Improved Synthesis of Functionalized Podand Ionophores

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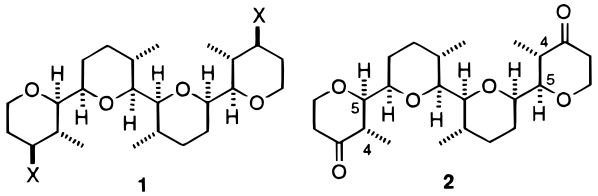
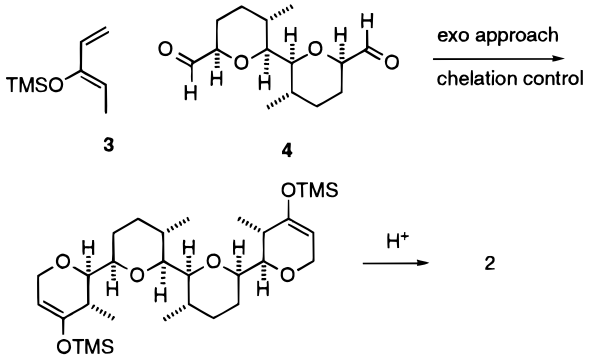
Enantiomerically pure podand ionophores **1**[1a−c] have been shown to be conformationally homogeneous and to bind salts of simple amino acid derivatives with significant enantioselectivity. The binding event is driven by electrostatic interactions between the ammonium group in the electron rich polyether cleft. Incorporation of additional groups having hydrogen bonding capabilities on the outer rings has led to hosts with enantioselectivities as high as 90% ee.[1a] Bis-ketone **2** has proven a valuable synthetic intermediate *en route* to such hosts, with the ketone functionality serving as an attachment point for the introduction of auxiliary hydrogen bonding groups (*e.g.* **1**, X = NHAc). Obtaining large quantities of **2** has taken considerable effort: 20 linear steps are required starting from (+)-L-diethyl tartrate with the tenth step having to be run on no greater than 1 g.



1 **2**

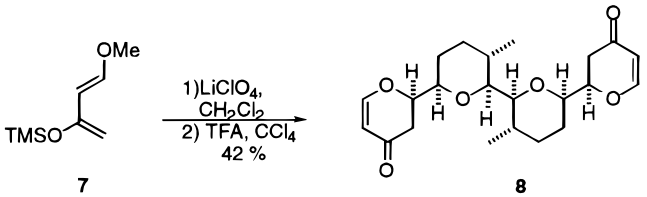
In this Note, we describe an improved synthesis of bis-ketone **2** which utilizes a hetero-Diels−Alder (HDA) reaction to rapidly access the four-ring system. Crucial to the successful implementation of the HDA strategy is the ability to exert stereocontrol in the formation of the C4 and C5 stereocenters in **2**. To obtain the desired stereochemistry, an *exo* addition of *Z* diene **3** to aldehyde **4** under conditions of chelation control is required.



3 **4**

The necessary bis-aldehyde **4** was obtained from known bis-ester **5**[1c] in four steps. Thus DIBAL reduction of **5** followed by Wittig reaction with *n*-butyltriphenylphosphonium bromide, deketalization, and $Pd(OAc)_2$-mediated cyclization[2] yielded diene **6**.[3] Ozonolysis of **6** with a sodium borohydride workup followed by Swern oxidation produced bis-aldehyde **4**. This compound was not stable to aqueous workup or silica chromatography but can be purified on fluorisil. The more direct ozonolysis of **6** followed by dimethyl sulfide workup was avoided, since it consistently produced a mixture of **4** and its *mono*- and bis-hydrates which could not be easily dehydrated (Scheme 1).

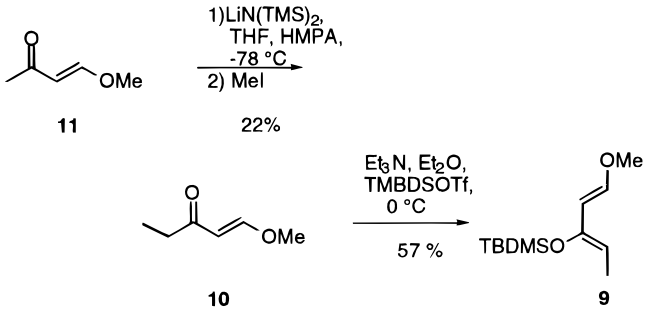
HDA reaction of **4** with known diene **3**[4] was attempted first, since it would give bis-ketone **2** directly. However, using $MgBr_2$[5] and $LiClO_4$[6] catalysis, no reaction could be induced. To see if the lack of reaction was simply due to inactive catalysts, HDA reaction of **4** with the more reactive bis-oxygenated diene **7**[7] was attempted. Under $MgBr_2$ catalysis, the reaction proceeded but with little stereocontrol. $LiClO_4$ catalysis, however, was more successful and resulted in formation of a single C_2-symmetric bis-enone **8** (42% yield). No other bis-enone products



7 **8**

could be detected in the crude reaction product. It was assumed that the product was the one expected from chelation control, but the issue of *endo* vs *exo* approach was less easily predicted. These HDA results implied that monoalkoxy diene **3** was simply not reactive enough to add to dialdehyde **4**. Furthermore, they suggested that the framework of **2** could be assembled by using a 1,3-bis-oxygenated diene bearing a C4 methyl, **9**.[8]

The precursor to diene **9**, 1-methoxypent-1-en-3-one (**10**) was obtained by methylation of the lithium enolate of commercially available 4-methoxybut-3-en-2-one (**11**).[9] Although the yield of the alkylation was low, gram quantities of **10** were easily prepared, and we used this method in preference to the known three-step preparation of **10.**[10] Enolsilylation of **10** following literature procedure[8] produced diene **9** as a *ca*. 4:1 *Z*:*E* mixture of enol silyl ethers.



11 **10** **9**

HDA reaction of bis-aldehyde **4** with diene **9** (5 equiv) and $LiClO_4$ (0.5 equiv) in CH_2Cl_2 (0.9 M) occurred over 6 h at rt. After desilylation and elimination promoted by TFA in CCl_4, we obtained the C_2-symmetric and non-

(1) (a) Burger, M. T.; Armstrong, A.; Guarnieri, F.; McDonald, D. Q.; Still, W. C. *J. Am. Chem. Soc.* **1994**, *116*, 3593−3594. (b) Armstrong, A.; Still, W. C. *J. Org. Chem.* **1992**, *57*, 4580−4582. (c) Wang, X.; Erickson, S. D.; Iomori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128−4137.

(2) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925−4928.

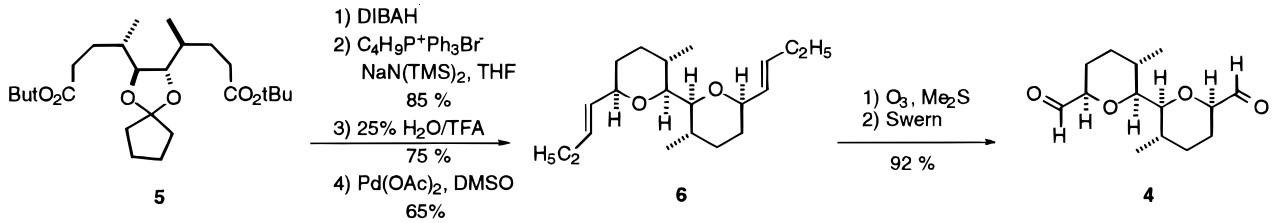
(3) The procedure for the preparation of the enantiomer of **6** was followed. Li, Ge, Ph.D. Thesis, Columbia University, 1993, p 92.

(4) Danishefsky, S. J.; Wan, C. F. *Synth. Commun.* **1978**, *8 (4)*, 211−218.

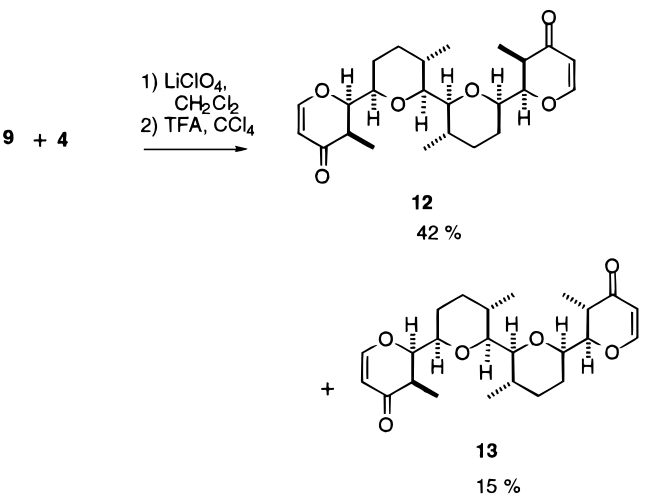
(5) Danishefsky, S. J.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256−1268.

0022-3263/96/1961-0775$12.00/0

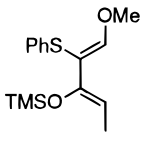
Scheme 1



symmetric bis-enones **12** and **13** in 42% and 15% yield, respectively. The relative C4,C5 *cis* stereochemistry in

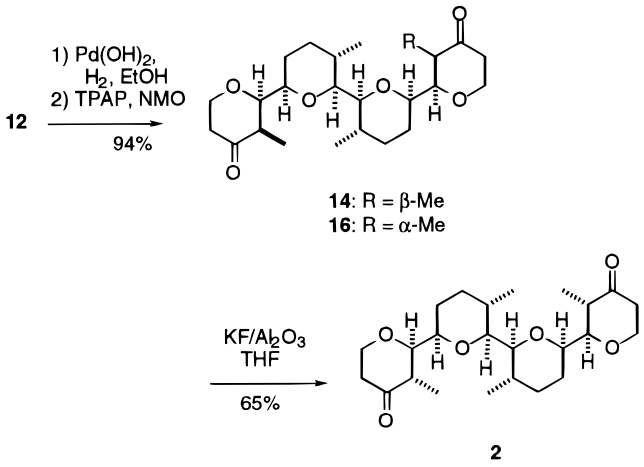


12 is supported by $J_{4,5}$ coupling constant of 2.9 Hz of **12** and furthermore by the equivalent coupling constant of 6.2 Hz of **14** produced by hydrogenation of **12**. Because this catalytic hydrogenation yielded some overreduced alcohol products, we oxidized the product mixture using TPAP[11] to produce a single bis-ketone **14**. The absolute stereochemistry of C4 and C5 was confirmed by conversion of **12** to **2** as described below. From the *cis* C4 and C5 stereochemistry of **12**, it is evident that the HDA reaction went with chelation control, setting C5, and with an *endo* approach of the diene, setting C4. Difficulties in obtaining *exo* Diels−Alder adducts with diene **9** in nonchelation control HDA reactions have been observed previously.[12] A solution to this problem has been proposed that employs diene **15** whose bulky C2 phenylthio substituent favors *exo* addition.[12]



15

Use of such an approach was not neccessary, however, because **14** could be readily epimerized to bis-ketone **2**. Thus, treatment of bis-ketone **14** with KF/Al_2O_3[13] in THF for 15 h gave **2** and the non-symmetric bisketone **16** in 57% and 21% yield respectively. After recycling **16** once, a 65% overall yield of **2** was obtained.



With this facile epimerizaion it was also possibe to convert the nonsymmetric HDA product **13** into **2**. In practice, the HDA products were not separated and the mixture was carried through the reduction and epimerization steps. Overall yields for the three-step conversion of bis-aldehyde **4** to the bis-ketone **2** are on the order of 40%. As compared to the prior synthesis of **2**, the HDA approach reduces the number of steps from 20 to 16 and more importantly increases the overall yield of **2** from (+)-L-diethyl tartrate by a factor of 3.

Experimental Section

Diene/Ketal. DIBAL (1 M in CH_2Cl_2, 10 mL, 10.0 mmol) was added dropwise to diester **5** (1.76 g, 4.0 mmol) at −78 °C under argon. After 20 min, methanol (2 mL) was added to quench the excess hydride. The resulting mixture was poured into a saturated Rochelle salt aqueous solution and stirred for 1 h until the organic layer became clear. The aqueous layer was then extracted three times with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. Removal of the solvents under reduced pressure and flash chromatography (50% Et_2O/hexanes) afforded bis-aldehyde as a colorless oil.

Sodium bis-trimethylsilylamide (1.0 M in THF, 11.0 mL, 11.0 mmol) was added slowly to *n*-butyltriphenylphosphonium bromide (4.8 g, 12.0 mmol) in 40 mL of THF under argon at −78 °C. After stirring at rt for 2 h, the orange suspension was recooled to −78 °C. The above bis-aldehyde (890 mg, 3.0 mmol) in 5 mL of THF was added dropwise via cannula to the stirred mixture. The reaction mixture was allowed to warm to rt and then stirred for 8 h. Ether (20 mL) and $NH_4Cl_{(sat.)}$ (30 mL) were added. The aqueous layer was extracted three more times with ether. The combined ethereal layers were washed with $NaCl_{(sat.)}$ and dried over $MgSO_4$. Removal of solvents, followed by chromatography (4% Et_2O/hexanes) yielded a diene/ketal (960

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(7) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996−7000.

(8) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, M. *J. Am. Chem. Soc.* **1985**, *107*, 1246−1255.

(9) Commercially available (Aldrich) 90% tech grade 1-methoxybut-1-en-3-one was distilled prior to use.

(10) (a) Hills, P. R.; McQuillan, F. *J. Chem. Soc.* **1953**, 4060−4065. (b) Harayama, T.; Cho, H.; Inubushi, Y. *Chem. Pharm. Bull.* **1978**, *26(4)*, 1201−1214.

(11) Griffith, W. F.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625−1627.

(12) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862−867.

(13) 40% KF/Al_2O_3 was prepared as described in Yamaka, J.; Ando, T. *Chem. Lett.* **1979**, 755−758.

mg, 85%). R_f = 0.35, 2% Et_2O/PE, silica gel; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (m, 4H), 3.60 (d, J = 6.3 Hz, 2H), 2.12 (m, 2H), 2.05−1.93 (m, 6H), 1.78−1.52 (m, 12H), 1.36 (dt, J = 7.4, 14.6 Hz, 4H), 1.18 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H), 0.88 (t, J = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.90, 129.78, 118.31, 83.74, 37.99, 36.02, 31.95, 29.31, 24.56, 23.45, 22.85, 16.22, 13.78; IR (neat) 2959, 2931, 2872, 1460, 1378, 1333, 1108, 981 cm^{-1}; HRMS calcd for $C_{25}H_{44}O_2$ 376.3341, found 376.3339.

Diene/Diol. The above diene/ketal (750 mg, 2.0 mmol) in 2 mL of TFA was treated with 0.4 mL of H_2O dropwise. After stirring at rt for 20 min, the reaction was quenched by adding 10 mL of 3 N NaOH. The aqueous solution was extracted with ether three times. The combined organics extracts were washed with $NaHCO_{3(sat.)}$, $NaCl_{(sat.)}$ and dried over $MgSO_4$ and chromatographed, yielding a diene/diol (460 mg, 75%). R_f = 0.65, 50% Et_2O/PE, silica gel; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (m, 4H), 3.37 (d, J = 5.8 Hz, 2H), 2.18−1.94 (m, 10H), 1.70−1.55 (m, 4H), 1.36 (dt, J = 7.4, 14.7 Hz, 4H), 1.21 (m, 2H), 0.93 (d, J = 6.8 Hz, 6H), 0.89 (t, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.95, 129.71, 75.19, 35.49, 31.77, 29.27, 24.62, 22.81, 15.91, 13.76; IR (KBr) 3361, 2960, 2929, 2871, 1654, 1455, 1404, 1378, 1302, 1067, 1018 cm^{-1}; HRMS calcd for $C_{20}H_{38}O_2$ 310.2872, found 310.2866.

Diene 6. $Pd(OAc)_2$ (730 mg, 3.25 mmol) was added to the above diene/diol (400 mg, 1.3 mmol) in 4 mL of DMSO under Ar. The reaction mixture was stirred in the dark at rt for 16 h, diluted with Et_2O (20 mL), and filtered through a small pad of SiO_2. The filtrate was washed with water three times and $NaCl_{(sat.)}$ once, dried over $MgSO_4$, and chromatographed (3% Et_2O/hexanes), yielding diene **6** (260 mg, 65%). R_f = 0.25, 2% Et_2O/PE, silica gel; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (dt, J = 5.9, 15.4 Hz, 2H), 5.52 (dd, J = 5.8, 15.5 Hz, 2H), 3.64 (dd, J = 5.8, 10.6 Hz, 2H), 3.03 (d, J = 9.0 Hz, 2H), 2.02 (m, 4H), 1.95−1.76 (m, 4H), 1.57 (m, 2H), 1.45 (m, 2H), 1.20 (m, 2H), 0.97 (t, J = 7.6 Hz, 6H), 0.80 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.27, 130.61, 82.60, 79.45, 33.15, 32.15, 30.11, 25.22, 17.13, 13.27; IR (neat) 2963, 2929, 2870, 2844, 1457, 1374, 1087, 1061, 1012, 966 cm^{-1}; HRMS calcd for $C_{20}H_{34}O_2$ 306.2559, found 306.2579.

Bis-aldehyde (4). A 1.9 g amount of bisdiene **6** (3.31 mmol, 1.0 equiv) in 220 mL of 4:1 CH_2Cl_2/MeOH was ozonized at −78 °C until a blue color persisted. At this time, 1.5 g of $NaBH_4$ (39.7 mmol, 12.0 equiv) was added, the bath was removed, and the solution was allowed to warm to rt with stirring over 45 min. Workup and extraction with $NH_4Cl_{(sat.)}$ and CH_2Cl_2 followed by drying over $MgSO_4$ and concentration yielded 916 mg of crude diol.

To 0.85 mL of $(COCl)_2$ (9.70 mmol, 2.94 equiv) in 58 mL of CH_2Cl_2 at −78 °C was added 1.38 mL of DMSO (19.45 mmol, 5.9 equiv) dropwise. The resultant solution was stirred for 5 min, upon which the preceding crude diol in 5 + 3 + 2 mL of CH_2Cl_2 was added dropwise. After stirring for 30 min at −78 °C, 3.4 mL of Et_3N (24.49 mmol, 7.4 equiv) was also added dropwise. After stirring at −78 °C for 25 min, the bath was removed and the solution was warmed to rt. Upon concentrating to 10 mL, the reaction mixuture was applied to a 3 cm × 4 in. column of fluorisil and was eluted with EtOAc, yielding 775 mg of bis-aldehyde **4** (92%). R_f = 0.25, EtOAc, silica gel; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 2H), 3.69 (dd, J = 12.0, 2.8 Hz, 2H), 3.20 (d, J = 9.2 Hz, 2H), 2.08−1.84 (m, 6H), 1.65−1.47 (m, 2H), 1.33−1.25 (m, 2H), 0.87 (d, J = 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.49, 82.80, 82.24, 32.00, 20.02, 26.70, 17.04; IR (thin film) 2927, 2850, 1738 cm^{-1}; MS m/e calcd for $C_{14}H_{23}O_4$ 255.1596, found 255.1600.

1-Methoxypent-1-en-3-one (10). To 248 mL of 1 M LiN(TMS)$_2$ in THF (248 mmoles, 1.2 equiv) in 1 L of THF at −78 °C was added 20.6 g of freshly distilled 4-methoxybut-3-en-2-one (**11**) (206 mmol, 1.0 equiv) dropwise. After stirring at −78 °C for 30 min, 102 mL of HMPA (586 mmol, 2.9 equiv) was added. After stirring 15 min at −78 °C, 36.5 mL of MeI (586 mmol, 2.9 equiv) was added. The resulting solution was stirred at −78 °C for 3 h. A 9 mL volume of $NH_4Cl_{(sat.)}$ was then added, and the bath was removed as the reaction was warmed to rt. The solution was diluted with Et_2O (1 L), washed with H_2O (3 × 500 mL), 1 M HCl, $NaHCO_{3(sat.)}$, and $NaCl_{(sat.)}$ (1 × 500 mL each), and dried over $MgSO_4$. Concentration and flash chromatography (25−30−35% E/PE) yielded 5.27 g of **10**, (22%). R_f = 0.45, 50% E/PE. Spectral characteristics are the same as reported.[10]

Bis-enone (12). To 203 mg of bis-aldehyde **4** (0.80 mmol, 1.0 equiv) and 42 mg of $LiClO_4$ (0.40 mmol, 0.5 equiv) in 1.9 mL of CH_2Cl_2 under argon was added 912 mg of diene **9** (4.0 mmol, 5.0 equiv). After stirring for 6 h, Et_2O (110 mL) and $NaHCO_{3(sat.)}$ (30 mL) were added. Upon being separated, the aqueous was extracted with Et_2O (2 × 60 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated. The crude product was dissolved in CCl_4 (25 mL), and 0.36 mL of TFA was added. After 5 min, CH_2Cl_2 (200 mL) was added and $NaHCO_{3(sat.)}$ (75 mL) was added in small portions to neutralize the reaction. Separation, extraction with CH_2Cl_2, drying over $MgSO_4$, and chromatography (70−80−90−100% E/PE) yielded 155 mg of C_2 enone **12** (42%) and 57 mg of non C-2 enone **13** (15%). R_f = 0.11 (**12**) and 0.17 (**13**), 75% E/PE, silica gel. Spectral data for **12**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 5.8 Hz, 2H), 5.31 (d, J = 5.8 Hz, 2H), 4.32 (dd, J = 7.6, 2.9 Hz, 2H), 3.52 (m, 2H), 3.05 (d, J = 9.2 Hz, 2H), 2.40 (m, 2H), 1.92 (m, 4H), 1.50 (m, 2H), 1.39 (m, 2H), 1.24 (m, 2H), 1.08 (d, J = 7.2 Hz, 6H), 0.84 (d, J = 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.46, 162.99, 105.20, 83.59, 82.47, 77.47, 41.02, 32.31, 29.24, 26.60, 16.84, 10.04; IR (thin film) 2931, 2851, 1682, 1594 cm^{-1}; MS m/e calcd for $C_{24}H_{34}O_6$ 418.2355, found 418.2343.

Bis-ketone (14). A 136 mg amount of bis-enone **12** (0.33 mmol, 1.0 equiv) and 47 mg of $Pd(OH)_2$/C in 35 mL of EtOH were placed under a balloon of H_2. After stirring for 55 min, the mixture was poured onto a 1 × 4 in. Celite column, eluting with EtOAc. All CAN-staining fractions were combined and concentrated. To the crude hydrogenation product were added 102 mg of *N*-methylmorpholine *N*-oxide (0.87 mmol, 2.6 equiv), 155 mg of 4 Å powdered molecular sieves, and 20.4 mL of CH_2Cl_2. After 5 min of stirring, 9 mg of tetrapropylammonium perruthenate (0.025 mmol, 0.07 equiv) was added. The reaction was stirred for 1 h. The mixture was then applied directly to a 5 cm × 4.5 in. SiO_2 column, eluting with Et_2O and then EtOAc, yielding 119 mg of bis-ketone **14**, (87%). R_f = 0.77, EtOAc, silica gel; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (m, 2H), 3.89 (m, 2H), 3.39 (m, 2H), 2.83 (d, J = 9.6 Hz, 2H), 2.68 (m, 2H), 2.52 (m, 2H), 2.20 (m, 2H), 1.97 (m, 2H), 1.80−1.66 (m, 4H), 1.46 (m, 2H), 1.15 (m, 2H), 1.05 (d, J = 6.8 Hz, 6H), 0.77 (d, J = 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.82, 83.19, 81.01, 77.37, 64.14, 46.38, 40.53, 32.73, 29.21, 26.75, 17.72, 9.74; IR (thin film) 2946, 2848, 1716 cm^{-1}; MS m/e calcd for $C_{24}H_{38}O_6$ 422.2668, found 422.2652.

Bis-ketone (2). A 112 mg amount of bis-ketone **14** (0.26 mmol, 1.0 equiv) and 280 mg of 40% KF/Al_2O_3 (1.93 mmol, 7.4 equiv) in 96 mL of THF was stirred for 15 h. The reaction mixture was poured onto a 2 × 4 in. Celite column, eluting with EtOAc. After concentrating, chromatography (75−90−100 EtOAc/hexanes) yielded 21 mg of non C-2 bis-ketone **16** (19%) and 62 mg of C_2 bis-ketone **2** (55%). Recycling the non C-2 bisketone **16** yielded an additional 11 mg of C_2 bis-ketone **2**; overall yield of **2** = 65%. R_f = 0.65 in EtOAc, silica gel, for nonsymmetric bis-ketone. R_f = 0.27 in EtOAc for α-Me bis-ketone; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (ddd, J = 11.3, 7.3, 1.4 Hz, 2H), 3.61 (ddd, J = 12.4, 11.3, 2.7 Hz, 2H), 3.36 (dd, J = 11.2, 1.8 Hz, 2H), 3.17 (dd, J = 10.0, 1.8 Hz, 2H), 3.05 (d, J = 9.0 Hz, 2H), 2.92 (m, 2H), 2.79 (m, 2H), 2.33 (d, J = 14.1 Hz, 2H), 2.01−1.87 (m, 6H), 1.40 (m, 2H), 1.22 (m, 2H), 1.01 (d, J = 6.7 Hz, 6H), 0.80 (d, J = 6.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.79, 85.03, 82.78, 76.70, 67.05, 46.54, 41.99, 32.95, 30.00, 27.27, 17.14, 9.37; IR (neat) 2969, 2929, 2852, 1713 cm^{-1}; MS m/e calcd for $C_{24}H_{38}O_6$ 422.2668, found 422.2678.

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Supporting Information Available: Copies of NMR spectra (7 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 ordering information.

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