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Total Synthesis of Cruentaren B

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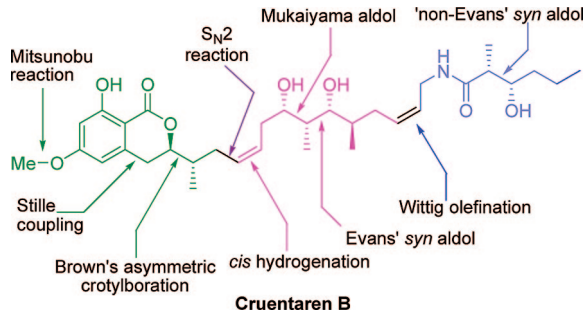


A convergent total synthesis of the cytotoxic natural product cruentaren B is completed in 26 steps (longest linear sequence) with an overall yield of 7.1%. For the construction of the C_1-C_{11} benzolactone fragment of the molecule, the key steps used were *O*-methylation, using a Mitsunobu reaction, a Stille coupling method to construct the C_7-C_8 bond, and a Brown's asymmetric crotylboration reaction for the direct enantioselective installation of the two chiral centers present in this fragment. For diastereoselective installation of the chiral centers in the $C_{12}-C_{20}$ polyketide fragment, an Evans *syn* aldol reaction on a chiral aldehyde, derived from methyl (*R*)-3-hydroxyl-2-methylpropionate, and subsequently a Mukaiyama aldol reaction were employed. For the construction of the $C_{21}-C_{28}$ tail, a "non-Evans" *syn* aldol reaction was used. The three fragments were coupled by an S_N2 reaction and a Wittig olefination reaction followed by standard functional group manipulations to furnish the target molecule.

In search of new biologically active natural products, myxobacteria have been proven to be a rich repertoire of innumerable secondary metabolites with novel structures and wide-ranging properties.[1,2] The benzolactones, cruentaren A (**1**) and its ring-contracted congener cruentaren B (**2**) (Figure 1), are two such molecules isolated from myxobacterium *Byssovorax cruenta*.[3,4] While cruentaren A strongly inhibited the growth of yeasts and

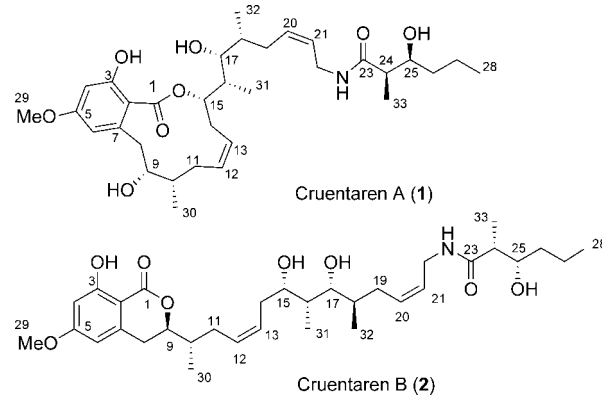
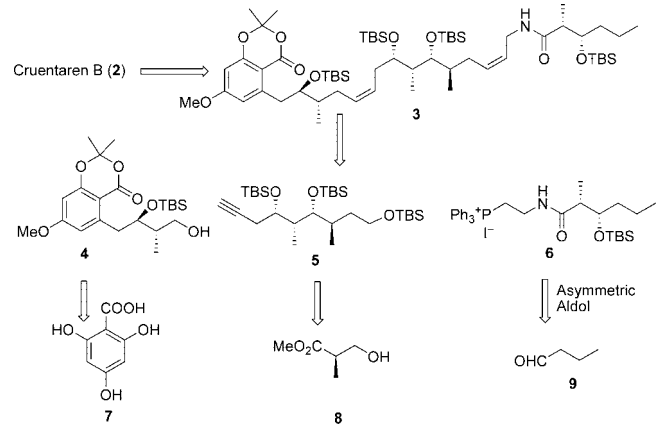


FIGURE 1. Structures of cruentarens.

SCHEME 1. Retrosynthetic Analysis of Cruentaren B (2)



filamentous fungi and showed high cytotoxicity against L929 mouse fibroblast cells, cruentaren B showed only marginal cytotoxicity and no antifungal activity.[4] However, thorough evaluation of other biological properties of cruentarens and their analogues can only be undertaken if a versatile synthetic route is devised for their syntheses. Because of their novel structures and wide-ranging biological activities,[5] cruentarens have attracted the attention of synthetic chemists worldwide. Synthesis of cruentaren A has been achieved by Maier et al.[6,7] and also by Fürstner's group.[8] In this paper, we describe a convergent total synthesis of cruentaren B.

A retrosynthetic analysis of cruentaren B (**2**) is shown in Scheme 1. We envisioned constructing the target molecule from the fragments **4**–**6** via an acetylide−triflate cross-coupling reaction (**4** + **5**), followed by selective hydrogenation to the *Z*-olefin and a Wittig olefination with **6**. The resulting product **3** after global deprotection of the protecting groups and a base-catalyzed cyclization was expected to furnish the target natural product **2**. While compound **4** could be built from 2,4,6-

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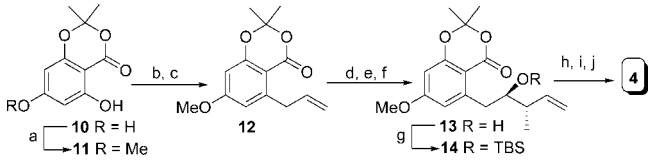
SCHEME 2. Synthesis of Fragment 4[a]



[a] Reagents and conditions: (a) DIAD, MeOH, Ph_3P, THF, 0 °C, 98%; (b) Tf_2O, pyridine, 0 °C, 90%; (c) Bu_3Sn(allyl), LiCl, TFP, $Pd_2(dba)_3$, NMP, rt, 72%; (d) OsO_4, NMO, acetone:water (1:1), rt, 92%; (e) $NaIO_4$, THF:H_2O (1:1), 0 °C, 93%; (f) (−)-Ipc_2BOMe, *trans*-but-2-ene, KO′Bu, *n*-BuLi, BF_3·Et_2O, THF:Et_2O (10:1), −78 to 0 °C, 89%; (g) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 92%; (h) same as in footnote d, 93%; (i) same as in footnote e, 90%; (j) $NaBH_4$, MeOH:THF (1:1), 0 °C, 97%.

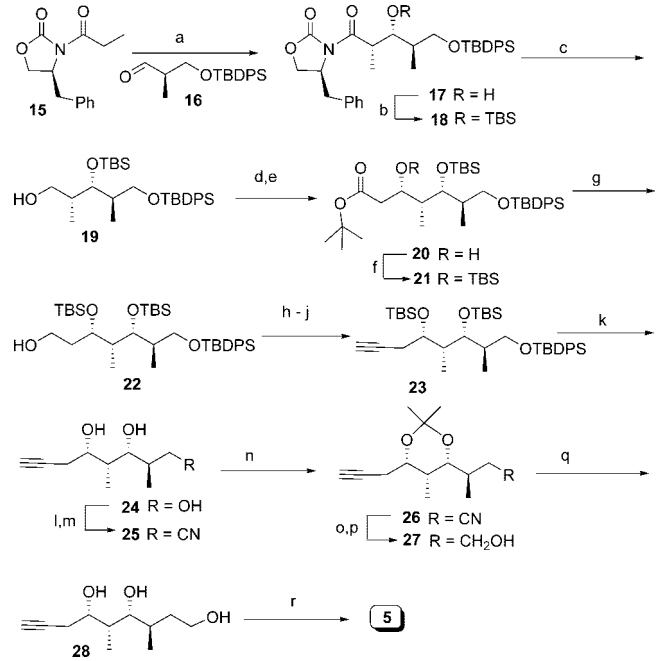
trihydroxybenzoic acid **7**, the acetylenic intermediate **5** could be derived from commercially available methyl (*R*)-3-hydroxyl-2-methylpropionate (**8**). An enantioselective aldol reaction on butyraldehyde **9** could furnish the ylide component **6**.

Our synthesis commenced with the construction of the benzolactone moiety **4** (Scheme 2). Selective *O*-methylation of **10**, derived from readily available acid **7**,[9] using diisopropylazodicarboxylate (DIAD) and methanol under Mitsunobu conditions,[10] gave **11** in an excellent yield of 98%.

Next, the alcohol **11** was treated with Tf_2O in pyridine to give the triflate compound, which upon Pd-catalyzed Stille coupling[11] with allylstannane in the presence of LiCl and tri(2-furyl)phosphine (TFP) in *N*-methylpyrrolidine (NMP) gave the desired product **12** in 65% yield. Dihydroxylation of **12** with *N*-methylmorpholine (NMO) and OsO_4 followed by oxidative cleavage with $NaIO_4$ gave an aldehyde, which on asymmetric crotylboration following Brown's protocol[12] and with (−)-isopinocamphenylborane, (−)-Ipc_2B(allyl), resulted in the formation of an *anti*-adduct, the homoallylic alcohol **13** in 76% overall yield in three steps and with an ee of 97% as determined by the Mosher ester method.[13] Silyl protection of the secondary hydroxyl group with TBSOTf and DIPEA in CH_2Cl_2 gave **14** in 92% yield. Compound **14** was converted to the primary alcohol **4** in three steps in 81% overall yield—dihydroxylation followed by oxidative cleavage and a $NaBH_4$ reduction.

Synthesis of **5** is depicted in Scheme 3. Aldehyde **16**, prepared from commercially available methyl (*R*)-3-hydroxyl-2-methylpropionate **8** by TBDPS protection and reduction,[14] was subjected to the Evans *syn* aldol reaction under modified conditions[15] with propanoyl oxazolidinone **15** to afford aldol product **17** in good yield and diastereoselectivity (92%, de 98%) after chromatographic purification. Silyl protection of the secondary hydroxyl group as TBS ether with TBSOTf and DIPEA followed by reductive removal[16] of the chiral auxiliary

SCHEME 3. Synthesis of Fragment 5[a]



[a] Reagents and conditions: (a) $TiCl_4$, (−)-sparteine, CH_2Cl_2, −78 °C, 92%; (b) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 94%; (c) $LiBH_4$, ether (cat. water), 0 °C, 90%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (e) TBS-enol ether of *tert*-butylacetate, BF_3·Et_2O, THF, −78 °C, 70% (in two steps); (f) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 93%; (g) DIBAL-H, CH_2Cl_2, −40 °C; (h) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C; (i) CBr_4, Ph_3P, CH_2Cl_2, Et_3N, 0 °C to rt; (j) *n*-BuLi, THF, −78 °C, 85% (in four steps); (k) TBAF, THF, 0 °C to rt, 85%; (l) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 96%; (m) NaCN, NaI (cat), DMSO, 90 °C, 82%; (n) 2,2-dimethoxypropane, CSA, 0 °C to rt, 98%; (o) (i) DIBAL-H, CH_2Cl_2, −78 °C; (ii) 3 N NaOH, −78 °C to rt; (p) $NaBH_4$, THF:MeOH (1:1), 0 °C, 92% (in three steps); (q) CSA, CH_2Cl_2:MeOH (1:1), 0 °C, 93%; (r) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 91%.

gave the alcohol **19** in 85% yield in two steps. Swern oxidation[17] of the alcohol **19** followed by Mukaiyama aldol[18] with TBS enol ether of *tert*-butyl acetate gave the required diastereomer **20** in 70% yield in two steps and diastereoselectivity of 81% after column chromatographic purification.

Protection of the secondary hydroxyl group of **20** as TBS ether followed by DIBAL-H reduction gave the alcohol **22**. The Dess−Martin periodinane (DMP) oxidation[19] of **22** gave an aldehyde, which was converted to the alkyne compound **23** by using Corey's protocol[20] (85% over four steps). Global deprotection of the silyl protecting groups was followed by selective monotosylation of the primary hydroxyl group and cyanation with NaCN in the presence of a catalytic amount of NaI at 90 °C in DMSO to give the cyano compound **25** in 67% yield in three steps. Acetonide protection followed by DIBAL-H reduction,[21] hydrolysis, and finally $NaBH_4$ reduction gave the alcohol **27** in 90% yield in four steps. Next, deprotection of the acetonide with CSA and global protection of the resulting triol with TBSOTf afforded **5** in 85% yield over two steps.

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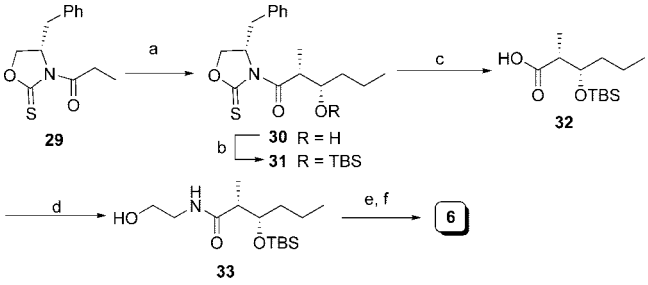
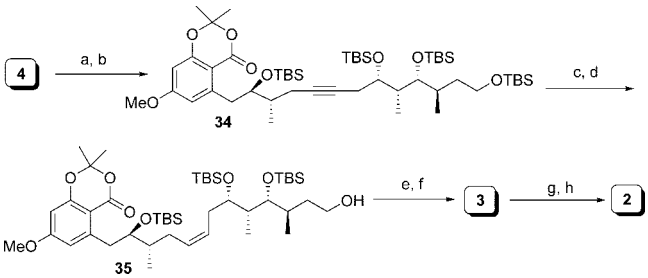
SCHEME 4. Synthesis of Fragment 6[a]



[a] Reagents and conditions: (a) $TiCl_4$, DIPEA, butanal, CH_2Cl_2, 0 °C, 87%; (b) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 94%; (c) LiOH, H_2O_2, THF: H_2O (3:1), 0 °C to rt, 86%; (d) EDCI, HOBt, DIPEA, 2-aminoethanol, CH_2Cl_2, 0 °C to rt, 80%; (e) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C to rt, 75%; (f) Ph_3P, 90 °C, 98%.

SCHEME 5. Coupling of Fragments 4, 5, and 6 and Completion of the Synthesis of Cruentaren B (2)[a]



[a] Reagents and conditions: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; (b) **5,** *n*-BuLi, HMPA, THF, then the triflate was added, −78 °C, 72%; (c) HF·py complex, THF, rt, 90%; (d) H_2, Pd-$BaSO_4$, quinoline (0.05 equiv), rt, 98%; (e) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 95%; (f) **6**, *n*-BuLi, HMPA, THF, then added the aldehyde, −78 °C, 64% (on the basis of recovered aldehyde); (g) HF·py, THF, −40 °C to –4 °C, 92%; (h) LiOH.H_2O, THF: H_2O:MeOH (3:1:1), 0 °C, 89%.

The synthetic route for the right-hand segment **6** is depicted in Scheme 4. The non-Evans *syn*-aldol reaction between **29** and butanal **9** with the Crimmins protocol[22] gave secondary alcohol **30**. Protection of the hydroxyl group as TBS ether, followed by oxidative removal of the chiral auxiliary with H_2O_2 and LiOH[23] gave **32** in 70% yield in three steps. This was identical in all respects with the one reported earlier.[7] The compound **32** was coupled with 2-aminoethanol using common amide bond forming protocol with EDCI and HOBt to afford **33** in 80% yield. The phosphonium salt **6** was generated in 73% yield in two steps with conversion of the hydroxyl group to an iodo with Ph_3P, I_2, and imidazole, followed by the reaction of the iodide with Ph_3P.

With all three segments **4**–**6** in hand, we undertook studies to couple them together to build the entire framework of the cruentaren B (Scheme 5). The triftate, generated from **4** with Tf_2O and 2,6-lutidine in CH_2Cl_2, was treated with the lithiated alkyne[24] moiety of **5** to afford the desired coupling product **34** with 72% yield.

After successful first coupling, we deprotected the primary TBS selectively with HF-py complex to give an intermediate alcohol, which was reduced by hydrogenation by using Pd-$BaSO_4$/quinoline to afford the *Z*-olefin **35** in 88% overall yield in two steps. Next, Dess−Martin periodinane (DMP)[19] oxidation followed by a selective *Z*-olefination[25] furnished the entire carbon framework **3** of the target molecule. Reaction between the ylide, generated from **6**, and aldehyde at −80 °C in THF−HMPA gave the required *Z*-olefin in 64% yield on the basis of recovered aldehyde. Exclusively, the *Z*-olefin was obtained when the reaction was carried out at −80 °C. When it was done at higher temperature (−40 to 0 °C), the *E*-isomer was also formed along with the *Z*-olefin and the aldehyde was unstable. Use of NaHMDS in THF gave only 5% of the required product after 12 h of reaction at −80 °C with extensive decomposition of the aldehyde. The product **3** was subjected to global deprotection of the TBS groups to afford the desilylated product, in 92% yields, which on treatment with LiOH·H_2O in THF afforded the target molecule, cruentaren B (**2**), in 89% yield. The spectral data of our synthetic product and its optical rotation data—found $[\alpha]^{26}_D$ −9.4 (*c* 0.41, MeOH), reported[4] $[\alpha]^{22}_D$ −9.1 (*c* 6.6 mg/mL, MeOH)—were virtually identical with those of the natural product.

In conclusion, we have achieved the stereoselective, convergent total synthesis of cruentaren B and a synthetic segment for the cruentaren A, through longest linear sequence of 26 steps in overall yields of 7.1%. We are now trying to cyclize the linear framework to 12-membered cruentaren A. We believe that this synthetic strategy can provide a practical route to many novel cruentaren analogues that can be used for biological screenings.

Experimental Section

Preparation of 3. To a solution of **35** (540 mg, 0.645 mmol) in CH_2Cl_2 (3 mL) were added $NaHCO_3$ (162 mg, 1.94 mmol) and DMP (411 mg, 0.97 mmol) sequentially at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched by addition of saturated aqueous Na_2SO_3 solution and stirred for 30 min. Then it was extracted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to dryness. The residue was chromatographed on silica gel with EtOAc in petroleum ether (1:20) to give aldehyde (511 mg, 95%) as a colorless oil.

To a stirred solution of **6** (1 g, 1.53 mmol) in THF (3 mL) was added *n*-butyl lithium (1.6 M, 0.84 mL, 1.35 mmol) at −80 °C. After being stirred for 30 min HMPA (0.7 mL, 3.67 mmol) followed by aldehyde (511 mg, 0.61 mmol) in THF (1 mL) were added in a dropwise manner to the reaction mixture at the same temperature and the resulting solution was stirred for an additional 12 h at −80 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. The organic layer was washed sequentially with water and brine and dried over anhydrous Na_2SO_4. The extract was concentrated to dryness under vacuum and chromatographed on silica gel with EtOAc−petroleum ether (1:32) to give **3** (351 mg) as a colorless liquid and unreacted aldehyde (95 mg). The yield is found to be 64% on the basis of recovered aldehyde. R_f 0.4 (SiO_2, 6% EtOAc in petroleum ether); $[\alpha]^{29}_D$ + 17.4 (*c* 0.61, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.50 (d, J = 2.6 Hz, 1H), 6.36 (t, J = 4.9 Hz, 1H), 6.31 (d, J = 2.6 Hz, 1H), 5.54–5.45 (m, 2H), 3.98–3.91 (m, 1H), 3.91–3.84 (m, 1H), 3.82 (s, 3H), 3.76 (m, 1H), 3.70 (q, J = 5.3 Hz, 1H), 3.55–3.48 (m, 2H), 2.71 (dd, J = 12.1, 9.5 Hz, 1H), 2.44 (qd, J = 6.8, 3.8 Hz, 1H), 1.75–1.55 (m, 5H), 1.70 (s, 3H), 1.67 (s, 3H), 1.41 (m, 2H), 1.08 (d, J = 7.2, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.91 (d, J =

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7.2 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 22H), 0.87 (t, $J = 4.93$ Hz, 3H), 0.80 (s, 9H), 0.08 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), −0.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.7, 164.2, 158.9, 147.1, 132.6, 126.1, 125.8, 115.1, 104.8, 104.7, 99.8, 75.2, 74.7, 72.8, 55.5, 45.6, 40.2, 39.8, 38.0, 37.1, 36.3, 34.8, 30.3, 29.7, 28.7, 26.2, 25.9, 25.8, 25.7, 25.6, 25.6, 19.2, 18.5, 17.9, 17.9, 17.4, 14.3, 14.2, 13.0, 10.4, −3.3, −3.4, −3.9, −4.6, −4.7, −5.2; IR (neat) 2955, 2930, 2856, 1731, 1654, 1612, 1577, 1464, 1381, 1381, 1254, 1205, 1159, 1065, 1030, 835, 772 cm^{-1}; MS (ESI) *m*/*z* (%) 1127 (100) $[M + Na]^+$; HRMS (ESI) calcd for $C_{60}H_{113}NO_9NaSi_4$ $[M + Na]^+$ *m*/*z* 1126.7390, found 1126.7356.

Preparation of Cruentaren B. To a stirred solution of **3** (200 mg, 0.181 mmol) in THF (2 mL) was added 70% aq HF−py complex (1.3 mL) at −40 °C. After being stirred for 3 h, the reaction mixture was warmed to −4 °C and stirred for an additional 20 h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution at 0 °C and extracted with EtOAc and washed sequentially with water and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The residue was chromatographed on silica gel with EtOAc−petroleum ether (7:10) to give tetrol (108 mg, 92%) as a colorless liquid.

To a stirred solution of the tetrol (20 mg, 0.03 mmol) in THF−water−MeOH (3:1:1) mixture (1.5 mL) was added LiOH·H_2O (4 mg, 0.09 mmol) at 0 °C. After being stirred for 3 h at the same temperature, solvent was removed in vacuo and the residue was dissolved in EtOAc. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The organic extract was concentrated to dryness under vacuum and chromatographed on silica gel with MeOH−$CHCl_3$ (1:20) to give **2** (16.2 mg, 89%) as a colorless oil.

R_f 0.45 (SiO_2, EtOAc); $[\alpha]^{26}_D$ −9.4 (*c* 0.41, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.16 (s, 1H), 6.41 (t, $J = 4.4$ Hz, 1H), 6.35 (d, $J = 2.2$ Hz, 1H), 6.26(d, $J = 2.2$ Hz, 1H), 5.68–5.45 (m, 4H), 4.34 (ddd, $J = 11.7$, 6.6, 3.3 Hz, 1H), 3.90– 3.80 (m, 4H), 3.80 (s, 3H), 3.47 (dd, $J = 9.9$, 1.5 Hz, 1H), 2.91 (dd, $J = 16.1$, 11.7 Hz, 1H), 2.81 (dd, $J = 16.1$, 3.3 Hz, 1H), 2.44–2.11 (m, 7H), 1.95–2.04 (m, 1H), 1.64–1.76 (m, 2H), 1.40–1.50 (m, 2H), 1.36–1.27 (m, 2H), 1.13 (d, $J = 7.3$ Hz, 3H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H), 0.91(t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3, 170.0, 165.7, 164.4, 141.1, 131.4, 129.6, 127,6, 126.3, 106.3, 101.7, 99.4, 82.3, 80.2, 77.3, 71.8, 55.6, 44.8, 37.3, 37.2, 36.4, 36.1, 35.7, 33.3, 30.6, 30.0, 29.7, 19.2, 15.7, 15.0, 14.0, 11.2, 4.3; IR (neat) 3446, 2954, 2929, 2857, 1687, 1631, 1459, 1375, 1249, 1208, 1158, 760 cm^{-1}; MS (ESI) *m*/*z* (%) 612 (100) $[M + Na]^+$; HRMS (ESI) calcd for $C_{33}H_{51}NO_8Na$ $[M + Na]^+$ *m*/*z* 612.3512, found 612.3517.

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Supporting Information Available: Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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