CHAPTER 3

THE FUTURE OF PURIFICATION

INTRODUCTION

The essence of research is to seek answers wherever there are questions. Regardless of what the answers are the experiments to be conducted must be carried out with utmost care. For this, one must ensure that the quality of the reactants used and the products obtained are of the highest possible purity. In general terms, one can broadly categorise experimental chemistry and biological chemistry into the following areas:

Isolation and identification of substances (natural products from nature, protein purification and characterisation, etc).

Synthesis of substances (organic, or inorganic in nature; these substances may be known substances or new compounds).

Analysis of substances (this is a key process in the identification of new or known chemical and biological substances. Methods of analysis include spectroscopic methods, derivatisation and sequencing methods).

Measurements of particular properties of a compound or substance (enzyme kinetics, reaction kinetics, FACS, fluorescence-activated cell sorting, assay).

Impressive and sophisticated strategies, in the form of new reagents, catalysts and chemical transformations, are currently available for the syntheses of molecules. In recent years there is a deviation in focus from developing new synthetic routes and reactions to improving methods for carrying out reactions. In particular, traditional reactions can be carried out in new ways such that those efficiencies of reactions are greatly improved. The efficiencies of reactions can be measured in terms of the yields of the desired product(s), or in terms of the time taken to obtain the desired product(s). Some of the 'new' lateral ways of thinking to improve efficiencies of reactions recognise the importance of purification of products in the planning of a synthetic sequence. Thus methods such as solid phase synthesis, fluorous chemistry as well as the use of ionic liquids minimise purification procedures and thus improve the ability to rapidly access pure compounds. These techniques also contribute to the efficiencies of reactions in terms of yields. In looking ahead to synthesis in the 21st century, a brief outline of the key aspects of these techniques are presented. In time many commercially available chemicals will be prepared using methods described in this chapter, and knowledge of these now should be useful to the experimenter. Some of these compounds (e.g. peptides) have already been synthesised by such methods (e.g. SPPS, see below).

SOLID PHASE SYNTHESIS

Solid phase synthesis (SPS) has emerged as an important methodology for the rapid and efficient synthesis of molecules. The ease of work-up and purification procedures in solid phase as compared to solution phase chemistry, as well as the scope for combinatorial chemistry provides impetus for further development in this field. The earliest studies on solid phase chemistry were focused on solid phase peptide synthesis (SPPS). The concept of carrying out reactions on a polymer support as distinct to reactants in solution, was conceived by R.B. Merrifield who received the Nobel Prize in Chemistry in 1984 for his pioneering work. However since the mid 1990's, advances in solid phase chemistry have moved beyond the routine (often robotic) synthesis of small to medium peptides and oligonucleotides. SPOS (solid phase organic synthesis) has gained much prominence due to the wealth of compounds (combinatorial libraries) that can be synthesised rapidly. This is especially important for pharmaceutical companies, screening for compounds with certain biological profiles or for chemical companies, screening for new catalysts or reagents. In SPOS, it is envisaged that difficult reactions can be driven to completion by using a large excess of reagents, which are easily removed by filtration. Furthermore, expensive reagents in the form of catalysts or chiral auxiliaries may be recycled easily if supported on a polymer and hence solid phase reactions provide economy in terms of costs and labour. Another strength of SPS is the ease in purification procedures which generally involves filtration of polymer supported products (solid) from soluble

reaction components (liquid) in what is effectively a solid-liquid extraction. In the final step of the synthetic sequence, the desired product is then cleaved from the polymer support.
Despite the relative infancy in the development of solid phase reactions, a wide range of functionalised resins are commercially available. The main uses of these functionalised resins can be roughly classified as follows:

SOLID PHASE PEPTIDE SYNTHESIS (SPPS)

Extensive studies on the synthesis of peptides on solid phase have been carried out, so much so that the technique of SPPS can be reliably and routinely used for the synthesis of short peptides by novices in the field. A large number of resins and reagents have been developed specifically for this purpose, and much is known on problems and avoidance of racemisation, difficult couplings, compatibility of reagents and solvents. Methods for monitoring the success of coupling reactions are available. Automated synthesisers are available commercially (e.g. from Protein Technologies, Rainin Inst Inc, Tuscon AZ; protan@dakotacom.net) which can carry out as many as a dozen polypeptide syntheses simultaneously. The most satisfactory chemistry currently used is Fmoc (9-fluorenylmethoxycarbonyl) chemistry whereby the amino group of the individual amino acid residues is protected as the Fmoc. A large number of Fmoc-amino acids are commercially available as well as polymer resins to which the specific Fmoc-amino acid (which will eventually become the carboxy terminal residue of the peptide) is attached. With automated synthesisers, the solvent used is *N*-methylpyrrolidone and washings are carried out with dimethylformamide. Deprotection of the polypeptide is carried out with anhydrous trifluoroacetic acid (TFA). A cycle for one residue varies with the residue but can take an hour or more. This means that 70-80 mer polypeptides could take more than a week to prepare. This is not a serious drawback because several different polypeptides can be synthesised simultaneously. The success of the synthesis is dependent on the amino acid sequence since there are some twenty or more different amino acids and the facility of forming a peptide bond varies with the pair of residues invloved. However, generally 70 to 80 mers are routinely prepared, and if the sequence is favourable, up to 120 mer polypeptides can be synthesised. After deprotection with TFA the polypeptide is usually purified by HPLC using a C18 column with reverse phase chromatography. There are many commercial firms that will supply custom made polypeptides at a price depending on the degree of purity required.

SOLID PHASE DEOXYRIBONUCLEOTIDE SYNTHESIS

The need for oligodeoxyribonucleotides mainly as primers for the preparation of deoxyribonucleic acids (DNA) and for DNA sequencing has resulted in considerable developments in oligodeoxyribonucleotide synthesis. The solid phase procedure is the method commonly used. Automated synthesisers are commercially avalable, but with the increase in the number of firms which will provide custom made oligodeoxyribonucleotides, it is often not economical to purchase a synthesiser to make one's own oligodeoxyribonucleotides. Unlike in polypeptide synthesis where there are some twenty different residues to "string" together, in DNA synthesis there are only four deoxyribonucleotides, consequently there is usually little difficulty is synthesising 100 mers in quantities from 10 μg to 10 milligrams of material. The deprotected deoxyribonucleic acid which is separated from the solid support is purified on an anion exchange column followed by reverse phase HPLC using C8 to C18 columns for desalting. As for the polypeptides, the cost of DNA will depend on the purification level required.

SOLID PHASE OLIGOSACCHARIDE SYNTHESIS

Although automated solid phase peptide and oligonucleotide synthetic procedures are well established, automated solid phase oligosaccharide synthesis is considerably more difficult. The current awareness of the importance of polysaccharides as surface recognition molecules and in glycoproteins and glycolipids has prompted much interest in oligosaccharide synthesis and some progress has been made (see Kochetkov *Russ Chem Rev* **69** 795 *2000;* Ito and Manabe *Curr Opin Chem Biol* **2** 701 *1998*; Seeberger and Danishefsky *Acc Chem Res* **31** 685 *1998*). A general method for automated oligosaccharide synthesis is not as yet availble. An example of an automated synthesis of *specific* glycosides has been reported by Seeberger (*Science* **291** 1523 *2001*; see also Houlton *Chem Br* **38** (**4**) 46 *2002*).

SOLID PHASE ORGANIC SYNTHESIS (SPOS)

At the time of writing this book, SPOS is in an area of relative infancy but has considerable potential. One of the main difficulties in SPOS lies in the lack of techniques available to monitor reactions carried out on polymer supports. Unlike reactions in solution phase, reactions on solid support cannot be monitored with relative ease and this has hindered the progress as well as the efficacy of solid supported synthesis of small non-peptidic molecules. Despite these difficulties, a large body of studies is available for SPOS. Recent reviews incorporate

information on the types of reactions that can be carried out, as well as outline the difficulties and differences with SP (solid phase) reactions as compared with their solution phase counterparts (see bibliography). An interesting application of such procedures is the synthesis of polymeric esters (e.g. polycaprolactones, polyhydroxybutyrates, polylactates) and starch- and cellulose- like polymers using a plasticised starch support. These have been useful for making biodegradable trays and containers for foodstuffs (BenBrahim *Chem Br* **38(4)** 40 *2002*).

POLYMER SUPPORTED REACTANTS

These have become of increasing importance in synthesis and a broad classification of polymer supported reactants are as follows: Polymer bound bases (e.g. dimethylaminopyridine, morpholine, piperidine); Polymer supported catalysts (e.g. Grubbs catalyst for metathesis reactions, palladium for hydrogenation reactions, tributylmethylammonium chloride for phase transfer reactions); Polymer supported condensation reagents {e.g. DEAD (diethyl azodicarboxylate) for Mitsonobu reactions, DEC [1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride] {or EDCI [1-ethyl-3-(3-di-methylaminopropyl) carbodiimide HCl]} for peptide synthesis, HOBt (1-hydroxybenzotriazole) for peptide synthesis; Polymer supported oxidizing agents (e.g. osmium tetroxide, perruthenate, pyridinium chlorochromate); Polymer supported reducing agents (e.g. borohydride, tributyltin fluoride); Polymer supported phosphines (for miscellaneous applications depending on the structure) and so on. Commercially available polymer supported reactants are identified in Chapters 4 and 5 of this book.

SCAVENGER RESINS

Though not as extensively utilised as polymer supported reactants, the use of resins to clean up reactions is gaining favour. The type of commercially available scavenger resins are electrophilic scavenger resins (e.g. benzaldehyde derivatised resins to scavenge amines; isocyanate resins to scavenge amines, anilines and hydrazines; tosyl chloride resins to scavenge nucleophiles) and nucleophilic scavenger resins (e.g. diethylenetriamine resins to scavenge acids, acid chlorides, anhydrides; sulfonyl amide resins to scavenge acids, acid chlorides, aldehydes, isocyanates and chloroformates).

RESIN SUPPORT

The common resin matrixes comprise of polystyrene crosslinked with divinylbenzene, graft polymers of polystyrene-polyethylene glycol (PS-PEG) and polyethyleneglycol acrylamide (PEGA) composite resins. For each type of resin matrixes, a range of functionalised polymer supports are available. In addition, a number of these resins are available with different percentage of crosslinking as well as a range of loadings of the reactive functionality. Polystyrene based resins are the most extensively used. Unfortunately these resins do not swell, i.e. do not imbibe water, in polar solvents such as water and methanol and thus cannot be used for carrying out reactions in these solvents. In contrast grafted PS-PEG resins swell in a range of solvents from toluene to water. Examples of grafted PS-PEG resins are NovaSyn® TG and NovaGel® resins. As the success of transformations to be carried out on SPOS depends in part on the swelling properties as well as the robustness of the resin, the choice of resin matrix to be used must be carefully considered. The swelling properties of a number of resin types in a variety of solvents have been documented (see NovaBiochem catalog and also Santini, Griffith and Qi *Tetrahedron Lett* **39** 8951 *1998*). For example, the swelling of a polystyrene resin in DMF is 3 mL/g of resin as compared to that in dichloromethane which is 7 mL/g of resin. It is thought that swelling of resins in the order of greater than 4 mL/g constitutes a good solvent, between 2-4 mL/g a moderate solvent and that less than 2 mL/g a poor solvent choice for carrying out solid phase reactions.
Lightly crosslinked resins are less robust but have greater ability to swell in appropriate solvents. Typically a 1-2% crosslinked divinyl benzene polystyrene resin is employed in organic synthesis.

An extensive list of the commercially available resins is available from Sigma-Aldrich (www.sigmaaldrich.com), Novabiochem (www.novabiochem.com), Fluka and other chemical companies. Sigma-Aldrich and Novabiochem have excellent catalogs. In addition, the Novabiochem catalog and website are a rich source of useful technical information.

CHOICE OF RESIN FOR SPOS

There is a large range of resins available for SPOS. These resins are derivatised polymer supports with a range of linkers. The roles of linkers are (i) to provide point(s) of attachment for the tethered molecule, akin to a solid supported protecting group(s), (ii) to provide distance from the polymeric backbone in order to minimise interactions with the backbone, (iii) to enable cleavage of product molecules under conditions compatible with the stability of the molecules and the reaction conditions employed for chemical transformations. Hence in order to

choose an appropriate resin for use in SPOS, one would need to consider the nature of the attachment of the reactant molecule onto the solid support (e.g. in order to tether the carboxy group in a reactant as an ester linkage on a solid support, one may choose to use a hydroxy functionalised linker), the stability of the resin under conditions employed in the chemical transformations (e.g. issues of orthogonality - will the conditions utilised cause premature cleavage of the linker or premature cleavage of the products?), the solvents and reactants needed in the transformations (e.g. will the solvents swell the resin?), conditions of cleavage of products (e.g. will this cause racemisation or rearrangement of the product?), the functionality of the resultant product after cleavage (e.g. will cleavage of the product result in a residual functionality in the molecule?) and so on. Linkers which leave no residual functionalities in the products upon cleavage are known as *traceless* linkers and those which need to be activated in order to be cleaved are known as *safety catch* linkers. A fascinating array of linkers (commercial or otherwise) is available and some excellent reviews are cited in the bibliography at the end of this chapter.

COMBINATORIAL CHEMISTRY

The major impetus for the development of solid phase synthesis centers around applications in combinatorial chemistry. The notion that new drug leads and catalysts can be discovered in a high throughput fashion has been demonstrated many times over as is evidenced from the number of publications that have arisen (see references at the end of this chapter). A number of approaches to combinatorial chemistry exist. These include the split-mix method, serial techniques and parallel methods to generate libraries of compounds. The advances in combinatorial chemistry are also accompanied by sophisticated methods in deconvolution and identification of compounds from libraries. In a number of cases, innovative hardware and software has been developed for these purposes.

Depending on the size of the combinatorial library to be generated as well as the scale of the reactions to be carried out, a wide range of specialised glassware and equipment are commercially available. For example, in order to carry out parallel combinatorial synthesis, reaction stations equipped with temperature and stirring control are available from a number of sources (e.g. www.fisher.co.uk; www.radleys.com; www.sigmaaldrich.com). These reaction stations are readily adapted, using appropriate modules, for conditions under reflux or under inert atmosphere. For automated synthesis of large libraries of compounds, reactions can be carried out using reaction blocks on microtiter plates.

Ready to use CombiKits™ which contain a variety of pre-weighed building blocks are available from Aldrich Chemical Company.

MONITORING SOLID PHASE REACTIONS

This remains the bane of solid phase reactions. Unlike solution phase reactions, where the progress of reactions can be monitored rapidly *via* TLC, GC or HPLC methods, procedures for the rapid monitoring of progress in solid phase reactions are limited. Although a number of spectroscopic methods have been developed for direct monitoring of reactions on solid supports, these methods usually require specialised equipment, not routinely available in chemical laboratories. These methods include on-bead IR analysis (e.g. Huber et al. *Anal Chim Acta* **393** 213 *1999*; Yan and Gremlich *J Chromatogr, B.* **725** 91 *1999*; Yan et al. *J Org Chem* **60** 5736 *1995*) and solid state magic angle spinning NMR techniques (e.g. Warrass and Lippens *J Org Chem* **65** 2946 *2000*; Rousselot-Pailley, Ede and Lippens *J. Comb. Chem.* **3** 559 *2001*).

The most common methods for monitoring solid phase reactions utilized in normal research laboratories are:

Infrared analysis of resin

This is a destructive method in which the resin is ground and pelleted as a KBr disc and analysed by FT-IR analysis. This method works best for systems where distinct functional group transformations (C=O, C-OH, C=C, etc) are expected. No special equipment is needed.

Qualitative and quantitative analyses

There are a number of colour or UV tests which are available for monitoring the presence or absence of certain functional groups. Although some of these tests are routinely used for the quantitative analysis of functional groups in solution phase, the quantification on solid phase is less than reliable. An exception to this is the Fmoc (9-fluorenylmethoxycarbonyl) assay, which is routinely used for quantification of coupling in SPPS using Fmoc amino acids. It should also be noted that the generality of some of these colour tests on a variety of solid phase resins is not known and hence these tests serve only as a *guide* to functional group identification. Some (not an exhaustive list) of the reported methods of analyses are outlined below.

DETECTION OF REACTIVE GROUPS ON RESINS

Detection of hydroxy groups on resin

A method in which the resin is treated with cyanuric chloride (trichlorotriazine, TCT) in DMF followed by a nucleophilic dye (AliR or Mordant Orange 1, beads appear red in the presence of hydroxyl groups, or with fuschin, beads appear fuschia, or with fluorescein, they become fluorescent) has been reported (Attardi and Taddei *Tetrahedron Lett* **42** 2927 *2001*; Attardi, Falchi and Taddei *Tetrahedron Lett* **41** 7395 *2001*). Another colorimetric test for the detection of polymer supported tertiary alcohols utilizes the conversion of the alcohols to the polymer supported diphenylsilylchloride ether, followed by subsequent treatment with methyl red. The beads form a readily distinguishable orange/red colour. The test is also positive for the hydroxy Wang resin and the aminomethylpolystyrene resin [Burkett, Brown and Meloni *Tetrahedron Lett* **42** 5773 *2001*]. Alternatively the conversion of polymer supported alcohols to the tosylate followed by displacement by *p*-nitrobenzylpyridine (PNBP) gives a strongly coloured salt upon treatment with bases such as piperidine, followed by gentle heating [Kuisle et al. *Tetrahedron* **55** 14807 *1999*].

Detection of aldehyde groups on resin

The use of an acidic solution of *p*-anisaldehyde in ethanol to detect aldehyde functionalities on polystyrene polymer supports has been reported (beads are treated with a freshly made solution of *p*-anisaldehyde (2.55 mL), ethanol (88 mL), sulfuric acid (9 mL), acetic acid (1 mL) and heated at 110°C for 4 min). The colour of the beads depends on the percentage of CHO content such that at 0% of CHO groups, the beads are colourless, ~50% CHO content, the beads appear red and at 98% CHO the beads appear burgundy [Vázquez and Albericio *Tetrahedron Lett* **42** 6691 *2001*]. A different approach utilises 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole (Purpald) as the visualizing agent for CHO groups. Resins containing aldehyde functionalities turn dark brown to purple after a 5 min reaction followed by a 10 minute air oxidation [Cournoyer et al. *J Comb Chem* **4** 120 *2002*].

Detection of carboxy groups on resin

The presence of a COOH functionality on a polystyrene resin can be detected using a 0.25% solution of malachite green-oxalate in ethanol in the presence of a drop of triethylamine. Beads with COOH functionalities are coloured dark green or appear as clear gel beads [Attardi, Porcu and Taddei *Tetrahedron Lett* **41** 7391 *2000*].

Detection of amino groups on resin

The methods for the detection of amine functional groups are well established. For example the Kaiser test can be used to detect the presence of amine groups on resins (blue colour is observed). In the Kaiser test, two reagents are prepared. Reagent 1 comprises of a mixture of two solutions: A and B. A is a solution of phenol in absolute ethanol (40g of phenol in 10 mL of absolute ethanol, followed by treatment of this clear solution with 4g of Amberlite mixed bed resin MB-3 for 45 mins. The solution is then filtered.). Solution B is made up of 65 mg of KCN in 100 mL water; 2 mL of this solution is diluted to 100 mL of freshly distilled pyridine. The solution is then stirred with 4 g of Amberlite mixed-bed resin MB-3 and filtered. Solutions A and B are then mixed. Reagent 2 is a solution of ninhydrin (2.5g) in absolute ethanol (50 mL). For a qualitative Kaiser test, 6 drops of reagent 1 and 2 drops of reagent 2 are added to the well washed dried resin (2-5 mg) and mixed, followed by heating to 100°C for 4-6 min. A method for the quantitative determination of amino groups using this test has also been reported [Sarin et al. *Anal Biochem* **117** 147 *1981*]. It is however known that the Kaiser test does not give a positive test with a secondary amino acid such as proline or some 'unnatural' amino acids. In addition some deprotected amino acids (Ser, Asn, Asp) do not show the expected intense blue colour typical of free primary amino groups.

A test for secondary amines (e.g. proline) is the Chloranil test (1 drop of a 2% acetaldehyde solution in DMF, followed by one drop of a 2% solution of *p*-chloranil in DMF, leave for 5 mins). A positive test gives blue stained beads.

Other tests for the detection of amino functionalities on solid supports include the TNBS (2,4,6-trinitrobenzenesulfonic acid, picrylsulfonic acid) [Hancock and Battersby *Anal Biochem* **71** 260 *1976*], the DABITC [Shah et al. *Anal. Commun.* **34** 325 *1997*] and the NF31 [Madder et al. *Eur J Org Chem* 2787 *1999*] tests.

Detection of thiol groups on resin

For quantitative analysis of solid supported thiol residues on free macroporous or PEG grafts, Ellman's reagent has been used [5,5'-dithio-*bis*-(2-nitrobenzoic acid]. However only qualitative information can be gained using lightly crosslinked polystyrene resins [Badyal et al. *Tetrahedron Lett* **42** 8531 *2001*].

Fmoc assay

This is a very important and well tested method for the quantitative determination of loading of Fmoc protected compounds particularly that of Fmoc (fluorenylmethoxycarbonyl) amino acids on solid support. Fmoc groups can

be readily deprotected in the presence of base. Generally, in the deprotection and quantification procedures, a known amount of resin is treated with 20% piperidine in DMF at room temperature for 30 mins. The resin is washed with more DMF and the pooled filtrates are combined in a volumetric flask and made up to an accurate volume (e.g. to 10 mL) with more DMF. The UV absorbance at 301 nm of the piperidine-dibenzofulvene adduct which is formed can then be measured against a blank solution of piperidine in DMF [Meienhofer et al. *Int J Pept Protein Res* **13** 35 *1979*]. The loading **L** is then determined using the equation :

$$\mathbf{L} = \frac{\text{(Absorbance value) x (Solution volume in litres)}}{\text{7.8 x (Weight of resin in mg)}}$$

IONIC LIQUIDS

Ionic liquids are organic or inorganic salts that are liquid at room or reaction temperatures. Although ionic liquids are themselves not new discoveries (e.g. the ionic liquid $[EtNH_3]$ $[NO_3]$ was described in 1914), the use of ionic liquids in synthesis is only recent. In particular, the potential applications of ionic liquids as solvents in synthesis and in catalysis have recently been realised. The physical properties of ionic liquids make them unique solvents for synthesis. For example, ionic liquids are good solvents for both organic and inorganic substances and hence can be used to bring reagents into the same phase for reaction. Ionic liquids are also immiscible with a number of organic solvents and thus provide a non-aqueous, polar alternative for two-phase extraction systems. As ionic liquids are non-volatile, they can be used in high vacuum systems without the possibility of loss or contaminants. In addition, this also facilitates the isolation of products as the products can be distilled from the ionic liquid or alternatively extracted with an organic solvent that is immiscible with the ionic liquid. Although ionic liquids are frequently composed of poorly coordinating ions, they are highly polar which are important characteristics in the activation of catalysts.
Commonly used ionic liquids are *N*-alkylpyridinium, *N,N'*-dialkylimidazolium, alkylammonium and alkylphosphonium salts.

To date a number of reactions have been carried out in ionic liquids [for examples, see Dell'Anna et al. *J Chem Soc, Chem Commun* 434 *2002*; Nara, Harjani and Salunkhe *Tetrahedron Lett* **43** 1127 *2002*; Semeril et al. *J Chem Soc Chem Commun* 146 *2002*; Buijsman, van Vuuren and Sterrenburg *Org Lett* **3** 3785 *2001*]. These include Diels-Alder reactions, transition-metal mediated catalysis, e.g. Heck and Suzuki coupling reactions, and olefin metathesis reactions. An example of ionic liquid acceleration of reactions carried out on solid phase is given by Revell and Ganesan [*Org Lett* **4** 3071 *2002*].

FLUOROUS CHEMISTRY

This new approach to synthesis was introduced by Curran early in 1997 and involves the attachment of fluorous phase labels to substrates such that the subsequent fluorinated products can be extracted into the fluorous phase. For example in liquid-liquid extractions (typical work-up procedures), a three-phase extraction is now possible (organic, fluorous and aqueous phases). As organic and inorganic compounds have little or no tendency to dissolve in highly fluorinated solvents and compounds, phase labeling a compound as fluorous will enable successful extraction into the fluorous phase. However in order to carry out homogenous reactions with these fluorinated compounds, organic solvents with a good dissolving power for fluorous compounds or miscible organic and fluorous solvents can be used. Alternatively organic solvents with a few fluorine atoms e.g. trifluoroethanol, benzotrifluoride ('hybrid solvents') will dissolve both organic and fluorous compounds. A number of synthetic applications utilising fluorous chemistry have been reported in the literature. [For examples, see Schneider and Bannwarth *Helv Chim Acta* **84** 735 *2001*; Galante, Lhoste and Sinou *Tetrahedron Lett* **42** 5425 *2001*; Studer and Curran *Tetrahedron* **53** 6681 *1997*; Studer et al. *J Org Chem* **62** 2917 *1997*; Crich and Neelamkavil *Tetrahedron* **58** 3865 *2002*].

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