Synthesis of (+)-(4az,6az,7az)-Hexahydro-6-hydroxy-7-methylcyclopenta[c]pyran-3(1H)-one, a Structure Common to Abelalactone, Aglykon A1, and Isobooine

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Synthesis of (+)-(4az,6az,7az)-hexahydro-6-hydroxy-7-methylcyclopenta[c]pyran-3(1H)-one [(+)-I] has been achieved through an 8-step route starting from 6,7-dihydrocyclopenta-1,3-dioxin-5(4H)-one (4). The identities of synthetic (+)-I with abelalactone, Aglykon A1, and isobooine permitted the unequivocal assignment of this common structure and the relative stereochemistry to these cyclopentano-monoterpenes lactones.

Key words: abelalactone; Aglykon A1; isobooine; cyclopentano-monoterpenes lactone; 1,3-dioxin vinlylogous ester; carboxyolefination

In 1985, Murai and Tagawa reported the isolation of abelalactone, a member of the cyclopentano-monoterpenes lactones, from Abelia grandiflora (Caprifoliaceae) and proposed the structure [4aR-(4az,6az,7az,7az)]-hexahydro-6-hydroxy-7-methylcyclopenta[c]pyran-3(1H)-one [(+)-I] for it on the basis of an X-ray crystallographic analysis and its chemical correlation with loganin. Thereafter, other research groups announced the isolation of two lactones, named Aglykon A1 (no chiroptical data presented) and isobooine, from Cephalis ipecacuanha (Rubiaceae) and from Rawolphia grandiflora (Apocynaceae), respectively, and independently assigned the same structure as (+)-I to them. These three lactones seem to be identical by comparison of the reported spectral data, but unambiguous establishment by chemical synthesis is desirable. In a preparatory study for the synthesis of (+)-I, we presented the stereoselective syntheses of cis-hexahydrocyclopenta[c]pyran-3(1H)-one (2), one of the parent frameworks common to a large number of cyclopentano-monoterpenes lactones, and its trans-isomer (3) starting from 2-(hydroxymethyl)cyclopentanone by adopting the "carboxyolefination/laeotization" technology, which was shown later by us to be very effective for the syntheses of several analogous natural lactones. Herein we wish to record the details of the synthesis of (+)-I achieved by exploiting this technology.

In designing a synthetic route to (+)-I, the 1,3-dioxin vinlylogous ester 4, which had already served successfully as a key intermediate for the syntheses of some natural products, seemed most attractive as a starting material because of the diversity of its chemical reactivity. Smith et al. have reported that hydroxylation of the enolate, generated via treatment of 4 with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), with (+)-(10-camphorsulfonyl)oxaziridine [(+)-5] was effected at the α'-position, giving (+)-6 (14% ee) as a major product in 37% yield. In the present study, however, addition of hexamethylenediamine (HMDA) to a similar hydroxylation of 4 with (+)-5 raised the yield of 6 to 46%. Methylative 1,3-carbonyl transposition of 6 was then achieved with methyl lithium in THF at −78°C followed by aqueous HCl treatment, affording the cyclopentenone 7 in 92% yield.

It is known that catalytic hydrogenation of the 2,3-disubstituted cyclopentenones containing a hydroxy group at the 4-position (e.g., 7) provides the cyclopentanone derivatives with the 3,4-trans-disposition of substituents due to the addition of hydrogen syn to the hydroxy group. Therefore, the two hydroxy groups of 7 were first protected to give the corresponding tert-butyldimethylsilyl ether 8 in 93% yield. Hydrogenation of 8 using Adams catalyst and hydrogen in AcOEt occurred predominantly from an orientation opposite to the bulky tert-butyldimethylsilyloxy group at the 4-position, giving the 2,3-cis-isomer (9) and the 2,3-trans-isomer (10) in 59% and 33% yields, respectively. The structures of 9 and 10 were assigned on the basis of the following NMR spectral and chemical evidence. (i) As shown in formulas 9 and 10 (Chart 1), nuclear Overhauser effect (NOE) experiments revealed cis relationships for the vicinal protons at the 3- and 4-positions in both isomers, a cis disposition for the two substituents at the 2- and 3-positions of 9, and a trans disposition for the corresponding substituents of 10. (ii) The C(3)-methyl carbon (δ 9.1) of 9 resonated at higher field than the corresponding carbon (δ 13.8) of 10 due to a steric effect. (iii) On treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene at room temperature for 19 h, the 2,3-cis-isomer (9) provided the 2,3-trans-isomer (10) in 84% yield.

For the purpose of effecting carboxyolefination reaction of 10, a route via addition–dehydration seemed to be a favorable choice, based on our previous experiments. Thus, addition of the lithium enolate derived from ethyl acetate to 10 was carried out in THF at −78°C for 2 h, affording the tertiary alcohol 11 in 70% yield as a 57:43 mixture of the two possible diastereoisomers. Dehydration of 11 using Martin sulfurane in CH2Cl2 proceeded smoothly at room temperature, providing the (E)-α,β-unsaturated ester 12a as a sole product in 93% yield. The

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assignment of geometry in 12a was based on the fact that an (E)-isomer was a major product formed in a similar dehydration reaction and on a comparison of the chemical shift for the C(2)-proton (δ 2.46) in 12a with those in analogous (E)- and (Z)-isomers.6,7 Catalytic hydrogenation of 12a over Adams catalyst provided the ester 13a as a 16:84 diastereoisomeric mixture, which was then subjected to deprotection with AcOH–H₂O–THF (3:1:1, v/v/v) at room temperature for 24 h. However, a main product obtained in 72% yield (from 12a) was the 1,2-trans-diol 14, and the yield of the desired (±)-1 derived from subsequent cyclization was only 14% (from 12a) (Table 1). Since the structurally analogous cis-lactone 17 had been prepared from 16 in 71% yield together with 18 (20% yield) by a similar hydrogenation–deprotective cyclization,7 poor yield of (±)-1 was presumed to be due to steric bulkiness of the tert-butylidimethylsilyloxy group at the 4-position of 12a. Prior to hydrogenation, deprotection of 12a was therefore performed with AcOH–H₂O–THF (3:1:1, v/v/v) to furnish the diol 12b (89% yield), which was then subjected to catalytic hydrogenation and subsequent acid-promoted cyclization. Contrary to our expectation, the 1,2-trans-diol 14 was still the main product (75% yield). We next anticipated that introduction of a bulky substituent at the primary hydroxy group of 12b could depress hydrogenation from the same side as the C(2)-substituent. Toward this end, tert-butylidimethylsilyl and tert-butylidiphenylsilyl groups were selected and introduced to 12b to afford 12c and 12d in 82% and 94% yields, respectively. As expected, separate catalytic hydrogenations of 12c,d and subsequent deprotective cyclizations of the resulting esters 13c,d provided the cis-lactone (±)-1 predominantly in both cases (Table 1). The small coupling constants (J = 3.5 and 4.5 Hz) between
C(1)-H's and C(7a)-H measured in the 'H-NMR spectrum of (+)-1 in CDCl₃ indicate that this lactone adopts an iridomyrmecin-type conformation, as previously proposed on the basis of NOE experiments. The 1,2-trans-diol 14 was finally subjected to alkaline hydrolysis followed by cyclization with dicyclohexylcarbodiimide (DCC), affording the trans-lactone 15 in 80% yield as a labile (to hydrolysis) solid.

The 'H-NMR (CDCl₃) and 13C-NMR (CDCl₃) spectra of the synthetic (+)-1 were virtually identical with those of natural abelia lactone [monohydrate: mp 79.5–80°C; [a]D +138.8° (MeOH)] 14 and Aglykon A1 (mp 93–95°C). The 'H-NMR spectral data for (+)-1 were also found to match those of natural isoboeicenin [oil; [a]D +65.0° (c=0.2, MeOH)] reported in the literature. In 1985, Murai et al. reported the structural elucidation of abeloside A isolated, along with abelia lactone, from A. grandiflora and postulated a bis-iridoid structure, in which secoligasic acid is esterified with the hydroxy group of (+)-1. The identical structure was recently proposed for lacinnatioside II isolated from Dispasia lacinniata (Dispasiaceae). 15 Again, the 'H-NMR (CDCl₃) spectral data for (+)-1 were in agreement with those of (+)-1 derived from lacinnatioside II.

In conclusion, the above synthesis of (+)-1 exploiting the “carboxyoxyelation/lactonization” technology for the 2-(hydroxymethyl)cyclopentanone derivative has established unambiguously the structures and relative stereochemistry of abelia lactone, Aglykon A1, and isoboeicenin as (4αz,6α,7α,7αZ)-hexahydro-6-hydroxy-7-methylcyclopenta[c][pyran-3(1H)-one]. It should also be emphasized that the synthetic potential of the 1,3-dioxin vinylogous ester 4, exemplified previously by the syntheses of several cyclopentanono-monoterpenic lactones, has now been extended to cover the synthesis of the more highly substituted analogue (+)-1.

**Experimental**

**General Notes** All melting points were determined by using a Büchi model 530 capillary melting point apparatus and are corrected. TLC was run on Merck precoated silica gel 60 F254 plates (0.25-mm thickness). Flash chromatography was carried out by using Merck silica gel 60 (No. 9385). Spectra reported herein were recorded on a Hitachi M-80 mass spectrometer, either a JASCO A-202 or a Shimazu FTIR-8100 IR spectrophotometer, or a JEOL JNM-EX-270 (100 MHz, 67.8 MHz) or a JEOL JNMGX-500 (1H 500 MHz, 13C 125.65 MHz) NMR instrument. Chemical shifts are reported in ppm downfield from internal Me₄Si. Elemental analyses and MS measurements were performed by Mr. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, dddd = doublet-of-doublets-of-doublets, dddd = doublet-of-doublets-of-doublets-of-doublets, dm = doublet-of-quartets, m = multiplet, q = quartet, s = singlet, t = triplet. **(±)-(10-Camphorsulfon)-oxaziridine [(±)-5]** This compound was prepared from (±)-(10-camphorsulfonic acid in a manner similar to that described in the literature for (+)-5. Recrystallization from 2-propanol afforded an analytical sample as colorless prisms, mp 156–157°C; MS m/z: 229 (M⁺), 99. Calcul. For C₂₂H₃₅NO₂S: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.20; H, 6.78; N, 5.97. The 'H-NMR (CDCl₃) and 13C-NMR (CDCl₃) spectra of this sample were virtually identical with those of (+)-5 reported in the literature.

**(±)-4,6-Dihydro-6-hydroxy-cyclopentan-1,3-dioxin-5(4H)-one (6)** A stirred solution of disopropylamine (3.7 ml, 26.4 mmol) in dry THF (100 ml) was cooled to 0°C in an atmosphere of Ar, and a 1.60 M solution (16.5 ml, 26.4 mmol) of n-BuLi in hexane was added dropwise. After 20 min, the mixture was cooled to −78°C, and a solution of the 1,3-dioxin vinylogous ester 4 (3.08 g, 22.0 mmol) in dry THF (45 ml) containing HMPA (4.6 ml, 26.4 mmol) was added dropwise over 20 min. After 1 h, a solution of (±)-5 (10.1 g, 44.0 mmol) in dry THF (80 ml) was added dropwise over 20 min, and the mixture was further stirred at −78°C for 4 h and at 0°C for 30 min. The reaction was quenched by adding saturated aqueous NH₄Cl (30 ml), and the mixture was warmed to room temperature. The aqueous layer was separated from the organic layer and extracted with CH₂Cl₂. The CH₂Cl₂ extracts and the above organic layer were combined, dried over anhydrous MgSO₄, and concentrated in vacuo to leave a yellow solid, which was then subjected to flash chromatography [AcOEt-hexane (2:1, v/v)], Earlier fractions afforded the starting vinylogous ester 4 (920 mg, 30% recovery). Later fractions of the above chromatography gave a yellow solid (2.09 g), which was recrystallized from AcOEt-hexane (1:1, v/v) to provide a first crop (0.95 g) of 6 as slightly yellow needles, mp 95–96°C. The IR (CHCl₃) and 'H-NMR (CDCl₃) data for this sample were virtually identical with those of authentic 6 (mp 95–96°C) reported in the literature. A second crop (0.03 g) was obtained by concentration of the mother liquor from the above recrystallization under reduced pressure and subsequent precipitation of the residue by flash chromatography [CH₃Cl₂–EtOH (20:1, v/v)]. The total yield of 6 was 1.58 g (46%).
Isomerization of 9 to 10 A mixture of 9 (56 mg, 0.15 mmol), DBN (4 mg, 0.03 mmol), and benzene (2.5 ml) was stirred at room temperature for 19 h. The reaction mixture was then washed successively with 5% aqueous HCl and saturated aqueous Na2SO4, dried over anhydrous MgSO4, and concentrated in vacuo. Purification of the residual oil by flash chromatography[19] (Hexane-Ch2Cl2, 1:1, v/v) provided 10 (47 mg, 84%) as a colorless solid, mp 47.5−48.5 °C, which was identical (by comparison of the IR and 1H-NMR spectra and TLC behavior) with the material isolated by preparative TLC from 9 by using 1% ethyl acetate in hexane as eluent.

(±)-[2S,3R,4S]-[4]-[(1,1-Dimethylcyclohexyl)[1]-[1,1-dimethylcyclohexyl][1]-[oxy]-1-hydroxy-3-methylcyloptene-2-acetic Acid Ethyl Ester (11) A stirred solution of diisopropylamine (0.21 ml, 1.5 mmol) in dry THF (5 ml) was cooled to −78 °C in an atmosphere of Ar, and a 1.50 m solution (1.0 ml, 1.5 mmol) of n-BuLi in hexane was added dropwise. After the mixture had been stirred for 30 min, Acid (10) (0.14 mmol) was added, and warming was continued for 20 min. A solution of 10 (418 mg, 1.12 mmol) in dry THF (2 ml) was then added dropwise over 5 min, and the mixture was stirred at −78 °C for a further 2 h. The reaction was quenched by adding saturated aqueous NH4Cl (2 ml), and the mixture was allowed to warm to room temperature. The aqueous layer was separated from the organic layer and extracted with ether (3 × 10 ml). The ether extracts and the above organic layer were washed, with saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. Purification of the residual oil by flash chromatography[19] (hexane-AcOEt (15:1, v/v)) furnished 11 (362 mg, 70%) as a colorless oil, MS m/z: 415 (M−OEt), 403 (M−tert-But), IR νmax cm−1: 3250 (OH), 1736 and 1719 (diesteriocoef ester COs); 1H-NMR (CDCl3) δ: 0.03, 0.04, 0.06, and 0.08 (s each, two 5Me2S); 0.87 and 0.89 (s each, two 5Me2S); 1.12 (s, 3H); 1.17 (s, 3H); 1.27 (H, t, J = 7-Hz, OCH3Me); 1.34 (H, d, J = 3.5 Hz, OH); 1.92 (H, m, C-2H); 2.60 and 2.75 (d each, J = 14.5 Hz, CH2COEt), 3.55 (dd, J = 10.5, 4.5 Hz) and 3.83 (dd, J = 10.5, 3.5 Hz) (C2H2O4); 3.95 (s, OH), 4.1−4.2 [m, OMe, Me and C(OH)]; minor isomer δ: 0.04, 0.07, and 0.08 (s each, two 5Me2S); 0.80 and 0.90 (s each, two tert-Buts); 0.94 (d, J = 7-Hz, C-3-Me); 1.26 (s, J = 7-Hz, OMe, Me); 1.71 (dd, J = 11.6, 4.5 Hz, C-2H2); 1.9−2.05 (m, 5H, C-3-H); 1.97 (dd, J = 13.5 Hz, and 2.07 (dd, J = 14.5, 2.5 Hz) (C5-H5s); 2.57 and 2.80 (d each, J = 14.5 Hz, CH2COEt), 3.80 (dd, J = 10.5, 6.5 Hz) and 3.90 (dd, J = 10.5, 4.5 Hz) (C2H2O4); 4.1−4.2 [m, OMe, Me, C(OH)]; 4.4 Hz (C5-H5s).

The 1H-NMR spectrum indicated that the major isomer (±) was 74.3% of the mixture of the two possible diastereoisomers.

(±)-[2S,3R,4S]-[4]-[(1,1-Dimethylcyclohexyl)[1]-[1,1-dimethylcyclohexyl][1]-[oxy]-1-hydroxy-3-methylcyloptene-2-acetic Acid Ethyl Ester (12a) A mixture of 11 (437 mg, 0.95 mmol), bis(2,2,2-trifluoro-1-phenyl-1-(trifluoromethoxy)ethoxy) diphenyl sulfuranate[19] (770 mg, 1.14 mmol), and dry CH2Cl2 (18 ml) was stirred in an atmosphere of N2 at room temperature for 3 h. The reaction mixture was then poured into H2O (10 ml) and extracted with CH2Cl2. The CH2Cl2 extracts were washed with saturated aqueous NaCl, dried over anhydrous MgSO4, and concentrated in vacuo. Purification of the residual oil by flash chromatography[19] (hexane-AcOEt (20:1, v/v)) gave 12a (390 mg, 93%) as a colorless oil, MS m/z: 442 (M+); IR νmax cm−1: 1717 (ester CO), 1655 (C=C); 1H-NMR (CDCl3) δ: 0.03, 0.036, 0.039, and 0.042 (1H, each, two SiMe3S); 0.86 and 0.87 (18H, each, two tert-Buts); 1.02 (3H, d, J = 6.5 Hz, C-3-Me); 1.27 (H, t, J = 7-Hz, OCH3Me); 1.88 [1H, m, C-3-H]; 2.46 [1H, m, C-2H]; 2.69 (1H, ddd, J=19, 5, 3, 2.5 Hz) and 3.08 (1H, ddd, J=19, 2, 1.5 Hz) (C5-H5s); 3.67 and 3.74 [1H each, dd, J=10, 5 Hz, C2-H2O4]; 4.14 and 4.16 (2H, dq each, J=10.5, 7.5 Hz, OCH2Me), 4.19 [1H, m, C(4-H)], 5.88 (1H, ddd, J=2.5, 2.5, 2.5 Hz, C5-H5s).
2 Hz) and 2.18 (1H, dd, J = 13.5, 10, 5.7 Hz) [C(5)-H's], 1.59 [1H, m, C(2)-H], 1.71 [1H, m, C(3)-H], 1.78 (br, two OH's), 2.266 [1H, m, C(1)-H], 2.49 (1H, dd, J = 16.5, 6 Hz) and 2.65 (1H, dd, J = 16.5, 7.5 Hz) [C(6)-H(2)], 3.57 (1H, dd, J = 11, 6 Hz) and 3.71 (1H, dd, J = 11.5, 3.5 Hz) [C(1)-H(OH)], 4.09 [1H, dd, J = 5, 2.7 Hz, C(4)-H], 4.14 (2H, q, J = 7 Hz, OCH₂Me).

Later fractions of the above chromatography furnished (±)-1 (34.0 mg, 64% from 12c) as a colorless solid. Recrystallization of the solid from hexane-AcOEt (2:1, v/v) afforded an analytical sample as colorless needles, mp 99–101°C; MS m/z (rel. intensity): 170 (M⁺), 7 (12), 139 (100), 126 (44), 124 (43), 111 (47), 110 (31), 97 (55), 83 (26), 81 (41), 69 (35), 55 (31), 43 (40); IR νC=O cm⁻¹: 3620 (OH), 1740 (CO). 3¹H-NMR (CDCl₃) δ: 1.08 [3H, d, J = 7 Hz, C(7)-Me], 1.41 (1H, dd, J = 14, 10.5, 3.5 Hz) and 2.06 (1H, dd, J = 14, 8 Hz) [C(5)-H's], 1.68 (1H, br, OH), 1.92 [1H, ddg, J = 10, 5.5, 3.7 Hz, C(7)-H], 2.16 [1H, ddg, J = 10.5, 10.5, 4.5 Hz, C(7)-H], 2.38 [1H, dd, J = 15, 4.7 Hz] and 2.64 (1H, dd, J = 15, 11.5 Hz) [C(4)-H's], 2.94 [1H, ddg, J = 10.5, 8.5, 8.7 Hz, C(4)-H], 4.13 [1H, dd, J = 3.5 Hz each, C(6)-H], 4.15 (1H, dd, J = 11.5, 3.5 Hz) and 4.32 (1H, dd, J = 11.5, 4.5 Hz) [C(1)-H(3)]; 13C NMR (CDCl₃) δ: 12.7 [C(7)-Me], 32.7 [C(4a), 34.5 [C(4)], 41.5 [C(5)], 41.7 [C(7)], 68.6 [C(11)], 75.6 [C(6)], 173.4 [C(3)]; high-resolution MS Calcd for C₁₀H₁₆O: 170.0943, Found: 170.0965. Anal. Calcd for C₁₀H₁₆O: C, 63.61; H, 8.29. Found: C, 63.83; H, 8.36. This sample was found to revert slowly to the hydroxy carbonylic acid on standing at room temperature.

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References and Notes
16) The [3]-C-NMR spectrum of abelalactone in CDCl₃ was newly measured by Professor F. Murai for comparison with that of (±)-1.
17) The [3]-H-NMR spectral data of Aglykon A1 in CDCl₃ have been recorded at higher field than those of (±)-1 by 0.10–0.12 ppm.
18) The carbon signals, except for the (C(7)-Me) signal, of isoboenone in CDCl₃ have been reported at higher field than those of (±)-1 by 1.0–1.2 ppm.

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