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TETRAZOLE-FRAGMENTATION FOR THE GENERATION OF ALKYLIDENE CARBENES FROM CYANOPHOSPHATES UNDER NEUTRAL CONDITIONS AND ITS APPLICATION TO ORGANIC SYNTHESIS

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Abstract – The generation of alkylidene carbenes through tetrazole-fragmentation from cyanophosphates (CPs) under neutral conditions and its application to organic synthesis are reviewed. The following topics are covered: 1) The formation of α -azidotetrazoles and their transformation into alkynes under microwave heating conditions, 2) the transformation of carbonyl compounds into homologous alkynes *via* CPs, 3) the synthesis of five-membered unsaturated cyclic compounds from ketones *via* CPs, 4) the synthesis of C4-linked C_n -triazole ribonucleoside phosphoramidites from β -ribofuranosyl- C_n -acetylenes, and 5) the synthesis of (-)-neplanocin A and one of its important synthetic intermediates using cyclopentene-formation from CPs.

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1. INTRODUCTION

Alkylidene carbenes (**1**) are reactive intermediates in organic chemistry. The carbenic center of **1** is located on the terminus of a carbon-carbon double bond. The carbenic carbon atom of **1** is effectively sp hybridized and exists in a singlet state with both electrons located in the sp non-bonding orbital; the p orbital is empty (Figure 1).¹ The singlet state is lower in energy than the triplet state by 48 kcal/mol² and can react in a single concerted step. Because the carbenic carbon is in an electron-deficient state, it is electrophilic.

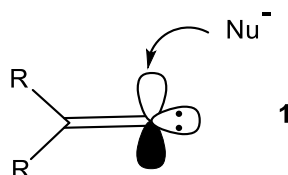
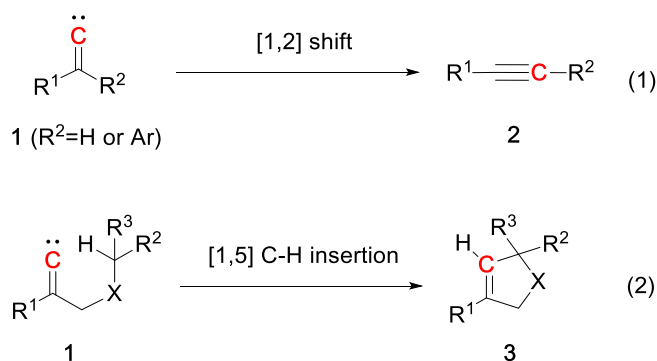


Figure 1. Carbenic carbon in a singlet state

Alkylidene carbenes (**1**) can be used in many synthetically valuable reactions including [1,2]-migration, ylide formation, alkyne cyclopropanation and [1,5]-C-H bond insertion.³ Notably, [1,2]-migrations occurring with alkylidene carbenes (**1**) are useful for the preparation of homologous alkynes (**2**), which are extensively utilized in organic synthesis (Scheme 1, eq. 1).³ Meanwhile, alkylidene carbenes (**1**) undergo regio- and stereoselective [1,5]-C-H bond insertions, which are well suited for the synthesis of cyclopentenes (**3**, X = CH₂) (eq. 2).³ In the case that a heteroatom is present in the connecting chain, five-membered unsaturated heterocycles (**3**, X = O or N-R) are produced. The high reactivity of alkylidene carbenes necessitates *in situ* generation, typically *via* the use of diazo olefination reagents, haloalkenes, or alkynyliodonium salts.³ One of the most widely employed methods to access alkylidene

carbenes is the loss of N₂ from a double bond terminus, particularly from 1-diazoalkenes. These reactions employ dimethyl(diazomethyl)phosphonate esters [(MeO)₂P(O)CHN₂: DAMP] (Seyferth-Gilbert reagent) or trimethylsilyldiazomethane (TMSCHN₂), but require strongly basic conditions, which is as a potential drawback.⁴⁻⁶



Scheme 1. [1,2]-Migration and [1,5]-C-H insertion reactions of alkylidene carbenes

In 1984, one of the authors (S. Harusawa) reported an easy synthetic method for the preparation of α -cyanophosphates (**5**, cyanohydrin-*O*-phosphates, CPs)⁷ by the reaction of carbonyl groups with diethyl phosphorocyanidate (DEPC)⁷ in the presence of a catalytic amount of lithium cyanide (LiCN).⁸ Since then, CPs have been widely utilized as useful synthetic intermediates in organic synthesis.⁷ In continuation of our program of using CPs, we have recently reported novel synthetic methods for homologous alkynes (**2**)⁹ or five-membered unsaturated cyclic compounds (**3**)¹⁰ from carbonyl compounds (**4**) based on the reactions of CPs (**5**) with trimethylsilylazide (TMSN₃) in the presence of Bu₂SnO as a catalyst (the Wittenberger method),^{11a} as shown in Scheme 2. In this two-step transformation, CPs (**5**) may form tetrazolylphosphates (**6**), which subsequently undergo successive fragmentation to generate alkylidene carbenes (**1**) that then undergo [1,2]-migration or [1,5]-C-H insertions to produce homologous alkynes (**2**) or five-membered cyclic compounds (**3**), respectively. The scope of these reactions, which occur under neutral conditions, could be extended towards a variety of alkynes and cyclopentene products that are not usually accessible from the corresponding carbonyl compounds *via* the lithium trimethylsilyldiazomethane [TMSC(Li)N₂] procedure¹² used currently in organic synthesis. In addition, the TMSC(Li)N₂ procedure requires basic conditions. This review covers our study of the generation of alkylidene carbenes under neutral condition through tetrazole fragmentation from CPs including [1,2]-migration or [1,5]-C-H bond insertion.^{9,10} Furthermore, their synthetic applications for the preparation of triazole C_n-ribonucleoside phosphoramidites (PAs)¹³ for use as probes of RNA catalysis and the preparation of cyclopentyl nucleoside (-)-neplanocin A¹⁴ are described.

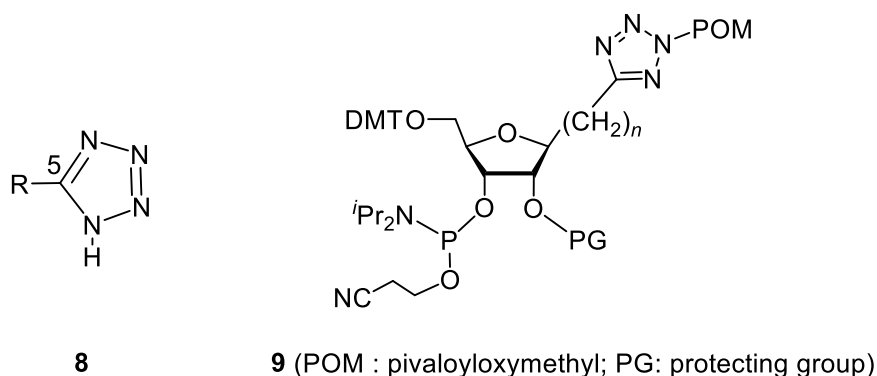
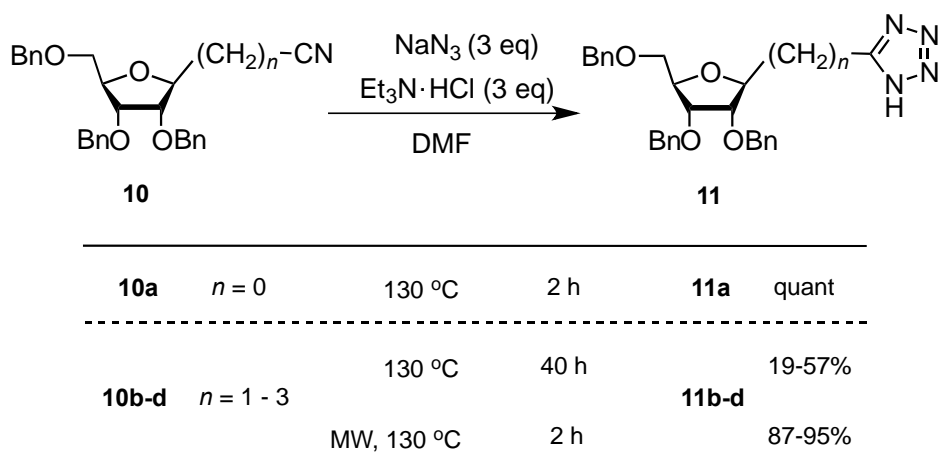


Figure 2. 5-Substituted tetrazoles **8** and tetrazole C_n -PAs **9**

activation of the neighboring electron-withdrawing oxygen in the sugar moiety. In contrast, transformations of inactive ribofuranosyl alkyl cyanides **10b**, **c**, and **d** ($n = 1-3$) into tetrazoles **11b**, **c**, and **d**, respectively, proceeds slowly (40 h, 130 °C, DMF) and has low to modest yields (19–57%). In contrast, the microwave (MW) activated reactions (2 h, 130 °C, DMF) achieve much higher yields (87–95%) of tetrazoles **11b**, **c**, and **d** from alkylcyanides **10b**, **c**, and **d** (Table 1), respectively.¹⁷

Table 1. Synthesis of tetrazole C_n -ribonucleosides **11** from ribofuranosyl alkyl cyanides **10**



Encouraged by the efficient synthesis of **11b-d**, we examined a variety of structurally different nitriles to understand the scope and generality of the reaction conditions for the MW-assisted synthesis of 5-substituted tetrazoles (Table 2).¹⁷ As a result, we have reported a practical method for the MW-assisted formation of 5-substituted tetrazoles from inactive nitriles.

Table 2. Synthesis of 5-substituted tetrazoles (**8**) from inactive nitriles (**12**) using MW irradiation

$$\text{R-CN} \xrightarrow[\text{DMF}]{\text{MW, 130 }^\circ\text{C, 2 h}} \text{R-C}_5\text{H}_3\text{N}_4$$

12 **8**

entry	product	8 (%)	entry	product	8 (%)
1		69	6		34
2		83	7-11	$\text{Me-(CH}_2\text{)}_n\text{-C}_5\text{H}_3\text{N}_4$	$n = 1$ 81
3		<i>o</i> - : 93			$= 2$ 95
4		<i>m</i> - : 81			$= 3$ 63
5		<i>p</i> - : 99			$= 4$ 85
					$= 5$ 85

3. TRANSFORMATION OF CARBONYL COMPOUNDS INTO HOMOLOGOUS ALKYNES UNDER NEUTRAL CONDITIONS VIA TETRAZOLE-FRAGMENTATION

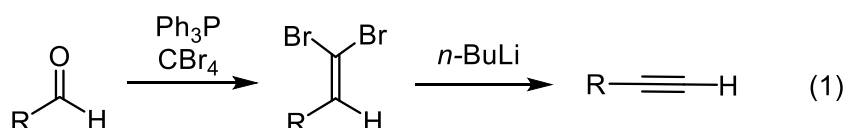
3-1. Current methods for the transformation of carbonyl compounds into homologous alkynes

The lessons learned in the synthesis of the corresponding tetrazoles from inactive nitriles encouraged us to look again at CPs (**5**) as potential precursors of alkylidene carbenes.⁷ The nitrile group in a CPs is activated by the presence of an adjoining phosphate group. Thus, the reaction of the CN moiety with an azide source might afford tetrazolylphosphates (**6**), as illustrated in Scheme 2. The resulting tetrazoles **6** could spontaneously generate alkylidene carbene species (**1**) through successive tetrazole fragmentation, producing homologous alkynes (**2**) or cyclopentenes (**3**).

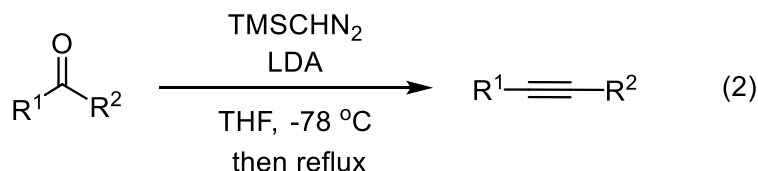
The preparation of internal and terminal alkynes from carbonyl compounds is a beneficial synthetic pathway.¹⁹ A widely used method for accessing alkynes is the one-carbon homologation of aldehydes or ketones.²⁰ Following the pioneering two-step procedure of Corey and Fuchs for alkyne synthesis (Scheme 3, eq. 1),²¹ the Colvin rearrangement using either TMSCHN₂^{6,12a} or dimethyl (diazomethyl)phosphonate (DAMP),³ and Seyferth-Gilbert homologation (using DAMP) were developed.^{4,5} Later, Shioiri and

co-workers reinvestigated Colvin rearrangement and established general conditions for alkyne synthesis in the reaction of aldehydes or aryl alkyl ketones with $\text{TMSC}(\text{Li})\text{N}_2$ (eq. 2).^{12a} Aliphatic ketones do not give the corresponding alkynes under these conditions.^{12b} A common drawback of these methods is the need for a strong base, which is problematic for highly functionalized substrates.²⁰ Meanwhile, the Ohira-Bestmann procedure, in which DAMP is produced *in situ* from dimethyl (1-diazo-2-oxopropyl)phosphonate, has become the most popular method of transforming an aldehyde into the corresponding alkyne under mildly basic reaction condition ($\text{K}_2\text{CO}_3/\text{MeOH}$) (eq. 3).²² However, using this method, ketones cannot be transformed into internal alkynes, and α,β -unsaturated aldehydes do not yield enynes.^{20,22b}

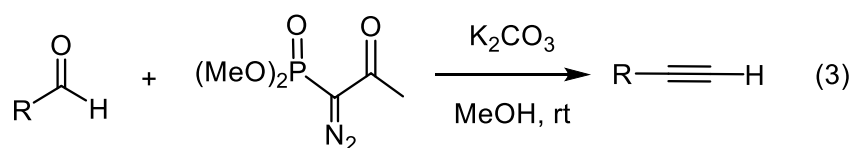
Corey - Fuchs method



Shioiri modification



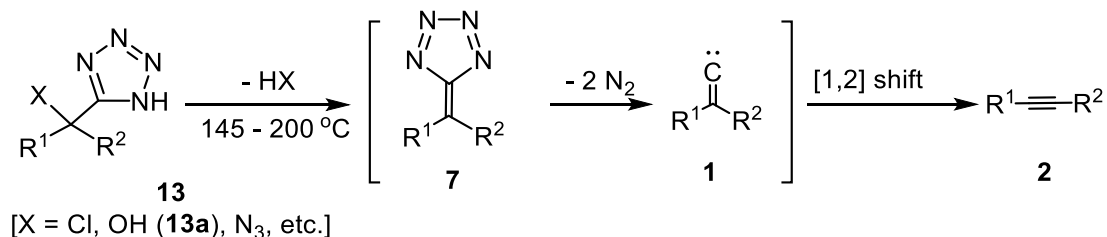
Ohira-Bestmann modification



Scheme 3. Current procedures for homologous alkyne synthesis from carbonyl compounds

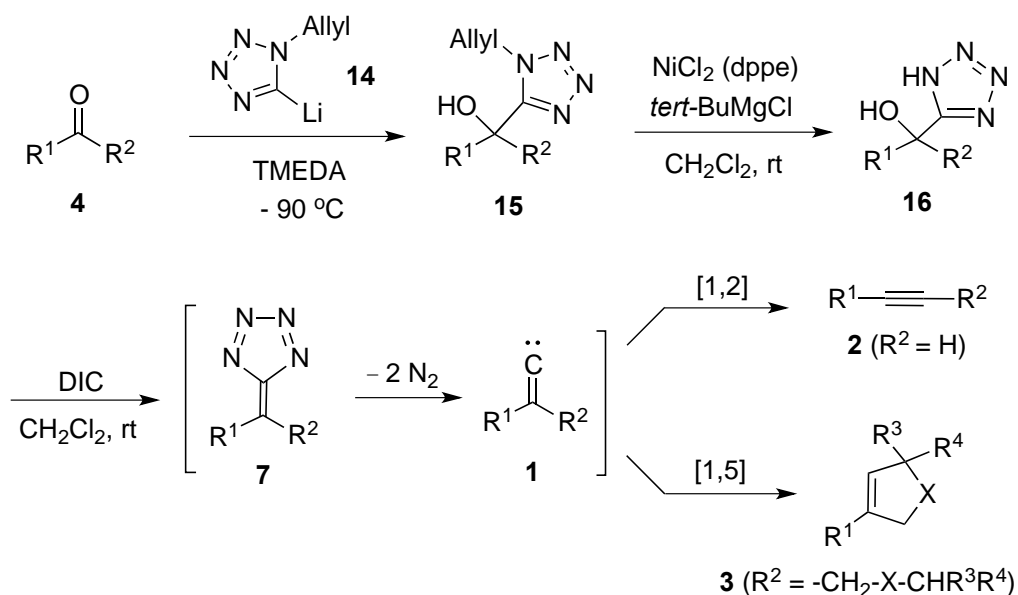
3-2. Alkyne synthesis using tetrazole fragmentation

On the other hand, the use of tetrazoles to produce alkylidene carbenes under base-free conditions is also known.^{3a} It is necessary to generate alkylidene carbenes *in situ* from more stable precursors. In 1966, Behringer and Matner first reported that tetrazole derivatives (**13**) give alkylidene carbenes (**1**) *via* the fragmentation of unstable tetraazafulvenes (**7**), thus producing alkynes (**2**) (Scheme 4).²³



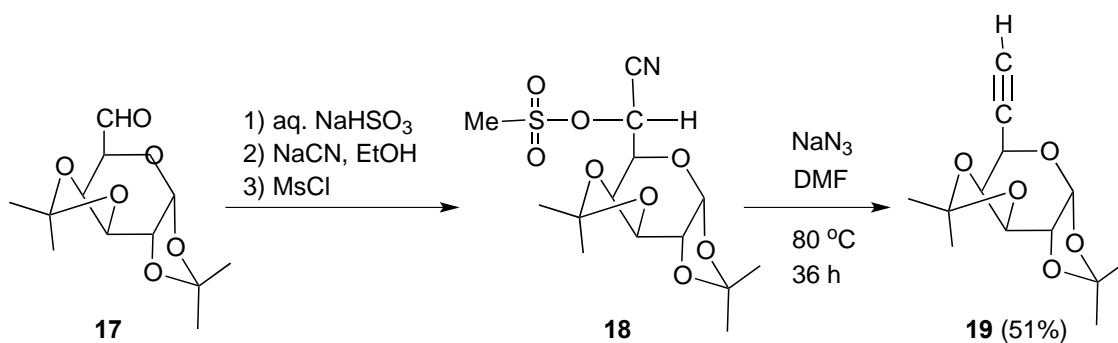
Scheme 4. First terazole-fragmentation of tetraazafulvenes reported by Behringer

After more than four decades (2012), Wardrop and Komenda reported synthetic methods for alkynes (**2**) or five-membered rings (**3**) from carbonyl compounds (**4**) in three steps by the generation of alkylidene carbenes (**1**), which are accessed through the dehydration of 5-hydroxyalkyl-1*H*-tetrazoles (**16**) with diisopropyl carbodiimide (DIC) (Scheme 5).²⁴ However, this methodology requires two additional steps for the preparation of the key intermediate (**16**): the addition of 1-allyl-5-tetrazoyllithium (**14**) to carbonyl compound **4** at -90 °C, and the subsequent de-*N*-allylation of the addition product (**15**).



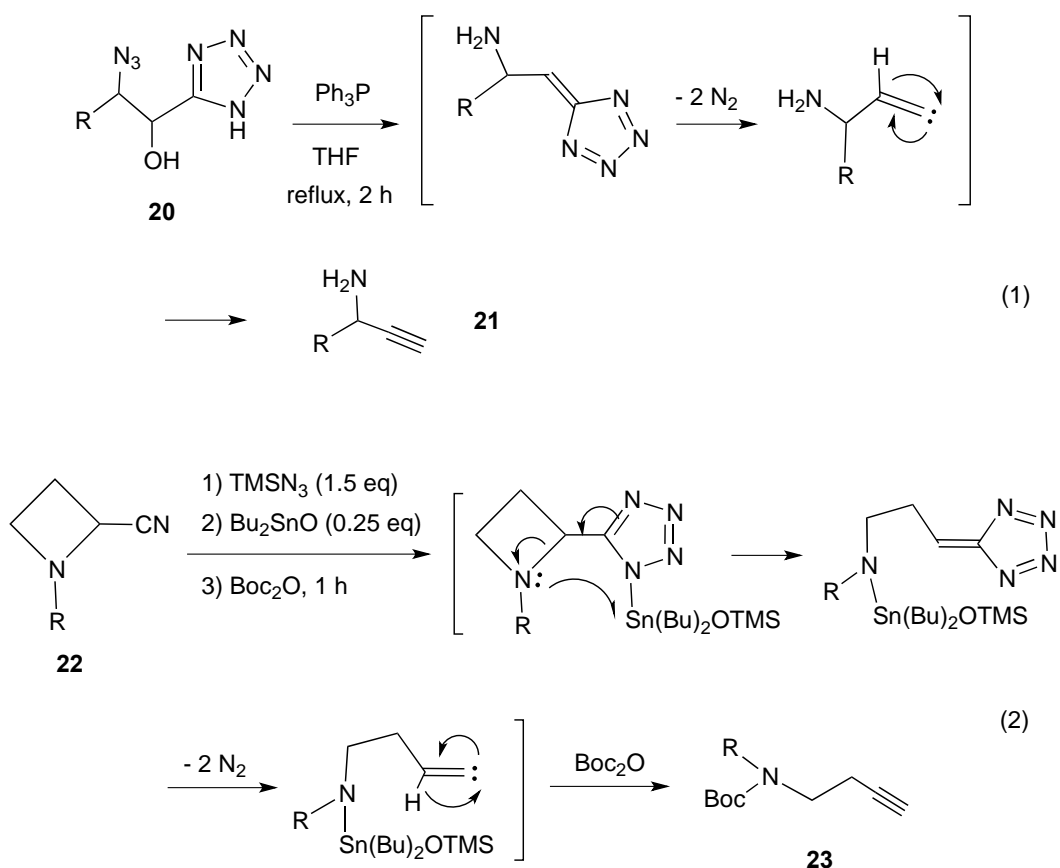
Scheme 5. Dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles (**16**), as reported by Wardrop

In addition, Czernecki and Valéry showed that reaction of cyanomesylate (**18**) with sodium azide in DMF gave an unusual single formation of an acetylenic sugar (**19**),^{25a} suggesting the formation of alkylidene carbene species (Scheme 6).²⁵



Scheme 6. Formation of acetylenic sugar **19**, as reported by Czernecki

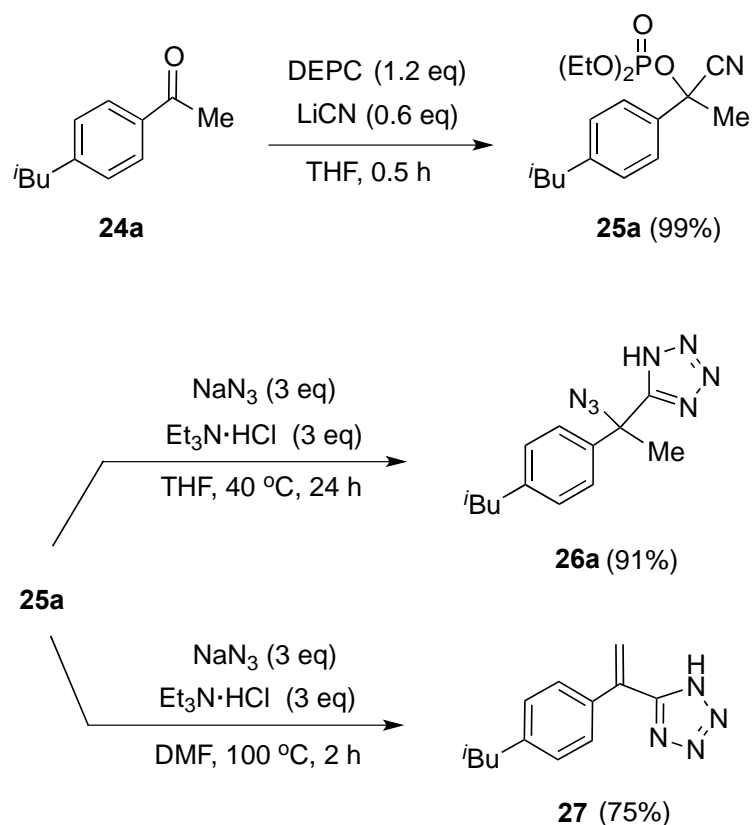
Other applications of the tetrazole-fragmentation can be found in the studies of Couty and co-workers: the transformation of α -hydroxy- β -azidotetrazoles (**20**) into propargylic amines (**21**) (Scheme 7, eq. 1)^{26a} and the synthesis of homopropargylamines (**23**) from 2-cyanoazetidines (**22**) (eq. 2).^{26b}



Scheme 7. Synthesis of propargylic amines **21** and homopropargylamines **23** by Couty

3-3. Formation of α -azidotetrazoles and their transformations into alkynes under microwave heating conditions⁹

Based on the previous reports of alkyne syntheses *via* the generation of alkylidene carbenes, we tested the reaction of CPs with sodium azide (NaN_3) in the presence of $\text{Et}_3\text{N}\cdot\text{HCl}$. Excess DEPC (3 equiv.) and LiCN (3 equiv.) have repeatedly been used for the cyanophosphorylation of different ketones and aldehydes since our original report.⁸ First, we optimized the reaction conditions and found that 1.2 equiv. of DEPC and 0.6 equiv. of LiCN were sufficient for the synthesis of CPs from ketones, whereas 1.2 equiv. of DEPC and 0.1 equiv. of LiCN were required when aldehydes were employed. Indeed, the treatment of 4-isobutylacetophenone **24a** with DEPC (1.2 equiv.) in the presence of LiCN (0.6 equiv.) afforded CP **25a** in 99% yield at room temperature (rt) within 0.5 h in tetrahydrofuran (THF) (Scheme 8). The reaction of benzylic CP **25a** with sodium azide (NaN_3 , 3 equiv.) in the presence of $\text{Et}_3\text{N}\cdot\text{HCl}$ (3 equiv.)¹⁶ gave α -azidotetrazole (AT) **26a** in 91% yield at 40 °C after 24 h in THF, as illustrated in Scheme 8. However, in the reaction of CP **25a** with the same reagent system, only vinyltetrazole (VT) **27** was obtained in 75% yield in DMF at 100 °C after 2 h.



Scheme 8. Synthesis of α -AT **26a** and VT **27** from CP **25a**

The stability of AT **26a** was studied by differential scanning calorimetry (DSC) and the results indicated that **26a** is thermally unstable at temperatures above its melting point (mp 119–120 °C).⁹ However, it was

not explosive and could be stored for over a year at rt ¹H NMR and mp measurements of the stored compound did not indicate any substantial decomposition, indicating that **26a** has long-term stability.

As shown in entry 1 of Table 3, the reaction of AT **26a** under MW irradiation in DMF-pyridine (5:2, v/v) at 150 °C gave the expected alkyne **28a** in 76% yield after 1 h. This result indicates that carbonyl compounds can be converted into alkynes under MW activation. ATs **26b** and **26c** bearing electron donating groups at the *para*-position of phenyl groups, as well as AT **26d** with a 6-methoxy naphthalene moiety, similarly provided alkynes **28b-d** in good yields (65-82%; entries 2-4). In the case of AT **26e**, which contains a nitro group, the reaction was suppressed, and the yield of alkyne **28e** was only 40% (entry 5). ATs **26f** and **26g**, prepared from hexaphenone and benzophenone CPs **25f** and **25g** respectively, provided the respective alkynes **28f** (81%) and **28g** (88%) in good yields (entries 6 and 7). However, AT **26h**, which was obtained from 4-phenyl-2-butanone CP **25h**, gave the corresponding alkyne (**28h**) in low yield (17%, entry 8). The reaction of 2,2,2-trifluoroacetophene CP (**25i**) with NaN₃-Et₃N·HCl was unusual, and as tetrazolylphosphate **32i** was obtained in 83% yield without further substitution of the azide anion (entry 9). Subsequently, **32i** was decomposed by MW treatment. Formation of a terminal alkyne **31a** in 62% yield was possible starting from 4-isobutylbenzaldehyde AT **30a**. The product mixture also contained a triazole **33a** (19%), which seems to have formed by the [2 + 3] cyclization of alkyne **31a** with hydrazoic acid (HN₃) generated *in situ* (entry 10). The aldehyde derived ATs **30b** and **30c** gave triazoles **33b** (33%) and **33c** (25%) in low yields (entries 11 and 12).

Although one-pot synthesis of alkynes **28** and **31** from CPs **25** and **29**, respectively, could be carried out without the isolation of the corresponding ATs **26** and **30**, respectively, the yields of the alkynes were lower compared to the two-step method, as shown in Scheme 9.

In addition, hydrogenation of the aforementioned vinyltetrazole VT **27** and AT **30c** afforded tetrazole analogs (**34** and **35**) of ibuprofen²⁷ and phenylalanine²⁸ in 94% and 91% yields, respectively (Scheme 10). The former exhibits twice the analgesic activity of ibuprofen,²⁹ while the latter acts as a tyrosine hydroxylase inhibitor.³⁰

3-4. Transformation of ketones into homologous alkynes *via* CPs

The procedure outlined above still requires the isolation of unstable ATs and relatively harsh conditions in the MW reactor. In the search for a milder variant, we investigated the reaction of CP **25a** with different organic azides such as tributyltin azide (Bu₃SnN₃), diphenyl phosphorazidate (DPPA), *p*-toluenesulfonyl azide (TsN₃), and trimethylsilyl azide (TMSN₃). It was found that CP **25a** could be transformed directly into the corresponding alkyne **28a** (60%) under Wittenberger conditions,^{11a} i.e., by using 1 equiv. of TMSN₃ in the presence of a catalytic amount of Bu₂SnO (0.1 equiv.) at reflux in toluene, as shown in Scheme 11.

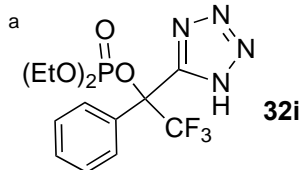
Table 3. Transformation of CPs **25** and **29** into alkynes **28** and **31** under MW conditions

25 (R¹ = H) → **26** (R¹ = H) → **28** (R¹ = H)

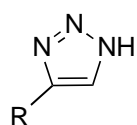
29 (R¹ = H) → **30** (R¹ = H) → **31** (R¹ = H)

entry	Ar	R ¹	temp. (°C)	time (h)	26 or 30 (%)	28 or 31 (%)
1		Me	40	24	26a 91	28a 76
2		Me	40	24	26b 91	28b 72
3		Me	40	8	26c 88	28c 65
4		Me	40	24	26d 96	28d 82
5		Me	40	24	26e 73	28e 40
6		<i>n</i> -pentyl	40	48	26f 82	28f 81
7			60	48	26g 54	28g 88
8		Me	40	48	26h 82	28h 17
9		CF ₃	15	48	(32i) 83) ^a	– dec.

10		H	rt	24	30a 98	31a 62 (33a , 19) ^b
11		H	rt	24	30b 81	– – (33b , 33) ^b
12		H	40	48	30c 71	– trace (33c , 25) ^b



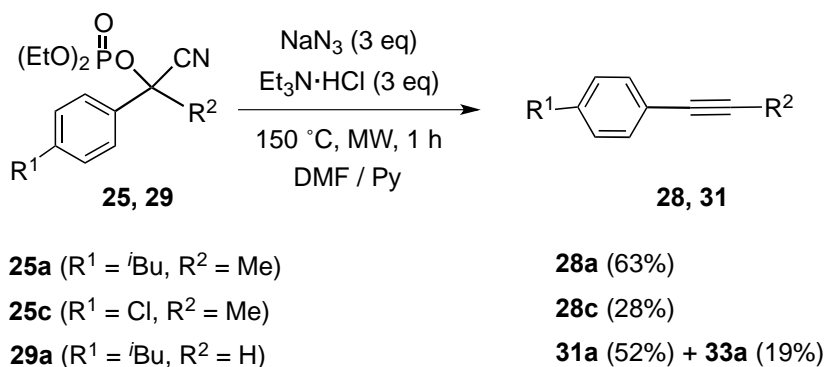
^bTriazoles **33** were obtained as by-products.



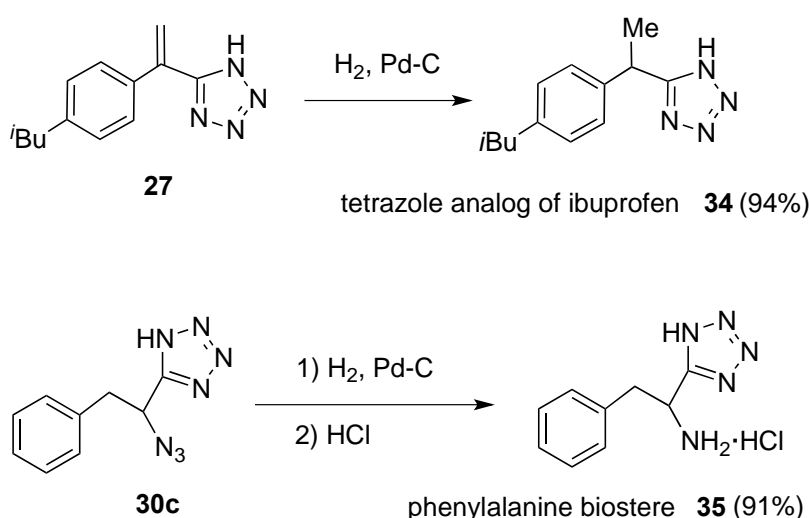
33a: R = 4-*t*-Bu-Ph-

33b: = Ph-

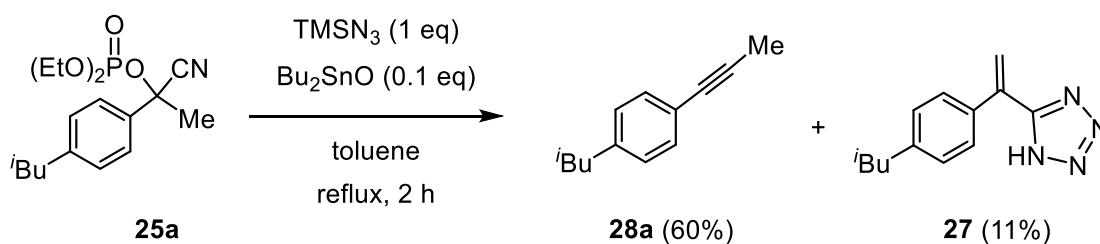
33c: = PhCH₂-



Scheme 9. One-pot synthesis of alkynes **28** and **31** from CPs **25** and **29**



Scheme 10. Conversion of VT **27** and AT **30c** into tetrazole analog and phenylalanine bioisostere



Scheme 11. The reaction of CP **25a** with $\text{TMSN}_3/\text{Bu}_2\text{SnO}$ (cat.)

The effect of the choice of solvent on the same reaction was also investigated. Using toluene, xylene or cyclopentyl methyl ether (CPME: b.p. = 106 °C) as solvents, alkyne **28a** was obtained in better yields compared to reactions performed in benzene or acetonitrile. These results suggest that a solvent with a boiling points >100 °C may be necessary for the efficient conversion to alkyne **28a**, while suppressing the formation of VT **27**.

Thus, several ketones (**24**) can be transformed into the corresponding alkynes (**28**) in moderate to high yields using $\text{TMSN}_3\text{-Bu}_2\text{SnO}$ (cat.) in toluene at reflux (Table 4). Acetophenones **24c**, **e**, and **j-l** ($\text{R} = \text{Cl}$, NO_2 , CN , CF_3 , and CO_2Me , respectively) and **24n-v** [$\text{R} = \text{OMe}$, NO_2 , *O*-methoxyethoxymethyl (OMEM), *OBn*, *OTs*, *NHTs*, *NHBoc*, and *O-tert*-butylmethylsilyl (OTBDMS), respectively] readily afforded the corresponding alkynes **28c**, **e**, **j-l** and **28n-v**, demonstrating that the reaction was relatively tolerant towards a range of functional groups on aromatic rings (entries 1-5 and 7-15). The reaction could not be applied in the case of *p*-methoxyacetophenone (**24m**; entry 6), because of the instability of the corresponding CP.

Notably, pyridine-containing ketones **24w-z** were transformed into alkynes **28w-z** in 73%, 49%, 80%, and 41% overall yields, respectively, in two steps (entries 16-19). In contrast, the overall yield of **28w** was merely 12% after three-steps from ketone **24w** following the Wardrop method.²⁴ The reduced yield due to the pyridine moieties, which are known to undergo ring opening in the presence of carbodiimides.³¹ Benzophenone CP (**25g**) and diketone CP **25aa** were efficiently converted into the respective alkynes **28g** (87%) and **28aa** (84%) (entries 20, 21).

The potential of the reaction methodology has been further explored by applying it to the synthesis of a selective mGlu5 receptor antagonist, 2-methyl-6-(phenylethynyl)pyridine (**28bb**: MPEP).³² Starting from 6-methylpicolinaldehyde, MPEP was obtained in 68% overall yield over four steps, as shown in Scheme 12.

Interestingly, β -ketoester **24cc**, which possesses readily enolizable α -protons, could also be converted into the corresponding alkyne **28cc** (68%) by the present method (Scheme 13). In contrast, the reaction of **24cc** under Shioiri conditions [TMSCHN_2 /lithium diisopropylamide (LDA)]^{12a} only resulted in the unreacted starting material.

Colvin and Hamill's original procedure used either TMSCHN_2 or DAMP, and its modifications cannot be applied to dialkyl ketones.^{4,5} Furthermore, the Ohira-Bestmann reaction of ketones does not afford alkynes; instead, enol ethers are formed.²² As shown in Scheme 14, the method developed in this work furnished the corresponding 1,6-diphenylhexen-3-yne (**28dd**) from 1,5-diphenylpentan-3-one (**24dd**) in 77% overall yield (eq. 1). In contrast, the Ohira-Bestmann reaction of **24dd** gave methyl enol ether **36** in 40% yield (eq. 2),²² while the Shioiri procedure yielded allenylsilane **37** (31%),³³ and a homologous aldehyde **38** (23%),^{12b} as well as unreacted **24dd** (46%) (eq. 3). The formation of allenylsilanes or homologous aldehydes from ketones utilizing TMSCHN_2 has been reported independently by the Lee³³ and Shioiri groups.^{12b} These results indicate the versatility of our method.

Table 4. Transformation of ketones (**24**) into alkynes (**28**) via CP **25**

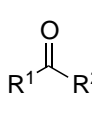
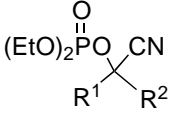

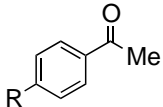
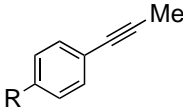
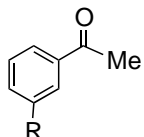
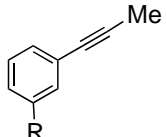
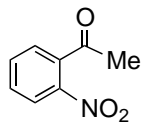
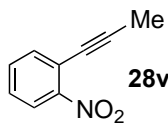
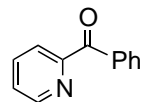
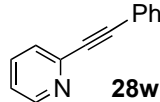
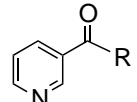
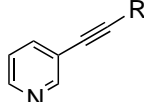
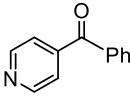
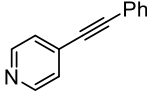
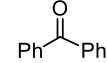
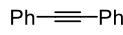
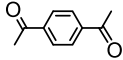
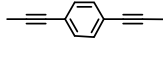
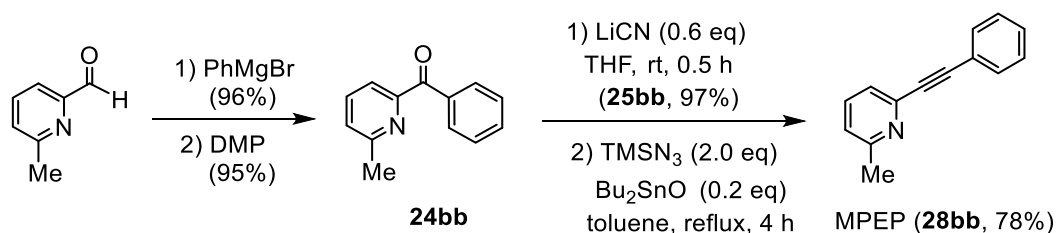
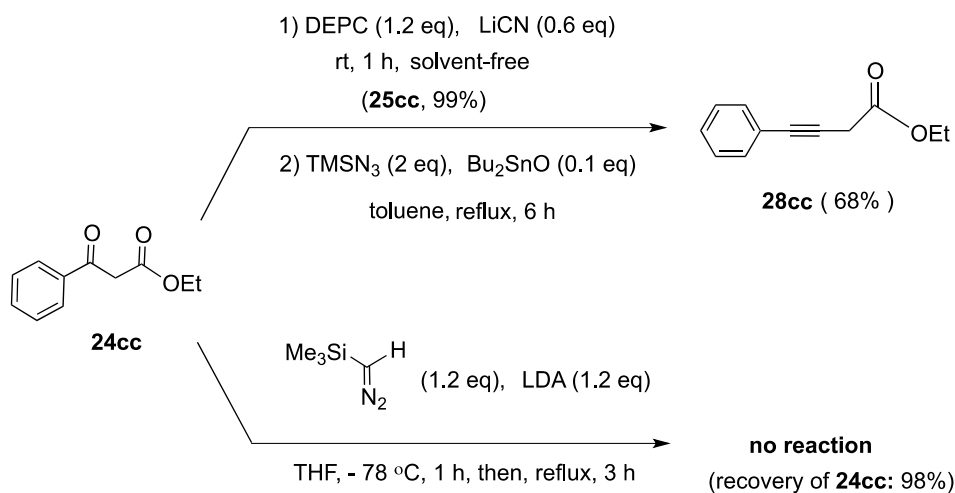
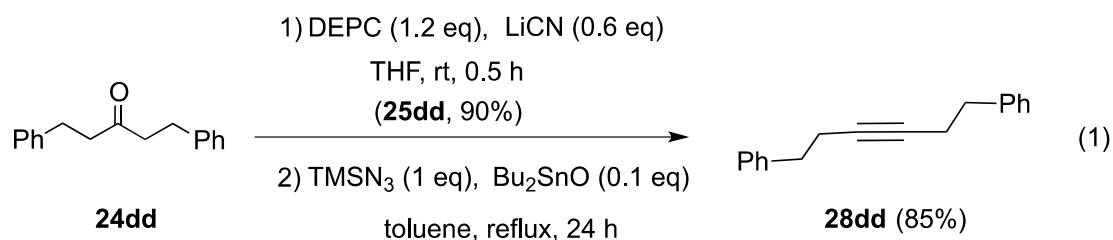
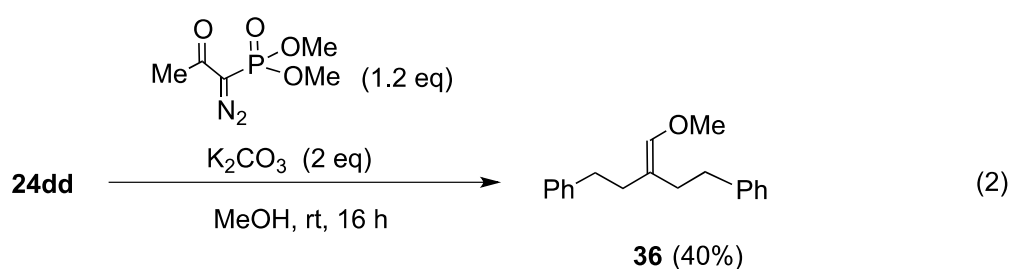
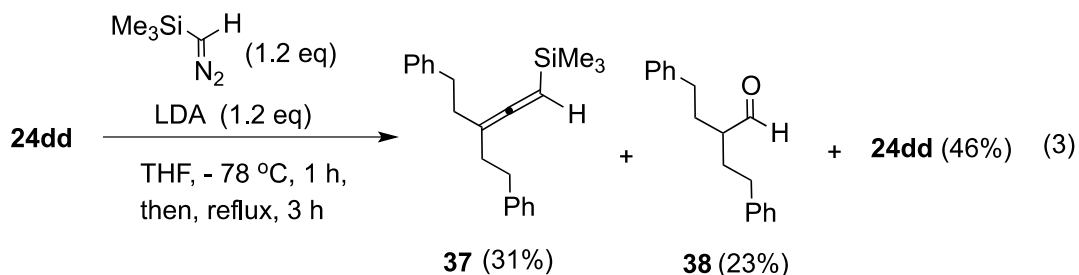
entry	24	CP 25 (%) ^a	28 (%) ^a
	 24	 25	 28
	DEPC (1.2 eq) LiCN (0.6 eq) THF, rt, 0.5 h		TMSN ₃ (1.0 eq) Bu ₂ SnO (0.1 eq) toluene, reflux, 2 h
1	 24c R = Cl	25c 86	 28c 63
2	24e R = NO ₂	25e 97	28e 88
3	24j R = CN	25j 99	28j 70
4	24k R = CF ₃	25k 99	28k 85
5	24l R = CO ₂ Me	25l 93	28l 82
6	24m R = OMe	dec	–
7	 24n R = OMe	25n 85	 28n 72
8	24o R = NO ₂	25o 99	28o 85
9	24p R = OMEM	25p 99 ^b	28p 78 ^c
10	24q R = OBn	25q 98	28q 88 ^c
11	24r R = OTs	25r 95	28r 82 ^c
12	24s R = NHTs	25s 95	28s 72 ^d
13	24t R = NHBoc	25t 96	28t 47 ^d
14	24u R = OTBDMS	25u 67 ^e	28u 80 ^c
15	 24v	25v 99	 28v 50
16	 24w	25w 97 ^b	 28w 75 ^{f,g}
17	 24x R = Me	25x 81	 28x 61
18	24y R = Ph	25y 90 ^b	28y 89 ^f

Table 4. (Continued)

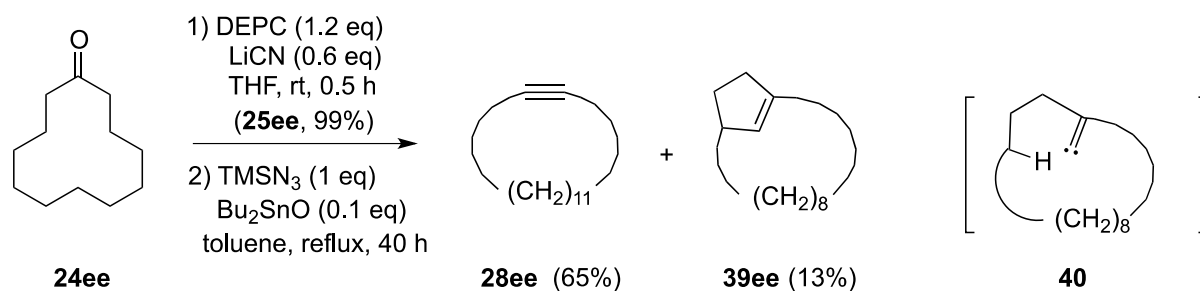
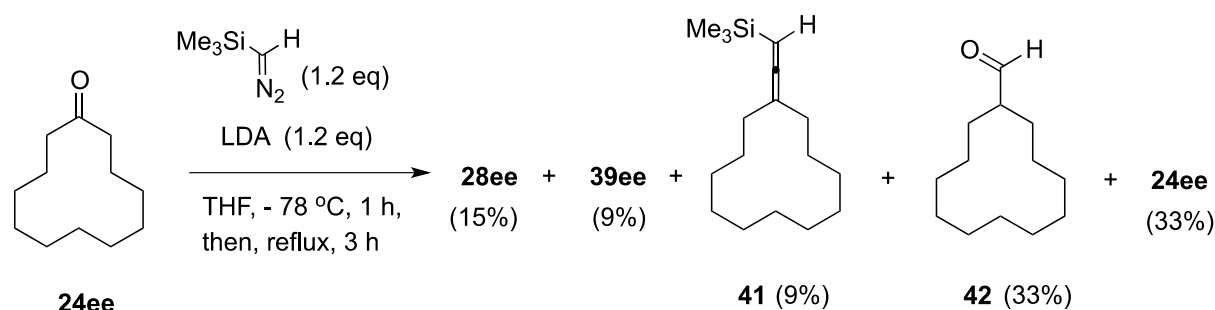
entry	24	CP 25 (%) ^a	28 (%) ^a
19	24z 	25z 71 ^b	28z 58 ^f 
20	24g 	25g 99	28g 87 
21	24aa 	25aa 85 ^h	28aa 84 ⁱ 

^aIsolated yield. ^bDEPC (3.0 eq.) and LiCN (3.0 eq.). ^cTMSN₃ (3.0 eq.), Bu₂SnO (0.1 eq.), reflux, 4 h. ^dTMSN₃ (2.0 eq.), Bu₂SnO (0.2 eq.), reflux, 2 h. ^eDEPC (3.0 eq.) and LiCN (3.0 eq.), reflux, 0.5 h. ^fTMSN₃ (2.0 eq.), Bu₂SnO (0.2 eq.), reflux, 4 h. ^gSee text. ^hDEPC (3.0 eq.) and LiCN (1.2 eq.). ⁱTMSN₃ (3.0 eq.), Bu₂SnO (0.1 eq.), reflux, 21 h.

**Scheme 12.** Synthesis of the mGlu5 receptor antagonist, MPEP**The present method****Shioiri method****Scheme 13.** Transformation of β -ketoester **24cc** to its corresponding acetylenic compound (**28cc**)

The present method**Ohira-Bestmann reaction****Shioiri method****Scheme 14.** Reactivity of dialkyl ketone **24dd** under three different conditions

Furthermore, the reaction of 12-membered cyclic ketone **24ee** yielded cyclotridecyne **28ee** in 64% overall yield via CP **25ee**. Bicyclo[8.2.1]tridecene (**39ee**, 13%) was also formed in this transformation, which is possibly due to a [1,5]-C–H insertion mediated by the alkylidene carbene **40**, as illustrated in Scheme 15. In contrast, when the same ketone (**24ee**) was subjected to Shioiri conditions, cyclotridecyne **28ee** was obtained in only 15% yield, along with the bicyclo compound **39ee** (9%), allenylsilane **41** (9%), homologous aldehyde **42** (33%), and the starting material (**24ee**, 33%).

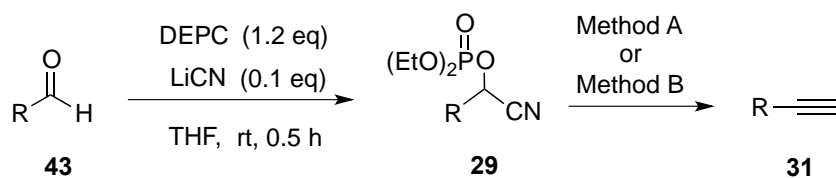
The present method**Shioiri condition****Scheme 15.** Transformation of cyclic ketone **24ee** to cyclic alkyne **28ee**

3-5. Transformation of aldehydes into homologous alkynes via CPs

The present method was successfully extended to the transformation of aldehydes (**43**) into homologous terminal alkynes (**31**), as shown in Table 5. In our studies on the synthesis of novel triazole-containing RNA or DNA,¹³ we sought access to alkynes **31d-g** from β -D-ribofuranosyl C_n-aldehydes **43d-f** ($n = 0-2$) and deoxyribofuranosyl carbaldehyde (**43g**). The reaction of CP **29d** with NaN₃ (3 equiv.) and Et₃N·HCl (3 equiv.) gave β -ribofuranosyl alkyne **31d** in 68% yield (method A). Alternatively, treatment of **29d** with TMSN₃ (1 equiv.) in the presence of Bu₂SnO (0.1 equiv.) gave **31d** in 47% yield (method B) (entry 1). Thus, method A is favorable for the preparation of homologous alkynes (**31e-g**) from their corresponding aldehydes (**43e-g**, entries 2-4). Both methods A and B may be employed equally for primary aldehydes (**43h**, entry 5), but method A is slightly more useful for aldehydes **43i-k** (entries 6-8). Furthermore, method A is superior to method B for the transformation of diphenylacetaldehyde (**43l**) into the corresponding alkyne **31l** in quantitative yield (entry 9). Conversely, in the case of the aromatic and α,β -unsaturated aldehyde CPs **29a** and **29n**, respectively, method B is favorable, providing alkynes **31a** and **31n** in 71% and 80% yields, respectively (entries 10 and 12). The reason for the preference towards

either method A or B depending on the aldehyde is unknown at present. Homologation of geranial and neral CPs **29o** and **29p** using method B gave moderate yields of the alkynes **31o** and **31p**, i.e., 68%, *E/Z* = 15/1 and 53%, *E/Z* = 1/10, respectively (entries 13 and 14).

Table 5. Transformation of aldehydes **43** into terminal alkynes **31** via CP **29**



Method A : NaN₃ (3 eq), Et₃N·HCl (3 eq), THF, reflux, 16 h.

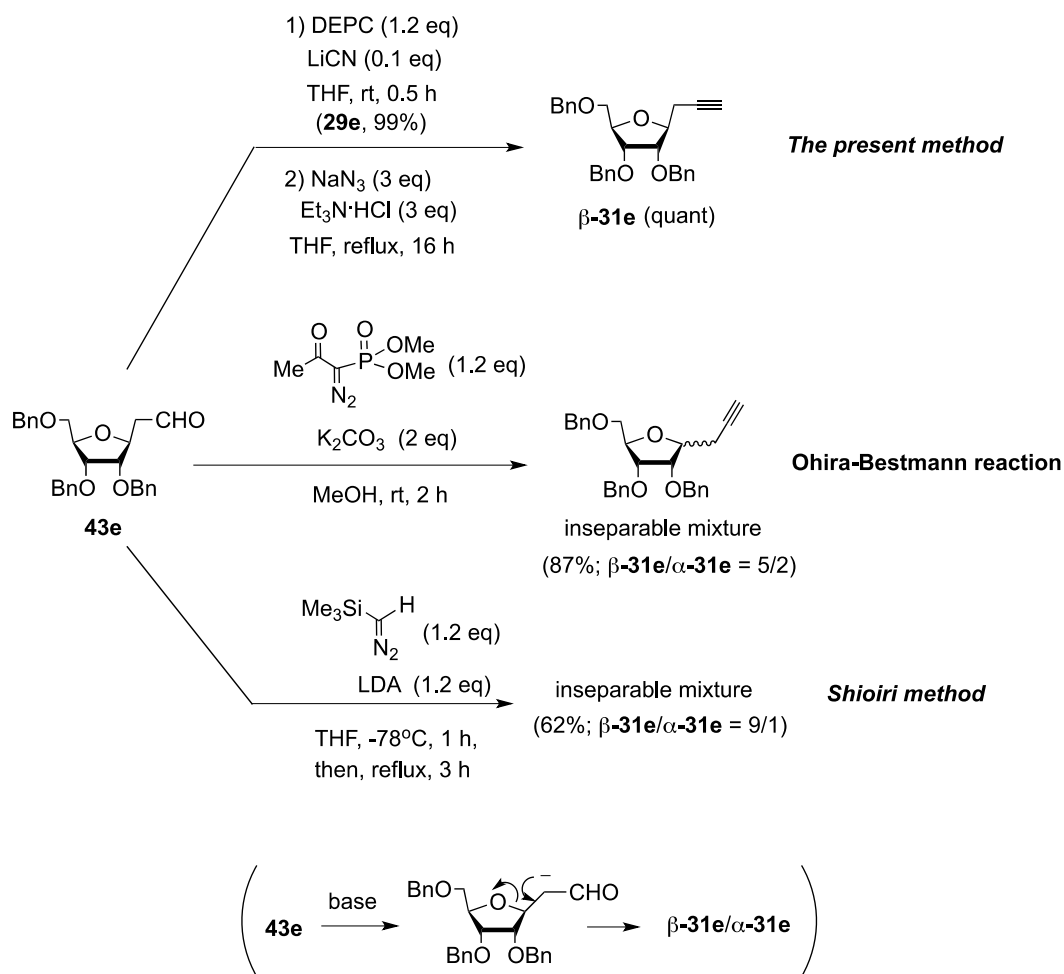
Method B : TMSN₃ (1eq), Bu₂SnO (0.1eq), toluene, reflux, 2 h.

entry	43	29 (%) ^a	Method	31	(%) ^a
1		29d 91	A		68
			B		31d
2		29e 99	A		quant
			B		31e
3		29f 96	A		quant
			B		31f
4		29g quant	A		31g 74
5		29h 99	A		57
			B		31h
6		29i 88	A		88
			B		31i
7		29j quant	A		74
			B		31j
8		29k 92	A		71
			B		31k
9		29l quant	A		quant
			B		31l

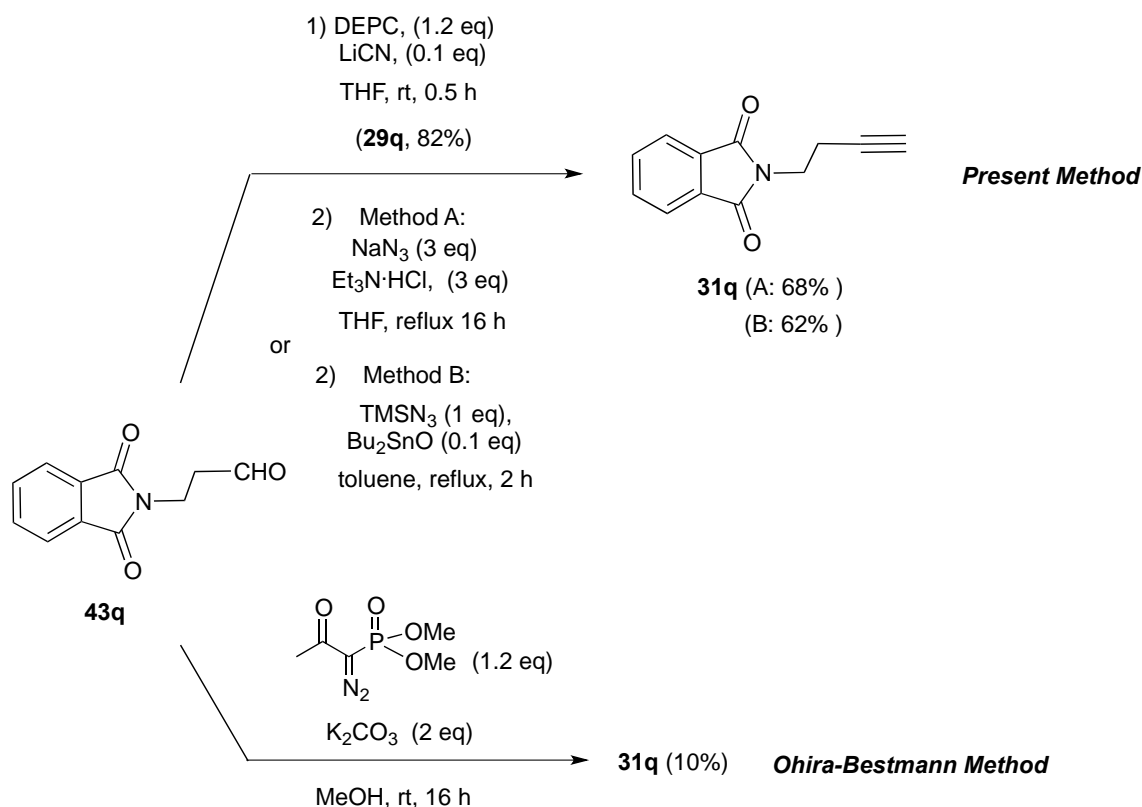
Table 5 (Continued)

entry	43	29 (%) ^a	Method	31	(%) ^a
10		29a 98	A B ^b		31a 29 71
11		29m quant	B		31m 88
12		29n 98	A B ^c		31n 17 80
13		29o 99	B ^c		31o 68 (E/Z=15/1)
14		29p 99	B ^c		31p 53 (E/Z=1/10)

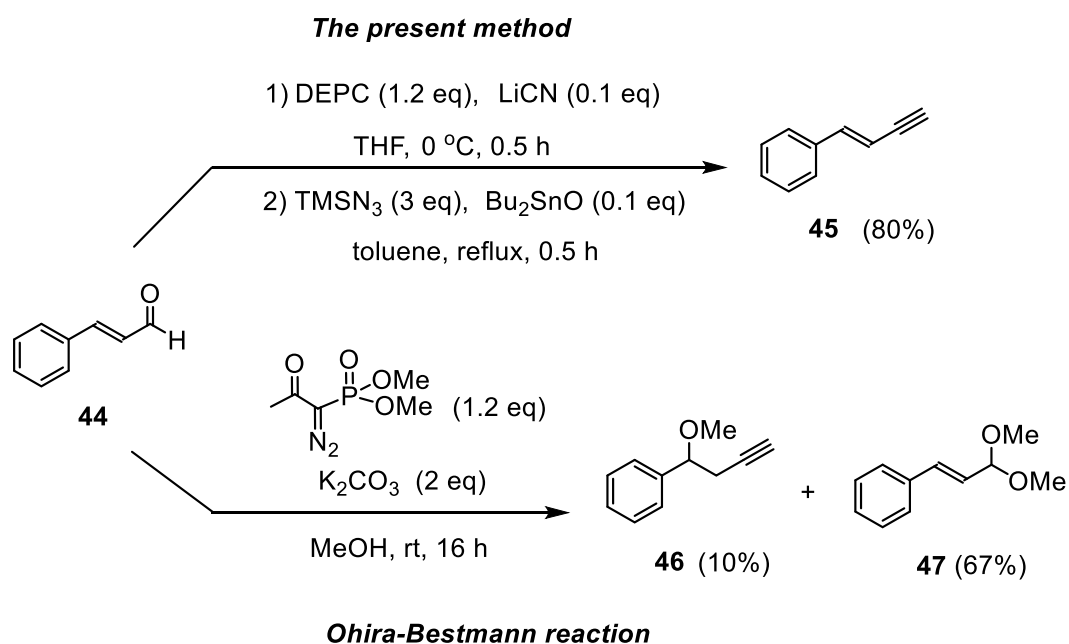
^aIsolated yield. ^bReflux, 0.5 h. ^cTMSN₃ (3 eq.), Bu₂SnO (0.1 eq), reflux, 0.5 h.



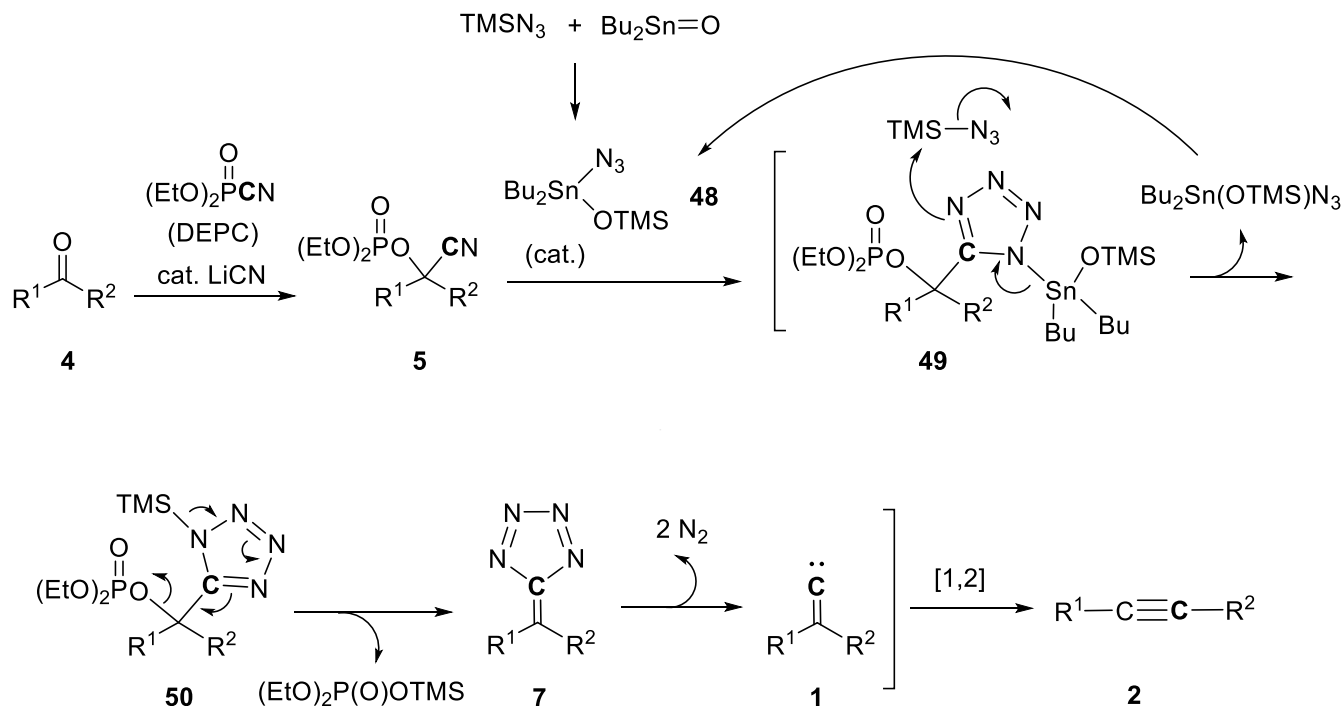
Scheme 16. Reactivity of β-D-ribofuranosyl C₁-carbaldehyde (**43e**) under different conditions



Scheme 17. Transformation of phthalimide-containing propanal **43q** into alkyne **31q** using the present method and the Ohira-Bestmann procedure



Scheme 18. Reactivity of cinnamaldehyde (**44**) using the present and Ohira-Bestmann methods



Scheme 19. Proposed mechanism for the formation of alkynes (**2**) mediated upon tetrazole-fragmentation from CPs (**5**)

As shown in Scheme 16, the transformation of aldehyde **43e** into alkyne β -**31e** in overall 99% yield is of particular interest, because the Ohira-Bestmann reaction and Shioiri modification procedures gave only inseparable 5:2 and 9:1 epimeric mixtures of β -**31e** and α -**31e**, respectively. The formation of the epimeric mixtures presumably occurs because of the extraction of α -acidic proton of **43e** followed by β -elimination under basic conditions.

Phthalimide-containing propanal **43q** similarly provided the terminal alkyne **31q** in 68% from CP **29q** by method A, but the Ohira-Bestmann reaction of **43q** gave **31q** in only 10% yield (Scheme 17).

As mentioned before, the Ohira-Bestmann reaction does not give enynes from α,β -unsaturated aldehydes.^{19,22} In contrast, it is possible to synthesize the corresponding enyne (**45**) from cinnamaldehyde (**44**) in 78% overall yield following the method described in this work (Scheme 18). Furthermore, the Ohira-Bestmann reaction using **44** as substrate gave (1-methoxybut-3-ynyl)benzene (**46**) in 10% yield, together with dimethyl acetal (**47**, 67%).

The mechanism of Bu_2SnO -catalyzed cycloaddition of TMSN_3 on nitriles has been studied in detail by Kappe and co-workers.^{11b} It was demonstrated that the active catalytic species is $\text{Bu}_2\text{Sn}(\text{OTMS})\text{N}_3$ (**48**), and that regeneration of this catalyst occurs through $\text{S}_{\text{N}}2$ displacement at the silicon atom followed by fast ligand exchange at the tin atom. A plausible mechanism that would account for the formation of alkynes

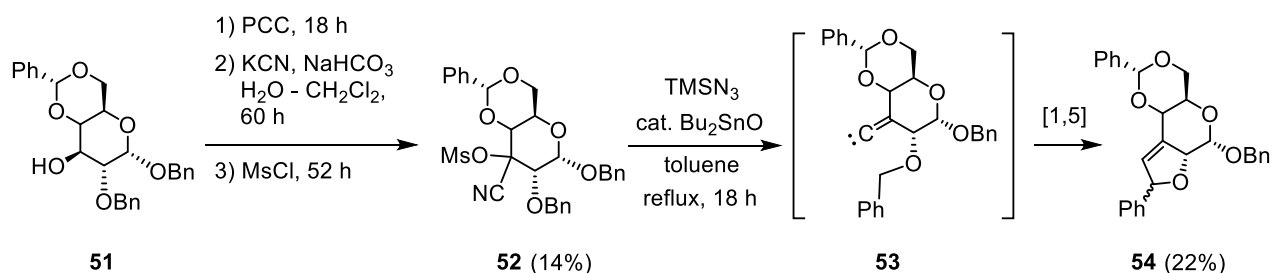
from CPs (**5**) is shown in Scheme 19. Tetrazolyolphosphates (**50**) would spontaneously lead to alkynes (**2**) upon tetrazole-fragmentation: that is, elimination of $(\text{EtO})_2\text{P}(\text{O})\text{OTMS}$ from **50**, the formation of unstable tetraazafulvene **7**, and loss of two moles of N_2 , thus generating alkylidene carbenes (**1**), which finally undergo a [1,2]-rearrangement to furnish alkynes **2**. The proposed mechanism also indicates that the C_1 unit of homologous alkynes **2** arises from the CN-carbon of DEPC.

4. SYNTHESIS OF FIVE-MEMBERED UNSATURATED CYCLIC COMPOUNDS FROM KETONES VIA CPs

4-1. [1.5]-C-H insertion reactions *via* the generation of alkylidene carbenes

Synthesis of five-membered unsaturated cyclic compounds from ketones by the [1.5]-C-H insertion of alkylidene carbenes has been carried out using $(\text{MeO})_2\text{P}(\text{O})\text{CHN}_2$ or TMSCHN_2 in the presence of a strong base.³ Wardrop and Komenda also reported the synthetic method for five-membered rings (**3**) from carbonyl compounds (**4**) in three steps by the generation of alkylidene carbenes (**1**) accessed through the dehydration of 5-hydroxyalkyl-1*H*-tetrazoles (**16**) with DIC, as shown in Scheme 5.²⁴ Meanwhile, Van Nhien and Postel reported a method for the generation of alkylidene carbenes based on the reaction of cyanomesylates with $\text{TMSN}_3/\text{Bu}_2\text{SnO}$.^{25c-f} As an example (Scheme 20), cyanomesylate **52**, which was prepared in only 14% yield from sugar template **51** in three steps in an aqueous condition, was converted into dihydrofuran derivative **54** through the [1,5]-C-H bond insertion of alkylidene carbene **53** in a low yield.^{25d} However, the scope and limitations of this method have not been clarified.

We have demonstrated the facile generation of the alkylidene carbenes from CPs in the efficient transformation of carbonyl compounds into homologous alkynes. Therefore, the formation of a variety of five-membered unsaturated carbocyclic or heterocyclic compounds *via* CPs will be addressed in the next section.

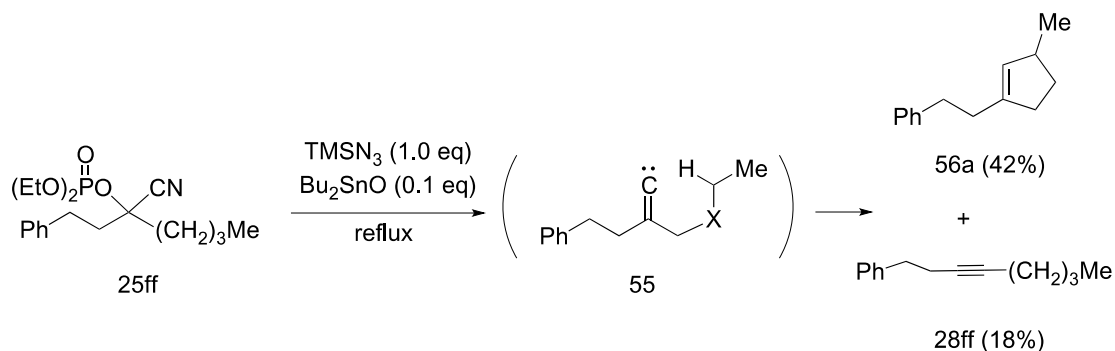


Scheme 20. Generation of alkylidene carbenes based on the reaction of cyanomesylates

4-2. Synthesis of five-membered unsaturated cyclic compounds¹⁰

We initially investigated the synthesis of cyclopentene **56a** from CP **25ff** (Scheme 21). In a previous study on alkyne synthesis, we found that solvents with boiling points greater than 100 °C may be required

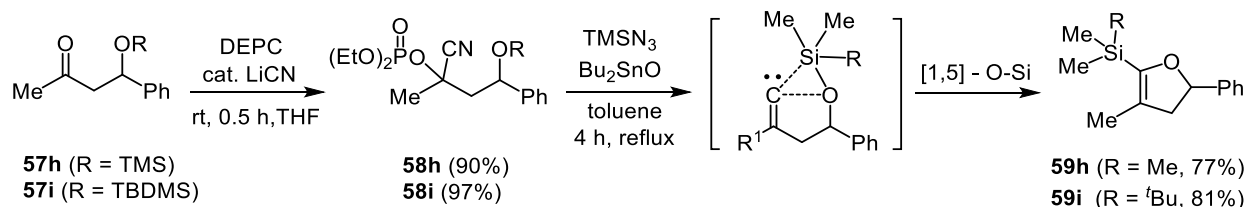
for the efficient generation of alkylidene carbenes from CPs. Accordingly, when CP **25ff** was treated with TMSN_3 (1.0 equiv.) in the presence of Bu_2SnO (0.1 equiv.) at reflux for 2 h in toluene, cyclopentene **56a** was obtained as the major product in 42% yield, together with alkyne **28ff** (18%). Alkyl-substituted alkylidene carbenes generally undergo [1,5]-C-H insertions rather than [1,2]-migrations.³



Scheme 21. Formation of cyclopentene **56a** from CP **25ff**

In the case of a dialkyl ketone CP like **25ff**, competitive reactions between the insertion and migration of carbene **55** take place. Methyl alkyl ketones (**57**) with lower migratory aptitudes³⁴ were thus chosen as substrates for the formation of various five-membered compounds, as summarized in Table 6. Cyanophosphorylation of methyl ketones **57b-g** yielded CPs **58b-g**, respectively, in 82% to 99% yields. Thus, CPs **58b-g** could be transformed into the corresponding five-membered compounds **59b-g** in moderate to high yields using TMSN_3 - Bu_2SnO (cat.) in toluene at reflux (Table 6). In the case of methyl ketones **57b-e** (entries 1-4), cyclopentene **59b**, 2,5-dihydrofuran **59c**, and 2,5-dihydropyrroles **59d**, and **59e** were readily obtained in 66%, 59%, 75%, and 74% overall yields in two steps. Meanwhile, the respective overall yields of **59b-e** obtained *via* the Wardrop method were lower 23%, 43%, 43%, and 49%, respectively, in three-steps from ketones **57b-e** (see values in parentheses of the right column of entries 1-4).²⁴ In the formation of 4-azaspiro[2.4]heptane **59f** from cyclopropylbenzenesulfonamide **57f**, a significant amount of the [1,2]-rearrangement product **60f** was produced as an inseparable mixture with **59f** and alkyne **60f** (54% overall yield from **57f**, **59f/60f** = 4/5), which is similar to the results obtained *via* the Wardrop method (38% overall yield from **57f**, **59f/60f** = 5/4) (entry 5).²⁴ Furthermore, the present method was successfully applied to the conversion of (4*S*)-2,2-dimethyl-4-(3-oxobutyl)-1,3-dioxolane (**57g**) into spiro[4.4]nonene (**59g**, 89% overall yield, entry 6), which is a versatile intermediate in the total synthesis of (-)-malyngolide^{35a} or (-)-frontalin^{35b} as reported by Ohira and co-workers.³⁵ They employed Shioiri conditions ($\text{TMSCHN}_2/n\text{-BuLi}$)¹² or the Seyferth-Gilbert procedure ($\text{DAMP}/t\text{-BuOK}$)^{4,5} for the preparation of **59g** from ketone **57g**, obtaining the products in 73% and 68% yields, respectively. The results summarized in Table 6 indicate that our method is preferable to the existing methods.

Shioiri and co-workers reported that alkylidene carbenes generated from β -trimethylsiloxy ketones undergo [1,5]-O-SiMe₃ bond insertion to produce 5-trimethylsilyl-2,3-dihydrofurans.^{12c} The present method could be used to similarly generate 5-trialkylsilyl-2,3-dihydrofurans **59h** (77%) and **59i** (81%) from the corresponding CPs **57h** (R = TMS) and **57i** (R = TBDMS), respectively (Scheme 22).

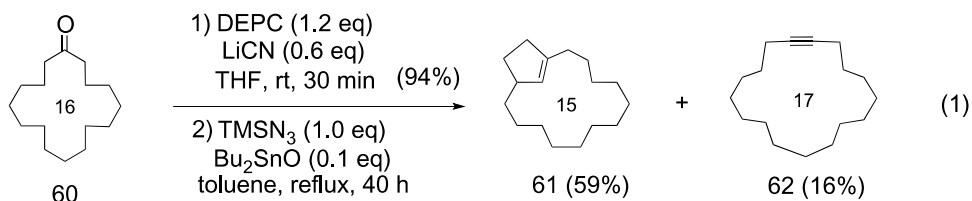


Scheme 22. Formation of 5-trialkylsilyl-2,3-dihydrofurans **59h** and **59i** using the present method

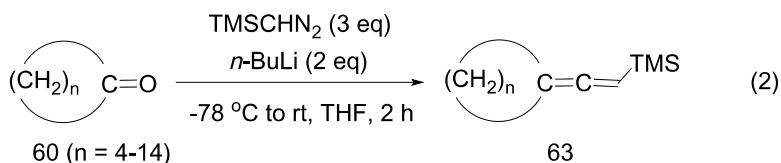
Furthermore, the 16-membered cyclic ketone **60** yielded bicyclo[12.2.1]heptadecene (**61**, 59%) *via* a CP together with cyclic alkyne homolog **62** (16%), in which [1,5]-C-H insertion mediated by alkylidene carbene from CP was preferred to the formation of cyclic alkyne homolog **62**, as shown in eq 1 of Scheme 23. In contrast, Lee and co-workers reported that the reaction of small- to medium-sized cyclic ketones (**60**, $n = 4 - 14$) with TMSCLiN₂ led to allenylsilanes (**63**, 10 - 81%) as per eq. 2.³³

Notably, β -ketoester **64**, which possesses readily enolizable α -protons, could be converted into cyclopentenyl acetate **65** in 95% overall yield using the present method (Scheme 24, eq 1). In contrast, the reaction of **64** under Shioiri conditions (TMSCH₂/LDA) only resulted in the unreacted starting material (**64**), as per eq. 2.¹²

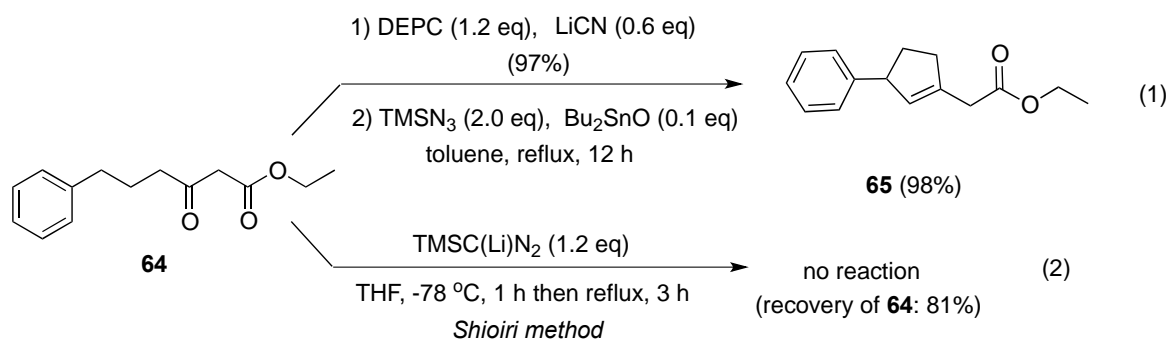
Lee and co-workers reported that the reaction of a dienyl ketone (**66**) with TMSCLiN₂ produced linearly fused triquinones **67** and **68** (54%, **67/68** = 3/1) (Scheme 25, eq. 2).³⁶ This reaction can be rationalized in that alkylidene carbene **69** undergoes an intramolecular [2+1] cycloaddition with the tethered alkene to generate methylenecyclopropane (**70**), and the fragmentation of this strained ring system provides trimethylenemethane diyls **71a** and **71b**, which afford linearly fused triquinanes **67** and **68**, respectively, through intramolecular [2+3] cycloaddition reactions.³⁶ Alternatively, cyanophosphorylation of dienyl ketone **66** followed by treatment of the CP with TMSN₃/Bu₂SnO (cat.) affords triquinanes **67** and **68** in 61% overall yield in the same ratio (**67/68** = 3/1), as per eq. 1.



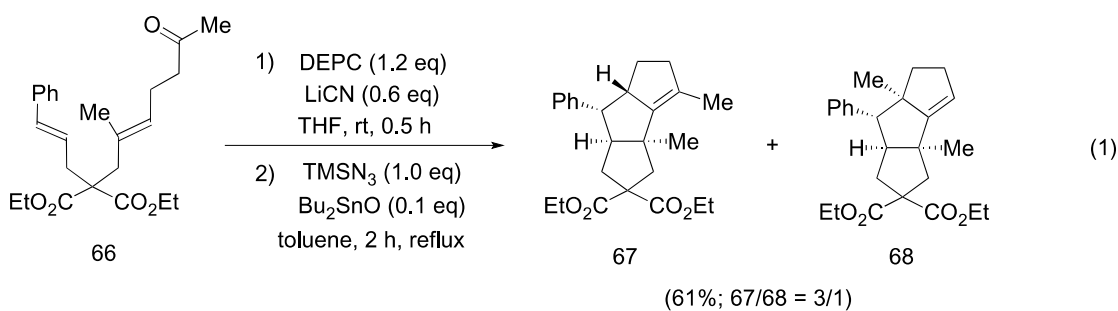
Cf. Lee and co-workers³³



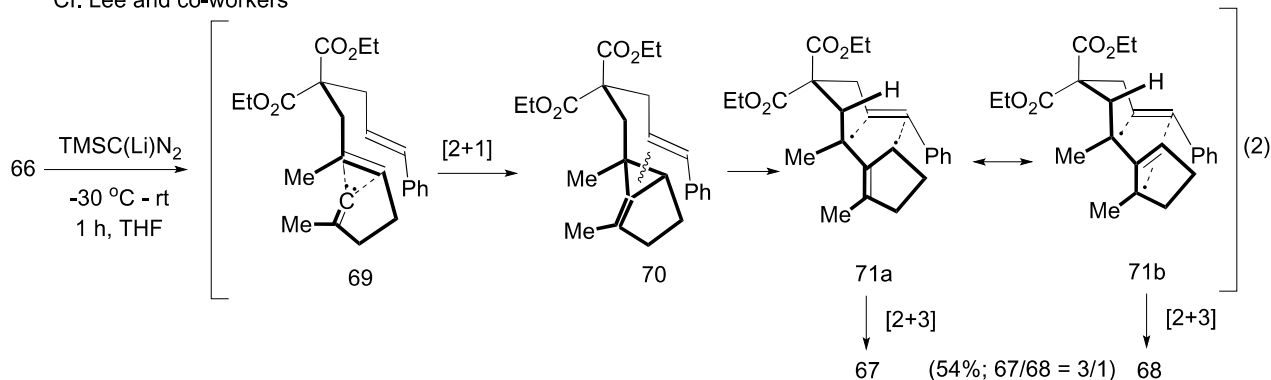
Scheme 23. Transformation of cyclic ketone **60** into bicyclic compound **61**



Scheme 24. Transformation of β-ketoester **64** into cyclopentenyl acetate **65**



Cf. Lee and co-workers³⁶



Scheme 25. Transformation of dieny ketone **66** into triquinanes **67** and **68** using the present method

5. SYNTHESIS OF C4-LINKED C_n -TRIAZOLE RIBONUCLEOSIDE PHOSPHoramidites FROM β -RIBOFURANOSYL- C_n -ACETYLENES¹³

We recently reported the efficient synthesis of C4-linked C_0 - to C_3 -imidazole ribonucleoside phosphoramidites [Imz- C_n -PAs (**72a-d**)], which were introduced into RNA using solid-phase *t*-BDMS chemistry implemented on an automated synthesizer, as shown in Figure 3.³⁷ Because imidazoles (p*K*_a of 7.1) are both excellent proton donors and acceptors,³⁸ we developed a novel chemogenetic approach using Imz- C_n -PAs **72** for the study of the catalytic mechanism of Varkud satellites (VS)^{39a} and hairpin ribozymes,^{39b} where conventional nucleobases are replaced by imidazoles.

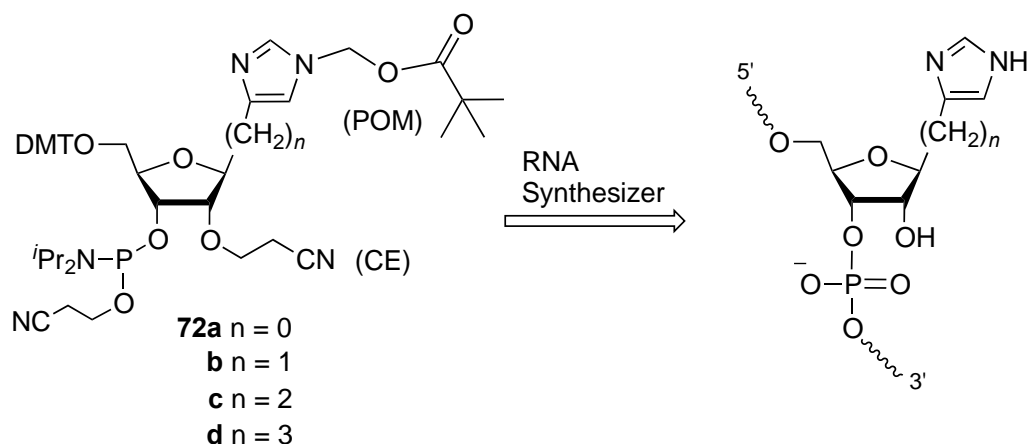


Figure 3. Incorporation of a C_n -imidazole to a ribozyme using PAs **72a-d** by solid-phase RNA synthesis

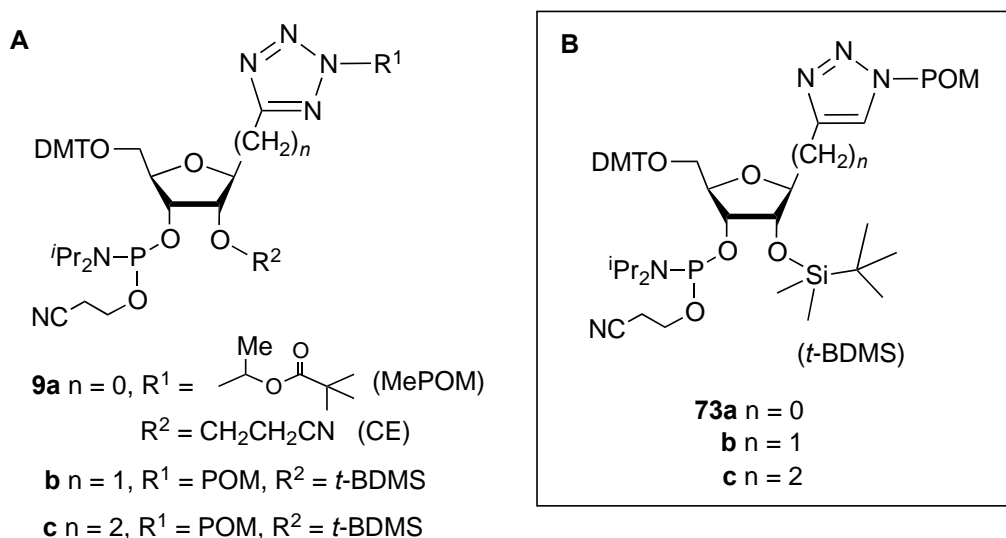
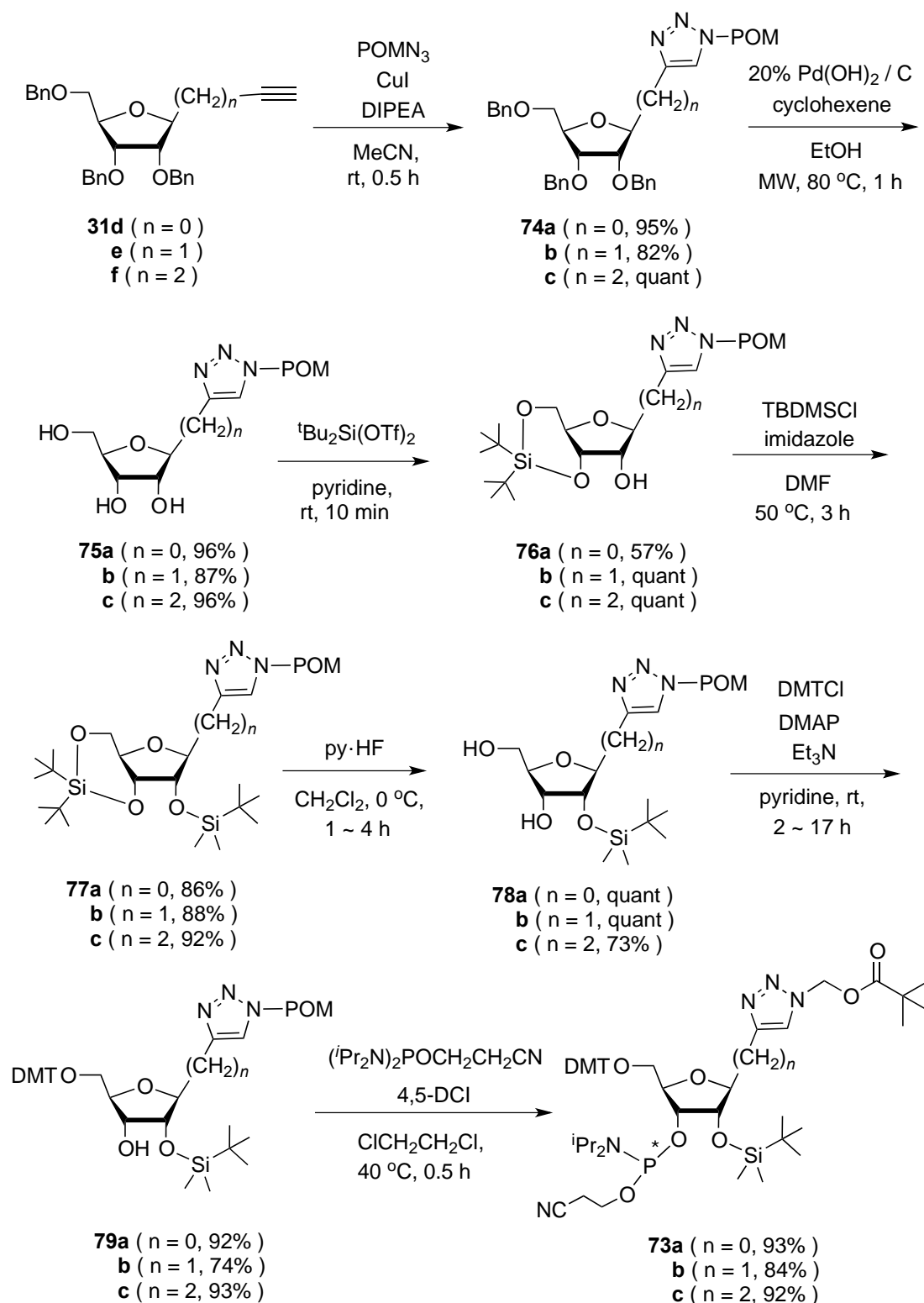


Figure 4. (A) Structure of C5-linked tetrazole- C_n -ribonucleoside PAs
(B) Structure of C4-linked triazole- C_n -ribonucleoside PAs



Scheme 26. Synthesis of triazole- C_n -ribonucleoside PAs (**73**) from terminal acetylenes (**31**)

There are powerful tools to probe general acid–base catalysis in the active sites of ribozymes.⁴⁰ However, it is impossible to use by this approach to determine which nucleobases function as acids or bases when imidazole species are employed as nucleobases. On the other hand, tetrazoles having a pK_a of 4.9 are

often used as metabolism-resistant isomeric replacements for carboxylic acids in medicinal chemistry.⁴¹ Therefore, after the preparation of ribose-(CH₂)_{*n*}-tetrazole (Tez) PAs **9a–c** (*n* = 0–2) (Figure 4–A),¹⁶ C5-linked C₀- and C₂-tetrazoles were incorporated successfully into the VS ribozyme substrate to determine more specifically which nucleobases of the ribozyme function as general acids in the chemistry of the natural ribozyme.¹⁶ However, the tetrazole-containing VS ribozymes exhibited poor catalytic activity. This might be attributed to the strongly acidic nature of tetrazoles, producing the corresponding salt between the tetrazole and nucleobase. With these results in hand, we directed our attention to 1,2,3-triazoles as alternative acid surrogates, because triazoles are less acidic (p*K*_a of 9.3).⁴² We therefore carried out the synthesis of novel C4-linked C₀-, C₁-, and C₂-triazole ribonucleoside PAs (**73a–c**, respectively) (Figure 4–B).¹³ In this study, β-ribofuranosyl-C_{*n*}-acetylenes **31d–f** (*n* = 0–2) were employed as key intermediates. They were efficiently prepared by the [1,2]-rearrangement of alkylidene carbenes generated upon fragmentation of tetrazoles derived from CPs **29d–f**, as shown in entries 1–3 in Table 5.⁹

With the C₀-, C₁-, and C₂-ribonucleoside acetylenes (**31d–f**, respectively) in hand, we turned our attention to the synthesis of C_{*n*}-triazole-ribonucleoside PAs **73a–c** (*n* = 0–2), as shown in Scheme 26. *N*-Pivaloyloxymethyl (POM)-1,2,3-triazole-C_{*n*}-nucleosides **74a–c** (82%–quantitative) were prepared via 1,3-dipolar cycloaddition of the terminal acetylenes **31** and azidomethyl pivalate (POMN₃).⁴³ Subsequent debenzoylation of **74a–c** with Pd(OH)₂-C/cyclohexene under MW irradiation furnished *N*-POM-triazole-C_{*n*}-nucleosides **75a–c** (87–96%).¹⁶ 3',5'-*O*-Di-*tert*-butylsilylanediyl (DTBS) protection of C-nucleosides **75a–c** afforded 3',5'-*O*-protected compounds **76a–c** (57%–quant.), allowing for the selective introduction of 2'-hydroxy protecting groups. The silylation reaction of **76a–c** with *tert*-butyldimethylsilyl chloride (TBDMSCl) afforded the fully protected intermediates **77a–c** (86–92%). The DTBS groups of **77a–c** were selectively removed by treatment with pyridine·HF to give 3',5'-unprotected ribonucleoside derivatives **78a–c** (73%–quantitative). After dimethoxytritylation under standard conditions, the 3'-hydroxy groups of derivatives **79a–c** (74–93%) were subjected to phosphitylation. Treatment of **79a–c** with 2-*O*-cyanoethyl-*N,N,N',N'*-tetraisopropylphosphodiamidite in the presence of 4,5-dicyanoimidazole (4,5-DCI) proceeded smoothly to afford the final product C4-linked-C_{*n*}-triazole PAs **73a–c** (84–93%). Subsequent studies on triazole-modified VS and hairpin ribozymes using triazole PAs **73a–c** are underway in our laboratory and will be published in due course.

6. SYNTHESIS OF (–)-NEPLANOCIN A THROUGH TETRAZOLE-FRAGMENTATION FROM CPs¹⁴

6-1. Synthesis of a crucial synthetic precursor for (–)-neplanocin A

(–)-Neplanocin A (NPA, **80**) is a naturally occurring carbocyclic nucleoside that was first isolated from

the culture filtrate of the soil fungus *Ampullariella regularis* in 1981.⁴⁴ NPA and other natural analogs have received considerable attention because of their interesting biological properties, such as their potent antiviral and antitumor properties (Figure 5).⁴⁵ (-)-NPA, one of the most potent *S*-adenosylhomocysteine hydrolase inhibitors, has broad-spectrum antiviral activity. However, NPA itself is cytotoxic to host cells and is also rapidly deaminated by adenosine deaminase to a chemotherapeutically inactive inosine congener.^{45c,46} This may account for its reduced therapeutic potency. Therefore, the chemical synthesis and structural modification of NPA have been investigated extensively,^{45,47} and several total syntheses have been achieved.

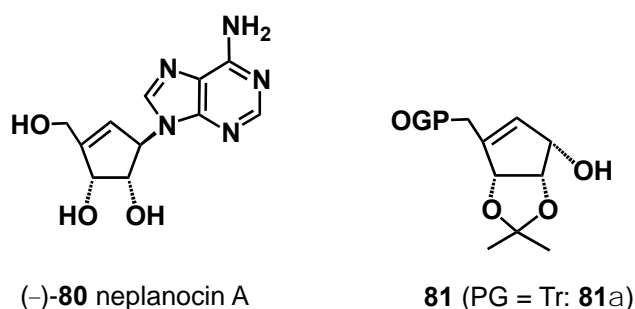


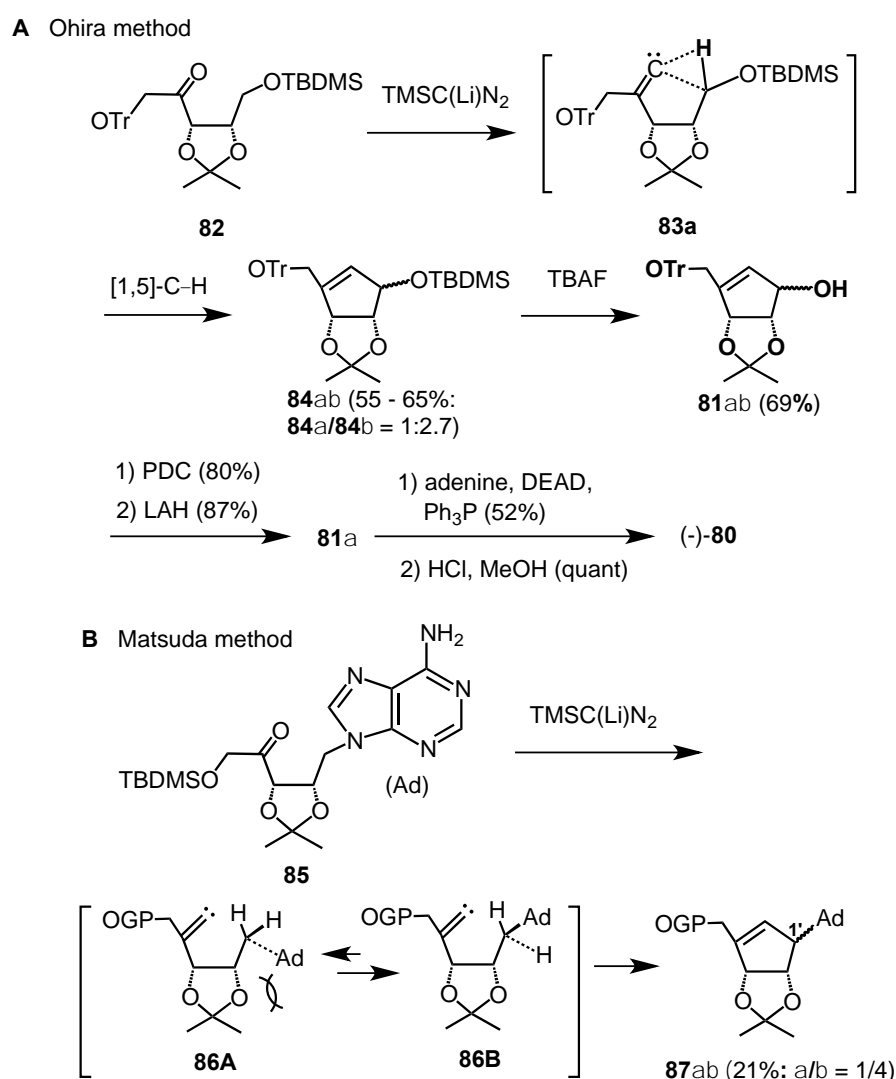
Figure 5. (-)-Neplanocin A (**80**) and crucial synthetic precursor (**81**) for neplanocin derivatives

Protected cyclopentenyl tetrol **81** has been widely used as a synthetic precursor not only for (-)-**80**, but also its analogs.⁴⁷⁻⁵⁶ The shortest method thus far was reported by Ohira and co-workers, who synthesized of (-)-**80** from **81a** [protecting group (PG) = triphenylmethyl (Tr)] by employing a C–H insertion reaction of alkylidene carbene **83a** (Scheme 27-A).⁵⁷ In this method, ketone **82**, which is derived from D-ribose, is reacted with $\text{TMSC}(\text{Li})\text{N}_2$,¹² affording cyclopentene derivative **84aβ** in 55–65% yield (**84a**/**84β** = 1:2.7).⁵⁷ Removal of the TBDMS group of **84aβ** with tetrabutylammonium fluoride (TBAF) furnished the protected tetrol **81aβ** (69%). Subsequent pyridinium dichromate (PDC) oxidation (80%) of **81aβ** followed by lithium aluminum hydride (LAH) reduction (87%), provided the desired tetrol (**81a**) as a single stereoisomer. Then, Mitsunobu reaction of **81a** with adenine using the Nokami procedure,^{47a} followed by deprotection of the hydroxy groups, afforded (-)-**80**. Using the Ohira method, Liao and co-workers also described the syntheses of 2'-β-C-methyl-neplanocin derivatives.⁵⁸ Alternatively, Matsuda and co-workers employed ketone **85** derived from adenosine for the C–H insertion reaction of alkylidene carbene **86** using $\text{TMSC}(\text{Li})\text{N}_2$ (Scheme 27-B).⁵⁹ The reaction of ketone **85** with $\text{TMSC}(\text{Li})\text{N}_2$ afforded a 1:4 epimeric mixture (**87aβ**) of **87a** and **87β** at the 1'-position in only 21% yield. The generated carbene (**86**) has two conformers, **86A** and **86B**. Steric repulsion between the isopropylidene and adenine groups in conformer **86A** could lead to the preferential adoption of conformer **86B**, which would afford desired β-diastereomer **87β** (Scheme 27-B). However, desired isomer **87β** was,

unfortunately, not isolated from the epimeric mixture of **87 $\alpha\beta$** , presumably because of the difficulty of separation through column chromatography on silica gel. As a result, this second synthetic study employing a C–H insertion reaction of an alkylidene-carbene was unsuccessful.⁶⁰

In addition, Postel and co-workers have reported the preparation of cyclopentene derivatives as the intermediates for the syntheses of NPA stereoisomers from D-mannose using similar [1,5]-C–H insertions of alkylidene carbenes generated from α -cyanomesylates.^{25e}

Based on these reports and to demonstrate the synthetic utility of the alkylidene carbenes generated under neutral conditions from CPs, we attempted to apply the CP method to ketones **82** and **85** employed by Ohira and Matsuda, respectively.^{57,59}



Scheme 27. (A) Synthesis of neplanocin A (**80**) from synthetic precursor **81 α** using the Ohira method; (B) Synthesis of epimeric mixture **87 $\alpha\beta$** at the 1'-position using the Matsuda method

Ketone **82**, which was prepared via Tr ether **88**⁶⁰ from D-ribose in five steps (71% overall yield), was

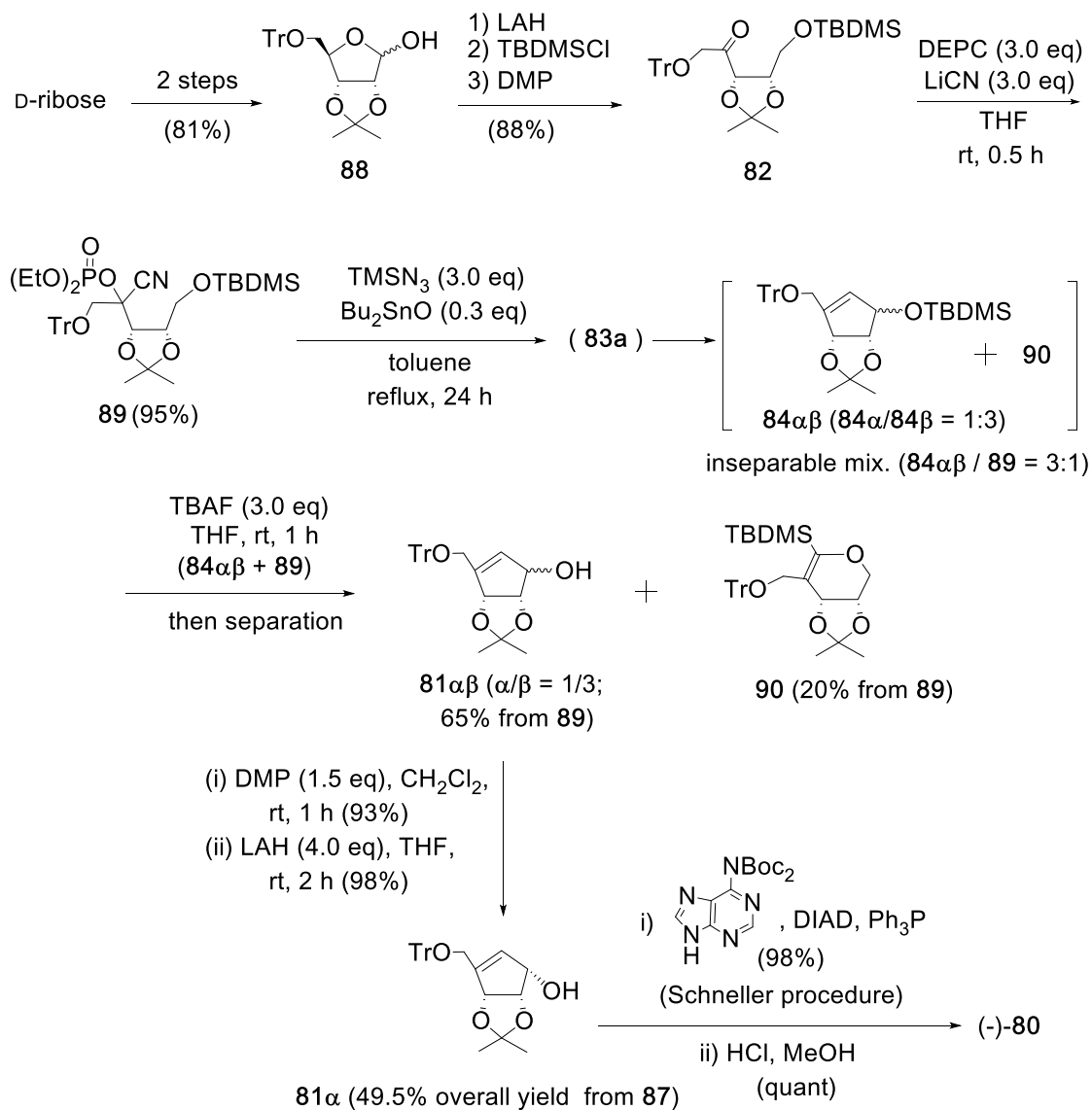
subjected to the CP method, as illustrated in Scheme 28. The reaction of ketone **82** with DEPC (3.0 equiv.) in the presence of LiCN (3.0 equiv.) easily afforded CP **89** in 95% yield. The reaction of CP **89** with TMSN₃ (3.0 equiv.) in the presence of Bu₂SnO (0.3 equiv.) in refluxing toluene for 24 h afforded an inseparable mixture of epimeric cyclopentenenes (**84αβ**), which was the result of the C–H insertion reaction of alkylidene carbene **83a**, along with unexpected compound (**90**). The ratio of **84αβ** to **90** was 3:1 based on ¹H-NMR measurements. After the mixture was treated with TBAF to remove the TBDMS group, deprotected cyclopentenenes **81αβ** (**81α/81β** = 1/3) and compound **90** were separated using column chromatography on silica gel and obtained in 65% and 20% yields, respectively, from CP **89**. Compound **90** was determined to be a dihydropyran derivative and the stereochemical assignment was made based on nuclear Overhauser effect spectroscopy (NOESY) analysis. As illustrated in Figure 6, the unexpected formation of **90** may have been caused by [1,6]-O-Si bond insertion of the carbene **83a** or 1,2-TBDMS shift of ylide **83b**,⁶¹ as opposed to the usual [1,5]-O-Si insertion that generates dihydrofuran derivatives.^{3,12c}

Ohira and co-workers reported only the formation of **84αβ** in the reaction of ketone **82** with TMSC(Li)N₂ and did not mention the production of dihydropyran **90**, as shown in Scheme 27-A.⁵⁷ The unusually broad yield range (55–65%) of **84αβ** reported by Ohira may be a combined yield of **84αβ** and **90** owing to the difficulty of their separation. Indeed, when we attempted to reproduce Ohira's result [i.e., the reaction of ketone **82** with TMSC(Li)N₂ (3 equiv.) in THF for 1 h at 0 °C],⁵⁷ an inseparable mixture of **84αβ** (**84α / 84β** = 1/3) and **90** was produced in 61% combined yield.

Transformation of **81αβ** into the desired cyclopentenol **81α** using Dess–Martin periodinane (DMP) oxidation (93%) and subsequent LAH reduction (98%) was more effective than the corresponding reactions in the Ohira method (Scheme 27-A). Cyclopentenol **81α** was obtained in 49.5% overall yield in eight steps from protected D-ribose (**88**). This result is superior to that achieved by Ohira method (18–23% overall yield of **81α** from **88**); that is, the overall yield was more than two times higher. Alcohol **81α** can be converted to (–)-**80** through efficient Mitsunobu coupling with *N*-6 amino bis-Boc-protected adenine using the Schneller procedure,⁶² followed by deprotection in acidic conditions.

6-2. Synthesis of (–)-neplanocin A from CP

We next investigated the synthesis of (–)-NPA (**80**) via CP **94** from adenine-containing ketone **85**, starting from 2',3'-*O*-isopropylidene-adenosine (**91**) using Matsuda's approach (Scheme 29). Matsuda used the reductive tetrahydrofuran-ring cleavage reaction reported by Maki.⁶³ Treatment of **91** with diisobutyl aluminum hydride (DIBAL) in THF afforded acyclic nucleoside **92** in 57% yield.



Scheme 28. Synthesis of (-)-neplanocin A from CP **89**

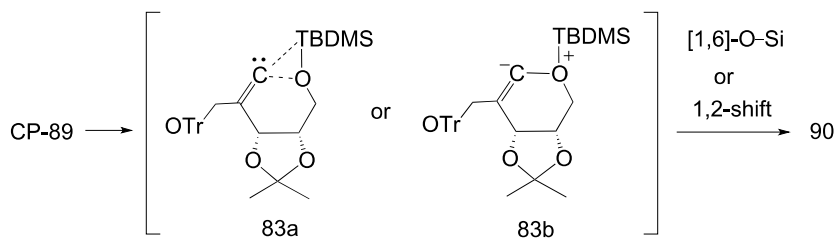
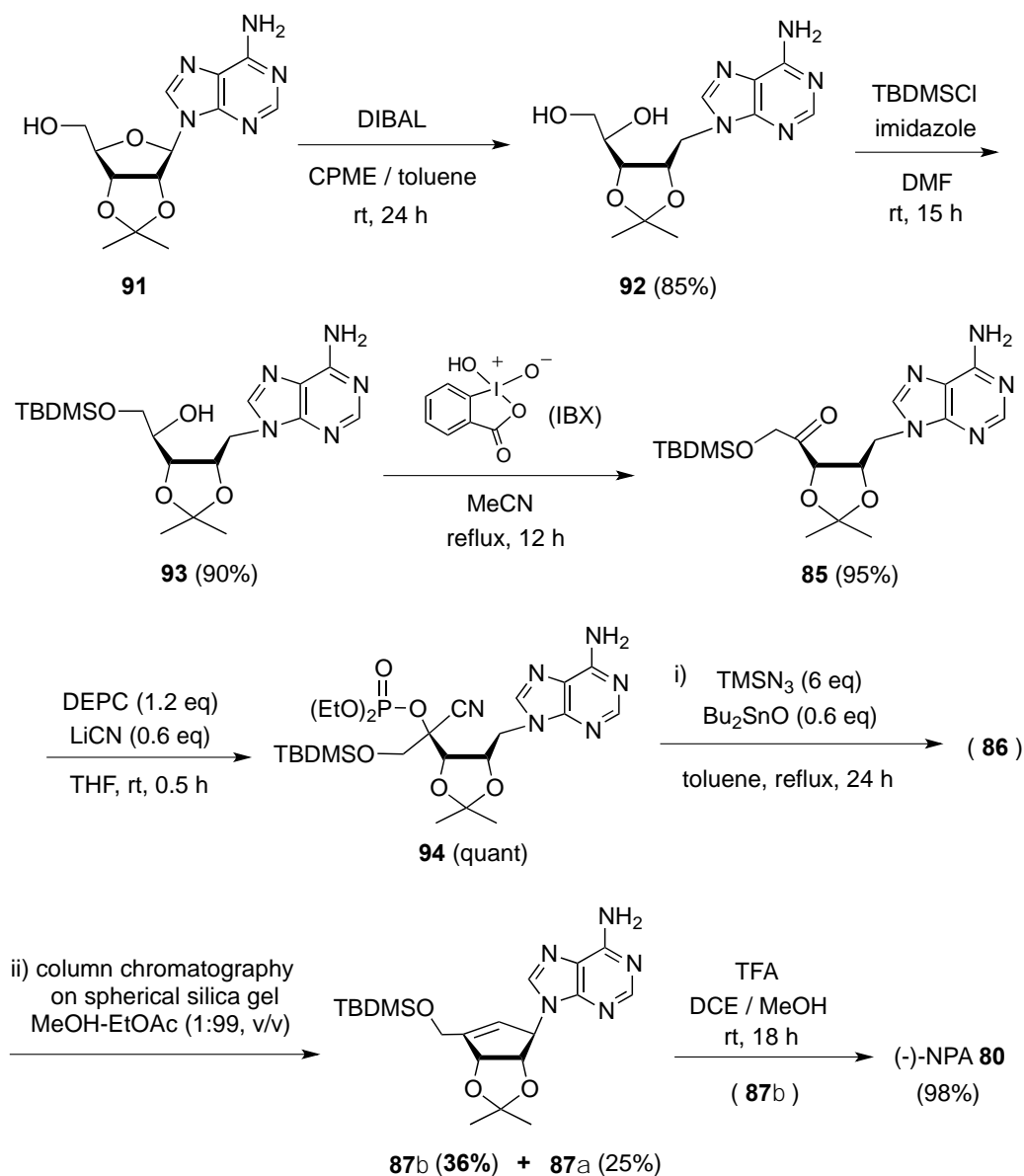


Figure 6. Two possible pathways for the formation of **90**

Meanwhile, we found that the use of a CPME-toluene (1:1, v/v) solvent system for the ring-cleavage reaction of **91** led to improved yields of **92** to 85% owing to the much easier extraction. After selective

protection (90%) of the primary hydroxyl group of **92** with TBDMSCl, we oxidized secondary alcohol **93** with *o*-iodoxybenzoic acid (IBX) to furnish ketone **85** (95%). Cyanophosphorylation (quantitative) of **85** with DEPC catalyzed by LiCN followed by the treatment of CP **94** with TMSN₃ (6 equiv.) catalyzed by Bu₂SnO in refluxing toluene for 24 h afforded an epimeric mixture (**87αβ**) of carbocyclic nucleosides through a [1,5]-C-H insertion reaction of alkylidene carbene **86**. Although the desired product **87β** was not isolated successfully from mixture **87αβ** in the Matsuda approach, it could be chromatographed over spherical silica gel⁶⁴ [MeOH-EtOAc (1:99, v/v)] and was obtained in 36% yield in this study, with 25% yield of **87α**. Deprotection of the obtained β-epimer (**87β**) under acidic conditions afforded (-)-**80** in high purity in an overall yield of 25.6% in six steps from protected adenosine **91**.⁴⁹ⁱ



Scheme 29. Synthesis of (-)-neplanocin A from CP **94**

7. CONCLUSIONS

CPs (**5**) can be readily prepared from either ketones or aldehydes, and their reaction with $\text{NaN}_3\text{-Et}_3\text{N}\cdot\text{HCl}$ results in the formation of azidotetrazoles **26**. On MW irradiation, the successive fragmentation of **26** generates alkylidene carbenes (**1**), which undergo [1,2]-rearrangement to yield homologous alkynes **2**. More importantly, CPs (**5**) react with $\text{TMSN}_3/\text{Bu}_2\text{SnO}$ (cat.) to form putative tetrazoylphosphates, which similarly generate alkylidene carbenes (**1**) through the tetrazole-fragmentation to produce homologous alkynes (**2**).

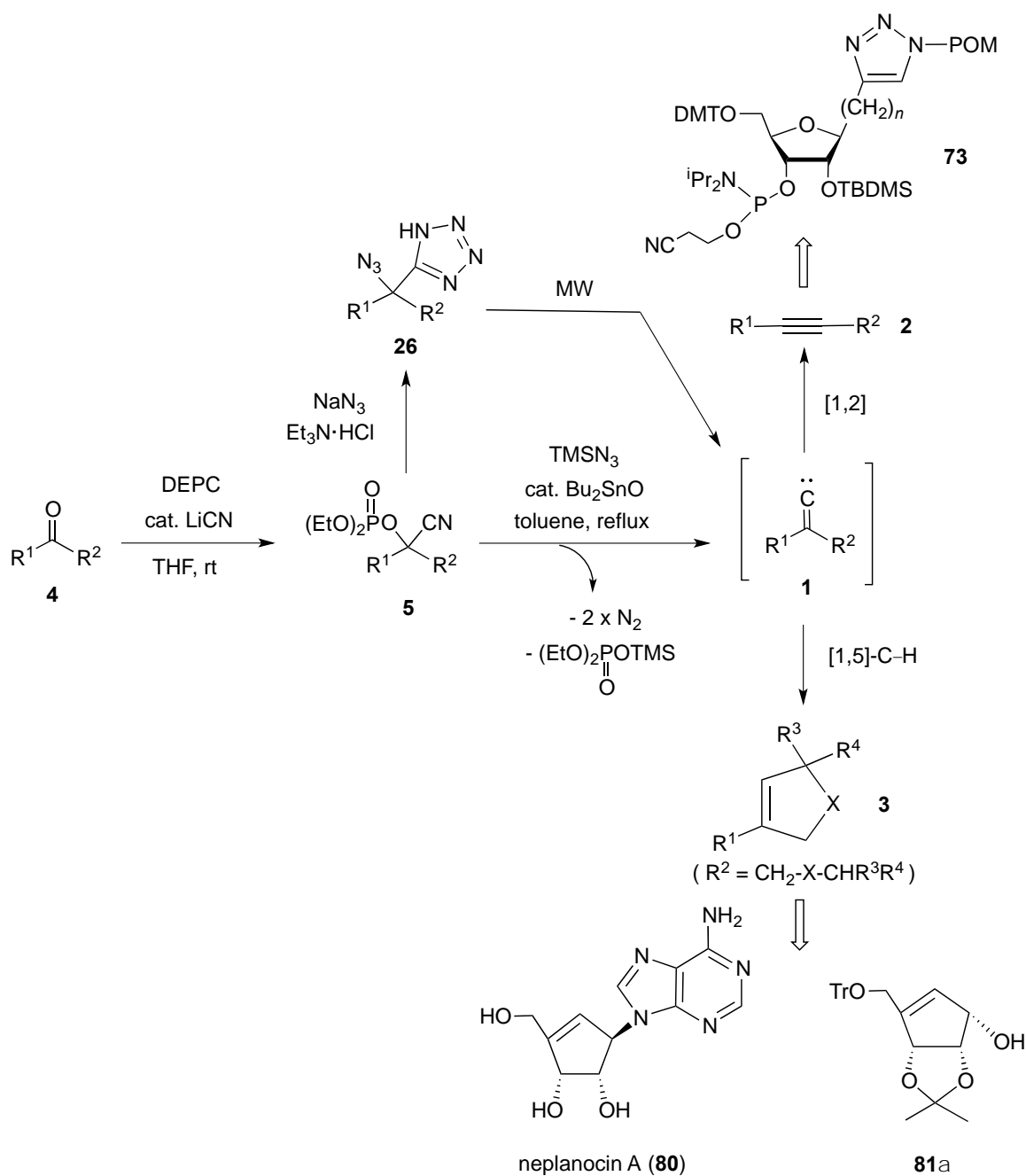


Figure 7. Generation of alkylidene carbenes (**1**) from CPs **5** and their synthetic applications to homologous alkynes (**2**) and five membered unsaturated cyclic compounds (**3**)

This reaction takes place under neutral conditions and can be successfully extended to obtain alkynes that are not usually accessible from the corresponding carbonyl compounds by the Ohira-Bestmann or Shioiri procedures, which require basic conditions. Alternatively, the carbenes (**1**) from ketone-derived CPs (**5**) undergo [1,5]-C-H insertions to yield five-membered unsaturated carbocycles **3** (X = CH₂) or heterocyclic systems (**3**, X = O or NH) in good yields. The results of the present study are summarized in Figure 7. Comparison with the existing methods for these two transformations demonstrates the superiority of the CP method over the Wardrop method, which uses tetrazole fragmentation, or the Shioiri method, which requires basic conditions. In the synthetic applications of the present method, novel C4-linked triazole C_n-ribonucleoside PAs (**73**, n = 0-2) for probing RNA catalysis were efficiently synthesized. Furthermore, the efficient and practical syntheses of neplanocin A (**80**) and widely applicable intermediate **81α** were achieved from CPs *via* the tetrazole-fragmentation. We hope that the synthetic method developed herein will be applied fruitfully to other synthetic targets. The less studied chemistry of tetrazole-fragmentation is presently under active investigation in our group because it opens perspectives for the smooth generation of alkylidene carbenes from CPs. In addition, the present study demonstrated the further applicability of CPs as intermediates in organic synthesis.⁷

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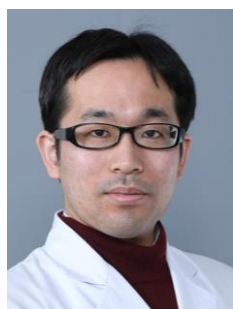
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