Electrophilic cyclization of 1,6-Enynes

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General experimental details: All reactions were carried out in sealed reaction vials. CH$_2$Cl$_2$ was passed through activated alumina columns. All other commercial reagents were used as received. Thin-layer chromatography (TLC) was conducted with precoated glass-backed plates (silica gel 60 F$_{254}$) and visualized by exposure to UV light (254 nm) or stained with ceric ammonium molybdate. Flash chromatography was performed with silica gel. The eluent used is reported in parentheses. $^1$H NMR spectra were recorded on 360 MHz spectrometers. $^{13}$C NMR spectra were recorded at 91 MHz. Chemical shifts are reported in ppm relative to solvent signal. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); sep (septet). Low resolution mass spectra were recorded applying GC-MS, EI or ESI technique. High resolution mass spectra were obtained using EI or ESI ionization method.
Electrophilic cyclization of 1,6-enzyme 1.

**(E)**-Dimethyl 5-(iodomethylene)-3-methylcyclohex-3-ene-1,1-dicarboxylate (2).

{[chemical structure image]}

Enyne 1 (48.9 mg, 218 µmol) were dissolved in 2.2 mL CH$_2$Cl$_2$ and 54.0 mg NIS (240 µmol, 1.1 equiv.) were added. The solution was stirred at room temperature in the dark until TLC indicated full consumption of the starting material. The reaction mixture was diluted with 10 mL CH$_2$Cl$_2$ and 10 mL of a saturated aqueous Na$_2$S$_2$O$_3$-solution were added. The phases were separated and the aqueous phase was extracted with 2×10 mL of CH$_2$Cl$_2$. The combined organic phases were washed with brine and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel (pentane/Et$_2$O 99:1 → 95:5). The product was isolated as yellow oil (29.0 mg, 82.8 µmol, 38%).

R$_f$ = 0.46 (pentane/Et$_2$O 80:20) [UV, CAM]. $^1$H NMR (360 MHz, CDCl$_3$): δ = 1.77 (s, 3H), 2.58 (s, 2H), 2.87 (d, $J$ = 1.6, 2H), 3.73 (s, 6H), 5.94 (dd, $J$ = 2.6, 1.3, 1H), 6.08 (s, 1H). $^{13}$C NMR (91 MHz, CDCl$_3$): δ = 23.3, 36.3, 37.5, 53.0, 54.7, 78.0, 124.0, 136.0, 142.7, 171.1. LRMS (GC-MS): m/z = 350 (54%) [M$^+$], 290 (72%), 231 (100%), 163 (49%), 105 (40%). HRMS (ESI): m/z calcld for C$_{12}$H$_{16}$O$_4$I (M$^+$+H): 351.0088; found: 351.0089.

General procedure for the electrophilic cyclization of 1,6-enynes 5.

**(E)**-2-(Iodomethylene)-8,8-dimethyl-3-(prop-1-en-2-yl)-7,9-dioxaspiro[4.5]decane (6a)

{[chemical structure image]}

Enyne 5a (20.8 mg, 93.6 µmol) were dissolved in 1 mL CH$_2$Cl$_2$ and 42.1 mg NIS (187 µmol, 2 equiv.) were added. The solution was stirred at room temperature in the dark until TLC
indicated full consumption of the starting material. The reaction mixture was diluted with 10 mL CH₂Cl₂ and 10 mL of a saturated aqueous Na₂S₂O₃-solution were added. The phases were separated and the aqueous phase was extracted with 2×10 mL of CH₂Cl₂. The combined organic phases were washed with brine and dried over Na₂SO₄. The solvent was evaporated and the residue was purified by flash-chromatography on silica gel (pentane/Et₂O 98:2). The product was isolated as a white solid (22.1 mg, 63.5 µmol, 68%).

Rᶠ = 0.52 (P/Et₂O 90:10) [UV, CAM]. ¹H NMR (360 MHz, CDCl₃): δ = 1.43 (s, 3H), 1.45 (s, 3H), 1.57 (d, J = 12.6, 1H), 1.61 – 1.64 (m, 3H), 2.08 (dt, J = 18.2, 2.7, 1H), 2.21 (ddd, J = 12.9, 7.8, 1.5, 1H), 2.42 – 2.49 (m, 1H), 3.25 – 3.32 (m, 1H), 3.60 – 3.76 (m, 4H), 4.83 – 4.85 (m, 1H), 4.87 – 4.89 (m, 1H), 5.85 – 5.88 (m, 1H). ¹³C NMR (91 MHz, CDCl₃): δ = 18.3, 23.3, 24.5, 39.0, 39.9, 44.6, 52.5, 67.7, 69.6, 72.9, 98.2, 114.2, 144.2, 154.4. LRMS (EI): m/z = 348 (6%) [M⁺], 334 (11%), 333 (100%), 273 (49%), 260 (8%), 245 (24%), 231 (6%), 163 (34%), 146 (77%), 131 (53%), 117 (22%), 105 (43%), 91 (59%), 77 (16%), 65 (7%), 55 (11%), 43 (43%). HRMS (EI): m/z calcd for C₁₄H₂₁IO₂ (M⁺): 348.0586; found: 348.0572.

(E)-Dimethyl-3-(iodomethylene)-4-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate (6b)

Following the general procedure, 6b was isolated as a white solid (55%) after flash-chromatography on silica gel (pentane/Et₂O 98:2).

Rᶠ = 0.53 (pentane/Et₂O 80:20) [UV, CAM]. ¹H NMR (360 MHz, CDCl₃): δ = 1.63 (dd, J = 1.2, 0.7, 3H), 2.25 (dd, J = 12.8, 12.1, 1H), 2.65 (dd, J = 12.9, 7.3, 1.9, 1H), 2.83 (dt, J = 18.2, 2.8, 1H), 3.12 (ddt, J = 18.3, 2.2, 0.9, 1H), 3.27 – 3.34 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 4.84 – 4.86 (m, 1H), 4.90 – 4.92 (m, 1H), 5.89 (dd, J = 5.2, 2.4, 1H). ¹³C NMR (91 MHz, CDCl₃): δ = 18.2, 39.7, 44.9, 53.1, 53.2, 58.0, 72.6, 115.1, 143.1, 152.6, 171.6, 171.9. LRMS (EI): m/z = 364 (12%) [M⁺], 304 (10%), 237 (6%), 177 (100%), 145 (17%), 117 (58%), 115 (7%), 91 (15%), 77 (9%), 59 (8%), 44 (13%). HRMS (EI): m/z calcd for C₁₃H₁₇IO₄ (M⁺): 364.0172; found: 364.0161.
(E)-(3-(Iodomethylene)-4-(prop-1-en-2-yl)cyclopentane-1,1-disulfonyl)dibenzene (6c)

Following the general procedure, 6c was isolated as a white solid (47%) after flash-chromatography on silica gel (pentane/Et2O 80:20).

R_f = 0.51 (pentane/Et2O 50:50) [UV, CAM]. ^1H NMR (360 MHz, CDCl₃): δ = 1.56 (s, 3H), 2.74 – 2.82 (m, 2H), 3.20 – 3.26 (m, 1H), 3.53 – 3.60 (m, 1H), 4.84 – 4.86 (m, 1H), 4.88 – 4.91 (m, 1H), 5.92 (dd, J = 4.9, 2.4, 1H), 7.60 – 7.65 (m, 4H), 7.71 – 7.78 (m, 2H), 8.05 – 8.09 (m, 4H). ^13C NMR (91 MHz, CDCl₃): δ = 17.6, 37.0, 42.6, 53.0, 73.6, 90.9, 115.8, 129.1, 129.1, 131.2, 131.4, 134.9, 135.1, 135.7, 136.7, 142.6, 151.0. LRMS (ESI): m/z = 1078 (15%) [2M⁺+Na], 550 (42%) [M⁺+Na], 528 (3%) [M⁺], 310 (15%), 282 (100%), 256 (10%). HRMS (ESI): m/z calcd for C₂₁H₂₂IO₄S₂ (M⁺+H): 528.9999; found: 528.9995.

(Z)-3-(Iodomethylene)-4-(prop-1-en-2-yl)tetrahydrofuran (6d)

Following the general procedure while stirring at 50 °C, 6d was isolated as a yellow oil (40%) after flash-chromatography on silica gel (pentane/Et2O 99:1).

R_f = 0.64 (P/Et2O 90:10) [CAM]. ^1H NMR (360 MHz, CDCl₃): δ = 1.69 – 1.70 (m, 3H), 3.40 – 3.45 (m, 1H), 3.89 (dd, J = 8.7, 7.0, 1H), 4.17 (dd, J = 8.7, 7.4, 1H), 4.23 – 4.29 (m, 1H), 4.31 – 4.35 (m, 1H), 4.87 – 4.90 (m, 2H), 5.93 (dd, J = 4.8, 2.6, 1H). ^13C NMR (91 MHz, CDCl₃): δ = 19.0, 54.8, 68.7, 73.9, 76.3, 114.5, 142.6, 153.3. LRMS (GC-MS): m/z = 250 (22%) [M⁺], 123 (38%), 91 (93%), 77 (100%), 67 (31%), 53 (30%). HRMS (ESI): m/z calcd for C₈H₁₂IO (M⁺+H): 250.9927; found: 250.9927.
(Z)-3-(Iodomethylene)-4-(prop-1-en-2-yl)-1-tosylpyrrolidine (6e)

Following the general procedure while stirring at 50 °C, 6e was isolated as a yellow oil (46%) after flash-chromatography on silica gel (pentane/Et₂O 99:1).

R_f = 0.51 (P/EtO 60:40) [UV, CAM]. ¹H NMR (360 MHz, CDCl₃): δ = 2.45 (s, 3H), 3.21 (dd, J = 9.5, 7.5, 1H), 3.32 – 3.37 (m, 1H), 3.62 (dd, J = 9.4, 7.7, 1H), 3.70 (dt, J = 15.5, 2.3, 1H), 3.87 (ddd, J = 15.4, 2.5, 0.9, 1H), 4.83 – 4.84 (m, 1H), 4.87 – 4.89 (m, 1H), 5.96 (dd, J = 4.8, 2.5, 1H), 7.36 (d, J = 8.2, 2H), 7.73 (d, J = 8.2, 2H). ¹³C NMR (91 MHz, CDCl₃): δ = 18.8, 21.7, 52.8, 53.0, 56.9, 72.3, 115.5, 128.0, 130.0, 132.6, 141.6, 144.1, 149.5. LRMS (EI): m/z = 403 (1%) [M⁺], 276 (5%), 222 (9%), 155 (33%), 122 (100%), 91 (95%). HRMS (EI): m/z calcd for C₁₅H₁₈NO₂S (M⁺ – I): 276.1053; found: 276.0151.