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The First Example of Nazarov Reactions of Vinyl Cumulenyl Ketones

Eric Leclerc and Marcus A. Tius*

Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822, and The Cancer Research Center of Hawaii, 1236 Lauhala Street, Honolulu, Hawaii 96813

tius@gold.chem.hawaii.ed

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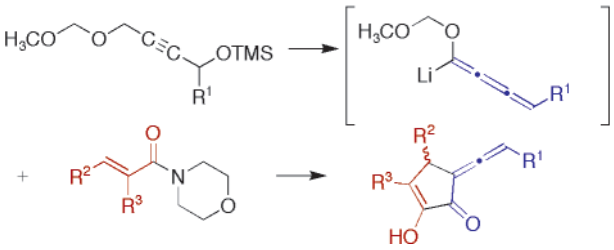
ABSTRACT



α-Lithio cumulenyl ethers can be prepared in situ and converted to α-allenyl cyclopentenones. Isomerization of the product of one such reaction has led to a furanyl cyclopentenone, the core structure of nakadomarin A.

Our research group has had a long standing interest in applying the cyclopentannelation methodology that we have developed to natural products total synthesis.[1] One of our targets is the marine alkaloid nakadomarin A, which was isolated in 1997 by Kobayashi and co-workers from an Okinawan *Amphimedon* sp. sponge.[2] Nakadomarin A has a fairly complicated bridged system of six heterocyclic and carbocyclic rings, and is without precedent, although it appears to be biosynthetically related to the manzamines[3] and ircinals.[4] It is cytotoxic in the L1210 assay with an IC_{50} of 1.3 μg/mL and shows inhibitory activity against cyclin-dependent kinase 4 (IC_{50} = 9.9 μg/mL). Some antifungal activity against *Trichophyton mentagrophytes* and some antibacterial activity against Gram-positive *Corynebacterium xerosis* was also determined. For a chemical structure of this complexity there will obviously be a large number of possible retrosynthetic disconnections. We focused on the central cyclopentene ring (highlighted in the structure of nakadomarin A in Figure 1) and reasoned that furanyl cyclopentanone **1** might serve as an advanced intermediate in a nakadomarin A synthesis. Since a number of methods are

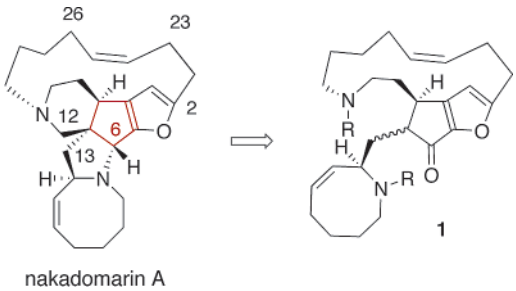


Figure 1. Nakadomarin A retrosynthesis.

* Address correspondence to this author at the University of Hawaii.

(1) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem Soc.* **2002**, *124*, 10091 and references cited. therein

(2) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236. Several approaches to the nakadomarin skeleton have been described: (a) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (b) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2001**, *7*, 4811. (c) Nagata, T.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, *42*, 8345. (d) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

(3) (a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. (b) Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Sasaki, T.; Mikami, Y. *J. Nat. Prod.* **1994**, *57*, 1737.

(4) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.

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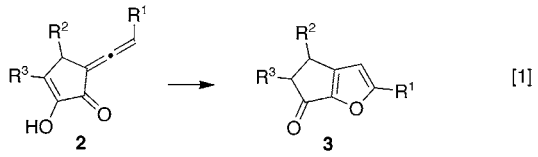
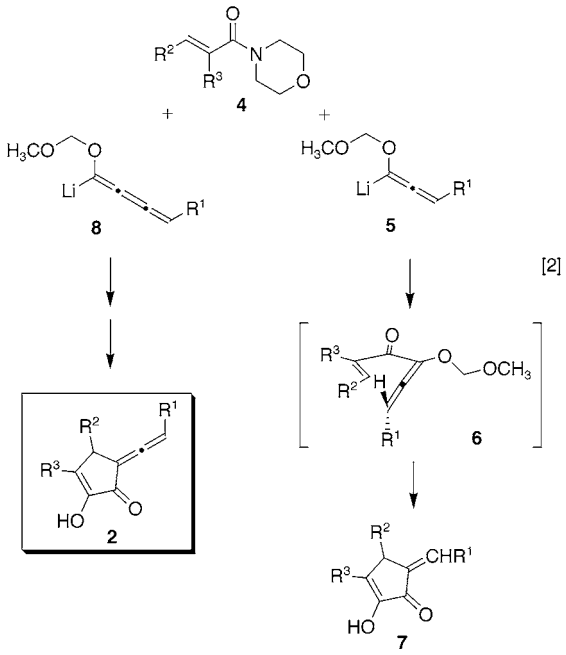
known to isomerize α-allenyl ketones to furans,[5] we further reasoned that **1** might be accessible through an isomerization of the type that is summarized in eq 1. Such a process would



[1]

require us to solve two problems. First, we would have to demonstrate a synthesis of α-allenyl cyclopentenones such as **2**, and second, we would have to develop conditions for the isomerization step leading to **3**. In this Letter we report solutions to each of these problems.

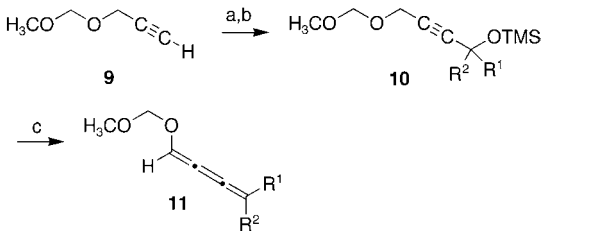
The preparation of α-allenyl cyclopentenones such as **2** appears to be a straightforward extension of the cationic cyclopentannelation, a process that we have developed and used successfully in the context of several total syntheses (eq 2).[6] In brief, addition of lithioallene **5** to morpholino



amide **4** produces cyclopentenone **7** following acidic workup, presumably via intermediate allenyl ketone **6**, that undergoes spontaneous cyclization. To adapt this method to the synthesis of **2**, all that needs to be done is to "extend" **5** to include a third cumulated π bond. We postulated that the combination of morpholino amide **4** with butatrienyl anion **8** would lead to **2** through a similar series of steps. The fundamental difficulty in putting this into practice is related to the lability of the cumulenes. Allenyl ethers are generally air-stable, but somewhat sensitive to acid. They can be purified and isolated by flash column chromatography on silica gel, provided one or two percent of triethylamine is added to the mobile phase so as to inhibit hydrolysis of the enol ether function. By contrast, we were unable to purify the butatrienyl ethers by chromatography, as they underwent oxidative degradation on the column.

We chose Brandsma and co-workers' simple and convenient method for preparing the butatrienyl ethers (Scheme 1).[7] (Methoxy)methoxypropargyl ether **9** was first converted

Scheme 1[a]



[a] Reaction conditions: (a) *n*-BuLi, THF, −78 °C; add R^1COR^2; (b) TMSCl, Et_2O, Et_3N (+ cat. DBU when R^1 = *t*-Bu, R^2 = H or $R^1 = R^2$ = Et, or $R^1 = R^2 = -(CH_2)_{11}-$); (c) 2.3−2.5 equiv of *n*-BuLi, THF, −40 °C, 30 min; aq NH_4Cl workup.

to the lithioacetylide, then quenched with a ketone or an aldehyde. Silylation of the free hydroxyl group of the product led to silyl ethers **10**. Exposure to a small excess of *n*-butyllithium in THF at −40 °C led to the desired cumulenes **11** through initial selective deprotonation of the propargylic methylene group α to the methoxymethyl group, followed by elimination of silyloxide. It is necessary to use at least 2 equiv of *n*-butyllithium because deprotonation of **11** is faster than deprotonation of **10**. All cumulenes in which R^2 = H were isolated as 3−1.5/1 mixtures of geometrical isomers. Stereochemistry of the cumulene ethers has been assigned by ^{1}H NMR, by following Brandsma's reasoning.[7c] Brandsma mentions that the *trans* isomer of ethyl or *tert*-butyl cumulenyl ethers is the favored product, and he assigned stereochemistry based on the fact that "Of the isomers, *cis* presumably has a somewhat smaller $J_{1,4}$ than *trans*." In the examples Brandsma reported, $\Delta J_{1,4}$ for the two isomers was never greater than 0.9 Hz; however, of the three cumulenyl ethers that we have described in no case was $\Delta J_{1,4}$ greater than 0.1 Hz. This suggests that any assignment of cumulene stereochemistry be considered tentative at this time. The crude cumulenes were characterized by ^{1}H NMR and IR spectroscopy. Diagnostic absorbances in the IR for the cumulene and the enol ether functions occurred at 2055 and

(5) For example, see: Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450.

(6) (a) Tius, M. A.; Astrab, D. P.; Fauq, A. H.; Ousset, J.-B.; Trehan, S. *J. Am. Chem. Soc.* **1986**, *108*, 3438. (b) Tius, M. A.; Trehan, S. *J. Org. Chem.* **1989**, *54*, 46. (c) Tius, M. A.; Astrab, D. P. *Tetrahedron Lett.* **1989**, *30*, 2333. (d) Tius, M. A.; Drake, D. J. *Tetrahedron* **1996**, *52*, 14651. (e) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509. (f) Nakazaki, A.; Sharma, U.; Tius, M. A. *Org. Lett.* **2002**, *4*, 3363.

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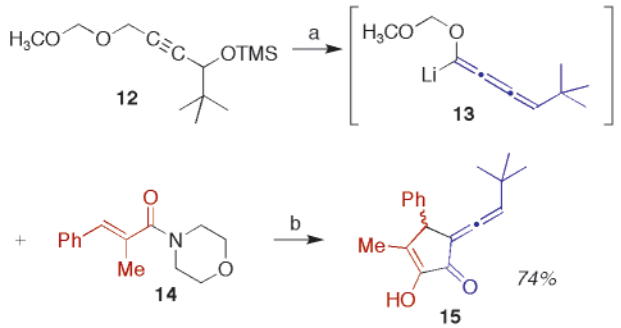
1640 cm^{-1}, respectively. The proton at C1 appeared near 6.50 ppm in the ^1H NMR spectrum ($CDCl_3$). The terminally disubstituted cumulene in which $R^1 = R^2 = Et$ was also characterized by ^{13}C NMR (157.6, 142.3, 119.6, and 116.9 ppm for the sp- sp^2-hybridized carbon atoms).

For the cyclopentannelation reaction it was not necessary to isolate the cumulenyl ethers. This represents a major simplification of the procedure. For example, treatment of ether **12** with slightly more than 2 equiv of *n*-butyllithium at −40 °C in carefully degassed THF led to lithio cumulene **13**. Addition of a solution of 0.75 equiv of morpholino amide **14**, relative to **12**, followed by warming to −40 °C and quenching into aq KH_2PO_4 led to allenyl cyclopentenone **15**

Scheme 2[a]



[a] Reaction conditions: (a) *n*-BuLi, −40 °C, THF; (b) add **14** at −78 °C; 1 h; −40 °C, 30 min; add to aq KH_2PO_4.

in 74% yield based on **14**, following purification by flash column chromatography. Because both the allene and the sp^3-hybridized ring carbon atom in the product are stereogenic, **15** was isolated as a ca. 4/1 mixture of diastereoisomers.[8] There were some differences between cyclopentannelations leading to allenyl cyclopentenones **2** and those leading to cyclopentenones **7**. When R^2 was an alkyl group, it was necessary to induce cyclization with 1 M HCl. Whereas cyclization to **7** invariably took place upon exposure to phosphate during workup, this was only true for cyclopentenones **2** in which R^2 was aromatic. Figure 2 summarizes our results.

Cyclopentenones **15**−**22** were isolated as mixtures of diastereomers (dr ca. 2/1−4/1) that were inseparable by flash column chromatography. The terminally disubstituted cumulenes and the cumulene substituted by a single *tert*-butyl group were a bit less labile than the monosubstituted ones, and were more easily manipulated. The reason for the low yield for brominated cyclopentenone **17** is not clear to us. In the case of the allene cyclization, bromine is well tolerated at that position, and leads to no diminution of the yield. It is likely that the yields in Figure 2 are not fully optimized. Although some of these are modest, it should be pointed out that these are overall yields from the respective morpholino amides for the two steps, addition and cyclization. The synthesis of **15** has been scaled up to 3.4 mmol of amide with only a small erosion of the yield (>600 mg of **15**; 66% yield). This version of the cyclopentannelation reaction generates a great deal of molecular complexity in a single operation.

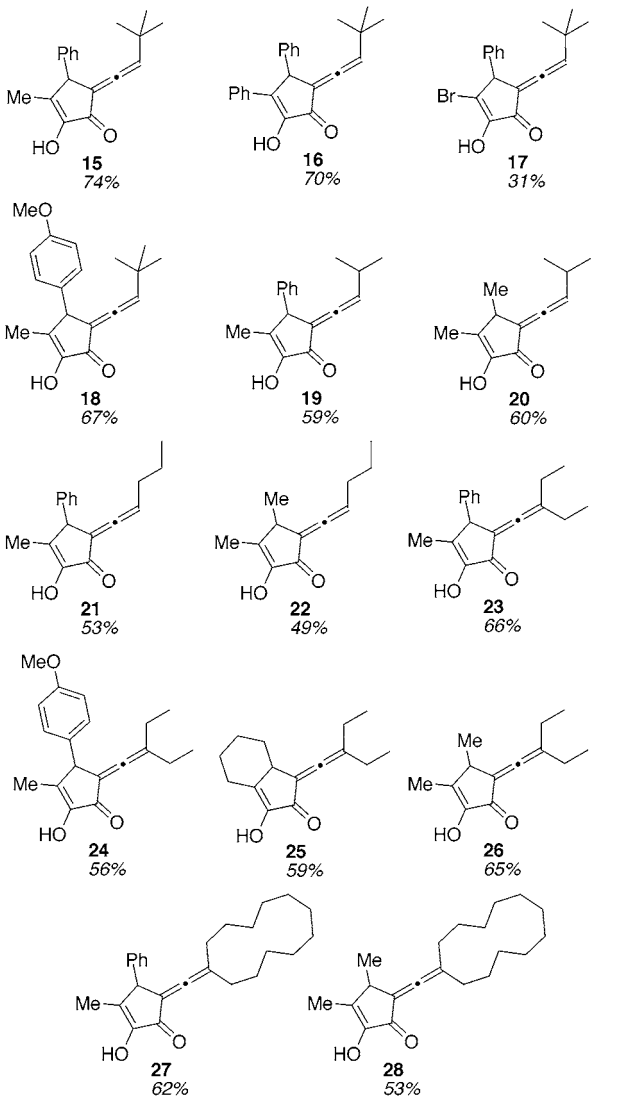


Figure 2. α-Allenyl cyclopentenones. Yields were calculated from the corresponding amides.

The first goal for this project having been realized, we turned our attention to the second goal, conversion of a (monosubstituted) allenyl product of the Nazarov reaction to a fused bicyclic furanyl cyclopentanone. Allenyl ketones are known to be easily isomerized to furans under mild conditions with Rh(I),[5] Ag(I),[9] Pd(II),[10] Au(III),[11] or Cu(I)

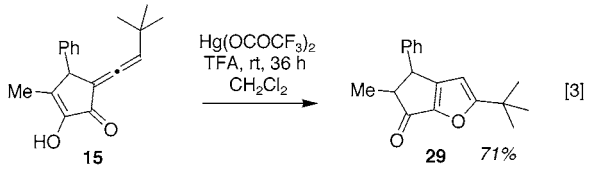
(8) The relative stereochemistry of major and minor isomers has been determined in the case of **15** and **16**. See Supporting Information.

(9) (a) Marshall, J. A.; Wang, X. *J. Org. Chem.* **1991**, *56*, 960. (b) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169.

(10) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295.

(11) (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590.

catalysis.[12] We were surprised to find that Marshall's conditions, $AgNO_3$ in refluxing acetone, failed to convert **15** to furan **29** (eq 3). A limited survey of silver salts



[3]

($AgSbF_6$, $AgClO_4$) and solvents (acetonitrile, 3-pentanone) did not lead to success. Protection of the free hydroxyl group in **15** as the benzoate led to no improvement. Several attempts to use $PdCl_2(MeCN)_2$ to catalyze the isomerization of **15** resulted in complex mixtures that were devoid of **29**. The failure of these methods that have been used successfully to isomerize open chain allenyl ketones to furans suggested that the conformational rigidity of **15** was frustrating our efforts. We next decided to explore mercuric salts as alternative catalysts for the isomerization.[13] Simply exposing **15** to 0.2 equiv of mercuric trifluoroacetate and 1 equiv of trifluoroacetic acid (TFA) in dichloromethane at room temperature led to slow but clean conversion to furanyl cyclopentanone **29** in 71% yield, as a 1/1 mixture of *cis* and *trans* isomers. This result suggests that a nakadomarin A synthesis based on the cumulene ether cyclization may be possible.

In conclusion, we have demonstrated a method that transforms a cumulene ether to a furanyl cyclopentanone, the core of the structure of nakadomarin A. Cumulenes are not much exploited for synthesis.[14] Most of the work in this area during the past 10 years or so has been done in the context of the neocarzinostatin chromophore.[14e,f,15] The activated form of neocarzinostatin incorporates a butatriene. Cumulenes would appear to have much to offer in synthesis. They are easily prepared, they can react along a large number of mechanistic manifolds, and their reactions are facilitated by the loss of strain.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support. E.L. thanks the Association pour la Recherche Contre le Cancer (A.R.C.) for a fellowship.

Supporting Information Available: General procedures for the synthesis of cumulenes **11**, allenylcyclopentenones **15**−**28**, and furan **29**; spectroscopic data for **15**−**28**; reproductions of ^{1}H NMR, ^{13}C NMR, IR and mass spectra of **15**, **25**, and **29**; reproductions of ^{1}H NMR, ^{13}C NMR, and IR spectra of **11** ($R^1 = R^2 =$ Et). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95.

(13) The conversion of an allenyl carbinol to a furan by mercury(II) chloride has been described: Tso, H.-H.; Tsay, H. *Tetrahedron Lett.* **1997**, *38*, 6869.

(14) For some syntheses of cumulenes, see: (a) Aurrecoechea, J. M.; Pérez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564. (b) Le Strat, F.; Maddaluno, J. *Tetrahedron Lett.* **2000**, *41*, 5367. (c) Wang, K. K.; Liu, B.; Lu, Y.-d. *J. Org. Chem.* **1995**, *60*, 1885. (d) Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* **1994**, *35*, 6977. (e) Saito, I.; Yamaguchi, K.; Nagata, R.; Murahashi, E. *Tetrahedron Lett.* **1990**, *31*, 7469. (f) Ziegler, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 2983. (g) Nader, F. W.; Wacker, C.-D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 851. (h) Arnold, R. D.; Baldwin, J. E.; Ziegler, C. B., Jr. *J. Chem. Soc., Chem. Commun.* **1984**, 152. (i) Saalfrank, R. W.; Welch, A.; Haubner, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2709. (j) Bienz, S.; Enev, V.; Huber, P. *Tetrahedron Lett.* **1994**, *35*, 1161.

(15) For a review of some of the early work, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.