A Further Improved Synthesis of a Dibenzodioxocinone CETP Inhibitor

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Abstract: A newly improved synthesis of a dibenzodioxocinone CETP inhibitor is described. Key features of the synthetic route include a chiral ligand induced alkyl addition to aldehyde and the use of triethylborane for improved selective alkylation of brominated phenyl ring.

Key words: total synthesis, asymmetric synthesis, natural products, inhibitors, drugs

The natural product penicillide {11-hydroxy-3-[(1*S*)-1-hydroxy-3-methylbutyl]-4-methoxy-9-methyl-5*H*,7*H*-dibenzo[*b*,*g*][1,5]dioxocin-5-one, Figure 1} is a dibenzodioxocinone first reported by Sassa et al.[1] Derivatives of penicillide were reported to have a variety of biological activities including lipid lowering,[2] ACAT inhibition,[3] oxytocin antagonism,[4] and antihypertensive potential.[5] Recently, certain derivatives of dibenzodioxocinone were found to be a new class of CETP (cholesterol ester transfer protein) inhibitors.[6] Inhibition of CETP can lead to an increased level of high-density lipoprotein cholesterol (HDL-C) and is an alternative way to prevent coronary heart disease as opposed to lowering the level of low-density lipoprotein cholesterol (LDL-C).[7] In particular, compound **1** was reported to be a promising candidate for in vivo study with an IC_{50} of 15 nM toward CETP inhibition and long plasma stability.[6]

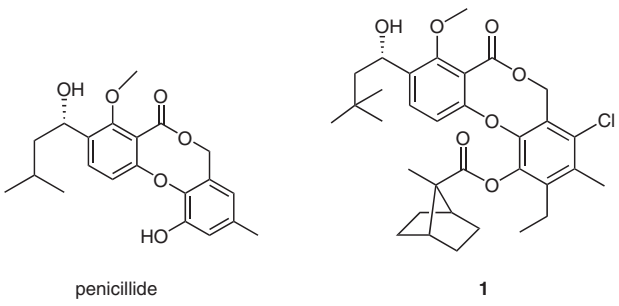


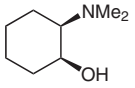
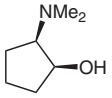
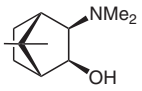
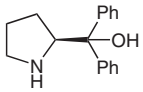
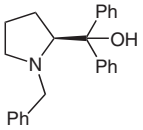
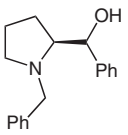
Figure 1

The original synthesis of **1** was a 17-step protocol with an overall yield of 0.1%, starting from 5-methylsalicylic acid.[8] We previously developed an 15-step route with a much better overall yield of 1.6%.[9] In this work, we report a further improved procedure that combines early introduction of the chiral functional group and borane-based alkylation to reach an overall yield of 4.5%.

The overall synthetic route is described in Scheme 1. Starting from **2**, aldehyde **3** can be obtained in seven steps with an overall yield of 24.2%, following the procedures described before.[8,9] Of these seven steps, the first three steps to arrive at 3-benzyloxy-5-methylsalicylic acid are identical to the original route developed by Bayer HealthCare AG.[8] However, in our hand, we performed the reactions at kg scale and achieved a combined yield of 61.3% as compared to a 18.3% yield at gram scale reported in the original patent.[8] The desired chlorine atom was introduced during this stage,[9] marking a difference between our work and the original route.

In our previous work, alkyl addition to aldehyde **3** was carried out in a racemic manner. As a consequence, chiral separation of intermediate enantiomers is required at

Table 1 Chiral Amino Alcohol Induced Asymmetric Addition

Amino alcohol **4**	Isolated yield of **5** (%)	ee (%)
 **4a**	64	92
 **4b**	66	86
 **4c**	60	>99
 **4d**	58	95
 **4e**	50	96
 **4f**	46	82

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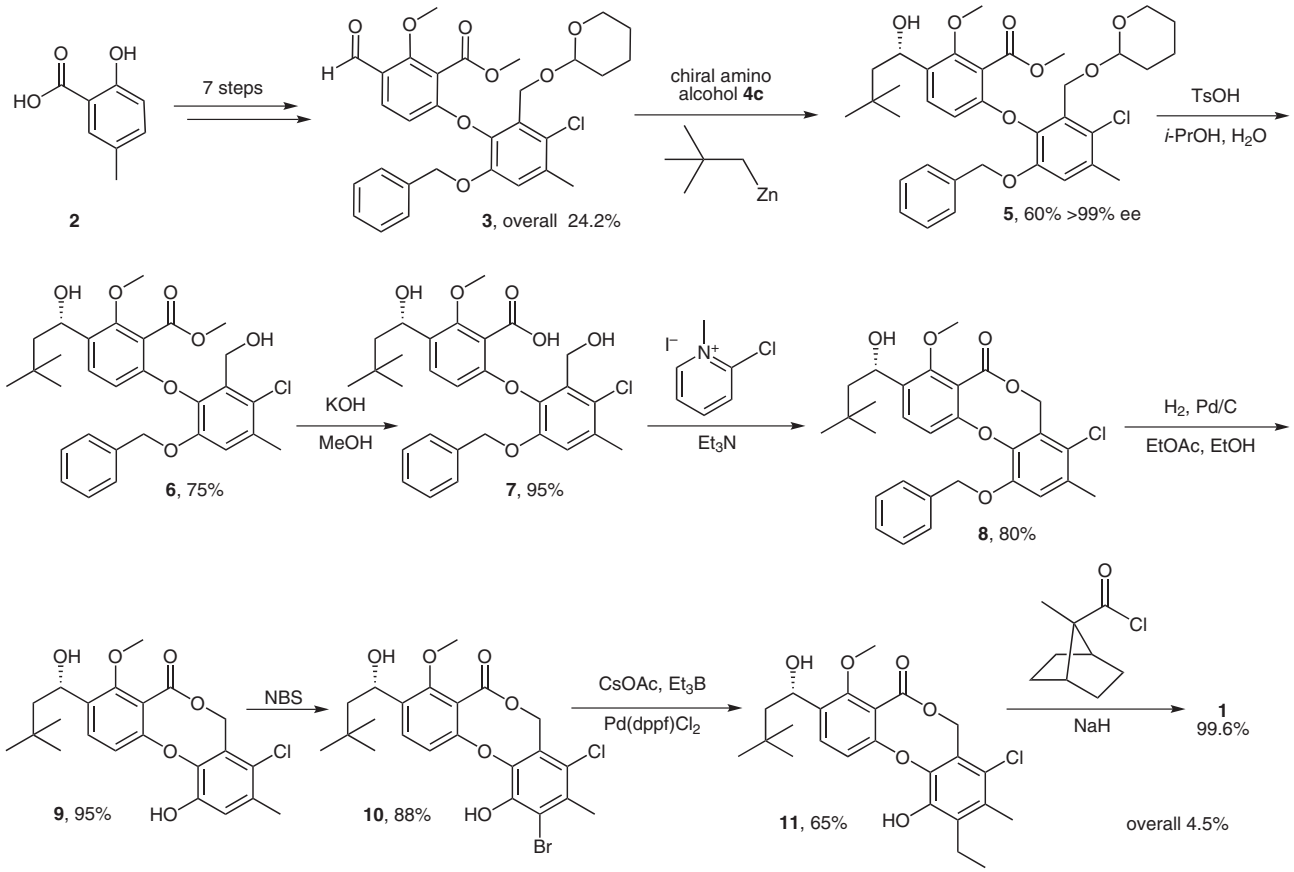

Scheme 1 Improved synthetic route for compound **1**

some stage before reaching the final product **1**. This drawback not only wastes starting material and lowers the overall yield, but also makes it much harder to adapt the procedure for potential large-scale production. Therefore, we decided to explore asymmetric alkyl addition conditions in hope to discover protocols that can produce the desired *S*-enantiomer in high yield and avoid chiral separation procedures.

We explored a variety of chiral amino alcohols **4** to induce asymmetric addition of 2,2-dimethylpropyl zinc to aldehyde **3**. The results are summarized in Table 1. It is gratifying to find that **4c** can induce the formation of **5** exclusively with an acceptable yield of 60%.[10] Figure 2 shows the optical purity of **5** by chiral chromatography.

From **5** to **10**, the procedures are identical to our previous work.[9] It is worth noting that in spite of the presence of the chlorine atom, the benzyl protection can be efficiently removed using Pd/C-catalyzed hydrogenation in EtOAc and EtOH to afford **9** with a high yield of 95%, a substantial improvement over the original protocol using $FeCl_3$ with a 65% yield.[8]

From compound **10**, introduction of the ethyl group was achieved using triethylborane and $Pd(dppf)_2Cl_2$ to afford **11** with a yield of 65%.[11] This is improved over our previous protocol that utilized the Negishi coupling[12] with a 40% yield,[9] as well as the original Bayer protocol that utilized the Stille coupling[13] with a 22% yield.[8] The formation of the target compound **1** was finally achieved after a 99.6% acylation step.

In summary, compound **1** as a potent CETP inhibitor was prepared starting from **2** with a significantly improved overall yield of 4.5% over previous methods.[8,9] With a highly enantioselective protocol for asymmetric alkylation of aldehyde **3**, our synthetic route avoids chiral separation of intermediates. Combined with other improvements to optimize individual reaction steps, this improved synthetic sequence opens up the opportunity to large-scale production of **1** or its analogues.

References and Notes

(1) Sassa, T.; Niwa, G.; Unno, H.; Ikeda, M.; Miura, Y. *Tetrahedron Lett.* **1974**, *45*, 3941.
(2) Taisho Pharmaceutical Ltd.; WO 1994012175, **1994**.
(3) Tomoda, H.; Nishida, H.; Masuma, R.; Cao, J.; Okuda, S.; Omura, S. *J. Antibiot.* **1990**, *44*, 136.
(4) Salituro, G. M.; Pettibone, D. J.; Clineschmidt, B. V.; Williamson, J. M.; Zink, D. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 337.
(5) (a) Bayer AG; DE 4039860, **1992**. (b) Bayer AG; EP 0411268, **1995**.
(6) Bruckner, D.; Hafner, F.-T.; Li, V.; Schmeck, C.; Telser, J.; Valalopoulos, A.; Wirtz, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3611.

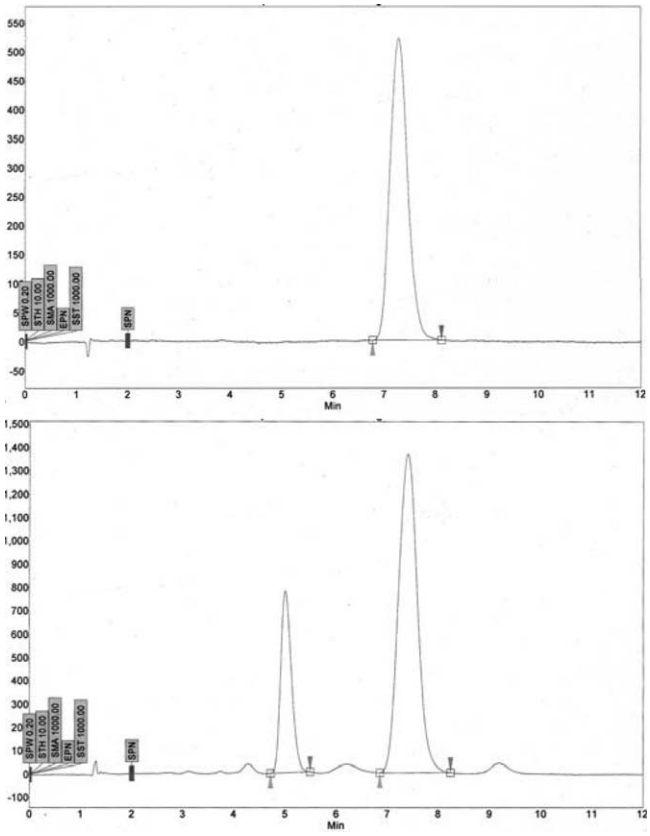

Figure 2 Optical purity of **5** analyzed using a Chiralpak AD-H column, mobile phase: *n*-hexane–EtOH (80:20). Top: compound **5**; bottom: mixture of **5** and a racemic sample based on our previous work.[9]

(7) (a) Dullaart, R. P. F.; Dallinga-Thie, G. M.; Wolffenbuttel, B. H. R.; van Tol, A. *Eur. J. Clin. Invest.* **2007**, *37*, 90. (b) Linsel-Nitschke, P.; Tall, A. R. *Nature Rev. Drug Discov.* **2005**, *4*, 193.

(8) Bayer HealthCare AG; WO 2004039453, **2004**.

(9) Fudan University; CN 101066967, **2007**.

(10) **Experimental Procedure**
To a stirred solution of **4c** (74.1 mg, 0.4 mmole) in dry toluene at 15 °C under argon, a solution of 2,2-dimethyl-propyl zinc (4.76 g, 23 mmole) in toluene was added. After 15 min, the temperature was lowered to –78 °C, followed by the addition of a toluene solution (10 mL) of compound **3** (10.4 g, 18.8 mmol). The mixture was allowed to slowly warm to 0 °C, and stirred for another 6 h. The reaction was slowly quenched by a sat. solution of NH_4Cl, and then extracted three times with EtOAc. The combined organic phase was washed by H_2O and brine, dried over anhyd $MgSO_4$, filtered and concentrated. The product **5** was purified using silica gel chromatography (CH_2Cl_2–EtOAc, 50:1). Yield 7.06 g, 60%, $[a]_D^{20}$ +22.5 (*c* 1.0, $CHCl_3$; >99% ee, as analyzed by chiral HPLC, see Figure 2). ESI-MS: *m/z* = 627.1 $[M + H]^+$. ^1H NMR (400 MHz, CD_3Cl): δ = 1.01 (s, 9 H), 1.20–1.70 (m, 8 H), 2.02 (s, 1 H), 2.37 (s, 3 H), 3.45 (m, 1 H), 3.86 (s, 3 H), 3.92 (s, 3 H), 4.50 (dd, 1 H), 4.65 (m, 1 H), 4.93 (dd, 1 H), 5.02 (s, 2 H), 5.08 (m, 1 H), 6.38 (d, 1 H), 6.90 (s, 1 H), 7.18–7.35 (m, 6 H) ppm. ^{13}C NMR (100 MHz, CD_3Cl): δ = 20.4, 20.5, 25.4, 27.1, 30.1 (3 C), 30.5, 51.5, 52.4, 58.6, 62.3, 63.3, 66.5, 71.1, 114.5, 116.9, 118.8, 121.3, 123.6, 127.1 (2 C), 127.6, 128.9 (2 C), 131.0, 131.6, 131.8, 136.7, 138.3, 142.3, 144.1, 151.1, 154.2, 168.2 ppm.

(11) Under argon, compound **10** (18.0 g, 36 mol), CsOAc (35.2 g, 108 mmol), and $Pd(dppf)_2Cl_2$ (0.54 g, 0.72 mmol) was dissolved in dry THF. To this was added a solution of Et_3B (1 M, 108 mL, 108 mmol) in THF. The mixture was heated to reflux for 4 h. Then it was cooled to 0 °C, and the reaction was quenched with 10% NaOH and 30% H_2O_2. After stirring at r.t. for 30 min, the mixture was neutralized with diluted HCl, followed by extraction with EtOAc for three times. The combined organic phase was washed with brine, dried over anhyd $MgSO_4$, and concentrated. Purification using silica gel chromatography (PE–EtOAc, 8:1 to 1:1) afforded **11**. Yield 10.5 g (65%). HRMS (MALDI/DHB): *m/z* = 471.1550 $[M + Na]^+$. ^1H NMR (400 MHz, CD_3Cl): δ = 1.03 (s, 9 H), 1.15 (t, 3 H), 1.57 (m, 1 H), 1.61 (m, 1 H), 1.93 (d, 1 H), 2.31 (s, 3 H), 2.77 (q, 2 H), 3.99 (s, 3 H), 5.16 (m, 1 H), 5.37 (dd, 1 H), 5.48 (dd, 1 H), 6.26 (s, 1 H), 6.84 (d, 1 H), 6.95 (s, 1 H), 7.59 (d, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3Cl): δ = 13.3; 16.2; 20.7, 30.1 (3 C), 30.8, 52.4, 62.3, 65.9, 66.6, 116.9, 118.8, 121.3, 123.6, 131.0, 131.6, 131.8, 138.3, 142.3, 144.1, 151.1, 154.2, 167.4 ppm.

(12) (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) *Handbook of Organo-palladium Chemistry for Organic Synthesis*, Part III, Vol. 1; Negishi, E., Ed.; Wiley-Interscience: New York, **2002**.

(13) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.