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Total synthesis of isotopically labelled flavonoids. Part 5: Gram-scale production of ^{13}C-labelled (−)-procyanidin B3†

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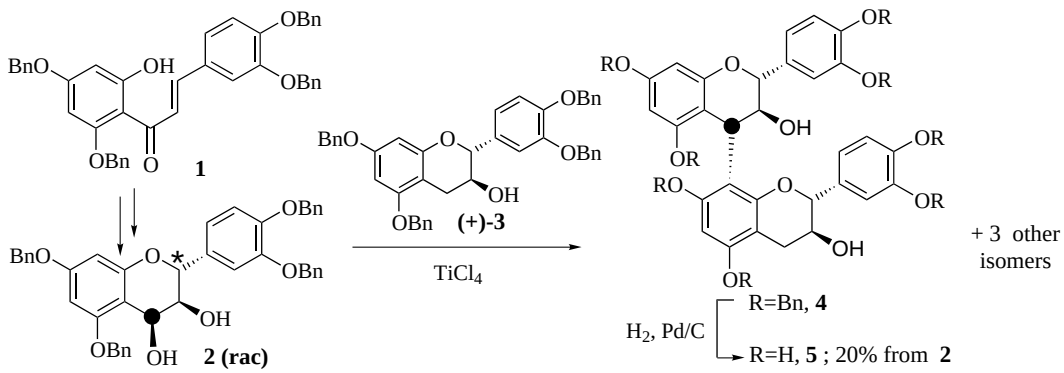
Abstract—Gram amounts of ^{13}C-labelled dimer (−)-procyanidin B3 **5** were prepared from 1-[^{13}C]acetic acid by coupling the optically labelled flavan-3,4-diol (+)-**7** with protected natural catechin (+)-**3** in acidic medium.

We recently described the synthesis of ^{13}C-labelled (−)-procyanidin B3 **5**, through the coupling of a racemic labelled flavan-3,4-diol derivative **2** with protected natural (+)-catechin[2] under Kawamoto's conditions.[3] However, this route could not be used to obtain this dimer in large amounts as needed for biological studies. Since we had in hand gram-amounts of labelled (+)-catechin,[1] it was conceivable to use it as a 'corner stone' intermediate to synthesise the dimer. The crucial glycol (+)-**7** was obtained by reoxidation of the protected ^{13}C-labelled catechin (+)-**6**[1,3] allowing its coupling with benzylated (+)-catechin to yield the enantiomerically pure labelled dimer B3 **5**.

Our former total synthesis of the dimer **5**[2] required the coupling of the racemic flavan-3,4-diol **2** with benzylated catechin (+)-**3** (Scheme 1). Since the access to this intermediate could never be obtained directly under an enantiomerically pure form from chalcone **1**,[2,4] the resolution of the racemic mixture was performed at the coupling step with (+)-catechin. Unfortunately, this led to three other dimers in addition to **4**. Not only had this a detrimental effect on the yields, but it also gave rise to very tough problems of purification, making this strategy unusable at large scale. Having in hand gram-amounts of benzylated labelled catechin (+)-**6**,[2] it was viewed as a precursor of such an optically pure glycol (Scheme 2). The best conditions to reoxidise the C-4 atom turned out to be those described by Ferreira (DDQ, CH_2Cl_2/MeOH),[5] giving the flavan-3,4-diol methyl ether derivative (+)-**7**[6] after centrifugal chro-



Scheme 1. Former total synthesis of ^{13}C-labelled dimer B3 (via the racemic glycol **2**).

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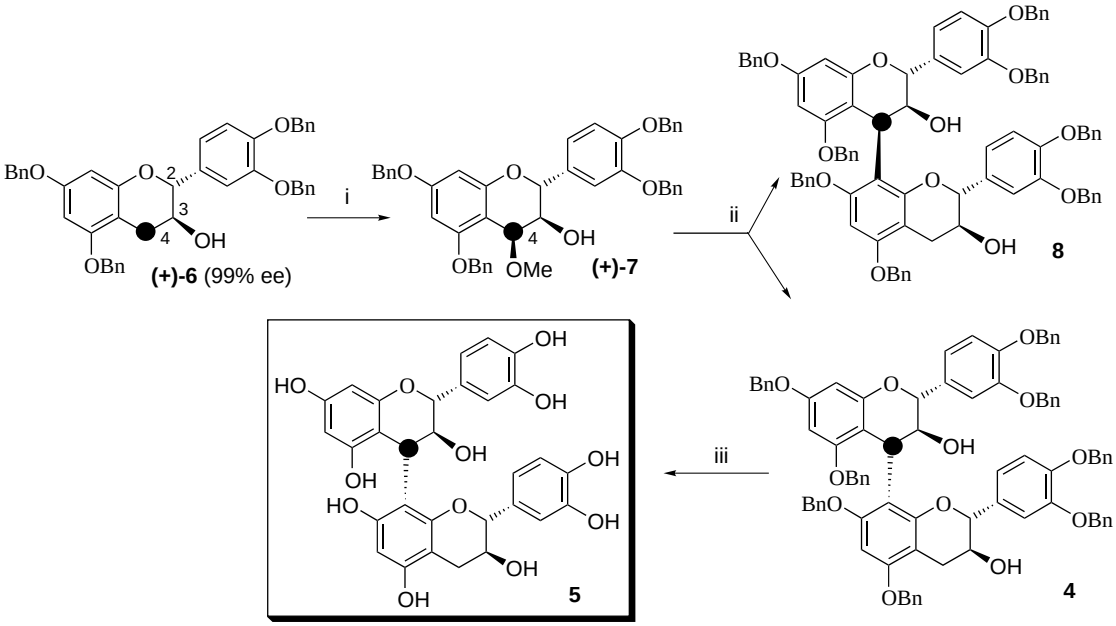

Scheme 2. Synthesis of labelled procyanidin B3 **5** from (+)-**6** (38%, from **7**). (i) DDQ (2 equiv.), CH_2Cl_2/MeOH 3:1, 56%. (ii) (+)-**3** (5 equiv.), $TiCl_4$ (1 equiv.), CH_2Cl_2, 82% coupling yield, **8**:**4** = 1:2. (iii) $Pd(OH)_2$/C, THF/H_2O 20:1, H_2 (atm. pressure), rt, 71%.

matography on gypsum-containing silica gel (4.8 g; 56% yield). This oxidation method was clearly stereoselective, leading exclusively to the 3,4-*cis* diastereomer, as deduced from NMR coupling constant value ($J = 3.5$ Hz). **7** was obtained in higher yields (up to 76%), in preliminary studies on smaller quantities. We have shown that this activated benzylic methyl ether decomposed rapidly upon storage at room temperature.

$TiCl_4$-catalysed condensation[2,3] of (+)-**7** (4.7 g) with optically pure (2*R*,3*S*)-tetrabenzyloxycatechin (+)-**3** (benzylated natural (+)-catechin) yielded dimers **8** and **4** in a 1:2 ratio (82% coupling yield). Purification by silica gel centrifugal chromatography led to pure benzylated dimer B3 **4** (4.8 g, 55%) and to its diastereomer **8** (2.4 g, 27%). Hydrogenolysis of dimer **4** provided 1.52 g of the native (−)-4*C*-[^{13}C]-procyanidin B3 **5** (71%) after purification by chromatography on Sephadex LH-20 (EtOH). The use of $Pd(OH)_2$/C in THF/H_2O at rt,[7] instead of Pd/C in dioxanne at 90°C,[2] for deprotection, allowed us to avoid the formation of benzylated catechin by-product resulting from the cleavage of the interflavanolic linkage.

We could then synthesise Gram amounts of ^{13}C-labelled dimer B3 **5** (in three steps and 21% yield from [^{13}C]-catechin **2**), thanks to our efficient resolution process of synthetic racemic flavan-3-ol **6**. We now reached our ultimate goal of preparing a large amount of labelled dimer B3, a major dimer present in wine, in addition to labelled (+)-catechin and (−)-epicatechin.[1] The use of this labelled flavonoid is under process in experiments aimed at assessing its bioavailability from red wine sources in humans and to investigate its pharmacological properties at a molecular level on cell cultures.

Acknowledgements

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6. Data for (+)-**7**: white solid. $[\alpha]_D = +48$ (*c* 1, CH_2Cl_2). ^{1}H HR-NMR ($CDCl_3$, 500 MHz), δ ppm: 2.39 (dd, $J = 3.5$, 9 Hz, 3-OH), 3.47 (d, $J = 4.5$ Hz, 4-*O*-CH_3), 3.86 (m, 3-H), 4.77 (dd, $J = 3.5$, 150 Hz, 4-H), 4.98 (dd, $J = 1.5$, 10.5 Hz, 2-H), 5.02 and 5.05 (2 d, $J = 12$ Hz, 7-*O*-$C\underline{H}_a\underline{H}_b$-$C_6H_5$), 5.06 and 5.12 (2 d, $J = 11.5$ Hz, 5-*O*-$C\underline{H}_a\underline{H}_b$-$C_6H_5$), 5.20 (m, 3′- and 4′-*O*-$C\underline{H}_2$-C_6H_5), 6.22 (d, $J = 2$ Hz, 8-H), 6.32 (d, $J = 2$ Hz, 6-H), 7.01 (d, $J = 8$ Hz, 5′-H), 7.05 (dd, $J = 1.5$, 8 Hz, 6′-H), 7.13 (d, $J = 1.5$ Hz, 2′-H), 7.32–7.50 (m, 20 *O*-CH_2-$C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$, 125 MHz), δ ppm: 58.8 (4-*O*-CH_3), 70.3 (C-4), 70.5 (7-*O*-$\underline{C}H_2$-C_6H_5), 70.8 (5-*O*-$\underline{C}H_2$-C_6H_5), 70.9 (C-3),

71.7 and 71.8 (3′- and 4′-*O*-$\underline{C}H_2$-C_6H_5), 77.2 (C-2), 93.9 (C-6), 94.9 (C-8), 103.6 (d, $J=48$ Hz, C-4a), 115.1 (C-2′), 115.4 (C-5′), 121.7 (C-6′), 127.6, 127.9, 128.0, 128.2, 128.5, 128.6, 128.8, 129.0 (4 *para*-, 8 *ortho*- and 8 *meta*-*O*-CH_2-$\underline{C}_6H_5$), 132.1 (C-1′), 136.9, 137.0, 137.6, 137.7 (4 *ipso*-*O*-CH_2-$\underline{C}_6H_5$), 149.6 (C-3′), 149.9 (C-4′), 156.7 (C-8a), 159.2 (C-5), 131.4 (C-7). MS (HR-FAB+, nitrobenzyl alcohol) m/z: calcd for $^{13}C_1^{12}C_{43}H_{40}O_7$ 681.2852; found 681.2826.

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