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Chabrolols A, B and C, three new norditerpenes from the soft coral *Nephthea chabroli*

Wei-Han Zhang,[a] Ian D. Williams[a] and Chun-Tao Che[a,b,*]

[a]*Department of Chemistry, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong*
[b]*School of Chinese Medicine, the Chinese University of Hong Kong, Shatin, Hong Kong*

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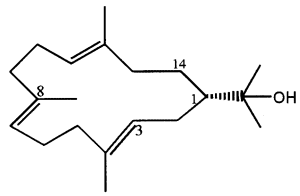
Abstract—Three new norditerpenes, chabrolols A–C, were isolated along with three cembrane diterpenes from the soft coral *Nephthea chabroli* collected from the South China Sea. Their structures were determined on the basis of spectral data and confirmed by X-ray crystallographic analysis. © 2001 Elsevier Science Ltd. All rights reserved.

Soft corals are a rich source of terpenoids with diverse chemical structures and interesting biological activities.[1] Prior investigations have shown that members of the *Nephthea* genus (family Acyonaceae, sub-family Nephtheidae) produce sesquiterpenes,[2] diterpenes[3] and polyhydroxylated steroids.[4] Chemical studies on *N. chabroli*



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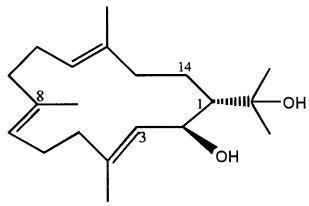

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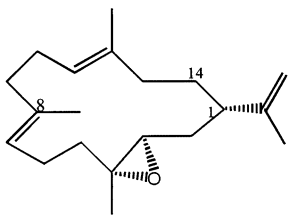

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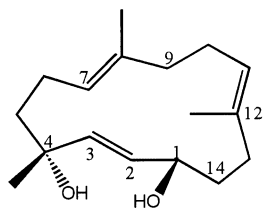

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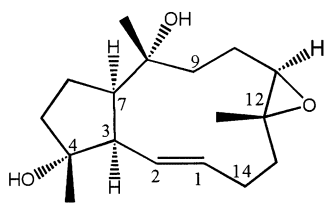

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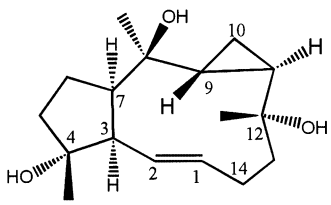

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Keywords: norditerpene; chabrolol; marine natural product; *Nephthea*.

* Corresponding author. Tel.: (852) 2609-8130; fax: (852) 2603-7203; e-mail: chect@cuhk.edu.hk

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have resulted in the identification of a tetraprenyl benzoquinone derivative,[5] meso-1,3-diphenyl-1,3-propanediol,[6] (1*S*)-acetoxygermacra-3*Z*,10(15)-diene, (1*S*)-acetoxygermacra-3*Z*,5*E*,10(15)-triene, (1*S*,4*R*,5*S*)-guia-6,9-dien-4-ol, (1*S*,5*R*,6*R*)-guia-3,10(15)-dien-7,11-epoxy-6β-acetate, nephthenols A and B,[7] hydroxycolorenone, methoxycolorenone,[8] 24-methylcholesta-5,24(28)-diene-1α,3β,19-triol and 24-methylcholesta-5,24(28)-diene-3β,7β,9α,19-tetraol.[9] We now report the isolation and structural determination of six terpenoids (**1**–**6**) from a sample of *N. chabroli* collected from the South China Sea.

An EtOH extract of the soft coral was partitioned between aqueous MeOH and $CHCl_3$. The $CHCl_3$ soluble fraction, after passing through a bed of silica gel by vacuum-liquid chromatography, was separated by repeated chromatography on silica gel, Sephadex LH-20 and RP-18 silica gel to afford three known compounds (**1**–**3**). Their structures were determined as nephthenol (**1**),[10] 2-hydroxynephthenol (**2**),[11] and (7*E*,11*E*)-3,4-epoxycembra-7,11,15-triene (**3**).[12] During the course of investigation, three new compounds (**4**–**6**) were also isolated, which we named chabrolol A, B, and C, respectively.

Table 1. ^{13}C NMR spectral data of compounds **4**–**6**[a]

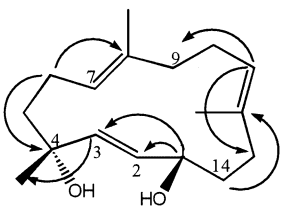
Position	4	5	6
1	71.9 d	131.5 d	132.3 d
2	127.5 d	130.8 d	132.4 d
3	140.0 d	58.8 d	59.6 d
4	73.0 s	81.6 s	82.8 s
5	43.3 t	38.4 t	38.8 t
6	22.9 t	23.3 t	23.9 t
7	124.8 d	53.8 d	57.2 d
8	132.6 s	73.5 s	74.9 s
9	35.0 t	25.1 t	26.3 t
10	23.4t	38.1 t	8.6 t
11	127.3 d	64.7 d	32.9 t
12	132.8 s	59.2 s	75.4 s
13	38.6 t	30.3 t	45.6 t
14	32.3 t	32.9 t	31.5 t
15	28.4 q	26.1 q	26.9 q
16	14.7 q	31.5 q	25.5 q
17	14.7 q	16.0 q	21.6 q

[a] Spectra were recorded in $CDCl_3$ on 100 MHz NMR for carbon, using TMS as internal standard

Chabrolol A (**4**)[13] was obtained as colorless needles. The EIMS results (M^+ at m/z 264) together with the ^{13}CNMR data (Table 1) were consistent with a molecular formula of $C_{17}H_{28}O_2$. The functional groups present in the molecule included two hydroxyl groups (IR, ν_{max} 3300 cm^{-1}; δ_C 71.9, 73.0) and three tertiary methyls (δ_C 14.7, 14.8, 28.4; δ_H 1.32, 1.59, 1.62). The ^{13}C NMR spectrum displayed six olefinic carbon signals for two trisubstituted and disubstituted double bonds. These spectroscopic data are reminiscent of 14-membered carbocyclic cembrane diterpenes.[14]

The locations of the double bonds were determined from HMBC long-range coupling results (Fig. 1). Thus, the disubstituted olefinic carbons at δ 127.5 and 140.0 displayed coupling with H-1 (δ 3.96), while the signal at δ 140.0 showed further coupling to the C-4 methyl protons (δ 1.32). This information led to the assignment of a double bond between the C-2/C-3 positions. The HMBC data also provided evidence for the determination of unsaturation at C-7/C-8 and C-11/C-12 (Fig. 1).

Chabrolol A is therefore a norditerpene of the cembrane-type with the loss of the isopropyl side-chain. The first natural norditerpene possessing a 4,8,12-trimethyl-2,7,11-cyclotetradecatriene ring system, the structure of chabrolol A was confirmed by X-ray crystallographic analysis,[15] and shows a 14-membered ring



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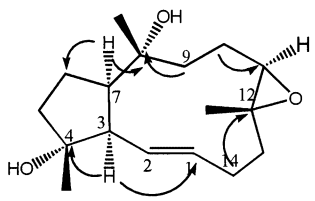

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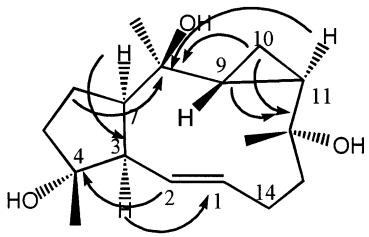

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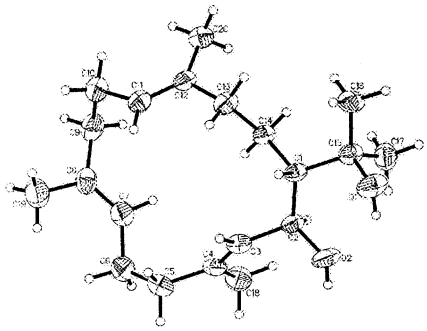
Figure 1. Key HMBC correlations of **4**, **5** and **6**.

with three exocyclic methyl groups and double bonds at the 2, 7 and 11 positions (Fig. 2).

Chabrolol B (**5**)[16] was found to have a molecular formula $C_{17}H_{28}O_3$ on the basis of positive FABMS [m/z 281 (M^+)] and ^{13}C NMR data. The IR spectrum contained absorption bands at ν_{max} 3450 cm^{-1} (hydroxyl) and ν_{max}1650 cm^{-1} (unsaturation). The ^{13}C and ^1H NMR spectra (Tables 1 and 2) displayed signals for three tertiary methyl groups, a disubstituted double bond [δ_H 5.32 (1H, m, H-1) and 5.18 (1H, dd, $J=15.0$, 4.5 Hz, H-2), δ_C 131.5, 130.8], two oxymethines (δ_C 81.6, 73.5), and a pair of carbons bearing an epoxy group (δ 64.7 d, 59.2 s). From this information, it



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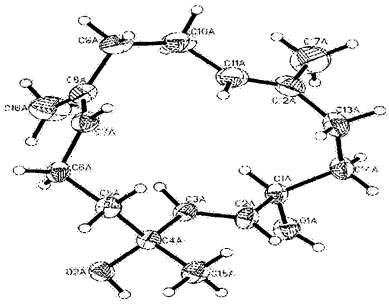

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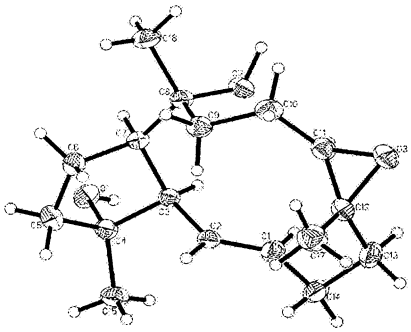

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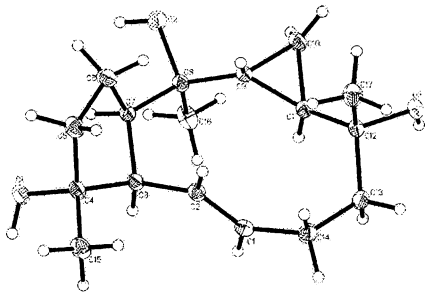

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Figure 2. ORTEP views of **2**, **4**, **5** and **6**.

Table 2. ^1H NMR spectral data of compounds **4–6**[a]

Position	4	5	6
1	3.96 m	5.32 m	5.38 m
2	5.25 (dd, $J=8$, 15.1 Hz)	5.18 (dd, $J=15.0$, 4.5 Hz)	5.17 (dd, $J=5.1$, 10.3 Hz)
3	5.87 (d, $J=15.1$ Hz)	2.60 m	2.27 (dd, $J=6$, 12 Hz)
4	–	–	–
5	1.85 m, 1.92 m	1.82 m	1.77 m, 1.86 m
6	2.12 m	1.53 m, 1.81 m	1.85 m
7	5.00 brs	2.81 m	2.80 m
8	–	–	–
9	2.02 m, 2.10 m	1.24 m, 2.20 m	1.11 m
10	2.02m	1.08 m, 2.07 m	0.63 m
11	5.18 (t, $J=7.2$ Hz)	3.25 (dd, $J=4.4$, 9.8 Hz)	0.98 m
12	–	–	–
13	2.05 m	1.98 m, 2.38 m	1.76 m
14	1.62 m, 1.83 m	1.41 m, 2.04 m	2.05 m, 2.22 m
15	1.32 s	1.22 s	1.15 s
16	1.59 s	1.22 s	0.90 s
17	1.61 s	1.28 s	0.84 s

[a] Spectra were recorded in $CDCl_3$ on 400 MHz NMR for ^1H, using TMS as internal standard.

followed that the compound is bicyclic in order to account for the required degrees of unsaturation. Indeed, the single crystal structure of chabrolol B (Fig. 2)[17] revealed a five-membered ring fused to an 11-membered ring, corresponding to a closure between C-3 and C-7 of a cembrane structure. The presence of the epoxy group was confirmed by bond lengths [O(3)–C(11) = 1.458(2), O(3)–C(12) = 1.467 (2), C(11)–C(12) = 1.468(2) Å]. The COSY and HMBC (Fig. 1) experiments provided coupling information completing the chemical shift assignments (Tables 1 and 2).

Chabrolol C (**6**)[18] was purified as colorless crystals from $CH_3OH/CHCl_3$. The molecular formula $C_{17}H_{28}O_3$ was deduced from DEPT spectra and EIMS [m/z 280 (M^+)]. The ^{13}C and ^1H NMR spectra (Tables 1 and 2) suggested the presence of a *trans* disubstituted double bond [δ_C 132.4, 132.3, δ_H 5.38 m, 5.17 (1H, dd, J = 15.1, 10.3 Hz)] and three oxymethine groups (δ_C 82.8, 74.9, 75.4). A comparison of the NMR spectral data of compound **6** with those of chabrolol B suggested that the two molecules share similar structures. The major difference between the two appeared to be the presence of a cyclopropyl group (δ_C 8.3 t, δ_H 0.63 m) in **6**, instead of an epoxy function in chabrolol B. In the HMBC spectrum, the signal for C-8 (δ_C 74.9) displayed coupling to both protons at δ_H 0.63 (H-10) and 0.98 (H-11), inferring bonding between C-9 and C-11 (Fig. 1). In addition, H-9 (δ_H 1.11) and H-10 (δ_H 0.63) showed long-range coupling with C-12 (δ_C 75.4), confirming the presence of a hydroxyl group on C-12.

The structure of chabrolol C was confirmed by X-ray crystallographic analysis (Fig. 2),[19] which clearly showed the presence of the same fused bicylic system present in **5** as well as the cyclopropyl function [C(9)–C(10) = 1.513(2), C(10)–C(11) = 1.506(2), C(9)–C(11) = 1.517 (2) Å].

Surprisingly, despite the large optical rotation values recorded for compounds **4**–**6**, their crystal structures were found to be centrosymmetric with triclinic space group $P1$. This is consistent with each natural product existing as an intimate mixture of enantiomers, though not with a 50:50 racemic ratio. Further investigation of the relative enantiomeric ratios for each compound by use of chiral separation methods is warranted.

During the course of investigation, the single crystal X-ray structure of 2-hydroxynephenol (**2**) was also determined (Fig. 2).[20] The result confirmed the *anti* orientation between the isopropanol group at C-1 and the hydroxyl at C-2.

Acknowledgements

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References

1. Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155–189.
2. Bowden, B. F.; Coll, J. C.; Mitchell, S. J. *Aust. J. Chem.* **1980**, *33*, 1833–1989.
3. Blackman, A. J.; Bowden, B. F.; Coll, J. C.; Frick, B.; Mahendran, M.; Mitchell, S. J. *Aust. J. Chem.* **1982**, *35*, 1873–1880.
4. Wang, G.; Li, F.; Zeng, L.; Ma, L.; Tu, G. *Chem. J. Chin. Univ.* **1992**, *13*, 623–627.
5. Bowden, B. F.; Coll, J. C. *Aust. J. Chem.* **1981**, *34*, 2677–2681.
6. Ray, A. K.; Datta, P. K.; Das, T.; Bhattacharyya, P.; Barua, A. K. *J. Nat. Prod.* **1991**, *54*, 854–855.
7. Anjaneyulu, A. S. R.; Prakash, C. V. S. *Indian J. Chem.* **1995**, *34B*, 32–39.
8. Handayani, D.; Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Ofwegen, L. V.; Kunzmann, A. K. *J. Nat. Prod.* **1997**, *60*, 716–718.
9. Rao, M. R.; Venkatesham, U.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 1584–1585.
10. Carmely, S. *J. Org. Chem.* **1981**, *46*, 4279–4281.
11. Tursch, B.; Braekman, J. C.; Daloze, D. *Bull. Soc. Chim. Belg.* **1975**, *84*, 767.
12. Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Kazlauskas, R. *Aust. J. Chem.* **1981**, *34*, 1551–1556.
13. Chabrolol A (**4**): colorless needle (hexane); mp 124–125°; $[\alpha]_D^{25} = +109$ (c 1.48, $CHCl_3$); IR (film) ν_{max} 3330, 2980, 1640 cm^{-1}; EIMS m/z (rel. int.): 264 (4), 246 (38), 229 (35), 213 (18), 203 (20), 188 (25), 175 (30), 163 (40), 147 (42), 138 (55), 109 (100).
14. Coll, J. *Chem. Rev.* **1992**, *92*, 613–631.
15. X-ray intensity data were collected at 295 K with a Bruker P4-RA diffractometer, Mo–Kα radiation. Crystal data for **4**: $C_{17}H_{29}O_{2.5}$, MW 273.4; triclinic; space group $P\bar{1}$, a = 9.609 (3), b = 11.328 (5), c = 17.553 (6) Å, α = 75.07 (3), β = 75.62 (3), γ = 70.14 (4)°; V = 1709.0 (11) Å^3, Z = 4, D_{calc} = 1.063 Mg m^{-3}; 2θ = 57°. For 7704 data and 352 parameters, the structure refined to $R_1 = 0.0604$ [$I \geq 2\sigma(I)$, $wR_2 = 0.1544$ (all data)]. The supplementary material has been deposited at the Cambridge Crystallographic Data Center (CCDC 146812).
16. Compound (**5**): colorless crystal ($CHCl_3$); mp 224–225°; $[\alpha]_D^{25} = +23.5$ (c 0.047, $CHCl_3$); IR (film) ν_{max} 3446, 2968, 1654, 1376, 1066 cm^{-1}; EIMS m/z (rel. int.): 280 (3), 262 (8), 244 (11), 187 (14), 161 (32), 147 (45), 121 (70), 107 (80), 95 (100), 85 (84).
17. Crystal data for **5**: $C_{17}H_{28}O_3$, MW 280.39; triclinic; space group $P\bar{1}$, a = 8.186 (1), b = 9.654 (1), c = 10.662 (1) Å, α = 82.67 (10), β = 82.35 (2), γ = 67.98 (2)°; V = 771.41 (14) Å^3, Z = 2, D_{calc} = 1.207 Mg m^{-3}. 2θ = 55°. For 3480 data and 181 parameters, the structure refined to $R_1 = 0.0445$ [$I \geq 2\sigma(I)$, $wR_2 = 0.1342$ (all data)]. The supplementary material has been deposited at the Cambridge Crystallographic Data Center (CCDC 146809).
18. Compound (**6**): colorless crystal ($CHCl_3/CH_3OH$), mp 195–196°; $[\alpha]_D^{25} = -278.2$ (c 0.052, CH_3OH); IR (film) ν_{max} 3440, 2970, 1638, 1380, 1080 cm^{-1}; EIMS m/z (rel. int.):

280 (1), 262 (4), 237 (8), 226 (32), 195 (40), 181 (56), 165 (96), 131 (100).

19. Crystal data for **6**: $C_{17}H_{30}O_4$, MW298.41; triclinic; space group $P\bar{1}$, $a=6.5350$ (10), $b=10.3370$ (10), $c=12.679$ (2) Å, $\alpha=84.23$ (10), $\beta=76.58$ (2), $\gamma=73.28$ (2)°; $V=797.4$ (2) Å^3, $Z=2$, $D_{calc}=1.243$ Mg m^{-3}, $2\theta=55°$. For 3608 data and 192 parameters, the structure refined to $R_1=0.043$ [$I\geq 2\sigma(I)$, $wR_2=0.1334$ (all data)]. The supplementary material has been deposited at the Cambridge Crystallographic Data Center (CCDC 146810).
20. Crystal data for **2**: $C_{20}H_{34}O_2$, MW 306.47; orthorhombic; space group $P2_12_12_1$, $a=9.836$ (1), $b=9.835$ (2), $c=22.334$ (1) Å, $\alpha=90$, $\beta=90$, $\gamma=90°$; $V=1962.8(3)$ Å^3, $Z=4$, $D_{calc}=1.037$ Mg m^{-3}, $2\theta=59.5°$. For 3135 data and 199 parameters, the structure refined to $R_1=0.0495$ [$I\geq 2\sigma(I)$, $wR_2=0.1235$ (all data)]. The supplementary material has been deposited at the Cambridge Crystallographic Data Center (CCDC 146811).