

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

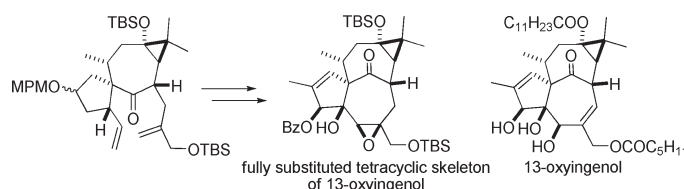
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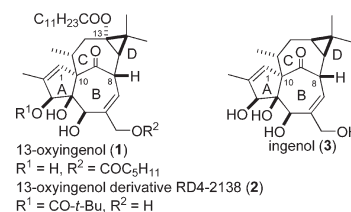
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ABSTRACT



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



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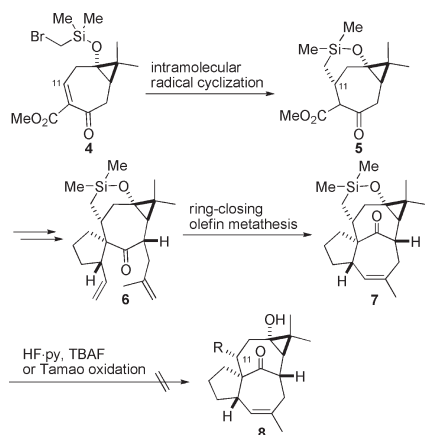
Figure 1. Structures of ingenol, 13-oxyingenol, and 13-oxyingenol derivative.

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

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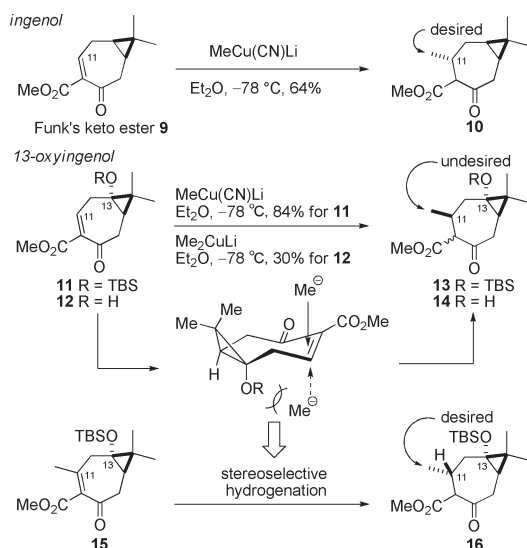
cyclization and ring-closing metathesis.⁷ We describe herein an improved synthetic route to the 13-oxyingenol skeleton.

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

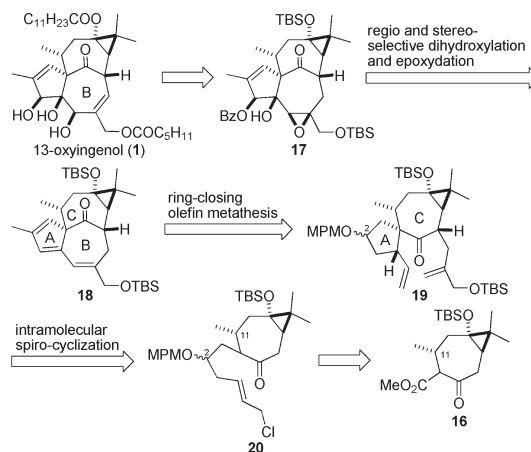


On the other hand, in the synthetic study of ingenol by Funk, the methyl group can be introduced from the α face

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

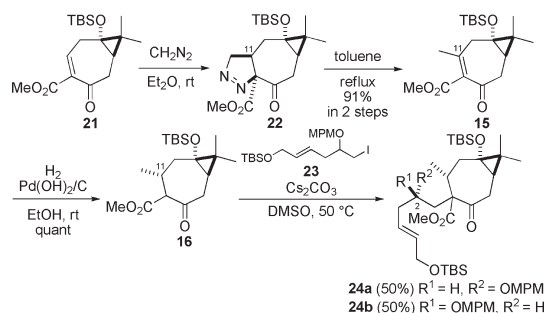
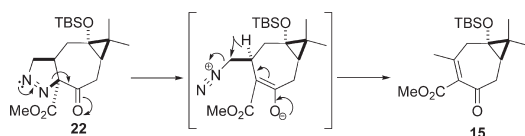
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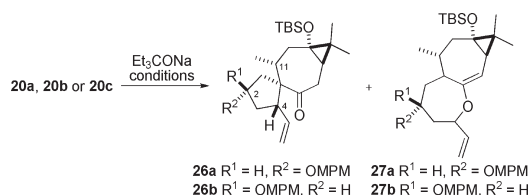
(11) X-ray crystallographic analysis of cycloadduct **22** is shown in the SI.

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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 ¹H 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	xylylene	reflux	26a = 5%, 27a = 5%
2	20a	toluene	rt to reflux	26a = 86%
3	20b	xylylene	reflux	26b = 11%, 27b = 11%
4	20b	toluene	rt to reflux	27b = 42%
5	20c	xylylene	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.

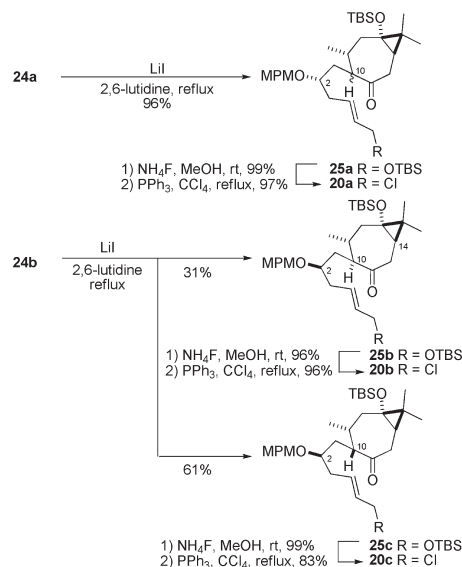
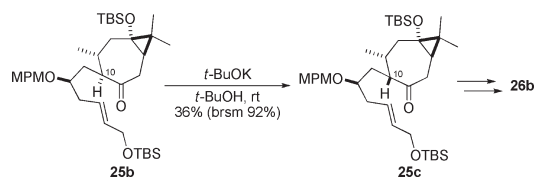
Scheme 6. Syntheses of Chlorides **20a–c**, Precursors of Intramolecular Spiro-Cyclization

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 Et₃CONa 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 Et₃CONa 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.

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

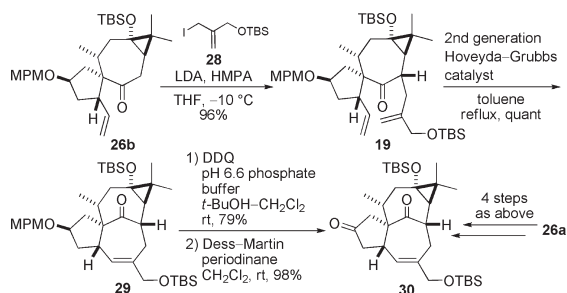


stereochemistry of spiro ketone **26b** was determined by the NOE correlation between H-11 and allylic H-4 (see SI). The stereoselectivity of this spiro-cyclization can be explained by our previous proposed transition state model.⁶

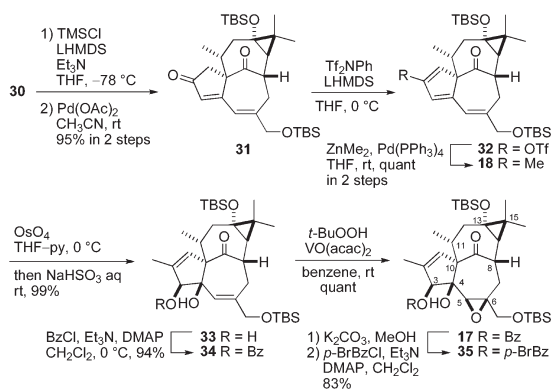
Alkylation of **26b** by LDA and iodide **28** gave the desired ketone **19** as the sole product (Scheme 8). The ring-closing olefin metathesis of **19** with the second-generation Hoveyda–Grubbs catalyst¹⁴ gave tetracyclic ketone **29** in quantitative yield. The stereochemistry of **29** was determined 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 OsO₄ 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 epoxidation 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).

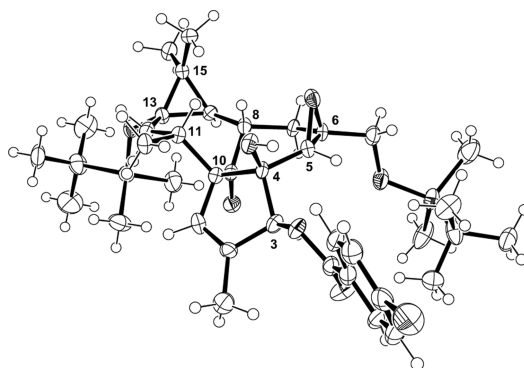


Figure 2. X-ray crystallographic structure of **35**.

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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