acting through inhibition of basic fibroblast growth factor-stimulated endothelial cell proliferation, may be active in diabetic retinopathy [US Dept Health and Human Services, WO 95/08327].

With so many approaches being actively investigated across the world, new therapies for the long-term complications of diabetes are clearly within reach of pharmaceutical companies.

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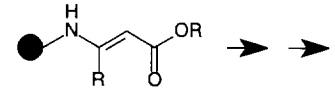
Combinatorial chemistry

Synthesis of dihydropyridines

Combinatorial chemists have rapidly increased the range of chemistry on solid-phase to include a number of classical pharmacophoric series. One such class of compound is the dihydropyridines (DHPs), a structure synonymous with calcium channel blocking activity. Recently workers from Affymax have described a successful synthesis of DHPs on solid-phase [Gordeev, M. F. *et al. J. Org. Chem.* (1996) 61, 924–928]. Using an amino-derivatized resin, formation of an amino crotonate **1** was followed by condensation with a ketoester and an aldehyde to produce the DHP **2**. The route



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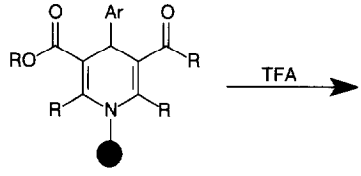

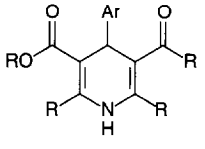

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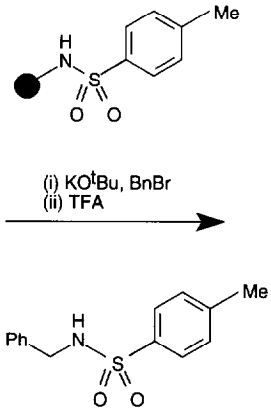
was exemplified by the synthesis of a number of DHPs including the well-known agents nifedipine, nitrendipine and nimodipine.

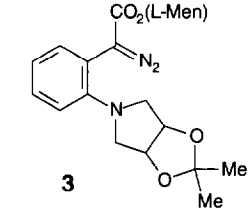
Linkers for increased diversity

Linkers are a particularly effective way of enhancing combinatorial library diversity, as the ability to reveal a new functionality following cleavage from the solid phase may readily generate new classes of structure. A novel use of the ubiquitous Rink resin has been described that yields sulphonamides following acid-catalysed cleavage [Spear, K.L. *et al. Tetrahedron Lett.* (1996) 37, 1145–1148]. The authors demonstrated that the sulphonamide functionality was compatible with N-alkylation and the use of Heck and Stille couplings, and this is likely to be a valuable extension of the utility of this solid phase.



Reaction optimization

Combinatorial chemistry is being widely used to generate new compounds for screening and drug discovery. However, it is only now beginning to be used as a method for reaction optimization, and thus for process development. Burgess and coworkers' reactions [*Angew. Chem. Int. Ed. Engl.* (1996) 35, 220–222] have described the use of a combinatorial approach to the discovery of new metal-based catalysts for carbene C-H insertion. Some 96 different reaction conditions were examined in microtitre plate format to convert compound **3** into **4**. HPLC was used to derive both chemical yield and stereoselectivity data that assisted the choice of optimum reaction conditions.



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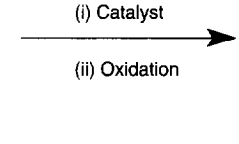

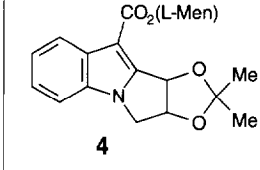

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About *Monitor*..... *Therapeutic Profiles*

This month's *Monitor* includes the first in a series of *Profiles* on specific disease states which aims to review succinctly the state-of-the-art in an especial therapeutic area and provide an insight to the likely direction of future research. We welcome offers of contributions; brief outlines of proposed *Therapeutic Profiles* should be directed to: Dr Andrew W. Lloyd, *Monitor* Editor, Department of Pharmacy, University of Brighton, Moulsecoomb, Brighton, BN2 4GJ UK. tel: +44 1273 642049, fax: +44 1273 679333, e-mail: a.w.lloyd@brighton.ac.uk