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Total Synthesis of (-)-Dactylyne and (-)-Isodactylyne

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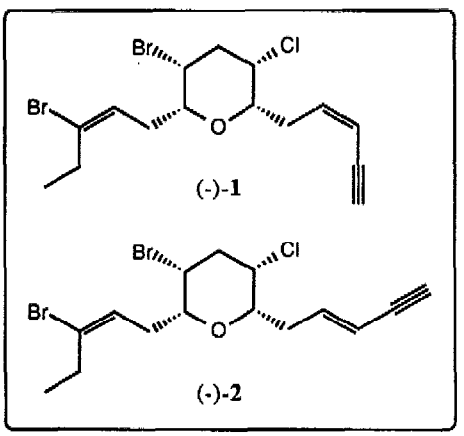
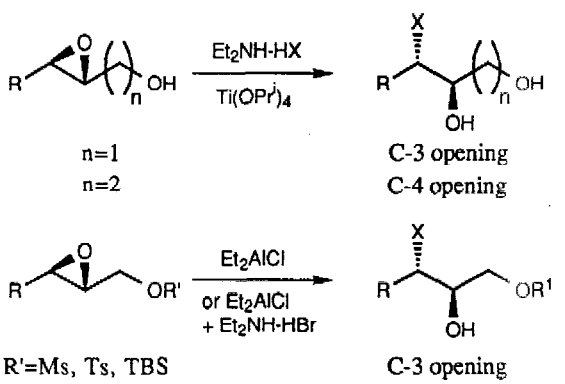
Key words: (-)-Dactylyne; (-)-Isodactylyne; Total synthesis; Epoxy alcohol.

Abstract: The first total synthesis of (-)-dactylyne (**1**) and (-)-isodactylyne (**2**), which are isolated from sea hare, is described via intermediates **3**-**15** and **17**-**18**. Critical steps in the synthesis include a stereoselective construction as well as an intramolecular ring closure of **12**, and the effective double elongation reactions (**15** → **17** and **17** → **18**).

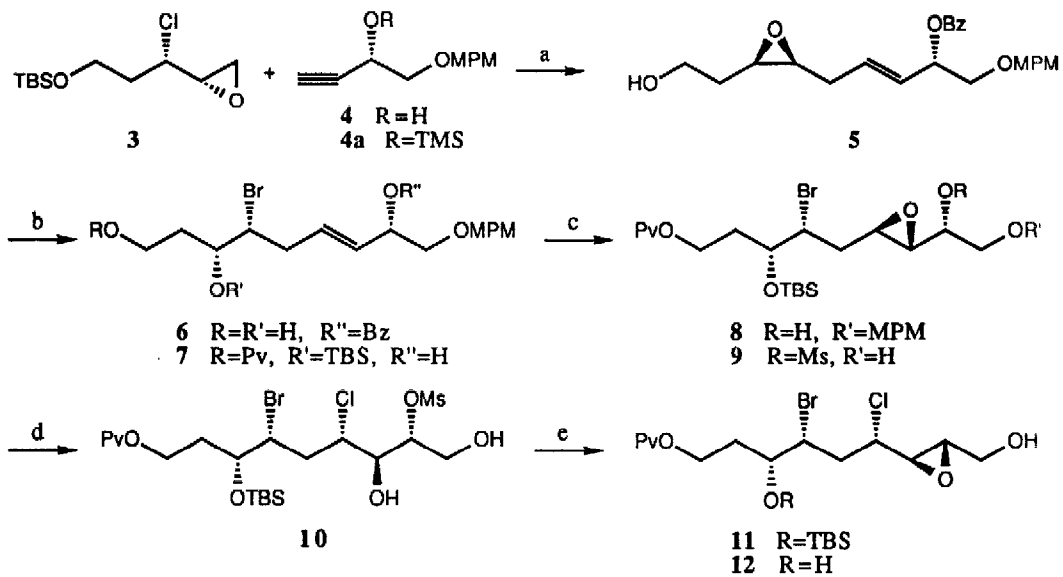
The title compounds, **1** and **2**, have been isolated from the digestive tract of sea hare, *Aplysia dactylomela*.[1] They are characterized structurally by a tetrahydropyran with all α-oriented, four substituents and possess central nervous system depressent activity, as evidenced by the potentiation of pentobarbital hypnosis.[2] In view of the structural features and biological activity, these are attractive synthetic targets. In this communication the first total synthesis of (-)-**1** and (-)-**2** is presented. The synthetic key step constitutes our developed regioselective ring opening reactions of 3,4-epoxy alcohols[3] as well as 2,3-epoxy alcohols[3,4] and their derivatives[4a] with halogeno-nucleophiles (Scheme 1).





Scheme 1. X=Cl or Br

The synthesis started from a combination of the chloro-oxirane (**3**)[4a] and the TMS ether (**4a**) of **4**, prepared from unnatural D-(-)-tartaric acid.[5] According to the Yamaguchi method,[6] compound **4a** was reacted with BuLi, with BF_3-OEt_2, and with **3**, followed by treatment with aq. AcOH to afford a chlorohydrin alcohol in 98% yield. The compound was converted to *cis*-3,4-epoxy alcohol (**5**) in a four step process (K_2CO_3; Red-Al; BzCl; TBAF, 91%). When compound **5** was treated with Et_2NH-HBr and $Ti(OPr^i)_4$ in CH_2Cl_2,[3,4b] the opening reaction of the oxirane proceeded regioselectively to yield a 92:8 separable mixture of C-4-(**6**) and C-3-opening products in 78% combined yield. The bromohydrin (**6**) was smoothly transformed by a usual three-step sequence (PvCl; TBSOTf; K_2CO_3, 86.5%) into the (*E*)-olefin alcohol (**7**), which, on Sharpless oxidation [D-(-)-DIPT],[7] gave rise to β-epoxide (**8**) as a sole product (97%). The corresponding 2,3-epoxy alcohol mesylate (**9**, regarded also as the 3,4-epoxy alcohol system) provided exclusively the desired chlorohydrin (**10**) on reaction with Et_2AlCl in 3:1 CH_2Cl_2-hexane (90-100%).[4a] Compound **10** was smoothly converted to the corresponding 2,3-epoxy alcohol (**11**), with K_2CO_3, which was deprotected to afford the desired hydroxy 2,3-epoxy alcohol (**12**). Overall yield of **12** amounted to 45% from the starting coupling reaction (Scheme 2).



3

4 R=H
4a R=TMS

5

6 R=R'=H, R"=Bz
7 R=Pv, R'=TBS, R"=H

8 R=H, R'=MPM
9 R=Ms, R'=H

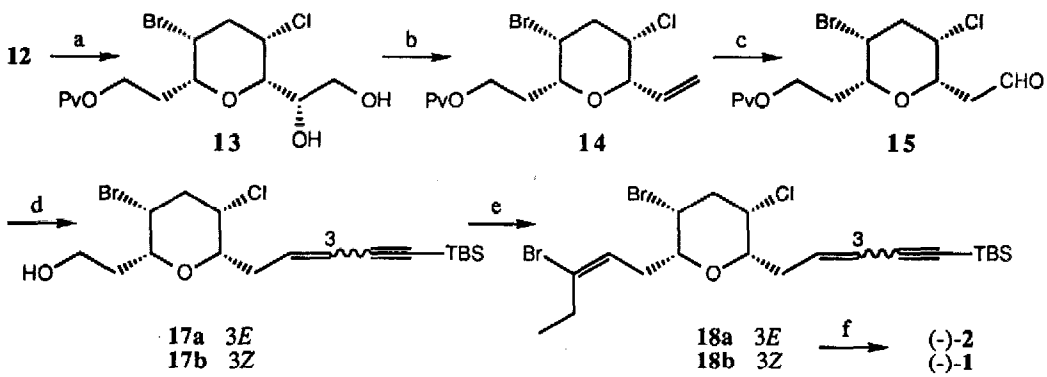
10

11 R=TBS
12 R=H

Reagents and conditions: a) **4a** (1.5 eq), BuLi, THF, -78 °C, 15 min; BF_3-OEt_2, -78 °C, 15 min; **3** (1.0 eq), -78 °C, 1.5 h; 20% aq. AcOH, -78 °C → 20 °C, 2 h, 98%; K_2CO_3, MeOH, 20 °C, 6 h, 98%; Red-Al, ether, 0 °C, 1 h, 98%; BzCl, TEA, DMAP, CH_2Cl_2, 0 °C, 3 h, 98%; TBAF, THF, -10 °C, 3 h, 97%. b) Et_2NH-HBr (4.0 eq), $Ti(OPr^i)_4$ (1.5 eq), CH_2Cl_2, 25 °C, 12 h, 78%; PvCl, Py, CH_2Cl_2, 0 °C, 12 h, 98%; TBSOTf, TEA, DMAP, CH_2Cl_2, -20 °C, 4 h, 97%; K_2CO_3, 95% aq. MeOH, 20 °C, 3 h, 91%. c) D-(-)-DIPT, $Ti(OPr^i)_4$, 4Å-MS, CH_2Cl_2, -20 °C, 3 days, 97%; MsCl, TEA, DMAP, CH_2Cl_2, -40 °C, 1 h, 100%; DDQ, 18:1 CH_2Cl_2-H_2O, 20 °C, 4 h, 94%. d) Et_2AlCl (3.0 eq), 3:1 CH_2Cl_2-hexane, 0 °C, 3 h, 90-100%. e) K_2CO_3, MeOH, 20 °C, 1 h, 96%; TBAF-HF, pH 4.0, THF, 20 °C, 28 h, 100%.

Scheme 2.

We have intended to close **12** intramolecularly with some Lewis acids as one of the most crucial steps. Initial reactions with $Ti(OPr^i)_4$ (0.25 eq) in toluene (with or without 4Å-MS, 100 °C, 3-18 h) led to formation of the desired ring closure product (**13**)[8] in only 10-20% yield. Next, reactions with use of the softer Lewis acid, $Sn(OTf)_2$ (1.0 eq), provided **13** in better yields. However, the by-products were produced as well. Eventually, the reaction with $Zn(OTf)_2$ (1.1 eq) in the presence of the Aldrich septum (Z-10,076-5)[9] (benzene, reflux, 5 h) gave rise to *only* **13** (38% isolated yield and 74% corrected yield based on the recovered starting material). The vicinal diol part of the compound (**13**) was then converted into the vinyl derivative (**14**), via thiocarbonate, by a modification of the Corey procedure ($CSCl_2$; 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine][10] in 80% total yield. Compound **14** was naturally transformed into the aldehyde (**15**) on hydroboration reaction and Swern oxidation. Conversion of **15** into (-)-**1** and (-)-**2** was commenced by introduction of enyne units. Modification of the Corey method ($TBSCH_2C{\equiv}C\text{-}TBS$, BuLi, THF, -78 → 5 °C, 6 h)[11] led to formation of a 1:1 mixture of (3*E*)- and (3*Z*)-enynes in only 19% combined yield. Accordingly, we have devised to prepare a new Horner-Wittig-type reagent [$(CF_3CH_2O)_2P(O)CH_2C{\equiv}CTBS$ (**16**)].[12] Compound **15**, when treated with **16** (1.4 eq), $KN(TMS)_2$ (1.2 eq), and 18-crown-6 (1.4 eq) in THF at -78 °C for 45 min, gave rise to a 62:38 mixture of (3*E*)- and (3*Z*)-enynes in 85% combined yield. The mixture was then derived to separable alcohols (**17a** and **17b**) on DIBAH reduction. Next, the (*E*)-olefin alcohol (**17a**) was oxidized by the Swern method to another aldehyde, which, on reaction with Smithers' reagent[13] and BuLi in a 5:1 mixture of THF and DMSO[14] at -78 °C for 45 min, provided a 83:17 separable mixture of (*E*)-bromo-olefin (**18a**) and its (*Z*)-isomer in 87% yield. Finally, deprotection of **18a** (TBAF-HF, pH 4.0) afforded a colorless oil, $[\alpha]_D^{25}$ -8.2° (c=2.45, $CHCl_3$),[15] which was identified as (-)-isodactylyne (**2**)[1b] in all respects. On the other hand, the (*Z*)-olefin alcohol (**17b**) was transformed into a 82:18 mixture of (*E*)-vinyl bromide (**18b**) and its (*Z*)-isomer in 76% total yield under the same condition as mentioned above. Compound **18b** obtained thus was deprotected similarly to give crystalls, 62.5-63.2 °C



Reagents and conditions: a) $Zn(OTf)_2$ (1.0 eq), benzene, reflux, 5 h, 38% (74%). b) $CSCl_2$, DMAP, 0 °C, 1 h; 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine, toluene, 20 °C, 2 h, 80%. c) 9-BBN, THF, 20 °C, 2 h; 5% NaOH, H_2O_2, 20 °C, 1 h, 96%; Swern oxid., 89%. d) **16** (1.4 eq), $KN(TMS)_2$ (1.2 eq), 18-crown-6 (1.4 eq), THF, -78 °C, 45 min, 85%; DIBAH, CH_2Cl_2, -78 → -40 °C, 1 h, 99%. e) Swern oxid., 100%; $Ph_3P^+CBr_2\text{-}EtBr^-$, BuLi, 5:1 THF-DMSO, -78 °C, 45 min, 87%. f) TBAF-HF, pH 4.0, -5 → 0 °C, 2 h, 79%.

Scheme 3.

(hexane-ether),[16] $[\alpha]_D^{25}$ -37.6° (c=2.10, $CHCl_3$),[17] which was identical with (-)-dactylyne (**1**)[1a] in every respect. The result indicates completion of the first total synthesis of (-)-**1** and (-)-**2** (Scheme 3).

It should be emphasized that the present synthesis involved 25 steps and the overall yields amounted to 9.7% for (-)-**1** and 10.9% for (-)-**2**, respectively, from the initial coupling reaction.

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7. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
8. The structure of **13** was determined from the NOE experiments as well as measurements of vicinal coupling constants in ^1H NMR.
9. Unless the septum was added, the yield of **13** resulted in only 13%.
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11. Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719-722.
12. The reagent (**16**) was prepared as follows: readily available propargyl alcohol tetahydropyranyl ether was converted to 3-t-butyldimethylsilyl-2-propyn-1-ol in a two-step process [(i) BuLi, TBSCl, THF, 20 °C, 2 h; (ii) PTS, MeOH, 20 °C, 1 h] in 90% total yield. The alcohol was reacted with NBS and Me_2S (CH_2Cl_2, 20 °C, 7 h) to yield the corresponding bromo derivative (86%), which gave rise to **16** in 11% yield on reaction with tris(2,2,2-trifluoroethyl) phosphite at 130 °C (neat) for 48 h. **16**: bp 86-87 °C/0.05 mmHg.
13. Smithers, R. H. *J. Org. Chem.* **1978**, *43*, 2833-2838.
14. Unless DMSO was used, the requisite ratio amounted to only 1:1 in only 23% combined yield.
15. Natural sample of (-)-**2**: $[\alpha]_D^{25}$ -8.06° (c=7.97, $CHCl_3$).[1b]
16. Natural sample of (-)-**1**: mp 62.2-63.3 °C (hexane-ether).[1a]
17. Natural sample of (-)-**1**: $[\alpha]_D^{25}$ -36° (c=15.2, $CHCl_3$).[1a]

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