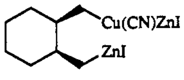
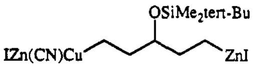
equiv) is added to the reaction mixture, furnishing the desired monocoupling product with less than 5% of symmetrical dicoupling adduct ($E^1(CH_2)_nE^1$). The addition of pentane was found to be critical for this selectivity and can be rationalized by assuming that this low dielectric constant solvent favors the formation of higher aggregates of **5** having lower reactivities.[7] As shown in Table I, bimetallic reagents in which the two metals are separated by 4, 5, or 6 carbon atoms display excellent selectivities. More substituted reagents such as **4d** can be readily prepared.[8] The coupling of **4d** with electrophiles yields pure *cis*-1,2-cyclohexane derivatives (entries 13 and 14). Finally, the functionalized[9] heterobimetallic **4e** (entry 15) reacts selectively with diethyl benzylidenemalonate and allyl bromide, affording the desired coupling product **6o** in 75% yield.

$IZn(CN)Cu(CH_2)_nZnI$

4a: n = 4
4b: n = 5
4c: n = 6


4d


4e

We have observed that the zinc and the copper homobimetallics ($IZn(CH_2)_4ZnI$ (**8**) and $IZn(CN)Cu(CH_2)_4Cu(CN)ZnI$ (**9**)) did not undergo selective reactions. Thus the *dicopper reagent* **9** reacts with benzaldehyde (0.7 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2 equiv) and leads to a mixture of the desired monoadduct **5a** and the diadduct $PhCH(OM)(CH_2)_4CH(OM)Ph$ (60:40 ratio by GLC analysis of an hydrolyzed reaction aliquot). The remarkable aspect of the reactivity of the *heterobimetallics* of zinc and copper **4** is the broad range of electrophiles[10] which react selectively to give functionalized organometallics of type **5** (Table I). Nevertheless, we observed that electrophiles which react with organozinc halides (RZnX) in the presence of *a catalytic amount* of $CuCN{\cdot}2LiCl$ such as acyl chlorides or allylic halides[6] did not display this selectivity and their reaction with **4** afforded a mixture of mono- and diadducts under various reaction conditions. The unique selectivity displayed by the reagents **4** can be explained by the high reactivity of the carbon–copper bond (compared to the carbon–zinc bond) toward electrophiles leading to intermediate organometallics **5** (Table I), the structures of which are best viewed as being mixed copper–zinc clusters also containing lithium salts coming from $CuCN{\cdot}2LiCl$. These reagents have a diminished reactivity,[11] which is accentuated by the presence of pentane as cosolvent and in some cases by chelating interactions (as for the compounds **5a–b,f–i,k,m,n**). This preliminary study shows that the two primary carbon–metal bonds of a 1,*n*-heterobimetallic reagent of zinc and copper (*n* = 4–6) can be differentiated by a variety of electrophiles E^1 allowing a new approach to various types of new highly functionalized intermediate zinc and copper organometallics **5** (Table I). After their coupling with a second, different electrophile E^2 a broad range of polyfunctional molecules are obtained. Extensions of this method are currently underway in our laboratories.

Acknowledgment. We thank the National Science Foundation (Grant CHE-8818704) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supplementary Material Available: Characterization data for all new compounds (10 pages). Ordering information is given on any current masthead page.

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(7) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H.-R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. (c) Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597. (d) Bates, T. F.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5109.

(8) 1,2-Diiodomethylcyclohexane was prepared from 1,2-dihydroxymethylcyclohexane via the dimesylate: (a) Haggis, G. A.; Owen, L. N. *J. Chem. Soc.* **1953**, 389. (b) Bailey, W. F.; Gagnier, P. R.; Patricia, J. J. *J. Org. Chem.* **1984**, *44*, 2098.

(9) 1,5-Diiodo-3-[(*tert*-butyldimethylsilyl)oxy]pentane was prepared from diethyl 1,3-acetonedicarboxylate via standard procedures (see supplementary material).

(10) Symmetrical di-Grignard reagents do not react selectively with electrophiles (see: (a) Bickelhaupt, F. In *Organometallics in Organic Synthesis 2*; Springer: Berlin-Heidelberg, 1989; p 145. (b) Raston, C. L.; Salem, G. In *The Chemistry of the Metal–Carbon Bond*; Hartley, F. R., Ed.; John Wiley: New York 1987; Vol 4, Chapter 2, p 159) and only *unsymmetrical* dimetallics bearing two carbon–metal bonds having a very different reactivity undergo selective reactions (see ref 1f, 10a and Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109).

(11) It has been observed in related studies that the reactivity of the copper reagents $RCu(CN)ZnI$ is strongly reduced in the presence of an excess of zinc halides. Since 1 equiv of ZnX_2 is liberated in the reaction of the bimetallics **4** with E^1, the reactivity of compounds **5** is expected to be lower than the one of **4**.

A Direct Preparation of Vinylogous Acyl Anion Equivalents

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Received April 25, 1991

Summary: Unmasked vinylogous acyl anion equivalents **2** were prepared by the insertion of zinc to various β-halo, α,β-unsaturated ketones and esters **1**. The new reagents **2** react with various electrophiles in the presence of $CuCN{\cdot}2LiCl$ or catalytic amounts of Pd(0) complexes in excellent yields.

Acyl anion equivalents[2] form an important class of reagents that display an umpolung of the carbonyl group reactivity (d^1 reagents).[3] Many acyl anion equivalents are masked carbonyl derivatives, which, after the reaction with an electrophile, have to be converted to the free carbonyl

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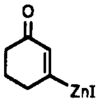
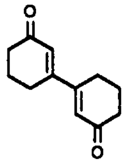
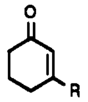
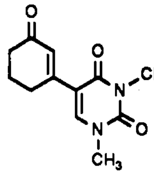
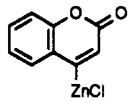
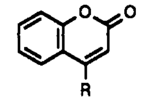
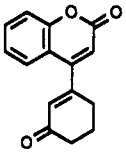
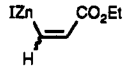
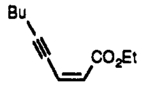
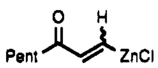
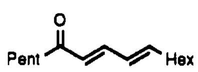
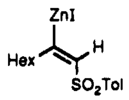
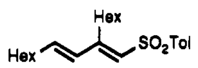
(1) Permanent address: Nizam College, Osmania University, Hyderabad, India.

(2) For a comprehensive list of acyl anions, see: *Umpolung Synthons*; Hase, T. A., Ed.; John Wiley and Sons: New York, 1987.

(3) Seebach, D. *Angew. Chem.* **1979**, *91*, 259; *Angew Chem., Int. Ed. Engl.* **1979**, *18*, 239.

0022-3263/91/1956-4593$02.50/0

Table I. Products 9–13 Obtained by the Copper(I)-Mediated and Palladium(0)-Catalyzed Reaction of the Organozinc Reagents 4–8 with Electrophiles

entry	organozinc reagent	electrophile	product	yield[a] (%)
1	 **4**	(thermolysis of the copper derivative)	 **9a**	83
2	**4**	Me$_3$SnCl[b]	 **9b**: R = SnMe$_3$	93
3	**4**	1-iodohexyne[b]	**9c**: R = C≡CBu	92
4	**4**	ethyl α-(bromomethyl)acrylate[b]	**9d**: R = $CH_2C(CO_2Et){=}CH_2$	83
5	**4**	1-nitro-1-pentene[b]	**9e**: R = $CH(Pr)CH_2NO_2$	76
6	**4**	1,3-dimethyl-5-iodouracil[c]	 **9f**	97
7	 **5**	ethyl α-(bromomethyl)acrylate[d]	 **10a**: R = $CH_2C(CO_2Et){=}CH_2$	71
8	**5**	(*E*)-1-iodooctene[c]	**10b**: R = (*E*)-CH=C(H)Hex	71
9	**5**	3-iodo-2-cyclohexen-1-one[d]	 **10c**	70
10	 **6** (*E*:*Z*, 11:89)	Me$_3$SnCl[b]	 **11a** (100% *Z*)	99
11	**6**	(*E*)-1-iodooctene[c]	 **11b** (100% 2*Z*,4*E*)	81
12	**6**	1-iodohexyne[b]	 **11c** (*E*:*Z*, 11:89)	81
13	 **7** (*E*:*Z*, 1:1)	(*E*)-1-iodooctene[c]	 **12** (100% *EE*)	55
14	 **8** (100% *E*)	(*E*)-1-iodooctene[c]	 **13** (100% *EE*)	40

[a] All yields refer to isolated yields of analytically pure products. Satisfactory spectra data (IR, ^1H and ^{13}C NMR, mass spectra and high-resolution mass spectra) were obtained for all new compounds (supplementary material). [b] The organozinc halide was first treated with CuCN·2LiCl (1.0 equiv) in THF–Me$_2$S (1:1) at −30 °C. [c] The reaction was performed in the presence of 1–2 mol % of bis(dibenzylideneacetone)palladium(0) (Pd(dba)$_2$) and 2–8 mol % of PPh$_3$. [d] The organozinc halide was first treated with CuCN·2LiCl (1.0 equiv) in THF at −30 °C.

functionality by an extra deprotection step.[2,4] Herein, we report a new direct preparation of a variety of vinylogous acyl anions[5] (d^3 reactivity)[3] obtained by using a very efficient insertion of zinc metal into the carbon–halogen bond of a β-halo unsaturated carbonyl derivative of type **1**. The organozinc halides of type **2a** (Met = ZnX), such as **4–8**, formed by this procedure undergo palladium(0)-catalyzed or copper(I)-mediated reactions with various

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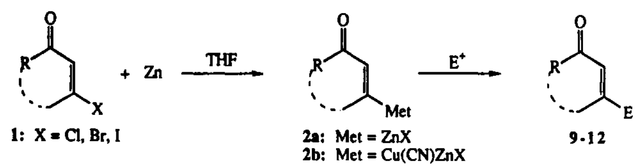
(4) For the preparation of unmasked acyl anions see: (a) Seyferth, D.; Hui, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4551. (b) Seyferth, D.; Hui, R. C. *Tetrahedron Lett.* **1986**, *27*, 1473. (c) Schwartz, J. *Tetrahedron Lett.* **1972**, 2803.

Scheme I

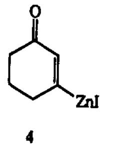


1: X = Cl, Br, I

2a: Met = ZnX
2b: Met = Cu(CN)ZnX

9-12

electrophiles affording products of type **9–12** in high yields (Scheme I and Table I). Thus the dropwise addition of a 3 M THF solution of 3-iodo-2-cyclohexen-1-one[6] to zinc dust[7] (3 equiv) at 25 °C led to an exothermic reaction (the reaction temperature rises from 25 °C to 50 °C). After 1 h of stirring at 25 °C, the GC analysis of a hydrolyzed reaction aliquot indicates the complete formation of (3-oxo-1-cyclohexenyl)zinc iodide, **4**. The addition of a THF solution of CuCN·2LiCl[7] to **4** leads to an unstable vinylic copper derivative of type **2b**, which reductively dimerizes at 0 °C, producing the dienic diketone **9a**, in 83% isolated yield. However, the addition of CuCN·2LiCl in a 1:1 mixture of THF and Me_2S at −40 °C leads to a stabilized copper reagent, which reacts readily with Me_3SnCl (0.8 equiv; −78 °C to 0 °C, 1 h) affording 3-(trimethylstannyl)cyclohexenone (**9b**) in 93% yield (entry 2). Its coupling with 1-iodohexyne[8] (0.8 equiv, −60 °C, 24 h) leads to the keto–enyne **9c** in 92% yield (entry 3). The allylation with ethyl α-(bromomethyl)acrylate[9] (0.8 equiv, −60 °C to 0 °C, 0.5 h) gives the keto ester **9d** in 83% yield (entry 4). The Michael addition to 1-nitropentene[10] (0.8 equiv, −60 °C to 0 °C, 3 h) affords the nitro ketone **9e** in 76% yield (entry 5). The zinc reagent **4** can also be coupled in the presence of a catalytic amount of $Pd(dba)_2$ (1–2 mol %)[11] and PPh_3 (4–8 mol %) with alkenyl and aryl iodides. Thus the reaction of **4** with 1,3-dimethyl-5-iodouracil[12] (0.8 equiv, 25 °C, 24 h) gives the heterocycle **9f** in quantitative yield (entry 6). Compared to the zinc insertion to nonfunctional alkenyl iodides, which requires high temperatures (60–70 °C) and the use of a polar solvent (DMF or DMAC),[13] the zinc insertion to 3-iodo-2-cyclohexen-1-one proceeds under very mild conditions. The presence of the carbonyl group greatly facilitates the initial electron transfer from the zinc metal to the organic substrate. This effect is so important that a direct zinc insertion into the *carbon–chloride* bond of 4-chlorocoumarin[14] occurs readily (45 °C, 4 h) and furnishes the desired organozinc chloride **5** in over 80% yield (determined by GLC analysis of hydrolyzed and iodolyzed reaction aliquots). The preparation of the corresponding copper reagent does not require the presence of Me_2S as cosolvent and after allylation with ethyl α-(bromomethyl)acrylate (0.7 equiv, −78 °C to 0 °C, 0.5 h) the 4-substituted coumarin **10a** is obtained in 71% yield (entry 7). An addition–elimination reaction of this copper reagent to 3-iodo-2-cyclohexen-1-one (0.7 equiv, −30 °C to −5 °C, 16 h) furnishes the dienic keto ester **10c** in 70% yield (entry 9). The Pd(0)-catalyzed coupling of (*E*)-1-iodooctene (0.7 equiv, 25 °C, 5 h) leads to the coumarin derivative **10b** in 71% yield (entry 8).



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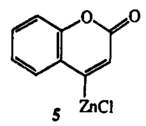
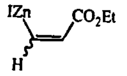
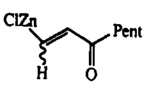


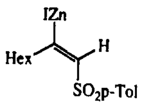
5



6



7



8

In order to examine the stereoselectivity of the zinc insertion, (*Z*)-ethyl 3-iodoacrylate[15] was treated with zinc dust (3 equiv) and the formation of a *E*:*Z* mixture (11:89) of the zinc reagent **6** (THF, 25 °C, 2–3 h; ca. 90% yield) was observed. Interestingly, the treatment of this mixture with CuCN·2LiCl (1 equiv) followed by the addition of Me_3SnCl (0.8 equiv, −30 °C to 0 °C, 3 h) leads to the formation of pure (*Z*)-ethyl 3-(trimethylstannyl)acrylate (**11a**) in quantitative yield (entry 10), indicating a higher reactivity of the intermediate (*Z*)-copper organometallic derived from **6**. The same type of kinetic differentiation is observed in the case of the palladium(0)-catalyzed coupling of 1-iodooctene with **6**, which afforded only the (2*Z*,4*E*)-dienic ester **11b** ($Pd(dba)_2$ (2 mol %), PPh_3 (8 mol %), 1-iodooctene (0.8 equiv), 25 °C, 2 h; 81%; entry 11). In the case of other electrophiles such as 1-iodohexyne, an *E*/*Z* ratio reflecting the initial *E*/*Z* ratio of the zinc organometallic is observed for the product **11c** ((i) CuCN·2LiCl in THF–Me_2S (1:1); (ii) 1-iodohexyne (0.8 equiv), −55 °C, 48 h; 81%; entry 12). Acyclic β-chloro enones such as 1-chloro-1-octen-3-one[16] can be converted to the corresponding zinc ragent **7** (THF, −15 °C to 10 °C, 2 h);[17] however, this compound is unstable and slowly decomposes under the reaction conditions. The Pd(0)-catalyzed coupling of **7** with (*E*)-1-iodooctene (0.7 equiv, 25 °C, 4 h) affords the dienic ketone **12** (100% *EE* isomer) in only 55% yield (entry 13). Interestingly, a β-iodo sulfone[18] rapidly undergoes the zinc insertion (THF, 25 °C, 4 h) providing the organozinc iodide **8**. This reagent shows a relatively good thermal stability and undergoes only a slow elimination of p-$TolSO_2ZnI$ ($t_{1/2}(25°C)$ = ca. 5 h). Its reaction with (*E*)-1-iodooctene (0.7 equiv, $Pd(dba)_2$ 2 mol %, PPh_3 8 mol %, 25 °C, 24 h) gives the stereochemically

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(5) (a) Piers, E.; Morton, H. E. *J. Org. Chem.* **1979**, *44*, 3437. (b) Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78. (c) Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612. (d) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1007, 1397. (e) Kondo, K.; Saito, E.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 2275. (f) Iwai, K.; Kosugi, H.; Miyazaki, A.; Uda, H. *Synth. Commun.* **1976**, *6*, 357. (g) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *J. Org. Chem.* **1976**, *41*, 2506. (h) Debal, A.; Cuvigny, T.; Larchevêque, M. *Tetrahedron Lett.* **1977**, 3187. (i) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346. (j) Bakuzis, P.; Bakuzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett.* **1978**, 2371. (k) Saddler, J. C.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1978**, 5079. (l) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 5167. (m) Baker, W. R.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 1022.

(6) (a) Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193. (b) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210.

(7) Zinc dust was purchased from Aldrich (−325 mesh) and activated with 5 mol % of 1,2-dibromoethane: Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(8) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799.

(9) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.

(10) (a) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017. (b) Retherford, C.; Yeh, M. C. P.; Schipor, I.; Chen, H. G.; Knochel, P. *J. Org. Chem.* **1989**, *54*, 5200.

(11) (a) Takahashi, Y.; Ito, T.; Sakai, S.; Ishii, Y. *J. Chem. Soc., Chem. Commun.* **1970**, 1065. (b) Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 134. (c) Mignani, ; Leising, F.; Meyrueix, R.; Samson, H. *Tetrahedron Lett.* **1990**, *31*, 4743. (d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (e) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.

(12) Olgilvie, K. K.; Beaucage, S.; Gillen, M. F. *Tetrahedron Lett.* **1978**, *35*, 3203.

(13) Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.

(14) Anschutz, v. R. *Liebigs Chem. Ann.* **1909**, *367*, 169.

(15) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 1643.

(16) Price, C. C.; Pappalardo, J. A. *Organic Syntheses*; Willey: New York, 1963; Collect Vol. IV, p 186.

(17) An iodolysis of **7** affords a 1:1 mixture of two *E* and *Z* isomeric β-iodo enones.

(18) (a) Truce, W. E.; Wolf, G. C. *J. Org. Chem.* **1971**, *36*, 1727. (b) Whitmore, F. C.; Thurman, N. *J. Am. Chem. Soc.* **1923**, *45*, 1068.

pure (*EE*) dienic sulfone **13** in 40% yield (entry 14).

Other electrophiles such as aldehydes, acid chlorides, and alkyl halides did not react in satisfactory yields with the alkenylcopper reagents **2b** due to their moderate reactivity.[19]

In summary, the facile insertion of zinc into the carbon–halogen bond of alkenyl halides bearing an electron-withdrawing substituent led to a very general preparation of new vinylogous *unmasked* acyl anion equivalents. Their reaction in the presence of Pd(0) or CuCN·2LiCl with various classes of electrophiles led to highly functionalized molecules. Extensions of this methodology are currently underway in our laboratories.

Acknowledgment. We thank the National Institutes of Health (GM 41908) and the Chemistry Department of the University of Michigan for their generous support of this work.

Supplementary Material Available: Typical experimental procedure and spectral data for all new compounds (8 pages). Ordering information is given on any current masthead page.

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[19] Alkenylcopper reagents are less reactive than alkylcopper derivatives limiting somewhat the range of electrophiles reacting with **2b**. See: Normant, J. F. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Salle and Sauerländer: Frankfurt, 1983, Vol. 3, p 139.

Wakayin: A Novel Cytotoxic Pyrroloiminoquinone Alkaloid from the Ascidian *Clavelina* Species

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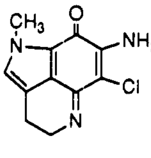
Summary: Wakayin (**3**) is the first reported example of a pyrroloiminoquinone alkaloid to be isolated from an ascidian.

Ascidians have been the recent source of many iminoquinone-bearing polycyclic aromatic alkaloids.[2] These structurally related compounds typically exhibit a wide range of biological activities, including murine cell-line cytotoxicity,[2] topoisomerase II,[2e] and microbe/fungus[2d] inhibition. The related pyrroloiminoquinone alkaloids, isobatzellines (e.g., isobatzelline C (**1**)), and discorhabdins/prianosins (e.g., discorhabdin C (**2**)) are, however, known only from phylum Porifera.[3]



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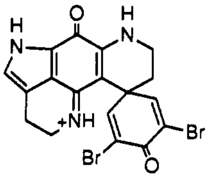

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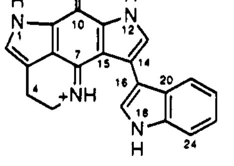

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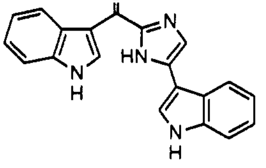

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In continuation of our search for biologically active secondary metabolites from ascidians, we now report the structure of a new pyrroloiminoquinone derivative, wakayin (**3**), isolated from the ascidian *Clavelina* sp. Wakayin exhibited in vitro cytotoxicity against the human colon tumor cell line (HCT116 IC_{50} 0.5 μg/mL). Inhibition of topoisomerase II enzyme (250 μM) and the observation of a 3-fold differential toxicity toward the CHO cell line EM9[4] (sensitive to DNA-damaging genotoxic agents) versus BR1[5] (resistant to BCNU) provided preliminary evidence that wakayin exhibits its cytotoxicity by interfering with or damaging DNA. Antimicrobial activity against *Bacillus subtilis* (MIC ≈ 0.3 μg/mL) was also observed.

The methanol–chloroform extract of the ascidian[6] was crudely partitioned by reversed-phase flash chromatography using methanol–aqueous trifluoroacetic acid solvent mixtures.[7] Biologically active fractions were combined and purified by repeated elution through Sephadex LH-20,

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[6] *Clavelina* species (Chordata, Aplousobranchia, Clavelinidae) was collected from shallow reef waters off Wakaya Island in the Fiji Group and was identified by Dr. F. Monniot, Museum National d'Histoire Naturelle, Paris, France.

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