Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1637–1641

TETRAHEDRON: *ASYMMETRY*

Conjugate addition to (α,β)(α′,β′)-diendioate esters by lithium (α-methylbenzyl)benzylamide: tandem addition–cyclisation versus double addition

Julio G. Urones,[a] Narciso M. Garrido,[a,*] D. Díez,[a] Sara H. Dominguez [a] and Stephen G. Davies [b]

[a]*Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain*
[b]*The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK*

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Abstract

Strategies for obtaining either the products from tandem conjugate addition–cyclisation or from double addition in the highly stereoselective addition of lithium (*R*)-(α-methylbenzyl)benzylamide to (α,β)(α′,β′)-diendioate esters are demonstrated.

(α,β)(α′,β′)-Diendioate esters are potential substrates for tandem conjugate addition–cyclisation processes or for double conjugate addition reactions (Scheme 1): which reaction manifold is followed will obviously depend on the rate of intramolecular cyclisation of the intermediate ester enolate formed in the first addition versus the rate of intermolecular conjugate addition to the second α,β-unsaturated ester. Conjugate addition–cyclisation reactions with (α,β)(α′,β′)-diendioate esters as substrates have been studied in the racemic series using lithium (benzyl)trimethylsilylamide as initiating nucleophile for the generation of cyclopentane and cyclohexane derivatives.[1] Asymmetric versions have also been reported for (α,β)(α′,β′)-diendioyl derivatives of chiral auxiliaries.[2] The double addition manifold has not been reported although monoaddition without cyclisation has been reported for an (*E*,*E*)-deca-2,5-diendioate ester with lithium (benzyl)trimethylsilylamide rather than cyclisation to a cycloheptane derivative.[1] The diamino bisadducts obtained are very versatile intermediates[3] due to the fact that a class of C_2-symmetric molecules that contains 1,*n*-diamino functions (*n*=3−5) as structural features has been found to efficiently inhibit HIV-protease.[4] C_2-Symmetric diamines are also of importance in asymmetric synthesis as ligands and ligand building blocks for transition metal catalysts.[5]

We have demonstrated the use of homochiral lithium (α-methylbenzyl)benzylamide **1** to initiate the asymmetric conjugate addition–cyclisation of dimethyl (*E*,*E*)-octa-2,5-dienoate **2** to generate the

* Corresponding author. E-mail: nmg@gugu.usal.es

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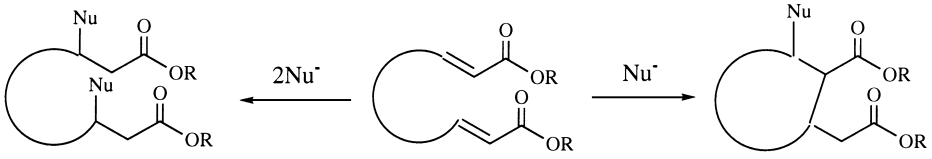
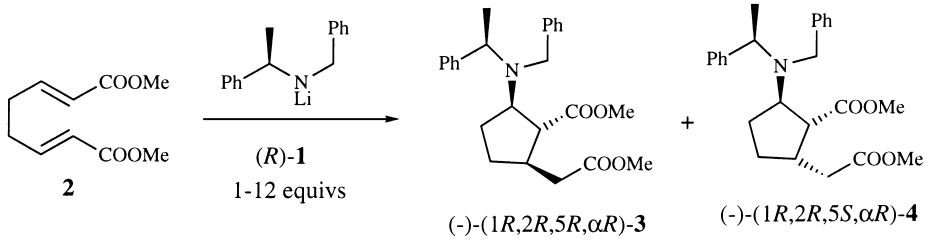


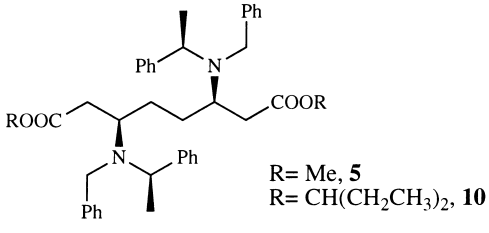
Scheme 1.

homochiral cyclopentane derivative **3** with complete control over the configuration of C-1 and C-2 and excellent control over C-5 with only a small amount of the C-5 epimer **4** being formed[6] (Scheme 2).

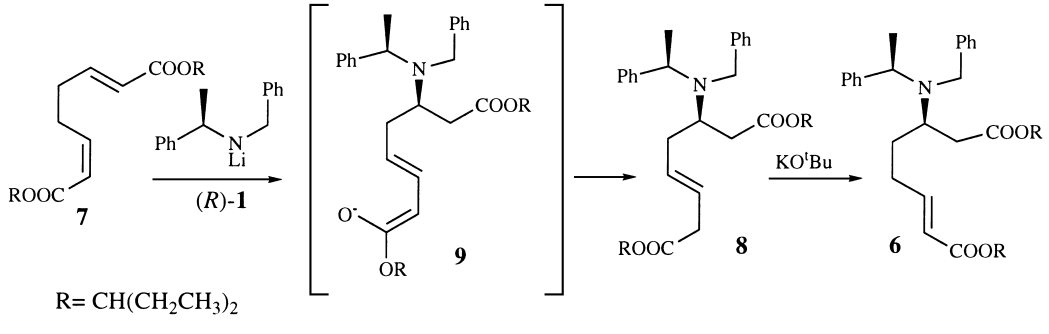


Scheme 2.

Addition of dimethyl (*E*,*E*)-octa-2,5-dienoate **2** to a large excess (12 equiv.) of the lithium amide (*R*)-**1** similarly resulted in the exclusive formation of the cyclised products **3** and **4** with no double addition product **5** being found.

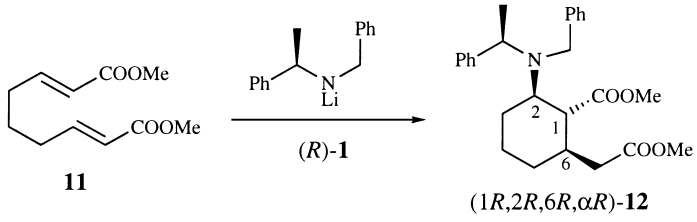


Whereas (*E*)-α,β-unsaturated esters are very susceptible to conjugate addition, their (*Z*)-counterparts are highly susceptible to γ-deprotonation.[1b,7] This suggested a strategy towards the monoadduct **6** from di-3-pentyl (*E*,*Z*)-octa-2,6-diendioate **7**. Addition of **7** to an excess (3 equiv.) of (*R*)-**1** generated, in 76% yield after work-up, the (*E*)-β,γ-unsaturated monoadduct **8**, $[\alpha]_D^{26}$=−12.8 (*c* 1.54, $CHCl_3$),[8] as expected from α-protonation of the intermediate dienoate **9**, which on treatment with base under protic conditions rearranged to the (*E*)-α,β-unsaturated ester monoadduct **6** in 72% yield (Scheme 3). The bisadduct **10** $[\alpha]_D^{26}$=−2.8 (*c* 0.21, $CHCl_3$), was now accesssible in 51% yield by subsequent conjugate addition of (*R*)-**1** to **6**.



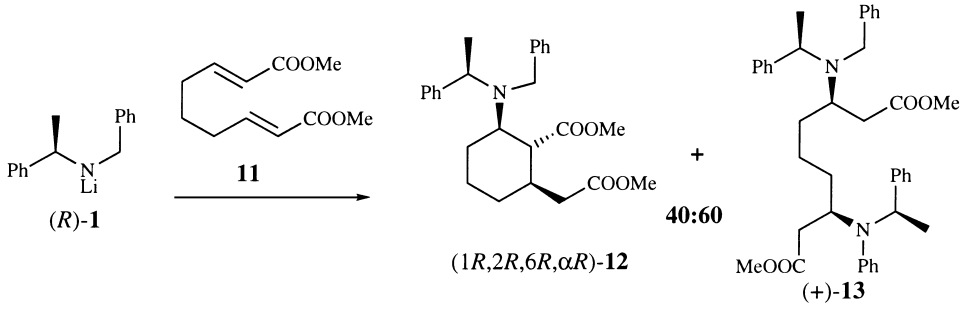
Scheme 3.

Addition of a slight excess of lithium amide (*R*)-**1** to dimethyl (*E*,*E*)-nona-2,7-diendioate **11** gave (+)-(1*R*,2*R*,6*R*,α*R*)-**12**, $[\alpha]_D^{26}$=+3.9 (*c* 1.86, $CHCl_3$), as the sole product completely stereoselectively in 72% yield. The absolute configuration of the α-methylbenzyl centre derives from (*R*)-**1**, while that of C-2 is assigned by analogy with all other conjugate additions of (*R*)-**1** to α,β-unsaturated esters.[9] The absolute configurations of C-1 and C-6 are assigned by determining their configurations relative to C-2 by ^{1}H NMR spectroscopy including two-dimensional homonuclear COSY, heteronuclear HMQC and HMBC, NOE and ROESY experiments. The C-1 configuration is consistent with the established *anti*-addition to the first α,β-unsaturated ester initiated by the lithium amide[10] (Scheme 4).



Scheme 4.

On the other hand, addition of dimethyl (*E*,*E*)-nona-2,7-diendioate **11** to a large excess (12 equiv.) of the lithium amide (*R*)-**1** generated a 40:60 mixture of the cyclised adduct (1*R*,2*R*,6*R*,α*R*)-**12** to the double addition product (+)-**13**, $[\alpha]_D^{26}$=+7.4 (*c* 2.00, $CHCl_3$) in 70% yield (Scheme 5).

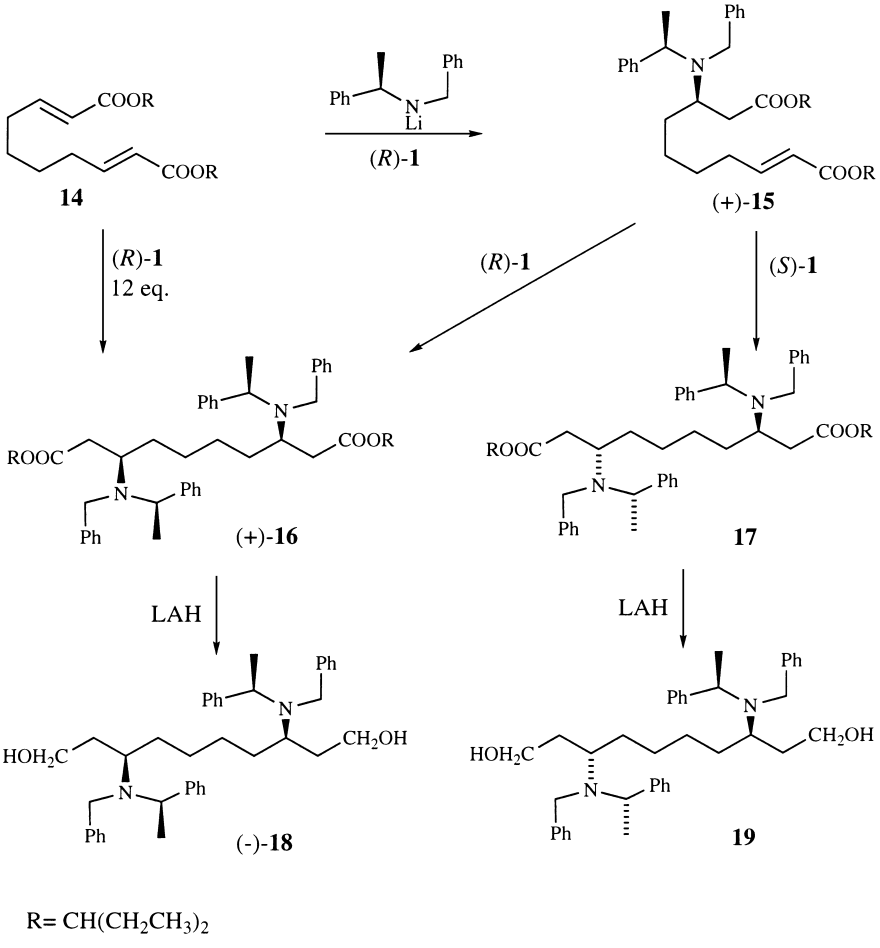


Scheme 5.

When lithium amide (*R*)-**1** (1.2 equiv.) was added to di-3-pentyl (*E*,*E*)-deca-2,8-diendioate **14**, no cyclisation products were obtained, with only the monoaddition product **15**, $[\alpha]_D^{26}$=+6.2 (*c* 0.62, $CHCl_3$), being formed in 25% yield (Scheme 6) and 65% of **14** was recovered. Addition of **14** to a large excess (12 equiv.) of lithium amide (*R*)-**1** generated the bisadduct (+)-**16**, $[\alpha]_D^{26}$=+7.1 (*c* 0.86, $CHCl_3$), as the sole product in 67% isolated yield. Analysis of the crude product by ^{1}H NMR (400 MHz) confirmed it to be diastereomerically pure (>95% d.e.) as no trace was found of any of the other (β,β′)-stereoisomers independently prepared[11] by adding (*R*)-α-methylbenzylamine to **14** non-stereoselectively.[9a,12] Bisadduct (+)-**16** was also obtained on addition of (*R*)-**1** to the monoadduct **15**. The bisadduct **17**, precursor to the *meso*-diaminodiacid derivative was obtained on treatment of **15** with (*S*)-**1** in 71% yield, $[\alpha]_D^{26}$=−0.1 (*c* 0.86, $CHCl_3$). Reduction of (+)-**16** and **17** with $LiAlH_4$ generated the diols: (−)-**18**, $[\alpha]_D^{26}$=−47.5 (*c* 1.57, $CHCl_3$) and **19**, in 84% and 77% yields, respectively.

The analogous series of reactions starting from (*S*)-**1** generated (−)-**16**, $[\alpha]_D^{26}$=−6.6 (*c* 3.80, $CHCl_3$), and, by reduction, the diol (+)-**18**, $[\alpha]_D^{26}$=+46.2 (*c* 1.18, $CHCl_3$).

In conclusion, we have demonstrated strategies for obtaining either the products from tandem conjugate addition–cyclisation (cyclopentane and cyclohexane derivatives) or from double addition in the highly stereoselective addition of (*R*)- and (*S*)-(α-methylbenzyl)benzylamide to (α,β)(α′,β′)-



Scheme 6.

diendioate esters. In this way the asymmetric synthesis of precursors to all three stereoisomers of (β,β′)-diaminodiacids is achieved in good yield.

Acknowledgements

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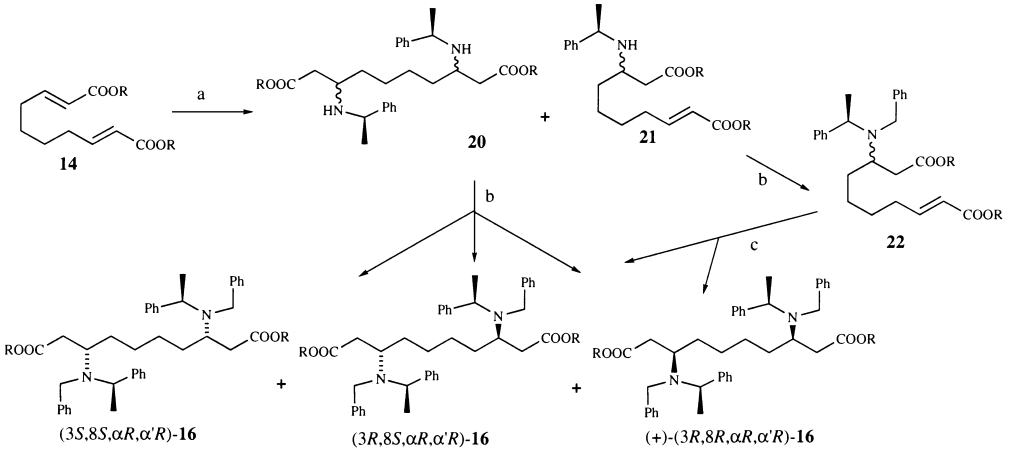
11. The mixture of (+)-(3*R*,8*R*,α*R*,α′*R*)-**16** together with the other two stereoisomers ((3*R*,8*S*,α*R*,α′*R*)-**16** and (3*S*,8*S*,α*R*,α′*R*)-**16**) was prepared according to the following:†



R= $CH(CH_2CH_3)_2$ a: (*R*)-α-methylbenzylamine/EtOH. b: $BnCl/CH_3CN/NaHCO_3$. c: (*R*)-**1**

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† By reaction of **14** with (*R*)-α-methylbenzylamide in EtOH at reflux, the monoaddition product **21** together with the diaddition product **20** were obtained. Subsequent benzylation of the secondary amines gave **22** from **21** and the mixture of three stereoisomers, (+)-(3*R*,8*R*,α*R*,α′*R*)-**16**, (3*R*,8*S*,α*R*,α′*R*)-**16** and (3*S*,8*S*,α*R*,α′*R*)-**16**, from **20**. Treatment of **22** with (*R*)-**1** gave the mixture: (+)-(3*R*,8*R*,α*R*,α′*R*)-**16** and (3*R*,8*S*,α*R*,α′*R*)-**16**.