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Generation of *N*-Acyliminium Ions via Intramolecular Conjugate Addition Reactions: A Strategy for the Total Synthesis of Nakadomarin A

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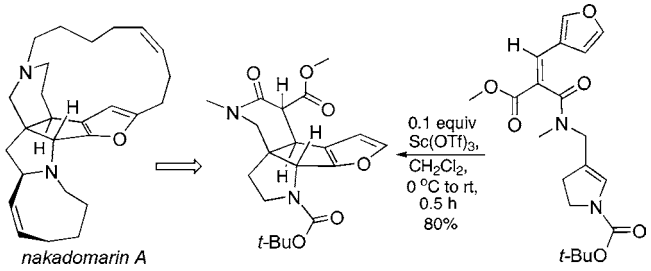
ABSTRACT



The rapid construction of the tetracyclic core ring system of nakadomarin A via a tandem enecarbamate Michael addition/*N*-acyliminium ion cyclization is described.

N-Acyliminium ions have been extensively utilized for the construction of nitrogen-containing ring systems. Accordingly, a number of methods have been developed for the generation of these versatile electrophiles.[1] A particularly attractive protocol involves the treatment of an enamide/enecarbamate **1** (Scheme 1) with an electrophile to afford the *N*-acyliminium ion **2** that is then trapped by a nucleophile to afford amide/carbamate **3**, a product of tandem vicinal difunctionalization.[1] Typically, the enamides/enecarbamates **1** are activated by protonation, halogenation, or oxidation, but examples using the arguably more valuable carbon electrophiles are scarce.[2] Examples of vicinal difunctionalization of enamides/enecarbamates using a carbon electrophile *and* a carbon nucleophile are even more limited, most likely because of the incompatibility of these two reactive species.[3,4] In fact, the three-component coupling method recently reported by Suga and Yoshida[5] was accomplished

(1) For a review, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, T. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(2) (a) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S. I.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697. (b) Eberson, L.; Malmberg, M.; Nyberg, K. *Acta Chem. Scand.* **1984**, *38*, 391. (c) Meth-Cohn, O.; Westwood, K. T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1173. (d) Katritzky, A. R.; Belyakov, S. A.; Rachwal, B.; Moutou, J.-L. *J. Org. Chem.* **1997**, *62*, 700. (e) Taylor, R. E.; Risatti, C. A.; Engelhardt, C.; Schmitt, M. J. *Org. Lett.* **2003**, *5*, 1377. (f) Prashad, M.; Lu, Y.; Repîc, O. *J. Org. Chem.* **2004**, *69*, 584. (g) García, A.; Gómez, E.; Domínguez, D. *Synlett* **2004**, 2331. (h) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 12216. (i) Matsubara, R.; Vital, P.; Nakumura, Y.; Kiyohara, H.; Kobayashi, S. *Tetrahedron* **2004**, *60*, 9769. (j) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814.

(3) For vicinal difunctionalization of enamides or enecarbamates with carbon electrophiles and carbon nucleophiles via indirect routes, see: (a) Seebach, D.; Stucky, G.; Pfammatter *Chem. Ber.* **1989**, *122*, 2377. (b) Wieber, G. M.; Hegedus, L. S.; Åkermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649. (c) Masters, J. J.; Hegedus, L. S.; Tamariz, J. *J. Org. Chem.* **1991**, *56*, 5666. (d) Harrison, T.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023. (e) Matos, M. N.; Afonso, C. A. M.; Batey, R. A. *Tetrahedron* **2005**, *61*, 1221.

(4) For examples of the enamine variant of this transformation, see: Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193.

(5) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. This transformation is the converse of the much more well-known tandem vicinal difunctionalization reactions of unsaturated carbonyl systems wherein addition of a nucleophile generates an enolate that is then intercepted by an electrophile.

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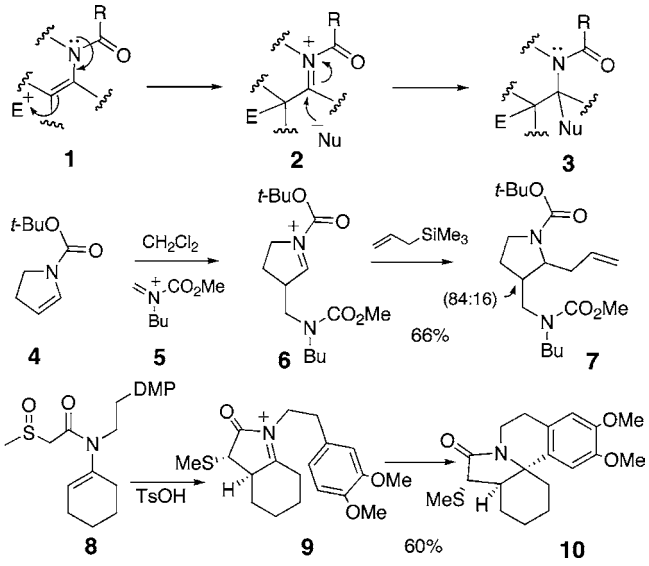
Scheme 1

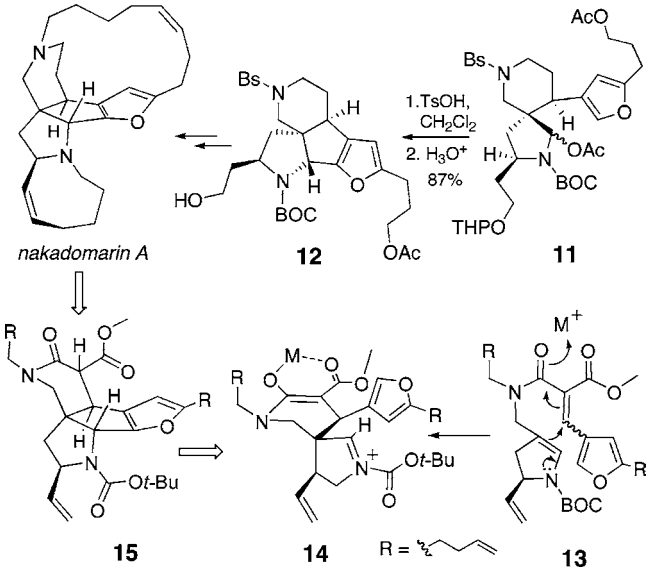


by the sequential addition of an electrochemically generated iminium ion **5** to the enecarbamate **4** to produce the *N*-acyliminium ion **6** followed by allyl silane addition to afford the difunctionalized product **7**. An alternative scenario for circumventing this hypothetical incompatibility problem is to design enecarbamates capable of undergoing intramolecular activation and capture processes wherein geometric constraints preclude the self-destruction of the electrophilic and nucleophilic components. This strategy also may permit the utilization of less electrophile/nucleophile-reactive species. These factors are no doubt at play in the Pummerer-type cyclization of enamide **8** and the subsequent closure of the resultant *N*-acyliminium ion **9** with the modest dimethoxyphenyl nucleophile en route to erythrinan alkaloids reported by Tamura and Ishibashi.[6a]

A synthesis effort directed toward the marine cytotoxin nakadomarin A[7] represents an excellent opportunity for further exploring the tandem cyclization reactions of enecarbamates. A number of groups are pursuing the total synthesis of this structurally fascinating compound[8] whose biological evaluation has been restricted by its limited availability from the natural source (*Amphimedon* sponge).[7]

Most notably, Nishida and co-workers have reported the total syntheses of both nakadomarin A and *ent*-nakadomarin A by conceptually different routes.[9] In particular, they demonstrated that the core ring system, tetracycle **12**, could be assembled by cyclization of an *N*-acyliminium ion generated from carbamate **11** in their synthesis of *ent*-nakadomarin A (Scheme 2).[9a] We were intrigued by the possibility of generating an analogous *N*-acyliminium **14** by a Lewis acid-promoted intramolecular conjugate addition of the enecarbamate functionality of amide **13** to the doubly activated Michael acceptor.[10] Upon the basis of the Nishida precedent, the *N*-acyliminium **14** should undergo concomitant cyclization with the proximate furan substituent to afford the tetracycle **15** that is suitably functionalized for the olefin metathesis-driven transformation to nakadomarin A. Of paramount concern was the stereochemical consequence of the proposed conjugate addition reaction. Although it seemed likely that the conjugated double bond would approach the enecarbamate moiety from the face opposite to the vinyl substituent (or, if necessary, alkoxymethyl), it was by no means certain that the iminium ion would prefer to emerge cis to the furan substituent on the six-membered ring. It was anticipated that the stereochemistry would be dependent upon the unsaturated amide configuration, and inspection of molecular models suggested that the *E*-isomer might lead to a more favorable outcome (vide infra).

Scheme 2



(6) (a) Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209. The Padwa group has proposed that the *N*-acyliminium ion **9** arises from a 4π-conrotatory electrocyclization. For additional examples of these Pummerer cyclizations/*N*-acyliminium ion cyclizations, see: (b) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. *J. Org. Chem.* **2003**, *68*, 929 and references therein. For a review on Pummerer chemistry, see: (c) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003.

(7) (a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236. (b) Kobayashi, J.; Tsuda, M.; Ishibashi, M. *Pure Appl. Chem.* **1999**, *71*, 1123. Extraction of 1.0 kg of the sponge *Amphimedon* sp. (SS-264) afforded 6.0 mg of nakadomarin A (0.0018%). Nakadomarin A exhibited cytotoxicity against murine lymphoma L1210 cells (IC_{50} 1.3 μg/mL), inhibitory activity against cyclin-dependent kinase 4 (IC_{50} 9.9 μg/mL), and antimicrobial activity against a fungus (*Trichophyton mentagrophytes*, MIC 23 μg/mL) and a Gram-positive bacterium (*Corynebacterium xerosis*, MIC 11 μg/mL).

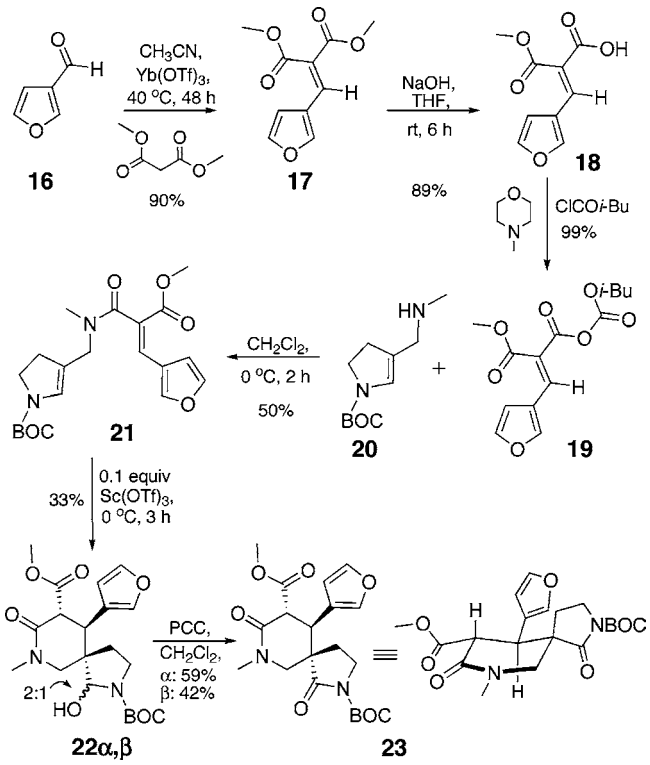
(8) (a) Fürstner, A.; Guth, O.; Duffels, A.; Seidel, G.; Liebl, M.; Gabor, B.; Mynott, R. *Chem.*−*Eur. J.* **2001**, *7*, 4811. (b) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (c) Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 1171. (d) Ahrendt, K. A.; Williams, R. M. *Org. Lett.* **2004**, *6*, 4539.

(9) (a) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (b) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *42*, 2020. Nishida and co-workers actually prepared the enantiomers of carbamates **11** and **12**.

(10) For other examples of intramolecular conjugate addition reactions of α-alkylidene-β-carboxyamides, see: (a) Tietze, L. F.; Schünke, C. *Eur. J. Org. Chem.* **1998**, 2089. (b) Hourcade, S.; Ferdenzi, A.; Retailleau, P.; Mons, S.; Marazano, C. *Eur. J. Org. Chem.* **2005**, 1302.

We began this investigation by preparing the more accessible *Z*-unsaturated model amide **21** that lacks the three alkenyl substituents present in amide **13** (Scheme 3). Thus,

Scheme 3



a ytterbium(III)-catalyzed Knovenagel condensation of dimethyl malonate with 3-furaldehyde (**16**) gave the unsaturated diester **17**. Saponification of the less-hindered ester group of diester **17** gave the monoacid **18**, a species that was converted to the chromatographically stable mixed anhydride **19**. Condensation of the mixed anhydride **19** with the amine **20**[11] gave the desired amide **21** in moderate yield due, in part, to competitive attack of the amine on the other carbonyl group of mixed anhydride **19** (15%). A variety of Lewis acids [$Yb(OTf)_3$, $Mg(OTf)_2$, $Zn(OTf)_2$, BF_3, $ZnCl_2$] were surveyed for effecting the key conjugate addition/*N*-acyliminium ion cyclization of the *Z*-unsaturated amide. The best results were observed when $Sc(OTf)_3$ was employed: a mixture of two hemi-aminals **22**α and **22**β that derived from conjugate addition and capture of the *N*-acyliminium ion by adventitious water was isolated, despite extensive efforts to maintain rigorously anhydrous conditions. Addition of water (2 equiv) to the reaction mixture gave hemi-aminals **22**α,β in improved yield but required a longer reaction period (0 °C, 12 h, 54%). Each of the hemi-aminals was independently converted to the same imide **23** by oxidation with PCC. Most importantly, the major isomer, hemi-aminal **22**β,

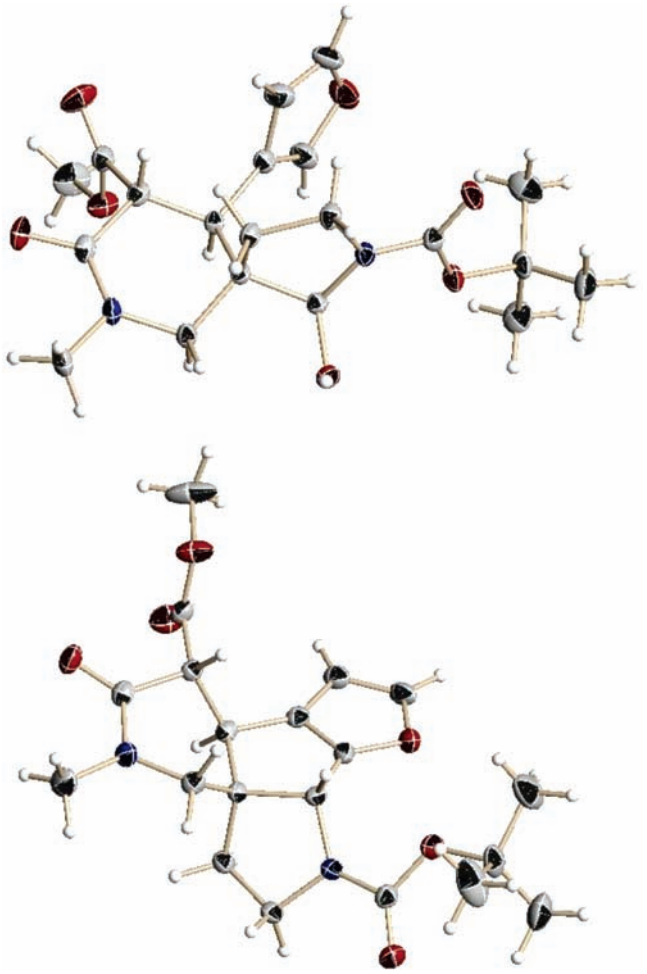


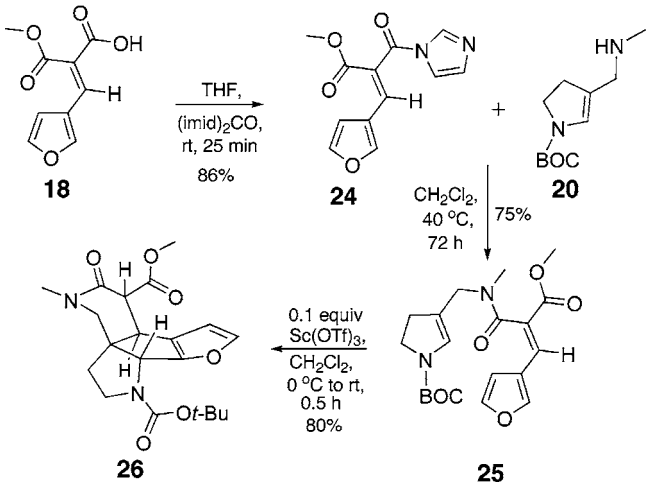
Figure 1. X-ray structures of hemiaminal **22**β and tetracycle **26**.

afforded crystals suitable for X-ray crystallographic analysis (Figure 1). Thus, the *N*-acyliminium ion resulting from the conjugate addition reaction emerges trans to the furan substituent and its closure to the relatively flat trans-5,6 ring system may be inhibited by a significant steric interaction in the corresponding Wheland intermediate between the furonium ion ring and the ester substituent. Moreover, subjection of the acetate derivative of hemi-aminal **22**β to the Nishida conditions, cf. **11** → **12**, only returned the hemi-aminal **22**β.

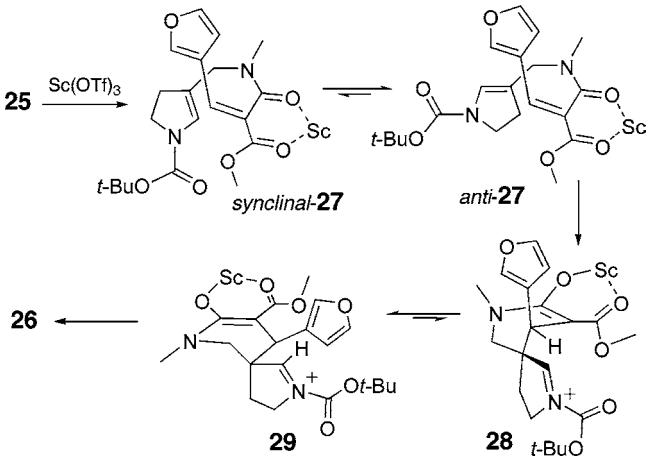
We now directed our attention to the preparation of *E*-unsaturated amide **25** (Scheme 4) which was made easier by a serendipitous discovery. Thus, in an attempt to improve the yield of *Z*-amide **21**, we converted the acid **18** to the acylimidazole derivative **24**. The acylimidazole **24** underwent a slow but clean transformation upon heating in methylene chloride in the presence of amine **20** to the *E*-unsaturated amide **25**. In control experiments, we independently heated the *Z*-amide **21** and the *Z*-acylimidazole **24** in methylene chloride (40 °C, 48 h) but did not observe any olefin isomerization. However, treatment of *Z*-amide **21** with 1 equiv of diethylamine under these conditions led to complete

(11) Prepared by reductive amination ($MeNH_3Cl$, NEt_3, $NaBH_4$, MeOH, rt, 3 h, 81%) of the readily available 3-formylpyrroline; see: Greshock, T. G.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946. For the reductive amination with 3-butynylamine hydrochloride, see ref 8b.

Scheme 4



Scheme 5



conversion to *E*-amide **25**. This fortuitous thermodynamic control has been previously observed for related α-alkylidene-*β*-carboxyamides[10a,12] and can be attributed to, in part, the better overlap of the ester substituent with the adjacent double bond in *E*-amide **25** in comparison to the carbonyls of *Z*-amide **21**, both of which are twisted out of conjugation. Our good fortune carried over to the next step where it was found that treatment of enecarbamate **25** with 10% scandium triflate in methylene chloride (0 °C → rt, 0.5 h) gave tetracycle **26**, whose relative stereochemistry was determined by X-ray crystallographic analysis (Figure 1) and shown to be that desired for the synthesis of nakadomarin A.

Our current working model for this favorable stereochemical outcome is diagrammed in Scheme 5. Thus, cyclization can take place through one of two boatlike transition states, *synclinal*-**27** or *anti*-**27**. Two effects might conspire to destabilize *synclinal*-**27**, a steric interaction between the BOC and ester substituents as well as an electrostatic interaction between the developing positive charge on the enecarbamate nitrogen and the carbonyl carbon of the chelated ester. These interactions are not present in *anti*-**27**, and so cyclization leads directly to the boat conformer **28** of the *N*-acyliminium ion intermediate. Conformational adjustment by rotation to the alternative boat conformer **29** possessing an equatorial furan substituent (or even further to the corresponding half-chair conformer) before closure to tetracycle **26** then rationalizes the observed diastereoselectivity. Further experimentation is clearly required to substantiate and/or refine this conjecture.[13]

In conclusion, we have demonstrated that an intramolecular Michael addition of an enecarbamate constitutes a new pathway to *N*-acyliminium ions. It remains to be seen whether other polycyclic systems can be constructed by the strategic placement of the enecarbamate, the Michael acceptor, and various nucleophilic components for the interception of the *N*-acyliminium ion intermediate. These studies as well as the completion of a potentially concise synthesis of nakadomarin A are underway.

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

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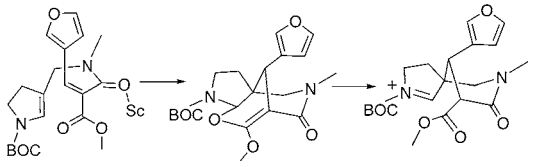
(12) (a) Brown, J. M.; Guiry, P. J.; Laing, J. C. P.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron* **1995**, *51*, 7423. (b) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M. *Tetrahedron Lett.* **1998**, *39*, 2047.

(13) A type 2 intramolecular hetero Diels−Alder reaction pathway is not operative because it can only afford the product with an *N*-acyliminium ion trans to the furyl substituent upon ring opening of the strained cycloadduct.



For an attempt to obtain such a cycloadduct, see: Bear, B. R.; Shea, K. J. *Org. Lett.* **2001**, *3*, 723.