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EXCLUSIVE γ-COUPLING IN THE ALDOL REACTION OF α,β-UNSATURATED ESTERS

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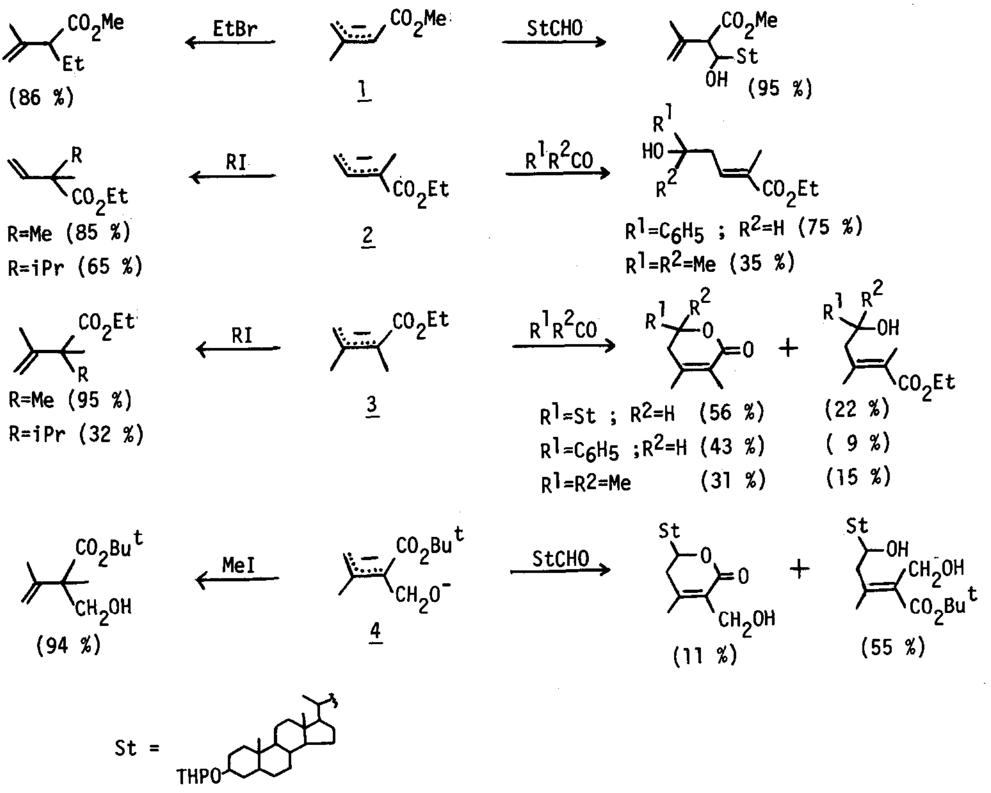
Direct alkylation of α,β-unsaturated esters have become increasingly attractive in synthetic organic chemistry. Although allylic carbanion might react with electrophiles either at α or γ carbons[1], the lithium dienolates derived from crotonate[2,3] and its α-isopropyl[2] or β-propyl[4] homologs have been reported to undergo alkylation regioselectively at the α position[3]. During the synthetic studies on withanolides[5], we have found exclusive γ-coupling in the aldol reaction of some of α,β-unsaturated esters[6] which is described in this report.

By the method of Herrman et al.[3], four esters 1 - 4 (Scheme) were reacted with 1 equivalent of lithium diisopropylamide-hexamethylphosphoramide complex at -78° and the resulting lithium dienolates, after 20 min, were treated with 1.2 equivalents of electrophiles in tetrahydrofuran at -78° for 1 hr. The results are summarized in the Scheme. On reaction with alkyl halides, all of the esters examined gave exclusively α-alkylation products as shown by the single peak on gas chromatography and nmr signals of exomethylene at 4.9 ppm. The "α-preference" was still observed in the aldol reaction of the dienolate 1 with the steroidal aldehyde. However, the regioselectivity was markedly changed when the lithium dienolates derived from α,β-unsaturated esters 2 - 4 which have methyl group at both α and β carbons were treated with various carbonyl electrophiles. Thus the products from ethyl tiglate 2 contained one vinyl proton (6.8 ppm, triplet, J = 8 Hz) and no exomethylene, consistent with the structure of α,β-unsaturated δ-hydroxyesters. Similarly the tetrasubstituted analogs 3 and 4 underwent γ-coupling to give the corresponding hydroxyesters and the α,β-unsaturated δ-lactones where vinyl methyls appeared at around 2.0 ppm. The complete absence of exomethylene signal assured the severe regioselectivity in these aldol reactions and would suggest the major utility in organic synthesis. The steroidal lactones produced from 3 and 4 have identical structure with withanolides side chain except for the stereochemistry at C-22[7].



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7. CD of the steroidal lactone from 3 showed Δε, -3.72 at 258 nm and C-22 proton appeared at 4.42 ppm (d,d, J = 13 and 3 Hz).