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Syntheses of (−)-(7*S*)- and (+)-(7*R*)-K252a dimers

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Abstract—This letter describes syntheses of (−)-(7*S*)-and (+)-(7*R*)-K252a dimers wherein a convergent bis-indole-*N*-glycosidic coupling step was used for the resolution of the C(7) substituted (±)-aglycon. Dimerization of the derived monomers was achieved via olefin methathesis.

K252a (**1**) (Fig. 1),[1] isolated originally from the culture broth of *Actinomadura* by Sezaki and then reisolated from *Nocardiopsis* by Kase in a screen for antagonists of Ca^{2+} mediated signaling, has been implicated in the inhibition of several tyrosine kinases (Trks) and has been shown to be a potent PKC inhibitor.[2] Trk mediated PDGF signal transduction is potentially a novel therapeutic inroad for the treatment of human gliomas and follows the general motif of receptor tyrosine kinases (i.e. dimerization and autophosphorylation).[3] Based on recent work demonstrating that dimeric natural product probes function particularly efficiently as tools for chemical biology,[4–6] we became curious as to whether multivalent analogs of K252a would have a selective influence on receptor-type kinases. Thus, we initiated an effort to prepare K252a analogs poised for subsequent conversion to dimeric or higher valent species. Recently, efforts to access novel K252a analogs have resulted in a convergent route to C7 and C2′ alkylated K252a analogs.[7a–d] Herein, we describe a synthesis of (−)-(7*S*)-and (+)-(7*R*)-K252a dimers (**2** and **3**) utilizing olefin methathesis. The requisite monomers were prepared using an expansion of our strategy for the construction of C7 alkylated K252a analogs.[7b,c]

The synthesis of (±)-aglycon **11** is outlined in Scheme 1. Thus, alkylation of known imine **4** with 8-bromo-1-octene according to O'Donnel's procedure followed by hydrolysis of the imine afforded ethyl 2-amino-9-decenoate hydrochloride (**5**) in 72% overall yield.[8] A two-step reductive amination utilizing 3,4-dimethoxybenzaldehyde and $NaBH_4$ gave DMB (3,4-dimethoxybenzyl) protected amine **6** in 81% yield. Acylation with ethyl hydrogen malonate under standard coupling conditions (DCC/DMAP) afforded **7** in 92% yield. Dieckmann cyclization (NaOEt/EtOH) followed by decarboalkoxylation in wet CH_3CN gave *N*-DMB-protected tetramic acid **8** (84%, two steps). Subsequent diazotransfer with 4-nitrobenzenesulfonyl azide in the presence of Et_3N smoothly gave diazolactam **9** in 93% yield.[9] According to previous protocols, **9** and biindole **10** were treated with $Rh_2(OAc)_4$ in degassed pinacolone under reflux for 8 h. Successive C–H insertion, electrocyclization and aromatization gave the desired *N*-DMB

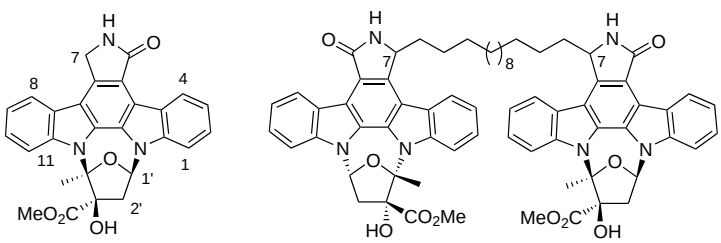

Figure 1.

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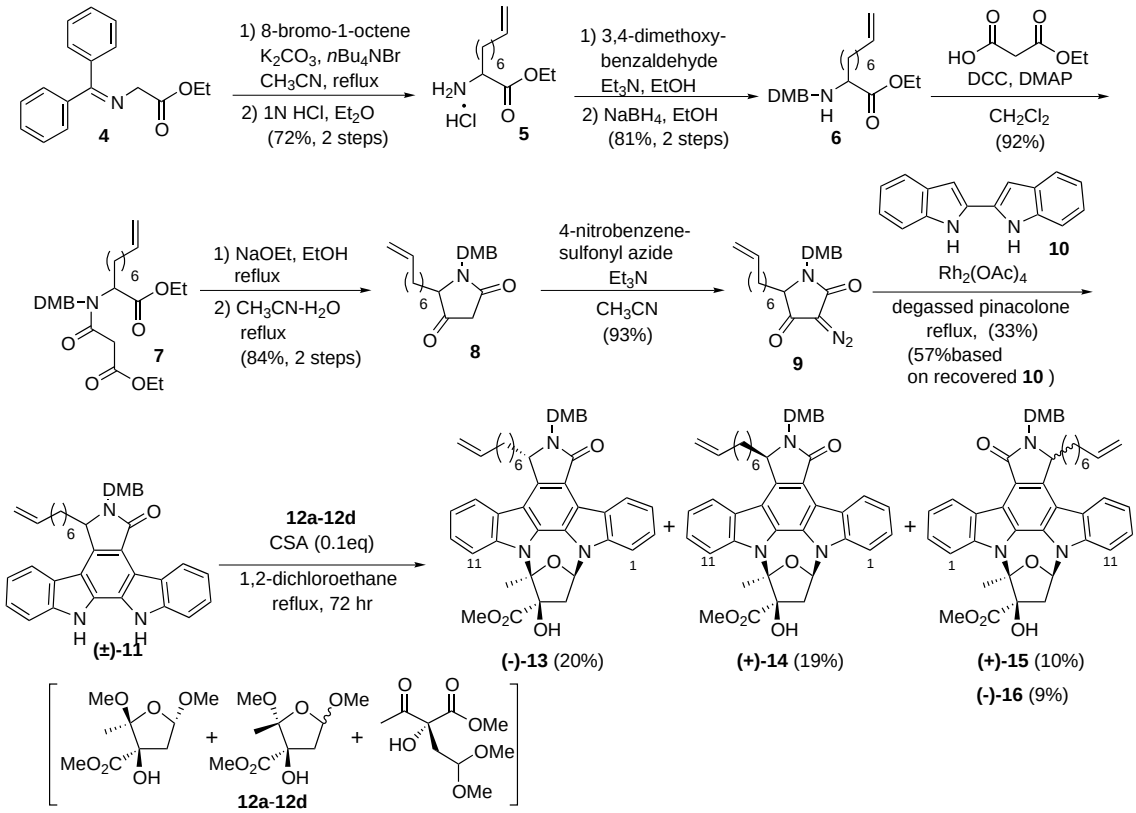
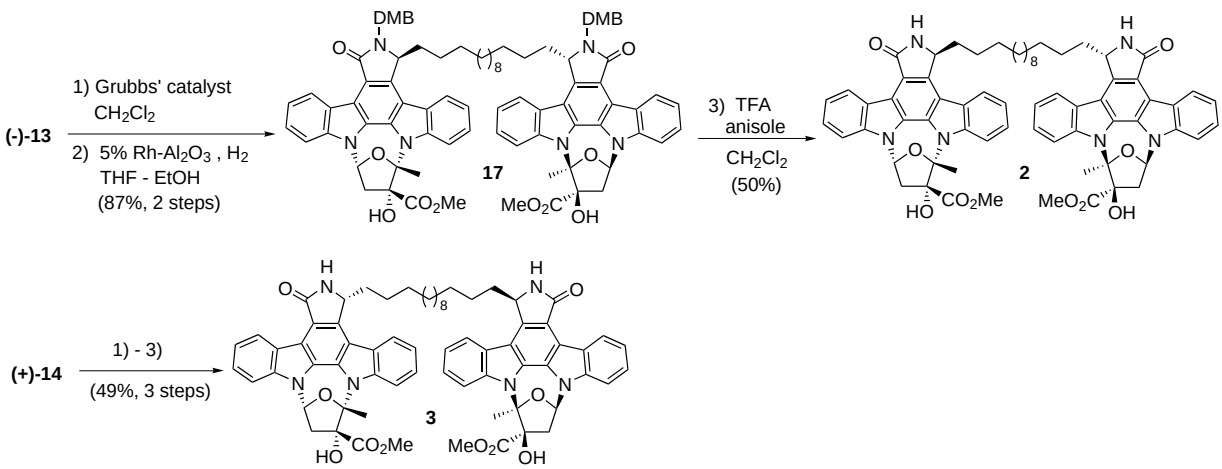


Scheme 1.

protected aglycon (±)-**11** in 33% yield (57% based on recovered **10**).[7a] With **11** in hand we explored the one-step acid catalyzed bis-indole-*N*-glycosidic coupling with enantioenriched **12a**–**12d**.[7a,10] Slow addition (24 h) of **12a**–**12d** (a solution in 1,2–dichloroethane) to **11** and CSA (0.1 equiv.) in 1,2-dichloroethane followed by an additional 48 h at reflux gave a 2:2:1:1 diastereomeric mixture of methathesis precursors (**13**–**16**). Following isolation of the individual diastereomers by careful preparative TLC,[11–14] the initial regiochemical assignment for **13**–**16** was made based on ^{1}H NMR analysis. Subsequent assignment of the relative stereochemistry to the major regioisomers (–)-**13** and (+)-**14** was made by comparison to previously prepared C7-methyl-6-*N*-DMB-K252a[7b,c] and C7-benzyl-6-*N*-DMB-K252a[7c] analogs. The relative stereochemistry of (+)-**15** and (–)-**16** remains ambiguous due to a lack of comparison data.

Treatment of (–)-**13** with Grubbs' catalyst (Scheme 2)[15] (8 mol%) at room temperature in CH_2Cl_2 for 43 h gave the desired dimer as a mixture of *E* and *Z* isomers.[16] Subsequent hydrogenation with 5% Rh/Al_2O_3 afforded (7*S*)-6-*N*-DMB-dimer **17** in 87% overall yield. Final



Scheme 2.

DMB deprotection was carried out with TFA in the presence of anisole to provide the (−)-(7*S*)-K252a dimer (**2**) in 50% yield.[17] An identical reaction sequence utilizing (+)-**14** furnished the corresponding (+)-(7*R*)-K252a dimer (**3**) in 49% overall yield.[18]

In conclusion, the first total synthesis of a C7 linked dimer of K252a has been completed. The synthesis expands the scope of our aglycon synthesis and establishes the feasibility of using cyclofuranosylation with enentioenriched carbohydrate precursors as a means to resolve racemic aglycons. Evaluation of the biological activity of these dimers is underway and has already established them to be potent kinase inhibitors.

Acknowledgements

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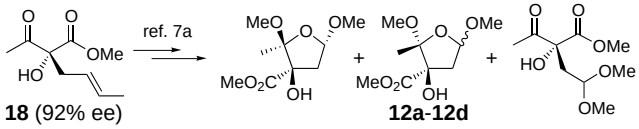
10. The four diasteromers (**12a**–**12d**) were all derived from alcohol **18** (92% ee) and lead to identical cyclofulanosylation products. See Ref. 7a.



18 (92% ee) **12a-12d**

11. (−)-(7*S*)-(1-Octenyl)-*N*-DMB-K252a (**13**): a pale yellow powder; $[\alpha]_D^{20}$ −36.0 (*c* 0.30, $CHCl_3$); IR (thin film/NaCl) 3298 (br w), 2930 (m), 2854 (w), 1733 (m), 1673 (s), 1646 (s), 1585 (m), 1515 (m), 1459 (s), 1392 (m) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 9.51 (d, *J*=7.9 Hz, 1H), 8.09 (d, *J*=7.3 Hz, 1H), 8.00 (d, *J*=8.2 Hz, 1H), 7.81 (d, *J*=8.1 Hz, 1H), 7.51 (app t, *J*=7.8 Hz, 1H), 7.43 (app t, *J*=7.8 Hz, 1H), 7.36–7.26 (m, 2H), 7.17 (dd, *J*=5.0, 7.6 Hz, 1H), 7.11 (d, *J*=1.8 Hz, 1H), 7.01 (dd, *J*=1.8, 8.3 Hz, 1H), 6.92 (d, *J*=8.3 Hz, 1H), 5.60 (ddt, *J*=10.2, 17.0, 6.8 Hz, 1H), 5.34 (app t, *J*=3.2 Hz, 1H), 5.34 (d, *J*=15.1 Hz, 1H), 5.27 (s, 1H), 4.80 (m, 1H), 4.76 (m, 1H), 4.42 (d, *J*=15.1 Hz, 1H), 4.01 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.49 (dd, *J*=7.6, 14.2 Hz, 1H), 2.52 (m, 1H), 2.41 (m, 1H), 2.23 (s, 3H), 2.20 (m, 1H), 1.82–1.73 (m, 2H), 1.12–0.92 (m, 7H), 0.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 169.8, 149.0, 148.2, 140.3, 138.9, 137.0, 134.2, 130.4, 128.9, 126.4, 125.6, 125.0, 124.5, 124.0, 122.6, 121.9, 120.6, 120.1, 119.6, 119.3, 116.7, 114.8, 114.2, 113.9, 111.0, 110.7, 107.3, 98.9, 85.3, 84.7, 60.0, 55.8, 55.8, 53.7, 43.6, 42.2, 33.5, 29.2, 29.0, 28.6, 28.5, 22.8, 21.6; HRMS (FAB) *m*/*z* 728.3339 [calcd for $C_{44}H_{46}N_3O_7$ (M+H) 728.3336].
12. (+)-(7*R*)-(1-Octenyl)-*N*-DMB-K252a (**14**): a pale yellow powder; $[\alpha]_D^{20}$ +74.8 (*c* 0.21, $CHCl_3$); IR (thin film/NaCl) 3485 (br w), 3304 (br w), 3069 (w), 2998 (m), 2928 (s), 2854 (m), 1732 (s), 1673 (s), 1585 (m), 1515 (s), 1452 (s), 1392 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 9.51 (d, *J*=7.8 Hz, 1H), 8.12 (d, *J*=7.6 Hz, 1H), 8.01 (d, *J*=8.5 Hz, 1H), 7.80 (d, *J*=8.3 Hz, 1H), 7.51 (app t, *J*=7.4 Hz, 1H), 7.43 (app t, *J*=7.5 Hz, 1H), 7.36–7.27 (m, 2H), 7.15 (dd, *J*=5.1, 7.3 Hz, 1H), 7.12 (d, *J*=1.8 Hz, 1H), 7.02 (dd, *J*=1.8, 8.2 Hz, 1H), 6.93 (d, *J*=8.2 Hz, 1H), 5.61 (ddt, *J*=10.3, 17.1, 6.8 Hz, 1H), 5.39 (s, 1H), 5.36 (m, 1H), 5.34 (d, *J*=15.2 Hz, 1H), 4.81 (m, 1H), 4.76 (m, 1H), 4.42 (d, *J*=15.2 Hz, 1H), 4.02 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.51 (dd, *J*=7.3, 14.2 Hz, 1H), 2.54–2.35 (m, 2H), 2.36 (dd, *J*=5.1, 14.2 Hz, 1H), 2.18 (s, 3H), 1.82–1.75 (m, 2H), 1.12–0.83 (m, 7H), 0.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 169.8, 149.2, 148.3, 140.1, 139.0, 137.2, 134.7, 130.3, 128.8, 126.9, 125.8, 125.0, 124.4, 124.3, 123.3, 122.4, 120.6, 120.3, 120.2, 117.1, 114.9, 114.0, 113.9, 111.0, 111.0, 107.3, 98.5, 85.0, 84.3, 58.7, 55.9, 55.8, 54.2, 43.6, 41.5, 33.6, 29.2, 29.1, 28.8, 28.6, 22.8, 21.6; HRMS (FAB) *m*/*z* 728.3339 [calcd for $C_{44}H_{46}N_3O_7$ (M+H) 728.3336].

13. (+)-Indolocarbazole **15** (isomer 1): a pale yellow powder; $[\alpha]_D^{20}$ +68.7 (*c* 0.31, $CHCl_3$); IR (thin film/NaCl) 3485 (br m), 3333 (br m), 3056 (m), 2999 (m), 2928 (s), 2854 (m), 1732 (s), 1671 (s), 1585 (m), 1514 (s), 1451 (s), 1400 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 9.76 (d, $J=8.0$ Hz, 1H), 8.14 (d, $J=7.8$ Hz, 1H), 7.94 (d, $J=8.6$ Hz, 1H), 7.88 (d, $J=8.5$ Hz, 1H), 7.51 (app t, $J=7.7$ Hz, 1H), 7.44 (app t, $J=7.8$ Hz, 1H), 7.35–7.27 (m, 2H), 7.16 (dd, $J=5.0$, 7.3 Hz, 1H), 7.10 (d, $J=1.9$ Hz, 1H), 7.01 (dd, $J=1.9$, 8.2 Hz, 1H), 6.91 (d, $J=8.1$ Hz, 1H), 5.60 (ddt, $J=10.2$, 17.0, 6.8 Hz, 1H), 5.34 (d, $J=14.9$ Hz, 1H), 5.30 (app t, $J=3.7$ Hz, 1H), 5.26 (s, 1H), 4.81 (m, 1H), 4.76 (m, 1H), 4.42 (d, $J=14.9$ Hz, 1H), 4.00 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.49 (dd, $J=7.3$, 13.8 Hz, 1H), 2.53 (m, 1H), 2.42 (m, 1H), 2.26 (m, 1H), 2.23 (s, 3H), 1.82–1.74 (m, 2H), 1.13–0.94 (m, 7H), 0.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 170.0, 149.2, 148.3, 139.9, 138.9, 137.2, 135.2, 130.4, 127.0, 126.7, 126.4, 125.6, 125.2, 125.1, 122.9, 122.5, 120.4, 120.4, 120.2, 120.0, 117.8, 114.3, 114.0, 112.8, 111.0, 110.9, 108.4, 98.5, 85.1, 84.6, 58.3, 55.9, 55.8, 54.0, 43.6, 41.7, 33.5, 29.2, 29.2, 28.7, 28.6, 22.9, 21.5; HRMS (FAB) *m/z* 728.3339 [calcd for $C_{44}H_{46}N_3O_7$ (M+H) 728.3336].

14. (−)-Indolocarbazole **16** (isomer 2): a pale yellow powder; $[\alpha]_D^{20}$ −30.0 (*c* 0.26, $CHCl_3$); IR (thin film/NaCl) 3485 (br m), 3334 (br w), 3056 (m), 2998 (m), 2928 (s), 2854 (m), 1732 (s), 1671 (s), 1585 (m), 1515 (s), 1487 (m), 1450 (s), 1400 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 9.76 (d, $J=8.0$ Hz, 1H), 8.16 (d, $J=8$, 1 Hz, 1H), 7.94 (d, $J=8.5$ Hz, 1H), 7.88 (d, $J=8.5$ Hz, 1H), 7.51 (app t, $J=7.8$ Hz, 1H), 7.44 (app t, $J=7.7$ Hz, 1H), 7.37–7.26 (m, 2H), 7.15 (dd, $J=5.0$, 7.3 Hz, 1H), 7.11 (d, $J=1.8$ Hz, 1H), 7.02 (dd, $J=1.8$, 8.1 Hz, 1H), 6.92 (d, $J=8.1$ Hz, 1H), 5.57 (ddt, $J=10.2$, 17.0, 6.8 Hz, 1H), 5.39 (s, 1H), 5.32 (d, $J=15.1$ Hz, 1H), 5.32 (app t, $J=3.5$ Hz, 1H), 4.78 (m, 1H), 4.75 (m, 1H), 4.43 (d, $J=15.1$ Hz, 1H), 4.00 (s, 3H), 3.76 (s, 3H), 3.75 (s, 3H), 3.54 (dd, $J=7.3$, 13.8 Hz, 1H), 2.56 (m, 1H), 2.47–2.33 (m, 2H), 2.18 (s, 3H), 1.79–1.67 (m, 2H), 1.07–0.87 (m, 7H), 0.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 170.0, 149.3, 148.3, 140.0, 138.9, 137.4, 135.1, 130.4, 127.1, 126.6, 126.6, 125.7, 125.3, 125.2, 122.7, 122.6, 120.6, 120.4, 120.2, 120.0, 118.1, 114.4, 114.0, 113.0, 111.1, 111.0, 108.3, 98.6, 85.1, 84.3, 58.3, 55.9, 55.9, 54.0, 43.6, 42.1, 33.5, 29.2, 28.9, 28.7, 28.6, 22.8, 21.5; HRMS (FAB) *m/z* 728.3340 [calcd for $C_{44}H_{46}N_3O_7$ (M+H) 728.3336].

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16. Due to signal overlap in ^1H NMR, *E*/*Z* ratio was not determined.

17. (−)-(7*S*)-K252a dimer (**2**): a white powder: $[\alpha]_D^{20}$ −145 (*c* 0.10, $CHCl_3$); IR (thin film/NaCl) 3223 (br m), 3051 (m), 2924 (s), 2851 (m), 1731 (s), 1678 (s), 1583 (m), 1487 (m), 1453 (s), 1392 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 9.37 (d, $J=7.8$ Hz, 2H), 8.13 (d, $J=7.8$ Hz, 2H), 8.10 (s, 2H), 8.00 (d, $J=8.5$ Hz, 2H), 7.74 (d, $J=8.3$ Hz, 2H), 7.48–7.40 (m, 4H), 7.34 (app t, $J=7.4$ Hz, 2H), 7.26 (app t, $J=7.6$ Hz, 2H), 7.12 (dd, $J=4.8$, 7.4 Hz, 2H), 5.38 (s, 2H), 5.33 (dd, $J=2.2$, 7.8 Hz, 2H), 4.00 (s, 6H), 3.49 (dd, $J=7.4$, 14.0 Hz, 2H), 2.51 (m, 2H), 2.30 (dd, $J=4.8$, 14.0 Hz, 2H), 2.20 (s, 6H), 1.74 (m, 2H), 1.61 (m, 2H), 1.47–0.99 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 171.1, 140.7, 137.0, 136.7, 129.3, 125.4, 125.3, 124.8, 123.7, 121.1, 120.8, 120.4, 118.7, 116.2, 115.9, 115.8, 113.4, 107.0, 100.0, 86.2, 85.0, 57.2, 53.1, 42.6, 34.2, 29.3, 29.2, 29.1, 28.7, 28.7, 26.6, 22.7; HRMS (FAB) *m/z* 1129.5073 [calcd for $C_{68}H_{69}N_6O_{10}$ (M+H) 1129.5075].

18. (+)-(7*R*)-K252a Dimer (**3**): a white powder: $[\alpha]_D^{20}$ +107 (*c* 0.10, $CHCl_3$); IR (thin film/NaCl) 3499 (w), 3405 (br m), 3205 (br m), 3053 (m), 2924 (s), 2853 (s), 1732 (s), 1680 (s), 1584 (m), 1488 (w), 1458 (s), 1393 (s) cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ 9.42 (d, $J=8.0$ Hz, 2H), 8.17 (s, 2H), 8.15 (d, $J=8.3$ Hz, 2H), 8.01 (d, $J=8.4$ Hz, 2H), 7.78 (d, $J=8.3$ Hz, 2H), 7.48 (app t, $J=7.8$ Hz, 2H), 7.44 (app t, $J=7.9$ Hz, 2H), 7.34 (app t, $J=7.3$ Hz, 2H), 7.28 (app t, $J=7.6$ Hz, 2H), 7.15 (dd, $J=5.1$, 7.3 Hz, 2H), 5.46 (s, 2H), 5.38 (dd, $J=1.9$, 8.1 Hz, 2H), 4.00 (s, 6H), 3.52 (dd, $J=7.3$, 14.3 Hz, 2H), 2.56 (m, 2H), 2.34 (dd, $J=5.1$, 14.3 Hz, 2H), 2.20 (s, 6H), 1.74–1.55 (m, 6H), 1.53–1.06 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 172.4, 140.2, 137.8, 137.1, 129.1, 126.8, 125.7, 124.9, 124.4, 124.2, 123.3, 122.1, 120.6, 120.1, 117.1, 115.0, 114.1, 107.3, 98.7, 85.1, 84.4, 57.7, 53.9, 41.9, 34.3, 29.3, 29.3, 29.2, 29.2, 29.2, 26.4, 22.9; HRMS (FAB) *m/z* 1129.5073 [calcd for $C_{68}H_{69}N_6O_{10}$ (M+H) 1129.5075].