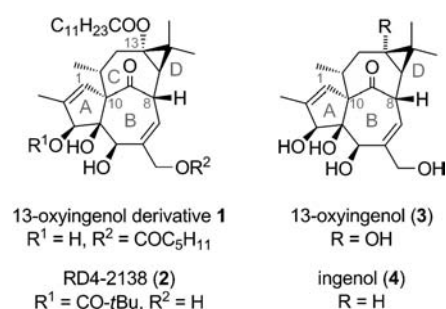


Total Synthesis of (–)-13-Oxyingenol and its Natural Derivative**

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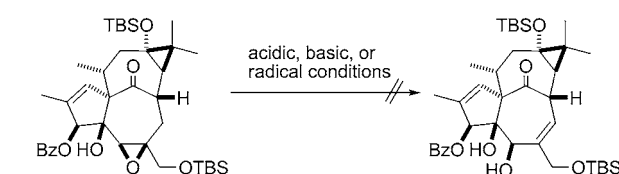
13-Oxyingenol derivative **1**^[1] and ingenol (**4**)^[2] are diterpenoids isolated from the plants of *Euphorbia* sp. The main structural features of ingenols are a bicyclo[4.4.1]undecane skeleton with inside–outside intrabridgehead stereochemistry and a high degree of oxygenation (Scheme 1). Ingenols and

Recently, we reported the construction of the fully substituted tetracyclic inside–outside framework of 13-oxyingenols.^[10] We attempted the ring-opening reaction of an epoxide to construct the allylic alcohol part of the B ring under acidic, basic, or radical conditions (Scheme 2). How-



Scheme 1. Structures of 13-oxyingenols and ingenol.

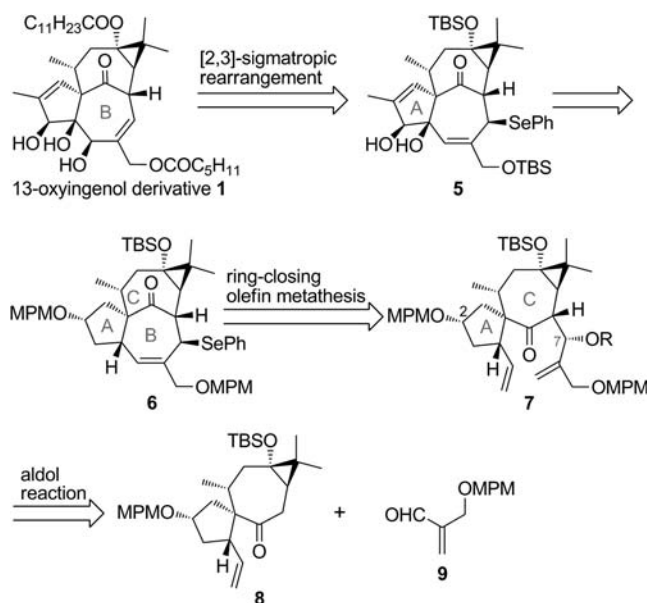
their analogues show strong bioactivities, such as protein kinase C activation.^[3] Furthermore, related compounds, such as RD4-2138 (**2**), have strong anti-HIV activity.^[4] The unique structures of ingenol derivatives along with their potent biological activity have made them attractive targets for total synthesis. Several synthetic studies, including total syntheses of ingenol (**4**), have been reported.^[5–8] However, the total synthesis of 13-oxyingenols has not been reported to date, despite the fact that 13-oxyingenol derivative **1** was isolated over 30 years ago.^[9]



Scheme 2. Unsuccessful attempts to convert the epoxide into the allylic alcohol in the previous synthetic studies. Bz = benzoyl, TBS = *tert*-butyldimethylsilyl.

ever, the desired ring-opened allylic alcohol could not be obtained. Herein, we describe an improved synthetic route and the first total synthesis of optically active (–)-13-oxyingenol (**3**) and its natural derivative **1**.

According to our retrosynthetic analysis of 13-oxyingenol derivative **1** (Scheme 3), the B ring of **1** could be constructed by a Mislow–Evans-type [2,3]-sigmatropic rearrangement of a selenoxide that was generated from **5**.^[11,12] The A-ring part at diol **5** can be established from tetracyclic ketone **6** by a strategy similar to the one we used in our previous



Scheme 3. Retrosynthetic analysis of 13-oxyingenol derivative **1**.

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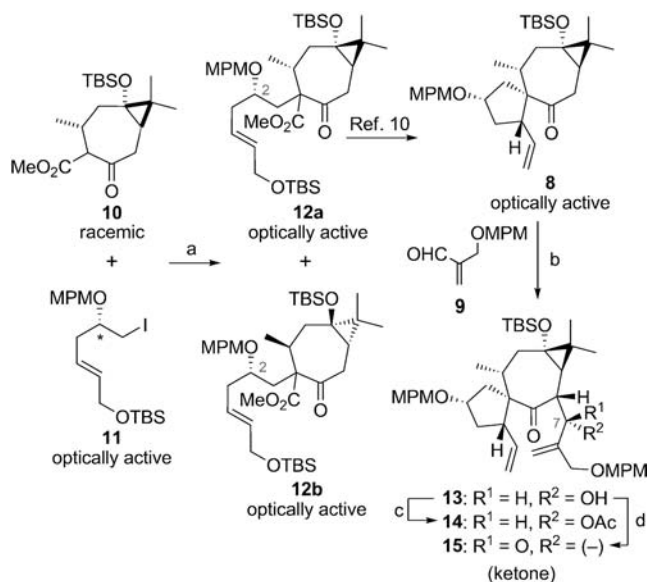
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synthesis.^[10] Tetracyclic ketone **6** would be synthesized by using an aldol reaction between spiro ketone **8** and aldehyde **9**,^[11] followed by the ring-closing olefin metathesis (RCM) of **7**. In this work, we introduced two hydroxy groups at C2 and C7, and used them to introduce the requisite functional groups at the A- and B-ring parts.

The synthesis started with the preparation of the optically active spiro ketone **8** (Scheme 4). We synthesized **8** in racemic



Scheme 4. Syntheses of precursors of ring-closing olefin metathesis. Reagents and conditions: a) **11**, Cs_2CO_3 , DMSO, 50°C ; 2) chromatographic separation, **12a**: 45%, **12b**: 46%; b) **9**, NaHMDS, THF, -78°C ; c) Ac_2O , pyr, DMAP, 50°C , 83% (2 steps); d) Dess–Martin periodinane, CH_2Cl_2 , RT, 81% (2 steps). Ac = acetyl, DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide, MPM = *p*-methoxyphenylmethyl, NaHMDS = sodium bis(trimethylsilyl)amide, pyr = pyridine, THF = tetrahydrofuran.

form in our previous work, in which we found that alkylated compounds **12a** and **12b** could be easily separated chromatographically. Thus, the racemic keto ester **10** was alkylated with optically active iodide **11**^[13] to give alkylated compounds **12a** and **12b** as single stereoisomers that were separated by silica gel chromatography. Optically active compound **12a** was converted into spiro ketone **8** in the same manner as in our previous work.^[10] With optically active spiro ketone **8** in hand, we then prepared the precursors for the RCM. The aldol reaction between spiro ketone **8** and unsaturated aldehyde **9** gave aldol **13** as a single diastereomer.^[11] The stereochemistry at C7 in **13** was determined by ^1H NMR analysis of the corresponding 7-hydroxy tetracyclic ketone **16** (see Table 1 and the Supporting Information). Aldol **13** was converted into acetate **14** and α,β -unsaturated ketone **15** as the precursors of RCM.

We next examined the crucial construction of the inside-outside framework of 13-oxyingenol by RCM (Table 1). RCM of **13** with the second-generation Hoveyda–Grubbs catalyst (**19**)^[14] gave 7-hydroxy tetracyclic ketone **16**, but the yield was moderate (54%; entry 1). The stereochemistry of **16** was

Table 1: Ring-closing olefin metathesis of dienes **13**–**15**.

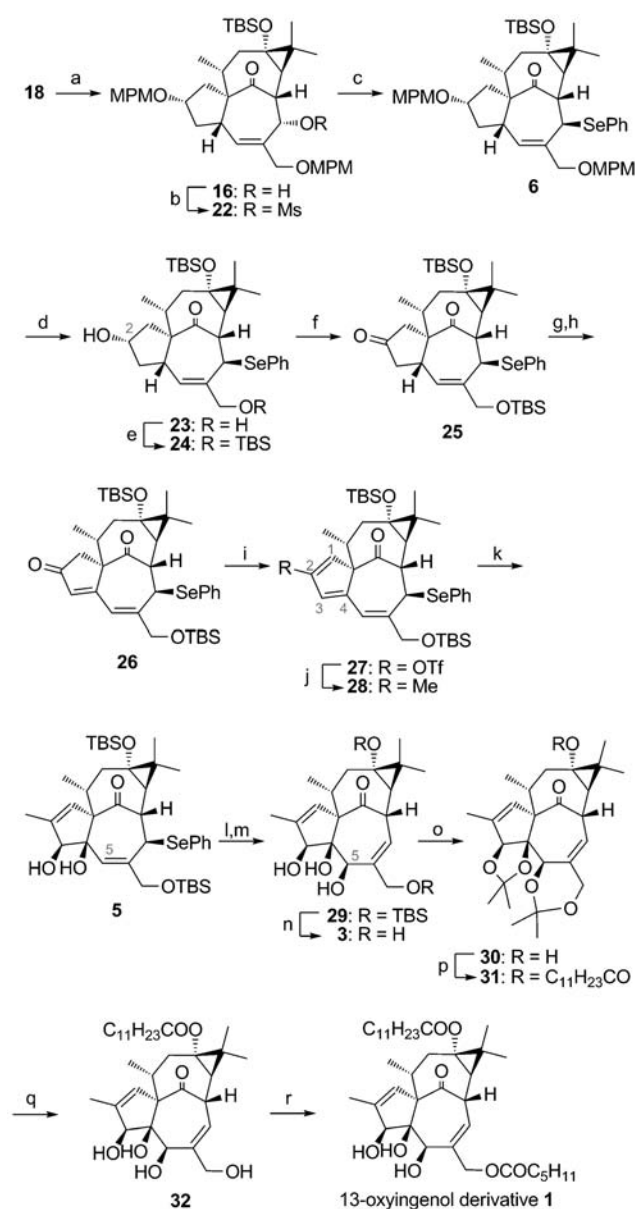
Entry	Precursor of RCM	Catalyst	Yield [%]
1	13	19	54 (16)
2	14	19	64 (17)
3	14	20	51 (17)
4	14	21	0 (17)
5	15	19	86 (18)

13: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OH}$
14: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OAc}$
15: $\text{R}^1 = \text{O}$, $\text{R}^2 = \text{O}$
16: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OH}$
17: $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{OAc}$
18: $\text{R}^1 = \text{O}$, $\text{R}^2 = \text{O}$ (ketone)

19: $\text{Mes}_2\text{N}(\text{CH}_2)_2\text{N}(\text{Mes})_2$
20: $\text{Mes}_2\text{N}(\text{CH}_2)_2\text{N}(\text{Mes})_2$
21: $\text{Mes}_2\text{N}(\text{CH}_2)_2\text{N}(\text{Mes})_2$

determined by ^1H NMR analysis (see the Supporting Information). Under these RCM conditions, a small amount of spiro ketone **8** was obtained because a retro-aldol reaction occurred. Thus, we next investigated the RCM of acetate **14** by screening an assortment of Ru catalysts (entries 2–4). The reaction with the second-generation Hoveyda–Grubbs catalyst (**19**) gave 7-acetoxy tetracyclic ketone **17** in 64% yield (entry 2). Use of highly active Ru catalyst **20**^[15] in this reaction afforded 7-acetoxy tetracyclic ketone **17** (entry 3). However, the reaction was not as successful as expected and the yield of product **17** was moderate. Treatment of acetate **14** with the less hindered Ru catalyst **21**^[16] (Stewart–Grubbs catalyst) did not result in the formation of 7-acetoxy tetracyclic ketone **17**. Next, we tried this cyclization with α,β -unsaturated ketone **15**, in which the reactivity of one olefin is different and the steric hindrance of the cyclization is lowered. The reaction of α,β -unsaturated ketone **15** with Hoveyda–Grubbs catalyst **19** proceeded smoothly to give the desired 7-keto tetracyclic ketone **18** in 86% yield (entry 5). It is noteworthy that no epimerization of β -diketone moiety in **15** and **18** was observed.

We next attempted the functionalization of the A and B rings in 13-oxyingenol derivative **1** (Scheme 5). Reduction of the carbonyl group at C7 in compound **18** gave allylic alcohol **16** as a single diastereomer. Mesylation of alcohol **16** by the method described by Tanabe and co-workers^[17] afforded mesylate **22**, and the introduction of a phenyl selenyl group with a selenide anion generated from $(\text{PhSe})_2$ and NaBH_4 gave selenide **6**. The stereochemistry of selenide **6** was determined by ^1H NMR analysis (see the Supporting Information). The removal of both MPM groups in selenide **6** and subsequent selective protection of the primary hydroxy group afforded alcohol **24**. The remaining secondary hydroxy group at C2 in alcohol **24** was oxidized by Parikh–Doering oxidation^[18] to give diketone **25**. Substrate **25** was trans-



Scheme 5. Total synthesis of 13-oxyingenol derivative **1**. Reagents and conditions: a) DIBAL, toluene, -78°C , 96%; b) MsCl , $\text{Me}_2\text{N}-(\text{CH}_2)_3\text{NMe}_2$, toluene, 0°C ; c) $(\text{PhSe})_2$, NaBH_4 , THF/EtOH , RT, quant. (2 steps); d) DDQ, pH 6.6 phosphate buffer, $t\text{BuOH}/\text{CH}_2\text{Cl}_2$, RT, quant.; e) TBSCl, Et_3N , DMAP, CH_2Cl_2 , RT, 97%; f) SO_3 -pyr, DMSO, Et_3N , CH_2Cl_2 , RT, quant.; g) TMSCl, LHMDS, Et_3N , THF, -78°C ; h) $\text{Pd}(\text{OAc})_2$, DMSO, RT, 64% (2 steps); i) Tf_2NPh , LHMDS, THF, -40°C ; j) Me_2Zn , $\text{Pd}(\text{PPh}_3)_4$, THF, RT; k) OsO_4 , THF/pyr , 0°C , then aq. NaHSO_3 , RT, 64% (3 steps); l) *m*CPBA, THF, -78°C ; m) $\text{P}(\text{OMe})_3$, MeOH , 0°C , 61% (2 steps) (borsm quant.); n) $\text{HF}\cdot\text{pyr}$, THF/pyr , RT, quant.; o) 2,2-dimethoxypropane, PPTS, CH_2Cl_2 , RT; p) $\text{C}_{11}\text{H}_{23}\text{CO}_2\text{H}$, EDCI, DMAP, CH_2Cl_2 , RT, 63% (2 steps); q) HCl (1 M), THF, RT, 99%; r) $(\text{C}_5\text{H}_{11}\text{CO})_2\text{O}$, Et_3N , CH_2Cl_2 , -20°C , 85%. borsm = based on recovered starting material, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, LHMDS = lithium bis(trimethylsilyl)amide, *m*CPBA = *m*-chloroperoxybenzoic acid, Mes = 2,4,6-trimethylphenyl, Ms = methanesulfonyl, *o*-Tol = *o*-tolyl, PPTS = pyridinium *p*-toluenesulfonate, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

formed into enone **26** by using the Ito–Saegusa oxidation.^[19] Enone **26** was converted into enol triflate **27**, which was subjected to a Negishi coupling^[20] to afford triene **28**. Regio- and stereoselective dihydroxylation of triene **28** with a stoichiometric amount of OsO_4 gave diol **5**. The high regio- and stereoselectivity could be explained by considering that steric hindrance at the C11 methyl group shielded the olefin at C1/C2, and that the strain and pyramidal distortion of the olefin at C3/C4 enhance its reactivity (see the Supporting Information). The phenyl selenyl group was not affected during the conversion of selenide **6** into diol **5** under different oxidizing conditions, including the use of DDQ, Parikh–Doering oxidation, and OsO_4 . The introduction of the hydroxy group at C5 by using a Mislow–Evans-type rearrangement was next attempted. The oxidation of the aromatic selenide group in **5** with *m*CPBA and subsequent [2,3]-sigmatropic rearrangement with $\text{P}(\text{OMe})_3$ afforded triol **29**. The removal of both TBS groups in **29** afforded 13-oxyingenol (**3**), a parent compound of 13-oxyingenol derivatives, such as **1**. 13-oxyingenol (**3**) was protected as two acetonide groups to afford compound **30**. Acylation of the remaining tertiary hydroxy group at C13 gave dodecanoyl ester **31**. Hydrolysis of two acetonides with aqueous HCl , followed by selective acylation of the primary hydroxy group, led to the formation of 13-oxyingenol derivative **1**. The spectral data of synthetically obtained 13-oxyingenol derivative **1** (^1H NMR, ^{13}C NMR, HRMS) were in full agreement with those of the natural product. The optical rotation of **1** ($[\alpha]_{\text{D}}^{23} = -25.0$ ($c = 0.10$, CHCl_3)) was in good agreement with that of the isolated sample ($[\alpha]_{\text{D}}^{23} = -24.6$ ($c = 0.17$, CHCl_3)).

In conclusion, we have achieved the first total synthesis of (–)-13-oxyingenol (**3**) and its natural derivative **1** in 21 steps from spiro ketone **8**. The presence of the hydroxy groups at C2 and C7 enables the efficient functionalization of the A and B rings. The highlights of this approach are the use of an RCM for the construction of an inside–outside framework and a Mislow–Evans-type [2,3]-sigmatropic rearrangement for the introduction of a hydroxy group at C5. This synthetic strategy is also applicable to the synthesis of ingenol (**4**) and more concise than the method we used in our previous work.^[6]

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