

Cyclisation of α,β,γ,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 (\pm)-Dihydronepetalactone and (\pm)-Isodihydronepetalactone.

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A stereoselective total synthesis of (\pm)-dihydronepetalactone and (\pm)-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.

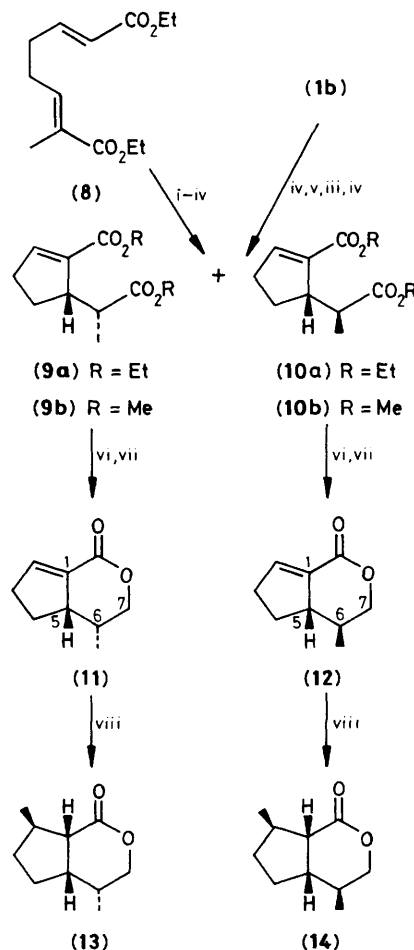
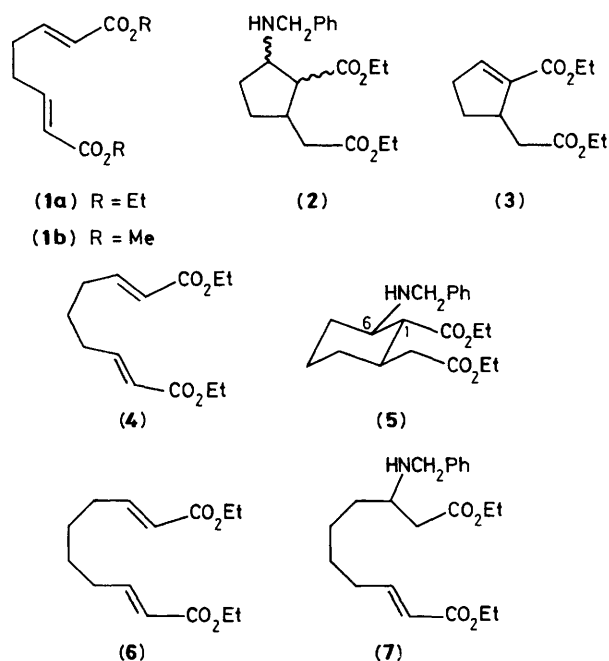
When a crotonic acid ester is treated with a metal amide derived from an alkyl amine, the reactions expected are deprotonation of the γ -position to give the dienolate, conjugate addition to give the β -amino acid ester, and carboxamide formation. Recently, it has been reported that lithium *N*-benzyltrimethylsilylamide (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,γ,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 ^1H 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



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

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, $(\text{CH}_3)_2\text{CuLi}$.

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 ^1H 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 (\pm)-dihydronepetalactone (13)^{4,5} in 90% yield and (\pm)-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-trig⁷ 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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References

- 1 T. Ueyhara, N. Asao, and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, 1987, 1410; *Tetrahedron*, 1988, **44**, 4173.
- 2 For recent examples and leading references of intramolecular conjugate addition of α,β -unsaturated esters, see S. T. Nugent, M. M. Baizer, and R. D. Little, *Tetrahedron Lett.*, 1982, **23**, 1339; G. Stork, J. D. Winkler, and N. A. Saccomano, *ibid.*, 1983, **24**, 465; G. Majetich, R. Desmond, and A. M. Casares, *ibid.*, 1983, **24**, 1913; M. Ihara, M. Toyota, K. Fukumoto, and T. Kametani, *ibid.*, 1984, **25**, 2167; M. P. Cooke, Jr., *J. Org. Chem.*, 1984, **49**, 1144.
- 3 For a synthesis of the related compounds, see H. Amri and J. Villieras, *Tetrahedron Lett.*, 1987, **28**, 5521.
- 4 T. Sakan, S. Isoe, S. B. Hyeon, R. Katsumura, T. Maeda, J. Wolinsky, D. Dickerson, M. Slabaugh, and D. Nelson, *Tetrahedron Lett.*, 1965, 4097, and references cited therein.
- 5 J. Wolinsky and E. J. Eutace, *J. Org. Chem.*, 1972, **37**, 3376.
- 6 J. Ficini and J. d'Angelo, *J. Org. Chem.*, 1976, 6087.
- 7 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.