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The first total synthesis of acutifolone A, a pinguisane-type sesquiterpenoid isolated from the Japanese liverwort *Porella acutifolia* subsp. *tosana*

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Abstract—The first total synthesis of acutifolone A, a sesquiterpenoid carrying the bicyclo[4.3.0]nonane structure **1**, was successfully achieved from the intermediate **6** produced by the intramolecular Diels–Alder reaction.

Liverworts produce a variety of sesquiterpenoids, possessing the bicyclo[4.3.0]nonane moiety such as acutifolone A **1**,[1] bisacutifolone C **2**,[1] pinguisenol **3**,[2] and chiloscyphone **4**[3] (Fig. 1). These natural products have unique structures including the *cis*-oriented continuous-substitutions in the bicyclo[4.3.0]nonane structure, which provide fish-killing, anticancer, and antimicrobial[4] activities. Until now, synthetic studies of these sesquiterpenoids have adopted intramolecular cycloaddition-approaches of the corresponding cyclopentane rings to construct the bicyclo[4.3.0]nonane structure,[5] although laborious manipulation of the undesired cycloadducts co-obtained was required. Furthermore, assembly of structures carrying highly oxygenated functional groups at the bridgehead position has not been reported as yet. Against such background, we undertook an efficient synthesis of these sesquiterpenoids with our own approach different from the conventional methodology. Thus, we developed construction methodology of the bicyclo[4.3.0]nonane system (type-**6**) by using the intramolecular Diels–Alder reaction of **5**,[6a] and reported its application to total synthesis of chiloscyphone **4** (Scheme 1).[6b] This protocol enabled us not only to synthesize the bicyclo[4.3.0]nonane framework, but also to introduce a variety of functional groups to desired positions. We describe herein the synthetic availability

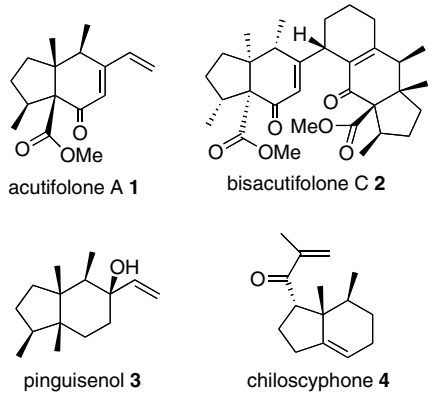
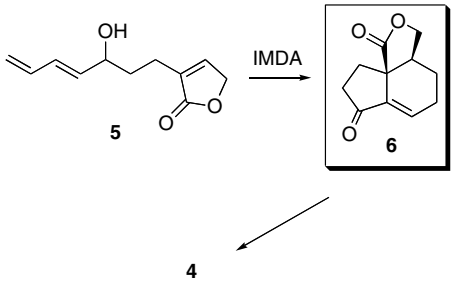


Figure 1.



Scheme 1.

Keywords: Liverwort; Acutifolone; Pinguisane; Sesquiterpenoid; Total synthesis; Intramolecular Diels–Alder reaction; Mukaiyama aldol reaction; Desulfurization; Allylic oxidation.
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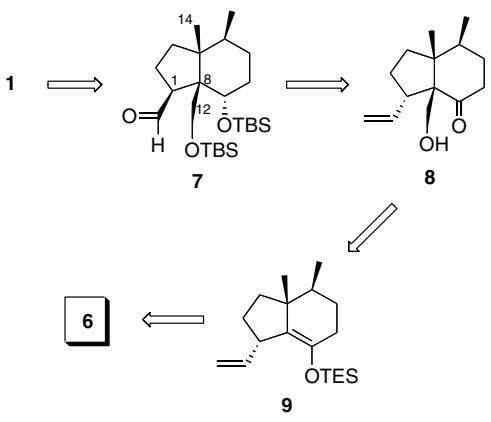
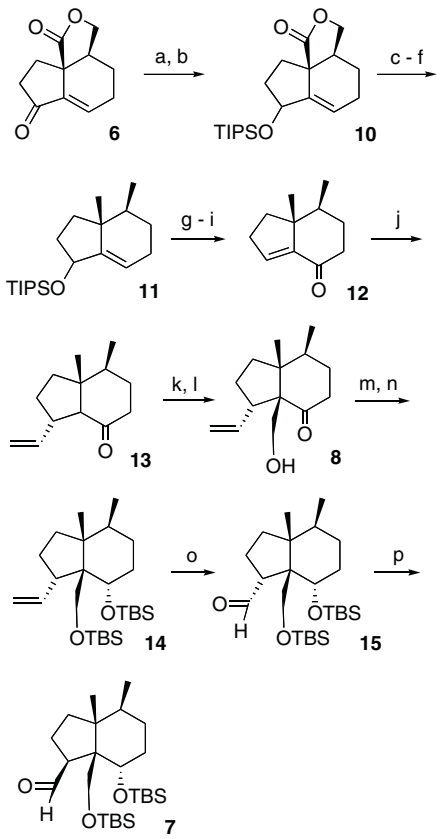
of **6** to synthesize complicated natural products, such as acutifolone A **1**, which was isolated from the Japanese liverwort *Porella acutifolia* subsp. *tosana*. In addition to construction of the all-*cis* four-carbon sequence including two quaternary centers and the unsaturated ketone moiety, the successful introduction of the oxygenated function at the C-8 position by the Mukaiyama aldol reaction effected the first total synthesis of **1** through **6**.

In retrosynthetic analysis, we envisaged the stereocenter at the C-1 position of **7** would be constructed by isomerization of the corresponding α-aldehyde (Scheme 2). The functionalized carbon atom at the C-8 position of **8** would be synthesized stereoselectively by the Mukaiyama aldol reaction of the silyl enol ether **9**, which would be obtained by successive manipulation of **6**.

Along this line, synthesis of the all-*cis* tetramethyl moiety of **7** from **6** is outlined in Scheme 3. Thus, **6** was reduced under the Luche conditions,[7] followed by TIPS-protection to afford **10**. After reduction of the lactone moiety with DIBAL-H, mesylation, conversion into the corresponding cyclic sulfide, and desulfurization with Raney Ni W-4[8] gave **11**.[6b] The tri-substituted olefin was exposed to hydroboration, followed by oxidative work-up to give a secondary alcohol. After oxidation of the alcohol, elimination of the siloxy moiety led to the unsaturated ketone **12**. Michael addition of a vinyl functional group gave the ketone **13** as a single isomer. The stereochemical control might be governed by steric hindrance of the β-face dimethyl moiety. Compound **13** was converted with TESI and Et_3N into a mixture of the TES ethers (**9**:the tri-substituted isomer = 2.6:1), which was submitted to coupling with HCHO under the Mukaiyama aldol conditions[9] to give the alcohol **8**.[10] The coupling reaction was extensively assessed to obtain the desired alcohol **8** in acceptable yields (Table 1). Among such reactions that with aq formaldehyde and the water-tolerant Lewis acid $Yb(OTf)_3$ gave the desired **8** in 36% yield (entry 1). Upon using a similar Lewis acid $Sc(OTf)_3$, the diluted reaction condition increased the product yield (45% in 0.1 M, 88% in 0.05 M, entries 2 and 3). When reacted with $(HCHO)_n$, no desired product was obtained (entry 4). Reactions with other nucleophilic reagents (HCO_2Et, MeI, $ClCO_2Me$) were also unsuccessful. In the case of other activated reagents, $CaCl_2$ in DMF[11] or CSA in THF, these protocols did not provide the expected **8** (entries 5 and 6). In all of the entries, **8** was obtained as a single diastereomer by steric hindrance of the adjacent α-face vinyl moiety



Scheme 2.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −70 °C; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91% in two steps; (c) DIBAL-H, CH_2Cl_2, −40 °C; (d) MsCl, pyridine, 0 °C; (e) Na_2S, DMF, rt; (f) Raney Ni W-4, THF, reflux, 61% in four steps; (g) $BH_3{\cdot}$THF, THF, 0 °C, then H_2O_2, NaOH, rt; (h) TFAA, DMSO, Et_3N, CH_2Cl_2, −60 °C; (i) DBU, PhMe, 0 °C, 56% in three steps; (j) $CH_2{=}CHMgCl$, CuI, THF, −78 °C, 79%; (k) TESCl, Et_3N, LiI, CH_2Cl_2, 40 °C; (l) HCHO aq, $Sc(OTf)_3$, THF, 65 °C, 54% (88% conversion) in two steps, see Table 1; (m) $LiAlH(OtBu)_3$, THF, 0 °C; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96% in two steps; (o) OsO_4, Me_3NO, acetone, H_2O, 0 °C, then $NaIO_4$, rt, 71%; (p) DBU, PhH, 50 °C, 99%.

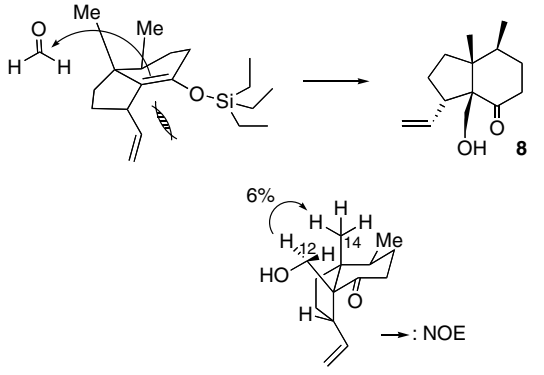
Table 1. Diastereoselective introduction at C-8 position by using the Mukaiyama aldol reaction

Entries	Reagents and conditions[a]	Yields (%) of **8**[b]
1	$Yb(OTf)_3$, HCHO aq	36
2	$Sc(OTf)_3$, HCHO aq	45
3	$Sc(OTf)_3$, HCHO aq	88
4	$Sc(OTf)_3$, $(HCHO)_n$	0
5	$CaCl_2$, HCHO aq	0
6	CSA, HCHO aq	0

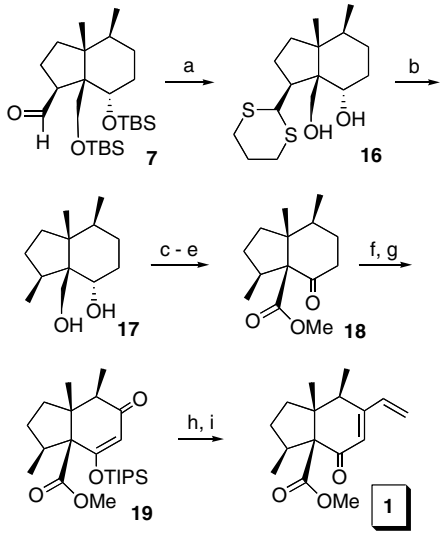
[a] THF was used as a solvent (65 °C), without entry 5 (DMF was used). A ratio of HCHO aq to a solvent was ca. 1:2. 0.1 M concentrations of the substrate was used, without entry 3 (0.05 M concentration).
[b] Conversion yield in two steps from **13**.

(Scheme 4). The stereostructure of **8** was confirmed by the NOE correlation between H-12 and H-14. Reduction of a ketone in **8** with $LiAlH(OtBu)_3$ gave a diol as a single isomer, followed by protection to furnish **14**, although $NaBH_4$ afforded both α- and β-alcohols (α/β = 4:3). Oxidative cleavage of the terminal olefin and isomerization under the basic conditions provided the desired β-aldehyde **7**.[12]

Deoxygenation of the aldehyde and completion of the total synthesis are displayed in Scheme 5. Reaction of **7** with 1,3-propanedithiol in the presence of $BF_3{\cdot}OEt_2$ furnished the TBS-deprotected dithiane **16**, which was submitted to desulfurization with Raney Ni W-4 to provide the desired *cis*-tetramethyl alcohol **17**. In attempts for this deoxygenation, both dehydroxylation of the alcohol moiety and deoxygenation of the corresponding xanthate were unsuccessful, leading to complicated mixtures by undesired rearrangements. Methyl ester **18** was then produced via sequential oxidation (PDC, $NaClO_2$) and methylation. Conversion of **18** into a TIPS ether and the following allylic oxidation by the Corey protocol gave the β-siloxy unsaturated ketone **19**.[13] 1,2-Addition of a vinyl group using Grignard reagent in the presence of $CeCl_3$,[14] followed by deprotection of the TIPS group gave **1**,[15] which was superimposable to the reported spectroscopic data.[1b]



Scheme 4. Structural determination of **8**.



Scheme 5. Reagents and conditions: (a) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 93%; (b) Raney Ni W-4, THF, reflux, 78%; (c) PDC, DMF, rt; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH–H_2O, 0 °C; (e) $TMSCHN_2$, MeOH, 0 °C, 54% in three steps; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt; (g) TBHP, 20% $Pd(OH)_2$–C, Cs_2CO_3, CH_2Cl_2, O_2, 0 °C, 75% in two steps; (h) $CH_2{=}CHMgCl$, $CeCl_3$, THF, 0 °C; (i) CSA, MeOH, rt, 70% in two steps.

In conclusion, the first total synthesis of acutifolone A **1**was achieved by using the Mukaiyama aldol reaction as a key step. Furthermore, the synthetic availability of **6** was demonstrated by the stereocontrolled synthesis of the natural product carrying the bicyclo[4.3.0]nonane structure. Synthetic studies of other sesquiterpenoids **2** and **3** carrying the related structure are now in progress.

Acknowledgements

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10. Compound **8**: IR (film): 3483, 2956, 2875, 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 5.78 (1H, complex), 5.04 (1H, d, $J = 16.8$ Hz), 4.98 (1H, d, $J = 10.4$ Hz), 3.94 (1H, dd, $J = 3.2$, 10.8 Hz), 3.38–3.28 (3H, m), 2.35 (1H, m), 2.25 (1H, m), 1.98–1.47 (7H, complex), 0.93 (3H, d, $J = 6.8$ Hz), 0.84 (3H, s).
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12. Compound **7**: IR (KBr): 2954, 2927, 2856, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 9.95 (1H, d, $J = 1.6$ Hz), 4.16 (1H, d, $J = 10.8$ Hz), 3.61 (1H, d, $J = 10.8$ Hz), 3.51 (1H, dd, $J = 5.6$, 11.2 Hz), 3.12 (1H, t, $J = 9.2$ Hz), 2.12–2.04 (2H, complex), 1.83–1.13 (7H, complex), 0.88 (3H, s), 0.87 (9H, s), 0.85 (9H, s), 0.81 (3H, d, $J = 6.8$ Hz), 0.04 (6H, s), 0.01 (6H, s).
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15. Compound **1**: IR (KBr): 2927, 1736, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 6.47 (1H, dd, $J = 10.8$, 17.6 Hz), 5.99 (1H, s), 5.69 (1H, d, $J = 17.6$ Hz), 5.45 (1H, d, $J = 10.8$ Hz), 3.67 (3H, s), 2.62 (1H, q, $J = 7.0$ Hz), 2.20 (1H, m), 1.70–1.50 (4H, complex), 1.25 (3H, d, $J = 6.8$ Hz), 1.18 (3H, d, $J = 6.8$ Hz), 1.10 (3H, s).