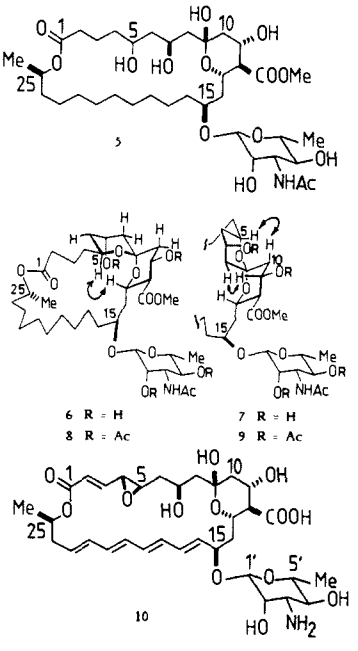

Figure 2.

three NOE distance constraints, a situation already observed in the stereostructural study of nystatin A_1.[12c] Consequently, the 7*R*, 9*S*, 11*S*, 12*R*, 13*S*, and 15*R* configurations were assigned for the pimaricin aglycon.

A precise definition of the local geometry of the C_{22}–C_{25} portion was easily derived from combined data taken from the DQF-COSY ($J_{23,24a}$ = 8.8, $J_{23,24e}$ = 2.5, $J_{24a,25}$ = 11.0, and $J_{24e,25}$ = 5.6 Hz) and NOESY experiments (H_{22}–H_{24a} and H_{23}–H_{25} NOE contacts, structure **4**). The *all-E* extended C_{16}–C_{23} tetraene (H_{17}–H_{18}, H_{19}–H_{20}, and H_{21}–H_{22} all antiperiplanar by pairs) behaves indeed as a long-range sensor which defines the orientation of H_{23} relative to H_{16} and hence to the C_9–C_{15} chiral segment. This observation combined with the C_{22}–C_{25} relative geometry described above defined the diastereotopicity of the H_{24} protons and, therefore, the *R* configuration at C_{25}.

Due to the quasi-planar arrangement of the epoxide function, the spectroscopic study left the C_4–C_5 configurations undetermined. At this point, it was anticipated that the disjunction of the macrocycle structural rigidity allied with a regioselective epoxide opening would permit the formation of a bicycloketal, a conformationally biased skeletal framework ideally suited for structural investigation. Hydrogenolysis (H_2, Pd/C, MeOH, room temperature, 1.5 h) and methyl ester formation (CH_2N_2, MeOH) on *N*-acetylpimaricin (**2**) led to the single saturated polyol **5**, $[\alpha]_D$ −70°, with a hydroxyl group located at C_5[20,21] (Figure 2). Acid-catalyzed bicycloketalization (CSA cat., $CHCl_3$–MeOH, 9:1, room temperature) gave two easily separated isomers **6**, $[\alpha]_D$ −88°, and **7**, $[\alpha]_D$ −105°, in a ratio of 2:1 (2-h reaction) transformed to a 40:1 ratio (72-h reaction, 85% yield). This chemical behavior strongly suggested a 5,7-*syn*-diol system.[22] Proton NMR analysis of tetra-*O*-acetates **8** (major isomer), $[\alpha]_D$ −71°, and **9** (minor isomer), $[\alpha]_D$ −47°, fully confirmed this prediction. The *J* coupling pattern observed (not shown) led to chair–chair bicycloketals with a characteristic splitting pattern for an equatorial proton at C_7 in both isomers. This conformational and configurational situation was fully validated by long-range space contacts derived from NOESY (ROESY) maps (H_5–H_{13} in **8** and H_5–H_{10e} and H_{8e}–H_{11} in **9**). The 5*R* configuration was then determined, and by extension the 4*S* configuration, thus defining the complete stereostructure of pimaricin as **10**.

Analyzing through-space contacts between a well-characterized carbohydrate and a chiral aglycon of unknown absolute configuration represents a simple and powerful method of general interest for three-dimensional assignments of naturally or artifically glycosylated structures. In polyene macrolides containing polyhydroxy ketonic structural segments, bicycloketalization of saturated macrocycles may provide a useful protocol for stereostructure determination.

Acknowledgment. We express our gratitude to Gist-Brocades (The Netherlands) for a generous supply of pimaricin.

Supplementary Material Available: Physical data for **3** and **5**–**7**, phase-sensitive DQF-COSY data for **1**, **2**, **5**, **8**, and **9**, and NOESY/ROESY data for **1**, **2**, **8**, and **9** (5 pages). Ordering information is given on any current masthead page.

(20) Information obtained by the phase-sensitive DQF-COSY spectrum of **5** in DMSO-d_6 (15 mM, 298 K): H_5 (3.60 ppm), OH_5 (4.54). 2 H_6 (1.39–1.49). H_7 (4.08). and OH_7 (4.92).

(21) The same degradation sequence was described to give an hydroxyl group at C_4[18a] in contradiction with the previous findings of Golding et al.[2] placing the OH group at C_5 in the allylic hydrogenolysis of the epoxide function of *N*-acetylpimaricin (**2**).

(22) A 5,7-*anti*-diol system would cyclize in two isomers equilibrating under mild acidic conditions to a ratio of approximately 1:1, as no differences in electronic effects (stabilizing) and steric effects (destabilizing) between the two isomers would be observed.[23]

(23) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

[7.7]Paracyclophanes from Blue-Green Algae

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[*m.n*]Paracyclophanes[1] were first described by Cram and Steinberg in 1951.[2] These carbocyclic compounds, known to date only through synthesis, have provided interesting vehicles for host–guest chemistry. We report here the isolation and identification of [7.7]paracyclophanes from two species of cytotoxic blue-green algae belonging to the Nostocaceae. This marks the first time that this class of macrocyclic compounds has been found in Nature.

In an evaluation of blue-green algae for antitumor activity, extracts of two species belonging to the Nostocaceae, viz., *Cylindrospermum licheniforme* Kutzing (ATCC 29204) and *Nostoc linckia* (Roth) Bornet (UTEX B1932), were found to exhibit moderate cytotoxicity against KB and LoVo tumor cell lines at <20 μg/mL.[3,4] Each freeze-dried cyanophyte[5] was extracted with 70% aqueous ethanol and the resulting extract subjected to normal-phase (silica gel) and/or reverse-phase (C-18) column chromatography, to give a mixture of cytotoxic [7.7]para-

(1) Keehn, P. M.; Rosenfield, S. M. *Cyclophanes*; Academic Press: New York, 1983.

(2) Cram, D. J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691–5704.

(3) Moore, R. E.; Banarjee, S.; Bornemann, V.; Caplan, F. R.; Chen, J.-L.; Corley, D. G.; Larsen, L. K.; Moore, B. S.; Patterson, G. M. L.; Paul, V. J.; Stewart, J. B.; Williams, D. E. *Pure Appl. Chem.* **1989**, *61*, 521–524.

(4) The extracts do not show selective cytotoxicity against solid tumor cell lines in the Corbett assay (Corbett, T. H.; Polin, L.; Wozniak, A. J.; Bissery, M.; LoRusso, P. M.; Valeriote, F. A.; Baker, L. H. *Proc. Am. Assoc. Cancer Res.* **1988**, *29*, 533–535).

(5) The cyanophytes were grown in mass culture by using the procedure described for *Hapalosiphon fontinalis* (Moore, R. E.; Cheuk, C.; Yang, X.-Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036–1043). Typical harvest times for *C. licheniforme* ATCC 29204 and *N. linckia* UTEX B1932 grown on A_3M_7 were 15–16 and 18–20 days, respectively; typical yields were 0.2 and 0.16 g/L, respectively.

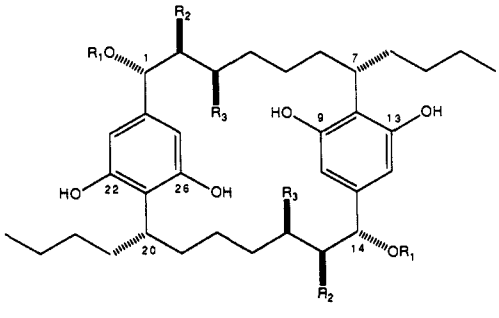
0002-7863/90/1512-4061$02.50/0

Table I. ^1H and ^{13}C Nuclear Magnetic Resonance Data in Dimethyl Sulfoxide-d_6

proton or carbon positions	cylindrocyclophane A		nostocyclophane D	
	^1H	$^{13}C^a$	^1H	^{13}C
1,14	3.54 dd	79.0 (81.9) d	4.05 dd	80.9 d
OH on 1,14	4.87 d			
OMe on 1,14			3.05 s	55.6 q
2,15	1.31	41.0 (42.1) d	1.85, 2.08	45.5 t
Me on 2,15	0.96 d	16.6 (17.0) q		
3,16	0.56	33.8 (35.3) t	2.82	62.6 d
4,17	0.68, 1.36	28.5 (30.0) t	1.51, 1.62	40.3 t
5,18	0.61, 0.88	29.9 (30.7) t	0.54, 1.48	26.5 t
6,19	1.28, 1.89	33.8 (35.5) t	1.58, 1.85	32.7 t
7,20	3.05	34.9 (36.9) d	3.10	34.8 d
8,21		115.0 (117.8) s		116.1 s
9,22[b]		157.2 (158.9) s		155.6 s
10,23[c]	6.16 s	103.8 (105.1) d	6.10 s	102.8 d
11,24		143.4 (143.9) s		138.0 s
12,25[c]	5.94 s	106.9 (109.0) d	6.15 s	107.3 d
13,26[b]		155.1 (157.0) s		157.5 s
1′(7,20)	1.43, 1.82	33.1 (34.9) t	1.36, 1.81	32.5 t
2′(7,20)	1.00, 1.08	30.1 (31.7) t	1.03, 1.21	30.0 t
3′(7,20)	1.16, 1.21	22.3 (23.9) t	1.16, 1.25	22.1 t
4′(7,20)	0.76 t	14.1 (14.5) q	0.77 t	13.9 q

[a] Chemical shifts in parentheses for methanol-d_4. [b] Phenolic OH signals at 8.56 and 8.59 ppm for **1** and 8.80 and 8.82 ppm for **2**. [c] It has not been determined whether H-1 and H-14 are anti to H-23 and H-10 and syn to H-25 and H-12, as arbitrarily shown in Figure 1, or syn to H-23 and H-10 and anti to H-25 and H-12.

cyclophanes. After reverse-phase HPLC on C-18, cylindrocyclophane A (**1**) was isolated as one of the major cytotoxic compounds from *C. licheniforme* in 0.11% yield and nostocyclophane D (**2**) was obtained as the major cytotoxin from *N. linckia* in 0.13% yield (yields based on weights of the dried algae).[6]



	R_1	R_2	R_3
1	H	Me	H
2	Me	H	Cl

Cylindrocyclophane A was assigned the molecular formula $C_{36}H_{56}O_6$ from the field-desorption mass spectrum (M^+ at m/z 584) and a high-resolution EI mass measurement of the $[M - 2H_2O]^+$ ion (−0.4 mmu error). Since only 18 carbon signals were visible in the ^{13}C NMR spectrum, the molecule had to have a 2-fold axis of symmetry. DEPT experiments indicated the presence of two methyl, seven methylene, and five methine carbon signals, and comparison of ^1H NMR in DMSO-d_6 and MeOH-d_4 showed the presence of three exchangeable proton signals. From these data it was evident that **1** possessed four methyls, 14 methylenes, 10 methines, eight unsubstituted carbons, and six hydroxyls.

The proton and carbon NMR data for **1** (Table I) indicated the presence of a disubstituted dihydroxybenzene unit where the phenolic groups were symmetrical relative to the two other substituents. Two-dimensional ^1H–^1H COSY and ^1H–^{13}C CSCM

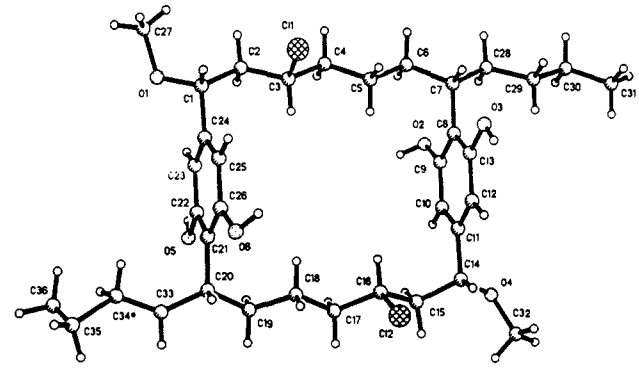


Figure 1.

spectra established three additional partial structures for **1**, viz., $CH_3CH_2CH_2$, $CH_2CHArCH_2$, and $ArCHOHCHCH_3CH_2$, where the methines of the latter two units were connected to the dihydroxybenzene unit. The FABMS indicated the loss of C_4H_9, thus connecting the propyl group to $CH_2CHArCH_2$. The remaining two carbons (methylenes) had to connect $CH_2CHArCH_2$ to $ArCHOHCHCH_3CH_2$ by a process of elimination.

An INADEQUATE spectrum (MeOH-d_4) of cylindrocyclophane A, which had been uniformly enriched with ^{13}C to 28% by growing *C. licheniforme* on $NaH^{13}CO_3$ (99 atom %),[7] enabled us to determine the structure of the aromatic portion of the molecule unambiguously and to confirm the expanded structure implied above. The ^{13}C–^{13}C connectivities clearly showed that the two phenolic groups were meta to each other, the methine in the CH_2CHCH_2 unit was between the two phenolic groups, and the hydroxyl-bearing methine in the $CHOHCHCH_3CH_2$ unit was meta to both phenolic groups. The gross structure of **1** was therefore as shown.

Similar arguments were used to deduce the gross structure of **2** ($C_{36}H_{54}O_6Cl_2$; FABMS shows a 3:1 MH^+ ion cluster at m/z 653/655).

The relative and absolute stereochemistry of **2** was determined by an X-ray crystallographic study. Nostocyclophane D crystallized from aqueous ethanol as clear colorless cubes in space group $P2_1$ with a = 11.659 (2) Å, b = 13.861 (1) Å, c = 13.226 (10) Å, and β = 93.79 (2)°. A complete set ($2\theta \leq 114°$) of Friedel redundant data (5801 reflections, 5732 observed) was collected by using 2θ–θ scans and graphite-monochromated Cu Kα radiation. The data were corrected for absorption, and the structure was solved routinely by using direct methods. Full-matrix least-squares refinements with anisotropic heavy atoms, isotropic riding hydrogens, and anomalous scattering corrections converged to a conventional crystallographic discrepancy index of 5.17% for the enantiomer shown. The opposite enantiomer had a significantly higher discrepancy index: 6.55%. The η-factor for the enantiomer shown was +0.98 (4) and, for the opposite enantiomer, −0.99 (4). Figure 1 is a computer-generated perspective drawing of the final X-ray model. The model has molecular, but not crystallographic, 2-fold symmetry.

Cylindrocyclophane A appears to have the same relative stereochemistry at C1, C7, C14, and C20. The protons on these carbons are pseudoaxial for two reasons: (1) The signal for H-7 and H-20, which appears to be a very broad triplet of triplets, shows large coupling (~10 Hz) to the signals for the pseudoaxial protons on the adjacent methylenes. (2) The signal for H-1 and H-14 shows large coupling (9.5 Hz) to the signal for H-2 and H-15. This means that the methyl substituents on C-2 and C-15 are pseudoequatorial.

Acknowledgment. This research was supported by PHS Grants CA12623 (R.E.M.) and CA24487 (J.C.), awarded by the Na-

(6) Compounds **1** and **2** show cytotoxicity against the KB cell line at 0.5 μg/mL. Detailed cytotoxicity data for the cyclophanes will be presented in our full paper.

(7) Uniform ^{13}C enrichment was carried out by using the procedure described for *Anabaena* sp. BQ-16-1 (Moore, R. E.; Bornemann, V.; Niemczura, W. P.; Gregson, J. M.; Chen, J.-L.; Norton, T. R.; Patterson, G. M. L.; Helms, G. L. *J. Am. Chem. Soc.* **1989**, *111*, 6128-6132).

tional Cancer Institute, DHSS, and by a New York Sea Grant (J.C.).

Supplementary Material Available: Tables of fractional coordinates, interatomic distances, interatomic angles, and thermal parameters for nostocyclophane D (6 pages). Ordering information is given on any current masthead page.

Ligand Exchange between Cyanocuprates and Allylic Stannanes: A Novel, Direct Route to Allylic Cuprates Possessing Remarkable Reactivity and Stability

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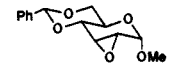
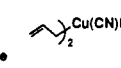
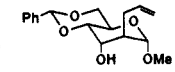
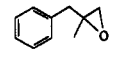
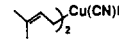
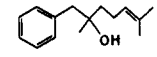
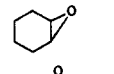
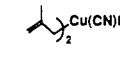
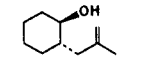
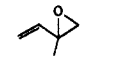
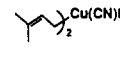
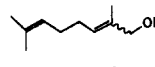
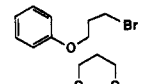
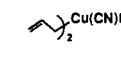
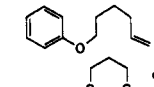
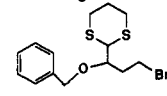
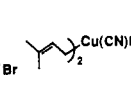
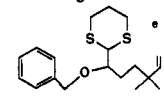
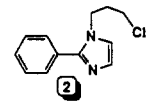
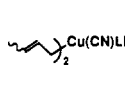
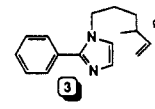
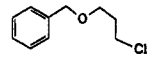
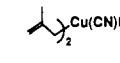
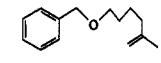
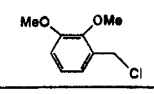
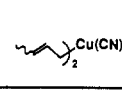
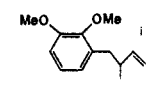
Received November 13, 1989

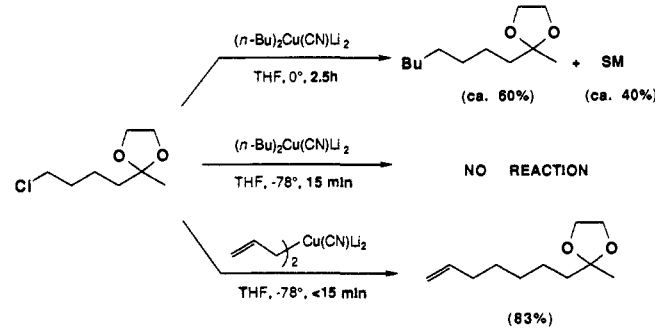
The lack of thermal stability associated with Gilman reagents (R_2CuLi) composed of allylic ligands, recently demonstrated in these laboratories,[2] can be used to rationalize the scarcity of successful organocopper reactions involving allylic cuprates in the past decade.[3] Indeed, even the preparation of dimeric $(allyl)_2CuLi$ at −78 °C affords significant percentages of Wurtz-like coupling material (1,5-hexadiene) together with aggregate $(allyl)_3Cu_2Li$,[2] which as a class of reagents is known to have considerably different chemical reactivities.[4] To circumvent these problems of reagent preparation and thermal instability, we now report a novel route to higher order (HO) allylic cyanocuprates based on direct transmetalations of precursor allylstannanes. The species so formed by this process (i.e., $R_2Cu(CN)Li_2$, R = an allylic group) are stable at 0 °C yet are extremely reactive toward substitution reactions (vide infra).[5]

Table I. Substitution Reactions of Allylic Cuprates Formed via Transmetalations of Allylic Stannanes with $Me_2Cu(CN)Li_2$ at 0 °C in THF for 30 min

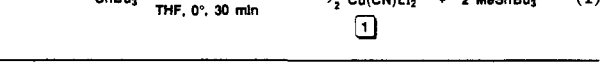
Entry	Educt	Reagent	Conditions	Product(s)[a]	Yield(%)[b]
1			0° to rt, 12h		98
2			-78°, 15 min		89
3			0°, 1 h		90
4			-78°, 15 min		74[c]
5			-78°, 5 min		86
6			-78 to -40°, 2.5 h[d]		77(95)[f]
7			-78°, 1 h[d]		84(0)[h]
8			-78°, 15 min		88
9			-78°, 1 h		84

[a] Chromatographically pure; fully characterized by IR, NMR, MS, and HRMS data. [b] Isolated. [c] A 5:1 ratio of *E*:*Z* isomers. [d] Ten equivalents of Me_2S added. [e] Also contained 20% of the product of α-attack. [f] Based on recovered educt. [g] A 2:1 mix of γ:α (*Z* + *E*) isomers. [h] Yield obtained by using the corresponding LO crotylcuprate.[15] [i] A 9:1 mix of γ:α (*E*) isomers.

Scheme I



Treatment of allyltributylstannane with 0.5 equiv of the trivial, MeLi-derived cyanocuprate $Me_2Cu(CN)Li_2$[6] at 0 °C for 30 min affords cuprate **1** essentially quantitatively, as judged from ^1H NMR analysis (complete disappearance of the methyl signal at δ −1.50 ppm)[7] and assessment by quantitative VPC (measurement of $MeSnBu_3$ formed vs an internal standard). Similar conditions can be employed with other allylic stannanes, including those containing methallyl,[8] crotyl, and prenyl groups (eq 1).[9]



(1)

(1) Proctor & Gamble Predoctoral Fellow; awarded by the American Chemical Society, 1989-1990.

(2) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Org. Chem.* **1989**, *54*, 4977.

(3) Lipshutz, B. H.; Sengupta, S. *Org. React. (N.Y.)*, in press.

(4) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351. Lipshutz, B. H.; Kozlowski, J. A.; Breneman, C. M. *Ibid.* **1985**, *107*, 3197. Ashby, E. C.; Watkins, J. J. *Ibid.* **1977**, *99*, 5312. House, H. O.; Chu, C. Y. *J. Org. Chem.* **1976**, *41*, 3083. House, H. O.; Respess, W. L.; Whitesides, G. M. *Ibid.* **1966**, *31*, 3128. San Filippo, J. *Inorg. Chem.* **1978**, *17*, 275.

(5) For some examples of substitution reactions involving allylic cuprates, see the following. (a) Lithium-based: Schauman, E.; Kirschning, A. *Tetrahedron Lett.* **1988**, *29*, 4281. Corriu, R. J. P.; Guerin, C.; M'Boula, J. *Ibid.* **1981**, *22*, 2985. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137. (b) Grignard-based: Larcheveque, M.; Petit, Y. *Bull. Soc. Chim. Fr.* **1989**, 130. Beau, J.-M.; Aburaki, S.; Pougny, J.-R.; Sinay, P. *J. Am. Chem. Soc.* **1983**, *105*, 621. Cahiez, G.; Alexakis, A.; Normant, J. F. *Synthesis* **1978**, 528. Bourgain-Commercon, M.; Normant, J. F.; Villieras, J. *J. Chem. Res., Synop.* **1977**, 183. Fujisawa, T.; Sato, T.; Kawashima, M.; Nakagawa, M. *Chem. Lett.* **1981**, 1307. Sato, T.; Kawashima, M.; Fujisawa, T. *Ibid.* **1984**, 1851. Sato, T.; Takeuchi, M.; Itoh, T.; Kawashima, M.; Fujisawa, T. *Tetrahedron Lett.* **1981**, *22*, 1817. Fujisawa, T.; Sato, T.; Kawara, T.; Kawashima, M.; Shimizu, H.; Ito, Y. *Ibid.* **1980**, *21*, 2181. Sato, T.; Kawashima, M.; Fujisawa, T. *Ibid.* **1981**, *22*, 2375. Fujisawa, T.; Sato, T.; Kawashima, M.; Naruse, K.; Tamai, K. *Ibid.* **1982**, *23*, 3583. Klein, J.; Levene, R. *Ibid.* **1974**, 2935. Normant, J. F.; Alexakis, A.; Cahiez, G. *Ibid.* **1980**, *21*, 935. Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Ibid.* **1979**, 1503. Linstrumelle, G.; Lorne, R.; Dant, H. P. *Ibid.* **1978**, 4069. Derguini-Boumechal, F.; Lorne, R. Linstrumelle, G. *Ibid.* **1977**, 1181. Brockway, C.; Kocienski, P.; Pant, C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 875. Drouin, J.; Leyendecker, F.; Conia, J. M. *Tetrahedron* **1980**, *36*, 1195. Courtois, G.; Harama, M.; Miginiac, L. *J. Organomet. Chem.* **1980**, *198*, 1.

(6) Lipshutz, B. H. *Synthesis* **1987**, 325. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.

(7) Lipshutz, B. H.; Kozlowski, J. A.; Wilhelm, R. S. *J. Org. Chem.* **1984**, *49*, 3943.

(8) VPC analysis of the transmetalation of methallyltributyltin indicated that this exchange went to the extent of ca. 85%. Due to the large difference in reactivities between the allylic cuprate and $Me_2Cu(CN)Li_2$, however, there was no competition by the alkylcuprate in subsequent alkylations (i.e., no methyl transfer under the conditions employed).

(9) The transmetalation process is sensitive to the quality and the manner in which the stannanes are stored. Hence, for maximum results, allylic tin reagents should be as pure as reasonably possible and stored in glass containers *without using rubber septa* (polyethylene stoppers are acceptable).

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