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Total synthesis and determination of the absolute configuration of (+)-neoisoprelaurefucin

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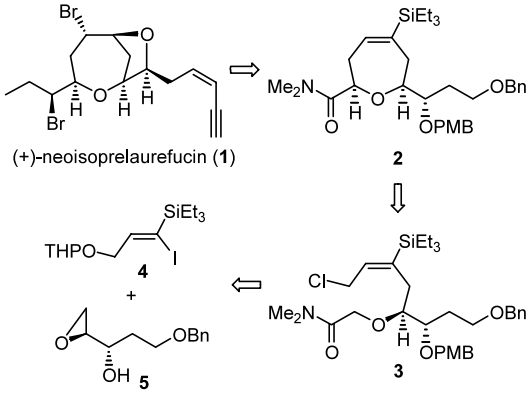
Abstract—The first total synthesis of the seven-membered ring ether marine natural product (+)-neoisoprelaurefucin (**1**) has been achieved employing a regioselective internal alkylation of amide **3**, a novel sequence for removal of the triethylsilyl group from the resulting triethylsilyloxepene **2**, and a bromoetherification of alcohol **16** as key steps. In addition, the absolute stereochemistry of the natural product was assigned.

(+)-Neoisoprelaurefucin (**1**), isolated from *Laurencia nipponica* by Suzuki et al. in 1996, is a seven-membered ring ether marine natural product with a unique 2,7-dioxabicyclo[4.2.1]nonane skeleton.[1] The structure of (+)-neoisoprelaurefucin was proposed on the basis of an extensive NMR spectroscopic analysis and biosynthetic considerations although its absolute stereochemistry was not determined.[1] In this paper, we report the first asymmetric total synthesis of (+)-neoisoprelaurefucin (**1**), which also led to the assignment of its absolute configuration.[2] As shown in our retrosynthetic plan (Scheme 1), we envisaged that the desired triethylsilyloxepene **2** might be secured regioselectively by internal alkylation of (*E*)-allylic chloride **3** using a strategically placed bulky silyl group to inhibit the otherwise favored S_N2' alkylation. Further analysis suggested key alkylation substrate **3** should in turn be readily accessible from vinyl iodide **4** and known epoxy alcohol **5**.[3]

As shown in Scheme 2, protection of alcohol **5** with PMB-Cl (88%), followed by regioselective opening of the resulting epoxide **6** with the vinyl lithium generated from readily available vinyl iodide **4**[4] by treatment with *t*-BuLi, furnished homoallylic alcohol **7** in 71% yield.[5] The key internal alkylation substrate **3** was prepared from alcohol **7** in three straightforward steps in 70% overall yield: (1) *O*-alkylation of alcohol **7** with 2-bromo-*N*,*N*-dimethylacetamide, (2) removal of THP protecting group of **8** under standard acidic conditions, and (3) chlorination of the resulting allylic alcohol **9** with CCl_4 and Ph_3P.[6]

To our delight, the crucial intramolecular alkylation of amide **3** could be effected by treatment with KHMDS in THF at room temperature to furnish a 3:1 mixture of the desired triethylsilyloxepene **2** and tetrahydrofuran derivative **2′**.[7] Furthermore, the regioselectivity could be increased to a 6:1 by using toluene as solvent (78% total yield).[8]



Scheme 1. Retrosynthetic plan for (+)-neoisoprelaurefucin (**1**).

Keywords: internal alkylation; total synthesis; marine natural product; seven-membered ether ring.

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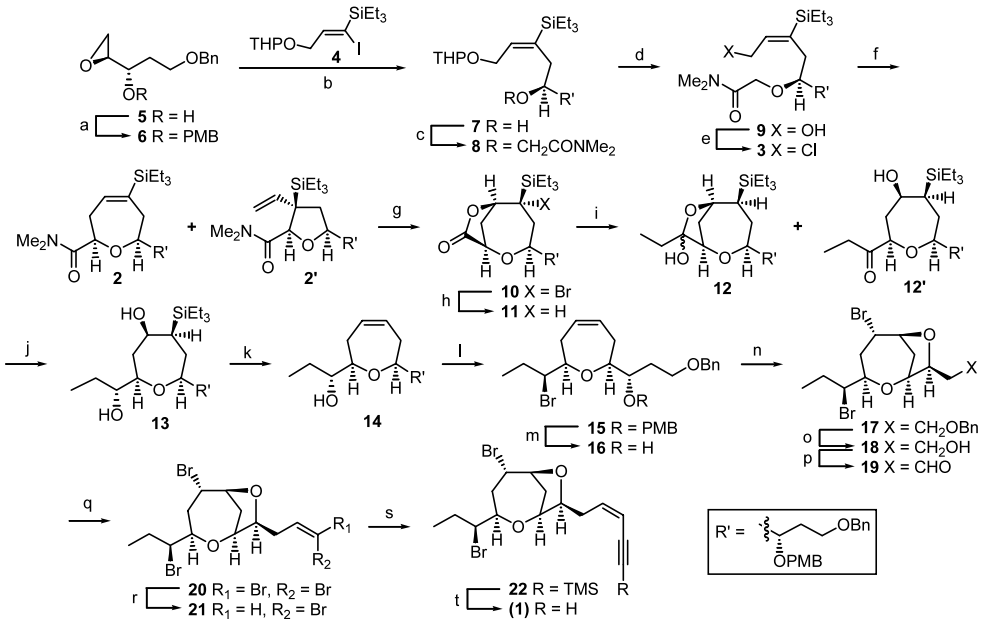

Scheme 2. *Reagents and conditions*: (a) PMBCl, NaH, DMF, 0°C, 2 h, 88%; (b) *n*-BuLi, Et_2O, $BF_3{\cdot}Et_2O$, THF, −78°C, 1 h, 71%; (c) 2-bromo-*N*,*N*-dimethylacetamide, NaH, THF, rt, 24 h, 86%; (d) PTSA, MeOH, rt, 30 min, 94%; (e) Ph_3P, CCl_4, reflux, 20 min, 87%; (f) KHMDS, $PhCH_3$, rt, 30 min, 67%; (g) NBS, CH_3CN, rt, 10 min, 96%; (h) *n*-Bu_3SnH, PhH, reflux, 30 min, 93%; (i) EtMgBr, THF, 0°C, 30 min; (j) L-Selectride®, THF, −78°C, 2 h, 57% (for two steps); (k) *t*-BuOK, THF, 0°C, 1.5 h, 70%; (l) CBr_4, 1-methyl-cyclohexene, *n*-Oct_3P, $PhCH_3$, 70°C, 3 h, 77%; (m) DDQ, CH_2Cl_2/pH 7.4 buffer (10:1), 0°C, 1 h, 99%; (n) NBS, CH_3CN, rt, 10 min, 99%; (o) H_2, Pd/C, EtOH, rt, 2 h, 95%; (p) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min, 87%; (q) CBr_4, Ph_3P, CH_2Cl_2, rt, 1 h, 99%; (r) $Pd(PPh_3)_4$, *n*-Bu_3SnH, $PhCH_3$, rt, 20 min, 59%; (s) $Pd(PPh_3)_4$, Et_2NH, CuI, trimethylsilylacetylene, rt, 3 h, 78% after three cycles; (t) TBAF, THF, 0°C, 20 min, 97%.

We overcame serious difficulties encountered in removal of the triethylsilyl group from triethylsilyloxepene **2** by using a novel five-step sequence leading to key intermediate **14** as follows: (1) bromolactonization[9] of γ,δ-unsaturated amide **2** with NBS (96%), (2) stereoselective debromination of bromolactone **10** with *n*-Bu_3SnH (93%),[7] (3) addition of EtMgBr to γ-lactone **11**, (4) stereoselective L-Selectride® reduction of the resulting mixture of hemiketal **12** and ketone **12′** (3:1) in a Felkin–Ahn sense (57% for two steps),[10] and (5) Peterson-like elimination of *syn*-silyl alcohol **13** by treatment with potassium *t*-butoxide in THF (70%).[7]

With key intermediate **14** in hand, we addressed the remaining task of construction of the 2,7-dioxabicyclo[4.2.1]nonane skeleton and (*Z*)-enyne unit present in (+)-neoisoprelaurefucin (**1**). Bromination of alcohol **14** with inversion of configuration by the procedure of Murai,[10a] removal of the PMB protecting group of **15** under conditions of Yonemitsu,[11] and stereoselective bromoetherification of the resulting unsaturated alcohol **16** by the action of NBS provided the desired bicyclic bromo ether **17** in 76% overall yield for the three steps.[7] Introduction of the (*Z*)-enyne moiety of (**1**) into **17** was accomplished employing Sonogashira methodology as a key step. Thus, hydrogenolysis of the benzyl group of **17** followed by Dess–Martin oxidation[12] of the resulting alcohol **18** gave aldehyde **19** (83% for two steps). Conversion of aldehyde **19** to the corresponding 1,1-dibromoalkene **20** (99%) and subsequent stereoselective Uenishi's debromination[13] produced the requisite (*Z*)-bromoalkene **21** (59%).[14] Finally, Sonogashira coupling[15] of (*Z*)-bromoalkene **21** with ethynyltrimethylsilane (78% after three cycles) and removal of the TMS group of the resulting TMS-enyne **22** with TBAF produced (+)-neoisoprelaurefucin (97%). The spectroscopic data (^1H and ^{13}C NMR, IR) and specific rotation of our synthetic (+)-neoisoprelaurefucin were in good agreement with those reported for the natural product ($[\alpha]_D^{23}$ +17.3 (*c* 0.15. $CHCl_3$); lit.[1] ($[\alpha]_D^{23}$ +17.2 (*c* 1.30. $CHCl_3$)).

In conclusion, we have accomplished the first asymmetric total synthesis of the seven-membered ring ether marine natural product (+)-neoisoprelaurefucin (**1**). The approach features an efficient internal alkylation to form the oxepene skeleton with good regio- and stereocontrol, a novel sequence for removal of a silyl group from a vinylsilane, and a stereoselective bromoetherification step. In addition, the absolute stereochemistry of the natural product was established to be as shown in Scheme 1.

Acknowledgements

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4. Prepared in two steps from known 3-triethylsilylprop-2-yn-1-ol: (1) Red-Al®, Et_2O, then IBr, Et_2O; (2) DHP, PPTS, CH_2Cl_2. (a) Denmark, S. E.; Jones, T. K. *J. Org. Chem*. **1982**, *47*, 4595–4597; (b) Kim, K. D.; Magriotis, P. A. *Tetrahedron Lett*. **1990**, *31*, 6137–6140.
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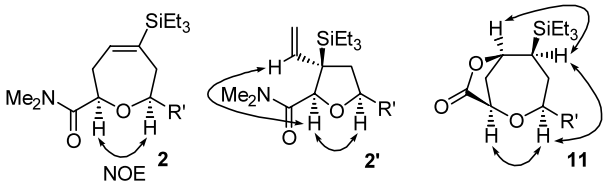
7. All new synthetic compounds gave satisfactory analytical and spectral data. The relative stereochemistry of triethylsilyloxepene **2**, tetrahydrofuran **2′** and lactone **11** were established via two-dimensional NOE experiments.



Selected spectral data for triethylsilyloxepene **2**: $[\alpha]_D^{25}=-32.5$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.37 (m, 5H), 7.21 (d, $J=8.5$ Hz, 2H), 6.86 (d, $J=8.5$ Hz, 2H), 6.23 (td, $J=3.0$, 8.2 Hz, 1H), 4.56 (d, $J=11.1$ Hz, 2H), 4.50 (d, $J=11.9$ Hz, 1H), 4.44 (d, $J=11.9$ Hz, 1H), 4.40 (d, $J=11.1$ Hz, 1H), 4.02 (d, $J=10.3$ Hz, 1H), 3.81 (s, 3H), 3.64–3.67 (m, 1H), 3.60 (dd, $J=5.0$, 7.1 Hz, 2H), 3.40 (dd, $J=4.6$, 9.6 Hz, 1H), 3.02 (s, 3H), 2.93 (s, 3H), 2.79 (ddd, $J=2.1$, 10.6, 14.7 Hz, 1H), 2.52 (dd, $J=8.6$, 16.0 Hz, 1H), 2.44 (d, $J=15.5$ Hz, 1H), 2.34 (dd, $J=9.8$, 15.4 Hz, 1H), 2.03 (dtd, $J=2.6$, 7.5, 15.0 Hz, 1H), 1.71 (tdd, $J=4.9$, 9.9, 14.0 Hz, 1H), 0.94 (t, $J=7.9$ Hz, 9H), 0.60 (q, $J=7.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.1, 141.7, 139.8, 138.5, 130.4, 129.5, 128.2, 127.5, 127.4, 113.6, 79.8, 78.2, 72.6, 72.3, 67.0, 55.1, 37.0, 35.8, 34.8, 32.8, 30.0, 7.4, 2.3; IR (neat) 2951, 1656, 1613, 1513, 1458, 1215, 1250, 1105, 823, 731 cm^{-1}; HRMS (EI) found 567.3387 [M$^+$; calcd for $C_{33}H_{49}NO_5Si$: 567.3380]. For tetrahydrofuran derivative **2′**: $[\alpha]_D^{25}=-79.9$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.37 (m, 5H), 7.24 (d, $J=8.5$ Hz, 2H), 6.84 (d, $J=8.6$ Hz, 2H), 5.79 (dd, $J=10.8$, 17.4 Hz, 1H), 5.04 (d, $J=10.8$ Hz, 2H), 5.00 (d, $J=17.4$ Hz, 1H), 4.93 (s, 1H), 4.70 (d, $J=11.2$ Hz, 1H), 4.41–4.47 (m, 3H), 4.09 (ddd, $J=5.8$, 8.2, 9.7 Hz, 1H), 3.80 (s, 3H), 3.67 (dt, $J=2.9$, 8.5 Hz, 1H), 3.56–3.60 (m, 1H), 3.48–3.52 (m, 1H), 3.21 (s, 3H), 3.00 (s, 3H), 2.29 (dd, $J=10.2$, 11.9 Hz, 1H), 2.08 (dd, $J=5.7$, 12.0 Hz, 1H), 1.76–1.80 (m, 1H), 1.66–1.71 (m, 1H), 0.97 (t, $J=7.9$ Hz, 9H), 0.67 (q, $J=7.9$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 158.9, 143.1, 138.5, 131.5, 129.7, 128.3, 127.8, 127.4, 113.5, 111.1, 83.0, 81.6, 79.4, 72.9, 72.7, 66.9, 55.2, 44.9, 37.8, 35.9, 35.4, 31.9, 8.1, 3.4; IR (neat) 2951, 1656, 1513, 1458, 1401, 1247, 1071, 902, 822, 732 cm^{-1}. For lactone **11**: $[\alpha]_D^{25}=-31.6$ (*c* 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–2.39 (m, 5H), 7.20 (d, $J=8.6$ Hz, 2H), 6.86 (d, $J=8.7$ Hz, 2H), 5.03 (dd, $J=2.4$, 7.5 Hz, 1H), 4.43–4.54 (m, 4H), 4.33 (d, $J=6.8$ Hz, 1H), 4.06 (dd, $J=3.9$, 10.1 Hz, 1H), 3.81 (s, 3H), 3.72 (td, $J=3.5$, 9.7 Hz, 1H), 3.55–3.58 (m, 1H), 2.45 (d, $J=14.7$ Hz, 1H), 2.34 (td, $J=7.3$, 14.6 Hz, 1H), 1.97–2.04 (m, 2H), 1.77–1.83 (m, 2H), 1.64 (tdd, $J=4.8$, 9.5, 14.3 Hz, 1H), 0.99 (t, $J=8.0$ Hz, 9H), 0.67 (q, $J=7.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 159.2, 138.6, 130.4, 129.6, 128.3, 127.7, 127.4, 113.7, 82.2, 77.2, 75.5, 72.7, 72.6, 71.0, 66.9, 55.3, 30.3, 29.4, 39.2, 24.5, 7.6, 3.4; IR (neat) 2954, 1772, 1612, 1513, 1456, 1249, 1107, 948, 740 cm^{-1}. For oxepene **14**: $[\alpha]_D^{25}=-10.4$ (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.35 (m, 5H), 7.21 (d, $J=8.6$ Hz, 2H), 6.85 (d, $J=8.6$ Hz, 2H), 5.75 (t, $J=4.0$ Hz, 2H), 4.42–4.52 (m, 4H), 3.79 (s, 3H), 3.61 (td, $J=4.5$, 7.9 Hz, 1H), 3.50–3.56 (m, 3H), 3.36–3.40 (m, 1H), 3.18 (ddd, $J=1.9$, 6.8, 10.0 Hz, 1H), 2.9 (s, 1H), 2.18–2.38 (m, 4H), 1.96 (dtd, $J=4.3$, 6.9, 14.1 Hz, 1H), 1.78 (tdd, $J=5.5$, 8.0, 13.5 Hz, 1H), 1.53–1.59 (m, 1H), 1.41 (tt, $J=7.5$, 15.0 Hz, 1H), 0.97 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 138.4, 130.4, 129.6, 129.2, 128.6, 128.3, 127.7, 127.5, 113.7, 83.5, 80.9, 78.2, 75.3, 72.9, 72.2, 66.7, 55.2, 33.3, 32.3, 30.4, 26.0, 9.8; IR (neat) 2869, 1612, 1513, 1457, 1248, 1100, 1033, 821, 698 cm^{-1}; HRMS (EI) found 440.2536 [M$^+$; calcd for $C_{27}H_{36}O_5$: 440.2563]. For bicyclic bromo ether **17**: $[\alpha]_D^{25}=0.74$ (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.38 (m, 5H), 4.55 (s, 2H), 4.50 (dd, $J=4.6$, 8.4 Hz, 1H), 4.36 (dd, $J=3.3$, 3.8 Hz, 1H), 4.30 (q, $J=3.3$ Hz, 1H), 4.04–4.10 (m, 2H), 3.94 (dd, $J=3.4$, 9.1 Hz, 1H), 3.60–3.68 (m, 2H), 2.78 (d, $J=15.1$ Hz, 1H), 2.41 (ddd, $J=3.6$, 9.2, 16.1 Hz, 1H), 2.11–2.19 (m, 3H), 2.03–2.07 (m, 1H), 1.82–1.91 (m, 2H), 1.11 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.3, 127.6, 127.5, 83.9, 80.1, 75.7, 72.8, 71.9, 67.3, 62.5, 51.2, 36.2, 30.4, 29.3, 28.5, 12.5; IR (neat) 2929, 2867, 1453, 1365, 1194, 1095, 836, 739, 698, 636 cm^{-1}; HRMS (EI) found 382.1137 [(M$^+$+H)–Br; calcd for $C_{19}H_{27}O_3{}^{79}Br$: 382.1144 or M$^+$–HBr; calcd for $C_{19}H_{25}O_3{}^{81}Br$: 382.1144].
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