Synthesis of Alkaloid Natural Products Using Solid-Supported Reagents and Scavengers

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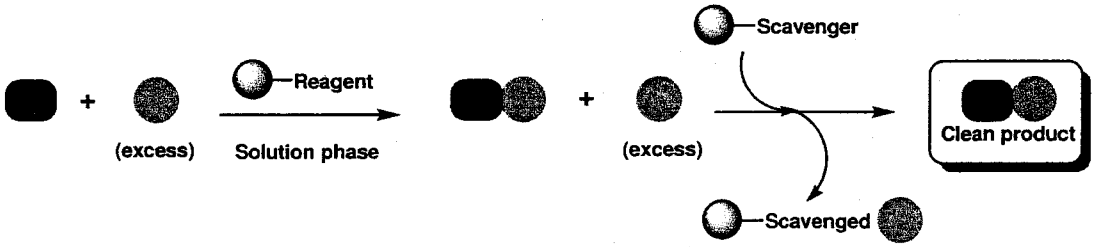
Abstract: Supported reagents and scavengers have become key tools for the synthesis of biologically important molecular entities. The complexity of the target molecules attainable and the synthetic flexibility afforded by these systems now rivals any solution phase approach whilst offering the added advantage of rapid purification and work-up. This short review highlights the application of these immobilized reagents to the preparation of alkaloid natural products.

The phenomenal rate of change in organic synthesis is, for the most part, being driven by the demand for more efficient and sustainable chemical manufacturing processes [1]. Major advances in enabling technologies such as automation, informatics software and robotics are rapidly becoming standard features in chemical synthesis. The new generation of tools emerging from these technologies, such as microfluidic devices and the use of microwave dielectric heating, means that organic synthesis can be greatly accelerated resulting in enhanced compound generation. In addition, these approaches are required by the chemical industry to be complementary to, and to capitalise on, opportunities created by high-throughput biological screening.

work using these immobilized systems has been to devise practical solutions for the clean preparation of drug substances and to synthesise more complex natural products in multi-step sequences [4].

Using immobilized reagents and scavengers as well as the catch-and-release concept when required, avoids many of the conventional purification techniques, such as chromatography, distillation and crystallization: techniques that require considerable practical experience and skill. The illustration shown in scheme **1** demonstrates how clean products can be obtained from a reaction, when all that is required in terms of purification is the filtration of the reaction mixture to remove the supported reagent. By-products or excess reactants can be scavenged by the



Scheme 1.

Natural products, and particularly the alkaloids, have provided an intellectual stimulus for many drug discovery programmes over the years. Materials nature has already optimised often provide the basis for a considered starting point in that process. The unique properties of alkaloid natural products in controlling cell cycles and other biological events makes them invaluable probes for mechanistic studies [2]. Conscious of this, our group has been amongst those in the vanguard discovering and developing new tools and protocols to facilitate more expedient organic synthesis; especially by amplifying the concepts of reagent immobilization [3]. The key goals of our

subsequent treatment with an appropriately functionalised resin. Alternatively it may be more convenient or advantageous to capture the desired product by transiently binding it to a suitably functionalised polymer, then washing the bound material and re-releasing it to give a pure product; free from contamination of starting materials, reagents or any reaction by-product.

While long linear syntheses are feasible with reactions that can be monitored in real-time, other opportunities for supported reagents continue to present themselves; for example, the ability to perform multiple reactions in one-pot with combinations of otherwise mutually incompatible reagents (Scheme **2**). Why this becomes a realistic possibility is due to the fact that supported reagents are site-isolated. That is, the reagents cannot interact with one another to any significant extent, only with the substrates present in the solution, which are able to diffuse between the

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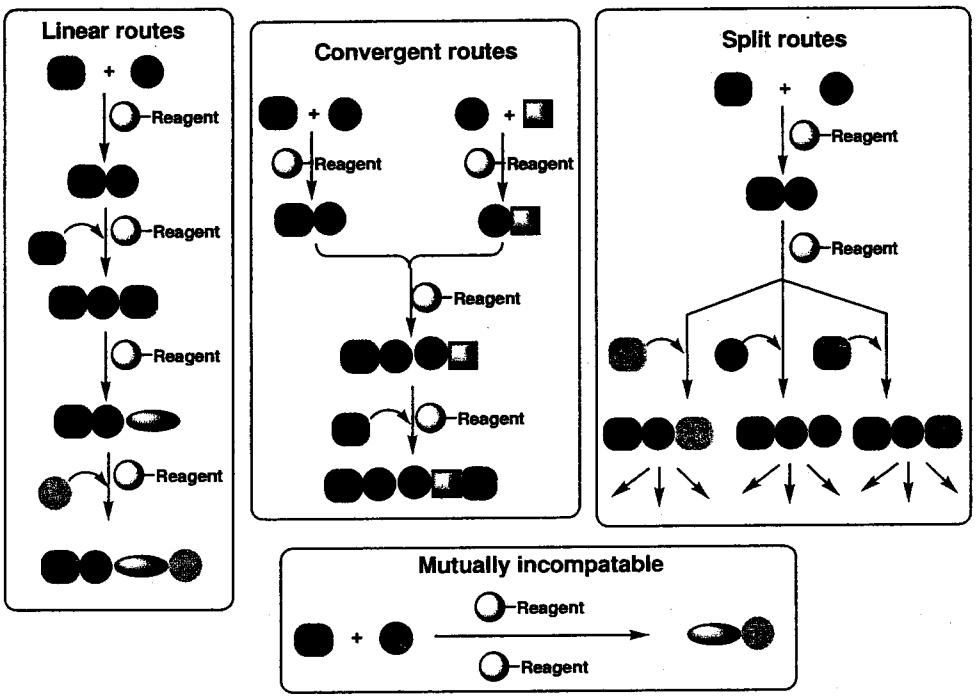
1385-2728/05 $50.00+.00

various polymeric reagents. This approach delivers many advantages in terms of synthetic flexibility. Conventional work-up procedures such as quenching, washing and extraction are avoided, which can be particularly useful when sensitive intermediates are involved. Substantial savings in terms of volumes of solvent and silica gel can also be made. Needless to say these one-pot procedures are therefore very attractive for the rapid preparation of architecturally elaborate structures. Convergent syntheses, where the products of reactions carried out in individual reaction vessels are ultimately combined to form more complex materials, are also possible using polymer-supported reagents. Moreover, these systems can accommodate the splitting of intermediate products into other useful building blocks or fragment sets, enabling new pathways for analogue preparation.



Scheme 2.

Immobilised reagents can be delivered in a variety of formats *e.g.* as loose beads, or as beads contained within pouches or formed into plugs, and also as coatings on laminar materials. The same reagents can be readily packed into tubes and flow systems resulting in tremendous versatility; particularly so for complex molecule assembly where rapid reaction and reagent optimisation is essential for efficient and high yielding production.

The introduction of new immobilising supports and alternative presentation formats is a crucial component to the continued development of this area of chemistry. The commonly used micro-bead reagent configuration is not always the most practical of materials to work with. Measuring and dispensing operations are often associated with problems of static charge and calibration of the stoichiometry. Additional difficulties can also be encountered during the reactions with possible fragmentation and grinding of the beads which can complicate the work-up protocol. Another issue which is often highlighted is one of product recovery which may involve extensive washing of the support in order to fully extract the desired molecules. A compounding factor to this is often the low loading levels of the reagents meaning large quantities of support material may be required for a given reaction. For these reasons there is often a resistance to the adoption of these techniques in a number of laboratories. However, in recent years significant progress has been made that resolves many of these issues. There are now many commercially available reactors and work-up stations which have been developed through collaboration with experienced end users that accelerate and facilitate the handling and usage of immobilised reagents. The requirement for higher loadings of the reagents and more robust materials has also been addressed by manufactures. Indeed, whereas, only three years ago a loading of 1.2 mmol/g was considered good now these same reagents are available at levels of 3-4 mmol/g and are prepared using methods that yield reagents which are more consistent and thus give better reproducibility. Another crucial facilitating aspect has been the considerable expansion of the associated literature and the resulting better understanding of the immobilised support and tethered reagents themselves. With this appreciation has come the development of many improved practical techniques and enhanced synthetic procedures. As an example; one such area has been the evaluation and selection of suitable solvents and their compatibility with the chemistry and support. Traditionally the majority of immobilised reagent transformations were conducted using only a few limited solvents such as DMF, toluene and DCM because of the need to 'swell the support'. The application of new approaches such as microwave heating and pressurised flow reactors as well as the introduction of more macroporous resins and non swelling supports such as silica and other inorganic matrices has

permitted the use of a wider range of solvents. Not only does this increased scope help with the specific chemistries but it also significantly assists in extraction of product following the reaction. It is well documented that the correct selection of solvent can significantly reduce the necessity for successive and extended washing sequences of the matrix at the time of product isolation.

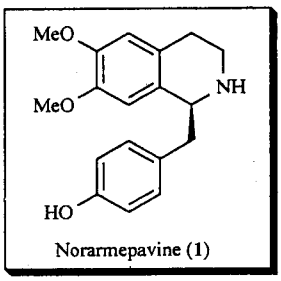
One final factor which requires addressing is one of cost, a major criticism and stumbling block to the wider usage of these immobilised reagents is the *perceived* prohibitive price. This is often an issue of supply where the common distributors of chemical have placed a heavy premium on the reagents. The authors have encountered many examples where the prices of essentially identical reagents have been listed by secondary retail sources at a significant multiple of the initial purchase price. This also includes situations where kilogram quantities can be bought for the same price as batches sold in 25 or 100 grams lots. This is not an easily overcome problem because unlike simple monomeric reagents which are relatively simple to compare a greater knowledge of the support architecture and its preparation is often required in order to trace a viable manufacturing source. Much of this is information is proprietary to a few individuals which permits the leverage of price multiples by many distributors.

The maturing of the area of immobilised reagent technology has certainly led to an increase in the applicability and availability of these species; however there is still scope for improvement in both expanding the range of reagents and in the continued development of the more physical characteristics such as loading, support identity, and general material format.

In this review we describe how this methodology has proved highly effective for the synthesis of numerous alkaloid natural products, and how these same approaches have a wider significance for organic synthesis in general [5].

(–)-Norarmepavine (1)

Norarmepavine (1) is a tetrahydrobenzylisoquinoline alkaloid isolated in 1963 from the American lotus plant *Nelumbo lutea* [6]. During the biological evaluation of norarmepavine (1) in mice it was shown to promote mydriasis (pupil dilation) and a corresponding decrease in spontaneous motor activity when administrated orally at high dosage. At lower levels (50mg/kg) compound (1) exerted only weak analgesic action in rats and failed to produce anti-pyresis or diminish oedema in the Randall-Sellitto anti-inflammatory test [7].



Norarmepavine (1)

We were interested in developing an enantioselective route [8] to (–)-norarmepavine (1), as this had not been achieved previously; moreover it constituted a useful test for the supported reagent, scavenging and quenching techniques described above.

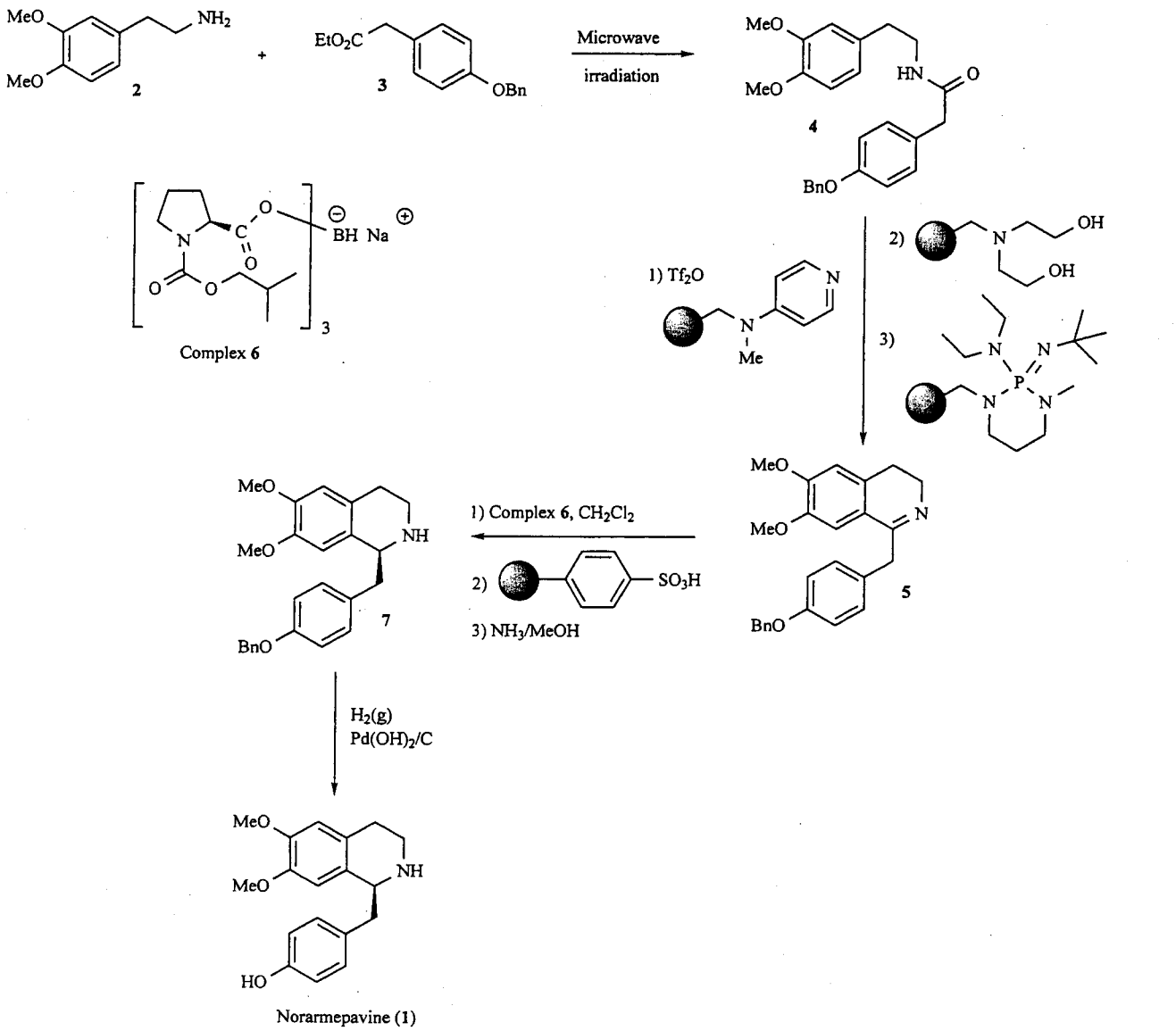
The synthesis makes use of a Bischler-Napieralski cyclisation to install the core heterocyclic structure and an enantioselective reduction to set in place the required stereogenic center. The synthesis begins by the coupling of the commercially available amine (2) with ethyl-4-benzyloxyphenylacetate (3) to afford the amide (4). This was achieved through the application of focussed microwave irradiation under solvent free conditions yielding (4) in better than 90% yield, with the material being of sufficient quality to be carried through to the next reaction (Scheme **3**).

The Bischler-Napieralski reaction was effected by the use of a polymer-supported version of 4-dimethylaminopyridine (PS-DMAP) and triflic anhydride in CH_2Cl_2 at 0 °C giving the cyclic imine (5). Scavenging with polymer-supported *N*-(2-aminoethyl)aminomethyl polystyrene to destroy the excess triflic anhydride and treatment with supported 2-tert-butylimino-2-diethylamino-1, 3-dimethylperhydro-1, 2, 3-diazaphosphazene (PS-BEMP) [9] generated the free base (5). Next a stereoselective reduction was achieved by use of a chiral sodium acyloxyborohydride reagent (6). The reagent was readily prepared by the reaction of (*S*)-*N*-isobutyloxycarbonylproline with sodium borohydride (Scheme **4**).

The stereoselective reduction of the imine (5) to amine (7) could be achieved with a modest 78% enantiomeric excess by slow addition the imine (5) in to the preformed complex (6) (Scheme **3**). A catch-and-release procedure using a sulfonic acid resin to trap the amine (7) as the salt and after washing release of the amine (7) in 82% isolated yield by treatment with methanolic ammonia. Finally, the benzyl protecting group was cleanly removed by hydrogenolysis with palladium(II) hydroxide on charcoal to give the natural product (–)-norarmepavine (1) [10]

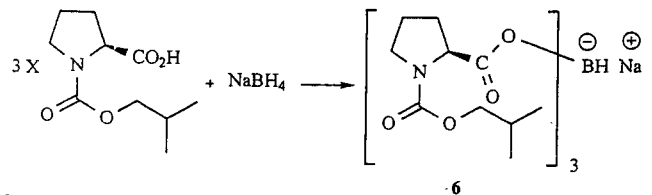
Oxomaritidine (8) and Epimaritidine (9)

The Amaryllidaceae alkaloids have been extensively studied owing to the interest generated by their structural diversity and biological activity [11]. In addition there have been a number of syntheses reported [12]. Our route to these alkaloids was based on the solution phase synthesis described by Holton [13], however it translates the synthesis into an immobilised reagent version to avoid conventional work-up methods (Scheme **5**). The first step in the synthesis involves the polymer-supported perruthenate (PSP) reagent that we developed in these laboratories for the catalytic oxidation of alcohols to carbonyl compounds. [14] Here, the benzylic primary alcohol (10) was converted in essentially quantitative yield to the aldehyde (11). This was then reacted with the amine (12) under reductive amination conditions with polymer-supported borohydride, to afford the norbelladine derivative (13) also in very high yield. Other immobilised systems such as a polymer-supported cyanoborohydride [15] were equally effective in this reduction process. Next, trifluoroacetylation of the amine (13) was accomplished using trifluroacetic anhydride and PS-DMAP to generate (14) in 99% yield. For the key intramolecular phenolic oxidation cyclization of (14) to the spirodienone (15) we developed a set of polymer-supported

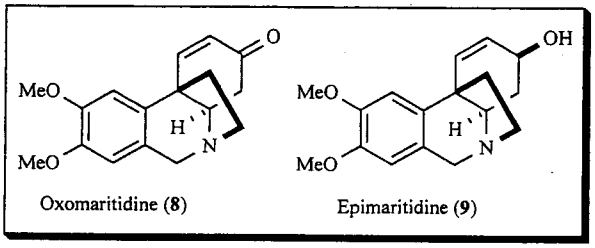


Scheme 3.

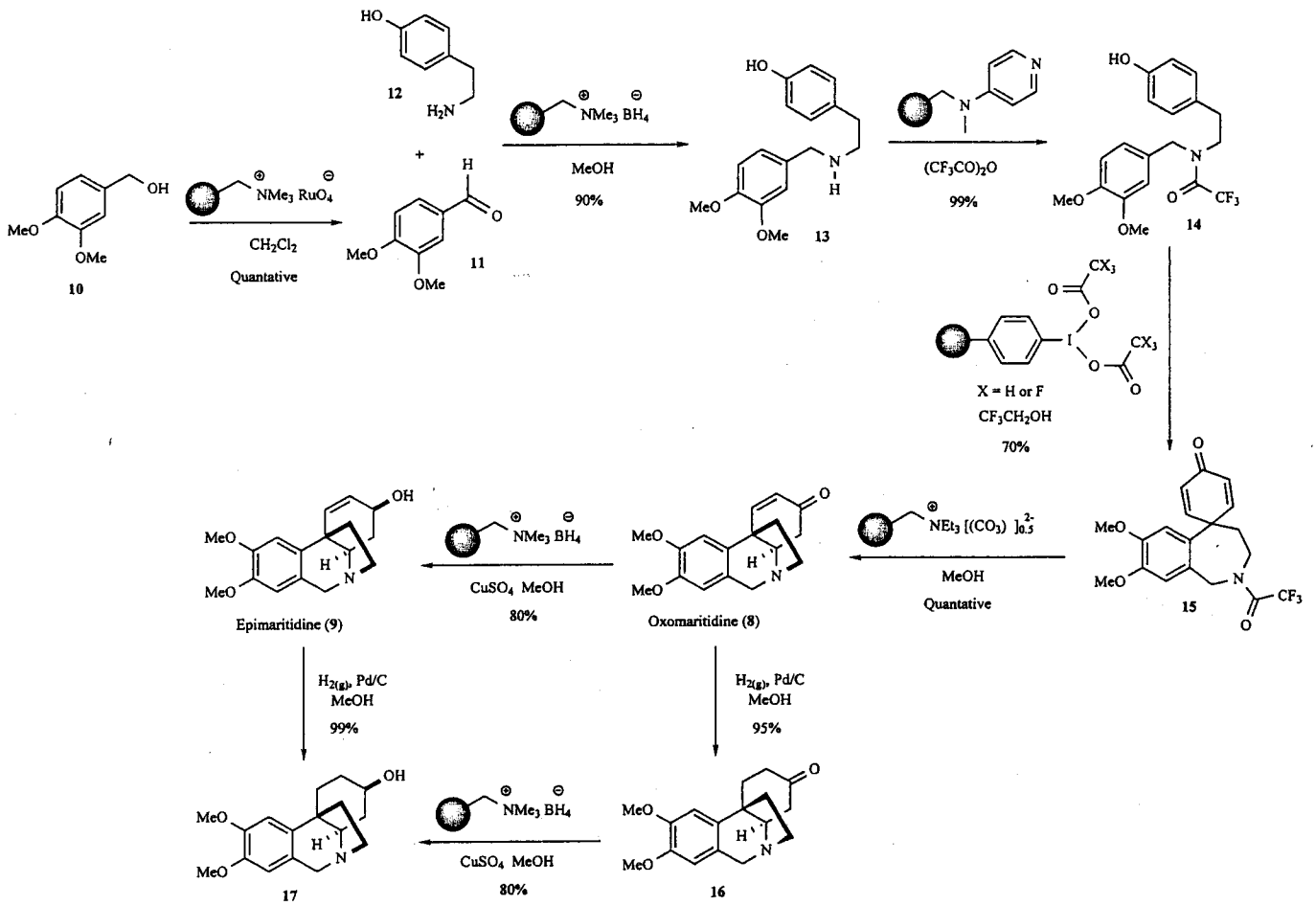
hypervalent oxidants specifically to effect this transformation [16]. Accordingly, polystyrene-supported diacetoxyiodobenzene or even better, the bis(trifuoroacetoxyiodo)benzene version, in trifluoroethanol gave excellent conversion to the spirodienone (15). In this process the desired *para, para* coupled product was the only observed compound by LC-MS and no other products were detected. Following a simple filtration to remove spent reagent and solvent evaporation (15) was obtained in 70% yield. When this reaction was conducted with reagents in solution we were unable to obtain the product in anything greater than 55% yield. Finally, treatment of (15) with polymer-supported carbonate in methanol resulted in the rapid deprotection and spontaneous intramolecular conjugate addition to give oxomaritidine (8) as a pure crystalline product in 99% yield identical to authentic material [17] (Scheme 5).



Scheme 4.



Stereoselective reduction of (8) with polymer-supported borohydride in the presence of a catalytic amount of

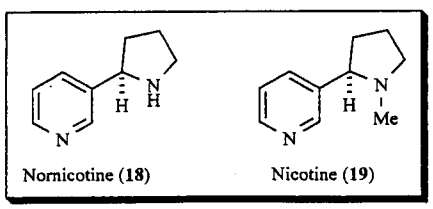


Scheme 5.

$Cu(SO_4)_2.5H_2O$ or $NiCl_2.6H_2O$ in methanol gave the natural product epimaritidine (9), also in high yield and identical to the authentic compound. The dihydro analogues (16) and (17) of these natural products [18] were also obtained by further reduction using hydrogenation with palladium on carbon (Scheme **5**). Once again all products were produced with high purity without recourse to conventional chromatographic work-ups. In addition it was demonstrated that all the compounds can be prepared on a gram scale such that they are available for further chemical modification and decoration and hence become useful for biological evaluation [19].

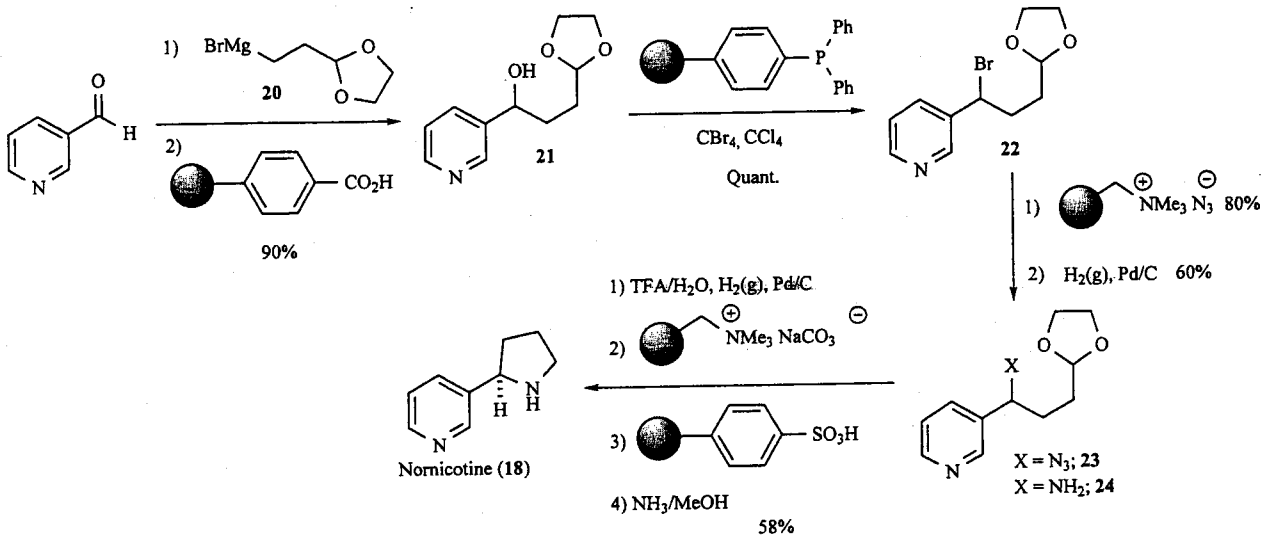
Nornicotine (18) and Nicotine (19)

The natural products nornicotine (18) and nicotine (19) are of considerable interest to medicinal chemists owing to their interactions with nicotinic acetylcholine receptors [20]. They have been shown to improve cognitive function and give neuroprotection [21]. Additionally they have shown substantial therapeutic benefits in the specific treatment of

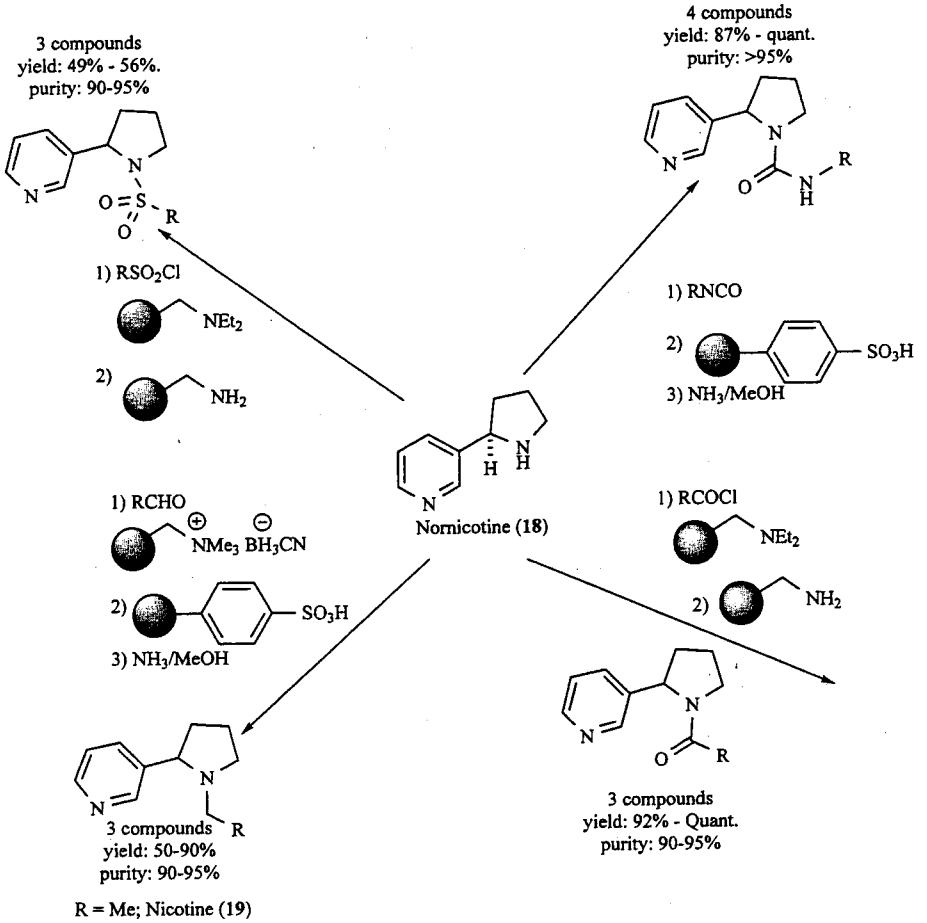


Tourette's syndrome, Alzheimer's and Parkinson's disease [22] and in a more general application as anxiolytic, antidepressive and schizophrenic agents [23]. It is therefore not surprising that chemists have devised many synthetic approaches to these compounds and related their analogues. We have also developed two routes to these interesting nicotinic compounds [24].

Firstly we investigated the addition of the Grignard reagent (20) to pyridine-3-carbaldehyde (Scheme **6**). After warming to room temperature the reaction was quenched by the addition of a carboxylic acid functionalised resin (Amberlite IRC-50) to give (21). This, on treatment with a mixture of carbon tetrabromide and polymer-supported triphenylphosphine in CH_2Cl_2 gave the reactive bromide (22) in quantative yield (Scheme **6**). In order to complete the synthesis, the bromide (22) was firstly transformed to the azide (23) by use of an azide ion exchange resin. Reduction of the azide (23) by hydrogenation with palladium on carbon readily afforded the primary amine (24). Use of an ion exchange azide in this way followed by the direct reductive work-up, is an attractive and safer way to manipulate azides in chemical reactions, since there is no need to isolate the potentially hazardous adduct. Acid catalysed hydrolysis of the acetal protecting group using trifluoroacetic acid (TFA) furnished the aldehyde which underwent spontaneous cyclisation to the imine. This material was further transformed *via* an *in-situ* reduction with palladium on



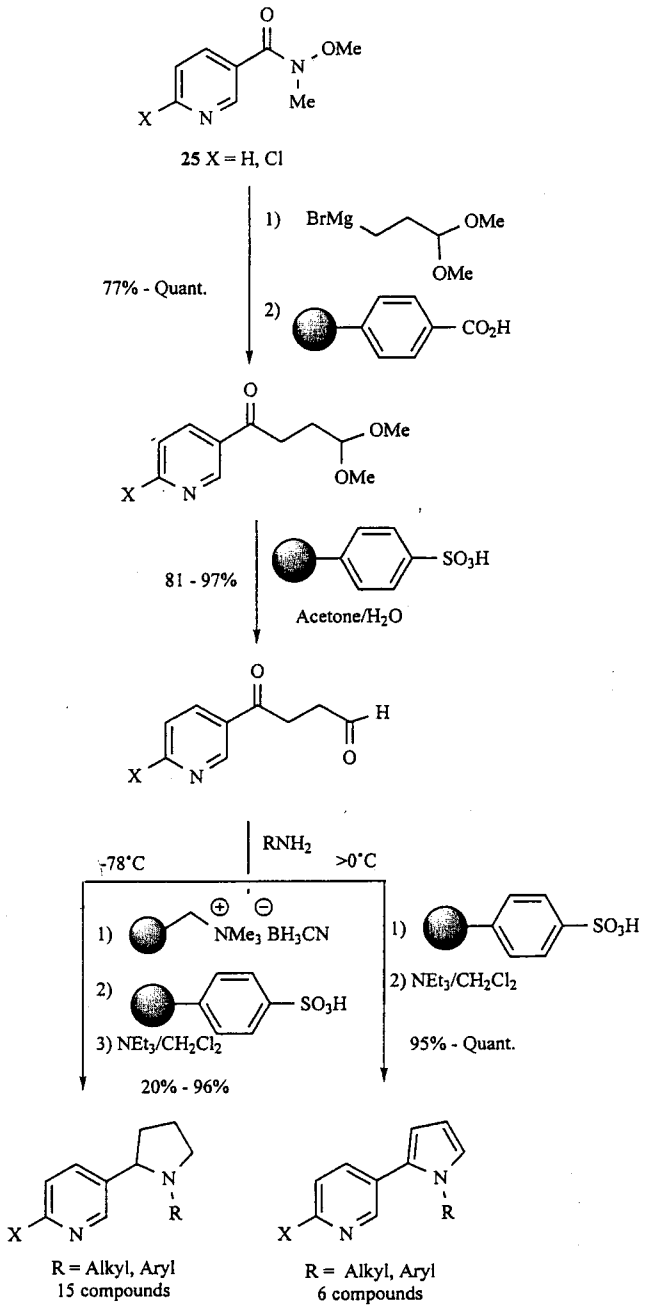
Scheme 6.



Scheme 7.

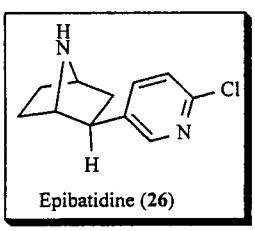
carbon under a hydrogen atmosphere to give nornicotine (18) as its TFA salt. Evaporation of the solution followed by dissolution of the residue in ethyl acetate and addition of a polymer-supported carbonate base liberated the free amine base (18), which in turn was captured on to a sulfonic acid resin (Amberlyst 15). This allowed easy purification of the bound material by filtration of the resin and washing with CH_2Cl_2 to remove impurities. Release of nornicotine (18) from the resin was achieved by suspending the polymer in a 2M solution of ammonia in methanol, filtration and concentration of the filtrate under reduced pressure yielded (18) as high quality product (Scheme **6**).

Starting from nornicotine (18) several analogues were also prepared using a suite of supported reagents and scavengers (Scheme **7**). In one of these analogue channels



Scheme 8.

when nornicotine (18) was reacted with formaldehyde followed by a reductive amination with polymer-supported cyanoborohydride, nicotine (19) itself was obtained also in high purity by direct filtration and evaporation.



During these investigations we also embarked on a second synthetic approach to nicotinic derivatives which began with the Weinreb amides (25). These were then transformed in a series of steps, again using immobilised reagents and quenching agents, to form a collection of nicotine derivatives; or by a slight modification to yield pyridine-pyrrole hybrids (Scheme **8**).

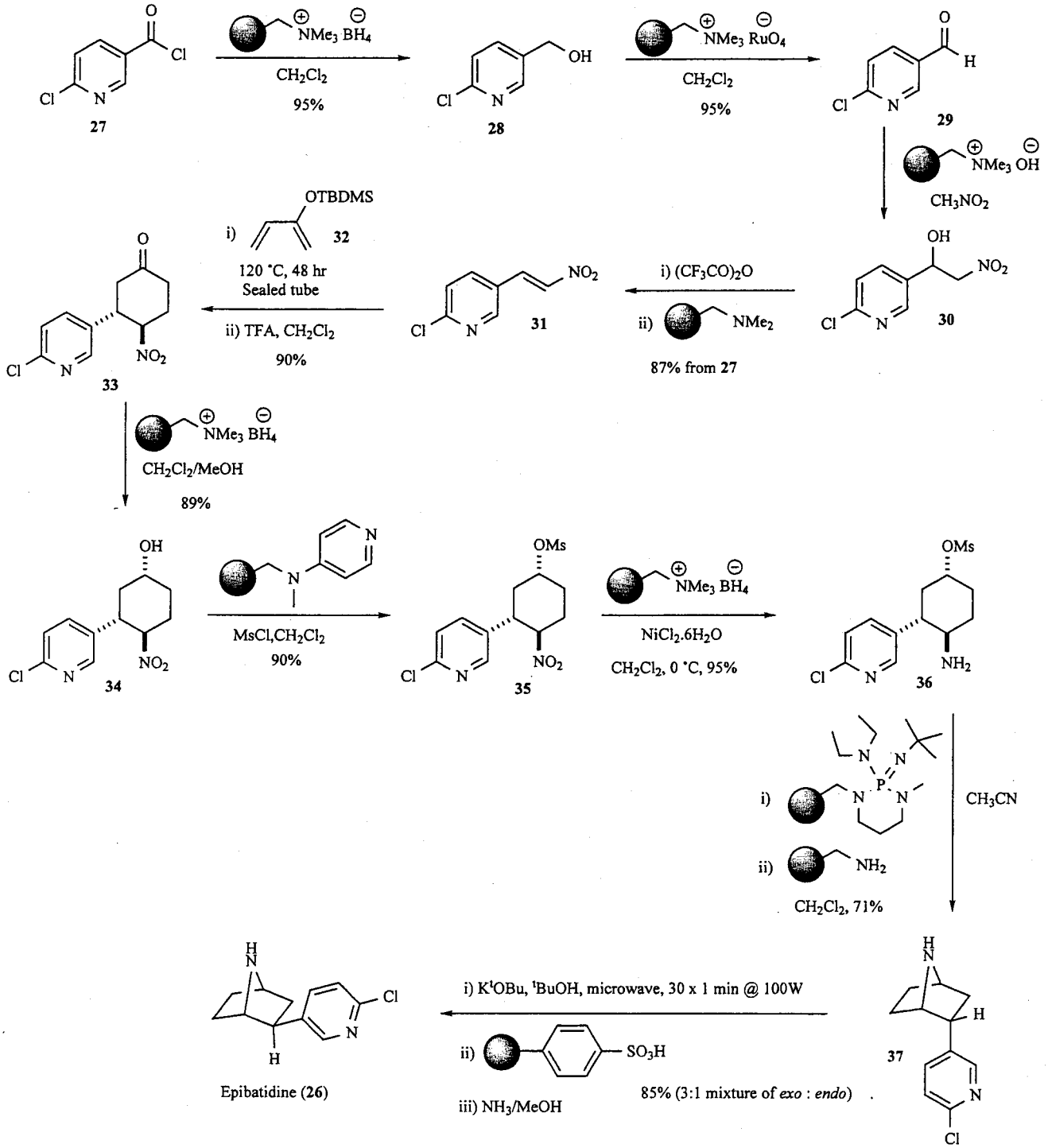
Epibatidine (26)

Epibatidine (26) is a potent analgesic compound isolated from the Equadorian poison frog *Epipedobates tricolour* [25]. Epibatidine (26) and its analogues have been the centre of a significant synthetic effort [26]. In our work we used an array of polymer-supported reagents and sequestering agents to achieve a synthesis in only ten steps without the use of any chromatography (Scheme **9**) [27].

Treatment of the commercially available acid chloride (27) with polymer-supported borohydride [28] cleanly afforded the corresponding alcohol (28) in good isolated yield (Scheme **9**). A number of protocols were investigated for the oxidation of (28) to the pyridyl aldehyde (29). The polymer-supported perruthenate [14] (PSP) and polymer-supported permanganate [29] (PSM) reagents (first introduced by our group) as well as polymer-supported (diacetoxyiodo)benzene [16] were found to be extremely efficient with no over-oxidation to the corresponding carboxylic acid. Alternatively, 'clean' oxidants such as Magtrieve [30] (magnetised CrO_2 filaments) were also suitable for this reaction, however, reaction times were considerably longer under comparable reaction conditions.

A basic Amberlite resin (IRA 420-OH^- form) was found to be a suitable base for the Henry reaction between aldehyde (29) and nitromethane [31]. Removal of the resin by filtration and evaporation of excess nitromethane afforded the unstable nitro alcohol (30). Derivatisation with trifluoroacetic anhydride cleanly afforded the corresponding acetate, with TFA and excess trifluoroacetic anhydride being simply removed *in vacuo*. Treatment with PS-DMAP in CH_2Cl_2 promoted elimination to give exclusively the *trans* configured alkene (31). Reactions were monitored by LC-MS which indicated product purity of in excess of 95% in all steps *en route* to the alkene adduct (31). Confirmation of the purity by NMR analysis was confirmed to be in excess of 95% for all the intermediates. In an important modification, it was found that by encapsulating quantities of the polymer-supported reagents in sealed porous pouches, the reaction sequence of acid chloride (27) to the key alkene intermediate (31) could be carried out in a one-pot procedure. When the reaction had gone to completion, the pouch containing the immobilised reagent was removed, washed with solvent and the next pouch was added to the flask. This removed the need for filtration between individual steps.

With the alkene (31) in hand, construction of the cyclohexyl ring system was achieved *via* a thermal Diels–Alder reaction. Heating two equivalents of the TBDMS-protected 2-oxadiene (32) with alkene (31), in toluene in a sealed vial at 120 °C, reproducibly afforded quantitative yields of the TBDMS-protected Diels–Alder adduct. Removal of excess diene *in vacuo* followed by TFA-catalysed hydrolysis of the silyl enol ether afforded the ketone (33) with exclusively the *trans*-geometry. Reduction



Scheme 9.

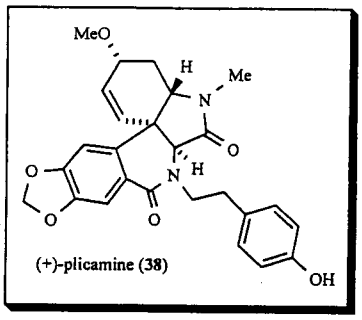
of the ketone (33) with polymer-supported borohydride gave a 7:1 diastereomeric ratio in favour of the all equatorial substituted cyclohexanol (34). Conversion of the alcohol (34) to the corresponding mesylate (35) was achieved by adding a solution of the alcohol in dichloromethane to a preformed mixture of PS-DMAP and mesyl chloride and then stirring the reaction mixture at room temperature until the reaction was complete. Reduction of the aliphatic nitro functionality of mesylate (35) with retention of configuration initially proved problematic. In addition as reported previously [32] the lability of the 2-chloro substituent of the pyridyl ring also frustrated a range of attempted hydrogenation (rhodium on alumina, palladium on carbon, platinium oxide) and transfer hydrogenation (ammonium formate and palladium on carbon) conditions. However, using Raney Nickel as the catalyst with hydrogen, the transformation could be accomplished without concommitant reductive dechlorination of the pyridyl ring, albeit with an

extended reaction time. However, the best method for this transformation proved to be *via* the use of polymer-supported borohydride with $NiCl_2.6H_2O$ [33]. This reproducibly furnished the desired amino mesylate (36) rapidly and under mild conditions, and was found to be superior to the use of sodium borohydride with $NiCl_2$ under the usual reduction conditions [34]. The commercially available PS-BEMP allowed the key transannular cyclisation to proceed in higher yield and more rapidly than under the attempted thermal conditions (toluene, D, overnight, 46%) previously reported [35]. As no trace of the potential by-product arising from intermolecular amino-mesylate displacement was observed in these reactions (LC-MS, ^{1}H NMR), the most significant impurity remaining was the epimeric *cis* amino mesylate of (36) (approximately 10%). This is derived from the minor diastereoisomer obtained from the reduction of ketone (33) to alcohol (34) which has the incorrect configuration for intramolecular cyclisation. This and any acidic impurities were conveniently removed by sequestration with a basic aminomethyl polystyrene resin which effected an intermolecular displacement of the mesylate to remove the unwanted residual diastereomer of mesylate (36) from solution. Filtration then afforded the *endo* isomer of (37) of epibatidine in excess of 85% purity as determined by LC-MS.

The final step required the epimerisation of the α-pyridyl proton of (37) to give the thermodynamically more stable *exo* isomer (26); namely epibatidine (26) itself. Previous reports indicated that even under forcing conditions (*t*BuOK, *t*BuOH, D, 30 h, 50%), this reaction could not be driven beyond 50% completion and the *endo* and *exo* isomers had to be separated by chromatography. In contrast, we have found the use of microwave irradiation (using a Labwell Microwell 10 system) of a sample in a sealed vessel formed a 3:1 ratio in favour of the desired *exo* isomer of epibatadine (26) in faster reaction times (30 min). This was one of the first applications of focused microwaves to be reported in the literature. The reaction work-up for this step involved sequestering both the potassium salts and the product amine (26) onto an acidic ion-exchange resin (Amberlyst 15); discarding the resultant solution containing neutral impurities. The product was displaced from the resin by treatment with methanolic ammonia to afford epibatidine (26) in excess of 90% purity (LC-MS, ^{1}H NMR) as a 3:1 mixture of *exo* and *endo* isomers. This sequence of reactions again nicely illustrates the use of the full armory of supported reagents, scavengers and catch-and-release techniques available for natural product synthesis.

(+)-Plicamine (38)

A recent study [36] of the Turkish Amayllidaceae *Glanthus plicatus* (Byzantinus) has led to the isolation of a new alkaloid (+)-plicamine (38). This compound is the first representative of a new subgroup of Amaryllidaceae alkaloids possessing a distinct dinitrogenous skeletal arrangement. Currently no biological activity for plicamine (38) has been reported, however related structures, such as tazettine, pretazettine, criwelline, percriwelline and 6a-epipretazettine have shown a wide spectrum of medicinal properties, which include anticholinergic, antitumour, immunosuppressive and analgesic activity [37]. There is also evidence that these compounds inhibit various cell cycle mechanisms and may therefore find application in the therapeutic treatment of Alzheimer's disease.

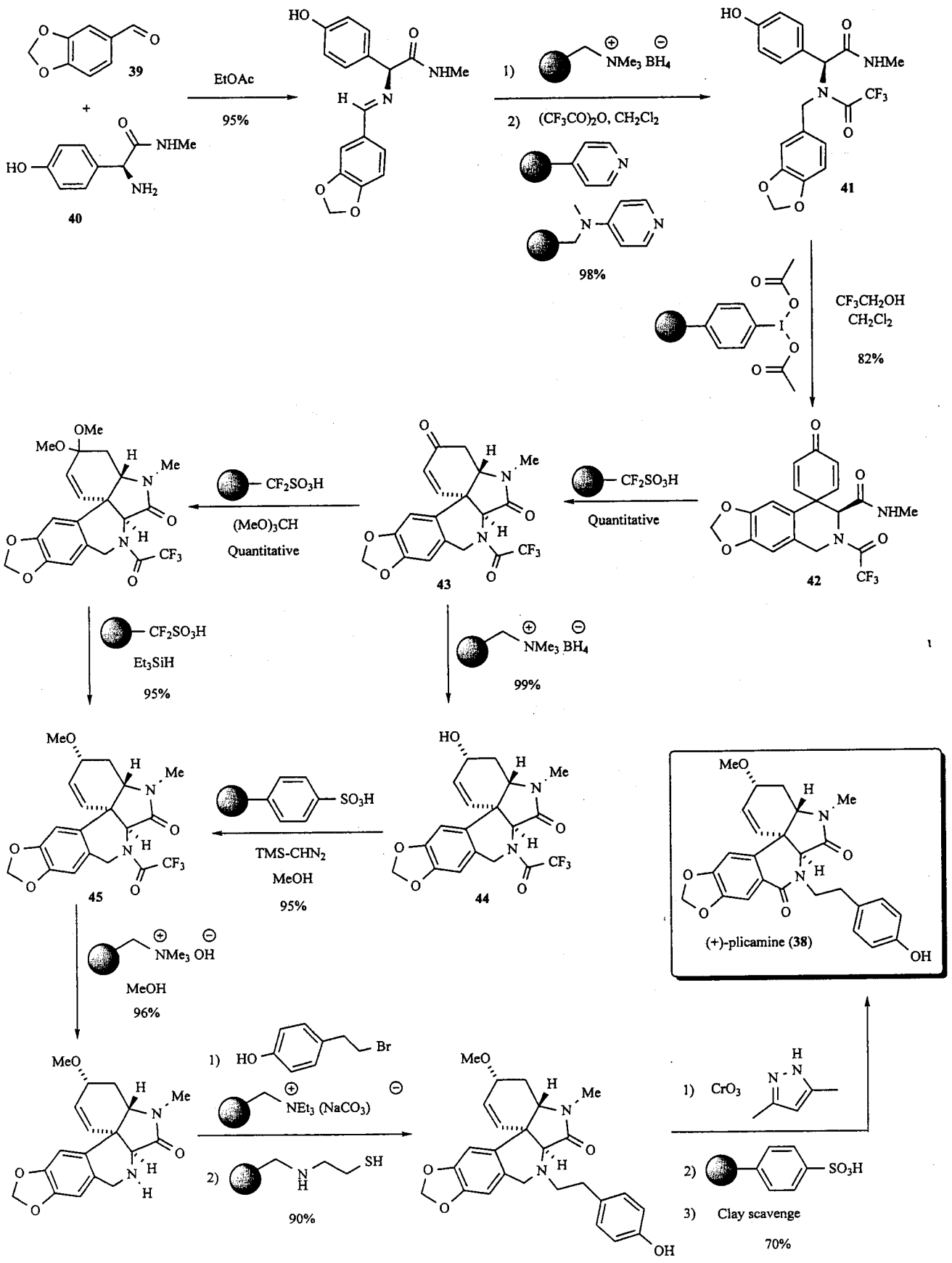


(+)-plicamine (38)

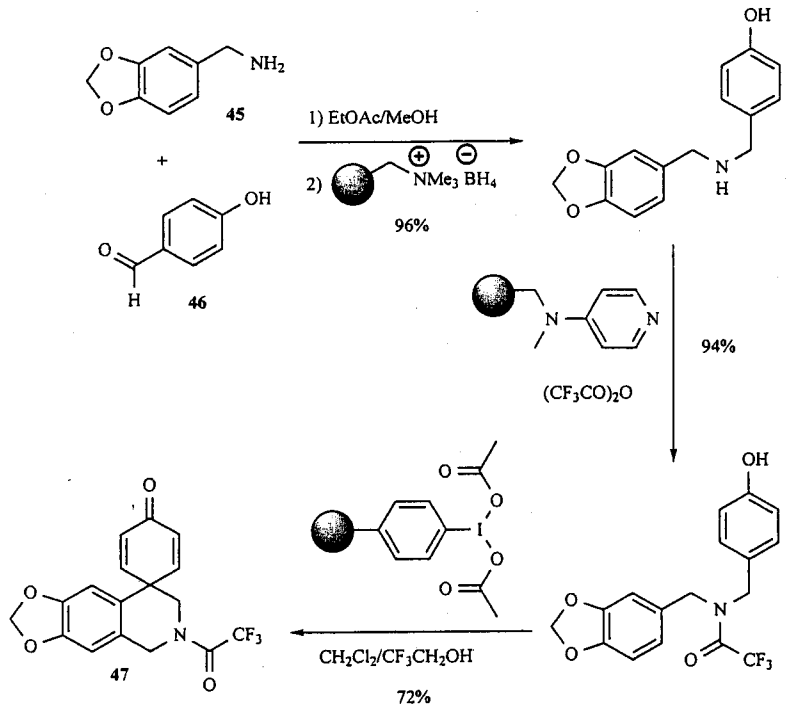
(+)-Plicamine (38) presents a significant challenge for supported reagents and scavengers in that there are four stereogenic centers around a 6,6-spirocyclic core and a high level of functional substituents including a very hindered methyl ether. No previous synthesis of plicamine (38) has been described. Key features of our synthesis are summarized in scheme **10**.

The plicamine (38) synthesis [38] follows a similar strategy to that used for oxamaritidine; an early reductive amination to bring together the key the aldehyde (39) and chiral aminoamide (40) components. In this initial step the absolute stereochemistry was defined which was used to control the remaining stereocenters. It was also at this stage that the antipodal unnatural configuration of the aminoamide could be used to prepare the corresponding (–)-plicamine. The synthesis continues *via* protection of the amino group as its trifluoroacetamide (41) prior to phenolic oxidative coupling with the polymer-supported hypervalent iodonium diacetate to give the spirodienone (42). The commercially available Nafion-H resin was then used as a proton source to catalyse the conversion of the dienone (42) to the polycyclic enone (43). This could then be progressed to the key methylether derivative (45) *via* two alternative pathways (Scheme 10). Of particular note is the use of trimethylsilyl diazomethane and a sulfonic acid resin (Amberlyst 15) to achieve the direct methylation of the hindered alcohol (44). The remaining steps of the synthesis of (+)-plicamine (38) are relatively straightforward, although considerable experimental work was necessary to find the optimal procedures. For this work extensive use of parallel reaction equipment was made to rapidly scan different reagent conditions and combinations. This greatly facilitated the optimisation processes and is well suited to the use of polymer-supported reagents. It is worth consulting the full paper for further details relating to these optimisation studies as great rate enhancements were observed when focussed microwave heating was employed.

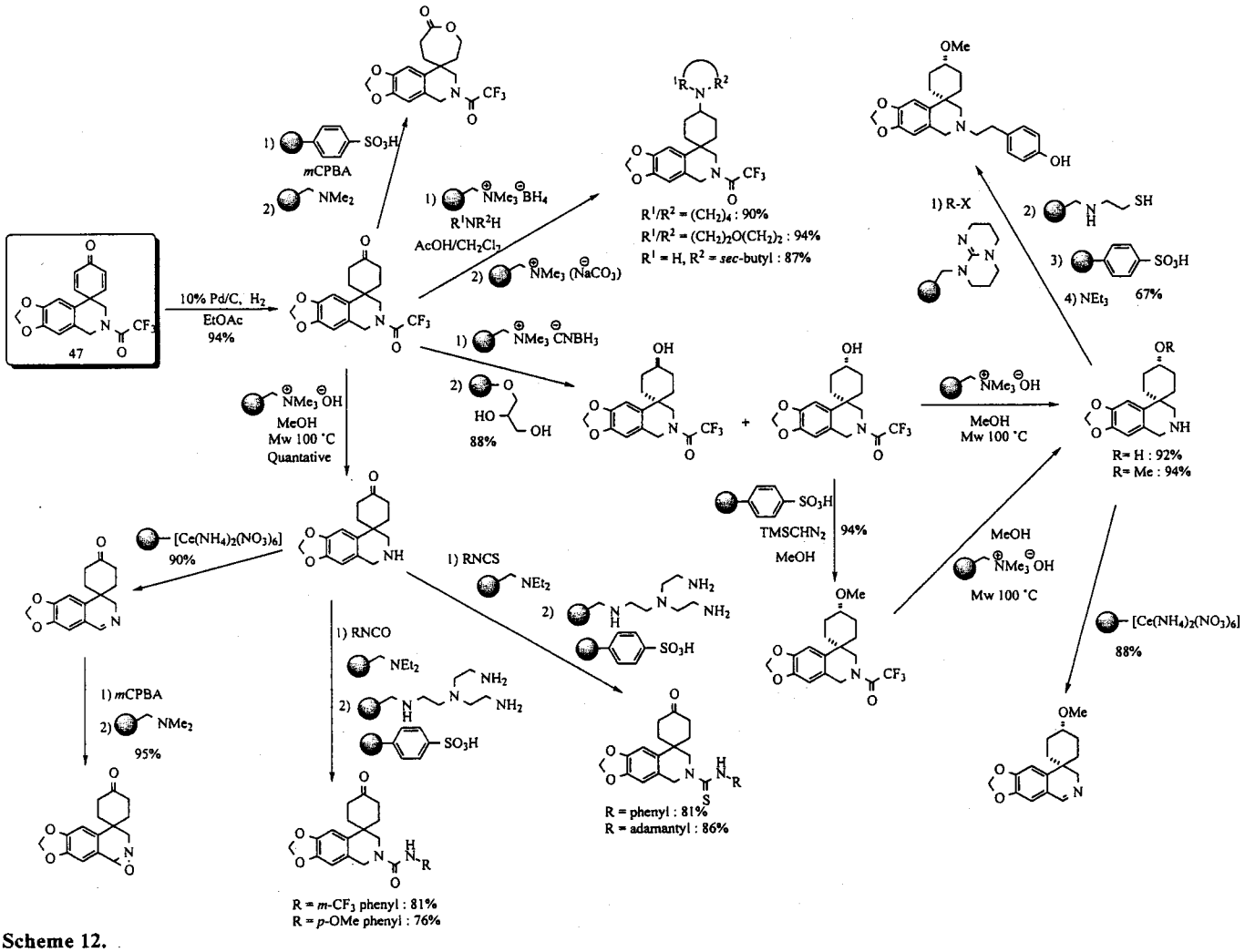
In addition a simplified structure based on the plicamine (38) template was prepared which lent itself very well to combinatorial decoration and the generation of a whole variety of analogues. Accordingly, we coupled the amine (45) with the aldehyde (46) and progressed this in multigramme quantities to the model spirodienone (47) (Scheme **11**). Then in a divergent fashion this key building block (47) was converted to a whole range of new structures as part of a combinatorial chemistry program (Scheme **12**).


39
40
EtOAc
95%
1) NMe3 BH4
2) (CF3CO)2O, CH2Cl2
98%
41
CF3CH2OH
CH2Cl2
82%
42
Quantitative
CF2SO3H
43
(MeO)3CH
Quantitative
99%
Et3SiH
95%
45
TMS-CHN2
MeOH
95%
44
MeOH
96%
1) HO Br
NEt3 (NaCO3)
2)
90%
1) CrO3
2) SO3H
3) Clay scavenge
70%
(+)-plicamine (38)

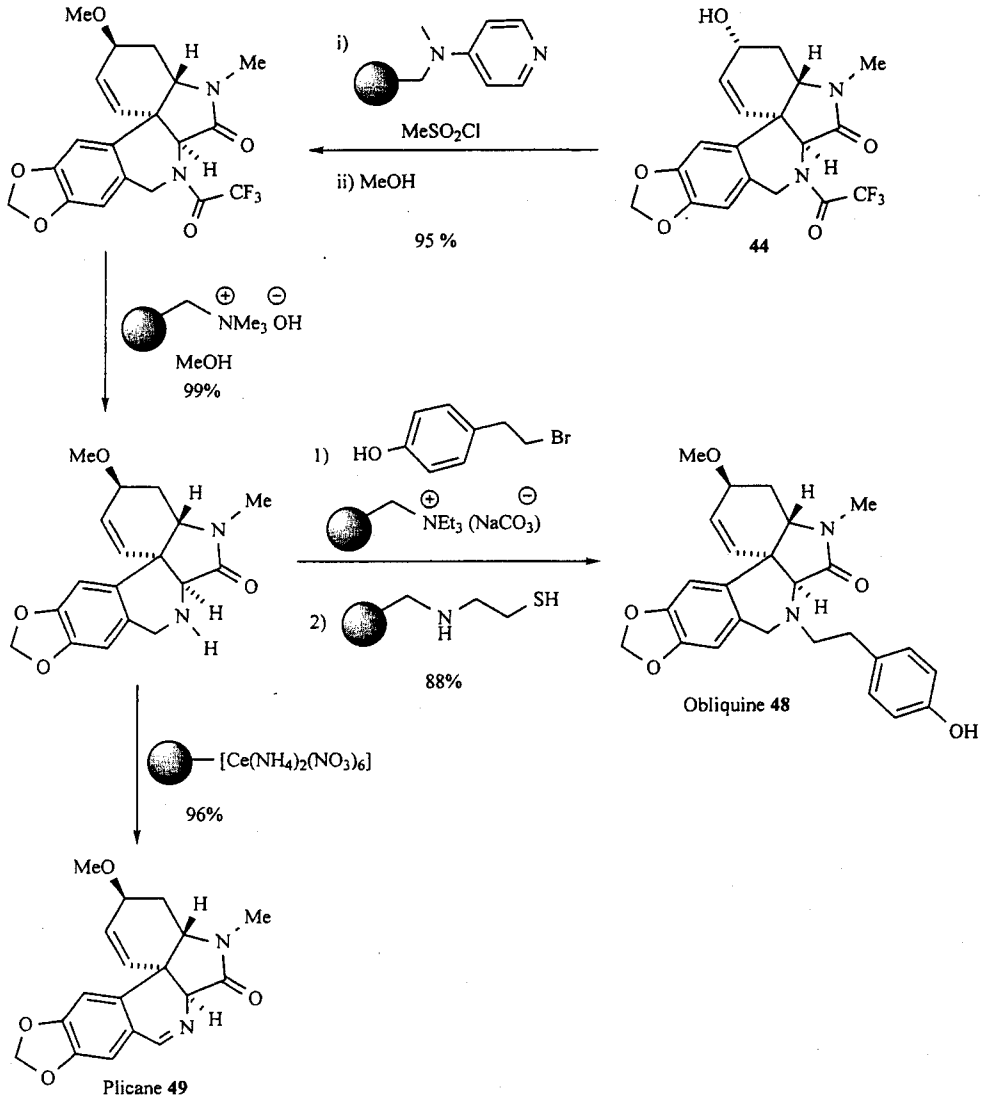
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

Research on (+)-plicamine (38) uncovered two additional dinitrogenous alkaloids, which had also been isolated from plant sources. The structurally related compounds obliquine [39] (48) and plicane [40] (49) could be readily accessed through simple manipulation of the core structure (44) as described in Scheme **13** [41].

CONCLUSIONS

While this review has focussed on the use of supported reagents and scavengers for the preparation of alkaloid, these methods are equally applicable to the synthesis of many other molecules. For example, in our laboratories we have used immobilised reagents to prepare 1,2,3,4-tetrasubstituted pyrroles [42], isoxazolidines [43], aminothiazoles [44], benzodioxanes [45], pyrazoles [46], piperidinothiomorpholines [47], benzofurans [48], bicyclo(2,2,2)octane derivatives [49], and the pharmaceuticals Sildenafil [50], Salmeterol [51] and various HDAc [52] and MMP inhibitors [53]. The most complex natural product synthesised by these methods is the potential anticancer agent epothilone C, achieved in no less than 29 steps [54].

Synthesis is changing and there is an absolute requirement to respond to the new challenges. As the global emphasis towards more eco-efficient and sustainable practices unfolds before us, so does the new remit for chemistry. We are already applying the principles of this new paradigm to environmentally cleaner and more efficient chemical processes. In that vein, it is our belief that the future of organic synthesis will increasingly incorporate the use of supported reagents and scavengers in both batch and flow modes.

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