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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6221–6224

Synthetic study on 13-oxyingenol: construction of the full carbon framework

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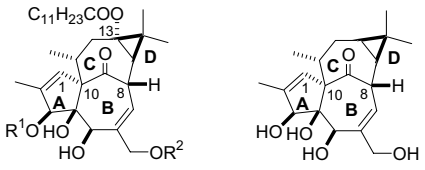
Received 23 May 2007; revised 12 June 2007; accepted 15 June 2007
Available online 3 July 2007

Abstract—13-Oxyingenol is a diterpenoid isolated from *Euphorbia kansui*, and its derivatives have strong anti-HIV activity. We achieved the construction of *inside–outside* framework of 13-oxyingenol by using ring-closing olefin metathesis.

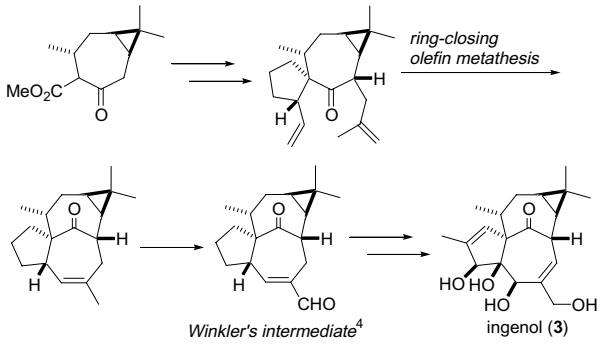
13-oxyingenol (**1**) and ingenol (**3**) are diterpenoids isolated from the plants of *Euphorbia* sp. (Fig. 1).[1] They and their analogs have interesting bioactivities such as protein kinase C activation and anti-HIV activities.[2] Particularly, 13-oxyingenol derivatives such as **2** have strong anti-HIV activity. The structural features of ingenol and 13-oxyingenol are a high degree of oxygenation and a highly strained *inside–outside* bicyclic ring system. The molecular complexity of ingenol derivatives, in conjunction with their potent biological activities, has made them attractive synthetic targets. Several groups have reported approaches to synthesize the ingenol skeleton.[3] In 2002, Winkler et al. first achieved the total synthesis of **3** by using the de Mayo reaction and subsequent fragmentation.[4] The next year, Tanino–Kuwajima et al. accomplished the total synthesis of **3** by using the tandem cyclization-rearrangement reaction.[5] In 2004, we reported the formal total synthesis of optically active ingenol by using ring-closing olefin metathesis as a key step (Scheme 1).[6] Wood et al. have reported the total synthesis of **3** by a similar metathesis strategy.[7]



13-oxyingenol (**1**)
R^1 = H, R^2 = COC_5H_{11}
13-oxyingenol derivative RD4-2138 (**2**)
R^1 = CO-*t*-Bu, R^2 = H

ingenol (**3**)

Figure 1. Structures of ingenol, 13-oxyingenol and its derivatives.



Scheme 1. Formal total synthesis of optically active ingenol by our group.

A number of synthetic approaches to ingenol (**3**) have been made as stated above. However, synthetic approaches to 13-oxyingenol derivatives have never been reported so far. We planned the synthesis of 13-oxyingenol (**1**) and its derivatives **2** by using our ring-closing olefin metathesis strategy.

The starting point for this work was the construction of the enone **9** (Scheme 2). Two hydroxy groups in 2-(4-hydroxyphenyl)ethanol (**4**) were successively protected, and the aromatic ring was reduced in Birch conditions

Keywords: 13-Oxyingenol; Anti-HIV activity; Ring-closing olefin metathesis.
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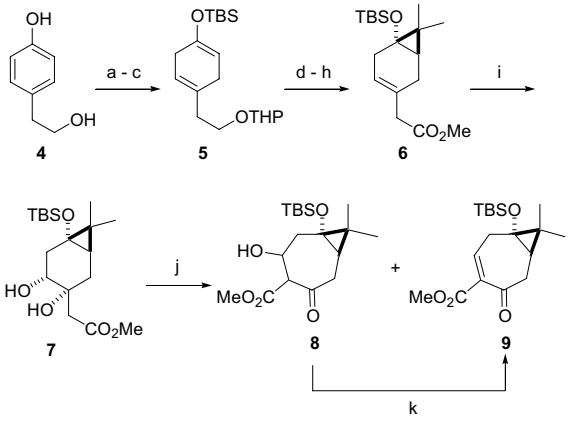
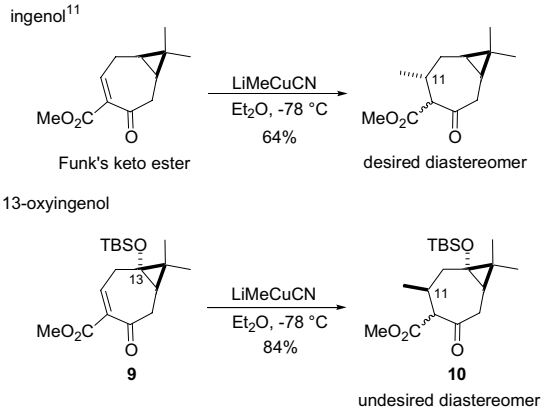
doi:10.1016/j.tetlet.2007.06.135



Scheme 2. Reagents and conditions: (a) DHP, *p*-TsOH·H_2O, CH_2Cl_2, rt, 70%; (b) TBSCl, imidazole, DMF, rt, 100%; (c) Li, *liq*. NH_3, *t*-BuOH, THF, −33 °C, 100%; (d) $(CH_3)_2CBr_2$, *n*-BuLi, Et_2O, −78 °C, 83%; (e) propylene glycol, 100 °C, 15 min, 86%; (f) DMP, CH_2Cl_2; (g) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, *t*-BuOH; (h) $TMSCHN_2$, MeOH, rt, 90% in three steps; (i) OsO_4, NMO, acetone–H_2O, 86%; (j) $Pb(OAc)_4$, benzene; (k) Ac_2O, pyridine, rt, 74% in two steps.

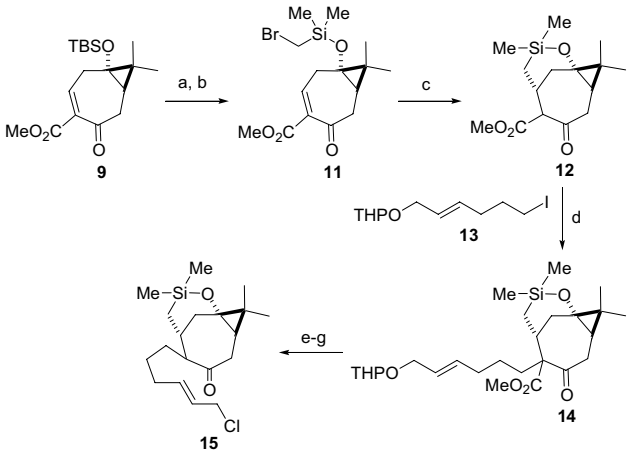


Scheme 3.

to give diene **5**. Regioselective cyclopropanation[8] of **5** and selective removal of the THP group[9] gave an alcohol, which was transformed into methyl ester **6** by a three-step sequence of reactions. Dihydroxylation of **6** gave diol **7**.[10] Oxidative cleavage of **7** by $Pb(OAc)_4$ and a spontaneous intramolecular aldol reaction afforded the seven-membered aldol **8** and the seven-membered enone **9**. The former was converted into the latter on acetylation.[6]

In the synthetic study of ingenol reported by Funk, the methyl group can be introduced from the α face of Funk's keto ester stereoselectively (Scheme 3).[11] However, in the case of 13-oxyingenol, the methyl group was introduced from the β face of enone **9** exclusively, maybe because of steric hindrance of the C-13 substituent.[12] The corresponding hydroxy enone gave the same result.

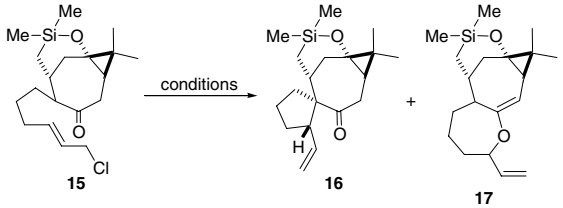
We next tried the stereoselective introduction of the C1 unit at C-11 by using intramolecular radical cyclization of **11** to give silicon–tethered compound **12** (Scheme 4).



Scheme 4. Reagents and conditions: (a) HF·pyr., pyridine, THF, rt, 97%; (b) $BrCH_2Si(CH_3)_2Cl$, Et_3N, CH_2Cl_2, rt, 84%; (c) AIBN, Bu_3SnH, benzene, reflux, 91%; (d) **13**, NaH, DMF, 100 °C, 67%; (e) LiI, 2,6-lutidine, reflux, 66%; (f) PPTS, EtOH, 50 °C, 90%; (g) PPh_3, CCl_4, reflux, 92%.

The TBS protecting group in **9** was removed in good yield, and the resulting alcohol was reacted with bromomethyldimethylsilyl chloride to afford silyl ether **11**. Radical cyclization of **11** using AIBN and Bu_3SnH gave the desired compound **12** in good yield.[13] This silicon–tethered compound **12** enabled not only the introduction of the C1 unit from the α face in enone **9** but also the suitable protection of the C-13 hydroxy group. Keto ester **12** was alkylated with iodide **13**[6] to give alkylated compound **14**. The methoxycarbonyl group of **14** was removed by heating with lithium iodide to afford a ketone.[14] The THP group was removed, and the resulting allylic alcohol was converted into chloride **15**. Attempts toward the intramolecular spiro-cyclization of **15** are summarized in Table 1. In our previous reports,[6] similar intramolecular spiro-cyclization was carried out by Et_3CONa in boiling xylene. Intramolecular spiro-cyclization of **15** under the same conditions gave the desired ketone **16** (46%) and the undesired

Table 1. Study of spiro-cyclization



Entry	Base	Solvent	Temperature	Time (min)	Yield (%)	
					16	**17**
1	Et_3CONa (3 equiv)[a]	Xylene	rt→reflux	10	46	18
2	Et_3CONa (3 equiv)[b]	Xylene	rt→reflux	10	72	2

[a] Et_3CONa prepared from the alcohol and NaH in 60% mineral oil (1:1) in xylene.

[b] Et_3CONa prepared from the alcohol and oil free NaH (1:1) in xylene.

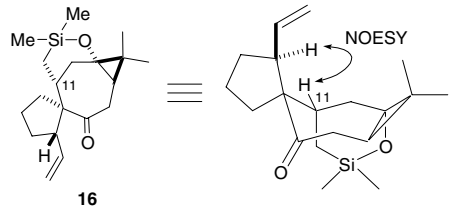
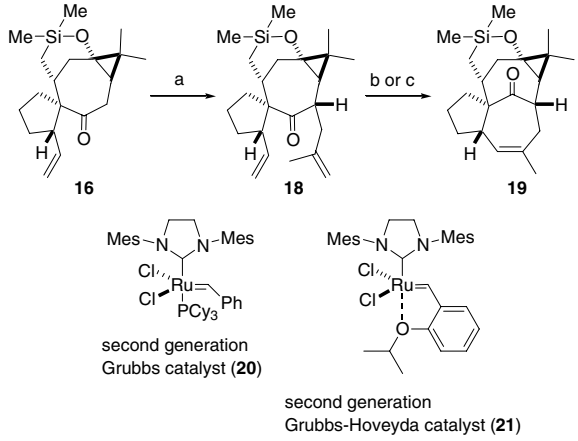


Figure 2. Relative stereochemistry of **16**.



Scheme 5. Reagents and conditions: (a) methallyl iodide, LDA, HMPA, −10 °C, 72%; (b) **20**, toluene, reflux, 86%; (c) **21**, toluene, reflux, 3%.

seven-membered ether **17** (18%) (entry 1). By use of oil-free NaH (washed with *n*-hexane), efficient spiro-cyclization of **15** has been realized (entry 2).

The stereochemistry of **16** was determined by the NOESY correlation between the allylic methine proton and the C-11 methine proton (Fig. 2).

Methallylation of spiroketone **16** with LDA and methallyl iodide gave the desired ketone **18** as the sole product (Scheme 5). The ring-closing olefin metathesis of **18** with the second-generation Grubbs catalyst (**20**)[15] provided the desired pentacyclic ketone **19** in 86%.[16] Another olefin metathesis catalyst, second-generation Hoveyda–Grubbs catalyst (**21**),[17] was less effective in this case.

The stereochemistry of **19** was determined by the NOESY correlations (Fig. 3). Thus, we achieved the construction of an *inside–outside* framework of 13-oxyingenol by using ring-closing olefin metathesis as a key step. Efforts toward the completion of the total synthesis are currently under way.[18]

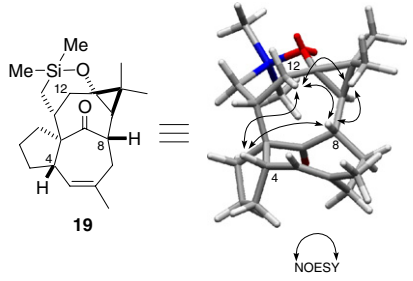


Figure 3. Relative stereochemistry of **19**.

Acknowledgments

This work was supported in part by the 21st COE program and Grant-in-Aid for Scientific Research on Priority Areas (No. 16073204, 'Creation of Biologically Functional Molecules') from the Ministry of Education, Culture, Sports, Science, and Technology, Japan and University of Tsukuba Projects.

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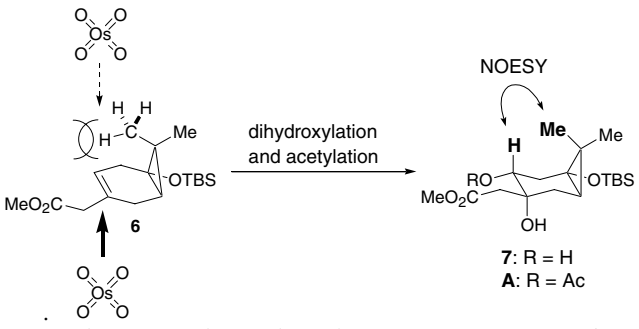
10. The stereochemistry of **7** was determined as follows. Diol **7** was converted into acetate **A**, the NOESY spectrum of which indicated the important correlation to determine the stereochemistry of the diol moiety.



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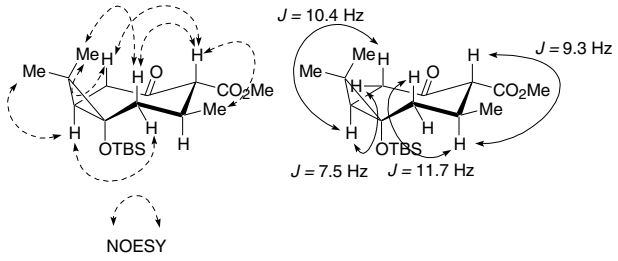

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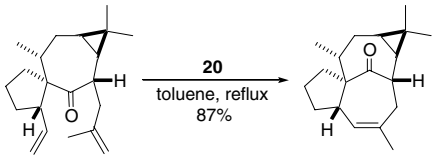
16. In the previous work,[6a] we achieved the construction of *inside–outside* framework of ingenol by using ring-closing olefin metathesis in 87%. The siloxy–tether group in this study does not participate in the olefin metathesis.



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