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# New route to the synthesis of the illudane skeleton by Michael–Michael-elimination reaction

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**Abstract**

A new route to the synthesis of an optically active illudane skeleton from (*R*)-(–)-pantolactone (**4**) is established. The tricyclic ring system was constructed by Michael–Michael-elimination reaction of the enolate of (3*S*,5*R*)-3-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-1-propionylcyclopentene (**10**) with ethyl cyclopropylidenacetate (**3**). 

*Keywords:* Michael reactions; terpenes and terpenoids; antitumor compounds.

Illudin M (**1**) and illudin S (**2**), produced by the bioluminescent mushroom *Omphalous illuens* (synonymous with *Lampteromyces japonicus*), are highly toxic sesquiterpenes, each possessing a rare tricyclic ring system (illudane skeleton).[1] Selective toxicity toward tumor cells of illudins and certain derivatives of illudins has been reported.[2] Their unique structural features and biological significance have attracted much interest in synthetic studies on these products.[3] This paper describes a new synthetic route to the illudane skeleton having most of the functionalities necessary for producing illudins from (*R*)-(–)-pantolactone (**4**). The concept for constructing the tricyclic ring system was based on Michael–Michael-elimination reaction of the enolate of **i** having a leaving group at C-5 with ethyl cyclopropylideneacetate (**3**),[4] to give enone **iii** via enolate **ii**, as shown in Fig. 1.

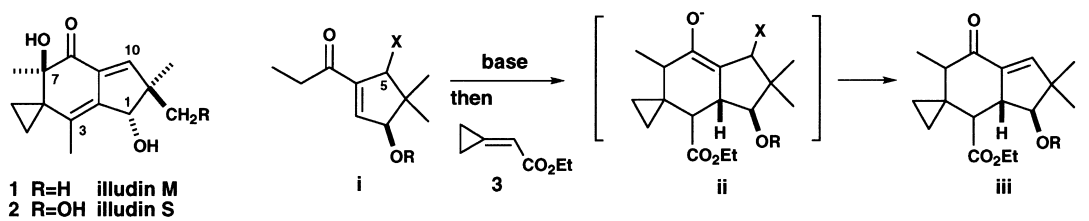


Figure 1.

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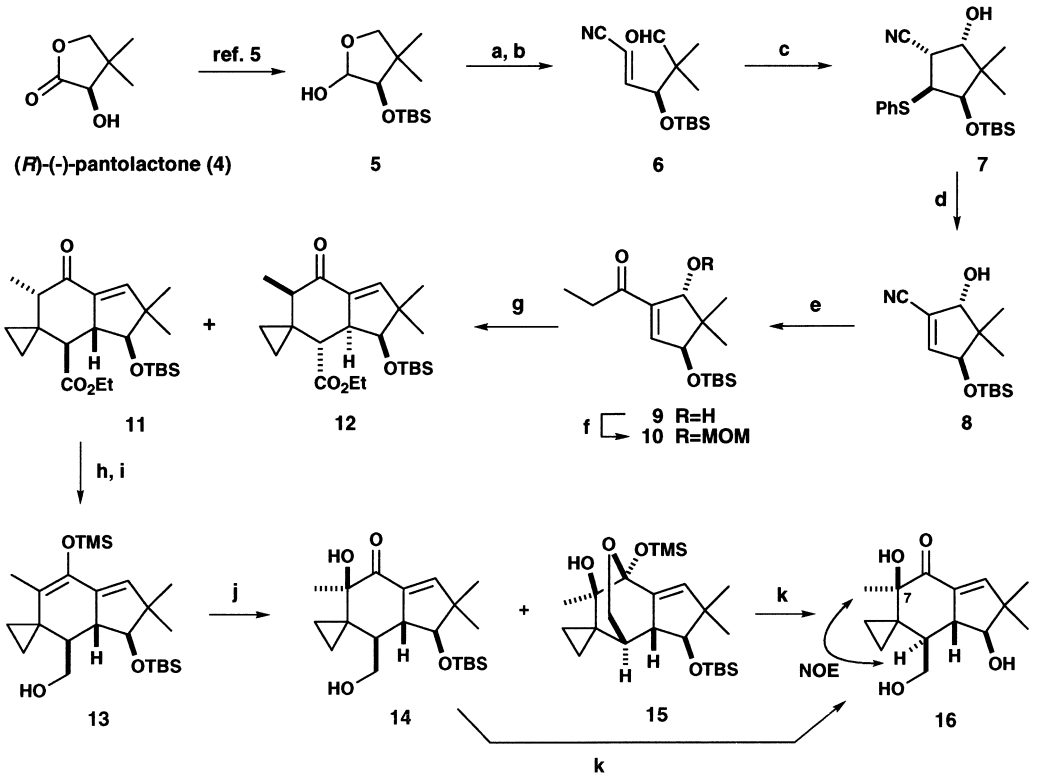
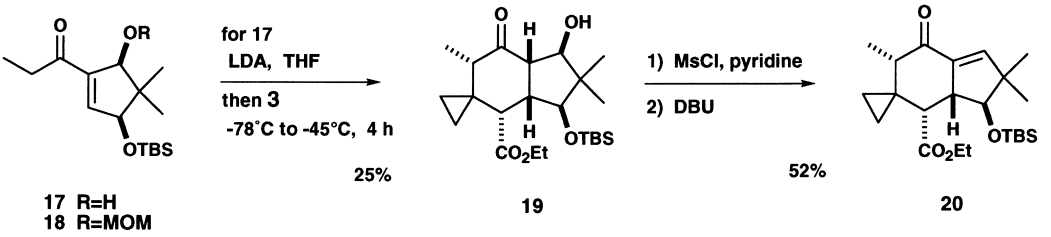
Enone **10** corresponding to **i** was synthesized via Michael–aldol reaction of cyano aldehyde **6** obtained from hemiacetal **5**[5] through the Wittig reaction and Swern oxidation. Reaction of **6** with Oshima's reagent ($PhS^{-}AlMe_3{\cdot}Li^{+}$)[6] in THF proceeded stereoselectively to afford cyclopentanol **7**[7] (93%) with a trace amount of its diastereomer, and treatment of **7** with potassium *tert*-butoxide gave **8** (Scheme 1). The Baylis–Hillman reaction of **6** with DABCO[8] for the direct formation of **8** failed to proceed. Transformation of the cyano group in **8** into a propionyl group was carried out by reaction with ethyl lithium to give **9**, whose secondary hydroxy group at C-5 was activated as a methoxymethyl ether to form **10**.[9]




Scheme 1. Reagents and conditions: (a) $Ph_3P{=}CHCN$, $CH_2ClCH_2Cl$, 70°C, 8 h; (b) $(COCl)_2$, DMSO, $CH_2Cl_2$, –78 to –45°C, 1 h, then $Et_3N$, 0°C, 20 min (two steps, 82%); (c) $PhS^{-}AlMe_3{\cdot}Li^{+}$, THF, 0–22°C, 8 h, **7** (93%), stereoisomer of **7** (trace); (d) *t*-BuOK, THF, 24°C, 1 h, 79%; (e) EtLi, THF, –20°C, 30 min, then $NH_4Cl$ aq, 24°C, 10 h, 77%; (f) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, 22°C, 88%; (g) LHMDS, THF–HMPA then **3**, –78 to 0°C; (h) TMSOTf, $Et_3N$, $CH_2Cl_2$, rt, 1 h, 90%; (i) DIBAH, $CH_2Cl_2$, –78°C, quant.; (j) $VO(acac)_2$, TBHP, $CH_2Cl_2$, rt, 12 h, 63% (**14**: 31%; **15**: 32%); (k) TBAF, THF, rt, 1 h, quant.

Reaction of the kinetic enolate generated from **10** with LHMDS with cyclopropylideneacetate **3** at –78 to –5°C in a 3:2 mixture of THF and HMPA proceeded to produce enone **11**,[7] $[\alpha]_D^{25}$ –43.2 (*c* 0.84; $CHCl_3$) in 31% yield, and its stereoisomer **12**[7] (10%) with tandem Michael reaction and elimination of the methoxymethyloxy group. On the other hand, attempts to effect the reaction of the enolate of **18** bearing a 5β-methoxymethyloxy group, prepared from **8**,[10] with **3** to produce **20** met with failure. However, the enolate of **17** was found to react with **3** to give **19**[7] in 25% yield, and this product could be converted to enone **20** by mesylation of the hydroxy group and

successive DBU treatment (Scheme 2). Stereoselectivity in the reaction of **17** with **3** may be explained based on transition state **C** leading to **19**, as shown in Fig. 3. In this state, α,β-unsaturated ester **3** approaches the dienolate of **17** from the less hindered side with coordination between the lithium cation in the enolate of **17** and carbonyl oxygen of **3**. Reaction of **10** with **3** appeared to proceed via transition state **B** (Fig. 2). In this case, transition state **A** corresponding to **C** (Fig. 3) would be disfavored owing to steric repulsion between the ethoxycarbonyl group in **3** and the 5*a*-methoxymethyloxy group of **10**.




Scheme 2.

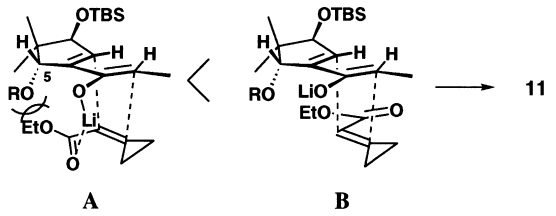



Figure 2.

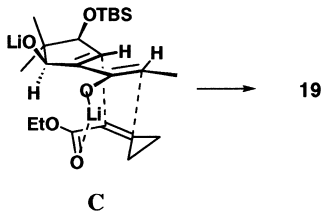



Figure 3.

Stereoselective introduction of the β-hydroxy group at C-7 was achieved by the neighboring effect of the 3β-hydroxymethyl group in **13**, which was converted from **11** by formation of the corresponding silyl enol ether followed by DIBAH reduction. The double bond of the enol ether was readily oxidized with *tert*-butyl hydroperoxide in the presence of a catalytic amount of $VO(acac)_2$ to give a mixture of keto alcohol **14** and acetal **15**,[11] both of which were subsequently converted to triol **16**, $[\alpha]_D^{25}$ +40.8 (*c* 0.5; $CHCl_3$), by removal of the silyl group in quantitative yield.

In conclusion, suitably functionalized illudane skeleton **16** was synthesized in optically active form from hemiacetal **5** in 11 steps via Michael–Michael-elimination reaction of **10** with **3** as the crucial step. The total synthesis of **1** using **16** is presently being attempted at this laboratory.

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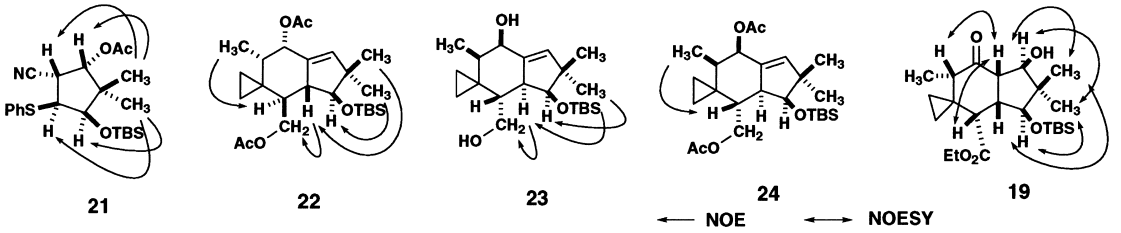
7. Relative configurations of **7**, **11** and **12** were determined by NOE experiments of **21**, derived from **7** by acetylation, **22**, derived from **11** in two steps (i. DIBAH; ii. $Ac_2O$, $Et_3N$, DMAP), **23** and **24**, which were derived from **12**, respectively. The relative configuration of **19** was determined by NOESY experiment.

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9. Attempts at mesylation and tosylation of the hydroxy group in **9** were unsuccessful.
10. Compound **18** was prepared from **8** in four steps: (1) Dess–Martin reagent, $CH_2Cl_2$, 23°C, 94%; (2) DIBAH, $CH_2Cl_2$, –78°C, 15–40%; (3) EtLi, $Et_2O$, –78°C, 90%; (4) MOMCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, 0°C, 33%.
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