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Facile and practical synthesis of optically pure 1D-*chiro*-inositol from *myo*-inositol

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Abstract—Optically pure 1D-*chiro*-inositol (DCI) has been synthesized from optically inactive *myo*-inositol practically in four steps. The crystalline nature of most intermediates and the utilization of inexpensive reagents facilitate the economical mass production of DCI, which is expected to be used in the future for treatment of Type 2 diabetes and polycystic ovary syndrome (PCOS). © 2001 Elsevier Science Ltd. All rights reserved.

Kasugamycin,[1] discovered by Umezawa et al. in 1965, has been used as an agricultural antibiotic. While its constituent cyclitol, 1D-*chiro*-inositol (DCI), is expected to have potential to treat Type 2 (adult-onset) diabetes,[2] it was reported[3] that the Phase II clinical trials of DCI for women with polycystic ovary syndrome (PCOS), the most common female endocrine disorder that affects up to 6 million women in the United States,[4] had been successfully conducted. These significant results put kasugamycin in the spotlight as the natural source of DCI, but its present fermentation scale is too small to meet the expected demand. Although 4-*O*-methyl-DCI, (+)-pinitol, has been found in the extract of sugar pine,[5] its limited availability hinders its use for the production of DCI on a large scale. Other reported methods to yield DCI or protected DCI include enzymatic conversion from *myo*-inositol[6] or D-*chiro*-3-inosose,[7] a combination of a biocatalytic approach and chemical modification starting from halobenzene,[7,8] and chemical synthesis from methyl α-D-glucoside via 6-*O*-acetyl-5-enopyranoside[9] or via 5-enopyranoside,[10] from *myo*-inositol,[11] and from cyclohexene.[12] In the light of the anticipated problems such as cost, purity and availability associated with the above processes, it was deemed worthwhile to investigate a new synthetic route applicable to the mass production of DCI.

As shown in Scheme 1, we chose inexpensive and readily available *myo*-inositol as the starting compound. First, *myo*-inositol was converted into its 2,3-(+)-camphor acetal (**1**) in 63% yield (43% after recrystallization in MeOH–H_2O) by modifying the methods described in recent papers.[13–15] The mixture of byproduct acetals was readily hydrolyzed in an acidic solution to recover *myo*-inositol.

In order to introduce a leaving group at the C-1 position, compound **1** was treated with Tf_2O in pyridine–CH_2Cl_2 (1:1) at −20°C to give unstable 1-triflate (**2a**)[16] as the main product. Similar selectivity was observed on treatment with TsCl to give 1-tosylate (**2b**)[17] in 85% yield. This higher reactivity of the 1-hydroxyl group may be attributed to its intramolecular hydrogen bonding with *cis*-vicinal oxygen at C-2.[18] Suami and co-workers reported[19] an analogous selectivity in tosylation of 1,2-*O*-cyclohexylidene-DL-*myo*-inositol by obtaining the 3-tosylate.

Treatment of **2a** with BzOLi in DMF afforded anhydrides **3**[20] and **4**,[21] instead of forming a benzoyl derivative with inversion of the stereochemistry at C-1. The structures of **3** and **4** were unambiguously confirmed by X-ray diffraction. These two compounds were also obtained from 1-tosylate (**2b**) (Table 1, entries 1 and 2). It was concluded, therefore, the oxygen anions at 4 or 6 intramolecularly attacked the C-1 more easily than the benzoyloxy anion under these conditions. Formation of similar anhydrides was also observed[22] when 1,2-*O*-cyclohexylidene-3- or 3,4-di-*O*-tosyl-DL-*myo*-inositol was treated with MeONa in MeOH.

Keywords: inositols; cyclitols; resolution; sulfonyl compounds; inversion reactions; 1D-*chiro*-inositol; diabetes.

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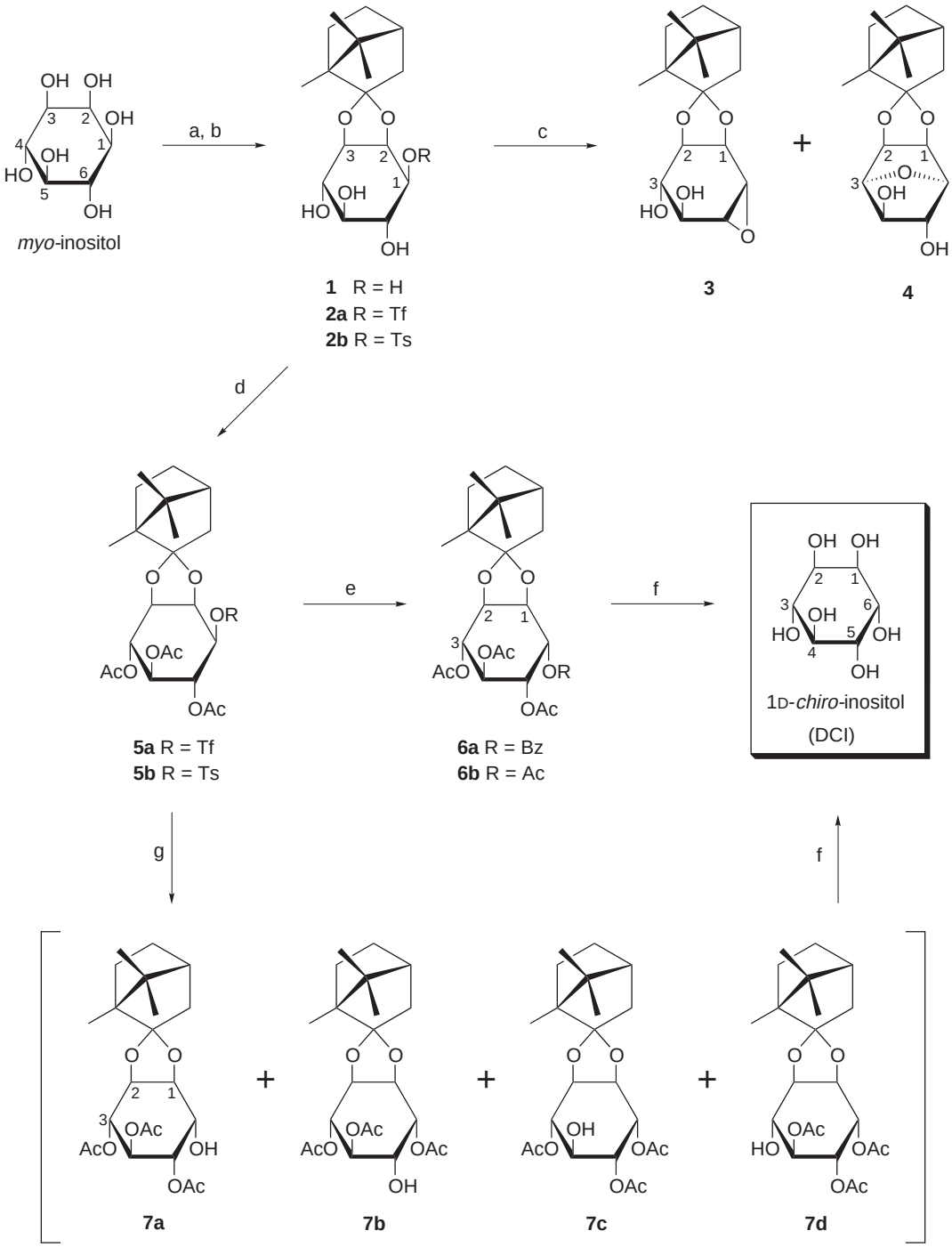
For suppression of these undesirable attacks of the oxygen anions, the remaining three hydroxyl groups of **2a** were protected by addition of Ac_2O into the reaction mixture of sulfonylation, after monitoring disappearance of **1** on a TLC plate, to yield triacetate (**5a**).[23] Compound **5b**[24] was also produced from **1** in a similar manner.

A few representative results of inversion reactions at C-1 of **5a** and **5b** are summarized in Table 1. Our concern that a *muco*-inositol would be formed[25] by the neighboring group participation fortunately proved to be groundless, and these two compounds successfully underwent displacement by the benzoate or acetate anion to give **6a**[26] and **6b**,[27] respectively (entries 3–9),



Scheme 1. Reaction conditions: (a) 1. (1*R*)-(+)-camphor dimethyl acetal, H_2SO_4, DMSO, 70°C, 3 h, 2. MeONa, 3. *p*-TsOH, $CHCl_3$–MeOH–H_2O, 17 h, 63%; (b) Tf_2O (or TsCl), pyr–CH_2Cl_2, –20°C, 2 h (or 20 h), 76% (or 85%); (c) see Table 1; (d) Ac_2O, pyr–CH_2Cl_2; (e) see Table 1; (f) 1. MeONa, MeOH, 1 h, 2. 50% AcOH–H_2O, 80°C, 0.5 h, 88–93%; (g) see Table 1.

Table 1. Inversion reactions of the 1-hydroxyl group of *myo*-inositol derivatives

Entry	Substrate	Reagent	Solvent	Temp. (°C)	Time (h)	Product	Yield[a] (%)
1	**2a**	BzOLi	DMF	80	1	**3**, **4** (1:6)	61
2	**2b**	BzOLi	DMF	120	3	**3**, **4** (1:2)	52
3	**5a**	BzOLi	DMF	80	2	**6a**	83
4	**5b**	BzOLi	DMF	Reflux	20	**6a**	51
5	**5b**	BzONa	DMF	Reflux	10	**6a**	57
6	**5b**	BzOK	DMF	Reflux	5	**6a**	56
7	**5a**	AcOK	DMF	80	1	**6b**	81
8	**5b**	AcOK	DMF	150	8	**6b**	57
9	**5b**	AcOK	DMSO	140	3	**6b**	57
10	**5a**	NaF	DMF	100	2	**7a**, **7b**, **7c** (1:1.5:0.1)	56
11	**5b**	NaF	DMSO	170	15	**7a**, **7b**, **7c**, **7d** (1:1:0.7:0.4)	65

[a] From **1** after purification by silica-gel chromatography.

which have the same configuration as DCI. The rate of displacement by the benzoate anion depends on its counter cations ($K^+ > Na^+ > Li^+$, entries 4–6). Moreover, using DMSO instead of DMF for a solvent gave the same yield of **6b** at lower temperature in a shorter time (entries 8 and 9). Optimization of the reaction conditions is now under study.

When **5a** was treated with NaF, the desired inversion products (**7a**, **7b**, **7c**) were also obtained by participation of the adjacent 6-acetoxyl group followed by hydrolysis and acetyl migration (entry 10).[28] Treatment of **5b** with NaF in DMSO gave **7a**–**c** accompanied with **7d**, which was produced by rather drastic conditions to complete the inversion at C-1 (entry 11).

Finally, compounds **6a**, **6b** and the mixture of **7a**–**c**(**d**) were respectively deprotected in a basic, and subsequently acidic, medium to give DCI almost quantitatively. DCI thus obtained showed the same specific rotation, $[\alpha]_D^{25}$+64 (*c* 1, H_2O), (lit.[7] +63.2), and NMR spectra as those of authentic DCI from kasugamycin.

In conclusion, we have successfully developed a new synthetic route to optically pure 1D-*chiro*-inositol (DCI) from optically inactive *myo*-inositol, in total 47% (via **5a** and **6a**), 33% (via **5b** and **6a**) and 36% (via **5b** and **7a**–**d**) yields, practically in four steps: (1) selective monoacetalization with chiral ketone and resolution; (2) selective introduction of a leaving group at C-1 and subsequent esterification of the remaining hydroxyl groups; (3) inversion at C-1; (4) deprotection. The total yields become higher when *myo*-inositol recovered in the first step is taken into the calculation. The crystalline nature of most intermediates, the utilization of inexpensive reagents and the environmentally-friendly recycling of the undesired acetal isomers, (1*R*)-(+)-camphor, and solvents facilitate the economical mass production of DCI. We believe the above synthetic route will meet the great demand for manufacturing DCI, which is expected to be used in the future for treatment of Type 2 diabetes and polycystic ovary syndrome (PCOS).

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16. Compound **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84, 0.87 and 0.97 (s, Me each), 3.39 (t, $J=10$ Hz, H-5), 3.61 (dd, $J=7$, 10 Hz, H-4), 3.95 (dd, $J=5.5$, 7 Hz, H-3), 3.99 (t, $J=10$ Hz, H-6), 4.47 (apparent t, $J=5$, 5.5 Hz, H-2), 4.94 (dd, $J=5$, 10 Hz, H-1).
17. Compound **2b**: colorless needles (from $CHCl_3$–*n*-hexane); mp 143–144°C; $[\alpha]_D^{21}$ −32 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.73, 0.81 and 0.85 (s, Me each), 2.41 (s, Me of Ts), 3.02 (dt, $J=5$, 9.5, 9.5 Hz, H-5), 3.17 (ddd, $J=5$, 7, 9.5 Hz, H-4), 3.42 (dt, $J=5$, 9.5, 9.5 Hz, H-6),

3.73 (dd, $J=6$, 7 Hz, H-3), 4.06 (dd, $J=4.5$, 6 Hz, H-2), 4.62 (dd, $J=4.5$, 9.5 Hz, H-1), 4.93 (d, $J=5$ Hz, HO-4), 4.95 (d, $J=5$ Hz, HO-5), 5.24 (d, $J=5$ Hz, HO-6).

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20. Compound **3**: colorless columns (from $CHCl_3$–*n*-hexane); mp 136–137°C; $[\alpha]_D^{24}$ −22 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.84, 0.86 and 1.01 (s, Me each), 2.67 (d, $J=11$ Hz, HO-3), 3.12 (d, $J=11$ Hz, HO-4), 3.26 (H-6), 3.52 (H-5), 4.08 (H-3), 4.19 (dt, $J=3$, 3, 11 Hz, H-4), 4.26 (H-2), 4.63 (d, $J=6$ Hz, H-1). Some signals were collapsed with long-range couplings between H-1 and 5, H-2 and 6 and H-3 and 5. Anal. calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.92; H, 8.08.
21. Compound **4**: colorless columns (toluene–*n*-hexane); mp 180–181°C; $[\alpha]_D^{24}$ −11 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.87, 0.98 and 1.02 (s, Me each), 2.09 (d, $J=6.5$ Hz, HO-5), 4.17 (dddd, $J=1.5$, 2.5, 5, 11.5 Hz, H-4), 4.26 (d, $J=11.5$ Hz, HO-4), 4.39 (broad d, 5 Hz, H-6), 4.41 (t, $J=5$ Hz, H-3), 4.47 (dd, 2.5, 6.5 Hz, H-5), 4.67 (dddd, $J=1$, 1.5, 5, 8.5 Hz, H-2), 4.72 (dd, $J=5$, 8.5 Hz, H-1). The 2D-COSYLR spectrum showed long-range correlations between H-1 and 3, H-1 and 5, H-2 and 4, H-2 and 6, H-3 and 5 and H-4 and 6. Anal. calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.88; H, 8.10.
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23. Compound **5a**: colorless needles (from $CHCl_3$–*n*-hexane); mp 121–122°C (decomp.); $[\alpha]_D^{23}$ −42 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88, 0.99 and 1.02 (s, Me each), 2.04, 2.08 and 2.10 (s, Me of Ac each), 4.18 (dd, $J=5$, 6.5 Hz, H-3), 4.58 (dd, $J=4$, 6.5 Hz, H-2), 5.07 (dd, $J=6$, 8 Hz, H-5), 5.12 (dd, $J=4$, 10.5 Hz, H-1), 5.16 (dd, $J=5$, 6 Hz, H-4), 5.61(dd, $J=8$, 10.5 Hz, H-6). Anal. calcd for $C_{23}H_{31}F_3O_{11}S$: C, 48.25; H, 5.46. Found: C, 48.07; H, 5.38.
24. Compound **5b**: colorless needles (from $CHCl_3$–*n*-hexane); mp 226–227°C; $[\alpha]_D^{23}$ −36 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85, 0.91 and 0.96 (s, Me each), 1.89, 1.99 and 2.06 (s, Me of Ac each), 2.44 (s, Me of Ts), 4.05 (t, $J=6$ Hz, H-3), 4.42 (dd, $J=4$, 6 Hz, H-2), 4.91 (dd, $J=4$, 10.5 Hz, H-1), 5.00 (t, $J=8$ Hz, H-5), 5.12 (dd, $J=6$, 8 Hz, H-4), 5.44 (dd, $J=8$, 10.5 Hz, H-6). Anal. calcd for $C_{29}H_{38}O_{11}S$: C, 58.57; H, 6.44. Found: C, 58.71; H, 6.50.
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26. Compound **6a**: colorless needles (from *n*-hexane); mp 138–139°C; $[\alpha]_D^{23}$ +64 (*c* 1, $CHCl_3$);^1H NMR (500 MHz, $CDCl_3$) δ 0.87, 0.99 and 1.00 (s, Me each), 1.98, 2.04 and 2.10 (s, Me of Ac each), 4.21 (t, $J=6.5$ Hz, H-2), 4.33 (dd, $J=3$, 6.5 Hz, H-1), 5.25 (dd, $J=6.5$, 7.5 Hz, H-3), 5.40 (dd, $J=3$, 9 Hz, H-5), 5.43 (dd, $J=7.5$, 9 Hz, H-4), 5.81 (t, $J=3$ Hz, H-6). Anal. calcd for $C_{29}H_{36}O_{10}$: C, 63.96; H, 6.66. Found: C, 63.70; H, 6.60.
27. Compound **6b**: $[\alpha]_D^{21}$ +46 (*c* 1, $CHCl_3$);^1H NMR (500 MHz, $CDCl_3$) δ 0.86, 0.94, 0.97 (s, Me each), 2.01, 2.03, 2.07 and 2.13 (s, Me of Ac each), 4.14 (t, $J=6.5$ Hz, H-2), 4.18 (dd, $J=3$, 6.5 Hz, H-1), 5.17 (apparent t, $J=7$, 8 Hz, H-3), 5.25 (dd, $J=2.5$, 8 Hz, H-5), 5.28 (t, $J=8$ Hz, H-4), 5.56 (apparent t, $J=2.5$, 3.5 Hz, H-6).
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