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Synthetic Studies toward 13-Oxyingenol: Construction of the Fully Substituted Tetracyclic Compound

Takayuki Ohyoshi,† Yamato Miyazawa, Kenta Aoki, Satomi Ohmura, Yuki Asuma, Ichiro Hayakawa, and Hideo Kigoshi*

Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, Tennodai, Tsukuba 305-8571, Japan

kigoshi@chem.tsukuba.ac.jp

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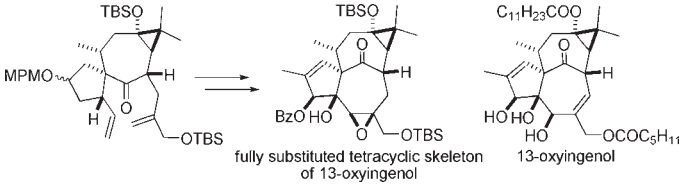
ABSTRACT



13-Oxyingenol and its derivatives have high levels of anti-HIV activity. A fully substituted tetracyclic skeleton of 13-oxyingenol is constructed by using spiro-cyclization and ring-closing olefin metathesis as key steps.

13-Oxyingenol (**1**)[1] and ingenol (**3**) are diterpenoids isolated from the plants of *Euphorbia* sp. The main structural features of ingenols are a highly strained *inside–outside* bicyclic ring system and a high degree of oxygenation (Figure 1). They and their analogues showed strong bioactivity against protein kinase C activation and anti-HIV activity.[2] In particular, 13-oxyingenol derivatives such as RD4-2138 (**2**) have strong anti-HIV activity. The unique structures of ingenol derivatives, along with their potent biological activity, have made them attractive targets for synthesis. Although several total syntheses and synthetic studies of **3** have been reported,[3−5] the total synthesis of **1** has not been reported thus far. In 2004, we achieved the formal synthesis of optically active ingenol by using ring-closing metathesis.[6] This synthesis provides the first synthetic access to optically active ingenol. In 2007, we reported the construction of the *inside–outside* framework of 13-oxyingenol by using intramolecular radical

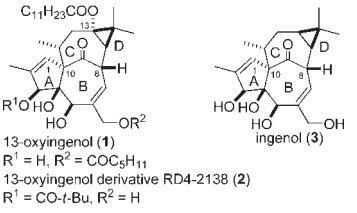


Figure 1. Structures of ingenol, 13-oxyingenol, and 13-oxyingenol derivative.

† Research fellow of the Japan Society for the Promotion of Science (JSPS).

(1) Uemura, D.; Ohwaki, H.; Hirata, Y.; Chen, Y.-P.; Hsu, H.-Y. *Tetrahedron Lett.* **1974**, *24*, 2529.

(2) Fujiwara, M.; Okamato, M.; Ijichi, K.; Tokuhisa, K.; Hanasaki, Y.; Katuura, K.; Uemura, D.; Shigeta, S.; Konno, K.; Yokota, T; Baba, M. *Arch. Virol.* **1998**, *143*, 2003.

(3) Review: (a) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387. (b) Kuwajima, I; Tanino, K. *Chem. Rev.* **2005**, *105*, 4661. (c) Cha, J. K.; Epstein, O. L. *Tetrahedron* **2006**, *62*, 1329.

(4) Total synthesis of ingenol: (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jean, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726. (b) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. (c) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300.

(5) Successful construction of *inside–outside* skeleton: (a) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (b) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927. (c) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799. (d) Epstein, O. L.; Cha, J. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 121.

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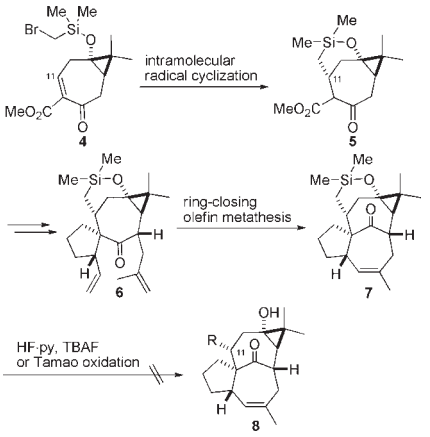
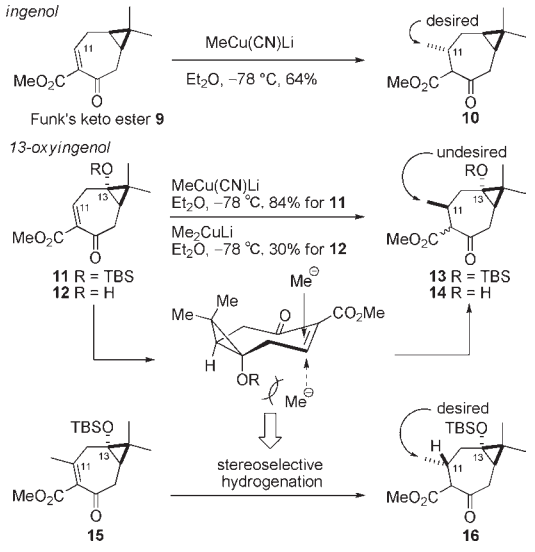
cyclization and ring-closing metathesis.[7] We describe herein an improved synthetic route to the 13-oxyingenol skeleton.

Scheme 1. Our Previous Synthesis of the Pentacyclic Carbon Framework of 13-Oxyingenol



The outline of our previous synthesis of the pentacyclic carbon framework of 13-oxyingenol is shown in Scheme 1. This strategy had a serious problem: the silicon-tether group in compound **7** could not be successfully cleaved by HF·py, TBAF, or Tamao oxidation.[8] Thus, we could not yet introduce a methyl group at C-11 into the *inside–outside* framework.

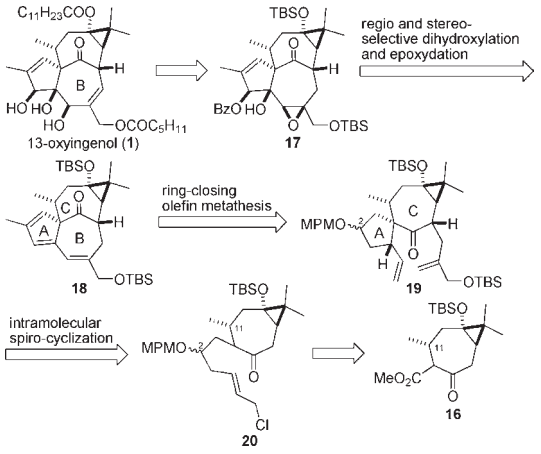
Scheme 2. Synthetic Strategy of 13-Oxyingenol



On the other hand, in the synthetic study of ingenol by Funk, the methyl group can be introduced from the α face of Funk's keto ester **9** stereoselectively (Scheme 2).[5a] However, in the case of 13-oxyingenol, the methyl group was introduced from the β face of enones **11** and **12** exclusively, possibly because of the steric hindrance of the C-13 substituent. Therefore, we planned the synthesis of desired keto ester **16** by hydrogenating seven-membered enone **15**, where hydrogen could be introduced from the β face of **15** because of the above-mentioned steric hindrance.

Our new retrosynthetic analysis of 13-oxyingenol (**1**) is shown in Scheme 3. We planned to construct the B ring of **1** by a ring-opening reaction of epoxide **17**. Epoxide **17** might be obtained from triene **18** by regio- and stereoselective dihydroxylation and epoxidation. The *inside–outside* ABC ring system could be synthesized by intramolecular spiro-cyclization of **20** and the ring-closing olefin metathesis reaction of **19**. In this work, we decided to introduce a hydroxy group at C-2, which we utilized for the introduction of the requisite functional group at the A ring. Chloride **20** can be prepared from keto ester **16**.

Scheme 3. Retrosynthetic Analysis of 13-Oxyingenol



The starting point for this work was the construction of keto ester **16**. Therefore, we attempted to introduce the methyl group at C-11 in seven-membered enone **21**, an intermediate in our previous synthesis,[7,9] by using 1,3-dipolar cycloaddition and subsequent thermolysis (Scheme 4).[10] Treatment of **21** with diazomethane afforded the cycloadduct **22**,[11] which was thermolyzed in toluene to give the desired enone **15** in 91% yield. A plausible reaction mechanism of the thermolysis of **22** to **15** is illustrated in Scheme 5. Stereoselective hydrogenation of **15** occurred from the opposite side against the OTBS group to afford the keto ester **16** as the desired diastereomer at C-11. The stereochemistry of C-11 in **16** was confirmed by the NOESY correlation between H-11 and the methyl group

(7) Hayakawa, I.; Asuma, Y.; Ohyoshi, T.; Aoki, K.; Kigoshi, H. *Tetrahedron Lett.* **2007**, *48*, 6221.

(8) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694.

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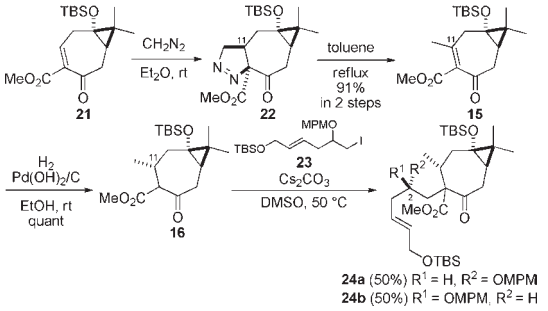
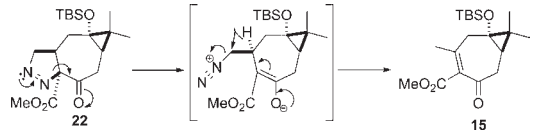
(11) X-ray crystallographic analysis of cycloadduct **22** is shown in the SI.

Scheme 4. Syntheses of Alkylated Compounds **24a** and **24b**

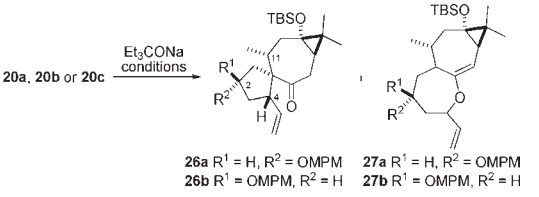


Scheme 5. Plausible Reaction Mechanism of Thermolysis of Cycloadduct **22**



of the cyclopropane part. **16** was alkylated with iodide **23**[12] to give alkylated compounds **24a** and **24b**, which were the diastereomers of the secondary hydroxy group at C-2. The stereochemistry of C-2 in **24a** and **24b** was determined by the ^{1}H NMR analysis of corresponding spiro ketone **26a** and **26b**, respectively (Table 1 and Supporting Information (SI)).

Table 1. Study of Intramolecular Spiro-Cyclization



entry	chloride	solvent	temp	yield
1	**20a**	xylene	reflux	**26a** = 5%, **27a** = 5%
2	**20a**	toluene	rt to reflux	**26a** = 86%
3	**20b**	xylene	reflux	**26b** = 11%, **27b** = 11%
4	**20b**	toluene	rt to reflux	**27b** = 42%
5	**20c**	xylene	reflux	**26b** = 57%
6	**20c**	toluene	rt to reflux	**26b** = 33%

The syntheses of precursors for intramolecular spiro-cyclization are illustrated in Scheme 6. The methoxycarbonyl group of **24a** was removed by heating with lithium iodide to afford ketone **25a**, which was obtained as a 3:1 inseparable mixture of C-10 diastereomers.[13] Selective removal of the primary TBS group in **25a** gave an allylic alcohol, which was converted into chloride **20a**, a precursor for intramolecular spiro-cyclization. The alkylated compound **24b** was also converted into **25b** and **25c**, which were separated by silica gel chromatography. Compounds **25b** and **25c** were converted into the corresponding chlorides **20b** and **20c** in the same manner, respectively. The stereochemistry of C-10 in **25b** was determined by the NOE correlation between H-10 and H-14.

Scheme 6. Syntheses of Chlorides **20a**–**c**, Precursors of Intramolecular Spiro-Cyclization

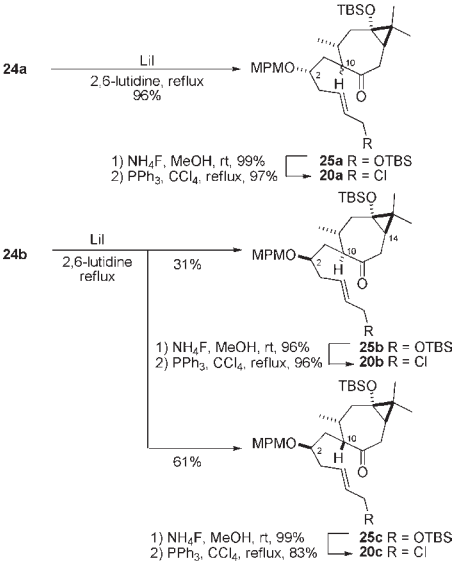
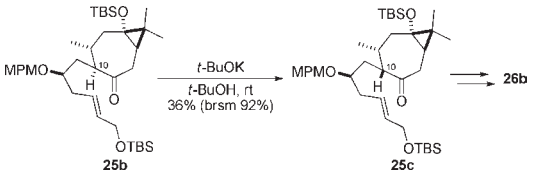


Table 1 summarizes the attempts at the intramolecular spiro-cyclization of chlorides **20a**–**c**. In our previous reports,[6,7] similar intramolecular spiro-cyclization was carried out by Et_3CONa in boiling xylene. In entries 1, 3, and 5, we examined cyclization under these conditions. The spiro-cyclization of **20a** afforded the desired spiro ketone **26a** (5%) and the undesired seven-membered ether **27a** (5%) (entry 1). Also, the spiro-cyclization of **20b** gave similar results to that of **20a** (desired **26b** = 11%, undesired **27b** = 11%) (entry 3). Treatment of **20c** with Et_3CONa gave the desired **26b** (57%) as the sole product (entry 5). These results indicated that the stereochemistry of the C-2 and C-10 positions in spiro-cyclization precursors **20a**–**c** is an important factor in the yield of this cyclization. The desired spiro ketones **26a** and **26b** are obtained from the thermodynamic enolate. Therefore, **20a** in toluene was heated from room temperature to the boiling point in 20 min to give the desired **26a** in 86% yield (entry 2). However, treatment of **20b** under the same conditions gave only the undesired **27b** (entry 4). On the other hand, treatment of **20c** under the same conditions gave the desired **26b**, but the yield was low (33%) (entry 6). Although we could not convert **20b** into the desired spiro ketone under these conditions, the epimerization of the C-10 position in **25b** by using *t*-BuOK afforded **25c**, which was converted into **26b** through **20c** (Scheme 7). The

(12) Iodide **23** was prepared from commercially available β-hydroxy-γ-butyrolactone. The detailed synthetic procedures for **23** are given in the SI.
(13) Elsinger, F. *Org. Synth., Coll. Vol. V*. **1973**, 76.

Scheme 7. Epimerization of C-10 Position in Compound **25b**

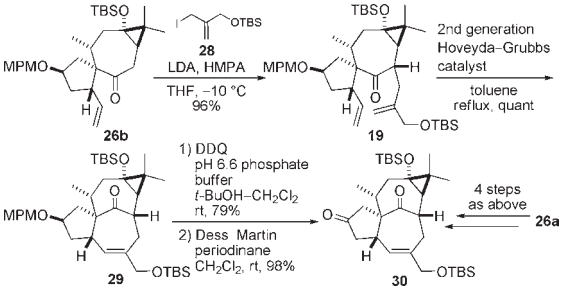


stereochemistry of spiro ketone **26b** was determined by the NOE correlation between H-11 and allylic H-4 (see SI). The stereoselectivity of this spiro-cyclization can be explained by our previous proposed transition state model.[6]

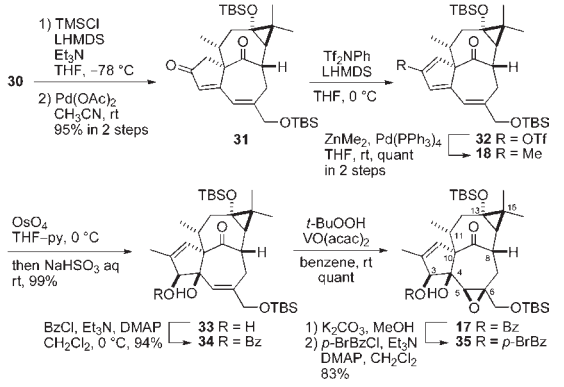
Alkylation of **26b** by LDA and iodide **28** gave the desired ketone **19** as the sole product (Scheme 8). The ring-closing olefin metathesis of **19** with the second-generation Hoveyda–Grubbs catalyst[14] gave tetracyclic ketone **29** in quantitative yield. The stereochemistry of **29** was determined by NOESY correlations (see SI). Thus, we achieved the construction of an *inside–outside* framework of 13-oxyingenol. The MPM group in **29** was removed, and the resulting hydroxy group was oxidized by Dess–Martin periodinane to afford diketone **30**. Spiro-ketone **26a** was converted into **30** in the same manner.

Next, we attempted to construct an A ring of 13-oxyingenol (**1**) (Scheme 9). Diketone **30** was oxidized to enone **31** by Ito–Saegusa oxidation.[15] **31** was converted into enol

Scheme 8. Synthesis of Diketone **30**



Scheme 9. Synthesis of Epoxy Alcohol **17**



triflate **32**, which was transformed into triene **18** by the Negishi coupling.[16] Regio- and stereoselective dihydroxylation of **18** with a stoichiometric amount of OsO_4 gave diol **33**, and the resulting secondary hydroxy group in **33** was protected by a benzoyl group to afford allyl alcohol **34**. Epoxidation of **34** by using *t*-BuOOH and $VO(acac)_2$ gave epoxy alcohol **17**. This epoxydation proceeded regio- and stereoselectively. The benzoyl group of **17** was transformed into *p*-bromobenzoate **35**, and the stereochemistry of **35** was determined by X-ray crystallographic analysis (Figure 2).

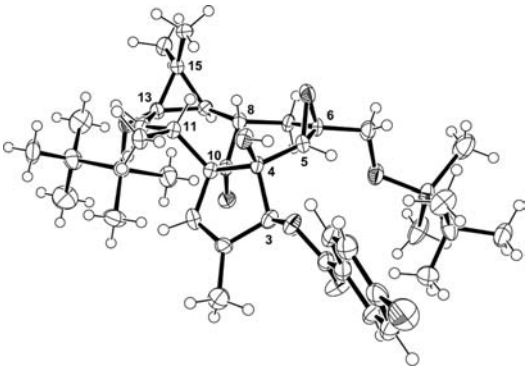


Figure 2. X-ray crystallographic structure of **35**.

In conclusion, we have achieved the synthesis of the fully substituted tetracyclic skeleton of 13-oxyingenol by using intramolecular spiro-cyclization and ring-closing olefin metathesis as key steps. The construction of the A ring part was established by using the C-2 hydroxy group. As a preliminary work, we attempted the ring-opening reaction of epoxide **17** to construct the allylic alcohol part of the B ring under acidic, basic, or radical conditions. However, the desired ring-opening compound could not be obtained. A further approach toward the synthesis of 13-oxyingenol is currently underway in our group.

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Supporting Information Available. Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(15) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.