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Total synthesis of 7-*O*-methyldehydropinguisenol by palladium–catalyzed 1,7-enyne cycloisomerization

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Abstract—Efficient synthesis of 7-*O*-methyldehydropinguisenol, a typical pinguisane-type sesquiterpene with a furan moiety, was accomplished by applying palladium-catalyzed 1,7-enyne cycloisomerization for the construction of six-membered ring bearing an exomethylene as well as of adjacent quaternary centers.

Pinguisane-type sesquiterpenes whose carbon skeleton (**1**) is not consistent with the biogenetic isoprene rule occurs exclusively in liverworts.[1] In addition to many pinguisanes possessing the basic carbon skeleton (**1**),[2] a number of furanopinguisanes such as 7-*O*-methyldehydropinguisenol (**2**),[3] dehydropinguisenol (**3**),[4] deoxopinguisone (**4**),[5] and furanopinguisanol (**5**) (Fig. 1) were isolated mainly from *Lejeuneaceae*, *Prellaceae*, *Trichocoleaceae* and *Ptilidiaceae*.[1] These compounds have novel tricyclic furan skeleton with a *cis*-junction between the five- and six-membered rings and four or three adjacent *cis*-oriented methyl groups. Their unique carbon frameworks have stimulated extensive efforts of synthetic works.[6–9]

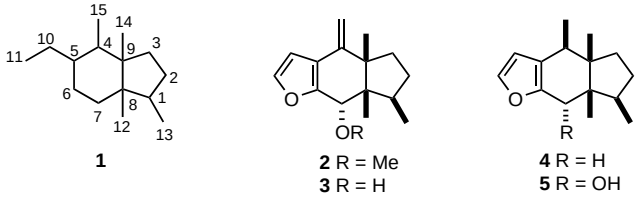
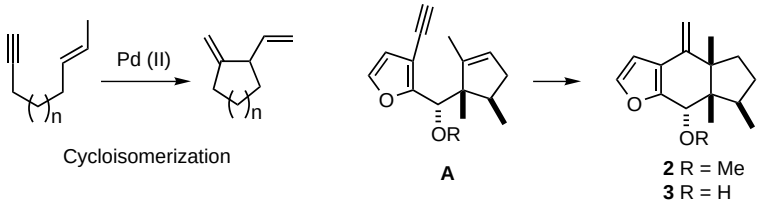


Figure 1. Pinguisane skeleton **1** and furanopinguisanes **2**–**5**.

In 1986, T. Uyehara et al. reported the first total synthesis of a furanopinguisane, deoxopinguisone (**4**), by employing light-induced rearrangement reaction.[10] Recently, Srikrishna et al. reported the first enantiospecific synthesis of pinguisenol, belonging to the primitive carbon skeleton **1**, by applying carbene reaction to the construction of the *cis*-fused five- and six-membered rings.[11,12] Herein, we describe the first and efficient synthesis of (±)-7-*O*-methyldehydropinguisenol (**2**) bearing a furan ring and a methoxyl group at C-7 on pinguisane framework.

Our synthetic strategy, outlined in Scheme 1, involves palladium-catalyzed 1,7-enyne cycloisomerization[13] of **A** which can not only construct the *cis*-fused five- and six-membered rings with an exomethylene but also control the *cis*-relationship of two vicinal methyl groups on the ring junction in **2**. Generally speaking, isomerization is expressed as 'Atom Economical Reaction' that



Scheme 1. Synthetic plan of **2** and **3** by Pd-catalyzed cycloisomerization.

Keywords: 7-*O*-methyldehydropinguisenol; pinguisane; palladium; 1,7-enyne; cycloisomerization.

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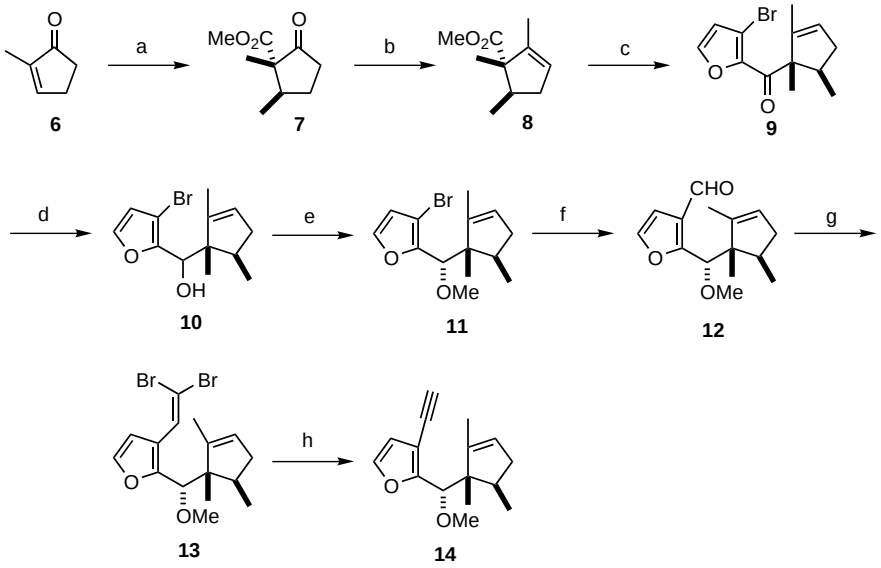
means no increase or decrease of atoms before and after the reaction.[14] Thus, ring formation by Pd-catalyzed isomerization of enyne can be regarded as an efficient procedure. Palladium-catalyzed cycloisomerization of our 1,7-enyne system involving tri-substituted olefin and furan ring conjugated with triple bond has not been investigated, and thus offers a challenge to apply this strategy toward the synthesis of **2**.

Methyl ester **7**[15] obtained from **6** was methylated by methylmagnesium iodide, followed by dehydration with P_2O_5, giving rise to **8** in 89% over four steps (Scheme 2). Compound **8** was coupled with 2-lithio-3-bromofuran prepared in THF in situ from 3-bromofuran by treatment of LDA at −78°C to afford **9** as a sole product in 66% yield. Reduction of **9** with $NaBH_4$ provided alcohols **10** as a mixture (α:β = 2:1). A α **11** and its β isomer were readily separated by silica gel column chromatography after *O*-methylation of **10** under the standard conditions. Treatment of **11** with *n*-BuLi and then addition of DMF gave rise to the aldehyde **12**. Subsequent Wittig-type reaction of **12** using CBr_4/PPh_3 yielded dibromoalkene **13**, which was then treated with *n*-BuLi to 1,7-enyne **14** in 75% yield over two steps.[16]

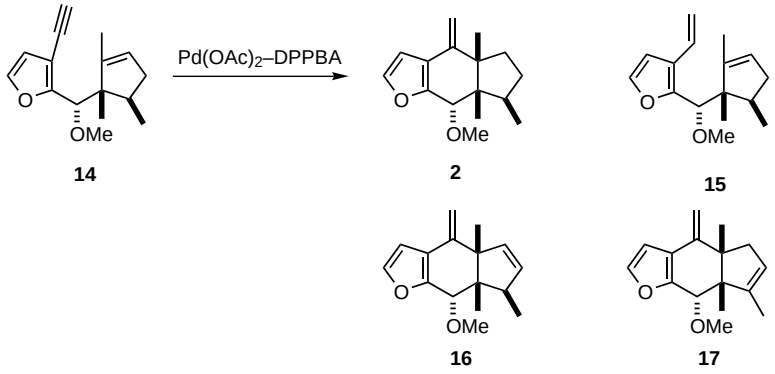
Subsequently, we have investigated 1,7-enyne cycloisomerization of **14** using $Pd(OAc)_2$ catalysts (Table 1). At first, reductive cycloisomerizations of **14** aiming at the direct conversion of **14** to **2** were employed under a catalytic system of $Pd(OAc)_2$–DPPBA–ligands in the presence of PMHS as a hydride reagent.[17,18] As results, the desirable product **2** was obtained in poor yield (6%) when dppe was used as a ligand (Table 1, entry 2). The formation of six-membered ring appears less efficient than that of five-membered ring due to the poor ability of 1,7-enyne to function as bidentate ligands to Pd(II).[19] Thus, the triple bond of **14** was reduced with hydride reagent prior to cyclization, resulting in the formation of the noncyclized **15** as main product. Our next attention focused on two-step conversion of **14** to **2**. Compound **14** was reacted under the same Pd-catalytic combination without PMHS as entry 2 in Table 1, thereby cyclization slowly proceeding to give **17** in 62% after 10 h (Table 1, entry 3). However, **17** resulted in losing the correct stereochemistry on C-1 by an undesirable migration of double bond. Slow Pd-catalyzed cyclization to six-membered ring presumably allowed competing a variety of noncyclization reactions.[20] This means that selection of ligand and reaction period are essential for this cyclization. After being attempted a variety of conditions (Table 1), we were pleased to find a Pd catalytic condition using 20 mol% tris(2-methylphenyl)phosphine as a ligand in 1,2-dichloroethane (10^{-3} M) and the reaction period of 5 h effected to **16** in 60% yield accompanying **17** in 6% (entry 6). Finally, selective hydrogenation of **16** (Scheme 3) over Wilkinson's complex in benzene–ethanol smoothly proceeded to give 7-*O*-methyldehydropinguisenol (**2**) in 90% yield.[22] The synthesized compound **2** is identical in all respects with the natural one.

In conclusion, we have developed the efficient procedure for construction of pinguisane framework by applying Pd-catalyzed 1,7-enyne cycloisomerization and have accomplished the first synthesis of (±)-7-*O*-methyldehydropinguisenol in overall yield of 9%. We are now applying this synthetic strategy to enantiospecific synthesis of other pinguisane-type sesquiterpenes.



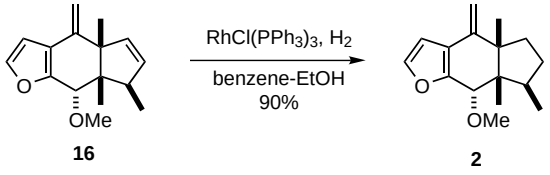
Scheme 2. (a) 1. Me_2CuLi, THF, 0°C then CO_2, 2. CH_2N_2, ether, 99%; (b) 1. MeMgI, ether, 2. P_2O_5, benzene, 90%; (c) 3-bromofuran, LDA, THF, −78°C, 66%; (d) $NaBH_4$, MeOH, 100%; (e) NaH, MeI, THF, 91% (**11**: 61%); (f) *n*-BuLi, DMF, THF, −78°C, 80%; (g) CBr_4, PPh_3, CH_2Cl_2, 83%; (h) *n*-BuLi, THF, −78°C, 90%.

Table 1. Palladium-catalyzed cycloisomerization of **14**[a]



Entry	Ligand	Hydride reagent (10 equiv.)	Time (h)	Products (%)[b]			
				2	**15**	**16**	**17**
1	$(o\text{-Tol})_3$P[c]	PMHS	10	–	65	–	–
2	Dppe[d]	PMHS	10	6	49	–	–
3	Dppe[d]	–	10	–	–	–	62
4	Dppe[d]	–	5	–	–	21	21
5	BBEDA[d]	–	5	–	–	16	14
6	$(o\text{-Tol})_3$P[c]	–	5	–	–	60	6

[a] All reactions were carried out with $Pd(OAc)_2$-DPPBA (10 mol %) in 1,2-dichloroethane at 80°C.
[b] Isolated yield after chromatographic purification.
[c] 20 mol%.
[d] 10 mol%. PMHS: polymethylhydrosiloxane; DPPBA: diphenylphosphinobenzoic acid; dppe: diphenylphosphinoethane; BBEDA: *N*,*N*′-bis(benzylidene)ethylenediamine.[21]



Scheme 3. Synthesis of **2**.

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