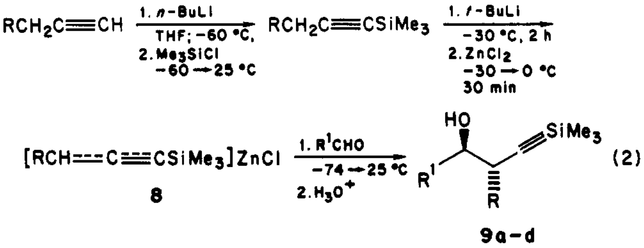
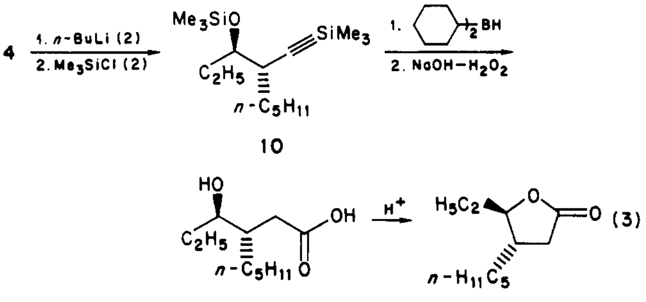
Recently, Yamamoto and co-workers[12] reported that condensations of 1-(trimethylsilyl)-1-propyne or 3-(trimethylsilyl)-2-propyn-1-yl 2-tetrahydropyranyl ether derived zinc reagents with cyclohexanecarbaldehyde were only moderately regioselective or only moderately stereoselective, respectively.[13] Having access to an efficient, one-pot procedure for the conversion of 1-alkynes into the zinc reagents 8[14] via treatment of the corresponding lithium reagents[15] with anhydrous zinc chloride, we briefly examined their reaction with aldehydes (eq 2). In the cases investigated, the condensations proceeded in a regio- and diastereoselective manner producing the threo alcohols **9a–d** in 92% to 99% stereoisomeric purities (Table I). Apparently the presence of a γ-alkyl group in **8** has a marked influence on both the regio- and diastereoselectivities of the reaction.



Finally, it should be noted that 3-alkyn-1-ols **4** and **9** are valuable intermediates for use in a variety of synthetic transformations. For example, conversion of **4a** into the bis-silylated derivative **10** followed by hydroboration and oxidation produces the γ-hydroxy acid **11**.[16] Lactonization stereoselectively affords the *trans*-3,4-disubstituted γ-butyrolactone **12** in 91% yield containing less than 5% of the cis isomer (eq 3).[17]



Acknowledgment. We thank the National Science Foundation (CHE 82-05954) for financial support of this investigation.

Registry No. 1 (R = $CH_3(CH_2)_4$), 80472-36-2; 1 (R = $CH_3(CH_2)_5$), 92490-11-4; 1 (R = c-C_6H_{11}), 92490-12-5; 1 (R = *t*-Bu), 81363-95-3; **2** (R = $CH_3(CH_2)_4$), 92490-13-6; **2** (R = $CH_3(CH_2)_5$), 92490-14-7; **2** (R = c-C_6H_{11}), 92490-15-8; **2** (R = *t*-Bu), 78389-91-0; **4a**, 92490-16-9; **4b**, 92490-17-0; **4c**, 92490-18-1; **4d**, 92490-19-2; **4e**, 92490-20-5; **4f**, 92490-21-6; **8** (R = $CH_3(CH_2)_4$), 92490-22-7; **8** (R = $CH_3(CH_2)_2$), 92490-23-8; **9a**, 92490-24-9; **9b**, 92490-25-0; **9c**, 92490-26-1; **9d**, 92524-59-9; **10**, 92490-27-2; **11**, 92490-28-3; **12**, 92490-29-4; $CH_3(CH_2)_4CH{=}C{=}CH_2$, 1072-19-1; $CH_3(CH_2)_5CH{=}C{=}CH_2$, 22433-33-6; c-$C_6H_{11}CH{=}C{=}CH_2$, 5664-17-5; $(CH_3)_3CCH{=}C{=}CH_2$, 26981-77-1; $CH_3(CH_2)_4CH_2C{\equiv}CH$, 629-05-0; $CH_3(CH_2)_2CH_2C{\equiv}CH$, 693-02-7; $CH_3(CH_2)_5C{\equiv}CLi$, 21433-45-4; $CH_3(CH_2)_3C{\equiv}CLi$, 17689-03-1; $CH_3(CH_2)_5C{\equiv}CSiMe_3$, 15719-55-8; $CH_3(CH_2)_3C{\equiv}CSiMe_3$, 3844-94-8; CH_3CH_2CHO, 123-38-6; $(CH_3)_2CHCHO$, 78-84-2; $(CH_3)_3CCHO$, 630-19-3; $CH_3(CH_2)_2CHO$, 123-72-8.

Supplementary Material Available: Full experimental and spectral details for compounds **4a–f**, **9a–d**, and **12** (9 pages). Ordering information is given on any current masthead page.

George Zweifel,* Gregory Hahn

Department of Chemistry
University of California, Davis
Davis, California 95616

Received June 4, 1984

---

[11] Spectral data for **4c**: IR (neat) 3460 (OH), 3335 (≡CH), 2110 (C≡C), 630 (≡CH); ^1H NMR (CCl_4, 360 MHz) δ 3.11 (dt, *J* = 3.7, 7.1 Hz, 1 H, H_a), 2.58 (m, 1 H, H_b), 2.12 (d, *J* = 2.4 Hz, 1 H, H_c), 1.84 (sextet, *J* = 7.1 Hz, 1 H), 1.64 (m, 1 H), 1.57 (s, 1 H), 1.53 (m, 1 H), 1.38–1.26 (m, 8 H), 1.03 (d, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 6.5 Hz, 3 H); exact mass, *m/e* 196.1796 (calcd for $C_{13}H_{24}O$, 196.1828).

[12] Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.

[13] For additional examples of condensations of aldehydes with 1-(trimethylsilyl)-1-alkyne derived organometallics, see: (a) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579 and references cited therein. (b) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568. (c) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (d) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376 and references cited therein.

[14] The zinc reagent **8** (R = *n*-C_5H_{11}) at 25 °C showed a strong IR absorption at 1890 cm^{-1} characteristic for the allenic structure.[5,12]

[15] Rajagopalan, S.; Zweifel, G. *Synthesis* **1984**, 111.

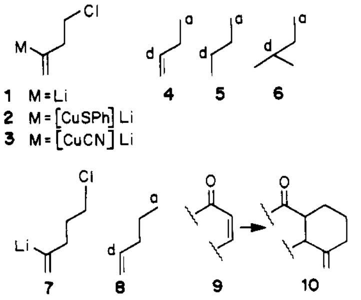
[16] Zweifel, G.; Backlund, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 3184.

[17] The precursor **10** for the lactone **12** may also be prepared by treatment of **8** (R = *n*-C_5H_{11}) with propanal followed by addition of chlorotrimethylsilane at 25 °C.

5-Chloro-2-lithio-1-pentene and Related Reagents. Efficient Methylenecyclohexane Annulation Sequences

Summary: 5-Chloro-2-lithio-1-pentene (**7**), obtained by transmetalation of the (trimethylstannyl)alkene **11**, can be converted into the corresponding Grignard and organocopper reagents. Conjugate addition of the latter species to the enones **13–19**, followed by ring closure of the resultant adducts **20–26**, provides the methylenecyclohexane annulation products **27–37**.

Sir: A recent report[1a] from this laboratory described, inter alia, the preparation of the unusual donor–acceptor reagent 4-chloro-2-lithio-1-butene (**1**). Subsequently, it was shown[1b] that the cuprate reagents **2** and **3**, derived from **1**, could serve as pivotal species in the development of a new five-membered-ring annulation method. Furthermore, application of the latter operation to the synthesis of the structurally interesting sesquiterpenoids (±)-$\Delta^{9(12)}$-capnellene[1c] and (±)-pentalenene[1d] has demonstrated clearly the utility of the process. In fact, in these syntheses, reagents derived from **1** served as efficient synthetic equivalent to the three donor–acceptor synthons **4–6**.



A potentially important extension to the methodology summarized above involved the possibility of preparing

---

[1] Piers, E.; Karunaratne, V. (a) *J. Org. Chem.* **1983**, *48*, 1774; (b) *J. Chem. Soc., Chem. Commun.* **1983**, 935; (c) *Can. J. Chem.* **1984**, *62*, 629; (d) *J. Chem. Soc., Chem. Commun.* **1984**, 959.

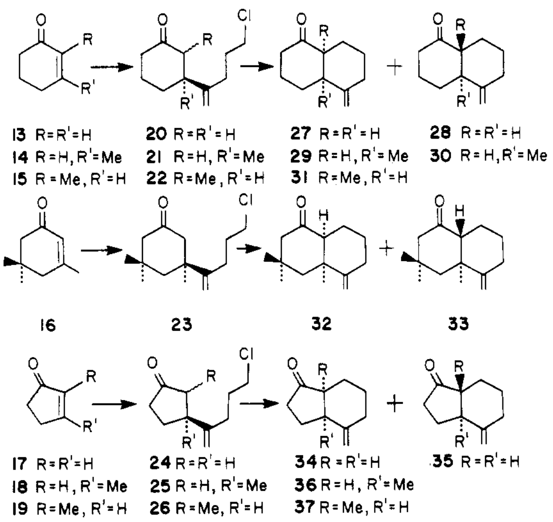
0022-3263/84/1949-4567$01.50/0

Table I. Methylenecyclohexane Annulation of Cyclic Enones

entry	enone	conjugate addition product (method, yield[a] (%))	cyclized product(s) (ratio,[b] yield[a] (%))	cyclized product(s) (ratio[b] after equilibration)
1	**13**	**20** (A, 81; B, 61)	**27**, **28** (1:2, 86)	**27**, **28** (⟨1:⟩99)
2	**14**	**21** (A,[c] 37; B, 55)	**29**, **30** (3.5:1, 82)	**29**, **30** (1:2.8)
3	**15**	**22** (A,[c] 55; B, 58)	**31** (78)	
4	**16**	**23** (A,[c,d] 45; B,[c] 21)	**32**, **33**, (8:1, 89)	**32**, **33** (1:2)
5	**17**	**24** (A, 54; B, 65)	**34**, **35** (4.9:1, 84)	**34**, **35** (4.9:1)
6	**18**	**25** (A,[c] 54; B, 38)	**36** (88)	no change
7	**19**	**26** (A,[c] 33; B,[c] 67)	**37** (90)	

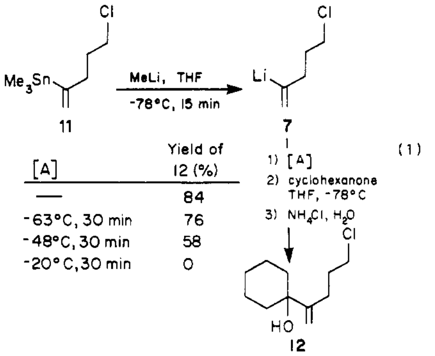
[a] Yield of distilled, purified product(s). [b] Ratios were determined by gas–liquid chromatography. [c] $BF_3\cdot Et_2O$ (1.2 equiv) was added immediately after addition of the enone. [d] The reaction time was 4.5 h.

Chart I



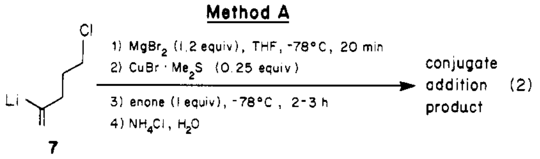
homologues of the reagents **1**–**3**. For example, it was of considerable interest to determine whether or not one could prepare and employ synthetically 5-chloro-2-lithio-1-pentene (**7**) and related Grignard and/or copper reagents. Clearly, these materials could serve as synthetic equivalents to the 1-pentene d^2,a^5-synthon **8** and, if the proposed use of these species were to be successful, one could, presumably, perform methylenecyclohexane annulations shown in general terms by **9** → **10**. We report herein some of the results which we have thus far obtained from this study.

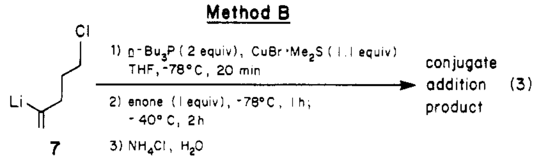
Successive treatment of a cold (−78 °C) solution of 5-chloro-2-(trimethylstannyl)-1-pentene (**11**)[2] with methyllithium (15 min) and cyclohexanone (2–3 h), followed by suitable workup, provided the alcohol **12**[3] in 84% yield (eq 1). However, as shown in eq 1, when the reaction mixture was allowed to warm to −63, −48, and −20 °C prior to addition of the ketone, the yield of the alcohol **12** decreased to 76%, 58%, and 0%, respectively. Thus, although it was gratifying to find that **7** could be prepared and employed synthetically, it was also clear that low temperatures had to be maintained. It appears that even at −50 °C, this substance decomposes slowly.[4]



[A]	Yield of 12 (%)
—	84
-63°C, 30 min	76
-48°C, 30 min	58
-20°C, 30 min	0

Considerable effort was expended to find procedures suitable for effecting conjugate transfer of the 2-(5-chloro-1-pentenyl) group to cyclic α,β-unsaturated ketones. Eventually, two methods were established as being reasonably satisfactory. The first of these (method A, eq 2) involved $CuBr\cdot Me_2S$ catalyzed conjugate addition of the Grignard reagent obtained by treatment of **7** with anhydrous magnesium bromide. The second procedure (method B, eq 3) was modeled on work done by Noyori and co-workers.[5] For some substrates, $BF_3\cdot Et_2O$ was employed as an additional catalyst[6] to improve the efficiency of the addition.





A number of enones (**13**–**19**, see Chart I) were subjected to methylenecyclohexane annulation and the results are summarized in Table I. In general, the yields of the conjugate addition reactions (**13**–**19** → **20**–**26**, respectively) using methods A and/or B were satisfactory but not particularly high. However, even addition to the highly hindered enone isophorone (**16**) (entry 4) could be accomplished in reasonable yield. In those cases in which $BF_3\cdot Et_2O$ was used as a catalyst,[6] the yields were significantly improved over similar reactions in the absence of the Lewis acid.

The conjugate addition products **20**–**26** were cyclized smoothly and efficiently by treatment with KH (~2.5 equiv) in THF at room temperature for 2 h.[7] As expected,[8] the "kinetic" products possessed a cis ring fusion

---

(2) Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934.

(3) All compounds reported herein exhibited spectral data in full accord with structural assignments. New compounds gave satisfactory molecularmass determinations (high-resolution mass spectrometry).

(4) Although the fate of **7** at higher temperatures is not known at present, it seems reasonable to suppose that it is converted into methylenecyclobutane.

(5) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1247.

(6) Smith, A. B., III; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845.

(7) In theory, one would expect that the direct conversion of enones to cyclized product(s) could be accomplished by warming the conjugate addition reaction mixtures. However, in related work[1b–d] we have found that the overall annulation processes are more efficient if the conjugate addition products are isolated and then cyclized via a separate (simple) step. This protocol was followed in the present investigation.

and, indeed, in each case in which subsequent equilibration was not possible (entries 3 and 7), a single, cis-fused annulation product (**31** and **37**) was produced in high yield. In other experiments (entries 1, 2, and 4–6) varying degrees of equilibration occurred under the conditions of ring closure. In each of these cases, the cyclized product(s) were equilibrated (MeONa, MeOH, reflux, 18 h) and the equilibrium ratios were determined (Table I). Interestingly, the equilibrium **27** $\rightleftharpoons$ **28** favored exlusively the trans isomer **28**, while attempted equilibration of the cis-fused ketone **36** gave no detectable amount of the corresponding trans-fused isomer.[9]

The "best" overall yields of the annulation sequences summarized in Table I varied from 40% (entry 4) to 70% (entry 1). Taking into account the brevity of the process and the fact that the methylenecyclohexane moiety is a fairly common structural feature in the terpenoid family of natural products, it appears that the methodology described herein should find use in organic synthesis. We are actively investigating a number of possible applications.

Acknowledgment. We are very grateful for financial support from the Natural Sciences and Engineering Research Council of Canada and from Merck and Co., Inc., and Merck Frosst Canada, Inc.

Registry No. **7**, 92490-53-4; **11**, 89045-21-6; **12**, 92490-54-5; **13**, 930-68-7; **14**, 1193-18-6; **15**, 1121-18-2; **16**, 78-59-1; **17**, 930-30-3; **18**, 2758-18-1; **19**, 1120-73-6; **20**, 92490-55-6; **21**, 92490-56-7; **22**, 92490-57-8; **23**, 92490-58-9; **24**, 92490-59-0; **25**, 92490-60-3; **26**, 92490-61-4; **27**, 92490-62-5; **28**, 92490-63-6; **29**, 92490-64-7; **30**, 92490-65-8; **31**, 92490-66-9; **32**, 92490-67-0; **33**, 92490-68-1; **34**, 92490-69-2; **35**, 92490-70-5; **36**, 92490-71-6; **37**, 92490-72-7; cyclohexanone, 108-94-1.

Supplementary Material Available: Representative experimental procedures for the preparation of compounds **20**, **27**, and **28** and spectral data for compounds **20** and **27**–**37**, inclusive (3 pages). Ordering information is given on any current masthead page.

---

[8] Conia, J. M.; Rouessac, F. *Tetrahedron* **1961**, *16*, 45, Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

[9] Treatment of **36** with MeONa–MeOD gave the expected (cis-fused) trideuterio ketone.

Edward Piers,* Bik Wah Anissa Yeung

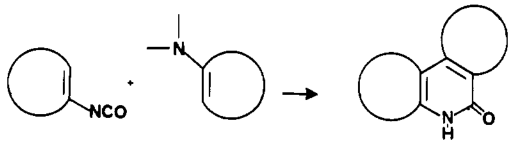
Department of Chemistry
University of British Columbia
Vancouver, British Columbia, Canada V6T 1Y6

Received June 21, 1984

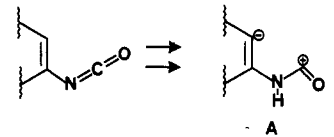
Vinyl Isocyanate Cyclization Reactions in Synthesis. An Expedient Construction of the Octahydrophenanthridinone Ring System

Summary: The octahydrophenanthridinone ring system is assembled in one step via a thermally induced reaction of vinyl isocyanates and enamines.

Scheme I

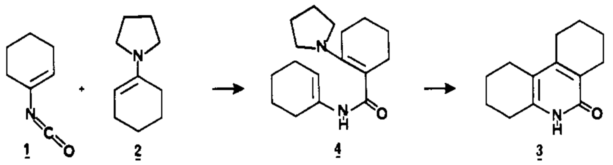


Sir: Vinyl isocyanates are particularly attractive intermediates for application to synthetic problems by virtue of their high degree of reactivity and relative ease of preparation. However, to date this grouping has received relatively little attention in this context.[1] We were particularly intrigued with the possibility of exploiting this functionality as an equivalent for the useful 1,4-dipolar species A. This type of species could be envisioned to participate in a highly convergent ring forming process which would quickly assemble complex heterocyclic systems. To demonstrate this concept, we report herein the facile reaction of substituted vinyl isocyanates with enamines to provide highly substituted 2-pyridones[2] (Scheme I). The 2-pyridone moiety is a prominent structural feature in a number of interesting natural products,[3] and the hydrophenanthridine systems made available by this route are displayed in one form or another by several classes of alkaloids.



A

Simply heating an equal molar mixture of 1-isocyanato-1-cyclohexene (1) and 1-pyrrolidino-1-cyclohexene (2)[4] in refluxing toluene provided the octahydrophenanthridinone 3[5] as the principle isolable product in 81% yield. A variety of other isocyanate and enamine partners also yield pyridone products in a similar fashion (Table I), and in most cases, the polycyclic pyridone compounds produced in this apparently general reaction can be isolated by filtration and recrystallization. The simplicity and mildness of this technology for the construction of relatively elaborate hydrophenanthridinone systems can be contrasted with many of the "classical" preparations of 2-pyridones which are often not amenable to generating such substitution patterns.[6]



In a typical procedure, 1-cyclohexenecarboxylic acid (10 mmol) is stirred with 10 mmol of triethylamine in 10 mL of toluene. DPPA (diphenylphosphoryl azide)[7] (10 mmol) is added via syringe; and after 1 h of stirring at room

---

[1] (a) Dondoni, A.; Kniezo, L.; Medici A. *J. Org. Chem.* **1982**, *47*, 3994. (b) Takaki, K.; Okamura, A.; Ohshiro, Y.; Agawa, T. *Ibid.* **1978**, *43*, 402. (c) Fuks, R. *Tetrahedron* **1970**, *26*, 2161.

[2] For other pyridone syntheses, see: (a) Earl, R. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6991. (b) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *Ibid.* **1983**, *105*, 5390. (c) Sainte, F.; Poncin, B. S.; Frisque, A. H.; Ghosez, L. *Ibid.* **1982**, *104*, 1428. (d) Overman, L. E.; Tsuboi, S.; Roos, J. P.; Taylor, G. F. *Ibid.* **1980**, *102*, 747.

[3] (a) Lednicer, D.; Mitscher, L. A. "The Organic Chemistry of Drug Synthesis"; Wiley: New York, 1977; Vol. 1; 1980, Vol. 2. (b) Grundon, M. F. "The Alkaloids"; The Chemical Society: London, 1977; Vol. 7.

[4] Enamine additions to the carbonyl carbon of aryl isocyanates have been observed previously: (a) Ried, W.; Kappeler, W. *Liebigs Ann. Chem.* **1964**, *673*, 132. (b) Ried, W.; Kappeler, W. *Ibid.* **1965**, *688*, 177.

[5] This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR, UV, mass spectrum) and analytical data in complete accord with the assigned structure.

[6] Tieckelmann, H. In "Pyridine and its Derivatives", Supplement, Part 3; Abramovitch, R. A., Ed.; Wiley: New York, 1975; Chapter 12, pp 599–728.

[7] Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

0022-3263/84/1949-4569$01.50/0