Construction of the CDE-Ring Framework of Erinacine E through a Pummerer-Type Cyclization

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Abstract: The CDE-ring framework of erinacine E, a potent stimulator against nerve growth factor (NGF) synthesis, was constructed using stereocontrolled Grignard addition, silicon-promoted Pummerer-type cyclization, and ring-closing metathesis as key transformations.

Key words: erinacine, Pummerer reaction, ring-closing metathesis, stereoselective addition, cyathane diterpene

Cyathane diterpenes have attracted immense attention among chemists and biologists alike because of their unique chemical structures and fascinating biological activities involving stimulation of nerve growth factor (NGF) synthesis.[1] Erinacine E (**1**), erinacine F (**2**), and erinacine G (**3**) isolated from the cultured myceria of *Hericium erinaceum* are representative of this family (Figure 1).[2,3] The attractive features of these molecules lie not only within the complicated chemical structure that involves a five- to seven-membered ring-fused multicyclic skeleton with ten chiral centers, but also in that erinacine E exerts selective κ-opioid receptor agonistic activity.[4] Despite the numerous synthetic endeavors in this area,[5–8] only two successful total syntheses have been reported for the sugar-containing erinacines.[5] Total synthesis of pentacyclic or hexacyclic cyathanes such as **1**, **2**, or **3** has never been achieved.[9] We report herein a strategy to form the central CDE-ring system of erinacine E (**1**) featuring the intramolecular Pummerer-type reaction as a key transformation.

From a retrosynthetic point of view, the chemically stable tricyclic *O*,*S*-acetal **5** was considered to be a suitable precursor of the CDEF-ring moiety (**4**) of **1** and selected as a prime synthetic target (Scheme 1). We planned to apply ring-closing metathesis (RCM) for the formation of the C ring due to its mildness and high chemoselectivity within polyfunctionalized molecules.[10] The requisite *O*,*S*-acetal **6** can be prepared through the intramolecular Pummerer-type reaction,[11] although the analogous cyclization to achieve polysubstituted hydroisobenzofurans has not been reported. The highly oxygenated nature and demanding stereochemistry of several of the proposed intermediates required an elaborate protecting group strategy as well as many stereoselective transformations. Thus, the

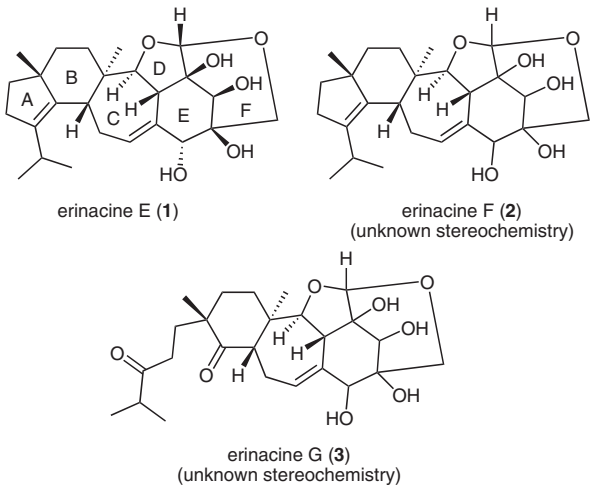
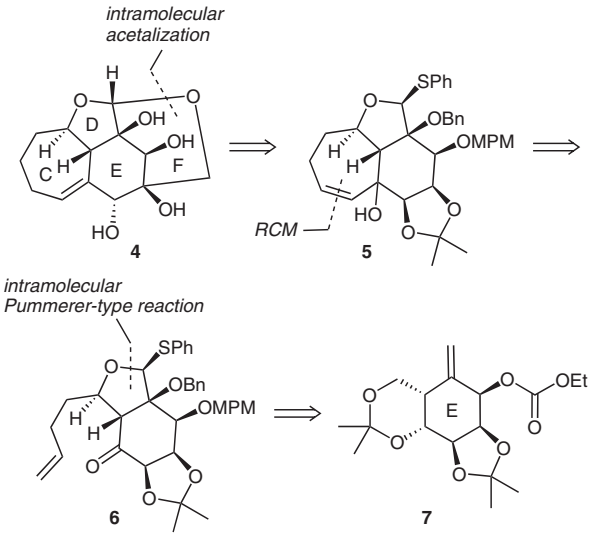


Figure 1 Structures of erinacine E (**1**), erinacine F (**2**), and erinacine G (**3**)



Scheme 1 Strategy for constructing the CDEF ring moiety (**4**) of erinacine E (**1**). MPM = *p*-methoxybenzyl

optically active acetonide-protected methylenecyclohexyl ethyl carbonate **7**,[12] which was prepared from D-mannose via radical cyclization in a stereoselective manner, was chosen as the starting material.

Sequential protecting group manipulation involving (a) selective cleavage of the 1,3-acetonide, (b) selective protection of the primary alcohol as a TBDPS ether, (c)

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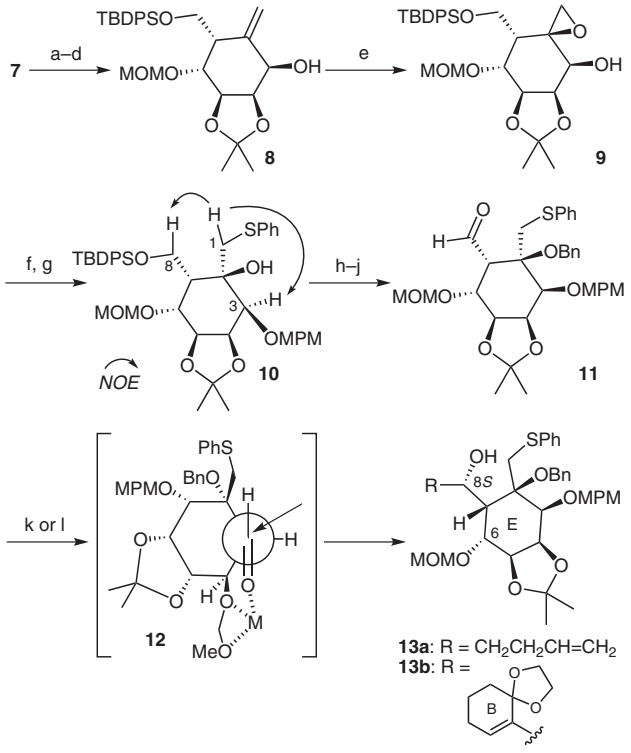
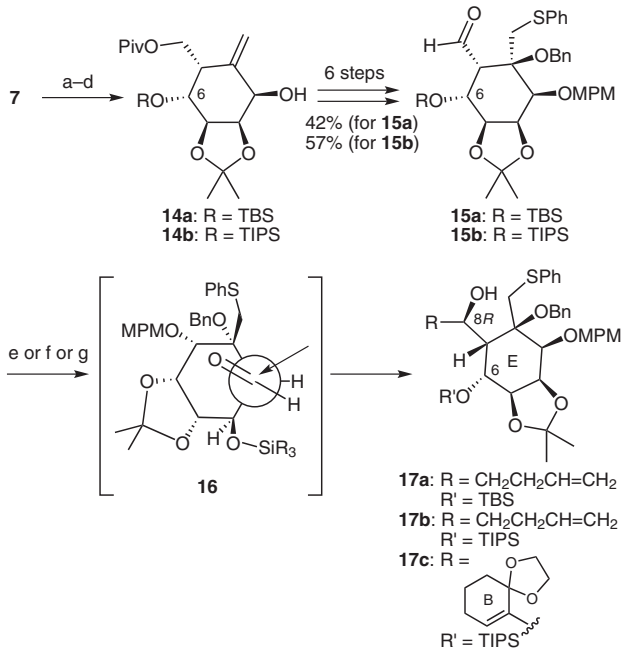
MOM protection of the secondary alcohol, and (d) methanolysis of ethyl carbonate, provided allylic alcohol **8** (Scheme 2). Diastereoselective epoxidation of **8** under Sharpless conditions[13] afforded the requisite β-epoxide **9** in a 9:1 ratio. MPM protection of the secondary alcohol **9** followed by thiol-assisted epoxide opening gave phenyl sulfide **10** in high yield. Strong NOE correlations between H1 and H3, and H1 and H8, confirmed the relative stereochemistry of **10**. The remaining tertiary alcohol of **10** was protected as a benzyl ether, and desilylation and oxidation afforded the suitably functionalized aldehyde **11**. Addition of homoallylmagnesium bromide, which corresponds to the C-ring chain, to **11** occurred in an undesired manner to give 8*S*-alcohol **13a** exclusively.[14] A similar tendency was observed when the cyclohexyllithium derivative[15] was employed, leading to a mixture of 8*S*- (**13b**) and 8*R*-alcohols in a 3.8:1 ratio. This unfavorable selectivity can be explained by the chelation transition state **12**, which causes the nucleophiles to approach from the *si* face of the aldehyde. Since neither inversion of the C8-alcohol of **13a** under a variety of Mitsunobu conditions[16] nor an oxidation–reduction sequence were effective,[17] we resorted to changing the C6-protective group from a MOM ether to bulky silyl ethers to reduce this unfavorable chelation.



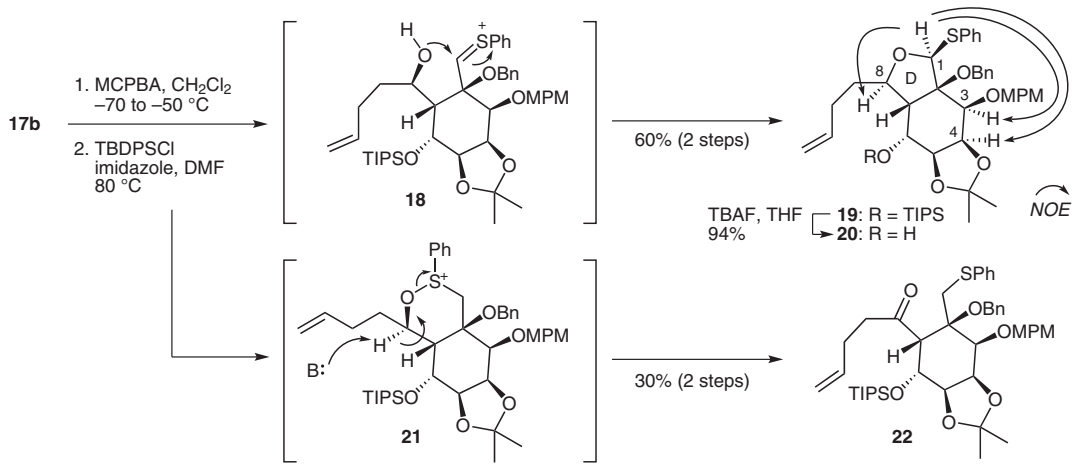
Scheme 2 *Reagents and conditions*: (a) CSA, MeOH, 0 °C, 65% (3 cycles); (b) TBDPSCl, imidazole, DMF, 0 °C to r.t., 93%; (c) MOM-Cl, *i*-Pr_2NEt, CH_2Cl_2, 94%; (d) K_2CO_3, MeOH, 99%; (e) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, reflux, 96% (dr = 9:1); (f) MPMBr, NaH, TBAI, THF, 92%; (g) PhSH, K_2CO_3, DMF, 92%; (h) BnBr, NaH, TBAI, THF, reflux, 97%; (i) TBAF, THF, 100%; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –70 to –20 °C, 84%; (k) homoallylmagnesium bromide, THF, 0 °C, **13a**: 90% (single diastereomer); (l) 2-iodocyclohexen-1-one ethylene ketal, *t*-BuLi, Et_2O, –78 °C, **13b**: 91% (dr = 3.8:1).

The silyl-protected aldehydes **15a** and **15b** were prepared in a similar manner as above, except that a pivaloyl group was used for the protection of the primary alcohol (Scheme 3).[18] In sharp contrast to our observation with the C6-MOM ether **11**, addition of homoallylmagnesium bromide to the TBS-protected aldehyde **15a** proceeded in the desired fashion to give a mixture of 8*R*- (**17a**) and 8*S*-alcohols in a 4:1 ratio.[14] The use of the more bulky TIPS ether **15b** improved diastereoselectivity up to 10:1. It should be noted that the high stereoselection established here could be extended to another nucleophile involving oxygen-containing cyclohexenyllithium, which corresponds to the B ring of **1**, and the reaction generated the 8*R*-alcohol **17c** in 99% yield with a diastereomeric ratio of 4.8:1. It is likely that the nucleophiles approached from the *re* face of the aldehyde to avoid the steric hindrance of the bulky silyl ethers **16**.



Scheme 3 *Reagents and conditions*: (a) CSA, MeOH, 0 °C, 55% (3 cycles); (b) PivCl, pyridine, 0 °C; (c) TBSOTf or TIPSOTf, 2,6-lutidine, CH_2Cl_2; (d) K_2CO_3, MeOH, 59% (for **14a**, 3 steps), 64% (for **14b**, 3 steps); (e) homoallylmagnesium bromide, THF, 0 °C, **17a**: 55% (dr = 4:1); (f) homoallylmagnesium bromide, THF, –50 °C, **17b**: 78% (dr = 10:1); (g) 2-iodocyclohexen-1-one ethylene ketal, *t*-BuLi, Et_2O, –78 °C, **17c**: 99% (dr = 4.8:1).

Having realized the stereoselective installation of the homoallyl moiety into the E ring, we then focused our attention on the formation of the D ring. We first attempted direct cyclization of **17b** by activating the phenyl sulfide moiety with NCS.[19] However, no cyclization products were detected even if the uncharacterized reaction product, which can be thought as an α-chlorosulfide, was treated with AgOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) without purification.[20] Therefore, indirect methods via phenyl sulfoxide were investigated.[11] The standard conditions of the Pummerer reaction, including the use of trifluoroacetic anhydride or



Scheme 4 Intramolecular Pummerer-type reaction

triflic anhydride in the presence of pyridine, 2,6-lutidine, DTBMP, or *i*-Pr_2NEt, gave disappointing results, most likely due to competition with acylation or sulfonation of the secondary alcohol. Treatment with TBDPSCl[11b] or TIPSCl, however, in the presence of imidazole at high temperature gave rise to the cyclized product **19** in 60% yield (Scheme 4). It is likely that the bulky silyl chlorides are less reactive toward the secondary alcohol and hence the hydroxyl group could attack the thionium cation **18** without any loss of its nucleophilicity. We also isolated ketone **22** as a minor product, which presumably arose through the six-membered oxathianium intermediate **21**.[21] The NOE correlations between H1 and H3, and H1 and H8, in connection with the singlet signal at δ = 5.10 corresponding to H1 confirmed the structure of **19**. Moreover, for the desilylated product **20**, strong positive NOEs at H4 and H5 upon irradiation at H1 and H8, respectively, indicated that the E ring was in the boat conformation (Figure 2).[22] In order to obtain more detailed stereochemical information, the acetonide group of **19** was removed by *p*-TsOH in MeOH, leading to diol **23** (53% yield) (Figure 2). The intensive NOEs between H8 and H3, and H8 and H5, in addition to indicated coupling constants, confirmed the C8-stereochemistry and the chair conformation of the E ring.

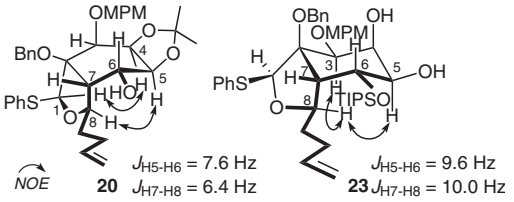
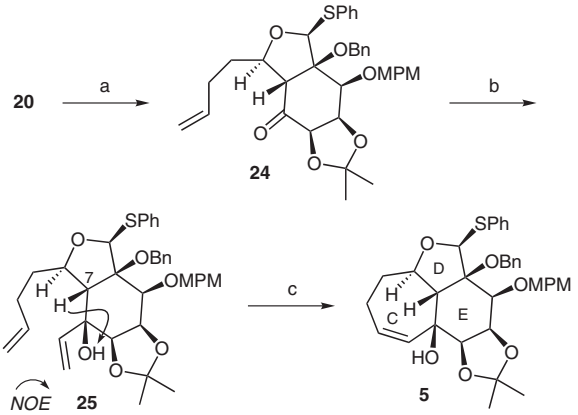


Figure 2 Conformational analyses of the cyclized products

With the DE ring **20** in hand, construction of the C ring was undertaken. The secondary alcohol **20** was oxidized to ketone **24** under Swern conditions (Scheme 5). Addition of vinyllithium, which was prepared in situ from tetravinyltin and MeLi at –78 °C, to **24** took place from the less hindered α face to give tertiary alcohol **25**, whose stereochemistry was determined by NOE experiments. Irradiation at H7 caused enhancement of the OH signal. RCM of **25** with Grubbs' second generation catalyst proceeded smoothly at room temperature to furnish the tricyclic compound **5** in good yield.[23] Further investigations directed toward the CDEF ring as well as assembly of the AB ring are currently underway.



Scheme 5 *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –70 to –50 °C, 100%; (b) tetravinyltin, MeLi, THF, –78 °C, 80%; (c) Grubbs' 2nd generation catalyst (5 mol%), CH_2Cl_2, 84%.

In conclusion, we have developed an efficient route to the CDE ring system **5** of erinacine E (**1**) via substrate-controlled stereoselective Grignard addition, Pummerer-type cyclization, and RCM. The latter cyclization sequence will serve as a powerful tool for the synthesis of valuable multicyclic hydroisobenzofurans.[24]

Acknowledgment

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(14) The C8-stereochemistry of each product was confirmed by NOE experiments after the Pummerer-type cyclization.

(15) 2-Iodocyclohexen-1-one ethylene ketal was synthesized from 2-cyclohexen-1-one as follows: (i) I_2, pyridine, THF, r.t., 12 h, 80%; (ii) 1,2-bis(trimethylsilyloxy)ethane, TMSOTf, CH_2Cl_2, –20 °C, 72 h, 86%.

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(17) At best, a 1:1 selectivity was obtained for reduction of the C8-ketone of **13a** with $LiAlH_4$ in THF at 0 °C (98% yield). Other reductants including $Zn(BH_4)_2$, $NaBH_4$, L-Selectride, or Red-Al gave inferior yields and selectivity.

(18) Pivaloate was cleaved with DIBAL in CH_2Cl_2 at –78 °C.

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(22) To a solution of **17b** (108 mg, 0.139 mmol) in CH_2Cl_2 (2 mL) was added MCPBA (65%, 111 mg, 0.417 mmol) at –78 °C. The mixture was stirred at –78 °C to –50 °C for 1 h, followed by addition of sat. $Na_2S_2O_3$ solution, Et_2O, and sat. $NaHCO_3$ solution. The resulting mixture was stirred at r.t. for 30 min and extracted with Et_2O. The combined organic phase was washed with sat. $NaHCO_3$ solution, brine, and dried over anhyd $MgSO_4$. Concentration of the solution gave the corresponding sulfoxide (117 mg), which was used without further purification. To a solution of sulfoxide (117 mg) and imidazole (94.6 mg, 1.39 mmol) in DMF (1.4 mL) was added TBDPSCl (107 μL, 0.417 mmol). The mixture was stirred at 80 °C for 3 h, and diluted with Et_2O and sat. $NaHCO_3$ solution. After separation of the organic phase, the aqueous phase was extracted with Et_2O and the combined organic phase was washed with sat. NH_4Cl solution, brine, and dried over anhyd $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel; hexane–EtOAc, 40:1 → 25:1 → 10:1) to give *O*,*S*-acetal **19** (64.7 mg, 0.0835 mmol, 60%) and ketone **22** (32.3 mg, 0.0417 mmol, 30%). To a solution of **19** (33.3 mg, 0.0430 mmol) in THF (1.4 mL) was added TBAF (1.0 M solution in

THF, 64.4 μL, 0.0644 mmol). The mixture was stirred at r.t. for 1.5 h. After concentration, the residue was purified by flash column chromatography (silica gel; hexane–EtOAc, 10:1 → 5:1 → 3:1 → 1:1) to give alcohol **20** (24.9 mg, 0.0403 mmol, 94%). Compound **20**: $[\alpha]_D^{29}$ –2.4° (*c* = 0.822, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 3 H, Me), 1.51 (s, 3 H, Me), 1.93 (q, *J* = 7.6 Hz, 2 H, H9), 2.15–2.25 (m, 1 H, H10), 2.28–2.38 (m, 1 H, H10), 2.77 (dd, *J* = 6.4, 6.8 Hz, 1 H, H7), 3.80 (s, 3 H, MPM), 4.00 (q, *J* = 6.4 Hz, 1 H, H8), 4.10 (d, *J* = 3.6 Hz, 1 H, H3), 4.25 (dd, *J* = 7.6, 8.0 Hz, 1 H, H5), 4.40 (dd, *J* = 3.6, 8.0 Hz, 1 H, H4), 4.57 (br dd, *J* = 6.8, 7.6 Hz, 1 H, H6), 4.60 (d, *J* = 11.0 Hz, 1 H, MPM), 4.83 (d, *J* = 11.0 Hz, 1 H, MPM), 4.89 (d, *J* = 12.0 Hz, 1 H, Bn), 4.95 (d, *J* = 12.0 Hz, 1 H, Bn), 4.97 (br dd, *J* = 1.0, 10.0 Hz, 1 H, H12), 5.05 (br dd, *J* = 1.6, 17.0 Hz, 1 H, H12), 5.05 (s, 1 H, H1), 5.78–5.89 (m, 1 H, H11), 6.81 (d, *J* = 8.8 Hz, 2 H, MPM), 7.21–7.40 (m, 10 H), 7.53–7.56 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 26.6, 30.8, 35.5, 48.8, 55.4, 68.3, 70.7, 74.4, 75.2, 77.3, 78.1, 80.2, 88.8, 94.6, 110.0, 113.7, 114.9, 127.06, 127.13, 127.2, 128.3, 129.1, 129.3, 130.9, 131.0, 136.1, 138.3, 139.4, 159.1. FT-IR (film): 3465, 3062, 3031, 2978, 2932, 2913, 2875, 2837, 1640, 1613, 1585, 1514, 1497, 1481, 1463, 1454, 1440, 1381, 1351, 1302, 1248, 1209, 1173, 1161, 1121, 1064, 1029, 913, 880, 822, 777, 739, 695 cm^{-1}. HRMS (FAB): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{42}NaO_7S$: 641.2549; found: 641.2563.

(23) To a solution of diene **25** (27.9 mg, 0.0433 mmol) in CH_2Cl_2 (4.3 mL) was added second generation Grubbs' catalyst (1.4 mg, 1.6 μmol). The mixture was stirred at r.t. for 9 h and quenched with Et_3N (1 mL). After concentration, the residue was purified by flash column chromatography (silica gel; hexane–EtOAc, 5:1 → 3:1) to give the tricyclic product **5** (22.4 mg, 0.0363 mmol, 84%); $[\alpha]_D^{29}$ +21.8° (*c* = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H), 1.58 (s, 3 H), 1.79–1.88 (m, 1 H), 2.08–2.23 (m, 1 H), 2.29–2.43 (m, 2 H), 3.02 (d, *J* = 10.0 Hz, 1 H), 3.53 (dt, *J* = 3.0, 10.0 Hz, 1 H), 3.78 (s, 3 H), 4.10 (d, *J* = 4.0 Hz, 1 H), 4.18 (d, *J* = 8.4 Hz, 1 H), 4.41 (dd, *J* = 4.0, 8.4 Hz, 1 H), 4.73 (d, *J* = 10.0 Hz, 1 H), 4.78 (d, *J* = 10.0 Hz, 1 H), 4.91 (br s, 1 H), 4.94 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 5.29 (br s, 1 H), 5.66 (ddd, *J* = 4.0, 6.8, 13.0 Hz, 1 H), 5.77 (br d, *J* = 13.0 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 7.24–7.35 (m, 5 H), 7.45 (br d, *J* = 7.6 Hz, 2 H), 7.54 (br d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 24.9, 26.2, 31.7, 55.4, 68.2, 71.0, 74.2, 76.3, 76.8, 78.5, 79.7, 88.7, 94.4, 110.4, 113.9, 127.0, 127.3, 127.4, 128.3, 129.2, 129.4, 130.1, 131.1, 135.3, 135.6, 139.0, 159.5. FT-IR (KBr): 3398, 3060, 2984, 2933, 2871, 2837, 1612, 1585, 1514, 1481, 1457, 1439, 1379, 1303, 1250, 1211, 1173, 1136, 1118, 1075, 1026, 970, 881, 845, 822, 738, 694 cm^{-1}. HRMS (FAB): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{40}NaO_7S$: 639.2392; found: 639.2413.

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