Japanese group have found that the *E* lithium enolate of ethyl propionate reacts with ethyl (*E*)-crotonate to give the anti and syn 1,4 adducts in a ratio of 71:29[16a] and that the stereoselectivity is increased to 10:1 if HMPT is added *subsequent* to enolate formation and to >20:1 if HMPT is added prior to enolate formation.[16b] The latter observation is consistent with our finding that the *Z* enolate **1**, formed by deprotonation of *tert*-butyl propionate in the presence of HMPT,[4] gives predominantly the anti-Michael adduct. However, we observe high syn selectivity with the enolate formed in THF alone and have not observed a reversal to anti selectivity if HMPT is added after formation of the enolate. In agreement with our results, Yamaguchi and co-workers also found that the *E* enolate of *tert*-butyl propionate (**2**), formed by deprotonation of *tert*-butyl propionate in the absence of HMPT, reacts with ethyl (*E*)-crotonate to give the syn diastereomer (stereoselectivity >20:1).[16b]

In summary, our investigations with the stereoisomeric *E* and *Z* enolates of *tert*-butyl propionate have demonstrated that there is a relationship between enolate geometry and Michael adduct stereostructure, as has been previously found in the aldol addition reactions of lithium enolates.[3] Experiments aimed at further defining the mechanism and scope of the kinetic Michael reaction and at the synthetic exploitation of the stereoselective processes reported in this communication are in progress.

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Supplementary Material Available: A listing of the ^{13}C NMR chemical shifts of the products summarized in Table I (1 page). Ordering information is given on any current masthead page.

(16) (a) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Chem. Lett.* **1984**, 375. (b) Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661.

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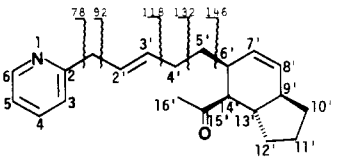
An Intriguing C_{16}-Alkadienone-Substituted 2-Pyridine from a Marine Mollusk[1]

Summary: A minor metabolite of the caphalaspidean mollusk *Philinopsis speciosa* is an uncommon pyridine derivative, substituted at C-2 by a bicyclic polyketide derived C_{16}-alkadienone. Its structure was elucidated largely by ^1H NMR techniques.

Sir: Our search for ecologically meaningful metabolites of coral reef invertebrates has prompted us to study the endemic Hawaiian opisthobranch mollusk *Philinopsis speciosa*. *P. speciosa* belongs to the order Cephalaspidea, characterized by a prominent head shield; it has a thin shell enclosed in the mantle and feeds on other mollusks at night, when it may be found in sandy tidepools during June and July.[2] Its principal organic constituents are C_{24}- and C_{25}-polypropionate compounds to be described elsewhere. Here we report on the structure of pulo'upone[3] (**1**),



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a minor (0.008% of freeze-dried animal) metabolite, which is an uncommon pyridine derivative substituted at C-2 by a bicyclic C_{16}-polyketide. Hexane extraction of 59 freeze-dried animals (77.5 g) yielded 1.17 g of residue. Chromatography on Sephadex LH-20 (1:1 CH_2Cl_2/2-PrOH) yielded four fractions; the last (613 mg) was triturated with MeCN and then passed through a C_{18} Bond Elut[4] cartridge (MeCN). The eluate after HPLC on Bondapak C_{18} (MeCN) was split into three fractions. Rechromatography of the middle fraction on Bondapak C_{18} (85:15 MeCN/H_2O) furnished pulo'upone (**1**, 6.5 mg) as a colorless oil, $[\alpha]_D$ −10° (*c* 0.20, hexane).

HRMS revealed a composition of $C_{21}H_{27}NO$ (*m/z* 309.2095, calcd 309.2093), which together with UV bands (EtOH) at 260 (ε 10 700), 257 (3870), 263 (4200), and 269 (3130) nm suggested a substituted pyridine. MS fragments[6] at *m/z* 78, 92, 118, 132, and 146 (see formula *1*) were indicative of an unbranched C_5 monoolefinic side chain. Four downfield proton signals in the ^1H NMR spectrum of **1** (Table I) require a monosubstituted pyridine; an acetyl group (δ 2.09 (s, 3 H) and ν_{max} 1713 cm^{-1}) defines the terminus of the side chain. Full ^1H NMR data are given in Table I.

A ^1H NMR COSY experiment and extensive decoupling in C_6D_6 showed that the pyridine ring was 2-substituted

Table I. ^1H NMR Data (300 MHz) for 1 in Cd_2Cl_2 and C_6D_6

	CD_2Cl_2		C_6D_6	
^1H	δ	*J*	δ	*J*
3	7.14 br d	8.2	6.78 d	7.6
4	7.63 ddd	1.7, 7.7, 8.2	7.02 ddd	1.8, 7.3, 7.6
5	7.13 br dd	5.0, 7.7	6.56 dd	4.9, 7.3
6	8.48 dd	0.8, 5.0	8.46 dd	1.8, 4.9
1′a,b	3.50 br d	6.6	3.51 d	6.9
2′	5.65 br dd	6.6, 15.3	5.72 ddd	6.9, 6.9, 15.0
3′	5.51 ddd	5.3, 6.6, 15.3	5.36 ddd	6.7, 6.8, 15.0
4′a	2.15 m		2.05 m	
4′b	2.00 m		1.87 m	
5′a	1.3 m		1.38 m	
5′b	1.2 m		1.28 m	
6′	2.65 m		2.35 m	
7′	5.70 ddd	2.6, 3.9, 9.9	5.57 ddd	2.4, 3.3, 9.8
8′	5.86 d	9.9	5.82 d	9.8
9′	2.0 m		2.3 m	
10′a	1.3 m		1.4 m	
10′b	1.2 m		1.4 m	
11′a	1.7 m		1.6 m	
11′b	1.6 m		1.6 m	
12′a	0.93 m		1.1 m	
12′b	1.15 m		0.9 m	
13′	1.54 m	6, 9, 10, 11.0	1.6 m	
14′	2.75 dd	6.2, 11.0	2.40 br d	7.3
16′	2.09 s	CH_3	1.71 s	CH_3

(1) A preliminary account was presented at the PacChem Congress, Honolulu, HI, Dec 16-21, 1984, Abstract *ORGN* 10 E 23.

(2) Kay, E. A. "Hawaiian Marine Shells"; Bishop Museum Press: Honolulu, HI, 1979; p 430.
(3) Pulo'u is the Hawaiian word for head covering.
(4) Analytichem International, Harbor City, CA.
(5) Waters Associates, Inc., Milford, MA.
(6) EIMS, *m/z* 309 (5%), 267 (18), 266 (91), 173 (7), 172 (6), 147 (10), 146 (62), 133 (66), 132 (39), 131 (15), 130 (28), 119 (30), 118 (72), 106 (15), 93 (59), 92 (13), 91 (44), 79 (22), 78 (10), 77 (15), 67 (11), 43 (100).
(7) IR (film) ν_{max} 2924, 2856, 1713, 1456, 1435, 1354, 970 cm^{-1}.

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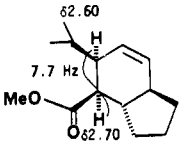
and that the benzylic methylene at C-1′, which upon irradiation caused sharpening of H-3 and H-4, was coupled to an olefinic proton at δ 5.72 (H-2′). This olefinic proton also is coupled to H-3′ (δ 5.36, J = 15 Hz), thus defining trans geometry. The ^{1}H NMR decoupling data readily extend the structure to C-8′, which forms a *cis*-olefin with C-7′ (J = 9.8 Hz). H-8′ shows no further coupling.

Change of solvent from C_6D_6 to CD_2Cl_2, while obscuring the lowfield region, clarified the remaining upfield ^{1}H NMR signals. The multiplet at δ 2.65 (H-6′) is coupled by 6.2 Hz to a doublet of doublets at δ 2.75 (H-14′). This chemical shift suggests that C-14′ bears the acetyl group. H-14′ is further coupled to a multiplet at δ 1.54 (H-13′) by 11.0 Hz. This proton (H-13′) is further coupled to ^{1}H signals at δ 1.15 (J = 6 Hz) and 0.93 (J = 9 Hz) assigned to CH_2-12′ and also to a signal at δ 2.0 (J = 10 Hz) assigned to H-9′. Chemical shifts and coupling constants define the six-membered ring of the hydrindene system and the relative stereochemistry of the four chiral carbons: the three protons at C-14′, C-13′, and C-9′ must be axial, while the 6.2-Hz coupling between H-6′ and H-14′ indicates a cis relationship and hence an equatorial H-6′.[8] Synthetic analogue **2** supports this assignment.[9] Absence of coupling



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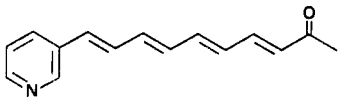
between H-9′ and H-8′ is necessitated by a dihedral angle of 90° as seen in a Dreiding model of **1**. Three remaining methylene groups at C-10′, C-11′, and C-12′ give rise to complex and overlapping multiplets (Table I) but uniquely encompass the five-membered ring.

Pulo'upone has no close analogue among natural or synthetic products. Aside from nicotine and related alkaloids, simple substituted pyridines other than the common coal tar substituents are rare in nature. The closest structural relative of pulo'upone (**1**) is navenone A (**3**), the



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major constituent of the alarm pheromone of *Navanax inermis*, a related cephalaspidean mollusk.[10,11] Because of the small quantity of pulo'upone available to us, we could not evaluate its biological activity in an ecological or anthropocentric context. Interestingly, 2-alkylpyridines of various chain lengths have been evaluated as antibacterials.[12]

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(8) We thank one of the referees for this suggestion.
(9) Roush, W. R.; Gillis, H. G.; Ko. A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269–2283.
(10) Sleeper, H. L.; Fenical, W. *J. Am. Chem. Soc.* **1977**, *99*, 2367–2368.
(11) Sleeper, H. L.; Paul, V. J.; Fenical, W. *J. Chem. Ecol.* **1980**, *6*, 57–70.
(12) Birchenough, M. J. *J. Chem. Soc.* **1951**, 1263–1266.

Application of Kinetic, Asymmetric Selection to the Breaking of Molecular Symmetry

Summary: Reaction of the chiral glyoxylate **1** with 1 equiv of diene **2** in dichloromethane at −78 °C in the presence of a stoichiometric amount of stannic chloride afforded the ene adduct **3** in 74% chemical yield after chromatographic purification. The combination of the face selectivity of the glyoxylate with that of the bicyclo[3.3.0]octadiene provided for selection between the enantiotopically related rings of **2** and effected a selective breaking of molecular symmetry.

Sir: In recent articles[1,2] Bertz has drawn attention to disadvantages attending the presence of symmetrically related but remote functionality within a synthetic intermediate. While his conclusions are valid in general, such molecular properties in fact can be turned to advantage when the symmetry element present is a mirror plane. In this case, the symmetrically disposed portions of the molecule are actually enantiotopic rather than identical and thus, in theory, can be differentiated by reagents capable of chiral recognition. The application of such selectivity not only has the advantage that the reaction is controlled to only one site but also, and as a direct consequence, that it results in the creation of new elements of chirality with induction of asymmetry. While the utility of enzymes for the differentiation of enantiotopically related functionality has already been realized,[3] we know of no example of the application of the recently developed and powerful methods for asymmetric induction such as the Sharpless oxidation[4] to such selection.

In 1982 we reported[5] on the reactions of 8-phenylmenthol glyoxylate (**1**) for the induction of asymmetry through both Grignard addition to and ene reactions of the aldehyde functionality. Subsequently, we discovered that this same reagent is capable of effecting kinetic resolution of selected alkenes and wish to illustrate this feature here as it applies to the selective breaking of molecular symmetry in diene **2**. Note that the two double bonds are enantiotopically related by reflection through the mirror plane of symmetry present in **2** and that the bridgehead atoms are thus prochiral (Figure 1). Reaction of the glyoxylate **1** with 1 equiv of diene **2** in dichloromethane at −78 °C in the presence of a stoichiometric amount of stannic chloride afforded the ene adduct **3** in 74% chemical yield after chromatographic purification. The ^{13}C NMR

(1) Bertz, S. H. *Tetrahedron Lett.* **1983**, *24*, 5577.
(2) Bertz, S. H. *J. Chem. Soc., Chem. Commun.* **1984**, 218.
(3) For a recent example using pig liver esterase and a compilation of other enzymatic applications, see: Francis, C. J.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 579.
(4) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
(5) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988. Whitesell, J. K.; Bhattacharya, A.; Aguilar, D. A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 989.

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