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# Electrostatic Effects on the Reactions of Cyclohexanone Oxocarbenium Ions

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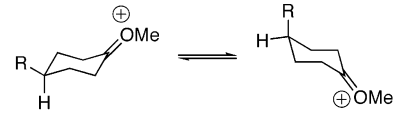
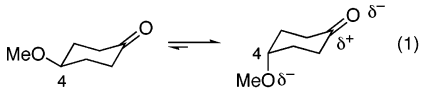



Nucleophilic substitution reactions of 4-substituted cyclohexanone acetals display different selectivities depending upon the electronic nature of the substituent. Alkyl groups favor equatorial positions in the oxocarbenium ions, but alkoxy groups prefer axial conformers. The reactions of acetals with alkoxy groups constrained to either equatorial or axial positions suggest that the presence of an axial alkoxy group distorts the oxocarbenium ion, changing its inherent preferences for facial attack.

## Introduction

Electrostatic effects exert powerful influences on conformational equilibria. For example, 4-methoxycyclohexanone prefers the pseudoaxial conformation **2** in a number of solvents despite the fact that this conformer is sterically disfavored (eq 1).[1,2] Similar conformational preferences are exhibited by 4-halocyclohexanones, with the fluoro derivative having the highest axial preference.[3,4] This trend indicates that electrostatic forces between the partially negatively charged substituent and the partially positively charged carbonyl carbon atom are most likely the origin of the contrasteric conformational preference.[5] In addition to ketones, other cyclic carbonyl compounds bearing heteroatom substituents also favor axial conformers.[6−10] The counterintuitive preference for the axial conformer influences nucleophilic additions to 4-alkoxycyclohexanones and related structures, which exhibit different stereoselectivities than additions to their alkyl analogues.[11−19]




Our studies of oxocarbenium ion reactivity have shown that electrostatic effects dramatically influence the conformational preferences of these cations. Structural evidence[20] confirms that electronegative heteroatoms such as oxygen atoms favor conformers that bring the negatively charged substituent close to the positively charged oxocarbenium ion carbon,[21] in accord with theoretical studies.[22,23] Once the conformer is defined,

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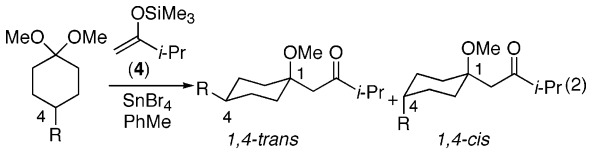
stereoelectronic effects of the ring system determine which face is attacked by nucleophiles.[24−28] In this paper, we provide evidence that electrostatic effects dictate the conformational preferences of alkoxy-substituted cyclohexanone-derived oxocarbenium ions. Because the stereoelectronic bias for nucleophilic addition in these systems is not high, the electrostatic effects appear to be strong enough to alter the inherent facial preference for nucleophilic attack by deforming the shape of the electrophile.

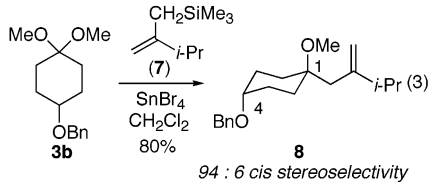
## Results and Discussion

The conformational preferences of cyclohexanone oxocarbenium ions were evaluated by analysis of the stereoselectivities of reactions of substituted acetals. Only substrates with substituents at C-4 were analyzed because steric effects that emerge in the transition state for nucleophilic attack complicate the analysis of C-3 and C-2-substituted electrophiles. The syntheses of the acetals are provided as Supporting Information. Stereoselectivities were typically determined by a combination of gas chromatography (GC) or gas chromatography/mass spectrometry (GCMS) and were confirmed by $^1$H NMR spectroscopy. In the case of enol ether nucleophiles, control experiments verified that the selectivities were the result of kinetic control. Because the stereocenter formed in each reaction was a quaternary carbon atom, spectroscopic methods were not generally useful for determining stereochemistry, so X-ray crystallography was typically employed. In some cases, chemical correlation and spectroscopic methods could be used to define stereochemical configurations. Details of the stereochemical proofs are provided as Supporting Information.

The major products observed for nucleophilic substitution reactions of 4-substituted cyclohexanone acetals with sterically large nucleophiles depend dramatically upon the electronic nature of the substituent. With 4-alkylcyclohexanone acetal **3a**, the nucleophile was incorporated trans to the substituent (eq 2).[29,30] The reaction of 4-alkoxy-substituted acetal **3b**, however, provided cis products preferentially. This cis selectivity with the alkoxy-substituted acetal **3b** was also observed when the analogous allylic silane[31] **7** was employed as the nucleophile (eq 3).[32]

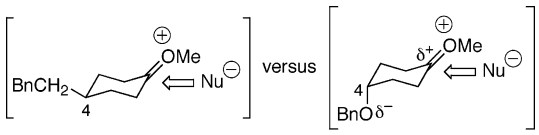



| substrate | R | 5 : 6 | yield (%) |
|---|---|---|---|
| **3a** | $CH_2Bn$ | 96 : 4 | 71 |
| **3b** | OBn | 4 : 96 | 86 |




94 : 6 cis stereoselectivity

The contrasting selectivities shown in eq 2 provide insight into the conformational preferences of the oxocarbenium ion intermediates. The reaction with the alkyl-substituted acetal **3a** is consistent with equatorial attack of the large nucleophile on the equatorially substituted cation (as shown in structure **9**).[29] Equatorial attack is anticipated because the large nucleophile develops destabilizing steric interactions if it approaches from the axial face (with smaller nucleophiles, axial approach is generally favored).[33,34] The opposite selectivity exhibited by the 4-alkoxy-substituted oxocarbenium ion most likely results from a change in conformational preference. Because a considerable amount of positive charge resides on the carbon atom of an oxocarbenium ion,[21] electrostatic forces bring the alkoxy group close to the carbocationic carbon in the axial isomer (cation **10**). This electrostatic effect, observed for 4-alkoxycyclohexanones (eq 1)[1,2] and related substrates,[4,6−10] should be higher for the oxocarbenium ion.[35] An axial preference for the alkoxy-substituted oxocarbenium ion is consistent with our studies of endocyclic oxocarbenium ions[20,24−26,28,36] and is supported by ab initio calculations that show the axial conformer (**10**) to be favored by 4.6 kcal/mol over the equatorial conformer.[37] Subsequent equatorial attack on the axial conformer **10** would give rise to the observed product. Studies with conformationally constrained substrates provide additional evidence to support this analysis (vide infra).




**9** **10**

When a smaller nucleophile was employed, alkyl- and alkoxy-substituted acetals again displayed opposite selectivities, but the magnitudes of the selectivities were higher for the alkyl acetal than for the alkoxy acetal. The reactions of alkyl-substituted cyclohexanone acetals **3a** and **3c** provided the trans products **11a** and **11c**,[38] respectively, with selectivities that compared to

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(30) The products are drawn to indicate relative stereochemistry, not necessarily the conformational preference of the product. This convention was chosen because in many cases it evokes the conformation of the oxocarbenium ion from which the product was formed.

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(34) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377−1386.

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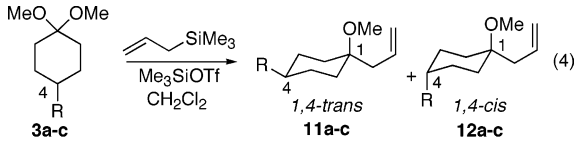
(37) The geometry optimizations were performed at the HF/6-31G* level using MacSpartan (Wavefunction, Irvine, CA). The structure of the low-energy axial conformer is provided as Supporting Information.

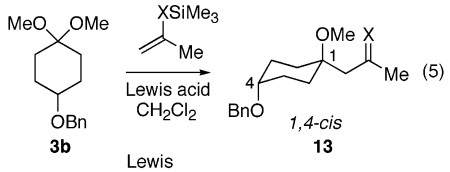
(38) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899−3910.

those exhibited by larger nucleophiles (eq 2). The substitution with the alkoxy-substituted acetal **3b** provided the cis product as observed for the larger nucleophiles (eqs 2 and 3), but the reaction was not as selective. Similar modest cis-selectivities were observed with other $\pi$-nucleophiles (eq 5).[32]




| substrate | R | **11** : **12** | yield (%) |
|---|---|---|---|
| **3a** | $CH_2Bn$ | 95 : 5 | 55 |
| **3c**[a] | *t*-Bu | 95 : 5 | 80 |
| **3b** | OBn | 20 : 80 | 85 |

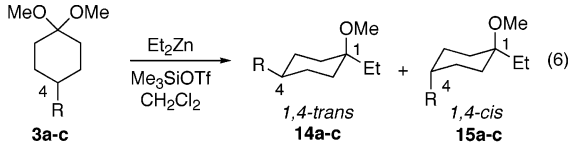
[a]Reference 38.



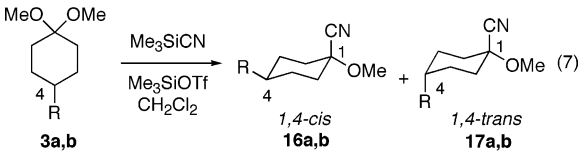

| X | Lewis acid | diastereoselectivity | yield (%) |
|---|---|---|---|
| O | $BF_3{\cdot}OEt_2$ | 61 : 39 | 81 |
| $CH_2$ | $SnBr_4$ | 88 : 12 | 70 |

The variation in selectivity depending upon nucleophile size for the alkoxy-substituted acetal **3b** was not anticipated. Because the conformational preference for the oxocarbenium ion intermediates should be independent of the nucleophile, similar selectivities should be observed. It is unlikely that the types of nucleophiles employed have inherently different preferences for axial versus equatorial selectivity in additions. This proposal can be discounted as the primary cause of the unusual behavior of acetal **3b**, since selectivities for the alkyl-substituted acetal **3a** are independent of the nucleophile. An alternative explanation for the lower selectivity with smaller nucleophiles would invoke the Curtin−Hammett principle[39] to propose that equatorial attack on the axial conformer **10** would be slower than equatorial attack on the corresponding equatorial conformer. To be correct, this dependence must operate only with small nucleophiles and not large nucleophiles, and it would not occur with alkyl-substituted cations. These conditions are severely limiting, making this argument unsatisfying.

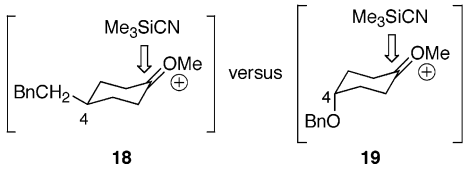
Other nucleophiles also showed different selectivities with the different acetals. Additions of $Et_2Zn$[40] provided only low selectivity with the alkyl-substituted acetals **3a** and **3c** but favored the trans product **14b** with the alkoxy-substituted system (eq 6). This result is likely due to axial attack of the alkylzinc reagent,[17] as would be expected from application of torsional and stereoelectronic considerations.[33,34] Using $Me_3SiCN$ as the nucleophile, the cis product was favored for the alkyl substrate,[38] but the trans product was again preferred with the alkoxy substrate. The reactions with $Me_3SiCN$ demonstrate a contrasting trend to the behavior of the silyl enol ethers in eq 2: this nucleophile attacks oxocarbenium ions with a significant preference for the axial face[38] (structures **18** and **19**), as would be expected with a small nucleophile.[33,34]




| substrate | R | **14** : **15** | yield (%) |
|---|---|---|---|
| **3a** | $CH_2Bn$ | 65 : 35 | 80 |
| **3c** | *t*-Bu | 50 : 50 | 75 |
| **3b** | OBn | 87 : 13 | 70 |

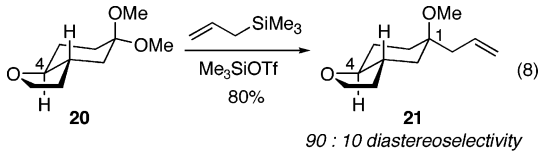


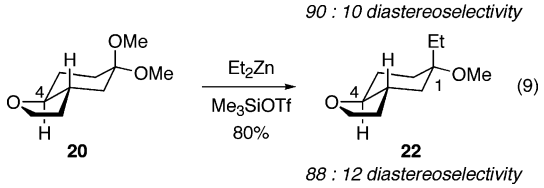

| substrate | R | **16** : **17** | yield (%) |
|---|---|---|---|
| **3a** | $CH_2Bn$ | 81 : 19 | 94 |
| **3b** | OBn | 24 : 76 | 89 |




Analyses of the reactions of conformationally flexible substrates **3a** and **3b** are complicated by the fact that the reactive conformers cannot be determined with ease. The alkyl-substituted oxocarbenium ions should favor the equatorial isomer, and an alkoxy group in an oxocarbenium can have a strong preference for the axial orientation.[22,25,26] The reactions of alkoxy-substituted oxocarbenium ions, however, might be complicated by electronic differences on facial selectivity caused by the remote alkoxy group.[17] Consequently, it would be valuable to know the influence on selectivity exerted by an alkoxy group in the equatorial and axial orientations.

Reactions of the conformationally constrained acetal **20** reveal that the presence of an equatorially disposed alkoxy group at C-4 provides products with selectivities similar to those exhibited by 4-alkyl-substituted acetals. Allyltrimethylsilane attacked the electrophile from the equatorial face to provide the 1,4-trans product (eq 8). This facial preference contrasts with the 1,4-cis selectivity observed for the unconstrained 4-alkoxy-substituted acetal (eq 4). Axial attack was favored for additions of $Et_2Zn$ (eq 9). The results shown in eqs 8 and 9 both show an increase in the amount of products formed by axial attack as compared to the 4-alkyl counterparts (eqs 4 and 6, respectively). This perturbation in selectivity is likely the result of flattening of the six-membered ring by the fused five-membered ring, which has been shown to increase the amount of axial attack to ketones.[34,41]

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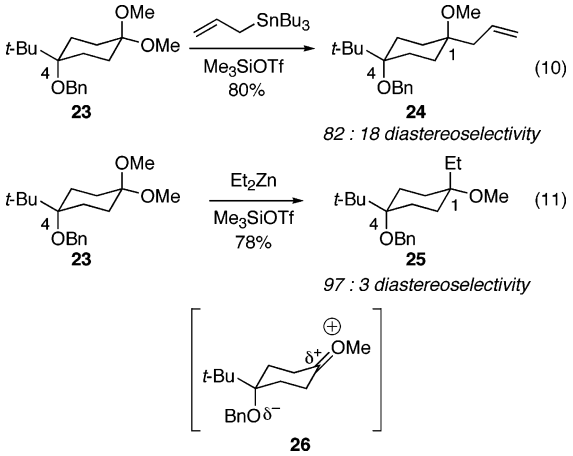
(40) Powell, N. A.; Rychnovsky, S. D. *J. Org. Chem.* **1999**, *64*, 2026−2037.
(41) Casadevall, E.; Pouet, Y. *Tetrahedron Lett.* **1976**, 2841−2844.

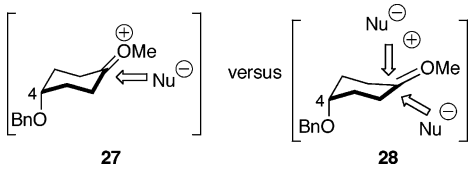
Nucleophilic substitutions of substrates with the C-4-alkoxy group constrained to an axial position exhibit selectivities that are almost identical to those of the unconstrained acetal **3b**. Substitution reactions of acetal **23** with allyltributylstannane occurred with modest selectivity for equatorial attack (eq 10); the relative stereochemistry and its magnitude compare closely to unconstrained example shown in eq 4.[42] Substitution with $Et_2Zn$ proceeded with high selectivity, favoring axial addition to the oxocarbenium ion **26**. The unconstrained system (eq 6) provided the analogous product with 87:13 selectivity.




The control experiments with alkyl-substituted acetals **3a**,**c** and constrained 4-alkoxy acetals **20** and **23** reveal the conformational preference and the facial selectivity for nucleophilic attack of the unconstrained 4-alkoxy oxocarbenium ion **10**. The strong correlation between the selectivities for the axially constrained alkoxy acetal **23** and the unconstrained alkoxy acetal **3b** indicate that the constrained oxocarbenium ion **26** resembles the reactive conformer of the unconstrained oxocarbenium ion (namely **10**). Larger nucleophiles favored equatorial attack with all substrates examined (see, for example, eq 2). On the other hand, oxocarbenium ions bearing an axial alkoxy group at C-4 showed more axial attack than a substrate with an alkyl group at C-4 (compare, for example, eqs 4 and 10 to eq 2).

The enhanced axial selectivity exhibited by the axially disposed 4-alkoxy oxocarbenium ions could be the result of interactions between the nucleophile and the remote substituent. The axial alkoxy group, bearing partial negative charge on oxygen, could repel the nucleophile electrostatically. This phenomenon has been invoked to explain the selective reductions of alkoxycyclohexanone derivatives with metal hydride ions,[15,43] although the importance of this effect has been questioned.[16] Electrostatic repulsion, however, should be smaller with $\pi$-nucleophiles, because they are neutral, so this effect is unlikely in the cases reported here.

The enhanced axial attack on alkoxy-substituted oxocarbenium ions could result from a powerful electrostatic effect influencing the structure of the electrophile. The electrostatic attraction that biases the cation to the axial conformer (**27**) by 4.6 kcal/mol[37] should draw the cationic carbon toward the benzyloxy group in this conformer. Computational studies[37] reveal significant flattening of the dihedral angle at the $sp^2$-hybridized carbon atom of the oxocarbenium ion **27** (39°) compared to cyclohexanone (54°).[14] This distortion of the cation from a more idealized chair conformer (**27**) to a flattened conformer (as depicted in **28**)[37] should alter the inherent facial selectivity[34,41] of the cyclohexanone oxocarbenium ion by exposing the axial face to nucleophilic attack. Such flattening of the ring of a cyclohexanone is known to increase the proportion of axial attack,[14,34,41] and electrostatic distortion has also been invoked to explain the enhanced axial reductions of ketones bearing electronegative substituents at C-4.[14−16,34] The electrostatic attraction and the resulting distortion should be more pronounced for oxocarbenium ions, since one component now bears a full positive charge.[44]




## Conclusion

Studies of 4-alkoxy-substituted cyclohexanone acetals reveal that the alkoxy group exerts a powerful influence on the conformational preference and reactivity of exocyclic oxocarbenium ions. The preference for axial conformers is consistent with observations of the corresponding cyclohexanones[1,2] and our studies of tetrahydropyran and tetrahydrofuran oxocarbenium ions.[24−26,28] This study also revealed a new influence of an alkoxy substituent. The electrostatic forces that favor axial conformers appear to distort the oxocarbenium ion, therefore changing its inherent preference for facial attack.

## Experimental Section

Details of the syntheses of substrates and stereochemical proofs are provided as Supporting Information.

**Ketones 5a and 6a.** To a cooled (−78 °C) solution of **3a** (0.100 g, 0.402 mmol) in toluene (1 mL) was added enol ether **4**[45] (0.08 g, 0.5 mmol), the mixture was allowed to stir for 2 min, then a solution of $SnBr_4$ (1 M in $CH_2Cl_2$, 0.48 mL, 0.48 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (1 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 1 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 4:96 (**6a**/**5a**) was determined by subjecting the unpurified oil to GCMS: $t_R$ (major) 19.9 min, $t_R$ (minor) 19.8 min. The resulting oil was purified by flash chromatography (95:5 to 91:9 hexanes/EtOAc) to afford the product as a colorless oil (0.087 g, 71%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31−7.25 (m, 2H), 7.21−7.14 (m, 3H), 3.21 (s, 3H), 2.67 (sep, $J$ = 6.9, 1H), 2.62−2.61 (m, 2H), 2.57 (s, 2H), 1.83−1.81 (m, 2H), 1.57−1.51-(m, 4H), 1.44 (ddd, $J$ = 13.6, 13.4, 3.1, 2H), 1.26−1.23 (m, 3H), 1.06 (d, $J$ = 6.9, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ 213.4, 143.0,

(42) The substitution with allyltrimethylsilane provided mostly decomposition products arising from elimination of the benzyloxy group. The reaction with allylstannane proceeded with few side products, so this result makes a better comparison.

(43) For a discussion comparing the models for nucleophilic attack to cyclohexanones and examination of the reactions of conformationally constrained 2-substituted cyclohexanones, see: Rosenberg, R. E.; Abel, R. L.; Drake, M. D.; Fox, D. J.; Ignatz, A. K.; Kwiat, D. M.; Schaal, K. M.; Virkler, P. R. *J. Org. Chem.* **2001**, *66*, 1694−1700.

(44) Comparing the charges of acetaldehyde and its methyl oxocarbenium ion using Mulliken population analysis shows the oxocarbenium ion to have larger charge on the carbon, although an AIM analysis shows acetaldehyde has a larger charge at carbon. See ref 21 and: Wiberg, K. B.; Rablen, P. R. *J. Comput. Chem.* **1993**, *14*, 1504−1518.

(45) Beutelman, H. P.; Xie, L.; Saunders, W. H., Jr. *J. Org. Chem.* **1989**, *54*, 1703−1709.

128.3, 128.2, 125.5, 75.0, 48.6, 47.5, 42.2, 38.8, 36.2, 33.6, 33.2, 27.8, 18.0; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_2Na$ $(M + Na)^+$ 325.2144, found 325.2140. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.58; H, 10.03.

**Ketones 5b and 6b.** To a cooled (−78 °C) solution of **3b** (0.050 g, 0.200 mmol) in toluene (1 mL) was added enol ether **4**[45] (0.076 g, 0.24 mmol), the mixture was stirred for 2 min, and then $SnBr_4$ (1 M in $CH_2Cl_2$, 0.24 mL, 0.24 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 94:6 (**6b**/**5b**) was determined by subjecting the unpurified oil to GCMS: $t_R$ (major) 19.9 min, $t_R$ (minor) 20.4 min. The resulting oil was purified by flash chromatography (97:3 to 96:4 hexanes/EtOAc) to afford the product as a colorless oil (0.05 g, 86%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.32 (m, 4H), 7.28−7.25 (m, 1H), 4.50 (s, 2H), 3.61−3.58 (m, 1H), 3.23 (s, 3H), 2.70 (sep, $J$ = 6.9, 1H), 2.62 (s, 2H), 1.85−1.69 (m, 6H), 1.64−1.61 (m, 2H), 1.07 (d, $J$ = 6.9, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 213.1, 139.1, 127.3, 127.3, 75.2, 72.7, 69.7, 49.0, 46.5, 42.1, 29.1, 25.6, 18.0; IR (thin film) 2925, 1705, 1456, 1368, 1062 cm$^{-1}$; HRMS (ES) *m/z* calcd for $C_{19}H_{29}O_3$ $(M + H)^+$ 305.2117, found 305.2102. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.80; H, 9.15.

**Alkene 8.** To a cooled (−78 °C) solution of **3b** (0.15 g, 0.60 mmol) in $CH_2Cl_2$ (3 mL) was added silane **7**[31] (0.19 g, 1.2 mmol), the mixture was stirred for 2 min, and then $SnBr_4$ (1 M in $CH_2Cl_2$, 0.72 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C) and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 94:6 was determined by subjecting the unpurified oil to GCMS: $t_R$ (major) 18.7 min, $t_R$ (minor) 19.4 min. The resulting oil was purified by flash chromatography (98:2 to 97:3 hexanes/EtOAc) to afford the product as a colorless oil (0.15 g, 80%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35−7.32 (m, 4H), 7.28−7.23 (m, 1H), 4.90−4.89 (m, 1H), 4.81−4.80 (m, 1H), 4.50 (s, 2H), 3.62−3.56 (m, 1H), 3.20 (s, 3H), 2.28 (sep, $J$ = 6.8, 1H), 2.21 (s, 2H), 1.73−1.64 (m, 6H), 1.58−1.54 (m, 2H), 1.03 (d, $J$ = 6.8, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ 152.1, 139.3, 128.3, 127.34, 127.28, 110.0, 75.6, 73.3, 69.7, 48.5, 40.1, 34.1, 29.0, 25.9, 22.0; IR (thin film) 3085, 3030, 2958, 2870, 1637, 1455 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{20}H_{30}O_2$ Na $(M + Na)^+$ 325.2144, found 325.2139. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.01; H, 10.22.

**Alkenes 11a and 12a.** To a cooled (−78 °C) solution of **3a** (0.100 g, 0.402 mmol) in $CH_2Cl_2$ (2 mL) was added allyltrimethylsilane (0.26 mL, 1.6 mmol), the mixture was allowed to stir for 2 min, and then TMSOTf (0.09 mL, 0.50 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 2 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 5:95 (**12a**/**11a**) was determined by subjecting the unpurified oil to GCMS: $t_R$ (major) 17.2 min, $t_R$ (minor) 17.4 min. The resulting oil was purified by flash chromatography (99:1 to 98:2 hexanes/EtOAc) to afford the product (as a 95:5 mixture as determined by GCMS) as a colorless oil (0.057 g, 55%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28−7.24 (m, 2.66H), 7.17−7.14 (m, 3.71H), 5.81 (ddt, $J$ = 17.5, 10.3, 7.3, 1.01H), 5.07−5.01 (m, 2.11H), 3.21 (s, 0.13H), 3.16 (s, 3H), 2.63−2.60 (m, 2.49H), 2.33−2.30 (m, 0.08H), 2.18 (dt, $J$ = 7.4, 1.2, 2.11H), 1.84−1.81 (m, 2.32H), 1.56−1.51 (m, 4.61H), 1.28−1.15 (m, 5.77H); $^{13}$C NMR (125 MHz, $CDCl_3$), $\delta$ 143.1, 134.0, 128.3, 128.2, 125.5, 117.2, 74.4, 48.1, 41.9, 38.9, 36.6, 33.4, 33.3, 27.8; IR (thin film) 2853, 1455, 1079, 699 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{17}H_{23}$ $(M - CH_3O)^+$ 227.1800, found 227.1809.

**Alkenes 11b and 12b.** To a cooled (−78 °C) solution of **3b** (0.150 g, 0.600 mmol) in $CH_2Cl_2$ (3 mL) was added allyltrimethylsilane (0.39 mL, 2.4 mmol), the mixture was stirred for 2 min, and then TMSOTf (0.13 mL, 0.72 mmol) was added. The solution was warmed (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 80:20 (**12b**/**11b**) was determined by subjecting the unpurified oil to GC: $t_R$ (major) 15.4 min, $t_R$ (minor) 16.0 min. The resulting oil was purified by flash chromatography (97:3 to 96:4 hexanes/EtOAc) to afford the products separately as colorless oils. **12b** (0.104 g, 67%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38−7.31 (m, 4H), 7.28−7.24 (m, 1H), 5.82 (ddt, $J$ = 17.4, 10.2, 7.2, 1H), 5.10−5.03 (m, 2H), 4.50 (s, 2H), 3.61−3.57 (m, 1H), 3.18 (s, 3H) 2.26 (d, $J$ = 7.2, 2H), 1.77−1.64 (m, 6H), 1.56 (dt, $J$ = 13.2, 4.0, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.2, 133.7, 128.3, 127.30, 127.25, 117.3, 74.7, 73.4, 69.7, 48.4, 40.3, 28.8, 25.8; IR (thin film) 2931, 1454, 1369, 1075 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{14}H_{19}O_2$ $(M - C_3H_5)^+$ 219.1385, found 219.1383. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.67; H, 9.56. **11b** (0.028 g, 18%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36−7.32 (m, 4H), 7.28−7.25 (m, 1H), 5.80 (ddt, $J$ = 17.5, 10.3, 7.3, 1H), 5.08−5.02 (m, 2H), 4.56 (s, 2H), 3.32 (tt, $J$ = 10.4, 4.0, 1H), 3.17 (s, 3H) 2.20−2.18 (m, 2H), 1.88−1.81 (m, 4H), 1.65−1.58 (m, 2H), 1.25−1.19 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.1, 133.8, 128.3, 127.5, 127.3, 117.5, 73.9, 69.8, 48.2, 40.9, 34.3, 31.6, 27.2; IR (thin film) 2941, 1449, 1364, 1070 cm$^{-1}$. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.31; H, 9.44.

**Ketone 13 (X = O).** To a cooled (−78 °C) solution of **3b** (0.050 g, 0.20 mmol) in $CH_2Cl_2$ (1 mL) was added 2-(trimethylsiloxypropene) (0.08 g, 0.24 mmol), the mixture was stirred for 2 min, and then $BF_3{\cdot}OEt_2$ (0.21 mL, 0.24 mmol) was added. The solution was allowed to warm to (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 61:39 was determined by subjecting the unpurified oil to $^1$H NMR spectroscopy. The resulting oil was purified by flash chromatography (91:9 to 83:17 hexanes/EtOAc) to afford the ketone **13** (X = O) and a mixture of ketone **13** (X = O) and its minor diastereomer (as an 8:92 mixture as determined by NMR) as colorless oils. **Ketone 13 (X = O)** (0.023 g, 42%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35−7.34 (m, 4H), 7.29−7.25 (m, 1H), 4.50 (s, 2H), 3.62−3.59 (m, 1H), 3.26 (s, 3H), 2.59 (s, 2H), 2.20 (s, 3H), 1.81−1.69 (m, 6H), 1.65−1.62 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 207.6, 139.1, 128.3, 127.33, 127.32, 75.0, 72.8, 69.8, 49.6, 49.0, 32.2, 29.2, 25.7; IR (thin film) 3067, 3023, 1705, 1433, 1422, 1068 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{16}H_{20}O_2$ $(M - MeOH)^+$ 244.1463, found 244.1475. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.12; H, 8.97. **Minor diasteroeomer of 13 (X = O)** (0.021 g, 38%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35−7.30 (m, 4.29H), 7.28−7.23 (m, 1.7H), 4.55 (s, 2H), 3.62−3.59 (m, 0.1H), 3.35 (ddt, $J$ = 10.2, 8.3, 4.0, 1H), 3.25 (s, 0.24H), 3.24 (s, 3H) 2.58 (s, 0.17H), 2.54 (s, 2H), 2.20 (s, 0.23H), 2.19 (s, 3H), 1.90−1.68 (m, 4.87H), 1.75−1.66 (m, 0.63H) 1.67−1.59 (m, 2.61H), 1.41 (ddd, $J$ = 13.5, 13.4, 3.8, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 207.7, 139.0, 128.31, 127.5, 127.4, 76.1, 74.2, 69.9, 49.5, 48.6, 32.2, 31.8, 27.1; IR (thin film) 2933, 2844, 1706, 1450, 1228 cm$^{-1}$; HRMS (EI) *m/z* calcd for $C_{13}H_{21}O_2$ $(M - MeOH)^+$ 244.1463, found 244.1461. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.74; H, 8.83.

**Alkene 13 (X = $CH_2$).** To a cooled (−78 °C) solution of **3b** (0.150 g, 0.600 mmol) in $CH_2Cl_2$ (3 mL) was added 2-methallyltrimethylsilane (0.31 mL, 2.4 mmol), the mixture was allowed to stir for 2 min, and then $SnBr_4$ (1 M in $CH_2Cl_2$, 0.72 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The

organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 88:12 was determined by subjecting the unpurified oil to GC: $t_R$ (major) 16.3 min, $t_R$ (minor) 17.0 min. The resulting oil was purified by flash chromatography (98:2 to 96:4 hexanes/EtOAc) to afford the products (**13**, X = $CH_2$, and its diastereomer) separately as colorless oils. **Alkene 13 (X = $CH_2$)** (0.099 g, 60%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.33 (m, 4H), 7.27−7.23 (m, 1H), 4.86−4.85 (m, 1H), 4.70 (s, 1H), 4.50 (s, 2H), 3.61−3.56 (m, 1H), 3.18 (s, 3H), 2.20 (s, 2H), 1.81 (s, 3H), 1.76−1.64 (m, 6H), 1.58−1.55 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.2, 139.2, 128.3, 127.3, 127.2, 114.1, 75.3, 73.4, 69.7, 48.5, 42.7, 29.2, 26.0, 24.2; IR (thin film) 3063, 2930, 1643, 1491,1367 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{17}H_{22}O$ (M − MeOH)$^+$ 242.1671, found 242.1668. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.52; H, 9.68. **Minor diastereomer of 13 (X = $CH_2$)** (0.017 g, 10%): $^1$H NMR (500 MHz, $CDCl_3$), $\delta$ 7.36−7.31 (m, 4H) 7.27−7.24 (m, 1H), 4.84 (dt, $J$ = 3.9, 1.5, 1H), 4.66 (m, 1H), 4.56 (s, 2H), 3.31 (tt, $J$ = 10.4, 4.0, 1H), 3.19 (s, 3H), 2.14 (s, 2H), 1.89−1.79 (m, 7H) 1.65−1.58 (m, 2H), 1.22 (ddd, $J$ = 13.7, 13.4, 3.7, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.4, 139.2, 128.3, 127.5, 127.3, 114.2, 76.8, 74.4, 69.8, 48.1, 43.4, 32.1, 27.3, 24.3; IR (thin film) 2934, 1637, 1457, 1367, 1076 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}O_2$ (M − $C_4H_7$)$^+$ 201.1279, found 201.1276. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.57; H, 9.72.

**Methyl Ethers 14a and 15a.** To a cooled (−78 °C) solution of **3a** (0.15 g, 0.60 mmol) in $CH_2Cl_2$ (3 mL) was added a solution of $Et_2Zn$ (1 M in hexanes, 0.7 mL, 0.7 mmol), the mixture was stirred for 10 s, and then TMSOTf (0.13 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 35:65 (**15a**/**14a**) was determined by subjecting the unpurified oil to GCMS: $t_R$ (major) 16.3 min, $t_R$ (minor) 17.0 min. The resulting oil was purified by flash chromatography (97:3 hexanes/EtOAc) to afford the products (as a 2:1 mixture as determined by NMR) as a colorless oil (0.12 g, 80%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.27−7.22 (m, 3.21H), 7.20−7.11 (m, 4.44H), 3.14 (s, 3H), 3.09 (s, 1.37H), 2.63−2.58 (2.96H), 1.83−1.79 (m, 0.97H), 1.76−1.66 (m, 4.19H), 1.56−1.52 (m, 6.07H), 1.42−1.31 (4.12H), 1.29−1.18 (m, 1.57H), 1.14−1.01 (m, 3.01H), 0.84−0.80 (m, 4.51H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 143.1, 142.9, 128.29, 128.25, 128.24, 128.18, 125.6, 125.5, 75.8, 74.4, 47.9, 47.8, 38.9, 37.6, 36.9, 36.1, 33.6, 33.3, 33.1, 32.8, 29.5, 28.9, 27.9, 24.3, 7.1, 6.7; IR (thin film) 2928, 1495, 1128 cm$^{-1}$. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.96; H, 10.66.

**Methyl Ethers 14b and 15b.** To a cooled (−78 °C) solution of **3b** (0.15 g, 0.60 mmol) in $CH_2Cl_2$ (3 mL) was added a solution of $Et_2Zn$ 1 M in hexanes (0.7 mL, 0.7 mmol), the mixture was stirred for 10 s, and then TMSOTf (0.13 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 87:13 (**14b**/**15b**) was determined by subjecting the unpurified oil to GC: $t_R$ (major) 15.2 min, $t_R$ (minor) 14.6 min. The resulting oil was purified by flash chromatography (97:3 hexanes/EtOAc) to afford the product (as a 8:1 mixture as determined by NMR) as a colorless oil (0.11 g, 70%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.30 (m, 4.10H), 7.28−7.23 (m, 1.20H), 4.56 (s, 2H), 4.50 (s, 0.14H), 3.62−3.58 (m, 0.06H), 3.32 (tt, $J$ = 10.0, 3.8, 1H), 3.12 (s, 0.18H), 3.11 (s, 3H), 1.88−1.79 (m, 3.96H), 1.67−1.57 (m, 2.40H), 1.49 (q, $J$ = 7.5, 0.21H), 1.41 (q, $J$ = 7.5, 2H), 1.18−1.10 (m, 1.96H), 0.85−0.81 (m, 3.15H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 139.3, 139.2, 128.2, 127.4, 127.27, 127.25, 127.2, 77.2, 77.0, 74.7, 73.8, 73.7, 69.7, 48.2, 47.8, 31.3, 28.6, 28.5, 27.2, 25.9, 7.2, 6.9; IR (thin film) 2937, 1457, 1367, 1072 cm$^{-1}$; HRMS (ES) *m*/*z* calcd for $C_{16}H_{24}NaO_2$ (M + Na)$^+$ 271.1674, found 271.1682. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.57; H, 9.79.

**Methyl Ethers 14c and 15c.** To a cooled (−78 °C) solution of **3c** (0.126 g, 0.600 mmol) in $CH_2Cl_2$ (3 mL) was added diethylzinc (1 M in hexanes, 1.2 mL, 1.2 mmol), the mixture was stirred for 10 s, and then TMSOTf (0.13 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 50:50 (**14c**/**15c**) was determined by subjecting the unpurified oil to GC: $t_R$ (major) 8.5 min, $t_R$ (minor) 8.9 min. The resulting oil was purified by flash chromatography (98:2 hexanes/EtOAc) to afford the product (as a 50:50 mixture as determinded by NMR) as a colorless oil (0.09 g, 75%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.16 (s, 3H), 3.10 (s, 3H), 1.89−1.79, (m, 4H), 1.69−1.66 (m, 2H), 1.56 (q, $J$ = 7.4, 2H), 1.51−1.49 (m, 2H), 1.40 (q, $J$ = 7.5, 2H), 1.35−1.20 (m, 4H), 1.10 (ddd, $J$ = 13.9, 13.6, 3.6, 2H), 1.05−1.00 (m, 3H), 0.96−0.90 (m, 1.5H), 0.85−0.80 (m, 26H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 75.9, 74.1, 48.05, 47.98, 47.82, 47.80, 34.3, 33.8, 32.4, 32.2, 29.6, 27.61, 27.59, 24.0, 23.0, 22.2, 7.1, 6.7; IR (thin film) 2933, 1456, 1367 cm$^{-1}$; HRMS (ES) *m*/*z* calcd for $C_{13}H_{26}O$ (M)$^+$ 198.1984, found 198.1981.

**Nitriles 16a and 17a.** To a cooled (−78 °C) solution of **3a** (0.150 g, 0.600 mmol) in $CH_2Cl_2$ (3 mL) was added cyanotrimethylsilane (0.09 mL, 0.7 mmol), the mixture was stirred for 2 min, and then TMSOTf (0.13 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 81:19 (**16a**/**17a**) was determined by subjecting the unpurified oil to GC: $t_R$ (major) 15.1 min, $t_R$ (minor) 15.2 min. The resulting oil was purified by flash chromatography (83:17 to 75:25 hexanes/ $CH_2Cl_2$) to afford the product (as a 75:25 mixture as determined by NMR) as a colorless oil (0.14 g, 94%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.28−7.25 (m, 2.50H), 7.18−7.14 (m, 3.75H), 3.43 (s, 3H), 3.38 (s, 0.74H), 2.63−2.58 (m, 2.51H), 2.26−2.23 (m, 2H), 2.18−2.15 (m, 0.66H), 1.94−1.85 (m, 2H), 1.70 (td, $J$ = 13.6, 3.9, 0.51H), 1.64−1.51 (m, 3.14H), 1.47−1.41 (m, 2H), 1.35−1.43 (m, 3.97H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.3, 142.2, 128.3, 128.2 125.7, 125.6, 120.4, 119.4, 76.6, 73.0, 52.5, 52.3, 37.8, 37.7, 35.7, 35.0, 34.8, 33.2, 33.0, 33.0, 26.2; IR (thin film) 3022, 2928, 2859, 1495, 1106 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{15}H_{21}O$ (M − CN)$^+$ 217.1592, found 217.1585. Anal. Calcd for $C_{16}H_{21}$-ON: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.05; H, 8.84; N, 5.84.

**Nitriles 16b and 17b.** To a cooled (−78 °C) solution of **3b** (0.150 g, 0.600 mmol) in $CH_2Cl_2$ (3 mL) was added cyanotrimethylsilane (0.31 mL, 2.4 mmol), the mixture was stirred for 2 min, and then TMSOTf (0.13 mL, 0.72 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (3 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 3 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 24:76 (**16b**/**17b**) was determined by subjecting the unpurified oil to GC: $t_R$ (major) 15.1 min, $t_R$ (minor) 15.2 min. The resulting oil was purified by flash chromatography (97:3 to 96:4 hexanes/EtOAc) to afford the products **17b** and a mixture of **17b** and **16b** (as a 2:1 mixture as determined by NMR) separately as colorless oils. **17b** (0.04 g, 24%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36−7.31 (m, 4H), 7.29−7.26 (m, 1H), 4.50 (s, 2H), 3.60−3.54 (m, 1H), 3.44 (s, 3H), 2.06−2.01 (m, 2H), 1.94−1.88 (m, 4H), 1.81−1.74 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 138.6, 128.4, 127.5, 127.3, 119.6, 74.7, 72.2, 69.9, 52.5, 30.5, 25.6; IR (thin film) 2924, 2833, 1495, 1368 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{15}H_{20}O_2N$ (M + H)$^+$ 246.1494, found 246.1483. Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.01; H, 7.92; N, 5.68. **Mixture of 17b and 16b** (0.1 g, 65%): $^1$H NMR

(500 MHz, $CDCl_3$) $\delta$ 7.38−7.25 (m, 7.39H), 4.52 (s, 1.15H), 4.50 (s, 1.74H), 3.60−3.54 (m, 1H), 3.54−3.48 (m, 0.48H), 3.44 (s, 3.12H), 3.43 (s, 1.17H), 2.25−2.17 (m, 0.92H), 2.09−1.98 (m, 2.10H), 1.98−1.85 (m, 5.01H), 1.83−1.71 (m, 3.9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 138.57, 138.55, 128.4, 128.4, 127.5, 127.5, 127.4, 127.3, 119.7, 119.6, 74.7, 74.2, 73.0, 72.2, 70.1, 69.9, 52.8, 52.4, 30.5, 26.6, 26.0; IR (thin film) 2941, 2866, 1495, 1028 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{15}H_{20}O_2N$ $(M + H)^+$ 246.1494, found 246.1503. Anal. Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.58; H, 7.88; N, 5.76.

**Methyl Ether 21.** To a cooled (−78 °C) solution of **20** (0.10 g, 0.50 mmol) in $CH_2Cl_2$ (2 mL) was added allyltrimethylsilane (0.35 mL, 2.1 mmol), the mixture was allowed to stir for 2 min, and then TMSOTf (0.12 mL, 0.64 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (2 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 2 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 90:10 was determined by $^1$H NMR spectroscopy. The resulting oil was purified by flash chromatography (99:1 hexanes/EtOAc) to afford the products **21** and a mixture of **21** and its minor diastereomer (as a 5:1 mixture as determined by $^1$H NMR spectroscopy) separately as colorless oils. **21** (0.03 g, 26%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.81 (ddt, $J$ = 17.4, 10.3, 7.3, 1H), 5.10−5.04 (m, 2H), 3.94−3.89 (m, 2H), 3.19 (s, 3H), 2.99 (ddd, $J$ = 11.2, 10.2, 3.9, 1H), 2.28 (ddt, $J$ = 14.4, 7.2, 1.3, 1H), 2.20 (ddt, $J$ = 14.4, 7.2, 1.3, 1H), 2.10 (dt, $J$ = 13.6, 3.1, 1H), 1.99−1.88 (m, 3H), 1.83−1.74 (m, 1H), 1.63−1.48 (m, 2H), 1.24 (ddd, $J$ = 14.4, 13.3, 4.0, 1H), 1.08 (dd, $J$ = 13.5, 12.6, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 133.6, 117.6, 83.1, 75.5, 67.3, 48.1, 41.3, 39.8, 36.5, 31.7, 30.5, 26.4; IR (thin film) 3074, 2936, 1639, 1456, 1358, 1076 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{12}H_{21}O_2$ $(M + H)^+$ 197.1542, found 197.1549. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.72; H, 10.28. **21 and its minor diastereomer** (0.06 g, 54%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.87−5.76 (m, 1.18H), 5.14−5.04 (m, 2.43H), 3.98−3.81 (m, 2.44H), 3.24 (s, 0.54H), 3.19 (s, 3H), 3.09 (ddd, $J$ = 10.7, 9.9, 3.9, 0.20H), 2.99 (ddd, $J$ = 11.1, 10.3, 3.9, 1H), 2.43−2.42 (m, 0.34H), 2.28 (ddt, $J$ = 14.6, 7.2, 1.2, 1H), 2.20 (ddt, $J$ = 14.2, 7.3, 1.2, 1H), 2.12−2.00 (m, 1.49H), 1.99−1.88 (m, 3.67H), 1.79 (tddd, $J$ = 12.4, 10.0, 6.6, 3.3, 1H), 1.63−1.36 (m, 2.96H), 1.32−1.21 (m, 1.63H), 1.08 (t, $J$ = 13.4, 12.6, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 133.6, 133.4, 117.6, 117.5, 83.1, 83.1, 75.5, 67.7, 67.2, 48.8, 48.1, 41.6, 41.3, 39.7, 37.1, 36.4, 36.4, 32.4, 31.7, 30.7, 30.4, 27.0, 26.4; IR (thin film) 3074, 2938, 1640, 1358, 1075 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{12}H_{21}O_2$ $(M + H)^+$ 197.1542, found 197.1549. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.68; H, 10.55.

**Methyl Ether 22.** To a cooled (−78 °C) solution of **20** (0.10 g, 0.50 mmol) in $CH_2Cl_2$ (2 mL) was added a solution of $Et_2Zn$ (1 M in hexanes, 0.64 mL, 0.64 mmol), the mixture was allowed to stir for 10 s, and then TMSOTf (0.12 mL, 0.64 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (2 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 2 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 88:12 was determined by subjecting the unpurified oil to GC: $t_R$ (major) 9.3 min, $t_R$ (minor) 9.1 min. The resulting oil was purified by flash chromatography (99:1 hexanes/EtOAc) to afford the products **22** and a mixture of **22** and its minor diastereomer (as a 5:1 mixture as determined by NMR) separately as colorless oils. **22** (0.05 g, 45%): $^1$H NMR (500 MHz, $CDCl_3$), $\delta$ 3.98−3.91 (m, 2H), 3.18 (s, 3H), 3.09 (ddd, $J$ = 10.5, 10.0, 3.9, 1H), 2.06 (dt, $J$ = 12.4, 2.8, 1H), 2.04−1.93 (m, 2H), 1.89 (dtd, $J$ = 12.2, 2.8, 2.5, 1H), 1.66 (q, $J$ = 7.4, 2H), 1.61−1.34 (m, 4H), 1.25 (t, $J$ = 12.5, 1H), 0.85 (t, $J$ = 7.4, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 83.4, 77.2, 67.7, 48.5, 41.7, 36.2, 32.3, 30.8, 27.2, 24.6, 6.8; IR (thin film) 2937, 1460, 1357, 1257 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_9H_{15}O_2$ $(M - C_2H_5)^+$ 155.1072, found 155.1078. **22 and its minor diastereomer** (0.03 g, 33%) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 3.98−3.91 (m, 2H), 3.18 (s, 3H), 3.13 (s, 0.58H), 3.09 (ddd, $J$ = 10.4, 10.3, 3.9, 1H), 3.04−3.98 (m, 0.23H), 2.13−1.86 (m, 4.83H), 1.84−1.74 (m, 0.44H), 1.66 (q, $J$ = 7.4, 2H), 1.61−1.34 (m, 5.01H), 1.25 (t, $J$ = 12.5, 1H), 1.21−1.14 (m, 0.41H), 1.03−0.98 (m, 0.23H), 0.87−0.84 (m, 3.54H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 83.38, 83.36, 77.2, 75.7, 67.7, 67.2, 48.5, 47.9, 41.7, 39.8, 36.2, 36.1, 32.3, 31.6, 30.8, 30.5, 29.1, 27.2, 26.5, 7.3, 6.8; IR (thin film) 2937, 1461, 1357, 1128 cm$^{-1}$; HRMS (EI) *m*/*z* calcd for $C_{10}H_{17}O$ $(M - MeO)^+$ 153.1279, found 153.1279. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.75; H, 10.73.

**Benzyl Ether 24.** To a cooled (−78 °C) solution of **23** (0.076 g, 0.248 mmol) in $CH_2Cl_2$ (2 mL) was added allyltributyltin (0.3 mL, 0.8 mmol), and the mixture was allowed to stir for 2 min, then TMSOTf (0.05 mL, 0.4 mmol) was added. The solution was warmed (0 °C), and $NaHCO_3$ (2 mL saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 2 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 82:18 was determined by subjecting the unpurified oil to GC: $t_R$ (major) 18.1 min, $t_R$ (minor) 17.7 min. The resulting oil was purified by flash chromatography (99:1 to 98:2 hexanes/EtOAc) to afford the products **24** and a mixture of **24** and its minor diastereomer (as a 3.7:1 mixture as determined by NMR) separately as colorless oils. **24** (0.051 g, 65%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36−7.30 (m, 4H), 7.25−7.22 (m, 1H), 5.74 (ddt, $J$ = 16.9, 10.4, 7.3, 1H), 5.03−4.99 (m, 2H), 4.61 (s, 2H), 3.17 (s, 3H), 2.16−2.14 (m, 2H), 1.79−1.60 (m, 6H), 1.53 (ddd, $J$ = 13.8, 13.6, 4.6, 2H), 1.02 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 140.4, 133.9, 128.2, 126.8, 126.7, 117.2, 79.7, 73.9, 65.7, 48.4, 41.7, 38.7, 29.3, 27.1, 24.0; IR (thin film) 3071, 2957, 1639, 1496, 1368, 1082 cm$^{-1}$. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.54; H, 10.33. **Mixture of 24 and its minor diastereomer** (0.020 g, 15%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.40−7.31 (m, 5.25H), 7.27−7.22 (m, 3.53H), 5.87 (ddt, $J$ = 17.2, 10.2, 7.1, 1H), 5.74 (ddt, $J$ = 17.6, 10.4, 7.3, 0.27H), 5.12−5.06 (m, 2H), 5.04−4.98 (m, 0.57H), 4.65 (s, 2H), 4.62 (s, 0.54H), 3.18−3.17 (m, 3.91H), 2.34−2.33 (m, 2H), 2.16−2.15 (m, 0.55H), 1.99−1.94 (m, 2H), 1.80−1.66 (m, 3.5H), 1.66−1.48 (m, 6.29H) 1.03−1.02 (m, 11.88H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 140.2, 140.1, 134.2, 133.9, 128.3, 128.2, 126.94, 126.91, 126.86, 126.7, 117.2, 117.0, 79.7, 79.1, 76.8, 75.4, 65.7, 65.7, 48.4, 48.3, 41.8, 41.7, 38.7, 36.1, 29.7, 29.4, 27.1, 26.0, 24.0; IR (thin film) 3070, 3029, 2957, 1638, 1496, 1454 cm$^{-1}$. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.47; H, 10.40.

**Benzyl Ether 25.** To a cooled (−78 °C) solution of **23** (0.100 g, 0.33 mmol) in $CH_2Cl_2$ (2 mL) was added a solution of $Et_2Zn$ (1 M in hexanes, 0.39 mL, 0.39 mmol), the mixture was allowed to stir for 10 s, and then TMSOTf (0.09 mL, 0.39 mmol) was added. The solution was allowed to warm (0 °C), and $NaHCO_3$ (2 mL, saturated, aqueous) was added. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (5 × 2 mL). The organic layers were combined, filtered through $Na_2SO_4$, and concentrated in vacuo. A selectivity of 97:3 was determined by subjecting the unpurified oil to GCMS: $t_R$ (major) 19.4 min, $t_R$ (minor) 19.0 min. The resulting oil was purified by flash chromatography (98:2 to 97:3 hexanes/EtOAc) to afford the product as a colorless oil (0.078 g, 79%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.41−7.39 (m, 2H), 7.34−7.31 (m, 2H), 7.26−7.22 (m, 1H), 4.66 (s, 2H), 3.13 (s, 3H), 1.98−1.92 (m, 2H), 1.72 (ddd, $J$ = 13.6, 13.5, 3.9, 2H), 1.62−1.55 (m, 4H), 1.48 (td, $J$ = 14.3, 4.0, 2H), 1.01 (s, 9H), 0.85 (t, $J$ = 7.4, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 140.1, 128.2, 126.9, 79.3, 75.4, 65.6, 48.0, 38.7, 29.6, 27.2, 26.1, 23.2, 6.9; IR (thin film) 2963, 2875, 1120, 1070 cm$^{-1}$. Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.00; H, 10.56.

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**Supporting Information Available:** Complete experimental procedures, product characterization, stereochemical proofs, and GC and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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