Pergamon

Tetrahedron, Vol. 52, No. 44, pp. 13901-13908, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00852-6

Vallartanone B: Synthesis and Related Studies

Hirokazu Arimoto*, Rieko Yokoyama, Kazuhiko Nakamura†, Yasuaki Okumura and Daisuke Uemura

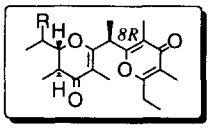
Department of Chemistry, Faculty of Science, Shizuoka University, 836 Ohya, Shizuoka 422 Japan

†Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi Yokohama 223 Japan

Abstract: The synthesis of vallartanone B, a γ-pyrone-containing polypropionate from the marine mollusc *Siphonaria maura*, is described. A γ-pyrone moiety, which was constructed by PPh_3-CCl_4 cyclization of a β-triketone, and a C1-C6 segment were joined by a $Sn(OTf)_2$ aldol reaction and converted to vallartanone B. This synthesis allows for revision of the stereochemistry at C8. A conformational analysis was performed using PM3 to examine the proposed interpretation of its CD spectrum. Copyright © 1996 Elsevier Science Ltd

Introduction

Marine pulmonate molluscs are known to produce various polypropionate metabolites.[1,2] Among these, the cytotoxic pyrones have attracted considerable attention as possible defense allomones,[3] although not all of them possess ichthyodeterrent properties. It has often been difficult to determine their stereochemistries due to the presence of isolated stereocenters. We previously reported efficient methods for constructing tetraalkylsubstituted γ-pyrones,[4] which have enabled the total synthesis of onchitriols.[5] Vallartanone B(**1**), isolated from *Siphonaria maura*, deters feeding by the fish *Thallasoma lunare*, and may be a defensive allomone of pulmonate molluscs.[6]



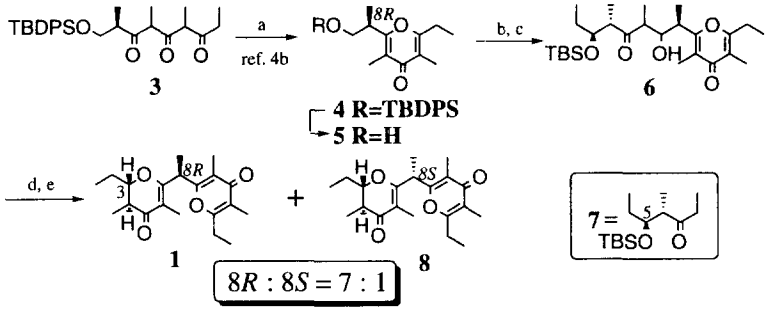
R= H Vallartanone B (**1**)
R= Me Vallartanone A (**2**)

The structure of vallartanone B was proposed to be **1** based on an interpretation of spectral data.[6] Although the absolute configuration was determined by analogy to that of the related vallartanone A (**2**), a CD exciton coupling method for the bis-pyrone system has not yet been fully established. In this report, we provide a detailed account of the revision of vallartanone B by our method,[7] along with PM3 conformational studies related to the results of a CD exciton coupling analysis.

Synthesis of (*8R*)-vallartanone B

Synthesis of the originally proposed structure **1** for vallartanone B began with β-triketone **3**, which was prepared from methyl (*R*)-3-hydroxy-2-methylpropionate. Compound **3** was converted to a pyrone **4** by PPh_3-CCl_4 cyclization, as reported previously.[4a,b] Dess-Martin oxidation of **5** gave an aldehyde. Since

the product was prone to racemization under silica gel chromatography, the reaction mixture was worked up conventionally (see Experimental section below), and used in the next step without further purification. An aldol reaction with a tin enolate of C_1-C_6unit **7**, which was prepared as described in the literature,[8] proceed successfully to furnish a diastereomixture of the adducts **6**. The mixture was again oxidized by the Dess-Martin procedure and then treated with TFA in $CHCl_3$. Deprotection and cyclization gave the desired dihydropyrone in give a good yield. ^1H NMR analysis of the product, which was not separable by either conventional silica gel chromatography or HPLC (ODS), revealed slight epimerization at the C8 stereocenter. Both of the isomers exhibited large coupling constants between protons attached to C3 and C4, which indicated that the isomers derived from C5-*epi*-**7** could be removed during purification by chromatography. Although the epimers exhibited very similar ^1H and ^{13}C NMR spectra, those of the minor 8*S* isomer **8** were in good agreement with those of natural vallartanone B.

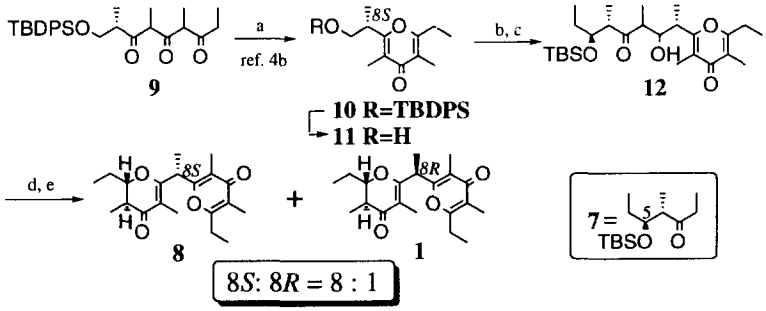


a. i) Ph_3P-CCl_4 / THF, ii) TBAF / THF. b. Dess-Martin periodinane / CH_2Cl_2. c. **7**, $Sn(OTf)_2$, Et_3N /CH_2Cl_2, -78° ℃ (43 % in 2 steps). d. Dess-Martin periodinane / CH_2Cl_2. e. TFA / $CHCl_3$ (72 % in 2 steps).

Scheme 1

Synthesis of (8*S*)-vallartanone B

(8*S*)-Vallartanone B (**8**) was prepared from methyl (*S*)-3-hydroxy-2-methylpropionate in essentially the same manner. The aldol reaction with ketone **7**[8] using 1-ethyl piperidine as a base proceeded smoothly to give a diastereomixture of aldol adducts in excellent yield. The resulting mixture of **12** was oxidized to β-diketones, and immediately treated with TFA to give bis-pyrones. Again, partial epimerization was observed, but (8*S*)-isomer **8** was stereospecifically obtained as a major product.



a. i) Ph_3P-CCl_4 / THF, ii) TBAF / THF. b. Dess-Martin periodinane / CH_2Cl_2. c. **7**, $Sn(OTf)_2$, 1-ethyl piperidine /CH_2Cl_2, -78 ℃ (82 % in 2 steps). d. Dess-Martin periodinane / CH_2Cl_2. e. TFA / $CHCl_3$ (67 % in 2 steps).

Scheme 2

Revised structure of vallartanone B

The resulting (8*R*)-and (8*S*)-vallartanone B could be separated by chiral HPLC (CHIRALCEL, Daicel Co., 75 % aq.MeOH). Since ^{1}H and ^{13}C NMR spectra of synthetic **8** were in good agreement with those of natural vallartanone B, the relative stereochemistry of vallartanone B was revealed to be (3*S**, 4*S**, 8*S**). The specific rotation of **8** ($[\alpha]_D^{20}$ -129°) was of the same sign and magnitude as that of the natural product[6] ($[\alpha]_D^{20}$ -133°). Based on these spectral data, we concluded that the stereochemistry of vallartanone B should be revised to **8** (3*S*, 4*S*, 8*S*).

Conformational analysis of vallartanones

Manker and Faulkner proposed that the absolute stereochemistry of vallartanones was 8*R* based on a CD spectrum of vallartanone A.[6] Since a CD spectrum of vallartanone B was not reported in their paper, we measured that of **8** (Fig. 1), which showed a split Cotton effect at 265 nm, quite similar to the reported spectrum[6] of natural vallartanone A, whereas (8*R*)-vallartanone B (**1**) showed a non-split complex Cotton curve at 268 nm.

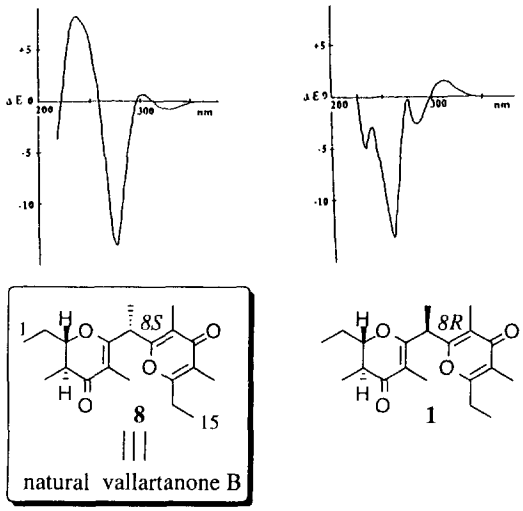


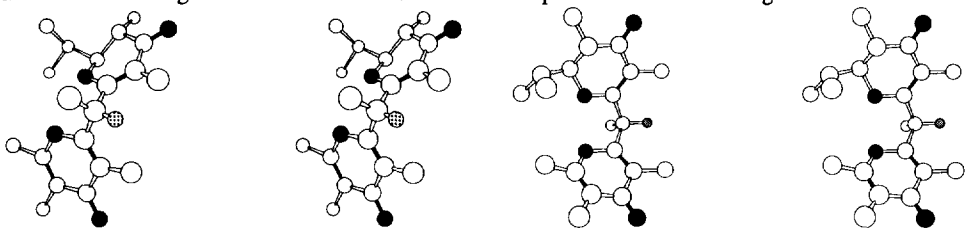
Figure 1: CD spectra of vallartanone B (8) and its C8 epimer (1).

Based on our synthetic studies, we concluded that vallartanone B must be revised to 8*S*. These results suggest the possibility that the structure of vallartanone A should also be reconsidered.

The originally proposed stereochemistry was based on the assumption that its most stable conformation was governed by steric repulsion between the C19 methyl adjacent to C6 and the substituents at C8. Thus, it was assumed that the CD spectrum of vallartanones was dominated by the C8 stereocenter. The quite different patterns of the CD spectra of our synthetic 8*R* and 8*S*-vallartanone B indicated that other stereocenters (C3, C4) also influenced the conformation.

Thus, we evaluated the conformation using theoretical calculations. The MOPAC program package[9] was used for semiempirical molecular orbital calculations. Model molecules of both 8*R* (**13**) and 8*S* (**14**) derivatives were constructed from vallartanone A (**2**). An ethyl group adjacent to C13 was changed to a methyl for simplification.

The conformational field was searched by driving the C7-C8 bond and the C8-C9 bond. Internal energies were minimized using an eigenvector following method under the PM3 Hamiltonian[10] for each conformer. The resulting most stable conformations for both epimers are shown in Fig. 2.

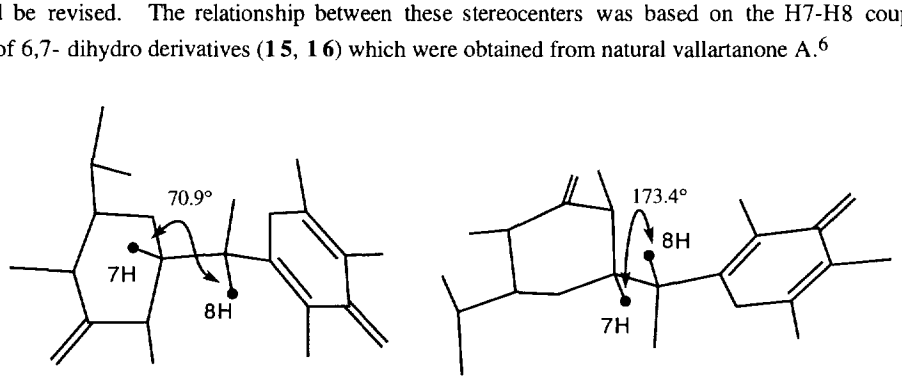


13 (8*R*) **14 (8*S*)**

Figure 2: The conformations of vallartanone derivatives obtained by PM3 (stereoview).

The resulting conformation of the 8*R* derivative is different from that proposed by Manker and Faulkner.[6] This may account for the misassignment of the absolute stereochemistry. The conformation of the vallartanone derivatives is governed by the configuration of C8, but is also clearly affected by those of C3 and C4. Since the dipole moment of the dihydropyrone ring has not been established precisely, interpretation of the CD spectrum of vallartanones is comlex. The electronic transition dipole moments of the chromophores were nearly on a plane in both **13** (8*R*) and **14** (8*S*). Thus, assignment of the absolute stereochemistry by an analysis of these CD spectra was difficult.

Although the absolute stereochemistry can be rationalized, the relative stereochemistries of C3, C4 and C8 should be revised. The relationship between these stereocenters was based on the H7-H8 coupling constants of 6,7- dihydro derivatives (**15**, **16**) which were obtained from natural vallartanone A.[6]



15 **16**

(3*S*, 4*S*, 6*R*, 7*R*, 8*S*) **(3*S*, 4*S*, 6*S*, 7*R*, 8*R*)**

Figure 3: The conformations of dihydrovallartanone derivatives obtained by PM3.

The results of the PM3 calculation for **15** and **16** are shown in Fig. 3. Since we concluded that **8** was natural vallartanone B, the 8*S* derivative **15** should correspond to the 6,7-dihydrovallartanone described by Manker and Faulkner.[6] The calculated coupling constant between H7 and H8 was 3.3 Hz based on the dihedral angle (see Experimental section),[11] and was in good agreement with the experimental value[6](4.0 Hz). 6,7-Dihydro-8-*epi*-vallatanone **16** gave calculated value of 10.1 Hz based on the dihedral angle (173.4°),

which was quite similar to the experimental value (9.8 Hz). These results support the conclusion that the relative stereochemistry of the vallartanones is (3*S*, 4*S*, 8*S*) .

Conclusion

In summary, the total synthesis of vallartanone B led to structural revision at C8. The stable conformations of both revised vallartanone B(**8**) and its *8R* epimer **1** were estimated by a PM3 computational analysis. The conformation of the *8R* isomer was differed from that of the originally proposed model, which was the basis for determining the absolute stereochemistry from the CD spectrum. Further studies on its role as a defensive allomone are in progress.

Experimental Section

General procedures

Unless otherwise indicated, all nonaqueous reactions were performed in oven-dried glassware under an inert atmosphere. NMR spectra were recorded on a Bruker AC-300 operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively, and are referenced to TMS. IR spectra were recorded on a JASCO IR-810 spectrometer using NaCl salt plates. Specific rotations were recorded on a JASCO DIP-360 spectrometer. CD spectra were recorded on a JASCO J-500 spectropolarimater at room temperature in methanol. Column chromatography was performed on a cica-Merck 60. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60F254, 0.25 mm. Tetrahydrofuran was distilled from benzophenone ketyl under nitrogen prior to use. Dichloromethane was passed through a column of activated alumina and stored over 4A molecular sieves. Where appropriate, reagents were purified prior to use.

(8*S*)-β-triketone 9 A solution of dienolate of 4-methylheptan-3,5-dione (3.80 mmol) was prepared by adding 4-methylheptan-3,5-dione to a solution of LDA (7.63 mmol) in 10 ml of THF at -15 ℃. The mixture was stirred for 30 min and then cooled to -60 ℃ before adding DMPU (33.1 mmol). The solution was then stirred for an additional 10 min.

To a solution of (2*S*)-3-*t*-butyldimethylsilyloxy-2-methylpropionic acid (519 mg, 1.52 mmol) in 15 ml of THF was added *N*, *N'*-carbonyl diimidazole (260 mg, 1.60 mmol), and the mixture was stirred for 3hr at room temperature. The resulting solution was recooled to -70 ℃ before the cold solution (-60 ℃) of the dienolate (3.80 mmol) was added dropwise. The reaction was stirred for 1hr at -70 ℃ and then quenched with 20 ml of a 2M HCl. The mixture was diluted with water (70 ml), partitioned with ether (20 ml), and the organic phase was collected. The aqueous phase was extracted with ether (20 ml), and combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the yellow residue by chromatography on silica gel (45g, hexane/ether 2:1) gave a tautomeric mixture of **9** as a pale yellow oil (530 mg, 75%): IR (film) 3410, 1710, 1660, 1608 cm^{-1}.

(8*S*)-γ-pyrone 10 To a solution of β-triketone **9** (290 mg, 0.622 mmol) in 5ml of THF was added PPh_3 (500 mg, 1.91 mmol), followed by CCl_4 (590 mg, 3.83 mmol). Stirring was continued at room temperature for 40hr before adding 30 ml of water. The mixture was extracted with 4 X 20 ml of ether, and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the product by chromatography on silica gel (30g, hexane/EtOAc 5:1) gave the desired γ-pyrone as a colorless oil (182 mg, 65%): $[\alpha]_D^{18}$ -5.6° (*c* 1.08, $CHCl_3$) HREIMS m/z (obs.) 433.2206(M^+-CH_3), calc. for $C_{27}H_{33}O_3Si$ 433.2198; IR (film) 1660, 1612 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.98 (9H, s), 1.13 (3H, t,

J= 7.3 Hz), 1.15 (3H, d, J= 6.6 Hz), 1.96 (6H, br.s), 2.52 (2H, complex), 3.26 (1H, m), 3.72 (1H, dd, J= 5.9, 9.6 Hz), 3.80 (1H, dd, J= 9.6, 9.6 Hz); ^{13}C-NMR (67.5MHz, $CDCl_3$) δ 9.5, 11.0, 13.9, 19.0, 24.6, 38.5, 66.3, 117.7, 119.2, 127.6, 129.6, 133.2, 135.4, 163.9, 164.0, 179.8

Alcohol 11[4b] A 1.0 M solution of $^{n}Bu_4NF$ in THF (0.55 ml, 0.55 mmol) was added dropwise to a solution of **10** in 3 ml of THF at 0 ℃. The solution was allowed to warm to room temperature over 40 min and then concentrated *in vacuo*. Purification by PTLC on silica gel ($CHCl_3$/MeOH 10:1) furnished **11** (53.6 mg, 92 %) as a colorless oil.

β-silyloxy ketone 7 To a solution of (4*S*)-5-hydroxy-4-methyl-heptan-3-one (593 mg, 4.12 mmol, 5*S*/5*R* 5:1) in 6 ml of DMF was added imidazole (560 mg, 8.23 mmol), followed by *t*-butylchlorodimethylsilane (750 mg, 4.98 mmol). After stirring at room temperature for 2days, the mixture was diluted with water (30 ml) and extracted with 3 X 30 ml of ether. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by chromatography on silica gel (25g, hexane/$CHCl_3$ 2:1) gave **7** as a slightly yellow oil (884 mg, 83%, 5*S*/5*R* 5:1): IR (film) 1720 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ -0.03 (3H, s), 0.04 (3H, s), 0.85 (9H, s), 0.88 (3H, t, J= 7.3 Hz), 0.95 (3H, d, J= 7.1 Hz), 1.04 (3H, t, J= 7.2 Hz), 1.48 (2H, m), 2.49 (2H, q, J= 7.2 Hz), 2.75 (1H, dq, J= 7.6, 7.1 Hz), 3.89 (1H, dt, J= 7.6, 4.3 Hz): signals attributed to contaminant 5*R* isomer were observed at δ 0.87 (s), 1.01 (t), 3.82 (dt); ^{13}C-NMR (75MHz, $CDCl_3$) δ -4.6, -5.0, 7.3, 7.5, 12.7, 18.0, 25.7, 26.0, 36.9, 49.8, 74.5, 214.5: signals attributed to contaminant 5*R* isomer were observed at δ 9.7, 12.1, 18.0, 27.4, 35.7, 50.6, 74.8, 214.0

(8*S*)-vallartanone B (8) To a solution of alcohol **11** (88.5 mg, 0.42 mmol) in 3.0 ml of CH_2Cl_2 was added the Dess-Martin periodinane (250 mg, 0.58 mmol) at room temperature. The mixture was stirred for 1hr and then quenched by addition of 20 ml of saturated $NaHCO_3$-$Na_2S_2O_3$ solution. The organic layer was collected, and the aqueous phase was extracted with 2 X 5 ml of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated to a pale yellow oil under reduced pressure. The product was azeotropically dried with benzene at room temperature and used without further purification.

To a suspension of $Sn(OTf)_2$ (385 mg, 0.924 mmol) in 2.5 ml of CH_2Cl_2 was added 1-ethylpiperidine (0.14 ml, 1.02 mmol) at room temperature. The mixture was cooled to -30 ℃ and a solution of ketone **7** (217 mg, 0.841 mmol) in 2.0 ml of CH_2Cl_2 was added. The reaction was gradually warmed to 0℃ over 2hr with stirring. Upon recooling the resulting yellow solution to -78 ℃, a solution of the unpurified aldehyde in 2.0 ml of CH_2Cl_2 was added to the mixture. Stirring at -78 ℃ was continued for an additional 2.5hr, and the reaction was quenched with cold (0 ℃) PH7 phosphate buffer solution (30 ml). The mixture was filtered through a pad of celite. The organic phase was separated, and the aqueous phase was extracted with 2 X 10 ml of CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude products were purified by chromatography on silica gel (10g, hexane/EtOAc 1:1) to give a diastereomixture of aldol adducts **12** as a colorless oil (102 mg, yield based on the consumed aldehyde 82%) along with the aldehyde (33 mg).

To a solution of the aldol adducts **12** (27 mg, 0.061 mmol) in 2.0 ml of CH_2Cl_2 was added Dess-Martin periodinane (73 mg, 0.17 mmol) at room temperature. The mixture was stirred for 15 min and the reaction was quenched by adding 20 ml of saturated $NaHCO_3$-$Na_2S_2O_3$ solution. The organic layer was collected, and the aqueous phase was extracted with 2 X 15 ml of Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated to a pale yellow oil under reduced pressure. The residue was immediately

dissolved in 1.5 ml of $CHCl_3$ and trifluoroacetic acid (0.5 ml) was added at room temperature. The resulting mixture was stirred at this temperature for 30 min before adding 20 ml of water. The mixture was extracted with 3 X 15 ml of $CHCl_3$. The combined extracts was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by PTLC on silica gel (hexane/EtOAc 1:1) gave (8*S*)-vallartanone B **8** as a colorless oil (13 mg, 67%; 8*S*/8*R* 8:1, based on the ^{1}H-NMR integral ratio of the singlets at δ 1.79 and 1.77 in C_6D_6), which was repurified by chiral HPLC (CHIRALCEL, Daicel Co., 75% aq.MeOH): $[\alpha]_D^{20}$ -129° (*c* 0.35, $CHCl_3$); HREIMS; *m/z* 332.1977, calc. for $C_{20}H_{28}O_4$ 332.1987; IR (film) 1650, 1600 cm^{-1}; UV(MeOH) 217 nm (ε 12715), 265 nm (ε 21663), ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.97 (3H, t, J= 7.3 Hz), 1.09 (3H, d, J= 6.9 Hz), 1.23 (3H, t, J= 7.6 Hz), 1.47 (3H, d, J= 7.1 Hz), 1.64 (1H, m), 1.76 (3H, s), 1.81 (1H, m), 1.93 (3H, s), 1.96 (3H, s), 2.30 (1H, dq, J= 12.3, 6.9 Hz), 2.63 (2H, q, J= 7.6 Hz), 3.86 (1H, ddd, J= 3.3, 8.1, 12.3 Hz), 4.16 (1H, q, J= 7.1 Hz); ^{1}H-NMR (300MHz, C_6D_6) δ 0.78 (3H, t, J= 7.3 Hz), 0.94 (3H, t, J= 7.7 Hz), 0.98 (3H, d, J= 7.0 Hz), 1.19 (3H, d, J= 7.0 Hz), 1.26 (1H, m), 1.35 (1H, m), 1.79 (3H, s), 1.96 (3H, s), 2.01 (3H, s), 2.04 (1H, dq, J= 11.9, 7.0 Hz), 2.14 (2H, complex), 3.40 (1H, ddd, J= 3.7, 8.4, 11.9 Hz), 3.75 (1H, q, J= 7.0 Hz); ^{13}C-NMR (75MHz, $CDCl_3$) δ 8.9, 9.0, 9.3, 9.5, 10.6, 11.2, 14.3, 24.8, 25.5, 38.6, 42.7, 84.4, 108.7, 118.2, 118.9, 160.8, 164.5, 168.6, 179.6, 195.3

Data for (8*R*)-vallartanone B (1) $[\alpha]_D^{20}$ -52° (*c* 0.42, $CHCl_3$); HREIMS; *m/z* 332.1970, calc. for $C_{20}H_{28}O_4$ 332.1987; IR (film) 1650, 1600 cm^{-1}; UV(MeOH) 217 nm (ε 7503), 268 nm (ε 10967), ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.96 (3H, t, J= 7.3 Hz), 1.08 (3H, d, J= 6.9 Hz), 1.23 (3H, t, J= 7.8 Hz), 1.49 (3H, d, J= 7.2 Hz), 1.69 (1H, m), 1.74 (3H, s), 1.78 (1H, m), 1.96 (3H, s), 1.96 (3H, s), 2.36 (1H, dq, J= 11.8, 6.9 Hz), 2.62 (2H, q, J= 7.8 Hz), 3.80 (1H, ddd, J= 3.4, 7.9, 11.8 Hz), 4.14 (1H, q, J= 7.2 Hz); ^{1}H-NMR (300MHz, C_6D_6) δ 0.77 (3H, t, J= 7.3 Hz), 0.92 (3H, t, J= 7.7 Hz), 0.99 (3H, d, J= 7.0 Hz), 1.21 (3H, d, J= 7.0 Hz), 1.33 (2H, complex), 1.77 (3H, s), 1.97 (3H, s), 2.01 (3H, s), 2.07 (1H, dq, J= 11.9, 7.0 Hz), 2.13 (2H, q, 7.7 Hz), 3.45 (1H, ddd, J= 3.7, 8.1, 11.9 Hz), 3.72 (1H, q, J= 7.0 Hz); ^{13}C-NMR (75MHz, $CDCl_3$) δ 8.9, 8.9, 9.3, 9.5, 10.7, 11.3, 14.4, 24.8, 25.5, 38.7, 42.8, 84.3, 109.1, 118.2, 118.7, 161.0, 164.5, 168.6, 179.6, 195.2

MOPAC calculations The initial conformers were constructed using the Chem3D[12] molecular modeling program for Macintosh personal computers with reference to Dreiding Models. The generated input files were submitted to the MOPAC 6.01 program package for the CONVEX C4620 supercomputer[9]. Geometry optimizations were carried out with keywords EF and PRECISE using the PM3 Hamiltonian[10]. The existance provabilities were calculated by a Boltzman distribution at 300 K. The calculated results were visualized using Chem3D.[12]

Methods for the conformational field search The conformational fields were searched by driving the dihedral angles C6-C7-C8-C9 and C7-C8-C9-C10 by 30-degree steps using grid-scan options for reaction coordinate searching. After energy minimization, the lowest conformation was selected and full energy optimization was applied. Conformers with energy differences less than 2.0 kcal/mol (3.5:100 existance provability versus the lowest conformation) were also selected and their internal energies were minimized.

*Conformational analysis of **13**;* The conformation of the global minimum is depicted in Fig. 2. The second most-stable conformer has an energy difference of 1.56 kcal/mol, which equates to an existence probability of 7.3:100.

*Conformational analysis of **14**;* Two conformations were obtained in addition to the lowest one. The

second conformer has an energy difference of 0.07 kcal/mol and the third has an energy difference of 0.48 kcal/mol. These two conformers were judged to be near the global minimum in conformational space, since only slight differences were observed in the dihedral angles (*ca.* ± 20°). It can be concluded that these conformations are interconvertible with each other at ambient temperature and are essentially the same. Other conformers have much higher heats of formation.

Conformational analysis of 15; The global minimum is shown in Fig. 3. The second most-stable conformation (ΔE = 0.93 kcal/mol) is also depicted in Fig. 4 and the corresponding coupling constant is 10.2 Hz. The corrected coupling constant calculated from the existence probability (21:100) is 3.3 Hz.

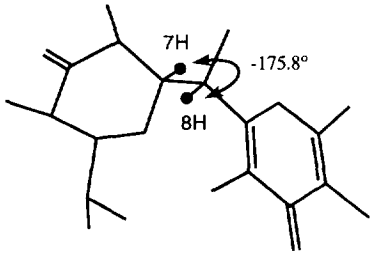


Figure 4: The second most-stable conformation of dihydrovallartanone derivative 15 based on PM3.

Conformational analysis of 16; The global minimum is shown in Fig. 3. Other conformers have a much higher heat of formation.

Acknowledgment: The authors thank Prof. D. J. Faulkner, Scripps Institution of Oceanography, University of California, for providing a sample of vallartanone B and for his helpful discussions.

REFERENCES AND NOTES

1. Faulkner, D. J. *Nat. Prod. Rep.* **1995**, 223 and previous articles in this series.
2. Garson, M. *Chem. Rev.* **1993**, 93, 1699-1733.
3. Pawlik, J. R. *Chem. Rev.* **1993**, *93*, 1911-1922.
4. a) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5619-5620.
   b) Arimoto, H.; Cheng, J.-F.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 5781-5784.
5. a) Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 9581-9584.
   b) Arimoto, H.; Okumura, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1995**, *36*, 5357-5358.
6. Manker, D. C.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5374-5377.
7. Part of this work has been previously communicated: Arimoto, H.; Yokoyama, R.; Okumura, Y. *Tetrahedron Lett.* **1996**, *37*, 4749-4750.
8. Narasaka, K.; Miwa, T. *Chem. Lett.* **1985**, 1217-1220.
9. MOPAC Ver. 6, Stewart, J. J. P. *QCPE Bull.* **1989**, *9*, 10; Revised as Ver. 6.01 for CONVEX supercomputers.
10. Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209.
11. Haasnoot, C. A. G.; de Leeuw, F. A. A. M., Altona, C. *Tetrahedron* **1980**, *36*, 2783.
12. Cambridge Scientific Computing, Inc.

(*Received in Japan* 5 *August* 1996; *accepted* 6 *September* 1996)