Cyclisation of α,β,χ,ψ-Unsaturated Dioic Acid Esters *via* Tandem Conjugate Additions by using Lithium *N*-Benzyltrimethylsilylamide (LSA) as a Nitrogen Nucleophile and its Application to a Total Synthesis of (±)-Dihydronepetalactone and (±)-Isodihydronepetalactone.

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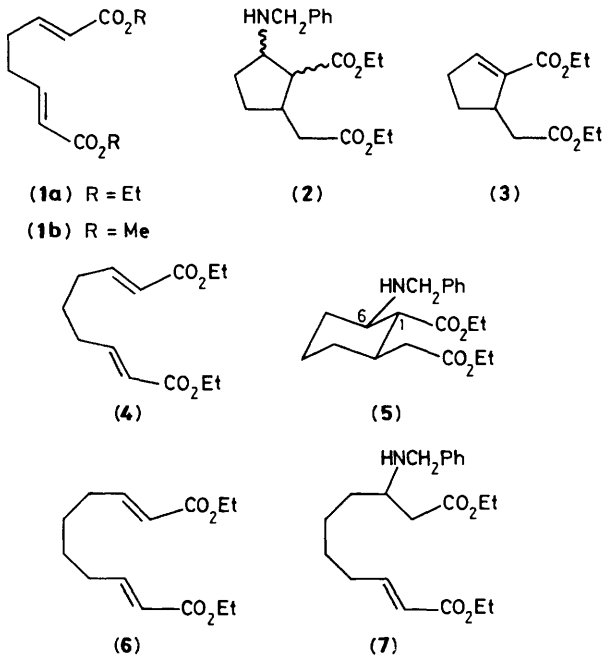
A stereoselective total synthesis of (±)-dihydronepetalactone and (±)-isodihydronepetalactone has been accomplished by utilising a novel cyclisation procedure; a reaction of octadiene-2,6-dioic acid esters with lithium *N*-benzyltrimethylsilylamide (LSA) induces 5-exo-Trig ring-closure *via* tandem conjugate additions.

When a crotonic acid ester is treated with a metal amide derived from an alkyl amine, the reactions expected are deprotonation of the γ-position to give the dienolate, conjugate addition to give the β-amino acid ester, and carboxamide formation. Recently, it has been reported that lithium *N*-benzyltrimethylsilylamide (LSA) is an excellent nucleophile adding only in a 1,4-manner to crotonate derivatives.[1] This finding has promise for new metal-amide chemistry in organic synthesis. For instance, the products of the conjugate addition followed by alkylation are synthetically useful β-amino acid esters which can be transformed into β-lactams and trisubstituted enoates.[1] We report here a new method for cyclisation by means of tandem conjugate addition of α,β,χ,ψ-unsaturated dioic acid esters initiated by LSA.[2]

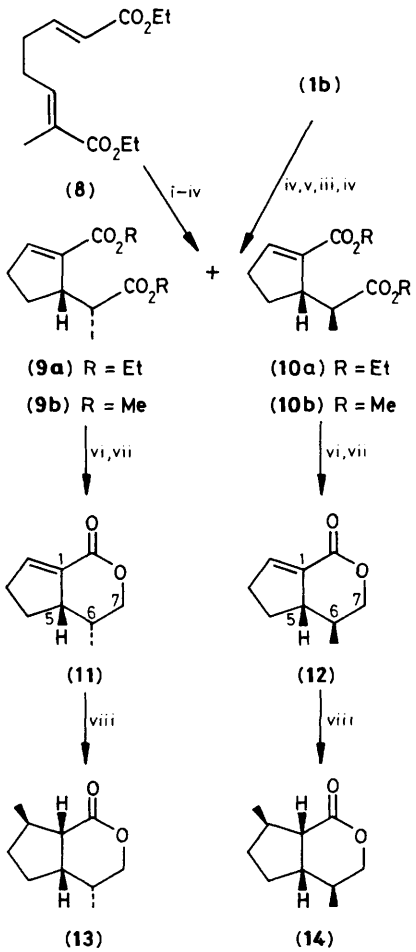
The reaction of the diester (**1a**)† with LSA (1.1 equiv.) in tetrahydrofuran (THF) at −78 °C for 1 h followed by treatment with acetic acid gave a 7:3 mixture of the cyclised products (**2**) in 78% yield. This mixture was converted into the cyclopentene (**3**)[3] in 83% yield by treatment with iodomethane and potassium carbonate in ethanol for 7 h at room temperature to give the *N*-methylated products followed by heating under reflux in xylene overnight with silica gel to eliminate the dialkylamino group.



A similar reaction of the homologous diester (**4**) with LSA gave only the *r*-1,*t*-2,*t*-6 trisubstituted cyclohexane (**5**) in 93% yield. The stereostructure of (**5**) was confirmed on the basis of its ^{1}H n.m.r. spectrum [δ 2.79 (ddd) *J* 11.5, 10.5, and 4 Hz (H-6_{ax}), and 2.04 (t), *J* 10.5 Hz (H-1_{ax})].

The reaction of the higher homologue (**6**) with LSA at −78 °C for 1 h gave the 1,4-addition product (**7**) in 59% yield without detectable amounts of the cycloheptanes expected. With longer reaction times at room temperature, the yield of (**7**) was greatly diminished.

Treatment of the unsymmetrical diester (**8**) with LSA followed by *N*-methylation and β-elimination gave a 26:74 mixture of (**9a**) and (**10a**) in 64% overall yield. The initial



Scheme 1. *Reagents*: i, LSA; ii, H^+; iii, MeI, K_2CO_3; iv, SiO_2, xylene, reflux; v, MeI; vi, $LiAlH_4$; vii, MnO_2; viii, $(CH_3)_2CuLi$.

† All new compounds gave satisfactory spectral, microanalytical, and/or high-resolution mass data.

conjugate addition of LSA to (**8**) proceeded only at the crotonate system. On the other hand, the reaction of the ester enolate derived from (**1b**) and LSA with iodomethane, at −78 °C for 3 h and then at room temperature overnight, followed by *N*-methylation and then deamination gave (**9b**) and (**10b**) in a ratio of 61 to 39 in 69% overall yield.

The esters (**9**) and (**10**) were transformed into the lactones [(**11**) and (**12**), in 69 and 58% yields, respectively] by successive treatment with lithium aluminium hydride and active manganese dioxide to establish the assignment of their stereostructures. The ^{1}H n.m.r. spectrum of (**11**) shows nuclear Overhauser enhancement (n.O.e.) only between the signals due to the methyl group [δ 0.97, (d), *J* 7.0 Hz] and those due to one of the C-7 methylene protons [δ 4.25, (dd), *J* 11.4 and 2.6 Hz], while that of (**12**) shows n.O.e. between the signals due to the methyl group [δ 0.97, (d), *J* 6.6 Hz] and those due to each of the C-7 methylene protons [δ 3.94, (dd), *J* 11.6 and 11.6 Hz, and 4.29, (dd), *J* 11.6 and 4.6 Hz] and the C-5 methine proton [δ 2.56, (m)]. Accordingly, the methyl group of (**12**) is *cis* to the ring-juncture proton.

On treatment with Me_2CuLi, these lactones (**11**) and (**12**) were converted into (±)-dihydronepetalactone (**13**)[4,5] in 90% yield and (±)-isodihydronepetalactone (**14**)[4–6] in 83% yield, respectively, physiologically active components for the Felidae animals isolated from the leaves and galls of *Actinidia polygama* Miq. and from the essential oil of *Nepeta catraria*.

A new and practical method for 5- and 6-exo-trig[7] ring closure of α,β,χ,ψ-unsaturated dioic acid esters has thus been developed by using LSA as a nitrogen nucleophile. This methodology opens up many possibilities in the synthesis of biologically important cyclopentane monoterpenes.

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