141.5-142.5 °C (EtOAc);[17] ^{1}H NMR ($CDCl_3$) δ 6.03 (dd, J = 3.7, 11.5 Hz, 1 H, =CH—), 3.74 and 3.57 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 167.0 (s, C-3), 152.9 (d, C-9), 132.7 (s, C-1), 97.3 (s, C-2). This compound has been described as the cis,cis-isomer by Brannock et al. (mp 109.5-110.5 °C),[8] Paquette and Begland (mp 139-141 °C),[18] and Hirsch and Cross (mp 140-142 °C).[19] Compound **3d**, mp 102-106 °C (Et_2O), was characterized by its ^{1}H NMR [($CDCl_3$) δ 5.82 (dd, J = 5.0, 12.2 Hz, 1 H, =CH—), 3.72 and 3.57 (s, 3 H, OCH_3)][20] and ^{13}C NMR spectrum [($CDCl_3$) δ 163.7 (s, C-3), 147.3 (d, C-10), 132.7 (s, C-1), 98.0 (s, C-2)]. From the reaction of 1-(1-cyclopenten-1-yl)pyrrolidine with DMAD in diethyl ether we obtained dimethyl 3-(1-pyrrolidinyl)-*cis*,*cis*-2,7-cycloheptadiene-1,2-dicarboxylate[8] without observing the corresponding cis,trans isomer by ^{1}H NMR spectroscopy as an intermediate, possibly because of a fast isomerization of the cis,trans to the cis,cis isomer.

When the thiocin **3b** was heated in toluene for 4 h at 100 °C *in the dark* the cis,cis-isomer **4b** was isolated in a 44% yield as a crystalline solid, mp 169-170 °C (toluene). Upon irradiation at room temperature, however, **3b** isomerized to dimethyl 3,8-dihydro-6-(1-pyrrolidinyl)-2*H*-thiocin-4,5-dicarboxylate (**5**). Under the prevailing reaction conditions both isomers were not interconvertible.[23] Therefore, we concluded that **5** has to be formed by a photochemical [1,5] hydrogen shift. As can be seen from Dreiding models and from the X-ray structure of **3b**, the 4π system in **3b** is twisted, thus making the antarafacial hydrogen shift sterically possible. To our knowledge this is the first example of a photochemical [1,5] hydrogen shift in a cyclic system.[25]

Our results clearly show that the ring opening of cis-fused 3-aminocyclobutenes proceeds in a *conrotatory* mode, giving (strained) cis,trans-cycloalkadienes. The rate of isomerization and the relative equilibrium concentrations of **2** and **3** at ambient temperature depend on the ring size. These results make a revision of the structural assignment of a number of compounds obtained by reaction of enamines and DMAD[8,18,19,22] necessary. Also the stereochemistry published of several other compounds[18,26] might be incorrect. Moreover the formation of "abnormal" ring opening products like **5** that have previously been reported[24,27,28] can be rationalized in terms of the intermediacy of a cis,trans isomer and a subsequent [1,5] hydrogen shift.

Registry No. 1a, 1125-99-1; **1b**, 3417-64-9; **1c**, 14092-11-6; **1d**, 942-81-4; **2a**, 3603-83-6; **3a**, 83585-93-7; **3b**, 83585-90-4; **3c**, 42205-54-9; **3d**, 42205-55-0; **4a**, 83585-94-8; **4b**, 83585-91-5; **5b**, 83585-92-6; DMAD, 762-42-5.

Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, and a list of observed and calculated structure factors (30 pages). Ordering information is given on any current masthead page.

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(21) Reaction of 1-(1-cyclohexen-1-yl)piperidine and -morpholine with DMAD gave the corresponding cyclobutenes as oils.[22] At room temperature these compounds produce slowly the *cis*,*cis*-2,8-cyclooctadienes, but the corresponding cis,trans-isomers could not be detected by ^{1}H NMR spectroscopy.
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General Synthesis of Chiral Borinic Acid Esters. Asymmetric Synthesis of Acyclic Ketones via Asymmetric Hydroboration-Carbenoidation

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Asymmetric hydroboration of prochiral alkenes with monoisopinocampheylborane in the molar ratio of 1:1, followed by a second hydroboration of nonprochiral alkenes with the intermediate dialkylboranes, provides the chiral mixed trialkylboranes. Treatment of these trialkylboranes with acetaldehyde under mild conditions results in the selective, facile elimination of the 3-pinanyl group, providing the corresponding chiral borinic acid esters with enantiomeric purities of 73-100% ee. Treatment of these intermediates with base and dichloromethyl methyl ether provides the chiral ketones, following oxidation of the intermediates, with enantiomeric purities as high as 90%.

The asymmetric synthesis of ketones has been extensively studied in the past decade.[2,3] The activity, however, is achieved primarily by the enantioselective alkylation of appropriate ketones. In the case of enantioselective alkylation of acyclic ketones, the most favorable results are realized only in the alkylation of symmetrical ketones, thereby limiting seriously the generality of the method. The present study reports a new, more general approach for the asymmetric synthesis of acyclic ketones involving asymmetric hydroboration-carbenoidation, as well as the first general synthesis of chiral borinic acid esters.

Asymmetric hydroboration has now been known for more than 2 decades,[4] and many applications of the reaction have been reported.[5] However, the high asymmetric induction achieved in the reaction has not hitherto been utilized for the asymmetric formation of carbon-carbon bonds.

It is known that under vigorous conditions trialkylboranes react with benzaldehyde to form the borinic acid esters.[6,7] Recently this reaction has been applied for a direct chiral synthesis of boronic esters.[8] However, the selective reaction of aldehydes with mixed trialkylboranes is not known.

Consequently, the strategy of the present method depends upon the successful synthesis of chiral mixed trialkylboranes, followed by selective elimination of the starting chiral auxiliary, the 3-pinanyl group, from the boron intermediate. Thus, hydroboration of *trans*-2-butene with monoisopinocampheylborane[9-11] ($IpcBH_2$) in the molar ratio of 1:1 results in the formation of 3-pinanyl-2-butylborane, which then rapidly hydroborates 1-pentene at -25 °C to provide the corresponding chiral mixed trialkylborane.

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Table I. Synthesis of Chiral Borinic Esters via Asymmetric Hydroboration Displacement[a]

olefin A	olefin B	borinate ester	yield, % (isolated)	bp, °C (mmHg)	$[\alpha]^{23}_D$, deg	ee, %	config
trans-2-butene	1-pentene	ethyl 2-butyl-*n*-pentylborinate	75	47 (1)	−4.7 (*c* 7.4, THF)	73	*R*
1-methylcyclohexene	1-pentene	ethyl *trans*-(2-methylcyclohexyl)-*n*-pentylborinate	72	65 (0.01)	−24.7 (*c* 8.6, THF)	75	1*R*,2*R*
1-phenylcyclopentene	ethylene	ethyl *trans*-(2-phenylcyclopentyl)-ethylborinate	67	85 (0.01)	−26.6 (*c* 11.8, THF)	100	1*R*,2*R*

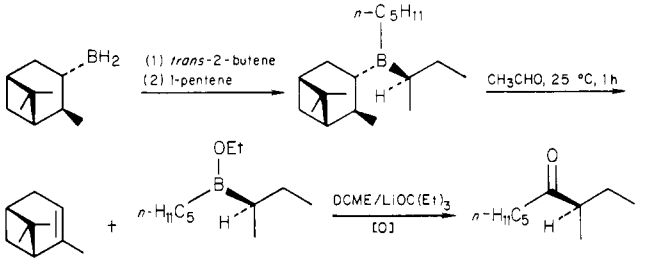
[a] $IpcBH_2$, prepared from (−)-α-pinene, was used for asymmetric hydroboration.

Table II. Asymmetric Synthesis of Representative Acyclic Ketones via Asymmetric Hydroboration[a]–Carbenoidation

		product ketones				
olefin A	olefin B	ketone	yield, % (isolated)	$[\alpha]^{23}_D$, deg	ee, %	config
trans-2-butene	ethylene	4-methyl-3-hexanone	78[b]	−19.2 (*c* 3.67, Et_2O)	60[c]	*R*
trans-2-butene	1-pentene	3-methyl-4-nonanone	66	−15.7 (*c* 5, Et_2O)	70[d]	*R*
trans-2-butene	5-hexenylacetate	8-methyl-7-oxo-1-decanol[e]	65	−11.92 (*c* 5.11, EtOH)	*f*	*R*
1-methylcyclohexene	1-pentene	*trans*-2-methylcyclohexyl *n*-pentyl ketone	70	−14.7 (*c* 5.2, EtOH)	75[g]	1*R*,2*R*
1-phenylcyclopentene	1-pentene	*trans*-2-phenylcyclopentyl *n*-pentyl ketone	78	−103.8 (*c* 5.2, EtOH)	90[g]	1*R*,2*S*
1-phenylcyclopentene	*h*	*trans*-2-phenylcyclopentyl methyl ketone	66	−106.8 (*c* 5, EtOH)	90[g]	1*R*,2*S*

[a] $IpcBH_2$, prepared from (−)-α-pinene, was used for asymmetric hydroboration. [b] GC yield. [c] Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 397. These authors report $[\alpha]^{23}_D$ +30.2° (*c* 3.7, Et_2O) for 94% ee 4-methyl-3-hexanone. [d] Seebach, D.; Steinmüller, D. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 619. These authors report maximum rotation for 3-methyl-4-nonanone $[\alpha]^{23}_D$ +22.4° (*c* 5, Et_2O). [e] The acetoxy group is hydrolyzed under DCME oxidation conditions. [f] Attempts to determine % ee by ^1H NMR in the presence of chiral shift reagent Eu(hfc)$_3$ were unsuccessful. [g] As determined by ^1H NMR in the presence of chiral shift reagent Eu(hfc)$_3$ by using Varian XL-200 spectrometer.[18] [h] Methyllithium is used to prepare the trialkylborane containing methyl as one of the alkyl groups.

Reaction of the resulting trialkylborane with acetaldehyde under very mild conditions (25 °C, 1 h) occurs with selective, facile elimination of only the 3-pinanyl group to provide ethyl 2-butyl-*n*-pentylborinate and α-pinene (eq 1).



(1)

The α-pinene eliminated is readily removed by distillation under vacuum. It may be noted that the α-pinene thus recovered is optically pure, $[\alpha]^{23}_D$ −51.5° (neat). Distillation of the residue yields (*R*)-(−)-ethyl 2-butyl-*n*-pentylborinate (bp 47 °C (1 mmHg), $[\alpha]^{23}_D$ −4.7° (*c* 7.4, THF)] in 73% ee as estimated by its oxidation to (*R*)-(−)-2-butanol. Similarly, we have prepared ethyl *trans*-(2-methylcyclohexyl)-*n*-pentylborinate and ethyl *trans*-(2-phenylcyclopentyl)ethylborinate in 75% and 100% ee, respectively (Table I).

Treatment of the ethyl 2-butyl-*n*-pentylborinate with α,α-dichloromethyl methyl ether (DCME) and lithium triethylcarboxide,[12] followed by the alkaline hydrogen peroxide oxidation of the intermediate, furnished (*R*)-(−)-3-methyl-4-nonanone in 70% ee.

In a similar manner, we have prepared several other chiral borinic esters, and converted them, without isolation, into the ketones (Table II) including an alarm pheromone of the ant *Manica mutica*[13] (Table II, entry 1).

The synthesis of the borinic acid esters and the corresponding chiral alkyl ketones containing methyl groups is readily achieved as follows. The dialkylborane, obtained by the hydroboration of 1-phenylcyclopentene with $IpcBH_2$, was methanolyzed and the borinate ester in *n*-pentane treated with methyl lithium at −78 °C. The "ate" complex, on warming to room temperature (25 °C), precipitated lithium methoxide, forming the trialkylborane bearing methyl as one of the alkyl groups.[14] The trialkylborane then on successive treatment with acetaldehyde, DCME,[12] and oxidation with alkaline hydrogen peroxide provided *trans*-2-phenylcyclopentyl methyl ketone in 90% ee.

The following experimental procedure is representative.[15] $IpcBH_2$ of 100% optical purity was prepared from (−)-α-pinene[16] ($[\alpha]^{23}_D$ −48.7° (neat), 94.9% ee) following the reported procedure.[9,17] To a 40-mL solution of 0.75 M (30 mmol) $IpcBH_2$ at −25 °C was added 4.4 mL (30 mmol) of 1-phenylcyclopentene, followed by addition of 3.3 mL (30 mmol) of 1-pentene after 48 h at −25 °C. The hydroboration of 1-pentene was complete after stirring for 6 h at −25 °C (^{11}B NMR δ +83). The trialkylborane was then treated with 3.5 mL (60 mmol) of acetaldehyde at 0 °C. The formation of borinate was complete after 3.5 h at 0 °C. The excess acetaldehyde was pumped off (25 °C (14 mmHg), 1 h), the flask filled with nitrogen, and the residue dissolved in THF (25 mL). The reported procedure[12] was followed for conversion of the borinate to the ketone.

The method provides a convenient procedure for the general synthesis of acyclic chiral ketones in a very high enantiomeric purities. The high asymmetric induction realized in the asymmetric hydroboration reaction is retained in the carbon–carbon bond-forming reaction. Even though the chiral center is in the α position to the keto group, there is only 2–6% racemization under alkaline conditions utilized for the hydrogen peroxide oxidation. The unique advantage of the present method over the known enantioselective alkylation procedures is its application to the asymmetric synthesis of ketones containing two chiral centers (Table I, entries 3–6). Moreover, ketones with chiral centers of opposite configuration can be readily synthesized by using $IpcBH_2$ derived from (+)-α-pinene. The simplicity of the method is evidenced by joining two alkyl groups from two olefinic fragments into a ketone in a one-pot synthesis via this asymmetric hydro-

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boration–carbenoidation–oxidation reaction. The chiral auxiliary, α-pinene, can be readily recovered and recycled, making the asymmetric synthesis exceptionally efficient. With the increasing knowledge of organoboranes, the asymmetric synthesis of chiral products via carbon–carbon bond formation has now become more attractive. We are continuing to explore asymmetric synthesis via chiral organoboranes.

(18) The Varian XL-200 spectrometer was purchased with funds from NSF Grant CHE-8004246. This support is gratefully acknowledged.

Isolation and Structure of Bryostatin 1[1]

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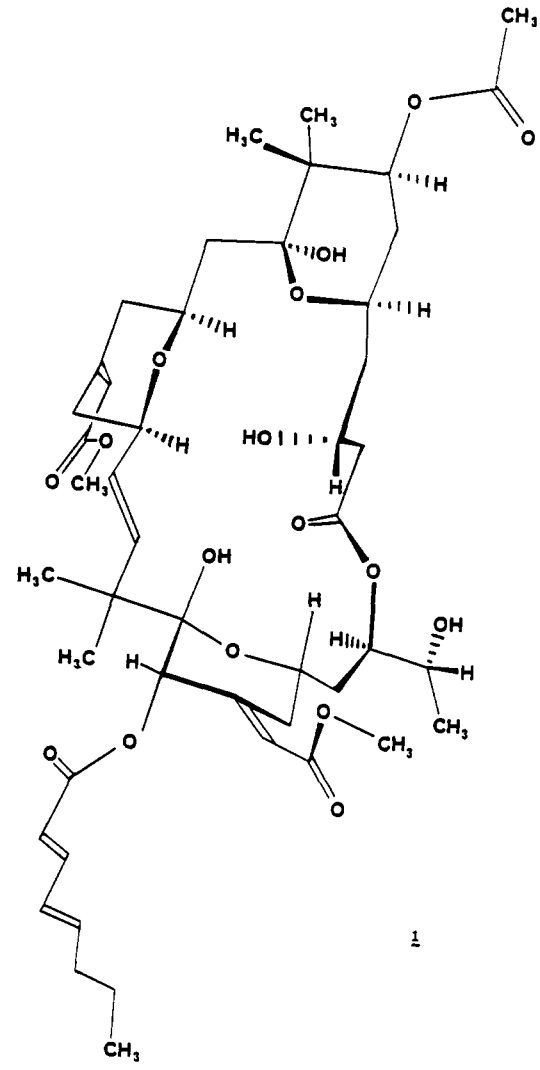
Marine animals of the phylum Ectoprocta (usually termed Bryozoa or Polyzoa) are colonial filter-feeders and each member (polypide) is enclosed in a separate unit (zooecium). Because of their superficial appearance Bryozoa are commonly known as sea-mats and false corals.[2] The genus *Bugula*[3] contains very prominent mosslike colonies, and *Bugula neritina* (Linnaeus) is well-known for its ability to attach to ship hulls.[4] Our initial report[5] that certain Bryozoa such as *B. neritina* L. contain anticancer constitutents, preliminary study of an adrenochrome-like pigment in the same species,[6] and isolation of indoles such as flustramines A and B from *Flustra foliacea*[7] appear to represent the only prior chemical investigations of Bryozoan metabolites.

We now report the structure of a remarkable[8] anticancer constituent of *Bugula neritina* designated bryostatin 1. The study began in 1968 with a Gulf of Mexico collection and has recently culminated in the structural elucidation of bryostatin 1 (**1**) by crystallographic and spectroscopic techniques. The biological activity of bryostatin 1 (**1**) is noteworthy. In the murine P388 lymphocytic leukemia (PS system)[9] macrocyclic lactone **1** shows 52–96% life extension at 10–70 μg/(kg/injection dose) levels and an ED_{50} of 0.89 μg/mL against the P388 in vitro cell line.

An initial methylene chloride extract prepared from 500 kg of wet animals was further fractioned by the solvent partition sequence 9:1 → 4:1 methanol–water with ligroin → carbon tetrachloride.[10] The carbon tetrachloride fraction (214 g) was purified by column chromatography using both Sephadex LH-20 and silica gel monitored by bioassay (PS system). Recrystallization from methylene chloride–methanol gave crystals of bryostatin 1 (**1**): melting at 230–235 °C. TLC (silica gel) R_f 0.7 (9:1 CH_2Cl_2–CH_3OH); EI MS *m/z* 886 ($M-H_2O$, $C_{47}H_{66}O_{16}$), exact mass 886.4376 amu (calcd. 886.4351 for $C_{47}H_{66}O_{16}$); FAB MS *m/z* 904 (M); $[\alpha]^{25}_D$ + 34.1° (*c* = 0.044, CH_3OH); UV (CH_3OH) λ_{max} 233 nm (ε 25 700) and 263 (ε 28 700); IR (KBr) 3470, 3400, 2970, 2950, 1735, 1716, 1700, 1640, 1600, 1433, 1385, 1365, 1245, 1160, 1100, 1080, 1000 cm^{-1}. Detailed high-resolution (400 MHz) NMR data has been included in a subsequent report.[11]



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Stout parallelepiped crystals were obtained from slow mixing of a layered solution of bryostatin 1 in methylene chloride under methanol. When maintained in the mother liquor, these crystals were found to belong to space group $P2_12_12_1$ with *a* = 21.782 (5), *b* = 20.428 (4) and *c* = 23.664 (6) Å and *Z* = 8. As the crystals dried, the *c* axis appeared to halve, and the relatively poor diffraction pattern conformed to $P2_12_12$.[12] A total of 5464 reflections was collected at −100 °C by using 1° ω scans and graphite-monochromated Mo Kα (0.710 69 Å) radiation. Of these data, 3553 (65%) were judged observed ($|F_o| > 3\sigma(F_o)$) and used in subsequent calculations. By means of the program system

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