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NEODOLABELLINE, A METHYL MIGRATED DOLABELLANE-TYPE DITERPENE FROM THE OKINAWAN SOFT CORAL *CLAVULARIA KOELLIKERI*

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Summary: A new diterpene named neodolabelline (5), having a methyl migrated dolabellane-type skeleton, was isolated from the stoloniferan soft coral *Clavularia koellikeri*, together with clavukerins (trinor-sesquiterpenes) and bicyclogermacrene, and the absolute configuration was determined.

In the course of chemical studies on the constituents of Okinawan marine organisms,[1)] we isolated three new trinor-sesquiterpenes named clavukerins A (1), B (2), and C (3) together with bicyclogermacrene (4) from the stolonifer *Clavularia koellikeri* and elucidated their absolute configurations.[2)] In a continuing study of the same soft coral (collected in July 1983, at Kohamajima, Okinawa Prefecture), we isolated a new diterpene named neodolabelline (5), which possessed a methyl migrated dolabellane-type skeleton, and elucidated the absolute configuration as described in this communication.

An acetone extract of the fresh soft coral was partitioned into an AcOEt-water mixture and the AcOEt soluble portion was repeatedly chromatographed on SiO_2 to furnish neodolabelline (5) (7.5% from the AcOEt extract), clavukerins, and bicyclogermacrene.[3)] The IR spectrum of neodolabelline (5), a colorless amorphous solid, $C_{20}H_{30}O_4$,[4)] $[\alpha]^{19}_D$ +53° ($CHCl_3$), showed hydroxyl and carbonyl absorption bands [3595, 3410 (br), 1710 cm^{-1}], while the ^{13}C NMR spectrum (22.5 MHz, d_6-DMSO), showed signals due to one carbonyl carbon [δc 208.3 (s), C-9], two olefinic carbons [147.7 (s), C-1; 124.4 (d), C-14], five carbons having an oxygen function [77.0 (s), C-8; 77.0 (d), C-3; 66.0 (d), C-7; 58.6 (s), C-4; 58.2 (d), C-5], four methylene carbons [38.6 (t), C-10; 34.1, 25.0, 23.4 (all t), C-2, 6, 13], two methine carbons [47.8 (d), C-12; 28.9 (d), C-18], one quaternary carbon [52.6 (s), C-11], five methyl carbons [22.8, 22.3, 21.6, 20.7, 15.9 (all q)]. The ^1H NMR spectrum (500 MHz)[5)] of 5 showed signals assignable to two *sec*.methyls [δ 1.04, 0.90 (both 3H, d, J=6.5, $18\text{-}(CH_3)_2$], three *tert*. methyls [1.26, 0.94, 0.85 (each 3H, s, 4, 8, $11\text{-}CH_3$)], one olefinic proton [5.41 (1H, br s, 14-H)], three protons geminal each to an oxygen function [3.82 (1H, dd, J=11.5, 3.5, 3-H), 3.29 (1H, br s, 5-H), 3.97 (1H, d, J=10.5, 7-H)] and the decoupling experiments in detail revealed that 5 was a tetracyclic diterpene.

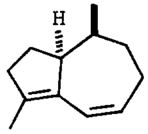
Deuteration ($NaOCH_3$-CH_3OD) of neodolabelline (5) resulted in the loss of signals due to 10-H_2 and C-10 (^1H, ^{13}C NMR), and acetylation of 5 provided the monoacetate (6), $C_{22}H_{32}O_5$ (δ 2.03, 3H, s). The comparison of ^{13}C NMR data for 5 and 6 led us to presume the presence of an α-ketol moiety [■-CH_2-CO-C(OH)(CH_3)-] in 5. $NaBH_4$ reduction of 5 yielded a *trans*-diol (7)(45%), $C_{20}H_{32}O_4$ (δ 3.94, 1H, br s, 9-H) and a *cis*-diol (8)(15%), $C_{20}H_{32}O_4$ (3.95, 1H, d, J=9.0, 9-H). Upon irradiation of the 8-CH_3 signal of 8, 7% NOE was observed on the 9-H signal. $NaIO_4$ oxidation of 7 and 8 afforded quantitatively an identical keto-aldehyde (9), $C_{20}H_{30}O_4$ (δ 9.68, 1H, dd, J=4.0, 2.0, 9-H; 2.14, 3H, s, 8-CH_3). $NaBH_4$ reduction followed by acetylation of 9 yielded a pair of epimeric diacetates: 10, $C_{24}H_{38}O_6$ [δ 3.50 (1H, ddd, J=10.5, 6.0, 2.5, 7-H), 4.77 (1H, dq, J=6.0, 6.0, 8-H), 4.13 (1H, ddd, J=10.5, 10.0, 6.5, 9-Ha), 3.89 (1H, ddd, J=10.5, 10.5, 5.0, 9-Hb), 2.04, 2.03 (both 3H, s, 8, 9-OAc)], and 8-epimer(11), $C_{24}H_{38}O_6$. Thus, the partial structure of 5 from C-6 to C-10 [▨-CH_2-CO-C(OH)(CH_3)-CH(O-)-CH_2-] was elucidated.

Treatment of neodolabelline (5) with 47% aq. HBr cleaved the 4,5-epoxide ring to furnish two bromohydrins: 12, $C_{20}H_{31}O_4Br$ [δ 4.64 (1H, dd, J=11.5, 4.5, 5-H), 2.20 (1H, br dd, J=12.5, 4.5, 6α-H), 1.75 (1H, m, 6β-H), 1.29 (3H, s, 4-CH_3)], and 13, $C_{20}H_{31}O_4Br$ [δ 4.11 (1H, br s, 5-H), 2.09 (1H, dd, J=13.0, 11.5, 6α-H), 1.61 (1H, dd-like, J=13.0, 2.0, 6β-H), 1.78 (3H, s, 4-CH_3)]. Thus, the elucidated partial structure of 5 was extended from C-4 to C-10.

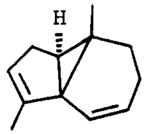
NBS treatment with irradiation[6)] of neodolabelline (5) in 90% aq. dioxane provided 1,14-dibromo-neodolabelline (14), mp 154-155°C (hexane), $C_{20}H_{30}O_4Br_2$ [δ 5.32 (1H, dd, J=9.0, 3.5, 14-H), 2.91 (1H, ddd, J=16.0, 9.0, 6.5, 13β-H), 2.08 (1H, ddd, J=16.0, 10.0, 3.5, 13α-H), 2.17 (1H, m, 12-H)], and a bromohydrin (15), $C_{20}H_{31}O_5Br$ [δ 4.71 (1H, dd, J=8.0, 2.0, 14-H)], whereas OsO_4 oxidation of 5 yielded a triol (16), $C_{20}H_{32}O_6$, δ 3.92 (1H, m, 14-H).

^1H NMR examinations (500 MHz) of neodolabelline (5) and its derivatives (6-16), which included decoupling experiments, NOE examinations (Table I), and pyridine-induced solvent shifts[7)] (*e.g.* for 7-H in 8; for 5-H and 7-H in 12; for 2β-H and 7-H in 16), finally led us to presume a methyl migrated (C-1 → C-11) dolabellane structure (5) for neodolabelline.

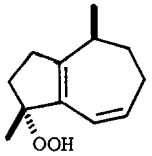
In order to substantiate the presumption and to establish the absolute stereochemistry of neodolabelline (5), the molecular structure with its absolute configuration of 1,14-dibromo-neodolabelline (14) was determined by the X-ray crystal structure analysis (Fig. 1).[8)] Bond distances and angles were all normal. The C3, C4, C5, and C6 atoms were in a plane with the maximum deviation of 0.004 Å. The absolute structure of 5 was further confirmed by means of the cyclic α-glycol chirality method.[9)] Thus, the CD curve [in CCl_4 with Eu(fod)$_3$] of *trans*-glycol (7) showed a positive Cotton effect: $[\theta]_{305}$ +19000 (pos. max.), while that of *cis*-glycol (8) showed only a weak Cotton curve: $[\theta]_{331}$ -1500 (neg. max.), $[\theta]_{302}$ +4000 (pos. max.). Consequently, the 8(R) and 9(S) configurations in 7 were confirmed.



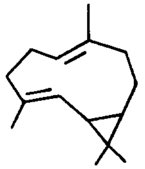
clavukerin A (1)



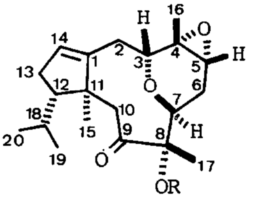
clavukerin B (2)



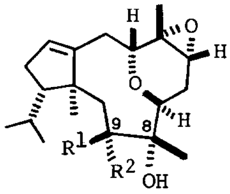
clavukerin C (3)



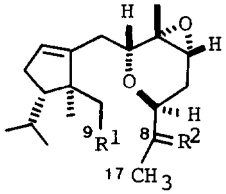
bicyclogermacrene (4)



5, R= H : neodolabelline
6, R= Ac

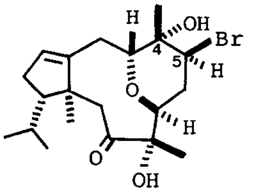


7, R^1= OH, R^2= H
8, R^1= H, R^2= OH

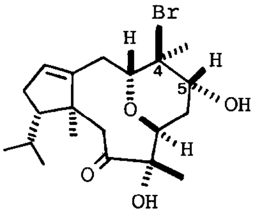


9, R^1= CHO, R^2= O
10, R^1= CH_2OAc, R^2= $<^{OAc}_{H}$

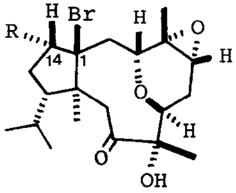
11, R^1= CH_2OAc, R^2= $<^{H}_{OAc}$
(C-8 epimer of 10)



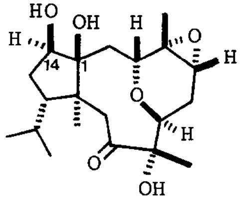
12



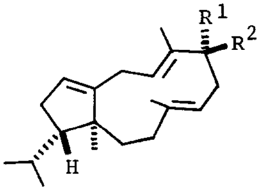
13



14, R= Br
15, R= OH



16



17, R^1= H, R^2= OH
18, R^1= OH, R^2= H

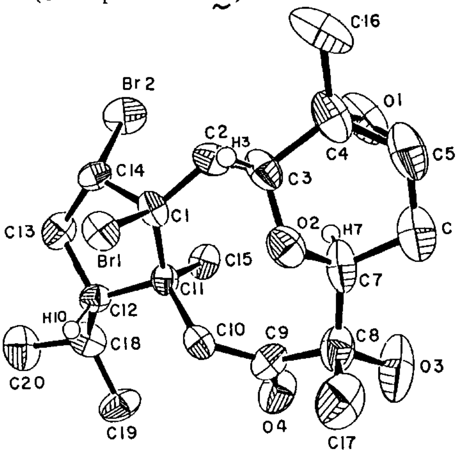


Figure 1. ORTEP drawing of 1,14-dibromoneodolabelline (14). Thermal ellipsoids are drawn at the 50 % probability. Only three hydrogen atoms are shown to represent the absolute structure clearly.

Table I. NOE Data 500 MHz on $5^{a)}$, $7^{a)}$, $8^{b)}$, and $16^{b)}$

	2α-H	3-H	5-H	6β-H	7-H	14-H	18-H
5 NOE (%) c)	6 [7-H]	10 [2α-H] 8 [2β-H] 6 [4-CH_3]	12 [6α-H] 14 [6β-H] 14 [4-CH_3]	15 [6α-H] 5 [8-CH_3]	5 [2α-H]	5 [13α-H] 11 [13β-H]	13 [11-CH_3] 13 [18-CH_3]
7 NOE (%) c)		8 [4-CH_3]	12 [4-CH_3] 6 [6α-H]				8 [11-CH_3]
8 NOE (%) c)		8 [4-CH_3] 7 [2β-H]	9 [4-CH_3]	5 [8-CH_3]		4 [2β-H]	9 [11-CH_3]
16 NOE (%) c)	7 [11-CH_3]	11 [4-CH_3]	8 [4-CH_3]		9 [11-CH_3]	10 [11-CH_3]	6 [11-CH_3]

a) In d_6-DMSO solution. b) In $CDCl_3$ solution.
c) Saturated signals were shown in square brackets.

Various dolabellane-type diterpenes were isolated from sea hare,[10] brown algae,[11] sea whip (sea fan),[12] and moss.[13] Neodolabelline (5) has a carbon skeleton, in which a CH_3 residue at C-1 in the dolabellane skeleton is migrated to C-11. A few diterpenes such as 17 and 18, which have these methyl migrated dolabellane skeletons, were reported so far from soft corals, *Clavularia inflata*[14] and *Cespitularia* sp.[14]

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References and Notes

1) M. Kobayashi, Y. Kiyota, S. Orito, Y. Kyogoku, and I. Kitagawa, Tetrahedron Lett., in the press.
2) a) M. Kobayashi, B. W. Son, M. Kido, Y. Kyogoku, and I. Kitagawa, Chem. Pharm. Bull., 31, 2160 (1983); b) M. Kobayashi, B. W. Son, Y. Kyogoku, and I. Kitagawa, Chem. Pharm. Bull., 32, 1667 (1984).
3) It should be mentioned here that the composition of clavukerins (1,2,3) and neodolabelline (5) in *Clavularia koellikeri* varied depending upon the year (1981-1983) collected, although the soft corals investigated were collected in the same waters and in the same season.
4) The molecular compositions of compounds with the chemical formulae were determined by high resolution mass spectrometry.
5) The spectra of 5, 6, 7, 8, 12, and 13 were measured in d_6-DMSO while those of 9, 10, 11, 14, 15, and 16 were taken in $CDCl_3$.
6) B. W. Finucane and J. B. Thomson, Chem. Commun., 1969, 1220.
7) a) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, J. Am. Chem. Soc., 90, 5480 (1968); b) M. Kobayashi, T. Yasuzawa, Y. Kyogoku, M. Kido, and I. Kitagawa, Chem. Pharm. Bull., 30, 3431 (1982).
8) A colorless crystal with dimensions of 0.16x0.34x0.25 mm was used for collection of the X-ray diffraction data, and the color changed purple at the end of X-ray exposure. Two sets of intensity data were measured with the same crystal on a Rigaku AFC-5 diffractometer with the graphite monochromatized Cu-Kα radiation (1701 reflections, $2\theta \leq 125°$, and $Fo \geq 3\sigma Fo$) and Mo-Kα(2201 hkl and $h\bar{k}l$ reflections, $2\theta \leq 41.4°$), the former was used for determination of the structure and the latter for that of the absolute structure, respectively. The crystallographic data were, $C_{20}H_{30}O_4Br_2$, M_W=494.26, monoclinic $P2_1$, a=9.328(3), b=15.233(3), c=7.395(2)Å, β=99.66(2)°, V=1035.9(5) $Å^3$, D_x=1.585 gcm^{-3}, Z=2, μ=56.98 and 41.67 cm^{-1} for Cu-Kα and Mo-Kα radiation, respectively. The structure was solved by the heavy atom method and refined by block-diagonal least-squares procedure with all hydrogen atoms except those on the methyl groups by setting them on their calculated positions. The final R and Rw values with 2201 Friedel pair reflections were 0.045 and 0.053, respectively, whereas the enantiomeric structure refined under identical conditions gave R and Rw values of 0.063 and 0.072, respectively. Tables of atomic coordinates, temperature factors, structure factors, bond lengths and angles, planarity of atoms, have been deposited with the Cambridge Crystallographic Data Centre.
9) K. Nakanishi and J. Dillon, J. Am. Chem. Soc., 93, 4058 (1971).
10) *e.g.* A. G. González, J. D. Martin, M. Norte, R. Pérez, V. Weyler, S. Rafii, and J. Clardy, Tetrahedron Lett., 24, 1075 (1983).
11) *e.g.* C. Tringali, M. Piattelli, and G. Nicolosi, Tetrahedron, 40, 799(1984).
12) S. A. Look and W. Fenical, J. Org. Chem., 47, 4129 (1982).
13) A. Matsuo, K. Uohama, S. Hayashi, and J. D. Connolly, Chemistry Lett.,1984, 599.
14) B. F. Bowden, J. C. Braekman, J. C. Coll, and S. J. Mitchell, Aust. J. Chem., 33, 927 (1980).

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