Stereocontrolled Construction of Either Stereoisomer of 12-Oxatricyclo[6.3.1.0^{2,7}]dodecanes Using Prins-Pinacol Reactions.

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Supporting Information

Experimental procedures and characterization data for the preparation of compounds 12-21 and 27-37.1

rel-\((2R,6R)-(6-\text{\textregistered}\text{-Methoxytetrahydropyran}-2-\text{yl})\text{-cyclohex-1-enyl methanol (12 and 15). To a solution of tert-butyllithium (4.3 mL, 6.42 mmol, 1.5 M in pentane) in THF (32 mL, 0.1 M) was added a solution of vinyl iodide 11 (0.74 g, 3.56 mmol)\(^2\) in THF (2 mL) dropwise at \(-78 \, ^\circ\text{C}\). The reaction was maintained at \(-78 \, ^\circ\text{C}\) for 20 min followed by the dropwise addition of aldehyde 10 (0.47 g, 3.24 mmol)\(^3\) in THF (2 mL). The cooling bath was removed and the reaction was maintained at rt for 18 h. The reaction mixture was treated with \(\text{H}_2\text{O} (20 \, \text{mL})\), the aqueous layer was extracted with \(\text{Et}_2\text{O} (2 \times 20 \, \text{mL})\), the combined organic extracts were dried (\(\text{MgSO}_4\)), filtered and concentrated. The residue (380 mg, 52%) was purified by HPLC (10% ethyl acetate-hexane isocratic; Novapack 6 \(\text{M}\) Silica, 300 x 50 mm ID). Major diastereomer 12, \(R_T =

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47 min: \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \[ \delta \, 5.77 \, (s, \, 1 \, H), \, 4.76 \, (s, \, 1 \, H), \, 4.00 \, (d, \, J = 4.24 \, Hz, \, 1 \, H), \, 3.37 \, (s, \, 3 \, H), \, 2.05–1.97 \, (m, \, 4 \, H), \, 1.80–1.75 \, (m, \, 1 \, H), \, 1.67–1.46 \, (m, \, 9 \, H), \, 1.44–1.41 \, (m, \, 1 \, H); ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \[ \delta \, 136.4, \, 123.7, \, 99.1, \, 77.5, \, 70.2, \, 54.9, \, 29.9, \, 25.6, \, 25.2, \, 24.6, \, 22.9, \, 17.8; \) IR (neat) 3466 cm\(^{-1}\); HRMS (EI) m/z 226.1570 (M, 226.1569 calc for C\(_{13}\)H\(_{22}\)O\(_3\)). Anal. Calcd for C\(_{13}\)H\(_{22}\)O\(_3\): C, 68.99; H, 9.80. Found: C, 68.71; H, 9.85.

Minor diastereomer 15, \( R_T = 55 \, min: \) \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \[ \delta \, 5.73 \, (s, \, 1H), \, 4.78 \, (s, \, 1H), \, 3.78 \, (d, \, J = 7.7 \, Hz, \, 1H), \, 3.72–3.69 \, (m, \, 1H), \, 3.38 \, (s, \, 3H), \, 2.21–2.17 \, (m, \, 1H), \, 2.10–1.98 \, (m, \, 2H), \, 1.90–1.75 \, (m, \, 2H), \, 1.73–1.43 \, (m, \, 9H), \, 1.40–1.23 \, (m, \, 1H); ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \[ \delta \, 136.3, \, 126.6, \, 98.8, \, 80.2, \, 70.5, \, 54.8, \, 29.8, \, 27.3, \, 25.4, \, 24.2, \, 22.9, \, 22.8, \, 17.8; \) IR (neat) 3486 cm\(^{-1}\); HRMS (EI) m/z 226.1577 (M, 226.1569 calc for C\(_{13}\)H\(_{22}\)O\(_3\)). Anal. Calcd for C\(_{13}\)H\(_{22}\)O\(_3\): C, 69.24; H, 9.79.

\( \textit{rel-(2R,6R)-[(6-Methoxytetrahydropyran-2-yl)cyclohex-1-eny1]-rel-(S)-methoxy triethylysilane (13).} \) Chlorotriethylysilane (0.48 mL, 2.83 mmol) was added to a solution of alcohol \( 12 \) (0.32 g, 1.42 mmol) and imidazole (0.29 g, 4.26 mmol) in DMF (7 mL). The reaction was maintained at rt for 18 h. Water (10 mL) was added and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were washed with H\(_2\)O (4 x 15 mL), brine (20 mL), dried (MgSO\(_4\)), filtered and concentrated. The residue was purified on silica gel (2% ethyl acetate-hexanes) to yield 0.42 g (87%) of tetrahydropyran \( 13: \) \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \[ \delta \, 5.65 \, (s, \, 1 \, H), \, 4.68 \, (s, \, 1 \, H), \, 3.76 \, (d, \, J = 7.8 \, Hz, \, 1 \, H), \, 3.70–3.65 \, (m, \, 1 \, H), \, 3.33 \, (s, \, 3 \, H), \, 2.16–1.98 \, (m, \, 4 \, H), \, 1.66–1.54 \, (m, \, 9 \, H), \, 1.27–1.24 \, (m, \, 1 \, H), \, 0.95 \, (t, \, J = 7.9 \, Hz, \, 9 \, H), \, 0.58 \, (q, \, J = 7.9 \, Hz, \, 6 \, H); ^{13}C \) NMR (125 MHz, CDCl\(_3\)) \[ \delta \, 138.7, \, 124.8, \, 98.7, \, 80.4, \, 69.9, \, 54.7, \, 30.1, \, 27.9, \, 25.4, \, 23.9, \, 23.0, \, 22.9, \, 18.1, \, 7.1, \, 5.1; \) IR (neat) 2952, 2836 cm\(^{-1}\); HRMS (EI) m/z 363.2328 (M+Na, 363.2332 calc for C\(_{19}\)H\(_{36}\)O\(_3\)SiNa).

\( \textit{rel-(2R,6R)-[(6-Methoxy-tetrahydropyran-2-yl)cyclohex-1-eny1]-4-nitrobenzoic acid–rel-(R)-methylester (14).} \) 4-Nitrobenzoyl chloride (110 mg, 0.60 mmol) was added to a solution of \( 12 \) (90 mg, 0.40 mmol), pyridine (130 \[ mL, \, 1.60 \, mmol) and 2,6-dimethyl-aminopyridine (5.0 mg, 0.04 mmol) in CH\(_2\)Cl\(_2\) (4 mL) at rt. After 2 h, the reaction mixture was added to saturated aqueous NH\(_4\)Cl (5 mL) and the resulting mixture was extracted with CH\(_2\)Cl\(_2\) (2 x 5 mL). The organic extract was washed
sequentially with saturated aqueous CuSO₄ (2 x 10 mL) and brine (2 x 10 mL), dried (Na₂SO₄), filtered and concentrated. The residue was purified by flash chromatography on silica gel (5% ethyl acetate-hexanes) to afford 125 mg (83%) of 14 as a yellow solid: 

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\begin{align*}
^1H\ \text{NMR} &\quad (500\ MHz, CDCl₃) \delta 8.29 (d, J = 8.7\ Hz, 2H), 8.22 (d, J = 8.7\ Hz, 2H), 5.82 (s, 1H), 5.31 (d, J = 6\ Hz, 1H), 4.74 (s, 1H), 4.05–4.02 (m, 1H), 3.36 (s, 3H), 2.16–1.81 (m, 4H), 1.69–1.26 (m, 10H); \\
^13C\ \text{NMR} &\quad (125\ MHz, CDCl₃) \delta 163.9, 150.7, 136.2, 133.8, 130.9, 126.9, 123.8, 98.9, 81.3, 68.6, 54.8, 29.9, 26.7, 25.5, 25.2, 22.7, 22.5, 17.8; \text{IR (neat)} 2933, 1726, 1608, 1529 \text{ cm}^{-1}; \text{HRMS (ESI)} m/z 398.1580 (M+Na, 398.1586 \text{ calcd for } C_{20}H_{25}NO_6Na).
\end{align*}
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**rel-(2R,6R)-[(6-Methoxytetrahydropyran-2-yl)cyclohex-1-enyl]-rel-(R)-methoxytriethylsilane (16).** Chlorotriethylsilane (0.24 mL, 1.42 mmol) was added to a solution of alcohol 15 (0.16 g, 0.71 mmol) and imidazole (0.15 g, 2.13 mmol) in DMF (4 mL). The reaction was maintained at rt for 18 h. Water (15 mL) was added and the aqueous phase was extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with H₂O (4 x 8 mL), brine (10 mL), dried (MgSO₄), filtered and concentrated. The residue was purified on silica gel (2% ethyl acetate-hexanes) to yield 0.22 g (87%) of tetrahydropyran 16: 

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\begin{align*}
^1H\ \text{NMR} &\quad (500\ MHz, CDCl₃) \delta 5.59 (s, 1\ H), 4.73 (s, 1\ H), 4.12 (d, J = 8.9\ Hz, 1H), 3.80–3.78 (m, 1\ H), 3.35 (s, 3\ H), 2.25–2.15 (m, 1\ H), 2.03–1.95 (m, 2\ H), 1.90–1.72 (m, 2\ H), 1.70–1.48 (m, 7\ H), 1.38–1.35 (m, 1\ H), 1.29–1.22 (m, 1\ H), 0.95 (t, J = 9.8\ Hz, 9\ H), 0.58 (q, J = 9.8\ Hz, 6\ H); \text{IR (neat)} 2948, 1196 \text{ cm}^{-1}; \text{HRMS (ESI)} m/z 363.2349 (M+Na, 363.2332 \text{ calcd for } C_{19}H_{36}O_3SiNa).
\end{align*}
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**Prins-pinacol Rearrangement of 16.** Tin (IV) chloride (42 mL, 0.23 mmol) was added dropwise to a solution of tetrahydropyran 16 (0.16 g, 0.46 mmol) and CH₂Cl₂ (9.5 mL, 0.025 M) at 0 °C. After maintaining the reaction at 0 °C for 30 min, the reaction mixture was poured into saturated aqueous NaHCO₃ (5 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica gel (2% ethyl acetate-hexanes) to give the following fractions: 

**12-oxatricyclo[6.3.1.0₂⁷]dodecane aldehyde 17:** 30 mg (33%) as a clear pale yellow oil: 

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\begin{align*}
^1H\ \text{NMR} &\quad (500\ MHz, CDCl₃) \delta 9.53 (s, 1\ H), 4.38 (m, 1\ H), 4.20 (d, J = 4.2
\end{align*}
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Supporting Information: Stereocontrolled Construction of 12-Oxatricyclo[6.3.1.0\(^{2,7}\)]dodecanes; Overman and Velthuisen, September 1, 2004

13-oxatricyclo[7.3.1.0\(^{2,7}\)]tridecane-8-one 19: 50 mg (55%) as a clear yellow pale oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) □4.43 (dd, \(J = 10.4, 5.7\) Hz, 1 H), 4.06 (d, \(J = 4.4\) Hz, 1 H), 3.29–3.26 (m, 1 H), 2.90–2.83 (m, 1 H), 2.32–2.29 (m, 1 H), 2.08–2.04 (m, 1 H), 1.88–1.49 (m, 8 H), 1.34–1.25 (m, 3 H), 1.24–1.08 (m, 1 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) □219.2, 78.6, 71.1, 43.2, 38.9, 26.9, 26.7, 26.2, 25.8, 22.9, 22.5, 18.3; IR (neat) 1724 cm\(^{-1}\); HRMS (EI) \(m/z\) 194.1316 (M, 194.1307 calcd for C\(_{12}\)H\(_{18}\)O\(_2\)).

13-oxatricyclo[7.3.1.0\(^{2,7}\)]tridecane-8-one 20: 1,8-Diazabicyclo[5.4.0]undec-7-ene (15 □L, 0.10 mmol) was added to a solution of 19 (19 mg, 0.10 mmol) in C\(_6\)D\(_6\) (2 mL). The reaction mixture was heated to 50 °C. After 19 h, \(^1\)H NMR analysis showed the complete consumption of starting material. The reaction was concentrated, and the residue was purified by flash column chromatography on silica gel (1% ethyl acetate-hexanes) to give 19 mg (100%) of 20 as a pale yellow oil: \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) □4.23 (d, \(J = 5.8\) Hz, 1H), 3.57–3.55 (m, 1H), 2.40 (d, \(J = 13.5\) Hz, 1H), 1.91–1.89 (m, 2H), 1.74–1.43 (m, 3H), 1.49–1.45 (m, 1H), 1.38–1.22 (m, 4H), 1.14 (d, \(J = 12.3\) Hz, 1H), 1.07–0.93 (m, 3H), 0.72–0.64 (m, 1H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)) □108.4, 78.1, 71.5, 53.4, 48.9, 29.5, 28.8, 26.7, 26.5, 26.0, 24.0, 18.8; IR (neat) 1713 cm\(^{-1}\); HRMS (EI) \(m/z\) 194.1309 (M, 194.1307 calcd for C\(_{12}\)H\(_{18}\)O\(_2\)).
13-Oxatricyclo[7.3.1.0\(^{2,7}\)]tridecan-8-tosylhydrazone 21. A solution of 20 (40 mg, 0.21 mmol), glacial acetic acid (2.0 mL) and tosyl hydrazone (76 mg, 0.42 mmol) was maintained at rt for 18 h. The reaction was diluted with heptane (1 mL), concentrated, and the residue was purified by flash column chromatography on silica gel (10% ethyl acetate-hexanes) to give 37 mg (50%) of 21 as an off-white solid: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.88 (d, \(J = 8.2\) Hz, 2 H), 7.36 (d, \(J = 8.2\) Hz, 2 H), 7.10 (bs, 1 H), 4.66–4.65 (m, 1 H), 3.75–3.73 (m, 1 H), 2.49 (s, 3 H), 2.42–2.40 (m, 2 H), 2.04–1.75 (m, 6 H), 1.16–0.93 (m, 8 H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 129.6, 128.5, 71.6, 65.7, 47.1, 45.8, 29.5, 28.1, 26.4, 26.3, 26.2, 23.6, 18.3; IR (neat) 3435, 3261, 3157, 2937, 1594, 1524 cm\(^{-1}\); HRMS (EI) \(m/z\) 363.1736 (M+H, 363.1742 calcd for C\(_{19}\)H\(_{26}\)NO\(_3\)SH).

rel-(7R,9S)-7-Methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undecane-9-carboxylic acid methyl ester (27). m-CPBA (23.7 g, 80.1 mmol) was added to a solution of 2-methyl-3,4-dihydro-2H-pyran-2-carboxylic acid methyl ester 24 (12.5 g, 137 mmol)\(^4\) in methyl alcohol (800 mL) at 0 °C. After 3 h, dimethyl sulfide (10.0 mL, 137 mmol) was added and the reaction mixture was stirred for 1 h. The reaction mixture was then concentrated and the resulting solids were dissolved in a minimal amount of CH\(_2\)Cl\(_2\) (10 mL). The crude mixture was then filtered through a plug of silica gel (50% ethyl acetate-hexanes) to yield 14.8 g (90%) of alcohol 25 as a mixture of anomers (4:1; \(\square:\square\)) as determined by \(^1\)H NMR analysis: \(\square\) anomere, \(\square\) 4.5 ppm (d, \(J = 3.2\) Hz); \(\square\) anomere; \(\square\) 4.32 ppm (d, \(J = 7.7\) Hz).

To a solution of oxalyl chloride (7.6 mL, 87 mmol) in CH\(_2\)Cl\(_2\) (725 mL) at −78 °C was added DMSO (13.5 mL, 174 mmol) dropwise over 5 min.\(^5\) After stirring 10 min at −78 °C, a solution of alcohol 25 (14.8 g, 72.5 mmol) in CH\(_2\)Cl\(_2\) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, triethylamine (27.9 mL, 218 mmol) was then added and the reaction mixture was allowed to warm to rt. After stirring for 30 min, the reaction mixture was poured into saturated aqueous NH\(_4\)Cl (100 mL) and the layers were separated. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL) and the combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated to yield 14.6 g


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(100%) of ketone 26 as a pale yellow oil. The material was used without any further purification.

To a solution of ketone 26 (14.8 g, 73.3 mmol) and propanedithiol (7.0 mL, 73.3 mmol) in CH₂Cl₂ (730 mL) was added BF₃•OEt₂ (1.90 mL, 14.6 mmol) and the reaction was maintained at rt for 18 h. The solution was poured into saturated aqueous NaHCO₃ (200 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate-hexanes) to give 7.0 g (35%) of dithiane 27 as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 4.57 (s, 1 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.45–3.26 (m, 2 H), 2.62–2.49 (m, 2 H), 2.20–2.00 (m, 3 H), 1.92–1.80 (m, 2 H), 1.66–1.58 (m, 1 H), 1.50 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 108.9, 78.4, 52.5, 48.1, 35.1, 29.2, 28.2, 27.6, 27.1, 25.7; IR (neat) 1733 cm⁻¹; HRMS (CI) m/z 292.0797 (M, 292.0830 calcd for C₁₂H₂₀O₄S₂).

rel-(7R,9R)-Methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undec-9-yl methanol (28). A solution of LiAlH₄ (36.0 mL, 36 mmol, 1 M in THF) was added dropwise to a stirring solution of ester 27 (7.0 g, 24.0 mmol) in Et₂O (240 mL) at 0 °C. After stirring for 30 min, the reaction mixture was quenched by sequential addition of H₂O (1.4 mL), aqueous NaOH (4.2 mL, 2.5 M) and finally H₂O (1.4 mL) with a 30 min period in between each addition. After vigorously stirring for 2 h, the suspension was filtered through a pad of Celite. Upon concentration, 5.6 g (89%) of alcohol 28 as a colorless oil was recovered. The material was used without further purification: ¹H NMR (500 MHz, CDCl₃) δ 4.62 (s, 1H), 3.48 (s, 3H), 3.45–3.39 (dd, J = 11.3, 3.2 Hz, 2 H), 2.94–2.86 (m, 2 H), 2.82–2.68 (m, 2 H), 2.30–2.23 (m, 1 H), 2.16–2.08 (m, 2 H), 2.04 (br s, 1 H), 2.00–1.90 (m, 2 H), 1.50–1.44 (m, 1 H), 1.29 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 103.9, 75.4, 68.7, 56.7, 51.3, 28.6, 27.0, 26.4, 26.3, 25.4, 24.0; IR (neat) 3460, 2931 cm⁻¹; HRMS (Cl) m/z 264.0845 (M, 264.0853 calcd for C₁₁H₂₀O₃S₂). Anal. Calcd for C₁₁H₂₀O₃S₂: C, 49.97; H, 7.62. Found: C, 50.14; H, 7.71.

rel-(7R,9R)-7-Methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undecane-9-carbaldehyde (29). To a solution of oxalyl chloride (0.40 mL, 4.7 mmol) in CH₂Cl₂ (39 mL) at −78 °C was added DMSO (0.7 mL, 9.4 mmol) dropwise over 5 min. After stirring 10 min at −78 °C, a solution of alcohol 28 (1.0 g, 3.9 mmol) in CH₂Cl₂ was added
dropwise. The reaction mixture was stirred at –78 °C for 30 min, triethylamine (1.50 mL, 11.8 mmol) was then added and the reaction mixture was allowed to warm to rt. After stirring for 30 min, the reaction mixture was poured into saturated aqueous NH₄Cl (100 mL) and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were dried (Na₂SO₄), filtered and concentrated. The residue was purified by flash chromatography on silica gel (10% ethyl acetate-hexanes) to give 0.85 g (83%) of aldehyde 29 as a white solid: ¹H NMR (500 MHz, CDCl₃) δ 9.60 (s, 1 H), 4.52 (s, 1H), 3.65 (s, 3 H), 3.40–3.27 (m, 2H), 2.60–2.52 (m, 2H), 2.17–2.11 (m, 1 H), 2.06–1.97 (m, 2 H), 1.92–1.79 (m, 2 H), 1.60 (ddd, J = 13.9, 13.9, 4.7 Hz, 1 H), 1.33 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 203.4, 109.1, 81.0, 57.3, 48.1, 34.0, 28.1, 27.4, 25.59, 25.55, 22.8; IR (neat) 1735 cm⁻¹; HRMS (CI) m/z 262.0695 (M, 262.0697 calcd for C₁₁H₁₈O₃S₂). Anal. Calcd for C₁₁H₁₈O₃S₂: C, 50.35; H, 6.91. Found: C, 50.54; H, 6.93.

rel-(7R,9R)-[(7-Methoxy-9-methyl-8-oxa-1,5-dithia-spiro[5.5]undec-9-yl)cyclohex-1-enyl]methanol (30 and 33). To a solution of tert-butyllithium (1.3 mL, 6.4 mmol, 1.1 M in pentane) in THF (8 mL, 0.1 M) was added a solution of vinyl iodide 11 (0.16 g, 0.76 mmol) in THF (2 mL) dropwise at –78 °C. The reaction was maintained at –78 °C for 20 min, followed by the dropwise addition of a solution of aldehyde 29 (0.2 g, 0.76 mmol) in THF (2 mL). The cooling bath was removed and the reaction was maintained at rt for 18 h. The reaction mixture was treated with H₂O (20 mL) and the aqueous layer was extracted with Et₂O (2 x 20 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated. The residue (0.22 g, 84%) was purified via HPLC (10% ethyl acetate-hexane isocratic; Novapack 6 M Silica, 300 x 50 mm ID): Major diastereomer 30, Rₜ = 34 min: ¹H NMR (500 MHz, CDCl₃) δ 5.75 (s, 1 H), 4.73 (s, 1 H), 3.90 (s, 1 H), 3.47 (s, 3 H), 2.91–2.75 (m, 5 H), 2.48 (ddd, J = 12.5, 12.5, 4.9 Hz, 1 H), 2.33 (ddd, J = 13.7, 13.7, 3.7 Hz, 1 H), 2.28–2.18 (m, 2 H), 2.07–1.85 (m, 5 H), 1.70–1.48 (m, 4 H), 1.35–1.29 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 135.7, 127.8, 102.9, 82.7, 78.8, 56.5, 52.2, 26.9, 26.1, 25.99, 25.91, 25.6, 25.5, 25.4, 23.6, 23.1, 22.8; IR (neat) 3529 cm⁻¹; HRMS (CI) m/z 327.1446 ([M-OH]+, 327.1453 calcd for C₁₇H₂₇O₂S₂). Anal. Calcd for C₁₇H₂₈O₃S₂: C, 59.26; H, 6.19. Found: C, 59.06; H, 8.46.
Minor Diastereomer 33, R_T = 39 min: \(^1\)H NMR (500 MHz, CDCl\(_3\)) □ 5.62 (s, 1 H), 4.74 (s, 1 H), 3.78 (s, 1 H), 3.49 (s, 3 H), 2.92 (dd, \(J = 7.3, 3.7 \text{ Hz}, 1 \text{ H}\)), 2.89 (dd, \(J = 7.1, 4.4 \text{ Hz}, 1 \text{ H}\)), 2.84–2.74 (m, 3 H), 2.35–2.14 (m, 4 H), 2.07–1.92 (m, 4 H), 1.69–1.49 (m, 5 H), 1.45–1.42 (m, 1 H), 1.25 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) □ 136.9, 126.9, 103.5, 81.1, 78.2, 56.8, 51.4, 28.7, 28.5, 26.4, 26.3, 25.5, 25.4, 25.3, 23.0, 22.83, 22.80; IR (neat) 3543 cm\(^{-1}\); HRMS (CI) \(m/z\) 327.1459 ([M-OH]\(^+\), 327.1453 calcd for C\(_{17}\)H\(_{27}\)O\(_2\)S\(_2\)).

\(\text{rel-}(7R,9R)-[(7\text{-methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undec-9-yl)}\) -cyclohex-1-enyl]-\(\text{rel-}(S)\)-methoxy triethylsilane (31). Chlorotriethylsilane (49 □L, 0.15 mmol) was added to a solution of alcohol 30 (50 mg, 0.30 mmol) and imidazole (30 mg, 0.45 mmol) in DMF (0.7 mL) and the reaction was maintained at rt for 18 h. Water (10 mL) was added and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The combined organic layers were washed with H\(_2\)O (4 x 15 mL), brine (20 mL), dried (MgSO\(_4\)), filtered and concentrated. The residue was purified on silica gel (2% ethyl acetate-hexanes) to yield 66 mg (100%) of tetrahydropyran 31 as a white solid: \(^1\)H NMR (500 MHz, CDCl\(_3\)) □ 5.66 (s, 1H), 4.70 (s, 1H), 4.12 (s, 1H), 3.43 (s, 3H), 3.26–3.13 (m, 2H), 2.68–2.56 (m, 2H), 2.30–2.23 (m, 1H), 2.14–2.01 (m, 5H), 2.00–1.85 (m, 3H), 1.77–1.58 (m, 3H), 1.50–1.40 (m, 2H), 1.31 (s, 3H), 0.94 (t, \(J = 7.9 \text{ Hz}, 9 \text{H}\)), 0.61–0.52 (m, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) □ 138.6, 126.7, 105.6, 78.9, 78.5, 56.4, 49.9, 32.4, 29.4, 27.7, 27.2, 25.8, 25.6, 24.1, 23.1, 22.9, 7.1, 5.1; IR (neat) 2935, 1050 cm\(^{-1}\); HRMS (CI) \(m/z\) 458.2335 (M, 458.2345 calcd for C\(_{23}\)H\(_{42}\)O\(_3\)S\(_2\)Si).

\(\text{rel-}(7R,9R)-[(7\text{-methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undec-9-yl)}\) -cyclohex-1-enyl]-\(\text{rel-}(S)\)-methoxy triisopropylsilane (32). Pyridine (150 □L, 1.9 mmol), triisopropylsilyl trifluoromethanesulfonate (220 □L, 0.81 mmol), and 2,6-dimethylaminopyridine (8 mg, 0.06 mmol) were added sequentially to a solution of 30 (214 mg, 0.62 mmol) in CH\(_2\)Cl\(_2\) (6 mL). After stirring for 18 h, the solution was poured into H\(_2\)O (10 mL) and the layers were separated. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 5 mL) and the combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was purified by flash chromatography on silica gel (5% ethyl acetate-hexanes) to give 240 mg (77%) of tetrahydropyran 32 as a pale yellow oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) □ 5.69 (s, 1 H), 4.63 (s, 1 H), 4.28 (s, 1 H), 3.42 (s, 3 H), 3.24–3.13 (m, 2 H), 2.68–5.78 (m, 2 H), 2.35–2.29 (m, 1 H), 2.19–1.86 (m, 8 H), 1.78–1.64
(m, 3 H), 1.47–1.41 (m, 2 H), 1.38 (s, 3 H), 1.06 (s, 21 H); \(^\text{13}^\text{C}\) NMR (125 MHz, CDCl\(_3\)): \[138.8, 127.2, 105.5, 79.2, 78.6, 56.3, 49.8, 32.3, 29.7, 27.7, 27.1, 25.9, 25.8, 25.5, 24.2, 22.9, 22.8, 18.48, 18.46, 12.9; IR (neat) 1460, 1050 cm\(^{-1}\); HRMS (CI) \(m/z\) 500.2812 (M, 500.2814 calcd for C\(_{26}\)H\(_{48}\)O\(_3\)S\(_2\)Si). Anal. Calcd for C\(_{26}\)H\(_{48}\)O\(_3\)S\(_2\)Si: C, 62.35; H, 9.66. Found: C, 62.36; H, 9.66.

**rel-(7R,9R)-[(7-Methoxy-9-methyl-8-oxa-1,5-dithiaspiro[5.5]undec-9-yl)-cyclohex-1-enyl]-rel-(R)-methoxy triisopropylsilane (34).** Pyridine (64 mL, 0.76 mmol), triisopropylsilyl trifluoromethanesulfonate (92 mL, 0.34 mmol), and 2,6-dimethylaminopyridine (4 mg, 0.03 mmol) were added sequentially to a solution of 33 (214 mg, 0.62 mmol) in CH\(_2\)Cl\(_2\) (3 mL). After stirring for 18 h, the solution was poured into H\(_2\)O (5 mL) and the layers were separated. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 5 mL) and the combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was purified by flash chromatography on silica gel (5% ethyl acetate-hexanes) to give 100 mg (75%) of tetrahydropyran 34 as a yellow oil: \(^1^H\) NMR (500 MHz, CDCl\(_3\)): \[5.65 (s, 1 H), 4.76 (s, 1 H), 4.04 (s, 1 H), 3.48 (s, 3 H), 2.92–2.72 (m, 3 H), 2.29–2.21 (m, 2 H), 2.06–1.88 (m, 5 H), 1.69–1.62 (m, 2 H), 1.55–1.44 (m, 2 H), 1.32 (s, 3 H), 1.12–1.05 (m, 25 H); \(^\text{13}^\text{C}\) NMR (125 MHz, CDCl\(_3\)): \[137.9, 126.8, 103.8, 85.2, 78.5, 56.6, 52.3, 29.4, 28.7, 26.5, 26.4, 26.2, 25.6, 25.5, 23.1, 22.9, 21.9, 18.44, 18.42, 12.9; IR (neat) 1449, 1052 cm\(^{-1}\); HRMS (CI) \(m/z\) 500.2885 (M, 500.2814 calcd for C\(_{26}\)H\(_{48}\)O\(_3\)S\(_2\)Si). Anal. Calcd for C\(_{26}\)H\(_{48}\)O\(_3\)S\(_2\)Si: C, 62.35; H, 9.66. Found: C, 62.61; H, 9.75.

**Tricyclic acetal 35.** Tin (IV) chloride (24 mL, 0.13 mmol) was added dropwise to a stirring solution of tetrahydropyran 30 (44 mg, 0.13 mmol) and CH\(_2\)Cl\(_2\) (1.3 mL) at 0 °C. After maintaining the reaction at 0 °C for 30 min, the reaction mixture was poured into saturated aqueous NaHCO\(_3\) (5 mL) and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated. The residue was purified on silica gel (10% ethyl acetate-hexanes) to yield 38 mg (99%) of 35 as a clear oil: \(^1^H\) NMR (500 MHz, CDCl\(_3\)): \[6.12 (s, 1 H), 5.54 (s, 1 H), 4.00 (s, 1 H), 2.98 (ddd, \(J = 13.7, 9.0, 4.4\) Hz, 1H), 2.85 (ddd, \(J = 14.4, 7.4, 4.4\) Hz, 1H), 2.77 (ddd, \(J = 14.4, 7.4, 4.1\) Hz, 1H), 2.67 (ddd, \(J = 14.4, 6.1, 4.1\) Hz, 1H), 2.35–2.27 (m, 1H), 2.12–2.05 (m, 2H), 2.00–1.80 (m, 6H), 1.75–1.47 (m,
Supporting Information: Stereocontrolled Construction of 12-Oxatricyclo[6.3.1.0²⁷]dodecanes; Overman and Velthuisen, September 1, 2004

5H), 1.39 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 130.9, 123.4, 101.2, 86.9, 80.4, 52.0, 31.1, 29.0 26.2, 26.0, 25.8, 25.0, 24.9, 23.8, 22.8, 22.7; IR (neat) 2933, 2360, 2332, 1380, 1090 cm⁻¹; HRMS (ESI) m/z 335.1107 (M+Na, 335.1115 calcd for C₁₆H₂₄O₂S₂Na).

trans-12-oxatricyclo[6.3.1.0²⁷]dodecane aldehyde 36. Tin (IV) chloride (30 mL, 0.17 mmol) was added dropwise to a stirring solution of tetrahydropyran 32 (166 mg, 0.33 mmol) and CH₂Cl₂ (3.3 mL) at 0 °C. After maintaining the reaction at 0 °C for 30 min, the reaction mixture was poured into saturated aqueous NaHCO₃ (5 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated. The residue was purified on silica gel (10% ethyl acetate-hexanes) to yield 83 mg (81%) of 36 as a pale yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 9.61 (s, 1 H), 4.03 (s, 1 H), 3.09–3.04 (m, 1 H), 2.95–2.84 (m, 2 H), 2.79–2.70 (m, 2 H), 2.09–1.96 (m, 4 H), 1.82–1.57 (m, 6 H), 1.50–1.35 (m, 2 H), 1.31 (s, 3 H), 1.28–1.22 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ 202.5, 84.8, 83.6, 61.2, 51.6, 40.8, 32.3, 30.8, 26.1, 26.0, 25.9, 25.4, 22.2, 22.1, 18.2, 16.8; IR (neat) 1715 cm⁻¹; HRMS (CI) m/z 312.1217 (M+H, 312.1218 calcd for C₁₆H₂₄O₂S₂).

Tosyl Hydrazone 37. A solution of 36 (83 mg, 0.27 mmol), glacial acetic acid (3.0 mL) and tosyl hydrazine (100 mg, 0.53 mmol) was maintained at rt for 4 h. The reaction was diluted with heptane (10 mL) and concentrated. The residue was purified by flash column chromatography on silica gel (10% ethyl acetate-hexanes) to yield 103 mg (81%) of 37 as an off-white solid: ¹H NMR (500 MHz, CDCl₃) δ 8.18 (s, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 4.12 (s, 1 H), 2.92–2.80 (m, 3 H), 2.70–2.62 (m, 2 H), 2.43 (s, 3 H), 2.00–1.88 (m, 2 H), 1.80–1.74 (m, 1 H), 1.68–1.58 (m, 3 H), 1.51–1.35 (m, 5 H), 1.09–1.03 (m, 6 H); ¹³C NMR (125 MHz, CDCl₃) δ 153.0, 144.4, 135.3, 130.2, 128.2, 84.3, 52.5, 51.9, 42.2, 32.3, 30.7, 26.6, 26.2, 25.6, 25.4, 25.4, 25.0, 21.8, 21.4, 18.2, 17.1; HRMS (CI) m/z 481.1651 (M+H, 481.1653 calcd for C₂₃H₃₂N₂O₃S₃H). Anal. Calcd for C₂₃H₃₂N₂O₃S₃: C, 57.47; H, 6.71; N, 5.83. Found: C, 57.29; H, 6.87; N, 5.77.