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

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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[5.3.0.0₁⁴]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)." 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[5.3.0.0₁⁴]decenone ring system.
BF$_3$·Et$_2$O-Mediated Intramolecular Allylstannane-Ketone Cyclizations

[3 + 4] annulation using a combination of (Z)-(β-(tributylstannnyl)acryloyl)silanes 10 and alkenyl methyl ketone enolate 11 proceeded in the same manner to give cycloheptenone derivative 12, which upon treatment with BF$_3$·Et$_2$O, afforded bicyclo[4.1.0]heptenols 13, an intramolecular addition product of the allylstannane system to the carbonyl group (Scheme 3).

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\begin{align*}
\text{BF}_3 \cdot \text{Et}_2\text{O-Mediated Intramolecular Allylstannane-ketone Cyclizations}\n\end{align*}
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\begin{align*}
\text{Scheme 3 BF}_3 \cdot \text{Et}_2\text{O-Mediated intramolecular allylstannane-ketone cyclizations.}
\end{align*}
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Stereoselective Construction of Eight-Membered Carbocycles and Oxygen-Heterocycles

The use of the enolate 15 (X = CH$_2$) 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]decanone 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). 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.
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). 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 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,\textsuperscript{10} which features a further extension of a stereocontrolled anion relay.\textsuperscript{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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