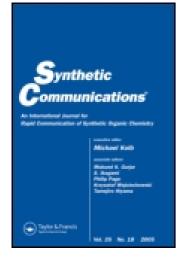
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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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Synthesis of Trisaccharide of Incanoside from Caryopteris incana

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To cite this article: Jubiao Li & Yanguang Wang (2004) Synthesis of Trisaccharide of Incanoside from Caryopteris incana, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:3, 515-522, DOI: <u>10.1081/SCC-120027292</u>

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SYNTHETIC COMMUNICATIONS[®] Vol. 34, No. 3, pp. 515–522, 2004

Synthesis of Trisaccharide of Incanoside from Caryopteris incana

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ABSTRACT

Trisaccharide phenyl 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyl- $(1 \rightarrow 2)$ -3,4-di-*O*-benzoyl- α -L-rhamnopyranosyl- $(1 \rightarrow 3)$ -2-*O*-acetyl-4,6-*O*-benzylidene-1-thio- β -D-glucopyranoside, the sugar core of incanosides from *Caryopteris incana* (T_{HUNB.}), was synthesized via a concise route. The key step of this route involved the preparation of decisive disaccharide acceptor from the phenyl 2-acetyl-3,4-di-*O*-benzoyl- α -L-rhamnopyranosyl- $(1 \rightarrow 3)$ -2-*O*-acetyl-4,6-*O*-benzylidene-1-thio- β -D-glucopyranoside by regioselective and chemoselective deacetylation method.

Key Words: Trisaccharide; Incanoside; Caryopteris incana; Synthesis.

In recent years, evidence has accumulated suggesting that free radicals are involved in many deterioration processes. They attack the unsaturated fatty

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acids in the biomembranes resulting in membrane lipid peroxidation, which is strongly connected with aging, carcinogenesis and atherosclerosis.^[1,2] It was also reported that many diseases of fruits and vegetables, including cancer and cardio- and cerebrovascular diseases, were ascribed to the oxidation resulting from the active oxygen molecules. Free radicals also attack DNA and cause mutation leading to cancer.^[3] Thus it is desirable to look for effective radical scavengers.

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In 1999, Janjun Gao et al.^[4] isolated incanoside C, D and E (Fig. 1) from the whole plant of *Caryopteris incana* ($T_{HUNB.}$) which was proved to exhibit good radical scavenging activities against DPPH radical and inhibitory actives against the oxidation of linoleic acid.^[5] Here, for the first time we report the synthesis of trisaccharide of incanosides C, D and E.

Although the linear trisaccharide structure is not very complex, the high stereoselective and regioselective coupling for the construction of $\beta(1 \rightarrow 2)$ and $\alpha(1 \rightarrow 3)$ linkages remains challenge. Our strategy is based on a regioselective deacetylation as shown in Sch. 1. The D-Glucose and L-Rhamnose were chosen as the starting materials. 1,2,3,4,6-Penta-O-acetyl- β -D-glucopyranose (1) and phenyl 4,6-O-benzylidene-1-thio- β -D-glucopyranoside (2) were prepared as previously reported.^[6] Acetylation of 2 with acetic anhydride in pyridine (\rightarrow 3), followed by our regioselective deacetylation method with hydrazine acetate in THF and CH₂Cl₂, afforded phenyl 2-Oacetyl-4,6-O-benzylidene-1-thio- β -D-glucopyranoside (4) in good yield. Allyl 2-O-acetyl-3,4-di-O-benzoyl- α -L-rhamnopyranoside (6) was synthesized via a four-step sequential reaction. 6 was then deally lated with $PdCl_{2}$,^[7] followed by trichloroacetimidation with CCl₃CN in the presence of DBU,^[8] to give 2-*O*-acetyl-3,4-di-*O*-benzoyl- α -L-rhamnopyranosyl trichloacetimidate (7). Similarly, the glycosyl donor 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl trichloacetimidate (5) was readily obtained by the selective 1-O-deacetylation of 1 via the method of Excoffier^[9] with hydrazine acetate and trichloroacetimidation.^[10]

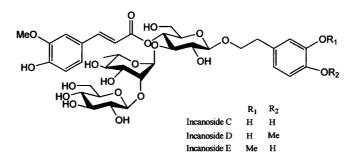
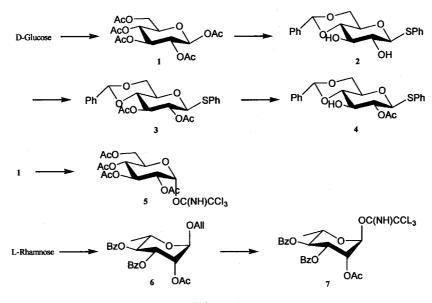


Figure 1. Structures of incanosides C, D and E.

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Synthesis of Trisaccharide of Incanoside from *Caryopteris incana*

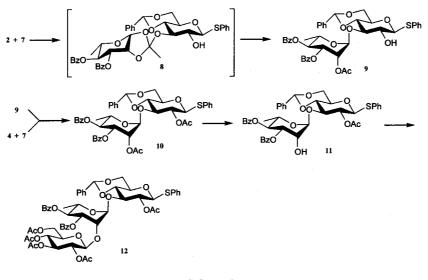
Scheme 1.

With the glucosyl acceptors 2 and 4 and rhamnosyl donor 7 in hand, the key disaccharide 10 was directly synthesized by coupling of 7 with the acceptor 4 in the presence of a catalytic amount of trimethylsilyl triflate (TMSOTf) with high stereoselectivity in excellent yield. We also obtained 10 by the acetylation of 9 resulting from the regioselective coupling of 7 and 2 under BF₃. OEt₂ as the catalyst. In our case, we have not isolated the intermediate orthoester 8.^[11] This may be due to the long reaction time and excess of catalyst (Sch. 2).

Disaccharide **11** is also a significant building block to synthesis of many natural products, such as ballotetroside^[12] and phenylpropanoid glycosides from Lamiophlomis rotata^[13] and Fernandoa adenophylla.^[14] To get the free 2'-OH of disaccharide, the chemoselective 2'-O-deacetylation was usually carried out in acid conditions,^[15] which resulted in a undesired removing of 4,6-protecting group. Based on our regioselective and chemoselective deacetylation method,^[16] **10** was treated with 85% hydrazine hydrate in THF to afford disaccharide **11** in good yield. Further glycosylation of **11** with donor **5** gave target trisaccharide **12** with an anomeric leaving group in excellent yield.

In summary, we present the first synthesis of trisaccharide of natural antioxidants and free radical scavengers incanosides C, D and E. The key step of this concise and effective method involved the preparation of decisive

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Scheme 2.

disaccharide acceptor from the phenyl 2-acetyl-3,4-di-*O*-benzoyl- α -L-rhamnopyranosyl- $(1 \rightarrow 3)$ -2-*O*-acetyl-4,6-*O*-benzylidene-1-thio- β -D-gluco-pyranoside by regioselective and chemoselective deacetylation. The total syntheses of incanosides C, D and E are in process.

EXPERIMENTAL

¹H NMR spectra were determined in CDCl₃ on a Bruker AVANCE DMX-500 (500 MHz) with tetramethylsilane (Me₄Si) as the internal standard. Chemical shifts are expressed in ppm downfield from the internal Me₄Si absorption. Mass spectra were recorded with Bruker Daltonics APEXIII FT-ICR mass spectrometer or Bruker Daltonics DataAnalysis 3.0 mass spectrometer using the ESI technique to introduce the sample. Thin-layer chromatography (TLC) was performed on silica gel GF₂₅₄, detection being affected by charring with 30% (v/v) sulfuric acid in methanol or sometimes by UV detection. Column chromatography was conducted by elution of a column (8/100 mm, 16/240 mm, 35/400 mm) of silica gel (100–200 mesh) and EtOAc/petroleum ether (b.p. 60–90°C) as the eluent. Melting points were determined with a YANACO apparatus and were uncorrected. Elemental analyses were performed at Carlo-Erba 1106 instrument.





Synthesis of Trisaccharide of Incanoside from Caryopteris incana

Phenyl 2-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (4). To a solution of phenyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside 3 (600 mg, 1.35 mmol) in dry THF and CH₂Cl₂ (1/1, 15 mL) was added hydrazine acetate (124 mg, 1.35 mmol). The mixture was stirred at 30°C for 4 h, then diluted with CH₂Cl₂ and washed with water and brine. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude oil was subject to column chromatography on silica gel with petroleum ether/ethyl acetate (3 : 1) as the eluent to give 4 (350 mg, 64.4%) as a white solid. m.p. 192.4–194.5°C ¹H NMR δ7.48–7.32 (m, 10H, 2Ph-H), 5.53 (s, 1H, PhCH), 4.93 (dd, 1H, H-2), 4.73 (s, 1H, 10.0 Hz, H-1), 4.36 (dd, 1H, H-6a), 3.88 (t, 1H, H-6b), 3.76 (t, 1H, H-4), 3.57–3.50 (m, 2H, H-3 and H-5), 2.17 (s, 3H, CH₃CO) ppm.

Allyl 2-O-acetyl-3,4-di-O-Benzoyl- α -L-rhamnopyranoside (6). The solution of trifluoromethanesulphonic acid (0.5 mL) and L-rhamnose monohydrate (5 g, 27.4 mmol) in allyl alcohol (100 mL) was stirred at reflux for 3.5 h. After having cooled, the reaction mixture was neutralized with triethylamine (1 mL), filtered and concentrated. After co-distillation with toluene $(3 \times 30 \text{ mL})$, the residue was dissolved in a mixture of dry acetonitrile (25 mL) and trimethyl orthoacetate (1.5 mL). p-Toluenesulfornic acid (50 mg) was added, and the mixture was placed under partial vacuum on rotatory evaporator and heated to 50°C, and then stirred at 50°C for 12 h. Triethylamine (1 mL) was added and the mixture was concentrated to give a syrup. The syrup was dissolved in 80% aqueous acetic acid (30 mL) and after 10 min the solution was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ and water. The organic phase was dried and concentrated in vacuum to give a syrup. The syrup was then dissolved in pyridine (7 mL). The solution of benzoyl chloride (7 mL) in CH₂Cl₂ (10 mL) was added at 0°C. The mixture was stirred overnight and then washed with ¹NHCl, saturated aqueous NaHCO₃ and water. The purification of crude product through silica gel column with petroleum ether/ ethyl acetate (7 : 1, v/v) as the eluent gave **6** (8.22 g, 66%) as crystals. ¹H NMR δ7.97-7.32 (m, 10H, Bz-H), 5.93 (m, 1H, CH₂=CH-CH₂), 5.71 (dd, 1H, H-3), 5.53 (t, 1H, H-4), 5.47 (dd, 1H, H-2), 5.39–5.35 (m, 2H, CH₂=CH– CH₂), 4.90 (s, 1H, H-1), 4.28-4.24 (m, 1H, H-5), 4.16-4.06 (m, 2H, CH₂=CH-CH₂), 2.18 (s, 3H, CH₃CO), 1.32 (d, 3H, H-6) ppm.

2-O-acetyl-3,4-di-O-benzoyl-\alpha-L-rhamnopyranosyl trichloacetimidate (7). Allyl 2-O-acetyl-3,4-di-O-benzoyl- α -L-rhamnopyranoside (6) (454 mg, 1 mmol) in 90% acetic acid (20 mL) containing sodium acetate (586 mg, 3 mmol) was added PdCl₂ (178 mg, 1 mmol) and the mixture was stirred overnight. The mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NaHCO₃ and water. The organic layer was concentrated under reduced pressure and the obtained residue was passed eluent to give crude 2-O-acetyl-3,4-di-O-benzoyl- α -L-rhamnopyranose, which was dis-

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solved in dry CH₂Cl₂ (40 mL), then CCl₃CN (0.2 mL, 2 mmol) and DBU (28 μ L, 0.18 mmol) were added. The reaction mixture was stirred at 0°C for 3 h. Concentration of the reaction mixture followed by purification on flash chromatography (2/1 petroleum ether/ethyl acetate as the eluent) gave 7 (507 mg, 91% for two steps) as crystals. ¹H NMR δ 8.79 (s, 1H,C==*NH*), 7.99–7.34 (m, 10H, Bz-H), 6.33 (s, 1H, H-1), 5.77–5.74 (m, 1H, H-3), 5.69–5.63 (m, 2H, H-2 and H-4), 4.34-4.31 (m, 1H, H-5), 2.19 (s, 3H, CH₃CO), 1.37 (d, 3H, H-6) ppm.

Phenyl 2-*O*-acetyl-3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl-(1 → 3)-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (9). 2-*O*-acetyl-3,4-di-*O*benzoyl-α-L-rhamnopyranosyl trichloroacetimidate 7 (335 mg, 0.6 mmol) and phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside 2 (180 mg, 0.5 mmol) were together dried under high vacuum for 2–3 h, then dissolved in dry CH₂Cl₂ (30 mL) and BF₃·OEt₂ (60 µL) was added dropwise at -30° C under N₂ atmosphere. The reaction mixture was stirred for 3 h. The reaction mixture was neutralized with triethylamine, concentrated under reduced pressure to dryness. Further purification by silic gel column chromatography (1/1.5 petroleum ether/ethyl acetate as eluent) gave 9 (333 mg, 88%) as a colorless solid. m.p. 171.6–173.4°C; ¹H NMR δ 7.87–7.19 (m, 20H, Bz-H and Ph-H), 5.63–5.61 (m, 2H, H-3' and PhCH), 5.53 (dd, 1H, H-2'), 5.41 (t, 1H, H-4'), 5.35 (s, 1H, H-1'), 4.61 (dd, 1H, 9.75 Hz, H-1), 4.46–4.41 (m, 2H, H-6a and H-5'), 3.98 (t, 1H, H-6b), 3.81 (t, 1H, H-4), 3.64 (t, 1H, H-3), 3.61–3.55 (m, 2H, H-2 and H-5), 2.12 (s, 3H, CH₃CO), 0.92 (d, 3H, 6.10 Hz,H-6') ppm.

Phenyl 2-O-acetyl-3,4-di-O-benzoyl- α -L-rhamnopyranosyl- $(1 \rightarrow 3)$ -2-O-acetyl-4,6-O-benzylidene-1-thio- β -D-glucopyranoside (10). *Method* A. Disaccharide 9 (302.5 mg, 0.4 mmol) was dissolved in a solution of fresh pyridine/acetic anhydride (2/1, v/v, 8 mL), and the mixture was stirred overnight at room temperature, then concentrated to dryness. Further purification by column chromatography (2/1 petroleum either/ethyl acetate) gave 10 (313 mg, 98%).

Method B. The mixture of **7** (335 g, 0.6 mmol) and phenyl 2-*O*-acetyl-4,6-*O*-benzylidene-1-thio- β -D-glucopyranoside **4** (201 mg, 0.5 mmol) was dried under high vacuum for 2–3 h, then dissolved in dry CH₂Cl₂ (30 mL). TMSOTf (10 μ L, 0.1 equiv) in CH₂Cl₂ (mL) was added dropwise at –45°C under N₂. The reaction mixture was stirred for 4 h and then neutralized with triethylamine, concentrated under reduced pressure to dryness. Further purification by column chromatography (1/1.5 petroleum ether/ethyl acetate as eluent) gave **10** (367 mg, 92%) as a colorless solid. m.p. 186.7–189.3°C; ¹H NMR δ 7.88–7.16 (m, 20H, Bz-H and Ph-H), 5.69 (dd, 1H, H-3'), 5.61 (s, 1H, PhCH), 5.38 (t, 1H, H-4'), 5.18–5.14 (m, 2H, H-2 and H-4'), 5.04 (s, 1H, H-1'), 4.74 (dd, 1H, 10.08 Hz, H-1), 4.44–4.40 (dd, 1H, H-6a), 4.35–4.31 (m, 1H, H-5'), 4.01 (t, 1H, H-6b), 3.82 (t, 1H, H-4), 3.75 (t, 1H, H-3), 3.57



Synthesis of Trisaccharide of Incanoside from Caryopteris incana

(m, 1H, H-5), 2.17 (s, 3H, CH₃CO), 2.13 (s, 3H, CH₃CO), 0.72 (d, 3H, 6.09 Hz, H-6') ppm.

Phenyl 3,4-di-*O*-benzoyl- α -L-rhamnopyranosyl- $(1 \rightarrow 3)$ -2-*O*-acetyl-4,6-O-benzylidene-1-thio-β-D-glucopyranoside (11). To a solution of 10 (1.6 g, 2.0 mmol) in 25 mL THF was added 3.0 equiv of 85% hydrazine hydrate (0.38 mL). The mixture was stirred at room temperature for 11 h, then quenched by the addition of H₂O (20 mL) and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was subject to column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) as the eluent to give **11** (1.12 g, 73.8%). m.p. 170.2–172.5°C; ¹H NMR δ 7.95-7.17 (m, 20H, Bz-H and Ph-H), 5.61 (s, 1H, PhCH), 5.53 (dd, 1H, H-3'), 5.41 (t, 1H, H-4'), 5.09 (t, 1H, H-2), 5.00 (s, 1H, H-1'), 4.74 (dd, 1H, 10.09 Hz, H-1), 4.44-4.40 (dd, 1H, H-6a), 4.37-4.34 (m, 1H, H-5'), 4.15 (br, 1H, H-2'), 4.08 (t, 1H, H-6b), 3.82 (t, 1H, H-4), 3.71 (t, 1H, H-3), 3.60-3.56 (m, 1H, H-5), 2.14 (s, 3H, CH₃CO), 0.80 (d, 3H, 6.15 Hz, H-6'). Anal. Calcd for C₄₁H₄₀O₁₂S: C, 65.07; H, 5.23; S, 4.24. Found: C, 64.38; H, 5.33; S, 4.17. MS(ESI): 779 $([M + Na]^+)$.

Phenyl 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl- $(1 \rightarrow 2)$ - 3,4-di-Obenzoyl- α -L-rhamnopyranosyl- $(1 \rightarrow 3)$ -2-O-acetyl-4,6-O-benzylidene-1thio-β-D-glucopyrano side (12). The disaccharide acceptor 11 (151 mg, 0.2 mmol) and glucosyl donor 5 (128 mg, 0.26 mmol) were dried under high vacuum for 2-3 h, then dissolved in dry CH₂Cl₂ (15 mL) and 24 μ L of a 0.2N solution of BF₃·OEt₂ was added dropwise at -30° C under N₂. The reaction mixture was stirred for 3 h, and then neutralized with triethylamine, concentrated under reduced pressure to dryness. Further purification by column chromatography (1/1.5 petroleum ether/ethyl acetate as eluent) gave 12 (197 mg, 91%) as a colorless solid. m.p. $264.3-275.8^{\circ}$ C; ¹H NMR δ 7.95-7.19 (m, 20H, Bz-H and Ph-H), 5.61 (s, 1H, PhCH), 5.53 (dd, 1H, H-3'), 5.45 (t, 1H, H-3"), 5.40 (br, 2H, H-1' and H-4'), 5.12-5.10 (m, 2H, H-2 and H-2"), 4.62 (dd, 1H, 9.74 Hz, H-1), 4.44-4.40 (m, 2H, H-6a and H-4"), 4.33 (br, 1H, H-2'), 4.23–4.20 (m, 2H, H-5' and H-6a"), 4.08 (dd, 1H, 6.74 Hz, H-1"), 4.01 (t, 1H, H-6b), 3.87-3.80 (m, 2H, H-6b" and H-4), 3.63 (t, 1H, H-3), 3.60-3.56 (m, 2H, H-5" and H-5), 2.11-2.00 (5s, 15H, 5CH₃CO), 0.98 (d, 3H, 6.70 Hz, H-6'). HRMS(ESI): Calcd for $C_{56}H_{60}O_{20}S$: 1083.3320([M-H]⁺). Found: 1083.3344([M-H]⁺).

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ACKNOWLEDGMENTS

The work was supported by The National Natural Science Foundation of China (No. 20272051) and by The Teaching and Research Award Program

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