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Directed Diastereoselectivity in the Asymmetric Claisen/Metathesis Reaction Sequence

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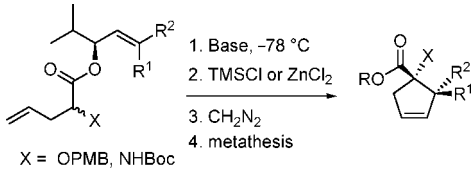


The Claisen/metathesis sequence is a versatile synthetic tool for the synthesis of quaternary hydroxy and amino acid carbocycles. By correctly choosing both the configuration of the allylic alcohol and the double bond geometry, specific access to any one of four possible stereoisomers is possible in good yield and excellent diastereoselectivity. The enantiomerically pure allylic alcohols are easily obtained by addition of terminal alkynes to aldehydes. Controlled reduction of the triple bond then gives the desired double bond geometry.

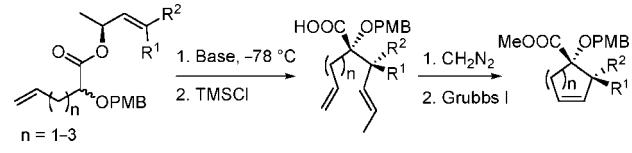
Since its introduction in 1972, the Ireland−Claisen rearrangement has proven to be an invaluable tool for the stereoselective formation of carbon−carbon bonds.[1] This rearrangement has been widely used in natural product synthesis, and has also been shown to be extremely useful in the formation of quaternary stereogenic centers. When esters are prepared from chiral allylic alcohols and carboxylic acids, an efficient chirality transfer occurs from the carbinol center to the newly formed stereocenter(s) at C2 and/or C3 of the acid product.

When the Claisen rearrangement is associated with ring closing metathesis, a powerful tandem reaction sequence can be generated in which access to a large number of asymmetric unsaturated carbocycles is possible, depending on the starting substrate. In 1998, two groups simultaneously described this sequence. Piscopio et al. reported the approach with nonchiral substrates for the synthesis of a variety of cyclic systems, including both carbo- and heterocycles in fair to good diastereoselectivities.[2] Burke et al. reported the synthesis of substituted dihydropyran-2-carboxylates starting from several enantiopure allylic alcohols and obtained selectivities of up to >20/1 for the rearrangement step.[3] Since then, several other groups have described examples in which the reaction sequence is performed with nonchiral substrates.[4]

In their total synthesis of Pancratistatin, Kim et al. used an enantiopure substrate in an Ireland−Claisen/metathesis sequence with only moderate diastereoselectivity (6/1) in the rearrangement step.[5] More recently, in the synthesis of (−)-Perrottetinene, the key cis-disubstituted cyclohexene ring was obtained by a highly diastereoselective (>20/1) Ireland−Claisen/metathesis sequence.[6] The absolute stereochemistry was derived from the starting chiral γ-hydroxy vinylstannane building block.

It was recently shown that the asymmetric Ireland−Claisen/metathesis sequence can be used to synthesize various cyclic quaternary α-alkoxyacids/esters with excellent diastereoselectivities from enantiomerically pure allylic alcohols and unsaturated α-alkoxy acids (Scheme 1).[7]

SCHEME 1. The Ireland−Claisen/Metathesis Sequence



This asymmetric sequence has been successfully used in both the formal total synthesis of fumagillin[8] and that of a spirotetronate subunit of the quartromicins.[9]

While the Ireland−Claisen rearrangement is technically limited to silyl ketene acetal intermediates, many variations have been reported. For example, with allylic esters having α-heteroatoms, an enolate Claisen rearrangement is evoked, in the presence or absence of trimethylsilyl chloride.[10] The rearrangement usually proceeds via a highly ordered six-member chairlike transition state. The α-heteroatom stabilizes the enolate through

(1) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650–657. (d) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572–3582. (e) McFarland, C. M.; McIntosh, M. C. In *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2007; pp 177−210.

(2) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158–3159.

(3) Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160–3161.

(4) (a) Srikrishna, A.; Khan, I. A.; Babu, R. R.; Sajjanshetty, A. *Tetrahedron* **2007**, *63*, 12616–12620. (b) Srikrishna, A.; Babu, R. R. *Tetrahedron Lett.* **2007**, *48*, 6916–6919. (c) Srikrishna, A.; Lakshmi, B. V.; Mathews, M. *Tetrahedron Lett.* **2006**, *47*, 2103–2106. (d) Srikrishna, A.; Lakshmi, B. V. *Tetrahedron Lett.* **2005**, *46*, 7029–7031. (e) Srikrishna, A.; Lakshmi, B. V. *Tetrahedron Lett.* **2005**, *46*, 4879–4881. (f) Srikrishna, A.; Lakshmi, B. V. *Synlett* **2005**, 1173–1175. (g) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465–3468. (h) Beaulieu, P.; Ogilvie, W. W. *Tetrahedron Lett.* **2003**, *44*, 8883–8885. (i) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. C.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716–3721.

(5) Ko, H.; Kim, E.; Park, J. E.; Kim, D.; Kim, S. *J. Org. Chem.* **2004**, *69*, 112–121.

(6) Song, Y.; Hwang, S.; Gong, P.; Kim, D.; Kim, S. *Org. Lett.* **2008**, *10*, 269–271.

(7) Français, A.; Bedel, O.; Picoul, W.; Meddour, A.; Courtieu, J.; Haudrechy, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1141–1155.

(8) (a) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797–4800. (b) Picoul, W.; Bedel, O.; Haudrechy, A.; Langlois, Y. *Pure Appl. Chem.* **2003**, *75*, 235–249.

(9) Bedel, O.; Français, A.; Haudrechy, A. *Synlett* **2005**, 2313–2316.

(10) Kazmaier, U. In *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, Germany, 2007; pp 233−299..

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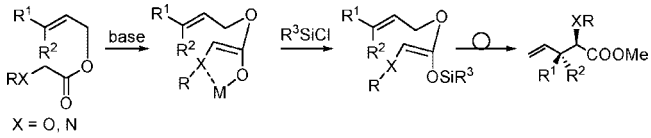
a five-member chelate ring, and (*Z*)-enolates are almost exclusively obtained (Scheme 2). The relative stereochemistry of the newly formed centers can then be controlled by simply changing the olefin geometry of the starting allylic alcohol.

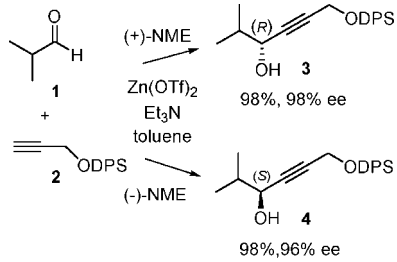
SCHEME 2. *Z*-Enolate Formation



If the starting ester is prepared from both a chiral allylic alcohol and an unsaturated α-hydroxy or α-amino acid, excellent diastereoselectivity can be expected in the Claisen rearrangement. A sequential metathesis reaction would lead to a large number of diverse unsaturated carbocycles with the stereoselective formation of a quaternary carbon center α to the carboxyl group. Herein, we wish to report our results on the directed diastereoselective synthesis of cyclic quaternary α-hydroxy and α-amino acid derivatives.

For the purpose of our study, γ-unsaturated α-hydroxy or α-amino acids were chosen for the acid moiety, which, after ring closing metathesis, would lead to the formation of the corresponding unsaturated cyclopentenes. To easily access the desired chiral allylic alcohols in both configurations, we chose to use the method developed by Carreira et al.[11] for the enantioselective synthesis of propargylic alcohols by the addition of terminal alkynes to aldehydes (Scheme 3).

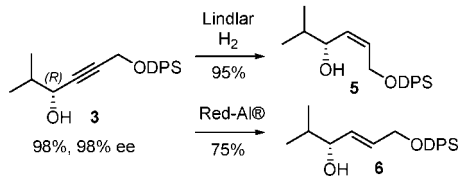
SCHEME 3. Propargylic Alcohol Synthesis



Isobutyraldehyde was chosen as the coupling partner with alkyne **2**[12] for strictly practical purposes as the coupling reaction works best with secondary aldehydes, and the isopropyl moiety is eliminated in the metathesis step.

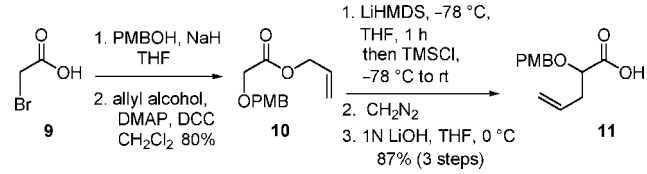
The double bond configuration was then established through partial reduction of the alkyne by either hydrogenation in the presence of Lindlar's catalyst (*Z*-olefins) or treatment with Red-Al in THF (*E*-olefins) (Scheme 4).

SCHEME 4. Alkyne Reduction



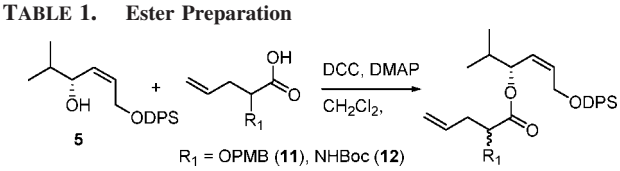
Compared to our previously reported conditions,[7] the synthesis of the protected α-hydroxy acid **11** was modified to optimize product yield. The unsaturated acid was prepared in 5 steps in 70% overall yield starting from bromoacetic acid **9** (Scheme 5). Intermediate esterification was performed solely to facilitate purification.

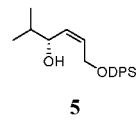
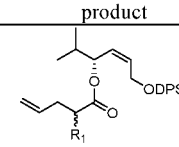
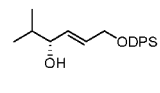
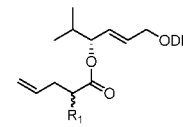
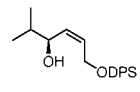
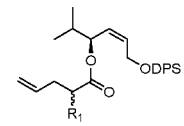
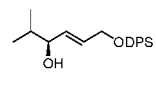
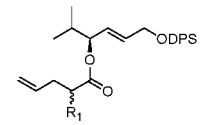
SCHEME 5. Synthesis of γ-Unsaturated α-Alkoxy Acid 11



Preparation of the unsaturated α-amino acid **12** was done in a straightforward manner from DL-2-amino-4-pentenoic acid and di-*tert*-butyl dicarbonate.[13] Esterification was then carried out with the four chiral allylic alcohols with use of standard DCC coupling techniques, giving the desired compounds in good yield (Table 1).

TABLE 1. Ester Preparation



alcohol	acid	product	yield (%)
 **5**	**11** **12**		R_1= OPMB, **13a**; 93% NHBoc, **13b**; 92%
 **6**	**11** **12**		R_1= OPMB, **14a**; 94% NHBoc, **14b**; 93%
 **7**	**11** **12**		R_1= OPMB, **15a**; 95% NHBoc, **15b**; 89%
 **8**	**11** **12**		R_1= OPMB, **16a**; 92% NHBoc, **16b**; 95%

When our model ester **17** was subjected to standard rearrangement conditions (1.5 equiv of KHMDS (commercial solution), toluene, TMSCl −78 °C)[7] the rearranged methyl ester **18** was obtained in 77% yield after treatment with diazomethane. The presence of 10−15% of unreacted ester leads us to further optimize reaction conditions. It was found that addition of the ester to LiHMDS, generated in situ from *n*-BuLi and freshly distilled 1,1,1,3,3,3-hexamethyldisilazane in toluene, increased the reaction yield to 91% with no recovered starting material (Scheme 6).

These conditions were then applied to esters **13a**−**16a** to give the rearranged products in excellent yield and diastereoselectivity (Table 2).[14] Ring closing metathesis was performed by using

(11) Frantz, D. E.; Fässler, R.; Carreira, E. M *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

(12) Bekele, T.; Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 8471–8479.

(13) Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Veerman, J. J. N.; Kamphuis, J.; Peggion, C.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2001**, *57*, 6567–6577.

(14) Diastereoselectivities were calculated from 500 MHz ^{1}H NMR spectra.

SCHEME 6. Optimized Rearrangement Conditions

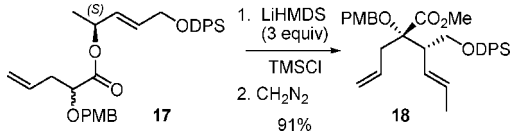
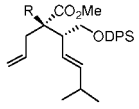
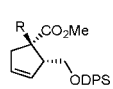
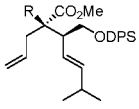
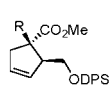
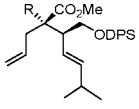
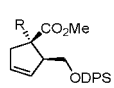
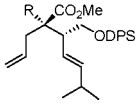
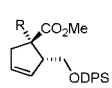


TABLE 2. The Claisen/Methathesis Sequence with α-Alkoxy and α-Amino Esters[a]

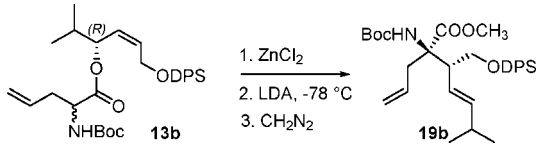
ester	rearrangement product	yield (%)	metathesis produit	yield (%)
13a*		**19a,** 75%; 99% de		**20a**, 92%
13b		**19b**, 61%; 97% de		**20b**, 95%
14a		**21a**, 87%; 92% de		**22a**, 94%
14b		**21b**, 67%; 96% de		**22b**, 94%
15a		**23a**, 73%; 95% de		**24a**, 97%
15b		**23b**, 67%; 95% de		**24b**, 97%
16a		**25a**, 88%; 99% de		**26a**, 96%
16b		**25b**, 63%; 99% de		**26b**, 95%

[a] See the asterisk in the first column: series a: R = OPMB; series b: R = NHBoc.

Grubb's first generation catalyst, and the cyclized products were obtained in excellent yields.

Chelate Claisen rearrangement of the chiral α-aminoesters **13b**−**16b** was performed by slightly modifying the procedure reported by Kazmaier et al. in the presence of zinc chloride (Scheme 7).[15]

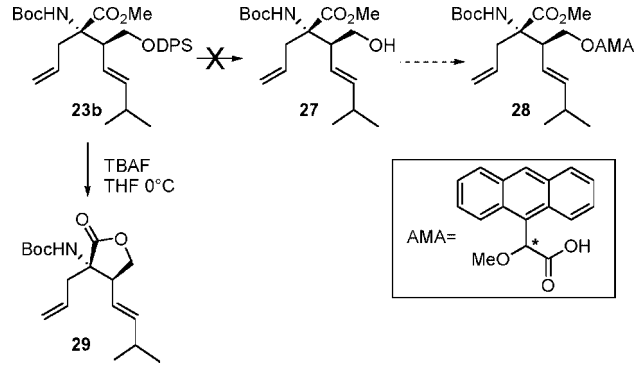
SCHEME 7. Chelate Claisen Rearrangement of 13b



The corresponding methyl esters **19b**, **21b**, **23b**, and **25b** were obtained in fair yield and excellent diastereoselectivity (Table 2). Ring closing metathesis then proceeded smoothly in the presence of Grubb's catalyst.

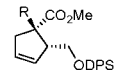
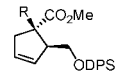
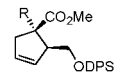
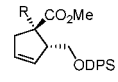
The relative and absolute stereochemistry depicted in Table 2 is based on our previous work in the (*S*)-OPMB series, in which several six-member rings issued from the Ireland−Claisen/metathesis sequence were analyzed by using deuterium NMR in chiral liquid crystals.[7] Although we felt confident about predicting stereochemistry based on this and the highly ordered transition states involved, we also felt that it was necessary to unequivocally confirm the stereochemistry of all of the obtained products. To do so, we used the chiral shift reagents (*R*)- or (*S*)-9-anthrylmethoxyacetic acid (9-AMA) to determine the absolute configuration of the *β*-chiral primary alcohol, a method developed by Riguera et al.[16] Unfortunately, but perhaps not surprisingly, TBAF deprotection of the DPS group gave 74% of lactone **29** instead of the expected alcohol **27** (Scheme 8).

SCHEME 8. Alcohol Deprotection and Lactone Formation



To avoid lactonization it was necessary to either "deactivate" the methyl ester or to deprotect the alcohol in a situation where cyclization was impossible. Two of the four cyclopentenes in each series (**22a**, **22b**, **26a**, and **26b**) were ideal candidates for deprotection without cyclization. If the methyl ester and the alcohol were in a trans configuration, lactone formation would be difficult because of the strain involved in closing the fused ring system. This would, of course, also confirm the relative stereochemistry of the adjacent chiral centers. If lactonization occurred, the cis relationship of the primary alcohol and the methyl ester would thus be established. These results are presented in Table 3.

TABLE 3. Relative Configuration of the Adjacent Stereocenters[a]

cyclopentene	product	yield (%)
		**30a***, 77%
		30b, 70%
		**31a**, 64%
		31b, 83%
		**32a**, 79%
		32b, 74%
		**33a**, 64%
		33b, 82%

[a] See the asterisk in the last column: series a: R = OPMB; series b: R = NHBoc.

The absolute configuration of the primary alcohols was then determined as follows. Alcohols **31a**, **31b**, **33a**, and **33b** were coupled to both the (*R*)- and (*S*)-9-AMA acids, and ^{1}H NMR spectra were recorded for the esters. This method is based on the observation that the sign of $\Delta\delta^{RS}$ is consistently positive or negative depending on the spatial arrangement of the substituents in relation to the anthryl ring of the chiral shift reagent. Figure 1 shows the $\Delta\delta^{RS}$ values experimentally obtained for the NHBoc

(15) (a) Kazmaier, U.; Schneider, C. *Synlett* **1996**, 975–977. (b) Kazmaier, U.; Schneider, C. *Synthesis* **1998**, 1321–1326. (c) Kazmaier, U.; Schneider, C. *Tetrahedron Lett.* **1998**, *39*, 817–818. (d) Schneider, C.; Kazmaier, U. *Eur. J. Org. Chem.* **1998**, 1155–1159.

(16) Latypov, S. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R *J. Am. Chem. Soc.* **1998**, *120*, 4741–4751.

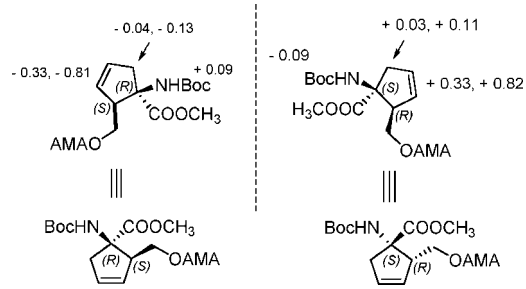


FIGURE 1. Comparison of the $\Delta\delta^{RS}$ values of the 9-AMA esters.

(*R*)- and (*S*)-9-AMA derivatives and clearly confirms the absolute configuration of the chiral center.

In conclusion, we have shown that an enolate Claisen metathesis sequence is a versatile synthetic tool for the synthesis of quaternary hydroxy and amino acid carbocycles. The judicious choice of both the configuration of the allylic alcohol and the double bond geometry gives access to any one of four stereoisomers in good yield and excellent diastereoselectivity. The enantiomerically pure chiral allylic alcohols are easily obtained by using the synthetic method developed by Carreira. Controlled reduction of the triple bond then gives the desired *E* or *Z* geometry. While this method has been exemplified for five-member rings, it is clear that changing the position of the unsaturation in the acid partner can give access to six, seven, or higher member rings in a completely controlled manner. Work is currently in progress to apply this sequence to the synthesis of biologically active natural products.

Experimental Section

General Procedure for the Ireland−Claisen/Metathesis Sequence (OPMB Esters). *n*-BuLi (3 equiv, 2.3 M solution in hexanes) was added to a solution of HMDS (4 equiv) in dry toluene cooled to 0 °C under argon and stirred for 15 min. The solution was then further cooled to −78 °C. The starting ester (1 equiv) dissolved in dry toluene (3 mL) was added dropwise via a canula to the reaction vessel at −78 °C. The reaction mixture was stirred for 45 min before freshly distilled TMSCl (3 equiv) was introduced via syringe and maintained at this temperature for an extra 10 min before gradually warming to rt. After 2 h, the reaction mixture was quenched by a saturated aqueous solution of ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether, dried over $MgSO_4$, filtered, and concentrated. The crude acid was immediately treated with a solution of diazomethane in ether to give the corresponding methyl ester, which was purified by flash chromatography (petroleum ether/EtOAc 95:5). The methyl ester (1 equiv) was then dissolved in CH_2Cl_2 (0.2 M solution). First generation Grubbs catalyst (0.1 equiv) was added and the reaction heated to 40 °C for 1 h. After cooling, the mixture was concentrated, and the crude product was purified by flash chromatography to afford the pure compound.

(*E*)-(2*R*,3*S*)-2-Allyl-3-(*tert*-butyldiphenylsilanyloxymethyl)-2-(4-methoxybenzyloxy)-6-methylhept-4-enoic Acid Methyl Ester (19a). Yield 75% (99% de), colorless oil. $[\alpha]^{20}_D$ −15.8 (*c* 0.69, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.00 (s, 6H), 1.02 (s, 9H), 2.33 (m, 1H), 2.70 (m, 3H), 3.61 (s, 3H), 3.70 (dd, J = 7.9, 9.9 Hz, 1H), 3.79 (s, 3H), 4.06 (dd, J = 3.8, 9.9 Hz, 1H), 4.41 (s, 2H), 5.08 (s, 1H), 5.14 (s, 1H), 5.34 (dd, J = 9.5, 15.3 Hz, 1H), 5.55 (dd, J = 6.7, 15.3 Hz, 1H), 5.79 (m, 1H), 6.82 (d, J = 8.6 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.30−7.43 (m, 6H), 7.64−7.67 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 22.4, 22.6, 26.8, 31.4, 37.1, 51.5, 51.9, 55.2, 63.0, 66.1, 82.9, 113.5, 118.6, 124.1, 127.5, 128.6, 129.4, 130.8, 132.5, 133.8, 133.9, 135.6, 142.1, 158.8, 172.7; IR (neat) ν_{max} 2956, 2931, 2858, 1737, 1514 cm^{-1}; ESI-MS *m*/*z* 623.3 [M + Na]$^+$. Anal. Calcd for $C_{37}H_{48}O_5Si$: C 73.96, H 8.05. Found: C 74.27, H 8.07.

(1*R*,2*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-1-(4-methoxybenzyloxy)cyclopent-3-enecarboxylic Acid Methyl Ester (20a). Yield 92% (colorless oil). $[\alpha]^{20}_D$ −95.5 (*c* 0.93, $CHCl_3$); R_f 0.74 (petroleum ether/EtOAc 8:2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.03 (s, 9H), 2.76 (d, J = 17.6 Hz, 1H), 3.14 (d, J = 17.6 Hz, 1H), 3.19 (br s, 1H), 3.65 (s, 3H), 3.66 (d, J = 6.2 Hz, 2H), 3.77 (s, 3H), 4.43 (d, J = 11.37 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 5.61 (d, J = 3.7 Hz, 1H), 5.78 (d, J = 3.7 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.34−7.42 (m, 6H), 7.64 (d, J = 7.3 Hz, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 19.2, 26.8, 41.1, 51.9, 55.3, 59.0, 63.3, 66.9, 88.7, 113.7, 127.6, 128.9, 129.6, 135.6, 135.6, 159.1, 172.6; ESI HRMS *m*/*z* calcd for $C_{32}H_{38}O_5Si$ (M + Na)$^+$ 553.2386, found 553.2384.

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Supporting Information Available: General experimental procedures and copies of NMR spectra (^{1}H and ^{13}C) of all of the new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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