Stereochemistry of Conjugate Addition to 4- and 5-Substituted α,β-Unsaturated δ-Lactones†

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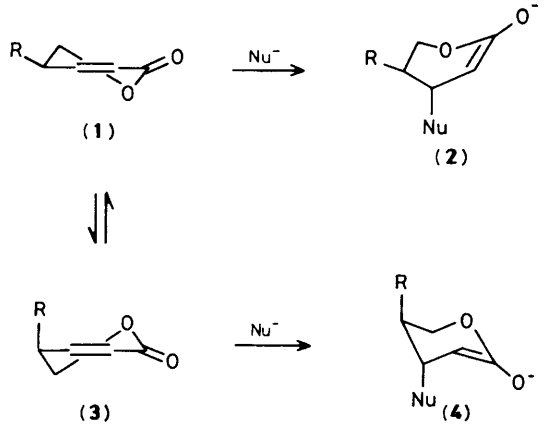
Conjugate addition, especially of the phenyldimethylsilylcuprate reagent, to 4- and 5-substituted α,β-unsaturated δ-lactones [(**5**) and (**18**)] is highly selective for the formation of the *trans*-products [(**6**), (**7**), (**9**), (**10**), and (**19**)], the silicon-containing products having ^{1}H n.m.r. coupling constants indicative of distortions from the chair conformation; the silyl group can be converted into a hydroxy group to give the lactones (**8**) and (**20**).

We reasoned that conjugate addition to 4-substituted δ-valerolactones should be highly stereoselective for the formation of the *trans*-product. If reaction takes place in the conformation in which the substituent R is pseudoequatorial (**1**), axial attack leading to a boat conformation (**2**) does not suffer from flagpole interactions. Alternatively, if reaction takes place in the conformation in which the substituent R is pseudoaxial (**3**), axial attack leading to a chair conformation (**4**) has no 1,3-diaxial interactions to the group R either in the starting conformation (**3**) or in the product conformation (**4**). We expected, therefore, that the occasionally poor selectivity found in conjugate additions to 4-substituted cyclohexenones[1] would be less of a problem in the corresponding lactones.

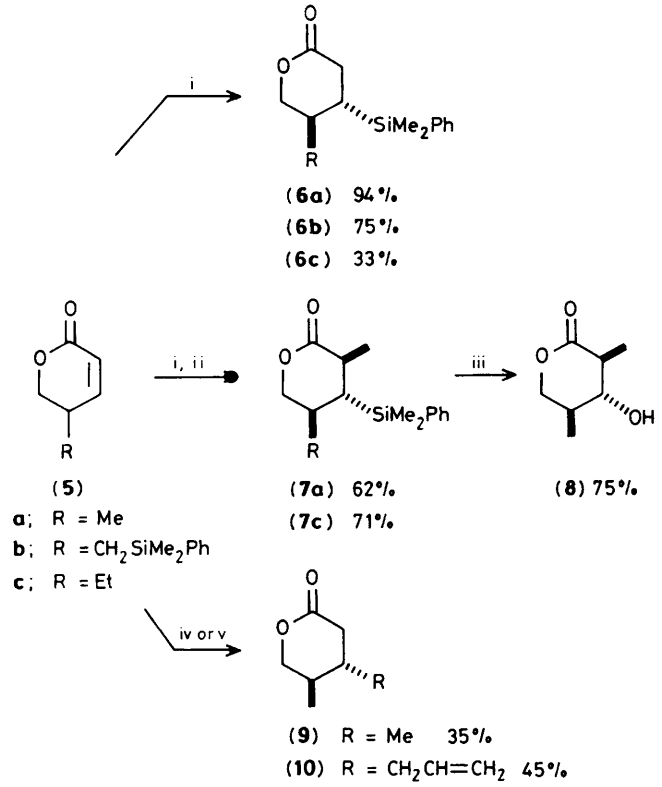
Our silylcuprate reagent[2] adds to the lactone (**5a**) to give only the *trans*-isomer (**6a**). We proved the stereochemistry of this adduct in two ways. First we prepared its stereoisomer (**13**) (Scheme 2) from the ester (**11**) of known configuration.[3] With well resolved signals present in the ^{1}H n.m.r. spectra of the two lactones, we can say that the selectivity for the formation of (**6a**) is at least 99.5 : 0.5. Second, we repeated the conjugate addition but quenched the enolate produced with methyl iodide to give, as far as we can tell, only the lactone (**7a**). Replacement of the phenyldimethylsilyl group by a hydroxy group,[4] a reaction that is known to take place with retention of configuration, then gave the known hydroxy lactone (**8**).[5] We draw attention to the efficiency with which three adjacent chiral centres have been set up in this sequence, which we have used to prepare the lactone (**7c**) having the correct relative configuration for C-10 to C-12 of ebelactone A.[6]

Conjugate addition to the lactone (**5b**) gives the lactone (**6b**); again we synthesised the isomer (**14**) (Scheme 2) using open-chain alkylation of β-silyl enolates.[7] In this case, with less well resolved signals in the n.m.r. spectra, we can only put a lower limit of 95 : 5 on the selectivity, but it is almost certainly better than that. The lactones (**6b**) and (**14**) have the correct relative configuration for syntheses of talaromycin B and A, respectively.[8] Thorough proof of stereochemistry was necessary in these compounds, because the vicinal coupling constants from the methylene hydrogen atoms adjacent to the oxygen atom, which might reasonably be expected to be diagnostic, were misleading. The *cis*- and *trans*-couplings were nearly equal to each other in all the silicon-containing lactones (**6a—c**), (**7a**), (**7c**), (**13**), and (**14**).‡ No doubt the silyl group seriously distorts the conformation of the lactone ring, with the result that the methylene group no longer has clear axial and equatorial hydrogen atoms.

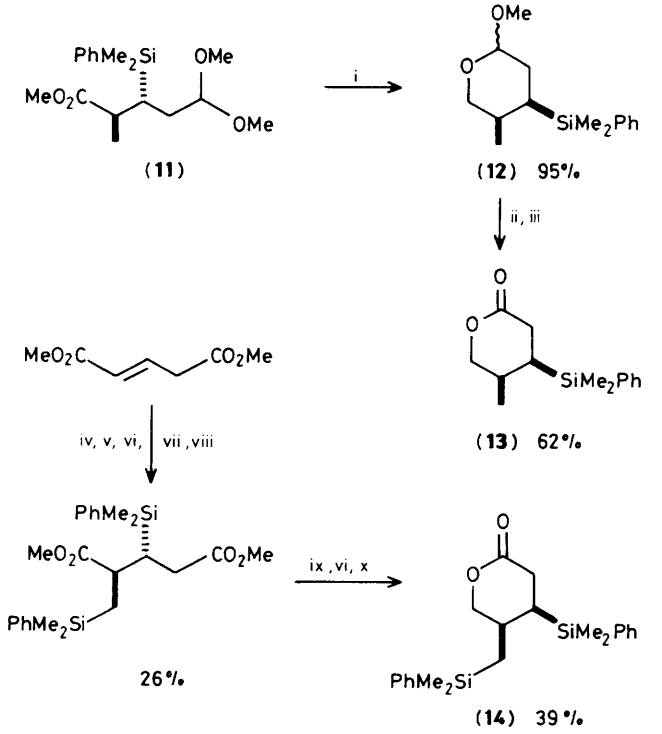


† No reprints available.

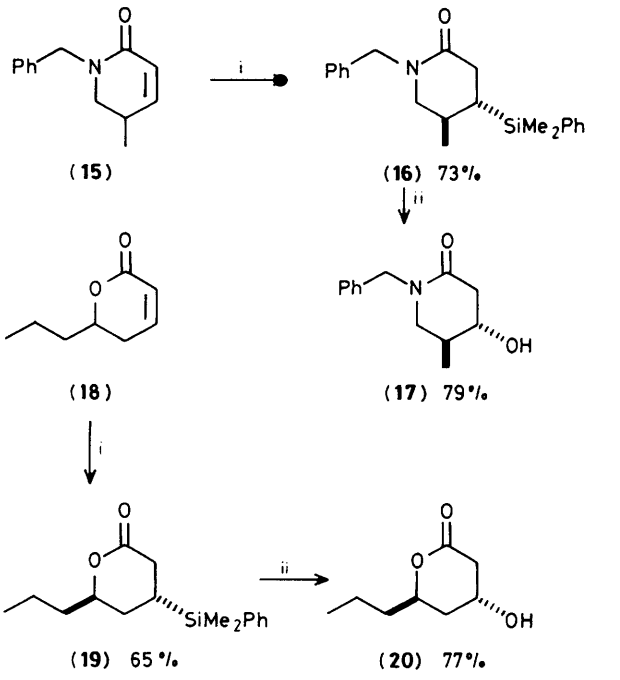
‡ The values are: 5.7 and 4.4 Hz for (**6a**); 5.3 and 4.3 Hz for (**6b**); 4.0 and 3.9 Hz for (**6c**); 3.4 and 3.2 Hz for (**7a**); 3.1 and 2.2 Hz for (**7c**); 3.5 and 2.6 Hz for (**13**); and 3.3 and 2.5 Hz for (**14**).



Scheme 1. *Reagents:* i, $(PhMe_2Si)_2CuLi{\cdot}LiCN$, tetrahydrofuran (THF), −78 °C, 2 h; ii, MeI, −78 °C, 2 h; iii, Br_2, AcOOH, AcOH, NaOAc; iv, MeMgI, CuI (cat.), Et_2O; v, $CH_2{=}CHCH_2SiMe_3$, Bu_4NF, Me_2NCHO, $PO(NMe_2)_3$.



Scheme 2. *Reagents:* i, $LiAlH_4$; ii, MoO_3, H_2O_2, room temp., 16 h; iii, Ac_2O, C_5H_5N, room temp., 12 h; iv, $(PhMe_2Si)_2CuLi{\cdot}LiCN$, THF, −23 °C, 2 h (77%); v, 2 equiv. $LiNPr^i_2$, THF; vi, Me_3SiCl (79 and 86%); vii, $PhSCHClSiMe_2Ph$, $ZnBr_2$, CH_2Cl_2, room temp., 2 h (69%); viii, Raney Ni, EtOH, 3 h (63%); ix, 1 equiv. $LiNPr^i_2$, THF; x, $LiAlH_4$, THF, room temp., 1 h (45%).



Scheme 3. *Reagents:* i, $(PhMe_2Si)_2CuLi{\cdot}LiCN$, THF, −78 °C, 2 h and 12 h; ii, $Hg(OAc)_2$, AcOOH, AcOH.

The control is not specific to the silicon reagent. Copper-catalysed addition of the methyl Grignard reagent to the lactone (**5a**) gave only the *trans*-lactone (**9**), but the yield was low because of polymerisation, which we did not attempt to overcome. The ^1H n.m.r. spectrum of our product was clearly different from that of an authentic sample of the corresponding *cis*-isomer.[9] Conjugate addition of an allyl group, using allyltrimethylsilane and fluoride ion catalysis,[10] gave a 6:1 mixture of lactones, in which the *trans*-isomer (**10**) was the major product. The lactones (**8**)—(**10**), incidentally, having no unusually large groups on the ring, show diagnostically normal vicinal coupling constants from the methylene group adjacent to the oxygen atom.§

The stereoselectivity carries over from the lactone series to the lactam (**15**), which gave only one product (**16**). In this case, the distortions in the chair conformation occasioned by the presence of the silyl group are less severe, and the coupling constants from the methylene hydrogen atoms adjacent to the nitrogen atom are diagnostic for the *trans*-configuration both for the silicon-containing lactam and for the derived hydroxy compound (**17**).¶ Finally, the 5-substituted lactone (**18**) also reacted selectively, giving the lactone (**19**), from which we made the lactone (**20**),** showing that this is a simple method for setting up the relative stereochemistry of the lactone ring of compactin.[13]

§ The values are 4.8 and 10.1 Hz for (**8**); 4.5 and 10.2 Hz for (**9**); and 9.3 and 4.4 Hz for (**10**), typical for axial–axial and equatorial–axial couplings for a ring more or less in a chair conformation.[11] The *cis*-isomer of (**10**) had coupling constants of 4.2 and 3.4 Hz.

¶ The values are 9.5 and 5.0 Hz for (**16**); and 9.2 and 5.2 Hz for (**17**).

** The ^{13}C n.m.r. spectrum was identical (±0.9 p.p.m.) with that reported for this compound[12].

We prepared the 4-substituted unsaturated lactones (**5**) from the corresponding saturated lactones by selenenylation followed by oxidation and pyrolytic elimination,[14] and the saturated lactones by the reaction of methyl acrylate with the appropriate aldehyde enamine,[15] followed by hydrolysis, reduction of the aldehyde group with sodium borohydride, and lactonisation with acid.

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