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Development of silicon-tethered anionic reaction and its application to the synthesis of chiral A-ring moieties of Taxol™

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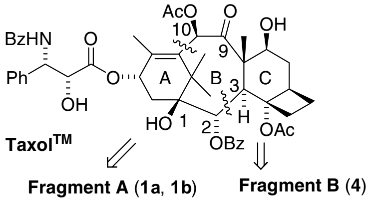
Abstract—Silicon-tethered intramolecular nucleophilic additions of a hydroxymethyl unit to ketones in β-hydroxyketones have been developed. The product obtained by this protocol was successfully converted to chiral A-ring moieties of Taxol™. Also developed was a promising silicon-tethered intramolecular α-alkylation reaction of the cyclic hydroxyketone.

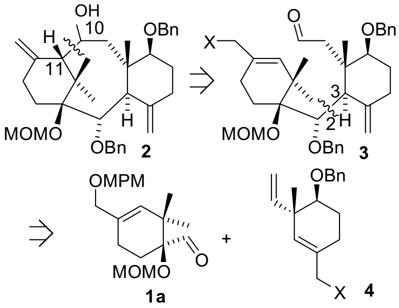
Construction of a stereogenic quaternary carbon is a challenging problem in natural product synthesis.[1] Among various stereogenic quaternary carbons, a chiral tertiary alcohol can be prepared by enantioselective addition of nucleophiles to ketones, and when the ketone is chiral, asymmetric induction is an efficient method. However, since the diastereoselective addition to chiral ketones predominantly occurs from the less hindered side, preferential addition from the more hindered side has rarely been reported.[2]

We have been studying the asymmetric total synthesis of Taxol™ via a convergent route,[3] and disconnection of Taxol™ in our plan results in the coupling of two fragments, Fragment A and B (Scheme 1). Since compounds **2** and **5** were surmised to convert to Taxol™, the B-ring of Taxol™ was envisioned to form between the C10 and C11 bonds by the intramolecular Nozaki–Hiyama reaction (Scheme 2) or the intramolecular Suzuki–Miyaura coupling reaction (Scheme 3). Hence, **3** and **6** must be prepared to examine these ring-closing reactions. Addition of Fragment B as the allylic organometallic reagent to aldehydes **1a** and **1b** would stereoselectively generate the C2 stereogenic center in a chelation-controlled manner; hence aldehydes **1a** and **1b** were needed for the synthesis of **3** and **6**.

In the synthesis of **1a** and **1b**, construction of the chiral tertiary alcohol was a problem. Although (*S*)-3-hydroxy-2,2-dimethylcyclohexanone **7** was readily prepared by baker's yeast,[4] a new method for the diastereoselective addition of a hydroxymethyl unit to the ketone in **7** had to be developed. We expected the silicon-tethered



Scheme 1.



Scheme 2.

Keywords: Silicon tethered; Intramolecular reaction; Taxol™; Carbanion; Nucleophilic addition; Alkylation.

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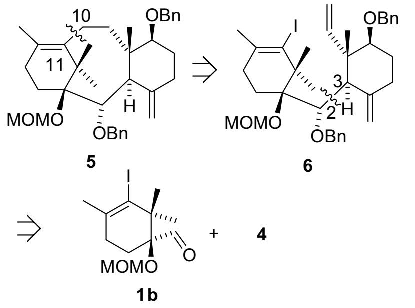
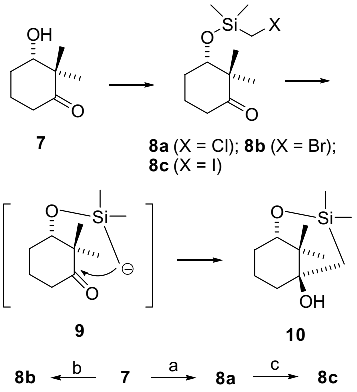


Scheme 3.



Scheme 4. Reagents and conditions: (a) $ClMe_2SiCH_2Cl$, imidazole, CH_2Cl_2, 1.5h, 96%; (b) $ClMe_2SiCH_2Br$, imidazole, CH_2Cl_2, 1.5h, 85%; (c) NaI, acetone, reflux, 10h, 98%.

intramolecular nucleophilic additions to chiral ketones would be a good solution to the stereoselective generation of the chiral tertiary alcohol. That is, as shown in Scheme 4, the anion **9** generated from **8a** to **c** by the halogen–lithium exchange reaction could react intramolecularly with the ketone in **9** to afford the tertiary alcohol **10**.

Since the silicon-tethered C–C bond-forming reaction is a useful method in terms of diastereo- and regioselectivity, a variety of the tethered reactions have been studied;[5,6] however, only a limited number of C–C bond-forming reactions of carbonyl compounds have been reported.[7] Although the allylation reactions[7a,c] and the SmI_2-mediated Barbier-type reactions[7b] have been reported as the reactions of carbonyl groups, the silicon-tethered nucleophilic addition has never been reported as far as we know. Nevertheless, we surmised the tethered reaction shown in Scheme 4 would proceed in practical yield because the halogen–lithium exchange reaction proceeds rapidly enough to permit the intramolecular C–C bond-forming reactions;[8] furthermore, the α-silyl carbanion is known to be stabilized by silicon.[9] Hence, we prepared the silyl ethers **8b** and **8c** from **7**, and investigated the silicon-tethered nucleophilic addition. The silyl ethers **8a** and **8b** were prepared by the reactions of **7** with $ClSiMe_2CH_2Cl$ and $ClSiMe_2CH_2Br$, respectively, and the iodide **8c** was easily prepared from **8a** by the halogen exchange reaction (Scheme 4, 98%).

Table 1. Preparation of **10** by the silicon-tethered nucleophilic addition

$$\mathbf{8} \xrightarrow{\text{conditions}} \mathbf{10}$$

Entry	8	Reagents (equiv)	Solvent	Temp (°C)	Time (min)	Yield (%)[a]
1	**8c**	*n*-BuLi (1.0)	THF	−78	5	61
2	**8c**	*n*-BuLi (1.0)	Et_2O	−78	30	43
3	**8c**	*n*-BuLi (1.0)	THF/Et_2O (4/1)	−78	15	55
4	**8c**	*n*-BuLi (1.0) HMPA (2.0)	THF	−78	15	33
5	**8b**	*t*-BuLi (1.95)	THF	−78	5	84
6	**8c**	*t*-BuLi (1.95)	THF	−78	5	86
7	**8c**	Li (10.0)	THF	0	60	40
8	**8c**	LiNp[b] (3.0)	THF	−78	30	—[c]
9	**8c**	LiDBB[d] (3.0)	THF	−78	10	38
10	**8b**	SmI_2 (2.2) HMPA (4.0)	THF	−78	15	50
11	**8c**	SmI_2 (3.0) HMPA (12.0)	THF	−78	5	18
12	**8c**	$SmBr_2$ (3.0)	THF	0	15	50

[a] Isolated yield.
[b] Lithium naphthalenide.
[c] Decomposed.
[d] Lithiunm 4,4′-di-*t*-butylbiphenyl.

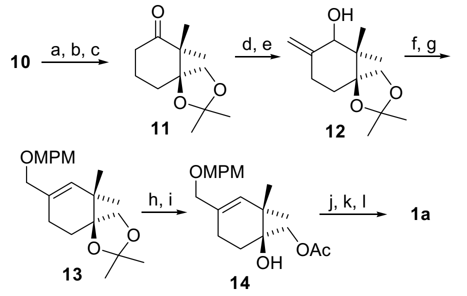
With **8b** and **8c** in hand, we first examined the halogen–lithium exchange reaction of **8c** with *n*-BuLi. As shown in Table 1, the reaction in THF proceeded in good yield, and the yield decreased in Et_2O (entries 1–3). Use of HMPA as the additive also decreased the yield (entry 4).

In these reactions (entries 1–4), a certain amount of unidentified side products formed. These by-products were surmised to arise from the side reactions, that is, addition reaction of *n*-BuLi to **8c** and reactions of the lithium enolate of **8c** generated by *n*-BuLi.[10] Next, *t*-BuLi was employed for this reaction because not only is its halogen–lithium exchange reaction faster than that of *n*-BuLi, but also no halogenated compounds remain, and the reaction of bulky *t*-BuLi with the ketone would be slow. As expected, the yield with *t*-BuLi increased to 86% (entry 6), and even the bromide **8b** afforded the desired product **10** in a comparable yield (84%, entry 5).

The halogen–lithium exchange reaction using Li powder also proceeded at 0 °C to afford **10**, but the yield was rather low (40%, entry 7). Lithium naphthalenide[11] afforded no desired product (entry 8), but LiDBB (lithiunm 4,4′-di-*t*-butylbiphenyl)[11] gave **10** in 38% yield (entry 9). In entries 7–9, a certain amount of unidentified by-products formed, and the yields did not exceed that of entry 6.

The reaction under Kim's conditions using SmI_2[7b] produced **10** in 50% yield with unidentified side products (entry 10). Use of 4 equiv of HMPA to SmI_2 (entry 11), or use of $SmBr_2$ (entry 12) did not improve the yield.[12]

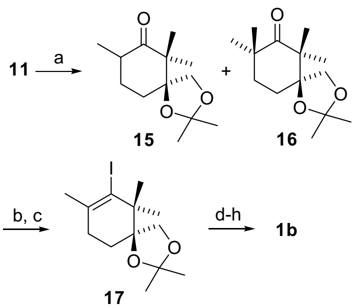
Since the desired product **10** was thus prepared in high yield, **10** was transformed to **1a**. As shown in Scheme 5, **10** was converted to the corresponding triol under



Scheme 5. Reagents and conditions: (a) 30% H_2O_2, $KHCO_3$, KF, THF/MeOH, 10h ; (b) cat. CSA, acetone, 1h, 96% (two steps); (c) Dess–Martin periodinane, CH_2Cl_2, 2h, 97%; (d) LDA, Eschenmoser's salt, THF, −78 to 0°C, 1h, then MeI, acetone, 10h, 64%; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 5min, 96%; (f) $SOCl_2$, Py, Et_2O, 3h, 84%; (g) MPMONa, TBAI, THF/DMF, 60°C, 5h, 92%; (h) cat. PTSA, MeOH/H_2O, 50°C, 3h, 98%; (i) Ac_2O, Py, DMAP, CH_2Cl_2, 20min, 91%; (j) MOMCl, DIPEA, NaI, CH_2Cl_2, 45h, 98%; (k) K_2CO_3, MeOH, 3h, 98% ; (l) Dess–Martin periodinane, CH_2Cl_2, 99%.

Tamao's conditions,[13] and the crude triol was treated with acetone under acidic condition to form the acetonide selectively (96%, two steps). Subsequent Dess–Martin oxidation gave ketone **11** (97%), followed by methylenation with Eschenmoser's salt (64%) and then the Luche reduction[14] to afford **12** in 96% yield. Alcohol **12** was converted to the chloride by $SOCl_2$ (84%), and then reacted with sodium *p*-methoxyphenylmethoxide to form **13** (92%). Deprotection of the acetonide (98%), acetylation (91%), protection of the tertiary alcohol by the MOM group (98%), removal of the acetyl group by K_2CO_3 in methanol (98%), and finally Dess–Martin oxidation afforded **1a** (99%).

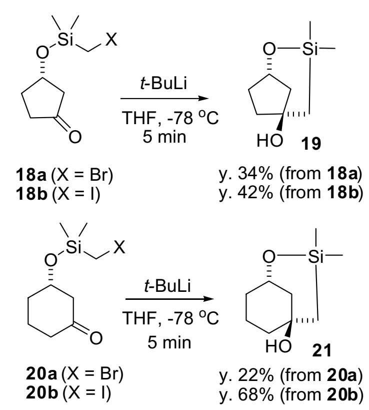
Another Taxol™ A-ring moiety **1b** was also prepared as shown in Scheme 6. The ketone **11** was methylated with MeI and NaH to afford an inseparable mixture of **15** and **16**. This mixture was reacted with hydrazine in a sealed tube, followed by the reaction with I_2 and DBU to generate iodide **17** (54%, three steps).[15] Treatment of **17** with a catalytic amount of *p*-TsOH in methanol removed the acetonide group (93%), and the following acetylation (85%), MOM protection of **17** (90%), deacetylation (96%), and Dess–Martin oxidation gave **1b** (quant.).[16]



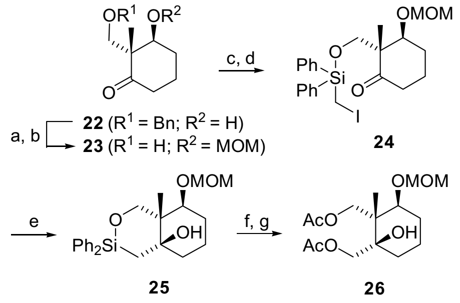
Scheme 6. Reagents and conditions: (a) MeI, NaH, THF/DMF, 19h; (b) hydrazine, TEA, EtOH, sealed tube, 130°C, 4d; (c) I_2, DBU, Et_2O, rt, 15min, then PhH, reflux, 3h, 54% (three steps); (d) cat. PTSA, MeOH/H_2O, 13h, 93%; (e) Ac_2O, Py, DMAP, CH_2Cl_2, 20min, 85%; (f) MOMCl, DIPEA, NaI, CH_2Cl_2, 45h, 90%; (g) K_2CO_3, MeOH, 3h, 96%; (h) Dess–Martin periodinane, CH_2Cl_2, quant.

This silicon-tethered reaction of some simple cyclic hydroxyketones was examined, and it was found that only β-hydroxyketones gave the desired products. As shown in Scheme 7, simple β-hydroxyketones having no substituent at their α-position gave the desired products.[10] Compared with the iodides **18b** (42%) and **20b** (68%), yields by bromides **18a** (34%) and **20a** (22%) were low. These results could be explained by the different rate of the halogen–lithium exchange reaction between iodide and bromide. These reactions in Scheme 7 also suggest that the high yield of **10** (Table 1, entry 6) arose from the structure of ketone **8c** having dimethyl substituents at the α-position of the ketone. The dimethyl substituents are so bulky that such side reactions as addition of *t*-BuLi to the ketone and reactions of the lithium enolate formed by *t*-BuLi would be suppressed.

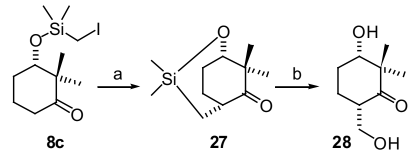
We applied this silicon-tethered protocol to α-hydroxymethylketone **23**, too (Scheme 8). Previously reported **22**[1b] was converted to **23** by MOM protection of the secondary alcohol and subsequent hydrogenation (95%, two steps). The chloromethyldimethylsilyl ether[17] of



Scheme 7.



Scheme 8. Reagents and conditions: (a) MOMCl, DIPEA, NaI, CH_2Cl_2, reflux, 2d, 95%; (b) H_2, Pd/C, MeOH, 10h, quant. (c) $ClPh_2SiCH_2Cl$, imidazole, CH_2Cl_2, 1h, 74%; (d) NaI, acetone, reflux, 10h, 96%; (e) *t*-BuLi, −78°C, 5min, 64% ; (f) 30% H_2O_2, $KHCO_3$, KF, THF/MeOH, 10h; (g) Ac_2O, DMAP, CH_2Cl_2, 10h, quant. (two steps).



Scheme 9. (a) LDA, THF, −78 to 0 °C, 1 h, 80%; (b) 30% H_2O_2, $KHCO_3$, KF, THF/MeOH, rt, 3.5 h.

the primary alcohol **23** was found to be too unstable to purify by silica gel chromatography; hence, a more stable chloromethyldiphenylsilyl ether was prepared (74%), and the silyl ether was converted to iodide **24** (96%). Reaction of **24** with *t*-BuLi afforded **25** in 64% yield.[10] This rather low yield could arise from the bulky phenyl groups of the silyl ether; that is, the large phenyl groups was surmised to slow down not only the halogen–lithium exchange reaction but also the addition reaction, resulting in the decrease of the yield. Tamao oxidation of **25** proceeded smoothly, and subsequent acetylation afforded **26** quantitatively (two steps).[18]

It should be noted that we have also found another silicon-tethered anionic reaction of **8c** (Scheme 9). Thus, treatment of **8c** with LDA instead of *t*-BuLi caused intramolecular alkylation to afford **27** in 80% yield,[10] and the following Tamao oxidation gave **28** (71%). Since the intramolecular reaction is fast and the C–Si bond is rather long, this reaction would not suffer from the steric hinderance around the silicon atom, giving the product in high yield. This tethered reaction is expected to be a general method for the regio- and stereoselective installation of a hydroxymethyl group at the α-position of ketones in cyclic as well as acyclic hydroxyketones; hence, its scope and limitations are now under investigation.

In summary, we have developed intramolecular silicon-tethered nucleophilic additions of a hydroxymethyl unit to ketones in cyclic β-hydroxyketones, and the products obtained by this protocol were successfully converted to chiral A-ring moieties of Taxol™. Also found was the promising diastereoselective silicon-tethered α-alkylation of the cyclic hydroxyketone. To our knowledge, these silicon-tethered anionic reactions have not been reported; therefore, now our attention is focused on their further development and applications including the studies in an acyclic system. The further development will be reported in due course.

Acknowledgements

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References and notes

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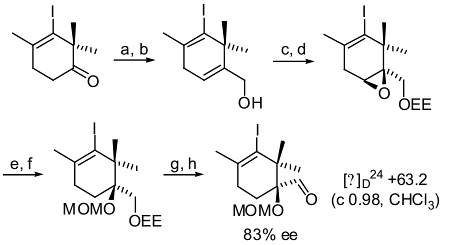
16. Absolute structure of **1b** ($[\alpha]_D^{27}$ −76.2 (*c* 0.98, $CHCl_3$)) was elucidated by the reaction mechanism and comparison of its $[\alpha]_D$ value with that of the same compound as prepared below.



(a) Me_3SI, NaH, DMSO/THF, 19 h, 85%; (b) 2,2,6,6-tetramethylpiperidine, *n*-BuLi, Et_2AlCl, toluene, 0 °C, 6 h, 67%; (c)TBHP, L-(+)-DET, Ti(O–*i*-Pr)$_4$, MS 4 Å, CH_2Cl_2, −20 °C, 1 h, 90%, 83% ee; (d) EVE, cat. PPTS, CH_2Cl_2, 20 min, 96%; (e) $LiAlH_4$, Et_2O, 20 min, 91%; (f) MOMCl, DIPEA, NaI, CH_2Cl_2, 15 h, quant.; (g) cat. PPTS, MeOH, 1.5 h, 80%; (h) Dess–Martin periodinane, CH_2Cl_2, 1 h, 96%.

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