Pure & Appl.Chem., Vol.53, pp.2371-2378.
Printed in Great Britain.

0033-4545/81/122371-08$02.00/0
Pergamon Press Ltd
©1981 IUPAC

PALLADIUM CATALYSIS IN NATURAL PRODUCT SYNTHESIS

Jiro Tsuji

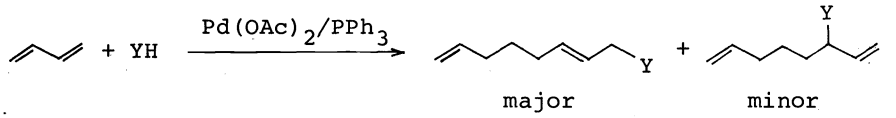
Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Abstract - New synthetic methods for natural products, mainly steroids, based on the palladium-catalyzed reactions are presented.

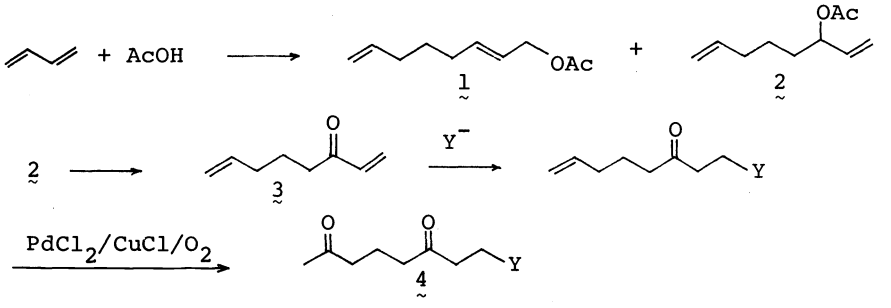
A variety of organic reactions promoted by palladium compounds have been discovered in the last decade, and palladium compounds play important roles in organic synthesis especially as catalysts (Ref.1). Among numerous reactions catalyzed by palladium compounds, we use two reactions extensively for organic synthesis. The first one is the oxidation of olefins to carbonyl compounds. The original reaction is well-known as the Wacker reaction and actually acetaldehyde is produced on an industrial scale from ethylene and oxygen by using $PdCl_2/CuCl_2$ as a catalyst system (Ref.2). Application of this oxidation method to higher 1-olefins affords methyl ketones selectively (Ref.3). We use $PdCl_2/CuCl$ system, rather than $PdCl_2/CuCl_2$, in DMF for the oxidation of 1-olefins to methyl ketones (Ref.4). This reaction is a very useful synthetic method, and terminal olefins can be regarded as masked methyl ketones.

$$RCH{=}CH_2 + O_2 \xrightarrow{PdCl_2/CuCl} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3$$

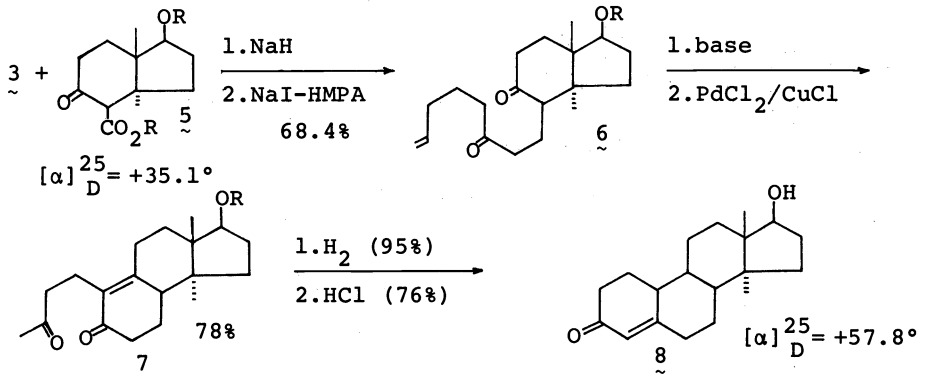
The second reaction is the telomerization of butadiene catalyzed by $Pd(OAc)_2/PPh_3$ (Ref.5 & 6). In this telomerization, dimerization of butadiene with incorporation of various nucleophiles takes place to give the following telomers in high yields.



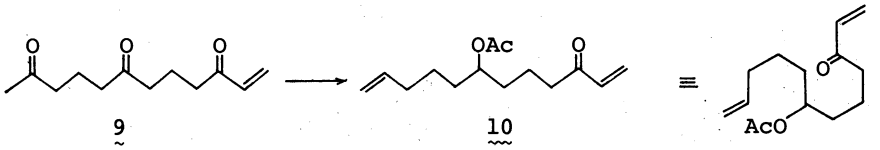
We have applied the above reactions and other palladium-catalyzed reactions to natural product synthesis (Ref.7). Here we wish to report new synthetic methods, mainly for steroids, using palladium-catalyzed reactions in key steps. The palladium-catalyzed telomerization of butadiene with acetic acid affords the following two telomers 1 and 2 (Ref.8 & 9). The telomer 2 was converted to 1,7-octadien-3-one by hydrolysis and oxidation (Ref.10). This is a new and easily prepared bisannulation reagent. After initial Michael reaction at the enone moiety, the terminal double bond is converted into the desired methyl ketone 4 in one step by the palladium-catalyzed oxidation in high yield under mild conditions.



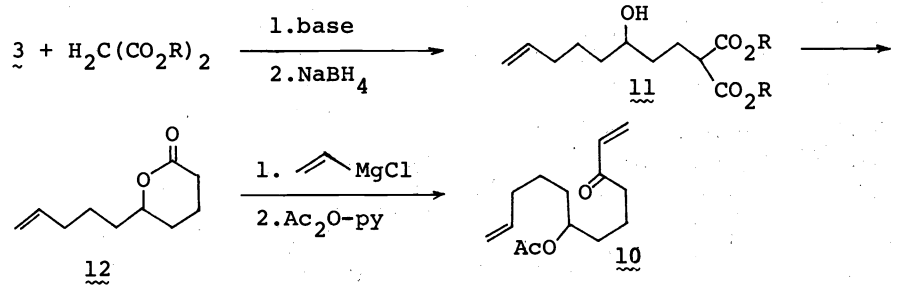
The synthesis of (+)-19-nortestosterone (8) started with the Michael addition of the optically active oxo ester 5 to 3, the ester group being removed by heating in aqueous HMPA with sodium iodide to give the dione 6. The aldol condensation proceeded in 90% yield. The terminal double bond was oxidized with $PdCl_2/CuCl$ to the methyl ketone and the internal olefinic bond subsequently hydrogenated. Finally the aldol condensation afforded (+)-19-nortestosterone (8) (Ref.10).



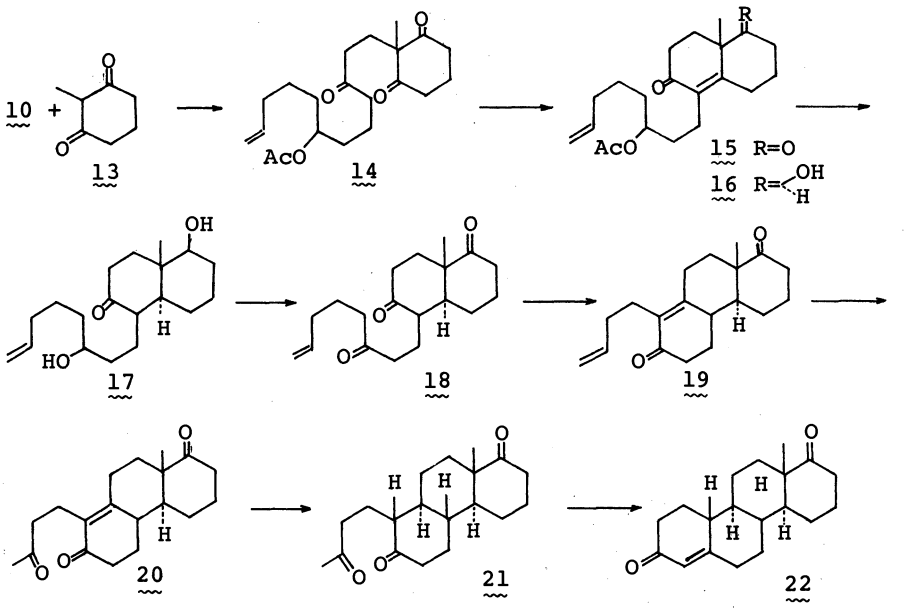
Then we prepared the trisannulation reagent 10 from the bisannulation reagent 3 (Ref.11). The trisannulation in steroid synthesis is a method of constructing three fused six-membered cyclic ketones from one reagent. The trisannulation reagent is a synthetic equivalent of 11-dodecene-2,6,10-trione (9). In other words, the trisannulation reagents are linear 12-carbon frameworks having a terminal enone or its equivalent, a masked methyl ketone, and an oxygen function at the position 6. The usefulness of trisannulation reagents depends upon the easy accessibility of the reagent itself, its stability to acids and bases, and facile procedure of the unmasking. Our trisannulation reagent is 7-acetoxy-1,11-dodecadien-3-one (10). This compound undergoes Michael reaction and then the acetoxy group is converted to a ketone by hydrolysis and oxidation. Finally the terminal double bond is converted to a methyl ketone by the $PdCl_2$-catalyzed oxidation.



The synthesis of 10 was carried out by the reaction scheme shown below. The Michael addition of dimethyl malonate to the enone 3 was carried out and the product was reduced to dimethyl (3-hydroxy-7-octenyl)malonate (11) in 65% yield. Hydrolysis of the diester, followed by heating caused decarboxylation and lactonization to afford 9-decen-5-olide (12) in 77% yield. The lactone 12 was treated with vinylmagnesium chloride and the crude product was acetylated to give the trisannulation reagent 10 in 61% yield.



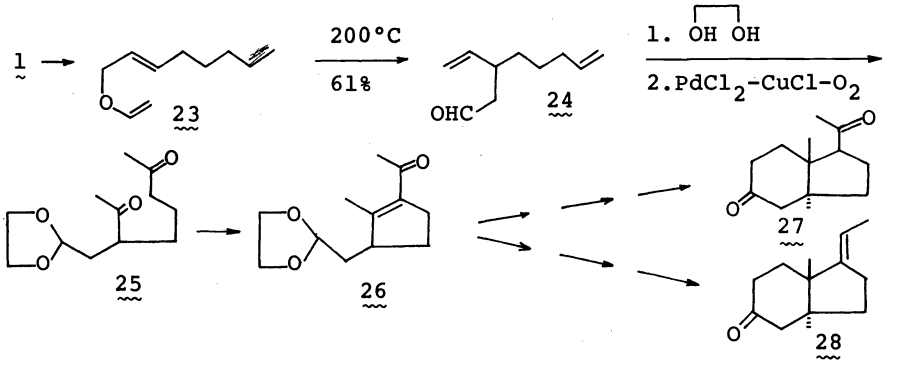
We have carried out the synthesis of (±)-D-homo-19-norandrosta-4-en-3-one (22) from the trisannulation reagent 10 by the following sequence of reactions.



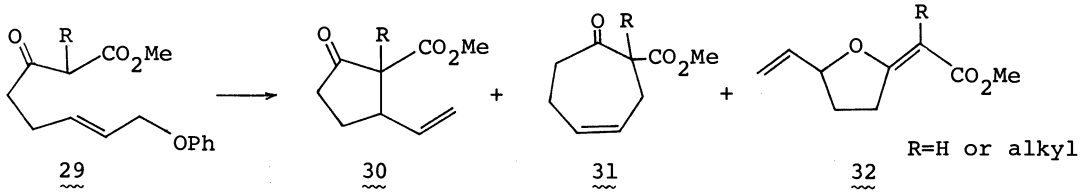
The Michael reaction of 10 with 2-methylcyclohexane-1,3-dione (13) in a mixed solvent of ethyl acetate and triethylamine (2 : 1) produced the trione 14 in 91% yield. Then the aldol condensation of 14 was carried out in a refluxing mixed solvent of toluene and acetic acid (4 : 1) containing β-alanine (2 equiv) to give 15 in 94% yield. The unconjugated ketone of 15 was selectively reduced with sodium borohydride to give 16. Then the enone system of 16 was subjected to the Birch reduction to give the desired trans-fused CD ring. The crude reduction product was hydrolyzed to give the dialcohol 17 in 67% yield from 15. The Jones oxidation of 17 produced the trione 18. The NMR spectrum of the trione 18 showed one singlet peak assignable to the angular methyl group at 1.31 ppm, which clearly demonstrates that the trione 18 is homogeneous and has the trans-fused junction. The intramolecular aldol condensation of 18 using p-toluenesulfonic acid gave the diketone 19 in 76% yield. Then the oxidation of the terminal double bond with $PdCl_2$ and CuCl in aqueous DMF afforded the crystalline trione 20 in 84% yield. Hydrogenation of the enone 20 over Pd on carbon in a mixture of THF-ethanol-triethylamine (100 : 100 : 1) afforded the trione 21 as crystals. The aldol condensation of 21 with 4N-hydrochloric acid produced the crystalline steroid 22 in 90% yield from 20.

As described above, new methods for the facile construction of AB or BC and ABC rings of steroids have been developed by using the bis- and tris-annulation reagents easily prepared from the butadiene telomer. Next, we tried to devise new methods for preparing D ring of steroids based on the palladium-catalyzed reactions.

The telomer 1 was converted to the allyl vinyl ether 23. Its [3,3]-sigmatropic rearrangement afforded the diene aldehyde 24. After protection of the aldehyde, two terminal double bonds were oxidized with $PdCl_2$-CuCl to give the diketone 25, which underwent aldol condensation to give the cyclopentenone 26 (Ref.12). This compound is a very suitable compound for the synthesis of hydrindanones (27, 28), or CD rings of steroids.



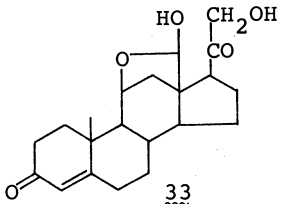
We have investigated another synthetic method for D rings based on the palladium catalyzed cyclization (Ref.13). We prepared five-membered cyclic ketones by the palladium-catalyzed intramolecular reaction of active methylene compounds with allylic ether moities. We have synthesized methyl (E)-3-oxo-8-phenoxy-6-octenoate (29) by the reaction of the dianion of methyl acetoacetate with (E)-1-chloro-4-phenoxy-2-butene (77% yield), and carried out its cyclization using 5-10 mol% of $Pd(OAc)_2$-phosphine or phosphite as a catalyst at the refluxing temperature of various solvents without using a base.



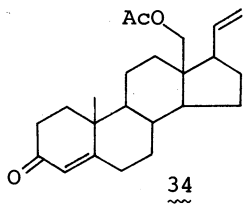
29 30 31 32

2-Carbomethoxy-3-vinylcyclopentanone (30) and 2-carbomethoxy-4-cycloheptenone (31) were obtained as the C-alkylated product. The ratio of 30 and 31 changed depending on the conditions. The desired 30 was obtained with 87% selectivity when acetonitrile or propionitrile was used. The five-membered ketones were obtained predominantly when 2-alkylated derivatives were subjected to the cyclization. In addition to 30 and 31, formation of 2-carbomethoxymethylidene-5-vinyltetrahydrofuran (32) was detected as the O-alkylation product, which was rearranged to 30 and 31 during the reaction by the palladium catalyst. The cyclization reaction proceeds under neutral conditions, and hence tolerates the presence of various functional groups without protection.

This palladium-catalyzed reaction offers a very good synthetic approach to naturally occurring cyclopentanone derivatives disubstituted at the 2 and 3 positions such as jasmonoids and prostanoids. Furthermore, these cyclopentanones 30 are very suitable starting materials for facile synthesis of CD rings of steroids; particularly those which have functionalized 18-methyl groups (steroid numbering). The ester and vinyl groups in 30 can be transformed into several functional groups present in various steroids. A number of naturally occurring steroids functionalized at 18 methyl are known: aldosterone (33), 18-acetoxypregna-1,4,20-trien-3-one (34), and 20-hydroxypregn-4-en-3-one are typical examples. Also conessine has a nitrogen function at the 18-methyl.

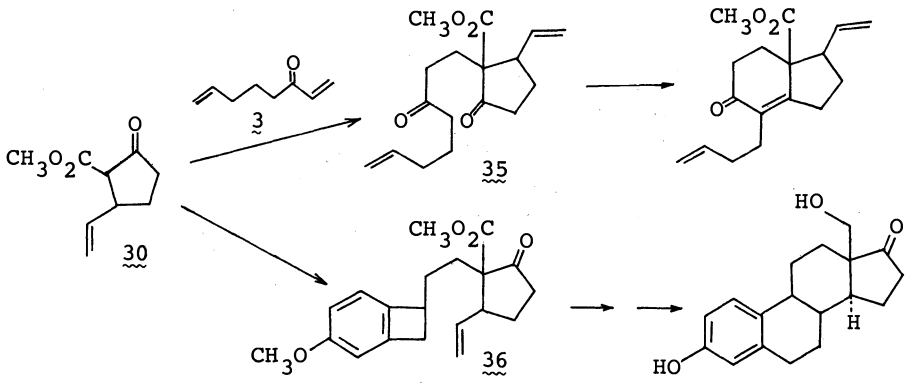


33

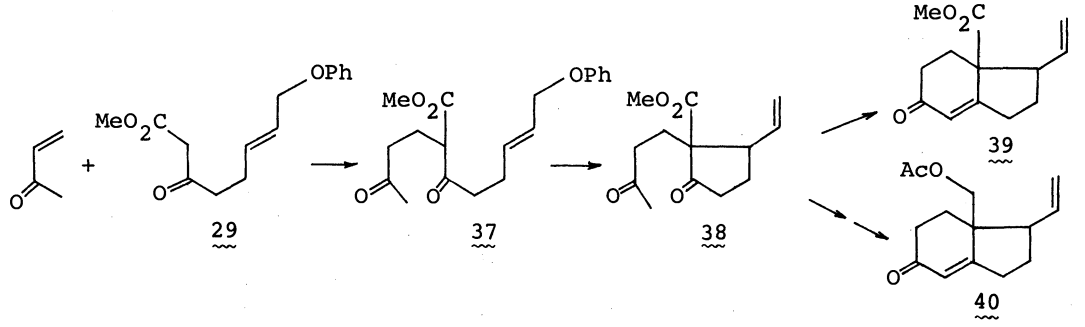


34

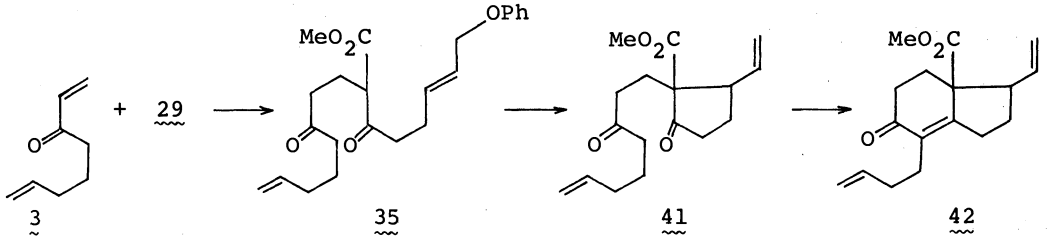
The compound 30 can be utilized for the steroid synthesis in two ways. In one way, the vinyl group is used for the preparation of a side chain attached to the D ring, and the ketone is used for aldol condensation to construct the C ring. We have prepared the following cyclopentanone derivative 35 from 30 by the Michael addition of the bisannulation reagent 3. The second way is based on the utilization of the vinyl group in 30 for the intramolecular cycloaddition with benzocyclobutene 36 via an o-quinodimethane intermediate, and the ketone group becomes the 17-oxo group.



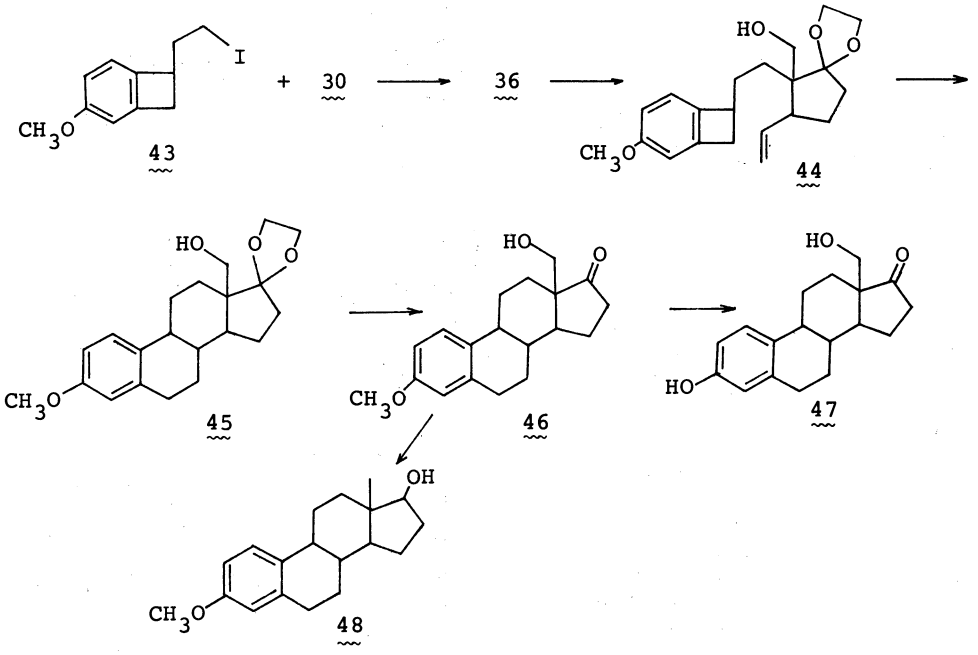
The new bisannulation reagent 37 was prepared in 74% yield by the addition of methyl vinyl ketone to methyl 3-oxo-8-phenoxy-6-octenoate (29)(Ref.14). The cyclization of 37 using $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%) as the catalyst in refluxing acetonitrile for 1 hr afforded the cyclopentanone 38 in 91% yield. The cyclization conditions are so mild that no side reaction such as retro-Dieckmann or aldol condensation took place. The aldol condensation of 38 in toluene using a mixture of acetic acid and β-alanine produced the CD rings 39 in 74% yield. There are a number of possible modifications of the functional groups. For example, the ester group in 38, after protection of the ketones, was reduced to an alcohol and the acetoxymethyl derivative 40 was prepared.



The new trisannulation reagent 35 was also prepared in 81% yield using 1,7-octadien-3-one (3), instead of methyl vinyl ketone. The palladium-catalyzed cyclization of 35 produced the cyclopentanone 41 in 60% yield. Finally the CD rings 42 were obtained by the aldol condensation in 80% yield.



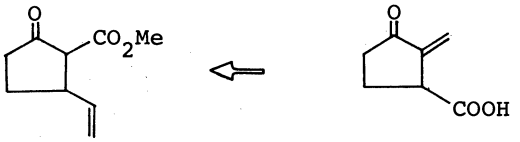
We have carried out the total synthesis of 18-hydroxyestrone (47) based on the second way (Ref.15). 18-Hydroxyestrone (47) was isolated from urine of pregnant women and identified by Marrian and coworker (Ref.16). Two partial syntheses (Ref.17 & 18) and one formal total synthesis (Ref.19) of 47 have been reported. Our synthesis is based on the well-known thermal cycloaddition of benzocyclobutene developed by Kametani (Ref.20) and Oppolzer (Ref.21). In this methodology, one problem to be solved is the facile synthesis of the D ring component with right stereochemistry between the vinyl and the 18-methyl groups. The D ring component should be prepared to secure the formation of the trans junction of the CD rings. In a number of syntheses reported before, the reactions were not selective and separation of a trans isomer from a cis isomer was required. Thus further elaboration is necessary in this respect. Our synthesis has been carried out by the following sequence of reactions.



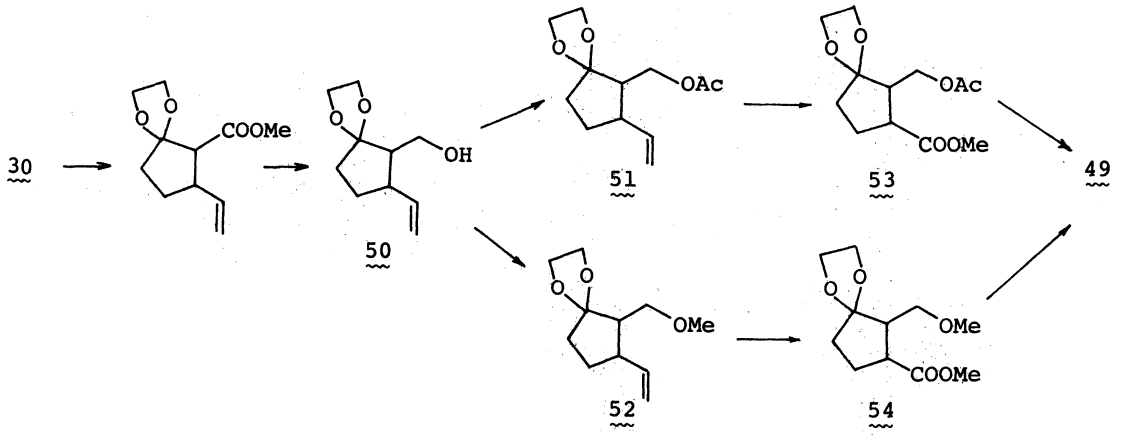
The alkylation of 30 with the iodide 43 in refluxing acetone in the presence of K_2CO_3 for 36 h afforded 2-methoxycarbonyl-3-vinyl-2-[2-(3-methoxybicyclo-[4.2.0]octa-1,3,5-trien-7-yl)ethyl]cyclopentanone (36) in 62% yield. The alkylation is expected to proceed preferentially in trans manner to the vinyl group, and the main product was assumed to be the desired trans isomer 36. Actually, the content of the cis isomer was less than 10%, and it was easily removed from the trans isomer by column chromatography.

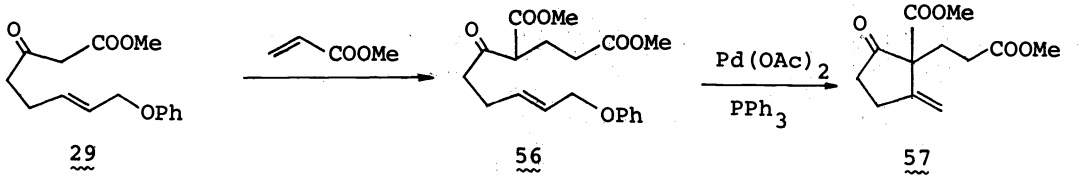
The ketone group of 36 was protected as the acetal and the ester group was reduced to the alcohol 44 with $LiAlH_4$ in 73% yield. The cycloaddition of 44 in refluxing o-dichlorobenzene produced the steroid skeleton 45 in 75% yield. Careful analysis by HPLC showed that the product was a single compound. On the other hand, the cycloaddition of the ester 36 afforded in 75% yield two products which were the cis and trans isomers of the BC ring junction in a ratio of 1 : 4. Then the acetal group of 45 was removed to give 46 in 89% yield. Then 18-hydroxyestrone (47) was obtained from 46 by the treatment with BBr_3 in dichloromethane at -78°C. Also the structure of 46 was confirmed by converting it into 3-methoxyestra-1,3,5(10)-trien-17-ol (48).

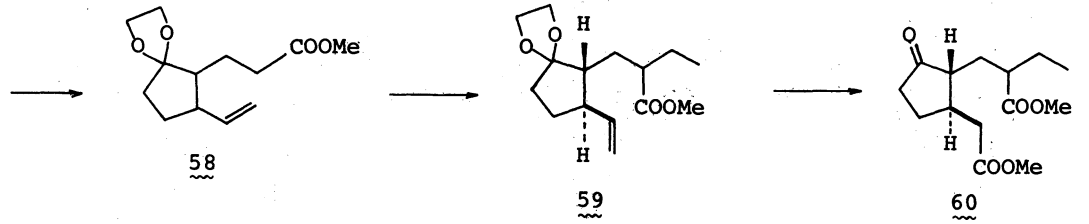
Sarkomycin (49) is a natural product which shows powerful inhibitory effect on Ehrlich ascites tumor. It contains a rather unstable α-methylene-β-carboxylic acid moiety. Our cyclopentanone 30 has very suitable functionality for a simple synthesis of sarkomycin.

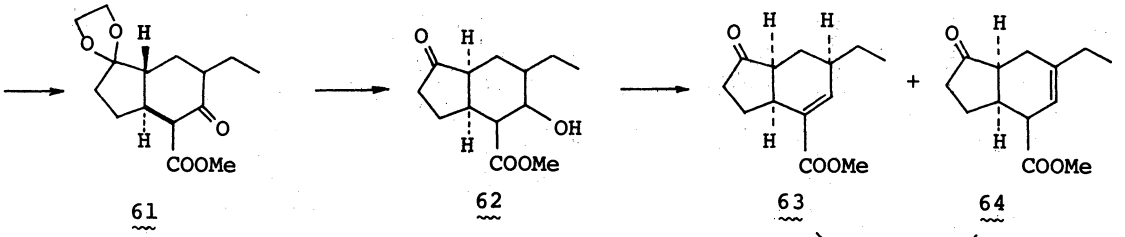


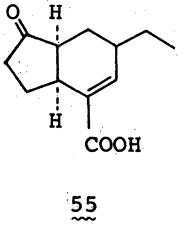
The synthesis of sarkomycin was carried out by the following sequence of reactions (Ref. 22).


30
COOMe
OH
50
OAc
51
OAc
COOMe
53
49
OMe
52
OMe
COOMe
54


COOMe
OPh
29
COOMe
COOMe
OPh
56
Pd(OAc)2
PPh3
COOMe
COOMe
57


COOMe
58
H
COOMe
59
H
COOMe
COOMe
60


H
O
COOMe
61
H
OH
COOMe
62
H
H
COOMe
63
+
H
COOMe
64


H
H
COOH
55

At first the ketone was protected and the ester was reduced to the alcohol 50. The alcohol was protected by acetylation and methyl ether formation to give 51 and 52. Then the vinyl group was converted to the methyl ester by ozonization, oxidation with Jones reagent, and esterification to give 53 and 54. The last step of the synthesis was carried out by treating 53 with 3N HCl in ether at room temperature. Sarkomycin (49) was obtained in 48% crude yield from 53. Purification by chromatography gave pure sarkomycin in 24% yield.

Coronafacic acid (55) is another good synthetic target for the palladium-catalyzed cyclization (Ref. 23). Michael addition of methyl acrylate to the keto ester 29 afforded the diester 56. The cyclized product 57 was obtained in 98% yield from 56 using 1 mol% of $Pd(OAc)_2$ and 4 mol% of PPh_3 in acetonitrile. After demethoxycarbonylation, the ketone was protected to give 58. The ethyl group was introduced in 89% yield by the treatment with LDA and ethyl iodide to give 59. The vinyl group was converted to acetate moiety to form the diester 60 by hydroboration, oxidation with Jones reagent, and esterification. After reprotection of the ketone, the diester was subjected to the Dieckmann condensation by using potassium t-butoxide in THF to give the keto ester 61 in 74% yield. Reduction of the ketone with $NaBH_4$ and hydrolysis of the acetal produced the keto alcohol 62, which has the cis ring junction. Dehydration of the alcohol with $POCl_3$ afforded a mixture of double bond isomers 63 and 64, which were converted to coronafacic acid (55) by acid catalyzed hydrolysis of the methyl ester.

REFERENCES

1. J. Tsuji, Organic Syntheses with Palladium Compounds., Springer Verlag, 1980.
2. J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, and A. Sabel, Angew. Chem. Intern. Ed., 1, 80-88 (1962).
3. W. H. Clement and C. M. Selwitz, J. Org. Chem., 29, 241 - 243 (1964).
4. J. Tsuji, I. Shimizu, and K. Yamamoto, Tetrahedron Lett., 2975-76 (1976).
5. J. Tsuji, Acc. Chem. Res., 6, 8-15 (1973).
6. J. Tsuji, "Advances in Organometal. Chem.". Vol.17, Academic Press, New York, N.Y., 1979, p.141-193.
7. J. Tsuji, Ann. New York Acad. Sci., 333, 250-263 (1980).
8. S. Takahashi, T. Shibano, and N. Hagihara, Tetrahedron Lett., 2451-2453 (1967).
9. W. E. Walker, R. M. Manyik, K. E. Atkins, and M. L. Farmer, Tetrahedron Lett., 2451-2454 (1967).
10. J. Tsuji, I. Shimizu, H. Suzuki, and Y. Naito, J. Am. Chem. Soc., 101, 5070-5072 (1979).
11. J. Tsuji, Y. Kobayashi, and T. Takahashi, Tetrahedron Lett., 483-486 (1980).
12. unpublished
13. J. Tsuji, Y. Kobayashi, H. Kataoka, and T. Takahashi, Tetrahedron Lett., 21, 1475-1478 (1980).
14. J. Tsuji, Y. Kobayashi, H. Kataoka, and T. Takahashi, Tetrahedron Lett., 21, 3393-3394 (1980).
15. J. Tsuji, H. Okumoto, Y. Kobayashi, and T. Takahashi, Tetrahedron Lett., 22, 1357-1358 (1981).
16. K. H. Loke, E. J. D. Watson, and G. F. Marrian, Biochim. Biophys. Acta, 26, 230-231 (1957).
17. J. E. Baldwin, D. H. R. Barton, I. Dainis, and J. L. C. Pereira, J. Chem. Soc. C, 2283-2289 (1968).
18. H. Breuer and K. Engel, Liebigs Ann. Chem., 580-584 (1978).
19. D. K. Banerjee, S. D. Venkataramu, and P. K. Sen, Steroids, 24, 627-636 (1974).
20. T. Kametani, Pure Appl. Chem., 51, 747-768 (1979).
21. W. Oppolzer, Synthesis, 793-802 (1978).
22. J. Tsuji and Y. Kobayashi, in preparation.
23. J. Tsuji and Y. Kobayashi, in preparation.