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Total Synthesis of (+)-Cyclomyltaylan-5α-ol Isolated from the Taiwanese Liverwort *Reboulia hemisphaerica*

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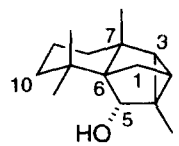
Abstract: The novel tetracyclic sesquiterpenoid (+)-cyclomyltaylan-5α-ol **1** has been synthesized starting from (*S*)-(+)-Hajos-Wiechert ketone analogue **3** *via* SmI_2-promoted reductive cyclization as a key step. Thus, the absolute configuration has been established to be 2*R*,3*R*, 4*R*,5*S*,6*R*,7*R* (cyclomyltaylane numbering) as depicted in structure **1**.

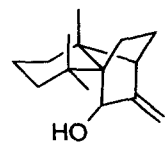
Keywords: polycyclic aliphatic compounds; radicals and radical reactions; terpenes and terpenoids: samarium and compounds

Liverworts contain structurally as well as physiologically interesting organic molecules. Among them are cyclomyltaylane and myltaylane sesquiterpenoids which have unique tetracyclic and tricyclic carbon frameworks respectively. Following the first isolation of cyclomyltaylenol[1a] (cyclomyltaylan-15-ol) from the *Mylia taylorii* (Hook.) by Matsuo *et al.* in 1988, Wu *et al.* subsequently reported the isolation of tetracyclic (+)-cyclomyltaylan-5α-ol **1**[1d] from the Taiwanese liverwort *Reboulia hemisphaerica* in 1995. Similarly, Asakawa *et al.* reported the isolation of tricyclic (–)-myltayl-4(12)-en-5-ol **2** from the French *Bazzania trilobata*[2b] in 1996 (Figure 1). Though the relative stereochemistries of these natural products **1** and **2** have been determined by using modern NMR techniques, the absolute configurations have not been established yet. Intrigued by its novel carbon framework containing tricyclo[2.2.1.$0^{2,6}$]- or bicyclo[2.2.1]heptane fused to cyclohexane ring with three contiguous quaternary carbon centers and an absence of successful total synthesis of cyclomyltaylane-type sesquiterpenoids in literature, we set out our synthetic study and report herein an enantioselective first total synthesis of (+)-**1** thereby establishing the absolute stereochemistry as depicted in structure **1**.

Figure 1



1

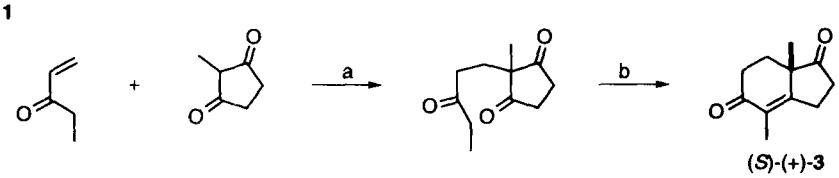


2

PII: S0040-4039(99)00338-X

We previously reported the synthesis of optically pure Wieland-Miescher ketone analogue by amino acid assisted asymmetric cyclization followed by subsequent recrystallization.[3] In a similar manner, an optically pure (*S*)-(+)-**3** (98%ee)[4] was prepared from 2-methyl-2-(3-oxopentyl)-1,3-cyclopentanedione (Scheme 1).

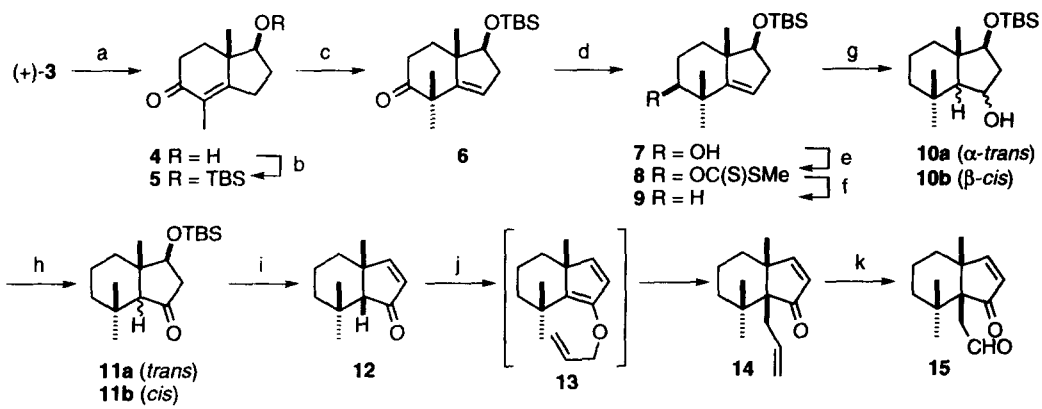
Scheme 1



Reagents and Conditions: a) cat. AcOH, cat. hydroquinone, H_2O, 75 °C, 100%. b) i) L-phenylalanine (1.0 eq), D-CSA (0.5 eq), CH_3CN, r.t. to 70 °C, 5 days, 98%, ii) recrystallization from hexane-ether, 45% (98%ee).

Though the absolute stereochemistry of the natural product **1** was unknown, we employed the optically active (*S*)-(+)-**3** as a starting material (Scheme 2). The saturated carbonyl group in **3** was regio- and stereoselectively reduced with 0.26 equiv. of $NaBH_4$ to give β-alcohol **4** which was then protected with TBSCl to afford TBS ether **5**. Methylation with excess iodomethane in the presence of *t*-BuOK in *t*-BuOH at reflux temperature provided dimethylketone **6**. After reduction of the carbonyl group in enone **6**, removal of the hydroxyl group of **7** was accomplished by applying Barton's radical protocol[5] *via* xanthate **8** to give olefin **9** in 98% yield (2 steps). Hydroboration of **9** and subsequent PCC oxidation followed by treatment with DBU gave cyclopentenone **12**.

Scheme 2

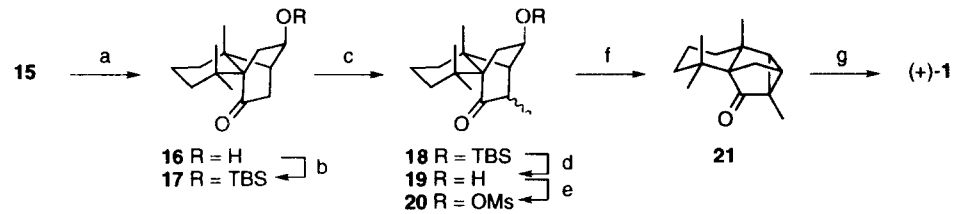


Reagents and Conditions: a) $NaBH_4$ (0.26 eq), MeOH, –20 °C, 30 min, 100%; b) TBSCl, imidazole, cat. DMAP, DMF, r.t., overnight, 98%; c) *t*-BuOK, *t*-BuOH, reflux, 30 min then MeI, 2 h, reflux, 65%; d) LAH, ether, –78 °C, 30 min, 99%; e) *n*-BuLi, CS_2, MeI, THF, 0 °C; f) *n*-Bu_3SnH, cat. AIBN, PhMe, 150 °C, 10 min, 98% (from **7**); g) BH_3•THF, reflux, 20 h then H_2O_2, NaOH, r.t., overnight, 61% (**10a**:**10b**=1:1.2); h) PCC, 4Å MS, CH_2Cl_2, r.t., 89% (from **10a**), 98% (from **10b**); i) DBU, *t*-BuOH, reflux, 88% (from **11a**), 90% (from **11b**); j) NaH, allylbromide, 15-c-5, THF, 40 °C to reflux, overnight then PhMe, reflux, 3 h, 65% based on recovered **12**; k) cat. OsO_4, $NaIO_4$, *t*-BuOH-H_2O (2:1), r.t., 2 days, 75%.

Next, we investigated alkylation reaction at an angular position of enone**12**. Though deuterium was incorporated at the angular position by D_2O addition after treatment with LDA, attempted allylation with allylbromide resulted in the recovery of the starting enone **12**. On the other hand, treatment of **12** with

allylbromide and excess NaH in the presence of 15-crown-5 at 45 °C afforded an acid labile *O*-alkylated allyldienolether **13** which after an addition of toluene was subjected to Claisen rearrangement at reflux temperature to give the desired allylenone **14** as a sole product. The stereoselective introduction of the allyl group with β-configuration at this stage can be judged in view of the transformation of **14** into the natural product **1**. Oxidative cleavage of the allyl group of **14** with a catalytic amount of OsO_4 and excess $NaIO_4$ in *t*-BuOH-H_2O (2:1) gave aldehyde **15** in 75% yield. Thus the crucial intermediate **15** for a key samarium diiodide (SmI_2) cyclization reaction was synthesized in 11 steps from the optically active (*S*)-(+)-**3**.

Scheme 3



Reagents and Conditions: a) SmI_2 (3 eq), *t*-BuOH, HMPA-THF (1:10), –78 °C, 10 min, 52% (β/α=2.4/1); b) TBSCl, imidazole, cat. DMAP, DMF, r.t., overnight, 94%; c) LDA, MeI, 0 °C, 30 min; d) TBAF, THF, r.t., 12 h; e) MsCl, Et_3N, CH_2Cl_2, r.t., 3 h; f) NaOMe, MeOH, r.t., 14 h; g) LAH, ether, 0 °C, 50 min, 25% (from **16**).

Efficiency of reductive cyclization of alkyl or ketyl radical species generated by SmI_2 is well precedented.[6] However, a successful cyclization involving cyclic enone moiety and formyl group has been rare, because in SmI_2-promoted ketyl olefin coupling reaction, the unsaturated carbonyl compound is not a good ketyl acceptor.[6] With excess HMPA in order to enhance the reducing ability of SmI_2,[7] the intramolecular reaction of enone aldehyde **15** with SmI_2 at –78 °C for 10 min gave tricyclic hydroxyketone **16** as a separable mixture of β- and α-alcohol (β/α=2.4:1) (Scheme 3). The relative stereochemistry of the major β-hydroxyketone **17** was confirmed by the successful intramolecular S_N2 displacement leading to cyclopropane derivative **21** (*vide infra*). W-type coupling between protons α to carbonyl group and a proton on a carbon having the hydroxyl group, established the orientation of the hydroxyl group as α in the minor hydroxyketone **16**. When the reaction was run without HMPA, reductive elimination proceeded to give only enone **12**. Presumably, the reduction potential of the formyl group in **15** is lower than that of the unsaturated carbonyl group. Supposing that the reaction proceeds by chelation control through one electron transfer to formyl group followed by intramelecular conjugate addition to the cyclopentenone moiety of **15**, then the α-alcohol should predominate. However, obtaining β-hydroxy ketone **16** as a major isomer in the present SmI_2-promoted reaction, indicates that the present reaction might have proceeded through thermodynamic vinylogous pinacol coupling pathway after two-electron transfer to **15**, and not *via* the conjugate addition reaction of formyl ketyl radical to cyclopentenone moiety, judging from the result that an equivalent amount of SmI_2 gave poor yield in a structurally similar compound. Steric repulsion between the two Sm metal atoms coordinated to intermediary two alkoxy groups may provide β-alcohol **16** preferentially.

With the common intermediate **16** for cyclomyltaylane and myltaylane natural products in hand, the final transformation to the natural product **1** was carried out as follows. TBS protection of keto alcohol **16** with TBSCl furnished in 94% yield TBS ether **17** which was then methylated with LDA and methyl iodide in

THF at 0 °C to afford **18** as a diastereomeric mixture. Without separation, subsequent deprotection followed by mesylation yielded mesylate **20**. The mesylate **20** was subjected to cyclization using sodium methoxide[8] to give cyclomyltaylane-5-one **21**. Stereoselective reduction of ketone **21** with LAH furnished (+)-cyclomyltaylan-5α-ol **1** { $[\alpha]_D^{20}$ +33 ° (*c* 0.3, $CHCl_3$)} in 24% overall yield from **17**. Spectral data of the synthetic **1** were in complete agreement with those of natural product **1** {$[\alpha]_D$ +36 ° (*c* 0.2, $CHCl_3$)} thereby establishing the absolute stereochemistry of the natural product **1** as depicted in Figure 1.

In conclusion, we have achieved an enantioselective first total synthesis of (+)-cyclomyltaylan-5α-ol **1** starting from the optically active (*S*)-(+)-Hajos-Wiechert ketone analogue **3** *via* SmI_2-promoted reductive coupling as a key step in ca. 1.2% overall yield over 18 steps. The absolute configuration of the natural product **1** was established as 2*R*,3*R*,4*R*,5*S*,6*R*,7*R* (cyclomyltaylane numbering) as shown in structure **1**. Further work to synthesize the tricyclic myltaylane sesquiterpenoid such as **2** from the common intermediate **15** are now in progress.

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References and Note

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4 The absolute configuration of (+)-**3** was determined by an exciton chirality method. An enantiomeric excess was obtained by GLC analysis on a chiral stationary phase (Cyclodextrine-β-236M-19). These results will be reported in due course.

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