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# Absolute Stereochemistry of Aplaminone and Neoaplaminone, Cytotoxic Bromodopamines from a Marine Mollusc: Enantioselective Synthesis of Debromoneoaplaminone

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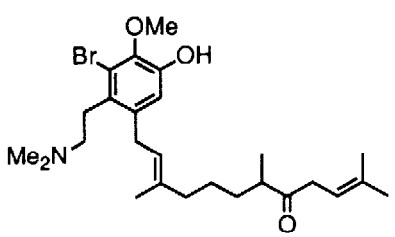
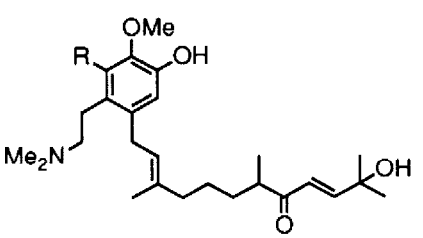
**Abstract:** The absolute stereochemistry of potent cytotoxic bromodopamines, aplaminone and neoaplaminone has been determined by means of enantioselective synthesis of debromoneoaplaminone, a derivative of aplaminone and neoaplaminone.

Aplaminone (**1**) and neoaplaminone (**2**) were isolated from a marine mollusc *Aplysia kurodai* as minute components and were found to exhibit potent cytotoxicity against HeLa-S3 cells ($IC_{50}$: **1** 0.28 μg/mL; **2** $1.6 \times 10^{-7}$ μg/mL).[1] Aplaminone and neoaplaminone were shown to have the novel structures consisting of a brominated dopamine moiety and a sesquiterpenoid part, as depicted in **1** and **2**, respectively. We describe herein the enantioselective synthesis of debromoneoaplaminone (**3**) and determination of the absolute stereochemistry of **1** and **2**.

The synthesis of optically active debromoneoaplaminone (**3**) is shown in Scheme 1. The Evans procedure[2] was utilized for the rational construction of the chiral center in the synthesis of debromoneoaplaminone (**3**). Thus, (–)-imide **4** was converted into alcohol **5**,[2] which was subsequently transformed into chloride **6**.[3]

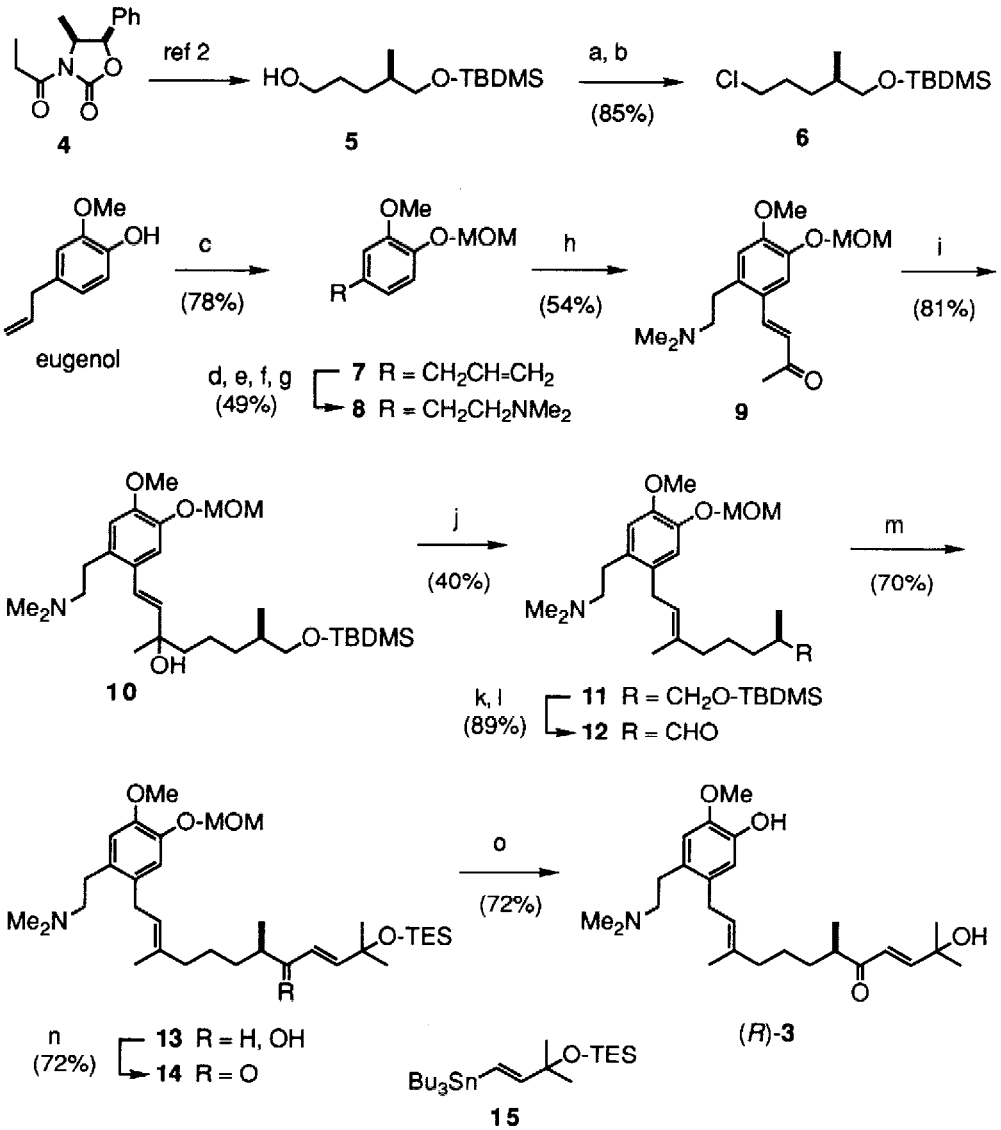



**1**




**2** R = Br
**3** R = H

**Scheme 1.**




Reagents and Conditions: (a) TsCl, Py, 23 °C, 3 h; (b) LiCl, $CaCO_3$, 2-butanone, reflux, 23 h; (c) MOM-Cl, NaH, THF, 23 °C, 3 h; (d) $O_3/O_2$, MeOH, -78 °C, 2 h; $Me_2S$, -78 → 23 °C, 3.5 h; (e) $KMnO_4$, 1 M phosphate buffer (pH 7), *t*-BuOH, 23 °C, 10 min; (f) $Im_2CO$, THF, 50 °C, 1 h; 50% $Me_2NH$, 23 °C, 10 min; (g) $LiAlH_4$, ether, 23 °C, 30 min; (h) $Pd(OAc)_2$, benzene, 23 °C, 86 h; NaCl, acetone–$H_2O$, 23 °C, 4 h; $CH_3COCH{=}CH_2$, $Et_3N$, toluene, reflux, 1 h; (i) **6**, Li (1% Na), ether, -50 → 23 °C, 1.5 h; **9**, THF, -78 °C, 10 min; (j) Na, liquid $NH_3$–THF, -78 °C, 10 min; (k) $Bu_4NF$, THF, 23 °C, 14 h; (l) DMSO, $(COCl)_2$, $CH_2Cl_2$, -65 °C, 15 min; $Et_3N$, -65 → 23 °C, 20 min; (m) **15**, *n*-BuLi, THF, -78 °C, 20 min; -50 °C, 1 h; **12**, -78 °C, 10 min; (n) $MnO_2$, $CH_2Cl_2$, 23 °C, 14 h; (o) AcOH–$H_2O$ (1:7), 60 °C, 20 h.

The aromatic moiety of debromoneoaplaminone (**3**) was prepared from eugenol (Scheme 1). Protection of the hydroxyl group of eugenol gave methoxymethyl ether **7**, the allyl group of which was converted into a 2-(dimethylamino)ethyl group in a four-step sequence, affording amine **8**. *ortho*-Palladation[4] of amine **8** followed by addition of 3-buten-2-one provided enone **9**.

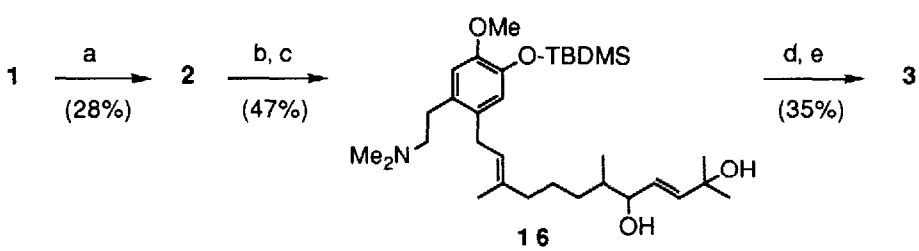
Lithiation of chloride **6** with lithium (–50 °C to room temperature, ether, 1.5 h) followed by addition of enone **9** afforded allyl alcohol **10**.[5] Deoxygenation of allyl alcohol **10** with concomitant migration of the double bond was effected by sodium in liquid $NH_3$–THF to give a mixture of (*E*)-olefin **11** (40%) and the corresponding (*Z*)-olefin (45%), which was separated by HPLC.[6] Deprotection of the silyl ether group of **11** and subsequent Swern oxidation provided aldehyde **12**. Addition of the vinyllithium compound generated from stannane **15**[7] to aldehyde **12** gave allyl alcohol **13**.[5]

Oxidation of allyl alcohol **13** under the Swern conditions or with DMSO–$SO_3$·Py–$Et_3N$ or with imidazolium dichromate afforded enone **14** in low yields owing to the instability of the product **14** under the oxidation conditions, whereas oxidation of **13** with $MnO_2$ gave enone **14** in a moderate yield. Acidic hydrolysis of **14** provided (*R*)-debromoneoaplaminone[8] [(*R*)-**3**] as an oil, $[\alpha]^{25}_{365}$ –42.7° (*c* 0.30, MeOH).

(*S*)-Debromoneoaplaminone [(*S*)-**3**] was also synthesized from the enantiomer of **4** in the same manner as described above: $[\alpha]^{23}_{365}$ +36.4° (*c* 0.25, MeOH).

Since autoxidation of aplaminone (**1**) gave neoaplaminone (**2**) (Scheme 2), the absolute stereochemistry of both compounds is identical. In order to correlate the absolute stereochemistry of aplaminone (**1**) and neoaplaminone (**2**) to that of debromoneoaplaminone (**3**), transformation of natural **2** to debromoneoaplaminone (**3**) was executed as follows (Scheme 2): 1) protection of the phenol group of **2**; 2) $LiAlH_4$ reduction to give allyl alcohol **16**[5]; 3) $MnO_2$ oxidation of **16**; 4) deprotection of the silyl ether group. Natural debromoneoaplaminone (**3**), $[\alpha]^{25}_{365}$ –20° (*c* 0.04, MeOH), thus obtained was identical with synthetic (*R*)-debromoneoaplaminone [(*R*)-**3**] in every respect ($^1H$ NMR, IR, MS, $[\alpha]_{365}$, and TLC) including the sign of the specific rotation.

**Scheme 2.**




Reagents and Conditions: (a) air, neat, -20 °C, 2 months; (b) TBDMS-Cl, imidazole, DMF, 23 °C, 2 h; (c) $LiAlH_4$, THF, 23 °C, 1.5 h; (d) $MnO_2$, $CH_2Cl_2$, 23 °C, 8 h; (e) AcOH–$H_2O$ (2:1), 50 °C, 18 h.

In summary, we have determined the absolute stereochemistry of aplaminone (**1**) and neoaplaminone (**2**) to be *R* by the enantioselective synthesis of debromoneoaplaminone (**3**).

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## References and Notes

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2. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.
3. Satisfactory spectral (IR, $^1$H NMR, and mass spectra) and analytical (microanalyses or high-resolution mass spectra) data were obtained for all new compounds described in this paper.
4. (a) Liang, C. D. *Tetrahedron Lett.* **1986**, *27*, 1971. (b) Holton, R. A.; Davis, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 4175.
5. This compound was obtained as a mixture of diastereomers.
6. Develosil 30–10, hexane–ethyl acetate–methanol–triethylamine (49.5:49:1:0.5), recycles.
7. Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, *113*, 3096.
8. $C_{26}H_{41}NO_4$ [*m/z* 431.3053 ($M^+$)]; IR ($CHCl_3$) 3540, 1685, 1660, 1625, and 1595 $cm^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) δ 6.93 (1H, d, *J* = 15.7 Hz), 6.72 (1H, s), 6.65 (1H, s), 6.42 (1H, d, *J* = 15.7 Hz), 5.70 (1H, br s), 5.20 (1H, t, *J* = 6.9 Hz), 3.85 (3H, s), 3.26 (2H, d, *J* = 6.9 Hz), 2.78—2.62 (3H, m), 2.44 (2H, m), 2.30 (6H, s), 2.01 (2H, t, *J* = 7.5 Hz), 1.67 (3H, s), 1.65 (1H, m), 1.50—1.22 (3H, m), 1.37 (3H, s), 1.36 (3H, s), and 1.08 (3H, d, *J* = 6.9 Hz); EIMS *m/z* 431 ($M^+$, 40%) and 58 (100%).

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