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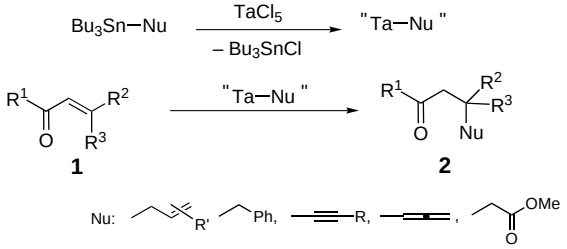
Generation of Organotantalum Reagents and Conjugate Addition to Enones**

Ikuya Shibata,* Takeyoshi Kano, Nobuaki Kanazawa, Shoji Fukuoka, and Akio Baba*

Organotin compounds are good precursors for generating active organometallic agents through transmetalation.[1, 2] For example, active allylic titanium complexes generated from allylic tin complexes have performed effective allylation of carbonyl compounds.[1] In contrast, generation and synthetic use of similar early transition metal complexes such as tantalum reagents[3] have not been reported so far, although Ta–C bonds are known to be moderately reactive to electrophiles.[4, 5] We report here on the preparation of active tantalum reagents by the transmetalation of organotin compounds with tantalum(v) chloride. Of particular interest is that certain tantalum reagents promote the conjugate allylation of enones (Scheme 1).



Scheme 1. Generation of an active tantalum–nucleophile complex and subsequent addition to an enone.

Compared with the direct allylation of carbonyl groups, little has been reported on the selective conjugate allylation of enones.[6] The only choice for this purpose has been the Hosomi–Sakurai reaction (allylsilane and $TiCl_4$).[7a] Later, modified reagents such as allylbarium[7b] and allylcopper[7c] were developed to avoid strong acidic conditions. However, with these modified reagents the allylation of acyclic enones is far more difficult than that of cyclic ones. The present system could be the method of choice for conjugate addition of allylic nucleophiles including sterically hindered ones to enones.[8]

The results of the conjugate allylation of enones, both acyclic and cyclic substrates, are given in Table 1. Under the conditions described in the Experimental Section, benzalacetone (**1a**) was allylated to give the conjugate adduct **2a** in 91% yield (entry 1, Table 1). The yield decreased to 50%

[*] Dr. I. Shibata, Prof. Dr. A. Baba, T. Kano, N. Kanazawa, S. Fukuoka
Department of Molecular Chemistry & Frontier Research Center
Graduate School of Engineering, Osaka University
2–1 Yamadaoka, Suita, Osaka, 565-0871 (Japan)
Fax: (+81) 6-6879-7387
E-mail: shibata@ap.chem.eng.osaka-u.ac.jp

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Table 1. Conjugate allylation of enones **1** according to Scheme 1 (Nu = allyl, $R^3 = E$ or Z H).[a]

Entry	Starting compound	R^1	$R^{2[b]}$	Solvent	Product	Yield [%]
1	**1a**	Me	Ph	CH_3CN	**2a**	91 (50[c])
2	**1a**	Me	Ph	CH_2Cl_2	**2a**	trace
3	**1a**	Me	Ph	THF	**2a**	49
4	**1a**	Me	Ph	Et_2O	**2a**	7
5	**1b**	Ph	Ph	CH_3CN	**2b**	99
6	**1c**	Ph	Me	CH_3CN	**2c**	63
7	**1d**	Ph	H	CH_3CN	**2d**	48
8	**1e**	Ph	PhMeCH	CH_3CN	**2e**	63[d]
9	**1f**	Et	Me	CH_3CN	**2f**	83
10	**1g**		$-(CH_2)_2-$	CH_3CN	**2g**	56
11	**1h**		$-(CH_2)_3-$	CH_3CN	**2h**	81

[a] Conditions: allyltributyltin (2 mmol), $TaCl_5$ (1 mmol), enone **1** (1 mmol), solvent (1 mL). [b] Entries 1–9: E isomers; entries 10 and 11: Z isomers. [c] Allyltin (1 mmol). [d] d.r. = 89:11.

when one instead of two equivalents of the allyltin reagent was used. Acetonitrile is the solvent of choice (see entries 2–4 for the results with other solvents). Aromatic and aliphatic enones are similarly applicable to this conjugate allylation to give **2b**–**2h** (entries 5–11). In all cases, the 1,2-adduct was not obtained.

The use of allyltrimethylsilane in place of allyltri-*n*-butyltin under the identical conditions resulted in lower yield of **2b** (27%), perhaps because $TaCl_5$ does not interact with allylsilane. The reaction of allylmagnesium bromide, $TaCl_5$, and **1b** in THF at $-40\,^\circ C$ afforded only 1,2-adduct (34%). Furthermore, attempted allylation with allyltitanium generated from allyltri-*n*-butyltin and $TiCl_4$ did not afford any products. Thus, the allyltin–tantalum system seems to be the one efficient combination for conjugate allylation.

That the transmetalation of the tin species with $TaCl_5$ is facile is evident in Table 2. When equimolar amounts of $TaCl_5$ and allyltri-*n*-butyltin were stirred at $-40\,^\circ C$ in THF or CH_3CN for 30 min, quantitative yields of nBu_3SnCl were obtained but the transmetalation is faster in the latter solvent (entries 1 and 2, Table 2). When an excess of allyltin was used, nBu_3SnCl was formed in over 100% yield based on $TaCl_5$, which indicates that several Ta–Cl bonds are responsible for the transmetalation (entries 3 and 4). The ^{119}Sn NMR spectrum confirmed the formation of nBu_3SnCl ($\delta = 123$) and complete disappearance of allyltri-*n*-butyltin ($\delta = 20$). Unfortunately, no actual reacting species has been identified by ^1H NMR spectroscopy, as in the case for allylic titanium.[1] We observed only the completely demetalated product, propene. Although the actual structure of the tantalum species, whether the allyl ligand is σ- or π-bound, is not clear as yet, the active tantalum species is formed by transmetalation.[9] In addition to allyltin, benzyl- and alkynyltin compounds also reacted to give benzyl- and alkynyltantalum compounds, respectively (entries 5 and 6, Table 2).

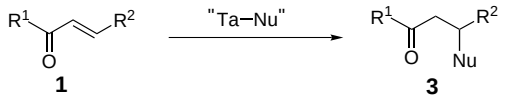
Table 2. Generation of active tantalum reagents "Ta–Nu" according to Scheme 1.[a]

Entry	Nu	Solvent	nBu_3SnR [equiv]	Yield of nBu_3SnCl [%]
1	allyl	THF	1	99 (16[b])
2	allyl	CH_3CN	1	99 (99[b])
3	allyl	CH_3CN	2	189
4	allyl	CH_3CN	3	250
5	$PhCH_2$	CH_3CN	2	76
6	PhC≡C	CH_3CN	2	83

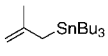
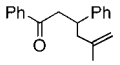
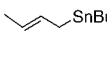
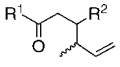
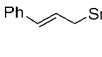
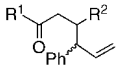
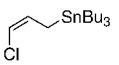
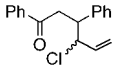
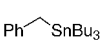
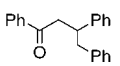
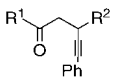
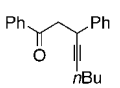
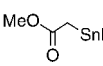
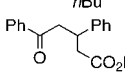
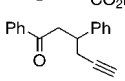
[a] Yields are from GLC and based on $TaCl_5$. The reactions were carried out in 1 mL of solvent using $TaCl_5$ (1 mmol) and allyltin at $-40\,^\circ C$ for 30 min. [b] Reaction time of 5 min.

The synthetic advantage of this tin–tantalum system is the stability and easy availability of various tin precursors.[1, 2] Thus various groups could be introduced to enones by conjugate addition [Eq (1), Table 3]. Methallyltri-*n*-butyltin gave the corresponding adduct **3a** (entry 1, Table 3). When γ-substituted allyltin derivatives were used, the addition occurred at the γ-position selectively to give **3b**–**3f** (entries 2–6). Besides allylic reagents, benzyltri-*n*-butyltin, alkynyltri-*n*-butyltin derivatives, and α-stannyl esters could be used to give the conjugate adducts **3g**–**3k**, respectively (entries 7–11). In the case of allenyltri-*n*-butyltin, the β-propargylated adduct **3l** was obtained (entry 12).

Table 3. Conjugate addition of tantalum reagents to enone [Eq (1)].[a]



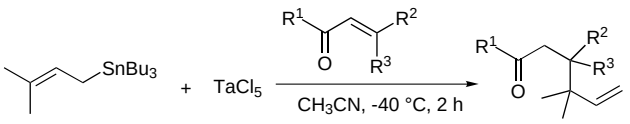
1 **3**

Entry	Tin precursor	Enone	Product			Yield [%]
1		**1b**			**3a**	54
2		**1b**		R^1,R^2 = Ph,Ph	**3b**	70[b]
3		**1f**		R^1,R^2 = Et,Me	**3c**	79[c]
4		**1b**		R^1,R^2 = Ph,Ph	**3d**	89[d]
5		**1f**		R^1,R^2 = Et,Me	**3e**	97[e]
6		**1b**			**3f**	83[f]
7		**1b**			**3g**	97
8		**1b**		R^1,R^2 = Ph,Ph	**3h**	76
9		**1f**		R^1,R^2 = Et,Me	**3i**	99
10		**1b**			**3j**	57
11		**1b**			**3k**	50
12		**1b**			**3l**	60

[a] All reactions were carried out in CH_3CN (1 mL) using tin compound (2 mmol), $TaCl_5$ (1 mmol), and enone **1** (1 mmol) at $-40\,^\circ C$ for 2 h. [b] d.r. = 56:44. [c] d.r. = 77:23. [d] d.r. = 82:18. [e] d.r. = 69:31. [f] d.r. = 77:23.

  1433-7851/02/4108-1390 $ 20.00+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 8

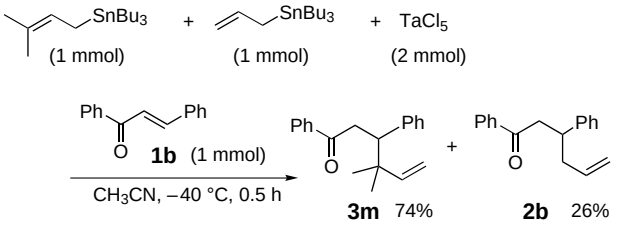
As shown in Scheme 2, even tri-*n*-butylprenyltin effectively gave the corresponding products **3m**–**3p** in high yields in spite of the bulky *gem*-dimethyl substituents at the γ-position.



R^1= Ph	R^2= Ph	R^3= H	**3m**	92%
R^1= Ph	R^2= Me	R^3= Me	**3n**	82%
R^1= Me	R^2= Ph	R^3= H	**3o**	56%
R^1= Et	R^2= Me	R^3= H	**3p**	90%

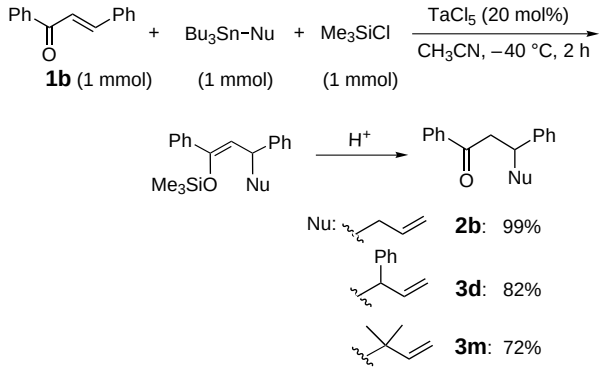
Scheme 2. Conjugate prenylation of enones.

In particular, the product **3n** bearing contiguous quaternary carbon centers could be obtained in 82% yield.[10] We confirmed that the Sakurai–Hosomi reagent, trimethylprenylsilane/$TiCl_4$, under the standard conditions[7] resulted in lower yields of **3n** (11% at $-78\,^\circ$C. 17% at $-40\,^\circ$C). Interestingly, in the competition experiment shown in Scheme 3, more sterically demanding prenyltin reacted predominantly over allyltin to give **3m**.[11]



Scheme 3. Competition experiment between conjugate prenylation and allylation.

In all cases discussed above, the required molar ratio of $TaCl_5$ to the allylic tin reagent was 1:2. However, we found that addition of an equimolar amount of trimethylsilyl chloride (Me_3SiCl) enabled the catalytic use of $TaCl_5$ (Scheme 4). Careful isolation afforded the conjugate adducts as silyl enolates, which were converted to **2b**, **3d**, and **3m** by simple protonolysis. As a tentative catalytic cycle, it can be assumed that the conjugate adduct, tantalum enolate, is trapped by Me_3SiCl to form silyl enolate along with the regeneration of $TaCl_5$.



Scheme 4. Catalytic version of the $TaCl_5$-mediated conjugate addition.

In conclusion, various tantalum reagents could be generated from organotin compounds by transmetalation. In particular, the system described is more broadly applicable on the conjugate allylation of enones than conventional methods.

Experimental Section

Representative procedure of conjugate addition: To a dry nitrogen-filled 10-mL round-bottomed flask containing $TaCl_5$ (0.358g, 1 mmol) in MeCN (1 mL) was added allyltri-*n*-butyltin (0.662 g, 2 mmol) at $-40\,^\circ$C. $TaCl_5$ was partly insoluble. The mixture was stirred at $-40\,^\circ$C for 30 min, before benzalacetone (**1a**) (0.146 g, 1 mmol) was added. As the reaction proceeded, the mixture gradually turned homogeneous and very pale yellow; a drastic change in color was not observed. After the mixture had been stirred at $-40\,^\circ$C for 2 h, MeOH (2 mL) was added and the volatiles were removed under reduced pressure. The residue was chromatographed on a silica-gel column (FL100-DX (Fuji silysia)); eluting with hexane/EtOAc (3/1) gave conjugate adduct **2a** (0.171 g, 91%).

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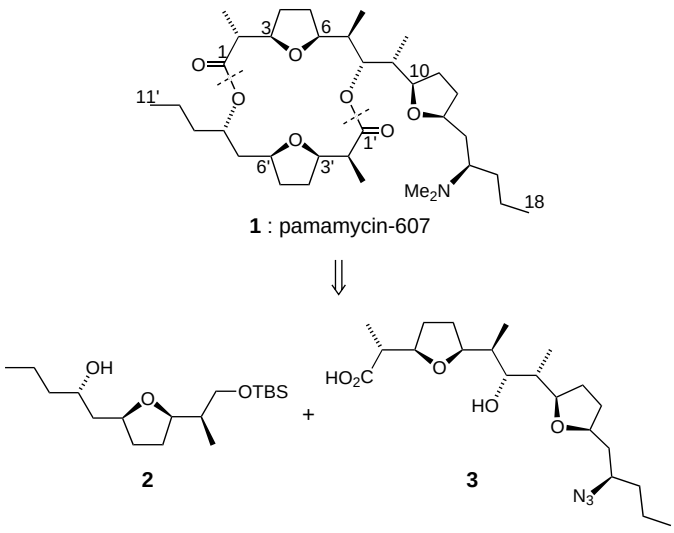


Scheme 1.

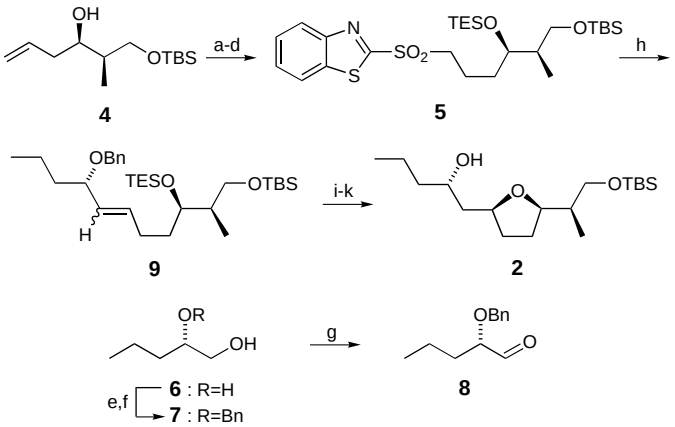
Total Synthesis of (+)-Pamamycin-607**

Sung Ho Kang,* Joon Won Jeong, Yu Sang Hwang, and Sung Bae Lee

The pamamycins are a novel family of naturally occurring homologous macrodiolides, which are found in *Streptomyces sp*.[1–9] They induce the aerial mycelium formation in *S. alboniger* to display autoregulatory activity.[1–3]. They also exhibit antibiotic activity against Gram-positive bacteria and pathogenic fungi,[1,2] inhibit myosin light chain kinase,[5] and mediate hydrophilic ion transport through lipophilic phases.[6] In addition, they show vasodilating,[7] anionophoric,[2–7] protonophoric,[8] and autolytic properties.[9] A major component of the family is pamamycin-607 (**1**), which has a molecular weight of 607. While the structure and relative stereochemistry of pamamycin-607 were elucidated by NMR spectroscopy, its absolute stereochemistry was later determined by a correlation study.[10] The remarkable biological activity of pamamycin-607 and its unique structural features led us to choose **1** as a synthetic target.[11] Herein we report an asymmetric total synthesis of **1**.

The two ester linkages of **1** were disconnected by retrosynthetic analysis to provide alcohol **2** and carboxylic acid **3** as the precursors of the C1′ – C11′ and C1 – C18 subunits, respectively (Scheme 1). As we envisaged that the three *cis*-2,5-disubstituted tetrahydrofurans comprising **2** and **3** could be formed[12] by iodoetherification of γ-triethylsilyloxyalkenes,[13] **9** (see Scheme 2) and **21** (see Scheme 3) were proposed as the intermediates. Construction of the double bonds in **9** and **21** was planned by means of a sulfone olefination[14] and the Horner – Emmons reaction. The C2 methyl group could be installed by the cuprate epoxide opening of **23** (see Scheme 4), in which the regioselectivity was assumed to be dictated by the bulky substituent. In addition, while the adjacent hydroxyl and methyl functional groups of **9** were expected to be delivered from the known alcohol **4** (Scheme 2),[15] those of **21** would be transformed by a Paterson[16] aldol reaction and Evans *anti* reduction.[17]

To prepare the bottom subunit **2**, alcohol **4** (78 % *de*) was consecutively subjected to silylation, hydroboration, Mitsunobu reaction, and *m*CPBA oxidation to afford sulfone **5** (Scheme 2). The requisite aldehyde **8** (the coupling partner of **5**) was obtained from the known diol **6**[18] by a sequence of benzylidene formation, DIBAH reduction,[19] and Swern



Scheme 2. a) TESCl, imidazole, DMF, RT, 83 % of desired diastereomer; b) $H_3B \cdot SMe_2$, THF, RT, then aqueous NaOH, H_2O_2, RT, 85 % ; c) Ph_3P, 2-mercaptobenzothiazole, DEAD, THF, 0 °C → RT, 87 %; d) *m*CPBA, CH_2Cl_2, RT, 90 %; e) TsOH, PhCHO, PhMe, reflux ($-H_2O$), 94 %; f) DIBAH, PhMe, 0 °C, 88 % for **7**; g) Swern oxidation; h) LiHMDS, THF, −78 °C, then **8**, RT, 80 %; i) I_2, Ag_2CO_3, Et_2O, RT, 92 %; j) Ph_3SnH, Et_3B, THF, 0 °C, 90 %; k) H_2, 10 % Pd/C, MeOH, RT, 99 %. TES = triethylsilyl, DMF = N,N-dimethylformamide, DEAD = diethyl azodicarboxylate, *m*CPBA = 3-chloroperoxybenzoic acid, Ts = toluenesulfonyl, DIBAH = diisobutylaluminum hydride, LiHMDS = lithium bis(trimethylsilyl)amide.

[*] Prof. Dr. S. H. Kang, J. W. Jeong, Yu. S. Hwang, S. B. Lee
Center for Molecular Design and Synthesis
Department of Chemistry, School of Molecular Science
Korea Advanced Institute of Science and Technology, Taejon 305-701 (Korea)
Fax: (+82) 42-869-2810
E-mail: shkang@kaist.ac.kr

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