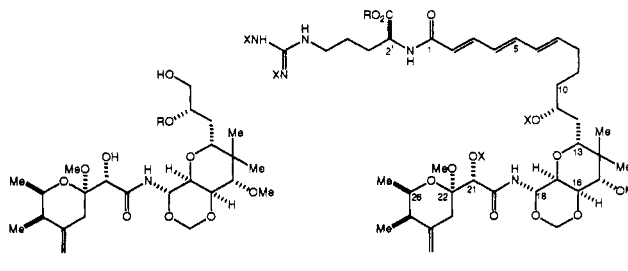
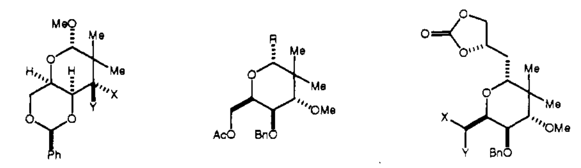
Chart I



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

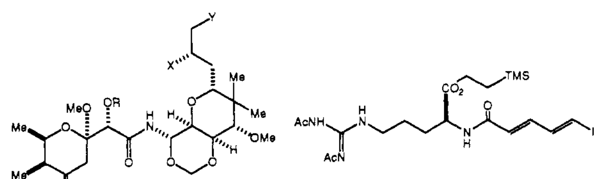
3 : R = X = H (onnamide A)
15 : X = Ac, R = CH_2CH_2TMS



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



14

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*)

(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.
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(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.

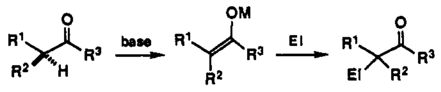
(1) For example, see: Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021.
(2) It is reported that the alkylation of an aspartic acid derivative proceeded without complete racemization; see: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.
(3)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

Table I. Enantioselective Alkylation of **1**[a]

entry	RX	product[b]	yield, %	ee,[c] %	$[\alpha]^{20}_D$ (c)[d]	confign
1	MeI	**4a**	48	66	−15.8° (2.3)	*R*
2	EtI	**4b**	27	65	+18.5° (1.3)	*R*
3	$PhCH_2Br$	**4c**	31	67	+25.6° (2.3)	*e*
4	$CH_2{=}CHCH_2Br$	**4d**	36	48	+13.9° (1.8)	*e*

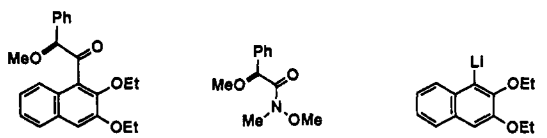
[a] Chiral ketone **1** of 93% ee was used. For the experimental procedure, see ref 9. [b] Enol ethers were also obtained in 12–30% yield. [c] Determined by HPLC analysis (CHIRALPAK AD, hexane:2-propanol = 95:5). [d] Measured in chloroform. [e] Not determined.

Scheme I

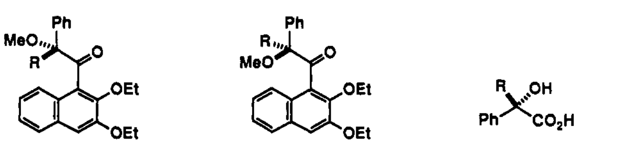


chiral achiral racemic

Chiral ketone **1**[4] was prepared from the Weinreb amide **2**[5] derived from (*S*)-mandelic acid and aryllithium **3** in 54% yield. Treatment of **1** (93% ee) with potassium hydride[6] and methyl iodide in the presence of 18-crown-6[7] afforded **4a** of 66% ee without any additional chiral source (Table I, entry 1). Similarly, the reaction with ethyl iodide afforded **4b** of 65% ee (entry 2). The absolute configurations of **4a** and **4b** were both determined to be *R* by independent preparation of their enantiomers **5a** and **5b**. Thus, (*S*)-atrolactic acid (**6a**)[8] and (*S*)-2-hydroxy-2-phenylbutanoic acid (**6b**)[8] were converted into **5a** and **5b**, respectively, through methylation followed by addition of **3**. This proved that both methylation and ethylation of **1** occurred with inversion of configuration. Reaction of **1** with benzyl bromide or allyl bromide also afforded alkylated products **4c** or **4d** in 67% or 48% ee, respectively (entries 3 and 4).[9]



1 **2** **3**

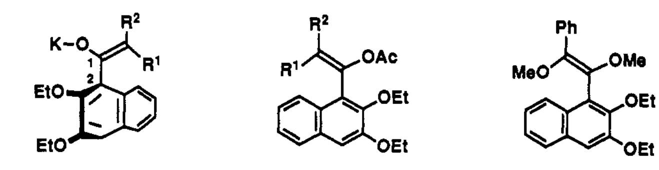


4 a : R= Me
b : R= Et
c : R= CH_2Ph
d : R= $CH_2CH{=}CH_2$

5a : R=Me $[\alpha]_D^{20}$ +22.2° (c 1.6, $CHCl_3$)
5b : R=Et $[\alpha]_D^{20}$ -28.4° (c 1.3, $CHCl_3$)

6a : R=Me (89% op)
6b : R=Et (97% op)

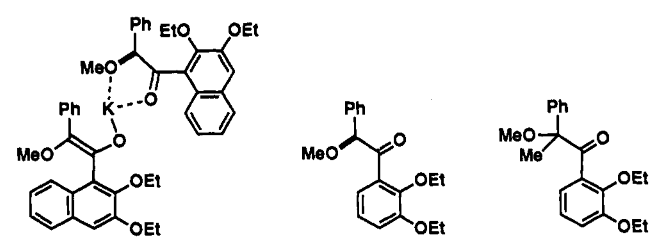
This novel asymmetric induction can be rationalized in terms of a two-step transfer of chirality. In the first step, the central chirality of **1** is transferred to axial chirality about the C_1–C_2 bond of the enolate **7** and/or **8**.[10] To determine the geometry of the enolate, trapping experiments were performed. When **1** (93% ee) was treated with potassium hydride and acetic anhydride[11] in the presence of 18-crown-6, (*E*)-enol acetate **9** and the *Z* isomer **10**[12] were obtained in 59% and 6% yields, respectively. The ee of the recovered **1** (27% recovery) had remained intact. These observations indicated that the (*E*)-enolate was the major intermediate under kinetically controlled conditions. Enol acetate **9** did not show optical rotation at either 589 or 405 nm. However, enol ether **11**,[12] which was obtained as one of the byproducts[13] in the experiment (Table I, entry 1), has been disclosed to be optically active. A rapid HPLC analysis[14] of the reaction mixture showed that the ee of **11** was at least 65% in the reaction medium below −20 °C. The enantiomeric purity of **11** gradually decreased at ambient temperature (e.g., 34% ee after 1 h). Thus, (*E*)-enolate **7** is considered to have transient axial chirality. The second step includes regeneration of central chirality in **4** by reaction of the chiral enolate with the electrophile. The bulkiness of the electrophile does not seem to affect the enantioselectivity (entries 1–3). These observations imply that the direction and degree of asymmetric induction are mainly controlled by enolate formation. Another possible rationale for the present asymmetric induction involves participation of **1** as a chiral bidentate ligand for the potassium cation of the enolate as shown in **12**. This is, however, less plausible since the chiral ketone **13** (96% ee) afforded the methylated product **14** in completely racemized form (51% yield) under the same conditions as those employed for **1**. Studies on the detailed mechanism are currently under way in our laboratory.



7 : R^1= OMe, R^2= Ph
8 : R^1= Ph , R^2= OMe

9 : R^1= OMe, R^2= Ph
10 : R^1= Ph , R^2= OMe

11



12 **13** **14**

In summary, chiral ketone **1** was converted into chiral alkylated ketones **4** in 48–67% ee without any additional chiral source. We propose that *central chirality at a carbon α to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product*

(4) Conformational atropisomerism in **1** due to restricted rotation about the Ar—C(=O) bond was not observed in either ^1H or ^{13}C NMR at room temperature.

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(6) Attempted enolate formation using bases such as LDA or potassium hexamethyldisilazide was unsuccessful. Thus, treatment of **1** with either of the bases followed by a mixture of CD_3CO_2D and CD_3OD afforded undeuterated starting material and decomposed products.

(7) In the absence of 18-crown-6, impure reaction products and starting material (34%) were recovered.

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(9) The following procedure is representative: A mixture of potassium hydride (35% oil dispersion, 57 mg, 0.50 mmol) and 18-crown-6 (132 mg, 0.50 mmol) in tetrahydrofuran (THF) (1 mL) was stirred at room temperature for 30 min and then cooled to −78 °C. To the suspension was added a THF (1 mL) solution of **1** (91 mg, 0.25 mmol) and methyl iodide (0.31 mL, 5.0 mmol). The resultant mixture was gradually warmed to −20 °C. Usual extractive workup followed by purification by preparative TLC (silica gel, ethyl acetate:hexane = 1:5) afforded **4a** (45 mg, 48%).

(10) Steric interaction between R^1 and the naphthalene ring would prevent free rotation of the C_1–C_2 bond as well as coplanarity of the enolate double bond with the aromatic ring.

(11) Attempts to trap the enolate as a silyl enol ether using trialkylsilyl chloride or triflate were totally unsuccessful.

(12) The geometry was determined by NOE studies. The details will be published elsewhere.

(13) **11** was obtained in 15–27% yield and the *Z* isomer in 2–5% yield.

(14) Usual workup followed by purification with preparative TLC afforded **11** whose ee was less than 1%. Direct HPLC analysis of the residue resulting from the rapid (<3 min) workup has made it possible to measure the enantiomeric purity of **11**. The experimental details will be published elsewhere.

(*memory of chirality*). We believe that this concept can lead to new developments in asymmetric synthesis.

Acknowledgment. We are grateful to Dr. Akito Ichida, Daicel Chemical Industries, Ltd., for the determination of the enantiomeric excess of compounds **1** and **4a–d** by HPLC analysis.

Supplementary Material Available: Analytical and spectral data for **1**, **4a–d**, **13**, and **14** and synthetic procedure for **1** (10 pages). Ordering information is given on any current masthead page.

The Nonstatistical Dissociation Dynamics of $Cl^-(CH_3Br)$: Evidence for Vibrational Excitation in the Products of Gas-Phase S_N2 Reactions

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Gas-phase bimolecular nucleophilic substitution (S_N2) reactions of halide ions with methyl halides have been the subject of numerous experimental[1-10] and theoretical[11-15] studies. Results of recent theoretical studies by Vande Linde and Hase have led to the suggestion that these reactions may exhibit vibrational mode specific reaction rate enhancement.[11] If this is true, then the dynamics of these reactions may display measurable deviations from predictions of statistical theories such as RRKM[16] and phase space theory.[17] One approach to examining the dynamics of reactive bimolecular collisions is to study the unimolecular dissociation of a species that corresponds to the reaction intermediate.[18,19] We have recently succeeded in measuring the kinetic energy release distribution (KERD) for metastable dissociation of the $Cl^-(CH_3Br)$ species, which may serve as a model for the intermediate in the bimolecular reaction (1). Comparison of the

$$Cl^- + CH_3Br \rightleftarrows [Cl^-(CH_3Br)]^* \rightarrow Br^- + CH_3Cl \quad (1)$$

experimental distribution with the distribution predicted by phase space theory reveals significant deviations, which we believe can be attributed to vibrational excitation of the CH_3Cl product.

The KERD measurements were carried out for second field-free region unimolecular dissociations in a reverse geometry sector mass spectrometer (V.G. Analytical ZAB-2F), using methods that have been described previously.[20] The $Cl^-(CH_3Br)$ species are formed by means of thermal energy (~300 K) ion–molecule capture collisions of Cl^- (generated by dissociative electron attachment

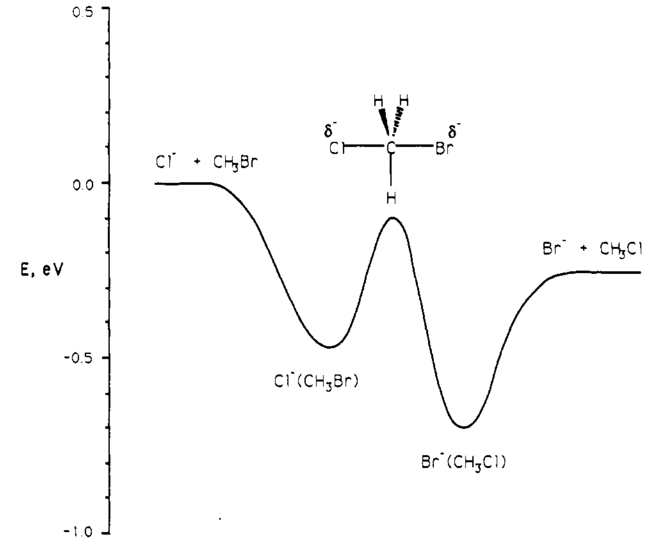

Figure 1. The schematic reaction coordinate diagram used to model the S_N2 reaction $Cl^- + CH_3Br \rightarrow Br^- + CH_3Cl$. The energies of the $Cl^-(CH_3Br)$ and $Br^-(CH_3Cl)$ complexes and of the S_N2 transition state have been determined experimentally.[7,23] The relative energies of the Cl^- + CH_3Br reactants and the Br^- + CH_3Cl products are taken from ref 24.

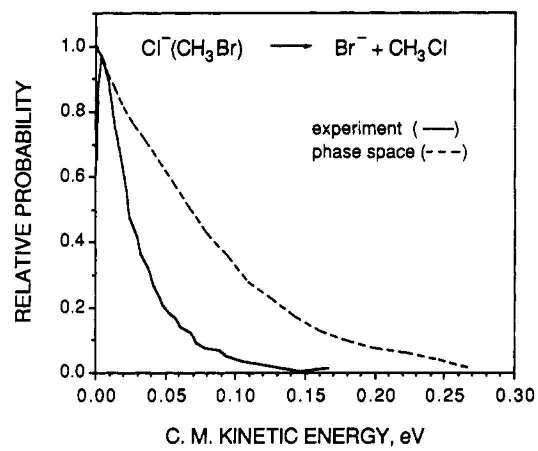

Figure 2. Experimental and theoretical kinetic energy release distributions for the metastable displacement reaction of $Cl^-(CH_3Br)$. The theoretical curve is calculated for $Cl^-(CH_3Br)$ complexes with internal energies between 0.4 and 0.5 eV (see text).

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