



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

Kazuo Tokuzaki, Yasuhiro Kanemitsu, Takehiko Yoshimitsu and Hiroto Nagaoka*

Meiji Pharmaceutical University, Noshio, Kiyose, Tokyo 204-8588, Japan

Received 8 May 2000; revised 8 June 2000; accepted 9 June 2000

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 cyclopropylideneacetate (**3**). © 2000 Elsevier Science Ltd. All rights reserved.

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

Illudin M (**1**) and illudin S (**2**), produced by the bioluminescent mushroom *Omphalotus 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.

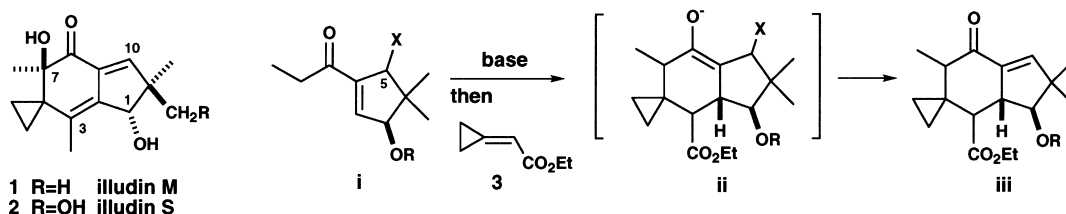
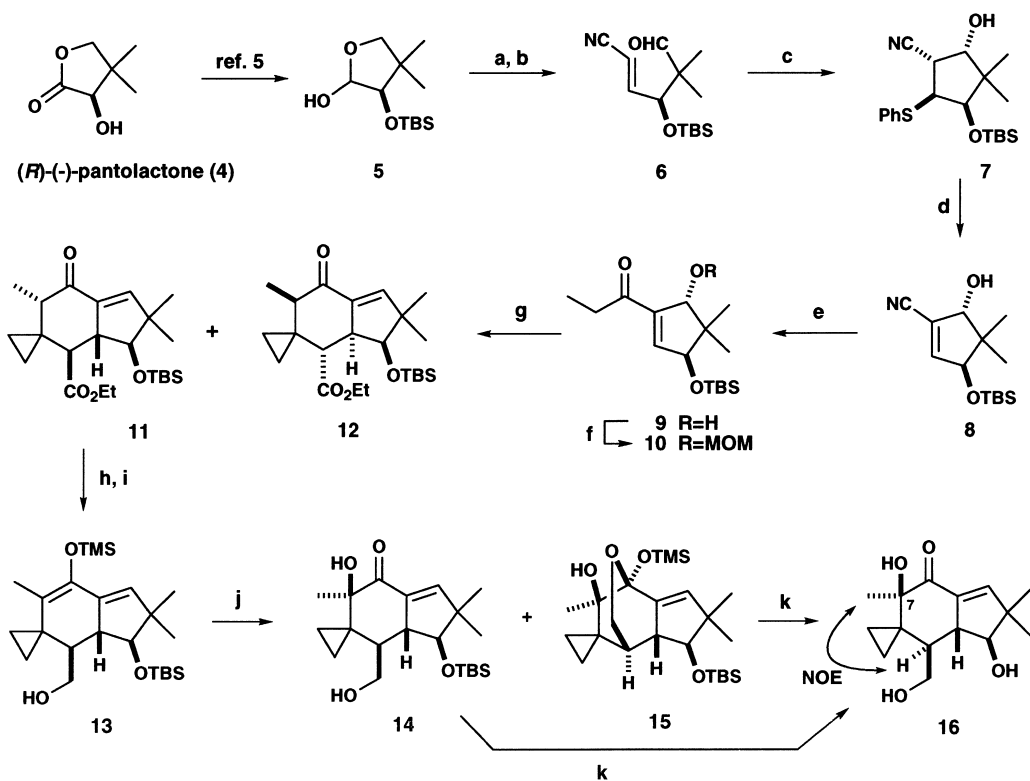


Figure 1.

* Corresponding author. Fax: +00-81-424-95-8796; e-mail: nagaoka@my-pharm.ac.jp

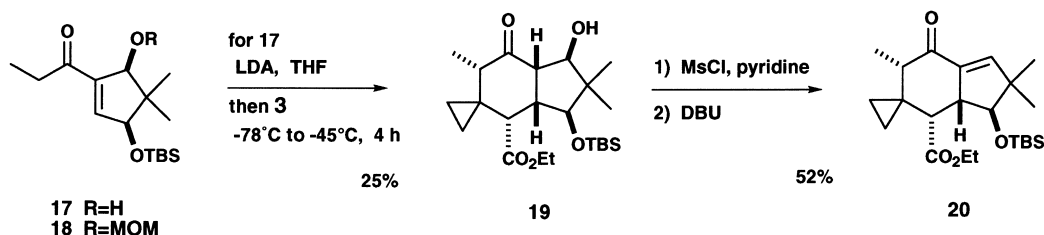
Enone **10** corresponding to **i** was synthesized via Michael–aldol reaction of cyano aldehyde **6** obtained from hemiacetal **5**⁵ through the Wittig reaction and Swern oxidation. Reaction of **6** with Oshima's reagent ($\text{PhS}^-\text{AlMe}_3\cdot\text{Li}^+$)⁶ in THF proceeded stereoselectively 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 DABCO⁸ 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) $\text{Ph}_3\text{P}=\text{CHCN}$, $\text{CH}_2\text{ClCH}_2\text{Cl}$, 70°C , 8 h; (b) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78 to -45°C , 1 h, then Et_3N , 0°C , 20 min (two steps, 82%); (c) $\text{PhS}^-\text{AlMe}_3\cdot\text{Li}^+$, 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*-Pr₂NEt, 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) DIBALH, 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 methoxymethoxy group. On the other hand, attempts to effect the reaction of the enolate of **18** bearing a 5β -methoxymethoxy 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 α -methoxymethoxy group of **10**.



Scheme 2.

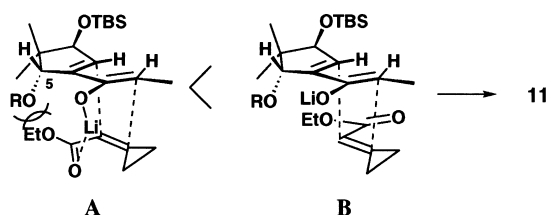


Figure 2.

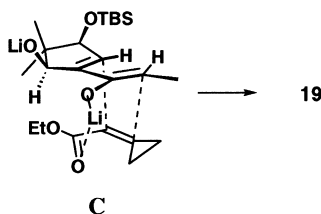


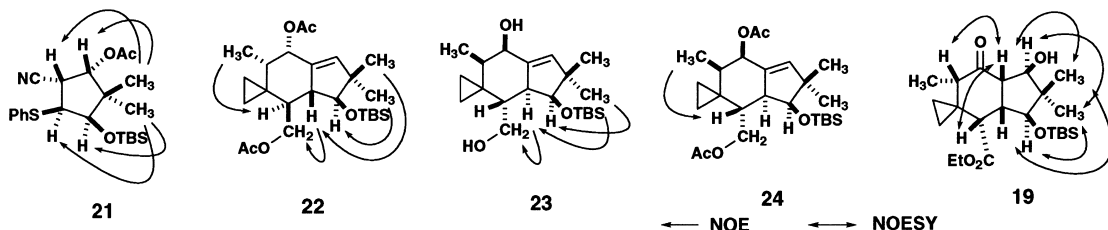
Figure 3.

Stereoselective introduction of the β -hydroxy group at C-7 was achieved by the neighboring effect of the 3 β -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; CHCl₃), 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.

References

- (a) Anchel, M.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. USA* **1952**, *38*, 927–928. (b) Shirahama, H.; Komatsu, T. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1047–1048. (c) Nakanishi, K.; Tada, M.; Yamada, Y.; Ohashi, M.; Komatsu, N.; Terakawa, H. *Nature* **1963**, *197*, 292. (d) Nakanishi, K.; Ohashi, M.; Tada, M.; Yamada, Y. *Tetrahedron*, **1965**, *21*, 1231–1246. (f) McMorris, T. C.; Anchel, M. *J. Am. Chem. Soc.* **1963**, *85*, 831–832. (g) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Fukuoka, Y.; Takahashi, Y.; Mori, Y.; Watanabe, M. *Tetrahedron* **1965**, *21*, 2671–2676.
- (a) McMorris, T. C.; Kelner, M. J.; Wang, W.; Estes, L. A.; Montoya, M. A.; Taelte, R. *J. Org. Chem.*, **1992**, *57*, 6876–6883. (b) Kelner, M. J.; McMorris, T. C.; Estes, L. A.; Montoya, M. A.; Wang, W.; Samson, K. M.; Taetle, R. *Investigational New Drugs* **1996**, *14*, 161–167. (c) McMorris, T. C.; Yu, J.; Hu, Y. *J. Org. Chem.* **1997**, *62*, 3015–3018.
- (a) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Matsumoto, S.; Nishida, S. *J. Am. Chem. Soc.* **1968**, *90*, 3280–3281; (b) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Miyano, K. *Tetrahedron Lett.* **1971**, *23*, 2049–2052. (c) Kinder Jr., F. R.; Bair, K. W. *J. Org. Chem.* **1994**, *59*, 6965–6967. (d) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667–2668. (e) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317–1325.
- (a) Salaün, J.; Bennani, F.; Compain, J. C.; Fadel, A.; Ollivier, J. *J. Org. Chem.* **1980**, *45*, 4129–4135. (b) Spitzner, D.; Swoboda, H. *Tetrahedron Lett.* **1986**, *27*, 1281–1284.
- Miyaoka, H.; Sagawa, S.; Nagaoka, H.; Yamada, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 587–594.
- Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274–278.
- 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. Ac₂O, Et₃N, DMAP), **23** and **24**, which were derived from **12**, respectively. The relative configuration of **19** was determined by NOESY experiment.



- Basavaiah, D.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1986**, *27*, 2031–2032.
- Attempts at mesylation and tosylation of the hydroxy group in **9** were unsuccessful.
- Compound **18** was prepared from **8** in four steps: (1) Dess–Martin reagent, CH₂Cl₂, 23°C, 94%; (2) DIBAH, CH₂Cl₂, –78°C, 15–40%; (3) EtLi, Et₂O, –78°C, 90%; (4) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, 0°C, 33%.
- Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741–2744.