Synthesis of Tridensone, a Sesquiterpene Ketone Isolated from the Liverwort *Bazzania tridens*. Structure Revision and Absolute Configuration

Motoo Tori, Kazuhiro Kosaka and Yoshinori Asakawa*
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro cho, Tokushima 770, Japan

The title compound and its isomer have been synthesized as optically active forms. The spectral data of the natural compound **1** were identical with those of our synthetic isomer **1a** showing that its structure should be revised and its absolute configuration was established as an antipode of the synthetic one as depicted in the formula **9**.

Recently Wu and Chen reported isolation and structure determination of tridensone **1** from the liverwort *Bazzania tridens*.[1] However, the absolute configuration has not been established. The structure of **1** is very rare and unique from the biogenetic standpoint. It is considered as a seco-eudesmane-type skeleton derived from the C–C bond fission of C-6 and -7 (Fig. 1). The same group have already reported the isolation of tridensenal **2** from the same liverwort.[2] This is considered to be derived from an eremophilane-type sesquiterpene by C–C bond fission of C-5 and -6 (Fig. 1). These two sesquiterpenoids are thus closely related from the biogenetic point of view. Establishment of the absolute configuration of either terpenoid presumably suggests all the absolute configurations of these family of sesquiterpenoids. We have been interested in the absolute configuration of the terpenoids from the liverwort[3] and have started on a synthesis of tridensone **1**. We have now found that the original structural assignment is wrong and we here report the revised structure of tridensone **1** and its absolute configuration in detail.

Optically active compounds having a quaternary chiral centre next to a carbonyl group can be synthesized by 1,4-addition of the enamines of the chiral amine auxiliary.[4] This methodology using (*S*)-(−)-phenylethylamine was reported by d'Angelo *et al.*[5] and we utilized this strategy to construct the chiral centre at C-5 of tridensone **1**; namely, we started from the known chiral ketone **3**.[5]

The chiral ketone (+)-**3** was synthesized by a literature route[5] in 80% yield. The ketone (+)-**3** was then reduced by $LiAlH_4$ to afford a mixture of diols **4**. The primary alcohol function of this diol **4** was selectively protected by a TBDMS† group (TBDMSCl–Et_3N–DMAP–CH_2Cl_2) after which the compound was oxidized by PDC to give the ketone (+)-**5**. Methylation (LDA–MeI) of (+)-**5** at this stage afforded a mixture of the diastereoisomers (*ca.* 3:2) **6** after several trials using different conditions. This ratio could not be altered by quenching the enolate or equilibration conditions. Thus, the mixture of **6** when treated with triphenylmethylphosphonium bromide–BuLi followed by deprotection (Bu_4N^+F–THF) afforded a mixture of alcohols **7**. Swern oxidation of **7** to an aldehyde, alkylation by isopropylmagnesium bromide and Jones oxidation gave a mixture of the diastereoisomers of the desired ketone and its isomer, which was separated by silver nitrate-impregnated silica gel column chromatography to afford pure (+)-**1a** and (−)-**1b** (Scheme 1).

The relative stereochemistry of these ketones were unambiguously established by NOESY experiments (Fig. 2) as shown in the formula. Namely, in the case of (+)-**1a**, NOEs are observed between the higher part methyl group signals (13- and 15-H) and both of the *exo*-methylene signals (14-H). On the other hand, only one NOE between the lower field *exo*-methylene signal (14-H) and one of the higher part of the methyl signals (13- or 15-H) was observed, in the case of (−)-**1b**. Furthermore, the other NOE between the higher field *exo*-methylene signal

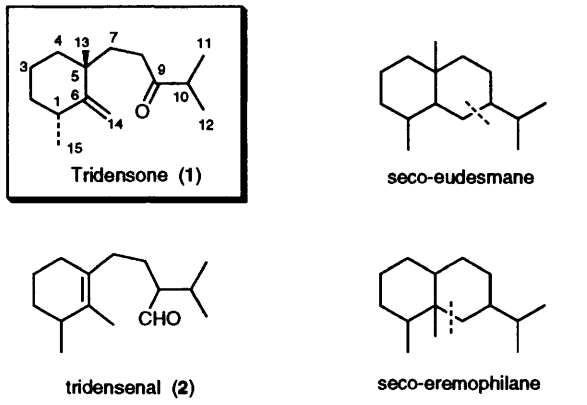
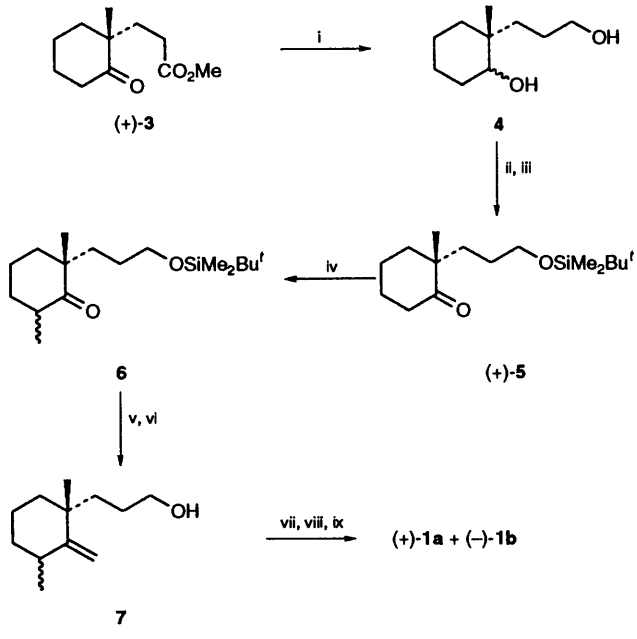


Fig. 1 Tridensone (**1**) and tridensenal (**2**) and their presumed skeletons



Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, Et_2O; ii, TBDMSCl, NEt_3, DMAP; iii, PDC–CH_2Cl_2; iv,LDA–MeI; v, $Ph_3PMe^+Br^-$, BuLi; vi, $Bu_4N^+F^-$; vii, Swern oxid.; viii; MeCH(Br)Me–Mg,Et_2O; ix, Jones oxid., then $AgNO_3$–SiO_2

† *Acronyms*: TBDMS, *tert*-butyldimethylsilyl; DMAP, 4-dimethylaminopyridine; PDC, pyridinium dichromate; THF, tetrahydrofuran; LDA, lithium diisopropylamide; DMSO, dimethyl sulfoxide.

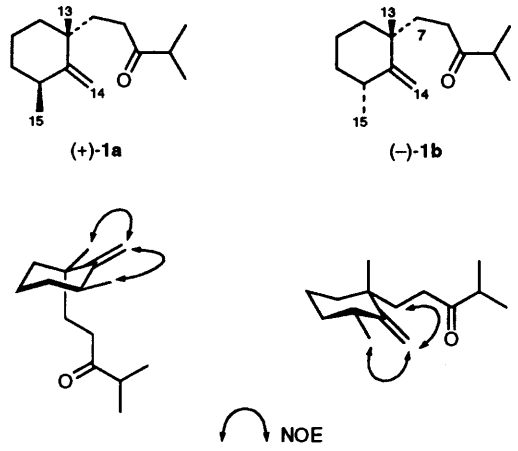


Fig. 2 NOEs detected for (+)-**1a** and (−)-**1b** by NOESY experiment

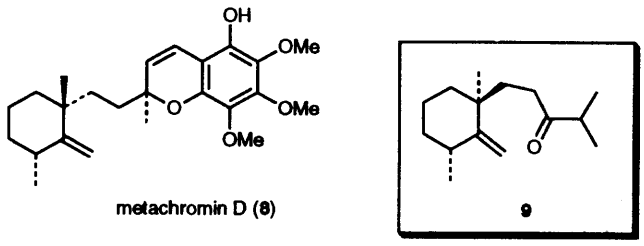
Table 1 NMR data for tridensone and synthetic compounds

	1	1a	1b	8[a]
1	33.4	33.4	34.0	33.98
2	37.3	37.3	37.1	37.20
3	21.8	21.8	21.8	21.89
4	41.4	41.4	38.7	38.72
5	39.5	39.6	39.1	39.05
6	158.1	158.2	158.8	159.42
7	30.7	30.7	34.6	35.35
8	35.4	35.5	35.5	35.40
9	215.3	215.5	215.4	
10	41.0	41.0	41.0	
11	18.4	18.4	18.4	
12	18.3	18.3	18.4	
13	26.3	26.3	25.0	24.98
14	104.9	104.9	103.8	103.71
15	19.2	19.3	19.5	19.61

[a] Only the corresponding data are cited and the numbering is applied for the tridensone system [1]

and one of the methylene signals assigned to 7-H (by COSY experiment) was observed. These results clearly show that compound (+)-**1a** has two methyl groups *cis* to each other and adopts the conformation shown in Fig. 2. The other compound (−)-**1b** has *trans*-dimethyl groups and is recognized as having the conformation shown in Fig. 2. The ^{1}H NMR spectrum of natural tridensone (**1**) was identical with that of synthetic (+)-**1a**, not with (−)-**1b**, which has the desired *trans*-dimethyl groups. Then we compared the ^{13}C NMR data of the natural product with those of the synthetic products and the compound having the similar partial structure, metachromin D **8**, which was isolated from the marine sources.[6] The results are shown in Table 1. On comparison, the chemical shifts of synthetic (+)-**1a** were identical with those of the natural compound **1** reported by Wu and Chen.[1] The data of (−)-**1b** can be compared with the cyclohexane part of those of metachromin D **8**.[6] The ^{13}C NMR data also indicate that the assignment of the relative configuration of the natural tridensone **1** was incorrect and should, therefore, be revised to the isomer **1a** having *cis*-dimethyl groups.

Since the specific rotation of synthetic (+)-**1a** was $[\alpha]_D$ + 12.7 (*c* 0.85, $CHCl_3$) {lit.,[1] $[\alpha]_D$ −15.1 (*c* 0.93, $CHCl_3$)}, the absolute configuration of the natural compound should be the antipode of (+)-**1a** as shown in the formula **9**.



Experimental

The IR spectra were measured with a JASCO FT/IR-5300 spectrophotometer. The ^{1}H and the ^{13}C NMR spectra were taken with a Varian Unity 200 (200 MHz), a JEOL JNM GX400 (400 MHz) or a Varian Unity 600 (600 MHz) spectrometer. The mass spectra, including high resolution mass spectra, were taken with a JEOL JMS AX-500 spectrometer. The CD spectra were carried out with a JASCO J-500 spectrometer. The specific rotations were measured by a JASCO DIP-140 polarimeter. Silica gel 60 (70–230 mesh, Merck) was used for column chromatography and silica gel 60 F_{254} plates (Merck) were used for TLC. (*S*)-(−)-phenylethylamine was purchased from Wako Pure Chemical Industries, Ltd. and used without further purification.

Methyl 3-(1-*Methyl*-2-*oxocyclohexyl*)*propionate* (+)-**3**.—According to the literature,[4] 2-methylcyclohexanone (10 g) was treated with (*S*)-(−)phenylethylamine (11.3 cm^3) in benzene (100 cm^3) in the presence of TsOH (1 g) in a Dean–Stark water separator for 3 h. The imine (8 g) was obtained after reduced pressure distillation. The mixture of imine (4 g) and methyl acrylate (1.6 cm^3) was stirred for 4 days at room temp. without any solvent under an atmosphere of Ar, followed by hydrolysis (AcOH–H_2O, 9:1; 20 cm^3) and silica gel column chromatography (hexane–EtOAc, gradient) to afford the ketone (+)-**3** (5.3 g); $[\alpha]_D^{22}$ +21.3 (*c*. 1.08, $CHCl_3$); $[\alpha]_D^{22}$ +35.0 (*c*. 1.03, EtOH); ν_{max}(film)/cm^{-1} 1740 1705 and 1440; δ_H(200 MHz; $CDCl_3$) 1.08 (3 H, s, Me) and 3.68 (3 H, s, OMe); *m/z* 198 (M^+), 167, 154, 112 (100%), 96, 81, 74, 69 and 55; CD $[\theta]_{299nm}$ +1200 (EtOH).

2-(3-*Hydroxypropyl*)-2-*methylcyclohexanol* **4**.—The ketone (+)-**3** (3 g) was added to a suspension of $LiAlH_4$ (1.5 g) in dry Et_2O (100 cm^3) and stirred for 30 min. Ethyl acetate, H_2O (0.8 cm^3), 10% NaOH (0.8 cm^3), and H_2O (2.4 cm^3) were added successively and the mixture was filtered to give a residue, which was filtered through a short column of silica gel with $CHCl_3$–MeOH (9:1) as the eluent to afford the diol **4** (1.8 g) (a mixture of diastereoisomers). [HR-MS (GC-CI, $C_4H_{10}{}^i$) Found: *m/z* 173.1523 $(M + 1)^+$. $C_{10}H_{21}O_2$ requires 173.1541]; ν_{max}(film)/cm^{-1} 3340; δ_H(200 MHz; $CDCl_3$) 0.87 (s), 0.92 (s), 3.41 (m) and 3.61 (m); δ_C(40 MHz; $CDCl_3$) 17.2 (q), 21.1 (t × 2), 21.2 (t), 22.8 (t), 23.6 (q), 24.6 (t), 25.9 (t), 26.0 (t), 29.4 (t), 30.3 (t), 34.2 (t), 35.1 (t), 36.7 (t), 36.9 (s), 37.6 (s), 63.3 (t), 63.4 (t), 75.1 (d) and 75.8 (d); GC-MS first peak at 9.30 min, *m/z* 154 $(M - 18)^+$, 142, 129, 121, 110, 95, 82 (100%), 69, 55, 43 and 41; second peak at 9.37 min, *m/z* 154 $(M - 18)^+$, 142, 129, 121, 110, 95, 82 (100%), 69, 55, 43 and 41.

2-(3-tert-*Butyldimethylsiloxypropyl*)-2-*methylcyclohexanone* (+)-**5**.—The diol **4** (1.8 g) was treated with TBDMSCl (2.5 g), Et_3N (2 cm^3), and DMAP (180 mg) in CH_2Cl_2 (20 cm^3) overnight. Work-up afforded a silyl ether (3.17 g), which was used without purification. The silyl ether was treated with PDC (19 g) in dry CH_2Cl_2 (30 cm^3) overnight. The mixture was passed through a column of Celite and silica gel (ether as the eluent). The solution was washed with 1 mol dm^{-3} HCl, 10% aq. $NaHCO_3$, and NaCl. After removal of the solvent, a residue (2.5 g) was obtained. Purification of the residue by column chromatography of silica gel (hexane–EtOAc, gradient) afforded the ketone (+)-**5** (1 g). [HR-MS (CI-CH_4) Found:

285.2241 (M + 1)$^+$. $C_{16}H_{33}O_2Si$ requires 285.2250]; $[\alpha]_D^{22}$ +47.0 (*c* 1.15, $CHCl_3$); ν_{max}(film)/cm^{-1} 1710, 1100, 840 and 780; δ_H(200 MHz; $CDCl_3$) 0.03 (6 H, s), 0.88 (9 H, s), 1.03 (3 H, s) and 3.57 (2 H, t, *J* 6.0); δ_C(50 MHz; $CDCl_3$) −5.3 (q × 2), 18.3 (s), 21.0 (t), 22.5 (q), 25.9 (q × 3), 27.2 (t), 27.5 (t), 33.6 (t), 38.7 (t), 39.4 (t), 48.3 (s), 63.3 (t) and 215.9 (s); *m/z* 227 [(M − 57)$^+$, 100%], 212, 185, 159, 131, 109, 93, 75 and 41; CD $[\theta]_{260nm}$ +3320 (EtOH).

2-(3-tert-*Butyldimethylsiloxypropyl*-2,6-*dimethylcyclohexanone* **6**.—The ketone (+)-**5** (3.1 g) was treated with LDA prepared from BuLi (1.6 mol dm^{-3}; 20.6 cm^3) and diisopropyl amine (4.33 cm^3) in dry THF (30 cm^3) at −78 °C for 1 h. MeI (1.37 cm^3) was added to the reaction mixture and left overnight. Work-up and purification by silica gel column chromatography (hexane–EtOAc, gradient) gave the methylated ketone **6** (1.75 g) (a mixture of diastereoisomers) [HR-MS (GC-CI, CH_4) first peak at 11.34 min Found: *m/z* 299.2416. $C_{17}H_{35}O_2Si$ requires 299.2407. Second peak at 12.02 min Found: *m/z* 299.2391. $C_{17}H_{35}O_2Si$ requires 2 99.2407]; ν_{max}(film)/cm^{-1} 1710, 1100 and 840; δ_H(200 MHz; $CDCl_3$) 0.00 (s), 0.10 (s), 0.85 (s), 0.94 (d, *J* 6.6), 0.96 (s), 2.57 (m) and 3.53 (m); δ_C(50 MHz; $CDCl_3$) −5.3 (q), 14.9 (q), 15.0 (q), 18.2 (s), 18.3 (s), 21.1 (t), 21.2 (t), 22.4 (q), 23.2 (q), 25.9 (q), 26.0 (q), 27.2 (t), 27.4 (t), 33.7 (t), 34.3 (t), 36.4 (t), 36.8 (t), 38.7 (t), 40.9 (t), 41.0 (d), 41.1 (d), 47.7 (s), 48.5 (s), 63.0 (t), 64.0 (t) and 217.2 (s); GC-MS first peak at 10.43 min, *m/z* 241 (M − 57)$^+$, 171, 159 (100%) and 75; second peak at 10.85 min, *m/z* 241 (M − 57)$^+$, 171, 159 (100%) and 75.

3-(1,3-*Dimethyl*-2-*methylenecyclohexyl*)*propanol* **7**.—The ketone **6** (500 mg) was treated with Wittig reagent prepared by methyltriphenylphosphonium bromide (3 g) and BuLi (1.6 mol dm^{-3}; 5.25 cm^3) in dry THF (30 cm^3) at reflux overnight. Work-up afforded an olefin (150 mg), which was used without purification in the next step. The olefin was treated with $Bu_4N^+F^-$ (THF soln., 2.7 cm^3) at room temp. overnight. Work-up and purification over silica gel (hexane–EtOAc, gradient) afforded the alcohol **7** (33 mg) (a mixture of diastereoisomers) [HR-MS (GC-CI, CH_4) first peak at 7.53 min Found: *m/z* 182.1674.$C_{12}H_{22}O$ requires 182.1671. Second peak at 8.16 min Found: *m/z* 182.1689. $C_{12}H_{22}O$ requires 182.1671]; ν_{max}(film)/cm^{-1} 3350, 1630 and 890; δ_H(200 MHz; $CDCl_3$) 1.02 (d, *J* 6.7), 1.03 (d, *J* 6.0), 1.03 (s), 1.04 (s), 3.57 (t, *J* 5.9), 3.64 (t, *J* 5.7) and 4.70 (m); δ_C(50 MHz; $CDCl_3$) 19.3, 19.5, 21.8, 21.9, 24.6, 26.4, 27.2, 27.4, 33.1, 33.3, 33.8, 37.2, 37.3, 37.4, 38.6, 39.0, 39.6, 41.3, 63.5, 63.7, 103.3, 104.4, 158.6 and 159.6; GC-MS: first peak at 8.08 min, *m/z* 182 (M)$^+$, 123 (100%), 109, 107, 95, 81, 67, 57 and 55; second peak at 8.43 min, *m/z* 182 (M)$^+$, 123, 109, 107, 95, 81 (100%), 67, 57 and 55.

2-(1,3-*Dimethyl*-2-*methylenecyclohexyl*)*ethyl Isopropyl Ketone* (*Tridensone*) *and its Isomer*.—The alcohol **7** (160 mg) was treated with oxalyl chloride (0.3 cm^3) and DMSO (0.34 cm^3) in CH_2Cl_2 (3 cm^3) at −78 °C. Then Et_3N (1.8 cm^3) was added at 0 °C and work-up afforded an aldehyde (160 mg), which was added without purification into a Grignard reagent solution prepared from Mg (0.1 g) and isopropyl bromide (0.41 cm^3) in dry diethyl ether (3 cm^3). The mixture was stirred for 3 h and work-up afforded an alcohol (95 mg), which was used without purification in the next step. The alcohol was treated with Jones reagent (1.5 cm^3) in acetone (2 cm^3) at 0 °C for 20 min. Work-up afforded a residue (36 mg). The residue was purified by silver nitrate-impregnated silica gel column chromatography (hexane–EtOAc, gradient) to yield (+)-**1a** (8.5 mg) and (−)-**1b** (12.1 mg). (+)-**1a**. $[\alpha]_D^{22}$ +12.7 (*c* 0.85, $CHCl_3$); ν_{max}(film)/cm^{-1} 1715 and 1634; δ_H(600 MHz; $CDCl_3$) 1.008 (3 H, s, 13-H), 1.013 (3 H, d, *J* 6.4, 15-H), 1.06 (3 H, d, *J* 6.3, 12- or 11-H), 1.07 (3 H, d, *J* 7.1, 11- or 12-H), 2.58 (1 H, sept, *J* 6.7, 10-H), 4.70 (1 H, s, 14b-H) and 4.76 (1 H, s, 14a-H); δ_C(150 MHz; $CDCl_3$) (Table 1); *m/z* 222 (M$^+$), 123 (100%), 109, 81, 67 and 43. (−)-**1b** [HR-MS Found: *m/z* 222.2206. $C_{15}H_{26}O$ requires 222.1984]; $[\alpha]_D^{22}$ −1.9 (*c* 1.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 1715, 1635 and 895; δ_H(600 MHz; $CDCl_3$) 1.03 (3 H, d, *J* 6.6, 15-H), 1.04 (3 H, s, 13-H), 1.10 (6 H, d, *J* 7.1, 11- and 12-H), 2.63 (1 H, sept, *J* 6.8, 10-H), 4.68 (1 H, s, 14b-H) and 4.71 (1 H, s 14a-H); δ_C(150 MHz; $CDCl_3$) (Table 1); *m/z* 222 (M)$^+$, 204, 189, 179, 161, 151, 123 (100%), 109, 95, 81, 71, 55 and 43.

Acknowledgements

We thank Professor Wu, Tamkang University, Taiwan, for sending us the ^{1}H NMR spectrum of natural tridensone (**1**). The NOESY experiments were carried out at this University using a Varian Unity 600 (600 MHz) spectrometer by Miss Y. Kan and the mass spectra were taken by Miss Y. Okamoto, to whom many thanks are due. We also thank Dr. M. Ishibashi, Hokkaido University, for a valuable discussion about the structure of metachromin D. This work was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, Japan.

References

1 C.-L. Wu and C.-L. Chen, *Phytochemistry*, 1992, **31**, 4213.
2 C.-L. Wu, S.-J. Chan, M. Tori, H. Furuta, A. Sumida and Y. Asakawa, *J. Chi. Chem. Soc.* (*Taipei*), 1990, **37**, 387.
3 M. Tori, *Revista Latinoamerica Química*, 1991, **22/3**, 73.
4 M. Pfau, G. Revial, A. Guingant and J. d'Angelo, *J. Am. Chem. Soc.*, 1985, **107**, 273.
5 J. d'Angelo, D. Desmaële, F. Dumas and A. Guingant, *Tetrahedron: Asymmetry*, 1992, **3**, 459.
6 M. Ishibashi, Y. Ohizumi, J.-F. Chen, H. Nakamura, Y. Hirata, T. Sasaki and J. Kobayashi, *J. Org. Chem.*, 1988, **53**, 2855; J. Kobayashi, K. Naitoh, T. Sasaki and S. Shigemori, *J. Org. Chem.*, 1992, **57**, 5773.

Paper 4/00156G
Received 11*th January* 1994
Accepted 22*nd March* 1994