Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 16, pp. 2683–2685, 1997

Printed in Great Britain
PII: S0957-4166(97)00340-6
0957-4166/97 $17.00 + 0.00

Asymmetric synthesis of (*R*)- and (*S*)-methyl (2-methoxycarbonylcyclopent-2-enyl)acetate and (*R*)- and (*S*)-2-(2-hydroxymethyl-cyclopent-2-enyl)ethanol

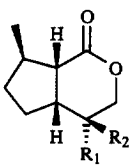
Julio G. Urones,[a] Narciso M. Garrido,[a,*] D. Díez,[a] Sara H. Dominguez [a] and Stephen G. Davies [b]

[a] Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1–5, 37008 Salamanca, Spain

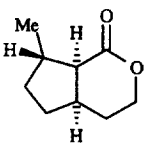
[b] The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, UK

Abstract: (*R*)- and (*S*)-Methyl (2-methoxycarbonylcyclopent-2-enyl)acetate **1** and (*R*)- and (*S*)-2-(2-hydroxymethyl-cyclopent-2-enyl)ethanol **2** have been obtained from dimethyl (E,E)-octa-2,6-diendioate **3** by a diastereoselective *tandem* conjugate addition protocol, from (*R*)- and (*S*)-lithium (α-methylbenzyl)benzylamide **4** respectively. © 1997 Elsevier Science Ltd

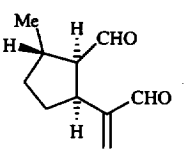
The compounds methyl (2-methoxycarbonylcyclopent-2-enyl)acetate **1** and 2-(2-hydroxymethyl-cyclopent-2-enyl)ethanol **2** have been obtained previously in non-racemic form from resolution of ethyl 5-hydroxycyclopent-1-enecarboxylate by lipase PS and vinyl acetate,[1] and are viable building blocks for naturally ocurring iridoid monoterpenes (+)-mitsugashiwalactone[2] and (−)-dolichodial[3] and the pentacyclic monoterpenes nepetalactones.[4]



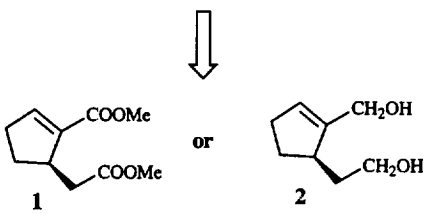
R_1=Me, R_2=H
Dihydronepetalactone
R_1=H, R_2=Me
Isodihydronepetalactone



Mitsugashiwalactone



(-) Dolichodial

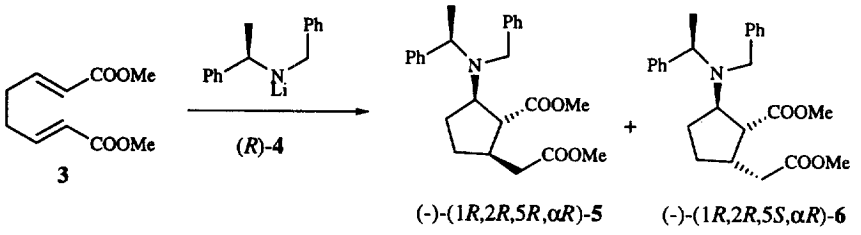


1 or **2**

Yamamoto *et al.* have previously reported in the racemic series that lithium N-benzyltrimethylsilylamide (LSA) mediates the tandem conjugate addition cyclisation of dimethyl (E,E)-octa-2,6-diendioate **3**,[5] and this methodology has been adapted by Meijere *et al.* to the asymmetric synthesis of anellated *cis*-pentacin derivatives.[6] We have previously shown that the addition of lithium (α-methylbenzyl)benzylamide to α,β-unsaturated esthers is highly stereoselective.[7] We describe herein a combination of these strategies for the asymmetric synthesis of methyl (2-methoxycarbonylcyclopent-2-enyl)acetate **1** and 2-(2-hydroxymethyl-cyclopent-2-enyl)ethanol **2** in both enantiomeric forms utilising a highly stereoselective tandem conjugate addition protocol from dimethyl (E,E)-octa-2,6-diendioate initiated by lithium (α-methylbenzyl)benzylamide.

* Corresponding author.

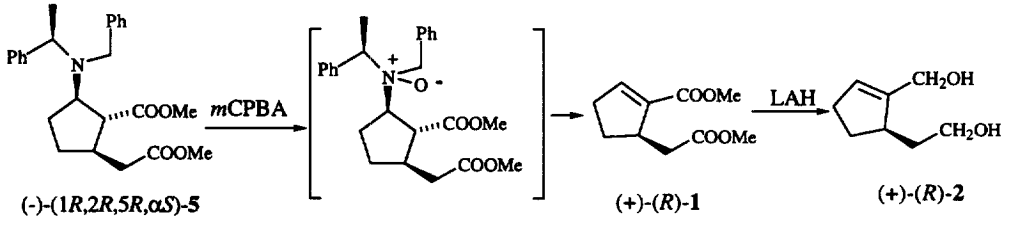
Addition of dimethyl (E,E)-octa-1,5-diendioate **3** to homochiral lithium (*R*)-(α-methylbenzyl)benzylamide (*R*)-**4** [prepared by treatment of (*R*)-(α-methylbenzyl)benzylamine with *t*-butyllithium] at −78°C followed by quenching with saturated aqueous ammonium chloride gave the readily separable, by flash chromatography (silica; 5% Et_2O in hexane), (−)-(1*R*,2*R*,5*R*,α*R*)-**5**,[8] $[\alpha]_D^{26}$=−51.3 (c 0.97, $CHCl_3$), together with a small amount of the C-5 epimer (−)-(1*R*,2*R*,5*S*,α*R*)-**6**,[8] $[\alpha]_D^{26}$=−15.5 (c 2.05, $CHCl_3$), in 86% isolated yield and 10:1 ratio. (Scheme 1).



Scheme 1.

The absolute configuration of the α-methylbenzyl centre derives from (*R*)-**4**, while that of C-2 is assigned by analogy with all other conjugate additions of (*R*)-**4** to α,β-unsaturated esters.[7] The absolute configurations of C-1 and C-5 are assigned by determining their configurations relative to C-2 by ^1H NMR spectroscopy including 2-dimensional homonuclear COSY, heteronuclear HMQC and HMBC, nOe and ROESY experiments. The products **5** and **6** have the same C-1 configuration consistent with the established anti addition to the first α,β-unsaturated ester initiated by the lithium amide.[9] Compounds **5** and **6** are epimeric at C-5, their ratio reflecting high stereoselectivity in the second conjugate addition step.

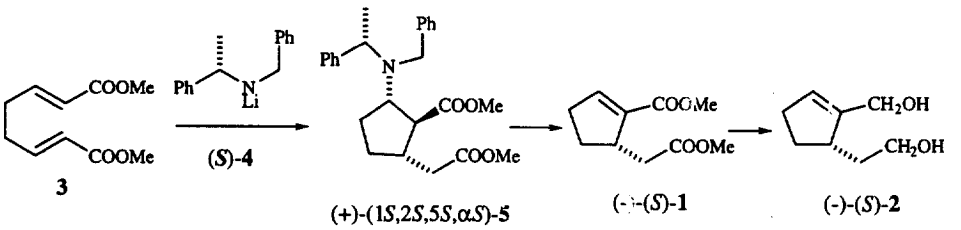
The *trans*-β-amino ester moiety within **5** suggested a *syn*-elimination protocol for the conversion of **5** to **1**.[10] Thus oxidation of (−)-(1*R*,2*R*,5*R*,α*R*)-**5** with *m*-chloroperbenzoic acid generated, presumably *via* the N-oxide and a Cope elimination, the desired ester (+)-(*R*)-**1**,[8] $[\alpha]_D^{26}$=+38.7 (c 0.60, $CHCl_3$), in 80% isolated yield (Scheme 2). Reduction of (+)-(*R*)-**1** with $LiAlH_4$ generated the diol (+)-(*R*)-**2**,[8] $[\alpha]_D^{26}$=+11.3 (c 0.60, MeOH),[11] in 70% isolated yield and ^1H NMR on the derived diester formed with R(+)-α-trifluoromethyl-phenylacetic chloride (MTPA; Mosher's reagent) confirmed it as homochiral (>95% e.e.).



Scheme 2.

The analogous series of reactions (Scheme 3) starting from (*S*)-**4** generated sequentially (+)-(1*S*,2*S*,5*S*,α*S*)-**5**, $[\alpha]_D^{26}$=+50.8 (c 1.34, $CHCl_3$), (−)-(*S*)-**1**, $[\alpha]_D^{26}$=−43.5 (c 1.30, $CHCl_3$), and (−)-(*S*)-**2**,[11] $[\alpha]_D^{26}$=−13.0 (c 0.25, MeOH)[11].

In conclusion, we have demonstrated the asymmetric synthesis of (*R*)- and (*S*)-methyl (2-methoxycarbonylcyclopent-2-enyl)acetate **1** and (*R*)- and (*S*)-2-(2-hydroxymethyl-cyclopent-2-enyl)ethanol **2**, useful homochiral synthons for monoterpenes, from dimethyl (E,E)-octa-2,6-diendioate **3** by a diastereoselective *tandem* conjugate addition protocol, initiated by (*R*)- and (*S*)-lithium (α-methylbenzyl)benzylamide **4** respectively.



Scheme 3.

Acknowledgements

We thank the Spanish Ministerio de Educación y Ciencias and the British Council for 'acción integrada' HB 18-B and Dr A. M. Lithgow for performing two dimensional experiments.

References

1. Yamane, T.; Takahashi, M.; Ogasawara, K., *Synthesis*, 1994, 444.
2. Sakan, T.; Murai, F.; Asoe, S.; Hyeon, S. B.; Hayashi, Y., *J. Chem. Soc. Jpn.*, 1969, **90**, 507.
3. (a) Cavill, G. W. K.; Hinterberger, H., *Aust. J. Chem.* 1960, **13**, 514; 1961, **14**, 143.(b) Pagnoni, U. M.; Pinetti, A.; Trave, R.; Garanti, C., *Aust. J. Chem*, 1976, **29**, 1375.
4. Sakan, T.; Isoe, S.; Hyeno, S.; Katsumura, R.; Maeda, T.; Wolinsky, J.; Dickerson, D.; Slabaugh, M.; Nelson, D., *Tetrahedron Letters*, 1965, 3376 and the references cited therein.
5. (a) Uyehara, T.; Shida, N.; Yamamoto, Y., *J. Chem. Soc., Chem. Commun*, 1989, 113.(b) Uyehara, T.; Shida, N.; Yamamoto, Y., *J. Org. Chem.*, 1992, **57**, 3139.
6. Voight, K.; Lansky, A.; Woltemeyer, M.; Meijere, A., *Liebigs Ann.*, 1996, 899.
7. (a) Davies, S. G.; Ichihara, O., *Tetrahedron: Asymmetry*, 1991, **2**, 183. (b) Bunnage, M.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1*, 1993, 1375; 1994, 2373. (c) Davies, S. G.; Costello, J. F.; Ichihara, O., *Tetrahedron: Asymmetry*, 1994, **5**, 1999. (d) Davies, S. G.; Walters, I. A. S., *J. Chem. Soc. Perkin Trans. I*, 1994, 1129.
8. All new compounds were fully characterised including elemental analysis or high resolution mass spectrometry.
9. (a) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S., *J. Chem. Soc. Chem. Commun.*, 1993, 1154. (b) Davies, S. G.; Ichihara, O.; Walters, I. A. S., *Synlett*, 1993, 461. (c) Davies, S. G.; Ichihara, O.; Walters, I. A. S., *Synlett*, 1994, 117. (d) Davies, S. G.; Walters, I. A. S., *J. C. S. Perkin Trans. I*, 1994, 1129. (e) Davies, S. G.; Lenoir, I.; Walters, I. A. S., *J. C. S. Perkin Trans. I*, 1994, 1411. (f) Davies, S. G.; Edwards, A. J.; Walters, I. A. S., *Recl. Trav. Chim. Pays-Bas*, 1994, 1141.
10. (a) Cope, A. C.; Foster, T. T.; Towle, P. H., *J. Am. Chem. Soc.*, 1949, **71**, 3929. (b) Cope, A. C.; Ciganek, E.; Howell, C. F.; Schweizer, E. E., *J. Am. Chem. Soc.*, 1960, 82, 4663. (c) Cram, D. J.; McCarty, J. E., *J. Am. Chem. Soc.*, 1954, **76**, 5740. (d) Davies, S. G.; Smyth, G. D., *Tetrahedron: Asymmetry*, 1996, **7**, 1001. (e) Davies, S. G.; Smyth, G. D., *J. C. S. Perkin Trans. I*, 1996, 2467.
11. Our values for the specific rotations of **2** (+)-(*R*)-**2**, $[\alpha]_D^{26}$=+11.3 (c 0.60, MeOH), and (−)-(*S*)-**2**, $[\alpha]_D^{26}$=−13.0 (c 0.25, MeOH) while significantly different from each other are both greater than the literature value for (*R*)-**2**[1] $[\alpha]_D^{20}$=+9.2 (c=0.68, MeOH). Our samples of **2** were pure by ^{1}H NMR analysis and homochiral (>95% e.e.) by ^{1}H NMR analysis of the diester derivatives formed with Mosher's reagent from (*R*)-**2**, (*S*)-**2** and racemic.

(Received in UK 15 July 1997)