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A NEW TRIS-ANNULATION REAGENT PREPARED FROM A BUTADIENE TELOMER, AND ITS APPLICATION TO STEROID SYNTHESIS

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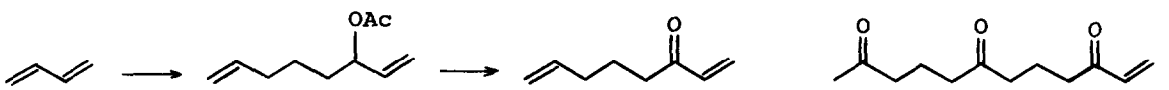
Summary: Reaction of 1,7-octadien-3-one with dimethyl malonate, followed by the reduction of the ketone produced dimethyl (3-hydroxy-7-octenyl)malonate, which was converted to 9-decen-5-olide after hydrolysis and decarboxylation. Reaction of vinylmagnesium chloride with the lactone and the subsequent acylation afforded 7-acetoxy-1,11-dodecadien-3-one. This is a new tris-annulation reagent. (±)-D-homo-19-norandrosta-4-en-3-one was synthesized by using this tris-annulation reagent.

In our continuous effort to utilize butadiene telomers as building blocks of natural products, we have reported the synthesis of 1,7-octadien-3-one (2) as a new bis-annulation reagent, and its application to facile synthesis of steroid.[1] The reagent 2 is easily prepared from 3-acetoxy-1,7-octadiene (1) obtained by the palladium catalyzed telomerization of butadiene with acetic acid. In this reagent, the terminal double bond is the masked ketone, which can be unmasked by the $PdCl_2$-catalyzed oxidation. We now wish to report the synthesis of a new tris-annulation reagent 4 from 2. The tris-annulation in steroid synthesis is a method of constructing three fused six-membered cyclic ketones from one reagent.[2] The tris-annulation reagent is a synthetic equivalent of 11-dodecene-2,6,10-trione (3). In other words, the tris-annulation reagents are linear 12-carbon framework having a terminal enone or its equivalent, a masked methyl ketone, and an oxygen function at the position 6. Depending on masking method of the methyl ketone and kinds of the oxygen function, several tris-annulation reagents have been reported.[3,4]



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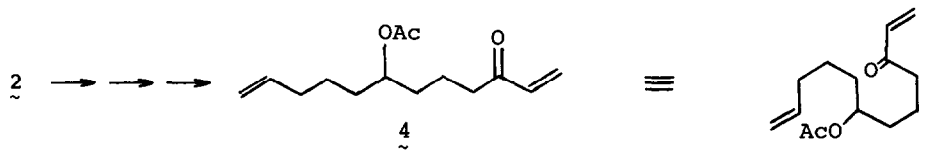
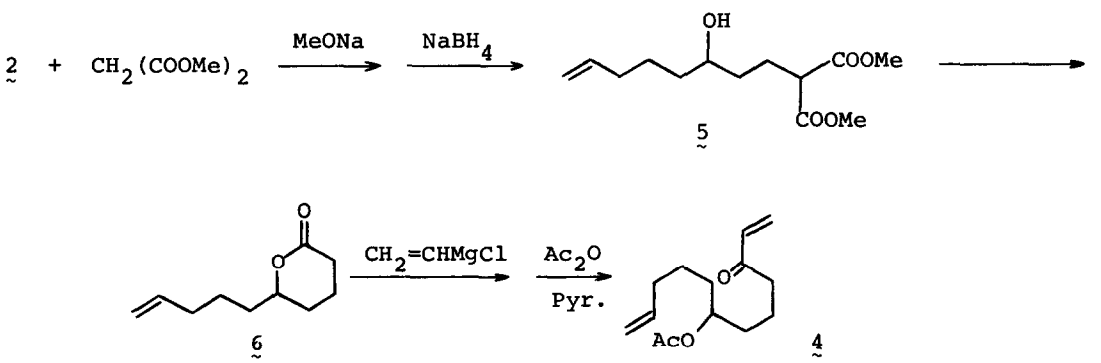
The usefulness of the tris-annulation reagents is determined by easy accessibility of the reagent itself, stability to acids and bases, and facile procedure

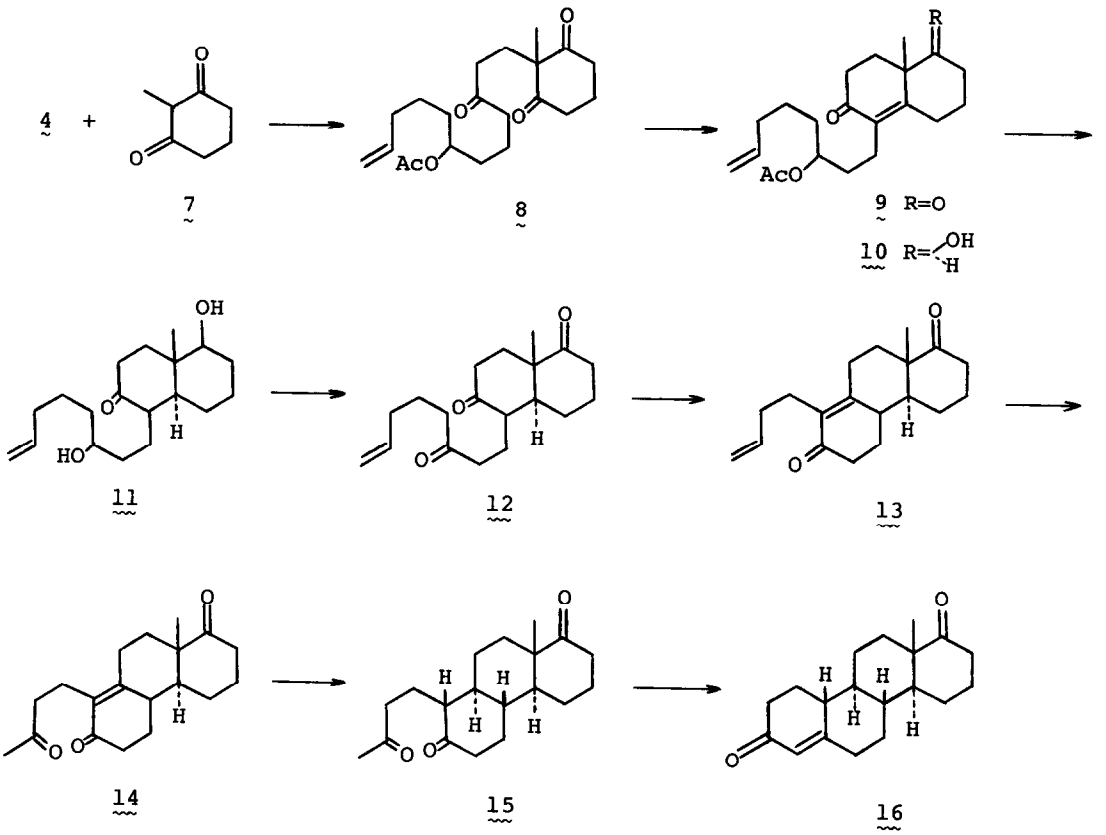
of the unmasking. The tris-annulation reagent, we now introduce, is 7-acetoxy-1,11-dodecadien-3-one (4). Our tris-annulation reagent can be prepared easily from butadiene, and the terminal olefin is the masked ketone, which is stable to acids and bases, and can be unmasked in one step by the $PdCl_2$-catalyzed oxidation.[5] This compound undergoes Michael reaction and then the acetoxy group is converted to ketone by hydrolysis and oxidation. Finally the terminal double bond is converted to methyl ketone by the $PdCl_2$-catalyzed oxidation.



The synthesis of 4 was carried out by the reaction scheme shown below. The Michael addition of dimethyl malonate to the enone 2 was carried out in methanol using sodium methoxide as a catalyst and the product, without purification, was reduced with sodium borohydride to give dimethyl (3-hydroxy-7-octenyl)malonate (5) in 65% yield. Hydrolysis of the diester, followed by heating caused decarboxylation and lactonization to afford 9-decen-5-olide (6) in 77% yield. The lactone 6 was treated with vinylmagnesium chloride (2 equiv) at -60 to -70°C[4] and the crude product was acetylated (acetic anhydride-pyridine) to give the tris-annulation reagent 4 in 61% yield: bp 126-130°C, 2 Torr; IR (film) 1748, 1701, and 1681 cm^{-1}; NMR (CCl_4) δ 2.01 (s, 3H, CH_3), 1.03-2.78 (m, 12H), and 4.66-6.40 (m, 7H).



Then we have carried out the synthesis of (±)-D-homo-19-norandrosta-4-en-3-one (16) by the following tris-annulation reaction using 4.



The Michael reaction of 4 with 2-methylcyclohexane-1,3-dione (7) in a mixed solvent of ethyl acetate and triethylamine (2 : 1) at room temperature produced the trione 8 in 91% yield: NMR ($CDCl_3$) δ 1.20 (s, 3H), 2.01 (S, 3H), 1.07-2.86 (m, 22H), and 4.63-6.24 (m, 4H). Then the aldol condensation of 8 was carried out in a refluxing mixed solvent of toluene and acetic acid (4 : 1) containing β-alanine (2 equiv) for 2 h to give 9 in 94% yield. The unconjugated ketone of 9 was selectively reduced with sodium borohydride in methanol at -7 to -8°C to give 10. Then the enone system of 10 was subjected to the Birch reduction in liquid ammonia with lithium to give the desired trans-fused CD ring (steroid nomenclature). The crude reduction product was hydrolyzed to give the dialcohol in 67% yield from 9. The Jones oxidation of 11 produced the trione 12: NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.02-3.02 (m, 22H), and 4.72-6.12 (m, 3H). The NMR spectrum of the trione 12 showed one singlet peak assignable to the angular methyl group at 1.31 ppm which clearly demonstrates that the trione 12 is homogeneous and has the trans-fused junction. The intramolecular aldol condensation of 12 using *p*-toluenesulfonic acid as a catalyst in refluxing benzene for 3 h gave the diketone

13 in 76% yield. Then the oxidation of the terminal double bond with $PdCl_2$ (0.1 equiv) and CuCl (1 equiv) in aqueous DMF afforded the crystalline trione 14 in 84% yield: mp 121-122°C; IR (KBr) 1711, 1692, and 1659 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (s, 3H), 2.09 (s, 3H), and 1.07-3.08 (m, 20H). Hydrogenation of the enone 14 over Pd on carbon in a mixture of THF-ethanol-triethylamine (100 : 100 : 1) afforded the trione 15 as crystals, mp 98-99°C. The aldol condensation of 15 with 4N-hydrochloric acid in refluxing methanol produced the crystalline steroid 16 in 90% yield from 14. The spectral data (IR, Mass, NMR) of 16 support the structure and were identical with those reported for the optically active form:[6] mp 171-172°C (reported for the optically active one, 164°C); mass spectrum m/e 286 (M^+); IR (KBr) 1700, 1660, and 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 3H, CH_3), 0.53-2.98 (m, 22H), 5.66-5.81 (m, 1H, CH=C); ^{13}C NMR ($CDCl_3$) δ 16.8, 23.0, 25.4, 25.8, 26.2, 30.4, 32.2, 35.4, 36.5, 37.1, 40.1, 42.7, 48.1, 48.7, 50.1, 124.3, 165.7, 199.6, 215.8.

References:

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