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A new approach to the bicyclo[4.3.0] ring system of natural products from the liverwort: total synthesis of (±)-chiloscyphone and (±)-isochiloscyphone

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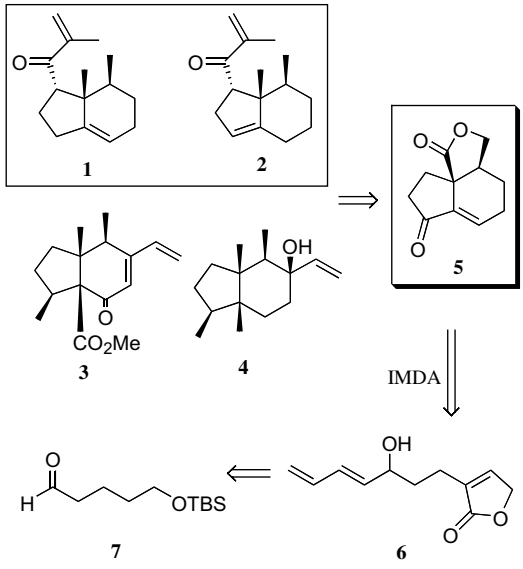
Abstract—Construction of the tricyclic derivative **5**, a common intermediate for the synthesis of sesquiterpenoids **1**–**4**, was accomplished by using the intramolecular Diels–Alder reaction. Availability of **5** was demonstrated by effective total synthesis of chiloscyphone **1** and isochiloscyphone **2**.

The genus liverwort produces a variety of sesquiterpenoids, such as chiloscyphone **1**,[1] isochiloscyphone **2**,[2] acutifolone A **3**[3] and pinguisenol **4**,[4] which possess fish killing, anticancer and antimicrobial activities, along with inhibition of ornithine decarboxylase and cathepsin B.[5] Among them, chiloscyphone **1** was isolated from *Chiloscyphus polyanthos* in 1969. After revision of its structure as depicted in Scheme 1,[2] total synthesis of **1** has been reported by several groups.[6] Their approach generally included intramolecular cycloaddition of appropriate cyclopentane rings. Construction of the skeleton by using intramolecular, 1,4-addition,[6a] aldol reaction,[6b–d] and cyclization of haloalkane derivatives[6e] was reported. However, in their synthesis, the undesired diastereomers of the cycloadduct, which could not be converted into useful forms, were co-produced. Against such background, we envisaged a more efficient synthesis of the liverwort-type sesquiterpenoids than the conventional methodology. We initiated a synthesis of a common precursor **5** of the sesquiterpenoid by using intramolecular Diels–Alder reaction for simultaneous construction of the *cis*-oriented continuous substitutions in the bicyclo[4.3.0] structure of this sesquiterpenoid family. In a previous paper,[7] asymmetric synthesis of the Diels–Alder product (type-**5**) was accomplished.



Scheme 1.

We describe herein an improved synthetic protocol of the racemic **5** and its application to total synthesis of (±)-**1** and (±)-**2**.

Retrosynthetic analysis of chiloscyphone **1** and isochiloscyphone **2** is illustrated in Scheme 1. The key intermediate **5** of **1** and **2** would be obtained by the intramolecular Diels–Alder reaction of the precursor **6**.

Keywords: Chiloscyphone; Total synthesis; Intramolecular Diels–Alder reaction; Sesquiterpenoid; Desulfurization.
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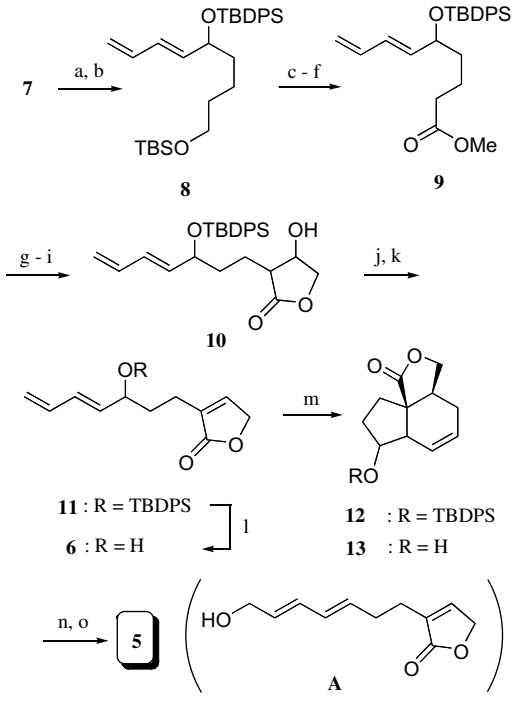
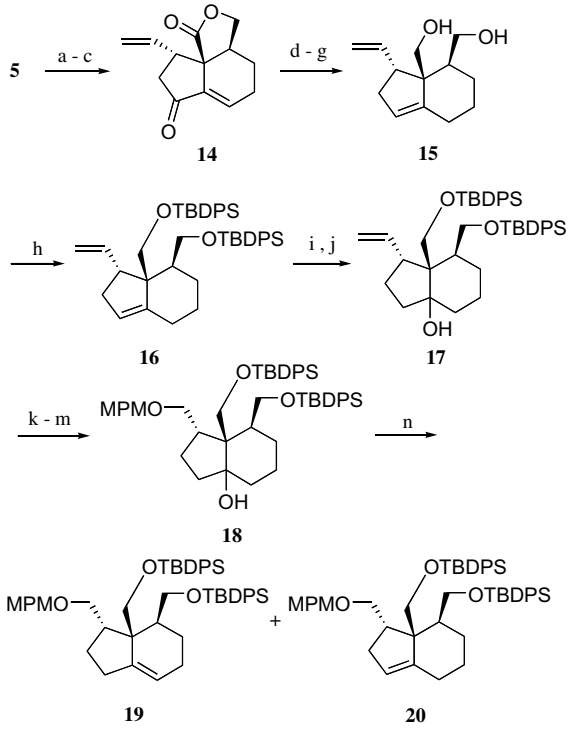
Triene **6** would be prepared from aldehyde **7**, readily available from 1,5-pentanediol.

Along this line, synthesis of the tricyclic compound **5** was commenced from **7**, which was produced by the known manipulation of 1,5-pentanediol[8] (Scheme 2). Thus, reaction of **7** with butadienyl lithium[9] gave the corresponding alcohol, which was protected as a TBDPS ether to furnish **8**. Selective removal of the TBS group, followed by oxidation, gave the corresponding aldehyde, which was further oxidized with PDC, leading to the methyl ester **9**. Compound **9** was submitted to the aldol reaction with $THPOCH_2CHO$, followed by removal of the THP group and cyclization under basic conditions to afford **10**. The lactone **10** was acetylated, followed by elimination under DBU conditions to give the triene **11**, which was submitted to the Lewis acid or thermal-mediated intramolecular Diels–Alder reactions. Attempts using Et_2AlCl in refluxing CH_2Cl_2 or $LiClO_4$ in refluxing PhMe, provided no expected cyclization product. Reaction of **11** with a stronger Lewis acid, $EtAlCl_2$, at ambient temperature was unsuccessful, owing to deprotection of the TBDPS group and rearrangement of the diene moiety to give the product **A**. Among reactions of **11** carrying a TBDPS group under thermal conditions, an inseparable mixture of cycloadduct **12** and unreacted **11** (**12**/**11** = 1:5, 94% yield) was obtained under heating (180 °C) in a sealed tube. The low yield of **12** might be owing to steric hindrance of the protecting group.[10] On the other hand, after deprotection of the siloxy group, heating of **6** in the presence of BHT in a sealed tube (0.1 M in PhMe), produced cycloadduct **13** in 65% yield, as a diastereomeric mixture (1:1.1:0.6). The tricyclic compound **13** in hand was oxidized, followed by isomerization with DBU to furnish the desired intermediate (±)-**5** in excellent yield.

Synthesis of **19** and **20** from **5** is outlined in Scheme 3. The tricyclic compound **5** was converted with TMSOTf into a TMS enol ether, followed by oxidation with $Pd(OAc)_2$,[11] and the Michael addition to give ketone **14** as a single isomer, owing to steric hindrance of the lactone moiety. Successive process involving reduction, mesylation and elimination, selectively afforded a trisubstituted olefin, according to the Saytzeff rule. Reduction of the lactone moiety gave the diol **15**, which was protected as a TBDPS ether to furnish **16**. Selective epoxidation of the electron-rich trisubstituted olefin of **16**,[12] and the epoxide opening by $LiEt_3BH$ afforded the tertiary alcohol **17**.[13] Oxidation of the terminal olefin by OsO_4 and oxidative cleavage gave an aldehyde, which was reduced with $NaBH_4$ and etherified as an MPM ether to afford **18**. Dehydroxylation of the tertiary alcohol was attempted to obtain the tri-substituted olefins **19**



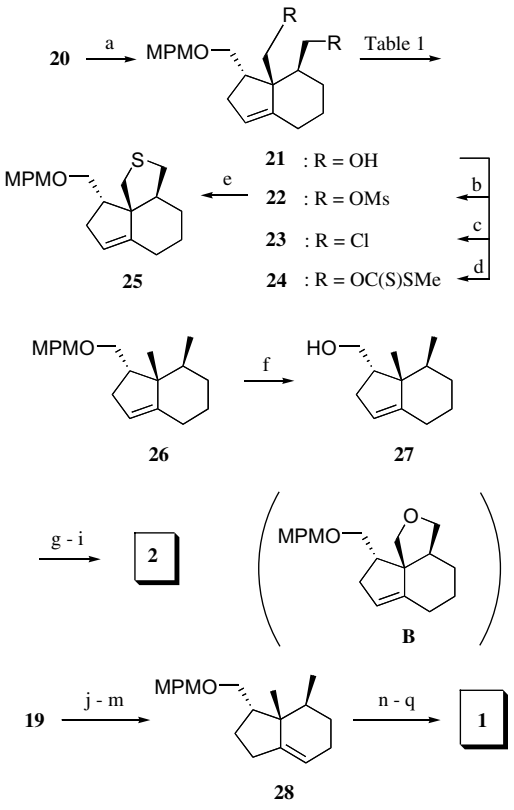
Scheme 2. Reagents and conditions: (a) (*E*)-nBu$_3$SnCH=CHCH=CH$_2$, nBuLi, THF, −78 °C, 93%; (b) TBDPSCl, Imid, DMF, rt, 92%; (c) PPTS, EtOH, rt, 95%; (d) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C; (e) PDC, DMF, rt, 92% in two steps; (f) K_2CO_3, MeI, DMF, 0 °C, 91%; (g) LDA, $THPOCH_2CHO$, THF, −78 °C; (h) PPTS, MeOH, rt; (i) Et_3N, MeOH, rt, 69% in three steps; (j) Ac_2O, py, CH_2Cl_2, rt; (k) DBU, PhMe, 0 °C, 93% in two steps; (l) TBAF, AcOH, THF, rt, 83%; (m) BHT, PhMe, in a sealed tube, 180 °C, 65%; (n) TFAA, DMSO, Et_3N, CH_2Cl_2, −60 °C; (o) DBU, PhMe, 0 °C, 64% in two steps.



Scheme 3. Reagents and conditions: (a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; (b) $Pd(OAc)_2$, CH_3CN, rt, 98% in two steps; (c) CH_2=CHMgBr, CuI, THF, −70 °C, 75%; (d) $NaBH_4$, MeOH, 0 °C; (e) MsCl, py, rt; (f) AcOK, DMF, H_2O, 80 °C; (g) DIBAL, CH_2Cl_2, 0 °C; (h) TBDPSCl, Imid, DMF, rt, 73% in five steps; (i) mCPBA, NaH_2PO_4, CH_2Cl_2, 0 °C; (j) $LiEt_3BH$, THF, rt, 53% in two steps; (k) OsO_4, Me_3NO, acetone, H_2O, rt, then $NaIO_4$, 0 °C; (l) $NaBH_4$, MeOH, 0 °C, 57% in two steps; (m) MPMCl, NaH, nBu$_4$NI, DMF, 0 °C, 70%; (n) $POCl_3$, py, 50 °C, 94%.

and **20**. The regiochemistry of the olefin was confirmed by transformation of **20** into the precursor **16** (1. DDQ; 2. IBX; 3. Ph_3PMeBr, NaHMDS). Reaction with $POCl_3$ at 50 °C gave **19** and **20** in the ratio of 1:10. Upon using $SOCl_2$ in pyridine, lower reaction temperature decreased the ratio of **20** (**19/20** in the ratio of 1:7 at 23 °C, 1:5 at 0 °C and 1:3.5 at −30 °C). Reaction of a mixture of **19** and **20** in the presence of Wilkinson catalysts effected no olefin isomerization. Although, at this stage, specific production of each product could not be achieved, both compounds could be used for synthesis of **1** and **2**, as follows.

In the case of **20**, removal of the TBDPS group provided the diol **21** (Scheme 4). Deoxygenation of **21** to the syn-dimethyl derivative **26** was examined (Table 1). When the mesylate **22** produced from **21** was reacted with $LiAlH_4$ or $LiEt_3BH$, the desired product **26** was not obtained (entries 1 and 2). In contrast to general deoxygenation, which cleaves the C–O bond, cleavage of the S–O bond[14] gave an alcohol and successive cyclization afforded the product **B**. After conversion of the diol **21** into the corresponding dichloride, radical reduction provided no desired **26** (entry 3). Radical reduction of the xanthate **24** was also unsuccessful, owing to an intramolecular radical coupling to obtain a complicated mixture (entry 4). When the alcohols were activated stepwise, the intramolecular cycloadducts were obtained. Finally, reaction of **22** with $Na_2S{\cdot}9H_2O$ furnished the cyclic sulfide **25**, which was submitted to desulfurization with Raney Ni W-4[15] to give the desired **26** in 60% yield (entry 5). Oxidative removal of the MPM group afforded the primary alcohol **27**. Compound **27** was oxidized with IBX, followed by alkylation with $CH_2{=}C(Me)MgBr$ and oxidation with PCC[6e] to give (±)-**2**. By employing essentially the same procedure, total synthesis of **1** was accomplished from **19** (Scheme 4). Synthetic (±)-**1** and (±)-**2** were superimposable to the reported data.[1,2]



Scheme 4. Reagents and conditions: (a) TBAF, THF, 50 °C, 94%; (b) MsCl, py, rt; (c) $SOCl_2$, py, rt; (d) NaH, CS_2, MeI, THF, 0 °C; (e) $Na_2S{\cdot}9H_2O$, DMF, 50 °C; (f) DDQ, CH_2Cl_2, H_2O, 0 °C, 85%; (g) IBX, DMSO, THF, rt; (h) $CH_2{=}C(Me)MgBr$, THF, 0 °C; (i) PCC, CH_2Cl_2, rt, 60% in three steps; (j) TBAF, THF, 50 °C, 90%; (k) MsCl, py, rt; (l) $Na_2{\cdot}9H_2O$, DMF, 50 °C; (m) Raney Ni W-4, THF, reflux, 66% in three steps; (n) DDQ, CH_2Cl_2, H_2O, 0 °C, 92%; (o) IBX, DMSO, THF, rt; (p) $CH_2{=}C(Me)MgBr$, THF, 0 °C; (q) PCC, CH_2Cl_2, rt, 62% in three steps.

Table 1. Deoxygenation of *cis*-oriented diol **21** using its derivatives **22**–**25**

Entry	Substrate	Conditions	Result
1	**22**	$LiAlH_4$, THF, reflux	**B**[a]
2	**22**	$LiEt_3BH$, THF, reflux	**B**[a]
3	**23**	nBu$_3$SnH, AIBN, PhMe, reflux	No reaction
4	**24**	nBu$_3$SnH, AIBN, PhMe, reflux	Unknown
5	**25**	Raney Ni W-4, THF, reflux	**26** (60%)

[a] Compound **B** was not purified, due to its instability.

In conclusion, tricyclic compound **5** was synthesized by using the intramolecular Diels–Alder reaction as the key step in far better yield than that of a previous report.[7] Efficiency of **5** for synthesis of the sesquiterpenoids carrying the bicyclo[4.3.0] system was demonstrated by the total synthesis of (±)-chiloscyphone **1** and (±)-isochiloscyphone **2**. Synthesis of sesquiterpenoids **3** and **4** carrying the related structures is now in progress.

Acknowledgements

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