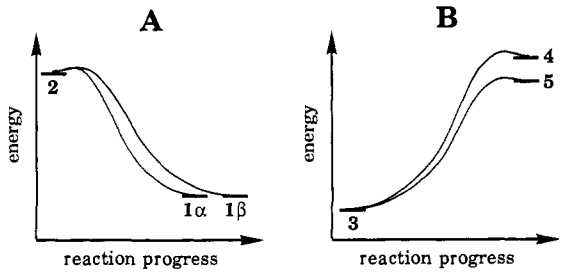
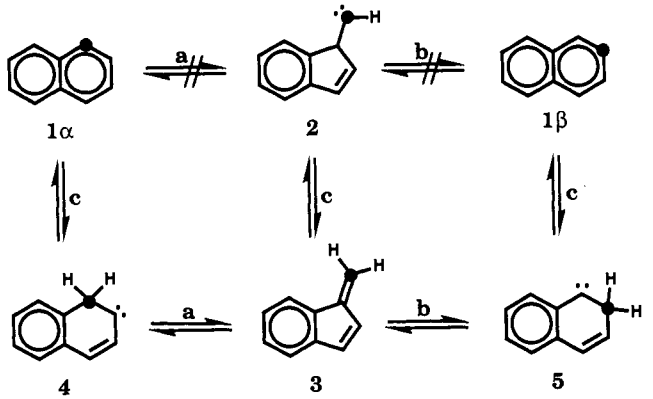


Figure 1. (A) Early transition states of similar energy for competing exothermic reactions. (B) Late transition states of different energies for competing endothermic reactions.

Scheme I[a]



[a] ● = ^{13}C; a = aryl shift, b = vinyl shift, c = hydrogen shift.

quently, since benzofulvene appears to aromatize via the six-membered-ring carbenes **4** and **5**, rather than via the indenyl carbene **2** (vida supra), it follows that all four of the other transition states in Scheme I must likewise lie lower in energy than the transition states separating **2** from either **1**α or **1**β. The lowest energy pathway between **1**α and **1**β in Scheme I, therefore, is **1**α $\rightleftharpoons$ **4** $\rightleftharpoons$ **3** $\rightleftharpoons$ **5** $\rightleftharpoons$ **1**β.

All the experimental and theoretical evidence to date is consistent with (but does not "prove") this pathway for the automerization of naphthalene. One cannot exclude the direct "dyotropic" rearrangement[23] of naphthalene to benzofulvene (simultaneous carbon and hydrogen shifts), bypassing carbene intermediates entirely, but in either case, benzofulvene would be an obligatory intermediate in the naphthalene automerization. Alternative pathways involving reversible isomerization of naphthalene to azulene or to isonaphthvalene have already been disproven.[5,7] We conclude, therefore, that the thermal automerization of naphthalene probably occurs by reversible formation of benzofulvene, either via carbenes **4** and **5** or by direct dyotropic rearrangements.

Acknowledgment. We thank the Department of Energy and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work. Valuable discussions with R. S. Sheridan are also gratefully acknowledged.

Registry No. **1**α, 20526-83-4; **1**β, 29571-13-9; **3**, 137175-13-4; naphthalene, 91-20-3; benzofulvene, 2471-84-3.

(22) Kjell, D. P.; Sheridan, R. S. *J. Am. Chem. Soc.* **1986**, *108*, 4111-4114. Extrapolation to high temperatures could lead to a reversal of the observed preference for hydrogen shift over carbon shift only if the hydrogen shift were to have a significantly more negative $\Delta S^{\ddagger}$, which we deem unlikely.

(23) Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 129-130. Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 130-131. Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 2, Chapter 9.

Total Synthesis of Onnamide A

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Antiviral and antitumor natural products mycalamides A (**1**) and B (**2**) and onnamide A (**3**) were isolated from marine sponges.[1,2] Structurally, they strikingly resemble pederin.[3] We recently reported an enantioselective total synthesis of mycalamides A and B, which unambiguously established their absolute stereochemistry and structural link to pederin.[4] In this context, we turned our attention to onnamide A, whose structure has been elucidated primarily by spectroscopic methods. However, its relative stereochemistry at the C-11 and C-21 positions and absolute stereochemistry except at the C-2′ position still remain unknown.[5] In the synthetic studies leading to mycalamides A and B, we recognized that the diol **10** might be a useful substance to establish not only the stereochemistry of onnamide A but also the structural link between these three classes of natural products. However, we also realized that its synthesis, particularly the synthesis of **9**, needed to be improved for this purpose, and we first studied an alternative synthesis of **9**.

Sodium triacetoxyborohydride reduction [$NaBH(OAc)_3$/$CeCl_3$/MeOH/0 °C] of the ketone **4**,[6] followed by methylation (MeI/NaH/THF/room temperature), yielded the desired methyl ether **5** in 78% overall yield (stereoselectivity = 12:1). It is notable that this reduction did not proceed in the absence of $CeCl_3$. Furthermore, various reduction conditions, including $NaBH_4$ (desired/undesired = 0/1), LAH (0/1), L-Selectride (0/1), BH_3·THF (0/1), $Zn(BH_4)_2$ (1/3), $NaBH_3CN$ (1/5), $NaBH_4$–$CeCl_3$ (1/1), and $NaBH_3CN$–$CeCl_3$ (3/2), neither yielded the desired diastereomer nor gave a satisfactory level of stereoselectivity. The required protecting group manipulation at the C-16 and C-18 positions, i.e. **5** → **6**, was possible in two steps [(1) LAH/$AlCl_3$/Et_2O–CH_2Cl_2/reflux and (2) Ac_2O/BF_3·Et_2O/room temperature]. However, for large-scale preparation, this transformation was carried out in four steps [(1) H_2/$Pd(OH)_2$ on C/MeOH/room temperature, (2) MMTrCl/(*i*-Pr)$_2$EtN/CH_2Cl_2/room temperature, (3) BnBr/NaH/DMF/room temperature, and (4) Ac_2O/BF_3·Et_2O/0 °C → room temperature] in 75–80% overall yield because of its better reproducibility. C-Glycosidation of **6** (CH_2=$CHCH_2TMS$/TMSOTf/BF_3·Et_2O/MeCN/0 °C)[7] gave exclusively the expected, axially substituted product **7** in 93% yield. Corey asymmetric osmylation of **7** [OsO_4/*S*,*S* Corey ligand/CH_2Cl_2/−90 °C],[8,9] followed by carbonate formation (Im_2CO/C_6H_6/reflux) and separation by silica gel chromatography, afforded the desired diastereomer **8**

(1) (a) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850. (b) Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem.* **1990**, *55*, 223.

(2) Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy, G.; Higa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4851.

(3) (a) Cardani, C.; Ghirinhelli, D.; Mondelli, R.; Quilico, A. *Tetrahedron Lett.* **1965**, 2537. (b) Matumoto, T.; Yanagiya, M.; Maeno, S.; Yasuda, S. *Tetrahedron Lett.* **1968**, 6298. (c) Furusaki, A.; Watanabe, T.; Matsumoto, T.; Yanagiya, M. *Tetrahedron Lett.* **1968**, 6301.

(4) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242.

(5) The numbering of compounds used in this paper corresponds to that of onnamide A: see structure **3**. Satisfactory spectroscopic data (^1H and ^{13}C NMR, HRMS, MS, IR, UV, α_D) were obtained for all the new compounds reported.

(6) Rocherolle, V.; Lopez, J. C.; Olesker, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1988**, 513.

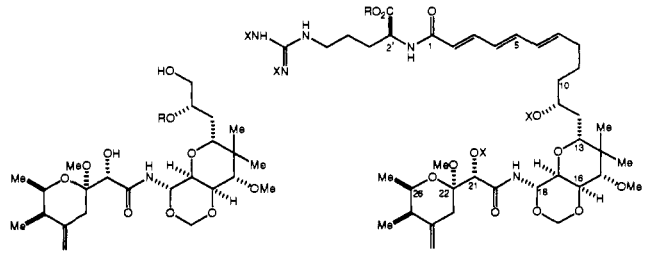
(7) For the stereochemical outcome of this type of C-glycosidation, see: Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

(8) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. For recent papers on asymmetric osmylation, see references cited in ref 4.

(9) We are indebted to Professor Sharpless for a sample of new ligands prior to publication (Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585). The stereoselectivity with the DHQD-MEQ ligand was approximately 2:1, favoring the desired diastereomer.

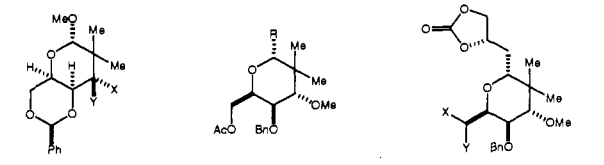
0002-7863/91/1513-9693$02.50/0

Chart I



1 : R = H (mycalamide A)
2 : R = Me (mycalamide B)

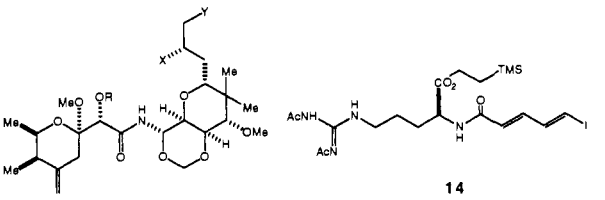
3 : R = X = H (onnamide A)
15 : X = Ac, R = CH_2CH_2TMS



4 : X = Y = O
5 : X = OMe, Y = H

6 : R = OAc
7 : R = $CH_2CH{=}CH_2$

8 : X = OAc, Y = H
9 : X = Y = OMe



10 : X = Y = OH, R = 3,4-$(MeO)_2PhCH_2$
11 : X = Y = O (epoxide), R = 3,4-$(MeO)_2PhCH_2$
12 : X = OAc, Y = $(CH_2)_2C{\equiv}C$-TMS, R = 3,4-$(MeO)_2PhCH_2$
13 : X = R = OAc, Y = $(CH_2)_2CH{=}CHSn(n\text{-}Bu)_3$ (*trans*)

14

(65% yield) along with the undesired diastereomer (21% yield).[10] Hydrolysis (*p*-TsOH/MeOH/reflux) of the acetate in **8**, Swern oxidation,[11] and acetalization [$(MeO)_3CH$/*p*-TsOH/MeOH/0 °C → room temperature] furnished the dimethyl acetal **9** (84% overall yield), which was shown to be identical with the intermediate used in the synthesis of mycalamides.[4] This 10-step synthesis provided **9** in approximately 31% direct overall yield from **4** or 39% overall yield including one recycling at the osmylation step[10] and is suitable for large-scale preparation.

The dimethyl acetal **9** was then transformed into the diol **10**, using the route previously described.[4] In order to facilitate the C-9–C-10 bond formation, the diol **10** was converted to the epoxide **11** by treatment with tosylimidazole (*p*-TsIm/NaH/imidazole/THF/0 °C → room temperature; 85% yield). The epoxide **11** exhibited the expected reactivity toward various cuprates. Indeed, **11** smoothly reacted at −30 °C → room temperature with a mixed cuprate prepared from $TMSC{\equiv}CCH_2CH_2Li$ and lithium 2-thienylcyanocuprate (Aldrich), to yield the desired coupled product, which was isolated as its acetate **12** in 78% overall yield. Since deprotection of the 3,4-dimethoxybenzyl group at the C-21 position in the later stage of synthesis had proven difficult, this protecting group was removed at this stage by DDQ treatment [DDQ/CH_2Cl_2–phosphate buffer (pH = 7.0)/room temperature;[12] 85% yield]. Standard functional group transformations [(1) $Ac_2O/Et_3N/CH_2Cl_2$/room temperature, (2) TBAF/THF/room temperature, (3) *n*-Bu_3SnH/AIBN/C_6H_6/reflux] were then applied to convert **12** into **13** in 76% overall yield.

The Suzuki coupling reaction[13] appeared to be well suited for the synthesis of the C-2–C-7 triene of onnamide A, which requires a vinylboronic acid or ester as the coupling component. In spite of substantial efforts, however, we were unable to prepare the requisite vinylboronic acid on either the left or right half in a satisfactory fashion. Therefore, our attention was shifted to the Stille coupling reaction.[14] The required δ-iodo amide **14**[15] was readily prepared by coupling (*p*-TsCl/DMAP/CH_2Cl_2/room temperature) of 5-iodopentadienoic acid[16] and N^{ω},$N^{\omega'}$-diacetyl-L-arginine trimethylsilylethyl ester.[17] Stille coupling of **13** with **14** in the presence of $Pd(PPh_3)_4$ in DMF at room temperature gave the coupled product as a mixture of geometric isomers. Iodine treatment of this mixture in methylene chloride at room temperature furnished the pure trans,trans,trans product **15** in 51% overall yield. Tetrabutylammonium fluoride (THF/room temperature) and lithium hydroxide (MeOH/room temperature) treatments of **15** gave synthetic onnamide A (**3**) in 59% overall yield.

The spectroscopic data (^1H NMR, ^{13}C NMR, MS, IR, UV, and α_D[18]) of the synthetic onnamide A was found to be identical with those of the authentic sample from natural sources,[19] establishing the complete structure of onnamide A as depicted in **3**. Thus, this work, coupled with the previously reported synthesis of mycalamides, establishes the structural link between the pederin, mycalamide, and onnamide classes of natural products.

Acknowledgment. Financial support from the National Institutes of Health (CA-22215) is gratefully acknowledged.

(10) For recycling the undesired diastereomer, see ref 4.
(11) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(12) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885, 889.
(13) (a) Miyaura, N.; Yamada, Y.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, *22*, 127. (c) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972. (d) For rate enhancement of Suzuki coupling reactions, see: Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.
(14) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
(15) The product was a 4:1 mixture of trans and cis isomers, which was separated by silica gel chromatography.
(16) This substance was prepared from 2-penten-4-yn-1-ol (Farchan Laboratories) in three steps [(1) *n*-Bu_3SnH/AIBN/C_6H_6/reflux, (2) I_2/CH_2Cl_2/room temperature, (3) Jones oxidation]. The product was a 4:1 mixture of trans and cis isomers.
(17) This substance was synthesized from N^{α}-*t*-BOC-N^{ω}-nitro-L-arginine (Sigma) in three steps [(1) $HOCH_2CH_2TMS$/DCC/DMAP/CH_2Cl_2/room temperature, (2) $H_2/Pd(OH)_2$ on C/AcOH–MeOH/room temperature, (3) Ac_2O/Py/room temperature].
(18) α_D of the synthetic onnamide A: +62° (MeOH, *c* 0.15). α_D of the natural onnamide A: +63° (MeOH, *c* 0.32).
(19) We are indebted to Dr. G. Saucy for a sample of natural onnamide A.

Memory of Chirality: Enantioselective Alkylation Reactions at an Asymmetric Carbon Adjacent to a Carbonyl Group

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It is widely accepted that chirality at a carbon α to a carbonyl group is lost in the corresponding enols or enolates because they are achiral. Thus, subsequent reaction with electrophiles should give products totally racemized even though enantiomerically enriched starting materials are used (Scheme I).[1,2] This means that chiral sources such as chiral auxiliaries, chiral ligands, or chiral electrophiles must be used to obtain optically active products by alkylation of enolates.[3] However, we describe here a conceptually novel asymmetric induction which does not fall into any of the above-mentioned categories.

(1) For example, see: Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021.
(2) It is reported that the alkylation of an aspartic acid derivative proceeded without complete racemization; see: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.
(3) For example, see: Morrison, J. D. *Asymmetric Synthesis*; Academic Press: Orlando, 1984; Vol. 3.

0002-7863/91/1513-9694$02.50/0