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Design and synthesis of a *trans*-fused polycyclic ether skeleton as an α-helix mimetic scaffold

Hiroki Oguri,*,† Akifumi Oomura, Shintaro Tanabe and Masahiro Hirama*

Department of Chemistry, Graduate School of Science, Tohoku University, and SORST, Japan Science and Technology Corporation (JST), Sendai 980-8578, Japan

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Abstract—Inspired by the common skeletal feature of potent marine toxins, a ladder-like polycyclic ether scaffold was designed as the basis for the synthesis of structurally defined α-helix mimics. A synthetic route to *trans*-fused 6/6/6/6/6 pentacyclic ether skeletons is presented, involving the iterative assembly of tetrahydropyran rings via the SmI_2-mediated coupling reaction of α-sulfonyl ketones with aldehydes.

The potent ladder-like polycyclic ether marine toxins are based on a common *trans*/*syn*-fused cyclic ether array, with ring sizes ranging from five to nine members.[1] Among these potent toxins, brevetoxins[2,3] and ciguatoxins[4,5] (Fig. 1) are believed to bind to a common site (site 5) on the α subunit of voltage-sensitive sodium channels (VSSCs),[6] where the α subunit consists of 24 transmembrane helices. Although the three-dimensional structure of the receptor site in the VSSC remains unknown, and the extremely limited availability of the toxins has hampered further biological investigation, recent studies have suggested a relationship between the size of the polycyclic ether skeleton and the inhibitory activity against the binding of labeled brevetoxins with the VSSC.[7] It appears that both the length and the relatively straight conformation of the cyclic ether skeletons are critical factors in this relationship, and are required for the binding and modulation of the VSSC function.[8] The interactions between the polycyclic ethers and the receptor site are surmised to be primarily hydrophobic and to be supplemented by hydrogen bonding between skeletal oxygen atoms and the OH/NH groups of the α-helical peptides.[8] In addition to this hydrogen bonding, axially oriented CH groups adjacent to the skeletal oxygen atoms are also expected to play an important role in molecular recognition of the aromatic amino acid residues through CH/π interactions, as exemplified by the crystal structures of complexes between the carbohydrate-binding proteins and specific substrates.[9,10]

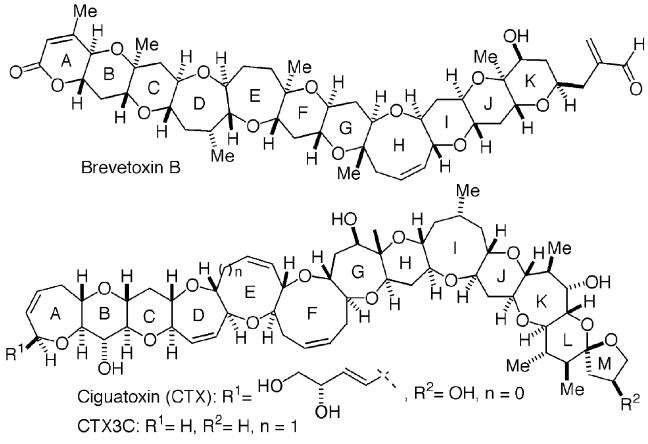

Figure 1. Structures of brevetoxin B, ciguatoxin and CTX3C.

On analysis of the mode of action of these ladder-like toxins, it was noticed that the *trans*-fused cyclic ethers may be topologically analogous to the α-helical peptides. In the 6/6/6 tricyclic system (Fig. 2a), the distance between skeletal oxygen atoms on the same side (4.8 Å) in the cyclic ethers is almost identical to the interval

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* Corresponding authors. Tel.: +81 22 217 6563; fax: +81 22 217 6566; e-mail addresses: oguri@sci.hokudai.ac.jp; hirama@ykbsc.chem.tohoku.ac.jp
† Present address: Division of Chemistry, Graduate School of Science, Hokkaido University.

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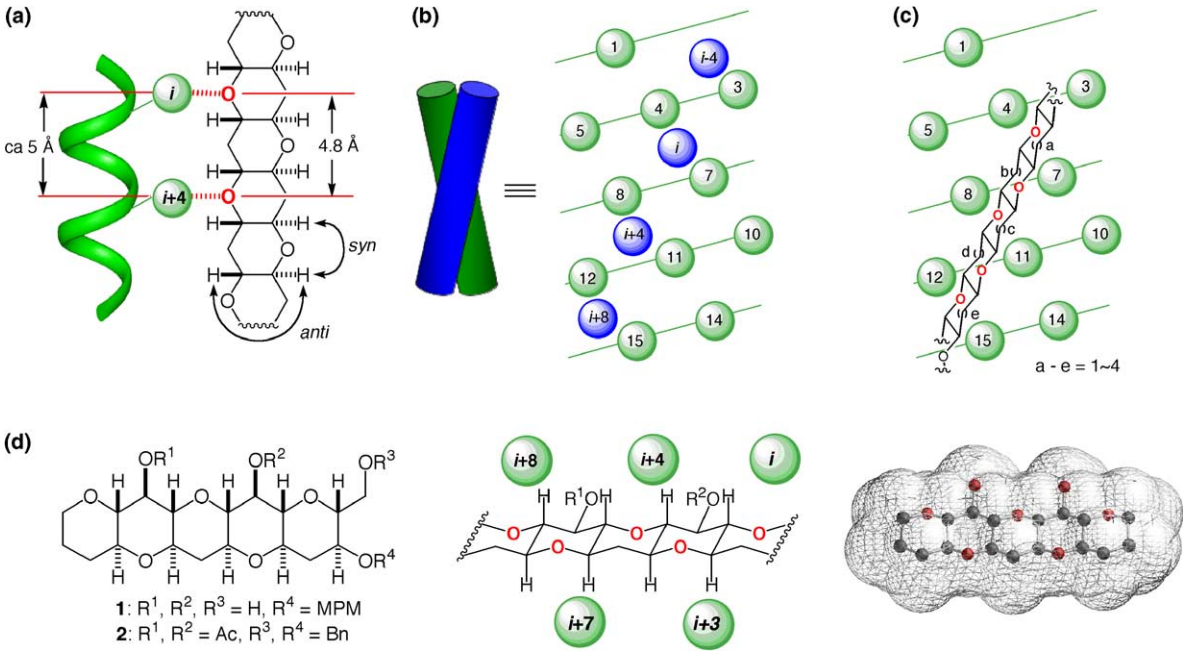


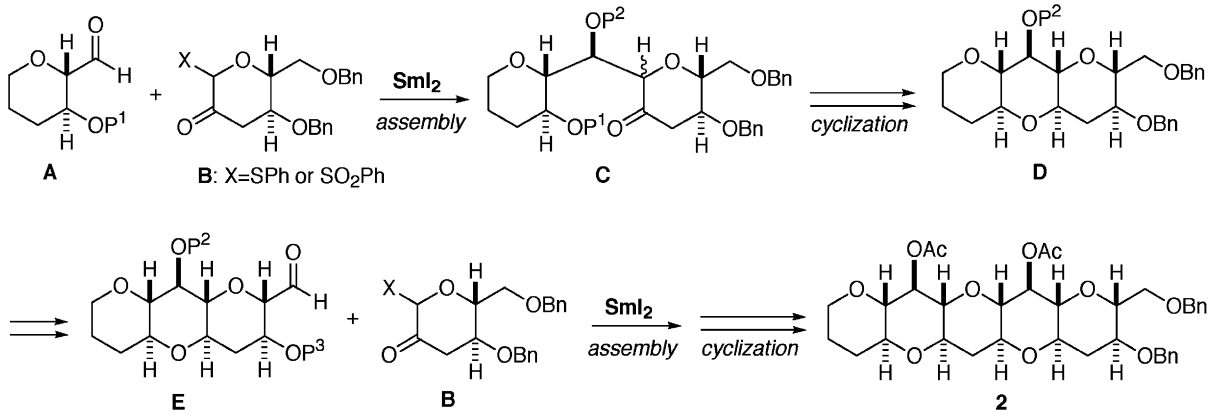
Figure 2. (a) Structural features of a cyclic ether skeleton and an α-helix; (b) Typical helix–helix interaction, showing projection of the surface defined by the ridges and grooves of two helices (green and blue); (c) Hypothetical binding model for the cyclic ether with an α-helix; (d) Design of cyclic ether **1** as an α-helix mimetic scaffold. The water-accessible surface (Connolly surface) for the skeletal cyclic ether part of **1** was generated by Chem 3D Ver. 5.0 using a probe radius of 1.4 Å.

between side-chains in the α-helical peptides in the canonical *i*, *i*+4 relationship (ca. 5 Å). As illustrated in Figure 2b, a typical mode of packing between α-helices (green and blue) involves insertion of the ridges of one helix (blue) into the grooves of an adjacent helix (green).[11] Inspired by this potentially analogous topology, the hypothetical binding model shown in Figure 2c was derived. In this model, the ladder-like polycyclic ether fits into the grooves of the helix.

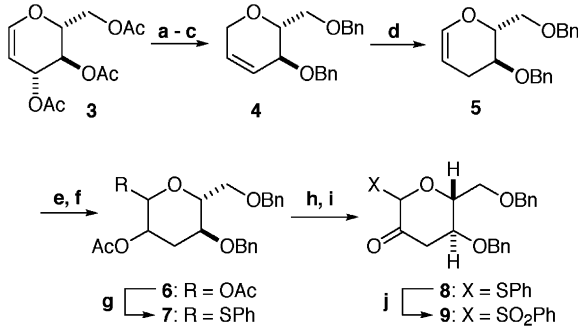
As a first step in the investigation of this model, a 6/6/6/6/6 pentacyclic ether skeleton (**1**) was designed as a structurally defined α-helix mimetic scaffold[12] having two equatorial hydroxyl groups separated by a distance of 4.8 Å (Fig. 2d). Installation of a variety of substituents (R^1 and R^2) is possible via the hydroxyl groups, and the consequent undulation of the molecular surface is expected to be analogous to the ridges formed by side-chains of α-helices in the *i*, *i*+4 relationship.

The strategy for the iterative synthesis of the cyclic ether scaffolds is outlined in Scheme 1. A SmI_2-mediated Reformatsky-type reaction of α-ketosulfide **B** with aldehyde **A** was employed for the assembly of the two hydropyrans.[13] Subsequent hydroxy-ketone cyclization of the compound **C** would afford tricyclic **D**.[14] After conversion of **D** into aldehyde **E**, the second assembly of two cyclic ethers **E** and **B** followed by the hydroxy-ketone cyclization would yield the 6/6/6/6/6/6 cyclic ether skeleton **2** with two equatorial hydroxy groups.

The key coupling component, α-ketosulfide **8**, was synthesized from tri-*O*-acetyl-D-glucal **3** (Scheme 2). Reduction of **3** with triethylsilane and $BF_3{\cdot}Et_2O$ followed by



Scheme 1. Strategy for iterative synthesis of cyclic ether skeleton **3**.

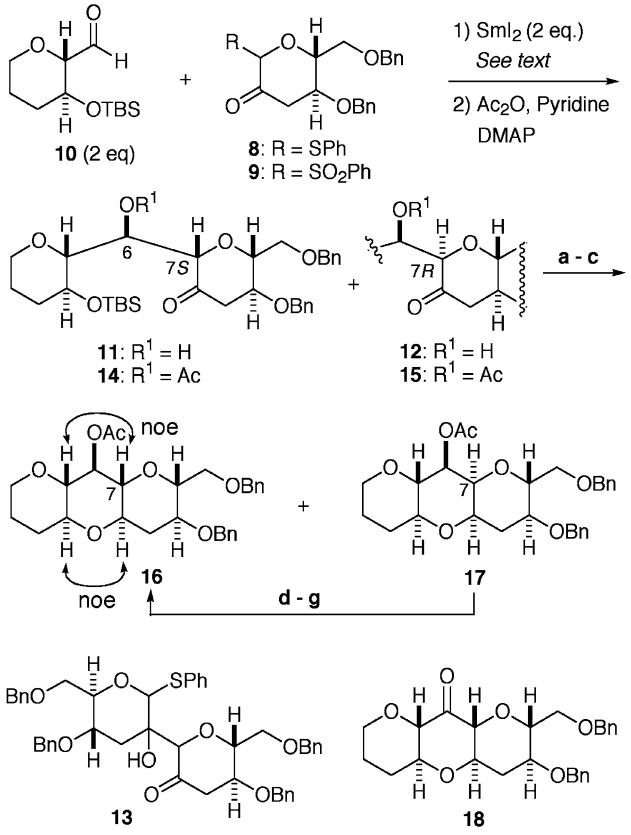


Scheme 2. Reagents and conditions: (a) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_3CN, −20 °C, 78%; (b) K_2CO_3, MeOH; (c) NaH, BnBr, THF/DMF(1/1), 90% (two steps); (d) $RhCl(PPh_3)_3$ (15 mol %), DBU, EtOH, 60 °C, 83%; (e) cat. OsO_4, NMO, acetone; (f) Ac_2O, pyridine, DMAP, 93% (two steps); (g) PhSH, $SnCl_4$ (10 mol %), CH_2Cl_2, −20 to 0 °C, 90%; (h) K_2CO_3, MeOH; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 92% (two steps); (j) *m*-CPBA, CH_2Cl_2, −40 to 0 °C, 88%.

methanolysis and benzylation gave **4**. The allylic ether **4** was then converted into enol ether **5** in the presence of Wilkinson's catalyst and DBU in 83% yield.[15] Dihydroxylation of **5** and subsequent acetylation yielded **6**, which was then subjected to $SnCl_4$-catalyzed thioacetalization to afford **7**.[16] Conversion of **7** to the α-ketosulfide **8** was achieved by methanolysis and subsequent Swern oxidation in 92% yield (two steps).

The tetrahydropyran rings were assembled by Reformatsky-type coupling of the α-ketosulfide **8** with the aldehyde **10**[17] using Mastuda's protocol (Scheme 3).[13] A solution of **8** in THF was added dropwise to a solution of SmI_2 (2 equiv) in THF at −78 °C to generate the samarium enolate regioselectively, and the resulting solution was treated with **10** (2 equiv). Unfortunately, homocoupled **13** was the major product (34% yield), and the desired coupling products **11** were obtained in only low yield (18%).[18] Thus, the samarium enolate was trapped immediately after generation by adding a mixture of **8** and **10** (2 equiv) to a solution of SmI_2 (2 equiv) at −78 °C. Although the yield of the desired **11** was improved (up to ~40%), significant amounts of **13** (~20%) were still produced.[18] To suppress the formation of **13**, sulfone **9**[19] was used in place of sulfide **8** to accelerate the generation of the samarium enolate. Treatment of a mixture of **9** and **10** (2 equiv) with SmI_2 (2 equiv) promoted the Reformatsky-type reaction smoothly at −78 °C, affording the desired coupling products without formation of **13**. Subsequent in situ acetylation gave a 3:2 diastereomeric mixture of **14** and **15** in 79% yield (two steps). A highly stereo-controlled addition at C6 occurred in this synthesis, presumably due to 1,2-chelation of **10** with the samarium species. The mixture of **14** and **15** was subsequently subjected to hydroxy-ketone cyclization followed by reductive etherification to afford separable tricyclic ethers **16**[20] and **17**. The *trans*, *cis*-fused **17** was converted to *trans*, *trans*-fused **16** in four steps involving the epimerization of ketone **18** under Swern oxidation conditions.[14b]

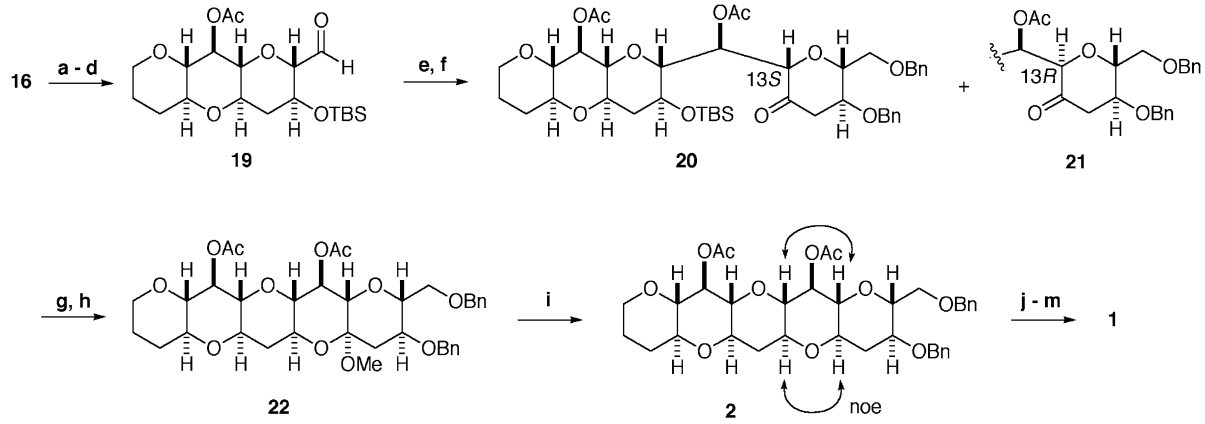
With tricyclic **16** in hand, iterative assembly with **9** was performed, leading to **1** (Scheme 4). Functional group



Scheme 3. Reagents and conditions: (a) CSA, $MeOH/CH_2Cl_2$ (1:7); (b) Ac_2O, pyridine, DMAP; (c) Et_3SiH, TMSOTf, CH_2Cl_2, −20 °C, **16** 34% (three steps), **17** 9% (three steps); (d) K_2CO_3, MeOH; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 57% (two steps); (f) $NaBH_4$, $CeCl_3$, MeOH/THF (4:1), −20 °C; (g) Ac_2O, pyridine, DMAP, 50% (two steps).

manipulation of **16** gave aldehyde **19** via a four-step procedure involving (i) removal of benzyl groups, (ii) protection of the hydroxyl groups as TBS ethers, (iii) selective removal of the primary silyl group, and (iv) Swern oxidation. The SmI_2-mediated coupling reaction of **19** (1.2 equiv) with sulfone **9** and subsequent acetylation furnished a 1:1 diastereomeric mixture of **20** and **21** in 72% yield (two steps). Exposure of the mixture to CSA in $MeOH/CH_2Cl_2$ (1:4) effected the removal of the TBS and in situ methyl ketal formation, as well as partial deacetylation. The desired methyl ketal **22** was isolated after acetylation in 52% yield. The products possessing 13*R* stereochemistry could not be isolated. Reduction of **22** with Et_3SiH and TMSOTf gave the *trans*-fused 6/6/6/6/6 pentacyclic ether **2** in 91% yield.[21] Finally, protecting-group manipulation under standard conditions led to the scaffold **1**.

In conclusion, a polycyclic ether scaffold was designed as an α-helix mimic, inspired by the topological similarity between ladder-like cyclic ether marine toxins and α-helical peptides. The synthesis presented here provides an efficient strategy for the stereo-controlled construction of *trans*-fused polycyclic ether skeletons via SmI_2-mediated Reformatsky-type coupling of α-sulfonyl ketones with aldehydes. Further investigation of the synthesis



Scheme 4. Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, MeOH/AcOEt (1/4); (b) TBSCl, imidazole, DMF, 99% (two steps); (c) CSA, MeOH, −5 °C, 75%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C; (e) **19** (1.2 equiv), **9**, SmI_2 (2 equiv), THF, −100 °C; (f) Ac_2O, pyridine, DMAP, **20:21** = 1:1, 72% (two steps); (g) CSA, MeOH/CH_2Cl_2 (1:4); (h) Ac_2O, pyridine, DMAP, **22** 52% (two steps); (i) Et_3SiH, TMSOTf, CH_2Cl_2, −20 °C, 91%; (j) H_2, $Pd(OH)_2$/C, MeOH/AcOEt (1/4); (k) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, DMF, 71% (two steps); (l) DIBAL, CH_2Cl_2, −78 to −15 °C, then Ac_2O, pyridine, DMAP, 80%; (m) K_2CO_3, MeOH/THF (4/1), 99%.

of a variety of α-helix mimics based on cyclic ether scaffolds and evaluation of the interaction with α-helical peptides will be presented in future reports.

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20. Data for **16**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46–1.58 (m, 1H), 1.49 (dt, 1H, J = 12.0, 9.0 Hz), 1.65–1.76 (m, 2H), 2.09 (s, 3H), 2.11–2.12 (m, 1H), 2.57 (dt, 1H, J = 12.0, 4.0 Hz), 3.04 (t, 1H, J = 9.0 Hz), 3.13 (t, 1H, J = 9.0 Hz), 3.23 (td, 2H, J = 9.0, 4.5 Hz), 3.30 (td, 1H, J = 11.5, 3.5, Hz), 3.40 (ddd, 1H, J = 9.0, 5.5, 2.0 Hz), 3.49 (td, 1H, J = 9.0, 4.5 Hz), 3.62 (dd, 1H, J = 11.0, 5.5 Hz), 3.80 (dd, 1H, J = 11.0, 2.0 Hz), 3.95 (ddd, 1H, 11.0, 3.5, 1.0 Hz), 4.44 (d, 1H, J = 11.0 Hz), 4.52 (d, 1H, J = 11.0 Hz), 4.58 (d, 2H, J = 11.0 Hz), 5.11 (t, 1H, J = 9.0 Hz), 7.23–7.34 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.00, 24.90, 29.06, 35.03, 67.80, 68.93, 71.05, 71.97, 73.05, 73.17, 73.93, 75.94, 79.41, 80.13, 80.92, 127.28, 127.42, 127.57, 127.71, 127.86, 128.10, 128.17, 128.30, 137.71, 138.42, 170.32; IR (neat) ν.3030, 2948, 1741, 1454, 1367, 1237, 1099 cm^{-1}; MALDI-TOFMS calcd for $C_{28}H_{34}O_7Na$ $[M+Na]^+$ 505.220; found 505.218; $[\alpha]_D^{26}$ +26.4 (*c* 1.00, $CHCl_3$).
21. Data for **2**: ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37–1.48 (m, 1H), 1.46 (dt, 1H, J = 11.5, 9.5 Hz), 1.51 (dt, 1H, J = 11.5, 9.5 Hz), 1.59–1.70 (m, 2H), 1.97 (s, 3H), 2.01 (s, 3H), 2.01–2.08 (m, 1H), 2.38 (dt, 1H, J = 11.5, 4.5 Hz), 2.51 (dd, 1H, J = 11.5, 4.5 Hz), 2.98 (t, 1H, J = 9.5 Hz), 3.02 (t, 1H, J = 9.5 Hz), 3.03 (t, 1H, J = 9.5 Hz), 3.07 (t, 1H, J = 9.5 Hz), 3.12–3.20 (m, 2H), 3.21–3.30 (m, 3H), 3.34 (ddd, 1H, J = 9.5, 5.5, 1.5 Hz), 3.44 (td, 1H, J = 9.5, 4.5 Hz), 3.57 (dd, 1H, J = 11.0, 5.0 Hz), 3.71 (dd, 1H, J = 11.0, 1.5 Hz), 3.89 (m, 1H), 4.38 (d, 1H, J = 11.5 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.52 (d, 1H, J = 11.5 Hz), 4.52 (d, 1H, J = 12.0 Hz), 5.04 (t, 1H, J = 9.5 Hz), 5.07 (t, 1H, J = 9.5 Hz), 7.17–7.28 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.66, 20.75, 24.98, 29.09, 34.91, 35.03, 67.90, 68.97, 71.22, 71.98, 72.40, 72.72, 73.29, 74.00, 74.31, 74.56, 76.33, 79.23, 79.99, 80.04, 80.08, 81.02, 127.42, 127.56, 127.82, 127.84, 128.29, 128.42, 137.72, 138.42, 169.43, 169.75; MALDI-TOFMS calcd for $C_{36}H_{44}O_{11}Na$ $[M+Na]^+$ 675.273; found 675.289.