Determination of the Absolute Configurations of Norte's Obtusenynes by Total Syntheses of (12*R*,13*R*)-(-)- and (12*S*,13*R*)-(+)-Obtusenynes

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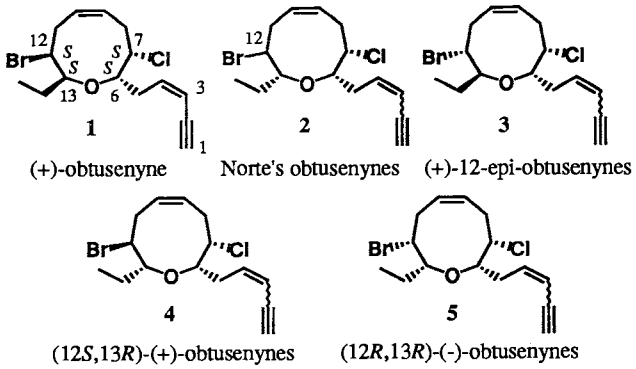
(Received March 10, 1999; CL-990158)

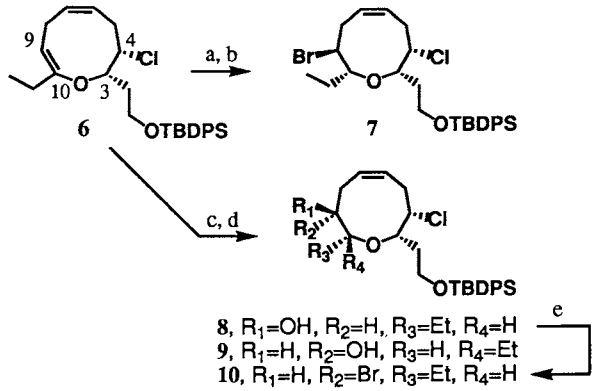
The total syntheses of (12*R*,13*R*)-(-)-obtusenynes and (12*S*,13*R*)-(+)-obtusenynes were achieved. The absolute configurations of the obtusenynes isolated by Norte from *Laurencia pinnatifida* were clarified as the former.

Some 9-membered cyclic ether C-15 acetogenins, represented by (+)-obtusenyne **1**,[1] having halogen atoms as well as ethyl and pentenyl side chains with various stereochemistries on the ether ring have been isolated from red algae (*Laurencia* sp.) and sea hare (*Aplysia* sp.). In 1991, the analogues **2** of **1**, possessing the same structural feature, were isolated as (3*Z*)- and (3*E*)-isomers by Norte *et al.* from *Laurencia pinnatifida* and their structural analyses was performed,[2] {(3*Z*)-**2**, $[\alpha]_D^{25}$ -15.4 (c 0.31, $CHCl_3$); (3*E*)-**2**, $[\alpha]_D^{25}$ -39.7 (c 0.80, $CHCl_3$)}. The absolute cofigurations of C6 and C7 have been confirmed by accordance of the acyclic product provided by chemical degradations of **2** with that derived from natural (3*Z*)-pinnatifidienyne of which the absolute structure was determined by X-ray analysis.[2] The stereochemistry of C13 has also been deduced by comparison of chemical shifts in ^{1}H NMR spectra with those of **1**[1] and its isomer **3**.[3] The respective structures of Norte's obtusenynes have thus been proposed to be **2** except the undefined configuration of C12.[2] We describe herein the establishment of the absolute configurations of Norte's obtusenynes.



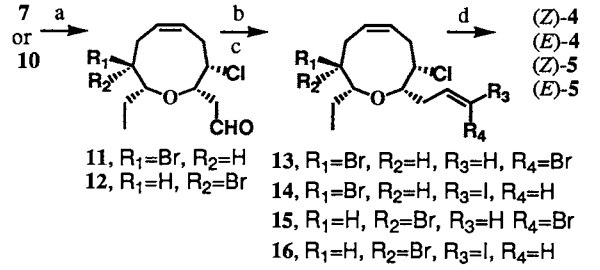
In order to clarify their absolute cofigurations, we aimed to synthesize (12*S*,13*R*)-(+)-obtusenynes **4** and (12*R*,13*R*)-(-)-obtusenynes **5** as the respective diastereoisomers on C12 of the proposed structures **2**. Our synthesis was commenced with bromination of the known cyclic dienyl ether **6**,[4] from which we have recently succeeded in the first total synthesis of (+)-**1**.[4] Compound **6** was brominated in two different ways: i) NBS in MeOH; Et_3SiH, $SnCl_4$;[5] ii) dimethyldioxirane, acetone-Et_2O;[4,6] DIBAH; CBr_4, Oct_3P[7] to give one pair of diastereoisomers at C12, **7**[8] and **10**,[8] respectively (Scheme 1).

The subsequent stereoselective construction of the respective *E* and *Z* conjugated enyne moieties is demonstrated in Scheme 2. Compounds **7** and **10** were converted to aldehydes



Scheme 1. Reagents and conditions: a) NBS, MeOH, 0 °C, 1 h; b) $SnCl_4$, Et_3SiH, CH_2Cl_2, -78 °C, 2.5 h, 60% for 2 steps; c) dimethyldioxirane, acetone-Et_2O (1:1), -78 °C, 10 min, then -10 °C, 20 min, then 2-methyl-2-butene, 0 °C, 10 min, then solvent removal at 0 °C (20 Torr); d) DIBAH, CH_2Cl_2, -78 °C, 10 min, then 0 °C, 14 h, 60% for 2 steps (**8**:**9**=1.5:1); e) CBr_4, Oct_3P, toluene, rt, 30 min, then 75 °C, 22 h, 83%.

11 and **12**, which supplied *Z*-bromo olefins **13** and **15** *via* dibromo olefins by the Uenishi method[9] and *E*-iodo olefins **14** and **16** by the Takai method,[10] respectively, as the coupling precursors. Each halo-olefin was coupled with ethynyltrimethylsilane according to the Sonogashira procedure,[11] accompanied by



Scheme 2. Reagents and conditions: a) **7** → **11**: TBAF, rt, 1 h, 96%; $(COCl)_2$, DMSO, Et_3N, -78 °C, 1 h, 92%; a) **10** → **12**: HF-CH_3CN (3:7), 0 °C, 1 h, then rt, 2 h, 96%; Dess-Martin periodinane, CH_2Cl_2, rt, 2 h, 83%; b) **11** → **13**: CBr_4, PPh_3, CH_2Cl_2, 0 °C, 3.3 h, 98%; Bu_3SnH, $Pd(PPh_3)_4$, CH_2Cl_2, rt, 4 h, 79%; b) **11** → **14**: CHI_3, $CrCl_2$, THF, rt, 21.5 h, 89%; b) **12** → **15**: CBr_4, PPh_3, CH_2Cl_2, 0 °C, 30 min, ~100%; Bu_3SnH, $Pd(PPh_3)_4$, CH_2Cl_2, rt, 5 h, 77%; b) **12** → **16**: CHI_3, $CrCl_2$, THF, 0 °C, 2 h, 82%; d) **13** → (*Z*)-**4**: ethynyltrimethylsilane, $Pd(PPh_3)_4$, CuI, $^iPr_2NH$, THF, rt, 19 h, 61%; TBAF, THF, rt, 30 min, 70% ; d) **14** → (*E*)-**4**: ethynyltrimethylsilane, $Pd(PPh_3)_4$, CuI, $^iPr_2NH$, THF, rt, 3 h, then separation, 54% (*E*:*Z*=84:16); TBAF, THF, rt, 30 min, ~100%; d) **15** → (*Z*)-**5**: ethynyltrimethylsilane, $Pd(PPh_3)_4$, CuI, $^iPr_2NH$, THF, rt, 8 h, ~100%; TBAF-HF (pH 4.5), 0 °C, 30 min, then 33 °C, 14.5 h, 77%; d) **16** → (*E*)-**5**: ethynyltrimethylsilane, $Pd(PPh_3)_4$, CuI, $^iPr_2NH$, THF, rt, 6 h, 35% (*E*:*Z*=97:3); TBAF-HF (pH 4.5), 37 °C, 3 h, 56%.

Table 1. ^{13}C and ^{1}H NMR data of Norte's obtusenynes **2** and synthetic (12*S*,13*R*)-(+)- **4** and (12*R*,13*R*)-(-)-obtusenynes **5**

	^{13}C NMR			^{1}H NMR		
	δ (3*Z*)-**2**[a]	δ (3*Z*)-**4**[b]	δ (3*Z*)-**5**[b]	δ (3*Z*)-**2**[a]	δ (3*Z*)-**4**[c]	δ (3*Z*)-**5**[c]
1	82.8	79.9	82.5	3.15 (d, 2.4)	3.18 (brd, 2.0)	3.16 (brd, 1.5)
3	111.1	111.5	111.3	5.56 (m)	5.57 (brdt, 10.8, 1.1)	5.55 (brd, 9.5)
4	140.1	139.7	140.3	6.03 (dt, 10.6, 7.5)	5.99 (dt, 10.8, 7.4)	6.03 (dtd, 10.8, 7.6, 0.9)
5a	34.7	34.1	34.6	2.84 (m)	2.72 (ddd, 13.5, 9.4, 7.4)	2.77-2.95 (m)
5b					2.84-2.92 (m)	
6	80.9	82.8	81.4	3.58 (ddd, 8.9, 5.9, 3.2)	3.66 (ddd, 9.4, 5.5, 3.1)	3.59 (brddd, 8.8, 5.6, 3.3)
7	61.8	61.9	62.2	4.06 (ddd, 8.9, 5.7, 3.2)	4.06 (ddd, 10.6, 5.9, 3.1)	4.07 (ddd, 10.6, 5.4, 3.3)
8a	33.5	32.1	33.5	2.44 (m)	2.54 (dt, 13.0, 5.9)	2.46 (brddd, 13.0, 5.4, 5.4)
8b					3.01-3.11 (m)	3.18-3.49 (m)
9	128.6	127.9	128.5	5.57 (m)	5.62 (td, 10.9, 5.9)	5.52-5.69 (m)
10	130.0	129.8	130.0	5.60 (m)	5.91 (td, 10.9, 7.7)	5.52-5.69 (m)
11a	34.1	34.1	34.3	2.59 (m)	2.36-2.44 (m)	2.58 (brddd, 13.0, 5.4, 5.4)
11b					3.32-3.41 (m)	3.18-3.49 (m)
12	54.1	55.0	54.7	4.26 (ddd, 8.9, 5.6, 3.2)	4.28 (dt, 9.0, 4.1)	4.27 (ddd, 10.5, 5.4, 3.1)
13	83.4	85.9	84.0	3.22 (m)	3.58 (brdt, 9.0, 4.1)	3.23 (ddd, 8.4, 5.9, 3.1)
14a	27.6	26.0	27.9	1.89 (qd, 7.8, 7.6)	1.83 (dqd, 14.8, 7.4, 4.8)	1.82-1.98 (m)
14b					1.91 (dqd, 14.8, 7.4, 3.6)	
15	9.6	8.1	9.7	0.85 (7.4)	0.97 (t, 7.4)	0.86 (t, 7.5)
	δ (3*E*)-**2**[a]	δ (3*E*)-**4**[b]	δ (3*E*)-**5**[b]	δ (3*E*)-**2**[a]	δ (3*E*)-**4**[c]	δ (3*E*)-**5**[c]
1	77.0	79.9	77.0	2.84 (d, 2.2)	2.85 (brd, 2.2)	2.84 (brd, 2.2)
3	112.3	112.4	112.3	5.64 (m)	5.58-5.67 (m)	5.53-5.68 (m)
4	140.6	140.3	140.6	6.12 (ddd, 15.5, 7.6, 7.6)	6.09 (brdt, 15.9, 7.7)	6.12 (dt, 16.0, 8.0)
5a	37.1	36.8	37.3	2.51 (m)	2.46-2.57 (m)	2.52-2.63 (m)
5b				2.71 (m)	2.65 (brddd, 13.9, 9.0, 9.0)	2.78 (brddd, 9.1, 8.0, 1.2)
6	80.8	82.5	81.9	3.51 (ddd, 8.8, 5.3, 3.2)	3.61 (brddd, 9.8, 5.1, 2.9)	3.51 (brddd, 9.1, 5.6, 3.3)
7	61.6	61.5	61.8	4.08 (ddd, 10.5, 5.7, 3.2)	4.06 (ddd, 10.8, 5.9, 2.9)	4.08 (brddd, 10.5, 5.6, 3.3)
8a	33.4	31.8	33.4	2.45 (m)	2.36-2.44 (m)	2.41-2.52 (m)
8b					3.29-3.40 (m)	3.14-3.29 (m)
9	128.5	127.9	128.5	5.59 (m)	5.58-5.67 (m)	5.53-5.68 (m)
10	130.1	129.9	130.0	5.61 (m)	5.91 (td, 10.6, 5.5)	5.53-5.68 (m)
11a	34.2	34.0	34.2	2.57 (m)	2.46-2.57 (m)	2.52-2.63 (m)
11b					3.00-3.10 (m)	3.30-3.46 (m)
12	54.2	55.0	54.4	4.21 (ddd, 8.8, 5.5, 3.3)	4.27 (brddd, 8.7, 3.9, 3.9)	4.25 (ddd, 10.4, 5.5, 3.5)
13	83.3	85.8	83.5	3.20 (ddd, 8.8, 5.3, 3.3)	3.58 (brddd, 8.7, 4.6, 4.6)	3.20 (brddd, 9.2, 5.5, 3.5)
14a	27.7	26.0	27.9	1.88 (m)	1.74 (dqd, 14.9, 7.4, 4.6)	1.78-1.83 (m)
14b					1.89 (dqd, 14.9, 7.4, 3.9)	1.84-1.91 (m)
15	9.7	8.1	9.7	0.85 (t, 7.5)	0.94 (t, 7.4)	0.86 (t, 7.4)

a) Reported by Norte's group in ref. 2. b) Measured in $CDCl_3$ at 75 MHz. c) Measured in $CDCl_3$ at 300 MHz.

detachment of the TMS groups,[12] to provide stereoselectively each isomer having 3*E*- and 3*Z*-enyne moieties, (3*Z*,12*S*, 13*R*)-(+)-obtusenyne {(3*Z*)-**4**, $[\alpha]_D^{24}$ +153 (c 0.11, $CHCl_3$)} and (3*E*,12*S*,13*R*)-(+)-obtusenyne {(3*E*)-**4**, $[\alpha]_D^{22}$ +52.3 (c 0.10, $CHCl_3$)}, (3*Z*,12*R*,13*R*)-(-)-obtusenyne {(3*Z*)-**5**, $[\alpha]_D^{24}$ -16.7 (c 0.54, $CHCl_3$)}, and (3*E*,12*R*,13*R*)-(-)-obtusenyne {(3*E*)-**5**, $[\alpha]_D^{22}$ -41.3 (c 0.08, $CHCl_3$)}. Thus, we could synthesize the possible four isomers of Norte's obtusenynes **2**, including two pairs of diastereoisomers on C12 and geometrical isomers on C3.

We compared the optical rotations and ^{13}C, and ^{1}H NMR data reported for natural Norte's obtusenynes **2** with those of synthetic **4** and **5** as revealed in Table 1 and found out that the optical rotation values as well as the chemical shifts and coupling patterns in their NMR spectra of (3*Z*)-**5** and (3*E*)-**5** were coincident well with those of naturals (3*Z*)-**2** and (3*E*)-**2**, respectively, while the respective data of (3*Z*)-**4** and (3*E*)-**4** had several differences from those of the naturals, especially in the left sides of the ether rings. Accordingly, the absolute stereochemistries of Norte's obtusenynes[2] were able to be determined unambiguously as (3*Z*)-**5** and (3*E*)-**5** including *R* configurations at C12, respectively.

This work was supported by Grants-in-Aid for Scientific Research (No. 08245103, No. 10308027, A.M.) from the Ministry of Education, Science, Sports, and Culture of Japan.

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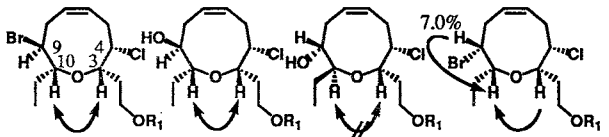
8 The stereochemistries of **7**, **8**, **9**, and **10** were predicted with the respective NOE experiments and their requisite coupling constants ($J_{9\text{-}10}$).



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