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Stereoselective formal synthesis of aspergillide A

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ABSTRACT

The stereoselective formal synthesis of aspergillide A (**1**), a cytotoxic 14-membered macrolide, is disclosed. The key intermediate, a trisubstituted tetrahydropyran core is prepared by SmI_2-induced intramolecular reductive cyclization as well as by using sequential α-aminooxylation, Horner–Wadsworth–Emmons olefination, and followed by Oxa-Michael cyclization. Other notable transformations in the synthesis include the use of Jacobsen's hydrolytic kinetic resolution, esterification, ring-closing metathesis (RCM), and cross-metathesis (CM) reactions.

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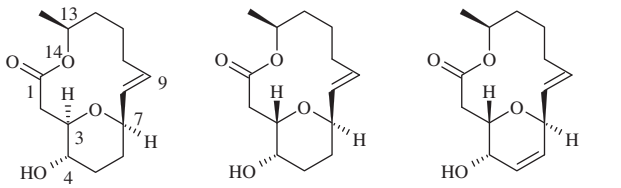
Recently, three novel 14-membered macrolides, named aspergillides A, B, and C (Fig. 1, **1**–**3**) were isolated by Kusumi and coworkers[1] from marine-derived fungus *Aspergillus ostianus* strain 01F313, cultured in a 1/2PD medium containing bromine-modified artificial sea-water. These compounds were shown to exhibit significant cytotoxic activity against mouse lymphocytic leukemia cells with an IC_{50} value of 2.1, 70, and 2.0 μg/mL, respectively. The structures originally proposed for aspergillides A (**1**) and B (**2**) were revised[2] by X-ray crystallography studies and the structure for aspergillide C (**3**) was confirmed to be correct by performing its synthesis.[3] Both their unique pharmaceutical profile and challenging chemical architectures have attracted considerable interest, leading to numerous attempts and several successful syntheses of **2** and **3**,[4] but the synthesis of **1** is rare[5] so it has driven us to take-up the synthesis of aspergillide A (**1**).

From a retrosynthetic perspective (Scheme 1), we planned that the side chain installation onto trisubstituted tetrahydropyran core **4** would be the late stage reaction. Thus, the 14-membered macrolide **1** can be achieved from two fragments, **4** and **5**, via esterification followed by a ring-closing metathesis reaction or cross-metathesis reaction and Yamaguchi lactonization. The trisubstituted tetrahydropyran core **4** was prepared by two different routes using a SmI_2-induced intramolecular reductive cyclization or sequential α-aminooxylation followed by in situ Horner–Wadsworth–Emmons olefination and Oxa-Michael reaction from **6** and **7**, respectively. The **6** in turn could be prepared from the known epoxide **8**, whereas the aldehyde **7** could be obtained from the epoxide **9**.

In route A (Scheme 2), our synthesis commenced from chiral epoxide **8**, prepared from 4-pentene-1-ol following the literature procedure.[6] Opening of epoxide[7] **8** using trimethylsulfonium iodide, *n*-BuLi in dry THF at −10 °C provided secondary allylic alcohol **10** in 75% yield. The plan for the diastereoselective construction of **13** was based on SmI_2 reductive cyclization[8,9] of aldehydes such as **6**. To this end, the allylic alcohol **10** was condensed with methyl propiolate. This was achieved by slow addition of methyl propiolate[10] to compound **10** via syringe pump over 16 h to deliver the intermediate **11** in 90% isolated yield. Next, deprotection of the THP ether **11** by using PTSA in MeOH released the primary alcohol **12**, which was immediately oxidized using IBX in $DMSO/CH_2Cl_2$ to provide aldehyde **6**. As anticipated, the SmI_2-mediated cyclization of **6** proceeded to give 1**3** with high diasterocon-



Aspergillide A (1) **Aspergillide B (2)** **Aspergillide C (3)**
revised structures

Figure 1.

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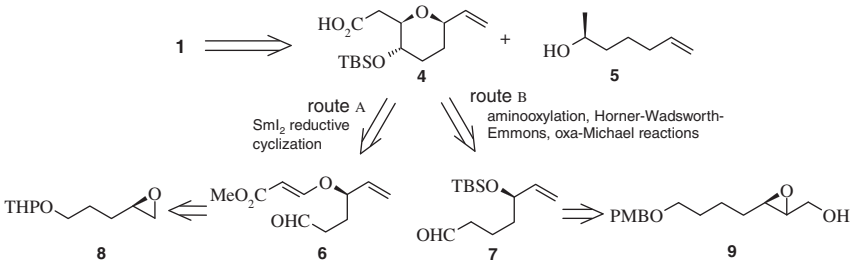
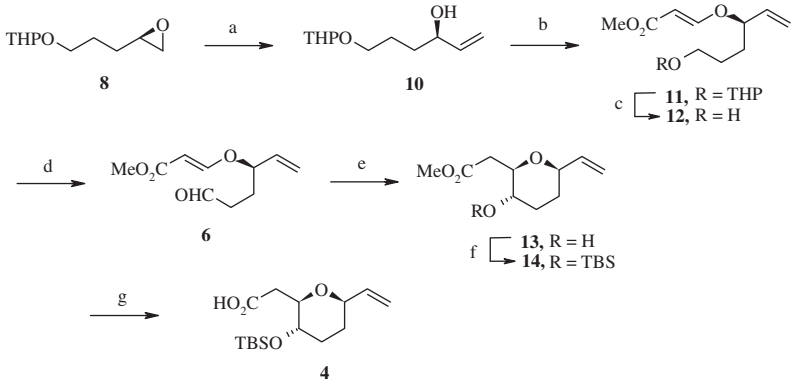


Scheme 1. Retrosynthesis.



Scheme 2. Reagents and conditions: (a) trimethylsulfonium iodide, *n*-BuLi, THF, −10 °C, 4 h, 75%; (b) methyl propiolate, DMAP, CH_3CN, rt, 16 h, 90%; (c) PTSA, MeOH, 0 °C to rt, 12 h, 81%; (d) IBX (*o*-iodoxybenzoic acid), DMSO, CH_2Cl_2, 0 °C to rt, 1 h, 78%; (e) SmI_2 (0.1 M solution) (3 equiv), MeOH (3 equiv), THF, 0 °C, 1 h, 92%; (f) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 20 h, 88%; (g) LiOH, MeOH/H_2O (8:2), 0 °C to rt, 10 h, 78%.

trol. Thus treatment of **6** with 3 equiv of SmI_2[11] in the presence of 3 equiv of dry MeOH in THF effected reductive cyclization to give 2,6-*syn*-2,3-*anti*-tetrahydropyran **13** in 92% yield as the single product. The hydroxy group was protected as TBS ether **14** and cleavage of the methyl ester furnished acid **4** in excellent yield.

Product **14** was thoroughly characterized with the help of 2-D nuclear Overhauser effect spectroscopy (NOESY) and double quantum filter correlation spectroscopy (DQF-COSY) experiments. J_{H2-H3} = 9.1 Hz, J_{H5-H6} = 12.2, and $J_{H5'-H6}$ = 1.7 Hz suggest that the H-2 and H-6 are diaxially disposed with respect to each other, which is further confirmed by exclusive, strong NOE cross-peaks between H2 and H6. Hence *R*- and *S*-stereocenter for C2 and C3, respectively. Further NOE correlation H2/H4 and H4/H6 is consistent with the chair conformation for six-membered pyran ring. The minimum energy structure is adequately supported by NMR data. These data (Figs. 2 and 3) suggest that the structure of the newly formed ring in **14**[12] is the desired 2,6-*syn*-2,3-*anti* tetrahydropyran.

In route B (Scheme 3), the synthesis of the key intermediate **13** started from the epoxy alcohol **9** (98% ee, measured by chiral HPLC) prepared as reported in our Letter.[13] The alcohol was treated with TPP and I_2 in Et_2O/CH_3CN (3:1) in the presence of imidazole to get the 2,3-epoxy iodide **15** in good yield, which on refluxing in MeOH with Zn yielded the allylic alcohol **16**. The allylic alcohol was protected as TBS ether **17** followed by removal of PMB group that provided the primary alcohol **18**, which on oxidation using IBX in $DMSO/CH_2Cl_2$ afforded the aldehyde. The aldehyde without isolation was subjected to the crucial MacMillan[14] α-aminooxylation using nitrosobenzene and 20 mol % D-proline in DMSO followed by in situ Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate and Cs_2CO_3 as base to furnish γ-anilinoxy-α,β-unsaturated ester **19a**, which was further treated with $Cu(OAc)_2$ in ethanol at room temperature to cleave the O–N bond providing the ester **19** with high enantiopurity (dr, >95:<5). Exposure of compound **19** to TBAF for 20 h effected a silyl group removal and a smooth Oxa-Michael cyclization under thermodynamic conditions in one-pot provided exclusively the 2,6-*syn*-2,3-*anti* tetrahydropyran **13** (70%). The hydroxy group was protected as TBS ether **14** and cleavage of the methyl ester furnished acid **4** in excellent yield. The analytical and optical rotation values of **13**, **14**, and **4** exactly matched with those of **13**, **14**, and **4** synthesized by Scheme 2.

Now, the stage is set to the synthesis of **1** to fasten the desired fragments **4** and the known alcohol **5**[15] together to obtain the 14-membered macrocycle **1** (Scheme 4). Thus, the esterification of alcohol **5** with carboxylic acid **4** was carried out under Yamaguchi conditions[16] to produce compound **20** in 79% yield. This set the stage for the macrocyclization by ring-closing metathesis.

Reaction of diene **20** with second or first generation Grubbs' catalyst[17] in refluxing dichloromethane or using Grubbs–Hoveyda (G–H) catalyst in the presence of 1,4-benzoquinone[18] also resulted in the exclusive formation of *Z*-isomer **21** in 90% yield. Finally, the (*Z*)-isomer **21** was subjected to desilylation under TBAF conditions to give the macrocyclic core **22** (*J* = 10.5 Hz) in 85% yield. The structure of macrolactone **22** was fully characterized by ^1H NMR, ^{13}C NMR, and mass spectral data.

In addition, the cross-metathesis of hydroxy acid **4** with alcohol **5** carried out in the presence of 10 mol% of Grubbs-II catalyst afforded **23** in 15 min as a mixture of *E*/*Z* in a ratio of 9:1. The formation of the product was confirmed by ^1H NMR analysis and comparison with the literature data.[5a]

It is noteworthy to mention that when our work was under progress, a note appeared[5b] on the synthesis of aspergillide A **1** indicating similar results on RCM and cross-metathesis reactions. The spectral and analytical (^1H, ^{13}C NMR, mass, IR, and optical rotation) data of our synthetic materials **22** and **23** were in complete agreement with those reported.[5a,5b] As per the literature, the macrolactonization of **23** proved to be a difficult task. Only in the case of TBS-ether and MOM-ether the product was obtained in 30% and 20% yields, respectively, under Yamaguchi conditions.[5a,5c] The seco

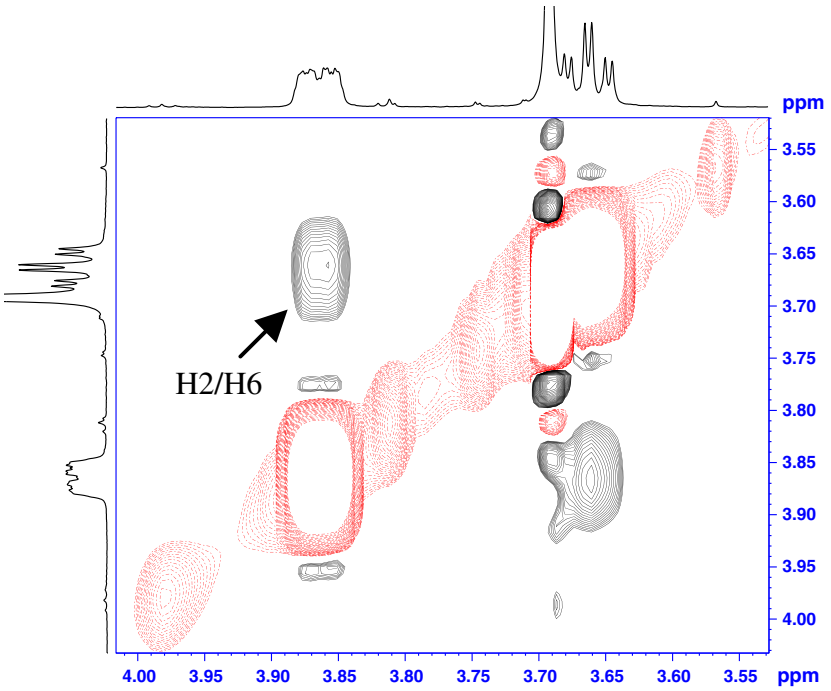


Figure 2. Expansion of the NOESY spectrum showing the characteristic NOE correlations.

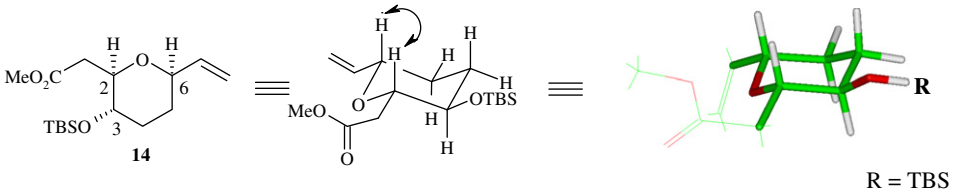
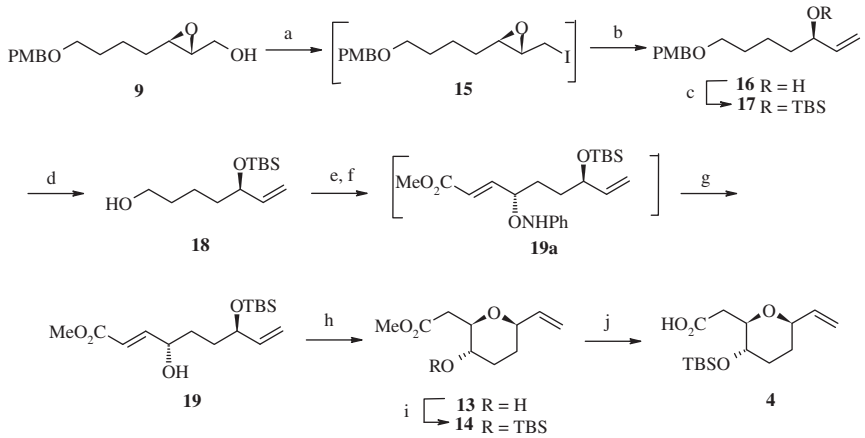


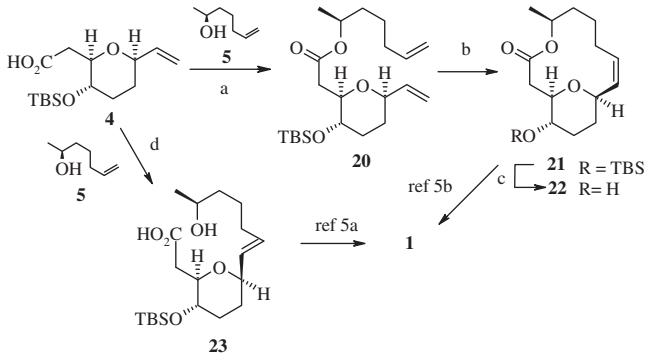
Figure 3. Chemical structure and energy-minimized structure of **14**.



Scheme 3. Reagents and conditions: (a) TPP, imidazole, iodine, Et_2O/CH_3CN (3:1), 0 °C, 1 h; (b) Zn, MeOH, reflux, 1 h, (92% overall from **9**); (c) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 4 h, 96%; (d) DDQ, CH_2Cl_2/H_2O (9:1), 0 °C, 1 h, 91%; (e) IBX (*o*-iodoxybenzoic acid), DMSO, CH_2Cl_2, 0 °C to rt, 10 h; (f) (i) PhNO, D-proline, DMSO, rt, 15 min, (ii) trimethyl phosphonoacetate, cesium carbonate, rt, 2 h (60% overall from **18**); (g) $Cu(OAc)_2$, EtOH, rt, overnight, 85%; (h) TBAF, THF, 20 h, rt, 70%; (i) TBSCl, Imidazole, CH_2Cl_2, 0 °C to rt, 20 h, 88%; (j) LiOH, $MeOH/H_2O$ (8:2), 0 °C to rt, 10 h, 78%.

acid bearing benzyl ether as per the report is not stable under any macrolactonization conditions.[5b] Since the conversion of **22** and **23** to aspergillide A **1** has already been reported in the literature,[5a,5b] the present sequence herein constitutes a formal synthesis of aspergillide A **1**.

In conclusion, a formal synthesis of the 14-membered macrolide, aspergillide A (**1**) has been demonstrated. This synthesis features a key SmI_2 reductive cyclization step and sequential α-aminooxylation–Horner–Wadsworth–Emmons olefination and oxa-Michael cyclization reactions to access the trisubstituted pyr-



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 6 h, 79%; (b) Ru-I, CH_2Cl_2, reflux, 2 h, 90%; (c) TBAF, THF, rt, overnight, 85%; (d) Ru-II, CH_2Cl_2, reflux, 15 min, 42%.

an core. Other salient features of the approach include the use of ring-closing metathesis and cross-metathesis reactions. We believe that this approach sets the stage not only for the total synthesis of aspergillide A (**1**) but also entry to a diversity of analogues through the installation of various side chains. Studies in this direction are underway.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.013.

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12. *Spectral data: methyl 2-((2R,3S,6R)-3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-6-vinyltetrahydro-2H-2 pyranyl)acetate* (**14**): $[\alpha]_D^{25}$ +24.3 (*c* 0.01 g/mL, $CHCl_3$); ^1H NMR: ($CDCl_3$, 600 MHz): δ 5.81 (ddd, *J* = 5.1, 10.7, 17.4 Hz, 1H), 5.20 (td, *J* = 1.6, 17.4 Hz, 1H), 5.06 (td, *J* = 1.6, 17.4 Hz, 1H), 3.85 (m, 1H), 3.68 (s, 3H), 3.65 (dt, *J* = 3.2, 9.1 Hz, 1H), 3.35 (ddd, *J* = 4.4, 9.1, 10.3 Hz, 1H), 2.82 (dd, *J* = 3.3, 15.2 Hz, 1H), 2.39 (dd, *J* = 9.2, 15.2 Hz, 1H), 2.02 (qd, *J* = 3.8, 12.6 Hz, 1H), 1.77 (qd, *J* = 2.8, 12.6 Hz, 1H), 1.62–1.41 (m, 2H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 172.2, 138.3, 114.8, 79.0, 77.6, 70.6, 51.5, 37.9, 33.2, 30.9, 25.7, 17.8, −4.0, −4.8; IR (Neat): 3060, 2933, 2858, 1744, 1640, 1464, 1437, 1342, 1194, 1095, 990,927, 897, 840, 775, 671 cm^{-1}; LC–MS: 315 $[M+H]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{16}H_{31}O_4Si$: 315.1991; found: 315.1991.
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    Selected spectral data: (3R)-6-(tetrahydro-2H-2-pyranyloxy)-1-hexen-3-ol (**10**): $[\alpha]_D^{25}$ −6.2 (*c* 0.01 g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.91–5.78 (m, 1H), 5.22 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.60–4.56 (m, 1H), 4.16–4.08 (m, 1H), 3.87–3.72 (m, 2H), 3.53–3.44 (m, 1H), 3.43–3.34 (m, 1H), 2.23 (br s, 1H, OH), 1.89–1.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): 141.0, 114.4, 98.8, 72.7, 67.5, 62.2, 34.2, 30.5, 25.8, 25.3, 19.4; IR (Neat): 3430, 3060, 2941, 2866, 1640, 1442, 1352, 1266, 1200, 1123, 1071, 1027, 988, 913, 868, 810, 758, 669 cm^{-1}; ESIMS: *m/z* 223 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{11}H_{20}O_3Na$: 223.1310; found: 223.1303.
    Methyl (E)-3-[(1R)-1-(3-hydroxypropyl)-2-propenyl]oxy-2-propenoate (**12**): $[\alpha]_D^{25}$ −5.3 (*c* 0.009 g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.46 (d, *J* = 12.0 Hz, 1H), 5.82–5.69 (m, 1H), 5.32–5.19 (m, 3H), 4.39–4.31 (m, 1H), 3.70–3.61 (m, 5H), 1.85–1.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): 168.4, 161.6, 136.2, 118.2, 97.6, 83.7, 62.3, 51.1, 31.2, 28.1 ; IR (Neat): 3431, 3055, 3020, 2947, 1705, 1635, 1438, 1334, 1292, 1199, 1139, 1054, 967, 900, 832, 754 cm^{-1}; LC–MS: *m/z* 223 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{10}H_{16}O_4Na$: 223.0946; found: 223.0940.
    ((2R,3R)-3,4-[(4-Methoxybenzyl)oxy]butyloxiran-2-yl)methanol (**9**): $[\alpha]_D^{25}$ +11.1 (*c* 0.0135 g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.39 (s, 2H), 3.83 (dd, *J* = 1.9, 12.5, Hz, 1H), 3.79 (s, 3H), 3.57 (dd, *J* = 4.8, 12.5 Hz, 1H), 3.41 (t, *J* = 6.7 Hz, 2H), 2.91–2.67 (m, 1H), 2.86–2.82 (m, 1H), 1.66–1.46 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.0, 130.4, 129.1, 113.6, 72.4, 69.6, 61.6, 58.4, 55.8, 55.2, 31.2, 29.3, 22.6 ; IR: 3424, 2932, 2860, 1611, 1513, 1460, 1248, 1096, 1032, 822, 757 cm^{-1}; LC–MS: 289 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{15}H_{22}O_4Na$: 289.1415; found: 289.1407.
    (5R)-5-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-6-hepten-1-ol (**18**): $[\alpha]_D^{25}$ −5.6 (*c* 0.0115 g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.82–5.69 (m, 1H), 5.15–5.07 (m, 1H), 5.03–4.98 (m, 1H), 4.17–4.03 (m, 1H), 3.61 (t, *J* = 6.7 Hz, 2H), 1.61–1.30 (m, 6H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 141.5, 113.6, 73.7, 62.5, 37.6, 32.6, 25.8, 21.2, 18.2, −4.4, −4.9 ; IR (Neat): 3351, 3080, 2934, 2859, 1643, 1466, 1418, 1253, 1087, 1034, 924, 837, 775, 676 cm^{-1}; LC–MS: 245 $[M+H]^+$; HRMS: *m/z* $[M+H]^+$ calcd for $C_{13}H_{29}O_2Si$: 245.1936; found: 245.1938.
    Methyl (2E,4S,7R)-7-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-hydroxy-2,8-nonadienoate (**19**): $[\alpha]_D^{25}$ −28.4 (*c* 0.0225 g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.94 (dd, *J* = 4.5, 15.8 Hz, 1H), 6.07 (dd, *J* = 2.2, 15.8 Hz, 1H), 5.86–5.72 (m, 1H), 5.21–5.05 (m, 2H), 4.35–4.19 (m, 2H), 3.75 (s, 3H), 2.80 (br s, 1H, OH), 1.75–1.55 (m, 4H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.1, 150.4, 140.5, 119.7, 114.5, 73.5, 71.0, 51.5, 33.8, 31.8, 25.8, 18.2, −4.4, −4.9 ; IR (Neat): 3446, 2925, 2855, 1726, 1656, 1462, 1258, 1170, 1077, 923, 836, 775 cm^{-1}; LC–MS: 337 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{16}H_{30}O_4NaSi$: 337.1811; found: 337.1799.
    (1R,5S,11R,14S)-14-Hydroxy-5-methyl-4,15-dioxabicyclo-[9.3.1]pentadec-9(Z)-en-3-one (**22**): $[\alpha]_D^{25}$ +38.2 (*c* 0.006 g/mL, $CHCl_3$), lit[5b] $[\alpha]_D^{25}$ +42.9 (*c* 0.077, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.64–5.53 (m, 1H), 5.16 (dd, *J* = 2.2, 10.5 Hz, 1H), 5.06–4.93 (m, 1H), 4.08–4.00 (m, 1H), 3.56–3.47 (m, 1H), 3.35–3.25 (m, 1H), 2.81 (dd, *J* = 2.2, 11.3 Hz, 1H), 2.30 (t, *J* = 11.3 Hz, 1H), 2.32–2.09 (m, 2H), 2.00 (br s, OH) 1.83–1.74 (m, 1H), 1.72–1.40 (m, 7H), 1.25 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 173.3, 135.7, 128.0, 81.5, 74.8, 70.1, 69.8. 39.0, 34.4, 33.6, 31.9, 28.0, 25.7, 20.9; IR (Neat): 3431, 3020, 2923, 2854, 1725, 1655, 1459, 1371, 1275, 1183, 1133, 1075, 969, 758, 678 cm^{-1}; LC–MS: 277 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{14}H_{22}O_4Na$: 277.1415; found: 277.1427.
    2-(2R,3S,6R)-3-hydroxy-6-[(E,6S)-6-hydroxy-1-heptenyl]tetrahydro-2H-2-pyranyl acetic acid (**23**): $[\alpha]_D^{25}$ +48.4 (*c* 0.005 g/mL, $CHCl_3$), ^1H NMR ($CDCl_3$, 500 MHz): δ 5.67–5.52 (m, 1H), 5.39 (dd, *J* = 5.2, 15.6 Hz, 1H), 3.85–3.71 (m, 2H), 3.60–3.53 (m, 1H), 3.36–3.28 (m, 1H), 2.77 (dd, *J* = 3.1, 14.5 Hz, 1H), 2.39–2.33 (m, 1H), 2.15–1.95 (m, 4H), 1.75–1.60 (m, 1H), 1.57–1.34 (m, 5H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); LC–MS: 409 $[M+Na]^+$; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{20}H_{38}O_5NaSi$: 409.5902; found: 409.5893.