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

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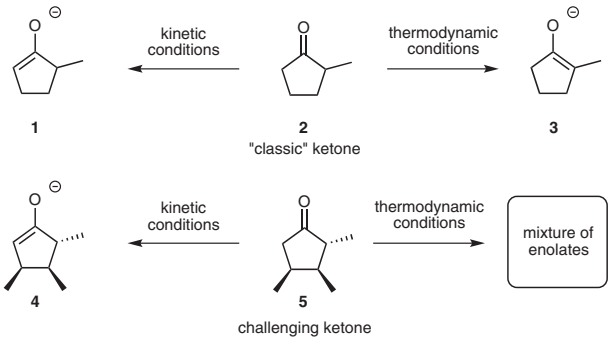
Abstract: Some ketones, especially 2,3-*trans*-3,4-*cis*-trisubstituted cyclopentanones, have strong inherent preferences to react through their less-substituted enolates, with neither kinetic nor thermodynamic conditions being able to selectively functionalize their more-substituted enolate isomers. Herein we report a synthetic strategy to overcome this limitation and selectively access the more-substituted alkylation products of these ketones. The strategy's key feature is to utilize a $MeOCH_2O$ group to temporarily block the more-reactive α position and to direct the ketone to react through its inherently less-reactive enolate isomer. The products formed by this strategy are useful synthetic intermediates on the path to multiple families of natural products.

Key words: ketones, alkylation, regioselectivity, neighboring-group effects, natural products



Scheme 1 Accessing enolate isomers: different reaction conditions can provide selective access to either the more- or the less-substituted enolate isomer for some, but not all ketones

Enolate alkylation is a classic and powerful method for constructing carbon–carbon bonds.[1] In addition to the challenges of forming these bonds stereoselectively, alkylating ketones can present additional challenges of regioselectively due to the fact that ketones can have deprotonable α hydrogens on either side of their carbonyl groups. Fortunately, many ketones can be selectively functionalized at either their more-substituted or less-substituted α positions by using thermodynamic or kinetic conditions to favor either the lower-energy or more rapidly formed enolate isomers.[2,3] 2-Methylcyclopentanone (**2**, Scheme 1) provides a classic example of this dichotomy.[2]

Some ketones, however, can be especially challenging to selectively functionalize because one of their enolate isomers is neither favored by thermodynamic nor kinetic conditions. For example, functionalizing the more-substituted α-position of cyclopentanones with the substitution pattern shown in molecule **5** (Scheme 1) is especially challenging because most enolization conditions produce the less-substituted enolates or give mixtures.[4,5] Herein, we report a strategy to selectively alkylate the more-substituted α position of these difficult-to-control cyclopentanone structures.

Various strategies for alkylating cyclopentanones have been developed. Enamines[6] and metalated imines[7] each generally favor alkylation at their less-substituted α-positions. Enolates derived from α,β-unsaturated enones can selectively react without enolate equilibration to the other α position.[8] Also, 1,3-dicarbonyls can allow preferential reaction at their more or less acidic α positions by using single or double deprotonation.[9] Despite these methods, performing selective chemical reactions on the more-substituted α positions of cyclopentanones like **5** has provided substantial challenges during the syntheses of several exciting natural products.

One telling example, reported by Jin and Qiu, is the synthesis of terpestacin (**7**, Scheme 2), a naturally occurring sesterterpene with potential anti-HIV and anti-angiogenesis activity.[4] A key fragment-coupling step in their synthetic route requires alkylation of cyclopentanone **6** at the more-substituted α position, yet they report that most attempted enolate-forming conditions favor reaction at the less-substituted and undesired α position. After substantial optimization, they were able to identify conditions that favor the desired product isomer, but by only a 3:1 ratio. Unsurprisingly, these isomers are 'difficult' to separate by chromatography.

A second illustrative example, reported by Ley and coworkers, is the synthesis of members of the thapsigargin family of sesquiterpene lactones, including nortrilobolide (**9**, Scheme 2).[5] Their synthetic strategy requires oxidation of the more substituted α position in cyclopentanone **8** to form the corresponding α,β-unsaturated enone; however, all attempts to form the required silyl enol ether exclusively produced the undesired silyl enol ether on the less-substituted α position. They were able to work around this reactivity by first installing a trimethylsilyloxy group to block the less substituted α position and then forming the desired silyl enol ether on the more substituted α position,

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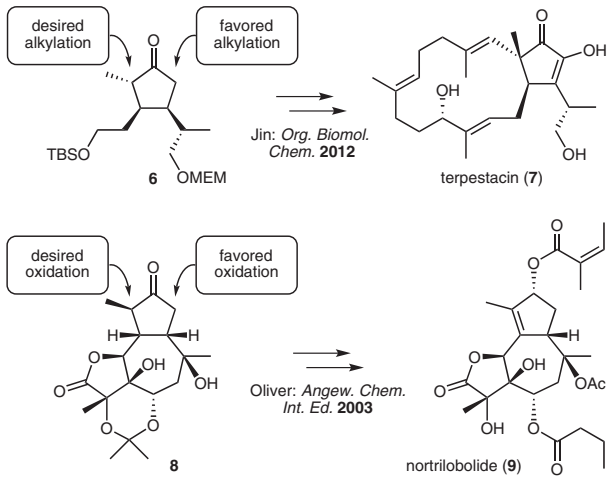
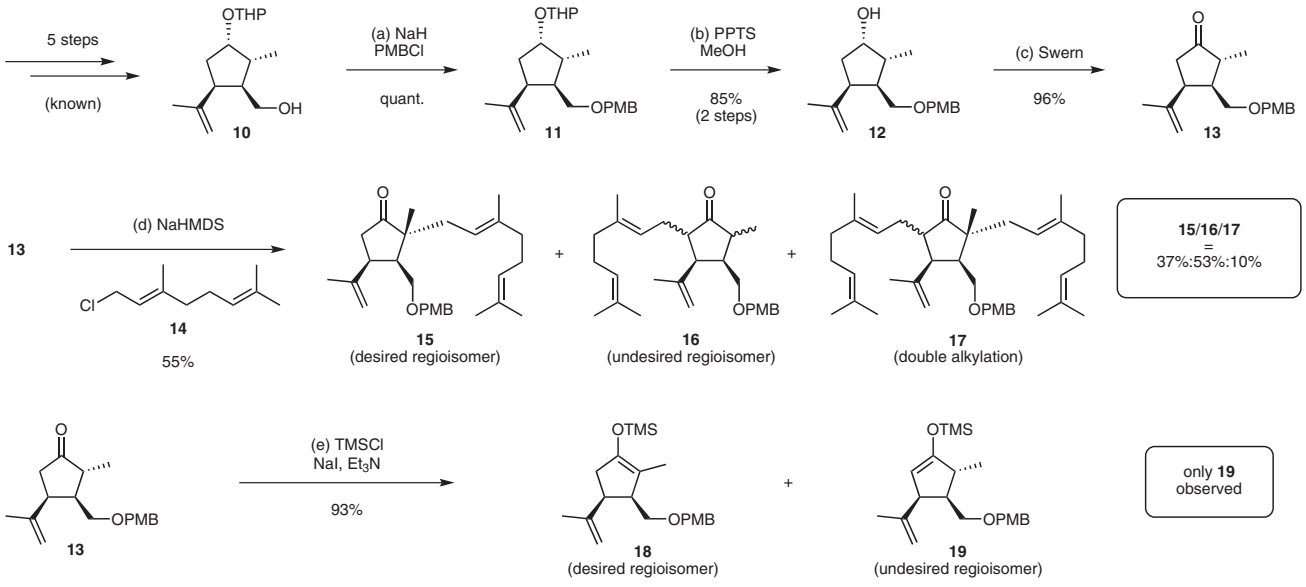


Scheme 2 Example challenges from natural product syntheses: summaries of syntheses of terpestacin by Jin and Qiu[4] and of nortrilobolide by Oliver, Ley, and co-workers,[5] both of which highlight the unmet need for methods to selectively functionalize this type of cyclopentanone at the more-substituted α position

although this transformation required the ketone to be heated with trimethylsilyl chloride to 150 °C.

In our research program, we are aiming to synthesize certain bioactive members of the dolabellane family of diterpenes, and a key step of our synthetic strategy involves selectively alkylating the more-substituted α position of cyclopentanone **13** (Scheme 3). We were able to efficiently access cyclopentanone **13** in three steps from known alcohol **10**,[10] but consistent with the previously described systems,[4,5] this molecule shows a strong inherent preference to react at the less-substituted α position. Under conditions known to favor alkylation of thermodynamically favored enolate intermediates (slow addition of sodium hexamethyldisilazane at ambient temperature followed by time for equilibration before adding the electrophile),[4,11] alkylation with geranyl chloride (**14**) favors formation of the less-substituted alkylation product **16** by a ratio of 1.4:1 and also produces doubly alkylated product **17**. Under conditions known to form thermodynamically favored silyl enol ethers (trimethylsilyl chloride, sodium iodide, and triethylamine or pyridine at ambient temperature),[12] reaction of cyclopentanone **13** exclusively forms the less-substituted silyl enol ether **19**. The desired silyl enol ether **18** was not observed by ^{1}H NMR spectroscopy. Although a small amount of the desired alkylation product **15** can be isolated by silica gel chromatography, we did not find this approach to be an efficient way to produce larger quantities of product **15**, and therefore sought a strategy that could more selectively produce this desired product.

We hypothesized that a multistep strategy (outlined in Scheme 4) could be used to reverse the inherent preference of cyclopentanone **13** and cause it to favor alkylation at the more-substituted α position. Similar to using a chiral auxiliary to control the stereochemistry of a reaction,[13] this strategy utilizes an 'auxiliary directing group', to force the alkylation to occur on the inherently less-reactive α position (to form **21**). Based on reported examples of α-alkoxyketones preferentially reacting at their nonoxygenated α positions,[5,14] we focused on oxygen-based auxiliary groups. Using auxiliary groups based on other atoms, including sulfur, was less promising because α-thioketones are known to preferentially react at their sul-



Scheme 3 Challenging alkylation towards the dolabellane core structure: synthesis of ketone **13** and example reactions that illustrate its inherent preference to react at the less-substituted α position. *Reagents and conditions*: (a) NaH (1.5 equiv), **10**, DMF (0.6 M), 0 °C, 1 h, then *p*-methoxybenzyl chloride (1.2 equiv), 3 h, full conversion and quantitative mass recovery, used directly in the next step; (b) MeOH (0.2 M), pyridinium *p*-toluenesulfonate (0.6 equiv), 15 h, 85% yield (2 steps); (c) oxalyl chloride (2 equiv), CH_2Cl_2 (0.4 M), DMSO (4 equiv), –84 °C, 25 min, then **12**, then Et_3N (5.5 equiv), to 0 °C, 1.5 h, 96% yield; (d) THF (0.4 M), sodium bis(hexamethylsilyl)amide (1.1 equiv), 30 min, r.t., then to 40 °C, then **14** (1.3 equiv), 1 h, 55% total yield, mixture of **15**, four diastereomers of **16**, and **17**; (e) NaI (2 equiv), MeCN (0.3 M), Et_3N (4.6 equiv), 0 °C, then Me_3SiCl (3 equiv), 3 h, 93% crude yield, single isomer.

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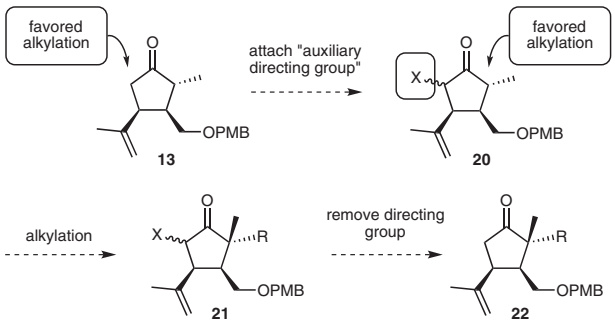
fur-bearing α positions,[15] which may be influenced by sulfur's superior ability to stabilize adjacent negative charges.[16]



Scheme 4 Hypothesized strategy to use an auxiliary directing group to force alkylation to occur at the more-substituted and inherently less-reactive α position of ketone **13**

We found that the methoxymethoxy group ($MeOCH_2O$, MOMO) can effectively function as an auxiliary directing group that is easy to install and remove and that is able to completely control alkylation of cyclopentanone **20** to favor alkylation at the more-substituted α position. Our initial attempts to use a trimethylsilyloxy group as the auxiliary produced undesired byproducts including elimination of the trimethylsilyloxy group and migration of the trimethylsilyl group, but these problems were not observed when using a MOMO group as the auxiliary.

Starting with cyclopentanone **13** (Scheme 5), we were able to take advantage of the molecule's natural preference to selectively form silyl enol ether **19** to install the MOMO auxiliary in three steps. Alkylation of α-MOMO-cyclopentanone **24** with geranyl chloride (**14**) provides clean conversion into the desired alkylation product **25** with full regioselectivity. No alkylation at the MOMO-functionalized α position was observed by ^1H NMR spectroscopy.

In addition to controlling the regioselectivity, this alkylation establishes the new carbon–carbon bond with complete control of stereochemistry, which we were able to determine by using through-space NOE couplings (Figure 1). Although the stereochemistry at the MOMO-functionalized carbon becomes a mixture of epimers (**25a** and **25b**) during the alkylation, fortunately this stereocenter is irrelevant because it is removed when the auxiliary is removed in the following step. Treatment of alkylation products **25a** and **25b** with samarium diiodide[17] removes the MOMO group and produces clean conversion to ketone **15** as a single stereoisomer.

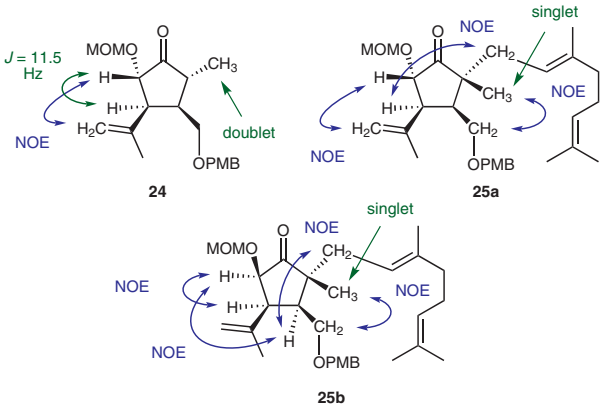
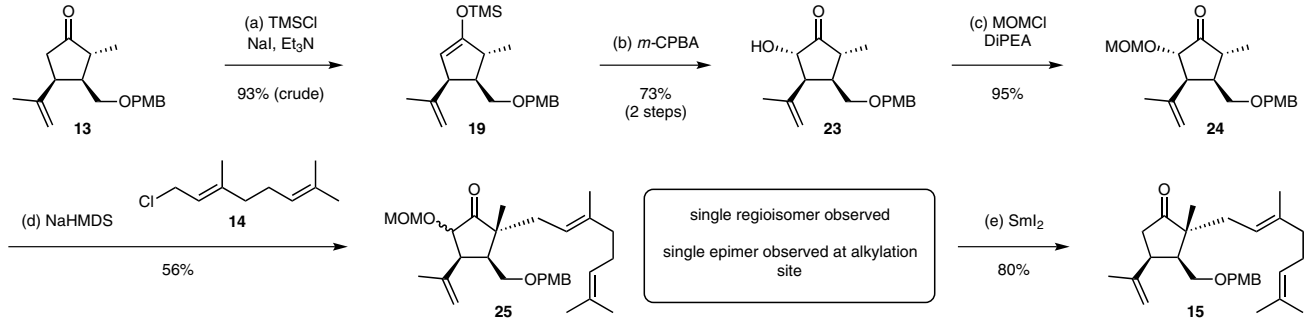


Figure 1 Product structures: select ^1H (green) and NOESY (blue) NMR data from alkylation precursor **24** and products **25a** and **25b**

To study the scope of this alkylation reaction, we tested the reaction using two additional electrophiles. Reacting ketone **24** with benzyl bromide at a slightly cooler temperature (0 °C instead of 30 °C) gives an analogous result. The ketone reacts exclusively at the more-substituted α position to produce a single stereoisomer of the monoalkylation product (**26**, 58% yield). Using iodomethane as the electrophile, on the other hand, is less successful. At cooler temperature (0 °C), the reaction is sluggish, yet at warmer temperature (30 °C), in addition to the desired monoalkylation product **27** some alkylation at the MOMO-protected α position and double alkylation occur. These data suggest that allylic and benzylic electrophiles are most appropriate for this transformation.



Scheme 5 Regio- and stereoselective alkylation controlled by an auxiliary directing group: selective synthesis of alkylated ketone **15**. *Reagents and conditions*: (a) NaI (2 equiv), MeCN (0.3 M), Et_3N (4.6 equiv), 0 °C, then Me_3SiCl (3 equiv), 3 h, 93% crude yield, single isomer; (b) THF (0.2 M), 2-methylbut-2-ene (0.9 equiv), 0 °C, *m*-CPBA (1.3 equiv), 1.5 h, then HCl, 20 min, 73% yield (2 steps), single stereoisomer; (c) CH_2Cl_2 (0.5 M), *i*-Pr_2NEt (4.5 equiv), 0 °C, then chloromethyl methyl ether (4 equiv), to r.t., 15 h, 95% yield; (d) geranyl chloride (**14**; 2.5 equiv), THF (2 M), 30 °C, sodium bis(trimethylsilyl)amide (1.5 equiv), 56% yield, 8:1 mixture of epimers at CHOMOM; (e) THF–MeOH (2:1, 0.03 M), freshly prepared SmI_2 (9.4 equiv), 15 min, 80% yield, single stereoisomer.

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Overall, utilizing a MOMO group as an auxiliary directing group allows for reversal of the inherent alkylation preference of a stubborn type of cyclopentanone structure and allows the desired alkylation of the more-substituted α position to be completed with full regio- and stereochemical control of the product. We are optimistic that this method will enable easier access to multiple families of interesting natural products including the dolabellanes and related sesterterpenes.

Full experimental details and spectra of synthesized compounds are provided in the Supporting Information. All novel structures were characterized by ^{1}H NMR, ^{13}C NMR, IR, TLC, and HRMS. Additional data for select compounds were obtained from COSY and NOESY NMR experiments. Column chromatography was performed with 60 Å 40–63 μm silia-P flash silica gel. Solvents for reactions (DMF, CH_2Cl_2, Et_2O, 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 $CDCl_3$ at ambient temperature unless otherwise noted. ^{1}H NMR spectra were recorded on either a 600 or 200 MHz Varian spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS using the solvent as a reference.^{13}C 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 TMS using the solvent as a reference. IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer with PerkinElmer Spectrum software. Spectra are partially reported (cm^{-1}). HRMS were obtained at The University of Illinois Urbana-Champaign. TLC was performed on 60 Å F_{254} precoated silica gel plates. Samples were visualized by either ultraviolet irradiation, $KMnO_4$ staining, or cerium ammonium molybdenate staining.

2-[(1*S*,2*S*,3*R*,4*S*)-2-{[(*p*-Methoxyphenyl)methoxy]methyl}-3-methyl-4-(tetrahydro-2*H*-pyran-2-yloxy)cyclopentyl]prop-1-ene (11)

Into a flame-dried flask was added NaH (60% dispersion, 1.38 g, 34.6 mmol, 1.5 equiv). The flask was capped with a rubber septum, maintained under a N_2 atmosphere and cooled in an ice 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 flask (over 25 min, evolving gas, final concentration = 0.6 M). The mixture was stirred (1 h) and *p*-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 aq 1 M potassium phosphate monobasic (10 mL, producing pH 5), diluted with H_2O (80 mL), and extracted with hexane (3 × 50 mL). The combined organic phases were washed with H_2O (2 × 40 mL) and dried (Na_2SO_4). Volatiles were removed under reduced pressure, and the crude material was passed through a short pad of silica gel (10 mL silica gel, 6:1 hexane–EtOAc) to yield crude ether **11** (8.79 g, quantitative mass recovery, colorless oil) as a 1:1 mixture of diasteromers at the THP group; R_f = 0.50. (5:1 hexane–EtOAc, UV or CAM). The crude material was used directly in the next step. An enriched aliquot of ether **11** was used for analysis. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

IR (neat): 2927, 2852, 1645, 1513, 1454, 1247, 1113, 1034, 1001 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.5 Hz, 2 H, Ar), 6.86 (d, *J* = 8.5 Hz, 2 H, Ar), 4.80 (s, 0.5 H, C=CH), 4.78 (s, 0.5 H, C=CH), 4.69–4.67 (m, 0.5 H, OCHO), 4.64 (s, 1 H, C=CH), 4.59–4.57 (m, 0.5 H, OCHO), 4.38 (d, *J* = 11.5 Hz, 1 H, ArCH_2), 4.32 (d, *J* = 11.5 Hz, 1 H, ArCH_2), 4.13 (t, *J* = 5.0 Hz, 0.5 H, C*H*OTHP), 4.07–4.04 (m, 0.5 H, C*H*OTHP), 3.92–3.86 (m 1 H, CH_2O), 3.51–3.47 (m, 1 H, CH_2O), 3.80 (s, 3 H, OCH_3), 3.51–3.46 (m 1 H, CH_2O), 3.31 (m, 1 H, CH_2OPMB), 3.19–3.14 (m 1 H, CH_2OPMB), 2.96 (q, *J* = 9.3 Hz, 0.5 H, C=CCH), 2.90–2.86 (m, 0.5 H, C=CCH), 2.13–2.04 (m, 1 H, C*H*COPMB), 2.02–1.98 (m, 1 H, C*H*CH_3), 1.77 (s, 1.5 H, C=CCH_3), 1.76 (s, 1.5 H, C=CCH_3), 1.88–1.49 (m, 8 H, 4 × CH_2), 1.15 (d, *J* = 7.4 Hz, 1.5 H, CH_3), 1.04 (d, *J* = 7.4 Hz, 1.5 H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 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, 42.37, 37.33, 34.68, 31.13, 30.79, 25.65, 25.53, 23.91, 23.82, 19.89, 19.27, 14.93, 14.83.

HRMS-ESI: *m*/*z* calcd for $[C_{23}H_{34}O_4 + Na]^+$: 397.2355; found: 397.2354.

(1*S*,2*R*,3*S*,4*S*)-4-Isopropenyl-3-{[(*p*-methoxyphenyl)methoxy]methyl}-2-methylcyclopentanol (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 × 130 mL) of brine and sat. aq $NaHCO_3$, washed with NaCl (50% saturated, 2 × 130 mL), and dried (Na_2SO_4). 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**) as a white solid; mp 54.5–56.0 °C; R_f = 0.21 (4:1 hexane–EtOAc, UV/CAM). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY and by comparison to signals from the starting materials.

IR (neat): 3426, 2956, 2925, 2855, 3077, 1645, 1613, 1513, 1247, 1097 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H, Ar), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar), 4.81 (s, 1 H, C=CH), 4.65 (s, 1 H, C=CH), 4.39 (d, *J* = 11.4 Hz, 1 H, CH_2Ar), 4.31 (d, *J* = 11.4 Hz, 1 H, CH_2Ar), 4.22–4.13 (m, C*H*OH), 3.80 (s, 3 H, OCH_3), 3.33 (dd, J_1 = 9.2 Hz, J_2 = 6.0 Hz, 1 H, CH_2OPMB), 3.18 (dd, J_1 = 9.2 Hz, J_2 = 7.1 Hz, 1 H, CH_2OPMB), 3.05 (q, *J* = 9.1 Hz, 1 H, C=CCH), 2.08 (quint, *J* = 7.8 Hz, 1 H, C*H*COPMB), 2.00–1.67 (m, 3 H, C*H*Me, CH_2COH), 1.76 (s, 3 H, C=CCH_3) 1.33 (d, *J* = 2.5 Hz, 1 H, OH), 1.09 (d, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.17, 145.80, 131.07, 129.23, 113.86, 110.40, 74.95, 72.87, 71.97, 55.49, 45.73, 45.16, 43.22, 39.13, 24.17, 14.63.

HRMS-ESI: *m*/*z* calcd for $[C_{18}H_{26}O_3 + Na]^+$: 313.1780; found: 313.1776.

(2*R*,3*S*,4*S*)-4-Isopropenyl-3-{[(*p*-methoxyphenyl)methoxy]-methyl}-2-methylcyclopentanone (13)

A flame-dried flask was capped with a rubber septum, maintained under a N_2 atmosphere, and cooled in an EtOAc/N_2 bath (–84 °C). Into the flask were added oxalyl chloride (1.54 mL, 17.9 mmol, 2 equiv), CH_2Cl_2 (45 mL, 0.4 M), and DMSO (2.54 mL, 35.8 mmol, 4 equiv). The mixture was stirred (25 min). Alcohol **12** (2.57 g, 8.95 mmol, 1 equiv) was dissolved in CH_2Cl_2 (22 mL, 0.4 M) and added. The mixture was stirred (25 min) and Et_3N (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 °C), stirred (1.5 h), quenched with sat. aq $NaHCO_3$ (60 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (60 mL) and dried (Na_2SO_4). Volatiles were removed under reduced pressure, and the crude material was passed through a short plug of silica gel (15 mL silica gel, 4:1 hexane–EtOAc) to yield pure ketone **13** (2.48 g, 8.61 mmol, 96%) as a yellow oil. R_f = 0.37 (5:1 EtOAc–hexane, UV/CAM). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY.

IR (neat): 3083, 2968, 2918, 2849, 1739, 1612, 1514, 1455, 1248, 1172 cm^{-1}.

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^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.6 Hz, 2 H, Ar), 6.87 (d, *J* = 8.6 Hz, 2 H, Ar), 4.89 (s, 1 H, C=CH), 4.69 (s, 1 H, C=CH), 4.38 (s, 2 H, CH_2Ar), 3.80 (s, 3 H, OCH_3), 3.42 (dd, J_1 = 9.2 Hz, J_2 = 5.9 Hz, 1 H, CH_2OPMB), 3.36 (dd, J_1 = 9.2 Hz, J_2 = 5.9 Hz, 1 H, CH_2OPMB), 3.03 (q, *J* = 7.5 Hz 1 H, CHC=C), 2.50 (dd, J_1 = 18.1 Hz, J_2 = 7.5 Hz, 1 H, CH_2C=O), 2.38–2.23 (m, 3 H, CH_2C=O, C*H*C*H*Me), 1.78 (s, 3 H, C=CCH_3), 1.14 (d, *J* = 7.1 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 221.21, 159.27, 144.42, 130.40, 129.27, 113.89, 112.00, 73.09, 70.22, 55.39, 46.67, 45.74, 42.45, 42.22, 22.85, 15.82.

HRMS: *m*/*z* calcd for $[C_{18}H_{24}O_3 + Na]^+$: 311.1623; found: 311.1618.

(3*R*,4*S*,5*R*)-3-Isopropenyl-4-{[(*p*-methoxyphenyl)methoxy]methyl}-5-methyl-1-trimethylsiloxycyclopentene (19)

Into a flame-dried flask were added ketone **13** (552 mg, 1.91 mmol, 1 equiv), NaI (dried in a vacuum oven, 100 °C, 50 mbar, 12 h; 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 N_2 atmosphere, and cooled in an ice bath (0 °C). Into the flask were added anhydrous MeCN (distilled from CaH_2 and stored over activated 3 Å molecular sieves; 6.5 mL, 0.3 M) and Et_3N (1.22 mL, 8.73 mmol, 4.6 equiv). Me_3SiCl (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 sat. aq $NaHCO_3$ (7 mL), diluted with brine (7 mL), and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with a mixture of brine and potassium phosphate monobasic (1 M aqueous) (1:1, 20 mL) and dried (Na_2SO_4). Volatiles were removed under reduced pressure, and the crude silyl enol ether **19** (643 mg, 1.80 mmol, 93% crude yield, brown oil) was used directly in the next step; R_f = 0.54 (hexane–EtOAc, 8:1, UV/CAM). A single isomer was observed by ^{1}H NMR spectroscopy. No signals from the more-substituted isomeric product were observed. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY and by comparison to signals from the starting materials. Some analytical data was not obtained for silyl enol ether **19** due to its moderate instability.

IR (neat): 3078, 2961, 2917, 2851, 1644, 1513, 1250, 1091, 1040 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.6 Hz, 2 H, Ar), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar), 4.79 (s, 1 H, C=CH), 4.74 (s, 1 H, C=CH), 4.52–4.48 (br s, 1 H, TMSOC=C*H*), 4.42 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 4.34 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 3.80 (s, 3 H, OCH_3), 3.40–3.28 (m, 3 H, CH_2OPMB, CHC=C), 2.36 (pent, *J* = 6.8 Hz, 1 H, C*H*Me), 2.21 (pent, *J* = 7.2 Hz, 1 H, C*H*COPMB), 1.68 (s, 3 H, C=CCH_3), 1.08 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.22 (s, 9 H, TMS).

^{13}C NMR (50 MHz, $CDCl_3$): 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.

(2*S*,3*S*,4*S*,5*R*)-2-Hydroxy-3-isopropenyl-4-{[(*p*-methoxyphenyl)methoxy]methyl}-5-methylcyclopentanone (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-methylbut-2-ene (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 N_2 atmosphere, and cooled in an ice bath (0 °C). *m*-CPBA (519 mg, 2.32 mmol, 1.3 equiv) was added, and the mixture was stirred (1.5 h). Aq 0.5 M HCl (8 mL) was then added. The mixture was stirred (20 min), extracted with EtOAc (9 mL), washed with aq 10% Na_2CO_3 (10 mL) and brine (8 mL), and dried (Na_2SO_4). 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 **23** (417 mg, 1.38 mmol, 73% from ketone **13**) as a pale yellow oil; R_f = 0.24 (4:1 EtOAc–hexane, UV/CAM). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY. Stereochemistry of the alcohol was determined after the subsequent step.

IR (neat): 3434, 2964, 2917, 2856, 1747, 1612, 1514, 1248, 1097, 1035 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.7 Hz, 2 H, Ar), 6.86 (d, *J* = 8.7 Hz, 2 H, Ar), 5.08 (s, 1 H, C=CH), 5.00 (s, 1 H, C=CH), 4.59 (dt, J_d = 12.6 Hz, J_t = 2.5 Hz, 1 H, C*H*OH), 4.36 (s, 2 H, CH_2Ar), 3.81 (s, 3 H, OCH_3), 3.43 (dd, J_1 = 9.4 Hz, J_2 = 3.9 Hz, 1 H, CH_2OPMB), 3.35 (dd, J_1 = 9.4 Hz, J_2 = 5.5 Hz, 1 H, CH_2OPMB), 2.71–2.52 (m, 3 H, C*H*Me, C*H*C=C, OH), 2.25–2.13 (m, 1 H, C*H*COPMB), 1.81 (s, 3 H, C=CCH_3), 1.21 (d, *J* = 8.2 Hz, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): 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.

HRMS-ESI: *m*/*z* calcd for $[C_{18}H_{24}O_4 + Na]^+$: 327.1572; found: 327.1575.

(2*S*,3*S*,4*S*,5*R*)-3-Isopropenyl-2-methoxymethoxy-4-{[(*p*-methoxyphenyl)methoxy]methyl}-5-methylcyclopentanone (24)

Into a flame dried flask were added α-hydroxy ketone **23** (560 mg, 1.86 mmol, 1 equiv), CH_2Cl_2 (4 mL, 0.5 M), and *i*-Pr_2NEt (1.45 mL, 8.37 mmol, 4.5 equiv). The flask was capped with a rubber septum, maintained under a N_2 atmosphere, and cooled in an ice bath (0 °C). Chloromethyl methyl ether (0.42 mL, 5.58 mmol, 3 equiv) was added, the reaction mixture was stirred (10 h, gradually returning to r.t.), and additional chloromethyl methyl ether (0.14 mL, 1.86 mmol, 1 equiv) was added. The mixture was stirred (additional 5 h), quenched with 50% aq NH_4Cl (10 mL), stirred (10 min), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with a mixture (1:1, 15 mL) of aq 1 M potassium phosphate monobasic and brine, and dried (Na_2SO_4). Volatiles were removed under reduced pressure, and the crude material was purified by column chromatography (25 mL silica gel, 5:1 hexane–EtOAc) to yield ketone **24** (615 mg, 1.76 mmol, 95%) as a pale yellow oil; R_f = 0.47 (4:1 hexane–EtOAc, UV/CAM). ^{1}H 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.

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

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2 H, Ar), 6.85 (d, *J* = 8.4 Hz, 2 H, Ar), 5.04 (s, 1 H, C=CH), 5.02 (d, *J* = 7.1 Hz, 1 H, OCH_2O), 4.98 (s, 1 H, C=CH), 4.69 (d, *J* = 7.2 Hz, 1 H, OCH_2O), 4.58 (d, *J* = 11.7 Hz, 1 H, C*H*OMOM), 4.40 (d, *J* = 11.6 Hz, 1 H, CH_2Ar), 4.31 (d, *J* = 11.6 Hz, 1 H, CH_2Ar), 3.80 (s, 3 H, ArOCH_3) 3.39 (s, 3 H, OCH_3) 3.36–3.30 (m, 2 H, CH_2OPMB), 2.87 (dd, J_1 = 11.4 Hz, J_2 = 7.9 Hz, 1 H, CHC=C), 2.46 (q, *J* = 7.8 Hz, 1 H, C*H*Me), 2.21–2.10 (m, 1 H, C*H*COPMB), 1.80 (s, 3 H, C=CCH_3), 1.20 (d, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): 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.

HRMS-ESI: *m*/*z* calcd for $[C_{20}H_{28}O_5 + Na]^+$: 371.1834; found: 371.1829.

(2*R*,3*S*,4*S*)-2-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-4-isopropenyl-5-methoxymethoxy-3-{[(*p*-methoxyphenyl)methoxy]methyl}-2-methylcyclopentanone (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 H_2O. The flask was fitted with a condensing column, capped with a rubber septum, and maintained under a N_2 atmosphere. THF (0.10 mL, 2 M) was added, and the mixture was warmed to 30 °C 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

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aq 1 M potassium phosphate monobasic (5 mL, producing pH 5), and extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (8 mL) and dried (Na_2SO_4). 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%) as a mixture of epimers at the CHOMOM stereocenter (8:1 **25a**/**25b**); colorless oil. An aliquot of each epimer was isolated by column chromatography. ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY. Stereochemistry of each epimer was assigned by ^{1}H–^{1}H NOESY. No other stereoisomers, constitutional isomers, or double-alkylation products were observed by NMR spectroscopy.

Stereoisomer 25a (*S*-Stereochemistry at CHOMOM)
R_f = 0.36 (8:1 EtOAc–hexane, $KMnO_4$).

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

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.0 Hz, 2 H, Ar), 6.83 (d, *J* = 8.0 Hz, 2 H, Ar), 5.11 (t, *J* = 7.9 Hz, 1 H, C=CH), 5.05–5.03 (m, 4 H, C=CH, C=CH_2, OCH_2O), 4.69 (d *J* = 6.7 Hz, 1 H, OCH_2O), 4.62 (d, *J* = 11.0 Hz, 1 H, C*H*OMOM), 4.30 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 4.19 (d, *J* = 11.7 Hz, 1 H, CH_2Ar), 3.79 (s, 3 H, ArOCH_3) 3.37 (s, 3 H, OCH_3) 3.28–3.24 (m, 2 H, CH_2OPMB), 2.94 (dd, J_1 = 10.8 Hz, J_2 = 7.4 Hz, 1 H, CHC=C), 2.34 (dd, J_1 = 14.4 Hz, J_2 = 9.0 Hz, 1 H, C=CCH_2), 2.14 (dt, J_d = 7.3 Hz, J_t = 2.1 Hz, 1 H, C*H*COPMB), 2.10–2.02 (m, 5 H, CH_2CH_2, C*H*Me), 1.94 (dd, J_1 = 14.4 Hz, J_2 = 6.2 Hz, 1 H, C=CCH_2), 1.79 (s, 3 H, C=CCH_3), 1.65 (s, 3 H, C=CCH_3), 1.62 (s, 3 H, C=CCH_3), 1.59 (s, 3 H, C=CCH_3), 1.09 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): 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.

HRMS-ESI: *m*/*z* calcd for $[C_{30}H_{45}O_5 + H]^+$: 485.3267; found: 485.3263.

Stereoisomer 25b (*R*-Stereochemistry at CHOMOM)
R_f = 0.30 (8:1 hexane–EtOAc, $KMnO_4$).

IR (neat): 3078, 2929, 2855, 1749, 1613, 1514, 1455, 1248, 1035 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.2 Hz, 2 H, Ar), 6.88 (d, *J* = 8.2 Hz, 2 H, Ar), 5.06–5.02 (m, 3 H, 2 × C=CH, C=CH_2), 4.73 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.68 (d, *J* = 6.7 Hz, 1 H, OCH_2O), 4.67 (s, 1 H, C=CH_2), 4.45 (d, *J* = 11.3 Hz, 1 H, CH_2Ar), 4.39 (d, *J* = 11.3 Hz, 1 H, CH_2Ar), 4.24 (d, *J* = 8.1 Hz, 1 H, C*H*OMOM), 3.81 (s, 3 H, ArOCH_3), 3.53–3.49 (m, 2 H, CH_2OPMB), 3.36 (s, 3 H, OCH_3), 3.24 (t, *J* = 7.8 Hz, 1 H, C=CCH), 2.54 (q, *J* = 7.7 Hz, 1 H, C*H*COPMB), 2.14 (d, *J* = 7.7 Hz, 1 H, CH_2), 2.15–1.95 (m, 4 H, C=CCH_2), 1.99 (d, *J* = 7.7 Hz, 1 H, CH_2), 1.74 (s, 3 H, C=CCH_3), 1.68 (s, 3 H, C=CCH_3), 1.59 (s, 3 H, C=CCH_3), 1.09 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 218.90, 159.29, 140.80, 140.16, 131.76, 130.42, 129.32, 124.17, 118.79, 116.61, 113.89, 96.11, 81.63, 73.01, 68.67, 55.96, 55.4, 45.95, 45.73, 41.75, 40.13, 26.80, 25.88, 24.49, 19.65, 17.82, 16.40.

HRMS-ESI: *m*/*z* calcd for $[C_{30}H_{44}O_5 + Na]^+$: 507.3100; found: 507.3094.

(2*R*,3*S*,4*S*)-2-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-4-isopropenyl-3-{[(*p*-methoxyphenyl)methoxy]methyl}-2-methylcyclopentanone (15)
MeOH was distilled over Na_2SO_4 prior to use. Reaction flasks were washed in a base-bath (NaOH in propan-2-ol) for 2 h and then dried in an oven overnight prior to use. Rubber septa were dried in a desiccator overnight prior to use.

SmI_2 Generation: Sm 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 CH_2I_2 (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 MeOH (3 mL). This mixture was stirred (2 h, to remove any remaining H_2O). 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 H_2O. Into this flask was added by cannula the THF–MeOH mixture (9 mL, 0.03 M). O_2 was removed from this mixture by a freeze-pump-thaw procedure (freezing with liquid N_2 and backfilling with argon, 3 times). The freshly prepared SmI_2 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 mixture was stirred (additional 15 min), quenched with sat. aq NH_4Cl (12 mL), and diluted with EtOAc (30 mL) and H_2O (50 mL). Insoluble material was removed by filtration. The organic phase was isolated, the aqueous phase was further extracted with EtOAc (additional 2 × 30 mL), and the combined organic phases were washed with brine (50 mL) and dried (Na_2SO_4). 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) as a colorless oil; R_f = 0.48 (6:1 hexane–EtOAc, $KMnO_4$). ^{1}H NMR signals were assigned by ^{1}H–^{1}H COSY and by comparison to signals from the starting materials.

IR (neat): 3083, 2966, 2915, 2858, 1737, 1613, 1514, 1455, 1248, 1093, 1036 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.4 Hz, 2 H, Ar), 6.83 (d, *J* = 8.4 Hz, 2 H, Ar), 5.13 (t, *J* = 7.7 Hz, 1 H, C=CH), 5.06 (t, *J* = 6.6 Hz, 1 H, C=CH), 4.95 (s, 1 H, C=CH_2), 4.79 (s, 1 H, C=CH_2), 4.26 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 4.21 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 3.79 (s, 3 H, OCH_3), 3.38–3.34 (m, 2 H, CH_2OPMB), 3.01 (dt, J_d = 11.1 Hz, J_t = 7.4 Hz, 1 H, C=CCH), 2.71 (dd, J_1 = 18.1 Hz, J_2 = 12.1 Hz, 1 H, CH_2C=O), 2.28–2.22 (m, 3 H, C*H*COPMB, O=CCH_2, C=CCH_2), 2.11–2.03 (m, 4 H, CH_2CH_2), 1.95 (dd, J_1 = 14.1 Hz, J_2 = 6.6 Hz, 1 H, CH_2C=C), 1.78 (s, 3 H, C=CCH_3), 1.66 (s, 3 H, C=CCH_3), 1.62 (s, 3 H, C=CCH_3), 1.60 (s, 3 H, C=CCH_3), 1.11 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 221.74, 159.14, 143.13, 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.

HRMS-ESI: *m*/*z* calcd for $[C_{30}H_{41}O_3 + H]^+$: 425.3056; found: 425.3065.

Characterization Data for Benzyl Alkylation Product 26 and Methyl Alkylation Product 27
See Supporting Information for experimental procedures.

(2*R*,3*S*,4*S*,5*S*)-2-Benzyl-4-isopropenyl-5-methoxymethoxy-3-{[(*p*-methoxyphenyl)methoxy]methyl}-2-methylcyclopentanone (26)
R_f = 0.51 (4:1 hexane–EtOAc, UV/$KMnO_4$).

IR (neat): 2938, 1742, 1611, 1513, 1247, 1097, 1023 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.3 Hz, 2 H, Ph), 7.25 (t, *J* = 7.3 Hz, 1 H, Ph), 7.13 (d, *J* = 7.3 Hz, 2 H, Ph), 7.09 (d, *J* = 8.4 Hz, 2 H, Ar), 6.82 (d, *J* = 8.4 Hz, 2 H, Ar), 5.08 (d, *J* = 6.8 Hz, 1 H, OCH_2O), 5.07 (s, 1 H, C=CH), 5.05 (s, 1 H, C=CH), 4.73 (d, *J* = 6.8 Hz, 1 H, OCH_2O), 4.66 (d, *J* = 10.7 Hz, 1 H, C*H*OMOM), 4.28 (d, *J* = 11.6 Hz, 1 H, MeOArCH_2), 4.15 (d, *J* = 11.6 Hz, 1 H, MeOArCH_2), 3.78 (s, 3 H, ArOCH_3), 3.40 (s, 3 H, OCH_3), 3.21 (d,

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J = 9.6 Hz, 1 H, CH_2OPMB), 3.11 (d, J = 9.6 Hz, 1 H, CH_2OPMB), 2.99 (dd, J_1 = 10.7 Hz, J_2 = 7.5 Hz, 1 H, CHC=C), 2.89 (d, J = 13.8 Hz, 1 H, PhCH_2), 2.58 (d, J = 13.8 Hz, 1 H, PhCH_2), 2.18 (br d, J = 7.5 Hz, 1 H, C*H*COPMB), 1.80 (s, 3 H, C=CCH_3), 1.11 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 219.14, 159.18, 141.35, 136.85, 130.68, 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, 22.88, 17.45.

HRMS-ESI: m/z calcd for $[C_{27}H_{34}O_5 + H]^+$: 439.2484; found: 439.2478.

(3*S*,4*S*,5*S*)-4-Isopropenyl-5-ethoxymethoxy-3-{[(*p*-methoxyphenyl)methoxy]methyl}-2,2-dimethylcyclopentanone (27)

R_f = 0.47 (4:1, hexane–EtOAc, UV/$KMnO_4$).

IR (neat): 2973, 2912, 1745, 1614, 1513, 1247, 1100, 1027 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.12 (d, J = 8.6 Hz, 2 H, Ar), 6.83 (d, J = 8.6 Hz, 2 H, Ar), 5.05 (br s, 2 H, C=CH_2), 5.02 (d, J = 6.6 Hz, 1 H, OCH_2O), 4.68 (d, J = 6.6 Hz, 1 H, OCH_2O), 4.60 (d, J = 11.0 Hz, 1 H, C*H*OMOM), 4.30 (d, J = 11.7 Hz, 1 H, ArCH_2), 4.21 (d, J = 11.7 Hz, 1 H, ArCH_2), 3.79 (s, 3 H, ArOCH_3), 3.37 (s, 3 H, OCH_3), 3.36 (dd, J_1 = 9.4 Hz, J_2 = 2.5 Hz, 1 H, CH_2OPMB), 3.26 (dd, J_1 = 9.4 Hz, J_2 = 2.5 Hz, 1 H, CH_2OPMB), 2.97 (dd, J_1 = 11.0 Hz, J_2 = 7.5 Hz, 1 H, CHC=C), 2.04 (dt, J_1 = 7.5 Hz, J_2 = 2.5 Hz, 1 H, C*H*COPMB), 1.80 (s, 3 H, C=CCH_3), 1.18 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): 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.

HRMS-ESI: m/z calcd for $[C_{21}H_{30}O_5 + H]^+$: 363.2171; found: 363.2166.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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