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# Improved synthesis of enantiopure pseudo-$C_2$-symmetric 1,4-bis-epoxide building blocks from arabitol

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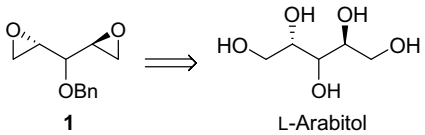
**Abstract**—An improved large-scale synthesis of 1,2:4,5-dianhydro-3-benzylarabitol and 1,2:4,5-dianhydroarabitol from arabitol is described.

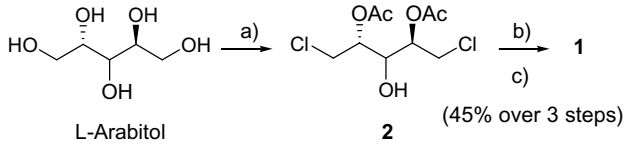

## 1. Introduction

Small chiral bis-epoxides are useful building blocks in organic synthesis. Many examples have been reported of their use as starting materials in traditional and bidirectional syntheses.[1–12] Such bis-epoxides are not commercially available, and have to be synthesised.[2,4,6,8,10,12] Carbohydrates are often used as starting materials, but catalytic enantioselective methods are also available.

The chiral, pseudo-$C_2$-symmetric bis-epoxide **1** (Scheme 1) is an important building block. Existing preparative methods for **1** are based on arabitol, which has the added advantage that both enantiomers are commercially available at similar cost. Schreiber reported a three-step synthesis involving the treatment of arabitol with Moffatt's reagent to yield the dichloro diacetate intermediate **2** (Scheme 2). Epoxide formation initiated by saponification with sodium methoxide, and alkylation with benzyl bromide afforded **1** in 45% overall yield.[4b]

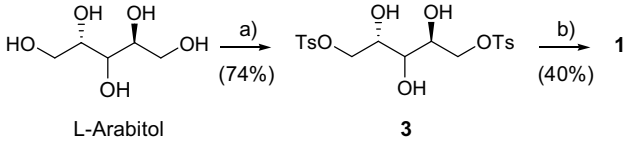



**Scheme 1.**




**Scheme 2.** Reagents and conditions: (a) $Me_2C(OAc)COCl$, MeCN, rt, 15 h; (b) NaOMe, THF, rt, 0.5 h; (c) NaH, BnBr.

An alternative route was described by Dreyer,[4a] in which arabitol was initially converted into the corresponding bis-tosylate (Scheme 3). Subsequent intramolecular tosylate displacement followed by benzylation of the remaining alkoxide group delivered **1** in 30% yield from arabitol.




**Scheme 3.** Reagents and conditions: (a) TsCl, pyridine, 0 °C, 3 h; (b) NaH, THF, 0 °C, 1 h; then BnBr, rt, overnight.

For ongoing research within our group, large quantities of **1** were required. However, neither procedure mentioned above were reproducible in our hands, with **1** obtained in low yields (<18%). Given L-arabitol is

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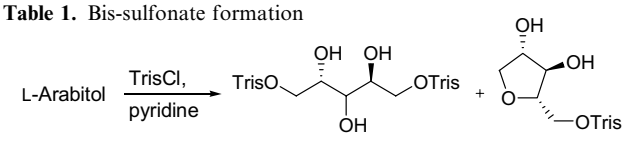
moderately expensive, it prompted us to reinvestigate and optimise the formation of **1**. We report herein, a high yielding, reproducible and straightforward synthesis of **1** on a large scale, based on modifications of Dreyer's protocol.

## 2. Results and discussion

### 2.1. Optimisation of bis-sulfonate 4 formation

In order to ensure selective sulfonylation at the primary alcohol groups, the synthesis of known[13] 1,5-di-*O*-(2,4,6-triisopropylbenzene sulfonyl)arabitol **4**, was investigated. The reaction of L-arabitol with 2,4,6-triisopropylbenzene sulfonyl chloride (TrisCl) at rt for 18 h yielded the desired bis-sulfonate **4** as the major product in modest yield, together with a side product which was identified as the tetrahydrofuran derivative **5** (Table 1, entry 1).[14] Increasing or decreasing the concentration led to decreased yields of **4** with equally unacceptable high returns of **5** (entries 2 and 3). As **5** clearly originated from the intramolecular cyclisation of **4**, a shorter reaction time was investigated (entry 4). This led to a considerable reduction in the yield of side-product **5**, but unfortunately this did not lead to a big increase in yield for **4** (entry 4 vs 1). Finally, it was found that the reaction temperature was the decisive parameter with the cyclisation being largely suppressed at 0 °C (entry 5). Addition of DMAP to facilitate the sulfonylation further improved the yield of **4** to 80%, with 10% of cyclised by-product **5** (entry 6).

**Table 1.** Bis-sulfonate formation



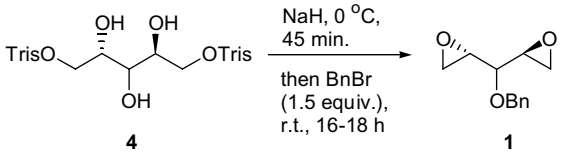

| Entry | TrisCl (equiv) | Conc. (M) | Time (h) | Temp (°C) | **4** (%) | **5** (%) |
|---|---|---|---|---|---|---|
| 1 | 2.2 | 0.44 | 18 | rt | 48 | 32 |
| 2 | 2.2 | 1.31 | 18 | rt | 44 | 27 |
| 3 | 2.2 | 0.22 | 18 | rt | 32 | 39 |
| 4 | 2.2 | 0.44 | 5 | rt | 55 | 13 |
| 5 | 2.4 | 0.44 | 20 | 0 | 73 | 7 |
| 6 | 2.2[a] | 0.44 | 24 | 0 | 80 | 10 |

[a] 10 mol % DMAP added.

### 2.2. Optimisation of bis-epoxide 1 formation

Using purified **4**, the base-mediated double cyclisation process was investigated (Table 2). Following Dreyer's conditions, treatment of **4** with 3 equiv of sodium hydride in THF initiated bis-epoxide formation and subsequent benzylation of the resulting alkoxide afforded **1** in 46% yield (entry 1), similar to that of Dreyer's observations.[4a] A sharp improvement was observed when the reaction solvent was changed to DMF (entry 2). An increase in dilution was found to effect a general increase in yield (entries 3 and 4). The efficiency of the benzylation was further enhanced by the addition of sodium iodide (entry 5), leading to an excellent yield of 83%.

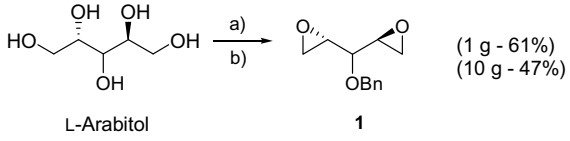
**Table 2.** Bis-epoxide formation




| Entry | Conc. (M) | Solvent | NaI (equiv) | Yield (%) |
|---|---|---|---|---|
| 1 | 0.061 | THF | 0 | 46 |
| 2 | 0.073 | DMF | 0 | 62 |
| 3 | 0.050 | DMF | 0 | 74 |
| 4 | 0.033 | DMF | 0 | 77 |
| 5 | 0.033 | DMF | 1.5 | 83 |

### 2.3. Large-scale optimisation

Having found high yielding conditions for the individual operations, the process was further optimised for scale-up. Importantly, it was aimed to avoid using column chromatography for the purification of the bis-sulfonate **4**. To this end, arabitol was subjected to bis-sulfonylation with TrisCl in pyridine, followed by aqueous work-up and direct subjection of the obtained crude material to the bis-epoxide formation/benzylation sequence. Starting with 1 g of arabitol and using DMF as solvent for the second step, an overall yield of 61% was obtained (Scheme 4). However, an overall yield of only 47% was obtained on a 10-g scale.

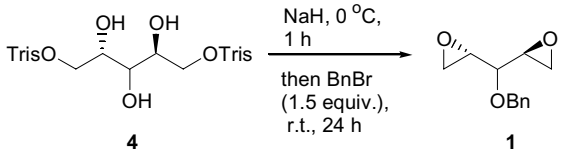



**Scheme 4.** Reagents and conditions: (a) TrisCl (2.2 equiv), pyridine (0.44 M), DMAP (10%), 0 °C, 24 h; (b) NaH (3.5 equiv), DMF (0.03 M), 0 °C, 1 h; then BnBr (1.5 equiv), NaI (1.5 equiv), rt, 24 h.

Also, a practical limitation of the conditions used became apparent in that for 10 g of arabitol, 2.2 L of DMF was needed for the second step. In order to decrease the required amount of DMF, the use of solvent mixtures was investigated (Table 3). A 1:1 mixture of DMF/THF was found to effect yields comparable to DMF (entry 1), but further reducing the amount of DMF led to a decrease in yield (entries 2 and 3). In addition, another practical difficulty still existed, that the use of these water soluble solvents did not facilitate the aqueous work-up of this reaction. However, by utilising a 1:1 mixture of DMF and $Et_2O$, the extraction procedure was greatly simplified with the yield remaining equally high (entry 4).

Having successfully determined a suitable solvent system, a large-scale synthesis (10 g) of **1** was attempted under the optimised conditions from Table 3. In addition, the amount of TrisCl used in the first step was reduced

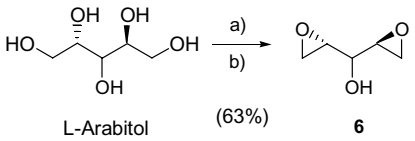
**Table 3.** Solvent optimisation




4 1

| Entry | Conc. (M) | Solvent | NaI (equiv) | Yield (%) |
|---|---|---|---|---|
| 1 | 0.030 | DMF/THF 5:5 | 1.5 | 83 |
| 2 | 0.030 | DMF/THF 3.7:6.3 | 1.5 | 81 |
| 3 | 0.030 | DMF/THF 2.7:7.3 | 1.5 | 66 |
| 4 | 0.030 | DMF/$Et_2O$ 5:5 | 1.5 | 85 |

from 2.2 to 2.05 equiv in order to avoid a possible sulfonylation side reaction of residual TrisCl with the alkoxide obtained before benzylation in the second step. This resulted in the formation of **1** in 63% overall yield. The by-product **5** was easily removed after purification by column chromatography.




**Scheme 5.** Reagents and conditions: (a) TrisCl (2.05 equiv), pyridine (0.44 M), DMAP (10%), 0 °C, 24 h; (b) NaH (3.5 equiv), THF (0.03 M), 0 °C, 1 h; then satd $NH_4Cl$.

With the optimised conditions for the synthesis of **1** established, the conversion of L-arabitol to the unprotected hydroxy bis-epoxide **6** was also investigated. Hence, bis-sulfonylation (Scheme 5) and NaH treatment of the crude bis-sulfonate was followed by acidic work-up to give **6** in a 63% overall yield. Importantly, DMF was not a useful solvent for the second step, as an aqueous extraction could not be used given **6** is water soluble. Instead, THF was used as solvent.

## 3. Conclusion

In conclusion, we have successfully established a significantly improved synthesis for bis-epoxide **1** over existing methods. The methodology is high yielding, reproducible and suitable for scaling up. Chromatographic purification of the large molecular weight bis-sulfonate intermediate **4** is not required, while the use of a DMF/$Et_2O$ solvent mixture for the second step—necessary to achieve high benzylation yields—allows for an easy aqueous extraction to remove salts and DMF. The unprotected bis-epoxide **6** was also synthesised under similar conditions. Multigram quantities of these compounds can be easily obtained in straightforward steps over a short period of time.

## 4. Experimental

Arabitol was obtained from CMS Chemicals, and used without further purification. Pyridine was distilled from $CaH_2$ and stored in a Schlenk flask. $Et_2O$ and THF were distilled from Na/benzophenone immediately prior to use. Extra dry DMF (water < 50 ppm) was purchased from commercial sources. Glassware was flame-dried immediately before use. Column chromatography was performed on 230–400 mesh silica gel. Reactions were monitored by TLC (Merck) with alkaline $KMnO_4$ and anisaldehyde dyes.

### 4.1. Preparation of (2*S*,4*S*)-1,5-di-*O*-(2,4,6-triisopropylbenzenesulfonyl)-arabitol 4

Triisopropylbenzensulfonyl chloride (4.47 g, 14.8 mmol) was added to a solution of L-arabitol (1.06 g, 6.70 mmol) and DMAP (84.0 mg, 0.685 mmol) in pyridine (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. HCl (2M, 95 mL) and $Et_2O$ (30 mL) were added. The aqueous layer was extracted with $Et_2O$ (2 × 30 mL), washed with 2 M HCl (30 mL), 5% $NaHCO_3$ (30 mL) and brine (30 mL) before drying over $MgSO_4$. Filtration, concentration in vacuo and purification by column chromatography (acetone/petroleum ether 2:8) afforded **4** (3.84 g, 80%) and **5** (256 mg, 10%) as a white solid.

**4.1.1. Data for 4.** Mp 127.5–128.5 °C, lit.[13] 111–112; $[\alpha]_D^{24} = -1.4$ (*c* 2.2, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) 7.19 (4H, s, ArH), 4.33 (1H, dd, $J = 11.0$, 3.0 Hz), 4.27–4.06 (8H, m), 3.98 (1H, ddd, $J = 8.5$, 6.0, 3.0 Hz), 3.60 (1H, dd, $J = 8.0$, 1.0 Hz), 2.91 (2H, septet, $J = 7.0$ Hz), 2.67 (4H, s), 1.26 (24H, d, $J = 7.0$ Hz), 1.25 (12H, d, $J = 7.0$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) 154.3, 151.1, 129.0, 124.1, 70.9, 70.5, 70.2, 70.0, 68.3, 34.4, 29.8, 24.8, 23.6; IR ($cm^{-1}$): 3517 br, 2959 m, 1600 m, 1341 m and 1173 s; LRMS ($ES^+$) 707.6 ($M+Na^+$, 100); HRMS ($ES^+$) for $C_{35}H_{56}O_9S_2Na$ $(M+Na)^+$: calcd 707.3258. Found 707.3259

**4.1.2. Data for 5.** Mp 163.5–164.0 °C; $^1H$ NMR (400 MHz, acetone) 7.36 (1H, s), 7.35 (1H, s), 4.46–4.48 (1H, m, OH), 4.08–4.23 (3H, m), 3.91–3.96 (2H, m), 3.72 (1H, dt, $J = 9.5$, 2.0 Hz), 2.99 (2H, septet, $J = 7.0$ Hz), 2.98 (1H, septet, $J = 7.0$ Hz), 2.87 (1H, m, OH), 1.26 (12H, d, $J = 7.0$ Hz), 1.25 (6H, $J = 7.0$ Hz); $^{13}C$ NMR (100 MHz, acetone) 154.9, 151.7, 130.5, 124.8, 84.1, 79.6, 78.3, 74.7, 70.4, 35.0, 30.4, 25.0, 23.8; LRMS ($ES^+$) 423 ($M+Na^+$, 100); Anal. Calcd for $C_{20}H_{32}O_6S$: C, 59.98; H, 8.05. Found: C, 60.14; H, 8.21.

### 4.2. Preparation of (2*S*,4*S*)-1,2:4,5-dianhydro-3-(benzyl)-arabitol 1

**4.2.1. From bis-sulfonate 4.** NaH (60% dispersion in mineral oil, 0.120 g, 3.00 mmol) was added to a solution of bis-sulfonate **4** (0.50 g, 0.734 mmol) in DMF/$Et_2O$ (1:1, 24.4 mL) at 0 °C and the mixture stirred at 0 °C for 1 h. BnBr (0.14 mL, 1.18 mmol) was added and the reaction mixture warmed to room temperature. NaI (0.164 g, 1.10 mmol) was added and the mixture stirred for 24 h. Satd $NH_4Cl$ (5 mL) and $H_2O$ (5 mL) were added. The aqueous layer was extracted with $Et_2O$ (3 × 10 mL) and dried over $Na_2SO_4$. Filtration and

concentration in vacuo delivered crude **1**, which was purified by column chromatography (EtOAc/petroleum ether 2:8) to afford a clear oil (128 mg, 85%).

**4.2.2. From arabitol.** Triisopropylbenzensulfonyl chloride (41.4 g, 0.137 mol) was added to a solution of L-arabitol (10.0 g, 66.0 mmol) and DMAP (0.840 g, 6.88 mmol) in pyridine (150 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. HCl (2M, 920 mL) and $Et_2O$ (600 mL) were then added. The aqueous layer was extracted with $Et_2O$ ($2 \times 500$ mL), washed with 2 M HCl (100 mL), 5% $NaHCO_3$ (1 L) and brine (400 mL). Filtration and concentration in vacuo led to a white solid, which was dissolved in $Et_2O$/DMF (1:1, 2190 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 9.47 g, 0.237 mol) was added and the mixture was stirred at 0 °C for 1 h. BnBr (11.8 mL, 99.2 mmol) was added and the reaction mixture warmed to room temperature. NaI (14.7 g, 98.7 mmol) was added and the mixture stirred for 24 h. Satd $NH_4Cl$ (300 mL) and $H_2O$ (1.2 L) were then added. The aqueous layer was extracted with $Et_2O$ ($2 \times 300$ mL), washed with brine (500 mL) and dried over $Na_2SO_4$. Filtration, concentration in vacuo and purification by flash column chromatography (EtOAc/petroleum ether 2:8) delivered **1** as a clear oil (8.56 g, 63%). Bis-epoxide **1** can be further purified by distillation under reduced pressure (116 °C, 0.6 mbar).

**4.2.3. Data for *ent*-1.** $[\alpha]_D^{22} = +29.8$ (*c* 1.0, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) 7.25–7.37 (5H, m), 4.76 (1H, d, $J = 12.0$ Hz), 4.65 (1H, d, $J = 12.0$ Hz), 3.17 (1H, ddd, $J = 6.0$, 4.5, 3.0 Hz), 2.99 (1H, ddd, $J = 5.5$, 4.0, 2.5 Hz), 3.07 (1H, ddd, $J = 5.5$, 3.5, 2.5 Hz), 2.99 (1H, dd, $J = 6.5$, 5.5 Hz), 2.79–2.84 (2H, m), 2.64–2.68 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) 137.9, $128.3 \times 2$, $127.7 \times 3$, 79.7, 72.2, 52.6, 50.9, 45.2, 43.1; IR ($cm^{-1}$): 3062 m, 3031 m, 2998 s, 2927 m, 2873 m, 1602 w, 1496 m and 1455 s; LRMS (CI) 224 ($M + NH_4^+$, 60), 91 (100); HRMS ($ES^+$) for $C_{12}H_{14}O_3Na$ $(M+Na)^+$: calcd 229.08406. Found 229.08315.

### 4.3. Preparation of (2*S*,4*S*)-1,2:4,5-Dianhydroarabitol 6

Triisopropylbenzensulfonyl chloride (4.29 g, 14.1 mmol) was added to a solution of L-arabitol (1.05 g, 6.90 mmol) and DMAP (83.0 mg, 0.68 mmol) in pyridine (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. HCl (2M, 92 mL) and $Et_2O$ (50 mL) were then added. The aqueous layer was extracted with $Et_2O$ ($2 \times 50$ mL), washed with 2 M HCl (30 mL), 5% $NaHCO_3$ (10 mL) and brine (50 mL). Filtration and concentration in vacuo led to a white solid, which was dissolved in THF (219 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil, 0.92 g, 23.0 mmol) was added and the mixture was stirred at 0 °C for 1 h. Satd $NH_4Cl$ (3 mL) was added and the slurry filtered through a column of $Na_2SO_4$. Concentration in vacuo and purification by column chromatography (EtOAc/toluene 3:7) afforded a colourless liquid (0.509 g, 63%).

$^1H$ NMR data corresponded to previously reported values.[4b]: $^1H$ NMR (300 MHz, $CDCl_3$) 3.52 (1H, q, $J = 5.0$ Hz), 3.14 (1H, td, $J = 4.0$, 2.5 Hz), 3.09 (1H, ddd, $J = 4.5$, 4.0, 2.5 Hz), 2.75–2.85 (4H, m), 2.62 (1H, d, $J = 5.0$ Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) 70.2, 52.6, 52.1, 44.6, 44.1.

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