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Synthetic studies on the seven- and eight-membered rings by the intramolecular Nozaki–Hiyama reaction of the allylic phosphates

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Abstract—Synthetic studies on the seven- and eight-membered rings by the intramolecular Nozaki–Hiyama reaction of the allylic phosphates are described. The yield greatly depends on the structure of substrate; however, some complex substrates afforded desired products in high to excellent yield.

Some biologically important natural products, particularly terpenoids, contain seven- or eight-membered carbocyclic ring in their structures. For example, these carbon skeletons can be found in Taxol™, guanacastepene, erinacine E, and variecolin (Fig. 1).[1]

These ring systems, especially eight-membered rings, are difficult to construct because of entropy reasons, ring strain, and the transannular interaction; hence, their synthesis has been a challenging problem.

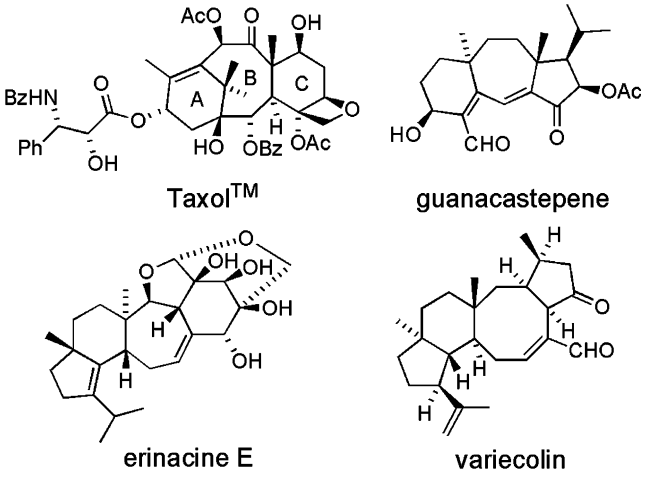

Figure 1.

Nozaki–Hiyama reaction is a Cr(II) mediated C–C bond forming reaction of various halides with aldehydes.[2] This reaction has been studied extensively because of their potential utility, and has also been applied to numerous total syntheses of complex natural products due to their high chemoselectivity, high yield, and excellent compatibility with various functional groups. However, to prepare both functional groups, an allylic halide and an aldehyde, in a same molecule is sometimes troublesome because of their high reactivity. Hence, application of the intramolecular Nozaki–Hiyama allylation (Fig. 2) to natural product synthesis has been limited.[3]

Nozaki and co-workers and Knochel and co-workers reported the intermolecular Nozaki–Hiyama reaction of allylic phosphates with aldehydes. To our knowledge, however, the intramolecular Nozaki–Hiyama reaction of allylic phosphates has never been reported so far.[4] This intramolecular reaction would be useful for the

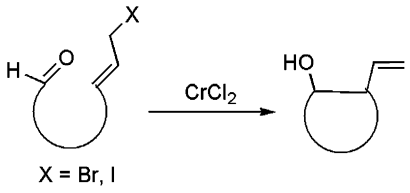

Figure 2.

Keywords: Nozaki–Hiyama reaction; Intramolecular reaction; Allylic phosphate; Carbocyclic ring, Seven- and eight-membered ring.
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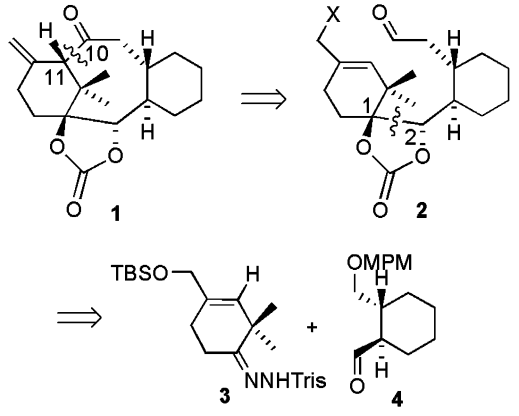
construction of cyclic compounds because the allylic phosphate is stable and easy to handle.

We have been investigating a new total synthesis of Taxol™, however, development of a synthetic method for the central eight-membered ring of Taxol™ (B-ring) has been a problem. Since Nozaki–Hiyama allylation has been an effective C–C bond forming reaction, we have started to investigate the intramolecular Nozaki–Hiyama allylation as a method for constructing the B-ring of Taxol™. During this study, we have found the intramolecular Nozaki–Hiyama reaction of allylic phosphates is a good method for constructing seven- and eight-membered carbocyclic rings. Herein we report the results obtained so far.

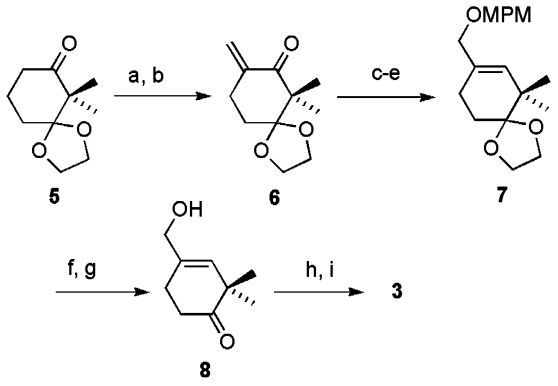
We have studied the construction of the eight-membered ring in Taxol™ model compound **1**, whose retrosynthetic analysis is shown in Scheme 1. Since the intramolecular Nozaki–Hiyama allylation of allylic phosphate **2** was expected to provide **1**, and **2** was envisioned to be prepared from trisyl hydrazone **3** and aldehyde **4** via Shapiro reaction (Scheme 1). Aldehyde **4** would be prepared from the known compound.[5]

Preparation of the trisyl hydrazone **3** is shown in Scheme 2. The known compound **5**[6] was alkylated by LDA and iodomethyl pivalate, followed by the β-elimination induced with DBU to afford α,β-unsaturated ketone **6** (84%, two steps).[7] Luche reduction of **6** (87%),[8] subsequent transformation to the corresponding chloride (87%), and the following reaction with sodium *p*-methoxyphenylmethoxide afforded **7** (94%). MPM group of **7** was removed by DDQ (90%), and the dioxolane was hydrolyzed with *p*-TsOH in aqueous acetone to afford **8** (96%). Alcohol **8** was protected as a TBS ether, and the following condensation with trisyl hydrazine gave trisyl hydrazone **3** (87%).

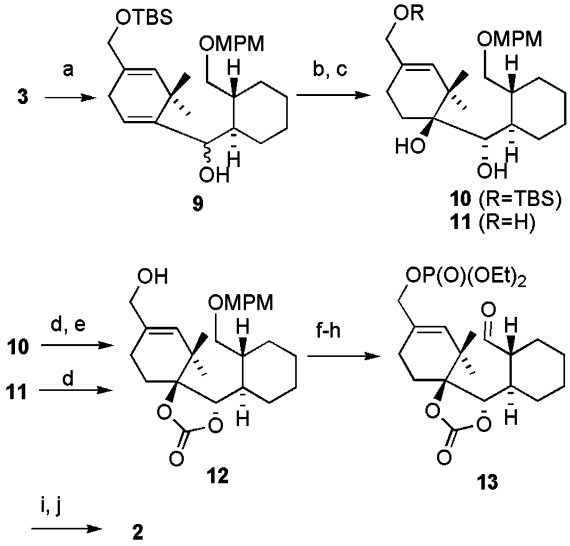
Preparation of aldehyde **13** is shown in Scheme 3. Trisyl hydrazone **3** was converted to the corresponding alkenyllithium by *n*-butyllithium (2 equiv), and which was reacted with aldehyde **4** to produce **9** as a mixture of diastereomers (91%, 6:1). The diastereoselective epoxidation of the isolated major diastereomer with TBHP



Scheme 1.



Scheme 2. Reagents and conditions: (a) LDA, THF, 0 °C, 15 min, then $PivOCH_2I$, −78 to 0 °C, 1 h; (b) DBU, CH_2Cl_2, 12 h, 84% (two steps); (c) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 5 min, 87%; (d) Py, $SOCl_2$, Et_2O, 0 °C to rt, 1 h, 87%; (e) MPMONa, TBAI, THF/DMF, 10 h, 94%; (f) DDQ, CH_2Cl_2/*t*-BuOH/potassium phosphate buffer $pK_a = 8$ (KPB 8), 1 h, 90%; (g) cat. PTSA, acetone/H_2O, 50 °C, 2 d, 96%; (h) TBSCl, imidazole, CH_2Cl_2, 9 h, 98%; (i) $TrisNHNH_2$, THF, 2 d, 87%.



Scheme 3. Reagents and conditions: (a) *n*-BuLi, THF, −78 to 0 °C, then **4**, −78 to 0 °C, 1 h, 91% (6:1); (b) cat. $VO(acac)_2$, TBHP, toluene, 0 °C, 0.5 h, 94%; (c) 1 N $LiAlH_4$ (in Et_2O), $Al(O\text{–}i\text{-}Pr)_3$, Et_2O, 33 h (**10**) 50% (**11**) 44%; (d) $(Cl_3CO)_2CO$, Py, CH_2Cl_2, −78 °C to rt, 10 h, quant.; (e) THF/2 N HCl, rt, 40 min, 80%; (f) $(EtO)_2P(O)Cl$, Py, CH_2Cl_2, 3 h, 74%; (g) DDQ, CH_2Cl_2/*t*-BuOH/KPB 7, 2 h, 91%; (h) Dess–Martin periodinane, CH_2Cl_2, 1 h, 95%; (i) LDA, (methoxymethyl)triphenyl phosphonium chloride, −78 °C to rt, 2 h, 50%; (j) PTSA, CH_2Cl_2, 0.5 h, quant.

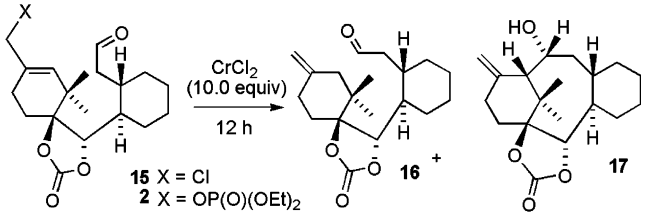
and $VO(acac)_2$,[5] followed by $LiAlH_4$ reduction in the presence of $Al(O\text{–}i\text{-}Pr)_3$ to give diol **10** (50%)[9] along with triol **11** (44%). Diol **10** was converted to the cyclic carbonate with triphosgene (quant.), followed by the treatment with diluted hydrochloric acid to produce **12** (80%), and triol **11** was independently converted to **12** by the treatment with triphosgene (quant.). Reaction of **12** with chlorodiethylphosphate (74%), removal of MPM with DDQ (91%), and the following Dess–Martin oxidation generated aldehyde **13** (95%). Wittig reaction of **13** (50%) and the following hydrolysis of the alkenyl

ether under acidic condition afforded allylic phosphate **2** (quant.).

With allylic phosphate **2** in hand, the intramolecular Nozaki–Hiyama reaction was carried out, but no reaction occurred in the absence of LiI[4c] (Table 1, entry 2). Although the reaction in the presence of LiI at room temperature only produced protonated product **16** (entry 3), a cyclized product **17** formed in 15% yield at 60 °C (entry 4).[10] In other solvents, DMF, DMSO, and DMPU, a complicated mixture of undesired products formed, and no product was obtained. We also prepared allylic chloride **15**[11] from **14** as shown in Scheme 4, and subjected to this reaction, however, surprisingly no product was obtained (entry 1), and the starting material was recovered. The reaction of **2** in DME at 70 °C proceeded smoothly, and the starting material disappeared after 1 h to afford the desired product **17**[12] (11%) along with **16** (39%)[13] (entry 5).

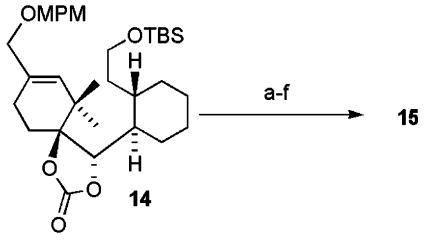
To examine the generality of this intramolecular Nozaki–Hiyama allylation, we applied this reaction to other substrates. First, **13** was subjected to this reaction,

Table 1. Intramolecular Nozaki–Hiyama reaction of **15** and **2**

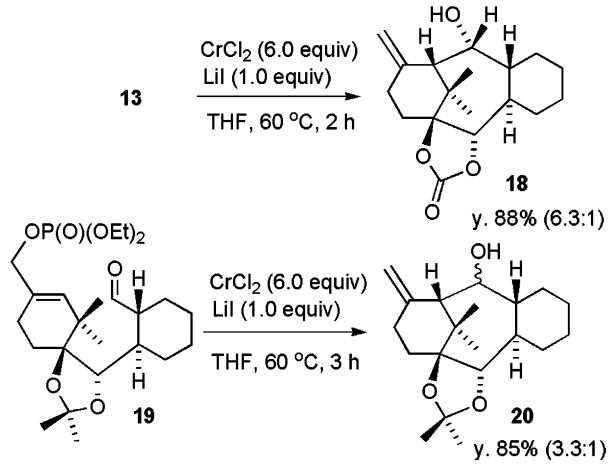


Entry	Substrate	LiI (equiv)	Solvent	Temp (°C)	Yield[a]	
					16 (%)	**17** (%)
1[b]	**15**	1.0	THF	60	—	—
2[b]	**2**	—	THF	60	—	—
3[c]	**2**	1.0	THF	Rt	30	—
4	**2**	1.0	THF	60	60	15
5[d]	**2**	1.0	DME	70	39	11

[a] Isolated yield.
[b] Starting material was recovered.
[c] Starting material (45%) was recovered.
[d] Reaction time was 1 h. Unidentified products also formed.



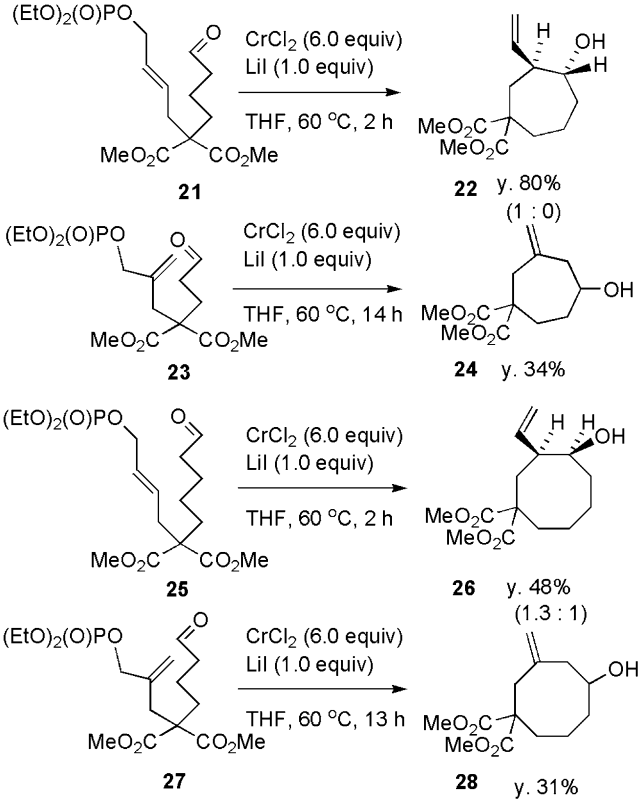
Scheme 4. Reagents and conditions: (a) 1 N H_2SO_4, THF, 1 h, 98%; (b) Dess–Martin periodinane, CH_2Cl_2, 1 h, quant.; (c) cat. PTSA, $CH(OMe)_3$, CH_2Cl_2, MeOH, 10 h, 89%; (d) DDQ, CH_2Cl_2, *t*-BuOH, KPB 7, 88%; (e) LiCl, 2,6-lutidine, MsCl, DMF, 3 h, 91%; (f) 2 N HCl, THF, 1 h, 85%.



Scheme 5.

and a diastereomeric mixture of seven-membered products **18**[12] was obtained in 88% yield (6.3:1) (Scheme 5). Reaction of the corresponding acetonide **19** also afforded a diastereomeric mixture of seven-membered products **20** in 85% yield, but interestingly the ratio of diastereomers changed (3.3:1).

We succeeded thus in the synthesis of 6-8-6 tricyclic compound **17**, 6-7-6 tricyclic compounds **18** and **20**. This is a first synthesis of a cyclic compound by the intramolecular Nozaki–Hiyama allylation using the allylic phosphate.[14]



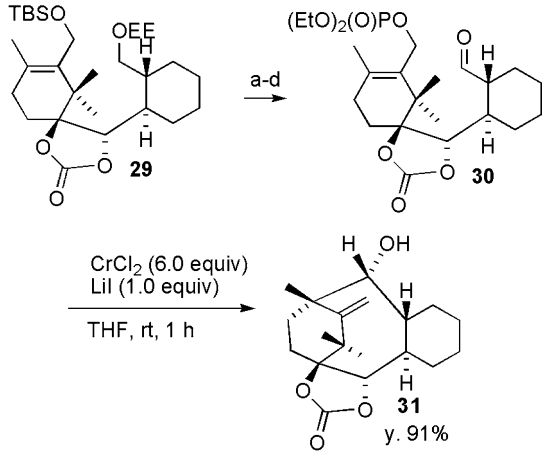
Scheme 6.

Next, we examined the intramolecular Nozaki–Hiyama allylation of rather simple substrates **21**, **23**, **25**, and **27** (Scheme 6).[15] As shown in Scheme 6, **21** and **23** gave the seven-membered products **22** (80%, a single isomer)[12] and **24** (34%),[16] respectively; furthermore, **25** and **27** gave the eight-membered products **26** (48%)[12,17] and **28** (31%),[18] respectively.

Reactions of **21**, **23**, **25**, and **27** suggest that the substrates affording the product with a vinyl group on its formed ring, that is, **21** and **25**, give the better yield. Considering the Nozaki–Hiyama allylation proceeds via a six-membered transition state, this tendency is probably because the chromium reagent derived from **23** would cyclize via the more strained 6-7 fused transition state in contrast with that of **21**; hence, the yield of **24** was lower than that of **22**. The difference in yield in the reactions of **25** and **27** could be explained by the same assumption.

The intramolecular Nozaki–Hiyama allylation using the allylic phosphate affording the eight-membered ring in excellent yield is shown in Scheme 7. Phosphate **30** was prepared from **29**,[19] and was subjected to this reaction. The substrate **30** is the same type of allylic phosphate as **27**, however, the reaction of **30** completed at room temperature within 1 h to afford **31**[12] as a sole product (91%). This result could suggest that the conformational requirement is critical for good yielding in this reaction.

In summary, we have developed the intramolecular Nozaki–Hiyama reaction of the allylic phosphates to afford the compounds containing the seven- or eight-membered carbocyclic ring. The yield greatly depends on the structure of substrate, however, rather complex substrates, **13**, **19**, and **30**, afforded products containing seven- or eight-membered carbon skeleton in high to excellent yield. The allylic phosphate was stable under some reaction conditions; therefore, the intramolecular Nozaki–Hiyama reaction of the allylic phosphates would be a useful method in the synthesis of complex natural products. Further studies on the intramolecular Nozaki–Hiyama reaction of some other allylic phosphates are now in progress.



Scheme 7. Reagents and conditions: (a) TBAF, THF, 50 °C, 1.5 d, 99%; (b) $(EtO)_2P(O)Cl$, Py, CH_2Cl_2, 1 d, 62%; (c) excess PPTS, MeOH, 0 °C, 0.5 h, 97%; (d) Dess–Martin periodinane, CH_2Cl_2, 1 h, 97%.

Acknowledgements

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7. This method requires two steps, but could be applied to a variety of ketones, so we are now investigating its scope and limitation. For preparation of $PivOCH_2I$, see: Bodor, N.; Solan, K. B.; Kaminiski, J. J.; Shin, C.; Pogany, S. *J. Org. Chem.* **1983**, *48*, 5280–5284.
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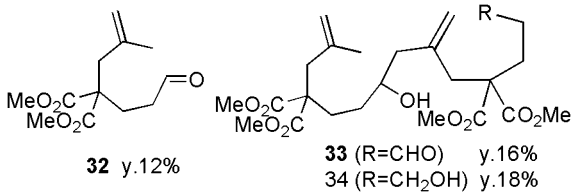
9. No reduction proceeded in the absence of Al $(O\text{–}i\text{-}Pr)_3$.
10. Prolonged reaction time (3 days) did not improve the yield of 17 (14%, with formation of **16** (45%)).
11. Preparation of the chloride **15** from **12** was attempted, but the yield was very low; hence, **14** was prepared through a different route.

12. Relative configuration was elucidated by NOE experiment.
13. Since we were interested in the formation of this protonated product **16**, the reaction was carried out under the same conditions as in entry 4 and quenched with D_2O. The result of this experiment showed no incorporation of deuterium into the product; hence, the formed allylic chromium was surmised to react with water existing somewhere in the reaction mixture to afford **16**.
14. Now we are studying the ring-enlargement reaction of the seven-membered rings in **18** and **20** to the eight-membered rings to construct the 6-8-6 ring system required for the synthesis of Taxol™.
15. Allylic phosphate **21** was synthesized from malonic acid dimethyl ester in six steps as follows: (i) $I(CH_2)_4OTBS$, NaH, THF, rt, 55%; (ii) 1-(4-bromo-2-butenyloxymethyl)-4-methoxy-benzene, NaH, THF, rt, 82%; (iii) DDQ, CH_2Cl_2/*t*-BuOH/KPB 7, rt; (iv) $(EtO)_2P(O)Cl$, Py, CH_2Cl_2, rt, 66% (two steps); (v) 2 N HCl/THF; (vi) Dess–Martin periodinane, CH_2Cl_2, 82% (two steps). Allylic phosphates **23**, **25**, and **27** were synthesized similarly.
16. By-products were shown below. The intermolecular reaction was neglected even under diluted conditions (0.002 M).



17. Configuration of **26** shown in Scheme 6 is that of the major diastereomer.
18. By-products possessing similar structure to **32** and **33** were obtained in 12% each.
19. Compound **29** was prepared according to the method in Ref. 5.