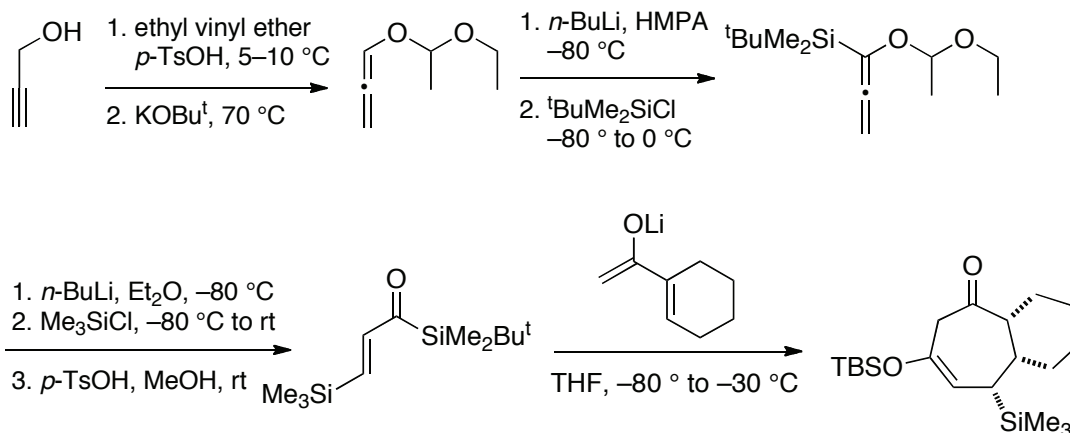


Discussion Addendum for:
[3 + 4] Annulation Using a [β -(Trimethylsilyl) acryloyl]silane and
the Lithium Enolate of an α,β -Unsaturated Methyl Ketone:
(1*R*,6*S*,7*S*)-4-(*tert*-Butyldimethylsiloxy)-6-
(trimethylsilyl)bicyclo [5.4.0]undec-4-en-2-one



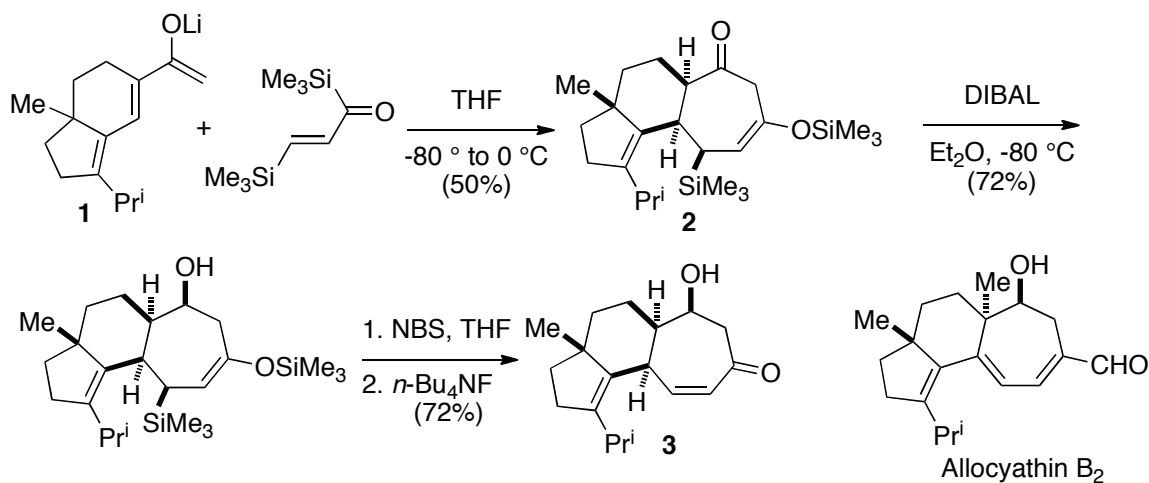
Prepared by Kei Takeda* and Michiko Sasaki.¹

Original article: Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E.; *Org. Synth.* **1999**, *76*, 199–213.

Brook rearrangement-mediated [3 + 4] annulation has evolved as a unique methodology for the construction of not only seven-membered carbocycles but also eight-membered carbo- and oxygen-heterocycles and has been applied to the synthesis of natural products after clarification² of the precise reaction mechanism accounting for the stereospecificity.

Synthesis of the Tricyclic Skeleton of Allocyathin B₂

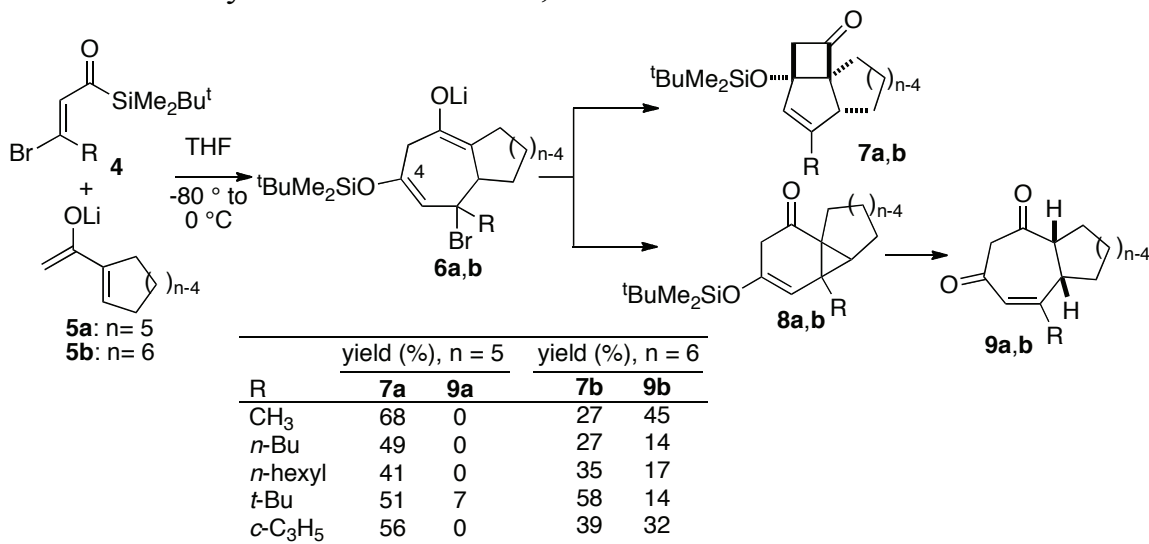
The synthetic utility of annulation was first demonstrated by the synthesis of the unusual 5-6-7 tricyclic ring skeleton of allocyathin B₂, a compound that has been shown to have potent nerve growth factor synthesis-stimulating activity and to be a κ opioid receptor agonist (Scheme 1). The key [3 + 4] annulation proceeded smoothly even with a relatively complex four-carbon unit **1** to afford **2** as a single diastereomer in 50% yield, which was transformed to **3**.³



Scheme 1 Synthesis of the tricyclic skeleton of allocyathin B₂.

Construction of a Tricyclo[5.3.0.0^{1,4}]decenone Ring System

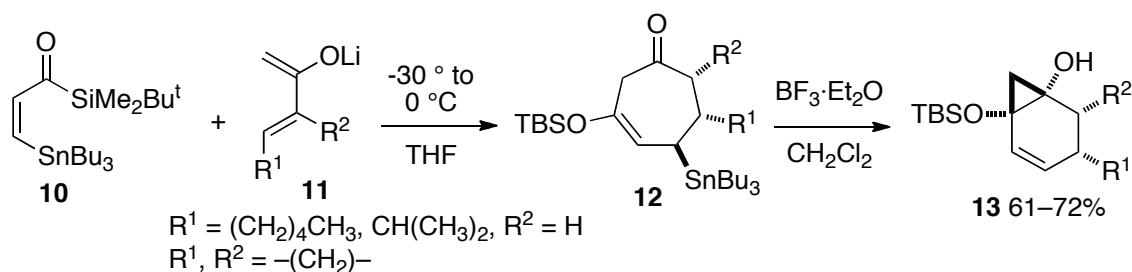
The use of acryloylsilanes **4** with a leaving group such as a halogen atom at the β -position as a three-carbon unit in the [3 + 4] annulation afforded tricyclic ketone derivatives **7a,b** in yields dependent upon the β -substituent of **4**, in addition to the [3 + 4] annulation–debromosilylation products **9a,b** (Scheme 2).⁴ Small structural changes in the four-carbon unit significantly affect the product distribution. Thus, whereas cyclopentyl methyl ketone enolate gave **7a** in almost all cases, **9b** was formed as a byproduct in the case of the corresponding cyclohexyl derivative. Mechanistic studies including low-temperature quenching experiments suggested that **7a,b** can be formed via an S_N'-like intramolecular attack of the enolate at the C-4 position in the intermediate **6a,b**, and **9a,b** can be formed via tricyclic intermediate **8a,b**.



Scheme 2 Construction of a tricyclo[5.3.0.0^{1,4}]decenone ring system.

BF₃·Et₂O-Mediated Intramolecular Allylstannane-Ketone Cyclizations

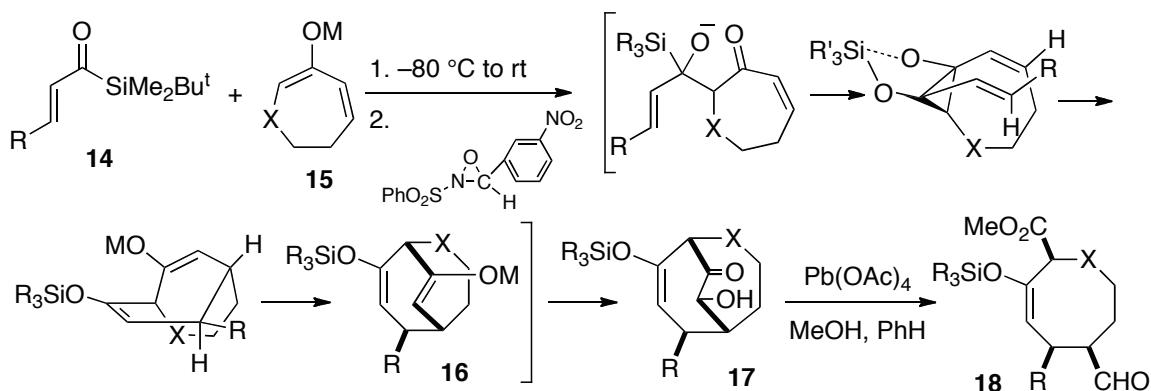
[3 + 4] annulation using a combination of (Z)-(β -(tributylstannanyl)acryloyl)silanes **10** and alkenyl methyl ketone enolate **11** proceeded in the same manner to give cycloheptenone derivative **12**, which upon treatment with BF₃·Et₂O, afforded bicyclo[4.1.0]heptenols **13**, an intramolecular addition product of the allylstannane system to the carbonyl group (Scheme 3).⁵



Scheme 3 BF₃·Et₂O-Mediated intramolecular allylstannane-ketone cyclizations.

Stereoselective Construction of Eight-Membered Carbocycles and Oxygen-Heterocycles

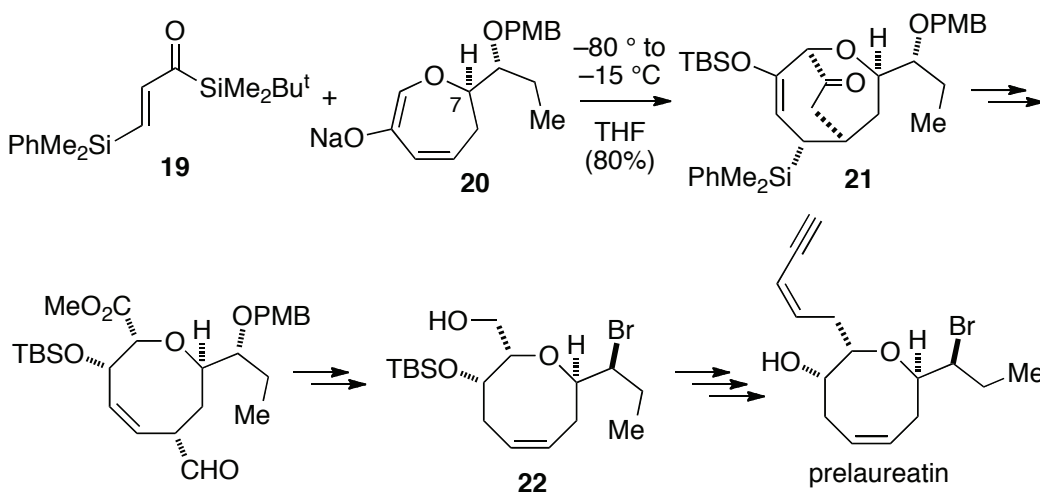
The use of the enolate **15** (X = CH₂) derived from 2-cycloheptenone as the four-carbon unit in [3 + 4] annulation instead of the enolates of alkenyl methyl ketones produced bicyclo[3.3.2]decenone derivatives **16**. The two-atom internal tether in these products could be oxidatively cleaved after conversion to α -hydroxy ketone **17** to give the *cis*-3,4,8-trisubstituted cyclooctenone enol silyl ethers **18** stereoselectively (Scheme 4).⁶ This methodology has also been successfully applied to the construction of oxygen eight-membered heterocycles using enolates of 6-oxacyclohept-2-en-1-one **15** (X = O), affording eight-membered oxygen heterocycles **18** (X = O) possessing functionality that can easily be manipulated to generate other functionalized eight-membered ring products.⁷



Scheme 4 Stereoselective construction of eight-membered carbocycles and oxygen-heterocycles.

Formal Total Syntheses of (+)-Prelaureatin and (+)-Laurallene

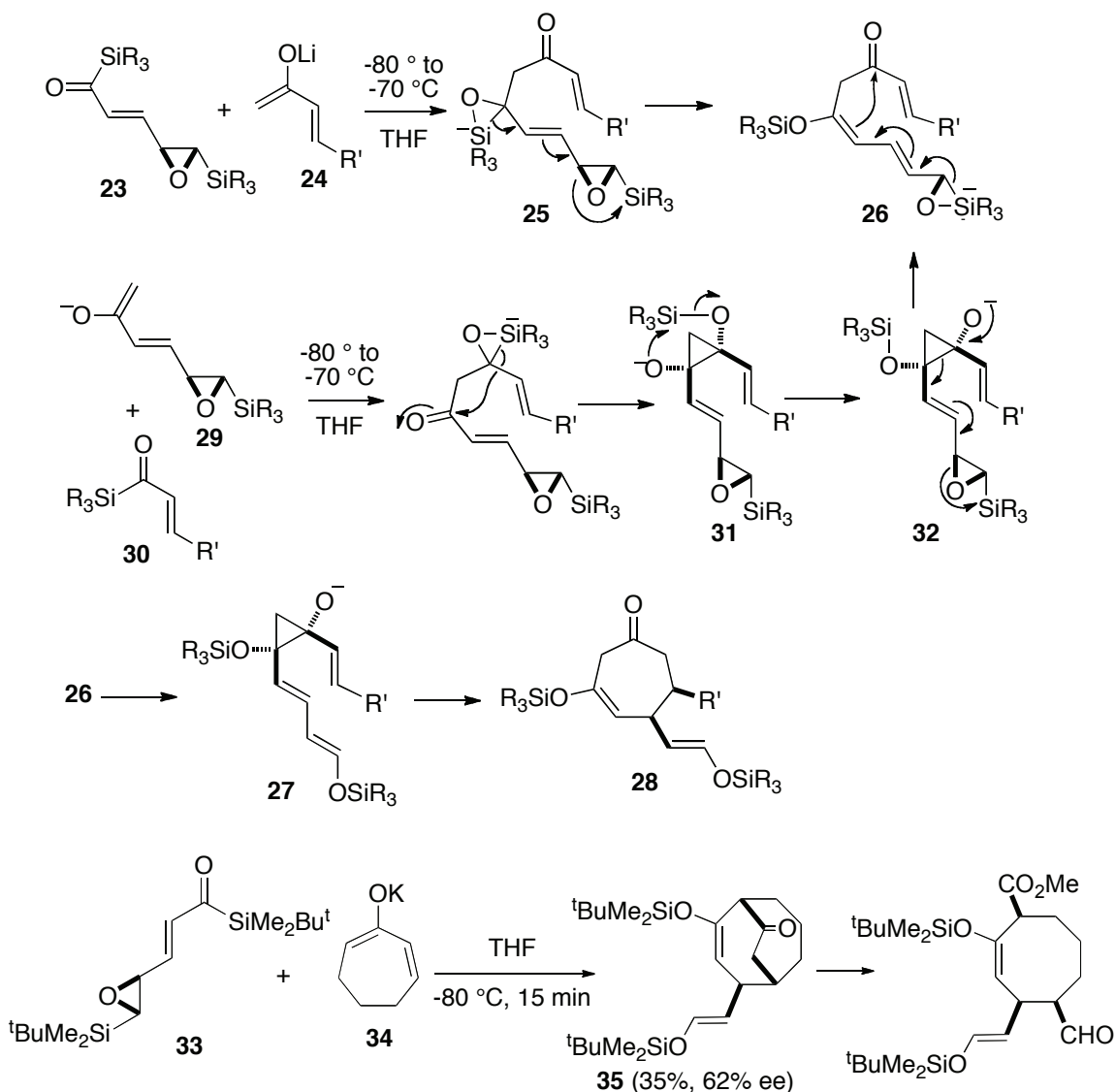
The versatility of the annulation has been highlighted through the formal total synthesis of (+)-prelaureatin, a biogenetic precursor of several members of the laurenan structural subclass (Scheme 5).⁸ The annulation of **19** and sodium enolate **20** proceeded in a highly diastereoselective manner to afford exclusively **21** in 80% yield. The observed excellent selectivity could be explained in terms of the approach of the acryloylsilane from the same side as the C-7 substituent in **20** that is sterically less hindered because of pseudo equatorial disposition of the substituent on the seven-membered ring. The bicyclic derivative **21** was transformed into Crimmins' intermediate **22**⁹ after oxidative cleavage of the two-carbon tether.



Scheme 5 Formal total syntheses of (+)-prelaureatin.

Stereocontrolled Construction of Seven- and Eight-Membered Carbocycles Using a Combination of Brook Rearrangement-Mediated [3 + 4] Annulation and Epoxysilane Rearrangement

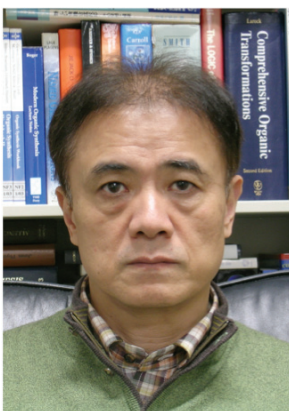
The [3 + 4] annulation has also been expanded to include the construction of densely functionalized seven- and eight-membered carbocycles by combining it with an epoxysilane rearrangement,¹⁰ which features a further extension of a stereocontrolled anion relay.¹¹ Reactions of δ -silyl- γ,δ -epoxy- α,β -unsaturated acylsilane **23** with alkenyl methyl ketone enolate **24** afforded highly functionalized cycloheptenone derivative **28** via a tandem process that involves Brook rearrangement followed by the resulting carbanion-induced ring-opening of the epoxide (**25** \rightarrow **26**), a second Brook rearrangement, the formation of divinylcyclopropanediolate derivative **27** via internal carbonyl attack by the resulting carbanion, and an anionic oxy-Cope rearrangement (Scheme 6). The reactions using an alternative combination of three and four carbon units (**29** + **30**), in which an epoxysilane moiety was incorporated in the four-carbon unit, also give satisfactory results, via 1,4-*O*-to-*O* silyl migration (**31** \rightarrow **32**). Use of enantioenriched acylsilane **33** and 2-cycloheptenone enolate **34** gave a moderate level (62% ee) of asymmetric induction in the bicyclic ketone **35**.



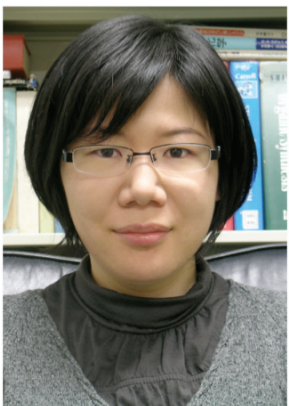
Scheme 6 Stereocontrolled construction of seven- and eight-membered carbocycles using a combination of Brook rearrangement-mediated [3 + 4] annulation and epoxysilane rearrangement.

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