Communications

Transformations of α,α-Dichlorocyclopentanones Obtained by Three-Carbon Annelation

Summary: α,α-Dichlorocyclopentanones and α,α-dichloro-β-[(trimethylsilyl)oxy]cyclopentanones, readily available by three-carbon annelation, are cleanly transformed under mild conditions via α-chloro enolates and α-chloro enones to a variety of alkylated and nonalkylated ketones and enones.

Sir: Among the numerous methods of constructing the five-membered ring, there are few effective procedures for regio- and stereoselectively attaching a functionalized three-carbon unit onto an olefin or ketone.[1] In addition, there is the problem that the available techniques often do not permit the rational modification of the annelated ring, a drawback which of course can severely limit their incorporation into the synthesis of any complex organic molecule.

An important feature of the recently described three-carbon annelation (one-carbon homologation of α,α-dichlorocyclobutanones, secured by [2 + 2] cycloaddition,[2] which affords α,α-dichlorocyclopentanones and thence cyclopentanones)[3] is that both the regio- and the stereochemical outcomes of the process usually show considerable selectivity and are generally predictable for any given substrate.[2,3] We now report several modifications of the intermediate α,α-dichloro- and α,α-dichloro-β-[(trimethylsilyl)oxy]cyclopentanones which should serve to broaden substantially the usefulness of this method of annelation.

A prototypical dichloro ketone, hydrindanone **2**,[4] was examined in some detail and yielded the diverse results indicated in Figure 1.[5] The initial objective of cleanly generating the α-chloro enolate corresponding to the dichloride **2** was readily achieved by using lithium dimethylcuprate[6] (1–2 equiv) in THF or Et_2O at −78 °C,

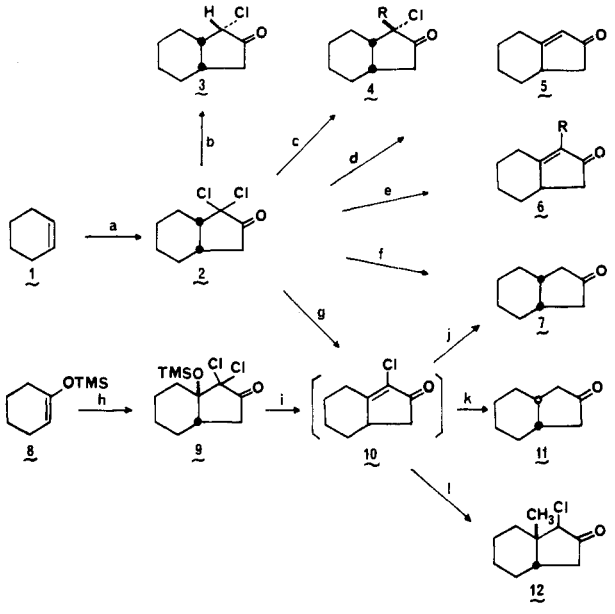
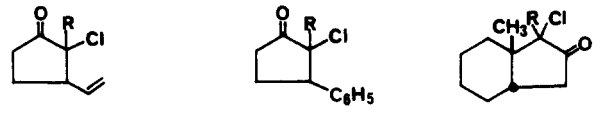


Figure 1. Elaboration of Dichlorocyclopentanones. (a) See ref 4. (b) $Li(CH_3)_2Cu$, THF or Et_2O, −78 °C; AcOH. (c) $Li(CH_3)_2Cu$, THF, −78 °C; CH_3I or C_3H_5Br, HMPA, −78 to −40 °C. (d) $Li(CH_3)_2Cu$, THF–EtO, −78 °C; $LiI{\cdot}2H_2O$, HMPA, −78 °C to room temperature. (e) $Li(CH_3)_2Cu$, THF, −78 °C; CH_3I or C_3H_5I, HMPA, −78 °C to room temperature. (f) Zn, AcOH, 70 °C. (g) DMF, Li_2CO_3, 85 °C. (h) Reference 13. (i) Zn, AcOH, room temperature. (j) **9**, H_2, Pd/C, MeOH. (k) **9**, Li, NH_3; Zn, AcOH or Ca, NH_3, MeOH; $C_5H_5NH^+$, $ClCrO_3^-$, CH_2Cl_2. (l) **9**, $Li(CH_3)_2Cu$, Et_2O-hexane.

affording α-chloro ketone **3**[7] quantitatively following protonation. Dichloro ketones **13** and **15**[3] are similarly



13 R = Cl; **14** R = H; **15** R = Cl; **16** R = H; **17** R = Cl; **18** R = CH_3

transformed in excellent yields to chloro ketones **14** and **16**, respectively. This procedure not only is substantially easier and higher yielding than the alternative stoichiometric Zn–AcOH[3] and *n*-Bu_3SnH[2b,c] methods but, in addition, offers the possibility for effecting monoalkylation regioselectively, which is often quite difficult to achieve

(1) See M. E. Jung, *Tetrahedron*, **32**, 3 (1976), and references cited therein. See also: (a) M. E. Jung and J. P. Hudspeth, *J. Am. Chem. Soc.*, **99**, 5508 (1977); (b) Y. Hayakawa, K. Yokoyama, and R. Noyori, *ibid.*, **100**, 1791 (1978); (c) A. Marfat and P. Helquist, *Tetrahedron Lett.*, 4217 (1978); (d) T. Hiyama, M. Shinoda, and H. Nozaki, *ibid.*, 771 (1978); (e) E. J. Corey and D. L. Boger, *ibid.*, 13 (1978); (f) R. M. Jacobson, R. A. Raths, and J. H. McDonald, III, *J. Org. Chem.*, **42**, 2545 (1977); R. M. Jacobson, A. Abbaspour, and G. P. Lahm, *ibid.*, **43**, 4650 (1978); R. M. Jacobson and G. P. Lahm, *ibid.*, **44**, 462 (1979); (g) B. M. Trost, Y. Nishimura, and K. Yamamoto, *J. Am. Chem. Soc.*, **101**, 1328 (1979); (h) T. Hiyama, M. Shinoda, and Nozaki, *ibid.*, **101**, 1599 (1979); (i) F. Cooke, J. Schwindeman, and P. Magnus, *Tetrahedron Lett.*, 1995 (1979); (j) W. E. Fristad, D. S. Dime, T. R. Bailey, and L. A. Paquette, *ibid.*, 1999 (1979), and references cited therein.

(2) (a) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.*, **87**, 5257 (1965); (b) W. T. Brady and O. H. Waters, *J. Org. Chem.*, **32**, 3703 (1967); W. T. Brady, *Synthesis*, 415 (1971); D. A. Bak and W. T. Brady, *J. Org Chem.*, **44**, 107 (1979); W. T. Brady and R. M. Lloyd, *ibid.*, **44**, 2560 (1979); (c) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971); R. A. Minns, *Org. Synth.*, **57**, 117 (1977); (d), L. R. Krepski and A. Hassner, *J. Org. Chem.*, **43**, 2879, 3173 (1978); A. Hassner and L. R. Krepski, *ibid.*, **44**, 1376 (1979), and references cited therein.

(3) A. E. Greene and J. P. Deprés, *J. Am. Chem. Soc.*, **101**, 4003 (1979).

(4) This material was easily secured in 80–90% yield from 8,8-dichlorobicyclo[4.2.0]octan-7-one[2c] by using diazomethane in Et_2O–MeOH;[3] mp 60–61 °C (hexane).

(5) All compounds displayed spectral properties in full agreement with the assigned structures. Crystalline derivatives had melting points in accord with those reported in the literature. No attempt has been made to maximize any yield reported in this paper.

(6) To the best of our knowledge, this is the first report of the reaction of a cuprate with α,α-dichloro ketones. Cuprates have been used, however, with the following. Bromo ketones: (a) J. E. Dubois, C. Lion, and C. Moulineau, *Tetrahedron Lett.*, 177 (1971); C. Lion and J. E. Dubois, *Tetrahedron*, **31**, 1223 (1975); J. E. Dubois and C. Lion, *ibid.*, **31**, 1227 (1975); (b) O. P. Vig, S. D. Sharma, and J. C. Kapur, *J. Indian Chem. Soc.*, **45**, 1026 (1968); (c) M. Audouin and J. Levisalles, *Bull. Soc. Chim. Fr.*, 695 (1975); (d) G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 3076 (1973); G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, *ibid.*, **97**, 107 (1975); G. H. Posner and C. M. Lentz, *ibid.*, **101**, 934 (1979). α-Acetoxy ketones: (e) J. R. Bull and A. Tuinman, *Tetrahedron Lett.*, 4349 (1973). α,β-Epoxy ketones: (f) J. R. Bull and H. H. Lachmann, *ibid.*, 3055 (1973); R. P. Szajewski, *J. Org. Chem.*, **43**, 1819 (1978). Coupling has been observed with an α-chloro ketone and lithium diisopropenylcuprate. See O. P. Vig, J. C. Kapur, and S. D. Sharma, *J. Indian Chem. Soc.*, **45**, 734 (1968).

(7) E. J. Moriconi, J. P. St. George, and W. F. Forbes, *Can. J. Chem.*, **44**, 759 (1966). Chloro ketone **3** contains ca. 10% of the exo isomer.

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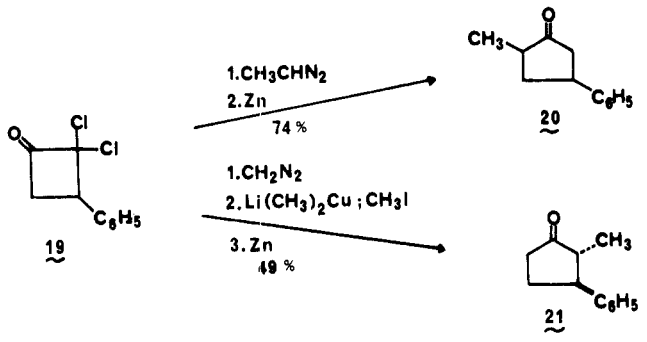
with cyclopentanones.[6d] Thus the addition of MeI in HMPA to the solution of the α-chloro enolate afforded the α-chloro-α-methyl ketone **4** (R = CH_3) in 78% yield after purification. Similarly, addition of allyl bromide provided chloro ketone **4** (R = allyl) in 71% yield. In spite of the steric congestion, alkylation could also be successfully carried out with dichloro ketone **17**, leading to **18** in 70% yield. This ability to introduce α-alkyl substituents complements the diazoalkane procedure for introducing α′ substituents.[3] Thus, for example, the pure regioisomers **20**[3] and **21**[8] become readily available from a common precursor.



Prompted by the simplicity of this reduction–protonation or alkylation method, we have also examined various means of converting the chloro ketones to the corresponding enones. The solution in most cases examined proved to be surprisingly simple, reflecting the favorable trans stereochemistry for elimination in the reduction products,[9] viz., in the case of nonalkylated chloro ketones, the enone is produced in situ through addition of $LiI{\cdot}2H_2O$ and HMPA to the reaction mixture (**2** → **5**,[1f] 60%); with α-alkyl-α-chloro ketones the mixture is merely stirred at room temperature overnight [**2** → **6** (R = CH_3),[1f] 86%; **2** → **6** (R = allyl), 68%].[10] In that α-methylcyclopentenones of this type are common to many naturally occurring hydroazulenes,[11] it is of potential synthetic importance that this simple one-step protocol also served to convert ketone **22** to the corresponding α-methyl enone **23**[1f] in 65% yield after chromatography.

22 **23**

The versatile[12] chloro enone **10** can be readily secured in excellent yield from the α,α-dichloro ketone **2** (DMF, Li_2CO_3, 85 °C, 30 min, 96%) and, importantly, also from the α,α-dichloro-β-[(trimethylsilyl)oxy]cyclopentanone **9**[13] (Zn, AcOH, room temperature, 30 min, 90%). *Direct* treatment of **9** with (a) H_2 and Pd/C in MeOH afforded the cis-fused bicyclic ketone **7**[7,14] in 80% yield (also available from **2** by using Zn in AcOH, 90%). Treatment with (b) Li in NH_3 followed by Zn in AcOH, or Ca in NH_3–MeOH followed by pyridinium chlorochromate in CH_2Cl_2, yielded the trans-fused bicyclic ketone **11**[7,14,15] in 55–60% yield.[16] (c) Excess lithium dimethylcuprate in Et_2O–hexane gave the angularly substituted cis-fused chloro ketone **12**,[3] mp 85–7 °C, in 50–60% yield. Of course, chloro enone **10**, an intermediate in a–c, would be expected to react similarly.

The mild, high-yield transformations of α,α-dichlorocyclopentanones described in this paper add to the value of this three-carbon annelation process, especially for use in the construction of complex natural products. We anticipate pursuing such goals.

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Registry No. 2, 72952-33-1; **3**, 72952-34-2; **4** (R = CH_3), 72952-35-3; **4** (R = allyl), 72952-36-4; **5**, 39163-29-6; **6** (R = CH_3), 24730-98-1; **6** (R = allyl), 72952-37-5; **7**, 5689-04-3; **9**, 72952-38-6; **10**, 72952-39-7; **11**, 16484-17-6; **12**, 72952-40-0; **13**, 72952-41-1; **14**, 72952-42-2; **15**, 72952-43-3; **16**, 72952-44-4; **17**, 72952-45-5; **18**, 72952-46-6; **22**, 72952-47-7; **23**, 67722-29-6.

(8) A. M. El-Abbady and S. H. Doss, *Can. J. Chem.*, **43**, 2408 (1965); T. Shomo, M. Okawa, and I. Nishiguchi, *J. Am. Chem. Soc.*, **97**, 6144 (1975).

(9) The stereochemistry of compounds **3** and **4** in Figure 1 has been assigned on the basis of attack of the electrophile from the less hindered side of the chloro enolate intermediate. The facile loss of HCl [**4** (R = CH_3) was totally converted to **6** (R = CH_3) on standing at 0 °C for a few weeks] and the kinetic formation[6d] of the chloro ketone **3** (δ_{CCl_4} 4.30, d, J = 7.5 Hz), which upon epimerization (Al_2O_3, $CHCl_3$) affords predominently the isomeric product (δ_{CCl_4} 3.90, d, J = 6.0 Hz), support the assignments.

(10) Of course, the commonly used techniques can also be applied. See C. Djerassi, "Steroid Reactions", Holden-Day, San Francisco, 1963, Chapter 4, and references cited therein. In the case of **2** → **6** (R = allyl) allyl iodide was used, and the conversion was incomplete.

(11) See T. K. Devon and A. I. Scott, "Handbook of Naturally Occuring Compounds", Academic Press, New York, 1972.

(12) G. Stork and T. L. Macdonald, *J. Am. Chem. Soc.*, **97**, 1264 (1975); G. Stork and V. Nair, *ibid.*, **101**, 1315 (1979); T. L. Macdonald, *J. Org. Chem.*, **43**, 4241 (1978). See also: T. Kametani, K. Sazuki, H. Nemoto, and K. Fukumoto, *ibid.*, **44**, 1036 (1979); Y. Tamura, T. Kawasaki, N. Gohda, and Y. Kita, *Tetrahedron Lett.*, 1129 (1979); P. Blatcher and S. Warren, *ibid.*, 1247 (1979).

(13) We have found that these compounds can be synthesized in excellent yield by treatment of the corresponding dichloroketene–trimethyl silyl enol ether adducts[2b,d] with diazomethane [**9**, 92%, mp 62–64 °C (hexane)]. This extends considerably the scope of the annelation process making it now applicable to ketones (i.e., enol ethers) as well as olefins. Silyl enol ethers are available *regioselectively* through a variety of procedures. See: J. K. Rasmussen, *Synthesis*, 91 (1977); E. W. Colvin, *Q. Rev., Chem. Soc.*, **7**, 15 (1978), and references cited therein.

(14) A. Kandiah, *J. Chem. Soc.*, 922 (1931).

(15) R. S. Thakur, *J. Chem. Soc.*, 1485 (1933).

(16) The cis-fused hydrindanone **7** was also formed in approximately 5% yield in these reactions.

Jean-Pierre Deprés, Andrew E. Greene*
Laboratoire de Chimie Organique, CERMO
Université Scientifique et Médicale
38041 Grenoble, France

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A Synthesis of Moenocinol[1]

Summary: The fluoride-induced elimination of a β-silyl sulfone and the reductive elimination of a β-acyloxy sulfone are key olefin-forming reactions in a new synthesis of moenocinol [(2*Z*,6*E*,13*E*)-3,8,8,14,18-pentamethyl-11-methylenenonadeca-2,6,13,17-tetraen-1-ol].

Sir: The moenomycins and prasinomycin are members of a group of relatively nontoxic phosphorus-containing antibiotics which have the remarkable property of long duration of action in vivo against Gram-positive bacteria.[2,3]

(1) Reprints of this paper will not be available.

(2) W. A. Slusarchyk, J. A. Osband, and F. L. Weisenborn, *Tetrahedron*, **29**, 1465 (1973).

(3) Witteler et al. [F.-J. Witteler, P. Welzel, H. Duddeck, G. Höfle, W. Riemer, and H. Budzikiewicz, *Tetrahedron Lett.*, 3493 (1979)] have proposed a complete structure for moenomycin A.

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