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Convergent synthesis of *trans*-fused 6/*n*/6/6 (*n*=7, 8) tetracyclic ether system via α-cyano ethers

Tohru Oishi,* Koji Watanabe and Michio Murata

Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

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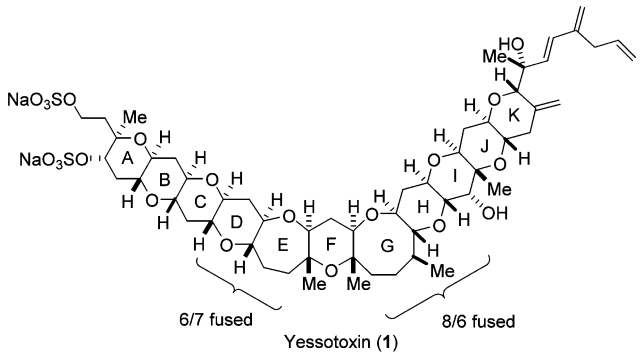
Abstract—A convergent method for synthesizing 6/*n*/6/6 (*n*=7, 8) tetracyclic ether system via two-rings construction of the central *n*/6 ring system was developed. The key steps of the present synthesis involve a ring-closing metathesis reaction for the construction of the seven- and eight-membered rings, and reductive etherification for the tetrahydropyrans. Unification of the two fragments through acetal formation, followed by regioselective cleavage of the acetal using TMSCN/TMSOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, afforded the α-cyano ether, of which the nitrile group was manipulated to give the precursors of the ring-closing reactions.

Because of their unique structures and potent biological activities,[1] ladder polyether toxins of marine origin have attracted much attention among synthetic chemists. In 1987, yessotoxin (**1**) was isolated from the digestive glands of the scallop *Patinopecten yessoensis* in association with diarrhatic shellfish poisoning (DSP).[2] Recent reports on its apoptosis-inducing activities[3] and unique arched molecular structure have prompted us to synthesize **1** and its analogs.[4] Although significant advancements in the total syntheses of polyether natural products have been made in the last decade,[5] practical and reliable methods based on the convergent strategy via two-rings construction[6] are still required for the efficient synthesis of **1**, because the yields and stereoselectivities of the precedent coupling reactions (e.g. alkylative-coupling[6a–d]) or subsequent ring-forming reactions (e.g. radical cyclization[6h–k] and intramolecular allylation[6l]) are highly depending on the substrates. It is worth noting that Nakata[7a,b] and Mori[7c,d] have reported on alternative approaches that involve the convergent and iterative strategies. Herein, we describe a convergent method for synthesizing the 6/7/6/6 and 6/8/6/6 tetracyclic ether systems (**2a** and **2b**), as a model case for the construction of the CDEF- and FGHI-ring frameworks of **1** via α-cyano ether **3** through the convergent assemblage of diol **4** and aldehyde **5** (Scheme 1).

As shown in Scheme 2, the synthesis of the diol **4** and the aldehyde **5** commenced with a common intermediate **6**,[8] which was prepared from 2-deoxy-D-ribose. For the diol **4**, *p*-methoxybenzylidene acetal **6** was converted to the corresponding di-*tert*-butylsilylene **7**, then subjected to rhodium catalyzed hydroboration[9] using catecholborane to give the diol. Alternatively, for the aldehyde **5**, ozonolysis of **6** followed by benzylation of the resulting diol gave **8**. Regioselective opening of the *p*-methoxybenzylidene acetal of **8** with DIBAL-H gave the primary alcohol, which was converted to nitrile **9** through mesylation followed by treatment with NaCN. Reduction of the nitrile **9** with DIBAL-H afforded the aldehyde **5** in 83% yield.



Keywords: convergent synthesis; polyether; α-cyano ether; acetal cleavage; ring-closing metathesis; reductive etherification; yessotoxin.
* Corresponding author. Tel.: +81-6-6850-5775; fax: +81-6-6850-5785; e-mail: oishi@ch.wani.osaka-u.ac.jp

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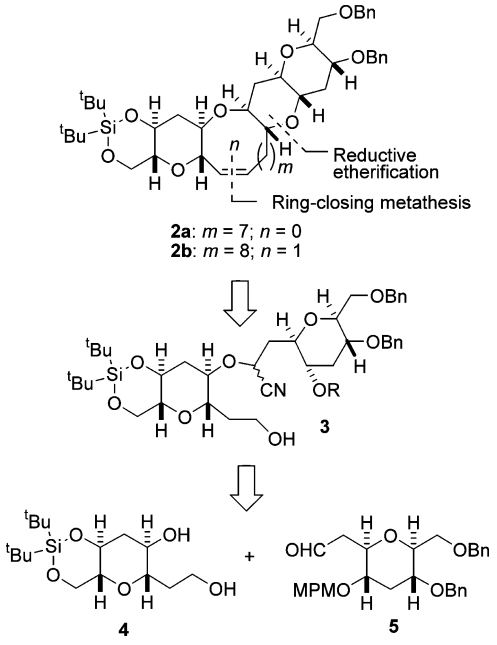
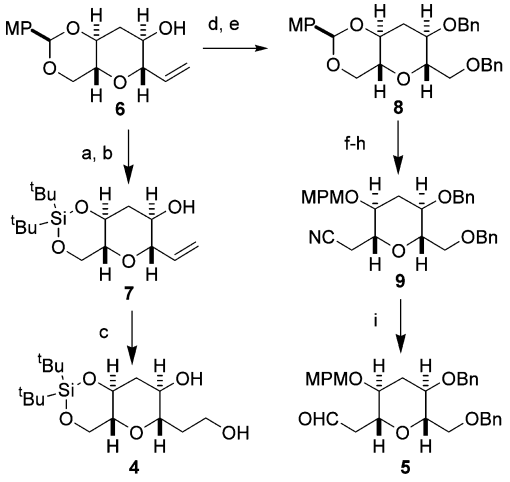


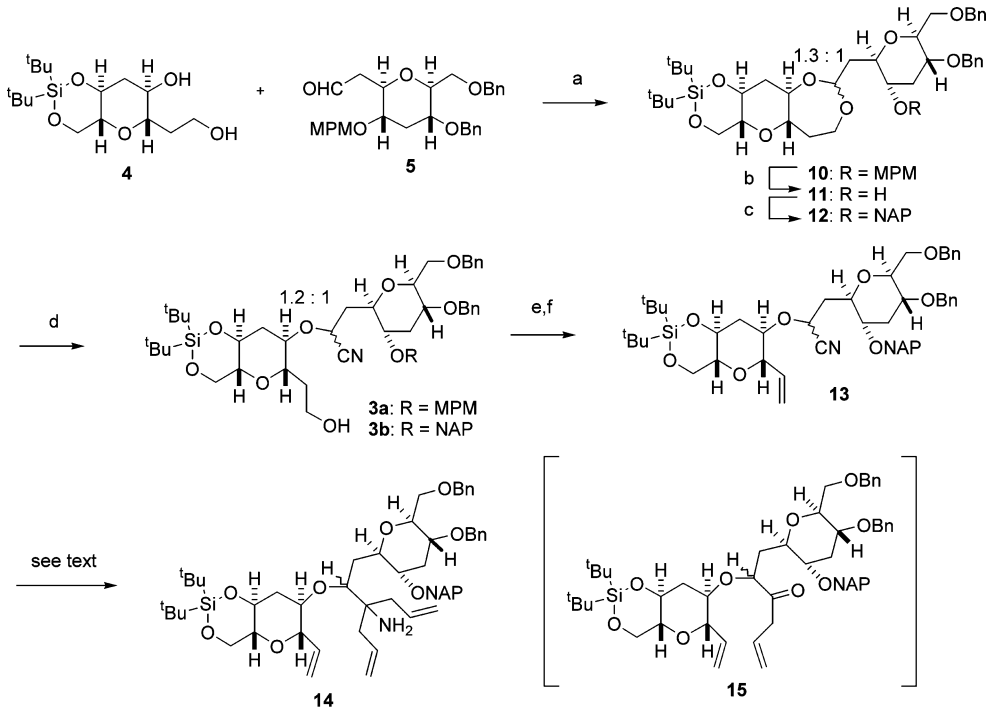
Scheme 1. Synthesis plan.



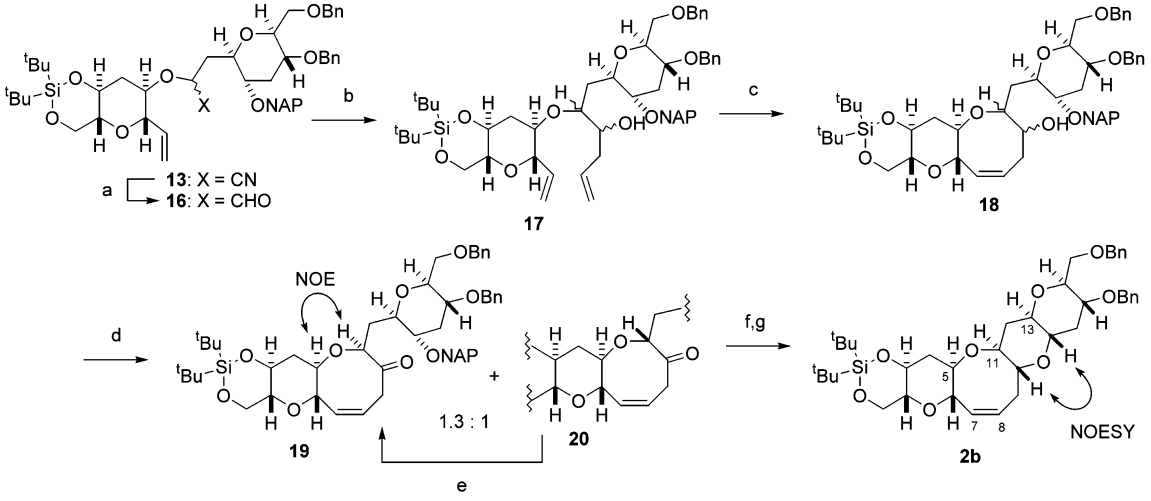
Scheme 2. *Reagents and conditions*: (a) *p*-TsOH, H_2O, MeOH, rt, 30 min; (b) *t*-$Bu_2Si(OTf)_2$, 2,6-lutidine, DMF, 0°C, 30 min, 97% (two steps); (c) catecholborane, $Rh(PPh_3)_3Cl$, THF, rt, 14 h, then 30% H_2O_2, $NaHCO_3$ (aq.), 66%; (d) O_3, CH_2Cl_2, MeOH, −78°C, then, $NaBH_4$, 96%; (e) BnBr, NaH, THF, DMF, rt, 24 h, 96%; (f) DIBAL-H, CH_2Cl_2, −78 to −20°C, 20 h, 90%; (g) MsCl, Et_3N, CH_2Cl_2, 0°C to rt; (h) NaCN, DMF, 50°C, 24 h, 84% (two steps); (i) DIBAL-H, CH_2Cl_2, −78°C, 83%.

The synthesis of 6/8/6/6 tetracyclic ether **2b** is shown in Schemes 3 and 4. Condensation of **5** using 2 equiv. of **4** was successfully achieved by treating with $Sc(OTf)_3$[10] in benzene to give seven-membered ring acetal **10** in 84% yield as a mixture of diastereomers (1.3:1) with respect to the stereogenic center on the acetal carbon.[5a,b,6j] Attempts to obtain nitrile **3a** by means of regioselective opening of acetal **10** using TMSCN in the presence of $TiCl_4$[11] was unsuccessful due to the formation of a complex mixture with concomitant removal of the MPM group. Alternatively, after converting the MPM to the NAP (2-naphthylmethyl) group,[5b,12] regioselective cleavage[6i–k] of the acetal **12** was successfully achieved using TMSCN and TMSOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine and MS 4 Å in CH_2Cl_2 to afford nitrile **3b** in 87% yield without the removal of the NAP group. Subsequently, primary alcohol **3b** was converted to terminal olefin **13** via 2-nitrobenzenselenide through the elimination of the selenoxide.[13] Attempts to obtain ketone **15** directly from **13** using allylmagnesium bromide or allylzinc chloride[14] were unsuccessful due to the formation of diallylamine **14**, and, therefore, stepwise reaction was examined via aldehyde **16** (Scheme 4). Nitrile **13** was reduced with the careful gradual addition of DIBAL-H at −78°C (carefully monitored by TLC) to afford **16** in 63% yield, which was treated with allylmagnesium bromide at −50°C to give alcohol **17** as an inseparable mixture of four diastereomers in 81% yield. Ring-closing metathesis reaction of diene **17** using Grubbs catalyst[15] proceeded smoothly to give eight-membered ring alcohol **18**, which was further oxidized to enones **19** and **20** as an inseparable mixture (**19**:**20** = 1.3:1). Undesirable epimer **20** was successfully isomerized to **19** by treating with DBU in toluene at 80°C for 15 h. Finally, construction of the tetrahydropyran ring was achieved through the removal of the NAP group in 72% yield, followed by the reductive etherification of the resulting hemiacetal to give 6/8/6/6 tetracyclic ether **2b** as a single isomer in 68% yield.[16]

In an analogous sequence, 6/7/6/6 tetracyclic ether **2a** was synthesized as shown in Scheme 5. Treatment of aldehyde **16** with vinyllithium, generated from tetravinylstannane and methyllithium, followed by ring-closing metathesis reaction of the resulting diene using Grubbs catalyst[15] gave **21** in 20% yield along with **22** as an inseparable mixture of three diastereomers in 44% yield. Dess–Martin oxidation of **21** gave enone **23**, whose stereochemistry was unambiguously determined using NOE experiments. Removal of the NAP group of **23** yielded an equilibrium mixture of the corresponding hydroxy ketone and hemiacetal in a 1.3:1 ratio, which were subjected to reductive etherification using triethylsilane and TMSOTf to give **2a** as a single isomer.[16] On the other hand, oxidation of **22** gave an inseparable mixture of enones **24** and **23** with a ratio of 4.4:1. Although isomerization of **24** using DBU or imidazole afforded the β,γ-unsaturated enone **25** in low yield (~40%) as compared to the eight-membered ring system, conversion to the desired isomer was achieved through the 1,4-reduction of the enones using $NaBH_4/CoCl_2$,[17] followed by treatment with DBU to yield the desired ketone **26** (7.7:1). Successive removal of the NAP group and reductive etherification gave saturated 6/7/6/6 tetracyclic system **27** in 70% yield.

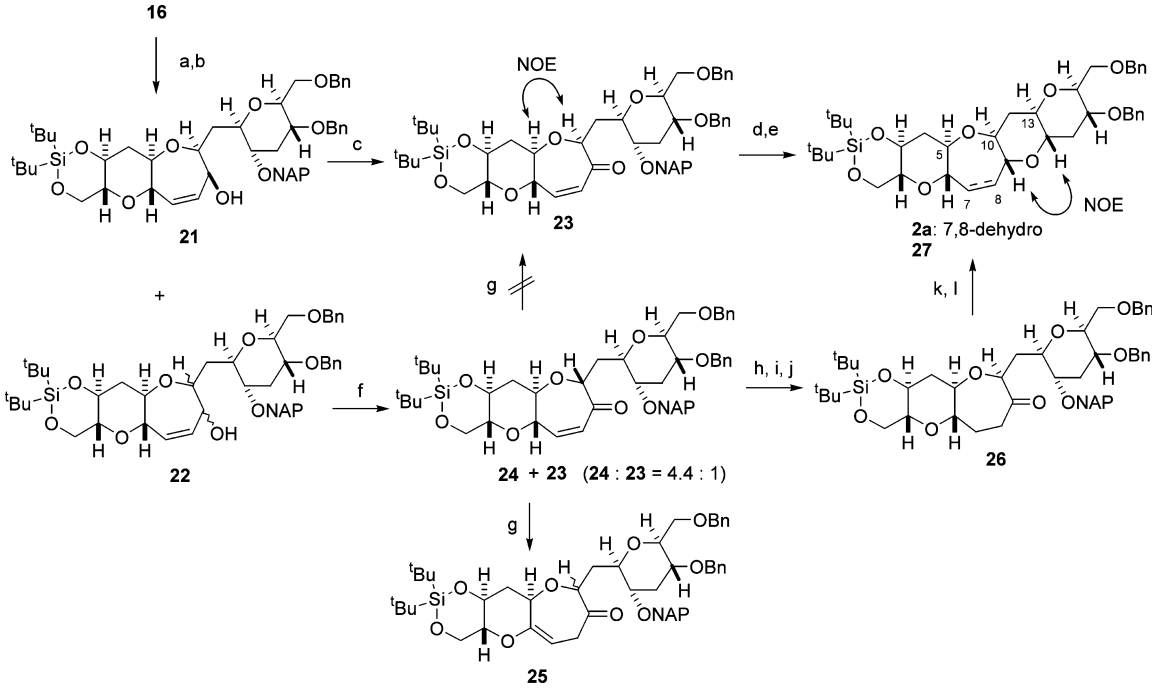


Scheme 3. *Reagents and conditions*: (a) $Sc(OTf)_3$, benzene, 1.5 h, 84% (**11**: 11%); (b) DDQ, $NaHPO_3$ (aq.), CH_2Cl_2; (c) 2-naphthylmethyl bromide, NaH, TBAI, THF, DMF, 82% (two steps); (d) TMSCN, TMSOTf, 2,6-di-*tert*-butyl-4-methylpyridine, MS 4 Å, CH_2Cl_2, rt, 36 h, then, K_2CO_3, MeOH, 87%; (e) 2-$NO_2C_6H_4SeCN$; Bu_3P, THF; (f) 30%H_2O_2, $NaHCO_3$ (aq.), THF, 40°C, 69% (two steps).



Scheme 4. *Reagents and conditions*: (a) DIBAL-H, −78°C, CH_2Cl_2, 63%; (b) CH_2=$CHCH_2MgBr$, THF, −50°C, 35 min, 81%; (c) $(PCy_3)_2Cl_2Ru$=CHPh, CH_2Cl_2, 40°C, 93%; (d) Dess–Martin periodinane, CH_2Cl_2, quant.; (e) DBU, toluene, 80°C, 15 h, 71%; (f) DDQ, CH_2Cl_2, H_2O, 72%; (g) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −45°C, 68%.

In conclusion, convergent synthesis of the 6/*n*/6/6 (*n*=7, 8) ring system has been achieved via pivotal α-cyano ethers through the construction of the central *n*/6 ring system based on the ring-closing metathesis and reductive etherification with control of the newly formed stereogenic centers. The present method would be useful for synthesizing ladder polyether natural products, and further studies directed towards the total synthesis of yessotoxin will be reported in due course.



Scheme 5. *Reagents and conditions*: (a) $(CH_2{=}CH)_4Sn$, MeLi, THF, −78°C, 81%; (b) $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 40°C, 24 h, 20% (for **21**), 44% (for **22**); (c) Dess–Martin periodinane, CH_2Cl_2, quant.; (d) DDQ, CH_2Cl_2, H_2O, 90%; (e) Et_3SiH, TMSOTf, CH_2Cl_2, −50°C, 30 min, 77%; (f) Dess–Martin periodinane, CH_2Cl_2, quant. (**23**:**24** = 1:4.4); (g) DBU, toluene, 80°C, 15 h, ~40% (for **25**); (h) $NaBH_4$, $CoCl_2$, MeOH, 0°C, 15 h (ketone 40%, alcohol 38%); (i) Dess–Martin periodinane, CH_2Cl_2, 85%; (j) DBU, toluene, reflux, 12 h, 74%; (k) DDQ, CH_2Cl_2, H_2O, 83%; (l) Et_3SiH, TMSOTf, CH_2Cl_2, −50°C, 30 min, 70%.

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16. Sterochemistry of the tetracyclic ethers was determined by ^{1}H NMR analysis and NOE experiments. **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (9H, s, ^{t}Bu), 1.01 (9H, s, ^{t}Bu), 1.43 (1H, ddd, J=11.5, 11.5, 11.5 Hz, $H14_{ax}$), 1.52–1.59 (2H, m, $H4_{ax}$, $H11_{ax}$), 2.32 (1H, dt, J=12.0, 4.5 Hz, $H11_{eq}$), 2.41 (1H, dt, J=12.0, 4.5 Hz, $H4_{eq}$), 2.52 (1H, dt, J=11.5, 4.5 Hz, $H14_{eq}$), 2.96 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H13), 3.03 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H12), 3.24 (1H, ddd, J=10.5, 10.0, 5.0 Hz, H4), 3.29–3.34 (2H, m, H5, H10), 3.40 (1H, ddd, J=9.5, 5.0, 1.5 Hz, H2), 3.50 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H15), 3.63 (1H, dd, J=10.5, 5.0 Hz, H17), 3.73 (1H, dd, J=10.5, 1.5 Hz, H17), 3.74 (1H, ddd, J=11.5, 10.0, 4.5 Hz, H3), 3.78 (1H, t, J=10.5 Hz, $H1_{ax}$), 3.81 (1H, d, J=9.0 Hz, H6 or H9), 3.86 (1H, d, J=9.5 Hz, H6 or H9), 4.12 (1H, dd, J=10.5, 5.0 Hz, $H1_{eq}$), 4.37 (1H, d, J=11.5 Hz), 4.53 (1H, d, J=12.0 Hz), 4.55 (1H, d, J=11.5 Hz), 4.59 (1H, d, J=12.0 Hz), 5.58 (1H, d, J=15.0 Hz), 5.61 (1H, d, J=15.0 Hz), 7.17–7.32 (10H, m, Ph); ESI MS calcd for $C_{39}H_{54}O_8SiNa$ ($M+Na^+$) 701, found 701; **2b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (9H, s, ^{t}Bu), 1.02 (9H, s, ^{t}Bu), 1.44 (1H, td, J=11.5, 11.0 Hz, $H15_{ax}$), 1.53–1.61 (2H, m, $H4_{ax}$, $H12_{ax}$), 2.27 (1H, dt, J=11.5, 4.5 Hz, $H12_{eq}$), 2.32 (1H, ddd, J=14.0, 6.5, 2.0 Hz, H9), 2.43 (1H, dt, J=12.0, 4.5 Hz, $H4_{eq}$), 2.50 (1H, dt, J=11.0, 4.5 Hz, $H15_{eq}$), 2.67 (1H, ddd, J=14.0, 9.5, 4.5 Hz, H9), 2.90–2.98 (2H, m, H13, H14), 3.22 (1H, ddd, J=10.5, 10.0, 5.5 Hz, H2), 3.26 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H5), 3.33 (1H, ddd, J=9.5, 4.5, 2.0 Hz, H2), 3.36 (1H, ddd, J=10.0, 5.0, 2.0 Hz, H17), 3.44 (1H, ddd, J=11.5, 9.5, 4.5 Hz, H11), 3.48 (1H, ddd, J=11.5, 10.0, 4.5 Hz, H16), 3.62 (1H, dd, J=10.0, 5.0 Hz, H18), 3.72 (1H, dd, J=10.0, 2.0 Hz, H18), 3.75 (1H, ddd, J=11.5, 10.0, 4.5 Hz, H3), 3.78 (1H, t, J=10.5 Hz, $H1_{ax}$), 3.93 (1H, ddd, J=9.5, 5.0, 2.0 Hz, H6), 4.12 (1H, dd, J=10.5, 5.5 Hz, $H1_{eq}$), 4.35 (1H, d, J=11.5 Hz), 4.52 (1H, d, J=12.5 Hz), 4.53 (1H, d, J=11.5 Hz), 4.59 (1H, d, J=12.5 Hz), 5.63 (1H, dd, J=11.5, 5.0 Hz, H7), 5.68 (1H, dddd, J=11.5, 9.5, 6.5, 2.0 Hz, H8), 7.16–7.31 (10H, m, Ph); ESI MS calcd for $C_{40}H_{56}O_8SiNa$ ($M+Na^+$) 715, found 715.
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