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Graphical Abstract

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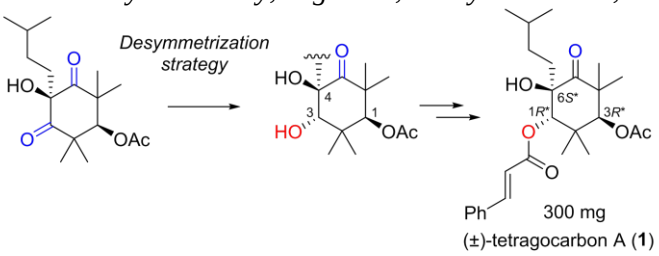

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ABSTRACT

Stereoselective total synthesis of (±)-tetragocarbon A isolated from the propolis of an Australian stingless bee, *Tetragonula carbonara*, has been developed by focusing on the latent symmetry of **1**. The requisite 1*R**, 3*R**, 6*S** stereogenic centers were selectively installed by hydroxy group directing reactions including the late stage desymmetrization of the 1,3-diketone. The target natural product was successfully prepared in 12 steps from phloroglucinol on 300 mg.

1. Introduction

Tetragocarbone A (**1**) was isolated from the propolis of an Australian stingless bee, *Tetragonula carbonara*.[1] Among several highly substituted cyclic polyketides that have been isolated, such as **2**~**5**, **1** features a highly complex cyclohexanone skeleton with eight substituents and a cinnamic acid ester (Figure 1).[2,3] The relative structure of **1** was proposed by NMR analysis and the first total synthesis of **1**. The absolute stereochemistry of 1 was elucidated by X-ray structure analysis of the key synthetic intermediates and comparison of the chiral HPLC profiles of the synthetic and naturally occurring **1**. [1]

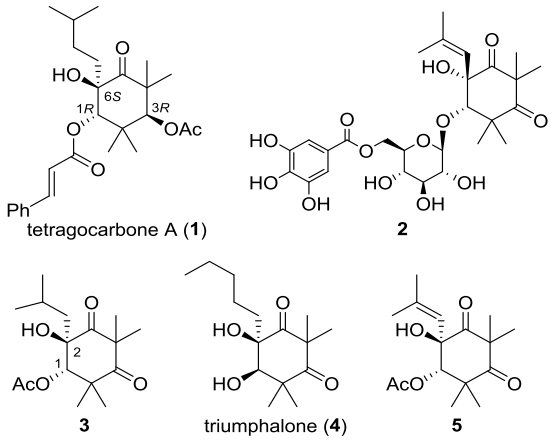
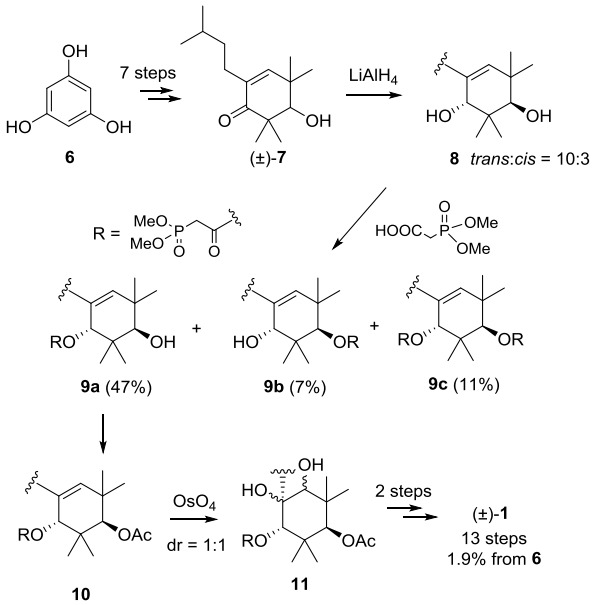


Figure 1. Structures of cyclic polyketides sharing a tetramethylcyclohexanone skeleton. No names are given for **2**, **3**, and **5**.

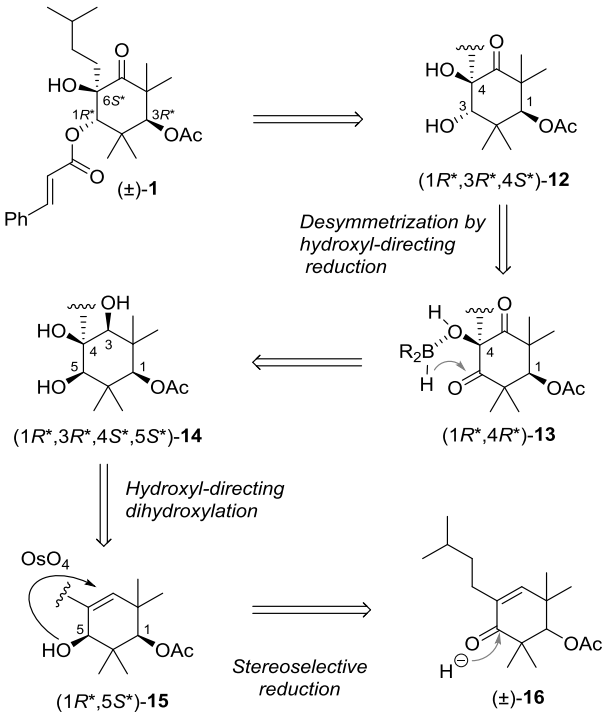
The first total synthesis of **1** was achieved in 13 steps starting from phloroglucinol (**6**) in 1.9 % overall yield (Scheme 1).[1] Although the first synthesis contributed to the structure elucidation, it suffered from low stereoselectivities in the following steps: (i) $LiAlH_4$ reduction of **7** (dr = 10:3), (ii) esterification of diol **8** to give a mixture of mono- and diesters, and (iii) dihydroxylation of **10** to give **11** (dr = 1:1). These results suggested that the above intermolecular reactions would not be suitable for the practical synthesis of **1**.



Scheme 1. First total synthesis of **1** from phloroglucinol.

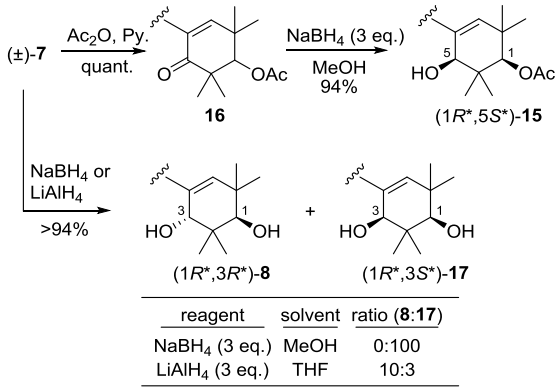
2. Results and Discussion

In this paper, we would like to report a stereoselective total synthesis of (±)-**1** focusing on the latent symmetry of the natural product (Scheme 2).[4] Tetragocarbone (**1**) was initially divided into the cinnamic acid and the cyclohexanone core **12** in a retrosynthetic manner. The molecular complexity of **12** was thought to be reduced to **13** and **14** possessing symmetrical elements. We set hydroxyl-directing reactions: the late stage desymmetrization of **13** and dihydroxylation of **15**, for the introduction of the requisite stereocenters. Alcohol **15** would be elaborated by the stereoselective reduction of enone **16**.



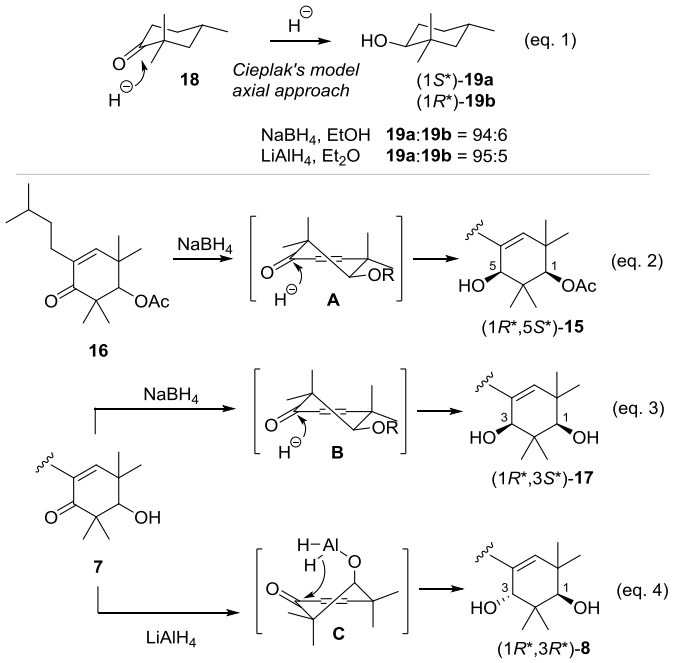
Scheme 2. Retrosynthetic analysis.

The synthesis commenced with the stereoselective synthesis of acetate **15**. Alcohol **7** was prepared from phloroglucinol (**6**) according to the literature (Scheme 3).[1] Alcohol **7** was smoothly reduced using $NaBH_4$ in MeOH to give (1*R**,3*S**)-**17** in a stereoselective manner. On the other hand, switching to $LiAlH_4$ afforded a 10:3 mixture of (1*R**,3*R**)-**8** and (1*R**,3*S**)-**17**.[1] Reduction of acetate **16** with $NaBH_4$ in MeOH gave (1*R**,5*S**)-**15** as a single isomer. The stereochemistry of **15** was unambiguously determined by the total synthesis of **1** from **15**.



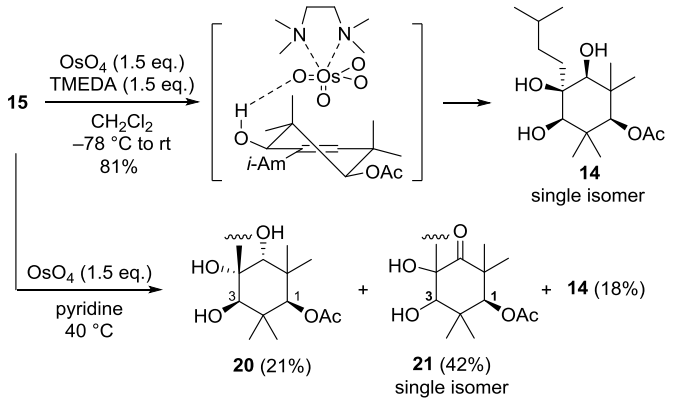
Scheme 3. Stereoselective reduction of **7** and **16**.

Proposed reaction mechanism for the stereoselective reductions of **7** and **16** is depicted in Scheme 4. Senda *et al*. reported that reduction of ketone **18** with $LiAlH_4$ or $NaBH_4$ to give **19a** in a stereoselective manner (eq. 1).[5,6] The stereochemical outcomes were rationalized by the Cieplak effect in which the orbital interaction between the axial carbon-carbon bond and the carbonyl π-orbital plays an important role in the selective hydride approach.[7] We assumed that the Cieplak effect would be adopted to the stereoselective reduction of **7** and **16** (eqs. 2 and 3, model A and B). On the other hand, reduction with $LiAlH_4$ instead of $NaBH_4$ afforded (1*R**,3*R**)-**8** as a major product from **7** (eq. 4). The selectivity switching would be ascribed to the hydroxyl-directing model C in which the hydride is predominantly transferred in an intramolecular fashion.



Scheme 4. Proposed reaction mechanism.

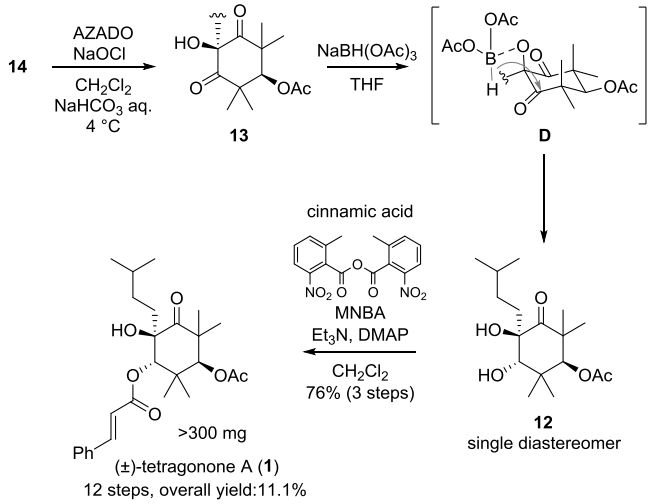
With the key intermediate (1*R**,5*S**)-**15** in hand, we next examined stereoselective transformation of **15** to the symmetrical triol **14** (Scheme 5). Dihydroxylation of **15** using a stoichiometric amount of OsO_4 in pyridine was not fruitful to give a mixture of **14**, **20**, and the unexpected ketone **21**. Although the stereochemistry of **21** could not be determined, these results implied that the intermolecular oxidation was not effective. These results led us to examine the hydroxyl-directing dihydroxylation reaction developed by Donohoe et al.[8,9]



Scheme 5. Hydroxy group directing dihydroxylation.

Pleasingly, the stereoselectivity was significantly improved by treatment of **15** with OsO_4 in the presence of TMEDA in CH_2Cl_2 at low temperature to provide the desired triol **14** in 81% yield as a single isomer. In addition, the undesired formation of **21** was suppressed under the conditions.

Triol **14** was smoothly converted to the symmetrical 1,3-diketone **13** by AZADO-catalyzed oxidation reaction[10,11] (Scheme 6). The stereoselective reduction of **13** was successfully achieved under the Saksena reduction condition[12] using $NaBH(OAc)_3$ in AcOH to give **12** as a sole product. It is conceivable that the tertiary hydroxy group participates to the directing effect to conduct the preferential intramolecular hydride transfer (model D). *trans*-Diol **12** was found to be labile and immediately employed for the next esterification reaction. Although diol **12** did not react with cinnamic acid under the conventional esterification condition using EDCI, DMAP, and Et_3N, the esterification was significantly promoted by the Shiina's esterification.[13,14] Treatment of **12** with 2-methyl-6-nitrobenzoic anhydride (MNBA) in the presence of DMAP furnish (±)-tetragocarbone A (**1**) in 76% from **14** in 3 steps. Spectroscopic data of the synthetic **1** were identical with those of the authentic data.[1]



Scheme 6. Total synthesis of (±)-tetragocarbone A (**1**).

3. Conclusion

We have developed an efficient stereoselective synthesis of **1** from phloroglucinol (**6**). Highlights of the new total synthesis includes: (i) the synthetic design focusing on latent symmetry to reduce the molecular complexity, (ii) stereoselective installation of the three stereogenic centers on the highly substituted cyclohexane ring by taking advantage of the hydroxyl-directing reactions, and (iii) scalable synthesis of **1** on 300 mg. Biological investigation of **1** has not been implemented due to the low availability of **1** from the propolis. The present improved synthesis would aid to study the biological function of **1** in the propolis.

4. Experimental Section

4.1. General Information

All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Kanto Kagaku Co., Inc., Merck & Co., Inc., Nacalai Tesque Company, Ltd., Peptide Institute, Tokyo Kasei Kogyo Co., Ltd., or Wako Pure Chemical Industries, Ltd., and used without further purification unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide (P_2O_5). Methanol (MeOH), tetrahydrofuran (THF), and pyridine of anhydrous grade were used. FTIR spectra was measured on a JASCO FT/IR-6200 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on an either Bruker AVANCE 300 (300 MHz) or Bruker AVANCE 600 (600 MHz) spectrometer. Chemical shifts of ^{1}H NMR were reported in parts per million (ppm, δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. ^{13}C NMR spectra were recorded on an either Bruker AVANCE 300 (75 MHz) or Bruker AVANCE 600 (150 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to $CHCl_3$ (δ = 77.0) in $CDCl_3$. High resolution mass spectra (HRMS) were obtained on an either JEOL JMS-AX500 for fast atom bombardment ionization (FAB) or Bruker solariX XR (9.4T) for electrospray ionization (ESI). All reactions were monitored by thin layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm thickness, manufactured by Merck). TLC visualization was accompanied using UV lamp (254 nm) or a charring solution (ethanoic phosphomolybdic acid). Daiso IR-60 1002W (40/63 μm) was used for flash column chromatography on silica gel. Precoated plate (silica gel 60 F-254, 0.5 mm thickness, manufactured by Merck) was used for preparative TLC.

4.2. Synthetic Procedures and Characterization Data

*4.2.1. 4-Isopentyl-2,2,6,6-tetramethyl-5-oxocyclohex-3-en-1-yl acetate (**16**)*

To a solution of (±)-**7** (500 mg, 2.10 mmol) in pyridine (10 mL) was added Ac_2O (2.0 mL, 21.2 mmol) at room temperature. The mixture was stirred for 21 h at 40 °C. The mixture was concentrated under reduced pressure to give **16** (589 mg, quant.) as a colorless oil; R_f 0.50 (hexane/AcOEt = 10:1); FTIR (neat) 2956, 2871, 1748, 1677, 1468, 1367, 1236, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (t, *J* = 1.1 Hz, 1 H, H-3), 5.02 (s, 1 H, 1-H), 2.15 (m, 2 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 2.13 (s, 3 H, OAc), 1.53 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.23 (m, 2 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.15 (s, 3 H, Me), 1.10 (s, 9 H, Me × 3), 0.89 (d, *J* = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.1, 170.4, 149.6, 135.3, 79.7, 46.6, 37.8, 37.4, 29.7, 27.9, 27.7, 23.9, 23.4, 22.5 × 2, 21.7, 20.8; HRMS (ESI) *m/z* (M + H)$^+$ calcd for [$C_{17}H_{28}O_3$ + H]$^+$ 281.2111, found 281.2112.

4.2.2. (1R,5S*)-5-Hydroxy-4-isopentyl-2,2,6,6-tetramethylcyclohex-3-en-1-yl acetate (**15**)*

To a solution of **16** (589 mg, 2.10 mmol) in MeOH (10 mL) was added $NaBH_4$ (397 mg, 10.5 mmol) at room temperature. The mixture was stirred for 30 min, quenched with brine (15 mL), and extracted with AcOEt (15 mL × 1, 5 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give **15** (558 mg, 94%) as a colorless oil; R_f 0.21 (hexane/AcOEt = 15:1); FTIR (neat) 3481, 2958, 2871, 1744, 1721, 1469, 1367, 1241, 1025, 976, 910, 879, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, *J* = 1.2 Hz, 1 H, H-3), 4.81 (s, 1 H, H-1), 3.70 (s, 1 H, H-5), 2.24–1.98 (m, 2 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 2.10 (s, 3 H, OAc), 1.55 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.31 (m, 2 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.002 (s, 3 H, Me), 0.995 (s, 3 H, Me), 0.97 (s, 6 H, Me × 2), 0.904 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.896 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 136.4, 130.2, 81.3, 75.3, 39.3, 37.5, 36.7, 31.6, 30.0, 27.9, 25.6, 25.0, 22.8, 22.3, 20.9, 19.3; HRMS (ESI) *m/z* (M + Na)$^+$ calcd for [$C_{17}H_{30}O_3$ + Na]$^+$ 305.2087, found 305.2089.

4.2.3. (1R,3R*,4S*,5S*)-3,4,5-Trihydroxy-4-isopentyl-2,2,6,6-tetramethylcyclohexyl acetate (**14**)*

To a solution of **15** (409 mg, 1.45 mmol) in CH_2Cl_2 (10 mL) were added TMEDA (323 mL, 2.17 mmol) and OsO_4 (522 mg, 2.05 mmol) at −78 °C. The mixture was gradually warmed up to room temperature over 12 h. The mixture was diluted with CH_2Cl_2 (20 mL), washed with 10% $NaHSO_3$ aq. (10 mL × 4), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give the corresponding osmate of **14**. THF (5.0 mL), water (5.0 mL), and solid $NaHSO_3$ (910 mg) were added to the osmate. The mixture was stirred for 2 h at room temperature, quenched with brine (15 mL), and extracted with AcOEt (20 mL × 2). The combined organic layers were washed with 10% $NaHSO_3$ (15 mL × 2) aq. and brine (15 mL × 1), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give **14** (370 mg, 81%) as a brown solid; R_f 0.23 (hexane/AcOEt = 4:1); FTIR (neat) 3416, 2960, 1734, 1465, 1366, 1253, 1233, 1024, 1006, 993, 977, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.50 (s, 1 H, H-1), 3.21 (brd, *J* = 6.6 Hz, 2 H, H-3 and H-5), 2.14 (s, 3 H, OAc), 2.06 (m, 2 H, OH), 1.69 (m, 2 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.51 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.15 (m, 2 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.11 (s, 6 H, Me × 2), 0.94 (s, 6 H, Me × 2), 0.90 (d, *J* = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 79.9, 77.7, 74.2 × 2, 40.8 × 2, 35.4, 33.8, 28.9 × 2, 28.6, 22.6 × 2, 20.8, 15.7 × 2; HRMS (ESI) *m/z* $(M + Na)^+$ calcd for $[C_{17}H_{32}O_5 + Na]^+$ 339.2142, found 339.2142.

*4.2.4. Dihydroxylation of **15** with OsO_4 in pyridine*

To a solution of **15** (30.0 mg, 106 mmol) in pyridine (1.0 mL) was added OsO_4 (41.0 mg, 161 mmol) at room temperature. The mixture was stirred for 21 h at 40 °C, quenched with 10% $NaHSO_3$ aq. (3 mL), and extracted with AcOEt (3 mL × 2). The combined organic layers were washed with 10% $NaHSO_3$ aq. (3 mL × 1) and brine (3 mL × 1), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give a mixture of the corresponding osmate of **14**, **20**, and **21**. THF (3.0 mL), water (2.0 mL), and solid $NaHSO_3$ (135 mg) were added to the residue. The mixture was stirred for 30 min at room temperature and extracted with AcOEt (3 mL × 2). The combined organic layers were washed with brine (3 mL × 1), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (hexane/AcOEt = 4:1) to give **14** (6.0 mg, 18%), **20** (7.0 mg, 21%), and **21** (14.0 mg, 42%). Ketone **21** was obtained as a single isomer. The stereochemistry of **21** has not been determined.

20: FTIR (neat) 3446, 2958, 1718, 1457, 1374, 1260, 1092, 1024, 983, 803, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 1 H, H-1), 3.59 (s, 1 H, H-3 or H-5), 3.55 (s, 1 H, H-3 or H-5), 2.11 (s, 3 H, OAc), 1.91 (dt, *J* = 13.4, 4.5 Hz, 1 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.75 (dt, *J* = 13.4, 4.3 Hz, 1 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.52 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.41 (m, 1 H, one of CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.25 (m, 1 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.23 (s, 3 H, Me), 1.16 (s, 3 H, Me), 1.05 (s, 3 H, Me), 1.04 (s, 3 H, Me), 0.92 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.91 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 79.9, 78.2, 77.3, 74.3, 40.8, 40.2, 35.4, 31.5, 28.9, 28.7, 22.7 × 2, 22.6, 20.8, 15.7; HRMS (ESI) *m/z* $(M + Na)^+$ calcd for $[C_{17}H_{32}O_5 + Na]^+$ 339.2142, found 339.2142.

21: FTIR (neat) 3466, 2953, 2872, 1739, 1705, 1469, 1452, 1373, 1236, 1030, 989, 908 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 1 H, H-1), 3.94 (s, 1 H, OH), 3.89 (d, *J* = 6.3 Hz, 1 H, H-3 or OH), 3.11 (d, *J* = 6.3 Hz, 1 H, H-3 or OH), 2.14 (s, 3 H, OAc), 1.86 (dt, *J* = 13.2, 4.2 Hz, 1 H, one of C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.68 (dt, *J* = 13.2, 4.4 Hz, 1 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.48 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.35 (m, 1 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.30 (s, 3 H, Me), 1.10 (s, 3 H, Me), 1.08 (s, 3 H, Me), 0.99 (m, 1 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 0.88 (d, *J* = 6.5 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.86 (d, *J* = 6.5 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.80 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.7, 170.3, 81.2, 78.1, 77.0, 46.2, 39.4, 38.9, 31.4, 28.1, 28.0, 23.8, 23.1, 22.5, 22.4, 20.6, 20.1; HRMS (ESI) *m/z* $(M + Na)^+$ calcd for $[C_{17}H_{30}O_5 + Na]^+$ 337.1985, found 337.1985.

4.2.5. (1R,4R*)-4-Hydroxy-4-isopentyl-2,2,6,6-tetramethyl-3,5-dioxocyclohexyl acetate (**13**)*

To a solution of **14** (370 mg, 1.17 mmol) in CH_2Cl_2–water (2:1, 15 mL) were added AZADO (18.0 mg, 0.118 mmol), KBr (153 mg, 1.29 mmol), and ca. 10% NaOCl aq.–5% $NaHCO_3$ aq. (1:1, 4.0 mL) at 4 °C. The mixture was stirred for 30 min at 4 °C. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (5 mL × 1). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give **13** (366 mg, quant.) as a brown oil; R_f 0.34 (hexane/AcOEt = 4:1); FTIR (neat) 3481, 2957, 2871, 1735, 1703, 1468, 1387, 1367, 1231, 1214, 1032, 910, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (s, 1 H, H-1), 3.84 (brs, 1 H, OH), 2.18 (s, 3 H, OAc), 1.84 (m, 2 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.48 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.22 (s, 6 H, Me × 2), 1.16 (s, 6 H, Me × 2), 1.11 (m, 2 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 0.84 (d, *J* = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3 × 2, 170.3, 85.6, 75.6, 48.2 × 2, 35.6, 31.2, 27.9, 25.8 × 2, 22.4 × 2, 21.2 × 2, 20.6; HRMS (ESI) *m/z* $(M + Na)^+$ calcd for $[C_{17}H_{28}O_5 + Na]^+$ 335.1829, found 335.1828.

*4.2.6. Total synthesis of (±)-Tetragocarbone A (**1**) via (1R*,3R*,4S*)-3,4-Dihydroxy-4-isopentyl-2,2,6,6-tetramethyl-5-oxocyclohexyl acetate (**12**)*

To a solution of **13** (366 mg, 1.17 mmol) in THF (15 mL) was added $NaBH(OAc)_3$ (743 mg, 3.51 mmol) at room temperature. The mixture was stirred for 18 h, quenched with brine (20 mL), and extracted with AcOEt (20 mL × 2). The combined organic layers were washed with sat. $NaHCO_3$ (15 mL × 1) and brine (15 mL × 1), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give **12** (368 mg, quant.) as a brown oil; R_f 0.38 (hexane/AcOEt = 4:1); FTIR (neat) 3474, 2957, 2873, 1742, 1715, 1452, 1387, 1370, 1236, 1025, 990, 910, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1 H, H-1), 3.81 (s, 1 H, H-3 or OH), 3.71 (s, 1 H, H-3 or OH), 2.43 (brs, 1 H, OH), 2.11 (s, 3 H, OAc), 1.99 (m, 1 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.69 (ddd, *J* = 14.4, 12.6, 4.5 Hz, 1 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.48 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.30 (m, 2 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.21 (s, 3 H, Me), 1.15 (s, 3 H, Me), 1.11 (s, 3 H, Me), 1.04 (s, 3 H, Me), 0.87 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.85 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$); HRMS (ESI) *m/z* $(M + Na)^+$ calcd for $[C_{17}H_{30}O_5 + Na]^+$ 337.1985, found 337.1985. This material was subjected to the next step without further purification.

To a solution of Et_3N (490 mL, 3.52 mmol) in CH_2Cl_2 (5.0 mL) were added DMAP (13.0 mg, 0.106 mmol), MNBA (451 mg, 1.31 mmol), and cinnamic acid (194 mg, 1.31 mmol) at room temperature. The mixture was stirred for 10 min. A solution of **12** (368 mg, 1.17 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture at room temperature and stirred for 20 h. The mixture was washed with 10% citric acid aq. (15 mL × 3) and sat. $NaHCO_3$ (15 mL × 4), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/AcOEt = 10:1) to give **1** (397 mg, 76% over 3 steps) as a yellow oil; R_f 0.60 (hexane/AcOEt = 4:1); FTIR (neat) 3488, 2957, 2872, 1709, 1635, 1372, 1235, 1153, 1027, 910, 767, 731 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 15.9 Hz, 1 H, OC(O)CH=C*H*Ph), 7.58 (m, 2 H, Ph-H-2), 7.41 (m, 3 H, Ph-H-3 and Ph-H-4), 6.53 (d, *J* = 15.9 Hz, 1 H, OC(O)C*H*=CHPh), 5.38 (s, 1 H, H-3), 5.24 (s, 1 H, H-1), 3.62 (brs, 1 H, OH), 2.14 (s, 3 H, OAc), 1.76 (dt, *J* = 13.3, 4.3 Hz, 1 H, C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.68 (dt, *J* = 13.3, 4.7 Hz, 1 H,

C*H*$_2$CH$_2$CH(CH$_3$)$_2$), 1.43 (m, 1 H, CH$_2$CH$_2$C*H*(CH$_3$)$_2$), 1.35 (s, 3 H, C4-Me), 1.22 (m, 1 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 1.17 (s, 3 H, C4-Me), 1.02 (s, 3 H, C2-Me), 0.98 (s, 3 H, C2-Me), 0.91 (m, 1 H, CH$_2$C*H*$_2$CH(CH$_3$)$_2$), 0.821 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.817 (d, *J* = 6.6 Hz, 3 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz, CDCl$_3$) δ 216.1 (C5), 170.7 (O<u>C</u>(O)CH$_3$), 166.0 (O<u>C</u>(O)CH=CHPh), 146.3 (OC(O)CH=<u>C</u>HPh), 134.1 (Ph-C1), 130.6 (Ph-C4), 128.9 × 2 (Ph-C3), 128.3 × 2 (Ph-C2), 117.1 (OC(O)<u>C</u>H=CHPh), 79.8 (C1), 79.14 (C3), 79.10 (C6), 47.7 (C4), 39.4 (C2), 34.3 (<u>C</u>H$_2$CH$_2$CH(CH$_3$)$_2$), 31.1 (CH$_2$<u>C</u>H$_2$CH(CH$_3$)$_2$), 28.3 (CH$_2$CH$_2$<u>C</u>H(CH$_3$)$_2$), 27.0 (C4-Me), 23.7 (C2-Me), 22.6 (CH(<u>C</u>H$_3$)$_2$), 22.4 (CH(<u>C</u>H$_3$)$_2$), 21.9 (C4-Me), 20.8 (C2-Me), 20.7 (OC(O)<u>C</u>H$_3$); HRMS (FAB) *m*/*z* (M + H)$^+$ calcd for [C$_{26}$H$_{36}$O$_6$ + H]$^+$ 445.2590, found 445.2589.

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Appendix A.

Supplementary data associated with this article can be found in the online version, at https://doi.org////// . These data include ^{1}H- and ^{13}C-NMR data of the new compounds described in this article.

References

1. Nishimura, E.; Murakami, S.; Suzuki, K.; Amano, K.; Tanaka, R.; Shinada, T. *Asian J. Org. Chem*. **2016**, *5*, 855.
2. Singh, I. P.; Bharate, S. B. *Nat. Prod. Rep*. **2006**, *23*, 558.
3. Singh, I. P.; Sidana, J.; Bharate, S. B.; Foley, W. J. *Nat. Prod. Rep*. **2010**, *27*, 393.
4. Wang, M.; Feng, M.; Tang, B.; Jiang, X. *Tetrahedron Lett*. **2014**, *55*, 7147.
5. Senda, Y.; Nakano, S.; *J. Chem. Soc. Perkin Trans. 2* **1993**, 1009.
6. Senda, Y.; Kikuchi, N.; Inui, A.; Itoh, H. *Bull. Chem. Soc. Jpn*. **2000**, *73*, 237.
7. Cieplak, A. S. *J. Am. Chem. Soc.*, **1981**, *103*, 4540
8. Donohoe, T. J.; Garg, R.; Moore, P. R. *Tetrahedron Lett*. **1996**, *37*, 3407.
9. Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett*. **1997**, *38*, 5027.
10. Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc*. **2006**, *128*, 8412.
11. Iwabuchi, Y. *Chem. Pharm. Bull*. **2013**, *61*, 1197.
12. Saksena, A.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.
13. Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett*. **2002**, *31*, 286.
14. Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem*. **2004**, *69*, 1822.