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Synthesis of the Tricyclic Skeleton of Cyathins Using Brook Rearrangement-Mediated [3 + 4] Annulation

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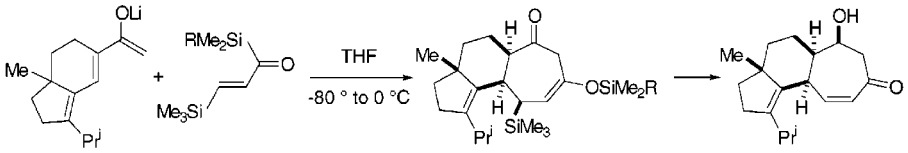
ABSTRACT



The tricyclic core of cyathins has been synthesized using a Brook rearrangement-mediated [3 + 4] annulation that we previously developed.

Cyathins,[1] isolated from bird nest fungi, and other members[2−4] of this family, including erinacins (**1**, **2**),[5] which are collectively called cyathins, continue to be of interest because of their unusual 5−6−7 tricyclic ring system coupled with their important biological activities (Figure 1). Recently, erinacine E (**2**), one of the complex members of the cyathin family, was shown to have potent nerve growth factor (NGF) synthesis-stimulating activity[5] and to be a *k* opioid receptor agonist.[6] Synthetic efforts have been described by several groups,[7] and two total syntheses of allocyathin B_2 (**3**) have been reported.[8,9]

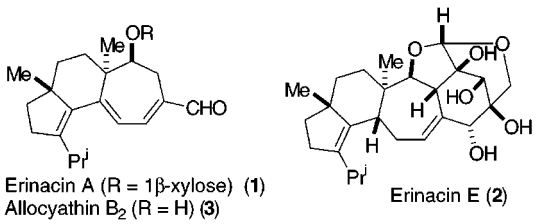


Figure 1.

We have recently developed a Brook rearrangement-mediated [3 + 4] annulation for the stereoselective synthesis

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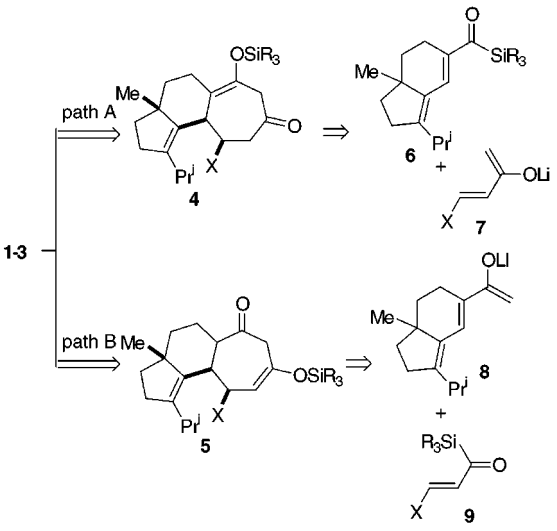
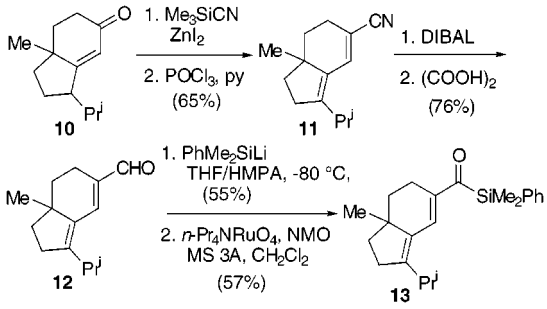
of seven-membered carbocycles by the reaction of α,β-unsaturated acylsilanes with the lithium enolates of alkenyl methyl ketones.[10] To demonstrate the effectiveness of the methodology for the synthesis of functionalized cycloheptenones, we decided to apply this method to the synthesis of the tricyclic skeleton of the cyathin ring system. As a target we selected the tricyclic compounds **4** and **5** bearing the appropriate functionalities necessary for their conversion to natural products, and we addressed two retrosynthetic pathways defined as A and B that use the 5−6 ring systems **6** and **8** as three-carbon and four-carbon units in the key [3 + 4] annulation, respectively (Scheme 1).

Scheme 1



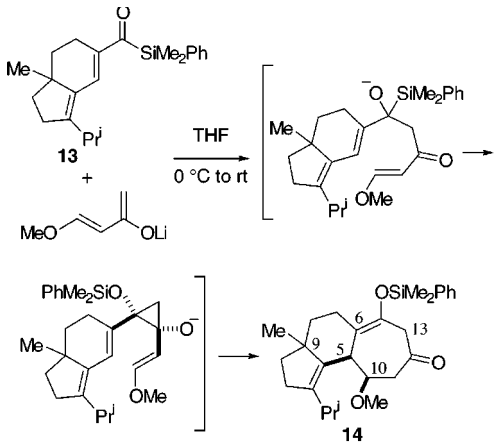
Path A. Acylsilane **13** was prepared by a four-step sequence starting with known enone **10**[11] (Scheme 2). When **10** was reacted with Me_3SiCN in the presence of ZnI_2 followed by elimination of silanol with $POCl_3$,[12] unsaturated nitrile **11** was obtained in 65% yield. Reduction of **11** with DIBAL followed by an acid quench afforded aldehyde **12** in 76% yield. Conversion of **12** into acylsilane **13** was carried out by reaction with dimethyl(phenyl)silyllithium[13] followed by oxidation of the generated α-silyl alcohol. Oxidation with DMSO/$(COCl)_2$, PCC, and MnO_2 resulted in a low yield of **14** with the concomitant formation of **12**. The best result was obtained when 1 equiv of *n*-Pr_4NRuO_4 (TPAP)[14] was used to provide **13** in 57% yield along with 14% of **12**. The use of a catalytic amount of TPAP and/or a longer reaction time resulted in increased formation of **12**.

Scheme 2



As a four-carbon unit in the [3 + 4] annulation, we initially examined several vinyl methyl ketone derivatives **7** which have a leaving group such as a phenylthio or phenylsulfonyl group at the β-position, anticipating that facile elimination of LiX would occur to lead to an enone derivative in the annulation product. Not unexpectedly, significant decomposition of the substrate occurred during the formation of the enolate. Next, we turned to the use of the lithium enolate of 4-methoxy-3-buten-2-one. When the lithium enolate was added to a THF solution of **13** at 0 °C and the solution was then warmed to room temperature, tricyclic ketone **14** was obtained as an epimeric mixture at C(9) in 47% yield along with recovery of **13** (14%) (Scheme 3).

Scheme 3



The structures were assigned by analogy with structurally related compounds,[10c] and the 5,10-cis stereochemistry of

(7) (a) Ayer, W. A.; Ward, D. E.; Browne, L. M.; Delbaere, L. T. J.; Hoyano, Y. *Can. J. Chem.* **1981**, *59*, 2665−2672. (b) Ward, D. E. *Can. J. Chem.* **1987**, *65*, 2380−2384. (c) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885−899. (c) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553−3560. (d) Wright, D. L.; Whitehead, C. R.; Hampton, E. *Org. Lett.* **1999**, *1*, 1535−1538. (e) Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407−1410.

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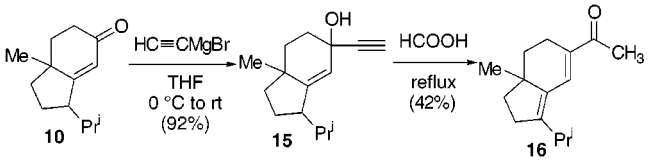
14 was based on $J_{5,10}$ (ca. 0 Hz for both isomers) and NOESY experiments.

Path B. Bicyclic methyl ketone **16** was prepared from **10** via a two-step sequence: (1) addition of ethynylmagnesium bromide and (2) Rupe rearrangement[15] (Scheme 4).

Scheme 4



The key [3 + 4] annulation proceeded smoothly when **16** was added to a solution of acryloylsilane **17a** at −80 °C and allowed to warm to 0 °C to afford **20a** as a single diastereomer in 60% yield (Scheme 5). The 6,5,10-cis stereochemistry was assigned on the basis of $J_{5,6}$ = 7.3 Hz, $J_{5,10}$ = 6.6 Hz, and a NOESY correlation between H-6 and H-10. The relative stereochemisty of Me-15 was tentatively assigned as trans to H-5 and H-6 since no NOESY correlation between the 9-Me and H-5 was observed. The observed stereoselectivity can be rationalized by a concerted pathway of the anionic oxy-Cope rearrangement of the *cis*-1,2-divinylcyclopropanediolate intermediate **19** which was stereoselectively derived from 1,2-adduct **18** by Brook rearrangement, followed by internal trapping of the generated carbanion by the ketone carbonyl.[10c] The stereoselectivity, which is different from that in the reaction of **13**, remains unclear at the present time. Although the trimethylsilyl group at C-10 could be removed by exposure to NBS followed by *n*-Bu_4NF to give an enone derivative,[10c] the reaction turned out to produce a low yield and to have poor reproducibility. We then decided to use trimethylsilyl derivative **17b**, anticipating a more facile conversion into the enone derivative. The [3 + 4] annulation using **17b** proceeded in a similar manner to give **20b** as a single isomer in 50% yield. Oxidative desilylation of **20b** was realized after DIBAL

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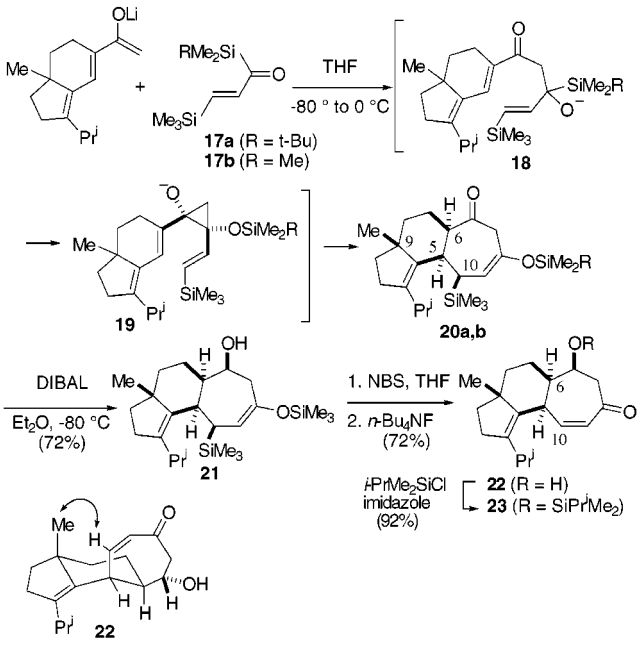
Scheme 5



reduction to alcohol **21** to afford enone **22** in 79% yield. The configuration of 9-Me was assigned on the basis of a NOESY correlation between 9-Me and H-10 and a comparison of ^{1}H NMR of its *O*-silylated derivative **23** with that of 6-methyl derivative of **23**, which is known.[8b]

In summary, we have demonstrated the synthetic utility of our Brook rearrangement-mediated [3 + 4] annulation by application to the synthesis of the tricyclic ring system of cyathins.

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Supporting Information Available: Full experimental details and characterization data for all new compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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