ORGANIC LETTERS

1999
Vol. 1, No. 1
63−66

Novel Strategies to Construct the γ-Hydroxy Lactone Moiety of the CP Molecules. Synthesis of the CP-225,917 Core Skeleton

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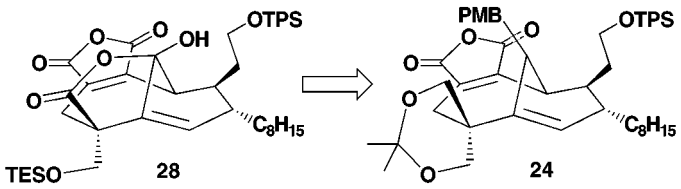
Received March 26, 1999

ABSTRACT



The array of challenging structural lineaments embodied in the CP molecules (1 and 2, Figure 1) offers synthetic chemists uncharted realms of exploration and discovery. In this communication, we focus on the chemical hurdles posed by the γ-hydroxy lactone moiety of these exciting targets. Thus, the examination of the general reactivity of these systems, the development of a novel tandem oxidation sequence to construct the γ-hydroxy lactone moiety, and the successful construction of the complete polycyclic core of 2 (compound 28, Scheme 5) is enumerated within.

The structures of the CP molecules (**1**, CP 263,114; **2**, CP-225,917; Figure 1) represent unprecedented molecular frameworks of exotic connectivity and functional group interposition. Isolated from an unidentified fungus by Pfizer scientists,[1] the CP molecules were found to inhibit the enzymes squalene synthase and ras farnesyl transferase and, therefore, are lead compounds for potential new drugs for the treatment of cardiovascular diseases and cancer. Several strategies toward the chemical synthesis of these molecules have already appeared.[2] Herein we disclose our explorations and discoveries en route to the γ-hydroxy lactone moiety of the CP molecules.

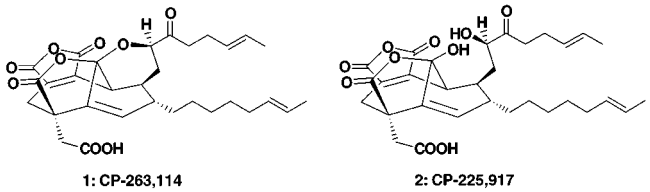


Figure 1. Structures of the CP molecules.

Our initial forays toward the synthesis of the γ-hydroxy lactone moiety utilized model compound **3**[3] extensively (Scheme 1). Attempts to mask the bridgehead alcohol **6**,[4] derived from ketone **3** upon treatment with DDQ (for abbreviations see the legends in the schemes), either through inversion of stereochemistry or simple protection of the

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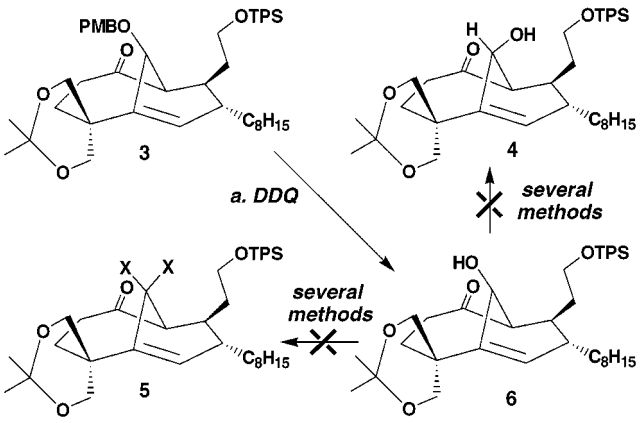
(1) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594. Dabrah, T. T.; Harwood, H. J., Jr.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J.-C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. *J. Antibiot.* **1997**, *50*, 1.

10.1021/ol990551y CCC: $18.00
Published on Web 05/24/1999

Scheme 1. Failed Attempts To Protect the Bridgehead Enone or Invert the Bridgehead Hydroxyl Group[a]

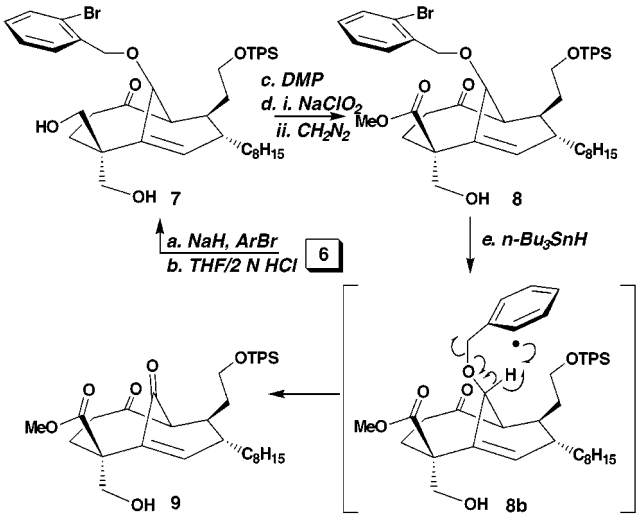


[a] Reagents and conditions: (a) DDQ (2.0 equiv), CH_2Cl_2/H_2O (18:1), 25 °C, 2 h, 50%. Abbreviations: DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; PMB = *p*-methoxybenzyl; TPS = *tert*-butyldiphenylsilyl.

corresponding enone failed, presumably due to the extreme steric screening in the vicinity of the bridgehead alcohol.[5]

Application of Curran's elegant, yet rarely employed, self-oxidizing protecting group[6] yielded promising results (Scheme 2). Thus, treatment of alcohol **6** with sodium hydride in DMF followed by addition of 2-bromobenzyl bromide led, after

Scheme 2. Arrival at Model Compound **9** Using a Self-Oxidizing Protecting Group[a]



[a] Reagents and conditions: (a) (i) NaH (5.0 equiv), DMF, 25 °C, 0.5 h, (ii) 2-bromobenzyl bromide (1.5 equiv), 1 h, 75%; (b) THF/2 N HCl (2:1), 25 °C, 1 h, 90%; (c) DMP (1.2 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 90% (5:1 convex (desired):concave aldehyde); (d) $NaClO_2$ (3.0 equiv), NaH_2PO_4 (1.5 equiv), 2-methyl-2-butene (50 equiv), THF, *t*-BuOH/H_2O (5:1), 25 °C, 1.5 h, then CH_2N_2 (ca. 100 equiv, solution in Et_2O), 0 °C, 5 min, 85%; (e) *n*-Bu_3SnH (20 equiv), AIBN (1.0 equiv), benzene, 80 °C, 0.5 h, 80%. Abbreviations: DMP = Dess−Martin periodinane, AIBN = 2,2′-azobis(isobutyronitrile).

acidic hydrolysis, to diol **7** in 68% overall yield. The convex alcohol could be selectively oxidized (ca. 5:1 convex:concave, 90% yield) using Dess−Martin periodinane (DMP)[7] followed by $NaClO_2$-mediated oxidation and workup with diazomethane to furnish hydroxy methyl ester **8** in 85% yield. Treatment of **8** with *n*-Bu_3SnH/AIBN in refluxing benzene for 0.5 h cleanly led to enone **9**, a surrogate of the γ-hydroxy lactone moiety, in 80% yield. A caveat of this useful transformation was, however, discovered while screening a number of different substrates as a prelude to enlist this method in a total synthesis of the CP molecules. Specifically, we found that the reaction was quite sensitive to subtle changes on the periphery of the molecule. In several instances, we observed significant amounts of the reduced product resulting from *n*-Bu_3SnH-mediated debromination.[8] In addition, we found that the presence of the maleic anhydride served to completely suppress any product formation.[9] This result, coupled with the unpredictability of the reaction as a function of the substrate employed, forced us to abandon this approach.

Next, we turned our attention to a strategy predicated on the ring-chain tautomerism of hydroxy ketones.[10] Thus, 1,4-diol **13** was targeted as a suitable model for a sequence which would ultimately involve construction of the γ-hydroxy lactone after maleic anhydride installment (Scheme 3). Under the auspices of DDQ with rigorous exclusion of water, the seven-membered benzylidene acetal **11** was formed (81% yield) from **10**,[11] protected as the pivaloate **12**, and easily

(2) (a) Nicolaou, K. C.; Härter, M. W.; Boulton, L.; Jandeleit, B. *Angew. Chem.* **1997**, *109*, 1243; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1194. (b) Nicolaou, K. C.; Postema, M. H. D.; Miller, N. D.; Yang, G. *Angew. Chem.* **1997**, *109*, 2922; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2821. (c) Davies, H. M. L.; Calvo, R.; Ahmed, G. *Tetrahedron Lett.* **1997**, *38*, 1737. (d) Sgarbi, P. W. M.; Clive, D. L. J. *Chem. Commun.* **1997**, 2157. (e) Armstrong, A.; Critchley, T. J.; Mortlook, A. A. *Synlett* **1998**, 552. (f) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem.* **1998**, *110*, 1978; *Angew. Chem., Int. Ed.* **1998**, *37*, 1877. (g) Kwon, O.; Su, D.-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem.* **1998**, *110*, 1981; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1880. (h) Waizumi, N.; Itoh, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 6015. (i) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784. (j) Fontier, A. J.; Danishefsky, S. J.; Koppel, G. A.; Meng, D. *Tetrahedron* **1998**, *54*, 12721. (k) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890. (l) Nicolaou, K. C.; Baran, P. S.; Jautelat, R.; He, Y.; Fong, K. C.; Choi, H.-S.; Yoon, W. H.; Zhong, Y.-L. *Angew. Chem.* **1999**, 111, 532; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 549.

(3) The synthesis of **3** via a route similar, yet superior, to that reported in ref 2a will be reported in due course.

(4) All new compounds were fully characterized spectroscopically.

(5) Inversion of the stereochemistry would prevent the formation of "conformationally locked" structures (vide infra). Mitsunobu, oxidation−reduction, and S_N2 displacement were among the failed strategies. Protection of the bridgehead enone as both cyclic and acyclic thio- and oxyketals failed despite repeated attempts.

(6) Curran, D. P.; Yu, H. *Synthesis* **1992**, 123.

(7) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

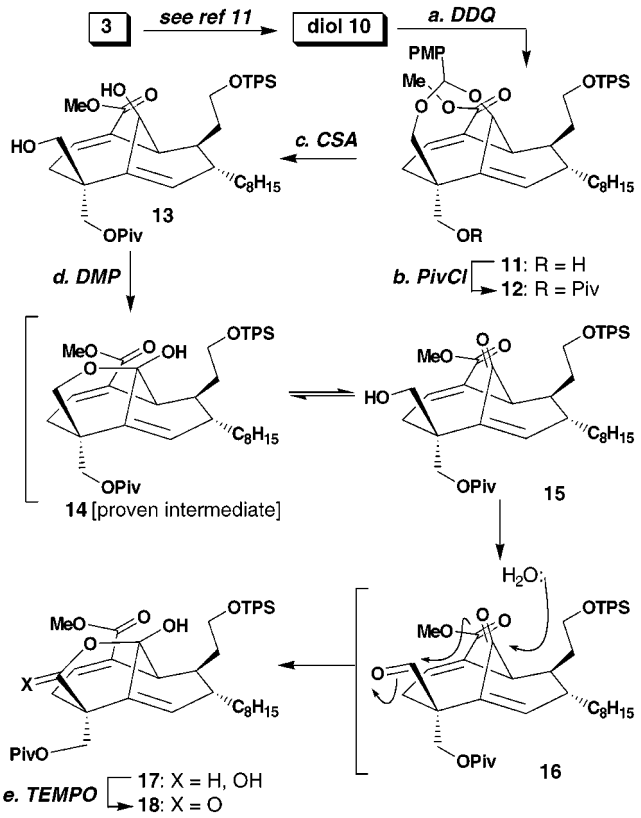
(8) The use of high-dilution syringe pump techniques and even alternative initiators/reductants could not reduce the amount of this byproduct.

(9) The starting material was recovered; longer reaction times resulted in decomposition.

(10) (a) Whiting, J. E.; Edward, J. T. *Can. J. Chem.* **1971**, *49*, 3799. (b) Hurd, C. D.; Saunder, W. *J. Am. Chem. Soc.* **1952**, *74*, 5324.

(11) The conversion of ketone **3** into the conjugated ester was accomplished via enol triflation and palladium-catalyzed carboxymethylation, as reported in ref 2l. Hydrolysis of the acetonide using THF/2 N HCl at 25 °C for 1 h afforded **10** in 90% yield.

Scheme 3. Construction of the γ-Hydroxy Lactone Moiety in Two Steps via a Novel One-Pot Dess−Martin Oxidation[a]



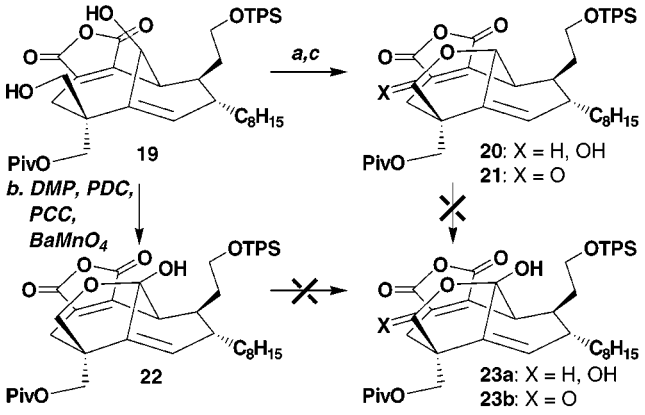
[a] Reagents and conditions: (a) DDQ (1.2 equiv), 4 Å molecular sieves (500 mg/mmol), CH_2Cl_2, 25 °C, 1 h, 81%; (b) PivCl (5.0 equiv), Et_3N (10 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 12 h, 90%; (c) CSA (0.2 equiv), MeOH, 25 °C, 1 h, 90%; (d) DMP (10 equiv), CH_2Cl_2, 16 h, 82%; (e) TEMPO (20 equiv), KBr (0.1 equiv), cyclooctene (50 equiv), NaOCl (3.0 equiv), acetone/5% $NaHCO_3$ (2:1), 0 °C, 0.5 h, 68%. Abbreviations: Piv = 2,2,2-trimethyl acetyl, CSA = camphorsulfonic acid, TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxy, PMP = *p*-methoxyphenyl, 4-DMAP = 4-(dimethylamino)pyridine.

hydrolyzed under acidic conditions, thus setting the stage for the critical DMP-mediated oxidation of **13**.

In the event,[12] the reaction succeeded in furnishing diol **17** (single isomer of unassigned stereochemistry) in 82% yield via the proven intermediate **14**. This tandem reaction sequence requires the initial selective oxidation of the sterically hindered bridgehead alcohol followed by ring closure to furnish the isolable hemiketal **14**. Further oxidation (10 equiv of DMP, 16 h) funnels hemiketal **14** to keto aldehyde **16** via the ring-chain tautomer **15**. Trace quantities of water terminate the cascade, forming the stable diol **17**, which cannot be oxidized further with DMP. After several methods were screened,[13] only the *N*-oxoammonium ion-mediated (TEMPO) oxidant[14] was able to efficiently (68% yield) bring about the conversion of diol **17** to the coveted γ-hydroxy lactone **18**.

With this success in hand, we set out to probe the effects of the maleic anhydride moiety on the course of the oxidation reaction. The synthesis of compound **19** (Scheme 4) from

Scheme 4. Attempted Construction of the γ-Hydroxy Lactone Moiety in the Presence of the Maleic Anhydride[a]



[a] Reagents and conditions: (a) to access **21** directly, $(COCl)_2$ (5.0 equiv), DMSO (10 equiv), Et_3N (10 equiv), −78 °C, 1 h, 90%, or to access **20**, SO_3·pyr. (2.0 equiv), DMSO (8.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2, 0 °C, 0.5 h, 82%; (b) oxidant (2.0−10 equiv), CH_2Cl_2, 25−35 °C, 70−90%; (c) to access **21** from either **19** or **20**, TEMPO (20 equiv), KBr (0.1 equiv), cyclooctene (50 equiv), NaOCl (3.0 equiv), acetone/5% $NaHCO_3$ (2:1), 0 °C, 20−30 min, 75−85%. Abbreviations: PDC = pyridinium dichromate, PCC = pyridinium chlorochromate.

24[15] (see Scheme 5) was accomplished using a sequence similar to that used to construct compound **13** from compound **3** (vide supra). An array of oxidation procedures failed to provide bis-lactol **23a** or γ-hydroxy lactone **23b** and instead resulted in the formation of "conformationally locked" intermediates **20**−**22** (Scheme 4).[16]

To establish the relative stability of the γ-hydroxy lactone harboring the maleic anhydride, we designed a stepwise route to **28** as depicted in Scheme 5. Titanium-assisted hydrolysis of both the acetonide and PMB ether of **24**[15] followed by bis-TES protection of the resulting primary alcohols and acetylation of the bridgehead hydroxyl group provided compound **25** in 69% overall yield. Selective removal of the convex TES group followed by oxidation and dithiane masking of the resulting aldehyde furnished **26** (45% overall yield). Methanolysis (K_2CO_3) of the acetate residue followed by oxidation and Stork−Zhao dithiane deprotection[17] permit-

(12) **General procedure for the preparation of bis-lactols from 1,4-diols** (those embedded in the CP skeleton as in **13**): The 1,4-diol **13** in CH_2Cl_2 (0.1−0.01 M) was stirred at 25 °C while being exposed to air. Freshly prepared DMP[7] (5.0 equiv) was then added without rigorous removal of trace acid (no base added). The reaction could be easily monitored by TLC, with formation of intermediate lactol **14** after only a few minutes. DMP (5.0 equiv) was added, and stirring was continued for 12−16 h at 25 °C to furnish bis-lactol **17** in 82% yield after column chromatography.

(13) PDC, PCC, DMP/CH_2Cl_2 reflux, Swern, SO_3·pyr., $KMnO_4$, Jones, and TPAP were among the reagents tried.

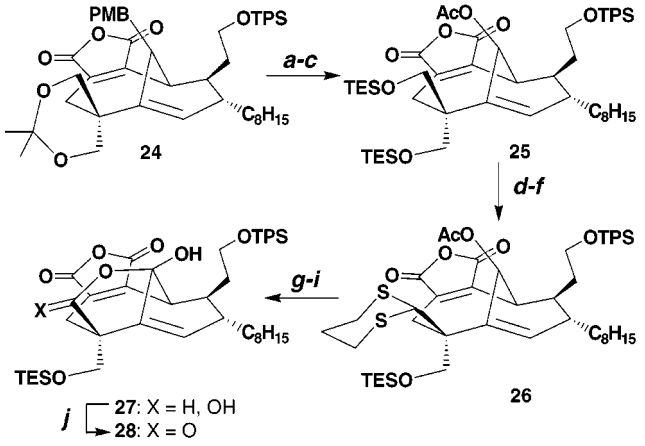
(14) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

(15) See ref 2l for synthesis and characterization of this intermediate.

(16) Despite the barrage of conditions aimed at opening, oxidizing, or transforming these compounds into the sought-after γ-hydroxy lactone moiety, these compounds remained "locked".

(17) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

Scheme 5.[18] Stepwise Construction of the γ-Hydroxy Lactone Moiety (compound **28**) in the Presence of the Maleic Anhydride[a]



[a] Reagents and conditions: (a) $TiCl_4$ (3.0 equiv), 1,3-propanedithiol (5.0 equiv), cyclooctene (20 equiv), CH_2Cl_2, −15 °C, 10 min, 84%; (b) TESCl (2.2 equiv), imidazole (3.0 equiv), CH_2Cl_2, 25 °C, 85%; (c) Ac_2O (20 equiv), Et_3N (30 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 12 h, 97%; (d) $TiCl_4$ (1.0 equiv), cyclooctene (20 equiv), CH_2Cl_2, −78 °C, 67% (+23% starting material) (3.8:1 convex (desired):concave deprotected -TES); (e) DMP (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 94%; (f) $TiCl_4$ (3.0 equiv), 1,3-propanedithiol (5.0 equiv), cyclooctene (20 equiv), CH_2Cl_2, −78 °C → −15 °C, 0.5 h, 71%; (g) K_2CO_3 (5.0 equiv), MeOH, 25 °C, 4 h, 89%; (h) PDC (20 equiv), CH_2Cl_2, 25 °C, 1 h, 90%; (i) $(CF_3CO_2)_2IPh$ (3.0 equiv), CH_3CN, 25 °C, 10 min, 80%; (j) TEMPO (20 equiv), KBr (0.1 equiv), cyclooctene (50 equiv), NaOCl (3.0 equiv), acetone/5% $NaHCO_3$ (2:1), 0 °C, 0.5 h, 70%.

ted us to arrive at diol **27** (64% overall yield). Oxidation of diol **27** with TEMPO under the conditions described above for **17** generated γ-hydroxy lactone **28** in 70% yield.

To rationalize why anhydride diol **19** is so resistant to direct oxidation, we carried out in-depth model studies correlating the efficacy of the tandem DMP reaction with the substrate employed. From these studies,[19] we conclude that the angle θ illustrated in Figure 2 plays a decisive role

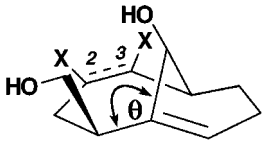


Figure 2. The angle θ, which appears to be a decisive factor in the formation of the γ-hydroxy lactone moiety.

in the oxidation of these systems, leading to either "conformationally locked" structures or the desired bis-lactols. On the basis of molecular models and experimental results, it appears that a decrease in conformational freedom at C2−C3 is directly proportional to the size of the angle θ (e.g. **19** vis-à-vis **13**), which must reflect the propensity for ring-chain tautomerization (rate-determining step of the DMP cascade).

In conclusion, we have delineated parameters for the conversion of 1,4-diols into the corresponding γ-hydroxy lactone moiety present in the CP molecules by a variety of methods leading to compound **28**, representing the complete core skeleton of CP-225,917 (**2**). A more detailed understanding of the observed reactivity and lack thereof demonstrated in these model systems, a computational verification of our hypothesis relating the angle θ (Figure 2) to the ease of ring-chain tautomerization, and a more efficient solution to the challenge of installing the γ-hydroxy lactone in the presence of the maleic anhydride moiety will be issues of paramount importance when formulating a total synthesis of the CP molecules and designed analogues.

Acknowledgment. We thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. This work was supported by the National Institutes of Health, The Skaggs Institute for Chemical Biology, and fellowships from the Korea Science and Engineering Foundation (H.-S.C.), the National Science Foundation (P.S.B.), and Boehringer Ingelheim (Y.H.).

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(18) Selected data for compounds are as follows. **27**: R_f = 0.21 (silica gel, EtOAc:hexane 1:4); IR (film) ν = 3411, 2927, 2855, 1766, 1650, 1460, 1428, 1384, 1265, 1109, 1005, 968, 909, 820, 741, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.70 (m, 4 H), 7.42−7.37 (m, 6 H), 5.78 (d, J = 3.0 Hz, 1 H), 5.40−5.38 (m, 2 H), 5.21 (d, J = 3.0 Hz, 1 H), 4.01 (d, J = 10.0 Hz, 1 H), 3.98 (t, J = 5.5 Hz, 2 H), 3.92 (d, J = 10.0 Hz, 1 H), 3.77 (s, 1 H), 3.48 (s, 1 H), 3.35 (s, 1 H), 2.78 (d, J = 20.0 Hz, 1 H), 2.54 (d, J = 20.0 Hz, 1 H), 2.38−2.30 (m, 1 H), 1.98−1.82 (m, 4 H), 1.63 (d, J = 3.5 Hz, 3 H), 1.60−1.11 (m, 11 H), 1.05 (s, 9 H), 0.98 (t, J = 8.0 Hz, 9 H), 0.65 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.3, 166.0, 144.6, 142.6, 140.6, 135.6 (4C), 133.7, 133.6, 131.3, 129.7, 129.6 (2C), 127.6 (4C), 124.8, 106.1, 103.4, 63.1, 61.9, 54.3, 48.4, 41.8, 40.1, 38.9, 36.2, 33.8, 32.5, 29.5, 29.1, 27.6, 26.8 (2C), 19.1, 17.9, 6.7 (3C), 4.2 (3C); HR-MS (FAB) calcd for $C_{46}H_{64}O_8Si_2Cs$ [M + Cs^+] 933.3194, found 933.3226. **28**: R_f = 0.43 (silica gel, EtOAc:hexane 1:4); IR (film) ν = 3416, 2956, 2928, 2855, 1836, 1768, 1466, 1427, 1385, 1260, 1172, 1109, 1006, 967, 817, 740, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.77−7.69 (m, 4 H), 7.48−7.41 (m, 6 H), 6.07 (d, J = 3.5 Hz, 1 H), 5.73 (s, 1 H), 5.39−5.30 (m, 2 H), 4.12−4.06 (m, 1 H), 4.09 (d, J = 10.0 Hz, 1 H), 3.99 (d, J = 10.0 Hz, 1 H), 3.96−3.88 (m, 1 H), 3.93 (s, 1 H), 2.97 (d, J = 19.0 Hz, 1 H), 2.86 (d, J = 19.0 Hz, 1 H), 2.65−2.58 (m, 1 H), 2.13−2.05 (m, 1 H), 1.98−1.82 (m, 2 H), 1.82−1.75 (m, 1 H), 1.71−1.11 (m, 11 H), 1.64 (d, J = 3.5 Hz, 3 H), 1.07 (s, 9 H), 0.98 (t, J = 8.0 Hz, 9 H), 0.65 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 174.9, 165.6, 164.8, 144.6, 140.3, 137.6, 135.7 (2C), 133.0, 132.7, 131.2, 130.1, 130.0, 127.9 (4C), 124.8, 105.0, 62.9, 61.8, 52.5, 48.6, 42.6, 38.7, 37.5, 35.9, 33.5, 32.4, 29.5, 29.0, 27.5, 26.8 (2C), 19.1, 17.9, 6.7 (3C), 4.2 (3C); HR-MS (FAB) calcd for $C_{46}H_{62}O_8Si_2Cs$ [M + Cs^+] 931.3038, found 931.3063.

(19) Due to space limitations, details will be provided in a full account of this work.