Total Synthesis of (−)-Nakadomarin A

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Supporting Information: Experimental Procedures

General Procedures

Unless otherwise noted, all reactions were carried out under an argon atmosphere using flame-dried glassware. All moisture sensitive reagents were added via a dry syringe or cannula where possible. Anhydrous acetonitrile (CH_3CN), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), benzene, toluene, and triethylamine (Et_3N) were from obtained from a solvent dispensing system. All other solvers and reagents were used as obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were obtained on Bruker 300, 400 or 600 MHz spectrometers. Infrared spectra were obtained using a Perkin-Elmer 1600 FTIR. Chromatographic purification was performed using Silicycle SiliaFlash® P60 (230-400 mesh) silica gel. Optical rotations were recorded in a cell of 50 mm path length on a Rudolph Research Analytical Autopol® II automatic polarimeter.

S1

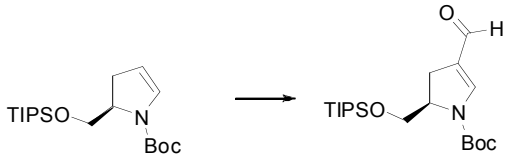
Silyl ether S1. To a solution of D-pyroglutaminol[1] (33.8 g, 294 mmol) and imidazole (40 g, 588 mmol) in a 2:1 mixture of CH_2Cl_2/DMF (600 mL) at rt was added dropwise TIPSCl (75.5 mL, 353 mmol). The solution was stirred overnight at rt. The reaction mixture was poured into H_2O and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc) gave silyl ether **S1** as a clear oil (70.2 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 21H), 1.74 (dddd, *J* = 13.1, 9.4, 5.5, 3.9 Hz, 1H), 2.17 (ddd, *J* = 7.7, 13.0, 15.4 Hz, 1H), 2.34 (dd, *J* = 6.5, 5.3 Hz, 1H), 2.36 (7.5, 5.3 Hz, 1H), 3.52 (dd, *J* = 9.8, 8.0 Hz, 1H), 3.72 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.75-3.82 (m, 1H), 5.78 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 17.8, 22.6, 29.7, 55.9, 67.0, 178.1; IR (neat) 3223 (br), 2942, 2865, 1697, 1462, 1383, 1258, 1121 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{30}NO_2Si$ 272.2046, found 272.2039; $[\alpha]_D$ = -36.6 (*c* = 0.328, $CHCl_3$).

S1 **10**

Imide 10. To a solution of lactam **S1** (41.91 g, 154 mmol) in MeCN (260 mL) at rt was added and DMAP (1.88 g, 15.4 mmol) and di-*tert*-butyl dicarbonate (38.84 g, 185 mmol). The solution was stirred at rt for 3 h then concentrated. Purification by silica gel chromatography (EtOAc-hexanes 20:80) gave imide **10** as a clear oil (51.24 g, 90%). ^{1}H NMR ($CDCl_3$, 400.13 MHz, amide rotamers) δ 1.05 (s, 21 H), 1.52 and 1.56 (s, 9H), 2.01-2.16 (m, 1H), 2.36 (ddd, *J* = 12.0, 8.9, 3.0 Hz, 1H), 2.74 (dt, *J* = 17.5, 10.5 Hz , 1H), 3.78 (dd, *J* = 12.4, 10.1 Hz, 1H), 4.01 (dd, *J* = 10.1, 4.1 Hz, 1H), 4.14-4.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 17.8, 20.9, 27.9, 32.2, 58.9, 64.5, 82.5, 149.9, 174.8; IR (neat) 2943, 2866, 1790, 1753, 1711, 1462, 1366, 1312, 1257, 1161 cm^{-1}; HRMS (M+Na$^+$) calcd for $C_{19}H_{37}NO_4SiNa$ 394.2390, found 394.2379; $[\alpha]_D$ = +62.5 (*c* = 0.32, $CHCl_3$).

10 **11**

Enecarbamate 11. To a solution of imide **10** (51.14 g, 138 mmol) in toluene (275 mL) at -78 °C was added dropwise Super Hydride (146 mL of a 1.0 M solution in THF, 146 mmol). The solution was stirred at -78 °C for 0.5 h, then diisopropylethylamine (137 mL, 787 mmol), DMAP (337 mg, 2.76 mmol) and trifluoroacetic anhydride (23.4 mL, 166 mmol) were added. The solution was allowed to warm to rt and stirred for 3 h. The reaction mixture was then washed with water, brine, dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et_3N, 2.5:95:2.5) to give enecarbamate **11** as a yellow oil (43.38 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 21H), 1.47 (s, 9H), 2.62-2.84 (br m, 2H), 3.76-3.93 (br m, 2H), 4.13 and 4.21 (br s, 1H), 4.88 and 4.97 (br s, 1H), 6.39 and 6.53 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, amide rotamers) δ 11.8, 17.8, 28.3, 31.8 (major) and 33.1 (minor), 58.0, 63.0 (major) and 63.1 (minor), 79.7 (major) and 79.9 (minor), 106.6 (major) and 106.8 (minor), 129.6 (major) and 129.4 (minor), 151.4 (major) and 151.9 (minor); IR (neat) 2942, 2866, 1703, 1623, 1463, 1402, 1179, 1129 cm^{-1}; HRMS (MH$^+$) calcd for $C_{19}H_{38}NO_3Si$ 356.2621, found 356.2631; $[\alpha]_D$ = +56.8 (*c* = 0.352, $CHCl_3$).



11 **12**

Aldehyde 12. To a solution of DMF (45.7 mL, 590 mmol) in CH_2Cl_2 (590 mL) at 0 °C was added oxalyl chloride (12.4 mL, 142 mmol). The solution was stirred at 0 °C for 10 min. To the resultant white suspension was then added enecarbamate **11** (41.98 g, 118 mmol) in CH_2Cl_2 (118 mL). After 15 minutes, the solution was poured into saturated aqueous Na_2CO_3 (480 mL) and the mixture was stirred vigorously

for 1 h. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 20:80) gave aldehyde **12** as a yellow oil (39.2 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz, amide rotamers) δ 1.05 (s, 21H), 1.51 (s, 9H), 2.93 (br m, 2H), 3.64-3.97 and 4.04-4.20 (br m, 2H), 4.23-4.47 (br m, 1H), 7.37 and 7.51 (br s, 1H) 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.7, 17.7, 27.4, 28.2, 60.8, 63.1 (broad), 82.3, 124.1, 147.6, 150.2 (broad), 185.6; IR (neat) 2943, 2866, 1719, 1662, 1613, 1462, 1412, 1314, 1154 cm^{-1}; HRMS (MH^+) calcd for $C_{20}H_{38}NO_4Si$ 384.2570, found 384.2569; $[\alpha]_D$ = +38.7 (*c* = 0.672, $CHCl_3$).

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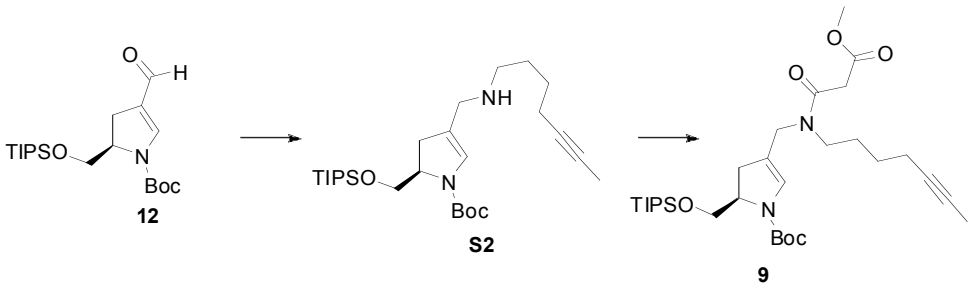

Amide 9. To a solution of aldehyde **12** (20.0 g, 52.1 mmol) in MeOH (260 mL) at rt was added 5-heptynyl amine[2] (6.95 g, 62.5 mmol). The solution was stirred at rt for 3 h, cooled to 0 °C and $NaBH_4$ (2.96 g, 78.2 mmol) was added in one portion. The solution was allowed to warm to rt and stirred for 5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give amine **S2** (24.6 g) as a yellow oil which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz, amide rotamers) δ 1.05 (s, 21H), 1.46 (s, 9H), 1.47-1.67 (br m, 4H), 1.77 (t, J = 2.5 Hz, 3H), 2.08-2.20 (br m, 2H), 2.52-2.87 (br m, 4H), 3.75-3.94 (br m, 2H), 4.10-4.31 (br m, 1H), 6.29 and 6.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, amide rotamers, major rotamer resonances reported) δ 3.0, 11.5, 17.6, 18.2, 26.5, 28.0, 28.8, 30.9, 47.3, 48.6, 58.3, 62.8, 75.0, 78.9, 79.2, 119.5, 125.2, 151.0; IR (neat) 3323 (br), 2941, 2865, 1698, 1462, 1413, 1366, 1247, 1165, 1120 cm^{-1}; HRMS (MH^+) calcd for $C_{27}H_{51}N_2O_3Si$ 479.3669, found 479.3659.

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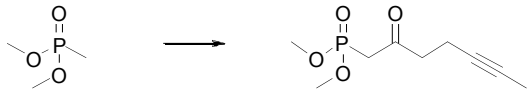
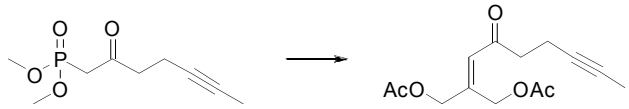
To a solution of amine **S2** (24.6 g, 51.4 mmol) and Et_3N (14.4 mL, 103 mmol) in CH_2Cl_2 (510 mL) at 0 °C was added dropwise methyl malonyl chloride (6.60 mL, 61.7 mmol). The solution was stirred at 0 °C for 1 h and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et_3N, 27.5:70:2.5) gave amide **9** as a yellow oil (19.56 g, 66%, two steps). ^{1}H NMR ($CDCl_3$, 400 MHz, multiple amide rotamers) δ 1.04 (s, 21H), 1.39-1.52 (br m, 2H), 1.46 (s, 9H), 1.57-1.72 (br m, 2H), 1.72-1.82 (br m, 3H), 2.08-2.24 (br m, 2H), 2.49-2.81 (br m, 2H), 3.13-3.50 (br m, 2H), 3.44, 3.46 and 3.47 (s, 2H), 3.60-4.33 (br m, 5H), 3.73 and 3.74 (s, 3H), 6.28, 6.36 and6.47 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, amide rotamers, major rotamer resonance reported) δ 2.7, 11.4, 17.4,

17.9, 25.1, 26.7, 27.8, 33.7, 40.2, 44.6, 46.0, 51.6, 58.4, 62.7, 75.0, 78.1, 79.3, 115.3, 126.8, 151.1, 165.1, 167.5 ; IR (neat) 2942, 2865, 1746, 1698, 1651, 1414, 1366, 1330, 1251, 1162 cm^{-1}; HRMS (MH^+) calcd for $C_{31}H_{55}N_2O_6Si$ 579.3829, found 579.3835; $[\alpha]_D$ = +56.1 (*c* = 0.57, $CHCl_3$).



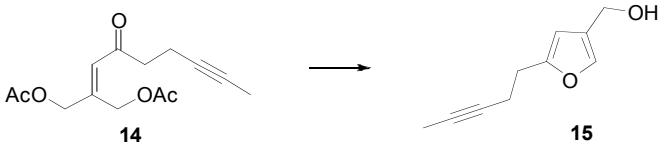
13

β-ketophosphonate 13. To a solution of dimethyl methyl phosphonate (20.3 mL, 190 mmol) in THF (475 mL) at -78 °C was added dropwise *n*-BuLi (76 mL of a 2.5 M solution in hexanes, 190 mmol). The reaction mixture was stirred for 0.5 h at -78 °C, then a solution of methyl 4-hexynoate[3] (20.0 g, 159 mmol) in THF (160 mL) was added dropwise. The solution was stirred for 1 h at -78 °C, then allowed to warm to rt and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl, extracted with EtOAc, dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc) gave β-ketophosphonate **13** as a yellow oil (22.5 g, 54%, 94% based on recovered methyl 4-hexynoate). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.74 (t, 2.5 Hz, 3H), 2.40 (tq, 7.4, 2.5 Hz, 2H), 2.80 (t, 7.4 Hz, 2h), 3.11 (d, *J* = 22.7 Hz, 2H), 3.77 (d, 11.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.1, 12.9, 41.5 (d, *J* = 128.3 Hz), 43.0, 52.8 (d, *J* = 6 Hz), 76.0, 77.0, 199.9 (d, *J* = 6 Hz); IR (neat) cm^{-1}; HRMS (MH^+) calcd for $C_9H_{16}O_4P$ 219.0786, found 219.0804.



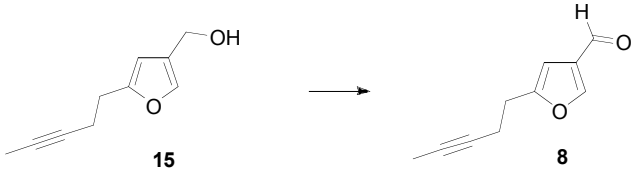
13 **14**

Enone 14. To a solution of NaH (60% wt in mineral oil, 4.52 g, 113 mmol) in THF (225 mL) at 0 °C was added dropwise β-ketophosphonate **13** (22.5 g, 103 mmol) in THF (65 mL). The solution was allowed to warm to rt and stirred for 1 h. A solution of 1,3-diacetoxy-2-propanone[4] (18.8 g, 108 mmol) in THF (85 mL) was added dropwise, and the solution was stirred for 1 h. The reaction mixture was poured into water, the layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 25:75) gave enone **14** as a yellow oil (22.5 g, 82%). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.74 (t, *J* = 2.5Hz, 3H), 2.06 (s, 3H), 2.12 (s, 3H), 2.41 (tq, *J* = 7.4, 2.5 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 4.72 (s, 2H), 5.19 (s, 2H), 6.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.1, 13.0, 20.3, 20.4, 43.0, 61.7, 63.2, 75.8, 77.2, 123.9, 147.3, 169.8, 170.0, 198.2; IR (neat) 2922, 1744, 1692, 1629, 1371, 1221 cm^{-1}; HRMS (MH^+) calcd for $C_{14}H_{19}O_5$ 267.1232, found 267.1224.



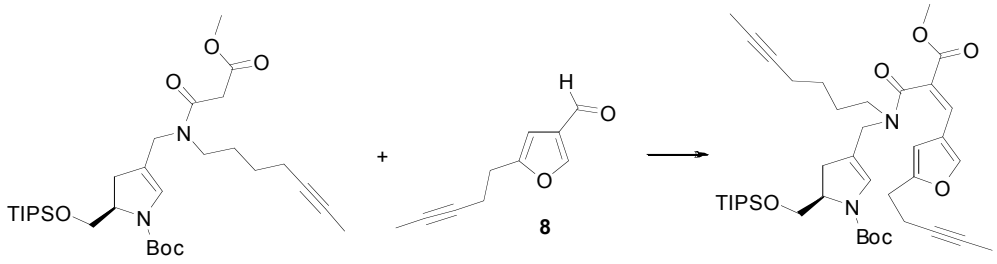
14 **15**

Furan 15. To a solution of enone **14** (22.5 g, 84.2 mmol) in MeOH (840 mL) at rt was added conc. HCl (1.4 mL, 16.8 mmol). The solution was heated at 50 °C overnight. The reaction mixture was concentrated to about one-quarter of its original volume, then poured into saturated aqueous $NaHCO_3$ and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 30:70) gave furan **15** as an orange oil (11.3 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (br s, 1H), 1.77 (t, *J* = 2.4 Hz, 3H), 2.44 (tq, *J* = 7.5, 2.4 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 4.5 (s, 2H), 6.12 (s, 1H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.2, 17.6, 27.8, 56.3, 76.1, 77.8, 105.5, 125.6, 138.1, 155.4,; IR (neat) 3241 (br), 2920, 1759, 1638, 1442 cm^{-1}; HRMS (M^+) calcd for $C_{10}H_{13}O_2$ 165.2090, found 165.2120.



15 **8**

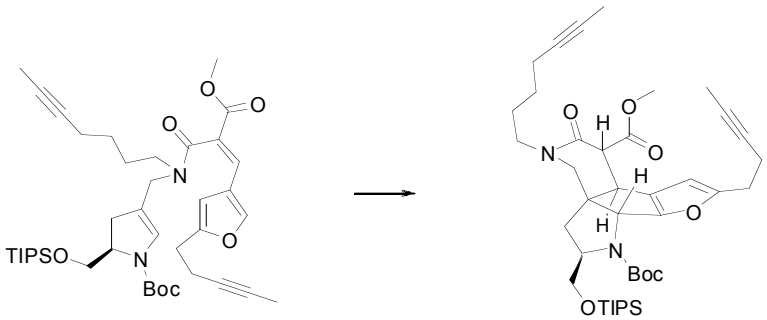
Furaldehyde 8. To a solution of oxalyl chloride (12.0 mL, 138 mmol) in CH_2Cl_2 (275 mL) at -78 °C was added DMSO (19.5 mL, 275 mmol). The solution was stirred for 15 minutes, then furan **15** (11.3 g, 68.8 mmol) in CH_2Cl_2 (46 mL) was added, followed by Et_3N (57.6 mL, 413 mmol). The solution was allowed to warm to rt and stirred for 30 minutes before being poured into water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 10:90) gave furaldehyde **8** as a yellow oil (8.39 g, 75%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.75 (t, *J* = 2.5 Hz, 3H), 2.47 (tq, *J* = 7.5, 2.5 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H), 6.48 (s, 1H), 7.94 (s, 1H), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.2, 17.3, 27.5, 76.6, 77.0, 102.5, 129.3, 150.4, 157.5,184.3; IR (neat) 3123, 2919, 2844, 2735, 1686, 1544, 1442, 1408, 1134 cm^{-1}; HRMS (MH^+) calcd for $C_{10}H_{11}O_2$ 163.1961, found 163.1931.



9 **7**

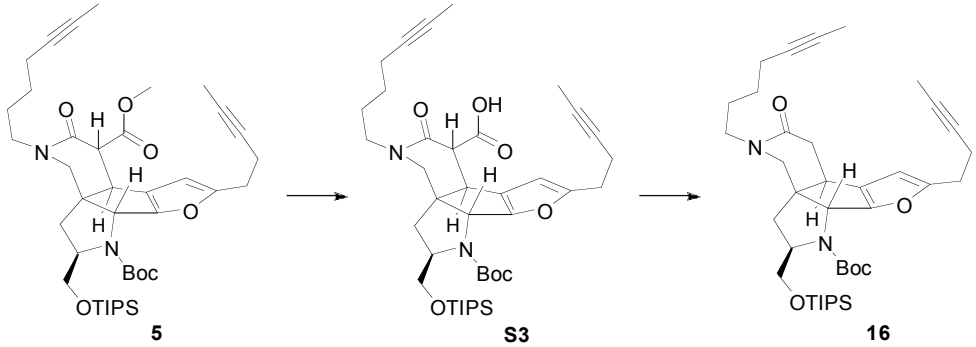
Enoate 7. To a solution of amide **9** (11.58 g, 20.0 mmol) and furaldehyde **8** (6.49 g, 40.0 mmol) in benzene (200 mL) at rt was added benzoic acid (1.06 g, 8.80 mmol) and piperidine (1.30 mL, 13.2 mmol). The flask was equipped with a Dean-Stark trap and a condenser, and the solution was heated at reflux overnight. The solution was allowed to cool to room temperature, and then poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes-Et_3N, 17.5:80:2.5) gave **7** as an orange oil (12.68 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz, multiple amide rotamers) δ 1.03 (s, 21

H), 1.18-1.32 (br m, 2H), 1.45 (s, 9H), 1.48-1.60 (br m, 2H), 1.65-1.87 (br m, 6H), 1.90-2.06 (br m, 2H), 2.12-2.27 (br m, 2H), 2.27-2.57 (br m, 2H), 2.60-2.92 (br m, 2H), 3.00-3.27 (br m, 2H), 3.27-4.34 (br m, 8H), 6.16-6.50 (br m, 1H), 6.21 (br s, 1H), 7.50 (br s, 1H), 7.58 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, amide rotamers, major rotamer resonance reported) δ 2.9, 3.0, 11.5, 17.2, 17.5, 18.1, 25.5, 25.9, 27.4, 27.9, 33.6, 41.1, 46.2, 51.7, 58.5, 63.0, 75.5, 76.0, 77.7, 78.2, 79.6, 104.5, 114.9, 121.0, 125.1, 128.3, 131.4, 144.9, 151.2, 156.5, 164.6, 166.6; IR (neat) 2943, 2865, 1698, 1634, 1414, 1366, 1239, 1163 cm^{-1}; HRMS (MH^+) calcd for $C_{41}H_{63}N_2O_7Si$ 723.4405, found 723.4410; $[\alpha]_D$ = +34.8 (*c* = 0.689, $CHCl_3$).



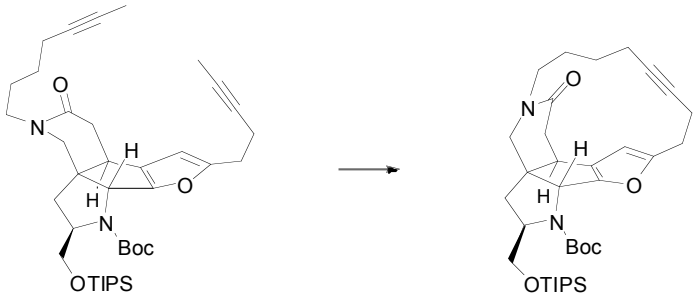
7 **5**

Tetracycle 5. To a solution of **7** (12.18 g, 16.8 mmol) in CH_2Cl_2 (336 mL) at rt was added $InCl_3$ (372 mg, 1.68 mmol) in one portion. The solution was heated at reflux overnight, cooled to rt and poured over saturate aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, the combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 20:80) gave **5** as an orange gum (9.62 g, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 21 H), 1.37-1.48 (br m, 2H), 1.51 (br s, 9H), 1.55-1.67 (br m, 2H), 1.76 (br t, *J* = 2.5 Hz, 6H), 2.08-2.18 (br m, 2H), 2.19-2.28 (br m, 2H), 2.37-2.47 (br m, 2H), 2.75 (br t, *J* = 7.4 Hz, 2H), 3.24-3.33 (br m, 1H), 3.31 (d, 6.7 Hz), 3.41 (d, 6.7 Hz), 3.45-3.57 (br m, 2H), 3.59-3.75 (br m, 2H), 3.76-3.86 (br m, 1H), 3.81 (s, 3H), 3.97-4.06 (br m, 1H), 4.13-4.23 (br m, 1H), 4.71 (br s, 1H) 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.2, 3.2, 11.8, 17.6, 17.7, 18.2, 25.9, 27.1, 27.9, 28.1, 28.6, 39.8, 45.9, 47.3, 52.3, 53.6, 54.2, 58.8, 59.1, 62.9, 64.9, 75.5, 76.2, 77.4, 78.3, 79.7, 102.6, 127.2, 153.6, 154.5, 167.4, 169.5; IR (neat) 2942, 2865, 1745, 1695, 1674, 1435, 1383, 1257, 1173, 1108, 1062 cm^{-1}; HRMS (MH^+) calcd for $C_{41}H_{63}N_2O_7Si$ 723.4405, found 723.4419; $[\alpha]_D$ = +43.8 (*c* = 0.32, $CHCl_3$).



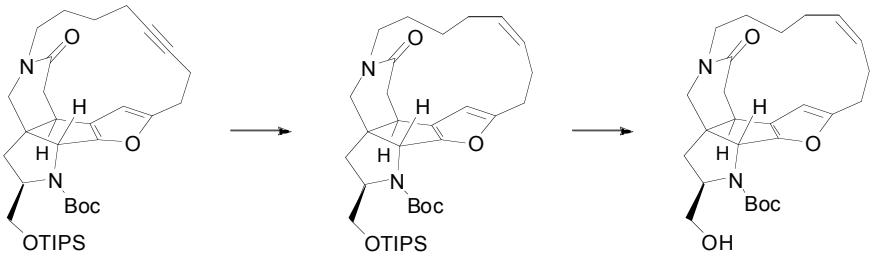
5 **S3** **16**

Lactam 16. To a solution of ester **5** (9.21 g, 12.99 mmol) in MeOH (260 mL) at rt was added KOH (43.3 mL of a 3M aqueous solution, 130 mmol). The solution was heated at reflux overnight, cooled to 0 °C, and acidified with 1M HCl until a pH of about 4 was obtained. The reaction mixture was extracted with EtOAc, dried and concentrated to give a mixture of carboxylic acid **S3** and the decarboxylated lactam **16**. This mixture was dissolved in toluene (260 mL) and the solution was heated at reflux overnight. The solution was then concentrated. Purification by silica gel chromatography (EtOAc-hexanes, 30:70) gave lactam **16** as an orange gum (6.94 g, 80%, two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (s, 21H), 1.34-1.45 (br m, 2H), 1.51 (s, 9H), 1.52-1.63 (br m, 2H), 1.75 (br t, *J* = 2.5 Hz, 3H), 1.76 (br t, *J* = 2.5 Hz, 3H), 2.07-2.23 (br m, 4H), 2.33 (dd, *J* = 14.9, 5.0, 1H), 2.38-2.47 (br m , 2H), 2.67 (dd, *J* = 14.9, 7.0, 1H), 2.76 (br t, *J* = 7.5 Hz, 2H), 2.97-3.05 (br m, 1H), 3.11-3.23 (br m, 1H), 3.45-3.61 (br m, 1H), 3.50 (br d, *J* = 13.3 Hz, 1H), 3.56 (br d, *J* = 13.3 Hz, 1H), 3.71 (br d, *J* = 9.5 Hz, 1H), 3.93-4.05 (br m, 1H), 4.15 (br d, *J* = 9.5 Hz, 1H), 4.68 (s, 1H), 5.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 3.3, 11.9, 17.7, 17.8, 18.4, 26.0, 27.3, 28.2, 28.7, 37.3, 39.4, 43.3, 46.9, 54.1, 58.8, 59.5, 63.1, 64.9, 75.5, 76.2, 77.6, 78.4, 79.7, 102.5, 128.7, 153.7, 154.3, 160.1, 171.2; IR (neat) 2941, 2865, 1694, 1656, 1446, 1384, 1257, 1176, 1141, 1103 cm^{-1}; HRMS (MH^+) calcd for $C_{39}H_{61}N_2O_5Si$ 665.4350, found 665.4348; $[\alpha]_D$ = +49.1 (*c* = 0.448, $CHCl_3$).

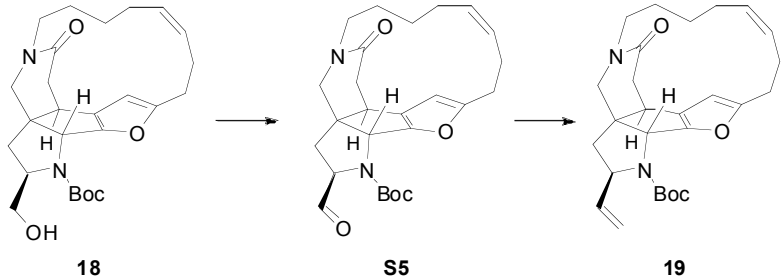


Cycloalkyne 17. **Method A:** To a solution of diyne **16** (1.00 g, 1.50 mmol) in PhCl (240 mL) at 80 °C was added a solution of Schrock carbyne catalyst[5] (178 mg, 0.376 mmol) in PhCl (1 mL). The solution was heated at 80 °C for 3 h, then allowed to cool to rt and concentrated. Purification by silica gel chromatography (EtOAc-hexanes 70:30) gave cycloalkyne **17** as a foam (705 mg, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 21H), 1.07-1.18 (br m, 1H), 1.18-1.37 (br m, 3H), 1.50 (s, 9H), 1.85-2.04 (br m, 2H), 2.07-2.23 (br m, 2H), 2.32-2.55 (br m, 3H), 2.57 (dd, *J* = 14.9, 4.6 Hz, 1H), 2.64 (dd, *J* = 14.9, 2.5 Hz, 1H), 2.68-2.85 (br m, 2H), 3.25 (d, *J* = 14.0 Hz, 1H), 3.27 (br s, 1H), 3.63 (d, *J* = 14.0 Hz, 1H), 3.87-4.02 (br m, 3H), 4.12-4.26 (br m, 1H), 4.65 (s, 1h), 5.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.8, 17.8, 18.2, 18.8, 25.9, 27.5, 28.0, 34.6, 37.5, 42.2, 46.5, 57.4, 58.7, 59.4, 62.7, 67.8, 79.3, 79.5, 102.7, 129.9, 153.7, 155.0, 159.4, 170.2; IR (neat) 2939, 2864, 1696, 1669, 1458, 1426, 1390, 1364, 1255, 1146, 1104 cm^{-1}; HRMS (MH^+) calcd for $C_{35}H_{55}N_2O_5Si$ 611.3880, found 611.3906; $[\alpha]_D$ = +37.5 (*c* = 0.16, $CHCl_3$).

Method B: To a solution of diyne **16** (48 mg, 0.072 mmol) in toluene (3.6 mL) was added [(pyridine)($Ph_3SiO)_3$Mo≡N][6] (16 mg, 0.014 mmol). The solution was heated at 80 °C overnight, then allowed to cool to rt and concentrated. Purification by silica gel column chromatography (EtOAc-hexanes 70:30) gave cycloalkyne **17** as a foam (35 mg, 80%).

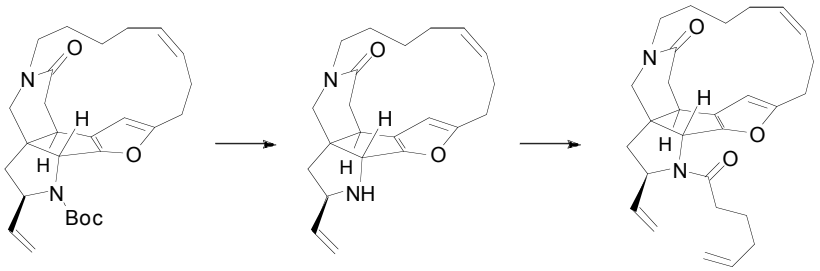


Alcohol 18. A solution of cycloalkyne **17** (1.00 g, 1.64 mmol), quinoline (1.0 mL,) and Lindlar catalyst (500 mg) in MeOH (82 mL) at rt was placed under an atmosphere of H_2 and stirred for 4 h. The reaction mixture was filtered through Celite and concentrated. The crude cycloalkene **S4** could not be separated from quinoline by silica gel chromatography and was thus used without further purification. To a solution of silyl ether **S4** (1.00 g, 1.64 mmol) in THF (82 mL) at 0 °C was added dropwise TBAF (4.92 mL of a 1.0 M solution in THF, 4.92 mmol). The solution was allowed to rt and stirred 1 h. The reaction was quenched with saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 20:80) gave alcohol **18** as a colorless solid (600 mg, 80%, two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90-1.19 (m, 2H), 1.39 (app t, *J* = 12.3 Hz, 2H), 1.56 (s, 9H), 1.85 (ddd, *J* = 16.5, 11.3, 5.1 Hz, 1H), 1.95 (dd, *J* = 12.6, 5.0, 1H), 2.06-2.16 (m, 1H), 2.35-2.46 (m, 1H), 2.47-2.58 (m, 2H), 2.63 (d, *J* = 15.4, 2.4 Hz, 1H), 2.67-2.87 (m, 1H), 2.80 (dd, *J*= 14.5, 5.8 Hz, 1H), 3.16 (d, *J* = 13.8 Hz, 1H), 3.21-3.26 (m, 1H), 3.61 (d, *J* = 13.8 Hz, 1H), 3.65-3.80 (m , 2H), 3.82-3.90 (m, 1H), 4.0 (ddd, *J* = 14.0, 11.2, 2.8 Hz, 1H), 4.74 (s, 1H), 5.25 (ddd, 10.4, 10.4, 6.2 Hz, 1H), 5.34 (ddd, 11.0, 11.0, 4.5), 5.44 (br d, *J* = 9.6 Hz, 1H), 5.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 27.5, 28.0, 28.4, 28.6, 30.3, 34.3, 38.1, 41.4, 46.7, 57.1, 57.5, 60.7, 64.7, 67.6, 80.7, 103.4, 126.0, 129.6, 132.1, 154.5, 155.2, 160.2, 170.4; IR (neat) 3392 (br), 2929, 1665, 1554, 1477, 1455, 1427, 1404, 1365, 1255, 1152, 1089, 912 cm^{-1}; HRMS (MH^+) calcd for $C_{26}H_{37}N_2O_5$ 457.2702, found 457.2686; $[\alpha]_D$ = +33.3 (*c* = 0.12, $CHCl_3$).



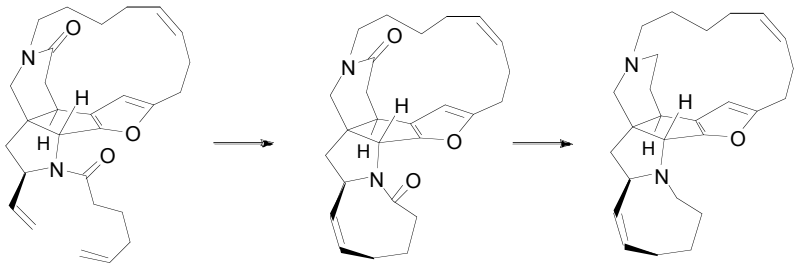
Olefin 19. To a solution of alcohol **18** (486 mg, 1.06 mmol) in DMSO (53 mL) at rt was added IBX (1.52 g, 5.30 mmol). The solution was stirred overnight at rt. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. The crude aldehyde **S5** was found to be unstable to silica gel chromatography and was used without further purification. To a solution of aldehyde **S5** (481 mg, 1.06

mmol) in THF (53 mL) at 0 °C was added dropwise Tebbe reagent (2.54 mL of a 0.5 M solution in PhMe, 1.27 mmol). The solution was stirred for 10 minutes, then poured into saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 5:95) gave olefin **19** as a yellow foam (324 mg, 68%, two steps). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77-1.67 (m, 7H), 1.53 (s, 9H), 1.87 (ddd, *J* = 12.1, 11.0, 5.0 Hz, 1H), 2.03 (dd, *J* = 13.8, 5.5 Hz, 1H), 2.04-2.16 (m, 1H), 2.32-2.45 (m, 1H), 2.46-2.57 (m, 2H), 2.64 (dd, *J* = 15.3, 2.5 Hz, 1H), 2.68-2.85 (m, 2H), 3.20 (d, *J* = 13.9 Hz, 1H), 3.23-3.29 (m, 1H), 3.64 (d, *J* = 13.9 Hz, 1H), 4.04 (ddd, *J* = 15.3, 8.0, 3.0 Hz, 1H), 4.23 (ddd, *J* = 12.1, 6.5, 5.5 Hz, 1H), 4.75 (s, 1H), 5.05-5.30 (m, 3H), 5.35 (ddd, *J* = 10.8, 10.8, 4.3 Hz, 1H), 5.77-5.93 (m, 1H), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 27.4, 28.0, 28.3, 28.5, 30.1, 34.2, 41.3, 42.3, 46.6, 57.2, 58.4, 59.7, 66.7, 79.7, 103.2, 114.0, 125.9, 129.2, 132.0, 138.5, 153.7, 154.7, 159.9, 170.4; IR (neat) 2927, 2359, 1698, 1664, 1553, 1477, 1425, 1388, 1364, 1299, 1170, 1146 cm^{-1}; HRMS (MH^+) calcd for $C_{27}H_{37}N_2O_4$ 453.2753, found 453.2760; $[\alpha]_D$ = +28.6 (*c* = 0.14, $CHCl_3$).



19 **S6** **20**

Amide 20. To a solution of carbamate **19** (324 mg, 0.716 mmol) in CH_2Cl_2 (27 mL) at rt was added TFA (9 mL). The solution was stirred for 1 h at rt, then cooled to 0 °C and quenched with saturated aqueous Na_2CO_3. The layers were separated and the aqueous phase extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. The crude pyrrolidine was used without further purification. To a solution of pyrrolidine **S6** (252 mg, 0.716 mmol) in benzene (36 mL) at rt was added Et_3N (300 µL, 2.15 mmol) and 5-hexenoyl chloride (122 µL, 0.931 mmol). The solution was stirred for 10 minutes, then quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 5:95) gave amide **20** as a yellow foam (238 mg, 74%, two steps). ^{1}H NMR ($CDCl_3$, 400 MHz amide rotamers) δ 0.78-1.18 (br m, 3H), 1.20-1.47 (br m, 2H), 1.48-1.90 (br m, 6H), 1.91-2.27 (br m, 5H), 2.28-2.42 (br m, 1H), 2.43-2.57 (br m, 3H), 2.44-2.92 (br m, 4H), 3.13-3.30 (br m , 2H), 3.55-3.74 (br m, 1H), 3.91-4.11 (br m , 1H), 4.27-4.47 (br m, 1H), 4.73-5.40 (br m, 7H), 5.61-5.92 (br m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, amide rotamers) δ 23.8 and 23.9, 24.9 and 25.2, 27.3 and 27.5, 28.3, 28.5, 29.7 and 30.3, 32.8 and 33.1, 33.9, 34.1, 41.3 and 41.7, 43.3, 47.0, 57.4, 60.0, 60.4 and 60.6, 66.9 and 67.4, 103.0 and 103.6, 113.1, 114.7 and 115.8, 126.1 and 126.5, 129.1 and 130.1, 131.9, 138.1, 138.6 and 139.0, 153.6 and 155.4, 160.5 and 160.7, 170.3, 172.6 and 172.9; IR (neat) 2923, 1654, 1553, 1479, 1424, 1406, 1349, 1274, 1169, 1104, 995 cm^{-1}; HRMS (MH^+) calcd for $C_{28}H_{37}N_2O_3$ 449.2804, found 449.2822; $[\alpha]_D$ = +30.8 (*c* = 0.13, $CHCl_3$).



(−)-Nakadomarin A (1). To a solution of diene **20** (50 mg, 0.111 mmol) in CH_2Cl_2 (111 mL) at reflux was added Grubbs 1st generation catalyst (91 mg, 0.111 mmol) in CH_2Cl_2 (3 mL) by syringe over 5 h. The solution was stirred at reflux overnight. The reaction mixture was concentrated and subjected to silica gel column chromatography (MeOH-EtOAc, 5:95) to afford bislactam **21** contaminated with triphenylphosphine (38 mg total). To a suspension of $AlCl_3$ (63 mg, 0.469 mmol) in THF (11 mL) at 0 °C was added $LiAlH_4$ (1.42 mL of a 1.0 M solution in THF, 1.42mmol). The resulting mixture was allowed to warm to rt and stir for 1 h. The solution was then cooled to 0 °C, and a solution of bislactam **21** (38 mg of the above mixture) in THF (3.4 mL) was added dropwise. The reaction mixture was allowed to warm to rt and stirred 2 h. The solution was cooled to 0 °C and quenched by dropwise addition of H_2O (1 mL) to precipitate aluminum salts. After the mixture had been stirred for 15 min, 3 M aqueous KOH (1 mL) was added to coagulate the precipitate. The reaction mixture was filtered through Celite and the solid residue was extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (MeOH-EtOAc, 67:33) gave (−)-nakadomarin A **1** as a foam (25 mg, 57%, two steps). ^{1}H NMR (CD_3OD, 600 MHz) δ 0.82-0.93 (m, 1H), 1.01-1.10 (m, 2H), 1.28-1.36 (m, 2H), 1.36-1.43 (m, 1H), 1.49 (dd, *J* = 12.4, 10.0 Hz, 1H), 1.56-1.75 (m, 4H), 1.82 (ddd, *J* = 14.0, 7.1, 2.8 Hz, 1H), 1.88-1.95 (m, 1H), 1.91 (dd, *J* = 12.4, 4.8 Hz, 1H), 1.96-2.02 (m, 1H), 2.04-2.10 (m, 1H), 2.10-2.19 (m, 2H), 2.29-2.38 (m, 2H), 2.30 (d, *J* = 12.2 Hz, 1H), 2.40 (ddd, *J* = 11.8, 3.7, 3.7 Hz, 1H), 2.44-2.53 (m, 1H), 2.57-2.65 (m, 2H), 2.71 (ddd, *J* = 14.3, 7.3, 2.2 Hz, 1H), 2.75-2.82 (m, 1H), 2.84 (br s, 1H), 2.97-3.07 (m, 1H), 3.04 (d, *J* = 12.2 Hz, 1H), 3.71-3.76 (m, 1H), 3.94 (s, 1H), 5.22-5.29 (m, 1H), 5.40-5.47 (m, 1H), 5.50 (dd, *J* = 9.6, 8.9 Hz, 1H), 5.81 (br q, *J* = 17.1, 9.4 Hz, 1H), 5.87 (s, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 23.0, 25.8, 25.9, 27.1, 27.2, 28.8, 29.1, 29.2, ,29.5, 43.1, 43.4, 46.1, 50.9, 58.3, 59.3, 60.6, 63.6, 74.7, 104.7, 129.3, 131.4, 132.2, 134.7, 135.3, 156.4, 162.5; IR (neat) 3003, 2923, 2855, 2791, 1443, 1132, 1081, 952 cm^{-1}; HRMS (M^+) calcd for $C_{26}H_{37}N_2O$ 393.2906, found 393.2918, found; $[\alpha]_D$ = -72.7 (*c* = 0.12, MeOH), [lit.[7] $[\alpha]_D$ = -73.0 (*c* = 0.08, MeOH)].

Comparison of observed ^{13}C-NMR signals with those reported by Nishida (*Angew. Chem.* **2004**, *116*, 2054; *Angew. Chem. Int. Ed.* **2004**, *42*, 2020):

Nishida	Funk
23.0	23.0
25.8	25.8
25.9	25.9
27.1	27.1
27.2	27.2
28.8	28.8
29.1	29.1
29.2	29.2
29.5	29.5
43.1	43.1
43.4	43.4
46.1	46.1
50.9	50.9

Nishida	Funk
58.4	58.3
59.3	59.3
60.6	60.6
63.6	63.6
74.8	74.7
104.8	104.7
129.3	129.3
131.3	131.4
132.2	132.2
134.8	134.7
135.4	135.3
156.3	156.4
162.6	162.5

References:

1. Purchased from Amfinecom Inc.
2. A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108.
3. Prepared by Fischer esterification of 4-hexynoic acid, which was prepared by isomerization of 5-hexynoic acid with potassium hydroxide. See: E. R. H. Jones, G. H. Whitham, M. C. Whiting, *J. Chem. Soc.* **1954**, 3201.
4. P. H. Bentley, W. McCrae, *J. Org. Chem.* **1970**, *35*, 2082.
5. Purchased from Strem Chemicals Inc.
6. M. Bindl, R. Stade, E. K. Heilmann, A. Picot, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2009**, *131*, 9468.
7. K. Ono, M. Nakagawa, A. Nishida, *Angew. Chem.* **2004**, *116*, 2054; *Angew. Chem. Int. Ed.* **2004**, *42*, 2020.