Tetrahedron Letters, Vol 32 No 42, pp 5861 5864 1991
Printed in Great Britain

0040-4039/91 $3 00 + 00
Pergamon Press plc

A Novel Synthesis of Unsaturated Spiro Compounds Based on Reactions of Bifunctional Organometallic Reagents.

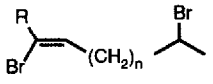
Perséphone Canonne*, Raynald Boulanger and Paul Angers

Département de chimie, Université Laval, Ste-Foy, Québec, Canada, G1K 7P4

Abstract *Z-allylic dibromides regio- and stereoselectively prepared were reacted with the sodium enolate of ethyl acetoacetate or di(α-ethoxyvinyl)cuprate to yield, after hydrolysis, and decarboxylation in the case where the enolate of ethylacetoacetate was the nucleophile, the corresponding ketones After reduction and bromination, the products were converted into the appropriate organometallic compounds and reacted with selected cyclic anhydrides and β-halo-α,β-unsaturated cyclic ketones The spiro compounds so obtained are key intermediates for the synthesis of naturally occurring spiro sesquiterpenes*

Many natural spiro compounds or key intermediates[1] in the preparation of these natural products possess a double bond in the α position of the quaternary center The desired orientation of this double bond often causes some difficulty, mainly because of a possible isomerization during its formation To circumvent this problem, we established a general method for the preparation of Z-vinyl alkyl dibromides which can be made to react at selected dielectrophilic sites after conversion into the appropriate bisorganometallic reagents Moreover, depending on the dibromide chosen, it is possible to construct five or six membered rings

The dibromides have the general structure represented hereafter, where R is a hydrogen atom or an alkyl group and n is either 1 or 2, and can rapidly provide key intermediates in the synthesis of natural products, as selected examples will illustrate

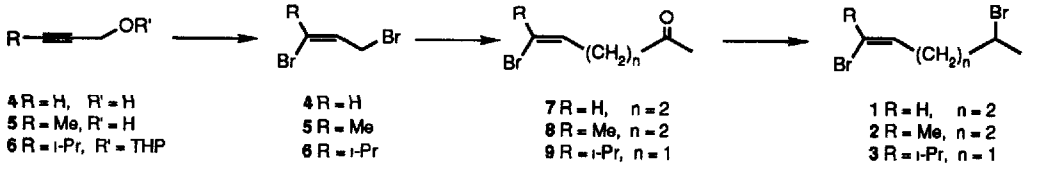


1 R = H, n = 2
2 R = Me, n = 2
3 R = *i*-Pr, n = 1

In order to demonstrate the general applicability of this approach, we prepared Z-dibromides **1**, **2** and **3**, as shown in Scheme 1 The first step in this synthesis consisted in the easy formation of compounds **4**, **5** and **6** by the regio- and stereoselective addition of hydrogen bromide to the triple bond[2] and by bromination of the primary allyl alcohol or the corresponding derivative In the case of compound **4**, the starting material was

propargyl alcohol itself, while for compound **5**, it was 2-butyn-1-ol Finally, the introduction of an isopropyl group on the terminal acetylenic carbon of 1-tetrahydropyranyl-2-propyne, according to Brown's method,[3] led to 4-methyl-1-tetrahydropyranyl-2-pentyne Addition of hydrogen bromide to the latter provided **6** with a high degree of stereoselectivity

Scheme 1



The next step consisted in the homologation of the primary allylic site by displacement of bromine For compounds **4** and **5**, the sodium enolate of ethyl acetoacetate acted as the nucleophile Hydrolysis of the resultant intermediate, followed by decarboxylation, led to ketones **7** and **8** In the case compound **6**, di(α-ethoxyvinyl)cuprate[4] effected a quantitative displacement to yield an enol ether which was then hydrolysed,[5] giving ketone **9** in high yield

A quantitative reduction of methylketones with sodium borohydride, followed by bromination of the resulting alcohols, using carbon tetrabromide and triphenylphosphine in methylene chloride,[6] completed the preparation of compounds **1**, **2** and **3** in good to high yields

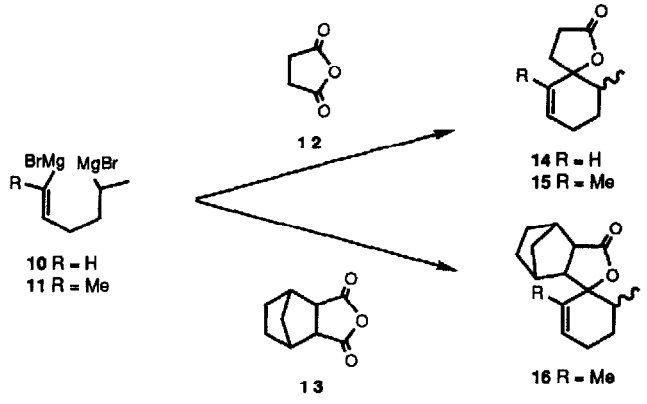
In connection with the development of a fundamentally new synthesis of spiro compounds, we extended our spiroannulation methodology to the formation of unsaturated spiro compounds based on the use of unsaturated di-Grignard reagents That the created ring contains a double bond adjacent to the spirocenter and two methyl groups is the major advantage and the specific feature of this present method. Alternative methods to accomplish this overall process require multistep processes involving sequential attachment of two rings and the creation of the double bond [7]

Di-Grignard reagents **10** and **11** were respectively prepared by reaction of dibromides **1** and **2** (8 8 mmoles) in 70ml of anhydrous tetrahydrofuran with magnesium turnings (18,2 mmoles) at 10°C under vigourous stirring and a nitrogen atmosphere The resulting di-Grignard solution was stirred at room temperature over a three hour period To this stirred and cooled solution (0°C) was then added anhydride **12** or **13** (7 mmoles) diluted in anhydrous tetrahydrofuran (30 ml) over a one hour period The reaction mixture was allowed to warm to room temperature for three hours and then was submitted to a standard work-up procedure, leading to the formation of spirolactones **14**, **15** and **16** in good yield (Scheme 2) Spirolactone **14** is a key intermediate in the synthesis of cubebene [9]

The second major goal of this study concerned the synthesis of unsaturated spiroketones based on the use of 3-halo-2-cycloalken-1-ones which, as is well established, react with cuprates 3-Halo-2-cyclopenten-1-one (**17**) was easily prepared from the corresponding 1,3-cyclopentanedione, according to the procedures previously reported.[10] Notable examples are found in the synthesis of β-vetivone, hinesol and agarospirol

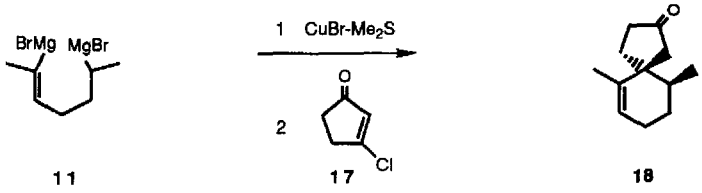
Thus, in order to obtain the important key intermediate 6,10-dimethylspiro[4 5]-6-decen-2-one (**18**), the dibromo compound **2** was selected as precursor of the appropriate annulating reagent

Scheme 2



In the present study, it was important to examine factors that influence the efficiency of the process, including the nature of the organometallic reagent as well as that of the halogen in the 3-halo-2-cyclen-1-one It resulted that di-Grignard **11**, in the presence of a catalytic amount of the copper(I) bromide-dimethyl sulfide complex, treated with 3-chloro-2-cyclopenten-1-one at -30°C in tetrahydrofuran,[11] led to the preparation of 6,10-dimethyl[4 5]-6-decen-2-one (**18**) in a 65% yield, after purification by flash chromatography on silica gel After analysis of the product, it was observed that the reaction proceeded stereospecifically, indeed only the cis-isomer was formed The stereochemistry was confirmed by ^{1}H-NMR and IR spectra which were compared to those previously reported by professors P Deslongchamps[12] and D. Caine [13] This spiroketone also gave a mixture of two 2,4-dinitrophenylhydrazone derivatives (m.p 76-86°C, lit 78-88°C[12]) which can be separated

The observed stereochemistry can mainly be attributed to the selective displacement of the halogen by the secondary alkyl organometallic function, leading to a uniquely favoured conformation due to the steric hindrance caused by the presence of the introduced methyl group Consequently, the conjugate addition of the vinyl organometallic function, responsible for the ring closure, is completely stereoselective



Furthermore, in studies related to this spiroannulation process, it was found that replacement of the di-Grignard reagent by 1,5-dilithioalkane and two equivalents of copper(I) thiophenoxide led to more side products and, accordingly, lower yields [14]

A new application of our methodology has been developed, based on the reaction of cyclic anhydrides and β–halocycloalkenones with unsaturated vinyl alkyl organodimagnesium compounds This method affords the concise synthesis of the spiro[4 5] decane squeleton found in many sesquiterpenes

ACKNOWLEDGMENT We thank Professors P Deslongchamps and L Ruest for the ^{1}H-NMR and IR spectra of **18** This work was supported by Natural Sciences and Engineering Research Council of Canada and the Fonds F C A R , Ministère de l'éducation du Québec A postgraduate scholarship (NSERC, Canada) to P Angers is also gratefully acknowledged.

REFERENCES

1 (a) Heathcock, C H , In *The Total Synthesis of Natural Products*, Vol 2, Edited by J ApSimon, John Wiley & Sons Inc, New-York, 1973, pp 466-474
(b) Marshall, J A , Brady, S F , Andersen, N H , In *Progress in the Chemistry of Organic Natural Products*, Vol 31, Springer-Verlag, Wien and New-York, 1974, pp 283-371
2 Shi, L, Narula, C K , Mak, K T , Kao, L K , Xu, Y , Heck, R F , *J Org Chem* , **48**, 3894 (1983)
3 Suzuki, A , Miyaura, N , Abiko, S , Itoh, M , Brown, H C , Sinclair, J A , Midland, M. M *J Am Chem Soc* , **95**, 3080 (1973)
4 Chavdarian, C G , Heathcock, C H , *J Am Chem Soc* , **97**, 3822 (1975)
5 Boeckman Jr , R K , Bruza, K J , *J Org Chem* , **44**, 4781 (1979)
6 (a) Tomoskozi, I , Gruber, L , Radus, L , *Tetrahedron Lett* , 2473 (1975).
(b) Aneja, R , Davies, A P , Knaggs, J A , *Tetrahedron Lett* , 67 (1975)
7 (a) Marshall, J A , Johnson, P C , *Chem Commun* , 391 (1968)
(b) Marshall, J A , Brady, S F , *Tetrahedron Lett* , 1387 (1969)
(c) Marshall, J A , Brady, S F , *Tetrahedron Lett* , 1387 (1969)
(d) Ibuka, T , Hayashi, K , Ito, Y , Inubushi, Y , *Can J Chem* , **57**, 1579 (1979)
(e) Ibuka, T , Hayashi, K, Minakata, H , Inubushi, Y , *Tetrahedron Lett* , **2**, 159 (1979)
(f) Posner, G H , Frye, L L , Hulce, M , *Tetrahedron*, **40**, 1401 (1984)
(g) Posner, G H , Hamill, T G , *J Org Chem* , **53**, 6031 (1988)
8 Canonne, P , Bélanger, D , Lemay, G , Foscolos, G B , *J Org Chem* , **46**, 3091 (1981)
9 (a) Brown, H C , Garg, C P , *J Am Chem Soc* , **83**, 2952 (1961)
(b) Tanaka, A , Uda, H , Yoshikoshi, A , *Chem Comm* , 308 (1969)
(c) Tanaka, A , Tanaka, R , Uda, H , Yoshikoshi, A , *J Chem Soc Perkin I*, 1721 (1972)
10 (a) Piers, E , Nagakura, I , *J Org Chem* , **40**, 2694 (1975)
(b) Kowalski, C J , Fields, K W , *J Org Chem* , **46**, 197 (1981)
(c) Piers, E , Cheng, K, F , Nagakura, I , *Can J Chem* , **60**, 1256 (1982)
11 (a) Normant, J F , Bourgain, M , *Tetrahedron Lett* , 2583 (1971)
(b) Normant, J F , Cahiez, G , Bourgain, M , Chuit, C , Villeras, J V , *Bull Soc Chim Fr* , 1656 (1974)
(c) Westmijze, H , Meier, J , Bos, H J T , Vermeer, P , *Recl, Trav Chim Pays-Bas*, **95**, 299 (1976)
(d) Ashby, E C , Smith, R S , Goel, A B , *J Org Chem* , **46**, 5133 (1981)
(e) Ashby, E C , Goel, A B , *J Org Chem* , **48**, 2125 (1983)
12 Lafontaine, J , Mongrain, M , Guay, M S , Ruest, L , Deslongchamps, P , *Can J Chem* , **58**, 2460 (1980)
13 Caine, D , Boucugnani, A A , Chao, S T , Bawson, J B , Ingwalson, P F , *J Org Chem* , **41**, 1539 (1976)
14 Wender, P A , White, A W , *J Am Chem Soc* , **110**, 2218 (1989)

(Received in USA 16 July 1991)