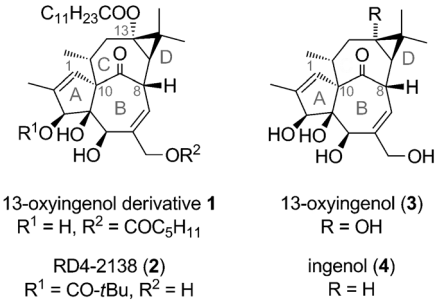
Natural Product Synthesis

DOI: 10.1002/anie.201201383

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

*Takayuki Ohyoshi, Shota Funakubo, Yamato Miyazawa, Keisuke Niida, Ichiro Hayakawa, and Hideo Kigoshi**

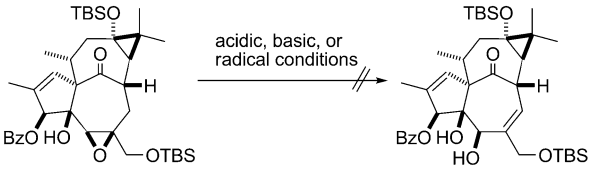
13-Oxyingenol derivative **1**[1] and ingenol (**4**)[2] are diterpenoids isolated from the plants of *Euphorbia* sp. The main structural features of ingenols are a bicyclo[4.4.1]undecane skeleton with inside–outside intrabridgehead stereochemistry and a high degree of oxygenation (Scheme 1). Ingenols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



Scheme 1. Structures of 13-oxyingenols and ingenol.

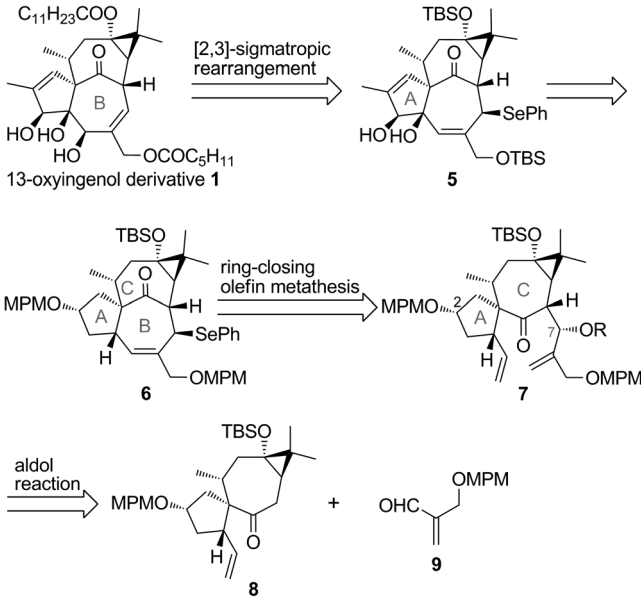
their analogues show strong bioactivities, such as protein kinase C activation.[3] Furthermore, related compounds, such as RD4-2138 (**2**), have strong anti-HIV activity.[4] The unique structures of ingenol derivatives along with their potent biological activity have made them attractive targets for 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]

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). However, 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**.



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

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**.

[*] Dr. T. Ohyoshi,[+] S. Funakubo, Y. Miyazawa, K. Niida, Dr. I. Hayakawa, Prof. Dr. H. Kigoshi
Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba
1-1-1 Tennodai, Tsukuba 305-8571 (Japan)
E-mail: kigoshi@chem.tsukuba.ac.jp

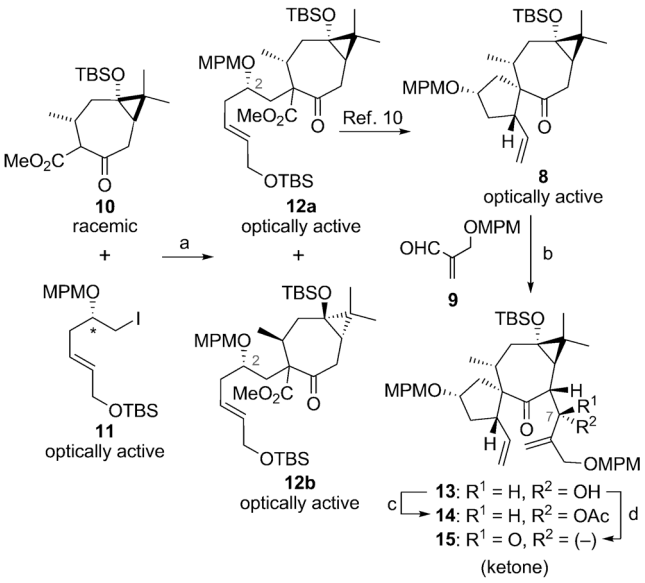
[+] Research fellow of the Japan Society for the Promotion of Science (JSPS).

[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT; Japan); by a grant from the Uehara Memorial Foundation, and by a grant from the Suntory Institute for Bioorganic Research (SUNBOR GRANT). We thank the Takasago International Corp. for their gift of (*S*)-β-hydroxy γ-butyrolactone. We would also like to thank Prof. Daisuke Uemura (Kanagawa University) for providing a sample of the 13-oxyingenol derivative and for his helpful discussion.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201383.

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

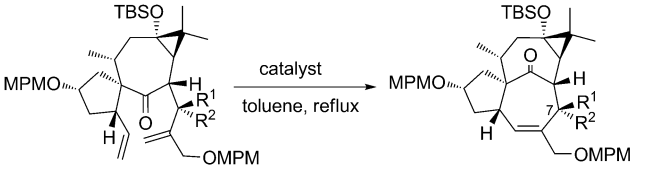


Scheme 4. Syntheses of precursors of ring-closing olefin metathesis. Reagents and conditions: a) 1) **11**, Cs_2CO_3, DMSO, 50 °C; 2) chromatographic separation, **12a**: 45 %, **12b**: 46 %; b) **9**, NaHMDS, THF, −78 °C; c) Ac_2O, pyr, DMAP, 50 °C, 83 % (2 steps); d) Dess–Martin periodinane, CH_2Cl_2, 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 ^{1}H 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

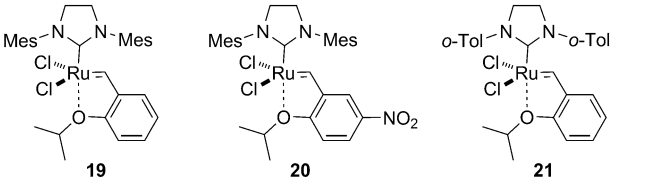
Table 1: Ring-closing olefin metathesis of dienes **13**–**15**.



13: R^1 = H, R^2 = OH
14: R^1 = H, R^2 = OAc
15: R^1 = R^2 = O

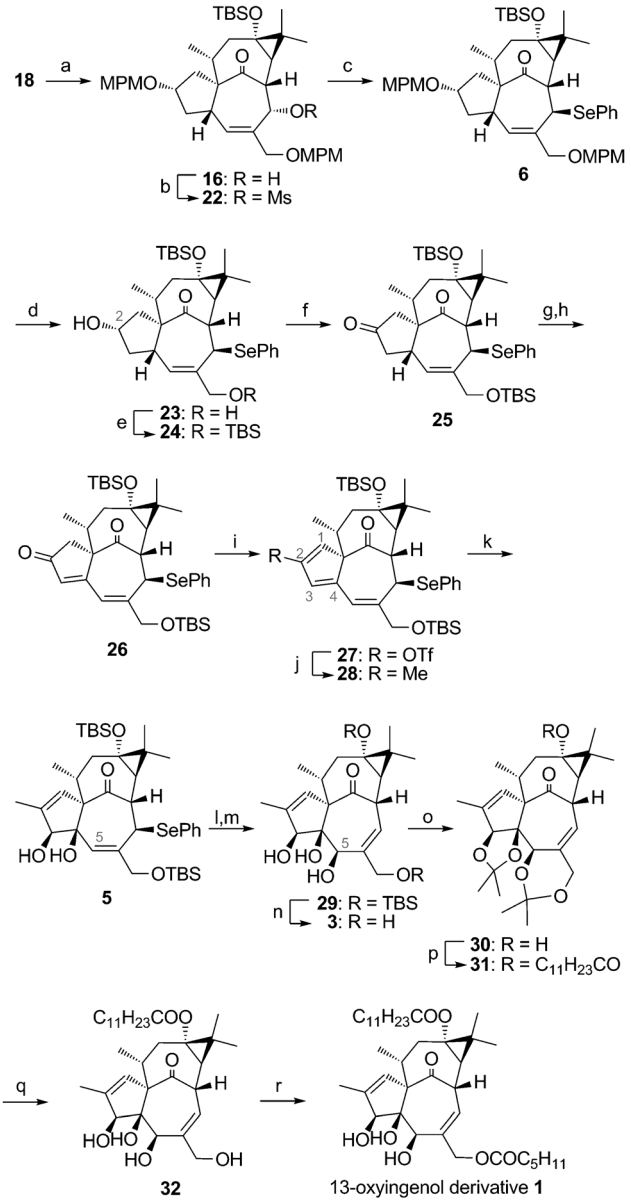
16: R^1 = H, R^2 = OH
17: R^1 = H, R^2 = OAc
18: R^1 = O, R^2 = (–) (ketone)

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**)



determined by ^{1}H 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 $(PhSe)_2$ and $NaBH_4$ gave selenide **6**. The stereochemistry of selenide **6** was determined by ^{1}H 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, $Me_2N(CH_2)_3NMe_2$, toluene, 0 °C; c) $(PhSe)_2$, $NaBH_4$, THF/EtOH, RT, quant. (2 steps); d) DDQ, pH 6.6 phosphate buffer, *t*BuOH/CH_2Cl_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) $Pd(OAc)_2$, DMSO, RT, 64% (2 steps); i) Tf_2NPh, LHMDS, THF, −40 °C; j) Me_2Zn, $Pd(PPh_3)_4$, THF, RT; k) OsO_4, THF/pyr, 0 °C, then aq. $NaHSO_3$, RT, 64% (3 steps); l) *m*CPBA, THF, −78 °C; m) $P(OMe)_3$, MeOH, 0 °C, 61% (2 steps) (borsm quant.); n) HF·pyr, THF/pyr, RT, quant.; o) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, RT; p) $C_{11}H_{23}CO_2H$, EDCI, DMAP, CH_2Cl_2, RT, 63% (2 steps); q) HCl (1 M), THF, RT, 99%; r) $(C_5H_{11}CO)_2O$, 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*-chloroperbenzoic 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 $P(OMe)_3$ 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** (^{1}H NMR, ^{13}C NMR, HRMS) were in full agreement with those of the natural product. The optical rotation of **1** ($[\alpha]_D^{23} = -25.0$ ($c = 0.10$, $CHCl_3$)) was in good agreement with that of the isolated sample ($[\alpha]_D^{23} = -24.6$ ($c = 0.17$, $CHCl_3$)).

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]

Received: February 20, 2012
Published online: April 5, 2012

Keywords: 13-oxyingenol · inside–outside framework · metathesis · sigmatropic rearrangement · terpenoids

[1] a) D. Uemura, H. Ohwaki, Y. Hirata, Y.-P. Chen, H.-Y. Hsu, *Tetrahedron Lett.* **1974**, *15*, 2529; b) Y. Hirata, *Pure Appl. Chem.* **1975**, *41*, 175.
[2] K. Zechmeister, F. Brandl, W. Hoppe, E. Hecker, J. H. Opferkuch, W. Adolf, *Tetrahedron Lett.* **1970**, *11*, 4075.
[3] C. M. Hasler, G. Acs, M. Blumberg, *Cancer Res.* **1992**, *52*, 202.
[4] M. Fujiwara, M. Okamato, K. Ijichi, K. Tokuhisa, Y. Hanasaki, K. Katuura, D. Uemura, S. Shigeta, K. Konno, T. Yokota, M. Baba, *Arch. Virol.* **1998**, *143*, 2003.
[5] For a review, see: a) S. Kim, J. D. Winkler, *Chem. Soc. Rev.* **1997**, *26*, 387; b) I. Kuwajima, K. Tanino, *Chem. Rev.* **2005**, *105*, 4661; c) J. K. Cha, O. L. Epstein, *Tetrahedron* **2006**, *62*, 1329.

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

[7] For a formal synthesis of ingenol by our group, see: K. Watanabe, Y. Suzuki, K. Aoki, A. Sakakura, K. Suenaga, H. Kigoshi, *J. Org. Chem.* **2004**, *69*, 7802.

[8] For the successful construction of an inside–outside skeleton, see: a) R. L. Funk, T. A. Olmstead, M. Parvez, *J. Am. Chem. Soc.* **1988**, *110*, 3298; b) H. Kigoshi, Y. Suzuki, K. Aoki, D. Uemura, *Tetrahedron Lett.* **2000**, *41*, 3927; c) J. H. Rigby, B. Bazin, J. H. Meyer, F. Mohammadi, *Org. Lett.* **2002**, *4*, 799; d) O. L. Epstein, J. K. Cha, *Angew. Chem.* **2005**, *117*, 123; *Angew. Chem. Int. Ed.* **2005**, *44*, 121.

[9] For our approaches to synthesize the 13-oxyingenol skeleton, see: a) I. Hayakawa, Y. Asuma, T. Ohyoshi, K. Aoki, H. Kigoshi, *Tetrahedron Lett.* **2007**, *48*, 6221; b) I. Hayakawa, Y. Miyazawa, T. Ohyoshi, Y. Asuma, K. Aoki, H. Kigoshi, *Synthesis* **2011**, 769.

[10] T. Ohyoshi, Y. Miyazawa, K. Aoki, S. Ohmura, Y. Asuma, I. Hayakawa, H. Kigoshi, *Org. Lett.* **2011**, *13*, 2160.

[11] A. Nickel, Ph.D. Thesis, Yale University, **2005**: Nickel described the synthetis of ingenol by using an aldol reaction and a Mislow–Evans-type [2,3]-sigmatropic rearrangement. His successful aldol reaction was effected with a simpler aldehyde, methacrolein.

[12] a) K. B. Sharpless, R. F. Lauer, *J. Am. Chem. Soc.* **1972**, *94*, 7154; b) H. J. Reich, *J. Org. Chem.* **1975**, *40*, 2570.

[13] Iodide **10** was prepared from (*S*)-β-hydroxy γ-butyrolactone. The detailed synthetic procedures for **10** are given in Ref. [9].

[14] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168.

[15] K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem.* **2002**, *114*, 4210; *Angew. Chem. Int. Ed.* **2002**, *41*, 4038.

[16] I. C. Stewart, T. Ung, A. A. Pletnev, J. M. Berlin, R. H. Grubbs, Y. Schrodi, *Org. Lett.* **2007**, *9*, 1589.

[17] Y. Yoshida, Y. Sakakura, N. Aso, S. Okada, Y. Tanabe, *Tetrahedron* **1999**, *55*, 2183.

[18] J. P. Parikh, W. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505.

[19] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.

[20] E. Negishi, A. O. King, N. Okukado, *J. Org. Chem.* **1977**, *42*, 1821.

