Supplementary Material

Synthesis of nucleoside analogues using acyclic diastereoselective reactions

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Part I. Stereoc hemical Proofs

Diastereoselective Mukaiyama Aldol Reaction - The anti-stereochemistry of methyl ester 8a,b obtained in the Mukaiyama aldol reaction was previously confirmed by our lab.1

Diastereoselective Atom Transfer Cyclization - The syn stereochemistry of methyl ester 12 for the intramolecular vinyl transfer reaction was indirectly confirmed from the X-ray structure of acetonide S20a. See below for experimental procedures and full characterization of S20a. In addition, the stereochemistry for this transformation was confirmed in the final nucleoside analogues.

Diastereoselective Cyanation - The relative stereochemistry of the racemic cyanohydrins (Table 1) was determined by relevant nuclear Overhauser effect [nOe] enhancements and supported by 13C NMR data. The two cyanohydrin diastereomers were separated, deprotected to the corresponding diols and then protected as an acetonide. See below for experimental procedures and full characterization. The relative stereochemistry of the syn and anti acetonides was determined from 1D NOESY and the 13C chemical shifts of the acetal carbon and the gem-dimethyl substituents. According to Rychnovsky’s study,2 the difference in chemical shifts between the gem-dimethyl groups is an indicator of stereochemistry, with syn acetonides having a difference of >9 ppm (methyl shifts around 19 and 30 ppm) and anti-isomers showing a difference of <5 ppm (methyl shifts around 25 ppm). The chemical shift of the acetal carbon is also an indicator of the relative stereochemistry, with syn-acetonides having chemical shifts below 99.5 ppm and anti-acetals above 100.5 ppm. In Rychnovsky’s study, some inconsistencies were observed in the presence of a nitrile substituent. In this study, the shift of the acetal carbon of all syn acetonides was around 100.5 ppm and around 102 ppm for anti acetonides. In addition, for substrates in which the gem-dimethyl groups of the acetonide could be clearly identified, the syn acetonides had a difference of 9 ppm between the methyl groups located around 19 and 30 ppm while the anti acetonides showed a difference of 5 ppm with methyl shifts around 25 ppm, consistent with Rychnovsky’s study. Based on this and NOESY correlations, the proof of structures for cyanohydrins 5a,b, 20a,b, 22a,b, 26a,b and 28a,b were determined.
The proof of structure for cyanohydrins 24a,b was determined through X-ray crystallography of the corresponding acetone.
Diastereoselective Thioaminal Formation and Intramolecular Cyclization - Proof of structure for the protected nucleoside analogue 32 and the final deprotected analogue 36 was determined by 2D NOESY experiments thus confirming the 1,2-syn diastereoselectivity for nucleobase addition to the dithioacetal followed by O4'-C1 cyclization with inversion of configuration providing the 1',2'-trans nucleoside analogue.

Cyanohydrins 5a,b, 20a,b and 22a,b:

To a solution of cyanohydrin 5a (24 mg, 0.064 mmol, 1.0 equiv.) in dry THF (0.64 mL, 0.10 M) at 0 °C, HF-pyridine (0.13 mL, 0.13 mmol, 2.0 mL/mmol) was added. The solution was warmed to room temperature and stirred overnight. An aqueous solution of NaHCO3 was added and the aqueous layer extracted with Et2O (3x). The organic layers were combined, dried with MgSO4, filtered and concentrated in vacuo. Purification
by flash chromatography using 35:65 EtOAc:Hex provided 22a (10 mg, 59% yield) as a clear oil. Characterization data for 22a can be found in the experimental section.

Cyanohydrin 20a was diluted in MeOH and a few drops of TFA were added. Concentration of the reaction mixture provided 22a.

(±)-(4R,5R,6S)-6-(benzyloxymethyl)-2,2,5-trimethyl-5-vinyl-1,3-dioxane-4-carbonitrile (S15a):

\[
\text{OH} \quad \text{CN} \quad \text{O} \\
\text{OBn} \quad \text{Me} \quad \text{OBn} \quad \text{Me}
\]

To a solution of diol 22a (8.4 mg, 0.032 mmol, 1.0 equiv.) in dry CH₂Cl₂ (0.3 mL, 0.1 M) at 0 °C, 2-methoxypropene (12 µL, 0.13 mmol, 4.0 equiv.) and camphor sulfonic acid (1.5 mg, 0.0060 mmol, 0.20 equiv.) were added. The solution was stirred 15 minutes at 0 °C then warmed to room temperature for 45 minutes. An aqueous solution of NH₄Cl was added and the aqueous layer was extracted with Et₂O (3x). The organic layers were combined, dried with MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography using 20:80 EtOAc:Hex provided acetonide S15a as a clear oil (8.3 mg, 86% yield): \( R_f = 0.21 \) (20:80 EtOAc:Hex); Molecular Formula: C₁₈H₂₃NO₃; MW: 301.39; IR (neat) \( \nu \text{max} \) 2251 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.38 – 7.27 (m, 5H), 6.26 (dd, \( J = 17.8, 11.0 \) Hz, 1H), 5.42 (d, \( J = 11.0 \) Hz, 1H), 5.25 (d, \( J = 17.8 \) Hz, 1H), 4.60 (s, 1H), 4.56 (d, \( J = 12.1 \) Hz, 1H), 4.45 (d, \( J = 12.1 \) Hz, 1H), 3.92 (dd, \( J = 6.3, 3.6 \) Hz, 1H), 3.50 (dd, \( J = 10.8, 3.6 \) Hz, 1H), 3.34 (dd, \( J = 10.7, 6.3 \) Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.11 (s, 3H) ppm; \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 138.1, 134.0, 128.6, 127.9, 127.8, 118.7, 115.8, 100.7, 76.4, 73.6, 70.6, 70.4, 40.9, 29.5, 18.8, 17.0 ppm; HRMS calcd for C₁₈H₂₃O₃Na \[M+Na^+\]: 324.1570, found 324.1572 (+0.5 ppm).

Cyanohydrin 20b was diluted in MeOH and a few drops of TFA were added. Concentration of the reaction mixture provided 22b.

(±)-(4S,5R,6S)-6-((benzyloxy)methyl)-2,2,5-trimethyl-5-vinyl-1,3-dioxane-4-carbonitrile (S15b):

\[
\text{OH} \quad \text{CN} \quad \text{O} \\
\text{OBn} \quad \text{Me} \quad \text{OBn} \quad \text{Me}
\]

To a solution of diol 22b (9.4 mg, 0.036 mmol, 1.0 equiv.) in dry CH₂Cl₂ (0.6 mL, 0.1 M) at 0 °C, 2-methoxypropene (14 µL, 0.14 mmol, 4.0 equiv.) and camphor sulfonic acid (1.7 mg, 0.0070 mmol, 0.20 equiv.)
equiv.) were added. The solution was stirred for 15 minutes at 0°C then warmed to room temperature for 45 minutes. An aqueous solution of NH₄Cl was added and the aqueous layer was extracted with Et₂O (3x). The organic layers were combined, dried with MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography using 20:80 EtOAc:Hex provided acetonide S15b as a clear oil (9.3 mg, 86% yield): R_f = 0.32 (20:80 EtOAc:Hex); Molecular Formula: C₁₈H₂₃NO₃; MW: 301.39; IR (neat) υ_max 2992, 2873, 1383 cm⁻¹; 
¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 6.08 (dd, J 17.6, 11.0 Hz, 1H), 5.27 (d, J 10.9 Hz, 1H), 5.20 (d, J 17.6 Hz, 1H), 4.58 (d, J 12.1 Hz, 1H), 4.47 (d, J 12.1 Hz, 1H), 4.42 (s, 1H), 4.04 (dd, J 6.9, 3.7 Hz, 1H), 3.45 (dd, J 10.8, 3.7 Hz, 1H), 3.39 (dd, J 10.8, 7.0 Hz, 1H), 1.62 (s, 3H), 1.45 (s, 3H), 1.24 (s, 3H) ppm; 
¹³C NMR (126 MHz, CDCl₃) δ 138.1, 136.6, 128.6, 127.8, 127.7, 117.29, 117.28, 102.4, 74.5, 73.5, 69.8, 68.4, 42.1, 27.4, 22.4, 17.8 ppm; HRMS calcd for C₁₈H₂₄O₃NNa [M+H⁺]: 302.17507, found 302.17510 (+0.1 ppm).

Cyanohydrins 24a,b:
The relative stereochemistry of cyanohydrins 24a and 24b was determined by X-ray diffraction of syn-acetonide S20a. Acetonides S20a,b were obtained from the corresponding diols S19a,b resulting from cyanation of aldehyde S18. From this, the relative stereochemistry of cyanohydrid 24a could be determined. Cleavage of the two silyl protecting groups of 24a resulted in the corresponding triol. The primary alcohol was selectively protected providing S19a which corresponded to the diol with syn relative stereochemistry. The X-ray structure of S20a also confirms the relative 3,4-syn stereochemistry for the intramolecular vinyl transfer.

(±)-(S)-methyl 2-(S)-3,3-diethyl-9,9-dimethyl-8,8-diphenyl-4,7-dioxo-3,8-disiladecan-5-yl)-2-methylbut-3-enoate (S16):
To a solution of (S)-methyl 2-((S)-2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-2-methylbut-3-enoate\(^3\) (0.35 g, 0.84 mmol, 1.0 equiv.) in anhydrous CH\(_2\)Cl\(_2\) (28 mL, 0.10 M) at 0°C, 2,6-lutidine (0.13 mL, 1.1 mmol, 1.3 equiv.) and TBSOTf (0.21 mL, 0.92 mmol, 1.2 equiv.) were added. The solution was stirred 4 hours at 0°C. An aqueous solution of NH\(_4\)Cl was added to the reaction mixture and the aqueous layer was extracted with Et\(_2\)O (3x). The organic layers were combined, dried over MgSO\(_4\), filtered and concentrated in vacuo.

Purification by flash chromatography using 10:90 EtOAc:Hex provided protected ester S16 as a clear oil (0.38 g, 85% yield): R\(_f\)= 0.5 (10:90 EtOAc:Hex); Molecular Formula: C\(_{30}\)H\(_{46}\)O\(_3\)Si\(_2\); MW: 526.86; IR (neat) \(\nu_{max}\) 1737 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68 – 7.63 (m, 4H), 7.46 – 7.36 (m, 6H), 6.11 (dd, J 17.6, 10.8 Hz, 1H), 5.14 (dd, J 10.9, 1.0 Hz, 1H), 5.04 (dd, J 17.7, 1.0 Hz, 1H), 4.21 (t, J 5.6 Hz, 1H), 3.58 (s, 3H), 3.58 – 3.53 (m, 1H), 3.47 (dd, J 10.8, 5.6 Hz, 1H), 1.24 (s, 3H), 1.05 (s, 9H), 0.88 (t, J 8.0 Hz, 6H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 175.1, 139.1, 135.83, 135.78, 133.44, 133.35, 129.82, 129.79, 127.80, 127.78, 114.8, 77.7, 66.5, 53.7, 52.0, 27.0, 19.3, 16.1, 7.0, 5.2 ppm; HRMS calcd for C\(_{30}\)H\(_{47}\)O\(_4\)Si\(_2\) [M+H\(^+\)]: 527.3007, found 527.3010 (+0.4 ppm).

(\(\pm\)-(R)-2-((S)-3,3-diethyl-9,9-dimethyl-8,8-diphenyl-4,7-dioxo-3,8-disiladecan-5-yl)-2-methylbut-3-en-1-ol (S17):

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OTES} & \quad \text{CO}_2\text{Me} \\
\text{S16} & \quad \text{Me} \\
\text{TBDPSO} & \quad \text{OTES} & \quad \text{OH} \\
\text{S17} & \quad \text{Me}
\end{align*}
\]

Following General Procedure A and purification by flash chromatography using 10:90 EtOAc:Hex, primary alcohol S17 was obtained as a clear oil (0.47 g, 89% yield): R\(_f\)= 0.28 (10:90 EtOAc:Hex); Molecular Formula: C\(_{29}\)H\(_{46}\)O\(_3\)Si\(_2\); MW: 498.85; IR (neat) \(\nu_{max}\) 3454 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.68 – 7.64 (m, 4H), 7.47 – 7.35 (m, 6H), 5.83 (dd, J 17.7, 11.0 Hz, 1H), 5.04 (dd, J 11.0, 1.4 Hz, 1H), 4.98 (dd, J 17.7, 1.4 Hz, 1H), 3.76 – 3.69 (m, 2H), 3.61 (dd, J 10.9, 6.5 Hz, 1H), 3.54 (dd, J 10.0, 3.9 Hz, 1H), 3.50 (dd, J 10.9, 6.1 Hz, 1H), 2.72 (t, J 6.0 Hz, 1H), 1.06 (s, 9H), 1.04 (s, 3H), 0.89 (t, J 7.9 Hz, 9H), 0.56 (q, J 7.9 Hz, 6H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 141.4, 135.9, 135.8, 133.2, 133.1, 129.92, 129.91, 127.86, 127.83, 114.5, 79.8, 68.7, 66.7, 45.8, 27.0, 19.3, 18.4, 7.0, 5.1 ppm; HRMS calcd for C\(_{29}\)H\(_{47}\)O\(_3\)Si\(_2\) [M+H\(^+\)]: 499.3058, found 499.3057 (-0.3 ppm).

(\(\pm\) -(S)-2-((S)-3,3-diethyl-9,9-dimethyl-8,8-diphenyl-4,7-dioxo-3,8-disiladecan-5-yl)-2-methylbut-3-enal (S18):

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OTES} & \quad \text{OH} \\
\text{S17} & \quad \text{Me} \\
\text{TBDPSO} & \quad \text{OTES} & \quad \text{O} \\
\text{S18} & \quad \text{Me}
\end{align*}
\]

Following General Procedure B and purification by flash chromatography using 5:95 EtOAc:Hex provided aldehyde S18 as a clear oil (0.35 g, 85 % yield): R\(_f\)= 0.28 (5:95 EtOAc:Hex); Molecular Formula: C\(_{29}\)H\(_{44}\)O\(_3\)Si\(_2\); MW: 496.84; IR (neat) \(\nu_{max}\) 1728 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.66 (s, 1H), 7.69 – 7.62 (m, 4H), 7.48 – 7.37 (m, 6H), 6.07 (dd, J 17.8, 10.9 Hz, 1H), 5.27 (dd, J 11.0, 0.9 Hz, 1H), 5.11 (dd, J 17.8, 0.9 Hz, 1H), 4.04 (dd, J 6.6, 4.7 Hz, 1H), 3.58 (dd, J 10.7, 6.6 Hz, 1H), 3.52 (dd, J 10.7, 4.7 Hz, 1H), 1.19 (s, 3H), 1.05 (s, 9H), 0.85 (t, J 7.9 Hz, 9H), 0.49 (q, J 7.9 Hz, 6H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 201.7, 137.2, 135.82, 135.79, 133.04, 132.96, 129.9, 127.86, 127.85, one aromatic carbon missing, 117.1, 76.7, 65.6, 56.9, 26.9, 19.2, 14.3, 6.9, 5.1 ppm; HRMS calcd for C\(_{29}\)H\(_{44}\)O\(_3\)Si\(_2\) [M+H\(^+\)]: 497.2902, found 497.2898 (-0.7 ppm).
\((\pm)-(2R, 3R)-3-(\text{S}-2-\text{(tert-butylidiphenylsilyloxy)}-1\text{-hydroxyethyl})-2\text{-hydroxy-3-methylpent-4-enenitrile (S19a)}\) and \((\pm)-(2S, 3R)-3-(\text{S}-2-\text{(tert-butylidiphenylsilyloxy)}-1\text{-hydroxyethyl})-2\text{-hydroxy-3-methylpent-4-enenitrile (S19b)}:\)

\[
\text{S18} \xrightarrow{\text{OTES}} \text{S19a} + \text{S19b}
\]

To a solution of aldehyde \text{S18} (70 mg, 0.14 mmol, 1.0 equiv.) in anhydrous CH\text{2}Cl\text{2} (1.9 mL, 0.10 M) at 0 °C, BF\text{3}·OEt\text{2} (36 µL, 0.29 mmol, 1.5 equiv.) was added. The reaction mixture was stirred 5 minutes for precomplexation. TMSCN (51 µL, 0.38 mmol, 2.0 equiv.) was then added and the solution was stirred 1 hour at 0 °C. An aqueous solution of NaHCO\text{3} was poured into the reaction mixture and the aqueous layer was extracted with Et\text{2}O (3x). The organic layers were combined, dried over MgSO\text{4}, filtered and concentrated in vacuo. \text{1H NMR} spectroscopic analysis of the crude reaction indicated a ~1:2.5 mixture of 2,4-diastereomers. Purification by flash chromatography using 25:75 EtOAc:Hex provided cyanohydrins \text{S19a,b}.

\((\pm)-(4R, 5R, 6S)-6-(\text{(tert-butylidiphenylsilyloxy)methyl})-2,2,5\text{-trimethyl-5-vinyl-1,3-dioxane-4-carbonitrile (S20a)}\) and \((\pm)-(4S, 5R, 6S)-6-(\text{(tert-butylidiphenylsilyloxy)methyl})-2,2,5\text{-trimethyl-5-vinyl-1,3-dioxane-4-carbonitrile (S20b)}:\)

\[
\text{S19a,b} \xrightarrow{\text{S18}} \text{S20a,b}
\]

To a solution of diol \text{S19a,b} (33 mg, 0.081 mmol, 1.0 equiv.) in dry CH\text{2}Cl\text{2} (0.8 mL, 0.1 M) at 0 °C, 2-methoxypropene (31 µL, 0.32 mmol, 4.0 equiv.) and camphor sulfonic acid (4.0 mg, 0.016 mmol, 0.20 equiv.) were added. The solution was stirred for 15 minutes at 0 °C then warmed to room temperature for 45 minutes. An aqueous solution of NH\text{4}Cl was added and the aqueous layer was extracted with Et\text{2}O (3x). The organic layers were combined, dried over MgSO\text{4}, filtered and concentrated in vacuo. Purification by flash chromatography using 10:90 EtOAc:Hex provided acetonide \text{S20a,b} (39.5 mg, quantitative yield). 

\text{S20a}: R\text{f} = 0.23 (10:90 EtOAc:Hex); Molecular Formula: C\text{27}H\text{35}NO\text{3}Si; MW: 449.67; \text{IR} (neat) \nu_{\text{max}} 1782, 1459 cm\text{\textsuperscript{-1}}; \text{1H NMR} (500 MHz, CDCl\text{3}) \delta 7.67 – 7.63 (m, 4H), 7.47 – 7.35 (m, 6H), 6.17 (dd, J 17.8, 11.0 Hz, 1H), 5.35
Cyanohydrins 26a,b:

(±)-(2R,4R)-2,4-dihydroxy-3,3-dimethyl-7-phenylheptanenitrile (S21a):

To a solution of cyanohydrin 26a (75 mg, 0.21 mmol, 1.0 equiv.) in dry THF (2 mL, 0.1 M) at 0 °C, HF-pyridine (0.42 mL, 2.0 mL/mmol) was added. The solution was warmed to room temperature and stirred overnight. An aqueous solution of NaHCO₃ was added and the aqueous layer extracted with Et₂O (3x). The organic layers were combined, dried with MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography using 35:65 EtOAc:Hex provided S21a as a clear oil (36 mg, 70 % yield): Rf = 0.19 (35:65 EtOAc:Hex); Molecular Formula: C₁₅H₂₁NO₂; MW: 247.34; IR (neat) νmax 3442, 2243 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.16 (m, 3H), 4.48 (d, J 3.2 Hz, 1H), 3.96 (s, 1H), 3.60 (ddd, J 10.6, 5.0, 1.8 Hz, 1H), 2.74 – 2.59 (m, 2H), 2.18 (s, 1H), 1.93 – 1.80 (m, 1H), 1.73 – 1.57 (m, 2H), 1.54 – 1.40 (m, 1H), 1.07 (s, 3H), 0.99 (s, 3H) ppm; ¹³C NMR (100.6 MHz, CDCl₃) δ 142.0, 128.6, 128.5, 126.1, 119.0, 78.3, 70.5, 41.7, 35.7, 31.4, 28.3, 21.6, 16.0 ppm; HRMS calcld for C₁₅H₂₂O₂N [M⁺H⁺]: 248.1645, found 248.1655 (+3.9 ppm).

(±)-(2S,4R)-2,4-dihydroxy-3,3-dimethyl-7-phenylheptanenitrile (S21b):

To a solution of cyanohydrin 26b (29 mg, 0.079 mmol, 1.0 equiv.) in dry THF (0.8 mL, 0.1 M) at 0 °C, HF-pyridine (0.16 mL, 2.0 mL/mmol) was added. The solution was warmed to room temperature and stirred overnight. An aqueous solution of NaHCO₃ was added and the aqueous layer extracted with Et₂O (3x). The organic layers were combined, dried with MgSO₄, filtered and concentrated in vacuo. Purification by flash chromatography using 35:65 EtOAc:Hex provided S21b as a clear oil (14 mg, 70 % yield): Rf = 0.19 (35:65 EtOAc:Hex); Molecular Formula: C₁₅H₂₁NO₂; MW: 247.34; IR (neat) νmax 3442, 2243 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.30 (t, J 7.5 Hz, 2H), 7.23 – 7.15 (m, 3H), 4.53 (d, J 8.7 Hz, 1H), 4.25 (d, J 8.6 Hz, 1H), 3.93 (ddd, J 10.6, 4.5, 1.9 Hz, 1H), 2.75 – 2.60 (m, 2H), 2.15 (s, 1H), 1.92 – 1.82 (m, 1H), 1.73 – 1.61 (m, 1H), 1.60 – 1.52 (m, 1H), 1.50 – 1.39 (m, 1H), 1.04 (s, 3H), 1.00 (s, 3H) ppm; ¹³C NMR (100.6 MHz, CDCl₃) δ 141.8, 128.6, 128.5, 126.2, 119.3, 77.7, 71.9, 40.9, 35.7, 31.3, 28.0, 22.1, 17.8 ppm; HRMS calcld for C₁₅H₂₂O₂N [M⁺H⁺]: 248.1645, found 248.1650 (+2.0 ppm).
(±)-(4R,6R)-2,2,5,5-tetramethyl-6-(3-phenylpropyl)-1,3-dioxane-4-carbonitrile (S22a):

![Diagram]

To a solution of diol S21a (18.7 mg, 0.076 mmol, 1.0 equiv.) in dry CH2Cl2 (0.8 mL, 0.1 M) at 0 °C, 2-methoxypropene (30 µL, 0.30 mmol, 4.0 equiv.) and camphor sulfonic acid (4 mg, 0.02 mmol, 0.2 equiv.) were added. The solution was stirred for 15 minutes at 0 °C then warmed to room temperature for 45 minutes. An aqueous solution of NH4Cl was added and the aqueous layer was extracted with Et2O (3x). The organic layers were combined, dried with MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography using 10:90 EtOAc:Hex provided acetonide S22a as a clear oil (22.1 mg, quantitative yield):

Rf = 0.38 (10:90 EtOAc:Hex); Molecular Formula: C18H25NO2; MW: 287.40; IR (neat) $\nu_{\text{max}}$ 2250 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.32–7.27 (m, 2H), 7.22–7.15 (m, 3H), 4.41 (s, 1H), 3.47 (dd, $J$ 9.6, 2.0 Hz, 1H), 2.66–2.55 (m, 2H), 1.89–1.80 (m, 1H), 1.60–1.45 (m, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.14 (s, 3H), 0.91 (s, 3H) ppm; $^{13}$C NMR (100.6 MHz, CDCl3) $\delta$ 142.4, 128.5, one aromatic carbon missing, 126.0, 116.5, 100.4, 77.0, 70.9, 36.1, 35.9, 29.7, 28.9, 28.3, 21.1, 18.8, 14.7 ppm; HRMS calcd for C18H26O2N [M+H$^+$]: 288.1958, found 288.1962 (+1.3 ppm).

(±)-(4S,6R)-2,2,5,5-tetramethyl-6-(3-phenylpropyl)-1,3-dioxane-4-carbonitrile (S22b):

![Diagram]

To a solution of diol S21b (14 mg, 0.055 mmol, 1.0 equiv.) in dry CH2Cl2 (0.6 mL, 0.1 M) at 0 °C, 2-methoxypropene (21 µL, 0.22 mmol, 4.0 equiv.) and camphor sulfonic acid (3.0 mg, 0.011 mmol, 0.2 equiv.) were added. The solution was stirred for 15 minutes at 0 °C then warmed to room temperature for 45 minutes. An aqueous solution of NH4Cl was added and the aqueous layer was extracted with Et2O (3x). The organic layers were combined, dried with MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography using 10:90 EtOAc:Hex provided acetonide S22b as a clear oil (15.8 mg, quantitative yield):

Rf = 0.5 (10:90 EtOAc:Hex); Molecular Formula: C18H25NO2; MW: 287.40; IR (neat) $\nu_{\text{max}}$ 3061, 2991, 2943, 2866, 2991 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl3) $\delta$ 7.29 (t, $J$ 7.6 Hz, 2H), 7.22–7.16 (m, 3H), 4.27 (s, 1H), 3.75 (dd, $J$ 9.9, 2.5 Hz, 1H), 2.64 (t, $J$ 7.9 Hz, 2H), 1.92–1.81 (m, 1H), 1.65–1.60 (m, 1H), 1.58 (s, 3H), 1.51–1.42 (m, 2H), 1.40 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H) ppm; $^{13}$C NMR (100.6 MHz, CDCl3) $\delta$ 142.3, 128.5, 128.5, 126.0, 118.4, 101.8, 74.2, 70.3, 36.4, 35.9, 28.6, 28.4, 28.2, 22.2, 21.9, 19.2 ppm; HRMS calcd for C18H26O2N [M+H$^+$]: 288.1958, found 288.1959 (+0.4 ppm).

Cyanohydrins 28a,b:

(±)-(2R, 4S)- 5-(benzyloxy)-2,4-dihydroxy-3,3-dimethylpentanenitrile (S23a) and (±)-(2S, 4S)- 5-(benzyloxy)-2,4-dihydroxy-3,3-dimethylpentanenitrile (S23b):

![Diagram]
To a solution of cyanohydrin 28a,b (3:1 syn:anti) (54 mg, 0.15 mmol, 1.0 equiv. prepared following General Procedure C with BF3·OEt2) in dry THF (1.5 mL, 0.1 M) at 0 °C, HF-pyridine (0.30 mL, 0.29 mmol, 2.0 mL/mmoll) was added. The solution was warmed to room temperature and stirred overnight. An aqueous solution of NaHCO3 was added and the aqueous layer extracted with Et2O (3x). The organic layers were combined, dried with MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography using 40:60 EtOAc:Hex provided S23a and S23b as clear oils (23.1 mg, 63 % yield). S23a: Rf = 0.32 (40:60 EtOAc:Hex); Molecular Formula: C14H19NO3; MW: 249.31; IR (neat) wmax 3440, 2244 cm–1; 1H NMR (500 MHz, CDCl3) δ 7.42 – 7.29 (m, 5H), 4.58 (s, 2H), 4.50 (d, J 4.2 Hz, 1H), 4.22 (d, J 4.3 Hz, 1H), 3.82 (dt, J 7.8, 3.1 Hz, 1H), 3.64 (dd, J 9.5, 3.4 Hz, 1H), 3.58 (dd, J 9.5, 7.9 Hz, 1H), 2.87 (d, J 2.8 Hz, 1H), 1.11 (s, 3H), 1.07 (s, 3H) ppm; 13C NMR (100.6 MHz, CDCl3) δ 137.1, 128.8, 128.4, 128.0, 118.7, 76.6, 73.9, 70.3, 70.1, 40.6, 22.0, 17.3 ppm; HRMS calcd for C14H20O3N [M+H]+: 250.1438, found 250.1439 (+0.8 ppm).

(±)-(4R, 6S)- 6-(benzyloxymethyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carbonitrile (S24a) and (4S, 6S)- 6-(benzyloxymethyl)-2,2,5,5-tetramethyl-1,3-dioxane-4-carbonitrile (S24b):

To a solution of diol S23a,b (23 mg, 0.093 mmol, 1.0 equiv.) in dry CH2Cl2 (1.1 mL, 0.10 M) at 0 °C, 2-methoxypropene (41 µL, 0.43 mmol, 4.0 equiv.) and camphor sulfonic acid (5.0 mg, 0.021 mmol, 0.2 equiv.) were added. The solution was stirred for 15 minutes at 0 °C then warmed to room temperature for 45 minutes. An aqueous solution of NH4Cl was added and the aqueous layer was extracted with Et2O (3x). The organic layers were combined, dried with MgSO4, filtered and concentrated in vacuo. Purification by flash chromatography using 10:90 EtOAc:Hex provided acetonide S24a (16.6 mg) and S24b (8.7 mg) as a clear oils in 94% overall yield (25.3 mg). S24a: Rf = 0.11 (10:90 EtOAc:Hex); Molecular Formula: C17H22NO3; MW: 289.38; IR (neat) wmax 2251 cm–1; 1H NMR (500 MHz, CDCl3) δ 7.39 – 7.27 (m, 5H), 4.60 (d, J 12.1 Hz, 1H), 4.49 (d, J 12.1 Hz, 1H), 4.46 (s, 1H), 3.81 (dd, J 6.6, 3.3 Hz, 1H), 3.59 (dd, J 10.6, 3.3 Hz, 1H), 3.42 (dd, J 10.6, 6.6 Hz, 1H), 1.47 (s, 3H), 1.47 (s, 3H), 1.13 (s, 3H), 1.00 (s, 3H) ppm; 13C NMR (100.6 MHz, CDCl3) δ 138.0, 128.6, 127.9, 127.8, 116.2, 100.5, 76.6, 73.7, 70.7, 69.9, 35.1, 29.5, 21.1, 18.8, 15.0 ppm; HRMS calcd for C17H23O3NNa [M+Na]+: 312.1570, found 312.1573 (+0.8 ppm).
Part II. X-ray information for acetonide S20a

Single crystals of $\text{C}_{27}\text{H}_{35}\text{NO}_3\text{Si}$ were prepared from a mixture of ethyl acetate and hexanes. A suitable crystal was selected and mounted on a diffractometer. The crystal was kept at 150 K during data collection. A mixture of enantiomers were crystallized with both enantiomers observed in the cell matrix. All non-H atoms were refined by full-matrix least-squares with anisotropic displacement parameters. The H atoms were generated geometrically ($\text{C}-\text{H} \ 0.95$ to $1.00\,\text{Å}$) and were included in the refinement in the riding model approximation; their temperature factors were set to 1.5 times those of the equivalent isotropic temperature factors of the parent site (methyl) and 1.2 times for others. A final verification of possible voids was performed using the VOID routine of the PLATON program (Spek, 2000). Data collection: APEX2 (Bruker, 2004). Cell refinement: APEX2 (Bruker, 2004). Data reduction: SAINT (Bruker, 2004). Program(s) used to solve structure: SHELXS97 (Sheldrick, 1997). Program(s) used to refine structure: SHELXL97 (Sheldrick, 1997). Molecular graphics: SHELXTL (Bruker, 1997). Software used to prepare material for publication: UdMX (local program).

<table>
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<td>$b = 8.5601(3),\text{Å}$, $b = 93.899(2)^\circ$</td>
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<td></td>
<td>$c = 22.4586(8),\text{Å}$, $g = 90^\circ$</td>
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<tr>
<td>Z</td>
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<td>Density (calculated)</td>
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<td>Full-matrix least-squares on $F^2$</td>
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<td>Goodness-of-fit on $F^2$</td>
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<td>Final R indices [$I&gt;2\sigma(I)$]</td>
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<tr>
<td>R indices (all data)</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.365 and -0.629 e/Å$^3$</td>
</tr>
</tbody>
</table>

Bruker (2004). APEX2 Release 1.1.2.2; Bruker Molecular Analysis Research Tool, Bruker AXS Inc., Madison, USA.
Part III. Computational Data

Density functional theory (DFT) calculations were performed in Gaussian 09 (D.01) with tight SCF convergence. The different possible -OiPr and -Cl ligand coordination positions were examined, the complex with the lowest energy is presented below. The energy reported is from the fully optimized structure at the M062XII/6-31G* level of theory in DCM using the polarizable continuum model (PCM).

# of imaginary frequency (vi): none
Energy (E, Ha): \(-5156.489258\)
Energy + zero-point energy (E + ZPE, Ha) at 273.15 K: \(-5155.989905\)
Energy + thermal free energies (G, Ha) at 273.15 K: \(-5156.052957\)

Symbol XYZ
O 0.21977300 -0.43997600 0.21725600
C 0.78371600 -1.36857100 0.66695800
C 1.37435100 -2.18340300 -0.50536200
C 0.26941700 -2.97981000 -1.15186900
O -0.92403200 -2.83035600 -0.94640900
Ti -2.23246100 -1.22018900 -0.15527700
Ti 0.22009200 1.43318800 -0.01177400
O 2.10685400 0.56809200 0.68333700
C 1.79474700 -0.58301200 1.47180500
C 2.05386300 -1.34917700 -1.57373800
C 2.38574600 -3.21989700 0.03364200
C 1.49635400 -0.96465600 -2.72021900
Cl -2.00759400 -0.44481800 -2.34877100


| Cl | 1.54324700 | 2.49125000 | -1.52900200 |
| C | 3.27145700 | 1.29689400 | 1.14963100 |
| C | 5.21968000 | 0.55339100 | 0.77133900 |
| C | 6.08340100 | -0.14249600 | -0.94079100 |
| C | 7.73482200 | -0.90853500 | -0.00019800 |
| H | 0.58429600 | -3.76763900 | -1.85253900 |
| H | 1.35445700 | 1.90039200 | 1.3466100 |
| H | 3.27145700 | 2.26973700 | 0.66016100 |
| H | 4.41785000 | 2.36696000 | 0.55339100 |
| C | 5.21968000 | 0.55339100 | 0.77133900 |
| C | 6.08340100 | -0.14249600 | -0.94079100 |
| C | 7.73482200 | -0.90853500 | -0.00019800 |
| H | 0.58429600 | -3.76763900 | -1.85253900 |
| H | 1.35445700 | 1.90039200 | 1.3466100 |
| H | 3.27145700 | 2.26973700 | 0.66016100 |
H -3.80200500 1.68321100 3.35459700
H -2.83871100 0.19531800 3.17771700
H -2.29448000 1.70586800 2.41054100
Cl -4.00732200 -2.54835800 -0.73864300
Part IV. $^1$H and $^{13}$C spectra
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

OTBS

OBn

OBz

15

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

OTBS

O

OBn

Me

Residual CDCl$_3$

f1 (ppm)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

TBSO OH
O\(\text{Me}\)
OBn

Residual CDCl$_3$
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$

![NMR Spectrum](image-url)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^{1}$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
\[^{13}\text{C}-\text{NMR (126 MHz, CDCl}_3\text{)}\]

\[
\begin{align*}
\text{OBn} & \\
\text{O} & \\
\text{Me} & \\
\text{S4} & \\
\end{align*}
\]
$^1$H-NMR (500 MHz, CDCl$_3$)
\(^{13}\)C-NMR (126 MHz, CDCl\(_3\))

![Chemical structure diagram]
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

![Chemical structure diagram](Image)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl₃)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

OPMB

OBn

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

![NMR spectrum image]
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)

![Chemical Structure](image-url)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
\(^1\)H-NMR (500 MHz, CDCl\(_3\))
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$

OTBS

TBDPSO

CO$_2$Me

Me

S7
$^{13}$C-NMR (126 MHz, CDCl$_3$)

OTBS
TBDPSO

CO$_2$Me

Me

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (126 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (126 MHz, CDCl$_3$)

![Screenshot of a 13C-NMR spectrum showing a spectrum with peaks labeled.]
$^1$H-NMR (500 MHz, CDCl$_3$)
\[ ^{13}\text{C-NMR (126 MHz, CDCl}_3 \text{)} \]

- TBSO
- TBDPSO
- OH
- CN
- 24a
- Me

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl₃)
$^1$H-NMR (500 MHz, CDCl$_3$)
\(^{13}\text{C}-\text{NMR (100.6 MHz, CDCl}_3\text{)}}$

\[\text{S10}\]

OTBS

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{CO}_2\text{Me} & \quad \text{OC}_2\text{Me}
\end{align*}
\]
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)

![Chemical Structure](image)
\( ^1\text{H-NMR} \ (500\ \text{MHz, CDCl}_3) \)

![Chemical structure](image)

Residual CDCl\(_3\)
\(^{13}\)C-NMR (100.6 MHz, CDCl\(_3\))
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

OTBS
BnO
CO$_2$Me
S13
Me
Me

Residual CDCl$_3$
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)

![Chemical Structure Image]
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$

[Chemical structure image]

Page S94
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)

![Chemical Structure](image)

28a
$^1$H-NMR (500 MHz, CDCl$_3$)

![NMR spectrum](image)

TBSO OH
BnO Me Me

28b
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
\(^{13}\)C-NMR (126 MHz, CDCl\(_3\))

Residual CDCl\(_3\)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (126 MHz, CDCl$_3$)

![C-NMR spectrum](image-url)
$^1$H-NMR (500 MHz, CDCl$_3$)
\(^{13}\)C-NMR (126 MHz, CDCl\(_3\))

\[\text{Residual CDCl}_3\]
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CD$_3$OD)
$^{13}$C-NMR (126 MHz, CD$_3$OD)

Residual CD$_3$OD
$^1$H-NMR (500 MHz, CD$_3$OD)
$^{13}$C-NMR (126 MHz, CD$_3$OD)

![Chemical structure](image)
$^{1}$H-NMR (500 MHz, CD$_3$OD)
13C-NMR (126 MHz, CD$_3$OD)

Residual CD$_3$OD

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

![NMR Spectrum](image_url)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (126 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)

Residual CDCl$_3$
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
\[^{13}\text{C}-\text{NMR} (100.6\ \text{MHz, CDCl}_3)\]

TBDPSO

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{CN} & \quad \text{Me}
\end{align*}
\]

S20a
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

\begin{center}
\includegraphics[width=\textwidth]{chemical_structure}
\end{center}
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)

![NMR Spectrogram]

S23a

Residual CDCl$_3$
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)

![Chemical Structure](image)

Residual CDCl$_3$
^1H-NMR (500 MHz, CDCl₃)
$^{13}$C-NMR (100.6 MHz, CDCl$_3$)

Residual CDCl$_3$
$^1$H-NMR (500 MHz, CDCl$_3$)
$^{13}$C-NMR (126 MHz, CDCl$_3$)
REFERENCES


   http://dx.doi.org/10.1039/c5ra19080k.