Supporting Material

Overcoming the Inherent Alkylation Selectivity of 2–3-trans-3–4-cis-Trisubstituted Cyclopentanones

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1. Synthetic Procedures

1.1 Abbreviations

DCM = dichloromethane
DMF = N,N-dimethylformamide
DMSO = dimethylsulfoxide
EtOAc = ethyl acetate
MeOH = methanol
Quant. = quantitative conversion
PPTS = pyridinium para-toluenesulfonate
TEA = triethylamine
THF = tetrahydrofuran
y = yield

1.2 General Procedures

Column chromatography was performed with 60 Å 40–63 μm silica-P flash silica gel. Solvents for reactions (DMF, DCM, ether, THF, and toluene) were dried using a LC Technology Solutions purification system. Other solvents were used as received unless noted otherwise. Chemicals were purchased from Fisher, VWR, or Sigma–Aldrich and used as received unless noted otherwise.

NMR Spectra were measured in CDCl₃ at ambient temperature unless otherwise noted. ¹H NMR spectra were recorded on either a 600 or 200 MHz Varian spectrometer. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane using the solvent as a reference (CDCl₃ = 7.26 ppm, DMSO-d₆ = 2.49 ppm, D₂O = 4.80 ppm, CD₃OD = 3.30). The following is an example data point: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sext = sextet, sept = septet, oct = octet, m = multiplet, br = broad, and combinations thereof], coupling constants [Hz], integration, assignment [if any]).

¹³C NMR spectra were recorded on a 600 or 200 MHz (150 or 50 MHz) Varian spectrometer with complete proton decoupling. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane using the solvent or MeOH as a reference (CDCl₃ = 77.0 ppm, DMSO-d₆ = 39.5 ppm, CD₃OD = 49.0 ppm, MeOH = 49.5).

IR spectra were recorded on a Perkin Elmer Spectrum 100 FT–IR spectrometer with Perkin Elmer Spectrum software. Spectra are partially reported (υₘₐₓ cm⁻¹).

HRMS were obtained at The University of Illinois Urbana–Champaign.

TLC was performed on 60 Å F₂₅₄ precoated silica gel plates. Samples were visualized by either ultraviolet irradiation, potassium permanganate staining, or cerium ammonium molybdenate staining.

Yield refers to isolated material.

Quantitative recovery means that mostly pure material was recovered in approximately the expected mass, and the material was used directly for the next step without purification.
1.3. Synthesis of Ketone 15

Scheme S1.  

Scheme S1 shows the synthetic strategy used to access ketone 15.

Synthesis of alcohol 10  Following previously reported procedures,\(^1\) alcohol 10 (colorless oil) was synthesized and purified via silica column chromatography as a 1:1 mixture of diastereomers on the THP protecting group.

Synthesis of ether 11  Into a flame dried flask was added sodium hydride (60% dispersion, 1.38 g, 34.6 mmol, 1.5 equiv). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere and cooled in an ice

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bath (0 °C). DMF (18 mL, 1.2 M) was added to the flask. Alcohol 10 (5.70 g, 22.4 mmol, 1 equiv) was dissolved in DMF (18 mL) and added dropwise to the reaction (over 25 min, evolving gas, final concentration = 0.6 M). The mixture was stirred (1 h) and para-methoxybenzyl chloride (3.64 mL, 26.9 mmol, 1.2 equiv) was added dropwise (over 10 min). The mixture was stirred (additional 2.5 h), quenched with potassium phosphate monobasic (1 M, 10 mL, producing pH = 5), diluted with water (80 mL), and extracted with hexane (3 x 50 mL). The combined organic phases were washed with water (2 x 40 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was passed through a short pad of silica gel (10 mL silica, 6:1 hexane/EtOAc) to yield crude ether 11 (quantitative mass recovery, colorless oil) as a 1:1 mixture of diasteromers at the THP group. The crude material was used directly in the next step. An enriched aliquot of ether 11 was used for analysis. 

1H NMR signals were assigned by 1H–1H COSY.

1H NMR (CDCl3, 600 MHz) \(\delta\) 7.23 (d, \(J = 8.5\) Hz, 2H, Ar), 6.86 (d, \(J = 8.5\) Hz, 2H, Ar), 4.80 (s, 0.5H, C=CH), 4.78 (s, 0.5H, C=CH), 4.69–4.67 (m, 0.5H, O–CH–O), 4.64 (s, 1H, C=CH), 4.59–4.57 (m, 0.5H, O–CH–O), 4.32 (d, \(J = 11.5\) Hz, 1H, Ar–CH2), 4.13 (t, \(J = 2.5\) Hz, 1H, Ar–CH2), 3.92–3.86 (m, 1H, CH2–O), 3.51–3.47 (m, 1H, CH2–O), 3.31 (m, 1H, CH2–OPMB), 3.19–3.14 (m, 1H, CH2–OPMB), 2.96 (q, \(J = 9.3\) Hz, 0.5H, C=C–CH), 2.90–2.86 (m, 0.5H, C=C–CH), 2.13–2.04 (m, 1H, CH–C–OPMB), 2.02–1.98 (m, 1H, CH–CH3), 1.77 (s, 1.5H, C=C–CH3), 1.76 (s, 1.5H, C=C–Me), 1.88–1.49 (m, 8H, 4 x CH2), 1.15 (d, \(J = 7.4\) Hz, 1.5H, CH3), 1.04 (d, \(J = 7.4\) Hz, 1.5H, CH3).

13C NMR (CDCl3, 600 MHz) \(\delta\) 158.90, 145.90, 145.77, 130.91, 128.96, 113.60, 109.89, 100.13, 94.82, 80.84, 76.39, 72.59, 71.85, 71.12, 62.72, 61.71, 55.24, 45.95, 45.82, 44.98, 44.90, 43.22, 37.33, 34.68, 31.13, 30.79, 25.65, 25.53, 23.91, 23.82, 19.89, 19.27, 14.93, 14.83.

IR (neat, cm\(^{-1}\)) 2927, 2852, 1645, 1513, 1454, 1247, 1113, 1001.

HRMS calculated for [C23H34O4Na]+, requires \(m/z = 397.2355\), found \(m/z = 397.2354\) (ESI).

TLC (5:1) hexane/EtOAc, UV or CAM, \(R_f = 0.50\).

1H NMR (CDCl3, 200 MHz) \(\delta\) 7.23 (d, \(J = 8.6\) Hz, 2H, Ar), 6.86 (d, \(J = 8.6\) Hz, 2H, Ar), 4.81 (s, 1H, C=CH), 4.65 (s, 1H, C=CH), 4.39 (d, \(J = 11.4\) Hz, 1H, CH2–Ar), 4.31 (d, \(J = 11.4\) Hz, 1H, CH2–Ar), 2.08 (quint, \(J = 7.8\) Hz, 1H, CH–C–OPMB), 2.00–1.67 (m, 3H, CH–Me, CH2–C–OH), 1.76 (s, 3H, C=C–CH3), 1.33 (d, \(J = 1.2\) Hz, 1H, OH), 1.09 (d, \(J = 6.9\) Hz, 3H, CH3).

13C NMR (CDCl3, 200 MHz) \(\delta\) 159.17, 145.80, 74.95, 72.87, 71.97, 55.49, 45.73, 45.16, 24.17, 14.63.

IR (neat, cm\(^{-1}\)) 3426, 2956, 2925, 2855, 3077, 1645, 1513, 1247, 1097.

HRMS calculated for [C18H26O3Na]+, requires \(m/z = 313.1780\), found \(m/z = 313.1776\) (ESI).

TLC (4:1) hexane/EtOAc, UV or CAM, \(R_f = 0.21\).

MP 54.5–56.0 °C.

Synthesis of alcohol 12  Into a flask were added crude ether 11 (22.4 mmol, 1 equiv), MeOH (130 mL, 0.2 M), and PPTS (3.30 g, 13.1 mmol, 0.58 equiv). The mixture was stirred (15 h), diluted with EtOAc (260 mL), washed with a mixture (1:1, 2 x 130 mL) of brine and sodium bicarbonate (saturated aqueous), washed with sodium chloride (50% saturated, 2 x 130 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (100 mL silica gel, 6:1 to 1:1 hexane/EtOAc) to yield alcohol 12 (5.51 g, 19.0 mmol, 85% from alcohol 10, white solid). 

1H NMR signals were assigned by 1H–1H COSY and by comparison to signals from the starting materials.

1H NMR (CDCl3, 200 MHz) \(\delta\) 7.23 (d, \(J = 8.6\) Hz, 2H, Ar), 6.86 (d, \(J = 8.6\) Hz, 2H, Ar), 4.81 (s, 1H, C=CH), 4.65 (s, 1H, C=CH), 4.39 (d, \(J = 11.4\) Hz, 1H, CH2–Ar), 4.31 (d, \(J = 11.4\) Hz, 1H, CH2–Ar), 2.08 (quint, \(J = 7.8\) Hz, 1H, CH–C–OPMB), 2.00–1.67 (m, 3H, CH–Me, CH2–C–OH), 1.76 (s, 3H, C=C–CH3), 1.33 (d, \(J = 1.2\) Hz, 1H, OH), 1.09 (d, \(J = 6.9\) Hz, 3H, CH3).

13C NMR (CDCl3, 200 MHz) \(\delta\) 159.17, 145.80, 131.07, 129.23, 113.86, 110.40, 74.95, 72.87, 71.97, 55.49, 45.73, 45.16, 24.17, 14.63.

IR (neat, cm\(^{-1}\)) 3426, 2956, 2925, 2855, 3077, 1645, 1513, 1247, 1097.

HRMS calculated for [C18H26O3Na]+, requires \(m/z = 313.1780\), found \(m/z = 313.1776\) (ESI).

TLC (4:1) hexane/EtOAc, UV or CAM, \(R_f = 0.21\).

MP 54.5–56.0 °C.
Synthesis of ketone 13  A flame dried flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an EtOAc / N₂ bath (-84 ºC). Into the flask were added oxalyl chloride (1.54 mL, 17.9 mmol, 2 equiv), DCM (45 mL, 0.4 M), and DMSO (2.54 mL, 35.8 mmol, 4 equiv). The mixture was stirred (25 min). Alcohol (2.57 g, 8.95 mmol, 1 equiv) was dissolved in DCM (22 mL, 0.4 M) and added. The mixture was stirred (25 min) and TEA (6.81 mL, 49.2 mmol, 5.5 equiv) was added dropwise (over 10 min). The mixture was stirred (5 min), transferred into an ice bath (0 ºC), stirred (1.5 h), quenched with sodium bicarbonate (saturated aqueous, 60 mL), and extracted with ether (3 x 50 mL). The combined organic phases were washed with brine (60 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was passed through a short plug of silica (15 mL silica, 4:1 hexane/EtOAc) to yield pure ketone (2.48 g, 8.61 mmol, 96% yield, yellow oil).  

\[ \delta \begin{align*} & \text{7.21 (d, } J = 8.6 \text{ Hz, } 2H, \text{ Ar}) \text{, 6.87 (d, } J = 8.6 \text{ Hz, } 2H, \text{ Ar}) \text{, 4.89 (s, } 1H, \text{ C}=\text{CH}) \text{, 4.74 (s, } 1H, \text{ C}=\text{CH}) \text{, 4.52–4.48 (brs, } 1H, \text{ TMSO }–\text{C}=\text{CH}) \text{, 4.34 (d, } J = 11.7 \text{ Hz, } 1H, \text{ CH}_2–\text{OPMB}) \text{, 3.80 (s, } 3H, \text{ O–CH}_3) \text{, 3.40–3.28 (m, } 3H, \text{ CH}_2–\text{OPMB, CH–C}=\text{C}) \text{, 2.36 (pent, } J = 6.8 \text{ Hz, } 1H, \text{ CH–Me}) \text{, 2.21 (pent, } J = 7.2 \text{ Hz, } 1H, \text{ CH–C}=\text{OPMB}) \text{, 1.68 (s, } 3H, \text{ C}=\text{C–CH}_3) \text{, 1.08 (d, } J = 6.8 \text{ Hz, } 3H, \text{ CH}_3) \text{, 0.22 (s, } 9H, \text{ TMS).} \end{align*} \]

Synthesis of silyl enol ether 19  Sodium iodide was dried in a vacuum oven (100 ºC, 50 mBar, 12 h). Acetonitrile was distilled from calcium hydride and stored over activated 3Å molecular sieves. Into a flame-dried flask were added ketone (552 mg, 1.91 mmol, 1 equiv), sodium iodide (582 mg, 3.88 mmol, 2.0 equiv), and toluene (5 mL). The toluene was removed under reduced pressure to remove any remaining moisture. The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 ºC). Into the flask were added acetonitrile (6.5 mL, 0.3 M) and TEA (1.22 mL, 8.73 mmol, 4.6 equiv). Chlorotrimethylsilane (0.74 mL, 5.82 mmol, 3.0 equiv) was added dropwise (over 5 min). The mixture was stirred (3 h), diluted with EtOAc (13 mL), quenched with sodium bicarbonate (saturated aqueous, 7 mL), diluted with brine (7 mL), and extracted with EtOAc (2 x 10 mL). The combined organic phases were washed with a mixture (1:1, 20 mL) of brine and potassium phosphate monobasic (1 M aqueous) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and crude silyl enol ether (643 mg, 1.80 mmol, 93% crude yield, brown oil) was used directly in the next step. A single isomer was observed by NMR. Some analytical data was not obtained for silyl enol ether 19 due to its moderate instability.  

\[ \delta \begin{align*} & \text{7.24 (d, } J = 8.6 \text{ Hz, } 2H, \text{ Ar}) \text{, 6.86 (d, } J = 8.6 \text{ Hz, } 2H, \text{ Ar}) \text{, 4.79 (s, } 1H, \text{ C}=\text{CH}) \text{, 4.74 (s, } 1H, \text{ C}=\text{CH}) \text{, 4.52–4.48 (brs, } 1H, \text{ TMSO }–\text{C}=\text{CH}) \text{, 4.42 (d, } J = 11.7 \text{ Hz, } 1H, \text{ CH}_2–\text{Ar}) \text{, 4.34 (d, } J = 11.7 \text{ Hz, } 1H, \text{ CH}_2–\text{Ar}) \text{, 3.80 (s, } 3H, \text{ O–CH}_3) \text{, 3.40–3.28 (m, } 3H, \text{ CH}_2–\text{OPMB, CH–C}=\text{C}) \text{, 2.36 (pent, } J = 6.8 \text{ Hz, } 1H, \text{ CH–Me}) \text{, 2.21 (pent, } J = 7.2 \text{ Hz, } 1H, \text{ CH–C}=\text{OPMB}) \text{, 1.68 (s, } 3H, \text{ C}=\text{C–CH}_3) \text{, 1.08 (d, } J = 6.8 \text{ Hz, } 3H, \text{ CH}_3) \text{, 0.22 (s, } 9H, \text{ TMS).} \end{align*} \]
**13C NMR** (CDCl₃, 200 MHz) δ 159.13, 158.56, 145.73, 130.96, 129.30, 113.80, 111.74, 104.07, 72.84, 72.31, 55.38, 49.04, 47.49, 42.89, 22.52, 17.81, 0.19.

**IR** (neat, cm⁻¹) 3078, 2961, 2917, 2851, 1644, 1513, 1250, 1091, 1040.

**TLC** (8:1) Hexane/EtOAc, UV/CAM, Rₓ = 0.54.

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**Synthesis of α-hydroxy ketone 23**

Into a flame-dried flask were added crude silyl enol ether 19 (643 mg, 1.80 mmol, 1 equiv), THF (9 mL, 0.2 M), and 2-methyl 2-butene (2 M in THF, 0.8 mL, 1.6 mmol, 0.9 equiv, to quench excess peracid). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 °C). *meta*-Chloroperoxybenzoic acid (519 mg, 2.32 mmol, 1.3 equiv) was added, and the mixture was stirred (1.5 h). Hydrochloric acid (0.5 M aqueous, 8 mL) was added. The mixture was stirred (20 min), extracted with EtOAc (9 mL), washed with sodium carbonate (10% aqueous, 10 mL) and brine (8 mL), and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (15 mL silica gel, [4:1] hexane/EtOAc) to yield α-hydroxy ketone 23 (417 mg, 1.38 mmol, 73% from ketone 13, pale yellow oil). 1H NMR signals were assigned by 1H–1H COSY. Stereochemistry of the alcohol was determined after the subsequent step.

**13C NMR** (CDCl₃, 200 MHz) δ 219.68, 159.27, 140.96, 130.21, 129.23, 113.88, 112.20, 75.42, 73.09, 69.85, 55.39, 50.13, 42.16, 42.06, 22.31, 16.78.

**IR** (neat, cm⁻¹) 3434, 2964, 2917, 2856, 1747, 1612, 1514, 1248, 1097, 1035.

**HRMS** calculated for [C₁₈H₂₄O₄Na]⁺, requires m/z = 327.1572, found m/z = 327.1575 (ESI).

**TLC** (4:1) EtOAc/hexane, UV/CAM, Rₓ = 0.24.

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**Synthesis of MOM ether 24**

Into a flame-dried flask were added α-hydroxy ketone 23 (560 mg, 1.86 mmol, 1 equiv), DCM (4 mL, 0.5 M), and diisopropylethylamine (1.45 mL, 8.37 mmol, 4.5 equiv). The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 °C). Chloromethyl methyl ether (0.42 mL, 5.58 mmol, 3 equiv) was added, the reaction was stirred (10 h, gradually returning to ambient temperature), and additional chloromethyl methy ether (0.14 mL, 1.86 mmol, 1 equiv) was added. The reaction was stirred (additional 5 h), quenched with ammonium chloride (50% saturated, 10 mL), stirred (10 min), and extracted with DCM (2 x 10 mL). The combined organic phases were washed with a mixture (1:1, 15 mL) of potassium phosphate monobasic (1 M aqueous) and brine and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified via column chromatography (25 mL silica gel, 5:1 hexane/EtOAc) to yield ketone 24 (615 mg, 1.76 mmol, 95%, pale yellow oil). 1H NMR signals were assigned by 1H–1H COSY and by comparison to signals from the starting materials. Stereochemistry was determined by 1H–1H NOESY.

**13C NMR** (CDCl₃, 200 MHz) δ 219.68, 159.27, 140.96, 130.21, 129.23, 113.88, 112.20, 75.42, 73.09, 69.85, 55.39, 50.13, 42.16, 42.06, 22.31, 16.78.

**IR** (neat, cm⁻¹) 3434, 2964, 2917, 2856, 1747, 1612, 1514, 1248, 1097, 1035.

**HRMS** calculated for [C₁₈H₂₄O₄Na]⁺, requires m/z = 327.1572, found m/z = 327.1575 (ESI).

**TLC** (4:1) EtOAc/hexane, UV/CAM, Rₓ = 0.24.
2.46 (q, J = 7.8 Hz, 1H, CH–Me), 2.21–2.10 (m, 1H, CH–C–OPMB), 1.80 (s, 3H, C=C–CH 3), 1.20 (d, J = 7.5 Hz, 3H, CH3).

13C NMR (CDCl 3, 200 MHz) δ 218.81, 159.25, 141.24, 130.23, 129.22, 113.71, 111.87, 96.11, 78.16, 73.05, 69.91, 56.15, 55.40, 48.53, 43.53, 42.16, 22.77, 17.12.

IR (neat, cm-1) 2962, 2930, 1749, 1514, 1248, 1097, 1035.

HRMS calculated for [C20H28O5Na]+, requires m/z = 371.1834, found m/z = 371.1829 (ESI).

TLC (4:1 hexane/EtOAc, UV/CAM, Rf = 0.47.

Synthesis of ketone 25 
Into a flame-dried flask were added ketone 24 (63 mg, 0.181 mmol, 1 equiv), geranyl chloride (14, 78 mg, 0.453 mmol, 2.5 equiv), and toluene (5 mL). Volatiles were removed under reduced pressure to remove any traces of water. The flask was fitted with a condensing column, capped with a rubber septum, and maintained under a nitrogen atmosphere. THF (0.10 mL, 2 M) was added, and the mixture was warmed to 30 ºC in a water bath. Sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.27 mL, 0.27 mmol, 1.5 equiv) was added dropwise (over 1.5 h). The mixture was stirred (additional 1 h), quenched with potassium phosphate monobasic (1 M aqueous, 5 mL, producing pH = 5), and extracted with EtOAc (3 x 5 mL). The combined organic phases were washed with brine (8 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure and the crude material was purified via column chromatography (18 mL silica gel, 6:1 hexane/EtOAc) to yield ketone 25 (48 mg, 0.102 mmol, 56% yield, colorless oil) as a mixture of epimers at the CH–OMOM stereocenter (8:1 25A / 25B). An aliquot of each epimer was isolated by column chromatography. 1H NMR signals were assigned by 1H–1H COSY. Stereochemistry of each epimer was assigned by 1H–1H NOESY. No other stereoisomers, constitutional isomers, or double-alkylation products were observed by NMR.

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1H NMR (CDCl 3, 600 MHz) δ 7.12 (d, J = 8.0 Hz, 2H, Ar), 6.83 (d, J = 8.0 Hz, 2H, Ar), 5.11 (t, J = 7.9 Hz, 1H, C=CH), 5.05–5.03 (m, 4H, C=CH, C=CH 2, O–CH 2–O), 4.69 (d J = 6.7 Hz, 1H, O–CH 2–O), 4.62 (d, J = 11.0 Hz, 1H, CH–OMOM), 4.30 (d, J = 11.7 Hz, 1H, CH=Ar), 4.19 (d, J = 11.7 Hz, 1H, CH=Ar), 3.79 (s, 3H, Ar–O–CH 3) 3.37 (s, 3H, O–CH 3) 3.28–3.24 (m, 2H, CH 2–OPMB), 2.94 (dd, J 1 = 10.8 Hz, J 2 = 7.4 Hz, 1H, CH–C–CH), 2.34 (dd, J 1 = 14.4 Hz, J 2 = 9.0 Hz, 1H, C=C–CH2), 2.14 (dt, J 1 = 7.3 Hz, J 2 = 2.1 Hz, 1H, CH–C–OPMB), 2.10–2.02 (m, 5H, CH 2–CH 2–CH 2–Me), 1.94 (dd, J 1 = 14.4 Hz, J 2 = 6.2 Hz, 1H, C=C–CH3), 1.79 (s, 3H, C=C–CH3), 1.65 (s, 3H, C=C–CH3), 1.62 (s, 3H, C=C–CH3), 1.59 (s, 3H, C=C–CH3), 1.09 (s, 3H, CH3).

13C NMR (CDCl 3, 200 MHz) δ 219.77, 159.15, 141.53, 139.29, 131.64, 130.06, 129.22, 124.22, 118.78, 113.74, 111.54, 96.15, 73.00, 67.13, 55.92, 55.39, 51.04, 49.38, 42.31, 40.16, 35.62, 26.60, 25.60, 22.95, 17.86, 16.77, 16.37.

IR (neat, cm-1) 3085, 2965, 2916, 2856, 1744, 1651, 1612, 1514, 1451, 1249, 1100, 1028.

HRMS calculated for [C30H45O5H]+, requires m/z = 485.3267, found m/z = 485.3263 (ESI).

TLC (8:1 EtOAc/hexane, permanganate, Rf = 0.36.
**Synthesis of ketone 15**

Methanol was distilled over sodium sulfate prior to use. Reaction flasks were washed in a base-bath (sodium hydroxide in 2-propanol) for 2 h and then dried in an oven overnight prior to use. Rubber septa were dried in a desiccator overnight prior to use.

Samarium diiodide generation: Samarium metal (510 mg, 3.23 mmol, 1.4 equiv, cut into small pieces) was placed in a flame-dried flask and dried under vacuum (5 min). The flask was capped with a rubber septum and maintained under an argon atmosphere. Into the flask were added THF (6.5 mL, 0.4 M) and CH₂I₂ (0.189 mL, 2.38 mmol, 1 equiv). The mixture was stirred (6 h, becoming dark blue and dissolving most of the metal solid).

3 Å Molecular sieves (0.5 g) were flame-dried in a flask. The flask was capped with a rubber septum and maintained under an argon atmosphere. To this flask were added THF (6 mL) and methanol (3 mL). This mixture was stirred (2 h, to remove any remaining water). Into a separate flame-dried flask were added ketone 25 (122 mg, 0.253 mmol, 1 equiv) and toluene (5 mL). Volatiles were removed under reduced pressure to remove any water. Into this flask was added the THF/methanol mixture (9 mL, 0.03 M). Oxygen was removed from this mixture by a freeze-pump-thaw procedure (freezing with liquid nitrogen and backfilling with argon, 3 times). The freshly prepared samarium diiodide solution (2.38 mmol, 9.4 equiv) was added via cannula (over 10 min, initially the blue color disappears instantly, but by the end of the addition process, the blue color remained in the reaction for a couple minutes before fading into a yellow color). The reaction was stirred (additional 15 min), quenched with ammonium chloride (saturated aqueous, 12 mL), and diluted with EtOAc (30 mL) and water (50 mL). Insoluble material was removed by filtration. The organic phase was isolated, the aqueous phase was further extracted with EtOAc (additional 2 x 30 mL), and the combined organic phases were washed with brine (50 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (10 mL silica gel, 10:1 hexane/EtOAc) to yield ketone 15 (85 mg, 0.202 mmol, 80% yield, colorless oil). ¹H NMR signals were assigned by ¹H–¹H COSY and by comparison to signals from the starting materials.

**¹H NMR (CDCl₃, 600 MHz) δ 7.72 (d, J = 8.2 Hz, 2H, Ar), 6.83 (d, J = 8.2 Hz, 2H, Ar), 5.13 (t, J = 7.7 Hz, 1H, C=CH), 5.06 (t, J = 6.6 Hz, 1H, C=CH), 4.95 (s, 1H, C=CH₂), 4.79 (s, 1H, C=CH₂), 4.26 (d, J = 11.5 Hz, 1H, CH₂=Ar), 4.21 (d, J = 11.5 Hz, 1H, CH₂=Ar), 3.79 (s, 3H, O–CH₃), 3.38–3.34 (m, 2H, CH₂–OPMB), 3.01 (dt, J₁ = 11.1 Hz, J₂ = 7.4 Hz, 1H, C=C=CH), 2.71 (dd, J₁ = 18.1 Hz, J₂ = 12.1 Hz, 1H, CH₃–C=O), 2.28–2.22 (m, 3H, CH–C=OPMB, O=C=CH₂, C=C=CH₂), 2.11–2.03 (m, 4H, CH₂–CH₂), 1.95 (dd, J₁ = 14.1 Hz, J₂ = 6.6 Hz, 1H, CH₂–C=), 1.78 (s, 3H, C=C=CH₃), 1.66 (s, 3H, C=C=CH₃), 1.62 (s, 3H, C=C=CH₃), 1.60 (s, 3H, C=C=CH₃), 1.11 (s, 3H, C=CH₃).

**¹³C NMR (CDCl₃, 200 MHz) δ 221.74, 159.14, 141.02, 138.94, 131.74, 130.55, 128.97, 124.33, 119.28, 113.82, 111.10, 73.09, 68.43, 55.49, 55.43, 53.31, 45.74, 42.46, 40.27, 35.54, 26.74, 25.96, 23.06, 17.96, 17.03, 16.60.

**IR** (neat, cm⁻¹) 3078, 2966, 2958, 1737, 1613, 1514, 1455, 1248, 1093, 1036.

**HRMS** calculated for [C₃₀H₄₄O₅Na⁺], requires m/z = 507.3100, found m/z = 507.3094 (ESI).

**TLC** (6:1) hexane/EtOAc, permanganate Rₚ = 0.30.
Unselective alkylation of ketone 13  Into a flame-dried flask were added ketone 13 (75 mg, 0.260 mmol, 1 equiv) and toluene (5 mL). Volatiles were removed under reduced pressure to remove any remaining water. The flask was capped with a rubber septum and maintained under a nitrogen atmosphere. THF (0.6 mL, 0.4 M) was added into the flask, and then sodium bis(trimethylsilyl)amide (1 M in THF, 0.29 mL, 0.29 mmol, 1.1 equiv) was added dropwise (10 mins). The reaction was stirred (30 min) and warmed to 40 °C in an oil bath. Geranyl chloride (14, 59 mg, 0.34 mmol, 1.3 equiv) was added, and the mixture was stirred (1 h), quenched with potassium phosphate monobasic (1 M, 5 mL, giving pH = 5), and extracted with ether (3 x 4 mL). The combined organic phases were washed with brine (5 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure and the mixture of products was separated from starting materials by column chromatography (25 mL silica gel, [8:1 to 6:1] hexane/EtOAc) to yield a mixture of ketone 15, 4 stereoisomers of ketone 16, and one stereoisomer of ketone 17 (total mass = 60 mg, approximately 0.14 mmol, approximately 55% yield, 15:16:17 = 37:53:10). The ratio of products was determined by integrating the 1H NMR signals from the α-methyl groups (doublets for product 16 and singlets for products 15 and 17).

<table>
<thead>
<tr>
<th>Product</th>
<th>CH$_3$-$^1$H NMR</th>
<th>relative integration</th>
<th>percent of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (desired mono-alkylation)</td>
<td>1.11 (s)</td>
<td>1</td>
<td>37%</td>
</tr>
<tr>
<td>16 (undesired regioisomer, first stereoisomer)</td>
<td>1.20 (d, $J=7.3$)</td>
<td>0.17</td>
<td>6%</td>
</tr>
<tr>
<td>16 (undesired regioisomer, second stereoisomer)</td>
<td>1.16 (d, $J=7.2$)</td>
<td>0.47</td>
<td>18%</td>
</tr>
<tr>
<td>16 (undesired regioisomer, third stereoisomer)</td>
<td>1.13 (d, $J=7.1$)</td>
<td>0.50</td>
<td>19%</td>
</tr>
<tr>
<td>16 (undesired regioisomer, fourth stereoisomer)</td>
<td>1.08 (d, $J=7.7$)</td>
<td>0.27</td>
<td>10%</td>
</tr>
<tr>
<td>17 (double alkylation)</td>
<td>1.10 (s)</td>
<td>0.28</td>
<td>10%</td>
</tr>
</tbody>
</table>

TLC (6:1) hexane/EtOAc, permanganate, $R_f = 0.48-0.61$. 

S9
1.4 Scope of the Alkylation Reaction

Synthesis of ketone 26  Into a flame dried flask were added ketone 24 (64 mg, 0.18 mmol, 1 equiv) and toluene (3 mL). Volatiles were removed under reduced pressure to remove any water. The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 °C). To the reaction were added THF (0.33 mL, 0.5 M) and benzyl bromide (43 μL, 0.36 mmol, 2.0 equiv). Using a syringe pump, sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.234 mL, 0.234 mmol, 1.3 equiv), was added drop-wise over 1.5 h. The reaction was stirred (additional 1 h), diluted with EtOAc (3 mL), and quenched with potassium phosphate monobasic (1 M aqueous, pH 5, 5 mL). The organic phase was isolated, the aqueous phase was extracted with additional EtOAc (2 x 3 mL), and the combined organic phases were washed with brine (4 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (15 mL silica gel, 5:1 hexane/EtOAc) to yield pure ketone 26 (46 mg, 0.11 mmol, 58% yield, colorless oil). 1H NMR signals were assigned by 1H–1H COSY and by comparison to signals from the starting materials. Stereochemistry was determined by 1H–1H NOESY. No other stereoisomers, constitutional isomers, or double-alkylation products were observed by NMR.

$$\delta$$ 7.29 (t, $J = 7.3$ Hz, 2H, Bn), 7.25 (t, $J = 7.3$ Hz, 1H, Bn), 7.13 (d, $J = 7.3$ Hz, 2H, Bn), 7.09 (d, $J = 8.4$ Hz, 2H, PMB), 6.82 (d, $J = 8.4$ Hz, 2H, PMB), 5.08 (d, $J = 6.8$ Hz, 1H, O–CH$_2$–O), 5.07 (s, 1H, C=CH), 5.05 (s, 1H, C=CH), 4.73 (d, $J = 6.8$ Hz, 1H, O–CH$_2$–O), 4.66 (d, $J = 10.7$ Hz, 1H, CH–OMOM), 4.28 (d, $J = 11.6$ Hz, 1H, MeOAr–CH$_2$), 4.15 (d, $J = 11.6$ Hz, 1H, MeOAr–CH$_2$), 3.78 (s, 3H, Ar–OCH$_3$), 3.40 (s, 3H, O–CH$_3$), 3.21 (d, $J = 9.6$ Hz, 1H, CH$_2$–OPMB), 3.11 (d, $J = 9.6$ Hz, 1H, CH$_2$–OPMB), 2.99 (dd, $J_1 = 10.7$ Hz, $J_2 = 7.5$ Hz, 1H, CH–C=CH), 2.89 (d, $J = 13.8$ Hz, 1H, Ph–CH$_2$), 2.58 (d, $J = 13.8$ Hz, 1H, Ph–CH$_2$), 2.18 (br d, $J = 7.5$ Hz, 1H, CH–C–OPM), 1.80 (s, 3H, C=C–CH$_3$), 1.11 (s, 3H, CH$_3$).

$^{13}$C NMR (CDCl$_3$, 200 MHz) $\delta$ 219.14, 159.18, 141.35, 136.85, 129.97, 129.16, 128.33, 126.97, 113.75, 111.60, 96.24, 73.00, 66.92, 55.94, 55.35, 51.24, 49.28, 42.95, 41.75, 41.75, 22.88, 17.45.

IR (neat, cm$^{-1}$) 2938, 1742, 1611, 1513, 1427, 1097, 1023;
HRMS calculated for [C$_{27}$H$_{34}$O$_5$H]+, requires m/z = 439.2484, found m/z = 439.2478 (ESI).

TLC (4:1) hexane/EtOAc, UV/permanganate, $R_f$ = 0.51.

Synthesis of ketone 27: Procedure 1: Into a flame dried flask were added ketone 24 (99 mg, 0.28 mmol, 1 equiv) and toluene (3 mL). Volatiles were removed under reduced pressure to remove any water. The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and cooled in an ice bath (0 °C). To the reaction were added THF (0.41 mL, 0.6 M) and iodomethane (35 μL, 0.57 mmol, 2 equiv). Using a syringe pump, sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.340 mL, 0.340 mmol, 1.2 equiv), was added drop-wise over 1.5 h. The reaction was stirred (additional 2 h), diluted with EtOAc (3 mL), and quenched with potassium phosphate monobasic (1 M aqueous, pH 5, 5 mL). The organic phase was isolated, the aqueous phase was extracted with additional EtOAc (2 x 3 mL), and the combined organic phases were washed with brine (4 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (22 mL silica gel, 6:1 hexane/EtOAc) to yield pure ketone 27 (32 mg, 0.088 mmol, 32% yield, colorless oil). 1H NMR signals were assigned by $^1$H–$^1$H COSY and by comparison to signals from the starting materials. Stereochemistry was determined by $^1$H–$^1$H NOESY. Trace amounts of products with alkylation at the MOMO-protected $\alpha$-position were observed by NMR of the crude material.
Procedure 2: Into a flame dried flask were added ketone 24 (127 mg, 0.364 mmol, 1 equiv) and toluene (3 mL). Volatiles were removed under reduced pressure to remove any water. The flask was capped with a rubber septum, maintained under a nitrogen atmosphere, and warmed in a water bath (30 °C). To the reaction were added THF (0.60 mL, 0.6 M) and iodomethane (45 μL, 0.73 mmol, 2 equiv). Using a syringe pump, sodium bis(trimethylsilyl)amide (1.0 M in THF, 0.546 mL, 0.546 mmol, 1.5 equiv), was added drop-wise over 1.5 h. The reaction was stirred (additional 2 h), diluted with EtOAc (3 mL), and quenched with potassium phosphate monobasic (1 M aqueous, pH 5, 5 mL). The organic phase was isolated, the aqueous phase was extracted with additional EtOAc (2 x 3 mL), and the combined organic phases were washed with brine (4 mL) and dried with sodium sulfate. Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (22 mL silica gel, 6:1 hexane/EtOAc) to yield pure ketone 27 (70 mg, 0.19 mmol, 54% yield, colorless oil). Measureable amounts of products with alkylation at the MOMO-protected α-position (17 mg, 13% yield) or with double alkylation (9 mg, 7% yield) were also isolated.

**1H NMR (CDCl₃, 600 MHz)** δ 7.12 (d, J = 8.6 Hz, 2H, Ar), 6.83 (d, J = 8.6 Hz, 2H, Ar), 5.05 (br s, 2H, C=CH₂), 5.02 (d, J = 6.6 Hz, 1H, O–CH₂–O), 4.68 (d, J = 6.6 Hz, 1H, O–CH₂–O), 4.60 (d, J = 11.0 Hz, 1H, CH–OMOM), 4.30 (d, J = 11.7 Hz, 1H, Ar–CH₂), 4.21 (d, J = 11.7 Hz, 1H, Ar–CH₂), 3.79 (s, 3H, Ar–OCH₃), 3.37 (s, 3H, O–CH₃), 3.36 (dd, J₁ = 9.4 Hz, J₂ = 2.5 Hz, 1H, CH₂–OPMB), 2.97 (dd, J₁ = 11.0 Hz, J₂ = 7.5 Hz, 1H, CH–C=), 2.04 (dt, J₁ = 7.5 Hz, J₂ = 2.5 Hz, 1H, CH–C–OPMB), 1.80 (s, 3H, C=C–CH₃), 1.18 (s, 3H, CH₃), 1.13 (s, 3H, CH₃).

**13C NMR (CDCl₃, 200 MHz)** δ 220.17, 159.17, 141.49, 130.02, 129.12, 113.76, 111.64, 96.11, 73.03, 66.88, 55.88, 55.39, 49.26, 46.91, 46.24, 27.24, 22.97, 19.80.

**IR** (neat, cm⁻¹) 2973, 2912, 1745, 1614, 1513, 1247, 1100, 1027.

**HRMS** calculated for [C₂₁H₃₀O₅H]+, requires m/z = 363.2171, found m/z = 363.2166 (ESI).

**TLC** (4:1) hexane/EtOAc, UV/permanganate, Rₛ = 0.47.
2. Spectra

2.1 From the Synthesis of Ketone 15

$^1$H NMR Spectrum of 11 (mix of 2 diastereomers on the THP group)

$^{13}$C NMR Spectrum of 11 (mix of 2 diastereomers on the THP group)
$^1$H–$^1$H COSY Spectrum of 11 (mix of 2 diastereomers on the THP group)

$^1$H NMR Spectrum of 12
$^{13}$C NMR Spectrum of 12

$^{1}H-^{1}H$ COSY Spectrum of 12
$^1$H NMR Spectrum of 13

$^{13}$C NMR Spectrum of 13

$^1$H–$^1$H COSY Spectrum of 13
$^1$H NMR Spectrum of 15

$^{13}$C NMR Spectrum of 15

$^1$H–$^1$H COSY Spectrum of 15
\(^1\)H NMR Spectrum of 19

\(^{13}\)C NMR Spectrum of 19

\(^1\)H–\(^1\)H COSY Spectrum of 19
$^1\text{H NMR Spectrum of 23}$

$^{13}\text{C NMR Spectrum of 23}$
\( ^1\text{H} - ^1\text{H} \text{ COSY Spectrum of 24} \)
$^1\text{H}$$^1\text{H}$ NOESY Spectrum of 24

Black rectangles highlight noteworthy NOE signals.

$^1\text{H}$ NMR Spectrum of 25A

$^{13}\text{C}$ NMR Spectrum of 25A
$^1$H–$^1$H COSY Spectrum of 25A
$^1$H–$^1$H NOESY Spectrum of 25A

Black rectangles highlight noteworthy NOE signals.

$^1$H NMR Spectrum of 25B

$^{13}$C NMR Spectrum of 25B
$^1$H–$^1$H NOESY Spectrum of 25B

Black rectangles highlight noteworthy NOE signals.
2.2 From the Scope of the Alkylation Reaction

$^1$H NMR Spectrum of 26

$^{13}$C NMR Spectrum of 26

$^1$H–$^1$H COSY Spectrum of 26
$^1$H–$^1$H NOESY Spectrum of 26

Black rectangles highlight noteworthy NOE signals.

$^1$H NMR Spectrum of 27

$^{13}$C NMR Spectrum of 27
$^1$H–$^1$H COSY Spectrum of 27
$^1$H–$^1$H NOESY Spectrum of 27

Black rectangles highlight noteworthy NOE signals.