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Synthesis of C1—C9 Domain of the Nominal Didemnaketal A

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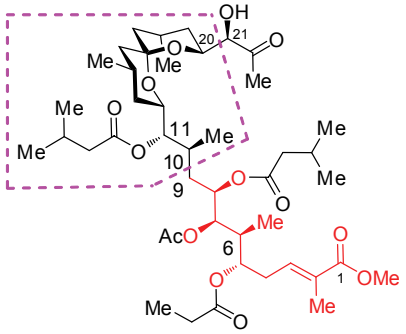
Based on chiral pool strategy, a synthesis of the C1—C9 domain of the proposed structure of didemnaketal A, a natural product with potent HIV-1 protease inhibitory activity, has been achieved. Key transformations are a Sharpless asymmetric dihydroxylation and a chelation-controlled allylation.

Keywords didemnaketal, chiral pool, chelation-controlled allylation, natural products, Sharpless AD

Introduction

Didemnaketals are a seven-membered family of natural products, three of which were isolated from the magenta ascidian *Didemnum sp.* by Faulkner and co-workers,[1] and the others from marine ascridian species belonging to the genus *Didemnum* by Youseff and co-workers.[2] Didemnaketals A (**1**) and B showed potent HIV-1 protease inhibitory activities (IC_{50} 2—10 μmol/L) presumably via a dissociative mechanism (Figure 1).



didemnaketal A (**1**)

Figure 1 The structure of didemnaketal A (**1**).

The densely functionalized structures and interesting biological activities of didemnaketals have stimulated several groups to pursue the chemical synthesis.[3] The Tu group has accomplished the synthesis of the proposed didemnaketal A in 2012 and the Fuwa group the nominal didemnaketal B in 2013.[4] Both groups reported disagreement of NMR spectroscopic data between the synthetic samples and the natural ones, and therefore, devoting much effort on disclosing the real structures through synthesis.[5] Recently, the Fuwa group revised the structure of didemnaketal B by total synthesis, pointing out that the absolute configuration of its C10—C20 domain has been erroneously assigned.[6]

Despite their structural issues, didemnaketals posed many challenges and opportunities for synthetic chemists. To us, four methyl groups of **1** exhibited huge attraction because we have been focusing on the development of chiral methyl building blocks for a long time.[7] Herein, we report a synthesis of the C1—C9 domain (**2**) of the original didemnaketal A (**1**).

Experimental

Methyl (4*R*)-5-(benzyloxy)-4-methyl-2-((methylsulfonyl)-oxy)pentanoate (6)

To a solution of **4** (5.2 g, 20.6 mmol) in dry DCM (40 mL) under argon were added Et_3N (8.9 mL, 62 mmol) and MsCl (2.4 mL, 31 mmol) at 0 ℃. The reaction mixture was stirred for 1 h, quenched with diluted HCl solution, and extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to give **6** (6.20 g, 18.8 mmol, 91%, inseparable mixture of epimers) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37—7.26 (m, 5H), 5.14 (dd, J=18.0, 4.0 Hz, 1H), 4.49 (s, 2H), 3.77 (s, 3H), 3.46—3.34 (m, 2H), 3.13 (s, 3H), 2.16—1.99 (m, 2H), 1.78—1.69 (m, 1H), 1.02 (d, J=8.8 Hz, 3H); IR (KBr) ν: 2961, 1755, 1361, 1177, 1101, 959, 741, 699 cm^{-1}; MS (EI, *m/z*) (%): 209 ($[M–BnOCH_2]^+$) (1), 330 (M^+) (3); HRMS-EI: M^+ calcd for $C_{15}H_{22}O_6S$: 330.1137, found 330.1140.

Methyl (4*R*)-5-(benzyloxy)-2-bromo-4-methylpentanoate (8)

A solution of **6** (9.90 g, 30 mmol) and LiBr•H_2O (9.5 g, 90.5 mmol) in acetone (150 mL) was heated at reflux for 18 h. The mixture was concentrated in vacuo, added

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water, extracted with ethyl acetate for three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel (petroleum ether/EtOAc: 10/1) to give bromide **8** (8.93 g, 28 mmol, 95%, inseparable mixture of epimers) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38－7.26 (m, 5H), 4.48 (s, 2H), 4.45－4.37 (m, 1H), 3.75 (s, 3H), 3.39－3.27 (m, 2H), 2.29－1.87 (m, 3H), 0.98 or 0.94 (d, J=12.4 Hz, 3H); IR (KBr) v: 2957, 2858, 1743, 1455, 1438, 1158, 1099, 738, 699 cm^{-1}; MS (EI, *m/z*) (%): 193 ([M–BnOCH$_2$]$^+$) (6); HRMS-EI: M$^+$ calcd for $C_{14}H_{19}O_3Br$: 314.0515, found 314.0518.

Methyl (*R*,*E*)-5-(benzyloxy)-4-methylpent-2-enoate (7)

A solution of bromide **8** (17.3 g, 55 mmol) in dry HMPA (40 mL) was stirred at 100 ℃ for 4 h. Removal of the solvent and purification through column chromatography on silica gel (petroleum ether/EtOAc: 15/1) afforded alkene **7** (8.47 g, 36 mmol, 66%, known compound[8]) as a colorless oil. $[\alpha]_D^{28}$ ＋14.6 (*c* 1.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.37－7.26 (m, 5H), 7.00－6.93 (dd, J=21.2, 8.0 Hz, 1H), 5.90－5.85 (d, J=21.2 Hz, 1H), 4.51 (2H), 3.73 (s, 3H), 2.73－2.60 (m, 1H), 1.10－1.08 (d, J=8.8 Hz, 3H); IR (KBr) v: 3066, 3032, 2952, 2858, 1724, 1659, 1497, 1455, 1436, 1359, 1315, 1274, 1196, 1180, 1154, 1099, 1029, 985, 918, 862, 738, 699 cm^{-1}; MS (EI, *m/z*) (%): 113 ([M–BnOCH$_2$]$^+$) (8), 219 (M$^+$) (1). For compound **9** (mixture of isomers): ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34－7.25 (m, 5H), 5.65 (t, J=9.2 Hz, 1H), 4.45 (s, 2H), 3.94 (s, 2H), 3.69 (s, 3H), 3.12 (d, J=10 Hz, 2H), 1.70 (s, 3H); IR (KBr) v: 2952, 2856, 1741, 1454, 1436, 1202, 1166, 1072, 738, 699 cm^{-1}; MS (EI, *m/z*) (%): 234 (M$^+$) (5); HRMS-EI: M$^+$ calcd for $C_{14}H_{18}O_3$: 234.1256, found 234.1254.

Methyl (2*S*,3*R*,4*S*)-5-(benzyloxy)-2,3-dihydroxy-4-methylpentanoate (10)

A suspension of $K_3Fe(CN)_6$ (15.5 g, 47 mmol), $(DHQD)_2PHAL$ (0.12 g, 0.15 mmol), K_2CO_3 (47 mmol), $MeSO_2NH_2$ (1.5 g, 15.8 mmol) and **7** (3.66 g, 15.6 mmol) in *t*-BuOH (30 mL)/water (20 mL) was added a solution of OsO_4 in water (7.9 mL, 1.0 mg/mL, 0.2 mol%) at 0 ℃. The reaction was warmed to ambient temperature and stirred for 12 h before Na_2SO_3 was added. The mixture was extracted with ethyl acetate for three times; the extracts were combined, washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel (petroleum ether/EtOAc: 2/1) to afford diol **10** (3.6 g, 13 mmol, 86%, *d.r.*＞19/1 by ^{1}H NMR) as a colorless liquid. $[\alpha]_D^{27}$ ＋6.8 (*c* 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40－7.27 (m, 5H), 4.51 (s, 2H), 4.32－4.31 (d, J=2.8 Hz, 1H), 3.90 (dd, J=8.0, 2.8 Hz, 1H), 3.81 (s, 3H), 3.54 (d, J=3.6 Hz, 1H), 3.52 (s, 1H), 3.09 (s, 2H), 2.19－2.05 (m, 1H), 1.06 (d, J=9.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.0, 137.9, 128.5 (2C), 127.8, 127.7 (2C), 74.8, 73.4, 73.2, 71.8, 52.7, 37.0, 13.3; IR (KBr) v: 3400, 2959, 1742, 1455, 1216, 1142, 1097, 1048, 738, 699 cm^{-1}; MS (EI, *m/z*) (%): 268 (M$^+$) (1); HRMS-EI: M$^+$ calcd for $C_{14}H_{20}O_5$: 268.1311, found 268.1310.

(1*R*,2*S*)-3-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropan-1-ol (11)

A solution of **10** (500 mg, 1.9 mmol) in THF (20 mL) was treated with $LiAlH_4$ (90 mg, 2.3 mmol, added at 0 ℃) at room temperature under argon for 12 h. The reaction was quenched with diluted HCl solution, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was dissolved in dry acetone (30 mL) and treated with TsOH•H_2O (35 mg, 0.19 mmol) at ambient temperature for 10 h before being quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with ethyl acetate for three times, the combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel (petroleum ether/EtOAc: 5/1) to afford **11** (300 mg, 1.1 mmol, 57%) as a colorless oil. $[\alpha]_D^{24}$ ＋20.4 (*c* 1.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36－7.26 (m, 5H), 4.49 (s, 2H), 4.02－3.98 (m, 1H), 3.92－3.88 (m, 1H), 3.77－3.72 (m, 1H), 3.64 －3.58 (m, 1H), 3.42 (d, J=5.6 Hz, 2H), 2.09－2.07 (m, 1H), 2.00－1.94 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.03 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.2, 128.4 (2C), 127.7, 127.6 (2C), 108.5, 79.4, 78.6, 73.2, 73.1, 62.9, 36.2, 27.2, 27.2, 12.7; IR (KBr) v: 3449, 2985, 2934, 1455, 1370, 1247, 1215, 1103, 1054, 738, 699 cm^{-1}; MS (EI, *m/z*) (%): 265 ([M–Me]$^+$) (5); HRMS-EI: [M–Me]$^+$ calcd for $C_{15}H_{21}O_4$: 265.1440, found 265.1443.

(*R*)-4-((1*R*,2*S*)-3-(Benzyloxy)-1-(methoxymethoxy)-2-methylpropyl)-2,2-dimethyl-1,3-dioxolane (12)

To a solution of **11** (7.2 g, 25.7 mmol) and *i*-Pr_2NEt (18 mL, 103 mmol) in dry DCM (100 mL) was added MOMCl (7.7 mL, 102 mmol) at 0 ℃. The mixture was stirred at ambient temperature for 12 h, then quenched with a saturated aqueous solution of NH_4Cl and concentrated. The residue was extracted with ethyl acetate for three times, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography on silica gel (petroleum ether/EtOAc: 9/1) afforded **12** (8.12 g, 25 mmol, 98%) as a colorless oil. $[\alpha]_D^{24}$ ＋16.7 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36－7.26 (m, 5H), 4.64 (s, 2H), 4.50 (s, 2H), 4.09－4.05 (m, 1H), 3.89 (dd, J=8.4, 4.8 Hz, 1H), 3.65 (dd, J=10.8, 3.6 Hz, 1H), 3.58 (dd, J=10.4, 2.8 Hz, 1H), 3.47－3.38 (m, 2H), 3.34 (s, 3H), 2.02－1.96 (m, 1H), 1.40 (s, 6H), 1.02 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.4, 128.4 (2C), 127.6 (3C), 108.8, 96.6, 78.9, 77.8, 73.1, 73.1, 68.6, 55.3, 35.9, 27.1, 27.1, 12.2; IR (KBr) v: 2985, 2933, 2885, 1455, 1369, 1214, 1109, 1043, 919, 738, 699 cm^{-1}; MS (EI, *m/z*) (%): 309 ([M–Me]$^+$) (5); HRMS-EI:

$[M–Me]^+$ calcd for $C_{17}H_{25}O_5$: 309.1702, found 309.1703.

(2*S*,3*R*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2-methylpropan-1-ol (13)

A reaction flask containing **12** (1.7 g, 5.2 mmol), Pd/C (5%, 400 mg), and MeOH (40 mL) was evacuated and back-filled with hydrogen (1 atm). The reaction mixture was stirred at ambient temperature under hydrogen for 12 h and then filtered over a plug of silica gel topped with Celite (MeOH eluent). The filtrate was concentrated and purified by flash column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to give **13** (1.2 g, 5.1 mmol, 98%) as a colorless oil. $[\alpha]_D^{24}$ +18.0 (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.67 (s, 2H), 4.12—4.06 (m, 1H), 3.95 (dd, *J*=8.0, 4.0 Hz, 1H), 3.66—3.65 (m, 4H), 3.38 (s, 3H), 2.18 (s, 1H), 1.96—1.87 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.02 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 109.0, 96.8, 80.4, 77.3, 68.7, 66.3, 55.5, 37.3, 27.2, 27.2, 11.7; IR (KBr) *v*: 3446, 2935, 2887, 1380, 1371, 1251, 1215, 1153, 1042, 1109 cm^{-1}; MS (EI, *m/z*) (%): 219 ($[M–Me]^+$) (17); HRMS-EI: $[M–Me]^+$ calcd for $C_{10}H_{19}O_5$: 219.1232, found 219.1231.

(2*R*,3*R*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(methoxymethoxy)-2-methylpropanal (3)

To a solution of **13** (180 mg, 0.77 mmol) in DCM (20 mL) were added $NaHCO_3$ (260 mg, 3.1 mmol) and Dess-Martin reagent (500 mg, 1.2 mmol) at 0 ℃. The mixture was stirred for 1 h and quenched with a saturated aqueous solution of $Na_2S_2O_3$ and separated. The aqueous layer was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel (petroleum ether/EtOAc: 12/1) to afford aldehyde **3** (120 mg, 0.52 mmol, 67%) as a colorless oil. $[\alpha]_D^{25}$ +12.6 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.74 (s, 1H), 4.65 (s, 2H), 4.27 (dd, *J*=8.0, 4.4 Hz, 1H), 4.09—4.00 (m, 1H), 3.68 (d, *J*=5.2 Hz, 2H), 3.37 (s, 3H), 2.66—2.59 (m, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.22 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 202.8, 109.7, 96.9, 77.4, 68.2, 55.5, 48.2, 27.1, 27.1, 8.6; IR (KBr) *v*: 2986, 2937, 1728, 1458, 1371, 1216, 1153, 1111, 1043, 919 cm^{-1}; MS (EI, *m/z*) (%): 217 ($[M–Me]^+$) (5); HRMS-EI: $[M–Me]^+$ calcd for $C_{10}H_{17}O_5$: 217.1076, found 217.1070.

(1*R*,2*S*,3*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)-2-methylhex-5-en-3-ol (14)

To a solution of **13** (190 mg, 0.8 mmol) in DMSO/DCM (10 mL/10 mL) were added Et_3N (0.61 mL, 4.2 mmol) and SO_3•py complex (400 mg, 2.5 mmol) at 0 ℃. The mixture was stirred for 1 h and quenched with an aqueous NH_4Cl solution and extracted with ether for three times. The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give aldehyde **3**. The crude **3** was dissolved in dry DCM (15 mL) and treated with $MgBr_2$•Et_2O (630 mg, 2.4 mmol) and $Bu_3SnCH_2CHCH_2$ (0.50 mL, 1.6 mmol) at ambient temperature for 12 h. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$, extracted with ethyl acetate for three times. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel (petroleum ether/EtOAc: 8/1) to afford **14** (180 mg, 0.66 mmol, 81%, *d.r.*>19/1 by ^{1}H NMR) as a colorless oil. $[\alpha]_D^{24}$ +20.2 (*c* 1.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.90—5.80 (m, 1H), 5.16 (d, *J*=6.0 Hz, 1H), 5.13 (s, 1H), 4.66 (s, 2H), 4.17—4.14 (m, 1H), 4.08—4.03 (m, 1H), 3.64—3.62 (m, 3H), 3.37 (s, 3H), 2.44—2.39 (m, 2H), 2.25—2.18 (m, 1H), 1.81—1.77 (m, 1H), 1.41 (s, 6H), 1.01 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.9, 118.0, 109.1, 96.7, 78.0, 77.1, 73.4, 68.3, 55.3, 39.7, 38.2, 27.1, 27.0, 10.7; IR (KBr) *v*: 3492, 2985, 2935, 1380, 1370, 1244, 1215, 1042, 918 cm^{-1}; MS (EI, *m/z*) (%): 259 ($[M–Me]^+$) (1); HRMS-EI: $[M–Me]^+$ calcd for $C_{13}H_{23}O_5$: 259.1545, found 259.1546.

(4*S*,5*S*,6*R*)-4-Allyl-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,5-trimethyl-1,3-dioxane (15)

A solution of **14** (700 mg, 1.8 mmol) in MeOH (80 mL) was treated with aqueous HCl solution (4 N, 80 mL) at room temperature for 2 h. The mixture was concentrated and dissolved with acetone (100 mL) and treated with TsOH-H_2O (200 mg) at room temperature for 12 h. After being quenched with a saturated solution of $NaHCO_3$, the mixture was concentrated to remove acetone and extracted with ethyl acetate for three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel to afford a diol (178 mg, 0.8 mmol, 43%). Diol was treated with PPTS (20 mg) in DMP/DCM (10 mL/10 mL) at room temperature for 12 h. The solution was concentrated and purified on silica gel (petroleum ether/EtOAc: 12/1—8/1) to afford **15** (154 mg, 0.57 mmol, 74%) as a colorless oil. $[\alpha]_D^{26}$ +27.3 (*c* 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.93—5.82 (m, 1H), 5.09 (s, 1H), 5.06 (d, *J*=1.2 Hz, 1H), 4.51—4.45 (m, 1H), 4.09 (dd, *J*=12.0, 5.6 Hz, 1H), 3.63 (dd, *J*=9.2, 8.4 Hz, 2H), 3.37 (dd, *J*=12.0, 10.4 Hz, 1H), 2.35—2.24 (m, 2H), 1.78—1.68 (m, 1H), 1.41 (s, 3H), 1.36 (s, 6H), 1.32 (s, 3H), 1.02 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.3, 117.4, 107.4, 100.5, 84.5, 76.7, 71.7, 65.5, 43.0, 38.3, 27.3, 26.9, 25.8, 24.01, 15.1; IR (KBr) *v*: 2988, 2934, 1374, 1255, 1212, 1061, 1034, 912, 836 cm^{-1}; MS (EI, *m/z*) (%): 255 ($[M–Me]^+$) (12); HRMS-EI: $[M–Me]^+$ calcd for $C_{14}H_{23}O_4$: 255.1596, found 255.1595.

(5*R*,6*R*,7*S*)-7-Allyl-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-6,9,9,10,10-pentamethyl-2,4,8-trioxa-9-silaundecane (16)

To a solution of **14** (170 mg, 0.60 mmol) in dry DMF (5 mL) were added imidazole (180 mg, 2.6 mmol) and TBSCl (200 mg, 1.3 mmol). The reaction was stirred at

room temperature for 12 h, then quenched with water and extracted with ether for three times. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated in vacuo, and purified on silica gel (petroleum ether/EtOAc: 12/1) to afford **16** (200 mg, 0.52 mmol, 83%) as a colorless oil. $[\alpha]_D^{25}$ +48.3 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.93−5.82 (m, 1H), 5.08 (d, *J*=5.2 mmol, 1H), 5.05 (s, 1H), 4.66 (s, 2H), 4.09 (dd, *J*=9.6, 2.0 Hz, 1H), 3.96−3.91 (m, 1H), 3.72−3.68 (m, 1H), 3.63−3.54 (m, 2H), 3.37 (s, 3H), 2.37−2.23 (m, 2H), 1.68−1.58 (m, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H), 0.89 (d, *J*=6.0 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 134.6, 117.2, 109.1, 96.8, 77.6, 77.4, 73.4, 68.7, 55.5, 39.1, 38.6, 27.3, 27.3, 26.0 (3C), 18.29, 9.1, –4.1, –4.7; IR (KBr) *v*: 2931, 2888, 1473, 1463, 1379, 1369, 1256, 1046, 913, 837, 776 cm^{-1}; MS (EI, *m/z*) (%): 373 ([M–Me]$^+$) (1); HRMS-EI: [M–Me]$^+$ calcd for $C_{19}H_{37}O_5Si$: 373.2410, found 373.2412.

(3*S*,4*R*,5*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(methoxymethoxy)-4-methylpentanal (17)

A solution of **16** (575 mg, 1.48 mml) in MeOH/DCM (50 mL/50 mL) was treated with ozone at −78 ℃ until the blue color sustained. To the mixture were added Et_3N (0.32 mL, 2.2 mmol) and Me_2S (3.3 mL, 44.7 mmol). The solution was stirred at ambient temperature for 5 h and concentrated and purified on silica gel (petroleum ether/EtOAc: 15/1) to give aldehyde **17** (570 mg, 1.46 mmol, 99%) as a colorless oil. $[\alpha]_D^{26}$ +18.8 (*c* 1.18, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.83 (dd, *J*=2.8, 1.6 Hz, 1H), 4.65 (s, 2H), 4.21 (dd, *J*=10.8, 6.0 Hz, 1H), 3.98−3.92 (m, 2H), 3.65−3.57 (m, 2H), 3.37 (s, 3H), 2.69−2.54 (m, 2H), 1.89−1.81 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 0.96 (d, *J*=7.2 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}CNMR ($CDCl_3$, 100 MHz) δ: 202.4, 109.4, 96.9, 78.0, 77.3, 70.9, 68.4, 55.5, 47.9, 40.4, 27.2, 27.2, 25.9 (3C), 18.1, 8.0, –4.5, –4.6; IR (KBr) *v*: 2932, 2888, 1728, 1473, 1463, 1380, 1370, 1254, 1046, 838, 777 cm^{-1}; MS (EI, *m/z*) (%): 375 ([M–Me]$^+$) (1); HRMS-EI: [M–Me]$^+$ calcd for $C_{18}H_{35}O_6Si$: 375.2203, found 375.2207.

Methyl (5*S*,6*R*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-(methoxymethoxy)-2,6-dimethylhept-2-enoate (2)

A solution of **18** (690 mg, 3.1 mmol) in dry DME (10 mL) was treated with *n*-BuLi (1.0 mL, 2.4 mol/L in hexane, 2.4 mmol) at 0 ℃ for 10 min, then a solution of **17** (480 mg, 1.23 mmol) in DME (10 mL) was added. The resulting mixture was stirred at room temperature for 30 min and quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate for three times. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified on silica gel (petroleum ether/EtOAc: 10/1) to give **2** (550 mg, 1.19 mmol, 97%). $[\alpha]_D^{26}$ +34.4 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.90 (t, *J*=8.0 Hz, 1H), 4.66 (s, 2H), 4.04 (dd, *J*=8.4, 1.6 Hz, 1H), 3.96−3.91 (m, 1H), 3.81−3.77 (m, 1H), 3.74 (s, 3H), 3.63−3.55 (m, 2H), 3.38 (s, 3H), 2.42−2.39 (m, 2H), 1.85 (s, 3H), 1.73−1.66 (m, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 0.90 (d, *J*=9.6 Hz, 1H), 0.89 (s, 9H), 0.07 (s, 3H), 0.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 139.2, 128.8, 109.2, 96.9, 77.8, 73.6, 68.6, 55.5, 51.8, 39.9, 33.4, 27.3, 27.3, 25.9 (3C), 18.2, 12.8, 8.7, –4.3, –4.6; IR (KBr) *v*: 2986, 2931, 1717, 1472, 1463, 1436, 1379, 1370, 1253, 1046, 836, cm^{-1}; MS (ESI, *m/z*): 483.4 ([M+Na]$^+$); HRMS-ESI: [M+Na]$^+$ calcd for $C_{23}H_{44}O_7Si$: 483.2749, found 483.2761.

Results and Discussion

To exclude the use of CrO_3 in Marker degradation, we have developed a green oxidation which enabled us to obtain potassium salt **5** on multikilogram scale as side product.[9] Compound **5** is a versatile compound and could easily be transformed into a series of 4C−6C chiral pool molecules including **4** on a 100 g scale.[10] From **4** we started our synthesis of **2**, as shown in Figure 2 the synthetic plan. The C2−C3 (*Z*)-double bond was to be introduced through a Horner–Wadsworth–Emmons (HWE) olefination and the C4−C5 bond through a chelation-controlled allylation of aldehyde **3**. The desired chiral vicinal diol in **3** was to be introduced by Sharpless asymmetric dihydroxylation of C2−C3 double bond derived from **4** by dehydration.

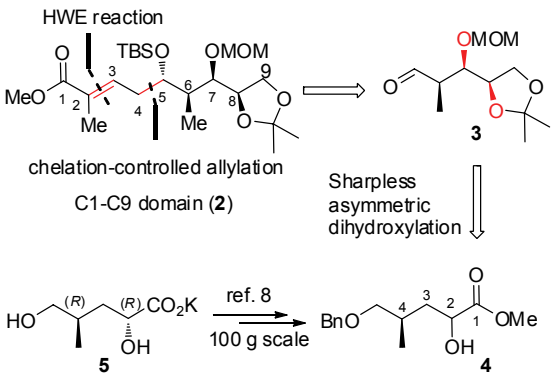

Figure 2 A retrosynthetic analysis of C1−C9 domain (**2**).

To implement the dehydration of **4**, as depicted in Scheme 1, its exposed hydroxyl group was first transformed into mesylate **6** in excellent yield, however, elimination of **6** did not proceed to afford **7**, even under harsh condition. Then we prepared bromide **8**, by heating **6** with lithium bromide in acetone at reflux for 18 h, and put it through several typical conditions. Treatment of **8** with DBU in DMF at 80 ℃ delivered completely **9**, a deconjugated product of **7**. After much optimization, we found that treating **8** with exact one equivalent of $NaHCO_3$ in HMPA at 100 ℃ for 4 h afforded the desired **7** in good yield without forming **9**. Under the standard condition of Sharpless asymmetric dihydroxylation,[11] diol **10** was prepared from **7** in high

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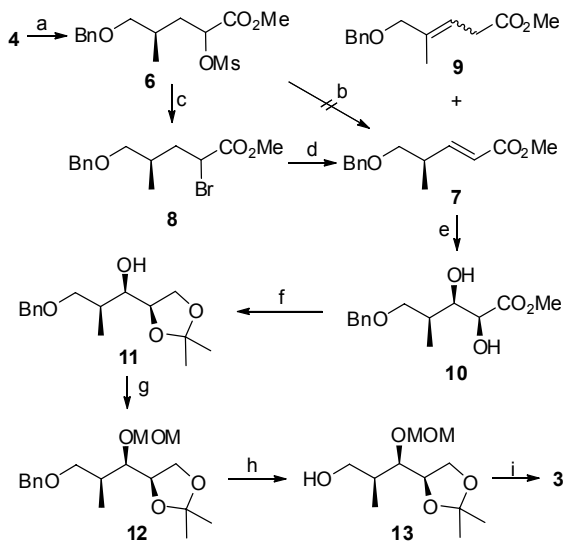
yield and stereoselectivity (86%, *d.r.*＞19∶1 by ^{1}H NMR).

We then set out to prepare aldehyde **3**. Ester **10** was reduced with $LiAlH_4$ and the resulting triol was protected as acetonide selectively to give **11**, the more thermodynamically stable isopropylidene derivative, in 57% yield. The exposed secondary hydroxyl group in **11** was protected as a MOM ether to form a chelation site we needed later. The benzyl ether was removed by catalytic hydrogenation and the exposed hydroxyl group was oxidized with Dess-Martin periodinane to afford aldehyde **3** in moderate yield.

Scheme 1

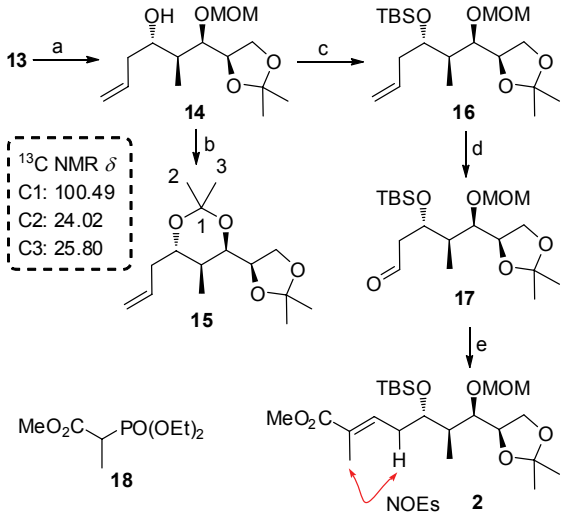


Conditions and reagents: (a) MsCl, Et_3N, CH_2Cl_2, 0 ℃, 1 h, 91%; (b) LiBr, Li_2CO_3, DMF, 120 ℃, 8 h; (c) LiBr, acetone, reflux, 18 h, 95%; (d) $NaHCO_3$, HMPA, 100 ℃, 4 h, 66%; (e) $K_3Fe(CN)_6$, K_2CO_3, OsO_4, $(DHQD)_2PHAL$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 ℃ to r.t., 12 h, 86%, *d.r.*＞19∶1 by NMR; (f) $LiAlH_4$, THF, 0 ℃ to r.t., 12 h; then TsOH•H_2O, acetone, r.t., 10 h, 57%; (g) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 ºC to r.t., 12 h, 98%; (h) H_2, Pd/C, MeOH, r.t., 12 h, 98%; (i) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 ℃, 1 h, 67%.

To minimize the possible *α*-epimerization and *β*-elimination, **3** was used without purification to give better result, as in Scheme 2. Allylation of crude **3**, with allyltributyltin in the presence of magnesium bromide etherate in CH_2Cl_2 at room temperature, gave **14** in high yield and stereochemical control.[12] To confirm the stereochemistry of the newly generated hydroxyl in **14**, we prepared diacetonide **15** and analyzed its ^{13}C NMR spectroscopy. The chemical shift of the acetal carbon in the 1,3-dioxolane appearing at *δ* 100.5 and the methyl groups at *δ* 24.0 and 25.8 suggested the presence of *anti*-1,3-diol.[13] The allylation step was therefore confirmed to be chelation-controlled. As both chirality at *α*- and *β*-positions induced the same stereochemical outcome under chelation conformation, the stereochemical control was reinforced to give **14** as the sole product.

To prepare for the forthcoming HWE olefination, the free hydroxyl in **14** was protected as TBS ether and the terminal double bond was cleaved with ozone to give aldehyde **17** in high yield. HWE reaction of **17** with phosphonate **18** delivered *α*,*β*-unsaturated ester **2** effectively (97% yield, *E*/*Z*: 5/1). The major isomer was isolated by flash column chromatography and its geometry of the C2—C3 double bond was confirmed to be *E* by an NOE experiment.

Scheme 2



Conditions and reagents: (a) SO_3•py, DMSO, Et_3N, CH_2Cl_2, 0 ℃, 1 h; then $MgBr_2$•Et_2O, $Bu_3SnCH_2CHCH_2$, CH_2Cl_2, r.t., 12 h, 81%, *d.r.*＞19∶1 by NMR; (b) MeOH, 4 N HCl, r.t., 2 h, concentration, acetone, TsOH, r.t., 12 h, 43%, then DMP, PPTS, CH_2Cl_2, r.t., 12 h, 74%; (c) TBSCl, imidazole, DMF, r.t., 12 h, 83%; (d) O_3, MeOH, CH_2Cl_2, −78 ºC, then Et_3N, Me_2S, r.t., 5 h, 99%; (e) **18**, *n*-BuLi, DME, 0 ℃, 10 min, **17**, 97%, *E*/*Z*: 5/1.

Conclusions

The C1—C9 domain **2** of the nominal didemnaketal A was synthesized from *α*-OH ester **4**, a chiral pool molecule which passed its methyl on to the target, in 12 steps with an overall yield of 14%. Both key reactions, the introduction of the 7,8-*syn*-diol through Sharpless asymmetric dihydroxylation and the C4-OH through chelation-controlled allylation, proceeded with high yields and stereoselectivities. Currently, developing more and useful chiral pool molecules from **5** and applying them in the syntheses of natural products are ongoing in this laboratory.

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