Monitor

Monitor provides an insight into the latest developments in the pharmaceutical and biotechnology industries. ***Chemistry*** examines and summarises recent presentations and publications in medicinal chemistry in the form of expert overviews of their biological and chemical significance, while ***Profiles*** provides commentaries on promising lines of research, new molecular targets and technologies. ***Biology*** reports on new significant breakthroughs in the field of biology and their relevance to drug discovery. ***Business*** reports on the latest patents and collaborations, and ***People*** provides information on the most recent personnel changes within the drug discovery industry.

Chemistry

Molecules

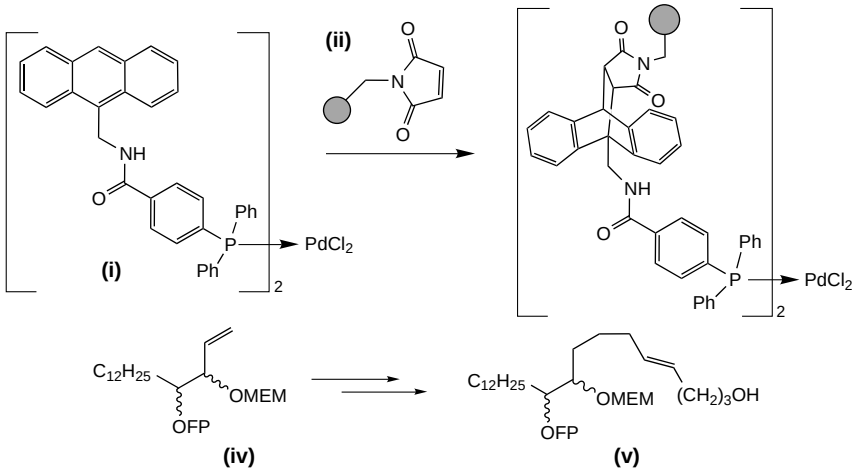
New solution-phase parallel synthesis methods

Solution-phase chemistry has largely supplanted solid-phase chemistry as the method of choice for parallel synthesis of small organic molecules. However, there are many powerful organic reactions that have not been successfully adapted to a solution-phase parallel format. In addition, much of the power of solid-phase synthesis (i.e. the split/mix technique and ease of purification) has been lost. Recently, some new solution-phase techniques have been developed that address some of these issues.

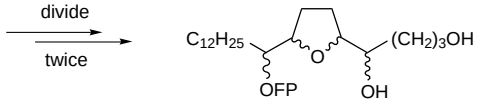
Purification facilitated by anthracene-tagging

All synthetic chemists know that clean reactions, with no byproducts or excess reagents to remove from the reaction mixture, are the exception to the rule. The purification techniques used historically, such as aqueous extractions and chromatography, are not very amenable to a parallel format. The Suzuki reaction is a powerful choice for the formation of aryl–aryl bonds, but so far its use in parallel synthesis has been limited because so many undesired components must be removed from the reaction mixture: the palladium catalyst, unreacted starting materials and side products. Parlow and coworkers have recently reported on the adaptation of Suzuki couplings to a polymer-assisted solution-phase (PASP) format [1].

Adaptation of the Suzuki coupling to a PASP format relied on a strategy where some of the undesired components in the final reaction mixture were tagged with anthracene. The anthracene-tagged components were removed from the mixture by chemoselective Diels-Alder reaction with PS-maleimide resin. Thus, an anthracene-tagged palladium catalyst, compound **i**, was synthesized. Catalyst **i** proved to affect the Suzuki coupling efficiently between numerous aryl bromides and arylboronic acids to produce biaryl compounds. Upon completion of the



Each of the 4 isomers tagged with a different fluorinated protecting group (FP)
OMEM = methoxyethoxymethyl



(iii)

Four mixtures of four, separable based on the fluorous tag

coupling reaction, PS-maleimide resin **ii** was added. Diels-Alder reaction of **i** and **ii**, followed by filtration, removed the catalyst from the reaction mixture. An anthracene-tagged boronic acid was used in a similar fashion to remove excess aryl bromide. Polymer-bound carbonate was used as a base, a strategy that replaced the usual aqueous workup; the polymer-bound carbonate also effectively scavenged excess boronic acid and other borane-containing byproducts. Workup after scavenging consisted of filtration and evaporation of solvents. This anthracene-tagging strategy could conceivably be applied to many other organic transformations.

Solution-phase split/mix synthesis facilitated by fluorous tagging

For the combinatorial chemist, the split/mix technique is one of the strengths of solid-phase synthesis: a 10x10 split/mix sequence can yield 100 compounds from only 20 synthetic manipulations. Using various techniques, active compounds can be deconvoluted relatively easily. In recent years, the emphasis has shifted to solution-phase parallel synthesis, and the power of the split/mix technique has been lost. Recently, Curran and coworkers demonstrated that the use of fluorine-tagged protecting groups can facilitate solution-phase split/mix synthesis [2] and reported an elegant example of this technique to synthesize 16 stereoisomers of the natural product (+)-murisolin.

All three known murisolins possess the same stereochemistry about a hydroxy butenolide. The split/mix strategy was utilized to obtain all 16 possible stereoisomers of the dihydroxy tetrahydrofuran fragment **iii** (represented here in its protected form). The synthetic transformations employed were straightforward and included hydroboration/oxidation, Negishi coupling, Shi epoxidation and Mitsunobu inversion. The advantage of the present strategy is the use of the split/mix technique in solution phase. In pre-mix stage, all four isomers of the protected diol **iv** were synthesized. Each isomer was tagged with a different fluorous protecting group, with the fluorine content of the tag serving as a code for the configuration at the hydroxyl positions. The four isomers of **iv** were mixed together and carried through several synthetic steps to intermediate **v**, which is still a single mixture of four isomers at this point. Mixture **v** was divided in two, and Shi epoxidation with enantiomeric catalysts was performed. These two epoxidation reaction mixtures were each split in two, and one was subjected to Mitsunobu inversion. Ultimately, four mixtures of four isomers of fragment **iii** were obtained.

The mixtures of fragment **iii** were carried on to the final natural product murisolin in parallel fashion, so four mixtures of four isomers of murisolin were obtained. Each mixture was deconvoluted by chromatography on FluoroFlash silica gel. At this stage, the individual isomers separate based on the fluorine content of their tags. The fluorous tag is then removed. The identity of each stereoisomer is provided by its synthetic series coupled with its elution order on demixing. Using this strategy, all 16 isomers of murisolin were synthesized in a total of 39 synthetic steps, followed by four fluorous phase columns to demix. If performed in traditional solution-phase parallel fashion, this would have required 156 synthetic steps and 16 purification steps. If proven to be generally applicable, this technique could potentially bring the power of the split/mix technique to solution-phase chemistry, facilitating the synthesis and deconvolution of mixtures of compounds without resorting to synthesis "on-the-bead".

1 Lan, P. *et al.* (2003) Polymer-assisted solution-phase (PASP) Suzuki couplings employing an anthracene-tagged palladium catalyst. *J. Org. Chem.* 68, 9678–9686

2 Zhang, Q. *et al.* (2004) Fluorous mixture synthesis of stereoisomer libraries: total syntheses of (+)-murisolin and 15 diastereoisomers. *J. Am. Chem. Soc.* 126, 36–37

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Biology

Cancer Biology

A new cancer drug in the pipeline?

Antibodies directed against growth factor receptor molecules possess strong therapeutic potential in the treatment of cancer. The anti-Her2 antibody Trastuzumab (Herzeptin) is currently used for the treatment of metastatic breast cancer. Evidence suggests that resistance to Herzeptin in some forms of breast cancer could be due to activation of insulin-like growth factor I receptor (IGF-IR) signalling. The IGF-IR activates mitogenic and antiapoptotic pathways and has been shown to play a pivotal role in the development and progression of cancer. Apart from breast cancer, overexpression of the IGF-IR can be observed in several tumour types and is correlated with bad prognosis. Burtrum *et al.* now report the engineering of a new fully human monoclonal antibody directed against IGF-IR [1].

A candidate, 2F8, for optimal binding to IGF-IR and competitive ligand locking was identified by screening a naïve human Fab phage display library. The light-chain shuffling technique was used to improve binding properties. The resulting Fab (A12) was chosen for further investigation and converted into IgG.

Western blot analysis and cell culture experiments revealed inhibition of IGF-IR induced mitogenesis and cell proliferation. Mechanistically, A12 was shown to prevent binding of receptor ligands IGF-I and IGF-II and to induce receptor internalization and degradation, thus blocking downstream signalling cascades. The first *in vivo* data from xenograft tumour models in mice show >70% tumour growth inhibition and no detectable toxicity.

The published data suggest that the new IGF-IR antibody A12 might be a good candidate for a broad-spectrum anticancer drug. Clinical investigation will show if it lives up to the promise.

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