Pergamon

Tetrahedron Letters 42 (2001) 7325–7328

TETRAHEDRON LETTERS

1,4-Addition of chiral 2-propenylphosphonamide anions to α-substituted cyclopentenones: use in enantioselective syntheses of methyl dihydrojasmonates and methyl jasmonates

Helen C. Hailes,[a,*] Ben Isaac[b] and M. Hashim Javaid[a]

[a]*Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, UK*
[b]*Bush Boake Allen Ltd., Blackhorse Lane, London E17 5QP, UK*

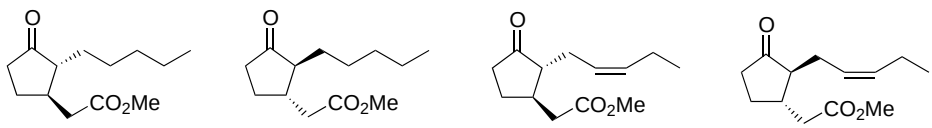
Received 2 July 2001; revised 25 July 2001; accepted 3 August 2001

Abstract—The addition of chiral 2-propenylphosphonamide anions, generated from the reaction products of (1*R*,2*S*)-ephedrine and 2-propene-1-phosphonyl dichloride, to α-substituted cyclopentenones is described. Ozonolysis of the addition products led to the synthesis of both enantiomers of methyl dihydrojasmonate and methyl jasmonate.

The methyl jasmonates[1] are key natural products occurring in *Jasminium grandiflorum* L. and the blossoms of many flowers, and are used widely in the formulation of many perfumes. In addition, key biological roles have been noted[2] including roles in gene expression,[3] odour production[4] and growth inhibition.[5] The unnatural analogue, methyl dihydrojasmonate possesses important olfactory properties, biological activities have been reported[4] and it is a constituent of famous fragrances.[6] Enantioselective syntheses of the dihydrojasmonates (−)-**1** and (+)-**2** have been reported, for example using solid–liquid asymmetric phase transfer catalysis where a range of e.e.s was obtained depending on the phase transfer catalyst and reaction conditions utilised.[7] Syntheses of (−)-**3** and (+)-**4** have also been published using, for example, bis(8-phenylmenthyl) malonate as an enantiopure precursor which was converted into cyclopropane intermediates,[8] or the optically pure precursor cyclopent-2-ene-1,3-diol monoacetate and Montforts et al. enantiodivergent alkylation route;[9] however, these syntheses are multistep and therefore low yielding overall.

With the intense interest in these compounds and their analogues, there is a continuing desire to develop versatile, short, selective syntheses. We have recently investigated the 1,4-addition of chiral 2-propenylphosphonamide anions to α-substituted cyclopentenones which highlighted their use in the synthesis of α,β-disubstituted cyclopentanones. Herein, we report the results of this investigation and demonstrate the effectiveness of such a transformation in affording a direct and flexible route to the jasmonates.

The conjugate addition of chiral phosphonamide anions to α,β-unsaturated carbonyl compounds has been reported by for example Haynes,[10] Denmark who used 1,3,2-oxazaphosphorane 2-oxides,[11] Hanessian who used C_2-symmetrical phosphonamides[12] and Hua.[13] Hua et al. have described the conjugate addition of extended lithium anions of chiral phosphonamides to 2-cyclopentenone, 2-cyclohexenone and 2-cycloheptenone leading to β-substituted acids and aldehydes in 28–98% e.e. (depending on the phosphonamide and *N*-alkyl group used and the enone).[13] Notably, the use



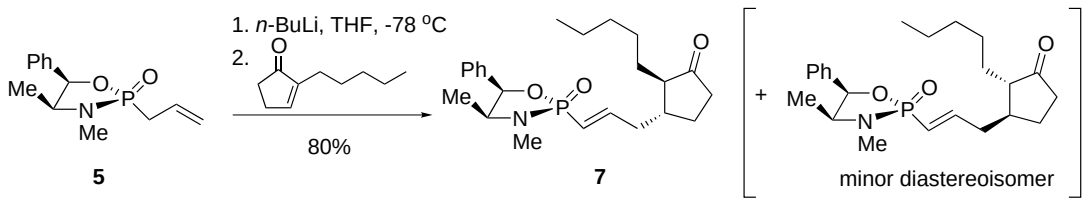
(-)-1 (+)-2 (-)-3 (+)-4

Keywords: flavours and fragrances; chiral propenylphosphonamides; ozonolysis.
* Corresponding author. Fax: +44 (0)20 7679 7463; e-mail: h.c.hailes@ucl.ac.uk

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01437-X

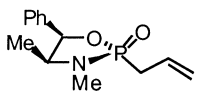
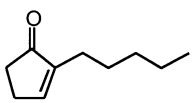
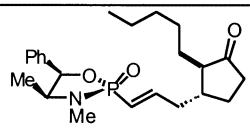
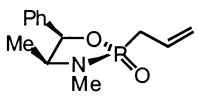
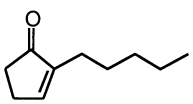
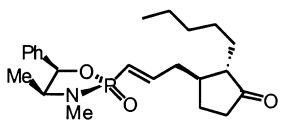
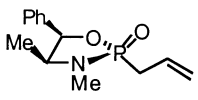
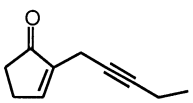
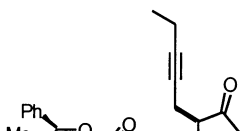
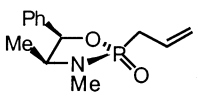
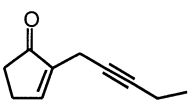
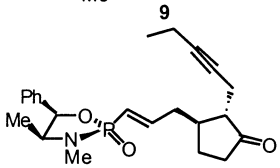
of phosphonamides derived from (1*R*,2*S*)-ephedrine (with an *N*-methyl group) led to the formation of products in approximately 70% d.e. (from analysis of the aldehydes, the ozonolysed compounds). However, those prepared from (1*R*,2*R*)-norpseudoephedrine and an *N*-^{i}propyl group led to excellent diastereoselectivities with one of the diastereomeric phosphonamides but much lower reaction selectivities with the other. We rationalised that the introduction of an alkyl group at the α-position on the enone system could enhance facial stereodifferentiation, since chelation of the lithium ion with the cyclopentenone is likely to be on the O=P–O face of the phosphonamide due to the *N*-alkyl group present. This could result in the formation of adducts in overall higher diastereoselectivities and would also provide rapid access to α,β-cyclopentanones.

Our initial studies focused on the use of the enone, 2-pentyl-2-cyclopenten-1-one. The chiral phosphonamides (2*R*,4*S*,5*R*)-3,4-dimethyl-5-phenyl-2-(2-propenyl)-1,3,2-oxazaphospholidin-2-one **5** and (2*S*,4*S*,5*R*)-3,4-dimethyl-5-phenyl-2-(2-propenyl)-1,3,2-oxazaphospholidin-2-one **6**, were selected since high reaction selectivities were sought when using both diastereoisomeric phosphonamides. These were prepared from 2-propene-1-phosphonyl dichloride and (1*R*,2*S*)-ephedrine, as previously reported[14] in a 1:1 ratio and were readily separated by flash column chromatography. Whilst in our studies both diastereoisomers were required, a stereospecific synthesis of phosphonamides has also been described.[15] Deprotonation of the phosphorous template **5** using *n*-butyllithium at −78°C to generate the anion and addition of 1 equivalent of 2-pentyl-2-cyclopenten-1-one led to the formation of **7** as the major addition product, together with a minor diastereoisomer in a combined yield of 80% (Scheme 1 and Table 1). The relative configuration of **7** was determined by correlation to the final product. Attempts to separate the isomeric products were not successful. The use of template **6** led to the formation of **8** and a minor diastereoisomer in 86% yield.



Scheme 1.

Table 1. Selectivities observed for addition of phosphonamide anions to α-substituted cyclopentenones

Phosphonamide	α-Substituted cyclopentenone	Major Diastereomer	Diastereomeric ratio major:minor	Yield
 **5**		 **7**	95:5	80%
 **6**		 **8**	93:7	86%
 **5**		 **9**	94:6	76%
 **6**		 **10**	92:8	83%

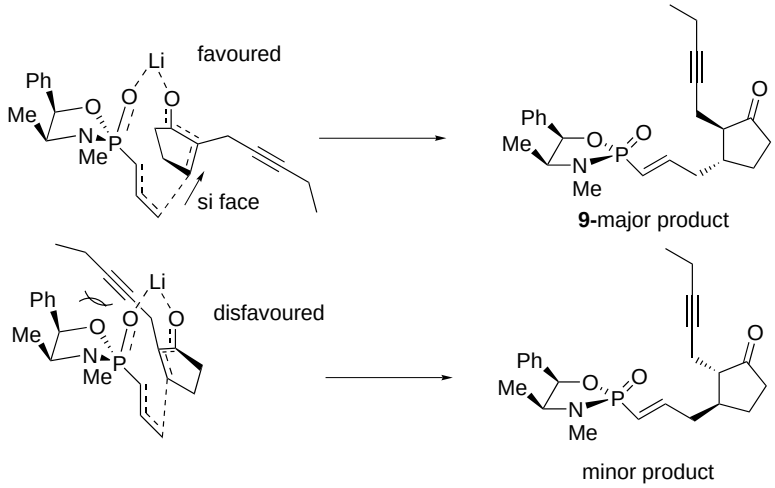
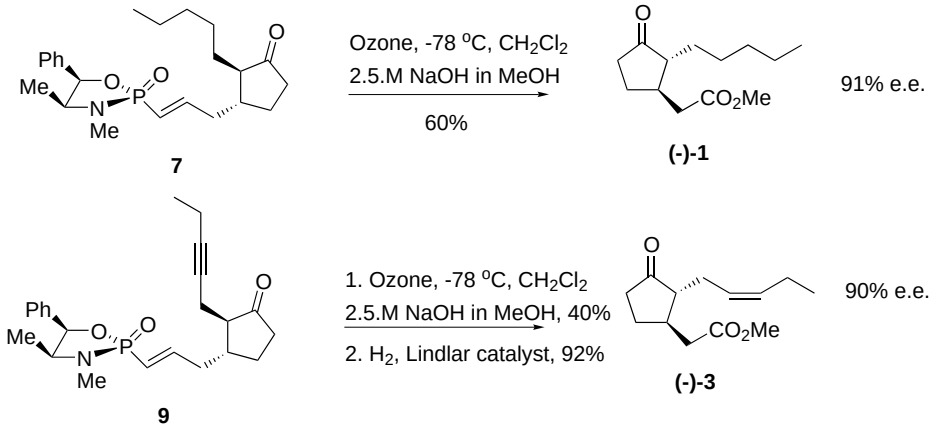


Figure 1.



Scheme 2.

2-(2-Pentynyl)-2-cyclopenten-1-one was prepared as previously reported.[16] Reaction of the extended enolates generated by the addition of *n*-butyllithium to **5** and **6** and the subsequent addition of 2-(2-pentynyl)-2-cyclopenten-1-one led to the formation of **9** and **10**, together with minor diastereoisomers, in 76 and 83% yield, respectively. The high reaction selectivities observed, compared to those reported by Hua of approximately 70% d.e., were consistent with the higher facial stereodifferentiation due to the presence of an alkyl chain at the α-position, as outlined in Fig. 1.

Cleavage of the phosphonamide template from **7** and **8** using ozonolysis under oxidative conditions with hydrogen peroxide generated a mixture of products. However, under reductive conditions (dimethyl sulfide) the corresponding aldehyde, 3-oxo-2-pentanylcyclopentyl ethanal, was produced in 62% yield. Whilst a stepwise oxidation of the aldehyde with subsequent methyl ester formation was explored, it resulted in the formation of **2** in only 20% yield from **8**. A more direct procedure was investigated, performing the ozonolysis in a 2.5 M solution of sodium hydroxide in methanol, together with dichloromethane as solvent.[17,18] This afforded (−)-methyl dihydrojasmonate **1** in 60% yield from **7** (Scheme 2) and **2** in 57% yield from **8**. The optical purity of the products **1** and **2** was shown to be 91 and 85% e.e., respectively, using chiral HPLC.[19]

Oxidative cleavage of the phosphonamides **9** and **10** was less straightforward due to potential oxidation of the alkyne moiety. Use of the azo-dye Sudan Red III[20] indicated phosphonamide cleavage under reductive ozonolysis conditions to give the corresponding aldehyde in 39% yield. However, Sudan III was observed to be unstable under the conditions used above to generate **1** and **2**. Therefore, to avoid the formation of several over-oxidised products, the reaction was carried out as before (Scheme 2) but was closely followed by TLC analysis and rapidly quenched. The corresponding methyl esters were then isolated in 39–40% yield and subsequent Lindlar reduction afforded **3** and **4** in 92% yield. Again HPLC analysis was used to indicate the optical purity of **3** and **4** as 90 and 84% e.e., respectively.

In summary, we have demonstrated that the 1,4-addition of chiral 2-propenylphosphonamide anions to α-substituted cyclopentenones can be achieved with high diastereoselectivities. In addition, the reaction products

can be readily converted using a one-step conversion to (−)- and (+)-methyl dihydrojasmonate and a two-step route to (−)- and (+)-methyl jasmonate.

Acknowledgements

We thank Bush Boake Allen for a studentship (M.H.J.) and John Janes for helpful discussions. The ULIRS Mass Spectrometry Facility at the University of London School of Pharmacy are acknowledged for high resolution mass spectra.

References

1. Demole, E. P.; Lederer, E.; Mercier, D. *Helv. Chim. Acta* **1962**, *45*, 675–685.
2. Beale, M. H.; Ward, J. L. *Nat. Prod. Rep.* **1998**, 533–548.
3. Boland, W.; Hopke, J.; Donath, J.; Nüske, J.; Bublitz, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1600–1602.
4. Miersch, O.; Kramell, R.; Parthier, B.; Wasternack, C. *Phytochemistry* **1999**, *50*, 353–361.
5. Koda, Y.; Kikuta, Y.; Kitahara, T.; Nishi, T.; Mori, K. *Phytochemistry* **1992**, *31*, 1111–1114.
6. Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633–7703.
7. Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.* **2000**, *2*, 2959–2962.
8. Quinkert, G.; Adam, F.; Durner, G. *Angew. Chem., Int. Ed.* **1982**, *21*, 856–856.
9. Montforts, F.-P.; Gesling-Zibulak, I.; Grammenos, W.; Schneider, M.; Laumen, K. *Helv. Chim. Acta* **1989**, *72*, 1852–1859.
10. Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411–5423.
11. Denmark, S. E.; Kim, J.-O. *J. Org. Chem.* **1995**, *60*, 7535–7547.
12. Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623–5631.
13. Hua, D. H.; Chan-Yu-King, R.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026–5029.
14. Cooper, D. B.; Hall, C. R.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969–1979.
15. Hua, D. H.; Chen, J. S.; Saha, S.; Wang, H.; Roche, D.; Bharathi, S. N.; Chan-Yu-King, R.; Robinson, P. D.; Iguchi, S. *Synlett* **1992**, 817–820.
16. Buchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021–2023.
17. Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675–3680.
18. Typical procedure: To a solution of the phosphonamide (800 mg, 2.0 mmol) in CH_2Cl_2 was added a solution of NaOH in MeOH (2.5 M NaOH, 4.1 ml). The reaction temperature was decreased to −78°C and ozone bubbled through the solution for ca. 40 min, after which nitrogen was passed through the solution for 30 min. The product was extracted with Et_2O (4×50 ml), and the combined organic extracts were dried and concentrated in vacuo to afford a colourless oil which was purified by flash column chromatography (eluent: hexane/EtOAc, 25:1) to yield **1** (0.27 g, 60%).
19. Optical purities were monitored using HPLC (Chiralcel OD, 250×4.6 mm, detection UV, λ 226 nm) and confirmed using optical rotations, **1**- $[\alpha]_D^{25}$ −48.2 (*c* 0.90 $CHCl_3$), **2**- $[\alpha]_D^{25}$ +38.2 (*c* 0.48 $CHCl_3$), **3**- $[\alpha]_D^{25}$ −85.5 (*c* 1.5 MeOH), **4**- $[\alpha]_D^{25}$ −80.5 (*c* 1.1 MeOH).
20. Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–809.