Supporting Information

Double Michael Addition Reactions of the Nazarov Reagent with 2-Cyano-2-Cycloalkenones: An Alternative Approach to cis-Fused Bicyclic Systems

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The General Procedure of the double Michael addition reaction in the

Synthesis of Compound 3a-3i

The general procedure is illustrated immediately below with compound 3a as a specific example.

(4aS*,8aS*)-4a-Cyano-2-hydroxy-5-oxo-3,4,4a,5,6,7,8,8a-octahydropyrene-1-carboxylic acid methyl ester (3a)

Under N₂ atmosphere, DBU (0.5 equiv, 0.6 mmole) was added slowly to a solution of Nazarov reagent 1 (1.5 equiv, 1.8 mmole) and cycloalkenone 2a (1.2 mmole) in anhydrous THF (0.2M in 2a) at -78 °C. After 2 h, the reaction was quenched with water (5 mL), followed by extraction (ethyl acetate 3 x 10 mL). The combined organic layers are washed with brine solution (5 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed under reduced pressure providing crude residue that was purified flash column chromatography (silica gel; ethyl acetate:hexane = 1:4) to provide the desired product 3a: Mp 115.0-116.0 °C; IR (CH₂Cl₂ cast, cm⁻¹) νmax 3405 (br), 2955, 2244, 1722, 1660, 1652, 1615; ¹H NMR (CDCl₃, 400 MHz): δ12.36 (s, 1H), 3.72 (s, 3H), 2.74 (dd, J = 12.0, 4.0 Hz, 1H), 2.71-2.62 (m, 1H), 2.50-2.36 (m, 3H), 2.28 (td, J = 13.2, 6.4 Hz, 1H), 2.17-2.12 (m, 1H), 2.02-1.96 (m, 1H), 1.90 (dd, J = 13.2, 6.0 Hz, 1H), 1.67 (ddt, J = 13.6, 8.0, 4.4 Hz, 1H), 1.62-1.40 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ202.8 (C), 171.5 (C), 170.7 (C), 118.3 (C), 99.5 (C), 52.2 (C), 51.8 (CH₃), 40.1 (CH), 37.1 (CH₂), 28.6 (CH₂), 26.2 (CH₂), 24.0 (CH₂), 23.7 (CH₂); HRMS (EI) C₁₃H₁₅NO₄: 249.1001; found: 249.1002.

(4aS*,8aS*)-4a-Cyano-2-hydroxy-6,6-dimethyl-5-oxo-3,4,4a,5,6,7,8,8a-octahydropyrene-1-carboxylic acid methyl ester (3b)

IR (neat) : νmax 2956 (br), 2242, 1714, 1668, 1660, 1622 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 12.38 (s, 1H), 3.76 (s, 3H), 3.15 (dd, J = 19.6, 8.4 Hz, 1H), 2.67 (ddd, J = 22.2, 12.0, 6.8 Hz, 1H), 2.48-2.38 (m, 2H), 2.30-2.22 (m, 1H), 2.14-2.03 (m, 1H), 1.91 (dd, J = 13.4, 6.8 Hz, 1H), 1.88-1.63 (m, 1H), 1.61-1.53 (m, 1H), 1.13 (s, 3H), 1.12 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 208.1 (C), 171.7 (C), 170.9 (C), 119.1 (C), 99.0 (C), 51.8 (CH₃), 51.2 (C), 44.2 (C), 40.1 (CH), 37.3 (CH₂), 27.4 (CH₂), 27.1 (CH₃), 26.7 (CH₂), 25.9 (CH₂), 25.1 (CH₂); HRMS (EI) calecd. for C₁₅H₁₉NO₄: 277.1314; found: 277.1316.

(4aS*,8aS*)-4a-Cyano-2-hydroxy-7,7-dimethyl-5-oxo-3,4,4a,5,6,7,8,8a-octahydropyrene-1-carboxylic acid methyl ester (3c)

Mp 160.9-161.4 °C, IR (neat) : νmax 2958 (br), 2244, 1717, 1661, 1655, 1619 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 12.36 (s, 1H), 3.76 (s, 3H), 3.26 (dd, J = 12.8, 4.4 Hz, 1H), 2.72-2.62 (m,
1H), 2.47 (dd, J = 18.8, 6.0 Hz, 2H), 2.37-2.18 (m, 2H), 1.95-1.76 (m, 2H), 1.44 (t, J = 13.4 Hz, 1H), 1.02 (s, 3H), 0.94 (s, 3H); 13C NMR (CDCl3, 100 MHz) δ 202.1 (C), 171.3 (C), 170.6 (C), 118.2 (C), 98.9 (C), 51.8 (CH3), 51.2 (C), 49.7 (CH2), 41.7 (CH2), 36.0 (CH), 34.1 (C), 31.1 (CH3), 26.1 (CH2), 25.0 (CH3), 23.7 (CH2); HRMS (EI) calcd. for C15H19NO4: 277.1314; found: 277.1309; Anal.: calcd. for C15H19NO4: C: 64.97; H: 6.91; N: 5.05; found: C: 64.98; H: 7.12; N: 5.06

\[(1R,3R,4aS,8aS)-4a-Cyano-7-hydroxy-9,9-dimethyl-4-oxo-1,2,3,4,4a,5,6,8a-octahydronaphthalene-8-carboxylic acid methyl ester (3d)\]

IR (neat): \(\tilde{\nu}_{\text{max}}\) 2960 (br), 2238, 1716, 1652, 1615 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 400 MHz) δ 12.54 (s, 0.5H), 3.77 (s, 3H), 3.51 (d, J = 12.0 Hz, 0.5H), 3.43 (s, 0.5H), 2.84 (t, J = 4.8 Hz, 0.5H), 2.81-2.62 (m, 2H), 2.55-2.38 (m, 2H), 1.75 (d, J = 6.4 Hz, 0.5H), 1.72 (d, J = 11.6 Hz, 0.5H), 1.40 (s, 3H), 1.14 (s, 3H), 1.06 (s, 3H); 13C NMR (CDCl3, 100 MHz) δ 204.0 (C×2), 203.0 (C), 171.9 (C), 171.7(C), 168.5 (C), 120.1 (C), 119.8 (C), 95.7 (C), 56.3 (CH×2), 56.3 (CH), 52.6 (CH3), 52.0 (CH3), 45.7 (CH), 45.6 (C), 45.2 (CH), 42.5 (C×2), 41.1 (C), 39.7 (CH), 36.6 (CH), 35.8 (CH2), 31.8(CH2), 30.1 (CH2), 26.2 (CH3), 25.8 (CH3), 25.4 (CH2), 23.1 (CH2), 23.0 (CH2), 21.8 (CH2×2); HRMS (EI) calcd. for C16H19NO4: 289.1314; found: 289.1318.

\[(4aS*,6S*,8aS*)-4a-Cyano-2-hydroxy-6-methyl-5-oxo-3,4,4a,5,6,7,8,8a-octahydonaphthalene-1-carboxylic acid methyl ester (3e)\]

Mp 152.0-153 °C, IR (neat) : \(\tilde{\nu}_{\text{max}}\) 2937 (br), 2246, 1716, 1659, 1652, 1615 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 400 MHz) δ 12.39 (s, 1H), 3.77 (s, 3H), 3.15 (dd, J = 12.0, 4.2 Hz, 1H), 2.73 (ddd, J = 19.2, 12.1, 7.1 Hz, 1H), 2.56-2.48 (m, 2H), 2.40-2.29 (m, 1H), 2.20-2.16 (m, 1H), 1.95 (d, J = 13.3, 7.1 Hz, 1H), 1.60-1.53 (m, 1H), 1.44 (qd, J = 13.3, 3.1 Hz, 1H), 1.08 (d, J = 6.4 Hz, 3H); 13C NMR (CDCl3, 150 MHz) δ 204.4 (C), 171.6 (C), 171.0 (C), 118.4 (C), 99.7 (C), 52.7 (C), 51.9 (CH3), 40.9 (CH×2), 32.9 (CH2), 29.2 (CH2), 26.5 (CH2), 24.4 (CH2), 14.5 (CH3); HRMS (EI) calcd. for C14H17NO4: 263.1158; found: 263.1162; Anal.: calcd. for C14H17NO4: C: 63.87; H: 6.51; N: 5.32; found: C: 64.21; H: 6.55; N: 5.17.

\[(4aS*,8R*,8aS*)-4a-Cyano-2-hydroxy-8-methyl-5-oxo-3,4,4a,5,6,7,8,8a-octahydonaphthalene-1-carboxylic acid methyl ester (3f)\]

Mp 152.0-153 °C, IR (neat) : \(\tilde{\nu}_{\text{max}}\) 2961 (br), 2244, 1715, 1668, 1652, 1634 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 400 MHz) δ 12.46 (s, 1H), 3.72 (s, 3H), 2.95 (d, J = 10.8 Hz, 1H), 2.69-2.37 (m, 5 H), 2.00-2.90 (m, 2H), 1.79-1.71 (m, 1H), 1.73 (ddd, J = 21.6, 13.2, 4.8 Hz, 1H), 0.89 (d, J = 6.4 Hz, 3H); 13C NMR (CDCl3, 100 MHz) δ 202.0 (C), 171.9 (C), 171.0 (C), 118.2 (C), 99.0 (C), 52.3 (C), 51.5 (CH3), 44.3 (CH), 36.8 (CH2), 35.4 (CH), 32.6 (CH2), 25.6 (CH2), 24.7 (CH2), 18.6 (CH3); HRMS (EI) calcd. for C14H17NO4: 263.1158; found: 263.1158.
(3a$^S$,7a$^S$*)-7a-Cyano-5-hydroxy-1-oxo-2,3,3a,6,7,7a-hexahydro-1H-indene-4-carboxylic acid methyl ester (3g)

Mp 136-137 °C, IR (neat) : $\nu_{max}$ 3475 (br), 2920, 2241, 1756, 1661, 1652, 1634 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 12.31 (s, 1H), 3.79 (s, 3H), 3.38 (dd, $J = 10.8, 6.4$ Hz, 1H), 2.71-2.37 (m, 5H), 2.00-1.85 (m, 2H), 1.67-1.56 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 207.8 (C), 171.7 (C), 171.0 (C), 118.3 (C), 97.1 (C), 51.9 (CH$_3$), 47.1 (C), 40.1 (CH), 36.5 (CH$_2$), 27.7 (CH$_2$), 26.0 (CH$_2$), 23.2 (CH$_2$); HRMS (EI) calcd. for C$_{12}$H$_{13}$NO$_4$: 235.0845; found: 235.0844; Anal.: calcd. for C$_{12}$H$_{13}$NO$_4$: C: 61.27; H: 5.57; N: 5.95; found: C: 61.13; H: 5.75; N: 5.95.

(4a$^S$,9a$^S$*)-4a-Cyano-2-hydroxy-5-oxo-4,4a,5,6,7,8,9,9a-octahydro-3H-benzocyclohepten e-1-carboxylic acid methyl ester (3h)

Mp 121-122 °C, IR (neat) : $\nu_{max}$ 2950 (br), 2231, 1728, 1668, 1652, 1622 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 12.27 (s, 1H), 3.80 (s, 3H), 3.24 (d, $J = 13.2$ Hz, 1H), 3.04-2.97 (m, 1H), 2.62-2.53 (m, 2H), 2.43 (d, $J = 9.6$ Hz, 1H), 2.40-2.32 (m, 1H), 2.04-2.00 (m, 1H), 1.90-1.81 (m, 1H), 1.71-1.53 (m, 3H), 1.43-1.40 (m, 1H), 1.00-0.96 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 202.9 (C), 171.9 (C), 170.8 (C), 118.4 (C), 99.3 (C), 51.9 (CH$_3$), 49.6 (C), 39.7 (CH$_2$), 39.4 (CH), 33.7 (CH$_2$), 29.4 (CH$_2$), 28.0 (CH$_2$), 26.0 (CH$_2$), 21.5 (CH$_2$); HRMS (EI) calcd. for C$_{14}$H$_{17}$NO$_4$: 263.1158; found: 263.1154; Anal.: calcd. for C$_{14}$H$_{17}$NO$_4$: C: 63.87; H: 6.51; N: 5.32; found: C: 63.66; H: 6.68; N: 5.32.

(1R*,4aR*,10aR*)-4a-Cyano-2,5-dioxododecahydrobenzocyclooctene-1-carboxylic acid methyl ester (3i)

Mp 169-170 °C, IR (neat) : $\nu_{max}$ 2940, 2246, 1748, 1715 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 3.78 (s, 3H), 3.42 (d, $J = 12.0$ Hz, 1H), 3.04 (td, $J = 17.6, 6.4$ Hz, 1H), 2.81 2.59 (m, 3H), 2.51-2.47 (m, 1H), 2.22-2.15 (m, 2H), 1.99-1.93 (m, 1H), 1.89-1.82 (m, 2H), 1.80-1.69 (m, 2H), 1.55-1.46 (m, 1H), 1.36-1.21 (m, 1H), 1.20-1.13 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 206.5 (C), 201.3 (C), 168.8 (C), 116.6 (C), 60.7 (CH), 56.5 (C), 52.4 (CH$_3$), 42.1 (CH), 37.2 (CH$_2$), 36.9 (CH$_2$), 32.4 (CH$_2$), 31.8 (CH$_2$), 28.9 (CH$_2$), 25.6 (CH$_2$), 23.2 (CH$_2$); HRMS (EI) calcd. for C$_{15}$H$_{19}$NO$_4$: 277.1314; found: 277.1314; Anal.: calcd. for C$_{15}$H$_{19}$NO$_4$: C: 64.97; H: 6.91; N: 5.05; found: C: 65.13; H: 7.16; N: 5.13.

The General Procedure for the Synthesis of Compound 4a, 4b, 4d and 4f

The general procedure is illustrated immediately below with compound 4a as a specific example.

(4a$^S$,8a$^S$*)-2-Acetoxy-4a-cyano-5-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid methyl ester (4a)
To a stirred solution of 3a (0.200 g 0.8 mmol) in THF (5 mL) were added pyridine (2.0 mL) and acetic anhydride (0.76 mL) at 0 °C under N2 atmosphere. The reaction mixture was stirred at room temperature for 18 hours. Then the reaction was quenched with water (20 mL), followed by extraction (ethyl acetate 2 x 20 mL). The combined organic layers are washed with brine solution (10 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvent was removed under reduced pressure providing crude residue that was purified flash column chromatography (silica gel; ethyl acetate:hexane = 1:2) to provide the desired product 4a.

Mp 149-150 °C, IR (neat) : \( \tilde{\nu}_{\text{max}} \) 2959, 2245, 1780, 1713, 1674 cm\(^{-1}\); \( ^1\text{H NMR} \) (CDCl\(_3\), 600 MHz) \( \delta \) 3.70 (s, 3H), 3.35 (dd, \( J = 11.4, 4.0 \) Hz, 1H), 2.58-2.33 (m, 5H), 2.15-2.11 (m, 4H), 1.99-1.93 (m, 2H), 1.73 (ddt, \( J = 13.2, 7.6, 4.1 \) Hz 1H), 1.62-1.51 (m, 1H); \( ^{13}\text{C NMR} \) (CDCl\(_3\), 150 MHz) \( \delta \) 202.2 (C), 168.3 (C), 164.0 (C), 155.3 (C), 118.8 (C), 117.9 (C), 52.0 (CH\(_3\)), 51.1 (C), 42.1 (CH), 37.2 (CH\(_2\)), 27.8 (CH\(_2\)), 26.4 (CH\(_2\)), 24.7 (CH\(_2\)), 23.6 (CH\(_2\)), 20.7 (CH\(_3\)); HRMS (EI) calcd. for C\(_{15}\)H\(_{17}\)NO\(_5\): 291.1107; found: 291.1101; Anal. calcd. C: 61.85; H: 5.88; N: 4.81; found: C: 61.81; H: 6.16; N: 4.86.

\( (4a^S,8a^S^*)-2\text{-Acetoxy-4a-cyano-6,6-dimethyl-5-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid methyl ester (4b)} \)

Mp 156-157 °C, IR (neat) : \( \tilde{\nu}_{\text{max}} \) 2953, 2242, 1771, 1728, 1715, 1660 cm\(^{-1}\); \( ^1\text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) 3.72 (s, 3H), 3.42 (d, \( J = 6.0 \) Hz, 1H), 2.74-2.37 (m, 3H), 2.17-2.09 (m, 4H), 1.94-1.90 (m, 1H), 1.77-1.63 (m, 3H), 1.25 (s, 3H), 1.17 (s, 3H); \( ^{13}\text{C NMR} \) (CDCl\(_3\), 100 MHz) \( \delta \) 206.9 (C), 168.3 (C), 164.4 (C), 154.7(C), 119.0 (C), 118.8(C), 52.0 (CH\(_3\)), 48.8 (C), 44.9 (C), 42.1 (CH), 36.5 (CH\(_2\)), 27.6 (CH\(_3\)), 26.9 (CH\(_2\)), 26.8 (CH\(_2\)), 26.4 (CH\(_3\)), 23.9 (CH\(_2\)), 20.6 (CH\(_3\)); HRMS (EI) calcd. for C\(_{17}\)H\(_{21}\)NO\(_5\): 319.1420; found: 319.1419; Anal.: calcd. for C\(_{17}\)H\(_{21}\)NO\(_5\): C: 63.94; H: 6.63; N: 4.39; found: C: 64.31; H: 6.45; N: 4.33.

\( (1R,3R,4aS,8aS^*)-7\text{-Acetoxy-4a-cyano-9,9-dimethyl-4-oxo-1,2,3,4,4a,5,6,8a-octahydro-1,3-methanonaphthalene-8-carboxylic acid methyl ester (4d)} \)

Mp 154-155 °C, IR (neat) : \( \tilde{\nu}_{\text{max}} \) 2957, 2240, 1767, 1728, 1724, 1661 cm\(^{-1}\); \( ^1\text{H NMR} \) (CDCl\(_3\), 400 MHz) \( \delta \) 3.71 (s, 3H), 3.60 (s, 1H), 2.75 (t, \( J = 5.2 \) Hz, 1H), 2.62-2.54 (m, 1H), 2.50-2.39 (m, 2H), 2.30 (dd, \( J = 11.4, 4.0 \) Hz, 1H), 2.19-2.15 (m, 2H), 2.13 (s, 3H), 1.75 (d, \( J = 12.0 \) Hz, 1H), 1.37 (s, 3H), 1.04 (s, 3H); \( ^{13}\text{C NMR} \) (CDCl\(_3\), 100 MHz) \( \delta \) 203.2 (C), 168.3 (C), 165.2 (C), 153.9 (C), 119.7 (C), 117.6 (C), 57.0 (CH), 52.0 (CH\(_3\)), 45.4 (C), 44.4 (CH), 42.5 (C), 38.9 (CH), 31.1 (CH\(_2\)), 26.0 (CH\(_3\)), 25.2 (CH\(_2\)), 23.3 (CH\(_2\)), 21.8 (CH\(_3\)), 20.6 (CH\(_3\)); HRMS (EI) calcd. for C\(_{18}\)H\(_{21}\)NO\(_5\): 331.1420; found: 331.1424; Anal.: calcd. for C\(_{18}\)H\(_{21}\)NO\(_5\): C: 65.24; H: 6.39; N: 4.23; found: C: 65.00; H: 6.44; N: 4.19.

\( (4a^S,8R^*,8a^S^*)-2\text{-Acetoxy-4a-cyano-8-methyl-5-oxo-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylic acid methyl ester (4f)} \)
Mp 196-197 °C, IR (neat): $\nu_{\text{max}}$ 2973, 2242, 1774, 1722, 1670 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 3.71 (s, 3H), 3.19 (d, $J = 10.9$ Hz, 1H), 2.63-2.49 (m, 4H), 2.46-2.42 (m, 1H), 2.16 (s, 3H), 2.03 -1.99 (m, 1H), 1.95-1.92 (m, 2H), 1.56-1.52 (m, 1H), 0.92 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 202.5 (C), 168.7 (C), 165.1 (C), 154.3(C), 119.4 (C), 117.7 (C), 52.0 (CH$_3$), 51.4 (C), 46.8 (CH), 36.9 (CH$_2$), 35.2 (CH), 32.8 (CH$_2$), 26.0 (CH$_2$), 25.3 (CH$_2$), 20.7 (CH$_3$), 18.3 (CH$_3$); HRMS (EI) calcd. for C$_{16}$H$_{19}$NO$_5$: 305.1263; found: 305.1263; Anal.: calcd. for C$_{16}$H$_{19}$NO$_5$: C: 62.94; H: 6.27;
NMR Spectrum of 3a
NMR Spectrum of 3b
NMR Spectrum of 3c
NMR Spectrum of 3d
NMR Spectrum of 3e
NMR Spectrum of 3f
NMR Spectrum of 3g
NMR Spectrum of 3h
NMR Spectrum of 3i
NMR Spectrum of 4a
NMR Spectrum of 4b
NMR Spectrum of 4d
NMR Spectrum of 4f