Pergamon

Tetrahedron Letters 41 (2000) 3927–3930

TETRAHEDRON LETTERS

Synthetic studies of ingenol: synthesis of *in,out*-tricyclo[7.4.1.0^{1,5}]tetradecan-14-one

Hideo Kigoshi,[a,*] Yuto Suzuki,[b] Kenta Aoki [b] and Daisuke Uemura [b,*]

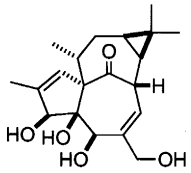
[a]*Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*
[b]*Department of Chemistry, Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*

Received 1 March 2000; accepted 24 March 2000

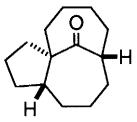
Abstract

in,out-Tricyclo[7.4.1.0^{1,5}]tetradecan-14-one was synthesized from γ-butyrolactone in 12 steps using ring-closing olefin metathesis as the key step.

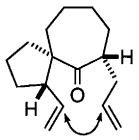
Ingenol (**1**) is a diterpenoid isolated from *Euphorbia ingens*, possessing a bicyclo[4.4.1]undecane skeleton with a highly strained *inside-outside* intrabridgehead stereochemistry.[1] Many derivatives have also been isolated.[1] Ingenol and its derivatives interest organic chemists not only because of their unique framework but also their biological activities, such as protein kinase C (PKC)-activating and anti-HIV activities.[2,3] Despite many synthetic studies,[4] ingenol has not been synthesized and only a few strategies for the construction of the unique *in,out*-bicyclo[4.4.1]undecane skeleton have been disclosed by Winkler,[5] Funk,[6] Rigby,[7] and Kuwajima.[8]



ingenol (**1**)



2



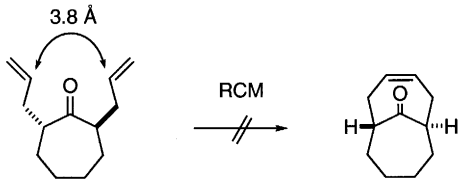
3

The strategies for the *inside-outside* intrabridgehead stereochemistry, such as the de Mayo reaction and fragmentation,[5] the Ireland–Claisen rearrangement for ring contraction,[6] the 1,5-H sigmatropy to change the intrabridgehead stereochemistry from *out–out* to *in–out*,[7] and the tandem cyclization–rearrangement reaction,[8] have appeared, however, the direct cyclization to the *in,out*-bicyclo[4.4.1]undecane system has not been reported. We describe herein the synthesis of *in,out*-tricyclo[7.4.1.0^{1,5}]tetradecan-14-one (**2**) by direct cyclization using olefin metathesis.

* Corresponding author.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00519-0

The key reaction of this synthesis was the ring-closing olefin metathesis with a Grubbs' ruthenium catalyst, $RuCl_2(=CHPh)(PCy_3)_2$, which provides a new strategy for the synthesis of cyclic natural products.[9] In the ring-closing olefin metathesis, it is important that the two olefins being connected to each other should be closely arranged. In the preliminary study, we found that ring-closing olefin metathesis of *trans*-2,7-diallylcycloheptanone did not afford *in*,*out*-bicyclo[4.4.1]undecene but dimeric compounds (Scheme 1). Thus, we chose olefin **3** as a key intermediate, in which the distance between the two terminal olefins is closer, about 3.6 Å based on a molecular mechanics calculation,[10] than that of *trans*-2,7-diallylcycloheptanone.



Scheme 1. Ring-closing olefin metathesis of *trans*-2,7-diallylcycloheptanone

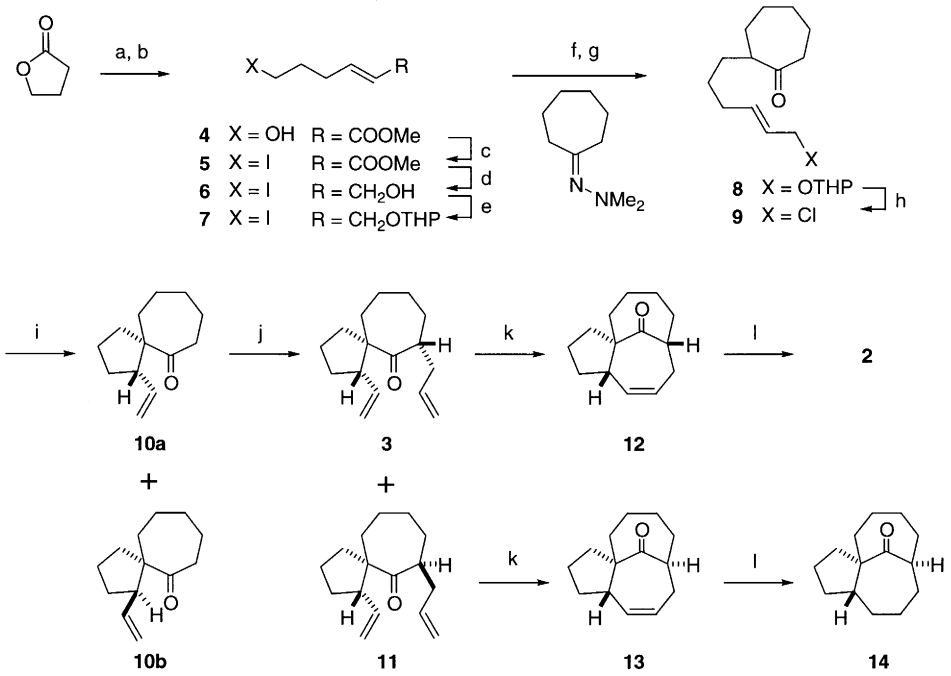
The synthesis of **2** is illustrated in Scheme 2.[11] γ-Butyrolactone was reduced with DIBAL to give a hemiacetal, the Wittig reaction of which afforded the unsaturated ester **4** (61%, two steps). Iodination of the hydroxy group in **4** and subsequent reduction with DIBAL afforded the allylic alcohol **6**. The hydroxy group in **6** was protected to provide the THP ether **7** (71%, three steps). The alkylation reaction[12] of cycloheptanone *N*,*N*-dimethylhydrazone with **7** (*n*-BuLi) followed by hydrolysis with silica gel[13] gave the alkylated ketone **8** in 92% yield. Treatment of **8** with concentrated hydrochloric acid in 1,4-dioxane readily afforded the allylic chloride **9**[14] (94%), which was treated with *t*-BuOK in *t*-BuOH to give the spiroketones **10a** (28%) and **10b** (43%).[15,16] Allylation of **10a** with KHMDS and allyl iodide provided a 7:1 mixture of the allyl ketones **3** and **11** in 81% yield, which were separated by silica gel column chromatography. We could not determine the stereochemistry of **3** and **11** by the spectroscopic analysis, however, we predicted that the allylation of **10a** should occur from the less hindered side of the corresponding enolate, and the allyl ketone **3** should be predominantly obtained.

The ring-closing olefin metathesis of the allyl ketones **3** and **11** was investigated, respectively, and it was proved that this reaction required a relatively higher temperature. The allyl ketone **3** reacted with Grubbs' ruthenium catalyst in boiling toluene to give the tricycloketone **12** in 20% yield, whereas the ring-closing olefin metathesis of **11** gave the tricycloketone **13** in 76% yield. The tricycloketones **12** and **13** were catalytically hydrogenated to afford the previously reported compound **2**[5c,17] (55%) and compound **14**[18] (68%), respectively. Thus, the structures of **3** and **12** were confirmed.

In summary, we have synthesized *in*,*out*-tricyclo[7.4.1.$0^{1,5}$]tetradecan-14-one (**2**), the framework of ingenol, in 12 steps from γ-butyrolactone using a Grubbs' ring-closing metathesis. Application of this strategy to the total synthesis of ingenols is currently underway in our laboratory.

Acknowledgements

We thank Mr Jun Yamamoto for his efforts on the preliminary study. This work was supported in part by Grants-in-Aid for COE Research and Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

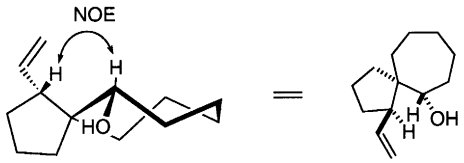


Scheme 2. Reagents and conditions. (a) DIBAL, toluene, −78°C, 1 h, 95%; (b) Ph_3P=CHCOOMe, benzene, 23°C, 1 h, 64%; (c) I_2, Ph_3P, imidazole, toluene, 23°C, 1 h, 79%; (d) DIBAL, toluene, −78°C, 1 h; (e) DHP, *p*-TsOH, CH_2Cl_2, 23°C, 1 h, 90% in two steps; (f) cycloheptanone *N*,*N*-dimethylhydrazone, *n*-BuLi, THF, 23°C, 2 h; (g) silica gel, CH_2Cl_2, 23°C, 19 h, 92% in two steps; (h) conc. HCl, dioxane, 23°C, 5 h, 94%; (i) *t*-BuOK, *t*-BuOH, reflux, 3.5 h, 28% for **10a**, 43% for **10b**; (j) allyl iodide, KHMDS, THF, 0°C, 3 h, 81% (**3**:**11**=7:1); (k) $RuCl_2$(=CHPh)$(PCy_3)_2$, toluene, reflux, 20% for **12**, 76% for **13**; (l) H_2, Pd/C, EtOH, 23°C, 1 h, 55% for **2**, 68% for **14**

References

1. Zeichmeister, K.; Brandl, F.; Hoffe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, 4075–4078. Uemura, D.; Hirata, Y. *Tetrahedron Lett.* **1971**, 3673–3676. Opferkuch, H.; Hecker, E. *Tetrahedron Lett.* **1974**, 261–264. Uemura, D.; Ohwaki, H.; Hirata, Y.; Chen, Y.-P.; Hsu, H.-Y. *Tetrahedron Lett.* **1974**, 2527–2528. Uemura, D.; Hirata, Y.; Chen, Y.-P.; Hsu, H.-Y. *Tetrahedron Lett.* **1974**, 2529–2532. Upadhyay, R. R.; Mohadded, J. *Curr. Sci.* **1987**, *56*, 1058–1059.
2. Hasler, C. M.; Acs, G.; Blumberg, M. *Cancer Res.* **1992**, *52*, 202–208.
3. Fujiwara, M.; Ijichi, K.; Tokuhisa, K.; Katsuura, K.; Shigeta, S.; Konno, K.; Wang, G.-Y.-S.; Uemura, D.; Yokota, T.; Baba, M. *Antimicrob. Agents Chemother.* **1996**, *40*, 271–273. Fujiwara, M.; Ijichi, K.; Tokuhisa, K.; Katsuura, K.; Wang, G.-Y.-S.; Uemura, D.; Shigeta, S.; Konno, K.; Yokota, T.; Baba, M. *Antiviral Chemistry & Chemotherapy* **1996**, *7*, 230–236.
4. Review: Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387–399.
5. (a) Winkler, J. D.; Hey, J. P.; Williard, P. G. *J. Am. Chem. Soc.* **1986**, *108*, 6425–6426. (b) Winkler, J. D.; Henegar, K. E.; Williard, P. G. *J. Am. Chem. Soc.* **1987**, *109*, 2850–2851. (c) Winkler, J. D.; Henegar, K. E.; Hong, B.-C.; Williard, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 4183–4188. (d) Winkler, J. D.; Hong, B.-C.; Bahador, A.; Kazanietz, M. G.; Blumberg, P. M. *J. Org. Chem.* **1995**, *60*, 1381–1390. (e) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296–300.
6. (a) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298–3300. (b) Funk, R. L.; Olmstead, T. A.; Parvez, M.; Stallman, J. B. *J. Org. Chem.* **1993**, *58*, 5873–5875.
7. (a) Rigby, J. H.; de Sainte Claire, V.; Cuisiat, S. V.; Heeg, M. J. *J. Org. Chem.* **1996**, *61*, 7992–7993. (b) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265–2268.
8. Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032–3033.
9. Review: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
10. The global minima were calculated in a Multiconformer conformational search using MacroModel (Version 6.0).

11. All new compounds exhibited spectral (^{1}H NMR, ^{13}C NMR, IR, MS) and analytical (HRMS) data fully consistent with the assigned structures.
12. Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3–6.
13. Kotsuki, H.; Miyazaki, A.; Kadota, I.; Ochi, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 429–430.
14. Compound **9** was obtained as a mixture of α- and γ-allylic chlorides, which was employed for the next step without separation.
15. Although the reaction conditions for the spirocyclization were investigated, such as *t*-BuONa/*t*-BuOH, *t*-BuOLi/*t*-BuOH, NaH/toluene, BrMgN(*i*-Pr)$_2$/THF, *t*-BuOK-KI/*t*-BuOH, and *t*-BuOK, 18-crown-6/*t*-BuOH, none of them were found to be more effective.
16. The stereochemistry of **10a** and **10b** was determined as follows. The spiroketone **10b** was reduced with $NaBH_4$ in EtOH to give alcohol **15** (39%) and its diastereomeric alcohol (37%). Alcohol **15** exhibited an NOE between the oxymethine proton and the allylic proton, suggesting that the oxymethine group and the vinyl group in **15** are on the opposite side of the cyclopentane ring to each other. This finding indicates that the carbonyl group and the vinyl group in **10b** are on the opposite side of the cyclopentane ring to each other and thus **10a** possesses the desired stereochemistry for the synthesis of **2**.



15

17. Compound **2**: IR ($CHCl_3$) 2945, 2860, 1720, 1450, 1380 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.88 (br tt, *J*=11.9, 2.0 Hz, 1 H), 2.04–0.86 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.0, 63.5, 54.3, 50.3, 41.1, 36.2, 35.0, 30.8, 30.6, 30.54, 30.51, 30.48, 26.0, 25.2; EIMS *m/z* 206 (M^+, 100), 188 (21).
18. Compound **14**: IR ($CHCl_3$) 2930, 2860, 1680, 1460, 1360 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.73 (m, 1H), 2.19–2.12 (m, 2H), 1.95–1.17 (m, 19H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 219.2, 63.4, 54.7, 43.3, 38.8, 35.0, 34.1, 34.0, 30.0, 28.7, 26.6, 26.3, 24.7, 20.9; EIMS *m/z* 206 (M^+, 100), 188 (31); HREIMS calcd for $C_{14}H_{22}O$ (M^+) 206.1671, found 206.1643.