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NEW BIS- AND TRIS-ANNULATION REAGENTS FOR THE SYNTHESES OF CD RINGS OF STEROIDS, BEARING A FUNCTIONALIZED 18-METHYL GROUP, BY THE PALLADIUM-CATALYZED CYCLIZATION

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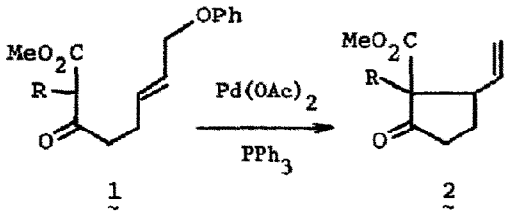
Summary: 2-Substituted 2-alkoxycarbonyl-3-vinylcyclopentanones (2), easily prepared by the palladium-catalyzed cyclization of 2-substituted 3-oxo-8-phenoxy-6-octenoates (1), are very suitable building blocks for CD rings of steroids, bearing particularly a functionalized 18-methyl group.

In a previous paper we have reported a new synthetic method for 2-alkoxycarbonyl-3-vinylcyclopentanone and its 2-substituted derivatives (2) by the palladium-catalyzed cyclization of 3-oxo-8-phenoxy-6-octenoate and its derivatives (1).[1] The cyclization reaction proceeds under neutral conditions and hence tolerates the presence of various functional groups without protection.



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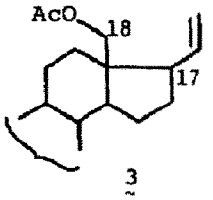

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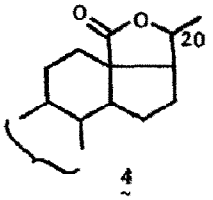

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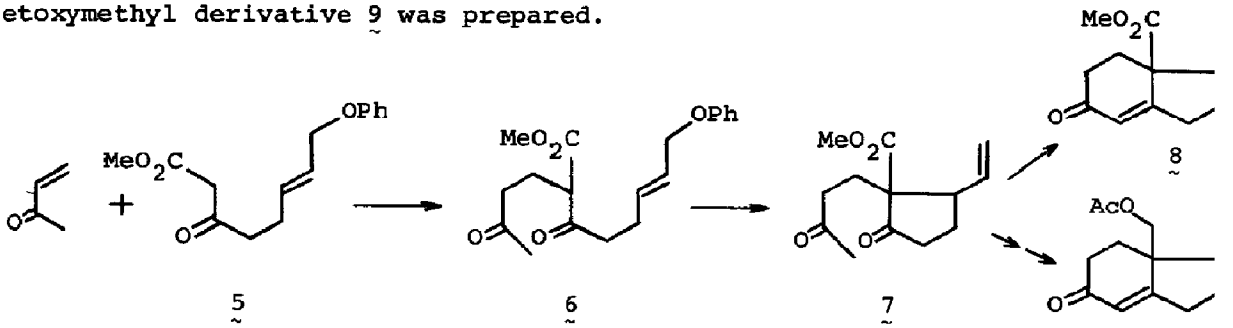
There exist in nature many cyclopentanone derivatives disubstituted at 2 and 3 positions such as jasmonoids and prostanoids. The above-mentioned palladium-catalyzed reaction offers a very good synthetic methodology for these natural products. Furthermore, we now wish to report that these cyclopentanones are very suitable starting materials for facile synthesis of CD rings of steroids; particularly those which have functionalized 18-methyl group (steroid numbering). The ester and vinyl groups in 2 can be transformed to several functional groups present in various steroids. A number of naturally occurring steroids functionalized at 18-methyl are known: aldosterone, 18-acetoxypregna-1,4,20-trien-3-one (3), and 20-hydroxy-3-oxopregn-4-en-18-oic acid γ-lactone (4) are typical examples. Also conessine has a nitrogen function at the 18-methyl. Several syntheses for these steroids have been reported,[2,3] but still they needs further elaboration.

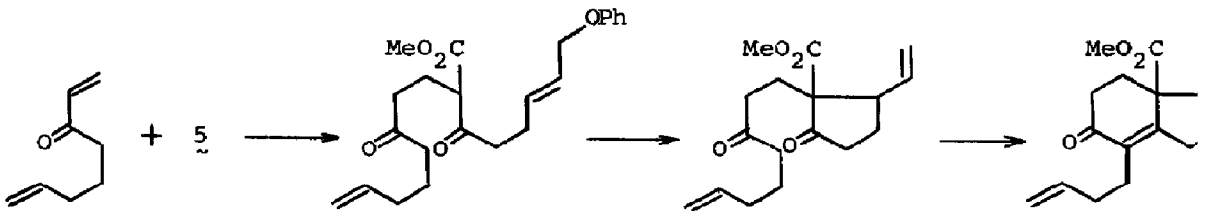
The new bisannulation reagent 6 was prepared in 74% yield by the addition of methyl vinyl ketone to methyl 3-oxo-8-phenoxy-6-octenoate (5). The cyclization of 6 using $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%) as the catalyst in refluxing acetonitrile in one h afforded the cyclopentanone 7 in 91% yield. The cyclizatio

conditions are so mild that no side reaction such as retro-Dieckmann or aldol condensation took place. The aldol condensation of 7 in toluene using a mixtu of acetic acid and ß-alanine produced the CD rings 8 in 74% yield. There are number of possible modifications of the functional groups. For example, the e group in 7, after protection of the ketones, was reduced to alcohol and the acetoxymethyl derivative 9 was prepared.



5 6 7 8 9

The new trisannulation reagent 11 was also prepared in 81% yield using 1, octadien-3-one (10), which is easily prepared from butadiene,[4] instead of meth vinyl ketone. The palladium-catalyzed cyclization of 11 produced the cyclopent none 12 in 60% yield. Finally the CD rings 13 were obtained by the aldol conde sation in 80% yield.



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References

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