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Studies toward the total synthesis of gambieric acids: convergent synthesis of the GHIJ-ring fragment having a side chain

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ABSTRACT

A stereocontrolled synthesis of the GHIJ-ring fragment having a side chain of gambieric acids, which are potent antifungal polycyclic ether natural products, has been achieved. The synthesis features convergent assembly of the tetracyclic polyether skeleton by using aldol coupling and stereoselective construction of the J-ring side chain by a cerium chloride-promoted Julia–Kocienski reaction.

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Gambieric acids A–D (**1**–**4**, Fig. 1) are marine polycyclic ether natural products isolated from the ciguatera causative dinoflagellate *Gambierdiscus toxicus* by Nagai, Yasumoto, and co-workers.[1] These polycyclic ethers exhibit extremely potent antifungal activity against *Aspergillus niger* 2000 times greater than that of amphotericin B, whereas they show only moderate toxicity against mice or cultured mammalian cells.[2] It has also been reported that gambieric acid A enhances the cell concentration of *G. toxicus* in a dose-dependent manner with inhibition at higher concentrations, suggesting the possible role of gambieric acid A as an endogenous growth regulator of *G. toxicus*.[3] Moreover, Inoue et al. have recently reported that gambieric acid A inhibits the binding of tritiated brevetoxin-B derivative ([^{3}H]PbTx-3) to voltage-sensitive sodium channels, although its binding affinity is significantly lower than those of brevetoxins and ciguatoxins.[4] Their extraordinary complex molecular architecture coupled with highly potent antifungal activity has prompted considerable interest from the synthetic community.[5–9] As part of our continuing studies toward the total synthesis of gambieric acids, we have recently reassigned the absolute configuration of the polycyclic ether domain of gambieric acids.[5e,f] We describe herein a convergent synthesis of the GHIJ-ring system having a side chain.

Our synthesis plan toward the GHIJ-ring fragment **5** is outlined in Scheme 1. Stereocontrolled construction of a trisubstituted alkene in the J-ring side chain poses a significant synthetic challenge. The only synthesis of the J-ring side chain has been reported by Kadota et al.,[6b] but their synthesis suffered from low yield. Therefore, the development of an efficient method for synthesis of the side chain is indispensable for the total synthesis. We envisioned that introduction of the side chain to the J-ring would be achieved by Julia–Kocienski olefination[10] of ketone **6** and 1-phenyl-1*H*-tetrazol-5-yl sulfone **7**. Although we have previously described a synthesis of the GHIJ-ring fragment in its antipodal form based on acetylide–aldehyde coupling,[5b,c] the present synthesis relied on an alternative convergent strategy. It was planned that the tetracyclic polyether **6** would be synthesized through aldol coupling of the G- and J-rings (**8** and **9**, respectively), a cyclodehydration to form the H-ring, and reductive etherification to build the I-ring.

The synthesis of the G-ring is shown in Scheme 2. The known alcohol **10**[11] was protected as the TES ether **11**. Subsequent ozonolysis of the double bond afforded aldehyde **8** in 96% yield for the two-steps.

The synthesis of the J-ring **9** started with the known epoxy alcohol **12**.[12] Regioselective epoxide ring-opening with $Ti(OBn)_4$[13] afforded diol **13** in 79% yield (Scheme 3). Selective sulfonylation of the primary alcohol followed by treatment with K_2CO_3 gave epoxide **14** (91%, two-steps), which was then treated with dimethylsulfonium methylide (Me_3SI, *n*-BuLi)[14] to afford allylic alcohol **15** in 94% yield. Protection as the PMB ether using $PMBOC(=NH)CCl_3$ in the presence of $La(OTf)_3$[15] was followed by hydroboration of the double bond with disiamylborane to afford alcohol **16** in 81% yield for the two-steps. Benzyl protection and removal of the TBDPS group provided primary alcohol **17** (77%, two-steps), which was subjected to Swern oxidation and a one-pot Wittig reaction to afford (*E*)-enoate **18** in 95% yield. DIBALH reduction followed by Sharpless asymmetric epoxidation[16] of the resultant allylic alcohol gave epoxy alcohol **19** (81%, two-steps), which was oxidized with

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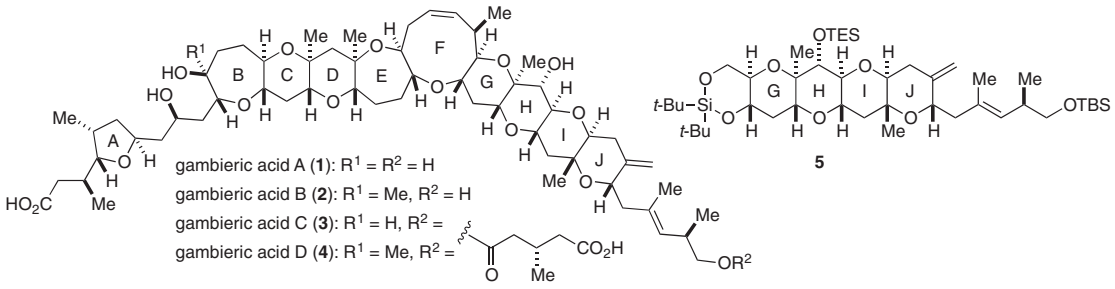
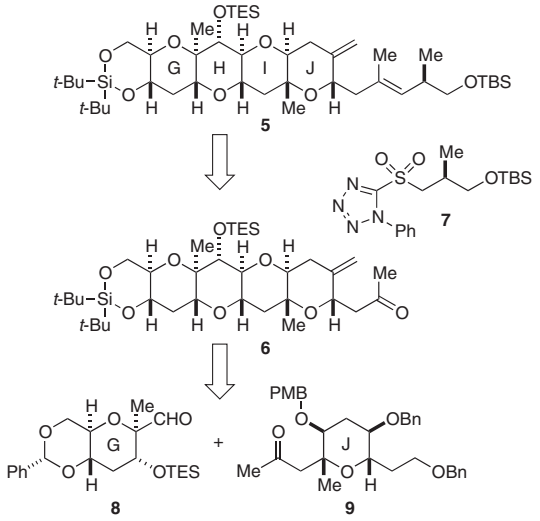
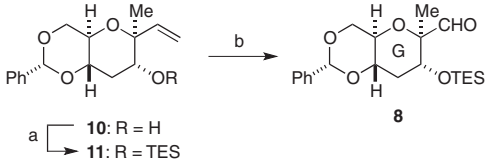


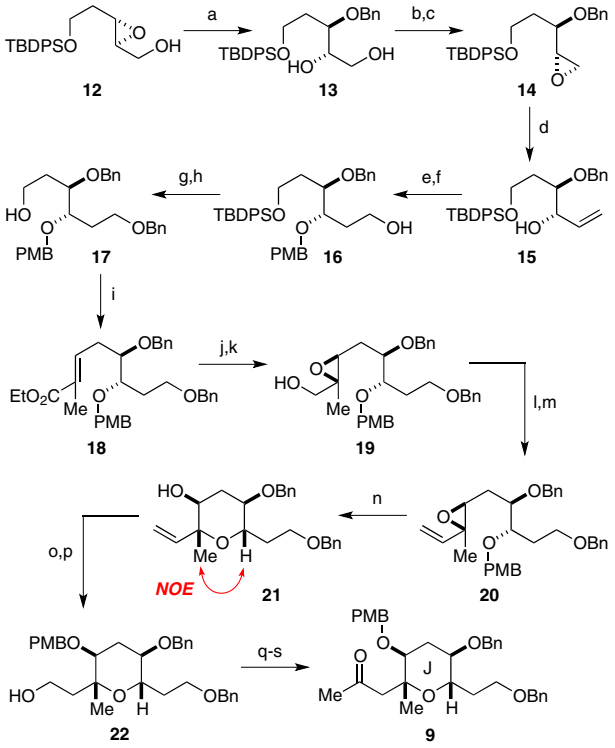
Figure 1. Structures of gambieric acids A–D (**1**–**4**) and the GHIJ-ring fragment **5**.



Scheme 1. Synthesis plan for the GHIJ-ring fragment **5**.



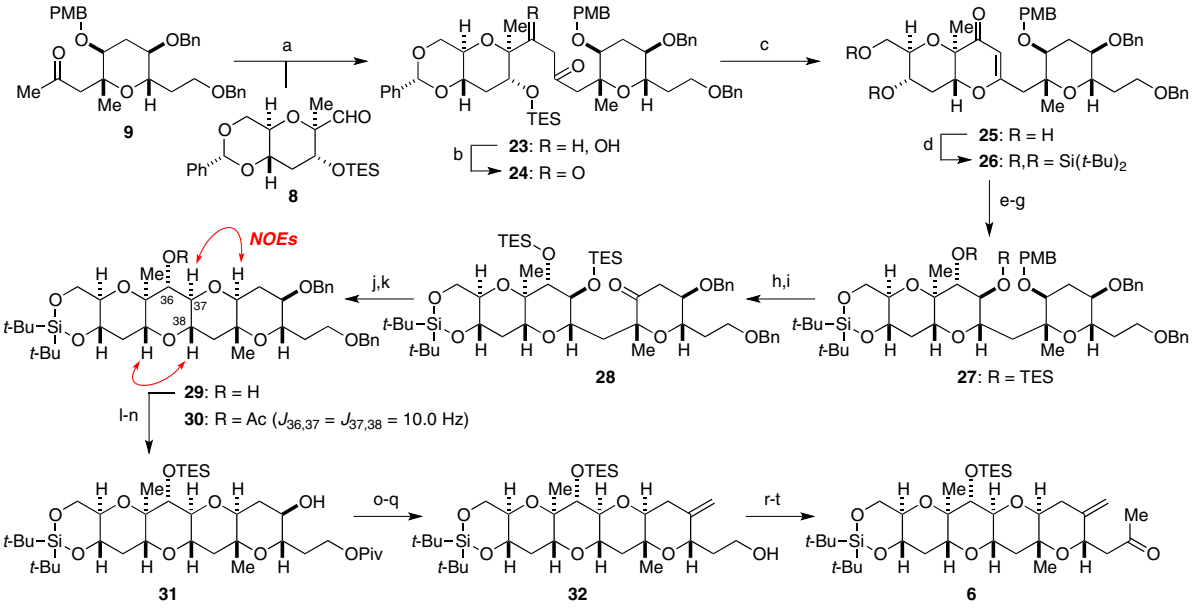
Scheme 2. Reagents and conditions: (a) TESCl, imidazole, CH_2Cl_2, rt, 100%; (b) O_3, CH_2Cl_2, −78 °C; then PPh_3, −78 °C to rt, 96%.



Scheme 3. Reagents and conditions: (a) Ti(O*i*-Pr)$_4$, BnOH, toluene, 85 °C, 79%; (b) $MesSO_2Cl$, pyridine, rt; (c) K_2CO_3, MeOH, rt, 91% (two-steps); (d) Me_3SI, *n*-BuLi, THF, −30 °C to rt, 94%; (e) PMBOC(=NH)CCl_3, La(OTf)$_3$, toluene, rt; (f) (Sia)$_2$BH, THF, 0 °C to rt; then 3 M aq NaOH, H_2O_2, 0 °C to rt, 81% (two-steps); (g) KO*t*-Bu, BnBr, THF, rt; (h) 10% aq KOH, THF/MeOH, 70 °C, 77% (two-steps); (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt; then $Ph_3P{=}C(Me)CO_2Et$, rt, 95%; (j) DIBALH, CH_2Cl_2, −78 °C, 99%; (k) (+)-DET, Ti(O*i*-Pr)$_4$, TBHP, 4 Å molecular sieves, CH_2Cl_2, −40 °C, 82%; (l) TEMPO, aq NaClO, KBr, aq $NaHCO_3$, CH_2Cl_2, 0 °C; (m) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 93% (two-steps); (n) DDQ, CH_2Cl_2/H_2O, rt, 72%; (o) KO*t*-Bu, PMBCl, TBAI, DMF, rt, 98%; (p) (Sia)$_2$BH, THF, 0 °C to rt; then 3 M aq NaOH, H_2O_2, rt, 100%; (q) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, rt; (r) MeMgBr, Et_2O, −78 °C; (s) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, rt, 83% (three-steps).

TEMPO/NaClO[17] and subsequently subjected to a Wittig reaction to afford vinyl epoxide **20** in 93% yield for the two-steps. Upon treatment with DDQ, cleavage of the PMB group with concomitant 6-*endo* cyclization[18] took place to give tetrahydropyran **21** in 72% yield.[19] The stereochemistry of **21** was confirmed by an NOE as shown. Protection of the secondary alcohol as the PMB ether and hydroboration of the terminal olefin afforded primary alcohol **22** (98%, two-steps), which was then converted into methyl ketone **9** in a three-step sequence involving oxidation to the aldehyde, a reaction with MeMgBr, and TPAP/NMO oxidation[20] (83% for the three-steps).

With the two desired fragments in hand, their aldol coupling was then undertaken. Treatment of dibutylboron enolate derived from the methyl ketone **9** (*n*-Bu_2BOTf, *i*-Pr_2NEt, Et_2O)[21] with aldehyde **8** (1.5 equiv) afforded the desired aldol adduct **23** as an inconsequential 5:1 mixture of diastereomers in 74% combined yield (Scheme 4). Oxidation of the secondary alcohol with Dess–Martin periodinane[22] afforded diketone **24** in 91% yield. Treatment of **24** with PPTS in methanol at 80 °C effected deprotection of the TES and benzylidene acetal protective groups with concomitant cyclodehydration[23] to form the H-ring, leading to dihydropyrone **25** in 95% yield. Construction of the I-ring was carried out without incident following the previously described route.[5b,c,24] The diol within **25** was protected as its di-*tert*-butylsilylene to afford **26** in 93% yield. Luche reduction (97%),[25] hydroboration of the derived enol ether with BH_3·THF (80%), followed by protection as the bis-TES ether, afforded **27** in 94% yield. Removal of the PMB group with DDQ followed by oxidation of the resultant alcohol provided ketone **28** in 85% yield for the two-steps. After cleavage of the TES ethers with TsOH (93%), treatment of the resultant ketodiol with Et_3SiH and TMSOTf in propionitrile at −78 °C led to the desired GHIJ-ring skeleton **29** as a single diastereomer in 87% yield.[26]

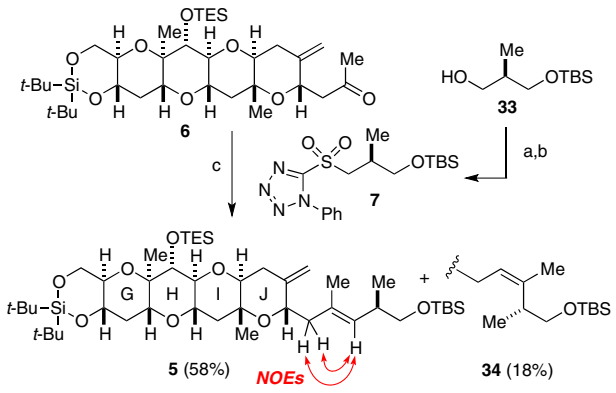


Scheme 4. Reagents and conditions: (a) **9**, Bu_2BOTf, *i*-Pr_2NEt, Et_2O, 0 °C; then **8**, −78 °C, 74%; (b) Dess–Martin periodinane, CH_2Cl_2/*t*-BuOH, rt, 91%; (c) PPTS, MeOH, 80 °C, 95%; (d) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DMF, rt, 93%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH/CH_2Cl_2, 0 °C, 97%; (f) $BH_3{\cdot}$THF, THF, 0 °C; then 3 M aq NaOH, H_2O_2, 0 °C to rt, 80%; (g) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 94%; (h) DDQ, CH_2Cl_2/H_2O, 0 °C; (i) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 0 °C to rt, 85% (two-steps); (j) TsOH, CH_2Cl_2/MeOH, rt, 93%; (k) Et_3SiH, TMSOTf, EtCN, −78 °C, 87%; (l) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 97%; (m) H_2, $Pd(OH)_2$/C, EtOAc, rt, 97%; (n) PivCl, pyridine, 0 °C, 85%; (o) Dess–Martin periodinane, CH_2Cl_2, rt, 80%; (p) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 83%; (q) DIBALH, CH_2Cl_2, −78 °C, 96%; (r) Dess–Martin periodinane, CH_2Cl_2, rt; (s) MeMgBr, THF, −78 °C; (t) Dess–Martin periodinane, CH_2Cl_2, rt, 51% (three-steps).

The stereochemistry of **29** was unambiguously established based on the NMR analysis of the corresponding acetate **30** (Ac_2O, pyridine, 95%) as shown.

Having constructed the tetracyclic ether skeleton, we next turned our attention to introduction of the side chain to the J-ring. Thus, the alcohol **29** was elaborated to the requisite precursor, methyl ketone **6** (Scheme 4). Protection of **29** as the TES ether, removal of the benzyl ethers by hydrogenolysis, followed by selective protection of the primary alcohol as the pivaloate ester led to alcohol **31** in 80% overall yield. Dess–Martin oxidation and Wittig methylenation, followed by reductive removal of the pivaloyl group with DIBALH, afforded primary alcohol **32** in 64% yield for the three-steps. Alcohol **32** was then transformed to methyl ketone **6** by a three-step sequence (51% overall yield), setting the stage for appending the side chain by Julia–Kocienski olefination.

The required sulfone **7** was prepared from the known alcohol **33**[27] by the reaction with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions, followed by oxidation with *m*CPBA as shown in Scheme 5. After extensive experimentation on model compounds, we finally found that the Julia–Kocienski reaction of methyl ketone **6** with sulfone **7** was best accomplished under modified conditions using cerium chloride.[28,29] Thus, the lithiation of sulfone **7** with LDA (THF, −78 °C), followed by addition to ketone **6** in the presence of cerium chloride (−78 to 0 °C), gave rise to the desired trisubstituted (*E*)-olefin **5**[30] in 58% yield, along with the corresponding (*Z*)-isomer **34** (18%). The stereochemistry of **5** was established by NOEs, as shown. To the best of our knowledge, there is no previous example of Julia–Kocienski olefination using organocerium derivatives.



Scheme 5. Reagents and conditions: (a) 1-phenyl-1*H*-tetrazole-5-thiol, diisopropyl azodicarboxylate, Ph_3P, THF, rt, 88%; (b) *m*CPBA, CH_2Cl_2, rt, 89%; (c) **7**, LDA, $CeCl_3$, THF, −78 to 0 °C, **5**: 58%, **34**: 18%.

In summary, we have synthesized the gambieric acids GHIJ-ring fragment having a side chain through a convergent strategy. Key reactions of the synthesis include: (i) aldol reaction to couple the G- and J-rings; (ii) acid-catalyzed cyclodehydration to form the H-ring; and (iii) a cerium chloride-promoted modified Julia–Kocienski reaction for stereoselective introduction of the J-ring side chain. Further studies toward the total synthesis of gambieric acids are currently underway and will be reported in due course.

Acknowledgments

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26. Direct treatment of **28** with Et_3SiH and TMSOTf in propionitrile at −78 °C afforded **29** as a single diastereomer in a somewhat lower yield (72%).
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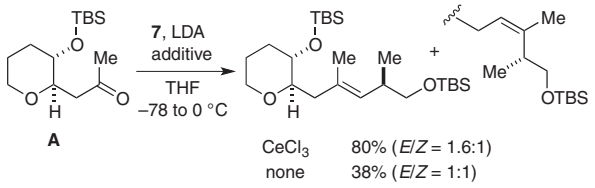
28. Pioneering works on organocerium reagents in organic synthesis, see: (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904; (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392; (c) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747; For a recent review, see: Bartoli, G.; Marcantoni, E.; Marcolini, M.; Sambri, L. *Chem. Rev.* **2010**, *110*, 6104.
29. The Julia–Kocienski reaction of model ketone **A** and sulfone **7** without cerium chloride resulted in a significant decrease in yield of the trisubstituted alkene products. The scope and limitations of the cerium chloride-mediated Julia–Kocienski reaction will be reported in a full account of this study.



Attempted introduction of the side chain to ketone **A** by other methods, including Wittig and Horner–Wittig olefinations using phosphonium salt **B** or phosphonate **C** under various conditions (base: *n*-BuLi, NaHMDS, or LiHMDS; solvent: THF, DME, or THF/HMPA), proved fruitless and resulted in the recovery of starting material, most probably due to the enolizable nature of **A**.

30. *Physical data for* **5**: $[\alpha]_D^{24}$ −23.1 (*c* 0.28, $CHCl_3$); IR (neat) 3441, 2954, 1645, 1471, 1083, 835 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 5.09 (d, *J* = 8.2 Hz, 1H), 4.82 (s, 1H), 4.77 (s, 1H), 4.26 (dd, *J* = 10.0, 4.8 Hz, 1H), 4.14 (dd, *J* = 8.6, 3.4 Hz, 1H), 3.90 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.79 (ddd, *J* = 11.0, 9.6, 4.4 Hz, 1H), 3.73 (ddd, *J* = 10.0, 9.6, 4.8 Hz, 1H), 3.56 (d, *J* = 9.3 Hz, 1H), 3.51 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.39 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.21 (ddd, *J* = 11.6, 9.6, 4.4 Hz, 1H), 3.14 (dd, *J* = 12.7, 4.5 Hz, 1H), 3.09 (dd, *J* = 9.6, 9.3 Hz, 1H), 2.82 (dd, *J* = 12.4, 3.8 Hz, 1H), 2.68 (m, 1H), 2.58 (dd, *J* = 13.1, 4.5 Hz, 1H), 2.45 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.37 (dd, *J* = 13.1, 12.7 Hz, 1H), 2.32 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.25 (ddd, *J* = 11.7, 4.4, 3.8 Hz, 1H), 2.18 (dd, *J* = 11.4, 4.4 Hz, 1 H), 1.85 (ddd, *J* = 12.4, 11.7, 11.0 Hz, 1H), 1.69–1.65 (m, 4H), 1.27 (s, 3H), 1.21 (s, 3H), 1.14 (s, 9H), 1.13 (t, *J* = 7.9 Hz, 9H), 1.08 (s, 9H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.99 (s, 9H), 0.78 (q, *J* = 7.9 Hz, 6H), 0.07 (s, 3 H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 146.0, 132.8, 130.1, 110.0, 83.8, 82.3, 78.5, 78.4, 77.9, 77.2, 74.4, 72.9, 70.3, 69.4, 68.4, 68.2, 43.9, 42.5, 35.9, 35.5, 33.8, 27.7 (3C), 27.3 (3C), 26.1 (3C), 22.8, 20.1, 18.5, 17.7, 16.9, 15.9, 10.5, 7.2 (3C), 5.5 (3C), −5.1, −5.2; HRMS (ESI) calcd for $C_{45}H_{84}O_8Si_3Na$ [(M+Na)$^+$] 859.5366, found 859.5388.