Conjugate Addition of Lithium Phenylthio- and Cyano-[2-(4-chlorobut-1-enyl)]cuprate to Cyclic Enones. An Efficient Methylenecyclopentane Annulation Process

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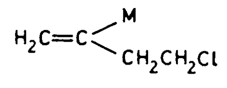
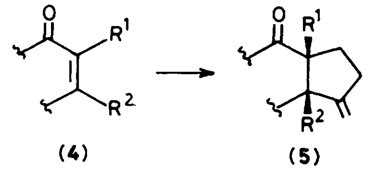
Reaction of the cyclic enones (**6**)—(**11**) with the structurally interesting cuprate reagents (**2**) and (**3**) provides very good yields of the conjugate addition products (**12**)—(**17**); treatment of the latter substances with potassium hydride in tetrahydrofuran affords the methylenecyclopentane annulation products (**18**)—(**23**), respectively.

In the preceding communication[1] we reported that the reaction of ω-substituted 1-alkynes with trimethylstannylcopper–dimethyl sulphide provides good to excellent yields of the corresponding 2-(trimethylstannyl)-1-alkenes which we believed could serve as useful precursors of reagents corresponding to donor–acceptor[2] synthons. We report herein that one of the products, 4-chloro-2-trimethylstannylbut-1-ene (**1**) can be converted readily into the novel cuprate reagents (**2**) and (**3**), which are convenient reagents for effecting the annulation (**4**) → (**5**).[3]

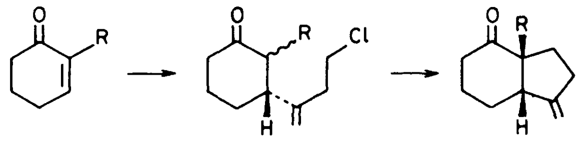
Transmetallation (1.1 equiv. of MeLi, tetrahydrofuran, −78 °C, 10 min) of compound (**1**),[4] followed by addition of 1.1 equiv. of phenylthiocopper[5] or copper(I) cyanide to the resulting solution of 4-chloro-2-lithiobut-1-ene,[4] provided clear solutions of the cuprate reagents (**2**) and (**3**). Importantly, these reagents proved sufficiently stable to allow for their reaction with cyclic enones to afford good to excellent yields of the



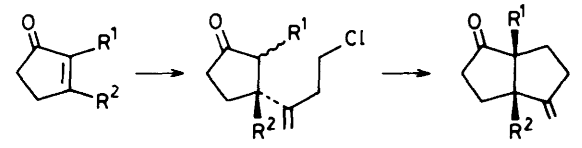
(**1**) M = $SnMe_3$
(**2**) M = Cu(SPh)Li
(**3**) M = Cu(CN)Li



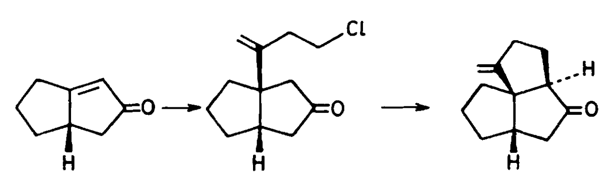
(**4**) (**5**)



(**6**) R = H (**12**) R = H (**18**) R = H
(**7**) R = Me (**13**) R = Me (**19**) R = Me



(**8**) $R^1 = R^2 = H$ (**14**) $R^1 = R^2 = H$ (**20**) $R^1 = R^2 = H$
(**9**) $R^1 = Me, R^2 = H$ (**15**) $R^1 = Me, R^2 = H$ (**21**) $R^1 = Me, R^2 = H$
(**10**) $R^1 = H, R^2 = Me$ (**16**) $R^1 = H, R^2 = Me$ (**22**) $R^1 = H, R^2 = Me$



(**11**) (**17**) (**23**)

Table 1. Preparation of methylenecyclopentane annulation products.

Enone	Conjugate addition product and yields, %[a]	Annulation product and yield, %[b]
(**6**)	(**12**) 83, 80	(**18**) 75
(**7**)	(**13**) 77, 78	(**19**) 75
(**8**)	(**14**) 75, 77	(**20**) 68
(**9**)	(**15**) 77, 75	(**21**) 75
(**10**)	(**16**) 80, 78[c]	(**22**) 70[d]
(**11**)[e]	(**17**) 70, 72	(**23**) 65

[a] The appropriate enone (1.2 equiv.) was allowed to react in tetrahydrofuran with 1.0 equiv. of reagent (**2**) (−78 °C, 2—3 h) or (**3**) (−78 °C, 1 h; −48 °C, 1.5 h). In each case, the two yields refer to those obtained by use of reagents (**2**) and (**3**), respectively. The yields, which were not optimized, are based on the amount of compound (**1**) employed, and refer to purified (chromatography, distillation) materials. [b] A tetrahydrofuran solution of the appropriate conjugate addition product was treated with potassium hydride (2.5 equiv.) and the resultant mixture was stirred at room temperature for 2.5 h. In each case, the yield (not optimized) refers to purified (chromatography, distillation) material. [c] In these cases, it was necessary to catalyse the reactions with boron trifluoride–diethyl ether (see text). [d] In this case, the reaction was not complete after 2.5 h, and the mixture was therefore stirred for an additional 5 h. [e] D. K. Klipa and H. Hart *J. Org. Chem.*, 1981, **46**, 2815.

corresponding conjugate addition products. Thus, when cyclohex-2-en-1-one (**6**) was allowed to react (tetrahydrofuran, −78 °C, 2 h) with reagent (**2**), and the resultant solution was treated with saturated aqueous ammonium chloride, the cyclohexanone derivative (**12**)† was obtained in 83% yield. Under similar conditions (−78 °C, 1 h; −48 °C, 1.5 h), reagent (**3**) converted (**6**) into (**12**) in 80% yield. Treatment of compound (**12**) with potassium hydride in tetrahydrofuran (room temperature, 2.5 h) afforded the bicyclic ketone (**18**) (75%).

Subjection of the cyclic enones (**7**)—(**11**) to the overall methylenecyclopentane annulation process provided the results summarized in Table 1. In all cases studied, the annulation sequence was quite efficient and experimentally straightforward. One minor difficulty arose when it was found that treatment of 3-methylcyclopent-2-en-1-one (**10**) with either of the reagents (**2**) or (**3**), under the conditions outlined above, failed to produce the desired addition product (**16**). However, when the solutions containing reagents (**2**) and (**3**) were treated with *ca.* 1 equiv. of boron trifluoride–diethyl ether prior to addition of the enone (**10**), conjugate addition proceeded smoothly [reagent (**2**), −20 °C, 2 h; reagent (**3**), −78 °C, 2 h] and, in each case, the cyclopentane derivative (**16**) was obtained in excellent yield.

In order to characterize fully all isolable synthetic intermediates, we have thus far carried out most of the annulation processes *via* two distinct steps, as described above. However, the conversion of the enones into the corresponding methylenecyclopentane derivatives can be accomplished without isolation of the intermediate chloro ketones. For example, addition of 1.5 equiv. of hexamethylphosphoramide to the solutions derived from addition of reagent (**2**) to the enones (**6**) and (**8**), followed by warming the resultant mixtures to room temperature (3 h), provided directly the annulation products (**18**) and (**20**) in yields of 55—60%. Clearly, this one-step method is particularly attractive.

The methylenecyclopentane moiety and the structurally related methyl- and *gem*-dimethyl-cyclopentane units are common structural features of many terpenoid natural products. It seems clear that the new annulation method described herein should prove to be useful for the synthesis of such naturally occurring substances.

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2 D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 239.

3 For a recent report describing, *inter alia*, a methylenecyclopentane annulation sequence, see P. Magnus and D. A. Quagliato, *Organometallics*, 1982, **1**, 1243.

4 For a preparation of (**1**) alternative to that described in reference 1, and for the reaction of 4-chloro-2-lithiobut-1-ene with electrophilic substrates, see E. Piers and V. Karunaratne, *J. Org. Chem.*, 1983, **48**, 1774.

5 G. H. Posner, D. J. Brunelle, and L. Sinoway, *Synthesis*, 1974, 662.

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† All isolable compounds reported herein exhibited spectra consistent with assigned structures (including stereochemistry). New compounds gave satisfactory molecular mass determinations (high resolution mass spectrometry).