Notes

Homochiral Ketals in Organic Synthesis. Diastereoselective Cyclopropanation of Medium and Large Ring α,β-Unsaturated Ketals Derived from 1,4-Di-*O*-benzyl-L-threitol[1]

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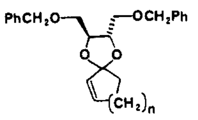
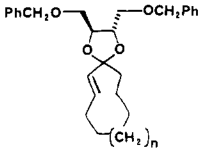
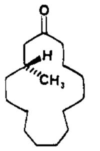
Recently there has been much interest in the diastereoselective manipulation of medium and large ring systems.[2] Recognition of the fact that substituents on such rings can control the conformational preference of the ring system has brought about the use of internal asymmetric induction for construction of macrocyclic natural products. However, general enantioselective routes to conformationally "anchored" medium and large carbocycles are not available.

Following our early studies of the diastereoselective Simmons–Smith cyclopropanation of common[3] homochiral 2-cycloalken-1-one 1,4-di-*O*-benzyl-L-threitol ketals **1a–c**,[4a] we examined the cyclopropanation of (*E*)-2-cyclopentadecen-1-one ketal **1l**.[4b] The observed diastereoselectivity (>20:1) was surprising in view of the minimal diastereoselectivity obtained for cyclopropanation of acyclic ene ketals and ene acetals using the Simmons–Smith reagent.[4,5] This result led to an efficient enantioselective synthesis of (*R*)-muscone (**2**).[6] Recently, we have returned to examine the general applicability of this diastereoselective cyclopropanation process to other medium and large ring systems. Results of this study are described herein.





	n		*n*
1a	1	**1f**	1
1b	2	**1g**	2
1c	3	**1h**	3
1d	4	**1j**	4
1e	5	**1j**	5
		1k	6
		1l	7
1n	12	**1m**	8



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The general route by which ene ketals **1** were produced is outlined in Scheme I. Ketalization[7] of the commercially available cycloalkanones **3**[8] using 1,4-di-*O*-benzyl-2,3-bis-*O*-(trimethylsilyl)-L-threitol[9] produced the corresponding ketals **4**. Bromination using phenyltrimethylammonium tribromide[10] in tetrahydrofuran gave mixtures of diastereomeric α-bromo ketals **5**. Elimination using sodium methoxide in dimethyl sulfoxide[11] produced the desired ene ketals **1**. For the 2-cycloocten-1-one ketal **1d**, the (*Z*)-alkene geometry was predominant, while for the 2-cyclononen-1-one and larger ketals, the (*E*)-alkene stereochemistry was predominant. All product ene ketals **1** were purified to homogeneity by column chromatography on silica gel and were fully characterized. Yields are summarized in Table I.

Treatment of ene ketals **1** with freshly prepared zinc–copper couple,[12] diiodomethane, and a crystal of iodine in refluxing diethyl ether gave in good to excellent chemical yields mixtures of diastereomeric cyclopropane ketals **6** and **7** (Chart I). Diastereomer ratios were determined by 62.9-MHz ^{13}C NMR spectroscopy.[13,14] Yields and dia-

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[1] Portions of this work are taken from the Ph.D. Thesis of Shivanand K. Math, University of Arizona, 1989.

[2] (a) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275. (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (c) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774. (d) Still, W. C.; Novak, V. *J. Am. Chem. Soc.* **1984**, *106*, 1148. (e) Cameron, A.; Knight, D. *J. Chem. Soc., Perkin Trans. I* **1986**, 161. (f) Neeland, E.; Ounsworth, J.; Sims, R.; Weiler, L. *Tetrahedron Lett.* **1987**, 35. (g) Funk, R. L.; Abelman, M. M.; Munger, J. D. *Tetrahedron* **1986**, *42*, 2831. (h) Schreiber, S. L.; Hulin, B.; Liew, W. *Tetrahedron* **1986**, *42*, 2945. (i) Mehta, G.; Rao, K. *J. Am. Chem. Soc.* **1986**, *108*, 8015. (j) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625. (k) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038. (l) Vedejs, E.; Gapinski, D. *J. Am. Chem. Soc.* **1983**, *105*, 5058. (m) Corey, E. J.; Nicolaou, K. C.; Melvin, L. *J. Am. Chem. Soc.* **1975**, *97*, 654. (n) Doskotch, R.; Keely, S.; Hufford, C. *J. Chem. Soc., Chem. Commun.* **1972**, 1137. (o) Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. *J. Org. Chem.* **1986**, *51*, 3393. (p) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315. (q) Maryanoff, B.; Almond, H. *J. Org. Chem.* **1986**, *51*, 3295. (r) Marshall, J. A.; Henson, T.; DeHoff, B. *J. Org. Chem.* **1986**, *51*, 4316. (s) Raucher, S.; Chi, K.; Hwang, K.; Burks, J. *J. Org. Chem.* **1986**, *51*, 5503. (t) Paquette, L.; Lin, H.; Belmont, D.; Springer, J. *J. Org. Chem.* **1986**, *51*, 4807. (u) Coates, R.; Muskopf, J.; Senter, P. *J. Org. Chem.* **1985**, *50*, 3541. (v) Quinkert, G.; Neim, M.; Glenneberg, J.; Billhardt, V.; Autze, V.; Bats, J.; Dunner, G. *Angew. Chem.* **1987**, *26*, 362. (w) Vedejs, E.; Dent, W.; Gapinski, D.; McClure, C. *J. Am. Chem. Soc.* **1987**, *109*, 5437. (x) Winkler, J.; Sridar, V. *J. Am. Chem. Soc.* **1986**, *108*, 1708. (y) Winkler, J.; Sridar, V. *Tetrahedron Lett.* **1988**, *29*, 6219–6222.

[3] Ring compounds have been classified into four catagories, namely, "small rings" (three- and four-membered), "common rings" (five-, six-, and seven-membered), "medium rings" (8- to 11-membered), and "large rings" (12-membered and larger). See: Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 189.

[4] (a) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256–8258. (b) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679–692.

[5] Studies by Arai et al. have demonstrated that greater diastereoselectivity for acetal systems can be obtained at lower temperatures (−20 °C to 0 °C) by using diethyl zinc/methylene iodide as the cyclopropanating reagent and hexanes as the solvent; see: (a) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254–8256. (b) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447–6458.

[6] Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721–2724.

[7] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

[8] Available from Aldrich Chemical Company.

[9] Mash, E. A.; Nelson, K. A.; VanDeusen, S.; Hemperly, S. B. *Org. Synth.*, in press.

[10] Marquet, A.; Jaques, J. *Tetrahedron Lett.* **1959**, *9*, 24–26.

[11] Garbisch, E. W. *J. Org. Chem.* **1965**, *30*, 2109–2120.

[12] Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825–1826.

0022-3263/89/1954-4951$01.50/0

Table I. Syntheses of Ene Ketals 1

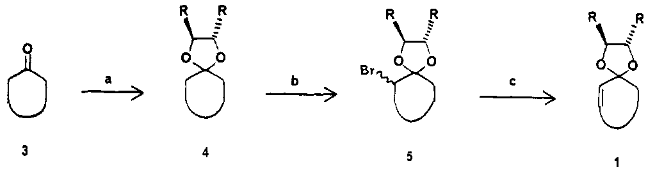
entry	ene ketal	alkene geometry	ring size	yield, % ketalization	yield, % α-bromination	yield, % elimination
1	**1a**	*Z*	5		from ref 4a	
2	**1b**	*Z*	6		from ref 4a	
3	**1c**	*Z*	7		from ref 4a	
4	**1d**	*Z*	8	72	100	68
5	**1e**	*Z*	9	90	100	22
6	**1f**	*E*	9			57
7	**1g**	*E*	10	62	90	30
8	**1h**	*E*	11	96	82	60
9	**1i**	*E*	12	75	48	69
10	**1j**	*E*	13	94	58	69
11	**1k**		14		not prepared	
12	**1l**	*E*	15		from ref 4b	
13	**1m**	*E*	16	98	100	51
14	**1n**	*Z*	16			13

Table II. Simmons-Smith Cyclopropanations

entry	alkene geometry	ring size	product cyclopropane ketals	yield, %	diastereomer[a,b] ratio
1	*Z*	5	**6a/7a**	72	9:1
2	*Z*	6	**6b/7b**	98	9:1
3	*Z*	7	**6c/7c**	90	8:1
4	*Z*	8	**6d/7d**	80	>20:1
5	*Z*	9	**6e/7e**	96	>20:1
6	*E*	9	**6f/7f**	93	>20:1
7	*E*	10	**6g/7g**	84	13:1
8	*E*	11	**6h/7h**	94	10:1
9	*E*	12	**6i/7i**	89	>20:1
10	*E*	13	**6j/7j**	88	10:1
11		14	**6k/7k**	not determined	
12	*E*	15	**6l/7l**	94	>20:1
13	*E*	16	**6m/7m**	98	>20:1
14	*Z*	16	**6n/7n**	70	>20:1

[a] Determined by 62.9-MHz ^{13}C NMR spectroscopy. [b] Predominant absolute stereochemistry confirmed for entries 2 and 12 only (see text).

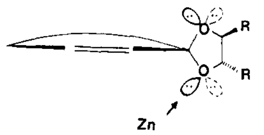
Scheme I. Syntheses of Ene Ketals 1 (R = CH_2OCH_2Ph)[a]



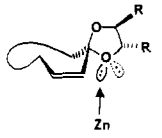
[a] (a) 1,4-Di-*O*-benzyl-2,3-bis-*O*-(trimethylsilyl)-L-threitol, TMSOTf, CH_2Cl_2; (b) $PhNMe_3^+Br_3^-$, THF; (c) $NaOCH_3$, DMSO.

stereomer ratios are summarized in Table II. The absolute configurations of the major diastereomers **6b** and **6l** have been independently established.[4,6] The others are assigned by analogy.

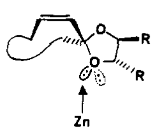
For all medium and large ring 2-cycloalken-1-one 1,4-di-*O*-benzyl-L-threitol ketals examined, diastereoselectivity exceeded that previously observed for common ring ene ketals (Table II). Diastereoselectivity for common ring ene ketals is presumably due to effective chelation-controlled positioning of the reagent[15] with respect to the two faces of the alkene, which are both sterically accessible but spatially constrained by the backbone of the common ring.[4,5,16]



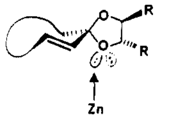
For medium and large ring *Z* ene ketals, conformers A and B are likely, while for *E* ene ketals, conformers C and D are likely.[2b] In conformer A, the 2*si*,3*si* face of the alkene is exposed, while the 2*re*,3*re* face of the alkene is exposed in conformer B. In conformer C, the 2*si*,3*re* face of the alkene is exposed, while the 2*re*,3*si* face of the alkene is exposed in conformer D. Apparently, one of each pair of conformers is predominant and/or more reactive. For 2-cyclopentadecen-1-one ketal **1l**, the major diastereomer of the product cyclopropane ketal is known to be (1*R*,15*R*)-bicyclo[13.1.0]hexadecan-2-one ketal **6l**.[4,6] This is the expected product from cyclopropanation of **1l** via conformer D. A computational study[2b] of the conformations available to ene ketals **1** when complexed to the Simmons-Smith reagent might provide additional insight regarding conformational preferences for each of the ene ketals **1**.



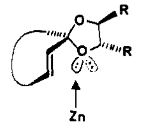
A



B



C



D

Enantiomerically enriched medium and large ring cyclopropyl ketones are now available via diastereoselective cyclopropanation of the corresponding 2-cycloalken-1-one 1,4-di-*O*-benzylthreitol ketals. Since the chiral auxiliary is available in both enantiomeric forms,[9] either enantiomer of a particular cyclopropyl ketone can be prepared via this method.

Diastereoselective functionalizations of medium and large ring systems conformationally "anchored" by a fused

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[13] Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183-2186.

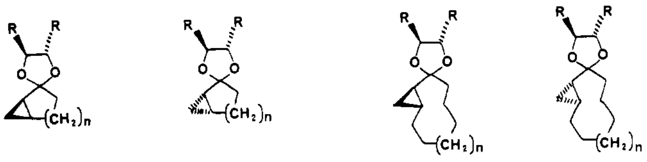
[14] Where possible, authentic diastereomeric mixtures were prepared for comparison purposes, (e.g., see Experimental Section).

[15] For reviews of the Simmons-Smith reaction, see: (a) Furukawa; J. Kawabata, N. In *Advances in Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic Press: New York, 1974; Vol. 12, Chapter 3. (b) Simmons, H. E.; Cairns, T. L.; Vladuchich, S. A.; Hoiness, C. H. *Org. React.* **1972**, *20*, 1-131.

[16] An increase in the bulk of the dioxolane appendages should result in increased diastereoselectivity; such is the case for common ring systems. See: Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250-253.

Chart I

$R = CH_2OCH_2Ph$



	n		*n*		*d*		*n*
6a	1	**7a**	1	**6f**	1	**7f**	1
6b	2	**7b**	2	**6g**	2	**7g**	2
6c	3	**7c**	3	**6h**	3	**7h**	3
6d	4	**7d**	4	**6i**	4	**7i**	4
6e	5	**7e**	5	**6j**	5	**7j**	5
				6k	6	**7k**	6
				6l	7	**7l**	7
6n	12	**7n**	12	**6m**	8	**7m**	8

cyclopropane ring are currently under study in our laboratory.[17]

Experimental Section

Benzene was distilled from calcium hydride and diethyl ether was distilled from phosphorus pentoxide or sodium benzophenone ketyl under an inert atmosphere. Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over 3-Å molecular sieves. Zinc–copper couple was prepared according to the method of Shank and Schechter[12] immediately before use. ^1H NMR spectra were recorded at 250 MHz and ^{13}C NMR spectra at 62.9 MHz. Optical rotations were measured at 589 nm on a Rudolph Research Autopol III polarimeter. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70–230-mesh ASTM). Merck silica gel 60 (70–230-mesh ASTM) was used for column chromatography.

The synthesis and cyclopropanation of ene ketal **1d** serves as a typical example.

Cyclooctanone 1,4-Di-*O*-benzyl-L-threitol Ketal (4d). To a well-stirred solution of TMSOTf (100 μL, 5 mol %) in CH_2Cl_2 (1 mL) at −78 °C were added 1,4-di-*O*-benzyl-2,3-bis-*O*-(trimethylsilyl)-L-threitol (3.57 g, 8.40 mmol) and a solution of cyclooctanone **3d**[8] (1.27 g, 10.1 mmol) in CH_2Cl_2 (1 mL) dropwise. The reaction mixture was warmed from −78 °C to 25 °C over several hours. After 5 h the reaction was quenched by the addition of dry pyridine (500 μL) and volatiles were removed in vacuo. Chromatography of the residue on silica gel 60 (400 g) eluted with 20% EtOAc/hexanes gave the ketal **4d** as a pale yellow oil homogeneous by TLC (R_f 0.39, 20% EtOAc/hexanes): $[\alpha]^{25}{}_D$ −7.08° (*c* 4.01, $CHCl_3$); yield 2.46 g, 6.00 mmol, 72%; IR ($CHCl_3$) cm^{-1} 3015, 3012, 2926, 1537, 1493, 1451, 1365, 1096, 698; ^1H NMR ($CDCl_3$) δ 1.54–1.83 (14, m), 3.59 (4, m), 4.00 (2, m), 4.57 (4, s), 7.31 (10, s); ^{13}C NMR ($CDCl_3$) δ 21.98 (CH_2), 24.33 (CH_2), 27.86 (CH_2), 35.33 (CH_2), 70.59 (CH_2), 73.29 (CH_2) 77.12 (CH), 113.41 (C), 127.43 (CH), 128.21 (CH), 137.99 (C).

(*Z*)-2-Cycloocten-1-one 1,4-Di-*O*-benzyl-L-threitol Ketal (1d). To a well-stirred solution of ketal **4d** (1.66 g, 4.05 mmol) in THF (2 mL) at 0 °C was added phenyltrimethylammonium tribromide (1.67 g, 4.45 mmol) in one portion. After 2 h at 0 °C the reaction mixture was diluted with CH_2Cl_2 (200 mL). The organic phase was washed with 5% aqueous K_2CO_3 (100 mL) and 5% aqueous $Na_2S_2O_3$ (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude α-bromo ketal **5d** was isolated as a pale yellow oil. Yield 1.98 g, 4.05 mmol, 100%.

To a well-stirred solution of the above α-bromo ketal (1.98 g, 4.05 mmol) in DMSO (20 mL) was added NaOMe (2.2 g, 40.5 mmol) at 25 °C. The reaction mixture turned brown. After 6 days the reaction mixture was poured into saturated aqueous NaCl (200 mL), extracted with hexanes (2 × 200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (200 g) eluted with CH_2Cl_2 gave the product **1d** as a pale yellow oil homogeneous by TLC (R_f 0.30, CH_2Cl_2): $[\alpha]^{25}{}_D$ +6.39° (*c* 8.6, $CHCl_3$); yield 1.13 g, 2.77 mmol, 68%; IR ($CHCl_3$) cm^{-1} 3063, 3014, 2928, 1652, 1494, 1452, 1091, 1006, 780; ^1H NMR ($CDCl_3$) δ 1.51–1.61 (16, m), 1.85–1.88 (2, m), 2.39 (2, m), 3.55–3.62 (4, m), 4.01 (2, m), 5.57–5.65 (2, m), 7.29 (10, s); ^{13}C NMR ($CDCl_3$) δ 21.45 (CH_2), 23.84 (CH_2), 24.43 (CH_2), 27.75 (CH_2), 40.45 (CH_2), 70.50 (CH_2), 71.20 (CH_2), 73.28 (CH_2), 77.12 (CH), 77.73 (CH), 110.64 (C), 127.47 (CH), 128.23 (CH), 130.90 (CH), 134.72 (CH), 137.99 (C).

Anal. Calcd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.89. Found: C, 76.71; H, 7.92.

(1*R,8*S**)-Bicyclo[6.1.0]nonan-2-one 1,4-Di-*O*-benzyl-L-threitol Ketal (6d/7d).** To a well-stirred suspension of freshly prepared Zn(Cu) couple (774 mg, 5.74 mmol) and anhydrous K_2CO_3 (418 mg, 3.03 mmol) in ether (10 mL) at reflux were added a large crystal of I_2 and CH_2I_2 (250 μL, 3.03 mmol). After 7 h at reflux the ene ketal **1d** (413 mg, 1.01 mmol) was added as a solution in ether (3 mL). After 24 h the reaction mixture was cooled to 0 °C and quenched with saturated aqueous K_2CO_3 (500 μL). After being stirred room temperature for 30 min, the gray-black precipitate was removed by filtration and the residue was washed well with CH_2Cl_2. The organic extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (100 g) eluted with 10% EtOAc/hexanes gave the product **6d** as a colorless oil homogeneous by TLC (R_f 0.29, 10% EtOAc/hexanes): $[\alpha]^{25}{}_D$ −19.67° (*c* 4.82, $CHCl_3$); yield 341 mg, 0.808 mmol, 80%; IR ($CHCl_3$) cm^{-1} 3030, 3017, 3009, 2926, 1494, 1452, 1363, 1220, 1092, 966; ^1H NMR ($CDCl_3$) δ 0.23 (1, m), 0.51 (1, m), 0.53 (1, m), 1.08–1.83 (12, m), 3.60 (4, m), 3.98 (2, m), 4.55 (4, d, J = 10 Hz), 7.28 (5, s), 7.30 (5, s); ^{13}C NMR ($CDCl_3$) δ 5.28 (CH_2), 15.33 (CH), 20.60 (CH_2), 23.64 (CH_2), 23.74 (CH), 25.57 (CH_2), 28.33 (CH_2), 29.59 (CH_2), 42.50 (CH_2), 70.61 (CH_2), 70.83 (CH_2), 73.20 (CH_2), 73.35 (CH_2), 75.49 (CH), 76.49 (CH), 79.35 (CH), 112.51 (C), 127.31 (CH), 127.45 (CH), 127.57 (CH), 128.27 (CH), 138.02 (C), 138.11 (C); mass spectrum (70 eV) m/z (rel intensity) 422 (7), 158 (55), 139 (43), 130 (61), 120 (25), 91 (100), 54 (6); exact mass calcd for $C_{27}H_{34}O_4$ 422.2458, obsd 422.2453.

Anal. Calcd for $C_{27}H_{34}O_4$: C, 76.73; H, 8.11. Found: C, 76.38; H, 7.97.

Bicyclo[6.1.0]nonan-2-one 1,4-Di-*O*-benzyl-DL-threitol Ketals. To a solution of ketal **6d** (103 mg, 0.24 mmol) in CH_3OH (2 mL) at room temperature was added 2.7 M aqueous HCl (100 μL). After 24 h the reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL) and the mixture was extracted with ether (3 × 25 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (100 g) eluted with 10% EtOAc/hexanes gave the product bicyclo[6.1.0]nonan-2-one as a colorless oil homogeneous by TLC (R_f 0.28, 20% EtOAc/hexanes); yield 28 mg, 0.210 mmol, 88%.

To a well-stirred solution of the above cyclopropyl ketone (33 mg, 0.24 mmol) in dry benzene (20 mL) were added 1,4-di-*O*-benzyl-DL-threitol (150 mg, 0.48 mmol) and pyridinium *p*-toluenesulfonate (60 mg, 0.24 mmol). The mixture was heated under argon and water was removed azeotropically using a Dean–Stark trap. After 3 days the reaction mixture was cooled to room temperature and diluted with ether (100 mL), and the ether layer was washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatography of the residue on silica gel 60 (50 g) eluted with 1% $MeOH/CH_2Cl_2$ gave the product as an oil: yield 28 mg, 0.067 mmol, 28%; ^{13}C NMR ($CDCl_3$) δ 4.90 (CH_2), 5.25 (CH_2), 14.37 (CH), 15.01 (CH), 20.68 (CH_2), 21.68 (CH_2), 23.57 (CH), 23.72 (CH_2), 23.82 (CH), 24.32 (CH_2), 25.51 (CH_2), 25.65 (CH_2), 28.42 (CH_2), 29.04 (CH_2), 41.50 (CH_2), 42.59 (CH_2), 70.18 (CH_2), 70.52 (CH_2), 70.71 (CH_2), 70.95 (CH_2), 73.25 (CH_2), 73.32 (CH_2), 73.47 (CH_2), 75.58 (CH), 76.73 (CH), 78.26 (CH), 79.46 (CH), 111.96 (C), 112.28 (C), 127.44 (CH), 127.59 (CH), 128.33 (CH), 138.05 (C).

Supplementary Material Available: Physical and spectral data for compounds **1e–n**, **4e–n**, and **6e/7e–6n/7n** (8 pages). Ordering information is given on any current masthead page.

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