Carbon−Carbon Bond Formation with Allylmagnesium Chloride

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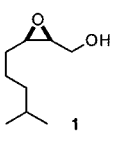
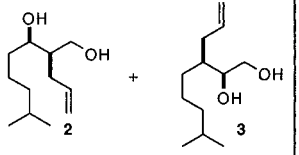
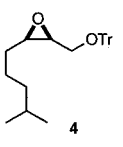
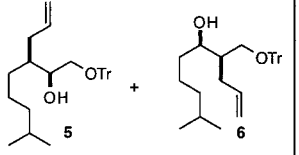
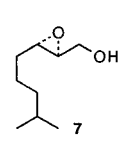
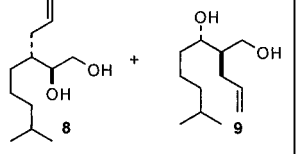
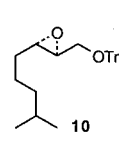
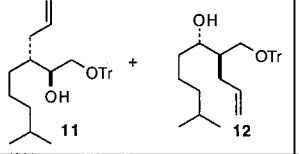
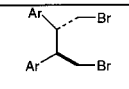
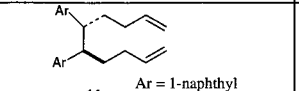
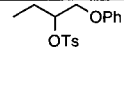
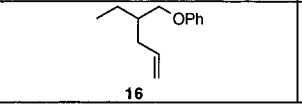
Preparative organic chemistry centers on nucleophilic carbon−carbon bond formation. Most commonly, stabilized anions (e.g. enolates) are used as nucleophiles. In contrast, simple organometal derivatives such as alkyllithiums and alkylmagnesium halides (Grignard reagents) are usually *not* effective for the displacements of ordinary halides or sulfonates. This problem has been circumvented by the use of, for instance, lithium dialkyl cuprates. We would like to draw attention to an underappreciated exception to this rule, allylmagnesium chloride.[2]

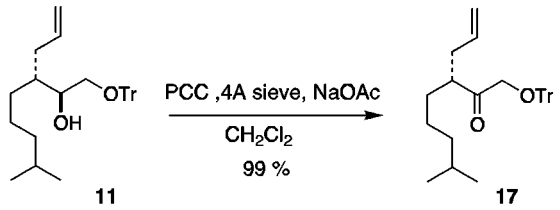
We report that *uncatalyzed* allylmagnesium chloride is not only nucleophilic enough to attack both glycidyl alcohols and their trityl ethers, but is also nucleophilic enough to displace primary bromides and secondary tosylates (Table 1). Usually, the opening of an epoxide, including the glycidyl derivatives described here, with a Grignard reagent *requires* Cu catalysis.[3,4] Although the nucleophilic opening of epoxides with allylmagnesium chloride has been recognized,[5] there have been no reports on the addition of allylmagnesium chloride to glycidyl alcohols.

A major concern in our work was the regioselectivity of the nucleophilic addition of allylmagnesium chloride to cis- and trans-substituted glycidyl alcohols and their trityl ethers. Four epoxides were studied for this purpose, **1**, **4**, **7**, and **10** (Table 1). The regioselectivity of the addition was found to depend on the relative configurations of the glycidyl alcohols.[3,4] In each case, the reaction proceeded with clean inversion of configuration.[6]

Table 1. Nucleophilic Coupling with Allylmagnesium Chloride

entry	starting material	product	ratio	% yield
1	 **1**	 **2** + **3**	3.6 : 1	87
2	 **4**	 **5** + **6**	8.1 : 1	93
3	 **7**	 **8** + **9**	2.5 : 1	97
4	 **10**	 **11** + **12**	9.9 : 1	74
5	 **13**	 **14** Ar = 1-naphthyl	-	75
6	 **15**	 **16**	-	76

The substitution pattern of the product diols was determined by tritylating the primary alcohols of the 1,2-diols **3** and **8** (Table 1). The derived monotrityl alcohols were then compared to the products from the opening of the trityl ethers **4** and **10** (Table 1). Independent PCC oxidation of the monotrityl ethers **5** and **11** (Table 1) resulted in a single ketone that was unequivocally **17**.



11 **17**

Although others have reported that the coupling of allyl Grignard with primary bromides *requires* Cu(I) catalysis,[7] our experience has been that the coupling occurs smoothly *without* Cu(I) catalysis (**13**, Table 1).[8] The remarkable nucleophilicity of allylmagnesium chloride then led us to consider the possibility of direct displacement of a secondary tosylate. Previously, we had observed that allylmagnesium chloride would displace a primary tosylate.[9] In fact, allylmagnesium chloride coupled cleanly with the secondary tosylate **15** (Table 1).

The efficient couplings documented here should emphasize the central role the commercially available and inexpensive allylmagnesium chloride could play in organic synthesis. The terminal vinyl group so introduced is a versatile site for further transformation. *Inter alia*, the work outlined here establishes new avenues for

(1) Undergraduate research participant.

(2) The efficient participation of allylmagnesium bromide in S_N2 displacement was noted almost 50 years ago: Letsinger, R. L.; Traynham, J. G. *J. Am. Chem. Soc.* **1950**, *72*, 849. This work has not been pursued, with the exception of a report of similar reactivity for allyllithium: Sommer, L. H.; Korte, W. D. *J. Org. Chem.* **1970**, *35*, 22.

(3) For the first report of Grignard addition to a glycidyl alcohol, see: (a) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131. For more recent results, see: (b) Kato, K.; Nagai, M.; Takita, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 119. (c) Kvarnstrom, I.; Svansson, L. *J. Org. Chem.* **1991**, *56*, 2993. (d) Katsuki, T.; Okamura, H.; Kuroda, S.; Ikegami, S.; Ito, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 5141. (e) Pattenden, G.; Kiefel, M. J.; Maddock, J.. *Tetrahedron Lett.* **1992**, *33*, 3227. (f) Miyashita, M.; Irie, H.; Yoshihara, K.; Kawamine, K.; Hoshino, M. *Tetrahedron Lett.* **1993**, *34*, 6285. (g) Nishizawa, M.; Minagawa, R.; Garcia, D. M.; Hatakeyama, S.; Yamada, H. *Tetrahedron Lett.* **1994**, *35*, 5891. (h) Rychnovsky, S. D.; Richardson, T. I. *J. Org. Chem.* **1996**, *61*, 4219.

(4) For references to Grignard ring openings of the trityl ether derivitives of glycidyl alcohols, see: (a) Schneider, G.; Horvath, T.; Sohar, P. *Carbohydr. Res.* **1977,** *56*, 43. (b) Sato, F.; Kitano, Y.; Kobayashi, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 498. (c) Rich, D. H.; Tung, R. D. *Tetrahedron Lett.* **1987**, *28*, 1139. (d) Heathcock, C. H.; Hoagland, S.; Morita, Y.; Bai, D. L.; Marki, H.-P.; Kees, K.; Brown, L. *J. Org. Chem.* **1988**, *53*, 3, 4730. (e) Katsuki, T.; Okamura, H.; Kuroda, S.; Ikegami, S.; Tomita, K.; Sugimoto, Y.; Sakaguchi, S.; Ito, Y.; Yamaguchi, M. *Tetrahedron* **1993**, *49*, 10531. (f) Schore, N. E.; Casainuovo, J. A.; Scott, R. W.; Harwood, E. A. *Tetrahedron Lett.* **1994**, *35*, 1153. (g) Nakata, M.; Ishiyama, T.; Akamatsu, S.; Hirose, Y.; Maruoka, H.; Suzuki, R.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 8, 967.

(5) Boto, A.; Betancor, C.; Prange, T.; Suarez, E.; *J. Org. Chem.* **1994**, *59*, 4393.

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synthesizing highly functionalized, enantiomerically enriched starting materials, through the use of enantiomerically enriched glycidyl derivatives.[10]

Experimental Section[11]

(*R,*R**)-7-Methyl-2-(2-propenyl)-1,3-octanediol (2) and (*R**,*R**)-3-(4-Methylpentyl)-5-hexene-1,2-diol (3).** Allylmagnesium chloride (3.4 mL of 2.0 M in THF, 6.73 mmol) was added dropwise over 15 min to epoxide **1** (213 mg, 1.35 mmol) in THF (1 mL) at 0 °C. After being stirred at rt overnight, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give a mixture of the C-2-allylated product **2** and its C-3 regioisomer **3** (3.6:1)[12] (232 mg, 1.16 mmol, 87% yield) as an opaque white oil. **2**: TLC R_f (50% MTBE/25% CH_2Cl_2/petroleum ether) = 0.50; ^{1}H NMR δ 0.88 (d, J = 6.5 Hz, 6H), 1.71−1.15 (m, 7H), 1.75 (m, 1H), 2.10 (t, J = 6.8 Hz, 2H), 3.36 (bs, 2H), 3.87−3.67(m, 3H), 5.05 (m, 2H), 5.83 (m, 1H); ^{13}C NMR δ 116.2, 64.2, 38.9, 33.6, 30.0, 24.0; d 137.0, 74.4, 44.0, 27.8, 22.5; IR (cm^{-1}) 3346, 3078, 2954, 2932, 2870, 1641, 1467; MS *m*/*z* 185 (0.14), 169 (0.15), 151 (0.30), 140 (0.42), 115 (12), 97 (38), 95 (18); HRMS calcd for $C_{12}H_{25}O_2$ 201.1855, obsd 201.1857. **3**: TLC R_f (50% MTBE/25% CH_2Cl_2/petroleum ether) = 0.37; ^{1}H NMR δ 0.87 (d, J = 6.6 Hz, 6H), 1.41−1.10 (m, 6H), 1.52 (m, 2H), 1.70 (bs, 1H), 2.17 (m, 4H), 3.71−3.52 (m, 3H), 5.06 (m, 2H), 5.83 (m, 1H); ^{13}C NMR δ u 116.3, 65.0, 39.2, 34.0, 29.8, 24.7; d 137.2, 74.1, 40.6, 27.9, 22.6, 22.5; IR (cm^{-1}) 3362, 3076, 2929, 2869, 1640, 1468; MS *m*/*z* 201 (0.51), 170 (2.0), 169 (18), 151 (12), 123 (6.7), 109 (36), 95 (100); HRMS calcd for $C_{12}H_{25}O_2$ 201.1855, obsd 201.1831.

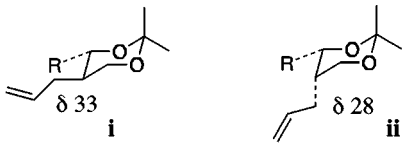
(*R,*R**)-3-(4-Methylpentyl)-1-(triphenylmethoxy)-5-hexen-2-ol (5) and (*R**,*R**)-9-Methyl-4-[(triphenylmethoxy)methyl]-1-decen-5-ol (6).** Allylmagnesium chloride (2.5 mL of 2.0 M in THF, 5.01 mmol) was added dropwise over 10 min to epoxide **4** (403 mg, 1.00 mmol) in THF (1.4 mL) at 0 °C. The mixture was allowed to warm to rt (30 min), stirred for an additional 20 min, and then partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give a mixture of the C-3-allylated product **5** and its C-2 regioisomer **6** (8.1:1)[10] (414 mg, 0.93 mmol, 93% yield) as a thick opaque white oil. Further chromatography led to analytical samples. **5**: TLC R_f (10% MTBE/5% CH_2Cl_2/petroleum ether) = 0.63; ^{1}H NMR δ 0.82 (d, J = 6.6 Hz, 6H), 1.27−1.07 (m, 6H), 1.57−1.41 (m, 2H), 2.08 (t, J = 6.4 Hz, 2H), 2.37 (s, 1H), 3.19 (m, 2H), 3.77 (bs, 1H), 4.95 (m, 2H), 5.30 (m, 1H), 7.46−7.11 (m, 15H); ^{13}C NMR δ u 143.9, 115.9, 86.7, 65.9, 39.2, 33.7, 29.6, 24.6; d 137.3, 128.6, 127.8, 127.1, 72.4, 40.4, 27.8, 22.6; IR (cm^{-1}) 3581, 3472, 3060, 3033, 2927, 2868, 1639, 1597; MS *m*/*z* 442 (0.00040), 424 (0.0027), 365 (0.13), 274 (0.087), 243 (100), 183 (12), 165 (30); HRMS calcd for $C_{31}H_{38}O_2$ 442.2872, obsd 442.2864. **6**: TLC R_f (10% MTBE/5% CH_2Cl_2/petroleum ether) = 0.58; ^{1}H NMR δ 0.87 (s, 6H), 1.56−1.15 (m, 7H), 1.79 (bs, 1H), 2.20 (q, J = 5.5 Hz, 2H), 2.78 (bs, 1H), 3.26 (s, 2H), 3.75 (bs, 1H), 4.97 (m, 2H), 5.69 (m, 1H), 7.44−7.22 (m, 15H); ^{13}C NMR δ u 143.7, 116.1, 87.1, 64.7, 39.0, 33.9, 30.6, 23.9; d 137.2, 128.6, 127.8, 127.1, 127.0, 74.0, 43.5, 27.9, 22.6; IR (cm^{-1}) 3464, 3085, 3059, 3033, 2950, 2868, 1640, 1597.

(*R,*S**)-3-(4-Methylpentyl)-5-hexene-1,2-diol (8) and (*R**,*S**)-7-Methyl-2-(2-propenyl)-1,3-octanediol (9).** Allylmagnesium chloride (3.2 mL of 2.0 M in THF, 6.45 mmol) was added dropwise over 10 min to epoxide **7** (204 mg, 1.29 mmol) in THF (1 mL) at 0 °C. After being stirred at rt overnight, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give a mixture of the C-3-allylated product **8** and its C-2 regioisomer **9** (2.5:1)[10] (251 mg, 1.25 mmol, 97% yield) as an opaque white oil. **8**: TLC R_f (50% MTBE/25% CH_2Cl_2/petroleum ether) = 0.28; ^{1}H NMR δ 0.86 (d, J = 6.7 Hz, 6H), 1.38−1.10 (m, 6H), 1.52 (m, 2H), 2.05 (m, 1H), 2.19 (m, 1H), 3.31 (bs, 1H), 3.38 (bs, 1H), 3.72−3.50 (m, 3H), 5.05 (m, 2H), 5.77 (m, 1H); ^{13}C NMR δ u 116.3, 64.8, 39.2, 34.5, 29.2, 24.9; d 137.0, 74.0, 40.7, 27.8, 22.6, 22.5; IR (cm^{-1}) 3362, 3077, 2954, 2928, 2869, 1640, 1468; MS *m*/*z* 200 (0.05), 199 (0.09), 188 (0.03), 169 (17), 158 (2.6), 151 (10), 127 (7.6); HRMS calcd for $C_{12}H_{24}O_2$ 200.1776, obsd 200.1755. **9**: TLC R_f (50% MTBE/25% CH_2Cl_2/petroleum ether) = 0.41; ^{1}H NMR δ 0.88 (d, J = 6.5 Hz, 6H), 1.69−1.06 (m, 8H), 2.21 (m, 2H), 2.94 (s, 2H), 3.69 (m, 2H), 3.92 (dd, J = 2.9 Hz, J = 11.0 Hz, 1H), 5.07 (m, 2H), 5.80 (m, 1H); ^{13}C NMR δ u 116.5, 63.7, 38.9, 35.7, 33.4, 23.5; d 136.6, 75.1, 43.9, 27.9, 22.6, 22.5; IR (cm^{-1}) 3342, 3078, 2953, 2869, 1641, 1468; MS *m*/*z* 200 (3.7), 200 (1.0), 199 (6.4), 183 (20), 165 (10), 159 (21), 158 (16), 151 (18); HRMS calcd for $C_{12}H_{24}O_2$ 200.1776, obsd 200.1752. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.68; H, 12.07.

(*R,*S**)-3-(4-Methylpentyl)-1-(triphenylmethoxy)-5-hexen-2-ol (11) and (*R**,*S**)-9-Methyl-4-[(triphenylmethoxy)-methyl]-1-decen-5-ol (12).** Allylmagnesium chloride (1.3 mL of 2.0 M in THF, 2.63 mmol) was added dropwise over 10 min to epoxide **10** (212 mg, 0.526 mmol) in THF (0.75 mL) at 0 °C. After being stirred at rt overnight, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give a mixture of the C-3 allylated product **11** and its C-2 regioisomer **12** (9.9:1)[10] (173 mg, 0.388 mmol, 74% yield) as a thick opaque white oil. Further chromatography led to analytical samples. **11**: TLC R_f (5% ethyl acetate/petroleum ether) = 0.35; ^{1}H NMR δ 0.84 (d, J = 6.5 Hz, 6H), 1.53−1.09 (m, 8H), 1.87 (m, 1H), 2.10 (m, 1H), 2.25 (s, 1H), 3.16 (m, 2H), 3.78 (bs, 1H), 4.90 (m, 2H), 5.70 (m, 1H), 7.45−7.20 (m, 15H); ^{13}C NMR δ u 143.9, 116.0, 86.8, 65.8, 39.2, 34.5, 28.9, 24.9; d 137.1, 128.6, 127.8, 127.1, 72.4, 40.6, 27.8, 22.7, 22.6; IR (cm^{-1}) 3581, 3467, 3060, 3033, 3023, 2927, 2868, 1639, 1597; MS *m*/*z* 442 (0.06), 424 (0.05), 365 (0.70), 323 (0.07), 244 (56), 243 (100), 183 (11), 165 (25); HRMS calcd for $C_{31}H_{38}O_2$ 442.2872, obsd 442.2874. **12**: TLC R_f (5% ethyl acetate/petroleum ether) = 0.31; ^{1}H NMR δ 0.83 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H), 1.73−1.04 (m, 8H), 2.34 (m, 2H), 2.76 (d, J = 6.3 Hz, 1H), 3.30 (m, 2H), 3.60 (m, 1H), 5.02 (m, 2H), 5.73 (m, 1H), 7.46−7.20 (m, 15H); ^{13}C NMR δ u 143.7, 116.4, 87.2, 63.6, 39.1, 35.3, 33.7, 23.7; d 136.9, 128.6, 127.9, 127.1, 73.9, 43.5, 27.9, 22.7; IR (cm^{-1}) 3470, 3060, 3033, 2952, 2930, 2868, 1959, 1820, 1640, 1597, 1490, 1467, 1449.

(*R,*R**)-(1-(3-Butenyl)-2-naphthyl-5-hexenyl)naphthalene (14).** Allylmagnesium chloride (12.6 mL of 2.0 M in THF, 25.2 mmol) was added dropwise to dibromide **13** (1.08 g, 3.15 mmol) in THF (20 mL) at rt. The mixture was heated to reflux for 10 min and then allowed to cool to rt. After being stirred at rt overnight, the mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The combined organic extract was dried (K_2CO_3) and concentrated. The residue was chromatographed to give the diallylated product **14** (920 mg, 2.36 mmol, 75% yield) as a clear colorless oil: TLC R_f (10% ethyl acetate/petroleum ether) = 0.56; ^{1}H NMR δ 2.25−1.65 (m, 8H), 3.99 (bs, 2H), 4.83 (m, 4H), 5.78−5.62 (m, 2H), 8.14−7.01 (m, 14H); ^{13}C NMR δ u 139.9, 133.6, 132.6, 114.4, 32.7, 31.6, 29.7; d 138.7,

(6) The relative configurations of the product 1,3-diols described here were readily established from the ^{13}C spectra of the derived acetonides **i** and **ii**. Consistently, the allylic carbon, axial on the ring, of the acetonide **ii** derived from the syn diol resonates at higher field than the allylic carbon (equatorial) of the acetonide **i** derived from the anti diol.



(7) Johnson, D. K.; Ciavarri, J. P.; Ishmael, F. T.; Schillinger, K. J.; van Geel, T. A. P.; Stratton, S. M. *Tetrahedron Lett.* **1995**, *47*, 8565. For an alternative allyl nucleophile, see: DeShong, P.; Pilcher, A. S. *J. Org. Chem.* **1996**, *61*, 6901.

(8) For the preparation of dibromide **13**, see: Nanasawa, M.; Hu, L.; Vogl, O. *Polymer* **1987,** *28*, 514. Dibromide **13** is a particularly impressive test case. Our attempts to use **13** to alkylate more conventional nucleophiles (malonate, lithiated ethyl acetate) led to only the doubly eliminated diene.

(9) Taber, D. F.; Deker, P. B., Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488.

(10) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55* (11), 1823.

(11) For general experimental procedures, see Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

(12) Ratios were determined by quantitative ^{13}C NMR (relaxation delay = 3 min) of the crude reaction product.

128.7, 126.2, 125.2, 124.9, 123.6; IR (cm^{-1}) 3071, 2918, 2850, 1640, 1597, 1511, 1456; MS *m/z* 390 (5.4), 196 (16), 195 (93), 194 (17), 154 (16), 153 (27), 142 (12), 141 (100); HRMS calcd for $C_{30}H_{30}$ 390.2348, obsd 390.2333.

(2-Ethyl-4-pentenoxy)benzene (16). Allylmagnesium chloride (4.2 mL of 2.0 M in THF, 8.3 mmol) was added dropwise over 10 min to 4-toluenesulfonate **15** (535 mg, 1.67 mmol) in THF (2.5 mL) at 0 °C. After being stirred at rt overnight, the mixture was partitioned between saturated aqueous NH_4Cl and MTBE. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give the allylated product **16** (198 mg, 1.04 mmol, 76% yield) as a clear colorless oil: TLC R_f (100% petroleum ether) = 0.65; ^{1}H NMR δ 0.95 (t, J = 7.4 Hz, 3H), 1.48 (m, 2H), 1.82 (m, 1H), 2.23 (m, 2H), 3.84 (d, J = 5.8 Hz, 2H), 5.04 (m, 2H), 5.90−5.73 (m, 1H), 6.91 (m, 3H), 7.27 (m, 2H); ^{13}C NMR δ u 159.0, 116.4, 69.7, 35.2, 23.5; d 136.6, 129.4, 120.4, 114.5, 39.4, 11.2; IR (cm^{-1}) 3075, 2963, 1640, 1600; MS *m/z* 190 (24), 94 (100), 81 (24); HRMS calcd for $C_{13}H_{18}O$ 190.1355, obsd 190.1358. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.25; H, 9.40.

3-(4-Methylpentyl)-1-(triphenylmethoxy)-5-hexen-2-one (17). Pyridinium chlorochromate (75 mg, 0.35 mmol), powdered 4 Å molecular sieves (75 mg), and sodium acetate (75 mg, 0.91 mmol) were combined together and added to a solution of alcohol **11** (51 mg, 0.116 mmol) in CH_2Cl_2 (2.5 mL) at rt. After being stirred at rt overnight, the mixture was chromatographed to give the ketone product **17** (50 mg, 0.114 mmol, 99% yield) as a clear colorless oil: TLC R_f (5% ethyl acetate/petroleum ether) = 0.54; ^{1}H NMR δ 0.82 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H), 1.62−1.04 (m, 10H), 2.90−2.05 (m, 2H), 2.85 (m, 1H), 3.75 (s, 2H), 4.96 (m, 2H), 5.71−5.55 (m, 1H), 7.48−7.20 (m, 15H); ^{13}C NMR δ u 211.0, 143.3, 116.8, 70.1, 39.0, 35.5, 31.1, 25.1; d 135.6, 128.6, 128.0, 127.3, 47.6, 27.8, 22.7, 22.6; IR (cm^{-1}) 3060, 3033, 2925, 2868, 1714, 1641, 1598; MS *m/z* (CI, NH_4^+) 458 (7.0), 279 (18), 262 (46), 243 (100), 233 (32), 216 (97); HRMS calcd for $C_{31}H_{41}NO_2$ (M + NH_4^+) 458.3059, obsd 458.3076.

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for information.

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