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Palladium-catalysed Direct Synthesis of Optically Active Dienols

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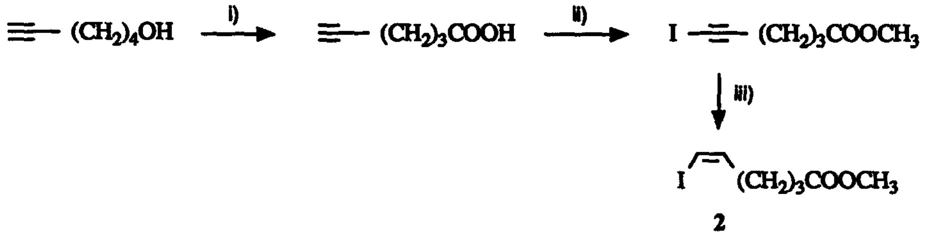
Abstract: A direct and highly chemo, regio and stereocontrolled method for constructing optically active conjugated dienols is described and illustrated by a short, convenient and efficient synthesis of methyl (9R)-9-hydroxytetradeca-5Z,7E-dienoate (-)-1.

An optically active conjugated dienol moiety (or derivatives thereof) constitutes a partial structure of many natural and/or biologically active products.[1]

We have recently reported an efficient method for synthesizing (E,E) and (E,Z) conjugated dienols which is realised with high chemo, regio and stereoselectivities with respect to the two double bonds.[2]

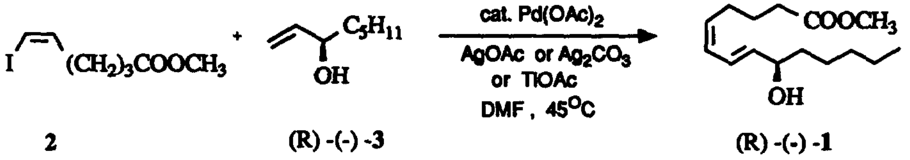
We now report that the described reaction can be achieved with retention of the absolute configuration of the carbon bearing the alcohol functional group. This result is illustrated by an efficient synthesis of methyl (9R)-9-hydroxytetradeca-5Z,7E-dienoate (-)-**1** whose acid has been isolated from *Securidaca longipedunculata* seed oil.[3]

Methyl-6-iodo-5Z-hexenoate **2** was conveniently synthesized (Scheme 1) from commercially available 5-hexyn-1-ol by a sequence of (i) chromic acid oxidation[4] to the corresponding alkynoic acid, (ii) esterification by methyl iodide and direct iodination by molecular iodine[5] which can be conducted in a one-pot experiment and (iii) stereospecific diimide reduction.[6] (3R)-1-octen-3-ol (-)-**3** was readily prepared from racemic 1-octen-3-ol by Sharpless kinetic resolution.[7] Treatment in N,N-dimethylformamide of the vinylic iodide **2** with the allylic alcohol (R)-(-)-**3**, in the presence of silver acetate (or carbonate) and a catalytic amount of palladium acetate, easily led to the formation, in good yield, of the optically active methyl (9R)-9-hydroxytetradeca-5Z,7E-dienoate (-)-**1** [8] (Scheme 2). The asymmetric carbon atom bearing the alcohol functional group has thus maintained its configurational integrity throughout the vinylation of the allylic alcohol: no racemization was observed during the process. A similar yield of (R)-(-)-**1** was obtained when thallium (I) acetate[10,11] was used instead of silver acetate or silver carbonate.



i) CrO_3/H^+, acetone, 80% ; ii) CH_3I, K_2CO_3, DMF, then CuI (0.10 equiv.), n-Bu_4NCl (0.5 equiv.), I_2, 85% ; iii) $KO_2CN{=}NCO_2K$, AcOH in MeOH, then n-$BuNH_2$, 54%.

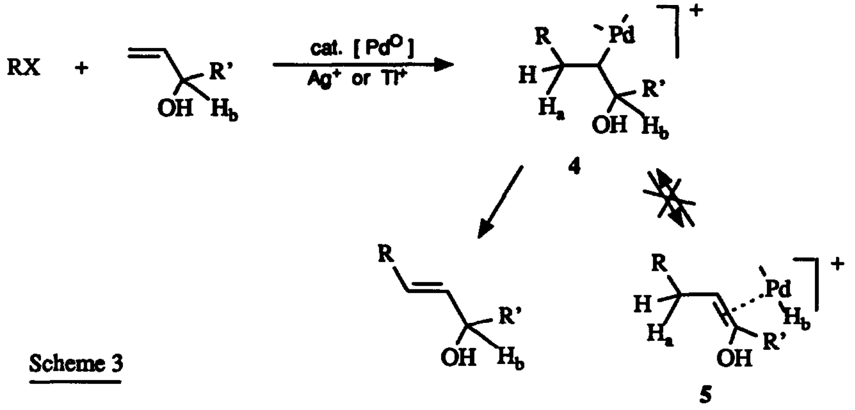
Scheme 1



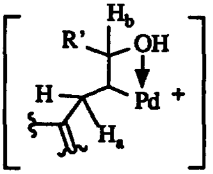
Scheme 2

Retention of the configuration of the carbon bearing the alcohol functional group provides further evidence for a regiospecific elimination of the β hydrogen (H_a) which is not on the carbon bearing the alcohol group, in the coupling of organic halides with allylic alcohols performed in the presence of silver (I) [2,12] or thallium (I) salts (scheme 3). This result excludes the possibility of an equilibrium between palladium complexes such as **4** and **5**. Formation of a palladium intermediate such as **6** with hydroxyl coordination which prevents H_b from assuming the syn-relationship with Pd required for the palladium hydride elimination, has recently been proposed[13] to account for the highly selective elimination of H_a in palladium-catalysed reactions of allylic alcohols with either vinyltriflates[13] or vinylhalides in the presence of silver salts.[2]

In conclusion, the described methodology for constructing a stereodefined optically active dienol functionality has many advantages which should give it an important synthetic potential in the synthesis of numerous compounds having relevant biological activities. It is most direct since the conjugated dienol functionality results from a single carbon-carbon bond formation which, moreover, can be achieved without any protection of the alcohol group. The reaction is catalytic and operationally convenient. Furthermore, only one alkene needs to be functionalized and pure (E) and (Z) vinylic halides are easily accessible. Optically active allylic alcohols can be readily prepared by Sharpless kinetic resolution,[7] and the tellurium method recently described by Dittmer[14,15] should further enhance the availability of this type of compound.[16] Additionally, the described coupling proceeds with a particularly high chemo, regio and stereocontrol: the geometry of the organic halide double bond is retained, only an (E) double bond is formed α to the alcohol center and the absolute configuration of the carbon bearing the alcohol functional group is retained throughout the reaction.



Scheme 3



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Experimental procedure: Under an inert atmosphere, to a solution in dry N,N-dimethylformamide (1 ml/mmol of 2) of methyl 6-iodo-5Z-hexenoate 2 (1 equivalent), (3R)-1-octen-3-ol[7,17] (1.4 equivalent) and palladium acetate (0.06 equivalent), was added silver carbonate (0.8-1 equivalent). The suspension was stirred at room temperature for about 2h then heated overnight at 40-45°C. The reaction mixture was then cooled to room temperature, diluted with ether and filtered through a pad of celite. The organic phase was washed (H_2O), dried ($MgSO_4$) and the volatiles evaporated under reduced pressure. Purification by flash chromatography afforded methyl (9R)-9-hydroxy-tetradeca-5Z,7E-dienoate (-)-1[8] in 75% yield.

Similar yields (70% - 75%) were obtained when the reaction was effected using silver (I) acetate (1.2 equivalent) or thallium (I) acetate (1.2 equivalent) instead of silver carbonate.

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8. *^{1}H NMR (250 MHz, $CDCl_3$/TMS)*: δ(ppm)= 6.45 (dd, 1H, J= 15.1 Hz, J'= 11 Hz); 6.02 (dd, 1H, J= 11 Hz, J'= 10.8 Hz); 5.68 (dd, 1H, J= 15.1 Hz, J'= 6.78 Hz); 5.40 (dt, 1H, J= 10.8 Hz, J'= 7.66 Hz); 4.15 (td, 1H, J= 6.2 Hz, J'= 6.3 Hz); 3.67 (s, 3H); 2.32 (t, 2H, J= 7.5 Hz); 2.23 (td, 2H, J= 7.38 Hz, J'= 7.58 Hz); 1.73 (q, 2H, J= 7.5 Hz); 1.65 - 1.22 (m); 0.89 (t, 3H, J= 6.6 Hz).

   ^{13}C NMR ($CDCl_3$/TMS): δ(ppm)= 173.9; 136.6; 130.6; 128.8; 125.0; 72.4; 51.3; 37.1; 33.1; 31.6; 26.8; 24.9; 24.5; 22.4; 13.8 .

   IR (neat): ν (cm^{-1})= 3430 (broad, OH); 1730 (C=O) .

   $[\alpha]_D$ = -13.7° (c= 0.95; $CHCl_3$); Lit[9]: $[\alpha]_D^{25}$= -13.9° (c= 0.98; $CHCl_3$).

   The optical purities were estimated by chiral shift analysis in $CDCl_3$ using $Eu(tfc)_3$.[9] No splittings of the vinylic hydrogen H_7 and the OCH_3 signals were observed for (-)-**1**, in the presence of 0.7 equivalent of $Eu(tfc)_3$. Under the same conditions, the racemic compound prepared from methyl-6-iodo-5Z-hexenoate and racemic 1-octen-3-ol, shows net splittings of the same protons.
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17. $[\alpha]_D$= - 8.5° (c 1.23, $CHCl_3$); Lit[18]: $[\alpha]_D^{24}$= - 8.8° (c 1.50, $CHCl_3$).
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