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PREPARATION AND ALKYLATION OF CYCLIC β-TRIMETHYLSTANNYL α,β-UNSATURATED ESTERS. A NEW, GENERAL ANNULATION SEQUENCE

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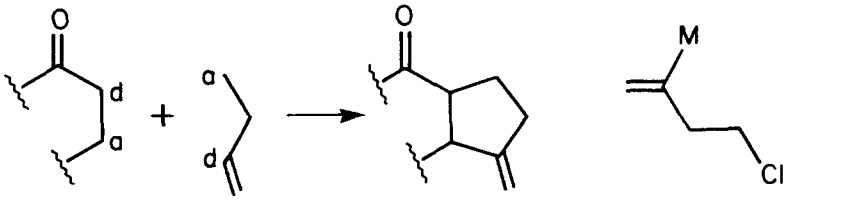
ABSTRACT: The key steps of a newly developed annulation method involve (a) reaction of cyclic β-trifluoromethanesulfonyloxy α,β-unsaturated esters (e.g. 14-16) with lithium (phenylthio)(trimethylstannyl)cuprate, (b) alkylation of the resultant products (e.g. 17-19) with 1,ω-dihaloalkanes, and (c) transmetalation-cyclization of suitable substrates (e.g. 25, 26, 28, 30) derived from the alkylation products (e.g. 20-24).

Annulation methods, involving the construction of rings onto cyclic or acyclic substrates, have been, and continue to be, of great importance in synthetic organic chemistry. Indeed, it is difficult to overstate the centrality of such processes in the area of natural product synthesis. Since the introduction of the Robinson annulation sequence nearly 50 years ago,[1] many different six-membered ring annulation processes have been developed.[1,2] More recently, however, primarily in connection with research programs aimed at the synthesis of naturally occurring substances containing five- and seven-membered carbocycles, a significant number of annulation methods leading to functionalized cyclopentane and cycloheptane ring systems have been described.[3,4]

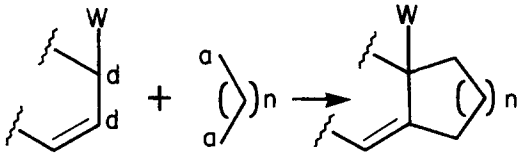
Recently, we developed a new 5-membered ring annulation method based on the (theoretical) combination of a d^2,a^3-synthon[5] 1 with the 1-butene d^2,a^4-synthon 2. In this process, which produces efficiently the methylenecyclopentane products 3, α,β-unsaturated ketones serve as equivalents to the generalized substrate synthon 1, while the structurally interesting organocuprates 4 and/or 5 function as efficient equivalents to the reagent synthon 2. Reagents 4 and 5 are derived from 4-chloro-2-lithio-1-butene (6),[6] which, in turn, can be produced conveniently by low-temperature transmetalation of 4-chloro-2-(trimethylstannyl)-1-butene (7).[7]



1 2 3

4 M = Cu(CN)Li
5 M = Cu(SPh)Li
6 M = Li
7 M = $SnMe_3$

We describe herein a new annulation sequence which, although also based on organotin chemistry, is quite different from that outlined above (1 → 3). The present method can be represented in general terms by the union of a d,d-synthon 8 (W = CO_2R or a functional group derived therefrom) with an a,a-synthon 9. In practice, species equivalent to 8 are obtained from β-trimethylstannyl α,β-unsaturated esters, while 1,ω-dihaloalkanes serve as convenient equivalents to 9. Clearly, it should be possible to have various functional groups incorporated into both 8 and 9. Furthermore, the size of the ring which is formed in the annulation sequence depends upon the value of n in 9 and, in our work thus far, 5-, 6- and 7-membered rings have been formed.



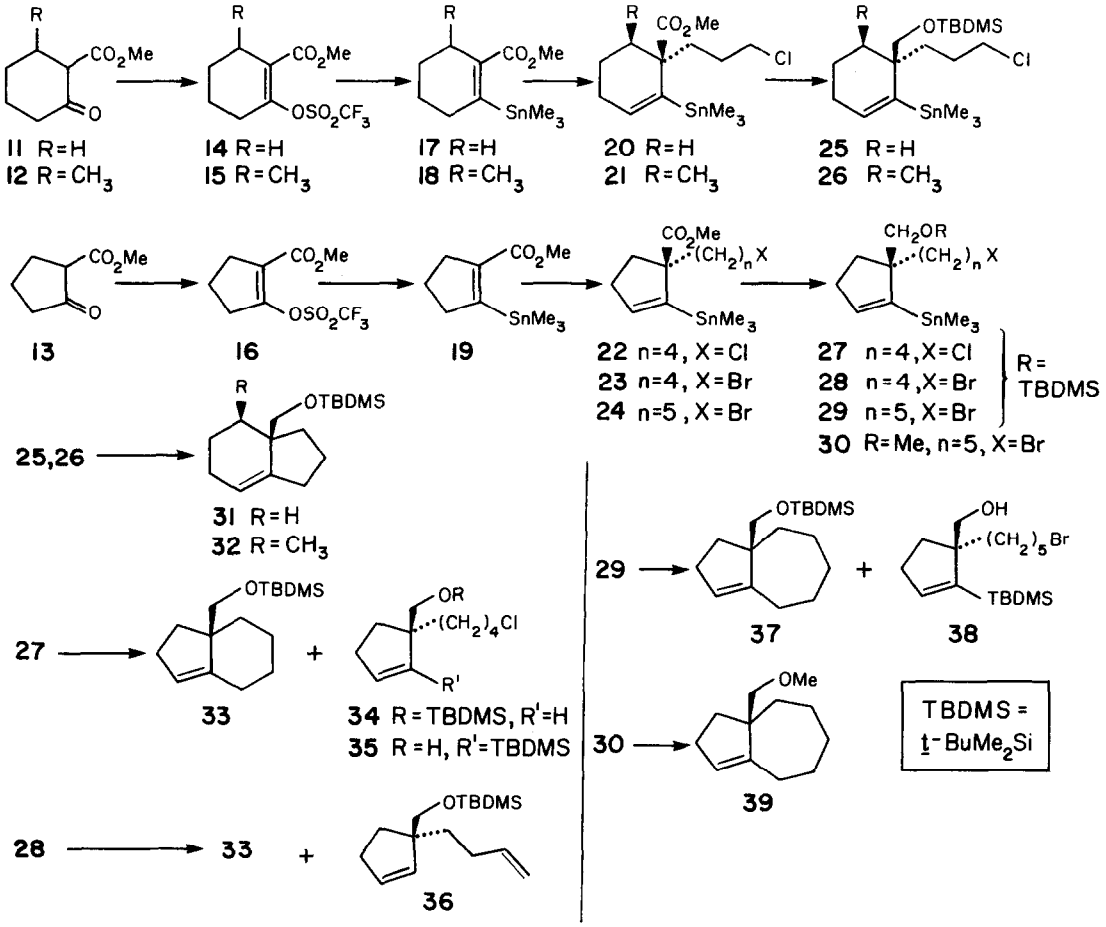
8 9 10

The cyclic β-trimethylstannyl α,β-unsaturated esters 17-19 were prepared conveniently and efficiently from the corresponding β-keto esters. Thus, for example, conversion [NaH, Et_2O, 0°C; $(CF_3SO_2)_2O$] of 2-carbomethoxycyclohexanone (11) into the trifluoromethanesulfonate 14,[8] followed by reaction of the latter substance with lithium (phenylthio)(trimethylstannyl)-cuprate[9] in tetrahydrofuran (-20°C, 1 h., add 3 equiv. hexamethylphosphoramide, then 0°C, 1 h.), gave compound 17 in 59% overall yield. In similar fashion, the keto esters 12[10] and 13 were transformed, via 15 and 16, into the trimethylstannyl derivatives 18 (81%) and 19 (58%).

Alkylation [lithium diisopropylamide, tetrahydrofuran, hexamethylphosphoramide (3 equiv.), -48°C; $Cl(CH_2)_3I$, -48°C, 40 min.] of esters 17 and 18 provided 20 (78%) and 21 (89%). The latter product consisted of a single isomer and, since the alkylating agent would be expected to approach the enolate anion from the side of the molecule opposite to the adjacent methyl group, the stereochemistry of 21 can be assigned with confidence. Alkylation, under similar reaction conditions, of the unsaturated ester 19 with 1-bromo-4-chlorobutane, 1,4-dibromobutane, and 1,5-dibromopentane afforded compounds 22 (84%), 23 (77%), and 24 (72%), respectively.

In order to allow for attempted completion of the annulation processes via transmetalation-intramolecular alkylation, the esters 20-24 were reduced (i-Bu_2AlH, Et_2O, -20°C) to the corresponding alcohols, which were then transformed into the ethers 25-30.[11] All of these reactions were very efficient.

Transmetalation-cyclization [MeLi (1.5 equiv.), hexamethylphosphoramide (3 equiv.), tetrahydrofuran, -20°C, 30 min.] of substrates 25 and 26 proceeded smoothly and efficiently, providing the substituted bicyclo[4.3.0]non-1-enes 31 (92%) and 32 (94%). However, subjection of compound 27 to similar reaction conditions gave three products, two of which were formed in minor amounts (12%, 10%) and proved to be the desired annulation material 33 and the transmetalation-protonation product 34. The major product, 35, was that resulting from transfer of the t-$BuMe_2Si$ group from oxygen to carbon. Interestingly, the competition between ring closure (6-centered transition state, chloride ion as leaving group) and silyl



group transfer (5-centered transition state) favored the latter process. This unsatisfactory result could be largely overcome simply by changing the leaving group. Thus, when the bromide 28 was treated with methyllithium, a 6:1 mixture of the annulation product 33 and the diene 36 was produced in good yield. None of the corresponding silyl group transfer product was formed. Presumably, the diene 36 was derived from an intramolecular elimination process (6-centered transition state) involving the vinyl anion produced by transmetalation.

Although attempted transmetalation-ring closure of substrate 29 did afford the desired product 37 (35%), the latter substance was again accompanied by a significant amount (17%) of the product 38 resulting from migration of the t-BuMe$_2$Si group from oxygen to carbon. In this case, apparently, even though the leaving group on the 5-carbon side chain was bromide, the rate of ring closure (7-centered transition state) was only about twice that of the alternative process. However, 7-membered ring formation did take place quite efficiently when the alcohol protecting group was changed from t-BuMe$_2$Si to Me. Thus, treatment of 30 with methyllithium afforded the substituted bicyclo[5.3.0]dec-7-ene 39 in 54% yield.

The preliminary results reported herein demonstrate clearly the viability of annulation sequences represented in general terms by 8 + 9 → 10. Extension of this work to the

preparation of more highly functionalized annulation products is being pursued.

ACKNOWLEDGEMENT. We are indebted to the Natural Sciences and Engineering Research Council of Canada for financial support.

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8. All compounds reported herein exhibited spectra in accord with assigned structures. Accurate molecular mass determinations (high resolution mass spectrometry) were carried out on all new compounds.
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10. The keto ester 12 was prepared by addition of lithium dimethylcuprate to 2-carbomethoxy-2-cyclohexen-1-one [H.J. Reich, J.M. Renga, and I.L. Reich, J. Am. Chem. Soc., 97, 5434 (1975)].
11. For the preparation of 25-27, the alcohols were treated with t-butyldimethylsilyl chloride - imidazole in dimethylformamide; for ethers 28 and 29, t-butyldimethylsilyl triflate-2,6-lutidine in dichloromethane [E.J. Corey, H. Cho, C. Rücker, and D.H. Hua, Tetrahedron Lett., 22, 3455 (1981)] was employed; the methyl ether 30 was obtained by treating the corresponding alcohol with KH-Me_2SO_4 in refluxing tetrahydrofuran.

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