Stereocontrolled synthesis of quaternary cyclopropyl esters†

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Received 10th May 2010, Accepted 22nd June 2010
DOI: 10.1039/c0cc01333a

Treatment of a variety of enantiopure terminal epoxides with the anion of a range of 2-substituted triethylphosphonoacetates leads to an array of quaternary cyclopropyl esters with high yield and diastereocontrol.

In 1961, Wadsworth and Emmons described the utility of phosphonate carbanions in synthesis.[1] The olefination method they described is now a cornerstone reaction in synthetic chemistry, so it is astonishing that the related conversion of epoxides to *trans*-cyclopropyl esters also disclosed in this seminal paper is seldom employed.[2] Cyclopropanes are found widely in natural products, medicinally active compounds, drugs, agrochemicals, foods and fragrances (Fig. 1),[3] as well as being highly versatile synthetic intermediates.[4] As such, there exists a substantial number of elegant methods for the stereocontrolled synthesis of cyclopropanes[5] which are now widely employed in natural product syntheses and medicinal chemistry.

In spite of these advances, the continued prevalence of routes involving wasteful enzymatic resolution methods at pilot-plant capacity and above stands as an indictment of the current methods with respect to scale.[6] Alternative (industrially applicable) methods for the stereocontrolled preparation of cyclopropanes are therefore still of significant interest. In light of this, the Wadsworth–Emmons cyclopropanation process has received far less interest than it might merit. The reaction is stereospecific and so levels of enantiomeric excess in the epoxide starting materials are reliably translated into the cyclopropane products.[2a–e] Additionally, the scaleability of this process has been demonstrated by Merschaert[2a] and Singh[2e] and their respective colleagues at Bristol-Myers-Squibb and Eli Lilly, who carried out Wadsworth–Emmons reactions at pilot-plant scale to give up to 14 kg of cyclopropane product. Thus, the excellent yields and high *trans*-selectivities obtained for this process coupled with the ready availability of enantiopure epoxides[7] and phosphonate esters provide potential access to a range of enantiopure cyclopropanes in a very straightforward manner. In spite of this, at present, the reaction is almost exclusively limited to the synthesis of cyclopropanes from triethylphosphonoacetate,[2] little is known of the substrate generality and the origin of the high *trans*-selectivity remains a fundamental unanswered question. More importantly from a synthetic point of view, there are no reports of the formation of quaternary cyclopropyl esters from terminal epoxides other than for oxirane itself[2g,h] and hence nothing is known of the diastereoselectivity of such a process.

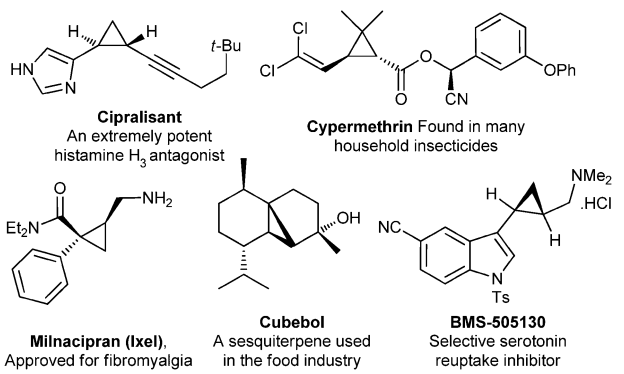
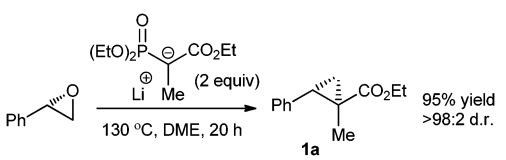


Fig. 1 Important cyclopropane containing molecules.

In the present work, we have sought to investigate the origin of the diastereocontrol and have explored whether the Wadsworth–Emmons cyclopropanation provides a feasible route to quaternary cyclopropyl esters. We began by examining the reaction between the lithium anion of commercially available triethyl phosphonopropionate (generated by deprotonation with *n*-BuLi (1.05 equiv.)) and (*S*)-styrene oxide (Scheme 1). Optimal reaction conditions were found when heating this anion (2.00 equiv.) with the epoxide at 130 °C in DME for 20 h.[8] This gave the known[9] cyclopropane **1a** in 95% yield and with a dr of >98 : 2 (GCMS).[10]

We next sought to determine if this method of generating trisubstituted cyclopropanes had broad scope (Table 1). Ethyl, propyl, benzyl and allyl substituted phosphononate esters all gave excellent yields (86–97%) for the corresponding quaternary stereocentre containing cyclopropanes **1b–e** (entries 2–5). It is of note that despite the increasing steric bulk of these substituents, the diastereoselectivity of this process was not unduly affected. In each case, prior to and following chromatographic purification, the cyclopropane product was obtained with >98 : 2 dr. In the case of cyclopropane **1e**, one could envisage using the allyl substituent as a synthetic handle either by way of a metathesis (*vide infra*) or *via* an oxidative process *e.g.* ozonolysis. We next examined the scope of the epoxide in

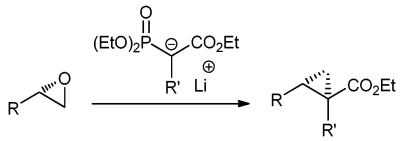


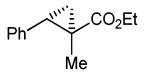
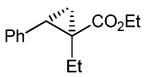
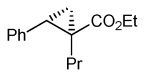
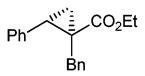
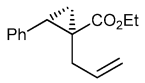
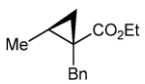
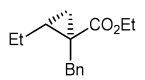
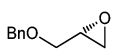
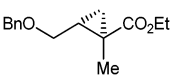
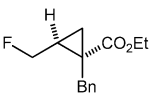
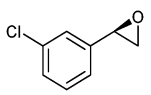
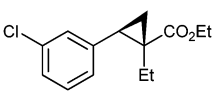
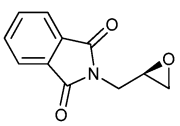
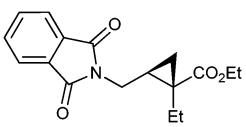
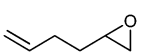
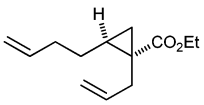
Scheme 1 Stereocontrolled synthesis of a quaternary cyclopropyl ester.

Queen Mary University of London, School of Biological and Chemical Sciences, Mile End Road, London, E1 4NS, UK. E-mail: c.bray@qmul.ac.uk; Fax: +44 (0)20 7882 7427; Tel: +44 (0)20 7882 3271

† Electronic supplementary information (ESI) available: Spectroscopic data along with ^{1}H and ^{13}C NMR spectra for compounds **1a–l** and **2**. See DOI: 10.1039/c0cc01333a

Table 1 Examination of reaction scope[a]



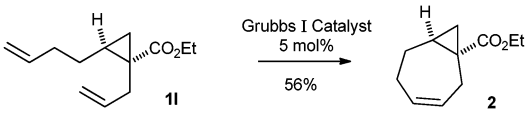
Entry	Epoxide	R′	Cyclopropane		Yield[b] (%)
1		Me		**1a**	95
2		Et		**1b**	97
3		Pr		**1c**	93
4		Bn		**1d**	98
5		Allyl		**1e**	86
6		Bn		**1f**	75
7		Bn		**1g**	76
8		Me		**1h**	78
9		Bn		**1i**	75
10		Et		**1j**	73
11		Et		**1k**	57
12		Allyl		**1l**	86

[a] Reactions carried out with phosphonate (2 equiv.) at 130 °C in DME for 20 h. [b] Percentage isolated yield following column chromatography.

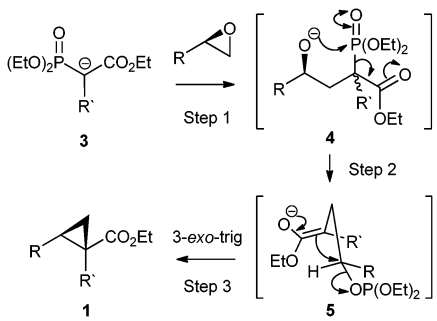
this process. Owing to their volatility, substrates such as (*R*)-propylene oxide and (*S*)-1,2-epoxybutane were potentially challenging, however these were successfully converted to the corresponding α-benzylcyclopropyl esters **1f** and **1g** (entries 6 and 7) albeit in slightly diminished yields to those obtained when using (*S*)-styrene oxide.[11] (*R*)-Benzyl glycidyl ether was uneventfully converted to cyclopropane **1h** (entry 8), which in its debenzylated form[12] has previously been used in the synthesis of cyclopropyl carbocyclic nucleosides containing quaternary stereogenic centres. Epifluorohydrin and (*R*)-3-chlorostyrene oxide also gave the expected cyclopropanes **1i**[13] and **1j** (entries 9 and 10) in good yield. The conversion of (*R*)-*N*-(2,3-epoxypropyl)phthalamide to cyclopropylamine **1k** (entry 11) is of note since Kennewell *et al.* have described how related compounds function as unusual γ-aminobutyric acid analogues with restricted rotation that proved to be potent in GABA receptor binding studies.[14] Epoxides bearing simply alkyl chains were also effectively converted to cyclopropanes *e.g.* **1l** (entry 12), which opens up the possibility of synthesising a range of unusual cyclopropane-containing fatty acids.

Unequivocal evidence of the *syn*-relationship between the alkenyl substituents of cyclopropane **1l** was established by conversion to cycloheptene **2** (Scheme 2) *via* ring-closing metathesis with Grubbs 1st generation catalyst (5 mol%). This process therefore also demonstrates the potential of the present method for the synthesis of (enantiopure) medium-sized rings bearing cyclopropanes.

For the reaction of epoxides with the anion of 2-substituted triethylphoshonoacetates **3**, cyclopropane formation would appear to proceed *via* S_N2-opening of the epoxide ring (Scheme 3, step 1), transfer of $P(O)(OEt)_2$ to the resultant alkoxide of **4** to give **5** (step 2), and finally ring-closure with loss of diethylphosphate (step 3). In reactions involving the triethylphosphonoacetate anion (**3**, R′ = H), Wadsworth and Emmons attributed *trans*-selectivity to initial formation of a mixture of cyclopropane ring geometries followed by equilibration to the thermodynamically more stable *trans*-isomer under the reaction conditions.[1] Barring the unlikely possibility that once formed, the cyclopropane ring reversibly reopens either *via* an ionic or even a radical process, the present work does not support this original hypothesis, but rather, it is consistent with a highly diastereoselective elimination of diethylphosphate during the reaction pathway *i.e.* **5** → **1**. Given that the steric requirements for an ethyl ester and R′ in **5** are not vastly different, this selectivity would not appear to



Scheme 2 Formation of a [5.1.0]-bicyclic ester.



Scheme 3 Reaction pathway for cyclopropane formation.

be solely due to steric interactions but rather, it would imply a more deep seated stereoelectronic effect.[15] We are endeavouring to obtain experimental as well as computational evidence for the origin of this diastereocontrol, including the possible existence of chelated intermediates during the reaction process such as those suggested by Merschaert and Krawczyk.[16,17]

In conclusion, we have demonstrated that quaternary cyclopropyl esters can be formed in high yield using the Wadsworth–Emmons cyclopropanation from readily available epoxides and 2-substituted phosphonoacetates. The stereochemistry of the epoxide is transferred into the newly formed all carbon stereocentre with high diastereocontrol. This control likely arises due to an electronically governed diastereoselective ring-closure rather than an equilibration of the products as was originally suggested by Wadsworth and Emmons. The present method proceeds without the need for hazardous precursors (*e.g.* diazo compounds) or any costly metals or ligands and since the process is under substrate control, laborious optimisation of conditions is not required for each reaction. The Wadsworth–Emmons cyclopropanation might now be considered as one of simplest methods for the synthesis of an all carbon stereocentre.

Notes and references

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2 Examples of Wadsworth–Emmons cyclopropanation are: (*a*) L. Delhaye, A. Merschaert, P. Delbeke and W. Briône, *Org. Process Res. Dev.*, 2007, **11**, 689; (*b*) M. Khurram, N. Qureshi and M. D. Smith, *Chem. Commun.*, 2006, 5006; (*c*) A. Armstrong and J. N. Scutt, *Chem. Commun.*, 2004, 510; (*d*) A. Armstrong and J. N. Scutt, *Org. Lett.*, 2003, **5**, 2331; (*e*) A. K. Singh, M. N. Rao, J. H. Simpson, W. S. Li, J. E. Thornton, D. E. Kuehner and D. J. Kacsur, *Org. Process Res. Dev.*, 2002, **6**, 618; (*f*) T. E. Jacks, H. Nibbe and D. F. Wiemer, *J. Org. Chem.*, 1993, **58**, 4584; (*g*) R. C. Petter, S. Banerjee and S. Englard, *J. Org. Chem.*, 1990, **55**, 3088; (*h*) R. C. Petter, *Tetrahedron Lett.*, 1989, **30**, 399; (*i*) B. J. Fitzsimmons and B. Fraser-Reid, *Tetrahedron*, 1984, **40**, 1279; (*j*) R. G. Ghirardelli, *J. Am. Chem. Soc.*, 1973, **95**, 4987; (*k*) R. A. Izydore and R. G. Ghiradelli, *J. Org. Chem.*, 1973, **38**, 1790; (*l*) I. Tömösközi, *Tetrahedron*, 1966, **22**, 179. For the analogous, but less facile use of phosphoranylidenes, see: (*m*) D. B. Denney, J. J. Vill and M. J. Boskin, *J. Am. Chem. Soc.*, 1962, **84**, 3944. For related approaches, see: ; (*n*) C. Clarke, D. J. Fox, D. S. Pedersen and S. Warren, *Org. Biomol. Chem.*, 2009, **7**, 1329; (*o*) C. Clarke, S. Foussat, D. J. Fox, D. S. Pedersen and S. Warren, *Org. Biomol. Chem.*, 2009, **7**, 1323; (*p*) H. Krawczyk, K. Wąsek and J. Kędzia, *Synthesis*, 2009, 1473; (*q*) H. Krawczyk, K. Wąsek, J. Kędzia, J. Wojciechowski and W. M. Wolf, *Org. Biomol. Chem.*, 2008, **6**, 308; (*r*) D. J. Fox, S. Parris, D. J. Pedersen, C. R. Tyzack and S. Warren, *Org. Biomol. Chem.*, 2006, **4**, 3108.

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7 (*a*) M. Amatore, T. D. Beeson, S. P. Brown and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2009, **48**, 5121; (*b*) O. A. Wong and Y. Shi, *Chem. Rev.*, 2008, **108**, 3958; (*c*) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.

8 (1*R*,2*S*)-Ethyl 1-methyl-2-phenyl-cyclopropanecarboxylate **1a**: to a solution of triethyl 2-phosphonopropionate (0.42 cm^3, 2.00 mmol) in DME (4.0 cm^3) at 25 °C was added *n*-butyllithium (2.5 M, 0.82 cm^3, 2.05 mmol) dropwise over 5 min. (*S*)-Styrene oxide (114 μl, 1.00 mmol) was added in one portion. The reaction was heated to 130 °C for 20 h. The reaction was cooled before sat. aq. NH_4Cl (8 cm^3) was added. The reaction was extracted three times with Et_2O (3 × 20 cm^3). The organic layers were combined, dried over $MgSO_4$ and filtered before the solvent was removed *in vacuo*. The residue was dry loaded onto silica (5 cm^3) and purified by flash column chromatography (4% EtOAc/petrol) to give the title compound **1a** (195 mg, 95%) as colourless oil: $[\alpha]_D$ −142.0 (*c* 1.7, Me_2CO); ν_{max}/cm^{-1} 1714, 1603, 1499, 1454, 1381, 1311, 1240, 1206, 1151, 1112, 1078, 1060, 1026; δ_H (400 MHz, $CDCl_3$) 7.26–7.08 (5H, m, Ph), 4.10 (2H, q, *J* 7.1, OCH_2), 2.73 (1H, dd, *J* 9.2 and 7.0, CH), 1.61 (1H, dd, *J* 9.2 and 4.5, C*H*(H)), 1.21 (3H, t, *J* 7.1, CH_2*Me*), 1.08 (1H, dd, *J* 7.0 and 4.5, CH(*H*)), 0.91 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 175.6, 137.0, 129.3, 128.1, 126.6, 60.7, 31.6, 25.1, 19.9, 14.5, 14.2; *m*/*z* 205.1223 (M + H^+. $C_{13}H_{17}O_2$ requires 205.1223).

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10 The assignment of the *syn*-relationship between the phenyl ring and the methyl group of **1a** was based on ^{1}H NMR spectroscopy where the methylene hydrogens of the ester functionality resonated with a highly diagnostic chemical shift of 4.10 ppm. The corresponding methylene protons of the epimer display a diagnostic upfield shift to 3.74 ppm due to the proximity of the phenyl group. For a detailed explanation of how this, and further diagnostic differences, can be used to distinguish *cis* and *trans*-cyclopropyl esters, see the ESI of ref. 9.

11 We believe that the lower yields are on account of the volatility of the products, which possessed fruity odours.

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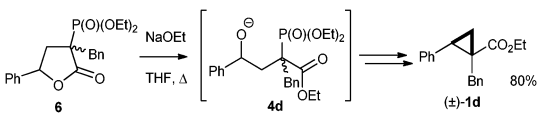
15 On the assumption that initial epoxide ring-opening by the phosphonate anion is not entirely diastereoselective, then these results are consistent with those of Krawczyk and co-workers who demonstrated that a mixture of diastereomers of a range of lactones, such as **6**, converged to give cyclopropanes *e.g.* (±)-**1d** in which the alkyl/aryl substituents are *cis*-oriented, presumably proceeding *via* **4d** on treatment with NaOEt, see ref. 2*q*



16 A 7-membered chelate intermediate has been proposed by Merschaert *et al.* to explain the high diastereoselectivities (>98 : 2) obtained in the synthesis of (*R*,*R*)-2-methylcyclopropanecarboxylic acid where only moderate steric effects are involved, see ref. 2*a*. A closely related 9-membered ring chelate has also been used to explain the high levels of *trans*-stereochemical control seen when cyclopropyl esters are formed when independently prepared analogues of **4** are generated with base, see: ref. 2*q*.

17 There are two examples of 1-(benzotriazol-1-yl)alkyldiphenyl phosphine oxide anions reacting with styrene oxide. This also gave a single diastereomer of the cyclopropane product in which the aryl/alkyl groups are *cis*-oriented, see: A. R. Katrizky, H. Wu, L. Xie and J. Jiang, *J. Heterocycl. Chem.*, 1995, **32**, 595.