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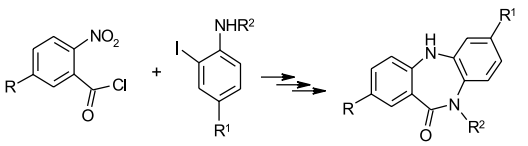
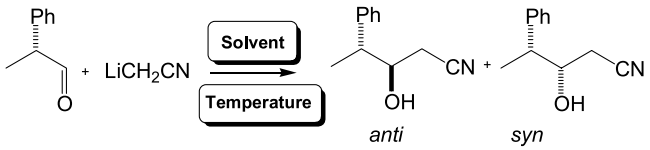
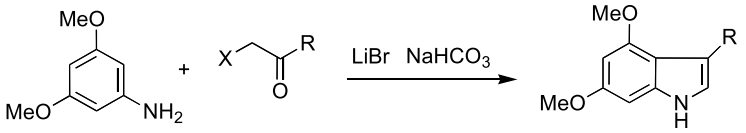
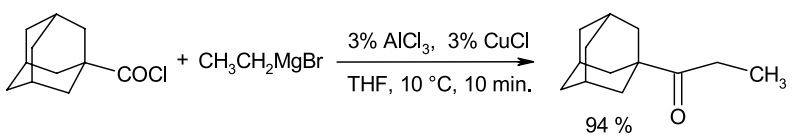
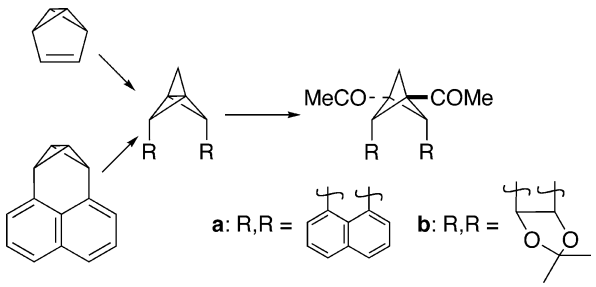
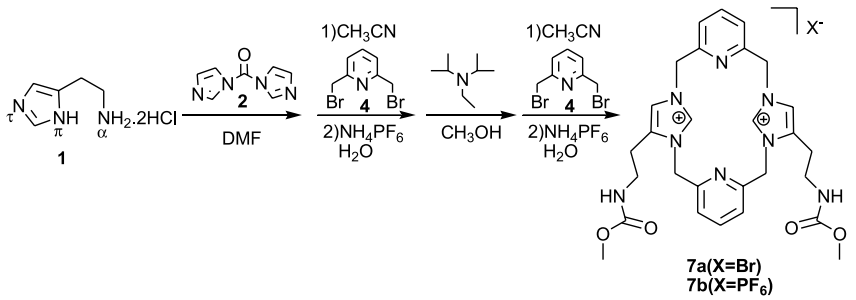


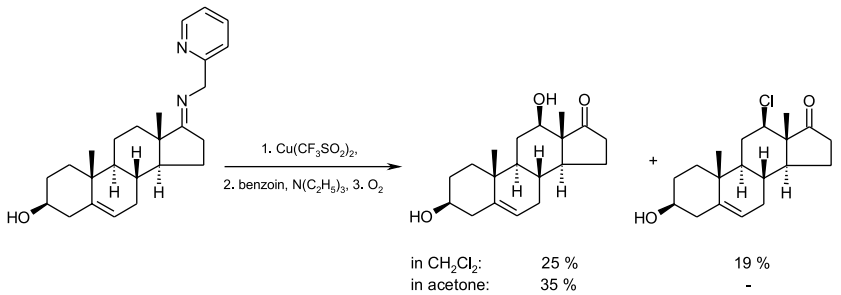


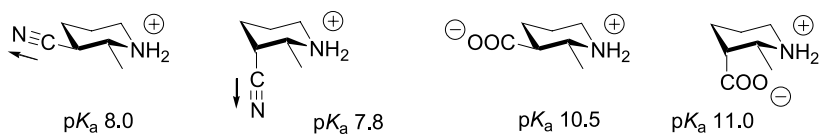


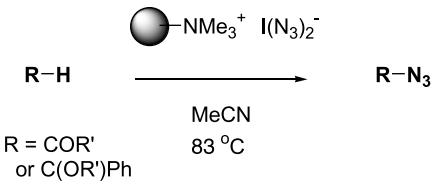


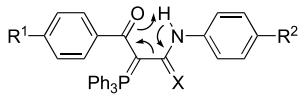




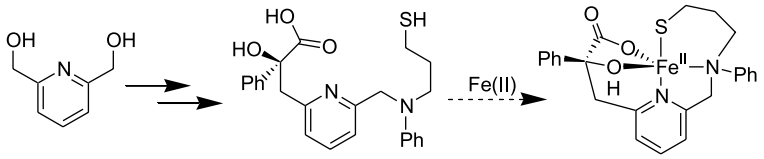


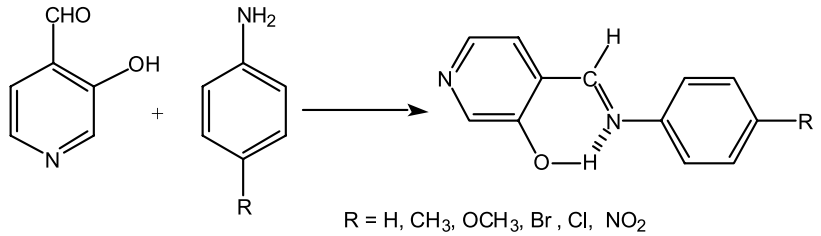




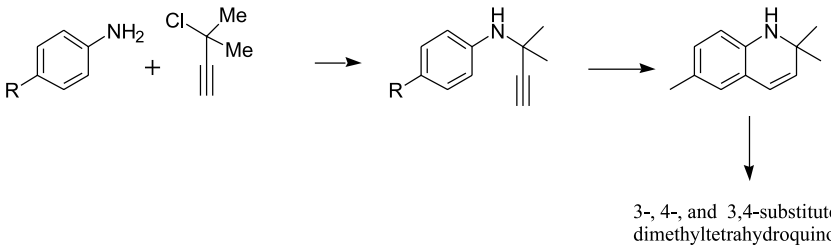


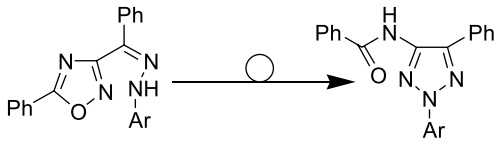
Rates measured as a function of X, R^1, R^2

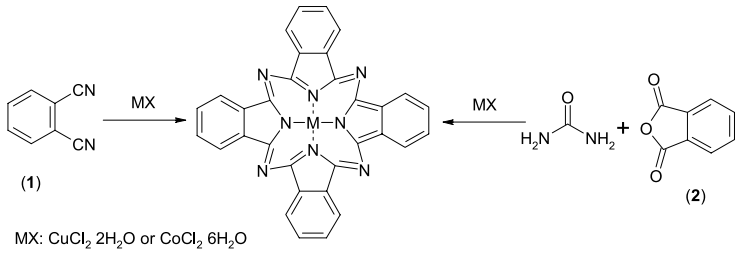


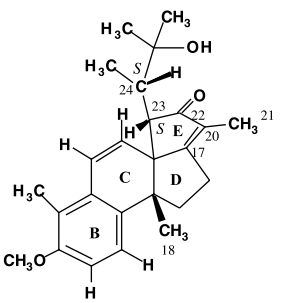


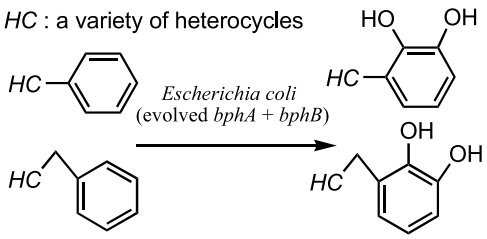
R = H, CH_3, OCH_3, Br , Cl, NO_2

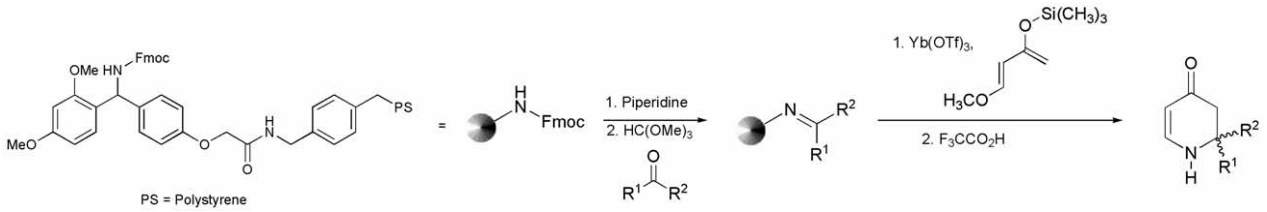


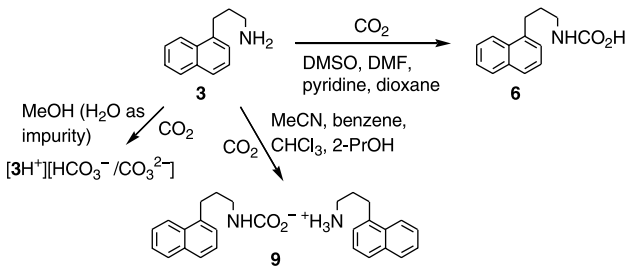




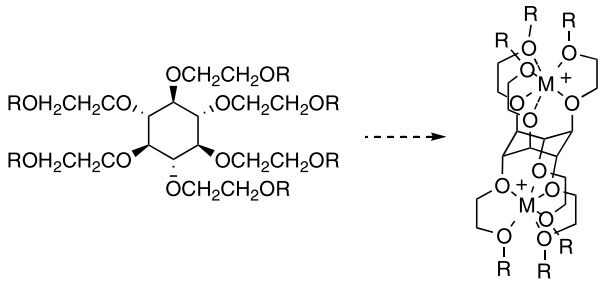


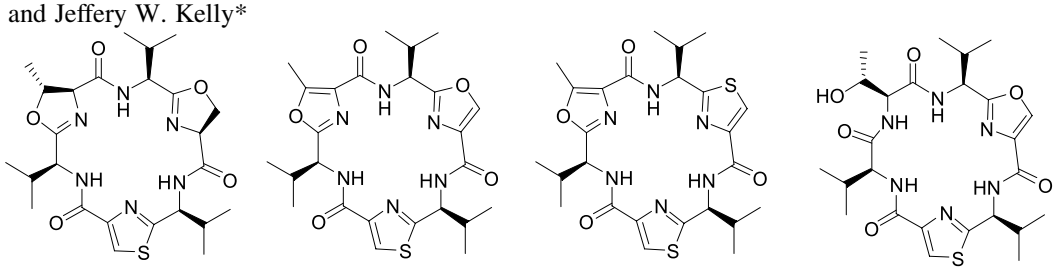






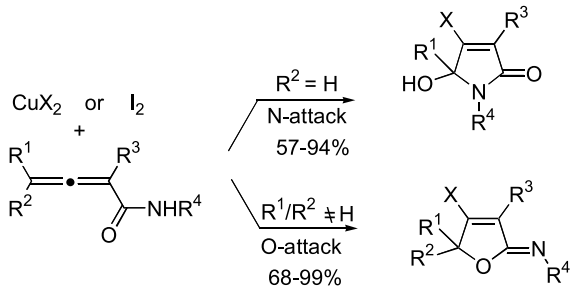
Probably due to $pK_a(\mathbf{6}) > pK_a(\mathbf{3})$ in protophilic dipolar aprotic solvents, the conversion **3**→**6** is nearly complete while the formation of **9** is minimal.

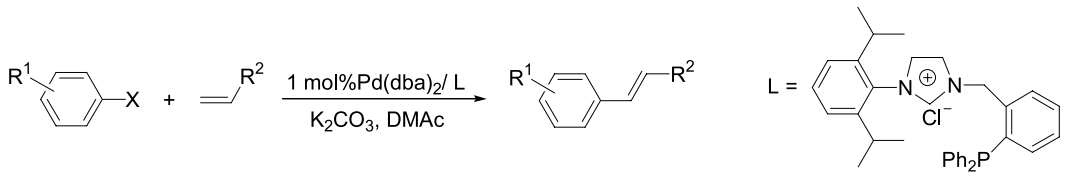


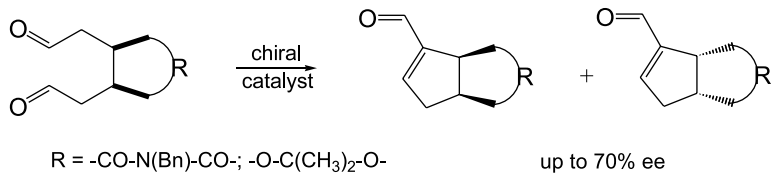


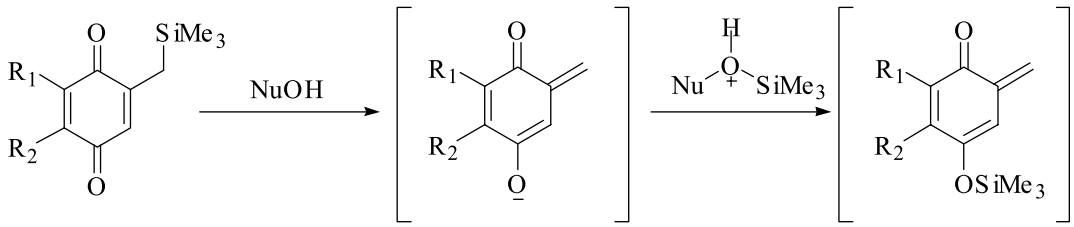
2 **3** **4** **5**

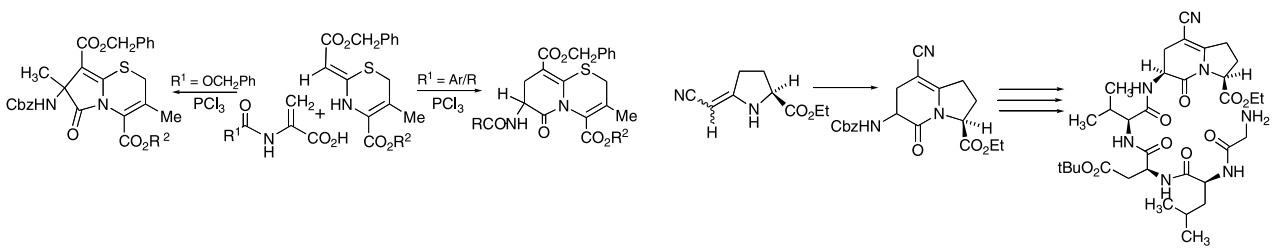
Total syntheses of bistratamides F–I (**2**–**5**) have been achieved in overall yields of 3, 10, 13, and 27%, respectively, from readily available amino acids.

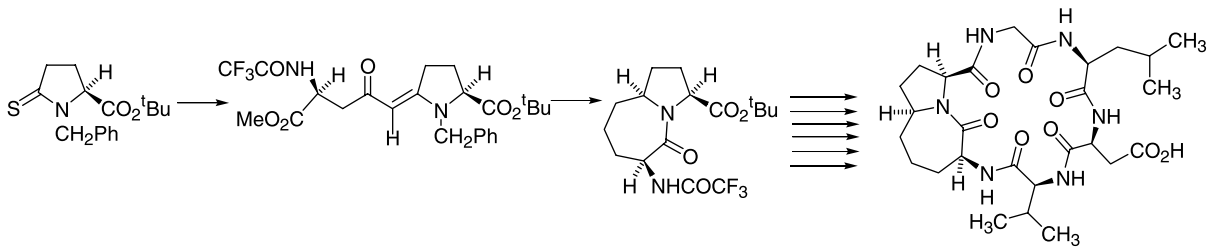












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Publisher's Note

On behalf of Elsevier, welcome to another exciting year for *Tetrahedron* and the Tetrahedron family of publications. This first issue of 2005 provides an opportunity for us to reflect on the year just passed, and to touch on the challenges of the year ahead.

Accessibility and Readership

During 2004 the Tetrahedron journals continued to experience considerable success. The number of institutes subscribing to the journals and gaining access to the content online continued to grow; many thousands of organisations are now able to access the journals in print or online.

Renewals of ScienceDirect accounts have progressed very well too, with many high profile institutes renewing their access to the Tetrahedron family of titles, along with other leading journals published by Elsevier.

The number of downloads from the Tetrahedron journals continues to increase—a clear indication of the relevance, quality and accessibility of the articles published in these internationally renowned titles. During 2004 alone, an estimated ten million articles were downloaded from these journals via ScienceDirect.

Journal Developments

The journal has again seen an increase in both citations and impact factor.

The journal's international prestige and the exceptional service received by authors has also resulted in a further and substantial increase in submissions, which has necessitated an increase in rejection rates. As submissions continue to grow, there is likely to be an increased need to reject more papers in future, which will result in an overall increase in quality.

Despite this considerable growth in submissions, production times have been further improved, providing even faster publication of authors' research. Articles are frequently published online just 3 weeks after acceptance, with many appearing faster than this.

The journal continues to publish an international mix of papers from academia and industry, including many contributions from leading authorities in the field.

Recent Developments

In response to feedback from researchers worldwide, several important developments have been implemented during the past year, including:

Cover Graphics

Regular readers of the journal will notice the eye-catching new cover designs, frequently featuring images provided by authors of papers published in a given issue. This development allows greater attention to be drawn to commissioned Symposia-in-Print, reviews and perspectives, or individual articles of particular interest.

New Design of Graphical Abstracts

The contents pages of the journal have been redesigned to provide a clearer, quicker overview of the contents of each issue. The new design has made both print and online browsing more appealing and easier.

Tetrahedron Computer Methodology (TCM)

In September last year, *Tetrahedron Computer Methodology*, a Tetrahedron publication published between 1988 and 1990, became available on ScienceDirect. An international journal for research in computer chemistry, *TCM* was the first scientific journal to be published simultaneously in print and electronic form, with the latter being enhanced by supplementary information. It is perhaps appropriate that this pioneering and somewhat experimental journal from Tetrahedron Publications becomes accessible, many years on, through the internet.

Presentation of Figures in ScienceDirect

Functionalities for online browsing on ScienceDirect have been reviewed and improved: for example, the reader can now choose whether to view either thumb-nail or full size graphics when viewing a paper in HTML format.

Tetrahedron Activities

During 2004 there have been a number of significant activities dedicated to the Tetrahedron Publications. These have been well supported by the organic chemistry community, and have proved to be highly successful events.

doi:10.1016/j.tet.2004.11.033

5th Tetrahedron Symposium

Last year's Tetrahedron Symposium was held in New York on 18 June 2004. The theme of the meeting was 'interaction of chemistry and biology', and the event was co-sponsored by *Drug Discovery Today*. The presentations from the invited speakers, including Professors Boger, Danishefsky, Jorgensen, Lipinski, Maryanoff, Posner, Schreiber and Scolnick, enthralled the many delegates attending this international event.

Tetrahedron Chair 2004

The Tetrahedron Chair was awarded to Professor Alois Fürstner, Director of the Max-Planck Institut für Kohlenforschung, Mülheim/Ruhr, Germany. The presentation was made on the opening day of the Tenth Belgium Organic Synthesis Symposium, held in Louvain-la-Neuve, Belgium. As part of the occasion, Professor Fürstner presented a full day lecture entitled 'Metathesis and Beyond' to an estimated 500 symposium delegates.

Tetrahedron Prize Symposium

The 2003 Tetrahedron Prize for Creativity was presented jointly to Professor Robert Grubbs (CALTECH, Pasadena) and Professor Dieter Seebach (ETH, Zürich). The associated Prize Symposium was held at the ACS National Meeting in Philadelphia on 23 August 2004, with over 1000 conference delegates attending their scientific presentations, and those of their co-presenters, Professor Seeberger and Professor Swager.

Tetrahedron Young Investigator Awards

Following the annual meeting of the Executive Board of Editors for Tetrahedron Publications, two new awards were created. These two awards are intended to recognise exceptional creativity and dedication to the scientists' field of research, covering 'Organic Synthesis' and 'Bioorganic & Medicinal Chemistry', respectively. In addition to a cash prize, the two awardees will be invited to present a plenary lecture at the 6th Tetrahedron Symposium being held in Bordeaux (29 June–1 July 2005). A call for nominations is already underway, with a closing date for nominations of 15 January 2005.

2005—The year Ahead

2005 will also see some exciting new developments and activities, several of which are focussed on further improving services to authors, reviewers and readers.

New Chairman

As we enter 2005, Professor Bruce Ganem of Cornell University takes over as Chairman of the Executive Board of Tetrahedron Publications. We congratulate Professor Ganem on his appointment and wish him an enjoyable term as Chairman.

New Online Submission System

Author services will be further improved through the launch of Elsevier's next generation e-submission system. The new system promises improved functionality, stability, and technical support for both authors and reviewers. Publications times are expected to continue to decrease as the benefits of this new submission system are realised.

6th Tetrahedron Symposium—Challenges in Organic Chemistry

The 6th Tetrahedron Symposium will be held in Bordeaux, 29 June–1 July 2005. Previous symposia have been held in Munich, Kyoto, Shanghai, Oxford and New York. Already an impressive list of speakers has been confirmed, and a 'Call for Abstracts' is underway for the symposium poster sessions. Further details may be found at: www.tetrahedron-symposium.elsevier.com

Tetrahedron Prize for Creativity in Organic Chemistry, 2004

The Tetrahedron Prize for 2004 will be presented to Professor Nakanishi at the Fall ACS National Meeting in Washington. The provisional date for the Prize Symposium and presentation of the Award is Monday 29 August 2005.

ScienceDirect and Scopus

ScienceDirect will continue to be enhanced in response to feedback from the community, and new search tools such as Scopus™ promise great advancements in the identification and evaluation of the best articles from all parts of the publishing world. During the year, we plan to launch clickable graphical abstracts within ScienceDirect.

On behalf of Elsevier and the journal Editors, I would like to thank our authors, reviewers and Editorial Board members for their continued support during 2004, and we look forward to 2005 being another successful year for Tetrahedron Publications.

Wishing you all a Happy New Year.

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Dynamic supramolecular porphyrin systems

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Received 19 October 2004

Contents

1. Introduction

In this report, we review recent dynamic supramolecular porphyrin systems in which weak and exchangeable interactions are used for their structure formation. Even though each interaction is weak and easily exchangeable, their accumulation provides thermodynamically stable structures of multi-porphyrins. The functional targets may include, for example, ligand-induced molecular switch, sensor, chiral recognition, and many others. Porphyrins have strong absorption bands in the visible light region, and their remarkable photoelectronic properties provide various molecular devices. In particular, since free base, zinc, and magnesium porphyrins have long singlet excited lifetimes, various systems directed toward artificial photosynthesis have been demonstrated. Zinc and magnesium porphyrins are coordinated by nitrogen ligands, and the coordination

Keywords: Porphyrin; Supramolecule; Non-covalent bond; Dynamic system.
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bond can exchange rapidly. This feature has been applied to the formation of dynamic supramolecular porphyrin complexes. Other stable metal porphyrins, such as Fe(III), Co(III), and Ru(II)CO porphyrins, also bind nitrogen ligands strongly. They are not, however, suitable for dynamic systems because their exchange rates are too slow. We therefore concentrate here on zinc and magnesium porphyrins allowing rapid dynamic processes. Other non-covalent interactions using the large π-plane of porphyrin and peripheral functional groups with outer functional molecules are also rapidly exchangeable and can therefore be used for the dynamic supramolecular porphyrin systems.

Several excellent reviews of supramolecular porphyrin systems have already been published.[1–6] Here, we will focus on how dynamic interactions are assembled to obtain functional expressions of reasonable stability just by mixing in solution. In Section 2, non-covalent bonds which can be used in dynamic supramolecular porphyrin systems are classified and illustrated with their association constants. In Section 3, the formation and characterization of supramolecular multi-porphyrins are introduced. In Section 4, recent functionalized supramolecular porphyrin systems in which a non-covalent bond plays an important role are described.

2. Association constants of non-covalent bonds in supramolecular porphyrin systems

How large an association constant is required for supramolecular porphyrin systems? The answers depend certainly on the concentration of supramolecules to be evaluated. Various spectroscopic methods are used to examine supramolecular porphyrin systems. The concentration limits are determined by the detection limit of each method. In porphyrin systems, the concentration range is generally 10^{-2}–10^{-4} M for high-field NMR, 10^{-4}–10^{-7} M for UV–vis spectra, and 10^{-5}–10^{-8} M for steady-state fluorescence spectra. Although the equilibrium between association and dissociation can be shifted if one side of the component is added in excess amounts, it produces problems in that the excess molecules affect the supramolecular structure and properties. Ideally, it is desirable that the porphyrin and its partner are mixed as an exact ratio to give their composite quantitatively. In these cases, we can treat the composite as a single component, and various analyses are simplified. For example, if two components having an association constant $K_1=10^5\,M^{-1}$ for 1:1 complexation are mixed in a ratio of 1:1, the percentages of the composite are 90.5, 73, and 38.2% in concentrations of 10^{-3}, 10^{-4}, and 10^{-5} M, respectively. In order to obtain the composite in more than 99% yield, 2, 20, and 200 equiv of the partner must be added in concentrations of 10^{-3}, 10^{-4}, and 10^{-5} M, respectively. If the formation of the composite is required in more than 99% yield by mixing in a 1:1 ratio, $K_1=10^7$, 10^8, and $10^9\,M^{-1}$ are required in concentrations of 10^{-3}, 10^{-4}, and 10^{-5} M, respectively. It is very important to obtain association constants higher than 10^8 or $10^9\,M^{-1}$ by elaborate molecular designs. Association constants of supramolecular composites constructed using more than two components have different dimensional units, such as M^{-2} and M^{-3}. In the case of self-organized trimeric porphyrin systems, more than 99% will exist as composites in concentrations of 10^{-3}, 10^{-4}, and 10^{-5} M if the association constants K_2 (K_2 (M^{-2})=[trimer]/[monomer]^3) are larger than 10^{12}, 10^{14}, and $10^{16}\,M^{-2}$, respectively. Similarly, in the case of self-organized tetrameric systems, the association constants K_3 (K_3 (M^{-3})=[tetramer]/[monomer]^4) for the concentrations of 10^{-3}, 10^{-4}, and 10^{-5} M, are required to be larger than 10^{17}, 10^{20}, and $10^{23}\,M^{-3}$, respectively, to obtain the same yield.

In Section 2.1, the association constants of zinc porphyrin with nitrogen ligands are summarized. Zinc porphyrin is one of the most frequently used and important templates for dynamic supramolecular systems. Having a so-called 'labile bond', the zinc porphyrin/nitrogen composite is generally considered to be unstable and difficult to isolate. Tactics for stabilizing 'labile bonds', however, have recently been reported. Many examples are described in order to understand the methods for obtaining high association constants. In Section 2.2, the interaction of porphyrins and fullerenes is described. Relatively strong interactions have been reported recently, and their applications are developing. In Section 2.3, the formation of other labile non-covalent bonds and exchangeable covalent bonds is described.

2.1. Zinc porphyrin/nitrogen ligand coordination

2.1.1. Monotopic interactions. Nitrogen ligands form relatively stable complexes with zinc porphyrin. Since the ligands have no d-orbitals, there is no stabilizing of back donation of electrons from the metal to the ligand. The association constant is therefore determined primarily by the electron donating ability of the ligand. In Table 1, the association constants of substituted pyridines with Zinc octaethylporphyrin (ZnOEP) are listed (see also Fig. 1).

Table 1. Association constants of ZnOEP with pyridine derivatives[7,a]

Run	Porphyrin	Ligand[b]	pK_a[c]	log K	K (M^{-1})
1	ZnOEP	3,5-Cl_2Py	0.67[d]	2.10	1.26×10^2
2	ZnOEP	4-CNPy	1.90	3.01	1.02×10^3
3	ZnOEP	Pyridine	5.17	3.37	2.34×10^3
4	ZnOEP	2-MePy	5.96	1.84	6.93×10^1
5	ZnOEP	4-MePy	6.00	3.67	4.68×10^3
6	ZnOEP	2,4-Me_2Py	6.74	2.25	1.78×10^2
7	ZnOEP	4-NMe_2Py	9.71[d]	4.66	4.57×10^4
8	ZnOEP	Piperidine	11.1	4.55	3.56×10^4

[a] Conditions: 298 K, toluene, UV–vis.
[b] Abbreviations: see Figure 1.
[c] Lange's Handbook of Chemistry, 5th ed. Dean, J. A. McGraw-Hill, 1999.
[d] Ref. 7.

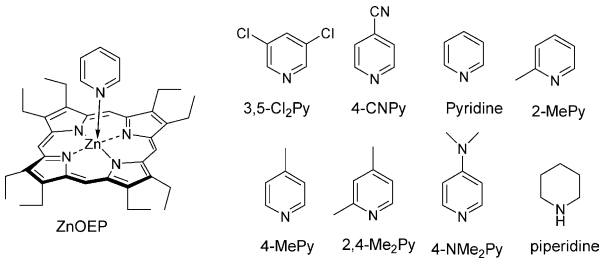

Figure 1. ZnOEP and pyridine derivatives in Table 1.

Except for the 2-substituted pyridines, the association constants increase with increase of the pK_a values (3,5-Cl_2Py < 4-CNPy < Pyridine < 4-MePy < 4-NMe_2Py). In the case of the 2-substituted pyridines (2-MePy, 2,4-Me_2Py), the association constants decrease significantly, because of steric repulsion between the porphyrin plane and the substituent α to the N atom.[7]

In Table 2, the association constants of aromatic and aliphatic amines with zinc tetraarylporphyrins (TPP and TTP) are listed (see also Fig. 2). The relative magnitudes of the association constants of aromatic amines can be estimated from their pK_a values. The more basic (larger pK_a) imidazole has an order of magnitude larger association constant than that of pyridine. In the case of aliphatic amines, the steric effect becomes significant rather than the basicity for determining the association constant. The aliphatic primary amine, *n*-$BuNH_2$, has almost the same association constant as that of imidazole because of its high basicity and low steric hindrance. The association constants decrease significantly, however, for the secondary and tertiary analogues. Cyclic amines have larger association constants than those of non-cyclic amines because of decreased repulsion between the substituents and the porphyrin plane. In particular, dabco has a very large association constant, even though its pK_a is smaller than those of the other aliphatic amines.

Association constants in non-coordinating solvents decrease in the order cyclohexane > benzene = toluene = CH_2Cl_2 > $CHCl_3$ (Table 3). Commercially available $CHCl_3$ includes a small amount of coordinating ethanol as a stabilizer and its removal or not must be noted. In weakly coordinating solvents, such as benzonitrile, DMF, and THF, the determination of association constants becomes difficult. A coordination interaction having strong association constants is, however, sometimes observed in such coordinating solvents.

Table 2. Association constants of ZnTPP and ZnTTP with amines[a]

Run	Porphyrin	Ligand	pK_a[b]	log *K*	*K* (M^{-1})	Solvent	Reference
1	ZnTTP	Pyridine	5.17	3.52	3.3×10^3	Toluene	8
2	ZnTTP	1-MeIm	7.06	4.66	4.6×10^4	Toluene	8
3	ZnTPP	1-MeIm	7.06	4.73	5.4×10^4	Toluene	9
4	ZnTPP	Im	6.99	4.73	5.4×10^4	Toluene	10
5	ZnTTP	*n*-$BuNH_2$	10.64	4.4	2.5×10^4	Toluene	8
6	ZnTTP	Et_2NH	10.8	3.15	1.4×10^3	Toluene	8
7	ZnTPP	Et_3N	10.72	1.1	1.3×10^1	Benzene	11
8	ZnTTP	Azetidine	11.29	5.51	3.2×10^5	Toluene	8
9	ZnTTP	Pyrrolidine	11.3	3.32	2.1×10^3	Toluene	8
10	ZnTTP	Piperidine	11.1	4.84	6.9×10^4	Toluene	8
11	ZnTPP	Dabco[c]	8.60, 2.90	5.2	1.6×10^5	Benzene	11

[a] Conditions: 298 K, UV–vis.
[b] Lange's Handbook of Chemistry, 5th ed. Dean, J. A. McGraw-Hill, 1999.
[c] dabco = 1,4-diazabicyclo[2.2.2]octane.

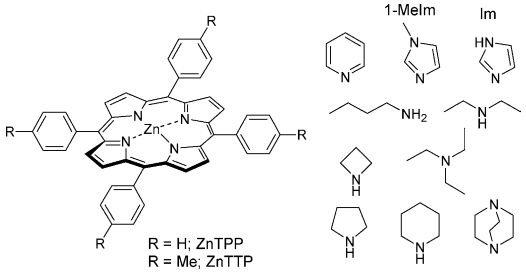

Figure 2. ZnTPP, ZnTTP, and amines in Table 2.

2.1.2. Ditopic interactions. Ditopic interactions, in which two porphyrins linked by appropriate spacers interact with a bisnitrogen ligand, raise the association constant by the operation of proper cooperativity.[5] The magnitude of the association constants depends on the mutual agreement of distance and orientation between the host (bisporphyrin) and guest (bisnitrogen ligand), and their rigidity. Sanders examined the association constants of bisporphyrins linked

Table 3. Association constant of ZnTPP with pyridine in various solvents[a]

Run	Solvent	log *K*	*K* (M^{-1})	Reference
1	Cyclohexane	4.4	2.51×10^4	12
2	CH_2Cl_2	3.84	6.92×10^3	13
3	Toluene	3.78	6.03×10^3	10
4	Benzene	3.7	5.01×10^3	14
5	$CHCl_3$	2.79	6.17×10^2	15

[a] Conditions: 298 K, UV–vis.

by rigid acetylene bonds. The association constant of bipyridine and bisporphyrin **2** linked by one bisacetylene bond is $6\times10^{6}\ M^{-1}$, which is three orders of magnitude larger than that of the monotopic system **1**. In the case of bisporphyrin **3** linked by two bisacetylene bonds, the association constant increases to $1\times10^{9}\ M^{-1}$ (Fig. 3).

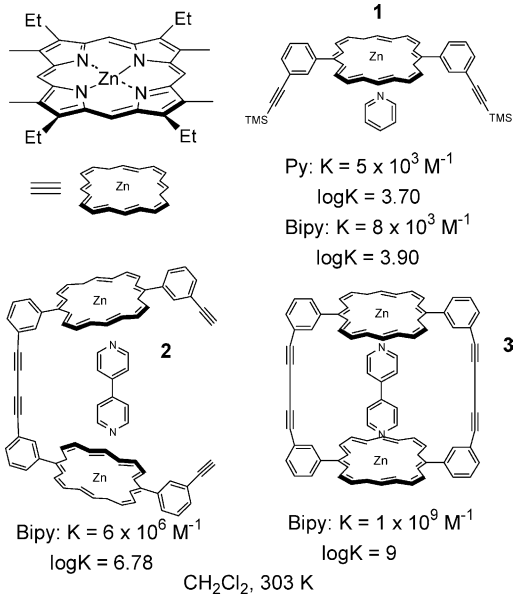

Figure 3. Mono- and bisporphyrins linked by bisacetylene.[5]

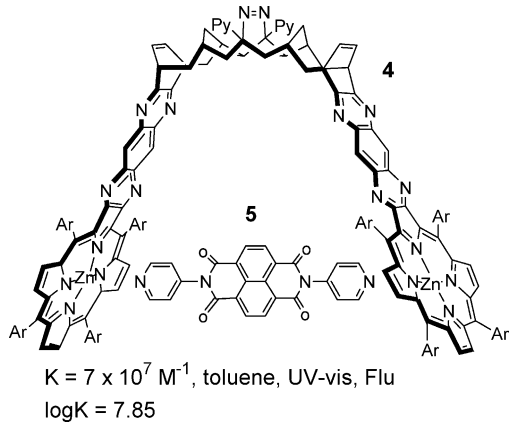

Figure 4. V-shaped bisporphyrin and bispyridyl(naphthalenediimide).[16]

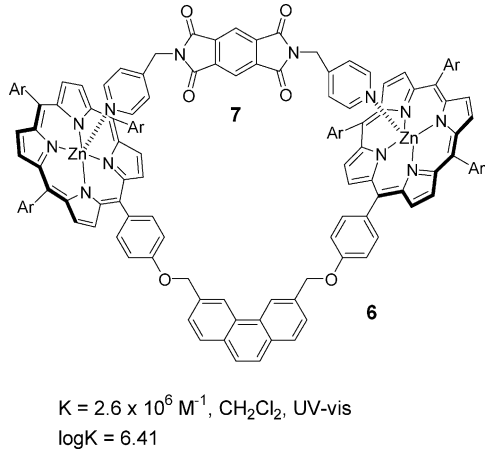

Figure 5. Zinc porphyrin dimer and bispyridylpyromellitimide.[17]

A combination of a bisporphyrin and a bisnitrogen ligand having an electron acceptor can form a stable supramolecular photo-excited electron transfer system. In the case of the composites **4/5** and **6/7**, the association constant exceeds $10^{6}\ M^{-1}$ (Figs. 4 and 5), and photophysical measurements are possible by mixing the two components under dilute conditions around 10^{-6} M. In both examples, fast electron transfer rates ($>10^{10}\ s^{-1}$) are reported.[16,17]

2.1.3. Tritopic and tetratopic interactions. Tritopic systems, in which three porphyrins are linked to one another, can interact with trisnitrogen ligands with very large association constants ($>10^{8}\ M^{-1}$). In such systems, only the mixing of host e.g. **8**, **10** and **12** and guest **9**, **11**, and **13** in a 1:1 ratio is enough to afford a complete composite, even in micromolar concentrations. Various sizes of ring were synthesized by the choice of spacers between the zinc porphyrins (Figs. 6–8).[5,18,19]

Further, tetratopic systems **14** and **16** have also been

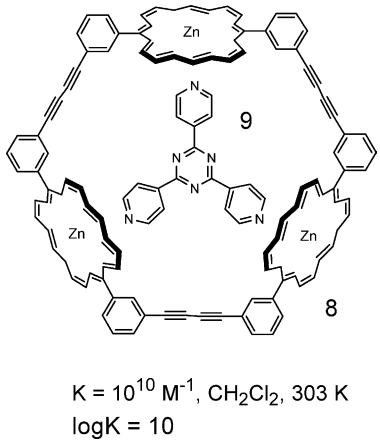

Figure 6. Trisporphyrin **8** linked by bisacetylene and a guest **9**.[5]

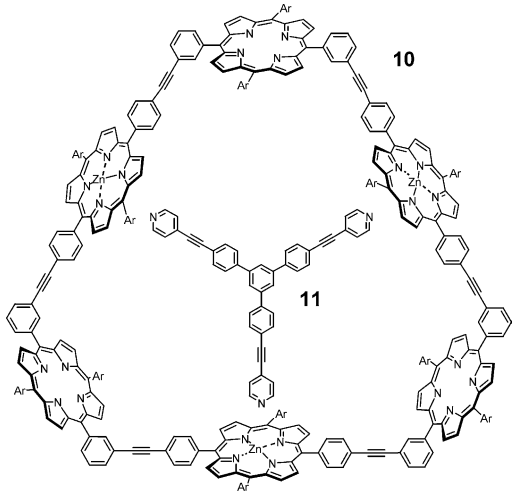

Figure 7. Cyclic porphyrin hexamer **10** and a tripyridyl guest **11**.[18]

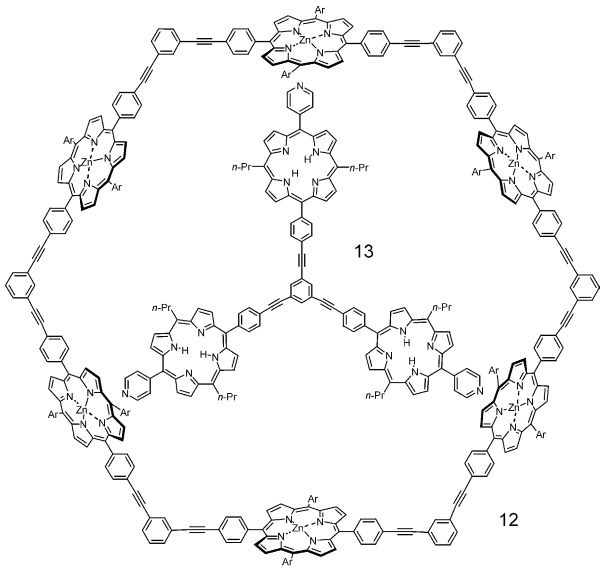

Figure 8. Cyclic porphyrin hexamer **12** and star-shaped porphyrin array **13**.[19]

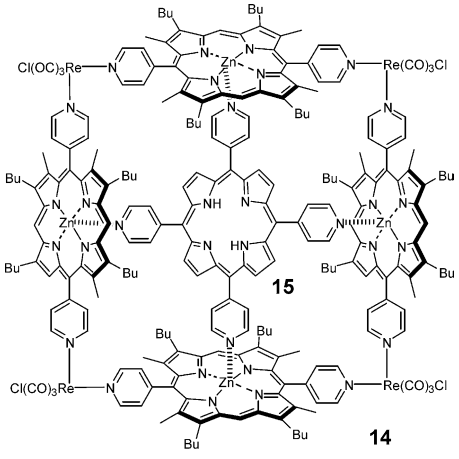

Figure 9. Zinc tetraporphyrin square **14** and tetrapyridylporphyrin **15**.[20]

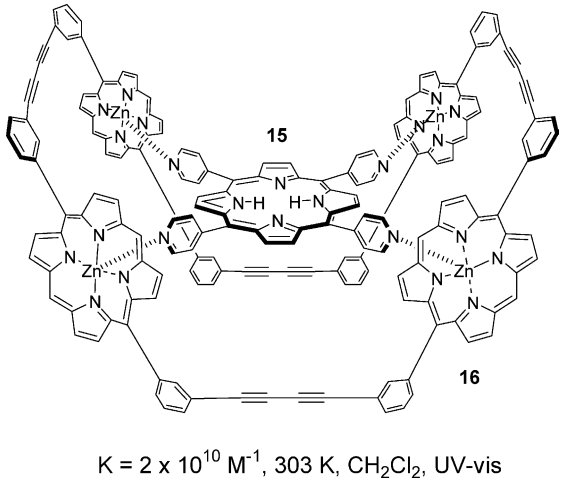

Figure 10. Tetraporphyrin **16** linked by bisacetylene.[5,21]

reported with high association constants. *meso*-Tetra-(4-pyridyl)porphyrin **15** was used as a rigid tetratopic guest (Figs. 9 and 10).[20–22]

2.1.4. Complementary coordination. Zinc porphyrins appended with nitrogen ligands interact with each other to form complementary dimers or multi-composites, more than two participating. In general, a large association constant is expected by the complementary nature.

When the coordination angle of the nitrogen ligand is adjusted to approximately 90° from the zinc porphyrin plane, an ideal geometry for dimer formation is expected. The stability of the dimer depends mainly on the directional angle of the lone pair and the rigidity of the spacer linking the ligand and porphyrin. Porphyrins to which 2-imidazolyl and 2-pyridyl groups are directly attached can afford complementary dimers. In the dimer, two porphyrins take a slipped co-facial form, and the Soret band is characteristically split by excitonic coupling between two porphyrin chromophores. The characteristic bands are a good indicator of dimer formation, and are useful for effective light-harvesting of visible light by expanded absorption bands and play a key role in photoinduced charge separation.[23] The dimer structure has a very close similarity to that of a special pair in photosynthetic bacteria. Schugar reported dimer formation of a 2-pyridylporphyrin **17** in a 5.2×10^{-5} M solution of CH_2Cl_2,[24] without mentioning its self-association constant (Fig. 11). Although we tried to follow the dimer formation by use of 5-(2-pyridyl)-10,20-(4-ethoxycarbonylphenyl)porphyrin, the characteristic split Soret band was not observed at a concentration of 5×10^{-5} M in $CHCl_3$. We concluded that the self-association constant of 2-pyridylporphyrin was not very high and its dimer formation might be sensitive to the substituents and experimental conditions. On the other hand, various

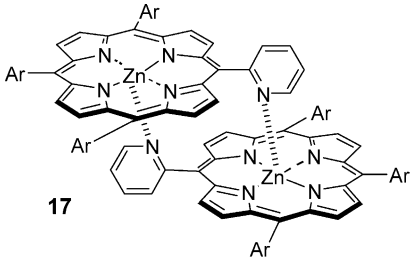

Figure 11. Self-coordinating Zn 2-pyridylporphyrin dimer **17**.[24]

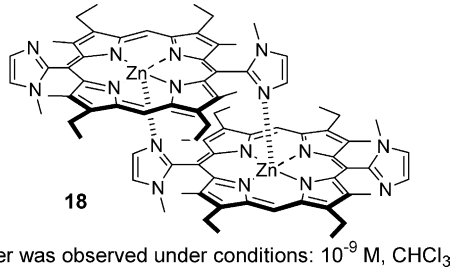

Figure 12. Complementary coordination dimer of Zn imidazolylporphyrin **18**.[25]

2-imidazolylporphyrins afford complementary dimers **18** almost completely even in 10^{-6} M or more dilute solutions of $CHCl_3$ (Fig. 12).[25] Competitive titration by 1-methylimidazole indicated the self-association constant was over 10^{10} M^{-1}, and dilution experiments (up to 10^{-8} M) also supported this order of values. There are some differences between 2-pyridyl- and 2-imidazolyporphyrins. In the former, the coordination angle from the porphyrin plane should be 60° and 72° in the latter (Fig. 13). Strain from the ideal coordination angle, 90° and steric hindrance of the hydrogen atom at α to the nitrogen atom on coordination should decrease significantly the association constant of 2-pyridylporphyrin.

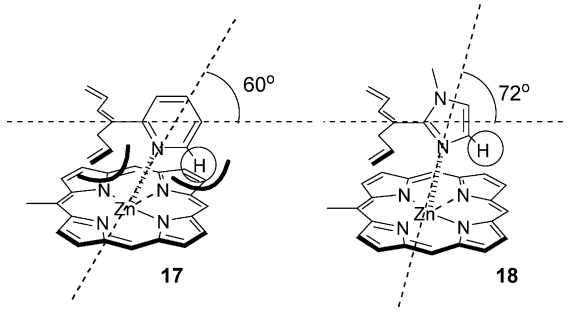

Figure 13. Comparison of coordination angle of dimers **17** and **18**.

The geometry of the imidazolyl group affects also the association constant.[26] The association constants for 2-imidazolyl- and 4-imidazolylporphyrins **19** and **20** in $CHCl_3$ were determined as 3.3×10^{11} and 8.1×10^{9} M^{-1}, respectively, by competitive UV–vis titration with *N*-methylimidazole (Fig. 14) and a stereoelectronic effect is considered to be operating. In any event, zinc 2-imidazolylporphyrin (**ZnImPor**) is one of the strongest self-assembly units, and its dimer motif is employed as a useful scaffold for further applications, which are described in the later parts of this report.

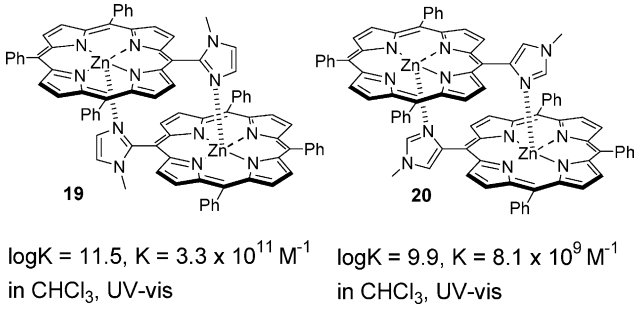

Figure 14. Comparison between dimers of Zn 2- and 4-imidazolylporphyrins **19** and **20**.[26]

When pyridine is linked at the 4-position through appropriate spacers to porphyrin to satisfy the angle requirement, stable complementary dimers are formed. Hunter reported stable dimers **21** by linking with pyridineamide spacers.[27,28] Since the two porphyrins are separated from each other, no excitonic coupling is observed (Fig. 15).

Other complementary dimers are reported for anilino-zincporphyrins **22** and **23**,[29] diaza-18-crown-6-zinc porphyrins **24**,[30] pyridine-3-boronic acid derivatives **25**,[31]

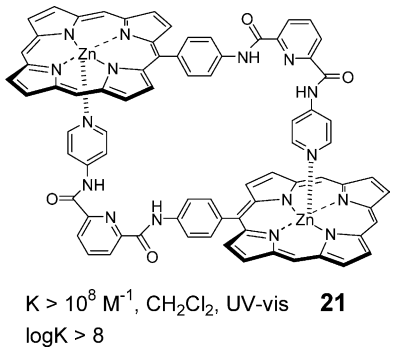

Figure 15. Macrocyclic porphyrin dimer **21**.[27,28]

ferrocene derivatives,[32] and amine-tethered zinc porphyrins **26** (Figs. 16–19).[33] Although complementarity was observed to some extent, the association constants were not very high. The dimer of amine-tethered zinc porphyrins

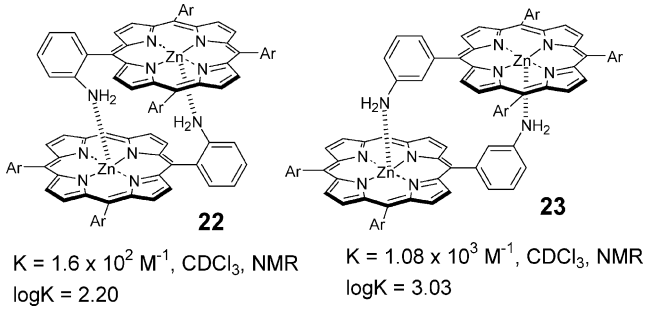

Figure 16. Complementary coordination dimer of Zn anilino-porphyrins **22** and **23**.[29]

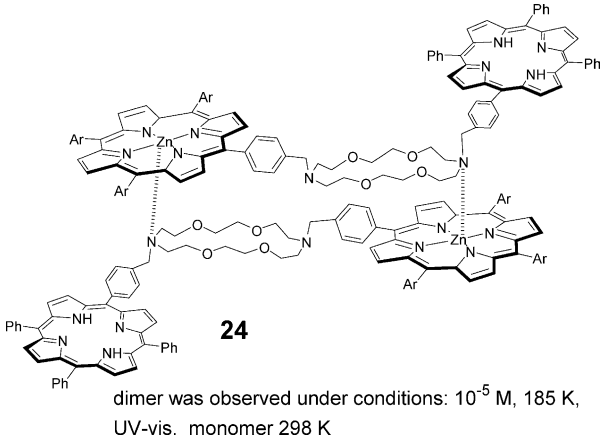

Figure 17. Dimerization of azacrownoporphyrin **24**.[30]

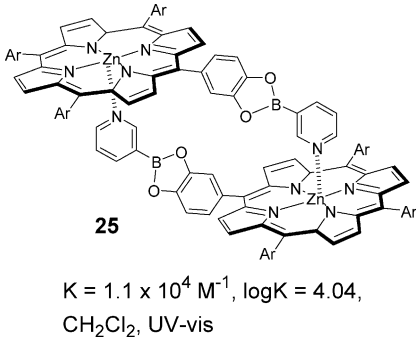

Figure 18. Self-assembled dimer composed of Zn catechol porphyrin and pyridine-3-boronic acid.[31]

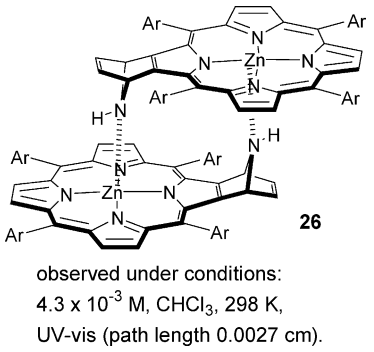

Figure 19. Amine-tethered porphyrin dimer **26**.[33]

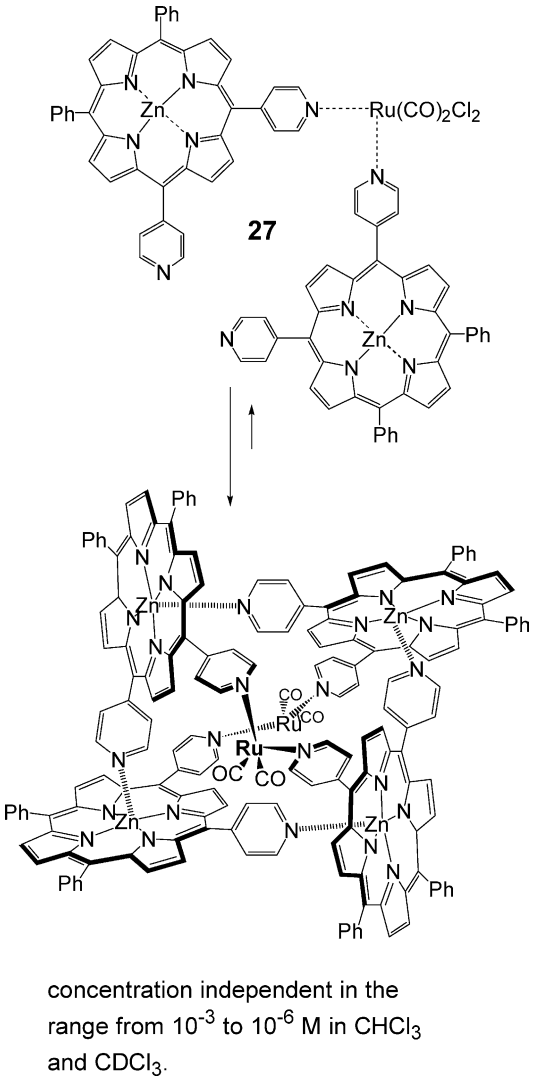

Figure 20. Dimerization of bis 4-(pyridylporphyrin) **27**.[34]

26 showed excitonic coupling in the Soret band. Alessio reported dimerization of bis(4-pyridylporphyrin) **27** linked by a ruthenium/pyridine bond (Fig. 20).[34]

When the coordination angle of the nitrogen ligand is adjusted to 120 and 180°, cyclic trimers **28**[35–37] and tetramers **29**[36] are formed, respectively (Figs. 21 and 22). Although Fleischer and Shachter[38] reported the formation of a linear polymer of 4-pyridyltriphenylporphyrin **30** in the solid state, Hunter,[36] Imamura,[39] and Ercolani[40] concluded that **30** gave a cyclic tetramer exclusively in solution. Computer simulation by Hunter predicted that the linear polymer should appear at a high concentration range (>1 M).[35] Osuka reported an X-ray crystal structure of the cyclic tetramer of **31** (Fig. 23).[41] As the number of components increases, the formation of a cyclic multi-porphyrin in solution becomes unfavorable and the cyclic hexamer of **26** was obtained only as crystals (Fig. 24).[33] Osuka developed the cyclic tetramer strategy to *meso–meso* linked bis(pyridylporphyrin) **32** to give box-type porphyrins (Fig. 25).[41]

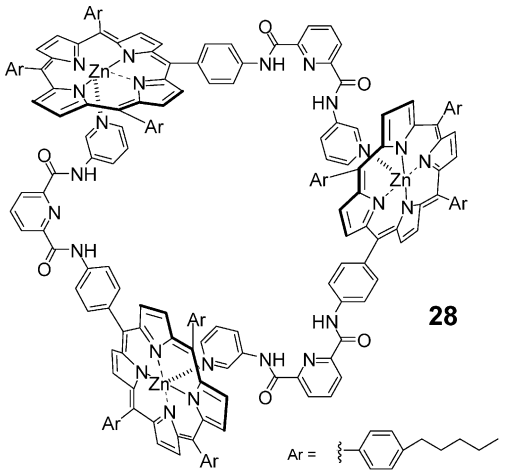

Figure 21. Cyclic trimer of **28**.[36]

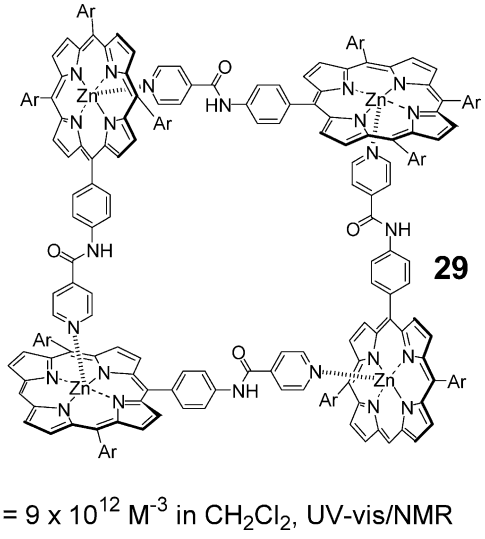

Figure 22. Cyclic tetramer of **29**.[36]

2.1.5. Combination with other interactions. The association constants of zinc porphyrin and pyridine in $CHCl_3$ are approximately of the order of $10^3\ M^{-1}$. Combination with other interactions increases an association constant significantly.

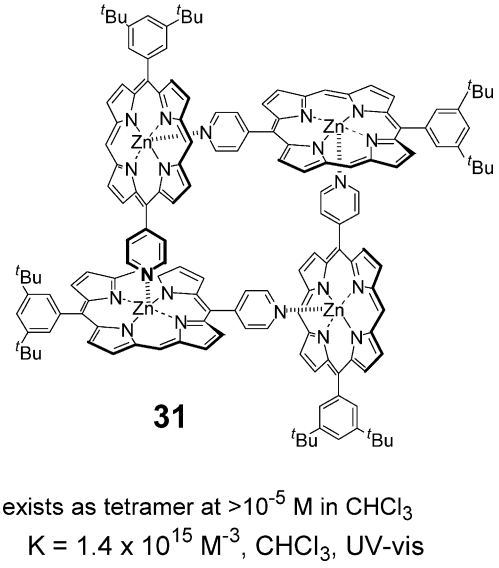

Figure 23. Cyclic tetramer of **31**.[41]

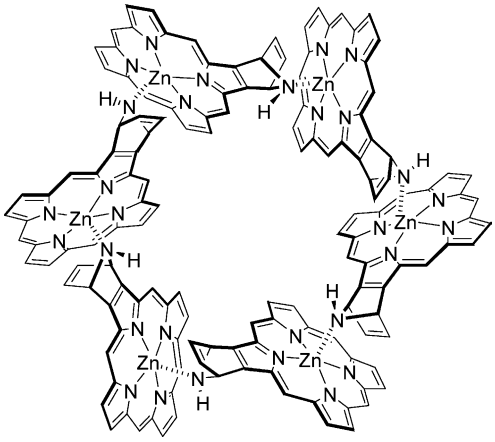

Figure 24. Cyclic hexamer of amine-tethered porphyrin **26**.[33]

Hydrogen bonding between zinc porphyrin and a ligand assists the coordination. D'Souza prepared zinc porphyrin having carboxylic acid (**33**) and amide groups (**34**), and examined the interaction with nicotine and cotinine. The association constant of **33** and the nicotine composite was 60-fold larger than that of ZnTPP and nicotine. In the case of **34**, 2- to 9-fold larger values are observed (Fig. 26 and Table 4).[42]

A porphyrin clip **35** derived from diphenylglycoluril (Fig. 27) interacts with some guests by a variety of interactions, namely by hydrogen-bonding with the carbonyl functions, by π–π interactions with the aromatic walls, by hydrogen-bonding and dipole interactions with the crown ether moieties, and by coordination to the zinc metal ion. The association constant with pyridine was two orders of magnitude larger than that of ZnTPP. Coordination of 3-hydroxypyridine is further assisted by hydrogen bonding to a carbonyl group to bring a 300-fold increase over that of pyridine.[43] A cavity effect of Zn(II) picket fence porphyrin was also reported by Kyuno. The association constant of

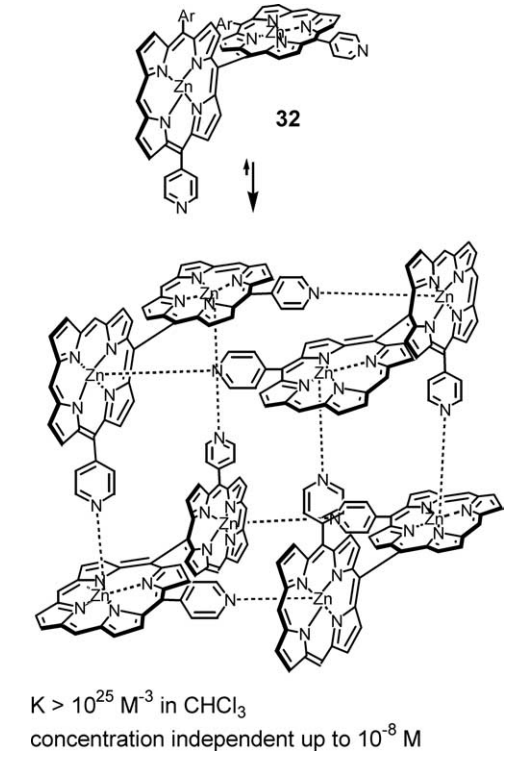

Figure 25. Self-assembled porphyrin box $(\mathbf{32})_4$.[41]

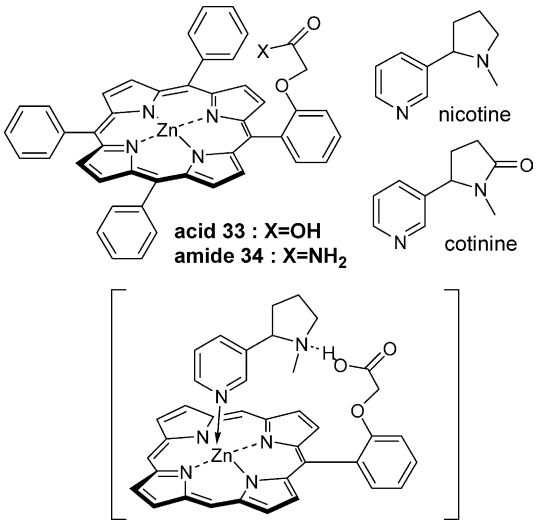

Figure 26. Structure of acid **33**, amide **34**, nicotine, and cotinine in Table 4.[42]

pyridine was enhanced by a CH–π interaction between pivalamide groups and pyridine.[44]

Ikeda noticed the assistance of hydrogen bonding between ester porphyrins and pyrazole.[37] The association constant of pyrazole with the ester porphyrin **36** is 10-fold larger than that with ZnTTP. This system was applied to the stabilization of the cyclic trimer of **37**, and the structure could be analyzed by ^{1}H NMR (Fig. 28).

In water, a hydrophobic interaction among alkyl chains affects the association constant significantly. Mizutani

Table 4. Association constants of nicotine and cotinine to porphyrins **33** and **34**[a,42]

Run	Porphyrin	Ligand	log K	K (M^{-1})
1	ZnTPP	Nicotine	3.84	6.9×10^3
2	ZnTPP	Cotinine	3.85	7.0×10^3
3	Acid **33**	Nicotine	5.65	4.5×10^5
4	Acid **33**	Cotinine	4.62	4.2×10^4
5	Amide **34**	Nicotine	4.80	6.3×10^4
6	Amide **34**	Cotinine	4.23	1.7×10^4

[a] Conditions: 298 K, toluene, UV–vis.

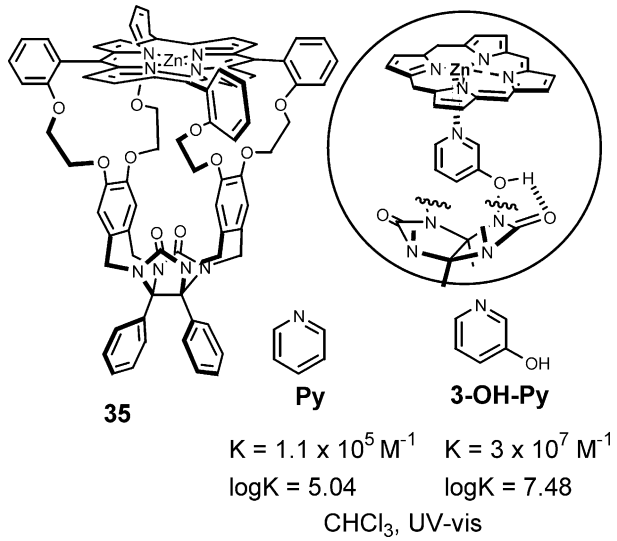

Figure 27. Binding of porphyrin clip **35** with pyridines.[43]

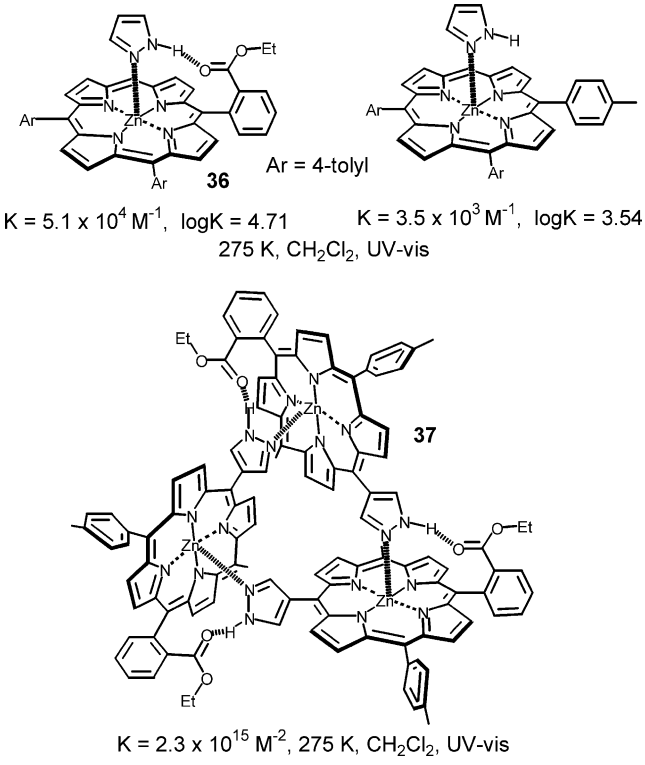

Figure 28. Binding of ester porphyrin **36** with pyrazole, and self-assembled trimer of **37**.[37]

reported association constants of 4-alkylpyridines with amphiphilic zinc porphyrin (Table 5). In the case of 4-pentylpyridine with porphyrin **38**, the association constant increases by >150-fold, compared with simple pyridine. This hydrophobic interaction almost disappears in porphyrin **39** (Fig. 29).[45]

2.2. Fullerene/porphyrin interactions

Fullerenes are known as excellent electron acceptors because of their small re-organization energy. Various reports are available for photo-excited electron-transfer systems of porphyrins and fullerene by covalent[46] and coordination[47–50] methodologies. A direct π–π interaction of porphyrins and fullerene was first reported in the crystal of a covalently linked composite,[51,52] and a strong interaction of bisporphyrins with fullerenes has subsequently been reported in solution. The association constant of the relatively flexible bisporphyrins **40**, **41**, and **42** with C_{60} was approximately $5\times10^3\ M^{-1}$ (in toluene).[53–55] When two porphyrins were tightly connected by two pillars, the value increased to $6\times10^5\ M^{-1}$ (**43**, M=Zn) (Figs. 30–33).[56,57] Interestingly, the association constants are altered by changing the central metal ion of the porphyrin. The strongest association constant, $2.5\times10^7\ M^{-1}$, was obtained with Rh(III) porphyrin (Table 6).[57] In general, the association constant of C_{70} is larger than that of C_{60}. It arises from an oval shape of C_{70}, since a larger contacting area of the π–π interaction is obtained by a side-on conformation of C_{70}.

The strength of the interaction between porphyrin and fullerene is affected by peripheral substituents on the porphyrin. Shirai reported that the association constant of the monoporphyrin **44** having dendritic substituents with C_{60} was $2.57\times10^4\ M^{-1}$, although no interaction was observed in the first-generation dendrimer **45** (Fig. 34).[58]

Porphyrin/fullerene composites having amide or carboxylic acid groups gave one-dimensional wires by self organization. Shinkai reported that a 2:1 composite of an octaamide porphyrin **46** and C_{60} grew perpendicularly to give a linear wire by a hydrogen-bonding interaction (Fig. 35). SEM and TEM showed direct images of the fibrous structures.[59] Aida synthesized bisporphyrin **47** having six carboxylic acid groups and large dendritic substituents (Fig. 36).[60] In this case, the composite with C_{60} is extended horizontally by hydrogen-bonding interactions. The TEM image shows uniform fibers with a diameter of 15 nm corresponding to supramolecular wire, as shown in Figure 36. The fiber is only formed in the presence of both C_{60} and carboxylic acid groups.

Table 5. Association constants of alkylpyridines to **38** and **39** in water[a,45]

Run	Pyridine	Porphyrin **38**		Porphyrin **39**	
		log K	K (M^{-1})	log K	K (M^{-1})
1	Py	3.8	6.31×10^{3}	2.5	3.16×10^{2}
2	4-MePy	4.2	1.58×10^{4}	2.9	7.94×10^{2}
3	4-EthylPy	4.7	5.01×10^{4}	3.0	1.00×10^{3}
4	4-PropylPy	5.3	2.00×10^{5}	3.2	1.58×10^{3}
5	4-ButylPy	6.0	1.00×10^{6}	3.2	1.58×10^{3}
6	4-PentylPy	>6	$>1.00\times10^{6}$	3.1	1.26×10^{3}

[a] Conditions: 298 K, pH 7 phosphate buffer, UV–vis.

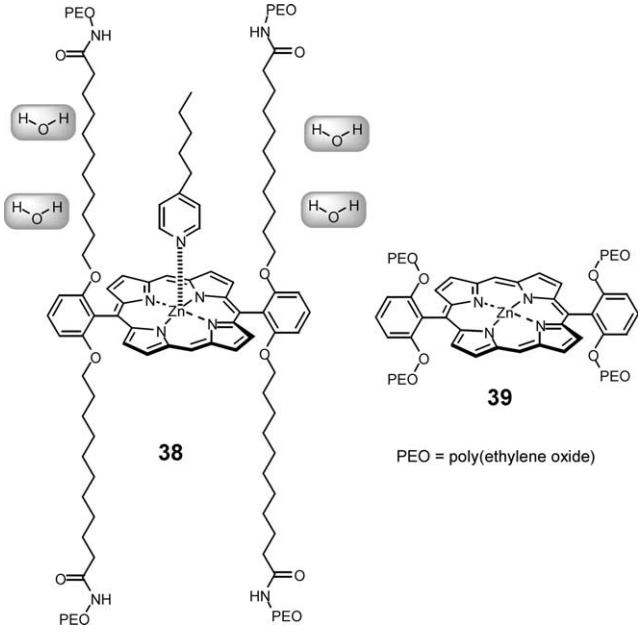

Figure 29. Binding of porphyrins **38** and **39** with alkylpyridines in water.[45]

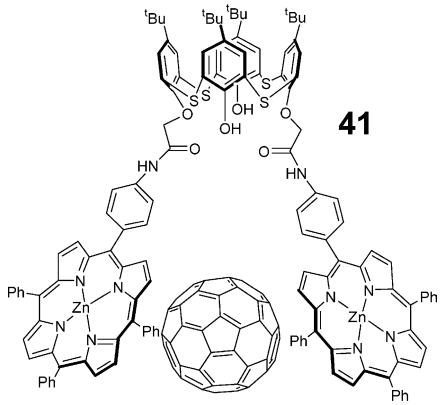

Figure 31. Association of bisporphyrin **41** with fullerenes.[54]

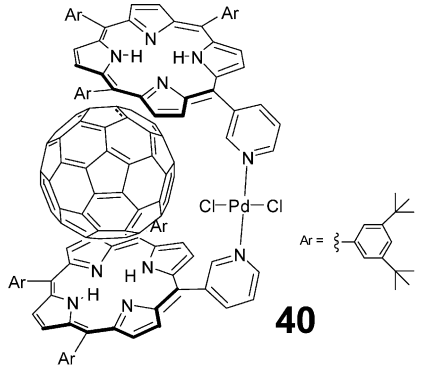

Figure 30. Association of bisporphyrin **40** with C_{60}.[53]

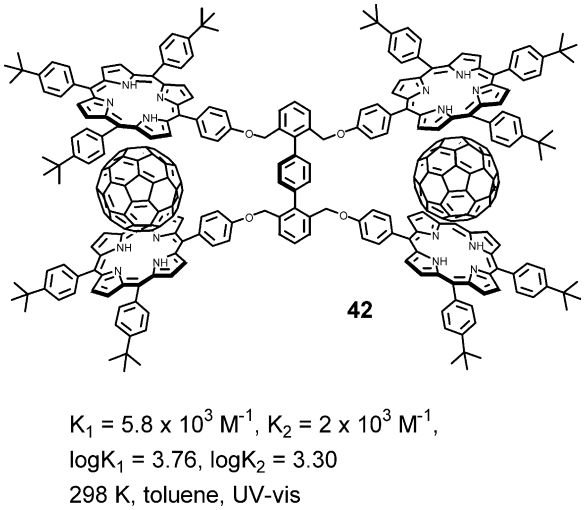

Figure 32. Association of tetraporphyrin **42** with two fullerenes.[55]

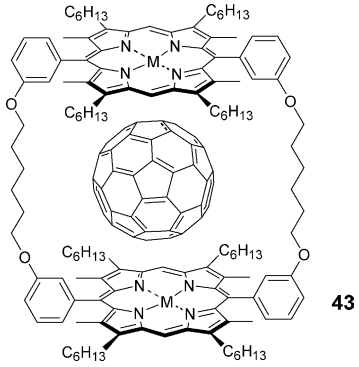

Figure 33. Association of bisporphyrin **43** (M=2H, Co(II), Rh(III), Ni(II), Cu(II), Ag(II), or Zn(II)) with fullerenes (see Table 6).[57]

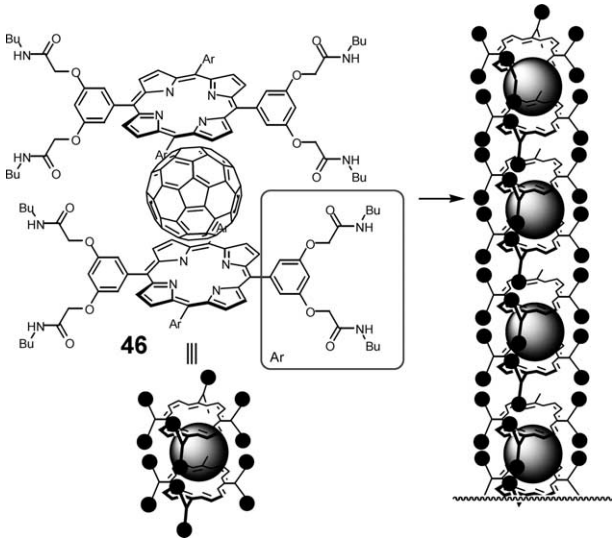

Figure 35. Structure of octa-amide porphyrin **46** and its supramolecular aggregate in the presence of C_{60}.[59]

Table 6. Association constants of porphyrins **43** with fullerenes[a,57]

Run	Porphyrin **43**	Fullerene	log *K*	*K* (M^{-1})
1	M=2H	C_{60}	5.9	7.9×10^5
2	M=2H	C_{70}	7.2	1.6×10^7
3	M=Co(II)	C_{60}	6.3	2.0×10^6
4	M=Co(II)	C_{70}	7.1	1.3×10^7
5	M=Rh(III)	C_{60}	7.4	2.5×10^7
6	M=Rh(III)	C_{70}	8.0	1.0×10^8
7	M=Ni(II)	C_{60}	5.4	2.5×10^5
8	M=Ni(II)	C_{70}	6.3	2.0×10^6
9	M=Cu(II)	C_{60}	5.7	5.0×10^5
10	M=Cu(II)	C_{70}	6.7	5.0×10^6
11	M=Ag(II)	C_{60}	5.1	1.3×10^5
12	M=Ag(II)	C_{70}	6.5	3.2×10^6
13	M=Zn(II)	C_{60}	5.8	6.3×10^5
14	M=Zn(II)	C_{70}	7.3	2.0×10^7

[a] Conditions: 298 K, benzene, UV–vis.

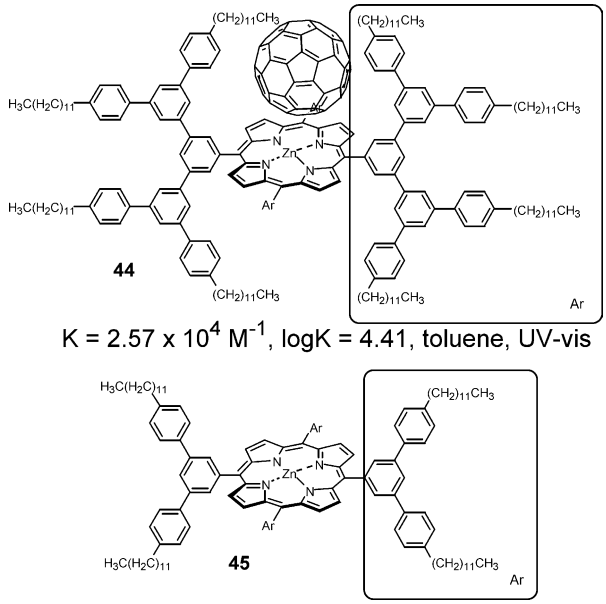

Figure 34. Structures of dendritic porphyrins **45** and **45**.[58]

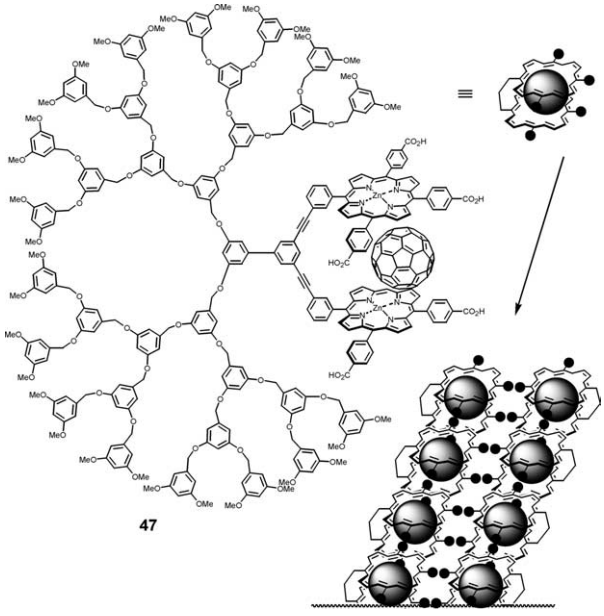

Figure 36. Structure of dendritic hexacarboxylic acid bisporphyrin **47** and its supramolecular aggregate in the presence of C_{60}.[60]

2.3. Other interactions

2.3.1. Hydrogen bonding. There are many examples of non-covalently linked porphyrin/acceptor systems.[1,2,61,62] Hayashi and Ogoshi reported a strong hydrogen-bonding interaction between α,α,α,α-hydroxynaphthylporphyrin **48** and tetramethoxy-*p*-benzoquinone ($2\times10^4\ M^{-1}$ in $CHCl_3$ at 298 K, UV–vis) (Fig. 37). This value is 670-fold larger than that of *p*-benzoquinone.[63]

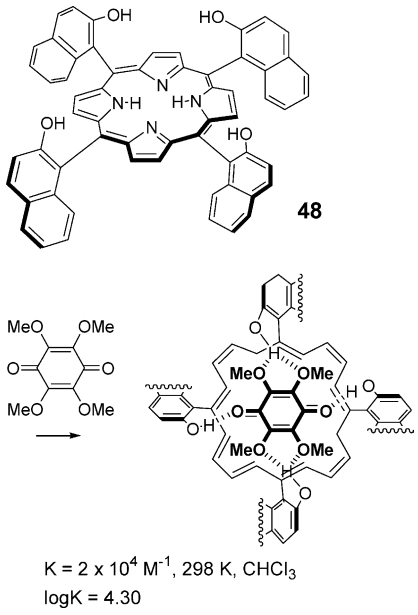

Figure 37. α,α,α,α-Hydroxynaphthylporphyrin **48** and tetramethoxy-*p*-benzoquinone.[63]

Carboxylic acids tend to form dimers in less polar solvents. The association constant of the porphyrin-carboxylic acid **49** and dinitrobenzoic acid is $5.5\times10^2\ M^{-1}$ (Fig. 38). Although this value is not very large, it is noteworthy that the electron-transfer rate through the non-covalent bond is of a high magnitude ($>10^{10}\ s^{-1}$).[64]

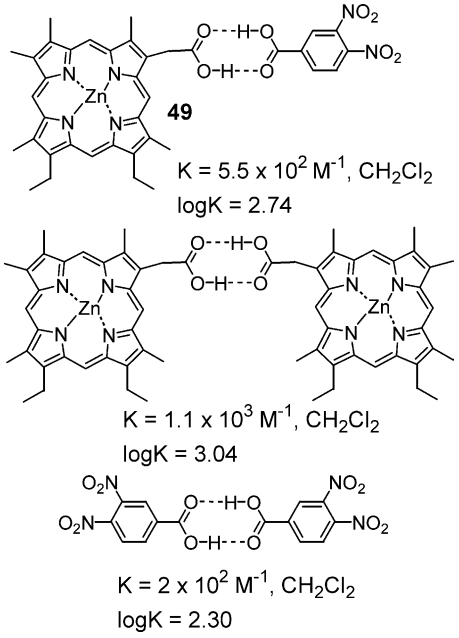

Figure 38. Porphyrin-carboxylic acid **49** and dinitrobenzoic acid.[64]

The heterolinking of two different carboxylic acids is always accompanied by the formation of two different homodimers. The use of a complementary pair elegantly selects the heterodimer formation. Nocera reported the selective formation of heterocomposite of amidine porphyrin and 3,4-dinitrobenzoic acid ($3.5\times10^3\ M^{-1}$ in DMSO-d_6 at 23.5 °C).[65] Other heterocomposites were synthesized by the use of a Watson–Crick base pair **50/51** (Fig. 39)[66] and a barbiturate/bisdiamidopyridine system **52/53**. In the latter case, a large association constant was obtained by the use of a multi-hydrogen bonding interaction (Fig. 40).[67] Sapphyrin **54**, an energy acceptor of porphyrin, can form a hetero-composite with the carboxylic acid **55** (Fig. 41).[68]

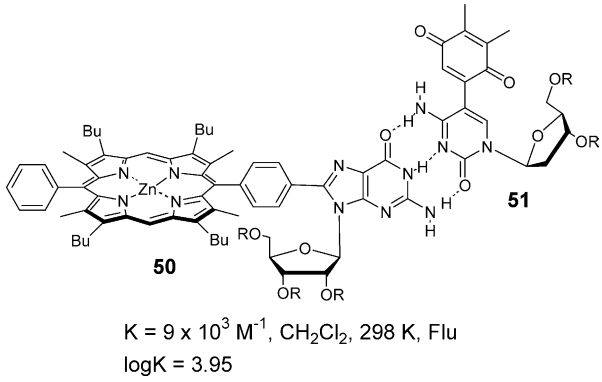

Figure 39. Heterocomposites **50/51** by Watson–Crick base pair.[66]

The α,α,α,α-tetra-urea-functionalyzed porphyrin **56** interacts strongly with sugars in non-polar solvents. Since the addition of water and methanol decreases the association constant, hydrogen bonding between the urea and hydroxyl groups is considered to stabilize their complex (Fig. 42).[69]

The tetrahydroxy-calix[4]arene **57** and tetra(2-pyridyl)porphyrin **58** give a complex by a tetratopic hydrogen bonding interaction (Fig. 43).[70]

Branda synthesized a stable porphyrin/ferrous-terpyridine complex **59/60** by the use of two hydrogen-bonding couples between the urea and carboxylic acid (Fig. 44).[71]

The zinc α,α,α,α-tetra(2-carboxyphenyl)porphyrin **61** forms a very stable dimer ($K>10^7\ M^{-1}$) by cooperative hydrogen bonding (Fig. 45). Since the zinc complex **61** interacts strongly with pyrazine ($K>10^7\ M^{-1}$), this system was applied to non-covalent light-harvesting antenna, as will be described later.[72]

Drain has reported the cyclic tetramers $(\mathbf{62})_4$ and $(\mathbf{62})_2/(\mathbf{63})_2$ by the use of self dimerization of 2,6-diacetamidopyridine and a complementary interaction with uracil (Fig. 46).[73,74]

Lehn synthesized a cyclic hexaporphyrin **64** based on a strategy of complementary hydrogen bonding among three triaminotriazines and three dialkylbarbituric acids

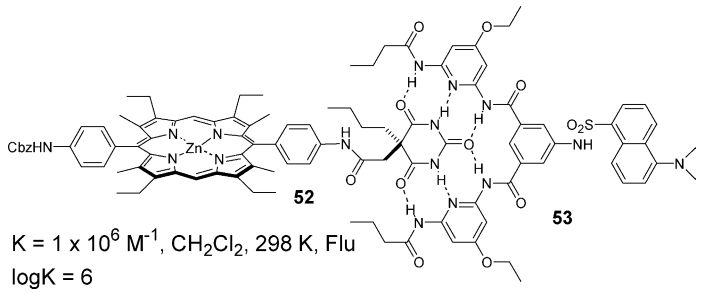

Figure 40. Heterocomposites **52/53** by barbiturate/bisdiamidopyridine pair.[67]

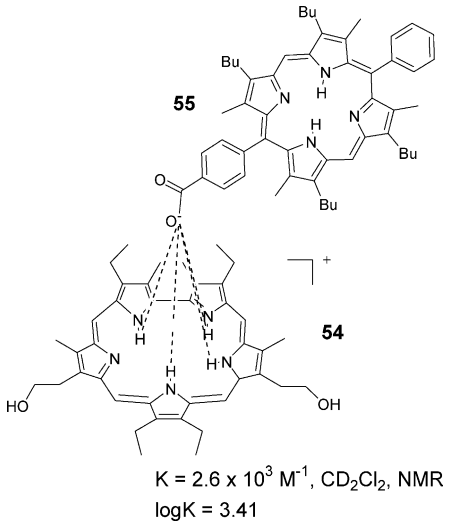

Figure 41. Sapphyrin **54** and porphyrin benzoic acid **55**.[68]

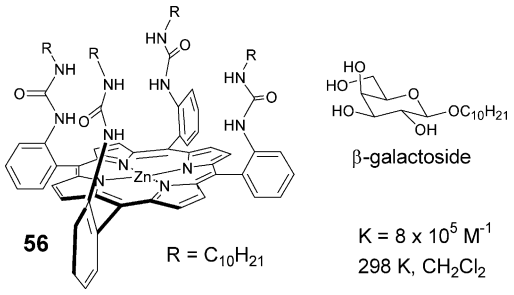

Figure 42. α,α,α,α-Tetraurea-functionalyzed porphyrin **56** and β-galactoside.[69]

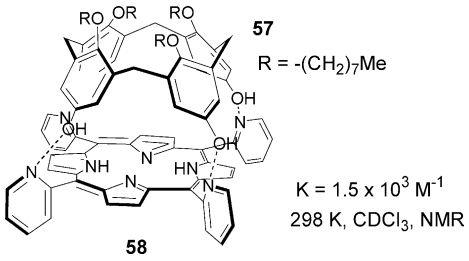

Figure 43. Tetrahydroxy calix[4]arene **57** and tetra(2-pyridyl)porphyrin **58**.[70]

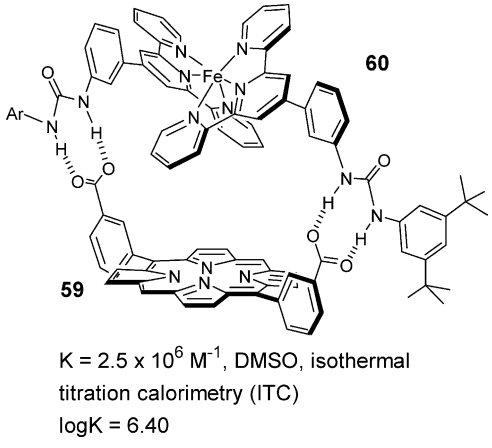

Figure 44. Porphyrin/ferrous terpyridine complex **59/60**.[71]

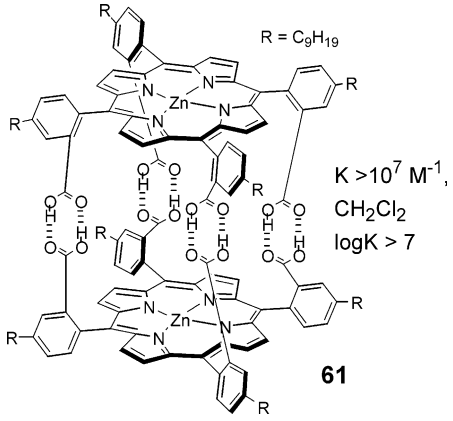

Figure 45. Dimer of α,α,α,α-tetra(2-carboxyphenyl)porphyrin **61**.[72]

(Fig. 47).[75] The cyclic structure was observed in a concentration of >100 μM in CH_2Cl_2.

2.3.2. Crown ether derivatives. Several non-covalent multi-porphyrin[76–79] and phthalocyanine[80,81] systems have employed crown ethers as units interacting with various cationic ions and molecules, such as ammonium and pyridinium derivatives. When an electron acceptor having a cationic moiety is used, a non-covalent donor/acceptor system can be constructed by using a crowned porphyrin.

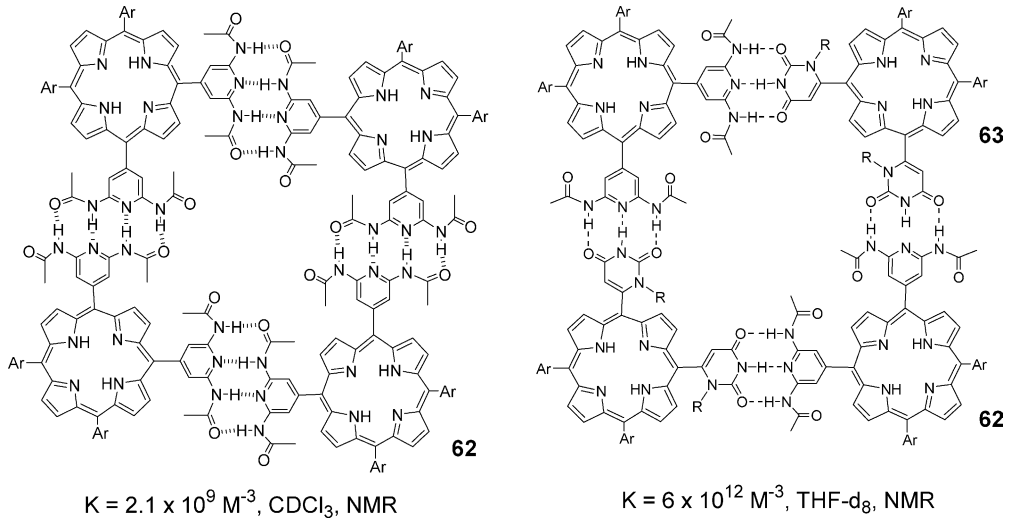

Figure 46. Cyclic tetramers $(\mathbf{62})_4$ and $(\mathbf{62/63})_2$ by self-dimerization of 2,6-diacetamidopyridine and complementary interaction with uracil.[73,74]

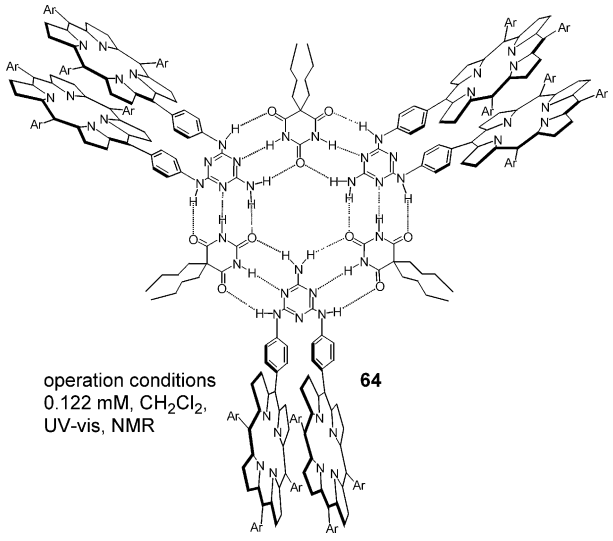

Figure 47. Cyclic hexaporphyrin **64** with three triaminotriazines and three dialkylbarbituric acids.[75]

The association constant of fullerene derivatives **65** having an ammonium group with the crowned porphyrin **66** was enhanced by 100-fold ($K=3.7\times10^5\ M^{-1}$) compared with the non-porphyrin system **67** ($K=3.5\times10^3\ M^{-1}$) by the additional porphyrin/C_{60} interaction (Fig. 48).[82]

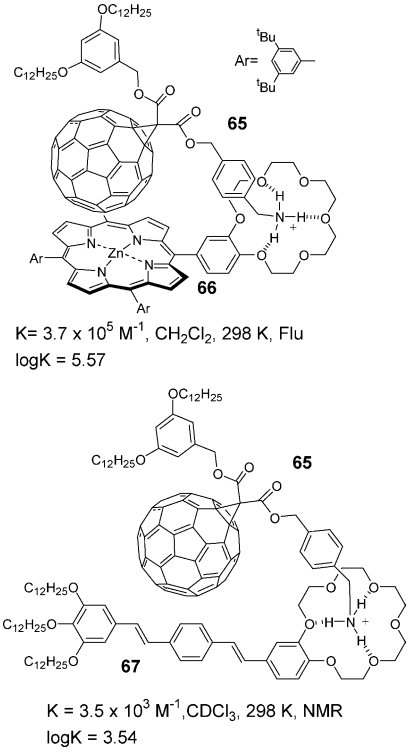

Figure 48. Crowned porphyrin **66** and ammonium fullerene **65**.[82]

Nolte synthesized porphyrin clips using a diphenylglycoluril **35Fb** unit to form stable charge transfer complexes with viologens. In particular, the association constant with (dihydroxyethyl)viologen (HEV) is 10-fold larger than that with methylviologen (MV) by incremental hydrogen-bonding interactions between the hydroxy and carbonyl groups (Fig. 49).[43]

2.3.3. Interactions in water. Although the interaction energy of hydrogen bonding weakens in protic solvents, the electrostatic interaction remains effective, even in aqueous solutions. In addition, the large hydrophobic π-plane of the porphyrin plays significant roles in molecular recognition in water. Mizutani synthesized a *m*-phenylene bridged bis-porphyrin **68** having 12 carboxylic acids which interact

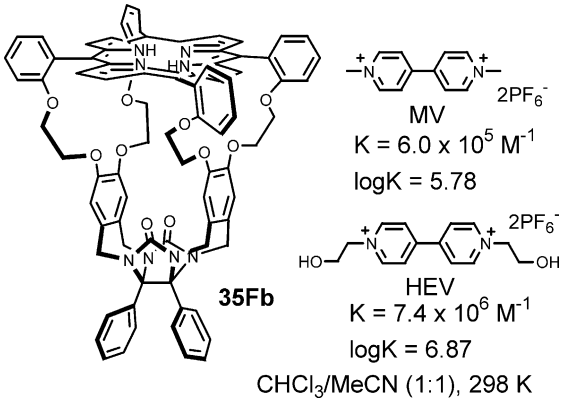

Figure 49. Porphyrin clips **35Fb** using diphenylglycoluril and viologens.[43]

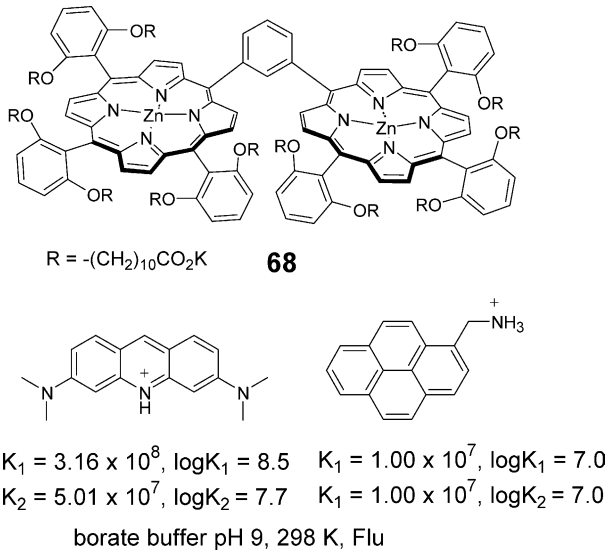

Figure 50. 12-Carboxylate porphyrin **68** and cationic π-aromatics.[83]

strongly with cationic π-aromatics to give 1:1 and 1:2 complexes (Fig. 50).[83]

Jux et al. reported stable 1:1 complex formation between an

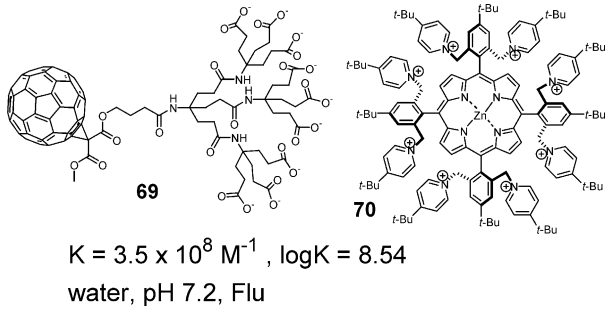

Figure 51. Octa-anionic fullerene **69** and octapyridinium zinc porphyrin **70**.[84]

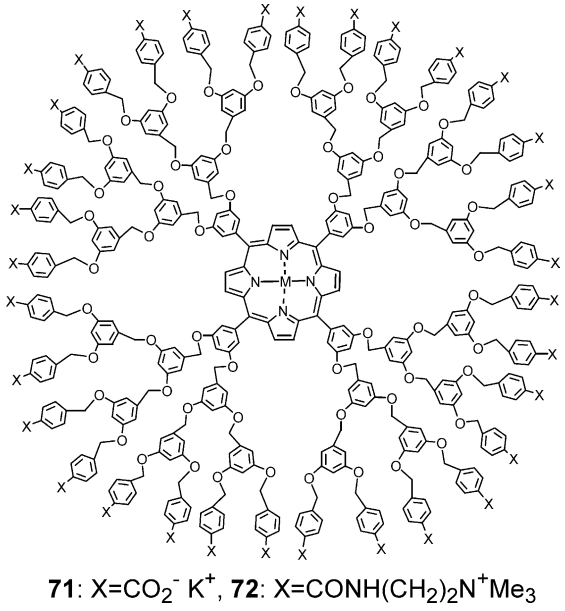

Figure 52. Porphyrins with 32 anions and cations, **71** and **72**.[85]

octa-anionic dendritic fullerene oligocarboxylate **69** and an octapyridinium zinc porphyrin salt **70** (Fig. 51). The association constant was 3.5×10^8 M^{-1} in de-ionized water, and decreased when the ionic strength of the solution was increased.[84]

Aida examined electrostatic assembly between porphyrins having 32 dendritic anions **71** and cations **72** (Fig. 52).[85] An equimolar mixture of **71** and **72** generated large infinite aggregates (10–20 μm), which were detectable by fluorescence microscope.

2.3.4. Exchangeable covalent bonds. Reversible covalent bonds, the exchange rate of which is relatively rapid, are used in dynamic supramolecular systems. Boronic acid and a diol form a boronic ester, and they are in equilibrium in protic solvents, such as water and methanol (Fig. 53). These systems were used in cooperative molecular recognition, details of which will be described later (Section 4.2).

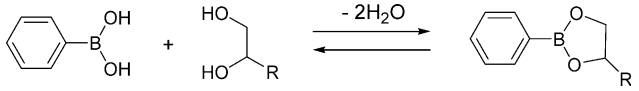

Figure 53. Equilibrium among a boronic acid, a diol and a boronic ester.

Disulfides are exchangeable with each other in the presence of a catalytic amount of thiol (Fig. 54). The S–S bond is also used in dynamic systems. Sanders demonstrated the selective formation of a dimer, trimer and tetramer of porphyrin **73** in the presence of dabco, tripyridyltriazine, and tetrapyridylporphyrin, respectively (Fig. 55).[86]

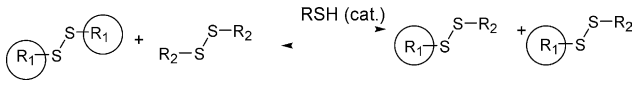

Figure 54. Exchange between disulfides.

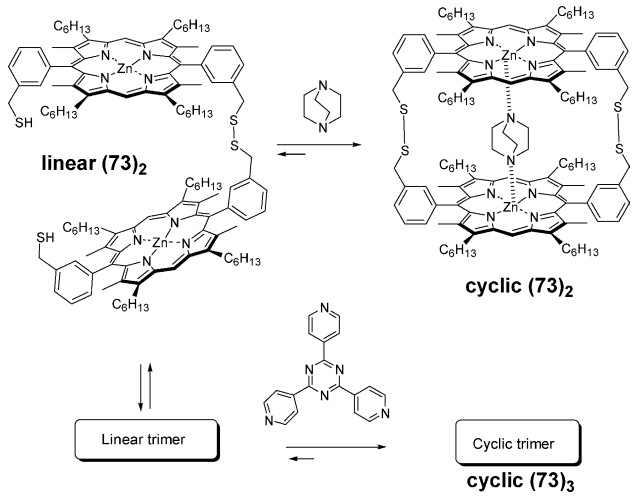

Figure 55. Template synthesis of cyclic dimer $(\mathbf{72})_2$ and trimer $(\mathbf{72})_3$.[86]

3. Dynamic formation and characterization of polymeric porphyrins

In Section 2, reversible non-covalent and covalent bonds for obtaining supramolecular porphyrins were introduced. If molecules A and B form a strong non-covalent bond, their combined molecules A–B in which A and B cannot interact intramolecularly produce polymeric porphyrins (Fig. 56).

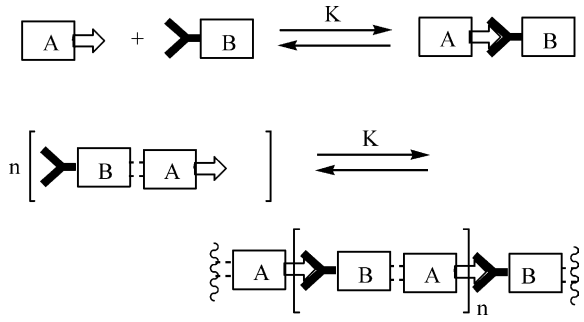

Figure 56. Schemes of formation of dimer and polymer.

We demonstrated this concept with the use of the complementary dimer of zinc imidazolylporphyrin (**ZnImPor**) **74**, which has a very large self-association constant $>10^{11}\,M^{-1}$ (**19** in Section 2). When two **ZnImPor 74** units are linked at their *meso*-positions (**BisZnImPor 75**), a huge porphyrin array was formed reflecting the large association constant in $CHCl_3$ (Fig. 57).[87] Since the coordination bond can be cleaved in coordinating solvents, the polymer can be dissociated to monomer units via oligomers by the addition of methanol and pyridine. When the coordinating solvent is removed, the long polymer can be regenerated. The reversible feature can be applied to synthesize oligomers with appropriate terminal units. When **ZnImPor 74** is added as a terminator to **BisZnImPor 75**, oligomers **76** are obtainable (Fig. 58).

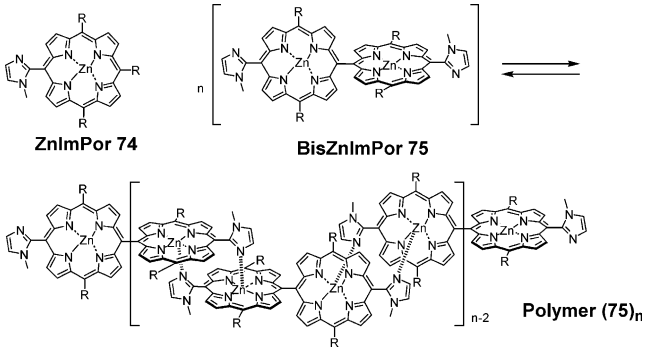

Figure 57. Linear porphyrin polymer of **BisZnImPor 75**.[87]

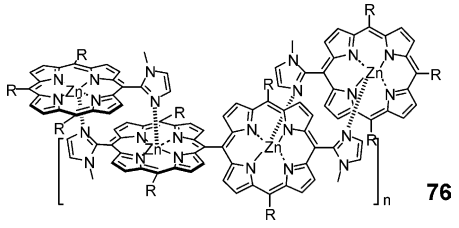

Figure 58. Porphyrin oligomer **76** terminated by **ZnImPor**.[87]

In the case of *meso–meso*-linked **BisZnImPor 75**, linear polymers and oligomers were formed by successive complementary coordination. When two zinc imidazolylporphyrins are linked by a spacer with the appropriate angle, cyclic oligomers are obtained by the re-organization method. *m*-Gable porphyrin **77**, in which two imidazolylporphyrins are linked with an angle of 120°, gives a polymer immediately after zinc insertion. The polymer is dissociated into monomers and a few oligomers in the presence of a coordinating solvent, such as methanol, in dilute concentrations. Gradual evaporation then causes reformation of the oligomers on decreasing the coordinating solvent and increasing the total concentration. Since complementary coordination is thermodynamically favored, free zinc imidazolylporphyrin terminals attempt to find their counterparts. When the number of oligomeric units reaches to five or six, intramolecular coordination is more favored than intermolecular coordination under high dilution conditions to afford the cyclic pentamer **78** and hexamer **79** (Fig. 59).[88] The cyclic heptamer has no chance to form for kinetic reasons. A similar methodology was applied to the trisporphyrins **80**, in which three porphyrin units were connected by two *m*-phenylene moieties. In this case, the cyclic trimer **81** was the sole product, because angle strain does not allow dimer formation (Fig. 60).[89]

3.1. Purification and characterization

In supramolecular systems, separation and characterization methods are, in general, limited because of the lability of the bond. Adsorption chromatography based on SiO_2 or Al_2O_3 is not applicable in most cases. Even if the association constant is very large, dissociated species are adsorbed on supports during chromatography, and the supramolecular structure gradually loses its relative contribution during the purification. Size exclusion chromatography (SEC) or gel permeation chromatography (GPC) can be applied when the supramolecular structure has unusually large association constants and when the components are not adsorbed on the supporting polymer. GPC analyses are reported for two types of multiporphyrin systems by Hunter[90] and by our group.[87] In both cases, calibration plots were prepared by oligomers to estimate the molecular weight and the assembly number.

Various characterization methods have been applied to determine or estimate the supramolecular structure. Since each method has its own characteristics and limitation on determining the molecular weight and the size as the most basic information, some of these must be combined based on the multi-facets principle with due consideration of the analytical conditions, and the resolution.

In Table 7, analytical methods applied or applicable to the characterization of the supramolecular structures are listed. When the exact molecular or assembly number is not obtained from normal mass spectroscopy, appropriate methodologies must be attempted. The following analytical methods are available: (1) vapor phase osmometry (VPO), (2) analytical ultracentrifugation (AUC), (3) NMR diffusion experiments, (4) small angle X-ray scattering (SAXS), and (5) dynamic light scattering (DLS). Since they are operated in solution phases, dynamic behavior of the supramolecules

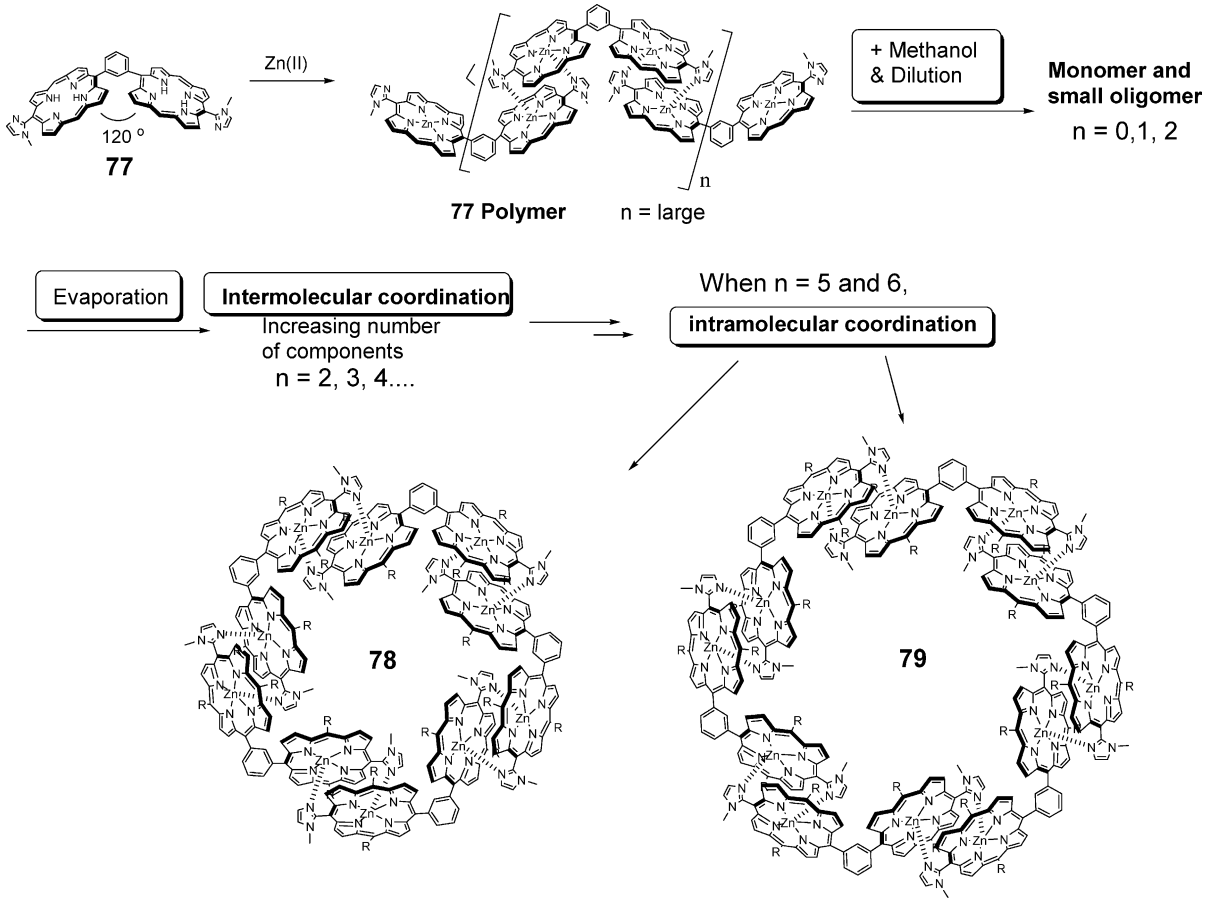

Figure 59. Re-organization procedure of *m*-gable porphyrin **77**.[88]

can be directly obtained by changing various conditions, such as concentration, temperature, and pH. (1) The VPO method can be applied most generally to self-assembled porphyrin systems. Although the accuracy is not high (ca.10%) enough to estimate especially high-molecular-weight samples, this method may be the best to try first. Many examples are reported from dimeric to nonameric porphyrins.[25,28,31,36,37,41,74,75,92–94] (2) Analytical ultracentrifugation (AUC) can analyze molecular weight and the distribution in the sample of relatively large molecular weights (MW $1500 \sim 10^7$). The association of large proteins or polymers is generally examined, but there are also examples of relatively small molecular weights (1600 Da).[98] The sedimentation velocity method is sensitive to the heterogeneity of the sample, and gives the distribution of the sedimentation coefficient. The molecular weight of a single component is obtained by the sedimentation equilibrium method with a knowledge of the partial specific volume of the sample. The accuracy of the molecular weight determined depends on the accuracy of the partial specific

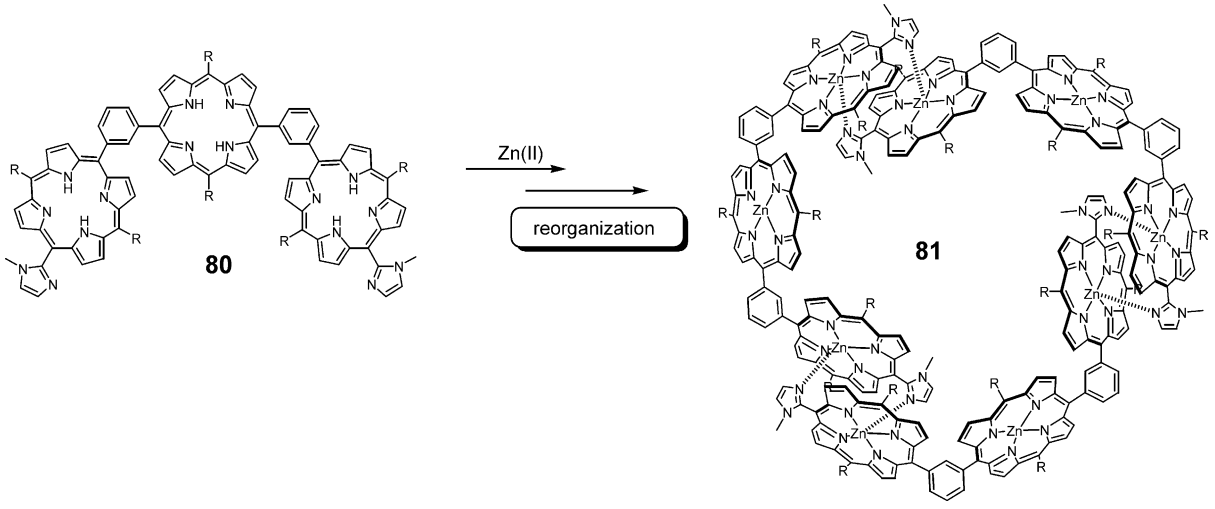

Figure 60. Trisporphyrin **80** and cyclic trimer **81**.[89]

Table 7. Estimation methods of molecular weight or size of supramolecular systems

Method	Appropriate MW or size	Accuracy	Separation ability for mixture	Limitation for measurement	References
Mass CSI-mass	$\sim 10^5$ Da	$<0.01\%$	Excellent	Cleavage to component under ionization	37,41,74,91
VPO	$\sim 10^4$ Da	$\pm 10\%$	No (number-averaged MW)	Solubility; sensitivity	25,28,31, 36,37,41, 74,75,92, 93,94
GPC	$\sim 10^6$ Da	Depending on reliability of standards	Very good	Adsorption of sample on supporting polymer; indirect estimation	41,87,88, 90,92,95
AUC	$1{,}500 \sim 10^7$ Da	3–20% Depending on accuracy of partial specific volume	Good	Requirement of sample enough to determine the partial specific volume	96,97,98,99
SAXS	1–100 nm	nm order	Possible by deconvolution of data	Sensitivity	88,95
DLS	1–6 μm	nm order	Possible by deconvolution of data	No fluorescent sample	31,92,100
NMR diffusion DOSY	Low $\sim 10^5$ Da	Depending on reliability of standards	Good	Sensitivity	90,101,102
SEM	50 nm-μm order	1 ~ several nm	Good	Decomposition by electron beam; no height information	59,103
TEM	10 nm-μm order	<1 nm resolution	Good	Decomposition by electron beam; no height information	59,60,100, 104
AFM	1 nm-μm order	<1 nm (height) 20 nm (width)	Good	Fixation on substrate	88,92,105, 106
STM	nm order	<1 nm resolution	Good	Fixation on substrate; sample preparation from solution; narrow sweep area	107,108

volume. A mixture gives a weight-averaged molecular weight. (3) For the NMR diffusion method, the peak resolution is generally large and various nuclei can be selected. A mixture of components can therefore be directly analyzed and, additionally, a DOSY (diffusion-ordered spectroscopy) method gives a spectrum of each component.[102] (4) Small angle X-ray scattering (SAXS) in solution can be applied to nm sizes of molecules and the scattering profile also includes information on the molecular shape and conformation. (5) Dynamic light scattering (DLS) has been used to estimate the size and the distribution of the sample as a particle and the suitable range of particle sizes is large (1 nm-several μm). Unfortunately, a fluorescent sample is not applicable because of its interference. Nonetheless, mass spectrometry is certainly one of the best methods to obtain direct evidence of the exact molecular weight. Recent mild and soft ionization methods, such as cold spray ionization (CSI), or electrospray ionization (ESI), sometimes enable the detection of the supramolecular structure.[37,41,74,91] There are some excellent examples where supramolecular assemblies were identified. Even so, the ionization conditions are still too harsh for many supramolecular assemblies employing labile non-covalent bonds and only dissociated species are detected. When mass spectrometry gives information different from other evidence obtained in solution, suitable alternative methodologies must be sought. This may be a major drawback of supramolecular assembly formation. In the case of the complementary dimer of **ZnImPor 74**, all the data suggests the complete dimerization in solution, but

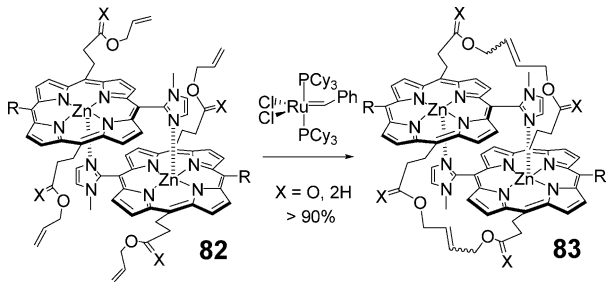

Figure 61. Covalent linking of complementary dimer by ring-closing metathesis.[109]

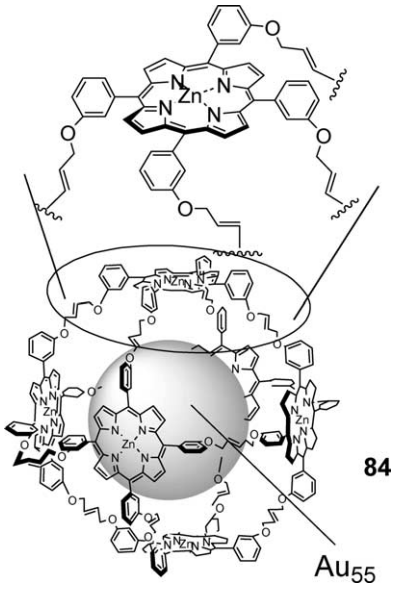

Figure 62. Covalently linked multiporphyrins on gold nanocluster.[111]

only a dissociated monomeric peak is observed in MALDI-TOF and ESI mass spectrometry. In order to prove the supramolecular structure by mass spectrometry, we recently developed a covalent linking of the complementary dimer.[109] Allylic groups introduced at appropriate positions in **82** were subjected to a ring-closing metathesis reaction in the presence of a Grubbs catalyst to give the covalently linked porphyrin dimer **83** in excellent yields (Fig. 61). This method is applicable to the macrocyclic pentamer **78** and hexamer **79**, affording the exact mass number.[110] It is interesting to note that a combination of self organization and covalent linking of supramolecular porphyrins may be applicable not only to structural proof, but also to develop coordination-assisted structure formation reactions.[89,110] Konishi has reported the metathesis linking of multi-porphyrins **84** assembled on a gold nanocluster (Fig. 62).[111]

If the supramolecular structure has a characteristic shape like a wire, rod, and ring and it is large enough to observe by various microscopes, single-molecule observation is an interesting methodology to estimate the real form. Scanning electron microscopy (SEM) and transmittance electron microscopy (TEM) have a very high resolution. A one- or two-dimensional aggregate composed of a porphyrin and phthalocyanine was observed by SEM and TEM.[59,60,100,103,104] Observation of the detailed molecular structure by magnification is associated with difficulties because of structure destruction by the focused electron beam. Scanning probe microscopy (SPM) is a milder method compared with electron microscopy and has frequently been used to estimate the supramolecular aggregation structure. Atomic force microscopy (AFM) can analyze the molecular height with <1 nm resolution, but information along the lateral directions, such as the width and length, probe curvature (diameter: ca. 20 nm), which should not be identical for each experiment. Scanning tunnel microscopy (STM) can provide high-resolution images at the atomic level. Kawai has successfully observed covalently linked multiporphyrin sheets,[112,113] tapes,[114] and rings[108] by a pulse injection technique[115] and this may be applied to supramolecular porphyrin systems. In SPM methods, the samples interact fairly strongly with the substrate and the stability of the non-covalent bond and immobilization of the sample on the substrate are critical for successful observations.

4. Recent functionalized supramolecular porphyrin systems

4.1. Mimics of photosynthesis

4.1.1. Light-harvesting antenna and energy/electron transfer. Mimics of photosynthetic functions, such as light harvesting and charge separation by the use of a supramolecular assembly of porphyrins, have been reported, and good reviews have been published in the field.[116] In this section, we introduce mimics of light-harvesting antenna assembled by relatively strong non-covalent bonds.

Hunter reported self-assembly of the free base porphyrin **85** having four pyridinyl groups and two biszincporphyrins linked by pyridine dicarboxylic amide.[93] In their molecular design, hydrogen bondings were effectively used to fix the conformation and to raise the association constants. The pentaporphyrin composite **85** (Fig. 63) was formed by mixing two components as a 1:2 complex with an association constant $K=2\times10^6\ M^{-1}$ for each dimer formation. When zinc porphyrin was selectively excited, fluorescence from the free base porphyrin was observed. The rate of energy transfer k_{ENT} was obtained as $2\times10^9\ s^{-1}$ by steady state and fluorescence lifetime measurements, and the quantum yield Φ_{ENT} was 73%.

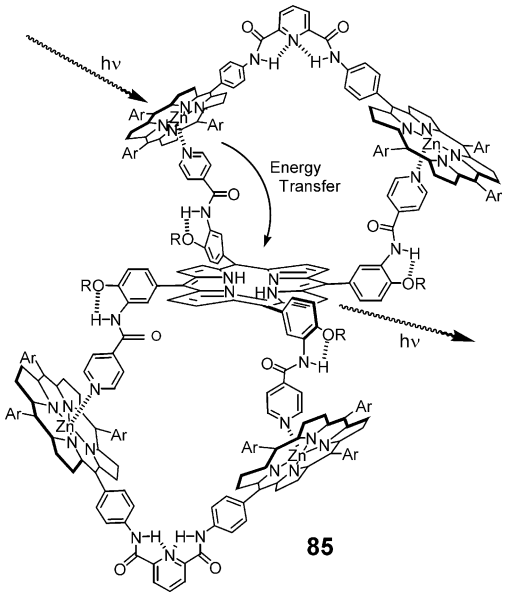

Figure 63. Energy transfer in pentaporphyrin composite **85**.[93]

Kuroda reported self-assembly of zinc porphyrin dimer **61** formed by four hydrogen bondings and free base porphyrin **86** having eight pyrazines (Fig. 64).[117,118] The large association constant between the dimer **61** and pyrazine ($K=4\times10^7\ M^{-1}$) gave a 1:8 complex of (**86/61**) quantitatively. Excitation of the Zn porphyrin part (564 nm) enhanced the fluorescence emission from the central free base porphyrin by 77-fold.

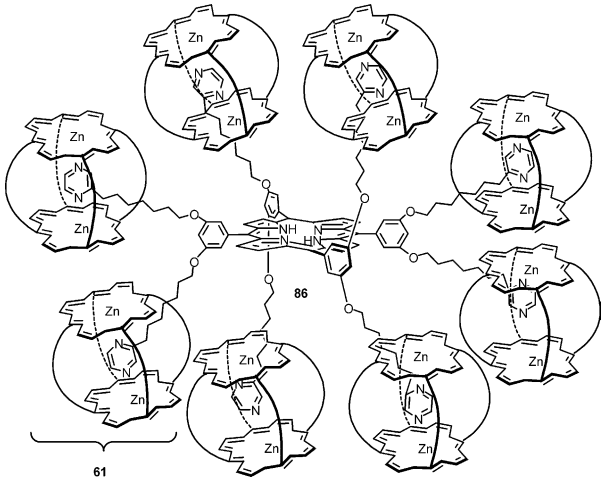

Figure 64. A composite of 16 zinc porphyrins **61** and one Fb porphyrin **86**.[117,118]

We have introduced supramolecular light-harvesting antenna into a lipid bilayer.[119] Three complementary **ZnImPor** dimers were attached to free base porphyrin and the former were directed to the membrane surface by the terminal carboxylate substituents (Fig. 65). The porphyrin heptamer **87** incorporated in large unilamellar vesicles (LUVs) showed energy transfer from zinc porphyrin to the free base porphyrin by selective excitation of the **ZnImPor** dimer.

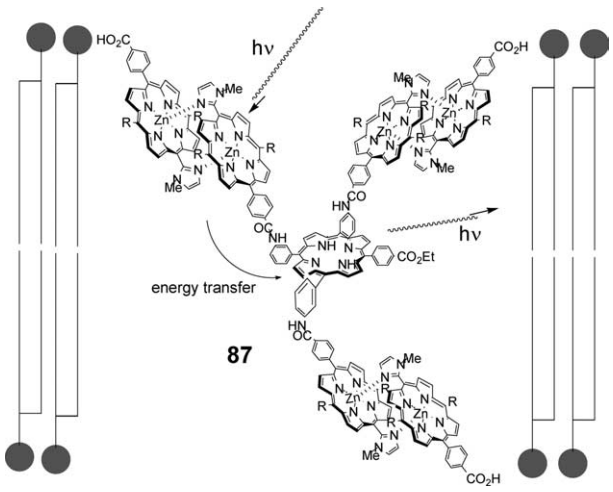

Figure 65. Energy transfer in porphyrin heptamer **87** incorporated in large unilamellar vesicles.[119]

The cyclic oligomers **78** and **79** (Fig. 59) were synthesized as mimics of light-harvesting antenna complex II (LH II).[88,120] In the complex (Fig. 66), six pairs of slipped co-facial dimers are arranged in a large ring with close Zn-to-Zn distances similar to natural LH II. To evaluate the energy delocalization in the ring, fluorescence quenching with benzoquinone was carried out. The quenching efficiency referred to TPP was proportional to the surface area and suggested a rapid excited energy migration in the ring within the life time of 2.0 ns.

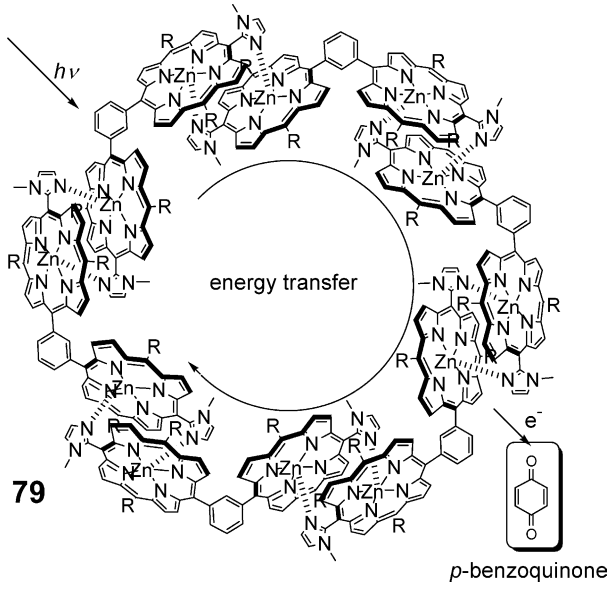

Figure 66. Energy migration in cyclic porphyrin dodecamer **79** as a model of B850 in LH2.[88,120]

The formation of the cyclic oligomer does not decrease the inherent fluorescence quantum yield. In the case of the cyclic trimer **81**, the fluorescence quantum yield ($\Phi=5.1\%$, toluene) was almost same as that of the dimer **ZnImPor** ($\Phi=4.9\%$, toluene).[89] No decrease of fluorescence was observed by assembling nine porphyrins and this indicated that the non-covalent coordination is suitable to construct a supramolecular light-harvesting complex. Compound **81** can accept one tetrapodal guest **88** in the cavity with a high association constant, $K=8\times10^8\ M^{-1}$, in toluene. This composite is expected to mimic the LH I/reaction center composite (Fig. 67).

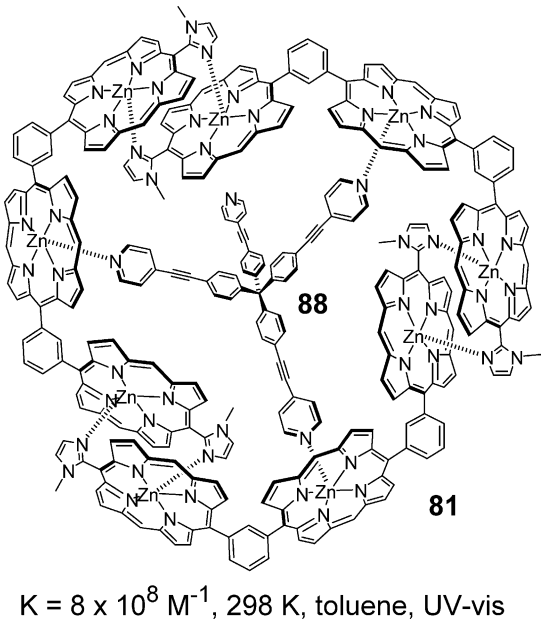

Figure 67. Composite of cyclic porphyrin nonamer **81** and tetrapodal guest **88**.[89]

The complementary **ZnImPor** dimer is useful as a mimic of a special pair in the photosynthetic reaction center, in addition to a fundamental unit of light-harvesting antenna in bacterial photosynthetic systems. When **ZnImPor 89** having an electron acceptor was dimerized by complementary coordination (Fig. 68), the photo-induced charge separation rate was accelerated, while the charge recombination rate was decreased, compared with those of the corresponding monomer. This is regarded as direct chemical

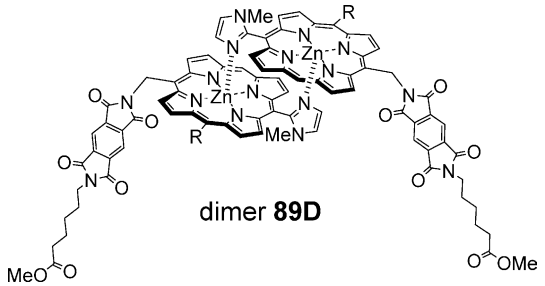

Figure 68. Mimic of special pair in reaction center.[23]

proof that Nature employed the special pair arrangement to increase the charge separation efficiency.[23]

4.1.2. Photocurrent generation. Supramolecular growth of porphyrins on the self-assembled monolayer (SAM) on an appropriate electrode surface is one of the interesting methods to introduce the antenna effect for photocurrent generation. Here, recent applications to photocurrent generation systems are introduced.

We applied a self-assembling system of **BisZnImPor 75** on a gold surface. First, the linker porphyrin **90** was attached to the gold surface by a thiol/gold interaction, and **BisZnImPor 75** was successively grown by a coordination bond (Fig. 69). Responding to the growth of the porphyrin layer, the photocurrent gradually increased. This antenna feature is desirable to absorb incident light effectively.[121]

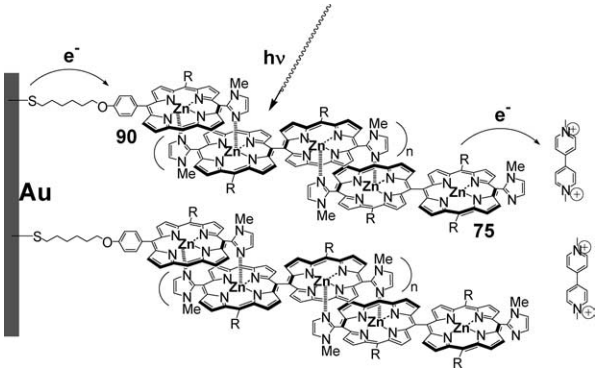

Figure 69. Complementary coordination assembly of antenna porphyrins on gold surface.[121]

In order to increase the efficiency of photocurrent generation, the vectorial arrangement of donor, porphyrin, and acceptor is essential. Thompson reported the ordered assembly of porphyrin and acceptor by a selective interaction of thiol/Cu(II) and phosphonic acid/Zr(IV) (Fig. 70).[122] We introduced vectorially an acceptor molecule by an imidazole/zinc coordination bond.[123] An increase of the photocurrent was observed by the introduction of acceptor molecules in both cases.

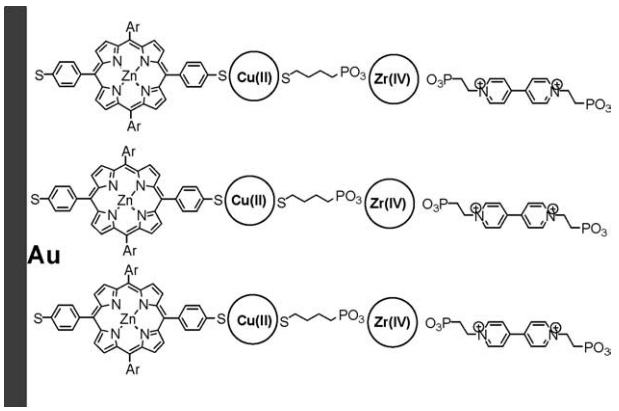

Figure 70. Ordered assembly of porphyrin and acceptor.[122]

Electrostatic interaction is convenient to assemble the components. Ikeda reported the electrostatic accumulation of fullerenes encapsulated in a cationic calixarene **91** and porphyrins supported by an anionic polymer **92** on indium-tin oxide (ITO) by a layer-by-layer accumulation method (Fig. 71).[124]

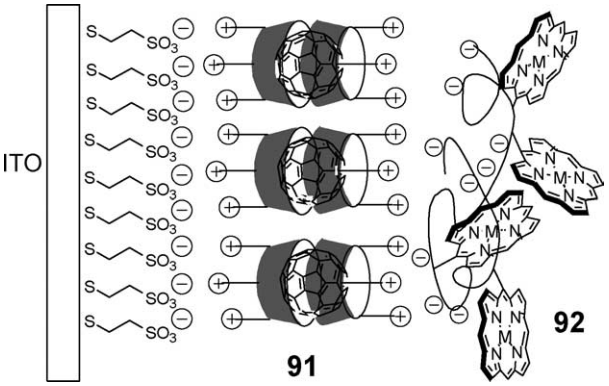

Figure 71. Electrostatic assembly of encapsulated fullerenes **91** and porphyrins **92**.[124]

Guldi and co-workers have reported the electrostatic assembly of four components by electrostatic forces. They prepared the anionic fullerene **69** (9−) as an electron acceptor, the cationic free base porphyrin **70** (8+) as an energy acceptor and photosensitizer, the anionic zinc porphyrin **93** (8−) as a photosensitizer, and the cationic ferrocene **94** (1+) as a donor. They were assembled

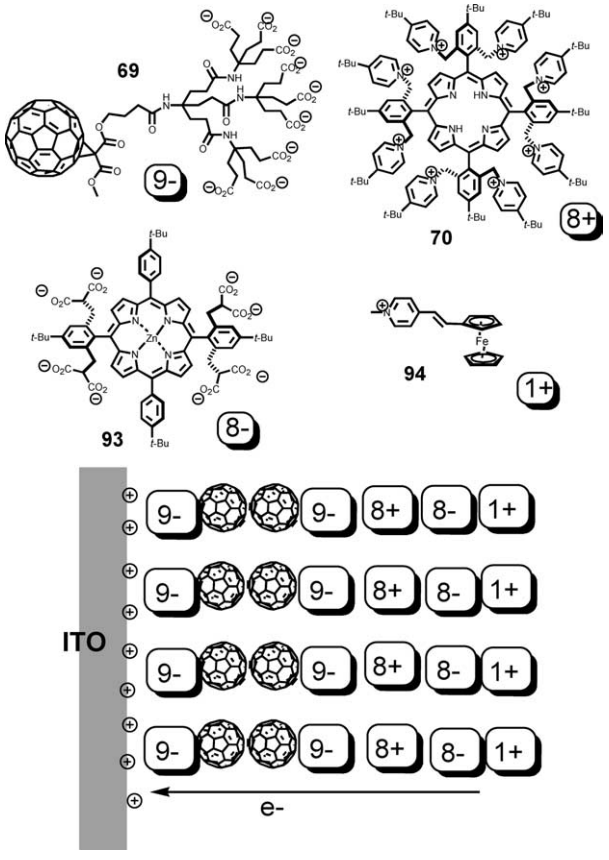

Figure 72. Electrostatic assembly of fullerene **69**, porphyrins **70** and **93**, and ferrocene **94**.[125]

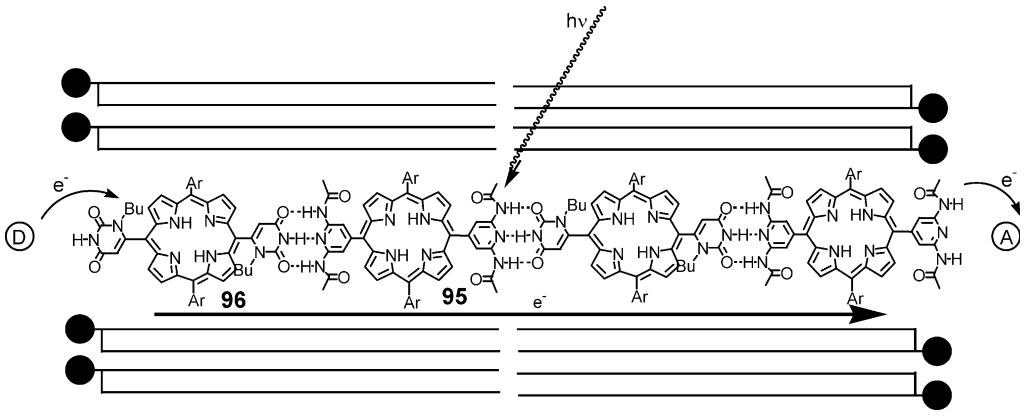

Figure 73. Photocurrent generation across the lipid bilayer membrane.[126]

stepwise as shown in Figure 72. As the assembled components increased, the IPCE (incident-photon-to-converted-electron efficiency) increased effectively, indicating that multistep electron transfer is occurring.[125]

Drain reported photocurrent generation across the lipid bilayer membrane.[126] Two kinds of porphyrins (**95** and **96**) having diacetoamidopyridines and uracils as hydrogen donor/acceptor pairs were incorporated into a membrane (Fig. 73), and $K_4Fe(CN)_6$ and anthraquinone sulfate solutions were placed at both ends as electron donor and acceptor, respectively. A clear on/off response was observed in response to white light irradiation. In the system, electrons are expected to pass through the four porphyrins by a hopping mechanism.

4.2. Sensing chirality

Porphyrin has a large extinction coefficient ($\varepsilon = 5\times10^5\ M^{-1}\ cm^{-1}$ at the Soret band for ZnTPP), and excitonic coupling between two porphyrins reaches a 50 Å distance.[127] These features enable a highly sensitive detection of chirality by the use of two porphyrins. Here, some applications for chiral sensing are introduced.

Berova and Nakanishi have developed a method to determine the absolute configuration of chiral diamines, amino acids, and aminoalcohols for practical use. A zinc porphyrin tweezer **97** (Fig. 74)-two zinc porphyrins connected by an alkyl chain-can coordinate chiral diamine, amino acid and aminoalcohol derivatives as ditopic

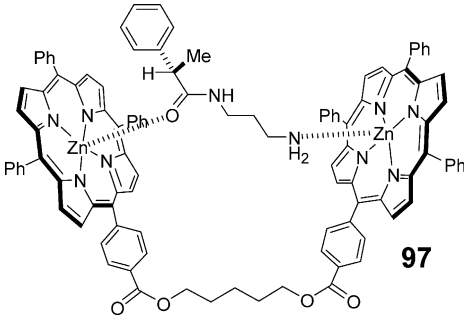

Figure 74. Zinc porphyrin tweezer **97** to determine the absolute configuration.[132]

coordination.[128–131] Based on the absolute configuration of the guest molecules, a positive or negative Cotton effect is observed. Various α-chiral amino acids can be analyzed, but the systems containing N, O, or halogens at the chiral center did not obey the rule. Recently, a Mg porphyrin tweezer was reported to exclude the exception.[132]

Inoue introduced another chiral sensing molecule by the use of bisporphyrin **98** bridged by an ethane group (Fig. 75).[133] The bisporphyrin **98** interacts with two chiral monoamines cooperatively. In the absence of a guest amine, the bisporphyrin takes a π-stacked conformation. When the first chiral amine coordinates to one of the zinc porphyrins, a strong CD is induced by the change to a chiral open conformation. This system has been developed to include a determination of the absolute configuration of a chiral secondary alcohol by using the highly oxophilic Mg bisporphyrin.[134]

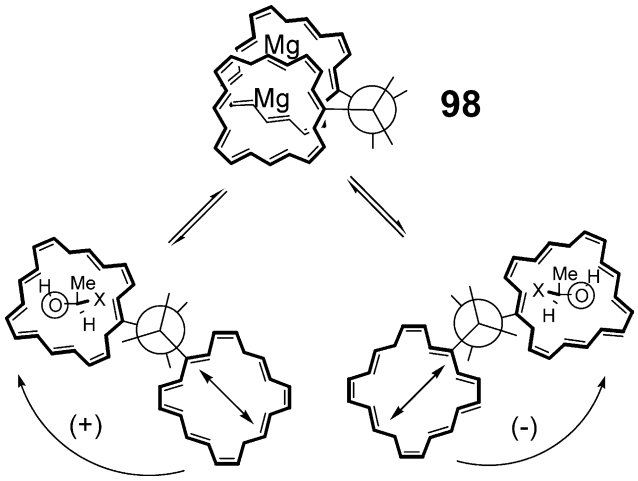

Figure 75. Interaction of metal bisporphyrin **98** bridged by ethane group with chiral guest.[133,134]

Aida has reported sensing of the helicity of peptides by the use of Zn bisporphyrin **99** connected by two helical peptides **100** (Fig. 76).[135] In the absence of the guest diamine, no CD activity of the bisporphyrin **99** is observed, because of the presence of equal amounts of D- and L-helices. When the chiral helical diamine is coordinated in a ditopic manner to

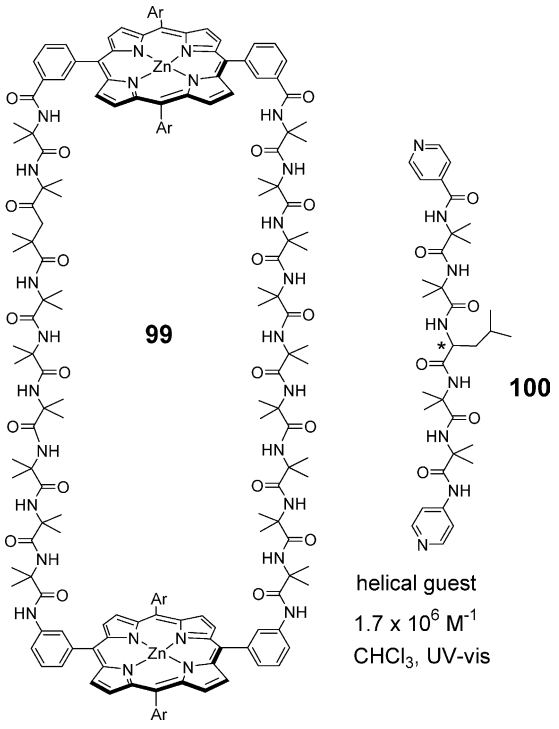

Figure 76. Bisporphyrin linked by helical posts and a helical guest.[135]

zinc porphyrins, the helicity of the pillars are harmonized with that of the guest, and induced CDs are observed for both the porphyrin and peptide parts.

Shinkai reported cooperative chiral sensing of chiral diacids and oligosaccharides by a double-decker porphyrin.[136] In this system, peripheral functional groups, such as pyridine and boronic acid, are used to interact with guest molecules. Electrostatic interaction was used in the former case, and reversible covalent bond formation between boronic acids and diols in the latter. The double-decker porphyrin **101** interacts with four chiral diacids cooperatively assisted by a twist motion to generate an induced CD (Fig. 77).

The double-decker porphyrin **102** interacts with oligosaccharides (Fig. 78). Various lengths of oligosaccharides[137] and Lewis oligosaccharides (Fig. 79)[138] were examined. It is interesting that the CD signals are inverted by the difference

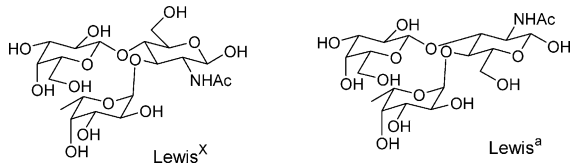

Figure 79. Structures of Lewis oligosaccharides.[138]

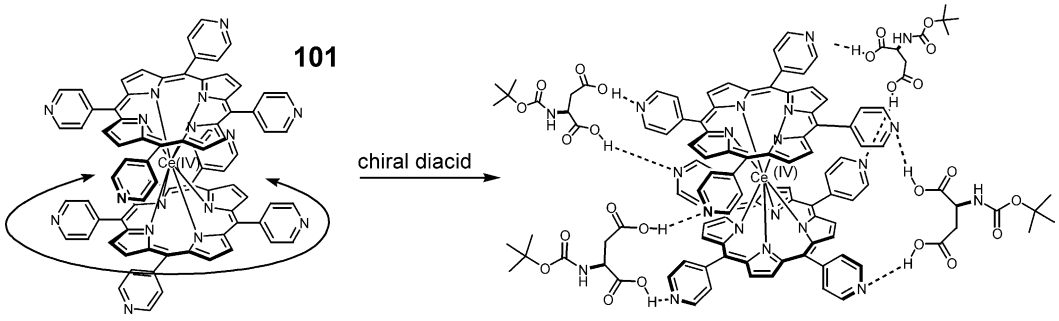

Figure 77. Cooperative binding of four chiral diacids by double-decker porphyrin **101**.[136]

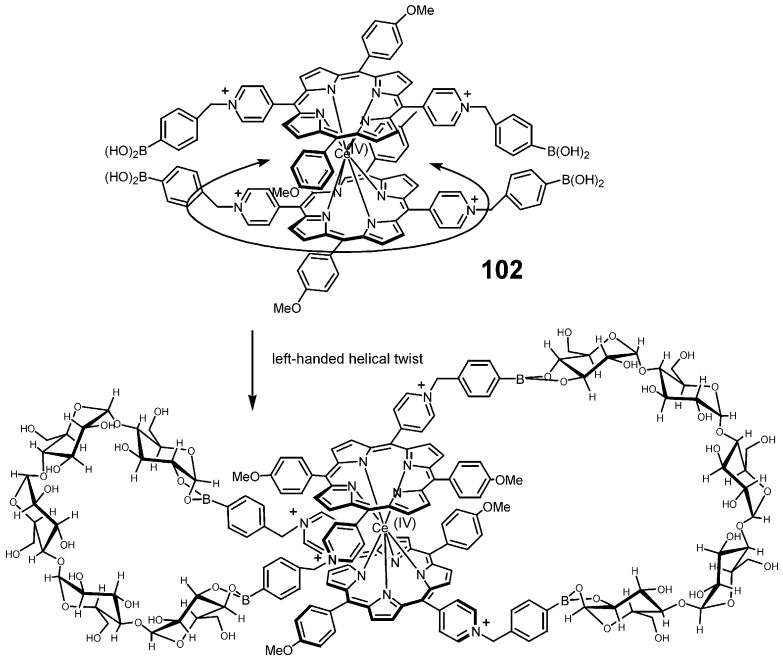

Figure 78. Cooperative binding of oligosaccharides by double-decker porphyrin **102**.[137]

of oligosaccharide lengths and Lewis oligosaccharide structures and this can be applied as a selective sensor for detecting oligosaccharides.

4.3. Specific extraction of carbon materials

As described in Section 2, porphyrin has been shown to interact with large π-conjugated materials such as fullerenes. Recently, the specific extractions of higher fullerenes and semiconducting carbon nanotubes were reported. Carbon soot contains higher fullerenes, $\geq C_{76}$, along with C_{60} and C_{70}. Although structure–property relationship of each discrete fullerene is interesting, the lack of a practical isolation method hampered such studies. Aida synthesized the bisporphyrin **103** (Fig. 80), the association constant of which with higher fullerenes was 10- to16-fold larger than those with C_{60} and C_{70}. They demonstrated the selective extraction of higher fullerenes, C_{96}–C_{110}, by a 3-fold repetitive process.[139]

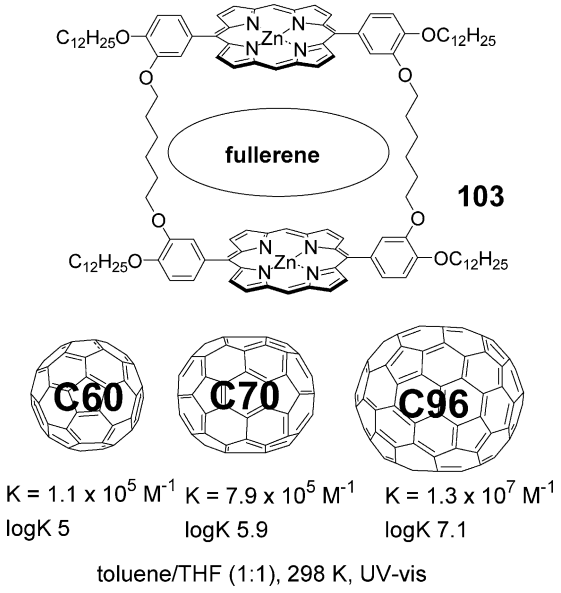

Figure 80. Association constants of C_{60}, C_{70}, and C_{96} with bisporphyrin **103**.[139]

Carbon nanotubes show excellent electronic properties and high tensile strengths, and various applications have been attempted. Since they are obtained as a mixture of metallic and semiconducting nanotubes, a practical separation method is highly desirable. Sun reported that tetra(hexadecyloxyphenyl)porphyrin extracts a semiconducting nanotube selectively.[140] Although the detailed mechanism of the selective interaction is not clear, this non-disruptive extraction is advantageous for the use of carbon materials.

4.4. Molecular switch

Coordination of ligands can induce a structural change in multi-porphyrin systems followed by a change in their electronic states. Reversible coordination can therefore be applied to molecular switch. Osuka examined the electronic properties of a *meso–meso*-linked zinc bisporphyrin **104** by coordination of various diamines in 1:1 complexation (Fig. 81).[141] In this system, the dihedral angle between the two porphyrins is changed by coordination of diamines with different separation distances. When heptamethylenediamine was used, the most distorted conformation was obtained. The Soret and Q-bands in the absorption spectrum are red shifted significantly and the fluorescence intensity is increased. These spectral changes were recovered on decomplexation by the addition of acetic acid.

We have reported a specific interaction of zinc hexaporphyrin **105**, produced by Ru coordination to the central bipyridyl part, with triamines (Fig. 82). The hexaporphyrin **105** has two tritopic binding pockets, and accepts two triamines accompanied by molecular motion. In a series of triamines, the association constants of triaminoethylamines **106** were the largest, and a specific spectral change was observed in the 1:2 complex formation. Structural analysis by NMR indicates that a distorted and rigid structure is formed by coordination of the two triamines **106**.[142]

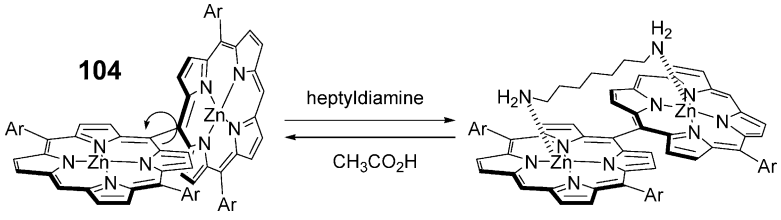

Figure 81. Distortional change of *meso–meso* linked zinc bisporphyrin by coordination of heptyldiamine.[141]

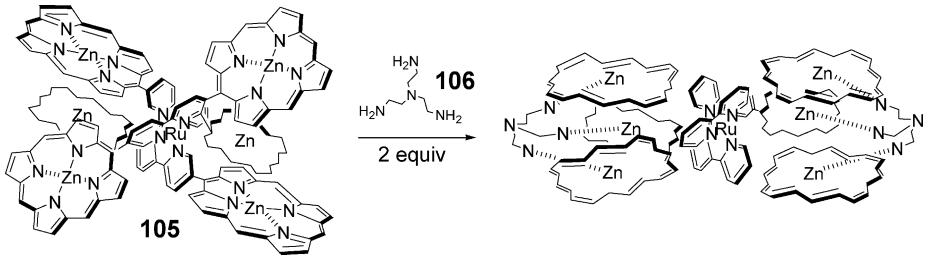

Figure 82. Distortional change of zinc hexaporphyrin **105** by coordination of triamine **106**.[142]

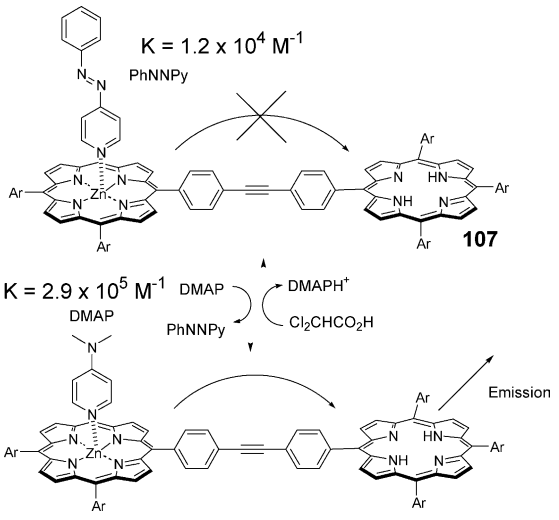

Figure 83. Reversible switching of intramolecular energy transfer in bisporphyrin **107**.[143]

Reversible coordination of an external ligand is useful for the replacement of functional ligands coordinated originally or guest interacted by other non-covalent bonds. Otsuki reported a switching system based on the difference of association constants and pK_as between azopyridine and dimethylaminopyridine (DMAP). Azopyridine (1 mM) is coordinated to the zinc porphyrin part in **107** (10 μM) in CH_2Cl_2 almost completely ($K_a = 1.2 \times 10^4\ M^{-1}$) (Fig. 83). Since coordination of azopyridine inhibits energy transfer from Zn porphyrin to the free base porphyrin, fluorescence from the free base porphyrin by excitation of the Zn porphyrin is suppressed. When 0.3 mM DMAP is added, azopyridine was replaced by DMAP having a larger association constant ($K_a = 2.9 \times 10^5\ M^{-1}$), and fluorescence from the free base porphyrin was recovered. Since the pK_a value of DMAP (10.1) is much larger than that of azopyridine (3.5), DMAP was protonated selectively by the addition of 1 equiv of dichloroacetic acid (0.3 mM), followed by coordination of azopyridine. The reversibility was confirmed several times by monitoring the fluorescence change.[143]

Yagi reported a dual-mode interaction of bisporphyrin **108** linked by two diarylureas (Fig. 84). The bisporphyrin **108** interacts strongly with a heptylviologen known as an electron acceptor ($K = 5.46 \times 10^5\ M^{-1}$ in $CHCl_3$/DMSO (10/1) at 293 K), and its fluorescence is quenched. A

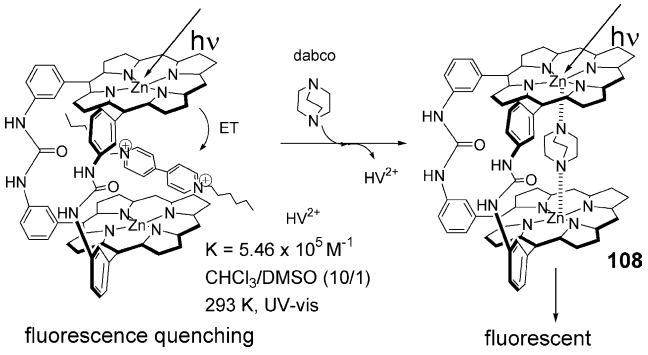

Figure 84. Dual-mode receptor of hexylviologen and dabco.[144]

charge–dipole interaction between heptylviologen and bisporphyrin **108** is supposed to be a major force to maintain the stable composite. When dabco was added to the composite, heptylviologen was replaced and fluorescence from the bisporphyrin **108** was recovered.[144]

5. Conclusions

We have reviewed various supramolecular porphyrin motifs constructed by using zinc porphyrin/nitrogen ligand coordination and other non-covalent bonds. Multiple and complementary coordination, associated with other intermolecular interactions, afford varieties of stable composites with large association constants of over $10^6\ M^{-1}$. Composite constructed by 'labile bonds' does not necessarily mean that they are observed only transiently, or as one of the composite mixtures, or that they are difficult to be isolated. If appropriately designed, an exchangeable property of the labile bond becomes a valuable method to construct dynamic systems, which cannot be achieved otherwise by covalent and inert coordinating bonds. In this review, we have introduced recent examples of dynamic supramolecular porphyrin systems. Such systems will undoubtedly be developed further in molecule-based devices for the advancement of science. Even so, the isolation and purification of supramolecular systems are still a tough target, and accurate determination of the molecular weight and the structure is successful only in limited cases. The development of technologies relevant to supramolecular sciences is definitely required for further progress in dynamic supramolecular systems.

References and notes

1. Takagi, S.; Inoue, H. Molecular and Supramolecular Photochemistry of Porphyrins and Metalloporphyrins. In *Multimetallic and Macromolecular Inorganic Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Molecular and Supramolecular Photochemistry; Maecel Decker, 1999; Vol. 4, Chapter 6, pp 215–342.
2. Chambron, J.-C.; Heitz, V.; Sauvage, J.-P. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic: New York, 2000; Vol. 6, pp 1–42.
3. Sanders, J. K. M. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic: New York, 2000; Vol. 3, pp 347–368.
4. Harvey, P. D. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Elsevier Science (USA), 2003; Vol. 18, pp 63–250.
5. Sanders, J. K. M. In Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Comprehensive Supramolecular Chemistry; Pergamon: Oxford, 1996; Vol. 9, pp 131–164.
6. Tabata, M.; Nishimoto, J. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic: New York, 2000; Vol. 9, pp 221–419.
7. Summers, J. S.; Stolzenberg, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 10559.

8. Imai, H.; Nakagawa, S.; Kyuno, E. *J. Am. Chem. Soc.* **1992**, *114*, 6719.
9. Brewer, C. T.; Brewer, G. *J. Chem. Soc., Dalton Trans.* **1990**, 843.
10. Bhyrappa, P.; Krishnan, V.; Nethaji, M. *J. Chem. Soc., Dalton Trans.* **1993**, 1901.
11. Sakuragi, M.; Ichimura, K.; Sakuragi, H. *Bull. Chem. Soc. Jpn* **1992**, *65*, 1944.
12. Vogel, G. C.; Stahlbush, J. R. *Inorg. Chem.* **1977**, *16*, 950.
13. Nappa, M.; Valentine, J. S. *J. Am. Chem. Soc.* **1978**, *100*, 5075.
14. Vogel, G. C.; Beckmann, B. A. *Inorg. Chem.* **1976**, *15*, 483.
15. Cole, S. J.; Curthoys, G. C.; Magnusson, E. A.; Phillips, J. N. *Inorg. Chem.* **1972**, *11*, 1024.
16. Flamigni, L.; Johnston, M. R. *New J. Chem.* **2001**, *25*, 1368.
17. Yamada, K.; Imahori, H.; Yoshizawa, E.; Gosztola, D.; Wasielewski, M. R.; Sakata, Y. *Chem. Lett.* **1999**, 235.
18. Ambroise, A.; Li, J.; Yu, L.; Lindsey, J. S. *Org. Lett.* **2000**, *2*, 2563.
19. Rucareanu, S.; Mongin, O.; Schuwey, A.; Hoyler, N.; Gossauer, A.; Amrein, W.; Hediger, H.-U. *J. Org. Chem.* **2001**, *66*, 4973.
20. Slone, R. V.; Hupp, J. T. *Inorg. Chem.* **1997**, *36*, 5422.
21. Anderson, S.; Anderson, H. L.; Bashall, A.; McPartlin, M.; Sanders, J. K. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1096.
22. Sanders, J. K. M. In Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vogtle, F., Eds.; Comprehensive Supramolecular Chemistry; Pergamon: Oxford, 1996; Vol. 9, pp 131–164.
23. Ozeki, H.; Nomoto, A.; Ogawa, K.; Kobuke, Y.; Murakami, M.; Hosoda, K.; Ohtani, M.; Nakashima, S.; Miyasaka, H.; Okada, T. *Chem. Eur. J.* **2004**, *10*, 6393.
24. Stibrany, R. T.; Vasudevan, J.; Knapp, S.; Potenza, J. A.; Emge, T.; Schugar, H. J. *J. Am. Chem. Soc.* **1996**, *118*, 3980.
25. Kobuke, Y.; Miyaji, H. *J. Am. Chem. Soc.* **1994**, *116*, 4111.
26. Inaba, Y.; Kobuke, Y. Unpublished results.
27. Hunter, C. A.; Low, C. M. R.; Packer, M. J.; Spey, S. E.; Vinter, J. G.; Vysotsky, M. O.; Zonta, C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2678.
28. Hunter, C. A.; Sarson, L. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2313.
29. Gardner, M.; Guerin, A. J.; Hunter, C. A.; Michelsen, U.; Rotger, C. *New J. Chem.* **1999**, 309.
30. Mårtensson, J.; Sandros, K.; Wennerström, O. *Tetrahedron Lett.* **1993**, *34*, 541.
31. Sarson, L. D.; Ueda, K.; Takeuchi, M.; Shinkai, S. *Chem. Commun.* **1996**, 619.
32. Bucher, C.; Devillers, C. H.; Moutet, J.-H.; Royal, G.; Saint-Aman, E. *Chem. Commun.* **2003**, 888.
33. Knapp, S.; Vasudevan, J.; Emge, T. J.; Arison, B. H.; Potenza, J. A.; Schugar, H. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2368.
34. Iengo, E.; Zangrando, E.; Geremia, S.; Graff, R.; Kieffer, B.; Alessio, E. *Chem. Eur. J.* **2002**, *8*, 4670.
35. Chi, X.; Guerin, A. J.; Haycock, R. A.; Hunter, C. A.; Sarson, L. D. *J. Chem. Soc., Chem. Commun.* **1995**, 2563.
36. Chi, X.; Guerin, A. J.; Haycock, R. A.; Hunter, C. A.; Sarson, L. D. *J. Chem. Soc., Chem. Commun.* **1995**, 2567.
37. Ikeda, C.; Tanaka, Y.; Fujihara, T.; Ishii, Y.; Ushiyama, T.; Yamamoto, K.; Yoshioka, N.; Inoue, H. *Inorg. Chem.* **2001**, *40*, 3395.
38. Fleischer, E. B.; Shachter, A. M. *Inorg. Chem.* **1991**, *30*, 3763.
39. Funatsu, K.; Imamura, T.; Ichimura, A.; Sasaki, Y. *Inorg. Chem.* **1998**, *37*, 1798.
40. Ercolani, G.; Ioele, M.; Monti, D. *New J. Chem.* **2001**, *25*, 783.
41. Tsuda, A.; Nakamura, T.; Sakamoto, S.; Yamaguchi, K.; Osuka, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 2817.
42. Deviprasad, G. R.; D'Souza, F. *Chem. Commun.* **2000**, 1915.
43. Elemans, J. A. A. W.; Claase, M. B.; Aarts, P. P. M.; Rowan, A. E.; Schenning, A. P. H. J.; Nolte, R. J. M. *J. Org. Chem.* **1999**, *64*, 7009.
44. Imai, H.; Kyuno, E. *Inorg. Chem.* **1990**, *29*, 2416.
45. Mizutani, T.; Kozake, K.; Wada, K.; Kitagawa, S. *Chem. Commun.* **2003**, 2918.
46. Imahori, H.; Mori, Y.; Matano, Y. *J. Photochem. Photobiol., C* **2003**, *4*, 51.
47. Ros, T. D.; Prato, M.; Guldi, D.; Alessio, E.; Ruzzi, M.; Pasimeni, L. *Chem. Commun.* **1999**, 635.
48. Armaroli, N.; Diederich, F.; Echegoyen, L.; Habicher, T.; Flamigni, L.; Marconi, G.; Nierengarten, J.-F. *New J. Chem.* **1999**, 77.
49. D'Souza, F.; Rath, N. P.; Deviprasad, G. R.; Zandler, M. E. *Chem. Commun.* **2001**, 267.
50. Ros, T. D.; Prato, M.; Guldi, D. M.; Ruzzi, M.; Pasimeni, L. *Chemistry* **2001**, *7*, 816.
51. Boyd, P. D. W.; Hodgson, M. C.; Rickard, C. E. F.; Oliver, A. G.; Chaker, L.; Brothers, P. J.; Bolskar, R. D.; Tham, F. S.; Reed, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 10487.
52. Sun, Y.; Drovetskaya, T.; Bolskar, R. D.; Bau, R.; Boyd, P. D. W.; Reed, C. A. *J. Org. Chem.* **1997**, *62*, 3642.
53. Sun, D.; Tham, F. S.; Reed, C. A.; Chaker, L.; Burgess, M.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2000**, *122*, 10704.
54. Dudić, M.; Lhoták, P.; Stibor, I.; Petříčková, H.; Lang, K. *New J. Chem.* **2004**, *28*, 85.
55. Kubo, Y.; Sugasaki, A.; Ikeda, M.; Sugiyasu, K.; Sonoda, K.; Ikeda, A.; Takeuchi, M.; Shinkai, S. *Org. Lett.* **2002**, *4*, 925.
56. Tashiro, K.; Aida, T.; Zheng, J.-Y.; Kinbara, K.; Saigo, K.; Sakamoto, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1999**, *121*, 9477.
57. Zheng, J.-Y.; Tashiro, K.; Hirabayashi, Y.; Kinbara, K.; Saigo, K.; Aida, T.; Sakamoto, S.; Yamaguchi, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1857.
58. Kimura, M.; Saito, Y.; Ohta, K.; Hanabusa, K.; Shirai, H.; Kobayashi, N. *J. Am. Chem. Soc.* **2002**, *124*, 5274.
59. Shirakawa, M.; Fujita, N.; Shinkai, S. *J. Am. Chem. Soc.* **2003**, *125*, 9902.
60. Yamaguchi, T.; Ishii, N.; Tashiro, K.; Aida, T. *J. Am. Chem. Soc.* **2003**, *125*, 13934.
61. Hayashi, T.; Ogoshi, H. *Chem. Soc. Rev.* **1997**, *26*, 355.
62. Ward, M. D. *Chem. Soc. Rev.* **1997**, *26*, 365.
63. Hayashi, T.; Miyahara, T.; Hashizume, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 2049.
64. Turró, C.; Chang, C. K.; Leroi, G. E.; Cukier, R. I.; Nocera, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 4013.
65. Kirby, J. P.; Van Dantzig, N. A.; Chang, C. K.; Nocera, D. G. *Tetrahedron Lett.* **1995**, *36*, 3477.
66. Sessler, J. L.; Wang, B.; Harriman, A. *J. Am. Chem. Soc.* **1993**, *115*, 10418.
67. Tecilla, P.; Dixon, R. P.; Slobodkin, G.; Alavi, D. S.; Waldeck, D. H.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 9408.

68. Kral, V.; Springs, S. L.; Sessler, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 8881.
69. Ladomenou, K.; Bonar-Law, R. P. *Chem. Commun.* **2002**, 2108.
70. Ohkawa, H.; Arai, S.; Takeoka, S.; Shibue, T.; Nishide, H. *Chem. Lett.* **2003**, *32*, 1052.
71. Norsten, T. B.; Chichak, K.; Branda, N. R. *Chem. Commun.* **2001**, 1794.
72. Kuroda, Y.; Kawashima, A.; Hayashi, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 4929.
73. Drain, C. M.; Shi, X.; Milic, T.; Nifiatis, F. *Chem. Commun.* **2001**, 287.
74. Shi, X.; Barkigia, K. M.; Fajer, J.; Drain, C. M. *J. Org. Chem.* **2001**, *66*, 6513.
75. Drain, C. M.; Russell, K. C.; Lehn, J.-M. *Chem. Commun.* **1996**, 337.
76. Feiters, M. C.; Fyfe, M. C. T.; Martínez-Díaz, M.-V.; Menzer, S.; Nolte, R. J. M.; Stoddart, J. F.; Van Kan, P. J. M.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8119.
77. Shinmori, H.; Yasuda, Y.; Osuka, A. *Eur. J. Org. Chem.* **2002**, 1197.
78. Shinmori, H.; Osuka, A. *Tetrahedron Lett.* **2000**, *41*, 8527.
79. Thanabal, V.; Krishnan, V. *J. Am. Chem. Soc.* **1982**, *104*, 3643.
80. Martinez-Diaz, M. V.; Rodriguez-Morgade, M. S.; Feiters, M. C.; Van Kan, P. J. M.; Nolte, R. J. M.; Stoddart, J. F.; Torres, T. *Org. Lett.* **2000**, *2*, 1057.
81. Sielcken, O. E.; Tilborg, M. M.; Roks, M. F. M.; Hendriks, R.; Drenth, W.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 4261.
82. Solladié, N.; Walther, M. E.; Gross, M.; Figueira Duarte, T. M.; Bourgogne, C.; Nierengarten, J.-F. *Chem. Commun.* **2003**, 2412.
83. Mizutani, T.; Wada, K.; Kitagawa, S. *J. Am. Chem. Soc.* **2001**, *123*, 6459.
84. Balbinot, D.; Atalick, S.; Guldi, D. M.; Hatzimarinaki, M.; Hirsch, A.; Jux, N. *J. Phys. Chem. B.* **2003**, *107*, 13273.
85. Tomioka, N.; Takasu, D.; Takahashi, T.; Aida, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 1531.
86. Kieran, A. L.; Bond, A. D.; Belenguer, A. M.; Sanders, J. K. M. *Chem. Commun.* **2003**, 2674.
87. Ogawa, K.; Kobuke, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 4070.
88. Takahashi, R.; Kobuke, Y. *J. Am. Chem. Soc.* **2003**, *125*, 2372.
89. Kuramochi, Y.; Satake, A.; Kobuke, Y. *J. Am. Chem. Soc.* **2004**, *126*, 8668.
90. Michelsen, U.; Hunter, C. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 764.
91. Fujita, N.; Biradha, K.; Fujita, M.; Sakamoto, S.; Yamaguchi, K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1718.
92. Drain, C. M.; Nifiatis, F.; Vasenko, A.; Batteas, J. D. *Angew. Chem. Int. Ed.* **1998**, *37*, 2344.
93. Haycock, R. A.; Yartsev, A.; Michelsen, U.; Sundström, V.; Hunter, C. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3616.
94. Drain, C. M.; Fischer, R.; Nolen, E. G.; Lehn, J.-M. *J. Chem. Soc., Chem. Commun.* **1993**, 243.
95. Sasaki, K.; Nakagawa, H.; Zhang, X.; Sakurai, S.; Kano, K.; Kuroda, Y. *Chem. Commun.* **2004**, 408.
96. Schnarr, N. A.; Kennan *J. Am. Chem. Soc.* **2003**, *125*, 6364.
97. Vandermeulen, G. W. M.; Tziatzios, C.; Klok, H.-A. *Macromolecules* **2003**, *36*, 4107.
98. Isaacs, L.; Witt, D.; Lagona, J. *Org. Lett.* **2001**, *3*, 3221.
99. Kleinekofort, W.; Germeroth, L.; Van den Broek, J. A.; Schubert, D.; Michel, H. *Biochim. Biophys. Acta* **1992**, *1140*, 102.
100. Ikeda, A.; Ayabe, M.; Shinkai, S. *Chem. Lett.* **2001**, 1138.
101. Viel, S.; Capitani, D.; Mannina, L.; Segre, A. *Biomacromolecules* **2003**, *4*, 1843.
102. Folmer, B. J. B.; Sijbesma, R. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2001**, *123*, 2093.
103. Ishi-i, T.; Iguchi, R.; Snip, E.; Ikeda, M.; Shinkai, S. *Langmuir* **2001**, *17*, 5825.
104. de la Escosura, A.; Martínez-Díaz, M. V.; Thordarson, P.; Rowan, A. E.; Nolte, R. J. M.; Torres, T. *J. Am. Chem. Soc.* **2003**, *125*, 12300.
105. Crusats, J.; Claret, J.; Díez- Pérez, I; El-Hachemi, Z.; García-Ortega, H.; Rubires, R.; Sagués, F.; Ribó, J. M. *Chem. Commun.* **2003**, 1588.
106. Ikeda, C.; Fujiwara, E.; Satake, A.; Kobuke, Y. *Chem. Commun.* **2003**, 616.
107. Lensen, M. C.; Van Dingenen, S. J. T.; Elemans, J. A. A. W.; Dijkstra, H. P.; Van Klink, G. P. M.; Van Koten, G.; Gerritsen, J. W.; Speller, S.; Nolte, R. J. M.; Rowan, A. E. *Chem. Commun.* **2004**, 762.
108. Peng, X.; Aratani, N.; Takagi, A.; Matsumoto, T.; Kawai, T.; Hwang, I.-W.; Ahn, T. K.; Kim, D.; Osuka, A. *J. Am. Chem. Soc.* **2004**, *126*, 4468.
109. Ohashi, A.; Satake, A.; Kobuke, Y. *Bull. Chem. Soc. Jpn* **2004**, *77*, 365.
110. Ikeda, C.; Satake, A.; Kobuke, Y. *Org. Lett.* **2003**, *5*, 4935.
111. Inomata, T.; Konishi, K. *Chem. Commun.* **2003**, 1282.
112. Kato, A.; Sugiura, K.; Miyasaka, H.; Tanaka, H.; Kawai, T.; Sugimoto, M.; Yamashita, M. *Chem. Lett.* **2004**, *33*, 578.
113. Sugiura, K.; Tanaka, H.; Matsumoto, T.; Kawai, T.; Sakata, Y. *Chem. Lett.* **1999**, *28*, 1193.
114. Takagi, A.; Yanagawa, Y.; Tsuda, A.; Aratani, N.; Matsumoto, T.; Osuka, A.; Kawai, T. *Chem. Commun.* **2003**, 2986.
115. Tanaka, H.; Kawai, T. *J. Vac. Sci. Technol. B* **1997**, *15*, 602.
116. Choi, M.; Yamazaki, T.; Yamazaki, I.; Aida, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 150.
117. Kuroda, Y.; Sugou, K.; Sasaki, K. *J. Am. Chem. Soc.* **2000**, *122*, 7833.
118. Sugou, K.; Sasaki, K.; Kitajima, K.; Iwaki, T.; Kuroda, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1182.
119. Ozeki, H.; Kobuke, Y. *Tetrahedron Lett.* **2003**, *44*, 2287.
120. Takahashi, R.; Kobuke, Y. Submitted for publication.
121. Nomoto, A.; Kobuke, Y. *Chem. Commun.* **2002**, 1104.
122. Abdelrazzaq, F. B.; Kwong, R. C.; Thompson, M. E. *J. Am. Chem. Soc.* **2002**, *124*, 4796.
123. Nomoto, A.; Mitsuoka, H.; Ozeki, H.; Kobuke, Y. *Chem. Commun.* **2003**, 1074.
124. Ikeda, A.; Hatano, T.; Shinkai, S.; Akiyama, T.; Yamada, S. *J. Am. Chem. Soc.* **2001**, *123*, 4855.
125. Guldi, D. M.; Zilbermann, I.; Anderson, G.; Li, A.; Balbinot, D.; Jux, N.; Hatzimarinaki, M.; Hirsch, A.; Prato, M. *Chem. Commun.* **2004**, 726.
126. Drain, C. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5178.
127. Matile, S.; Berova, N.; Nakanishi, K.; Fleischhauer, J.; Woody, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 5198.
128. Huang, X.; Rickman, B. H.; Borhan, B.; Berova, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1998**, *120*, 6185.
129. Huang, X.; Fujioka, N.; Pescitelli, G.; Koehn, F. E.; Williamson, R. T.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2002**, *124*, 10320.

130. Huang, X.; Borhan, B.; Rickman, B. H.; Nakanishi, K.; Berova, N. *Chem. Eur. J.* **2000**, *6*, 216.
131. Kurtan, T.; Nesnas, N.; Li, Y.-Q.; Huang, X.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2001**, *123*, 5962.
132. Proni, G.; Pescitelli, G.; Huang, X.; Nakanishi, K.; Berova, N. *J. Am. Chem. Soc.* **2003**, *125*, 12914.
133. Borovkov, V. V.; Lintuluoto, J. M.; Sugeta, H.; Fujiki, M.; Arakawa, R.; Inoue, Y. *J. Am. Chem. Soc.* **2002**, *124*, 2993.
134. Lintuluoto, J. M.; Borovkov, V. V.; Inoue, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13676.
135. Guo, Y.-M.; Oike, H.; Aida, T. *J. Am. Chem. Soc.* **2004**, *126*, 716.
136. Takeuchi, M.; Imada, T.; Shinkai, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2096.
137. Sugasaki, A.; Ikeda, M.; Takeuchi, M.; Shinkai, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3839.
138. Sugasaki, A.; Sugiyasu, K.; Ikeda, M.; Takeuchi, M.; Shinkai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10239.
139. Shoji, Y.; Tashiro, K.; Aida, T. *J. Am. Chem. Soc.* **2004**, *126*, 6570.
140. Li, H.; Zhou, B.; Lin, Y.; Gu, L.; Wang, W.; Shiral Fernando, K. A.; Kumar, S.; Allard, L. F.; Sun, Y.-P. *J. Am. Chem. Soc.* **2004**, *126*, 1014.
141. Shinmori, H.; Ahn, T. K.; Cho, H. S.; Kim, D.; Yoshida, N.; Osuka, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2754.
142. Kitagishi, H.; Satake, A.; Kobuke, Y. *Inorg. Chem.* **2004**, *43*, 3394.
143. Otsuki, J.; Yasuda, A.; Takido, T. *Chem. Commun.* **2003**, 608.
144. Yagi, S.; Ezoe, M.; Yonekura, I.; Takagishi, T.; Nakazumi, H. *J. Am. Chem. Soc.* **2003**, *125*, 4068.

Biographical sketch

Akiharu Satake was born in Tokyo, Japan. He received his PhD degree from Waseda University in 1995 working with Professor Isao Shimizu and Professor Akio Yamamoto. After two years with Professor Shimizu as an Assistant Professor at Waseda University, he joined the group of Dr. Tadashi Nakata in RIKEN (The Institute of Physical and Chemical Research) as a Special Postdoctoral Researcher in 1997. In this period, he studied novel metal catalysts and palladium-catalyzed reactions. He received the Award for Young Scientists in Coordination Chemistry from the Japan Society of Coordination Chemistry in 2000 for his study of a novel hapto-3-allylpalladium-pyridinylpyrazole complex. In 1999, he joined the group of Prof. Yoshiaki Kobuke in the Graduate School of Materials Science, Nara Institute of Science and Technology as an Assistant Professor. His present research interest is the construction of supramolecular multiporphyrin systems directed towards artificial photosynthesis and molecular devices.

Yoshiaki Kobuke completed his PhD in 1969 under the supervision of Professor Junji Furukawa at the Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, where he started research first as an Assistant and then as an Associate Professor in the groups of Profs. Furukawa, Iwao Tabushi and Hisanobu Ogoshi, successively. In this period, he studied topics on stereospecific polymerization, stereoselection of Diels–Alder reactions, binding and transport of metal ions by crown ethers, extraction of uranium from seawater, biomimetic recognition and biosynthetic chemistry. In 1972–1973, he contributed to the total synthesis of vitamin B_{12} and erythromycin as a visiting scientist under Professor Robert Burns Woodward, Department of Chemistry, Harvard University. In 1990, he was promoted to Professor at the Department of Materials Science, Faculty of Engineering, Shizuoka University, where he initiated the research on synthetic ion channels and artificial photosynthesis. In 1998, he moved to the Graduate School of Materials Science, Nara Institute of Science and Technology. During 1998–2003, he was nominated as a research director of Creative Research of Evolutional Science and Technology, Japan Science and Technology. In this period, he concentrated on supramolecular science. By using complementary coordination of porphyrins, he constructed artificial special pair and light-harvesting complexes of photosynthetic bacteria. This methodology was extended further to materials of nonlinear optics, especially two-photon absorption and construction of molecular electronics.

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Conversion of 1,3-oxathiolanes to 1,4-oxathianes using a silylated diazoester

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Abstract—Treatment of substituted 1,3-oxathiolanes with ethyl (triethylsilyl)diazoacetate in the presence of a copper catalyst effects one-carbon ring expansion to the corresponding 3-triethylsilyl-1,4-oxathiane-3-carboxylates. Subsequent desilylation can be brought about by treatment with tetrabutylammonium fluoride.
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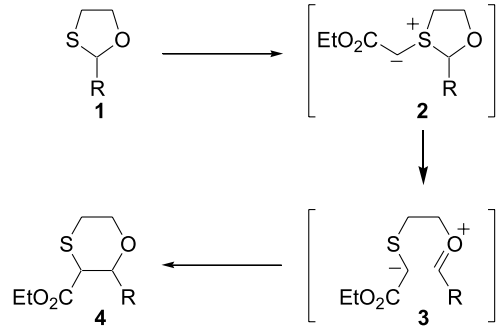
1. Introduction

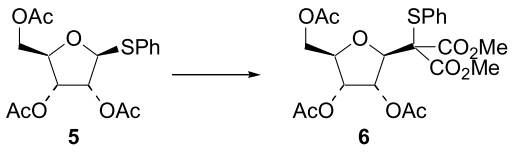
The metal-catalysed reaction of diazo compounds with sulfides is a well-established method for the generation of sulfur ylides.[1] The sulfur ylides generated in this fashion can undergo a variety of rearrangement reactions, the most common of which are [1,2]-and [2,3]-rearrangements. Alternatively, intermolecular reaction of the sulfur ylide can take place, for example reacting with an aldehyde to form an epoxide.[2]

As part of a project aimed towards the synthesis of the RNA polymerase inhibitor tagetitoxin,[3] we wished to develop a new method for the synthesis of 1,4-oxathianes such as **4**. We postulated that such compounds would be accessible through rearrangement of sulfur ylides derived from 1,3-oxathiolanes such as **1**. Thus, treatment of **1** with ethyl diazoacetate in the presence of a metal catalyst was expected to generate a sulfur ylide **2**, which would undergo a [1,2]-shift to produce the corresponding 1,4-oxathiane **4** (Scheme 1). This rearrangement could proceed via either the zwitterion **3** shown, or a diradical intermediate. The conversion of **1** to **4** corresponds to an overall insertion of the CH–CO_2Et unit into a C–S bond, and thus a one-carbon ring-expansion of the original substrate. In this paper we provide full details[4] of our studies into this ring-expansion reaction.

Previous related studies have shown that sulfur ylides derived from *S*,*S*-, *O*,*S*-, and *N*,*S*-acetals undergo this type of 1,2-shift to form new carbon–carbon bonds.[1] A ring expansion of 1,3-dithianes to 1,4-dithiepanes has been reported by Doyle,[5] and Kametani has shown that reaction of the ribose-derived thioglycoside **5** with dimethyl diazomalonate in the presence of rhodium(II) acetate gives rise to the *C*-glycoside **6**, which was used as an intermediate in a synthesis of showdomycin (Scheme 2).[6]



Scheme 1. Proposed ring expansion reaction. Reagents: ethyl diazoacetate, metal catalyst.



Scheme 2. Kametani's *C*-glycoside synthesis. Reagents and conditions: $(MeO_2C)_2CN_2$, $Rh_2(OAc)_4$ CH_2Cl_2, reflux, 71% yield.

Keywords: Ring expansion; Heterocycles; Sulfur ylides; Diazo compounds; Silicon.
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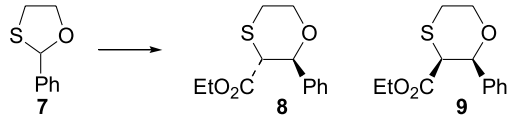
2. Results and discussion

2.1. Ring expansion with ethyl diazoacetate

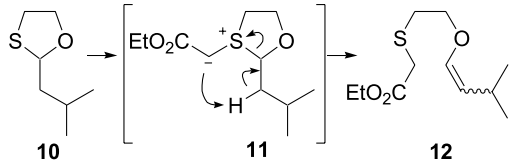
Initial investigations into the ring expansion reaction were carried out using 2-phenyl-1,3-oxathiolane (**7**), which was prepared by acid-catalysed reaction of benzaldehyde with 2-mercaptoethanol. A range of conditions were investigated for the reaction of this substrate with ethyl diazoacetate.

Under the best conditions found, conversion of **7** to the desired ring-expansion products **8** and **9** could be effected by slow addition of ethyl diazoacetate to a solution of **7** and copper(II) acetylacetonate in benzene under reflux (Scheme 3). Under these conditions, a 2:1 mixture of **8** and **9** was obtained, and this mixture could be isolated in 19% yield. However, in addition to the desired products, substantial amounts of diethyl maleate, diethyl fumarate and unreacted starting material were observed in the crude reaction mixture (although they were not isolated). Attempts to ensure the consumption of all the starting material by addition of further diazo compound led to complex, intractable mixtures. This result we attribute to a lack of discrimination shown by the metal carbene between the sulfur atom of the 1,3-oxathiolane **7** and those of the 1,4-oxathianes **8** and/or **9**; if all three heterocycles react with the metal carbene at a similar rate, addition of a large excess of diazo compound will lead to consumption of the desired products **8** and **9**, giving the corresponding sulfur ylides which decompose to unidentified side-products. Similar results were obtained with other 2-aryl-1,3-oxathiolanes.



Scheme 3. Reagents and conditions: EtO_2CCHN_2 (1.2 equiv), $Cu(acac)_2$ (12 mol%), benzene, reflux, 16 h, 19% yield (**8**:**9** 2:1).

When an alkyl-substituted 1,3-oxathiolane, **10**, was subjected to the same conditions, no products of ring expansion were observed; however, enol ether **12** could be obtained in 27% yield as a mixture of geometric isomers (Scheme 4). In this case it appears that the intermediate sulfur ylide **11**, rather than undergoing ring expansion, suffers an elimination reaction to produce the observed products.

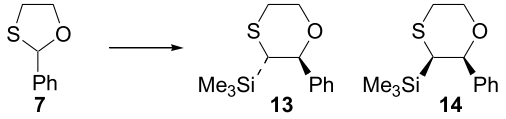


Scheme 4. Reagents and conditions: EtO_2CCHN_2 (1.2 equiv), $Cu(acac)_2$ (12 mol%), benzene, reflux, 24 h, 27% yield (*E*:*Z* 3.3:1).

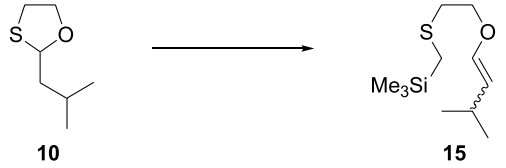
2.2. Ring expansion with (trimethylsilyl)diazomethane

In 1999, Aggarwal[7] and Van Vranken[8] independently reported that (trimethylsilyl)diazomethane offers marked advantages over ethyl diazoacetate in the formation and subsequent [2,3]-rearrangement of sulfur ylides from allylic sulfides. In particular, this diazo compound shows less of a tendency to form dimeric side-products (cf. diethyl maleate and diethyl fumarate from ethyl diazoacetate), and, more importantly, the desired products of the reaction do not react further with any excess diazo compound. A large excess of the diazo compound can thus be used with impunity.

Use of this diazo compound in the present study led to a marked improvement in the efficiency of the ring expansion reaction. Thus slow addition of an excess of (trimethylsilyl)diazomethane to a refluxing solution of 2-phenyl-1,3-oxathiolane (**7**) and copper(II) acetylacetonate[9] in benzene resulted in a clean ring expansion taking place, with complete consumption of starting material, and no apparent over-reaction of the 1,4-oxathiane products (Scheme 5). The desired compounds **13** and **14** could be isolated in 29% and 21% yield respectively by silica gel chromatography. Once again, however, isobutyl-substituted compound **10** yielded only the product of ring opening, enol ether **15** (Scheme 6).



Scheme 5. Reagents and conditions: Me_3SiCHN_2 (3.7 equiv), $Cu(acac)_2$ (10 mol%), benzene, reflux, 5.5 h, 29% **13**, 21% **14**.



Scheme 6. Reagents and conditions: Me_3SiCHN_2 (3.8 equiv), $Rh_2(OAc)_4$ (1.5 mol%), benzene, reflux, 17 h, 37% yield (*E*:*Z* 2.6:1).

2.3. Ring expansion with silylated diazoesters

The success of the ring expansion with a silylated diazo compound, combined with our desire to synthesise compounds containing an ester group, led us to consider the use of a silylated diazoester (**16**) in the ring expansion reaction. Such compounds, first reported by Schöllkopf in 1967,[10] have found use recently in a range of transition-metal catalysed reactions, including intermolecular cyclopropanation,[11] cyclopropenation,[12] carbonyl ylide formation,[13] oxazole synthesis,[13b,14] N–H insertion[15] and deoxygenation of epoxides.[16] In addition, a range of intramolecular reactions of compounds with the general structure **16** have been reported, including insertion into C–H bonds[16,17] and reactions with tethered alkenes[18] and alkynes.[19]

Ethyl diazo(trimethylsilyl)acetate (**17**) and its triethylsilyl analogue (**18**) (Fig. 1) are readily prepared by reaction of

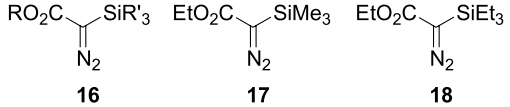
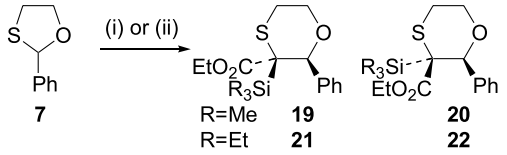


Figure 1. Silylated diazoesters.

ethyl diazoacetate with the corresponding trialkylsilyl triflate in the presence of Hünig's base.[20]

Treatment of phenyl-substituted oxathiolane **7** with ethyl diazo(trimethylsilyl)acetate (**17**) in the presence of copper(II) acetylacetonate led to a clean ring expansion, giving 1,4-oxathianes **19** and **20** in a 6:1 ratio (Scheme 7). After initial purification by passing the reaction mixture through a short plug of silica, recrystallisation from ethanol afforded the major diastereomer **19** in 46% yield. The minor isomer **20** could be obtained in 10% yield by chromatography of the mother liquors.



Scheme 7. Reagents and conditions: (i) **17** (1.04 equiv), $Cu(acac)_2$ (2 mol%), benzene, reflux, 29 h, 46% **19**, 10% **20**; (ii) **18** (1.2 equiv), $Cu(acac)_2$ (10 mol%), benzene, reflux, 22 h, 67% yield (**21**:**22** 8:1).

This ring expansion proved somewhat capricious; in particular, variable amounts of desilylation took place during the course of the reaction to give **8** and **9** in the crude reaction mixture. For this reason, our attention turned to the use of ethyl diazo(triethylsilyl)acetate (**18**), bearing the more robust triethylsilyl group. Treatment of **7** with 1.2 equiv of **18** and $Cu(acac)_2$ gave reproducibly the ring-expanded products **21** and **22**; the proton NMR spectrum of the crude reaction mixture showed this to be a 4:1 mixture of diastereomers, with no evidence of concomitant desilylation. These compounds proved resistant to purification by crystallisation, but chromatography on Florisil® allowed isolation of good yields of oxathiane products (67%, as an 8:1 mixture of stereoisomers). Markedly lower yields (ca. 30%) were obtained if the chromatography was carried out using either silica or alumina as the stationary phase.

The relative stereochemistry of compounds **21** and **22** was assigned with the aid of ^1H NMR and NOE experiments. The key NOE enhancements are shown in Figure 2. For both compounds, the coupling constants for the CH_2CH_2 portion of the six-membered ring were consistent with the adoption of a chair conformation. Irradiation of the *ortho*-protons of the phenyl ring in **21** led to NOE enhancements of the axial proton at C-6 and the methylene protons of the triethylsilyl group. Taken together, these indicate the relative configuration and conformation of **21** to be as depicted in Figure 2. It is noteworthy that in this structure, both the phenyl group and the ethyl ester occupy axial positions, with the silyl group residing equatorially. For compound **22**, NOE enhancements were observed between the axial C-6 proton and the benzylic proton, indicating an equatorial situation of the phenyl group in this compound.

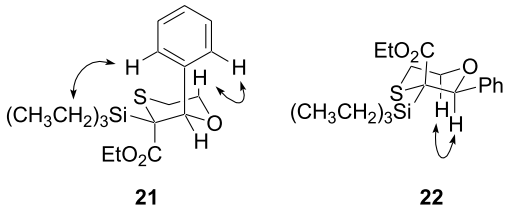
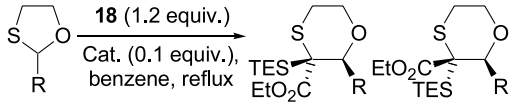


Figure 2. Selected NOE enhancements in compounds **21** and **22**.

A range of other 2-substituted 1,3-oxathiolanes was subjected to the optimised ring expansion conditions, and the results are summarised in Table 1. While good results were obtained with aryl substituents (compounds **23** and **24**), the yield of ring expansion products from the alkyl-substituted oxathiolane **10** was low and not entirely reproducible. Better results with this substrate were obtained when a copper(I) catalyst, $Cu(MeCN)_4$ PF_6, was used;[21] with this catalyst, a reproducible yield of 30% could be obtained. *tert*-Butyl oxathiolane **25** and unsubstituted oxathiolane **26** also underwent ring expansion in the presence of the copper(I) catalyst, although the product in the latter case proved unstable to chromatography, even on Florisil®.

Table 1. Ring expansion of 1,3-oxathiolanes using **18**

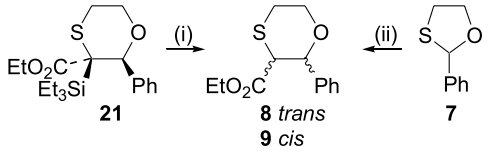


Substrate	R	Catalyst[a]	Time (h)	Product ratio[b]	Yield[c] (%)
7	Ph	Cu^{II}	24	4:1	67[d]
23	*p*-$NO_2C_6H_4$	Cu^{II}	22	4:1	62[e]
24	*p*-$MeOC_6H_4$	Cu^{II}	24	20:1	62
10	*i*-Bu	Cu^{II}	2	—[f]	7
		Cu^{I}	2.5	—[f]	30
25	*t*-Bu	Cu^{I}	4	—[f]	12
26	H	Cu^{I}	2.5	n/a	0[g]

[a] Catalysts: Cu^{II}=$Cu(acac)_2$, Cu^{I}=$Cu(MeCN)_4PF_6$.
[b] Determined by integration of ^1H NMR signals in crude reaction mixture.
[c] Isolated yields after chromatography on Florisil®. Unless otherwise stated, yields are of a single stereoisomer.
[d] 8:1 mixture of diastereoisomers.
[e] 3:1 mixture of diastereoisomers.
[f] Minor isomer not observed.
[g] Compound decomposed on attempted purification.

2.4. Desilylation of ring-expansion products

Having achieved the ring expansion of **7** in good yield by the introduction of a trialkylsilyl group, we now turned our attention to the removal of this extraneous substituent. Treatment of the major 1,4-oxathiane stereoisomer **21** with a solution of tetra-*n*-butylammonium fluoride in THF effected rapid desilylation, affording **8** and **9** as a 2:1 mixture, in quantitative yield (Scheme 8). All attempts to improve the ratio of stereoisomers, through variation of temperature, solvent or fluoride source,[22] were unsuccessful. Presumably, the silicon-bearing chiral centre in **21** is converted to a planar carbanion intermediate in the course of the reaction, leading to the loss of stereochemical purity.

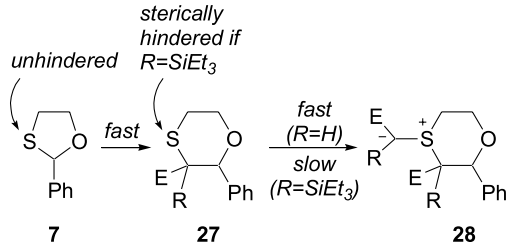


Scheme 8. Reagents and conditions: (i) Bu_4NF, THF, 0 °C, 100% yield (**8**:**9** 2:1); (ii) **18** (1.2 equiv), $Cu(acac)_2$ (0.1 equiv), benzene, reflux, 16 h then Bu_4NF, THF, 0 °C, 87% yield (**8**:**9** 2:1).

Desilylation could alternatively be carried out immediately after the ring expansion reaction, without purification of the intermediate silylated oxathiane. In this case, the desilylated products were obtained in an overall yield of 87% for two steps (Scheme 8).

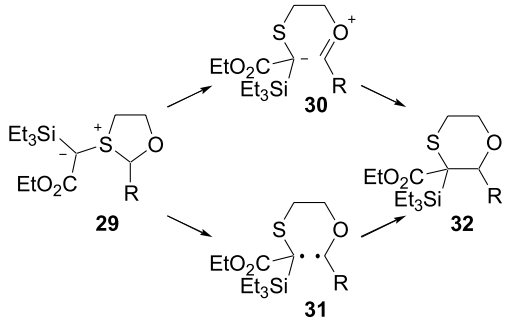
3. Discussion

In this work, we have developed an efficient method for the ring expansion of 2-aryl 1,3-oxathiolanes. The poor yields obtained when ethyl diazoacetate is used for this reaction arise from its tendency to form alkene by-products, but more pertinently to its lack of discrimination between the sulfur atoms in starting material (**7**, Scheme 9) and product (**27**, R=H). The complete conversion and high yields observed when the same substrates are treated with silylated diazoacetates **17** and **18** are indicative of an attenuation of both of these problems when the silylated reagents are used, and we ascribe both effects to the steric bulk of the silyl group; thus reaction of the bulky silylated metal carbene with the sterically hindered sulfur of 1,4-oxathiane **27** (R=$SiEt_3$) is markedly slower than its reaction with the starting material, 1,3-oxathiolane **7** (Scheme 9).



Scheme 9. Abbreviation: E=CO_2Et.

Mechanistically, the ring expansion reaction is presumed to proceed via a sulfur ylide intermediate **29**, or a metal-bound equivalent thereof (Scheme 10). Following formation of the ylide, the benzylic C–S bond breaks, either heterolytically to give zwitterion **30**, or homolytically to give a diradical **31**. In either case, a subsequent C–C bond formation completes the ring expansion. The lower yields obtained in the ring expansion of alkyl-substituted 1,3-oxathiolanes may be attributable, in part, to the lack of additional stabilisation which is afforded to intermediate **30** or **31** by an aromatic substituent.



Scheme 10.

4. Conclusion

The ring expansion of 1,3-oxathiolanes can be carried out by treatment with a diazo compound in the presence of a metal catalyst. While ring expansions with ethyl diazoacetate proceed with poor yield due to the relatively non-selective nature of the corresponding metal carbenoid, use of a silyl-substituted diazoester leads to cleaner reactions and higher yields of the desired products. Subsequent desilylation of the ring-expansion products can be carried out in quantitative yield.

5. Experimental

5.1. General

Reactions were performed under an atmosphere of nitrogen or argon. THF was distilled from sodium/benzophenone, and benzene was distilled from calcium hydride, immediately prior to use.

1,3-Oxathiolanes **7**, **10**, **23**, **24**, **25** and **26** were prepared from the corresponding aldehydes[23] and 2-mercaptoethanol in the presence of *p*-toluenesulfonic acid[24] or zirconium (IV) chloride[25] as acid catalyst. All other reagents were used as obtained from commercial sources.

5.2. Experimental procedures

5.2.1. Ring expansion with ethyl diazoacetate: ethyl *trans*-2-phenyl-1,4-oxathiane-3-carboxylate (8) and ethyl *cis*-2-phenyl-1,4-oxathiane-3-carboxylate (9). A solution of 2-phenyl-1,3-oxathiolane (**7**, 0.29 g, 1.7 mmol) and copper(II) acetylacetonate (54 mg, 0.21 mmol) in benzene (2.5 mL) was heated to reflux. A solution of ethyl diazoacetate (0.24 g, 2.1 mmol) in benzene (1.6 mL) was added dropwise over a period of 3.5 h, and reflux was

continued for a further 16 h. The solvent was evaporated under reduced pressure to afford a yellow oil, which was purified by flash chromatography (SiO_2; Et_2O/hexanes 30:70) to afford a 2:1 mixture of **8** and **9** (98 mg, 19%) (see below for spectroscopic data).

5.2.2. Ethyl 9-methyl-6-oxa-3-thiadec-7-enoate (12). A solution of 2-(2-methylpropyl)-1,3-oxathiolane (**10**, 0.30 g, 2.0 mmol) and copper(II) acetylacetonate (66 mg, 0.25 mmol) in benzene (2.5 mL) was heated to reflux. A solution of ethyl diazoacetate (0.29 g, 2.5 mmol) in benzene (1.6 mL) was added dropwise over a period of 3.5 h, and reflux was continued for a further 24 h. The solvent was evaporated under reduced pressure to afford a yellow oil, which was purified by flash chromatography (SiO_2; Et_2O/hexanes 5:95) to afford **12** as an inseparable 3.3:1 mixture of (*E*) and (*Z*) isomers (0.13 g, 27%); ν_{max} (film)/cm^{-1} 2959, 2869, 1731, 1651, 1298, 1270, 1176, 1156, 1126 and 1032; δ_H (300 MHz; $CDCl_3$; signals reported for (*E*)-isomer only) 1.00 (6H, d, $J=6.7$ Hz, $CH(CH_3)_2$), 1.30 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 2.19–2.30 (1H, m, $CH(CH_3)_2$), 2.90 (2H, t, $J=6.5$ Hz, SCH_2CH_2O), 3.30 (2H, s, SCH_2CO_2Et), 3.85 (2H, t, $J=6.5$ Hz, SCH_2CH_2O), 4.21 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.79 (1H, dd, $J=12.6$, 7.5 Hz, OCH=CH), 6.22 (1H, d, $J=12.5$ Hz, OCH=CH).

5.2.3. *trans*-2-Phenyl-3-trimethylsilyl-1,4-oxathiane (13) and *cis*-2-phenyl-3-trimethylsilyl-1,4-oxathiane (14). A mixture of 2-phenyl-1,3-oxathiolane (**7**, 0.23 g, 1.4 mmol) and copper(II) acetylacetonate (37 mg, 0.14 mmol) in benzene (2 mL) was heated to reflux. (Trimethylsilyl)-diazomethane (2 M in hexanes, 2.6 mL, 5.2 mmol) was added via syringe pump over a period of 4 h. Reflux was continued for a further 90 min, then the mixture was cooled and loaded directly onto a short column of flash silica. Elution with Et_2O/hexanes 20:80 afforded 0.37 g of a yellow oil. Flash chromatography (SiO_2; Et_2O/hexanes 3:97→10:90) afforded **13** (99 mg, 29%) and **14** (73 mg, 21%) as pale yellow oils.

Compound **13**. ν_{max} (liquid film)/cm^{-1} 2951, 2853, 1250, 1086, 847, 700; δ_H (300 MHz; $CDCl_3$) −0.26 (9H, s, $Si(CH_3)_3$), 2.32 (dt, $J=13.3$, 2.0 Hz, $SCH_{eq}H$), 2.69 (1H, d, $J=10.3$ Hz, TMSCH), 3.06 (ddd, $J=13.2$, 12.0, 3.5 Hz, $SCH_{ax}H$), 3.91 (td, $J=11.9$, 2.1 Hz, $OCH_{ax}H$), 4.31 (1H, ddd, $J=11.8$, 3.4, 2.0 Hz, $OCH_{eq}H$), 4.50 (1H, d, $J=10.3$ Hz, PhCH), 7.30 (1H, br s, C_6H_5); δ_c (75.4 MHz; $CDCl_3$) −2.7, 27.5, 33.2, 69.5, 84.3, 127.3, 128.5, 128.6, 141.5; *m/z* (FAB) 252.0994 (M^+, $C_{13}H_{20}OSSi$ requires 252.1004), 252 (31%), 154 (100).

Compound **14**. ν_{max} (liquid film)/cm^{-1} 2953, 2853, 1604, 1249, 1096, 846, 698; δ_H (300 MHz; $CDCl_3$) −0.17 (9H, s, $Si(CH_3)_3$), 2.06 (1H, d, $J=3.0$ Hz, TMSCH), 2.27 (1H, br d, $J=13.6$ Hz, $SCH_{eq}H$), 3.03 (1H, ddd, $J=13.7$, 11.4, 3.6 Hz, $SCH_{ax}H$), 3.93 (1H, td, $J=11.6$, 2.5 Hz, $OCH_{ax}H$), 4.43 (dt, $J=11.7$, 3.0 Hz, $OCH_{eq}H$), 5.14 (1H, d, $J=3.1$ Hz, PhCH), 7.18–7.39 (5H, m, C_6H_5); δ_C (75.4 MHz; $CDCl_3$) 0.2, 24.9, 31.8, 69.6, 82.1, 125.5, 127.2, 128.1, 142.0; *m/z* (EI) 252.1006 (M^+, $C_{13}H_{20}OSSi$ requires 252.1004), 252 (22%), 179 (29), 105 (53), 73 (100).

5.2.4. 2-Methyl-9-trimethylsilyl-5-oxa-8-thianon-3-ene (15). A mixture of 2-(2-methylpropyl)-1,3-oxathiolane (**10**, 0.11 g, 0.8 mmol), rhodium acetate dimer (5 mg, 12 μmol) and (trimethylsilyl)diazomethane (2 M in hexanes, 1.5 mL, 3.1 mmol) in benzene (2.5 mL) was heated to reflux for 17 h. The solvent was evaporated under reduced pressure to give an oil which was purified by flash chromatography (SiO_2; Et_2O/hexanes 5:95) to afford **15** as an inseparable 2.6:1 mixture of (*E*) and (*Z*) isomers (66 mg, 37%); ν_{max} (liquid film)/cm^{-1} 2957, 1653, 1261, 1250, 843; δ_H (400 MHz; $CDCl_3$) (signals quoted for (*E*)-isomer only) 0.12 (9H, s, $Si(CH_3)_3$), 1.00 (6H, d, $J=6.7$ Hz, $(CH_3)_2CH$), 1.87 (2H, s, $SiCH_2S$), 2.21–2.27 (1H, m, $(CH_3)_2CH$), 2.77 (2H, t, $J=6.9$ Hz, SCH_2CH_2O), 3.83 (2H, t, $J=6.9$ Hz, SCH_2CH_2O), 4.79 (1H, dd, $J=12.7$, 7.6 Hz, OCH=CH), 6.24 (1H, dd, $J=12.7$, 0.7 Hz, OCH=CH); δ_C (75.4 MHz; $CDCl_3$) −1.8, 23.7, 27.5, 35.0, 68.0, 112.4, 144.1; *m/z* (FAB^+) 233 (MH^+, 4%), 147 (37), 73 (100).

5.2.5. Ethyl diazo(trimethylsilyl)acetate (17).[20] A stirred solution of ethyl diazoacetate (1.14 g, 10.0 mmol) and ethyldiisopropylamine (1.75 mL, 10.0 mmol) in diethyl ether (50 mL) was cooled to −78 °C, and trimethylsilyl triflate (1.80 mL, 9.9 mmol) was added dropwise over 10 min. The reaction was stirred at −78 °C for 20 min then allowed to warm to room temperature. After a further 16 h, the white precipitate of ammonium salt was removed by filtration and washed with ether. The combined ether solutions were concentrated in vacuo to afford **17** as a yellow oil (1.55 g, 83%) which was used without further purification; δ_H (300 MHz; $CDCl_3$) 0.26 (9H, s, $Si(CH_3)_3$, 1.27 (3H, t, $J=7.1$ Hz, CH_2CH_3), 4.19 (2H, q, $J=7.1$ Hz, CH_2CH_3); δ_C (75.4 MHz; $CDCl_3$) 0.0, 15.9, 62.1, 97.0, 170.8.

5.2.6. Ethyl diazo(triethylsilyl)acetate (18).[20] A stirred solution of ethyl diazoacetate (3.48 g, 30 mmol) and ethyldiisopropylamine (4.1 mL, 30 mmol) diethyl ether (100 mL) was cooled to −78 °C, and triethylsilyl triflate (6.5 mL, 30 mmol) was added dropwise over 20 min. The mixture was stirred at −78 °C for 30 min then allowed to warm to room temperature. After a further 18 h, the white precipitate of ammonium salt was removed by filtration and washed with ether. The combined ether solutions were concentrated in vacuo to afford a yellow oil. Flash chromatography (alumina; Et_2O/hexanes 1:99) afforded **18** as a yellow oil (5.29 g, 77%); δ_H (300 MHz; $CDCl_3$) 0.72 (6H, q, $J=8.8$ Hz, $Si(CH_2CH_3)_3$), 0.93 (9 H, t, $J=8.8$ Hz, $Si(CH_2CH_3)_3$), 1.23 (3H, t, $J=7.1$ Hz, OCH_2CH_3), 4.15 (2H, q, $J=7.1$ Hz, OCH_2CH_3); δ_C (75.4 MHz; $CDCl_3$) 3.5, 6.8, 14.7, 60.9, 96.7, 169.6.

5.2.7. Ethyl 2-*t*-phenyl-3-trimethylsilyl-1,4-oxathiane-3-*r*-carboxylate (19) and ethyl 2-*c*-phenyl-3-trimethylsilyl-1,4-oxathiane-3-*r*-carboxylate (20). To a mixture of 2-phenyl-1,3-oxathiolane (**7**, 0.24 g, 1.4 mmol) and copper(II) acetylacetonate (8 mg, 31 μmol) was added ethyl diazo(trimethylsilyl)acetate (**17**, 0.28 g, 1.5 mmol) as a solution in benzene (2.5 mL). The mixture was heated to reflux for 29 h then cooled and applied directly to a short column of flash silica. Elution with Et_2O/hexanes 30:70 and concentration of the appropriate fractions gave a white solid (0.39 g). Recrystallisation from ethanol afforded **19** as a

white solid (0.21 g, 46%); mp 108–110 °C; δ_H (500 MHz, $CDCl_3$) −0.10 (9H, s, Si(CH_3)$_3$), 1.35 (3H, t, J=7.1 Hz, CH_2CH_3), 2.41 (1H, br d, J=13.3 Hz, SCHH_{eq}), 3.24 (1H, ddd, J=13.4, 11.3, 3.8 Hz, SCHH_{ax}), 3.69 (1H, dt, J=12.0, 3.4 Hz, OCHH_{eq}), 4.12 (1H, td, J=11.8, 2.9 Hz, OCHH_{ax}), 4.26 (dq, J=10.8, 7.1 Hz) and 4.34 (dq, J=10.8, 7, 1 Hz, OCH_2CH_3), 5.53 (1H, s, PhCH), 7.33–7.37 (3H, m) and 8.04–8.05 (2H, m, C_6H_5); δ_C (75.4 MHz, $CDCl_3$) −2.3, 14.3, 25.6, 47.8, 59.9, 61.9, 78.2, 127.8, 128.7, 131.4, 137.3, 172.8; m/z (FAB) 325.1306 (MH^+, $C_{16}H_{25}O_3SSi$ requires 325.1294), 325 (100%), 247 (47), 235 (80), 226 (77), 218 (86).

Flash chromatography of the mother liquors (SiO_2; CH_2Cl_2/hexanes 70:30) afforded **20** as a colourless oil (45 mg, 10%); δ_H (300 MHz, $CDCl_3$) 0.02 (9H, s, Si(CH_3)$_3$), 1.27 (3H, t, J=7.1 Hz, CH_2CH_3), 2.33 (1H, dt, J=13.2, 2.6 Hz, SCHH_{eq}), 3.52 (1H, ddd, J=13.2, 11.6, 3.6 Hz, SCHH_{ax}), 3.94 (1H, td, J=11.7, 2.4 Hz, OCHH_{ax}), 4.23 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.38 (1H, ddd, J=11.7, 3.4, 2.8 Hz, OCHH_{eq}), 4.90 (1H, s, PhCH), 7.28–7.35 (3H, m) and 7.37–7.42 (2H, m, C_6H_5); δ_C (75.4 MHz, $CDCl_3$) −1.8, 14.0, 24.6, 42.3, 60.8, 69.1, 84.0, 128.2, 128.3, 128.4, 140.0, 172.0.

5.2.8. Ring expansion with ethyl diazo(triethylsilyl)-acetate (18): general procedure. A mixture of 1,3-oxathiolane (1.5 mmol) and copper catalyst (0.15 mmol) in benzene (2 mL) was heated to reflux. A solution of **18** (0.41 g, 1.8 mmol) in benzene (1 mL) was added dropwise over 5 min. Reflux was continued for a further 22 h, then the mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash chromatography on Florisil®.

5.2.9. Ethyl 2-*t*-phenyl-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate (21) and ethyl 2-*c*-phenyl-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate (22). The general procedure was carried out with 2-phenyl-1,3-oxathiolane (**7**, 0.25 g, 1.5 mmol), copper(II) acetylacetonate (40 mg, 0.15 mmol) and ethyl (triethylsilyl)diazoacetate (**18**, 0.41 g, 1.8 mmol). Flash chromatography (Florisil®; petroleum ether/diethyl ether 9:1) afforded **21** and **22** as an 8:1 mixture of isomers (0.37 g, 67%); ν_{max} (film)/cm^{-1} 2954, 2877, 1726, 1631, 1193; δ_H (500 MHz, $CDCl_3$; signals quoted for **21** only) 0.47–0.58 (6H, m, Si(CH_2CH_3)$_3$), 0.85 (9H, t, J=7.9 Hz, Si(CH_2CH_3)$_3$), 1.40 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.31 (1H, br d, J=13.4 Hz, SCHH_{eq}), 3.30 (1H, ddd, J=13.3, 12.3, 4.0 Hz, SCHH_{ax}), 3.65 (1H, ddd, J=12.3, 4.0, 2.2 Hz, OCHH_{eq}), 4.10 (1H, td, J=12.2, 2.7 Hz, OCHH_{ax}), 4.31 (1H, dq, J=10.8, 7.2 Hz) and 4.37 (1H, dq, J=10.8, 7.2 Hz, OCH_2CH_3), 5.57 (1H, s, PhCH), 7.37–7.39 (3H, m) and 8.14–8.16 (2H, m, Ar-H); δ_C (75.4 MHz; $CDCl_3$; signals quoted for **21** only) 2.8, 7.5, 14.1, 25.6, 59.1, 61.7, 77.9, 127.6, 128.4, 131.6, 137.3, 172.6 (one signal too weak to be detected); m/z (FAB): 366 (M^+, 92%), 175 (100), 159 (91).

5.2.10. Ethyl 2-(4-nitrophenyl)-3-triethylsilyl-1,4-oxathiane-3-carboxylate. The general procedure was carried out with 2-(4-nitrophenyl)-1,3-oxathiolane (**23**, 0.32 g, 1.5 mmol), copper(II) acetylacetonate (40 mg, 0.15 mmol) and ethyl diazo(triethylsilyl)acetate (**18**) (0.41 g, 1.8 mmol). Flash chromatography (Florisil®; petroleum ether/diethyl ether 4:1) afforded ethyl 2-(4-nitrophenyl)-3-triethylsilyl-1,4-oxathiane-3-carboxylate (0.38 g, 62%) as an 4:1 mixture of isomers. A pure sample of ethyl 2-*t*-(4-nitrophenyl)-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate was obtained as an orange solid by recrystallisation from methanol, mp 62 °C (from MeOH); [Found: C, 55.4, H, 7.1, N, 3.4, S, 8.2. $C_{19}H_{29}NO_5SSi$ requires C, 55.45, H, 7.1, N, 3.4, S, 7.8%]; ν_{max} ($CHCl_3$ cast)/cm^{-1} 2955, 2877, 1725, 1519, 1193, 1016; δ_H (300 MHz; $CDCl_3$) 0.44–0.61 (6H, m, Si(CH_2CH_3)$_3$), 0.87 (9 H, t, J=7.9 Hz, Si(CH_2CH_3)$_3$), 1.40 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.39 (1H, dt, J=13.3, 2.5 Hz, SCHH_{eq}), 3.27 (1H, ddd, J=11.6, 4.0, 1.8 Hz, SCHH_{ax}), 3.69 (1H, ddd, J=12.3, 3.8, 1.0 Hz, OCHH_{eq}), 3.96 (1H, dt, J=11.7, 3.0 Hz, OCHH_{ax}), 4.29–4.40 (2H, m, OCH_2CH_3), 5.64 (1H, s, OCHAr), 8.14–8.37 (4H, m, Ar-H); δ_C (75.4 MHz; $CDCl_3$) 3.1, 7.7, 14.2, 25.6, 48.0, 59.9, 62.1, 122.1, 132.4, 144.6, 147.8, 172.3; m/z (FAB) 411 (M^+, 100%), 280 (74), 175 (55), 159 (61), 154 (76).

5.2.11. Ethyl 2-(4-methoxyphenyl)-3-triethylsilyl-1,4-oxathiane-3-carboxylate. The general procedure was carried out with 2-(4-methoxyphenyl)-1,3-oxathiolane (**24**, 0.30 g, 1.5 mmol), copper(II) acetylacetonate (40 mg, 0.15 mmol) and ethyl diazo(triethylsilyl)acetate (**18**) (0.41 g, 1.8 mmol). Flash chromatography (Florisil®; petroleum ether/diethyl ether 7:3) afforded ethyl 2-*t*-(4-methoxyphenyl)-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate (0.37 g, 62%) as a colourless oil; ν_{max} (film)/cm^{-1} 2953, 2877, 1725, 1511, 1250, 1180; δ_H (300 MHz; $CDCl_3$) 0.48–0.58 (6H, m, Si(CH_2CH_3)$_3$), 0.85 (9 H, t, J=7.9 Hz, Si(CH_2CH_3)$_3$), 1.39 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.28 (1H, br d, J=13.2 Hz, SCHH_{eq}), 3.30 (1H, ddd, J=13.2, 12.5, 4.0 Hz, SCHH_{ax}), 3.62 (1H, ddd, J=12.1, 4.0, 2.0 Hz, OCHH_{eq}), 3.85 (3H, s, OCH_3), 4.08 (1H, td, J=12.1, 2.4 Hz, OCHH_{ax}), 4.32 (1H, q, J=7.2, 1 Hz of OCH_2CH_3), 4.35 (1H, q, J=7.2, 1 Hz of OCH_2CH_3), 5.54 (1H, s, OCH(MeOPh)), 6.89–6.92 (2H, m) and 8.08–8.11 (2H, m, Ar-H); δ_C (75.4 MHz; $CDCl_3$) 2.8, 7.7, 14.3, 25.7, 49.0, 55.2, 58.8, 61.8, 112.9, 129.5, 133.1, 159.7, 172.7; m/z (FAB) 397.1883 (M^+, $C_{20}H_{32}O_4SSi$ requires 397.1869), 397 (15%), 131 (82), 115 (100).

5.2.12. Ethyl 2-*t*-(2-methylpropyl)-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate. A solution of 2-(2-methylpropyl)-1,3-oxathiolane (**10**, 0.22 g, 1.5 mmol), tetrakis-(acetonitrile)copper(I) hexafluorophosphate (50 mg, 0.15 mmol) and ethyl diazo(triethylsilyl)acetate (**18**, 0.34 g, 1.5 mmol) in 3 mL dry benzene was heated to reflux for 2.5 h under nitrogen atmosphere. The solvent was removed under reduced pressure and the residue purified by flash chromatography on Florisil® (petroleum ether/diethyl ether 9:1) to afford ethyl 2-*t*-(2-methylpropyl)-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate (0.16 g, 30%) as a colourless oil; δ_H (500 MHz; $CDCl_3$) 0.71 (6H, m, Si(CH_2CH_3)$_3$), 0.95 (3H, s) and 1.00 (3H, s, CH(CH_3)$_2$), 0.98 (9H, t, J=7.2 Hz, Si(CH_2CH_3)$_3$), 1.07 (1H, ddd, J=14.5, 10.6, 2.9, 1 Hz of CH_2(CHMe$_2$)), 1.32 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.75 (1H, m, CHMe$_2$), 2.06 (1H, ddd, J=13.2, 2.8, 1.9 Hz, SCHH_{eq}), 2.73 (1H, ddd, J=14.4, 12.2, 3.2, 1 Hz of CH_2(CHMe$_2$)), 3.17 (1H, ddd, J=13.2, 12.3, 4.0 Hz, SCHH_{ax}), 3.65 (1H, ddd, J=12.1, 4.1, 1.9 Hz, OCHH_{eq}), 3.94 (1H, dt, J=12.2, 2.7 Hz, OCHH_{ax}), 4.22

(1H, dq) and 4.30 (1H, dq, $J=12.2$, 2.7 Hz, OCH_2CH$_3$), 4.54 (1H, ddd, $J=12.2$, 2.9, 1.2 Hz, OCH(^{i}Pr)); δ_C (75.4 MHz; $CDCl_3$) 3.0, 7.8, 14.3, 21.3, 24.1, 25.5, 30.8, 38.1, 49.9, 59.1, 61.4, 74.1, 172.6; *m/z* (FAB): 346 (M^+, 42%), 317 (48), 289 (75), 215 (100), 175 (63), 159 (99).

5.2.13. Ethyl 2-*t*-*tert*-butyl-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate. A solution of 2-*tert*-butyl-1,3-oxathiolane (**25**, 0.22 g, 1.5 mmol), tetrakis(acetonitrile)copper(I) hexafluorophosphate (50 mg, 0.15 mmol) and ethyl diazo(triethylsilyl)acetate (**18**, 0.34 g, 1.5 mmol) in 3 mL dry benzene was heated to reflux for 4 h under nitrogen atmosphere. The solvent was removed under reduced pressure and the residue purified by flash chromatography on Florisil® (petroleum ether/diethyl ether 9:1) to afford ethyl 2-*t*-*tert*-butyl-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate (0.06 g, 12%) as a colourless oil; [Found: C, 59.2; H, 9.8; S, 9.0. $C_{17}H_{34}O_3SSi$ requires C, 58.9; H, 9.9; S, 9.25%]; ν_{max} (film)/cm^{-1} 2955, 1732, 1102; δ_H (300 MHz; $CDCl_3$) 0.97 (9H, s, C(CH_3)$_3$), 1.03–1.06 (15H, m, Si(CH_2-CH_3)$_3$), 1.29 (3H, t, $J=7.2$ Hz, OCH$_2$CH_3), 2.68 (1H, ddd, $J=13.7$, 5.7, 5.4 Hz, SCHH_{eq}), 3.04 (1H, ddd, $J=13.7$, 7.8, 5.1 Hz, SCHH_{ax}), 3.95 (1H, dt, $J=10.5$, 5.1 Hz, OCHH_{eq}), 4.09 (1H, s, OCH^{t}Bu), 4.11–4.20 (3H, m, OCHH_{ax} and OCH_2CH$_3$); δ_C (75.4 MHz; $CDCl_3$) 6.4, 9.0, 13.9, 23.8, 27.9, 37.4, 61.4, 68.7, 87.2; *m/z* (FAB) 346 (M^+, 8%), 317 (30), 289 (75), 215 (24), 175 (30), 159 (38), 131 (90), 115 (100).

5.2.14. Ethyl 3-triethylsilyl-1,4-oxathiane-3-carboxylate. A solution of 1,3-oxathiolane (**26**, 0.14 g, 1.5 mmol), tetrakis(acetonitrile)copper(I) hexafluorophosphate (50 mg, 0.15 mmol) and ethyl diazo(triethylsilyl)acetate (**28**, 0.34 g, 1.5 mmol) in 3 mL dry benzene was heated to reflux for 2.5 h under nitrogen atmosphere. The solvent was removed under reduced pressure to give ca. 0.1 g of a light yellow oil. Attempted purification by flash chromatography on Florisil® led to decomposition of the product. Data for crude ethyl 3-triethylsilyl-1,4-oxathiane-3-carboxylate. δ_H (300 MHz; $CDCl_3$) 0.62 (6H, q, $J=7.6$ Hz, Si(CH_2CH$_3$)$_3$), 0.90 (9H, t, $J=7.6$ Hz, Si(CH$_2$CH_3)$_3$), 1.22 (3H, t, $J=7.2$ Hz, OCH$_2$CH_3), 3.0 (1H, ddd, $J=11.0$, 10.0, 7.6 Hz, SCHH_{eq}), 3.29 (1H, ddd, $J=11.0$, 6.2, 1.4 Hz, SCHH_{ax}), 4.02 (2H, q, $J=7.2$ Hz, OCH_2CH$_3$), 4.39 (1H, ddd, $J=1.4$, 7.6, 10.5 Hz, OCHH_{eq}), 4.70 (1H, d, $J=5.7$, 1 Hz of OCH_2C(CO$_2$Et)(SiEt$_3$)), 4.85 (1H, dt, $J=10.0$, 6.2 Hz, OCHH_{ax}), 4.91 (1H, d, $J=5.7$, 1 Hz of OCH_2C(CO$_2$-Et)(SiEt$_3$)), contaminated with triethylsilyl residue at 0.52 (q, $J=8.1$ Hz, Si(CH_2CH$_3$)$_3$) and 0.93 (t, $J=8.1$ Hz, Si(CH$_2$CH_3)$_3$).

5.2.15. Desilylation of ring-expanded products: ethyl *trans*-2-phenyl-1,4-oxathiane-3-carboxylate (8) and ethyl *cis*-2-phenyl-1,4-oxathiane-3-carboxylate (9). A solution of ethyl 2-*t*-phenyl-3-triethylsilyl-1,4-oxathiane-3-*r*-carboxylate (**21**, 0.35 g, 0.95 mmol) in tetrahydrofuran (5 mL) was cooled to 0 °C and treated with tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 1.23 mL). After 30 min the reaction mixture was poured into ice/water overlaid with 5 mL diethyl ether. The aqueous layer was extracted with 3×5 mL diethyl ether. The combined extracts were dried using magnesium sulfate, and the solvent was evaporated under reduced pressure, affording **8** and **9** as a 2:1 mixture of isomers (0.24 g, quantitative). Recrystallisation from methanol afforded pure **8** as a white solid; ν_{max} ($CHCl_3$ cast)/cm^{-1} 3435, 1728, 1307, 1159; δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, $J=7.6$ Hz, OCH$_2$CH_3), 2.46 (1H, dt, $J=13.8$, 2.4 Hz, SCHH_{eq}), 3.07 (1H, ddd, $J=13.8$, 11.9, 3.3 Hz, SCHH_{ax}), 3.75 (1H, d, $J=9.5$ Hz, SCHCO$_2$Et), 3.85 (2H, q, $J=7.2$ Hz, OCH_2CH$_3$), 3.87–3.97 (1H, m, OCHH_{ax}), 4.30 (1H, ddd, $J=11.9$, 3.3, 2.4 Hz, OCHH_{eq}), 4.65 (1H, d, $J=9.5$ Hz, OCHPh), 7.23–7.27 (5H, m, Ar-H); δ_C (75.4 MHz; $CDCl_3$) 13.7, 27.1, 48.6, 61.2, 69.2, 82.3, 125.4, 127.0, 128.3, 139.0, 168.9.

Compound **9** (*colourless oil*). δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, $J=7.6$ Hz, OCH$_2$CH_3), 2.17 (1H, br d, $J=13.8$, 1 Hz of SCH_2), 3.29 (1H, d, $J=2.9$ Hz, SCH(CO$_2$Et)), 3.58 (1H, ddd, $J=11.9$, 3.8, 3.3, 1 Hz of SCH_2), 3.85 (2H, q, $J=7.2$ Hz, OCH_2CH$_3$), 3.87–3.97 (1H, m, 1 of OCH_2), 4.47 (1H, dt, $J=11.9$, 2.4, 1 Hz of OCH_2), 4.88 (1H, d, $J=2.9$ Hz, OCHPh), 7.23–7.27 (5H, m, Ar-H); δ_C (75.4 MHz; $CDCl_3$) 13.7, 23.1, 42.1, 60.5, 69.6, 79.4, 127.7, 128.2, 128.6, 139.6, 170.0.

5.2.16. One-pot ring-expansion/desilylation: ethyl *trans*-2-phenyl-1,4-oxathiane-3-carboxylate (8) and ethyl *cis*-2-phenyl-1,4-oxathiane-3-carboxylate (9). 2-Phenyl-1,3-oxathiolane (**7**) (0.25 g, 1.5 mmol) was subjected to ring expansion with **18** (0.58 g, 2.5 mmol) under the conditions outlined above. After 24 h, the reaction was cooled to 0 °C, and tetra-*n*-butylammonium fluoride (1 M in THF, 2.0 mL, 2.0 mmol) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h then poured into an ice/water mixture (5 mL) overlaid with diethyl ether (5 mL). The aqueous phase was extracted with diethyl ether (4×5 mL), then the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2; petroleum ether/diethyl ether 8:2) afforded **8** and **9** as a 2:1 mixture of isomers (0.33 g, 87%).

References and notes

1. For reviews, see (a) Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds; Wiley: New York, 1998. (b) *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002.
2. For an asymmetric version, see: Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H.; Fieldhouse, R. *J. Am. Chem. Soc.* **1998**, *120*, 8328–8339 and references cited therein.
3. (a) Mitchell, R. E.; Durbin, R. D. *Physiol. Plant Pathol.* **1981**, *18*, 157–168. (b) Mitchell, R. E.; Coddington, J. M.; Young, H. *Tetrahedron Lett.* **1989**, *30*, 501–504.
4. Preliminary communication: Ioannou, M.; Porter, M. J.; Saez, F. *Chem. Commun.* **2002**, 346–347.
5. Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917–1925.
6. Kametani, T.; Kawamura, K.; Honda, T. *J. Am. Chem. Soc.* **1987**, *109*, 3010–3017. For an intramolecular variant, see: Kim, G. C.; Kang, S. W.; Kim, S. N. *Tetrahedron Lett.* **1993**, *34*, 7627–7628.

7. Aggarwal, V. K.; Ferrara, M.; Hainz, R.; Spey, S. E. *Tetrahedron Lett.* **1999**, *40*, 8923–8927.
8. Carter, D. S.; Van Vranken, D. L. *Tetrahedron Lett.* **1999**, *40*, 1617–1620.
9. Similar results were obtained using 2 mol% $Rh_2(OAc)_4$.
10. Schöllkopf, U.; Rieber, N. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 884.
11. (a) Maas, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993**, *49*, 881–888. (b) Maas, G.; Alt, M.; Mayer, D.; Bergsträsser, U.; Sklenak, S.; Xavier, P.; Apeloig, Y. *Organometallics* **2001**, *20*, 4607–4615. (c) Braddock, D. C.; Badine, D. M.; Gottschalk, T.; Matsuno, A. *Synlett* **2003**, 345–348.
12. (a) Maier, G.; Volz, D.; Neudert, J. *Synthesis* **1992**, 561–564. (b) Arrowood, T. L.; Kass, S. R. *Tetrahedron* **1999**, *55*, 6739–6748.
13. (a) Alt, M.; Maas, G. *Chem. Ber.* **1994**, *127*, 1537–1542. (b) Alt, M.; Maas, G. *Tetrahedron* **1994**, *50*, 7435–7444. (c) Bolm, C.; Saladin, S.; Kasyan, A. *Org. Lett.* **2002**, *4*, 4631–4633.
14. Ducept, P. C.; Marsden, S. P. *Synlett* **2000**, 692–694.
15. Bolm, C.; Kasyan, A.; Drauz, K.; Günther, K.; Raabe, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2288–2290.
16. Bolm, C.; Kasyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Günther, K.; Wagner, C. *Org. Lett.* **2002**, *4*, 2265–2267.
17. (a) Kablean, S. N.; Marsden, S. P.; Craig, A. M. *Tetrahedron Lett.* **1998**, *39*, 5109–5112. (b) Marsden, S. P.; Pang, W.-K. *Tetrahedron Lett.* **1998**, *39*, 6077–6080. (c) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765–768. (d) Müller, P.; Lacrampe, F.; Bernardinelli, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1503–1510.
18. Maas, G.; Krebs, F.; Werle, T.; Gettwert, V.; Striegler, R. *Eur. J. Org. Chem.* **1999**, 1939–1946.
19. Gettwert, V.; Krebs, F.; Maas, G. *Eur. J. Org. Chem.* **1999**, 1213–1221.
20. (a) Emde, H.; Simchen, G. *Liebigs Ann. Chem.* **1983**, 816–834. (b) Allspach, T.; Gümbel, H.; Regitz, M. *J. Organomet. Chem.* **1985**, *290*, 33–39.
21. Doyle, M. P.; Peterson, C. S.; Parker, D. L. Jr. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1334–1336.
22. Fluoride sources employed were ammonium fluoride, potassium fluoride/tetra-*n*-butylammonium chloride and TAS-F (tris(dimethylamino)sulfonium difluorotrimethylsilicate).
23. Paraformaldehyde was used in the case of 1,3-oxathiolane **26**: Gokel, G. W.; Gerdes, H. M.; Dishong, D. M. *J. Org. Chem.* **1980**, *45*, 3634–3639.
24. Kipnis, F.; Ornfelt, J. *J. Am. Chem. Soc.* **1949**, *71*, 3555.
25. Karimi, B.; Seradj, H. *Synlett* **2000**, 805–806.

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Investigations into the utility of high-surface area silica pellets as potential solid-phase synthesis supports

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Abstract—Grace-Davidson silica pellets (SMR-057-015) are found to be optimal for surface grafting of $(RO)_3Si(CH_2)_3FG$ reagents. While loadings of up to 2.1 mmol g^{-1} can be attained (ca. 0.05 mmol per pellet) access of further reagents to the graft sites is problematic above loadings of 0.8 mmol g^{-1}. ^{13}C CPMAS NMR studies may be carried out on individual pellets (using natural abundance substrates) and the resulting spectra are diagnostic in identifying successful subsequent coupling reactions.
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1. Introduction

Combinatorial chemistry has heralded a near exponential growth in interest in applications of Solid-Phase Organic Synthesis (SPOS) in the last decade.[1] While considerable innovation has been achieved, the majority of this chemistry is still carried out on organic supports, mainly cross-linked polystyrene (and related species).[2] Approaches using alternative supports (especially silica and alumina, Fig. 1) have been investigated much less frequently, and often only in specialist areas. For example, silica powders serve as the basis for several commercial solid-phase scavenger reagents especially morpholine and related amines.[3] Use of these and related reagents is well documented.[4] A further significant number of reports deal with the attachment of metal complexes or organo-functions to silica surfaces to yield heterogeneous catalysts and sensors.[5] Finally, a few publications detail actual multi-step syntheses carried out on silica, notably Sucholeiki's Claisen rearrangement chemistry.[6] All of these investigations have used powdered supports. The powdered nature of such materials can make them difficult to handle, especially when drying under vacuum due to 'bumping'. Attempts have been made to overcome these problems through the use of glass beads, and related technologies,[7] but these have the limitation that only low levels (in mmol g^{-1}) of functionalisation have been attained. We believed that the alternative use of fused silica and alumina pellets or spheres, commonly used to prepare heterogeneous catalysts through salt impregnation, might offer advantages in chemistry leading to supported synthesis of ligands and catalyst discovery. The lack of literature precedent led us to make a full investigation of the scope and limitations of such approaches using simple model systems and these are reported here.

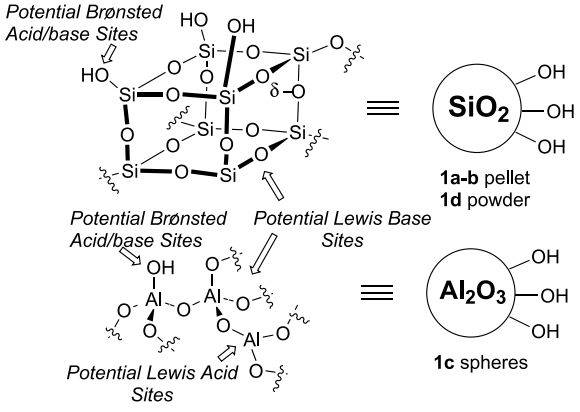

Figure 1. Schematic representation of silica and alumina surfaces.

Fused silica and alumina materials had not been used previously for supported reagents at the start of our studies. As their surfaces are not as innocent as those of polystyrene (and related) resins we were anxious to find out if the presence of residual Brønsted and Lewis acid/bases sites (Fig. 1) would affect the utility of these materials.

Keywords: Supported reagents; Silica; Coupling reactions.
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Table 1. Functionalisation of various inorganic supports **1**[a]

Inorganic support	Silane **2**, Y group	Loading[b]/mmol g^{-1}
High surface area silica extrudate [Grace-Davidson: SMR-057-015] **1a**	**2a**, NH_2	1.83
High surface area silica extrudate [Grace-Davidson: SMR-057-015] **1a**	**2c**, Cl	1.71
Low surface area silica extrudate [Criterion Catalysts: KL7200CY] **1b**	**2a**, NH_2	0.63
Low surface area silica extrudate [Criterion Catalysts: KL7200CY] **1b**	**2b**, NEt_2	0.44
High surface area alumina spheres [Rhodia (Axens): SPH501a] **1c**	**2a**, NH_2	1.18
High surface area alumina spheres [Rhodia (Axens): SPH501a] **1c**	**2c**, Cl	1.03
Chromatographic silica powder [Fluorochem 35-70u, 60A) **1d**	**2a**, NH_2	1.06

[a] Reaction on 1.00 g of support with 22–93 mmol of silane, 1.35–1.42 M silane in toluene, reflux 3 h.
[b] Mass change per gram assumed due to gain of $Si(CH_2)_3Y$ from **2** and loss of 3H from **1** normalized per gram of final product.

Additional questions to be answered were: (i) are sufficient reactive sites available to allow the synthetically useful loadings to be attained? (ii) would diffusion problems (of reagents into, or out of, the support) be encountered? and (iii) can the synthesis be monitored by standard diagnostic methods? Elements of our data have been the subject of a preliminary communication[8] in an area in which other groups have also been attracted to recently.[9]

2. Functionalisation of inorganic supports

To identify an optimal support, initial trials were made. Several different types of silica extrudate **1a–b** and alumina spheres **1c** were obtained from commercial suppliers [Criterion Catalysts, Grace-Davidson and Rhodia (Axens) all via Johnson-Matthey Ltd] and these were screened for grafting ability by reaction with $(RO)_3Si(CH_2)_3Y$ reagents (R=Et, Y=NH_2 **2a**, NEt_2 **2b**; R=Me, Y=Cl, **2c**) under standard conditions (reflux in toluene in the presence of excess silane[8]). A chromatographic grade silica powder **1d** was also reacted, under identical conditions, to allow direct comparison with known approaches. In all cases, derived loadings were calculated gravimetrically assuming the weight gain per gram of support was due to the attachment of $Si(CH_2)_3Y$ group and loss of 3H (Table 1).

The superiority of the Grace-Davidson high surface area silica extrudate SMR-057-015 (pellets approximately 6 mm long by 4 mm in diameter) was very clear from these preliminary runs. Low surface area extrudate performed worse than a typical silica powder while alumina spheres were only a little better. Both the latter support types were also rather fragile and easily damaged by mechanical stirring during functionalisation. Investigations on the optimal SMR-057-015 pellets revealed that the degree of grafting was essentially independent of the amount $(EtO)_3Si(CH_2)_2NH_2$ **2a** used at ratios above 20 mmol **2a**/g of pellets used. Commonly, before reaction with silanes, silica powders are activated by either heating or treatment with acids prior to heating.[10] In our case, heating (ca. 130 °C, 0.5 mmHg, 16–24 h) SMR-057-015 had little effect on the loading realised. However, 6 M $HCl_{aq.}$ acid treatment increased the apparent loading up to 2.15 provided excess **2a** and long reaction times were employed.[8] Even when low amounts of **2a** (1.2 mmol g^{-1}) were used, significant loadings of the Grace-Davidson pellets could be realised ($\sim$0.6 mmol g^{-1}, see Section 7). The Grace-Davidson SMR-057-015 material is reported as having a total pore volume of 1.39 mL g^{-1} with a distribution (based on mercury intrusion studies) favoring macropores in the 10–20 nm diameter range.[11] Because of the apparent superiority of this material in the initial grafting studies, further characterisation by BET (Brunauer–Emmett–Teller) isotherms were carried out both on the initial **1a** and with the pellets (**3a**) attained after treatment with $(EtO)_3Si(CH_2)_3NH_2$ **2a**. Typical data are compared in Table 2.

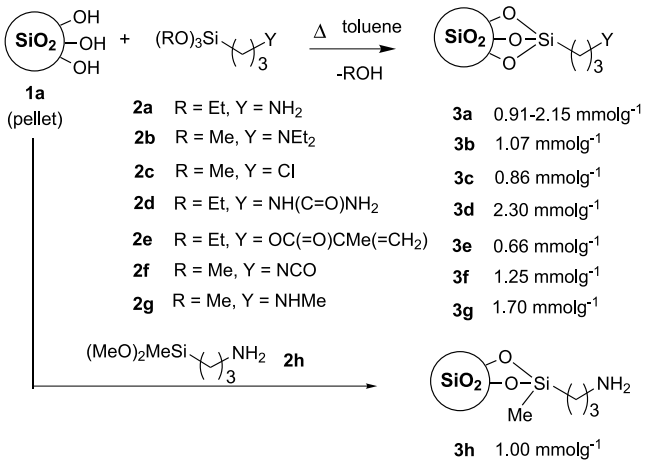
Table 2. Surface area and pore distribution data

Technique	Pellet **1a** (prior to grafting)	Pellet **3a** (grafted)[a]
BET surface area/m^2 g^{-1}	295	220
Langmuir surface area/m^2 g^{-1}	280	181
BJH pore distribution/mL g^{-1} (%)		
Under 10 nm	0.11 (9%)	0.10 (12%)
10–20 nm	0.22 (18%)	0.18 (22%)
20–80 nm	0.88 (70%)	0.48 (58%)
Over 80 nm	0.04 (3%)	0.07 (8%)
Total pore volume/mL g^{-1}	1.25	0.83
Hg intrusion pore distribution[b]/mL g^{-1} (%):		[c]
10–25 nm	1.00 (72%)	
25–50 nm	0.38 (27%)	
50–150 nm	0.10 (1%)	
Total pore volume/mL g^{-1}	1.39	

[a] After pre-treatment with 6 M HCl and reaction with $(EtO)_3Si(CH_2)_3NH_2$ **2a**; gravimetric loading 2.15 mmol g^{-1}.
[b] Literature data (Ref. 11).
[c] Data not available. BJH=Barret–Joyner–Halenda isotherm.

Unfunctionalised pellets **1a** typically displayed a BET surface area of ca. 295 m^2 g^{-1} but occasional batches with lower surface areas (down to 245 m^2 g^{-1}) were encountered. Clearly mesopores predominate in **1a** with the majority being 20–80 nm in diameter. These pores are of appropriate dimensions to accommodate $Si(CH_2)_3NH_2$ fragments whose molecular dimensions are of the order of 0.47×0.31 nm (based on molecular modeling studies[12]). Comparison of the BJH pore distribution data for **1a** and **3a** indicates: firstly, that it is the 20–80 nm pores that are the most functionalised (the distribution shifts to lower pore volumes upon reaction); and secondly, that HCl activation may operate by increasing the number of macropores (diameter above ca. 100 nm) in these pellet materials. Depending on the quality of the pellets **1a** used in the preparation of **3a** the pore distribution could be degraded. For example, when reduced surface area pellets (**1a**, 245 m^2 g^{-1}) were used, the fraction of 20–80 nm pores fell to 40% while those in the range up to 20 nm rose to 57%. Acid treated samples showed a slight rise (1–2%) in the number of large pores (>80 nm). Acid-treated pellets and samples with higher distributions of smaller pore sizes were found to be less effective in subsequent coupling reactions (see later).

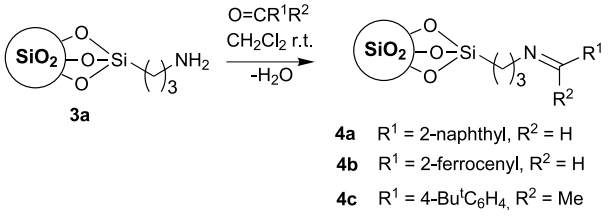
To test the generality of the apparent ease of silane binding to **1a** a range of derivatives was prepared by reaction with commercially available silanes $(RO)_3Si(CH_2)_3Y$ and in one case $(MeO)_2Si(Me)(CH_2)_3NH_2$ in refluxing toluene. Specific conditions for the couplings have already been reported in a preliminary communication,[8] so only the gravimetrically derived final loadings are given in Scheme 1. Typically, these functionalised materials displayed BET surface areas in the range 175–280 $m^2\ g^{-1}$ regardless of the anchor function in **3** (e.g. **3e** 225; **3 g** 174; **3 h** 242; 175–280 range over all pellets screened $m^2\ g^{-1}$).



Scheme 1. Silane grafted pellet materials based on SMR-057-015.

3. Pellet loading and characterisation studies

The loadings attained in the silane grafting studies (Scheme 1) are considerably higher that have been attained with many other non-powder inorganic supports. For example, glass beads have been used in combinatorial studies but here loadings of ~0.1 mmol g^{-1} are typical.[7] Because the data in Scheme 2 were determined gravimetrically there was a worry that the apparent high loadings may be in fact just due to physisorbed materials (unreacted starting materials, solvents or byproducts) and have little to do with the actual formation of **3**. To confirm the loadings of **3a** derived from weight gain studies we sought a simple titration approach through protonation of the amine function and back titration of the remaining free acid with NaOH. As silica is susceptible to dissolution under alkali conditions we selected bromocresol purple (pH change at 5.2–6.8) as a suitable indicator. Pelleted **3a** titrated thus gave amine loadings consistently 10–15% lower than those derived gravimetrically. We suspected that these reduced values were indicative of reduced accessibility of amines present in the smaller and more inaccessible pores. Grinding **3a** to a powder prior to assay increased the measured loading to the gravimetric value consistent with this idea. In these cases the ground silica had to be removed by filtration prior to titration to avoid erroneous results through alkali silica dissolution. The extent of pellet loading in **3a** (0.63–2.15) could be also be controlled by limiting the number of equivalents of **2a** (1.2 to 40 equiv) used in the preparation.



Scheme 2. Imine formation studies on amino pellets **2a**.

To confirm that the weight gains in the pellets **1a** after reaction with $(RO)_3Si(CH_3)_2Y$ **2** reagents were not due to simple physio adsorption of ROH by-products or toluene solvent TGA-MA (thermogravimetric analysis—mass analysis) studies were carried out on **3a** and **3c**. Pellets were heated from ambient temperature to 960 °C (at 10 °C min^{-1}) and the off-gas composition monitored by mass spectrometry in the range *m/z* 2–97 amu. Pellet **3a** (R=OEt; Y=NH_2) lost 2% of its initial weight below around 100 °C and a further 7% by the end of heating. No evidence of appreciable toluene or ethanol production was present in the MS data. Most material was cleaved in the region 490–560 °C. Pellet **3c** (R=OMe; Y=Cl) lost 7% of its weight on heating, the majority being lost at 350–500 °C. No evidence of thermal expulsion of methanol or toluene was observed. Tentative assignments for the major fragment losses are given in Figure 2. Control experiments in which pellets **1a** were placed in toluene or alcohols and then dried led to no weight gains or losses.

	From 3a		From 3c	
Temp/°C	*m/z*	Fragment	*m/z*	Fragment
up to 500			50/52	$Me^{35/37}Cl$
500	16	MeH		
550	26	HC≡CH		
	42	$^+CH_2CH{=}NH$		
600	56	$^+(CH_2)_3NH_2$	26	HC≡CH
650			64/66	$MeCH_2{}^{35/37}Cl$

Figure 2. Major fragments detected in TGA-MA analysis of pellets **3a** and **3c**.

Further confirmation that materials **3** have been correctly formulated is supplied by ^{13}C cross polarisation magic angle spinning (CPMAS) NMR spectroscopy. The data collected from the pellets in this study are summarised in Table 3. Appreciable background signals are always present in the spectra of polystyrene supported reagents, due to the resin itself.[13] However, only one very broad residual signal was encountered in the carbon spectra of **3** at $\delta_C \sim 175$. We believe this to be due to the residue from the organic formerly used in the sol-gel process to prepare **1a**. The presence of only this minimal background allowed ^{13}C data to be attained in 5–20 h on single pellets. In general aliphatic carbons gave sharp, well resolved, signals. A typical example is given in Figure 3. Poorer dispersion was obtained for the aromatic carbons due in part to spinning sidebands observed as expected at multiples of 53.0 ppm away from the isotropic peak at the MAS rate of 4 kHz used.[14] In some of our samples intrinsically weak signals

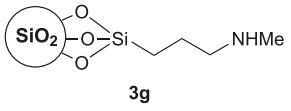
Table 3. Carbon-13 CPMAS NMR data (75.47 MHz, MAS rate 4 kHz) of various pellets **3–11**

Pellet	δ $SiCH_2$	δ CH_2cen.	δ YCH_2	δ Other Signals
3a	9.5	27.0	44.2	16.7, 58.0 (OEt)[a]
3b	11.2[b]	21.8	47.2[b]	54.1, 56.9 (OEt)[a]
3c	8.7	25.9	45.9	—
3d	10.3	24.0	43.0	161.4 (C═O)
3e	16.3	21.6	49.1	6.5 (Me), 124.1, 137.2 (C═C), 168.4 (C═O)[c]
3f	8.2	22.8	42.4	16.6, 58.2 (OEt)[d], 160.3 (C═O)
3g	10.1	23.0	34.4	54.9 (NMe)
3h	13.5	26.7	44.6	−3.2 (SiMe)
4a	10.9	20.0	24.8	127.7, 133.8 (Ar)[e], 186.8 (C═NR)
4b	—[f]	—	—	69.4br (Cp)
4c	9.7	22.8	40.9	9.7 (Bu^i), 124.8, 124.9 (Ar)[e], 174.5 (C═N); 16.7 56.6 (OEt)[g]
5	10.3	20.0	38.9	32.5 (CH_2CO), 53.2sh (CH_2O), 174.4 (C═O)[h]
6	9.4	23.4	—[i]	33.6, 43.7, 53.8 (NMe)
8	9.2	21.0, 24.8[j]	35.7, 42.3[j]	116.4, 124.9, 127.8, 143.5 (Ar^e), 162.0[j], 169.3[j] (C═O)
9	8.1	21.9br	44.3br	115.5, 125.9, 128.5, 158.1, (Ar^e), 161.8[j], 167.9[j], 169.9[j] (C═O)
11c	10.4	23.1	46.5	126.1 br (Ar^e), 179.4 (C═S)[e]
11d	9.9	19.7	34.4	53.5 (NMe), 126.4 br (Ar^e), 174.5 (C═S)[e]

[a] Due to residual SiOEt, only observed at partial conversion to **3**.
[b] SilylCH_2 overlapped by $MeCH_2N$; YCH_2 signal overlapped by $N(CH_2Me)_2$.
[c] A signal at 66.1 could not be assigned.
[d] Major product at extended reaction is $Y=NHCO_2Et$.
[e] The major aromatic signals (and carbonyls were indicated) show strong sidebands at ±53.0 ppm.
[f] The $(CH_2)_3$ tether showed only a broad signal at 21 ppm, imine signal not observed.
[g] Impurity derived from $HC(OEt)_3$.
[h] A signal at 17.1 could not be assigned.
[i] Overlapped by NMe signal.
[j] Ascribed to surface conformers or partial conversion (see text).

(C═O, C═S, and C═N) could not be detected within acceptable accumulation times (5–20 h).

The spectra confirmed the formation of single silica bound



3g

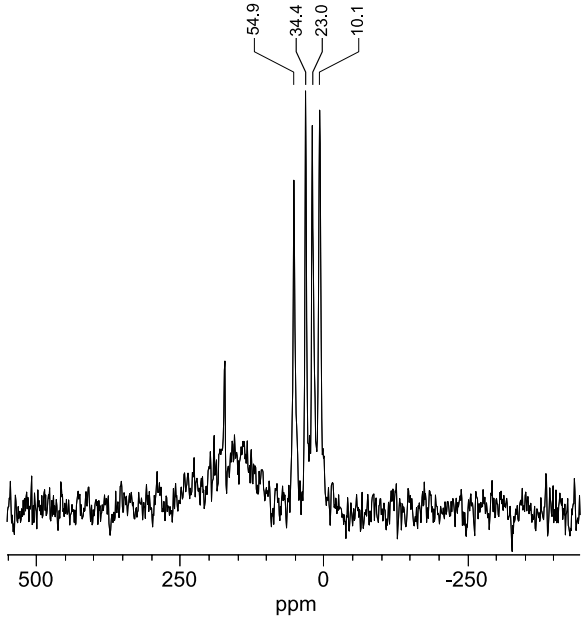


Figure 3. Typical solid-state ^{13}C CPMAS NMR spectra (75.47 MHz, MAS rate 4 kHz) of functionalised pellet **3g** (Y═NHMe). The sharp spike and associated very broad resonance at ca. 175 ppm are inate features of the silica pellets **1a** as supplied.

entities for the most of the materials screened. For **3a** occasional samples showed two extra peaks at 16.7 and 58.0 ppm which disappeared on extended reaction or storage of the pellets. These are assigned to residual Si-OEt in partially reacted **2a**. Similar features were encountered in the spectra of **3b** although in this case two residual OCH_2 signal were apparent. Nominal **3f** (Y═NCO) showed extra signals at 16.6 and 58.2 ppm revealing that long reaction times lead to smooth conversion to the alcoholysis product of **2f**, i.e. $Si(CH_2)_3NHCO_2Et$.

4. Coupling studies

As no organic syntheses on pelleted silica materials had been reported initial coupling studies concentrated on simple imine formation (Scheme 2). Representative results are given in Table 4. In general, the coupling efficiencies of **3a** having apparently high amine loadings (>1.0 mmol g^{-1}) were not good even when large excesses of aldehyde were used (compare runs 1 and 2 leading to **4a**). This situation was made worse if the pellets leading to **3a** had been acid pre-treated. Loadings of 0.6–0.8 mmol g^{-1} NH_2 led to the best, but not quantitative, yields. We speculate that **2a** having the highest loadings (>1.0 mmol g^{-1}) has a significant fraction of its amine groups in small pores that are not available for reaction through blocking of the pellet capillaries through over functionalisation with $(EtO)_3$-$Si(CH_2)NH_2$ **2a**. The ^{13}C CPMAS NMR spectra of poorly coupled **4a** are identical to those of high coupling efficiency indicating that formation of alternative products is not the cause of the poor performance. Acid pre-treatment also appears to promote small capillary blocking as very poor coupling efficiencies were always noted in reactions of **2a** prepared from acid-washed pellets. Ferrocene derivative **4b** was used to probe this idea. The ^{13}C CPMAS NMR spectra

Table 4. Imine preparations using pellet **2a**[a]

2a Loading/mmol g^{-1}	Conditions	**4** Loading[b]/mmol g^{-1}	Eff.[b]/%
1.48[c]	12.5 equiv $C_{10}H_8CHO$, 0.9 M, 28 h, rt	**4a** 0.63	42
0.63	3.1 equiv $C_{10}H_8CHO$, 0.1 M, 4 h, rt	**4a** 0.57	90
0.63	3.1 equiv $C_{10}H_8CHO$, 0.1 M, 1 h, rt	**4a** 0.50	79
1.05	3.1 equiv $C_{10}H_8CHO$, 0.07 M, 2 h, rt	**4a** 0.47	45
1.05	0.63 equiv $C_{10}H_8CHO$, 0.1 M, 1 h, rt	**4a** 0.25	38
2.02[c]	3.2 equiv FcCHO, 0.15 M, 16 h, rt	**4b** 0.45	22
0.63	3.2 equiv FcCHO, 0.02 M, 16 h, rt	**4b** 0.56	89
1.35	0.64 equiv 4-$Bu^tC_6H_4C(O)Me$ and $HC(OEt)_3$, 0.08 M, 1 h, rt	**4b** 1.08[d]	~60[d]

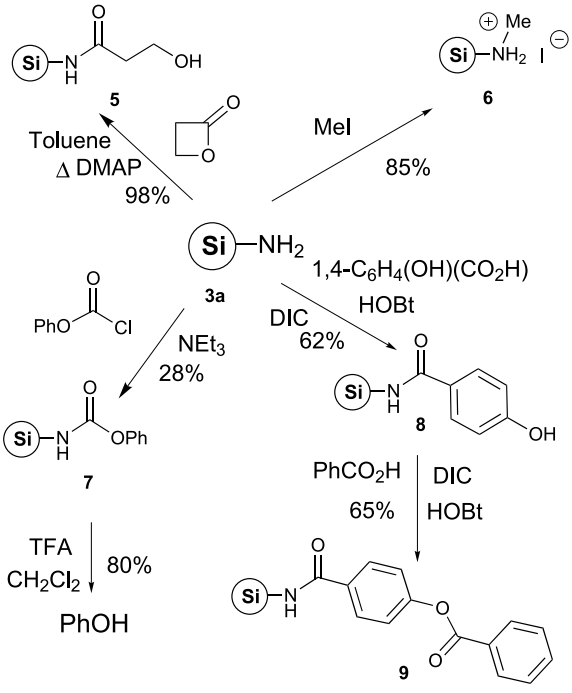
[a] In dry dichloromethane under argon.
[b] Loading based on weight gain. Eff. is coupling efficiency equivalent to chemical yield.
[c] Prepared from acid pre-treated **1a**.
[d] Contains orthoformate derived by-product, see text. Coupling yield based on NMR ratios.

of derived **4b** was uninformative, being rather broad, but it did confirm the presence of Cp-derived units. (There are suggestions that supported ferrocenes give inferior spectra from the limited polystyrene literature available.[15]). To probe if acid induced modification of the pellets does take place at the pellet surface, or throughout the sample, a pellet of **4b** (derived from acid treated **1a**) was cleaved across its diameter and subjected to EDX-backscatter techniques under electron microscopy. The pellet was imaged in 250×180 μm segments across its diameter. Functionalised silane linkers were detected at an equivalent %Fe density throughout the pellet indicating that homogeneous solutions do penetrate the core of the pellet. Within each segment small clusters (within 10^2 μm) of high iron concentration could be found in addition to an essentially random single Fe background sites across the segment. We interpret these as indicative of clusters of **4b** at pore defects that may block access to smaller capillaries and pores reducing coupling efficiency.

Support for these ideas comes from reactions of **4a** (ex **3a**, 1.05 mmol g^{-1}) with a second addition of 2-naphthaldehyde. Poor coupling yields are still realised as might be expected if some pores are inaccessible even under mild conditions. Formation of **4c** required the addition of a dehydrating agent [$HC(OEt)_3$] and the loading attained exceeds that expected from the reaction stoichiometry based on the weight of pellet **4c** recovered. However, the ^{13}C CPMAS NMR spectrum of this material shows ca. 40% of **3a** remains. The expected signals for **4c** are present except for the acyl methyl and CMe_3 resonance. In the starting ketone these signals resonate at 31.2 and 35.2 ppm and it is possible that they are coincident with the broad CH_2N imine signal observed at δ_C 40.9. Additionally, an OEt derived signal is present at 16.7 and 56.6 ppm. This is assigned to chemisorbed orthoformate (or derived products) on the basis that no other ethyl source is present in the preparation and it could not be removed even on extensive drying under high vacuum.

Propiolactone acylated **3a** with excellent coupling efficiency (Scheme 3) yielding amide **5**. Similarly, methyl iodide alkylations were highly effective to leading to salt **6** (83–96% coupling yield) based on gravimetric yield. However, additional signals were present in the ^{13}C CPMAS NMR spectra of pellet **6**. Use of ^{13}C-enriched MeI confirmed the presence of three ammonium methyl signals. The origin of this effect is unclear but it seems likely that adsorption of the polar head group onto more than one site on the silica surface is the likely explanation. The possibility of **3 g** formation (through HI loss) can be eliminated as this compound has been independently prepared and its δ_C (NMe) shift 54.9 ppm is not present in the spectra of **6**.

Acylation of **3a** with $PhOC(O)Cl/NEt_3$ was far less effective. Initial, gravimetrically determined yields of **7** appeared high but were masked by the the fact that the $NHEt_3Cl$ by-product is strongly absorbed onto the silica and this could only be removed by washing the pellets in 90 °C water. The final purified **7** was only attained with coupling efficiencies of 19–29% no matter what conditions were employed. Acceptable ^{13}C CPMAS NMR spectra of **7** were not obtained. To confirm the presence of the carbamate on **7** PhOH was cleaved from the support, in a subsequent step, by TFA and could be isolated by preparative TLC. We speculated that the low yields in the formation of **7** are due to blockage of the pellet capillaries by strongly adsorbed ammonium salt co-products. Cleavage of a single pellet of **7** after initial acylation and inspection under UV light



Scheme 3. Further solid-phase reactivity studies on **3a**.

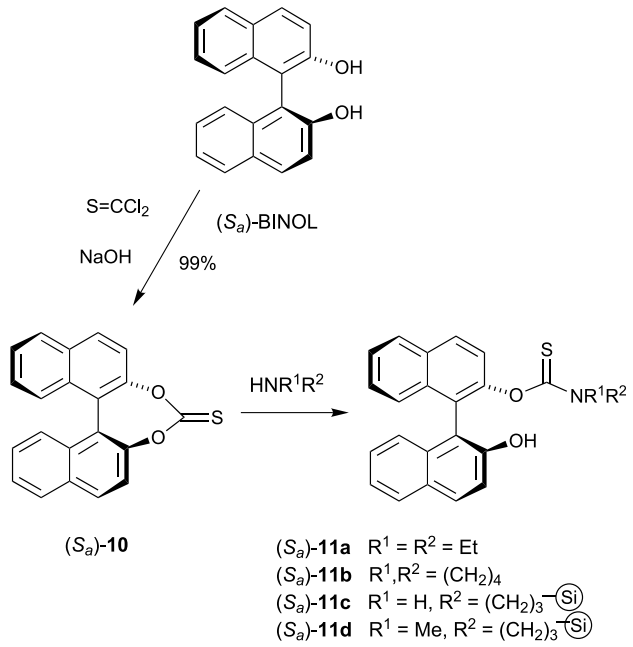
suggested reaction mainly at the pellet surface. This behaviour appears general and could be visualised easily in reactions with other coloured charged reagents. For example, reaction of **3a** or **3 g** with the diazonium salt [1,4-$Br(N_2)C_6H_4]BF_4$, which is yellow in colour, led (under Bräse's conditions[16]) only to a thin surface coating to the pellets.

In an attempt to overcome these problems amide formation from **3a** was attempted under Lee's conditions using DIC and HOBt in NMP (Scheme 3).[6a] Reaction with 1,4-hydroxybenzoic acid under these conditions led to some improvement in coupling efficiencies yielding up to 57–66% of nominal **8** based on weight gain. The ^{13}C CPMAS NMR spectrum of pelleted **8** revealed a doubling up of the CH_2N and carbonyl signals. We tentatively assign this as due to the partial conversion, but the possibility of different surface conformers cannot be excluded. Attempts to further functionalise **8** by reaction with PhOC(O)Cl/pyridine couplings were ineffective due to the same difficulties observed in the formation of **7**. Again the conditions of Lee[6a] provided a partial solution to this problem. While the majority of **8** was converted into a new material, assigned structure **9**, on the basis of ^{13}C CPMAS NMR spectroscopy. However, three carbonyl signal are present in these spectra. Again this may be due to the presence of surface conformers or partial conversion. We attempted to exclude the possibility of by-product formation but support cleavage reactions were unsuccessful. It was concluded that synthetic sequences on the pellets should be kept short and free of polar by-products.

5. Supported ligand preparation

Due to the problems encountered in reactions of **3a** with salt producing electrophiles, thiocarbonate (S_a)-**10** was selected as potentially the most effective route to silica-bound thiocarbamate ligands **11** (Scheme 4). Such species have shown some utility in copper-catalysed asymmetric additions of organozinc and organic aluminum reagents to enones.[17] Compound (S_a)-**10** was prepared by reaction of (S_a)-BINOL under conditions analogous to those used to prepare its biphenol analogue.[18] Solution ^{13}C NMR spectroscopy confirmed the symmetrical O–C(S)–O unit was present a conclusion reinforced by the presence of a strong ν(C=S) stretch at 1262 cm^{-1}. This reaction is somewhat capricious, and on occasions an uncharacterised C_1 binaphthyl product was formed, apparently a dimer of (S_a)-**10**. To confirm that (S_a)-**10** would open cleanly with amines, and without appreciable racemisation, to the desired thiocarbamates at the silica surface, the compound was treated with diethyl amine or pyrrolidine at room temperature as models for the surface reaction. In both cases, chiral HPLC confirmed that no appreciable racemisation took place during thiocarbamate opening. When **3a** or **3 g** were reacted with excess (S_a)-**10** the coupling efficiencies, based on net mass gain are very encouraging (>90%). However, extensive washing with dichloromethane led to much lower final yields (31–44%).

Our initial claim of efficient coupling for this reaction is therefore in error.[8] As highly loaded sources of **3**



Scheme 4. Preparation of silica supported thioamide ligands.

(1.7 mmol g^{-1} amine) were used for these studies it is likely that the reduced reactivity arises from the capillary blocking/accessibility problems in the pellet. Trials of these pellets in asymmetric conjugate addition studies have already been reported.[8] While ^{13}C CPMAS NMR studies confirmed the attachment of the binaphthyl fragment, broad spectra were encountered limiting the assignments that could be made.

6. Discussion and conclusions

It has been discovered that, in common with all supports, pelleted silica materials have both advantages and problems for use as solid-phase synthesis. They are of low cost and readily functionalised with a range of trialkoxysilane reagents. The ability to monitor the extent of reaction on single silica pellets by ^{13}C CPMAS NMR has been attained for the first time and this has proved extremely valuable in quantifying the purity of solid-phase bound materials (a very common problem in this area). The spectra are attained on natural abundance samples (within 5–20 h) and normally show sharp well resolved signals for aliphatic signals. Typically, poorer dispersion is attained for tethered aromatic species.

Grafting of the $(RO)_3Si(CH_2)_nY$ linkers to the pellets can be attained in a range 0.6–2.1 mmol g^{-1}. Prior activation of the pellets (through heating or acid treatment) was not found to be beneficial. The mesoporous and capillary nature of the pellets causes a significant fraction of the graft sites to be unavailable for further reaction once loadings over ca. 1.0 mmol g^{-1} are attained. The coupling efficiencies fall off dramatically in this case and complete functionalisation cannot be guaranteed even if excess reagents are used. This problem can be partially overcome if pellets with loadings of 0.6–0.8 mmol g^{-1} are used and no more than three synthetic reaction sequences using 'click'[19] reactions are

attempted. Couplings that generate polar by-products, or precipitates, are best avoided as these lead to surface adsorption and pore clogging preventing subsequent synthesis.

7. Experimental

7.1. General

General synthetic instrumentation has been described previously.[17a,b] Carbon-13 CPMAS NMR measurements were carried out on a Varian InfinityPlus spectrometer at a Larmour frequency of 75.47 MHz using a 7.5 mm double resonance MAS probe. Up to 9000 scans were recorded and CW proton decoupling at a field strength of 70 kHz was applied during acquisition. Other parameters were as follows: MAS rate 4 kHz, relaxation delay 8 s, contact time 1.7 ms, spectral width 75 kHz. The TGA-MS studies were carried out on Perkin Elmer Pyris 1 Thermogravimetric analyser. A ramp rate of 10 °C min^{-1} was used to heat each sample from ambient to 900 °C in a nitrogen gas stream of 35 mL min^{-1}. BET surface area studies were conducted on a Coulter SA 3200 Surface Area and Pore Size Analyzer. Electron microscopy studies were made on a FEI XL30 ESEM-FEG equipped with a EDAX DX4 system. Silica powder was chromatographic grade (Fluorochem 35-70u, 60A; 70–230 mesh powder). Silica extrudate were Criterion Catalysts (KL7200CY) and Grace-Davidson (SMR-057-015) products. Alumina spheres were from Rhodia (now Axens) product SPH501a. All inorganic supports were gifts from Johnson-Matthey but are commercially available. Moisture sensitive reactions were conducted under an argon atmosphere. Toluene was HPLC grade, further distillation from sodium did not improve reaction efficiencies. Dichloromethane was distilled from CaH_2. Other reagents were commercial products.

7.2. Representative approach to functionalisation of inorganic supports

A sample of 1.00 g of support (SiO_2 or Al_2O_3 extrudate/spheres or silica powder **1a–d**) was suspended in toluene (20.0 mL) and $(EtO)_3Si(CH_2)_3NH_2$ **2a** (10.0 mL, 9.46 g, 42.6 mmol) added. The mixture was stirred and heated to reflux under argon (3 h). The reaction was cooled and the functionalised support filtered off and subjected to Soxlet extraction with toluene or dichloromethane (2–6 h). For toluene extractions the final support was washed with dichloromethane (5×10 mL). The samples were dried under vacuum (0.5 mmHg, 100 °C, typically 16 h) to constant weight. Yield 1.122 g equiv to 1.22 mmol g^{-1}. Occasionally, silica samples of **1a** were activated by drying (0.5 mmHg, 110−140 °C, 2−16 h) or by treatment with aqueous 6M HCl (30 min.) followed by filtration, washing with copious distilled water, until the filtrate was pH 6.5 to 7.0, and final drying (0.5 mmHg, 120−140 °C, 24−48 h) to constant weight. Different loadings of **3a**,**c** could be achieved by changing the **1a**:**2** ratio and conditions (Table 5). Analogous compounds **3b**−**3 g** were prepared by identical procedures using trialkoxysilane concentrations and excesses already reported.[8]

7.3. Preparation of amide 5

Five pellets of **3a** (256.3 mg, loading 1.06 mmol g^{-1}, 0.27 mmol NH_2) were suspended in toluene (5 mL). Beta-propiolactone (13 μL, 18 mg, 0.25 mmol) and DMAP (4.5 mg, 0.05 mmol) were added. The reaction was refluxed under an inert atmosphere (18 h), the pellets filtered off, washed with dichloromethane (5×5 mL) and dried under vacuum (0.5 mmHg, 100 °C) to constant weight. Yield **5** 272.3 mg (indicating 1.05 mmol g^{-1}, 98%). Spectroscopic data for the compound is reported in Table 3.

7.4. Preparation of ammonium salt 6

Five pellets of **3a** (248.1 mg, loading 1.06 mmol g^{-1}, 0.26 mmol NH_2) were suspended in dichloromethane (3 mL). Neat MeI (21 μL, 47 mg, 0.33 mmol). The reaction was refluxed under an inert atmosphere (1 h), the pellets filtered off, washed with dichloromethane (5×5 mL) and dried under vacuum (0.5 mmHg, 100 °C) to constant weight. Yield **6** 261.1 mg (indicating 1.02 mmol g^{-1}, 91%) Spectroscopic data for the compound is reported in Table 3.

7.5. Preparation of carbamate 7

Five pellets of **2a** (250.0 mg, loading 0.66 mmol g^{-1}, 0.17 mmol NH_2) suspended in dichloromethane (5 mL) were treated with PhOC(=O)Cl (25 mg, 0.18 mmol) and NEt_3 (47 μL, 0.34 mmol) and occasionally DMAP (1 mg, 5 mol%). The reaction was stirred for 1−2 h, the pellets filtered off, washed with dichloromethane (5×5 mL) and dried under vacuum. The weight of the pellets (291.3 mg) suggested strong co-binding of the $NHEt_3Cl$ by-product. The pellets were suspended in hot water (90 °C, pH 7, 30 min), filtered off, washed with hot water (3×10 mL), dichloromethane (5×5 mL) and dried under vacuum

Table 5. Loadings of pellets **3a** and **3c** attained by varying conditions

2 (mmol g^{-1} pellets, conc./M)	Conditions	Loading[a] **3**/mmol g^{-1}
2a (1.2, 1.42)	Undried pellets,[b] toluene 110 °C, 2 h, CH_2Cl_2 Soxlet 2 h	0.63
2a (2.6, 0.32)	Undried pellets,[b] toluene 65 °C, 2 h, CH_2Cl_2 Soxlet 2 h	0.94
2a (2.7, 0.32)	Dried pellets,[c] toluene 110 °C, 2 h, toluene Soxlet 2 h	1.46
2a (41, 1.42)	Activated pellets,[d] toluene 110 °C, 65 h, toluene Soxlet 72 h	2.01
2c (2.2, 0.68)	Undried pellets,[b] toluene 110 °C, 1 h, toluene Soxlet 16 h	0.66

[a] Mass change per gram assumed due to effective gain of $Si(CH_2)_3Y$ from **2** and loss of 3H from **1** normalised per gram of final product.
[b] Pellets [Grace-Davidson: SMR-057-015] used as supplied.
[c] Heated 110 °C, 0.5 mmHg, 16 h.
[d] HCl treatment: 6 M, 0.5 h followed by washing with distilled water until neutrality and drying (140 °C, 0.5 mmHg, 63 h).

(0.5 mmHg, 100 °C) to constant weight. Yield **7** 256.1 mg (indicating 0.20 mmol g^{-1}).

Cleavage of pellets **7** (256.1 mg, loading 0.20 mmol g^{-1}, 0.05 mmol bound carbamate) with 1:3 TFA–dichloromethane (1 mL) led to formation of phenol within 30 min at room temperature by TLC (the pellet was ground up and destroyed in the reaction). Preparative TLC (4:1 Hexane/Et_2O) led to the recovery of phenol 4.2 mg (89)%.

7.6. Preparation of amides 8 and 9

Five pellets of **3a** (312.3 mg, loading 1.277 mmol g^{-1}, 0.40 mmol NH_2) were suspended in *N*-methylpyrrolidinone (6 mL). Solid 1,4-$HOC_6H_4CO_2H$ (0.32 g, 2.32 mmol), HOBt (0.42 g, 3.10 mmol) and 1,3-diisopropylcarbodiimide [DIC] (0.47 g, 3.75 mmol) was added. The reaction was stirred under an inert atmosphere (16 h), the pellets filtered off, and washed extensively with DMF, dichloromethane, MeOH and 10% w/w piperidine in THF. The pellets were subjected to soxlet extraction with dioxane (2 h), final washing with dichloromethane and dried under vacuum (0.5 mmHg, 100 °C) to constant weight. Yield **8** 342.0 mg (indicating 0.79 mmol g^{-1}, 62%) Spectroscopic data for the compound is reported in Table 3. Attempted coupling of **8** with PhOC(O)Cl/pyridine in dichloromethane led only to poor coupling uptakes (up to 28% yield of **9**) under a variety of conditions.

The coupling of **8** to **9** was completed more successfully in an analogous manner from **8** (342.0 mg, 0.79 mmol g^{-1}, 0.27 mmol OH), benzoic acid (255 mg, 2.09 mmol), HOBt (283 mg, 2.09 mmol) and DIC (317 mg, 2.53 mmol). Yield **9** 360.4 mg (indicating, 0.51 mmol g^{-1}, 65% coupling efficiency). Spectroscopic data for the compound is reported in Table 3.

7.7. 1,1′-Bis(2-naphthol)thiocarbonate (S_a)-10

Thiophosgene (0.4 g, 3.5 mmol) and a solution of NaOH (0.28 g, 7.0 mmol in 40 mL water) were added to a solution of (S_a)-BINOL (1.0 g, 3.5 mmol) in dichloromethane (140 mL) containing NBu_4Br (0.11 g, 0.35 mmol, 10 mol%). The reaction was stirred vigorously overnight. The organic phase was separated, dried (Na_2SO_4) and the solution evaporated to pale brown fluffy solid. Recrystallisation from dichloromethane/hexane (1:1) yielded analytically pure pale rose coloured microcrystals 1.13 g (99%). Prolonged storage or attempted chromatography led to decomposition. Mp 200–202 °C; $[\alpha]_D$ +172 (c=0.10 CH_2Cl_2, 29 °C); IR(KBr disc): ν_{max} 2924w, 2353w, 1461w, 1275m, 1260m (C═S), 1182w, 1122w, 764 s, 750 s cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ_H 7.36–7.42 (2H, m, H_8), 7.50–7.57 (4H, m, $H_{6,7}$), 7.60 (2H, d, J= 8.9 Hz, H_3), 7.98 (2H, d, J=7.9 Hz, H_5), 8.04 (2H, d, J= 8.9 Hz, H_4); ^{13}C NMR ($CDCl_3$, 126.0 MHz): δ_C 119.5, 122.4, 126.5, 127.0, 127.3, 128.7, 131.4, 131.5, 132.5, 152, 194.5 (C═S). Found: C, 76.83; H, 3.66. $C_{21}H_{12}O_2S$ requires: C, 76.40; H, 3.70. *m/z* (EI): 328 (M^+, 44%), 286(32), 269 (21), 268 (100), 239 (91), 120(22); [Found (HRMS, EI): M^+ 328.0550. $C_{21}H_{12}O_2S$ requires: *M* 328.0558.].

7.8. (S_a)-2-(*N*,*N*-Diethylthiocarbamoyloxy)-2′-hydroxy-1,1′-binaphthyl (S_a)-11a

Neat diethylamine (51.7 μL, 73.1 mg, 1.00 mmol) was added to a solution of thiocarbonate (S_a)-**10** (0.33 g, 1.00, mmol) in dichloromethane (6 mL). The reaction completed at room temperature within 2 h (TLC, hexane/dichloromethane 2:1). The presence (up to 1.2 equiv) of DMAP did not appreciably reduce the conversion time. The solution was filtered through a plug of silica gel, evaporated, and the solid recrystallised from EtOH giving colourless microcrystals 0.36 g (89%). Mp132–133 °C; $[\alpha]_D$ = −462 (c= 0.1, CCl_4, 28 °C); IR(KBr disc): ν_{max} 3438vs; 2358w; 1646m; 1518w; 1458w; 1272m; 1260m(C═S); 1210w; 818w; 764 s; 750 s cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ_H 0.46 (3H, t, J=7.2 Hz, Me); 1.06 (3H, t, J=7.1 Hz, Me); 2.82–2.89 (1H, m, CH_2Me); 3.13–3.2 (1H, m, CH_2Me); 3.57–3.68 (2H, m, CH_2Me); 5.93 (1H, s, OH); 7.08 (1H, d, J=8.4 Hz, $H_{8,8'}$); 7.21 (1H, d, J=7.1 Hz, $H_{8,8'}$); 7.23–7.28 (3H, m, $H_{6,6'\text{ or }7,7'}$); 7.31 (1H, d, J=8.8 Hz, $H_{3,3'}$); 7.41(1H, d, J=8.8 Hz, $H_{3,3'}$); 7.48 (1H, m, $H_{6,6'\text{ or }7,7'}$); 7.80 (1H, d, J=8.1 Hz, $H_{5,5'}$); 7.85 (1H, d, J=8.1 Hz, $H_{4,4'}$); 7.95 (1H, d, J=8.2 Hz, $H_{5,5'}$); 8.04 (1H, d, J=8.2 Hz, $H_{4,4'}$); ^{13}C NMR ($CDCl_3$, 126.0 MHz): δ_C 11.6; 12.2; 43.9; 48.1; 115.1; 119.5; 123.2; 123.5; 124.2; 124.7; 125.9; 126.3; 126.6; 127.3; 128.0; 128.4; 129.2; 130.0; 130.15; 132.2; 133.7; 133.9; 151.32; 152.3; 186.4 (C═S). Found: C, 74.81; H, 5.70; N, 3.34. $C_{25}H_{23}O_2SN$ requires: C, 74.72; H, 5.72; N, 3.49. *m/z* (EI): 401 (M^+, 54%), 286 (57), 268 (22), 239 (30), 116 (48), 88 (31), 58 (35) 72 (100). [Found (HRMS, EI): M^+ 401.1433. $C_{25}H_{23}O_2SN$ requires: *M* 401.1450.].

HPLC (Daicel AD, hexane/isopropanol 97:3, flow rate 0.5 mL min^{-1}): (S_a)-**11a** (37.9 min), (R_a)-**11a** (47.0 min). The crude reaction product showed 98% ee when compared against racemic material, (thiocarbonate (S_a)-**10** giving (S_a)-**11a** with retention of configuration). The retention times of the enantiomers were confirmed by the synthesis of the racemate. Formation (S_a)-**11a** was confirmed by comparison with an authentic sample of the S_a enantiomer prepared by an alternative route.[17]

7.9. (S_a)-2-(Pyrrolidine-1-carbothioyloxy)-2′-hydroxy-1,1′-binaphthyl (S_a)-11b

Prepared by an equivalent procedure to the synthesis of (S_a)-**11a** from thiocarbonate (S_a)-**10** (50.0 mg, 0.15 mmol) and pyrrolidine (12.5 μL, 0.15 mmol) in dichloromethane (5 mL) at room temperature (2 h). Recrystallisation from EtOH gave an off-white powder 41.9 mg (70%). Mp 276–278 °C; $[\alpha]_D$ = −307 (c=0.1, CH_2Cl_2, 29 °C). IR(KBr disc): ν_{max} 3422w, 2923w, 1716w, 1523w, 1454w, 1275m, 1260m (C═S), 764 s, 750 s cm^{-1}; ^{1}H NMR ($CDCl_3$, 500.1 MHz): δ_H 1.42–1.57 (1H, m, $NCH_{2\alpha}$) 1.71–1.79 (3H, m, $NCH_{2\alpha/\beta}$), 2.56–2.63 (1H, m, $NCH_2CH_{2\alpha}$), 3.23–3.29 (1H, m, $NCH_2CH_{2\beta}$), 3.5–3.59 (2H, m, $NCH_2CH_{2\alpha/\beta}$), 5.89 (1H, s, OH), 7.07 (1H, d, J=8.0 Hz, $H_{8\text{ or }8'}$), 7.23–7.37 (5H, m, Ar), 7.46 (1H, d, J=8.9 Hz, $H_{3\text{ or }3'}$), 7.50 (1H, broad apparent t, J=7.2 Hz, $H_{6,6'\text{ or }7,7'}$), 7.48 (1H, d, J= 8.0 Hz, $H_{5,5'}$), 7.88 (1H, d, J=8.9 Hz, $H_{4,4'}$) 7.97 (1H, d, J=8.5 Hz, $H_{5,5'}$), 8.05 (1H, d, J=8.8 Hz, $H_{4\text{ or }4'}$); ^{13}C NMR ($CDCl_3$, 126.0 MHz): δ_C 24.5, 25.6, 48.4, 52.4, 115.1, 119.4, 123.1, 123.6, 124.1, 125.0, 126.0, 126.3, 126.6,

127.4, 128.0, 128.4, 129.1, 130.1, 130.2, 132.3, 133.7, 133.8, 151.3, 152.4, 184.3 (C=S); *m/z* (EI): 399 (M^+, 91%), 284(78), 268 (41); 239(43%); 114(100%); 72(42%); 55(32%). [Found (EI, HRMS): M^+399.1284 $C_{25}H_{21}O_2SN$ requires 399.1293.]. Chiral HPLC under the conditions used for **11a** led to the observation of only a single peak.

7.10. Preparation of silica supported ligands 11c–d

Pelleted **3a** or **3 g** (0.15 g, loading 1.70 mmol g^{-1}, 0.25 mmol NHR; R=H, Me) in dichloromethane (1.5 mL) was treated with solid thiocarbonate (S_a)-**10** (2 equiv 0.50 mmol) under an argon atmosphere and the reaction allowed to stir at room temperature (2 h). The weight of the crude pellets indicated a high coupling yield (>90%). However, after extensive washing with dichloromethane and drying to constant weight much lower yields were attained. Yield for **11c**: 183.1 mg (indicating 0.54 mmol g^{-1}, 40%). Yield for **11d**: 176.0 mg (indicating 0.44 mmol g^{-1}, 31%).

Acknowledgements

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References and notes

1. Overviews of solid-phase organic (and combinatorial) synthesis (a): Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Handbook of Combinatorial Chemistry; Wiley-VCH: Weinheim, 2002; Vol. 1–2. (b) Zaragoza Dorwald, F. Organic Syntheses on Solid Phase; Wiley-VCH: Weinheim, 2000. (c) An extensive compilation of recent results is available at: www.combinatorial.com.
2. Overviews of polystyrene type supports: Haag, R., Hebel, A., Stumbé, J.-F., in Ref. 1a, p 46 and references therein.
3. Commercial silica supported products: Sigma-Aldrich list over 50 functionalised silica gels (scavengers, bases, and linkers) in their 2004 catalogue with loadings of 0.5–2.5 mmol g^{-1}. Additionally, morpholine and related supported bases may be obtained from SiliCycle Inc (www.silicycle.com).
4. Silica-powder supported reagents: (a) Carpino, L. A.; Mansour, E. M. E.; Knapczyc, J. *J. Org. Chem.* **1983**, *48*, 666–669. (b) Thompsona, L. A.; Combsa, A. P.; Trainor, G. L.; Wangb, Q.; Langloisb, T. J.; Kirkland, J. *Comb. Chem. High Through. Screen* **2000**, *3*, 107–115. (c) Carpino, L. A.; Ismail, M.; Truran, G. A.; Mansour, E. M. E.; Iguchi, S.; Ionescu, D.; ElFaham, A.; Riemer, C.; Warrass, R. *J. Org. Chem.* **1999**, *64*, 4324–4338.
5. Silica-powder supported catalysts: (a) Macquarrie, D. J. *Chem. Commun.* **1997**, 601–602. (b) Macquarrie, D. J.; Clark, J. H.; Lambert, A.; Mdoe, J. E. G.; Priest, A. *React. Funct. Polym.* **1997**, *35*, 153–158. (c) Tundo, P.; Venturello, P. *J. Am. Chem. Soc.* **1979**, *101*, 6607–6613. (d) Kurusu, Y. *Chin. J. Polym. Sci.* **1999**, *17*, 1–12. (e) Price, P. M.; Clark, J. H.; Macquarrie, D. J. *J. Chem. Soc. Dalton Trans.* **2000**, 101–110.
6. Solid-phase synthesis on silica powder: (a) Lee, J. W.; Louie, Y. Q.; Walsh, D. P.; Chang, Y-T. *J. Comb. Chem.* **2003**, *5*, 330–335. (b) Palmacci, E. R.; Hewitt, M. C.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4433–4436. (c) Keana, J. F. W.; Shimizu, M.; Jernstedt, K. K. *J. Org. Chem.* **1986**, *51*, 1642–1644. (d) Sucholeiki, I.; Pavia, M. R.; Kresge, C. T.; McCullen, S. B.; Malek, A.; Schramn, S. *Mol. Divers.* **1998**, *3*, 161–171.
7. Glass bead references and related: (a) Haag, R.; Hebel, A.; Stumbé, J.-F. in Ref. 1a, p 46 and references therein. (b) Anson, M. S.; Leese, M. P.; Tonks, L.; Williams, J. M. J. *J. Chem. Soc., Dalton Trans.* **1998**, 3529–3538.
8. Timofte, R. S.; Woodward, S. *Tetrahedron Lett.* **2004**, *45*, 39–42.
9. Hamaya, J.; Suzuchi, T.; Hoshi, T.; Shimizu, K.; Kitayama, Y.; Hagiwara, H. *Synlett* **2003**, 873–875.
10. Activation of silica: Kurusu, Y. *Chin. J. Polym. Sci.* **1999**, *17*, 1–12.
11. Hawker, S. Chemical Catalyst Development, Johnson Matthey Ltd. Personal communication.
12. Values determined through modelling on Spartan'02 from wavefun.com.
13. (a) Lippens, G.; Warrass, R.; Wieruszeski, J.-M.; Rousselot-Pailley, P.; Chessari, G. *Comb. Chem. High Through. Screen.* **2001**, *4*, 333–351. (b) Keifer, P. A. *Drug Discovery Today* **1997**, *2*, 468–478.
14. Khitrin, A. K.; Fung, B. M.; McGeorge, G. In *Encyclopedia of Nuclear Magnetic Resonance*; Wiley: UK, 2002; Vol 9, pp 91–98 and references within.
15. Butler, I. R.; Cullen, W. R.; Han, N. F.; Herring, F. G.; Jagannathan, N. R.; Ni, J. *Appl. Organomet. Chem.* **1988**, *2*, 263–275.
16. (a) Lormann, M.; Dahmen, S.; Bräse, S. *Tetrahedron Lett.* **2000**, *41*, 3813–3816. (b) Lazny, R.; Sienkiewicz, M.; Bräse, S. *Tetrahedron* **2001**, *57*, 5825–5832.
17. (a) Bennett, S. M. W.; Brown, S. M.; Cunningham, A.; Dennis, M. R.; Muxworthy, J. P.; Oakley, M. A.; Woodward, S. *Tetrahedron* **2000**, *56*, 2847–2855. (b) Bennett, S. M. W.; Brown, S. M.; Muxworthy, J. P.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 1767–1770. (c) Kodama, H.; Okazaki, A.; Segi, A.; Shimotsuki, A.; Ohta, T.; Furukawa, I. *Sci. Eng. Rev. Doshisha Uni.* **2000**, *41*, 26–32. (d) Kodama, H.; Okazaki, A.; Segi, A.; Shimotsuki, A.; Ohta, T.; Furukawa, I. *Chem Abs.* **2000**, *133*, 237651.
18. Yoder, C. M. S.; Zuckerman, J. J. *J. Hetrocycl. Chem.* **1967**, *4*, 166–167.
19. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.

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Palladium-mediated approach to dibenzo[*b*,*e*][1,4]diazepines and benzopyrido-analogues. An efficient synthesis of tarpane

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Abstract—An original synthetic route toward dibenzo[*b*,*e*][1,4]diazepin-11-ones and analogues pyridobenzodiazepinones has been developed. The method relies upon an intramolecular amination process between an (hetero)aryl halide and the appropriate aniline moiety.
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1. Introduction

1,4-Benzodiazepines constitute an important class of compounds due to their biological activities mostly based on their special affinity for serotonin (5-HT_2) and acetylcholine receptors. In fact, these compounds play a crucial role as anti-anxiety and antihistaminic agents.[1] In particular the dibenzo[*b*,*e*][1,4]diazepin-11-ones may be active as antidepressants (dibenzepine **1**),[2] antihistaminics (tarpane **2**),[3] antinflammatories,[4] antiarhytmics,[5] antitumors,[6] anticonvulsivants[7] and many of these derivatives have been patented. Other, pyrido[2,3-*b*]benzodiazepinones have been screened as cardioselective muscarinic receptor antagonists (pirenzepine **3**)[8] and explored as potential HIV-1 reverse transcriptase (RT) inhibitors as isomeric structures of the potent RT inhibitor nevirapine, a dipiridodiazepinone.

The interest associated with the pharmacological activities of the dibenzodiazepinones and pyridobenzodiazepinones justifies a continuation of the work on novel synthetic methodologies. While several strategies of access to 1,4-benzodiazepinones are known,[9] a few synthetic pathways were reported to obtain analogue tricyclic fused systems.[10]

We recently described an access to 1,4-benzodiazepin-5-ones based on Pd-catalyzed intramolecular amination of *N*-allyl antranilamides.[11] In continuation of our work to exploit the validity of Pd-catalysts as important tools in synthetic strategies to heteropolyciclic systems,[12] we report herein a novel approach to dibenzo[*b*,*e*][1,4]diazepinones (**7**) and pyridobenzodiazepinones (**11** and **15**) by an intramolecular Buchwald–Hartwig reaction between an (hetero)aryl halide and an aromatic amino group (Fig. 1).

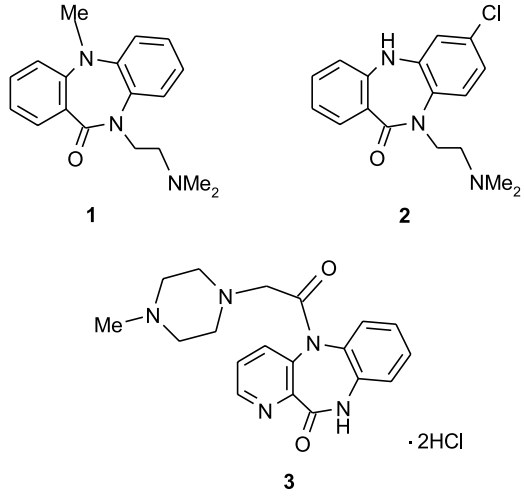

Figure 1.

2. Results and discussion

Starting from 2-nitrobenzoyl chloride and 2-iodoaniline, we thought to synthesize the 2-nitrobenzamides **4** following classic conditions (triethylamine as base in dichloromethane) (Scheme 1). In the case of compound **4c** the reaction gave quantitative yield using a zinc mediated method.[13] The obtained amides were then N-alkylated with NaH and the suitable alkyl halides in THF solution. In the case of compounds **5ab** and **5bb** a phase-transfer method

Keywords: Pd-catalyst; Dibenzodiazepines; Intramolecular cyclization; Tarpane; Buchwald–Hartwig amination.
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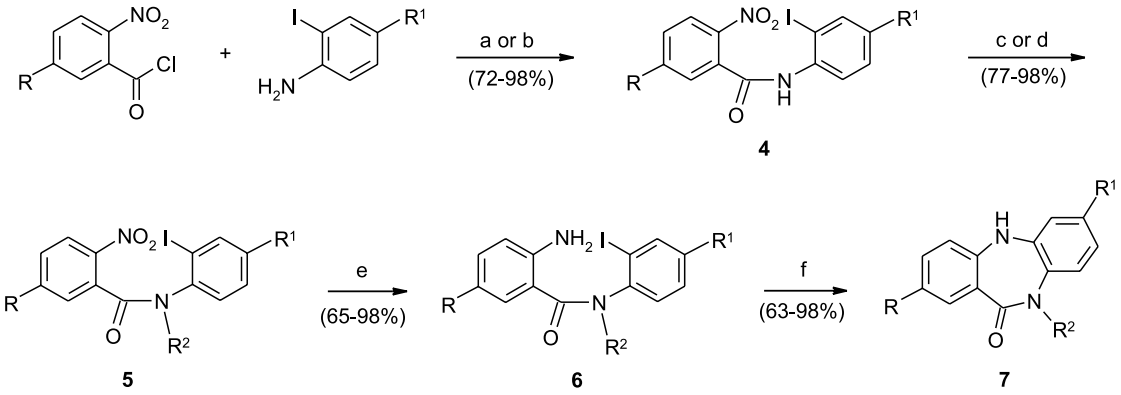
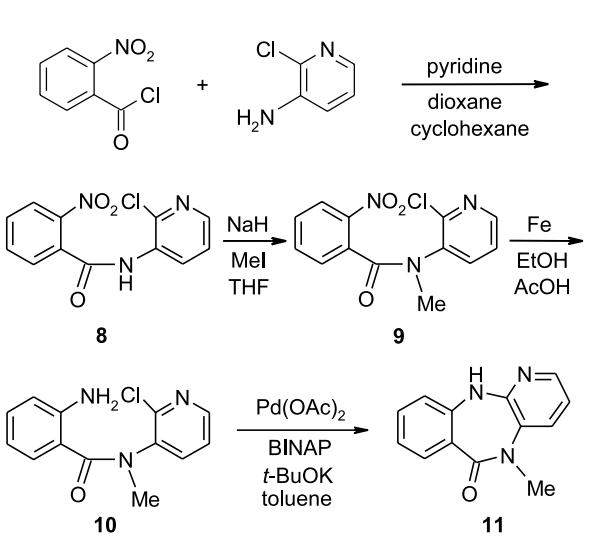


Compound	R	R^1	R^2
4a	H	H	—
5-7aa	H	H	Me
5-7ab	H	H	$-(CH_2)_2NMe_2$
4b	H	Cl	—
5-6bb	H	Cl	$-(CH_2)_2NMe_2$
5-7bc	H	Cl	Et
4c	Cl	H	—
5-7ca	Cl	H	Me
5-7cc	Cl	H	Et
4d	F	H	—
5-7da	F	H	Me
4e	F	Cl	—
5-7ea	F	Cl	Me

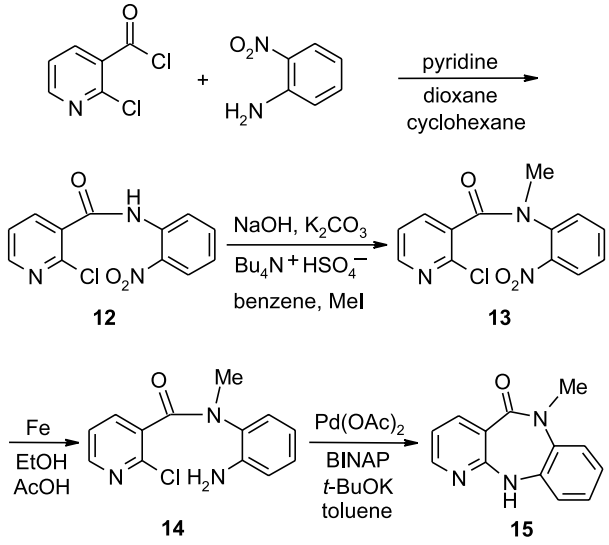
Scheme 1. Reagents and conditions: (a) TEA, CH_2Cl_2, rt; (b) Zn powder, dry toluene, rt; (c) NaH, dry THF, N_2 atmosphere, alkyl halide, rt; (d) NaOH, K_2CO_3, $Bu_4N^+HSO_4^-$, benzene, alkyl halide, reflux; (e) Fe, EtOH, AcOH, reflux; (f) $Pd(OAc)_2$, Cs_2CO_3, BINAP, dry toluene, reflux.

was necessary to obtain alkylated amides.[14] The resulting compounds **5** were submitted to nitro group reduction with Fe in AcOH resulting in the desired intermediates **6**. The cross-coupling amination reaction between amino and halogen groups, through the known Pd-catalyzed C–N bond formation, gave the desired products **7**. The tarpane **2** was obtained from the amino intermediate **6bb**. The yields of compounds **7** were in the range of 63–98% in the best cases. The $Pd(OAc)_2$/BINAP catalyst system remained the most active in the presence of the weak base cesium carbonate. The cyclization was performed in toluene at 110 °C for 24 h.

The method was also applicable to the synthesis of pyridobenzodiazepinones as depicted in Schemes 2 and 3. Amides **8** and **12** were synthesized respectively starting from 2-nitro-benzoyl chloride with 3-amino-2-chloro-pyridine and 2-chloronicotinoyl chloride with 2-nitro-aniline, using a mixture of dioxane–cyclohexane as solvent and pyridine as base. These intermediates were converted to **10** and **14**, respectively, by alkylation and reduction. The choice of the base in the ring closure reaction was fundamental and, for chloropyridines, potassium *tert*-butoxide was found effective to obtain cyclization



Scheme 2.



Scheme 3.

compounds **11** and **15**[10b] via a Pd-catalyzed amination procedure. Despite the prolonged reaction time at 48 h, the yields were lower with respect to the dibenzodiazepinone analogues.

In summary, a novel synthetic route to benzodiazepinones and pyridobenzodiazepinones by palladium-catalyzed amination was presented. Furthermore a variety of substituents can be present; in particular, halogen atoms (as observed for diazepam, tarpane, clozapine, flumazenil, tifluadom) can be very important for the biological activities. Once again, these results demonstrate the validity of the Buchwald–Hartwig methodology in intramolecular reactions. Different heterocyclic substrates are being evaluated for other intramolecular cyclizations.

3. Experimental

3.1. General

Melting points were determined on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Jasco IR Report 100 spectrophotometer, in nujol mull for solids and as a liquid film for oils. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer. Column chromatography was performed on Merck Kieselgel 60, 0.063–0.2 mm. Elemental analysis were executed on Perkin–Elmer CHN Analyzer Series II 2400. Where required, the use of the anhydrous solvents was specified.

3.2. General procedure for the preparation of 2-nitrobenzamides 4a,b,d,e

To a solution of the appropriate 2-nitro-benzoyl chloride (5 mmol) in CH_2Cl_2 (20 ml), a mixture of 2-iodo-4-substituted aniline (5 mmol) and triethylamine (7.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise at 0 °C. The reaction was stirred at room temperature for 5 h, then the mixture was diluted with H_2O (20 ml), the organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by crystallization.

3.2.1. *N*-(2-Iodo-phenyl)-2-nitro-benzamide (4a).[15] 80% Yield; mp 189–191 °C (white crystals from CH_2Cl_2–hexane); IR (nujol): ν 1640, 3195 cm^{-1}; ^{1}H NMR (DMSO): δ=7.01 (1H, dd, J=7.6, 7.7 Hz), 7.41 (1H, dd, J=7.7, 7.8 Hz), 7.56 (1H, d, J=7.8 Hz), 7.68 (1H, dd, J=7.5, 7.6 Hz), 7.70–7.82 (2H, overlapping), 7.86 (1H, d, J=7.8 Hz), 8.09 (1H, d, J=8.1 Hz), 10.12 (1H, br s, absent after deuteriation); ^{13}C NMR (DMSO): δ=97.0 (s), 124.8 (d), 128.2 (d), 128.8 (d), 129.4 (d), 129.7 (d), 131.3 (d), 133.5 (s), 134.4 (d), 139.5 (s), 139.7 (d), 147.2 (s), 165.4 (s). Anal. Calcd for $C_{13}H_9IN_2O_3$: C, 42.42; H, 2.46; N, 7.61. Found: C, 42.28; H, 2.51; N, 7.80.

3.2.2. *N*-(4-Chloro-2-iodo-phenyl)-2-nitro-benzamide (4b). 98% Yield; mp 188–190 °C (white crystals from Et_2O); IR (nujol): ν 1637, 3190 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.43 (1H, dd, J=2.1, 8.3 Hz), 7.62–7.75 (3H, overlapping, 2H after deuteriation), 7.80 (1H, d, J=7.3 Hz), 7.83 (1H, d, J=2.1 Hz), 8.17 (1H, d, J=8.1 Hz), 8.26 (1H, d, J=8.2 Hz); ^{13}C NMR ($CDCl_3$): δ=95.0 (s), 124.6 (d), 127.2 (d), 129.2 (d), 129.3 (d), 130.9 (d), 132.2 (s), 133.1 (s), 134.2 (d), 137.8 (s), 138.4 (d), 146.7 (s), 165.4 (s). Anal. Calcd for $C_{13}H_8ClIN_2O_3$: C, 38.79; H, 2.00; N, 6.96. Found: C, 38.91; H, 1.81; N, 7.07.

3.2.3. 5-Fluoro-*N*-(2-iodo-phenyl)-2-nitro-benzamide (4d). 96% Yield; mp 182–184 °C (white crystals from CH_2Cl_2–hexane); IR (nujol): ν 1646, 3174 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=6.97 (1H, dd, J=7.8, 8.0 Hz), 7.35 (1H, ddd, J=2.2, 7.8, 8.0 Hz), 7.39–7.48 (2H, overlapping), 7.67 (1H, br s, absent after deuteriation), 7.85 (1H, dd, J=1.2, 8.0 Hz), 8.21–8.29 (2H, overlapping); ^{13}C NMR ($CDCl_3$): δ=91.5 (s), 116.3 (dd, J_{C-F}=24.8 Hz), 118.3 (dd, J_{C-F}=23.0 Hz), 123.6 (d), 127.7 (d), 128.3 (dd, J_{C-F}=9.5 Hz), 129.9 (d), 135.7 (s), 137.7 (s), 139.3 (d), 142.7 (s), 163.3 (s), 165.5 (d, J_{C-F}=259.2 Hz). Anal. Calcd for $C_{13}H_8FIN_2O_3$: C, 40.44; H, 2.09; N, 7.26. Found: C, 40.41; H, 1.88; N, 7.17.

3.2.4. 5-Fluoro-*N*-(4-chloro-2-iodo-phenyl)-2-nitro-benzamide (4e). 97% Yield; mp 168–170 °C (pale yellow crystals from CH_2Cl_2–hexane); IR (nujol): ν 1647, 3404 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.25 (1H, dd, J=7.0, 7.0 Hz), 7.44 (1H, br s, absent after deuteriation), 7.50 (1H, dd, J=2.3, 8.5 Hz), 7.33 (1H, dd, J=2.2, 8.5 Hz), 7.50 (1H, dd, J=2.5, 8.5 Hz), 7.62 (1H, d, J=2.3 Hz), 7.85 (1H, d, J=2.2 Hz); ^{13}C NMR ($CDCl_3$): δ=101.7 (s), 115.2 (dd, J_{C-F}=31.3 Hz), 118.0 (dd, J_{C-F}=29.5 Hz), 127.8 (dd, J_{C-F}=9.8 Hz), 130.7 (d), 130.9 (d), 136.6 (s), 137.1 (s), 137.7 (s), 140.2 (d), 141.0 (s), 165.5 (d, J_{C-F}=259.8 Hz), 165.7 (s). Anal. Calcd for $C_{13}H_7ClFIN_2O_3$: C, 37.13; H, 1.68; N, 6.66. Found: C, 37.02; H, 1.89; N, 6.75.

3.2.5. 5-Chloro-*N*-(2-iodo-phenyl)-2-nitro-benzamide (4c)

5-Chloro-2-nitrobenzoyl chloride (5 mmol) and activate zinc powder (5 mmol) were stirred in anhydrous toluene (20 ml) for 10 min at room temperature. A solution of 2-iodo aniline (5 mmol) in anhydrous toluene (5 ml) was added slowly and the mixture stirred for 2 h. The reaction was filtered and the solid washed with ether (50 ml). The combined filtrate was washed with 10% $NaHCO_3$ solution, water and dried over Na_2SO_4. Evaporation of the solvent gave **4c**. 72% Yield; mp 190–192 °C (white crystals from Et_2O); IR (nujol): ν 1643, 3212 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=6.98 (1H, dd, J=7.6, 7.6 Hz), 7.45 (1H, dd, J=7.6, 7.6 Hz), 7.61–7.75 (3H, overlapping, 2H after deuteriation), 7.85 (1H, dd, J=1.0, 7.9 Hz), 8.15 (1H, d, J=8.7 Hz), 8.25 (1H, d, J=7.9 Hz); ^{13}C NMR ($CDCl_3$): δ=91.4 (s), 123.6 (d), 126.8 (d), 127.7 (d), 129.0 (d), 129.9 (d), 131.4 (d), 134.4 (s), 137.8 (s), 139.4 (d), 141.2 (s), 145.0 (s), 163.2 (s). Anal. Calcd for $C_{13}H_8ClIN_2O_3$: C, 38.79; H, 2.00; N, 6.96. Found: C, 38.72; H, 2.17; N, 7.18.

3.3. General procedure for the preparation of compounds 8 and 12

To a solution of 3-amino-2-chloropyridine or 2-nitroaniline (2 mmol) in a mixed solvent system of 1,4-dioxane (4 ml), cyclohexane (5 ml) and pyridine (0.16 ml, 2 mmol), a solution of 2-nitrobenzoyl chloride or 2-chloronicotinoyl

chloride (2 mmol) in 1,4-dioxane (3 ml) was added over 15 min. The reaction mixture was stirred overnight at room temperature under nitrogen. The solid product was filtered and purified by crystallization.

3.3.1. *N*-(2-Chloro-pyridin-3-yl)-2-nitro-benzamide (8).[16] *From 2-nitrobenzoyl chloride and 3-amino-2-chloro-pyridine*. 70% Yield; mp 154–156 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1637, 3251 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.37$ (1H, dd, $J=4.7$, 8.0 Hz), 7.73–7.68 (2H, overlapping), 7.80 (1H, dd, $J=7.3$, 7.3 Hz), 7.99 (1H, br s, absent after deuteriation), 8.17 (1H, d, $J=8.0$ Hz), 8.20 (1H, d, $J=4.7$ Hz), 8.81 (1H, d, $J=8.0$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=123.9$ (d), 125.4 (d), 128.7 (d), 130.3 (d), 131.8 (d), 132.3 (s), 134.6 (d), 140.8 (s), 140.9 (s), 145.2 (d), 146.8 (s), 165.0 (s). Anal. Calcd for $C_{12}H_8ClN_3O_3$: C, 51.91; H, 2.90; N, 15.13. Found: C, 52.04; H, 2.87; N, 15.21.

3.3.2. 2-Chloro-*N*-(2-nitro-phenyl)-pyridine-3-carboxamide (12). *From 2-chloronicotinoyl chloride and 2-nitroaniline*. 75% Yield; mp 150–152 °C (yellow crystals from AcOEt–hexane); IR (nujol): ν 1640, 3220 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=7.32$ (1H, ddd, $J=1.1$, 7.3, 7.7 Hz), 7.43 (1H, dd, $J=4.7$, 7.7 Hz), 7.74 (1H, ddd, $J=1.8$, 7.3, 7.3 Hz), 8.10 (1H, dd, $J=1.8$, 7.3 Hz), 8.28 (1H, dd, $J=1.8$, 8.4 Hz), 8.56 (1H, dd, $J=1.8$, 4.7 Hz), 8.90 (1H, dd, $J=1.1$, 8.4 Hz), 11.01 (1H, br s, absent after deuteriation); ^{13}C NMR ($CDCl_3$): $\delta=123.0$ (d), 123.2 (d), 124.8 (d), 126.3 (d), 131.8 (s), 134.3 (s), 136.4 (d), 137.5 (s), 139.1 (s), 139.6 (d), 152.1 (d), 164.1 (s). Anal. Calcd for $C_{12}H_8ClN_3O_3$: C, 51.91; H, 2.90; N, 15.13. Found: C, 52.09; H, 2.84; N, 15.22.

3.4. General procedures for the preparation of *N*-alkyl-2-nitro-benzamides 5aa, 5bc, 5cc, 5da, 5ea and 9

To a solution of compound **4** or **8** (4 mmol) in anhydrous THF (30 ml), 60% NaH (240 mg, 6 mmol) was added portionwise under nitrogen at 0 °C. After 15 min. at room temperature, the appropriate alkyl halide (8 mmol) was added. The reaction was stirred at 30–35 °C for 12 h, then the solvent was evaporated and the residue diluted with 1 M HCl and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by crystallization.

3.4.1. *N*-(2-Iodo-phenyl)-*N*-methyl-2-nitro-benzamide (5aa). 82% Yield; mp 149–151 °C (white crystals from Et_2O); IR (nujol): ν 1648 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.46$ (3H, s), 6.87 (1H, ddd, $J=1.5$, 7.9, 8.9 Hz), 7.14 (1H, ddd, $J=1.2$, 7.7, 8.9 Hz), 7.36–7.39 (2H, overlapping), 7.46 (1H, dd, $J=7.5$, 7.7 Hz), 7.60 (1H, ddd, $J=1.8$, 6.0, 7.5 Hz), 7.75 (1H, dd, $J=1.2$, 7.9 Hz), 7.92 (1H, dd, $J=1.8$, 8.2 Hz); ^{13}C NMR ($CDCl_3$): $\delta=37.1$ (q), 99.5 (s), 124.7 (d), 128.3 (d), 129.3 (d), 130.2 (d), 130.3 (d), 130.5 (d), 133.1 (s), 134.1 (d), 140.5 (d), 145.6 (s), 146.1 (s), 167.2 (s). Anal. Calcd for $C_{14}H_{11}IN_2O_3$: C, 44.00; H, 2.90; N, 7.33. Found: C, 43.84; H, 3.01; N, 7.39.

3.4.2. *N*-(4-Chloro-2-iodo-phenyl)-*N*-ethyl-2-nitro-benzamide (5bc). 80% Yield; mp 135 °C (white crystals from Et_2O–hexane); IR (nujol): ν 1650 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.32$ (3H, t, $J=7.1$ Hz), 3.25 (1H, dq, $J=14.1$, 7.1 Hz), 4.58 (1H, dq, $J=14.1$, 7.1 Hz), 7.15 (1H, dd, $J=2.4$, 8.4 Hz), 7.23 (1H, d, $J=8.4$ Hz), 7.41 (1H, ddd, $J=1.4$, 7.6, 8.1 Hz), 7.50 (1H, ddd, $J=1.0$, 7.4, 7.6 Hz), 7.58 (1H, dd, $J=1.4$, 7.4 Hz), 7.80 (1H, d, $J=2.4$ Hz), 8.01 (1H, dd, $J=1.0$, 8.1 Hz); ^{13}C NMR ($CDCl_3$): $\delta=12.0$ (q), 44.1 (t), 100.9 (s), 124.9 (d), 127.8 (d), 129.9 (d), 130.3 (d), 131.2 (d), 133.2 (s), 134.2 (d), 135.2 (s), 139.2 (s), 140.0 (d), 142.6 (s), 166.5 (s). Anal. Calcd for $C_{15}H_{12}ClIN_2O_3$: C, 41.84; H, 2.81; N, 6.51. Found: C, 41.71; H, 2.99; N, 6.34.

3.4.3. 5-Chloro-*N*-(2-iodo-phenyl)-*N*-methyl-2-nitro-benzamide (5ca). 98% Yield; mp 141–143 °C (white crystals from CH_2Cl_2–hexane); IR (nujol): ν 1643 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.44$ (3H, s), 6.94 (1H, ddd, $J=1.8$, 7.3, 7.7 Hz), 7.20 (1H, ddd, $J=1.1$, 7.3, 7.7 Hz), 7.27–7.35 (2H, overlapping), 7.71 (1H, d, $J=2.2$ Hz), 7.81 (1H, dd, $J=1.1$, 7.7 Hz), 7.92 (1H, d, $J=8.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=37.1$ (q), 99.5 (s), 126.1 (d), 128.6 (d), 129.2 (d), 130.3 (d), 130.6 (d), 130.7 (d), 134.6 (s), 140.7 (d), 144.1 (s), 144.4 (s), 145.1 (s), 165.7 (s). Anal. Calcd for $C_{14}H_{10}ClIN_2O_3$: C, 40.36; H, 2.42; N, 6.72. Found: C, 40.51; H, 2.24; N, 6.71.

3.4.4. 5-Chloro-*N*-ethyl-*N*-(2-iodo-phenyl)-2-nitro-benzamide (5cc). 82% Yield; mp 172–173 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1646 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.27$ (3H, t, $J=7.0$ Hz), 3.28 (1H, dq, $J=13.9$, 7.0 Hz), 4.55 (1H, dq, $J=13.9$, 7.0 Hz), 6.92 (1H, ddd, $J=1.7$, 7.6, 7.7 Hz), 7.19 (1H, ddd, $J=1.2$, 7.6, 7.7 Hz), 7.26 (1H, dd, $J=1.7$, 7.8 Hz), 7.31 (1H, dd, $J=2.2$, 8.8 Hz), 7.65 (1H, d, $J=2.2$ Hz), 7.85 (1H, dd, $J=1.2$, 7.8 Hz), 7.92 (1H, d, $J=8.8$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=$ 12.1 (q), 44.2 (t), 100.6 (s), 126.1 (d), 127.7 (d), 129.8 (d), 130.1 (d), 130.6 (d), 130.7 (d), 134.8 (s), 140.8 (d), 141.7 (s), 143.3 (s), 144.1 (s), 165.2 (s). Anal. Calcd for $C_{15}H_{12}ClIN_2O_3$: C, 41.84; H, 2.81; N, 6.51. Found: C, 41.84; H, 2.96; N, 6.42.

3.4.5. 5-Fluoro-*N*-(2-iodo-phenyl)-*N*-methyl-2-nitro-benzamide (5da). 98% Yield; mp 128–130 °C (cream crystals from Et_2O); IR (nujol): ν 1648 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.41$ (3H, s), 6.92 (1H, dd, $J=7.6$, 7.8 Hz), 7.02 (1H, ddd, $J=2.6$, 8.0, 9.0 Hz), 7.18 (1H, dd, $J=7.6$, 7.8 Hz), 7.31 (1H, d, $J=7.8$ Hz), 7.36 (1H, dd, $J=2.6$, 8.0 Hz), 7.79 (1H, d, $J=7.8$ Hz), 8.01 (1H, dd, $J=4.7$, 9.0 Hz); ^{13}C NMR ($CDCl_3$): $\delta=37.1$ (q), 99.5 (s), 115.6 (dd, $J_{C-F}=25.6$ Hz), 117.4 (dd, $J_{C-F}=23.2$ Hz), 127.7 (dd, $J_{C-F}=9.6$ Hz), 129.2 (d), 130.3 (d), 130.8 (d), 135.9 (s), 140.7 (d), 142.0 (s), 145.1 (s), 165.1 (d, $J_{C-F}=258.2$ Hz), 166.4 (s). Anal. Calcd for $C_{14}H_{10}FIN_2O_3$: C, 42.02; H, 2.52; N, 7.00. Found: C, 42.19; H, 2.51; N, 6.94.

3.4.6. 5-Fluoro-*N*-(4-chloro-2-iodo-phenyl)-*N*-methyl-2-nitro-benzamide (5ea). 89% Yield; mp 113–115 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1644 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.41$ (3H, s), 7.06 (1H, ddd, $J=2.6$, 8.1, 9.1 Hz), 7.17 (1H, dd, $J=2.3$, 8.4 Hz), 7.27 (1H, d, $J=8.4$ Hz), 7.35 (1H, dd, $J=2.6$, 8.1 Hz), 7.79 (1H, d, $J=2.3$ Hz), 8.05 (1H, dd, $J=4.8$, 9.1 Hz); ^{13}C NMR ($CDCl_3$): $\delta=37.1$ (q), 99.9 (s), 115.5 (dd, $J_{C-F}=25.5$ Hz), 117.5 (dd, $J_{C-F}=23.0$ Hz), 127.9 (dd, $J_{C-F}=9.7$ Hz), 129.7 (d), 130.5 (d), 135.2 (s), 135.6 (s), 140.1 (d), 142.0 (s), 143.9 (s), 165.3 (d, $J_{C-F}=258.7$ Hz), 166.5 (s). Anal. Calcd for

$C_{14}H_9ClFIN_2O_3$: C, 38.69; H, 2.09; N, 6.45. Found: C, 38.54; H, 2.00; N, 6.64.

3.4.7. *N*-(2-Chloro-pyridin-3-yl)-*N*-methyl-2-nitro-benzamide (9). 82% Yield; mp 127–128 °C (white crystals from AcOEt–hexane); IR (nujol): ν 1650 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.46$ (3H, s), 7.10 (1H, dd, $J=4.7$, 7.8 Hz), 7.41 (1H, ddd, $J=2.0$, 7.0, 8.0 Hz), 7.44–7.46 (2H, overlapping), 7.70 (1H, dd, $J=1.8$, 7.8 Hz), 7.96 (1H, d, $J=8.0$ Hz), 8.22 (1H, dd, $J=1.8$, 4.7 Hz); ^{13}C NMR ($CDCl_3$): $\delta=36.3$ (q), 123.9 (d), 124.9 (d), 127.9 (d), 130.7 (d), 132.7 (s), 134.5 (d), 137.8 (s), 138.5 (d), 146.1 (s), 149.8 (d), 150.1 (s), 167.1 (s). Anal. Calcd for $C_{13}H_{10}ClN_3O_3$: C, 53.53; H, 3.46; N, 14.41. Found: C, 53.72; H, 3.35; N, 14.29.

3.5. General procedures for the preparation of compounds 5ab, 5bb and 13

A mixture of amide **4** or **12** (4 mmol), benzene (50 ml), powdered NaOH (640 mg, 16 mmol), anhydrous K_2CO_3 (553 mg, 4 mmol) and tetrabutylammonium hydrogen sulphate (68 mg, 0.2 mmol) was stirred at 80 °C for 1 h. 2-(Dimethylamino)ethyl chloride (538 mg, 5 mmol) for compound **5ab** and **5bb** or dimethyl sulphate (0.4 ml, 4 mmol) for compounds **13**, was then added to the stirred mass at 70–80 °C over a period of 20 min. The mixture was stirred at this temperature for 12 h, the inorganic salts were filtered off and the filtrate washed with 1 M HCl, water and then dried (Na_2SO_4). Concentration of the solvent furnished the product purified by crystallization.

3.5.1. *N*-(2-Iodo-phenyl)-*N*-(dimethylamino-ethyl)-2-nitro-benzamide (5ab). 98% Yield; mp 187–189 °C (pale yellow crystals from diisopropyl alchool); IR (nujol): ν 1657 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=2.30$ (6H, s), 2.75 (2H, overlapping), 3.38 (1H, m), 4.60 (1H, m), 6.92 (1H, ddd, $J=1.8$, 7.7, 7.7 Hz), 7.15 (1H, ddd, $J=1.5$, 7.3, 7.3 Hz), 7.30–7.40 (2H, overlapping), 7.45 (1H, ddd, $J=1.8$, 7.7, 7.7 Hz), 7.57 (1H, dd, $J=1.8$, 7.7 Hz), 7.81 (1H, dd, $J=1.1$, 7.7 Hz), 7.98 (1H, dd, $J=1.1$, 7.7 Hz); ^{13}C NMR ($CDCl_3$): $\delta=44.3$ (q), 44.8 (t), 54.4 (t), 100.1 (s), 124.7 (d), 127.7 (d), 129.8 (d), 129.9 (d), 130.5 (d), 130.9 (d), 132.0 (s), 134.2 (d), 140.8 (d), 143.1 (s), 145.9 (s), 167.4 (s). Anal. Calcd for $C_{17}H_{18}IN_3O_3$: C, 46.49; H, 4.13; N, 9.57. Found: C, 46.34; H, 4.01; N, 9.59.

3.5.2. *N*-(4-Chloro-2-iodo-phenyl)-*N*-(dimethylamino-ethyl)-2-nitro-benzamide (5bb). 77% Yield; pale yellow oil; IR (film): ν 1655 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=2.26$ (6H, s), 2.69 (2H, t, $J=6.8$ Hz), 3.28 (1H, dt, $J=14.2$, 6.8 Hz), 4.58 (1H, dt, $J=14.2$, 6.8 Hz), 7.08 (1H, dd, $J=1.7$, 8.3 Hz), 7.29 (1H, d, $J=8.3$ Hz), 7.39 (1H, dd, $J=7.3$, 7.5 Hz), 7.48 (1H, dd, $J=7.3$, 7.3 Hz), 7.54 (1H, d, $J=7.4$ Hz), 7.75 (1H, d, $J=1.7$ Hz), 7.98 (1H, d, $J=8.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=45.9$ (q), 47.1 (t), 55.9 (t), 100.6 (s), 124.8 (d), 127.8 (d), 129.9 (d), 130.5 (d), 131.7 (d), 133.0 (s), 134.2 (d), 135.1 (s), 139.7 (d), 143.1 (s), 146.1 (s), 166.8 (s). Anal. Calcd for $C_{17}H_{17}ClIN_3O_3$: C, 43.11; H, 3.62; N, 8.87. Found: C, 43.20; H, 3.45; N, 8.73.

3.5.3. 2-Chloro-*N*-methyl-*N*-(2-nitro-phenyl)-pyridine-3-carboxamide (13). 88% Yield; mp 108–110 °C (yellow crystals from Et_2O); IR (nujol): ν 1646 cm^{-1}; ^1H NMR ($CDCl_3$, mixture 3:2 of rotamers): major rotamer $\delta=3.43$ (3H, s), 7.05 (1H, dd, $J=4.9$, 7.6 Hz), 7.34–7.41 (1H, m), 7.47–7.59 (2H, overlapping), 7.74 (1H, dd, $J=7.6$, 7.6 Hz), 7.84 (1H, d, $J=8.0$ Hz), 8.20 (1H, d, $J=3.8$ Hz); minor rotamer $\delta=3.26$ (3H, s), 7.34–7.41 (1H, m), 7.47–7.59 (3H, overlapping), 7.83 (1H, dd, $J=7.6$, 7.6 Hz), 8.07 (1H, d, $J=8.0$ Hz), 8.47 (1H, d, $J=3.8$ Hz); ^{13}C NMR ($CDCl_3$): major rotamer $\delta=37.5$ (q), 122.6 (d), 126.6 (d), 130.1 (d), 131.1 (d), 132.4 (s), 134.9 (d), 136.5 (s), 136.9 (d), 146.1 (s), 147.3 (s), 150.7 (d), 166.0 (s); minor rotamer $\delta=39.8$ (q), 123.4 (d), 126.6 (d), 129.4 (d), 129.9 (d), 132.1 (s), 135.2 (d), 136.1 (s), 137.5 (d), 146.5 (s), 147.1 (s), 151.0 (d), 166.9 (s). Anal. Calcd for $C_{13}H_{10}ClN_3O_3$: C, 53.53; H, 3.46; N, 14.41. Found: C, 53.52; H, 3.62; N, 14.29.

3.6. General procedure for the preparation of compounds 6, 10 and 14

To a solution of compound **5**, **9** or **13** (4 mmol) in EtOH (10 ml) heated at 50 °C, 20% AcOH (5 ml) and Fe dust (30 mmol) were added with vigorous stirring. The mixture was heated to reflux for 5 h, then filtered and the solvent evaporated. The residue was taken up with AcOEt (30 ml) and the organic layer washed with 5% $NaHCO_3$, water, dried (Na_2SO_4) and evaporated.

3.6.1. 2-Amino-*N*-(2-iodo-phenyl)-*N*-methyl-benzamide (6aa). 96% Yield; pale yellow oil; IR (film): ν 1620, 3358, 3457 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.38$ (3H, s), 4.80 (2H, br s, absent after deuteriation), 6.36 (1H, d, $J=7.1$ Hz), 6.64 (1H, d, $J=8.8$ Hz), 6.80–7.27 (5H, overlapping), 7.85 (1H, d, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=37.9$ (q), 98.8 (s), 116.7 (d), 119.1 (s), 120.9 (d), 129.2 (d), 129.6 (d), 129.7 (d), 130.0 (d), 131.0 (d), 140.2 (d), 146.9 (s), 147.1 (s), 171.5 (s). Anal. Calcd for $C_{14}H_{13}IN_2O$: C, 47.75; H, 3.72; N, 7.95. Found: C, 47.89; H, 3.51; N, 8.13.

3.6.2. 2-Amino-*N*-(2-iodo-phenyl)-*N*-(dimethylamino-ethyl)-benzamide (6ab). 70% Yield; pale yellow oil; IR (film): ν 1647, 3354, 3457 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=2.36$ (6H, s), 2.75 (1H, m), 2.87 (1H, m), 3.37 (1H, m), 4.55 (2H, absent after deuteriation), 4.65 (1H, m), 6.89 (1H, dd, $J=7.6$, 7.6 Hz), 7.13 (1H, dd, $J=7.6$, 7.6 Hz), 7.32–7.38 (2H, overlapping), 7.46 (1H, dd, $J=7.6$, 7.6 Hz), 7.59 (1H, d, $J=7.6$ Hz), 7.79 (1H, d, $J=8.1$ Hz), 7.98 (1H, d, $J=8.1$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=45.8$ (q), 47.0 (t), 55.6 (t), 100.2 (s), 124.7 (d), 128.0 (d), 129.6 (d), 130.1 (d), 130.4 (d), 130.9 (d), 133.2 (s), 134.0 (d), 140.5 (d), 144.1 (s), 146.1 (s), 166.9 (s). Anal. Calcd for $C_{17}H_{20}IN_3O$: C, 49.89; H, 4.93; N, 10.27. Found: C, 49.73; H, 5.11; N, 10.06.

3.6.3. 2-Amino-*N*-(4-chloro-2-iodo-phenyl)-*N*-(dimethyl-amino-ethyl)-benzamide (6bb). 65% Yield; mp 88–90 °C dec. (cream crystals from Et_2O); IR (nujol): ν 1626, 3357, 3458 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=2.35$ (6H, s), 2.60 (2H, overlapping), 3.48 (1H, m), 4.22 (2H, br s, absent after deuteriation), 4.48 (1H, m), 6.37 (1H, br s), 6.61 (1H, d, $J=8.2$ Hz), 6.82 (1H, br s), 7.03 (1H, dd, $J=7.1$, 7.1 Hz), 7.26 (2H, overlapping), 7.81 (1H, s); ^{13}C NMR ($CDCl_3$): $\delta=45.2$ (q), 48.5 (t), 56.0 (t), 100.0 (s), 116.7 (d), 116.9 (d), 119.3 (s), 128.3 (d), 129.5 (d), 131.2 (d), 131.4 (d), 134.0 (s), 139.5 (d), 144.0 (s), 146.6 (s), 171.2 (s). Anal. Calcd for

$C_{17}H_{19}ClIN_3O$: C, 46.02; H, 4.32; N, 9.47. Found: C, 45.90; H, 4.39; N, 9.63.

3.6.4. 2-Amino-*N*-(4-Chloro-2-iodo-phenyl)-*N*-ethyl-benzamide (6bc). 98% Yield; mp 212–214 °C (white crystals from CH_2Cl_2–hexane); IR (nujol): ν 1618, 3358, 3456 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.21$ (3H, t, $J=7.0$ Hz), 3.48 (1H, m), 4.25 (1H, m), 4.57 (2H, br s, absent after deuteriation), 6.39 (1H, br s), 6.61 (1H, d, $J=7.1$ Hz), 6.78–7.28 (4H, overlapping), 7.84 (1H, s); ^{13}C NMR ($CDCl_3$): $\delta=12.8$ (q), 44.7 (t), 100.3 (s), 116.9 (d), 117.2 (d), 128.6 (d), 129.5 (s), 129.6 (d), 131.3 (d), 131.5 (d), 139.1 (s), 139.8 (d), 141.1 (s), 147.1 (s), 168.3 (s). Anal. Calcd for $C_{15}H_{14}ClIN_2O$: C, 44.97; H, 3.52; N, 6.99. Found: C, 45.11; H, 3.37; N, 6.94.

3.6.5. 2-Amino-5-chloro-*N*-(2-iodo-phenyl)-*N*-methyl-benzamide (6ca). 98% Yield; mp 128–130 °C (cream crystals from Et_2O); IR (nujol): ν 1628, 3355, 3416 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.36$ (3H, s), 4.53 (2H, br s, absent after deuteriation), 6.55 (1H, br s), 6.79–7.01 (3H, overlapping), 7.18 (1H, br s), 7.28 (1H, br s), 7.86 (1H, d, $J=7.5$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=38.9$ (q), 98.9 (s), 118.2 (d), 120.4 (s), 128.9 (d), 129.5 (d), 129.6 (d), 130.0 (d), 130.4 (s), 131.1 (d), 140.6 (d), 145.7 (s), 146.2 (s), 170.1 (s). Anal. Calcd for $C_{14}H_{12}ClIN_2O$: C, 43.49; H, 3.13; N, 7.25. Found: C, 43.55; H, 3.04; N, 7.05.

3.6.6. 2-Amino-5-chloro-*N*-ethyl-*N*-(2-iodo-phenyl)-benzamide (6cc). 66% Yield; pale yellow oil; IR (film): ν 1620, 3357, 3461 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.24$ (3H, t, $J=6.9$ Hz), 3.53 (1H, dq, $J=13.9$, 6.9 Hz), 4.16 (1H, dq, $J=13.9$, 6.9 Hz), 4.22 (2H, br s, absent after deuteriation), 6.61 (1H, d, $J=8.0$ Hz), 7.08–7.18 (2H, overlapping), 7.08–7.26 (3H, overlapping), 7.89 (1H, d, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=12.7$ (q), 44.9 (t), 100.0 (s), 118.9 (d), 121.9 (s), 122.7 (s), 123.6 (d), 128.6 (d), 129.6 (d), 129.9 (d), 131.0 (d), 140.6 (d), 142.9 (s), 144.0 (s), 169.3 (s). Anal. Calcd for $C_{15}H_{14}ClIN_2O$: C, 44.97; H, 3.52; N, 6.99. Found: C, 45.19; H, 3.75; N, 6.87.

3.6.7. 2-Amino-5-fluoro-*N*-(2-iodo-phenyl)-*N*-methyl-benzamide (6da). 76% Yield; mp 110–112 °C dec. (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1625, 3351, 3448 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.41$ (3H, s), 4.41 (2H, br s, absent after deuteriation), 6.58 (2H, br s), 6.73 (1H, br s), 6.95 (1H, br s), 7.17 (1H, br s), 7.24 (1H, br s), 7.86 (1H, d, $J=7.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=38.9$ (q), 98.8 (s), 115.1 (dd, $J_{C-F}=23.9$ Hz), 118.3 (dd, $J_{C-F}=22.8$ Hz), 118.5 (dd, $J_{C-F}=8.1$ Hz), 120.4 (s), 129.6 (d), 129.8 (d), 130.0 (d), 140.6 (d), 143.1 (s), 143.9 (s), 154.4 (d, $J_{C-F}=233.8$ Hz), 170.3 (s). Anal. Calcd for $C_{14}H_{12}FIN_2O$: C, 45.43; H, 3.27; N, 7.57. Found: C, 45.39; H, 3.41; N, 7.38.

3.6.8. 2-Amino-5-fluoro-*N*-(4-chloro-2-iodo-phenyl)-*N*-methyl-benzamide (6ea). 65% Yield; mp 125–127 °C (cream crystals from Et_2O); IR (nujol): ν 1628, 3359, 3454 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.32$ (3H, s), 4.31 (2H, br s, absent after deuteriation), 6.58 (2H, overlapping), 6.77 (1H, br s), 7.10–7.25 (2H, overlapping), 7.84 (1H, br s); ^{13}C NMR ($CDCl_3$): $\delta=37.2$ (q), 99.0 (s), 114.8 (dd, $J_{C-F}=23.7$ Hz), 118.2 (dd, $J_{C-F}=7.9$ Hz), 118.6 (dd, $J_{C-F}=22.4$ Hz), 120.0 (s), 130.0 (d), 130.2 (d), 134.4 (s), 139.8 (d), 142.8 (s), 143.2 (s), 154.8 (d, $J_{C-F}=241.2$ Hz), 170.3 (s). Anal. Calcd for $C_{14}H_{11}ClFIN_2O$: C, 41.56; H, 2.74; N, 6.92. Found: C, 41.54; H, 2.62; N, 6.87.

3.6.9. 2-Amino-*N*-(2-chloro-pyridin-3-yl)-*N*-methyl-benzamide (10). 98% Yield; mp 189–191 °C dec. (pale yellow crystals from CH_2Cl_2–hexane); IR (nujol): ν 1647, 3355, 3441 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.40$ (3H, s), 4.40 (2H, br s, absent after deuteriation), 6.40 (1H, dd, $J=7.3$, 7.3 Hz), 6.63 (1H, d, $J=8.1$ Hz), 6.82 (1H, d, $J=7.3$ Hz), 7.01 (1H, dd, $J=7.3$, 7.3 Hz), 7.15 (1H, m), 7.45 (1H, dd, $J=6.6$ Hz), 8.23 (1H, dd, $J=1.5$, 4.4 Hz); ^{13}C NMR ($CDCl_3$): $\delta=39.2$ (q), 117.1 (d), 120.5 (s), 123.3 (d), 123.5 (d), 127.9 (d), 133.4 (d), 135.5 (d), 139.5 (s), 142.3 (d), 145.9 (s), 146.1 (s), 163.1 (s). Anal. Calcd for $C_{13}H_{12}ClN_3O$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.45; H, 4.71; N, 16.08.

3.6.10. *N*-(2-Amino-phenyl)-2-chloro-*N*-methyl-pyridine-3-carboxamide (14). 92% Yield; mp 138–140 °C (pale yellow needles from Et_2O); IR (nujol): ν 1647, 3357, 3443 cm^{-1}; ^1H NMR (DMSO): $\delta=3.28$ (3H, s), 4.60 (2H, br s, absent after deuteriation), 6.37 (1H, br s), 6.57 (1H, br s), 6.84 (1H, br s), 6.94–6.99 (2H, overlapping), 7.68 (1H, br s), 8.11 (1H, br s); ^{13}C NMR (DMSO): $\delta=35.4$ (q), 116.5 (d), 117.8 (d), 122.3 (d), 127.8 (s), 128.4 (d), 129.9 (d), 133.4 (s), 136.3 (d), 143.9 (s), 147.4 (s), 149.8 (d), 167.2 (s). Anal. Calcd for $C_{13}H_{12}ClN_3O$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.76; H, 4.47; N, 15.89.

3.7. General procedure for cyclization reaction of *N*-alkyl-2-amino-benzamides to give 2 and 7

A mixture of compound **6** (1 mmol), $Pd(OAc)_2$ (2 mol%), Cs_2CO_3 (2 mmol), BINAP (4 mol%) in anhydrous toluene was heated at 110 °C for 24 h. After cooling, water (10 ml) and Et_2O (10 ml) were added and the organic phase was separated, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (eluent from CH_2Cl_2 to CH_2Cl_2–MeOH 10:1).

3.7.1. 7-Chloro-10-(2-dimethylamino-ethyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (2).[3] 98% Yield; mp 163–165 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1613, 3272 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=2.31$ (6H, s), 2.67 (2H, t, $J=7.0$ Hz), 4.15 (2H, t, $J=7.0$ Hz), 5.51 (1H, br s, absent after deuteriation), 6.82 (1H, d, $J=7.9$ Hz), 6.98 (1H, s), 7.01–7.12 (2H, overlapping), 7.26–7.34 (2H, overlapping), 7.82 (1H, d, $J=7.9$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=46.0$ (q), 49.3 (t), 57.6 (t), 119.1 (d), 120.9 (d), 123.5 (d), 124.8 (d), 125.7 (s), 125.8 (d), 130.4 (s), 132.9 (d), 133.0 (d), 133.5 (s), 146.1 (s), 150.5 (s), 168.7 (s). Anal. Calcd for $C_{17}H_{18}ClN_3O$: C, 64.66; H, 5.75; N, 13.31. Found: C, 64.80; H, 5.66; N, 13.18.

3.7.2. 10-Methyl-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (7aa).[10a] 63% Yield; mp 205–207 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1616, 3306 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.56$ (3H, s), 5.38 (1H, br s, absent after deuteriation), 6.81 (1H, d, $J=8.0$ Hz), 6.93 (1H, m), 7.06 (1H, dd, $J=2.6$, 7.4 Hz), 7.07–7.26 (3H, overlapping), 7.34 (1H, dd, $J=1.8$, 7.4 Hz), 7.91 (1H, dd, $J=1.8$, 7.6 Hz); ^{13}C NMR ($CDCl_3$): $\delta=38.6$ (q), 118.7 (d),

120.5 (d), 122.8 (d), 123.5 (d), 124.5 (d), 125.0 (s), 125.9 (d), 132.8 (d), 133.1 (d), 135.8 (s), 143.5 (s), 151.0 (s), 168.9 (s). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.03; H, 5.52; N, 12.57.

3.7.3. 10-(2-Dimethylamino-ethyl)-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (7ab).[2] 76% Yield; mp 113–115 °C (cream crystals from Et_2O); IR (nujol): ν 1644, 3373 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=2.25$ (6H, s), 2.72 (2H, overlapping), 3.28 (1H, m), 4.60 (1H, m), 5.20 (1H, br s, absent after deuteriation), 6.84 (1H, ddd, $J=1.5$, 7.7, 7.7 Hz), 7.09 (1H, ddd, $J=1.5$, 7.7, 7.7 Hz), 7.27–7.35 (2H, overlapping), 7.43 (1H, ddd, $J=1.1$, 7.3, 8.1 Hz), 7.57 (1H, dd, $J=1.1$, 7.7 Hz), 7.76 (1H, dd, $J=1.1$, 8.1 Hz), 7.95 (1H, d, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=41.3$ (t), 45.8 (q), 55.5 (t), 115.7 (d), 122.2 (d), 123.3 (d), 124.3 (d), 124.5 (d), 124.8 (d), 125.4 (s), 131.6 (d), 132.8 (d), 137.5 (s), 142.6 (s), 151.3 (s), 163.6 (s). Anal. Calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.59; H, 6.73; N, 15.08.

3.7.4. 7-Chloro-10-ethyl-5,10-dihydro-dibenzo[*b*,*e*][1,4]-diazepin-11-one (7bc). 84% Yield; mp 180 °C dec. (cream crystals from Et_2O); IR (nujol): ν 1598, 3360 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.31$ (3H, t, $J=6.9$ Hz), 4.09 (2H, q, $J=6.9$ Hz), 5.45 (1H, br s, absent after deuteriation), 6.80 (1H, d, $J=7.4$ Hz), 6.98 (1H, s), 7.03–7.14 (2H, overlapping), 7.18 (1H, d, $J=8.0$ Hz), 7.29 (1H, d, $J=7.4$ Hz), 7.84 (1H, d, $J=6.5$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=14.2$ (q), 45.8 (t), 118.9 (d), 120.9 (d), 123.5 (d), 124.6 (d), 125.4 (d) 125.9 (s), 131.2 (s), 132.8 (d), 133.1 (d), 139.3 (s), 146.2 (s), 150.4 (s), 166.4 (s). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 65.91; H, 4.89; N, 10.31.

3.7.5. 2-Chloro-10-methyl-5,10-dihydro-dibenzo[*b*,*e*]-[1,4]diazepin-11-one (7ca). 77% Yield; mp 205–206 °C (cream crystals from Et_2O); IR (nujol): ν 1617, 3290 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.55$ (3H, s), 5.51 (1H, br s, absent after deuteriation), 6.77 (1H, d, $J=8.4$ Hz), 6.93 (1H, dd, $J=1.3$, 7.3 Hz), 7.09 (1H, ddd, $J=1.3$, 7.3, 7.9 Hz), 7.13 (1H, ddd, $J=1.3$, 7.3, 7.3 Hz), 7.19 (1H, dd, $J=1.3$, 7.9 Hz), 7.25 (1H, dd, $J=2.4$, 8.4 Hz), 7.86 (1H, d, $J=2.4$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=38.6$ (q), 120.3 (d), 120.7 (d), 123.8 (d), 125.0 (d), 126.3 (d), 128.2 (s), 132.7 (d), 132.8 (d), 135.6 (s), 135.7 (s), 143.2 (s), 149.6 (s), 167.8 (s). Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 65.11; H, 4.21; N, 10.62.

3.7.6. 2-Chloro-10-ethyl-5,10-dihydro-dibenzo[*b*,*e*][1,4]-diazepin-11-one (7cc). 98% Yield; mp 225–228 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1613, 3275 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=1.31$ (3H, t, $J=6.9$ Hz), 4.10 (2H, q, $J=6.9$ Hz), 5.48 (1H, br s, absent after deuteriation), 6.72 (1H, d, $J=8.8$ Hz), 6.81 (1H, s), 6.91 (1H, d, $J=8.2$ Hz), 6.96–7.14 (2H, overlapping), 7.19 (1H, d, $J=8.2$ Hz), 7.83 (1H, dd, $J=7.4$, 8.8 Hz); ^{13}C NMR ($CDCl_3$): $\delta=14.2$ (q), 45.8 (t), 120.2 (d), 121.0 (d), 124.4 (d), 124.9 (d), 126.5 (d), 132.3 (d), 132.6 (d), 132.9 (s), 133.7 (s), 143.4 (s), 144.8 (s), 149.7 (s), 167.4 (s). Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 65.98; H, 4.97; N, 10.19.

3.7.7. 2-Fluoro-10-methyl-5,10-dihydro-dibenzo[*b*,*e*]-[1,4]diazepin-11-one (7da). 63% Yield; mp 175–177 °C dec. (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1619, 3310 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.55$ (3H, s), 5.36 (1H, br s, absent after deuteriation), 6.78 (1H, dd, $J=4.4$, 8.7 Hz), 6.93 (1H, dd, $J=1.5$, 7.5 Hz), 7.03 (1H, ddd, $J=3.0$, 8.4, 9.0 Hz), 7.09 (1H, ddd, $J=1.4$, 7.3, 7.3 Hz), 7.13 (1H, ddd, $J=1.4$, 7.3, 7.3 Hz), 7.21 (1H, dd, $J=1.5$, 7.2 Hz), 7.59 (1H, dd, $J=3.0$, 9.0 Hz); ^{13}C NMR ($CDCl_3$): $\delta=38.6$ (q), 119.1 (dd, $J_{C-F}=23.9$ Hz), 120.0 (dd, $J_{C-F}=23.1$ Hz), 120.3 (dd, $J_{C-F}=7.2$ Hz), 120.7 (d), 123.7 (d), 124.8 (d), 126.4 (d), 135.8 (s), 143.8 (s), 143.9 (s), 147.3 (s), 158.7 (d, $J_{C-F}=239.5$ Hz), 167.9 (s). Anal. Calcd for $C_{14}H_{11}FN_2O$: C, 69.41; H, 4.58; N, 11.56. Found: C, 69.24; H, 4.77; N, 11.65.

3.7.8. 2-Fluoro-7-chloro-10-methyl-5,10-dihydro-dibenzo[*b*,*e*][1,4]diazepin-11-one (7ea). 75% Yield; mp 205–208 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1621, 3304 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.53$ (3H, s), 5.42 (1H, br s, absent after deuteriation), 6.75 (1H, dd, $J=4.4$, 8.8 Hz), 6.93 (1H, d, $J=1.8$ Hz), 7.04 (1H, ddd, $J=3.0$, 8.5, 9.0 Hz), 7.08–7.12 (2H, overlapping), 7.58 (1H, dd, $J=3.0$, 9.2 Hz); ^{13}C NMR ($CDCl_3$): $\delta=38.7$ (q), 119.2 (dd, $J_{C-F}=24.0$ Hz), 120.2 (dd, $J_{C-F}=24.0$ Hz), 120.4 (dd, $J_{C-F}=7.8$ Hz), 120.7 (d), 124.7 (d), 124.8 (d), 126.4 (s), 131.3 (s), 134.5 (s), 144.7 (s), 146.4 (s), 158.9 (d, $J_{C-F}=240.5$ Hz), 167.5 (s). Anal. Calcd for $C_{14}H_{10}ClFN_2O$: C, 60.77; H, 3.64; N, 10.12. Found: C, 60.73; H, 3.81; N, 9.97.

3.8. Synthesis of compounds 11 and 15

The reaction was performed as described for compound **7**, using *t*-BuOK (2 mmol) as base and heating at reflux for 48 h.

3.8.1. 5-Methyl-5,11-dihydro-benzo[*e*]pyrido[3,2-*b*][1,4]diazepin-6-one (11).[17] 55% Yield; mp 208–210 °C dec. (pale yellow crystals from CH_2Cl_2–hexane); IR (nujol): ν 1620, 3289 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.51$ (3H, s), 6.75 (1H, br s, absent after deuteriation), 6.87 (1H, d, $J=8.0$ Hz), 7.02–7.08 (2H, overlapping), 7.33 (1H, dd, $J=7.5$, 7.5 Hz), 7.46 (1H, d, $J=7.8$ Hz), 7.92 (1H, d, $J=7.8$ Hz), 8.02 (1H, d, $J=4.4$ Hz);^{13}C NMR ($CDCl_3$): $\delta=38.5$ (q), 119.5 (d), 119.9 (d), 123.1 (d), 124.1 (s), 130.1 (s), 131.4 (d), 133.3 (d), 133.4 (d), 144.0 (d), 148.1 (s), 154.9 (s), 168.5 (s). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.43; H, 5.07; N, 18.65.

3.8.2. 6-Methyl-6,11-dihydro-benzo[*b*]pyrido[2,3-*e*][1,4]diazepin-5-one (15).[10d] 42% Yield; mp 167–169 °C (cream crystals from CH_2Cl_2–hexane); IR (nujol): ν 1661, 3046 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=3.74$ (3H, s), 4.60 (1H, br s, absent after deuteriation), 7.01 (1H, dd, $J=5.2$, 7.1 Hz), 7.29–7.45 (3H, overlapping), 7.84 (1H, d, $J=7.9$ Hz), 7.94 (1H, d, $J=7.1$ Hz), 8.31 (1H, d, $J=3.3$ Hz); ^{13}C NMR ($CDCl_3$): $\delta=29.0$ (q), 109.9 (d), 115.7 (s), 116.8 (d), 120.0 (d), 122.6 (d), 123.1 (d), 134.4 (s), 136.4 (s), 141.9 (d), 143.1 (s), 149.0 (d), 161.3 (s). Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.26; H, 5.04; N, 18.45.

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References and notes

1. (a) Vida, J. A. In *Medicinal Chemistry Part III*; Wolf, M. V., Burger, A., Eds.; Wiley: New York, 1981. (b) Landquist, J. K. In Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 1, Ch. 1/06. (c) Sharp, J. T. In Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 7, Ch. 5/18. (d) Baldessarini, R. J. In *The Pharmacologic Basis of Therapeutics*; Gilman, A. G., Goodman, L. S., Ralland, T. W., Murad, F., Eds.; Macmillan: New York, 1985; Vol. 1, pp 391–413.
2. Lehner, H.; Gauch, R.; Michaelis, W. *Arzneim.-Forsch.* **1967**, *17*, 185–189.
3. Hunziker, F.; Lauener, H.; Smutz, J. *Arzneim.-Forsch.* **1963**, *13*, 324–328.
4. (a) Joergensen, T. K.; Andersen, K. E.; Andersen, H. S.; Hohlweg, R.; Madsen, P.; Olsen, U. B. (Novo Nordisk A/s, Den.) Patent No. WO 9631497, 1996; *Chem. Abstr.* **1997**, *126*, 8146. (b) Ohkuma, H.; Kobaru, S. (Bristol-Myers-Squibb Company, USA) U.S. Patent 94-249518, 1996; *Chem. Abstr.* **1996**, *125*, 140671.
5. Grigorseva, E. K.; Kaverina, N. V.; Likhosherstov, A. M.; Lyskovtsev, V. V.; Skoldinov, A. P.; Stavrovskaya, A. V.; Tolmacheva, E. A.; Chichkanov, G. G.; Barch, R.; et al. (Nauchno-Issiedovateiski Institut Farmakologi RAMN, Russia) Patent No. RU 2026862, 1995; *Chem. Abstr.* **1996**, *124*, 106663.
6. Yoshino, H.; Ueda, N.; Niijma, J.; Haneda, T.; Kotake, Y.; Yoshimatsu, K.; Watanabe, T.; Nagasu, T.; Tsukahara, N.; et al. (Eisai Co., Ldt., Japan) Patent No. WO 9503279, 1995; *Chem. Abstr.* **1995**, *122*, 314588.
7. Squires, R. F.; Saederup, E. *Neurochem. Res.* **1993**, *18*, 787–793.
8. Schmidt, G. (Boehringer Ingelheim G.m.h.H.) Patent No. U.S. 3,406,168, 1968; *Chem. Abstr.* **1969**, *70*, 87866d.
9. (a) Walser, A.; Fryer, R. I. In *Bicyclic Diazepines*; Wiley: New York, 1991; Ch. VII. (b) Beccalli, E. M.; Broggini, G.; Paladino, G.; Pilati, T.; Pontremoli, G. *Tetrahedron: Asymmetry* **2004**, *15*, 687–692. (c) Sugimori, T.; Okawa, T.; Eguchi, S.; Kakehi, A.; Yashima, E.; Okamoto, Y. *Tetrahedron* **1998**, *54*, 7997–8008. (d) Broggini, G.; Molteni, G.; Terraneo, A.; Zecchi, G. *Tetrahedron* **1999**, *55*, 14803–14806. (e) Keenan, R. M.; Callahan, J. F.; Samanen, J. M.; Bondinell, W. E.; Calvo, R. R.; Chen, L.; DeBrosse, C.; Eggleston, D. S.; Haltiwanger, R. C.; Hwang, S. M.; Jakas, D. R.; Ku, T. W.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M. F.; Southhall, L. S.; Uzinskas, I.; Vasko-Moser, J. A.; Venslavsky, J. W.; Wong, A. S.; Huffman, W. F. *J. Med. Chem.* **1999**, *42*, 545–559. (f) Matsunaga, N.; Harada, H.; Aoyama, T.; Shioiri, T. *Heterocycles* **1992**, *33*, 235–255. (g) Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *Org. Lett.* **2002**, *4*, 139–141. (h) Wang, T.; Lui, A. S.; Cloudsdale, I. S. *Org. Lett.* **1999**, *1*, 1835–1837. (i) Ammadi, F.; Boukhris, S.; Souizi, A.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 6517–6518. (j) Abrous, L.; Hynes, J., Jr.; Friederich, S. R.; Smith, A. B., III; Hirschmann, R. *Org. Lett.* **2001**, *3*, 1089–1092. (k) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539–3546. (l) Matthews, J. M.; Dyatkin, A. B.; Evangelisto, M.; Gauthier, D. A.; Hecker, L. R.; Hoekstra, W. J.; Liu, F.; Poulter, B.; Sorgi, K. L.; Maryanoff, B. E. *Tetrahedron: Asymmetry* **2004**, *15*, 1259–1267. (m) Hemming, K.; Loukou, C. *Tetrahedron* **2004**, *60*, 3349–3357. (n) Herrero, S.; García-López, M. T.; Herranz, R. *J. Org. Chem.* **2003**, *68*, 4582–4585.
10. (a) Hanze, A. R.; Strube, R. E.; Greig, M. E. *J. Med. Chem.* **1963**, *6*, 767–771. (b) Blanche, Y.; Hichour, M.; Di Blasi, G.; Chezal, J.-M.; Viols, H.; Chavignon, O.; Teulade, J.-C.; Chapat, J.-P. *Heterocycles* **1999**, *51*, 1003–1014. (c) Engel, W. W.; Eberlein, W. J.; Mihm, G.; Hammer, R.; Trummlitz, G. *J. Med. Chem.* **1989**, *32*, 1718–1724. (d) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fucha, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. *J. Med. Chem.* **1991**, *34*, 2231–2241. (e) Liégeois, J.-F.F.; Bruhwyler, J.; Damas, J.; Phuong Nguyen, T.; Chleide, E. M. G.; Mercier, M. G. A.; Rogister, F. A.; Delarge, J. E. *J. Med. Chem.* **1993**, *36*, 2107–2114. (f) Di Braccio, M.; Roma, G.; Ermili, A. *Farmaco* **1985**, *40*, 391–403. (g) Vanden Eynde, J. J.; Mayence, A.; Maquestiau, A.; Anders, E. *Bull. Soc. Chim. Belg.* **1992**, *101*, 801–806. (h) Kalyanam, N.; Likhate, M. A. *Res. Ind. J. Chem., Sect. B* **1988**, *27B*, 154–755. (i) Hirobe, M.; Ozawa, T. *Tetrahedron Lett.* **1971**, *47*, 4493–4494. (j) Hunziker, F.; Kuenzel, F.; Schindler, O.; Schmutz, J. *Helv. Chim. Acta* **1964**, *47*, 1163–1172.
11. Beccalli, E. M.; Broggini, G.; Paladino, G.; Penoni, A.; Zoni, C. *J. Org. Chem.* **2004**, 5627–5630.
12. (a) Beccalli, E. M.; Broggini, G.; Marchesini, A.; Rossi, E. *Tetrahedron* **2002**, *58*, 6673–6678. (b) Beccalli, E. M.; Broggini, G. *Tetrahedron Lett.* **2003**, *44*, 1919–1921. (c) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Zoni, C. *J. Org. Chem.* **2003**, *68*, 7625–7628.
13. Meshram, H. M.; Reddy, G. S.; Reddy, M. M.; Yadav, J. S. *Tetrahedron Lett.* **1998**, *39*, 4103–4106.
14. Ayyangar, N. R.; Choudhary, A. R.; Kalkote, U. R.; Natu, A. A. *Synth. Commun.* **1988**, *18*, 2011–2016.
15. Satzinger, G.; Herrmann, M. Patent No. Ger. Offen. 2012094; *Chem. Abstr.* **1972**, *76*, 3908g.
16. Flouzat, C.; Guillaumet, G. *Synthesis* **1990**, *1*, 64–66.
17. Schmidt, G. Patent No. Ger. 1204680; *Chem. Abstr.* **1966**, *64*, 3578a.

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Solvation-dependent diastereofacial selectivity: addition of lithioacetonitrile to 2-phenyl propanal

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Abstract—Diastereofacial selectivity in the addition of lithioacetonitrile to 2-phenyl propanal is temperature and solvent-dependent. Each solvent studied (benzene, toluene, *n*-hexane, cyclohexane, methylcyclohexane, THF, and diethyl ether) shows a different Eyring plot of ln(*anti*/*syn*) versus $1/T$ with specific differential activation parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$, and discloses the presence of inversion temperatures (T_{inv}s). We demonstrated that the opposite temperature behaviour of the diastereomeric ratio (dr) observed for *n*-hexane and methylcyclohexane does not depend on the base (*n*-BuLi, LDA and LiHMDS) used to generate the anion, but is exclusively due to the reaction solvent. A 5 mol% of an amine in *n*-hexane and methylcyclohexane deeply affects the *anti*/*syn* ratio, the differential activation parameters, and the T_{inv} values. For *n*-hexane we were able to connect the inversion temperature of the pure solvent and of the Bu_3N-mixture with dynamic solvation phenomena revealed by VT ^{13}C NMR measurements.
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1. Introduction

Nitrile-stabilized carbanions are important synthetic intermediates and several reactions with different electrophiles document their wide range of applications.[1] Among these reactions, the addition of lithiated nitriles to carbonyls, an aldol-like process, is a very useful way to simultaneously construct two stereocenters and install a latent amino functionality. In particular, with aldehydes the reaction products are β-hydroxy nitriles, which can be easily transformed into γ-aminoalcohols, useful synthetic building blocks and a common structural motif in antidepressant drugs.[2]

Since the studies of Trost[3] on the addition of lithiated acetonitrile and propionitrile to cyclohexanones, much attention has been focused on simple- and facial diastereoselectivity of this addition that can be carried out with high stereocontrol.[4] However, very little attention was paid to the solvent effect on the stereochemical outcome of this aldol-like process, despite the fact that a solvent may affect the preferential formation of one stereoisomer over the others. It has already been observed that the reaction solvent deeply influenced the stereoselectivity of nitrile anion cyclizations,[5] and an interesting example of a solvent induced reversion of enantioselectivity in asymmetric lithioacetonitrile addition to benzaldehyde was recently reported.[6]

Solvent effects are closely related to the nature and the extent of solute–solvent interactions locally developed in the microenvironment of the solute molecules; these solute–solvent interactions are able to differently modulate the free activation energies which lead to two different stereoisomers thus exerting a stereospecific solvation control on enantio- and diastereoselectivity.[7]

As part of our ongoing interest in solvent effects on stereoselectivity,[8] we report here the effects of temperature and solvent on the nucleophilic addition of lithioacetonitrile to 2-phenyl propanal. In particular, we studied the diastereofacial selectivity of this process in several different reaction solvents, such as ethers and hydrocarbons, and by the use of different bases generating the anion, discovered the presence of temperature-dependent dynamic solvent effects (Scheme 1).

2. Results and discussion

The stereoselectivity, S, of an asymmetric reaction can be defined as the ratio of the overall rate constants k and k'

Keywords: Solvent effect; Temperature effect; Acetonitrile anion; Aldehyde; Diastereoselectivity.
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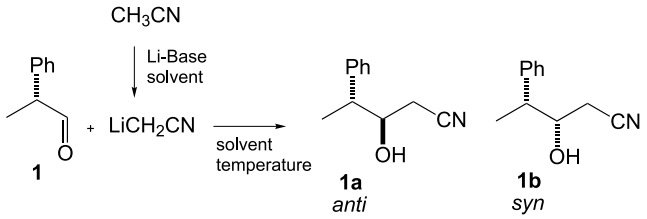


Scheme 1.

which lead to two different stereoisomers. S can be then connected to the differential free energy of activation $\Delta\Delta G^{\neq}$ through the modified Eyring equation (Eq. 1).[9] The usefulness of Eq. 1 relies on the evaluation of the differential activation parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ from temperature-dependent measurements of stereoselectivity. In the case of kinetically controlled processes, the stereoselectivity corresponds to the enantiomeric or diastereomeric ratio.

$$\ln S = \ln(k/k') = -\Delta\Delta G^{\neq}/RT$$

$$= -\Delta\Delta H^{\neq}/RT + \Delta\Delta S^{\neq}/R \quad (1)$$

Eq. 1 shows a linear correlation of the logarithm of selectivity versus $1/T$ but there are many experimental results that feature non-linear behaviour. In these cases, the corresponding Eyring plot of $\ln(k/k')$ versus $1/T$ generally consists of two linear regions intersecting at a point defining a temperature called the inversion temperature (T_{inv}).[10]

In previous papers, we demonstrated that the presence of a T_{inv} in temperature-dependent studies of enantio- and diastereoselectivity depends on dynamic solvation effects.[11] In our interpretation, an Eyring plot featuring a T_{inv} is the result of two intersecting linear trends produced by two different solvation clusters. These solute–solvent clusters are the real reacting species in solution and they have specific and different thermodynamic properties and hence different stereoselectivities.

The dynamic solvent effects have been confirmed by temperature-dependent studies of the ^{13}C NMR, CD and UV spectra of some solvated aldehydes in the absence of any reaction, revealing the presence of peculiar temperatures T_{NMR}, T_{CD}, and T_{UV}, whose values are identical and match with experimentally found T_{inv} and thus supporting the solvent-dependent substrate-related nature of T_{inv}.[12]

We report here a study on the diastereoselective addition of lithioacetonitrile (preformed by the use of different bases) to 2-phenyl propanal and in different reaction solvents, chosen among hydrocarbons and ethers (benzene, toluene, *n*-hexane, cyclohexane, methylcyclohexane, THF, and diethyl ether). The lithioacetonitrile (1 mmol) was generated at −78 °C by addition of acetonitrile to lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide (LiHMDS) or *n*-BuLi in 10 mL of the designed solvent; after 30 min, the anion was warmed to the operative temperature, kept at this temperature and then aldehyde **1** (1 mmol) was added. The reaction was repeated at different temperatures over the range permitted by the boiling and melting point of the solvent. Reactions proceeded smoothly in all solvents examined to give *anti* (**1a**) and *syn* (**1b**) 1,2-hydroxy nitriles. The diastereomeric *anti*/*syn* ratio within the crude reaction mixture was determined in each experiment by GC analysis with an average standard deviation less than 2% (see Section 4). The *anti* and *syn* configurations were determined by NMR analysis, by comparison with known products.[13] We took into account the possible reversibility of the reaction. To test for the presence of equilibration phenomena we followed the variation of the diastereomeric ratio for a long reaction time (2 h), but the dr remained constant. This result established that the diastereoselectivity is kinetically controlled and the stereoselectivity S can be calculated as the ratio *anti*/*syn*.

Data of ln(*anti*/*syn*) versus $1/T$ were then analysed by least-squares fitting to Eq. 1 to obtain linear correlations. For each data set we applied a residual analysis to evaluate the number of linear trends and to ascertain the presence of the inversion temperature, and we calculated the differential activation enthalpy and entropy ($\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$) for each reaction solvent (Table 1) corresponding to $\Delta\Delta H^{\neq} = \Delta H^{\neq}_{anti} - \Delta H^{\neq}_{syn}$, and $\Delta\Delta S^{\neq} = \Delta S^{\neq}_{anti} - \Delta S^{\neq}_{syn}$.

It is useful to remember that the enthalpic and/or entropic preference for one diastereoisomer over the other could be evaluated from the signs of the differential activation parameters. In particular, a negative $\Delta\Delta H^{\neq}$ derives from a $\Delta H^{\neq}_{syn} > \Delta H^{\neq}_{anti}$ and there is then a lower activation barrier in the formation of the *anti* diastereoisomer, that is to say, *anti* diastereoisomer is preferred by enthalpy. The opposite applies for $\Delta\Delta H^{\neq} > 0$: the enthalpy favours the *syn* diastereoisomer. Regarding the entropy, if it is assumed that an addition reaction is accompanied by a loss of activation entropy, a $\Delta\Delta S^{\neq} < 0$ derives from $|\Delta S^{\neq}_{anti}| > |\Delta S^{\neq}_{syn}|$: this means that the entropic loss in the formation of the *anti* diastereoisomer is larger than that of the *syn* one, so the entropy favours the formation of the *syn* stereoisomer. The opposite holds for $\Delta\Delta S^{\neq} > 0$: the entropy now favours the *anti* diastereoisomer.

Plots in Figure 1 refer to the experimental data of ln(*anti*/*syn*) versus $1/T$ in the reaction of lithioacetonitrile obtained with LDA and racemic 2-phenylpropanal in THF and diethylether (Fig. 1a), cyclohexane and methylcyclohexane (Fig. 1b), toluene and benzene (Fig. 1c).

In all solvents, at all temperature values, we obtained a predominance of the *anti* diastereoisomer **1a**, the highest diastereomeric ratio was exhibited at low T in THF ($T = -90$ °C *anti*/*syn* = 81:19). Each solvent gives a specific Eyring plot of diastereoselectivity, characterized by different values of slopes and intercepts, that is to say different activation parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ (Table 1). Moreover, all solvents showed specific inversion temperatures (T_{inv}), except benzene, but this may be due to a short temperature range of liquidity because of its high melting point. Cyclohexane and methylcyclohexane show very similar thermodynamic parameters but the latter offers a wider range of temperature to explore; the same holds for the benzene–toluene couple at high T.

Table 1. Differential activation parameters and inversion temperatures (T_{inv}) for the addition of $LiCH_2CN$ to 2-phenyl propanal

Entries	Solvent	Base	T_{inv} [°C]	$T>T_{inv}$		$T<T_{inv}$	
				$\Delta\Delta H^{\neq}$ (kcal/mol)	$\Delta\Delta S^{\neq}$ (cal/mol K)	$\Delta\Delta H^{\neq}$ (kcal/mol)	$\Delta\Delta S^{\neq}$ (cal/mol K)
1	THF	LDA	−18	−0.15±0.03	1.1±0.1	−0.83±0.03	−1.6±0.2
2	Et_2O	LDA	−64	−0.07±0.04	1.5±0.2	−0.37±0.03	0.0±0.2
3	Cyclohexane	LDA	+37	0.3±0.1	2.3±0.3	−0.9±0.1	−1.6±0.3
4	MeCy	LDA	−39	0.03±0.06	1.7±0.2	−1.20±0.02	−3.6±0.1
5	MeCy	LiHMDS	−39	0.05±0.01	1.7±0.1	−1.05±0.04	−3.0±0.2
6	MeCy	*n*-BuLi	−42	0.04±0.02	1.7±0.1	−1.03±0.03	−2.9±0.1
7	MeCy/Bu_3N	*n*-BuLi	−9	−0.19±0.02	0.6±0.1	−0.35±0.02	0.0±0.1
8	Benzene	LDA	—	−0.05±0.03	1.2±0.1	—	—
9	Toluene	LDA	+37	−0.04±0.04	1.3±0.2	−0.27±0.01	0.5±0.1
10	*n*-Hexane	LiHMDS	−20	−0.68±0.03	−0.8±0.1	0.01±0.03	2.0±0.1
11	*n*-Hexane	*n*-BuLi	−25	−0.5±0.1	−0.1±0.3	0.0±0.1	2.0±0.2
12	*n*-Hexane/Bu_3N	*n*-BuLi	−13	0.3±0.1	2.6±0.3	−0.68±0.04	−1.2±0.2

As clearly shown in the plots, T_{inv} constitutes a break point leading to two sets of activation parameters: one for $T>T_{inv}$ and one for $T<T_{inv}$ (Table 1). At temperatures higher than T_{inv}, all solvents present flattened plots with very similar diastereomeric ratios. This behaviour, a dr scarcely dependent on temperature, results from a predominant contribution of the differential entropy of activation to the stereoselectivity, especially in this reaction where little differential activation enthalpies occurred in the high temperature region (Table 1). At temperatures lower than T_{inv}, all solvents present differentiated plots with a significant enthalpic contribution to the diastereoselectivity.

Quite unexpected was the behaviour of *n*-hexane as reaction solvent. On exploring the addition of the acetonitrile anion obtained using LDA in *n*-hexane, we observed the formation of the reduced alcohol **2** (Scheme 2) and not of the hydroxy nitriles **1a** and **1b**. This side-reaction could derive from reducing properties of lithium diisopropylamide via a single electron transfer mechanism as already reported in the literature.[14]

On changing the base, using LiHMDS, the reaction in *n*-hexane proceeded smoothly to give the addition products **1a** and **1b**, thus allowing temperature-dependent measurements of the *anti*/*syn* ratio as reported in Figure 1d.

However, *n*-hexane behaves differently from the other solvents studied because it shows a flattened plot in the low temperature region, where the $\Delta\Delta S^{\neq}$ is the sole factor controlling stereoselectivity. In contrast, at $T>T_{inv}$ the diastereofacial selectivity drops down with an increase of the temperature. This arises from the equal negative signs of $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ which act in opposition: the negative

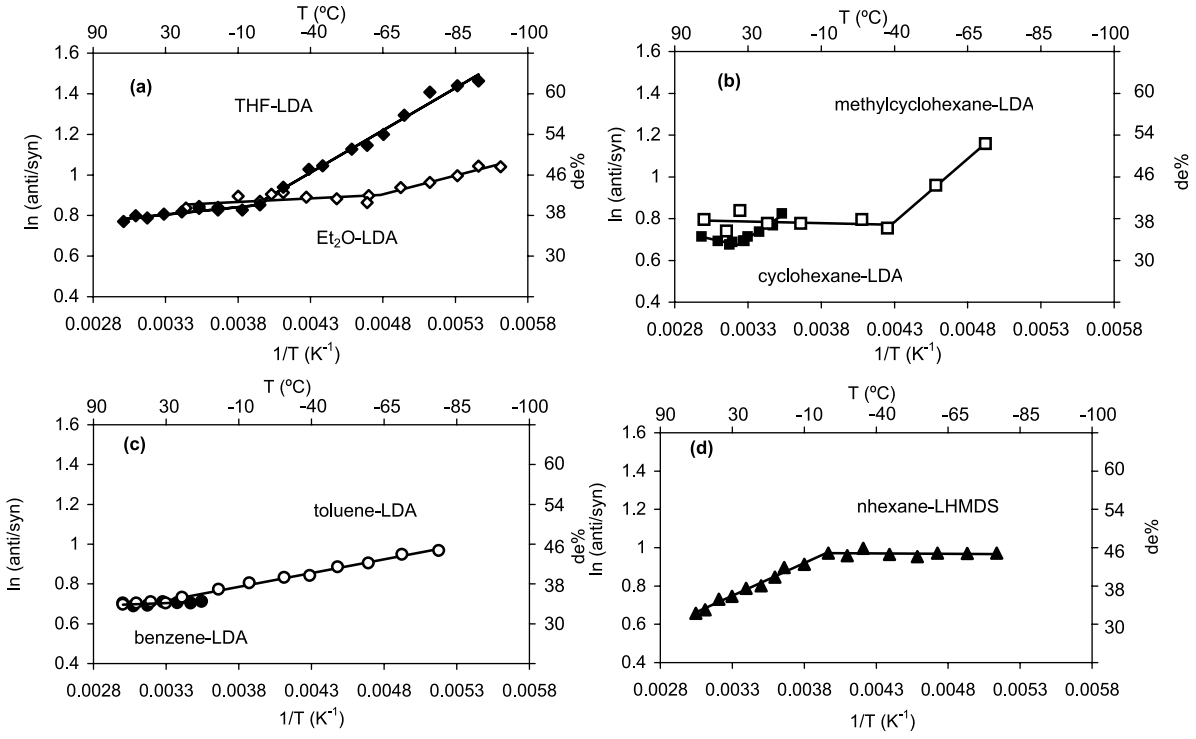
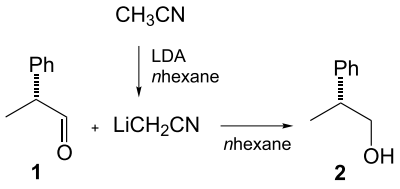


Figure 1. Eyring plots of the diastereomeric ratios obtained in the reaction of $LiCH_2CN$ to **1** in different solvents using the indicated base to form the anion: (a) THF–LDA (♦, solid diamond), Et_2O–LDA (◇, empty diamond); (b) methylcyclohexane–LDA (□, empty square), cyclohexane–LDA (■, solid square); (c) toluene–LDA (○, empty circle), benzene–LDA (●, solid circle); (d) *n*-hexane–LiHMDS (▲, solid triangle).



Scheme 2.

$\Delta\Delta H^{\neq}$ favours the *anti* diastereoisomer while the negative $\Delta\Delta S^{\neq}$ favours the *syn* one.

We already reported the opposite effect of linear versus cyclic hydrocarbons on the temperature-dependence of facial diastereoselectivity in the addition of *n*-BuLi to 2-phenyl propanal.[11b] This cyclic–acyclic effect of hydrocarbons derives from a complete change in values and signs of the differential activation parameters and it would deserve a deeper specific inspection. This effect, however, does not appear in the addition of $LiCH_2CN$ in ethers as clearly indicated by the plots of THF and Et_2O (Fig. 1a). These results show that the tuning of thermodynamic parameters exerted by the reaction solvent was significant.

We tested if the different behaviour of *n*-hexane would derive from the use of a different base to form the lithium anion. We choose two solvents, *n*-hexane and methylcyclohexane, that had shown in the first screening an opposite behaviour of the dr with the temperature, and we checked the effect of the base on the facial diastereoselectivity. Three different bases, *n*-BuLi, LDA and LiHMDS were used to form the lithioacetonitrile in methylcyclohexane, and two bases, *n*-BuLi and LiHMDS in *n*-hexane. The corresponding Eyring plots are reported in Figure 2. The data clearly show that the different bases did not affect the diastereomeric ratio and its temperature-dependence. In fact, the corresponding plots are superimposed as a consequence of similar thermodynamic parameters (Table 1).[15]

It is important to observe that the base does not influence the presence or the value of the inversion temperatures in the two solvents. Following our interpretation, the inversion

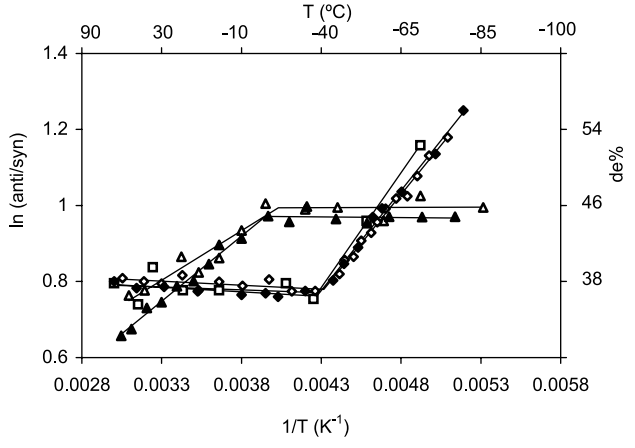


Figure 2. Eyring plots of the diastereomeric ratios obtained in the reaction of $LiCH_2CN$ to **1** in *n*-hexane using LiHMDS (▲, solid triangle) or *n*-BuLi (△, empty triangle) to form the anion; and in methylcyclohexane using LDA (□, empty square), LiHMDS (♦, solid diamond), or *n*-BuLi (◇, empty diamond).

temperature points out the presence of two different solvation clusters of the aldehyde, one at $T > T_{inv}$ and one at $T < T_{inv}$, which are in equilibrium at the T_{inv}.[8,11] The presence in solution of an equimolecular amount of a secondary amine (*iso*Pr_2NH or hexamethyldisilazane)[16] does not have any influence on those solute–solvent clusters and on their dynamic phenomena. Moreover, the superimposition with the Eyring plot obtained with the *n*-BuLi as a base, excludes the presence of these amines in the solvation sphere of the starting aldehyde.

The important role of solvents on structure and aggregation of organometallic reagents has been widely recognized. It is known for lithiophenylacetonitrile, that monomeric species predominate in THF, whereas dimeric aggregates are present in diethyl ether–toluene solutions.[17] Detailed solution studies of lithiophenylacetonitrile by NMR spectroscopy by Collum et al. showed a *N*-lithiated ketenimine dimer to be present in diethyl ether and diethylether–toluene, they also observed that mixed dimers were formed in the presence of TMEDA and hexamethyldisilazane.[18] Moreover, Hilmersson demonstrated that lithioacetonitrile and chiral lithium amides form mixed dimers in diethyl ether and THF according to NMR studies, and these mixed dimers underwent asymmetric addition to benzaldehyde with a change in enantioselectivity from diethyl ether to THF.[6]

In our case, the totally superimposed Eyring plots on changing the base, clearly demonstrate that the lithium amide, even if it could be present in mixed aggregate species of $LiCH_2CN$, has no influence on the facial diastereoselectivity of the aldol-like reaction, and neither on dynamic solvent effects of which the inversion temperature is the result. Moreover, this excludes the dependence of the T_{inv} on different aggregation states of the organometallic species.

Completely different is the result when a tertiary amine was used as a co-solvent in 5 mol% with respect to the hydrocarbon. Addition of 5 mol% Bu_3N to methylcyclohexane or *n*-hexane, has a dramatic effect (Fig. 3). In both cases, the resulting Eyring plots dramatically changed and consequently the differential activation parameters (Fig. 3 and Table 1). Especially in *n*-hexane, $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ change markedly and reverse their signs, thus reversing the preferred stereoisomer. In methylcyclohexane, the Bu_3N renders the presence of a T_{inv} much less evident, and in both methylcyclohexane and *n*-hexane the inversion temperatures present higher values than those obtained in the pure solvents (Table 1, entries 7 and 12). This result suggests that the tertiary amine is included in the solvation of the aldehyde and that the mixed-solvation cluster within the Bu_3N, requiring more energy for a cluster-interconversion (higher T_{inv}s), is thermodynamically more stable than that in pure solvents.

We already observed this effect by the use of different tertiary amines as co-solvent in the *n*-BuLi addition to 2-phenyl propanal in *n*-hexane,[19] and it could be attributed to a specific solvation due to the nitrogen atom. However, the same raising up of the inversion temperature has been observed even in binary mixtures of linear hydrocarbons,[20] thus confirming a higher stability of mixed-clusters than the

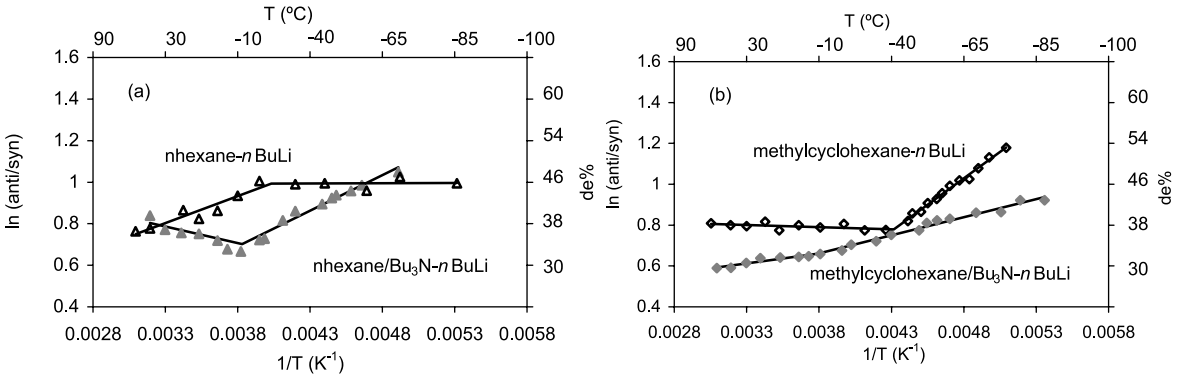


Figure 3. Eyring plots of the diastereomeric ratios obtained in the reaction of $LiCH_2CN$ to **1** in (a) pure *n*-hexane (△, empty triangle) and in a mixture *n*-hexane–Bu_3N 5 mol% (▲, grey triangle) using *n*-BuLi to form the anion; (b) pure methylcyclohexane (◇, empty diamond) and in a mixture methylcyclohexane–Bu_3N 5 mol% (◆, grey diamond) using *n*-BuLi.

corresponding homo-clusters independently on the presence of an eteroatom in the co-solvent.

Our proposed dependence of T_{inv} on solvation is reinforced by ^{13}C NMR experiments recording the evolution of chemical shifts with regard to the temperature.[11a] We recorded the ^{13}C NMR spectra of the sole aldehyde **1** in *n*-hexane–d_{14} on warming from −80 to 25 °C, and in *n*-hexane–d_{14}-Bu_3N (5 mol%) on warming from −60 to 15 °C. All spectra, after full assignments, showed a unique set of signals in the temperature range explored, which ensures the presence of a population-weighted average of rapidly interconverting conformers. In Figure 4 we report the evolution of the signal of the C═O with the temperature in the two cases. It could be easily recognized that the plots are composed of two linear segments. Using residual statistical analyses we confirmed that the correlation with two straight lines is always better than that with a single line and we determined the break points (T_{NMR}) at −22 °C in *n*-hexane–d_{14} and at −17 °C for *n*-hexane–d_{14}-Bu_3N. In both solvents the T_{NMR}s resulted fairly close to the T_{inv}s observed in the corresponding diastereoselective reactions (Table 1, entries 10, 11, and 12).

It appears clear that T_{inv} and T_{NMR}, even in this case, are linked as two independent experimental observations of the same reorganization cluster phenomenon. These results reinforce our hypothesis concerning the solvation-dependent nature of T_{inv} and T_{NMR}.

3. Conclusion

We have shown that the diastereofacial selectivity in the addition of lithioacetonitrile to 2-phenyl propanal is temperature and solvent-dependent. Each solvent studied (benzene, toluene, *n*-hexane, cyclohexane, methylcyclohexane, THF, and diethyl ether) shows a different Eyring plot of ln(*anti*/*syn*) versus $1/T$ with specific differential activation parameters $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$, and inversion temperature values (T_{inv}s). These measurements reveal that, in particular T ranges, the differential entropy of activation ($\Delta\Delta S^{\neq}$) plays an exclusive role in determining the preferential formation of the *anti* diastereoisomer.

We demonstrated that the opposite temperature behaviour of the diastereomeric ratio (dr) observed for *n*-hexane and methylcyclohexane does not depend on the base (*n*-BuLi, LDA and LiHMDS) generating the acetonitrile anion, but it is exclusively due to the reaction solvent.

The presence of 5 mol% Bu_3N co-solvent in *n*-hexane and methylcyclohexane has a dramatic effect on the temperature dependence of the diastereomeric ratio: it changed the thermodynamic parameters and the inversion temperature, and the T_{inv} values occur at higher temperatures than those seen in the pure solvents, thus confirming a higher stability of mixed solvation clusters.

For *n*-hexane we were able to connect the inversion temperature of the pure solvent and of the Bu_3N-mixture

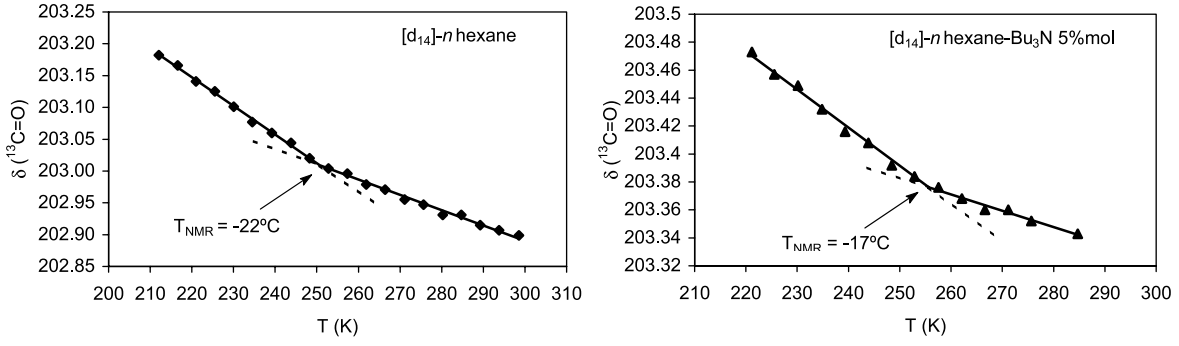


Figure 4. Plots of $\delta(^{13}C{=}O)$ versus temperature for **1** in deuterated *n*-hexane (◆, solid diamond), and in a mixture of deuterated *n*-hexane–Bu_3N 5 mol% (▲, solid triangle).

with dynamic solvation phenomena revealed by VT ^{13}C NMR measurements. The concomitance of T_{inv}s and T_{NMR}s revealed the presence of the amine in the solute–solvent clusters of the aldehyde and confirms the nature of the inversion temperature as due to dynamic solute–solvent clustering phenomena.

4. Experimental

4.1. General remarks

All reactions were performed in flame-dried glassware under an atmosphere of argon. – GC–MS: HP5980, capillar column HP-5 connected to HP5970 (70 eV). – GC: FISON G8000, column: HP-5 M.S. crosslinked 5% PhMeSilicone, 30 m × 0.25 mm × 0.25 μm. – TLC: Merck $60F_{254}$. – Column chromatography: Merck silica gel 200–300 mesh. During reactions, to set and maintain temperature in the range of ±0.5 °C, liquid N_2–acetone bath in Dewar containers or oily bath with water cooling was used. Temperature refers to the internal of reaction apparatus.

4.2. Starting materials

All solvents were purchased anhydrous from Fluka or dried by distillation from sodium and stored on Molecular Sieves 4 A, all amines were distilled and stored on KOH. *n*-BuLi (commercial 2.5 M solution in hexane) was titrated shortly before use. 2-Phenylpropanal **1** was purchased from Aldrich and distilled prior to use. The *n*-hexane–Bu_3N mixture was prepared in molar ratio *n*-hexane:Bu_3N = 95:5.

In a typical experiment, the lithioacetonitrile was generated as follows: acetonitrile (1 mmol, 52.5 μL) was added to a solution of LDA (1 mmol, prepared from diisopropylamine and *n*-BuLi) or LiHMDS (1 mmol, prepared from hexamethyldisilazane and *n*-BuLi) or *n*-BuLi (1 mmol, 0.4 mL) in the solvent of choice (10 mL) at −78 °C. After 30 min the lithio acetonitrile solution was brought to the desired constant temperature and after 15 min 2-phenylpropanal (1 mmol, 0.134 mL) was added dropwise via a gas-tight syringe. After 5 min, the reaction was quenched in 20 mL of saturated NH_4Cl solution and extracted with dichloromethane (3 × 25 mL). The reaction was repeated at different temperatures over the range permitted by the boiling and melting point of the solvent. The reactions proceeded smoothly in all solvents to give *anti* (**1a**) and *syn* (**1b**) 1,2-hydroxy nitriles.

From GC analysis of the crude products the *anti*/*syn* ratio and the de% value were obtained, (HP-5 M.S: 100 °C, 1 min, then 2 °C/min till 250 °C, rt: 22.2 min (**1a**), 23.1 min (**1b**)). The inverse addition of the preformed solution of $LiCH_2CN$ to the solution of aldehyde **1** did not change the *anti*/*syn* ratio. The average standard deviation for the ln(*anti*/*syn*) measurements was 2%. The 1,2-hydroxy nitriles obtained are known products and their configurations were determined in comparison with reported data.[13]

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.062

References and notes

1. (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1. (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.
2. (a) Yardley, J. P.; Husbands, G. E. M.; Butch, J.; Bicksler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H., III; James, M. N. G.; Sielecki, A. R. *J. Med. Chem* **1990**, *33*, 2899. (b) Koenig, T. M.; Mitchell, D. *Tetrahedron Lett.* **1994**, *35*, 1339.
3. (a) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613. (b) Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem.* **1988**, *53*, 2394.
4. (a) Leclerc, E.; Vrancken, E.; Mangeney, P. *J. Org. Chem* **2002**, *67*, 8928. (b) Mecozzi, T.; Petrini, M.; Profeta, R. *J. Org. Chem* **2001**, *66*, 8264. (c) Enders, D.; Kirchhof, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, 63. (d) Carlier, P. R.; Moon Lo, K.; Lo, M. M.-C.; Lo, P. C.-K.; Lo, C. W.-S. *J. Org. Chem.* **1997**, *62*, 6316. (e) Carlier, P. R.; Moon Lo, K.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511.
5. Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.
6. Sott, R.; Granander, J.; Hilmersson, G. *Chem. Eur. J.* **2002**, *8*, 2081.
7. See for instance: (a) Roland, S.; Mangeney, P. *Eur. J. Org. Chem.* **2000**, 611. (b) Cainelli, G.; Giacomini, D.; Galletti, P. *Eur. J. Org. Chem.* **1999**, 61. (c) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 10237. (d) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *Tetrahedron Lett.* **1995**, *36*, 2437. (e) Saito, T.; Kawamura, M.; Nishimura, J. *Tetrahedron Lett.* **1997**, *38*, 3231. (f) Wipf, P.; Jung, J.-K. *Angew. Chem., Int. Ed.* **1997**, *36*, 764. (g) Cainelli, G.; Giacomini, D.; Perciaccante, F. *Tetrahedron: Asymmetry* **1994**, *5*, 1913. (h) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. (i) Reetz, M. T.; Stanchev, S.; Haning, H. *Tetrahedron* **1992**, *48*, 6813.
8. (a) Cainelli, G.; Giacomini, D.; Galletti, P. *Chem. Commun.* **1999**, 567. (b) Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P. *Tetrahedron Lett.* **2001**, *42*, 7383.
9. (a) Eyring, H. *J. Phys. Chem.* **1935**, *3*, 107. (b) Glasstone, S.; Laidler, K. J.; Eyring, H. *The Theory of Rate Processes*; McGraw-Hill: New York, 1941.
10. For a review see: Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.
11. (a) Cainelli, G.; Giacomini, D.; Galletti, P.; Orioli, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 523. (b) Cainelli, G.; Giacomini, D.; Galletti, P.; Marini, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 2849. (c) Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Quintavalla, A. *Helv. Chim. Acta* **2003**, *86*, 3548.

12. Cainelli, G.; Galletti, P.; Pieraccini, S.; Quintavalla, A.; Giacomini, D.; Spada, G. P. *Chirality* **2004**, *16*, 50.
13. Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn* **1994**, *67*, 1126.
14. Ashby, E. C.; Goel, A. B.; DePriest, R. N. *Tetrahedron Lett.* **1981**, *22*, 4355.
15. In the case of simple diastereoselectivity Carlier already reported that the nature of the amide base (LDA or LiHMDS) did not appear to significantly affect the stereoselectivity in the addition of lithio phenylacetonitrile to aliphatic and aromatic aldehydes, see: Carlier, P. R.; Lo, K. M. *J. Org. Chem.* **1994**, *59*, 4053.
16. *iso*Pr_2NH and hexamethyldisilazane result as 1.3 mol% respect to *n*hexane.
17. (a) Strzalko, T.; Seyden-Penne, J.; Wartski, L. *J. Org. Chem.* **1998**, *63*, 3295. (b) Carlier, P. R.; Lo, K. M.; Lo, M. M.-C.; Williams, I. D. *J. Org. Chem.* **1995**, *60*, 7511. (c) Carlier, P. R.; Madura, J. D. *J. Org. Chem.* **2002**, *65*, 3832.
18. Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602.
19. Cainelli, G.; Giacomini, D.; Galletti, P.; Quintavalla, A. *Eur. J. Org. Chem.* **2003**, 1993.
20. Cainelli, G.; Galletti, P.; Giacomini, D.; Orioli, P.; Polidoro, M. A.; Righetti, M. C. *Helv. Chim. Acta* **2000**, *83*, 1951–1961.

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Synthesis of activated 3-substituted indoles: an optimised one-pot procedure

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Abstract—3-Substituted-4,6-dimethoxyindoles can be synthesised in a one-pot procedure from 3,5-dimethoxyaniline and 2-haloketones in the presence of lithium bromide and sodium bicarbonate.
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1. Introduction

The indole nucleus is present in a wide range of natural products, and consequently a variety of methods for the synthesis of indoles has been developed.[1,2] Amongst these numerous methods few practical and mild procedures are available for the construction of activated 3-substituted-4,6-dimethoxyindoles **6**, and in particular for 3-alkyl-4,6-dimethoxyindoles.[3–5] Indoles carrying this substitution pattern are of particular interest since they do not only activate C7 and C2, but also enhance the general reactivity of the indoles. An earlier study reported that 3-arylindoles can be synthesised via a modified Bischler procedure in four steps.[6,7] This approach involved condensation of 3,5-dimethoxyaniline **1** with phenacyl halides **2** (R = Ar) to afford arylamino ketones **3** which are consecutively protected giving the *N*-protected amido ketones **4**, prior to their cyclisation in acid yielding the *N*-protected indoles **5**. These are deprotected by base to yield the desired 3-arylindoles **6**. The *N*-protection is required to prevent Bischler rearrangement to give 2-arylindoles **7** instead.[6,8] This method has now been improved to provide a facile one-pot procedure that could also be extended to the preparation of 3-alkylindoles in good yields (Scheme 1).

2. Results and discussion

2.1. Scope of the four-step procedure

The modified Bischler synthesis has been successfully applied to 3,5-dimethoxyaniline and is an effective way for the preparation of 4,6-dimethoxyindoles with overall yields of 25–60% for aryl substituted indoles. Nevertheless, the presence of substituents carrying sensitive functions such as hydroxyl or ester groups contribute to a loss in yield, since chromatographic workup is needed for some of the intermediates prior to the next step in the reaction sequence. This also involves lengthy work-up, which adds to the accumulated reaction times needed for the four-step synthesis. Furthermore, there has been no general synthetic methodology for alkylindoles in this series.

After a close examination of the four-step synthesis the crucial step was identified as the formation of the anilino ketones **3**, where both the quality and quantity of the products were variable. Consequently, further investigations were undertaken to gain control over this step.

2.2. From a four-step procedure to a one-pot reaction

In order to synthesise 4,6-dimethoxy-3-methylindole **6a** via the modified Bischler procedure the reaction conditions in the first step had to be modified, eventually allowing the preparation of **6a** in 22% yield overall. Thus, in the crucial first step of its synthesis 1-chloroacetone **2a** was reacted with 3,5-dimethoxyaniline **1** in refluxing ethanol containing excess sodium bicarbonate and excess lithium bromide to produce the methyl anilinoketone **3a**, which ideally precipitated out of solution upon cooling affording the product in a variable yield of 30–67%. After a reaction period of only 3 h, the anilinoketone **3a** could be isolated in 70% yield, then cyclised using acetic anhydride to *N*-acetyl-4,6-dimethoxy-3-methylindole in 70% yield, and this could be hydrolysed with potassium hydroxide in ethanol to give indole **6a** in 90% yield. However, after longer reaction times

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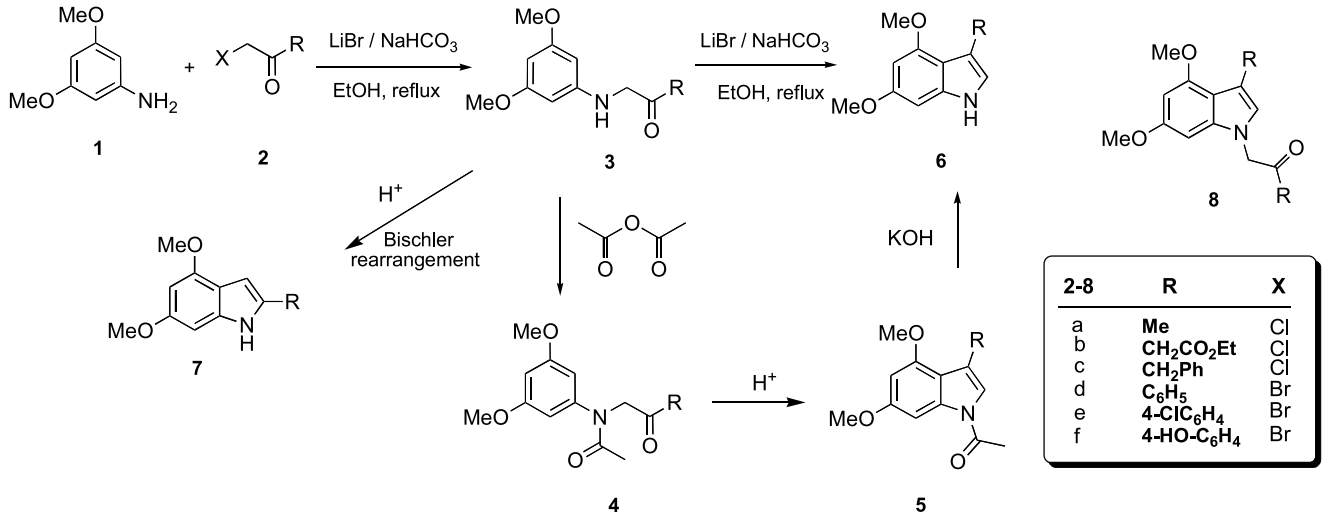

Scheme 1.

in the anilinoketone preparation and more appropriate stoichiometry, a major by-product appeared in the reaction mixture and was revealed by proton NMR spectroscopy to be the 3-methylindole **6a**. This was an interesting observation, since the cyclisation of amino ketones to indoles usually takes place under strongly acidic conditions. The absence of the corresponding 2-methylindole **7a** indicated that under the reaction conditions chosen no Bischler rearrangement could occur. With this information at hand the conditions could be adjusted to yield the indole **6a** in 74% yield, using molar equivalent amounts of all the reagents and reactants resulting in an efficient, shortened route to **6a**.

A similar observation was made for the reaction of 3,5-dimethoxyaniline **1** with ethyl 4-chloroacetoacetate **2b**. A reaction period of 3 h led to crude anilinoketone **3b**, which was converted with acetic anhydride to the *N*-acetyl compound **4b**, which was cyclised in trifluoroacetic acid to the *N*-acetylindole **5b** in an overall yield of 30%: hydrolysis with ethanolic potassium hydroxide gave indole **6b** in 70% yield. In contrast, a reflux period of 8 h in the initial step directly led to isolation of indole **6b** in 30% yield.

The one-pot method was also applied to the preparation of the 2-benzylindole **6c**, and the 3-arylindoles **6d–f**. Indole **6f** was also prepared by the stepwise process and intermediate compounds isolated and characterised.

Lithium bromide, being a crucial reagent, is assumed not only to exchange with the chloro group to facilitate the formation of the anilinoketone but also to act as a Lewis acid to allow cyclisation without rearrangement at neutral conditions and moderate temperatures.

Next, the scope and limitations of the lithium-mediated one-pot reaction were investigated. Depending on the reactivity of the desired substituent at C3 of the indole the conditions (temperature and ratio of the reactants and reagents) had to be slightly modified. Higher boiling solvents such as 1-propanol or ethylene glycol showed a significant decrease in the reaction times and increase in the yields, in examples incorporating less reactive, electron withdrawing aryl groups. A change of the ratio of the reactants and reagents would not only result in a shift of the equilibrium but also a change of pH, which plays an important role in the reaction. By use of excess amine **1** and/or sodium bicarbonate a basic pH is maintained throughout the reaction and this inhibits cyclisation and produces mostly the uncyclised intermediates **3**. If, on the other hand insufficient base is added to the reaction mixture to neutralise the released HBr completely, a moderate amount of the 2-arylindole **7** is produced. Therefore, it is important to maintain a neutral pH. An excess of the haloketone **2** had a positive effect on the rate and the yield of the reaction, but it also led to a new by-product, the *N*-substituted indole **8**. Because of this the excess of **2** was reduced to a minimum of 1.05 mequiv, giving good yields of **6**.

2.3. Comparison of the four-step procedure and the one-pot reaction

The lithium bromide templated one-pot synthesis can be alternatively used to synthesise a variety of different 3-substituted 4,6-dimethoxyindoles **6**. Depending on the reactivity of the substituent different alcohols had to be chosen as the solvent and also adjustments of the ratios of the reagents had to be made. Overall it was found to be a quicker, less labour-intensive and better yielding procedure than the four-step-procedure, especially for alkyl-substituted indoles as can be seen from Table 1.

3. Conclusions

The synthesis of activated indoles based on electron-rich arenes, e.g. dimethoxyanilines, can be achieved in a one-pot process by a direct cyclisation of an arylaminoketone, in the presence of lithium bromide and under essentially neutral conditions.

Table 1. Comparison of four-step and one-pot reaction

	Reaction time (h)		Overall yield (%)	
	Four-step	One-pot	Four-step	One-pot
6a	9[a]	6	22	74
6b	9[a]	9	14	30
6c	N/A	12	N/A	61
6d		18		65[b]
6e	23[a]	5	57	75[b]
6f	9.5[a]	12	26	29

[a] Plus four work-ups.
[b] Plus 5–10% of 2-substituted isomers **7** and 10–15% of *N*-substituted indoles **8**.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker FT-ICR MS (EI) or a Micromass ZQ2000 (ESI) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FTIR Spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan Spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel.

4.1.1. 4,6-Dimethoxy-3-methylindole (6a). *Method A (stepwise)*. A mixture of 3,5-dimethoxyaniline **1** (10.0 g, 65.3 mmol), chloroacetone **2a** (6.11 g, 66.0 mmol), sodium hydrogen carbonate (11.0 g, 130.6 mol) and lithium bromide (8.5 g, 98.0 mmol) in absolute ethanol (100 mL) was heated under reflux for 3 h with stirring. After cooling, the resulting precipitate was filtered off and washed with water to give 1-(3,5-dimethoxyphenylamino)-propan-2-one **3a** (9.6 g, 70%) as a white solid, mp 92–94 °C (ethanol) (Found: C, 63.2; H, 7.1; N, 6.7. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%). ν_{max}: 3400, 1720, 1620, 1590, 1510, 1510, 1480, 1266, 1210, 1170, 1160 cm^{-1}. λ_{max} (MeOH): 222 nm (ε 16,200 cm^{-1} M^{-1}), 236 (7500), 246 (8300). ^{1}H NMR spectrum ($CDCl_3$): δ 2.20 (s, 3H, Me), 3.32 (s, 6H, OMe), 3.93 (s, 2H, CH_2), 4.57 (bs, 1H, NH), 5.75 (d, J=2.0 Hz, 2H, H2, H6), 5.88 (t, J=2.0 Hz, 1H, H4). ^{13}C NMR spectrum ($CDCl_3$): δ 27.20 (Me), 54.06 (CH_2), 55.03 (OMe), 90.09 (C4), 91.64 (C2, C6), 148.70, 161.73 (C Ar), 203.80 (C=O). Mass spectrum (EI): *m/z* 210 (M+1, 15%), 209 (M, 60), 167 (20), 166 (100), 138 (20).

The anilino ketone **3a** (5.0 g, 23.9 mmol) was partially dissolved in acetic anhydride (10 mL) and stirred at room temperature for 3 h. Water (1 mL) was added and the solution was warmed to 50–60 °C. Water was then added slowly so that the temperature did not drop below 50 °C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate, the extract washed with water until neutral, saturated sodium hydrogen carbonate solution, saturated brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to yield an oil, which was dissolved in trifluoroacetic acid (20 mL). The solution was refluxed for 1 h after which ice/water was added and the resulting solid was filtered off. The precipitate was washed with water until neutral, dried and recrystallised from ethanol resulting in *N*-acetyl-4,6-dimethoxy-3-methylindole **5a** as a white solid (3.9 g, 70%), mp 144–145 °C (ethanol) (Found: C, 65.7; H, 6.3; N, 5.9. $C_{13}H_{15}NO_3 \cdot 0.25\ H_2O$ requires C, 65.7; H, 6.6; N, 5.9%). ν_{max}: 1750, 1710, 1660, 1560, 1500, 1270, 1200 cm^{-1}. ^{1}H NMR spectrum ($CDCl_3$): δ 2.35 (d, J=1.5 Hz, 3H, Me), 2.52 (s, 3H, CO*Me*), 3.84 and 3.86 (2s, 6H, OMe), 6.33 (d, J=2.0 Hz, 1H, H5), 6.85 (d, J=1.0 Hz, 1H, H2), 7.65 (d, J=2.0 Hz, 1H, H7). ^{13}C NMR spectrum ($CDCl_3$): δ 12.28 (Me), 23.95 (CO*Me*), 55.20 and 55.66 (OMe), 92.92 (C5), 95.12 (C7), 119.39 (C2), 114.60, 118.76, 137.82, 154.46, 159.46 (C Ar), 168.57 (C=O). Mass spectrum (EI): *m/z* 234 (M+1, 15%), 233 (M, 80), 191 (100), 190 (25), 176 (90).

The *N*-acetylindole **5a** (2.0 g, 8.6 mmol) was partially dissolved in ethanol (50 mL). An excess of crushed potassium hydroxide was added to the above mixture and allowed to stir for 2 h. The resulting precipitate was filtered off and the solvent was removed from the filtrate, both solids were combined to yield 4,6-dimethoxy-3-methylindole **6a** as a light tan solid (1.5 g, 90%), mp 72–73 °C (lit.[5] mp 73–74 °C). ^{1}H NMR spectrum ($CDCl_3$): δ 2.46 (d, J=1.0 Hz, 3H, Me), 3.83 and 3.89 (2s, 6H, OMe), 6.21 (d, J=2.0 Hz, 1H, H5), 6.37 (d, J=1.0 Hz, 1H, H7), 6.67–6.68 (m, 1H, H2), 7.69 (bs, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 11.98 (Me), 55.12, 55.51 (OMe), 86.81 (C5), 91.22 (C7), 118.84 (C2), 112.02, 112.69, 138.00, 155.43, 157.36 (C Ar).

Method B (one-pot). 3,5-Dimethoxyaniline **1** (2.00 g, 13.1 mmol), chloroacetone **2a** (1.03 mL, 13.1 mmol), $NaHCO_3$ (1.09 g, 13.1 mmol) and LiBr (1.10 g, 13.1 mmol) were partially dissolved in EtOH (36 mL) and refluxed for 6 h. The solvent was evaporated and the crude residue extracted with CH_2Cl_2 (40 mL). The extract was washed with water (3×20 mL), dried ($MgSO_4$) and evaporated to give a yellow-green solid (2.62 g), which was purified by column chromatography (CH_2Cl_2/light petroleum, 9:1), yielding indole **6a** as a yellow solid (1.84 g, 74%), mp 72–74 °C (lit.[5] 73–74 °C).

4.1.2. Ethyl (4,6-dimethoxyindol-3-yl)acetate (6b). *Method A (stepwise)*. A mixture of 3,5-dimethoxyaniline **1** (5.00 g, 32.6 mmol), ethyl 4-chloroacetoacetate **2b** (5.4 g, 32.6 mmol), sodium hydrogen carbonate (5.5 g, 65.3 mmol) and LiBr (4.25 g, 44.0 mmol) in absolute ethanol (50 mL) was heated under reflux for 3 h with stirring. After cooling, water was added to the reaction mixture, which was extracted with dichloromethane, dried and concentrated to yield the crude amino ketone **3b** as a dark golden oil, which was then dissolved in acetic anhydride (10 mL) and stirred at room temperature for 3 h. Water (1 mL) was added and the solution was warmed to 50–60 °C. Water was then added slowly so that the temperature did not drop below 50 °C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate. The organic phase was washed with water until neutral, saturated sodium hydrogen carbonate solution, saturated brine solution and dried

(Na_2SO_4). The solvent was removed under reduced pressure to yield the crude protected anilinoketone, which was then dissolved in trifluoroacetic acid (10 mL). The solution was refluxed for 1 h after which ice/water was added and the resulting solid was filtered off and purified by chromatography (silica plug) and recrystallisation from ethanol to yield ethyl *N*-acetyl-4,6-dimethoxyindole-3-acetate **5b** as a light tan solid (3.00 g, 30%), mp 106–107 °C (ethanol). ν_{max}: 1730, 1695, 1600, 1590, 1570, 1410, 1280, 1200, 1160 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): δ 1.25 (t, J= 7.1 Hz, 3H, CH_2*Me*), 2.55 (s, 3H, CO*Me*), 3.79 (d, J= 3.3 Hz, 2H, CH_2), 3.80 and 3.84 (2s, 6H, OMe), 4.17 (q, J=7.1 Hz, 2H, *CH*$_2$Me), 6.31 (d, J=1.9 Hz, 1H, H5), 6.71 (s, 1H, H2), 7.63 (d, J=1.9 Hz, 1H, H7). Mass spectrum (EI): *m/z* 306 (M+1, 5%), 305 (M, 50), 263 (45), 190 (100).

The *N*-acetylindole **5b** (2.00 g, 6.6 mmol) was partially dissolved in ethanol (20 mL). Crushed KOH (0.26 g, 6.6 mmol) was added to the above mixture which was allowed to stir for 2 h. The resulting precipitate was filtered off to yield ethyl (4,6-dimethoxyindol-3-yl)acetate **6b** as a light tan solid (1.21 g, 70%), mp 105–106 °C (ethanol) (Found: C, 60.8; H, 6.1; N, 5.1. $C_{14}H_{17}O_4N.0.65\ H_2O$ requires C, 61.1; H, 6.7; N, 5.1%). ν_{max}: 3360, 1725, 1362, 1585, 1550, 1510, 1390, 1335, 1260, 1200 cm^{-1}. λ_{max}: 225 nm (ε 21,900 $cm^{-1}\ M^{-1}$), 269 (4900). ^1H NMR spectrum ($CDCl_3$): δ 1.27 (t, J=7.1 Hz, 3H, CH_2*Me*), 3.79 and 3.82 (2s, 6H, OMe), 3.87 (s, 2H, CH_2), 4.18 (q, J= 7.1 Hz, 2H, *CH*$_2$Me), 6.15 (d, J=1.5 Hz, 1H, H5), 6.36 (d, J=1.5 Hz, 1H, H7), 6.82 (d, J=1.5 Hz, 1H, H2), 7.97 (bs, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$): δ 14.25 (CH_2*Me*), 32.50 (*CH*$_2$Me), 54.96, 55.50 (OMe), 60.37 (CH_2), 86.75 (C5), 91.43 (C7), 120.29 (C2), 108.65, 111.91, 137.67, 154.72, 157.49 (C Ar), 172.92 (C=O). Mass spectrum (EI): *m/z* 264 (M+1, 5%), 263 (M, 40), 190 (100), 160 (35), 145 (30).

Method B (one-pot): A mixture of 3,5-dimethoxyaniline **1** (2.00 g, 13.1 mmol), ethyl-4-chloroacetoacetate **2b** (1.85 mL, 13.7 mmol), $NaHCO_3$ (1.10 g, 13.1 mmol) and LiBr (1.14 g, 13.1 mmol) was refluxed in EtOH (60 mL) for 8 h, the solvent evaporated and the crude residue extracted with CH_2Cl_2 (40 mL). The extract was washed with water (3×20 mL), dried ($MgSO_4$) and evaporated to give a brown-green solid, which was purified by column chromatography (CH_2Cl_2/MeOH, 98:2), yielding indole **6b** as a yellow solid (1.03 g, 30%), mp 102–104 °C.

4.1.3. 3-Benzyl-4,6-dimethoxyindole (6c). A suspension of 3,5-dimethoxyaniline **1** (1.73 g, 11.3 mmol), 1-chloro-3-phenylpropan-2-one **2c** (2.00 g, 11.9 mmol), $NaHCO_3$ (0.95 g, 11.3 mmol) and LiBr (0.98 g, 11.3 mmol) in 1-propanol (25 mL) was refluxed for 16 h. The mixture was cooled to room temperature and the precipitated salts filtered off. The remaining solution was concentrated to about one quarter of its volume and kept at room temperature for some time before filtration of the crude product. It was purified by column chromatography (CH_2Cl_2), yielding indole **6c** as a pale brown solid (1.85 g, 61%), mp 114–116 °C (Found: C, 76.5; H, 6.5; N, 5.2. $C_{17}H_{17}Cl_2NO_2$ requires C, 76.4; H, 6.4; N, 5.2%). ν_{max} (KBr): 3369, 1619, 1590, 1510, 1459, 1221, 1201, 1155, 1138, 1081, 938, 813, 740, 715 cm^{-1}. λ_{max} (CH_2Cl_2): 228 nm (ε 13,500), 271 (3800), 475 (600). ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.82 (s, 6H, OMe), 4.24 (s, 2H, CH_2), 6.19 (d, J=1.5 Hz, 1H, H5), 6.40 (d, J= 1.9 Hz, 1H, H7), 6.53 (d, J=1.1 Hz, 1H, H2), 7.15–7.30 (m, 5H, Ph), 7.72 (s, 1H, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 32.9 (CH_2), 55.0 (OMe), 55.5 (OMe), 86.7 (C5), 91.5 (C7), 112.1, 116.6, 119.5 (C2), 125.4 (CH Ph), 128.0 (CH Ph), 128.8 (CH Ph), 138.0, 142.4, 155.2, 157.5. Mass spectrum (ES): *m/z* (%) 267.1 (100, M^+), 252.1 (39), 190.1 (49), 132.1 (20).

4.1.4. 2-4,6-Dimethoxy-3-phenylindole (6d) and 2-(4,6-di-methoxy-3-phenylindol-1-yl)-1-phenylethanone (8d). A mixture of 3,5-dimethoxyaniline **1** (1.0 g, 6.53 mmol), 2-bromoacetophenone **2d** (1.62 g, 8.16 mmol), LiBr (0.57 g, 6.53 mmol) and $NaHCO_3$ (0.55 g, 6.53 mmol) in 1-propanol (25 mL) was refluxed overnight. The solvent was removed in vacuo, the residue extracted into CH_2Cl_2 (25 mL) and washed with water (3×15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting product mixture was separated by column chromatography on silica gel (CH_2Cl_2) yielding compound **8d** as yellow crystals (0.36 g, 15%) in the first band, mp 54–56 °C. (Found: C, 77.8; H, 5.8; N, 3.6. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%). ν_{max} (KBr): 3427, 1699, 1600, 1501, 1450, 1340, 1219, 1201, 1144, 1060, 757, 690 cm^{-1}. λ_{max} (CH_2Cl_2): 237 nm (ε 38,000), 248 (10,000). ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 6H, OMe), 5.36 (s, 2H, CH_2), 6.25 (s, 1H, H5), 6.29 (s, 1H, H7), 6.88 (s, 1H, H2), 7.23–7.28 (m, 1H, Ph), 7.34–7.39 (m, 2H, Ph), 7.47–7.53 (m, 2H, Ph), 7.62–7.64 (m, 3H, Ph), 7.98–8.00 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4 (CH_2), 55.1 (OMe), 55.6 (OMe), 85.3 (C7), 92.2 (C5), 110.9, 118.7, 125.0 (C2), 125.6 (CH Ph), 127.4 (CH Ph), 128.0 (CH Ph), 128.9 (CH Ph), 129.5 (CH Ph), 133.9 (CH Ph), 134.7, 135.8, 139.1, 155.1, 157.7, 192.9 (CO). Mass spectrum (ES): *m/z* (%) 371.1 (47, M^+), 266.1 (100), 250.1 (36).

The second band eluted from the column yielded **6d** as a brown powder (1.08 g, 65%), mp 57–59 °C (lit.[7] 58 °C). ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 6H, OMe), 6.34 (d, J= 2.0 Hz, 1H, H5), 6.45 (d, J=2.0 Hz, 1H, H7), 6.97 (d, J= 2.1 Hz, 1H, H2), 7.32–7.72 (m, 5H, Ph), 8.07 (br s, 1H, NH).

4.1.5. 3-(4-Chlorophenyl)-4,6-dimethoxyindole (6e) and 1-(4-chlorophenyl)-2-[3-(4-chlorophenyl)-4,6-di-methoxy-indol-1-yl]ethanone (8e). A mixture of 3,5-dimethoxyaniline **1** (1.0 g, 6.53 mmol), 2-bromoacetophenone **2e** (1.9 g, 8.14 mmol), LiBr (0.57 g, 6.53 mmol) and $NaHCO_3$ (0.55 g, 6.53 mmol) in 1-propanol (25 mL) was refluxed overnight. The solvent was evaporated in vacuo, the residue extracted into CH_2Cl_2 (25 mL) and washed with water (3× 15 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The resulting product mixture was separated by column chromatography on silica gel (CH_2Cl_2/light petroleum, 7:3) yielding indole **8e** as yellow crystals (0.35 g, 0.80 mmol, 12%) in the first band, mp 74–76 °C. (Found: C, 65.5; H, 4.4; N, 3.2. $C_{24}H_{19}Cl_2NO_3$ requires C, 65.5; H, 4.4; N, 3.2%). ν_{max} (KBr): 3406 (br), 2933, 2838 (w), 1700, 1588, 1545, 1335, 1217 (s), 1146, 1092, 1060, 834 cm^{-1}. λ_{max} (CH_2Cl_2): 248 nm (ε 34,000). ^1H NMR spectrum

(300 MHz, DMSO-d_6): δ 3.71 (s, 3H, OMe), 3.75 (s, 3H, OMe), 5.83 (s, 2H, CH_2), 6.24 (d, $J=1.5$ Hz, 1H, H5), 6.62 (d, $J=1.5$ Hz, 1H, H7), 7.19 (s, 1H, H2), 7.36 (d, $J=8.7$ Hz, 2H, Ar), 7.51 (d, $J=8.7$ Hz, 2H, Ar), 7.67 (d, $J=8.7$ Hz, 2H, Ar), 8.09 (d, $J=8.7$ Hz, 2H, Ar). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 52.5 (CH_2), 55.1 (OMe), 55.6 (OMe), 85.0 (C5), 92.3 (C7), 117.8, 124.7 (C2), 127.5 (CH Ar), 129.3 (CH Ar), 129.4 (CH Ar), 130.1, 130.6 (CH Ar), 131.5, 132.8, 134.1, 139.0, 140.6, 155.0, 157.9, 191.7 (CO). Mass spectrum (ES): *m/z* (%) 440.95 (36), 438.96 (50, M^+), 302.05 (35), 300.06 (100).

The second band eluted from the column yielded indole **6e** a pale yellow solid (1.40 g, 75%), mp 188–190 °C (lit.[7] 185–187 °C). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.27 (d, $J=1.9$ Hz, 1H, H5), 6.49 (d, $J=1.9$ Hz, 1H, H7), 6.99 (d, $J=2.6$ Hz, 1H, H2), 7.32 (d, $J=8.6$ Hz, 2H, Ar), 7.53 (d, $J=8.6$ Hz, 2H, Ar), 8.08 (br s, 1H, NH).

4.1.6. 4,6-Dimethoxy-3-(4-hydroxyphenyl)indole (6f). *Method A (stepwise).* A mixture of 3,5-dimethoxyaniline **1** (10.0 g, 66.6 mmol), 4-hydroxyacetophenone[9] **2f** (15.0 g, 69.0 mmol) and $NaHCO_3$ (5.6 g, 66.6 mmol) in MeOH (160 mL) was refluxed for 3 h. A yellow precipitate was obtained after cooling to room temperature and was filtered off and washed with water (30 mL). Recrystallisation from EtOH yielded 2-(3,5-dimethoxyphenylamino)-1-(4-hydroxyphenyl)ethanone **3f** as a white powder (10.4 g, 36.2 mmol, 56%), mp 166–168 °C. (Found: C, 66.6; H, 6.1; N, 4.9. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 6.0; N, 4.9%). ν_{max} (KBr): 3456, 3405, 1667, 1626, 1579, 1518, 1315, 1254, 1209, 1195, 1168, 1158, 1072, 961, 809, 799, 676, 591 cm^{-1}. λ_{max} (MeOH): 219 nm (ε 32,500), 278 (18,600). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 3.63 (s, 6H, OMe), 4.49 (d, $J=5.3$ Hz, 2H, CH_2), 5.69–5.74 (m, 2H, NH and H4′), 5.87 (d, $J=1.5$ Hz, 2H, H2′ and H6′), 6.86 (d, $J=9.3$ Hz, 2H, ArOH), 7.94 (d, $J=9.3$ Hz, 2H, ArOH), 10.37 (br s, 1H, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): 49.8 (CH_2), 55.2 (OMe), 89.3, 91.8 (CH), 115.7 (CH), 127.0, 130.8 (CH), 150.3, 161.5 (CH), 162.7, 194.8 (CO). Mass spectrum (EI): *m/z* (%) 287 (25, M^+), 166 (100), 122 (42).

A solution of anilinoketone **3f** (10.0 g, 34.8 mmol) in acetic anhydride (50 mL) was stirred at room temperature for 3 h, after which water (10 mL) was added, the solution heated to 50–60 °C and kept at this temperature, while more water (150 mL) was added. The mixture was cooled to room temperature, extracted with EtOAc (40 mL), and washed with water (2×25 mL), saturated aqueous $NaHCO_3$ (2×25 mL) and brine (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Recrystallisation from EtOH yielded 2-(*N*-acetyl-3,5-dimethoxyphenylamino)-1-(4-hydroxyphenyl) ethanone **4f** as a white solid (9.5 g, 28.8 mmol, 82%), mp 186–188 °C. (Found: C, 65.5; H, 6.0; N, 4.1. $C_{18}H_{19}NO_5$ requires C, 65.6; H, 5.8; N, 4.3%). ν_{max} (KBr): 3178, 1696, 1608, 1578, 1425, 1341, 1242, 1192, 1156, 1154, 1078, 981, 849, 702, 561 cm^{-1}. λ_{max} (MeOH): 218 nm (ε 22,000), 278 (18,000). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 1.89 (s, 1H, COMe), 3.72 (s, 6H, OMe), 4.98 (s, 2H, CH_2), 6.46 (s, 1H, H4′), 6.53 (s, 2H, H2′ and H6′), 6.84 (d, $J=8.7$ Hz, 2H, ArOH), 7.83 (d, $J=8.7$ Hz, 2H, ArOH), 10.43 (br s, 1H, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 22.3 (Me), 55.7 (CH_2), 55.8 (OMe), 99.8 (CH), 106.4 (CH), 115.7 (CH), 126.8, 130.8 (CH), 145.6, 161.1, 162.8, 169.5, 192.5. Mass spectrum (EI): *m/z* (%) 329 (7, M^+), 208 (17), 166 (100), 121 (93).

A solution of *N*-acetylanilino ketone **4f** (5.0 g, 15.2 mmol) in TFA (25 mL) was stirred at room temperature for 1.5 h. A green ppt formed after quenching with ice/water (100 mL), which was filtered off and washed with water until rinsings were neutral. Recrystallisation from EtOH yielded *N*-acetyl-4,6-dimethoxy-3-(4-hydroxyphenyl)indole **5f** as a pale grey solid (3.89 g, 12.5 mmol, 83%), mp 210–212 °C. ν_{max} (KBr): 3252, 1681, 1574, 1508, 1426, 1310, 1208, 1167, 1042, 966, 825, 688 cm^{-1}. λ_{max} (MeOH): 209 nm (ε 41,500), 252 (31,600), 319 (7100). (Found: C, 69.2; H, 5.6; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 2.61 (s, 1H, COMe), 3.71 (s, 3H, OMe), 3.79 (s, 3H, OMe), 6.46 (d, $J=1.9$ Hz, 1H, H5), 6.75 (d, $J=8.3$ Hz, 2H, ArOH), 7.35 (d, $J=8.3$ Hz, 2H, ArOH), 7.47 (s, 1H, H2), 7.63 (d, $J=1.9$ Hz, 1H, H7), 9.34 (s, 1H, OH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 24.4 (CO*Me*), 55.6 (OMe), 55.8 (OCH_3), 93.2 (C5), 95.5 (C7), 112.3, 114.8 (CH Ar), 122.0 (C2), 123.0, 125.1, 130.8 (CH Ar), 137.8, 154.2, 156.8, 159.2, 170.0 (CO). Mass spectrum (EI): *m/z* (%) 311 (18, M^+), 269 (20), 254 (40), 69 (50), 43 (100).

A suspension of *N*-acetylindole **5f** (3.40 g, 10.9 mmol) and KOH (2.5 g, 44.6 mmol) in MeOH (55 mL) was stirred for 3 h, followed by the addition of aqueous HCl solution (5 M, 8–10 mL) until no further precipitation was observed. The salts were filtered off, the solvent removed under reduced pressure, the remaining mixture diluted with CH_2Cl_2 (50 mL), and washed with water (3×20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. The crude product was flash chromatographed (CH_2Cl_2/MeOH, 96:4) and recrystallised in EtOH to yield indole **6f** as a pale yellow solid (2.01 g, 7.47 mmol, 69%), mp 212–214 °C.

Method B (one-pot). A mixture of 3,5-dimethoxyaniline **1** (1.02 g, 6.66 mmol), 4-hydroxyphenacylbromide **2f** (1.50 g, 6.98 mmol), $NaHCO_3$ (0.56 g, 6.66 mmol) and LiBr (0.58 g, 6.66 mmol) in 1-propanol (20 mL) was refluxed for 12 h. The mixture was cooled to room temperature and the precipitated salts filtered off. The remaining solution was concentrated to about one quarter of its volume and kept at room temperature for 3 h, after which the crude product was filtered off. It was purified by column chromatography (CH_2Cl_2/MeOH, 96:4), yielding indole **6f** as pale brown needles (0.52 g, 29%), mp 210–212 °C. ν_{max} (KBr): 3443, 3334, 1541, 1501, 1320, 1199, 1161, 1149, 1041, 838, 811, 550 cm^{-1}. λ_{max} (MeOH): 231 nm (ε 27,000), 261 (13,500). (Found: C, 70.4; H, 5.7; N, 5.1. $C_{16}H_{15}NO_3\cdot(1/4)H_2O$ requires C, 70.2; H, 5.7; N, 5.1%). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 3.70 (s, 3H, OMe), 3.74 (s, 3H, OMe), 6.14 (d, $J=1.9$ Hz, 1H, H5), 6.47 (d, $J=1.9$ Hz, 1H, H7), 6.69 (dd, $J=6.4$, 1.9 Hz, 2H, Ar), 7.00 (d, $J=2.3$ Hz, 1H, H2), 7.29 (dd, $J=6.4$, 1.9 Hz, 2H, Ar), 9.09 (br s, 1H, OH), 10.89 (br s, 1H, NH); ^{13}C-NMR spectrum (75 MHz, DMSO-d_6): δ 55.2 (OMe), 55.5 (OMe), 87.6 (C5),

91.8 (C7), 110.2, 114.7 (CH Ar), 117.3, 120.8 (C2), 127.6, 130.3 (CH Ar), 138.8, 154.6, 155.5, 156.8. Mass spectrum (EI): *m*/*z* (%) 269 (100, M^+), 254 (48), 211 (20).

Acknowledgements

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References and notes

1. Sundberg, R. J. *Indoles*; Academic Press: New York, 1996.
2. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
3. Magnus, P.; Mitchell, I. S. *Tetrahedron Lett.* **1998**, *39*, 4595–4598.
4. Hall, R. J.; Shannon, P. V. R.; Oliveira-Campos, A. M. F.; Queiroz, M. J. R. P. *J. Chem. Res., Synop.* **1992**, 2–3.
5. Black, D. S. C.; Rothnie, N. E.; Wong, L. C. H. *Aust. J. Chem.* **1983**, *36*, 2407–2412.
6. Black, D. S. C.; Kumar, N.; Wong, L. C. H. *Aust. J. Chem.* **1986**, *39*, 15–20.
7. Black, D. S. C.; Bowyer, M. C.; Bowyer, P. K.; Ivory, A. J.; Kim, M.; Kumar, N.; McConnell, D. B.; Popiolek, M. *Aust. J. Chem.* **1994**, *47*, 1741–1750.
8. Brown, R. K. *Indoles Part One*; Wiley-Interscience: New York, 1972.
9. Malik, M. L.; Grover, S. K. *Indian J. Chem., Sect. B: Org. Chem. Include. Med. Chem.* **1976**, *14B*, 513–515.

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Influence of catalytic system composition on formation of adamantane containing ketones

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Dedicated to Professor Milan Kratochvíl on his 80th birthday

Abstract—The preparation of non-symmetrical ketones by the reaction of acyl chlorides and the corresponding Grignard reagents in the presence of catalytic amounts of metal halides is described. The composition of catalyst has a great influence on the yield of the required ketone as well as on side product formation. For each catalytic system, the yield of ketone and the number of side products changes with the time of addition of the Grignard reagent. We examined the influence of both factors in our model reaction of adamantane-1-carbonyl chloride with ethylmagnesium bromide and discussed the possible mechanisms from this point of view. We have found $ZnCl_2$, $MnCl_2$, $AlCl_3$ and CuCl to be active catalytic components and developed very efficient, cheap and fast methods for the preparation of alkyl adamantyl ketones. The procedure was also tested for the synthesis of other alkyl aryl ketones.
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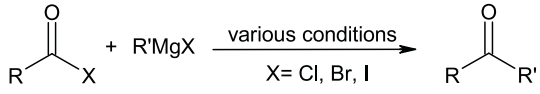
1. Introduction

One of the most important strategies to obtain a new carbon–carbon bond at a carbonyl group is a nucleophilic substitution of a good leaving group using an organometallic reagent (Scheme 1). Several modifications of the general procedure where an organometallic reagent reacts with acyl chlorides were studied[1–3] or used in synthesis[4,5] recently.



Scheme 1.

Typically, 'soft' organometallic reagents containing copper, zinc, manganese, etc. are used to support substitution of a good leaving group and to avoid the successive addition of an organometallic compound to an unsaturated carbonyl group. It is interesting that good yields of ketones can also be obtained when in situ transmetallation is carried out since this means that the Grignard reagent reacts with the acyl chloride in the presence of a suitable metal halide. This procedure can be improved using only a catalytic amount of the metal halide but in this case the rate of addition of the organomagnesium reagent was found to be important.[6]

2. Results and discussion

A few years ago, Cahiez and Laboue[6] described the preparation of various ketones using acyl chlorides and Grignard reagents in the presence of a catalytic amount of manganese chloride and copper(I) chloride. They optimized the rate of Grignard reagent addition to obtain the best yield of the required ketone. For any other than the optimal rate, the observed yields of the ketone decreased as the amount of tertiary alcohol formed increased. In this work, we carried out a number of experimental conditions for selected catalytic systems to discover the best combination of metals. This study led to the discovery of a new, efficient method for the preparation of adamantyl ketones. Our data from the reaction of Grignard reagents with adamantyl-1-carbonyl chloride (**1**) with similar manganese–copper catalysts are in good agreement with the observation of Cahiez and Laboue[6] (see Table 1, entries 8–13). The best yield (82%) we obtained when the addition took about 56 min. Surprisingly, we did not detect a significant amount of tertiary alcohol **4** anytime[†] and the main

Keywords: Ketones synthesis; Catalyst composition influence; 1-Adamantyl; Grignard reagent.
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[†] However, when the structure of Grignard reagent used eliminates the reduction of ketone, the corresponding tertiary alcohol was present.

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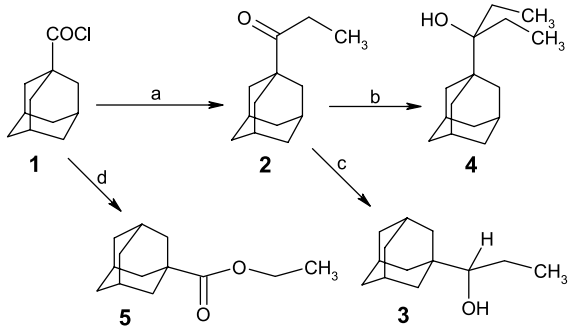
Table 1. Catalyst composition influence on the yield of ketone **2** and side-products distribution

A	B	Time (min)	C[a] **2**	Composition of crude product[b]			
				2	**5**	**3**	**4**
0	1	4.4	53	74.1	2.0	23.1	0.8
	2	17.0	59	90.6	5.8	3.4	0.2
	3	30.9	59	88.6	9.3	2.0	0.1
	4	39.9	60	84.3	13.9	1.6	0.2
	5	65.2	61	82.8	16.0	1.1	0.1
	6	91.5	57	78.3	20.9	0.7	0.1
	7	173.5	60	69.6	28.2	1.7	0.5
$MnCl_2 \cdot CuCl$	8	2.8	38	74.8	0.3	24.9	0.0
	9	18.5	49	84.6	0.6	14.8	0.0
	10	37.4	73	94.7	5.0	0.3	0.0
	11	55.8	82	97.8	1.3	0.9	0.0
	12	75.5	77	88.0	12.0	0.0	0.0
	13	100.0	55	87.6	12.4	0.0	0.0
$AlCl_3 \cdot CuCl$	14	0.25	95	>99.5	0.0	0.0	0.0
	15	12.2	73	91.6	8.4	0.0	0.0
	16	35.3	53	87.0	13.0	0.0	0.0
	17	47.9	52	86.0	14.0	0.0	0.0
	18	58.7	57	85.0	15.0	0.0	0.0
	19	66.3	59	84.0	16.0	0.0	0.0
	20	90.0	53	81.0	19.0	0.0	0.0
	21	105.4	51	78.0	22.0	0.0	0.0
$ZnCl_2 \cdot CuCl$	22	4.5	82	98.4	0.8	0.7	0.1
	23	15.8	80	98.3	1.2	0.5	0.0
	24	29.6	79	97.4	2.0	0.5	0.1
	25	44.8	80	96.2	3.3	0.4	0.0
	26	66.9	81	95.1	4.5	0.4	0.0
	27	82.9	76	93.9	5.8	0.3	0.0
	28	105.9	74	93.2	6.5	0.3	0.0
$AlCl_3$	29	0.3	49	97.0	1.9	0.0	1.1
	30	10.4	55	90.6	8.5	0.0	0.9
	31	19.1	57	89.5	9.6	0.0	0.7
	32	31.7	56	86.6	13.4	0.0	0.0
	33	47.1	53	85.6	14.4	0.0	0.0
	34	67.8	47	77.0	22.8	0.0	0.2
	35	87.0	50	75.4	24.5	0.0	1.0
	36	119.4	41	68.7	30.8	0.0	0.5
CuCl	37	0.3	77	95.5	0.3	2.9	0.0
	38	8.4	82	98.5	1.3	0.2	0.0
	39	15.1	80	98.0	1.5	0.5	0.0
	40	31.2	78	97.9	1.5	0.6	0.0
	41	42.9	82	94.1	5.5	0.4	0.0
	42	60.7	81	92.2	7.7	0.1	0.0
	43	93.5	74	92.9	6.9	0.3	0.0
$MnCl_2 \cdot AlCl_3$	45	4.15	68	94.9	0.3	4.3	0.4
	46	14.0	71	97.5	0.6	1.8	0.1
	47	31.4	67	96.7	1.4	1.7	0.2
	48	58.6	64	91.7	7.5	0.9	0.0
	49	70.1	56	89.5	9.9	0.6	0.0
	50	132.6	46	78.7	20.9	0.3	0.0

A=catalyst, B=entry number, C=yield.
[a] Determined by GC with cyclohexanone as an internal standard.
[b] Determined by GC (relative %).

side product at high addition rate was the secondary alcohol **3** arisen from reduction of ketone **2**. Furthermore, at a low addition rate we detected the ethyl adamantane-1-carboxylate **5** as the main side product. There are two possible routes to ester **5**. The first one is reaction between the acyl chloride and the corresponding alcoholate coming from impurities in the starting material (ethyl bromide) for Grignard reagent preparation. This pathway is proved by reactions where several different Grignard reagents were used and always the relevant ester was detected as well as the ketone. Nevertheless, this possibility cannot explain the increasing amount of ester with a prolonged time of addition. Thus, another pathway based on acylative cleavage of diethyl ether[7–11] is unambiguously present. The reaction pathways



Scheme 2. Supposed reaction pathways leading to main components of crude products. (a) Ethylmagnesium bromide substitution of chlorine, (b) Grignard reagent addition to carbonyl, (c) reduction of carbonyl group by Grignard reagent, (d) acylative cleavage of diethyl ether.

leading to the most important side products are shown in Scheme 2.

In case when no catalyst was used, the ketone **2** yield does not change significantly and for all the rates of the Grignard reagent addition varies around 60%. The distribution of products after reaction using $MnCl_2$/CuCl catalyst is very similar to that without any catalyst. The amount of ester **5** in the non-catalyzed reaction is even higher than that in the reaction catalyzed by manganese (compare entries 6 and 13). Use of aluminium trichloride with copper chloride (entries 14–21) led to a completely different situation. The highest ketone **2** yield (95%) was observed for the shortest addition time (entry 14) and for any lower rate of addition the yields were rapidly decreased.

Good yields (about 80%) were obtained when $ZnCl_2$ was used together with CuCl. They are nearly independent of the time of addition (entries 22–26). A small decrease of ketone **2** yield (caused by ester formation) was observed only for longer times of addition (entries 27 and 28).

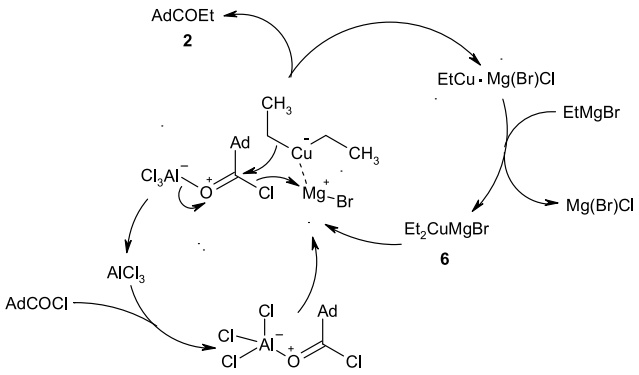
Sets of experiments where $AlCl_3$ (entries 29–36) and CuCl (entries 37–43) were used separately show that the influence of addition time with the $AlCl_3$ catalyst has no significant influence on the yield. However, the presence of CuCl increases ketone **2** yield for all rates by about 20% in comparison with the non-catalyzed reactions.

In the case of $AlCl_3$ catalyst, no significant amount of alcohols was detected in the product although the yield of ketone **2** was not higher than 60%. Appropriate unreacted starting material was recovered after hydrolysis and identified as adamantane-1-carboxylic acid. Finally, manganese chloride instead of copper chloride was used (entries 45–50) but the reactions were less successful. The best yield (71%) of ketone **2** in this case was obtained for 14 min lasting addition.

We can conclude, that the best result was observed when the strongest Lewis acid was used together with the most efficient organometallic reagent (formed in situ via transmetallation). This assertion is in good agreement with the trends indicated in Table 1. $AlCl_3$ as well as CuCl used separately decrease the amount of secondary alcohol, which is formed when excessive amount of Grignard reagent is present and that reacts not only with acyl chloride but consequently also with the already formed ketone **2**. When $AlCl_3$ and CuCl are used together, the absence of secondary alcohol **3** at all addition rates implies the presence of a mechanism that consumes Grignard reagent very rapidly, and so undesirable reductions or additions can not occur.

A reasonable explanation of our results leads to the formulation of a mechanism based on two joint cycles (Scheme 3). In the first cycle, aluminium trichloride reacts with acyl chloride to produce an acyl chloride–trichloro-aluminium complex.[12,13]

This activated alkyl carbonyl then interacts with organo-copper compound **6** to produce the expected ketone **2**, $EtCu{\cdot}MgX_2$ and regenerated aluminium trichloride. In the second joint cycle $EtCu{\cdot}MgX_2$ is alkylated by another molecule of Grignard reagent and the reactive



Scheme 3. Proposed mechanism of ketone **2** formation based on Lewis acid activated acyl chloride reaction with organocuprate.

organocuprate **6** is regenerated. Such a system can operate efficiently only when conversion of alkylcopper into **6** by action of Grignard reagent is sufficiently fast and when **6** reacts again very quickly with the activated acyl chloride rather than with other electrophiles present in the reaction mixture. The second assumption is acceptable because activated acyl chloride seems to be the most electrophilic species in the mixture.

Finally, we tested our new method in the synthesis of several ketones to eliminate the possible specific influence of the bulky adamantane moiety. These results are summarized in Table 2. In all the cases we obtained the expected ketones in good or excellent yields. It should be mentioned tertiary or secondary alcohols were not detected in any cases and the corresponding amounts of unreacted carboxylic acids were recovered (except acetic, propionic and pivalic acid).

3. Conclusion

A new, efficient, cheap and fast method for the synthesis of non-symmetrical ketones has been developed. In comparison with other methods, this one involves easily accessible reagents and provides very good yields. Ketones are obtained within 10 min at 10 °C and no special conditions or work-up procedures are required. In addition, no undesirable alcohols were present in crude product. Non-substituted ketones are produced very efficiently but the full scope of our reaction procedure remains a question for further research.

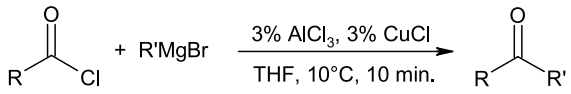
4. Experimental

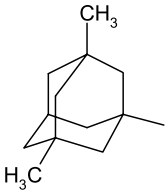
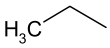
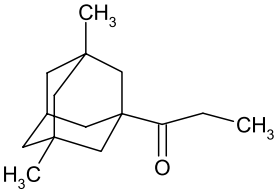
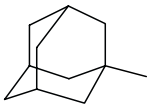
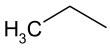
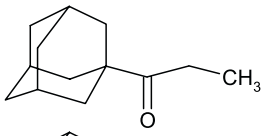
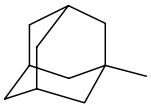
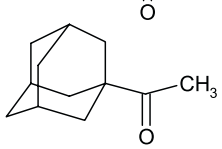
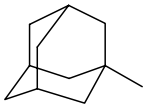
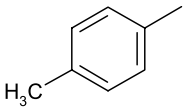
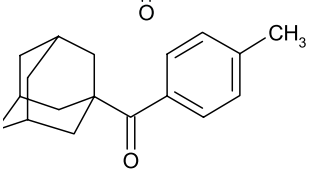
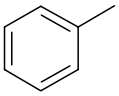
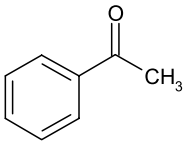
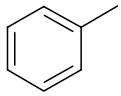
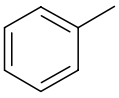
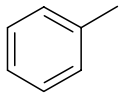
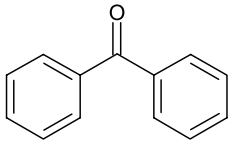
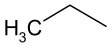
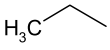
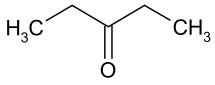
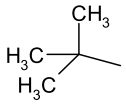
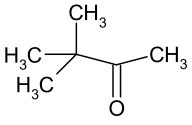
4.1. General data

All reactions were carried out under an argon atmosphere. Solvents were dried by the standard methods and were freshly distilled before use. LiCl, $MnCl_2$, $ZnCl_2$ were purchased from Fluka Co. and were dried before use under vacuum at 160 °C for 2 h. $AlCl_3$ was obtained from Merck.[‡] CuCl was prepared from $CuSO_4$ via reduction by $K_2S_2O_5$ in the presence of NaCl and was dried in the same way as

[‡] We used freshly crushed pale yellow coarse-grained crystals. White powder available from other sources was not suitable for our purpose (poor solubility).

Table 2. Summarized results of acyl chlorides reaction with organomagnesium compounds catalyzed by $AlCl_3 \cdot CuCl$



R	R′	Product	Yield (%)
			91[a]
			94[b]
			89[a]
			77[a]
			87[a]
			80[a]
			96[a]
			67[b]
			87[a]

[a] Isolated yields of purified product.
[b] Determined by GC.

the other chlorides. The white powder obtained can be stored under an argon atmosphere for several months.[§] Melting points are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75.5 (^{13}C) MHz (Bruker AM-300) or 500 (^{1}H) and 125.8 (^{13}C) MHz (Bruker DRX-500) respectively, using solvent as an internal standard. The IR spectra were recorded with FT-IR instrument Genesis ATI. GC analyses were run on a Shimadzu GC-17A instrument.

Ethylmagnesium bromide was prepared by refluxing ethyl bromide (10.90 g, 0.1 mol) with an excess of magnesium turnings (3.16 g, 0.13 mol) in diethyl ether.[14] The concentration of clear solution was determined by acid/base titration[15] before use.

[§] Commercial CuCl purchased from Fluka containing traces of $CuCl_2$ (colored light green) was not suitable for our experiments. It is not completely soluble in THF and caused low reproducibility and increasing amount of secondary alcohols.

4.2. General procedure for ketone preparation

Into a dry three-necked flask equipped with a magnetic stirring bar, thermometer and rubber septum, lithium chloride (5 mL of 0.03 M solution in THF) was transferred and the corresponding metal halide (0.075 mmol) was added and dissolved. Into the obtained clear solution, adamantane-1-carbonylchloride (**1**) (0.5 g, 2.5 mmol) was added and solution was stirred for 5 min. Then, Grignard reagent (2.5 mmol, 2 mL in ether) was added for the required time period using a syringe pump. After complete addition, the reaction mixture was quenched with hydrochloric acid (10 mL, 1 M solution). The water layer was extracted three times with 10 mL of diethyl ether. The collected organic layers were washed twice with potassium carbonate solution (10 mL, 1 M), once with ammonium chloride solution (10 mL, 3 M) and dried over sodium sulfate overnight. The solution was filtered from Na_2SO_4 and diluted to 50 mL with diethyl ether. The yield of ketone **2** and the composition of the crude product were then determined by gas chromatography. Cyclohexanone was used as an internal standard.

4.2.1. Adamantane-1-carbonyl chloride (1). Into a suspension of adamantane-1-carboxylic acid (25.0 g, 0.126 mol) in toluene (32 mL) at 70 °C, $SOCl_2$ (19.6 g, 0.164 mol) was added dropwise. The reaction mixture was stirred at this temperature for 8 h. Then dry toluene (30 mL) was added, the mixture was heated up and the $SOCl_2$/toluene azeotrope (30 mL) was distilled out. This procedure was repeated three times. Finally, 20 mL of solvent was distilled out, the residue was cooled down and allowed to crystallize at −15 °C. Pale yellow needles obtained were filtered and dried in a stream of an inert gas (yield 22.3 g, 89%, mp 47–48 °C, lit.[16] mp 49–51 °C). NMR data correspond with literature.[16]

4.2.2. 1-Adamantyl ethyl ketone (2). Used as a standard sample was prepared by the way described above scaled up to 25 mmol of starting acyl chloride **1**. $AlCl_3$ and CuCl were used as catalysts. Colorless flat crystals were obtained after crystallization from ethanol/water (4.3 g, 89%, mp 31–33 °C, lit.[17] 31–32 °C). NMR data correspond with literature.[18]

4.2.3. 1-(1-Adamantyl)propan-1-ol (3). Ketone **2** (1.32 g, 7 mmol) was treated with $LiAlH_4$ (0.2 g, 5 mmol) in 20 mL of dry diethyl ether at room temperature for 24 h according to literature procedure.[19] The reaction mixture was quenched by addition of 30% aq. KOH solution (20 mL). The resulting white suspension was filtered and washed with diethyl ether. The combined organic phases were washed with water and dried over Na_2SO_4. The solvent was removed and colorless needles were obtained in amount of 1.2 g (92%), mp 84–86 °C, lit.[20] mp 85–86 °C). NMR data correspond with literature.[20]

4.2.4. 3-(1-Adamantyl)pentan-3-ol (4). Into a solution of ethylmagnesium bromide (18.5 mL of 2.8 M diethyl ether solution), ketone **2** (10 mL of 1.04 M in THF) was dropwise added at 0 °C. The reaction mixture was well stirred for 20 h at 0–20 °C. After this period, the excess of Grignard reagent was destroyed by diluted hydrochloric acid. Organic layer was washed twice with solution of K_2CO_3 (20 mL, 1 M solution) and with brine (20 mL) and dried over Na_2SO_4. Colorless crystals obtained after solvent removing were crystallized from hexane to yield 2.03 g of alcohol **4** (88%), mp 67–69 °C, lit.[21] 68–69 °C. NMR data correspond with literature.[21]

4.2.5. Ethyl adamantane-1-carboxylate (5). The above title compound was prepared according to literature procedure[22] from adamantane-1-carboxylic acid (2.5 g, 0.014 mol). It was refluxed for 2 h in ethanol (20 mL, 0.343 mol) in the presence of catalytic amount of H_2SO_4. Crude product was purified by column chromatography (silica gel, chloroform) to yield 2.5 g of ester (86%) as a colorless liquid. Spectral data correspond with literature.[23]

4.2.6. 3,5-Dimethyladamantane-1-yl ethyl ketone. The above title compound was prepared by the same procedure like the ketone **2**. Colorless liquid was obtained after purification of the crude product by column chromatography (silica gel, 11% ethyl acetate/hexane); [Found: C, 81.8; H, 11.1. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98%]; ν_{max}(KBr) 2944–2844 (br), 1701, 1455, 1375, 1357, 1333, 1260, 1208, 1159, 1126, 1094, 1027, 895, 842, 804, 700, 514 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.39 (2H, q, J=7.2 Hz, $COCH_2CH_3$); 2.04–2.07 (1H, m, Ad); 1.57 (2H, m, Ad); 1.31–1.39 (4H, m, Ad); 1.28 (4H, m, Ad); 1.05–1.12 (2H, m, Ad); 0.94 (3H, t, J=7.2 Hz, $COCH_2CH_3$); 0.78 (6H, s, Ad-*Me*,); δ_C (75.5 MHz, $CDCl_3$) 216.2, 51.0, 48.5, 44.8, 43.1, 37.3, 31.1, 30.8, 29.6, 29.5, 8.1.

4.2.7. 1-Adamantyl 4-methylphenyl ketone. The above title compound was prepared by the same procedure like the ketone **2**. Colorless crystals were obtained after purification of the crude product by crystallization from methanol, mp 61–63 °C; [Found: C, 85.0; H, 8.8. $C_{18}H_{22}O$ requires C, 84.99; H, 8.72%]; ν_{max}(KBr) 2943–2846(br), 1657, 1606, 1452, 1342, 1271, 1238, 1176, 1103, 991, 928, 833, 812, 737, 607 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.53 (2H, m, Ph); 7.19 (2H, m, Ph); 2.39 (3H, m, Ad); 2.04–2.08 (9H, m, Ph-CH_3, Ad); 1.77 (6H, m, Ad); δ_C (75.5 MHz, $CDCl_3$) 209.5, 140.9, 136.8, 128.8, 127.8, 47.1, 39.5, 36.8, 28.5, 21.6.

Acknowledgements

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References and notes

1. Thibonnet, J.; Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787–4799.
2. Dieter, R. K.; Sharma, R. R.; Yu, H.; Gore, V. K. *Tetrahedron* **2003**, *59*, 1083–1094.
3. Kondo, J.; Inoue, A.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2002**, *43*, 2399–2402.
4. Kenning, D. D.; Mitchell, K. A.; Calhoun, T. R.; Funfar, M. R.; Sattler, D. J.; Rasmussen, S. C. *J. Org. Chem.* **2002**, *67*, 9073–9076.

5. Piazza, C.; Millot, N.; Knochel, P. *J. Organomet. Chem.* **2001**, *624*, 88–95.
6. Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1992**, *33*, 4439–4442.
7. Whitmore, F. C.; Wheeler, W. R. *J. Am. Chem. Soc.* **1938**, *60*, 2899–2900.
8. Whitmore, F. C.; Whitaker, J. S.; Mattil, K. F.; Popkin, A. H. *J. Am. Chem. Soc.* **1938**, *60*, 2790–2792.
9. Alper, H.; Huang, C.-C. *J. Org. Chem.* **1973**, *38*, 64–71.
10. Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *39*, 3728–3730.
11. Green, L.; Hemeon, I.; Singer, R. D. *Tetrahedron Lett.* **2000**, *41*, 1343–1346.
12. Jasien, P. G. *J. Phys. Chem.* **1995**, *99*, 6502–6508.
13. Le Carpentier, J.-M.; Weiss, R. *Acta Crystallogr. Sect. B* **1972**, *28*, 1437–1442.
14. Novakov, C. P.; Feierman, D.; Cederbaum, A. I.; Stoyanovsky, D. A. *Chem. Res. Toxicol.* **2001**, *14*, 1239–1246.
15. Gilman, H.; Wilkinson, P. D.; Fishel, W. P.; Meyers, C. H. *J. Am. Chem. Soc.* **1923**, *45*, 150–158.
16. Hoffmann, H. M. R.; Haase, K. *Synthesis* **1981**, *9*, 715–719.
17. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.
18. Qin, X.; Ishizuka, Y.; Lomas, J. S.; Teyuka, T.; Nakanishi, H. *Magn. Reson. Chem.* **2002**, *40*, 595–598.
19. Shiner, V. J.; Neumann, T. E. *Croat. Chem. Acta* **1996**, *69*, 1405–1420.
20. Kovalev, V. A.; Shokova, E. A. *Zh. Org. Khim.* **1981**, *17*, 109–116.
21. Dua, S.; Bowie, J. H.; Cerda, B. A.; Wesdemiotis, C. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1443–1448.
22. Marchand, A. P. *Tetrahedron* **1996**, *52*, 825–832.
23. Burkhard, J.; Janků, J.; Vodička, L. *Collect. Czech. Chem. Commun.* **1988**, *53*, 110–113.

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9,9-Dimethyl-8,10-dioxapentacyclo[5.3.0.0^{2,5}.0^{3,5}.0^{3,6}]decane and naphthotetracyclo[5.1.0.0^{1,6}.0^{2,7}]oct-3-ene: new substituted [1.1.1]propellanes as precursors to 1,2,3,4-tetrafunctionalized bicyclo[1.1.1]pentanes

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Abstract—Two new substituted [1.1.1]propellanes have been generated from the corresponding bicyclo[1.1.0]butanes in either single-step (**1a**) or four-step procedures (**1b**). The observed degree of double lithiation of the bicyclo[1.1.0]butanes is discussed in the context of DFT computational results. Addition reactions across the central C(1)–C(3) bonds of the propellanes were studied. Only the propellane **1b** gave the biacetyl addition product.
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1. Introduction

Polyfunctionalized bicyclo[1.1.1]pentanes (BCPs)[1] bearing functional substituents in addition to the two bridgehead ones are rare and sought-after as potential structural elements for molecular electronics and architecture.[2–4] Among a handful of such derivatives are 2,2-dichloro-[5] and polyfluoro derivatives,[6,7] which were obtained by direct halogenation of bicyclo[1.1.1]pentane-1,3-dicarboxylic acid or its esters.[8] Further transformations of the halogens to other groups have not been successful. In contrast, transformations of the carboxyl groups proceeded smoothly,[7,9] which enable the generation of 2,2-dichloro[1.1.1]propellane.[9] Recently, chlorination of the 2,4-dimethylene derivative of bicyclo[1.1.1]pentane-1,3-dicarboxylic acid and subsequent transformations of the halogenated products led to bicyclo[1.1.1]pentane-1,2,3,4-tetracarboxylic acid, the first example of tetrafunctionalized BCP **A**.[10]

A more versatile and general approach to polyfunctionalized BCPs **A** may, in principle, involve appropriately substituted [1.1.1]propellanes **B** (Fig. 1). Subsequent addition of biacetyl across the central bond of the propellane[11] introduces a carbonyl group amenable to further functional group manipulation.[12–14]

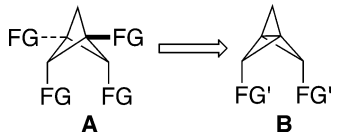
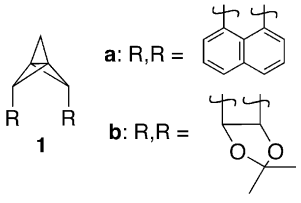


Figure 1. Retrosynthetic analysis for preparation of 1,2,3,4-tetrafunctionalized bicyclo[1.1.1]pentanes **A** through propellanes **B**.

Most [1.1.1]propellanes prepared to date are mono or geminally disubstituted derivatives of the parent [1.1.1]propellane or its 2,4-dimethylene or 2,4-trimethylene derivatives.[1,15] Only a handful of [1.1.1]propellanes are substituted with aryl,[16–18] vinyl[18] or alkoxymethyl[19,20] groups which are inert to propellane generation conditions and can be converted to the versatile carboxyl group. To our knowledge there is only one propellane with a benzyl group bridging the 2 and 4 positions,[16] which is a potential precursor to 1,2,3,4-tetrafuctionalized BCPs **A**. Unfortunately, the chemistry of this propellane has not been investigated.



Keywords: Substituted bicyclo[1.1.0]butanes and [1.1.1]propellanes; Theoretical models; Radical reactions.
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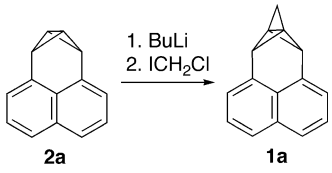
In order to develop synthetic access to tetrafunctionalized BCPs **A**, we focused on two new propellanes **1a** and **1b**. Here, we report the generation of the two substituted propellanes and some reactions at the central C–C bond with the emphases on the addition of biacetyl.

2. Results and discussion

2.1. Preparation of propellanes

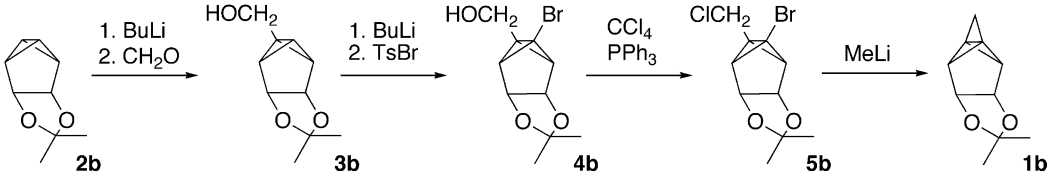
Propellanes **1a** and **1b** were prepared from appropriate bicyclo[1.1.0]butanes **2a** and **2b** using the methodology developed by Szeimies.[16] The former propellane was prepared in a single annelation step with $ClCH_2I$ taking advantage of the almost quantitative double deprotonation of **2a** (Scheme 1). The propellane **1a** was prepared in yields estimated at 30–40% and used as crude solutions in subsequent reactions.



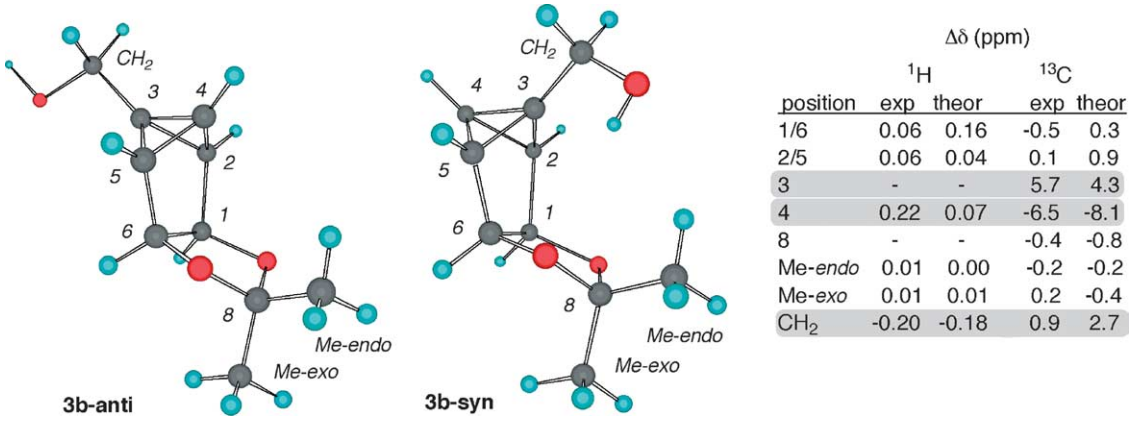
Scheme 1.

In contrast, propellane **1b** could not be prepared in the single-step procedure since the double deprotonation of **2b** was inefficient. Using *n*-BuLi, *sec*-BuLi or *tert*-BuLi at different temperatures, the double deprotonation occurred to less than 20%, as determined by quenching with D_2O and GCMS analysis.[21] Also prolonged reaction times led to decomposition of the precursor **2b**. This necessitated the use of the four-step route[16] shown in Scheme 2. Thus, hydroxymethylation of **2b** gave alcohol **3b** as a mixture of two isomers in about 2:1 ratio contaminated with a more polar compound presumably the corresponding bis(hydroxymethyl) derivative. After purification on alumina, the isomeric mixture of alcohols **3b** was brominated and the resulting **4b** was subsequently converted to the dihalide **5b** using the general literature conditions.[16] To improve the separation of the pure **5b**, small amounts of EtOH were added in the end of the reaction to convert the residual Ph_3P to the oxide. The overall average yield for the three steps was about 25%.

To assign stereochemistry of the two isomers formed during hydroxymethylation of **2b**, the minor isomer of **3b** was isolated chromatographically and the solid alcohol was purified by sublimation. NOESY experiments were inconclusive and the stereochemistry of the isomers was assigned based on a comparison of computational and experimental NMR data (Fig. 2). The analysis shows that the differences in theoretical chemical shifts $\Delta\delta$ (theor) for the *anti* and *syn* isomers follows the trend in the differences in experimental chemical shifts $\Delta\delta$ (exp) between the minor and major isomers. Perhaps the most diagnostic are the bridgehead positions of the bicyclo[1.1.0]butane ring and the hydroxymethyl group, which are most affected by the structural variation in the two isomers. Thus, the bridgehead carbon atom C(3) is significantly shielded, while C(4) is deshielded in the major and *syn* isomers relative to the minor and *anti*. Also, the CH_2 protons are significantly deshielded and the ^{13}C nucleus is shielded in the major and *syn* isomers relative to the minor and *anti*. This is consistent with general trends in exo/endo stereoisomers of bicycloalkanes.



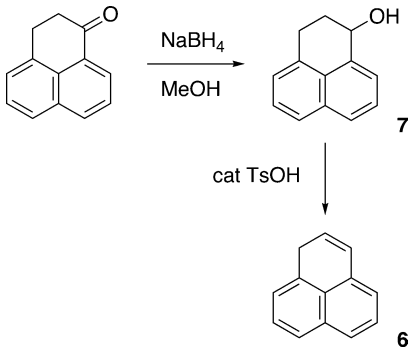
Scheme 2.



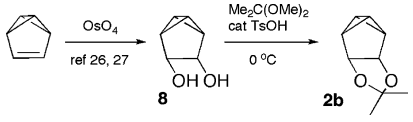
Δδ (ppm)

	^1H		^{13}C	
position	exp	theor	exp	theor
1/6	0.06	0.16	-0.5	0.3
2/5	0.06	0.04	0.1	0.9
3	-	-	5.7	4.3
4	0.22	0.07	-6.5	-8.1
8	-	-	-0.4	-0.8
Me-*endo*	0.01	0.00	-0.2	-0.2
Me-*exo*	0.01	0.01	0.2	-0.4
CH_2	-0.20	-0.18	0.9	2.7

Figure 2. Optimized gas phase geometries for **3b**-anti and **3b**-syn isomers and comparison of the difference in experimental and computed NMR chemical shifts: $\Delta\delta$ (exp)=δ (**3b**-minor)−δ (**3b**-major); $\Delta\delta$ (theor)=δ (**3b**-anti)−δ (**3b**-syn). Theoretical results obtained at the B3LYP/6-31G(d,p) level of theory.



Scheme 3.



Scheme 4.

Thus, the comparison indicates that the major isomer of **3b** has *syn* stereochemistry. This conclusion, however, is in contrast with previous reports on regioselectivity of methylation of a related carbocyclic system, where configuration of the major product was established to be *anti* based on independent synthesis.[22] Perhaps the dominance of the *syn* isomer in the present case results from the complexing ability of the 1,3-dioxolane ring oxygen atoms and preferential deprotonation of the pro-*syn* position.

Propellane **1b** was generated by treatment of a mixture of stereoisomers **5b** with MeLi and used as crude Et_2O/pentane solutions without further purification. ^{1}H NMR of **1b** shows that the propellane CH_2 group is deshielded by about 0.6 ppm relative to that in the parent [1.1.1]propellane.[16] For comparison, the CH_2 group in **1a** is shielded by about 0.25 ppm.

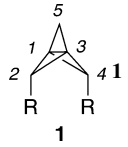
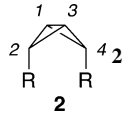
The bicyclo[1.1.0]butane **2a** was prepared from *1H*-phenalene (**6**), obtained by dehydration of 2,3-dihydro-*1H*-phenalen-1-ol[23] (**7**), following closely the literature procedure.[24] The alcohol **7** was conveniently prepared from 2,3-dihydro-*1H*-phenalen-1-one by substituting $NaBH_4$ for $LiAlH_4$ used in the original procedure[25] (Scheme 3).

Bicyclo[1.1.0]butane **2b** was prepared from benzvalene in two steps and 35% average overall yield (Scheme 4). Thus, **2b** was obtained by the reaction of glycol[26,27] **8** with 2,2-dimethoxypropane in the presence of TsOH for 30 min at 0 °C. Benzoic acid in benzene used in a similar procedure[26] was found to be ineffective in the present case. The preparation of benzvalene followed a literature procedure[28] except that a larger than recommended amount of MeLi was used in the third part of the reaction. When the second portion of MeLi was stoichiometric relative to CH_2Cl_2, the yields of benzvalene established by NMR[29] were 36–57% and similar to those reported in the literature.[28]

2.2. Molecular geometry and strain of 1 and 2

Structural effects on molecular geometry and strain energy of the parent [1.1.1]propellane (**1c**) and bicyclo[1.1.0]butane (**2c**) rings in **1** and **2** were assessed at the B3LYP/6-31G(d,p) level of theory and results are collected in Table 1. Analysis shows that the central C(1)–C(3) bond has virtually the same length in all three propellanes **1**, while in bicyclo[1.1.0]butanes **2a** and **2b** is shorter by about 0.02 Å than in the parent **2c**. The latter is consistent with experimental results for **2a**[30] and **2c**.[31] A comparison of the angles α indicates a modest contraction of

Table 1. Selected structural parameters and strain energies of propellanes **1** and bicyclo[1.1.0]butanes **2**

	d_{C1-C3} (Å)	α[a] (deg)	β[b] (deg)	SE[c] (kcal/mol)
 **1**				
a	1.576	118.6	124.3	94
b	1.576	112.4	112.2	92.5
c, R=H	1.578	120.0	122.6	98
	1.596(5)[d]			98[e]
 **2**				
a	1.471	118.0	124.6	62
	1.47(3)[f]	120(2)[f]	124(2)[f]	
b	1.472	110.9	113.0	60
c, R=H	1.491	121.9	124.7	66
	1.497(3)[g]	122.7(5)[g]	121.6(9)[g]	64[e]

[a] Angle between the two cyclopropane rings defined as C(2)-*-C(4), where * is the C(1)–C(3) midpoint.
[b] Angle defined as R-C(2)-*, where * is the C(1)–C(3) midpoint.
[c] Homodesmotic strain energies (SE) calculated according to Figure 3.
[d] Electron diffraction data; Hedberg, L.; Hedberg, K. *J. Am. Chem. Soc.* **1985**, *107*, 7257–7260.
[e] Ref 31.
[f] Solid state data; Ref. 30.
[g] Infrared data; Ref. 31.

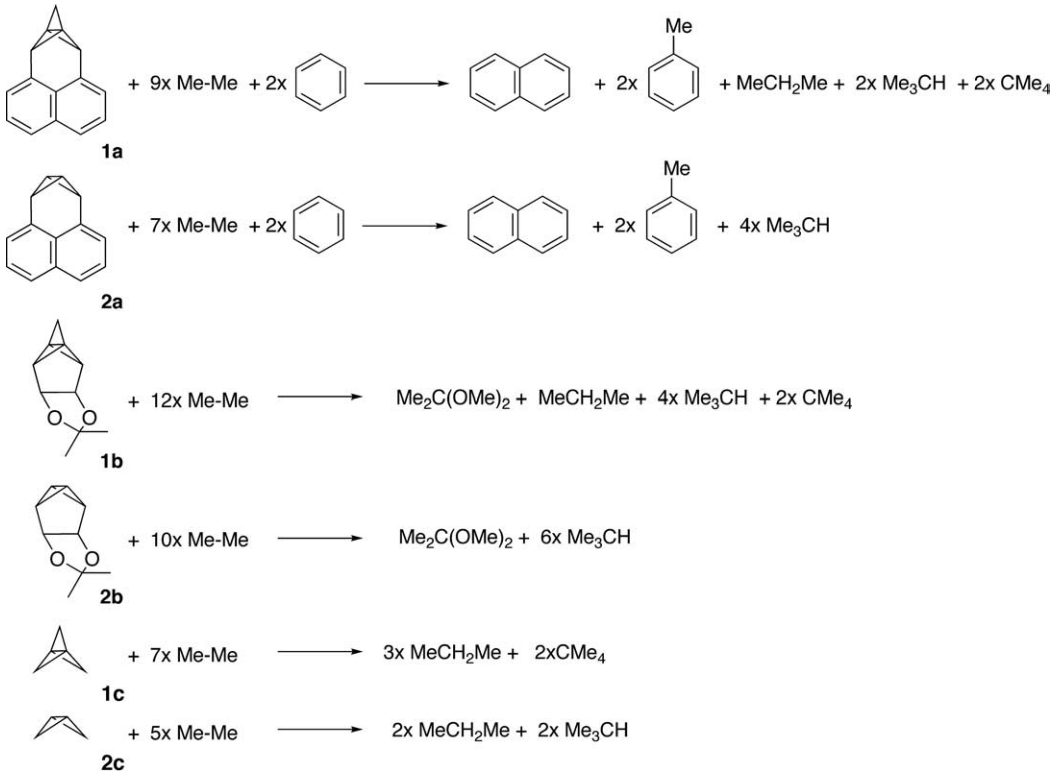


Figure 3. Homodesmotic reactions. Strain energies are listed in Table 1.

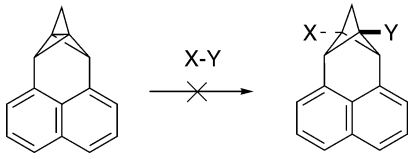
the angle between the cyclopropyl faces in the naphthalene derivatives **1a** and **2a** relative to the parent systems **1c** and **2c**. In contrast, the angle α in the dioxolane derivatives is smaller by about 7° for **1b** and 11° for **2b**, relative to the parent hydrocarbons. Similar results are obtained for the exocyclic bond angle β, which indicates a generally larger distortion of the propellane and bicyclobutane rings in the dioxolane (**b**) than in the naphthalene (**a**) derivatives.

In spite of significant deformation of the parent rings in the ketal derivatives **1b** and **2b**, the strain energies (SE) calculated using homodesmotic reactions[32] shown in Figure 3 are similar (within 6 kcal/mol) to those calculated in this work and previously reported[33] for the parent hydrocarbons.

The theoretical models for **1** and **2** provide an opportunity to analyze factors that may affect the efficiency of the double deprotonation of **2a** and **2b**. Previous studies concluded that a high degree of lithiation occurs for bicyclo[1.1.0]butanes carrying an sp^2 substituent, such as a phenyl ring, or those having a small angle between the cyclopropane faces.[21] Thus, the ease of double deprotonation of **2a** is in agreement with these empirical observations. In contrast, the low efficiency of complete deprotonation of **2b** is inconsistent with the previous conclusions and the 95% of double deprotonation observed[21] for 2,4-dimethylenebicyclo-[1.1.0]butane (tricyclo[3.1.0.0^{2,6}]hexane), a close analog of **2b**; both compounds have very similar small angle α of about 111°. Also, the computational analysis of the electronic structure of the bicyclobutanes is inconsistent with the deprotonation results. The NBO population analysis shows that the hybridization of the C(1/3) exocyclic hybrid is $sp^{1.81}$ in **2b** which has more s-character than the analogous orbital found in **2a** ($sp^{1.90}$). This would suggest enhanced C–H acidity of the bridgehead positions in the former and a more facile double deprotonation than in **2a**. For comparison, in the parent BCB the exocyclic orbital is $sp^{1.93}$ hybridized. Thus, the origin of the problem with the double deprotonation of **2b** is not clear.

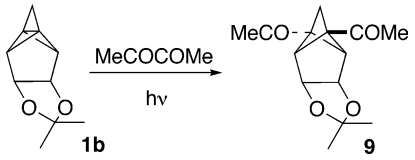
2.3. Reaction of propellanes 1

Initially, we investigated addition reactions to **1a**. Unfortunately, no radical or photochemical addition to this propellane gave a characterizable product (Scheme 5). Thus, the photochemically-induced addition of biacetyl[11] to **1a** in cyclohexane gave only highly colored decomposition products, even when a uranium glass filter was used to limit excitation of the naphthalene ring.[34] The colored products presumably resulted from the light-induced rearrangement of **1a** and subsequent polymerization of the olefins.[35] Addition of I_2 to **1a** in ether[36] resulted only in a black tar. Similarly, radical addition of PhSH or PhSSPh[36] to **1a** in ether at ambient temperature led to a brown complex mixture of unidentified products. Finally, attempts to introduce a carboxyl group at the bridgehead positions in **1a** first by lithiation either with *t*-BuLi[37] or lithium 4,4′-di-*t*-butylbiphenyl[13] followed by carboxylation with CO_2 was unsuccessful, and only a complex mixture of products was obtained.



Scheme 5.

In contrast, propellane **1b** underwent a smooth addition of biacetyl to form the diketone **9** in good yield (Scheme 6). The pure diketone **9** was separated from other by-products using column chromatography. The formation of polar by-products is promoted by large amounts of ether used as solvent, presumably due to light-induced radical reactions between biacetyl, ether and propellane.



Scheme 6.

3. Summary and conclusions

The preparation of both propellanes **1a** and **1b** was accomplished in about 5% overall yield starting from commercial 1-chloromethylnaphthalene (for **1a**) and cyclopentadiene (for **1b**) and using demanding seven-step procedures. Of the two propellanes, only **1b** proved useful for the formation of tetrasubstituted bicyclo[1.1.1]pentanes, and the diketone **9** was obtained in high yield from **1b**. In contrast, neither the photochemically- or thermally-induced radical additions to the central C(1)–C(3) bond in **1a**, nor a reaction with organometallic reagents led to isolable bicyclo[1.1.1]pentane derivatives.

The stereochemistry of the main isomer formed in hydroxymethylation of bicyclobutane **2b** was assigned as *syn* based on the comparison of experimental and theoretical chemical shifts for the *syn* and *anti* isomers. Simple analyses of molecular geometry and the hybridization of the C(1/3) exocyclic bond orbital in bicyclo[1.1.0]butanes **2a** and **2b** could not explain the observed marked difference in their ability to form dianions.

Thus, propellane **1b** is a promising precursor to 1,2,3,4-tetrafunctionalized bicyclo[1.1.1]pentanes. The functional group transformations of diketone **9** will be reported elsewhere.

4. Computational details

All quantum-mechanical calculations were carried out at the B3LYP/6-31G(d,p) level of theory[38,39] using the Linda–Gaussian 98 package[40] on a Beowulf cluster of 16 processors. Geometry optimizations were undertaken using appropriate symmetry constraints and default convergence limits. The isotropic shielding factors were obtained by using the GIAO algorithm.

5. Experimental

5.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively, in $CDCl_3$, unless specified otherwise. Chemical shifts were referenced to TMS (^{1}H) or solvent (^{13}C). IR spectra were recorded for neat samples on NaCl plates. Mass spectrometry data were acquired using a GCMS instrument. FAB/HRMS spectrometry was performed at Notre Dame University, IN. Elemental Analysis was provided by Atlantic Microlabs, GA. All reactions with organometallic reagents were performed under nitrogen and strictly anhydrous conditions. In these cases the glassware used was heated in vacuo to remove all residual moisture. All workup operations with propellanes **1a** and **1b** were performed in an inert atmosphere.

5.1.1. Naphthotetracyclo[5.1.0.0^{1,6}.0^{2,7}]oct-3-ene (1a). To a solution of the bicyclobutane[24] **2a** (145 mg, 0.814 mmol) in Et_2O (10 mL), *n*-BuLi solution in hexane (0.74 mL, 1.79 mmol, 2.44 M) was added at ambient temp and stirred for 6 h. The reaction mixture was cooled to −30 °C and chloroiodomethane (174 mg, 0.984 mmol) was added dropwise and stirred for 2 h at ambient temp. Then a 2 N aqueous NH_3 (5 mL) was added at 0 °C and stirred for 25 min. The aqueous layer was extracted with benzene (2×8 mL), the combined organic layers were dried (Na_2SO_4), and concentrated at reduced pressure. In case of visible precipitation, the solution can be filtered through a microfilter to remove polymeric materials. The resulting solid **1a** was about 90% pure by NMR: ^{1}H NMR (C_6D_6) major signals δ 1.81 (s, 2H), 3.57 (s, 2H), 6.86 (d, J=6.8 Hz, 2H), 7.06 (dd, J_1=8.4 Hz, J_2=6.8 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H). The crude solid propellane was dissolved in an appropriate solvent and used in subsequent reactions.

5.1.2. 9,9-Dimethyl-8,10-dioxapentacyclo[5.3.0.0^{2,5}.0^{3,5}.0^{3,6}]decane (1b). To a solution of dihalide **5b** (231 mg, 0.83 mmol) in Et_2O/pentane (15 mL, 2:1), MeLi in Et_2O (1.6 M, 0.62 mL, 0.99 mmol) was added at −30 °C and stirred for 2 h at ambient temp. Then a 2 N aqueous NH_3 (10 mL) was added at 0 °C and stirred for 20 min. The aqueous layer was extracted with Et_2O (2×10 mL) and the combined organic layers were dried (Na_2SO_4). The resulting solution of propellane **1b** was used directly for the next transformation to form **9**: ^{1}H NMR (ether/pentane/$CDCl_3$) δ 2.64 (s, 2H), 2.66 (s, 2H), 4.64 (s, 2H), the Me groups are obscured by the solvent peaks; MS, *m*/*z* (%) 163 (1) $[M-H]^+$, 149 (100) $[M-CH_3]^+$.

5.1.3. 8,8-Dimethyl-7,9-dioxatetracyclo[4.3.0.0^{2,4}.0^{3,5}]nonane (2b). To a solution of the diol **8** (16.2 g, 145 mmol) and 2,2-dimethoxypropane (500 mL) in $CHCl_3$ (500 mL), *p*-TsOH·H_2O (350 mg, 1.84 mmol) was added at −5 to 0 °C and the mixture was stirred for 30 min at the temperature below 0 °C. The reaction mixture was diluted with $CHCl_3$ (500 mL), washed with $NaHCO_3$ (2×300 mL) and brine (300 mL), dried (Na_2SO_4) and volatiles were removed under reduced pressure. Kugelrohr distillation (bp 40–44 °C/0.4–0.5 Torr) gave 19.9 g (90% yield) of the acetonide **2b** as a colorless low melting solid. For other four runs in 4–150 mmol scale the yields were 70–89%. Mp 19–21 °C; ^{1}H NMR δ 1.28 (s, 3H), 1.47 (s, 3H), 2.02 (dt, J_1=8.4 Hz, J_2=2.0 Hz, 1H), 2.29 (br s, 2H), 2.33–2.38 (m, 1H), 4.49 (br s, 2H); ^{13}C NMR δ 2.9, 8.6, 25.4, 26.9, 37.6, 82.4, 114.1; MS, *m*/*z* (%) 152 (2) $[M]^+$, 137 (100); HRMS, calcd

for $C_9H_{11}O_2$: 151.0759, found 151.0763. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.51: H, 7.62.

5.1.4. 8,8-Dimethyl-7,9-dioxatetracyclo[4.3.0.0^{2,4}.0^{3,5}]nonan-3-ylmethanol (3b). To a solution of the bicyclobutane **2b** (6.00 g, 39.4 mmol) in Et_2O (50 mL), *n*-BuLi solution in hexane (18.5 mL, 43.4 mmol, 2.35 M) was added at ambient temperature and stirred for 4 h. Gaseous formaldehyde, prepared by depolymerization of paraformaldehyde (6.00 g) at 170 °C, was introduced into the reaction mixture. After additional stirring for 1 h, water (25 mL) was added at ice bath cooling. The organic layer was washed with water (3× 10 mL) and the combined aqueous phases were extracted with ether (2×10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (Al_2O_3, Grade IV; CH_2Cl_2/MeOH 19:1 ratio containing 1% Et_3N, R_f=0.35) gave 4.09 g (57% yield) of alcohol **3b** as a 2:1 mixture of regio-isomers. For other four runs in 2–50 mmol scale the yields were 40–60%. The minor isomer was isolated as a slightly less polar fraction in the chromatographic purification of the mixture.

Minor isomer (**3b**-anti): mp 60.5–62 °C; ^{1}H NMR δ 1.26 (s, 3H), 1.45 (s, 3H), 2.42 (br s, 1H), 2.43 (s, 2H), 4.04 (s, 2H), 4.54 (s, 2H); ^{13}C NMR δ 7.0, 24.7, 25.3, 26.8, 40.7, 59.5, 82.1, 113.9; IR 3400 (br, OH), 1212 (C–O) cm^{-1}; GC/MS, rt 11.6 min, *m/z* (%) 182 (2) $[M]^+$, 167 (23) $[M-CH_3]^+$, 107 (55), 95 (100). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H 7.74. Found: C, 65.79; H, 7.79.

Major isomer (**3b**-syn) assigned from the mixture: ^{1}H NMR δ 1.25 (s, 3H), 1.44 (s, 3H), 2.19 (br s, 1H), 2.37 (s, 2H), 4.24 (s, 2H), 4.48 (s, 2H); ^{13}C NMR δ 13.5, 18.9, 25.1, 27.0, 40.6, 58.6, 82.6, 114.3; GC/MS, rt 10.9 min, *m/z* (%) 182 (1) $[M]^+$, 167 (100) $[M-CH_3]^+$, 95 (55).

5.1.5. 4-Bromo-8,8-dimethyl-7,9-dioxatetracyclo[4.3.0.0^{2,4}.0^{3,5}]nonan-3-ylmethanol (4b). To a solution of the isomeric mixture of alcohols **3b** (1.79 g, 9.83 mmol) in Et_2O (10 mL), *n*-BuLi solution in hexane (10 mL, 23.0 mmol, 2.3 M) was added and the mixture was stirred for 5 h. Solid *p*-toluenesulfonyl bromide[41] (2.70 g, 11.6 mmol) was added at 0 °C and the mixture was stirred for 1 h at ambient temperature. Then 10% NaOH (5 mL) was added dropwise. The aqueous layer was washed with Et_2O (3×20 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give 2.23 g (87% yield) of 85% pure (GCMS) **4b** as a yellowish oil, which was used without further purification for the next transformation. For other four runs in 1–15 mmol scale the yields were 60–82%. ^{1}H NMR δ (major signals) 1.26 (s, 3H), 1.44 (s, 3H), 2.67 (br s, 2H), 4.36 (br s, 2H), 4.62 (br s, 2H); MS, *m/z* (%) 260/262 (10/8) $[M]^+$, 187/185 (38/42), 67 (100); HRMS, calcd for $C_{10}H_{13}BrO_3$: 260.0048, found 260.0051.

5.1.6. 3-Bromo-4-(chloromethyl)-8,8-dimethyl-7,9-dioxatetracyclo[4.3.0.0^{2,4}.0^{3,5}]nonane (5b). A solution of crude bromo alcohol **4b** (1.69 g, 6.47 mmol) and Ph_3P (3.54 g, 13.5 mmol) in CCl_4 (35 mL) was stirred for 10 h at 80 °C. EtOH (2 mL) was added and stirring was continued for additional 3 h. After cooling, Celite (~5 g) was added and the mixture concentrated in vacuo. The solid residue was washed with petroleum ether containing CH_2Cl_2 (10%), the resulting solution was concentrated and the residue sublimed to give 1.19 g (66% yield) of **5b** as a white solid. For other four runs in 1–14 mmol scale the yields were 58–67%. Mp 55–65 °C; ^{1}H NMR δ major/minor 1.27/1.25 (s, 3H), 1.49/1.45 (s, 3H), 2.72/2.73 (s, 2H), 4.05/4.30 (s, 2H), 4.58/4.62 (s, 2H); ^{13}C NMR δ major/minor 22.7/22.9, 25.5/24.9, 27.0/26.7, 29.6/25.3, 40.0/39.4, 47.2, 82.2/81.7, 115.0/114.5; MS, *m/z* (%) 280/278 (3/2) $[M]^+$, 265/263 (10/8) $[M-CH_3]^+$, 77 (100). Anal. Calcd for $C_{10}H_{12}BrClO_2$: C, 42.96; H 4.33. Found: C, 43.19; H, 4.39.

5.1.7. 2,3-Dihydro-*1H*-phenalen-1-ol.[25] (7) 2,3-Dihydro-*1H*-phenalen-1-one[42] (3.64 g, 20.0 mmol) was added in one portion to a solution of $NaBH_4$ (984 mg, 26.0 mmol) in MeOH (50 mL) at 0 °C. The reaction mixture was stirred for 24 h at ambient temperature and quenched with 5% aq HCl (5 mL) and H_2O (200 mL). The precipitate was filtered and dissolved in Et_2O (80 mL). The organic phase was washed with H_2O (10 mL), dried (Na_2SO_4) and concentrated to yield the crude product. Flash column chromatography (SiO_2 3.5×30 cm, CH_2Cl_2, R_f=0.35) gave 3.17 g (86% yield) of alcohol **7** as an off-white light-sensitive solid: mp 81–83 °C (lit.[25] 85–86 °C); ^{1}H NMR δ 1.89 (br s, 1H), 2.09–2.26 (m, 2H), 3.07 (dt, J_1=16.4 Hz, J_2=5.9 Hz, 1H), 3.31 (ddd, J_1=16.4 Hz, J_2=8.2 Hz, J_3=5.4 Hz, 1H), 7.29 (dd, J_1=6.8 Hz, J_2=0.7 Hz, 1H), 7.39 (dd, J_1=7.7 Hz, J_2=6.8 Hz, 1H), 7.45 (dd, J_1=7.7 Hz, J_2=7.1 Hz, 1H), 7.54 (d, J=7.1 Hz, 1H), 7.69 (d, J=7.7 Hz, 1H), 7.78 (d, J=7.1 Hz, J_2=0.9 Hz, 1H).

5.1.8. 3,5-Diacetyl-9,9-dimethyl-8,10-dioxatetracyclo-[5.3.0.0^{2,5}.0^{3,6}]decane (9). Freshly distilled 2,3-butanedione (2 mL) was added to a solution of propellane **1b** in Et_2O/pentane prepared from 231 mg (0.83 mmol) of dihalide **5b**. The mixture was stirred at about 5 °C and irradiated with a 450 W medium-pressure Hanovia mercury lamp for 5 h. Volatiles were removed and the residue was short-path distilled (110 °C/0.01 Torr) giving 175 mg (85% based on **5b**) of hygroscopic diketone **9**. Alternatively, diketone was purified by column chromatography (neutral Alumina, Grade 1, hexane/CH_2Cl_2 9:1). For other three runs in 0.5–3 mmol scale the yields were 50–68% based on **5b**. ^{1}H NMR δ 1.28 (s, 6H), 2.08 (s, 3H), 2.21 (s, 3H), 2.42 (s, 2H), 3.33 (t, J=0.8 Hz, 2H), 4.85 (t, J=0.8 Hz, 2H); ^{13}C NMR δ 24.1, 24.3, 27.0, 27.4, 43.1, 47.7, 55.2, 65.0, 81.1, 114.7, 204.4; MS, *m/z* (%) 235 (100) $[M-CH_3]^+$; HRMS, calcd for $C_{14}H_{19}O_4$: 251.1283, found 251.1286.

Acknowledgements

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References and notes

1. Levin, M. D.; Kaszynski, P.; Michl, J. *Chem. Rev.* **2000**, *100*, 169–234.
2. Kaszynski, P.; Friedli, A. C.; Michl, J. *J. Am. Chem. Soc.* **1992**, *114*, 601–620.
3. Merkle, R. C. *Nanotechnology* **2000**, *11*, 89–99.

4. Schwab, P. F. H.; Levin, M. D.; Michl, J. *Chem. Rev.* **1999**, *99*, 1863–1933.
5. Robinson, R. E.; Michl, J. *J. Org. Chem.* **1989**, *54*, 2051–2053.
6. Shtarev, A. B.; Pinkhassik, E.; Levin, M. D.; Stibor, I.; Michl, J. *J. Am. Chem. Soc.* **2001**, *123*, 3484–3492.
7. Levin, M. D.; Hamrock, S. J.; Kaszynski, P.; Shtarev, A. B.; Levina, G. A.; Noll, B. C.; Newmark, R.; Moore, G. G. I.; Michl, J. *J. Am. Chem. Soc.* **1997**, *119*, 12750–12761.
8. 2,2-Dichlorobicyclo[1.1.1]pentane-1,3-dicarboxylic acid was also prepared through addition of CCl_2 to the appropriate bicyclo[1.1.0]butane; Applequist, D. E.; Wheeler, J. W. *Tetrahedron Lett.* **1977**, 3411–3412.
9. Hamrock, S. J.; Michl, J. *J. Org. Chem.* **1992**, *57*, 5027–5031.
10. Michl, J.; Mazal, C. Personal communication.
11. Kaszynski, P.; Michl, J. *J. Org. Chem.* **1988**, *53*, 4593–4594.
12. Kaszynski, P.; McMurdie, N. D.; Michl, J. *J. Org. Chem.* **1991**, *56*, 307–316.
13. Bunz, U.; Szeimies, G. *Tetrahedron Lett.* **1990**, *31*, 651–652.
14. Schwab, P. F. H.; Noll, B. C.; Michl, J. *J. Org. Chem.* **2002**, *67*, 5476–5485.
15. Kaszynski, P.; Michl, J. In Rappoport, Z., Ed.; The Chemistry of the Cyclopropyl Group; Wiley: New York, 1995; Vol. 2, pp 773–812.
16. Belzner, J.; Gareiß, B.; Polborn, K.; Schmid, W.; Semmler, K.; Szeimies, G. *Chem. Ber.* **1989**, *122*, 1509–1529.
17. Werner, M.; Stephenson, D. S.; Szeimies, G. *Liebigs Ann.* **1996**, 1705–1715.
18. Kenndoff, M.; Singer, A.; Szeimies, G. *J. Prakt. Chem.* **1997**, *339*, 217–232.
19. Klopsch, R.; Schlüter, A.-D. *Tetrahedron* **1995**, *51*, 10491–10496.
20. Kottirsch, G.; Polborn, K.; Szeimies, G. *J. Am. Chem. Soc.* **1988**, *110*, 5588–5590.
21. Schlüter, A.-D.; Huber, H.; Szeimies, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 404–405.
22. Paquette, L. A.; Taylor, R. T. *J. Am. Chem. Soc.* **1977**, *99*, 5708–5715.
23. Hempenius, M. A.; Lugtenburg, J.; Cornelisse, J. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 403–409.
24. Watson, C. R., Jr.; Pagni, R. M.; Dodd, J. R.; Bloor, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 2551–2562.
25. Boekelheide, V.; Larrabee, C. E. *J. Am. Chem. Soc.* **1950**, *72*, 1245–1249.
26. Christl, M.; Leiniger, H.; Kemmer, P. *Chem. Ber.* **1984**, *117*, 2963–2987.
27. Following footnote 10b in Bentley, T. W.; Norman, S. J.; Gerstner, E.; Kemmer, R.; Christl, M. *Chem. Ber.* **1993**, *126*, 1749–1757 is essential for achieving good yields.
28. Katz, T. J.; Roth, R. J.; Acton, N.; Carnahan, E. J. *J. Org. Chem.* **1999**, *93*, 7663–7664.
29. Miller, D. L.; Gross, M. L. *J. Am. Chem. Soc.* **1983**, *105*, 4239–4243.
30. Hazell, A. C. *Acta Cryst.* **1977**, *B33*, 272–274.
31. Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2184–2194.
32. George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Tetrahedron* **1976**, *32*, 317–323.
33. Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312–322.
34. Spanget-Larsen, J.; Gubernator, K.; Gleiter, R.; Thulstrup, E. W.; Bianco, B.; Gandillion, G.; Burger, U. *Helv. Chim. Acta* **1983**, *66*, 676–686.
35. Turro, N. J.; Ramamurthy, V.; Pagni, R. M.; Butcher, J. A., Jr. *J. Org. Chem.* **1977**, *42*, 92–96.
36. Wiberg, K. B.; Waddell, S. T. *J. Am. Chem. Soc.* **1990**, *112*, 2194–2216.
37. Schlüter, A.-D. *Macromolecules* **1988**, *21*, 1208–1211.
38. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
39. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
40. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.9, Gaussian, Inc., Pittsburgh, PA, 1998.
41. Poshkus, A. C.; Herweh, J. E.; Magnotta, F. A. *J. Org. Chem.* **1963**, *28*, 2766–2769.
42. Fieser, L. F.; Gates, M. D., Jr. *J. Am. Chem. Soc.* **1940**, *62*, 2335–2341.

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Synthesis of an imidazolium-linked cyclophane from histamine

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Abstract—The synthesis and structural characterization of a dicationic imidazolium-linked cyclophane **7** is reported. In **7**, two imidazolium units that have histamine dihydrochloride as a precursor are bridged by two 2,6-bis(bromomethyl)-pyridine.
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1. Introduction

Öfele[1] and Wanzlick[2] reported the first metal-*N*-heterocyclic carbene complexes synthesized from imidazolium salts in 1968. *N*-heterocyclic carbenes (NHC), also known as diaminocarbenes, are a class of ligands which have been shown to bind tightly to a wide variety of metals.[3] The synthesis of new imidazolium-linked cyclophanes is of interest to those working with *N*-heterocyclic carbenes because they serve as precursors which are easily converted to NHCs.

The chemistry of imidazolium-linked cyclophanes has been explored by our group[4] and others.[5] Our work involves the synthesis of cyclic ligand systems which can be reacted with a wide variety of transition metals in different oxidation states to afford new NHC metal complexes. Our interest in this area is the potential use of metal *N*-heterocyclic carbene complexes as medicinal agents. In 1998, Lin and co-workers reported the use of Ag_2O to produce silver *N*-heterocyclic carbenes.[6] Recently, we have demonstrated Ag(I)–carbene complexes have novel antimicrobial properties.[7] We have also reported the synthesis of rhodium carbene complexes as models for novel radiopharmaceuticals.[8] In accordance with our pursuit of medicinal agents, we report herein, the use of the biological molecule histamine to synthesize a dicationic imidazolium-linked cyclophane with side chains. These side chains could be linked to various targeting groups to produce a targeted radioimmunoconjugate.

2. Results and discussion

Pyman and Van Der Merwe[9] reported the alkylation of histamine at the various positions, N^{π}, N^{α} and N^{τ}[10] (Scheme 1). The selective alkylation of N^{τ} was obtained after the protection of N^{π} and N^{α}. Otherwise, electrophilic attack also occurs on both N^{π} and N^{α}. The reaction of histamine dihydrochloride (**1**) with 1,1′-carbonyl-diimidazole (**2**) gives the N^{π} and N^{α} protected histamine (**3**) (Scheme 1).[11] The ^1H and ^{13}C NMR spectra are consistent with the structure of **3**.[11] Compound **3** was crystallographically characterized by single crystal X-ray diffraction. Crystals suitable for X-ray diffraction were obtained from a saturated solution in acetonitrile. The thermal ellipsoid plot of compound **3** is illustrated in Figure 1.

The condensation of 2,6-bis(bromomethyl)-pyridine (**4**) with **3** in acetonitrile gives the dicationic imidazolium salt, **5a**. Compound **3** is considerably less reactive than other imidazole derivatives when forming imidazolium salts. This is likely due to the electron withdrawing effects of the diamide protecting group making N^{τ} less nucleophillic. Anion exchange of **5a** with ammonium hexa-fluorophosphate in water yields the hexafluorophosphate salt **5b** (Scheme 1). The ^1H and ^{13}C NMR spectra for $[\mathbf{5}][PF_6]_2$ are consistent with the proposed structure. The most notable feature of the ^1H NMR spectrum is the presence of the imidazolium proton resonance at 9.76 ppm. This value is in the range of C–H acidic proton shift of imidazolium salts ($\delta = 8$–10).[12] In the ^{13}C spectrum of compound $\mathbf{5}[Br]_2$, signals due to C1 (C=O) and C6 (N–C–N) were seen at 145.01 and 153.15 ppm, respectively. Crystals of $[\mathbf{5}][PF_6]_2$ suitable for X-ray crystallography were obtained from a concentrated 1:1 water–acetonitrile mixture. The thermal ellipsoid plot of compound **5** is shown in Figure 2.

Keywords: Histamine dihydrochloride; Imidazolium-linked cyclophane.
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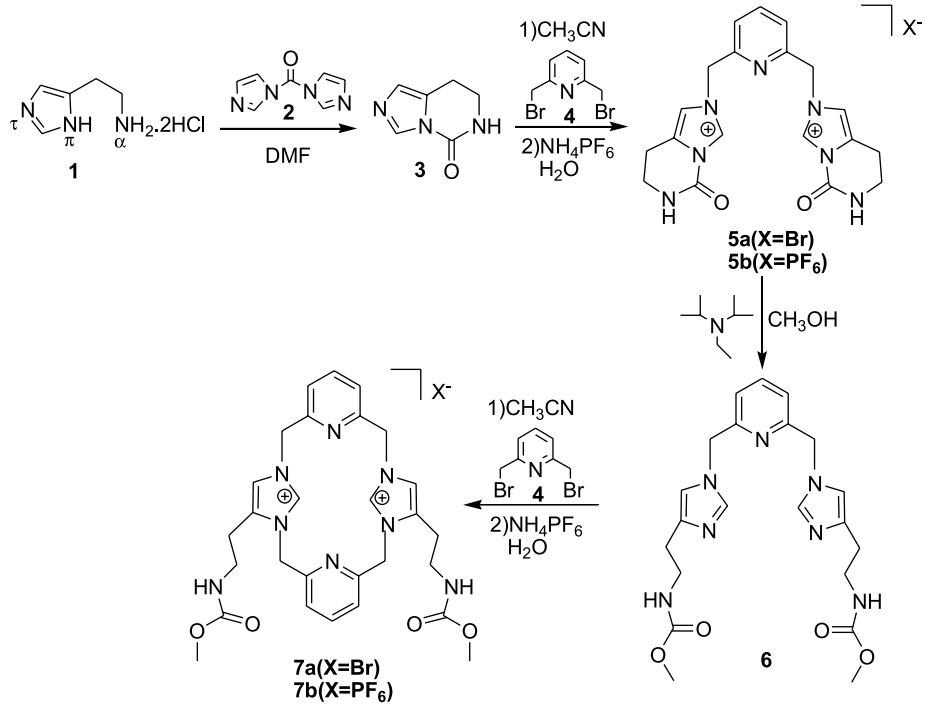


Scheme 1. Synthesis of **7**.

Compound **5a** was deprotected by refluxing in methanol in the presence of *N*,*N*-diisopropylethylamine to obtain compound **6**. Colorless crystals of compound **6** were obtained from concentrated CH_2Cl_2 solution. The thermal ellipsoid plot of compound **6** is illustrated in Figure 3. ^1H and ^{13}C NMR spectra (DMSO-d_6) of compound **6** are consistent with the crystal structure. In the ^1H NMR spectrum of compound **6**, signal due to the protons on C5 and C5A were observed at 7.62 ppm conforming the change from imidazolium proton (C–H^+) to imidazole proton (C–H).

Condensation of **6** and **4** in acetonitrile yields the dicationic cyclophane, **7**$[Br]_2$. The hexafluorophosphate salt, **7**$[PF_6]_2$ was isolated by anion exchange with ammonium hexafluorophosphate in water. Suitable crystals of [**7**]$[PF_6]_2$ for X-ray crystallography were obtained from a concentrated 1:1 water–acetonitrile mixture. The thermal ellipsoid plot of compound **7** is shown in Figure 4. Cyclophane [**7**]$[PF_6]_2$ has an inner cavity that is suitable for complexation to a variety of metals. The distances N1–N4 and C9–C19 (distance between the centroids of imidazolium rings) are 5.081 and 4.862 Å, respectively. ^1H and ^{13}C NMR spectra (DMSO-d_6) of [**7**]$[PF_6]_2$ are consistent with the proposed structure. The imidazolium proton appears at 8.95 ppm in the ^1H NMR spectrum of [**7**]$[PF_6]_2$.

The reaction of [**7**]$[PF_6]_2$ with Ag_2O in DMSO at 55 °C yields the silver complex of cyclophane **7**. The ESI-MS spectra showed $[M-H]^+$ at *m*/*z* 651.2. Further characterization of this compound is in progress.

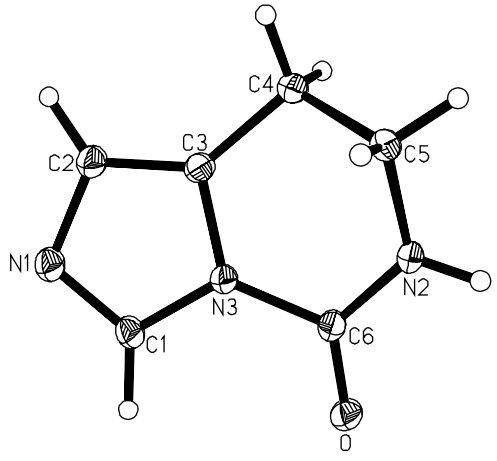


Figure 1. Molecular structure of **3** with thermal ellipsoids drawn at 50% probability.

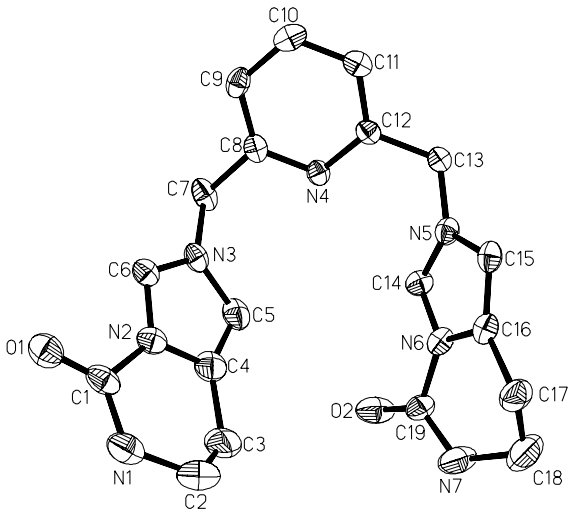


Figure 2. Molecular structure of dicationic portion of [**5**]$[PF_6]_2$ with thermal ellipsoids drawn at 50% probability. Hydrogen atoms have been omitted for clarity.

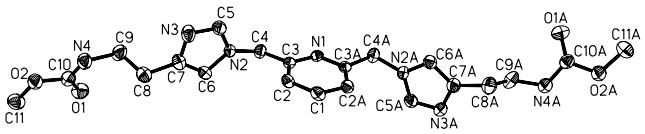


Figure 3. Molecular structure of **6** with thermal ellipsoids drawn at 50% probability. Hydrogen atoms have been omitted for clarity.

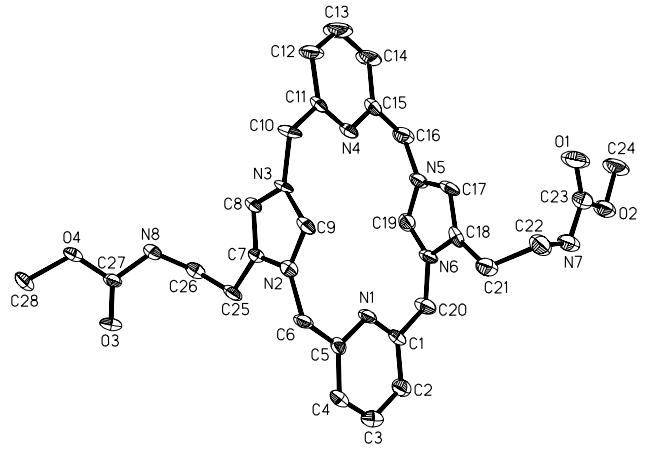
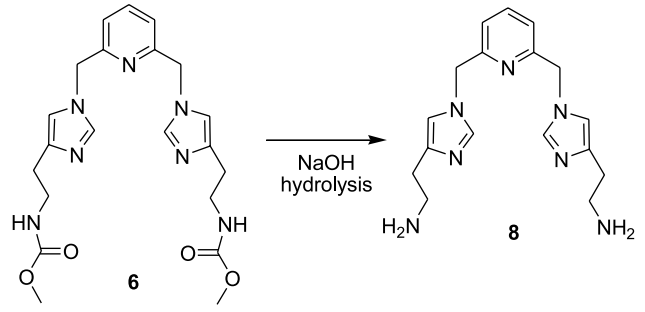


Figure 4. Molecular structure of dicationic portion of [**7**][PF6]$_2$ with thermal ellipsoids drawn at 50% probability. Hydrogen atoms have been omitted for clarity.

The base catalyzed hydrolysis of **6**, using sodium hydroxide, resulted in compound **8** (Scheme 2). The ESI-MS spectra showed [**8**+H]$^+$ at *m*/*z* 326.2 and [**8**+Na]$^+$ at *m*/*z* 348.2. The ^{1}H and ^{13}C NMR spectra easily confirm the cleavage of the ester groups by the absence of the resonances due to the methyl group (O–CH$_3$).



Scheme 2. Synthesis of **8**.

3. Conclusion

In this work, we have synthesized a dicationic imidazolium-linked cyclophane with side chains, [**7**][Br]$_2$, by condensing **6** with 2,6-bis(bromomethyl)-pyridine (**4**) in acetonitrile. [**7**][PF$_6$]$_2$ was obtained by exchanging bromide ions in the presence of $NH_4^+PF_6^-$. This ligand system should bind strongly to transition metals to make stable metal NHC complexes. A variety of targeting groups, including peptides, nitroimidazole, as well as other moieties, could be attached to the ligand through the ester functionality. Study of the metal binding chemistry of **5** and **7** as well as the attachment of targeting groups to **7** is currently underway.

4. Experimental

4.1. General procedures

All experiments were performed in air except for the synthesis of **6** was performed under a nitrogen atmosphere with Schlenk techniques. Histamine dihydrochloride was purchased from Aldrich and used as received. 1,1′-Carbonyldiimidazole was purchased from Acros and used as received. 2,6-Bis(bromomethyl)-pyridine was prepared by following literature procedures.[13]

^{1}H and ^{13}C NMR data were measured using a Varian300. Chemical shifts are in ppm. Mass spectra data were obtained from a Bruker Daltons (Billerica, MA) Esquire-LC mass spectrometer equipped with ESI and VG Autospec and Tandem Mass Spectrometer equipped with FAB. Micro-analyses laboratory at The University of Illinois and Galbraith Laboratories performed elemental analyses.

The data sets to determine crystal structures were collected on a Bruker Apex CCD diffractometer with graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The reflections from three different orientations were used to determine the unit cell. Multi-scan SADABS was used to make corrections. The Bruker SHELXTL computer program was used to solve structures, refine and model. The structures were obtained by full-matrix least-squares refinement of F^2 and the selection of appropriate atoms from the generated difference map.

4.1.1. Synthesis of 5,6,7,8-tetrahydro-5-oxoimidazo[1,5-*c*]pyrimidine (3). Compound **3** was prepared by following literature procedures.[11] Mp: 218–219 °C. (lit. Mp 220–221 °C); IR (cm^{-1}): 3114, 2893, 1734, 1709, 1456, 1409, 1344, 1209, 931, 833, 754, 651; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 8.19 (s, 1H, NH), 8.04 (s, 1H, 2-H), 6.78 (s, 1H, 4-H), 3.33 (m, 2H, CH$_2$), 2.86 (t, 2H, N–CH$_2$, J=6.6 Hz); ^{13}C NMR (60 MHz, DMSO-d$_6$): δ 148.4, 134.0, 127.3, 124.7, 38.7, 19.3; FAB-MS (*m*/*z*): calcd for $C_6N_3OH_8$ [M+H]$^+$:138.15. Found 138.00; Anal. calcd for $C_6N_3OH_7$ C, 52.57; H, 5.14; N, 30.65. Found: C, 52.32; H, 5.29; N, 30.54.

Crystal data for **3** $C_6H_7N_3O$: M_w=137.15, colorless crystal 1.00×0.40×0.20 mm, a=7.3860(6) Å, b=11.4148(10) Å, c=7.5885(6) Å, α=90°, β=110.1520(10)°, δ=90°, V=600.62(9) Å^3, D_{calcd}=1.517 mg m^{-3}, μ=0.110 mm^{-1}, Z=4, monoclinic, space group $P2_1/n$, λ=0.71073 Å, T=100 K, ω and ϕ scans, 7172 reflections collected, 1371 independent (R_{int}=0.0184), 119 refined parameters, $R1/wR2$ ($I\geq 2\sigma(I)$)=0.0374/0.0956 and $R1/wR2$ (all data)=0.0382/0.0965, maximum (minimum) residual electron density 0.301 (−0.533) e Å^{-3}.

4.1.2. Synthesis of 2,6-bis(5,6,7,8-tetrahydro-5-oxoimidazo[1,5-*c*]pyrimidiniummethyl)-pyridine bromide (5). The solution of compound **3** (0.979 g, 7.14 mol) and 2,6-bis(bromomethyl)-pyridine (**4**) (0.78 g, 2.98 mol) in 30 ml

of acetonitrile was stirred at 75 °C for 8 h to give [**5**][Br]$_2$ as a white solid (1.35 g, 84%). Mp: 236–238 °C; IR (cm^{-1}): 3408, 3162, 1748, 1442, 1320, 1168, 1131, 835, 749, 652; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 9.75 (s, 2H), 9.10 (s, 2H, NH), 7.98 (t, 1H, Ar-H, J=7.8 Hz), 7.59 (s, 2H, CH), 7.52 (d, 2H, Ar-H, J=7.8 Hz), 5.54 (s, 4H, bridge-CH$_2$), 3.49 (multiplet, 4H, N–CH$_2$), 3.01 (t, 4H, CH$_2$, J=6.3 Hz); ^{13}C NMR (60 MHz, DMSO-d$_6$): δ 153.1, 145.0, 138.9, 135.4, 130.7, 122.5, 118.8, 53.0, 38.2, 18.4; ESI-MS (*m*/*z*): calcd for $C_{19}N_7O_2H_{20}$ [M−2Br−H]$^+$: 378.41. Found 378.17; Anal. calcd for $C_{19}H_{23}F_{12}N_7O_3P_2C$, 33.20; H, 3.37; N, 14.26. Found: C, 33.80; H, 3.43; N, 14.32.

Crystal data for [**5**][PF$_6$]$_2$ $C_{19}H_{24}F_{12}N_7O_{3.50}P_2$: M_w=696.39, colorless crystal 0.30×0.20×0.05 mm, a=10.4302(9) Å, b=12.5948(11) Å, c=21.4179(19) Å, α=94.955(2)°, β=101.215(2)°, γ=90.842(2)°, V=2748.1(4) Å^3, D_{calcd}=1.683 mg m^{-3}, μ=0.280 mm^{-1}, Z=4, triclinic, space group $P-1$, λ=0.71073 Å, T=100 K, ω and ϕ scans, 33,996 reflections collected, 12,328 independent (R_{int}=0.0294), 762 refined parameters, $R1$/$wR2$ ($I\geq 2\sigma(I)$)=0.0841/ 0.2323 and $R1$/$wR2$ (all data)=0.0990/ 0.2418, maximum (minimum) residual electron density 1.124 (−0.874) e Å^{-3}.

4.1.3. Synthesis of 2,6-bis[*N*-α-(methoxycarbonyl)-histaminemethyl]-pyridine (6). *N*,*N*-diisopropylethylamine (0.35 ml, 2 mol) was added to the solution of [**5**][Br]$_2$ (0.5 g, 0.93 mol) in 12 ml of methanol. The reaction mixture was stirred at 60 °C for 48 h under a nitrogen atmosphere. After the volatiles were evaporated in vacuo, the residue was dissolved in 150 ml of dichloromethane. The dichloromethane solution was washed with 150 ml of water and dried over Na_2SO_4. After filtration, the volatiles were removed in vacuo, yielding **6** as a white solid (0.21 g, 51%). Mp: 136–137 °C; IR (cm^{-1}): 3228, 3051, 2962, 2946, 1704, 1575, 1503, 1458, 1428, 1287, 1261, 1235, 1171, 1044, 987, 834, 779, 649, 633; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.76 (t, 1H, Ar-H, J=8.1 Hz), 7.62 (s, 2H, CH), 7.14 (br s, 2H, NH), 7.01 (d, 2H, Ar-H, J=7.5 Hz), 6.93 (s, 2H, CH), 5.20 (s, 4H, bridge-CH$_2$), 3.48 (s, 6H, CH$_3$), 3.18 (multiplet, 4H, N–CH$_2$), 2.55 (t, 4H, CH$_2$, J=7.5 Hz); ^{13}C NMR (60 MHz, DMSO-d$_6$): δ 156.7, 156.6, 139.2, 138.5, 137.1, 120.4, 116.2, 51.1, 40.4, 28.5; FAB-MS (*m*/*z*): calcd for $C_{21}H_{28}N_7O_4$ [M+H]$^+$: 441.49. Found 442.00; Anal. calcd for $C_{21}H_{27}N_7O_4$ C, 57.13; H, 6.16; N, 22.21. Found: C, 57.16; H, 6.21; N, 21.22.

Crystal data for **6** $C_{21}H_{27}N_7O_4$: M_w=441.50, colorless crystal 0.40×0.10×0.04 mm, a=14.094(4) Å, b=8.188(3) Å, c=19.262(6) Å, α=90°, β=96.860(5)°, α=90°, V=2207.0(12) Å^3, D_{calcd}=1.329 mg m^{-3}, μ=0.095 mm^{-1}, Z=4, Monoclinic, space group $C2/c$, λ=0.71073 Å, T=100 K, ω and ϕ scans, 7738 reflections collected, 1950 independent (R_{int}=0.0329), 151 refined parameters, $R1$/$wR2$ ($I\geq 2\sigma(I)$)=0.0992/0.2705 and $R1$/$wR2$ (all data)=0.1117/0.2779, maximum (minimum) residual electron density 1.856 (−0.306) e Å^{-3}.

4.1.4. Synthesis of imidazolium-linked cyclophane (7). A mixture of compound **6** (0.15 g, 0.34 mol) and 2,6-bis(bromomethyl)-pyridine (**4**) (0.17 g, 0.64 mol) in 15 ml of acetonitrile was stirred at 75 °C for 18 h. The volatile materials were removed in vacuo, yielding [**7**][Br]$_2$ as a yellow solid (0.17 g, 70%). Mp: 186–187 °C; IR (cm^{-1}): 3440, 3160, 2961, 1718, 1582, 1525, 1446, 1251, 1177, 835, 779, 658, 651, 642; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 9.00 (s, 2H), 8.01 (t, 2H, Ar-H), 7.61 (d, 4H, Ar-H, J=8.4 Hz), 7.44 (s, 2H, CH), 7.25 (br s, 2H, NH), 5.57 (s, 4H, bridge-CH$_2$), 5.53 (s, 4H, bridge-CH$_2$), 3.46 (s, 6H, CH$_3$), 3.23 (m, 4H, N–CH$_2$), 3.16 (t, 4H, CH$_2$); ^{13}C NMR (60 MHz, DMSO-d$_6$): δ 156.7, 153.3, 153.0, 138.7, 138.6, 137.1, 132.4, 122.7, 122.5, 120.1, 52.4, 51.4, 50.1, 38.0, 23.7; ESI MS (*m*/*z*): calcd for $C_{28}N_8O_4H_{34}PF_6$ [M−PF$_6$]$^+$ 691.23. Found 691.30. Anal. calcd for $C_{28}H_{34}F_{12}N_8O_4P_2$ C, 40.18; H, 4.10; N, 13.40. Found: C, 39.60; H, 3.93; N, 12.52.

Crystal data for [**7**][PF6]$_2$ $C_{28}H_{34}F_{12}N_8O_4P_2$: M_w=836.57, colorless crystal 0.1×0.04×0.04 mm, a=21.297(5) Å, b=8.876(2) Å, c=36.582(9) Å, α=90°, β=90°, γ=90°, V=6915(3) Å^3, D_{calcd}=1.607 mg m^{-3}, μ=0.239 mm^{-1}, Z=8, orthorhombic, space group *Pcab*, λ=0.71073 Å, T=100 K, ω and ϕ scans, 33,656 reflections collected, 6785 independent (R_{int}=0.0990), 487 refined parameters, $R1$/$wR2$ ($I\geq 2\sigma(I)$)=0.0939/0.2086 and $R1$/$wR2$ (all data)=0.1316/0.2219, maximum (minimum) residual electron density 0.730 (−0.417) e Å^{-3}.

4.1.5. Synthesis of 2,6-bis(histaminemethyl)-pyridine (8). Compound **6** (0.20 g, 0.45 mol) was stirred with 30 ml of 0.04 N sodium hydroxide at 100 °C for 48 h. The mixture was dried in vacuo and the residue was dissolved in 100 ml of water. The aqueous solution was extracted two times with 100 ml portions of dichloromethane and dried over Na_2SO_4. After filtration, the volatiles were removed in vacuo yielding **8** as a yellow solid (0.09 g, 61%). Mp: 70–72 °C; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.78 (t, 1H, Ar-H, J=7.8 Hz), 7.62 (s, 2H, CH), 7.04 (d, 2H, Ar-H, J=7.8 Hz), 6.90 (s, 2H, CH), 5.21 (s, 4H, bridge-CH$_2$), 2.72 (m, 4H, N–CH$_2$), 2.51 (t, 4H, CH$_2$); ^{13}C NMR (60 MHz, DMSO-d$_6$): δ 156.4, 140.2, 138.3, 136.7, 120.3, 115.7, 50.9, 41.5, 32.2; ESI MS (*m*/*z*): calcd for $C_{17}H_{24}N_7$ [M+H]$^+$: 326.21. Found 326.20.

5. Supplementary data

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre. The CCDC nos. 228971, 228972, 228973, and 228974 have been assigned for the compounds **3**, [**5**][PF$_6$]$_2$, **6**, and [**7**][PF$_6$]$_2$ respectively. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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diffractometer used in this work. We would like to thank Dr. Wesdemiotis and Kathleen Wollyung for the mass spectrometry data.

References and notes

1. Öfele, K. *J. Organomet. Chem.* **1968**, *12*, 42–43.
2. Wanzlick, H. W.; Schonherr, H. J. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 141.
3. (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91. (b) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309.
4. (a) Garrison, J. G.; Simons, R. S.; Talley, J. M.; Wesdemiotis, C.; Tessier, C. A.; Youngs, W. J. *Organometallics* **2001**, *20*, 1276–1278. (b) Garrison, J. G.; Simons, R. S.; Kofron, W. G.; Tessier, C. A.; Youngs, W. J. *J. Chem. Soc., Chem. Commun.* **2001**, *18*, 1780–1781. (c) Garrison, J. C.; Simons, R. S.; Tessier, C. A.; Youngs, W. J. *J. Organomet. Chem.* **2003**, *673*(1-2), 1–4. (d) Simons, R. S.; Custer, P.; Tessier, C. A.; Young, W. J. *Organometallics* **2003**, *22*(9), 1979–1982.
5. (a) Alcalde, E.; Gisbert, M.; Alvarez-Rua, C.; Garcia, G. S. *Tetrahedron* **1996**, *52*(48), 15189–15196. (b) Alcalde, E.; Mesquida, N.; Perez-Garcia, L.; Ramos, S.; Alemany, M.; Rodriguez, M. L. *Eur. J. Chem.* **2002**, *8*(2), 474–484. (c) Baker, M. V.; Bosnich, M. J.; Williams, C. C.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1999**, *52*, 823–825. (d) Magill, A. M.; McGuinness, D. S.; Cavell, K. J.; Britovsek, G. J. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J.; White, A. H.; Skelton, B. W. J. *Organomet. Chem.* **2001**, *617–618*, 546–560. (e) Alcalde, E.; Alemany, M.; Perez-Garcia, L.; Rodriguez, M. L. *J. Chem. Soc., Chem. Commun.* **1995**, *12*, 1239–1240. (f) Alcalde, E.; Alvarez-Rua, C.; Garcia-Granda, S.; Garcia-Rodriguez, E.; Mesquida, N.; Perez-Garcia, L. *J. Chem. Soc. Chem. Commun.* **1999**, *3*, 295–296. (g) Alcalde, E.; Mesquida, N.; Vilaseca, M. *Rapid Commun. Mass Spectrom.* **2000**, *14*(16), 1443–1447. (h) Bitter, I.; Torok, Z.; Csokai, V.; Grun, A.; Balazs, B.; Toth, G.; Keseru, G. M.; Kovari, Z.; Czugler, M. *Eur. J. Org. Chem.* **2001**, *15*, 2861–2868.
6. Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972–975.
7. Melaiye, A.; Simons, R. S.; Milsted, A.; Pingitore, F.; Wesdemiotis, C.; Tessier, C. A.; Youngs, W. J. *J. Med. Chem.* **2004**, *47*, 973–977.
8. Quezada, C. A.; Garrison, J. C.; Panzner, M. J.; Tessier, C. A.; Youngs, W. J. *Organometallics* **2004**, *23*(21), 4846–4848.
9. Durant, G.; Emmett, J. C.; Ganellin, C. R.; Roe, A. M.; Slater, R. A. *J. Med. Chem.* **1976**, *19*, 923–928.
10. Noordam, A.; Maat, L.; Beyerman, H. C. *Recueil J. R. Netherlands Chem. Soc.* **1978**, *97*(11), 293–295.
11. Jain, R.; Cohen, L. A. *Tetrahedron* **1996**, *52*(15), 5363–5370.
12. Hermann, W. A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187.
13. Haeg, M. E.; Whitlock, B. J.; Whitlock, H. W. *J. Am. Chem. Soc.* **1989**, *111*(2), 692–696.

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Copper-mediated regio- and stereoselective 12β-hydroxylation of steroids with molecular oxygen and an unexpected 12β-chlorination

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Dedicated to Professor D. Walther on the occasion of his 65th birthday

Abstract—It is shown, that copper(I) complexes of 17-(2-iminomethyl)pyridino steroids (17-IMPY steroids) can react with molecular oxygen followed by a regio- and stereoselective γ-hydroxylation in 12β-position. After decomplexation and hydrolysis of the IMPY group 12β-hydroxy-17-ketones are available in practical useful yields. IMPY compounds are simple to prepare by condensation of oxo compounds with (2-aminomethyl)pyridine. In the cases of 17-IMPY steroids the yields in the hydroxylation procedure of an unactivated CH_2 group are higher by starting with copper(II) complexes, reduction with benzoin/triethylamine in acetone and reaction with molecular oxygen in comparison to the direct reaction of copper(I) complexes with molecular oxygen in acetone. Employing the procedure in dichloromethane as solvent starting with copper(II) complexes surprisingly the 12β-chloro compound could be isolated next to the hydroxylation product. This regio- and stereoselective γ-chlorination takes place also in acetone, when triethylammonium chloride is added to the reaction mixture. Oxygen is necessary for this reaction. The mechanistic and stereochemical aspects of these new reactions are discussed. Comparison of the different yields of steroids with different A-ring [3-methoxy-estra-1,3,5(10)-triene and 3β-hydroxy-androst-5-ene] pointed out to a subtle influence of the molecular structure far from the reaction centre on these reactions. The successful hydroxylation of the IMPY derivative of 3β-hydroxy-androst-5-ene-17-one shows the tolerance of a homoallylic system against this oxidation procedure. By Oppenauer oxidation 12β-hydroxy-androst-4-ene-3,17-dione is available. The hydroxylation procedure opens a short way to 12β-hydroxy-17-oxo steroids, which are difficult to obtain by other routes.
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1. Introduction

The activity of copper-containing enzymes (tyrosinase, dopamine-β-hydroxylase and bacterial particulate methane monooxygenase) for binding and activating molecular oxygen with a following insertion into C–H bonds of organic substrates under mild conditions is very remarkable.[1] Developing the ability to mimic this behavior with simpler copper(I) complexes and molecular oxygen has thus become an interesting research topic in the last few years.[2]

Despite considerable success in inducing intramolecular hydroxylations of aromatic[3] and benzylic[4] C–H bonds, analogous hydroxylations of nonactivated C–H bonds is much more difficult and only now is becoming possible. Using tri- or bidendate ligands with N-donor atoms for copper complexation, resulted in a hydroxylation at the β-position relative to the central N-atom in relatively low yields (Fig. 1).[5–9] Recently, we have successed, for the first time, in obtaining γ-hydroxylations of nonactivated C–H bonds in preparative useful yields (Fig. 2).[7,10]

Using the sterically more constrained bidentate iminomethylpyridine (IMPY)[10,11] and aminomethylenepyridine (AMPY)[10–12] ligands that possess a conformationally

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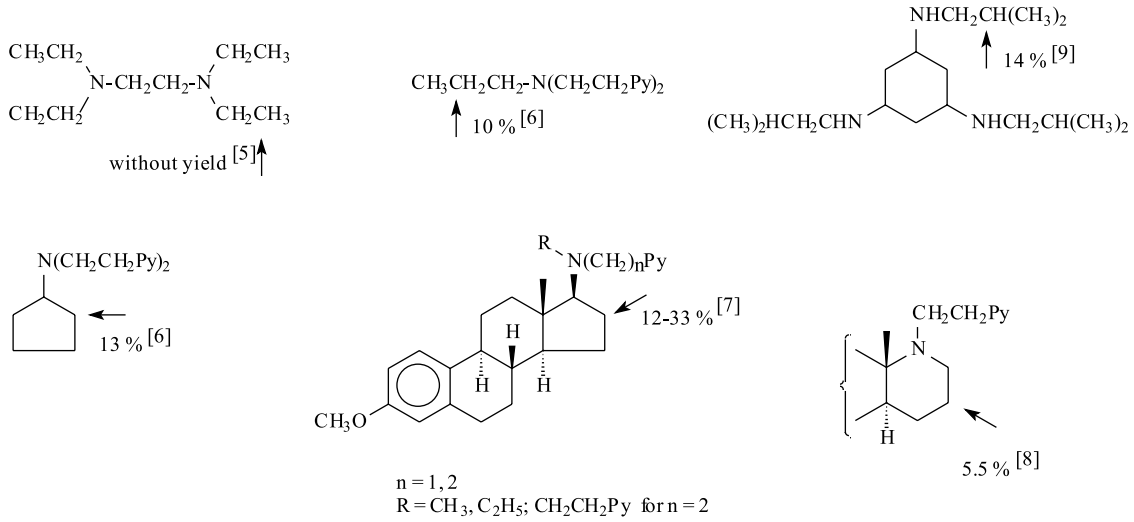


Figure 1. Examples for β-hydroxylation of nonactivated C–H bonds.

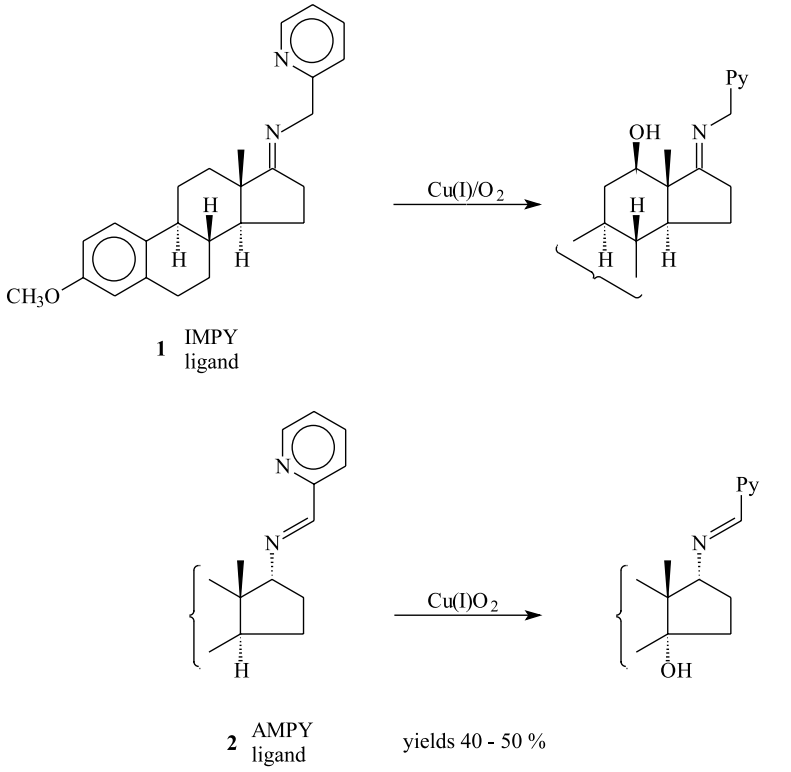


Figure 2. Examples for γ-hydroxylation of nonactivated C–H bonds.

well-defined steroid skeleton, we could develop a stereochemical model for this hydroxylation reaction.[7,10] Assuming a dinuclear complex with the well-known central $[Cu_2O_2]$ structure motive in which the four lone pairs of the coordinating nitrogens lie in a plane, we discovered that a hydrogen atom at a γ-C atom must also be in this plane and, in addition, be near a oxygen atom in order for a successful H abstraction followed by hydroxylation at the γ-C atom to take place (Fig. 3). In this way, a seven-membered transition state can be formulated. Six atoms are nearly in a plane. This could also confirmed by force field calculations.[10]

Using 17-IMPY-3-methoxy-estra-1,3,5(10)-triene **1**[7] as our model, the corresponding 17a-D-homo compound as well as the 13α-derivatives could be regio- and stereoselective hydroxylated in the 12β-position.[10] In addition, the 10-methyl group of (1R)-IMPY-camphor was hydroxylated.[10] Starting from 17α-AMPY-3-methoxy-estra-1,3,5(10)-triene **2** or 3α-AMPY-5α-cholestane, the γ-methine groups could be hydroxylated to the 14α-hydroxy and the 5α-hydroxy derivatives, respectively.[10]

Several aspects of this reactions are of interest from the practical point of view. IMPY and AMPY compounds are

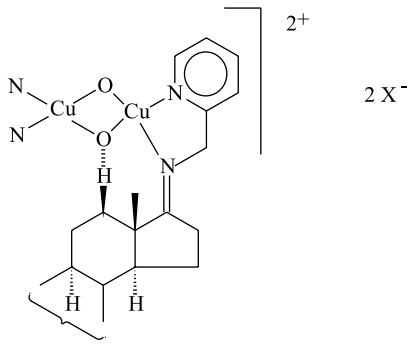


Figure 3. 17-IMPY-estra-1,3,5(10)-triene as a model for γ-hydroxylations.

quite easy to prepare by the condensation of oxo compounds with 2-(aminomethyl)pyridine or primary amines with pyridine-2-carboxaldehyde.[10,11] After the simple hydroxylation procedure (copper complexation and reaction with molecular oxygen at room temperature in an organic solvent) is performed, three variants become possible. In most cases the IMPY and AMPY groups could be hydrolyzed under the conditions of decomplexation (with aqueous ammonia) and chromatography. In this way 3-hydroxy-1-ones[7,10] or 3-hydroxy-1-primary amines[10] are available (Fig. 4, variant B). Using of (1R)-IMPY-camphor, 10-hydroxy-2-IMPY-camphor could be isolated (Fig. 4, variant A).[10] A third variant consists in the direct reduction of the C=N double bond of the hydroxylation product with $NaBH_4$ to give 3-hydroxy-1-(*N*-2-pyridylmethyl)amino compounds (Fig. 4, variant C).[7,10]

As Itoh and co-workers could demonstrate, two methods are successful for the hydroxylation of benzylic groups.[4b,d] Starting with copper(I) complexes followed by the addition of molecular oxygen (method A) the active dinuclear $[Cu_2O_2]$ species has been formed. Only one oxygen was transferred to generate the C–O bond. In this way, only 50% of ligand hydroxylation is possible; the other part should be unchanged. To improve the yield, Itoh and co-workers started with copper(II) complexes and an excess of benzoin and triethylamine [reducing agent for copper(II)]. After reaction with molecular oxygen, the hydroxylation took place in the same way. The excess of reducing agent can now reduce the formed copper(II) complex to copper(I) and further reaction with oxygen gave a complete ligand hydroxylation (method B).[4b,d] Reglier and co-workers found that unactivated CH_2 groups undergo β-hydroxylation only with method B.[6] However, we as well as Masuda et al. could recently demonstrate, that unactivated CH_2 groups can also be hydroxylated in β-position with method A.[8,9] We have now employed both methods to investigate the possibility of γ-hydroxylation of unactivated C–H bonds with IMPY and AMPY ligands.[10] An unexpected strong dependence on the structure of the compounds could be find. γ-Methine groups of AMPY ligands can be hydroxylated much more efficiently with method A than with method B. In contrast to this 17-IMPY-3-methoxy-estra-1,3,5(10)-triene **1** could be better hydroxylated with method B. Surprisingly enough, method A is considerably better for the other IMPY compounds. The active species for the hydroxylation procedure is probably a bis(μ-oxo)dicopper(III)

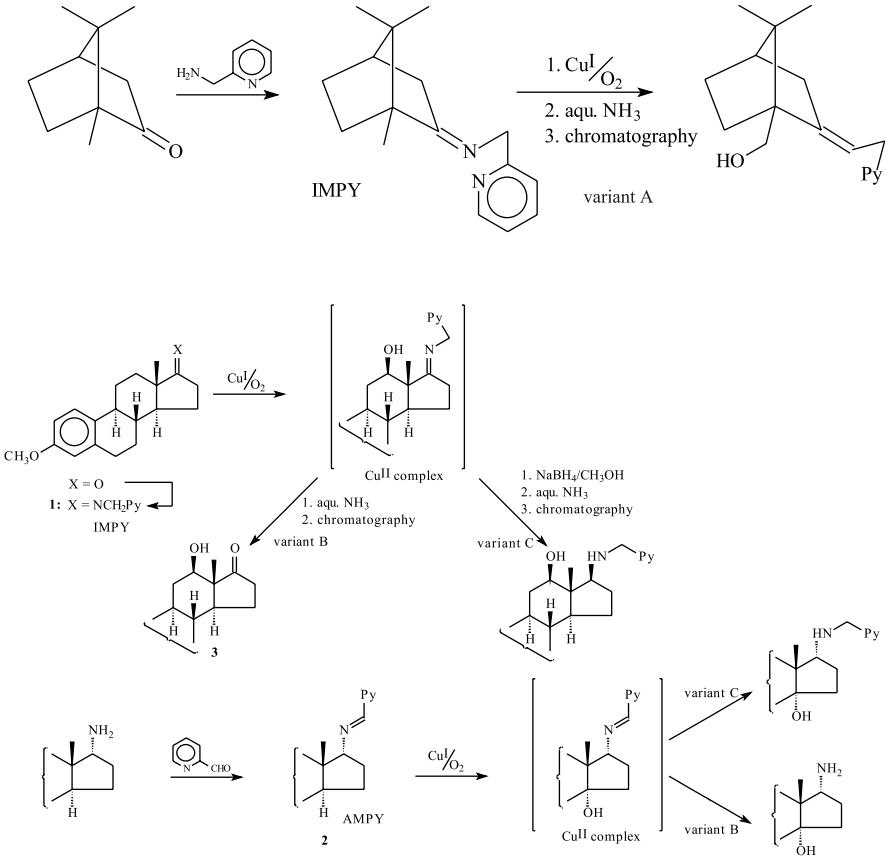


Figure 4. Synthesis of IMPY and AMPY compounds and their possible γ-hydroxylation products.

complex [in equilibrium with previously generated (μ–η^2:η^2–peroxo)dicopper(II) complexes] (Fig. 5).[4b,c,d] As discussed by Reglier and co-workers a mixed bis (μ-oxo)Cu(II), Cu(III) complex[6] is also possible (method B).

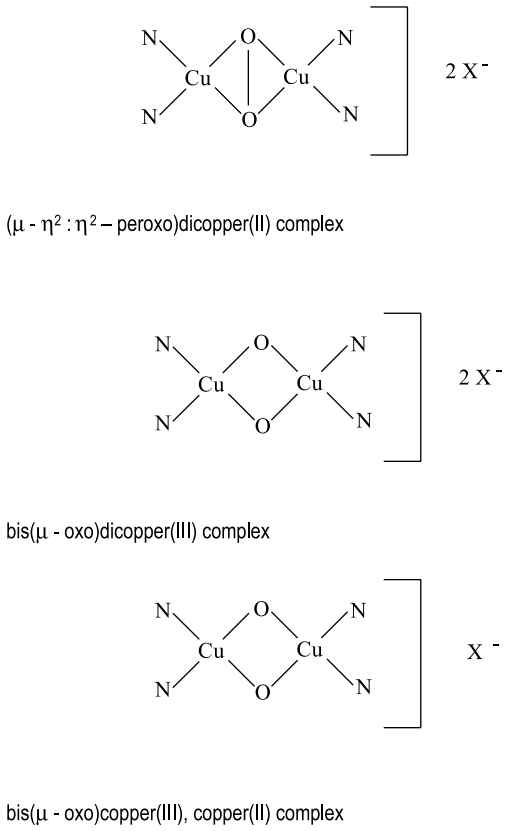


Figure 5. Structures of copper-O_2-complexes.

Our results indicate that a fine tuning by varying the surrounding of the ligand at the copper center[10,13] influences the structures of the active copper-oxygen species. The method employed (A or B) also directly affect the results. For these reasons, we decided to investigate additional γ-hydroxylations of the 12β-position of steroids. We chose 3β-hydroxy-androst-5-ene-17-one as the target, since different conformational effects of the estra-1,3,5(10)-triene and the androst-5-ene skeleton could be awaited. Furthermore, we were interested in the stability of the 3β-hydroxy-androst-5-ene system (a homoallyl alcohol) towards our hydroxylation procedure. The biological activity of, until now, difficult to obtain 12β-hydroxy-androstenes[14] is also of interest. After a successful 12β-hydroxylation it should be possible to transform the 3β-hydroxy-5-ene system into the 3-oxo-4-ene system by an Oppenauer oxidation.

2. Results and discussion

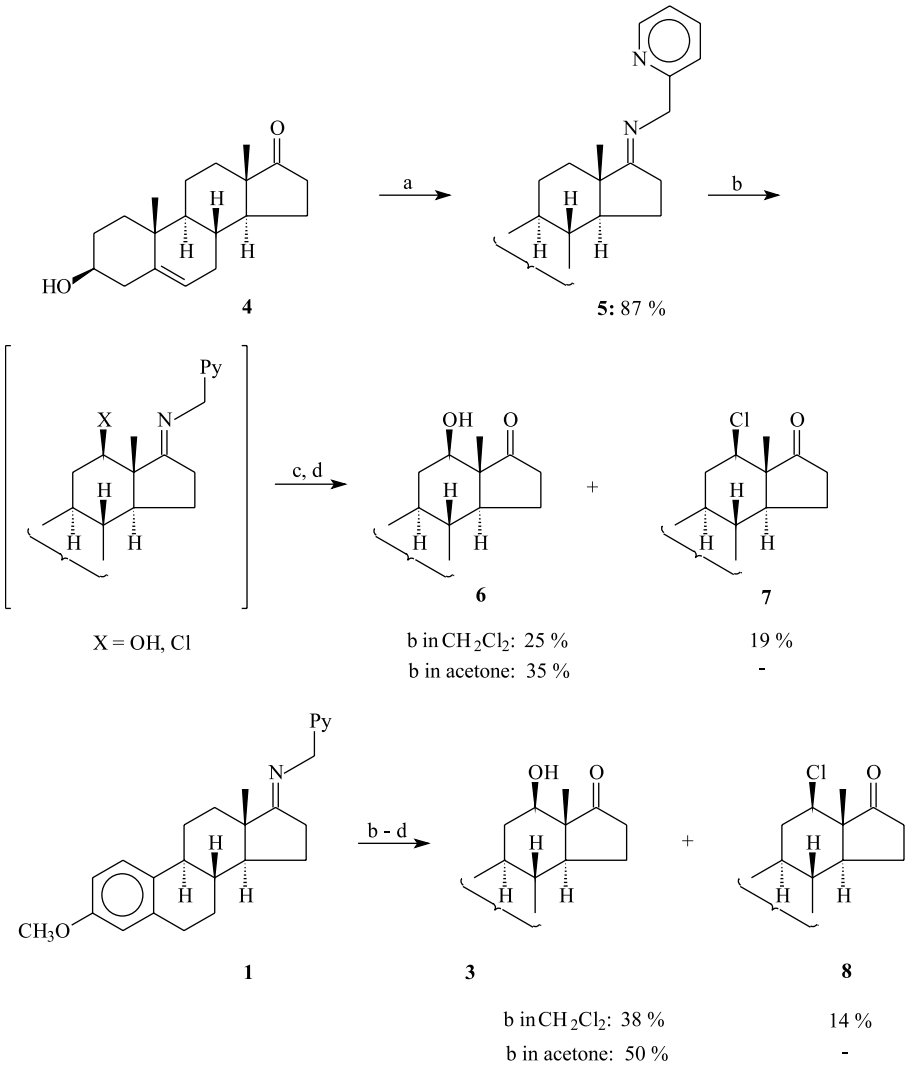
The IMPY compound **5** was synthesized by heating 3β-hydroxy-androst-5-ene-17-one **4** (dehydroepiandrosterone, DHEA) with 2-(aminomethyl)pyridine and *p*-toluensulfonic acid in toluene. **5** could be obtained in a yield of 87% and was reacted in CH_2Cl_2 with copper(II)triflate. The green complex thus obtained was directly reduced with an excess of benzoin/triethylamine to give a yellow copper(I) complex solution (method B). Reaction with pure oxygen then yielded a dark-green solution. After decomplexation and chromatography, DHEA **4** and two new polar compounds could be isolated in 25 and 19% yields, respectively (**6** and **7**, Scheme 1).

The more polar compound **6** was the expected 12β-hydroxy compound [comparison with **3** from the estra-1,3,5(10)-triene series]. Similarities in the ^1H and ^{13}C NMR spectra of **6** and **7** pointed to a 12β-substitution of **7**. MS spectra and elemental analysis of **7** indicated a 12β-chlorine substitution which could be confirmed by an X-ray analysis (Fig. 6).

This result was completely unexpected, because the only source for chlorine was the solvent (dichloromethane). To confirm this reaction, we reinvestigated the hydroxylation procedure of the IMPY derivative **1** of the estra-1,3,5(10)-triene series in CH_2Cl_2. Indeed, we could isolate, after careful chromatography (MPLC), the new 12β-chloro compound **8** in a yield of 14% in addition to the known 12β-hydroxy compound **3**. To exclude chlorine sources we changed the solvent to acetone. Using method B for the hydroxylation of **5** under these conditions yielded solely **6** which could be isolated in a yield of 35% after the work-up procedure (next to **4**). From compound **1**, only **3** was obtained in acetone in a yield of 50%. **6** could be transformed by an Oppenauer oxidation to the desired 12β-hydroxy-androst-4-ene-3,17-dion **9** (Scheme 2).

Interestingly enough, hydroxylation of **5** using method A in CH_2Cl_2 [$Cu(CH_3CN)_4PF_6$, O_2, decomplexation, chromatography] gave only compound **6** in nearly 20%. The same yield of **6** could be obtained with method A in acetone. Using method A for **1** in CH_2Cl_2 only **3** could be obtained (29%). We assume that the basic conditions of method B in CH_2Cl_2 (benzoin/triethylamin) are responsible for the generation of chloride ions. We could thus demonstrate, that triethylammonium chloride is indeed a source for the chlorination procedure. Adding three equivalents of triethylammonium chloride (method B) to the reaction of **5** in acetone resulted in a mixture of **7** and **6**; both in very low yields (5% of **6** and 10% of **7**). Method A in acetone with triethylammonium chloride gave the same (see Table 1).

It should be mentioned, that copper(I) complexes of tris(*N*-benzylaminoethyl)amine, tris(*N*-benzyl-*N*-methylaminoethyl)amine and tris(2-pyridylmethyl)amine are able to react with CH_2Cl_2 to generate copper(II)chloro complexes. 1,2-Dichlorethane (coupling product) can also be obtained under these conditions.[15] Copper(I) chloride coordinated with 1,1,4,7,10,10-hexamethylethylentetramine can act in DMF as a atom-transfer radical polymerization catalyst for poly(vinylchloride) and polyethylene glycol monomethacrylate.[16] In addition, other metal complexes are able to react with CH_2Cl_2 under oxidative addition.[17] Our experimental results (Table, entry 3 and 7) show that no chlorination product could be detected with method A in CH_2Cl_2. When chloride ions are added, a chlorination takes place (entry 9). Method B in acetone with added of chloride ions also results in chlorination (entry 5). Chlorination takes place only when pure oxygen is involved in the reaction. It



Scheme 1. γ-Hydroxylation and chlorination of 17-IMPY steroids. (a) $PyCH_2NH_2$, *p*-toluenesulfonic acid, refluxing toluene; (b) 1. $Cu(CF_3SO_2)_2$, CH_2Cl_2 or acetone; 2. benzoin, $N(C_2H_5)_3$, Ar; 3. O_2; (c) NH_4OH/H_2O; (d) chromatography on silica gel.

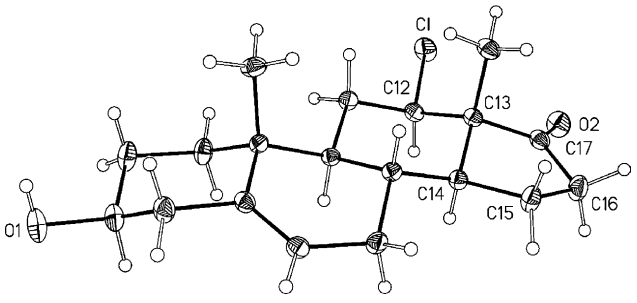
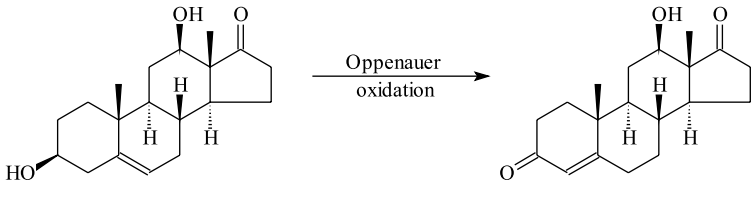


Figure 6. Molecular structure of 12β-chloro-3β-hydroxy-androst-5-ene-17-one **7**.

is therefore plausible, that an active complex with a $[Cu_2O_2]$ core is a common intermediate for both hydroxylation and chlorination. Similar to the recently calculated β-hydroxylation of benzylic groups,[18] abstraction of a hydrogen atom in γ-hydroxylation by one oxygen of the $[Cu_2O_2]$ core is an important step followed by creation of the C–O bond (Fig. 7). If chloride ions are present, it could be possible that the $[Cu_2O_2]$ core reacts to form a $[Cu_2O_2Cl]$ core containing an additional chloro bridge (Fig. 8). In this case, a five-coordinated copper intermediate similar to the oxidation product of $L_2[Cu_2Br_2]$ possessing a $[Cu_2Br_2O]$ core[19] could be present. The assumed $[Cu_2O_2Cl]$ core should have two



Scheme 2. Synthesis of 12β-hydroxy-androst-4-ene-3,17-dione **9**.

Table 1. Hydroxylation and chlorination in dependence of reaction conditions

Entry	IMPY compound	Method	Solvent	Addition	Yields
1	**1**	B	CH_2Cl_2	–	**3**: 38% (OH **8**: 14% (Cl)
2	**1**	B	Acetone	–	**3**: 50% (OH)
3	**1**	A	CH_2Cl_2	–	**3**: 29% (OH)
4	**5**	B	CH_2Cl_2	–	**6**: 25% (OH) **7**: 19% (Cl)
5	**5**	B	Acetone	–	**6**: 35% (OH)
6	**5**	B	Acetone	$[HNEt_3]^+Cl^-$	**6**: 5% (OH) **7**: 10% (Cl)
7	**5**	A	CH_2Cl_2	–	**6**: 22% (OH)
8	**5**	A	Acetone	–	**6**: 20% (OH)
9	**5**	A	Acetone	$[HNEt_3]^+Cl^-$	**6**: 6% (OH) **7**: 9% (Cl)

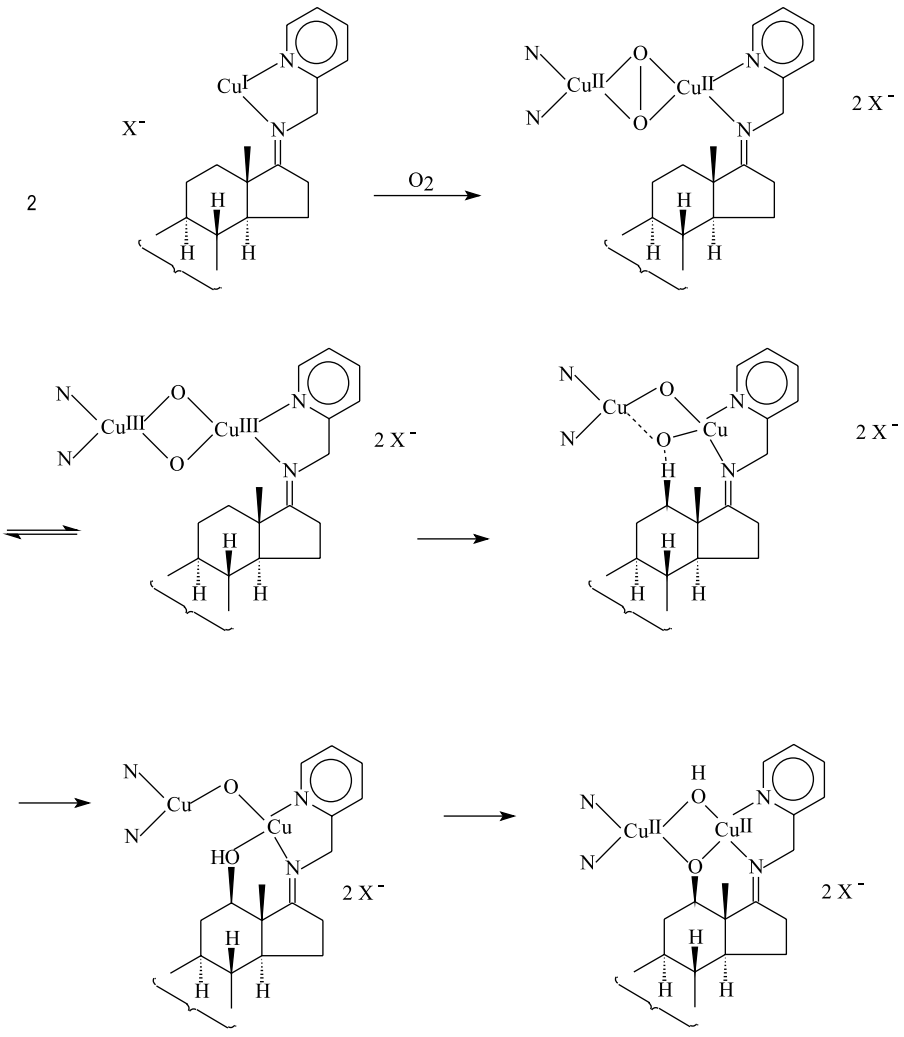


Figure 7. Mechanism for γ-hydroxylation.

possibilities for reaction after the H abstraction: reaction with the O-brigded oxygen to a hydroxylated product or reaction with the bridged chlorine to a chlorinated product. Whether the primary attack of the hydrogen is caused by an oxygen or the chlorine is an open question. Possible mechanisms are given in Figures 7 and 8.

This chlorination reaction has, in spite of the relatively low yields, a great potential for the functionalization of unactivated γ-CH_2 (maybe CH and CH_3 as well) groups in a regio- and stereoselective manner. Further investigations especially optimization of the reaction conditions (copper salts, source of chloride, solvent, temperature, etc.) is, however, necessary to improve this chlorination process. In addition, use of bromide or other bridging anions for functionalizations should be interesting.

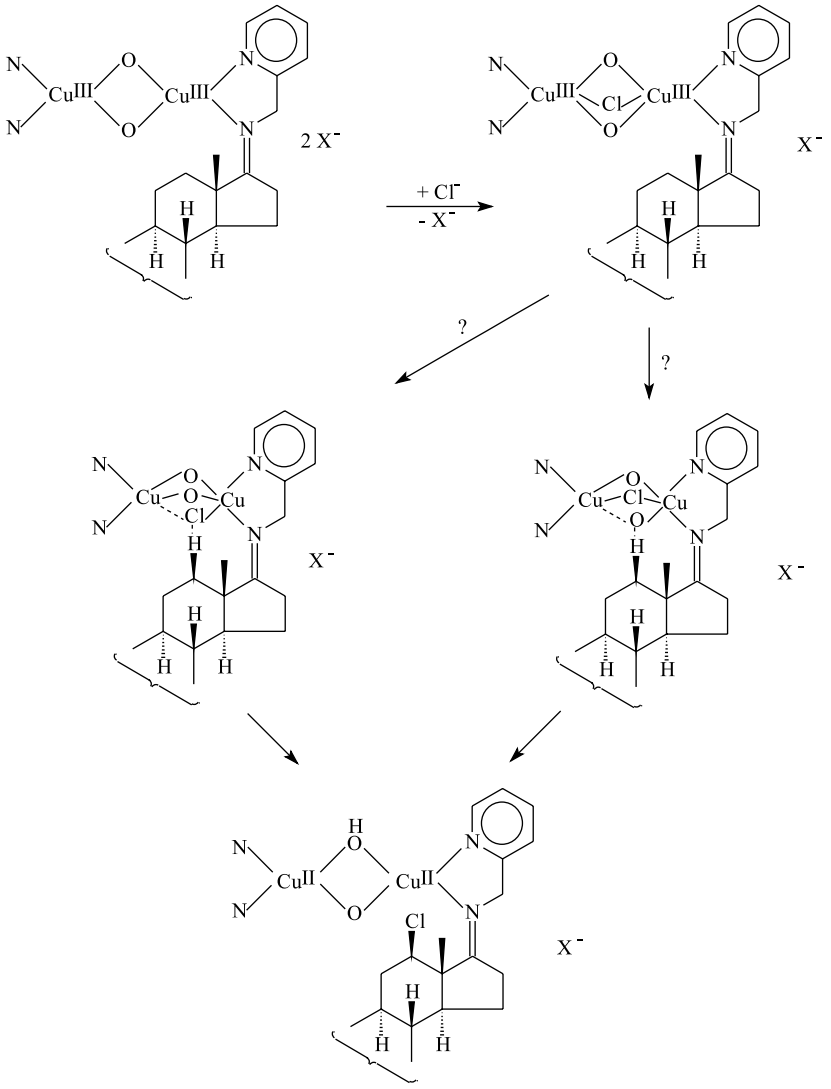


Figure 8. Mechanisms for γ-chlorination.

The regio- and stereoselective chlorination of unactivated CH bonds is not a process that is simple to achieve. Breslow and co-workers have described the chlorination of unactivated CH groups using suitable esters or silylethers of steroidal 3α- or 17α-alcohols and a chloride source ($SOCl_2$, $PhICl_2$). In this way, selective chlorination of the tertiary positions 9, 14 and 17 are possible.[20–22]

Selective C-chlorination of ligands with metal complexes are quite rare. As an examples, the C-chlorination of the pyrazole ring of a $CuCl_2$ complex with 3-phenyl-5-(6-methyl-2-pyridyl)pyrazole in DMF to a dinuclear copper complex containing chloride bridges[23] or a similar chlorination of a (2-pyridyl)pyrazol complex with $VOCl_3$ and *tert*.-BuOOH[24] need to be mentioned. The active chlorine species in the latter case should be formed in a vanadium haloperoxidase-like reaction.[24]

Similar to the regio- and stereoselective 12β-chlorination observed to 17-IMPY compounds (forms **7** and **8**) the 12β-hydroxylation to form the new compounds **6** and **3** is a practical useful procedure. 12β-hydroxylated estra-1,3,5(10)-trienes and androst-4-enes are metabolic products.[25] However, their synthesis is a difficult problem. 19-*nor*-3,17-dioxo-4-androstane can be converted in two microbial steps (12β-hydroxylation and aromatization) to 12β-hydroxy-estrone.[26] Cholanic acids with a 12α-hydroxy group serve as starting materials for multistep chemical syntheses to 12β-hydroxylated estra-1,3,5(10)-trienes.[27] Intermediates are 12-oxo-androstenes. 12β-Hydroxylated androstenes have been synthesized also in a multistep chemical procedure starting with the steroid alkaloid jervine.[28] Polyoxypregnanes with a 12β-hydroxy group are important natural products.[29] A remote oxidation in the 12-position of the androstane skeleton (12α-OH and 12-oxo) has been reported by P. A. Grieco and T. L. Shuk.[30] In addition the 14α-position has been hydroxylated. A 3α-phenylacetic ester with a synthetic manganeseporphyrin in meta-position of the phenyl ring and iodosylbenzene as oxygen source are responsible for the oxygen transfer.[30] With the corresponding 3α-benzoic acid ester, a tertiary 17α-hydroxy group could be introduced.[30] Recently, Breslow et al reported on manganeseporphyrin catalysts linked by spacers to cyclodextrin which are able to achieve a selective hydroxylation of steroids in 6α- and 9α-position.[31]

We could demonstrate that, with our procedure, the IMPY derivatives of 3-methoxy-estra-1,3,5(10)-triene-17-one **1** and 3β-hydroxy-androst-5-ene-17-one **5** can be regio- and stereoselective hydroxylated in the 12β-position using method B [starting with Cu(II) complexes in acetone, reduction with benzoin/triethylamine, reaction with molecular O_2, hydrolysis] in yields of 50 and 35%. The difference in the yields points to a subtle influence of the molecular structure. In principle, the hydroxylation procedure is also successful for molecules possessing an homoallylic alcohol group (as compound **4**).

3. Conclusion

The regio- and stereoselective 12β-hydroxylation of 17-(2-iminomethyl)pyridino steroids (IMPY compounds) via copper complexation and reaction with molecular oxygen described here is a model reaction for a hydroxylation of unactivated C–H bonds in γ-position to the IMPY nitrogen. The simple preparation of IMPY compounds from oxo compounds and their easy hydrolysis after the hydroxylation procedure allows the synthesis of 3-hydroxy-1-oxo compounds in a simple procedure and in satisfactory yields. Starting with the IMPY compounds of 3-methoxy-estra-1,3,5(10)-triene-17-one and 3β-hydroxy-androst-5-ene-17-one and using copper(II) triflate for complexation in acetone followed by reduction with benzoin/triethylamine and reaction with molecular oxygen, the 12β-hydroxy-17-ketones could be obtained after hydrolysis in yields of 50 and 35%, respectively. Using copper(I) salts for complexation the yields are clearly lower. This is in contrast to the recently described γ-hydroxylations of IMPY compounds of a D-homo-17a-ketone, a 13α-17-ketone, (1R)-camphor and 17α-, 16α- and 3α-aminomethylene steroids (AMPY steroids),[10] all of which react better with copper(I) complexes and molecular oxygen as compared to the use of copper(II) complexes and reduction. In summary, these results, point to subtle influences of the molecular structure on the reactive centre;[32] the yields maybe also be due to different active species.

A 12β-chlorination was oberserved in addition to the 12β-hydroxylation with the Cu(II) complexes in the presence of benzoin/triethylamine/O_2 when CH_2Cl_2 as solvent is employed. This chlorination also took place in acetone after the addition of triethylammonium chloride to the reaction mixture, but in lower yields. A chloro-bridge between the two copper centres together with oxygen bridges could possibly be responsible for these reactions. Further optimizations are necessary to improve the yields of this new γ-chlorination procedure. In addition the possibility of functionalization with other bridged atoms or groups should be quite interesting.

4. Experimental

4.1. General

Melting points were measured on a Boëtius micromelting point apparatus and are corrected values. Mass spectra were determined on an AMD 402 intectra instrument with direct electron impact (DEI) with 70 eV and electro spray ionization (ESI). Elemental analyses were performed with a CHNS-932 (LECO) instrument. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AC 250 or a DRX-400 spectrometer (^{1}H NMR 250 MHz, 400 MHz, ^{13}C NMR 62.5 MHz, 100 MHz). Signals were assigned by DEPT, COSY, TOCSY, NOESY and HMQC experiments. All reactions were carried out under inert conditions. The reactions were monitored by TLC aluminium sheets, silica gel 60 F_{254} (Merck.), 0.2 mm, detection by UV (254 nm) and spraying with methanolic sulfuric acid (methanol/H_2SO_4 4:1) and heating at 170 °C. For flash chromatography, silica gel 60 (Lichroprep Si 60, 40–63 μm, Merck.) was used. MPLC was performed on Lichroprep Si 60, 15–25 μm, Merck). Solvents were purified, dried and distilled according to convential methods.

4.2. Crystal structure analysis

Compound measurements were carried out at beamline ID11 at the European Synchrotron Radiation Facility (ESRF). Data were collected using a Bruker 'Smart' CCD-camera system at fixed 2θ, while the sample was rotated over 0.1° intervals during 2 s exposures, using monochromated radiation from $\lambda = 0.38745$ Å. Data were corrected for Lorentz and polarization effects, but not for absorption.[33] The structures were solved by direct methods (SHELXS[34]) and refined by full-matrix least squares techniques against Fo^2 (SHELXTL97-2[35]). The hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All non-hydrogen atoms were refined anisotropically.[35] *XP* (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

4.3. Synthesis of 17-IMPY steroids

4.3.1. 17-(*N*-2-Pyridylmethyl)imino-3-methoxy-estra-1.3.5(10)-triene (1). 3-Methoxy-estra-1,3,5(10)-triene-17-one (1.3 g, 4.5 mmol), 2-(aminomethyl)pyridine (0.97 mL, 9.0 mmol) and triethyl orthoformate[36] (25 mL) were heated at 80° for 5 h. After removing the liquids under reduced pressure the yellowish solid was crystallized from ethyl acetate giving white crystals of **1** (1.47 g, 86%). Mp 124–126 °C; $[\alpha]_D^{24} = +81.7$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (s, 3H, 18-H_3), 2.86 (m, 2H, 6-H_2), 3.76 (s, 3H, OCH_3), 4.60 (m, 2H, CH_2N), 6.60–6.65 (s, m, 2H, 4-H and 2-H), 7.10 (m, 3H, 1-H, 3-H_{py} and 5-H_{py}), 7.58 (m, 1H, 4-H_{py}), 8.52 (m, 1H, 6-H_{py}), 8.52 (m, 1H, 6-H_{py}). MS (EI): *m/z* (%): 374 (100%) [M^+]; $C_{25}H_{30}N_2O$ (374.5) calcd: C 80.18; H 8.07; N 7.48; found: C 80.52; H 8.16; N 7.42.

4.3.2. 17-(*N*-2-Pyridylmethyl)imino-3β-hydroxy-androst-5-ene-17-one (5). A mixture of dehydroepiandrosterone **4** (2.0 g, 6.9 mmol), 2-(aminomethyl)pyridine (3.5 mL, 34.7 mmol) and a catalytic amount of *p*-toluenesulfonic acid (30 mg) was dissolved in toluene (30 mL) and refluxed for 2 h using a Dean–Stark apparatus. After cooling the reaction mixture was diluted with ethyl acetate, washed twice with aqueous satured $NaHCO_3$ solution and water, dried and separated. The solvent was evaporated and the sticky brown residue purified by crystallization from ethyl acetate, giving pure 17-imine **5** (2.28 g, 87%) as light yellow crystals. Mp

172–175 °C (ethylacetate); $[\alpha]_D^{24} = -40.8$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (250 MHz, CD_2Cl_2): $\delta = 0.89$ (s, 3H, 18-H_3), 1.05 (s, 3H, 19-H_3), 3.47 (m, 1H, 3α-H), 4.49 (m, 2H, CH_2-N), 5.37 (m, 1H, 6-H), 7.14, 7.52, 7.68 and 8.48 (4×m, 4×1H, 4×H_{py}); MS (EI): *m/z* (%): 378 [M^+]; $C_{25}H_{34}N_2O$ (378.6): calcd: C 79.32; H 9.05; N 7.40; found: C 79.12; H 9.04; N 7.46.

4.4. Hydroxylation and chlorination procedures

4.4.1. Hydroxylation and chlorination of 17-IMPY-3β-hydroxy-androst-5-ene 5 (method B, CH_2Cl_2). To a solution of **5** (756 mg, 2.0 mmol) in abs. CH_2Cl_2 (30 mL) $Cu(CF_3SO_3)_2$ (880 mg, 2.4 mmol) was added. The dark-green solution was stirred at rt for about 1 h. Under an argon atmosphere and continual stirring benzoin (850 mg, 4.0 mmol) and triethylamine (0.6 mL, 4.0 mmol) were added. After 4 h pure oxygen was bubbled through the mixture for 10 min. The yellow-brown solution was stirred for further 24 h under O_2 during which it turned to dark-green. After removing the solvent a dark-sticky oil was obtained. The crude product was dissolved in ethyl acetate and extracted three times with aqueous NH_4OH (25%). The brown organic layer was washed with brine, dried with Na_2SO_4 and evaporated. The residue was redissolved in methanol (40 mL) and treated with acetic acid (40 mL) at 90° for 6 h. The methanol was removed and the mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine and dried (Na_2SO_4). Evaporation gave a dark oil which was purified by MPLC (Lichroprep Si 60, 15–20 μm, *n*-hexane/ethyl acetate 70:30). Dehydroepiandrosterone **4** (121 mg, 21%), 12β-chloro compound **7** (122 mg, 19%) and 12β-hydroxy compound **6** (152 mg, 25%) were obtained as white amorphous solids.

12β-Chloro-3β-hydroxy-androst-5-ene-17-one **7**: Mp 189–193 °C (diethyl ether); $[\alpha]_D^{24} = -60.1$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (s, 3H, 19-H_3), 1.06 (s, 3H, 18-H_3), 3.51 (m, 1H, 3α-H), 3.99 (m, 1H, 12α-H), 5.36 (m, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.15$ (CH_3), 19.5 (CH_3), 21.4 (CH_2), 30.3 (CH), 30.7 (CH), 31.6 (CH_2), 33.3 (CH_2), 35.6 (CH_2), 36.9 (C_q), 37.2 (CH_2), 42.2 (CH_2), 50.8 (CH), 51.4 (C_q), 52.2 (CH), 61.8 (C-12), 71.6 (C-3), 120.8 (C-6), 140.9 (C-5), 216.3 (C-17); $C_{19}H_{27}O_2Cl$ (322.2): calcd C 70.77; H 8.45; Cl 10.86; found: C 68.07; H 8.62; Cl 10.04.

Crystal data for **7**.[37] $C_{19}H_{27}ClO_2$, Mr = 322.86 g mol^{-1}, colourless prism, size 0.04×0.04×0.03 mm^3, orthorhombic, space group $P2_12_12_1$, $a = 5.9230$ (1) Å, $b = 11.4755$ (2) Å, $c = 24.8073$ (4) Å, $V = 1686.14(5)$ Å^3, $T = -153$ °C, $Z = 4$, $\rho_{calcd} = 1.272$ g cm^{-3}, μ ($\lambda = 0.38745$ Å) = 0.000 cm^{-1}, $F(000) = 696$, 10,716 reflections in $h(-7/7)$, $k(-15/14)$, $l(-32/32)$, measured in the range $2.42° \leq \Theta \leq 14.97°$, completeness $\Theta_{max} = 85.8\%$, 3630 independent reflections, $R_{int} = 0.031$, 3440 reflections with $F_o > 4\sigma(F_o)$, 308 parameters, 0 restraints, $R1_{obs} = 0.024$, $wR^2_{obs} = 0.062$, $R1_{all} = 0.027$, $wR^2_{all} = 0.063$, GOOF = 1.007, Flack-parameter 0.69 (6) (absolute configuration not determined), largest difference peak and hole: 0.208/−0.137 e Å^{-3}.

3β,12β-Dihydroxy-androst-5-ene-17-one **6**: Mp 192–196 °C (diethyl ether); $[\alpha]_D^{24} = -21.9$ ($c = 0.9$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H, 18-H_3), 1.03 (s, 3H, 19-H_3), 3.49 (m, 1H, 3α-H), 3.78 (m, 1H, 12α-H), 5.36 (m, 1H, 6-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.00$ (CH_3), 19.3 (CH_3), 21.7 (CH_2), 28.2 (CH_2), 30.3 (CH_2), 30.6 (CH), 31.6 (CH_2), 35.7 (CH_2), 36.7 (C_q), 37.1 (CH_2), 42.1 (CH_2), 49.1 (CH), 49.6 (CH), 51.4 (C_q), 71.5 (C-3), 72.7 (C-12), 120.7 (C-6), 141.0 (C-5), 222.6 (C-17); $C_{19}H_{28}O_3$ (304.2): calcd C 74.95; H 9.28; found: C 73.99, H 9.17.

4.4.2. Hydroxylation of 5 (method B, acetone). 5 (756 mg, 2.0 mmol) was reacted with $Cu^{II}(CF_3SO_3)_2$ (880 mg, 2.4 mmol), benzoin (850 mg, 4.0 mmol) and triethylamine (0.6 mL, 4.0 mmol) in absolute acetone (30 mL) as desribed above. Separation by MPLC yielded dehydroepiandrosterone **4** (127 mg, 22%) and 12β-hydroxy compound **6** (213 mg, 35%).

4.4.3. Hydroxylation and chlorination of 5 (method B, $NEt_3 \cdot HCl$, acetone). To a solution of **5** (756 mg, 2.0 mmol) in absolute acetone (30 mL) $Cu^{II}(CF_3SO_3)_2$ (880 mg, 2.4 mmol) and triethylamine hydrochloride (825 mg, 6.0 mmol) were added. The mixture was then treated with benzoin (850 mg, 4.0 mmol) and triethylamine (0.6 mL, 4.0 mmol) as described above. After working up and MPLC (Lichroprep Si 60, 15–20 μm, *n*-hexane/ethyl acetate 70:30) dehydroepiandrosterone **4** (231 mg, 40%), 12β-chloro compound **7** (64 mg, 10%) and 12β-hydroxy compound **6** (30 mg, 5%) were obtained.

4.4.4. Hydroxylation of 5 (method A, CH_2Cl_2). To a solution of **5** (378 mg, 1.0 mmol) in absolute dichloromethane (30 mL), tetrakis(acetonitrile)copper(I)hexafluorophosphate (447 mg, 1.2 mmol) was added. The resulting brown solution was stirred at rt. After 1 h the argon atmosphere was replaced by an O_2 atmosphere. Pure oxygen was then bubbled trough the reaction mixtures for approximately 10 min. The solution were stirred for about 24 h under O_2. During this time it turned to dark green. The solvent was distilled off and the oily dark residue was dissolved in ethyl acetate and extracted three times with aqueous NH_4OH (25%); the brown organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The brown oil was then redissolved in methanol (20 mL) and treated with acetic acid (20 mL) at 90 °C for 6 h. The methanol was removed and the mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine and dried (Na_2SO_4). Evaporation gave a dark oil which was separated by MPLC using Lichroprep Si 60, 15–20 μm, *n*-hexane/ethyl acetate 80:20 (column of 200×35 mm, rate 25 mL min^{-1}) yielding dehydroepiandrosterone **4** (130 mg, 45%) and 12β-hydroxy compound **6** (72 mg, 22%). No chlorination product could be found.

4.4.5. Hydroxylation of 5 (method A, acetone). 5 (378 mg, 1.0 mmol) was reacted with tetrakis(acetonitrile)copper-(I)hexafluorophosphate (447 mg, 1.2 mmol) in absolute acetone (30 mL) as described under Section 4.4.4. Separation by MPLC yielded dehydroepiandrosterone **4** (104 mg, 36%) and 12β-hydroxy compound **6** (61 mg, 20%).

4.4.6. Hydroxylation and chlorination of 5 (method A, $NEt_3 \cdot HCl$, acetone). To a solution of **5** (378 mg, 1.0 mmol) in absolute acetone (30 mL) tetrakis(acetonitrile)copper(I)hexafluoro-phosphate (447 mg, 1.2 mmol) and triethylamine hydrochloride (412 mg, 3.0 mmol) were added. The reaction and working up procedures were performed as described under Section 4.4.4. After separation by MPLC dehydroepiandrosterone **4** (155 mg, 54%), 12β-chloro compound **7** (29 mg, 9%) and 12β-hydroxy compound **6** (18 mg, 6%) were obtained.

4.4.7. Hydroxylation and chlorination of 17-IMPY-3-methoxy-estra-1.3.5(10)-triene 1 (method B, CH_2Cl_2). **1** (374 mg, 1.0 mmol) was reacted with $Cu(CF_3SO_3)_2$ (440 mg, 1.3 mmol), benzoin (425 mg, 2.0 mmol) and triethylamin (0.3 mL, 2.0 mmol) in abs. CH_2Cl_2 (20 mL) as desribed under Section 4.4.1. Also the working up procedure was performed as described. MLPC using Lichroprep Si60, 15–20 μm, *n*-hexane/ethyl acetate 75:25 (column of 200×35 mm, rate 25 mL min^{-1}) yielded 3-methoxy-estra-1.3.5(10)-triene (57 mg, 20%) and 12β-chloro compound **8** (45 mg, 14%) and 12β-hydroxy compound **3** (114 mg, 38%) as white amorphous solids.

12β-Chloro-3-methoxy-estra-1.3.5(10)-triene-17-one **8**: Mp 166–171 °C (CH_3OH); $[\alpha]_D^{24} = +33.4$ ($c=0.9$ in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.08$ (s, 3H, 18-H_3), 2.88 (m, 2H, 6-H_2), 3.76 (s, 3H, CH_3O), 4.14 (m, 1H, 12α-H), 6.63 (d, 1H, $J=2.7$ Hz, 4-H), 6.70 (dd, 1H, $J=2.7$, 8.6 Hz, 2-H), 7.13 (d, 1H, $J=8.6$ Hz, 1-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=9.3$ (C-18), 20.9, 25.8, 29.4, 35.3, 37.4, 37.8, 43.8, 50.7, 51.6 (C-13), 55.2 (H_3CO), 61.0 (C-12), 111.7 (C-2), 114.1 (C-4), 126.0 (C-1), 130.2 (C-10), 137.5 (C-5), 157.9 (C-3), 215.8 (C-17); MS (ESI): *m/z* (%): 341 (100) [M^+ + Na]; HRMS (ESI): *m/z* found 341.1278, calcd $C_{19}H_{23}O_2ClNa$ (M^+ + Na) 341.1287.

12β-Hydroxy-3-methoxy-estra-1.3.5(10)-triene-17-one **3**: Mp 153-155 °C (CH_3OH); $[\alpha]_D^{24} = +103.9$ ($c=0.9$ in CH_2Cl_2); ^1H NMR ($CDCl_3$): 0.96 (s, 3H, 18-H_3), 2.89 (m, 2H, 6-H_2), 3.76 (s, 3H, OCH_3), 3.96 (dd, $^3J_1=4.6$ Hz, $^3J_2=$ 11.3 Hz, 1H, 12α-H), 6.63 (s, 1H, 4-H), 6.70 (d, $^3J=8.5$ Hz, 1H, 2-H), 7.17 (d, $^3J=8.5$ Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$): 8.3 (C-18), 21.4 (C-15), 26.2 (C-16), 29.5 (C-7), 33.0 (C-6), 35.8 (C-11), 37.3 (C-8), 42.2 (C-9), 48.4 (C-13), 52.0 (C-14), 55.2 (OCH_3), 72.7 (C-12), 111.5 (C-2), 114.0 (C-4), 126.1 (C-1), 131.2 (C-10), 137.5 (C-5), 157.7 (C-3), 222.5 (C-17); IR (ATR): 3485 cm^{-1} (OH), 1736 cm^{-1} (C=O); HRMS (ESI): *m/z* found 323.16233, calcd $C_{19}H_{24}NaO_3$ (M + Na) 323.16231.

4.4.8. Hydroxylation of 1 (method A, CH_2Cl_2). To a solution of **1** (236 mg, 0.63 mmol) in degassed CH_2Cl_2 (30 mL) $Cu(CH_3CN)_4PF_6$ (230 mg, 0.63 mmol) was added under Ar. The red solution was stirred for 2 h. After bubbling with pure oxygen the solution was kept for 48 h under an oxygen atmosphere. To the green solution aqueous NH_4OH (25%, 20 mL) was added. After stirring for 4 h the organic layer was separated, washed with brine and dried (Na_2SO_4). The solvent was removed by distillation and the residue separated by column chromatography (silica gel; $CHCl_3$, $CHCl_3/CH_3OH$) giving 3-methoxy-estra-1.3.5(10)-triene-17-one (87 mg, 49%) and 12β-hydroxy compound **3** (55 mg, 29%).

4.5. Oppenauer oxidation of 6

To a solution of **6** (200 mg, 0.7 mmol) in anhydrous toluene (20 mL) and cyclohexanone (2 mL) a suspension of aluminium isopropoxide (200 mg, 1 mmol) in toluene (1 mL) was added. The reaction mixture was refluxed while stirring for 4 h. After cooling to room temperature the reaction mixture was washed with diluted sulfuric acid and water, dried over Na_2SO_4 and evaporated. The oily crude product was purified by MPLC on silica gel with *n*-hexane-ethyl acetate (50:50) giving pure 12β-hydroxy-androst-4-ene-3,17-dione **9** (100 mg, 50%) as white crystals. Mp 149–152 °C (*n*-hexane-ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.94$ (s, 3H, 18-H_3), 1.16 (s, 3H, 19-H_3), 3.74 (m, 1H, 12α-H), 5.70 (m, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=8.19$, 17.2, 21.6, 27.9, 30.2, 31.4, 32.4, 33.8, 34.2, 35.6, 38.5, 48.5, 51.4, 52.2, 72.3, 124.4, 169.3, 199.1, 222.1; HRMS (EI): *m/z* found 302.2062, calcd $C_{19}H_{26}O_3$ (M^+) 302.2065.

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References and notes

1. (a) Blain, I.; Slama, P.; Giorgi, M.; Tron, T.; Reglier, M. *J. Biotechnol.* **2002**, *90*, 95–112. (b) Gerdemann, C.; Eicken, C.; Krebs, B. *Acc. Chem. Res.* **2002**, *35*, 183–191. (c) Pascaly, M.; Jolk, I.; Krebs, B. *Chem. Unserer Zeit* **1999**, *33*, 334–341. (d) Klinmann, J. P. *Chem. Rev.* **1996**, *96*, 2541–2561. (e) Kaim, W.; Rall, J. *Angew. Chem.* **1996**, *108*, 47–64. *Angew. Chem., Int. Ed.* **1996**, *35*, 43–60.
2. (a) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. B. *Chem. Rev.* **2004**, *1104*, 1013–1045. (b) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *1104*, 1047–1076. (c) Itoh, S. In Comprehensive Coordination Chemistry II; Que, L., Jr., Tolman, W. B., Eds.; Elsevier: Amsterdam, 2004; Vol. 8, pp 369–393. (d) Komiyama, K.; Furutachi, H.; Nagatomo, S.; Hashimoto, A.; Hayashi, H.; Fujinami, S.; Suzuki, M.; Kitagawa, T. *Bull. Chem. Soc. Jpn* **2004**, *77*, 59–72. (e) Chufán, E. E.; Karlin, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 16160–16161. (f) Limberg, C. *Angew. Chem.* **2003**, *115*, 6112–6136. *Angew. Chem., Int. Ed.* **2003**, *42*, 5932–5954. (g) Itoh, S.; Fukuzumi, S. *Bull. Chem. Soc. Jpn* **2002**, *75*, 2081–2095. (h) Que, L. Jr.; Tolman, W. B. *Angew. Chem.* **2002**, *114*, 1160–1185. *Angew. Chem., Int. Ed.* **2002**, *41*, 1114–1137. (i) Blain, I.; Giorgi, M.; DeRiggi, I.; Reglier, M. *Eur. J. Inorg. Chem.* **2001**, 205–211. (j) Schindler, S. *Eur. J. Inorg. Chem.* **2000**, 2311–2326. (k) Holland, P. L.; Tolman, W. P. *Coord. Chem. Rev.* **1999**, *190–192*, 855–869. (l) Than, R.; Feldmann, A.; Krebs, B.

Coord. Chem. Rev. **1999**, *182*, 211–241. (m) Karlin, K. D.; Kaderli, S.; Zuberbühler, A. D. *Acc. Chem. Res.* **1997**, *30*, 139–147. (n) Tolman, W. B. *Acc. Chem. Res.* **1997**, *30*, 227–237. (o) Kitajima, N.; Moro-oka, Y. *Chem. Rev.* **1994**, *94*, 737–757.

3. (a) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1982**, *23*, 1573–1576. (b) Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1982**, *23*, 1577–1580. (c) Karlin, K. D.; Hayes, J. C.; Gultneh, Y.; Cruse, R. W.; McKown, J. W.; Hutchinson, J. P.; Zubieta, J. *J. Am. Chem. Soc.* **1984**, *106*, 2121–2128. (d) Gelling, O. J.; Bolhuis van, F.; Meetsma, A.; Feringa, B. L. *Chem. Commun.* **1988**, 522–554. (e) Casella, L.; Gullotti, M.; Pallanza, G.; Rigoni, L. *J. Am. Chem. Soc.* **1988**, *110*, 4221–4227. (f) Menif, R.; Martell, A. E. *Chem. Commun.* **1989**, 1521–1523. (g) Gelling, O. J.; Feringa, B. L. *J. Am. Chem. Soc.* **1990**, *112*, 7599–7604. (h) Menif, R.; Martell, A. E.; Squattrito, P. J.; Clearfield, A. *Inorg. Chem.* **1990**, *29*, 4723–4729. (i) Sorrell, Th. N.; Vankai, V. A.; Garrity, M. L. *Inorg. Chem.* **1991**, *30*, 207–210. (j) Sorrell, Th. N.; Garrity, M. L. *Inorg. Chem.* **1991**, *30*, 210–215. (k) Becker, M.; Schindler, S.; Eldik Van, R. *Inorg. Chem.* **1994**, *33*, 5370–5371. (l) Ryan, S.; Adams, H.; Fenton, D. E.; Becker, M.; Schindler, S. *Inorg. Chem.* **1998**, *37*, 2134–2140. (m) Becker, M.; Schindler, S.; Karlin, K. D.; Kaden, Th. A.; Kaderli, S.; Palanche, T.; Zuberbühler, A. D. *Inorg. Chem.* **1999**, *38*, 1989–1995. (n) Pidcock, E.; Obias, H. V.; Zhang, Ch. X.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1998**, *120*, 7841–7847. (o) Holland, P. L.; Rodgers, K. R.; Tolman, W. B. *Angew. Chem.* **1999**, *111*, 1210–1213. *Angew. Chem., Int. Ed.* **1999**, *38*, 1139–1142. (p) Santagostini, L.; Gullotti, M.; Monzani, E.; Casella, L.; Dillinger, R.; Tuczek, F. *Chem. Eur. J.* **2000**, *6*, 519–522. (q) Itoh, S.; Kumei, H.; Taki, M.; Nagatomo, S.; Kitagawa, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 6708–6709.
4. (a) Amadei, E.; Alilou, E. H.; Eydoux, F.; Pierrot, M.; Reglier, M.; Waegell, B. *Chem. Commun.* **1992**, 1782–1784. (b) Itoh, S.; Kondo, T.; Komatsu, M.; Ohshiro, Y.; Li, C.; Kanehisa, N.; Kai, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **1995**, *117*, 4714–4715. (c) Blain, I.; Bruno, P.; Giorgi, M.; Lojou, E.; Lexa, L.; Reglier, M. *Eur. J. Inorg. Chem.* **1998**, 1297–1304. (d) Itoh, S.; Nakao, H.; Berreau, L. M.; Kondo, T.; Komatsu, M.; Fukuzumi, S. *J. Am. Chem. Soc.* **1998**, *120*, 2890–2899. (e) Itoh, S.; Taki, M.; Nakao, H.; Holland, P. L.; Tolman, W. B.; Que, L. Jr.; Fukuzumi, S. *Angew. Chem.* **2000**, *112*, 409–411. *Angew. Chem., Int. Ed.* **2000**, *39*, 398–400. (f) Taki, M.; Teramae, S.; Nagatomo, S.; Tachi, Y.; Kitagawa, T.; Itoh, S.; Fukuzumi, S. *J. Am. Chem. Soc.* **2002**, *124*, 6367–6377. (g) Osaka, T.; Tachi, Y.; Doe, M.; Shiro, M.; Ohkubo, K.; Fukuzumi, S.; Itoh, S. *Chem. Eur. J.* **2004**, *10*, 237–246.
5. Thompson, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 8308–8309.
6. Blain, I.; Giorgi, M.; DeRiggi, I.; Reglier, M. *Eur. J. Inorg. Chem.* **2000**, 393–398.
7. Schönecker, B.; Zheldakova, T.; Liu, Y.; Kötteritzsch, M.; Günther, W.; Görls, H. *Angew. Chem.* **2003**, *115*, 3361–3365. *Angew. Chem., Int. Ed.* **2003**, *42*, 3240–3244.
8. Magyar, A.; Schönecker, B.; Wölfling, J.; Schneider, G.; Günther, W.; Görls, H. *Tetrahedron: Asymmetry* **2003**, *14*, 1925–1935.
9. Arii, H.; Saito, Y.; Nagatomo, S.; Kitagawa, T.; Funahashi, Y.; Jitsukawa, K.; Masuda, H. *Chem. Lett.* **2003**, *32*, 156–157.
10. Schönecker, B.; Zheldakova, T.; Lange, C.; Günther, W.; Görls, H.; Bohl, M. *Chem. Eur. J.* **2004**, in press.
11. Magyar, A.; Schönecker, B.; Wölfling, J.; Schneider, G.; Günther, W.; Görls, H. *Tetrahedron: Asymmetry* **2003**, *14*, 2705–2715.
12. Amendola, V.; Fabrizzi, L.; Linati, L.; Mangano, C.; Pallavicin, P.; Pedrazzini, V.; Zema, M. *Chem. Eur. J.* **1999**, *5*, 3679–3688.
13. Liang, H.-C.; Zhang, C. X.; Henson, M. J.; Sommer, R. D.; Hatwell, K. R.; Kaderli, S.; Zuberbühler, A. D.; Rheingold, A. L.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 4170–4171.
14. (a) Wilson, M. R.; Gallimore, W. A.; Reese, B. A. *Steroids* **1999**, *64*, 834–843. (b) Smith, K. E.; Latif, S.; Kirk, D. N. *J. Steroid Biochem.* **1990**, 115–120. (c) Owen, R. W.; Bilton, R. F. *J. Steroid Biochem.* **1985**, *22*, 817–822. (d) Owen, R. W.; Mason, A. N.; Bilton, R. F. *Tetrahedron* **1984**, *40*, 421–426. (e) Park, R. J. *Steroids* **1981**, *38*, 383–395. (f) Bilton, R. F.; Mason, A. N.; Tenneson, M. E. *Tetrahedron* **1981**, *37*, 2509–2513. (g) Murai, A.; Iwasa, N.; Masamune, T. *Bull. Chem. Soc. Jpn* **1980**, *53*, 259–262. (h) Murai, A.; Iwasa, N.; Masamune, T. *Chem. Lett.* **1977**, 235–236.
15. Jacobson, R. R.; Tyeklár, Z.; Karlin, K. D. *Inorg. Chim. Acta* **1991**, *181*, 111–118.
16. Mayes, A. M.; Hester, J. F.; Banerjee, P.; Akthakul, A., WO, 2002022712 (21.03.2002).
17. Bradd, K. J.; Heaton, B. T.; Jacob, C.; Sampanthar, J. T.; Steiner, A. *J. Chem. Soc., Dalton Trans.* **1999**, 1109–1112.
18. Spuhler, B.; Holthausen, M. C. *Angew. Chem.* **2003**, *115*, 6143–6147. *Angew. Chem., Int. Ed.* **2003**, *42*, 5961–5965.
19. Churchill, M. R.; Davies, G. E.; Sayed, M. A.; Fournier, J. A.; Hutchinson, J. P.; Zubieta, J. A. *Inorg. Chem.* **1984**, *23*, 783–787.
20. (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170–177. (b) Breslow, R. *Chemtracts—Org. Chem.* **1988**, *1*, 333–348. (c) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146–153. (d) Breslow, R.; Corcovan, R. J.; Snider, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 6791–6792. (e) Wiechert, R.; Kerb, U.; Stahnke, M.; Schulze, P.-E. *Angew. Chem.* **1981**, *93*, 89–90. *Angew. Chem., Int. Ed.* **1981**, *20*, 88–89.
21. Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045–2046.
22. Breslow, R.; Brandl, M.; Hunger, J.; Adams, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 3799–3801.
23. Pons, J.; Chadghan, A.; Alvarez-Larena, A.; Francesc Piniella, J.; Ros, J. *Inorg. Chem. Commun.* **2001**, *4*, 610–612.
24. Glas, H.; Herdtweck, E.; Artus, G. R. J.; Thiel, W. R. *Inorg. Chem.* **1998**, *37*, 3644–3646.
25. (a) Lee, A. J.; Kosh, J. W.; Conney, A. H.; Zhu, B. T. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 420–432. (b) Smeets, J. M. W.; Wamsteker, J.; Roth, B.; Everaarts, J.; van den Berg, M. *Chemosphere* **2002**, *46*, 163–172. (c) Wilson, M. R.; Gallimore, W. A.; Reese, P. B. *Steroids* **1999**, *64*, 834–843. (d) Smith, S. J.; Korzewka, K. R.; Aoyama, T.; Gonzalez, F. J.; Darbyshire, J. F.; Sugiyama, K.; Gillette, J. R. *Drug Metab. Dispos.* **1992**, *20*, 566–571. (e) Smith, K. E.; Latif, S.; Kirk, D. N. *J. Steroid Biochem.* **1990**, *35*, 115–120. (f) Owen, R. W.; Bilton, R. F. *J. Steroid Biochem.* **1985**, *22*, 817–822. (g) Owen, R. W.; Mason, A.; Bilton, R. F. *Tetrahedron* **1984**, *40*, 421–426. (h) Bilton, R. F.; Mason, A. R.; Tenneson, M. E. *Tetrahedron* **1981**, *37*, 2509–2513.
26. Pan, S. C.; Lerner, L. J.; Principe, P. A.; Junta, B. U.S. Patent 3324153, 1967.
27. Coombs, M. M.; Roderick, H. R. *J. Chem. Soc. (C)* **1967**, 1819–1821.
28. (a) Murai, A.; Iwasa, N.; Masamune, T. *Chem. Lett.* **1977**,

235–236. (b) Murai, A.; Iwasa, N.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 259–262.
29. (a) Wang, Y. Q.; Yan, X. Z.; Gong, S. S.; Fu, W. H. *Chin. Chem. Lett.* **2002**, *13*, 543–546. (b) Lee, D.-U. *Bull. Korean Chem. Soc.* **2002**, *23*, 9–10. (c) Lee, D.-W.; Kim, C.; Lee, D.-U. *Biol. Pharm. Bull.* **2001**, *24*, 1451–1453. (d) Lee, D.-U.; Kang, S.-I.; Yoon, S.-H.; Budesinsky, M.; Kasal, A.; Mayer, K. K.; Wiegrebe, W. *Planta Med.* **2000**, *66*, 480–482. (e) Zhang, R.-S.; Ye, Y.-P.; Shen, Y.-M.; Liang, H.-L. *Tetrahedron* **2000**, *56*, 3875–3879.
30. Grieco, P. A.; Snuk, T. L. *J. Am. Chem. Soc.* **1990**, *112*, 7799–7801.
31. (a) Breslow, R.; Fang, Z. *Tetrahedron Lett.* **2002**, *43*, 5197–5200. (b) Breslow, R.; Yan, J.; Belvedere, S. *Tetrahedron Lett.* **2002**, *43*, 363–365. (c) Breslow, R.; Yang, J.; Yan, J. *Tetrahedron* **2002**, *58*, 653–659. (d) Yan, J.; Breslow, R. *Angew. Chem.* **2000**, *112*, 2804–2806. *Angew. Chem., Int. Ed.* **2000**, *39*, 2692–2694.
32. Spencer, D. J. E.; Aboelella, N. W.; Reynolds, A. M.; Holland, P. L.; Tolman, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 2108–2109.
33. *SMART, Software for the CCD Detektor System*, version 5.05; Bruker AXS: Madison, WI, 1998.
34. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
35. Sheldrick, G. M. *SHELXTL97-2*; University of Göttingen: Germany, 1997.
36. Gonschior, M.; Kötteritzsch, M.; Rost, M.; Schönecker, B.; Wyrwa, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2159–2182.
37. CCDC 232442 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

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Stereochemical substituent effects: investigation of the cyano, amide and carboxylate group

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Abstract—Three pairs of diastereomeric piperidines, *cis*- and *trans*-2-methylpiperidine-3-carboxylate (**6a** and **6b**), *cis*- and *trans*-2-methylpiperidine-3-carboxylamide (**9a** and **9b**) and *cis*- and *trans*-2-methyl-3-cyanopiperidine (**11a** and **11b**), were synthesised for the purpose of investigating the effect of the axial versus equatorial carboxylate, carboxamide and cyano group on piperidine base strength. The pK_a values of the six compounds were determined to be 11.0 (**6a**), 10.4 (**6b**), 9.5 (**9a**), 9.3 (**9b**), 7.8 (**11a**) and 8.0 (**11b**). This shows that the strong electron-withdrawing effect of the cyano group and the effect of the amide group are relatively independent of spacial orientation. The carboxylate, on the other hand is considerably less electron-withdrawing when axial.
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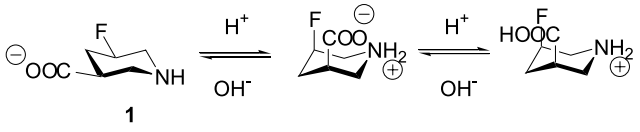
1. Introduction

Understanding the relationship between structure and properties is a fundamental issue in organic chemistry. Of central importance is the influence, in terms of electronic effects, of substituents on the chemistry of compounds. Substituent effects has been quantified by Hammett and Taft[1–3] and subsequently been refined so that very specific information is known about the electronic influence of functional groups.[4–6] However, relatively little attention has been given to the study of stereochemistry on substituent effects. While it was noted early that the base-strength of amines with polar groups varied widely, it was also concluded that they appeared to be unpredictable.[7,8] However, in recent work it has been observed that the basicity of piperidines and hexahydropyridazines was systematically affected by the axial or equatorial positioning of ring hydroxyl, fluorine or ester-groups.[9–11] An equatorial hydroxyl group was found to be three times more electron withdrawing than an axial hydroxyl group. This is exemplified in the difference in base strength of the epimeric glycosidase inhibitors isofagomine/galacto-isofagomine and 1-deoxynojirimycin/galactostatin (Fig. 1), in which the axial epimer is the stronger base. Similarly the piperidines with equatorial ester and fluorine groups were also found to be less basic than their axial isomers. An important and fascinating consequence of stereochemical substituent effects is, due to the principle of microscopic reversibility, that piperidines with polar substituents may change conformation on protonation.[10] Thus, as shown by Lankin and Snyder the fluoropiperidinecarboxylic acid **1** changes to the all axial conformation when the amino-group is protonated (Scheme 1).[12]



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Scheme 1. Conformational change of *cis*-3-fluoro-5-piperidinecarboxylic acid as a result of pH change.

It has been suggested that differences in charge–dipole interactions between the protonated amine and an axial or equatorial polar substituent is the prime reason for the influence of stereochemistry on piperidine base-strength. The present work is an effort to expand our knowledge about stereochemical substituent effects especially with the intent of determining the importance of charge–dipole interactions. For this purpose the nitrile-group was particularly interesting as it has a strong dipole and is a strongly electron-withdrawing group. If charge–dipole interactions are crucial for the base-strength a significant difference should be observed between piperidine isomers **A** and **B** (Fig. 1). We here report the influence of axial and equatorial positions on the base-lowering effect of carboxylic acid, carboxylic amide and nitrile groups. We have synthesised three pairs of stereoisomeric piperidines having a functional group in the 3-position and with restricted conformation and

Keywords: Electronic effect; Base strength; Piperidines; Conformation.
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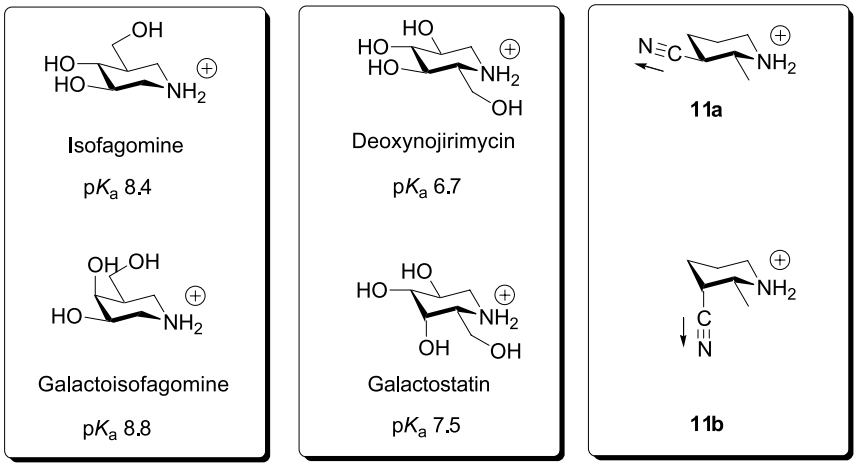


Figure 1. Base strength of epimeric glycosidase inhibitors and target molecules **11a** and **11b**.

recorded their pK_a values. We find that stereochemistry and/or conformation has a minor influence on the base-lowering effect of the cyano and carboxylic amide groups, while the base-lowering effect of the carboxylic acid is essentially eliminated in the axial position.

2. Results and discussion

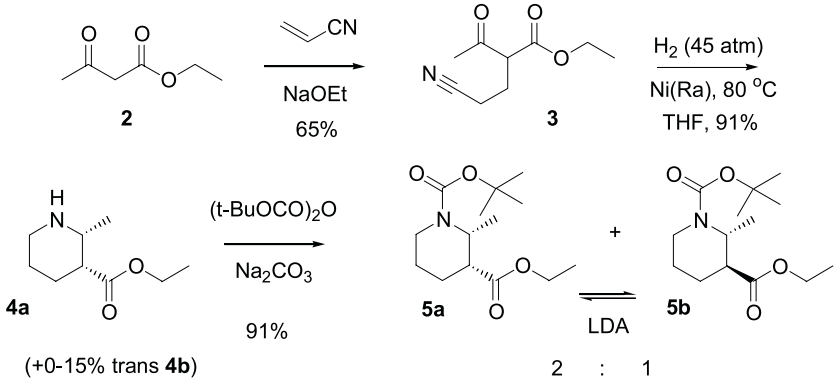
2.1. Synthesis

We decided to synthesise 3-substituted piperidines having a 2-methyl group, which should restrict the conformation of the molecule by inducing unfavourable 1,3-diaxial interaction when axial. These molecules should prefer a chair conformation with the methyl group equatorial and the 2,3-*cis* and *trans* isomers would therefore have the 3-substituent equatorial and axial, respectively. Here we rely on the work of Lapuyade et al. who studied the conformation of various methyl nipecotic acids and found that the methyl group preferred to be equatorial.[13]

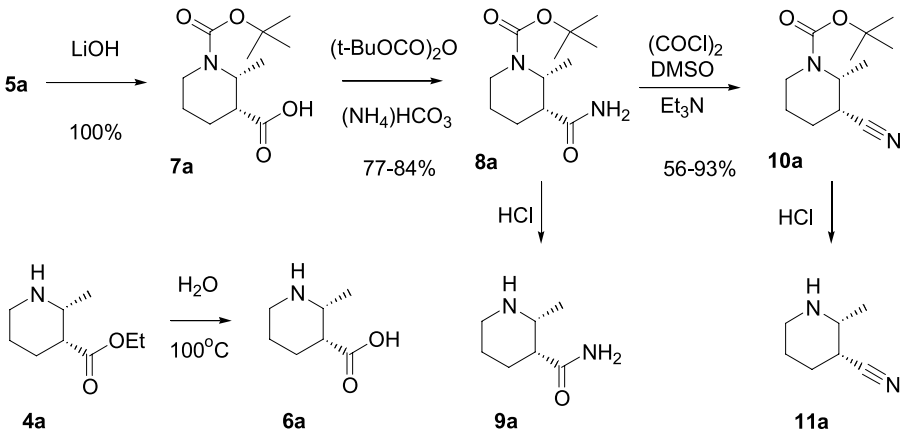
The acid, 2-methylnipecotic acid **6**, was prepared by Lapuyade et al.[13] as a mixture of *cis* and *trans* isomers. We decided to modify their synthesis to obtain all three sets of compounds with the anticipation that the stereoisomers could be separated. Thus the known Michael reaction between ethyl acetoacetate and acrylonitrile was used to obtain adduct **3** (Scheme 2).[14] Hydrogenation and reductive amination using Raney Nickel catalyst and 45 atm hydrogen pressure in EtOH gave the ester **4**, as previously reported,[14] in good yield. However, we observed that the *N*-ethyl derivative was formed as a byproduct in the reaction lowering yield and purity. This compound is presumably formed by metal catalysed dehydrogenation from ethanol to acetaldehyde and subsequent reductive amination of **4**. We therefore changed the solvent to THF which led to a yield of 91%. The reaction gives mainly the *cis*-isomer with the content of the *trans*-isomer not being entirely reproducible and varying between 0 and 15%. The catalysts Pd/C and Rh/C did not efficiently reduce the nitrile.

By careful chromatography in the polar solvent mixture EtOAc–EtOH–Et_3N 66:33:1 the *cis*- and *trans*-isomers of **4**, **4a** and **4b**, could be separated. However, it was typically more convenient to separate after protection of the amino group. The piperidine **4** was protected with Boc anhydride/Na_2CO_3 in the usual way giving **5** in 91% yield, and was separated to **5a** and **5b** by chromatography. To obtain more **5b**, the isomerization of **5a** with LDA was performed giving a product with a content of **5b** up to 37% (Scheme 2).

The *cis*-2-methylnipecotic acid **6a** was made, in 72% yield, by treatment of **4a** with boiling water as described for the mixture by Lapuyade et al. (Scheme 3).[13] The *cis* isomer **5a**, was converted, in quantitative yield, to the acid **7a** by



Scheme 2. Synthesis of esters **5a** and **5b**. The chiral compounds are racemic.



Scheme 3. Synthesis of *cis* isomers **6a**, **9a** and **11a**. All compounds are racemic.

hydrolysis with LiOH. By the use of Boc anhydride/$(NH_4)HCO_3$[15] on the acid **7a**, the primary amide **8a** was obtained in 84% yield. Dehydration of **8a** with oxalyl chloride/Et_3N[16] gave up to 93% yield of the nitrile **10a**. Deprotection of **8a** and **10a** with HCl gave the amines **9a** and **11a**, respectively.

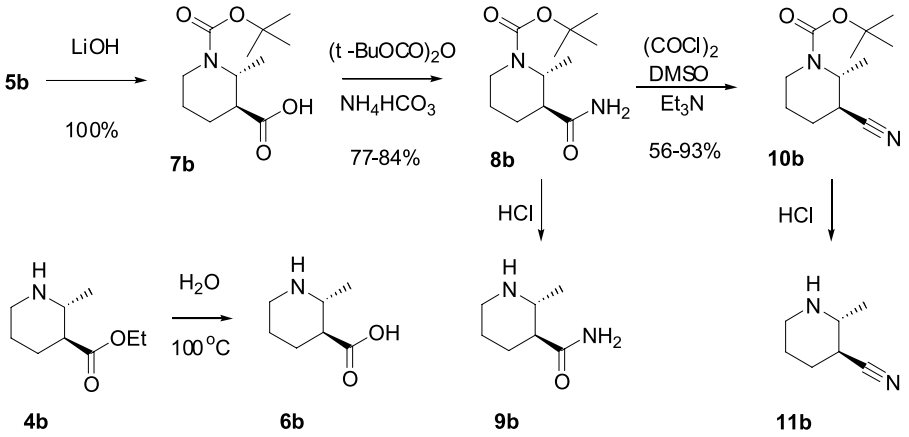
An identical sequence of reactions was carried out on the *trans*-isomeric compounds **4b** and **5b** leading to the corresponding acid, amide and nitrile **6b**, **9b** and **11b** (Scheme 4).

2.2. Configuration of the piperidines

The synthesised piperidines are all configurationally related in two families of *cis* and *trans* compounds obtained from the same two precursors **4a** and **4b**. Therefore determination of the configuration of a single member of each family is sufficient to establish the configuration of all. This determination is readily done with **6a** and **6b**. In **6b** J_{23} is 11 Hz showing that it must be diaxial coupling, which is only consistent with the 2,3-*trans* configuration of this molecule. In contrast in **6a** J_{23} is 2.3 Hz which is consistent with a axial-diequatorial coupling of the *cis*-configured molecule.

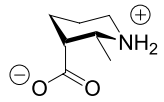
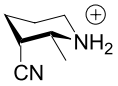
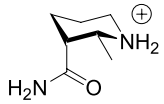
2.3. Conformation of the piperidines

As the conformation can influence the base-strength the conformational preference of the six piperidines as hydrochlorides and as free amines is important. If protonation of the piperidine is associated with a conformational change this may influence the base-strength and complicate the interpretation. In the following discussion we will, for simplicity, relate to the enantiomers shown in Schemes 3 and 4 despite the fact that the compounds are racemic. The arguments are, of course, equally valid for the antipodes. As mentioned previously, the conformation of **6a** and **6b** was determined by Lapuyade et al. to be mainly $^4C_1$ that is have the methyl group equatorial.[13] The *trans*-amide **9b** is clearly also in the diequatorial $^1C_4$ conformation both as hydrochloride and as free amine. This is readily seen by the large J_{23} proton coupling being 10 Hz in the amine and 10.8 Hz in the hydrochloride. The *cis*-amide **9a** is also in $^4C_1$ conformation in both protonated and neutral form. This is particularly evident from the H-3 proton which only has small couplings and thus must be equatorial. It is also seen that H-2 and H-3 has an essentially similar chemical shift, respectively, in both the amino and conjugate acid forms which confirm that they do not change from equatorial to axial or vice versa. Finally the 2-methyl group has a ^{13}C



Scheme 4. Synthesis of *trans* isomers **6b**, **9b** and **11b**. All compounds are racemic.

Table 1. pK_a values of the piperidines

Number	Structure	pK_a	Number	Structure	pK_a
6a		11.0	**9b**		9.3
6b		10.4	**11a**		7.8
9a		9.5	**11b**		8.0

chemical shift of 16–19 ppm in **9a** and **9b** both as amines and conjugated acids, in accordance with it being consistently equatorial. An axial methyl group is 5–7 ppm more shielded than an equatorial.[17] The *cis*- and *trans*-nitriles **11a** and **11b** were also found to be in the $^4C_1$ conformation. The ^{13}C spectra of the conjugate acids and amines quite clearly shows the 2-methyl group has essentially the same chemical shift as in **9a** and **9b**, and therefore must be predominantly equatorial. Also the H-2 proton in **11a** is found at a similar chemical shift as was the case in **9a**. In **11b** J_{23} is found to be 10.4 Hz in the amine form and 11.2 Hz in the conjugate acid form clearly consistent with $^4C_1$ conformation for both forms. So we conclude that the 2-methyl group serves its purpose as an conformational anchor and that the piperidines **6a**, **6b**, **9a**, **9b**, **11a** and **11b** are predominantly in the conformations as shown in Table 1.

2.4. Determination of base-strength

The pK_a values of amino groups of **6a**, **6b**, **9a**, **9b**, **11a** and **11b** were determined by titration and are shown in Table 1. The pK_a values of the carboxylic acid residues of **6a** and **6b** were found to 3.3 and 3.2, respectively. The data are the average of three determinations (error $\pm$0.1). The empirical formula p$K_a = 10.7 - \Sigma\sigma_s$[10] was applied to calculate the σ_s values for the new substituents, taking into account that the σ_s value of an equatorial 2-Me is -0.1. This gave the values shown in Table 2. The value for an equatorial 3-carboxylate has previously determined to 0.5 and from that value the pK_a was calculated to 10.3 and thus is underestimated by 0.1.

The results are remarkable in that only the nipecotic acids **6a** and **6b** show a significant difference in the base-strength of the amine. The difference (ΔpK_a) between the pK_a values of **6a** and **6b** is 0.5 (or 0.7 between σ_s values) which appears reasonable given the sizeable ΔpK_a found previously for the ester group in the 3-position of the piperidine.[10] However, surprisingly the ΔpK_a for the amides **9a/9b** is only 0.2, despite the fact that the very similar ester group differs largely in axial and equatorial substituent effect. Even more remarkable is the observation that the very electron-withdrawing and strongly dipolar nitrile group only has a pK_a difference of -0.2 for **11a/11b**, the *cis* isomer being slightly more basic.

Table 2. σ_s values of substituents in the β or 3-position of piperidines

Substituent	σ_s value (β, equat.)	σ_s value (β, axial)	σ_I (Ref. 5)
COO^-	0.5*	−0.2	0.58
$CONH_2$	1.5	1.3	1.78
CN	2.8	3.0	3.04
COOMe	1.2*	0.2*	1.7
OH	1.3*	0.5*	1.68
F	2.3*	1.5#	2.57

The pK_a of the piperidine is calculated using the formula p$K_a = 10.7 - \Sigma\delta_s$, *value taken from Ref. 10, #value taken from Ref. 11.

It is interesting to note that the σ_s values of the equatorial isomers are comparable in size or slightly smaller than the σ_I values determined by Grob[5] on 4-substituted quinuclidines (Table 2). Evidently an equatorial σ_s value can be estimated as 70–100% of a σ_I value. In contrast, in the axial position, the substituent effect varies widely. While the CN and $CONH_2$ groups are similar to σ_I values for the carboxylate, ester, hydroxyl and fluorine substituent a partial or complete elimination of the electron withdrawing effect takes place.

2.5. PM3 calculations

To get more insight into these differences semi-empirical calculations (MOPAC, PM3) were made on 3-substituted piperidine, in ammonium and amine form, with the substituent placed axial and equatorial. The results are shown in Table 3. These calculations are valid in the gas phase and their significance in solution must be interpreted with caution. Nevertheless some general trends are evident and consistent with the experimental facts. It is seen that while the axial and equatorially substituted amines essentially have similar heat of formation, the ammonium ions generally differ with the equatorial isomer being less stable. The smallest difference, 6 kJ/mol, is found for the cyano substituted piperidine, which explains why a large pK_a

Table 3. Heat of formation, in kJ/mol of monosubstituted piperidines calculated using PM3, MOPAC in Chem3D 6.0 Ultra

Substituent	Amine	Ammonium
3-CN (axial)	80.0	762.8
3-CN (equatorial)	79.6	768.9
3-$CONH_2$ (axial)	−222.1	400.6
3-$CONH_2$ (equatorial)	−224.2	437.4
3-COO^- (axial)	−539.7	−289.9
3-COO^- (equatorial)	−538.8	−189.0
3-COOMe (axial)	−404.3	245.5
3-COOMe (equatorial)	−404.3	273.2
3-OH (axial)	−251.8	399.7
3-OH (equatorial)	−253.1	413.6
3-F (axial)	−258.9	411.0
3-F (equatorial)	−256.4	423.6

difference not is found between **11a** and **11b**. Also the difference observed in the pK_a of **6a** and **6b** is qualitatively supported by the large difference observed in heat of formation for the ammonium ions. On the other hand the size of the pK_a difference (0.5–0.7) is relatively small compared to the huge energy difference calculated. Also the clear difference in heat of formation between the protonated amides is not very consistent with the insignificant difference found in pK_a (0.2) between **9a** and **9b**. This is contrasted by the ester were a similar energy difference is calculated between axial and equatorial isomer but a significant pK_a difference (1.0) is observed. It is proposed that these inconsistencies may be caused by effects of solvation of the carboxylate and amide groups reducing the electrostatic interaction with the ammonium ion compared to the gas phase.

3. Conclusion

It was found that the strong electron withdrawing power of the cyano group is not significantly influenced by its axial or equatorial orientation. The through space or solvent component of the electron withdrawing effect must be minor, and a charge dipole effect cannot be important. The substituent effect from the amide group was also found relatively independent on stereochemistry. In contrast the substituent effect from a carboxylate group was significantly different in the axial and equatorial positions.

4. Experimental

4.1. General

^{13}C-, ^{1}H- and H,H-COSY NMR were recorded on a Varian Gemini 200 (200 MHz) NMR instrument and when specifically noted on a Mercury 400 (400 MHz) NMR instruments. The spectra were referenced to solvent residues. MS was recorded on a Micromass LC-TOF instrument. Chromatography was performed in Merck 60 silica. TLC was performed on Merck silica 60 E_{254} coated glass plates and developed using either vanillin (3 g in 100 mL EtOH with 1 mL H_2SO_4 added), potassium permanganate (aq), Ce-mol (10 g Ce(IV)SO_4 and 15 g $(NH_4)_2MoO_4$ in 1 L 10% H_2SO_4) or ninhydrin (2% in *n*-BuOH) and subsequent heating.

4.1.1. Ethyl (2-cyanoethyl)-acetoacetate (3).[14] This product, a clear oil, was prepared as described in Ref. 14. ^{1}H NMR ($CDCl_3$): δ 4.23 (q, J=7.8 Hz, 2H, –OCH_2CH$_3$), 3.65 (t, J=6.8 Hz, 1H, H_2), 2.45 (t, J=6.8 Hz, 2H, H_6), 2.30 (s, 3H, H_4), 2.2 (m, 2H, H_5), 1.3 (t, J=7.8 Hz, 3H, OCH$_2$CH_3).

4.1.2. *cis* and *trans* Ethyl 2-methyl nipecotate (4a and 4b). *Compound* **3**. (2.52 g, 13.8 mmol) was dissolved in freshly distilled dry THF, and Raney nickel (0.5 g, prewashed in THF) was added. The mixture was transferred to an autoclave with magnet, and the atmosphere replaced by flushing with a stream of nitrogen. The container was closed and a pressure of 45 atm. H_2 was applied for 15 h at 80 °C. The mixture was filtered through Celite® and concentrated. The yield of **4** was 2.14 g (91%) and further purification was not necessary unless the pure stereoisomers were required. The *cis*/*trans* ratio (**4a**/**4b**) was normally 10/1 (as determined from ^{1}H NMR) but varied between 1:0 and 6:1 depending on the scale. Separation of the **4a** and **4b** was carried out by chromatography in EtOAc–EtOH 2:1 containing 1% Et_3N added. Separation of 1.0 g of the mixture gave 634 mg **4a** and 74 mg **4b**.

Compound **4a**. Clear oil, ^{1}H NMR ($CDCl_3$, assigned with COSY): δ 4.1 (q, J=7.3 Hz, 2H, –OCH_2CH$_3$), 3.02 (dt, J=13.6, 4.4 Hz, 1H, H_{6e}), 2.9 (dq, J=6.4, 3.5 Hz, 1H, H_{2a}), 2.62 (dt, J=10.2, 3.5 Hz, 1H, H_{6a}), 2.48 (q, J=3.5 Hz, 1H, H_{3e}), 2.05 (bs, 1H, N–H), 1.95 (dt, J=5.8, 1.5 Hz 1H, H_{4e}), 1.5–1.8 (m, 2H, H_{5e}, H_{4a}), 1.35 (m, 1H, H_{5a}), 1.22 (t, J=7.3 Hz, 3H, –OCH$_2$CH_3), 1.08 (d, J=7 Hz, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): **4a**: δ=174.3 (C=O), 60.1 (–OCH_2CH$_3$), 52.5 (C_3), 45.4 (C_2), 44.3 (C_6), 26.5 (C_4), 22.9 (–OCH$_2$CH_3), 19.2 (C_5), 14.5 (–CH_3).

Compound **4b**. Clear oil, ^{1}H NMR ($CDCl_3$) (assigned with COSY): δ 4.1 (q, J=7.3 Hz, 2H, –OCH$_2$CH_3), 3.05 (m, 1H, H_{6a}), 2.8 (dq, J=10, 5.8 Hz, 1H, H_{2a}), 2.68 (dt, J=12, 2.6 Hz, 1H, H_{6a}), 1.9–2.1 (m, 2H, H_{3a}, N–H), 1.4–1.7 (m, 5H, H_{4e}, H_{5e}, H_{4a}, H_{5a}), 1.25 (t, J=7.7 Hz, 3H, –OCH$_2$CH_3), 1.06 (d, J=5.8 Hz, 3H, –CH_3). MS: Calcd for $C_9H_{17}NO_2$ (M+H)=172.1338. Found: 172.1328.

4.1.3. *cis* and *trans* Ethyl *N*-*tert*-butoxycarbonyl-2-methylnipecotate (5a and 5b). A mixture of **4a** and **4b** (2.30 g, 13.4 mmol) was dissolved in 40 mL 50% aq THF. Na_2CO_3 (1.46 g, 13.7 mmol) was added under stirring at 0 °C. A mixture of 3.32 g (15.3 mmol) di-*tert*-butyl dicarbonate (boc-anhydride) and 1.43 g (16.1 mmol) Na_2CO_3 in 30 mL 50% aq THF was added, and the mixture stirred for 30 min at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 2 h and acidified with 1.0 M HCl. The mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$. After concentration a white crystalline product of **5a** and **5b** was obtained. Yield: 3.32 g (91%, mixture of *cis* and *trans*). Compounds **5a** and **5b** could be separated using chromatography in CH_2Cl_2/EtOAc 20:1 (see also below).

Compound **5a**. White crystals, mp=72 °C, ^{1}H NMR ($CDCl_3$): δ 4.84* (bs, 0.5H, H_2), 4.63* (bs, 0.5H, H_2), 4.12 (q, J=6.6 Hz, 2H, –CH_2CH$_3$), 3.99* (d, J=11.6 Hz, 0.5H, H_{6e}), 3.86* (d, J=13.2 Hz, 0.5H, H_{6e}), 2.77 (dt, J=11.6, 13.2 Hz, 1H, H_{6a})*, 2.60 (dt, J=3.6, 12.8 Hz, 1H, H_{3e}), 1.65–1.9 (m, 3H, H_{4e}, H_{5e}, H_{4a}), 1.46 (s, 9H, Boc), 1.40 (m, 1H, H_{5a}), 1.25 (t, J=6.6 Hz, 3H, –CH$_2$CH_3), 1.03 (d, J=7.2 Hz, 3H, –CH_3) (*Rotamers present).

Compound **5b**. White crystals, mp=74 °C, ^{1}H NMR ($CDCl_3$): δ 4.86 (q, J=6.4 Hz, 1H, H_{2e}), 4.12 (dq, J=2.4, 7.4 Hz, 2H, –CH_2CH$_3$), 3.92 (bd, J=13.2 Hz, 1H, H_{6e}), 2.79 (dt, J=3.2, 13.2 Hz, 1H, H_{6a}), 2.37 (bs, 1H, H_{3e}), 2.02 (dd, J=3.2, 14 Hz, 1H, H_{4e}), 1.74 (tt, J=4.0, 13.4 Hz, 1H, H_{4a}), 1.75 (m, 1H, H_{5e}) 1.62 (tk, J=4.0, 13.2 Hz, 1H, H_{5a}), 1.43 (s, 9H, Boc), 1.24 (t, J=6.8 Hz, 3H, –CH$_2$CH_3), 1.19 (d, J=7.2 Hz, 3H, –CH_3). MS: Calcd for $C_{14}H_{25}NO_4$ (M+Na)=294.1681. Found 294.1680.

4.1.4. Epimerisation of 5a. A 50 mL oven dried round-bottomed flask was purged with nitrogen and closed with septum. Then 20 mL freshly distilled THF and dry diisopropylamine (0.50 mL, 3.5 mmol) was injected. The mixture was cooled, and *n*-BuLi (2.20 mL, 3.5 mmol, 1.6 M in hexane) was added. The mixture was stirred on ice for 10 min. The LDA solution was cooled on dry ice/acetone and **5a** (800 mg, 3.0 mmol) in THF was added. The reaction mixture was stirred for 1 h and quenched with water. The mixture was acidified with 1.0 M HCl and extracted with CH_2Cl_2. The yellowish product was separated by chromatography in CH_2Cl_2/EtOAc 20:1 giving **5b** (160 mg, 27%) and **5a** (428 mg, 47%).

4.1.5. *cis*- and *trans*-2-Methylnipecotic acid (6a and 6b). These acids were prepared as described for the mixture in Ref. 13. Compund **4a** (133 mg) or **4b** (74 mg) was boiled in water for 5 h, concentrated and dried. This gave **6a** (115 mg) or **6b** (65 mg), respectively. Yield: 95–100%.

Compound **6a**. White solid, ^{1}H NMR (D_2O): δ 3.4 (dt, J= 1.9, 3.8 Hz, 1H, H_{6e}), 3.3 (dq, J=2.3, 6.8 Hz, 1H, H_{2a}), 3.0 (m, 1H, H_{6a}), 2.62 (bq, J=2.3 Hz, 1H, H_{3e}), 1.6–2.1 (m, 4H, H_{4a}, H_{4e}, H_{5a}, H_{5e}), 1.32 (d, J=6.8 Hz, 3H, H_7). ^{13}C NMR (D_2O): δ 180.1 (C=O), 53.1 (C_2), 44.0 (C_3), 43.5 (C_6), 24.7 (C_4), 18.3 (C_5), 15.6 (C_7).

Compound **6b**. White solid, ^{1}H NMR (D_2O): δ 3.4 (m, 1H, H_{6e}), 3.2 (dq, J=6.5, 11 Hz, 1H, H_{2a}), 2.95 (dt, J=3.2, 12.5 Hz, 1H, H_{6a}), 2.28 (dt, J=3.2, 11 Hz, 1H, H_{3a}), 1.5–2.1 (m, 4H, H_{4a}, H_{4e}, H_{5a}, H_{5e}), 1.27 (d, J=6.5 Hz, 3H, H_7). ^{13}C NMR (D_2O): δ 179.9 (C=O), 53.5 (C_2), 50.2 (C_6), 43.8 (C_3), 26.3 (C_4), 21.1 (C_5), 16.8 (C_7).

4.1.6. *cis*- and *trans*-*N*-*tert*-Butoxycarbonyl-2-methylnipecotic acid (7a and 7b). *Compound* **5a** or **5b** (1.69 g) was dissolved in THF and treated with excess 2 M LiOH solution. After 18 h at room temperature, the solution was acidified with 1.0 M HCl. The mixture was extracted with EtOAc, dried over $MgSO_4$ and concentrated giving a white solid of **7a** or **7b**. Yield: 1.50 g (100%).

Compound **7a**. White solid, mp=178 °C. ^{1}H NMR ($CDCl_3$): δ 9.2 (bs, 1H, –COO*H*), 4.8 (bs, 1H, H_2), 3.9 (bs, 1H, H_{6e}), 2.8 (bs, 1H, H_3), 2.65 (dt, J=4.8, 11.9 Hz, 1H, H_{6a}), 1.6–1.9 (m, 3H, H_{4e}, H_{5e}, H_{4a}), 1.46 (s, 9H, Boc), 1.24 (dt, J=1.6, 7.2 Hz, 1H, H_{5a}), 1.08 (d, J=6.7 Hz, 1H, –C*H*$_3$). IR (KBr): 1660 (–*CO*O^{t}Bu), 1734 (–*CO*NH$_2$), 2979 (C–H sp^3), 3000–2900 (small bands –COO*H*). MS: Calcd for $C_{12}H_{21}NO_4$ (M+Na)=266.1368. Found: 266.1367.

Compound **7b**. White crystals, mp=115 °C. ^{1}H NMR ($CDCl_3$): δ 4.82 (q, J=6.8 Hz, 1H, H_{2e}), 3.90 (d, J= 12 Hz, 1H, H_{6e}), 2.75 (dt, J=3.2, 13.2 Hz, 1H, H_{6a}), 2.38 (bs, 1H, H_{3e}), 2.00 (bd, J=13.2 Hz, 1H, H_{4e}), 1.73 (tt, J= 4.8, 13.6 Hz, 1H, H_{4a}), 1.58 (tq, J=4.0, 13.2 Hz, 1H, H_{5a}), 1.45 (bd, J=13.2 Hz, 1H, H_{5e}), 1.38 (s, 9H, Boc), 1.16 (d, J=7.2 Hz, 3H, –C*H*$_3$). IR (KBr): 1653 (–*CO*OH), 1730 (*CO*O^{t}Bu), 3000–2850 (small bands –CO*OH*). MS: Calcd for $C_{12}H_{21}NO_4$ (M+Na)=266.1368, Found: 266.1367.

4.1.7. *cis*- and *trans*-*N*-*tert*-Butoxycarbonyl-2-methylpiperidine-3-carboxylic amide (8a and 8b). *Compound* **7a** or **7b** (0.890 g, 3.27 mmol) was dissolved in 1,4-dioxane (6 mL) and (0.125 mL, 1.5 mmol) pyridine was added dropwise. Boc anhydride (0.75 g, 3.4 mmol) was added and the reaction was stirred for 15 min. Now ammonium hydrogencarbonate (0.27 g) was added and stirring continued for 18 h. EtOAc was added, the mixture separated and the organic layer washed with 5% H_2SO_4 and water. The organic phase was dried with $MgSO_4$ and concentrated. The products were thick yellowish syrups. After trituration with ether **8a** becomes crystalline and white. Yield: 0.745 g (84%).

Compound **8a**. White crystals, mp=163–165 °C. ^{1}H NMR ($CDCl_3$): δ 5.65 (bs, 1H, –N*H*$_2$), 5.5 (bs, 1H, –N*H*$_2$), 4.64 (dq, J=4.8, 6.4 Hz, 1H, H_{2e}), 3.92 (bd, J=13 Hz, 1H, H_{6e}), 2.8 (dt, J=3.2, 12 Hz, 1H, H_{6a}), 2.5 (dt, J=4.8, 11.2 Hz, 1H, H_{3e}), 1.8 (dq, J=13, 4.1 Hz, 1H, H_{4a}), 1.6–1.9 (m, 2H, H_{4e}, H_{5e}), 1.43 (s, 9H, Boc), 1.2–1.4 (m, 1H, H_{5a}), 1.1 (d, J=6.6 Hz, 3H, –C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 175.7 (*CO*NH$_2$), 154.9 (Boc), 80.7 (–O–*C*(CH$_3$)$_3$), 48.3 (C_2), 46.0 (C_6), 38.3 (C_3), 28.6 (O–C(*C*H$_3$)$_3$), 24.8 (C_4), 20.6 (C_5), 11.9 (–*C*H$_3$). IR (KBr): 1685 (–*CO*O^{t}Bu), 1625 (–*CO*NH$_2$), 2975/2944 (C–H sp^3), 3393 (–CO*N*H$_2$). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na)=265.1528, Found: 265.1516.

Compound **8b**. White solid, mp=165 °C. ^{1}H NMR ($CDCl_3$): δ 5.41 (bs, 1H, –N*H*$_2$), 4.71 (q, J=6.4 Hz, 1H, H_{2e}), 3.93 (bd, $J\approx$13.5 Hz, 1H, H_{6e}), 2.91 (dt, J=4.0, 13.2 Hz, 1H, H_{6a}), 2.35 (ddd, J=2.0 Hz, 1H, H_{3e}), 2.19 (bd, $J\approx$12.4 Hz, 1H, H_{4e}), 1.85 (tt, J=4.8, 12.8 Hz, 1H, H_{4a}), 1.46–1.53 (m, 2H, H_{5e}, H_{5a}), 1.46 (s, 9H, Boc), 1.26 (d, J= 6.8 Hz, 3H, –C*H*$_3$). ^{13}C NMR ($CDCl_3$): δ 177 (amide C=O), 156 (Boc C=O), 80.5 (–O–*C*(CH$_3$)$_3$), 46.5 (C_2), 45 (C_6), 39 (C_3), 29.5 (O–C(*C*H$_3$)$_3$), 22.4 (C_4), 22 (C_5), 16.5 (–*C*H$_3$). IR (KBr): 1684 (–*CO*O^{t}Bu), 1659 (–*CO*NH$_2$), 2975/2930 (C–H sp^3), 3389 (–CO*N*H$_2$). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na)=265.1528. Found: 265.1526.

4.1.8. *cis*- and *trans*-2-Methylpiperidine-3-carboxylic amide (9a and 9b). *Compound* **8a** or **8b** was treated with 0.2 M HCl in excess and concentrated to dryness to give the hydrochloride of **9a** or **9b**. To obtain the amine, the hydrochloride was dissolved in water and subjected to ion-exchange chromatography on Amberlite IR-120, H^+. The amine was eluted with 5% aq ammonia.

Compound **9a**. Clear syrup, ^{1}H NMR (D_2O): δ 3.19 (dq, J= 3.4, 6.6 Hz, 1H, H_{2a}), 2.96 (dt, J=4.2, 12.6 Hz, 1H, H_{6e}), 2.74 (ddd, J=3, 9.8, 12.6 Hz, 1H, H_{6a}), 2.62 (q, J=4.2 Hz, 1H, H_{3e}), 1.85 (m, 1H, H_{4e}), 1.48–1.8 (m, 3H, H_{4a}, H_{5e}, H_{5a}), 1.14 (d, J=6.8 Hz, 3H, –C*H*$_3$). (hydrochloride): δ= 3.42 (dq, J=6.4, 3.1 Hz, 1H, H_{2a}), 3.36 (m, 1H, H_{6e}), 3.02 (dt, J=4.6, 12 Hz, 1H, H_{6a}), 2.84 (q, J=3.1 Hz, 1H, H_{3e}), 1.7–2.05 (m, 4H, H_{4e}, H_{5e}, H_{4a}, H_{5a},), 1.32 (d, J=6.4 Hz, 3H, –C*H*$_3$). ^{13}C NMR (CD_3OD): δ 179.0 (*C*=O), 53.7 (C_2), 45.1 (C_6), 43.5 (C_3), 27.0 (C_4), 21.1 (C_5), 17.4 (–*C*H$_3$). (hydrochloride): δ 178 (*C*=O), 54.4 (C_2), 45.2 (C_6), 42.0 (C_3), 27.0 (C_4), 19.5 (C_5), 16.9 (–*C*H$_3$). IR (KBr, hydrochloride): 1608 (–CONH$_2$), 1660 (–*C*=*O*), 2753/ 2857 ($R_2N^+H_2$), 2960 (C–H sp^3), 3318/3151 (–CONH$_2$). MS: Calcd for $C_7H_{14}N_2O$ (M+H)=143.1184, Found: 143.1080.

Compound **9b**. Clear syrup, ^{1}H NMR (D_2O): δ 3.0 (bd, J= 12.8 Hz, 1H, H_{6e}), 2.74 (dq, J=6.4, 10 Hz, 1H, H_{2a}), 2.6 (dt, J=2.8, 12.4 Hz, 1H, H_{6a}), 2.08 (ddd, J=3.6, 10.0, 10.4 Hz, 1H, H_{3a}), 1.9 (bdd, J=2.8, 13.6 Hz, 1H, H_{4e}), 1.72 (dt, J= 2.8, 13.2 Hz, 1H, H_{5e}), 1.55 (dq, J=2.8, 13 Hz, 1H, H_{4a}), 1.42 (tq, J=2.8, 13 Hz, 1H, H_{5a}), 1.02 (d, J=6.4 Hz, 3H, CH_3). (hydrochloride): δ 3.06 (bd, J=12.8 Hz, 1H, H_{6e}), 2.94 (dq, J=6.4, 10.8 Hz, 1H, H_{2a}), 2.65 (dt, J=2.5, 12.4 Hz, 1H, H_{6a}), 2.19 (dt, J=3.6, 10.8 Hz, 1H, H_{3a}), 1.69 (bd, J=11.6 Hz, 1H, H_{4e}), 1.62 (bd, J=13.6 Hz, 1H, H_{5e}), 1.39 (ddd, J=3.2, 13.2 Hz, 1H, H_{5a}), 1.32 (dq, J=3.2, 11.4 Hz, 1H, H_{4a}), 0.95 (d, J=6.4 Hz, 3H, –CH_3). ^{13}C NMR (CD_3OD): δ 180 (C=O), 53 (C_2), 50 (C_6), 45 (C_3), 27 (C_4), 23 (C_5), 19 (–CH$_3$). (hydrochloride): δ 175.5 (C=O), 52.9 (C_2), 43.9 (C_6), 42.8 (C_3), 24.7 (C_4), 20.1 (C_5), 15.6 (–CH$_3$). IR (KBr, hydrochloride): 1613 (–$CONH_2$), 1667 (–C=O), 2807 ($R_2N^+H_2$), 2950 (C–H sp^3), 3368/3180 (–$CONH_2$). MS: Calcd for $C_7H_{14}N_2O$ (M+H): 143.1184. Found: 143.1086.

4.1.9. *cis*- and *trans*-*N*-*tert*-Butoxycarbonyl-3-cyano-2-methylpiperidine (10a and 10b). *Compound* **8a** or **8b** (0.58 g, 2.4 mmol) was dissolved in DCM (7 mL) and DMSO (0.27 mL, 0.30 g; 3.8 mmol) was added. The mixture was cooled to −78 °C and oxalylchloride (0.25 mL, 0.37 g; 2.88 mmol) was added. After 15 min triethylamine (1.0 mL, 0.73 g; 7.19 mmol) was added dropwise. After further 15 min of stirring, the reaction was quenched with 15 mL water and extracted with three times 15 mL EtOAc. The organic layer was washed with concd NaCl solution, dried over $MgSO_4$ and concentrated. Purification by chromatography—eluent DCM/EtOAc 50:1—gave 480 mg **10a** or **10b** (93%).

Compound **10a**. White crystals. mp=61 °C. ^{1}H NMR ($CDCl_3$): (assigned using Cosy) δ 4.64 (dq, J=3.5, 6.6, 6.6, 6.6 Hz, 1H, H_{2e}), 3.95 (bd, J=13.2 Hz, 1H, H_{6e}), 2.80 (dt, J=3.3, 13.2, 13.2 Hz, 1H, H_{6a}), 2.76 (dt, J=3.5, 3.5, 11.5 Hz, 1H, H_{3a}), 1.9–2.1 (m, 1H, H_{4e}), 1.90 (ddd, J=3.5, 13.2, 13.2 Hz, 1H, H_{4a}), 1.70 (ddd, J=2.0, 3.3, 13.2 Hz, 1H, H_{5e}), 1.46 (s, 9H, Boc), 1.38 (m, 1H, H_{5a}), 1.31 (d, J= 6.6 Hz, 3H, –CH_3) ^{13}C NMR ($CDCl_3$): δ 155 (Boc C=O), 120.5 (–C≡N), 80.5 (–O–C(CH_3)$_3$), 47 (C_6), 37.5 (C_2), 31.7 (C_3), 28.6 (O–C(CH_3)$_3$), 24.5 (C_5), 23.0 (C_4), 12.4 (–CH_3). IR (KBr): 1690 (C=O), 2240 (–C≡N), 2977 (C–H sp^2). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na)=247.1422. Found: 247.1415.

Compound **10b**. White crystals. mp=69 °C. ^{1}H NMR ($CDCl_3$): (assigned using Cosy) δ 4.63 (q, J=6.8 Hz, 1H, H_{2e}), 3.99 (bd, J=14 Hz, 1H, H_{6e}), 2.75 (dt, J=3.5, 13, 13 Hz, 1H, H_{6a}), 2.63 (bs, 1H, H_{3e}), 1.81 (m, 1H, H_{4e}), 1.75 (tt, J=3.6, 13 Hz, 1H, H_{4a}), 1.58 (m, 1H, H_{5e}), 1.41 (s, 9H, Boc), 1.22 (m, 1H, H_{5a}), 1.15 (d, J=6.8 Hz, 3H, –CH_3). ^{13}C NMR ($CDCl_3$): δ 155 (Boc C=O), 120.5 (–C≡N), 80.5 (–O–C(CH_3)$_3$), 48 (C_6), 38 (C_2), 31.6 (C_3), 28.5 (O–C(CH_3)$_3$), 21.8 (C_5), 21.6 (C_4), 15.6 (–CH_3). IR (KBr): 1693 (C=O), 2239 (–C≡N), 2977 (C–H sp^3). MS: Calcd for $C_{12}H_{22}N_2O_3$ (M+Na) 247.1422, Found: 247.1430.

4.1.10. *cis*- and *trans*-3-Cyano-2-methylpiperidine (11a and 11b). *Compound* **11a** or **11b** were prepared from **10a** or **10b** as described for **9** above.

Compound **11a**. Syrup, ^{1}H NMR (D_2O/CD_3OD): δ 3.2 (bd, J=12.2 Hz, 1H, H_{6e}), 2.97 (m, 1H, H_{3e}), 2.85 (dq, J=6.4, 3 Hz, 1H, H_{2a}), 2.65 (ddd, J=4, 10.4, 12.2 Hz, 1H, H_{6a}), 2.05 (bd, J=13 Hz, 1H, H_{4e}), 1.55–1.85 (m, 3H, H_{4a}, H_{5e}, H_{5a}), 1.24 (d, J=6.4 Hz, 3H, –CH_3). (hydrochloride) δ 3.55 (dq, J=3.7, 6.0 Hz, 1H, H_{2a}), 3.45 (bd, J=3.7 Hz, 1H, H_{3e}), 3.42 (dd, J=3, 13 Hz, 1H, H_{6e}), 3.05 (dt, J=3.6, 12 Hz, 1H, H_{6a}), 2.18 (m, 1H, H_{4e}), 1.7–2.1 (m, 3H, H_{4a}, H_{5e}, H_{5a}), 1.45 (d, J=6.4 Hz, 3H, –CH_3). ^{13}C NMR (CD_3OD): δ 121.8 (–C≡N), 52.9 (C_2), 46.5 (C_6), 35.0 (C_3), 28.3 (C_4), 22.9 (C_5), 20.7 (–CH_3). (hydrochloride): δ=118.7 (–C≡N), 52.5 (C_2), 45.1 (C_6), 33 (C_3), 26.2 (C_4), 20.1 (C_5), 17.7 (–CH_3). IR (KBr, hydrochloride): 2242 (–C≡N), 2700–2800 ($R2N^+H_2$), 2940 (C–H sp^3). For MS the *N*-acetate was prepared by treatment of 8–10 mg sample with 2 mL acetic anhydride/CH_2Cl_2 (1:1) for 18 h and evaporating. MS (*N*-acetate): Calcd for $C_9H_{14}NO$ (M+Na)=189.1004, Found: 189.1006.

Compound **11b**. Syrup, ^{1}H NMR (D_2O): δ 3.92 (dt, J=2.4, 12.8 Hz, 1H, H_{6e}), 2.75 (dq, J=6.4, 10.4 Hz, 1H, H_{2a}), 2.53 (dt, J=2.8, 12.4 Hz, 1H, H_{6a}), 2.35 (ddd, J=3.6, 10.4, 10.4 Hz, 1H, H_{3a}), 2.16 (m, 1H, H_{5e}), 1.58–1.75 (m, 2H, H_{4a}, H_{4e}), 1.33 (m, 1H, H_{5a}), 1.20 (d, J=6.4 Hz, 3H, –CH_3). (hydrochloride) δ 3.56 (dq, J=6.56, 11.2 Hz, 1H, H_{2a}), 3.47 (bd, J=12.9 Hz, 1H, H_{6e}), 3.08 (dd, J=3.6, 13.2 Hz, 1H, H_{6a}), 3.04 (dd, J=3.6, 11.2 Hz, 1H, H_{3a}), 2.34 (ddq, J=1.6, 3.6, 13.6 Hz, 1H, H_{4e}), 2.05 (dk, J=3.6, 14.4 Hz, 1H, H_{5e}), 1.95 (ddd, J=3.6, 12, 12 Hz, 1H, H_{4a}, 1.76 (m, 1H, H_{5a}). ^{13}C NMR (CD_3OD): δ 121.8 (–C≡N), 52.6 (C_2), 44.1 (C_6), 35.0 (C_3), 26.7 (C_4), 24.6 (C_5), 17.8 (–CH_3). (hydrochloride): δ=118.7 (–C≡N), 53.1 (C_2), 42.7 (C_6), 32.7 (C_3), 25.0 (C_4), 20.1 (C_5), 15.9 (–CH_3). IR (KBr): 2254 (–C≡N), 2650–2750 ($R_2N^+H_2$), 2939 (C–H sp^3). For MS the *N*-acetate was prepared by treatment of 8–10 mg sample with 2 mL acetic anhydride/CH_2Cl_2 (1:1) for 18 h and evaporating. MS (*N*-acetate): Calcd for $C_9H_{14}NO$ (M+Na)=189.1004, Found: 189.1005.

4.1.11. Determination of pK_a of piperidine hydrochlorides. The piperidine hydrochloride (30 mg) was dissolved in 15–20 mL distilled water and subjected to titration with 0.1 M NaOH following the pH with a pH electrode. The pK_a was determined from the resulting titration curve, and was the average of three determinations (error ±0.1).

References and notes

1. Alder, R. W.; Baker, R.; Brown, J. M. *Mechanisms in Organic Chemistry*; Wiley: London, 1971.
2. Hammett, L. P. *Chem. Rev.* **1935**, *17*, 125–136.
3. Taft, R. W. J. *J. Am. Chem. Soc.* **1957**, *79*, 1045–1049.
4. Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1–20.
5. Grob, C. A.; Schlageter, M. G. *Helv. Chim. Acta* **1976**, *59*, 264–276.
6. Grob, C. A.; Rich, R. *Helv. Chim. Acta* **1979**, *62*, 2793–2801.
7. Clark, J.; Perrin, D. D. *Q. Rev.* **1964**, *18*, 295–320.
8. Inouye, S. *Chem. Pharm. Bull.* **1968**, *16*, 1134–1137.
9. Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447–3449.

10. Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem. Eur. J.* **2002**, 1218–1226.
11. Bols, M.; Liang, X.; Jensen, H. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447–3449.
12. Lankin, D. C.; Chandrakumar, N. S.; Rao, S. N.; Spangler, D. P.; Snyder, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 3356–3357.
13. Laupade, G.; Schlewer, G. S.; Wermuth, C.-G. *Bull. Soc. Chim.* **1986**, *4*, 663–668.
14. Albertson, N. F. J. *Am. Chem. Soc.* **1950**, *72*, 2594–2597.
15. Pozdnev, V. F. *Tetrahedron Lett.* **1995**, *36*, 7115–7118.
16. Nakajima, N.; Ubukata, M. *Tetrahedron Lett.* **1997**, *38*, 2099–2102.
17. For several examples see: Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3201–3203. orDong, W.; Jespersen, T. M.; Skrydstrup, T.; Bols, M.; Sierks, M. R. *Biochemistry* **1996**, *35*, 2788–2795.

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Safe radical azidonation using polystyrene supported diazidoiodate(I)

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Abstract—Aldehydes are converted to acyl azides and benzyl ethers to azido ethers by treatment with polymer supported iodine azide in MeCN at 83 °C. The reaction provides a safe and convenient alternative to the use of iodine azide in radical azidonations.
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1. Introduction

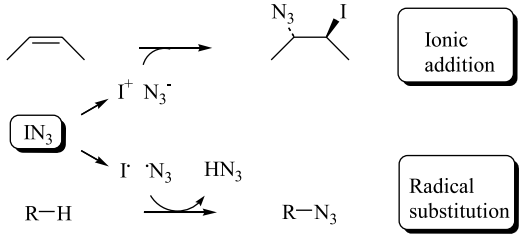
The azido group is a highly useful functionality in organic synthesis due to it ready conversion to amino groups and its photochemical or cycloaddition reactions.[1] Iodine azide is a very useful reagent for the introduction of the azido group. Besides the classical electrophilic reactions pioneered by Hassner,[2] that exploits the polarized character of IN_3 and allows addition of iodine and azide to double bonds, several radical azidonation reactions using iodine azide have recently been investigated by us.[3–5] In these reactions, homolysis of the weak I–N bond lead to radicals (Scheme 1) that cause azide substitution of active hydrogens. However, a considerable drawback with IN_3 as a reagent, is its potentially explosive nature, which inhibits its widespread use.

In 1999 Kirschning et al. described a stable electrophilic polymer-bound reagent that synthetically behaves like iodine azide (Scheme 1).[6] By reacting the polystyrene-bound iodide **1** with phenyliodonium diacetate in dichloromethane at room temperature and subsequently with trimethysilyl azide, the resin **3** was generated. They also obtained **3** by direct azido transfer after treatment of iodide **1** with (diazido)benzene (Scheme 2). The polymer **3** was shown to be unexplosive and a number of electrophilic IN_3 additions to alkenes could be performed simply by mixing **3** and the alkene.[6] It was presumed that the diazidoiodate ion was the active species in these reactions.

Being aware of the work from the Kirschning group we speculated whether the polymerically supported diazidoiodate could not only emulate ionic iodine azide, but also the radical reactions with which we have been focused. In the present work, we report the finding that the diazidoiodate(I) ion can indeed be used for radical azidonation, and hence that the Kirchning groups polymer **3** is a safe and efficient solid-phase reagent for radical azidonation reactions. The reactions provide a useful addition to the arsenal that can be carried out with solid supported reagents,[7] and used for parallel or solution-phase combinatorial chemistry.[8]

2. Results and discussion

Solution phase reactions. We first investigated whether the diazidoiodate ion could be employed in lieu of iodine azide in radical azidonation reactions in solution. For this purpose we prepared tetraethylammonium diazidoiodate(I) in situ in a similar manner to the solid-phase conversion of **2** to **3** (Scheme 2). Thus tetraethylammonium iodide was reacted with phenyliodonium diacetate to give tetraethylammonium diacetoxyiodate(I) (**4**, Scheme 3). Reaction of aldehyde **6** with 2.5 equiv of **4** and 2.8 equiv of $TMSN_3$ in MeCN at 83 °C gave the carbamoyl azide **7** in 76% yield, where IN_3



Scheme 1.

Keywords: Polymer supported reagent; Radical substitution; Solution phase combinatorial chemistry.
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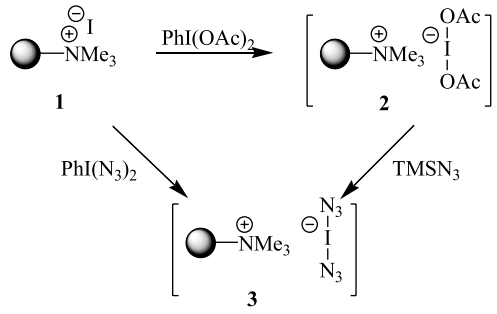
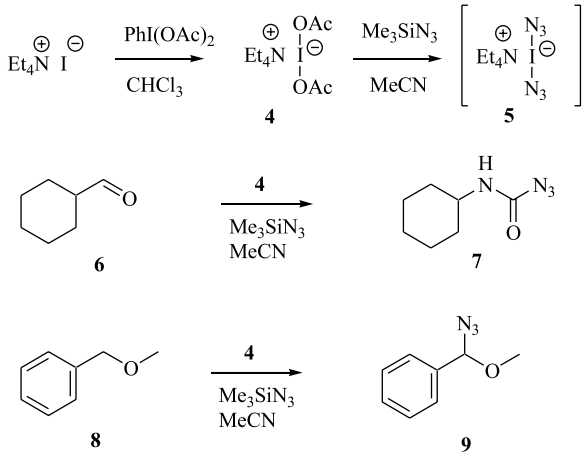


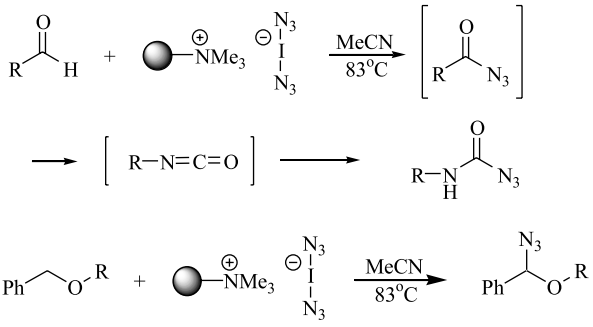
Scheme 2.

gives 89%.[4] This reaction occur by substitution of the aldehyde hydrogen atom with azide and subsequent Curtius rearrangement to an isocyanate that reacts with more azide (Schemes 3 and 4). Similarly the benzyl ether **8** was converted to azide **9** in 64% yield, where IN_3 gives the product in 93% yield.[2] It appears that the radical reactions in solution of **5** and IN_3 are essentially equivalent. Addition of a radical trap, *N-tert*-butyl-α-phenylnitrone, to the reaction of **8** prevented the formation of **9**, supporting a similarity of the reactions.

Solid phase reactions. We prepared the polymer **3** as described by Kirschning converting iodide **1** into diacetoxyiodate **2** and hence diazidoiodate **3** (Scheme 2).[1] Two different sources of **1** was employed; the Amberlite IR-900 (Fluka) and a microreticular Amberlyst A-26 resin (Lancaster). Both resins essentially gave similar results. The resin **3** was reacted with aldehydes **6** and **10–13** and benzyl ethers **8**, **14** and **15** giving carbamoyl azides **7** and **16–20** and azidobenzyl ethers **9**, **21** and **22**, respectively (Scheme 4, Table 1). Typically the reaction was carried out by heating the substrate under reflux for 4 h with 4 equiv of **3** in MeCN. The yields were excellent for the aldehydes (87–96%), but somewhat lower (57–66%) for the benzyl ethers, than can be obtained with IN_3. The solid-phase reaction did not work satisfactorily with benzylidene acetals, presumably because the polymer contained an unavoidable amount of water as seen by IR. Thus acetal **17** gave the alcohol **26** in 96% yield; a product that can be obtained by hydrolysis of the intermediate benzoxonium ion. On the other hand reaction of the tertiary amine **18** was found to lead to



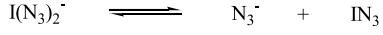
Scheme 3.



Scheme 4.

fragmentation and the Schiff base **27**. Adding *N-tert*-butyl-α-phenylnitrone to the reaction of **6** with **3** inhibited formation of carbamoyl azide **9**. The reaction is accompanied by the formation of a brown colour, presumably iodine. Besides MeCN the solvents CH_2Cl_2, THF, MeOH, EtOH and *t*-BuOH were tried, but only *t*-BuOH gave satisfactory results, probably because it also has a high boiling point. In this solvent, a carbamoyl azide is still obtained from an aldehyde, and not the carbamate.

It was observed that when the polymer was heated to reflux in acetonitrile, a faint brown color was formed and a UV spectrum of the solution confirmed that IN_3 was present. Furthermore when the polymer was reacted with an excess of substrate and recovered, IR spectroscopy showed that the spent polymer was polymerically bound azide. Therefore the polymer probably functions by slow release of IN_3 from the polymer bound diazidoiodate(I) ion (Scheme 5). This explanation fits with the polymer bound reagent usually reacting slower than IN_3 in solution and also explains the very similar reaction profile of the polymer compared to IN_3.



Scheme 5.

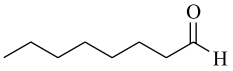
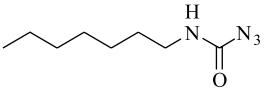
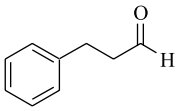
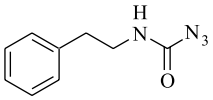
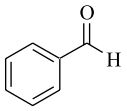
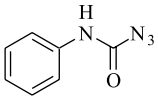
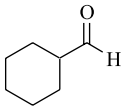
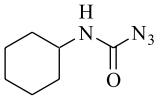
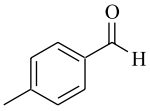
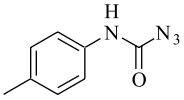
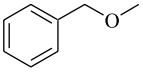
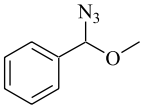
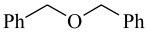
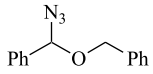
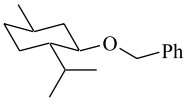
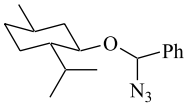
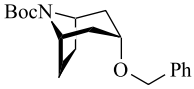
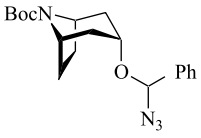
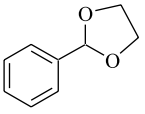
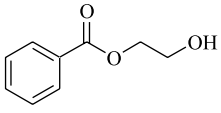
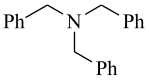
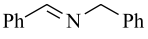
In conclusion, azidonation with polymer **3** is a convenient and safe alternative to the use of IN_3 in radical azidonations. It is also a useful reaction for parallel combinatorial synthesis since the requirements for purification are minimal when the reaction is carried out in this manner.

3. Experimental

3.1. General

Moisture sensitive reactions were carried out in flame-dried glassware under a N_2 atmosphere in solvents dried according to standard procedures. Commercially available compounds were used without further purification. Evaporation was carried out on a rotatory evaporator with the temperature kept below 40 °C. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC-plates (Merck, 60, F_{254}) were visualized by spraying with either A) phosphomolybdic acid hydrate (5% in EtOH), B) 2,4-dinitrophenylhydrazine (0.5% in 2 M HCl), or C) vanillin (3% in 1% H_2SO_4 in EtOH) and heating until

Table 1. Results of reaction of substrates with polymer 3 in MeCN at 83 °C

Substrate	Nr	Time (h)	Product	Nr	Yield[a] (%)
	**10**	4		**19**	95
	**11**	4		**20**	87
	**12**	4		**21**	87
	**6**	4		**7**	96
	**13**	4		**22**	96
	**8**	4		**9**	68[b]
	**14**	4		**23**	64
	**15**	4		**24**	60
	**16**	4		**25**	57
	**17**	4		**26**	96
	**18**	4		**27**	73

[a] Yields are after chromatography.
[b] Adjusted yield due to isolated starting material.

colored spots appeared. A is best for visualizing carbamoyl azides, while B is good for visualizing benzylic azides. NMR-spectra were recorded on a Varian Mercury 400 instrument. Mass spectra were run on a Micromass LC-TOF instrument.

3.2. Tetraethylammonium diacetoxyiodate(I) (4)

To a solution of tetraethylammonium iodide (4 g, 15.6 mmol) in dry chloroform (50 mL) was added iodosobenzene diacetate (5 g, 16 mmol) and the mixture was stirred at room temperature overnight. Then ethyl ether (60 mL) was added, and the reaction mixture was cooled to 0 °C, filtered and washed with cold dry ethyl ether (3× 20 mL). The light yellow product **4** was dried in vacuo and kept under nitrogen protected from light.

3.3. Procedure with 4 and Me_3SiN_3

3.3.1. Cyclohexylcarbamoyl azide (7). 0.94 g (2.5 mmol) of tetraethylammonium-salt **4** was dissolved in dry MeCN (4 mL) and 0.322 g (2.8 mmol, 0.367 mL) of Me_3SiN_3 and 0.112 g (1 mmol) cyclohexanecarbaldehyde were added, and the mixture heated to 83 °C for 2.5 h. The brown slurry was poured into 2 mL of water, and the mixture was extracted with dichloromethane (3×10 mL). The organic

extracts were combined and washed with 10 mL of 5% sodium thiosulfate leaving a light yellow solution, which was dried over magnesium sulfate. Removal of the solvent under reduced pressure followed by column chromatography (EtOAc/pentane 1:10) afforded the cyclohexylcarbamoyl azide[5] (**7**, 0.127 g, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (bs, 1H), 3.56–3.46 (m, 1H), 1.88–182 (m, 2H), 1.66 –1.60 (m, 2H), 1.57–1.51 (m, 2H), 1.34–1.23 (m, 2H), 1.14–1.04 (m, 2H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (*C*=O), 50.3 (C_1), 33.08 ($C_{2,6}$), 25.5 (C_4), 24.8 ($C_{3,5}$). IR (KBr, cm^{-1}): 1547.9(N–C=O), 1677.7 (strong C=O), 2140 (N_3), 3275.4 (NH). HRMS (ES): *m/z*: 191.0910 (calcd for $C_7H_{12}N_4ONa$ [M+ Na^+]: 191.0908), mp=105.1 °C.

3.3.2. α-Azidobenzyl methylether (9). 0.94 g (2.5 mmol) of tetraethylammonium-salt **4** was dissolved in dry MeCN (4 mL) and 0.322 g (2.8 mmol, 0.367 mL) of Me_3SiN_3 and 0.122 g (1 mmol) of benzyl methyl ether were added, and the mixture heated to 83 °C for 2.5 h. The reaction was followed on TLC (pentane/CH_2Cl_2 3/1), and found complete after 2 h. The reaction mixture was poured into water (2 mL), and the mixture was extracted with dichloromethane (3×10 mL). The organic extracts were combined and washed with 10 mL of 5% sodium thiosulfate, brine, dried over magnesium sulfate and concentrated in vacuo to give the desired α-azido benzyl ether. Additional purification by flash chromatography (pentane/EtOAc gradient 1/0:10/1) provided the desired α-azido benzyl methylether[3] as a light yellow oil (**9**, 0.104 g, 64%). ^{1}H NMR: δ 7.22–7.38 (m, 5H), 5.24 (s, 1H), 3.43 (s, 3H).[3]

When this reaction was performed in presence of 0.26 equiv of *N-tert*-butyl-α-phenylnitrone no azidonation product was observed.

3.4. Synthesis of polymer 3

The untreated (Amberlyst A-26 iodide-resin from Lancaster was previously washed with dry CH_2Cl_2 and dried in vacuum) polymer-bound iodide **1** (1 equiv) was shaken at 1000 rpm with $PhI(OAc)_2$ (1.8 equiv) in dry CH_2Cl_2 (2.5 mL/mmol iodide) at room temperature under nitrogen overnight. During this time the reaction mixture was protected from light. The resulting light yellow resin **2** was filtered and washed with dry CH_2Cl_2 (5×25 mL/g resin) and dried in vacuum.

The prepared resin **2** was treated with Me_3SiN_3 (2.6 equiv with respect to **1**) in dry CH_2Cl_2 (4 mL/mmol) and shaked at 1000 rpm under nitrogen overnight. The yellow resin was filtered and washed with dry CH_2Cl_2 (5×25 mL/g resin) and dried under vacuum. The calculated loading (from weight increase) was up to 2.1 mmol reagent per g resin for the Lancaster resin and up to 2.5 mmol reagent per g resin in the Fluka case. The resin was stored in a desiccator at room temperature.

3.5. Azidonation of compounds with resin 3, general procedure

To a suspension of resin **3** (5 equiv with respect to substrate) in dry MeCN (4 mL/g resin) was added 1 equiv of aldehyde, and the reaction mixture was heated to 83 °C. The reaction was followed on TLC (pentane/ CH_2Cl_2 1/1), and the time for a complete reaction was normally between 2 and 4 hours. The resin was filtered and washed with dry CH_2Cl_2. The resulting organic layer was washed with a solution of 5% sodium thiosulfate, dried over magnesium sulfate and concentrated under reduced pressure to give the crude azide. Additional purification by flash chromatography (pentane/ethyl acetate 10/1) provided the desired compound in the yield given in Table 1.

3.5.1. Heptyl carbamoylazide (19).[5] A colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.28 (bs, 1H), 3.2 (q, 2H, J= 8.0 Hz), 1.52–1.44 (m, 2H), 1.29 –1.21 (m, 8H), 0.84 (t, 3H, J=7.2 Hz).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6 (*C*=O), 41.3 (C_1), 31.8 (C_5), 29.6 (C_2), 29.05 (C_4), 26.8 (C_3), 22.7 (C_6), 14.1 (C_7). IR (KBr, cm^{-1}): 1702 (C=O), 2139.7 (N_3), 2858/2929 (C–H sp^3), 3331.8 (NH).

3.5.2. 2-Phenylethyl carbamoylazide (20).[5] White crystals. Mp=85.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.25–7.10 (m, 5H), 4.99 (bs, 1H), 3.42 (q, 2H, J=6.7 Hz), 2.75 (t, 2H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (*C*=O), 137.1 (Ar C_1), 127.6 (Ar $C_{3,4,5}$), 125.6 (Ar $C_{2,6}$), 41.1 (*C*H$_2$–NH), 34.5 (*C*H$_2$). IR (KBr, cm^{-1}): 1543 (N–C=O), 1671.8 (strong C=O), 2141.9 (N_3), 2930.2 (C–H sp^3), 3029 (C–H sp^2) 3280.3 (NH).

3.5.3. Phenyl carbamoylazide (21).[5] White crystals. Mp= 107.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.4 (m, 3H), 7.1 (m, 2H), 7 (bs, 1H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5 (*C*=O), 137.1 (Ar C_1), 129.3 (Ar $C_{3,5}$), 124.9 (Ar C_4), 119.7 (Ar $C_{2,6}$). IR (KBr, cm^{-1}): 1554 (N–C=O), 1688.6 (strong C=O), 2147.4 (N_3), 3325.6 (NH).

3.5.4. 4-Methylphenyl carbamoylazide (22).[5] Light yellow crystals. Mp=130.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.2 (d, 2H, J=8.0 Hz), 7 (d, 2H, J=8.0 Hz), 6.7 (bs, 1H), 2.2 (s, 3H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.2 (*C*=O), 134.6 (Ar C_1), 129.8 (Ar $C_{3,4,5}$), 119.6 (Ar $C_{2,6}$), 21.03 (*C*H$_3$).[5] IR (KBr, cm^{-1}): 3276 (NH), 2143, (medium, N_3), 1682 (strong, C=O), 1538 (N–C=O).[5]

3.5.5. α-Azidobenzyl benzyl ether (23). A light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7. 51 (m, 10H, Ar), 5.529 (s, 1H, Ar-C*H*–N_3), 4.93 (d, 1H$_a$, J=11.6 Hz, Ar-C*H*$_2$), 4.73 (d, 1H$_b$, J=11.6 Hz, Ar-C*H*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.9 (1 C, Ar C_1), 129.3–126.3 (11C,Ar),91.5(Ar-*C*H–N_3),70.4(Ar-*C*H$_2$).IR(KBr, cm^{-1}): ν=1495, 1587 (Ar), 2105 (–N_3), 2874 (C–H sp^3), 3033/3065 (C–H sp^2). GS–MS: 211 (–N_2). HR-MS: 262.0950 (calcd for $C_{14}H_{13}N_3O+Na^+$: 262.0956).

3.5.6. Azidobenzyl (−)-menthyl ether (24).[9] A light yellow oil. ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.79 (d, 3H, J=6.3 Hz), 0.98 (d, 6H, J=6.9 Hz), 1.0 (m, 2H), 1.2 (m, 1H), 1.4 (m, 2H), 1.65 (m, 2H), 2.1 (m, 1H), 2.2 (m, 1H), 3.65 (dt, 1H), 5.45 (s, 1H), 7.4 (m, 5H).[9]

3.5.7. 3-(Azido-phenyl-methoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (25).[10] A clear colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.36 (5H, m, Ar-*H*), 5.39 (1H, s, O–C*H*N_3-Ar), 4.19 (2H, br. s,

H-1,5), 4.13 (1H, t, J=4,4 Hz, H-3), 2.22–1.78 (8H, m, 2H-2,4,6,7), 1.46 (9H, s, $(CH_3)_3$, Boc). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6 (C=O, Boc), 137.5 (C(Ar)), 129.3; 129.2; 128.9 (CH(Ar)), 91.5 (O–CHN$_3$-Ar), 79.4 ($C(CH_3)_3$, Boc), 72.4 (C_3), 53.1/52.3 ($C_{1,5}$), 37.2/36.4 ($C_{2,4}$), 35.3/34.4 ($C_{6,7}$), 28.7/28.0 (($CH_3)_3$C, Boc).[10] IR (film, cm^{-1}): ν=3444, 2978 (C–H sp^3), 2103 (N$_3$), 1694, 1652, 1548 cm^{-1}.[10]

3.5.8. 2-Hydroxyethyl benzoate (26).[11] Colourless oil. ^{1}H NMR ($CDCl_3$): δ=8.1 (m, 2H, Ar; H$_2$, H$_6$), 7.5 (m, 1H, Ar; H$_4$), 7.4 (m, 1H, Ar; H$_3$, H$_5$), 4.4 (t, 2H, CH_2), 3.9 (t, 2H, CH_2) and 2.8 (bs, 1H, OH).[11]

3.5.9. Benzylidene benzyl amine (27).[12] Ligth yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.42 (s, 1H, =NH), 7.81 (m, 2H, Ar; H$_2$, H$_6$), 7.45–7.22 (m, 9H, Ar; H$_{2-5}$, H$'_{2-6}$), 4.85 (s, 1H, –Ar-CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 162.1 (C=N–), 139.4 (Ar C_1), 136.3 (Ar C'_1), 130.8 (Ar C_4), 128.7–128.1 (8 C, Ar $C_{2,3,5,6}$, $C_{2',3',5',6'}$), 127.1 (Ar-C_4'), 65.2 (Ar-CH$_2$). IR (KBr, cm^{-1}): ν=1580 (Ar), 1643 (–HC=N–), 2840/2872 (C–H sp^3), 3027/3085 (C–H sp^2). HR-MS: 196.1130 (calcd for $C_{14}H_{13}N+H^+$: 196.1126).

Acknowledgements

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References and notes

1. Eric, F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
2. Hassner, A. *Acc. Chem. Res.* **1971**, *4*, 9–16.
3. Viuf, C.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 623–625.
4. Baruah, M.; Bols, M. *Synlett* **2002**, *7*, 1111–1112.
5. Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* **2003**, *68*, 9453–9455.
6. Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2594–2696.
7. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815–4195.
8. An, H.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311–3340.
9. Baruah, M.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 509–512.
10. Pedersen, H.; Sinning, S.; Bülow, A.; Wiborg, O.; Falborg, L.; Bols, M. *Org. Biomol. Chem.* **2004**, *2*, 2861–2869.
11. Sharghi, H.; Sarvari, M. H. *J. Org. Chem.* **2003**, *68*, 4096–4099.
12. Goosen, A.; McCleland, C. W.; Sipamla, A. M. *J. Chem. Res. (S)* **1995**, 18–19.

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Synthesis, thermal reactivity and kinetics of substituted [(benzoyl)(phenylcarbamoyl)methylene]triphenylphosphoranes and their thiocarbamoyl analogues

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Abstract—A range of 16 substituted benzoyl/arylcarbamoyl and benzoyl/arylthiocarbamoyl stabilised ylides have been prepared. They are found under conditions of flash vacuum pyrolysis to fragment giving a benzoyl ylide and aryl isocyanate or isothiocyanate accompanied in some cases by secondary pyrolysis products. Kinetic studies show the thiocarbamoyl ylides to react consistently faster than their carbamoyl analogues and substituent effects suggest a polar cyclic transition state, which involves attack by the benzoyl oxygen on the carbamoyl/thiocarbamoyl NH.
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1. Introduction

In 1959 Trippett and Walker reported that stabilised phosphorus ylides of structure **1** react with phenyl isocyanate to form the carbamoyl stabilised ylides **2**.[1] There have since been several reports of the formation of such adducts between a variety of ylides and both isocyanates[2,3] and isothiocyanates.[4–7] Where R contains a carbonyl group, these are known to exhibit intramolecular hydrogen bonding as shown in structure **3**.[2–4,6] Apart from a brief note that compounds **4** revert to their starting components upon heating in boiling toluene,[8] there has been no systematic study of the thermal reactivity of these compounds. In view of our long-standing interest in synthetic applications of flash vacuum pyrolysis of stabilised phosphorus ylides,[9,10] we were interested to examine these compounds where the functional groups present could lead to several conceivable routes for thermal decomposition. In this paper, we describe the synthesis of a range of substituted benzoyl aryl(thio)carbamoyl ylides, a study of their pyrolysis behaviour and detailed kinetic measurements, almost the first for phosphorus ylides,[11] which provide evidence in support of the proposed reaction mechanism.

2. Results and discussion

A series of 16 ylides **8–23** were prepared by reacting benzoylmethylenetriphenylphosphorane **5a** or ring-substituted analogues **5b–e** with aryl isocyanates **6a–e**, and isothiocyanates **7a–e** (Scheme 1). The combinations were chosen so as to examine the effects that electron-donating and electron-withdrawing substituents in the *para* position of each ring would have on the kinetics. All products were obtained as stable crystalline solids and gave the expected analytical and spectroscopic data, although it should be noted that the melting points recorded for ylides **13**, **15** and **17** differed markedly from the values reported in an early paper[4] for samples characterised only by elemental analysis. In agreement with this paper, we found that the ylides **5b** and **5c** with electron-withdrawing substituents failed to react with phenyl isothiocyanate. As we have reported for other classes of stabilised ylides, the ^{13}C NMR spectra formed a highly informative and regular pattern (Table 3, Section 3) with ArNH*C*O giving signals in the range δ_C 167–169 (d, $J_{P-C}=10$ Hz), while for ArNH*C*S this moved to δ_C 189–190 (d, $J_{P-C}=17$–18 Hz). In the light of our previous work,[12] the fact that both these coupling constants and the value to Ar*C*O (16–22 Hz) are ≥ 10 Hz means that thermal extrusion of Ph_3PO or Ph_3PS is unlikely.

A clue to the likely pyrolysis behaviour was provided by the mass spectra of the compounds, which in most cases showed

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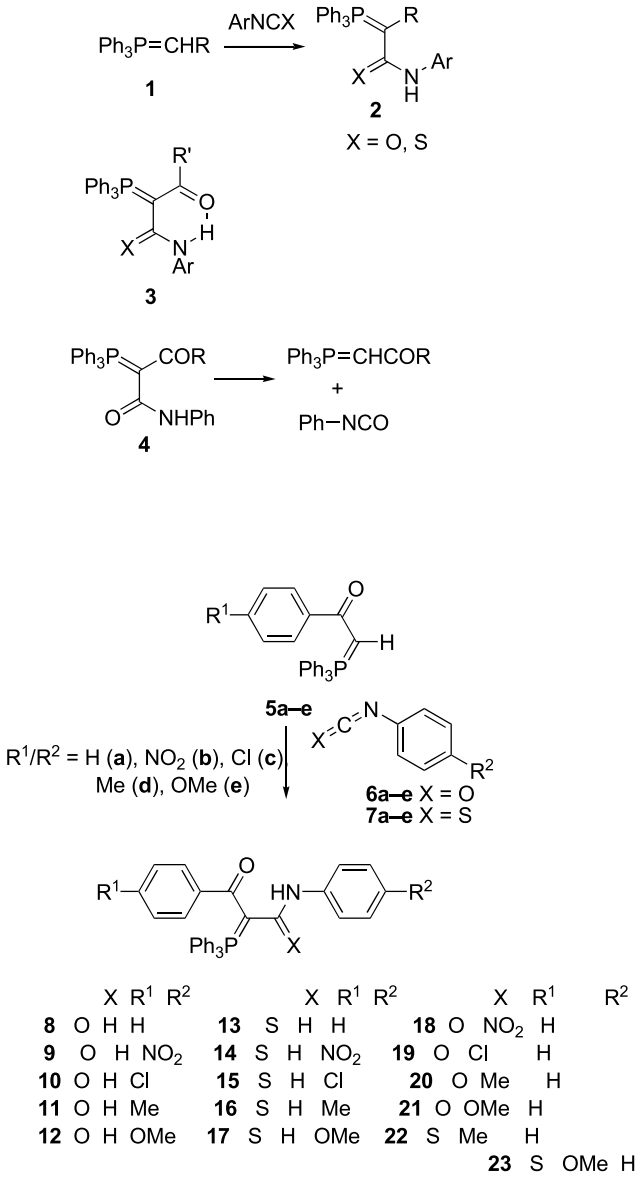
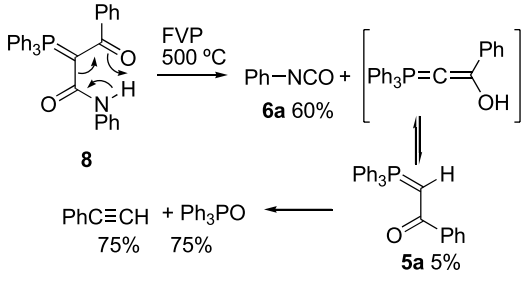
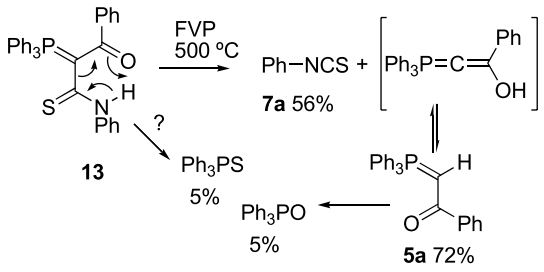


Scheme 1.

prominent loss of ArNCO or ArNCS. This was confirmed when the reactivity of the two parent compounds **8** and **13** was examined using flash vacuum pyrolysis. Both compounds were found to react completely at 500 °C and 10^{-2} Torr and the products are shown in Schemes 2 and 3 respectively. For ylide **8** the electrocyclic process shown leads to PhNCO and the enol form of ylide **5a**. The situation is complicated by the fact that the latter can then undergo



Scheme 2.



Scheme 3.

secondary reaction with extrusion of Ph_3PO to give phenylacetylene. Under FVP conditions a temperature of over 650 °C is usually required for this process.[13] The substantial extent of extrusion here at 500 °C is presumed to be due to the formation of **5a** in an activated state following the isocyanate elimination. For the thiocarbamoyl ylide **13** the situation is somewhat simpler: the same type of electrocyclic process gives PhNCS and the enol form of ylide **5a**, which are now isolated as the major products together with small amounts of Ph_3PO from decomposition of **5a**, and Ph_3PS formed by an unknown route. Despite the slight complication of secondary processes it seems clear that the primary thermal reaction for all these compounds is dissociation into the compounds **5** and **6** or **7** from which they were formed.

We now sought additional evidence in support of the proposed mechanism from kinetic measurements. If, as shown in Schemes 2 and 3, the initial step is nucleophilic attack of the keto oxygen on the carbamoyl or thiocarbamoyl NH, substituents on the ArCO ring should have a marked effect on the reaction rate whereas substituents on the ArNH ring should not affect the rate greatly. In addition, it is of interest to compare the rates for X=O and X=S.

Kinetic studies were performed using a sealed glass tube reactor over the range 330–440 K as detailed in Section 3. The resulting rates and Arrhenius parameters are shown in Table 4. Rate constants adjusted to 400 K are shown in Tables 1 and 2. Two points are immediately apparent from these results. In all cases, the reactions for the thiocarbamoyl ylides are considerably faster than for the corresponding carbamoyl ylides. In addition, while varying the substituent on the ArNH ring has no significant effect on the rates (Table 1), variation of the substituent on the ArCO

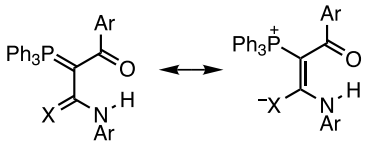
Table 1. Rate constants and relative rates at 400 K in the gas phase (R^1=H)

R^2	X=O 10^4k (s^{-1})	X=S 10^2k (s^{-1})	$k_{rel}=\frac{k(X=S)}{k(X=O)}$
H	3.69	1.34	36
4-NO_2	5.41	1.08	20
4-Cl	6.11	1.34	22
4-Me	4.32	2.35	54
4-OMe	7.12	2.32	33

Table 2. Rate constants and relative rates at 400 K in the gas phase (R^2=H)

R^1	X=O 10^4k (s^{-1})	X=S 10^2k (s^{-1})	$k_{rel}=\frac{k(X=S)}{k(X=O)}$
H	3.69	1.34	36
4-NO_2	0.90	—	—
4-Cl	3.42	—	—
4-Me	16.42	3.10	19
4-OMe	16.18	4.53	28

ring has the effect predicted from the mechanisms of Schemes 2 and 3, with electron-withdrawing groups reducing the rate and electron-donating groups increasing it (Table 2). The difference between carbamoyl and thiocarbamoyl ylides is most likely due to the former existing to a greater extent in the phosphonium enolate form **24** in which the C–C bond to be broken in the fragmentation is a double bond. Due to the lower electronegativity of sulfur, this form is likely to be less significant for the thiocarbamoyl ylides, a fact also supported by the higher values of J_{P-C}, thus leading to more rapid fragmentation.



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The molecularity, order and homogeneous nature of the reaction, as well as the Arrhenius parameters and product analysis combine to suggest a concerted transition state for the thermal elimination reaction of these ylides (Scheme 2). The relative contribution to the molecular reactivity of each of the three bonds involved in the electron flow described by the curved arrows in Scheme 2 has been documented in earlier studies,[14,15] where it was noted that any one of these bonds could be the prime contributor to molecular reactivity, or that the overall reactivity could be a product of synergism between two or all three bonds. Non-synchronous bond breaking would explain the polarity of the cyclic transition state, and an effective relative contribution from a particular bond might, under favourable structural constraints, lead to a linear Hammett correlation.[16,17] As shown in Figure 1, this is indeed the case and the data show a reasonably good Hammett relationship with values of $\rho=-1.2$ for X=O and $\rho=-2.1$ for X=S. In Scheme 2, the protophilicity of the C=O bond depends on the electronic effect of a substituent on the PhCO ring and an electron-donating group will enhance the protophilicity toward NH.

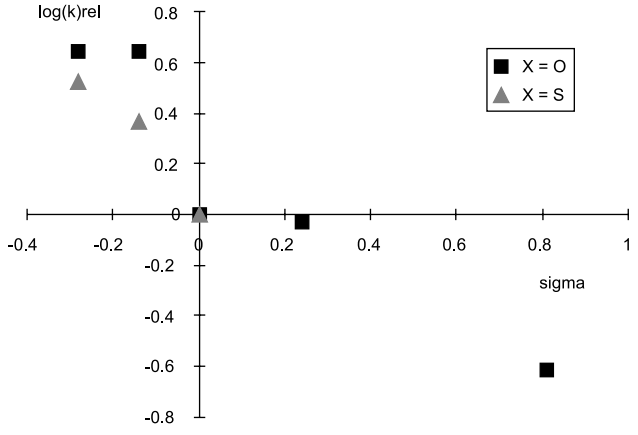

Figure 1. Hammett correlation for pyrolysis of ylides **18–23**

The thermal reactivity and kinetics of other classes of stabilised ylides are currently under investigation and the results will be reported shortly.

3. Experimental

Melting points were recorded on a Reichert hot-stage microscope and are uncorrected. Infra red spectra were recorded as Nujol mulls on a Perkin Elmer 1420 instrument. NMR spectra were obtained for ^{1}H at 300 MHz and for ^{13}C at 75 MHz using a Bruker AM300 instrument and for ^{31}P at 121 MHz using a Varian Gemini 2000 instrument. All spectra were run as solutions in $CDCl_3$, unless otherwise stated, with internal Me_4Si as reference for ^{1}H and ^{13}C and external 85% H_3PO_4 for ^{31}P. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants J are in Hz. Mass spectra were obtained on an AEI/Kratos MS-50 spectrometer using electron impact at 70 eV.

The benzoyl ylides **5** were prepared by the reported method,[18] and the aryl isocyanates **6a–e** and isothiocyanates **7a–e** were commercially available.

3.1. General procedure for synthesis of ylides 8–23

A solution of the ylide **5** (5 mmol) in CH_2Cl_2 (50 cm^3) was stirred at RT while a solution of the appropriate isocyanate **6** or isothiocyanate **7** (5 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise. After 2 h the mixture was evaporated and the residue recrystallised from ethyl acetate. In this way the following compounds were prepared:

3.1.1. [(Benzoyl)(phenylcarbamoyl)methylene]triphenylphosphorane 8. From **5a** and **6a** as colourless crystals (89%), mp 215–217 °C (lit.,[1] 189 °C) (Found: C, 79.3; H, 5.4; N, 2.8. $C_{33}H_{26}NO_2P$ requires C, 79.3; H, 5.2; N, 2.8%); ν_{max}/cm^{-1} (KBr) 3435, 1625, 1588, 1516, 1441, 1351, 1207, 1101, 747 and 691; δ_H (CD_3SOCD_3) 11.75 (1H, br s), 7.6–7.3 (17H, m), 7.15 (2H, t) and 7.0–6.8 (6H, m); δ_C see Table 3; δ_P 18.8; *m/z* 499 (M^+, 3%), 407 (M^+-PhNH, 100), 380 (M^+-PhNCO, 30), 379 (M^+-PhNHCO, 30), 303 (32), 183 (27) and 129 (63).

3.1.2. [(Benzoyl)(4-nitrophenylcarbamoyl)methylene]triphenylphosphorane 9. From **5a** and **6b** as pale yellow crystals (80%), mp 173–175 °C (Found: C, 72.5; H, 4.8; N, 4.95. $C_{33}H_{25}N_2O_4P$ requires C, 72.8; H, 4.6; N, 5.1%); ν_{max}/cm^{-1} (KBr) 3435, 1638, 1598, 1505, 1489, 1439, 1328, 1233, 1199, 1174, 1107 and 690; δ_H 12.76 (1H, br s), 8.09 (2H, half AB pattern, $J=9$ Hz), 7.75–7.30 (17H, m) and 7.02–6.80 (5H, m); δ_C see Table 3; δ_P 19.2; *m/z* (M^+544 not apparent), 380 (M^+-ArNCO, 100%), 379 (M^+-ArNHCO, 92), 351 (15), 303 (98), 277 (68), 183 (50) and 105 (72).

3.1.3. [(Benzoyl)(4-chlorophenylcarbamoyl)methylene]triphenylphosphorane 10. From **5a** and **6c** as colourless crystals (82%), mp 193–195 °C (Found: C, 74.2; H, 5.0; N, 2.6. $C_{33}H_{25}ClNO_2P$ requires C, 74.2; H, 4.7; N, 2.6%); ν_{max}/cm^{-1} (KBr) 3470, 1620, 1507, 1440, 1355, 1193, 1102, 750 and 693; δ_H ($CDCl_3$) 12.24 (1H, br s), 7.80–7.55 (6H, m), 7.50–7.25 (11H, m), 7.14 (2H, half AB pattern, $J=9$ Hz), 7.00–6.90 (3H, m) and 6.86–6.76 (2H, m); δ_C see Table 3; δ_P 18.9; *m/z* 535 ($^{37}Cl-M^+$, 0.1%), 533 ($^{35}Cl-M^+$, 0.3), 407 (M^+-ArNH, 15), 380 (M^+-ArNCO, 67), 379 (M^+-ArNHCO, 65), 303 (65), 277 (100) and 183 (45).

Table 3. ^{13}C NMR spectra of benzoyl/carbamoyl and thiocarbamoyl ylides **8–23**, δ_C (J_{P-C})

					P-Phenyl					
	X	R^1	R^2	P=C	COAr	CXNHAr	C-1	C-2	C-3	C-4
8[a]	O	H	H	75.9 (119)	191.7 (16)	168.1 (10)	126.2 (92)	134.0 (10)	129.6 (12)	132.8 (3)
9	O	H	NO_2	76.4 (130)	193.6 (18)	168.3 (10)	125.0 (93)	133.3 (10)	128.8 (13)	132.0 (2)
10	O	H	Cl	76.0 (122)	193.0 (18)	167.9 (10)	125.6 (93)	133.3 (10)	128.7 (13)	131.8 (3)
11	O	H	Me	76.0 (122)	192.8 (18)	167.8 (10)	126.0 (93)	133.4 (10)	128.6 (13)	131.6 (2)
12	O	H	MeO	75.8 (120)	192.7 (18)	167.6 (10)	126.0 (93)	133.3 (10)	128.6 (13)	131.6 (2)
13	S	H	H	88.1 (136)	192.7 (22)	189.8 (17)	126.8 (96)	133.5 (9)	128.3 (12)	131.3 (2)
14[a]	S	H	NO_2	89.3 (126)	192.6 (18)	189.6 (13)	126.4 (93)	134.2 (9)	129.6 (12)	132.7 (<2)
15	S	H	Cl	88.3 (135)	192.9 (22)	190.0 (17)	126.5 (95)	133.5 (9)	128.4 (13)	131.4 (2)
16	S	H	Me	87.7 (136)	192.6 (22)	189.9 (17)	126.9 (95)	133.5 (9)	128.3 (12)	131.3 (2)
17	S	H	MeO	87.4 (136)	192.5 (22)	190.0 (17)	126.9 (95)	133.5 (9)	128.3 (12)	131.3 (2)
18	O	NO_2	H	77.3 (120)	189.5 (18)	167.3 (10)	125.3 (93)	133.2 (10)	128.7 (13)	132.0 (3)
19	O	Cl	H	76.5 (122)	191.4 (18)	167.7 (10)	125.8 (94)	133.3 (9)	128.7 (13)	131.8 (2)
20	O	Me	H	75.8 (120)	193.0 (18)	168.0 (10)	126.0 (93)	133.4 (9)	128.5 (13)	131.9 (2)
21	O	OMe	H	75.4 (122)	192.5(18)	168.0 (10)	126.1 (93)	133.3 (10)	128.6 (12)	131.6 (2)
22	S	Me	H	87.9 (136)	192.8 (22)	189.8 (18)	126.9 (95)	133.5 (9)	128.2 (12)	131.3 (2)
23	S	OMe	H	87.6 (137)	192.4 (21)	189.9 (17)	127.2 (95)	133.6 (8)	128.7 (12)	131.5 (3)

	Ar signals
8[a]	144.4, 140.7, 129.5, 129.2, 128.3, 127.6, 122.9, 119.7 (11)
9	146.1, 143.7, 141.9 (4ry), 128.8 (CH), 127.9 (2CH), 127.0 (2CH), 125.0 (2CH), 118.9 (2CH)
10	144.0, 138.5, 129.4 (4ry), 128.9 (CH), 128.5 (2CH), 127.8 (2CH), 127.0 (2CH), 121.0 (2CH)
11	144.3, 137.3, 131.6 (all 4ry), 129.1 (2CH), 128.5 (CH), 127.8 (2CH), 127.1 (2CH), 119.8 (2CH), 20.8
12	154.9, 144.2, 128.5 (4ry), 128.3 (CH), 127.8 (2CH), 127.1 (2CH), 121.2 (2CH), 113.8 (2CH), 55.5
13	144.3, 140.4 (4ry), 129.0 (CH), 128.3 (2CH), 127.9 (2CH), 127.3 (2CH), 124.6 (CH), 123.8 (2CH)
14[a]	147.6, 143.5 (4), 143.2, 129.9 (CH), 128.5 (2CH), 127.8 (2CH), 125.1 (2CH), 122.1 (2CH)
15	144.1, 139.0, 129.5 (4ry), 129.1 (CH), 128.3 (2CH), 127.9 (2CH), 127.3 (2CH), 124.9 (2CH)
16	144.3, 137.8, 134.4 (all 4ry), 128.95 (CH), 128.87 (2CH), 127.9 (2CH), 127.4 (2CH), 124.0 (2CH), 21.0
17	156.7, 144.3, 128.9 (CH), 128.6 (4ry), 127.8 (2CH), 127.3 (2CH), 125.6 (2CH), 113.5 (2CH), 55.4
18	149.4 (4ry), 146.9 (4ry), 139.3 (4ry), 128.5 (2CH), 127.5 (2CH), 122.8 (2CH), 122.5 (CH), 119.8 (2CH)
19	142.5 (4ry), 139.7 (4ry), 134.4 (4ry), 128.6 (2CH), 128.4 (2CH), 127.9 (2CH), 122.3 (CH), 119.8 (2CH)
20	141.4 (4ry), 139.9 (4ry), 138.4 (4ry), 128.6 (2CH), 128.3 (2CH), 127.2 (2CH), 122.5 (CH), 119.8 (2CH), 21.2
21	160.0 (4ry), 139.9 (4ry), 137.1 (4ry), 128.9 (2CH), 128.6 (2CH), 122.1 (CH), 119.8 (2CH), 113.1 (2CH), 55.2
22	141.6 (4ry), 140.4 (4ry), 139.1 (4ry), 128.4 (2CH), 128.3 (2CH), 127.4 (2CH), 124.6 (CH), 123.8 (2CH)
23	160.7 (4ry), 140.6 (4ry), 137.4 (4ry), 129.4 (2CH), 128.4 (2CH), 124.7 (CH), 123.9 (2CH), 113.3 (2CH), 55.3

[a] In CD_3SOCD_3.

3.1.4. [(Benzoyl)(4-methylphenylcarbamoyl)methylene]-triphenylphosphorane 11. From **5a** and **6d** as colourless needles (76%), mp 206–209 °C (Found: C, 79.4; H, 5.6; N, 2.7. $C_{34}H_{28}NO_2P$ requires C, 79.5; H, 5.5; N, 2.7%); ν_{max}/cm^{-1} 3432, 1732, 1602, 1518, 1288, 1123, 1073, 740 and 722; δ_H 12.02 (1H, br s), 7.7–7.5 (6H, m), 7.5–7.2 (11H, m), 7.0 –6.7 (7H, m) and 2.24 (3H, s); δ_C see Table 3; δ_P 18.8; *m/z* 513 (M^+, 0.5%), 407 (40), 380 (45), 379 (44), 337 (30), 303 (45) and 277 (100).

3.1.5. [(Benzoyl)(4-methoxyphenylcarbamoyl)methylene]triphenylphosphorane 12. From **5a** and **6e** as pale yellow crystals (88%), mp 180–182 °C (Found: C, 77.4; H, 5.5; N, 2.5. $C_{34}H_{28}NO_3P$ requires C, 77.1; H, 5.3; N, 2.6%); ν_{max}/cm^{-1} (KBr) 3435, 1620, 1510, 1440, 1351, 1246, 1202, 1100, 760, 749, 738 and 693; δ_H 12.00 (1H, br s), 7.70–7.60 (6H, m), 7.50–7.25 (9H, m), 7.46 and 6.77 (4H, AB pattern, J=9 Hz), 7.00–6.90 (3H, m), 6.84–6.74 (2H, m) and 3.74 (3H, s); δ_C see Table 3; δ_P 18.7; *m/z* 529 (M^+, 2%), 407 (M^+ −ArNH, 75), 380 (100), 379 (90), 303 (90), 277 (77) and 183 (50).

3.1.6. [(Benzoyl)(phenylthiocarbamoyl)methylene]triphenylphosphorane 13. From **5a** and **7a** as yellow needles (90%), mp 186–187 °C (lit.,[4] 167–167.5 °C) (Found: C, 76.9; H, 4.95; N, 2.9; S, 5.8. $C_{33}H_{26}NOPS$ requires C, 76.9; H, 5.1; N, 2.7; S, 6.2%); ν_{max}/cm^{-1} (KBr) 3436, 1596, 1550, 1504, 1440, 1340, 1176, 1106, 752 and 690; δ_H 13.80 (1H, br s), 7.80–7.70 (8H, m), 7.45–7.25 (11H, m), 7.15–6.95 (4H, m) and 6.87–6.77 (2H, m); δ_C see Table 3; δ_P 13.3; *m/z* 515 (M^+, 1%), 380 (M^+ −PhNCS, 100), 379 (M^+ −PhNHCS, 96), 351 (20), 303 (98), 277 (80), 202 (35), 183 (75) and 77 (56).

3.1.7. [(Benzoyl)(4-nitrophenylthiocarbamoyl)methylene]triphenylphosphorane 14. From **5a** and **7b** as orange needles (82%), mp 186–187 °C (Found: C, 70.4; H, 4.4; N, 5.2; S, 5.3. $C_{33}H_{25}N_2O_3PS$ requires C, 70.7; H, 4.5; N, 5.0; S, 5.7%); ν_{max}/cm^{-1} (KBr) 3436, 1512, 1439, 1341, 1243, 1179, 1103, 745 and 690; δ_H 14.40 (1H, br s), 8.16 and 8.10 (4H, AB pattern, J=9 Hz), 7.80–7.65 (6H, m), 7.50–7.30 (9H, m), 7.10–7.00 (3H, m) and 6.90–6.80 (2H, m); δ_C see Table 3; δ_P 14.1; *m/z* (M^+ 560 not apparent) 380 (M^+ −ArNCS, 97%), 379 (95), 351 (16), 303 (100), 277 (50) and 183 (65).

3.1.8. [(Benzoyl)(4-chlorophenylthiocarbamoyl)methylene]triphenylphosphorane 15. From **5a** and **7c** as yellow needles (88%), mp 189–190 °C (lit.,[4] 151 °C) (Found: C, 71.8; H, 4.6; N, 2.5; S, 5.3. $C_{33}H_{25}ClNOPS$ requires C, 72.1; H, 4.6; N, 2.5; S, 5.8%); ν_{max}/cm^{-1} (KBr) 3436, 1584, 1546, 1497, 1439, 1338, 1283, 1173, 1105, 749 and 690; δ_H 13.92 (1H, br s), 7.80–7.65 (8H, m), 7.50–7.25 (9H, m), 7.24 (2H, half AB pattern, J=9 Hz), 7.08–6.98 (3H, m) and 6.87–6.78 (2H, m); δ_C see Table 3; δ_P 13.6; *m/z* (M^+ 551/549 not apparent), 380 (M^+ −ArNCS, 86), 379 (80), 351

(15), 303 (72), 294 (40), 277 (70), 171 (^{37}Cl–ArNCS, 38) and 169 (^{35}Cl–ArNCS, 100).

3.1.9. [(Benzoyl)(4-methylphenylthiocarbamoyl)methylene]triphenylphosphorane 16. From **5a** and **7d** as colourless crystals (36%), mp 192 °C (Found: C, 77.0; H, 5.35; N, 2.7. $C_{34}H_{28}NOPS$ requires C, 77.1; H, 5.3; N, 2.6%); ν_{max}/cm^{-1} 3432, 1732, 1584, 1287, 1120, 1072, 748 and 686; δ_H 13.70 (1H, br s), 7.85–7.7 (6H, m), 7.60 and 7.12 (4H, AB pattern, J=9 Hz), 7.5–7.3 (9H, m), 7.1–7.0 (3H, m), 6.9–6.8 (2H, m) and 2.33 (3H, s); δ_C see Table 3; δ_P 13.1; *m/z* (M$^+$529 not apparent) 380 (M$^+$ −ArNCS, 55%), 351 (10), 343 (10), 303 (50) and 277 (100).

3.1.10. [(Benzoyl)(4-methoxyphenylthiocarbamoyl)methylene]triphenylphosphorane 17. From **5a** and **7e** as yellow crystals (85%), mp 181–182 °C (lit.,[4] 149 °C) (Found: C, 74.85; H, 5.4; N, 2.5; S, 5.1. $C_{34}H_{28}NO_2PS$ requires C, 74.8; H, 5.2; N, 2.6; S, 5.9%); ν_{max}/cm^{-1} (KBr) 3436, 1512, 1439, 1341, 1243, 1179, 1103, 745 and 690; δ_H 13.56 (1H, br s), 7.80–7.67 (6H, m), 7.57 and 6.85 (4H, AB pattern, J=9 Hz), 7.50–7.25 (9H, m), 7.08–6.98 (3H, m), 6.86–6.78 (2H, m) and 3.78 (3H, s); δ_C see Table 3; δ_P 13.2; *m/z* (M$^+$545 not apparent), 467 (M$^+$ −Ph, 3%), 423 (M$^+$ −ArNH, 1), 380 (M$^+$ −ArNCS, 64), 379 (65), 375 (100), 303 (100), 277 (48) and 183 (70).

3.1.11. [(4-Nitrobenzoyl)(phenylcarbamoyl)methylene]triphenylphosphorane 18. From **5b** and **6a** as yellow crystals (50%), mp 215–217 °C (Found: C, 72.6; H, 4.6; N, 4.8. $C_{33}H_{25}N_2O_4P$ requires C, 72.8; H, 4.6; N, 5.1%); ν_{max}/cm^{-1} 1628, 1589, 1510, 1494, 1440, 1342, 1206, 1103, 857, 763, 746 and 692; δ_H 12.10 (1H, br s), 7.70–7.58 (9H, m), 7.55 and 7.47 (4H, AB pattern, J=9 Hz), 7.42–7.30 (6H, m), 7.24 (2H, t, J=7 Hz), 7.05 (2H, d, J=7 Hz) and 6.97 (1H, t, J=7 Hz); δ_C see Table 3; δ_P 18.2; *m/z* 544 (M$^+$, 2%), 452 (M$^+$ −PhNH, 96), 425 (60), 424 (58), 303 (80), 277 (100), 183 (86) and 174 (60).

3.1.12. [(4-Chlorobenzoyl)(phenylcarbamoyl)methylene]triphenylphosphorane 19. From **5c** and **6a** as colourless crystals (65%), mp 220 °C (Found: C, 74.4; H, 4.7; N, 2.7. $C_{33}H_{25}ClNO_2P$ requires C, 74.2; H, 4.7; N, 2.6%); ν_{max}/cm^{-1} 3432, 1732, 1627, 1586, 1289, 1280, 1073, 842, 745, 723 and 693; δ_H 12.14 (1H, br s), 7.75–7.35 (15H, m), 7.3–7.2 (3H, m), 7.03–6.9 (2H, m) and 6.90 and 6.80 (4H, AB pattern, J=9 Hz); δ_C see Table 3; δ_P 18.7; *m/z* 535 (^{37}Cl–M$^+$, 0.2%), 533 (^{35}Cl–M$^+$, 0.6), 443 (^{37}Cl–M$^+$ −PhNH, 6), 441 (^{35}Cl–M$^+$ −PhNH, 17), 414 (14), 343 (26), 303 (16), 277 (20) and 91 (100).

3.1.13. [(4-Methylbenzoyl)(phenylcarbamoyl)methylene]triphenylphosphorane 20. From **5d** and **6a** as colourless prisms (31%), mp 201–203 °C (Found: C, 79.8; H, 5.7; N, 2.7. $C_{34}H_{28}NO_2P$ requires C, 79.5; H, 5.4; N, 2.7%); ν_{max}/cm^{-1} 3436, 1632, 1514, 1441, 1342, 1208, 1101, 840, 766, 751 and 692; δ_H 12.18 (1H, br s), 7.75–7.15 (19H, m), 6.94 (1H, t, J=7 Hz), 6.85 (2H, d, J=7 Hz), 6.60 (2H, d, J=7 Hz) and 2.15 (3H, s); δ_C see Table 3; δ_P 18.9; *m/z* 513 (M$^+$, 1%), 421 (M$^+$ −PhNH, 40), 394 (M$^+$ −PhNCO, 50), 393 (M$^+$ −PhNHCO, 45), 351 (15), 303 (45), 277 (100), 121 (82) and 91 (87).

3.1.14. [(4-Methoxybenzoyl)(phenylcarbamoyl)methylene]triphenylphosphorane 21. From **5e** and **6a** as colourless crystals (80%), mp 197–199 °C (Found: C, 76.6; H, 5.15; N, 2.3. $C_{34}H_{28}NO_3P$ requires C, 77.1; H, 5.3; N, 2.6%); ν_{max}/cm^{-1} 3420, 1627, 1606, 1505, 1440, 1355, 1254, 1209, 1180, 1104, 1029, 850, 754 and 691; δ_H 12.10 (1H, br s), 7.75–7.60 (6H, m), 7.60–7.50 (2H, m), 7.50–7.30 (9H, m), 7.30–7.15 (2H, m), 7.00–6.90 (1H, m), 6.92 and 6.33 (4H, AB pattern, J=9 Hz) and 3.68 (3H, s); δ_C see Table 3; δ_P 18.9; *m/z* 529 (M$^+$, 0.4%), 437 (M$^+$ −PhNH, 12), 410 (M$^+$ −PhNCO, 35), 409 (M$^+$ −PhNHCO, 32), 303 (25), 277 (40) and 91 (100).

3.1.15. [(4-Methylbenzoyl)(phenylthiocarbamoyl)methylene]triphenylphosphorane 22. From **5d** and **7a** as pale yellow crystals (36%), mp 160–162 °C (Found: C, 76.65; H, 5.5; N, 2.5. $C_{34}H_{28}NOPS$ requires C, 77.1; H, 5.3; N, 2.6%); ν_{max}/cm^{-1} 3420, 1587, 1545, 1503, 1339, 1184, 1102, 828, 752 and 694; δ_H 13.85 (1H, br s), 7.80–7.70 (8H, m), 7.50–7.25 (11H, m), 7.10 (1H, t, J=7 Hz), 6.92 (2H, d, J=7 Hz), 6.62 (2H, d, J=7 Hz) and 2.18 (3H, s); δ_C see Table 3; δ_P 13.3; *m/z* (M$^+$529 not apparent) 394 (M$^+$ −PhNCS, 100%), 393 (M$^+$ −PhNHCS, 92), 365 (25), 303 (85), 277 (44), 202 (36), 183 (62), 135 (98) and 77 (82).

3.1.16. [(4-Methoxybenzoyl)(phenylthiocarbamoyl)methylene]triphenylphosphorane 23. From **5e** and **7a** as pale yellow crystals (58%), mp 169–171 °C (Found: C, 75.0; H, 5.3; N, 2.5. $C_{34}H_{28}NO_2PS$ requires C, 74.8; H, 5.2; N, 2.6%); ν_{max}/cm^{-1} 3418, 1603, 1500, 1348, 1245, 1172, 1106, 840, 748 and 691; δ_H 13.68 (1H, br s), 7.80–7.70 (8H, m), 7.45–7.25 (11H, m), 7.15–7.00 (1H, m), 7.03 and 6.36 (4H, AB pattern, J=9 Hz) and 3.68 (3H, s); δ_C see Table 3; δ_P 13.2; *m/z* (M$^+$545 not apparent), 410 (M$^+$ −PhNCS, 100%), 409 (M$^+$ −PhNHCS, 82), 381 (20), 303 (56), 277 (35), 209 (35) and 183 (42).

3.2. Flash vacuum pyrolysis

The sample was volatilised from a tube in a Büchi Kugelrohr oven through a 30×2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A at a temperature of 500 °C, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the centre of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≈10 ms.

Pyrolysis of **8** (100 mg) at 500 °C gave two fractions. In the cold trap there was a liquid, which proved to be a mixture of phenyl isocyanate **6a** (60%); δ_C 124.8 (2 C), 125.7, 129.5 (CO), 129.6 (2 C) and 133.6 (quaternary) and phenylacetylene (75%); δ_H 3.10. At the furnace exit there was a solid, which was a mixture of Ph_3PO (75%); δ_P 29.5 and the ylide **5a** (5%); δ_P 17.0.

Pyrolysis of **13** (60 mg) at 500 °C gave two fractions. In the cold trap there was a liquid which proved to be phenyl

Table 4. Kinetic data for the gas-phase elimination reaction of **8–23**

	X	R^1	R^2	10^4k (s^{-1}) at T (K)						$\log_{10}A$ (s^{-1})	E_a (kJ mol^{-1})
8	O	H	H	1.02	2.12	3.87	10.84	17.78	35.13	8.95±0.30	94.73±2.35
				382.25	391.65	400.25	415.85	422.25	433.75		
9	O	H	NO_2	1.08	3.05	7.11	12.71	32.17		9.93±0.35	101.01±2.65
				380.25	391.85	402.55	412.65	424.55			
10	O	H	Cl	2.16	5.41	8.62	17.58	37.79		9.86±0.45	100.15±3.48
				386.25	398.05	405.95	415.05	424.85			
11	O	H	Me	1.64	3.28	4.89	7.12	10.68	20.54	9.38±0.47	97.64±3.66
				388.35	395.05	401.05	407.35	413.55	422.25		
12	O	H	OMe	1.46	2.95	8.32	15.94	28.75		9.60±0.44	97.52±3.40
				378.95	389.05	400.15	410.95	419.95			
13	S	H	H	1.61	4.92	20.84	38.34	53.98		10.10±0.57	90.68±2.89
				341.45	352.35	369.25	378.59	383.95			
14	S	H	NO_2	1.70	3.72	6.76	15.05	26.06	51.53	10.05±0.57	92.02±3.90
				346.25	355.05	364.45	373.85	380.95	387.85		
15	S	H	Cl	4.28	10.69	17.78	34.87	63.49		10.40±0.35	93.85±2.48
				356.25	369.95	373.45	381.05	388.75			
16	S	H	Me	3.35	6.11	11.22	15.88	34.94		10.28±0.51	91.18±3.54
				346.30	352.35	360.40	365.15	373.15			
17	S	H	OMe	3.77	7.20	13.29	28.41	48.24		10.19±0.19	90.58±1.31
				347.15	355.25	362.25	371.35	377.85			
18	O	NO_2	H	2.34	5.30	9.81	17.87			10.66±0.34	112.62±2.78
				411.85	421.85	429.85	439.10				
19	O	Cl	H	4.54	6.75	10.14	18.11	31.21		10.12±0.34	104.02±2.67
				403.15	409.15	415.05	422.35	430.15			
20	O	Me	H	0.43	0.91	2.51	5.96	35.58		12.78±0.41	119.24±2.96
				362.35	371.05	380.05	389.40	408.25			
21	O	OMe	H	3.17	5.66	7.96	12.55	19.13		7.12±0.16	75.92±1.22
				373.65	381.95	388.00	395.45	403.20			
22	S	Me	H	0.98	1.36	4.44	11.98	32.62		12.09±0.69	104.18±4.63
				333.35	342.45	352.80	362.25	372.45			
23	S	OMe	H	0.52	1.70	5.44	14.84	35.29		12.93±0.42	109.33±2.83
				332.20	341.85	351.40	362.35	371.80			

isothiocyanate (56%); ν_{max}/cm^{-1} 2080, 1592, 1490, 752 and 685; δ_H 7.38–7.20 (5H, m, pattern identical to authentic sample). At the furnace exit there was a solid which was a mixture of Ph_3PS (ca. 5%); δ_P 43.7, Ph_3PO (ca. 5%); δ_P 29.5 and the ylide **5a** (72%); δ_P 17.0; δ_H 8.0–7.94 (2H, m), 7.8–7.6 (6H, m), 7.6–7.4 (9H, m), 7.4–7.3 (3H, m) and 4.40 (1H, br s).

3.3. Kinetic studies

Reaction set-up. Preliminary kinetic results were obtained on a system featuring a Eurotherm 093 pyrolysis unit coupled to a Perkin Elmer Sigma 115 Gas Chromatograph. The kinetic data reported are from a reactor set-up including an HPLC (BioRad Model 2700) fitted with a UV–vis detector (BioRad Model 1740) adjusted to 254 nm; HPLC column LC-8, 25 cm, 4.6 μm (Supelco); and CDS custom made pyrolysis unit for the thermolysis reactions. The pyrolysis tube is jacketed by an insulating aluminum block fitted with a platinum resistance thermometer and a thermocouple connected to a Comark microprocessor thermometer.

Kinetic runs and data analysis. Aliquots (0.2 cm^3) of very dilute solutions (ppm) of neat substrates in acetonitrile as solvent and chlorobenzene as internal standard were pipetted into the reaction tube, which was then sealed under vacuum (0.2 Torr). The tube was then placed inside the pyrolyzer for 600 s at a temperature at which 10–20% pyrolysis was deemed to occur. The contents of the tube were analyzed using HPLC.

At least three kinetic runs were carried out for each 5–10 °C rise in temperature of the pyrolyzer and for the same time interval until 90–95% pyrolysis was achieved. The reactions were ascertained to be homogeneous, unimolecular, and free of reactor surface effects. The homogeneous nature of the reactions was tested by comparing rates using a normal reactor with those obtained when the reactor vessel is packed with helices. Absence of free radical pathways in the elimination reactions was confirmed using established procedures.

The rates were followed over a temperature range of 30–40 K, and the rate coefficients were calculated using the expression for a first-order reaction: $kt=\ln(a_o/a)$ (Table 4). Each rate coefficient represents the mean of three kinetic runs in agreement to within $\pm 2\%$. The Arrhenius parameters were obtained from a plot of log k against $1/T$ (K). The Arrhenius plots were linear up to $\approx 95\%$ reaction. Rate constants adjusted to 400 K are given in Tables 1 and 2.

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References and notes

1. Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1959**, 3874–3876.
2. Blanchard, M.-L.; Strzelecka, H.; Martin, G. J.; Simalty, M.; Fugnitto, R. *Bull. Soc. Chim. Fr.* **1967**, 2677–2679.
3. Strzelecka, H. *Ann. Chim. (Paris)* **1966**, 201–220.
4. Shevchuk, M. I.; Zabrodskaya, I. S.; Dombrovskii, A. V. *Zh. Obshch. Khim.* **1969**, *39*, 1282–1287.
5. Bestmann, H. J.; Pfohl, S. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 762–763.
6. Tolochko, A. F.; Megera, I. V.; Zykova, L. V.; Shevchuk, M. I. *Zh. Obshch. Khim.* **1975**, *45*, 2150–2154. Saikachi, H.; Takai, K. *Yakugaku Zasshi* **1969**, *89*, 1401–1406.
7. Bollens, E.; Szönyi, F.; Trabelsi, H.; Cambon, A. *J. Fluorine Chem.* **1994**, *67*, 177–181.
8. Bestmann, H. J.; Schade, G.; Schmid, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 822–824.
9. Aitken, R. A.; Karodia, N.; Massil, T.; Young, R. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 533–541 and preceding parts in this series.
10. Reviews: Aitken, R. A.; Thomas, A. W. In *Chemistry of the Functional Groups, Supplement A3*; Patai, S., Ed.; Wiley: Chichester, 1997; pp 503–507. Symery, F.; Iorga, B.; Savignac, P. *Synthesis* **2000**, 185–213.
11. Kinetic data for a series of 8 β,δ′-dioxo ylides have been reported: Aitken, R. A.; Al-Awadi, N. A.; Balkovich, M. E.; Bestmann, H. J.; Clem, O.; Gibson, S.; Gross, A.; Kumar, A.; Röder, Th. *Eur. J. Org. Chem.* **2003**, 840–847.
12. Aitken, R. A.; Hérion, H.; Janosi, A.; Karodia, N.; Raut, S. V.; Seth, S.; Shannon, I. J.; Smith, F. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2467–2472.
13. Aitken, R. A.; Atherton, J. I. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1281–1284.
14. Al-Awadi, N. A.; Al-Bashir, R. F.; El-Dusouqui, O. M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 579–581.
15. Al-Awadi, N. A.; El-Dusouqui, O. M. *Int. J. Chem. Kinet.* **1997**, *29*, 295–298.
16. Al-Awadi, N. A.; El-Dusouqui, O. M.; Mathew, T. *Int. J. Chem. Kinet.* **1997**, *29*, 289–293.
17. Al-Awadi, N. A.; Al-Bashir, R. F.; El-Dusouqui, O. M. *Tetrahedron Lett.* **1989**, *30*, 1699–1702.
18. Dombrovskii, A. V.; Shevchuk, M. I. *Zh. Obshch. Khim.* **1963**, *33*, 1263–1269.

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Design and synthesis of an isopenicillin N synthase mimic

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Abstract—Towards the aim of creating a functional mimic of isopenicillin N synthase, a small molecule designed to coordinate around iron(II) and model the enzyme active site has been prepared in nine synthetic steps from 2,6-bis(hydroxymethyl)pyridine, (*S*)-(+)-mandelic acid and pivaldehyde. One aspartate, two histidines and a water ligand in the natural enzyme are replaced by an α-hydroxy acid, pyridine and aniline in the model compound. Additionally, a free thiol designed to simulate the enzyme substrate, δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine, is linked to the ligand by a three carbon chain. We postulate that in the presence of molecular oxygen, the complex formed between this synthetic ligand and iron(II) will display oxidative chemistry similar to that observed in the active site of isopenicillin N synthase.
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1. Introduction

Isopenicillin N synthase (IPNS) is a non-heme iron(II)-dependent oxidase that catalyzes the conversion of δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine (ACV) **1** to isopenicillin N (IPN) **2**, the precursor of all penicillin and cephalosporin antibiotics (Fig. 1).[1,2] IPNS uses the full oxidizing power of molecular oxygen to perform this remarkable bicyclization, producing 2 equiv of water over the course of the reaction. Comprehensive spectroscopic,[3] crystallographic,[4–6] and substrate-analogue turnover studies[7,8] have led to the proposal of a detailed mechanism for the enzymatic transformation (Fig. 2A).

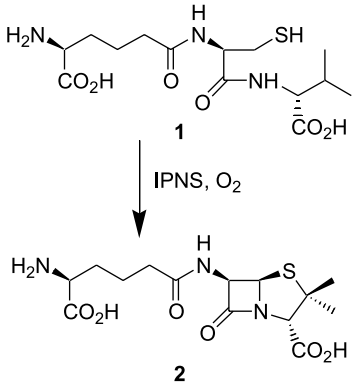

Figure 1. ACV **1** is converted to IPN **2** by IPNS in the presence of molecular oxygen.

Despite the development of a broad understanding of the IPNS active site, efforts to synthesize an iron-centered complex that mimics the activity of the enzyme have been unsuccessful.[9] Functional enzyme mimics can be important tools for advancing mechanistic knowledge as well as for testing existing hypotheses. Such mimics have recently been developed for several non-heme iron(II) oxidases including methane monooxygenase,[10] the extradiol-cleaving catechol dioxygenases[11,12] and the α-keto acid-dependent enzymes.[13] A detailed discussion of this topic appears in a recent review of the mechanisms and mimics of dioxygenase enzymes.[14]

The failure to create an equivalent IPNS mimic can be attributed primarily to the complexity of the reaction that this enzyme catalyzes. A major energetic hurdle must be overcome to hold an ACV-based substrate in the conformation required for the formation of such a strained system. When ACV is bound in the IPNS active site, multiple contacts between enzyme and substrate stabilize this conformation and promote formation of the bicyclic β-lactam product.[5] These stabilizing interactions cannot be easily replicated in a small model system, and efforts to mimic the entire reaction cycle of IPNS have consequently met with little success.[9]

A more achievable goal is the creation of a model system that mimics the early steps of the IPNS oxidation without requiring the system to duplicate the high-energy ring-closures. Recent studies with IPNS and the modified

Keywords: Enzyme mimic; Penicillin; β-Lactam; Isopenicillin N; IPNS.
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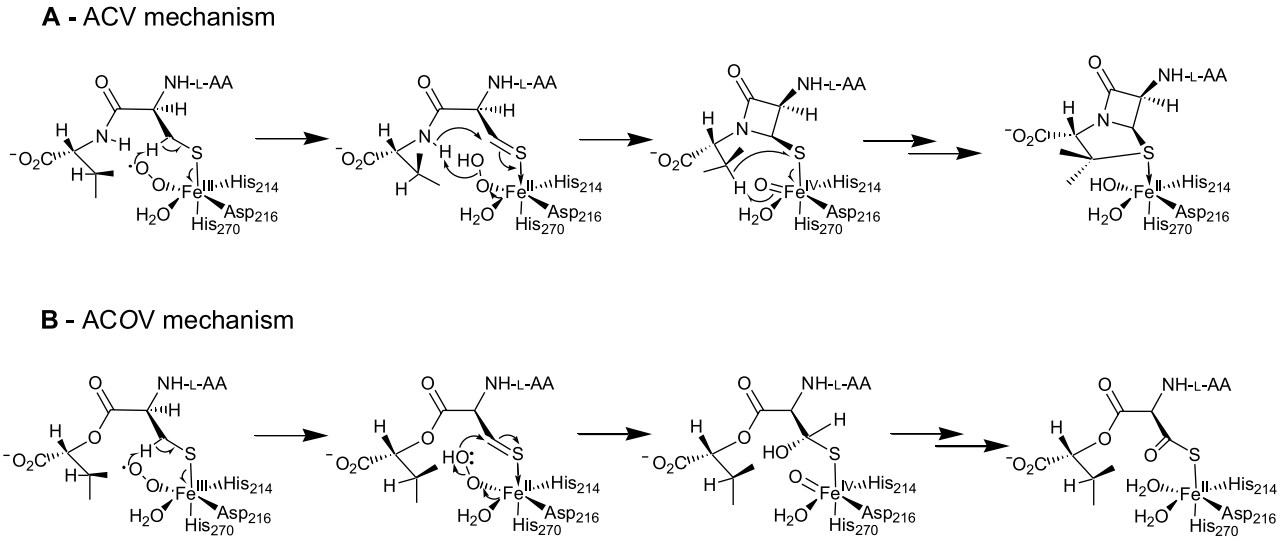


Figure 2. The reaction cycle of IPNS with ACV (A) and AC*O*V (B). With both substrates, it is proposed that initial hydrogen abstraction by an iron-bound superoxide results in the formation of a thioaldehyde bound to iron through the sulfur atom. With ACV, the valinyl amide nitrogen atom then attacks the thioaldehyde to form a β-lactam. In the reaction with AC*O*V, which lacks this internal nucleophile, the hydroperoxide formed after initial hydrogen abstraction itself attacks the thioaldehyde, and the resulting hydroxyl group is ultimately oxidized to give a thiocarboxylate.

substrate δ-(L-α-aminoadipoyl)-L-cysteine D-α-hydroxyisovaleryl ester (AC*O*V) provide support for a mechanism involving initial hydrogen abstraction by an iron(III)-bound superoxide species to give a thioaldehyde and an iron(II)-hydroperoxide (Fig. 2B).[15] In the absence of the substrate-derived nucleophile that is generated in the reaction of ACV, the hydroperoxide itself attacks the thioaldehyde, and the cysteine residue is ultimately oxidized to a thiocarboxylate.

We now report the synthesis of a pyridine-based ligand **3** designed to form a pentadentate complex **4** with iron(II) (Fig. 3). We postulate that in the presence of iron(II), the complex formed should display oxidative chemistry similar to that seen in the early stages of the IPNS reaction cycle (Scheme 1).

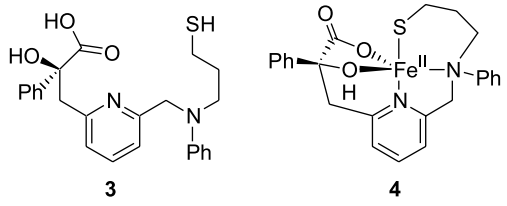
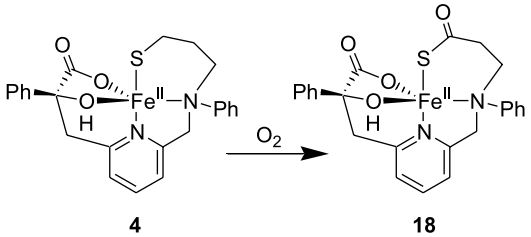


Figure 3. Ligand **3** and its complex **4** with iron(II), a proposed mimic for the IPNS active site.



Scheme 1. The proposed biomimetic oxidation of the IPNS enzyme mimic **4** upon exposure to molecular oxygen. We propose that the carbon adjacent to the iron-bound sulfur will be oxidized to a thiocarboxylate in the resulting complex **18**.

2. Results and discussion

Towards the goal of constructing an IPNS mimic, we designed a complex small molecule **3** to simulate the iron-coordinating ligands in the active site of the natural enzyme. The iron center in ACV-bound IPNS is coordinated by one aspartate (Asp_{216}) and two histidine (His_{214} and His_{270}) residues from the protein in a facial triad arrangement,[4] a motif that is conserved throughout the non-heme mononuclear iron(II) oxidases (Fig. 4).[16] A well-ordered water molecule is bound to iron opposite His_{214}, and ACV binds via the cysteinyl sulfur *trans* to His_{270}, giving a square pyramidal geometry around the metal center. Dioxygen is believed to initiate catalysis upon binding to iron in the site opposite Asp_{216}, creating an octahedral geometry that is maintained throughout the reaction cycle.[4,5]

Based on the requirements of this system, we designed the ligand **3** to form a pentadentate complex **4** with iron(II) while leaving a coordination site vacant for dioxygen binding (Fig. 3). The framework of this structure is based on a cobalt complex designed by Chin et al.[17] to stereospecifically bind amino acids. In our complex, pyridine and aniline ligands take the place of the histidine residues of IPNS, while an α-hydroxy acid moiety models both the

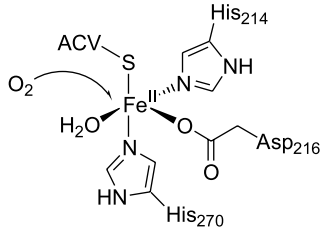
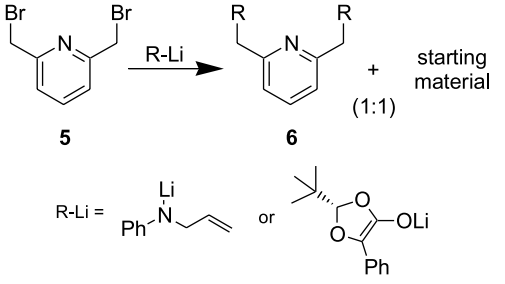


Figure 4. The active site of IPNS. The iron(II) center is coordinated by three endogenous protein ligands (His_{214}, Asp_{216}, and His_{270}), a water molecule, and the thiol sulfur of ACV in a square pyramidal arrangement. Molecular oxygen binds opposite Asp_{216}, giving the iron center an octahedral geometry.

carboxylate and water ligands. The design includes a thiol attached to the aniline nitrogen by a three-carbon linker. The sulfur atom was included to simulate binding of ACV, and it is at the adjacent carbon that we hope ultimately to achieve oxidation (Scheme 1).

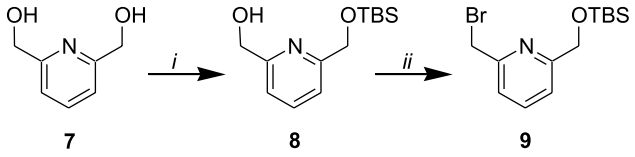
An important factor to be considered in the design of a ligand of this nature is the potential for intermolecular side reactions of the iron complex. Of particular concern is the propensity of free thiols and ferrous iron to undergo competing oxidation reactions to give disulfides and Fe(III)–O–Fe(III) species respectively, in the presence of atmospheric oxygen. Two phenyl groups are therefore included in the structure in order to increase steric bulk and inhibit intermolecular interactions that might render the complex inactive.

Initial efforts to synthesize the ligand were based on the approach taken by Chin et al., who reacted 2,6-bis(bromomethyl)pyridine **5** with the enolate of 2-(*N*-acetylamino)-diethylmalonate followed by dimethylamine to give a 2,6-hetero-disubstituted pyridine.[17] However, this approach did not prove effective in our hands, and treatment of 2,6-bis(bromomethyl)pyridine **5** with 1 equiv of an appropriate nucleophile resulted in a 1:1 mixture of homo-disubstituted product **6** and starting material (Scheme 2). This is not surprising as the mono-brominated species is highly reactive. 2-Bromomethylpyridine was found to be stable only as an HBr salt, forming polymers at pH 7 (data not shown). Conversely, 2,6-bis(bromomethyl)pyridine **5** is stable at neutral pH and can be stored indefinitely in its deprotonated form.



Scheme 2. Reaction of 2,6-bis(bromomethyl)pyridine **5** with 1 equiv of nucleophile to give a 1:1 ratio of the 2,6-homo-disubstituted pyridine **6** and the starting material.

In order to overcome this problem, the synthesis was modified to begin with 2,6-bis(hydroxymethyl)pyridine **7** (Scheme 3). The diol **7** was treated with 1 equiv of sodium hydride, and the resulting mono-anion reacted with 1 equiv of *tert*-butyldimethylsilyl chloride (TBS-Cl) to give the singly-protected diol **8** in moderate yield.[18] Mono-bromination of the protected diol proceeded smoothly with

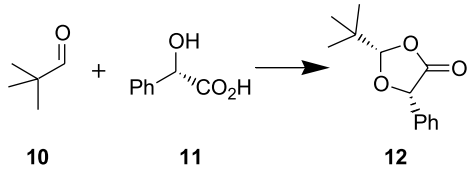


Scheme 3. Conditions: i. NaH, then TBS-Cl, DCM, RT, 5 h, 54%; ii. CBr_4, PPh_3, Et_2O, RT, 1.5 h, 81%.

triphenylphosphine and carbon tetrabromide, giving the bromide **9** in 81% yield.

At this stage, the α-hydroxy acid moiety was introduced stereoselectively in the masked form of a [1,3]-dioxolanone. Seebach and co-workers have shown that *cis*-2-*tert*-butyl-5-substituted-[1,3]-dioxolanones can be stereospecifically alkylated at the 5-position.[19,20] They have also demonstrated that these *cis*-2,5-disubstituted dioxolanones can be synthesized from pivaldehyde and enantiopure α-substituted-α-hydroxy acids in high diastereomeric purity. Hydrolysis under either acidic or basic conditions cleaves the pivaldehyde moiety, leaving an α-disubstituted-α-hydroxy acid as a single enantiomer.

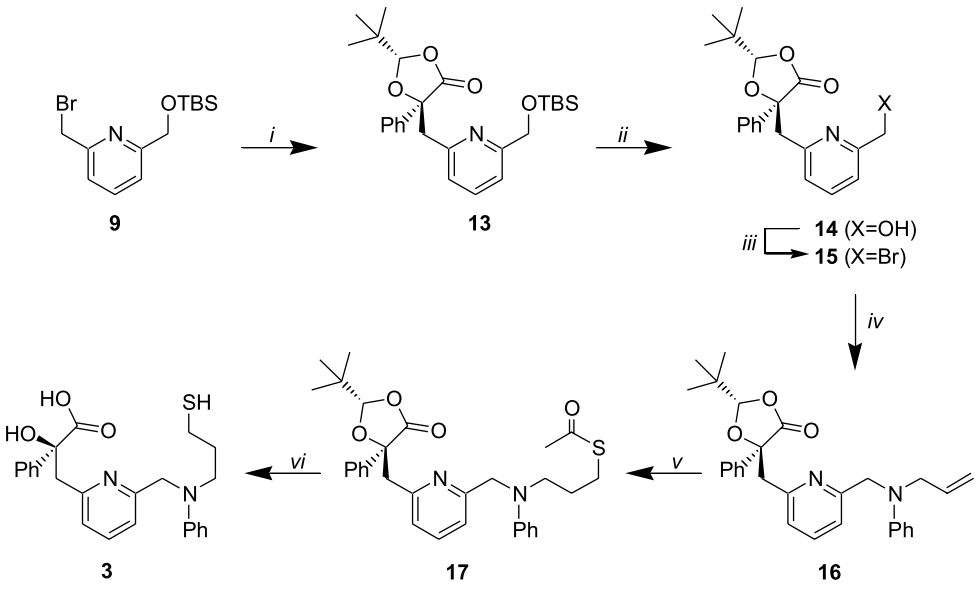
In order to introduce the phenyl group required to bring the desired steric bulk to the exterior of the mimic, a *cis*-2,5-disubstituted dioxolanone was synthesized from pivaldehyde **10** and (*S*)-(+)-mandelic acid **11** (Scheme 4). In the presence of catalytic triflic acid, these two reagents were refluxed in pentane with azeotropic removal of water to give the desired dioxolanone **12**,[21] which was isolated in diastereomerically pure form and 81% yield after a single recrystallization. Deprotonation of the dioxolanone **12** with LDA followed by addition to the mono-protected bromide **9** gave the 2,5,5-trisubstituted dioxolanone **13** in 84% yield (Scheme 5). The TBS group was then removed with tetra-*n*-butylammonium fluoride in high yield (93%), and the resulting alcohol **14** was brominated with triphenylphosphine and carbon tetrabromide to give the brominated dioxolanone **15** as a crystalline solid. The stereochemistry of all dioxolanone products was determined by nOe spectroscopy, and the solution of an X-ray crystal structure for the brominated dioxolanone **15** further confirmed that the (2*S*,5*S*)-dioxolanone system had been formed as anticipated (data not shown).



Scheme 4. Conditions: triflic acid (cat), pentane, reflux, 5 h, 81%.

Having prepared the bromide **15**, the aniline and thiol functionalities could be introduced. Deprotonation of *N*-allylaniline with *n*-butyllithium in the presence of *N*, *N*′-dimethyl-*N*, *N*′-propylene urea (DMPU), followed by addition to the bromide **15**, led to formation of the unsaturated amine **16** in 94% yield (Scheme 5). The sulfur functionality was then incorporated by radical addition of thiolacetic acid to the alkene **16**. To this end, a solution of the unsaturated compound **16** and thiolacetic acid in toluene was irradiated at 254 nm, and conversion to the thioester **17** proceeded in 56% yield.

The thioester **17** represents a protected form of the target molecule **3**, as unmasking of the thiol and the α-hydroxy acid by hydrolysis leads to the pentadentate ligand **3**. While it was originally thought that acid-catalyzed hydrolysis would be more effective in minimizing disulfide formation,



Scheme 5. Conditions: i. LDA-**12** (premixed), THF, −78 °C, 6 h, 84%; ii. TBAF, THF, 0 °C→RT; 1 h, 93%; iii. CBr_4, PPh_3, DCM, 0 °C→RT, 1.5 h, 81%; iv. *n*BuLi-*N*-allylaniline (premixed), THF, DMPU, −78 °C, 4 h, 90%; v. AcSH, toluene, *hv*, 4 h, 56%; vi. LiOH, H_2O–THF, reflux, 14 h.

the deprotection proceeded more smoothly when run under basic conditions using dilute lithium hydroxide in tetrahydrofuran-water. Mass spectrometric analysis of the crude product provides strong evidence that the pentadentate ligand **3** has been formed (HRMS: *m*/*z* found=423.1737, required for **3**=423.1742). However, separation of ligand **3** from reaction by-products was problematic, primarily due to poor solubility properties of the product. As a result, the NMR spectrum of the crude material is complicated by residual impurities (identified by HRMS as the starting material **17** and a partially deprotected product in which only the thioester has been hydrolyzed), precluding further characterization of the product by this method. Nonetheless, it is apparent from the HRMS data that the putative iron ligand **3** has indeed been formed.

3. Conclusion

We report the synthesis of a pentadentate ligand **3** to be used in the construction of a functional mimic of the key biosynthetic enzyme IPNS. Compound **3** has been prepared in nine steps from 2,6-bis(hydroxymethyl)pyridine, (*S*)-(+)-mandelic acid and pivaldehyde. We propose that the ligand **3** will bind to iron(II) and that in the presence of oxygen, the resulting complex may function as the first small molecule mimic of IPNS (Scheme 1). Further work is required to test this hypothesis.

4. Experimental

4.1. General

Reactions were carried out under an atmosphere of argon. All reagents and solvents were used as received from manufacturers unless otherwise specified. Trimethylacetaldehyde (pivaldehyde) and *N*-allylaniline were purified by Kugelröhr distillation at reduced pressure. Triphenylphosphine was recrystallized from heptane. Anhydrous dichloromethane (DCM) was obtained directly before use by refluxing over calcium hydride under an atmosphere of nitrogen, followed by distillation under those conditions. Anhydrous tetrahydrofuran (THF) and diethyl ether were similarly obtained by distillation from sodium/benzophenone ketyl. Hexane and *N*, *N*′-dimethyl-*N*, *N*′-propylene urea (DMPU) were dried with calcium hydride, fractionally distilled, and stored over 4.0 Å molecular sieves. Diisopropyl amine was similarly dried and distilled, and was stored over potassium hydroxide pellets. 'Petroleum ether' refers to the fraction of light petroleum boiling between 30 and 40 °C and was distilled prior to use. Concentrations of lithium diisopropylamide and *n*-butyllithium were determined by titration against 1,3-diphenylacetone-*p*-tosyl-hydrazone.

Melting points (mp) were measured using a Cambridge Instruments Gallen™ III Melting Point Microscope. Optical rotations ($[\alpha]_D$) were recorded on a Perkin–Elmer 241 polarimeter at 589 nm. Low-resolution mass spectra were recorded using a Micromass Platform spectrometer, and high-resolution mass spectra (HRMS) were recorded on Micromass Autospec, GCT, and LCT spectrometers. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer. Nuclear magnetic resonance spectra were recorded on Brüker DPX200 and Brüker DPX400 spectrometers, and nOe spectroscopy was performed on a Brüker DRX500 spectrometer. Elemental analysis was performed by Elemental Microanalysis Limited (Okehampton). Single-crystal X-ray diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo K_α radiation, λ=0.71073 Å) and processed using the DENZO-SMN package.[22]

4.1.1. 2-Hydroxymethyl-6-(*tert*-butyldimethylsilyloxymethyl)pyridine (8).[18] Sodium hydride (880 mg of a 60% dispersion in oil, 21.9 mmol) was washed with petroleum ether (3×25 mL), and residual solvent was removed under

reduced pressure. The resulting powder was added to a slurry of 2,6-bis(hydroxymethyl)pyridine **7** (3.01 g, 21.6 mmol) in DCM (25 mL), and this mixture was stirred at room temperature. After 45 min, a solution of *tert*-butyldimethylsilyl chloride (3.30 g, 21.9 mmol) in DCM (5 mL) was added to the reaction mixture, which was stirred at room temperature for 5 h. The mixture was diluted with DCM (250 mL) to dissolve all the solid material, and this solution was washed with saturated aqueous sodium bicarbonate (2×125 mL) and saturated brine (125 mL), and dried with magnesium sulfate. The solvent was evaporated under reduced pressure to give the crude product as an orange oil which was purified by column chromatography (petroleum ether/diethyl ether, 1:1) to give the mono-protected diol **8** as a yellow oil (2.96 g, 54%); R_f 0.25 (petroleum ether/diethyl ether, 1:1); ν_{max} (thin film): 3276 (m, br O–H str), 2955, 2932, 2886, 2857 (s, aliphatic C–H str), 1598, 1580, 1462 (m, ring str), 1257 (s), 1118, 838 (s, Si–O str); δ_H (400 MHz, $CDCl_3$): 0.14 (6H, s, $Si(CH_3)_2$), 0.97 (9H, s, $SiC(CH_3)_3$), 3.82 (1H, t, J=5.0 Hz, CH_2OH), 4.74 (2H, d, J=5.0 Hz, CH_2OH), 4.84 (2H, s, CH_2OSi), 7.10 (1H, d, J=7.5 Hz, one of $CH(Py)_{3,5}$), 7.42 (1H, d, J=7.5 Hz, one of $CH(Py)_{3,5}$), 7.71 (1H, t, J=7.5 Hz, $CH(Py)_4$); δ_C (100.6 MHz, $CDCl_3$): −5.37 ($Si(CH_3)_2$), 18.35 ($SiC(CH_3)_3$), 25.89 ($SiC(CH_3)_3$), 63.81 (CH_2OH), 65.90 (CH_2OSi), 118.40, 118.53 (2×$CH(Py)_{3,5}$), 137.27 ($CH(Py)_4$), 157.60, 160.30 (2×$C(Py)_{2,6}$); *m/z* (AP+): 254 (100%, $[MH]^+$); HRMS: found $[MH]^+$=254.1577, $C_{13}H_{24}NO_2Si$ requires 254.1576.

4.1.2. 2-Bromomethyl-6-(*tert*-butyldimethylsilyloxymethyl)pyridine (9). Carbon tetrabromide (6.70 g, 20.2 mmol) was added as a solid to a solution of the mono-protected diol **8** (4.70 g, 18.6 mmol) in diethyl ether (20 mL) and the resulting mixture was stirred at room temperature. A solution of triphenylphosphine (5.25 g, 20.0 mmol) in diethyl ether (10 mL) was added, and the reaction mixture was stirred for a further 90 min at room temperature, during which time a white precipitate formed. The precipitate (triphenylphosphine oxide) was removed by vacuum filtration, and the filtrate was concentrated under reduced pressure to give a crude orange oil. The product was purified by column chromatography (petroleum ether/diethyl ether, 20:1) to give the bromide **9** as a pale yellow oil (4.75 g, 81%); R_f 0.20 (petroleum ether/diethyl ether, 19:1); ν_{max} (thin film): 3063 (w, aromatic C–H str), 2955, 2929, 2886, 2856 (m-s, aliphatic C–H str), 1592, 1578, 1460, 1431 (m, ring str),1257 (s), 1123, 838 (s, Si–O str); δ_H (400 MHz, $CDCl_3$): 0.13 (6H, s, $Si(CH_3)_2$), 0.97 (9H, s, $SiC(CH_3)_3$), 4.52 (2H, s, CH_2Br), 4.84 (2H, s, CH_2OSi), 7.31 (1H, d, J=7.5 Hz, one of $CH(Py)_{3,5}$), 7.46 (1H, d, J=7.5 Hz, one of $CH(Py)_{3,5}$), 7.72 (1H, d, J=7.5 Hz, $CH(Py)_4$); δ_C (100.6 MHz, $CDCl_3$): −5.39 ($Si(CH_3)_2$), 18.33 ($SiC(CH_3)_3$), 25.89 ($SiC(CH_3)_3$), 33.85 (CH_2Br), 65.87 (CH_2OSi), 119.25, 121.50 (2×$CH(Py)_{3,5}$), 137.64 ($CH(Py)_4$), 155.56, 161.50 (2×$C(Py)_{2,6}$); *m/z* (AP+): 318 (80%, $[MH]^+$ for ^{81}Br), 316 (100%, $[MH]^+$ for ^{79}Br), 268 (82%), 237 (21%, $[MH–Br]^+$), 202 (41%, $[MH–SiC(CH_3)_3]^+$ for ^{79}Br), 154 (42%); HRMS: found $[MH]^+$=316.0729, $C_{13}H_{23}^{79}BrNOSi$ requires 316.0732.

4.1.3. (2*S*,5*S*)-2-*tert*-Butyl-5-phenyl-[1,3]-dioxolan-4-one (12).[21] Pivaldehyde **10** (2.65 g, 30.8 mmol) was added to a slurry of (*S*)-(+) mandelic acid **11** (3.92 g, 25.8 mmol) in pentane (45 mL). The mixture was stirred at room temperature while trifluoromethanesulfonic acid (100 μL, 1.1 mmol) was added dropwise, and then heated to reflux for 5 h under Dean-Stark conditions. The reaction mixture was cooled to room temperature and neutralized with aqueous sodium bicarbonate (8%, *w/v*) and then with solid sodium bicarbonate. During this process, a white precipitate formed from what had become an orange solution. The pentane was removed under reduced pressure, and the white solid was isolated from the aqueous suspension by vacuum filtration. Two recrystallizations of the solid (ethyl acetate–heptane) gave the dioxolanone **12** as large white needles (4.54 g, 81%); mp 138–140 °C; R_f 0.20 (petroleum ether/diethyl ether, 20:1); $[\alpha]_D^{25}$ +90.0 (chloroform, c=0.1; lit. $[\alpha]_D^{25}$ +88.7,[19] chloroform, c=1.2); ν_{max} (KBr disk): 3070, 3039 (w, aromatic C–H str), 2980, 2960, 2922, 2873 (m, aliphatic C–H str), 1799 (s, C=O str), 1483, 1457 (m, ring, str), 1206 (s), 1183 (s, C–O–C str); δ_H (400 MHz, $CDCl_3$): 1.10 (9H, s, $C(CH_3)_3$), 5.25 (1H, d, J=1.5 Hz, PhC*H*), 5.34 (1H, d, J=1.5 Hz, $(CH_3)_3CCH$), 7.38–7.49 (5H, m, 2×C*H* $(Ph)_o$, 2×$CH(Ph)_m$, $CH(Ph)_p$); δ_C (100.6 MHz, $CDCl_3$): 23.63 ($C(CH_3)_3$), 34.48 ($C(CH_3)_3$), 77.02 (PhCHC=O), 109.32 ($(CH_3)_3CCH$), 127.06, 128.74 (2×$CH(Ph)_o$, 2×$CH(Ph)_m$), 129.19 ($CH(Ph)_p$) 133.51 ($C(Ph)_i$), 171.86 (C=O); *m/z* (TOF+): 238 (100%, $[M+NH_4]^+$), 221 (20%, $[MH]^+$), 176 (18%), 152 (25%); HRMS: found $[M+NH_4]^+$=238.1444, $C_{13}H_{20}NO_3$ requires 238.1443; found C 70.67%, H 7.34%, $C_{13}H_{16}O_3$ requires C 70.89%, H 7.32%.

4.1.4. (2*S*,5*S*)-2-*tert*-Butyl-5-[6-(*tert*-butyldimethylsilyloxymethyl)pyridin-2-ylmethyl]-5-phenyl-[1,3]-dioxolan-4-one (13). A solution of the dioxolanone **12** (1.11 g, 5.0 mmol) in THF (25 mL) was cooled to −78 °C and a solution of lithium diisopropylamide (1.63 M solution in THF, 3.10 mL, 5.0 mmol) was added. The solution was stirred at −78 °C for 50 min, then added dropwise via cannula to a solution of 2-bromomethyl-6-(*tert*-butyldimethylsilyloxymethyl)pyridine **9** (1.59 g, 5.0 mmol) in THF (25 mL) at −78 °C. The reaction mixture was stirred at −78 °C for an additional 6 h. It was then poured into half-saturated aqueous ammonium chloride (40 mL), and the resulting solution was extracted with diethyl ether (4× 50 mL). The organic phase was dried with magnesium sulfate, and the solvent was removed under reduced pressure to give a peach-colored oil. The crude material was purified by column chromatography (petroleum ether/diethyl ether, 15:2) to yield the trisubstituted dioxolanone **13** as an off-white crystalline solid (1.93 g, 84%); mp 65–67 °C; R_f 0.15 (petroleum ether/diethyl ether, 8:1); $[\alpha]_D^{25}$ −37.3 (chloroform, c=0.9); ν_{max} (KBr disc): 3054, 3037 (w, aromatic C–H str), 2955, 2902, 2855 (m, aliphatic C–H str), 1787 (s, C=O str), 1578, 1549, 1483, 1460 (m, ring str), 1257 (m), 1192 (s, C–O–C str); δ_H (400 MHz, $CDCl_3$): 0.13 (6H, s, $Si(CH_3)_2$), 0.86 (9H, s, $HCC(CH_3)_3$), 0.97 (9H, s, $SiC(CH_3)_3$), 3.33 (1H, d, J=14.5 Hz, one of $PhCCH_2Py$), 3.65 (1H, d, J=14.5 Hz, one of $PhCCH_2Py$), 4.69 (1H, s, $HCC(CH_3)_3$), 4.81 (1H, d, J=15.5 Hz, one of $PyCH_2OSi$), 4.84 (1H, d, J=15.5 Hz, one of $PyCH_2OSi$), 6.99 (1H, d, J=7.5 Hz, one of $CH(Py)_{3,5}$), 7.30–7.35 (1H, m, $CH(Ph)_p$), 7.36–7.45 (3H, m, 2×$CH(Ph)_o$, one of $CH(Py)_{3,5}$), 7.63 (1H, t, J=7.5 Hz, $CH(Py)_4$), 7.74–7.78 (2H, m, 2×$CH(Ph)_m$); δ_C (100.6 MHz, $CDCl_3$): −5.37 ($Si(CH_3)_2$),

18.36 ($SiC(CH_3)_3$), 23.52 ($HCC(CH_3)_3$), 25.92 ($SiC(CH_3)_3$), 34.86 ($HCC(CH_3)_3$), 48.49 (PyCH_2CPh), 65.82 (PyCH_2OSi), 82.20 (PhCCH_2Py), 109.57 ($HCC(CH_3)_3$), 118.20, 122.31 (2×$CH(Py)_{3,5}$), 124.91 (2×$CH(Ph)$-$_m$), 127.92 ($CH(Ph)_p$), 128.24 (2×$CH(Ph)_o$), 137.06 ($CH(Py)_4$), 139.18 ($C(Ph)_i$), 154.11, 161.17 (2×$C(Py)_{2,6}$), 173.28 (C=O); *m/z* (ES+): 456 (100%, $[MH]^+$); HRMS: found $[MH]^+$=456.2572, $C_{26}H_{38}NO_4Si$ requires 456.2570; found C 68.50%, H 8.23%, N 3.19%, $C_{26}H_{37}NO_4Si$ requires C 68.35%, H 8.18%, N 3.07%.

4.1.5. (2*S*,5*S*)-2-*tert*-Butyl-5-(6-hydroxymethylpyridin-2-ylmethyl)-5-phenyl-[1,3]-dioxolan-4-one (14). A solution of the protected dioxolanone **13** (397 mg, 0.87 mmol) in THF (8 mL) was cooled to 0 °C, and TBAF (1.0 M solution in THF, 1.75 mL, 1.75 mmol) was added. The solution was stirred at 0 °C for 5 min and at room temperature for 70 min. It was then poured into water (10 mL) and extracted with DCM (3×20 mL). The organic layer was washed with saturated brine (10 mL), dried with magnesium sulfate, and the solvent was removed under reduced pressure to give a runny yellow oil. The crude product was purified by column chromatography (petroleum ether/diethyl ether, 1:1) to give the alcohol **14** (275 mg, 93%) as a viscous pale yellow oil; R_f 0.20 (petroleum ether/diethyl ether, 1:1); $[\alpha]_D^{25}$ −57.8 (chloroform, c=0.8); ν_{max} (thin film): 3422 (s, br, O–H str), 3064, 3029 (m, aromatic C–H str), 2974, 2935, 2908, 2874 (s, aliphatic C–H str), 1790 (s, C=O str), 1594, 1578, 1483, 1459 (s, ring str),1178 (s, C–O–C str); δ_H (400 MHz, $CDCl_3$): 0.88 (9H, s, $HCC(CH_3)_3$), 3.39 (1H, d, J=14.5 Hz, one of PhCCH_2Py), 3.66–3.72 (2H, m, one of PhCCH_2Py and CH_2OH), 4.73 (2H, d, J=4.5 Hz, PyCH_2OH), 4.85 (1H, s, CHC$(CH_3)_3$), 7.01 (1H, d, J=7.5 Hz, one of C$H(Py)_{3,5}$), 7.11 (1H, d, J=7.5 Hz, one of C$H(Py)_{3,5}$), 7.31–7.36 (1H, m, C$H(Ph)_p$), 7.37–7.42 (2H, m, C$H(Ph)_m$), 7.59 (1H, t, J=7.5 Hz, C$H(Py)_4$), 7.71–7.75 (2H, m, C$H(Ph)_o$); δ_C (100.6 MHz, $CDCl_3$): 23.49 ($HCC(CH_3)_3$), 34.88 ($HCC(CH_3)_3$), 47.81 (PyCH_2CPh), 63.98 (PyCH_2OH), 81.91 (PhCCH_2Py), 109.44 ($HCC(CH_3)_3$), 118.81, 122.91 (2×$CH(Py)_{3,5}$), 124.94 (2×$CH(Ph)_o$), 128.03 ($CH(Ph)_p$), 128.26 (2×$CH(Ph)_m$), 137.10 ($CH(Py)_4$), 128.74 ($C(Ph)_i$), 154.28, 158.49 (2×$C(Py)_{2,6}$), 173.24 (C=O); *m/z* (ES+): 364 (25%, $[M+Na]^+$), 342 (100%, $[MH]^+$); HRMS: found $[MH]^+$=342.1696, $C_{20}H_{24}NO_4$ requires 342.1705.

4.1.6. (2*S*,5*S*)-5-(6-Bromomethylpyridin-2-ylmethyl)-2-*tert*-butyl-5-phenyl-[1,3]-dioxolan-4-one (15). A solution of the alcohol **14** (1.45 g, 4.2 mmol) in DCM (30 mL) was cooled to 0 °C, and a solution of carbon tetrabromide (1.54 g, 4.6 mmol) in DCM (5 mL) was added to it via cannula. A solution of triphenylphosphine (1.23 g, 4.7 mmol) in DCM was then added via cannula, and the resulting yellow solution was stirred at 0 °C for 5 min, and then at room temperature for 90 min. The reaction mixture was diluted with diethyl ether (300 mL), causing the precipitation of triphenylphosphine oxide. The white precipitate was removed by vacuum filtration, and the solvent was evaporated under reduced pressure to give a thick yellow oil. This crude material was purified by column chromatography (petroleum ether/diethyl ether, 9:2) to give the bromide **15** (1.39 g, 81%) as a white crystalline solid; mp 101–102 °C; R_f 0.20 (petroleum ether/diethyl ether, 4:1); $[\alpha]_D^{25}$ −58.4 (chloroform, c=0.9); ν_{max} (KBr disc): 3068 (w, aromatic C–H str), 2970, 2905, 2872 (m, aliphatic C–H str), 1794 (s, C=O str), 1597, 1574, 1482, 1459 (m, ring str),1210 (m), 1172 (m, C–O–C str); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, $HCC(CH_3)_3$), 3.39 (1H, d, J=15.0 Hz, one of PyCH_2CPh), 3.66 (1H, d, J=15.0 Hz, one of PyCH_2CPh), 4.55 (2H, s, PyCH_2Br), 5.03 (1H, s, $HCC(CH_3)_3$), 7.04 (1H, d, J=7.5 Hz, one of C$H(Py)_{3,5}$), 7.31–7.36 (2H, m, $CH(Ph)_p$) and one of C$H(Py)_{3,5}$), 7.37–7.43 (2H, m, 2×C$H(Ph)_m$), 7.62 (1H, t, J=7.5 Hz, C$H(Py)_4$), 7.75–7.79 (2H, m, 2×C$H(Ph)_o$); δ_C (100.6 MHz, $CDCl_3$): 23.58 ($HCC(CH_3)_3$), 33.71 (PyCH_2Br), 34.96 ($HCC(CH_3)_3$), 48.41 (PyCH_2CPh), 81.95 (PyCH_2CPh), 109.72 ($HCC(CH_3)_3$), 121.97, 123.54 (2×$CH(Py)_{3,5}$), 124.91 (2×$CH(Ph)_o$), 127.98 ($CH(Ph)_p$), 128.29 (2×$CH(Ph)_m$), 137.55 ($CH(Py)_4$), 139.29 ($C(Ph)_i$), 155.48, 156.39 (2×$C(Py)_{2,6}$), 173.28 (C=O); *m/z* (ES+): 406 (100%, $[MH]^+$ for ^{81}Br), 404 (95%, $[MH]^+$ for ^{79}Br); HRMS: found $[M]^+$=403.0787, $C_{20}H_{23}^{79}BrNO_3$ requires 403.0783.

4.1.7. (2*S*,5*S*)-5-{6-[(*N*-Allyl-*N*-phenylamino)methyl]-pyridin-2-ylmethyl}-2-*tert*-butyl-5-phenyl-[1,3]-dioxolan-4-one (16). *N*-Allylaniline (442 mg, 3.32 mmol) in THF (25 mL) was cooled to 0 °C, and *n*BuLi (2.26 M in hexanes, 1.52 mL, 3.44 mmol) was added. The solution was stirred for 30 min, after which DMPU (445 mg, 3.47 mmol) was added. Stirring was continued at 0 °C for another 15 min, before the lithium amide solution thus formed was added dropwise via cannula to a solution of the bromide **15** (1.39 g, 3.4 mmol) in THF (25 mL) at −78 °C. The resulting solution was stirred at −78 °C for 4 h and then quenched by pouring into half-saturated ammonium chloride (40 mL). This mixture was extracted with diethyl ether (3×100 mL), and the organic phase was washed with brine (100 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil, which was purified by column chromatography (petroleum ether/diethyl ether, 6:1), giving the alkene **16** (1.43 g, 94%) as a viscous, colorless oil; R_f 0.10 (petroleum ether/diethyl ether, 8:1); $[\alpha]_D^{25}$ −44.5 (chloroform, c=1.0); ν_{max} (thin film): 3062, 3040 (w, aromatic C–H str), 2962, 2934, 2907, 2836 (m, aliphatic C–H str), 2361 (w, overtone of C–O–C str), 1792 (s, C=O str), 1643 (w, C=C str), 1599, 1576, 1506, 1482 (m-s, ring str), 1178 (s, br, C–O–C str); δ_H (400 MHz, $CDCl_3$): 0.90 (9H, s, $C(CH_3)_3$), 3.40 (1H, d, J=14.5 Hz, 1 of PyCH_2C), 3.72 (1H, d, J=14.5 Hz, 1 of PyCH_2C), 4.11 (2H, ddd, X of ABMX, J_{XM}=5.0 Hz, J_{XA}=1.5 Hz, J_{XB}=1.5 Hz, NCH_2CHCH_2), 4.63 (2H, s, PyCH_2N), 4.80 (1H, s, $(CH_3)_3CCH$), 5.22 (1H, ddt, B of ABMX, J_{BM}=10.0 Hz, J_{AB}=1.5 Hz, J_{BX}=1.5 Hz, H_{trans} of NCH_2-CHCH_2), 5.25 (1H, ddt, A of ABMX, J_{AM}=17.0 Hz, J_{AB}=1.5 Hz, J_{AX}=1.5 Hz, H_{cis} of NCH_2CHCH_2), 5.94 (1H, ddt, M of ABMX, J_{AM}=17.0 Hz, J_{BM}=10.0 Hz, J_{MX}=5.0 Hz, NCH_2CHCH_2), 6.65–6.75 (3H, m, 2×CH(Ph–N)$_o$, CH(Ph–N)$_p$), 7.01 (1H, d, J=7.5 Hz, one of C$H(Py)_{3,5}$), 7.14 (1H, d, J=7.5 Hz, one of C$H(Py)_{3,5}$), 7.16–7.23 (2H, m, 2×CH(Ph–N)$_m$), 7.32–7.38 (1H, m, CH(Ph–C)$_p$), 7.39–7.45 (2H, m, 2×CH(Ph–C)$_m$), 7.53 (1H, t, J=7.5 Hz, C$H(Py)_4$), 7.77–7.81 (2H, m, 2×CH(Ph–C)$_o$); δ_C (100.6 MHz, $CDCl_3$): 23.57 ($C(CH_3)_3$), 34.88 ($C(CH_3)_3$), 48.41 (PyCH_2C), 53.83 (NCH_2CHCH_2), 56.19 (PyCH_2N), 82.17 (PhCCH_2Py), 109.60 ($(CH_3)_3CCH$), 112.28 (2×CH(Ph–N)$_o$), 116.65 (NCH_2CHCH_2), 116.70 (CH(Ph–N)$_p$), 119.11,

122.50 (2×*C*H(Py)$_{3,5}$), 124.96 (2×*C*H(Ph–C)$_o$), 127.98 (*C*H(Ph–C)$_p$), 128.27 (2×*C*H(Ph–C)$_m$), 129.18 (2×*C*H(Ph–N)$_m$), 133.39 (NCH$_2$*C*HCH$_2$), 137.15 (*C*H(Py)$_4$), 139.13 (*C*(Ph–C)$_i$), 148.38 (*C*(Ph–N)$_i$), 155.22, 159.20 (2×*C*(Py)$_{2,6}$), 173.24 (*C*=O); *m/z* (AP+): 479 (15%, [M+Na]$^+$); 457 (100%, [MH]$^+$); HRMS: found [MH]$^+$=457.2497, $C_{29}H_{33}N_2O_3$ requires 457.2491.

4.1.8. Thiolacetic acid *S*-(3-{[6-((2*S*,4*S*)-2-*tert*-butyl-5-oxo-4-phenyl-[1,3]-dioxolan-4-ylmethyl)pyridin-2-ylmethyl]phenylamino}propyl) ester (17). To a solution of the alkene **16** (248 mg, 0.54 mmol) in toluene (1.25 mL) in a quartz flask was added thiolacetic acid (130 mg, 1.7 mmol). Argon was bubbled through the solution for 20 min to remove dissolved oxygen. The flask was then sealed and the solution was irradiated with 4×8 W bulbs at 254 nm for 4 h. The solvent was removed under reduced pressure to give a crude yellow oil which was purified by column chromatography (petroleum ether/diethyl ether, 2:1), giving the thioester **17** as a yellow oil (162 mg, 56%); R_f 0.30 (petroleum ether/diethyl ether, 2:1); $[\alpha]_D^{25}$ −48.4 (chloroform, c=0.5); ν_{max} (thin film): 3092, 3062, 3028 (w, aromatic C–H str), 2961, 2933, 2873 (aliphatic C–H str), 1790 (s, lactone C=O str), 1693 (s, thioester C=O str), 1599, 1576, 1505, 1456 (s, ring str), 1195 (s), 1177 (s, C–O–C str); δ_H (400 MHz, $CDCl_3$): 0.89 (9H, s, HCC(C*H*$_3$)$_3$), 1.98 (2H, quint, J=7.5 Hz, NCH$_2$C*H*$_2$CH$_2$S), 2.36 (3H, s, SC(=O)C*H*$_3$), 2.95 (2H, t, J=7.0 Hz, NCH$_2$-CH$_2$C*H*$_2$S), 3.38 (1H, d, J=14.5 Hz, one of PyC*H*$_2$CPh), 3.54 (2H, t, J=7.5 Hz, NC*H*$_2$CH$_2$CH$_2$S), 3.69 (1H, d, J=14.5 Hz, one of PyC*H*$_2$CPh), 4.59 (2H, s, PyC*H*$_2$N), 4.79 (1H, s, (CH$_3$)$_3$CC*H*), 6.61–6.65 (2H, m, 2×C*H*(Ph–N)$_o$), 6.67–6.72 (1H, m, C*H*(Ph–N)$_p$), 6.98 (1H, d, J=7.5 Hz, one of C*H*(Py)$_{3,5}$), 7.04 (1H, d, J=7.5 Hz, one of C*H*(Py)$_{3,5}$), 7.16–7.21 (2H, m, 2×C*H*(Ph–N)$_m$), 7.31–7.37 (1H, m, C*H*(Ph–C)$_p$), 7.38–7.44 (2H, m, 2×C*H*(Ph–C)$_m$), 7.49 (1H, t, J=7.5 Hz, C*H*(Py)$_4$), 7.74–7.79, (2H, m, 2×C*H*(Ph–C)$_o$); δ_C (100.6 MHz, $CDCl_3$): 23.57 (HCC(*C*H$_3$)$_3$), 26.56 (NCH$_2$CH$_2$*C*H$_2$S), 27.27 (NCH$_2$*C*H$_2$CH$_2$S), 30.63 (SC(=O)*C*H$_3$), 34.88 (HC*C*(CH$_3$)$_3$), 48.34 (Py*C*H$_2$CPh), 50.72 (N*C*H$_2$CH$_2$CH$_2$S), 56.73 (Py*C*H$_2$N), 82.15 (PyCH$_2$-*C*Ph), 109.53 (H*C*C(CH$_3$)$_3$), 112.24 (2×*C*H(Ph–N)$_o$), 116.67 (*C*H(Ph–N)$_p$), 119.12, 122.53 (2×*C*H(Py)$_{3,5}$), 124.96 (2×*C*H(Ph–C)$_o$), 127.97 (*C*H(Ph–C)$_p$), 128.25 (2×*C*H(Ph–C)$_m$), 129.25 (2×*C*H(Ph–N)$_m$), 137.11 (*C*H(Py)$_4$), 139.05 (*C*(Ph–C)$_i$), 147.76 (*C*(Ph–N)$_i$), 155.17, 158.92 (*C*(Py)$_{2,6}$), 173.15 (O–*C*=O), 195.47 (S–*C*=O); *m/z* (ES+): 533 (100%, [MH]$^+$); HRMS: found [MH]$^+$=533.2477, $C_{31}H_{37}N_2O_4S$ requires 533.2474.

4.1.9. (2*S*)-2-Hydroxy-3-(6-{[(3-mercaptopropyl)phenylamino]methyl}pyridin-2-yl)-2-phenylpropionic acid (3). Lithium hydroxide (15 mg, 0.63 mmol) was dissolved in water (2.5 mL) and a solution of the thioester **17** (106 mg, 0.20 mmol) in THF (2.5 mL) was added. The solution was then heated at reflux for 16 h and the solvent was removed under reduced pressure to give the deprotected molecule **3** as an off-white solid; *m/z* (ES+): 423 (100%, [MH]$^+$); HRMS: found [MH]$^+$=423.1737, $C_{24}H_{27}N_2O_3S$ requires 423.1742.

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References and notes

1. Samson, S. M.; Belagaje, R.; Blankenship, D. T.; Chapman, J. L.; Perry, D.; Skatrud, P. L.; VanFrank, R. M.; Abraham, E. P.; Baldwin, J. E.; Queener, S. W.; Ingolia, T. D. *Nature* **1985**, *318*, 191–194.
2. Cooper, R. D. G. *Bioorg. Med. Chem.* **1993**, *1*, 1–17.
3. Que, L. Jr.; Ho, R. Y. N. *Chem. Rev.* **1996**, *96*, 2607–2624.
4. Roach, P. L.; Clifton, I. J.; Fulop, V.; Harlos, K.; Barton, G. J.; Hajdu, J.; Andersson, I.; Schofield, C. J.; Baldwin, J. E. *Nature* **1995**, *375*, 700–704.
5. Roach, P. L.; Clifton, I. J.; Hensgens, C. M. H.; Shibata, N.; Schofield, C. J.; Hajdu, J.; Baldwin, J. E. *Nature* **1997**, 387.
6. Burzlaff, N. I.; Rutledge, P. J.; Clifton, I. J.; Hensgens, C. M. H.; Pickford, M.; Adlington, R. M.; Roach, P. L.; Baldwin, J. E. *Nature* **1999**, *401*, 721–724.
7. Baldwin, J. E.; Bradley, M. *Chem. Rev.* **1990**, *90*, 1079–1088.
8. Baldwin, J. E.; Schofield, C. J. In *The Biosynthesis of β-Lactams*; Page, M. I., Ed.; Blackie Academic and Professional: London, 1992; pp 1–78.
9. (a) Fung, K. W. D. Phil. Thesis, University of Oxford, 1993. (b) Chu, C. D. Phil. Thesis, University of Oxford, 1999.
10. Tshuva, E. Y.; Lee, D.; Bu, W.; Lippard *J. Am. Chem. Soc.* **2002**, *124*, 2416–2417.
11. Lin, G.; Reid, G.; Bugg, T. D. H. *J. Chem. Soc., Chem. Commun.* **2000**, 1119–1120.
12. Lin, G.; Reid, G.; Bugg, T. D. H. *J. Am. Chem. Soc.* **2001**, *123*, 5030–5039.
13. Hegg, E. L.; Ho, R. Y. N.; Que, L. Jr. *J. Am. Chem. Soc.* **1999**, *121*, 1972–1973.
14. Bugg, T. D. H. *Tetrahedron* **2003**, *59*, 7075–7101.
15. Ogle, J. M.; Clifton, I. J.; Rutledge, P. J.; Elkins, J. M.; Burzlaff, N. I.; Adlington, R. M.; Roach, P. L.; Baldwin, J. E. *Chem. Biol.* **2001**, *8*, 1231–1237.
16. Hegg, E. L.; Que, L. Jr. *Eur. J. Biochem.* **1997**, *250*, 625–629.
17. Chin, J.; Lee, S. S.; Lee, K. J.; Park, S.; Kim, D. H. *Nature* **1999**, *401*, 254–257.
18. McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390.
19. Seebach, D.; Naef, R. *Helv. Chim. Acta* **1981**, *64*, 2704–2708.
20. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324.
21. Grover, P. T.; Bhongle, B. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283–6287.
22. Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307–326.

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Synthesis and spectroscopic properties of Schiff bases derived from 3-hydroxy-4-pyridinecarboxaldehyde

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Abstract—A series of six new Schiff bases has been prepared by reacting aniline and 4-R-substituted anilines (R = CH_3, OCH_3, Br, Cl, NO_2) with 3-hydroxy-4-pyridinecarboxaldehyde. The ^{1}H, ^{13}C, ^{15}N and ^{17}O NMR data of these compounds are used to discuss the tautomerism. ^{15}N NMR and ^{17}O NMR chemical shifts established the tautomer existing in solution as the hydroxy/imino. ^{13}C CPMAS NMR confirms that the same tautomer is found in the solid state. The stabilities of the tautomeric forms have been approached using density functional calculations (B3LYP/6-31G**) in the gas phase. In all cases the neutral hydroxy/imino with *E* configuration is more stable than the oxo/enamino form (by ~22 kJ mol^{-1}) and significantly more stable than the betaine (by ~75 kJ mol^{-1}).
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1. Introduction

Pyridoxal (PL **1**) and its phosphate, pyridoxal-5′-phosphate (PLP **2**) are an essential part of several enzymatic systems (pyridoxal phosphate dependent enzymes) acting as cofactors or prosthetic groups. These systems are involved in the metabolism of amines and aminoacids. The mechanism and stereochemistry of the PLP-dependent enzymic reactions have been studied in great detail and many intermediates have been identified.[1–3] Some of these intermediates correspond to the formation of Schiff bases (imines) with the substrates. In the absence of the substrate, the formyl group at position 4 of the pyridine is forming a Schiff base with the ε-amino group of a specific residue of lysine in the active center.[4] When an aminoacid reach the active center, it displaces the lysine and forms a new Schiff base **3**, usually in the form of a pyridinium ion **4** (Scheme 1). From that step, the transaminations, decarboxylations, desaminations and aldolic cleavages take place.[5] There is also a considerable number of theoretical papers devoted to this topic.[6–8]

We decided to study the structure of the Schiff bases **7a–7f**, that belong to an interesting class of systems with intramolecular hydrogen bonds (IMHB) in which the bridge atoms are involved in the π-electron chelate ring, derived from a simple model of PL, the 3-hydroxy-4-pyridinecarboxaldehyde (3-hydroxyisonicotinaldehyde) (**5**), and 4-R-substituted anilines (R = H, CH_3, OCH_3, Br, Cl, NO_2). The final purpose is to reach some structural conclusions concerning tautomerism in such compounds transferable to PL.

2. Results and discussion

We have represented in Scheme 2 the synthetic part of this work. Besides imines **7a–7f** we have prepared the azine **8**.

The main difficulty is the synthesis of the common precursor **5**. This compound has been described by O'Learly and Payne from 4-picoline-*N*-oxide in a five step procedure (Scheme 3).[9] The procedure is tedious and the total yield is only 2%. From **5** it was easy to obtain the Schiff bases and the azine.

All the compounds of Schemes 2 and 3 have been characterized by NMR spectroscopy. We will first discuss the compounds of Scheme 3 including **5**. The ^{1}H NMR

Keywords: Schiff bases; Hydrogen bonds; Tautomerism; Multinuclear NMR; DFT calculations.
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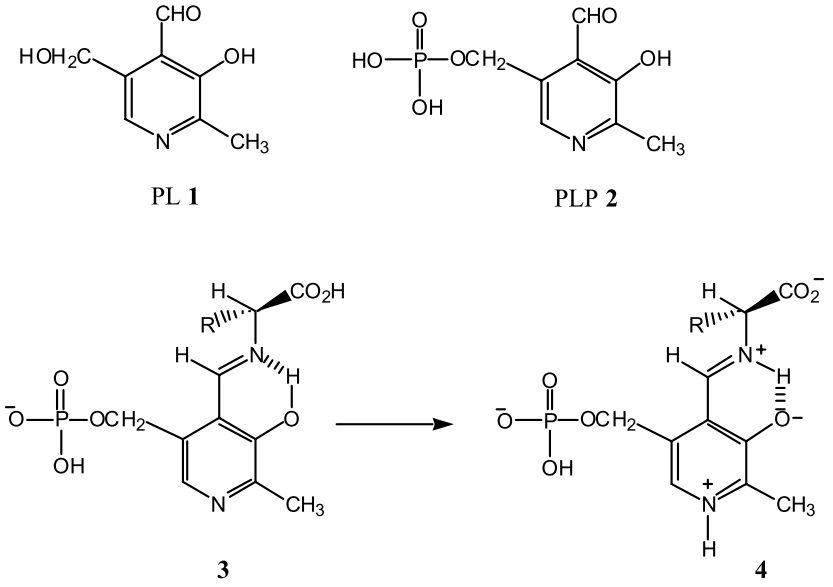
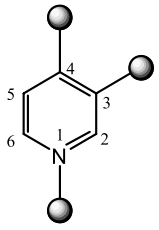


Scheme 1.

results are reported in Table 1 and the ^{13}C, ^{15}N and ^{17}O NMR in Table 2.

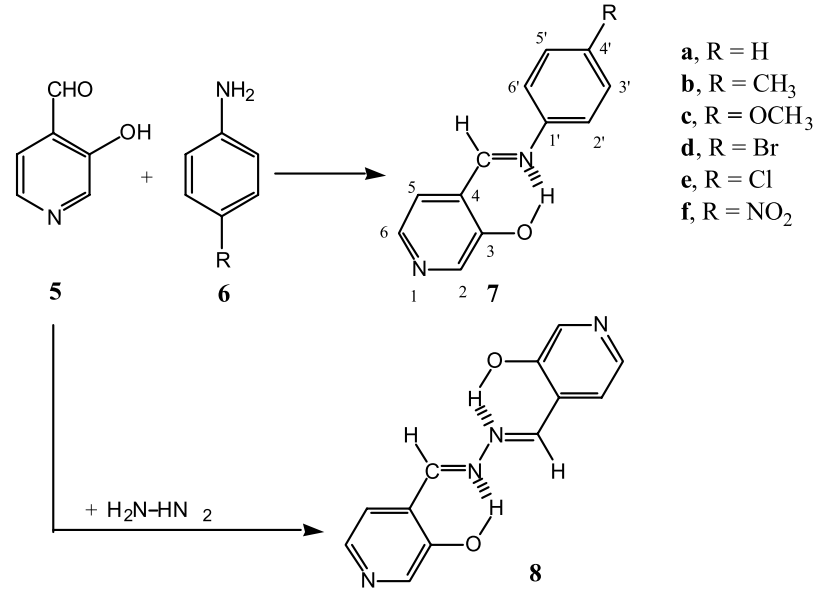


Due to the diversity of structures of the compounds of Tables 1 and 2 compounds, comparisons are not possible but, in any case, the assignments are unambiguous and structures have been established with certainty. The ^{1}H NMR spectrum of **5** in D_2O was described as early as 1968.[10] The ^{15}N NMR chemical shifts of pyridines are about −70 ppm and those of *N*-oxides about −90 ppm, in agreement with literature results.[11] The oxygen chemical shifts also are in the ranges of similar compounds.[11]

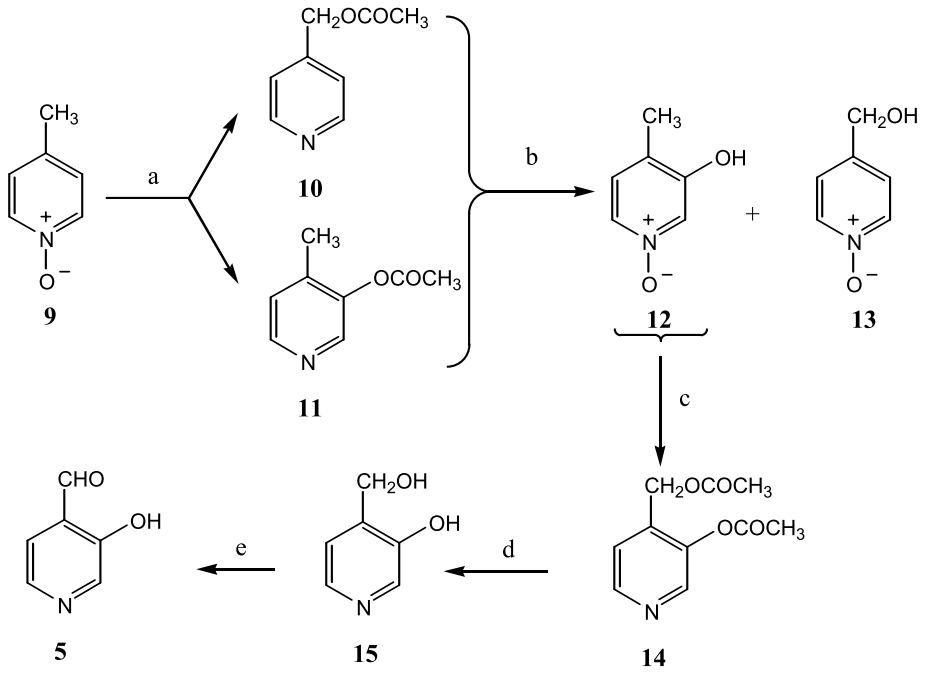
The results concerning the Schiff bases are reported in Table 3 (^{1}H NMR) and Table 4 (^{13}C NMR, ^{15}N NMR and ^{17}O NMR).

The first and most important conclusion from Tables 3 and 4 is that compounds **7** exist as hydroxy/imino tautomers forming an intramolecular O–H···N hydrogen bond.[12–14] The OH signals (both in ^{1}H and in ^{17}O NMR) and the CH=N signal (^{15}N NMR) are characteristic of such structure.[11]

Recently an important paper on the tautomerism of Schiff



Scheme 2.



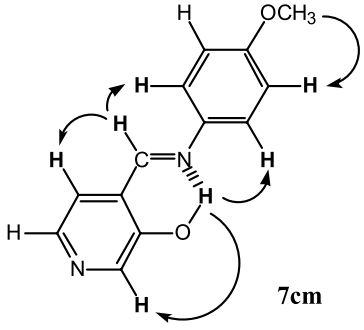
Scheme 3. (a) Ac_2O/C_6H_5Cl; (b) $AcOH/H_2O_2$; (c) Ac_2O; (d) H_2O/4% NaOH; (e) $MnO_2/CHCl_3/H_2O$.

Table 1. ^1H NMR chemical shifts (ppm) and ^1H–^1H coupling constants (Hz) of compounds **9**–**15** and **5**

Comp.	Solvent	H2	H3	H4	H5	H6
9	$CDCl_3$	7.54 (m)	6.57 (m)	1.75 (CH_3)	6.57 (m)	7.54 (m)
10	$CDCl_3$	8.54 (m)	7.20 (m)	5.06 (CH_2) 2.10 (CH_3)	7.20 (m)	8.54 (m)
11	$CDCl_3$	8.26 (s)	2.30 (CH_3)	2.16 (d, CH_3) ^4J=0.5 Hz	7.15 (qd) $^3J_{5,6}$=5.0 Hz	8.30 (d)
12	$CDCl_3$	8.16 (d) $^4J_{2,6}$=1.9 Hz	n.o. (OH)	2.24 (d, CH_3) ^4J=0.9 Hz	7.05 (qd) $^3J_{5,6}$=6.3 Hz	7.73 (dd)
12	DMSO-d_6	7.71 (d) $^4J_{2,6}$=1.7 Hz	10.78 (OH)	2.08 (CH_3)	7.10 (d) $^3J_{5,6}$=6.3 Hz	7.67 (dd)
13	$CDCl_3$	8.17 (m)	7.31 (m)	4.71 (CH_2)	7.31 (m)	8.17 (m)
13	DMSO-d_6	8.15 (m)	7.36 (m)	4.47 (CH_2) 5.56 (OH)	7.36 (m)	8.15 (m)
14	$CDCl_3$	8.41 (s)	2.33 (CH_3)	5.08 (CH_2) 2.11 (CH_3)	7.38 (d) $^3J_{5,6}$=4.8 Hz	8.48 (d)
15	DMSO-d_6	8.03 (s)	9.80 (OH)	4.47 (CH_2) 5.25 (OH)	7.21 (d) $^3J_{5,6}$=4.7 Hz	7.90 (d)
5	$CDCl_3$	8.56 (s)	10.03 (OH)	10.05 (d, CHO) $^4J_{H5,CHO}$=0.5 Hz	7.45 (dd) $^3J_{5,6}$=4.9 Hz	8.40 (d)

bases of *o*-hydroxy-benzaldehydes (salicylaldehydes, Scheme 4) has appeared.[15] Rather than of aniline derivatives, they are the methylimines **16**–**18**. Selecting conveniently the substituent of the aromatic part, the authors have almost pure hydroxy/imino **16m**, and depending on the temperature, mixtures of both tautomers **17m/17o** rich in **17m** and mixtures of both tautomers **18m/18o** rich in **18o**. Our data (for instance those of **7a**) are very similar to those of their hydroxy/imino tautomer **16m** and very different to those of their oxo/enamino tautomer **18o**.[16]

To prove, without ambiguity, that compound **7c** has the hydroxy/imino structure with the *E*-configuration (**7cm**) and the O–H···N IMHB (intramolecular hydrogen bond) we have recorded its NOESY spectra, the results obtained clearly establish this structure in solution:



7cm

The ^1H chemical shifts of Table 3 can be compared with

Table 2. ^{13}C NMR chemical shifts (ppm) and ^{1}H–^{13}C coupling constants (Hz), ^{15}N NMR chemical shifts (ppm) and ^{17}O chemical shifts of compounds **9–15** and **5**

Comp.	Solvent	C2	C3	C4	C5	C6	C4′(R4)	CH_3	CO	^{15}N	^{17}O
9	$CDCl_3$	137.3 $^{1}J=187.2$	125.7 $^{1}J=162.0$ Hz	136.5	125.7	137.3	19.9 $^{1}J=128.3$	—	—	−95.0	319.0 (NO)
10	$CDCl_3$	149.7 $^{1}J=178.2$ $^{3}J=11.9$	121.8 $^{1}J=162.7$ Hz $^{3}J=8.6$ Hz	144.9 $^{2}J=^{3}J_{CH_2}=4.4$	121.8	149.7	64.1 (CH_2) $^{1}J=148.1$ $^{3}J=4.0$	20.6 $^{1}J=129.8$	170.3	−71.5	163.4 (–O–) 362.4 (–CO–)
11	$CDCl_3$	143.0 $^{1}J=181.4$ $^{3}J=11.7$	146.5	140.0 $^{3}J_{CH_3}=6.9$	125.8 $^{1}J=162.5$	146.3 $^{1}J=179.3$ $^{3}J=12.2$ $^{2}J=2.6$	15.6 (CH_3) $^{1}J=128.6$ $^{3}J=4.5$	20.4 $^{1}J=130.4$	168.9 $^{2}J=6.9$	−77.1	189.5 (–O–) 371.8 (–CO–)
12	DMSO-d_6	126.2 $^{1}J=183.8$ $^{3}J=3.9$	153.9 $^{3}J=10.4$ Hz $^{3}J_{CH_2}=4.0$ Hz	124.7 $^{3}J=^{3}J=6.1$ $^{2}J_{CH_3}=6.1$	126.9 $^{1}J=164.3$ $^{2}J=^{3}J_{CH_3}=5.0$	130.0 $^{1}J=188.6$	14.5 (CH_3) $^{1}J=128.3$ $^{3}J=4.6$	—	—	−91.9	
13	DMSO-d_6	138.3 $^{1}J=188.9$	124.0 $^{1}J=162.5$ Hz	141.0	124.0 $^{1}J=162.5$	138.3 $^{1}J=188.9$	60.9 (CH_2) $^{1}J=141.9$ $^{3}J=3.5$			−90.4	
14	$CDCl_3$	143.8 $^{1}J=182.9$ $^{3}J=11.4$	144.7	136.9	122.7 $^{1}J=165.0$ $^{2}J=8.2$ $^{3}J_{CH_2}=3.6$	146.9 $^{1}J=180.6$ $^{3}J=12.3$	59.5 (CH_2) $^{1}J=149.5$ $^{3}J=3.9$	20.23 $^{1}J=127.6$ 20.18 $^{1}J=124.8$	168.2(3) $^{2}J_{CH_3}=7.2$ 169.8(4) $^{2}J_{CH_3}=7.2$ $^{3}J_{CH_2}=3.0$	−66.7	188.8 (–O-3) 159.3 (–O-4) 371.1(–CO-3) 362.4 (–CO-4)
15	DMSO-d_6	147.0	162.4	146.7	130.9	149.0	67.6 (CH_2)				
5	$CDCl_3$	142.3 $^{1}J=186.6$ $^{3}J=11.1$	154.5	123.8 $^{2}J=21.4$ $^{3}J=6.7$ $^{3}J=4.4$	123.7 $^{1}J=162.5$ $^{3}J=9.5$	141.3 $^{1}J=183.6$ $^{3}J=11.8$	196.9 (CHO) $^{1}J=181.0$ $^{3}J=6.2$	—	—	−44.8	72.5 (–OH) 547.3 (–CHO)

Table 3. ^{1}H NMR chemical shifts (ppm) and ^{1}H–^{1}H coupling constants (Hz) of compounds **7a–7f**

Comp.	CH=N	H2	H5	H6	H2′/6′	H3′/5′	H4′	OH/R
7a[a]	8.65 (s)	8.52 (s)	7.28 (d) $^3J_{5,6}$=4.8 Hz	8.27 (d)	7.33 (m)	7.46 (m)	7.35 (m)	12.76 (s, br)
7b[a]	8.64 (s)	8.50 (s)	7.24–7.26	8.25 (d) $^3J_{5,6}$=4.6 Hz	7.24–7.26		—	12.90 (s, br) 2.40 (CH_3)
7b[b]	8.84 (s)	8.36 (s)	7.36 (d) $^3J_{5,6}$=4.9 Hz	8.17 (d)	7.33 (m)	7.26 (m)	—	12.71 (s) 2.37 (CH_3)
7c[a]	8.55 (s)	8.42 (s)	7.17 (d) $^3J_{5,6}$=4.8 Hz	8.17 (d)	7.26 (m)	6.90 (m)	—	12.87 (s) 3.78 (OCH_3)
7c[b]	8.82 (s)	8.34 (s)	7.33 (d) $^3J_{5,6}$=4.9 Hz	8.16 (d)	7.42 (m)	6.99 (m)	—	12.79 (s) 3.81 (OCH_3)
7d[a]	8.63 (s)	8.52 (s)	7.28 (d) $^3J_{5,6}$=4.9 Hz	8.28 (d)	7.20 (m)	7.59 (m)	—	12.50 (s, br)
7e[a]	8.60 (s)	8.50 (s)	7.24 (d) $^3J_{5,6}$=4.9 Hz	8.26 (d)	7.25 (m)	7.41 (m)	—	12.50 (s, br)
7f[a]	8.67 (s)	8.57 (s)	7.34 (d) $^3J_{5,6}$=5.0 Hz	8.33 (d)	7.37 (m)	8.35 (m)	—	12.06 (s, br)
7f[c]	8.85 (s)	8.45 (s)	7.49 (d) $^3J_{5,6}$=4.9 Hz	8.27 (d)	7.56 (m)	8.32 (m)	—	12.15 (s, br)
7f[d]	9.08 (s)	8.44 (s)	7.60 (d) $^3J_{5,6}$=4.9 Hz	8.28 (d)	7.72 (m)	8.38 (m)	—	12.12 (s)

[a] $CDCl_3$.
[b] THF-d_8.
[c] CD_3CN.
[d] CD_3COCD_3.

Hammett σ_p of the seven substituents (H 0.00, CH_3 −0.17, OCH_3 −0.27, Br +0.23, Cl +0.23, NO_2 +0.78),[17] the aim being less to show that linear correlation exist that to determine how far the effect of R is perceived by the molecule.

CH=N, range 0.12 ppm, slope=0.06
H2, range 0.15 ppm, slope=0.10
H5, range 0.17 ppm, slope=0.12
H6, range 0.16 ppm, slope=0.12
H2′/6′, range 0.20 ppm, slope=0.08
H3′/5′, range 1.45 ppm, slope=1.23
OH, range 0.84 ppm, slope=−0.83

As can be seen, range and slope are roughly proportional. The most sensitive signals are H3′/5′ (*ortho* to R) and that of the OH (note that it is the only one with a negative slope). We have represented this last case below (Fig. 1).

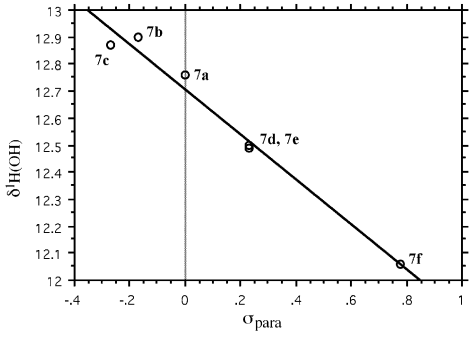


Figure 1. Plot of δ^1H(OH) vs. σ_p.

This sign change shows that the variation of δ_{OH} is not a direct electronic effect, as in the other signals, but the consequence of the modification of the hydrogen bond strength. It is stronger for **7c** (12.87 ppm) than for **7f** (12.06 ppm) probably because the iminic nitrogen is more basic in the *p*-methoxy than in the *p*-nitro derivative.

The only ^{13}C chemical shifts (Table 4, values in $CDCl_3$ except for **7f** in CD_3CN by reasons of solubility) that show acceptable correlations with σ_p is CH=N. On the other hand, both nitrogen atoms and the OH oxygen are correlated with σ_p. Even ^{17}O (Table 4) and ^{1}H (Table 3) for the OH are correlated. We have reported the values to those of the R=H derivative (**7a**, σ_p=0.00):

$$\delta^{13}\mathrm{C(CH=N)} = (6.9\pm1.0)\sigma_p,\quad n=6,\quad r^2=0.90 \qquad (1)$$

$$\delta^{15}\mathrm{N(CH=N)} = -(8.3\pm3.3)\sigma_p,\quad n=6,\quad r^2=0.56 \qquad (2)$$

$$\delta^{15}\mathrm{N(N1)} = (7.0\pm0.7)\sigma_p,\quad n=6,\quad r^2=0.95 \qquad (3)$$

$$\delta^{17}\mathrm{O(OH)} = -(5.8\pm0.1)\sigma_p,\quad n=6,\quad r^2=0.997 \qquad (4)$$

$$\delta^{17}\mathrm{O(OH)} = -(6.3\pm0.7)\delta^1\mathrm{H(OH)},\quad n=6,\quad r^2=0.997 \qquad (5)$$

We interpret the sensitivity of the OH group signals to the nature of *R* (as measured by σ_p) as an indication of slight tautomeric changes between the hydroxy/imino and the oxo/enamino forms.

The ^{13}C chemical shifts were measured in the solid state by the CPMAS NMR technique. The signals of the pyridine part (C1–C6 and CH=N) do not show any anomaly indicating that the structure of the solid is the same as that in solution, i.e. hydroxy/imino. Some carbons of the phenyl moiety show splittings: C2′/6′ and 4-CH_3 of **7b**, C3′/5′ of **7d**, C4′ of **7e**, and C2′/6′ of **7f** (the small splitting, 0.03 ppm, of C2 in **7e** is probably due to the ^{14}N linked to it). The pairs C2′/6′ and C3′/5′ are not equivalent in the solid state due to the IMHB that prevents free rotation about the N–C1′ bond. The

Table 4. ^{13}C NMR chemical shifts (ppm) and ^{1}H–^{13}C coupling constants (Hz), ^{15}N NMR chemical shifts (ppm) and ^{17}O chemical shifts of compounds **7a–7f**

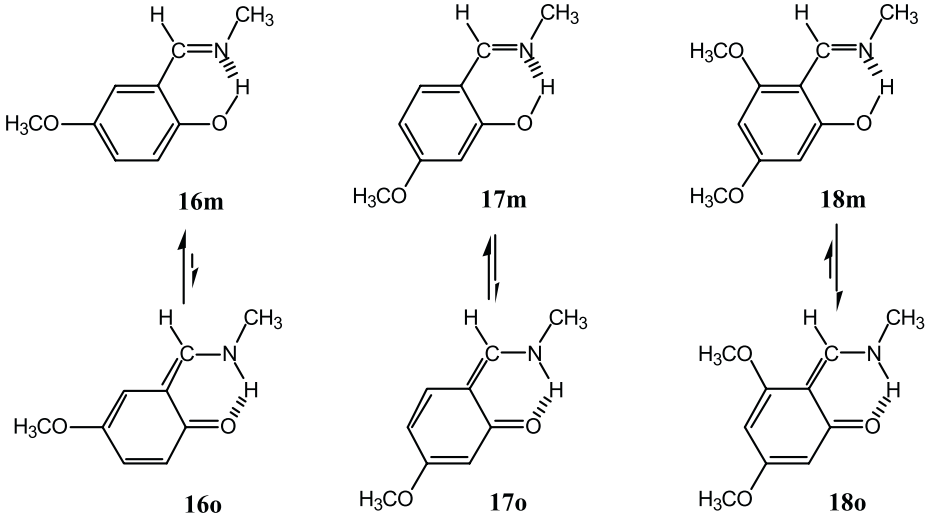
Comp.	C2	C3	C4	C5	C6	CH=N	C1′
7a[a]	141.2 $^{1}J=180.8$ $^{3}J=10.3$	155.1	123.6	123.6 $^{1}J=161.0$ $^{3}J=9.2$	140.3 $^{1}J=179.9$ $^{3}J=11.0$	160.9 $^{1}J=163.6$ $^{3}J=6.2$	147.6 $^{3}J=^{3}J=^{3}J=8.7$
7a[b]	142.3	155.4	123.5	124.6	140.4	159.9	144.7
7b[a]	140.9 $^{1}J=180.8$ $^{3}J=11.1$	155.1 $^{3}J=^{3}J=^{2}J=7.3$	123.6	123.4 $^{1}J=161.0$ $^{3}J=9.2$	140.2 $^{1}J=181.5$ $^{3}J=11.4$	159.6 $^{1}J=163.4$ $^{3}J=6.3$	144.8 $^{3}J=^{3}J=^{3}J=7.3$
7b[b]	140.5	154.7	123.8	125.0	138.1	156.6	144.0
7b[c]	141.8 $^{1}J=181.4$	156.3	124.8	124.5 $^{1}J=161.3$ $^{3}J=8.9$	141.4 $^{1}J=180.3$ $^{3}J=11.4$	162.2 $^{1}J=165.5$ $^{3}J=5.9$	146.6
7c[a]	141.1 $^{1}J=181.0$ $^{3}J=^{3}J=9.3$	155.1	123.8	123.4 $^{1}J=160.7$ $^{3}J=9.0$	140.4 $^{1}J=182.3$ $^{3}J=11.9$	158.2 $^{1}J=163.1$ $^{3}J=6.2$	140.4
7c[b]	141.8	154.8	123.8	127.6	139.7	161.4	141.6
7c[c]	141.7 $^{1}J=180.4$ $^{3}J=10.4$ $^{3}J=7.4$	156.2	125.0	124.4 $^{1}J=160.1$ $^{3}J=10.4$	141.3 $^{1}J=181.1$ $^{3}J=12.8$	160.4 $^{1}J=165.3$ $^{3}J=5.7$	141.8
7d[a]	141.2 $^{1}J=181.8$ $^{3}J=10.3$	154.9	123.3	123.6 $^{1}J=161.0$ $^{3}J=10.1$	140.4 $^{1}J=182.0$ $^{3}J=10.7$	161.3 $^{1}J=163.6$ $^{3}J=6.2$	146.5 $^{3}J=^{3}J=^{3}J=8.3$
7d[b]	143.4	154.9	123.1	126.9	138.7	155.6	143.4
7e[a]	141.0 $^{1}J=181.1$ $^{3}J=10.7$ $^{3}J=5.8$	154.8	123.2	123.5 $^{1}J=161.1$ $^{3}J=9.1$	140.3 $^{1}J=182.6$ $^{3}J=12.5$	161.1 $^{1}J=163.7$ $^{3}J=6.2$	145.8 $^{3}J=^{3}J=^{3}J=8.8$
7e[b]	139.6 139.9	155.7	124.1	122.2	138.9	158.9	142.5
7f[b]	140.6	155.0	124.0	124.0	138.0	164.4	155.0
7f[d]	141.8 $^{1}J=181.7$ $^{3}J=10.2$	155.9 $^{3}J=^{3}J=4.9$	124.6	125.8 $^{1}J=163.6$ $^{3}J=9.9$	141.7 $^{1}J=182.0$ $^{3}J=10.1$	166.8 $^{1}J=168.2$ $^{3}J=5.9$	154.5 $^{3}J=8.1$

Comp.	C2′/6′	C3′/5′	C4′	R	CH=N	N1	OH
7a[a]	121.2 $^{1}J=160.4$ $^{3}J=6.2$ $^{4}J=5.5$	129.5 $^{1}J=161.8$ $^{3}J=8.0$	128.0 $^{1}J=163.0$ $^{3}J=^{3}J=7.6$	—	−67.5	−56.6	86.0
7a[b]	114.6	130.8	129.6	—	—	—	—
7b[a]	121.1 $^{1}J=159.6$ $^{3}J=4.1$	130.1 $^{1}J=158.3$ $^{3}J=^{3}J=5.0$	138.3 $^{3}J=^{2}J=6.5$	21.0 (CH_3) $^{1}J=126.6$ $^{3}J=^{3}J=3.6$	−69.1	−57.7	87.0
7b[b]	117.4 113.0	129.1	140.8	21.3 20.0	—	—	—
7b[c]	122.4 $^{1}J=159.8$ $^{3}J=5.4$	131.0 $^{1}J=158.1$ $^{3}J=^{3}J=5.4$	139.0 $^{2}J=6.7$	21.3 (CH_3) $^{1}J=127.0$ $^{3}J=^{3}J=4.3$	−73.8	−53.5	—
7c[a]	122.7 $^{1}J=159.3$ $^{3}J=6.2$	114.8 $^{1}J=160.3$ $^{3}J=5.2$	159.8	55.6(OCH_3) $^{1}J=144.1$	−70.5	−57.5	87.8
7c[b]	119.0	111.7	160.0	56.4	−69.4	−45.1	—
7c[c]	123.8 $^{1}J=159.5$ $^{3}J=6.1$	115.6 $^{1}J=160.3$ $^{3}J=5.2$	161.2	55.9(OCH_3) $^{1}J=143.7$	−73.0	−50.8	
7d[a]	122.8 $^{1}J=161.6$ $^{3}J=5.8$	132.6 $^{1}J=167.2$ $^{3}J=6.0$	121.7 $^{3}J=^{3}J=9.8$	—	−71.4	−55.0	84.7
7d[b]	117.3	131.8 128.8	139.0 128.5 119.0 113.5	—	−80.5	n.o.	—
7e[a]	122.4 $^{1}J=163.2$ $^{3}J=5.8$	129.5 $^{1}J=167.6$ $^{3}J=5.4$	133.6 $^{3}J=^{3}J=10.1$ $^{2}J=^{2}J=3.2$	—	−70.6	−55.8	84.8
7e[b]	116.7	129.5	136.7 132.4	—	—	—	—
7f[b]	119.7 117.1	127.2	145.4	—	—	—	

Table 4 (*continued*)

Comp.	C2′/6′	C3′/5′	C4′	R	CH=N	N1	OH
7f[d]	123.6 ^1J=166.4 ^3J=5.7	126.2 ^1J=169.9 ^3J=4.6	147.8	—	−75.5	−50.5	—

[a] $CDCl_3$.
[b] Solid.
[c] THF-d_8.
[d] CD_3CN.



Scheme 4.

splitting of C4′ in **7d** and **7e** are due to the quadrupolar bromine and chlorine nuclei.[18,19] The only surprising result is the splitting of the methyl group in **7b**, that could be indicative of the presence of two independent molecules in the crystal asymmetric unit. It is noteworthy that the signal corresponding to C2′/6′ always appears about 5 ppm upfield in the solid state than in solution.

The NMR data of the azine **8** are reported in the experimental part. This compound exists in the *E*-bis-hydroxy/imino form; the most noticeable difference with respect to the Schiff bases **7** is the ^{15}N signal of the CH=N group (−19.7 ppm), because now it is linked to a second nitrogen atom.

2.1. Electronic spectra

The principal bands of compounds **5**, **7a–7f** and **8** in acetonitrile (absorption at <190 nm) are reported in Table 5. The bands do not correspond to any precise classification of the transitions involved, but to a simple homology. In the case of the Schiff bases **7**, the six bands of Table 5 are rather artificial because the maximum is very flat, being resolved into several peaks in some cases while in others they cannot be distinguished.

The UV spectrum of compound **5** has been described by Nakamoto and Martell using dioxane as solvent with very similar results (237 and 330 nm).[20] The starting anilines **6** have two main bands; the absorption frequencies of band 3 are roughly correlated with Hammett σ_p.[17] The Schiff bases **7** have a more complex structure. There are correlations between their bands 5 and 6, which seem to be related to the pyridine chromophore and between their band 3 and the corresponding band in anilines (Eq. (6)):

$$\text{Band 3}: \ \lambda_{max}(\mathbf{7}) = (379 \pm 6) - (0.48 \pm 0.03)[\lambda_{max}(\mathbf{6})], \quad n = 4, \quad r^2 = 0.994 \tag{6}$$

2.2. Theoretical calculations

As shown in Table 6, we have calculated by using DFT calculations at the B3LYP/6-31G** level, the three compounds of Scheme 4 (**16–18**: two tautomers, hydroxy/imino **m** and oxo/enamino **o**) as well as the four structures of Scheme 5 for the six compounds, **7a–7f** in their four structures: the hydroxy/imino *E* (with an IMHB) **m**, the hydroxy/imino *Z* **n**, the oxo/enamino (with an IMHB) **o** and the betaine **p**.

It is clear that the only structure present in the gas phase should be **7_m** (**7am**, **7bm**, **7cm**, **7dm**, **7em** and **7fm**). Taking into account the ZPE correction, the following one

Table 5. Electronic spectra in CH_3CN of compounds **5**, **6a–6f**, **7a–7f** and **8** [λ_{max} in nm, (log ε)]

Comp.	Band 1	Band 2	Band 3	Band 4	Band 5	Band 6
5		237.0 (3.79)			329.0 (3.55)	
6a			238.0 (4.07)	288.0 (3.35)		
6b			241.5 (3.98)	295.5 (3.26)		
6c			240.0 (3.98)	307.0 (3.38)		
6d			247.5 (4.14)	291.5 (3.62)		
6e			248.0 (4.02)	289.5 (3.64)		
6f	231.0 (3.74)		275.5 (4.01)	363.5 (4.09)		
7a	218.0 (4.19)		265.5 (4.04)			336.0 (3.84)
7b	222.0 (4.37)	241.0 (4.03)	263.5 (3.97)	293.5 (3.99)	329.0 (4.04)	344.0 (4.05)
7c	223.0 (4.23)				335.5 (4.15)	352.0 sh (4.19)
7d	223.5 (4.26)		261.0 (4.04)	289.5 (4.01)	330.0 (4.02)	343.4 (4.00)
7e	222.5 (4.33)		260.5 (4.03)		330.0 (4.09)	344.4 (4.04)
7f	219.5 sh (4.16)		285.5 (3.89)		354.5 (4.21)	
8	216.5 (4.30)			280.5 (4.44)		355.5 (4.06)

Table 6. Absolute energies (Hartree) and relative energies (kJ mol^{-1}) of the four structures

Comp.	R	Code		**7_m**	**7_n**	**7_o**	**7_p**
7a	H	**7am/n/o/p**		−648.0359 (0.0)	71.3	22.1	77.4
			+ZPE	−647.8395 (0.0)	69.8	20.5	77.0
7b	CH_3	**7bm/n/o/p**		−687.3571 (0.0)	72.0	22.1	78.1
			+ZPE	−687.1334 (0.0)	70.6	20.3	77.9
7c	OCH_3	**7cm/n/o/p**		−762.5614 (0.0)	73.6	23.6	78.1
			+ZPE	−762.3324 (0.0)	72.1	22.4	78.3
7d	Br	**7dm/n/o/p**		−3221.3147 (0.0)	70.1	23.9	74.0
			+ZPE	−3221.1286 (0.0)	68.5	22.1	73.6
7e	Cl	**7em/n/o/p**		−1107.6300 (0.0)	70.3	24.0	74.2
			+ZPE	−1107.4431 (0.0)	68.8	22.2	73.9
7f	NO_2	**7fm/n/o/p**		−852.5349 (0.0)	66.4	23.6	69.1
			+ZPE	−852.3360 (0.0)	65.0	22.0	68.9

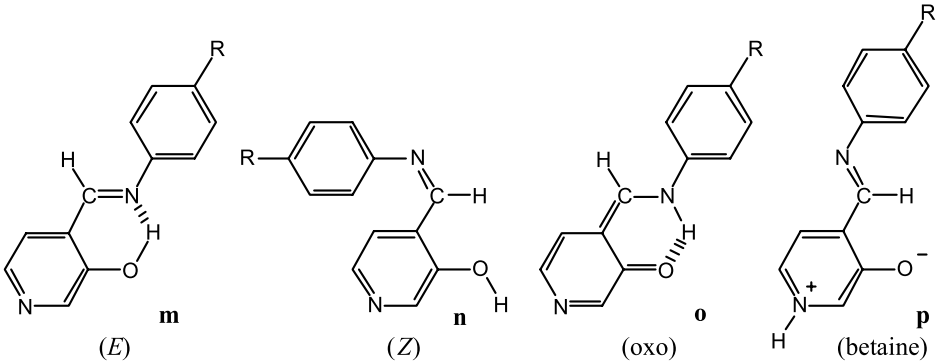
in stability is the oxo tautomer **7_o**, which lies about 20–22 kJ mol^{-1} higher. The two other forms can be neglected (65–80 kJ mol^{-1} higher than **7_m**). There is no clear correlation with the effect of the *para*-substituent (as defined by σ_p) but in any case, the difference in stability between tautomers **m** and **o** is rather insensitive to the nature of the substituent (the same value, 23.6 kJ mol^{-1} is found for OCH_3 and NO_2, see Table 6).

Schilf et al.[15] reported the percentages of hydroxy **m** and oxo (or NH) tautomers **o** at low temperature (about 218 K) and at room temperature (303 K). Their data at room temperature are **16** 97% of OH/3% of NH (estimated by us), **17** 85% of OH/15% of NH, **18** 50% of OH/50% of NH. They correspond to the following equilibrium constants and ΔG_{303} in kJ mol^{-1}: **16** 32.3, 8.76; **17** 5.7, 4.37 and **18** 1.0, 0.00. Our calculations carried out at the same level and including ZPE are: **16** 18.04, **17** 13.64 and **18** 8.40 kJ mol^{-1}. Although the calculations do not reproduce the experimental results (gas phase vs. chloroform solution) they are proportional (Eq. (7)):

$$\Delta G_{303} = (7.7 \pm 0.6) - (0.91 \pm 0.05)\Delta G + ZPE,$$

$$n = 3, \quad r^2 = 0.997 \tag{7}$$

Using Eq. (7) it is possible to transform the ΔG+ZPE of Table 6 into ΔG_{corr}, and from ΔG_{corr} and $T=303$, to calculate the equilibrium constant K and the percentage of the OH tautomer: R=H, **7am** 98.7%, R=CH_3 **7bm** 98.6%, R=OCH_3 **7cm** 99.3%, R=Br **7dm** 99.3%, R=Cl **7em** 99.3% and R=NO_2 **7fm** 99.2%.



Scheme 5.

3. Conclusions

NMR spectroscopy has proved to be a valuable tool to investigate the tautomerism in Schiff bases derived from 3-hydroxy-4-pyridinecarboxaldehyde (**5**) and six different anilines. On the other hand, UV spectroscopy is not such a valuable tool. All compounds have the neutral hydroxy/imino structure with the *E* configuration with intramolecular hydrogen bond between the hydroxyl group OH and the imine N=C nitrogen. The electronic nature of the *para*-substituent on the phenyl group bonded to the imine nitrogen does not significantly affect the tautomeric equilibria. Further studies on protonation and/or complexation effects able to modify the tautomeric equilibrium are needed to contribute to the PL or PLP Schiff bases understanding.

4. Experimental

4.1. General procedures

Melting points were determined both under microscope (Axiolab 'Zeiss' with a TMS 92 LINKAN heating stage) and by DSC on a SEIKO DSC 220C connected to a Model SSC5200H Disk Station. Thermograms (sample size 0.003–0.010 g) were recorded at the scanning rate of 2.0 °C min^{-1}. Unless otherwise stated, column chromatography was performed on silica gel (Merck 60, 70–230 mesh). Compounds **7** have been fully characterized by electrospray mass spectrometry.[21] Elemental analyses were performed using Perkin–Elmer 240 by 'Centro de Microanálisis Elemental-UCM, Madrid'. Room-temperature absorption spectra were obtained with a Shimadzu UV-2501PC spectrometer in CH_3CN Merck Uvasol grade.

4.2. DFT calculations

The optimization of the structures of all compounds discussed in this paper was carried out at the hybrid B3LYP/6-31G** level[22,23] with basis sets of Gaussian type functions using Spartan 2002 for Windows.[24]

4.3. NMR parameters

(400.13 MHz), ^{13}C (100.61 MHz), ^{15}N (40.56 MHz) and ^{17}O NMR (54.26 MHz) spectra in solution were obtained with a *Bruker DRX-400* instrument, with a 5-mm inverse-detection H-X probe equipped with a gradient coil, at 300 K [$Cr(acac)_3$ was not used in any experiment]. Chemical shifts (δ in ppm) are given from solvent $CDCl_3$ 7.26 for ^1H and 77.0 for ^{13}C, DMSO-d_6 2.49 for ^1H and 39.5 for ^{13}C, CD_3CN 1.38 for ^1H and 118.7.0 for ^{13}C, CD_3COCD_3 2.05 for ^1H and 29.9 for ^{13}C, THF-d_8 3.58 and 1.73 for ^1H and 67.6 and 25.4 for ^{13}C, external nitromethane (0.00) for ^{15}N NMR and external D_2O (0.00) for ^{17}O NMR. Coupling constants (J in Hz) are accurate to ± 0.2 Hz for ^1H and ± 0.6 Hz for ^{13}C. 2D-inverse-proton-detected homonuclear-shift-correlation spectra gs-COSY, and heteronuclear-shift-correlation spectra gs-HMQC and gs-HMBC were obtained with the standard pulse sequences.[25] Solid-state ^{13}C (100.73 MHz) CPMAS-NMR spectra have been obtained with a *Bruker WB-400* spectrometer at 300 K with a wide-bore 4-mm DVT probehead at rotational frequencies of ca. 12 kHz. Samples were carefully packed in ZrO_2 rotors, and the standard CPMAS pulse sequence and NQS technique (Non Quaternary Suppression to observe only the quaternary C-atoms) were employed.[25]

4.4. Synthesis of 3-hydroxy-4-pyridinecarboxaldehyde (5)

Compound **5** was prepared according to a literature procedure with similar yields in all steps,[9] but without inert atmosphere save in the last one going from **15** to **5**, where the reaction was carried out under Ar. Compound **5** was purified by crystallization mp = 123 °C (chloroform–hexane) and sublimation mp 117.8 °C, lit. mp = 112–123 °C.

4.4.1. Synthesis of Schiff bases 7. The compounds have been prepared by refluxing in toluene equimolar amounts of **5** and the corresponding aniline:

Compound **7a**. R = H, 7 h, 92% yield, mp 71.5 °C (microscope) and 72.4 °C (DSC). Anal. calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 71.67; H, 5.11; N, 13.83.

Compound **7b**. R = CH_3, 9 h, 72% yield, mp 87.5–92.5 (microscope) and 91.1 °C (DSC). Anal. calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.54; H, 5.72; N, 13.17.

Compound **7c**. R = OCH_3, 6.5 h, 88% yield, mp 97–98 °C (microscope) and 100.0 °C (DSC). Anal. calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.45; H, 5.36; N, 12.24.

Compound **7d**. R = Br, 5 h, 82% yield, mp 133–135 °C (microscope) and 133.6 °C (DSC). Anal. calcd for $C_{12}H_9N_2BrO$: C, 52.01; H, 3.27; N, 10.11. Found: C, 52.12; H, 3.32; N, 10.07.

Compound **7e**. R = Cl, 5.5 h, 78% yield, mp 106.5–108 °C (microscope) and 108.2 °C (DSC). Anal. calcd for $C_{12}H_9N_2ClO$: C, 61.95; H, 3.90; N, 12.04. Found: C, 62.03; H, 4.12; N, 11.73.

Compound **7f**. R = NO_2, 14 h, 75% yield, this compound melts at 181.1 °C with a phase transition at 121.0 °C (observed by DSC) Under the microscope, this compound changes its appearance at 148 °C and then at 183–184 °C decomposes. Anal. calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.14; H, 3.88; N, 17.03.

4.5. Synthesis of azine 8

This compound was prepared from **5** by treating it with hydrazine in EtOH at reflux for 2 h, 70% yield. Mp 261.7 °C decomposes (DSC); under the microscope the compound slowly changes its appearance until decomposition takes place at 286 °C. ^1H NMR (δ, ppm, solvent: DMSO-d_6): 8.37 (s, H2), 7.68 (d, H5, $^3J_{5,6}$ = 4.9 Hz), 8.17 (d, H6), 8.96 (s, CHz, N), 11.8 (s, OH). ^{13}C NMR (δ, ppm, solvent: DMSO-d_6): 140.0 (C2, ^1J = 179.5 Hz, ^3J = 11.1 Hz), 153.0 (C3), 124.6 (C4, $^3J = {}^3J$ = 7.4 Hz, ^2J = 4.1 Hz), 121.1 (C5, ^1J = 163.7 Hz, ^3J = 9.5 Hz, ^2J = 3.0 Hz), 140.5 (C6, ^1J = 181.6 Hz, ^3J = 11.3 Hz), 159.5 (CH=N, ^1J = 170.1 Hz). ^{15}N NMR (δ, ppm, solvent: DMSO-d_6): −51.4 (N1),

−18.7 (CH═N). Anal. calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 58.59; H, 4.23; N, 22.53.

Acknowledgements

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References and notes

1. Walsh, C. *Enzymatic Reaction Mechanism*; W.H. Freeman: San Francisco, CA, 1979; pp 777–833.
2. Metzler, D. E. *Biochemistry: The Chemical Reactions of Living Cells*; Academic: New York, 1977; pp 444–461.
3. Vederas, J. C.; Floss, H. G. *Acc. Chem. Res.* **1980**, *13*, 455.
4. Sun, S.; Toney, M. D. *Biochemistry* **1995**, *34*, 3362. Sun, S.; Toney, M. D. *Biochemistry* **1999**, *38*, 4058. Toney, M. D. *Biochemistry* **2001**, *40*, 1378.
5. Zabinski, R. F.; Toney, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 193.
6. Bach, R. D.; Canepa, C.; Glukhovtsev, M. N. *J. Am. Chem. Soc.* **1999**, *121*, 6542.
7. Salvà, A.; Donoso, J.; Frau, J.; Muñoz, F. *THEOCHEM* **2002**, *577*, 229.
8. Salvà, A.; Donoso, J.; Frau, J.; Muñoz, F. *J. Phys. Chem. A* **2003**, *107*, 9409.
9. O'Learly, M. H.; Payne, J. R. *J. Med. Chem.* **1971**, *14*, 773.
10. Gansow, O. A.; Holm, R. H. *Tetrahedron* **1968**, *24*, 4477.
11. Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Non-Metallic Elements*; Wiley: Chichester, 1997.
12. Alarcón, S. H.; Pagani, D.; Bacigalupo, J.; Olivieri, A. C. *J. Mol. Struct.* **1999**, *475*, 233.
13. Dziembowska, Z.; Rozwadowski, E.; Majewski, E.; Ambroziak, K. *Magn. Reson. Chem.* **2001**, *39*, 484.
14. Alarcón, S. H.; Olivieri, A. C.; Sanz, D.; Claramunt, R. M.; Elguero, J. *J. Mol. Struct.* **2004**, *705*, 1.
15. Schilf, W.; Bloxsidge, J. P.; Jones, J. R.; Lu, S.-Y. *Magn. Reson. Chem.* **2004**, *42*, 556 and references therein.
16. Compound **7a**: OH (^{1}H) = 12.76 ppm, PhN═CH (^{15}N) = −67.5 ppm. 5-Methoxy derivative (pure hydroxy/imino tautomer **16m**): OH (^{1}H) = 12.83 ppm, PhN═CH (^{15}N) = −87.7 ppm.[15] 4,6-Dimethoxy derivative (pure oxo/enamino tautomer **18o**): OH (^{1}H) = 14.05 ppm, PhN═CH (^{15}N) = −212.7 ppm.[15] The difference in ^{15}N chemical shifts between **7a** and **16m** (87.7–67.5 = 20.2 ppm) is very close to that between *N*-phenyl and *N*-methyl imines (20.9 ppm).[11]
17. Exner, O. The Hammett equation—the present position. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1972; pp 28–29.
18. Olivieri, A. C.; Elguero, J.; Sobrados, I.; Cabildo, P.; Claramunt, R. M. *J. Phys. Chem.* **1994**, *98*, 5207.
19. Claramunt, R. M.; López, C.; García, M. A.; Otero, M. D.; Torres, M. R.; Pinilla, E.; Alarcón, S. H.; Alkorta, I.; Elguero, J. *New J. Chem.* **2001**, *25*, 1061.
20. Nakamoto, K.; Martell, A. E. *J. Am. Chem. Soc.* **1959**, *81*, 5863.
21. Claramunt, R. M.; Sanz, D.; Perona, A.; Elguero, J.; Sanchez, P.; Enjalbal, C.; Martinez, J.; Aubagnac,. J.-L. Int. J. Mass Spectrom. **2005**, in press.
22. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200.
23. Hariharan, P. A.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
24. Spartan 2002 for Windows from Wavefunction Inc.
25. Braun, S.; Kalinowki, H.-O.; Berger, S. *150 and more Basic NMR Experiments*; Wiley-VCH: Weinheim, 1998.

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The preparation and some chemistry of 2,2-dimethyl-1,2-dihydroquinolines

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Abstract—The cyclisation of *N*-(1,1-dimethylpropargyl) anilines, using cuprous chloride in refluxing toluene, yields 6-substituted-2,2-dimethyl-1,2-dihydroquinolines. The reactivity of the double bond in the heterocyclic ring of these products is exemplified by chlorination, to yield 6-substituted-3,4-*cis*-dichloro-2,2-dimethyl-1,2,3,4-tetrahydroquinolines which can be selectively dechlorinated to provide 6-substituted-3-chloro-2,2-dimethyl-1,2,3,4-tetrahydroquinolines; epoxidation to yield an epoxide, which can be hydrogenolysed to the corresponding 3-hydroxy product and in turn oxidised to the 3-keto derivative; and oxymercuration to provide a 4-hydroxy product and hence a 4-keto derivative. Dehydrochlorination of a 3,4-dichloro product provides a 3-chloro-1,2-dihydroquinoline which can be hydrolysed to a 3-keto system. The formation of *cis* 3,4-dichloro products from the chlorination, as well as the formation of a *cis* chlorohydrin from the chlorination of *N*-acetyl-2,2,6-trimethyl-1,2-dihydroquinoline in partially aqueous solution, suggests that *N*-acetyl, or *N*-trifluoroacetyl groups, participate in the addition process.
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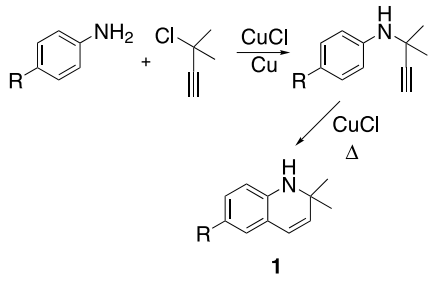
1. Introduction

The availability of 2,2-disubstituted-1,2-dihydroquinolines,[1–3] **1**, via the copper catalysed cyclisation of *N*-(1,1-substitutedpropargyl) anilines,[4,5] (Scheme 1) makes these compounds of interest as starting materials for the preparation of 2,2,3,4- and 2,2,3- or 2,2,4-substituted tetrahydroquinolines and related compounds. We have been interested for some time[3,6–9] in the development of general synthetic approaches to analogues of the antiviral compound Virantmycin,[10–16] **2**, and we were, as a consequence, particularly interested in methodology that would lead to 2,2-disubstituted-3-chlorotetrahydroquinolines. We have previously noted[5] that the size of the substituents attached to the carbon bearing the nitrogen atom affects the coupling of the amine to the acetylenic chloride (Scheme 1) such that when these groups are sufficiently bulky the coupling does not occur and for this reason we chose initially to investigate the chemistry of 2,2-dimethyl-1,2-dihydroquinolines in order to establish the range of reactions that these least sterically hindered 2,2-substituted-1,2-dihydroquinolines would undergo. Any addition reaction to the double bond that creates a 3-substituted product has also created a neopentyl system at the 3-position which has ramifications for substitutions at this position. Having established the chemistry of the dimethyl substituted dihydroquinolines we would then be in a position to evaluate how well these reactions would work when more bulky substituents, needed for the development of Virantmycin analogues, were present.



Scheme 1.

2. Results and discussion

Chlorination of the dihydroquinolines, **1**, was expected to be difficult to control as, at least in cases where an aromatic substituent that is electron donating is present, chlorination of both the double bond and the aromatic ring would be expected. Even the *N*-acetyl compound, **3**, gave the expected dichloro compound, **4**, together with some of the ring chlorinated material, **5**. Aromatic chlorination did not occur, however, when the N-protecting group was trifluoroacetyl rather than acetyl. Consequently a range of

Keywords: *N*-propargylanilines; Dihydroquinolines; Tetrahydroquinolines; Addition; Synthesis.
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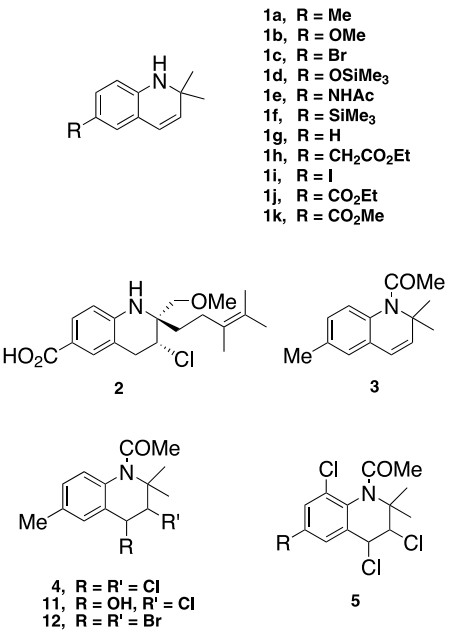
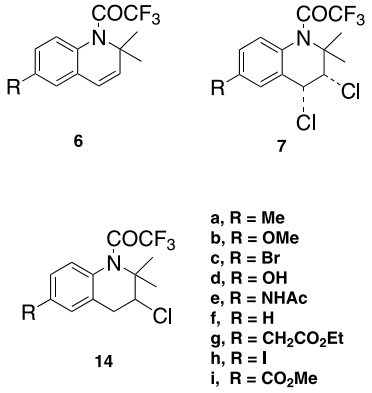
N-trifluoroacetyl derivatives, **6a**–**6h**, were prepared to investigate the reactivity of the dichloro compounds.

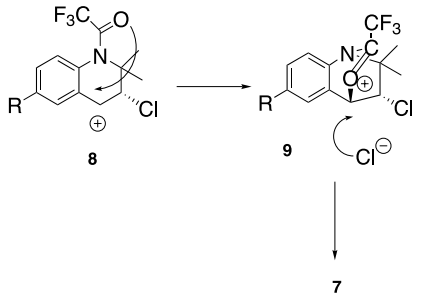


The ester-substituted dihydroquinoline, **1j**, cannot be N-protected due to the delocalisation of the lone electron pair on the nitrogen atom by the ester substituent. Attempts to chlorinate the dihydroquinoline double bond of the unprotected ester, **1j**, resulted in a complex mixture. However the iodo-substituted dihydroquinoline, **6h**, could be carbonylated to yield the methyl ester, **6i**, in moderate yield as well as a small amount of the deprotected compound, **1k**. This deprotection possibly involves methanolysis of the trifluoroacetamide facilitated by the triethylamine present in the reaction mixture.



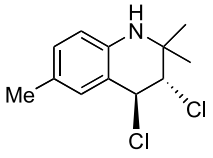
Chlorination of the *N*-trifluoroacetyldihydroquinolines **6a**–**6i** proceeded smoothly to give excellent yields of the 3,4-dichlorotetrahydroquinolines, **7a**–**7i**. The ^{1}H NMR spectra of the dichloro compounds showed two doublets at approximately δ 4.5 and 5.2, corresponding to the two methine hydrogens attached to chlorine-bearing carbon atoms. The coupling constants for these doublets were small, ranging from 4–6 Hz, suggesting *cis* stereochemistry. By the same criteria *cis* chlorination was also observed for the *N*-acetyl compound, **3**, and for its corresponding 6-methoxy substituted analogue.

This *cis* geometry of these dichlorotetrahydroquinolines, **7**, can be rationalised by invoking the participation of the N-protecting group, as shown in Scheme 2. The benzylic carbocation, **8**, and/or the corresponding chloronium ion, may be trapped by the carbonyl oxygen of the acyl group, giving the *trans*-intermediate, **9**, which is then attacked at the benzylic position by chloride ion to give the *cis*-product.



Scheme 2.

Support for this protecting-group participation explanation was provided by the chlorination, in acidic solution, of the unprotected dihydroquinoline, **1a**, which gave a dichloro product, **10**, whose coupling constant, $J_{3,4}$, was 9.2 Hz, typical of that expected for a *trans* product and showing that in the absence of the protecting group the chlorination proceeds via the expected chloronium ion mechanism.

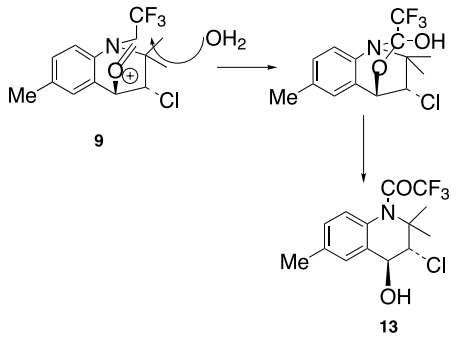


The dichloro compounds, **7**, were, in general, unstable and were used as soon as they had been isolated. The *N*-acetyldichloro compound, **4**, slowly crystallised on standing exposed to the atmosphere. Recrystallisation of this material gave the alcohol, **11**, whose structure, and the *trans* geometry of the chlorine and hydroxyl groups in the heterocyclic ring, were confirmed by an X-ray crystal structure determination.[17] In the solid state the heterocyclic ring is in a twist boat conformation. Such a conformation in solution would facilitate substitution of the benzylic chlorine by the carbonyl oxygen of either the acetyl or the trifluoroacetyl group. The coupling constant, $J_{3,4}$, was 9.7 Hz for the *trans* chlorohydrin, **11**, a value which is very similar to that of the *trans* dichloride, **10**, but considerably higher than the coupling constants of the *cis* dichlorides, **7**.

Bromination of the *N*-acetyl dihydroquinoline, **3**, gave an unstable dibromo compound, **12**, in high yield. A coupling constant of 3.9 Hz for the H3 and H4 doublets suggested that *cis*-addition had also occurred with bromine.

The facile conversion of the dichloride, **4**, to the chlorohydrin, **11**, prompted an examination of the chlorination in partially aqueous solvents. When the chlorination

of **3** was conducted in a tetrahydrofuran/water mixture the chlorohydrin, **11**, was produced in 96% yield. The *N*-trifluoroacetyl compound, **6a**, gave only a 36% yield of the corresponding chlorohydrin, **13**, under these conditions but the *cis*-3,4-dichloro compound, **7a**, was also obtained in a 47% yield. The *trans* geometry of the chlorohydrins, **11** and **13**, can either arise from the displacement of the benzylic chlorine in the *cis* dichloride or from attack on the intermediate, **9**, as shown in Scheme 3.

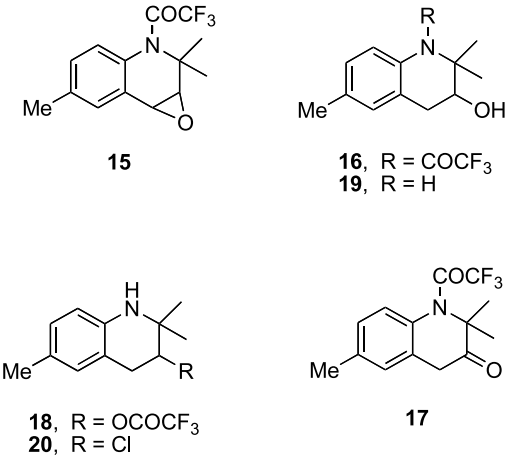


Scheme 3.

Treatment of the dichloro compounds, **7**, with zinc-modified cyanoborohydride[18] gave the corresponding 3-chlorotetrahydroquinolines, **14**, in moderate to excellent yields. The nature of the aromatic substituent was found to affect the rate of dechlorination, with electron-withdrawing substituents such as bromo, iodo and ester groups slowing the reaction to such an extent that only 50% conversion was observed after 10–12 days reaction time. Two doublet of doublets in the region δ 3.0–3.2, both with a large geminal coupling constant (15–16 Hz) and a smaller vicinal coupling constant (3–6 Hz), and a third doublet of doublets, at approximately δ 4.2, with two small vicinal coupling constants confirmed the removal of the benzylic chlorine in these products.

Epoxidation of the double bond of **6a**, to yield the epoxide **15**, was achieved using *meta*-chloroperoxybenzoic acid. Hydrogenolysis of the epoxide provided the alcohol, **16**, in good yield. The ^{1}H NMR spectrum of **16** resembled that of the related 3-chloro system, **14a**.

Oxidation of the alcohol, **16**, to the ketone, **17**, proceeded smoothly using Jones reagent. However, the ^{1}H NMR spectrum of the ketone did not show the expected sharp signals for the geminal dimethyl groups or the hydrogens of the benzylic methylene group, but rather four very broad singlets at δ 1.3, 1.7, 3.3 and 3.8, respectively, suggesting that a ring flipping process of the heterocyclic ring was creating two separate magnetic environments for the hydrogens attached to it, causing the broadening observed at room temperature. Heating the NMR sample to 50 °C saw coalescence of the two pairs of broadened signals to single resonances at δ 1.51 and 3.58, assigned to the hydrogens of the geminal dimethyl groups and the benzylic methylene group respectively. Cooling the sample to 0 °C caused all signals to sharpen considerably with the signals for the hydrogens of the two geminal dimethyl groups now appearing as two sharp singlets at δ 1.34 and 1.70, while the diastereotopic hydrogens of the benzylic methylene group were now well-defined doublets at δ 3.36 and 3.87. The signal for H5 was at δ 7.11.

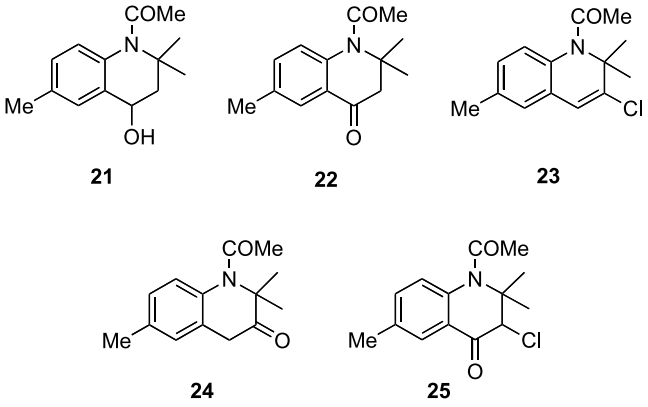


The alcohol, **16**, was subjected to Mitsunobu conditions in attempts to introduce a halogen atom into the 3-position. However using zinc chloride and tetrabutylammonium bromide or chloride as the halide source produced only the trifluoroacetate, **18**, presumably formed via trifluoroacetyl group transfer from the nitrogen atom to the oxygen atom. TLC and ^{1}H NMR of a sample of the alcohol, **16**, that had been standing for a few weeks revealed that the trifluoroacetyl transfer from the nitrogen atom to the oxygen atom is a relatively facile process as it also occurs on standing. Hydrolysis of the trifluoroacetate, **18**, using 10% methanolic potassium bicarbonate, provided the aminoalcohol, **19**. Treatment of this aminoalcohol with thionyl chloride[13] gave only an intractable product mixture as evidenced by tlc and ^{1}H NMR in which signals for the expected chloro compound could not be detected.

Direct S_N2 displacement of the trifluoroacetyl moiety of **18** with chloride ion (using tetrabutylammonium chloride as the chloride source) was very slow and the 3-chloroquinoline product, **20**, was unable to be separated from the starting trifluoroacetate. Evidence for the presence of the chloro compound, **20**, was seen in the ^{1}H NMR of the crude mixture. Two doublet of doublets were observed at δ 5.10 and 4.08, assigned to the methine hydrogen atoms of the trifluoroacetate, **18**, and the monochloride, **20**, respectively. A mass spectrum of the mixture showed molecular ions for both the trifluoroacetate, **18**, (*m*/*z* 287) and the chloro compound, **20**, (*m*/*z* 209/211).

It was also of interest to establish whether the double bond in the heterocyclic ring of the dihydroquinoline systems could undergo hydration and, if so, which carbon of the double bond was functionalised. Hydroboration of **3** gave a mixture of the *N*-ethyldihydroquinoline from reduction of the amide together with starting material. Hydroboration of the unprotected amine, **1a**, with excess diborane was unsuccesful with starting material being recovered. Oxymercuration of **3** gave a poor yield of an alcohol, **21**, whose NMR spectrum was quite different to that of the alcohol, **16**. In particular, the benzylic methylene hydrogens of **16** occur as two doublet of doublets at δ 2.82 and 2.94, with both

showing a vicinal and a geminal coupling, whereas the methylene signals of **21** were less deshielded and appeared as a multiplet in the region δ 2.1–2.4. The structure of this alcohol was confirmed by its oxidation to the ketone, **22**, in which the NMR signal for H5 showed the characteristic downfield shift (δ 7.75) expected for the anisotropic effect of the adjacent carbonyl. Oxidation of the chlorohydrin, **11**, gave the corresponding ketone, **25**, whose H5 signal in the NMR spectrum was at δ 7.85 (d, $J=2$ Hz).



The dichloride, **4**, could be dehydrochlorinated using potassium tertiary butoxide and gave the vinyl chloride, **23**. Confirmation of this structure was provided by its hydrolysis to the ketone, **24**, in which the NMR signal for H5 was at ca δ 7.2.

3. Conclusion

6-Substituted 2,2-dimethyl-1,2-dihydroquinolines can be readily prepared by the cyclisation of 4-substituted *N*-(1,1-dimethylpropargyl)anilines using cuprous chloride in refluxing toluene. These dihydroquinolines serve as convenient substrates from which to prepare 3-, 4- and 3,4-functionalised 2,2-dimethyl-1,2,3,4-tetrahydroquinolines with substituents at the 6-position of the quinoline system.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot stage apparatus equipped with a Reichert microscope and are uncorrected. Infrared spectra were recorded on a Jasco A102 grating spectrometer. *N*-acetyl-tetrahydro- and dihydroquinolines and *N*-trifluoroacetyl-tetrahydro- and dihydroquinolines showed carbonyl absorption in the region 1680–1705 cm^{-1}. The double bond in the heterocyclic ring of the dihydroquinolines absorbed in the region 1630–1640 cm^{-1}. The NH of N-unsubstituted di- and tetrahydroquinolines absorbed in the region 3370–3400 cm^{-1}. Only absorptions above 1600 cm^{-1}, other than those, are provided for individual compounds. Proton NMR spectra (δ_H) were recorded on a Bruker ACP300 spectrometer operating at 300 MHz in deuterochloroform solution using tetramethylsilane as an internal standard. Chemical shifts are quoted as δ in parts per million and coupling constants (J) are given in Hertz (Hz). Electron impact mass spectra (m/z) were recorded at 70 eV on a VG ZAB 2HF spectrometer. Accurate mass measurements (HRMS) were made using electron impact on either an AEI MS3074 spectrometer or by the University of Melbourne on a JEOL AX505H spectrometer. Where a formula contains bromine or chlorine atoms the accurate mass measurement was conducted on the major molecular ion peak corresponding to the halogen atom (or atoms) of lowest atomic weight. Flash chromatography refers to nitrogen pressure driven rapid chromatography[19] using Merck silica gel, pore diameter 60A. Organic extracts were dried using anhydrous magnesium sulfate.

4.2. General procedure for the synthesis of 2,2-dimethyl-1,2-dihydroquinolines 1a–1j

A stirred mixture of the N-substituted aniline[4,5] (11 mmol) and cuprous chloride (250 mg) in toluene (10 mL) was refluxed under an atmosphere of nitrogen for 0.5–16 h. The reaction mixture was cooled and water (10 mL) was added. The organic phase was separated and combined with the dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromotography; elution with light petroleum/ethyl acetate gave the dihydroquinolines, which partially decomposed, and/or rearranged, on attempted distillation under reduced pressure. By this method the following compounds were prepared:

4.2.1. 2,2,6-Trimethyl-1,2-dihydroquinoline 1a. (56%) as white needles, mp 36–37 °C (lit.[3] mp 36–37 °C).

4.2.2. 6-Methoxy-2,2-dimethyl-1,2-dihydroquinoline 1b. (41%) as a yellow oil; δ_H 6.35–6.60 (3H, m, ArH), 6.20 (1H, d, $J=9.1$ Hz, C=CH), 5.45 (1H, d, $J=9.1$ Hz, C=CH), 3.70 (3H, s, OMe), 2.25 (1H, br s (exchanges with D_2O), NH), 1.25 (6H, s, Me); m/z 189 (M, 20%), 174 (100), 159 (15), 131 (40); HRMS: M, found 189.1150. $C_{12}H_{15}NO$ requires 189.1154.

4.2.3. 6-Bromo-2,2-dimethyl-1,2-dihydroquinoline 1c. (43%) as orange prisms, mp 59–61 °C; δ_H 6.9–7.1 (2H, m, ArH), 6.28 (1H, d, $J=8.3$ Hz, ArH), 6.18 (1H, d, $J=9.7$ Hz, C=CH), 5.49 (1H, d, $J=9.7$ Hz, C=CH), 3.50 (1H, br s (exchanges with D_2O), NH), 1.29 (6H, s, Me); m/z 237/239 (M, 15%), 222/224 (100), 143 (50); HRMS: M, found 237.0146. $C_{11}H_{12}BrN$ requires 237.0153.

4.2.4. 2,2-Dimethyl-6-trimethylsilyloxy-1,2-dihydroquinoline 1d. (54%) as an unstable orange oil; δ_H 6.49 (1H, dd, $J=2.7$, 8.3 Hz, ArH), 6.43 (1H, d, $J=2.7$ Hz, ArH), 6.31 (1H, d, $J=8.3$ Hz, ArH), 6.20 (1H, d, $J=9.6$ Hz, C=CH), 5.50 (1H, d, $J=9.6$ Hz, C=CH), 3.50 (1H, br s (exchanges with D_2O), NH), 1.28 (6H, s, Me), 0.22 (9H, s, $SiMe_3$); m/z 247 (M, 15%), 232 (100), 160 (25), 73 (10); HRMS: M, found 247.1385. $C_{14}H_{21}NOSi$ requires 247.1392.

4.2.5. *N*-(2,2-Dimethyl-1,2-dihydro-6-quinolyl)acetamide 1e. (78%) as an orange oil. ν_{max} ($CDCl_3$) 1675 cm^{-1};

δ_H 7.98 (1H, br s (exchanges with D_2O), NH amide), 6.87–7.05 (2H, m, ArH), 6.33, (1H, d, J=8.2 Hz, ArH), 6.15 (1H, d, J=9.8 Hz, C=CH), 5.48 (1H, d, J=9.8 Hz, C=CH), 3.50 (1H, br s (exchanges with D_2O), NH amine), 2.02 (3H, s, COMe), 1.24 (6H, s, Me); *m/z* 216 (M, 15%); 201 (100); 160 (10); 159 (15); HRMS: M, found 216.1252. $C_{13}H_{16}N_2O$ requires 216.1263.)

4.2.6. 2,2-Dimethyl-6-trimethylsilyl-1,2-dihydroquinoline 1f. (30%) as an unstable orange oil; δ_H 7.07 (2H, m, ArH), 6.39 (1H, d, J=9.7 Hz, C=CH), 6.26 (1H, d, J=9.5 Hz, ArH), 5.45 (1H, d, J=9.7 Hz, C=CH), 3.70 (1H, br s (exchanges with D_2O), NH), 1.30 (6H, s, Me), 0.20 (9H, s, $SiMe_3$); *m/z* 231 (M, 1%), 216 (2), 178 (3), 158 (20), 144 (100).

4.2.7. 2,2-Dimethyl-1,2-dihydroquinoline 1g. Obtained from the same reaction. (21%) as an orange oil; δ_H 6.95 (1H, t, J=7.9 Hz, ArH), 6.87 (1H, d, J=7.5 Hz, ArH), 6.57 (1H, t, J=7.5 Hz, ArH), 6.40 (1H, d, J=7.9 Hz, ArH), 6.26 (1H, d, J=9.6 Hz, C=CH), 5.46 (1H, d, J=9.6 Hz, C=CH), 3.64 (1H, br s (exchanges with D_2O), NH), 1.30 (6H, s, Me); *m/z* 159 (M, 15%), 145 (15), 144 (100), 143 (10), 128 (5); HRMS: M, found 159.1043. $C_{11}H_{13}N$ requires 159.1048.

4.2.8. Ethyl 2-(2,2-dimethyl-1,2-dihydro-6-quinolyl)acetate 1h. (57%) as an unstable orange oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 6.87 (1H, dd, J=1.9, 8.0 Hz, ArH), 6.80 (1H, d, J=1.9 Hz, ArH), 6.36 (1H, d, J=8.0 Hz, ArH), 6.23 (1H, d, J=9.7 Hz, C=CH), 5.46 (1H, d, J=9.7 Hz, C=CH), 4.12 (2H, q, J=7.1 Hz, OCH_2), 3.64 (1H, br s (exchanges with D_2O), NH), 3.43 (2H, s, CH_2), 1.29 (6H, s, Me), 1.24 (3H, t, J=7.1 Hz, Me); *m/z* 246 (M+H, 80%), 245 (M, 20), 244 (M−H, 35), 230 (100), 202 (35), 172 (65), 157 (45).

4.2.9. 6-Iodo-2,2-dimethyl-1,2-dihydroquinoline 1i. (40%) as a light-sensitive orange oil; δ_H 7.19 (1H, d, J=2.0 Hz, ArH), 7.15 (1H, dd, J=2.0, 8.3 Hz, ArH), 6.19 (1H, d, J=8.3 Hz, ArH), 6.15 (1H, d, J=9.8 Hz, C=CH), 5.46 (1H, d, J=9.8 Hz, C=CH), 3.66 (1H, br s (exchanges with D_2O), NH), 1.29 (6H, s, Me); *m/z* 285 (M, 22%), 270 (100), 144 (90), 114 (10); HRMS: M, found 285.0024. $C_{11}H_{12}IN$ requires 285.0016.

4.2.10. Ethyl 2,2-dimethyl-1,2-dihydroquinoline-6-carboxylate 1j. (56%) as pale yellow prisms after crystallisation from ethanol/water, mp 106–107 °C; [Found: C, 72.6; H, 7.7; N, 6.0. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%]; ν_{max} ($CDCl_3$) 1690 cm^{-1}; δ_H 7.50 (2H, br s, ArH), 6.30 (1H, d, J=7.5 Hz, ArH), 6.20 (1H, d, J=9.5 Hz, C=C–H), 5.40 (1H, d, J=9.5 Hz, C=C–H), 4.30 (2H, q, J=7.2 Hz, CH_2), 3.45 (1H, br s, NH), 1.35 (3H, t, J=7.2 Hz, Me), 1.30 (6H, s, Me); *m/z* 231 (M, 50%).

4.2.11. Methyl 2,2-dimethyl-1-trifluoroacetyl-1,2-dihydroquinoline-6-carboxylate 6i and methyl 2,2-dimethyl-1,2-dihydroquinoline-6-carboxylate 1k. A mixture of the 6-iododihydroquinoline, **1i** (50 mg, 0.13 mmol), triphenylphosphine (100 mg, 0.39 mmol), triethylamine (37 µl, 0.26 mmol), methanol (0.5 mL) and dimethylformamide (1.5 mL) was purged with nitrogen for 10 min and then with carbon monoxide for 10 min. Palladium acetate (15 mg, 0.66 µmol) was added and the resulting mixture stirred at 100 °C under an atmosphere of carbon monoxide for 4 h. The reaction mixture was cooled and ether (5 mL) was added. Brine (5 mL) was added and the organic phase separated and combined with ethereal extracts of the aqueous phase. The combined organic extracts were washed with water (3×15 mL) and brine (2×15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) provided the N-substituted ester, **6i**, (16 mg, 39%) as colourless needles, mp 92–94 °C; ν_{max} (CH_2Cl_2) 1690 cm^{-1}; δ_H 7.85 (1H, dd, J=2.0, 8.2 Hz, ArH), 7.78 (1H, d, J=2.0 Hz, ArH), 6.88 (1H, d, J=8.2 Hz, ArH), 6.45 (1H, d, J=9.7 Hz, C=CH), 5.81 (1H, d, J=9.7 Hz, C=CH), 3.92 (3H, s, OMe), 1.57 (6H, s, Me); *m/z* 313 (M, 5%), 298 (100), 170 (31), 157 (16), 115 (22); HRMS: M, found 313.0934. $C_{15}H_{14}F_3NO_3$ requires 313.0926.

Further elution gave the N-unsubstituted ester, **1k** (10 mg, 25%) as unstable tan prisms, mp 85–87 °C; ν_{max} ($CDCl_3$) 3400, 1705 cm^{-1}; δ_H 7.65 (1H, dd, J=1.9, 8.4 Hz, ArH), 7.55 (1H, d, J=1.9 Hz, ArH), 6.34 (1H, d, J=8.4 Hz, ArH), 6.26 (1H, d, J=9.8 Hz, C=CH), 5.46 (1H, dd, J=1.9, 9.8 Hz, C=CH), 4.13 (1H, br s (exchanges with D_2O), NH), 3.83 (3H, s, OMe), 1.33 (6H, s, Me); *m/z* 217 (M, 8%), 202 (100), 143 (20), 115 (10); HRMS: M, found 217.1092. $C_{13}H_{15}NO_2$ requires 217.1103.

4.2.12. 1-Acetyl-2,2,6-trimethyl-1,2-dihydroquinoline 3. To a stirred solution of 2,2,6-trimethyl-1,2-dihydroquinoline,[1,3] **1a**, (5.8 mmol) in pyridine (10 mL) and dichloromethane (10 mL) cooled to 0 °C was added acetyl chloride (8.7 mmol) dropwise. The resultant mixture was stirred under nitrogen at room temperature for 1 h. Water (10 mL) was added and the organic layer was separated and washed with hydrochloric acid (5%, 4×25 mL). The organic layer was dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum yielded a yellow oil that crystallised on standing. Recrystallisation from ethanol/water afforded the acetamide, **3**, (1.00 g, 80%) as white needles, mp 67–68 °C; δ_H 6.50–7.05, (3H, m, ArH), 6.25 (1H, d, J=10 Hz, C=CH), 5.65 (1H, d, J=10 Hz, C=CH), 2.30 (3H, s, ArMe), 2.15 (3H, s, COMe), 1.55 (6H, s, Me); *m/z* 215 (M, 50%), 214 (25), 200 (10), 158 (50), 107 (100); HRMS: M, found 215.1301. $C_{14}H_{17}NO$ requires M, 215.1310.

4.3. General procedure for the synthesis of *N*-trifluoroacetyl dihydroquinolines

Trifluoroacetic anhydride (2.30 mmol) was added dropwise under an atmosphere of nitrogen to a solution of the corresponding dihydroquinoline (1.53 mmol) in dry dichloromethane (10 mL) and pyridine (0.5 mL) at 0 °C. The reaction was stirred at ambient temperature for 30–60 min, then quenched by the slow addition of water (10 mL). The organic phase was separated, washed with hydrochloric acid (10%, 3×15 mL) and water (15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate provided the *N*-trifluoroacetyldihydroquinolines. By this method, the following compounds were prepared:

4.3.1. 1-Trifluoroacetyl-2,2,6-trimethyl-1,2-dihydroquinoline 6a. (75%) as an orange oil; δ_H 6.96 (1H, dd, $J=1.5$, 8.0 Hz, ArH), 6.91 (1H, d, $J=1.5$ Hz, ArH), 6.76 (1H, d, $J=8.0$ Hz, ArH), 6.35 (1H, d, $J=9.7$ Hz, C=CH), 5.73 (1H, d, $J=9.7$ Hz, C=CH), 2.32 (3H, s, ArMe), 1.54 (6H, s, Me); *m/z* 269 (M, 5%), 254 (64), 172 (15), 157 (83), 156 (39), 115 (34), 69 (100); HRMS: M, found 269.1011. $C_{14}H_{14}F_3NO$ requires 269.1027.

4.3.2. 1-Trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2-dihydroquinoline 6b. (43%) as an orange oil; δ_H 6.82 (1H, d, $J=8.4$ Hz, ArH), 6.68 (2H, m, ArH), 6.35 (1H, d, $J=9.7$ Hz, C=CH), 5.78 (1H, d, $J=9.7$ Hz, C=CH), 3.81 (3H, s, OMe), 1.55 (6H, s, Me); *m/z* 286 (M+H, 20%), 272 (100), 173 (55), 158 (15), 130 (15); HRMS: (M+H), found 286.1061. $C_{14}H_{15}F_3NO_2$ requires 286.1055.

4.3.3. 6-Bromo-1-trifluoroacetyl-2,2-dimethyl-1,2-dihydroquinoline 6c. (86%) as an orange oil; δ_H 7.2–7.3 (2H, m, ArH), 6.74 (1H, d, $J=8.4$ Hz, ArH), 6.33 (1H, d, $J=9.7$ Hz, C=CH), 5.81 (1H, d, $J=9.7$ Hz, C=CH), 1.55 (6H, s, Me); *m/z* 333/335 (M, 100), 221/223 (40), 170 (15); HRMS: M, found 332.9965. $C_{13}H_{11}BrF_3NO$ requires 332.9976.

4.3.4. 1-Trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2-dihydroquinoline 6d. (86%) as pale orange needles, mp 117–120 °C; ν_{max} ($CDCl_3$) 3150 cm^{-1}; δ_H 6.78 (1H, d, $J=8.6$ Hz, ArH), 6.64 (2H, m, ArH), 6.33 (1H, d, $J=9.7$ Hz, C=CH), 5.78 (1H, d, $J=9.7$ Hz, C=CH), 5.33 (1H, br s (exchanges with D_2O), OH), 1.55 (6H, s, Me); *m/z* 271 (M, 25%), 256 (100), 159 (50), 130 (15), 69 (25); HRMS: M, found 271.0810. $C_{13}H_{12}F_3NO_2$ requires 271.0820.

4.3.5. *N*-(2,2-Dimethyl-1-trifluoroacetyl-1,2-dihydro-6-quinolyl)acetamide 6e. (51%) as orange needles, mp 157–159 °C; ν_{max} ($CDCl_3$) 1670 cm^{-1}; δ_H 7.92 (1H, br s (exchanges with D_2O), NH), 7.51 (1H, d, $J=2.3$ Hz, ArH), 7.20 (1H, dd, $J=2.3$, 8.5 Hz, ArH), 6.81 (1H, d, $J=8.5$ Hz, ArH), 6.34 (1H, d, $J=9.7$ Hz, C=CH), 5.77 (1H, d, $J=9.7$ Hz, C=CH), 2.18 (3H, s, COMe), 1.54 (6H, s, Me); *m/z* 312 (M, 15%), 298 (100), 255 (15),158 (50); HRMS: M, found 312.1092. $C_{15}H_{15}F_3N_2O_2$ requires 312.1086.

4.3.6. 1-Trifluoroacetyl-2,2-dimethyl-1,2-dihydroquinoline 6f. (67%) as a pale orange oil; δ_H 7.14 (3H, m, ArH), 6.87 (1H, d, $J=7.3$ Hz, ArH), 6.40 (1H, d, $J=9.7$ Hz, C=CH), 5.76 (1H, d, $J=9.7$ Hz, C=CH), 1.56 (6H, s, Me); *m/z* 255 (M, 15%), 240 (100), 170 (15), 143 (35); HRMS: M, found 255.0865. $C_{13}H_{12}F_3NO$ requires 255.0871. (Attempted trifluoroacetylation of **1f** produced only the reduced compound, **6f**).

4.3.7. Ethyl 2-(2,2-dimethyl-1-trifluoroacetyl-1,2-dihydro-6-quinolyl)acetate 6g. (72%) as a yellow oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 7.08 (2H, m, ArH), 6.82 (1H, d, $J=8.0$ Hz, ArH), 6.37 (1H, d, $J=9.7$ Hz, C=CH), 5.76 (1H, d, $J=9.7$ Hz, C=CH), 4.17 (2H, q, $J=7.1$ Hz, OCH_2), 3.58 (2H, s, CH_2), 1.55 (6H, s, Me), 1.27 (3H, t, $J=7.1$ Hz, Me); *m/z* 341 (M, 10%), 326 (100), 202 (40), 156 (60); HRMS: M, found 341.1227. $C_{17}H_{18}F_3NO_3$ requires 341.1239.

4.3.8. 1-Trifluoroacetyl-6-iodo-2,2-dimethyl-1,2-dihydroquinoline 6h. (75%) as a light-sensitive yellow oil; δ_H 7.48 (1H, dd, $J=2.0$, 8.3 Hz, ArH), 7.42 (1H, d, $J=2.0$ Hz, ArH), 6.61 (1H, d, $J=8.3$ Hz, ArH), 6.32 (1H, d, $J=9.7$ Hz, C=CH), 5.79 (1H, d, $J=9.7$ Hz, C=CH), 1.55 (6H, s, Me); *m/z* 381 (M, 15%), 366 (100), 269 (12), 240 (35), 170 (22); HRMS: M, found 380.9821. $C_{13}H_{11}F_3INO$ requires 380.9838.

4.4. General procedure for the preparation of 3,4-dichlorotetrahydroquinolines

A solution of chlorine in carbon tetrachloride (2.4 M, 0.83 mmol) was added dropwise under an atmosphere of nitrogen to a stirred solution of the corresponding dihydroquinoline (0.67 mmol) in dry dichloromethane (5 mL) and the mixture stirred at ambient temperature for 15–30 min. The solvent and excess chlorine were removed under reduced pressure and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate gave the 3,4-dichloro compounds as unstable solids or oils. By this method, the following compounds were prepared.

4.4.1. 1-Acetyl-3,4-dichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 4. (75%) as an unstable viscous yellow liquid; δ_H 6.80–7.35 (3H, m, ArH), 5.20 (1H, d, $J=5.5$ Hz, CHCl), 4.50 (1H, d, $J=5.5$ Hz, CHCl), 2.40 (3H, s, ArMe), 2.10 (3H, s, COMe), 1.85 (3H, s, Me), 1.40 (3H, s, Me); *m/z* 285/287/289 (M, 30%), 250/252/254 (30), 243/245/247 (30), HRMS: M, found 285.0675. $C_{14}H_{17}NOCl_2$ requires 285.0689.

4.4.2. 1-Acetyl-3,4,8-trichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 5. Obtained from the same reaction. (0.17 g, 13%) as a slightly impure yellow oil; δ_H 6.90–7.15, (2H, m, ArH), 5.10 (1H, d, $J=4.5$ Hz, CHCl), 4.70 (1H, d, $J=4.5$ Hz, CHCl), 2.40 (3H, s, ArMe), 2.05 (3H, s, COMe), 2.00 (6H, s, Me); *m/z* 321/323/325 (M, 15%).

4.4.3. 3,4-Dichloro-1-trifluoroacetyl-6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7b. (88%) as an unstable yellow oil; δ_H 7.04 (1H, d, $J=2.8$ Hz, ArH), 6.94 (1H, d, $J=8.8$ Hz, ArH), 6.88 (1H, dd, $J=2.8$, 8.8 Hz, ArH), 4.47 (1H, d, $J=4.5$ Hz, CHCl), 5.19 (1H, d, $J=4.5$ Hz, CHCl), 3.84 (3H, s, OMe), 1.81 (3H, s, Me), 1.51 (3H, s, Me); *m/z* 355/357/359 (M, 100%), 322/324/326 (70), 280/282 (100), 272 (50), 230 (55), 188 (55); HRMS: M, found 355.0343. $C_{14}H_{14}Cl_2F_3NO_2$ requires 355.0354.

4.4.4. 6-Bromo-3,4-dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7c. (90%) as an unstable pale yellow oil; δ_H 7.48 (1H, dd, $J=2.1$, 8.3 Hz, ArH), 6.85 (1H, d, $J=8.3$ Hz, ArH), 6.68 (1H, d, $J=2.1$ Hz, ArH, 5.21 (1H, d, $J=4.4$ Hz, CHCl), 4.44 (1H, d, $J=4.4$ Hz, CHCl), 1.77 (3H, s, Me), 1.56 (3H, s, Me); *m/z* 403/405/407 (M, 40%), 368/370/372 (100), 247 (60); HRMS: M, found 402.9334. $C_{13}H_{11}BrCl_2F_3NO$ requires 402.9353.)

4.4.5. 3,4-Dichloro-1-trifluoroacetyl-6-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7d. (100%) as unstable pale yellow needles, mp 100–102 °C; ν_{max} ($CDCl_3$) 3160 cm^{-1}; δ_H 7.03 (1H, d, $J=2.6$ Hz, ArH), 6.90 (1H, d, $J=8.6$ Hz, ArH), 6.84 (1H, dd, $J=2.6$, 8.6 Hz, ArH), 6.25 (1H, br s (exchanges with D_2O), OH), 5.16 (1H,

d, J=4.6 Hz, CHCl), 4.45 (1H, d, J=4.6 Hz, CHCl), 1.81 (3H, s, Me), 1.53 (3H, s, Me); *m/z* 341/343/345 (M, 100%), 306 (75), 266 (30), 264 (90), 216 (60), 174 (90).

4.4.6. *N*-(3,4-Dichloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetamide 7e. (75%) as unstable pale yellow needles, mp 145–147 °C; ν_{max} ($CDCl_3$) 1670 cm^{-1}; δ_H 8.14 (1H, br s (exchanges with D_2O), NH), 7.84 (1H, d, J=2.2 Hz, ArH), 7.52 (1H, dd, J=2.2, 8.7 Hz, ArH), 6.93 (1H, d, J=8.7 Hz, ArH), 5.20 (1H, d, J=4.4 Hz, CHCl), 4.46 (1H, d, J=4.4 Hz, CHCl), 2.20 (3H, s, COMe), 1.79 (3H, s, Me), 1.53 (3H, s, Me); *m/z* 382/384/386 (M, 100%), 347/349 (75), 312 (100), 305/307 (90), 297 (100); HRMS: M, found 382.0476. $C_{15}H_{15}Cl_2F_3N_2O_2$ requires 382.0463.

4.4.7. 3,4-Dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7f. (83%) as an unstable yellow oil; δ_H 7.54 (1H, dd, J=3.7, 5.8 Hz, ArH), 7.36 (2H, m, ArH), 6.98 (1H, m, ArH), 5.27 (1H, d, J=4.5 Hz, CHCl), 4.48 (1H, d, J=4.5 Hz, CHCl), 1.80 (3H, s, Me), 1.55 (3H, s, Me); *m/z* 325/327/329 (M, 25%), 290/292 (100), 253 (20), 239 (40); HRMS: M, found 325.0245. $C_{13}H_{12}Cl_2F_3NO$ requires 325.0248.

4.4.8. Ethyl 2-(3,4-dichloro-1-trifluoroacetyl-2,2-dimethyl-1,2,3,4-tetrahydro-6-quinolyl)acetate 7g. (92%) as an unstable yellow oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 7.48 (1H, d, J=1.8 Hz, ArH), 7.28 (1H, dd, J=1.8, 8.0 Hz, ArH), 6.93 (1H, d, J=8.0 Hz, ArH), 5.25 (1H, d, J=4.5 Hz, CHCl), 4.45 (1H, d, J=4.5 Hz, CHCl), 4.18 (2H, q, J=7.0 Hz, OCH_2), 3.65 (2H, s, CH_2), 1.78 (3H, s, Me), 1.55 (3H, s, Me), 1.27 (3H, t, J=7.0 Hz, Me); *m/z* 411/413/415 (M, 35%), 376/378 (100), 340 (25), 326 (55), 260 (40); HRMS: M, found 411.0596. $C_{17}H_{18}Cl_2F_3NO_3$ requires 411.0616.

4.4.9. 3,4-Dichloro-1-trifluoroacetyl-6-iodo-2,2-dimethyl-1,2,3,4-tetrahydroquinoline 7h. (68%) as unstable white prisms, mp 75–77 °C; δ_H 7.86 (1H, d, J=1.9 Hz, ArH), 7.66 (1H, dd, J=1.9, 8.4 Hz, ArH), 6.70 (1H, d, J=8.4 Hz, ArH), 5.19 (1H, d, J=4.4 Hz, CHCl), 4.43 (1H, d, J=4.4 Hz, CHCl), 1.77 (3H, s, Me), 1.56 (3H, s, Me); *m/z* 451/453/455 (M, 60%), 416/418 (55), 368 (22), 290 (26), 247 (22), 69 (100).

4.4.10. Methyl 3,4-dichloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-carboxylate 7i. (80%) as unstable yellow prisms, mp 104–106 °C; ν_{max} ($CDCl_3$) 1695 cm^{-1}; δ_H 8.23 (1H, d, J=1.9 Hz, ArH), 8.02 (1H, dd, J=1.9, 8.3 Hz, ArH), 6.99 (1H, d, J=8.3 Hz, ArH), 5.32 (1H, d, J=4.3 Hz, CHCl), 4.48 (1H, d, J=4.3 Hz, CHCl), 3.95 (3H, s, OMe), 1.77 (3H, s, Me), 1.59 (3H, s, Me); *m/z* 383/385/387 (M, 22%), 348/350 (100), 312 (13), 298 (20), 258 (16), 216 (15); HRMS: M, found 383.0303. $C_{15}H_{14}Cl_2F_3NO_3$ requires 383.0303.

4.4.11. 3,4-Dichloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 10. A solution of chlorine in carbon tetrachloride (2.4 M, 0.18 mL, 0.43 mmol) was added dropwise to a stirred solution of the dihydroquinoline, **1a**, (0.05 g, 0.29 mmol) in concentrated hydrochloric acid (5 mL) and the resulting mixture stirred vigorously at room temperature for 30 min. The mixture was neutralised with sodium hydroxide solution (10%) and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (85:15) gave the dichloro compound, **10**, (33 mg, 47%) as unstable white prisms, mp 107–109 °C; δ_H 7.25 (1H, d, J=1.5 Hz, ArH), 6.92 (1H, dd, J=1.5, 8.1 Hz, ArH), 6.49 (1H, d, J=8.1 Hz, ArH), 4.76 (1H, d, J=9.2 Hz, CHCl), 3.98 (1H, d, J=9.2 Hz, CHCl), 2.60 (1H, br s (exchanges with D_2O), NH), 2.25 (3H, s, ArMe), 1.39 (3H, s, Me), 1.24 (3H, s, Me); *m/z* 243/245/247 (M, 1%), 208/210 (25), 192/194 (100).

4.4.12. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-4-ol 11. A solution of chlorine in carbon tetrachloride (2.4 M, 0.15 mL, 0.35 mmol) was added dropwise to a solution of the dihydroquinoline, **3**, (50 mg, 0.23 mmol) in tetrahydrofuran (2 mL) and water (2 mL) and the resulting mixture stirred vigorously under an atmosphere of nitrogen for 24 h. Water (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (1:1) provided the chlorohydrin, **11**, (60 mg, 96%) as cream prisms, mp 139–141 °C; ν_{max} ($CDCl_3$) 3575 cm^{-1}; δ_H 7.39 (1H, d, J=1.8 Hz, ArH), 7.07 (1H, dd, J=1.8, 8.1 Hz, ArH), 6.84 (1H, d, J=8.1 Hz, ArH), 4.71 (1H, dd, J=3.0, 9.5 Hz, C*H*OH), 3.67 (1H, d, J=9.5 Hz, CHCl), 2.84 (1H, br s (exchanges with D_2O), OH), 2.37 (3H, s, ArMe), 2.11 (3H, s, COMe), 1.69 (3H, s, Me), 1.68 (3H, s, Me); *m/z* 267/269 (M, 44%), 225/227 (60), 210/212 (100), 198 (46); HRMS: M, found 267.1018. $C_{14}H_{18}ClNO_2$ requires 267.1026.)

This compound also formed slowly from the dichloride, **4**, if it was left exposed to the atmosphere.

4.4.13. 3-Chloro-1-trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-4-ol 13, and 1-trifluoroacetyl-3,4-dichloro-1,2,3,4-tetrahydroquinoline 7a. The chlorohydrin, **13**, was prepared, from **6a**, in a similar manner (43 mg, 36%) as a pale yellow gum; ν_{max} ($CDCl_3$) 3595 cm^{-1}; δ_H 7.43 (1H, d, J=1.6 Hz, ArH), 7.11 (1H, dd, J=1.6, 8.4 Hz, ArH), 6.89 (1H, d, J=8.4 Hz, ArH), 4.74 (1H, d, J=9.2 Hz, C*H*OH), 3.69 (1H, d, J=9.2 Hz, CHCl), 2.85 (1H, br s (exchanges with D_2O), OH), 2.39 (3H, s, ArMe), 1.68 (3H, s, Me), 1.67 (3H, s, Me); *m/z* 321/323 (M, 100%), 244 (54), 216 (45), 203 (63), 162 (86); HRMS: M, found 321.0733. $C_{14}H_{15}ClF_3NO_2$ requires 321.0743.)

4.4.14. 7a. Also obtained from this reaction was the dichloride. (59 mg, 47%) as a pale yellow oil; δ_H 7.33 (1H, d, J=1.5 Hz, ArH), 7.14 (1H, dd, J=1.5, 8.3 Hz, ArH), 6.87 (1H, d, J=8.3 Hz, ArH), 5.22 (1H, d, J=4.4 Hz, CHCl), 4.47 (1H, d, J=4.4 Hz, CHCl). 2.38 (3H, s, ArMe), 1.79 (3H, s, Me), 1.52 (3H, s, Me); *m/z* 339/341/343 (M, 32%), 304/306 (77), 262 (45), 214 (34), 172 (50), 69 (100); HRMS: M, found 339.0402. $C_{14}H_{14}Cl_2F_3NO$ requires 339.0404.)

4.4.15. 1-Acetyl-3,4-dibromo-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 12. Bromine (0.44 g, 2.7 mmol) was

added dropwise to a stirred solution of the dihydroquinoline, **3**, (0.59 g, 2.7 mmol) in dry dichloromethane (5 mL) and the resulting mixture stirred at ambient temperature for 1 h. The solvent and excess bromine were removed under reduced pressure and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) provided the dibromo compound, **12**, (0.94 g, 91%) as an unstable orange oil; δ_H 7.23 (1H, d, $J=1.7$ Hz, ArH), 7.11 (1H, dd, $J=1.7$, 8.2 Hz, ArH), 6.90 (1H, d, $J=8.2$ Hz, ArH), 5.55 (1H, d, $J=3.9$ Hz, CHBr), 4.89 (1H, d, $J=3.9$ Hz, CHBr), 2.36 (3H, s, COMe), 2.10 (3H, s, ArMe), 1.91 (3H, s, Me), 1.37 (3H, s, Me); *m/z* 373/375/377 (M, 2%), 314/316/318 (25), 294/296 (10), 236/238 (15), 200 (20), 158 (100).

4.5. General procedure for the synthesis of 3-chloro-tetrahydroquinolines

Sodium cyanoborohydride (1.75 mmol) was added to a solution of freshly dried zinc chloride[18] (0.87 mmol) in dry ether (10 mL) and the mixture stirred at ambient temperature under an atmosphere of nitrogen for 20 min. A solution of the dichlorotetrahydroquinoline (0.87 mmol) in dry ether (4 mL) was then added under an atmosphere of nitrogen and the resulting mixture stirred at ambient temperature for 3–10 days. The reaction was quenched with saturated sodium bicarbonate solution (15 mL), the organic phase separated and washed with water (15 mL) and brine (3× 15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate provided the 3-chloro compounds. By this method, the following compounds were prepared.

4.5.1. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline. As white plates after crystallisation from light petroleum (0.26 g, 65%), mp 74–76 °C; [Found: C, 67.0; H, 7.5; N, 5.6. $C_{14}H_{18}NOCl$ requires C, 66.9; H, 7.2; N, 5.6%.]; δ_H 6.96–7.02 (2H, m, ArH), 6.85 (1H, d, $J=8$ Hz, ArH), 4.15 (1H, dd, $J=3.4$, 6.7 Hz, CHCl), 3.15 (1H, dd, $J=3.4$, 15.3 Hz, 1H of CH_2), 3.01 (1H, dd, $J=6.7$, 15.3 Hz, 1H of CH_2–), 2.33 (3H, s, ArMe),2.11 (3H, s, COMe), 1.68 (6H, s, Me); *m/z* 251/253 (M, 60%), 9/211 (70), 196 (75), 194 (100).

4.5.2. 3-Chloro-2,2-dimethyl-6-methoxy-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14b. (78%) as a pale yellow oil; δ_H 6.93 (1H, d, $J=8.8$ Hz, ArH), 6.75 (2H, m, ArH), 4.17 (1H, dd, $J=3.6$, 6.3 Hz, CHCl), 3.81 (3H, s, OMe), 3.19 (1H, dd, $J=3.6$, 15.3 Hz, 1H of CH_2), 3.05 (1H, dd, $J=6.3$, 15.3 Hz, 1H of CH_2), 1.66 (6H, s, Me); *m/z* 321/323 (M, 60%), 286 (15), 270 (10), 244 (100), 232 (25), 188 (15); HRMS: M, found 321.0749. $C_{14}H_{15}ClF_3NO_2$ requires 321.0743.

4.5.3. 6-Bromo-3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14c. (20%) as white needles, mp 78–80 °C; [Found: C, 42.5; H, 3.3; N, 3.7. $C_{13}H_{12}BrClF_3NO$ requires C, 42.1; H, 3.3; N, 3.8%]; δ_H 7.37 (2H, m, ArH), 6.86 (1H, dd, $J=0.8$, 8.9 Hz, ArH), 4.21 (1H, dd, $J=3.5$, 5.8 Hz, CHCl), 3.24 (1H, dd, $J=3.5$, 15.8 Hz, 1H of CH_2), 3.09 (1H, dd, $J=5.8$, 15.8 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.63 (3H, s, Me); *m/z* 369/371/373 (M, 50%), 292/294 (75), 279/281 (25), 213 (100).

4.5.4. 3-Chloro-2,2-dimethyl-6-hydroxy-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14d. (88%) as a white powder, mp 118–119 °C; [Found: C, 50.5; H, 4.1; N, 4.7. $C_{13}H_{13}ClF_3NO_2$ requires C, 50.7; H, 4.3; N, 4.6%]; ν_{max} ($CDCl_3$) 3155 cm^{-1}; δ_H 6.89 (1H, d, $J=8.3$ Hz, ArH), 6.73 (1H, dd, $J=2.7$, 8.3 Hz, ArH), 6.70 (1H, d, $J=2.7$ Hz, ArH), 5.91 (1H, br s (exchanges with D_2O), OH), 4.18 (1H, dd, $J=3.5$, 6.2 Hz, CHCl), 3.17 (1H, dd, $J=3.5$, 15.4 Hz, 1H of CH_2), 3.04 (1H, dd, $J=6.2$, 15.4 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.65 (3H, s, Me); *m/z* 307/309 (M, 30%), 272 (5), 230 (100), 218 (25), 174 (12).

4.5.5. *N*-(3-Chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetamide 14e. (55%) as pale yellow prisms, mp 146–148 °C; [Found: C, 51.4; H, 4.5; N, 7.7. $C_{15}H_{16}ClF_3N_2O_2$ requires C, 51.6; H, 4.6; N, 8.0%]; ν_{max} ($CDCl_3$) 1675 cm^{-1}; δ_H 7.78 (1H, br s (exchanges with D_2O), NH), 7.65 (1H, d, $J=2.3$ Hz, ArH), 7.26 (1H, dd, $J=2.3$, 8.6 Hz, ArH), 6.93 (1H, d, $J=8.6$ Hz, ArH), 4.19 (1H, dd, $J=3.5$, 5.9 Hz, CHCl), 3.21 (1H, dd, $J=3.5$, 15.6 Hz, 1H of CH_2), 3.07 (1H, dd, $J=5.9$, 15.6 Hz, 1H of CH_2), 2.19 (3H, s, COMe), 1.67 (3H, s, Me), 1.63 (3H, s, Me); *m/z* 348/350 (M, 35%), 313 (5), 271 (60), 254 (45), 223 (100).

4.5.6. 3-Chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14f. (66%) as colourless prisms, mp 40–42 °C; [Found: C, 53.8; H, 4.4; N, 4.7. $C_{13}H_{13}ClF_3NO$ requires C, 53.5; H, 4.5; N, 4.8%]; δ_H 7.24 (2H, m, ArH), 6.99 (2H, m, ArH), 4.19 (1H, dd, $J=3.6$, 6.3 Hz, CHCl), 3.25 (1H, dd, $J=3.6$, 15.5 Hz, 1H of CH_2), 3.12 (1H, dd, $J=6.3$, 15.5 Hz, 1H of CH_2), 1.68 (3H, s, Me), 1.65 (3H, s, Me); *m/z* 291/293 (M, 20%), 256 (5), 240 (10), 214 (100), 202 (25), 158 (15).

4.5.7. Ethyl 2-(3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydro-6-quinolyl)acetate 14g. (76%) as a viscous, pale yellow oil; ν_{max} ($CDCl_3$) 1720 cm^{-1}; δ_H 7.15 (2H, m, ArH), 6.94 (1H, br s (not exchangeable with D_2O), ArH), 4.17 (3H, m, CHCl and OCH_2), 3.61 (2H, s, $ArCH_2$), 3.23 (1H, dd, $J=6.4$, 15.6 Hz, 1H of CH_2), 3.11 (1H, dd, $J=3.7$, 15.6 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.64 (3H, s, Me), 1.26 (3H, t, $J=7.2$ Hz, Me); *m/z* 378/380 (M+H, 35%), 342 (7), 300 (20), 288 (25), 226 (100); HRMS: M, found 377.0994. $C_{17}H_{19}ClF_3NO_3$ requires 377.1005.)

4.5.8. 3-Chloro-2,2-dimethyl-6-iodo-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline 14h. (33%) as a viscous, pale yellow oil; δ_H 7.56 (1H, br s (not exchangeable with D_2O), ArH), 7.24 (1H, m, ArH), 6.72 (1H, d, $J=8.8$ Hz, ArH), 4.19 (1H, dd, $J=3.6$, 5.8 Hz, CHCl), 3.22 (1H, dd, $J=3.6$, 15.8 Hz, 1H of CH_2), 3.07 (1H, dd, $J=5.8$, 15.8 Hz, 1H of CH_2), 1.67 (3H, s, Me), 1.62 (3H, s, Me); *m/z* 417/419 (M, 40%), 382 (5), 340 (40), 291 (20), 258 (25), 214 (85), 69 (100); HRMS: M, found 416.9585. $C_{13}H_{12}ClF_3INO$ requires 416.9606.

4.5.9. Methyl 3-chloro-2,2-dimethyl-1-trifluoroacetyl-1,2,3,4-tetrahydroquinoline-6-carboxylate 14i. (34%) as a colourless oil; ν_{max} (CH_2Cl_2) 1690 cm^{-1}; δ_H 7.92 (2H, m, ArH); 7.02 (1H, d, $J=7.9$ Hz, ArH), 3.93 (3H, s, OMe), 4.24 (1H, dd, $J=3.7$, 5.6 Hz, CHCl), 3.19 (1H, dd, $J=3.7$, 16.0 Hz, 1H of CH_2), 3.13 (1H, dd, $J=5.6$, 16.0 Hz, 1H of CH_2), 1.69 (3H, s, Me), 1.63 (3H, s, Me); *m/z* 349/351

(M, 38%), 272 (100), 260 (49), 240 (20), 228 (42); HRMS: M, found 349.0692. $C_{15}H_{15}ClF_3NO_3$ requires 349.0693.)

4.5.10. 3,4-Epoxy-1-trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 15. Sodium bicarbonate (255 mg, 3.0 mmol) and *m*-chloroperoxybenzoic acid (80%, 0.55 g, 2.4 mmol) were added to a solution of the dihydroquinoline, **6a**, (0.50 g, 1.9 mmol) in dichloromethane (25 mL) and the resulting mixture stirred under an atmosphere of nitrogen for 41 h. The mixture was diluted with dichloromethane (10 mL), washed with saturated sodium bicarbonate solution (3×15 mL) and water (2×15 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (70:30) afforded the epoxide, **15**, (0.39 g, 74%) as a pale orange oil; δ_H 7.26 (1H, d, J=1.8 Hz, ArH), 7.12, (1H, dd, J=1.8, 8.1 Hz, ArH), 6.77 (1H, d, J=8.1 Hz, ArH), 3.86 (1H, d, J=4.2 Hz, CHO), 3.41 (1H, d, J=4.2 Hz, CHO), 2.37 (3H, s, ArMe), 1.88 (3H, s, Me), 1.21 (3H, s, Me); *m*/*z* 285 (M, 46%), 214 (100), 145 (29), 144 (28), 69 (48); HRMS: M, found 285.0980. $C_{14}H_{14}F_3NO_2$ requires 285.0977.

4.5.11. 1-Trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinolin-3-ol 16. A solution of the epoxide, **15**, (0.39 g, 1.4 mmol) in ethyl acetate (10 mL) was stirred with 5% palladium on carbon (100 mg) under an atmosphere of hydrogen for 23 h. The mixture was filtered through a pad of celite and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (1:1) provided the alcohol, **16**, (0.27 g, 69%) as a colourless, unstable oil ν_{max} ($CDCl_3$) 3600 cm^{-1}; δ_H 7.04 (2H, m, ArH), 6.91 (1H, d, J=7.9 Hz, ArH), 3.89 (1H, m, C*H*OH), 2.82 (1H, dd, J=5.5, 14.4 Hz, 1H of CH_2), 2.94 (1H, dd, J=2.4, 14.4 Hz, 1H of CH_2), 2.35 (3H, s, ArMe), 1.59 (3H, s, Me), 1.56 (3H, s, Me), 1.43 (1H, d, J=7.8 Hz (exchanges with D_2O), OH); *m*/*z* 287 (M, 84%), 271 (48), 217 (25), 216 (30), 190 (35), 158 (100); HRMS: M, found 287.1123. $C_{14}H_{16}F_3NO_2$ requires 287.1133.

4.5.12. 1-Trifluoroacetyl-2,2,6-trimethyl-1,2,3,4-tetrahydro-3-quinolone 17. Jones reagent was added dropwise to a solution of the alcohol, **16**, (10 mg, 35 μmol) in acetone (5 mL) until the orange colour just persisted. Water (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) afforded the ketone, **17**, (7.3 mg, 74%) as a pale yellow oil; ν_{max} ($CDCl_3$) 1730 cm^{-1}; δ_H (acquired at 0 °C) 7.11 (2H, m, ArH), 7.01 (1H, d, J=8.0 Hz, ArH), 3.87 (1H, d, J=13.8 Hz, 1H of CH_2), 3.36 (1H, d, J=13.8 Hz, 1H of CH_2), 2.31 (3H, s, ArMe), 1.79 (3H, s, Me), 1.34 (3H, s, Me); *m*/*z* 285 (M, 30%), 257 (60), 242 (58), 188 (50), 160 (90), 145 (100); HRMS: M, found 285.0970. $C_{14}H_{14}F_3NO_2$ requires 285.0977.

4.5.13. 2,2,6-Trimethyl-1,2,3,4-tetrahydro-3-quinolyl trifluoroacetate 18. The alcohol, **16**, (100 mg, 0.35 mmol) and triphenylphosphine (270 mg, 1.1 mmol) were dissolved in dry tetrahydrofuran (5 mL) under an atmosphere of nitrogen. Anhydrous zinc chloride (48 mg, 0.35 mmol) in dry tetrahydrofuran (1 mL) and diethyl azodicarboxylate (0.18 g, 1.1 mmol) in dry tetrahydrofuran (1 mL) were added consecutively with stirring. The resulting mixture was stirred under an atmosphere of nitrogen for 2 h, the solvent removed in vacuo and the residue purified by flash chromatography; elution with light petroleum/ethyl acetate (80:20) gave the trifluoroacetate, **18**, (78 mg, 78%) as an unstable pale yellow oil; ν_{max} ($CDCl_3$) 1780 cm^{-1}; δ_H 6.84 (1H, d, J=8.1 Hz, ArH), 6.81 (1H, s, ArH), 6.46 (1H, d, J=8.1 Hz, ArH), 5.10 (1H, dd, J=5.5, 7.4 Hz, CHO), 3.56 (1H, br s (exchanges with D_2O), NH), 2.86 (1H, dd, J=7.4, 16.9 Hz, 1H of CH_2), 2.22, (3H, s, ArMe), 1.22 (3H, s, Me), 1.20 (3H, s, Me); *m*/*z* 287 (M, 9%), 272 (7), 173 (26), 158 (100), 132 (41).

Other attempts at the above reaction using the same conditions but replacing the zinc chloride with either tetrabutylammonium chloride or tetrabutylammonium bromide also gave the trifluoroacetate, **18**, as the sole product.

4.5.14. 2,2,6-Trimethyl-1,2,3,4-tetrahydroquinolin-3-ol 19. An aqueous solution of potassium bicarbonate (10%, 2.5 mL, 2.4 mmol) was added dropwise to a solution of the trifluoroacetate, **18**, (77 mg, 0.27 mmol) in methanol (5 mL) and the resulting mixture stirred at room temperature under an atmosphere of nitrogen for 40 min. Water (5 mL) was added and the mixture extracted with dichloromethane (3×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) provided the aminoalcohol, **19**, (40 mg, 78%) as cream prisms, mp 73–74 °C; ν_{max} ($CDCl_3$) 3500, 3370 cm^{-1}; δ_H 6.81 (2H, m, ArH), 6.43 (1H, d, J=8.7 Hz, ArH), 3.63 (1H, t, J=4.4 Hz, C*H*OH), 3.46, (1H, br s (exchanges with D_2O), NH), 2.99 (1H, dd, J=4.4, 17.0 Hz, 1H of CH_2), 2.71 (1H, dd, J=4.4, 17.0 Hz, 1H of CH_2), 2.21 (3H, s, ArMe), 2.18 (1H, br s (exchanges with D_2O), OH), 1.20 (3H, s, Me), 1.11 (3H, s, Me); *m*/*z* 191 (M, 69%), 176 (100), 158 (31), 146 (34), 132 (36); HRMS: M, found 191.1314. $C_{12}H_{17}NO$ requires 191.1310.

4.5.15. 3-Chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline 20. A mixture of the trifluoroacetate, **18**, (20 mg, 0.07 μmol), tetrabutylammonium chloride (28 mg, 0.10 mmol) and tetrahydrofuran (5 mL) was refluxed for 24 h. The reaction mixture was cooled, diluted with dichloromethane (5 mL), washed with water (2×10 mL) and brine (5 mL), dried and the solvent removed. The residue was purified by flash chromatography; elution with light petroleum/ethyl acetate (60:40) gave an inseparable mixture of the starting trifluoroacetate, **18**, and the 3-chloro compound, **20**, (6.5 mg); spectroscopic data for **20**; δ_H 6.83 (2H, m, ArH), 6.45 (1H, d, J=8.0 Hz, ArH), 4.08 (1H, dd, J=5.4, 8.4 Hz, CHCl), 3.60 (1H, br s (exchanges with D_2O), NH), 3.23 (1H, dd, J=5.4, 16.9 Hz, 1H of CH_2), 3.03 (1H, dd, J=8.4, 16.9 Hz, 1H of CH_2), 2.21 (3H, s, ArMe), 1.30 (3H, s, Me), 1.25 (3H, s, Me); *m*/*z* 209/211 (M, 29%), 194 (1), 174 (1), 158 (2).

4.5.16. 1-Acetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-4-ol 21. To a stirred solution of mercuric acetate (0.15 g, 0.5 mmol) in water (1 mL) was added tetrahydrofuran (1 mL); the resulting suspension was vigorously stirred and then the acetamide, **3**, (0.10 g, 0.5 mmol) was

added and the resultant mixture was stirred at room temperature for 24 h. Sodium hydroxide (3.0 M, 0.5 mL) was added followed by a solution of sodium borohydride (0.5 M) in sodium hydroxide (3.0 M, 0.5 mL). After 45 min the organic layer was separated and combined with dichloromethane extracts of the aqueous phase. The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:1) afforded an orange oil that solidified on standing. Recrystallisation of this solid from dichloromethane/light petroleum yielded the alcohol, **21**, (0.018 g, 15%) as cream-coloured prisms, mp 123–125 °C; ν_{max} ($CDCl_3$) 3550 cm^{-1}; δ_H 7.27 (1H, br s, ArH), 7.01, (1H, d, J=7.9 Hz, ArH), 6.83 (1H, d, J=7.9 Hz, ArH), 4.76 (1H, br d, J=11.2 Hz, CHO), 2.10–2.40 (2H, m, CH_2), 2.37 (3H, s, ArMe), 2.10 (3H, s, COMe), 1.73 (3H, s, Me), 1.53 (3H, s, Me), 1.46 (1H, br s, OH); *m/z* 233 (M, 50%), 217 (10), 176 (100), 158 (95); HRMS: M, Found 233.1426. $C_{14}H_{19}NO_2$ requires 233.1416.

4.5.17. 1-Acetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-4-one 22. A solution of chromium trioxide in sulfuric acid (30%, 0.014 mL, 0.04 mmol) was added to a stirred solution of the alcohol, **21**, (0.01 g, 0.04 mmol) in acetone (2 mL) and the mixture was stirred under nitrogen for 2 h. Water (3 mL) was then added and the mixture was extracted with dichloromethane (3×5 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:1) yielded the ketone, **22**, (7 mg, 71%) as a yellow oil; ν_{max} ($CDCl_3$) 1710 cm^{-1}; δ_H 7.75 (1H, d, J=2.0 Hz, ArH), 7.25 (1H, dd, J=2.0, 8.2 Hz, ArH), 6.80 (1H, d, J=8.2 Hz, ArH), 2.70 (2H, s, CH_2), 2.35 (3H, s, ArMe), 2.25 (3H, s, COMe), 1.51 (3H, s, Me), 1.50 (3H, s, Me); *m/z* 231 (M, 20%), 174 (100), 128 (50), 127 (25); HRMS: M, found 231.1251. $C_{14}H_{17}NO_2$ requires 231.1260.

4.5.18. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2-dihydroquinoline 23. Potassium *tert*-butoxide (0.17 g, 1.2 mmol) was added to a stirred solution of the dichloro compound, **4**, (0.22 g, 0.77 mmol) in tetrahydrofuran (10 mL) and the resultant mixture was stirred under nitrogen for 24 h. Water (10 mL) was added and the mixture extracted with dichloromethane (3×15 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:4) yielded the vinyl chloride, **23**, (0.065 g, 74%) as a yellow oil; δ_H 7.35 (1H, br s, ArH), 6.80–7.00 (2H, m, ArH), 5.85 (1H, s, C=CH), 2.40 (3H, s, ArMe), 2.15 (3H, s, COMe), 1.60 (6H, s, Me); *m/z* 249/251 (M, 20%), 234/236 (55), 192/194 (100); HRMS: M, found 249.0911. $C_{14}H_{16}ClNO$ requires 249.0920.

4.5.19. 1-Acetyl-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-3-one 24. A mixture of the vinyl chloride, **23**, (0.15 g, 0.60 mmol) and mercuric acetate (0.26 g, 0.83 mmol) in trifluoroacetic acid (15 mL) was stirred at room temperature under nitrogen for 24 h. The mixture was filtered and the solvent removed. Saturated sodium bicarbonate (15 mL) and saturated sodium chloride (15 mL) were cautiously added to the residue and the resulting mixture was extracted with dichloromethane (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (1:4) yielded a fraction which contained predominantly the ketone, **24**, (0.10 g, 70%) as a yellow oil; ν_{max} ($CDCl_3$) 1730 cm^{-1}; δ_H 6.67–7.32 (3H, m, ArH), 3.06 (2H, s, CH_2), 2.32 (3H, s, ArMe), 2.23 (3H, s, COMe), 2.18 (6H, s, Me); *m/z* 231 (M, 20%), 189 (15), 188 (29), 174 (100).

4.5.20. 1-Acetyl-3-chloro-2,2,6-trimethyl-1,2,3,4-tetrahydroquinoline-4-one 25. A solution of chromium trioxide in sulfuric acid (30%, 0.07 mL, 0.19 mmol) was added to a stirred solution of the chlorohydrin, **11**, (0.05 g, 0.19 mmol) in acetone (2 mL) and the mixture stirred under nitrogen for 24 h. The mixture was diluted with water (5 mL) and extracted with dichloromethane (2×10 mL). The combined organic extracts were dried and the solvent removed. The residue was purified by flash chromatography; elution with ethyl acetate/light petroleum (3:7) yielded the ketone, **25**, (0.036 g, 73%) as a pale yellow oil; ν_{max} ($CDCl_3$) 1740 cm^{-1}; δ_H 7.85 (1H, d, J=2.2 Hz, ArH), 7.30 (1H, dd, J=2.2, 8.0 Hz, ArH), 6.85 (1H, d, J=8.0 Hz, ArH), 4.10 (1H, s, CHCl), 2.35 (3H, s, ArMe), 2.30 (3H, s, COMe), 1.70 (3H, s, Me), 1.40 (3H, s, Me); *m/z* 265/267 (M, 20%), 223/225 (30), 208/210 (50), 138 (100); HRMS: M, found 265.0863. $C_{14}H_{16}ClNO_2$ requires 265.0870.

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References and notes

1. Easton, N. R.; Cassady, D. R. *J. Org. Chem.* **1962**, *27*, 4713–4714.
2. Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978–1032.
3. Williamson, N. M.; March, D. R.; Ward, A. D. *Tetrahedron Lett.* **1995**, *36*, 7721–7724.
4. Hennion, G. F.; Hanzel, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 4908–4912.
5. Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, 621–625.
6. Raner, K. D.; Skelton, B. W.; Ward, A. D.; White, A. H. *Aust. J. Chem.* **1990**, *43*, 609–616.
7. Raner, K. D.; Ward, A. D. *Aust. J. Chem.* **1991**, *44*, 1749–1760.
8. De Silva, A. N.; Francis, C. L.; Ward, A. D. *Aust. J. Chem.* **1993**, *46*, 1657–1671.
9. Francis, C. L.; Ward, A. D. *Aust. J. Chem.* **1994**, *47*, 2109–2117.
10. Omura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; KoJima, Y. *J. Antibiot.* **1980**, *33*, 1395–1396.
11. Nakagawa, A.; Omura, S. *Tetrahedron Lett.* **1981**, *22*, 2199–2202.
12. Nakagawa, A.; Iwai, Y.; Hashimoto, H.; Miyazaki, N.; Oiwa, R.; Takahashi, Y.; Hirano, A.; Shibukawa, N.; KoJima, Y.; Omura, S. *J. Antibiot.* **1981**, *34*, 1408–1415.

13. Hill, M. L.; Raphael, R. A. *Tetrahedron* **1990**, *46*, 4587–4594.
14. Morimoto, Y.; Oda, K.; Shirahama, H.; Matsumoto, T.; Omura, S. *Chem. Lett.* **1988**, *6*, 909–912.
15. Pearce, C. M.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 409–411.
16. Morimoto, Y.; Shirama, H. *Tetrahedron* **1996**, *52*, 10631–10652.
17. Williamson, N. M.; Ward, A. D.; Tiekink, E. R. T. *Z. Krist. NCS* **2002**, *217*, 347–348.
18. Kim, S.; Kim, Y. J.; Ahn, K. H. *Tetrahedron Lett.* **1983**, *24*, 3369–3372.
19. Harwood, L. M. *Aldrichim. Acta* **1985**, *18*, 25.

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On the application of the extended Fujita–Nishioka equation to polysubstituted systems. A kinetic study of the rearrangement of several poly-substituted *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles in dioxane/water

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Abstract—The rearrangement rates of several di-, tri-, tetra- or penta-substituted *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a–18a**) into the relevant 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles (**1b–18b**) have been determined in 1:1 (v:v) dioxane/water in a wide range of pS^+ (3.80–12.50) at different temperatures. The kinetic data obtained have been correlated with those previously collected for the rearrangement of *ortho*-, *meta*- and *para*-substituted *Z*-arylhydrazones (**19a–38a**) by means of an extension of the linear free-energy relationship (LFER) proposed by Fujita and Nishioka, thus considering steric (E_s) and field (F_o) proximity effects in addition to the normal electronic effects ($\sigma_{o,m,p}$). Excellent correlation coefficients have been calculated ($R \geq 0.999$), with susceptibility constants (ρ, δ and f) close to those previously obtained for **19a–38a**, when only excluding data for the 2,6-bis-*ortho*-substituted *Z*-arylhydrazones **11a** and **16–18a**, which show a reactivity much higher than foreseeable, evidencing the first case of 'steric acceleration' in mononuclear rearrangements of heterocycles. A rationale for such a behaviour is proposed.
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1. Introduction

Several drugs contain in their skeleton one or more polysubstituted aromatic (carbocyclic as well as heterocyclic) rings. Sometimes the polysubstitution causes an overcrowding, which can strongly influence the effect of the substituents themselves: for example, the electronic effects are often overwhelmed by steric and field effects. Moreover in some cases the occurrence of polysubstitution makes the additivity rule of the substituent effects non-effective and some kind of saturation can occur.[1–3]

For these reasons it may be difficult to evaluate the effect of the substituents and then to make previsions for their contribution to the overall properties of the molecules. In such cases it might become impossible to apply a quantitative structure-activity relationship (QSAR) for the understanding of the pharmacological activity.[2e,3] As a matter of fact, several other parameters have been introduced and some interesting reviews on this point have been reported in the last decades.[2,3] Problems can also arise when considering chemical reactivity, that is, in the application of linear free-energy relationships (LFER), resulting in the observation of non-linear or unexpected behaviours.[1–3] Thus, on going from *meta*- or *para*-disubstituted systems to *ortho*-disubstituted ones, additional parameters are required for a proper LFER treatment: for example parameters depending on proximity effects such as steric[4] (essentially deriving from primary steric effects, by using, e.g., the E_s constants) and field effects[5] (proximity polar effect, for example by using the F_o constants), as

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occurs in the Fujita and Nishioka[6] equation (Eq. 1). Often kinetic and/or equilibrium data for *ortho*-substituted compounds can be combined with those relevant to *meta*- and *para*-substituted ones as in the extended Eq. 2.

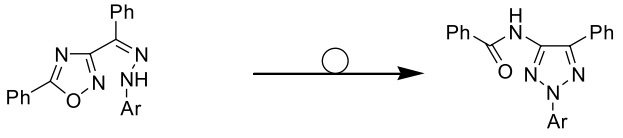
$$\log k_o/k_H = \rho\sigma_o + \delta E_s + fF_o + i \quad (1)$$

$$\log k_{o,m,p}/k_H = \rho\sigma_{o,m,p} + \delta E_s + fF_o + i \quad (2)$$

Usually these equations work quite well with *ortho*-disubstituted compounds, but their application to more extensively substituted systems has been rather scanty (Scheme 1).[1–6]

In the framework of our interest in structure-reactivity[7] and structure-activity[8] relationships in carbo- and hetero-cyclic systems we have now synthesized several poly-substituted *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**1a**–**18a**), addressing our attention to their rearrangement [monocyclic rearrangement of heterocycles (MRH) or Boulton–Katritzky reaction (BKR)][9] into the relevant triazoles (**1b**–**18b**). Thus we have examined the behaviour of fifteen 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-disubstituted (**1a**–**15a**), one 2,4,6-trisubstituted (**16a**), one 2,3,5,6-tetrasubstituted (**17a**) and one 2,3,4,5,6-pentasubstituted (**18a**) *Z*-arylhydrazones [the substituents on the benzene ring being in 1,2,3, 1,2,4, 1,2,5, 1,2,6, 1,3,4 and 1,3,5 (**1a**–**15a**), 1,2,4,6 (**16a**), 1,2,3,5,6 (**17a**) and 1,2,3,4,5,6 (**18a**) relationship, respectively].

By investigating kinetic (i.e., reactivity) and thermodynamic (i.e., equilibrium) aspects in polysubstituted compounds we have previously collected some interesting results in both carbo- and hetero-cyclic systems. For example, for the MRH of some *ortho*-, *meta*- or *para*-substituted *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**19a**–**38a**) into the relevant triazoles (**19b**–**38b**: see Table 1 for the definition of the structure) in dioxane/water at different pS^+ (an operational scale of proton concentration, see Section 4.2), the values observed[10a] in the pS^+-independent range (at pS^+ 3.80) were shown to fit in a single, common relationship of the Fujita–Nishioka type with the following susceptibility constants: $\rho_{o,m,p}$ −1.30, δ 0.54 and f −0.90. In contrast, in the base-catalysed range



1a-18a, 24a **1b-18b, 24b**

1: Ar = 2,3-$Me_2C_6H_3$
2: Ar = 2,4-$Me_2C_6H_3$
3: Ar = 2,5-$Me_2C_6H_3$
4: Ar = 3,4-$Me_2C_6H_3$
5: Ar = 2,4-$F_2C_6H_3$
6: Ar = 2,5-$F_2C_6H_3$
7: Ar = 3,5-$F_2C_6H_3$
8: Ar = 2,3-$Cl_2C_6H_3$
9: Ar = 2,4-$Cl_2C_6H_3$
10: Ar = 2,5-$Cl_2C_6H_3$
11: Ar = 2,6-$Cl_2C_6H_3$
12: Ar = 3,4-$Cl_2C_6H_3$
13: Ar = 3,5-$Cl_2C_6H_3$
14: Ar = 3-Cl-4-FC_6H_3
15: Ar = 2,4-$(NO_2)_2C_6H_3$
16: Ar = 2,4,6-$Cl_3C_6H_2$
17: Ar = 2,3,5,6-F_4C_6H
18: Ar = C_6F_5
24: Ar = C_6H_5

Scheme 1.

(for example, at pS^+ 11.50) two separate multiparameter relationships were evidenced:[10a] the first one for *Z*-arylhydrazones containing electron-withdrawing substituents, for which $\rho_{o,m,p}$ 2.23 and δ 1.51 were calculated, with an uncertain contribution of field effect (f 0.3±0.2), and the second one for *Z*-arylhydrazones containing electron-repelling substituents. In the latter case the very small number of substituents examined (moreover showing quantitatively similar effects) allowed only a qualitative indication of a significant steric effect and did not permit definitive conclusions concerning the field effect.

For a different example of MRH, that is, the ring-degenerate equilibration of some 3-aroylamino-5-methyl-1,2,4-oxadiazoles into 3-acetylamino-5-aryl-1,2,4-oxadiazoles in methanol in neutral as well as in basic solution we interestingly observed[11] no contribution of steric parameters in the Fujita–Nishioka treatment, because the strong internal conjugation of the amido group[12] leaves little role for the conjugation between the aryl group and the carbonyl carbon of the aroylamino moiety. However the contribution of the proximity polar effect with respect to the ordinary polar effect is very high in neutral solution, whilst a balance between the two effects occurs in basic solution.

Also of interest is the situation observed in other five-membered heterocyclic compounds: as a matter of fact, studying S_NAr reactions in some thiophenes we observed a strong attenuation or even the disappearance of kinetic steric effects (both primary[13] and secondary[14]) with respect to the well-known situation for benzene (or other six-membered aromatic compounds), and consequently we verified the occurrence of excellent LFER's in tri- as well as in tetra-substituted thiophenes.[15] Also studies on some series of *ortho*-substituted thiophenecarboxylic acids[16] (or their derivatives[17]) evidenced the occurrence of a simple LFER.

2. Results and discussion

2.1. Qualitative discussion of reactivity data

The rearrangement of **1a**–**18a** has been studied in 1:1 (v:v) dioxane/water, in the presence of buffers, in a large range of pS^+ (3.80–12.50) and at different temperatures. The kinetic data and the relevant thermodynamic parameters are reported in the Supplementary Material (Tables A–R). For all the substrates considered it was not possible to carry out kinetic experiments at pS^+ <3.80, where the hydrolysis to 3-benzoyl-5-phenyl-1,2,4-oxadiazole and arylhydrazine becomes the prevailing reaction.

In Table 1 the ratios of the logarithmic *A*pparent first-order rate constants for the *R*earrangement [$\log(k_{A,R})_X/(k_{A,R})_H$, calculated at 313.15 K from activation parameters] of **1a**–**18a**, at pS^+ =3.80 and 11.50, are collected together with the calculated substituent constants (σ_{calc}, see notes b and c in Table 1). For comparison, previous data for the arylhydrazones **19a**–**38a**[10] are also reported. In Figure 1 $\log k_{A,R}$ for **2a**, **5a** and **15a** as well as those for **24a**, **32a** and **38a** are plotted versus pS^+ values.

Table 1. Parameters used in LFER treatments for the rearrangement of the *Z*-arylhydrazones **1a–38a** into triazoles **1b–38b** in dioxane/water (1:1, v:v)

Comp.	Substituent	pS^+ 3.80		pS^+ 11.50		E_S[d]	F[d]
		$\log(k_{A,R})_X/(k_{A,R})_H$[a]	σ_{calc}[b]	$\log(k_{A,R})_X/(k_{A,R})_H$[a]	σ_{calc}[c]		
1a	2,3-Me_2	−0.367[e]	−0.193	−0.723[e]	−0.38	−1.24	−0.04
2a	2,4-Me_2	−0.270[e]	−0.248	−0.650[e]	−0.62	−1.24	−0.04
3a	2,5-Me_2	−0.339[e]	−0.193	−0.738[e]	−0.38	−1.24	−0.04
4a	3,4-Me_2	0.180[e]	−0.193	0.113[e]	−0.38		
5a	2,4-F_2	−1.037[e]	0.302	0.083[e]	0.266	−0.46	0.43
6a	2,5-F_2	−1.240[e]	0.491	0.521[e]	0.473	−0.46	0.43
7a	3,5-F_2	−0.881[e]	0.680	1.529[e]	0.68		
8a	2,3-Cl_2	−1.728[e]	0.642	0.050[e]	0.638	−0.97	0.41
9a	2,4-Cl_2	−1.549[e]	0.538	−0.092[e]	0.530	−0.97	0.41
10a	2,5-Cl_2	−1.679[e]	0.642	0.088[e]	0.638	−0.97	0.41
11a	2,6-Cl_2	−0.935[e]	0.538	0.560[e]	0.53	−1.94	0.82
12a	3,4-Cl_2	−0.795[e]	0.642	1.489[e]	0.638		
13a	3,5-Cl_2	−0.965[e]	0.746	1.637[e]	0.746		
14a	3-Cl-4-F	−0.682[e]	0.524	1.170[e]	0.506		
15a	2,4-$(NO_2)_2$			1.343[e]	2.10	−2.52	0.67
16a	2,4,6-Cl_3	−1.165[e]	0.807	1.355[e]	0.795	−1.94	0.82
17a	2,3,5,6-F_4			2.684[e]	0.946	−0.92	0.86
18a	2,3,4,5,6-F_5			2.819[e]	1.079	−0.92	0.86
19a	4-OMe	0.195[f]	−0.168	0.255[f]	−0.78[g]		
20a	4-Me	0.155[f]	−0.124	0.102[f]	−0.31[g]		
21a	4-Et	0.135[f]	−0.141	0.090[f]	−0.30[g]		
22a	3-Me	0.053[f]	−0.069[h]	0.023[f]	−0.069[h]		
23a	3-Et	0.065[f]	−0.070[h]	0.023[f]	−0.070[h]		
24a	H	0.000[f]	0.000[h]	0.000[f]	0.000[h]		
25a	4-F	−0.220[f]	0.151	0.320[f]	0.133		
26a	4-Cl	−0.339[f]	0.269	0.646[f]	0.265		
27a	4-Br	−0.390[f]	0.282	0.689[f]	0.273		
28a	3-Cl	−0.498[f]	0.373[h]	0.830[f]	0.373[h]		
29a	3-Br	−0.526[f]	0.391[h]	0.907[f]	0.391[h]		
30a	3-NO_2	−0.945[f]	0.710[h]	1.582[f]	0.710[h]		
31a	4-CN	−1.015[f]	0.775	1.854[f]	0.858		
32a	4-NO_2	−1.173[f]	0.895	2.426[f]	1.048		
33a	2-Me	−0.439[f]	−0.124	−0.774[f]	−0.31[g]	−1.24	−0.04
34a	2-Et	−0.491[f]	−0.141	−0.828[f]	−0.30[g]	−1.31	−0.05
35a	2-F	−0.772[f]	0.151	−0.234[f]	0.133	−0.46	0.43
36a	2-Cl	−1.258[f]	0.269	−0.728[f]	0.265	−0.97	0.41
37a	2-Br	−1.452[f]	0.282	−0.995[f]	0.273	−1.16	0.44
38a	2-NO_2	−3.153[f]	0.895	−1.231[f]	1.048	−2.52	0.67

[a] From $k_{A,R}$ (apparent rate constants for the rearrangement) values calculated at 313.15 K by the activation parameters. $(k_{A,R})_H$ 1.24×10^{-6} s^{-1} at pS^+ 3.80 and 2.52×10^{-3} s^{-1} at pS^+ 11.50.
[b] $\sigma_{calc}=\sum(\sigma^n+0.11\Delta\sigma_R^+ +0.26\Delta\sigma_R^-)$.[10b]
[c] $\sigma_{calc}=\sum(\sigma_H+0.60\Delta\sigma^-)$.[10b]
[d] Values from Ref. 6.
[e] This work.
[f] Values from Ref. 10a and references therein.
[g] Values of σ^+ from Ref. 2c.
[h] σ values defined by L. P. Hammett from Ref. 2a.

As shown in Figure 1 and in agreement with the mechanism proposed for the MRH process,[9f–k,10] the reactivity of compounds **1** is affected by the proton concentration. The trend of experimental data indicates that, similarly to the unsubstituted (**24a**) and, with few exceptions, to mono-substituted *Z*-arylhydrazones, also for all the polysubstituted *Z*-arylhydrazones examined herein but not for the 2,4-dinitrophenylhydrazone **15a** and the polyfluorophenylhydrazones **17a** and **18a**[18] two different reaction pathways can be evidenced: thus, in the 3.80–7.00 pS^+ range the reaction occurs via pS^+-independent route (that is, an uncatalysed process), while at p$S^+ > 8.00$ a pS^+-dependent route (that is, a general-base-catalysed pathway) is operating. Obviously, in the two cases, the structure of the transition state (see Fig. 2) should show a different degree of N(α)–N(2) bond formation and of N(α)–H bond breakage, actually depending both on the assistance provided by the solvent or by the base used and on the electronic effects of the substituents.[10b]

By studying the behaviour of some *ortho*-substituted arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**33a–38a**), we have previously shown that they are always less reactive than the corresponding *para*-substituted (**20a–21a**, **25a–27a**, **32a**) or unsubstituted (**24a**) substrates.[10] In the present study, an analysis of experimental data shows that, independent of the electronic nature of substituents, all 2,3-, 2,4-, 2,5- and 2,6-disubstituted arylhydrazones are always less reactive than the corresponding *meta*- and *para*-substituted derivatives, evidencing the importance of polar and/or steric proximity effects, caused by the *ortho* substitution.

For example, comparing the 2,4-disubstituted *Z*-arylhydrazones **2a** and **5a** [Ar=$Me_2C_6H_3$ and $F_2C_6H_3$, respectively] with the corresponding *para*-substituted derivatives (**20a** and **25a**) or with the unsubstituted phenylhydrazone **24a**, the following reactivity ratios at p$S^+=3.80$ can be calculated from the data in Table 1: $(k_{A,R})_{4\text{-}X}/(k_{A,R})_{2,4\text{-}X2}=2.7$ and 6.6 and $(k_{A,R})_H/(k_{A,R})_{2,4\text{-}X2}=1.9$ and 11, respectively.

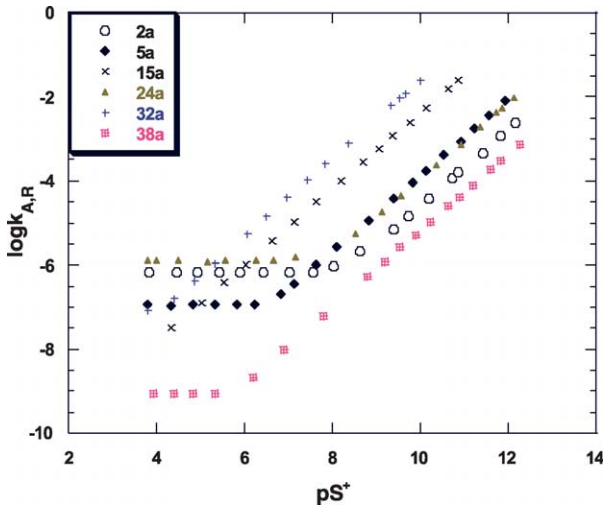
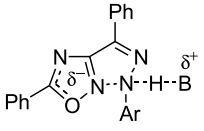


Figure 1. Plot of log $k_{A,R}$ for the rearrangement of **2a**, **5a**, **15a**, **24a**, **32a** and **38a** into the relevant triazoles in dioxane/water at 313.15 K versus pS^+.

On the other hand, at pS^+ = 11.50, where the comparison can be extended to the nitro-substituted derivatives **15a** [Ar = 2,4$(NO_2)_2C_6H_3$] and **32a**, a different behaviour has been observed: the disubstituted substrates are again less reactive than the *para*-substituted ones[10b] ($k_{4\text{-}X}/k_{2,4\text{-}X2}$ = 5.7, 1.7 and 12 for the couples **20a/2a**, **25a/5a** and **32a/15a**, respectively) while, in contrast, in the case of electron-repelling (**2a**) or -withdrawing (**5a** and **15a**) substituents, they are less or more reactive than the unsubstituted phenylhydrazone **24a** [$(k_{A,R})_H/(k_{A,R})_{2,4\text{-}X2}$ = 4.5, 0.83 and 0.045, respectively].

A comparison among the reaction profiles reported in Figure 1 shows that, in some cases, curves concerning *para*-substituted substrates intersect those concerning disubstituted ones. Furthermore, at a given pS^+ value, the rearrangement can follow different reaction pathways (uncatalysed or base-catalysed) depending on the nature of the substituents. Thus, at pS^+ = 7.00, the 2,4-dimethylphenylhydrazone (**2a**) and the 2,4-dinitrophenylhydrazone (**15a**) rearrange via uncatalysed and a base-catalysed pathway, respectively.

Looking at Figure 1, it is possible to see that in the pS^+-independent range the reactivity decreases while the electron-withdrawing power of the substituent and its *ortho*-steric effects increase. As a matter of fact, at pS^+ = 3.80, the reactivity order is **24a** > **2a** > **5a** > **32a** > **38a**. A different order has been observed in the base-catalysed range: for example, at pS^+ = 11.50 the reactivity order is **32a** > **15a** > **5a** ≈ **24a** > **2a** > **38a**.



B = base or solvent

Figure 2.

2.2. Quantitative treatment of reactivity data

Quantitative analysis has been carried out at pS^+ 3.80 and 11.50, that is at the two values previously used[10] for LFER studies in the uncatalysed and base-catalysed range for the rearrangement of several other *Z*-arylhydrazones, respectively. We would like to remember that kinetic data at different pS^+ values require different sets of substituent constants. As a matter of fact all the kinetic data at pS^+ 3.80 obey to Eq. 1 of Table 2,[10b] while at pS^+ 11.50 kinetic data for electron-withdrawing and -repelling substituents obey to Eqs. 1 and 2 of Table 3, respectively.[10b]

2.2.1. Use of LFER at pS^+ 3.80 (uncatalysed pathway). As previously shown by quantitative investigations on the rearrangement of *meta*-,[10b] *para*-[10b] (entry 1 of Table 2) and *ortho*-substituted[10a] (entries 2 and 3 of Table 2) *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole, a single relationship can be obtained, independent of the nature of the substituent (electron-repelling, that is with a negative Hammett substituent constant, or -withdrawing, that is with a positive Hammett constant).

Therefore, in order to examine the results obtained by studying the behaviour of the *Z*-arylhydrazones **1a**–**14a** and **16a**[18] we initially extended the LFER observed for *meta*- and *para*-substituted *Z*-arylhydrazones (**19a**–**32a**) to 3,5- (i.e., bis-*meta*-substituted: **7a** and **13a**) and 3,4-disubstituted (i.e., *meta*- and *para*-disubstituted: **4a**, **12a** and **14a**) substrates by applying the additivity rule to obtain the σ values useful to calculate the relevant ρ values. Interestingly, the inclusion of the new *Z*-arylhydrazones does not appreciably alter the susceptibility constants and the statistical data previously observed (compare entries 1 and 4 of Table 2). This first result has been confirmed by the behaviour observed including the abovementioned five *Z*-arylhydrazones in the LFER extended to *ortho*-, *meta*- and *para*-substituted *Z*-arylhydrazones previously examined by using Eq. 2: also in this case both susceptibility constants and statistical data remain practically unchanged (compare entries 3 and 5 of Table 2).

The encouraging results obtained induced us to attempt a LFER correlation (according to Eq. 2) inclusive of all the mono-, di- and tri-substituted *Z*-arylhydrazones **1a**–**14a**, **16a**, **19a**–**38a**, but a poor correlation coefficient was observed (R = 0.9077, see entry 6 of Table 2). A comparison between experimental and calculated (by using the susceptibility parameters of entry 6 of Table 2) rate constants (not reported) shows that the outlying points are those relevant to **11a** and **16a**. As a matter of fact, by excluding these two compounds a new LFER with an excellent correlation coefficient (R 0.9991) can be calculated, with susceptibility constants (ρ, δ and f) 'strictly' close to those previously obtained for the the monosubstituted (*ortho*, *meta* and *para*) *Z*-arylhydrazones (compare entries 3 and 7 of Table 2).

In order to provide better evidence of the outlying nature of kinetic data concerning **11a** and **16a** we have calculated the mean logarithmic residuals for $k_{A,R}$ values by applying Eq. 7 of Table 2. Interestingly we observed that while for compounds **1a**–**10a** and **12a**–**14a** the average of residuals is very low (<0.025), in contrast for **11a** and **16a** they are

Table 2. Linear free energy relationships[a] for the rearrangements **1a–38a → 1b–38b** at 313.15 K in dioxane/water (1:1, v:v) at pS^+ 3.80

No.	Equation used	$\rho \pm s_\rho$	$\delta \pm s_\delta$	$f \pm s_f$	$i \pm s_i$	r or R	n	Compounds
1	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho(\sigma^n + r^+\Delta\sigma^+ + r^-\Delta\sigma^-) + i$	−1.29±0.01			−0.02±0.01	0.9995	14	**19a–32a**
2	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sigma_o + \delta E_s + fF + i$	−1.36±0.17	0.55±0.04	−0.87±0.18	0.01±0.05	0.9994	7	**24a**,**33a–38a**
3	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sigma_{o,m,p} + \delta E_s + fF + i$	−1.30±0.02	0.54±0.01	−0.90±0.05	−0.01±0.01	0.9994	20	**19a–38a**
4	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + i$	−1.26±0.01			−0.02±0.01	0.9991	19	**4a**,**7a**,**12a–14a**,**19a–32a**
5	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + \delta E_s + fF + i$	−1.28±0.02	0.54±0.01	−0.92±0.05	−0.02±0.01	0.9992	25	**4a**,**7a**,**12a–14a**,**19a–38a**
6	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + \delta E_s + fF + i$	−1.29±0.17	0.46±0.11	−0.14±0.32	−0.08±0.08	0.9077	35	**1a–14a**,**16a**,**19a–38a**
7	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + \delta E_s + fF + i$	−1.29±0.02	0.52±0.01	−0.92±0.04	−0.01±0.01	0.9991	33	**1a–10a**,**12a–14a**,**19a–38a**

[a] s_ρ, s_δ, s_f, s_i represent standard errors, respectively, of ρ, δ, f and i (intercept); r or R, correlation coefficients; n, number of data points. The values of $\sigma_{calc.}$, E_S, F and $\log[(k_{A,R})_X/(k_{A,R})_H]$ used in correlations are shown in Table 1. $\sum\sigma$ represents summation of σ_{calc}.

very high (1.534 and 1.651, respectively). This situation appears evident by looking at a plot of experimental $\log(k_{A,R})_X/(k_{A,R})_H$ versus data calculated by using the above Eq. 7 (see Fig. 3): an excellent straight line with unitary slope has been of course obtained for all the points, but not for **11a** and **16a**.

Finally, an examination of thermodynamic parameters shows that the uncatalysed pathway is characterised by a practically constant activation enthalpy ($\Delta H^{\#}$ 98.0±1.4 kJ mol^{-1}) for all the *Z*-arylhydrazones examined: the reactivity being almost exclusively entropy-dependent ($\Delta S^{\#}$ ranging between −49 and −77 J K^{-1} mol^{-1}). Thus, the thermodynamic outcome (especially the high value of the activation entropy)[9f–j,10] is in agreement with the occurrence of an ordered and strongly solvated rate-determining transition state, as expected for a S_{Ni}-like process.

2.2.2. Use of LFER at pS^+ 11.50 (general-base-catalysed pathway). In the base-catalysed range we had observed, for *meta*- and *para*-substituted[10b] *Z*-arylhydrazones, two separate LFERs for electron-withdrawing and for electron-repelling substituents (entries 1 and 2 of Table 3), with the unsubstituted **24a** showing the lowest reactivity. The same situation was evidenced later also in the case of *ortho*-substituted *Z*-arylhydrazones[10a] (entries 3–5 of Table 3).

Such a peculiar behaviour (non-linear, concave-upward) of the linear free-energy correlation suggests a changeover of the mechanism with the nature of the substituent: electron-withdrawing substituents facilitating the hydrogen abstraction from the N(α)–H bond, electron-repelling substituents increasing the nucleophilic character of N(α) and then its ability to attack N(2). Consequently in the two situations the extent of formation of the new bond [N(α)–N(2)] and of

Table 3. Linear free energy relationships[a] for the rearrangements **1a–38a → 1b–38b** at 313.15 K in dioxane/water (1:1, v:v) at pS^+ 11.50

No.	Equation used	$\rho \pm s_\rho$	$\delta \pm s_\delta$	$f \pm s_f$	$i \pm s_i$	r or R	n	Compounds
1	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho(\sigma^n + r^-\Delta\sigma^-) + i$	2.22±0.05			0.03±0.03	0.9983	9	**24a–32a**
2	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sigma^+ + i$	−0.33±0.01			0.00±0.00	0.9997	6	**19a–24a**
3	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sigma_{o,m,p} + \delta E_S + fF + i$	2.30±0.01	1.55±0.01	0.41±0.01	0.00±0.00	0.9999	5	**24a**,**35a–38a**
4	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sigma_{o,m,p} + \delta E_S + fF + i$	2.23±0.04	1.51±0.05	0.31±0.16	0.02±0.02	0.9994	13	**24a–32a**,**35a–38a**
5	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sigma_{o,m,p} + \delta E_S + fF + i$	−0.33±0.01	0.71±0.00		0.00±0.00	0.9999	8	**19a–24a**,**33a**,**34a**
6	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + i$	2.22±0.04			0.03±0.02	0.9979	13	**7a**,**12a–14a**,**24a–32a**
7	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + \delta E_S + fF + i$	2.22±0.04	1.50±0.05	0.29±0.15	0.03±0.02	0.9993	17	**7a**,**12a–14a**,**24a–32a**,**35a–38a**
8	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + \delta E_S + fF + i$	2.35±0.27	1.90±0.24	2.56±0.55	−0.19±0.17	0.9021	27	**5a–18a**,**24a–32a**,**35a–38a**
9	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma + \delta E_S + fF + i$	2.30±0.04	1.50±0.04	0.32±0.12	−0.01±0.02	0.9986	23	**5a–10a**,**12a–15a**,**24a–32a**,**35a–38a**
10	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma^+ + i$	−0.32±0.01			0.00±0.00	0.9984	7	**4a**,**19a–24a**
11	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma^+ + \delta E_S + fF + i$	−0.32±0.01	0.70±0.04	0.19±0.99	0.00±0.00	0.9999	9	**4a**,**19a–24a**,**33a–34a**
12	$\log[(k_{A,R})_X/(k_{A,R})_H] = \rho\sum\sigma^+ + \delta E_S + fF + i$	−0.33±0.01	0.62±0.04	2.33±1.28	0.00±0.01	0.9998	12	**1a–4a**,**19a–24a**,**33a–34a**

[a] s_ρ, s_δ, s_f, s_i represent standard errors, respectively, of ρ, δ, f and i (intercept); r or R, correlation coefficients; n, number of data points. The values of $\sigma_{calc.}$, E_S, F and $\log[(k_{A,R})_X/(k_{A,R})_H]$ used in correlations are shown in Table 1. $\sum\sigma$ and $\sum\sigma^+$ represent summation of σ_{calc} and of σ^+_{calc}.

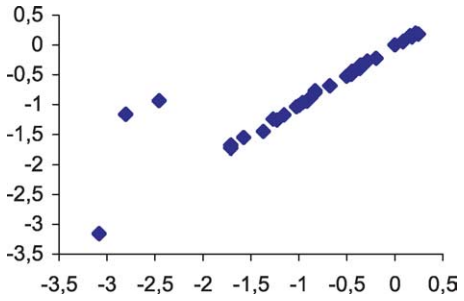


Figure 3. Plot of experimental log $(k_{AR})_X/(k_{AR})_H$ versus data calculated by using the Eq. 7 of Table 2.

breakage of the N(α)–H bond in the rate-determining transition state depends on the nature of the substituent itself.

The treatment of kinetic data at pS^+ 11.50 has been performed using the same rationale followed above for the data at pS^+ 3.80.

Thus, considering the case of electron-withdrawing substituents, we have extended the LFER concerning *meta*- and *para*-substituted *Z*-arylhydrazones (**24a**–**32a**) to the 3,5- (**7a** and **13a**) and the 3,4-disubstituted (**12a** and **14a**) ones, obtaining susceptibility constants and statistical data strictly comparable to those previously observed (compare entries 1 and 6 of Table 3). Moreover, the inclusion of the same four *Z*-phenylhydrazones also in the LFER concerning *ortho*-, *meta*- and *para*-substituted *Z*-phenylhydrazones does not affect the results of the correlation (compare entries 4 and 7 of Table 3). A further enlargement to all the mono-, di-, tri-, tetra- and penta-substituted *Z*-arylhydrazones (**24a**–**32a**, **35a**–**38a**, **5a**–**18a**) containing electron-withdrawing susbtituents gives a LFER with poor statistical results (R= 0.9021, see entry 8 of Table 3), but the exclusion of the points relevant to **11a** and **16a**–**18a** leads to susceptibility constants 'strictly' close to those of entry 4 of Table 3, with an excellent correlation coefficient (R 0.9986, see entry 9 of Table 3).

The treatment previously carried out for kinetic data at pS^+ 3.80 (2.2.1) has been now repeated, once more observing low mean logarithmic residuals (<0.042) in all cases but not for **11a** and **16a**–**18a** (2.000, 2.186, 1.626 and 1.462, respectively): the outlying character of these points being well evidenced in Figure 4.

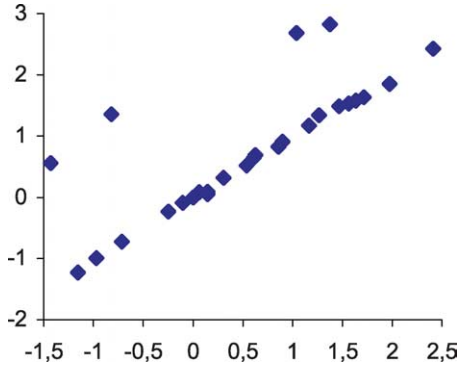


Figure 4. Plot of experimental log $(k_{AR})_X/(k_{AR})_H$ versus data calculated by using the Eq. 9 of Table 3.

Concerning the case of electron-repelling substituents, we have extended the LFER relevant to *meta*- and *para*-substituted *Z*-arylhydrazones (**19a**–**24a**) to the only 3,4-disubstituted one studied (**4a**): no significant change of the susceptibility constant together with an excellent statistical result (R=0.9984, see entry 10 of Table 3) has been observed and the same situation occurs including also the *ortho*-derivatives (**33a** and **34a**; R=0.9999, see entry 11 of Table 3). Moreover, at variance with the findings above, the enlargement to all the mono-, di- and tri-substituted *Z*-arylhydrazones (**19a**–**24a**, **33a**–**34a**, **1a**–**4a**) containing electron-repelling substituents gives a LFER with excellent statistical results (R=0.9998, see entry 12 of Table 3).

These two new sets of data at pS^+ 11.50 allow a better understanding of the proximity effects of *ortho*-substituents in the base-catalysed range. As a matter of fact in our previous paper,[10a] because of the limited number of *ortho*-derivatives examined [four electron-withdrawing and only two electron-repelling (moreover with similar effects: methyl and ethyl)] we could only collect uncertain data concerning field effects. Now, by adding nine electron-withdrawing substituents and four electron-donating substituents, we have been able to confirm (see entries 9 and 12 of Table 3) the occurrence of steric effects (δ=1.50±0.04 and 0.62±0.04, respectively) and to gain significant and interesting proofs in favour of the occurrence of field effects (f=0.32±0.12 and 2.33±1.28, respectively).

In this pathway, the discussion of thermodynamic parameters is less significant that in the uncatalysed one, because of their composite nature.[9f–j] Nevertheless it clearly appears that the reactivity variations (as a function of the nature of the substituents as well as of the value of pS^+) are more entropy- than enthalpy-dependent.

2.3. On the 'abnormal' reactivity of 2,6-dichloro-(11a), 2,4,6-trichloro-(16a), 2,3,5,6-tetrafluoro-(17a) and 2,3,4,5,6-pentafluoro-*Z*-phenylhydrazones (18a)

As shown above, **11a** and **16a**–**18a** (the only bis-*ortho*-substituted compounds) show a reactivity higher than that expected and behave as outlying in LFERs (see Figs. 3 and 4). As a matter of fact, by using the calculated susceptibility constants (line 7 of Table 2 and line 9 of Table 3, respectively) we calculated the following rate constants: at pS^+=3.80, $(k_{A,R})_{\mathbf{11a}}$ 4.42×10^{-9} s^{-1} and $(k_{A,R})_{\mathbf{16a}}$ 1.99×10^{-9} s^{-1}; at pS^+=11.50, $(k_{A,R})_{\mathbf{11a}}$ 9.04×10^{-5} s^{-1}, $(k_{A,R})_{\mathbf{16a}}$ 3.68×10^{-4} s^{-1}, $(k_{A,R})_{\mathbf{17a}}$ 0.0290 and $(k_{A,R})_{\mathbf{18a}}$ 0.0599, respectively: these values are 33 and 43 (at pS^+= 3.80) and 102, 155, 42 and 28 (at pS^+=11.50) times lower than those experimentally observed (e.g., at pS^+=3.80, $(k_{A,R})_{\mathbf{11a}}$ 1.44×10^{-7} s^{-1} and at pS^+=11.50, $(k_{A,R})_{\mathbf{11a}}$ 9.15×10^{-5} s^{-1}). Considering the occurrence of bis-*ortho*-substitution this acceleration, which represents the first evidence of 'steric acceleration' in mononuclear rearrangements of heterocycles, should be related to some steric effect operating in the starting substrates (that is increasing their energy content) or in the rate-determining transition states (that is decreasing the activation-energy barrier).

In an attempt to elucidate the previous point, we have subjected compounds **11a** and **36a**[19] to an ab initio computation (at DFT level and in the gas phase).[9k] It must be remarked that by applying Eq. 2 and by using the calculated susceptibility constants (line 7 of Table 2 and line 9 of Table 3, respectively) **11a** is expected to be less reactive than **36a** by a factor of 15.5 or 5.2 at pS^+ 3.80 or 11.50, respectively (i.e., its rearrangement requiring an energy barrier 7 or 4 kJ mol^{-1} higher) while we have observed that **11a** is more reactive than **36a** at pS^+ 3.80 and 11.50 by a factor of 2.1 and 19.4, experiencing 2 and 8 kJ mol^{-1} lower energy barriers, respectively.

We first optimised the geometry of **11a** and **36a**, observing that both are planar and at the same time do not show significant variations with respect to the structure of **24a**, thus excluding the influence of 2-monosubstitution or 2,6-disubstitution on the geometrical structure of the starting compounds and hence on its energy content. Secondly, by studying the course of the reaction (the recently deeply investigated uncatalysed pathway[9k] has been considered) we interestingly observed that in the case of **11a** the formation of the first transition state [relevant to the rate-determining nucleophilic attack of N(α) onto N(2)] requires an energy barrier some kJ mol^{-1} lower than that for **36a**. As we have recently pointed out,[9k] in this step a large part of the energy required depends on a rotation around the N(α)–N(β) bond to correctly orient the nitrogen lone pair of N(α) as well as on a rehybridation of N(α) (from sp^2 onto sp^3): both these two events can contribute, in **11a**, to release at least in part the steric strain due to the 2,6-disubstitution, thus explaining the abnormal reactivity of **11a** and, likewise, of **16a**–**18a**.[19] Interestingly, in agreement with the lower steric requirements of fluorine with respect to chlorine [for example, compare the E_S values for chlorine (−0.97) and fluorine (−0.46)] we have observed a larger steric acceleration in the case of **11a** and **16a** than in the case of **17a** and **18a** (see the reactivity ratios reported above), notwithstanding the fact that the fluorines at C(3) and C(5) should exert in the latter two arylhydrazones a buttressing effect.

Perhaps a similar effect could contribute to the higher-than-predicted acidity observed by Exner et al. for 2,6-dimethyl benzoic acid, attributed[20] to a better solvated non-planar structure of the relevant anion.

3. Conclusions

An accurate kinetic investigation of the rearrangement of several poly-substituted *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole **1a**–**18a** into the relevant triazoles **1b**–**18b** has been carried out in dioxane/water in the 3.80–12.50 pS^+ range. The results obtained have been treated according to the Fujita–Nishioka LFER (Eq. 2) together with previous data concerning **19a**–**38a**.

The following points have been evidenced:

(i) **15a**, **17a** and **18a** fail to show the uncatalysed (or solvent-catalysed) pathway;

(ii) at pS^+ 3.80 (uncatalysed pathway) the rate constants of **1a**–**14a** and **16a** give, together with those for **19a**–**38a**, an excellent correlation according to Eq. 2, after exclusion of the two bis-*ortho*-substituted derivatives (**11a** and **16a**; see Fig. 3) (line 7 of Table 2; $R=0.9991$);

(iii) at pS^+ 11.50 (general-base-catalysed pathway) the rate constants of **1a**–**18a** give separate correlations for electron-withdrawing and for electron-repelling substituents. Once again two excellent correlations have been calculated (see lines 9 and 12 of Table 3; $R=0.9986$ and 0.9998, respectively) after exclusion, in the first case, of the data for the four bis-*ortho*-substituted derivatives (**11a** and **16a**–**18a**; see Fig. 4);

(iv) the susceptibility constants (ρ, δ and f) previously calculated for *ortho*-, *meta*- and *para*-substituted *Z*-arylhydrazones **19a**–**38a** have been confirmed after inclusion in the computations of the polysubstituted ones **1a**–**18a** as appropriate [cf. points (ii) and (iii) above]: only in the instance of electron-repelling substituents at pS^+ 11.50 a further (probable) field effect has been evidenced;

(v) by examining the calculated susceptibility constants two interesting confirmations of previous conclusions have been achieved: (1) the δ values calculated at pS^+ 3.80 and 11.50 (in the second instance two separate LFER for electron-withdrawing and -repelling substituents being observed) are: 0.52, 1.50 and 0.62, respectively. For the general-base-catalysed pathway in the presence of electron-withdrawing substituents the highest δ has been calculated, in agreement with the suggested mechanism:[9f–j,10,24] as a matter of fact, owing to the participation of a base to the rate-determining transition state formation, it becomes more crowded and then more sensitive to steric strains. In the same pathway with electron-repelling substituents a changeover of the mechanism occurs (see discussion on this point at section 2.2.2), the N(α)–H bond breakage is less important and then the rate-determining transition state is less crowded and the δ value becomes similar to that observed in the uncatalysed pathway (δ 0.62 and 0.52, respectively); (2) concerning the calculated f values, we have observed at pS^+ 3.80 a large contribution of field effect comparable to that of the normal electronic one (ρ −1.29 and f −0.92); by contrast, at pS^+ 11.50, for electron-withdrawing substituents the normal electronic effect is largely prevailing (ρ 2.30 and f 0.32). For electron-repelling substituents the high f value is affected by a large error (f 2.33 ± 1.28) and appears opposite to the normal electronic effect (ρ −0.33);

(vi) in the whole, the obtained reactivity data have furnished a further quantitative confirmation of the additivity rule (without the occurrence of a saturation effect) also in the case of compounds in which the three substituents are in 1,2,3- or in a 1,3,4-relationship (see **1a** and **8a** as well as **4a**, **12a** and **14a**), which could, in principle, give stronger steric effects;

(vii) the particular kinetic behaviour of **11a** and **16a**–**18a** has been discussed and a rationale has been attempted

for such a 'steric acceleration' observed for the first time in mononuclear rearrangement of heterocycles.

4. Experimental

4.1. Synthesis and purification of compounds

Compounds **1a**–**18a** were prepared from 3-benzoyl-5-phenyl-1,2,4-oxadiazole and the appropriate substituted arylhydrazine in ethanol in the presence of acetic acid following a previous procedure.[21] Sometimes both *Z*- and *E*-isomers were obtained, the former with yields ranging between 50–70% and the latter with lower yields (20–30%). Purification was achieved by chromatography [silica gel: cycloexane/ethyl acetate (20/1)] and crystallization from ethanol.

The *Z*-arylhydrazones **1a**–**18a** were rearranged into the relevant 2-aryl-4-benzoylamino-5-phenyl-1,2,3-triazoles **1b**–**18b** by standing in ethanol in the presence of aqueous KOH (10%) at room temperature until disappearance of the starting product (tlc analysis) and/or by melting. Compounds **1b**–**18b** were purified by crystallization from ethanol.

4.1.1. Compound *Z*-1a. Yellow solid, mp 155–158 °C; ν_{max} (nujol) 3240 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 11.45 (1H, s, NH), 8.36–6.68 (13H, m, 2Ph, Ar), 2.36 (6H, s, $2CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.22, 164.02, 142.04, 136.95, 136.89, 133.26, 129.24, 128.47, 128.28, 128.00, 127.88, 126.48, 123.56, 123.30, 120.38, 111.30, 20.43, 12.75; MS(ESI): *m*/*z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.75; H, 5.40; N, 15.4%.

4.1.2. Compound *Z*-2a. Yellow solid, mp 142–144 °C; ν_{max} (nujol) 3220 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 11.35 (1H, s, NH), 8.21–7.09 (13H, m, 2Ph, Ar), 2.42 (3H, s, CH_3); 2.30 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.20, 164.11, 139.75, 136.94, 133.27, 131.13, 130.71, 129.28, 128.47, 128.32, 128.02, 127.85, 127.80, 126.18, 123.62, 121.80, 113.11, 20.67, 17.38; MS(ESI): *m*/*z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.68; H, 5.50; N, 15.32%.

4.1.3. Compound *Z*-3a. Yellow solid, mp 170 °C; ν_{max} (nujol) 3240 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.80 (1H, s, NH), 8.10–7.31 (13H, m, 2Ph, Ar), 2.44 (6H, s, $2CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.56, 164.37, 142.04, 137.34, 137.18, 133.57, 130.62, 129.56, 128.87, 128.60, 128.34, 128.25, 126.98, 123.88, 122.45, 119.23, 113.86, 21.74, 17.31; MS(ESI): *m*/*z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.85; H, 5.38; N, 15.35%.

4.1.4. Compound *E*-3a. Yellow solid, mp 145 °C; ν_{max} (nujol) 1610, 3320 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 8.20 (1H, s, NH), 8.20–6.72 (13H, m, 2Ph, Ar), 2.37 (3H, s, CH_3), 1.98 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.49; 168.68; 140.51; 137.00; 133.25; 132.73; 130.29; 129.77; 129.23; 128.54; 128.36; 128.27; 128.00; 127.93; 124.11; 122.07; 113.53; MS(ESI): *m*/*z* 367.2 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.95; H, 5.48; N, 15.25%.

4.1.5. Compound *Z*-4a. Yellow solid, mp 136–138 °C; ν_{max} (nujol) 3220 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.82 (1H, s, NH), 8.10–7.40 (13H, m, 2Ph, Ar), 2.42 (3H, s, CH_3), 2.36 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.20, 164.06, 141.87, 137.58, 136.93, 133.22, 130.35, 129.96, 129.21, 128.39, 127.99, 127.76, 125.48, 123.61, 115.29, 111.42, 20.00, 19.04; MS(ESI): *m*/*z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.70; H, 5.32; N, 15.35%.

4.1.6. Compound *Z*-5a. Yellow solid, mp 144–146 °C; ν_{max} (nujol) 3210 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 11.81 (1H, s, NH), 8.26–7.40 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.95, 164.14, 155.57, 151.70, 148.46, 136.63, 133.73, 129.60, 129.34, 128.72, 128.68, 123.65, 115.32, 115.25, 112.02, 111.98, 104.31; MS(ESI): *m*/*z* 375.4 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.12; H, 3.65; N, 14.95%.

4.1.7. Compound *Z*-6a. Yellow solid, mp 145–148 °C; ν_{max} (nujol) 3240 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.93 (1H, s, NH), 8.09–7.45 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.10, 164.05, 161.70, 148.40, 145.26, 130.72, 130.11, 129.53, 128.56, 127.98, 127.87, 127.66, 127.41, 117.11, 116.09, 115.69, 102.27; MS(ESI): *m*/*z* 375.3 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.15; H, 3.85; N, 14.80%.

4.1.8. Compound *Z*-7a. Yellow solid, mp158–160 °C; ν_{max} (nujol) 3205 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.98 (1H, s, NH), 8.10–7.41 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.77, 165.71, 165.51, 163.79, 162.45, 162.25, 146.46, 146.28, 136.01, 133.56, 129.33, 128.60, 128.41, 128.14, 123.24; MS(ESI): *m*/*z* 375.3 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.08; H, 3.82; N, 14.83%.

4.1.9. Compound *E*-7a. Colourless solid, mp 87–89 °C; ν_{max} (nujol) 3198 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.26 (1H, s, NH), 8.22–6.67 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.73; 168.41; 162.29; 162.09; 145.66; 134.44; 132.92; 129.40; 128.91; 128.79; 128.59; 128.49; 128.34; 123.93; 97.22; 96.88; 96.19; MS(ESI): *m*/*z* 375.3 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.00; H, 3.78; N, 14.93%.

4.1.10. Compound *Z*-8a. Yellow solid, mp 144–146 °C; ν_{max} (nujol) 3210 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.91 (1H, s, NH), 8.09–7.47 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.20, 163.93, 142.49, 136.48, 133.83, 133.20, 129.65, 128.95, 128.68, 128.46, 128.32, 123.63, 122.27, 117.22, 112.97; MS(ESI): *m*/*z* 407.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.72; H, 3.35; N, 13.74%.

4.1.11. Compound *Z*-9a. Yellow solid, mp 141–143 °C; ν_{max} (nujol) 3210 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.98 (1H, s, NH), 8.11–7.42 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.16, 163.69, 137.99, 136.52, 133.72, 130.21, 129.66, 129.61, 128.83, 128.69, 128.58,

128.44, 126.23, 124.17, 123.72; MS(ESI): *m/z* 407.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.45; H, 3.55; N, 13.80%.

4.1.12. Compound *Z*-10a. Yellow solid, mp 118 °C; ν_{max} (nujol) 3200 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.92 (1H, s, NH), 8.09–7.47 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.19, 163.94, 141.65, 136.33, 134.33, 133.81, 130.40, 130.09, 129.63, 129.05, 128.94, 128.68, 128.49, 123.61, 121.55, 116.98, 113.91; MS(ESI): *m/z* 407.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.58; H, 3.32; N, 13.84%.

4.1.13. Compound *E*-10a. Yellow solid, mp 115 °C; ν_{max} (nujol) 3310 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 8.76 (1H, s, NH), 8.24–7.05 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 176.12; 168.67; 140.21; 139.88; 135.94; 134.01; 132.89; 130.39; 129.78; 129.39; 129.00; 128.54; 128.34; 123.88; 121.37; 116.16; 114.92; MS(ESI): *m/z* 407.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.64; H, 3.42; N, 13.74%.

4.1.14. Compound *Z*-11a. Yellow-orange solid, mp 120 °C; ν_{max} (nujol) 3220 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.96 (1H, s, NH), 8.34–7.48 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.87, 163.39, 137.71, 136.23, 133.42, 129.93, 129.35, 129.32, 128.53, 128.28, 128.14, 125.96, 123.88, 123.43, 110.75; MS(ESI): *m/z* 406.7 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.60; H, 3.40; N, 13.74%.

4.1.15. Compound *Z*-12a. Yellow solid, mp 120–122 °C; ν_{max} (nujol) 3200 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.96 (1H, s, NH), 8.34–7.48 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.67, 163.86, 143.40, 136.13, 133.49, 133.27, 130.80, 129.84, 129.30, 129.04, 128.49, 128.41, 128.12, 124.31, 123.29, 115.35, 113.31; MS(ESI): *m/z* 406.8 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.65; H, 3.43; N, 13.70%.

4.1.16. Compound *Z*-13a. Yellow solid, mp 125 °C; ν_{max} (nujol) 3210 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.97 (1H, s, NH), 8.12–7.46 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.77, 163.75, 145.62, 135.93, 135.66, 133.53, 129.30, 128.85, 128.60, 128.52, 128.40, 128.11, 123.19, 121.18, 112.23; MS(ESI): *m/z* 406.9 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.75; H, 3.49; N, 13.64%.

4.1.17. Compound *E*-13a. Colourless solid, mp 155 °C; ν_{max} (nujol) 3310 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.21 (1H, s, NH), 8.21–7.06 (13H, m, 2Ph, Ar); MS(ESI): *m/z* 406.8 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.71; H, 3.46; N, 13.74%.

4.1.18. Compound *Z*-14a. Yellow solid, mp 129–130 °C; ν_{max} (nujol) 3220 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.92 (1H, s, NH), 8.33–7.44 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.50, 163.86, 154.94, 140.71, 140.68, 136.22, 133.42, 129.25, 128.43, 128.36, 128.29, 128.07, 127.47, 123.28, 117.07, 115.27, 113.04; MS(ESI): *m/z* 391.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OClF$: C, 64.21; H, 3.59; N, 14.26%. Found: C, 64.12; H, 3.50; N, 14.35%.

4.1.19. Compound *E*-14a. Colourless solid, mp 125 °C; ν_{max} (nujol) 3310 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.07 (1H, s, NH), 8.22–7.37 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.51; 163.84; 154.91; 140.69; 136.21; 133.43; 132.88; 129.24; 128.42; 128.36; 128.32; 128.06; 127.48; 123.25; 121.65; 117.08; 113.05; MS(ESI): *m/z* 391.2 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OClF$: C, 64.21; H, 3.59; N, 14.26%. Found: C, 64.22; H, 3.56; N, 14.31%.

4.1.20. Compound *Z*-15a. Yellow solid, mp 211–213 °C; ν_{max} (nujol) 3220 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 11.11 (1H, s, NH), 8.05–7.53 (13H, m, 2Ph, Ar); MS(ESI): *m/z* 429.3 (M−1). Anal. Calcd for $C_{21}H_{14}N_6O_5$: C, 58.61; H, 3.28; N, 19.53%. Found: C, 58.72; H, 3.33; N, 19.57%.

4.1.21. Compound *E*-15a. Yellow solid, mp 221–223 °C; ν_{max} (nujol) 3230 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 11.48 (1H, s, NH), 8.91–7.67 (13H, m, 2Ph, Ar); MS(ESI): *m/z* 429.4 (M−1). Anal. Calcd for $C_{21}H_{14}N_6O_5$: C, 58.61; H, 3.28; N, 19.53%. Found: C, 58.70; H, 3.29; N, 19.60%.

4.1.22. Compound *Z*-16a. Yellow solid, mp 154–155 °C; ν_{max} (nujol) 3220 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.97 (1H, s, NH), 8.10–7.43 (12H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.94, 163.33, 136.66, 136.01, 133.49, 130.42, 129.33, 129.14, 128.69, 128.38, 128.28, 128.17, 127.99, 126.15, 123.34; MS(ESI): *m/z* 441.2 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{13}N_4OCl_3$: C, 56.84; H, 2.95; N, 12.63%. Found: C, 56.75; H, 2.90; N, 12.74%.

4.1.23. Compound *E*-16a. Colourless solid, mp 147–149 °C; ν_{max} (nujol) 3223 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.93 (1H, s, NH), 8.15–7.45 (12H, m, 2Ph, Ar). MS(ESI): *m/z* 441.2 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{13}N_4OCl_3$: C, 56.84; H, 2.95; N, 12.63%. Found: C, 56.86; H, 2.93; N, 12.70%.

4.1.24. Compound *Z*-17a. Yellow solid, mp 168–170 °C; ν_{max} (nujol) 3200 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.99 (1H, s, NH), 8.41–7.49 (11H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.87, 166.73, 147.96, 144.95, 143.97, 142.66, 139.89, 132.97, 132.58, 129.53, 129.11, 128.66, 128.64, 127.98, 126.7; MS(ESI): *m/z* 410.9 (M−1). Anal. Calcd for $C_{21}H_{12}N_4OF_4$: C, 61.17; H, 2.93; N, 13.58%. Found: C, 61.07; H 2.96; N, 13.62%.

4.1.25. Compound *E*-17a. Yellow-orange solid, mp165 °C; ν_{max} (nujol) 3210 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 9.22 (1H, s, NH), 8.18–7.58 (11H, m, 2Ph, Ar).); ^{13}C NMR (300 MHz, $CDCl_3$) δ 175.04, 166.36, 136.30, 133.44, 130.11, 129.68, 129.48, 129.27, 128.05, 126.61, 123.50; MS(ESI): *m/z* 410.8 (M−1). Anal. Calcd for $C_{21}H_{12}N_4OF_4$: C, 61.17; H, 2.93; N, 13.58%. Found: C, 61.20; H 2.90; N, 13.60%.

4.1.26. Compound *Z*-18a. Yellow solid, mp 153–155 °C;

ν_{max} (nujol) 3310 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.99 (1H, s, NH), 8.08–7.46 (10H, m, 2Ph); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.72, 143.00, 132.94, 132.60, 129.58, 129.13, 128.85, 128.59, 127.98, 126.69; MS(ESI): *m/z* 428.9 (M−1). Anal. Calcd for $C_{21}H_{11}N_4OF_5$: C, 58.61; H, 2.57; N, 13.01%. Found: C, 58.65; H 2.60; N, 13.10%.

4.1.27. Compound *E*-18a. Colourless solid, mp 145 °C; ν_{max} (nujol) 3310 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 9.26 (1H, s, NH), 8.19–7.53 (10H, m, 2Ph); ^{13}C NMR (300 MHz, $CDCl_3$) δ 179.43, 166.73, 161.12, 146.95, 145.11, 143.00, 139.93, 132.94, 132.60, 129.58, 129.45, 129.13, 128.86, 128.59, 127.98, 126.69; MS(ESI): *m/z* 428.8 (M−1). Anal. Calcd for $C_{21}H_{11}N_4OF_5$: C, 58.61; H, 2.57; N, 13.01%. Found: C, 58.63; H 2.61; N, 13.15%.

4.1.28. Compound 1b. Colourless solid, mp 167–169 °C; ν_{max} (nujol) 3150, 3190, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.81 (1H, s, NH), 8.10–7.35 (13H, m, 2Ph, Ar), 2.43 (3H, s, CH_3); 2.25 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.17, 142.63, 140.40, 140.31, 139.32, 133.89, 132.97, 132.90, 131.42, 130.43, 129.40, 129.31, 128.17, 127.54, 126.58, 124.39, 21.06, 15.37; MS(ESI): *m/z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.78; H, 5.43; N, 15.45%.

4.1.29. Compound 2b. Colourless solid, mp 156–158 °C; ν_{max} (nujol) 3260, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.80 (1H, s, NH), 7.92–7.09 (13H, m, 2Ph, Ar), 2.45 (3H, s, CH3); 2.43 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.44, 141.81, 139.46, 138.76, 137.08, 133.31, 132.31, 132.26, 129.82, 128.72, 128.60, 127.16, 126.90, 124.85, 21.03, 18.89; MS(ESI): *m/z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.88; H, 5.58; N, 15.36%.

4.1.30. Compound 3b. Colourless solid, mp 160–162 °C; ν_{max} (nujol) 3210, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.81 (1H, s, NH), 8.12–7.30 (13H, m, 2Ph, Ar), 2.45 (3H, s, CH_3); 2.43 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.37, 141.87, 139.54, 139.10, 136.52, 133.34, 132.37, 131.58, 129.78, 129.56, 129.31, 128.84, 128.78, 128.68, 127.47, 126.96, 20.76, 18.66; MS(ESI): *m/z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.92; H, 5.53; N, 15.25%.

4.1.31. Compound 4b. Colourless solid, mp 193–195 °C; ν_{max} (nujol) 3160, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.84 (1H, s, NH), 8.10–7.40 (13H, m, 2Ph, Ar), 2.41 (3H, s, CH_3); 2.36 (3H, s, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.67, 142.40, 140.03, 137.97, 137.90, 136.43, 133.54, 132.66, 130.50, 130.01, 129.09, 129.04, 128.97, 127.77, 127.28, 119.95, 116.29, 20.15, 19.67; MS(ESI): *m/z* 367.3 (M−1). Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21%. Found: C, 74.76; H, 5.42; N, 15.30%.

4.1.32. Compound 5b. Colourless solid, mp 172–174 °C; ν_{max} (nujol) 3220, 1660 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.82 (1H, s, NH), 7.98–6.90 (13H, m, 2Ph, Ar, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.26, 142.96, 140.73, 133.08, 132.51, 129.23, 129.03, 128.86, 127.48, 127.06, 126.25, 126.12, 112.99, 111.69, 106.02, 105.70, 105.35; MS(ESI): *m/z* 375.4 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.22; H, 3.60; N, 14.92%.

4.1.33. Compound 6b. Colourless solid, mp 160–162 °C; ν_{max} (nujol) 3300, 1630 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.93 (1H, s, NH), 8.09–7.44 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.52, 143.52, 141.43, 133.29, 132.84, 129.42, 129.14, 128.62, 127.79, 127.38, 119.06, 118.94, 118.76, 118.64, 116.28, 115.95, 111.92; MS(ESI): *m/z* 375.3 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.25; H, 3.91; N, 14.84%.

4.1.34. Compound 7b. Colourless solid, mp197–198 °C; ν_{max} (nujol) 3282, 1660 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.98 (1H, s, NH), 8.10–7.42 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.86, 165.20, 164.97, 161.28, 161.04, 144.41, 142.47, 141.02, 140.81, 133.05, 132.63, 129.49, 129.08, 128.91, 128.02, 126.80; MS(ESI): *m/z* 375.3 (M−1). Anal. Calcd for $C_{21}H_{14}N_4OF_2$: C, 67.01; H, 3.75; N, 14.89%. Found: C, 67.08; H, 3.82; N, 14.83%.

4.1.35. Compound 8b. Colourless solid, mp 174 °C; ν_{max} (nujol) 3240, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.91 (1H, s, NH), 8.09–7.46 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.46, 143.10, 140.92, 139.64, 135.00, 133.42, 131.35, 129.56, 129.33, 129.16, 129.05, 127.77, 127.71, 127.36, 126.38; MS(ESI): *m/z* 407.4 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.62; H, 3.37; N, 13.78%.

4.1.36. Compound 9b. Colourless solid, mp 185–187 °C; ν_{max} (nujol) 3240, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.93 (1H, s, NH), 8.37–7.36 (13H, m, 2Ph, Ar, NH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.64, 143.36, 141.47, 136.98, 135.44, 133.90, 133.07, 132.31, 130.08, 129.66, 129.51, 129.38, 128.19, 127.82; MS(ESI): *m/z* 407.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.55; H, 3.50; N, 13.70%.

4.1.37. Compound 10b. Colourless solid, mp 123 °C; ν_{max} (nujol) 3220, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.96 (1H, s, NH), 8.07–7.40 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.21, 142.97, 140.05, 138.13, 133.11, 133.01, 132.50, 132.02, 129.92, 129.15, 129.08, 128.86, 128.83, 127.50, 127.30, 127.04, 126.99; MS(ESI): *m/z* 407.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.68; H, 3.42; N, 13.74%.

4.1.38. Compound 11b. Colourless solid, mp 136 °C; ν_{max} (nujol) 3240, 1650 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.94 (1H, s, NH), 8.10–7.46 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.50, 143.20, 141.14, 135.80, 134.40, 134.12, 132.90, 132.51, 129.14, 128.92, 128.76, 128.33, 128.03, 126.50, 116.50; MS(ESI): *m/z* 406.7 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.68; H, 3.49; N, 13.79%.

4.1.39. Compound 12b. Colourless solid, mp 212–214 °C; ν_{max} (nujol) 3240, 1659 cm^{-1}; ^1H NMR (250 MHz, DMSO) δ 10.97 (1H, s, NH), 8.23–7.10 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.25, 142.92, 140.84, 138.38, 133.33, 132.90, 132.52, 131.20, 130.82, 129.06, 128.79,

127.48, 126.95, 120.15, 117.44; MS(ESI): *m/z* 406.8 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: C, 61.63; H, 3.45; N, 13.69%. Found: C, 61.60; H, 3.41; N, 13.70%.

4.1.40. Compound 13b. Colourless solid, mp 150 °C; ν_{max} (nujol) 3180, 3220, 1650 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.97 (1H, s, NH), 8.14–7.48 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.29, 143.14, 141.08, 135.75, 135.50, 132.61, 131.03, 129.21, 128.36, 127.54, 127.17, 126.99, 120.70, 116.87, 110.75; MS(ESI): *m/z* 406.9 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OCl_2$: 61.63; H, 3.45; N, 13.69%. Found: C, 61.79; H, 3.42; N, 13.60%.

4.1.41. Compound 14b. Colourless solid, mp 181–183 °C; ν_{max} (nujol) 3240, 1660 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.93 (1H, s, NH), 8.32–7.48 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.84, 147.66, 143.01, 139.99, 139.57, 136.14, 136.08, 135.87, 134.50, 133.99, 129.04, 128.79, 127.77, 125.11, 125.01, 124.18, 123.87; MS(ESI): *m/z* 391.3 (M−1, ^{35}Cl isotope). Anal. Calcd for $C_{21}H_{14}N_4OClF$: C, 64.21; H, 3.59; N, 14.26%. Found: C, 64.32; H, 3.63; N, 14.25%.

4.1.42. Compound 15b. Yellow solid, mp 197 °C; ν_{max} (nujol) 3290 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.45 (1H, s, NH), 8.01–7.34 (13H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.41, 147.04, 146.95, 142.07, 139.51, 133.43, 132.88, 130.73, 130.62, 130.07, 129.31, 129.25, 129.11, 128.11, 126.58, 117.19, 114.68; MS(ESI): *m/z* 429.2 (M−1). Anal. Calcd for $C_{21}H_{14}N_6O_5$: C, 58.61; H, 3.28; N, 19.53%. Found: C, 58.69; H, 3.35; N, 19.59%.

4.1.43. Compound 16b. Colourless solid, mp 188–189 °C; ν_{max} (nujol) 3288, 1672 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.97 (1H, s, NH), 8.10–7.43 (12H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.61, 143.64, 141.64, 136.99, 134.67, 134.32, 133.17, 132.51, 129.53, 129.23, 129.06, 128.66, 128.03, 126.63; MS(ESI): *m/z* 441.2 (M−1). Anal. Calcd for $C_{21}H_{13}N_4OCl_3$: C, 56.84; H, 2.95; N, 12.63%. Found: C, 56.95; H, 2.85; N, 12.74%.

4.1.44. Compound 17b. Colourless solid, mp 170 °C; ν_{max} (nujol) 3161, 1657 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.99 (1H, s, NH), 8.43–7.49 (11H, m, 2Ph, Ar); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.83, 141.93, 132.91, 132.52, 129.30, 128.88, 128.81, 127.45, 127.11, 107.22, 106.66, 106.50; MS(ESI): *m/z* 410.8 (M−1). Anal. Calcd for $C_{21}H_{12}N_4OF_4$: C, 61.17; H, 2.93; N, 13.58%. Found: C, 61.20; H, 3.00; N, 13.62%.

4.1.45. Compound 18b. Colourless solid, mp 158 °C; ν_{max} (nujol) 3304, 1664 cm^{-1}; ^{1}H NMR (250 MHz, DMSO) δ 10.99 (1H, s, NH), 8.09–7.44 (10H, m, 2Ph); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.08, 145.17, 143.84, 142.13, 141.07, 139.90, 135.76, 132.78, 132.44, 129.30, 128.83, 128.67, 127.51, 127.02; MS(ESI): *m/z* 428.8 (M−1). Anal. Calcd for $C_{21}H_{11}N_4OF_5$: C, 58.61; H, 2.58; N, 13.02%. Found: C, 58.70; H, 2.62; N, 13.05%.

4.2. pS^+ and kinetic measurements

Dioxane and water were purified according to methods previously reported.[22]

The operational proton-concentration scale used (pS^+)[23a,24] was established in aqueous dioxane by employing the pK_a values of acids determined by interpolation from reported data.[23b] The meter reading after calibration against buffers required a correction of only +0.16.

A Varian Cary 1E spectrophotometer equipped with the rapid kinetic accessory SFA-11 was used in the 9.86–11.69 pS^+ range for the rearrangement of **18a** into **18b**.

The kinetics were followed spectrophotometrically as previously described[9h–k,24] by measuring the disappearance of **1a**–**18a** at the wavelengths of their absorption maxima, where the absorption of **1b**–**18b** was minimal. The rate constants are accurate to within ±3%. Tables A–R (Supplementary Materials) of the apparent first-order kinetic rate constants in 1:1 (v:v) dioxane/water, calculated at 313.15 K at various pS^+, together with thermodynamic parameters and optical properties are available on request from the authors (V. F. or D. S.). In Table 1 are collected the ratios of the logarithmic apparent first-order rate constants [log $(k_{A,R})_X/(k_{A,R})_H$] at pS^+ 3.80 and 11.50.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.054

References and notes

1. Shorter, J.; Stubbs, F. J. *J. Chem. Soc.* **1949**, 1180–1183. Dippy, J. F. J.; Hughes, S. R. C.; Laxton, L. W. *J. Chem. Soc.* **1956**, 2995–3000. Mather, J. G.; Shorter, J. *J. Chem. Soc.* **1961**, 4744–4757. Buckley, A.; Chapman, N. B.; Shorter, J. *J. Chem. Soc.* **1963**, 178–183. Dippy, J. F. J.; Hawkins, B. D.; Smith, B. V. *J. Chem. Soc.* **1964**, 154–163. Kalfus, K.; Kroupa, J.; Vecera, M.; Exner, O. *Coll. Czech. Chem. Commun.* **1979**, *40*, 3009–3019. Pytela, O.; Kulhánek, J.; Ludwig, M.; Riha, V. *Coll. Czech. Chem. Commun.* **1994**, *59*, 627–638. Pytela, O.; Kulhánek, J.; Ludwig, M. *Coll. Czech. Chem. Commun.* **1994**, *59*, 1637–1644. Bohm, S.; Exner, O. *New J. Chem.* **2001**, *25*,

250–254. Exner, O.; Fiedler, P.; Buděšinský, M.; Kulhánek, J. *J. Org. Chem.* **1999**, *64*, 3513–3518. Kulhánek, J.; Exner, O. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1397–1401. Kulhánek, J.; Pytela, O.; Lyčka, A. *Coll. Czech. Chem. Commun.* **2000**, *65*, 106–116. Kulhánek, J.; Pytela, O. *Coll. Czech. Chem. Commun.* **1997**, *62*, 913–924. Kulhánek, J.; Pytela, O. *Coll. Czech. Chem. Commun.* **1995**, *60*, 829–840.

2. (a) Hammett, L. P. Physical Organic Chemistry, 2nd ed.; McGraw Hill: New York, 1970. (b) Shorter, J. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1972; pp 71–117. (c) Shorter, J. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1978; pp 119–173. (d) Exner, O. Correlation Analysis of Chemical Data; Plenum: London, 1988. (e) Williams, A. Free Energy Relationships in Organic and Bio-organic Chemistry; RSC: London, 2003.
3. (a) Cammarata, A.; Rogers, K. S. In *Advances in Linear Free Energy Relationships*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1972; pp 401–444. (b) Hansch, C. In *Correlation Analysis in Chemistry*; Chapman, N. B., Shorter, J., Eds.; Plenum: London, 1978; pp 397–438. (c) Hadzi, D.; Jerman-Blazič, B. QSAR in Drugs Design and Toxycology; Elsevier: Amsterdam, 1987. (d) Kubinyi, H. QSAR: Hansch Analysis and Related Approach; VCH: New York, 1993.
4. Taft, R. W.; Jun In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; p 556.
5. Swain, C. G.; Lupton, E. *J. Am. Chem. Soc.* **1968**, *90*, 4328–4337.
6. Fujita, T.; Nishioka, T. *Prog. Phys. Org. Chem.* **1976**, *12*, 49–89.
7. Frenna, V.; Vivona, N.; Caronia, A.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1984**, 785–789. Frenna, V.; Vivona, N.; Cannella, L.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1183–1187. Frenna, V.; Vivona, N.; Macaluso, G.; Spinelli, D.; Consiglio, G. *J. Chem. Soc., Perkin Trans. 2* **1987**, 537–540. Lamartina, L.; Spinelli, D.; Guerrera, F.; Sarvà, M. C. *Magn. Reson. Chem.* **1995**, *33*, 883–888. Cosimelli, B.; Spinelli, D.; Costanzo, F.; Tonelli, D.; Lamartina, L.; Sarvà, M. C.; Seeber, R. *Tetrahedron* **2001**, *57*, 1857–1860. Mezzina, E.; Spinelli, D.; Lamartina, L.; Buscemi, S.; Frenna, V.; Macaluso, G. *Eur. J. Org. Chem.* **2002**, 203–208. Avellone, G.; Ceraulo, L.; Lamartina, L.; Cosimelli, B.; Spinelli, D.; Zuppiroli, L. *Rapid Commun. Mass Spectrom.* **1999**, *13*, 1360–1365. Consiglio, G.; Frenna, V.; Guernelli, S.; Macaluso, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **2002**, 965–970.
8. Hrelia, P.; Vigagni, F.; Maffei, F.; Fimognari, C.; Lamartina, L.; Spinelli, D.; Juric, P.; Guerra, M. C.; Cantelli-Forti, G. *Mutagenesis* **1995**, *10*, 171–177. Hrelia, P.; Fimognari, C.; Maffei, F.; Spinelli, D.; Lamartina, L.; Sarvà, M. C.; Cantelli-Forti, G. *Chem. Biol. Interact.* **1999**, *118*, 99–111.
9. (a) Boulton, A. J. *Lectures in Heterocyclic Chemistry*; Hetero Corporation: Provo, UT, 1973. (b) Boulton, A. J.; Katritzky, A. R.; Majid-Hamid, A. *J. Chem. Soc. C*, 2005–2007. (c) Katritzky, A. R.; Gordev, M. F. *Heterocycles* **1993**, *35*, 483–518. (d) Van der Plas, H. C. In *Ring Transformations of Heterocycles*; Academic: London, 1973; Vols. 1 and 2. (e) L'abbé, G. *J. Heterocycl. Chem.* **1984**, *21*, 621–638. (f) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141–169. (g) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49–154. (h) Cosimelli, B.; Guernelli, S.; Spinelli, D.; Buscemi, S.; Frenna, V.; Macaluso, G. *J. Org. Chem.* **2001**, *66*, 6124–6129. (i) Guernelli, S.; Laganà, M. F.; Spinelli, D.; Lo Meo, P.; Noto, R.; Riela, S. *J. Org. Chem.* **2002**, *67*, 2948–2953. (j) Cosimelli, B.; Frenna, V.; Guernelli, S.; Lanza, C. Z.; Macaluso, G.; Petrillo, G.; Spinelli, D. *J. Org. Chem.* **2002**, *67*, 8010–8018. (k) Bottoni, A.; Frenna, V.; Lanza, C. Z.; Macaluso, G.; Spinelli, D. *J. Chem. Phys. A* **2004**, *108*, 1731–1740.
10. (a) Frenna, V.; Macaluso, G.; Consiglio, C.; Cosimelli, B.; Spinelli, D. *Tetrahedron* **1999**, *55*, 12885–12896. (b) Spinelli, D.; Frenna, V.; Corrao, A.; Vivona, N. *J. Chem. Soc., Perkin Trans. 2* **1978**, 19–22. (c) Frenna, V.; Vivona, N.; Corrao, A.; Consiglio, C.; Spinelli, D. *J. Chem. Res.* **1981**, *S*, 308–309 see also pages (M) 3550–3578.
11. (a) Buscemi, S.; Frenna, V.; Pace, A.; Vivona, N.; Cosimelli, B.; Spinelli, D. *Eur. J. Org. Chem.* **2002**, 1417–1423. (b) Buscemi, S.; Frenna, V.; Vivona, N.; Petrillo, G.; Spinelli, D. *Tetrahedron* **1995**, *51*, 5133–5142.
12. Dell'Erba, C.; Mele, A.; Novi, M.; Petrillo, G.; Sancassan, F.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2055–2058 and references therein.
13. Consiglio, G.; Spinelli, D.; Noto, R. *J. Chem. Res.* **1979**, *S*, 242–243 and references therein.
14. Consiglio, G.; Frenna, V.; Mugnoli, A.; Noto, R.; Pani, M.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 309–316 and references therein.
15. (a) Spinelli, D.; Consiglio, G.; Noto, R.; Corrao, A. *J. Chem. Soc., Perkin Trans. 2* **1975**, 620–622. (b) Noto, R.; Frenna, V.; Consiglio, G.; Spinelli, D. *J. Chem. Res.* **1991**, *S*, 270–271 see also pages (M) 2701–2710. (c) Consiglio, G.; Frenna, V.; Guernelli, S.; Macaluso, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **2002**, 971–975. (d) Spinelli, D.; Consiglio, G.; Corrao, A. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1866–1869. (e) Consiglio, C.; Arnone, C.; Spinelli, D.; Noto, R.; Frenna, V.; Fisichella, S. *J. Chem. Soc., Perkin Trans. 2* **1985**, 519–522.
16. Consiglio, G.; Gronowitz, S.; Hörnfeldt, A.-B.; Noto, R.; Spinelli, D. *Chemica Scripta* **1980**, 117–121 and references therein.
17. Consiglio, G.; Spinelli, D.; Gronowitz, S.; Hörnfeldt, A.-B. *Chemica Scripta* **1984**, *23*, 116–119 and references therein.
18. Because of the absence of a pS^+-independent route (and therefore of 'plateau' values for the rate constants) the kinetic data concerning **15a**, **17a** and **18a** could not be used for the LFER treatment at pS^+ 3.80.
19. A complete ab initio computation of the course of the reaction is under investigation (Lanza, C. Z.; Spinelli, D.; Frenna, V. et al.).
20. Decourzon, M.; Ertl, P.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Am. Chem. Soc.* **1993**, *115*, 12071–12078. Fiedler, P.; Exner, O. *J. Phys. Org. Chem.* **1998**, *11*, 141–148.
21. Vivona, N.; Ruccia, M.; Frenna, V.; Spinelli, D. *J. Heterocycl. Chem.* **1980**, *17*, 401–402.
22. Weissberger, A. In *A Technique of Organic Chemistry*, 2nd ed.; Interscience: New York, 1963; Vol. 7.
23. (a) Bates, R. G. In *Solute–Solvent Interactions*; Coetze, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; p 46. (b) Harned, H. S.; Owen, B. B. The Physical Chemistry of Electrolytic Solution, 3rd ed.; ACS Monograph No. 137; Reinhold: New York, 1970; pp 716, 755.
24. Spinelli, D.; Corrao, A.; Frenna, V.; Vivona, N.; Ruccia, M.; Cusmano, G. *J. Heterocycl. Chem.* **1976**, *13*, 357–360.

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Improvement in the synthesis of metallophthalocyanines using microwave irradiation

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Abstract—A successful application of microwave irradiation, in which phthalocyanines were synthesized under solventless conditions from 1,2-phthalonitrile or phthalic anhydride and urea in the presence of metal templates is described. It was found that in comparison with conventional heating, the microwave process is a very useful alternative for cyclotetramerization processes because of reduction of the reaction time, better yield, and easy-to-perform procedure.
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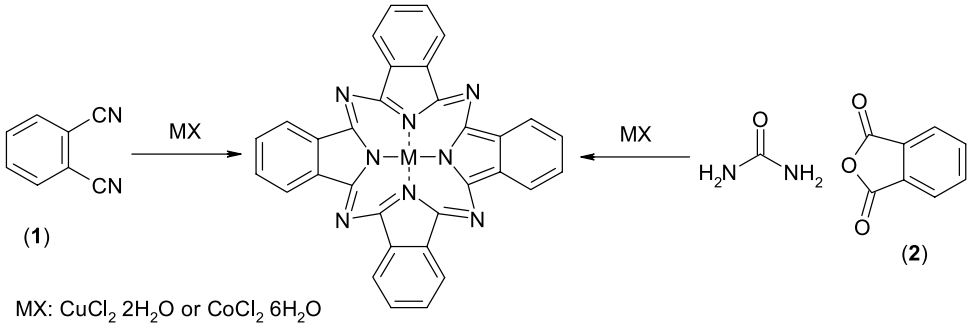
1. Introduction

Phthalocyanines form nowadays an important group of organic compounds that belongs to the most studied subjects of organic functional materials.[1] However, although phthalocyanines have been not identified in the nature yet, they were one of the first macrocycles that were synthesized and used as model compounds to mimic the biologically important porphyrines.[2] The most important industrial application of phthalocyanines is the formation of color complexes with metal cations that are used as highly stable pigments and dyes.[3] In addition, they can find commercial applications as: photovoltaic materials in solar cells,[4–6] systems for fabrication of light emitting diodes (LED),[7,8] liquid crystalline[9] and non-linear optical materials,[10,11] sensitizers for photodynamic (PDT) cancer therapy,[12,13] photoconductors in xerography,[14] dyes at recording layers for CD-R and DVD-R optical storage discs,[15] as well as diverse catalytic systems.[16,17] Recently, the synthesis, properties and potential application of phthalocyanine containing polymers were reviewed by McKeowon,[18] while an example of the preparation of nanoscale organic-inorganic composites containing rod-like phthalocyanine polymers was published by Kimura et al.[19]

Phthalocyanines are usually prepared by the high temperature cyclotetramerization processes of either phthalonitrile (**1**) or phthalic anhydride (**2**), in which the template effect afforded by a suitable metal cation is required (Scheme 1). The reactions can be carried out in a variety of solvents as



Scheme 1. Synthesis of phthalocyanines from phthalonitrile (**1**) or phthalic anhydride (**2**) and urea.

Keywords: Microwave irradiation; Phthalocyanines; Phthalonitrile; Phthalic anhydride; Solventless conditions.
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well as under solvent-free conditions, but both processes require temperature ca. 200 °C and long reaction times.[1] It is well known that microwave (MW) irradiation can accelerate a great number of chemical processes, and, in particular, the reaction time and energy input are supposed to be mostly reduced in the reactions that are run for a long time at high temperatures under conventional conditions.[20] On the other hand, the most successful examples of microwave applications are necessarily found to be related to the use of solvent-free systems, in which microwaves interact directly with reagents and, therefore, can more efficiently drive chemical reactions.[21,22] The possible accelerations of such reactions are expected to be optimal since they are not moderate or impeded by solvents. It was assumed and largely proven that specific (non-purely thermal) MW effects are related to mechanisms where the polarity is increased from the ground state to the transition state.[23] It is essentially the case of neutral reactants leading to a dipolar transition state. Thus, we have decided to apply microwave irradiation for the synthesis of phthalocyanine under solvent-less conditions in order to check whether such non-classical method of chemical activation might influence yield, selectivity and time of reaction in comparison with a conventional thermal treatment under strictly similar sets of conditions.

2. Results

The synthesis of phthalocyanines under microwave irradiation has been previously investigated by Shaabani[24] and Villemin et al.[25] In the former case, the reactions were carried out applying a domestic oven without any temperature control, whereas in the latter case the syntheses were run in a modified domestic oven and microwave resonance cavity without temperature control as well. It was found that the results depend upon the quantity of products and were difficult to reproduce when the reactions were conducted with small samples less then 5 g.[25] To solve this problem and control reasonably well temperature during syntheses under MW conditions so that it was possible to compare their results with experiments under conventional

Table 1. The synthesis of phthalocyanine–Cu from phthalonitrile (**1**) and copper (II) chloride dihydrate under microwave and conventional conditions

	Substrate	Quantity (mmol)	Conditions	Time (min)	Temp. (°C)	Conv.[a]/Yield (%)/(%)	CHN calc.	CHN found
1	**1**	8					C: 66.74	C: 66.01
	$CuCl_2 \cdot 2H_2O$	2.5	MW	10	200–220	86/82	H: 2.5	H: 2.59
							N: 19.2	N: 18.51
2	**1**	12					C: 66.74	C: 62.35
	$CuCl_2 \cdot 2H_2O$	2.5	MW	10	180–190	78/70	H: 2.5	H: 2.42
							N: 19.2	N: 18.35
3	**1**	12					C: 66.74	C: 17.49
	$CuCl_2 \cdot 2H_2O$	2.5	△	10	180	10/7	H: 2.5	H: 1.85
							N: 19.2	N: 4.84
4	**1**	12					C: 66.74	C: 66.21
	$CuCl_2 \cdot 2H_2O$	2.5	MW	10	200–230	90/81	H: 2.5	H: 2.83
							N: 19.2	N: 19.76
5	**1**	12					C: 66.74	C: 66.42
	$CuCl_2 \cdot 2H_2O$	2.5	MW	15	190–210	94/88	H: 2.5	H: 2.38
							N: 19.2	N: 19.06
6	**1**	12					C: 66.74	C: 46.67
	$CuCl_2 \cdot 2H_2O$	2.5	△	15	200	20/10	H: 2.5	H: 2.91
							N: 19.2	N: 13.91
7	**1**	8					C: 66.74	C: 66.31
	$CuCl_2 \cdot 2H_2O$	2.5	MW	6	230–240	76/74	H: 2.5	H: 2.58
	H_2O	3 drops (75 mg)					N: 19.2	N: 18.73
8	**1**	12					C: 66.74	C: 57.19
	$CuCl_2 \cdot 2H_2O$	2.5	MW	6	200–230	85/76	H: 2.5	H: 2.33
	H_2O	3 drops (75 mg)					N: 19.2	N: 17.28
9	**1**	12					C: 66.74	C: 66.81
	$CuCl_2 \cdot 2H_2O$	2.5	MW	10		90/86	H: 2.5	H: 2.85
	H_2O	3 drops (75 mg)					N: 19.2	N: 19.03
10	**1**	8					C: 66.74	C: 66.83
	$CuCl_2 \cdot 2H_2O$	2.5	MW	8	180	86/83	H: 2.5	H: 2.75
	DMF	3 drops (70 mg)					N: 19.2	N: 18.83
11	**1**	12					C: 66.74	C: 56.94
	$CuCl_2 \cdot 2H_2O$	2.5	MW	4	150–170	79/72	H: 2.5	H: 2.46
	DMF	3 drops (70 mg)					N: 19.2	N: 16.91
12	**1**	12					C: 66.74	C: 66.40
	$CuCl_2 \cdot 2H_2O$	2.5	MW	10	210–220	88/82	H: 2.5	H: 2.75
	DMF	3 drops (70 mg)					N: 19.2	N: 18.83

[a] Conversion based on the consumption of **1**.

Table 2. The synthesis of phthalocyanine–Co from phthalonitrile (**1**) and cobalt (II) chloride hexahydrate under microwave and conventional conditions

	Substrate	Quantity (mmol)	Conditions	Time (min)	Temp. (°C)	Conv[a]/Yield (%)/(%)	CHN calc.	CHN found
1	**1**	12					C: 67.28	C: 63.71
	$CoCl_2 \cdot 6H_2O$	2.5	MW	6	180	90/86	H: 2.80	H: 2.65
							N: 19.61	N: 17.89
2	**1**	12					C: 67.28	C: 67.30
	$CoCl_2 \cdot 6H_2O$	2.5	MW	6	210–220	81/75	H: 2.80	H: 2.70
							N: 19.61	N: 19.50
3	**1**	12					C: 67.28	C: 28.42
	$CoCl_2 \cdot 6H_2O$	2.5	△	6	210	10/5	H: 2.80	H: 2.41
							N: 19.61	N: 9.42
4	**1**	12					C: 67.28	C: 67.11
	$CoCl_2 \cdot 6H_2O$	2.5	MW	10	190–200	86/80	H: 2.80	H: 2.70
							N: 19.61	N: 19.40
5	**1**	12					C: 67.28	C: 32.20
	$CoCl_2 \cdot 6H_2O$	2.5	△	10	200	15/11	H: 2.80	H: 2.50
							N: 19.61	N: 10.45
6	**1**	12					C: 67.28	C: 61.78
	$CoCl_2 \cdot 6H_2O$	2.5	MW	5	180–200	88/83	H: 2.80	H: 2.51
	H_2O	3 drops (75 mg)					N: 19.61	N: 18.20
7	**1**	12					C: 67.28	C: 63.31
	$CoCl_2 \cdot 6H_2O$	2.5	MW	4	210–220	86/84	H: 2.80	H: 2.58
	H_2O	3 drops (75 mg)					N: 19.61	N: 18.73
8	**1**	12					C: 67.28	C: 67.20
	$CoCl_2 \cdot 6H_2O$	2.5	MW	10	180–200	90/86	H: 2.80	H: 2.71
	H_2O	3 drops (75 mg)					N: 19.61	N: 19.56
9	**1**	12					C: 67.28	C: 61.46
	$CoCl_2 \cdot 6H_2O$	2.5	MW	4	160	75/67	H: 2.80	H: 2.54
	DMF	3 drops (70 mg)					N: 19.61	N: 18.02
10	**1**	12					C: 67.28	C: 63.83
	$CoCl_2 \cdot 6H_2O$	2.5	MW	4	180–190	78/65	H: 2.80	H: 2.75
	DMF	3 drops (70 mg)					N: 19.61	N: 18.83
11	**1**	12					C: 67.28	C: 67.10
	$CoCl_2 \cdot 6H_2O$	2.5	MW	10	180	84/78	H: 2.80	H: 2.68
	DMF	3 drops (70 mg)					N: 19.61	N: 19.34

[a] Conversion based on the consumption of **1**.

conditions, we have decided to use the dedicated monomode microwave reactor Synthewave 402 (Prolabo) with accurate measurement of temperature by an infrared detection (calibrated using an optical fiber) during the reaction course. Moreover, such a reactor allows also maintaining of temperature at a constant value by modulation of emitted MW power and an efficient mechanical stirring.[21]

First, we decided to use two metal salts as templates for the formation of phthalocyanines, that is, cobalt (II) chloride hexahydrate and copper (II) chloride dihydrate, because these phthalocyanines are usually applied and commercially available. Moreover, phthalocyanines containing cobalt and copper templates can be used as effective catalysts in oxygenation[17] and oxyhalogenation processes,[16] which are also of research interest in our labs.[26,27]

In a typical experiment, the reactions were carried out by simply mixing and grinding phthalonitrile (**1**) (1,2-dicyanobenzene) with copper or cobalt chloride, and the mixtures were then irradiated in open vessels in the microwave reactor. In the case of phthalic anhydride (**2**), additionally, an excess of urea was added to the reaction mixture before it was subjected to microwave irradiation in an open vessel as well. All the substrates used in the syntheses were solid, and, in such a case, to initiate a chemical reaction under microwave conditions at least one of substrates need to be melting solid that absorbs relatively well microwaves.[28] These features can be ensured by phthalonitrile (**1**) or phthalic anhydride (**2**) that have melting points 139–141 °C and 131–134 °C,[29] respectively, provided that the reaction mixtures were irradiated strongly enough at the beginning of experiments. On the other hand, a small amount of a good microwave absorber added to substrates that do not absorb microwaves in solid state can initiate an increase of temperature and, in turn, a chemical reaction. Therefore, in the further stage of our investigations, we decided to check whether a small amount of water or DMF,[30] which are strong microwave absorbers, can influence reaction by faster increase of reaction temperature to level so high that is needed in the synthesis of phthalocyanines. Moreover, a small amount of solvent can provide better temperature homogeneity during the syntheses. The results and conditions of all the reactions are presented in Tables 1–3.

Regarding the reaction of phthalonitrile (**1**) (Tables 1 and 2), all the results under different reaction conditions (i.e., conventional and microwave) were compared on the basis of conversion of phthalonitrile (**1**), yield of the product after purification with water, acetone, methylene chloride, and

Table 3. The synthesis of phthalocyanine–Cu and Co from phthalic anhydride (**2**) and urea in the presence of ammonium molybdate under microwave and conventional conditions

	Substrate	Quantity (mmol)	Conditions	Time (min)	Temp. (°C)	Conv.[a]/Yield (%)/(%)	CHN calc.	CHN found
1	**2**	10					C: 66.74	C: 64.07
	Urea	20					H: 2.50	H: 2.82
	$CuCl_2 \cdot 2H_2O$	2.5	MW	10	200	88/80	N: 19.2	N: 19.04
	Ammonium molybdate	0.1						
2	**2**	15					C: 66.74	C: 66.81
	Urea	15					H: 2.50	H: 2.75
	$CuCl_2 \cdot 2H_2O$	2.5	MW	6	140–170	82/78	N: 19.2	N: 19.21
	Ammonium molybdate	2						
3	**2**	15					C: 66.74	C: 30.81
	Urea	15					H: 2.50	H: 2.05
	$CuCl_2 \cdot 2H_2O$	2.5	△	6	140–170	60/38	N: 19.2	N: 10.27
	Ammonium molybdate	2						
4	**2**	15					C: 67.28	C: 66.81
	Urea	15	MW	5	180	60/52	H: 2.80	H: 2.77
	$CoCl_2 \cdot 6H_2O$	2.5					N: 19.61	N: 19.48
	Ammonium molybdate	2						
5	**2**	15					C: 67.28	C: 19.68
	Urea	15	△	5	180	18/12	H: 2.80	H: 1.98
	$CoCl_2(6H_2O$	2.5					N: 19.61	N: 5.57
	Ammonium molybdate	2						

[a] Conversion based on the consumption of **2**.

concentrated sulfuric acid and final purity of the product (elemental analysis). For the reaction of phthalonitrile (**1**) and copper chloride, it was possible to optimize reaction conditions under microwave irradiation so that the phthalocyanine–Cu was obtained in a very good yield and high purity in a relatively short reaction time (Table 1, entries 1, 4, and 5). However, the reaction needed strong heating at the beginning and the final reaction temperature likely above 200 °C (for example, compare entries 1 and 2 in Table 1). A typical reaction temperature profile in which power of microwave irradiation and reaction temperature are shown is presented in Figure 1(a) (Table 1, entry 5). It can be seen that for the first half of the reaction, maximum MW power was applied to increase the reaction temperature from 20 to 100 °C, then when the reaction was initiated a fast temperature increase was observed together with a substantial reduction of MW power.

For those reactions under MW irradiation in which the best results were obtained, the experiments were run under conventional heating (Δ—oil bath) (Table 1, entries 2 vs. 3 and 5 vs. 6) with similar sets of conditions (for example, Fig. 1(a) and (b), respectively). In both cases, the yields of product under conventional conditions were much lower (7–10% instead of 70–88%), and, which is more important, purity of the product was unacceptable. Therefore, it was proven that the solvent-free procedure under microwave irradiation constitutes here an undeniable improvement for the reactions that were run with enhanced yields under MW conditions in comparison with conventional heating experiments.

The important specific MW effects observed here are consistent with the consideration of mechanisms and with the assumption that the MW effects are increased when the polarity of a system is enhanced. The rate-determining step consists of the addition of nitrile via its nitrogen site on the triple bond on the second nitrile group to form bipolar ions[31] that in turn can react with water molecules to produce 3-imino-2,3-dihydro-isoindol-1-one (**3**). The transition state is therefore more polar than ground state and consequently more prone to electrostatic interactions of dipole–dipole type with the electromagnetic field (Scheme 2). The stabilization of the transition state is therefore responsible of reactivity by a decrease of the activation energy.

It was found that molar ratios of the reagents (i.e., phthalonitrile (**1**) to the inorganic salt) influenced the conversion as well as yields, and the best results were obtained when **1** was used in an excess in comparison with copper chloride (Table 1, entries 4 and 5). However, in the opposite case (Table 1, entry 1), the purity of phthalocyanine–Cu was satisfactory, but it was obtained in lower yield.

As it can be seen in Figure 1(a) and (b), the increase of temperature at the beginning of phthtalonitrile reaction was relatively slow (as was mainly concerned with solid material), and, finally, lengthened the total reaction time under both microwave and conventional conditions. Therefore, we decided to add a small amount of a strong microwave absorber (water or DMF) to the reaction mixture in order to further reduce reaction time and improve temperature homogeneity (Table 1, entries 7–12). Applying water as a liquid microwave absorber, we obtained the best results when the reaction mixture was maintained for 10 min under microwave irradiation at 225 °C (Table 1, entry 9). Whereas the product, phthalocyanine–Cu, was prepared with lower yield when DMF was added to the reaction mixture under similar conditions (Table 1, entry 12).

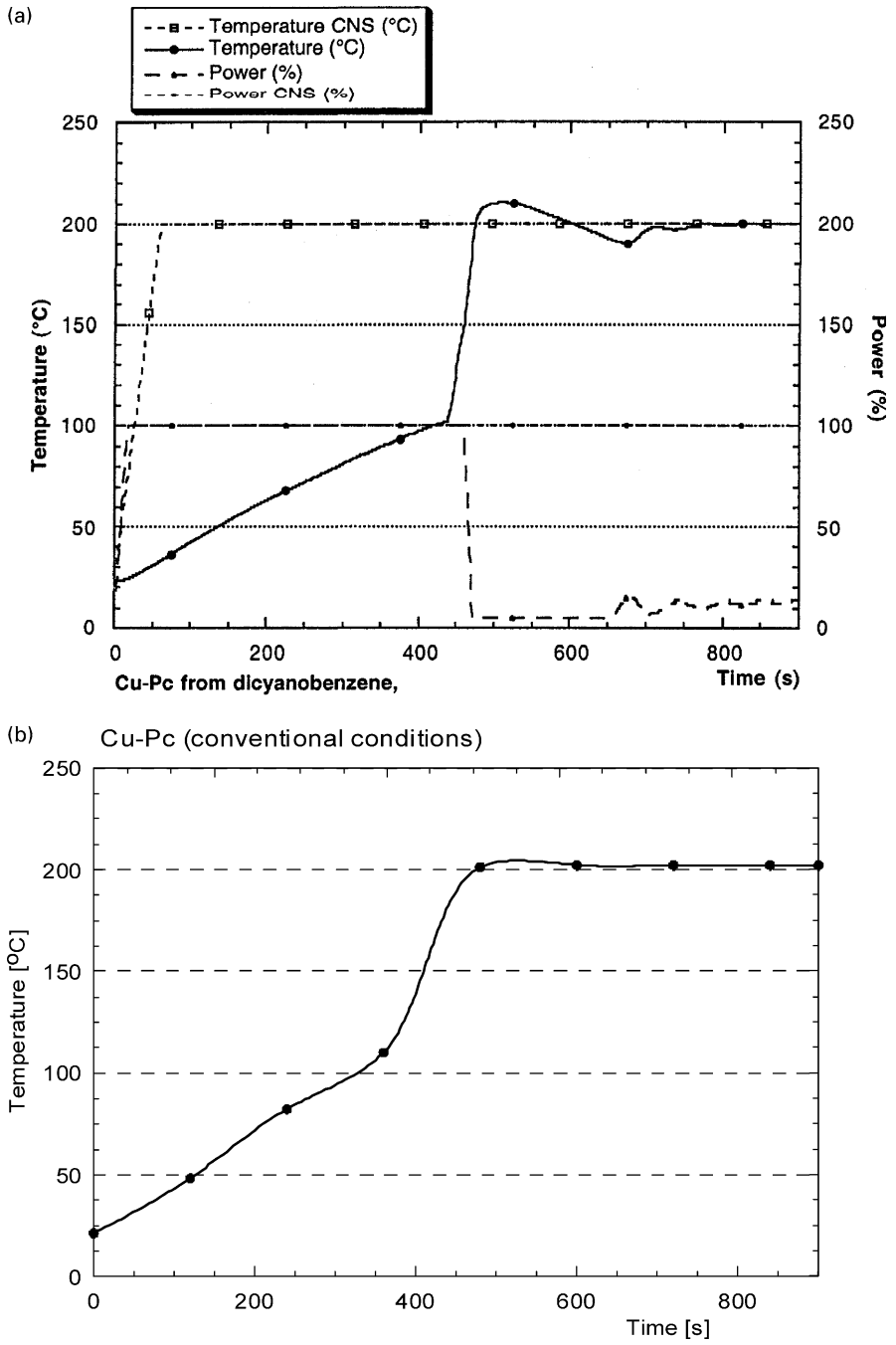
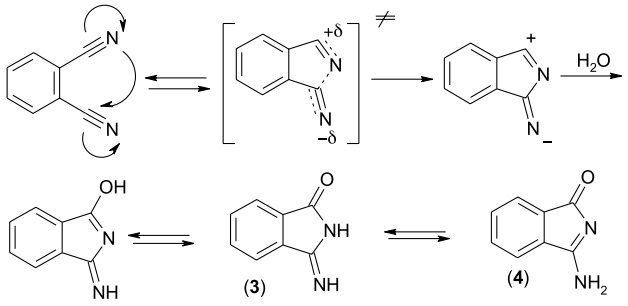


Figure 1. (a) Thermal profile during microwave-assisted solvent-free reaction of **1** with $CuCl_2 \cdot 2H_2O$ (Table 1, entry 5); temperature CNS and power CNS are programmed temperature and power profiles, respectively. (b) Thermal profile for the solvent-free reaction of **1** with $CuCl_2 \cdot 2H_2O$ (Table 1, entry 6) under conventional conditions.

The temperature profiles for the reactions with the addition of a small amount of water and DMF are presented in Figures 2 and 3, respectively. In comparison with Figure 1(a), it can be observed that in both cases further reduction in reaction times from 15 to 10 min was mainly due to the reduction of initial time of the reactions from 5 to 1 min, that is, time in which the reaction mixture reached appropriate reaction temperature ca.200 °C.

Similarly to the reaction with copper chloride, the reaction of phthalonitrile (**1**) with cobalt chloride needed to be carried out at temperature above 200 °C. However, it was possible to obtain the product, phthalocyanine–Co, with a good yield at temperature lower than 200 °C, but its purity was still unacceptable, which was proven by elemental analysis (for example: Table 2, entry 1).

Unlike in the synthesis with copper chloride, owing to the lack initial time in which the reaction temperature slowly increased from 20 to 100 °C (Fig. 1), the reaction time in the reaction with cobalt chloride was reduced to 10 min even in the absence of strong microwave absorbers (i.e., water or DMF). From the beginning, the reactions of cobalt chloride were characterized by a strong increase of reaction



Scheme 2. Mechanism of the activation of 1,3-dicyanobenzene during the formation of phthalocyanines.

temperature (Fig. 4; Table 2, entry 4), which was likely due to higher content of water in hydrated cobalt chloride than copper chloride. Thus, after addition of small amount of water or DMF, in comparison with the reactions of copper chloride (Figs. 1 and 2), a further reduction of reaction time was not observed and yields were similar (Table 2, entries 8 and 11). However, in the case of DMF, it was possible to decrease the reaction temperature to 190 °C (Table 2, entry 11).

Temperature profiles for the reaction of cobalt chloride with addition of a small amount of water and DMF (Figs. 5 and 6) were similar to temperature profiles for the reaction of copper chloride (Figs. 2 and 3). As soon as microwave irradiation was applied to the reaction mixtures, the reaction temperature increased within ca. 60 s from the room temperature to 200 °C and higher, in which the synthesis of phthalocyanines can be carried out with good yield and purity (for example, Table 2, entries 8 and 11). As before, for those reactions under microwave irradiation in which the best results were obtained, the experiments were run under conventional heating (oil bath) (Table 2, entries 3 and 5) with similar sets of conditions (time, temperature). In both cases, the yields of product under conventional conditions were much lower, and, which is more important, purity of the product was unacceptable. It was again shown that the solvent-free procedure under microwave irradiation in comparison with conventional heating experiments gives better results, which might be explained by a specific interaction of microwaves with substrates and an influence of non-thermal microwave effect[23] (i.e., increase of reaction rate that is non adequate to the reaction temperature) during microwave experiments.

The reactions of phthalic anhydride (**2**) under microwave irradiation were compared with those run under conventional conditions (oil bath) for both copper and cobalt chlorides (Table 3, entry 3 and 5). Similarly to the experiments described for phthalonitrile (**1**), the yields of phthalocyanines under conventional conditions were significantly lower and the purity was unacceptable. Eventually, it was proven that the solvent-free procedure under microwave irradiation in

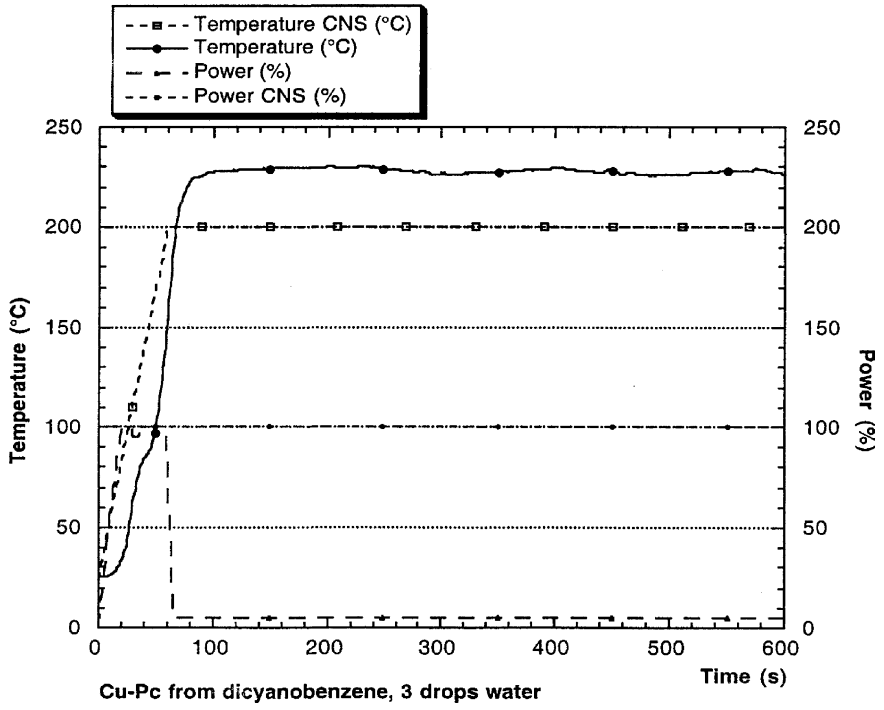


Figure 2. Thermal profile during microwave-assisted reaction of **1** with $CuCl_2 \cdot 2H_2O$ in the presence of 3 drops (75 mg) of water (Table 1, entry 9); temperature CNS and power CNS are programmed temperature and power profiles, respectively.

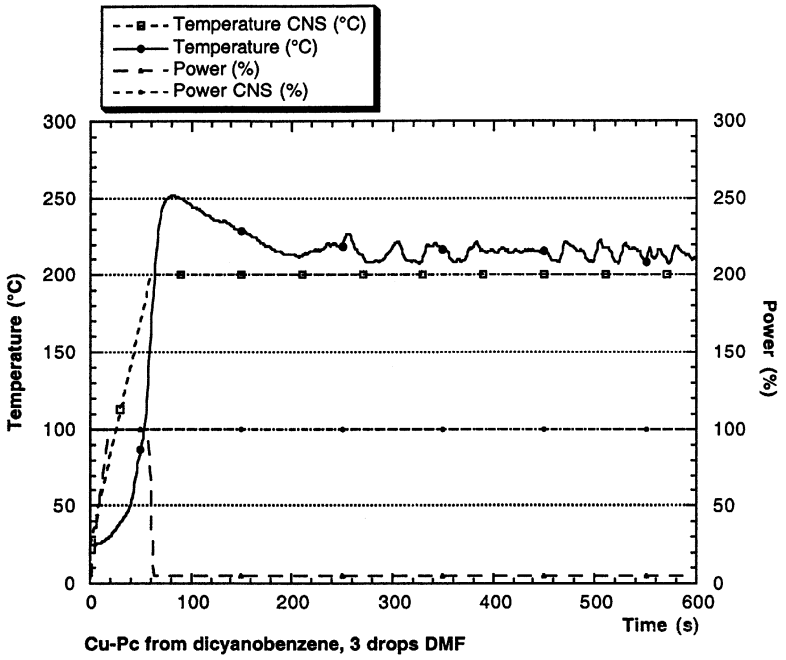


Figure 3. Thermal profile during microwave-assisted reaction of **1** with $CuCl_2 \cdot 2H_2O$ in the presence of 3 drops (70 mg) of DMF (Table 1, entry 12); temperature CNS and power CNS are programmed temperature and power profiles, respectively.

comparison with conventional heating experiments gave better results even as the substrate we used less reactive phthalic anhydride (**2**) in the presence of urea.

The specific non-thermal MW effects observed in this case are also clearly consistent with the more polar species generated during the course of the reaction. The reaction rate of the formation of phthalocyanine form urea and phthalic anhydride is proportional to the first power of the concentration of urea.[32] The urea molecule can be represented by one of the three tautomeric forms (Scheme 3). The polarized form could exist as transient or intermediate species in an excited state that decompose into ammonia and isocyanic acid in the presence of a catalyst (for example, ammonium molybdate). Ammonia react with phthalic anhydride to produce phthalimide, which in turn can react with isocyanic acid to give 3-imino-2,3-dihydro-isoindol-1-one (**3**). The reaction can proceed by passing through a concerted four center mechanism to form carbon dioxide.[32]

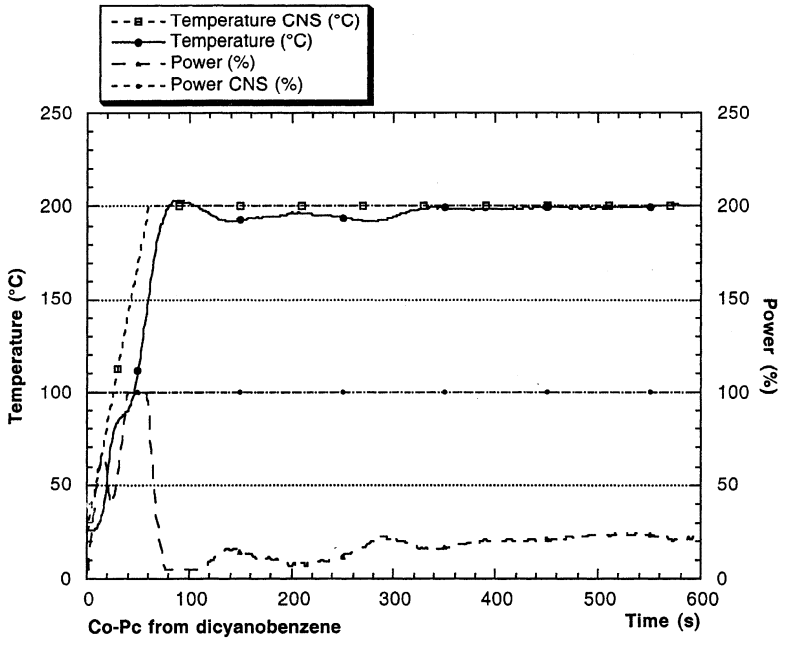


Figure 4. Thermal profile during microwave-assisted solvent-free reaction of **1** with $CoCl_2 \cdot 6H_2O$ (Table 2, entry 4); temperature CNS and power CNS are programmed temperature and power profiles, respectively.

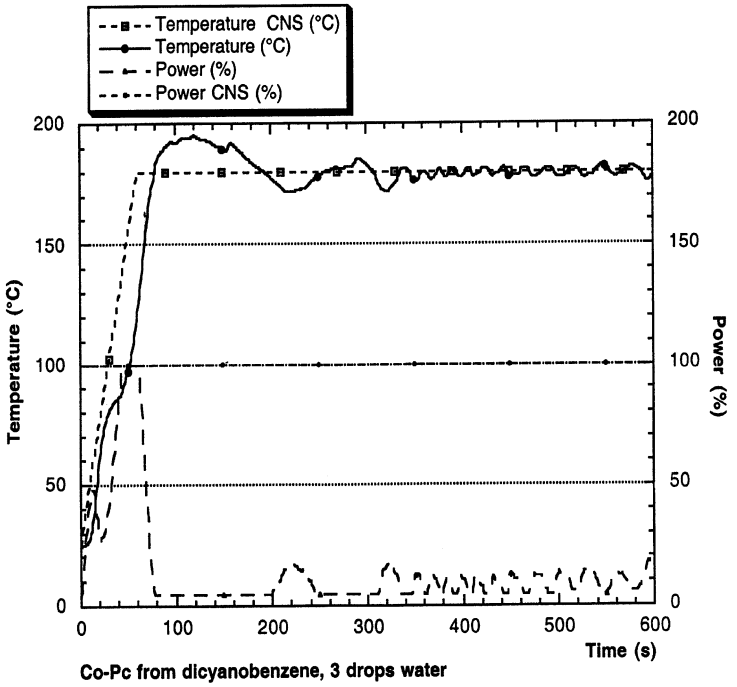


Figure 5. Thermal profile during microwave-assisted reaction of **1** with $CoCl2 \cdot 6H_2O$ in the presence of 3 drops (75 mg) of water (Table 2, entry 8); temperature CNS and power CNS are programmed temperature and power profiles, respectively.

Recently, the microwave-assisted procedure for the synthesis of phthalocyanine–Cu from phthalic anhydride (**2**) and urea in a solution of alkylbenzene was published by Park et al.[33] They found that under microwave irradiation phthalocyanine–Cu could be prepared at lower temperature and shorter time than those required under conventional conditions. Moreover, the samples synthesized under microwave conditions had smaller average size and narrower size distribution.

3. Conclusions

In summary, the synthesis of phthtalocyanines under

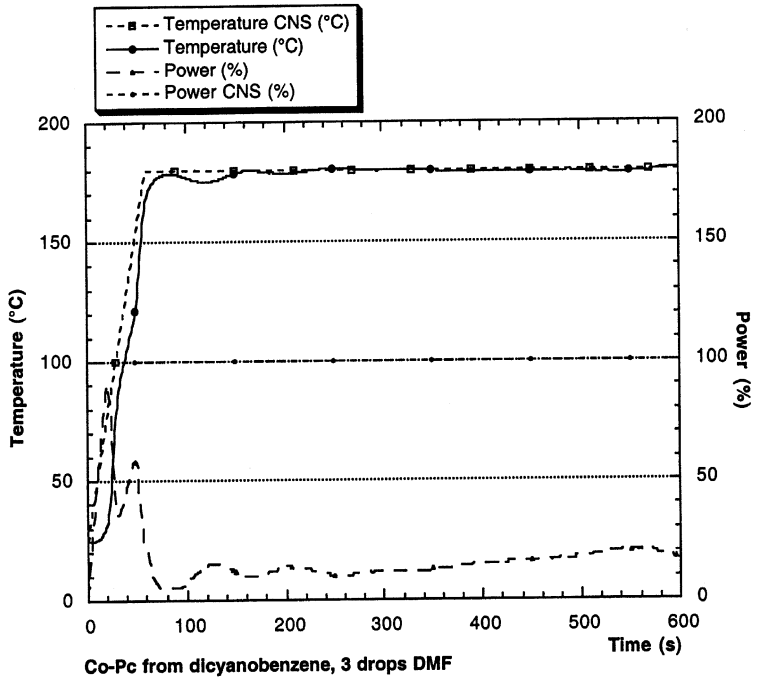
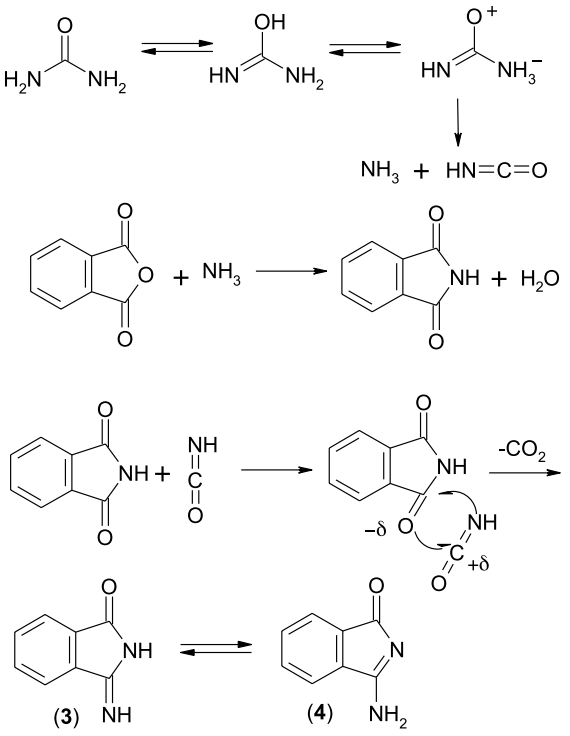


Figure 6. Thermal profile during microwave-assisted reaction of **1** with $CoCl_2 \cdot 6H_2O$ in the presence of 3 drops (70 mg) of DMF (Table 2, entry 11); temperature CNS and power CNS are programmed temperature and power profiles, respectively.



Scheme 3. Mechanism for condensation of urea with phthalic anhydride.

microwave irradiation can be performed easily in a reduced time scale applying phthalonitrile (**1**) or phthalic anhydride (**2**) as a substrate. Solvent-free conditions lead by far to the best results and to easy-to-perform procedures with considerable improvements over classical methods. Moreover, the application of the dedicated monomode microwave reactor (Prolabo 402) with temperature monitoring allowed directly comparing two activation modes (i.e., conventional heating and microwave irradiation) and showed that non-thermal microwave effects might be very favourable during microwave experiments. This can be explained when one considers the enhancement in the polarity of the system when the reaction is in progress thanks to a well-fitted mechanism. Eventually, the reactions under conventional conditions that were carried out in the same time scale gave products in much lower yields of unacceptable purity.

4. Experimental

4.1. Materials

1,2-Dicyanobenzene, phthalic anhydride, urea, copper (II) chloride dihydrate and cobalt (II) hexahydrate were purchased from the Aldrich Chemical and were used without further purification.

Infrared spectra were recorded on the BIORAD spectrophotometer model FTS-165 as KBr pastille. The elemental analyses were realized in CNRS (Centre National de la Recherche Scientifique in Gif sur Yvette) 91198, France). The microwave reactor was Synthewave 402 from Prolabo.

The preparation of copper phthalocyanine is representative of the general procedures.

4.1.1. Procedure A. Phthalodinitrile (**1**) (12 mmol, 1.54 g) and copper chloride dihydrate (2.5 mmol, 0.425 g) were ground together and placed in a tube. The mixture was then irradiated in the microwave reactor for time given in Tables 1 and 2. The crude product was washed successively with hot water, acetone, dichloromethane and then was dried. Next the product was twice dissolved in the concentrated H_2SO_4, precipitated from distilled water, filtrated off and washed with water to pH neutral. After drying under reduced pressure, the phthalocyanine–Cu was analysed.

4.1.2. Procedure B. Phthalic anhydride (**2**) (10 mmol, 1.49 g), urea (20 mmol, 1.2 g), copper chloride dihydrate (2.5 mmol, 0.425 g) and ammonium molybdate as a catalyst (2.0 mmol, 0.47 g) were ground together, placed in a tube and irradiated in the microwave reactor at high power for time reported in Table 3. After completion of the reaction, the product was washed hot water, acetone and dichloromethane. Finally, the product was twice dissolved in the concentrated H_2SO_4, precipitated from distilled water, filtrated off and washed with water to pH neutral. After drying under reduced pressure, the phthalocyanine–Cu was analysed.

Acknowledgements

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References and notes

1. McKeown, N. B. *Phthalocyanine Materials: Synthesis, Structure, and Function*; Cambridge University Press: Cambridge, 1998.
2. Moser, F. H.; Thomas, A. L. *The Phthalocyanines*; CRC: Boca Raton, 1983.
3. Leznoff, C. C.; Lever, A. B. P. *Phthalocyanines. Properties and Applications*; VCH: New York, 1996.
4. Anthopoulos, T. D.; Shafai, T. S. *Appl. Phys. Lett.* **2003**, *82*, 1628.
5. Wrobel, D.; Boguta, A. In *Molecular Low Dimensional and Nanostructured Materials for Advanced Technology*; Graja, A., Ed.; Kluwer Academic: The Netherlands, 2002.
6. Pannemann, Ch.; Dyakonov, V.; Parisi, J.; Hild, O.; Wohrle, D. *Synth. Met.* **2001**, *121*, 1585.
7. Ishii, M.; Taga, Y. *Appl. Phys. Lett.* **2002**, *80*, 3430.
8. Jung, S.-H.; Choi, J.-H.; , S.-M.; Yang, J.-H.; Cho, W.-J.; Ha, C.-S. *Mater. Sci. Eng. B* **2001**, *85*, 160.
9. Sluven, J.; Gorller-Walrand, Ch.; Binnemans, K. *Mater. Sci. Eng. C* **2001**, *18*, 229.
10. de la Torre, G.; Vazquez, P.; Agullo-Lopez, F.; Torres, T. *J. Chem. Mater.* **1998**, *8*, 1671.
11. Torres, T.; de la Torre, G.; Garcia-Ruiz, J. *Eur. J. Org. Chem.* **1999**, 2323.
12. Rosanthal, I. *Photochem. Photobiol.* **1991**, *53*, 859.
13. Muller, S.; Mantareva, V.; Stoichkova, N.; Kliesch, H.; Sobki,

A.; Wohrle, D.; Shopova, M. *J. Photochem. Photobiol. B* **1996**, *35*, 167.
14. Law, K.-Y. *Chem. Rev.* **1993**, *94*, 243.
15. Birkett, D. *J. Chem. Educ.* **2002**, *79*, 1081.
16. Raja, R.; Ratnasamy, P. *J. Catal.* **1997**, *170*, 244.
17. Sorokin, A.; Meunier, B. *Eur. J. Inorg. Chem.* **1998**, 1269.
18. McKeown, N. B. *J. Mater. Chem.* **2000**, *10*, 1979.
19. Kimura, M.; Wada, K.; Iwashima, Y.; Ohta, K.; Hanabusa, K.; Shirai, H.; Kobayashi, N. *Chem. Commun.* **2003**, 2504.
20. *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
21. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213.
22. Bogdal, D.; Pielichowski, J.; Penczek, P.; Prociak, A. *Adv. Polym. Sci.* **2003**, *163*, 193.
23. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
24. Shaabani, A. *J. Chem. Res. (S)* **1998**, 672. Shaabani, A.; Bahadoran, F.; Bazgir, A.; Safani, N. *Iran J. Chem.* **1999**, *18*, 104. Shaabani, A.; Bahadoran, F.; Safani, N. *Indian J. Chem.* **2001**, 195.
25. Villemin, D.; Hammadi, M.; Hachemi, M.; Bar, N. *Molecules* **2001**, *6*, 831.
26. Bogdal, D.; Lukasiewicz, M. *Synlett* **2000**, 143. Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Miciak, A.; Bednarz, S. *Tetrahedron* **2000**, 143.
27. Bogdal, D.; Lukasiewicz, M.; Pielichowski, J. *Green Chem.* **2004**, *6*, 110.
28. Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473.
29. Sigma-Aldrich Handbook of Fine Chemicals and Laboratory Equipment, 2003–2004.
30. Marquez, H.; Plutin, A.; Rodriguez, Y.; Perez, E.; Loupy, A. *Synth. Commun.* **2000**, *30*, 1067. Suarez, M.; Loupy, A.; Salfran, E.; Moran, L.; Rolando, E. *Heterocycles* **1999**, *51*, 21. Perez, R.; Perez, E.; Suarez, M.; Gonzalez, L.; Loupy, A.; Gimeno, M. L.; Ochoa, C. *Org. Prep. Proced. Int.* **1997**, *29*, 671. Dandia, A.; Sati, M.; Loupy, A. *Green Chem.* **2002**, *4*, 599.
31. Baumann, F.; Binert, B.; Roch, G. *Angew. Chem.* **1956**, *68*, 133. Baranski, A.; Lyubimtsev, A. *Zh. Org. Khim.* **1998**, *34*, 1535. Baranski, A.; Lyubimtsev, A. *Zh. Org. Khim.* **1998**, *34*, 1542. Baranski, A.; Lyubimtsev, A. *Zh. Org. Khim.* **2000**, *36*, 752 and references cited therein.
32. Bae, K. J.; Hahn, Ch. S. *J. Korean Chem. Soc.* **1972**, *16*, 84.
33. Jung, K. S.; Kwon, J. H.; Son, S. M.; Shin, J. S.; Lee, G. D.; Park, S. S. *Synth. Met.* **2004**, *141*, 259.

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Agariblazeispirol C from the cultured mycelia of the fungus, *Agaricus blazei*, and the chemical conversion of blazeispirol A

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Abstract—Agariblazeispirol C, which has a unique steroidal skeleton, has been isolated from the cultured mycelia of *Agaricus blazei* (Agaricaceae). The structure of agariblazeispirol C was established to be (23*S*,24*S*)-13,23-cyclo-25-hydroxy-14β-methyl-18-nor-des-*A*-ergosta-5,7,9,11,17(20)-pentaen-22-one by comparison of extensive 1D and 2D NMR spectral data with those of agariblazeispirols A and B. At the same time, agariblazeispirol C was synthesized by the reaction of blazeispirol A with $BF_3 \cdot OEt_2$ along with some interesting compounds.
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1. Introduction

Agaricus blazei is known as a precious fungus which produces many bioactive compounds in its fruiting bodies. The polysaccharides obtained from it have been revealed to have immuno-stimulating activities.[1–4] Ergosterol derivatives showed cytotoxity,[5] and linoleic acid derivatives were suggested to have antimutagenic and bactericidal effects.[6] In our previous papers we reported the isolation and structure elucidation of many blazeispirol derivatives, which have an unprecedented skeleton, from the cultured mycelia of *Agaricus blazei*.[7–11] In a preliminary paper, we reported the structure elucidation of agariblazeispirols A (**1**) and B (**2**) which have a new unique skeleton formed by migration of C-18 methyl from the position 13 to 14.[12] In further investigation of the same source, we found a new agariblazeispirol derivative (**3**), named agariblazeispirol C. In this paper, we describe the structure elucidation of the new compound, agariblazeispirol C. In addition, we also describe the structures of the reaction products (**3**–**6**) of blazeispirol A with $BF_3 \cdot OEt_2$ including the same structure moiety formed by migration of C-18 methyl from the position 13 to 14 as in compounds **1**–**3**.

2. Results and discussion

The cultured mycelia of *Agaricus blazei* Murill were extracted sequentially with methanol at room temperature. The concentrated methanolic extract was diluted with water and partitioned with chloroform and ethyl acetate. Each fraction was dried in vacuo. The chloroform extract (18.86 g) was chromatographed on silica gel and separated into fractions A–H. Further purification by silica gel column chromatography and reversed-phase HPLC afforded compound **3** from fraction D (Fig. 1).

Compound **3**, agariblazeispirol C, slight yellow oil (39.4 mg; 0.21% yield from the $CHCl_3$ extract), $[\alpha]_D^{23}$ −110° (*c*, 0.10, $CHCl_3$), had the molecular formula of $C_{25}H_{32}O_3$, with an 18 mass unit less relative to that of agariblazeispirol A ($C_{25}H_{34}O_4$) reported previously[12] by the high-resolution FAB mass spectrum. The presence of a hydroxyl group and a carbonyl group was indicated from its IR absorption at 3420 and 1690 cm^{-1}. Its ^{13}C NMR spectrum showed 25 carbons, and the DEPT spectrum suggested the presence of seven methyls, two methylenes, six methines, and 10 quaternary carbons identical with that of agariblazeispirol A[12] except for the number of the methine and quaternary carbons (Table 1). Although agariblazeispirol A showed four oxygenated carbon signals including an acetal carbon in the ^{13}C NMR spectrum, a carbonyl carbon (δ 212.5) and an oxygenated quaternary carbon (δ 72.5) signals were observed in the ^{13}C NMR spectrum of **3**. Therefore, compound **3** exhibits the structure moiety in which the furan ring seen in the agariblazeispirol

Keywords: *Agaricus blazei*; 14β-Methyl-18-nor-des-A-ergostane derivative; Agariblazeispirol C.
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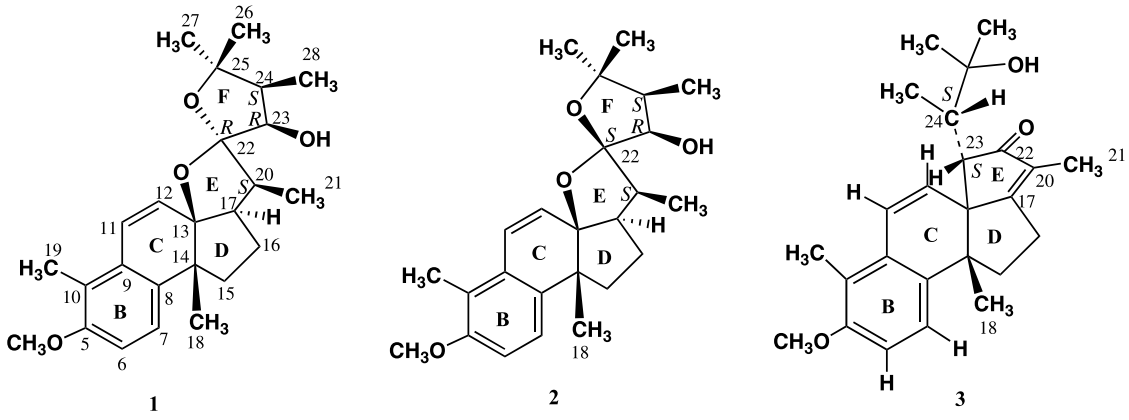

Figure 1. Structures of Agariblazeispirol A (**1**), B (**2**) and C (**3**).

A is opened and it was suggested that the diagnostic carbon signal (δ 187.1) was due to the five-membered olefinic carbon. As shown in Figure 2, NOEs were observed between methyl proton H-19 (δ 2.25) and H-11(δ 6.96), and H-11 and H-12(δ 5.55), methoxy methyl proton (δ 3.82) and H-6 (δ 6.72), H-6 and H-7 (δ 7.14), respectively, in the rings B and C in the NOESY spectra of **3**. These results lead to the conclusion that the rings B and C in **3** have a 5,7,9,11-tetraene structure the same as agariblazeispirol A. Depending on the evidence of HMBC spectral data that the methyl proton signal (δ 1.24) was correlated with four carbons (δ 42.8, 44.2, 61.7 and 133.6) supposed to be C-15, C-14, C-13 and C-8, its position was considered to be shifted from C-13 to C-14 and assigned to be an 18-methyl group like that of agariblazeispirols A and B.[12] Furthermore, in the NOESY spectrum of **3**, NOEs were observed between methyl proton H-18 (δ 1.24) and H-7 (δ 7.14), and H-15β (δ 1.71) (Fig. 2). These results lead to the conclusion that **3** has a 14β-methyl-18-nor-des-*A*-ergostane skeleton the same as that of agariblazeispirol A. In the ring E, the methyl proton signal H-21 (δ 1.77) which has coupling with methylene proton H-16, showed correlations with C-17 (δ 187.1: ^3J), C-20 (δ 133.2: ^2J) and C-22 (δ 212.5: ^3J), and also the proton signal H-23 (δ 2.86) correlated with C-13 (δ 61.7: ^2J), C-17 (δ 187.1: ^3J) and C-22 (δ 212.5: ^2J) in the HMBC spectrum (Table 1). From these results, the ring E was suggested to be cyclopentenone which was formed by cyclization of C-23 and C-13. Since NOE was observed between H-18 (δ 1.24) and H-23 (δ 2.86), **3** was determined to be (23*S*,24*S*)-13,23-cyclo-25-hydroxy-14β-methyl-18-nor-des-*A*-ergosta-5,7,9,11,17(20)-pentaen-22-one.

Table 1. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data (δ in ppm, J in Hz) for agariblazeispirol C (**3**)

C/H	$^{\delta}$H	$^{\delta}$C	^{1}H–^{13}C long-range correlations	
			^2J	^3J
5	—	156.5		
6	6.72 d (8.5)	109.4	C-5	C-8, C-10
7	7.14 d (8.5)	122.7	C-6	C-5, C-9, C-14
8	—	133.6		
9	—	130.2		
10	—	123.1		
11	6.96 d (10)	126.5	C-12	C-8, C-10, C-13
12	5.55 d (10)	130.1	C-13	C-9, C-14, C-17
13	—	61.7		
14	—	44.2		
15	2.29 ddd (13, 10.5, 9)	42.8	C-14, C-16	C-8, C-18
	1.71 ddd (13, 8, 2.5)		C-14, C-16	C-13, C-17, C-18
16	2.50 dddd (14, 10.5, 2.5, 1.5)	25.1	C-15, C-17	C-13, C-20
	2.58 dddd (14, 9, 8, 1.5)		C-15, C-17	C-13, C-20
17	—	187.1		
18	1.24 s	20.2	C-14	C-8, C-13, C-15
19	2.25 s	11.1	C-10	C-5, C-9,
20	—	133.2		
21	1.77 dd (1.5, 1.5)	8.9	C-20	C-17, C-22
22	—	212.5		
23	2.86 bs	53.7	C-13, C-22, C-24	C-12, C-17, C-20, C-25, C-28
24	1.26 dq (7, 1)	42.3	C-23, C-25, C-28	C-13, C-22, C-26, C-27
25	—	72.5		
26	1.04 s	27.9	C-25	C-24, C-27
27	0.91 s	30.4	C-25	C-24, C-26
28	0.92 d (7)	13.4	C-24	C-23, C-25
OCH_3	3.81 s	55.7		C-5
OH	4.08 bs			

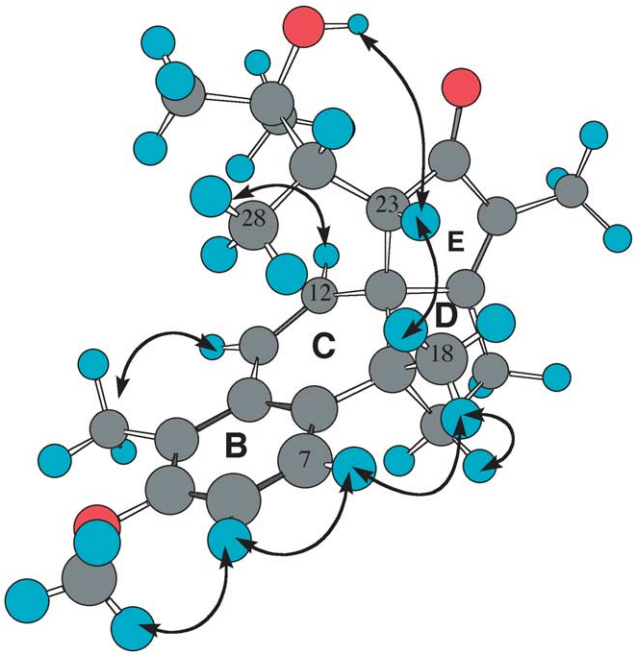

Figure 2. Key NOESY correlations of Agariblazeispirol C (**3**).

Agariblazeispirol A–C are novel des-*A*-ergostane type compounds and the occurrence of the 18-methyl group at C-14 is unprecedented.

Quite recently, Jayasinghe et al. reported the structure of diploclidine, which was a novel ecdysteroid with a pyridine ring as the fifth ring system and the occurrence of the 18-methyl group at C-14.[13] They proposed that the position of the methyl group can be accounted for by the fact that an ecdysteroid precursor having a 14α-hydroxyl group and a methyl group at the 13β-position promoted migration of the methyl group from C-13 to C-14 with concomitant elimination of the 14α-hydroxy group during the pyridine ring formation.[13] Agariblazeispirols A, B and C were suggested to be biosynthesized from blazeispirol A along with cleavage of the diepoxyl structure and rearrangement of the methyl from C-13 to C-14. In order to clarify this suggestion, we carried out a reaction of blazeispirol A with $BF_3 \cdot OEt_2$.[14,15] After work-up, four reaction products (RP-1–RP-4) were isolated by HPLC.

RP-1 (**3**), slight yellow oil, $[\alpha]_D^{22}$ −110° (*c*, 0.10, $CHCl_3$); had the molecular formula of $C_{25}H_{32}O_3$, identical with that of agariblazeispirol C ($C_{25}H_{32}O_3$) by the high-resolution FAB mass spectrum. Since the ^1H and ^{13}C NMR data of RP-1 were completely identical with that of agariblazeispirol C (Tables 1 and 2), RP-1 was identified to be agariblazeispirol C.

RP-2 (**4**) colorless powder, $[\alpha]_D^{28}$ +270° (*c*, 0.11, $CHCl_3$), had the molecular formula of $C_{25}H_{32}O_3Na$, the same as that of RP-1 (**3**) ($C_{25}H_{32}O_3$) by the high-resolution FAB mass spectrum. The presence of a five-membered ring carbonyl group was indicated from its IR absorption at 1755 cm^{-1}. Its ^{13}C NMR spectrum showed 25 carbons, and the DEPT spectrum suggested the presence of seven methyls, two methylenes, seven methines, and nine quaternary carbons identical with that of RP-1 (**3**) except for the number of the methine and quaternary carbons (Table 2). In the NOESY

Table 2. ^{13}C NMR (100 MHz) and ^1H NMR (400 MHz) data (δ in ppm, *J* in Hz) for RP-1 (**3**), RP-2 (**4**), RP-3 (**5**) and RP-4 (**6**)

C/H	**3**		**4**		**5**		**6**	
	$^{\delta}C$	$^{\delta}H$	$^{\delta}C$	$^{\delta}H$	$^{\delta}C$	$^{\delta}H$	$^{\delta}C$	$^{\delta}H$
5	156.5	—	155.7	—	152.4	—	152.7	—
6	109.4	6.72 d (8.5)	109.4	6.72 d (8.5)	115.7	7.35 s	114.3	7.12 s
7	122.7	7.14 d (8.5)	122.4	6.97 d (8.5)	131.9	—	133.3	—
8	133.6	—	139.1	—	126.6	—	127.0	—
9	130.2	—	131.5	—	132.4	—	132.4	—
10	123.1	—	122.2	—	118.3	—	118.4	—
11	126.5	6.96 d (10)	123.9	6.70 d (10)	121.3	7.73 d (8.5)	120.5	7.68 d (8.5)
12	130.1	5.54 d (10)	121.0	6.48 d (10)	128.8	7.30 d (8.5)	128.9	7.29 d (8.5)
13	61.7	—	139.1	—	129.3	—	129.0	—
14	44.2	—	49.5	—	132.1	—	133.8	—
15	42.8	2.30 ddd (13, 10.5, 9) 1.71 ddd (13, 8, 2.5)	38.7	2.03 ddd (11,10.5,8.5) 2.30 dd (11,6.5)	23.1	2.88 ddd (17.5,5.5,2.5) 2.79 ddd (17.5,13.5,5)	25.5	3.39 ddd (17,12,6) 2.83 ddd (17,6,3)
16	25.1	2.50 dddd (14,10.5,2.5, 1.5) 2.58 dddd (14, 9, 8, 1.5)	30.4	2.45 dd (16.5,8.5) 2.54 ddd (16.5,10.5,6,5)	24.3	1.97 dddd (13.5,13.5,5.5,5) 1.85 dddd (13.5,5,2.5,2.5)	25.1	2.12 m 2.04 ddd (13.5,6,3)
17	187.1	—	140.4	—	44.6	3.41 dd (5,2.5)	46.7	3.34 dd (4,4)
18	20.2	1.24 s	27.7	1.16 s	19.4	2.37 s	19.2	2.36 s
19	11.1	2.25 s	11.0	2.25 s	10.7	2.51 s	10.7	2.53 s
20	133.2	—	35.4	2.99 dq (7,7)	91.9	—	92.8	—
21	8.9	1.77 dd (1.5, 1.5)	15.6	1.06 d (7)	25.9	2.40 s	27.6	2.30 s
22	212.5	—	81.0	3.97 dd (7,1)	214.1	—	216.9	—
23	53.7	2.86 bs	217.6	—	36.2	1.44 dd (13.5,7.5) 1.99 dd (13.5,11.5)	41.3	1.83 dd (13.5,11.5) 2.36 dd (13.5,7)
24	42.3	1.27 dq (7, 1)	51.3	2.26 dq (7,1)	43.7	0.73 m	41.2	0.67 m
25	72.5	—	79.9	—	82.5	—	84.5	—
26	27.9	1.04 s	24.4	1.24 s	21.3	0.79 s	22.4	0.82 s
27	30.4	0.91 s	28.4	1.37 s	26.7	1.20 s	26.0	0.26 s
28	13.4	0.92 d (7)	10.4	1.07 d (7)	14.0	0.48 d (7)	13.8	0.59 d (7)
CH_3-O	55.7	3.81 s	55.8	3.80 s	56.6	3.97 s	57.2	3.91 s
OH		4.08 bs						

experiment, it was suggested that **4** has a 5,7,9,11-tetraene structure the same as RP-1 (**3**) in the rings B and C. The C-18 methyl proton at δ 1.16 showed HMBC correlation with C-8 (δ 139.1; ^3J), C-13 (δ 139.1; ^3J), C-14 (δ 49.5; ^2J) and C-15 (δ 38.7; ^3J), thus establishing the migration of the C-18 methyl group from the C-13 to C-14 position the same as RP-1 (**3**). In addition, correlations were observed of both H-16 (δ 2.45 and 2.54) and H-20 (δ 2.99) with C-13 (δ 139.1; ^3J), and also both H-12 (δ 6.48) and H-22 (δ 3.97) with C-17 (140.4; ^3J) in the HMBC spectrum of **4**. Therefore, C-13 and C-17 have composed a double bond in the ring D. Since H-22 (δ 3.97) showed the correlation with C-23 (δ 217.6; ^2J) and C-25 (δ 79.9; ^3J), and also H-28 (δ 1.07) with C-23 (δ 217.6; ^3J) and C-25 (δ 79.9; ^3J), ring E was suggested to be furanone. From these data, **4** was determined to be (20*S*,22*R*,24*R*)-22,25-epoxy-5-methoxy-14β-methyl-18-nor-des-*A*-ergosta-5,7,9,11,13(17)-pentaen-23-one.[16]

RP-3 (**5**) and RP-4 (**6**) colorless solid and slight yellow oil, $[\alpha]_D^{22}$ +39° (*c*, 0.10, $CHCl_3$) and $[\alpha]_D^{23}$ −42° (*c*, 0.11, $CHCl_3$), respectively, had the same molecular formula of $C_{25}H_{32}O_3$ as that of **4** by the high-resolution FAB mass spectra. In the NOESY spectrum **5**, NOEs were observed at methoxyl methyl (δ 3.97) and H-6 (δ 7.35), CH_3-19 (δ 2.51) and H-11 (δ 7.73), H-11 and H-12 (δ 7.30), H-12 and H-18 (δ 2.37), respectively. Furthermore, the 18-methyl proton, which was attached to the C-13 position (aromatic ring) correlated with C-12 (δ 128.8), C-13 (δ 129.3) and C-14 (δ 132.1) in the HMBC spectrum. These results lead to the conclusion that the B and C rings rise to be a dihydrophenalene skeleton formed by cyclization of C-17 and C-7 after cleavage of the C-13 and C-17 bonds. This cyclization was supported by the fact that H-17 methine proton, which coupled with H-16 (δ 1.85 and 1.97) methylene protons, was correlated with H-6 in the NOE experiment and also correlated with C-6 in the HMBC spectrum. In the HMBC spectrum, 21-methyl proton, which NOE was observed with H-17 methine proton, was correlated with C-20 (δ 91.9; ^2J), C-22 (δ 214.1; ^3J), and also H-23 (δ 1.44 and 1.99) methylene protons, which was coupled with H-24 (δ 0.73), were correlated with C-20 (δ 91.9; ^3J), C-22 (δ 214.1; ^2J) and C-25 (δ 82.5; ^3J). Furthermore, NOEs were observed among H-28, H-26, and H-21. Therefore, ring E is a pyranone and it was indicated that the relative stereochemistries of C-17, C-20 and C-24 should be *R**,*S** and *S**, respectively. These data led to the conclusion that the structure **5** was (17*R**, 20*S**, 24*S**)-17 (13→7)*abeo*-20,25-epoxy-5-methoxy-des-*A*-ergosta-5,7,9,11,13-pentaen-22-one as shown in Figure 3.

Since compounds **5** and **6** were synthesized from blazeispirol A reaction with $BF_3 \cdot OEt_2$, the orientation of C-24 of **5** and **6** is identical with that of blazeispirol A (Fig. 4). Therefore, RP-4 (**6**) was determined to be a stereoisomer of **5** at the C-17 position from the comparison with NOEs of **5** and **6** as shown in Figure 3.

It is interesting that agariblazeispirol C was demonstrated to be formed by the migration of the C-18 methyl group from the C-13 to C-14 position through opening the diepoxy ring of blazeispirol A.

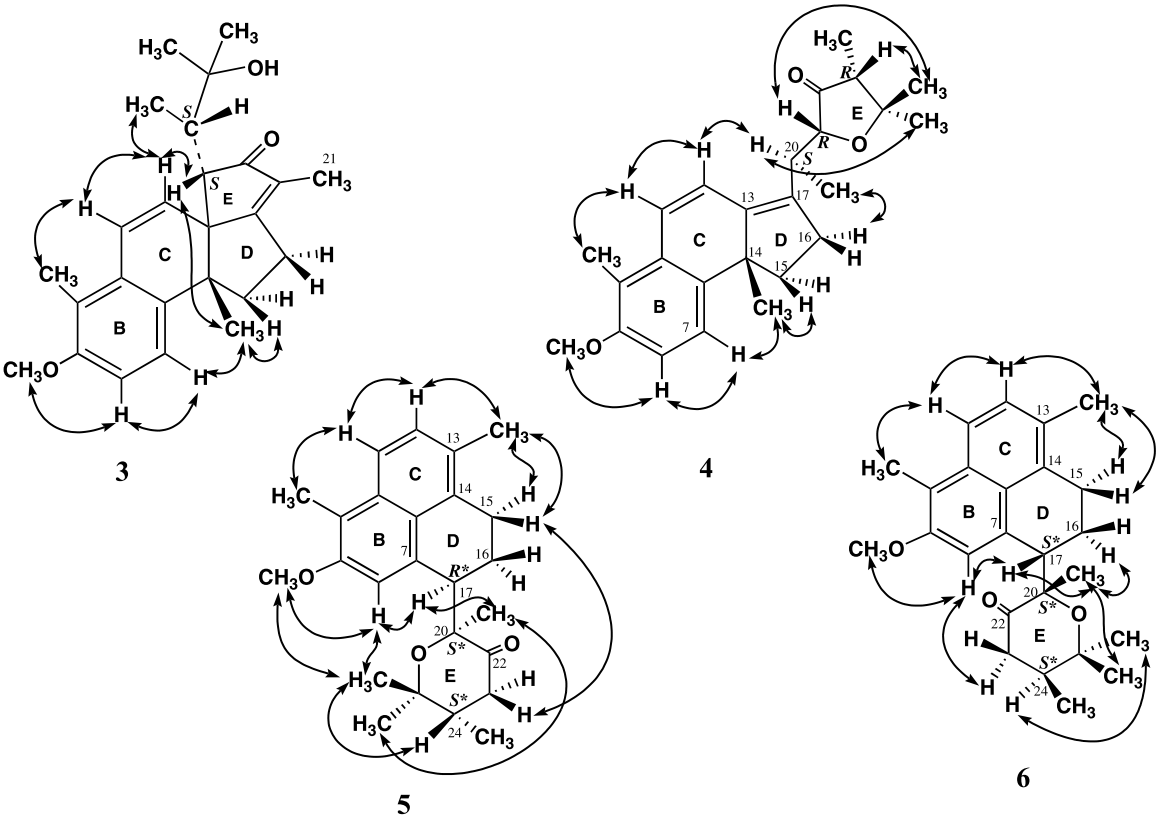

Figure 3. The structures and selected NOESY correlations for RP-1 (**3**), RP-2 (**4**), RP-3 (**5**) and RP-4 (**6**).

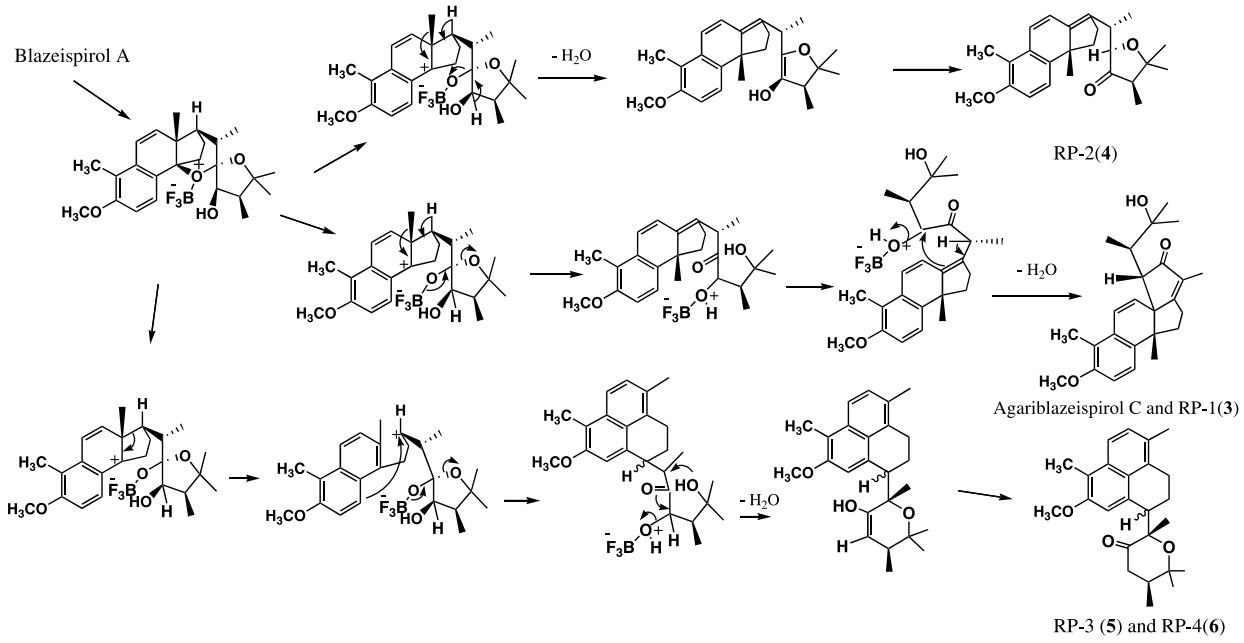

Figure 4. Plausible synthetic and biosynthetic mechanism of agariblazeispirol C (**3**), RP-1 (**3**), RP-2 (**4**), RP-3 (**5**) and RP-4 (**6**).

To explain this interesting conversion of the blazeispirol A side chain we propose a reaction as depicted in Figure 4.

3. Experimental

3.1. General

Optical rotation: JASCO DIP-370 ($CHCl_3$), UV: HITACHI 340 (alcohol), IR: JASCO FT/IR-200 (KBr discs), EIMS: JEOL JMS-AX505 H, FABMS: JEOL JMS-AX505 HA, ^1H and ^{13}C NMR: Varian UNITY 400 (400 and 100 MHz, respectively, in $CDCl_3$). TLC: 0.25 mm precoated silica-gel plates (MERCK silica-gel 60F254); detection by spraying the plates with 10% (v/v) H_2SO_4 solution followed by heating at 120 °C. Column chromatography (CC): Silica gel 60 (Cica-reagent, 40–100 μm, Kanto Chemical). HPLC was performed by Senshu Pak ODS (10 $\phi \times 300$ mm) coupled with a UV detector and a differential refractometer.

3.2. Culture conditions for *Agaricus blazei* mycelium

The pure mycelia were subcultured for 2 weeks and grown in a 500-ml Erlenmeyer flask with 125 ml of medium containing 10 g sucrose, 30 g malt extract, 5 g yeast extract in 1 l of distd H_2O according to the previous paper.[10] Usually, each flask was seeded with five of the 10 mm plugs cut from the potato dextrose agar culture.

3.3. Extraction procedure and separation of the MeOH extract of the mycelia

After 5 weeks culture (1027 flasks), the mycelia (12.77 kg, fr. wt) were harvested with nylon cloth, homogenized with MeOH (65.8 l) in a Waring blender and allowed to stand for 1 week at rt. The homogenate was filtered and the residue was re-extracted with the same solvent (46 l). The filtrates were combined and the organic solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ (five times in a total of 20 l), dried and evaporated to dryness. The $CHCl_3$ extract (18.86 g) was subjected to chromatography over silica gel (Silica gel 60, 720 g). Elution with 5.4 l toluene and 2.97 l toluene–AcOEt (19:1) (fraction A), 0.90 l (fraction B), 1.22 l and 3.67 l toluene–AcOEt (9:1) (fraction C), 2.07 l toluene–AcOEt (9:1) and 4.68 l toluene–AcOEt (8:2) (fraction D); 0.81 l toluene–AcOEt (8:2) and 3.44 l toluene–AcOEt (6:4) (fraction E); 3.44 l, 3.60 l toluene–AcOEt (4:6) and 3.60 l 100% AcOEt (fraction F), 1.80 l 100% MeOH (fraction G) yielded nine fractions A–G. In the previous paper, we reported the isolation and structure elucidation of blazeispirols G, U and Z_1 from fraction D (2.0 g), blazeispirol I from fraction E (0.98 g), blazeispirols V and V_1 from fraction F (1.91 g), and agariblazeispirols A (**1**) and B (**2**) from fraction B.[11,12] Further purification of fraction C (1.67 g) was achieved by silica gel column chromatography and reversed-phase HPLC. Fraction C was subjected to chromatography over silica gel (Silica gel 60, 100 g) to give 3 fractions C-1–C-3. Compound **3** (39.4 mg) was isolated from fraction C-2 (110.4 mg) by HPLC (Senshu Pak ODS, ϕ 10×300 mm, 90% MeOH, 3 ml min^{-1} flow rate, rt, 10.8 min).

3.3.1. Agariblazeispirol C (3). Slight yellow oil, $[\alpha]_D^{23}$ −110° (*c*, 0.10, $CHCl_3$) UV λ_{max} (MeOH) nm (log ε): 224 (4.39), 270 (3.88), 280 (3.81). IR ν_{max} (KBr) cm^{-1}: 3420, 2970, 2920, 1690, 1655, 1580, 1380, 1260, 1100. HRFABMS *m/z*: 403.2253 $[M+Na]^+$ ($C_{25}H_{32}O_3Na$ requires 403.2250). EI-MS *m/z* (rel. int.): 380 $[M]^{+s}$ (30), 365 $[M-CH_3]^+$(19), 347 (15), 322 (44), 321 (45), 307 (100), 292 (14), 279 (11), 249 (6), 199 (6), 149 (7), 84 (22), 83 (33). For ^{13}C and ^1H NMR spectral analyses, see Table 1.

3.4. Reaction of blazeispirol A with $BF_3 \cdot OEt_2$

A solution of blazeispirol A (100 mg; 0.25 mmol) in $CHCl_3$ (50 ml) was treated with $BF_3 \cdot OEt_2$(460 μl) at −10 to −15 °C and stirred for 30 min. To this solution was then added Et_3N (400 μl) and stirred for 5 min. The reaction mixture was diluted with $CHCl_3$ (200 ml), washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, concentrated in vacuo. The residue (108.1 mg) was separated. Four fractions containing the peak 1 (rt 11.2 min, 42.2 mg), peak 2 (rt 17.3 min, 4.6 mg), peak 3 (rt 19.4 min, 7.2 mg) and peak 4 (rt 23.8 min, 17.6 mg) were obtained by HPLC (Senshu pak ODS 10 $\phi \times 300$ mm, 90% MeOH 3 ml min^{-1} flow rate). RP-1 (42.2 mg) was isolated from the fraction containing peak 1 as the major reaction product (yield 44.2%). RP-4 (2.0 mg) was isolated from the fraction containing peak 3 (7.2 mg) by HPLC (Senshu Pak ODS, ϕ 10×300 mm, 90% CH_3CN, 3 ml min^{-1} flow rate, rt, 15.8 min). RP-2, 3 (1.9 and 4.4 mg, respectively) were isolated from the fraction containing peak 4 (17.6 mg) by HPLC (Senshu Pak ODS, ϕ 10×300 mm, 88% CH_3CN 3 ml min^{-1} flow rate, rt, 18.0 and 19.6 min, respectively).

3.4.1. RP-1 (3). Slight yellow oil, $[\alpha]_D^{22}$ −110° (*c*, 0.10, $CHCl_3$); UV λ_{max} (MeOH) nm (log ε): 224 (4.43), 270 (3.92), 280 (3.90). IR ν_{max} (KBr) cm^{-1}: 3420, 2970, 2920, 1690, 1655, 1580, 1470, 1380, 1260, 1100. HRFABMS *m/z*: 381.2422 $[M+H]^+$ ($C_{25}H_{33}O_3$ requires 381.2430). For ^{13}C and ^1H NMR spectral analyses, see Table 2.

3.4.2. RP-2 (4). Colorless powder, $[\alpha]_D^{28}$ +270° (*c*, 0.11, $CHCl_3$); UV λ_{max} (MeOH) nm (log ε): 232 (3.91), 307 (3.94), 316 (3.93). IR ν_{max} (KBr) cm^{-1}: 2960, 2950, 1755, 1460, 1370, 1260, 1100, 970. HRFABMS *m/z*: 403.2238 $[M+Na]^+$ ($C_{25}H_{32}O_3Na$ requires 403.2250). EIMS *m/z* (rel. int.): 380 $[M]^+$(12), 365 $[M–CH_3]^+$(80), 253 (93), 238 (100), 223 (11), 211 (10), 149 (12), 127 (6), 97 (6). For ^{13}C and ^1H NMR spectral analyses, see Table 2.

3.4.3. RP-3 (5). Colorless solid, $[\alpha]_D^{22}$ +39° (*c*, 0.10, $CHCl_3$); UV λ_{max} (MeOH) nm (log ε): 234 (4.92), 276 (3.78), 288 (3.93), 300 (3.93), 330 (3.71). IR ν_{max} (KBr) cm^{-1}: 2970, 2870, 1710, 1600, 1465, 1380, 1350, 1220, 1165, 1130. HRFABMS *m/z*: 403.2229 $[M+Na]^+$ ($C_{25}H_{32}O_3Na$ requires 403.2250). EIMS *m/z* (rel. int.): 380 $[M]^+$(5), 337 (2), 298 (24), 225 (100), 209 (22), 195 (17), 179 (14), 156 (11), 127 (6). For ^{13}C and ^1H NMR spectral analyses, see Table 2.

3.4.4. RP-4 (6). Slight yellow oil, $[\alpha]_D^{23}$ −42° (*c*, 0.11, $CHCl_3$); UV λ_{max} (MeOH) nm (log ε): 236 (5.09), 288 (3.78), 288 (4.12), 302 (4.12), 332 (3.93). IR ν_{max} (KBr) cm^{-1}: 2970, 2930, 1705, 1600, 1465, 1380, 1270, 1220, 1155, 1130, 1105, 1000. HRFABMS *m/z*: 403.2229 $[M+Na]^+$ ($C_{25}H_{32}O_3Na$ requires 403.2250). EIMS *m/z* (rel. int.): 380 $[M]^+$(12), 337 (4), 270 (4), 240 (5), 225 (100), 195 (14), 193 (12), 149 (19), 87 (12), 74 (13), 57 (11). For ^{13}C and ^1H NMR spectral analyses, see Table 2.

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References and notes

1. Kawagishi, H.; Inagaki, R.; Kanao, T.; Mizuno, T.; Shimura, K.; Ito, H.; Hagiwara, T.; Nakamura, T. *Carbohydr. Res.* **1989**, *186*, 267–273.
2. Mizuno, T.; Hagiwara, T.; Nakamura, T.; Ito, H.; Shimura, K.; Sumiya, T.; Asakura, A. *Agric. Biol. Chem.* **1990**, *54*, 2889–2896.
3. Ito, H.; Shimura, K.; Itoh, H.; Kawade, M. *Anticancer Res.* **1997**, *17*, 277–284.
4. Mizuno, M.; Morimoto, M.; Minato, K.; Tsuchida, H. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 434–437.
5. Kawagishi, H.; Katsumi, R.; Sazawa, T.; Mizumo, T.; Hagiwara, T.; Nakamura, T. *Phytochemistry* **1988**, *27*, 2777–2779.
6. Osaki, Y.; Kato, T.; Yamamoto, K.; Okubo, J.; Miyazaki, K. *Yakugaku Zasshi* **1994**, *114*, 342–350.
7. Hirotani, M.; Hirotani, S.; Takayanagi, H.; Yoshikawa, T. *Tetrahedron Lett.* **1999**, *40*, 329–332.
8. Hirotani, M.; Hirotani, S.; Yoshikawa, T. *Tetrahedron Lett.* **2000**, *41*, 5107–5110.
9. Hirotani, M.; Hirotani, S.; Yoshikawa, T. *Tetrahedron Lett.* **2001**, *42*, 5261–5264.
10. Hirotani, M.; Sai, K.; Hirotani, S.; Yoshikawa, T. *Phytochemistry* **2002**, *59*, 571–577.
11. Hirotani, M.; Sai, K.; Nagai, R.; Hirotani, S.; Takayanagi, H.; Yoshikawa, T. *Phytochemistry* **2002**, *61*, 589–595.
12. Hirotani, M.; Hirotani, S.; Takayanagi, H.; Komiyama, K.; Yoshikawa, T. *Tetrahedron Lett.* **2003**, *44*, 7975–7979.
13. Jayasinghe, L.; Jayasooriya, C. P.; Hara, N.; Fujimoto, Y. *Tetrahedron Lett.* **2003**, *44*, 8769–8771.
14. Corey, E. J.; Hong, B.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3149–3150.
15. Peakman, T. M.; Maxwell, J. R. *Tetrahedron* **1988**, *44*, 1559–1565.
16. In the previous paper,[12] our proposed structure of reaction product 2 (**4**) was correct, but the description of 20*R* was a typographical error. We have corrected the description to the *S*-configuration.

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Synthesis of vicinal diols from various arenes with a heterocyclic, amino or carboxyl group by using recombinant *Escherichia coli* cells expressing evolved biphenyl dioxygenase and dihydrodiol dehydrogenase genes

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Abstract—Various aromatic molecules, in which heterocycles are linked with a phenyl or benzyl group, were converted to their respective 2,3-diols (catechols) in the benzene ring by growing cell reactions using recombinant *Escherichia coli*, which expressed the evolved biphenyl dioxygenase [*bphA* (2072)] genes and the subsequent bacterial dihydrodiol dehydrogenase (*bphB*) gene. These vicinal diol products showed strong in vitro inhibitory activity against the lipid peroxidation induced by free radicals and strong scavenging activity towards DPPH radicals. The vicinal diols were also synthesized from ionized monocyclic aromatics incorporating an amino or carboxyl group.
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1. Introduction

We intend to develop a system for the comprehensive bioconversion of a series of organic chemicals by growing cell reactions using recombinant microbes which express different combinations of a sequence of biocatalytic genes. This intention attempts to perform comprehensive 'chemical synthesis' by using the multiple biocatalytic functions of the cells to link the diversity of genes (DNA) to that of chemicals. Figure 1 suggests the concept of such living cells-based combinatorial chemistry (CellCombiChem). CellCombiChem could significantly make it practical to synthesize chemicals, which are difficult or impractical to synthesize by chemical methods. It is also important to use an enzyme with broad substrate specificity or preference to achieve comprehensive bioconversion. Directed protein evolution could be one of the most powerful methods for generating such enzymes.[1]

It is usually difficult to introduce hydroxy group(s) into an aromatic ring *regio* or *stereo*-specifically by a chemical synthesis, although the industrial need for this is strong. For attempting such a hydroxylation reaction we have started our study on CellCombiChem with the biocatalytic genes mediating biphenyl catabolism, since carrying out the first dioxygenation reaction would be difficult by the extracted enzyme, which includes ferredoxin and ferredoxin reductase and needs $NAD(P)H^+$ that must be regenerated. The selection is also based on the following reasons: during the past 35 years, the *stereo* and *regio*-specific syntheses of *cis*-dihydrodiols (*cis*-dihydrocatechols, *cis*-cyclohexadiene-diols) have mainly been performed by toluene dioxygenase-mediated microbial conversion, so as to generate two hundred structurally diverse *cis*-dihydrodiols,[2] several of which have been applied as chiral intermediates for versatile synthetic applications by synthetic chemists worldwide.[2,3] These results show that toluene dioxygenase, which is an enzyme structurally similar to biphenyl dioxygenase, desirably has very broad substrate specificity; it may therefore be feasible to introduce hydroxy group(s) into a wide range of aromatic compounds *stereo*- and *regio*-specifically with biphenyl dioxygenase, and *regio*-specifically with the subsequent dehydrogenation enzyme. Many studies on the degradation of environmental pollutants such

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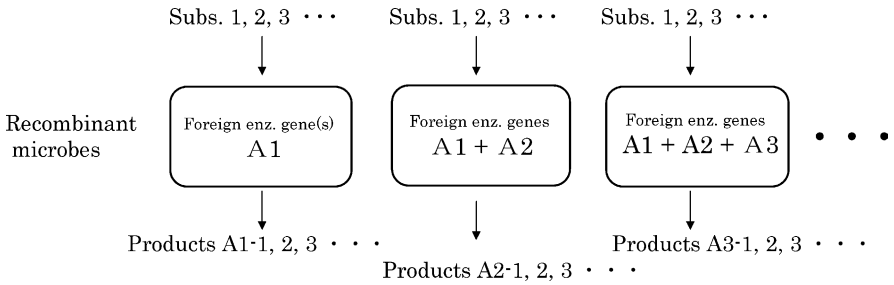


Figure 1. Concept of living cells-based combinatorial chemistry (CellCombiChem). Subs. 1, 2, 3… means a series of organic chemicals used as substrates. Foreign enz. gene(s) A1 represents foreign gene(s) coding for metabolic enzyme A1. Products A1-1, 2, 3… are generated from Subs. 1, 2, 3… through the living cells of recombinant microbes expressing the A1 gene(s). A2, which is usually a metabolic enzyme subsequent to A1, can convert A1-1, 2, 3… to A2-1, 2, 3… , which are further converted to A3-1, 2, 3… by enzyme A3.

as polychlorinated biphenyls (PCBs) have been performed by using biphenyl dioxygenases, but little work has been done on the synthesis of useful compounds by using this enzyme.[2,4]

The degradation of biphenyl and PCBs is enzymatically initiated by the action of biphenyl dioxygenase, as has been elucidated for the biphenyl-degrading bacteria, *Pseudomonas pseudoalcaligenes* KF707,[4,5] *Burkholderia* sp. strain LB400,[6] and *Sphingomonas yanoikuyae* strain B1.[2] Biphenyl dioxygenase is a multi-component enzyme consisting of BphA1, BphA2 [large α and small β subunits of iron–sulfur protein, respectively], BphA3 (ferredoxin), and BphA4 (ferredoxin reductase), as shown in Figure 2.[2,4,7–9] This enzyme (BphA) is responsible for the conversion of a biphenyl to its *cis*-dihydrodiol [(1*S*,2*R*)-dihydroxy-3-phenylcyclohexa-3,5-diene].[2,8] This compound is further converted to 3-phenylbenzene-1,2-diol by the subsequent desaturation reaction, which is catalyzed by BphB (biphenyl *cis*-dihydrodiol dehydrogenase).[7,9] The substrate-binding sites of biphenyl dioxygenase are considered to be present in its α-subunit (BphA1). This consideration is supported by the results of an X-ray structural analysis of naphthalene dioxygenase,[10] which is an enzyme with a topology slightly different from that of biphenyl dioxygenase, and by data obtained from DNA shuffling and in vitro mutagenesis experiments.[4,11] Modified *bphA1* genes were generated by DNA shuffling, using the *bphA1* genes derived from *P. pseudoalcaligenes* KF707 and *Burkholderia* sp. LB400.[11a] One of the shuffled genes, *bphA1* (2072), has been shown to mediate with broad substrate specificity, when expressed in combination with *bphA2A3A4* from *P. pseudoalcaligenes*.[8] We have shown for the first time that various molecular species, in which heterocyclic aromatics are linked with phenyl or benzyl groups, can be converted with high efficiency to the corresponding *cis*-dihydrodiols (*cis*-dihydrocatechols) by recombinant *Escherichia coli* or *Streptomyces lividans* strains carrying the evolved biphenyl dioxygenase genes [*bphA1*(2072)*A2A3A4*: *bphA* (2072)] (Fig. 3).[8,12] The *cis*-dihydrodiols generated may be capable of being used as substrates for BphB to synthesize their respective diols (catechols).

We report here the formation of vicinal diols (catechols) from various aromatic molecules, in which heterocycles including heteroaromatics are linked with phenyl or benzyl groups, through the growing cells of *E. coli* that express the *P. pseudoalcaligenes bphB* gene in addition to the *bphA* (2072) genes (Fig. 3). The antioxidative activity of these vicinal diols is examined. The vicinal diol formation from ionized monocyclic aromatics incorporating an amino or carboxyl group is also described.

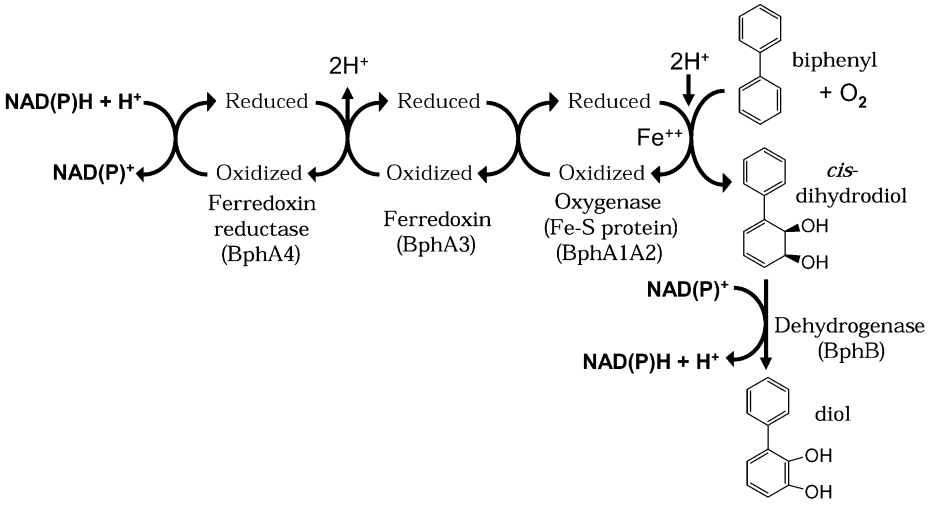


Figure 2. Catabolic pathway from biphenyl to diol (3-phenylbenzene-1,2-diol) via *cis*-dihydrodiol [(1*S*,2*R*)-dihydroxy-3-phenylcyclohexa-3,5-diene] for the biphenyl-degrading bacterium, *Pseudomonas pseudoalcaligenes* KF707. *Sphingomonas yanoikuyae* strain B1 seems to have the same pathway.[2]

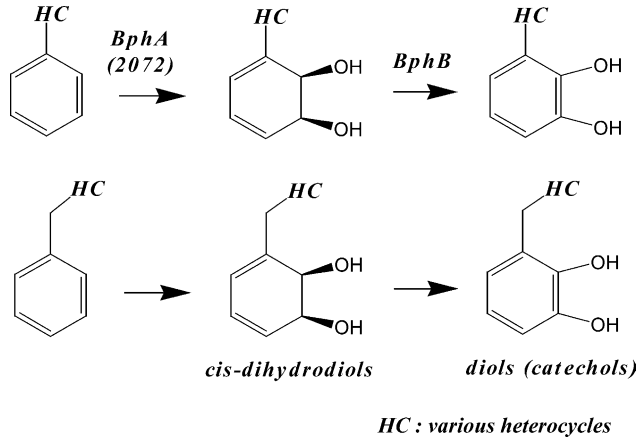


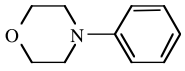
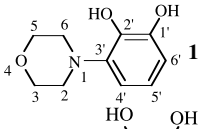
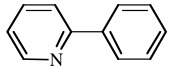
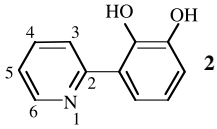
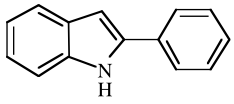
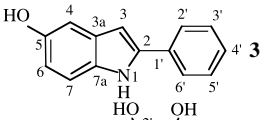
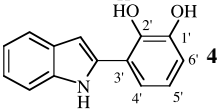
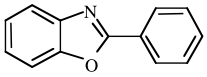
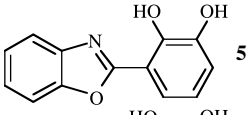
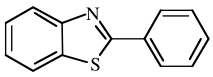
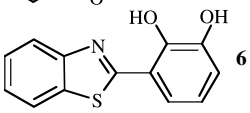
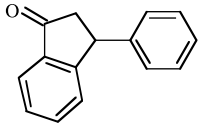
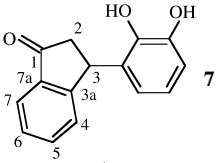
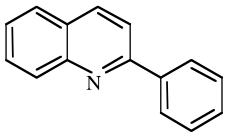
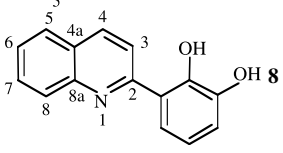
Figure 3. Bioconversion of a series of organic chemicals, in which various heterocycles are linked with phenyl or benzyl groups. The results of our study show that such compounds can be converted to the corresponding *cis*-dihydrodiols (*cis*-dihydrocatechols) by BphA (2072), these then being further converted to diols (catechols) by BphB.

2. Results and discussion

2.1. Biotransformation of heterocyclic compounds with phenyl moieties

4-Phenylmorpholine, 2-phenylpyridine, 2-phenylindole, 2-phenylbenzoxazole, 2-phenylbenzothiazole, and 2-phenylquinoline, whose structures are shown in Table 1, were used as examples of such substrates for bioconversion experiments. 3-Phenyl-1-indanone, in which not a heterocycle but a cyclic hydrocarbon substituted with oxygen is linked with a phenyl group, was also included in the experiments (Table 1). All of the substrates were converted by co-cultivation with recombinant *E. coli* cells possessing plasmid pBS2072B which carries the *bphA1*(2072)*A2A3A4* [*bphA* (2072)] and *bphB* genes. The structures of the biotransformed products were determined by HRMS (EI) and ^{1}H and ^{13}C NMR analyses, including a 2D spectral analysis. All the products were vicinal diols (catechols), except for one product converted from 2-phenylindole (Table 1). The yields of the respective purified products were 6.8–77% (Table 1). Products 2, 7 and 8 were found to be novel compounds according to the CAS database. In all the bioconversion experiments of this present study, we used 10 mg of each substrate per 100 ml culture (0.01%; w/v).

Table 1. Bioconversion of various aromatics, in which heterocycles are linked with phenyl groups, through the living cells of *E. coli* expressing the *bphA* (2072) and *bphB* genes

Substrate	Product	Yield (%)
 4-Phenylmorpholine	 **1**	30
 2-Phenylpyridine	 **2**	26
 2-Phenylindole	 **3**  **4**	9.0, 6.8
 2-Phenylbenzoxazole	 **5**	77
 2-Phenylbenzothiazole	 **6**	74
 3-Phenyl-1-indanone	 **7**	70
 2-phenylquinoline	 **8**	31

It may be thought that the substrate content is in a low level. However, the scale-up experiments in the substrates are easy to do up to 10-fold (0.1%; w/v), as needed (our unpublished results).[12]

When co-cultured with 2-phenylindole, a product with one hydroxy group in the indole ring (**3**) was obtained, in addition to the typical diol product (**4**). *E. coli* (pKF2072), which carries the *bphA1*(2072)*A2A3A4* genes, also generated the monohydroxylated product (**3**) in addition to the corresponding *cis*-dihydrodilol form (data not shown). We therefore consider that the indole ring has affinity for the active site facilitating an oxygenation reaction in the BphA (2072) enzyme and that the monohydroxy form is non-enzymatically generated from a *cis*-dihydrodiol due to the structural instability of the vicinal dihydrodiol in the indole ring. Such non-enzymatic dehydration from *cis*-dihydrodiols has often been observed.[8,9,12,13]

The results of our previous study show that heteroaromatic compounds with phenyl moieties were converted to their respective *cis*-dihydrodiols (*cis*-dihydrocatechols) when co-cultured with *E. coli* (pKF2072) carrying the *bphA* (2072) genes.[8] Examples of such substrates include 1-phenylpyrrole, 3-methyl-1-phenylpyrazole, and 4-phenylpyrimidine, in addition to the substrates shown in Table 1. 1-Phenylpyrrole, 3-methyl-1-phenylpyrazole, and 4-phenylpyrimidine are also very likely to be converted to the corresponding vicinal diols by *E. coli* (pBS2072B). Flavonoid pigments such as flavone and 6-hydroxyflavone can also be regarded as having a structure in which the heteroaromatic ring, the chromen-4-one ring, is linked to a phenyl group. We have shown that flavone and 6-hydroxyflavone were converted to their respective vicinal diols via *E. coli* or *S. lividans* carrying only the *bphA* (2072) genes[9,14] and via *E. coli* carrying the *bphA* (2072) and *bphB* genes more efficiently.[9] Seeger et al. have also shown that the isoflavonoids, 7-hydroxyisoflavone and 7-hydroxy-8-methyl-isoflavone, were biotransformed to the vicinal diol forms by *E. coli* harboring the *bphA* and *bphB* genes derived from *Burkholderia* sp. LB400.[15]

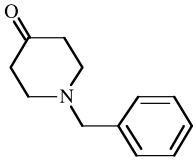
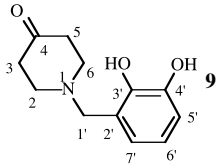
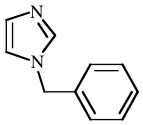
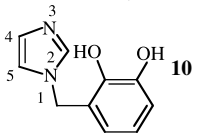
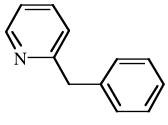
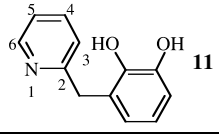
2.1.1. 4-Phenylmorpholine. The molecular formula of product **1** converted from 4-phenylmorpholine was determined to be $C_{10}H_{13}NO_3$ by HRMS (EI). In the ^{1}H NMR spectrum, signals derived from the morpholine moiety of 4-phenylmorpholine were completely preserved, while only the 3H sp^2 methine signals of the benzene ring were observed. Consistent with its molecular formula, the replacement of two phenolic OH functions in the benzene ring is proposed. The positions of these two phenolic OH functions were determined to be at C-1′ and C-2′ by the observation of a vicinal sp^2 spin network from H-4′ (δ 6.38) to H-6′ (δ 6.49) in the DQF COSY spectrum. Thus, **1** was identified to be 3-morpholin-4-ylbenzene-1,2-diol (Table 1).

2.1.2. 2-Phenylindole. The molecular formula of product **3** converted from 2-phenylindole was determined to be $C_{14}H_{11}NO$ by HRMS (EI). In the ^{1}H NMR spectrum, signals due to the phenyl moiety were completely conserved, while only 4H signals derived from the indole ring were observed. Consistent with its molecular formula, the replacement of a phenolic OH function in the indole ring is proposed. The position of this phenolic OH function was determined to be at C-5 by the observation of ^{1}H–^{13}C long-range coupling from H-4 (δ 6.82) to C-3 (δ 98.0) and the small coupling constant of H-4 (J=2.0 Hz, *meta* coupling between H-4 and H-6 (δ 6.61)). From these findings, **3** was determined to be 2-phenyl-1H-indole-5-ol (Table 1).

2.2. Biotransformation of heterocyclic compounds with benzyl moieties

Several heterocyclic compounds with benzyl moieties (1-benzylpiperidone, 1-benzylimidazole, and 2-benzylpyridine), whose structures are shown in Table 2, were also examined in the same manner and found to have been converted. The biotransformed products were identified as the vicinal diols shown in Table 2. The yields of the respective purified products were 20–68% (Table 2). Each of these three products was found to be a novel compound according to the CAS database. We have shown for the first time in the present study that heterocycles not having aromaticity and linked to a phenyl or benzyl moiety (4-phenylmorpholine and 1-benzylpiperidone) could be

Table 2. Bioconversion of several aromatics, in which heterocycles are linked with benzyl groups, through the living cells of *E. coli* expressing the *bphA* (2072) and *bphB* genes

Substrate	Product	Yield (%)
 1-Benzylpiperidone	 **9**	23
 1-Benzylimidazole	 **10**	68
 1-Benzylpyridine	 **11**	20

converted to the corresponding vicinal diols through the *E. coli* (pBS2072B) cells.

Several heteroaromatic compounds with benzyl moieties (1-benzylimidazole, 4-benzylisothiazole, and 2-benzylpyridine) have been shown to be converted to the corresponding *cis*-1,2-dihydrodiols when co-cultured with *E. coli* (pKF2072) carrying the *bphA* (2072) genes.[8] 4-Benzylisothiazole should also be converted to its vicinal diol by *E. coli* (pBS2072B) incorporating the *bphA* (2072) and *bphB* genes.

2.2.1. 1-Benzylpiperidone. The molecular formula of product **9** converted from 1-benzylpiperidone was determined to be $C_{12}H_{15}NO_3$ by HRMS (EI). In the ^{1}H NMR spectrum, signals due to the piperidone moiety of 1-benzylpiperidone were completely preserved, while only the 3H sp^2 methine signals of the benzene ring were observed. Consistent with its molecular formula, the replacement of two phenolic OH functions in benzene ring is proposed. The positions of these two phenolic OH functions were determined to be at C-3′ and C-4′ by the observation of a vicinal sp^2 spin network from H-5′ (δ 6.80) to H-7′ (δ 6.47) in the DQF COSY spectrum. From these findings, **9** was determined to be 1-(2,3-dihydroxy-benzyl)-piperidin-4-one (Table 2).

2.3. Biotransformation of a hetrocyclic aromatic compound

When heteroaromatic compounds with phenyl moieties, in which methyl or hydroxy groups are substituted, were used as the substrates for BphA (2072), these substrates were often converted to the hydroxylated forms in their heteroaromatic rings, e.g. 2-(2-hydroxyphenyl)benzoxazole was biotransformed to its *cis*-dihydrodiol in the benzoxazole ring [(4*R*,5*S*)-2-(2-hydroxyphenyl)-4,5-dihydro-1,3-benzoxazole-4,5-diol].[8] We show here that BphB was functional to produce the corresponding diol (**12**) from the *cis*-dihydrodiol (Table 3). The yield of the purified product was 20% (Table 3). This product was a novel compound.

2.3.1. 2-(2-Hydroxyphenyl)benzoxazole. The molecular formula of product **12** was determined to be $C_{13}H_9NO_4$ by HRMS (EI). In the ^{1}H and ^{13}C NMR spectra, signals due to C-1′–C-6′ were preserved, while only 2H signals derived from the benzoxazole ring were observed. Consistent with its molecular formula, the replacement of two phenolic OH functions in the benzoxazole ring is proposed. The positions of these two phenolic OH functions were determined to be at C-4 and C-5 by the coupling constant between H-4 and H-5 (J=8.5 Hz) and the ^{1}H–^{13}C long-range couplings from H-6 (δ 6.88) to C-3a (δ 129.2), C-5 (δ 142.2) and C-7a (δ 143.2). From these findings, **12** was determined to be 2-(2-hydroxyphenyl)benzoxazole-4,5-diol (Table 3).

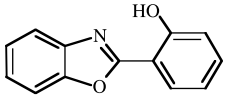
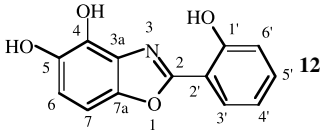
2.4. Biotransformation of aromatic compounds with an amino group

Ionized aromatic molecules incorporating carboxylic acid or primary amine moieties in their structures have frequently been used as building blocks for the chemical synthesis of pharmaceuticals, agrochemicals, and other industrially useful organic molecules. We further examined the ability of the evolved biphenyl dioxygenase [BphA (2072)] and dihydrodiol dehydrogenase (BphB) enzymes by bioconversion experiments on such ionized compounds. Primary amines such as aniline and benzylamine that incorporated an amino group in their molecules were not converted by the recombinant *E. coli* and *S. lividans* cells.[12] This could be due to their lack of permeability into the cell and/or to the stronger affinity of the amino group to the iron-incorporating active site of the enzyme. Therefore, the amino groups of aniline, benzylamine, and phenylethylamine were protected as a *tert*-butyl-carbamate by stirring with di-*tert*-butyl dicarbonate [(*t*-BOC)$_2$O] and NaOH in aqueous dioxane (Fig. 4(A)). Their protected groups should then be easy to remove by an acidic treatment. The *t*-BOC derivatives synthesized were successfully converted to the corresponding vicinal diols with high efficiency (75–85%) by the recombinant *E. coli* (pBS2072B) cells (Fig. 4(A)). All of the diol primary amines that were synthesized by the combination of biological and chemical methods are difficult to synthesize by purely chemical means. Indeed, the 3-(1-amino-ethyl)-benzene-1,2-diol was a novel compound according to the CAS database.

We used the racemic mixture of phenylethylamine as the substrates. The products (**15**) converted from their *t*-BOC derivatives were analyzed by HPLC in a Chiralcel OD-H column (10×250 mm, Daicel), which was developed with hexane-2-propanol (9:1). As a result, both the chiral products were found to generate from the *t*-BOC derivatives of racemic phenylethylamine, showing no enantio-selectivity of the *E. coli* cells expressing *bphA* (2072) and *bphB* towards bioconversion of such substrates.

2.4.1. Phenyl-carbamic acid *tert*-butyl ester. The molecular formula of product **13** was determined to be $C_{11}H_{13}NO_4$ by HRMS (EI). In the ^{1}H and ^{13}C NMR spectra, signals due to the *t*-BOC moiety (C-1′–C-6′) were preserved, while only 3H signals derived from the benzene ring were observed.

Table 3. Bioconversion of an aromatic, in which a heteroaromatic is linked with a phenyl group substituted with a hydroxyl group, through the living cells of *E. coli* expressing the *bphA* (2072) and *bphB* genes

Substrate	Product	Yield (%)
 2-(2-Hydroxyphenyl)benzoxazole	 **12**	20

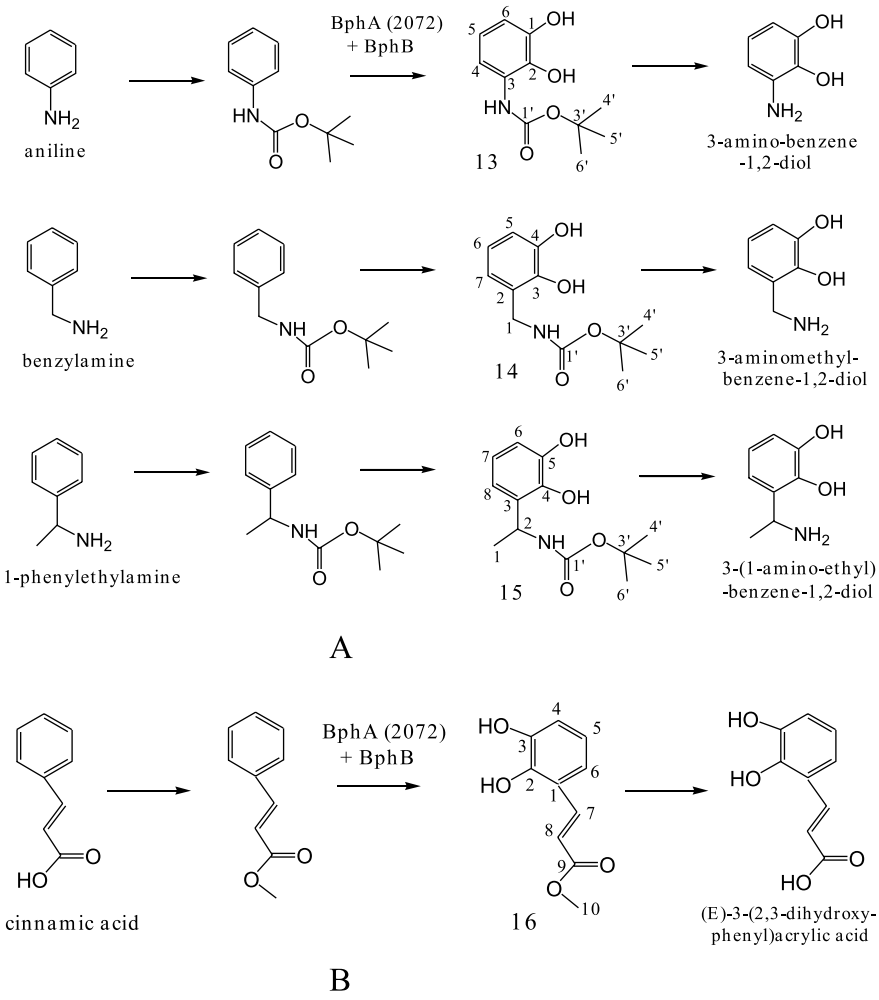


Figure 4. Bioconversion of several monocyclic aromatics incorporating an amino group (A) and a monocyclic aromatic incorporating a carboxyl group (B), by using the living cells of *E. coli* expressing the *bphA* (2072) and *bphB* genes, on the combination of the simple chemical methods.

Consistent with the molecular formula, the replacement of two phenolic OH functions in the benzene ring is proposed. The positions of these two phenolic OH functions were determined to be at C-1 and C-2 by observation of the vicinal sp^2 network of C-4 (δ 6.33)–C-5 (δ 6.66)–C-6 (δ 6.68). From these findings, **13** was determined to be (2,3-dihydroxy-phenyl)-carbamic acid *tert*-butyl ester (Fig. 4(A)).

2.5. Biotransformation of an aromatic compound with a carboxyl group

Cinnamic acid, which includes a carboxyl group in the molecule, was not converted by the recombinant *E. coli* cells. This could be due to its lack of permeability into the cells. Therefore, the carboxyl group of cinnamic acid was protected as a methyl ester by stirring in a 5% HCl–MeOH solution. The methyl ester should then be easy to hydrolyze by an alkaline treatment. The synthesized cinnamic acid methyl ester was converted to the corresponding vicinal diol with high efficiency (86%) by the recombinant *E. coli* (pBS2072B) cells (Fig. 4(B)).

2.5.1. Cinnamic acid methyl ester. The molecular formula of product **16** was determined to be $C_{10}H_{10}O_4$ by HRMS (EI). In the ^1H and ^{13}C NMR spectra, signals due to the side chain (C-7–C-10) were preserved, while only 3H signals derived from the benzene ring were observed. Consistent with its molecular formula, the replacement of two phenolic OH functions in the benzene ring is proposed. The positions of these two phenolic OH functions were determined to be at C-2 and C-3 by observation of the vicinal sp^2 network of C-4 (δ 6.83)–C-5 (δ 6.65)–C-6 (δ 7.05). From these findings, **16** was determined to be (*E*)-3-(2,3-dihydroxy-phenyl)-acrylic acid methyl ester (Fig. 4(B)).

2.6. Antioxidative activity of the converted products

The converted products described in 2.1–2.3 contained phenolic OH functions in their structures. We examined their in vitro inhibitory effects towards the lipid peroxidation induced by free radicals in a rat brain homogenate (Table 4A) and their scavenging activity towards DPPH (1,1-diphenyl-2-picrylhydrazyl) radicalsB). Each of the products showed much stronger antioxidative activity than to the corresponding substrate. Judging from the results shown in B, none of the substrates had antioxidative activity. The results suggest that our system of CellCombiChem would be effective for producing biologically active organic chemicals

Table 4

(A) Inhibitory effects of the respective compounds on lipid peroxidation in a rat brain homogenate

Substrate	IC_{50} (μg/ml)	Product	IC_{50} (μg/ml)
4-Phenylmorpholine	63	1	1.8
2-Phenylpyridine	140	2	3.5
2-Phenylindole	4.9	3	0.19
		4	0.038
2-Phenylbenzoxazole	>200	5	0.26
2-Phenylbenzothiazole	70	6	0.11
3-Phenyl-1-indanone	28	7	1.1
2-Phenylquinoline	>200	8	0.98
1-Benzylpiperidone	53	9	1.8
2-Benzylimidazole	>200	10	3.5
2-Benzylpyridine	78	11	1.6
2-(2-Hydroxyphenyl)benzoxazole	>200	12	0.18

(B) DPPH radical-scavenging activity of the respective compounds

Substrate	IC_{50} (μg/ml)	Product	IC_{50} (μg/ml)
4-Phenylmorpholine	>200	1	2.3
2-Phenylpyridine	>200	2	51
2-Phenylindole	>200	3	45
		4	30
2-Phenylbenzoxazole	>200	5	21
2-Phenylbenzothiazole	>200	6	13
3-Phenyl-1-indanone	>200	7	18
2-Phenylquinoline	>200	8	17
1-Benzylpiperidone	>200	9	33
2-Benzylimidazole	>200	10	24
2-Benzylpyridine	>200	11	51
2-(2-Hydroxyphenyl)benzoxazole	>200	12	78

which are difficult or impractical to synthesize by chemical methods.

3. Conclusions

The majority of pharmaceuticals and agrochemicals include a heterocycle not having aromaticity, an aromatic heterocycle (heteroaromatic), or a benzene ring in their molecular structures. We have shown that a wide array of aromatic molecules, in which a heterocycle with or without aromaticity is linked with a phenyl or benzyl group, can be biotransformed to the respective *cis*-2,3-dihydrodiols in the benzene ring by the growing cells of *E. coli* expressing the evolved *bphA* genes [*bphA* (2072)],[8] and further biotransformed to the respective 2,3-diols by those expressing the *bphB* genes in addition to the *bphA* (2072) genes (Fig. 3). It has also been shown that ionized monocyclic aromatics incorporating an amino group or a carboxyl group in their molecules can be converted to the respective 2,3-diols in the benzene ring, by using the *E. coli* cells that expresses the *bphA* (2072) and *bphB* genes, on the combination of the simple chemical methods. The results of this present and past study should enable CellCombiChem to be achieved when using the biphenyl-catabolic genes in the initial two steps (Fig. 1). CellCombiChem using the *bphC* gene, which mediates the third enzymatic step, in addition to the *bphA* (2072) and *bphB* genes, is already found to be successful to produce a series of aromatic compounds with a picolinic acid (pyridine-2-carboxylic acid) in their molecules, whose results will be presented elsewhere. The comprehensive production of such organic chemicals, which are difficult or impractical to chemically synthesize, could intend to serve as new starting materials for the chemical synthesis of pharmaceuticals, agrochemicals and other industrially useful compounds, or as a unique screening source for 'lead'-discoveries or ligand-hunting by pharmaceutical companies.

4. Experimental

4.1. Plasmids, bacterial strains, and chemicals

Plasmid pBS2072B, which contained the modified biphenyl dioxygenase [*bphA* (2072)] genes and the subsequent biphenyl-2,3-dihydrodiol 2,3-dehydrogenase (*bphB*) gene derived from *P. pseudoalcaligenes* KF707, has been described.[9] *E. coli* JM109 was used as the host for the plasmid. The chemicals used as substrates were purchased from Aldrich Chemical Co., Wako Pure Chemical Co., or Kanto Chemical Co. The respective substrates were each dissolved in a small volume of dimethyl sulfoxide (DMSO) and added to the culture.

4.2. Growing cell reactions

E. coli JM109 harboring pBS2072B was grown in an LB medium[16] containing Ampicillin (Ap; 150 μg/ml) at 30 °C with reciprocal shaking for 7–8 h. Five milliliters of this culture was inoculated into 100 ml of an M9 medium[16] with Ap (150 μg/ml), thiamine (10 μg/ml), and glucose (0.4%; w/v) in an Erlenmeyer flask at 30 °C with reciprocal shaking and left for 16–17 h, until the absorbance at OD 600 nm reached approximately 1. The cells were collected by centrifugation, resuspended in a fresh M9 medium (100 ml) with Ap (150 μg/ml), thiamine (10 μg/ml), 0.4% (w/v) glucose, and 1 mM (the final concentration) of isopropyl β-D-thiogalactopyranoside (IPTG) as well as each substrate (10 mg), and cultivated in the Erlenmeyer flask at 30 °C with reciprocal shaking for 2–3 days.

4.3. Extractions and HPLC analysis of the converted products

To extract the converted products and the substrates, an equal volume of methanol (MeOH) to that of the culture medium was added to the co-culture of the transformed cells of *E. coli*, and the mixture mixed for 30 min. After centrifuging to remove the cells, the liquid phase was analyzed by high-pressure liquid chromatography (HPLC) or used for further purification of the converted products. The liquid phase (80 μl) was applied to HPLC in an XTerra C_{18} column (4.6×150 mm, Waters) with a photodiode array detector (model L-7455, Hitachi). Development was at a flow rate of 1 ml/min with solvent A (5% acetonitrile (CH_3CN) and 20 mM phosphoric acid) for 3 min, then by a linear gradient from solvent A to solvent B (95% CH_3CN and 20 mM phosphoric acid) for 15 min, and finally with solvent B for 10 min, the maximum absorbance being monitored in the range of 200–500 nm.

4.4. Purification and identification of the products

The liquid phase (2,000 ml) which had been obtained by the procedure just described was concentrated in vacuo and then extracted with ethyl acetate (EtOAc) (500 ml×2). The organic layer was concentrated in vacuo, and analyzed by thin-layer chromatography (TLC) on silica gel [0.25 mm E. Merck silica gel plates (60F-254)]. The formed products were purified by column chromatography on silica gel [20× 250 mm^2, Silica Gel 60 (Merck)]. Their structures were analyzed by mass spectrometry (MS) [MS (EI) and HRMS (EI), Jeol AX-505W instrument] and nuclear magnetic resonance (NMR) (400 MHz, Bruker AMX400 instrument).

4.4.1. 3-Morpholin-4-ylbenzene-1,2-diol (1; the product converted from 1-phenylmorpholine). The crude extract (86.5 mg) was subjected to column chromatography (CH_2Cl_2–MeOH=30:1) to yield 30.0 mg of **1**. MS (EI) *m/z* 195 (M^+). HRMS (EI) calcd for $C_{10}H_{13}NO_3$ (M^+), 195.0896; found, 195.0899. ^{1}H NMR (DMSO-d_6) δ: 2.87 (m, 4H), 3.71 (m, 4H), 6.38 (dd, 1H, J=1.4, 7.8 Hz), 6.49 (dd, 1H, J=1.4, 8.1 Hz), 6.55 (dd, 1H, J=7.8, 8.1 Hz). ^{13}C NMR (DMSO-d_6) δ: 50.8 (C-2, C-6), 66.4 (C-3, C-5), 109.4 (C-4′), 110.5 (C-6′), 118.7 (C-5′), 138.0 (C-2′), 140.8 (C-3′), 145.5 (C-1′).

4.4.2. 3-(2-Pyridyl)benzene-1,2-diol (2; the product converted from 2-phenylpyridine). The crude extract (130.0 mg) was subjected to column chromatography (hexane–EtOAc=10:1) to yield 26.0 mg of **2**. MS (EI) *m/z* 187 (M^+). HRMS (EI) calcd for $C_{11}H_9NO_2$ (M^+), 187.0633; found, 187.0633. ^{1}H NMR ($CDCl_3$) δ: 6.92 (dd, 1H, J=1.2, 7.9 Hz), 6.75 (dd, 1H, J=7.9, 7.9 Hz), 7.18 (dd, 1H, J=5.3, 5.6 Hz), 7.27 (dd, 1H, J=1.2, 7.9 Hz), 7.76 (ddd, 1H, J=1.6, 5.3, 7.9 Hz), 7.83 (d, 1H, J=7.9 Hz), 8.42 (dd, 1H, J=1.6, 5.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 115.5 (C-6′), 116.8 (C-4′), 118.1 (C-3′), 118.6 (C-5′), 119.1 (C-3), 121.6 (C-5), 137.9 (C-4), 145.6 (C-6), 146.0 (C-1′), 147.4 (C-2′), 157.6 (C-2).

4.4.3. 2-Phenylindol-5-ol (3) and 2-indol-2-ylbenzene-1,2-diol (4) (the products converted from 2-phenylindole). The crude extract (191.0 mg) was subjected to column chromatography (hexane–EtOAc=3:1) to yield 6.8 mg of **3** and 9.0 mg of **4**.

3. MS (EI) *m/z* 209 (M^+). HRMS (EI) calcd for $C_{14}H_{11}NO$ (M^+), 209.0841; found, 209.0857. ^{1}H NMR (DMSO-d_6) δ: 6.61 (dd, 1H, J=2.0, 8.8 Hz), 6.70 (s, 1H), 6.82 (d, 1H, J=2.0 Hz), 7.17 (d, 1H, J=8.8 Hz), 7.27 (dd, 1H, J=7.7, 7.7 Hz), 7.42 (dd, 2H, J=7.7, 7.7 Hz), 7.79 (d, 2H, J=7.7 Hz), 8.70 (brs, 1H), 11.20 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ: 98.0 (C-3), 103.7 (C-4), 111.7 (C-7), 112.0 (C-6), 124.8 (C-2′, C-6′), 127.2 (C-4′), 128.9 (C-3′, C-5′), 129.4 (C-3a), 131.7 (C-7a), 132.5 (C-1′), 137.9 (C-2), 150.9 (C-5).

4. MS (EI) *m/z* 225 (M^+). HRMS (EI) calcd for $C_{14}H_{11}NO_2$ (M^+) 225.0790; found, 225.0786. ^{1}H NMR ($CDCl_3$) δ: 6.74 (dd, 1H, J=1.6, 7.8 Hz), 6.80 (s, 1H), 6.80 (dd, 1H, J=7.8, 7.9 Hz), 7.06 (dd, 1H, J=7.8, 7.8 Hz), 7.13 (dd, 1H, J=7.8, 7.8 Hz), 7.25 (dd, 1H, J=1.6, 7.8 Hz), 7.36 (d, 1H, J=7.8 Hz), 7.58 (d, 1H, J=7.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 100.0 (C-3), 111.0 (C-7), 114.1 (C-6′), 119.1 (C-3′), 120.0 (C-5), 120.0 (C-4′), 120.4 (C-4), 120.8 (C-5′), 122.1 (C-6), 128.2 (C-3a), 136.3 (C-7a), 141.0 (C-2′), 143.4 (C-1′).

4.4.4. 3-Benzoxazol-2-ylbenzene-1,2-diol (5; the product converted from 2-phenylbenzoxazole). The crude extract (155.0 mg) was subjected to column chromatography (CH_2Cl_2–MeOH=30:1) to yield 76.8 mg of **5**. MS (EI) *m/z* 227 (M^+). HRMS (EI) calcd for $C_{13}H_9NO_3$ (M^+), 227.0582; found, 227.0583. ^{1}H NMR (DMSO-d_6) δ: 6.88 (dd, 1H, J=7.8, 7.8 Hz), 7.03 (dd, 1H, J=1.8, 7.8 Hz), 7.45 (2H), 7.47 (dd, 1H, J=1.8, 7.8 Hz), 7.82 (dd, 1H, J=1.4, 8.0 Hz), 7.84 (1H). ^{13}C NMR (DMSO-d_6) δ: 110.1 (C-7), 110.5 (C-3′), 117.3 (C-4′), 119.3 (C-4), 119.5 (C-6′), 119.9 (C-5′), 125.4 (C-5), 125.8 (C-6), 139.4 (C-3a), 146.2 (C-1′), 146.9 (C-2′), 148.7 (C-7a), 162.8 (C-2).

4.4.5. 3-Benzothiazol-2-ylbenzene-1,2-diol (6; the product converted from 2-phenylbenzothiazole). The crude extract (165.0 mg) was subjected to column chromatography (hexane–EtOAc=20:1) to yield 73.5 mg of **6**. MS (EI) *m/z* 243 (M^+). HRMS (EI) calcd for $C_{13}H_9NO_2S$ (M^+), 243.0355; found, 243.0350. ^{1}H NMR (DMSO-d_6) δ: 6.82 (dd, 1H, J=7.2, 7.2 Hz), 6.96 (dd, 1H, J=1.2, 7.2 Hz), 7.44 (dd, 1H, J=7.3, 7.3 Hz), 7.53 (dd, 1H, J=7.3, 8.0 Hz), 7.54 (dd, 1H, J=1.2, 7.2 Hz), 8.05 (d, 1H, J=8.0 Hz). ^{13}C NMR (DMSO-d_6) δ: 117.7 (C-6′), 118.4 (C-3′), 118.5 (C-4′), 119.5 (C-5′), 122.0 (C-4), 122.1 (C-7), 125.2 (C-6), 126.6 (C-5), 133.9 (C-7a), 145.7 (C-2′), 146.3 (C-1′), 151.4 (C-3a), 166.4 (C-2).

4.4.6. 3-(2,3-Dihydroxyphenyl)indan-1-one (7; the product converted from 3-phenyl-1-indanone). The crude extract (148.0 mg) was subjected to column chromatography (hexane–EtOAc=2:1) to yield 70.3 mg of **7**. MS (EI) *m/z* 240 (M^+). HRMS (EI) calcd for $C_{15}H_{12}O_3$ (M^+), 240.0786; found, 240.0786. ^{1}H NMR (DMSO-d_6) δ: 2.60 (dd, 1H, J=3.4, 18.9 Hz), 3.09 (dd, 1H, J=8.2, 18.9 Hz), 4.80 (dd, 1H, J=3.4, 8.2 Hz), 6.34 (dd, 1H, J=1.9, 7.7 Hz), 6.52 (dd, 1H, J=7.5, 7.7 Hz), 6.66 (dd, 1H, J=1.9, 7.5 Hz), 7.28 (dd, 1H, J=0.8, 7.6 Hz), 7.41 (ddd, 1H, J=0.8, 7.6, 7.6 Hz), 7.60 (dd, 1H, J=7.6, 7.6 Hz), 7.65 (d, 1H, J=7.6 Hz). ^{13}C NMR (DMSO-d_6) δ: 39.5 (C-3), 44.3 (C-2), 113.8 (C-6′), 118.7 (C-4′), 118.9 (C-5′), 122.6 (C-7), 126.5 (C-4), 127.4 (C-6), 130.1 (C-3′), 136.3 (C-7a), 143.2 (C-2′), 145.2 (C-1′), 158.2 (C-3a), 205.8 (C-1).

4.4.7. 3-(2-Quinolyl)benzene-1,2-diol (8; the product converted from 2-phenylquinoline). The crude extract (210.0 mg) was subjected to column chromatography (hexane–EtOAc=10:1) to yield 31.3 mg of **8**. MS (EI) *m/z* 237 (M^+). HRMS (EI) calcd for $C_{15}H_{11}NO_2$ (M^+), 237.0790; found, 237.0788. ^{1}H NMR (DMSO-d_6) δ: 6.78 (dd, 1H, J=7.9, 7.9 Hz), 7.64 (d, 1H, J=7.9 Hz), 7.65 (dd, 1H, J=7.2, 7.2 Hz), 7.84 (dd, 1H, J=7.2, 8.0 Hz), 8.03 (d, 1H, J=8.0 Hz), 8.04 (d, 1H, J=7.2 Hz), 8.33 (d, 1H, J=8.7 Hz), 8.56 (d, 1H, J=8.7 Hz). ^{13}C NMR (DMSO-d_6) δ: 117.5 (C-6′), 117.9 (C-4′), 118.2 (C-3), 118.3 (C-5′), 118.7 (C-3′), 126.3 (C-4a), 126.8 (C-8), 127.0 (C-6), 128.0 (C-5), 131.0 (C-7), 138.4 (C-4), 143.9 (C-8a), 146.6 (C-1′), 149.1 (C-2′), 158.2 (C-2).

4.4.8. 1-[(2,3-Dihydroxyphenyl)methyl]piperidin-4-one (9; the product converted from 1-benzylpiperidone).

The crude extract (104.0 mg) was subjected to column chromatography (hexane–EtOAc = 1:1) to yield 22.5 mg of **9**. MS (EI) *m/z* 221 (M^+). HRMS (EI) calcd for $C_{12}H_{15}NO_3$ (M^+), 221.1053; found, 221.1055. ^{1}H NMR ($CDCl_3$) δ: 2.46 (t, 2H, J = 5.8 Hz), 2.83 (t, 2H, J = 5.8 Hz), 3.76 (s, 2H), 6.47 (dd, 1H, J = 0.9, 7.5 Hz), 6.65 (dd, 1H, J = 7.5, 7.5 Hz), 6.80 (dd, 1H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ: 40.7 (C-3, C-5), 52.5 (C-2, C-6), 60.3 (C-1′), 114.4 (C-5′), 119.7 (C-7′), 119.9 (C-6′), 120.8 (C-2′), 144.2 (C-3′), 144.7 (C-4′), 206.8 (C-4).

4.4.9. 3-(Imidazolylmethyl)benzene-1,2-diol (10; the product converted from 1-benzylimidazole). The crude extract (140.0 mg) was subjected to column chromatography (CH_2Cl_2–MeOH = 10:1) to yield 67.7 mg of **10**. MS (EI) *m/z* 190 (M^+). HRMS (EI) calcd for $C_{10}H_{10}N2O_2$ (M^+), 190.0742; found, 190.0748. ^{1}H NMR (DMSO-d_6) δ: 5.05 (s, 1H), 6.47 (d, 1H, J = 7.5 Hz), 6.57 (dd, 1H, J = 7.3, 7.3 Hz), 6.72 (d, 1H, J = 7.3 Hz), 6.85 (brs. 1H), 7.11 (brs, 1H), 7.65 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ: 45.0 (C-1′), 115.1 (C-5′), 119.0 (C-6′), 119.5 (C-7′), 119.7 (C-5), 124.6 (C-2′), 128.1 (C-4), 137.4 (C-2), 143.2 (C-3′), 145.2 (C-4′).

4.4.10. 3-(2-Pyridylmethyl)benzene-1,2-diol (11; the product converted from 2-benzylpyridine). The crude extract (109.7 mg) was subjected to column chromatography (hexane–EtOAc = 10:1) to yield 20.0 mg of **11**. MS (EI) *m/z* 201 (M^+). HRMS (EI) calcd for $C_{12}H_{11}NO_2$ (M^+), 201.0790; found, 201.0789. ^{1}H NMR (DMSO-d_6) δ: 4.00 (s, 2H), 6.54 (d, 1H, J = 7.2 Hz), 6.54 (d, 1H, J = 7.2 Hz), 6.64 (dd, 1H, J = 7.2, 7.2 Hz), 7.21 (dd, 1H, J = 4.8, 7.6 Hz), 7.22 (d, 1H, J = 7.6 Hz), 7.70 (ddd, 1H, J = 1.6, 7.6, 7.6 Hz), 8.45 (dd, 1H, J = 1.6, 4.8 Hz). ^{13}C NMR (DMSO-d_6) δ: 38.6 (C-1′), 113.9 (C-6′), 118.9 (C-5′), 120.9 (C-7′), 121.4 (C-5), 122.8 (C-3), 126.6 (C-2′), 137.0 (C-4), 143.4 (C-3′), 145.6 (C-4′), 148.4 (C-6), 160.8 (C-2).

4.4.11. 2-(2-Hydroxyphenyl)benzoxazole-4,5-diol (12; the product converted from 2′-hydroxy-2-phenylbenzoxazole). The crude extract (185.0 mg) was subjected to column chromatography (hexane–EtOAc = 4:1) to yield 19.5 mg of **12**. MS (EI) *m/z* 243 (M^+). HRMS (EI) calcd for $C_{13}H_9NO_4$ (M^+), 243.0532; found, 243.0531. ^{1}H NMR (DMSO-d_6) δ: 6.88 (d, 1H, J = 8.5 Hz), 7.05 (dd, 1H, J = 7.8, 8.5 Hz), 7.06 (d, 1H, J = 8.5 Hz), 7.10 (d, 1H, J = 8.5 Hz), 7.48 (ddd, 1H, J = 1.6, 8.5, 8.5 Hz), 7.93 (dd, 1H, J = 1.6, 7.8 Hz). ^{13}C NMR (DMSO-d_6) δ: 100.1 (C-6), 110.4 (C-2′), 114.3 (C-7), 117.2 (C-6′), 119.8 (C-4′), 126.9 (C-3′), 129.2 (C-3a), 133.5 (C-5′), 135.8 (C-4), 142.2 (C-5), 143.2 (C-7a), 157.6 (C-1′), 160.9 (C-2).

4.4.12. (2,3-Dihydroxy-phenyl)-carbamic acid *tert*-butyl ester (13; the product converted from phenyl-carbamic acid *tert*-butyl ester). The crude extract (132.5 mg) was subjected to column chromatography (hexane–EtOAc = 5:1) to yield 30.0 mg of **13**. MS (EI) *m/z* 225 (M^+). HRMS (EI) calcd for $C_{11}H_{13}NO_4$ (M^+), 225.1002; found, 225.1001. ^{1}H NMR ($CDCl_3$) δ: 1.46 (s, 9H), 6.33 (dd, 1H, J = 1.9, 7.0 Hz), 6.66 (dd, 1H, J = 7.0, 7.7 Hz), 6.68 (dd, 1H, J = 1.9, 7.7 Hz). ^{13}C NMR (CDCl3) δ: 28.2 (C-4′, C-5′, C-6′), 82.8 (C-3′), 111.2 (C-4), 112.6 (C-6), 120.8 (C-5), 125.1 (C-3), 135.2 (C-2), 147.6 (C-1), 155.6 (C-1′).

4.4.13. (2,3-Dihydroxy-benzyl)-carbamic acid *tert*-butyl ester (14; the product converted from benzyl-carbamic acid *tert*-butyl ester). The crude extract (86.5 mg) was subjected to column chromatography (hexane–EtOAc = 4:1) to yield 8.6 mg of **14**. MS (EI) *m/z* 239 (M^+). HRMS (EI) calcd for $C_{12}H_{17}NO_4$ (M^+), 239.1158; found, 239.1156. ^{1}H NMR ($CDCl_3$) δ: 1.37 (s, 9H), 4.12 (d, 2H, J = 6.9 Hz), 5.23 (brs, 1H), 5.79 (s, 1H), 6.52 (d, 1H, J = 7.5 Hz), 6.67 (dd, 1H, J = 7.5, 7.8 Hz), 6.81 (d, 1H, J = 7.8 Hz), 9.53 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 28.3 (C-4′, C-5′, C-6′), 50.0 (C-1), 81.6 (C-3′), 114.6 (C-5), 120.3 (C-6), 121.3 (C-7), 125.1 (C-2), 142.7 (C-3), 146.4 (C-4), 158.8 (C-1′).

4.4.14. [1-(2,3-Dihydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester [15; the product converted from (1-phenyl-ethyl)-carbamic acid *tert*-butyl ester]. The crude extract (183 mg) was subjected to column chromatography (CH_2Cl_2–EtOAc = 5:1) to yield 7.6 mg of **15**. MS (EI) *m/z* 253 (M^+). HRMS (EI) calcd for $C_{13}H_{19}NO_4$ (M^+), 253.1314; found, 253.1312. ^{1}H NMR ($CDCl_3$) δ: 1.37 (s, 9H), 1.49 (d, 3H, J = 6.9 Hz), 4.86 (d, 1H, J = 8.0 Hz), 4.92 (dq, 1H, J = 6.9, 8.0 Hz), 5.88 (s, 1H), 6.66 (dd, 1H, J = 1.3, 7.7 Hz), 6.75 (dd, 1H, J = 6.9, 7.7 Hz), 6.79 (dd, J = 1.3, 6.9 Hz), 9.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 19.4 (C-1), 28.3 (C-4′, C-5′, C-6′), 43.6 (C-2), 81.4 (C-3′), 113.8 (C-6), 116.1 (C-8), 120.7 (C-7), 129.7 (C-3), 142.0 (C-4), 146.5 (C-5), 157.9 (C-1′).

4.4.15. (*E*)-3-(2,3-Dihydroxy-phenyl)-acrylic acid methyl ester (16; the product converted from cinnamic acid methyl ester). The crude extract (130 mg) was subjected to column chromatography (CH_2Cl_2–MeOH = 40:1) to yield 80.0 mg of **16**. MS (EI) *m/z* 194 (M^+). HRMS (EI) calcd for $C_{10}H_{10}O_4$ (M^+), 194.0579; found, 194.0581. ^{1}H NMR ($CDCl_3$) δ: 3.69 (s, 3H), 6.55 (d, 1H, J = 15.8 Hz), 6.65 (dd, 1H, J = 7.8, 8.0 Hz), 6.83 (d, 1H, J = 7.8 Hz), 7.05 (d, 1H, J = 8.0 Hz), 7.90 (d, 1H, J = 15.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 51.3 (C-10), 116.7 (C-8), 116.9 (C-4), 118.8 (C-6), 119.2 (C-5), 121.3 (C-1), 140.4 (C-7), 145.5 (C-2), 145.7 (C-3), 167.2 (C-9).

4.5. In vitro inhibitory activity against lipid peroxidation

4.5.1. Inhibitory effect on lipid peroxidation. In vitro inhibitory activity of the respective diols against lipid peroxidation were measured using a rat brain homogenate as described.[9]

4.5.2. DPPH radical-scavenging activity. The scavenging activity towards DPPH (1,1-diphenyl-2-picrylhydrazyl) radicals was measured essentially according to the method described by Kubo et al.[17] A portion of the sample solution (100 μl) was mixed with a 100 mM MES buffer (pH 6.0, 50 μl) and 1 mM DPPH in ethanol (50 μl). The mixture was shaken vigorously and then left to stand for 30 min at room temperature in the dark. The absorbance at 515 nm (A_{515}) by DPPH was measured by UV–vis spectrophotometry. The concentration of the sample resulting in 50% radical-scavenging activity was determined.

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References and notes

1. (a) Kurtzman, A. L.; Govindarajan, S.; Vahle, K.; Jones, J. T.; Heinrichs, V.; Patten, P. A. *Curr. Opin. Biotechnol.* **2001**, *12*, 361–370. (b) Zhao, H.; Chockalingam, K.; Chen, Z. *Curr. Opin. Biotechonol.* **2002**, *13*, 104–110.
2. Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35–62.
3. (a) Hudlicky, T.; Thorpe, A. J. *Chem. Commun.* **1996**, 1993–2000. (b) Boyd, D. R.; Sheldrake, G. N. *Nat. Prod. Rep.* **1998**, 309–324. (c) Banwell, M. G.; McRae, K. J. *Org. Lett.* **2000**, *2*, 3583–3586. (d) Banwell, M. G.; McRae, K. J. *J. Org. Chem.* **2001**, *66*, 6768–6774.
4. Furukawa, K. *Curr. Opin. Biotechnol.* **2000**, *11*, 244–249.
5. Kimura, N.; Nishi, A.; Goto, M.; Furukawa, K. *J. Bacteriol.* **1997**, *179*, 3936–3943.
6. Seeger, M.; Zielinski, M.; Timmis, K. N.; Hofer, B. *Appl. Environ. Microbiol.* **1999**, *65*, 3614–3621.
7. Taira, K.; Hirose, J.; Hayashida, S.; Furukawa, K. *J. Biol. Chem.* **1992**, *267*, 4844–4853.
8. Misawa, N.; Shindo, K.; Takahashi, H.; Suenaga, H.; Iguchi, K.; Okazaki, H.; Harayama, S.; Furukawa, K. *Tetrahedron* **2002**, *58*, 9605–9612.
9. Shindo, K.; Kagiyama, Y.; Nakamura, R.; Hara, A.; Ikenaga, H.; Furukawa, K.; Misawa, N. *J. Mol. Catal. B: Enzym.* **2003**, *23*, 9–16.
10. Carredano, E.; Karlsson, A.; Kauppi, B.; Choudhury, D.; Parales, R. E.; Parales, J. V.; Lee, K.; Gibson, D. T.; Eklund, H.; Ramaswamy, S. *J. Mol. Biol.* **2000**, *296*, 701–712.
11. (a) Kumamaru, T.; Suenaga, H.; Mitsuoka, M.; Watanabe, T.; Furukawa, K. *Nat. Biotechnol.* **1998**, *16*, 663–666. (b) Barriault, D.; Plante, M.-M.; Sylvestre, M. *J. Bacteriol.* **2002**, *184*, 3794–3800. (c) Zielinski, M.; Kahl, S.; Hecht, H. J.; Hofer, B. *J. Bacteriol.* **2003**, *185*, 6976–6980.
12. Shindo, K.; Nakamura, R.; Chinda, I.; Ohnishi, Y.; Horinouchi, S.; Takahashi, H.; Iguchi, K.; Harayama, S.; Furukawa, K.; Misawa, N. *Tetrahedron* **2003**, *59*, 1895–1900.
13. Shindo, K.; Ohnishi, Y.; Chun, H.-K.; Takahashi, H.; Hayashi, M.; Saito, A.; Iguchi, K.; Furukawa, K.; Harayama, S.; Horinouchi, S.; Misawa, N. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 2472–2481.
14. Chun, H.-K.; Ohnishi, Y.; Shindo, K.; Misawa, N.; Furukawa, K.; Horinouchi, S. *J. Mol. Catal. B: Enzym.* **2003**, *21*, 113–121.
15. Seeger, M.; Gonzalez, M.; Camara, B.; Munoz, L.; Ponce, E.; Mejias, L.; Mascayano, C.; Vasquez, Y.; Sepulveda-Boza, S. *Appl. Environ. Microbiol.* **2003**, *69*, 5045–5050.
16. Sambrook, J.; Fritsch, E. F.; Maniatis, T. *Molecular Cloning: A Laboratory Manual*; Cold Spring Harbor: Cold Spring Harbor, New York, 1989.
17. Kubo, K.; Yoshitake, I.; Kumada, Y.; Shuto, K.; Nakamizo, N. *Arch. Int. Pharmacodyn.* **1984**, *272*, 283–295.

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One pot solid phase synthesis of 2-substituted 2,3-dihydropyridin-4(1*H*)-ones on Rinkamide-resin

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Abstract—A novel solid phase synthesis of 2-substituted 2,3-dihydropyridin-4(1*H*)-ones using Rinkamide-polystyrene-resin is described. The key step involves a hetero-Diels–Alder reaction of Danishefsky's diene with solid phase bound imines, which was carefully optimized. Using this method even ketones are transformed into 2,2-disubstituted dihydropyridones.
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1. Introduction

Many natural and synthetic compounds with biological activity possess a basic centre in the form of a nitrogen containing heterocycle. Among these heterocycles the piperidine ring is of particular interest for drugs like biperidene, pethidine, haloperidol, dexoxadrol or etoxadrol.[1] Our interest has been focused on the development of a novel method, which provides straightforward access to 2-substituted piperidine precursors. In the process of drug development and/or lead structure optimization it is most welcome to use a method, which allows easy access to diverse compounds. In this article, we present a novel one pot solid phase procedure that can be conducted in parallel form.

Our particular interest was the solid phase synthesis of N-unsubstituted piperidine derivatives from carbonyl compounds (aldehydes, ketones; Fig. 1). In the literature, several methods for the synthesis of 2-substituted piperidine derivatives are described.[2–4] In the liquid phase, these piperidines are accessible by reaction of aldehydes and amines with methyl 4-nitrobutyrate to yield 1,6-disubstituted 5-nitropiperidin-2-ones (path A).[2] This reaction is usually performed in polar protic solvents like EtOH, which is a drawback for the application on solid phase since swelling properties of mostly used polystyrene resins in polar protic solvents are poor. Additionally acidic reaction conditions are necessary which limit the choice of the linker.

In another method, carbonyl compounds are reacted with the Wittig reagent 4-(4-methylphenylsulfonyl)-1-triphenylphosphoranylidene-butan-2-one and subsequently with amines to yield 1,2-disubstituted piperidin-4-ones in a stepwise conjugate addition/β-elimination/conjugate addition (path B).[3] This concept allows parallel synthesis by replacement of the amine component by an amine functionalized resin. As a consequence a variety of α,β-unsaturated ketones has to be synthesized in solution, employing various aldehydes as diversity element. The resin bound amine then functions as a scavenger. Alternatively the Wittig-reagent was bound to the solid phase. Subsequent derivatization with aldehydes followed by a cyclization-cleavage with amines delivers N-substituted piperidin-4-ones.[3b]

In a third approach, the hetero-Diels–Alder (=HDA) reaction[4] of imines with activated dienes like Danishefsky's diene[5] led to 1,2-disubstituted 2,3-dihydroypridin-4(1*H*)-ones (path C). This type of reaction has previously been performed on solid phase,[6] yielding only N-substituted piperidine derivatives with aryl residues in position 2, thus limiting the diversity of the substituents in this position.

There is only one solid phase method, that leads to N-unsubstituted 2,3-dihydropyridin-4(1*H*)-ones. In this method, polymer bound pyridinium salts are used instead of a HDA-reaction.[7] The key step of this strategy is the addition of Grignard reagents to these pyridinium salts. However, according to this strategy 2,2-disubstituted

Keywords: Solid phase synthesis; Parallel synthesis; Hetero-Diels–Alder reaction; Dihydropyridones.
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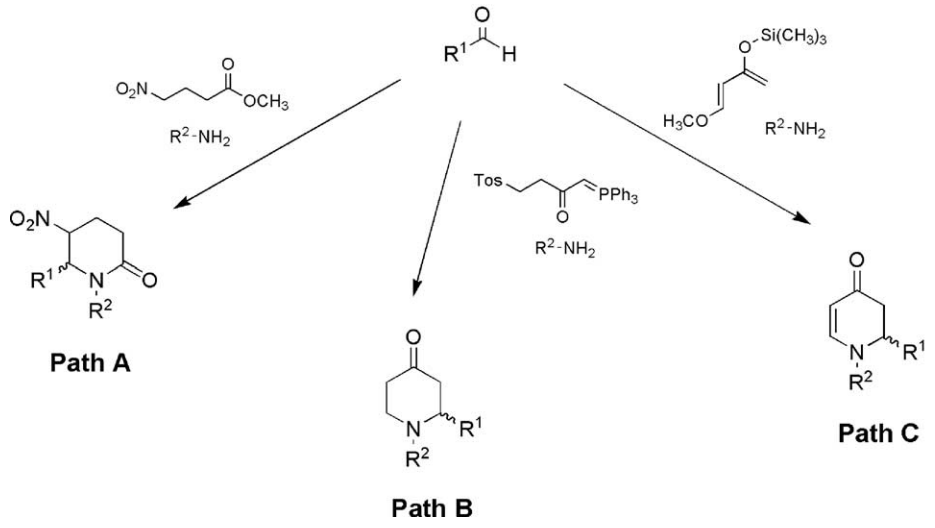


Figure 1.

piperidines or piperidines containing heteroatoms in the 2-substituent are not accessible.

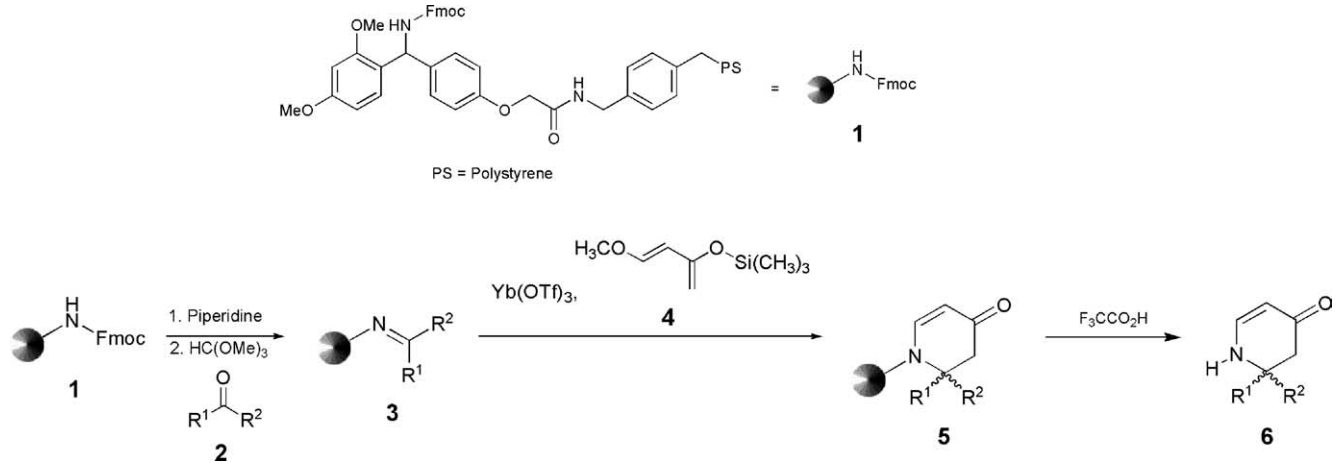
Thus, we decided to extend the HDA-concept to a new solid phase synthesis method to obtain N-unsubstituted pyridine derivatives with highly diverse 2-substituents including 2,2-disubstituion and heteroatom containing residues (e.g., ester, 2-bromophenyl).

As outlined in Scheme 1, Fmoc-protected Rinkamide-Resin **1** was used as amine component and therefore as N-donor. Deprotection with piperidine followed by condensation with various carbonyl compounds **2** using trimethyl orthoformate[8] led to the polymer bound imines **3**. Lewis acid catalyzed HDA-reaction with Danishefsky's-diene **4** provided the solid phase bound 2-substituted pyridones **5**. Finally, cleavage with trifluoroacetic acid yielded the N-unsubstituted 2,3-dihydropyridin-4(1*H*)-ones **6**.

In solution yields and diastereoselectivity of the HDA reaction (if chiral carbonyl compounds are used) are strongly dependent on the temperature and the solvent.[9] Additionally the kind of Lewis acid effects product yields. However, there are several reports showing ytterbium triflate $Yb(OTf)_3$ to be the most appropriate soluble catalyst.[6b,10] Therefore, the Lewis acid catalyst was not varied in our studies. A wide range of apolar as well as polar protic and aprotic solvents, including CH_2Cl_2,[11,12] THF,[10a,13] CH_3CN,[10b,14] MeOH[15] and even H_2O[16] has been used successfully. In most cases, the HDA-reaction has been performed at room temperature.[10,11b,15,16] However, performing the HDA-reaction at lower temperature has a positive effect on both diastereoselectivity and yield in solution.[9,11a,12–14]

On the other side, there are only few examples of the HDA-reaction on solid phase. These examples were always performed on polystyrene resins in THF, whereas the temperature varied from −60 °C to room temperature[6b] to +60 °C.[6a]

Obviously the HDA-reaction is the yield limiting step in this four step piperidine precursor synthesis. Therefore, we decided to optimize reaction conditions of the HDA-reaction. In particular, the solvent and the reaction temperature should be optimized. The optimized reaction



Scheme 1.

conditions then were applied to the synthesis of a small library.

2. Investigation of the solvent

In solid phase chemistry, THF is usually employed as solvent for the HDA-reaction with Danishefsky's diene **4**. However, it is described that in solution polar (protic) solvents (e.g. CH_3OH, CH_3CN) can increase yields in HDA-reactions, presumably by imine activation via hydrogen bonds[13,17] or by stabilization of a zwitterionic transition state, indicating that a nonconcerted stepwise Mannich–Michael reaction mechanism is operative.[10b,11a] According to poor swelling properties of polystyrene resins in polar (protic) solvents, THF/MeOH and THF/CH_3CN mixtures (1:1) were used within the solvent effect examination. Additionally, pure DMF and a DMF/CH_3CN mixture (1:1) were investigated (see Table 1).

Four different aldehydes were used, providing solid phase bound imines **3** differing in their reactivity in the HDA-reaction. At room temperature the resin bound imine **3** was preswelled in the dry solvent, the imine was activated by addition of 0.2 equiv of $Yb(OTf)_3$ and after 15 min, 5 equiv of freshly synthesized[18] Danishefsky's diene **4** were added and the mixture was agitated overnight at room temperature. The success of the HDA-reactions was evaluated by the product yields after F_3CCO_2H cleavage and flash chromatographic isolation. The results are shown in Table 1.

In all cases, the highest yields of **6** were obtained by performing the HDA-reaction in dry THF (entries 1, 6, 11 and 16). As a rule, increasing the solvent polarity decreases yields of **6**. Sterically demanding imines (e.g., **3b**, **3c**) led to reduced yields. Efficient Lewis acid imine activation seems to be crucial for high yields of dihydropyridones **6**. Using the Lewis basic solvent DMF, binding of the Lewis acid $Yb(OTf)_3$ resulted in very low yields of dihydropyridones **6** (entries 5, 10, 15 and 20).

Table 1. Influence of the solvent on the yields of **6**

Entry	R^1	R^2	Product	Solvent	Yield [%][a]
1	*i*Pr	H	**6a**	THF	43
2			**6a**	THF/MeOH=1:1	10
3			**6a**	THF/CH_3CN=1:1	21
4			**6a**	DMF/CH_3CN=1:1	26
5			**6a**	DMF	16
6	Cy	H	**6b**	THF	36
7			**6b**	THF/MeOH=1:1	31
8			**6b**	THF/CH_3CN=1:1	25
9			**6b**	DMF/CH_3CN=1:1	17
10			**6b**	DMF	8
11	*t*Bu	H	**6c**	THF	25
12			**6c**	THF/MeOH=1:1	0
13			**6c**	THF/CH_3CN=1:1	0
14			**6c**	DMF/CH_3CN=1:1	0
15			**6c**	DMF	0
16	Ph	H	**6d**	THF	58
17			**6d**	THF/MeOH=1:1	17
18			**6d**	THF/CH_3CN=1:1	37
19			**6d**	DMF/CH_3CN=1:1	24
20			**6d**	DMF	9

[a] Yields are given after FC-purification and are related to pure products.

3. Investigation of temperature effects

After optimization of the solvent (THF) the influence of the temperature on the HDA-reaction was investigated. For this purpose the HDA-reaction was performed at 50, −10, and 0–25 °C. In the last case temperature was held at 0 °C for 4 h, then the reaction mixture was allowed to reach 25 °C overnight. All other reaction parameters were not altered.

The results in Table 2 demonstrate that the highest yields of dihydropyridones **6** were obtained by using the temperature gradient from 0 to 25 °C. However, temperature variation seems to be less important for the aromatic benzaldehyde imine **3d** (entries 13 and 15). Performing the HDA-reaction with sterically less demanding aliphatic aldehyde imines **3a** and **3b** at various temperatures (−10, 25, 50 °C) had only little influence on the dihydropyridone yields (entries 1–3 and 5–7). However, the temperature gradient led to a considerable improvement of product yields (entries 4 and 8).

Table 2. Influence of the temperature on the yields of **6**

Entry	R^1	R^2	Product	Temp. [°C]	Yield [%][a]
1	*i*Pr	H	**6a**	50	36
2			**6a**	25	43
3			**6a**	−10	33
4			**6a**	0–25	55
5	Cy	H	**6b**	50	34
6			**6b**	25	36
7			**6b**	−10	42
8			**6b**	0–25	74
9	*t*Bu	H	**6c**	50	0
10			**6c**	25	25
11			**6c**	−10	42
12			**6c**	0–25	46
13	Ph	H	**6d**	50	69
14			**6d**	25	58
15			**6d**	−10	71
16			**6d**	0–25	71

[a] Yields are given after FC-purification and are related to pure products.

In contrary to these results the yields of **6c** resulting from the HDA-reaction of the sterically demanding pivalaldehyde imine **3c** strongly depended on the reaction temperature (entries 9–12). Decreasing the temperature increased yields, and the temperature gradient represented optimal reaction conditions. Thus, even products which are difficult to obtain at room temperature were synthesized in satisfactory yields by the temperature gradient.

Obviously at higher temperatures side reactions seem to be faster than the HDA-reaction. They can be suppressed by using lower temperatures at the beginning of the reaction. In order to drive the reaction to completion, the temperature has to be raised to 25 °C.

4. Scope and limitations

Next, the optimized reaction conditions were applied to the synthesis of a small dihydropyridone **6** library. The imines **3** were formed by condensation of deprotected **1** with a series of aliphatic, aromatic and heteroaromatic aldehydes as well

Table 3. Scope and limitations of the solid phase synthesis of dihydropyridones **6**

Entry	R^1	R^2	Product	Yield [%][a]
1	*i*Pr	H	**6a**	61±5 (n=3)[b]
2	Cy	H	**6b**	68±5 (n=3)[b]
3	*t*Bu	H	**6c**	46±8 (n=3)[b]
4	*n*Bu	H	**6e**	34
5	*i*Bu	H	**6f**	59
6	Ph	H	**6d**	52
7	4-NO_2–Ph	H	**6g**	67
8	2-Br–Ph	H	**6h**	63
9	Furan-2-yl	H	**6i**	26
10	Thiophen-2-yl	H	**6k**	30
11	Pyridin-2-yl	H	**6l**	40
12	Me	CO_2Et	**6m**	33

[a] Yields are given after FC-purification and are related to pure products.
[b] Average yields±standard deviation of three independent experiments.

as a ketone. Reactions with the aliphatic aldehydes used for the solvent- and temperature optimizing were repeated twice (n=3) to prove reproducibility of the transformation. The results are summarized in Table 3.

All kinds of aldehydes **2a**–**2l** and even the ketone ethyl pyruvate **2m** reacted to afford the desired 2-substituted dihydropyridones **6a**–**m** in good yields.

In the case of aromatic aldehydes, electron withdrawing aryl substituents seem to be favorable to high product yields (entries 7 and 8). This observation is confirmed by low yields that were obtained after the reaction of electron rich heteroaromatic carbaldehydes **2i** and **2k** (entries 9 and 10). The product **6m** resulting from the ketone ethyl pyruvate (**2m**, entry 12) is of particular interest, since two substituents are introduced in position 2 of the dihydropyridone moiety. To the best of our knowledge this is the first solid phase method for the synthesis of 2,2-disubstituted dihydropyridones from ketones.

5. Conclusion

We have developed a new solid phase method for the parallel synthesis of 2-substituted 2,3-dihydropyridin-4(1*H*)-ones **6**. Reaction conditions for the key step, that is, Lewis acid catalyzed HDA-reaction, were optimized to obtain the desired products in up to 68% overall yield (entry 2, Table 3), which implies an average yield of 91% for each of the four reaction steps. The chosen reaction sequence is applicable to all kinds of aldehydes. Even activated ketones reacted to yield disubstituted products, which were not accessible by other known methods. The novel strategy allows the introduction of additional functional groups in position 2, thus offering the possibility to access diverse structures. All described compounds were isolated by flash chromatography and are analytically pure.

6. Experimental

6.1. General

Thin layer chromatography (TLC): silica gel 60 F_{254} plates (Merck). Flash chromatography (FC):[19] Silica gel 60, 40–63 μm (Merck). MS: MAT GCQ (Thermo-Finnigan); EI=electron impact. Gas chromatography-high resolution MS (GC-HRMS): GCT (Waters-Micromass, Manchester, UK); EI=electron impact. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Unity Mercury Plus 400 NMR spectrometer (Varian); δ in ppm related to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques.

All dihydropyridone syntheses were performed in parallel on a 24-position Bohdan-MiniBlock (Mettler-Toledo). Temperature was controlled with a FP40-MV refrigerated circulator (Julabo). All solvents used were dried using standard procedures.

THF was dried over sodium and freshly distilled before use. Fmoc-Rinkamide-polystyrene-resin was purchased from Fluka and stored under N_2 at 4 °C. $Yb(OTf)_3$ (Aldrich) was stored in a desiccator over P_2O_5 in vacuo at room temperature. Danishefsky's diene **4** was stored under N_2 at −25 °C.

6.1.1. *trans*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene (=Danishefsky's diene) (4). Modified according to Ref. 20. Anhydrous LiBr (4.32 g, 49.8 mmol) was given to a 100 mL-Schlenk-flask, which was immediately sealed by a rubber septum, flushed with N_2 and heated to approx. 400 °C with a heat gun. The flask was allowed to cool down to room temperature under gentle N_2-flow, then 25 mL of dry THF were added. It was stirred until all LiBr was completely dissolved. Afterwards the mixture was cooled to −15 °C, 4.72 mL chlorotrimethylsilane (37.3 mmol) and 2.50 mL *trans*-4-methoxy-but-3-en-2-on (24.9 mmol) were added gradually and the mixture was stirred for 15 min. Then 5.18 mL triethylamine (37.3 mmol) were added directly into the solution, it was stirred at −15 °C for 1 h and another 24 h at 40 °C. After that the reaction mixture was transferred with 30 mL of cold (4 °C) pentane into a separating funnel loaded with 15 g ice, 15 mL cold saturated $NaHCO_3$, 15 mL cold brine and another 30 mL cold pentane (4 °C each). The organic layer was separated and the aqueous layer was extracted twice with 30 mL cold pentane. The combined organic layers were washed with 15 mL cold brine and five times with 15 mL cold water and dried over anhydrous $MgSO_4$. It was filtered, concentrated (400 mbar; 40 °C) and the resulting brownish oil was distilled in vacuo over a 10 cm-vigreux-column to yield 3.19 g (74%) of a clear colourless liquid, $bp._{10}$ 66–67 °C (Ref. 20 bp. 65–70 °C, 7 mm Hg).

6.2. General procedure for the one-pot parallel synthesis of 2,3-dihydropyridin-4(1*H*)-ones (6a–m)

Twelve glass-fritted tubes were loaded with 300 mg N-Fmoc-Rinkamide(aminomethyl)polystyrene-resin **1** (1.1 mmol/g, 0.33 mmol), suspended in 20% piperidine in DMF (3 mL) and shaken for 2 h at room temperature. It was filtered off and the resins were washed twice with 3 mL of DMF, CH_2Cl_2 and MeOH, respectively. Trimethylorthoformate (=$HC(OMe)_3$; 3 mL) was added to each tube, it was shaken for 15 min and filtered off. Another 3 mL of

$HC(OMe)_3$ were added as well as the carbonyl compounds **2a**–**m** (3.3 mmol each) and it was shaken for 18 h at room temperature (solid carbonyl compounds were dissolved in $HC(OMe)_3$ before use and if solubility was poor, CH_3CN was added). It was filtered off and the resins were washed three times each with dry CH_2Cl_2 (3 mL) and dry MeOH (3 mL) and once with dry THF (3 mL). They were suspended in 2 mL of dry THF before 1.0 mL of a 0.066 mM solution of anhydrous $Yb(OTf)_3$ (0.066 mmol) in dry THF was added to each tube. It was shaken while the reaction mixtures were cooled down to 0 °C. Then 315 μL **4** (1.65 mmol) were added to each resin, it was agitated for 4 h at 0 °C, then the reaction mixtures were allowed to warm to room temperature while it was shaken for additional 16 h. The reactions were quenched with approximately the same volume of water and shaken for 15 min. It was filtered off and washed as follows (3 mL each time): 2×THF, 2×CH_2Cl_2, 2×MeOH, 1×CH_2Cl_2. Products were cleaved from the resins with 20% TFA in CH_2Cl_2 for 3 h at room temperature. It was filtered off, the resins were washed with CH_2Cl_2 (3×2 mL) and cleavage reaction was repeated once. The combined filtrates were concentrated in vacuo and the obtained crude products were purified by column flash chromatography (eluent = ethyl acetate, exceptions: **6h** eluent = ethyl acetate/petroleum ether = 75:25, **6l** eluent = ethyl acetate/methanol/dimethylethylamine = 87.5:10:2.5).

6.2.1. 2-Isopropyl-2,3-dihydropyridin-4(1*H*)-one (6a).[7,21]

Yellow oil, R_f = 0.12 (EtOAc); yield: 27.3 mg (60%); purity > 99% (GC); UV: λ_{max} = 303 nm; IR (neat): 3284 (broad, –N–H), 3043 (w, –C=*C*–*H*), 2966 (m, –C–H), 1676 (s, amide I), 1561 (s, amide II), 1241 (s)/1212 (s)/1187 (s)/1138 cm^{-1} (s, characteristic dihydropyridone fingerprint); ^1H NMR (DMSO-d_6): δ 7.49 (s broad, 1H, NH), 7.25 (t, *J* = 6.9 Hz, 1H, 6-H), 4.63 (d, *J* = 7.1 Hz, 1H, 5-H), 3.30 (dt, *J* = 13.0, 5.6 Hz, 1H, 2-H), 2.15 (dd, *J* = 16.0, 13.0 Hz, 1H, 3-H), 2.06 (dd, *J* = 15.2, 5.6 Hz, 1H, 3-H), 1.85–1.74 (m, 1H, –C*H*(CH_3)$_2$), 0.87 (d, *J* = 6.8 Hz, 3H, –C*H*$_3$), 0.86 (d, *J* = 6.8 Hz, 3H, –C*H*$_3$); ^{13}C NMR (DMSO-d_6): δ 189.8 (C-4), 151.0 (C-6), 95.1 (C-5), 56.5 (C-2), 37.0 (C-3), 29.1 (–*C*H(CH_3)$_2$), 17.0, 16.8 (2C, –*C*H$_3$); MS (70 eV) *m/e* (rel.int.): 139 (M, 22), 96 (M − *i*Pr, 100), 68 (M − *i*Pr–CO, 56); HRMS (70 eV) *m/e* calcd for $C_8H_{13}NO$: 139.0997, found 139.0960.

6.2.2. 2-Cyclohexyl-2,3-dihydropyridin-4(1*H*)-one (6b).[22]

Pale-yellow oil, R_f = 0.16 (EtOAc); yield: 37.5 mg (63%); purity > 99% (GC); UV: λ_{max} = 316 nm; IR (neat): 3297 (br, –N–H), 3045 (w, –C=*C*–*H*), 2926 (s, –C–H), 2854 (m, –C–H), 1680 (s, amide I), 1559 (s, amide II), 1210 (s)/1185 (s)/1136 cm^{-1} (s, characteristic dihydropyridone fingerprint); ^1H NMR (DMSO-d_6): δ 7.47 (s broad, 1H, NH), 7.22 (t, *J* = 6.7 Hz, 1H, 6-H), 4.61 (d, *J* = 7.0 Hz, 1H, 5-H), 3.28 (dt, *J* = 12.5, 5.9 Hz, 1H, 2-H), 2.16 (dd, *J* = 16.0, 12.5 Hz, 1H, 3-H), 2.08 (dd, *J* = 16.0, 5.9 Hz, 1H, 3-H), 1.74–1.56 (m, 5H, –cyclohexyl), 1.52–1.42 (m, 1H, –C*H*(CH_2)$_5$), 1.23–0.91 (m, 5H, –cyclohexyl); ^{13}C NMR (DMSO-d_6): δ 189.8 (C-4), 150.9 (C-6), 95.0 (C-5), 55.9 (C-2), 39.0 (–*C*H(CH_2)$_5$), 37.3 (C-3), 27.1, 26.8, 24.8 (3C, –cyclohexyl), 24.6 (2C, –cyclohexyl); MS (70 eV) *m/e* (rel.int.): 179 (M, 33), 136 (M − *i*Pr, 27), 121 (M − butyl, 43), 96 (M − cyclohexyl, 100), 68 (M − cyclohexyl–CO, 52); HRMS (70 eV) *m/e* calcd for $C_{11}H_{17}NO$: 179.1310, found 179.1290.

6.2.3. 2-*tert*-Butyl-2,3-dihydropyridin-4(1*H*)-one (6c).[7]

Yellow oil, R_f = 0.23 (EtOAc); yield: 23.6 mg (47%); purity > 99% (GC); IR (neat): 3447 (broad, –N–H), 2968 (m, –C–H), 1684 (s, amide I), 1559 (s, amide II), 1253 (s)/1206 (s)/1146 cm^{-1} (s, characteristic dihydropyridone fingerprint); ^1H NMR (DMSO-d_6): δ 7.36 (s broad, 1H, NH), 7.26 (t, *J* = 6.8 Hz, 1H, 6-H), 4.65 (d, *J* = 7.1 Hz, 1H, 5-H), 3.19 (dd, *J* = 14.0, 5.5 Hz, 1H, 2-H), 2.17 (dd, *J* = 16.0, 14.3 Hz, 1H, 3-H), 2.08 (dd, *J* = 16.0, 5.4 Hz, 1H, 3-H), 0.89 (s, 9H, –C(C*H*$_3$)$_3$); ^{13}C NMR (DMSO-d_6): δ 191.7 (C-4), 153.3 (C-6), 96.6 (C-5), 61.9 (C-2), 37.8 (C-3), 33.6 (–*C*(CH_3)$_3$), 26.4 (3C, –CH_3); MS (70 eV) *m/e* (rel.int.): 153 (M, 24), 96 (M − *t*Bu, 100), 68 (M − *t*Bu–CO, 34); HRMS (70 eV) *m/e* calcd for $C_9H_{15}NO$: 153.1154, found 153.1137.

6.2.4. 2-Phenyl-2,3-dihydropyridin-4(1*H*)-one (6d).[7,22]

Yellow oil, R_f = 0.23 (EtOAc); yield: 29.8 mg (52%); purity > 99% (GC); UV: λ_{max} = 302 nm; IR (neat): 3234 (broad, –N–H), 3031 (w, –C=*C*–*H*), 2924 (w, –C–H), 1685 (s, amide I), 1556 (s, amide II), 1231 (s)/1203 (s)/1165 (s)/1134 (s, characteristic dihydropyridone fingerprint), 697 cm^{-1} (s, out-of-plane); ^1H NMR (DMSO-d_6): δ 7.84 (d broad, *J* = 5.5 Hz, 1H, NH), 7.41–7.28 (m, 6H, –Ph + 6-H), 4.76 (d, *J* = 7.4 Hz, 1H, 5-H), 4.71 (dd, *J* = 12.5, 5.9 Hz, 1H, 2-H), 2.49 (dd, *J* = 16.0, 12.5 Hz, 1H, 3-H), 2.38 (dd, *J* = 16.0, 5.9 Hz, 1H, 3-H); ^{13}C NMR (DMSO-d_6): δ 190.6 (C-4), 152.8 (C-6), 141.5 (C-1′), 129.2 (2C, –Ph, *ortho*), 128.4 (–Ph, *para*), 127.3 (2C, –Ph, *meta*), 97.7 (5-C), 57.0 (2-C), 44.6 (3-C); MS (70 eV) *m/e* (rel.int.): 173 (M, 100), 145 (M − CO, 55), 104 (M − NHCH=CHC(=O), styrene = Retro-Diels–Alder-fragment, 73), 78 (–Ph, 43); HRMS (70 eV) *m/e* calcd for $C_{11}H_{11}NO$: 173.0841, found 173.0856.

6.2.5. 2-Butyl-2,3-dihydropyridin-4(1*H*)-one (6e).

Pale-yellow oil, R_f = 0.13 (EtOAc); yield: 17.0 mg (34%); purity ~98% (GC); IR (neat): 3296 (broad, –N–H), 3046 (w, –C=*C*–*H*), 2959 (m, –C–H), 2930 (m, –C–H), 2861 (m, –C–H), 1676 (s, amide I), 1559 (s, amide II), 1241 (m)/1205 (s)/1186 (s)/1137 cm^{-1} (s, characteristic dihydropyridone fingerprint); ^1H NMR (DMSO-d_6): δ 7.47 (s broad, 1H, NH), 7.21 (t, *J* = 6.8 Hz, 1H, 6-H), 4.62 (d, *J* = 7.0 Hz, 1H, 5-H), 3.46 (tt, *J* = 12.2, 6.1 Hz, 1H, 2-H), 2.19 (dd, *J* = 16.0, 5.3 Hz, 1H, 3-H), 2.07 (dd, *J* = 16.0, 12.2 Hz, 1H, 3-H), 1.62–1.48 (m, 1H, –C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.48–1.36 (m, 1H, –C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.34–1.16 (m, 4H, –CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.91–0.76 (m, 3H, –CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (DMSO-d_6): δ 191.3 (C-4), 152.4 (C-6), 97.0 (C-5), 52.8 (C-2), 42.2 (C-3), 33.5 (–*C*H$_2$CH$_2$CH$_2$CH$_3$′), 27.6 (–CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.8 (–CH$_2$CH$_2$*C*H$_2$CH$_3$′), 14.6 (–CH$_2$CH$_2$CH$_2$*C*H$_3$); MS (70 eV) *m/e* (rel.int.): 153 (M, 13), 138 (M − CH_3, 20), 110 (M − C_3H_7, 21), 96 (M − Bu, 100), 68 (M − Bu–CO, 60); HRMS (70 eV) *m/e* calcd for $C_9H_{15}NO$: 153.1154, found 153.1134.

6.2.6. 2-(2-Methylpropyl)-2,3-dihydropyridin-4(1*H*)-one (6f).

Yellow oil, R_f = 0.14 (EtOAc); yield: 29.7 mg (59%); purity > 99% (GC); IR (neat): 3298 (broad, –N–H), 3052 (w, –C=*C*–*H*), 2960 (m, –C–H), 2928 (m, –C–H), 2874 (m,

–C–H), 1676 (s, amide I), 1559 (s, amide II), 1186 (s)/1137 cm^{-1} (s, characteristic dihydropyridone-fingerprint); ^1H NMR (DMSO-d_6): δ 7.49 (s broad, 1H, NH), 7.21 (t, J=6.8 Hz, 1H, 6-H), 4.63 (d, J=7.1 Hz, 1H, 5-H), 3.59–3.49 (m, 1H, 2-H), 2.21 (dd, J=16.0, 5.1 Hz, 1H, 3-H), 2.04 (dd, J=16.0, 12.1 Hz, 1H, 3-H), 1.73–1.60 (m, 1H, $-CH_2CH(CH_3)_2$), 1.55–1.46 (m, 1H, $-CH_2CH(CH_3)_2$), 1.29–1.19 (m, 1H, $-CH_2CH(CH_3)_2$), 0.85 (d, J=6.7 Hz, 3H, $-CH_3$), 0.84 (d, J=6.7 Hz, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6): δ 189.5 (C-4), 150.5 (C-6), 95.1 (C-5), 48.9 (C-2), 41.1 ($-CH_2CH(CH_3)_2$), 40.7 (C-3), 22.5 ($-CH_2CH(CH_3)_2$), 21.5, 21.1 (2C, $-CH_3$); MS (70 eV) *m/e* (rel.int.): 153 (M, 44), 138 (M−CH_3, 23), 110 (M−C_3H_7, 11), 96 (M−(2-methylpropyl), 100), 68 (M−(2-Methylpropyl)–CO, 100); HRMS (70 eV) *m/e* calcd for $C_9H_{15}NO$: 153.1154, found 153.1111.

6.2.7. 2-(4-Nitrophenyl)-2,3-dihydropyridin-4(1*H*)-one (6g). Yellow oil, R_f=0.12 (EtOAc); yield: 48.1 mg (67%); purity>99% (GC); IR (neat): 3274 (broad, –N–H), 3045 (w, –C=*C–H*), 2926 (w, –C–H), 1680 (s, amide I), 1561 (s, amide II), 1518 (s, $-NO_2$ asym.), 1347 (s, $-NO_2$ sym.), 1235 (m)/1204 (s)/1137 (s, characteristic dihydropyridone fingerprint), 698 cm^{-1} (m, out-of-plane); ^1H NMR (DMSO-d_6): δ 8.22 (d, J=9.0 Hz, 2H, 3′-H), 8.02 (d broad, J=5.9 Hz, 1H, NH), 7.67 (d, J=8.2 Hz, 2H, 2′-H), 7.44 (t, J=6.9 Hz, 1H, 6-H), 4.95–4.88 (m, 1H, 2-H), 4.78 (d, J=6.7 Hz, 1H, 5-H), 2.53 (dd, J=16.1, 6.4 Hz, 1H, 3-H), 2.46 (dd, J=16.1, 10.6 Hz, 1H, 3-H); ^{13}C NMR (DMSO-d_6): δ 189.9 (C-4), 152.8 (C-6), 149.3 (C-4′), 147.6 (C-1′), 128.6 (2C, C-2′), 124.4 (2C, C-3′), 98.1 (C-5), 56.1 (C-2), 43.9 (C-3); MS (70 eV) *m/e* (rel.int.): 218 (M, 100), 190 (M−CO, 55), 172 (M−NO_2, 7), 149 (M−NHCH=CHC(=O), 4-nitrostyrene=Retro-Diels–Alder-fragment, 17), 119 (Retro-Diels–Alder-fragment-NO, 23), 96 (M−(4-nitrophenyl), 11), 91 (C_7H_7, 38); HRMS (70 eV) *m/e* calcd for $C_{11}H_{10}N_2O_3$: 218.0691, found 218.0667.

6.2.8. 2-(2-Bromophenyl)-2,3-dihydropyridin-4(1*H*)-one (6h). Pale-yellow oil, R_f=0.18 (EtOAc/petroleum ether=75:25); yield: 52.0 mg (63%); purity>99% (GC); IR (neat): 3252 (broad, –N–H), 3036 (m, –C=*C–H*), 1676 (s, amide I), 1559 (s, amide II), 1236 (m)/1202 (s)/1187 (s)/1136 (s, characteristic dihydropyridone fingerprint), 720 cm^{-1} (m, out-of-plane); ^1H NMR (DMSO-d_6): δ 7.90 (d broad, J=5.5 Hz, 1H, NH), 7.63 (dd, J=8.0, 1.4 Hz, 1H, 3′-H), 7.56 (dd, J=7.6, 1.8 Hz, 1H, 6′-H), 7.48–7.39 (m, 2H, 6-H+5′-H), 7.25 (td, J=7.6, 2.0 Hz, 1H, 4′-H), 5.01–4.94 (m, 1H, 2-H), 4.80 (d, J=7.4 Hz, 1H, 5-H), 2.49 (dd, J=16.0, 6.3 Hz, 1H, 3-H), 2.39 (dd, J=16.0, 11.7 Hz, 1H-3-H); ^{13}C NMR (DMSO-d_6): δ 190.0 (C-4), 153.3 (C-6), 139.8 (C-1′), 133.7 (C-3′), 130.5 (C-4′), 128.9 (2C, C-5′+C-6′), 122.6 (C-2′), 97.8 (C-5), 56.5 (C-2), 42.6 (C-3); MS (70 eV) *m/e* (rel.int.): 253 (^{81}BrM, 78), 251 (^{79}BrM, 81), 225 (^{81}BrM−CO, 12), 223 (^{79}BrM−CO, 15), 184 (2-^{81}bromostyrene=Retro-Diels–Alder-fragment, 62), 182 (2-^{79}bromostyrene=Retro-Diels–Alder-fragment, 58), 172 (M−Br, 56), 144 (M−Br–CO, 55), 130 (isoquinolinium, 100), 103 (styrene, 91), 77 (–Ph, 12); HRMS (70 eV) *m/e* calcd for $C_{11}H_{10}BrNO$: 252.9925 (^{81}Br)/250.9946 (^{79}Br), found 252.9909 (^{81}Br)/250.9924 (^{79}Br).

6.2.9. 2-(Furan-2-yl)-2,3-dihydropyridin-4(1*H*)-one (6i). Yellow oil, R_f=0.22 (EtOAc); yield: 14.0 mg (26%); purity>99% (GC); IR (neat): 3247 (broad, –N–H), 3034 (m, –C=*C–H*), 2927 (w, –C–H), 1675 (w, amide I), 1560 (s, amide II), 1404 (m), 1281 (s)/1227 (s)/1205 (s)/1167 (s, characteristic dihydropyridone-fingerprint), 740 cm^{-1} (m, out-of-plane); ^1H NMR (DMSO-d_6): δ 7.89 (d broad, J=5.1 Hz, 1H, NH), 7.63 (dd, J=1.6, 0.8 Hz, 1H, 5′-H), 7.25 (dd, J=7.0, 0.8 Hz, 1H, 6-H), 6.41 (dd, J=3.1, 1.6 Hz, 1H, 4′-H), 6.30 (d, J=3.1 Hz, 1H, 3′-H), 4.78 (dt, J=7.0, 1.6 Hz, 1H, 2-H), 4.71 (dd, J=7.0, 0.8 Hz, 1H, 5-H), 2.53–2.47 (m, 2H, 3-H); ^{13}C NMR (DMSO-d_6): δ 190.1 (C-4), 153.7 (C-2′), 151.9 (C-6), 143.3 (C-5′), 111.1 (C-4′), 107.4 (C-3′), 97.6 (C-5), 49.9 (C-2), 40.5 (C-3); MS (70 eV) *m/e* (rel.int.): 163 (M, 39), 135 (M−CO, 93), 106 (Furo[2,3-c]pyrrole, 100), 94 (Retro-Diels–Alder-fragment, 61), 66 (pyrrole, 74); HRMS (70 eV) *m/e* calcd for $C_9H_9NO_2$: 163.0633, found 163.0590.

6.2.10. 2-(Thiophen-2-yl)-2,3-dihydropyridin-4(1*H*)-one (6k). Yellow oil, R_f=0.24 (EtOAc); yield: 14.6 mg (30%); purity>99% (GC); IR (neat): 3235 (broad, –N–H), 3025 (w, –C=*C–H*), 2924 (w, –C–H), 2852 (w, –C–H), 1684 (m, amide I), 1558 (s, amide II), 1232 (s), 1204 (s), 1179 (s), 1135 (s, characteristic dihydropyridone fingerprint), 702 cm^{-1} (m, out-of-plane); ^1H NMR (DMSO-d_6): δ 7.96 (d broad, J=5.1 Hz, 1H, NH), 7.44 (dd, J=5.1, 1.6 Hz, 1H, 3′-H), 7.29 (dd, J=7.4, 0.8 Hz, 1H, 6-H), 7.08–7.07 (m, 1H, 5′-H), 6.98 (dd, J=5.1, 3.1 Hz, 1H, 4′-H), 5.00 (ddd, J=9.8, 6.3, 1.6 Hz, 1H, 2-H), 4.76 (dd, J=7.4, 1.2 Hz, 1H, 5-H), 2.55 (dd, J=16.0, 6.3 Hz, 1H, 3-H), 2.48 (dd, J=15.7, 10.2 Hz, 1H, 3-H); ^{13}C NMR (DMSO-d_6): δ 190.1 (C-4), 152.0 (C-6), 145.0 (C-2′), 127.4 (C-4′), 126.0 (2C, C-3′+C-5′), 98.1 (C-5), 52.2 (C-2), 44.8 (C-3); MS (70 eV) *m/e* (rel.int.): 179 (M, 31), 162 (thiophen-2-ylpyridine·H^+, 61), 151 (M−CO, 72), 110 (Retro-Diels–Alder-fragment, 100), 106 (2-allylpyridine·H^+, 21), 96 (M−thiophenyl, 13), 84 (thiophen, 27), 66 (pyrrole, 53); HRMS (70 eV) *m/e* calcd for C_9H_9NOS: 179.0405, found 179.0381.

6.2.11. 2,3-Dihydro-2,2′-bipyridin-4(1*H*)-one (6l). Yellow oil, R_f=0.36 (EtOAc/MeOH/Me_2NEt=87.5:10:2.5); yield: 23.2 mg (40%); purity>99% (GC); IR (neat): 3226 (broad, –N–H), 3022 (m, –C=*C–H*), 2929 (w, –C–H), 1619 (m, amide I), 1562 (s, amide II), 1275 (w)/1236 (m)/1207 (s)/1166 (m, characteristic dihydropyridone fingerprint), 782, 748 cm^{-1} (m, out-of-plane); ^1H NMR (DMSO-d_6): δ 8.57–8.54 (m, 1H, 3′-H), 7.96 (d broad, J=5.5 Hz, 1H, NH), 7.80 (td, J=7.8, 2.0 Hz, 1H, 5′-H), 7.44 (d, J=7.8 Hz, 1H, 6′-H), 7.39 (t, J=6.9 Hz, 1H, 6-H), 7.33–7.29 (m, 1H, 4′-H), 4.78 (ddd, J=10.2, 6.3, 2.0 Hz, 1H, 2-H), 4.73 (d, J=7.4 Hz, 1H, 5-H), 2.64 (dd, J=16.0, 10.2 Hz, 1H, 3-H), 2.55 (dd, J=16.0, 6.3 Hz, 1H, 3-H); ^{13}C NMR (DMSO-d_6) δ 190.3 (C-4), 159.8 (C-1′), 152.4 (C-6), 149.8 (C-3′), 137.7 (C-5′), 123.5 (C-4′), 121.4 (C-6′), 97.8 (C-5), 57.5 (C-2), 42.0 (C-3); MS (70 eV) *m/e* (rel.int.): 174 (M, 14), 146 (M−CO, 63), 130 ([1,7]naphthyridine, 100), 106 (Retro-Diels–Alder-fragment, 18), 96 (M−pyridine, 18), 78 (pyridine, 15); HRMS (70 eV) *m/e* calcd for $C_{10}H_{10}N_2O$: 174.0793, found 174.0790.

6.2.12. Ethyl 2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate (6m). Yellow oil, R_f=0.23 (EtOAc); yield: 20.1 mg (33%); purity>99% (GC); IR (neat): 3291 (broad,

–N–H), 2985 (w, –C–H), 1732 (m, –(*C*═*O*)–O–), 1680 (s, amide I), 1624 (s), 1566 (s, amide II), 1294 (m, –*C*–*O*–(C═O)–), 1242 (s)/1186 (s)/1137 (s)/1106 cm^{-1} (s, characteristic dihydropyridone fingerprint); ^1H NMR (DMSO-d_6): δ 7.97 (d broad, $J=5.1$ Hz, 1H, NH), 7.26 (t, $J=6.9$ Hz, 1H, 6-H), 4.66 (d, $J=7.4$ Hz, 1H, 5-H), 4.08 (quart, $J=7.0$ Hz, 2H, –OCH_2CH$_3$), 2.58 (d, $J=16.0$ Hz, 1H, 3-H), 2.38 (d, $J=16.0$ Hz, 1H, 3-H), 1.38 (s, 3H, –CH_3), 1.14 (t, $J=7.0$ Hz, 3H, –OCH$_2$CH_3); ^{13}C NMR (DMSO-d_6): δ 189.8 (C-4), 174.3 (–*C*O$_2$Et), 152.0 (C-6), 97.6 (C-5), 61.9 (–O*C*H$_2$CH$_3$), 60.4 (C-2), 45.8 (C-3), 24.4 (–CH$_3$), 14.6 (–OCH$_2$*C*H$_3$); MS (70 eV) *m/e* (rel.int.): 183 (M, 16), 110 (M−ethoxycarbonyl, 100), 82 (M−ethoxycarbonyl–CO, 22); HRMS (70 eV) *m/e* calcd for $C_9H_{13}NO_3$: 183.0895, found 183.0879.

References and notes

1. Thurkauf, A.; Mattson, M. V.; Richardson, S.; Mirsadeghi, S.; Ornstein, P. L.; Harrison, E. A. Jr.; Rice, K. C.; Jacobson, A. E.; Monn, J. A. *J. Med. Chem.* **1992**, *35*, 1323–1329.
2. (a) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467–2473. (b) Bhagwatheeswaran, H.; Gaur, S. P.; Jain, P. C. *Synth. Commun.* **1976**, 615–616. (c) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831–5834. (d) Desai, M. C.; Lefkowitz, S. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2083–2086. (e) Rosen, T.; Seeger, T. F.; McLean, S.; Desai, M. C.; Guarino, K. J.; Bryce, D.; Pratt, K.; Heym, J. *J. Med. Chem.* **1993**, *36*, 3197–3201.
3. (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1998**, *39*, 1973–1976. (b) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1998**, *39*, 7591–7594.
4. For reviews concerning HDA-reactions see: (a) Jørgensen, K. A. *Angew. Chem.* **2000**, *112*, 3702–3733. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099–6138.
5. Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406.
6. (a) Wang, Y.; Wilson, S. R. *Tetrahedron Lett.* **1997**, *38*, 4021–4024. (b) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Org. Lett.* **2002**, *4*, 3667–3670.
7. Chen, C.; McDonald, I. A.; Munoz, B. *Tetrahedron Lett.* **1998**, *39*, 217–220.
8. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937–2940.
9. Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett.* **1997**, *38*, 2547–2550.
10. (a) Barluenga, J.; Mateos, C.; Aznar, F.; Valdés, C. *Organic Lett.* **2002**, *4*, 1971–1974. (b) Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633–9636.
11. (a) Kuethe, J. T.; Davies, I. W.; Dormer, P. G.; Reamer, R. A.; Mathre, D. J.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 29–32. (b) Kuethe, J. T.; Wong, A.; Davies, I. W.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 3871–3874.
12. (a) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264–3265. (b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749–1760.
13. Josephson, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019.
14. Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **2002**, *58*, 341–354.
15. Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309–3311.
16. Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574–575.
17. Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663.
18. Diene decomposes rapidly under standard storing conditions (4 °C, N_2, dark), but is stable for at least 21 days when stored under N_2 at −25 °C, dark (proved by NMR-analysis; purity $\geq$95% after 21 days).
19. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2325–2923.
20. Hansson, L.; Carlson, R. *Acta Chem. Scand.* **1989**, *43*, 188–192.
21. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679–3681.
22. Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728.

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Studies on the solvent dependence of the carbamic acid formation from ω-(1-naphthyl)alkylamines and carbon dioxide

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Abstract—Carbamic acid formation from amine and carbon dioxide in a variety of solvents was investigated by measuring NMR (^{1}H, ^{13}C, HMBC) and IR spectra in situ. Bubbling of CO_2 through solutions of naphthylalkylamines **1–3** in DMSO, DMF or pyridine (protophilic, highly dipolar, aprotic solvent) resulted in complete conversion of the amines to the corresponding carbamic acids **4–6**. In dioxane (protophilic, dipolar, aprotic solvent), the carbamic acid and a small amount of the ammonium carbamate were formed. By contrast, in MeCN (protophobic, dipolar, aprotic solvent), in benzene or $CHCl_3$ (apolar, aprotic solvent), or in 2-PrOH or MeOH (dipolar, amphiprotic solvent), ammonium carbamates **7–9** rather than **4–6** were formed, although the ammonium bicarbonates/carbonates were competitively formed in MeOH. The ammonium carbamates precipitated in many cases and hence they could be separated. The selective generation of the undissociated carbamic acids in preference to the ammonium carbamates in protophilic, dipolar, aprotic solvents (DMSO, DMF, pyridine, and dioxane) is rationalized by considering the acid–base equilibria between the amines **1–3** and the carbamic acids **4–6** in nonaqueous media. The obtained selectivity is likely due to the larger pK_a values for **4–6** than the amines **1–3** in these solvents. Interestingly, the fluorescence intensities for **1–3** were dramatically enhanced (4–50 times) in DMSO or DMF upon introduction of CO_2, while they were not altered very much in dioxane, MeCN, benzene, $CHCl_3$, 2-PrOH, and MeOH, except small to medium increases (1.3–3 times) for **1** in dioxane, MeCN, 2-PrOH and MeOH. As a whole, the solvent effects observed in these fluorescence studies are consistent with those observed in the above NMR and IR studies. Finally, methoxycarbonylation of amine **3** into the methyl carbamate was successfully accomplished by using (trimethylsilyl)diazomethane in the presence of CO_2.
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1. Introduction

Suitable amines can reversibly trap carbon dioxide through carbamic acids, which are important intermediates in view of their synthetic, industrial and biological applications.[1–5] In an attempt to accomplish new methods for irreversible fixation of carbon dioxide, we have been pursuing basic research on the reactivity of carbon dioxide with amines bearing an aromatic group as a chromophore and fluorophore. Mechanistic studies of amine–CO_2 reactions in organic solvents are scarce unlike in aqueous solutions, although carbamic acids have been known for a long time to be readily generated from a primary or secondary aliphatic amine $RR'NH$.[1–5] Because of their transient nature, however, their isolation in the free acid form $RR'NCO_2H$ is very difficult.† They are usually obtained as an ammonium carbamate salt $[RR'NCO_2^-][^+H_2NRR']$. Thus, bubbling of CO_2 gas through a solution of suitable amine in a variety of solvents such as chloroform ($CHCl_3$), methylene chloride, acetonitrile (MeCN), benzene, toluene, ethyl ether, tetrahydrofuran (THF), dioxane, and methanol (MeOH) (anhydrous), generally results in precipitation of the corresponding ammonium carbamate salt as a white solid. By contrast, we[6] and others[7] have recently found that in a particular solvent like dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF), where the carbamate salts are well soluble, the carboxylation of a primary aralkylamine into the carbamic acid $RNHCO_2H$ proceeds up to the complete (~100%) conversion. We have already studied a number of primary aralkylamines: for instance, ω-(1-naphthyl)alkylamines (ω=1–3) **1–3**, ω-(9-anthryl)alkylamines (ω=1–3), ω-phenylalkylamines (ω=1 or 2), tryptamines, and catecholamines.[6] Their N-carboxylation in DMSO by CO_2 bubbling proceeded smoothly to ~100% conversion. However, arylamines such as aniline and its derivatives did not undergo substantial N-carboxylation under similar conditions, although indoline and *p*-anisidine were N-carboxylated to a low conversion (22 and 11%,

Keywords: Carbon dioxide; Carbamic acid; Naphthylamines; Solvent effect; Carbon dioxide fixation; Fluorescence.
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† A successful isolation and the X-ray structure determination of *N*,*N*-dibenzylcarbamic acid Bn_2NCOOH was reported.[4] However, we were unable to reproduce its isolation. We obtained only the ammonium carbamate $[Bn_2NCO_2^-][^+H_2NBn_2]$.

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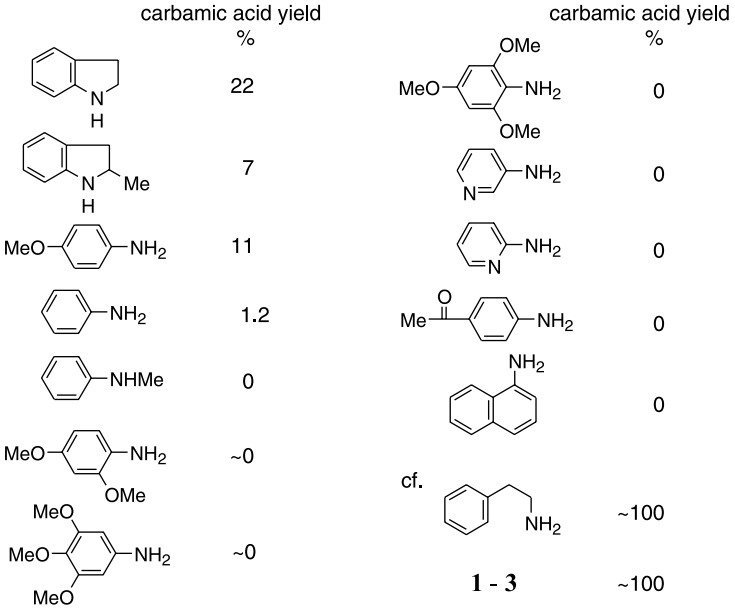
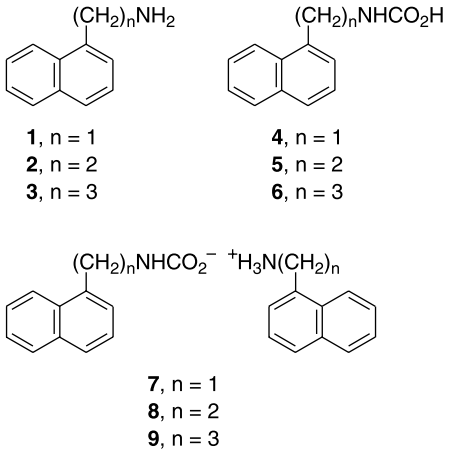


Chart 1. Carbamic acid formation from selected arylamines in DMSO-d_6 through bubbling of CO_2 at room temperature. The conversion or the carbamic acid yield was estimated in situ by ^{1}H NMR analysis.

respectively: Chart 1).[‡]



Since amine, carbamic acid, and ammonium carbamate are rapidly equilibrated in the solution phase (Eqs. 1 and 2),[2,5,8] we assumed that in the dissolving solvents (DMSO and DMF) all the free aralkylamine could finally be converted to the carbamic acid by excess CO_2. We now report that the observed complete transformation of the amine into the carbamic acid is not only due to the dissolving power of the solvent, but also is a consequence of the solvent effect on the acid–base equilibrium in Eq. 2. We investigated **1**–**3**, especially 3-(1-naphthyl)propylamine (**3**), because its ammonium carbamate **9** has been found to have relatively large solubility in various solvents, an advantageous property for spectroscopic studies. The solvents employed are (deuterated) DMSO, DMF, pyridine (Py), dioxane, MeCN, benzene, $CHCl_3$, 2-propanol (2-PrOH), and MeOH.

The carboxylation experiments were carried out by passing a large excess of CO_2 gas through a solution of amine (0.13–0.15 M for NMR and IR experiments and $\sim 6\times 10^{-5}$ M for absorption and fluorescence measurements) at room temperature for 0.5–1 h. Analyses for the products were performed in situ by measurements of ^{1}H and ^{13}C NMR including 2D NMR (COSY, NOESY, HMQC, and HMBC), IR, and absorption and fluorescence spectra.

$$RR'NH + CO_2 \overset{K_1}{\rightleftharpoons} RR'NCO_2H \quad (1)$$

$$RR'NCO_2H + RR'NH \overset{K_2}{\rightleftharpoons} \underset{\text{(precipitate in many solvents)}}{[RR'NCO_2^-][RR'NH_2^+]} \quad (2)$$

R = alkyl or aralkyl, R′ = H, alkyl or aralkyl.

2. Results and discussion

The NMR measurements in situ after bubbling of CO_2 through a solution of **3** in DMSO, DMF or Py revealed that 3-(1-naphthyl)propylcarbamic acid (**6**) was formed quantitatively in complete conversion (e.g., see Fig. 1 for the DMSO case; also see Fig. 2(a)–(c)). In dioxane, formation of the predominant product **6** (see Fig. 2(d)) was accompanied by precipitation of a small amount of ammonium carbamate **9**.[§] The carboxy carbon of **6** appeared at δ 157–160 and the NH proton appeared as a broad triplet at δ 6.0–7.8 (δ 6.9, 7.0, 7.8 and 6.0, respectively, in DMSO, DMF, Py and dioxane). The α-methylene protons resonanced as a quasi-quartet at δ 3.1–3.6, considerably lower than the corresponding signal of **3**, which occurred as a

[‡] It is reported that the efficiency for carbamate formation in water is controlled by both steric hindrance of the N-substituents and by electron densities on the nitrogen lone-pair.[9] The details of these structural effects, however, still remain to be elucidated.

[§] Like the dioxane solution of **3**, 3-(9-anthryl)propylamine in THF solution afforded, upon CO_2 bubbling, its carbamic acid (solution phase) and a little ammonium carbamate (precipitate and solution): Horiguchi, M.; Ito, Y.; Masuda, K.; unpublished data.

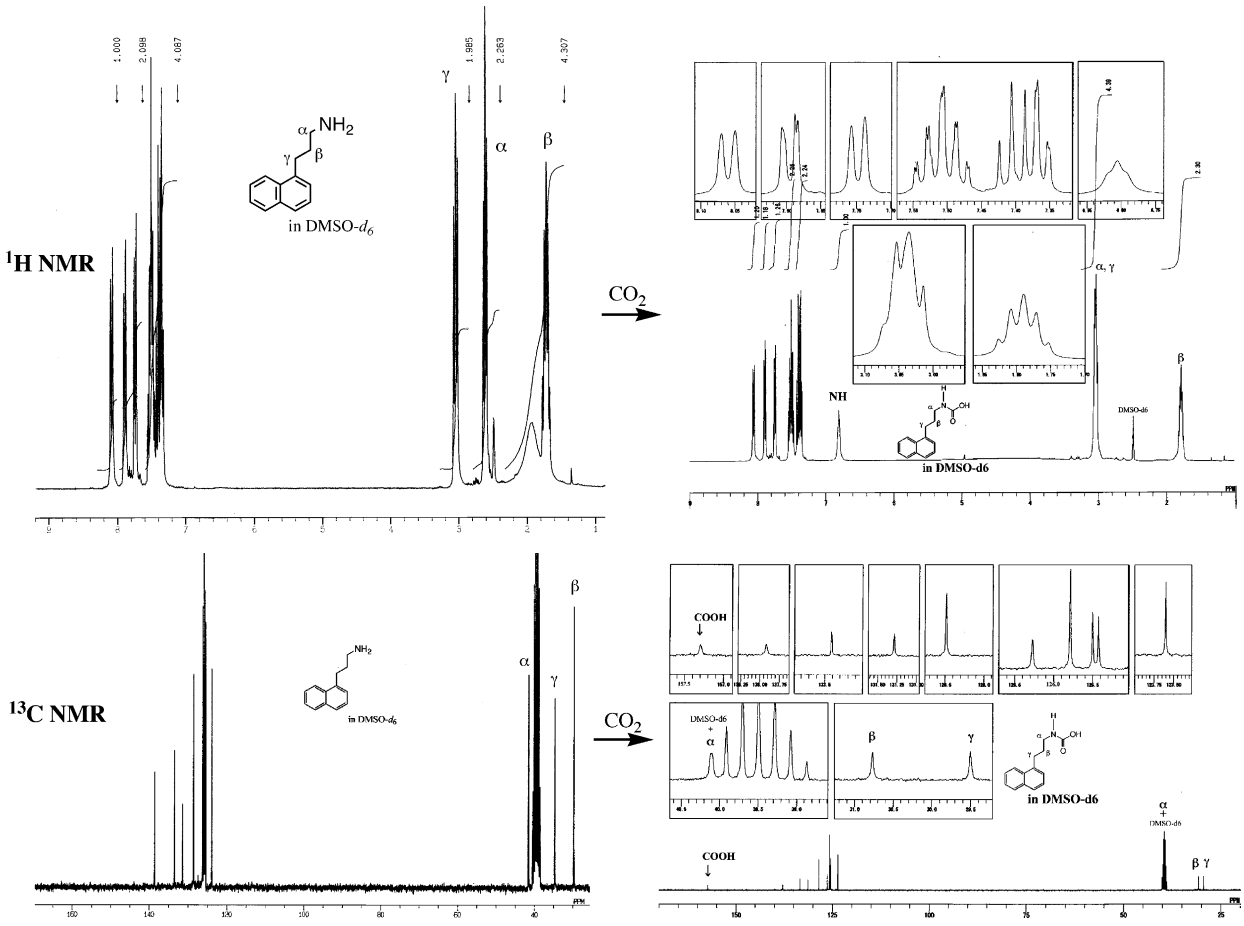


Figure 1. The ^{1}H and ^{13}C NMR spectra of **3** in DMSO-d_6 before and after CO_2 bubbling.

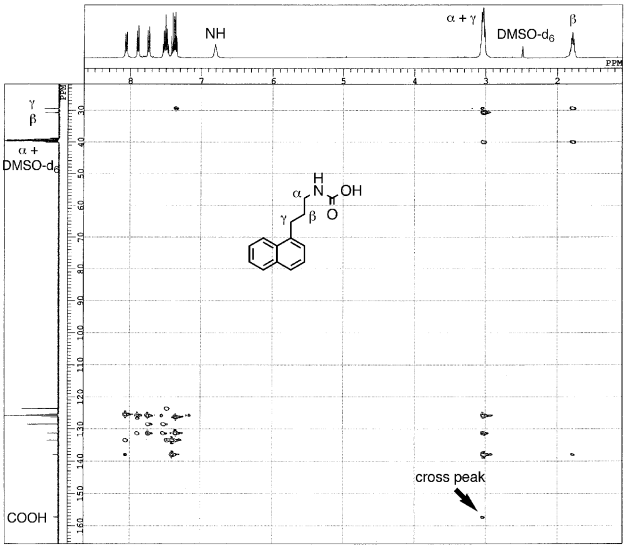
triplet at δ 2.6–2.8 ($\Delta\delta$ 0.40–0.81). The HMBC measurements demonstrate that there is a cross peak between the α-methylene proton and the carboxy carbon, unambiguously proving the N–C bond formation between the amine nitrogen and the CO_2 carbon. In Figure 2(a)–(d), the HMBC spectra in DMSO-d_6, DMF-d_7, Py-d_5 and dioxane-d_8 are displayed. The IR spectra for the solutions of **3** were likewise measured after CO_2 bubbling (Figs. 3 and 4). The spectra showed a strong band at 1700 cm^{-1} in DMSO (Fig. 4(a)) or Py (Fig. 3(b)) and at 1723 cm^{-1} in dioxane (Fig. 4(b)). These bands can be assigned to the CO_2H group of the carbamic acid **6**.[2] The IR measurement of the DMF solution was useless because of the presence of the strong absorption by DMF in this region.

Bubbling CO_2 through a solution of **3** in MeCN or benzene resulted in formation of 3-(1-naphthyl)propylammonium 3-(1-naphthyl)propylcarbamate (**9**) as a white precipitate. In the filtrate, only a trace of the free amine was detectable (in situ ^{1}H NMR). The precipitate **9** was characterized by ^{1}H and ^{13}C NMR (DMSO-d_6), IR (KBr) and elemental analysis. The NMR and elemental analyses revealed that a half of the amine is N-carboxylated. The IR spectrum in a KBr pellet (Fig. 3(e)) showed a broad band at about 1575 cm^{-1}, which is assignable to the $NHCOO^{-}$ group of the carbamate anion. It is to be noted that the IR spectrum of **9** dissolved in DMSO (Fig. 3 inset) or Py (Fig. 3(c)) showed a strong absorption at 1700 cm^{-1} corresponding to the carbamic acid **6**. Almost no absorption is visible around 1575 cm^{-1} in DMSO: this was more evident for the salts **7** and **8** dissolved in DMSO. Therefore, the carbamate salts change to the original carbamic acids when dissolved in DMSO or Py.

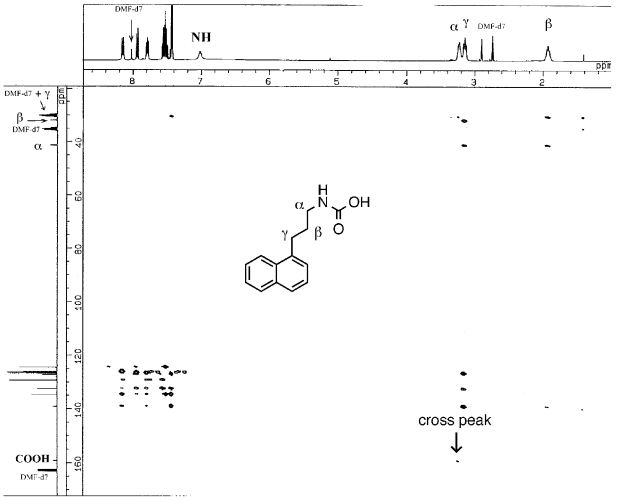
Although not precipitated from the solution, ammonium carbamate **9** was formed also in $CHCl_3$ or 2-PrOH, as was demonstrated in situ by the NMR and IR analyses. Thus, six methylene signals can be seen in the ^{1}H NMR spectra, corresponding to a mixture of the carbamate anion and the ammonium cation (Figs. 5 and 6). However, the reaction is not quantitative. Considering the presence of a small amount of the free amine which is undistinguishable from the ammonium species, the yield of **9** was estimated as 82 and 98%, respectively. The carboxy carbon of the carbamate anion is slightly more deshielded ($\delta \sim 163$) than that of **6** (δ 157–160).[¶] As seen from the HMBC spectra in $CDCl_3$ and 2-PrOH-d_8 (Fig. 2(e) and (f)), there is an expected cross peak between the α-methylene proton and the carboxy carbon. A strong support for the absence of the undissociated carboxy group is the IR spectrum. From inspection of Figure 3(d) ($CHCl_3$) and Figure 4(c) (2-PrOH), the absorption around 1700 cm^{-1} is negligible. Instead, we

[¶] The carbamyl carbon of butylammonium butylcarbamate is at δ 162.6 in benzene-d_6.[10a] The NMR spectra of the carbamate anions of homoveratrylamine, taurine, and various amino acids in D_2O containing K_2CO_3 was measured.[10b–d] Their carbamyl carbons occurred further downfield to δ 163–165 (measured with reference to dioxane δ 67.4).

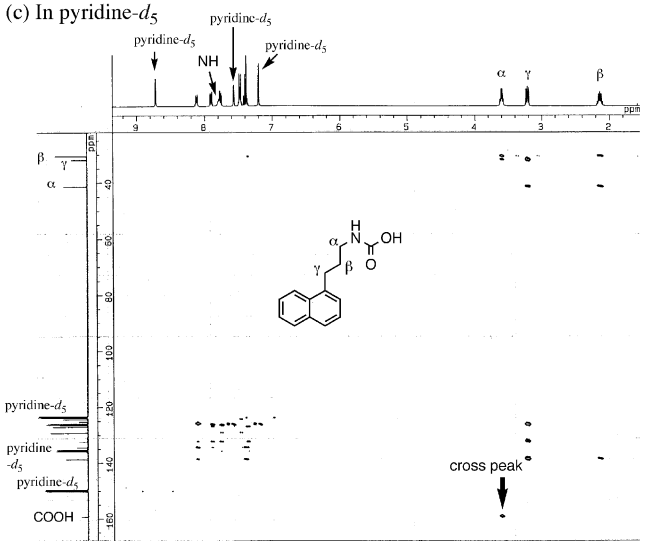
(a) In DMSO-d_6



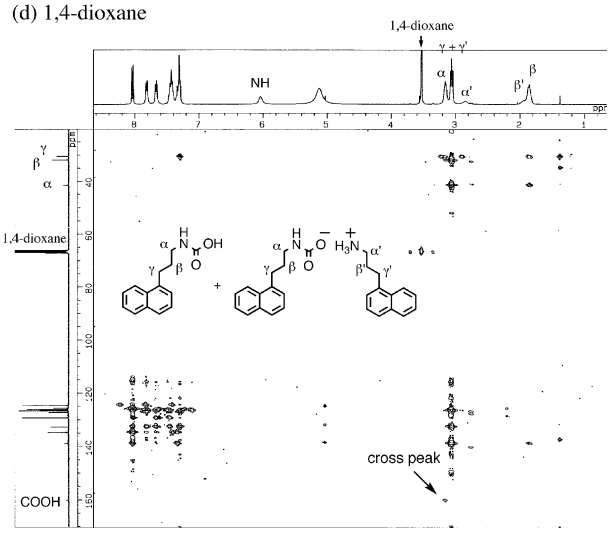
(b) In DMF-d_7



(c) In pyridine-d_5

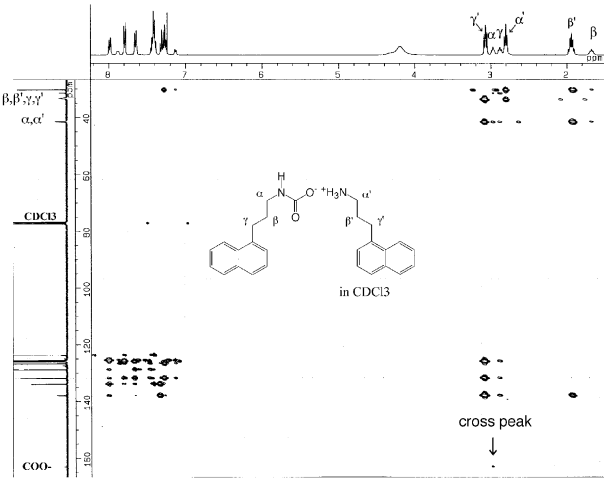


(d) 1,4-dioxane



A minor amount of the ammonium carbamate is present. The carbamate anion is indistinguishable from the carbamic acid.

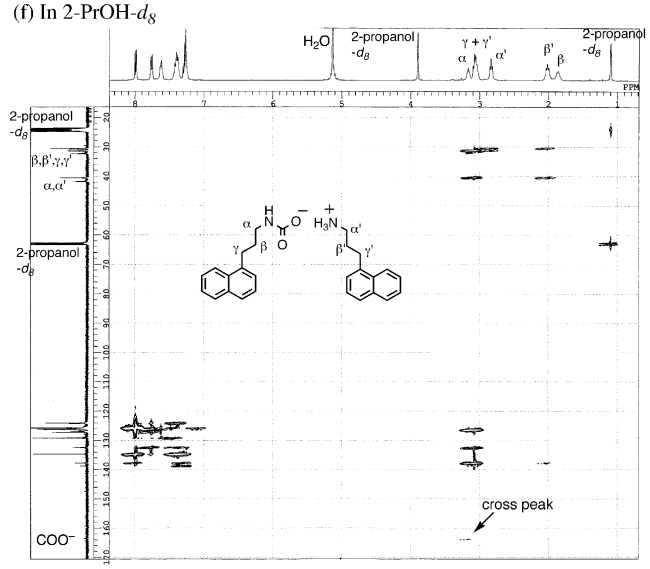
(e) In $CDCl_3$



The CO_2 gas was significantly lost during the storage before the HMBC measurement (compare with Figure 5). Therefore, a considerable amount of the free amine, which is undistinguishable from the ammonium species, is present.

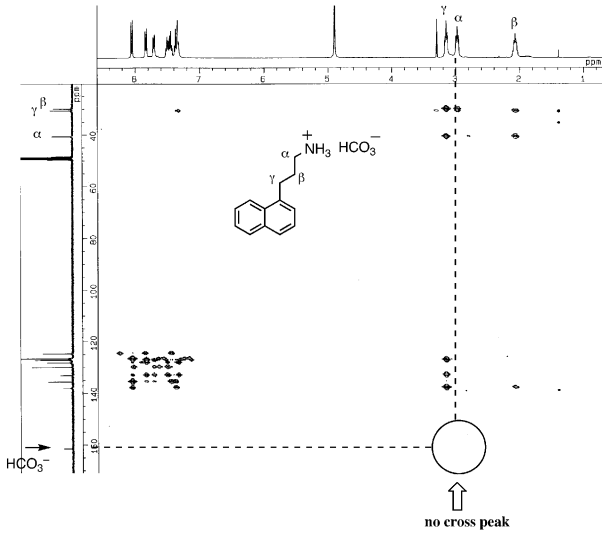
Figure 2. The HMBC spectra of **3** in a variety of solvents after CO_2 bubbling.

(f) In 2-PrOH-d_8



Some of the CO_2 gas escaped from the solution during the storage before the HMBC measurement (compare with Figure 6). Therefore, an excess of the free amine, which is undistinguishable from the ammonium species, is present.

(g) In methanol-d_4



Probably, some residual free amine coexists: see the IR spectra of Figure 4d.

Figure 2 (*continued*)

can clearly observe a broad band around 1575 cm^{-1}, being similar to that of **9** in KBr (Fig. 3(e)). From these spectral evidences, the carboxylated product is not the carbamic acid **6**, but the carbamate anion.

In MeOH-d_4, the downfield shift of the α-methylene protons by bubbling of CO_2 was relatively small ($\Delta\delta$ 0.29) and the ^{13}C NMR signal in the carboxy region appeared at 161.5 ppm. However, their correlation peak could not be observed in the HMBC spectrum (Fig. 2(g)). The IR spectrum showed strong bands at 1642 and 1310 cm^{-1} (Fig. 4(d)). These bands were also observed for Na_2CO_3 or $NaHCO_3$ suspended in MeOH or for the bicarbonate salt of DBU (=1,8-diazabicyclo[5.4.0]undec-7-ene)[11] in a KBr pellet or MeOH solution. Accordingly, the species that exists in the CO_2-saturated MeOH solution of **3** is almost doubtless a 3-(1-naphthyl)propylammonium bicarbonate or carbonate. It is well established that the bicarbonate formation is competitive with the carbamate formation in aqueous media, depending on pH.[5,8] In the present paper, all the experiments were done by using commercially available solvents without special precaution for drying them. Therefore, the bicarbonate could probably be formed by reaction with the contaminant water. In the case of amine **1** which reacts with CO_2 more rapidly than **2** or **3** (see Section 4), however, the corresponding ammonium carbamate **7** did precipitate from the MeOH solution upon bubbling of CO_2, as expected from the previously published results.[1f,1g]

Scheme 1 summarizes the effect of solvent changes on the reactions of **3** with CO_2. Virtually the same solvent dependence was observed for the amines **1** and **2**. As described below, many of these results may be rationalized by considering the acid–base reaction between amine and the corresponding carbamic acid (Eq. 2) in nonaqueous media.[12–15] It is known that the pK_a values of acids and bases are affected by the Brønsted/Lewis acid–base properties of the solvent (e.g., empirical parameters α and β or AN and DN), its dielectric constant (ε_r), and its solvation ability (Scheme 2).[12–14] As seen from consideration of the pK_a values in Table 1,[12] acetic acid AcOH is a stronger acid than butylammonium ion $BuNH_3^+$ in water or MeOH, that is, dipolar amphiprotic solvent. In sharp contrast, the opposite holds in DMSO, DMF or Py, that is, dipolar aprotic solvent. If the solvent influence on the acidity of carbamic acids is similar to that of carboxylic acids,[‖] this contrasting difference suggests that the equilibrium reaction **6**+**3**⇄**9** is in favor of carbamic acid **6** in DMSO, DMF or Py, while it is in favor of ammonium carbamate **9** in MeOH. As a result, since formation of the salt **9** is unfavorable in dipolar aprotic solvents, most of the amine **3** may be converted to **6** in the presence of CO_2, as was experimentally found (Scheme 1).[**]

Although MeCN is a dipolar aprotic solvent like DMSO, DMF and Py,[††] it is special in that (a) its hydrogen-bond acceptor basicity (β) is relatively poor and (b) considerable homoconjugation and heteroconjugation occur.[12,13,15] The first point is reflected on the large pK_a values of AcOH and $BuNH_2$ measured in MeCN (Table 1). As for the second point, since **9** precipitated from the MeCN solution (vide supra), it is probable that the relevant anion and cation are unusually stabilized in MeCN by the homo- and hetero-conjugation and they eventually combine, leading to the precipitation of **9**. Although dioxane is not polar in terms of the ε_r scale (Table 1), it is classified as a dipolar aprotic solvent due to its protophilicity.[††,12] A common feature of DMSO, DMF, Py, and dioxane is their high basicity and low

[‖] The pK_a for *p*-nitrophenylcarbamic acid is reported to be 4.2 in water,[8b] not very different from that of acetic acid (4.76) or benzoic acid (4.19).

[**] As distinct from the small K_2 value for the equilibrium **6**+**3**⇄**9** which is proposed here, the K_1 value for another equilibrium **3**+CO_2⇄**6** is presumably large in protophilic dipolar aprotic solvents (DMSO, DMF and Py), because **6** lasts pretty long in these solvents even under air (based on NMR in situ).

[††] According to the Kolthoff's review,[15] DMSO, DMF and Py as well as dioxane and THF are categorized as protophilic dipolar aprotic solvents, while MeCN is a protophobic dipolar aprotic solvent.

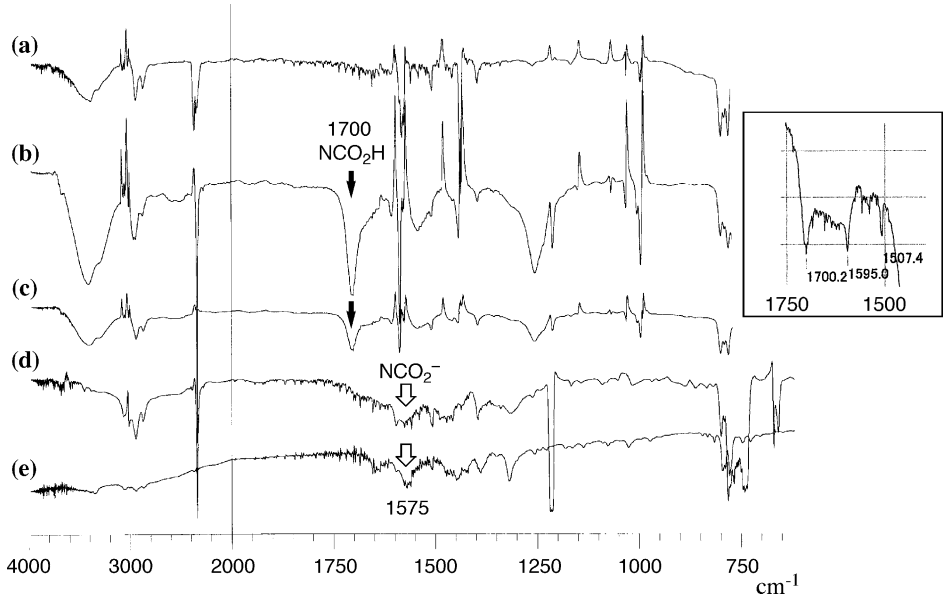
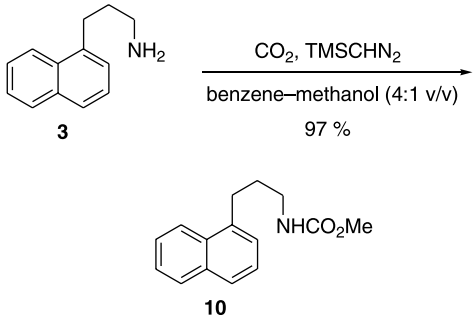


Figure 3. The IR spectra for (a) amine **3** in pyridine, (b) amine **3** in pyridine after CO_2 bubbling, that is, carbamic acid **6** in pyridine, (c) solid ammonium carbamate **9** dissolved in pyridine, (d) amine **3** in $CHCl_3$ after CO_2 bubbling, that is, ammonium carbamate **9** in $CHCl_3$, and (e) solid ammonium carbamate **9** in a KBr pellet (inset, solid ammonium carbamate **9** dissolved in DMSO). The backgrounds are pyridine for (a)–(c), $CHCl_3$ for (d), and air for (e) and inset.

acidity (Table 1). Hence, it does not seem strange that **6** was predominantly formed in dioxane. Also, it should be pointed out that CO_2 solubility in dioxane is relatively high (0.27 M, vide infra). The higher CO_2 concentration renders the free amine concentration lower and will shift the equilibrium of Eq. 2 to the left side. In apolar solvents like benzene, the ionic dissociation of acids is difficult but the salt formation with bases can nevertheless progress.[12] Therefore, formation of **9** in benzene is also not surprising.

Methoxycarbonylation of amine **3** into the carbamic acid methyl ester **10** was successfully accomplished by reaction with (trimethylsilyl)diazomethane in the presence of CO_2 (Eq. 3). $TMSCHN_2$ is a well-known reagent for preparation of methyl esters of carboxylic acids.[16] The reaction was virtually quantitative and complete in 20 min at room temperature. Like the carbamic acid **6**, the ester **10** showed an HMBC cross peak between the α-methylene protons and the carboxy carbon (Fig. 7). Solvent effects on this esterification reaction as well as application of this esterification method to other various amines are in progress.



3 **10** (3)

Quenching of arene fluorescence by amine donors via intramolecular electron transfer or exciplex formation is well studied.[17] Thus, we have measured the absorption and emission spectra of naphthylalkylamines **1**–**3** in a variety of solvents under Ar and CO_2.[6] Since the total amine concentrations are very low ($\sim 6\times10^{-5}$ M), precipitation of the ammonium carbamate was not visible in any solvent. The absorption spectra under Ar were found to remain unchanged by bubbling of CO_2. However, the intensity of fluorescence is expected to be affected by CO_2, provided that fluorescence quenching via intramolecular electron transfer (IET) from the amino group to the naphthalene moiety is the case. Table 1 (lines 7–9) shows the fluorescence intensity ratio between the CO_2-saturated solution and the Ar-saturated solution $I_F(CO_2)/I_F(Ar)$. Exciplex emission was not observed in all cases. The fluorescence intensity for **1**–**3** in DMSO solutions saturated with CO_2 was considerably stronger than that saturated with Ar, that is, $I_F(CO_2)/I_F(Ar)=$ 12.0 for **1**, 9.4 for **2**, and 3.6 for **3**. The fluorescence intensity for **1**–**3** in DMF solutions even more increased upon saturation with CO_2: $I_F(CO_2)/I_F(Ar)=50.0$, 15.3 and 8.2, respectively. A similar effect by CO_2 was recently reported for **1**.[7,18] In contrast, the ratio was not altered very much in dioxane, MeCN, benzene, $CHCl_3$, 2-PrOH, and MeOH, except small to medium increases for **1** in dioxane, MeCN, 2-PrOH and MeOH where $I_F(CO_2)/I_F(Ar)=1.3$, 1.6, 1.9 and 2.9, respectively (Table 1). Unfortunately, the fluorescence spectra in Py could not be measured because the absorption end of Py overshadowed the naphthyl group absorption.

The aforementioned remarkable increases in the fluorescence intensity upon saturation with CO_2 (observed for **1**–**3** in DMSO and DMF and for **1** in MeCN, 2-PrOH and MeOH) are completely unrelated with CO_2 solubility: the concentration of CO_2 is 0.13, 0.21, 0.15, 0.27, 0.32, 0.11, 0.14, 0.11 and 0.15 M in DMSO, DMF, Py, dioxane, MeCN, benzene, $CHCl_3$, 1-PrOH and MeOH, respectively, at 25 °C and 1 atm.[19] Instead, these increases may be ascribed to two reactions: (a) the carbamic acid formation in DMSO, DMF, MeCN, 2-PrOH and MeOH and (b) the bicarbonate/carbonate formation in MeOH. This inference is reasonable, because the lone pair on the nitrogen atom becomes hard to use for the IET quenching when the amino group is carboxylated or protonated. These situations are illustrated

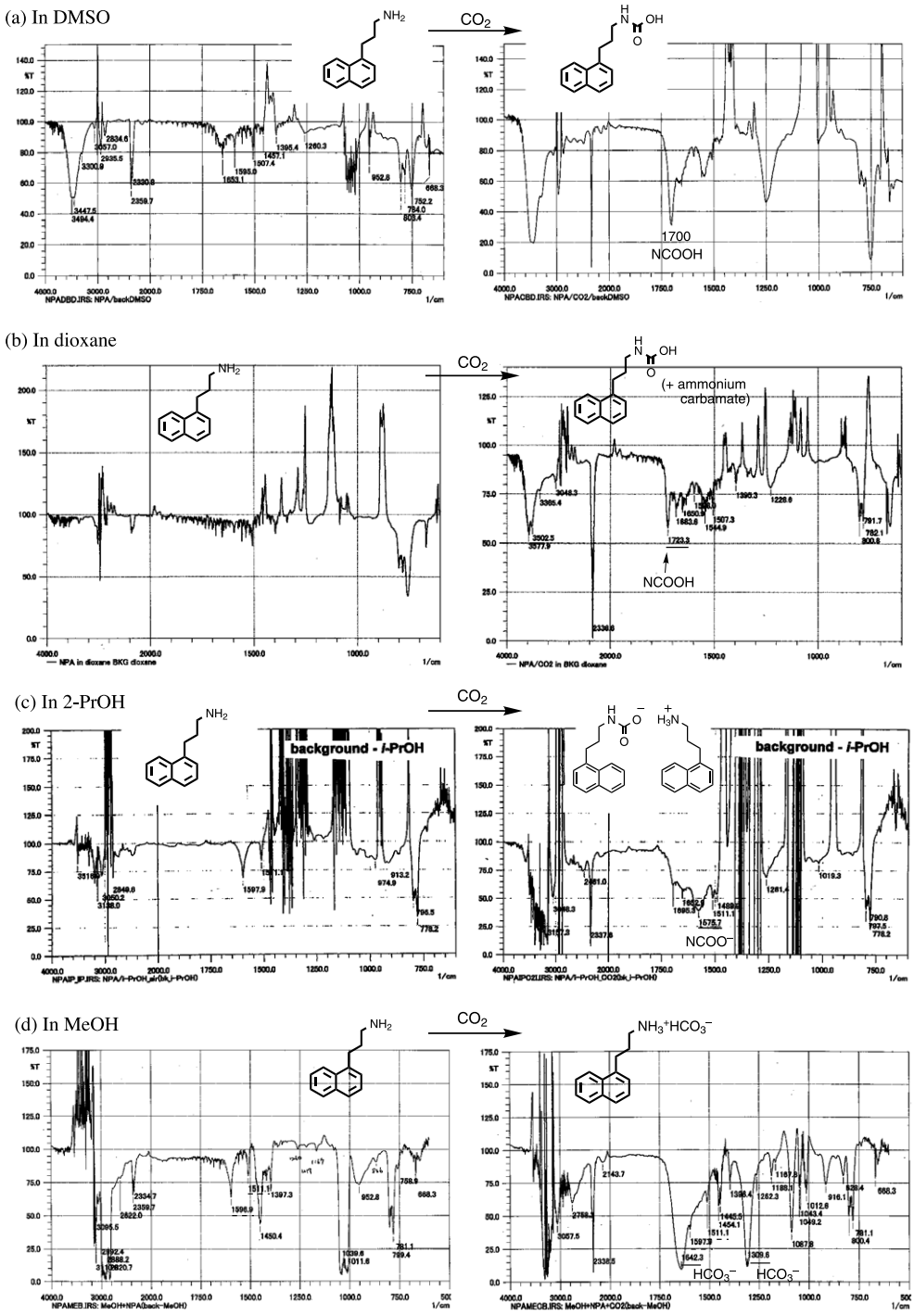


Figure 4. The IR spectra of **3** in DMSO, dioxane, 2-PrOH, or MeOH before and after CO_2 bubbling.

in Scheme 3. It is notable in Table 1 that the $I_F(CO_2)/I_F(Ar)$ values for **1** in DMSO (12) and DMF (50) are much larger than those in MeCN, 2-PrOH and MeOH (1.6–2.9). Probably, this difference partly originates in the fact that carbamic acid **4** is formed in DMSO or DMF whereas ammonium carbamate **7** is formed in MeCN, 2-PrOH or MeOH (compare B(i) and B(iii) in Scheme 3). The electron withdrawing property of the dissociated carboxyl group (COO^-) (the Hammett substituent constants σ-*meta* = −0.1, σ-*para* = 0.0) should be much smaller as comrared with the undissociated carboxyl group (COOH) (σ-*meta* = 0.37, σ-*para* = 0.45). Thereby, the IET quenching by $NHCOO^-$ may be much more efficient than by NHCOOH, leading to the stronger fluorescence emission from **4** than from **7**.

At this stage, it must be mentioned that, in those cases where $I_F(CO_2)/I_F(Ar) \approx 1$ as found for **2** and **3** in dioxane, MeCN, benzene, $CHCl_3$, 2-PrOH and MeOH and for **1** in benzene and $CHCl_3$ (Table 1), the occurrence of the IET event is

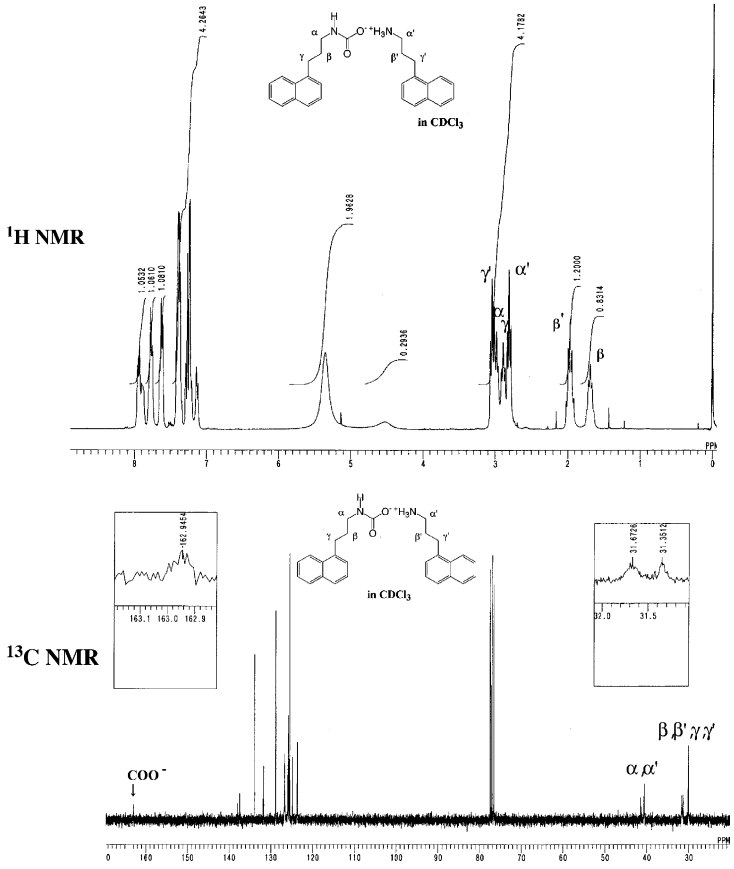


Figure 5. The ^{1}H and ^{13}C NMR spectra of **3** in $CDCl_3$ after CO_2 bubbling.

probably negligible even under Ar.[‡‡] In order to fully understand the fluorescence data in Table 1, quantitative data about the K_1 and K_2 values (Eqs. 1 and 2) and about the IET quenching efficiencies in various solvents are required. As a whole, however, the results of the present fluorescence study are well in line with those obtained from the NMR and IR studies, as schematically depicted in Scheme 3.

3. Conclusion

On the basis of the NMR and IR studies coupled with the fluorescence study, we conclude that bubbling of CO_2 through the solutions of naphthylalkylamines **1**–**3** in protophilic, highly dipolar, aprotic solvent (DMSO, DMF or pyridine) produces quantitatively the undissociated carbamic acids **4**–**6**. In dioxane (protophilic, dipolar, aprotic solvent), the carbamic acid and a minor amount of the ammonium carbamate are formed. By contrast, in MeCN (protophobic, dipolar, aprotic solvent), benzene or $CHCl_3$ (apolar aprotic solvent), and 2-PrOH or MeOH (dipolar amphiprotic solvent), the ammonium carbamates **7**–**9** are formed rather than **4**–**6**. It appears that these results can be well understood by considering the solvent effect on the acid–base reaction between amine (**1**–**3**) and carbamic acid (**4**–**6**). For more complete understanding, however, further information about K_1, K_2, the solubility of ammonium carbamate, and the IET quenching efficiency will be required. Carbamic acids are involved in various biological phenomena, for example, the CO_2 fixation by Rubisco or biotin,[20a,b] the CO_2 transport by hemoglobin,[20c] the urea cycle,[20d] and the neurotoxicity and chemical signaling.[20e] Therefore, the question as to whether the carboxyl group in the molecule is dissociated or undissociated will be physiologically an important matter. Recent studies on reversible organogels based on reversible uptake of CO_2[3b,c] may as well take into account such a solvent effect. Although the intermediacy of carbamic acid is not demonstrated, dipolar aprotic solvents are solvent of choice in many CO_2-fixation reactions through amines.[21] Aqueous solutions of amino alcohols are often employed for absorbing CO_2 from industrial gases, usually as bicarbonates rather than carbamates.[9,3a] Therefore, the present paper should be fundamental to these various aspects of mechanistic, biological and industrial interests.

[‡‡] On the basis of the Rehm–Weller equation, the estimated free energy for electron transfer from propylamine to naphthalene singlet or exciplex formation is 0.03 eV in MeCN, slightly endergonic ($\Delta G_{et}=E(D^+/D)-E(A/A^-)-E_{0,0}+\Delta E_{coul}=1.59-(-2.49)-3.99+(-0.06)=$ 0.03 eV).[17a] Therefore, the electron transfer will not be very efficient. The IET efficiency depends not only on ΔG_{et} but also on the solvent polarity and the relative geometry (configuration and distance) between the donor (D) and the acceptor (A).[17] As can be judged by the relative I_F(Ar) values (Table 1, lines 10–12), the quenching efficiency through IET is higher for **1** as compared with **2** and **3**, where I_F(Ar) is the fluorescence intensity of the Ar-saturated solution. This is expected, since **1** is a D–A system connected by the shortest polymethylene chain ($n=1$). For this kind of the system, IET is expected to occur in ethers and more polar solvents but not in nonpolar solvents.[17b]

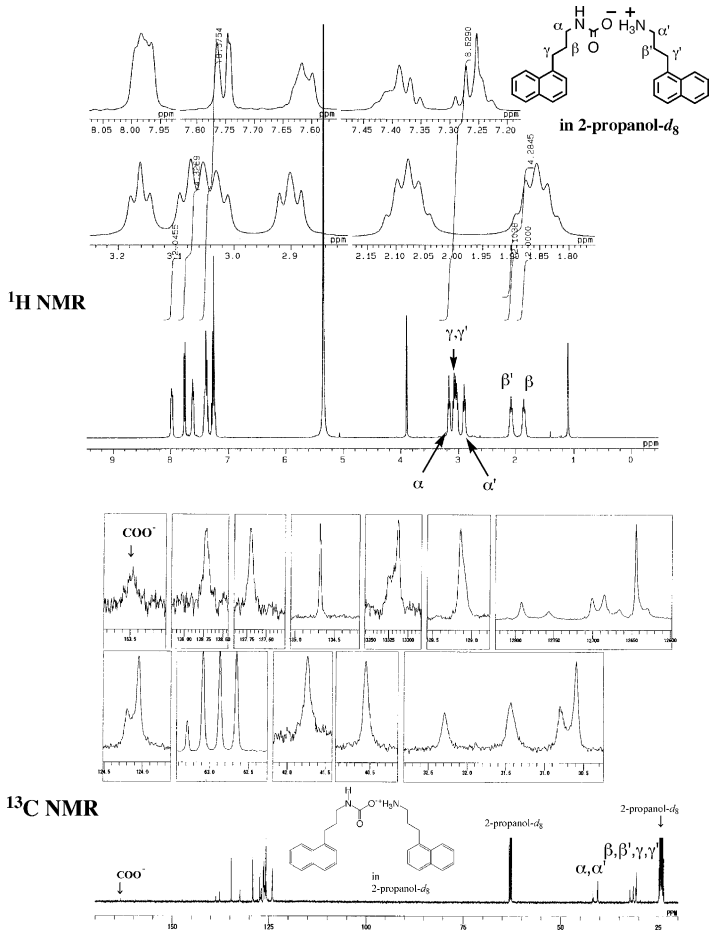
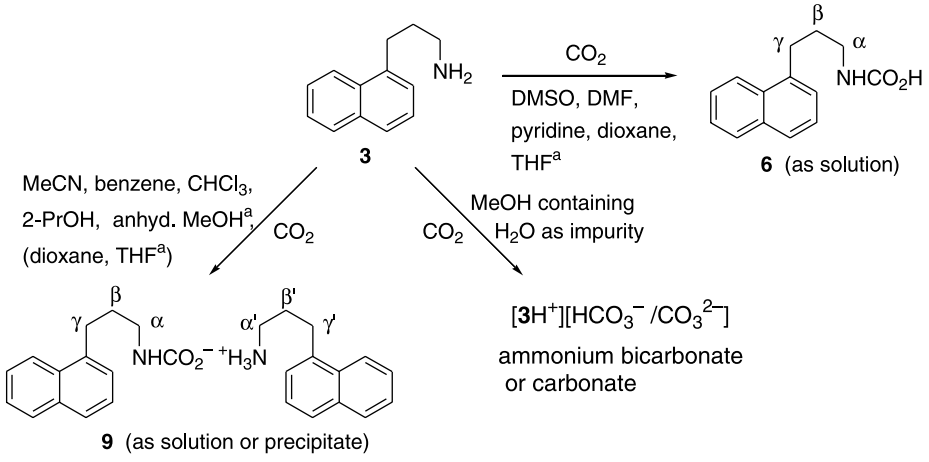


Figure 6. The ^{1}H and ^{13}C NMR spectra of **3** in 2-PrOH-d_8 after CO_2 bubbling.



[a]Not confirmed for amine 3.

Scheme 1.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were measured on a JEOL EX-270J, GSX-270, or AL-300 spectrometer. Measurements of 2D NMR were carried out with JEOL JUM-A400. Mass, IR, and absorption spectra were recorded on JEOL JMS-HX 110A, SHIMADZU FTIR-8400, and SHIMADZU UV-2400PC spectrometers, respectively. Fluorescence spectra were gathered with a SHIMADZU RF-5300PC spectrometer and excited at the absorption maximum (280–285 nm). Melting points were measured on a YANACO MP-S3 microscopic hot-stage and are uncorrected.

CO_2 gas (99.99%) was purchased from Ekika Tansan Co., Inc. All the solvents we employed (deuterated solvents, spectroscopic grade solvents, and dehydrated or anhydrous

$$HA + SH \rightleftharpoons SH_2^+ + A^- \qquad K_a = \gamma^2[SH_2^+][A^-]/[HA]$$

$$BH^+ + SH \rightleftharpoons SH_2^+ + B \qquad K_a = [SH_2^+][B]/[BH^+]$$

(HA: acid, B: base, SH: solvent)

The pK_a values of acids and bases are affected by the acidity or basicity of the solvent (e.g., α and β or AN and DN), its dielectric constant (ε_r), and its ability to solvate the species HA, A^-, BH^+, and B.

Scheme 2. The acid–base equilibria in a solvent (SH)[12–14].

solvents) are commercially available (from Aldrich, Sigma-Aldrich, Wako, Dojin, or Nakarai Tesque) and were used as received. The IR experiments were carried out by using dehydrated or anhydrous solvents and the absorption and fluorescence experiments by using spectroscopic grade solvents. The amine concentrations are 0.13–0.15 M for the NMR and IR measurements and $5.9–6.7\times10^{-5}$ M for the absorption and fluorescence ones. The CO_2 or Ar gas was introduced into a solution of amine through a needle. The bubbling was continued for 0.5–1 h at room temperature. After the bubbling, the tube or cell was tightly closed and the spectra were measured.

The IR spectra were taken with the background of either air or the respective solvent. In Figures 3 and 4, only the latter spectra are shown, unless otherwise specified. The original data of the fluorescence spectra are collected in Figures 8–10.

4.2. (1-Naphthyl)methylamine (1), 2-(1-naphthyl)-ethylamine (2) and 3-(1-naphthyl)propylamine (3)

These are known compounds. Commercial amine **1** was used. Amine **2** was prepared according to the literature

Table 1. Values of solvent dielectric constant ε_r, basicity β and acidity α,[a] solvent influence on the acidity constant K_a for acetic acid and butylamine,[b] and solvent dependence of the fluorescence intensity ratio $I_F(CO_2)/I_F(Ar)$ and the relative fluorescence intensity $I_F(Ar)$ for compounds **1–3**[c]

	DMSO	DMF	Py	Dioxane	MeCN	Benzene	$CHCl_3$	2-PrOH	MeOH	H_2O
ε_r	46.45	36.71	12.91	2.21	35.94	2.27	4.89	19.92	32.66	78.36
β	0.76	0.69	0.64	0.37	0.31	0.10	0.10	0.84	0.66	0.47
α	0.00	0.00	0.00	0.00	0.19	0.00	0.20	0.76	0.98	1.17
pK_a (AcOH)	12.6	13.5	10.1	—	22.3	—	—	—	9.7	4.76
pK_a ($BuNH_2$)	11.1	10.5	5.5	—	18.3	—	—	—	11.8	10.64
$\frac{I_F(CO_2)}{I_F(Ar)}$ **1**	12.0	50.0[d]	—	1.3[e]	1.6	1.0	1.0	1.9	2.9	—
2	9.4	15.3	—	1.2	1.0	1.0	1.0	1.0	1.0	—
3	3.6	8.2	—	1.1	1.2	1.1	1.0	1.0	1.0	—
relative $I_F(Ar)$ **1**	0.24	0.041	—	1.5	0.84	2.1	0.33	1.0	1.1	—
2	0.39	0.20	—	2.3	3.7	3.7	0.39	3.5	3.5	—
3	1.00[f]	0.45	—	2.7	2.9	3.4	0.35	3.2	3.5	—

[a] A β scale is a measure of the solvent hydrogen-bond acceptor (HBA) basicity, while an α scale is a measure of the solvent hydrogen-bond donor (HBD) acidity.[14] The values for the related solvent scales, donor number (DN) and acceptor number (AN), respectively, can also be derived from the same source.[14]
[b] Ref. 12.
[c] $I_F(Ar)$ and $I_F(CO_2)$ are the fluorescence intensities for the Ar-saturated and the CO_2-saturated solutions, respectively.
[d] >10 (Ref. 7).
[e] 1.5 (Ref. 18).
[f] Relative $I_F(Ar)$ for **3** in DMSO=1.00 as the reference.

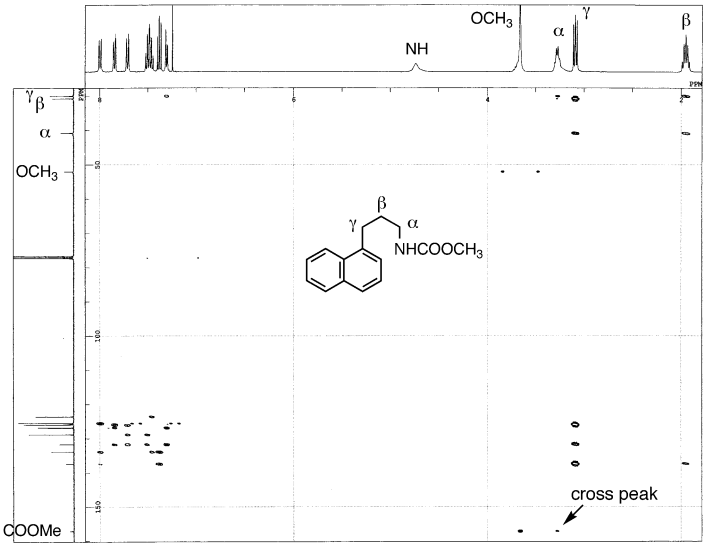
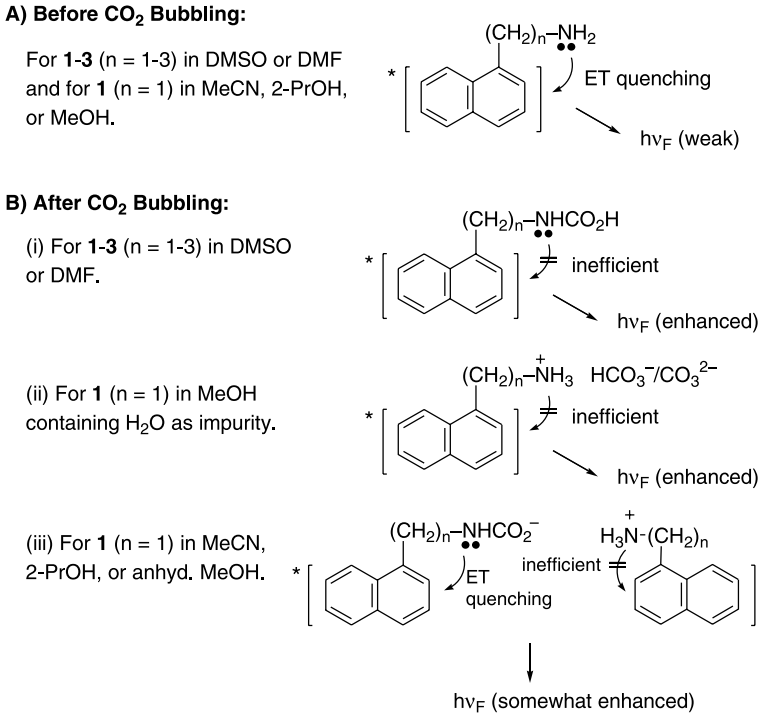


Figure 7. The HMBC spectrum for methyl 3-(1-naphthyl)propylcarbamate (**10**) in $CDCl_3$.



Scheme 3.

methods.[22] The preparation method for amine **3** was modified as outlined in Scheme 4. The spectral data were in accordance with those of the literatures: **11**,[23] **12**,[23b,24] **3**.[25]

4.2.1. Compound 2. Colorless oil, bp 136 °C (bath temperature) at 0.6 mm Hg ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.10 (1H, d, J=7.9 Hz), 7.89 (1H, finely split d, J=7.3 Hz), 7.75 (1H, d, J=7.9 Hz), 7.56–7.33 (4H, m), 3.11 (2H, t, J=7.4 Hz), 2.84 (2H, t, J=7.4 Hz); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 136.39, 133.31, 131.48, 128.38, 126.32, 126.26, 125.70, 125.42, 125.36, 123.73, 43.28, 37.16; MS (EI) m/z 171 (M^+, 14), 142 (100), 141 (42), 115 (34); HRMS (EI) calcd for $C_{12}H_{13}N$ 171.1048, found 171.1045.

4.2.2. Preparation of 3. A mixture of 1-naphthaldehyde (21.02 g, 0.136 mol), cyanoacetic acid (13.72 g, 0.161 mol) and morpholine (14 mL, 0.161 mol) in 120 mL of DMF was stirred at room temperature for 15 min. The stirring was continued at reflux for 5 h. After being left overnight, the reaction mixture was rotary-evaporated and the residue was distilled at 135 °C (bath temperature)/0.5 mm Hg to afford 10.80 g (0.0603 mol, 45% yield) of an *E*/*Z* mixture of 3-(1-naphthyl)acrylonitrile (**11**) (*E*/*Z* ratio=7:3 from NMR). This mixture, which solidified on standing, was recrystallized from MeOH to give 8.21 g (0.0458 mol, 34% yield) of (*E*)-**11** as pale yellow needles: mp 72–75 °C. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.24 (1H, d, J=16.3 Hz), 8.07–7.85 (3H, m), 7.69–7.47 (4H, m), 5.97 (1H, d, J=16.4 Hz); MS (EI) m/z 179 (M^+, 100), 178 (73), 152 (30), 151 (26); HRMS (EI) calcd for $C_{13}H_9N$ 179.0735, found 179.0734.

An *E*/*Z* mixture of **11** (5.47 g, 0.0305 mol) was dissolved in 56 mL of MeOH (predried with Molecular Sieves 3A)-distilled pyridine (1: 3 v/v). Then, 1.71 g (0.0452 mol) of $NaBH_4$ was added by portions with stirring. After refluxing for 2 h, the mixture was allowed to cool to room temperature and then poured into 100 mL of 10% aqueous HCl. The oily layer separated and it was taken up with 60 mL of ether. The ethereal layer was rotary-evaporated to afford 4.54 g (0.0251 mol, 82% yield) of crude 3-(1-naphthyl)propionitrile (**12**) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.95–7.76 (3H, m), 7.57–7.33 (4H, m), 3.41 (2H, t, J=7.5 Hz), 2.73 (2H, t, J=7.5 Hz).

A stirred solution containing 4.16 g (0.110 mol) of $LiAlH_4$ in 50 mL of dry THF was cooled in an ice bath. To this solution, a solution containing 4.54 g (0.0251 mol) of crude **12** in 20 mL of dry THF was added dropwise over a period of 15 min. The stirring was continued at reflux for 2 h, then at room temperature for 20 h. After quenching excess $LiAlH_4$ by careful addition of EtOH–water (1: 1 v/v), the mixture was filtered and the residue was washed with ether. The filtrate and the washings were combined and rotary-evaporated to afford a yellow oil. This yellow oil was treated with a mixture of 1 M aqueous HCl (100 mL) and EtOH (30 mL) at 90 °C for 1 h and an insoluble part of the oil was removed by extraction with ether (100 mL). The aqueous layer was rotary-evaporated and the resultant solid was washed with ether. 3-(1-Naphthyl)propylamine hydrochloride was obtained as a white solid: yield 1.38 g (0.0062 mol, 25%).

The above salt was dissolved in 150 mL of water and made alkaline (pH 14) with 1 M aqueous NaOH. Extraction with ether (40 mL×3), drying the ethereal layer with Na_2SO_4, and rotary-evaporation, followed by distillation at 133 °C (bath temperature)/0.5 mm Hg, afforded 0.404 g

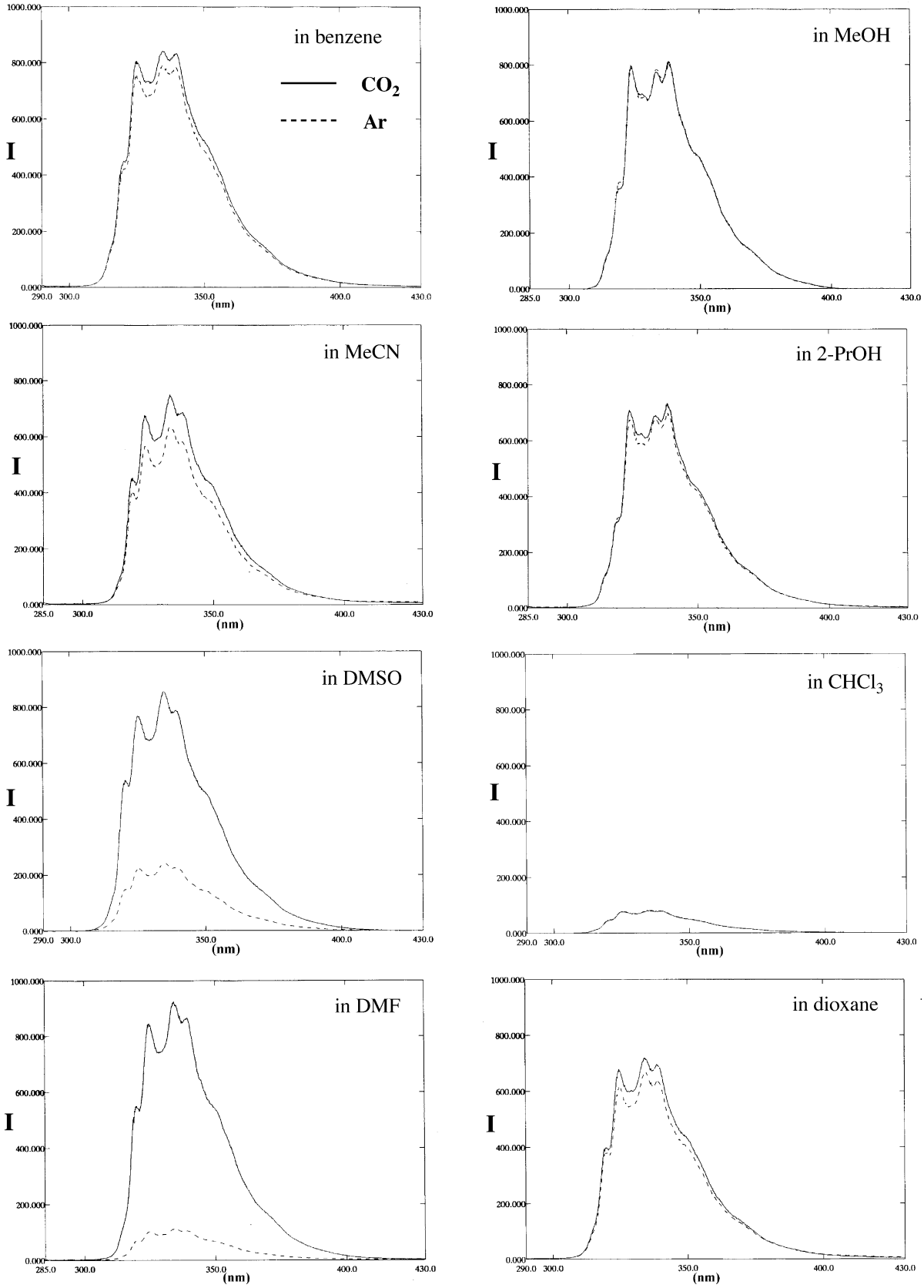


Figure 8. The fluorescence spectra for the CO_2-saturated and the Ar-saturated solutions of 3-(1-naphthyl)propylamine (**3**).

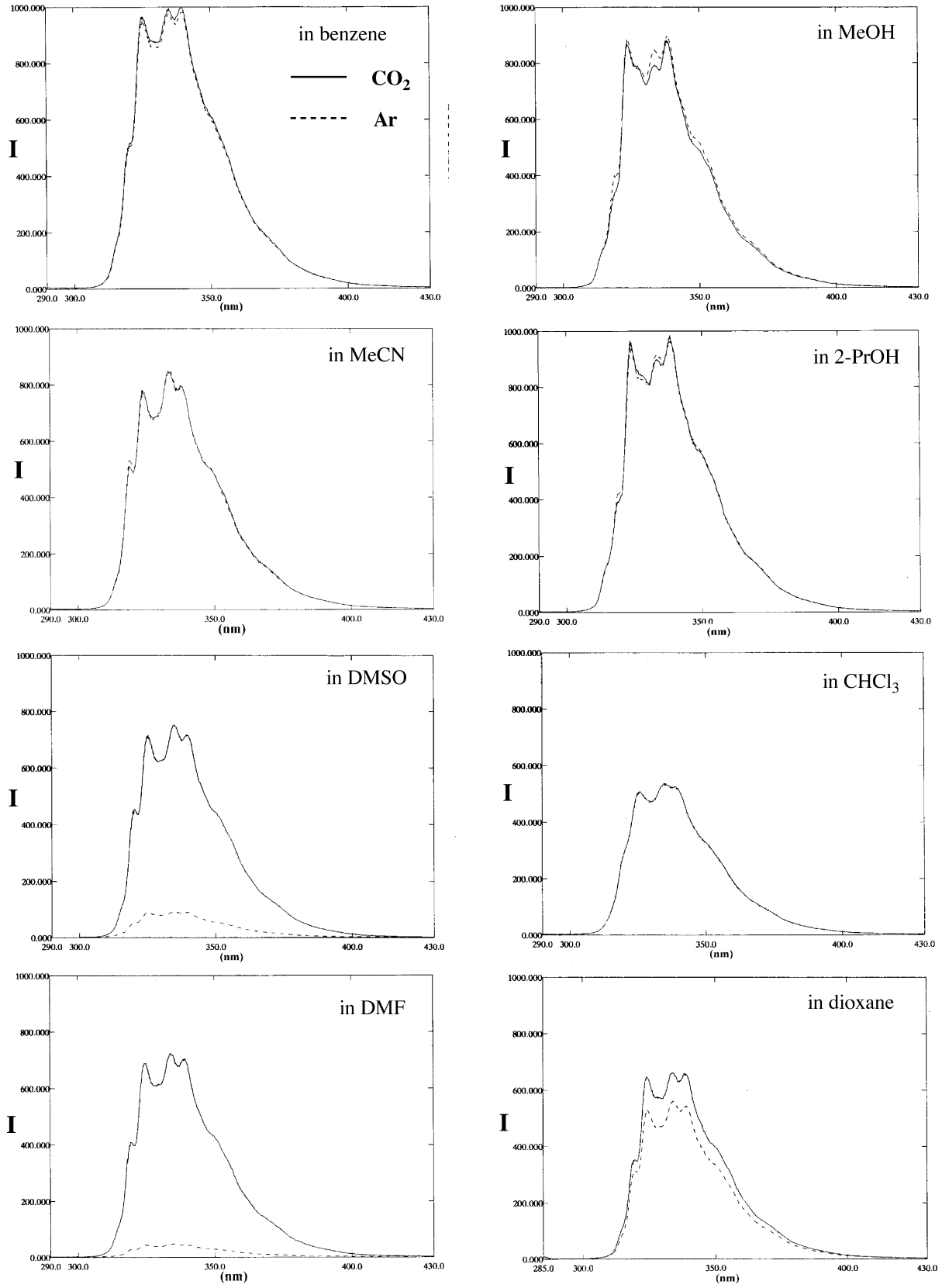


Figure 9. The fluorescence spectra for the CO_2-saturated and the Ar-saturated solutions of 2-(1-naphthyl)ethylamine (**2**).

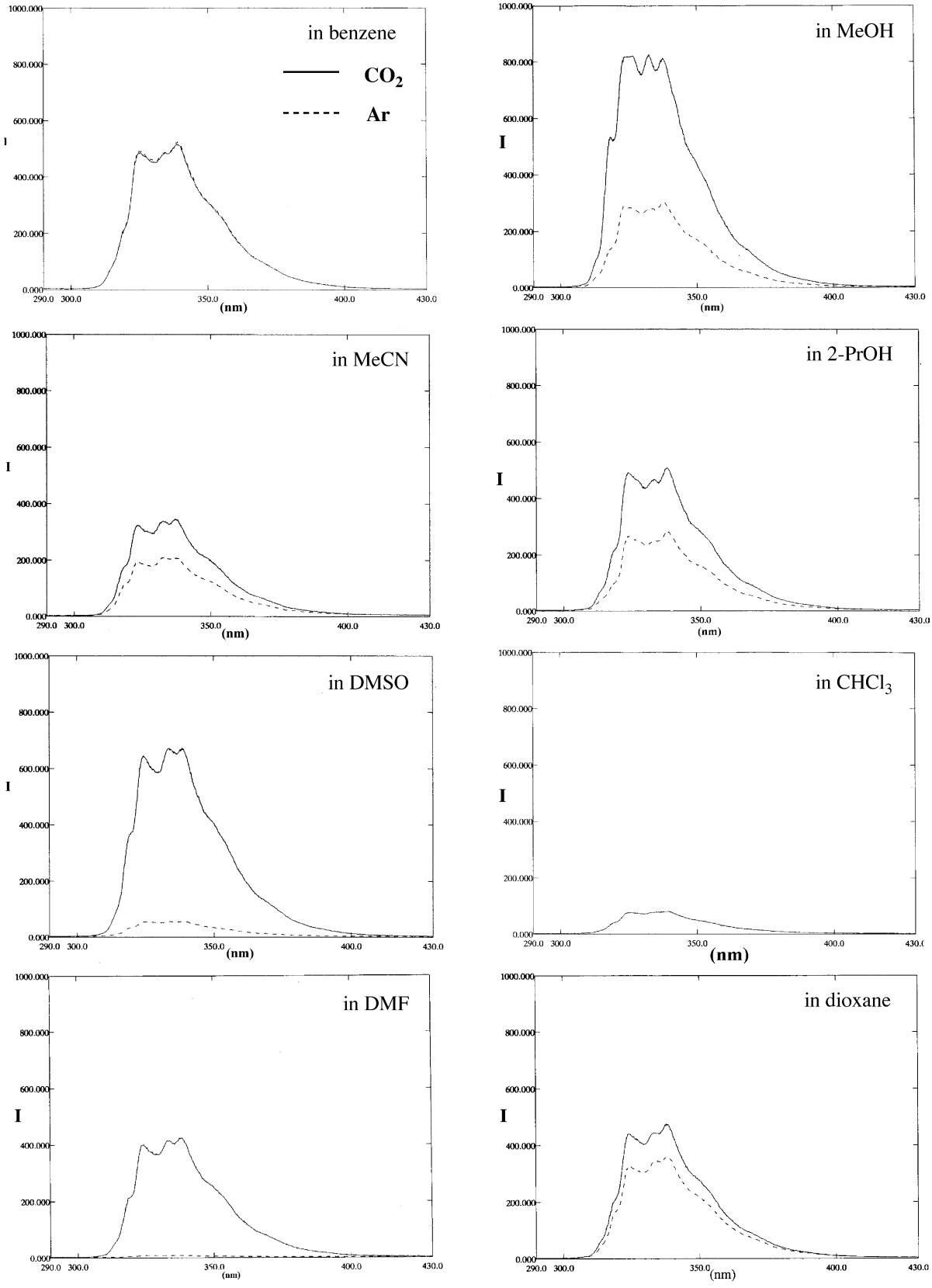
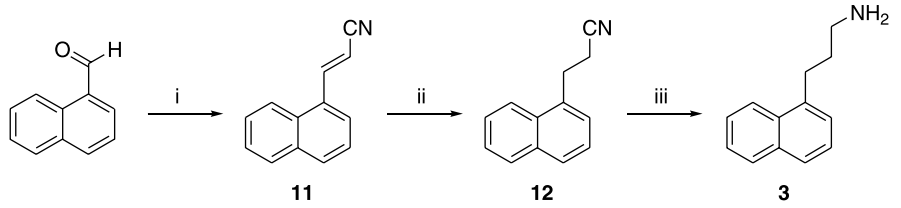


Figure 10. The fluorescence spectra for the CO_2-saturated and the Ar-saturated solutions of (1-naphthyl)methylamine (**1**).



Scheme 4. Reagents and conditions: (i) DMF, cyanoacetic acid, morpholine, reflux; (ii) MeOH, $NaBH_4$, pyridine; (iii) THF, $LiAlH_4$.

(0.0022 mol, 36%) of 3-(1-naphthyl)propylamine (**3**) as a colorless oil. ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.08 (1H, d, J=7.9 Hz), 7.89 (1H, d, J=7.3 Hz), 7.74 (1H, d, J=7.9 Hz), 7.32–7.56 (m, 4H), 3.05 (2H, t, J=7.8 Hz), 2.62 (2H, t, J=6.8 Hz), 1.72 (2H, m); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 138.55, 133.44, 131.38, 128.52, 126.18, 125.95, 125.79, 125.55, 125.45, 123.81, 41.53, 34.70, 29.71; MS (EI) m/z 185 (M^+, 40), 168 (100), 153 (87), 142 (54), 141 (54), 115 (41); HRMS (EI) calcd for $C_{13}H_{15}N$ 185.1204, found 185.1204.

Viscous oils of amines **1**–**3** reacted with CO_2 in the air, changing into a white solid of the corresponding ammonium carbamate, **7**–**9**, respectively. The solidification was rapid for **1** and was relatively slow for **2** and **3**, indicating that **1** reacts with CO_2 more efficiently.

4.3. Selected spectral data for ω-(1-naphthyl)alkylcarbamic acids 4–6

These carbamic acids were quantitatively generated by bubbling of CO_2 through the solutions of amines **1**–**3** in DMSO, DMF, or pyridine at room temperature for 0.5–1 h. Without delay after the CO_2 bubbling, their NMR, IR, absorption, and fluorescence spectra were directly measured. Evaporation of the solvent resulted in reversion to the original amine. Selected spectral data for **4**–**6** are as follows.

4.3.1. (1-Naphthyl)methylcarbamic acid (4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (1H, dd, J=7.1, 2.0 Hz), 7.93 (1H, dd, J=10.4, 2.4 Hz), 7.82 (1H, d, J=7.9 Hz), 7.58–7.33 (4H, m), 7.35 (1H, t, J=6.0 Hz), 4.61 (2H, d, J=6.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.18, 135.37, 133.28, 130.78, 128.49, 127.33, 126.12, 125.72, 125.43, 124.84, 123.43, 41.77; IR (DMSO) 3500–3100 (br, s), 1700 (s), 1545 (m), 1245 (br, s) cm^{-1}.

4.3.2. 2-(1-Naphthyl)ethylcarbamic acid (5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (1H, d, J=8.4 Hz), 7.90 (1H, dd, J=8.6, 1.5 Hz), 7.77 (1H, d, J=8.1 Hz), 7.57–7.48 (2H, m), 7.44–7.34 (2H, m), 6.85 (1H, br t, J=6 Hz), 3.30–3.23 (2H, m), 3.21–3.14 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.11, 135.50, 133.42, 131.58, 128.52, 126.67, 126.52, 125.97, 125.55, 125.53, 123.62, 41.31, 33.09; IR (DMSO) 3500–3100 (br, s), 1702 (s), 1544 (m), 1246 (br, m) cm^{-1}.

4.3.3. 3-(1-Naphthyl)propylcarbamic acid (6). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (1H, d, J=8.1 Hz), 7.89 (1H, dd, J=7.7, 1.6 Hz), 7.75 (1H, d, J=8.1 Hz), 7.55–7.47 (2H, m), 7.42–7.35 (2H, m), 6.81 (1H, br t, J=6 Hz), 3.08–3.00 (4H, m), 1.79 (2H, quin, J=7.3 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.30, 137.92, 133.41, 131.28, 128.48, 126.28, 125.79, 125.50, 125.43, 123.60, 40.10, 30.77, 29.50; IR (DMSO) 3600–3200 (br, s), 1700 (s), 1545 (br, m), 1250 (br, s) cm^{-1}.

4.4. Isolation of ω-(1-naphthyl)alkylammonium ω-(1-naphthyl)alkylcarbamates 7–9

Pure ammonium carbamates **7**, **8**, and **9** precipitated as a white solid upon bubbling of CO_2 through the solutions of **1** (in $CHCl_3$, MeCN, benzene, or 2-PrOH), **2** (in $CHCl_3$, MeCN, or benzene), and **3** (in MeCN or benzene), respectively. These were collected by filtration and were dried in vacuo at room temperature.

4.4.1. Compound 7. Mp 72.5–76 °C. ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.11 (2H, br), 7.92 (2H, m), 7.79 (2H, d, J=7.6 Hz), 7.57–7.43 (8H, m), 7.32 (1H, br t, J=5.8 Hz, carbamic NH), 4.61 (2H, d, J=5.8 Hz, carbamic α-CH_2), 4.21 (2H, s, free amine α-CH_2); ^{13}C NMR (67.7 MHz, DMSO-d_6) δ 157.60, 138.61, 135.50, 133.09, 130.73, 128.29, 127.07, 126.74, 125.91, 125.78, 125.53, 125.45, 125.38, 125.26, 124.64, 124.27, 123.39, 123.33, 42.64, 41.83; IR (KBr) 3314 (m), 3100–2000 (br s), 1611 (s, RNH_3^+), 1577 (m, $NCOO^-$), 1540 (m), 1499 (vs), 1465 (m), 1375 (br m), 1350 (s), 1286 (vs) cm^{-1}. Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82%. Found: C, 77.22; H, 6.26; N, 7.76%.

4.4.2. Compound 8. Mp 74–77.5 °C. ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.14 (2H, br), 7.90 (2H, m), 7.76 (2H, d, J=7.8 Hz), 7.56–7.34 (8H, m), 6.82 (1H, br, carbamic NH), 3.23–3.13 (6H, m), 2.88 (2H, br, free amine α-CH_2); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 158.07, 135.80, 133.26, 131.41, 128.37, 126.43, 126.36, 125.78, 125.42, 125.39, 123.62, 42.59, 41.61, 35.95, 33.41; IR (KBr) 3284 (m), 3100–2000 (br s), 1642 (m), 1577 (s, $NCOO^-$), 1469 (s), 1433 (m), 1395 (m), 1353 (m), 1334 (s) cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25%. Found: C, 77.73; H, 6.76; N, 7.20%.

4.4.3. Compound 9. Mp 65–69 °C. ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.10 (2H, br), 7.91 (2H, m), 7.76 (2H, d, J=7.7 Hz), 7.57–7.35 (8H, m), 6.83 (1H, br, carbamic NH), 3.05 (6H, br), 2.66 (2H, br t, J=6.7 Hz, free amine α-CH_2), 1.78 (4H, br); ^{13}C NMR (67.7 MHz, DMSO-d_6) δ 157.50, 138.07, 137.78, 133.18, 131.08, 128.29, 126.03, 125.59, 125.32, 125.24, 123.53, 40.99, 33.71, 30.81, 29.49; IR (KBr) 3344 (w), 3100–2000 (br), 1642 (m), 1570 (s br, $NCOO^-$), 1448 (s br), 1387 (m), 1318 (s) cm^{-1}. Anal. Calcd for $(\mathbf{9})_{1.0}(H_2O)_{0.3}$: C, 77.22; H, 7.34; N, 6.67%. Found: C, 77.31; H, 7.34; N, 6.67%.

4.4.4. Isolation of methyl 3-(1-naphthyl)propylcarbamate (10). Through a 5 mL methanolic benzene solution (benzene–MeOH 4:1 v/v) containing 73 mg (0.393 mmol) of amine **3** was bubbled CO_2 gas for 15 min. Into this solution was added 0.5 mL (1.0 mmol) of (trimethylsilyl)-diazomethane (Aldrich 2.0 M solution in hexanes) at room temperature with both stirring and CO_2 bubbling. The yellow color of $TMSCHN_2$ disappeared in 20 min. The mixture was stirred for additional 2 h under CO_2 bubbling. Then, it was rotary-evaporated to afford 93 mg of a colorless viscous oil, which was almost pure methyl 3-(1-naphthyl)-propylcarbamate (**10**) containing only a trace of **3** from the NMR analysis. Further purification was carried out by preparative TLC on silica gel ($CHCl_3$–MeOH 20:1 v/v) to give 93 mg (97% yield) of **10** as a colorless viscous oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, d, $J=8.2$ Hz), 7.85 (1H, dd, $J=8$, 1.7 Hz), 7.71 (1H, d, $J=8.1$ Hz), 7.53–7.44 (2H, m), 7.38 (1H, t, $J=7.6$ Hz), 7.31 (1H, d, $J=7$ Hz), 4.74 (1H, br s), 3.67 (3H, s), 3.28 (2H, quar, $J=6.5$ Hz), 3.10 (2H, t, $J=7.6$ Hz), 1.96 (2H, quin, $J=7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.13, 137.44, 133.91, 131.72, 128.84, 126.83, 125.97, 125.88, 125.53, 125.52, 123.58, 52.06, 40.95, 30.88, 30.11; IR (neat) 3336 (m), 1705 (br, s), 1538 (br, s), 1258 (s), 778 (s) cm^{-1}; MS (FAB^+) *m/z* 244 (MH^+, 100), 243 (M^+, 58), 212 (13), 168 (21); HRMS (FAB^+) calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1259.

References and notes

1. (a) Fichter, F.; Becker, B. *Chem. Ber.* **1911**, *44*, 3473–3480; see also pp 3481–3485. (b) Werner, E. A. *J. Chem. Soc.* **1920**, *117*, 1046–1053. (c) Hayashi, T. *Bull. Inst. Phys. Chem. Res. (Tokyo)* **1932**, *11*, 1391–1460. (d) Frankel, M.; Katchalski, E. *J. Am. Chem. Soc.* **1943**, *65*, 1670–1674. (e) Wright, H. B.; Moore, M. B. *J. Am. Chem. Soc.* **1948**, *70*, 3865–3866. (f) Wolfe, J. K.; Temple, K. L. *J. Am. Chem. Soc.* **1948**, *70*, 1414–1416. (g) Katchalski, E.; Berliner-Klibanski, C.; Berger, A. *J. Am. Chem. Soc.* **1951**, *73*, 1829–1831. (h) Gaines, G. L., Jr. *J. Org. Chem.* **1985**, *50*, 410–411.
2. Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515–1530.
3. (a) Bates, E. D.; Mayton, R. D.; Ntai, I.; Davis, J. H., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 926–927. (b) George, M.; Weiss, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 10393–10394. (c) Carretti, E.; Dei, L.; Baglioni, P.; Weiss, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 5121–5129. (d) Schimming, V.; Hoelger, C.-G.; Buntkowsky, G.; Sack, I.; Fuhrhop, J.-H.; Rocchetti, S.; Limbach, H.-H. *J. Am. Chem. Soc.* **1999**, *121*, 4892–4893.
4. Aresta, M.; Ballivet-Tkatchenko, D.; Dell'Amico, D. B.; Bonnet, M. C.; Boschi, D.; Calderazzo, F.; Faure, R.; Labella, L.; Marchetti, F. *J. Chem. Soc., Chem. Commun.* **2000**, 1099–1100.
5. Dell'Amico, D. B.; Calderazzo, F.; Labella, L.; Marchetti, F.; Pampaloni, G. *Chem. Rev.* **2003**, *103*, 3857–3897.
6. Ito, Y. *Photochemistry* **2002**, *33*, 205–212 and the abstracts for many symposiums mentioned therein.
7. (a) Hampe, E. M.; Rudkevich, D. M. *J. Chem. Soc., Chem. Commun.* **2002**, 1450–1451. (b) Hampe, E. M.; Rudkevich, D. M. *Tetrahedron* **2003**, *59*, 9619–9625.
8. The kinetics and mechanisms of carbamate formation in aqueous solution are well studied. The discussion is, however, complicated owing to, for instance, their pH dependency and the hydrolysis equilibrium of CO_2. See, for example, (a) Caplow, M. *J. Am. Chem. Soc.* **1968**, *90*, 6795–6803. (b) Johnson, S. L.; Morrison, D. L. *J. Am. Chem. Soc.* **1972**, *94*, 1323–1334. (c) Ewing, S. P.; Lockshon, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 3072–3084. (d) Crooks, J. E.; Donnellan, J. P. *J. Chem. Soc., Perkin Trans. 2* **1989**, 331–333.
9. (a) Yoon, S. J.; Lee, H. *Chem. Lett.* **2003**, *32*, 344–345. (b) Suda, T.; Zhang, Y.; Iwaki, T.; Nomura, M. *Chem. Lett.* **1998**, 189–190. (c) Chakraborty, A. K.; Bischoff, K. B.; Astarita, G.; Damewood, J. R. Jr. *J. Am. Chem. Soc.* **1988**, *110*, 6947–6954. (d) Sartori, G.; Savage, D. W. *Ind. Eng. Chem. Fundam.* **1983**, *22*, 239–249.
10. (a) Nomura, R.; Hasegawa, Y.; Ishimoto, M.; Toyosaki, T.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 7339–7342. (b) Kumamoto, Y.; Ito, Y., Unpublished data (c) Sherry, A. D.; Malloy, C. R.; Jeffrey, M. H.; Chavez, F.; Srere, H. K. *J. Magn. Reson.* **1990**, *89*, 391–398. (d) Armarego, W. L. F.; Milloy, B. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1905–1907.
11. Hori, Y.; Nagano, Y.; Fukuhara, T.; Teramoto, S.; Taniguchi, H. *Nippon Kagaku Kaishi* **1987**, 1408–1413.
12. (a) Izutsu, K. *Acid–Base Dissociation Constants in Dipolar Aprotic Solvents (IUPAC Chemical Data Series; No. 35)*; Blackwell: Boston, 1990. (b) Izutsu, K. *Electrochemistry in Nonaqueous Solutions*; Wiley: Weinheim, 2002; Chapter 3.
13. Zielinska, J.; Makowski, M.; Maj, K.; Liwo, A.; Chmurzynski, L. *Anal. Chim. Acta* **1999**, *401*, 317–321.
14. (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley: Weinheim, 2003. (b) Isaacs, N. S. *Physical Organic Chemistry*, 2nd ed.; Longman Scientific and Technical: Essex, 1995; Chapter 5.
15. Kolthoff, I. M. *Anal. Chem.* **1974**, *46*, 1992–2003.
16. Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478.
17. (a) Schneider, S.; Rehaber, H.; Schüßlbauer, W.; Lewis, F. D.; Yoon, B. A. *J. Photochem. Photobiol. A: Chem.* **1996**, *99*, 103–114. (b) Lewis, F. D.; Cohen, B. E. *J. Phys. Chem.* **1994**, *98*, 10591–10597. (c) Mataga, N.; Miyasaka, H. *Adv. Chem. Phys.* **1999**, *107*, 431–496.
18. Herman, P.; Murtaza, Z.; Lakowicz, J. R. *Anal. Biochem.* **1999**, *272*, 87–93.
19. (a) Pirig, Y. N.; Polyuzhin, I. V.; Makitra, R. G.; Russ *J. Appl. Chem.* **1994**, *66*, 691–695. (b) Gennaro, A.; Isse, A. A.; Vianello, E. *J. Electroanal. Chem.* **1990**, *289*, 203–215.
20. (a) Cleland, W. W.; Andrews, T. J.; Gutteridge, S.; Hartman, F. C.; Lorimer, G. H. *Chem. Rev.* **1998**, *98*, 549–561. (b) Attwood, P. V.; Wallace, J. C. *Acc. Chem. Res.* **2002**, *35*, 113–120. (c) Arnone, A. *Nature* **1974**, *247*, 143–145. (d) Holden, H. M.; Thoden, J. B.; Raushel, F. M. *Cell. Mol. Life Sci.* **1999**, *56*, 507–522. (e) Chen, J.-G.; Sandberg, M.; Weber, S. G. *J. Am. Chem. Soc.* **1993**, *115*, 7343–7350.
21. (a) Salvatore, R. N.; Chu, F.; Nagle, A. S.; Kapxhiu, E. A.; Cross, R. M.; Jung, K. W. *Tetrahedron* **2002**, *58*, 3329–3347. (b) Mizuno, T.; Ishino, Y. *Tetrahedron* **2002**, *58*, 3155–3158. (c) Prez, E. R.; da Silva, M. O.; Costa, V. C.; Rodrigues-Filho, U. P.; Franco, D. W. *Tetrahedron Lett.* **2002**, *43*, 4091–4093. (d) Tai, C.-C.; Huck, M. J.; McKoon, E. P.; Woo, T.; Jessop, P. G. *J. Org. Chem.* **2002**, *67*, 9070–9072. (e) Sudo, A.; Morioka, Y.; Koizumi, E.; Sanda, F.; Endo, T. *Tetrahedron Lett.* **2003**, *44*, 7889–7891.
22. (a) Smissman, E. E.; Makriyannis, A. C.; Walaszek, E. J. *J. Med. Chem.* **1970**, *13*, 640–644. (b) Ohta, K. *Yakugaku Zasshi* **1965**, *85*, 14–20.

23. (a) Hann, R. A. *J. Chem. Soc., Perkin Trans. I* **1974**, 1379–1380. (b) Cabri, W.; Ilaria Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1992**, *57*, 3558–3563.
24. Rhodes, R. A.; Boykin, D. W. *Synth. Commun.* **1988**, *18*, 681–687.
25. (a) Yao, Z.-J.; King, C. R.; Cao, T.; Kelley, J.; Milne, G. W. A.; Voigt, J. H.; Burke, T. R., Jr. *J. Med. Chem.* **1999**, *42*, 25–35. (b) Furet, P.; Gay, B.; Caravatti, G.; Garcia-Echeverria, C.; Rahuel, J.; Schoepfer, J.; Fretz, H. *J. Med. Chem.* **1998**, *41*, 3442–3449.

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Is potential coordination of alkali metal ions to stereodefined polyoxygenated cyclohexanes an adequate driving force for fostering the adoption of axial conformers?

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Abstract—Inositol orthoesters have been developed as precursors to stereodefined hexakis polyoxygenated cyclohexanes. The objective of the study was to determine if all-*trans* systems could be coaxed by alkali metal ions into adopting the all-*axial* coordinative features. This high level coordination cannot be matched by epimers whose only option is to experience monocomplexation. Only very low levels of coordination were exhibited in solution by the ligands in question. Electrospray ionization mass spectrometry was also used to evaluate the metal complexation properties of the inositol ligands based on competition experiments involving each ligand and one or more metals.
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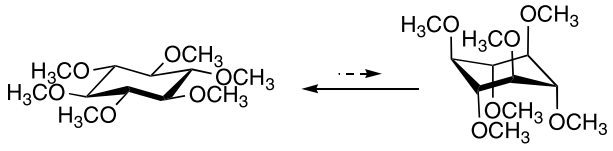
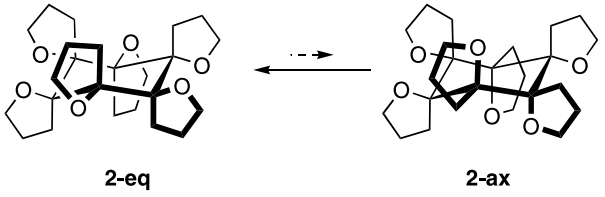
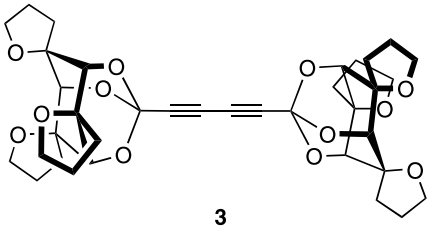
1. Introduction

The concept of bifacial ligation relates to the capacity of a single molecular entity to coordinate to a pair of metal ions residing on opposite faces of the organic core in an 'inside-out' sandwich relationship. The structural features intrinsic to this phenomenon hold fundamental interest and could potentially service a wide range of applications. However, progress in this area has been slow, largely because of the reluctance of candidate substrates to become involved in appropriate modes of geometric alignment. For example, the all-*trans* hexamethoxycyclohexane (**1**)[1] and its hexaspirotetrahydrofuran homolog **2**[2] are strikingly inert to alkali metal ions. The overwhelming preference for outward projection of the C–O bonds in **1** and **2** has been attributed[3] to the operation of six stabilizing *gauche* interactions[4] in the all-*O*-equatorial conformer. Analogous vicinal stereoelectronic contributions are absent in the axial counterparts. Another deterrent is the energetic cost associated with multiple projection of alkoxy groups axially on the same face of a cyclohexane (ca. 2 kcal/mol for each 1,3-interaction).[3] The inability to gain access to the all-*O-axial* arrangements dismisses any possibility of coordination to metal ions.







One way to skirt this complication is to rigidly enforce the proper conformational features as exemplified by **3**.[5] By taking advantage of an inositol orthoester platform, one finds it possible ultimately to link both halves into a dimeric arrangement.[5a,6] Much like its monomeric building block,

Keywords: Polyoxygenated cyclohexanes; Coordination; Alkali metal ions; Electrospray mass spectrometry; Conformational biases.
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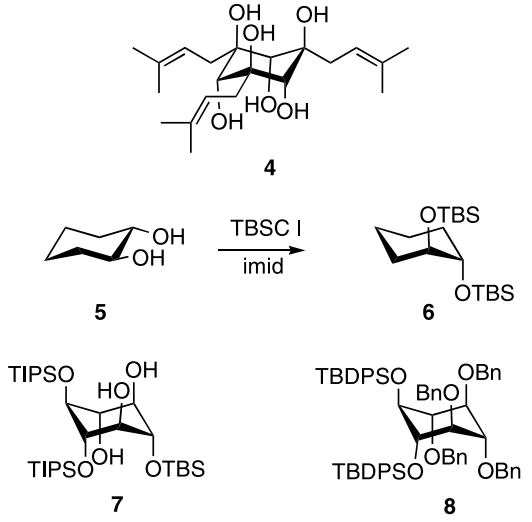
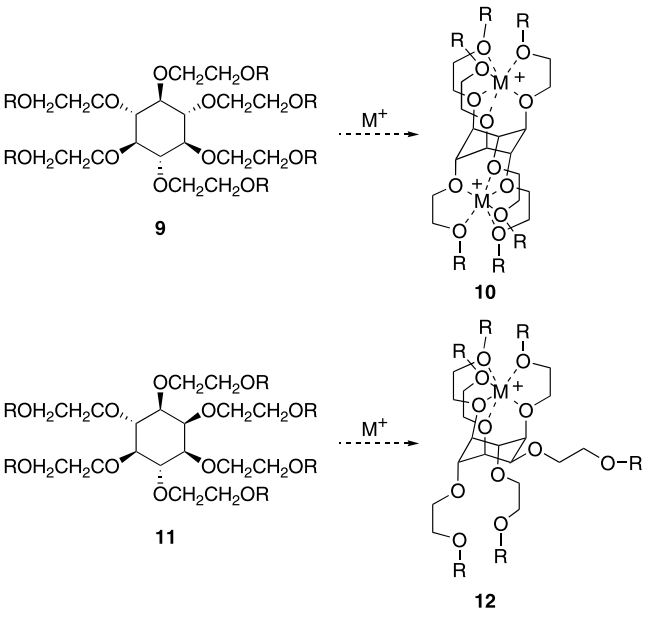
3 binds Li^+ ions very strongly. In addition, this homoditopic ionophore exhibits a strong preference for 2:1 stoichiometry and a propensity for conversion to a rodlike supramolecular ionic polymer. This reactivity conforms to expectations for a bifacial ligand.

Despite these successes, the allure offered by multifunctionalized cyclohexanes remains a siren call for more detailed investigation. Several discoveries have been reported that demonstrate the feasibility of projecting multiple oxygenated centers in *syn-axial* fashion under the proper circumstances. The first of these involves the natural product muellitol (**4**), its three prenyl substituents being adequate to predispose the peripheral hydroxyl groups for adoption of the desired axial-rich conformational bias.[7]

Ring inversion in this manner can also be achieved by introducing bulky silyl protecting groups. This phenomenon, known to occur already at the simple *trans*-1,2-cyclohexanediol level (as **5**→**6**),[8] is presently recognized to be operational as well in select *scyllo*-inositol derivatives represented by **7** and **8**.[9] These effects are in contrast to the state of affairs encountered in the corresponding alkyl ethers and have, on the basis of detailed MM3 calculations, been attributed to differences in repulsive and attractive steric interactions.[8b]



There is thus some degree of variability in the consequences of interactions between vicinal electron pairs or polar bonds upon the relative stability of cyclohexyl conformations. In the present exploratory study, we have sought to extend the length of the side chains in a manner that could allow metal ion complexation to materialize at sites more distal to the interconnective ring. At issue is the capacity for binding to two M^+ ions in the manner reflected in **10**. The differing stereochemistry of **11** disallows comparable bifacial ligation, but could possibly serve as a comparative test case for possible 1:1 complexation as in **12**. Alternatively, a number of factors such as solvation forces could conspire to preclude the formation of entities such as **10** and **11**. For this reason, we have evaluated the capacity of polyethers of generic formula **9** and **11** to bind to alkali metal ions both in solution and in the gas phase, the latter by electrospray ionization mass spectrometry.[10]

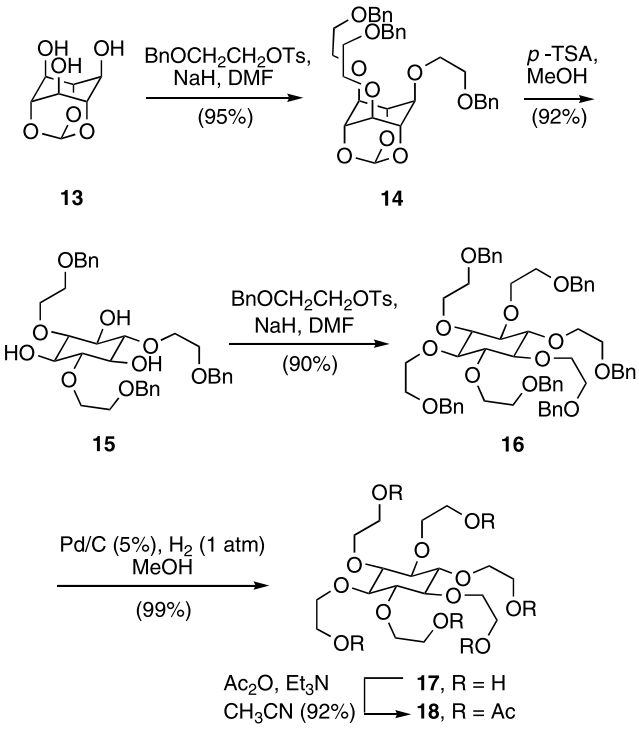


The use of electrospray ionization mass spectrometry (ESI-MS)[11] for the study of host–guest complexation and molecular recognition has expanded greatly over the past decade,[10,12–17] in large part because electrospray ionization is sufficiently gentle that non-covalent complexes can be transferred from the solution to the gas phase without disruption of the binding interactions of the complexes. Characterization of the binding properties and selectivities of new ligands has traditionally been undertaken by well-established NMR, potentiometric, spectrophotometric, and microcalorimetric methods,[18] but ESI-MS has gained popularity due to its sensitivity, low sample consumption, ability to give unambiguous information about the stoichiometries of complexes, and compatibility with a wide range of solvents.[12–17] Moreover, ESI provides a natural means to bridge the solution to gas-phase transition, thus giving a novel way to screen the binding properties of new ligands, to evaluate solvent effects, and to probe self-assembly strategies. One of our groups has been active in mapping the strengths and limitations of ESI-MS for applications related to molecular recognition,[5c,19–32] and we report the examination of the binding selectivities and stoichiometries of inositol derivatives in the present study.

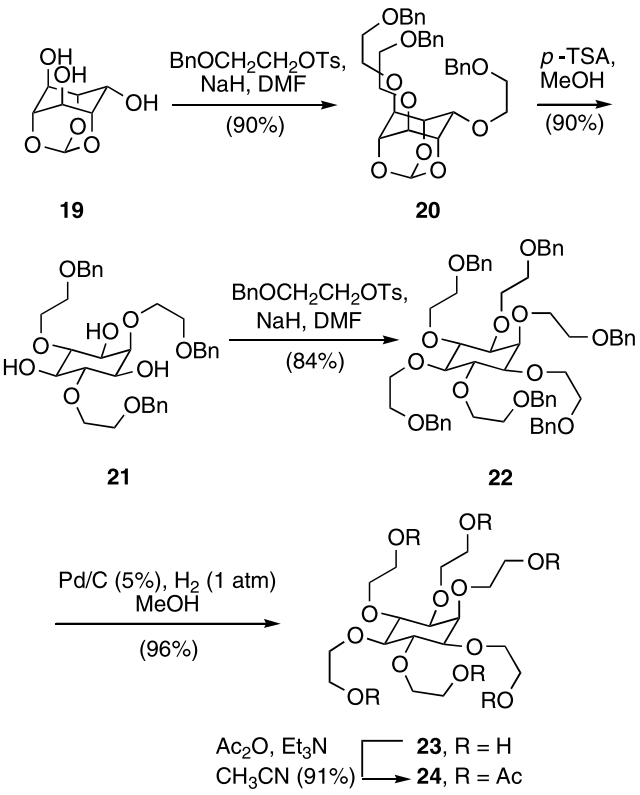
2. Results and discussion

2.1. Synthesis of the polyethers

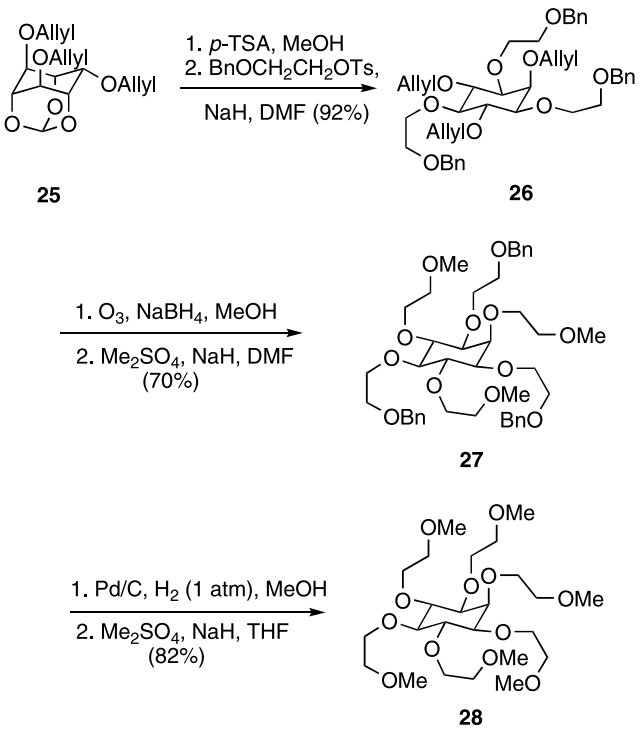
In contemplating workable routes to the target systems, pathways originating from the known inositol orthoesters **13** and **19**[33] came to be regarded as most feasible. Threefold alkylation of the hydroxyl groups resident in **13** with 2-(benzyloxy)ethyl tosylate[34] in DMF solution containing sodium hydride provided **14** efficiently (Scheme 1). This maneuver, in parallel with the like conversion of **15** to **16** had the purpose of proper chain elongation with positioning of a readily removable benzyl protecting group at the end of all six pendant β-alkoxy ethyl groups. Subsequent exhaustive hydrogenolysis of **16** could then be accomplished in a



Scheme 1.



Scheme 2.

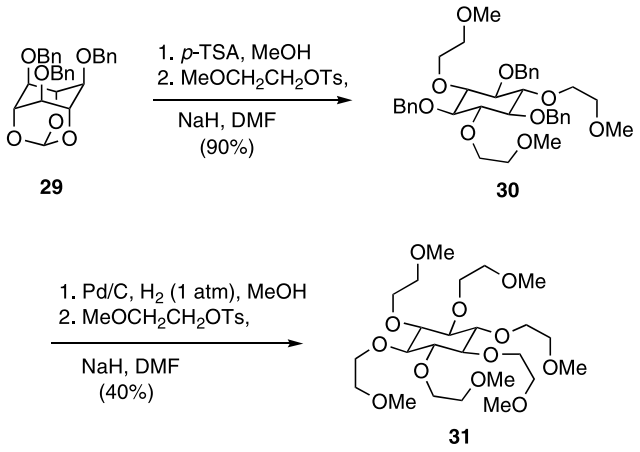


Scheme 3.

manner that conveniently skirted the problem of bringing **17** into contact with water, a medium in which it is freely soluble. Under the conditions adopted for the generation of **17**, it proved necessary only to remove the palladium catalyst by filtration and to evaporate the methanol in vacuo. The formation of hexaacetate **18** was routinely achieved by direct acylation of the solid so isolated.

A parallel thrust with triol epimer **19** proceeded with essentially identical efficiency at each of the five steps (Scheme 2). The capping of inositol by way of these symmetrical intermediates was unmistakingly diagnosed at each stage by ^{13}C NMR spectroscopy. Evidence that hydrolysis of the orthoester subunit in **14** and **20** was accompanied by conformational ring inversion was derived by comparison of ^{1}H NMR spectra. The most notable diagnostic is the appreciably deshielded nature of the cyclohexyl methine protons in **20** (4.28–4.47 ppm) relative to those in **21** (3.90–3.97 ppm).[35] Similarly, the conversion of **14** to **15** was accompanied by wholesale displacement of all six methine protons to higher field (as 4.19–4.41 to 3.49–3.64 ppm, respectively).

The stage was now set to proceed to the hexamethoxy derivatives **28** and **31**. To take advantage of the ready availability of triallyl orthoester **25**,[36] this heavily functionalized system was subjected to sequential acid hydrolysis and chain extension as before (Scheme 3). Once **26** became available, recourse was made to ozonolysis to degrade the allyl subunits. Direct reduction of the trialdehyde with sodium borohydride gave rise to an intermediate that could be processed without difficulty as in the conversion to polyether **27**. The route to **28** was completed uneventfully. The convenience associated with distributing side chain introduction into two distinctively separate operations holds advantages. However, a shorter means for accomplishing a comparable goal in a stereoisomeric series is available as illustrated in Scheme 4. In this instance, the two independent chain extensions were performed with 2-methoxyethanol tosylate.[37] By this means, tribenzyl



Scheme 4.

ether **29**[38] could be transformed into **31** by way of only four discrete steps. No yields reported herein are considered to be optimized.

2.2. Solution phase complexation studies

The solution-phase association constants (K_a) were determined for six of the polyethers defined above relative to Li^+, Na^+, and K^+ picrates in a H_2O–$CHCl_3$ solvent mixture according to Cram's extraction protocol.[39] The pair of polyols **17** and **23** proved to be too insoluble in the organic phase to allow measurements to be made. The data compiled in Table 1 were conservatively determined with relatively high concentrations of picrate salts so as to normalize matters to the level of 1:1 complexes only. From the outset, it became clear that the ability of the benzyl and methyl ethers as well as the acetates to extract any of the picrate salts was low. Compound **16** was defined as exhibiting a very modest capability to complex lithium ions. However, a K_a value of 2.38×10^{-4} represents a chelating ability roughly three orders of magnitude lower than that exhibited by **3**. At least in solution therefore, little tendency is seen for any of the alkali metal ions to position itself comfortably in a binding pocket of the type represented by **10** or **12**.

This conclusion is corroborated by NMR spectroscopy. The latter technique is recognized to be a powerful tool for

Table 1. Association constants (K_a) determined by picrate extraction from chloroform at 20 °C ($\times10^4$)

$$[M^+]_{aq} + [Pic^-]_{aq} + [host]_{org} \overset{K_a}{\rightleftarrows} [M^+\ Pic^-\ host]_{org}$$

Host	Li^+	Na^+	K^+
1. All-*trans* series			
16 (R=Bn)	2.38	1.17	0.53
17 (R=H)	[a]		
18 (R=Ac)	0.55	0.27	0.83
31 (R=Me)	0.93	0.48	0.28
2. *cis,trans*[2] series			
22 (R=Bn)	1.65	0.18	0.23
23 (R=H)	[a]		
24 (R=Ac)	0.96	1.40	0.10
28 (R=Me)	0.61	0.56	0.06

[a] This host exhibits extremely limited solubility in $CHCl_3$, thus precluding data collection.

dissecting changes in conformation brought on by ligation. In the present study, **16** dissolved in $CDCl_3/CH_3CN$ (1:1) was titrated with 0.25 M equiv of lithium perchlorate until an equimolar level had been reached. At each incremental stage, the ^1H and ^{13}C spectra of the resulting solution were recorded. Only very minor changes in carbon chemical shifts were noted at the maximum level of lithium salt. The same was true for the ^1H spectra except for the six equivalent protons on the cyclohexane ring which migrated upfield from δ 2.90 to 2.69. This singlet also underwent some slight line broadening. These observations are viewed as confirmatory of the absence of significant complexation of **16** to Li^+. The response of **22**, a key member of the *cis,trans*[2] series, proved to be entirely comparable.

2.3. Electrospray ionization-mass spectrometry measurements

The metal complexation properties of each potential ligand were assessed by analyzing solutions containing one host and one metal salt in 19:1 chloroform/methanol. This solvent mixture was employed to provide the closest possible correlation with binding affinity/selectivity determinations performed using conventional solution methods. Using this solvent, solutions containing KCl but no added NaCl produced signals consistent with complexation of sodium rather than potassium. Sodium is ubiquitous on glassware and in infusion tubing, and as a result sodium-cationized species are often observed in electrospray experiments even when no sodium is added. For comparison, 1:1 mixtures of ligand and metal salt were also analyzed in methanol, and potassium complexes were readily observed in this solvent.

In the presence of added NaCl or LiCl, the polyethers produced abundant complexes from the 19:1 chloroform/methanol solvent mixture. Electrospray spectra acquired for **17** and **23** (R=H) under these conditions are shown in Figure 1. The most abundant ions in these spectra are the metal-cationized ligands, $(L+M)^+$ where L=inositol ligand and M=metal, which suggests that the 1:1 stoichiometry is preferred for both ligand isomers.

Other stoichiometries were also observed at somewhat lower abundance, including the interesting bimetallic complexes of the general formula $(L+2M+Cl)^+$. In the all-*axial* conformation, the ligands potentially present two metal binding 'cavities', so the 1:2 ligand/metal stoichiometry was expected as a possibility. The observed retention of Cl^- counterions in these species is rationalized because the presence of the counterion reduces coulombic repulsion within the complex and should thereby improve its gas-phase stability. Ions of the general formulae $(2L+M)^+$ and $(2L+2M+Cl)^+$ are also observed in Figure 1A–D, indicating that complexes containing two ligand moieties exist for **17** and to a somewhat lesser extent for **23**.

The other inositol ethers ($R\neq H$) produced a smaller number of distinct complexes than **17** and **23** (spectra not shown). The $(L+M)^+$ ions were still the major species formed in the presence of both sodium and lithium, indicating that the 1:1 stoichiometry is again preferred. In many cases $(L+2M+Cl)^+$ ions were also major species. The $(2L+M)^+$

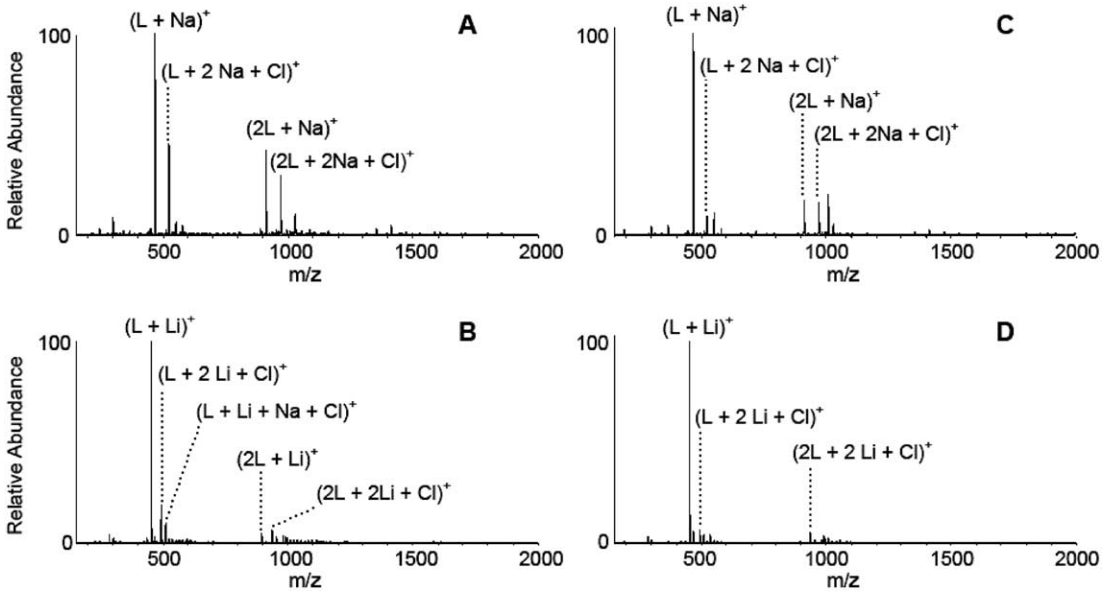


Figure 1. Electrospray ionization mass spectra for equimolar solutions of (A) **17** and NaCl, (B) **17** and LiCl, (C) **23** and NaCl, and (D) **23** and LiCl in 19:1 chloroform/methanol.

ions were far less significant for these ligands (R≠H), and the $(2L+2M+Cl)^+$ ions were not observed at all. This suggests that steric hindrance prevents the formation of the 2:1 and 2:2 ligand/metal complexes in the analogs containing ether or ester groups at the end of each pendant arm.

The signal abundance ratios for $(L+2M+Cl)^+$ to $(L+M)^+$ complexes observed upon ESI-MS of both the 19:1 chloroform/methanol and 100% methanol solutions were estimated for each ligand/metal combination, and the results are given in Table 2. Inspection of these data (also echoed in Fig. 1) shows that the bimetallic $(L+2M+Cl)^+$ ions were generally more abundant for the all-*trans* ligands than for the *cis*,*trans*[2] ligands. In fact, the enhancement ranges from a factor of 2 to 6 for the all trans-ligands versus the *cis*,*trans*[2] ligands in chloroform/methanol (19:1) up to an enhancement factor of 25 for **16** versus **22** in methanol. The greater $(L+2M+Cl)^+/(L+M)^+$ ratios for the all-*trans* ligands suggests that the three up–three down arrangement of chelating arms enhances the formation of the bimetallic complexes. The initial solvent environments also seem to influence the formation of the bimetallic complexes. The exaggeration of the $(L+2M+Cl)^+/(L+M)^+$ intensity ratios for the methanol solutions relative to the chloroform/methanol solutions suggests an increased stabilization of the bimetallic complexes in the more polar solvent. Furthermore, the $(L+2M+Cl)^+$ ions were observed with greater relative signal intensities for M=Na over M=Li, which implies that bimetallic coordination is less favored for smaller more charge-dense cations. Tight binding of a metal ion in one cavity may distort the cyclohexane ring in such a way as to disfavor coordination of a second metal.

Table 2. Signal abundance ratios, $(L+2M+Cl)^+/(L+M)^+$ by ESI-MS

R=	Ligand	Solvent=19:1 chloroform/methanol		Solvent=methanol		
		M=Na	M=Li	M=K	M=Na	M=Li
Bn	**16**	1.0	0.5	0.8	0.25	0.03
	22	0.2	0.25	0.03	0.01	0.01
Ac	**18**	0.3	0.1	1.2	0.2	0.15
	24	0.1	0.03	0.1	0.03	0.03
H	**17**	0.6	0.3	0.4	0.25	0.05
	23	0.1	0.1	0.3	0.05	0.1
Me	**31**	0.4	0.8	0.15	0.1	0.3
	28	0.1	0.3	0.3	0.02	0.1

To further characterize the ligand–alkali metal interactions, many of the complexes were individually isolated and subjected to collisionally activated dissociation (CAD). Typical results are shown in Figure 2 for the $(L+2Na+Cl)^+$ and $(2L+2Na+Cl)^+$ ions observed for **17**. For the $(L+2Na+Cl)^+$ parent species, two major fragmentation pathways are possible: loss of Cl^- to yield the doubly charged $(L+2Na)^{+2}$ ion, and loss of NaCl to yield the singly charged $(L+Na)^+$ ion. The spectrum in Figure 2A illustrates that the latter pathway is followed exclusively, which lends support to notion that coulombic effects destabilize $(L+2M)^{+2}$ species. The same result was obtained for all other $(L+2M+Cl)^+$ ions probed by CAD, regardless of the identity of either the ligand or the metal. For the $(2L+2Na+Cl)^+$ parent ions, several fragmentation pathways might be expected to give observable products, including loss of Cl^-, loss of NaCl, loss of L, and possibly loss of $(L+NaCl)^0$. Of these, only loss of one ligand was observed (Fig. 2B).

These CAD results shed some light on the structures of the gas-phase complexes. Based on the exclusive loss of NaCl from the bimetallic $(L+2Na+Cl)^+$ complexes, these structures are best rationalized as ones in which one metal is strongly coordinated via electrostatic interactions with the oxygen atoms on one face of the inositol plane, and NaCl is more loosely bound as an ion pair on the other face of the inositol plane. The $(2L+2Na+Cl)^+$ ions are likely sandwich complexes in which one Na^+ ion is bound between two inositol ligands, and a NaCl ion pair is loosely bound to the opposite faces of one of the inositol ligands.

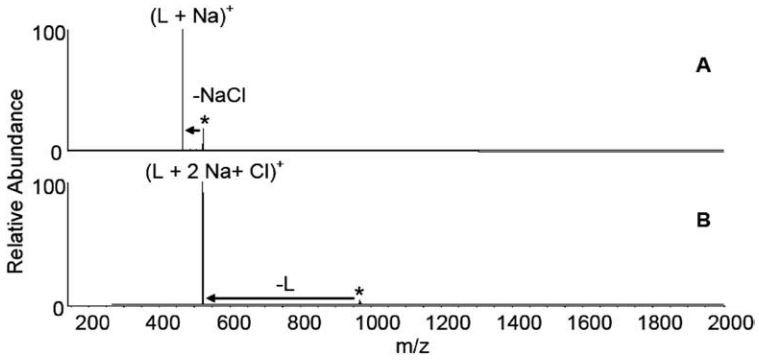


Figure 2. Collisionally activated dissociation of (A) $(\mathbf{17}+2\mathrm{Na}+\mathrm{Cl})^+$, *m/z* 525 and (B) $(2\times\mathbf{17}+2\mathrm{Na}+\mathrm{Cl})^+$, *m/z* 969. Asterisks mark the parent species.

Upon CAD, the exclusive loss of one of the inositol ligands suggests that steric factors prevent strong binding of both inositol ligands to the central metal ion.

To assess the metal dependence of ligand binding, solutions containing one inositol derivative and 1 equiv each of lithium, sodium, and potassium chloride were analyzed by ESI-MS. Results acquired for **17** and **23** are given in Figure 3, and clearly show that $(\mathrm{L}+\mathrm{Li})^+$ ions were the most abundant species. Similar results were obtained for all other analogs, indicating that the ligands in this series strongly prefer lithium to sodium and potassium; neither the identity of the substituents nor the arrangement of the chelating groups on the cyclohexane core significantly altered the metal selectivity.

2.4. Overview

The ionophoric potential of polyethers of type **9** or **11** is obviously dependent on recognition by the alkali metal ion of the availability of ligating sites at the termini of the other two chains residing in a 1,3-diequatorial relationship. For the cation-binding properties of these potential hosts to come into play in the manner defined in **10**, numerous solvent molecules require displacement so that a hold can be gained on achieving proximity for the appropriate oxygen atoms. The entropic and enthalpic costs of structural rigidification will also need to be paid. The fact that alkali metal ions, and particularly Li^+, are not well accommodated in an aqueous environment points up that these entities are not conducive to orienting their side chains axially in this medium. The ESI-MS results illustrate the enhanced ability of the all trans ligands to form bimetallic complexes of the type $(\mathrm{L}+2\mathrm{M}+\mathrm{Cl})^+$ where L=inositol ligand and M=metal. Dissociation of the bimetallic complexes suggests that one metal is coordinated to each face of the inositol plane.

3. Experimental

3.1. General

3.1.1. Compound 14. To triol **13**[33] (0.62 g, 3.2 mmol) dissolved in dry DMF (25 mL) was added sodium hydride (60%, 0.80 g, 19 mmol) followed by 2-(benzyloxy)ethyl tosylate (5.97 g, 19.5 mmol) at 0 °C. The mixture was stirred overnight with allowance for warming to rt, carefully quenched with saturated NH_4Cl solution, and extracted with ether (4×75 mL). The combined organic layers were washed with brine (4×100 mL), dried, and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 20% ethyl acetate in hexanes) to afford 1.84 g (95%) of **14** as a colorless oil; IR (film, cm^{-1}) 1602, 1584, 1496; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.24 (m, 6H), 7.17–7.12 (m, 6H), 7.08–7.03 (m, 3H), 5.65 (s, 1H), 4.41–4.29 (q, J=2.9 Hz, 3H), 4.32 (s, 6H), 4.22–4.19 (q, J=2.9 Hz, 3H), 3.45–3.41 (m, 6H), 3.38–3.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 128.2, 127.5, 127.3,

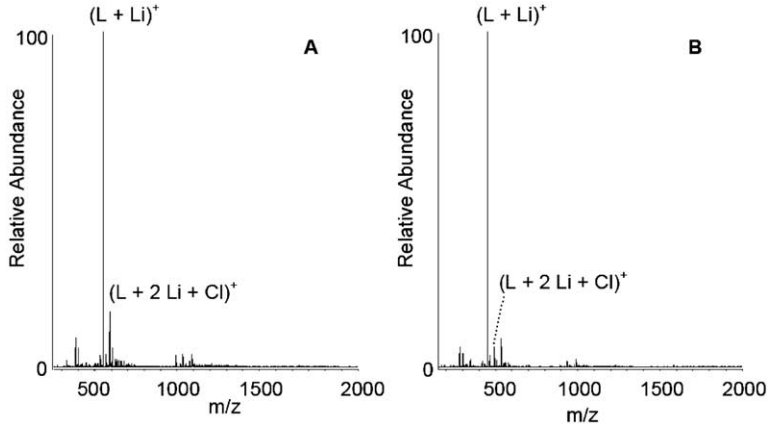


Figure 3. Electrospray ionization mass spectra for equimolar solutions of (A) **17**, LiCl, NaCl and KCl and (B) **23**, LiCl, NaCl, and KCl in 19:1 chloroform/methanol.

103.4, 73.8, 72.9, 69.7, 68.9, 68.8; HRMS (electrospray) *m/z* calcd for $C_{34}H_{40}O_9Na^+$ 615.2564, found 615.2510.

3.1.2. Compound 15. A solution of **14** (2.2 g, 3.7 mmol) and *p*-toluenesulfonic acid (0.04 g, 0.19 mmol) in methanol (75 mL) was refluxed for 4 h. The solvent was reduced to about 10 mL and the reaction mixture was quenched with saturated sodium carbonate solution (50 mL) and water (75 mL), and extracted with ether (3×100 mL). The organic extracts were combined, dried, and evaporated. The residue was purified by chromatography on silica gel (elution with 40% hexanes in ethyl acetate) to afford **15** as a colorless oil (2.0 g, 92%); IR (film, cm^{-1}) 3428, 1496, 1453; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 15H), 4.58 (s, 6H), 4.00–3.98 (t, J=4.7 Hz, 6H), 3.64–3.61 (t, J=4.7 Hz, 6H), 3.64–3.61 (t, J=9.4 Hz, 6H), 3.55–3.49 (t, J=9.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 128.4, 127.9, 127.8, 83.9, 73.7, 73.1, 72.2, 69.6; HRMS (electrospray) *m/z* calcd for $C_{33}H_{42}O_9Na^+$ 605.2721, found 605.2712.

3.1.3. Compound 16. Triol **15** (2.52 g, 4.32 mmol) was dissolved in dry DMF (100 mL), treated with sodium hydride (0.86 g, 22 mmol), and cooled to 0 °C. 2-(Benzyloxy)ethyl tosylate (5.30 g, 17.3 mmol) was introduced and the mixture was stirred overnight, quenched with methanol (10 mL), and poured into an ice–water mixture prior to extraction with ether (3×100 mL). The combined organic extracts were dried and freed of solvent to afford a residue that was purified by chromatography on silica gel (elution with 33% ethyl acetate in hexanes) to afford 3.84 g (90%) of **16** as a colorless oil that crystallized in the cold, mp 77–79 °C; (film, cm^{-1}) 1497, 1454, 1357; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 30H), 4.54 (s, 12H), 4.06–4.03 (m, 12H), 3.62–3.58 (m, 12H), 3.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 128.3, 127.7, 127.5, 83.1, 73.0, 72.9, 70.0; HRMS (electrospray) *m/z* calcd for $C_{60}H_{72}O_{12}Na^+$ 1007.4916, found 1007.4913.

3.1.4. Compound 17. To a solution of **16** (0.60 g, 0.61 mmol) in methanol (10 mL) was added palladium on charcoal (10%, 20 mg) and hydrogen was purged through the system followed by stirring under an atmosphere of hydrogen for 6 h. The mixture was filtered through a Celite plug and the solvent was removed in vacuo to afford polyol **17** in almost quantitative yield (0.27 g, 99%) as a white solid, mp 260 °C dec. Further purification was not required; IR (film, cm^{-1}) 3373, 1458, 1355; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57–4.54 (t, J=5.4 Hz, 6H), 3.70 (t, J=5.1 Hz, 12H), 3.54–3.45 (q, J=5.1 Hz, 12H), 3.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.2, 74.5, 60.8; HRMS (electrospray) *m/z* calcd for $C_{18}H_{36}O_{12}Na^+$ 467.2099, found 467.2098.

3.1.5. Hexaacetate 18. A suspension of **17** (0.88 g, 2.0 mmol) in acetonitrile (25 mL) cooled to 0 °C was treated with triethylamine (1.8 mL, 13 mmol) followed by acetic anhydride (1.15 mL, 12 mmol). The mixture was allowed to warm gradually to rt, freed of acetonitrile, and purified by flash chromatography on silica gel (15% methanol in ethyl acetate) to afford **18** (1.26 g, 92%) as a white solid, mp 157–159 °C; IR (film, cm^{-1}) 1738, 1464, 1384; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90–3.87 (t, J=4.7 Hz, 12H), 3.52–3.48 (t, J=4.9 Hz, 12H), 3.32 (s, 18H), 3.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.1, 72.6, 72.2, 58.7; HRMS (electrospray) *m/z* calcd for $C_{30}H_{48}O_{18}Na^+$ 719.2733, found 719.2738.

3.1.6. Compound 20. A solution of **19** (0.5 g, 2.6 mmol) in DMF (20 mL) was added dropwise to a stirred suspension of sodium hydride (60%, 0.4 g, 10 mmol) in DMF (30 mL) at 0 °C. the reaction mixture was stirred for 20 min prior to dropwise addition of solution of benzyloxyethyl tosylate (3.22 g, 10.5 mmol) in DMF (25 mL), stirred overnight with warming to rt, and quenched by careful addition of water (100 mL) followed by three extractions with diethyl ether (150 mL). The combined organic extracts were extracted with brine, dried, and evaporated. The residue was purified by flash chromatography on silica gel (5:1, hexanes/ethyl acetate) to afford **20** (1.40 g, 90%) as a colorless oil; IR (film, cm^{-1}) 1498, 1453, 1166; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 15H), 5.53 (d, J=1.2 Hz, 1H), 4.57 (s, 2H), 4.49 (s, H), 4.47–4.46 (m, 1H), 4.39–4.37 (m, 2H), 4.31–4.28 (t, J=3.5 Hz, 2H), 3.94–3.93 (d, J=1.5 Hz, 1H), 3.80–3.62 (m, 8H), 3.60–352 (t, J=4.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 138.1, 128.9, 128.2, 127.7, 127.6, 127.5, 103.9, 74.8, 73.2, 73.1, 70.4, 69.6, 69.4, 69.1, 69.0, 68.7, 67.9; HRMS (electrospray) *m/z* calcd for $C_{34}H_{40}O_9Na^+$ 615.2565, found 615.2551.

3.1.7. Compound 21. A solution of **20** (2.90, 4.89 mmol) and *p*-toluenesulfonic acid (7.6 mg, 0.04 mmol) in 100 mL of methanol was refluxed for 4 h and evaporated to leave a residue that was purified by chromatography on silica gel (elution with 1:1 ethyl acetate in hexanes). There was isolated 2.56 g (90%) of **21** as a colorless oil; IR (film, cm^{-1}) 3446, 1276, 1114; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 15H), 4.57–4.56 (m, 6H), 3.97–3.90 (m, 6H), 3.86 (s, 1H), 3.63–3.58 (m, 6H), 3.47–3.42 (m, 5H), 3.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.41, 137.35, 128.18, 128.16, 127.6, 127.5, 83.4, 81.0, 74.2, 72.9, 72.6, 72.1, 69.5, 69.4; HRMS (electrospray) *m/z* calcd for $C_{33}H_{42}O_9Na^+$ 605.2721, found 605.2669.

3.1.8. Compound 22. To triol **21** (2.56 g, 4.40 mmol), dissolved in dry DMF (100 mL) was added sodium hydride (60%, 1.2 g, 30 mmol) followed by 2-(benzyloxy)ethyl tosylate (6.74 g, 22 mmol) at 0 °C. The mixture was stirred overnight, allowed to warm up gradually to rt, quenched with saturated NH_4Cl solution, and extracted with ether (4×100 mL). The combined organic layers were washed with brine (4×100 mL), dried, and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 50% ethyl acetate in hexanes) to afford 3.61 g (84%) of **22** as a colorless oil; IR (film, cm^{-1}) 1602, 1496, 1453; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 30H), 4.60 (s, 2H), 4.54–4.53 (10H), 4.05–3.97 (m, 9H), 3.81–3.58 (m, 19H), 3.24–3.16 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 138.5, 138.4, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 99.7, 83.9, 82.0, 81.3, 76.4, 73.1, 72.9, 72.8, 72.85, 72.75, 72.5, 72.3, 70.4, 70.1, 70.0, 69.91, 69.88; HRMS (electrospray) *m/z* calcd for $C_{69}H_{72}O_{12}Na^+$ 1007.4916, found 1007.4834.

3.1.9. Polyol 23. To a solution of **22** (3.61 g, 3.66 mmol) in methanol (100 mL) was added palladium on charcoal (10%,

150 mg) and hydrogen was purged through the system followed by stirring under 1 atm for 6 h. The mixture was filtered through a Celite plug, solvent removed in vacuo, and the residue was purified by recrystallization (50% methanol in ethylacetate) to afford 1.57 g (96%) of **23** as a white solid, mp 104–106 °C; IR (film, cm^{-1}) 3386, 1461, 1361; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60–4.52 (m, 5H), 4.34–4.30 (t, $J=5.6$ Hz, 1H), 3.93 (s, 1H), 3.70–3.31 (m, 26H), 3.17–3.13 (m, 2H), 3.02–2.96 (t, $J=9.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 94.8, 83.0, 81.2, 80.1, 75.2, 74.5, 74.3, 73.9, 71.8, 60.84, 60.78, 60.7, 60.6; HRMS (electrospray) *m/z* calcd for $C_{18}H_{36}O_{12}Na^+$ 467.2099, found 467.2098.

3.1.10. Hexaacetate 24. A suspension of **23** (100 mg, 0.22 mmol) in dry acetonitrile (50 mL) was treated with triethylamine (0.4 mL, 2.70 mmol) and DMAP (2.7 mg, 0.02 mmol), and cooled to 0 °C. Following the addition of acetic anhydride (0.3 mL, 2.70 mmol), the reaction mixture was stirred for 2 h, quenched with saturated bicarbonate solution (30 mL), and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried and freed of solvent. The residue was chromatographed on silica gel (elution with 75% ethyl acetate in hexanes) to afford 142 mg (91%) of **24** as a white solid, mp 57–59 °C; (film, cm^{-1}) 1739, 1440, 1382; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11–4.01 (m, 12H), 3.85–3.63 (m, 12H), 3.50–3.43 (t, $J=9.4$ Hz, 2H), 2.98–2.90 (m, 3H), 1.92 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.63, 170.58, 83.2, 81.3, 80.7, 76.2, 71.1, 70.9, 70.7, 69.8, 63.9, 63.8, 63.53, 63.47, 20.7, 20.6; HRMS (electrospray) *m/z* calcd for $C_{30}H_{48}O_{17}Na^+$ 719.2733, found 719.2738.

3.1.11. Compound 26. A solution of **25** (2.64 g, 8.51 mmol) and *p*-toluenesulfonic acid (80 mg, 0.05 mmol) in methanol (150 mL) was refluxed for 4 h. The solvent was removed and the residue was dissolved in dry DMF (150 mL), treated with sodium hydride (1.36 g, 34.0 mmol), and cooled to 0 °C. 2-(Benzyloxy)ethyl tosylate (9.12 g, 29.77 mmol) was introduced and the reaction mixture was stirred overnight, quenched with methanol (10 mL), poured into an ice–water mixture, and extracted with ether (3×100 mL). The combined organic extracts were dried and evaporated. The residue was purified by chromatography on silica gel (elution with 25% ethyl acetate in hexanes) to afford 5.50 g (92% over two steps) of **26** as a colorless oil; IR (film, cm^{-1}) 1496, 1454, 1354; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 15H), 6.04–5.89 (m, 3H), 5.30–5.07 (m, 6H), 4.59–4.57 (m, 6H), 4.34–4.34 (m, 5H), 4.00–3.97 (m, 3H), 3.78–3.58 (m, 13H), 3.17–3.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.4, 136.0, 135.8, 128.5, 128.4, 128.3, 127.8, 127.6, 127.5, 116.4, 116.2, 84.3, 81.7, 81.2, 74.4, 74.2, 73.3, 73.2, 73.0, 72.9, 71.4, 70.5; HRMS (electrospray) *m/z* calcd for $C_{42}H_{54}O_9Na^+$ 725.3660, found 725.3684.

3.1.12. Compound 27. Ozone was bubbled through a solution of **26** (5.50 g, 7.83 mmol) in methanol/dichloromethane mixture (9:1, 100 mL) at −78 °C followed by the addition of sodium borohydride (1.48 g, 38.1 mmol) after reaction was complete. The mixture was stirred for 3 h and allowed to gradually warm to rt prior to quenching by slow addition of saturated NH_4Cl solution and extraction with ether (3×100 mL). The organic extracts were combined, dried, and freed of solvent to afford a residue that was dissolved in dry DMF (100 mL). The resulting solution was treated first with sodium hydride (1.25 g, 31.3 mmol) at −10 °C and then slowly with dimethyl sulfate (3 mL, 31.3 mmol). After overnight stirring, the reaction mixture was quenched with methanol (10 mL), poured into water (200 mL), and extracted with ether (3×100 mL). The organic extracts were combined, dried, and freed of solvent to afford crude product that was chromatographed on silica gel (elution with 60% ethyl acetate in hexanes) to afford **27** (4.15 g, 70% over three steps) as a colorless oil; IR (film, cm^{-1}) 1453, 1354, 1094; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 15H), 4.56 (s, 2H), 4.53 (s, 4H), 4.00–3.97 (m, 2H), 3.93–3.84 (m, 7H), 3.76–3.71 (m, 4H), 3.68–3.59 (m, 8H), 3.53–3.52 (m, 6H), 3.32 (s, 3H), 3.29 (s, 6H), 3.16–3.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.4, 128.3, 128.2, 127.6, 127.53, 127.50, 127.4, 83.4, 82.1, 81.3, 76.2, 73.1, 72.9, 72.7, 72.4, 72.2, 72.0, 70.4, 70.2, 69.9, 58.8, 58.7; HRMS (electrospray) *m/z* calcd for $C_{42}H_{60}O_{12}Na^+$ 779.3977, found 779.3958.

3.1.13. Hexamethoxy derivative 28. Compound **27** (2.0 g, 2.4 mmol) was dissolved in ethyl acetate (75 mL) followed by palladium on charcoal (10%, 200 mg). The mixture was purged with hydrogen and stirred in this atmosphere for 3 h. The catalyst was removed by filtration through a cotton plug and the filtrate was evaporated. The residue obtained was dissolved in THF, treated with sodium hydride (0.37 g, 9.25 mmol), and cooled to −20 °C prior to the addition of dimethyl sulfate (1.0 mL, 10.57 mmol). This mixture was stirred for 4 h, allowed to warm gradually, and quenched with methanol (5 mL). Solvent was removed in vacuo and the residue was purified by chromatography on silica gel (elution with 5% methanol in ethyl acetate) to afford **28** as a colorless oil (1.2 g, 82%); IR (film, cm^{-1}) 1454, 1356, 1267; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89–3.78 (m, 10H), 3.71–3.63 (m, 3H), 3.59–3.53 (t, $J=9.6$ Hz, 1H), 3.50–3.43 (m, 12H), 3.30–3.29 (m, 19H), 3.08–3.01 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.9, 81.9, 81.3, 76.0, 72.5, 72.3, 72.2, 72.1, 71.9, 70.2, 58.8, 58.7, 58.7, 58.6; HRMS (electrospray) *m/z* calcd for $C_{24}H_{48}O_{12}Na^+$ 551.3038, found 551.3037.

3.1.14. Compound 29. Triol **13**[33] (4.0 g, 21.0 mmol) dissolved in anhydrous DMF (100 mL) at 0 °C was treated with sodium hydride (60%, 3.0 g, 75.0 mmol), followed by benzyl bromide (8.35 mL, 70 mmol) after 30 min. The mixture was stirred overnight, quenched with saturated NH_4Cl solution (200 mL), and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried and concentrated to leave a residue that was purified by chromatography on silica gel (elution with 5% ethyl acetate in hexanes) to afford 8.55 g (88%) of **29** as a white solid, mp 117–119 °C; IR (film, cm^{-1}) 1497, 1453, 1167; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.17 (m, 5H), 5.55 (s, 1H), 4.66 (s, 6H), 4.60–4.57 (dd, $J=4.2$, 3.0 Hz, 3H), 4.38–4.36 (dd, $J=4.2$, 3.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.1, 127.7, 127.4, 103.1, 72.5, 71.2, 68.6; HRMS (electrospray) *m/z* calcd for $C_{28}H_{28}O_6Na^+$ 438.1778, found 483.1764.

3.1.15. Compound 30. A solution of **29** (2.4 g, 5.2 mmol) and *p*-toluenesulfonic acid (0.05 g, 0.26 mmol) in methanol

was refluxed for 3 h, cooled, and freed of solvent. The crude residue was dissolved in dry DMF (75 mL) followed by the addition of sodium hydride (0.73 g, 18.24 mmol) and cooling to 0 °C. 2-Methoxyethanol tosylate (4.20 g, 18.2 mmol) was introduced and the reaction mixture was allowed to warm gradually during overnight stirring, quenched with methanol (10 mL) and water (100 mL), and extracted with ether (3×100 mL). The organic extracts were combined, dried, and evaporated to afford a residue that was purified on silica gel (elution with 25% ethyl acetate in hexanes) to afford **30** (2.95 g, 90%) as a white solid, mp 95–97 °C; IR (film, cm^{-1}) 1454, 1356, 1198; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.26 (m, 15H), 4.90 (s, 6H), 3.99–3.95 (m, 6H), 3.55–3.48 (m, 9H), 3.35 (s, 9H), 3.30–3.24 (t, $J=9.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 128.4, 128.2, 127.6, 83.4, 82.5, 75.8, 73.0, 72.3, 59.0; HRMS (electrospray) *m/z* calcd for $C_{36}H_{48}O_9Na^+$ 647.3191, found 647.3205.

3.1.16. Hexamethoxy derivative 31. A solution of **30** (2.4 g, 3.84 mmol) in methanol (75 mL) containing palladium on charcoal (10%, 100 mg) was stirred under an atmosphere of H_2 for 3 h. The catalyst was removed by filtration through a cotton plug, the solvent was evaporated, and the residue was dissolved in dry THF (75 mL) and treated with sodium hydride (60%, 0.46 g, 11.5 mmol) at 0 °C. 2-Methoxyethanol tosylate (2.65 g, 11.52 mmol) was introduced and the mixture was stirred overnight with gradual warming to rt, quenched with methanol (10 mL) followed by water (100 mL), and filtered. The filtrate was evaporated in vacuo to afford a residue that was purified on silica gel (elution with 10% methanol in ethyl acetate) to afford **31** (0.82 g, 40%) as a colorless oil; IR (film, cm^{-1}) 1487, 1462, 1358; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90–3.87 (m, 12H), 3.52–3.48 (m, 12H), 3.32 (s, 18H), 3.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.0, 72.6, 72.2, 58.1; HRMS (electrospray) *m/z* calcd for $C_{24}H_{48}O_{12}Na^+$ 551.3038, found 551.3048.

3.2. Electrospray ionization-mass spectrometry

Lithium, sodium, and potassium chlorides were purchased from Aldrich Chemical Company (St. Louis, MO) and were used as received. Inositol derivatives were mixed with equimolar amounts of metal salts at a concentration of 10 μM in either methanol or 19:1 chloroform/methanol, and these samples were infused at 5 μL/min into the electrospray source of a ThermoFinnigan LCQ Duo quadrupole ion trap mass spectrometer operating in the positive ion mode. The needle voltage was set at 4.8 kV and the heated capillary temperature was set to 125 °C. Each mass spectrum acquired was an average of 100 scans. In CAD experiments, the ions of interest were isolated and fragmented using activation voltages between 0.7 and 1.25 V and an activation time of 30 ms.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.011

References and notes

1. (a) Anderson, J. E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 441. (b) Anderson, J. E.; Angyal, S. J.; Craig, D. C. *Carbohydr. Res.* **1995**, *272*, 141.
2. (a) Paquette, L. A.; Tae, J. S.; Branan, B. M.; Eisenberg, S. W. E.; Hofferberth, J. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 1412. (b) Paquette, L. A.; Tae, J.; Branan, B. M.; Bolin, D. G.; Eisenberg, S. W. E. *J. Org. Chem.* **2000**, *65*, 9172.
3. Rablen, P. R.; Paquette, L. A.; Borden, W. T. *J. Org. Chem.* **2000**, *65*, 9180.
4. (a) Zefirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953. (b) Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211. (c) Zefirov, N. S.; Samoshin, V. V.; Palyulin, V. A. *Zh. Org. Khim.* **1983**, *19*, 1888.
5. (a) Tae, J. S.; Rogers, R. D.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 139. (b) Paquette, L. A.; Tae, J. *J. Am. Chem. Soc.* **2001**, *123*, 4974. (c) Paquette, L. A.; Ra, C. S.; Gallucci, J. C.; Kang, H. J.; Ohmori, N.; Arrington, M. P.; David, W.; Brodbelt, J. S. *J. Org. Chem.* **2001**, *66*, 8629.
6. Paquette, L. A.; Tae, J.; Gallucci, J. C. *Org. Lett.* **2000**, *2*, 143.
7. (a) Fazideen, H.; Hegarty, M. P.; Lahey, F. N. *Phytochemistry* **1978**, *17*, 1609. (b) Fazideen, H. *Aust. J. Chem.* **1982**, *35*, 2589.
8. (a) Eliel, E. L.; Satici, H. *J. Org. Chem.* **1994**, *59*, 688. (b) Marzabadi, C. H.; Anderson, J. E.; Gonzales-Outeirino, J.; Gaffney, P. R. J.; White, C. G. H.; Tocher, D. A.; Todaro, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 15163.
9. Yamada, H.; Okajima, K.; Imagawa, H.; Mukae, T.; Kawamura, Y.; Nishizawa, M. *Tetrahedron Lett.* **2004**, *45*, 3157.
10. (a) Ryzhov, V.; Dunbar, R. C.; Cerda, B.; Wesdemiotis, C. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 1037. (b) Madhusudanan, K. P.; Raj, K.; Bhaduri, A. P. *Rapid Commun. Mass Spectrom.* **2000**, *14*, 885. (c) Cerda, B. A.; Hoyau, S.; Ohanessian, G.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1998**, *120*, 2437. (d) Cerda, B. A.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11884.
11. Fenn, J. B.; Mann, M.; Meng, C. K.; Wong, S. F.; Whitehouse, C. M. *Mass Spectrom. Rev.* **1990**, *9*, 48.
12. Veenstra, T. D. *Biophys. Chem.* **1999**, *79*, 63.
13. Loo, J. A. *Int. J. Mass Spectrom.* **2000**, *200*, 175.
14. Schalley, C. A. *Int. J. Mass Spectrom.* **2002**, *194*, 11.
15. Schalley, C. A. *Mass Spectrom. Rev.* **2001**, *20*, 253.
16. Pramanik, B. N.; Bartner, P. L.; Mirza, U. A.; Liu, Y. H.; Ganguly, A. K. *J. Mass Spectrom.* **1998**, *33*, 911.
17. Przybylski, M.; Glocker, M. O. *Angew. Chem., Int. Ed.* **1996**, *35*, 806.
18. Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. Comprehensive Supramolecular Chemistry. In Davies, J. E. D., Ripmeester, J. A., Eds.; Physical Methods in Supramolecular Chemistry; Elsevier: New York, 1996; Vol. 8; Chapter 10.

19. Blair, S. M.; Kempen, E.; Brodbelt, J. S. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 1049.
20. Brodbelt, J. S.; Kempen, E.; Reyzer, M. *Struct. Chem.* **1999**, *10*, 213.
21. Kempen, E. C.; Brodbelt, J. S.; Bartsch, R. A.; Jang, Y.; Kim, J. S. *Anal. Chem.* **1999**, *71*, 5493.
22. Blanda, M. T.; Farmer, D. B.; Brodbelt, J. S.; Goolsby, B. J. *J. Am. Chem. Soc.* **2000**, *122*, 1486.
23. Blair, S. M.; Brodbelt, J. S.; Marchand, A. P.; Kumar, K. A.; Chong, H. S. *Anal. Chem.* **2000**, *72*, 2433.
24. Kempen, E. C.; Brodbelt, J. S. *Anal. Chem.* **2000**, *72*, 5411.
25. Blair, S. M.; Brodbelt, J. S.; Marchand, A. P.; Chong, H. S.; Alidhodzic, S. *J. Am. Soc. Mass Spectrom.* **2000**, *11*, 884.
26. Reyzer, M. L.; Brodbelt, J. S.; Marchand, A. P.; Chen, Z. B.; Huang, Z. L.; Namboothiri, I. N. N. *Int. J. Mass Spectrom.* **2001**, *204*, 133.
27. Kempen, E. C.; Brodbelt, J. S.; Bartsch, R.; Blanda, M. T.; Farmer, D. B. *Anal. Chem.* **2001**, *73*, 384.
28. Marchand, A. P.; Huang, Z. L.; Chen, Z. L.; Hariprakasha, H. K.; Namboothiri, I. N. N.; Brodbelt, J. S.; Reyzer, M. L. *J. Heterocycl. Chem.* **2001**, *38*, 1361.
29. Williams, S.; Blair, S. M.; Brodbelt, J. S.; Huang, X. W.; Bartsch, R. A. *Int. J. Mass Spectrom.* **2001**, *212*, 389.
30. Williams, S. M.; Brodbelt, J. S.; Marchand, A. P.; Cal, D. *Anal. Chem.* **2002**, *74*, 4423.
31. Williams, S. M.; Brodbelt, J. S.; Bartsch, R. A. *J. Am. Soc. Mass Spectrom.* **2003**, *14*, 1215.
32. Williams, S. M.; Brodbelt, J. S.; Huang, Z.; Lai, H.; Marchand, A. P. *The Analyst* **2003**, *128*, 1352.
33. Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402.
34. Weber, E. *Liebigs Ann. Chem.* **1983**, 770.
35. Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. *J. Org. Chem.* **2000**, *65*, 9160.
36. Mills, S. J.; Backers, K.; Erneux, C.; Potter, B. V. L. *Org. Biomol. Chem.* **2003**, 3546.
37. Schultz, R. A.; White, B. D.; Dishong, D. M.; Arnold, K. A.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6659.
38. Prepared in a manner paralleling that reported for an epimer: Billington, D. C.; Baker, R. *J. Chem. Soc., Chem. Commun.* **1987**, 1011.
39. Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553.

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The total synthesis of bistratamides F–I

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Dedicated to Professor Li-Xin Dai on the occasion of his 80th birthday

Abstract—The total synthesis of bistratamides F–I (**2**–**5**) have been achieved in overall yields of 3, 10, 13, and 27%, respectively. The thiazole substructure was prepared utilizing a MnO_2 oxidation of a thiazoline, synthesized from a Val-Cys dipeptide using bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate. The serine-based oxazole substructure was prepared from a Val-Ser dipeptide using literature methods. The threonine-derived oxazole substructure was synthesized from a ketoamide dipeptide using the bisphosphonium salt employed for thiazoline preparation. Most of the amide bonds were formed using HBTU and HOBt in the presence of DIEA. The final macrocyclization step was accomplished efficiently by PyBOP and DMAP in all cases.
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1. Introduction

Many oxazole and/or thiazole-containing macrocycles have been recently isolated from marine organisms.[1–2] Their activities as cytotoxic agents and multiple drug resistance inhibitors, as well as their metal binding and transport properties have led to much synthetic interest.[3] Bistratamides are a family of macrolactams isolated from *Lissoclinum bistratum* in the southern Philippines.[4] Their interesting biological activities led to total syntheses of three bistratamide family members.[5] Bistratamides E–J (**1**–**6**) were very recently isolated and exhibit moderate cytotoxic activity against a human colon tumor (HCT-116) cell line (Fig. 1).[4c] The antimicrobial, antitumor and the anti-drug resistance properties of members of this family of natural products warrant the synthetic efforts published thus far to prepare natural products related to bistratamides E–J.

Construction of the thiazoles in these macrolactams is central to their total synthesis. Commonly used methods for the preparation of thiazolines and thiazoles include (1) a modification of Hantzsch's procedure using thioamides as intermediates,[6] (2) a condensation reaction between cysteine esters and *N*-protected imino esters,[7] and (3) the cyclodehydration of β-hydroxythioamides using either Mitsunobu conditions or the Burgess reagent.[8–9] Thiazolines are readily converted into thiazoles by oxidation.[3a–d] Recently, we reported a facile and efficient biomimetic synthesis of thiazolines accomplished by treating *N*-acylated cysteines with bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate.[10] Dendroamide A, as well as bistratamides E (**1**) and J (**6**) have been recently efficiently synthesized by taking advantage of this methodology.[11] In this paper, we report the synthesis of bistratamides F–I (**2**–**5**, respectively) using bis(triphenyl)-oxodiphosphonium trifluoromethanesulfonate to construct the thiazoline and threonine-derived oxazole precursors. Amide bond formation was utilized to stitch the heterocyclic amino acids together while PyBOP and DMAP were employed to facilitate the final macrolactamization.

2. Results and discussion

The retrosynthetic analysis for bistratamide F (**2**) is shown in Figure 2. Disconnections at the amide bonds result in two Fmoc-protected α-amino acids and two heterocyclic amino acids derived from dipeptides.

The thiazole-containing fragment (**7**) was synthesized as shown in Scheme 1. The synthesis commences with the protection of the carboxylic acid of *N*-Fmoc-*S*-trityl-L-cysteine as an allyl ester. Fmoc deprotection allows the resulting amine to be coupled with an activated ester of *N*-Fmoc-L-valine to afford the fully protected dipeptide **9** (84% overall, 3 steps). Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate was utilized to convert the trityl

Keywords: Bistratamide; Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate; Oxazole; Thiazole.
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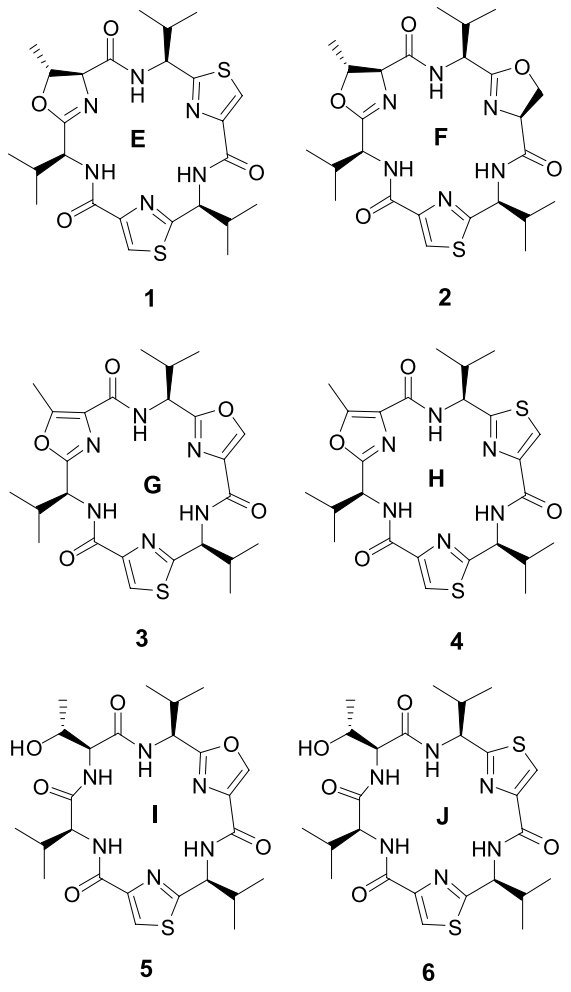


Figure 1. Bistratamides E–J (**1**–**6**).

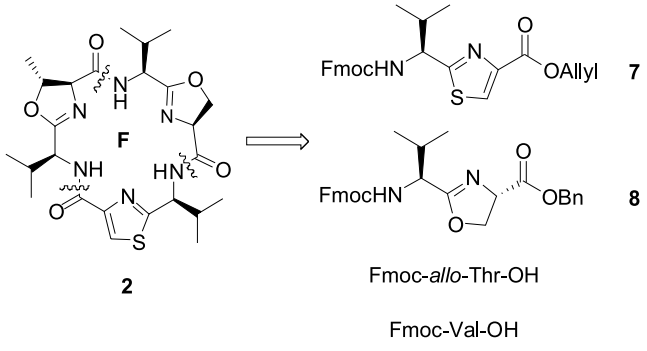
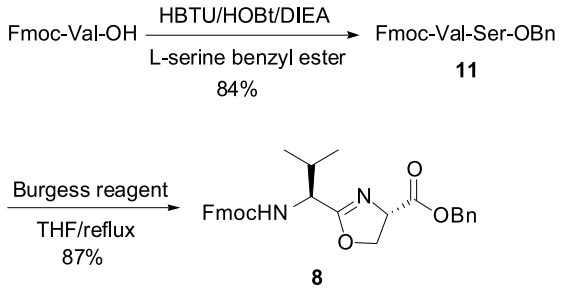


Figure 2. Retrosynthetic analysis for bistratamide F (**2**).

protected cysteine-containing dipeptide **9** into thiazoline **10** (89%). Thiazoline **10** was oxidized to a thiazole **7** employing activated manganese oxide (94%; >96% ee).[11b]

The synthesis of compound **8** is depicted in Scheme 2. Dipeptide **11** was synthesized by coupling *N*-Fmoc-L-valine and L-serine benzyl ester utilizing HBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and HOBt (*N*-hydroxybenzotriazole) in the presence of DIEA (*N*,*N*-diisopropylethylamine). Treating compound **11** with the Burgess reagent in refluxing THF afforded oxazoline **8** (87%).

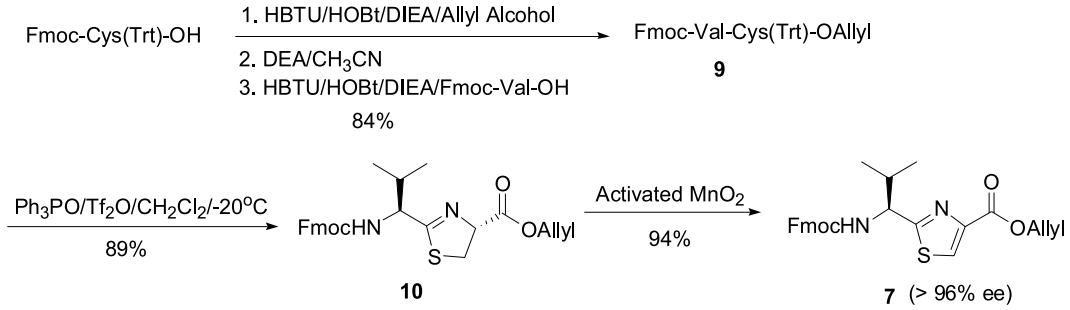


Scheme 2. Synthesis of the oxazoline-containing amino acid **8**.

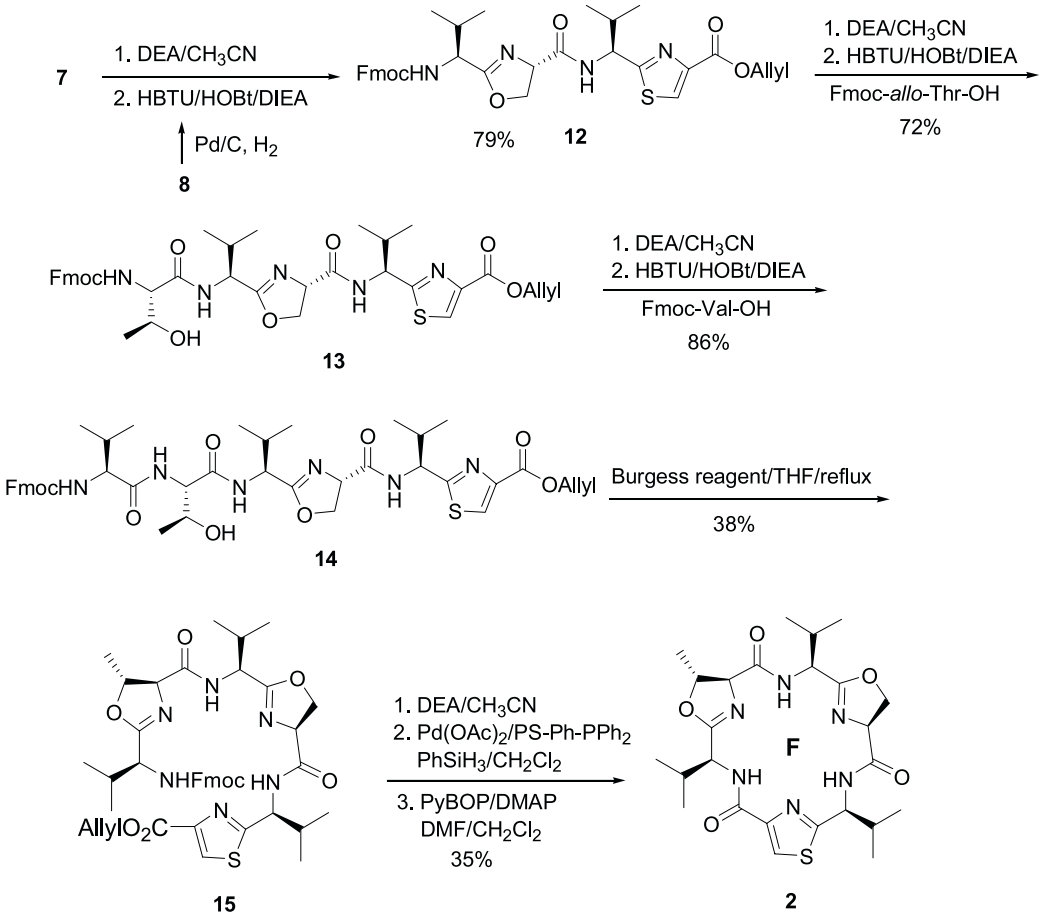
Thiazole **7** was coupled with the carboxylic acid resulting from removal of the benzyl protecting group from oxazoline **8** (using a Pd/C mediated hydrogenation) utilizing HBTU and HOBt in the presence of DIEA (Scheme 3). The resulting amide-linked bisheterocycle **12** was obtained in 79% yield. Compound **12** was coupled sequentially with *N*-Fmoc-*allo*-threonine and *N*-Fmoc-L-valine employing HBTU/HOBt/DIEA affording **13** (72%) and **14** (86%), respectively. Treating compound **14** with the Burgess reagent in refluxing THF afforded **15** (38%).

Removal of the Fmoc group in **15** using diethylamine followed by cleavage of the allyl ester using a palladium catalyst,[12] generated from $Pd(OAc)_2$ and polymer-supported triphenylphosphine, gave the amino acid macrolide precursor. The final cyclization mediated by PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and DMAP (4-dimethylaminopyridine) yielded **2** (35%). Bistratamide F (**2**) was obtained as a white semisolid having identical ^{1}H and ^{13}C NMR spectra to those reported in the literature.[4c]

The retrosynthetic analysis for bistratamide G (**3**) is outlined



Scheme 1. Synthesis of the thiazole-containing amino acid **7**.



Scheme 3. Completion of the synthesis of bistratamide F (**2**).

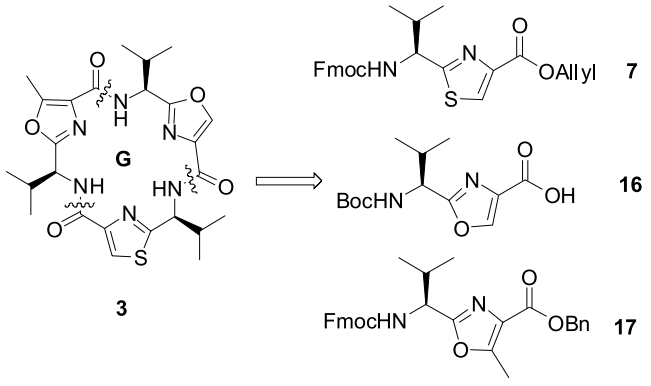
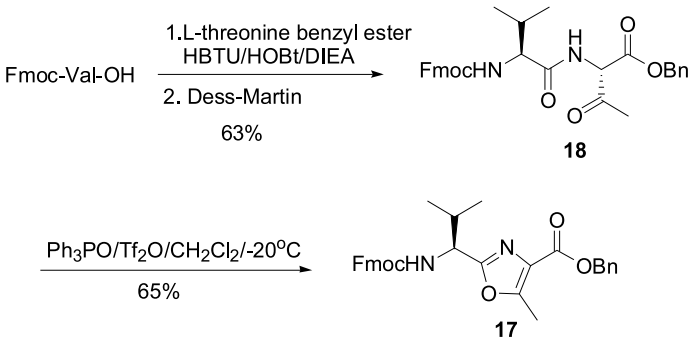


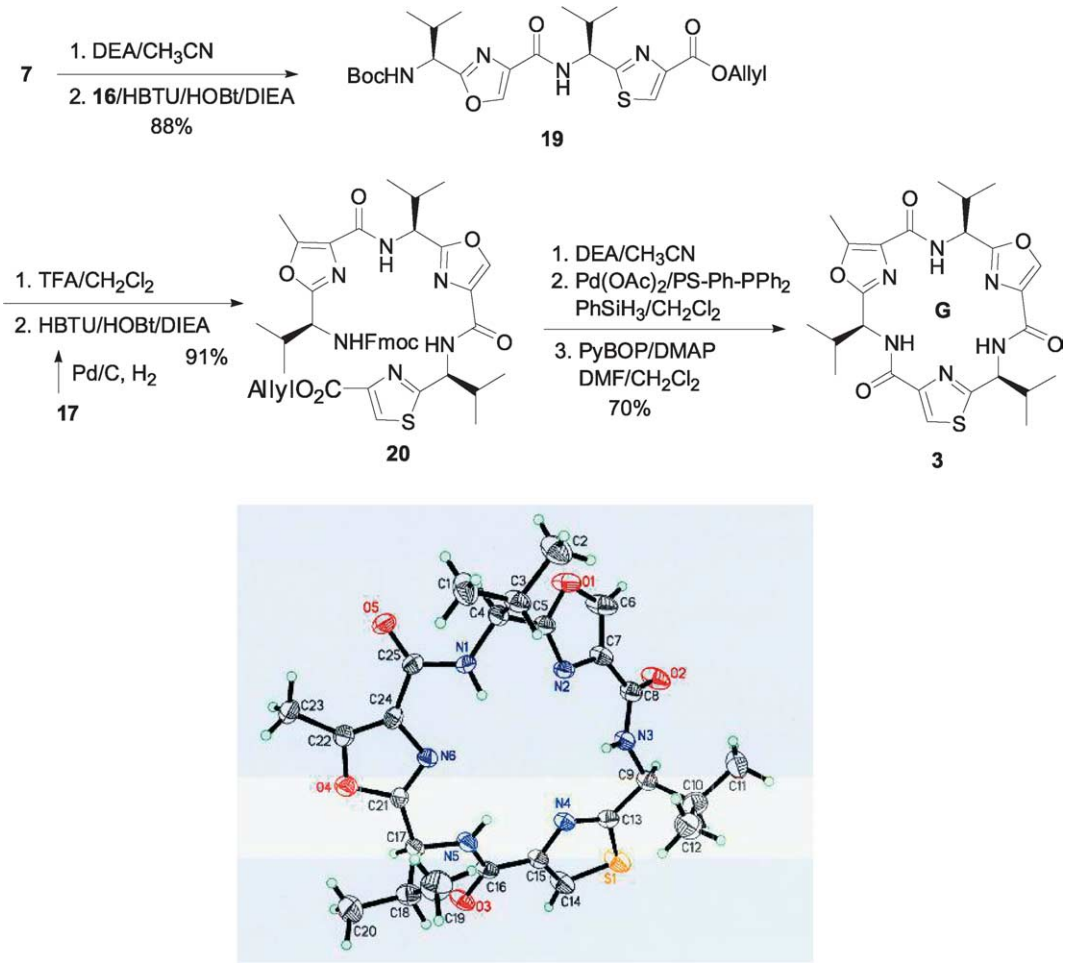
Figure 3. Retrosynthetic analysis for bistratamide G (**3**).

in Figure 3. Disconnections at the amide bonds result in three heterocyclic amino acids derived from dipeptides. The synthesis of compound **16** was performed following a known procedure.[5b,13] The synthesis of oxazole **17** is shown in Scheme 4. Coupling *N*-Fmoc-L-valine to L-threonine benzyl ester gave a dipeptide, which afforded ketone **18** when the dipeptide was subjected to a Dess–Martin oxidation.[14] Bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate was used to convert the β-ketodipeptide **18** to the protected oxazole amino acid **17** (65%) without compromising the valine-derived stereocenter.

The carboxylic acid **16** was coupled with the free amine generated by removing the Fmoc group from **7** (diethylamine) utilizing HBTU and HOBt in the presence of DIEA



Scheme 4. Synthesis of the oxazole-containing amino acid **17**.



Scheme 5. Completion of the synthesis of bistratamide G (**3**) and an ORTEP diagram of the X-ray structure of bistratamide G (**3**).

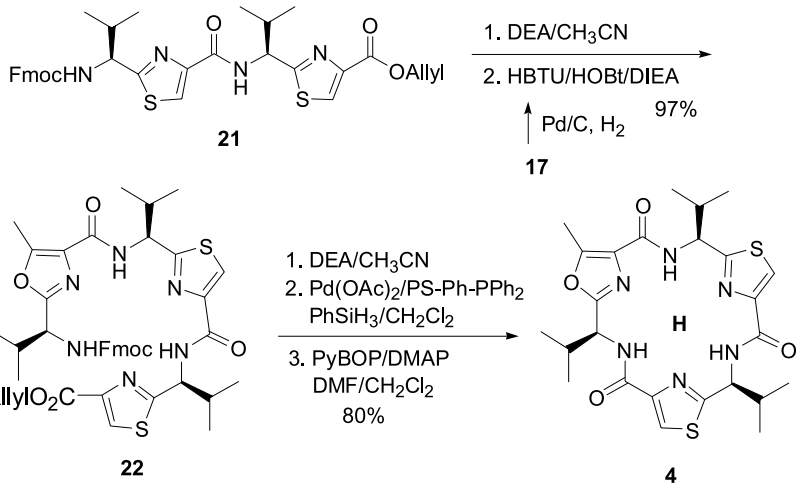
(Scheme 5). The bisheterocyclic amino acid **19** was thus obtained in 88% yield. The Boc group in **19** was removed by a TFA treatment. The resulting free amine was coupled with the amino acid generated from **17** by removal of the benzyl group (using a Pd/C mediated hydrogenation), yielding **20** (91%). Removal of the Fmoc and allyl groups in **20** as described above for **15** gave the amino acid macrolide precursor. The final macrolactamization was mediated by PyBOP and DMAP yielding **3** (70%). Bistratamide G (**3**) was obtained as a white solid having identical ^{1}H and ^{13}C NMR spectra to those reported in the literature.[4c] The structure of **3** was also verified by X-ray crystallography (Scheme 5).[15]

Bistratamide H (**4**) was synthesized from oxazole **17** and the bisheterocyclic amino acid **21** (Scheme 6), which was easily prepared from the coupling of two differentially protected molecules derived from thiazole **7**.[11b] The bisheterocyclic amino acid **21** was coupled with the carboxylic acid resulting from deprotection of **17**, affording **22** in 97% yield. Removal of the Fmoc and allyl groups in **22**, as described above, afforded the amino acid macrolide precursor. PyBOP and DMAP promoted the final macrolactamization yielding bistratamide H (**4**) (80%), which exhibited identical ^{1}H and ^{13}C NMR spectra to those reported in the literature.[4c]

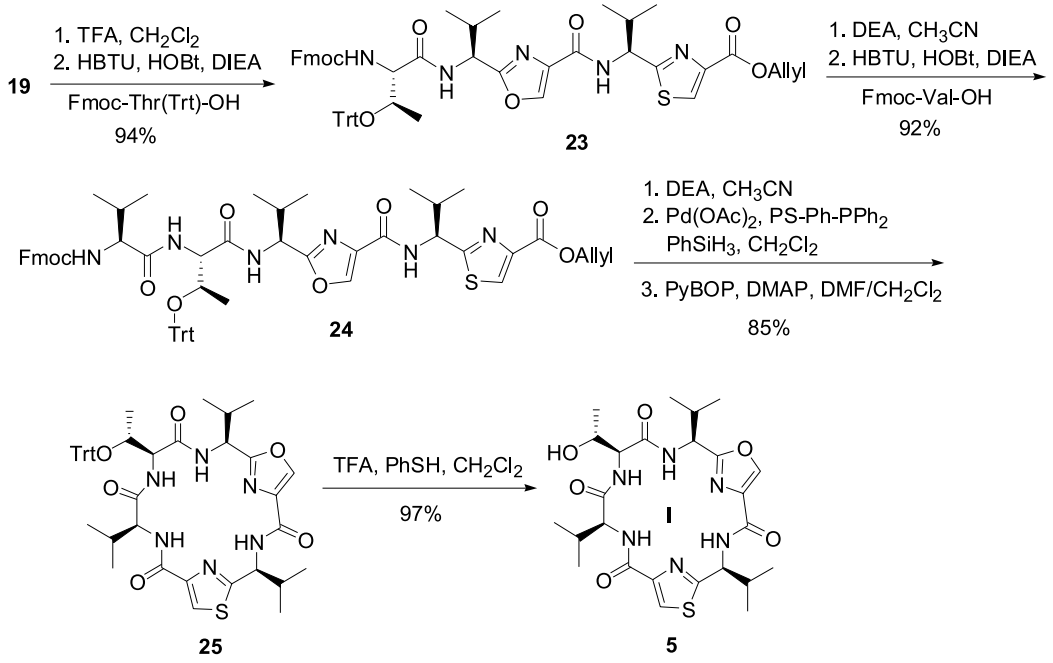
The synthesis of bistratamide I (**5**) is outlined in Scheme 7. The Boc-protected amine within **19**, liberated by TFA treatment, was coupled sequentially to *N*-Fmoc-*O*-trityl-L-threonine and *N*-Fmoc-L-valine employing HBTU/HOBt/DIEA affording **23** (94%) and **24** (92%), respectively. Removal of the Fmoc and allyl groups within **24** yielded the amino acid macrolide precursor. The final macrolactamization mediated by PyBOP and DMAP afforded **25** (85%). Bistratamide I (**5**) was obtained as a white semisolid after removing the trityl group from **25** utilizing 2% TFA in CH_2Cl_2 in the presence of 1 equiv of PhSH. Its ^{1}H and ^{13}C NMR spectra are identical to those reported in the literature.[4c]

3. Conclusions

The total synthesis of bistratamides F–I (**2**–**5**) have been accomplished for the first time. The thiazoles were prepared by oxidation of thiazolines. The latter were synthesized from cysteine containing amides wherein a Val-Cys dipeptide was converted to a thiazoline amino acid by bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate. The oxazole substructure was synthesized from a ketoamide dipeptide derived from a Val-Thr dipeptide (Dess–Martin oxidation) using the same bisphosphonium salt. The serine-derived oxazole amino acid, a known compound, was



Scheme 6. Completion of the synthesis of bistratamide H (**4**).



Scheme 7. Completion of the synthesis of bistratamide I (**5**).

prepared as described previously.[5b] PyBOP and DMAP efficiently promoted the final macrolactamizations in all cases.

4. Experimental

4.1. General methods

Unless stated otherwise, all reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purchased from Fisher and were dried prior to use. 'Regular workup' was as follows: the reaction mixture was diluted with EtOAc, washed with water, 10% $NaHCO_3$ (aq), and brine, the organic layer was dried over anhydrous Na_2SO_4 and then filtered and concentrated under reduced pressure to yield the crude product. ^1H NMR spectra were recorded at 600 MHz on a Bruker DRX spectrometer. ^{13}C NMR spectra were recorded at 150 MHz on a Bruker DRX-600 spectrometer. The chemical shift assignments for major diastereomers, not for minor diastereomers, were reported. Flash chromatography was performed on silica gel 60 (230–400 mesh, E. Merck no. 9385). Procedures for synthesis of compounds **7**, **9**, **10**, **21** were described elsewhere.[11b]

4.1.1. Compound 8. Compound **11** (413 mg, 0.8 mmol) and the Burgess reagent (214 mg, 0.9 mmol) were suspended in THF (10 mL). The mixture was refluxed for 2 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes = 1/2) to afford compound **8** (347 mg, 87%) as a white foam: $[\alpha]_D^{24} = +22.6$ (c 0.74, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 25 °C,

TMS) δ 0.91 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 2.12–2.15 (m, 1H), 4.21 (t, J=7.0 Hz, 1H), 4.36–4.45 (m, 4H), 4.52 (t, J=7.5 Hz, 1H), 4.78 (t, J=8.8 Hz, 1H), 5.16–5.23 (m, 2H), 5.53 (m, 1H), 7.24–7.39 (m, 9H), 7.60 (dd, J=8.3, 8.8 Hz, 2H), 7.75 (d, J=7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.2, 18.7, 31.6, 47.1, 54.2, 66.9, 67.3, 67.7, 70.3, 119.9, 125.1, 127.0, 127.6, 128.4, 128.5 (2C), 135.1, 141.2, 143.7, 143.9, 156.1, 169.9, 170.7; HRMS (MALDI-FTMS) calcd for $C_{30}H_{30}N_2O_5$ ($M+Na^+$) 521.2047, found 521.2048.

4.1.2. Compound 11. To a solution of *N*-Fmoc-L-valine (339 mg, 1 mmol), HBTU (417 mg, 1.1 mmol) and $HOBt\cdot H_2O$ (168 mg, 1.1 mmol) in DMF (4 mL), DIEA (0.54 mL, 3.1 mmol) and L-serine benzyl ester hydrochloride (232 mg, 1 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 8 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes=1/1) to afford compound **11** (433 mg, 84%) as a white foam: $[\alpha]_D^{24}=-14.0$ (c 0.25, DMSO); ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.85 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H), 1.97–2.03 (m, 1H), 3.67–3.71 (m, 1H), 3.76–3.79 (m, 1H), 4.02 (dd, J=7.0, 8.8 Hz, 1H), 4.20–4.23 (m, 2H), 4.27–4.31 (m, 1H), 4.44 (d, J=4.8, 11.8 Hz, 1H), 5.13–5.15 (m, 3H), 7.31–7.36 (m, 7H), 7.41 (t, J=7.5 Hz, 2H), 7.45 (d, J=9.2 Hz, 1H), 7.76 (d, J=7.5 Hz, 2H), 7.89 (d, J=7.5 Hz, 2H), 8.37 (d, J=7.5 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 18.1, 19.1, 30.5, 46.7, 54.8, 59.7, 61.2, 65.7, 65.9, 120.1, 125.4, 127.1, 127.6, 127.7, 127.9, 128.3, 135.9, 140.7 (2C), 143.8, 143.9, 156.1, 170.3, 171.5; HRMS (MALDI-FTMS) calcd for $C_{30}H_{32}N_2O_6$ ($M+Na^+$) 539.2152, found 539.2144.

4.1.3. Compound 12 (general procedure for Pd/C mediated hydrogenation, diethylamine-mediated deprotection of Fmoc group and HBTU, HOBt-mediated peptide coupling). Pd on activated carbon (30 mg) was added to a flask containing **8** (329 mg, 0.66 mmol) in MeOH (5 mL) and THF (5 mL). The reaction flask was fitted with H_2 balloon, and evacuated and purged with H_2 three times. The reaction progress was monitored by TLC and was complete in 1 h. After removing the solvent, the residue was passed through a short silica gel column and eluted with MeOH. The carboxylic acid was used in next step without further purification. In another flask, diethylamine (3 mL) was added to a solution of **7** (277 mg, 0.6 mmol) in CH_3CN (3 mL) and the resulting mixture was stirred at 25 °C for 30 min to ensure complete removal of the Fmoc protecting group. After concentration in vacuo, the reaction mixture was azeotroped to dryness with CH_3CN (2×3 mL) and the residue was dissolved in DMF (3 mL). This amine solution was added to a solution of above carboxylic acid, HBTU (277 mg, 0.73 mmol), $HOBt\cdot H_2O$ (112 mg, 0.73 mmol) and DIEA (0.24 mL, 1.4 mmol) in DMF (3 mL). The reaction mixture was stirred at 25 °C for 8 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes=1/2) to afford compound **12** (299 mg, 79%) as a white foam: $[\alpha]_D^{24}=-16.8$ (c 0.77, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.90 (d, J=6.6 Hz, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.98 (d, J=7.0 Hz, 3H), 1.00 (d, J=6.6 Hz, 3H), 2.14–2.18 (m, 1H), 2.44–2.50 (m, 1H), 4.25 (t, J=7.0 Hz, 1H), 4.35–4.38 (m, 1H), 4.42–4.47 (m, 2H), 4.52–4.59 (m, 2H), 4.74 (d, J=8.8, 10.5 Hz, 1H), 4.83 (d, J=5.3 Hz, 2H), 5.19 (dd, J=7.0, 8.3 Hz, 1H), 5.27 (d, J=10.5 Hz, 1H), 5.38 (d, J=17.1 Hz, 1H), 5.57 (d, J=8.8 Hz, 1H), 5.99–6.03 (m, 1H), 7.29–7.32 (m, 2H), 7.35 (d, J=8.8 Hz, 1H), 7.39 (t, J=7.5 Hz, 2H), 7.61 (d, J=7.9 Hz, 1H), 7.63 (d, J=7.5 Hz, 1H), 7.76 (d, J=7.5 Hz, 2H), 8.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7 (2C), 18.8, 19.3, 31.3, 32.9, 47.1, 54.6, 56.1, 65.9, 67.0, 68.2, 70.8, 118.9, 119.9, 125.0, 127.0, 127.6, 131.7, 141.2, 143.7, 143.8, 146.9, 156.1, 160.7, 169.7, 171.2; HRMS (MALDI-FTMS) calcd for $C_{34}H_{38}N_4O_6S$ ($M+H^+$) 631.2585, found 631.2566.

4.1.4. Compound 13. Compound **13** was synthesized from **12** in a 72% yield as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-23.2$ (c 0.34, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.88 (d, J=6.6 Hz, 3H), 0.93 (d, J=6.6 Hz, 3H), 0.96 (d, J=7.0 Hz, 3H), 1.01 (d, J=6.6 Hz, 3H), 1.27 (d, J=6.1 Hz, 3H), 2.28–2.31 (m, 1H), 2.35–2.40 (m, 1H), 3.92 (dd, J=6.1, 6.6 Hz, 1H), 4.21 (m, 2H), 4.33–4.41 (m, 2H), 4.60–4.62 (m, 2H), 4.68 (m, 1H), 4.73–4.75 (m, 1H), 4.86 (d, J=5.7 Hz, 2H), 4.96 (br, 1H), 5.16 (dd, J=6.1, 8.3 Hz, 1H), 5.30 (d, J=10.5 Hz, 1H), 5.41 (d, J=17.1 Hz, 1H), 5.91 (d, J=8.3 Hz, 1H), 6.01–6.05 (m, 1H), 7.27–7.30 (m, 3H), 7.39 (t, J=7.5 Hz, 2H), 7.51 (d, J=8.3 Hz, 1H), 7.58 (t, J=7.5 Hz, 2H), 7.75 (d, J=7.5 Hz, 2H), 8.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.2, 17.7, 18.9 (2C), 19.7, 30.0, 33.4, 38.5, 47.0, 52.9, 56.3, 59.6, 66.1, 67.1, 67.6, 69.3, 71.8, 119.0, 119.9, 125.0 (2C), 127.0, 127.3, 127.6, 131.6, 141.2, 143.6, 143.7, 146.4, 156.3, 160.8, 170.3, 170.7, 171.5; HRMS (MALDI-FTMS) calcd for $C_{38}H_{45}N_5O_8S$ ($M+H^+$) 732.3061, found 732.3045.

4.1.5. Compound 14. Compound **14** was synthesized from **13** in a 86% yield as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-23.1$ (c 0.85, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.87 (d, J=6.6 Hz, 3H), 0.92–0.95 (m, 12H), 0.97 (d, J=6.6 Hz, 3H), 1.24 (d, J=6.1 Hz, 3H), 2.09–2.12 (m, 1H), 2.21–2.23 (m, 1H), 2.36–2.41 (m, 1H), 3.98 (t, J=6.1 Hz, 1H), 4.15–4.20 (m, 2H), 4.30 (dd, J=7.0, 10.5 Hz, 1H), 4.40 (dd, J=7.5, 10.5 Hz, 1H), 4.51 (dd, J=7.9, 8.8 Hz, 1H), 4.54–4.59 (m, 2H), 4.65–4.70 (m, 2H), 4.85 (t, J=5.7 Hz, 2H), 4.93 (br, 1H), 5.16 (dd, J=6.1, 8.3 Hz, 1H), 5.28 (d, J=10.5 Hz, 1H), 5.40 (d, J=17.5 Hz, 1H), 5.74 (d, J=9.2 Hz, 1H), 5.98–6.04 (m, 1H), 7.26–7.30 (m, 3H), 7.36–7.39 (m, 2H), 7.41 (d, J=8.8 Hz, 1H), 7.51 (d, J=8.3 Hz, 1H), 7.57 (dd, J=7.0, 7.5 Hz, 2H), 7.74 (d, J=7.9 Hz, 2H), 8.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.4, 17.7, 17.8, 18.8, 18.9, 19.1, 19.8, 30.3, 31.4, 33.4, 47.0, 52.9, 56.3, 57.9, 60.1, 66.1, 67.0, 67.7, 68.9, 71.5, 119.0, 119.9, 125.0, 127.0, 127.3, 127.6, 131.7, 141.2, 143.7, 143.8, 146.5, 156.3, 160.8, 170.2, 170.4, 170.7, 170.0, 171.6; HRMS (MALDI-FTMS) calcd for $C_{43}H_{54}N_6O_9S$ ($M+H^+$) 831.3746, found 831.3756.

4.1.6. Compound 15. Compound **15** was synthesized from **14** in a 38% yield as a white foam by following the procedure used for the synthesis of **8**: $[\alpha]_D^{24}=-7.1$ (c 0.31, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.89 (d, J=7.0 Hz, 3H), 0.92–0.94 (m, 9H), 0.98 (d, J=8.3 Hz, 3H), 1.00 (d, J=7.5 Hz, 3H), 1.51 (d, J=6.1 Hz, 3H), 2.15–2.17 (m, 1H), 2.47–2.49 (m, 2H), 4.21–4.22 (m, 2H), 4.34–

4.44 (m, 3H), 4.55–4.59 (m, 2H), 4.67 (dd, J=5.7, 8.8 Hz, 1H), 4.73–4.77 (m, 1H), 4.78–4.80 (m, 3H), 5.19 (dd, J=6.6, 8.8 Hz, 1H), 5.26 (d, J=10.1 Hz, 1H), 5.36 (dd, J=17.1 Hz, 1H), 5.57 (d, J=8.8 Hz, 1H), 5.96–6.00 (m, 1H), 7.11 (d, J=9.2 Hz, 1H), 7.27–7.29 (m, 2H), 7.37–7.42 (m, 3H), 7.58 (t, J=6.6 Hz, 2H), 7.76 (d, J=7.5 Hz, 2H), 8.04 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.6, 17.7, 17.9, 18.8, 18.9, 19.4, 21.8, 31.2, 31.4, 33.0, 47.1, 52.2, 54.8, 56.2, 65.9, 67.0, 68.3, 70.8, 74.5, 80.7, 118.9, 120.0, 125.0 (2C), 127.0, 127.2, 127.7, 131.7, 141.2, 143.7, 143.8, 146.9, 156.0, 160.7, 168.9, 169.1, 171.0, 171.3, 171.5; HRMS (MALDI-FTMS) calcd for $C_{43}H_{52}N_6O_8S$ ($M+H^+$) 813.3640, found 813.3633.

4.1.7. Bistratamide F (2) (general procedure for removal of the allyl ester protecting group, PyBOP and DMAP-mediated macrocyclization). Deprotection of the Fmoc group in **15** (81.3 mg, 0.1 mmol) followed the procedure described in the synthesis of **12**. To remove the allyl group, $Pd(OAc)_2$ (1.12 mg, 5 μmol) and polystyrene-triphenylphosphine (25.2 mg, 1.59 mol/g, 0.04 mmol) were added to a flask containing CH_2Cl_2 (5 mL). After stirring for 10 min, the above amino ester in CH_2Cl_2 (2 mL) and $PhSiH_3$ (0.025 mL, 0.2 mmol) were added separately. The reaction progress was monitored by TLC and completed in 15 min. After removing the solvent, the residue was passed through a short silica gel column and eluted with $CHCl_3$/EtOH (1/2). After removing the solvents, the macrolide precursor was redissovled in CH_2Cl_2/DMF (5 mL, v/v: 2/1). This solution was added to a flask containing PyBOP (104 mg, 0.2 mmol) and DMAP (24.4 mg, 0.2 mmol) in CH_2Cl_2/DMF (20 mL, v/v: 2/1) over 8 h using a syringe pump. After the completion of addition, the mixture was stirred for 2 h. Regular workup and purification by flash chromatography (EtOAc/hexanes=4/1) gave **2** (18.6 mg, 35%) as a white foam: $[\alpha]_D^{24}=+25.3$ (c 0.30, MeOH) {lit[4c] $[\alpha]_D^{25}=+23.2$ (c 1.0, MeOH)}; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.76 (d, J=7.0 Hz, 3H), 0.80 (d, J=6.6 Hz, 3H), 0.81 (d, J=6.6 Hz, 3H), 0.84 (d, J=6.9 Hz, 3H), 0.85 (d, J=7.0 Hz, 3H), 0.89 (d, J=7.0 Hz, 3H), 1.48 (d, J=6.1 Hz, 3H), 2.12 (m, 1H), 2.21 (m, 1H), 2.33 (m, 1H), 4.31 (dd, J=2.2, 8.3 Hz, 1H), 4.38 (t, J=7.5 Hz, 1H), 4.60 (br, d, J=8.8 Hz, 1H), 4.78–4.85 (m, 4H), 5.30 (dd, J=4.8, 7.9 Hz, 1H), 7.64 (d, J=8.8 Hz, 1H), 7.73 (d, J=7.5 Hz, 1H), 7.99 (d, J=9.2 Hz, 1H), 8.37 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 15.9, 16.0, 17.2, 17.8, 18.5, 18.7, 21.4, 30.7, 30.8, 33.7, 51.1, 51.3, 54.7, 66.7, 72.4, 72.7, 81.8, 124.9, 147.9, 159.0, 160.4, 167.6, 168.9, 169.7, 169.8; HRMS (MALDI-FTMS) calcd for $C_{25}H_{36}N_6O_5S$ ($M+H^+$) 533.2541, found 533.2519.

4.1.8. Compound 17. To a solution of triphenylphosphine oxide (835 mg, 3 mmol) in dry CH_2Cl_2 (10 mL), trifluoromethanesulfonic anhydride (0.24 mL, 1.5 mmol) was added slowly at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then adjusted to −20 °C using a brine-ice bath. Then **18** (528 mg, 1 mmol) was added. The reaction progress was monitored by TLC and completed in 2 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes=1/3) to afford compound **17** (332 mg, 65%) as a white foam: $[\alpha]_D^{24}=+31.1$ (c 0.72, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.92 (d, J=7.0 Hz, 3H), 0.95 (d, J=6.6 Hz, 3H), 2.18–2.23 (m, 1H), 2.57 (s, 3H), 4.21 (t, J=7.0 Hz, 1H), 4.36–4.43 (m, 2H), 4.79 (dd, J=6.1, 6.8 Hz, 1H), 5.35 (AB, J_{AB}=12.3 Hz, 1H), 5.38 (AB, J_{AB}=12.3 Hz, 1H), 5.57 (d, J=8.8 Hz, 1H), 7.28–7.40 (m, 9H), 7.60 (dd, J=7.5, 7.9 Hz, 2H), 7.75 (d, J=7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.2, 18.0, 18.7, 32.7, 47.1, 54.6, 66.6, 67.0, 119.9, 125.0, 127.0, 127.4, 127.6, 128.3, 128.4, 128.5, 135.6, 141.2, 143.6, 143.8, 156.0, 156.3, 161.7, 161.9; HRMS (MALDI-FTMS) calcd for $C_{31}H_{30}N_2O_5S$ ($M+Na^+$) 533.2047, found 533.2060.

4.1.9. Compound 18. *N*-Fmoc-L-valine and L-threonine benzyl ester oxalate were coupled by following the procedure used for the synthesis of **12** to give the dipeptide (5 mmol scale). The resulting dipeptide was suspended in 150 mL CH_2Cl_2, then Dess–Martin periodinane (3.06 g, 97%, 7 mmol) was added. The resulting reaction mixture was stirred at 25 °C for 1 h. After regular workup, the resulting crude product was purified by flash chromatography (EtOAc/hexanes=1/3) to afford compound **18** (1.66 g, 63%) as a gel: $[\alpha]_D^{24}=-12.9$ (c 0.38, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.85–0.98 (m, 6H), 2.10–2.13 (m, 1H), 2.28 (s, 3H), 4.19–4.21 (m, 2H), 4.35–4.43 (m, 2H), 5.16–5.29 (m, 3H), 5.50–5.57 (m, 1H), 7.16–7.34 (m, 10H), 7.37–7.39 (m, 2H), 7.58–7.76 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.7, 19.1, 28.1, 31.3, 47.1, 59.8, 63.2, 67.1, 68.3, 119.9, 125.1, 127.0, 127.7, 128.5 (2C), 128.7, 128.8 (2C), 133.0, 134.4, 141.2, 141.6, 143.7, 143.8, 156.3, 165.5, 171.2, 197.7; HRMS (MALDI-FTMS) calcd for $C_{31}H_{32}N_2O_6$ ($M+Na^+$) 551.2152, found 551.2146.

4.1.10. Compound 19. Compound **19** was synthesized from **7** and **16** in a 88% yield as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-57.1$ (c 0.28, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.94 (d, J=6.6 Hz, 3H), 0.95 (d, J=8.3 Hz, 3H), 0.99 (d, J=7.0 Hz, 3H), 1.05 (d, J=6.6 Hz, 3H), 1.46 (s, 9H), 2.19–2.21 (m, 1H), 2.59–2.63 (m, 1H), 4.78 (dd, J=8.3, 6.1 Hz, 1H), 4.86 (d, J=5.7 Hz, 2H), 5.17 (d, J=8.3 Hz, 1H), 5.29–5.31 (m, 2H), 5.41 (d, J=17.1 Hz, 1H), 6.01–6.07 (m, 1H), 7.55 (d, J=9.2 Hz, 1H), 8.12 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.9, 18.1, 18.6, 19.6, 28.3, 32.7, 33.0, 54.2, 56.0, 65.9, 80.1, 118.8, 127.3, 131.8, 135.4, 141.2, 147.1, 155.3, 160.2, 160.8, 163.9, 171.3; HRMS (MALDI-FTMS) calcd for $C_{24}H_{34}N_4O_6S$ ($M+Na^+$) 529.2091, found 529.2093.

4.1.11. Compound 20. To a solution of **19** (507 mg, 1 mmol) in CH_2Cl_2 (10 mL), TFA (2.5 mL) was added. After stirring for 20 min, the solvent was removed. The residue was azeotroped with toluene to remove TFA. The resulting oil was dissolved in DMF (4 mL) and DIEA was added to neutralize. This amine was coupled with **17** yielding **20** (736 mg, 91%) as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-37.6$ (c 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.95 (d, J=6.6 Hz, 3H), 0.96–0.99 (m, 9H), 1.02 (d, J=7.0 Hz, 3H), 1.04 (d, J=6.6 Hz, 3H), 2.21–2.25 (m, 1H), 2.30–2.34 (m, 1H), 2.46 (br, 1H), 2.55–2.59 (m, 1H), 2.62 (s, 3H), 4.22 (dd, J=6.6, 7.0 Hz, 1H), 4.40–4.49 (m, 2H), 4.77 (dd, J=7.0, 8.8 Hz, 1H), 4.82 (m, 2H), 5.20 (dd, J=7.0, 9.2 Hz, 1H), 5.26–5.31 (m, 2H), 5.38 (d, J=17.1 Hz, 1H), 5.51 (d,

J=9.2 Hz, 1H), 5.98–6.02 (m, 1H), 7.26–7.29 (m, 2H), 7.36–7.39 (m, 3H), 7.58 (dd, J=7.5, 12.7 Hz, 2H), 7.61 (d, J=9.7 Hz, 1H), 7.75 (d, J=7.5 Hz, 2H), 8.06 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.6, 17.9, 18.0, 18.3, 18.8, 18.9, 19.5, 32.2 (2C), 32.9, 47.1, 52.1, 54.7, 56.0, 65.8, 66.8, 118.7, 119.9, 124.8 (2C), 126.9, 127.2, 127.6, 128.4, 131.7, 135.4, 141.2 (2C), 141.4, 143.5, 143.7, 146.9, 153.6, 155.9, 160.2, 160.4, 160.7, 161.4, 163.1, 171.4; HRMS (MALDI-FTMS) calcd for $C_{43}H_{48}N_6O_8S$ ($M+H^+$) 809.3327, found 809.3318.

4.1.12. Bistratamide G (3). Compound **3** was synthesized from **20** in a 70% yield as a white solid by following the procedure used for the synthesis of **2**: mp 224–226 °C; $[\alpha]_D^{24}=-84.4$ (c 0.97, MeOH) {lit[4c] $[\alpha]_D^{25}=-73.8$ (c 1.0, MeOH)}; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.88 (d, J=6.6 Hz, 3H), 0.91 (d, J=6.6 Hz, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.94 (d, J=7.0 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 0.97 (d, J=7.0 Hz, 3H), 2.15–2.22 (m, 2H), 2.27–2.31 (m, 1H), 2.54 (s, 3H), 5.01 (dd, J=4.4, 7.5 Hz, 1H), 5.09 (dd, J=5.7, 8.8 Hz, 1H), 5.39 (dd, J=6.1, 8.8 Hz, 1H), 8.30 (d, J=7.0 Hz, 1H), 8.32 (d, J=9.2 Hz, 1H), 8.35 (s, 1H), 8.44 (d, J=8.8 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 11.1, 18.0, 18.1, 18.2, 18.3, 18.6, 32.6, 32.9, 34.6, 52.1, 52.7, 54.8, 125.2, 128.0, 134.5, 142.9, 147.9, 152.8, 158.4, 159.3, 160.2, 160.5, 163.2, 168.3; HRMS (MALDI-FTMS) calcd for $C_{25}H_{32}N_6O_5S$ ($M+H^+$) 529.2228, found 529.2221.

4.1.13. Compound 22. Compound **22** was synthesized from **21** and **17** in a 97% yield as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-27.1$ (c 0.77, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.94 (d, J=6.6 Hz, 3H), 0.97 (d, J=7.0 Hz, 3H), 1.00 (d, J=7.0 Hz, 3H), 1.03 (d, J=7.5 Hz, 6H), 1.05 (d, J=7.9 Hz, 3H), 2.20–2.23 (m, 1H), 2.52–2.55 (m, 1H), 2.62–2.65 (m, 1H), 2.63 (s, 3H), 4.21 (dd, J=6.6, 7.0 Hz, 1H), 4.40–4.49 (m, 2H), 4.77 (dd, J=6.6, 9.2 Hz, 1H), 4.83 (m, 2H), 5.28 (d, J=10.1 Hz, 1H), 5.31 (dd, J=6.1, 9.2 Hz, 1H), 5.34 (dd, J=6.6, 9.2 Hz, 1H), 5.39 (d, J=17.1 Hz, 1H), 5.45 (m, 1H), 5.99–6.04 (m, 1H), 7.24–7.28 (m, 2H), 7.37 (t, J=7.5 Hz, 2H), 7.46 (d, J=8.8 Hz, 1H), 7.57 (dd, J=7.9, 8.3 Hz, 2H), 7.75 (d, J=7.5 Hz, 2H), 7.99 (d, J=9.2 Hz, 1H), 8.01 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.7, 17.8 (2C), 18.0, 18.9, 19.4, 19.6, 32.3, 32.8, 33.0, 47.1, 54.7, 55.8, 56.4, 65.8, 66.8, 118.7, 119.9, 123.5, 124.8, 124.9, 126.9, 127.2, 127.7, 128.4, 131.8, 141.2 (2C), 143.5, 143.7, 147.0, 149.3, 153.7, 155.9, 160.5, 160.7, 160.8, 161.6, 171.8, 171.9; HRMS (MALDI-FTMS) calcd for $C_{43}H_{48}N_6O_7S_2$ ($M+H^+$) 825.3098, found 825.3084.

4.1.14. Bistratamide H (4). Compound **4** was synthesized from **22** in a 80% yield as a gel-like solid by following the procedure used for the synthesis of **2**: $[\alpha]_D^{24}=-106.2$ (c 1.1, MeOH) {lit[4c] $[\alpha]_D^{25}=-92.9$ (c 1.0, MeOH)}; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.90 (d, J=6.6 Hz, 3H), 0.93 (d, J=7.0 Hz, 6H), 0.94 (d, J=8.3 Hz, 3H), 0.96 (d, J=7.0 Hz, 3H), 0.98 (d, J=7.0 Hz, 3H), 2.16–2.25 (m, 3H), 2.58 (s, 3H), 5.07 (dd, J=5.3, 8.3 Hz, 1H), 5.35 (dd, J=5.3, 8.3 Hz, 1H), 5.45 (dd, J=7.0, 9.6 Hz, 1H), 8.33 (s, 1H), 8.35 (s, 1H), 8.36 (d, J=9.2 Hz, 1H), 8.49 (d, J=8.3 Hz, 1H), 8.52 (d, J=9.7 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 12.2, 18.9, 19.0, 19.1, 19.2, 19.4, 33.7, 35.3, 35.5, 53.2, 55.5, 55.7, 125.7, 126.2, 128.7, 148.7, 149.2, 154.2, 159.9, 160.4, 160.6, 161.4, 169.4, 169.9; HRMS (MALDI-FTMS) calcd for $C_{25}H_{32}N_6O_4S_2$ ($M+Na^+$) 567.1819, found 567.1810.

4.1.15. Compound 23. Compound **23** was synthesized from **19** and *N*-Fmoc-*O*-trityl-threonine in a 94% yield as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-15.0$ (c 0.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.80 (d, J=7.0 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 1.00 (d, J=7.0 Hz, 3H), 1.17 (d, J=6.1 Hz, 3H), 2.21–2.27 (m, 1H), 2.56–2.62 (m, 1H), 3.44 (br, 1H), 4.13 (t, J=7.5 Hz, 1H), 4.22–4.29 (m, 2H), 4.35 (br, 1H), 4.82 (d, J=5.7 Hz, 2H), 5.08 (dd, J=8.8, 6.6 Hz, 1H), 5.26 (d, J=10.5 Hz, 1H), 5.37 (d, J=17.1 Hz, 1H), 5.41 (dd, J=8.8, 6.6 Hz, 1H), 5.73 (d, J=4.8 Hz, 1H), 5.97–6.02 (m, 1H), 7.23–7.30 (m, 12H), 7.35–7.38 (m, 2H), 7.52–7.57 (m, 9H), 7.72–7.74 (m, 2H), 8.09 (s, 1H), 8.22 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.1, 17.6, 18.2, 19.0, 19.5, 31.8, 33.0, 47.0, 53.1, 56.1, 65.9, 66.7, 69.8, 88.6, 118.9, 119.9, 125.0, 125.1, 126.9 (2C), 127.2, 127.5, 127.6, 128.2, 128.7, 131.8, 135.6, 141.2, 141.6, 143.7 (d), 147.2, 155.0, 160.3, 160.8, 163.7, 169.6, 171.9; HRMS (MALDI-FTMS) calcd for $C_{57}H_{57}N_5O_8S$ ($M+Na^+$) 994.382, found 994.3805.

4.1.16. Compound 24. Compound **24** was synthesized from **23** in a 92% yield as a white foam by following the procedure used for the synthesis of **12**: $[\alpha]_D^{24}=-25.6$ (c 1.21, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.79 (d, J=6.6 Hz, 3H), 0.84 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H), 0.88 (d, J=6.6 Hz, 3H), 0.94 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.6 Hz, 3H), 1.13 (d, J=6.1 Hz, 3H), 2.04–2.06 (m, 1H), 2.20–2.22 (m, 1H), 2.55–2.58 (m, 1H), 3.62 (br, 1H), 4.01 (t, J=6.1 Hz, 1H), 4.19 (m, 1H), 4.32 (dd, J=10.5, 7.0 Hz, 1H), 4.37–4.42 (m, 2H), 4.82 (d, J=5.7 Hz, 2H), 5.04 (dd, J=8.3, 6.6 Hz, 1H), 5.26 (d, J=10.5 Hz, 1H), 5.37 (d, J=17.1 Hz, 1H), 5.40 (dd, J=9.2, 6.1 Hz, 1H), 5.45 (d, J=8.8 Hz, 1H), 5.96–6.01 (m, 1H), 6.81 (d, J=4.8 Hz, 1H), 7.22–7.29 (m, 11H), 7.38 (t, J=7.0 Hz, 2H), 7.54–7.58 (m, 10H), 7.60 (d, J=9.2 Hz, 1H), 7.75 (d, J=7.5 Hz, 1H), 8.07 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.3, 17.5, 17.6, 18.2, 18.9, 19.1, 19.5, 31.3, 31.7, 33.0, 47.1, 53.2, 55.4, 56.0, 60.0, 65.9, 66.9, 69.2, 88.6, 118.8, 119.9, 125.0, 127.0, 127.2, 127.5, 127.6, 128.1, 128.7, 131.8, 135.5, 141.2, 141.6, 143.6, 143.7, 143.9, 147.1, 156.2, 160.3, 160.8, 163.6, 169.5, 170.2, 171.8; HRMS (MALDI-FTMS) calcd for $C_{62}H_{66}N_6O_9S$ ($M+Na^+$) 1093.4504, found 1093.4547.

4.1.17. Compound 25. Compound **25** was synthesized from **24** in a 85% yield as a white foam by following the procedure used for the synthesis of **2**: $[\alpha]_D^{24}=-115.5$ (c 0.27, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS) δ 0.75 (d, J=6.6 Hz, 3H), 0.90 (d, J=7.0 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H), 0.98 (d, J=6.6 Hz, 3H), 1.00 (d, J=7.0 Hz, 3H), 1.09 (d, J=7.0 Hz, 3H), 1.46 (d, J=6.6 Hz, 3H), 2.17–2.22 (m, 1H), 2.35–2.38 (m, 1H), 2.54–2.56 (m, 1H), 3.65 (dd, J=5.3, 4.4 Hz, 1H), 4.53–4.55 (m, 1H), 4.63 (dd, J=10.5, 3.5 Hz, 1H), 4.76 (dd, J=6.1, 4.4 Hz, 1H), 5.22 (dd, J=9.7, 7.0 Hz, 1H), 6.84 (d, J=5.3 Hz, 1H), 7.26–7.29 (m, 3H), 7.33–7.35 (m, 6H), 7.45 (d, J=10.1 Hz,

1H), 7.55–7.57 (m, 7H), 7.95 (s, 1H), 8.09 (s, 1H), 8.11 (d, $J=6.6$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.1, 16.8, 18.0, 18.6, 18.7, 18.8, 19.9, 30.3, 30.4, 34.1, 54.5, 55.0, 56.4, 57.6, 68.8, 89.5, 122.8, 127.6, 128.1, 128.2, 128.8, 135.5, 143.6, 149.7, 160.0, 160.1, 162.5, 168.8, 169.9, 170.1; HRMS (MALDI-FTMS) calcd for $C_{44}H_{50}N_6O_6S$ ($M+Na^+$) 813.3405, found 813.3376.

4.1.18. Bistratamide I (5). To a flask containing **25** (158 mg, 0.2 mmol) in CH_2Cl_2 (5 mL), TFA (0.1 mL) and PhSH (21 μL, 0.2 mmol) were added. TLC showed that **25** disappeared in 5 min. After removing all of the solvents, the residue was purified by flash chromatography. Bistratamide I (**5**) was obtained as a white semisolid (106 mg, 97%): $[\alpha]_D^{24}=-129.4$ (*c* 0.36, MeOH){lit[4c] $[\alpha]_D^{25}=-122$ (*c* 0.5, MeOH)}; ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C) δ 0.86 (d, $J=6.6$ Hz, 3H), 0.91 (d, $J=6.6$ Hz, 3H), 0.96 (d, $J=7.0$ Hz, 3H), 0.99 (d, $J=6.6$ Hz, 3H), 1.00 (d, $J=6.6$ Hz, 3H), 1.03 (d, $J=6.6$ Hz, 3H), 1.11 (d, $J=6.1$ Hz, 3H), 2.10–2.24 (m, 3H), 4.08–4.11 (m, 1H), 4.31 (dd, $J=10.1$, 3.1 Hz, 1H), 4.37 (t, $J=11.0$ Hz, 1H), 5.06 (dd, $J=8.8$, 6.1 Hz, 1H), 5.30 (dd, $J=9.2$, 7.0 Hz, 1H), 5.36 (d, $J=7.0$ Hz, 1H), 8.04 (d, $J=8.8$ Hz, 1H), 8.31 (s, 1H), 8.32 (d, $J=9.2$ Hz, 1H), 8.40 (d, $J=10.1$ Hz, 1H), 8.56 (d, $J=10.5$ Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 18.2, 18.3, 18.4, 18.9, 19.2, 19.8, 21.1, 30.9, 33.2, 34.7, 52.2, 55.3, 59.1, 61.2, 67.3, 125.6, 135.0, 141.9, 148.0, 159.4, 159.6, 163.2, 169.4, 170.1, 170.3; HRMS (MALDI-FTMS) calcd for $C_{25}H_{36}N_6O_6S$ ($M+Na^+$) 571.2309, found 571.2324.

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References and notes

1. Reviews: (a) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.
2. (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1991**, *32*, 2593. (c) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron* **1995**, *51*, 7321. (d) Ogino, J.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581. (e) Admi, V.; Afek, U.; Carmeli, S. *J. Nat. Prod.* **1996**, *59*, 396. (f) Banker, R.; Carmeli, S. *J. Nat. Prod.* **1998**, *61*, 1248. (g) Ishida, K.; Nakagawa, H.; Murakami, M. *J. Nat. Prod.* **2000**, *63*, 1315. (h) Rudi, A.; Chill, L.; Aknin, M.; Kashman, Y. *J. Nat. Prod.* **2003**, *66*, 575.
3. (a) Xia, Z.; Smith, C. D. *J. Org. Chem.* **2001**, *66*, 3459. (b) Bertram, A.; Pattenden, G. *Synlett* **2000**, 1519. (c) Bertram, A.; Pattenden, G. *Heterocycles* **2002**, *58*, 521. (d) Boden, C. D. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 875. (e) Wipf, P.; Fritchm, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (f) Mckeever, B.; Pattenden, G. *Tetrahedron Lett.* **2001**, *42*, 2573. (g) Wipf, P.; Uto, Y. *J. Org. Chem.* **2000**, *65*, 1037. (h) Wang, W.; Nan, F. *J. Org. Chem.* **2003**, *68*, 1636. (i) Yokokawa, F.; Sameshima, H.; Katagiri, D.; Aoyama, T.; Shioiri, T. *Tetrahedron* **2002**, *58*, 9445. (j) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 149. (k) Yoshihiro, H.; Tetsuo, S.; Takeo, K. *Bull. Chem. Soc. Jpn* **1970**, *43*, 1564.
4. (a) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354. (b) Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671. (c) Perez, L. J.; Faulkner, D. J. *J. Nat. Prod.* **2003**, *66*, 247.
5. (a) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2477. (b) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826. (c) At the same time we completed the synthesis of bistratamide F–I, there was a report on the synthesis of bistratamide G: Shin, C.-G.; Abe, C.; Yonezawa, Y. *Chem. Lett.* **2004**, *33*, 664.
6. (a) Schmidt, U.; Utz, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 725. (b) Schmidt, U.; Gleich, P. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 569. (c) Schmidt, U.; Utz, R.; Lieberknecht, A.; Griesser, H.; Potzolli, B.; Bahr, J.; Wagner, K.; Fischer, P. *Synthesis* **1987**, 233. (d) Bredenkamp, M. W.; Holzapfel, C. W.; van Zyl, W. J. *Synth. Commun.* **1990**, *20*, 2235. (e) Videnov, G.; Kaiser, D.; Brooks, M.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1506. (f) Li, G.; Warner, P. M.; Jebaratnam, D. J. *J. Org. Chem.* **1996**, *61*, 778.
7. (a) North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267. (b) Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett* **1995**, 417.
8. Mitsunobu conditions: (a) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (b) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.
9. Burgess reagent: (a) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397. (b) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358.
10. You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 83. For synthesis of thiazolines using $TiCl_4$ see: Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289. For synthesis of imidazoline-containing amino acids, see: You, S.-L.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 1681.
11. (a) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506. (b) You, S.-L.; Kelly, J. W. *Chem. Eur. J.* **2004**, *10*, 71.
12. Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741.
13. Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.
14. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
15. Crystallographic data for the structure **3** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 246784. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Study on halolactamization-γ-hydroxylation or haloiminolactonization of 2,3-alkadienamides

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Abstract—The reactions of 4-mono- or 4-unsubstituted 2,3-alkadienamides with CuX_2 afforded 5-hydroxypyrrol-2(5*H*)-ones via the sequential lactamization and γ-hydroxylation process in aqueous THF while those of 4,4-disubstituted 2,3-alkadienamides with CuX_2 in THF afforded iminolactones in high yields. Iodoiminolactonization and iodolactamization/γ-hydroxylation were achieved by the corresponding reaction with I_2 in THF at rt. The structures of the products depend on the steric hindrance at the 4-position of the starting allenamides. Relatively electron-rich allenes afforded the corresponding products in much higher yields under milder reaction conditions implying the intramolecular electrophilic nature of the cyclization reaction.
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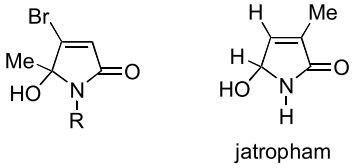
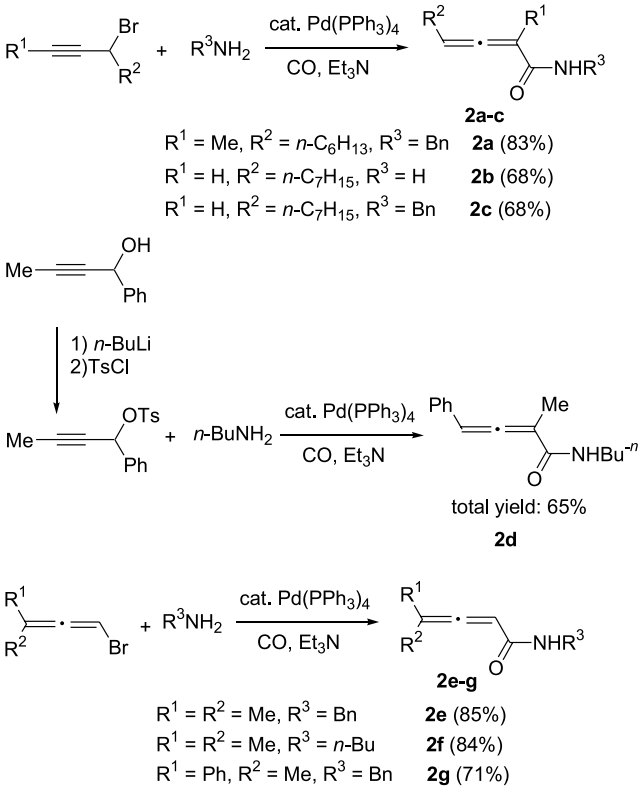
1. Introduction

Allenes are a class of compounds with interesting chemical and physical properties due to the presence of the unique cumulated diene unit.[1,2] For a long period of time or even now they are still considered unstable, which limits the study of their chemistry as compared to the chemistry of alkenes and alkynes.[1,2] During the last 5–10 years, much attention has been paid to the chemistry of allenes probably due to the observed fact during research that they are not so unstable and showed nice reactivities and selectivity in some cases.[3–5] We have developed some methodologies based on the ionic addition of allenes.[6] We have also develop the transition metal-mediated cyclization of allenes with an α-functionality, which provides efficient and diverse routes for the selective synthesis of aminoalcohols, carbocycles, and heterocycles.[7] Lactams especially 5-membered lactams are a class of important heterocycles, which exhibit interesting biological activities. Thus, we turned our attention to the chemistry of 2,3-allenamides, which may provide new methods for the synthesis of pyrrol-2(5*H*)-ones (Scheme 1).[1,8] In a preliminary communication,[9] we have shown that the reaction of 2,3-allenamides with CuX_2



Scheme 1.



Scheme 2.

Keywords: γ-Hydroxylation; Iminolactones; Allenes.
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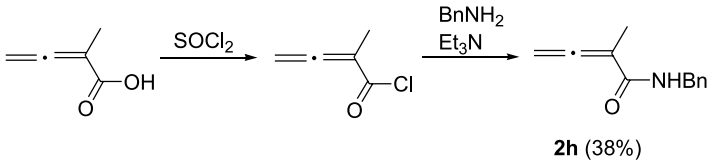


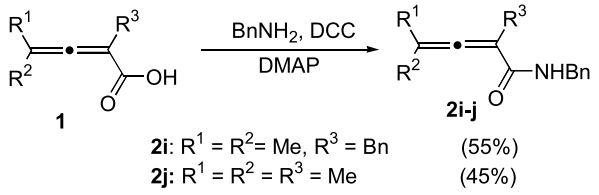
Scheme 3.

(X=Br, Cl) afforded 5-hydroxypyrrol-2(5*H*)-ones in THF–H_2O. In this paper we wish to disclose the details of this reaction.

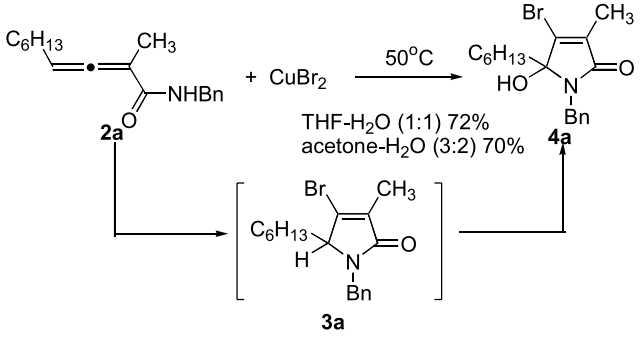
2. Results and discussion

2.1. Synthesis of starting materials

2,3-Allenamides **2a–g** were prepared by the $Pd(PPh_3)_4$-catalyzed carbonylation of 1,2-allenylic bromides or propargylic bromides/tosylate and amines in the presence of Et_3N and CO (Scheme 2).[10,11]



Scheme 4.



Scheme 5.

N-Benzyl 2-methyl-2,3-butadienamide **2h** was prepared by the reaction of 2-methyl-2,3-butadienoyl chloride with $BnNH_2$ (Scheme 3).[12]

2,3-Allenamides **2i–j** were synthesized by the DMAP-catalyzed amidation of the related carboxylic acids with amines (Scheme 4).[10]

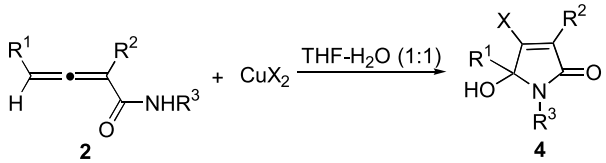
2.2. Cyclization of 2,3-allenamides with $CuBr_2$

Following our study of 2,3-allenoic acids with $CuBr_2$,[13,14] we studied the halolactamization of *N*-benzyl 2-methyl-deca-2,3-dienamide **2a** with 1.1 equiv of $CuBr_2$. After some screening, it was observed that the solvent is important. The reaction proceeded in aqueous THF or acetone to afford 5-hydroxypyrrol-2(5*H*)-one **4a** in ~70% yield. Obviously, a 5-hydoxylation reaction occurred to the initially formed pyrrol-2(5*H*)-one **3a** (Scheme 5).

Some typical results are summarized in Table 1. From the results in Table 1, it should be noted that (1) R^1 can be alkyl or aryl; R^2 can be H or alkyl; R^3 can be H, benzyl, or alkyl, (2) the reaction with $CuBr_2$ is usually faster than that with $CuCl_2$, (3) the yields are from moderate to good.

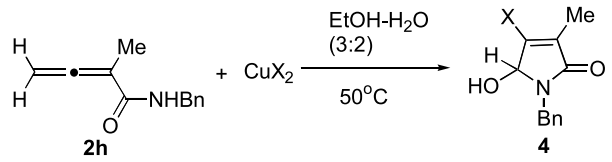
The reaction of $CuBr_2$ and a substrate without a substituent at 4-position, i.e. **2h**, afforded the corresponding products **4h** in THF/H_2O (1:1) in only 48% yield. Thus, optimization of the reaction condition was conducted. Finally EtOH–H_2O (3:2) was found to be a better reaction medium for this transformation with the results shown in Scheme 6.

Table 1. Halolactamization–hydroxylation reaction of 2,3-allenamides with CuX_2

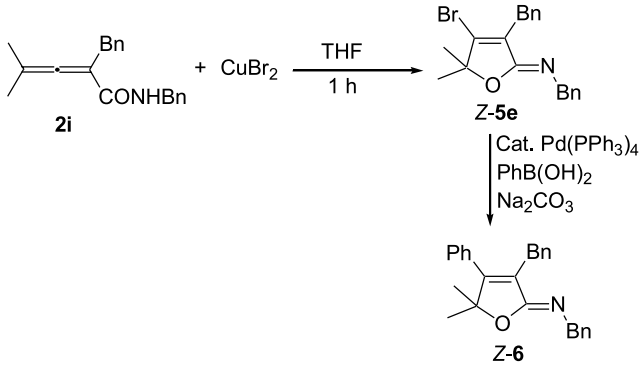


Entry	2			CuX_2, X (equiv)	Temperature (°C)	Time (h)	Yield of **4** (%)[a]
	R^1	R^2	R^3				
1	*n*-C_6H_{13}	Me	Bn (**2a**)	Br (1.1)	50	18.5	72 (**4a**)
2	*n*-C_6H_{13}	Me	Bn (**2a**)	Cl (1.1)	Reflux	21	57 (**4b**)
3	*n*-C_7H_{15}	H	H (**2b**)	Br (1.1)	50	22	69 (**4c**)
4	*n*-C_7H_{15}	H	Bn (**2c**)	Br (1.1)	50	32	78 (**4d**)
5	*n*-C_7H_{15}	H	Bn (**2c**)	Cl (2)	50	36	78 (**4e**)
6	Ph	Me	*n*-C_4H_9 (**2d**)	Br (2)	Reflux	24	94 (**4f**)
7	Ph	Me	*n*-C_4H_9 (**2d**)	Cl (4)	Reflux	60	71 (**4g**)

[a] Isolated yields.



Scheme 6.



Scheme 7.

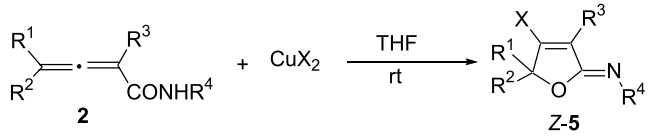
Furthermore, when we ran this reaction with 4,4-disubstituted 2,3-alkadienamides, instead of 5-hydroxypyrrol-2(5*H*)-one, iminolactones **5**[15] were formed smoothly in THF at rt in fairly high yield. In the preliminary communication,[9] we assigned it to pyrrol-2(5*H*)-ones, which was proven to be a wrong structure based on the further ^{13}C NMR analysis and its conversion to the known derivative **6**[16] by the related Pd-catalyzed coupling reaction (Scheme 7). It should be noted that only *Z*-**5e** was obtained in this reaction. The configuration of C=N bond in others products **5** was tentatively assigned based on this coupling result. From the typical results shown in Table 2, it can be concluded that the reaction was very fast (completed within 2 h) and the scope is broad.

2.3. Iodoiminolactonization/lactamization–hydroxylation of 2,3-alkadienamides

The reaction of 4,4-disubstituted 2,3-alkadienamides with I_2 in THF at rt also proceeded to produce 4-iodoiminolactones *Z*-**5k–n** in good yields (Table 3).

The reaction of 4-mono or 4-unsubstituted 2,3-alkadienamides with I_2 in THF followed by oxidation with O_2 at rt afforded 5-hydroxypyrrol-2(5*H*)-ones **4j–k** (Scheme 8).

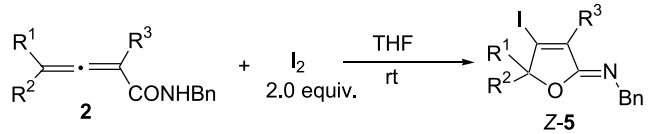
Table 2. Synthesis of iminolactones via the reaction of 4,4-disubstituted 2,3-alkadienamides with CuX_2



Entry	2				CuX_2		Time (h)	Yield of **5** (%)[a] (*Z*-**5**:*E*-**5**)[b]
	R^1	R^2	R^3	R^4	X=	(equiv)		
1	Me	Me	H	Bn (**2e**)	Br	1.1	1	85 (**5a**) (>97:3)
2	Me	Me	H	Bn (**2e**)	Cl	1.1	1	85 (**5b**) (>98:2)
3	Ph	Me	H	Bn (**2g**)	Br	3	1	99 (**5c**) (>99:1)
4	Ph	Me	H	Bn (**2g**)	Cl	3	2	98 (**5d**) (96:4)
5	Me	Me	Bn	Bn (**2i**)	Br	3	1	94 (**5e**) (100:0)
6	Me	Me	Bn	Bn (**2i**)	Cl	3	1	97 (**5f**) (100:0)
7	Me	Me	H	*n*-Bu (**2f**)	Br	1.1	1	78 (**5g**) (>98:2)
8	Me	Me	H	*n*-Bu (**2f**)	Cl	1.1	1	68 (**5h**) (>96:4)
9	Me	Me	Me	Bn (**2j**)	Br	1.1	2	82 (**5i**) (100:0)
10	Me	Me	Me	Bn (**2j**)	Cl	1.1	1	95 (**5j**) (100:0)

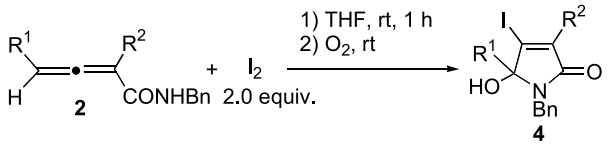
[a] Isolated yield.
[b] The ratios were determined by ^1H NMR spectra.

Table 3. Synthesis of 4-iodoiminolactones via the reaction of I_2 with 4,4-disubstituted 2,3-alkadienamides



Entry	2			Time (h)	Yield of **5** (%)[a] (*Z*-**5**:*E*-**5**)[b]
	R^1	R^2	R^3		
1	Me	Me	H (**2e**)	3	75 (**5k**) (95:5)
2	Me	Ph	H (**2g**)	26	84 (**5l**) (96:4)
3	Me	Me	Bn (**2i**)	16	92 (**5m**) (100:0)
4	Me	Me	Me (**2j**)	16	99 (**5n**) (100:0)

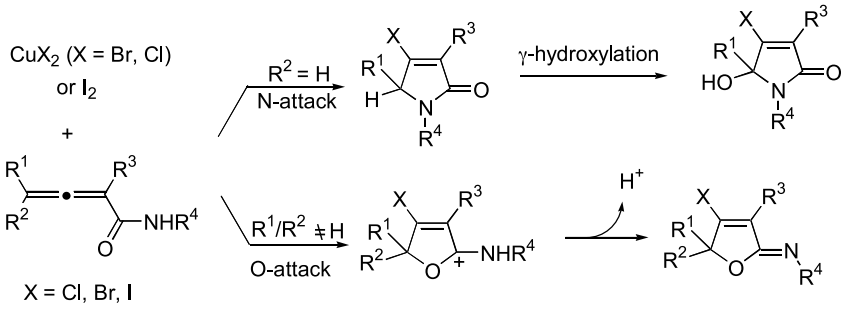
[a] Isolated yield.
[b] The ratios were determined by ^1H NMR spectra.



R^1	R^2	Time (h)	Yield (%)
n-C_7H_{15}	H (**2b**)	24	89 (**4j**)
H	Me (**2h**)	42	58 (**4k**)

Scheme 8.

It is quite obvious that the reaction is electrophilic in nature since the relatively electron richer amides provided the corresponding products in generally higher yields at a lower temperature (compare the results of Tables 1 and 2). Both the nitrogen and the carbonyl oxygen in starting materials may act as the intramolecular nucleophile. The selectivity clearly depends on the steric hindrance of 4-position of the amides, i.e. with 4-mono or 4-non-substituted 2,3-alkadienamides, pyrrol-2(5*H*)-ones were formed highly selectively, which was followed by γ-hydroxylation affording 5-hydroxypyrrol-2(5*H*)-ones while the reaction of 4,4-disubstituted 2,3-alkadienamides afforded iminolactones (Scheme 9).



Scheme 9.

In conclusion, we have developed the haloiminolactonization and halolactamization–hydroxylation reaction of 2,3-allenanimdes providing an efficient route for the highly selective synthesis of iminolactones or 5-hydroxypyrrol-2(5*H*)-ones, respectively, depending on the steric hindrance of 4-position of 2,3-allenamides. Further studies in this area are being carried out in our laboratory.

3. Experimental

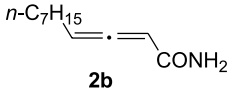
3.1. Synthesis of starting materials

The known compounds **2e**–**2g**, and **2i**–**2j** were prepared according to the reported procedure.[10]

3.1.1. *N*-Benzyl 2-methyl-2,3-decadienamide (2a). *Typical procedure A*. A stainless steel autoclave (250 mL) fitted with a glass reactor with a stirring bar inside was charged with THF (20 mL), 3-bromo-2-decyne (1.09 g, 5 mmol), $BnNH_2$ (0.6 mL, 5.5 mmol), Et_3N (0.77 mL, 5.5 mmol), and $Pd(PPh_3)_4$ (64 mg, 0.05 mmol) sequentially. The autoclave was charged with CO with a pressure of 18 atm. After the mixture was stirred for 1 h at rt, CO was released. The reaction was quenched with water followed by the addition of CH_2Cl_2. After separation, the organic phase was washed sequentially with 1 N HCl and brine. After evaporation, the residue was purified by flash chromatography on silica gel to afford 1.12 g (83%) of allenamide **2a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 6.32 (bs, 1H), 5.52–5.45 (m, 1H), 4.48 (d, J=6 Hz, 2H), 2.08 (q, J=7 Hz, 2H), 1.91 (d, J=2.7 Hz, 3H), 1.45–1.18 (m, 8H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 205.0, 166.8, 138.5, 128.5, 127.4, 127.2, 98.1, 96.0, 43.6, 31.4, 28.7, 28.7, 28.3, 22.5, 14.4, 14.0; MS m/z 271 (M^+, 19.43), 91 (100); IR (neat) 3347, 1955, 1655 cm^{-1}; HRMS cacld for $C_{18}H_{25}NO$ 271.1936; found 271.1949.

The following compounds **2b**–**2c** were prepared according to Typical procedures A.

3.1.2. 2,3-Undecadienamide (2b).



2b

The reaction of 3-bromo-1-decyne (1.02 g, 4.7 mmol), $NH_3\cdot H_2O$ (0.4 mL, 5.2 mmol), Et_3N (0.72 mL, 5.2 mmol), and $Pd(PPh_3)_4$ (54 mg, 0.047 mmol) in THF (25 mL) at rt for 2 h afforded 0.58 g (68% yield) of **2b**; white solid; mp 88–99 °C (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (bs, 1H), 5.67–5.52 (m, 3H), 2.18–2.10 (m, 2H), 1.55–1.20 (m, 10H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 208.4, 168.2, 96.5, 90.7, 31.6, 28.9, 28.9, 28.7, 27.7, 22.5, 13.9; MS m/z 180 (M^+-1, 1.46), 96 (100); IR (KBr) 3339, 3176, 1962, 1658 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.82; H, 10.64; N, 7.52.

3.1.3. *N*-Benzyl 2,3-undecadienamide (2c). The reaction of 3-bromo-1-decyne (1.09 g, 5.0 mmol), $BnNH_2$ (0.6 mL, 5.5 mmol), Et_3N (0.77 mL, 5.5 mmol), and $Pd(PPh_3)_4$ (64 mg, 0.05 mmol) in THF (20 mL) at rt for 1.5 h afforded 0.92 g (68% yield) of **2c**; white solid; mp 88–90 °C (*n*-hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5H), 6.22 (bs, 1H), 5.63–5.57 (m, 2H), 4.47 (d, J=5.7 Hz, 2H), 2.15–2.06 (m, 2H), 1.50–1.20 (m, 10H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 207.5, 165.1, 138.3, 128.6, 127.5, 127.3, 96.9, 91.2, 43.5, 31.6, 29.0, 28.9,

28.7, 27.8, 22.5, 14.0; MS *m/z* 271 (M^+, 22.04), 186 (100); IR (KBr) 3279, 1961, 1629 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.67; H, 9.23; N, 4.94.

3.1.4. *N*-Benzyl 4-phenyl-2,3-pentadienamide (2g). The reaction of 1-bromo-3-phenyl-1,2-butadiene (0.87 g, 4.1 mmol), $BnNH_2$ (0.5 mL, 4.5 mmol), Et_3N (0.65 mL, 4.5 mmol), and $Pd(PPh_3)_4$ (49 mg, 0.04 mmol) in THF (25 mL) at rt for 1.5 h afforded 0.77 g (71% yield) of **2g**; white solid; mp 139–140 °C (Et_2O–CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.26 (m, 10H), 6.04 (bs, 1H), 5.98 (q, $J=2.7$ Hz, 1H), 4.59–4.43 (m, 2H), 2.21 (d, $J=2.7$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 208.6, 164.5, 138.2, 134.0, 128.5, 128.5, 127.8, 127.4, 127.2, 125.9, 106.4, 92.9, 43.4, 16.3; MS *m/z* 263 (M^+, 19.88), 91 (100); IR (KBr) 3273, 1947, 1639 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.03; H, 6.26; N, 5.12.

3.1.5. *N*-Butyl 2-methyl-4-phenyl-2,3-butadienamide (2d). In a dry flask containing 1-phenyl-2-butyn-1-ol (580 mg, 4.0 mmol) in 40 mL THF was added *n*-BuLi (2.5 mL (1.6 M in hexane), 4.0 mmol) dropwise at −60 °C. After stirring for 30 min at −60 °C, TsCl (762 mg, 4.0 mmol) was added. The mixture was stirred for 15 min at −60 °C and then for 2 h at rt. Then, *n*-$BuNH_2$ (0.35 mL, 4.0 mmol), Et_3N (0.56 mL, 4.0 mmol), and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) were added sequentially at −78 °C. The autoclave was charged with CO with a pressure of 25 atm. After the mixture was stirred for 1 h at rt, CO was released. The reaction was quenched with water followed by the addition of CH_2Cl_2. After separation, the organic phase was washed sequentially with 1 N HCl and brine. After evaporation, the residue was purified by flash chromatography on silica gel to afford 0.59 g (65%) of **2d**: oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 5H), 6.48 (q, $J=3$ Hz, 1H), 6.07 (bs, 1H), 3.33–3.14 (m, 2H), 1.99 (d, $J=3$ Hz, 3H), 1.48–1.39 (m, 2H), 1.33–1.21 (m, 2H), 0.87 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 206.6, 165.3, 132.3, 128.7, 127.7, 126.9, 102.0, 98.4, 39.4, 31.5, 19.8, 14.2, 13.5; MS *m/z* 229 (M^+, 10.01), 84 (100); IR (neat) 3333, 1943, 1651 cm^{-1}; HRMS cacld for $C_{15}H_{19}NO$ 229.14666, found 229.14891.

3.1.6. *N*-Benzyl 2-methyl-2,3-butadienamide (2h). In a dry flask containing 2-methylbuta-2,3-dienoic acid (922 mg, 9.4 mmol) was added $SOCl_2$ (1.4 mL, 18.8 mmol). After stirring for 30 min at rt, the excess $SOCl_2$ was removed under reduced pressure to afford 2-methylbuta-2,3-dienoyl chloride, which was dissolved in dry ether (30 mL) for conversion in the next step.

To a mixture of benzylamine (1.1 mL, 10.3 mmol) and Et_3N (1.4 mL, 10.3 mmol) in dry ether (30 mL) was added 2-methyl buta-2,3-dienoyl chloride in dry ether dropwise at rt. After the mixture was stirred overnight, the reaction was quenched with water followed by the addition of ether. After separation, the water phase was extracted twice with ether and the combined organic layer was dried over $MgSO_4$. After evaporation, the residue was purified by flash chromatography on silica gel to afford 655 mg (38%) of **2h** white solid; mp 76–78 °C (*n*-hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 6.30 (bs, 1H), 5.09 (q, $J=3.0$ Hz, 2H), 4.48 (d, $J=6.0$ Hz, 2H), 1.92 (t, $J=3.0$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.7, 166.1, 138.4, 128.6, 127.6, 127.3, 97.6, 79.7, 43.7, 13.9; MS *m/z* 187 (M^+, 18.39), 91 (100); IR (KBr) 3422, 1944, 1641 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.91; H, 7.13; N, 7.35.

3.2. Halolactamization-γ-hydroxylation of 2,3-allenamides with CuX_2. General procedure B

A solution of 2,3-allenamide (**2**) (0.5 mmol) and CuX_2 (1.1–4 equiv) in THF/H_2O (1:1) (or enthanol/H_2O (3:2)) (8 mL) was stirred at 50 °C. When the reaction was complete, the mixture was then quenched with saturated NH_4Cl and extracted five times with chloroform. The organic layer was combined and dried over Na_2SO_4. After evaporation, the residue was purified via flash chromatography on silica gel to afford **4a**–**g**. All of the solid products were recrystallized from petroleum ether.

3.2.1. 4-Bromo-1-benzyl-5-*n*-hexyl-5-hydroxy-3-methyl-pyrrol-2(5*H*)-one (4a). The reaction of **1a** (75 mg, 0.28 mmol) and $CuBr_2$ (68 mg, 0.30 mmol) in THF (4 mL) and H_2O (4 mL) at 50 °C for 18.5 h afforded 73 mg (72% yield) of **2a**: white solid; mp 119–119.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.35–7.25 (m, 3H), 4.65 (d, $J=15.00$ Hz, 1H), 4.42 (d, $J=15.00$ Hz, 1H), 2.98 (s, 1H), 1.92 (s, 32H), 2.10–1.59 (m, 2H), 1.12–0.45 (m, 8H), 0.79 (t, $J=7.14$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.8, 139.2, 137.9, 134.1, 128.8, 128.5, 127.5, 92.5, 42.7, 34.3, 31.4, 28.5, 22.6, 22.4, 14.0, 10.5; MS *m/z* 368 ($M^+(^{81}Br)+1$, 22.17), 366 ($M^+(^{79}Br)+1$, 23.76), 91 (100); IR (KBr) 3303, 1677, 1072, 1026 cm^{-1}. Anal. Calcd for $C_{18}H_{24}BrNO_2$: C 59.02, H 6.60, N 3.82. Found: C 59.15, H 6.74, N 3.82.

The compounds **4b**–**4i**[9] were prepared according to Typical procedure B in the text, and the data of these compounds can be found in the supporting information of Ref. 2.

3.3. Haloiminolactonization of 2,3-alkadienamide. General procedure C

A solution of 2,3-allenamide (0.5 mmol) and CuX_2 (1.1–3 equiv) in THF (5 mL) was stirred at rt. When the reaction was complete, 10 mL of Et_2O and 10 mL of saturated NH_4Cl were added. The mixture was stirred for 5 min and extracted three times with Et_2O. The organic layer was combined and dried over Na_2SO_4. After evaporation, the residue was purified via flash chromatography on silica gel to afford **5a**–**5j**.

3.3.1. *Z*-2-Benzylimino-4-bromo-5,5-dimethyl-2,5-dihydrofuran (5a). The reaction of **2e** (112 mg, 0.56 mmol) and $CuBr_2$ (137 mg, 0.61 mmol) in THF (5 mL) at rt for 1 h afforded 132 mg (85% yield) of **5a** (*Z*-**5a**:*E*-**5a** > 97:3); light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**5a**: δ 7.37–7.22 (m, 5H), 6.25 (s, 1H), 4.51 (s, 2H), 1.51 (s, 6H). The following data were discernible for the *E* isomer, *E*-**5a**: 6.54 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.5, 144.3, 140.5, 128.3, 127.8, 126.4, 123.7, 90.8, 50.8, 25.4; MS *m/z* 281 ($M^+(^{81}Br)$, 30.18), 279 ($M^+(^{79}Br)$, 32.65), 91 (100); IR

(neat) 1687 cm^{-1}; HRMS cacld for $C_{13}H_{14}^{79}BrNO$ 279.0259; found 279.0264.

3.3.2. *Z*-2-Benzylimino-4-chloro-5,5-dimethyl-2,5-dihydrofuran (5b). The reaction of **2e** (119 mg, 0.59 mmol) and $CuCl_2 \cdot 2H_2O$ (111 mg, 0.65 mmol) in THF (5 mL) at rt for 1 h afforded 119 mg (85% yield) of **5b** (*Z*-**5b**:*E*-**5b**> 98:2), colorless oil; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**5b**: δ 7.37–7.25 (m, 5H), 6.09 (s, 1H), 4.53 (s, 2H), 1.51 (s, 6H). The following data were discernible for the *E* isomer, *E*-**5b**: δ 6.38 (s, 1H), 4.50 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.6, 154.1, 140.5, 128.3, 127.8, 126.4, 119.2, 89.5, 50.8, 25.0; MS *m/z* 237 ($M^+(^{37}Cl)$, 12.82), 235 ($M^+(^{35}Cl)$, 38.02), 91 (100); IR (neat) 1689, 1631 cm^{-1}; HRMS cacld for $C_{13}H_{14}^{35}ClNO$ 235.0764; found 235.0757.

3.3.3. *Z*-2-Benzylimino-4-bromo-5-phenyl-5-methyl-2,5-dihydrofuran (5c). The reaction of **2g** (67 mg, 0.25 mmol) and $CuBr_2$ (168 mg, 0.75 mmol) in THF (5 mL) at rt for 1 h afforded 86 mg (99% yield) of **5c** (*Z*-**5c**:*E*-**5c**>99:1); light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**5c**: δ 7.43–7.26 (m, 10H), 6.38 (s, 1H), 4.63 (s, 2H), 1.95 (s, 3H). The following data were discernible for the *E* isomer, *E*-**5c**: δ 6.63 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.7, 144.6, 140.3, 138.4, 128.6, 128.5, 128.3, 127.9, 126.5, 125.5, 123.8, 92.5, 51.1, 23.8; MS *m/z* 344 ($M^+(^{81}Br)+1$, 5.47), 342 ($M^+(^{79}Br)+1$, 6.58), 105 (100); IR (neat) 1687, 1602 cm^{-1}; HRMS cacld for $C_{18}H_{16}^{79}BrNO$ 341.04153; found 341.04516.

3.3.4. *Z*-2-Benzylimino-4-chloro-5-phenyl-5-methyl-2,5-dihydrofuran (5d). The reaction of **2g** (85 mg, 0.32 mmol) and $CuCl_2 \cdot 2H_2O$ (165 mg, 0.97 mmol) in THF (5 mL) at rt for 2 h afforded 94 mg (98% yield) of **5d** (*Z*-**5d**:*E*-**5d**= 96:4); light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**5d**: δ 7.34–7.20 (m, 5H), 6.14 (s, 1H), 4.57 (s, 2H), 1.87 (s, 3H). The following data were discernible for the *E* isomer, *E*-**5d**: δ 6.39 (s, 1H), 4.53 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.7, 154.0, 140.4, 138.4, 128.6, 128.5, 128.3, 127.8, 126.5, 125.3, 119.3, 91.2, 51.0, 23.6; MS *m/z* 299 ($M^+(^{37}Cl)$, 0.79), 297 ($M^+(^{35}Cl)$, 1.92), 105 (100); IR (neat) 1687, 1612 cm^{-1}; HRMS cacld for $C_{18}H_{16}^{35}ClNO$ 297.0920; found 297.0932.

3.3.5. *Z*-2-Benzylimino-3-benzyl-4-bromo-5,5-dimethyl-2,5-dihydrofuran (5e). The reaction of **2i** (62 mg, 0.21 mmol) and $CuBr_2$ (143 mg, 0.61 mmol) in THF (4 mL) at rt for 1 h afforded 74 mg (94% yield) of *Z*-**5e**; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.22 (m, 10H), 4.51 (s, 2H), 3.70 (s, 2H), 1.48 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.9, 141.0, 140.0, 137.7, 132.5, 128.8, 128.3, 128.1, 127.3, 126.3, 126.1, 88.4, 50.2, 31.1, 25.7; MS *m/z* 371 ($M^+(^{81}Br)$, 52.32), 369 ($M^+(^{79}Br)$, 54.98), 91 (100); IR (neat) 1682 cm^{-1}. Anal. Calcd for $C_{20}H_{20}BrNO$: C 64.87, H 5.44, N 3.78. Found: C 64.75, H 5.50, N 3.97.

3.3.6. *Z*-2-Benzylimino-3-benzyl-4-chloro-5,5-dimethyl-2,5-dihydrofuran (5f). The reaction of **2i** (48 mg, 0.16 mmol) and $CuCl_2 \cdot 2H_2O$ (84 mg, 0.45 mmol) in THF (4 mL) at rt for 1 h afforded 52 mg (97% yield) of *Z*-**5f**; yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.24 (m, 10H), 4.64 (s, 2H), 3.75 (s, 2H), 1.53 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.5, 148.2, 141.0, 137.8, 128.8, 128.8, 128.3, 128.1, 127.3, 126.3, 126.1, 87.3, 50.2, 29.8, 25.2; MS *m/z* 327 ($M^+(^{37}Cl)$, 36.93), 325 ($M^+(^{35}Cl)$, 84.57), 91 (100); IR (neat) 1683 cm^{-1}. Anal. Calcd for $C_{20}H_{20}ClNO$: C 73.72, H 6.19, N 4.30. Found: C 73.36, H 6.09, N 4.20.

3.3.7. *Z*-2-*n*-Butylimino-4-bromo-5,5-dimethyl-2,5-dihydrofuran (5g). The reaction of **2f** (119 mg, 0.71 mmol) and $CuBr_2$ (175 mg, 0.78 mmol) in THF (5 mL) at rt for 1 h afforded 137 mg (78% yield) of **5g** (*Z*-**5g**:*E*-**5g**>98:2); light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**5g**: δ 6.14 (s, 1H), 3.25 (t, J=6.9 Hz, 2H), 1.56–1.51 (m, 2H), 1.44 (s, 6H), 1.38–1.30 (m, 2H), 0.90 (t, J=7.4 Hz, 3H). The following data were discernible for the *E* isomer, *E*-**5g**: δ 6.42 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.7, 143.8, 123.7, 90.4, 46.4, 32.9, 25.4, 20.5, 13.8; MS *m/z* 248 ($M^+(^{81}Br)+1$, 23.52), 246 ($M^+(^{79}Br)+1$, 27.67), 160 (100); IR (neat) 1692, 1604 cm^{-1}; HRMS cacld for $C_{10}H_{16}^{79}BrNO$ 245.0415; found 245.0370.

3.3.8. *Z*-2-*n*-Butylimino-4-chloro-5,5-dimethyl-2,5-dihydrofuran (5h). The reaction of **2f** (126 mg, 0.75 mmol) and $CuCl_2 \cdot 2H_2O$ (142 mg, 0.83 mmol) in THF (6 mL) at rt for 1 h afforded 103 mg (68% yield) of **5h** (*Z*-**5h**:*E*-**5h**>96:4); colorless oil; ^1H NMR (300 MHz, $CDCl_3$) *Z*-**5h**: δ 5.96 (s, 1H), 3.24 (t, J=7.1 Hz, 2H), 1.52–1.46 (m, 2H), 1.41 (s, 6H), 1.34–1.27 (m, 2H), 0.86 (t, J=7.2 Hz, 3H). The following data were discernible for the *E* isomer, *E*-**5h**: δ 6.23 (s, 1H), 3.19 (t, J=7.2 Hz, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 158.8, 153.5, 119.1, 88.9, 46.3, 32.9, 24.9, 20.5, 13.8; MS *m/z* 203 ($M^+(^{37}Cl)$, 4.27), 201 ($M^+(^{35}Cl)$, 12.79), 130 (100); IR (neat) 1694, 1614 cm^{-1}; HRMS cacld for $C_{10}H_{16}^{35}ClNO$ 201.09204; found 201.08779.

3.3.9. *Z*-2-Benzylimino-3-methyl-4-bromo-5,5-dimethyl-2,5-dihydrofuran (5i). The reaction of **2i** (96 mg, 0.45 mmol) and $CuBr_2$ (110 mg, 0.49 mmol) in THF (5 mL) at rt for 2 h afforded 108 mg (82% yield) of *Z*-**5i**; light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 4.57 (s, 2H), 1.91 (s, 3H), 1.47 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.0, 140.8, 139.1, 129.7, 128.2, 127.6, 126.3, 88.4, 50.5, 25.6, 10.9; MS *m/z* 294 ($M^+(^{81}Br)-1$, 37.11), 292 ($M^+(^{79}Br)-1$, 36.26), 105 (100); IR (neat) 1691, 1655 cm^{-1}; HRMS cacld for $C_{13}H_{13}^{79}BrNO$ (M^+-CH_3) 278.0179; found 278.0177.

3.3.10. *Z*-2-Benzylimino-3-methyl-4-chloro-5,5-dimethyl-2,5-dihydrofuran (5j). The reaction of **2j** (105 mg, 0.49 mmol) and $CuCl_2 \cdot 2H_2O$ (92 mg, 0.54 mmol) in THF (5 mL) at rt for 1 h afforded 116 mg (95% yield) of *Z*-**5j**; light yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.23 (m, 5H), 4.60 (s, 2H), 1.92 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.7, 147.4, 140.8, 128.1, 127.6, 126.3, 125.8, 87.3, 50.4, 25.1, 9.3; MS *m/z* 251 ($M^+(^{37}Cl)$, 30.49), 249 ($M^+(^{35}Cl)$, 58.32), 91 (100); IR (neat) 1693,1664 cm^{-1}; HRMS cacld for $C_{14}H_{16}^{35}ClNO$ 249.0920; found 249.0932.

3.4. Iodoiminolactonization of 2,3-alkadienamide. General procedure D

A solution of 2,3-allenamide (0.5 mmol) and I_2 (2 equiv) in

THF (4 mL) was stirred at rt. When the reaction was complete, 10 mL of Et_2O was added, and then a solution of $Na_2S_2O_3$ was added to remove the excess I_2. After extraction with Et_2O, drying over Na_2SO_4, and evaporation, the residue was purified via flash chromatography on silica gel to afford **5k–5n**.

3.4.1. *Z*-2-Benzylimino-4-iodo-5,5-dimethyl-2,5-dihydrofuran (5k). The reaction of **2e** (106 mg, 0.53 mmol) and I_2 (268 mg, 1.06 mmol) in THF (4 mL) at rt for 3 h afforded 129 mg (75% yield) of **5k** (*Z*-**5k**:*E*-**5k**=95:5); light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) *Z*-**5k**: δ 7.37–7.20 (m, 5H), 6.43 (s, 1H), 4.50 (s, 2H), 1.47 (s, 6H). The following data were discernible for the *E* isomer, *E*-**5k**: 6.73 (s, 1H), 4.49 (s, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 162.03, 140.37, 131.86, 128.19, 127.70, 126.35, 119.54, 92.67, 50.75, 25.92; MS *m*/*z* 327 (M^+, 42.23), 95 (100); IR (neat) 1758, 1681 cm^{-1}; HRMS cacld for $C_{13}H_{14}INO$ 327.0120; found 327.0128.

3.4.2. *Z*-2-Benzylimino-4-iodo-5-methyl-5-phenyl-2,5-dihydrofuran (5l). The reaction of **2g** (47 mg, 0.18 mmol) and I_2 (91 mg, 0.36 mmol) in THF (5 mL) at rt for 26 h afforded 59 mg (84% yield) of **5l** (*Z*-**5l**:*E*-**5l**=96:4); light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.22 (m, 10H), 6.56 (s, 1H), 4.60 (s, 2H), 1.91 (s, 3H). The following data were discernible for the *E* isomer, *E*-**5l**: δ 6.84 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 162.4, 140.3, 138.6, 131.8, 128.6, 128.5, 128.3, 127.9, 126.5, 125.8, 120.7, 94.5, 51.1, 24.2; MS *m*/*z* 389 (M^+, 5.86), 129 (100); IR (neat) 1680 cm^{-1}; HRMS cacld for $C_{18}H_{16}INO$ 389.0277; found 389.0318.

3.4.3. *Z*-2-Benzylimino-3-benzyl-4-iodo-5,5-dimethyl-2,5-dihydrofuran (5m). The reaction of **2i** (78 mg, 0.27 mmol) and I_2 (136 mg, 0.54 mmol) in THF (5 mL) at rt for 16 h afforded 103 mg (92% yield) of *Z*-**5m**; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.26 (m, 10H), 4.63 (s, 2H), 3.77 (s, 2H), 1.50 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.5, 141.0, 139.3, 137.7, 128.9, 128.2, 128.1, 127.3, 126.3, 126.1, 118.4, 89.8, 50.3, 33.4, 26.3; MS *m*/*z* 417 (M^+, 25.25), 91 (100); IR (neat) 1681, 1629 cm^{-1}; HRMS cacld for $C_{20}H_{20}INO$ 417.0590; found 417.0569.

3.4.4. *Z*-2-Benzylimino-3-methyl-4-iodo-5,5-dimethyl-2,5-dihydrofuran (5n). The reaction of **2j** (21 mg, 0.10 mmol) and I_2 (50 mg, 0.20 mmol) in THF (3 mL) at rt for 16 h afforded 33 mg (99% yield) of *Z*-**5n**; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.21 (m, 5H), 4.55 (s, 2H), 1.94 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.5, 140.8, 136.7, 128.2, 127.7, 126.3, 117.3, 89.7, 50.6, 26.3, 13.8; MS *m*/*z* 341 (M^+, 43.86), 81 (100); IR (neat) 1686, 1639 cm^{-1}; HRMS cacld for $C_{14}H_{16}INO$ 341.0277; found 341.0253.

3.5. Iodolactamization-γ-hydroxylation of 2,3-allenamides. General procedure E

A solution of 2,3-allenamide (0.5 mmol) and I_2 (2 equiv) in THF (4 mL) was stirred at rt for 1 h, then 1 atm of O_2 was charged. When the reaction was complete, 10 mL of Et_2O was added, and then a solution of $Na_2S_2O_3$ was added to remove the excess I_2. After extraction with Et_2O, drying over Na_2SO_4, and evaporation, the residue was purified via flash chromatography on silica gel to afford **4j–k**.

3.5.1. 1-Benzyl-5-hydroxy-5-heptyl-4-iodopyrrol-2(5*H*)-one (4j). The reaction of **2b** (63 mg, 0.23 mmol) and I_2 (118 mg, 0.46 mmol) in THF (5 mL) at rt for 24 h afforded 85 mg (89% yield) of **4j**: light yellow solid; mp 106–108 °C (*n*-hexane–Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (m, 5H), 6.52 (s, 1H), 4.58 (d, J=15 Hz, 1H), 4.42 (d, J=15 Hz, 1H), 2.78 (s, 1H), 1.76–1.58 (m, 2H), 1.19–0.45 (m, 10H), 0.79 (t, J=7.4 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.0, 137.6, 135.3, 128.8, 128.4, 127.5, 123.1, 95.0, 42.8, 34.8, 31.5, 28.8, 28.7, 22.5, 22.2, 14.0; MS *m*/*z* 413 (M^+, 1.66), 91 (100); IR (KBr) 3197, 1673, 1652 cm^{-1}. Anal. Calcd for $C_{18}H_{24}INO_2$: C, 52.31; H, 5.85; N, 3.39. Found: C, 52.45; H, 6.02; N, 3.19.

3.5.2. 1-Benzyl-5-hydroxy-4-iodo-3-methylpyrrol-2(5*H*)-one (4k). The reaction of **2k** (70 mg, 0.37 mmol) and I_2 (191 mg, 0.75 mmol) in THF (5 mL) at rt for 42 h afforded 71 mg (58% yield) of **4k**: white solid; mp 108–109 °C (*n*-hexane–Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 5.03 (d, J=6.9 Hz, 1H), 4.94 (d, J=14.4 Hz, 1H), 4.26 (d, J=14.4 Hz, 1H), 4.11 (bs, 1H), 1.86 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.3, 142.0, 136.5, 128.7, 128.3, 127.7, 112.5, 84.7, 43.5, 13.3; MS *m*/*z* 329 (M^+, 11.56), 124 (100); IR (KBr) 3317, 1678 cm^{-1}. Anal. Calcd for $C_{12}H_{12}INO_2$: C, 43.79; H, 3.67; N, 4.26. Found: C, 43.89; H, 3.67; N, 4.06.

Acknowledgements

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References and notes

1. (a) Schuster, H. F.; Coppola, G. M. Allenes in Organic Synthesis; Wiley: New York, 1984. (b) *The Chemistry of Ketenes, Allenes, and Related Compounds, Part 1*; Patai, S., Ed.; Wiley: New York, 1980.
2. Krause, N. *Angew. Chem., Int., Ed.* **2004**, *43*, 1196–1216.
3. For some of the most recent reviews, see: (a) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067–3125. (b) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199–207. (c) Ma, S. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; p 1491.
4. For some of the most recent reports on the chemistry of allenes, see: (a) Löfstedt, J.; Franzén, J.; Bäckvall, J. E. *J. Org. Chem.* **2001**, *66*, 8015–8025. (b) Löfstedt, J.; Närhi, K.; Dorange, I.; Bäckvall, J. E. *J. Org. Chem.* **2003**, *68*, 7243–7248. (c) Baraero, A.; Castreño, P.; Pulido, F. J. *Org. Lett.* **2003**, *5*, 4045–4048. (d) Ohno, H.; Takeoka, Y.; Miyamura, K.; Kadoh, Y.; Tanaka, T. *Org. Lett.* **2003**, *5*, 4763–4766. (e) Franzén, J.; Bäckvall, J. E. *J. Am. Chem. Soc.*

2003, *125*, 6056–6057. (f) Franzén, J.; Löfstedt, J.; Falk, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2003**, *125*, 14140–14148. (g) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491–3494. (h) Jeganmohan, M.; Shanmugasundaram, M.; Chang, K.-J.; Cheng, C.-H. *Chem. Commun.* **2002**, 2552–2553. (i) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761–762. (j) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343–345. (k) Jeganmohan, M.; Shanmugasundaram, M.; Cheng, C.-H. *Chem. Commun.* **2003**, 1746–1747. (l) Yang, F.; Shanmugasundaram, M.; Chuang, S.-Y.; Ku, P.-J.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 12576–12583. (m) Ohno, H.; Takeoka, Y.; Miyamura, K.; Kadoh, Y.; Tanaka, T. *Org. Lett.* **2003**, *5*, 4763–4766.

5. For some of our most recent reports, see: (a) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775–1778. (b) Xu, D.; Li, Z.; Ma, S. *Chem. Eur. J.* **2002**, *8*, 5012–5018. (c) Ma, S.; Jiao, N. *Angew., Chem., Int. Ed.* **2002**, *41*, 4737–4740. (d) Ma, S.; Wang, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4215–4217. (e) Ma, S.; Ren, H.; Wei, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4817–4830. (f) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2003**, *42*, 1955–1957. (g) Ma, S.; Jiao, N.; Ye, L. *Chem. Eur. J.* **2003**, *9*, 6049–6056.
6. For an account on hydrohalogenation, see: Ma, S.; Li, L. *Synlett* **2001**, 1206–1213. For some of the most recent results, see: (a) Ma, S.; Yin, S.; Li, L.; Tao, F. *Org. Lett.* **2002**, *4*, 505–507. (b) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996–9002. (c) Ma, S.; Hao, X.; Huang, X. *Org. Lett.* **2003**, *5*, 1217–1219.
7. Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701–712.
8. (a) Ma, S.; Zhao, S. *Org. Lett.* **2000**, *2*, 2495–2497. (b) Ma, S.; Zhang, J. *Chem. Commun.* **2000**, 117–118. (c) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941–944. (d) Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933–8936.
9. Ma, S.; Xie, H. *Org. Lett.* **2000**, *2*, 3801–3803.
10. Ma, S.; Xie, H. *J. Org. Chem.* **2002**, *67*, 6575–6578.
11. Trieu, N. D.; Elsevier, C. J.; Vrieze, K. *J. Organomet. Chem.* **1987**, *325*, C23–C26.
12. (a) Himbert, G.; Schlindwein, H. J. *Z. Naturforsch* **1992**, *47b*, 1785–1793. (b) Himbert, G.; Schlindwein, H.-J. *Liebigs Ann. Chem.* **1997**, 435–439.
13. (a) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314–9317. (b) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441–442.
14. Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075–4077.
15. (a) Nedolya, N. A.; Schlyakhtina, N. I.; Zinov'eva, V. P.; Albanov, A. I.; Brandsma, L. *Tetrahedron Lett.* **2002**, *43*, 1569–1571. (b) Ohe, K.; Matsuda, H.; Ishihara, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Org. Chem.* **1993**, *58*, 1173–1177. (c) Hart, H.; Dickinson, D. A.; Li, W. Y. *Tetrahedron Lett.* **1975**, *16*, 2253–2256. (d) Skvortsov, Y. M.; Mal'kina, A. G.; Trofimov, B. A.; Kositsina, E. I.; Voronov, V. K.; Baikalova, L. V. *Zh. Org. Khim.* **1984**, *20*, 1108–1115.
16. The X-ray diffraction study of this compound was reported by us in Ref. 10.

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Triaryl phosphine-functionalized *N*-heterocyclic carbene ligands for Heck reaction

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Abstract—A new type of triaryl phosphine-functionalized imidazolium salts **6** were prepared. Their palladium complexes, generated in situ, were successfully applied in the palladium-catalyzed Heck reaction. Using 1 mol% of $Pd(dba)_2$ and 1 mol% **6c** in the presence of 2 equiv of K_2CO_3 in DMAc has proven to be highly efficient for the coupling of a wide array of aryl bromides and iodides with acrylates in excellent yield. The coupling of 4-bromotoluene with various styrene derivatives catalyzed by Pd/**6c** complex also gave good results.
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1. Introduction

Heck reaction has received intensive studies over the past several decades.[1] Especially the palladium-catalyzed arylation and vinylation have proven to be one of the most powerful means for the formation of carbon–carbon bond in organic synthesis.[2] Usually, Heck reaction is carried out in the presence of phosphine ligands, which stabilize the active palladium intermediates[3] and assist the initial oxidative-addition of C–X bonds.[4] Excellent results have been reported for the palladium-catalyzed Heck reactions when sterically bulky monophosphines,[5] diphosphines,[6] cyclometalated phosphines[7] or phosphites are used as ligands.[8] However, the phosphine ligands and the phosphine–palladium complexes are liable to air and moisture at elevated temperature, placing significant limits on their synthetic application. Therefore, in view of practical use, the development of more reactive and stable ligands is of importance for the palladium-catalyzed Heck reaction.

Recently, nucleophilic N-heterocyclic carbenes (NHC's),[9] with a stronger σ-donor electronic property than bulky tertiary phosphines,[10] have emerged as a new family of ligands. In contrast to metal complexes of phosphines, the metal–NHC complexes appeared to be extraordinarily stable toward heat, air and moisture due to their high dissociation energies of the metal–carbon bond.[11] This superiority of NHC's made them a potential type of ligands for Heck reaction. Since Herrmann[12] reported the first application of palladium–NHC complex in Heck reaction in 1995, various palladium complexes with monodente carbenes, chelating dicarbenes or tridentate pincer bis-carbenes, and even donor-functionalized NHC's have been synthesized and used as catalysts for the Heck reaction.[13] Most of the donor-functionalized NHC ligands had a N-donor, such as pyridine, imine or oxazoline as pendant groups. However, little attention has been paid to the synthesis of phosphine-functionalized NHC ligands,[14] though the theoretical calculation suggested that the chelating phosphine–carbene Pd complex might be a suitable catalyst for the Heck reaction.[15] So far as we know, there was one successful application of phosphine–NHC ligand in Heck reaction, which was reported by Nolan and co-workers.[14c] Herein, we describe the synthesis of a new type of phosphine-functionalized NHC ligands with stable triaryl phosphines as pendant functional groups and their application in palladium-catalyzed Heck reaction. The results revealed that the palladium-NHC species generated in situ from phosphine-functionalized imidazolium salts and $Pd(dba)_2$ in the presence of K_2CO_3 were highly effective for the coupling of a wide range of bromides and iodides with acrylates and the coupling of aryl bromides with styrene derivatives.

2. Result and discussion

2.1. Synthesis of phosphine-functionalized imidazolium salts

Initially, we attempted to synthesize triaryl phosphine-functionalized imidazolium salts **6** via the direct reduction

Keywords: Carbenes; Heck reaction; Palladium; Phosphine-functionalized.
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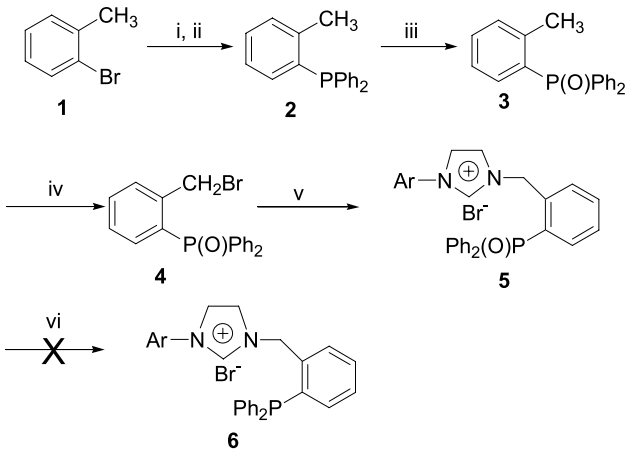
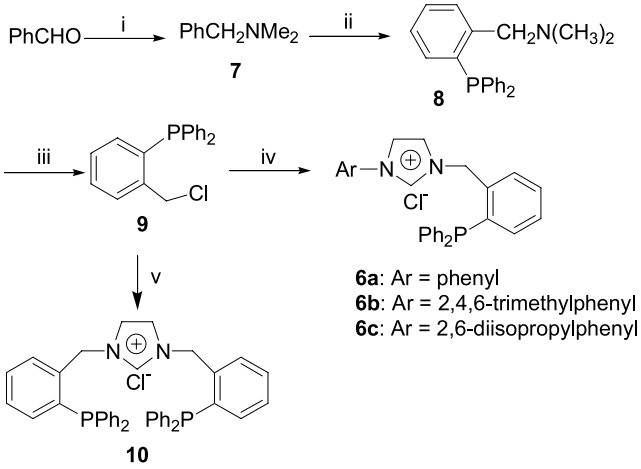


Scheme 1. Reagents and conditions: (i) Mg, THF, reflux; (ii) PPh_2Cl, −78 °C to room temperature; (iii) H_2O_2, CH_2Cl_2, room temperature; (iv) NBS, AIBN, CCl_4, reflux; (v) 1-arylimidazole, EtOH (abs), reflux; (vi) Cl_3SiH, EtOH, toluene, 120 °C.

of the phosphinoxide **5**[14d] (Scheme 1). Diphenyl-*o*-tolylphosphane (**2**), prepared from coupling of Ph_2PC1 with Grinard reagent of 2-bromotoluene, was treated with H_2O_2 to form the corresponding phosphinoxide **3** in excellent yield (97% for three steps). Bromination of compound **3** with NBS in the presence of AIBN provided *o*-(diphenylphosphinyl)-benzyl bromide (**4**) in 65% yield. Then, alkylation of 1-arylimidazole with bromide **4** gave imidazolium salts **5** in 70% yield. However, the direct reduction of compound **5** with Cl_3SiH was unsuccessful. Use of other reducing reagents, such as methyldichlorosilane, also gave disappointing results. It was very likely that the bulky steric effect around the phosphorus atom in compound **5** hindered its interaction with the reducing reagent.

Another synthetic route was then designed to make phosphine-functionalized imidazolium salts **6**, which started from benzaldehyde (Scheme 2). The benzaldehyde was condensed with dimethylamine, followed by the reduction with $NaBH_4$ to give benzyldimethylamine (**7**). Compound **7**

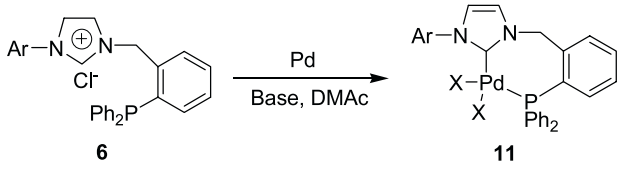


Scheme 2. Reagents and conditions: (i) (a) Me_2NH_2Cl, $Ti(Oi\text{-}Pr)_4$, NEt_3, EtOH (abs), room temperature; (b) $NaBH_4$, room temperature; (ii) (a) *n*-BuLi, Et_2O, room temperature; (b) Ph_2PCl, Et_2O, −78 °C to room temperature; (iii) $ClCO_2Et$, benzene, reflux; (iv) 1-arylimidazole, EtOH (abs), reflux; (v) 1*H*-imidazole, K_2CO_3, EtOH (abs), reflux.

was *ortho*-metallated by *n*-BuLi and reacted with Ph_2PC1 to afford 2-(diphenylphosphino)benzyldimethylamine (**8**). In the presence of ethyl chloroformate, **8** was converted to the key intermediate *o*-(diphenylphosphino)benzyl chloride (**9**) at refluxing condition. The yield was 42% for the three steps. Subsequently, alkylation of 1-arylimidazole with compound **9** in refluxing ethanol gave triaryl phosphine-functionalized imidazolium salts **6** in the yields of 46–63%. By using K_2CO_3 as the base, tridentate imidazolium salt **10** was obtained from 1*H*-imidazole and the compound **9** in 32% yield.

2.2. Heck reaction

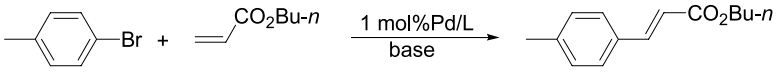
2.2.1. Arylation of acrylates. Having prepared the new phosphine-functionalized imidazolium salts **6** and **10**, we firstly tested the catalytic activity of the palladium complexes **11**[16] (Scheme 3) for the Heck reaction of *p*-tolyl bromide with *n*-butyl acrylate (Scheme 3). Preliminary experiment in DMAc in the presence of Cs_2CO_3 as the base at 120 °C showed that the catalyst **11a** generated in situ was efficient to yield coupling product (Table 1, entry 1). Controlled experiment indicated that the coupling reaction did not take place in the absence of imidazolium salt **6a**. A systematic investigation on the substituent effect in the imidazolium salts **6** indicated that the introduction of alkyl groups to the *N*-phenyl ring of NHC ligands notably increased the reaction rate and the yield of product, and imidazolium salt **6c** was found to be the most reactive one (entries 2 and 3). But the tridentate phosphine-functionalized imidazolium salt **10** showed a poor reactivity in this reaction (entry 4). As a comparison, the phosphinoxide **5b** was also tested for the reaction and poorer catalytic activity (24 h, 67% yield) was observed, indicating that the pendant phosphine group in ligands **6** is necessary for having a high reactivity.



Scheme 3.

Various palladium compounds, such as $Pd(dba)_2$, $Pd(OAc)_2$, $[Pd[(\eta\text{-}C_3H_5)Cl]]_2$ and $Pd_2(dba)_3\cdot CHCl_3$, were compared as catalyst precursors under the same reaction conditions (1 mol% [Pd], 1 mol% **6c**, 1 equiv *p*-tolyl bromide, 1.5 equiv *n*-butyl acrylate, 2.0 equiv Cs_2CO_3 and DMAc as solvent at 120 °C) (Table 1). The results showed that $Pd(dba)_2$ was the choice of catalyst precursor, which gave 100% conversion in the shortest reaction time (entry 3). The ratio of imidazolium salt **6c** to palladium precursor was also studied. The ratio of 1:1 was found to be optimal. When the ratio of **6c**/Pd changed from 1:1 to 2: 1, the coupling product was obtained in only 29% yield (entry 8). Further increasing the ratio to 3:1 or 4:1 led a very slow reaction (entries 9 and 10). These results suggested that NHC ligand **6c** coordinated to palladium with two coordinating atoms to form a chelating complex. When the ratio of **6c**/Pd exceeded 2:1, two bidentate P–C ligands occupied all of the four

Table 1. Heck reaction of 4-bromotoluene and *n*-butyl acrylate under various conditions[a]



Entry	Pd	Ligand	L/Pd	Base	Solvent	Time (h)	Conv. (%)[b]	Yield (%)[c]
1	$Pd(dba)_2$	**6a**	1	Cs_2CO_3	DMAc	18	91	62
2	$Pd(dba)_2$	**6b**	1	Cs_2CO_3	DMAc	14	99	82
3	$Pd(dba)_2$	**6c**	1	Cs_2CO_3	DMAc	12	100	85
4	$Pd(dba)_2$	**10**	1	Cs_2CO_3	DMAc	24	22	ND[d]
5	$Pd(OAc)_2$	**6c**	1	Cs_2CO_3	DMAc	24	54	28
6	$[Pd[(\eta\text{-}C_3H_5)Cl]]_2$	**6c**	1	Cs_2CO_3	DMAc	24	88	41
7	$Pd_2(dba)_3\cdot CHCl_3$	**6c**	1	Cs_2CO_3	DMAc	18	98	57
8	$Pd(dba)_2$	**6c**	2	Cs_2CO_3	DMAc	12	100	29
9	$Pd(dba)_2$	**6c**	3	Cs_2CO_3	DMAc	24	18	ND
10	$Pd(dba)_2$	**6c**	4	Cs_2CO_3	DMAc	24	5	ND
11	$Pd(dba)_2$	**6c**	1	NEt_3	DMAc	24	11	ND
12	$Pd(dba)_2$	**6c**	1	KOAc	DMAc	24	45	39
13	$Pd(dba)_2$	**6c**	1	K_3PO_4	DMAc	24	98	65
14	$Pd(dba)_2$	**6c**	1	KOH	DMAc	24	7	ND
15	$Pd(dba)_2$	**6c**	1	KF	DMAc	24	14	ND
16	$Pd(dba)_2$	**6c**	1	Na_2CO_3	DMAc	24	65	54
17	$Pd(dba)_2$	**6c**	1	K_2CO_3	DMAc	12	93	93
18[e]	$Pd(dba)_2$	**6c**	1	K_2CO_3	DMAc	11	99	99
19	$Pd(dba)_2$	**6c**	1	K_2CO_3	DMF	12	83	75
20	$Pd(dba)_2$	**6c**	1	K_2CO_3	DMSO	12	74	50
21	$Pd(dba)_2$	**6c**	1	K_2CO_3	Dioxane	24	56	39

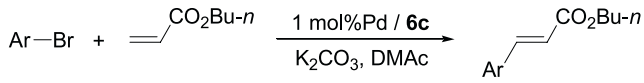
[a] Reaction conditions: 1 mol% [Pd], 1 mol% **6c**, 1 equiv *p*-tolyl bromide, 1.5 equiv *n*-butyl acrylate, 2.0 equiv base at 0.5 M at 120 °C.
[b] Determined by GC.
[c] Isolated yield.
[d] Not determined.
[e] At 140 °C.

coordination sites of palladium, hindering the oxidative addition of *p*-tolyl bromide to palladium, and consequently resulted in a slow or even no reaction. The base was found to significantly influence both the reaction rate and the yield of product. The highest yield was achieved by using K_2CO_3 (entry 17). Other inorganic bases, such as KOH, KF, KOAc, Na_2CO_3 and K_3PO_4, and organic base NEt_3 gave the coupling product in low yields (entries 11–16). The reaction was also solvent dependent when using K_2CO_3 as the base. DMAc was found to be the choice of solvent. Increasing the temperature from 120 to 140 °C accelerated the reaction rate and the yield of product (entry 18).

At the optimal reaction conditions, a wide array of aryl bromides bearing electron-donating or electron-withdrawing groups can react with *n*-butyl acrylate providing coupling products in excellent yields. As can be seen in the Table 2, most of the aryl bromides with electron-withdrawing substituents, such as CF_3, CN or NO_2, reacted completely at 120 °C in less than 6 h. While for the aryl bromides with electron-donating substituents, complete conversions were achieved only at 140 °C. These results showed that the electron-deficient bromides were beneficial to the reaction. The steric effect of substrates was also obvious. For the sterically congested substrates, such as 1-bromo-3,5-di-*tert*-butylbenzene (entry 6) and 1-bromo-3,5-di-*tert*-butyl-4-methoxybenzene (entry 9), longer reaction time were required. 1-Bromo-2-methyl naphthalene, another sterically congested bromide, could also couple with *n*-butyl acrylate using our catalyst system in high yield (entry 10). These results showed that the carbene ligands generated in situ from phosphine-functionalized imidazolium salt **6** have an activity, which is superior or comparable to the sterically demanding *ortho*-substituted arylphosphines, P(*o*-tol)$_3$[17] and the monodentate carbenes IMes.[18] It was noteworthy that in the coupling reaction of aryl bromides bearing another halide group, such as F or Cl, the mono-coupling products were formed predominantly. The bis-coupling products were isolated in just 3 and 7% yields in the reaction of *ortho*- and *para*-chlorophenyl bromides (entries 17 and 19). However, the reaction of dibromides, with excess *n*-butyl acrylate, produced di-coupling products in quantitative yields (entries 20 and 21). Bromides bearing carbonyl groups can couple with *n*-butyl acrylate leaving carbonyl group unchanged (entries 22 and 23). The aryl iodides had higher reactivities than bromides in the coupling reaction with *n*-butyl acrylate. The reactions were complete in 2 h at 120 °C and the yields were excellent (entries 24, 25 and 26). Double arylation products could be obtained in high yields when excess iodides were used (entries 27–29). However the reaction of aryl chlorides, such as 1-chloro-4-nitrobenzene and 2-chlorobenzaldehyde, with *n*-butyl acrylate provided very little amount of desired coupling products using Pd/**6c** system at the same conditions. Besides *n*-butyl acrylate, methyl acrylate and ethyl acrylate can also efficiently react with *p*-tolyl bromide providing the corresponding coupling products in 86 and 99% yields, respectively.

2.2.2. Arylation of styrenes. Using the same reaction conditions, we further studied the Heck reaction of 4-bromotoluene with styrene using in situ generated palladium complexes of phosphine-functionalized NHC ligands. The results are summarized in Table 3. Arylation

Table 2. Heck reaction of aryl bromides and iodides with *n*-butyl acrylate under optimal reaction conditions[a]



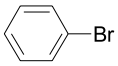
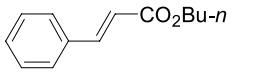
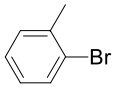
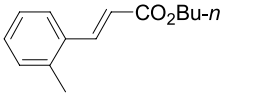
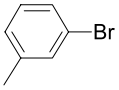
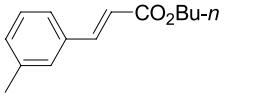
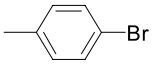
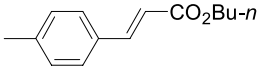
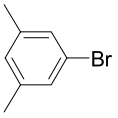
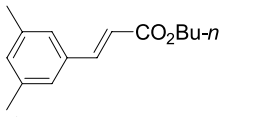
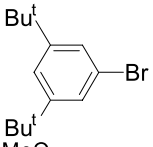
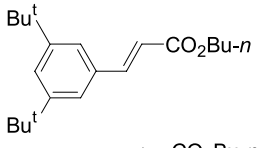
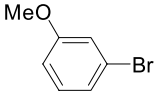
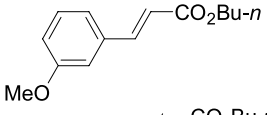
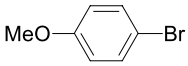
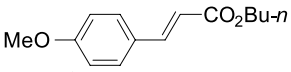
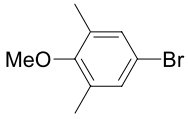
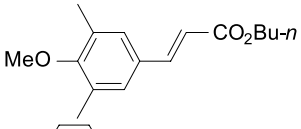
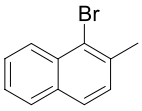
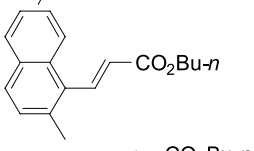
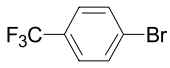
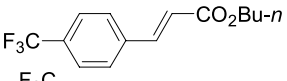
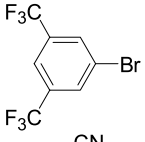
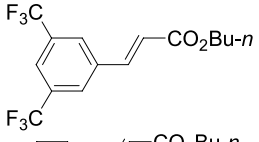
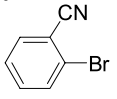
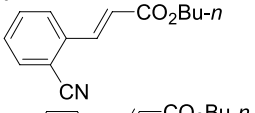
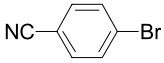
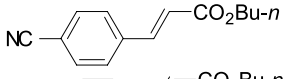
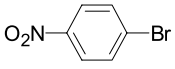
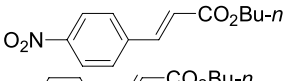
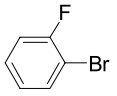
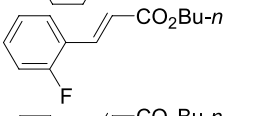
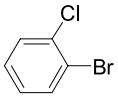
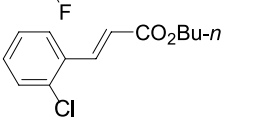
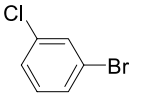
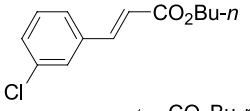
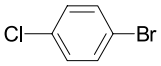
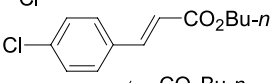
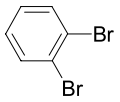
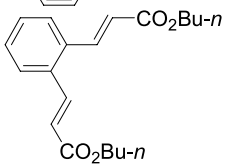
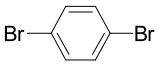
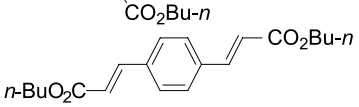
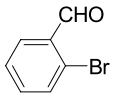
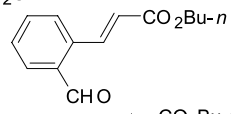
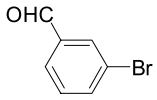
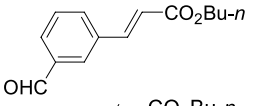
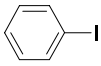
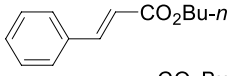
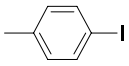
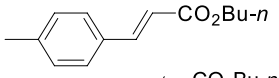
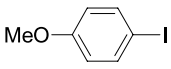
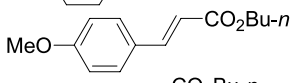
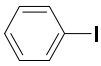
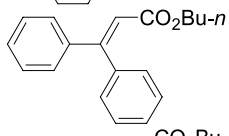
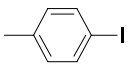
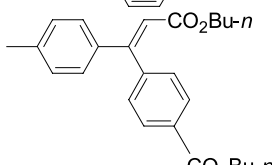
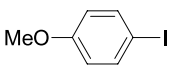
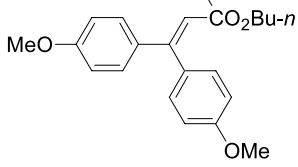
Entry	Aryl halide	Temperature (°C)	Time (h)	Conv. (%)[b]	Product	Yield (%)[c]	Ref.
1		140	11	99		99	19
2		140	12	100		98	17
3		140	12	100		98	20
4		140	11	99		99	18
5		140	12	100		98	18
6		140	24	100		100	21
7		140	12	100		100	18
8		140	12	100		96	18
9		140	24	100		94	22
10		140	24	100		100	23
11		120	6	100		99	24
12		120	6	100		96	25
13		120	10	97		89	23
14		120	5	100		93	18
15		120	6	100		85	25
16		120	6	97		92	25
17		120	10	96		87[d]	26

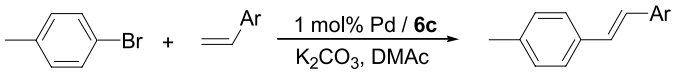
Table 2 (*continued*)

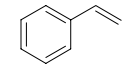
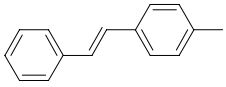
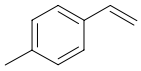
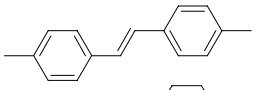
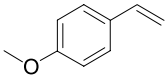
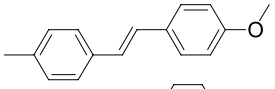
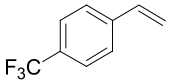
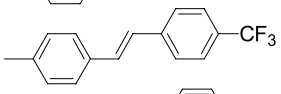
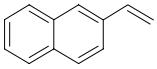
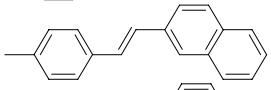
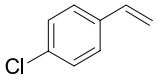
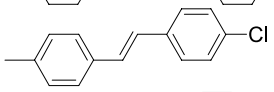
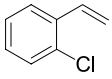
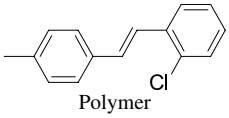
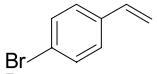
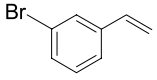
Entry	Aryl halide	Temperature (°C)	Time (h)	Conv. (%)[b]	Product	Yield (%)[c]	Ref.
18		120	5	100		100	27
19		120	5	100		93[e]	13a
20[f]		120	16	99		99	28
21[f]		120	12	100		99	28
22		120	12	100		83	23
23		120	5	100		93	29
24		120	2	100		97	19
25		120	2	100		92	18
26		120	2	100		93	18
27[g]		140	60	100		93	30
28[g]		140	140	100		99	30
29[g]		140	45	100		100	30

[a] Performed with 1.5 equiv acrylate, L/Pd = 1, 2.0 equiv base; 0.5 M.
[b] Determined by GC.
[c] Isolated yield.
[d] 3% Di-coupled product was obtained.
[e] 7% Di-coupled product was obtained.
[f] 4.0 equiv acrylate, 5.0 equiv base.
[g] 4.0 equiv halide, 5.0 equiv base.

of styrene with 4-bromotoluene at 140 °C gave 100% conversion and offered 96% yield of the coupling product (entry 1). A variety of styrene derivatives with electron-donating or electron-withdrawing groups on the phenyl ring were tested, and 100% conversions with good to excellent yields were obtained within 12 h. This revealed that the Pd catalysts bearing a chelating phosphine-functionalized NHC ligand were comparably good as the Pd catalysts containing a monodentate NHC ligand and a triarylphosphine in the arylation reaction of styrenes.[31] 4-Chlorostyrene was an exception, however, which gave a lower yield of coupling product (74%, entry 6). In the reaction of bromo-substituted styrenes, such as 4-bromostyrene and 3-bromostyrene, no cross-coupling products were isolated. On the contrary, the self-coupling of bromostyrenes occurred to form polymer PPV.[32] The lower yield in the reaction of 4-chlorostyrene can be also ascribed to some extent to its polymerization as a precipitation of a yellow solid was observed at the end of the reaction.

Table 3. Heck reaction of 4-bromotoluene with styrene derivatives[a]



Entry	Olefin	Product	Yield (%)[b]	Ref.
1			96	33
2			96	34
3			93	35
4			91	36
5			91	37
6			74[c]	38
7			99	39
9		Polymer	—	32
10		Polymer	—	32

[a] Performed with 1.5 equiv olefin, L/Pd=1, 2.0 equiv base, 0.5 M, 140 °C, 12 h.
[b] Isolated yield.
[c] Polymer was observed.

3. Conclusion

In summary, we have developed a new type of efficient triaryl phoshphine-funtionalized NHC ligands for the palladium-catalyzed Heck reactions. These phosphine-functionalized imidazole carbene ligands were easily prepared. Their palladium complexes, generated in situ, were applicable to the coupling reaction of bromides and iodides with acrylates and the coupling reaction of styrene derivatives with 4-bromotoluene in high yields. In these Heck reactions, the bulky substituents on the *N*-phenyl ring of the phoshphine-functionalized NHC ligands were found to be beneficial to the high activity of the catalyst. This might suggest that the introduction of bulky groups to the *P*-phenyl rings of the phoshphine-funtionalized NHC ligands is also helpful to increase the activity of the Pd catalyst, which is in progress in our laboratory.

4. Experimental

4.1. General

All reactions and manipulations were performed in an argon-filled glovebox or using standard Schlenk techniques, unless otherwise indicated. The aryl halides and styrene derivatives were purchased from Aldrich Co. or Acros Co. and used as received, with the exception of 2-bromotoluene, 3-bromotoluene and 4-bromotoluene, which were distilled prior to use. $Pd(OAc)_2$ and $[Pd[(\eta\text{-}C_3H_5)Cl]]_2$ were purchased from Acros Co. $Pd(dba)_2$ and $Pd_2(dba)_3\cdot CHCl_3$ were prepared according to the reported procedures.[40] Absolute EtOH was distilled from magnesium ethylate. 1,4-Dioxane was distilled from sodium benzophenone ketyl. Anhydrous DMSO, DMF, DMAc were freshly distilled from calcium hydride. K_3PO_4 was ground to a fine powder and dried in a vacuum oven prior to use. Cs_2CO_3, K_2CO_3, Na_2CO_3, KF, KOAc and KOH were used as received. NEt_3 was redistilled prior to use. ^1H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ on Varian Mercury Vx-300 spectrometers. HRMS were recorded on APEX II spectrometer. GC analyses were performed using a Hewlett Packard Model HP 6890 Series with HP-5 column.

4.1.1. Synthesis of 3-phenyl-1-(2-diphenylphosphinobenzyl)-3*H*-imidazol-1-ium chloride (6a). Under an atmosphere of argon, 8 mL abs. EtOH was added to a Schlenk tube charged with 1-phenylimidazole (288 mg, 2.0 mmol) and *o*-(diphenylphosphino)benzyl chloride (0.64 g, 2.05 mmol). The mixture was allowed to stir at 80 °C for 2 days. The ethanol was then removed under vacuum. The residue was purified by a flash chromatography

(CH_2Cl_2/MeOH) to give **6a** as a white solid (0.42 g, 46% yield). ^{1}H NMR δ 5.96 (s, 2H, CH_2), 6.90 (m, 1H, NCHCHN), 7.08–7.63 (m, 19H, Ar-H), 8.04 (m, 1H, NCHCHN), 11.12 (s, 1H, NCHN); ^{31}P NMR δ −16.58 (s); ^{13}C NMR δ 51.8, 52.1, 119.8, 121.9, 122.7, 122.8, 129.0, 129.1, 129.6, 130.3, 130.7, 130.8, 132.6, 132.7, 133.8, 134.1, 134.6, 134.7, 135.0, 135.1, 136.9, 137.0, 137.4, 137.8; HRMS for $C_{28}H_{24}N_2P^+$ $[M-Cl]^+$, calcd: 419.1672; found: 419.1672.

4.1.2. Synthesis of 3-mesityl-1-(2-diphenylphosphinobenzyl)-3*H*-imidazol-1-ium chloride (6b). The compound **6b** was prepared in 60% yield by the same procedure described for **6a** using 1-mesitylimidazole. ^{1}H NMR δ 2.02 (s, 6H, CH_3), 2.33 (s, 3H, CH_3), 6.20 (s, 2H, CH_2), 6.95 (s, 1H, Ar-H), 6.98 (s, 3H, Ar-H), 7.24–7.38 (m, 11H, Ar-H), 7.46 (m, 1H, NCHCHN), 7.59 (s, 1H, Ar-H), 8.11 (m, 1H, NCHCHN), 10.87 (s, 1H, NCHN); ^{31}P NMR δ −14.89 (s); ^{13}C NMR δ 17.8, 21.3, 51.1, 51.4, 122.6, 122.7, 129.1,129.2, 129.7, 130.0, 130.3, 131.0, 132.2, 132.3, 133.7, 133.9, 134.2, 134.5, 135.0, 135.1, 136.0, 136.5, 136.7, 136.9, 138.1, 138.5, 139.0, 141.4; HRMS for $C_{31}H_{30}N_2P^+$ $[M-Cl]^+$, calcd: 461.2141; found: 461.2143.

4.1.3. Synthesis of 3-(2,6-diisopropylphenyl)-1-(2-diphenylphosphinobenzyl)-3*H*-imidazol-1-ium chloride (6c). The compound **6c** was prepared in 63% yield by the same procedure described for **6a** using 1-(2,6-diisopropylphenyl)-imidazole. ^{1}H NMR δ 1.11 (d, J=7.2 Hz, 6H, CH_3), 1.23 (d, J=7.2 Hz, 6H, CH_3), 2.26 (m, 2H, CH), 6.26 (s, 2H, CH_2), 6.98 (m, 1H, NCHCHN), 7.00 (s, 1H, Ar-H), 7.24–7.55 (m, 15H, Ar-H), 7.75 (s, 1H, Ar-H), 8.14 (m, 1H, NCHCHN), 10.84 (s, 1H, NCHN); ^{31}P NMR δ −14.48 (s); ^{13}C NMR δ 24.4, 24.6, 28.7, 28.9, 51.1, 51.3, 122.7, 122.8, 123.6, 124.9, 129.2, 129.3, 129.7, 130.0, 130.5, 130.9, 132.1, 132.2, 133.9, 134.2, 135.0, 136.5, 136.7, 138.3, 138.6, 139.4, 145.6; HRMS for $C_{34}H_{36}N_2P^+$ $[M-Cl]^+$, calcd: 503.2610; found: 503.2609.

4.1.4. Synthesis of 1,3-bis(2-diphenylphosphinobenzyl)-imidazolidin-1-ium chloride (10). Under an atmosphere of argon, imidazole (0.20 g, 3.0 mmol), *o*-(diphenylphosphino)benzyl chloride (1.90 g 6.1 mmol) and K_2CO_3 (0.42 g 3.0 mmol) were mixed in 20 mL abs EtOH and refluxed for 2 days. The solvent was removed in vacuum, and the residue was extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvent was removed under vacuum, and the residue was purified by a flash chromatography (CH_2Cl_2/MeOH) to give **10** as a white solid (0.62 g, 32% yield). ^{1}H NMR δ 5.58 (s, 4H, CH_2), 6.89 (s, 4H, Ar-H), 6.95–7.46 (m, 22H, Ar-H), 7.70 (s, 2H, Ar-H), 7.74 (m, 2H, NCHCHN), 10.39 (s, 1H, NCHN); ^{31}P NMR δ −15.49 (s); ^{13}C NMR δ 51.4, 51.7, 121.7, 121.8, 129.1, 129.2, 129.5, 129.7, 130.3, 130.7, 131.6, 131.7, 133.8, 134.1, 134.7, 134.8, 135.3, 136.8, 136.9, 137.0, 137.2, 137.6; HRMS for $C_{41}H_{35}N_2P_2^+$ $[M-Cl]^+$, calcd: 617.2270; found: 617.2265.

4.2. General procedure for the Heck reaction of aryl halides with olefins

Under an atmosphere of argon, 2.0 mL DMAc was injected to a Schlenk tube charged with $Pd(dba)_2$ (0.01 mmol), imidazolium salt (0.01 mmol), and K_2CO_3 (2.0 mmol). The mixture was stirred for 30 min at 25 °C and then added 1.0 mmol of aryl halide, 1.5 mmol of olefin successively. The Schlenk tube was placed in a 120 °C or 140 °C oil bath and the reaction mixture was stirred and monitored by GC. After the reaction was complete, the reaction mixture was passed through a short plug of silica gel and washed with copious amount of Et_2O. The washings were concentrated and purified by flash chromatography on silica gel to offer the product. The products were identified by ^{1}H NMR.

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References and notes

1. (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314–321. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.
2. (a) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4745–4746. (b) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439–1442. (c) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499. (d) Shibasaki, M.; Boden, C. J. D.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411.
3. (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857. (b) Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859. (c) Kubas, G. J. *Acc. Chem. Res.* **1988**, *21*, 120–128. (d) Gonzales, A. A.; Mukerjee, S. L.; Chou, S. J.; Zhang, K.; Hoff, C. D. J. *J. Am. Chem. Soc.* **1988**, *110*, 4419–4421.
4. Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10–11.
5. (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000. (b) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123–2132. (c) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677–2678. (d) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589–1592.
6. (a) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995–1996. (b) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655–1664. (c) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734–4735. (d) Portnoy, M.; Ben-Dvid, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465–3479. (e) Shaw, B. L.; Perera, S. D. *Chem. Commun.* **1998**, 1863–1864.
7. For recent reviews on palladacycles for Heck reactions, see (a) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917–1927. (b) Benford, R. B. *Chem. Commun.* **2003**, 1787–1796.
8. For the use of tetraphenylphosphonium salts in Heck reactions,

see: Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481–483.
9. (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290–1309. (b) Herrmann, W. A.; Weskamp, T.; Böhm, V. P. W. *Adv. Organomet. Chem.* **2002**, *48*, 1–69. (c) Jafarpour, L.; Nolan, S. P. *Adv. Organomet. Chem.* **2001**, *46*, 181–222. (d) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91. (e) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187.
10. Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370–2375.
11. Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem. Eur. J.* **2000**, *6*, 1773–1780.
12. Herrmann, W. A.; Elison, M.; Fischer, J.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371–2374.
13. (a) Liu, J.; Zhao, Y.; Zhou, Y.; Li, L.; Zhang, T. Y.; Zhang, H. *Org. Biomol. Chem.* **2003**, *1*, 3227–3231. (b) Pytkowicz, J.; Roland, S.; Mangeney, P.; Meyer, G.; Jutand, A. *J. Organomet. Chem.* **2003**, *678*, 166–179. (c) Loch, J. A.; Albrecht, M.; Peris, E.; Mata, J.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2002**, *21*, 700–706. (d) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2002**, *21*, 5204–5208. (e) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031–3033. (f) Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079–2082. (g) Magill, A. M.; McGuinness, D. S.; Cavell, K. J.; Britovsek, G. J. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J.; White, A. H.; Skelton, B. W. *J. Organomet. Chem.* **2001**, *617*, 546–560. (h) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511–1514. (i) Grundemamm, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2001**, *20*, 5485–5488. (j) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201–202. (k) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741–748. (l) Clyne, D. S.; Jin, J.; Genest, E.; Gallucci, J. C.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 1125–1128. (m) Tulloch, A. A. D.; Danopoulos, A. A.; Tooze, R. P.; Cafferkey, S. M.; Kleinhenz, S.; Hursthouse, M. B. *Chem.Commun.* **2000**, 1247–1248.
14. (a) Seo, H.; Park, H.-J.; Kim, B. Y.; Lee, J. H.; Son, S. U.; Chung, Y. K. *Organometallics* **2003**, *22*, 618–620. (b) Danopoulos, A. A.; Winston, S.; Gelbrich, T.; Hursthouse, M. B.; Tooze, R. P. *Chem. Commum.* **2002**, 482–483. (c) Yang, C.; Lee, H. M.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1511–1514. (d) Herrmann, W. A.; Köcher, G. L. J.; Artus, G. R. J. *Chem. Eur. J.* **1996**, *2*, 1627–1636. (e) Tsoureas, N.; Danopoulos, A. A.; Tulloch, A. A. D.; Light, M. E. *Organometallics* **2003**, *22*, 4750–4758.
15. Albert, K.; Gisdakis, P.; Rösch, N. *Organometallics* **1998**, *17*, 1608–1616.
16. For example, **11c**: ^{1}H NMR δ 8.00 (m, 1H, NCH), 7.95 (s, 1H, Ar-H), 7.63–7.16 (m, 15H, Ar-H), 6.82 (m, 1H, NCH), 6.68 (s, 1H, Ar-H), 5.31 (s, 2H, CH_2), 2.40 (m, 2H, CH), 1.32 (d, J=6.0 Hz, 6H, CH_3), 1.26 (d, J=6.0 Hz, 6H, CH_3); ^{31}P NMR δ 16.52 (s).
17. Herrmann, W. A.; Broßmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1995**, *103*, 133–146.
18. Yang, C.; Nolan, S. P. *Synlett* **2001**, *10*, 1539–1542.
19. Ley, S. V.; Ramario, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134–1135.
20. Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Mol. Diversity* **2003**, *7*, 97–106.
21. Oil, ^{1}H NMR δ 7.64 (d, J=15.8 Hz, 1H, CHAr), 7.39 (s, 1H, Ar), 7.30 (s, 2H, Ar), 6.37 (d, J=15.8 Hz, 1H, $CHCO_2$), 4.14 (t, 6.8 Hz, 2H, CO_2CH_2), 1.62 (m, J=6.8 Hz, 6.8 Hz, 2H, CH_2CH_2), 1.37 (m, J=6.8, 7.5 Hz, 2H, CH_2CH_3), 1.26 (s, 18H, $C(CH_3)_3$), 0.89 (t, J=7.5 Hz, 3H, CH_2CH_3).
22. Oil, ^{1}H NMR δ 7.58 (d, J=15.8 Hz, 1H, CHAr), 7.20 (s, 2H, Ar), 6.33 (d, J=15.8 Hz, 1H, $CHCO_2$), 4.19 (t, 6.8 Hz, 2H, CO_2CH_2), 3.73 (s, 3H, OCH_3), 2.29 (s, 6H, CH_3), 1.68 (m, J=6.8, 6.8 Hz, 2H, CH_2CH_2), 1.43 (m, J=6.8, 7.5 Hz, 2H, CH_2CH_3), 0.96 (t, J=7.5 Hz, 3H, CH_2CH_3).
23. Feuerstein, M.; Doucet, H.; Santelli, M. *Synlett* **2001**, *12*, 1980–1982.
24. Lewis, F. D.; Oxman, J. D.; Gibson, L. L.; Hampsch, H. L.; Quillen, S. L. *J. Am. Chem. Soc.* **1986**, *108*, 3005–3015.
25. Feuerstein, M.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 5923–5925.
26. Terrian, D. L.; Mohammad, T.; Morrison, H. *J. Org. Chem.* **1995**, *60*, 1981–1984.
27. Murai, M.; Hashimoto, H.; Itoh, K.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2207–2211.
28. Ceccon, A.; Crociani, L.; Santi, S.; Venzo, A.; Biffis, A.; Boccaletti, G. *Tetrahedron Lett.* **2002**, *43*, 8475–8478.
29. Oil, ^{1}H NMR δ 10.05 (s, 1H, CHO), 8.03 (s, 1H, Ar), 7.89 (d, J=7.5 Hz, 1H, Ar), 7.78 (d, J=7.5 Hz, 1H, Ar), 7.73 (d, J=15.8 Hz, 1H, CHAr), 7.58 (t, J=7.5 Hz, 1H, Ar), 7.54 (d, J=15.8 Hz, 1H, $CHCO_2$), 4.23 (t, J=6.8 Hz, 2H, CO_2CH_2), 1.70 (m, J=6.8, 6.8 Hz, 2H, CH_2CH_2), 1.45 (m, J=6.8, 7.5 Hz, 2H, CH_2CH_3), 0.98 (t, J=7.5 Hz, 3H, CH_2CH_3).
30. Calo, V.; Nacci, A.; Monopoli, A.; Lopez, L.; di Cosmo, A. *Tetrahedron* **2001**, *57*, 6071–6077.
31. Herrmann, W. A.; Böhm, V. P. W.; Gstöttmayr, C. W. K. *J. Organomet. Chem.* **2001**, *617*, 616–628.
32. (a) Mikroyannidis, J. A. *Macromolecules* **2002**, *35*, 9289–9295. (b) Kim, J. H.; Lee, H. *Chem. Mater.* **2002**, *14*, 2270–2275. (c) Shim, H. K.; Ahn, T.; Lee, H. Y.; Lee, J. I. *Korea Polym. J.* **2001**, *9*, 116–121. (d) Liu, Y. B.; Lahti, P. M.; La, F. *Polymer* **1998**, *39*, 5241–5244.
33. Andrus, M. B.; Song, C.; Zhang, J. *Org. Lett.* **2002**, *4*, 2079–2082.
34. Spencer, A. *J. Organomet. Chem.* **1983**, *247*, 117–122.
35. Engler, T. A.; Gfesser, G. A.; Draney, B. W. *J. Org. Chem.* **1995**, *60*, 3700–3706.
36. Mp 188–191 °C, ^{1}H NMR δ 7.50 (s, 4H, Ar), 7.35 (d, J=7.5 Hz, 2H, Ar), 7.11 (d, J=7.5 Hz, 2H, Ar), 7.08 (d, J=16.6 Hz, 1H, CH=CH), 6.98 (d, J=16.6 Hz, 1H, CH=CH), 2.29 (s, 3H, CH_3).
37. Mp 178–180 °C, 1H NMR δ 7.76–7.64 (m, 5H, Ar), 7.40–7.33 (m, 4H, Ar), 7.16–7.10 (m, 4H, Ar, CH=CH), 2.29 (s, 3H, CH_3).
38. Mp 205–207 °C, 1H NMR δ 7.44–7.39 (m, 4H, Ar), 7.32–7.30 (m, 2H, Ar), 7.17 (d, J=7.5 Hz, 2H, Ar), 7.06 (d, J=15.8 Hz, 1H, CH=CH), 6.99 (d, J=15.8 Hz, 1H, CH=CH), 2.36 (s, 3H, CH_3).
39. Mallory, F. B.; Mallory, C. W. *J. Org. Chem.* **1983**, *48*, 526–532.
40. Takahashi, Y.; Ito, T.; Sakai, S.; Ishii, Y. *Chem. Commun.* **1970**, 1065–1066.

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A direct intramolecular asymmetric catalytic aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes

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Abstract—The intramolecular asymmetric catalytic aldol cyclodehydration of 1,6-dialdehydes to the corresponding cyclopentene carbaldehydes was accomplished for the first time on the cases of *meso*-3,4-disubstituted hexanedials. It was found that the presence of a hydroxyl group in the catalyst's molecule seems to be crucial to reach stereocontrol. The chiral centre, bearing the carboxylate functionality, in hydroxy amino acids controls the stereochemistry of the final product. In the case of amino alcohols, where carboxylate functionality does not exist, the configuration of the carbon, connected with the hydroxyl group, seems to be the key one. Additionally, it was observed that chiral phosphines and phosphites are effective catalysts for this cyclodehydration but without inducing stereocontrol.
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1. Introduction

In recent years the synthesis of carbocyclic nucleoside analogues has been the subject of great interest, due to their wide range of biological activity profiles.[1–4] In the same time, these compounds are chemically and enzymatically more stable than the corresponding nucleosides, according to the absence of a typical glucoside bond in their molecules.[5] The role of the methylene group in the carbocycle as a bioisostere of oxygen is justified by the observed antiviral and antitumor efficacies of some natural carbocyclic nucleosides, such as Arystomicin[6] and Neplanocin A,[7] as well as synthetic ones, as Carbovir[8–10] and Abacavir.[11–14] The latter shows great anti-HIV activity and therefore, it is used clinically to treat AIDS and AIDS-related complex.

As precursors of the carbocyclic moieties of compounds like nucleosides, carbohydrates and many other products of biological importance, cyclopentanoids play a fundamental role in synthetic organic chemistry. Among the broad range of organic transformations for the five-membered ring construction, the aldol condensation is an exceptionally useful C–C bond-forming reaction.[15–17] Its catalytic asymmetric variant is a strategic one both in chemistry and in biology, where it presents a critical biological transformation in the context of metabolism. The enzymatic reactions, catalysed by Type I aldolases, which accept hydrophobic organic substrates, utilise an enamine mechanism.[18] The aldolase antibodies synthesis and application in aldol reactions,[19–24] as well as their chemical oversimplified versions, have received considerable attention in recent years. Proline-catalysed asymmetric intramolecular condensation of dicarbonyl compounds, well known as Hajos–Parris–Eder–Sauer–Wiecher reaction, was discovered in the 1970s,[25–29] and afterward widely exploited both in its intermolecular[30–37] and intramolecular[38–46] variants. This reaction involves an enamine intermediate, with the C–C bond formation as the rate determining step and the stereodifferentiation occurring in this step, before dehydration. In the case of the Robinson annulating reaction it was found[45] that while proline, as well as a number of similar chiral compounds, like hydroxy proline, azetidine carboxylic acid etc., catalyse both steps of the transformation, the chiral amines tested catalyse the annulation but not the dehydration. It was suggested that chiral compounds containing a secondary amine of pyrrolidine type and a carboxylate functionality are the most efficient catalysts and that the carboxylic acid functionality appears to be the key to the dehydration step.

The asymmetric aldol reactions of diketones and ketoaldehydes are widely investigated, while the condensation of

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dialdehydes, well known in its non-chiral version reaction, is much less studied. To the best of our knowledge, the only paper on this subject reports the direct intramolecular asymmetric catalytic aldol condensation of dialdehydes on the case of proline-catalysed cyclisation of heptanedials.[46] The corresponding hydroxy cyclohexanecarbaldehydes are isolated with stereocontrol at the carbons, bearing the hydroxyl and carbaldehyde functionalities, while no dehydration products are detected, like in the most part of the cases of six-membered ring formation. In contrast, the direct catalytic intramolecular cross-aldol cyclisation of 1,6 dialdehydes, a widely exploited non-chiral transformation in the synthesis of a broad range of biologically active products,[47–55] leads to dehydration products in general, the corresponding cyclopentenecarbaldehydes. However, the asymmetric variant, requiring an asymmetricity to be induced at the β-carbon in respect to the aldehyde, is still unknown.

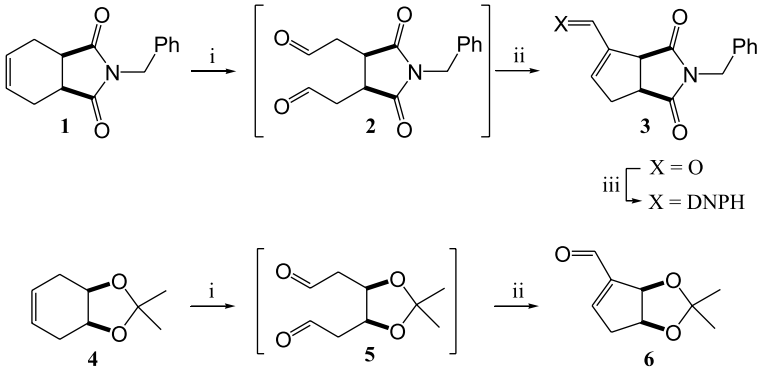
As a part of our study on the cyclopentanoid synthesis, an asymmetric version of the direct intramolecular catalytic aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes, leading to the corresponding cyclopentene carbaldehydes, is presented herein.

2. Results and discussion

The *meso*-3,4-disubstituted-1,6-dialdehydes were readily obtained by olefin oxidation of a series of differently *meso*-4,5-disubstituted cyclohexenes, applying ozonolysis and subsequent dimethyl sulphide (DMS) reductive work-up. Their asymmetric aldol cyclodehydration was conducted at ambient temperature in a time scale of 18–20 h, using different groups of compounds as catalysts (Scheme 1). In our previous work[56] several alkenes were tested in a non-chiral transformation. Among them the cyclic amide **1** appeared to be a good model compound for the detailed preliminary investigations, according to the observed high stability of the 2,4-dinitrophenylhydrazone of the aldol product (**3**, X=DNPH). Afterward the same catalysts were applied in the cyclodehydration of the dialdehyde **5**, where the corresponding cyclopentenecarbaldehyde **6** presents a direct precursor of a more functionalised cyclopentanoid unit with its two hydroxyl groups in the molecule. The difference in the behaviours of the dialdehydes **2** and **5** in respect to the catalysts used, observed in the non-chiral version,[56] gave an additional reason to concentrate our attention on the asymmetric transformation of these compounds.

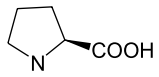
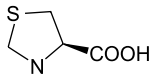
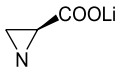
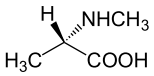
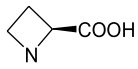
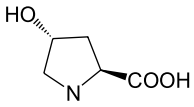
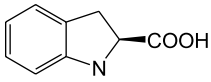
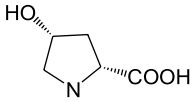
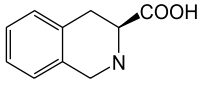
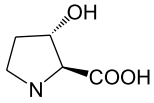
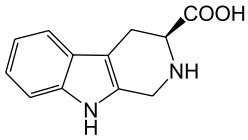
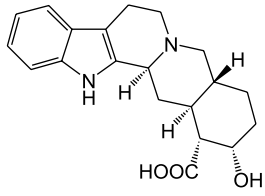
As a first series several amino acids activities were checked (Table 1), starting from (*S*)-proline as it has found to be a highly efficient catalyst in many transformations, including aldol cyclisation of heptanedials.[46] It was observed that it is also an effective catalyst in the formation of **3**, but without including stereocontrol (entry 1). By testing other amino acids it was observed, that **2**→**3** transformation is catalysed by simple acids, like (*S*)-(−)-aziridine carboxylic acid (entry 2), (*S*)-(−)-azetidine carboxylic acid (entry 3) and *N*-methyl-(*S*)-alanine (entry 8), leading to relatively high chemical yields but without enantiomeric excess. On the other hand, aromatic amino acids, such as (*S*)-(−)-2-indoline carboxylic acid (entry 4) and (*S*)-(−)-tetrahydro-3-isoquinoline carboxylic acid (entry 5), gave lower conversion but better stereoselectivities. The chiral yield observed with (*R*)-(−)-thiazolidin-4-carboxilic acid (36%, entry 7) in comparison with (*S*)-proline could be an indication that the sulphur atom in the catalyst molecule creates some stereocontrol. However, as the variability of commercially available sulphur containing chiral amino acids is very low, no further detailed investigation of this class of compounds were conducted.

The catalytic activities of different hydroxy prolines, which have shown similar efficiency to that of proline in an asymmetric Mannich reaction,[36] were studied (Table 1). It was observed that while both (2*S*,4*R*)-(+)-*trans*-4-hydroxyproline (entry 9) and (2*R*,4*R*)-(+)-*cis*-4-hydroxyproline (entry 10) catalysed the construction of **3** slowly but with significant stereocontrol, (2*S*,3*S*)-(−)-3-hydroxyproline (entry 11) promoted better conversion but with lower selectivity. When the diastereoisomers of 4-hydroxy prolines were used, where the difference in the configuration is only at C-2 centre, while that of the C-4 is the same, the major products showed the opposite stereochemistry. This could be an indication that the carbon, bearing the carboxylate functionality, controls the selectivity in this case, while that connected with the hydroxyl group has not significant influence. The latter is in agreement with the stereochemistry of the product of the reaction, catalysed by 3-hydroxy proline. In the cases of (*S*)-(−)-2,3,4,9-tetrahydro-1*H*-pyrido(3,4-*b*)indole-3-carboxilic acid (entry 6) and (+)-yohimbinic acid (entry 12), very low solubility in



Scheme 1. Aldol cyclodehydration of dialdehydes **2** and **5**: (i) O_3, dry CH_2Cl_2, −78 °C, DMS; (ii) catalyst (0.2 equiv), rt, 18–20 h; (iii) 2,4-dinitrophenylhydrazine, H_2SO_4, MeOH.

Table 1. Chiral amino acids and hydroxy amino acids, tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		73 (4)	0 (0)	7		58 (—)	36[a] (—)
2		73 (—[b])	0 (—)	8		85 (3)	16[c] (4[d])
3		88 (6)	0 (3[d])	9		26 (—)	52[a] (—)
4		57 (—)	58[a] (—)	10		19 (—)	66[c] (—)
5		42 (—)	26[a] (—)	11		60 (6)	30[a] (2[e])
6		18 (4)	6[a] (10[e])	12		10 (—)	4[c] (—)

[a] Major isomer $t_R = 52$ min.
[b] No reaction occurs.
[c] Major isomer $t_R = 60$ min.
[d] Major isomer $t_R = 29$ min.
[e] Major isomer $t_R = 22$ min.

the reaction media was observed, which could be an additional reason for the inefficiency of these compounds as catalysts. As phenylalanine has found to be an effective catalyst for the aldol condensation steps in the estrone[57] and (−)-ilimaquinone[58] syntheses, the primary amino acids (*S*)-valine and (*S*)-serine activities were ascertained, but racemic products in low reaction yields were isolated in both cases.

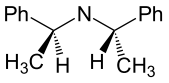
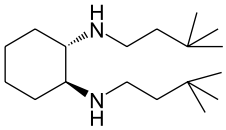
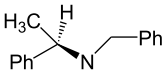
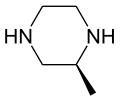
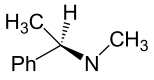
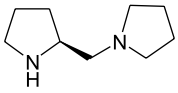
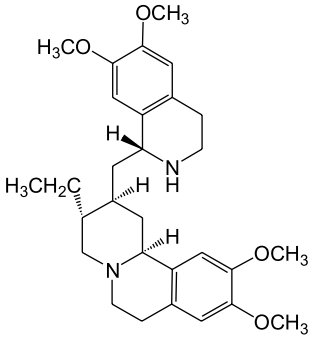
As a second series, the trifluoroacetates of various secondary amines were studied, due to their high effectiveness as catalysts in the non-chiral version. Starting with some chiral analogues of dibenzylamine (Table 2, entries 1–3), a strong dependence of the conversion on the steric hindrance in the catalyst molecule was observed, but without inducing stereocontrol. As all amines tested showed similar patterns, it could be summarised that these compounds, which have shown activity in Robinson annulation[45] but not in Manich condensation,[36] are not efficient catalysts for the asymmetric transformation, described herein.

Based on the observed better selectivities using hydroxy prolines in respect to proline, the trifluoroacetates of some amino alcohols activities were tested (Table 3). Variable conversion was observed without substantial selectivity, but some comments could be done. Comparing the efficiencies of some cyclic amino alcohols (Table 3, entries 1–3) with those of the corresponding carboxylic acids (Table 1, entries 1, 4 and 5), it could be summarised that while prolinol is more effective than proline, creating some stereocontrol in almost the same reaction extent, the indolyl derivatives show the opposite behaviour. As hydroxy pyrrolidine (Table 3, entry 5) catalysed the **2**→**3** conversion in the same extent as 3-hydroxy proline (Table 1, entry 11) but loosing the stereoselectivity (0 vs 30% ee), it could be suggested that the carboxylate functionality plays a crucial role in this case. Taking in consideration the stereochemistry of the major products in ephedrine and pseudoephedrine catalysed aldol condensation (Table 3), where (1*S*,2*R*)-(+)-ephedrine (entry 9) and (1*S*,2*S*)-(+)-pseudoephedrine (entry 10) originate mainly the product with a positive value of $[\alpha]_D$, while (1*R*,2*S*)-(−)-ephedrine (entry 8) led to the negative one, it could be suggested that the carbon, connected to the hydroxyl group, controls the selectivity in this case, where a carboxylate functionality does not exist. To ascertain this suggestion, as well as to study as wide as possible range of catalysts, several open chain secondary amino alcohols were prepared from commercially available primary ones (Fig. 1).

The racemic products were formed with all catalysts of this series, where the hydroxyl group is connected with a non-chiral centre. The latter supports the suggestion that the configuration of the carbon, bearing the hydroxyl group, is crucial for induction of stereocontrol in substrates studied.

Applying a part of the catalysts tested in **2**→**3** conversion to the construction of **6** from **5**, it was observed that the

Table 2. Chiral amines[a], tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		—[b]	—	5		78 (6)	4[c] (6[d])
2		59	0	6		10 (—)	4[e] (—)
3		97	0				
4		(8)	(14[d])	7		73 (10)	6[c] (0)

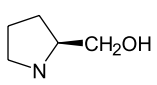
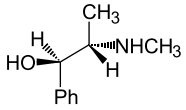
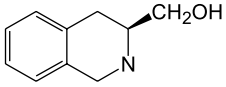
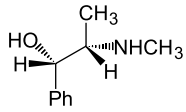
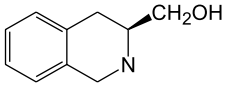
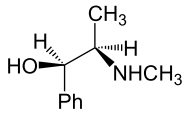
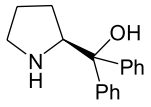
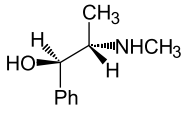
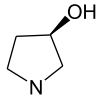
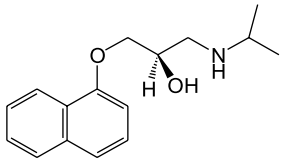
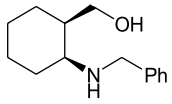
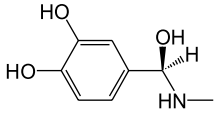
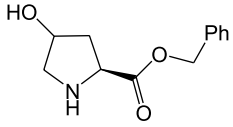
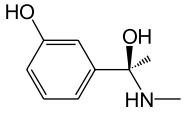
[a] As trifluoroacetates.
[b] No reaction occurs.
[c] Major isomer t_R=52 min.
[d] Major isomer t_R=22 min.
[e] Major isomer t_R=60 min.

transformation in this case is rather slow in general and without inducing significant stereocontrol. The only exception is in the case of 2-(diphenylhydroxymethyl)pyrrolidine (Table 3, entry 4), where 70% ee was observed but in very low conversion. An attempt to increase the reaction yield by prolonging the reaction time resulted in a significant decrease in the selectivity. The fact that no reaction occurred with several amino acids and ammonium trifluoroacetates is in accordance with the observed in our previous work[56] that dibenzylammonium trifluoroacetate does not catalyse the aldol condensation of **5**. As it was found that dibenzylamine itself is an efficient catalyst, the basic components of some of the catalysts used were checked. Thus, 2-methylpiperazine (Table 2, entry 6), which salt was inactive, created the product in almost the highest chemical yield, observed in this case, but with very low selectivity (34 and 8% ee). On the other hand, the ephedrines did not catalyse the reaction at all. The (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine, which salt gave the best chiral excess, generated the product in better extent but with reduced stereocontrol (6 and 70% ee vs 18 and 36% ee). The latter could be an indication that the faster reaction in this case leads to a loose of selectivity and/or that the acidic component of the catalyst controls it, but as such behaviour was observed only with this catalyst, no substantial conclusions could be done in general. Surprisingly, it was observed that the catalyst (*S*)-(−)-2-(pyrrolidinomethyl)-pyrrolidine, apart of giving some desired transformation (21 and 2% ee), originated 7,7a-dihydro-4-hydroxy-2,2-dimethylbenzo[*d*][1,3]dioxol-5(6*H*)-one as a main product. The same compound was found to be a side product in the non-chiral variant of this reaction performed in wet dichloromethane and the main one if hydroxycyclohexene was used as a starting material.[56]

Additionally, in a search of better catalysts, some chiral phosphites and phosphines were studied in both **2**→**3** and **5**→**6** cyclodehydration (Table 4). It was found that the transformation occurs in moderate to excellent yield, but without stereocontrol. The only exception was (2*S*,4*S*)-(−)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine (entry 6), which gave moderate selectivity (24% ee).

In an attempt to determine the absolute configuration of the aldol product **3**, which is explicit if a chiral centre with known configuration exists in the molecule as a norm, several derivatisations and transformations were performed. Chiral hydrazones (using SAMP and RAMP), chiral enamines and subsequent reduction to the corresponding amines, hydrogenation of the aldehyde followed by chiral ether or ester formation etc. were done, but a crystal of pure enantiomer was not isolated. When providing the cyclodehydration, starting from an analogue of **1**, having (*S*)-phenylethylamino group instead of benzylamino in the substituent part, the dinitrophenylhydrazone of the corresponding cyclopentene carbaldehyde was isolated in the same extent and stereochemistry as **3**. After several recrystallisations from ethylacetate, where racemic crystals were always formed, the enriched to the major isomer mother liquors were submitted to a PTLC using multiple developments of the plates, as both isomers have the same R_f-values. A pure isomer was isolated, but the crystals, created in several different solvent systems, were always rather small and thus, X-ray data were not obtained.

Table 3. Chiral amino alcohols[a], tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		81	12[b]	8		64 (11)	18[c] (20[d])
2		45	27[b]	9		73 (10)	44[b] (0)
3		70	22[b]	10		73 (25)	16[b] (6[e])
4		71 (6)	12[b] (70[e])	11		(14)	(6[d])
5		63 (12)	0 (10[d])	12		27 (15)	0 (2[d])
6		37 (—[f])	8[c] (—)	13		44 (3)	24[c] (32[d])
7		96 (16)	1[b] (8[e])	14		(9)	(10[d])

[a] As trifluoroacetates.
[b] Major isomer $t_R = 52$ min.
[c] Major isomer $t_R = 60$ min.
[d] Major isomer $t_R = 29$ min.
[e] Major isomer $t_R = 22$ min.
[f] No reaction occurs.

3. Conclusions

A first direct intramolecular asymmetric catalytic aldol cyclodehydration of 1,6-dialdehydes to the corresponding cyclopentene carbaldehydes was accomplished. Variable conversion was observed with dialdehyde **2**, having amide substituents, while in the case of acetonide protected diol **5**, the transformation was rather slow in general and without inducing substantial selectivity. Among the broad range of the catalysts tested, it appears that for the substrates studied some hydroxy amino acids, like hydroxy prolines, as well as amino alcohols, like ephedrines and pseudoephedrines, are the most efficient chiral ones for insertion of asymmetricity at the β-carbon in respect to the aldehyde. The results obtained clearly demonstrate that the chiral version is feasible and that to reach stereocontrol, the presence of a hydroxyl group in the catalyst's molecule seems to be crucial. The chiral centre in hydroxy amino acids, bearing the carboxylate functionality, controls the stereochemistry of the final product. In the case of amino alcohols, where carboxylate functionality does not exist, the configuration of the carbon, connected with the hydroxyl group, seems to be the key one. Additionally, it was found that chiral phosphines and phosphites are effective catalysts for this cyclodehydration but without inducing stereocontrol.

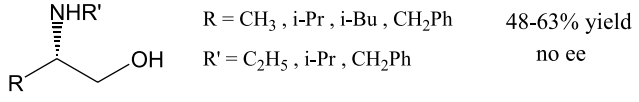
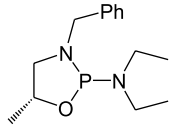
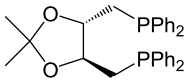
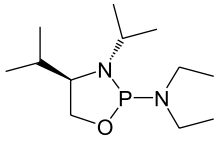
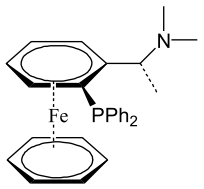
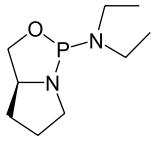
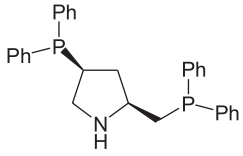


Figure 1. A series of chiral secondary amines.

4. Experimental

All reagents and the most part of the catalysts were purchased from Aldrich and Fluka and were used without any further purification. The chiral phosphites were prepared in the laboratory.[59] The amino alcohols, shown in Figure 1, were synthesised from (*S*)-(+)-alaninol, (*S*)-(−)-phenylalaninol, (*S*)-(+)-leucinol and (*S*)-(+)-valinol by azomethyne formation with benzaldehyde, acetaldehyde

Table 4. Chiral phosphites and phosphines, tested as catalysts in **2**→**3** and **5**→**6** conversions

Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %	Entry	Catalyst	Yield of **3** (**6**), %	ee of **3** (**6**), %
1		83 (17)	2[a] (0)	4		48 (—[b])	0 (—)
2		97 (13)	0 (4[c])	5		50	4[a]
3		64 (25)	0 (4[c])	6		93	24[d]

[a] Major isomer $t_R = 60$ min.
[b] No reaction occurs.
[c] Major isomer $t_R = 29$ min.
[d] Major isomer $t_R = 52$ min.

and acetone and subsequent $LiAlH_4$ reduction, following standard procedures. The dichloromethane was dried over P_2O_5. The ozonolysis were performed on a Fischer Ozon Generator 500 M using dry (in-steam molecular sieve-silica gel blue tube) oxygen. The HPLC analyses were carried out using Merck and Hitachi components L-600A, L-4250, T-6300, D-600 on a Chiralpak AD column, Diacel Chemical Industries, Ltd (0.46 and 25 cm). The optical rotations were recorded on a AA-100 Polarimeter, Optical Activity, Ltd (Na-lamp, $\lambda = 589$ nm, 0.5 dm cell, $c = 1$ in $CHCl_3$).

All experimental details and physical and spectroscopic data for the starting materials, intermediately formed dialdehydes and final products are given in our previous report.[56]

General procedure for **1**→**3** *and* **4**→**6** *transformation*. Through a solution of an alkene (1 mmol) in dry dichloromethane (5 ml) a steam of ozone in oxygen was bubbled at −78 °C until the solution turned blue. The system was purged with argon until the colour disappeared and dimethylsulphide (4 mmol, 0.3 ml) was then added. The solution was kept at rt for 2 h and a catalyst (0.2 mmol, 20%), was added. After 18–20 h at rt the solvent was removed in vacuo and the product was purified by chromatography directly in the case of **6** and after derivatisation as DNPH for **3**.

The selectivities were determined by chiral-phase HPLC analysis at 25 °C using the following conditions: (a) for the DNPH derivative of **3**: mobile phase 50% *i*-PrOH and 50% hexane, flow rate 0.6 ml/min, wave length 372 nm, retention times $t_R = 52$ min and $t_R = 60$ min; (b) for the product **6**: mobile phase 1% *i*-PrOH and 99% hexane, flow rate 1.5 ml/min, wave length 240 nm, retention times $t_R = 22$ min and $t_R = 29$ min.

Optical rotations of selected samples of the DNPH of **3**: Table 1, $[\alpha]_D = +137.0°$ (entry 4), $+59.0°$ (entry 5), $+79.3°$ (entry 7), $-38.7°$ (entry 8), $+119.5°$ (entry 9), $-169.0°$ (entry 10), $+61.7°$ (entry 11), $-11.9°$ (entry 12); Table 3, $[\alpha]_D = -48.4°$ (entry 8), $+97.2°$ (entry 9), $+39.2°$ (entry 10), $-56.1°$ (entry 13).

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References and notes

1. Borthwick, A.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571–623.
2. Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.; Earl, R.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611–10670.
3. Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272.
4. Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319–4348.
5. Jones, M. *Chem. Br.* **1988**, *24*, 1122–1126.
6. Kusaka, T.; Yamamoto, H.; Shibata, M.; Muroi, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255–263.
7. Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Otani, M. *J. Antibiot.* **1981**, *34*, 359–366.
8. Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17–21.
9. Jones, M.; Myers, P.; Robertson, C.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2479–2484.
10. Trost, B.; Madsen, R.; Guile, S.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947–5956.
11. Crimmins, M.; King, B. *J. Org. Chem.* **1996**, *61*, 4192–4193.
12. Daluge, S.; Good, S.; Faletto, M.; Miller, W.; Wayne, H.; St. Clair, M.; Boone, L.; Tisdale, M.; Parry, N.; Reardon, J.; Dornsife, R.; Averett, D.; Krenitsky, T. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082–1093.

13. Faletto, M.; Miller, W.; Garvey, E.; St. Clair, M.; Daluge, S.; Good, S. *Antimicrob. Agents Chemother.* **1997**, *41*, 1099–1107.
14. Foster, R.; Faulds, D. *Drugs* **1998**, 729–736.
15. Heathcock, C. H. In Morrison, J. D., Ed.; Asymmetric Synthesis; Academic: New York, 1984; Vol. 3, Chapter 2, pp 111–212.
16. Kim, B. M.; Williams, S. F.; Masamune, S. In Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 2, Chapter 1.7, pp 239–275.
17. Danheiser, R. In Lindberg, T., Ed.; Strategies and Tactics in Organic Synthesis; Academic: London, 1984; Vol. 1, pp 21–70.
18. Wong, C.-H.; Whitesides, G. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
19. Wagner, J.; Lerner, R.; Barbas, C., III *Science* **1995**, *270*, 1797–1800.
20. Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970–6979.
21. List, B.; Lerner, R.; Barbas, C. F., III *Org. Lett.* **1999**, *1*, 59–61.
22. List, B.; Lerner, R.; Barbas, C., III *Org. Lett.* **1999**, *1*, 1623–1626.
23. Machajewski, T.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374.
24. Heine, A.; DeSantis, G.; Luz, J.; Mitchell, M.; Wong, C.-H.; Wilson, I. *Science* **2001**, *294*, 369–374.
25. Hajos, Z.; Parris, D. German Patent DE 2102623, July 29, 1971.
26. Hajos, Z.; Parris, D. *J. Org. Chem.* **1973**, *38*, 3239–3243.
27. Hajos, Z.; Parris, D. *J. Org. Chem.* **1974**, *39*, 1615–1621.
28. Eder, U.; Sauer, G.; Wiecher; R. German Patent DE 2014757, Oct 7, 1971.
29. Eder, U.; Sauer, G.; Wiecher, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497.
30. List, B.; Lerner, R.; Barbas, C., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
31. Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529–532.
32. List, B. *Tetrahedron* **2002**, *58*, 5573–5590.
33. Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595–1601.
34. Northrup, A.; McMillan, D. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799.
35. Melchiorre, P.; Jørgensen, K. *J. Org. Chem.* **2003**, *68*, 4151–4157.
36. Notz, W.; Tanaka, F.; Watanabe, Sh.; Chowdari, N.; Turner, J.; Thayumanavan, R.; Barbas, C., III *J. Org. Chem.* **2003**, *68*, 9624–9634.
37. Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858–860.
38. Brown, K.; Damm, L.; Dunitz, J.; Eschenmoser, A.; Hobi, R.; Kratky, Chr. *Helv. Chim. Acta* **1978**, *61*, 3108–3135.
39. Woodward, R.; Logusch, E.; Nambiar, K.; Sakan, K.; Ward, D.; Au-Yeung, B.-W.; Balaran, P.; Browne, L.; Card, P.; Chen, C.; Chênevert, R.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D.; Hayakawa, K.; Heggie, W.; Hesson, D.; Hoppe, D.; Hoppe, I.; Hyatt, J.; Ikeda, D.; Jacobi, P.; Kim, K.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R.; Ong, B.; Press, J.; Rajan Babu, T.; Rousseau, G.; Sauter, H.; Suzuki, M.; Tatsuta, K.; Tolbert, L.; Truesdale, E.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A.; Vladuchick, W.; Wade, P.; Williams, R.; Wong, H. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213.
40. Agami, C.; Platzer, N.; Puchot, C.; Sevestre, H. *Tetrahedron* **1987**, *43*, 1091–1098.
41. Agami, C. *Bull. Soc. Chim. Fr.* **1988**, 499–507.
42. Reymond, J. *J. Mol. Catal. B* **1998**, *5*, 331–337.
43. Nelson, S. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.
44. Carreira, E. In Jacobsen, E., Pfaltz, A., Yamamoto, H., Eds.; Comprehensive Asymmetric Catalysis; Springer: Heidelberg, 1999; Vol. 3, Chapter 29.1.
45. Bui, T.; Barbas, C. F., III *Tetrahedron Lett.* **2000**, *41*, 6951–6954.
46. Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785–2788.
47. Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K. W.; McLamore, W. *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.
48. Barkley, L.; Farrar, M.; Knowles, W.; Raffelson, H.; Thompson, Q. *J. Am. Chem. Soc.* **1954**, *76*, 5014–5017.
49. Truesdale, L.; Swanson, D.; Sun, R. *Tetrahedron Lett.* **1985**, *26*, 5009–5012.
50. Hetmanski, M.; Purcell, N.; Stoodley, R.; Palfreyman, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2089–2096.
51. Corey, E.; Danheiser, R.; Chandrasekaran, S.; Siret, P.; Keck, G.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031–8034.
52. Tamura, N.; Natsugari, H.; Kawano, Y.; Matsushita, Y.; Yoshioka, K.; Ochiai, M. *Chem. Pharm. Bull.* **1987**, *35*, 996–1015.
53. Bryce, M.; Gardiner, J. *J. Chem. Soc., Chem. Commun.* **1989**, 1162–1164.
54. Hodgson, D.; Parsons, P.; Stones, P. *Tetrahedron* **1991**, *47*, 4133–4142.
55. Singh, R.; Cooper, R. *Tetrahedron* **1994**, *50*, 12049–12064.
56. Kurteva, V.; Afonso, C. *14th International Symposium on Homogeneous Catalysis*, July 5–9, **2004**, Munich, Germany, P108, Book of Abstracts, p 126; submitted for publication as a full paper.
57. Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *16*, 4975–4982.
58. Bruner, S.; Radeke, H.; Tallarico, J.; Snapper, M. *J. Org. Chem.* **1995**, *60*, 1114–1115.
59. Cabrita, E.; Afonso, C.; Santos, A. *Chem. Eur. J.* **2001**, *7*, 1455–1467 and unpublished results.

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Formation of reactive *o*-quinone methides from the reaction of trimethylsilyl(methyl)-substituted 1,4-benzoquinones with nucleophiles

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Abstract—*o*-Quinone methides are formed from the reaction of nucleophiles with trimethylsilyl(methyl)-1,4-benzoquinones. These reactive intermediates are trapped by excess nucleophile to form substituted quinones following oxidation. In addition, varying amounts of a symmetrical dimer and a xanthen derivative were observed. The influence of different nucleophiles and ring substituents on the rate of reaction have been studied, and are consistent with rate-limiting formation of a vinylogous enolate initiated by attack of the nucleophile on the silyl group.
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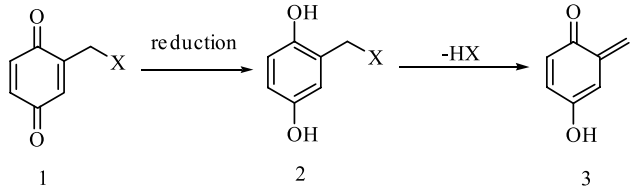
1. Introduction

The formation of *o*-quinone methides as reactive intermediates in biologically-active natural products has been reviewed.[1] For example, a proposed reactive quinone methide intermediate generated from the naturally occurring antitumor antibiotic, mitomycin C, is believed to be responsible for DNA alkylation.[2] Similarly, a quinone methide has been detected to arise from daunomycin and shown to function as an alkylating agent.[3] Apart from their involvement in biological processes, *o*-quinone methides have proven useful as synthetic intermediates. For example, electrophilic *o*-quinone methides of structural type **3** react with a variety of nucleophiles (Michael addition), resulting in substituted hydroquinones.[4] They also function as efficient heterodienes in Diels–Alder reactions and undergo a variety of self dimerization reactions.[5]

A common method for the generation of *o*-quinone methides **3** from appropriately substituted quinones, **1**, is initiated by their reduction to the corresponding hydroquinone **2** followed by intramolecular elimination of an equivalent of HX to form the *o*-quinone methide (Scheme 1). Variations of this method include the thermal dehydration of *o*-hydroxybenzyl alcohols and the fluoride-induced desilylation of silylated *o*-hydroxybenzyl bromide (X=Br) and bis-silylated *o*-hydroxybenzyl alcohol (X=OH).[6] Other methods of note involve oxidation of *o*-alkyl-substituted phenols and the thermal ring expansion of 4-allenyl-4-hydroxycyclobutenones.[7,8] Reported herein is a new method for the generation of *o*-quinone methides from (trimethylsilylmethyl or triarylsilylmethyl)-1,4-benzoquinones. This involves treatment of (trialkylsilylmethyl or triarylsilylmethyl)-1,4-benzoquinones with oxygen-nucleophiles such as alcohols or water. The reaction conditions are mild and the transformation can be accomplished under neutral conditions.[9]

A generalized mechanistic paradigm to account for the reaction is outlined in Scheme 2. The appropriately substituted quinone **4** reacts with nucleophiles to generate vinylogous enolate **5**, which provides *o*-quinone methide **6** upon silylation. The resulting *o*-quinone methide reacts further with the nucleophile to form substituted hydroquinone **7**, which is readily oxidized to the corresponding substituted quinone. Details of this study including synthetic applications and mechanistic details are now provided.



Scheme 1.

Keywords: *o*-Quinone methide; 1,4-benzoquinones; Trimethylsilyl; Michael addition; Diels–Alder; Dimerization.

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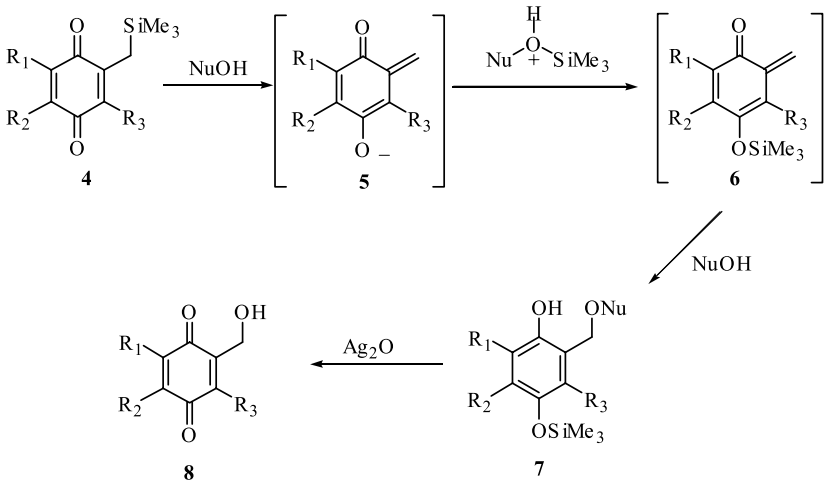
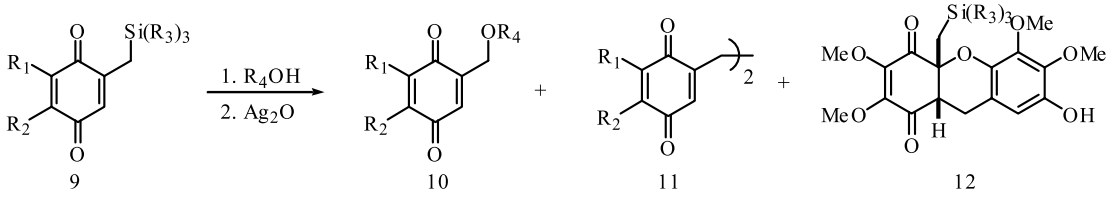


Scheme 2.

2. Results and discussion

A set of reactions illustrating the intermediacy of the *o*-quinone methides is outlined below (Scheme 3). When an ethanolic solution of quinone **9a** ($R_1=R_2=OMe$, $R_3=Me$) was refluxed for 45 min then worked up under oxidative conditions (Ag_20), the corresponding ethoxymethyl quinone **10a** ($R_1=R_2=OMe$, $R_4=Et$) was isolated in 82% yield along a minor amount (5%) of the symmetrical dimer **11a** ($R_1=R_2=OMe$). The symmetrical dimer **11a** may be envisaged to arise via a number of possible pathways. For example Diels–Alder dimerization of two *o*-quinone methides would result in a spiropyran. Subsequent ring opening would then provide the dimer in its half reduced form. Oxidative work up leads to **11a**. An alternate route would provide the half reduced dimer via Michael addition



a) $R_1=R_2=OMe$, $R_3=Me$
b) $R_1=OMe$, $R_2=n$Bu, $R_3=Me$
c) $R_1=n$Bu, $R_2=OMe$, $R_3=Me$
d) $R_1=R_2=OMe$, $R_3=Ph$

Compound	Conditions	9 (%)	10 (%)	11 (%)	12 (%)
9a	EtOH, reflux 45 min	0	82	5	0
9a	EtOH, RT 24 h	0	45	22	0
9a	10% EtOH/CH_3CN, reflux 44 h	44	trace	0	37
9a	10% H_2O/CH_3CN, reflux 1.5 h	0	18	67	trace
9a	5% H_2O/CH_3CN, reflux 8 h	0	12	46	22
9a	HOAc, reflux 4 h	10	54	0	0
9a	6 eq. NaOAc/HOAc, reflux 0.5 h	0	79	<2	0
9a	0.1 eq. NaOAc/HOAc, reflux 0.5 h	50	30	0	0
9b	EtOH, reflux 6 h	11	63	5	0
9c	EtOH, reflux 45 min	13	67	7	0
9d	EtOH, reflux 32 h	0	70	0	0

Scheme 3.

of the enolate to the *o*-quinone methide. At ambient temperature the reaction required 24 h and the above products were realized in 45 and 22%, respectively. In comparison, when the amount of ethanol was reduced to 10% in a solvent of acetonitrile, only a trace of **10a** was observed after refluxing for 44 h. The major product was the xanthene-1,4-dione **12** (37%), and a significant amount (44%) of starting material was recovered. In related studies ethanolic solutions of the quinones **9b** (R_1=OMe, R_2=*n*-Bu, R_3=Me) and **9c** (R_1=*n*-Bu, R_2=OMe, R_3=Me) gave the corresponding **10b** (R_1=OMe, R_2=*n*-Bu, R_4=Et) and **10c** (R_1=*n*-Bu, R_2=OMe, R_4=Et) in respective yields of 63 and 67% along with 5 and 7% of the dimers **11b** (R_1=OMe, R_2=*n*-Bu) and **11c** (R_1=*n*-Bu, R_2=OMe) after reaction times of 6 h for **9b** and 45 min for **9c** at reflux temperature. Quinone **9d** (R_1=R_2=OMe, R_3=Ph) also gave **10a** in 70% yield. However, the bulkier triphenylsilyl group significantly retarded the reaction rate; 32 h in refluxing ethanol was required as compared to 45 min for the trimethyl analogs, **9a**,**c** and 6 h for **9b**.

The steric bulk of the alcohol also influences the reaction course. For example, when solutions of **9a** in *iso*-propanol and *tert*-butanol were refluxed, the reaction times increased to 9 and 44 h, respectively. Also, the yields of the corresponding alkoxymethyl-substituted quinones decreased and the yield of the symmetrical dimer increased. In *iso*-propanol the quinone **10d** (R_1=R_2=OMe, R_4=*i*-Pr) and the dimer **11a** were obtained in 65 and 10%, respectively, as compared to yields of **10e** (R_1=R_2=OMe, R_4=*t*-Bu) (45%) and **11a** (16%) in *tert*-butanol.

In a related study a solution of **9a** in 5% aqueous acetonitrile was refluxed for 8 h followed by subsequent oxidation (Ag_2O). Here, the quinone **10f** (R_1=R_2=OMe, R_4=H) (12%), the symmetrical dimer **11a** (46%) and the xanthene-1,4-dione **12** (22%) were realized. Interestingly, the amount of water had a significant effect on the product distribution. For example, when 10% aqueous acetonitrile was employed, the dimer **11a** and quinone **10f** were realized in respective yields of 67 and 18%, and the xanthene-1,4-dione **12** was detected in only trace amounts.

Further data were obtained when a solution of **9a** in glacial acetic acid containing 6 equiv of sodium acetate was heated to reflux for 0.5 h. The major product detected was the quinone **10g** (R_1=R_2=OMe, R_4=Ac) (79%) along with $<$2% of dimer **11a**. When the amount of sodium acetate was reduced to 0.1 equiv the observed products were the quinone **10g** (30%) and recovered starting material. In acetic acid alone quinone **10g** was realized in 54% along with 10% recovered starting material. Dimer **11a** was not detected from the reactions containing 0.1% NaOAc or in pure acetic acid.

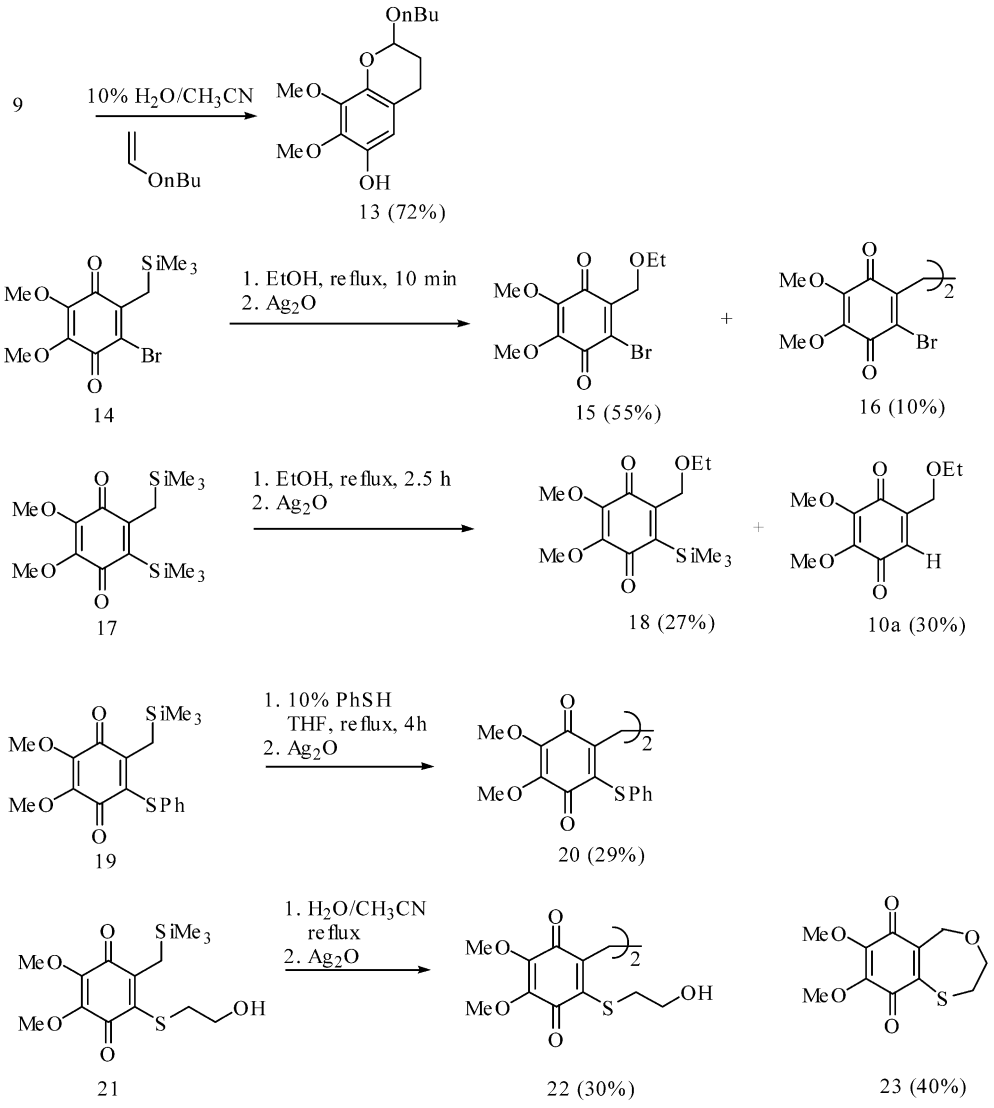
Additional examples are presented in Scheme 4. Treatment of **9a** with 10% aqueous acetonitrile in the presence of excess *n*-butyl vinyl ether gave the chromanol **13** in 72% yield. Quinone **14** was found to readily react with ethanol. After only 10 min at reflux followed by an oxidative (Ag_2O) workup, quinone **15** along with dimer **16** were realized in 55 and 10%, respectively. Under analogous conditions **17** was converted to **18** in 27% yield along with quinone **10a** in 30% yield.

Quinone **19** was found to be stable in dry refluxing THF after 7 h. However, addition of a catalytic amount (10 mol%) of thiophenol resulted in the formation of the symmetrical dimer **20** (29%) along with recovered starting material after an additional 4 h at reflux. Similar behavior was observed with the mercaptoethanol-substitued quinone **21**. Heating solutions of this quinone in refluxing THF for 5 h or toluene for 8 h failed to induce any reaction. However, heating a dilute aqueous acetonitrile solution of **21** for 3 h induced the formation of symmetrical dimer **22** and the annelated quinone **23** in respective yields of 30 and 40%.

The reaction rates of a variety of quinones with ethanol were studied to determine the influence of ring substitution. The reactions of **9a** as well as the regioisomeric *n*-butyl-substituted quinones **9b**, and **9c** were measured in ethanol-d_6 at 70° by ^{1}H NMR. The disappearance of the methylene group resonance as a function of time was monitored using the methyl group resonance of *p*-xylene as an internal standard. Due to the limited solubility of triphenylsilyl-substituted quinone **9d** in ethanol, the reaction rate of this quinone was followed by HPLC. In all cases, the reactions exhibited clean pseudo first-order kinetic behavior. The half lives of **9a**,**b**,**c**,**d** at 70 °C were calculated to be, respectively, 21 min, 85 min, 28 min and 15 h. The reaction of the bromoquinone **14** with ethanol was much too fast to be measured accurately at 70 °C. Therefore, the rate of reaction was studied by ^{1}H NMR at 30 °C in ethanol-d_6, revealing a half life of 13 min.

The data outlined above are consistent with the mechanism provided in Scheme 2. In this regard, the following points are of particular note:

1. The rate-limiting step is nucleophilic attack on the silyl group of quinone **4** to produce the enolate anion **5**. The difference in the reaction rates of **9a** and **9d** is particularly revealing in this regard. The data show the less bulky quinone **9a** to react approximately 43 times faster than its more hindered analog **9d** at 70 °C. The difference in rate between the other quinones is also noteworthy. For example, the half-life of the bromoquinone **14** is 13 min at 30 °C while that of **9a** is 21 min at 70 °C. Here again, the data suggest enolate anion formation in the rate-limiting step, that is, the electronegative bromine adds stability to the enolate and thus increases the reaction rate. The observed rate differences between the other quinones are less remarkable, but even here the data suggest the importance of enolate stability. Note, for example, the rate difference between the regioisomeric quinones, that is, **9b**/**9c**=1:3. This would be consistent with anion stabilization in **5**. Thus **9b** (R_1=OMe) would result in a vinylogous ester enolate while **9c** (R_1=*n*-Bu) would give a more stable keto enolate.[10]
2. Unambiguous data for the silyloxy quinone methide **6** as opposed to the protio analog was not obtained. However, the silyl analog is favored on the basis of the results obtained when **9a** was treated with acetic acid or acetic



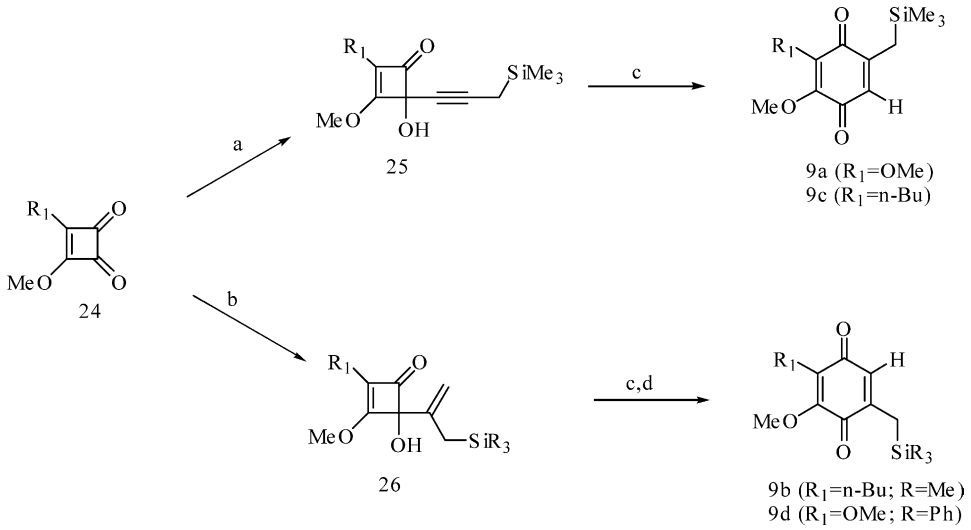
Scheme 4.

acid/sodium acetate. Under these acidic conditions no simple protio desilylated product (e.g., 2,3-dimethoxy-5-methyl-1,4-benzoquinone) was detected. These data are in agreement with the mechanistic paradigm outlined in Scheme 2, that is, *O*-silylation of the enolate **5** to give the quinone methide **6** is presumably favored over *O*-protonation. This intermediate then functions as the key precursor to the observed reaction products.

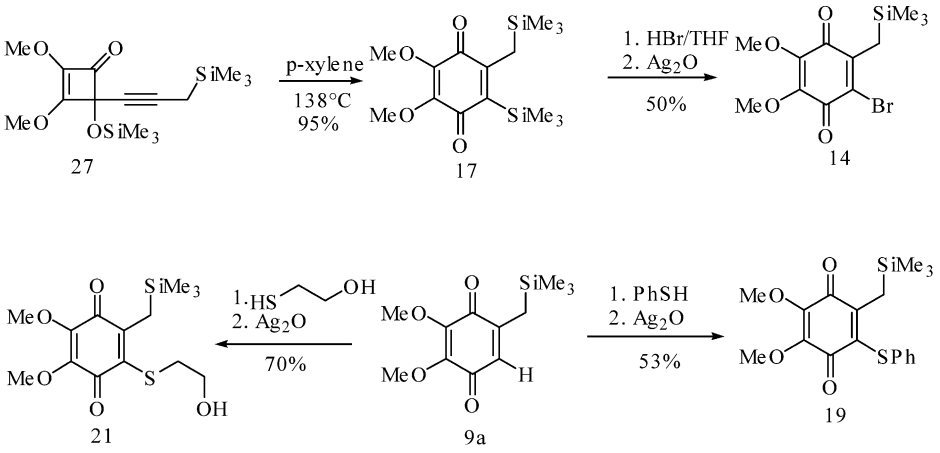
3. The above reactions are in agreement with an *o*-quinone methide precursor. Selected examples are noted below. Quinones of general structure **10** are envisaged to arise via Michael additions of ROH to the enone of the *o*-quinone methide followed by oxidation of the resulting silylated hydroquinone.[4g,11] As the concentration of ROH decreases (see, for example, entry b in Scheme 3) the *o*-quinone methide is competitively trapped by the starting quinone in a Diels–Alder reaction to give the xanthene-1,4-dione **12**. Analogously, the *o*-quinone methide can be intercepted to give **13** when generated in the presence of excess *n*-butylvinyl ether. The dimers of general structure **11** may arise via an initial Diels–Alder dimerization of the quinone methides, a known reaction pathway for such intermediates.[12] Alternatively, dimers **11** may be formed by Michael addition of enolate **5** to *o*-quinone methide **6**.

Quinones **9a**,**b**,**c**,**d**, **14**, **17**, **19** and **21**, needed for the study reported herein, find their synthetic genesis in the previously reported thermal rearrangement of 4-alkynyl and 4-alkenylcyclobutenones (Scheme 5).[13] For example, 3-*n*-butyl-4-methoxycyclobuten-1,2-dione (**24**) was converted to the corresponding adducts **25** and **26** (R_1 = *n*-Bu, R = Me) upon treatment with the appropriate alkynyl or vinyl lithium reagent to the more reactive carbonyl group. These then gave the respective regioisomeric quinone **9b** (92%) and **9c** (75%) upon thermolysis (*p*-xylene,138 °C). In a similar fashion **26** (R_1 = OMe, R = Ph) gave **9d** (92%) and **27** gave **17** (95%). Treatment of **17** with HBr in THF followed by oxidation (Ag_2O) of the resulting hydroquinone gave **14** (50%). Quinone **21** (70%) was obtained from **9a** upon treatment with mercaptoethanol followed by an oxidative work up. Quinone **19** (53%) was obtained analogously using thiophenol.

The facility of *o*-quinone methide formation from (trimethylsilyl)methyl-1,4-benzoquinones under mild and



Reagents: a) 1-lithio-3-(trimethylsilyl) propyne, THF, -78°C, then H_2O of TMSCl;
b) 2-lithio-3-(trimethylsilyl)propene, THF, -78°C; c) *p*-xylene, reflux; d) Ag_2O, *p*-xylene



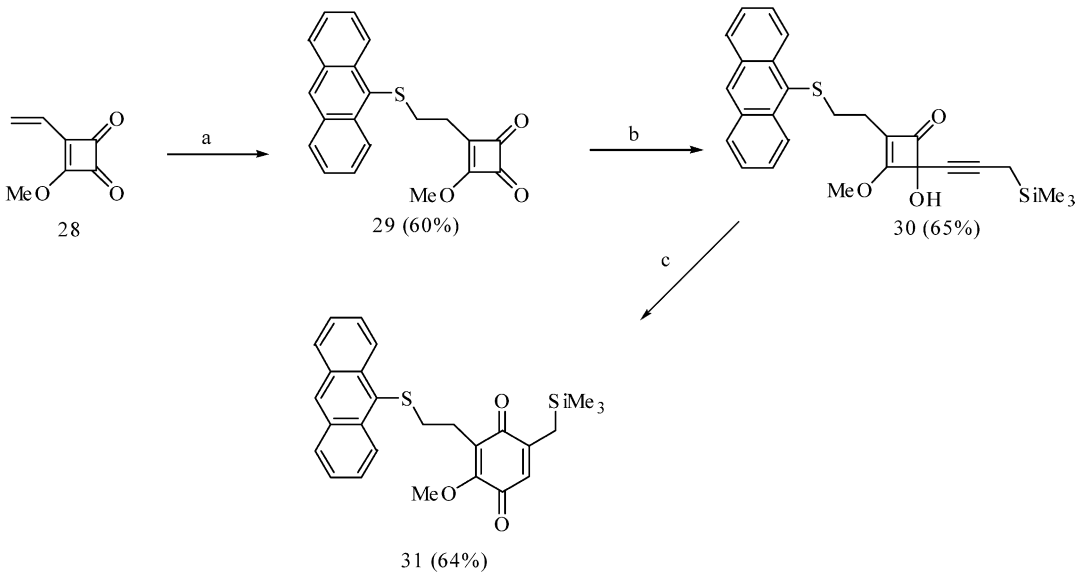
Scheme 5.

neutral conditions can be used as a paradigm to guide the design of potentially bioactive compounds. For example, quinones bearing an intercalating group as well as the (trimethylsilyl)methyl group might effectively cleave DNA. To this end, quinone **31** was prepared as outlined in Scheme 6. Addition of 9-thioanthracene to 3-methoxy-4-alkenylcyclobutene-1,2-dione gives **29** in 60% yield.[14] This was converted to **30** upon addition of 1-lithio-3-trimethylsilylpropyne, thermolysis of which (acetonitrile, reflux) gave the desired quinone **31** in 64% yield.

When quinone **31** was incubated with supercoiled DNA at 51 °C for 21 h cleavage to the relaxed circular form was observed as evidenced by agarose gel electrophoresis with ethidium bromide stain. Moreover, it was observed that added ethidium bromide inhibits cleavage of the supercoiled DNA by effectively competing for the intercalation sites.

3. Conclusions

In conclusion, the most significant aspects of this work include the following: (1) trialkylsilyl (or triarylsilyl)-methyl-1,4-benzoquinones **4** function as excellent precursors to *o*-quinone methide intermediates **6**; (2) the quinone methides can be generated under mild and neutral conditions; (3) the mechanism involves nucleophilic attack at the silyl group with displacement of the corresponding vinylogous enolate anion; (4) anion stabilizing groups on the quinone nucleus at those positions that enhance anion stabilization facilitate the rate of the reaction; (5) a general method for the synthesis of trialkylsilyl (or triarylsilyl)-methyl-1,4-benzoquinones from substituted cyclobuten-1,2-diones is presented; (6) quinone **31**, bearing an intercalating group as well as well as a (trimethylsilyl)-methyl substituent, was prepared and observed to cleave supercoiled DNA.



Reagents: a) 9-thioanthracene; b) 1-lithio-3-trimethylsilylpropyne; c) acetonitrile, reflux

Scheme 6.

4. Experimental

4.1. General

All air or water sensitive reactions were carried out under a slight pressure of nitrogen or argon. Dry solvents were distilled from calcium hydride. THF and ethyl ether were further distilled from sodium (benzophenone indicator). Unless specified as dry, solvents were unpurified reagent grade. Glassware was flame-dried under a stream of nitrogen or argon, where appropriate. In cases where products were isolated by 'aqueous work-up', the procedure was to quench the reaction by addition of 5% NH_4Cl to the reaction mixture followed by dilution with ethyl ether. The combined organic layers were washed with brine and dried with $MgSO_4$ before concentration in vacuo to yield the crude products. Flash column chromatography was performed using E.Merck silica gel (230–400 mesh) or Fisher Scientific florisil (100–200 mesh). Radial chromatography was performed on a model 7924T chromatotron from Harrison Research, Palo Alto, CA. Melting points were taken on a Buchi 50 melting point apparatus and are not corrected. NMR spectra were recorded on a Bruker 250 or 300 MHz or General Electric QE 300, QE 500 or Omega 500 MHz NMR spectrometers. IR spectra were obtained on a Perkin Elmer 1620 spectrophotometer (single beam). Low resolution mass spectra were obtained from a Finnigan 400 spectrometer; high resolution mass spectra were obtained on a VG Analytic 7070E spectrometer. Elemental analyses were performed by Robertson Laboratories, Inc., Madison, NJ.

4.1.1. 2,3-Dimethoxy-4-hydroxy-4-(3-trimethylsilylpropyn-1-yl)cyclobut-2-en-1-one 25, $R_1=OCH_3$—representative procedure for alkynyllithium addition. *n*-Butyllithium (1.8 mL of a 1.6 M solution in hexane, 2.88 mmol) was added to a solution of 3-trimethylsilylpropyne (331 mg, 2.96 mmol) in 50 mL of dry THF at −78 °C. After 10 min, a pre-cooled solution of dimethyl squarate (350 mg, 2.46 mmol) in 25 mL of THF was added via cannula over 5 min. The mixture was stirred for 10 min and then quenched with 5% NH_4Cl (20 mL) and allowed to warm to room temperature. Ether (100 mL) was added and the aqueous layer was extracted twice with ether (2× 20 mL). The combined organic layers were washed with brine and dried over anhyd. $MgSO_4$. Evaporation of the solvent followed by flash chromatography on silica gel (hexanes/ethyl acetate, 3:1) afforded 469 mg (75%) of the title compound as a cream colored solid: mp 75–76 °C; IR ($CDCl_3$) 3580, 1785 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (s, 3H), 3.96 (s, 3H), 2.79 (br s, 1H), 1.56 (s, 2H), 0.11 (s, 9H); ^{13}C NMR (500 MHz, CDCl3) δ 181.6, 165.2, 135.2, 89.1, 78.8, 73.2, 59.8, 58.5, 7.4, −2.0; LRMS *m/e* (rel. intens.) EI 239 (4), 73 (100); CI 255 (100), 237 (19), 223 (18); HRMS CI *m/e* calcd for $C_{12}H_{18}O_4Si$: (MH^+) 255.1052, found: 255.1040.

4.1.2. 2,3-Dimethoxy-4-hydroxy-3-(trimethylsilylpropen-2-yl)cyclobut-2-en-1-one, 26, $R_1=OCH_3$, R= CH_3—representative procedure for alkenyllithium addition. A solution of 2-bromoallyltrimethylsilane (1.20 g, 6.21 mmol) in 10 mL of dry THF was introduced dropwise to a solution of *t*-butyllithium (8.0 mL of a 1.5 M solution in hexanes, 12.0 mmol) in 100 mL of THF at −78 °C. After stirring for 30 min, a solution of dimethyl squarate (0.80 g, 5.63 mmol) in 50 mL of THF at −78 °C was added via cannula over 5 min. The resulting solution was stirred for 10 min and then quenched with 5% NH_4Cl and allowed to warm to ambient temperature. Ether (100 mL) was added and the aqueous layer was separated and back-extracted with ether (2×20 mL). The combined organic layers were washed with brine and dried with anhy. $MgSO_4$. Evaporation of the solvent followed by flash column chromatography (hexanes/ethyl acetate, 3:1) afforded 1.03 g (72%) of the title compound as a light yellow oil. IR ($CDCl_3$) 3580, 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (s, 1H), 4.91 (s, 1H), 4.10 (s, 3H), 3.96 (s, 3H), 2.71 (s, 1H), 1.64 (d, J=0.6 Hz, 2H), 0.05 (s, 9H); LRMS *m/e*

(EI, rel. intens.) 256 (M^+, 25), 241 (22), 225 (32), 73 (100). Anal. Calcd for $C_{14}H_{20}O_4Si$: 56.22% C; 7.86% H, found: 55.97% C, 7.94% H.

4.1.3. 2,3-Dimethoxy-4-(3-trimethylsilyl-1-propynyl)-4-trimethylsiloxycyclobenone, 27. 1-Lithio-3-trimethylsilylpropyne was generated and added to dimethyl squarate (150 mg, 1 mmol) as described for **25**. The resulting solution was stirred for ten min at −78 °C and then quenched by addition of trimethylsilylchloride (0.18 mL, 1.4 mmol). The solution was stirred at −78 °C for an additional ten min and then concentrated in vacuo. The residue was diluted with ether and quickly filtered through a plug of fluorisil. Concentration in vacuo gave 324 mg (95%) of the title compound as a clear oil. IR ($CDCl_3$) 1780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (s, 3H), 3.94 (s, 3H), 1.56 (s, 2H), 0.22 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 181.7, 166.2, 134.5, 88.5, 79.5, 74.3, 59.6, 58.4, 7.4, 1.2, −1.9; HRMS *m/e* (CI) calcd for $C_{15}H_{27}O_4Si_2$: 327.1428, found: 327.1427.

4.1.4. 2-*n*-Butyl-4-hydroxy-3-methoxy-4-(3-trimethylsilyl-1-propynyl)cyclobutenone, 25 R_1=*n*-butyl. The representative procedure for **25** was followed using 3-*n*-butyl-4-methoxycyclobut-3-ene-1,2-dione, **24**, R_1=*n*-butyl, as the starting material. Purification by flash column chromatography (hexanes/ethyl acetate, 3:1) gave 534 mg (54%) of the product as a yellow solid: mp 42–43 °C; IR ($CDCl_3$) 3580, 2230, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (s, 3H), 3.55 (bs, 1H), 2.04 (t, J=7.0 Hz, 2H), 1.55 (s, 2H), 1.49 (pentet, J=7.1 Hz, 2H), 1.30 (sextet, J=7.1 Hz, 2H), 0.87 (t, J=7.1 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 187.9, 180.7, 129.3, 89.9, 82.9, 73.5, 59.4, 28.9, 22.4, 21.5, 13.7, 7.5, −2.0 (3C); LRMS *m/e* (EI, rel. intens.) 280 (M^+, 1), 265 (17), 73 (100). CI 281 (MH^+, 100); HRMS (CI) *m/e* calcd for $C_{15}H_{24}O_3Si$: (MH^+) 281.1573, found: 281.1553.

4.1.5. 2-*n*-Butyl-4-hydroxy-3-methoxy-4-(3-trimethylsilylpropenyl)-cyclobutenone, 26 R_1=*n*-butyl. The representative procedure for **26** was followed using 4-*n*-butyl-3-methoxycyclobutenedione **24** (R=*n*-butyl) and 3-trimethylsilylpropyne as starting materials. Flash chromatography (hexanes/ethyl acetate, 4:1) gave 550 mg (53%) as a light yellow oil. IR ($CDCl_3$) 3580, 3460, 1760; ^1H NMR ($CDCl_3$) δ 5.15 (d, J=0.5 Hz, 1H), 4.89 (s, 1H), 4.04 (s, 3H), 2.07 (m, 2H), 1.60 (s, 2H), 1.47 (pentet, J=7.4 Hz, 2H), 1.30 (sextet, J=7.4 Hz, 2H), 0.87 (t, J=7.4 Hz, 3H), 0.02 (s, 9H); ^{13}C NMR (CDCl3) δ 191.6, 182.3, 143.6, 129.0, 111.2, 94.0, 59.3, 29.3, 22.5, 21.6, 21.5, 13.6, −1.0 (3C); LRMS *m/e* (EI, rel. intens.) 282 (M^+, 0.6), 208 (1.5), 73 (100); HRMS (EI) *m/e* calcd for $C_{15}H_{26}O_3Si$: (M^+) 282.1651, found: 282.1640.

Also isolated in 10% yield (101 mg) was the regioisomer as a yellow oil. IR ($CDCl_3$) 3590, 2960, 1765; ^1H NMR ($CDCl_3$) δ 5.07 (s, 1H), 4.88 (d, J=0.9 Hz, 1H), 4.00 (s, 3H), 2.32–2.45 (m, 3H overlapping methylene and hydroxy protons), 1.64 (quintet, J=7.1 Hz, 2H), 1.60 (d, J=1.0 Hz, 2H), 1.38 (sextet, J=7.4 Hz, 2H), 0.92 (t, J=7.3 Hz, 3H), 0.04 (s, 9H); ^{13}C (CDCl3) δ 188.7, 157.5, 154.8, 144.8, 111.1, 91.5, 58.1, 28.8, 25.1, 23.0, 22.1, 13.7, −1.0 (3C); LRMS *m/e* (EI, rel. intens.) 282 (M^+, 0.05), 239 (0.5), 73 (100); HRMS (EI) *m/e* calcd for $C_{15}H_{26}O_3Si$: (M^+) 282.1651, found: 282.1641.

4.1.6. 2-Bromo-3-triphenylsilyl-1-propene. Triphenylsilyllithium was prepared by mixing triphenylsilyl chloride (4.72 g, 16 mmol) with thinly sliced lithium metal wire (0.54 g, 80 mmol) in 20 mL of dry THF for 22 h at ambient temperature. The resulting green solution was cooled to 0 °C and then added to freshly dried CuI (1.52 g, 8 mmol). The mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. A pre-cooled solution of 2,3-dibromopropene (6.6 mmol) in 5 mL of THF was added to the mixture. The resulting mixture was stirred at −78 °C for 30 min and then allowed to warm to ambient temperature. The reaction mixture was poured into a mixture of 1:1 pentane/5% NH_4Cl (60 mL) and stirred vigorously. The mixture was filtered through glass wool and the layers were separated. The aqueous layer was back-extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting tan solid was purified by flash column chromatography (silica gel, hexanes/ethyl acetate, 12:1) followed by crystallization from boiling hexanes to afford 1.98 g (79%) of the title compound as white crystals: mp 91.5–92.5 °C; IR ($CDCl_3$) 3052, 3014, 1618, 1487, 1428, 1193, 1111, 872, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.50 (m, 6H), 7.50–7.26 (m, 9H), 5.34 (d, J=1.6 Hz, 1H), 5.30 (d, J=1.8 Hz, 1H), 2.98 (d, J=0.8 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 135.9, 133.5, 129.8, 129.2, 127.8, 117.4, 30.0; HRMS *m/e* (CI) calcd for $C_{21}H_{19}Si$: 299.1256, found: 299.1230; 341 (4), 340 (15), 339 (4), 338 (10), 302 (2), 301 (7), 263 (20), 261 (20), 260 (24), 259 (100).

4.1.7. 4-Hydroxy-2,3-dimethoxy-4-(1-((triphenylsilylmethyl)ethenyl)-2-cyclobutenone, 26, R_1=OMe, R=Ph. To a cooled (−78 °C) solution of *t*-butyllithium (3.7 mmol) in 50 mL of dry THF was added a pre-cooled (−78 °C) solution of 2-bromo-3-triphenylsilylprop-1-ene (644 mg, 1.7 mmol) in 40 mL of dry THF via cannula. The resulting solution was stirred for 15 min at −78 °C. A pre-cooled solution (−78 °C) of dimethyl squarate (200 mg, 1.4 mmol) in 50 mL of dry THF was added via cannula. The reaction mixture was stirred for 30 min at −78 °C and then worked up. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 1:1) provided the title compound as a white solid (365 mg, 59%): mp 112–113 °C; IR ($CDCl_3$) 3580, 1773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 1H), 2.51 (d, J=15 Hz, 1H), 2.6 (d, J=15 Hz 1H), 3.86 (s, 3H), 3.91 (s, 3H), 4.9 (s, 1H), 5.2 (s, 1H), 7.36–7.43 (m, 9H), 7.57–7.58 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 17.7, 58.5, 60.1, 89.1, 114.9, 127.95, 129.7, 134.4, 134.5, 136.0, 141.8, 165.8, 184.3; HRMS *m/e* (EI, rel. intens.) calcd for $C_{27}H_{26}O_4Si$: 442.1600, found: 442.1633; 442 (1.4), 410 (4.4), 411 (1.3), 364 (40.6), 365 (8.8), 349 (19), 350 (4.3), 259 (100), 260 (20.7), 261 (5.1), 180 (12.9), 181 (33.5), 182 (6.5), 105 (30.8).

4.1.8. 2,3-Dimethoxy-5-((trimethylsilylmethyl)-1,4-benzoquinone, 9a. Representative procedure for the rearrangement of 4-alkenyl substituted cyclobutenones to trimethylsilylmethyl-substituted benzoquinones. *Method A*. A solution of **26** (R_1=OMe, R=CH_3), (1.01 g, 3.94 mmol), in 100 mL of *p*-xylene was heated at reflux for

15 min. After cooling to ambient temperature, Ag_2O (2.0 g, 7.94 mmol) was added and the mixture was stirred for 15 min. Filtration and evaporation of the solvent gave the crude product. Purification by flash column chromatography (hexanes/ethyl acetate, 5:1) yielded 0.90 g (89%) of the title compound as a deep red oil. IR ($CDCl_3$) 2690, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.23 (t, $J=0.8$ Hz, 1H), 4.04 (s, 3H), 3.94 (s, 3H), 1.97 (d, $J=0.8$ Hz, 2H), 0.02 (s, 9H); LRMS *m/e* (EI, rel. intens.) 254 (M^+, 12), 239 (16), 226 (33), 211 (19), 195 (10), 73 (100). Anal. Calcd for $C_{12}H_{18}O_4Si$: C, 56.67; H, 7.13, found: C, 56.44; H, 6.99.

Method B. Heating a solution of 4-alkynyl substituted cyclobutenone, **25** ($R_1=OMe$), in *p*-xylene at reflux for 15 min followed by evaporation of the solvent and purification by flash column chromatography provided the title compound directly without the need for Ag_2O oxidation. The spectral properties were identical to the product derived from **26**.

4.1.9. 2,3-Dimethoxy-5-trimethylsilyl-6-((trimethylsilyl)-methyl)-1,4-benzoquinone, 17. A solution of cyclobutenone **27** (297 mg, 0.91 mmol) and 60 mL of dry *p*-xylene was heated at reflux for 1 h. Concentration in vacuo followed by flash column chromatography on silica gel (hexanes/ethyl acetate, 10:1) provided 190 mg (65%) of the product as an orange oil. IR ($CDCl_3$) 1641, 1564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9H), 0.28 (s, 9H), 2.27 (s, 2H), 3.90 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) Δ 188.15, 184.38, 156.17, 145.24, 143.19, 138.73, 60.95, 60.87, 21.19, 1.95, −0.23; HRMS (EI, rel. intens.) *m/e* calcd for $C_{15}H_{27}O_4Si_2$; 327.1475, found: 327.1421; 326 (0.8), 311 (7.8), 298 (22), 281 (4), 268 (3), 253 (11), 147 (8), 135 (11), 133 (12), 89 (12), 73 (100), 59 (13).

4.1.10. 2,3-Dimethoxy-6-((triphenylsilyl)methyl)-1,4-benzoquinone, 9d. A solution of cyclobutenone **6** ($R_1=$ OMe, R=Ph; 25 mg, 0.05 mmol)) in 1 mL of *p*-xylene was heated at reflux for 30 min. The solution was cooled to room temperature and treated with Ag_2O (350 mg, 1.5 mmol). After 15 min, the solution was filtered. Concentration followed by flash column chromatography (hexanes/ethyl acetate, 4:1) yielded 20.3 mg (92%) of the product as a yellow solid: mp 122.5–123 °C; IR ($CDCl_3$) 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.8 (s, 2H), 3.6 (s, 3H), 3.96 (s, 3H), 6.15 (s, 1H), 7.37–7.43 (m, 9H), 7.53–7.55 (m, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 183.5, 183.3, 146.9, 144.8, 144.2, 135.8, 132.9, 129.9, 128.5, 128.0, 60.9, 60.9, 16.7; LRMS (EI, rel. intens.) *m/e* 440 (4.98), 425 (9.9), 363 (7.1), 347 (3.9), 259 (100), 260 (22.4), 213 (18.1), 181 (36.9), 180 (13.3), 155 (14); Analysis calcd for $C_{27}H_{24}O_4Si$: C, 73.61; H, 5.49, found: C, 73.53; H, 5.42.

4.1.11. 3-*n*-Butyl-2-methoxy-5-((trimethylsilyl)methyl)-1,4-benzoquinone, 9c. This quinone was prepared by thermolysis of **25** ($R_1=n$-butyl) according to method B. Purification by flash column chromatography (hexanes/ethyl acetate, 95:5) gave 390 mg (75%) of the product as a golden yellow oil. IR ($CDCl_3$) 1650, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.22 (t, $J=0.9$ Hz, 1H), 4.01 (s, 1H), 2.43 (t, $J=$ 7.1 Hz, 2H), 1.98 (d, $J=0.9$ Hz, 2H), 1.35–1.32 (m, 4H), 0.91 (t, $J=7.0$ Hz), 0.01 (s, 9H); LRMS *m/e* (EI, rel. intens.) 280 (9), 265 (22), 209 (25), 73 (100); Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63, found: C, 64.24; H, 8.74.

4.1.12. 3-*n*-Butyl-2-methoxy-6-((trimethylsilyl)methyl)-1,4-benzoquinone, 9b. This quinone was prepared by thermolysis of **26** ($R_1=n$-butyl, $R=CH_3$) according to method A. Purification by flash column chromatography (hexanes/ethyl acetate, 95:5) provided 366 mg (92%) of the title compound as a golden yellow oil. IR ($CDCl_3$) 2980, 1670, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.30 (t, $J=1.0$ Hz, 2H), 3.92 (s, 3H), 2.40 (t, $J=7.1$ Hz, 2H), 1.95 (d, $J=$ 1.0 Hz, 2H), 1.34–1.38 (m, 4H), 0.90 (t, $J=7.1$ Hz, 3H), 0.02 (s, 9H); LRMS *m/e* (CI, rel. intens.) 281 (MH^+, 100), 267 (4). Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63, found: C, 64.24; H, 8.96.

4.1.13. 5,6-Dimethoxy-2-thiophenyl-3-((trimethylsilyl)-methyl)-1,4-benzoquinone, 19. A mixture of quinone **9a** (100 mg, 0.39 mmol), thiophenol (83.0 mg, 0.79 mmol) in 5 mL of THF was stirred at room temperature for 16 h. Evaporation of the solvent and flash column chromatography (hexanes/ethyl acetate, 3:1) gave the intermediate hydroquinone, which was oxidized with Ag_2O (218 mg, 0.867 mmol) in 10 mL of benzene. Filtration of the silver salts, evaporation of the solvent and purification by flash column chromatography (hexanes/ethyl acetate, 3:1) gave 75.0 mg (53%) of the product as a red solid: mp 61–62 °C; IR ($CDCl_3$) 1665, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–7.20 (m, 5H), 3.99 (s, 3H), 3.94 (s, 3H), 2.52 (s, 2H), 0.08 (s, 9H); LRMS *m/e* (CI, rel. intens.) 363 (MH^+, 100); Anal. Calcd for $C_{18}H_{20}O_4SSi$: C, 59.64; H, 6.12, found: C, 59.77; H, 5.94.

4.1.14. 5,6-Dimethoxy-2-(2-hydroxyethyl-1-thio)-3-trimethylsilylmethyl-1,4-benzoquinone, 21. A mixture of **9a** (100 mg, 0.39 mmol), mercaptoethanol (34.0 mg, 0.44 mmol) and 5 mL of absolute ethanol was stirred at room temperature for 15 min. Evaporation of the solvent followed by flash column chromatography (hexanes/ethyl acetate, 3:1) gave 110 mg of the intermediate hydroquinone, which was oxidized with Ag_2O (175 mg) in 10 mL of benzene at ambient temperature for 15 min. Purification of the quinone by flash column chromatography (hexanes/ethyl acetate, 3:2) furnished 92 mg (70%) of the product as a deep red oil in >96% purity (^1H NMR). IR ($CDCl_3$) 3500, 2960, 1670–1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (s, 3H), 3.96 (s, 3H), 3.74 (q, $J=5.9$ Hz, 2H), 3.13 (t, $J=6.0$ Hz, 2H), 2.45 (s, 2H), 2.28 (t, $J=6.1$ Hz, 1H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 181.7, 180.2, 150.3, 145.2, 144.0, 135.3, 61.6, 61.2, 61.0, 37.3, 22.3, −0.6 (3C); HRMS (EI, rel. intens.) *m/e* calcd for $C_{14}H_{22}O_5SSi$: 330.0957, found: 330.0960; 330 (1), 149 (40), 73 (100); LRMS (CI, rel. intens.) 331 (MH^+, 100), 287 (22).

4.1.15. Heterocyclic quinone 23 and symmetrical dimer 22. Quinone **21** (80 mg, 0.24 mmol) was heated at reflux in 200 mL of acetonitrile/water (197:3) for 3 h. The solvent was removed and the residue oxidized with Ag_2O (183 mg, 0.73 mmol) in 10 mL of benzene/acetonitrile (9:1) at ambient temperature for 30 min. After filtration and removal of the solvent, purification by flash chromatography (chloroform/methanol, 97:3) gave 24.7 mg (40%) of **23** as a red solid: mp 108–109 °C; IR ($CDCl_3$) 2950, 2860,

1650 (br), 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.70 (s, 2H), 4.03 (t, $J=5.5$ Hz, 2H), 4.02 (s, 3H), 3.94 (s, 3H), 3.18 (t, $J=5.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.1, 181.0, 148.1, 145.2, 143.6, 135.8, 71.2, 64.2, 61.4, 61.2, 33.5; MS (EI, rel. intens.) *m/e* 256 (M^+, 18), 213 (30), 185 (27), 129 (37), 85 (66), 69 (100), 57 (87); Anal. Calcd for $C_{11}H_{12}O_5S$: C, 51.55; H, 4.72, found: C, 51.41; H, 4.83. Further elution gave dimer **22** which was re-purified by flash column chromatography (chloroform/methanol, 20:1) to give 18.8 mg (30%) of **22** as an orange solid: mp 114–116 °C; IR ($CDCl_3$) 3540, 1660, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (s, 6H), 3.98 (s, 6H), 3.78 (m, 4H), 3.22 (t, $J=5.4$ Hz, 4H), 2.96 (s, 4H), 2.60 (br s, 2H); HRMS (EI, rel. intens.) *m/e* calcd for $C_{22}H_{26}O_{10}S_2$: 514.0967, found: 514.0947; 514 (M^+, 5), 257 (7), 227 (18), 215 (21), 60 (100).

4.1.16. Reaction of quinone 9a with *n*-butylvinyl ether. Chromanol, 13. A mixture of quinone **9a** (100 mg, 0.39 mmol), *n*-butylvinyl ether (800 mg, 8.0 mmol) and 10 mL of acetonitrile/water (9:1) was heated at reflux for 2.5 h. The mixture was concentrated in vacuo and 25 mL of ether was added. The layers were separated and the aqueous layer extracted twice with ether (2×10 mL). The combined organic layers were washed twice with brine (2×5 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification by flash column chromatography (hexanes/ethyl acetate, 3:1) gave 80 mg (72%) of **13** as a yellow oil. IR ($CDCl_3$) 3550, 2985, 1620–1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.46 (s, 1H), 5.26 (t, $J=2.7$ Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.84 (dt, $J=9.5$, 6.7 Hz, 1H), 3.59 (dt, $J=9.6$, 6.6 Hz, 1H), 2.91–2.84 (m, 1H), 2.54–2.49 (m, 1H), 2.02–1.97 (m, 1H); 1.92–1.85 (m, 1H), 1.54 (quintet, $J=7.0$ Hz, 2H), 1.30 (sextet, $J=7.3$ Hz, 3H), 0.87 (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 142.2, 141.2, 138.7, 138.5, 118.6, 108.9, 96.7, 68.0, 61.2, 60.8, 31.6, 26.4, 20.3, 19.2, 13.7; LRMS (EI, rel. intens.) *m/e* 282 (M^+, 21), 182 (100); Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85, found: C, 63.85; H, 7.80.

4.1.17. 5-Bromo-2,3-dimethoxy-6-((trimethylsilyl)-methyl)-1,4-benzoquinone, 14. Hydrogen bromide was bubbled through a methylene chloride solution (100 mL) of quinone **17**, (548 mg, 1.7 mmol) for five min. Nitrogen was then bubbled through the solution to purge any residual HBr. The solution was poured into 10% $NaHCO_3$, the layers were separated and the aqueous layer extracted with methylene chloride (3×15 mL). The solvent was evaporated in vacuo and the residue re-dissolved in benzene and treated with Ag_2O (1.2 g, 5.1 mmol) and K_2CO_3 (700 mg, 5.1 mmol) and stirred for 1.5 h. The mixture was filtered and concentrated in vacuo. The product was purified by flash column chromatography (florisil, hexanes/ethyl acetate, 10:1) to give 285 mg (50%) of the product as an orange solid: mp 54–55 °C; IR ($CDCl_3$) 1660, 1636, 1585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 3H), 3.97 (s, 3H), 2.31 (s, 2H), 0.08 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 180.9, 176.5, 148.7, 144.4, 144.3, 128.4, 61.5, 61.2, 23.7, −0.4; HRMS (EI, rel. intens.) *m/e* calcd for $C_{12}H_{18}O_4SiBr$: 333.0158, found: 333.0143; 334 (0.6), 332 (0.5), 317 (0.6), 319 (0.6), 304 (1.4), 306 (1.1), 253 (2.5), 223 (1.2), 195 (0.7), 139 (3), 137 (3), 73 (100).

4.2. General procedure for the reaction of ((trimethylsilyl)methyl)-1,4-benzoquinones with alcohols

A solution of the benzoquinone in 10 mL of the alcohol was heated at reflux for the appropriate time. The alcohol was removed in vacuo and the intermediate hydroquinone was re-dissolved in benzene and oxidized by the addition of 20 equiv of Ag_2O at room temperature for 15 min. Filtration of the solution and evaporation of the solvent gave the crude product which was purified by flash column chromatography.

4.2.1. 2,3-Dimethoxy-5-(ethoxymethyl)-1,4-benzoquinone, 10a. Quinone **9a** was heated at reflux in absolute ethanol for 45 min. After oxidation and purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 3:1), the title compound was isolated in 82% yield as an orange oil which solidified upon cooling: mp 38–39 °C; IR ($CDCl_3$) 1660, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63 (t, $J=2.2$ Hz, 1H), 4.32 (d, $J=2.2$ Hz, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.58 (q, $J=7.0$ Hz, 2H), 1.23 (t, $J=7.0$ Hz, 3H); LRMS (EI, rel. intens.) *m/e* 226 (95), 197 (69), 180 (100), 164 (49), 150 (41), 67 (60); Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24, found: C, 58.49; H, 6.32.

Further elution with hexanes/ethyl acetate, 2:1 gave 5% of the symmetrical dimer **11a** as an orange solid: mp 133–134 °C; IR ($CDCl_3$) 1660, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.39 (t, $J=0.8$ Hz, 1H), 4.06 (s, 3H), 4.00 (s, 3H), 2.63 (d, $J=0.8$ Hz, 2H); LRMS (EI, rel. intens.) *m/e* 362 (M^+, 8), 347 (13), 181 (14), 67 (100); Anal. Calcd for $C_{18}H_{18}O_8$: C, 59.67; H, 5.01: found: C, 59.38; H, 4.89.

4.2.2. 3-*n*-Butyl-6-(ethoxymethyl)-2-methoxy-1,4-benzoquinone, 10b. Quinone **9a** was heated in refluxing ethanol for 6 h according to the general procedure. Oxidation and purification by column chromatography (hexanes/ethyl acetate, 9:1) furnished 63% of the product as a yellow oil along with 11% of recovered starting material. IR ($CDCl_3$) 1660, 1655, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (t, $J=2.1$ Hz, 1H), 4.32 (d, $J=2.1$ Hz, 2H), 3.98 (s, 3H), 3.59 (q, $J=7.0$ Hz, 2H), 2.42 (t, $J=7.0$ Hz, 2H), 1.28–1.41 (m, 4H), 1.25 (t, $J=7.0$ Hz, 3H), 0.91 (t, $J=7.1$ Hz, 3H); MS (CI, rel. intens.) *m/e* 253 (MH^+, 100), 239 (16), 209 (13); Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99, found: C, 66.58; H, 8.30.

Further elution using hexanes/ethyl acetate, 2:1 gave 5% of the symmetrical dimer **11b** as a yellow oil. IR ($CDCl_3$) 1670, 1655, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.44 (s, 2H), 3.98 (s, 2H), 2.63 (s, 4H), 2.40 (t, $J=7.2$ Hz, 4H), 1.32–1.37 (m, 8H), 0.90 (t, $J=7.0$ Hz, 6H); HRMS (EI, rel. intens.) *m/e* calcd for $C_{24}H_{30}O_6$: 414.2042, found: 414.2044; 205 (26), 177 (14), 91 (31), 55 (100).

4.2.3. 3-*n*-Butyl-5-(ethoxymethyl)-2-methoxy-1,4-benzoquinone, 10c. According to the general procedure, **9c** was heated at reflux in absolute ethanol for 45 min. Oxidation and purification by flash column chromatography (hexanes/ethyl acetate, 9:1) furnished 67% of the title compound as a yellow oil that solidified upon cooling: mp 39–40 °C; IR ($CDCl_3$) 1660, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (t, $J=$

2.1 Hz, 1H), 4.33 (d, J=2.1 Hz, 2H), 4.02 (s, 3H), 3.59 (q, J=7.0 Hz, 2H), 2.41 (br. triplet, J=7.1 Hz, 2H), 1.38–1.32 (m, 4H), 1.25 (t, J=7.0 Hz, 3H), 0.91 (t, J=7.0 Hz, 3H); LRMS (CI, rel. intens.) *m/e* 253 (MH^+, 100), 209 (53), 137 (36); Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99, found: C, 66.51; H, 7.94.

Further elution with hexanes/ethyl acetate, 2:1) gave 7% of the symmetrical dimer **11c** as a yellow oil. IR ($CDCl_3$) 1670, 1650, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.36 (s, 2H), 4.01 (s, 6H), 2.62 (s, 4H), 2.43 (t, J=7.0 Hz, 4H), 1.30–1.43 (m, 8H), 0.92 (t, J=7.0 Hz, 6H); HRMS (EI, rel. intens.) *m/e* calcd for $C_{24}H_{30}O_6$ 414.2042, found: 414.2066; 209 (38), 207 (59), 165 (41), 55 (100).

4.2.4. 2,3-Dimethoxy-5-(*iso*-propoxymethyl)-1,4-benzoquinone, 10d. Quinone **9a** was heated in refluxing *iso* propanol for 10 h according to the general procedure. Oxidation and purification by column chromatography (hexanes/ethyl acetate, 3:1) gave 65% of the product as a red oil. IR ($CDCl_3$) 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.66 (t, J=2.3 Hz, 1H), 4.32 (d, J=2.3 Hz, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.67 (heptet, J=6.1 Hz, 1H), 1.19 (d, J=6.1 Hz, 6H); LRMS (EI, rel. intens.) *m/e* 240 (M^+, 6), 198 (38), 180 (23), 155 (25), 153 (39), 67 (100); Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71: found: C, 59.63; H, 6.83.

4.2.5. 5-(*tert*-Butoxymethyl)-2,3-dimethoxy-1,4-benzoquinone, 10e. Quinone **9a** was heated in *tert*-butanol at reflux for 44 h according to the general procedure. Oxidation and purification by flash column chromatography (hexanes/ethyl acetate, 3:1) gave 45% of the title compound as a red oil. IR ($CDCl_3$) 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.66 (t, J=2.3 Hz, 1H), 4.27 (d, J=2.3 Hz, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 1.23 (s, 9H); LRMS (EI, rel. intens.) *m/e* 254 (M^+, 1), 198 (21), 153 (24), 57 (100); Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14: found: C, 61.81; H, 7.39.

4.2.6. Reaction of benzoquinone 9a with water. 2,3-Dimethoxy-5-hydroxymethyl-1,4-benzoquinone, 10f. Quinone **9a** was heated in 10 mL of acetonitrile/water (9:1) at reflux for 1.5 h. Following oxidation with Ag_2O according to the general procedure and flash column chromatography (chloroform/methanol, 97:3) 18% of the title compound was isolated as an orange solid: mp 72–73 °C; IR ($CDCl_3$) 3610, 3520, 2960, 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.61 (s, 1H), 4.53 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 2.10 (br s, 1H); LRMS (EI, rel. intens.) *m/e* 198 (M^+, 12), 180 (11), 150 (17), 84 (47), 67 (67), 55 (100); Anal. Calcd for $C_9H_9O_5$: C, 54.55; H, 5.09, found: C, 54.28; H, 5.00. In addition to **10f**, 67% of the symmetrical dimer **11 a** was isolated.

Reaction of quinone **9a** in 95:5 acetonitrile/water for 8 h gave 22% of xanthen **12** after flash column chromatography (hexanes/ethyl acetate, 5:2) as a yellow solid: mp 144–145 °C; ^1H NMR ($CDCl_3$) δ 6.31 (s, 1H), 5.39 (s, 1H), 3.98 (s, 6H), 3.96 (s, 3H), 3.93 (s, 3H), 3.22 (dd, J=9.8, 6.6 Hz, 1H), 2.90 (dd, J=16.8, 6.7 Hz, 1H), 2.85 (dd, J=16.7, 10.0 Hz, 1H), 1.41 (d, J=14.9 Hz, 1H), 1.33 (d, J=14.8 Hz, 1H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 193.9, 193.0, 147.2, 146.4, 142.9, 141.2, 139.4, 113.5, 108.1, 81.9, 61.3, 60.9, 60.7, 60.5, 51.8, 27.9, 26.9, 0.0 (3C); IR ($CDCl_3$) 3545, 1695, 1600 cm^{-1}; MS (CI, rel. intens.) *m/e* 437 (MH^+, 100), 183 (35); Anal. Calcd for $C_{21}H_{28}O_8Si$: C, 57.78; H, 6.47, found: C, 57.40; H, 6.15.

Further with chloroform/methanol (1:1) followed by oxidation of the resulting product and purification by flash chromatography (chloroform/methanol, 97:3) gave 46% of the symmetrical dimer **11a** and 12% of the quinone **10f**.

4.2.7. 5-(Acetoxymethyl)-2,3-dimethoxy-1,4-benzoquinone, 10g. Sodium acetate (5 equiv) and quinone **9a** were dissolved in 10 mL of acetic acid and heated at reflux for 30 min. The acetic acid was evaporated with the aid of toluene and the residue was filtered through a short pad of silica gel, eluted with ethyl acetate. The crude hydroquinone was oxidized with Ag_2O and purified by flash column chromatography (hexanes/ethyl acetate, 3:1) to provide 79% of **10g** as an orange solid: mp 51–52 °C; IR ($CDCl_3$) 1755, 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (t, J=1.9 Hz, 1H), 4.97 (d, J=2.0 Hz, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 2.14 (s, 3H); LRMS (CI, rel. intens.) *m/e* 241 (MH^+, 100), 183 (63); Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04, found: C, 55.10; H, 4.96. In pure acetic acid the reaction gave 54% of **10g** after 4 h at reflux.

4.2.8. 2,3-Dimethoxy-6-ethoxymethyl-5-trimethylsilyl-1,4-benzoquinone, 18. The quinone **17** (67 mg, 0.21 mmol) was dissolved in 8 mL of absolute ethanol and then heated to reflux for 2 h according to the general procedure. Oxidation of the mixture followed by column chromatography (silica gel, hexanes/ethyl acetate, 4:1) gave 17 mg (27%) of the title compound as an orange oil. IR ($CDCl_3$) 1650, 1587 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (s, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.52 (q, J=7.1 Hz, 2H), 1.19 (t, J=7.1 Hz, 3H), 0.30 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 188.6, 183.3, 149.3, 148.6, 145.4, 143.8, 66.5, 63.3, 61.0, 60.9, 15.1, 0.8; HRMS CI (rel. intens.) *m/e* calcd for $C_{14}H_{23}O_5Si$: 299.1315, found: 299.1311, 300 (20), 299 (100), 284 (15), 283 (83), 255 (40), 183 (8).

4.2.9. Bis(5-bromo-2,3-dimethoxy-6-methylene-1,4-benzoquinone), 16 and 2-bromo-3-ethoxymethyl-5,6-dimethoxy-1,4-benzoquinone, 15. According to the general procedure, a solution of quinone **14** (53 mg, 0.16 mmol) in 10 mL of absolute ethanol was heated to reflux for 20 min. Oxidation with Ag_2O followed by flash column chromatography (silica gel, hexanes/ethyl acetate, 3:1) gave 4 mg (10%) of the symmetrical dimer, **16**, as an orange solid along with 27 mg (55%) of the ethanol addition product **15** as an orange oil.

Dimer **16**: mp 172–175 °C (decomp.); IR ($CDCl_3$) 1664, 1637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 6H), 4.00 (s, 6H), 2.97 (s, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 180.7, 176.4, 145.1, 144.2, 134.5, 61.6, 61.4, 28.7; HRMS (CI, rel. intens.) *m/e* calcd for $C_{18}H_{16}O_8{}^{81}Br^{79}Br$: 519.9191, found: 519.9224; 523 (47), 521 (62), 519 (26), 446 (14), 445 (71), 444 (25), 442 (21), 441 (40), 365 (53), 364 (23) 363 (100), 361 (21), 263 (55), 261 (54), 183 (44), 175 (47), 173 (52).

Quinone **15**. IR ($CDCl_3$) 1667, 1638, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.49 (s, 2H), 4.05 (s, 3H), 3.98 (s, 3H), 3.59 (q, $J=7.1$ Hz, 2H), 1.21 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 180.3, 176.8, 145.3, 144.1, 141.3, 137.4, 67.2, 65.6, 61.5, 61.3, 15.1; HRMS (EI, rel. intens.) *m/e* calcd for $C_{11}H_{13}O_5Br$: 303.9947, found: 303.9968; 306 (4), 304 (4), 288 (3), 286 (3), 277 (13), 275 (14), 260 (28), 258 (22), 247 (10), 245 (9), 233 (13), 219 (6), 217 (7), 197 (10), 179 (6), 119 (32), 117 (34), 66 (80), 53 (100).

4.2.10. ((2-Anthracenethio)ethyl)-4-hydroxy-3-methoxy-4-((3-trimethylsilyl)-1-propynyl)-2-cyclobuten-1-one, 30. To a cooled (−78 °C) solution of propargyltrimethylsilane (0.15 mL, 0.9 mmol) in 10 mL of dry THF was added *n*-BuLi (0.83 mmol) via syringe. The resulting solution was stirred for 5 min at −78 °C and then added via cannula to a cold solution of cyclobutenedione[15] **29** (200 mg, 0.58 mmol) in 40 mL of dry THF. Aqueous work-up after five min gave the crude product as a yellow oil. Purification by radial chromatography (silica gel, hexanes/ethyl acetate, 8:2) afforded 157 mg (63%) of the title product as an orange oil. IR (neat) 3308, 1758, 1622 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, $J=8.9$ Hz, 2H), 8.44 (s, 1H), 7.98 (d, $J=8.4$ Hz, 2H), 7.60–7.57 (m, 2H), 7.50–7.47 (m, 2H), 4.4 (br s, 1H), 4.02 (s, 3H), 3.09 (m, 2H), 2.18 (m, 2H), 1.58 (s, 2H), 0.08 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 187.9, 181.6, 134.6, 131.6, 128.9, 128.8, 128.2, 126.9, 126.6, 126.0, 125.2, 89.7, 82.7, 73.1, 59.3, 33.2, 22.9, 7.4, −2.1; HRMS (EI, rel. intens.) *m/e* calcd for $C_{27}H_{28}O_3SSi$: 460.1528, found: 460.1546; 462 (12), 461 (10), 460 (54), 325 (13), 252 (31), 251 (100), 210 (12), 179 (19), 178 (19), 165 (17), 161 (16), 73 (57).

4.2.11. 2-Methoxy-3-(2-anthracenethio)ethyl)-5-((trimethylsilyl)methyl)-1,4-benzoquinone, 31. A solution of **30** (129 mg, 0.28 mmol) in 10 mL of acetonitrile was heated to reflux for 1 h. The solution was cooled to room temperature and the solvent was removed in vacuo. Purification by radial chromatography (silica gel, hexanes/ethyl acetate, 10:1) yielded 82 mg (64%) of the title compound as a bright red oil. IR (neat) 1644, 1598, 1516 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, $J=8.8$ Hz, 2H), 8.46 (s, 1H), 8.00 (d, $J=8.5$ Hz, 2H), 7.6–7.46 (m, 4H), 6.12 (s, 1H), 3.66 (s, 3H), 2.96 (m, 2H), 2.64 (m, 2H), 1.89 (s, 2H), −0.04 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 186.9, 183.1, 155.4, 149.6, 134.4, 131.7, 129.2, 128.92, 128.89, 128.79, 127.6, 126.9, 126.5, 125.2, 60.6, 35.2, 24.0, 21.1, −1.6; HRMS (CI, rel. intens.) *m/e* calcd for $C_{27}H_{31}O_3SiS$: 463.1763, found: 463.1695; 464 (15), 163 (100), 461 (28), 255 (15), 253 (35), 211 (39), 179 (79), 112 (21), 97 (25), 95 (19), 91 (28), 85 (50), 83 (34), 81 (47).

4.3. General procedure for the measurement of reaction rates of (trialkylsilyl)methyl)-1-4-benzoquinones in EtOD-d_6

The quinone (10. mg) was dissolved in 0.50 mL of EtOD-d_6 in an NMR tube. To this solution was added 5 μL of dry *p*-xylene to serve as an internal standard. Proton NMR spectra of the solution were taken every 5–7 min on a 300 MHz instrument at a constant temperature of 70 °C. The integral of the reactant (cm) was divided by the integral of the methyl peak of *p*-xylene (cm) to standardize the measurements. The relative concentration of the reactant was taken to be the fraction of the initial standardized measurement (time 0=1.00). The natural log of the relative concentration was plotted against time. The k_{obs} was found from the slope of the line and the half life for the reaction was found by dividing the natural log of 2 by k_{obs}. An alternate procedure was required for the measurement of the reaction rate of the triphenylsilyl-substituted quinone **9d** due to the low solubility in ethanol. In this case, a solution of 40 mg of quinone **9d** was dissolved in 50 mL of absolute ethanol and heated to 70 °C in a jacketed flask equipped with a circulating bath. 20 μL of toluene was added to the solution to act as an internal standard. Samples of the solution were taken approximately every 3 h and diluted with acetonitrile for analysis by HPLC. A Hewlett–Packard HP 1050 equipped with a YMC ODS-AQ column was used for the analysis. The mobile phase consisted of acetonitrile/water containing 0.1% phosphoric acid. As with the ^1H NMR experiments, the peak area of the starting material was divided by the peak area of the toluene peak to standardize the measurement. The relative concentration of quinone **9d** was calculated in the same manner as the other quinones studied by NMR.

4.4. Procedure for the study of quinone 31 with supercoiled DNA

Ten microliters of a solution of 2 mg of quinone **31** in 1 μL of $CHCl_3$ was put into a microfuge tube. The solution was then concentrated to dryness in vacuo. To the residue was added 1.1 mL of ΦX174 supercoiled DNA and 18.9 μL of TE buffer (10 mM tris·HCl, 1mM EDTA, pH 7.2). The mixture was incubated at 51 °C for 21 h. The samples which contained ethidium bromide were composed of 10 μL of an ethidium bromide solution (1.4 μL of ethidium bromide in 28.6 μL of TE buffer), 1.1 μL of DNA and 8.9 μL of TE buffer. After the incubation, the mixtures were cooled to 0 °C and 2 μL of a loading buffer (0.25% bromophenol blue, 40% (w/v) sucrose in water) was added. A 7 μL portion of this mixture was loaded onto a 1% agarose gel and developed for 1 h at 101 V.

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References and notes

1. Moore, H. W. *Science* **1977**, *197*, 527.
2. (a) Tomasz, M.; Lipman, R. *Biochemistry* **1981**, *20*, 5056. (b) Tomasz, M. *Chem. Biol.* **1995**, *2*, 575.
3. (a) Gewirtz, D. A. *Biochem. Pharmacol.* **1999**, *57*, 727. (b) Taatjes, D. J.; Gaudiano, G.; Resing, K.; Koch, T. *J. Med. Chem.* **1997**, *40*, 1276. (c) Taatjes, D. J.; Gaudiano, G.; Resing, K.; Koch, T. *J. Med. Chem.* **1996**, *39*, 4135.
4. For reviews on the chemistry of quinone methides see: (a) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367. (b) Yasuda, M. *Kokagaku* **2000**, *31*, 30. (c) Wan, P.; Barker,

B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465. (d) Thompson, D. C.; Thompson, J. A.; Sugumaran, M.; Moldeus, P. *Chem.-Biol. Interact.* **1993**, *86*, 129. (e) Thompson, D.; Moldeus, P. *Adv. Exp. Med. Biol.* **1991**, 283. (f) *Biol. React. Intermed.*, 589 (g) Wagner, H. U.; Gompper, R. *Chem. Quinonoid Compd.* **1974**, 1145 [Part 2]. (h) Schleigh, W. R. *Org. Chem. Bull.* **1971**, *43*, 1.

5. (a) Giraud, L.; Giraud, A. *Synthesis* **1998**, *8*, 1153. (b) Jones, R. M.; Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2002**, *67*, 6911. (c) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502. (d) Talley, J. J. *J. Org. Chem.* **1985**, *50*, 1695.
6. (a) Rokita, S. E.; Yang, J.; Pande, P.; Greenberg, W. A. *J. Org. Chem.* **1997**, *62*, 3010. (b) Rokita, S. E.; Zeng, Q. *J. Org. Chem.* **1996**, *61*, 9080. (c) Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671. (d) Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435.
7. Angle, S. R.; Yang, W. *J. Am. Chem. Soc.* **1990**, *112*, 4524.
8. (a) Taing, M.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 329. (b) Ezcurra, J. E.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*, 6177.
9. Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372.
10. (a) Gero, A. *J. Org. Chem.* **1960**, *1954*, 19. (b) Matthews, W. S.; Bores, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006. (c) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327.
11. Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502.
12. Cook, C. D.; Butler, L. C. *J. Org. Chem.* **1969**, *34*, 227.
13. Moore, H. W.; Yerxa, B. R. In *Advanced Strain in Organic Chemistry*; 1995; Vol. 4, 81pp.
14. Xu, S. L.; Yerxa, B. R.; Sullivan, R. W.; Moore, H. W. *Tetrahedron Lett.* **1991**, *32*, 1129.

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Synthesis of external β-turn templates by reaction of protected dehydroamino acids with cyclic enaminoesters☆

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Abstract—Two external β-turn templates have been synthesised and one of them has been derivatised as a GLDV-tetrapeptide. In the course of the synthesis an interesting dichotomy was observed in the condensation of exocyclic enamines such as **4** and **19** with protected dehydroamino acids using phosphorus trichloride. When dehydroamido acids were condensed with the enamines **4** and **19** then 6/6 and 6/5 fused bicyclic compounds such as **5** and **20**, respectively, were obtained, whereas, when dehydroamino acid urethanes were used, the 5/6 and 5/5 fused products **7** and **23** were obtained. The bicyclic template **20** was converted to the GLDV-tetrapeptide derivative **31** but the sensitivity to base of the acyl–enamine system of the template reduced the yield in the synthesis of the external turn **35**.
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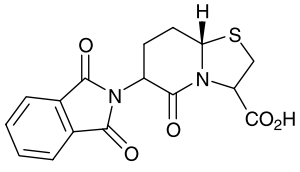
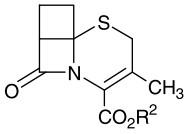
1. Introduction

Molecular recognition processes involving interaction between (i) proteins and nucleic acids; (ii) proteins and proteins; and (iii) proteins and small molecules are important in many biological regulatory mechanisms. Reverse turns connect elements of protein secondary structure such as α-helices and β-sheets and, since they usually occur on the surface of the protein, these turns are often important in molecular recognition processes,[2,3] such as those involved in immunological recognition, and in protein phosphorylation and glycosylation.

Native proteins are large, have poor transport properties and are prone to proteolysis and so their therapeutic use is limited. Small synthetic molecules which mimic the turns responsible for molecular recognition in these proteins may have the therapeutic effect of the protein they mimic but have none of the transport or other associated problems. Thus these compounds have become interesting as potential drugs and indeed incorporation of some dipeptide mimetics into peptide sequences has given compounds with highly constrained geometries and useful biological activity. The external turn mimetic BTD, **1**, prepared by Nagai[4–6] was an early example of such a compound and it was used successfully to replace the D-Phe-Pro dipeptide sequence in gramicidin S;[5] to prepare biologically active mimetics of enkephalin and luteinising hormone releasing factor (LRF);[6] and to replace residues 19 and 20 or 33 and 34 of hα $CGRP_{8-37}$, thus modelling the bioactive structure of the natural vasodilator peptide.[7]



1



2

During our work on the synthesis of the bridged β-lactam **2**,[8] we developed[9] a facile one-step synthesis of a series of bicyclic compounds **5** by the method summarised in Scheme 1. The products of this synthesis were all esters at C-4 and some, **5a**, **5b**, **5c** and **5d**, were substituted at C-7 with protected amino groups. It was evident, therefore, that suitably protected derivatives of these compounds might act as external β-turn mimetics, since selective deprotection might allow us to build an appropriate cyclic peptide on this framework. The fact that the compounds **5a–d** were not homochiral was evidently a drawback but we hoped that this problem might be solved by separation of the diastereoisomers produced as the turn was built up by reaction of the mimetic with suitably protected L-amino acids.

☆ See Ref. 1.

Keywords: GLDV-tetrapeptide; β-Turn templates; Annelation.
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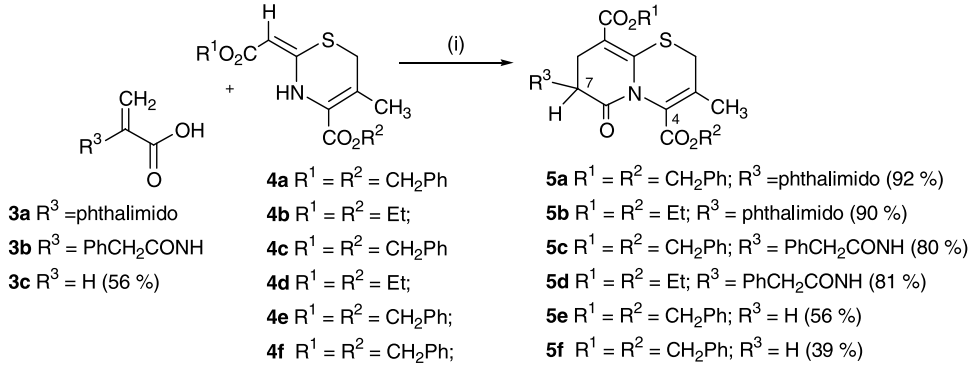
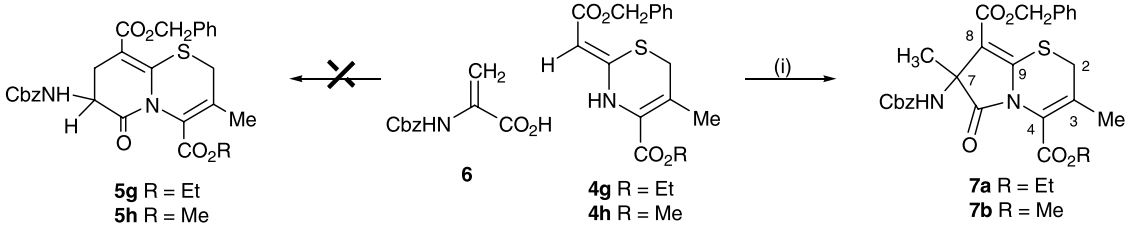


Scheme 1. Reagents and conditions—see Ref. 9.



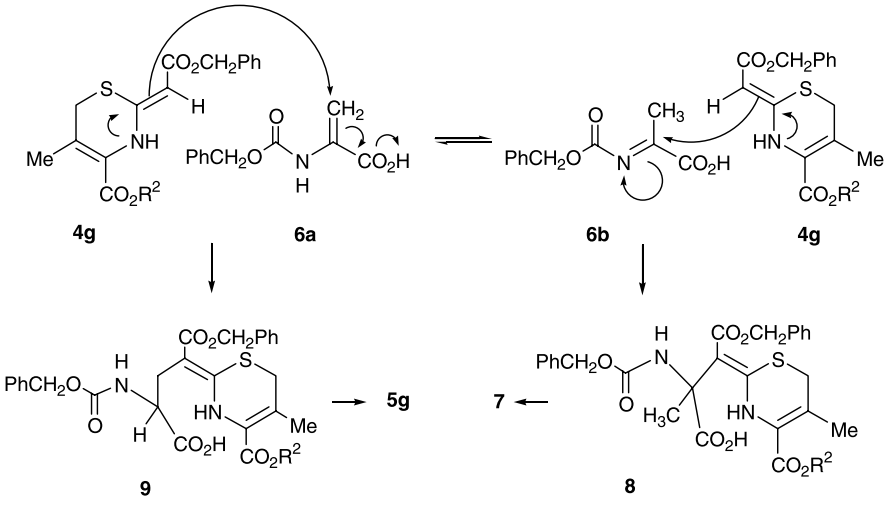
Scheme 2. Reagents and conditions: (i) PCl_3/dioxan/benzene/reflux (**7a** 57%, **7b** 53%).

2. Results and discussion

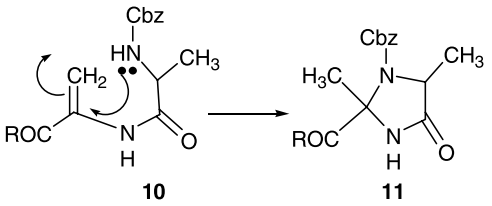
Our first targets were the benzyloxycarbonyl derivatives, **5g** and **5h**, and so we reacted 2-benzyloxycarbonylamino-acrylic acid **6**[10] with the esters **4g** and **4h**, respectively, in the presence of PCl_3 as shown in Scheme 2. The products, obtained in ca. 70% yields, were not the reduced pyridothiazines, **5g** or **5h**, expected by analogy with our previous work,[9] since the characteristic signals for H-7 and H-8, seen in the analogous compounds **5a**, **5b**, **5c** and **5d**, were absent in the ^{1}H NMR spectra. An additional methyl singlet was observed in the ^{1}H NMR spectra of both compounds, suggesting that the products were in fact the pyrrolinothiazines **7a** and **7b**, an assignment which was confirmed by single crystal X-ray structure analysis of the methyl ester **7b**.[1]

Our well-proven synthesis of pyridothiazines[9] had thus proceeded in an anomalous manner when the dehydroamino acid used was protected as a urethane. The structure of the product suggested that the reaction had proceeded by nucleophilic attack of the enamine **4** on the imine tautomer **6b** rather than by nucleophilic attack at C-3 of the tautomer **6a**, as shown in Scheme 3.

The ^{1}H NMR spectrum of the urethane **6** suggested that some of the imine tautomer **6b** might be present in $(C^2H_3)_2SO$ with time, as a singlet appeared at 1.89 ppm in the ^{1}H NMR spectrum on standing in this solvent. It is interesting to note that intramolecular attack by a nitrogen nucleophile has been observed to occur at the α-carbon atom of the dehydrodipeptide, **10**, giving the product **11**, as shown in Scheme 4.[11]

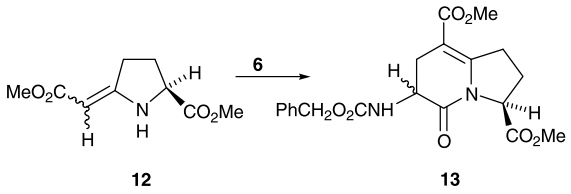


Scheme 3.



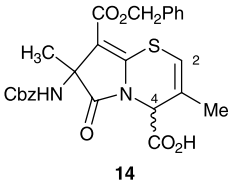
Scheme 4. Reagents and conditions—see Ref. 11.

Further, it has been shown that reaction of acetylamino-acrylic ester with HBr first gives the 2-bromo compound as the kinetic product and that this then rearranges to the 3-bromo compound, the product of thermodynamic control.[12] The nitrogen lone pair is certainly more available in the urethane derivative **6a**, allowing tautomerism to **6b**, than it is in the compounds **3a** and **3b** which form six membered ring products by Michael attack on **6a**. However, when Millet et al.[13] reacted the urethane **6** with the vinylogous urethane **12** using 1-ethyl-3-(3′-*N*,*N*-dimethylaminopropyl)-carbodiimide and HOBt, Michael addition occurred to give the 6/5 system **13** as shown in Scheme 5.



Scheme 5. Reagents and conditions—see Ref. 13.

Since the pyrrolinothiazines **7** might themselves be useful β-turn mimetics, attempts were made to remove the benzyloxycarbonyl group from **7a** and **7b** under a variety of conditions, but to no avail. When the methyl ester was treated with aqueous KOH in ethanol a crude product was obtained which had two sharp singlets at 6.1 and 6.2 ppm in the ^{1}H NMR spectrum characteristic of the protons H-2 and H-4 in double bond rearranged compounds such as **14**.[8]

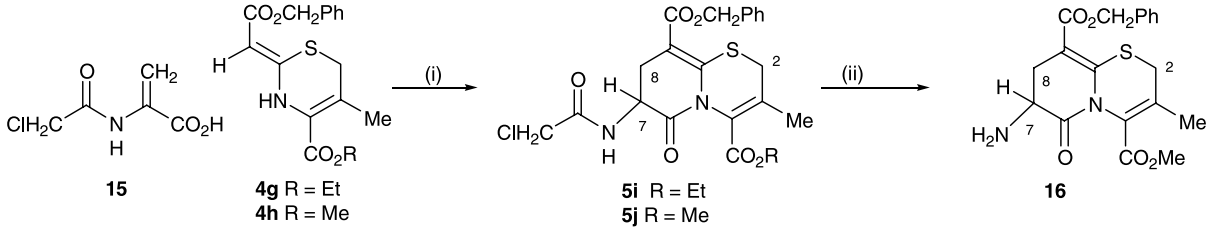


Because of the anomalous reaction observed when urethane protection was used, we decided to investigate the reaction using the chloroacetyl group to protect the amine function of the dehydroamino acid. The esters **4g** and **4h** were, therefore, reacted with 2-chloroacetylaminoacrylic acid **15**[14] in the presence of PCl_3 as shown in Scheme 6. The products obtained were those expected from 'normal' cyclisation, having all the spectral and analytical characteristics of the pyridothiazines **5i** and **5j**. An attempt to resolve these racemic products by selective hydrolysis of the L-chloroacetamide using immobilised acylase I from *Aspergillus* proved unsuccessful. The chloroacetylamine **5j** was converted to the free amine **16** by reaction with *ortho*-phenylenediamine.

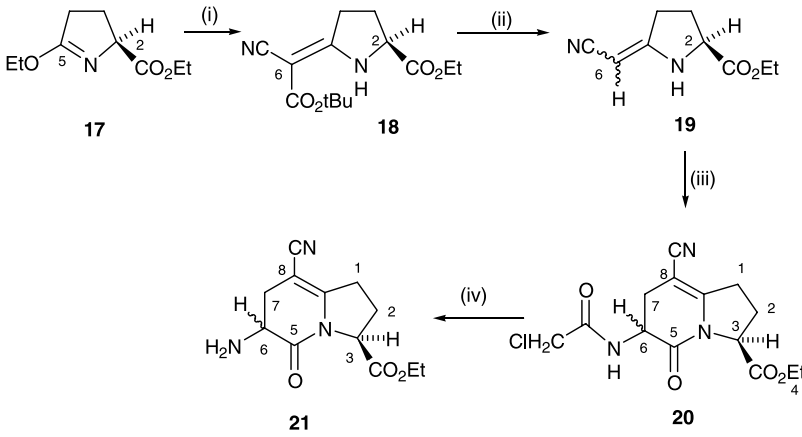
As we wished to make a series of β-turn templates, the 6/5-system **21** seemed to be a useful second series. It was also of interest to see whether the cyclisation method used in our synthesis might exhibit the same dichotomy between urethane protected amines and amides that we had observed in synthesis of the 6/6-ring system. Our starting point for the 6/5-system **21** was to prepare the imino ether **17** from ethyl (2*S*)-pyroglutamate[15] in 92% yield using Meerwein's reagent (Scheme 7). This was then reacted with *tert*-butyl cyanoacetate and triethylamine to yield the vinylogous urethane **18** as a single geometrical isomer in 58% yield. This was assumed to be the *Z*-isomer which was expected to be stabilised by hydrogen bonding. Treatment with trifluoroacetic acid gave a 1:1 mixture of the *E* and *Z* isomers **19a** and **19b**. The olefinic and NH protons in the ^{1}H NMR spectrum of the mixture diminished in intensity in the presence of ^2H_2O, indicating a dynamic equilibrium between the two isomers via the intermediate imine. The spectrum was assigned with the aid of a 2D-COSY spectrum, and the spectral peaks associated with the individual isomers were assigned with the aid of the NOE studies shown in Fig. 1 and reported in Section 3.1.9.

The mixed geometric isomers **19** were now reacted with chloroacetylaminoacrylic acid **15** and PCl_3 to afford the protected hexahydroindolizine **20** in 41% yield. Treatment of this with *ortho*-phenylenediamine gave the template amino acid **21**.

We had now prepared two β-turn templates **16** and **21** and were interested to see if an 'anomalous' cyclisation reaction might be observed if benzyloxycarbonylaminoacrylic acid **6** were reacted with the enamine **19**. When these compounds were reacted in the presence of PCl_3, a product was obtained in 21% yield which appeared to be a mixture of pairs of diastereoisomers of **22** and **23** (Scheme 8). The only pure product to be obtained by repeated column chromatography was one of the diastereoisomers of the 'anomalous product' **23**.



Scheme 6. Reagents and conditions: (i) PCl_3/dioxan/benzene/reflux (**5g** 72%, **5h** 71%); (ii) *ortho*-phenylenediamine/EtOH/aq LiOH/100 °C/48 h (51%).



Scheme 7. Reagents and conditions: $NCCH_2CO_2^tBu/NEt_3$/60 °C/24 h (92%); (ii) CF_3CO_2H/room temperature/8 min (68%); (iii) **15**+PCl_3/dioxan/benzene/reflux/90 min (41%); (iv) *ortho*-phenylenediamine/EtOH/aq LiOH/100 °C/48 h (43%).

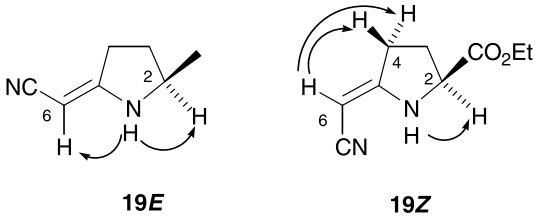
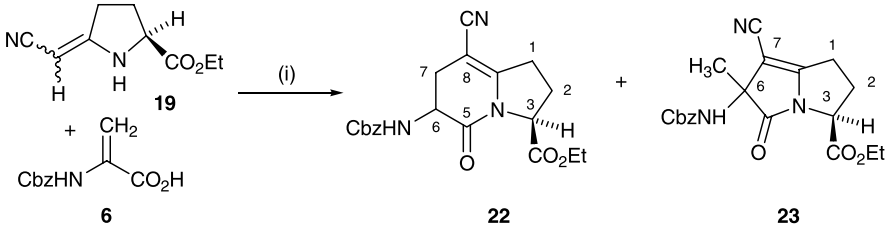
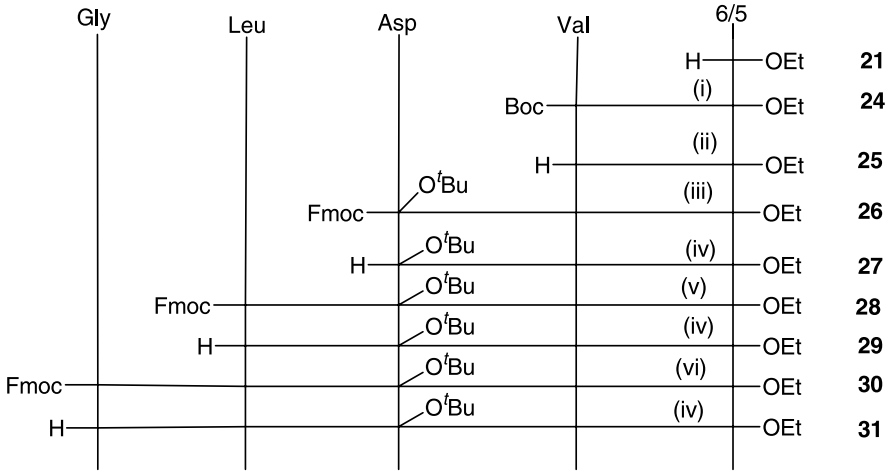


Figure 1. NOE experiments on the mixture of geometric isomers **19a** and **19b**.

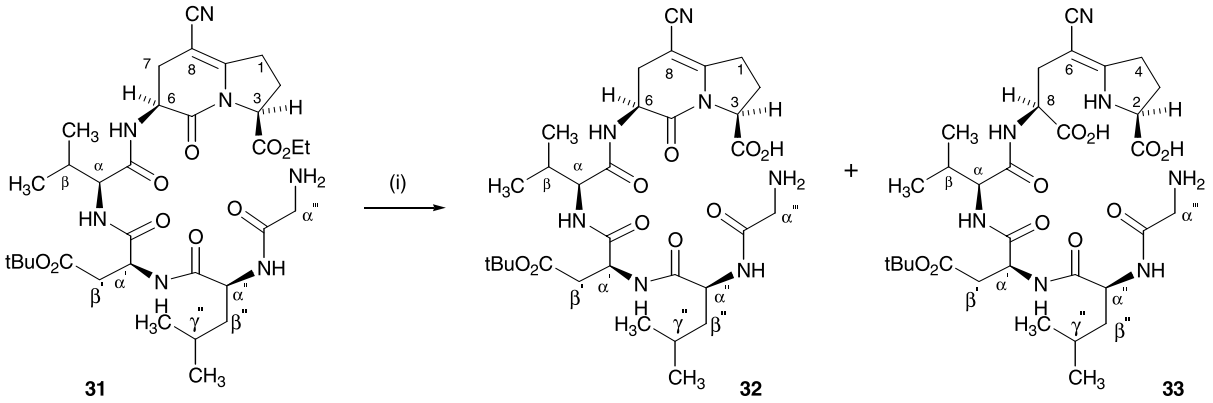
We were unable to resolve the enantiomers **16** or separate the diastereoisomers **21**, and so we decided to build an external turn motif on one of these templates and to attempt separation of the various diastereoisomers prepared as the peptide was built up. We chose the diastereoisomers **21** as our template and opted to build the cyclic peptide GLDV between the amino and carboxylic groups, since a turn incorporating this motif has been shown to inhibit the interaction of the integrin $\alpha_4\beta_1$ with vascular cell adhesion molecule-1.[16] The amine **21** was therefore reacted with (2*S*)-*N*-*tert*-butoxycarbonylvaline and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in DMF to give the adduct **24** in 76% yield as shown in Scheme 9. Deprotection with trifluoroacetic acid gave the amine **25** in 99% yield and condensation with 4-*tert*-butyl (2*S*)-*N*-Fmoc-aspartic acid gave the dipeptide adduct **26** in 70% yield. This was deprotected using piperidine in DMF to give a 70% yield of the amine **27** which was condensed with



Scheme 8. Reagents and conditions: (i) PCl_3/dioxan/benzene/reflux 24 h (21%).



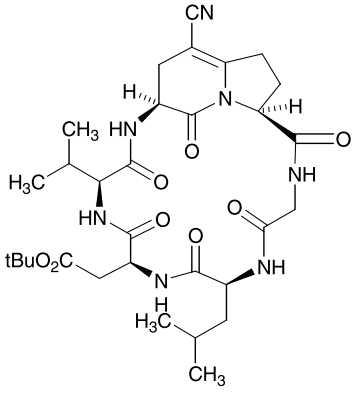
Scheme 9. Reagents and conditions: (i) TBTU/DIPEA/DMF/Boc-Val-OH/room temperature/12 h (76%); (ii) CF_3CO_2H/0 °C/15 min (74%); (iii) TBTU/DIPEA/Fmoc-Asp(O^tBu)-OH/room temperature/12 h (70%); (iv) piperidine/DMF/room temperature/90 min (>70%); (vi) TBTU/DIPEA/DMF/Fmoc-Leu-OH/room temperature/12 h (97%); (vii) TBTU/DIPEA/Fmoc-Gly-OH/room temperature/12 h (97%).



Scheme 10. Reagents and conditions: (i) NaOH/H_2O/EtOH/pH 11/room temperature/24 h (**32**, 3%; **33**, 14%).

(2*S*)-*N*-Fmoc-leucine to give the tripeptide adduct **28** in 97% yield. Deprotection to the amine **29** in 78% yield and condensation with *N*-Fmoc-glycine gave the tetrapeptide adduct **30** in 97% yield. None of the diastereoisomeric compounds in this synthesis could be separated.

Finally the GLDV-tetrapeptide amine **31** was prepared in 95% yield by treating the compound **30** with piperidine in dimethylformamide. The next stage was to hydrolyse the ethyl ester which we accomplished, obtaining the acid **32** in 3% yield (Scheme 10). The major hydrolysis product was the diacid **33**, the result of hydrolysis of the bicyclic lactam. The sensitivity of this functionality to base was presumably due to the fact that this was an enaminamide, a functionality which is thought to make the lactam system in cephalosporin more reactive.[17] Attempts to improve the yield of the acid **32** were unsuccessful. The small amount of acid **32** available was reacted with TBTU and DMAP in DMF at high dilution. The crude product showed an ion at *m/z* 667 in the mass spectrum corresponding $[M+Na]^+$ for the desired cyclic peptide **34** and further purification by HPLC gave a sample with *m/z* 645 ($[M+H]^+$ for **34**). There was however insufficient material for further characterisation. Reaction with trifluoroacetic acid and purification by HPLC gave material with *m/z* 610 ($[M+Na]^+$ for **35**) and 626 ($[M+K]^+$ for **35**) but again there was insufficient material for further characterisation.



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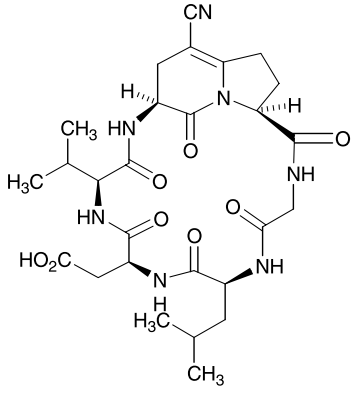

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In conclusion we have discovered an interesting dichotomy in the annelation of exocyclic enamines, depending on whether dehydroamino acid urethanes or dehydroamido acids are used. We have synthesised a series of potential external β-turn templates but when one of these was converted to a GLDV-tetrapeptide derivative, the sensitivity of the conjugated lactam system to base prevented the accumulation of sufficient bicyclic acid to fully characterise the product. In no case was separation of any of the diastereoisomeric products achieved.

3. Experimental

3.1. General

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotation measurements (in units of 10^{-1} deg cm^2 g^{-1}) were obtained on a Perkin Elmer PE241 polarimeter, using a 1 dm path length micro cell. IR spectra were recorded on Perkin Elmer 1720 and Bruker IFS 66 Fourier transform instruments. ^{1}H NMR spectra were recorded on Bruker WM360 (360 MHz), AMX500 (500 MHz), AC200 (200 MHz), AMX360 (360 MHz) and AMX600 (600 MHz) Fourier transform instruments. *J* values are given in Hz. NOE experiments were carried out on a Bruker AMX500 (500 MHz) Fourier transform instrument, and COSY experiments on a Bruker

AMX600 (600 MHz) Fourier transform instrument. ^{13}C NMR spectra were recorded on Bruker AMX500 (125.8 MHz) and Bruker AC200 (50 MHz) Fourier transform instruments. INEPT experiments were used to help assign ^{13}C NMR resonances where necessary. Residual solvent peaks were used as internal reference for all NMR spectra. Mass spectra were recorded on Kratos MS80F, MS50 and MS25 double focusing spectrometers and a VG Bio-Q spectrometer. Accurate mass measurements were recorded on a Concept Kratos spectrometer by Dr S. Chotai (Wellcome Research Laboratories). Microanalyses were performed by Miss M. Patel (Sussex) and Mrs. C. Longhurst and Miss W. C. Mann (Wellcome). Column chromatography was carried out on Merck Kieselgel 60 (239–240 mesh—ART 9385). Petroleum ether refers to the fraction of alkanes of bp 60–80 °C.

3.1.1. 2-Benzyloxycarbonylaminoacrylic acid (6). This was prepared by the method of Frankel and Reichmann[10] as a white solid in 53% yield, mp 110–112 °C (lit.[10] 105 °C); *m/z* [+ve FAB (thioglycerol)] 244 ($[M+Na]^+$); ν_{max} (KBr)/cm^{-1} 3424 (br, NH), 3300–2500 (NH, OH), 1749 (ester) and 1699 (acid); δ_H (360 MHz, $(C^2H_3)_2SO$) **6a** 5.09 (2H, s, OCH_2Ph), 5.60 (1H, s, olefinic), 5.83 (1H, s, olefinic), 7.30–7.40 (5H, m, ArH) and 8.53 (1H, br s, NH); signals for **6b** appeared with time 1.89 (3H, s, CH_3), 4.95 (2H, s, OCH_2Ph) and 7.4 (5H, m, ArH).

3.1.2. 8-Benzyl 4-ethyl (7*RS*)-7-benzyloxycarbonylamino-6,7-dihydro-3,7-dimethyl-6-oxo-2*H*-pyrrolo[2,1*b*]-[1,3]-thiazine-4,8-dicarboxylate (7a). Ethyl 2-benzyloxycarbonylmethylene-3,6-dihydro-5-methyl-2*H*-[1,3]-thiazine-4-carboxylate **4g**[9] (500 mg, 1.5 mmol) and 2-benzyloxycarbonylaminoacrylic acid **6** (500 mg, 2.25 mmol) were dissolved in dioxane (7.5 ml) and benzene (10 ml). Phosphorus trichloride (310 mg, 2.25 mmol) was added and the solution was heated at reflux under nitrogen for 5 h. The solvent was removed in vacuo to afford a dark red oil, which was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium hydrogen carbonate, 1 M hydrochloric acid and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo to afford an orange solid, which was recrystallised from dichloromethane/diethyl ether to yield 8-benzyl 4-ethyl (7*RS*)-7-benzyloxycarbonylamino-6,7-dihydro-3,7-dimethyl-6-oxo-2 -pyrrolo[2,1*b*][1,3]thiazine-4,8-dicarboxylate **7a** as a beige solid (460 mg, 57%), mp 158–160 °C; (Found: C, 63.05; H, 4.9; N, 5.1. $C_{28}H_{28}N_2O_7S$ requires C, 62.7; H, 5.0; N, 5.2%); *m/z* [+ve FAB (3-NBA)] 536 ($[M]^+$); ν_{max} (KBr)/cm^{-1} 3414 (br, NH), 1764 and 1732 (ester) and 1687 (lactam); λ_{max} (MeOH)/nm 328 (ε 6500); δ_H (360 MHz, C^2HCl_3) 1.27 (3H, t, $J=7.1$ Hz, CH_3), 1.55 (3H, s, CH_3), 2.14 (3H, s, CH_3), 3.10 (1H, d, $J_{2A,2B}=15$ Hz, H-2A), 3.60 (1H, d, $J_{2B,2A}=15$ Hz, H-2B), 4.20–4.35 (2H, m, $J=7.1$ Hz, OCH_2), 4.99 (1H, d, $J_{AB}=14$ Hz, OCH[A]Ph), 5.01 (1H, d, $J_{BA}=14$ Hz, OCH[B]Ph), 5.20 (1H, d, $J_{CD}=14$ Hz, OCH[C]Ph), 5.31 (1H, d, $J_{DC}=14$ Hz, OCH[D]Ph), 5.46 (1H, br s, NH, exchanges in ^2H_2O) and 7.29–7.35 (10H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 13.96 (CH_3), 18.74 (CH_3), 22.43 (CH_3), 30.59 (C-2), 59.48 (C-7), 61.69 (OCH_2), 65.99 and 67.07 (OCH_2Ph), 124.95 (C-9), 127.19 (C-3), 127.99–136.02 (aromatics), 153.00 (C-4), 154.13 (C-8) and 162.13, 162.20, 162.26 and 173.22 (4×C=O).

3.1.3. 8-Benzyl 4-methyl (7*RS*)-7-benzyloxycarbonylamino-6,7-dihydro-3,7-dimethyl-6-oxo-2*H*-pyrrolino-[2,1*b*][1,3]-thiazine-4,8-dicarboxylate (7b). Methyl 2-benzyloxycarbonylmethylene-3,6-dihydro-5-methyl-2*H*-[1,3]-thiazine-4-carboxylate **4h**[9] (1.0 g, 3.13 mmol) and 2-benzyloxycarbonylaminoacrylic acid **6** (1.4 g, 6.3 mmol) were dissolved in dioxane (15 ml) and benzene (20 ml). Phosphorus trichloride (900 mg, 6.3 mmol) was added and the solution was heated at reflux under nitrogen for 12 h. The solvent was removed in vacuo to afford a red oil, which was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium hydrogen carbonate, 1 M hydrochloric acid and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:2). The resulting orange foam was recrystallised from chloroform to yield 8-benzyl 4-methyl (7*RS*)-7-benzyloxycarbonylamino-6,7-dihydro-3,7-dimethyl-6-oxo-2*H*-pyrrolino-[2,1*b*][1,3]-thiazine-4,8-dicarboxylate **7b** as white crystals (870 mg, 53%), mp 147-149 °C; (Found: C, 61.6; H, 4.9; N, 5.2. $C_{27}H_{26}N_2O_7S$ requires C, 62.05; H, 5.0; N, 5.4%); *m/z* [+ve FAB (thioglycerol)] 545 ($[M+Na]^+$) and 523 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3311 (br, NH), 1764 and 1739 (ester) and 1691 (lactam); λ_{max} (MeOH)/nm 324 (ε 21,800); δ_H (360 MHz, C^2HCl_3) 1.55 (3H, s, CH_3), 2.12 (3H, s, CH_3), 3.13 (1H, d, $J_{2A,2B}=15.6$ Hz, H-2A), 3.59 (1H, d, $J_{2B,2A}=15.6$ Hz, H-2B), 3.80 (3H, s, OCH_3), 4.96 (2H, 2×d, $J_{AB}=12$ Hz, OCH_2Ph), 5.28 (2H, 2×d, $J_{AB}=12$ Hz, OCH_2Ph), 5.36 (1H, br s, NH) and 7.27–7.34 (10H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 18.77 (CH_3), 22.43 (CH_3), 30.44 (C-2), 52.30 (OCH_3), 59.48 (C-7), 65.97 and 66.89 (OCH_2Ph), 123.85 (C-9), 127.06 (C-3), 127.95–136.18 (aromatics), 152.55 (C-4), 154.19 (C-8) and 156.62, 162.25, 162.72 and 173.33 (4×C=O).

3.1.4. 9-Benzyl 4-ethyl (7*RS*)-7-(2-chloroacetylamino)-7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][1,3]-thiazine-4,9-dicarboxylate (5i). Ethyl 2-benzyloxycarbonylmethylene-3,6-dihydro-5-methyl-2*H*-[1,3]-thiazine-4-carboxylate **4g**[9] (2.0 g, 6 mmol) and 2-chloroacetylaminoacrylic acid **15**[14] (1.1 g, 6.6 mmol) were dissolved in dioxane (30 ml) and benzene (40 ml). Phosphorus trichloride (900 mg, 6.6 mmol) was added and the solution was heated at reflux under nitrogen for 156 h. The solvent was removed in vacuo to afford an oil which was dissolved in ethyl acetate. The solution was washed successively with saturated aqueous sodium hydrogen carbonate, 1 M hydrochloric acid and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel, eluting with ethyl acetate/chloroform (1:1) to yield 9-benzyl 4-ethyl (7*RS*)-7-(2-chloroacetylamino)-7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][1,3]thiazine-4,9-dicarboxylate **5i** as a pale yellow foam (2.1 g, 72%), mp 64–65 °C; *m/z* [EI] Found: 478.09564. $C_{22}H_{23}N_2O_6S^{35}Cl$ requires 478.09654; *m/z* [+ve FAB (EtOAc/3-NBA)] 479 and 481 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3414 (br, NH), 1725 (ester) and 1681 (lactam); λ_{max} (MeOH)/nm 316 (ε 17,800); δ_H (500 MHz, C^2HCl_3) 1.28 (3H, t, $J=7.1$ Hz, CH_3), 2.28

(3H, s, CH_3), 2.48 (1H, t, $J_{8A,8B}=J_{8A,7}=15$ Hz, H-8A), 2.87 (1H, d, $J_{2A,2B}=13.7$ Hz, H-2A), 3.50 (1H, d, $J_{2B,2A}=13.7$ Hz, H-2B), 3.52 (1H, AB, $J_{8B,7}=5.9$ Hz, $J_{8B,8A}=15$ Hz, H-8B), 4.09 (2H, s, CH_2Cl), 4.14–4.36 (2H, m, OCH_2), 4.59–4.64 (1H, m, $J_{7,8A}=15$ Hz, $J_{7,8B}=5.9$ Hz, H-7), 5.16 (1H, d, $J_{AB}=12.4$ Hz, OCH[A]Ph), 5.32 (1H, d, $J_{BA}=12.4$ Hz, OCH[B]Ph) and 7.29–7.40 (5H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 14.13 (CH_3), 18.74 (CH_3), 26.40 (C-2), 32.04 (C-8), 42.43 (CH_2Cl), 49.63 (C-7), 61.50 (OCH_2), 66.90 (OCH_2Ph), 106.44 (C-10), 126.76 (C-4), 128.39–135.84 (aromatics), 142.31 (C-3), 152.27 (C-9) and 162.13, 165.50, 166.38 and 167.97 (4×C=O).

3.1.5. 9-Benzyl 4-methyl (7*RS*)-7-(2-chloroacetylamino)-7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][1,3]-thiazine-4,9-dicarboxylate (5j). Methyl 2-benzyloxycarbonylmethylene-3,6-dihydro-5-methyl-2*H*-[1,3]-thiazine-4-carboxylate **4h**[9] (4.0 g, 13 mmol) and 2-chloroacetylaminoacrylic acid **15**[14] (2.3 g, 14 mmol) were dissolved in dioxane (60 ml) and benzene (80 ml). Phosphorus trichloride (1.9 g, 14 mmol) was added and the solution was heated at reflux under nitrogen for 90 min. The solvent was removed in vacuo to afford an oil, which was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium hydrogen carbonate, 1 M hydrochloric acid and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:2) to afford an off-white solid which was recrystallised from chloroform to yield 9-benzyl 4-methyl (7*RS*)-7-(2-chloroacetylamino)-7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][1,3]thiazine-4,9-dicarboxylate **5j** as a white solid (4.1 g, 68%), mp 202–204 °C; (Found: C, 53.9; H, 4.5; N, 5.9. $C_{21}H_{21}N_2O_6SCl$ requires C, 54.25; H, 4.55; N, 6.0%); *m/z* [+ve FAB (thioglycerol)] 487 and 489 ($[M+Na]^+$) and 465 and 467 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3354 (br, NH), 1730 (ester) and 1676 (lactam); λ_{max} (MeOH)/nm 318 (ε 9000); δ_H (360 MHz, C^2HCl_3) 2.25 (3H, s, CH_3), 2.51 (1H, t, $J_{8A,7}=J_{8A,8B}=17.5$ Hz, H-8A), 2.88 (1H, d, $J_{2A,2B}=15$ Hz, H-2A), 3.46 (1H, d, $J_{2B,2A}=15$ Hz, H-2B), 3.51 (1H, dd, $J_{8B,7}=7$ Hz, $J_{8B,8A}=17.5$ Hz, H-8B), 3.80 (3H, s, OCH_3), 4.10 (2H, s, CH_2Cl), 4.64 (1H, m, $J_{7,8A}=17.5$ Hz, $J_{7,8B}=7$ Hz, H-7), 5.15 (1H, d, $J_{AB}=12$ Hz, OCH[A]Ph), 5.38 (1H, d, $J_{BA}=12$ Hz, OCH[B]Ph) and 7.35–7.45 (5H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 18.73 (CH_3), 26.28 (C-2), 31.85 (C-8), 42.32 (CH_2Cl), 49.38 and 49.48 (C-7), 52.33 (OCH_3), 66.77 (OCH_2Ph), 106.40 (C-10), 126.32 (C-4), 128.22–135.68 (aromatics), 142.15 (C-3), 151.97 (C-9) and 162.66, 165.27, 166.24 and 167.72 (4×C=O).

3.1.6. 9-Benzyl 4-methyl (7*RS*)-7-amino-7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][1,3]thiazine-4,9-dicarboxylate (16). 9-Benzyl 4-methyl (7*RS*)-7-chloroacetamido-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][l,3] thiazine-4,9-dicarboxylate **5j** (600 mg, 1.25 mmol) was dissolved in ethanol (60 ml). A solution of *ortho*-phenylenediamine dihydrochloride (530 mg, 2.9 mmol) and lithium hydroxide (180 mg, 7.3 mmol) in water (50 ml) was added and the solution was stirred and heated at 100 °C for 48 h. The solution was concentrated in vacuo and the resulting aqueous solution was washed with diethyl ether. The aqueous phase was extracted with dichloromethane and the extracts were washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel, eluting with methanol/dichloromethane (4:96), to yield 9-benzyl 4-methyl (7*RS*)-7-amino-7,8-dihydro-3-methyl-6-oxo-2*H*,6*H*-pyrido[2,1*b*][1,3]thiazine-4,9-dicarboxylate **16** as a pale yellow foam (250 mg, 51%), mp 58–60 °C; *m/z* [EI] Found 388.10836. $C_{19}H_{20}N_2O_5S$ requires 388.10929; ν_{max} (KBr)/cm^{-1} 3413 (br, NH), 1728 (ester) and 1681 (lactam); λ_{max} (MeOH)/nm 232 and 315.0 (ε 11,900 and 3400); δ_H (360 MHz, C^2HCl_3) 2.28 (3H, s, CH_3), 2.51 (1H, t, $J_{8A,7}=J_{8A,8B}=15$ Hz, H-8A), 2.87 (1H, d, $J_{2A,2B}=13.7$ Hz, H-2A), 3.39 (1H, d, $J_{2B,2A}=13.7$ Hz, H-2B), 3.48 (1H, dd, $J_{8B,7}=5.6$ Hz, $J_{8B,8A}=15$ Hz, H-8B), 3.58 (1H, dd, $J_{7,8A}=15$ Hz, $J_{7,8B}=5.6$ Hz, H-7), 3.77 (3H, s, OCH_3), 5.25 (2H, s, OCH_2Ph) and 7.35–7.48 (5H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 18.67 (CH_3), 28.94 (C-2), 31.79 (C-8), 50.87 (OCH_3), 52.2 (C-7), 66.72 (OCH_2Ph), 106.22 (C-10), 126.89 (C-4), 128.22–135.87 (aromatics), 140.91 (C-3), 151.63 (C-9), 162.90, 165.64 and 172.35 (3×–C=O).

3.1.7. Ethyl (2*S*)-5-ethoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate (17). Ethyl (2*S*)-pyroglutamate[15] (44.4 g, 0.28 mol) was dissolved in dichloromethane (600 ml) and a solution of triethyloxonium tetrafluoroborate (76.7 g, 0.4 mol) in dichloromethane (300 ml) was added under nitrogen. The solution was stirred at room temperature for 40 h and saturated aqueous potassium hydrogen carbonate (225 ml) was added. When effervescence ceased, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo to yield ethyl (2*S*)-5-ethoxy-3, 4-dihydro-2*H*-pyrrole-2-carboxylate **17** as a dark yellow oil (48.3 g, 92%); *m/z* [EI] Found: 185.10494. $C_9H_{15}NO_3$ requires 185.10519; *m/z* [+ve FAB (3-NBA)] 186 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 1740 (ester) and 1684 (C=N); δ_H (360 MHz, C^2HCl_3) 1.17 and 1.25 (6H, 2×t, $J=7.1$ Hz, 2×CH_3), 2.00–2.52 (4H, m, H-3+H-4), 4.07–4.22 (4H, 2×q, $J=7.1$ Hz, 2×OCH_2) and 4.42 (1H, dd, $J_{2,3A}=1.9$ Hz, $J_{2,3B}=1.2$ Hz, H-2); δ_C (125.8 MHz, C^2HCl_3) 12.17 and 13.95 (2×CH_3), 29.52 (C-3), 36.48 (C-4), 57.93 and 60.65 (2×OCH_2), 59.25 (C-2), 171.89 (C-5) and 175.0 (C=O).

3.1.8. Ethyl (2*S*)-5-(*tert*-butoxycarbonylcyanomethylene)-pyrrolidine-2-carboxylate (18). Ethyl (2*S*)-5-ethoxy-3, 4-dihydro-2*H*-pyrrole-2-carboxylate **17** (45 g, 0.24 mol), *tert*-butyl cyanoacetate (68.6 g, 0.49 mol) and triethylamine (2.5 g, 24 mmol) were heated at 60 °C under nitrogen, for 24 h. The solvent was removed by distillation under reduced pressure. The resulting orange oil was purified by column chromatography on silica gel, eluting with diethyl ether/petroleum ether (1:1). The resulting yellow oil crystallised on standing and was recrystallised from dichloromethane/petroleum ether to yield ethyl (2*S*)-5-(*tert*-butoxycarbonylcyanomethylene)-pyrrolidine-2-carboxylate **18** as white crystals (39.1 g, 58%), mp 77–79 °C; $[\alpha]_D^{24}=-6.25$ (*c* 1, $CHCl_3$); (Found: C, 60.2; H, 6.8; N, 9.8. $C_{14}H_{20}N_2O_4$ requires C, 60.0; H, 7.2; N, 10.0%); *m/z* [+ve FAB (thioglycerol)] 281 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3344 (br, NH), 2199 (CN) and 1736 (ester); λ_{max} (MeOH)/

nm 273 (ε 16,300); δ_H (360 MHz, C^2HCl_3) 1.23 (3H, t, J= 7.1 Hz, CH_3), 1.43 (9H, s, $C(CH_3)_3$), 2.15 (1H, m, H-3A), 2.37 (1H, m, H-3B), 2.90 (2H, m, H-4), 4.17 (2H, q, J= 7.1 Hz, OCH_2), 4.48 (1H, dd, $J_{2,3A}$=5.5 Hz, $J_{2,3B}$=8.7 Hz, H-2) and 9.08 (1H, br s, NH, exchanges in ^2H_2O); δ_C (25.8 MHz, C^2HCl_3) 14.0 (CH_3), 25.2 (C-3), 28.2 ($C(CH_3)_3$), 32.3 (C-4), 61.96 (OCH_2), 62.02 (C-2), 70.4 (C-6), 81.2, ($OC(CH_3)_3$), 118.4 (CN), 166.9 (C-5) and 170.3 and 172.7 (2×C=O).

3.1.9. Ethyl (2*S*)-5-cyanomethylenepyrrolidine-2-carboxylate (19). Ethyl (2*S*)-5-(*tert*-butoxycarbonylcyanomethylene)-pyrrolidine-2-carboxylate **18** (16 g, 57 mmol) was stirred vigorously at room temperature in trifluoroacetic acid (80 ml) under argon for 8 min. Ice cold dichloromethane (200 ml) and saturated aqueous sodium hydrogen carbonate (200 ml) were carefully added. The reaction was cooled in an ice bath and solid sodium hydrogen carbonate was added until pH 6.0 was reached. Solid sodium chloride was added until the solution was saturated and it was filtered through Celite®. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with aqueous sodium hydrogen carbonate (2 g/100 ml H_2O) and dried ($MgSO_4$). The solvent was removed in vacuo to yield a yellow oil which was purified by column chromatography on silica gel, eluting with ethyl acetate/toluene (1:1), to afford ethyl (2*S*)-5-cyanomethylenepyrrolidine-2-carboxylate **19** as a pale oil (7.0 g, 68%); $[\alpha]_D^{29}$=+6.75 (*c* 1, MeOH); (Found: C, 60.25; H, 7.0; N, 15.8. $C_9H_{12}N_2O_2$ requires C, 60.0; H, 6.7; N, 15.5%); *m/z* [+ve FAB (thioglycerol)] 181 ($[M+H]^+$); ν_{max} film)/cm^{-1} 3344 (br, NH), 2192 (CN) and 1738 (ester); λ_{max} (MeOH)/nm 263 (ε 21,000); δ_H (500 MHz, C^2HCl_3, mixture of *E* and *Z* isomers) 1.23 and 1.27 (3H, 2×t, J=7.1 Hz, CH_3, *E*/*Z*), 2.10 (1H, m, $J_{3A,2}$=5.4 Hz, $J_{3A,3B}$=13.0 Hz, H-3A *E*/*Z*), 2.34 (1H, m, $J_{3B,2}$=8.3 Hz, $J_{3B,3A}$=13.0 Hz, H-3B *E*/*Z*), 2.60 (1H, m, H-4*Z*), 2.78 (1H, m, H-4*E*), 3.76 (0.5H, s, H-6*Z*, exchanges slowly in ^2H_2O), 4.09 (0.5H, s, H-6*E*, exchanges slowly in ^2H_2O), 4.13 and 4.22 (2H, m, J= 7.1 Hz, 2×OCH_2 *E*/*Z*), 4.25 (0.5H, dd, $J_{2,3A}$=5.4 Hz, $J_{2,3B}$=8.3 Hz, H-2*Z*), 4.30 (0.5H, dd, $J_{2,3A}$=5.4 Hz, $J_{32,3B}$=8.3 Hz, H-2*E*), 5.94 (0.5H, br, NH(*Z*), exchanges slowly in ^2H_2O) and 5.96 (0.5H, br, NH(*E*), exchanges slowly in ^2H_2O); δ_C (125.8 MHz, C^2HCl_3 mixture of *E* and *Z* isomers) 14.1 (CH_3), 26.7 and 27.1 (C-3), 29.98 and 30.5 (C-4), 55.7 and 58.1 (C-6), 60.0 and 60.4 (C-2), 61.6 (OCH_2), 119.9 and 121.3 (CN), 166.0 and 166.5 (C-5) and 171.6 and 171.96 (ester). Assignment of ^1H NMR spectral values to the individual isomers were made by a 2D COSY experiment and the following NOE experiment; (i) irradiation at δ 3.76 ppm for H-6*Z* gave a 4% NOE in both of H-4*Z* at δ 2.60 ppm; (ii) irradiation at δ 5.96 ppm for NH(*E*) gave an NOE at 4.30 for H-2*E* and at δ 4.09 for H-6*E*; (iii) irradiation at δ 4.09 ppm for H-6*E* resulted in a 2.6% NOE of NH(*E*) at δ 5.96 ppm; and (iv) irradiation at NH(*Z*) at δ 5.94 ppm resulted in a NOE at H-2*Z* (δ 4.25 ppm).

3.1.10. Ethyl (3*S*,6*RS*)-6-chloroacetylamino-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (20). Ethyl (2*S*)-5-cyanomethylenepyrrolidine-2-carboxylate **19** (5.5 g, 31 mmol) and 2-chloroacetylaminoacrylic acid **15**[14] (5.5 g, 34 mmol) were dissolved in dioxane (170 ml) and benzene (225 ml). Phosphorus trichloride (4.6 g, 34 mmol) was added and the solution was heated at reflux under nitrogen for 90 min. The solvent was removed in vacuo to afford a dark red oil which was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium hydrogen carbonate, 1 M hydrochloric acid and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel, eluting with dichloromethane/diethyl ether (1:1), to afford ethyl (3*S*,6*RS*)-6-chloroacetylamino-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **20** as a pale yellow foam (4.51 g, 41%), mp 40–42 °C; (Found: C, 51.8; H, 4.9; N, 12.9. $C_{14}H_{16}N_3O_4C1$ requires C, 51.6; H, 5.0; N, 12.9%); *m/z* [+ve FAB ($CHCl_3$/3-NBA)] 326 and 328 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3302 (br, NH), 2214 (CN), 1746 (ester) and 1670 (lactam); λ_{max} (MeOH)/nm 277 (ε 19,000); δ_H (500 MHz, C^2HCl_3, two diastereoisomers) 1.30 (3H, 2×t, J=7 Hz, CH_3), 2.24 (1H, m, $J_{2A,3}$=2.3, 3.1 Hz, $J_{2A,2B}$=13.5 Hz, H-2A), 2.41 (1H, m, $J_{2B,3}$=9.2, 9.4 Hz, $J_{2B,2A}$=13.5 Hz, H-2B), 2.55 (1H, m, $J_{7A,6}$=14.2 Hz, $J_{7A,7B}$=16 Hz, H-7A), 2.90–3.06 (2H, m, H-1), 3.15 (1H, 2×AB, $J_{7B,6}$=7.6 Hz, $J_{7B,7A}$=16 Hz, H-7B), 4.09 and 4.10 (2H, 2×s, CH_2Cl), 4.23 (2H, 2×q, J=7 Hz, OCH_2), 4.59–4.70 (1H, m, $J_{6,7A}$=14.2, 14.6 Hz, $J_{6,7B}$=7.4, 7.7 Hz, $J_{6,NH}$=6 Hz, 6 (m, simplifies to 2×q in ^2H_2O), H-7B), 4.80 (1H, 2×q, $J_{3,2A}$=2, 3 Hz, $J_{3,2B}$=9.1, 9.5 Hz, H-3) and 7.30–7.35 (1H, 2×d.br, $J_{NH,6}$=5.2, 5.8 Hz, NH exchanges in ^2H_2O); δ_C (125.8 MHz, C^2HCl_3) 14.05 (CH_3) 26.00 and 26.34 (C-2), 27.41 and 28.38 (C-1), 28.88 and 29.06 (C-7), 42.30 (CH_2Cl), 48.99 and 49.73 (C-6), 59.77 and 60.00 (C-3), 62.27 (OCH_2), 80.38 and 80.48 (C-8), 117.11 and 117.17 (CN), 154.59 and 154.81 (C-9) and 165.59–169.76 (3×C=O). The yellow foam was recrystallised from ethyl acetate/chloroform, affording one diastereoisomer as a white solid, mp 147–150 °C; λ_{max} (MeOH)/nm 277; δ_H (360 MHz, C^2HCl_3, single diastereoisomer) 1.28 (3H, t, J= 7 Hz, CH_3), 2.26–2.41 (2H, m, H-2), 2.46 (1H, m, $J_{7A,6}$= 14.3 Hz, $J_{7A,7B}$=16 Hz, H-7A), 2.98 (2H, m, H-1), 3.18 (1H, AB, $J_{7B,6}$=7.4 Hz, $J_{7B,7A}$=16 Hz, H-7B), 4.09 (2H, s, CH_2Cl), 4.22 (2H, q, J=7 Hz, OCH_2), 4.62 (1H, m, $J_{6,7A}$= 14.3 Hz, $J_{6,7B}$=7.4 Hz, H-6, simplifies in ^2H_2O), 4.84 (1H, dd, $J_{3,2A}$=1.5 Hz, $J_{3,2B}$=8 Hz, H-3) and 7.35 (1H, br d, $J_{NH,6}$=4.3 Hz, NH, exchanges in ^2H_2O); δ_C (125.8 MHz, C^2HCl_3) 14.05 (CH_3), 26.35 (C-2), 27.49 (C-1), 29.07 (C-7), 42.30 (CH_2Cl), 49.77 (C-6), 59.82 (C-3), 62.26 (OCH_2), 80.50 (C-8), 117.15 (CN), 154.78 (C-9) and 166.26 and 169.26 (3×C=O).

3.1.11. Ethyl (3*S*,6*RS*)-6-amino-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (21). Ethyl (3*S*,6*RS*)-8-cyano-6-chloroacetylamino-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **20** (4.54 g, 13 mmol) was dissolved in ethanol (30 ml). *ortho*-Phenylenediamine dihydrochloride (4.7 g, 26 mmol) and lithium hydroxide (1.54 g, 64 mmol) were added in water (80 ml) and the solution was stirred and heated at 100 °C for 48 h. The solution was concentrated in vacuo and the resulting aqueous solution was washed with ethyl acetate. The solvent was removed from the aqueous phase in vacuo to afford a brown foam. This was purified by preparative reverse phase HPLC on a Zorbax C8 column (25 cm× 22.2 mm), eluting with 0.2% TFA in acetonitrile and 0.2%

TFA/water, fractionating at 30 s intervals. Samples, judged to be homogeneous by analytical reverse phase HPLC on a Zorbax C8 column (25 cm×4.6 mm), were pooled and lyophilised. This resulted in ethyl (3*S*,6*RS*)-6-amino-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **21** as a pale yellow foam (1.5 g, 43%), mp 32–34 °C; *m/z* [EI] Found: 249.11155. $C_{12}H_{15}N_3O_3$ requires 249.11134; *m/z* [+ve FAB (thioglycerol)] 250 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3370 (br, NH), 2207 (CN), 1741 (ester) and 1664 (lactam); λ_{max} (MeOH)/nm 275 (ε 14,000); δ_H (360 MHz, C^2HCl_3) 1.27–1.32 (3H, 2×t, $J=7.1$ Hz, CH_3), 2.21 (1H, m, $J_{2A,3}=2$, 3 Hz, $J_{2A,2B}=13$ Hz, H-2A), 2.31–2.49 (1H, m, $J_{2B,3}=9.1$, 9.3 Hz, $J_{2B,2A}=13$ Hz, H-2B), 2.51–2.62 (1H, m, $J_{7A,6}=12.1$ Hz, $J_{7A,7B}=13.8$ Hz, H-7A), 2.75–2.83 (1H, m, $J_{7B.6}=7.3$ Hz, $J_{7B,7A}=13.8$ Hz, H-7B), 2.88–3.00 (2H, m, H-1), 3.59–3.74 (1H, 2×q, $J_{6,7A}=12.1$, 13.6 Hz, $J_{6,7B}=7.3$, 7.6 Hz, H-6), 4.18–4.26 (2H, m, $J=7.1$ Hz, OCH_2) and 4.72–4.82 (1H, 2×q, $J_{3,2A}=2$, 3 Hz, $J_{3,2B}=9.1$, 9.3 Hz, H-3); δ_C (50 MHz, C^2HCl_3) 14.08 (CH_3), 26.13 and 26.34 (C-2), 29.16 (C-1), 30.50 and 30.94 (C-7), 50.51 and 50.84 (C-3), 59.63 and 59.74 (C-6), 62.06 (OCH_2), 102.0 (C-8), 117.0 (CN), 121.0 (C-9), 155.0 and 171.0 (2×C=O).

3.1.12. Reaction of 2-benzyloxycarbonylaminoacrylic acid with ethyl (2*S*)-5-cyanomethylenepyrrolidine-2-carboxylate. Ethyl (2*S*)-5-cyanomethylenepyrrolidine-2-carboxylate **19** (500 mg, 2.8 mmol) and 2-benzyloxycarbonylaminoacrylic acid **6**[10] (920 mg, 4.2 mmol) were dissolved in dioxane (15 ml) and benzene (20 ml). Phosphorus trichloride (570 mg, 4.2 mmol) was added and the solution was heated at reflux under nitrogen for 24 h. The solvent was removed in vacuo affording a dark orange oil, which was dissolved in ethyl acetate. The solution was successively washed with saturated aqueous sodium hydrogen carbonate, 1 M hydrochloric acid and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and was purified by column chromatography on silica gel, eluting with dichloromethane/diethyl ether (2:1), yielding a mixture of four compounds as a foam (230 mg, 21%); *m/z* [+ve FAB (EtOAc/3-NBA)] 384 ($[M+H]^+$); ν_{max} (nujol)/cm^{-1} 3350 (br, NH), 2210 (CN), 1733 (ester), 1716 (γ-lactam) and 1665 (δ-lactam); λ_{max} (MeOH)/nm 282 and 283. Repeated column chromatography separated one diastereoisomer of the γ-lactam **23** as an off-white foam (44 mg, 5%); λ_{max} (MeOH)/nm 282; δ_H (360 MHz, C^2HCl_3) 1.28 (3H, t, $J=7.1$ Hz, CH_3), 1.50 (3H, s, CH_3), 2.51–3.00 (4H, m, H-1+H-2), 4.17–4.29 (2H, m, $J=7.1$ Hz, OCH_2), 4.53 (1H, m, H-3), 5.08 (2H, d, $J=7.4$ Hz, OCH_2Ph), 5.47 (1H, br s, NH) and 7.29–7.36 (5H, m, ArH); δ_C (125.8 MHz, C^2HCl_3) 13.9 (CH_3), 22.56 (CH_3), 23.93 (C-2), 30.88 (C-1), 55.65 (C-3), 62.23 (OCH_2), 65.84 (C-6), 67.24 (OCH_2Ph), 113.83 (CN), 127.99–135.8 (aromatics), 136.15 (C-7), 153.77 (C-8) and 161.7, 168.42 and 172.2 (3×C=O).

3.1.13. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-*tert*-butoxycarbonylamino-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (24). Ethyl (3*S*,6*RS*)-6-amino-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **21** (900 mg, 3.6 mmol) and (2*S*)-*N*-*tert*-butoxycarbonylvaline (780 mg, 3.6 mmol) were dissolved in dimethylformamide (35 ml). 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (1.2 g, 3.6 mmol) and di-isopropylethylamine (470 mg, 3.6 mmol) were added and the solution was stirred under nitrogen at room temperature for 12 h. The solvent was removed in vacuo (<50 °C) and the resulting oil was dissolved in ethyl acetate. The solution was successively washed with 5% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the resulting foam was purified by column chromatography on silica gel, eluting with methanol/dichloromethane (4:96), to yield ethyl (3*S*,6*RS*)-6-[(2*S*)-2-*tert*-butoxycarbonylamino-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **24** as a pale yellow powder (1.2 g, 76%), mp 83–84 °C; $[\alpha]_D^{28}=-32.5$ (*c* 1, $CHCl_3$); *m/z* [EI] Found: 448.23069, $C_{22}H_{32}N_4O_6$ requires 448.23219; *m/z* [EI] 487 ($[M+K]^+$), 471 ($[M+Na]^+$) and 449 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3412 (br, NH), 2210 (CN), 1748 (ester) and 1665 (lactam); λ_{max} (MeOH)/nm 277 (ε 14,300); δ_H (360 MHz, C^2HC1_3) 0.91–0.99 (6H, m, $J=6.7$ Hz, $C(CH_3)_2$), 1.25–1.33 (3H, 2×t, $J=7.1$ Hz, CH_3), 1.45–1.46 (9H, 2×s, $OC(CH_3)_3$), 2.15–2.30 (2H, m, $J_{7A,6}=7.1$ Hz, $J_{\beta,\alpha}=5.4$ Hz, H-7A+H-β), 2.39 (1H, m, $J_{2A,3}=9.1$ Hz, $J_{2A,2B}=13.3$ Hz, H-2A), 2.42–2.61 (1H, m, $J_{7B,6}=14.1$ Hz, $J_{7B,7A}=16.7$ Hz, H-7B), 2.94–3.14 (2H, m, H-1), 3.17–3.20 (1H, m, $J_{2B,3}=1.7$ Hz, $J_{2B,2A}=13.3$ Hz, H-2B), 3.90–4.10 (1H, m, $J_{\alpha,\beta}=5.4$ Hz, H-α), 4.21–4.28 (2H, m, $J=7.1$ Hz, OCH_2), 4.56–4.71 (1H, 2×q, $J_{6,7A}=7.1$ Hz, $J_{6,7B}=14.1$ Hz, H-6, simplifies to q in ^2H_2O), 4.73–4.76 (1H, 2×q, $J_{3,2A}=9.1$ Hz, $J_{3,2B}=1.7$ Hz, H-3), 5.02 (1H, br s, NH, exchanges in ^2H_2O) and 6.60–6.80 (1H, 2×br s, NH, exchanges in ^2H_2O); δ_C (125.8 MHz, C^2HC1_3) 14.05 (CH_3), 17.41, 17.54, 19.18 and 19.22 ($C(CH_3)_2$), 26.06 and 26.41 (C-2), 27.70 and 28.74 (C-1), 28.30 ($OC(CH_3)_3$), 28.91 and 29.10 (C-7), 30.73 and 30.90 (C-6), 31.23 ($OC(CH_3)_3$), 48.72 (C-3), 49.47 (C-β), 59.81 and 60.03 (C-α), 62.20 (OCH_2), 80.15 and 80.52 (C-8), 117.20 and 117.29 (CN), 154.49 and 154.72 (urethane), 155.80 (C-9), and 166.03, 166.62, 169.34, 169.83, 171.89 and 172.05 (3×C=O).

3.1.14. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-amino-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (25). Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-*tert*-butoxycarbonylamino-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **24** (300 mg, 0.67 mmol) was cooled to 0 °C. Trifluoroacetic acid (8 ml) was added and the solution was stirred under nitrogen at 0 °C, for 15 min. Stirring was continued at room temperature for a further 2 h. The solvent was removed in vacuo (<50 °C), affording an orange oil. This was triturated with diethyl ether and the solvent was decanted off, yielding the TFA salt of ethyl (3*S*,6*RS*)-6-[(2*S*)-2-amino-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **25** as an off-white solid (230 mg, 74%), mp 194–196 °C; $[\alpha]_D^{26}=-125.53$ (*c* 0.7, MeOH); *m/z* [EI] Found: 348.17809, $C_{17}H_{24}N_4O_4$ requires 348.17976; *m/z* [+ve FAB (thioglycerol)] 697 ($[2M+H]^+$), 371 ($[M+Na]^+$) and 349 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3414 (br, NH), 2213 (CN), 1750 (ester) and 1672 (lactam); λ_{max} (MeOH)/nm 276 (ε 5700); δ_H (360 MHz, C^2HC1_3) 0.89–0.99 (6H, m, $C(CH_3)_2$), 1.22–1.38 (3H, 2×t, $J=7.1$ Hz, CH_3), 2.12–2.30 (2H, m, $J_{7A,6}=5.8$ Hz, $J_{7A,7B}=14.2$ Hz, $J_{\beta,\alpha}=3.2$ Hz, H-7A+H-β), 2.37 (1H, m, $J_{2A,3}=8.8$ Hz,

$J_{2A,2B}$=15.8 Hz, H-2A), 2.43–2.62 (1H, m, $J_{7B,6}$=10.6 Hz, $J_{7B,7A}$=14.2 Hz, H-7B), 2.88–3.03 (2H, m, H-1), 3.04–3.22 (1H, m, $J_{2B,3}$=2.4 Hz, $J_{2B,2A}$=15.8 Hz, H-2B), 4.15–4.32 (2H, m, J=7.1 Hz, OCH_2), 4.53–4.84 (3H, m, $J_{\alpha,\beta}$=3.6 Hz, $J_{6,7A}$=5.8 Hz, $J_{6,7B}$=10.6 Hz, $J_{3,2A}$=8.8 Hz, $J_{3,2B}$=2.4 Hz, H-α+H-6+H-3) and 6.30–6.40 (1H, br s, NH, exchanges in ^2H_2O); δ_C (125.8 MHz, $C^2H_3O^2H$) 14.85 (CH_3), 18.37 and 19.37 ($C(CH_3)_2$), 27.49 and 27.61 (C-2), 29.15 and 29.72 (C-1), 30.61 and 31.26 (C-7), 32.05 and 32.20 (C-6), 50.94, 60.48 and 60.55 (C-3), 61.97 and 62.16 (C-α), 63.50 and 63.57 (OCH_2), 79.98 and 80.39 (C-8), 119.08 and 119.92 (CN), 157.64 and 157.88 (C-9), and 163.40, 163.67, 167.97, 168.40, 172.00 and 172.49 (3× C=O).

3.1.15. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((2*S*)-2-(9*H*)-fluoren-9-ylmethoxycarbonylamino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (26). Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-amino-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **25** (560 mg, 1.6 mmol) and 4-*tert*-butyl (2*S*)-*N*-(9*H*)-fluoren-9-ylmethoxycarbonylaspartate (660 mg, 1.6 mmol) were dissolved in dimethylformamide (22 ml). TBTU (520 mg, 1.6 mmol) and di-isopropylethylamine (210 mg, 1.6 mmol) were added and the solution was stirred under nitrogen at room temperature for 12 h. The solvent was removed in vacuo (<50 °C) and the resulting oil was dissolved in dichloromethane. The solution was successively washed with 5% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo and the resulting foam was triturated with diethyl ether, affording ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((2*S*)-2-(9*H*)-fluoren-9-ylmethoxycarbonylamino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **26** as a pale yellow solid (840 mg, 70%), mp 100–102 °C; $[\alpha]_D^{29}=-51.3$ (*c* 1, $CHCl_3$); *m/z* [EI] Found: 741.34168. $C_{40}H_{47}N_5O_9$ requires 741.33738; *m/z* [+ve FAB (thioglycerol)] 764 ($[M+Na]^+$); ν_{max} (KBr)/cm^{-1} 3414 (br, NH), 2210 (CN), 1710 (ester) and 1652 (lactam); λ_{max} (MeOH)/nm 265 (ε 24,000); δ_H (360 MHz, C^2HCl_3) 0.92–0.98 (6H, m, J=6.7 Hz, $C(CH_3)_2$), 1.21–1.33 (3H, m, J=7.1 Hz, CH_3), 1.43–1.45 (9H, 2×s, $OC(CH_3)_3$), 2.16–2.21 (2H, m, $J_{7A,6}$=6.6 Hz, $J_{\beta,\alpha}$=4.4 Hz, H-7A+H-β), 2.27–2.45 (1H, m, $J_{2A,3}$=9.2 Hz, $J_{2A,2B}$=13.4 Hz, H-2A), 2.54–3.00 (6H, m, $J_{2B,3}$=3.6 Hz, $J_{2B,2A}$=13.4 Hz, $J_{\beta',\alpha'}$=6 Hz, H-2B+H-7B+H-1+H-β′), 4.15–4.24 (3H, m, J=7.1 Hz, OCH_2, + $J_{\alpha,\beta}$=4.4 Hz, H-α), 4.28–4.75 (6H, m, $J_{6,7A}$=6.6, $J_{6,7B}$=2.3 Hz, $J_{\alpha',\beta'}$=6 Hz, $J_{3,2A}$=9.2 Hz, $J_{3,2B}$=3.6 Hz, H-6+H-α′+H-3+Ar_2CH+Ar_2CHCH_2), 6.12–6.14 (1H, br d, $J_{NH,6}$=8.4 Hz, NH, exchanges in ^2H_2O), 6.87–7.17 (2H, br m, 2×NH exchanges in ^2H_2O) and 7.29–7.78 (8H, ArH); δ_C (125.8 MHz, $C^2H_3O^2H$) 14.86 (CH_3), 18.87 and 18.93 ($C(CH_3)_2$), 27.47 and 27.55 (C-2), 28.85 ($OC(CH_3)_3$), 29.64 and 29.74 (C-1), 30.57 (C-7), 32.41 and 32.76 (C-β), 38.66 and 38.88 (C-β′), 39.03 and 39.37 (C-6), 53.53 (CAr_2), 58.81 ($OC(CH_3)_3$), 60.40 (C-3), 61.86 and 62.09 (C-α′), 63.43 and 63.51 (OCH_2), 68.71 ($CCHAr_2$), 79.96 (C-α), 82.92 and 83.01 (C-8), 119.11(CN), 121.44, 126.72, 128.69, 130.37 and 143.05 (Ar), 145.63 and 145.74 (C-9), and 157.5-173.9 (6×C=O).

3.1.16. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((2*S*)2-amino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (27). Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((2*S*)-2-(9*H*)-fluoren-9-ylmethoxycarbonylamino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **26** (750 mg, 1.01 mmol) was dissolved in dimethylformamide (12 ml) and piperidine (3 ml; 20% by volume). The solution was stirred at room temperature under a nitrogen atmosphere for 1.5 h. The solvent was removed in vacuo to yield an off-white solid, which was purified by column chromatography on silica gel, eluting with a gradient of methanol/dichloromethane (1:99) to methanol in dichloromethane (1:9). This yielded ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((2*S*)-2-amino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **27** as a white powder (370 mg, 70%), mp 102–104 °C; $[\alpha]_D^{28}=-72.46$ (*c* 1, $CHC1_3$); *m/z* [EI] Found: 519.26745. $C_{25}H_{37}N_5O_7$ requires 519.26930; *m/z* [+ve FAB (thioglycerol)] 520 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3411 (br, NH), 2210 (CN), 1710 (ester) and 1664 (lactam); λ_{max} (MeOH)/nm 275 (ε 5300); δ_H (360 MHz, C^2HC1_3) 0.94–0.99 (6H, m, J=6.7 Hz, $C(CH_3)_2$), 1.23–1.33 (3H, m, J=7.1 Hz, CH_3), 1.45 (9H, 2×s, $OC(CH_3)_3$), 2.19–2.29 (2H, m, $J_{7A,6}$=7.0 Hz, $J_{7A,7B}$=13.3 Hz, $J_{\beta,\alpha}$=3.7 Hz, H-7A+H-β), 2.36–2.49 (1H, m, $J_{2A,3}$=9.2 Hz, $J_{2A,2B}$=13.6 Hz, H-2A), 2.53–2.84 (3H, m, $J_{2B,3}$=1.9 Hz, $J_{\beta',\alpha'}$=3.8 Hz, H-2B+H-β′), 2.91–2.96 (2H, m, H-1), 3.00–3.12 (1H, m, H-7B), 3.68–3.74 (1H, m, $J_{\alpha',\beta'}$=3.8 Hz, H-α′), 4.18–4.28 (3H, m, J=7.1 Hz, OCH_2+H-α), 4.60–4.69 (1H, m, $J_{6,7A}$=7.0 Hz, $J_{6,7B}$=2.2 Hz, $J_{6,NH}$=5.7 Hz, H-6), 4.72–4.83 (1H, 2×d, $J_{3,2A}$=9.2 Hz, $J_{3,2B}$=1.9 Hz, H-3), 6.67–6.68 (1H, br d, J=6.2 Hz, NH, exchanges in ^2H_2O), 6.90–6.91 (1H, br d, $J_{NH,6}$=5.7 Hz, NH, exchanges in ^2H_2O) and 7.91–7.99 (1H, 2×br d, J=9 Hz, NH, exchanges in ^2H_2O); δ_C (125.8 MHz, C^2HC1_3) 14.05 (CH_3), 18.01 and 19.21 ($C(CH_3)_2$), 26.11 and 26.36 (C-2), 27.63 and 28.49 (C-l), 28.06 ($OC(CH_3)_3$), 28.92 and 29.14 (C-7), 29.67 (C-β′), 30.25 (C-α), 30.61 and 31.21 (C-β), 48.61 and 49.22 (C-6), 57.5 and 58.8 (C-3), 59.77 and 60.01 (C-α′), 62.18 (OCH_2), 80.31 (C-8), 117.20 and 117.29 (CN), 154.58 and 154.79 (C-9), and 166.0, 167.55, 169.91, 171.0, 171.1, 171.2 and 171.45 (5×C=O).

3.1.17. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-(9*H*)-fluor-9-enylmethoxycarbonylamino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (28). Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((2*S*)-2-amino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **27** (300 mg, 0.58 mmol) and *N*-(9*H*)-fluor-9-enylmethoxycarbonyl-(2*S*)-leucine (200 mg, 0.58 mmol) were dissolved in dimethylformamide (40 ml). TBTU (190 mg, 0.58 mmol) and di-isopropylethylamine (75 mg, 0.58 mmol) were added and the solution was stirred under nitrogen at room temperature for 12 h. The solvent was removed in vacuo (<50 °C) and the resulting oil was dissolved in dichloromethane. The solution was successively washed with 5% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in

vacuo affording ethyl (3*S*,6*RS*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-(9*H*)-fluor-9-enylmethoxycarbonylamino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **28** as a pale yellow solid (480 mg, 97%), mp 162–163 °C; $[\alpha]_D^{28} = -48.6$ (*c* 1, $CHCl_3$); *m/z* [+ve FAB (3-NBA)] 855 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3289 (br, NH), 2210 (CN), 1710 (ester) and 1641 (lactam); λ_{max} (MeOH)/nm 264 (ε 29,950); δ_H (360 MHz, C^2HCl_3) 0.92–0.96 (12H, m, $2\times C(CH_3)_2$), 1.25–1.30 (3H, m, $J=7.1$ Hz, CH_3), 1.34 and 1.39 (9H, 2×s, $OC(CH_3)_3$), 1.55–1.73 (3H, m, H-β′+H-β), 2.19–2.36 (3H, m, $J_{2A,3}=8.8$ Hz, $J_{2B,3}=2.8$ Hz, $J_{2A,2B}=13.3$ Hz, H-2+H-γ″), 2.61–2.72 (2H, m, $J_{7A,6}=7.2$ Hz, $J_{7B,6}=4.4$ Hz, $J_{7A,7B}=12.6$ Hz, H-7), 2.81–3.00 (3H, m, H-1+H-α″), 4.18–4.79 (11H, m, $J_{3,2A}=8.8$ Hz, $J_{3,2B}=2.8$ Hz, $J_{6,7A}=7.2$ Hz, OCH_2+H-α+H-6+H-α′+H-3+H-β″+Ar_2CH+Ar_2CHCH_2), 5.27–5.29 (1H, br d, NH, exchanges in ^2H_2O), 6.86–7.24 (3H, 6×br d, 3×NH, exchange in ^2H_2O) and 7.29–7.78 (8H, m, ArH); δ_C (125.8 MHz, $C^2H_3O^2H$) 14.86 (CH_3), 18.87, 20.26, 22.47 and 23.92 ($2\times C(CH_3)_2$), 26.37 (C-6), 27.5 (C-2), 28.83 ($OC(CH_3)_3$), 29.67 (C-1), 30.59 (C-7), 32.30 ($C(Ar)_2$), 32.61 (C-3), 37.91 (C-β″), 42.46 (C-β′), 51.90 (C-γ″), 55.52 (C-β), 58.82 ($OC(CH_3)_3$), 60.56 (C-α″), 61.70 (C-α′), 62.11 (C-α), 63.45 (OCH_2), 68.55 ($CCHAr_2$), 80.37 and 80.74 (C-8), 83.04 (quat C), 119.15 (CN), 121.43, 126.75, 128.69 and 129.30 (FmocCH), 143.10 (quat C), 145.62 and 145.89 (C-9), and 157.83–176.00 (6×C=O).

3.1.18. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-amino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (29). Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-(9*H*)-fluor-9-enylmethoxycarbonylamino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **28** (400 mg, 0.47 mmol) was dissolved in dimethylformamide (12 ml) and piperidine (3 ml, 20% by volume). The solution was stirred at room temperature under a nitrogen atmosphere for 1.5 h. The solvent was removed in vacuo to yield a pale yellow solid, which was purified by column chromatography on silica gel, eluting with a gradient of methanol/dichloromethane (1:99) to methanol in dichloromethane (4:96). This yielded ethyl (3*S*,6*RS*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-amino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **29** as a cream powder (260 mg, 87%), mp 92–94 °C; $[\alpha]_D^{29} = -86.94$ (*c* 1, $CHC1_3$); *m/z* [EI] Found: 632.35412. $C_{31}H_{48}N_6O_8$ requires 632.35336; *m/z* [+ve FAB (3-NBA)] 633 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3316 (br, NH), 2210 (CN), 1710 (ester) and 1662 (lactam); λ_{max} (MeOH)/nm 277 (ε 18,600); δ_H (360 MHz, C^2HC1_3) 0.94–0.97 (12H, m, $2\times C(CH_3)_2$), 1.26–1.33 (3H, m, $J=7.1$ Hz, CH_3), 1.44 and 1.45 (9H, 2×s, $OC(CH_3)_3$), 1.65–1.70 (3H, m, H-β+H-β′, masked by water peak), 2.22–2.26 (1H, m, $J=7$ Hz, H-γ″), 2.35–2.38 (1H, m, $J_{2A,3}=8.3$ Hz, H-2A), 2.50–2.90 (3H, m, H-7+H-2B), 2.94–3.03 (3H, m, H-α″+H-1), 3.43–3.45 (2H, d, $J=7.3$ Hz, H-β″), 4.20–4.84 (6H, m, $J_{6,7A}=9.9$ Hz, $J_{6,7B}=6.3$ Hz, $J_{3,2A}=8.3$ Hz, OCH_2+H-α+H-α′+H-6+H-3), 6.60, 7.0–7.1, 7.2 and 8.25–8,4 (4H, 4×br d, 4×NH, exchange in ^2H_2O); δ_C (125.8 MHz, C^2HC1_3) 14.06 (CH_3), 17.17, 17.61, 19.21, 21.28 and 21.32 ($2\times C(CH_3)_2$), 23.36 and 24.85 (C-6), 26.12 and 26.45 (C-2), 27.67 and 28.62 (C-1), 28.02 ($OC(CH_3)_3$), 28.90 and 29.13 (C-β′), 29.69 and 30.36 (C-3), 36.53 and 36.76 (C-7), 43.87 and 43.97 (C-β″), 48.70 and 49.10 (C-γ″) 49.32 and 49.76 (C-β), 53.39 and 53.47 (C-α), 58.48 and 58.85 (C-α′), 59.77 and 59.99 (C-α″), 62.15 (OCH_2), 64.0 ($OC(CH_3)_3$), 80.22 and 80.38 (C-8), 117.24 and 117.41 (CN), 154.55 and 154.75 (C-9) and 165.98-176.58 (6×C=O).

3.1.19. Ethyl (3*S*,6*RS*)-6-[(2*S*)-2-((((2*S*)-2-(((2*S*)-2-(2-(9*H*)-fluor-9-enylmethoxycarbonylaminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate (30). Ethyl (3*S*,6*RS*)-6-[(((2*S*)-2-((2*S*)-2-((2*S*)-2-amino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **29** (200 mg, 0.32 mmol) and N-(9*H*)-fluor-9-enylmethoxycarbonylglycine (94 mg, 0.32 mmol) were dissolved in dimethylformamide (25 ml). TBTU (100 mg, 0.32 mmol) and di-isopropylethylamine (41 mg, 0.32 mmol) were added and the solution was stirred under nitrogen at room temperature for 12 h. The solvent was removed in vacuo (<50 °C) and the resulting oil was dissolved in dichloromethane. The solution was successively washed with 5% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried ($MgSO_4$). The solvent was removed in vacuo affording a pale yellow foam. This was triturated with diethyl ether and dried in vacuo to yield ethyl (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-((2*S*)-2-(2-(9*H*)-fluor-9-enylmethoxycarbonylacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **30** as a cream solid (280 mg, 97%), mp 171–172 °C; $[\alpha]_D^{26} = -36.13$ (*c* 0.3, $CHC1_3$); *m/z* [+ve FAB (3-NBA)] 912 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3282 (br, NH), 2211 (CN), 1710 (ester) and 1638 (lactam); λ_{max} (MeOH)/nm 265 (ε 29,400); δ_H (360 MHz, $C^2H_3O^2H$) 0.94–0.99 (12H, m, $2\times C(CH_3)_2$),1.25–1.40 (3H, m, $J=7.1$ Hz, CH_3), 1.44 and 1.45 (9H, 2×s, $OC(CH_3)_3$), 1.50–1.62 (3H, m, H-β+H-β′), 2.10–2.25 (2H, m, H-γ″+H-2A), 2.30–2.48 (1H, m, $J_{2B,3}=3.7$ Hz, H-2B), 2.55–2.75 (2H, m, $J_{7A,6}=7.5$ Hz, H-7), 2.84–3.02 (3H, m, H-1+H-α″), 3.75 (2H, s, H-α‴), 4.15–4.85 (11H, m, $J_{6,7A}=7.5$ Hz, $J_{6,7B}=5.2$ Hz, $J_{3,2A}=8.6$ Hz, $J_{3,2B}=3.7$ Hz, OCH_2+H-α+H-6+H-3+H-α′+H-β″+Ar_2CH+Ar_2CHCH_2) and 7.25–7.80 (8H, m, ArH); δ_C (125.8 MHz, $C^2H_3O^2H$) 14.85 (CH_3), 15.92–22.41 ($2\times C(CH_3)_2$), 23.90 (C-6), 26.32 (CAr_2), 27.44 and 27.55 (C-α‴), 28.83 ($C(CH_3)_3$), 29.22 and 29.70 (C-2), 30.52 and 30.60 (C-1), 32.12 and 32.52 (C-3), 37.91 and 38.12 (C-7), 42.11 (C-β′), 45.46 (C-β″), 50.58 (C-γ″), 52.06 and 52.49 (C-β), 53.86 and 54.03 (C-α″), 60.52 and 60.85 (C-α′), 61.82 and 62.02 (C-α), 63.41 and 63.49 (OCH_2), 67.36 ($OC(CH_3)_3$), 68.75 ($CCHAr_2$), 80.36 and 80.71 (C-8), 82.94 and 83.05 (quat C), 119.09 (CN), 121.40–129.27 (FmocCH), 143.63 (quat C), 145.63 (C-9) and 157.50–175.19 (8×–C=O).

3.1.20. Ethyl (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-(((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate

(31). Ethyl (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-(((2*S*)-2-(2-(9*H*)-fluor-9-enylmethoxycarbonylacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **30** (250 mg, 0.27 mmol) was dissolved in dimethylformamide (8 ml) and piperidine (2 ml, 20% by volume). The solution was stirred at room temperature under a nitrogen atmosphere for 2 h. The solvent was removed in vacuo to yield a cream solid, which was purified by column chromatography on silica gel, eluting with a gradient of methanol/dichloromethane (1:99) to methanol/dichloromethane (1:9). This yielded ethyl (3*S*,6*RS*)-6-[((((2*S*)-(((2*S*)-2-(((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **31** as a white powder (180 mg, 95%), mp 103–105 °C; $[\alpha]_D^{26} = -65.24$ (*c* 1, $CHC1_3$); *m/z* [EI] Found: 689.37462. $C_{33}H_{51}N_7O_9$ requires 689.37483; *m/z* [+ve FAB (3-NBA)] 712 ($[M+Na]^+$) and 690 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3413 (br, NH), 2210 (CN), 1710 (ester) and 1639 (lactam); λ_{max} (MeOH)/nm 275 (ε 23,600); δ_H (600 MHz, $C^2H_3O^2H$) 0.90–1.05 (12H, m, $2\times C(CH_3)_2$), 1.25–1.30 (3H, m, $J=7.1$ Hz, CH_3), 1.44 and 1.45 (9H, 2× s, $OC(CH_3)_3$), 1.58–1.65 (2H, m, $J_{\beta',\alpha'}=8.8$ Hz, H-β′), 1.65–1.72 (1H, m, H-β), 2.12–2.26 (1.5H, m, H-γ″+H-1A), 2.40–2.50 (1H, m, H-1B), 2.61–2.77 (3H, m, $J_{2A,3}=8$ Hz, $J_{7A,6}=8.4$ Hz, H-2A+H-7), 2.80–3.03 (2.5H, m, H-2B+H-1A+H-α″), 3.38 (2H, s, H-α‴), 4.18–4.29 (4H, m, OCH_2+H-β″), 4.39–4.45 (2H, m, $J_{\alpha',\beta'}=8.8$ Hz, H-α+H-α′) and 4.63–4.75 (2H, m, $J_{6,7A}=8.4$ Hz, $J_{3,2A}=8$ Hz, H-6+H-3); δ_C (125.8 MHz, C^2HC1_3) 13.93 (CH_3), 17.74–22.66 ($2\times C(CH_3)_2$), 24.79 (C-6), 26.03 and 26.21 (C-α‴), 27.60 and 28.52 (C-2), 27.86 ($OC(CH_3)_3$), 28.85 and 29.04 (C-β′), 30.41 and 30.83 (C-γ″), 37.07 and 37.56 (C-1), 41.36 and 41.74 (C-β″), 44.63 (C-7), 48.17 and 49.02 (C-3), 49.43 and 49.70 (C-β), 51.57 and 51.74 (C-α″), 58.48 (C-α′), 59.67 and 59.87 (C-α), 61.87 (OCH_2), 79.69 and 79.75 ($OC(CH_3)_3$), 81.41 and 81.55 (C-8), 117.41 and 117.53 (CN), 154.79 (C-9) and 166.16-173.27 (7×C=O).

3.1.21. (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylic acid (32). Ethyl (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **31** (80 mg, 0.12 mmol) was dissolved in methanol/water (5:1, 24 ml) and the solution was stirred at room temperature. Aqueous sodium hydroxide (0.05 mol dm^{-3}) (7 ml) was added dropwise by means of an autoburette (Radiometer) with a fixed endpoint of pH 11.0 for 24 h. The solution was then acidified to pH 5.0 by addition of 5% aqueous citric acid and concentrated in vacuo. The resulting aqueous solution was washed with ethyl acetate and freeze-dried to yield a white solid. This was purified by preparative reverse phase HPLC on a Zorbax C8 column (25 cm×22.2 mm), eluting with 0.2% trifluoroacetic acid in acetonitrile and 0.2% trifluoroacetic acid in water, fractionating at 30 s intervals. Samples judged to be homogeneous by analytical reverse phase HPLC on a Zorbax C8 column (25 cm×4.6 mm) were pooled and lyophilised. This resulted in (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylic acid **32** as a white solid (2 mg, 3%), mp 180–183 °C; *m/z* [+ve FAB (thioglycerol)l 662 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3290 (br, NH), 3000–2600 (COOH), 2200 (CN), 1664 (CONH) and 1645 (C=O); λ_{max} (MeOH)/nm 275 (ε 12,000); δ_H (600 MHz, $C^2H_3O^2H$) 0.91–0.99 (12H, m, $2\times C(CH_3)_2$), 1.44 and 1.45 (9H, 2× s, $OC(CH_3)_3$), 1.59–1.65 (2H, m, H-β′), 1.67–1.75 (1H, m, H-β), 2.10–2.19 (1H, m, H-γ″), 2.20–2.29 (1H, m, H-1A), 2.39–2.48 (1H, m, H-1B), 2.61–2.69 (1H, m, H-2A), 2.70–2.79 (1H, m, H-7A), 2.81–2.89 (1H, m, H-2B), 2.90–2.98 (1H, m, H-7B), 2.99–3.08 (1H, m, H-α″), 3.71 (2H, s, H-α‴), 4.21–4.29 (2H, m, H-β″), 4.40–4.48 (2H, m, H-α+H-α′), 4.62–4.68 (0.5H, m, H-6), 4.70–4.74 (1H, m, H-3) and 4.75–4.78 (0.5H, m, H-6).

3.1.22. (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-6-cyano-5-pyrrolidinylidine-2,8-dicarboxylate (33). Ethyl (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-8-cyano-5-oxo-1,2,3,5,6,7-hexahydroindolizine-3-carboxylate **31** (80 mg, 0.12 mmol) was dissolved in ethanol/water (5:1) (24 ml) and stirred at room temperature. Aqueous sodium hydroxide (0.05 mol dm^{-3}) (8.2 ml) was added dropwise by means of an autoburette (Radiometer) with a fixed endpoint of pH 11.0 for 24 h. The solution was acidified to pH 5.0 by addition of 5% aqueous citric acid and concentrated in vacuo. The resulting aqueous solution was washed with ethyl acetate and freeze-dried to a white solid. This was purified by preparative reverse phase HPLC on a Zorbax C8 column (25 cm×22.2 mm), eluting with 0.2% trifluoroacetic acid in acetonitrile and 0.2% trifluoroacetic acid in water, fractionating at 30 s intervals. Samples judged to be homogeneous by analytical reverse phase HPLC on a Zorbax C8 column (25 cm×4.6 mm) were pooled and lyophilised. This resulted in (3*S*,6*RS*)-6-[((((2*S*)-2-(((2*S*)-2-((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-6-cyano-5-pyrrolidinylidine-2,8-dicarboxylate **33** as a white solid (11 mg, 14%), mp 203–205 °C; *m/z* [+ve FAB (thioglycerol)] 680 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3292 (br, NH), 3000–2600 (COOH), 2200 (CN), 1718 (COOH), 1670 (CONH) and 1659 (C=O); λ_{max} (MeOH)/nm 266 (ε 21,500); δ_H (600 MHz, $C^2H_3O^2H$) 0.91–1.01 (12H, m, $2\times OC(CH_3)_2$), 1.44 and 1.45 (9H, 2× s, $OC(CH_3)_3$), 1.60–1.62 (2H, m, H-β′), 1.65–1.72 (1H, m, H-β), 2.06–2.20 (2H, m, H-γ″+H-4A), 2.36–2.42 (1H, m, H-4B), 2.52–2.59 (1H, m, H-7A), 2.62–2.71 (2H, m, H-3A,+H-7B), 2.74–2.80 (1H, m, H-α″), 2.85–2.91 (1H, m, H-3B), 3.72 (2H, s, H-α‴), 4.23–4.28 (0.5H, m, H-8), 4.29–4.38 (2H, m, H-β″), 4.40–4.45 (1H, m, H-α′), 4.48–4.51 (0.5H, m, H-8), 4.52–4.59 (1H, m, H-α) and 4.68–4.72 (1H, m, H-2); δ_C (128.5 MHz, $C^2H_3O^2H$) 18.73–23.84 ($C(CH_3)_2$), 26.39 (C-8), 28.59 (C-4), 28.88 ($OC(CH_3)_3$), 31.43 (C-3), 32.44 (C-β″), 32.59 (C-γ″). 38.32 (C-7), 41.94 (C-β′), 42.59 (C-α‴), 51.97 (C-2), 53.48 (C-β), 53.89 (C-α″), 60.21 (C-α′), 62.49 (C-α), 67.07 ($OC(CH_3)_3$), 83.22 (C-6), 119.75 (CN), 166.81 (C-5) and 167.81-176.86 (7×C=O).

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References and notes

1. Part of this work has been published as a preliminary communication in: Berry, J. M.; Doyle, P. M.; Young, D. W. *Tetrahedron Lett.* **2002**, *43*, 8963–8966.
2. Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1–109.
3. Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem.* **1980**, *8*, 315–399.
4. Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647–650.
5. Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1231–1234.
6. Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577–3592.
7. Wisskirchen, F. M.; Doyle, P. M.; Gough, S. L.; Harris, C. J.; Marshall, I. *Br. J. Pharm.* **1999**, *126*, 1163–1170.
8. Capps, N. K.; Davies, G. M.; Loakes, D.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4373–4381.
9. Capps, N. K.; Davies, G. M.; Loakes, D.; McCabe, R. W.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3077–3086.
10. Frankel, M.; Reichmann, M. E. *J. Chem. Soc.* **1952**, 289–291.
11. Öhler, E.; Schmidt, U. *Chem. Ber.* **1977**, *110*, 921–941.
12. Love, A. L.; Olsen, R. K. *J. Org. Chem.* **1972**, *37*, 3431–3433.
13. Millet, R.; Domarkas, J.; Rombaux, P.; Rigo, B.; Houssin, R.; Hénichart, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5087–5088.
14. Bergmann, M.; Grafe, K. *Z. Physiol. Chem.* **1930**, *187*, 187–195.
15. Fischer, E.; Boehner, R. *Ber.* **1911**, *44*, 1332–1337.
16. Doyle, P. M.; Harris, C. J.; Moody, C. M.; Sadler, P. J.; Sims, M.; Thornton, J. M.; Uppenbrink, J.; Viles, J. H. *Int. J. Pept. Protein Res.* **1996**, *47*, 427–436.
17. Sweet, R. M. In *Cephalosporins and Penicillins—Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; pp 305–306; and references cited therein.

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Synthesis of an external beta-turn based on the GLDV motif of cell adhesion proteins☆

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Abstract—The (3*S*,6*S*,10*S*)-7/5 bicyclic lactam **8**, designed as an external turn constraint, was synthesised by a new stereoselective route involving Eschenmoser condensation. The cyclic peptide **35** containing the integrin recognition motif GLDV added across the amino and carboxyl groups of the lactam external constraint **8** was prepared.
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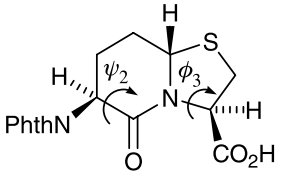
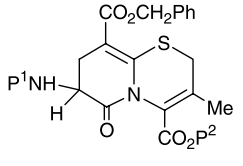
1. Introduction

Reverse turns connect elements of protein secondary structure and they usually occur on the surface of the protein. They can, therefore, be important in molecular recognition processes.[2,3] Synthetic molecules which mimic these turns, such as the classic 5/6 bicyclic lactam BTD, **1**, prepared by Nagai,[4–6] have been used to replace β-turns in various proteins without affecting their overall biological properties.[5–7] BTD, **1**, has been shown to be a type II′ β-turn mimic from the angles ψ_2 (−161°) and ϕ_3 (−69.4°) in the X-ray crystal structure.[8]



1

We have used BTD[9] as a structural constraint on which to build an external cyclic GLDV motif. This was shown induce a type I β-turn and to inhibit the interaction of the integrin $\alpha_4\beta_1$ with vascular cell adhesion molecule-1.[9] Using BTD as a model for an external β-turn, we have synthesised the putative external turn constraints, **2**, **3**, **4** and **5** (where P^1 and P^2 are protecting groups).[10]



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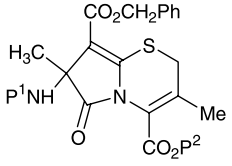

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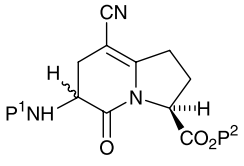

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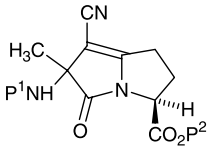

5

A linear GLDV construct was attached to the amino group of the template **4** but the acyl enamine nature of the template caused problems in the final hydrolysis and cyclisation steps which would have yielded the external GLDV turn. We therefore decided to prepare a homochiral bicyclic system in which the amide was not destabilised as an enamine and to use it as a template on which to build a cyclic GLDV turn.

Amino acid 7/5-bicyclic lactams of type **6** have found use as dipeptide surrogates in angiotensin-converting enzyme

☆ See Ref. 1.

Keywords: Bicyclic lactam; Integrin; Eschenmoser olefination.
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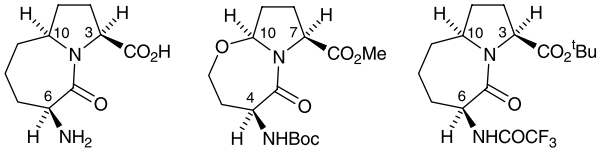
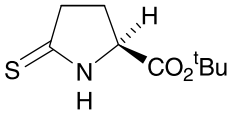
(ACE) inhibitors[11] and have been used as external constraints for tripeptide RGD turns which proved to be inhibitors of the $\alpha_V\beta_3$ integrin receptor.[12] The 7/5 bicyclic lactam **7** was synthesised using an electrochemical approach and conformational analysis showed that the (4*S*,7*S*,10*S*)-stereoisomer had families of minimum conformations with torsion angles close to those of classical β-turns.[13] We therefore decided to develop a new and stereoselective synthesis of the 7/5 bicyclic lactam, **8**, via a route involving Eschenmoser coupling and to use it as an external restraint for the GLDV motif present in the integrin family[14] of cell adhesion proteins.



6 **7** **8**

2. Results and discussion

As a first step in our synthesis of the bicyclic lactam **8**, we attempted to prepare the bromide **10** by the method used by Weygand[15] to obtain the corresponding ethyl ester bromide but without success. Modification of the method by reacting the diazoketone **9**[16] with HBr in $CHCl_3$, however, gave the α-bromoketone **10** in 89% yield, as shown in Scheme 1. On scale-up, the yield was reduced by the presence of the α-chloroketone **11**[17] but this could be separated out and converted to the α-bromoketone **10** in 85% yield by a Finkelstein reaction using lithium bromide in acetone.



12

A variety of methods were used in an attempt to complete the Eschenmoser olefination reaction between the bromoketone **10** and the thiolactone **12**.[18] When these compounds were heated at reflux in dichloromethane in the presence of solid sodium bicarbonate, then the only recognisable product was the disulfide **13**, obtained in 58% yield. When the bromide was heated at reflux with the thiolactam **12**[18] in CH_3CN, followed by addition of Ph_3P and triethylamine however, the desired product **14** was obtained as an oil. This was shown to be the *Z*-isomer by the NOE experiments summarised in Figure 1, since irradiation of the olefinic proton, H-6, caused enhancements to all four protons assigned to H-4 and H-8 in the ^{1}H NMR spectrum. The hydrogen bond between the N–H of the vinylogous amide and its carbonyl group, as shown, presumably accounts for this specificity. The highest yield of the product **14** that we could obtain was 30%.

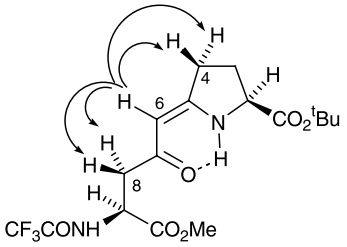
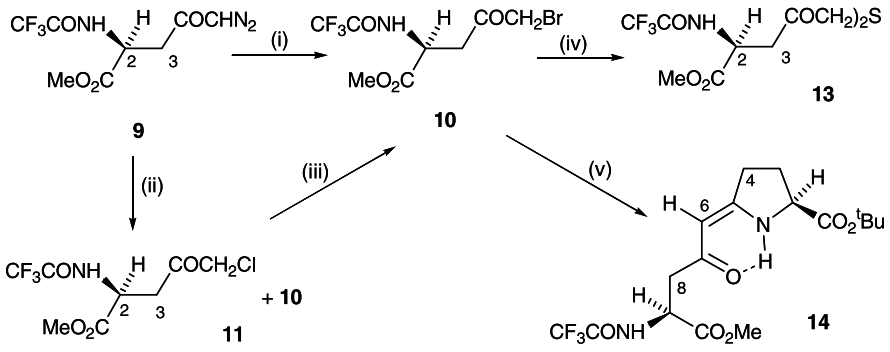


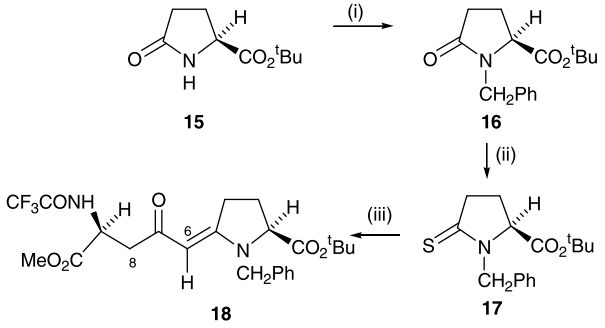
Figure 1. NOE experiments on compound **14**.

Since sulfur contraction reactions have been reported to be more effective when the thiolactam is trisubstituted,[19] we prepared the *N*-benzyl thiolactam **17** as shown in Scheme 2. This compound had previously been prepared by Rapoport[20] using a synthesis which involved *N*-alkylation of glutamic acid prior to cyclisation to avoid the danger of racemisation. We were able to alkylate *tert*-butyl (2*S*)-pyroglutamate **15** (prepared from commercial (2*S*)-pyroglutamic acid by the method of Miller[21]) directly to the *N*-benzyl derivative **16** in 64% yield using benzyl bromide and sodium hexamethyldisilazide. Reaction with P_4S_{10} then gave the thiolactam **17** in 95% yield with spectroscopic data similar to those reported by Rapoport.[20] Eschenmoser olefination using the bromide **10** and Ph_3P/Et_3N in CH_3CN then gave the vinylogous amide **18** as an oil in 91% yield.

NOE experiments on the *N*-benzyl derivative **18**, shown in Figure 2, indicated that it had *E*-stereochemistry. When the olefinic proton, H-6, was irradiated, both of the protons H-8 and one of the benzylic CH_2 protons showed enhancement, implying that, unlike the N–H analogue **14**, the *N*-benzyl compound **18** had *E*-geometry, as might be expected from



Scheme 1. Reagents and conditions: (i) HBr/$CHCl_3$, room temperature, (small scale) (89%); (ii) scale-up contains some **11**; (iii) LiBr/acetone/79 h/room temperature (80%); (iv) **12**/$NaHCO_3/CH_2Cl_2$, reflux (58%); (v) **12**/MeCN, reflux, then Ph_3P/Et_3N (30%).



Scheme 2. Reagents and conditions: (i) NaHMDS/$PhCH_2Br$/THF/−78 °C, (64%); (ii) P_4S_{10}/THF/room temperature (95%); (iii) **10**/Ph_3P/Et_3N/CH_3CN, room temperature (91%).

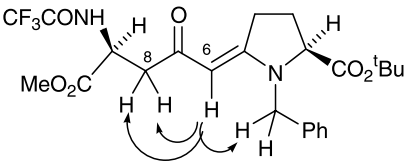


Figure 2. NOE experiments on compound **18**.

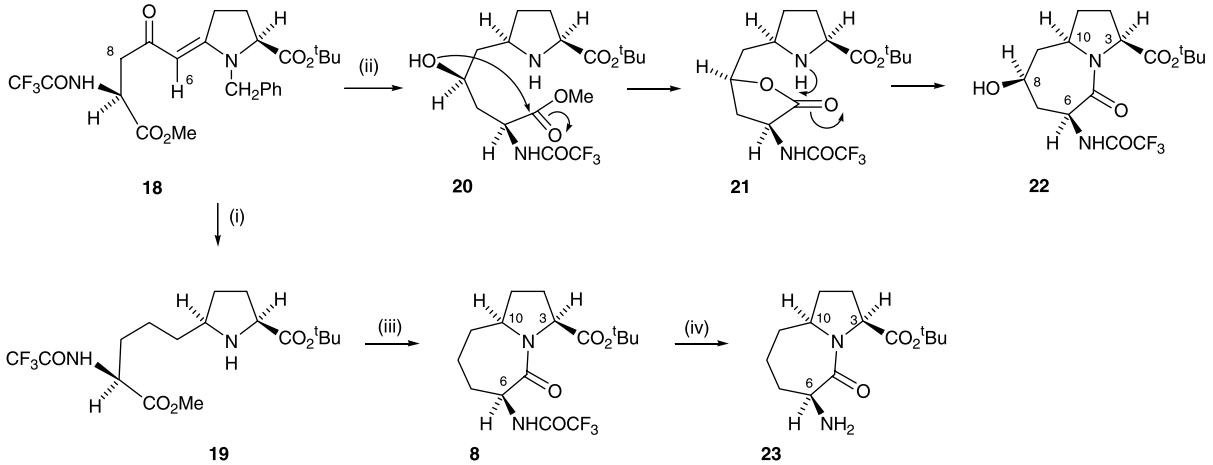
steric considerations in the absence of hydrogen bonding possibilities.

In order to reduce the vinylogous amide and hydrogenolyse the *N*-benzyl group in **18**, it was necessary to hydrogenate the compound at a pressure of 60–200 psi for 50 h using 10% palladium on activated carbon (75% by weight) in methanol containing trifluoroacetic acid as shown in Scheme 3. The resultant single diastereoisomeric product **19** was obtained as an oil in 65% yield, but NOE experiments were inconclusive as to its stereochemistry. Interestingly, in some of the hydrogenation experiments, a small yield of a by-product was obtained. This proved to be the bicyclic lactam alcohol **22**. The (3*S*,6*S*,8*S*,10*S*)-stereochemistry of this compound was implied from the NOE studies shown in Figure 3a, since irradiation at H-3 caused enhancement of H-10, and irradiation at H-10 caused enhancements at both H-8 and H-6. The fortuitous finding of the bicyclic compound **22** would have shortened our synthetic route to a homochiral 7/5-bicyclic external turn mimic but unfortunately we were unable to obtain it consistently and in good yield. The mechanism suggested in Scheme 3 would account for its formation. Here, incomplete reduction to the alcohol **20**, followed by lactonisation would give the product **21** which, on final cyclisation, would give the product **22**.

The amino ester **19** was cyclised using *t*BuMgCl in ether at 0 °C, giving the bicyclic lactam **8** in 29% yield. This was shown to have (3*S*,6*S*,10*S*) stereochemistry by the NOE studies summarised in Figure 3b, since H-10 showed enhancements when either H-3 or H-6 were irradiated. This stereochemistry was confirmed by the X-ray structure analysis, reported in our preliminary communication.[1]

Calculations of the conformational preferences of the compound **8**, reported in our preliminary communication,[1] indicated that the torsional minima for compound **8** were not compatible with it being a β-turn mimetic in its own right, and this was in agreement with the X-ray crystal structure analysis of the compound also reported in that paper.[1]

In order to examine the usefulness of the compound **8** as a constraint for an external β-turn involving the GLDV motif attached to its amino and carboxyl groups, we hydrolysed the trifluoroacetylamide using K_2CO_3 in methanol at reflux, as shown in Scheme 3. This gave the amine **23** in 86% yield. Synthesis of the linear GLDV tetrapeptide on the free amine group of compound **23** was now undertaken using Fmoc technology as shown in Scheme 4. Reaction of the amine **23** with Fmoc-valine, TBTU and DIPEA gave the product **24** in 80% yield, as shown in Scheme 4. Since it was essential to protect the β-carboxyl group of the aspartate residue in GLDV as the *tert*-butyl ester to prevent intramolecular cyclisation reactions, we now needed to change the orthogonality of our protecting groups. The Fmoc-*tert*-butyl ester **24** was therefore deprotected using TFA to give the acid **25** in quantitative yield. Reprotection using diphenyldiazomethane yielded the ester **26** as an oil in 64% yield. This was now sequentially deprotected with piperidine and reacted in turn with Fmoc-Asp(O^{t}Bu)-OH,



Scheme 3. Reagents and conditions: (i) most occasions, H_2/Pd–C/MeOH/TFA/60–200 psi (56%) of **19**; (ii) on some occasions up to 17% of **22** were obtained; (iii) ^{t}BuMgCl/Et_2O/0 °C (29%); (iii) K_2CO_3/MeOH/△ (86%).

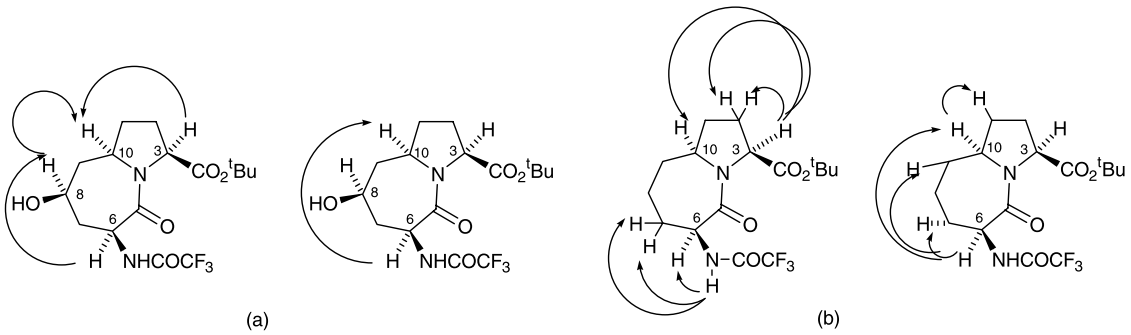
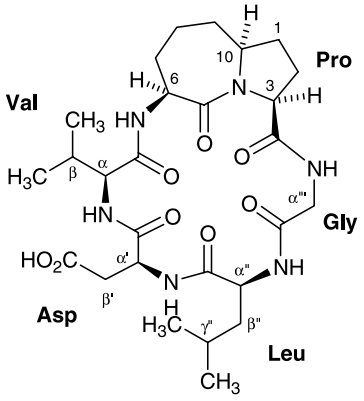


Figure 3. NOE experiments on (a) compound **22**, and (b) compound **8**.

Fmoc-Leu-OH and Cbz-Gly-OH to give the protected tetrapeptide **32**, as summarised in Scheme 4. Hydrogenolysis, cyclisation and final deprotection were then carried out, as in Scheme 4, and the final cyclic peptide **35** was purified by repeated reverse phase HPLC.



35

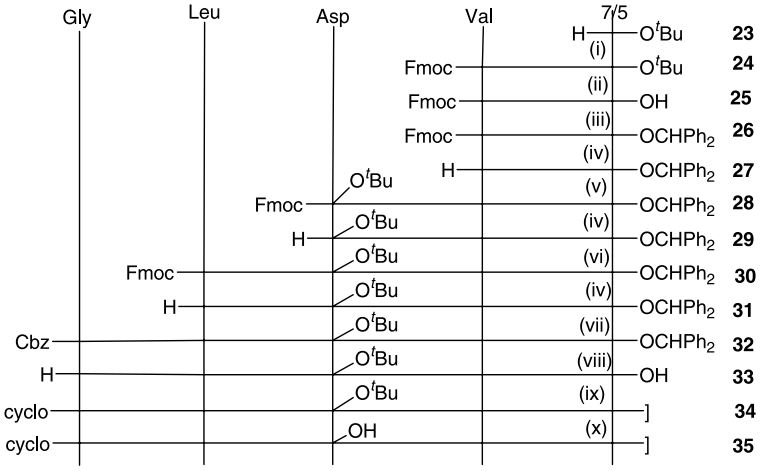
The high-resolution NMR spectroscopic data for this compound, reported in our preliminary communication, were consistent with a single backbone conformation with either type VI or type II′ β-turn properties.[22]

We have therefore prepared the homochiral external turn constraint **8** containing three chiral centres, and have affixed a cyclic GLDV sequence between the amino and carboxyl functionalities resulting in the presentation of the GLDV motif with either type VI or type II β-turn properties.

3. Experimental

3.1. General

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotation measurements (in units of 10^{-1} deg cm^2 g^{-1}) were measured on a Perkin Elmer PE241 polarimeter using a 1 dm path length micro cell. IR spectra were recorded on Perkin Elmer 1720 and Bio-Rad FTIR (FTS155) spectrometers. ^{1}H NMR spectra were recorded on Varian Inova 750 FT (750 MHz), and Bruker AMX500 FT (500 MHz), WM360 FT (360 MHz), DPX300 FT (300 MHz), ACP250 FT (250 MHz), AM250 FT (250 MHz) and DPX250 FT (250 MHz) instruments. *J* values are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on Bruker AMX500 FT (125.8 MHz), WM360 FT (100.5 MHz), DPX300 FT (75.5 MHz), DPX250 FT (62.9 MHz) and AM250 FT (62.9 MHz) instruments. DEPT experiments were used to help assign ^{13}C NMR spectra where necessary. Residual solvent peaks were used as internal reference for all NMR spectra. Microanalyses were performed by Ms. P. McDonough (GlaxoSmithKline) and



Scheme 4. Reagents and conditions: (i) TBTU/DIPEA/DMF/Fmoc-Val-OH (80%); (ii) CF_3CO_2H/CH_2Cl_2 (quant); (iii) Ph_2CHN_2/CH_2Cl_2 (64%); (iv) piperidine/DMF (>82%); (v) TBTU/DIPEA/Fmoc-Asp(O^{t}Bu)-OH (88%); (vi) TBTU/DIPEA/DMF/Fmoc-Leu-OH (82%); (vii) TBTU/DIPEA/Cbz-Gly-OH (81%); (viii) H_2/Pd–C/MeOH/THF (92%); (ix) TBTU/DMAP/DMF; (x) CF_3CO_2H/TES.

Medac Ltd. Mass spectra were recorded on Kratos MS80F and MS25 double focusing spectrometers by Dr. A. Abdul-Sada (Sussex) and a HP Engine (5989B) instrument operating in thermospray (positive ion) mode (GlaxoSmithKline). LC-mass spectra were obtained on a HP1100 HPLC coupled to a Micromass Platform II mass spectrometer operating in electrospray (positive and negative ion) mode. Accurate mass measurements were recorded by Mr. I. Davidson (GlaxoSmithKline), by Dr. A. Abdul-Sada (Sussex) and by the EPSRC National Mass Spectrometry Service, Swansea. Petroleum ether refers to that fraction of hexanes of bp 60–80 °C. HPLC studies on the cyclic peptide **35** were performed by Mr. Eric Horteuse (GlaxoSmithKline) and preparative HPLC was carried out using a Gilson Autoprep system and a Supelcosil LC-ABZ+ column.

3.1.1. Methyl (2*S*)-5-bromo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate (10). *Method A*. Methyl (2*S*)-5-diazo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **9** (3.6 g, 13.48 mmol) was dissolved in distilled chloroform (100 ml) and the mixture was stirred at room temperature. Hydrobromic acid (48%, ca. 25 ml) was added dropwise until nitrogen evolution ceased. The mixture was washed with de-ionised water (3×20 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give methyl (2*S*)-5-bromo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **10** as a pale yellow solid (3.83 g, 89%); mp 117–118 °C; $[\alpha]_D^{30}=+3.0$ (*c* 1.01, CH_2Cl_2). (Found: C 30.2; H 2.6; N 4.5. $C_8H_9NO_4BrF_3$ requires C 30.0; H 2.8; N 4.4%); *m/z* [+ve FAB (3-NBA)] 322 and 320 (1:1) ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 1750 (ester), 1727 (ketone) and 1705 (amide); δ_H (360 MHz, C^2HCl_3) 3.32 (1H, dd, $J_{3B,2}=4.1$ Hz, $J_{3A,3B}=18.6$ Hz, H-3A), 3.50 (1H, ABX, $J_{2A,3}=4.1$ Hz, $J_{3B,3A}=18.6$ Hz, H-3B), 3.80 (3H, s, OCH_3), 3.91 (2H, s, CH_2Br), 4.84 (1H, m, H-2) and 7.33 (1H, br s, NH, exchanges in ^2H_2O); δ_C (75.5 MHz, C^2HCl_3) 33.5 (CH_2Br), 40.9 (C-3), 48.9 (C-2), 53.5 (OCH_3), 169.7 (ester) and 200.5 (ketone).

On scale-up, varying amounts of methyl (2*S*)-5-chloro-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate, **11**, were obtained together with the bromide **10**. This compound had identical spectra to a sample prepared by Dr. R. A. August[17] with characterisation as follows: mp 131–133 °C, $[\alpha]_D^{23}=+55.9$ (*c* 1.1, $CHCl_3$). (Found C, 35.0; H. 3.1; N, 4.9. $C_8H_9ClF_3NO_4$ requires C, 34.9; H, 3.3; N, 5.1%); *m/z* (EI) 245 and 243 (1:3) ([M−MeOH]+); ν_{max} (KBr)/cm^{-1} 3301 (NH), 1747 (ester), 1739 (ketone) and 1708 (amide); δ_H (360 MHz, C^2HCl_3) 3.25 (1H, dd, $J_{3R,2}=4.2$ Hz, $J_{3R,3S}=18.9$ Hz, H-3*R*), 3.46 (1H, dd, $J_{3S,2}=4.2$ Hz, $J_{3S,3R}=18.9$ Hz, H-3*S*), 3.80 (3H, s, OCH_3), 4.11 (2H, s, CH_2Cl), 4.85 (1H, dt, $J_{2,3R}=J_{2,3S}=4.2$ Hz, $J_{2,NH}=7.8$ Hz, H-2) and 7.36 (1H, br d, NH).

Method B. Methyl (2*S*)-5-chloro-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **11** (3.79 g, 13.7 mmol) was dissolved in acetone (100 ml) with stirring at room temperature under nitrogen. Lithium bromide (11.9 g, 137 mmol) was added in one portion with vigorous stirring. After 19 h, a further portion of lithium bromide (5.97 g, 68.7 mmol) was added and the reaction mixture was vigorously stirred for a further 60 h. The solvent was removed in vacuo to yield an amber oil which was dissolved in dichloromethane (75 ml) and washed with water (75 ml). The aqueous layer was further washed with dichloromethane (2×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo to give methyl (2*S*)-5-bromo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **10** as a beige solid (3.752 g, 80%) with spectra identical to those of a sample prepared using method A.

3.1.2. Bis-[(2*S*)-2-oxo-4-(2,2,2-trifluoroacetamido)-4-carboxylmethylbutyl]sulfide (13). Methyl (2*S*)-5-bromo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **10** (426 mg, 1.33 mmol), *tert*-butyl (2*S*)-5-thioxoproline **12**[18] (116 mg, 0.57 mmol) and sodium bicarbonate (223 mg, 2.66 mmol) were heated at reflux in dichloromethane (15 ml) for 39 h. The mixture was allowed to cool to room temperature, filtered and the solvent was removed in vacuo. The resultant solid was purified by column chromatography, eluting with petroleum ether–ethyl acetate (1:1). Bis-[(2*S*)-2-oxo-4-(2,2,2-trifluoroacetamido)-4-carboxylmethylbutyl]sulfide **13** was collected as a yellow/orange solid which was recrystallised from chloroform (194 mg, 58%); $[\alpha]_D^{20}=-24.47$ (*c* 0.41, MeOH); *m/z* [+ve FAB (3-NBA)] 535 ($[M+Na]^+$) and 513 ($[M+H]^+$); *m/z* [EI] 512 ($[M]^+$); ν_{max} (film)/cm^{-1} 3311 (NH) and 1709 (br, amide and ketone); δ_H (500 MHz, $^2H_6$-DMSO) 3.06 (2H, dd, $J_{3A,2}=8.0$ Hz, $J_{3A,3B}=18.0$ Hz, H-3A), 3.22 (2H, dd, $J_{3B,2}=5.2$ Hz, $J_{3B,3A}=18.0$ Hz, H-3B), 3.47 (4H, d, $J=1.3$ Hz, CH_2S), 3.65 (6H, s, OCH_3), 4.71 (2H, ddd, $J_{2,3A}=8.0$ Hz, $J_{2,3B}=5.2$ Hz, $J_{2,NH}=7.6$ Hz, H-2) and 9.81 (2H, d, $J_{NH,2}=7.6$ Hz, NH); δ_C (125.8 MHz, $^2H_6$-DMSO) 40.56 (CH_2S), 40.74 (C-3), 48.12 (C-2), 52.55 (OCH_3), 114.50–116.80 (q, $^1J_{C,F}=288$ Hz, CF_3), 156.15 (q, $^2J_{C,F}=37$ Hz, CF_3CO), 169.99 (ester) and 201.63 (ketone).

3.1.3. Methyl (2*S*)-5-[(2*S*)-2-*tert*-butoxycarbonyl-5-pyrrolidinylidenyl]-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate (14). *tert*-Butyl (2*S*)-5-thioxoproline **12**[18] (49 mg, 0.25 mmol) and methyl (2*S*)-5-bromo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **10** (156 mg, 0.488 mmol) were heated at reflux in acetonitrile (5 ml) under nitrogen. After 1 h a solution of triphenylphosphine (258 mg, 0.975 mmol) and triethylamine (0.135 ml, 0.975 mmol) in acetonitrile (10 ml) was slowly added at a rate of ca. 0.5 ml/min. After addition was complete, the mixture was heated at reflux for 1 h and the solvent was removed in vacuo. The crude mixture was purified by column chromatography on silica gel, eluting with petroleum ether–ethyl acetate (2:1) to yield methyl (2*S*)-5-[(2*S*)-2-*tert*-butoxycarbonyl-5-pyrrolidinylidenyl]-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **14** as a yellow oil which foamed in vacuo (30 mg, 30%); $[\alpha]_D^{25}=+12.27$ (*c* 1, $CHCl_3$); *m/z* [EI] Found: 408.152141 ($[M]^+$). $C_{17}H_{23}N_2O_6F_3$ requires 408.150822; *m/z* [+ve FAB (3-NBA)] 409 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 3318 (NH), 3083 (=CH) and 1728 (ketone and amide); λ_{max} (MeOH)/nm 304 (ε 6604); δ_H (360 MHz, C^2HCl_3) 1.47 (9H, s, $C(CH_3)_3$), 2.05–2.32 (2H, m, H-3), 2.62–2.72 (2H, m, H-4), 2.79 (1H, dd, $J_{8A,9}=4.2$ Hz, $J_{8A,8B}=17.1$ Hz, H-8A), 3.17 (1H, dd, $J_{8B,9}=4.2$ Hz, $J_{8B,8A}=17.1$ Hz, H-8B), 3.75 (3H, s, OCH_3), 4.32 (1H, dd, $J_{2,3B}=5.4$ Hz, $J_{2,3A}=8.5$ Hz, H-2), 4.77 (1H, dt, $J_{9,8A}=J_{9,8B}=4.2$ Hz, $J_{9,NH}=7.2$ Hz, H-9), 5.09 (1H, s, =CH), 8.14 (1H, d, $J_{NH,9}=7.2$ Hz, NH, exchanges in ^2H_2O) and 9.78 (1H, s, NH, exchanges in

^2H_2O); δ_C (125.8 MHz, C^2HCl_3) 25.54 (C-3), 27.87 ($C(CH_3)_3$), 31.56 (C-4), 40.55 (C-8), 49.34 (C-2), 52.86 (C-9), 60.50 (*C*=CH), 61.82 (OCH_3), 82.53 ($OC(CH_3)_3$), 89.72 (C=*C*H), 111–119 (q, $^1J_{C,F}=287$ Hz, CF_3), 156–157 (q, $^2J_{C,F}=38$ Hz, CF_3*C*ONH), 167.69 (ester), 170.45 (ester) and 193.26 (ketone).

3.1.4. *tert*-Butyl (2*S*)-1-benzylpyroglutamate (16). *tert*-Butyl (2*S*)-pyroglutamate **15**[21] (5.1 g, 27.6 mmol) was dissolved in anhydrous THF (50 ml) in a flask purged with nitrogen. The solution was cooled to −78 °C and an approximately 1 M solution of sodium hexamethyldisilazide in THF (30.3 ml, 30.3 mmol) was slowly added via syringe, over a period of 20 min. After stirring for 1 h at −78 °C, benzyl bromide (3.2 ml, 27 mmol) was added over 3–4 min. After 2.5 h the solution was slowly allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate (50 ml). The solution was washed with water (50 ml) and the aqueous layer was extracted with ethyl acetate (3×25 ml). The combined organic layers were dried ($MgSO_4$) and the solvents were removed in vacuo to give an oil which was purified by column chromatography on silica gel, eluting with cyclohexane–ethyl acetate (3:2). *tert*-Butyl (2*S*)-1-benzylpyroglutamate **16** was obtained as a white solid (4.47 g, 59%); mp 59–61 °C, $[\alpha]_D^{25}=+36.87$ (*c* 1, $CHCl_3$) (lit. mp[20] 62–63 °C, lit.[23] $[\alpha]_D^{20}=+40.3$ (*c* 0.51, $CHCl_3$). (Found: C, 69.5; H, 7.7; N, 4.9. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7; N, 5.1%); *m/z* [electrospray] 276 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 1740 (ester) and 1676 (lactam); δ_H (300 MHz, C^2HCl_3) 1.37 (9H, s, $C(CH_3)_3$), 1.41–2.08 (1H, m, H-3A), 2.11–2.21 (1H, m, H-3B), 2.29–2.39 (1H, m, H-4A), 2.44–2.52 (1H, m, H-4B), 3.76 (1H, dd, $J_{2,3A}=3.3$ Hz, $J_{2,3B}=9.1$ Hz, H-2), 3.88 (1H, d, $J_{AB}=14.8$ Hz, $PhCH_AN$), 4.99 (1H, d, $J_{BA}=14.8$ Hz, $PhCH_BN$) and 7.13–7.29 (5H, m, aromatics); δ_C (75.5 MHz, C^2HCl_3) 23.2 (C-3), 28.3 ($C(CH_3)_3$), 30.0 (C-4), 45.9 (NCH_2Ph), 59.9 (C-2), 82.6 ($OC(CH_3)_3$), 128.1, 128.9, 129.1 and 136.3 (aromatics), 171.1 (ester) and 175.5 (amide).

3.1.5. *tert*-Butyl (2*S*)-1-benzyl-5-thioxoproline (17). This was prepared using the method of Rapoport[20] from *tert*-butyl 1-benzyl-(2*S*)-pyroglutamate **16** as a white solid (88% yield); mp 84.8–85.9 °C (lit.[20] 78–79 °C). (Found: C, 65.8; H, 7.4; N, 4.8; S, 10.9. $C_{16}H_{21}NO_2S$ requires C, 65.95; H, 7.3; N, 4.8; S, 11.0%); *m/z* [+ve electrospray] 292 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 1730 (ester); δ_H (300 MHz, C^2HCl_3) 1.43 (9H, s, $C(CH_3)_3$), 2.10–2.35 (2H, m, H-3) 3.05–3.2 (2H, m, H-4), 4.08 (1H, dd, $J_{2,3B}=3.3$ Hz, $J_{2,3A}=9.3$ Hz, H-2), 4.21 (1H, d, $J_{AB}=14.6$ Hz, $PhCH_AN$), 4.75 (1H, d, $J_{BA}=14.6$ Hz, $PhCH_BN$) and 7.20–7.30 (5H, m, aromatics); δ_C (75.5 MHz, C^2HCl_3) 23.8 (C-3), 26.8 ($C(CH_3)_3$), 42.48 (C-4), 49.45 (NCH_2Ph), 65.33 (C-2), 81.87 ($OC(CH_3)_3$), 127.16–133.65 (aromatics), 168.17 (ester) and 202.59 (C=S).

3.1.6. Methyl (2*S*)-5-[(2*S*)-1-benzyl-2-*tert*-butoxycarbonyl-5-pyrrolidinylidenyl]-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate (18). *tert*-Butyl (2*S*)-1-benzyl-5-thioxoproline **17** (2.49 g, 8.55 mmol) and methyl (2*S*)-5-bromo-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **10** (4.10 g, 12.8 mmol) were mixed in a flask purged with nitrogen. Acetonitrile (25 ml) was added via syringe and the solution was stirred under nitrogen, at room temperature, for 46 h. The mixture was diluted with dichloromethane (15 ml). A solution of triphenylphosphine (4.45 g, 17 mmol) in dichloromethane (10 ml) was added via syringe and, after stirring for 10 min, triethylamine (3.6 ml, 25.6 mmol) was slowly added. The mixture was stirred under nitrogen for a further 24 h at room temperature and the solvents were removed in vacuo to yield a yellow/brown solid which was purified by column chromatography on silica gel eluting with cyclohexane–ethyl acetate (2:1). This afforded methyl (2*S*)-5-[(2*S*)-1-benzyl-2-*tert*-butoxycarbonyl-5-pyrrolidinylidenyl]-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **18** as an amber oil (3.86 g, 91%); $[\alpha]_D^{32}=+122.6$ (*c* 1.025, $CHCl_3$); *m/z* [EI] Found: 498.198641 ($[M]^+$). $C_{24}H_{29}N_2O_6F_3$ requires 498.197772; *m/z* [+ve FAB (3-NBA)] 499 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 3315 (NH), 3065 (NH) and 1735 (br, ester); λ_{max} (MeOH)/nm 305 (ε 24,750); δ_H (300 MHz, C^2HCl_3) 1.41 (9H, s, $C(CH_3)_3$), 2.06–2.26 (2H, m, H-3), 2.81 (1H, dd, $J_{8A,9}=4.0$ Hz, $J_{8A,8B}=17.0$ Hz, H-8A), 3.03–3.12 (1H, m, H-4A), 3.21 (1H, dd, $J_{8B,9}=4.0$ Hz, $J_{8A,8B}=17.0$ Hz, H-8B), 3.38–3.47 (1H, m, H-4B), 3.75 (3H, s, OCH_3), 3.98 (1H, dd, $J_{2,3B}=3.1$ Hz, $J_{2,3A}=9.1$ Hz, H-2), 4.22 (1H, d, $J_{AB}=15.6$ Hz, $PhCH_AN$), 4.61 (1H, d, $J_{BA}=15.6$ Hz, $PhCH_BN$), 4.71 (1H, ddd, $J_{9,8A}=J_{9,8B}=4.0$ Hz, $J_{9,NH}=7.7$ Hz, H-9), 5.18 (1H, s, =CH), 7.14–7.38 (5H, m, aromatics) and 7.99 (1H, d, $J_{NH,9}=7.7$ Hz, NH, exchanges in ^2H_2O); δ_C (75.5 MHz, C^2HCl_3) 26.46 (C-3), 28.26 ($C(CH_3)_3$), 32.66 (C-4), 42.82 (C-8), 49.73 (C-2), 49.89 (NCH_2Ph), 53.25 (C-9), 60.42 (*C*=CH), 65.30 (OCH_3), 82.94 ($OC(CH_3)_3$), 90.23 (C=*C*H), 111–123 (q, $^1J_{C,F}=289$ Hz, CF_3), 128.00–129.34 and 135.03 (aromatics), 156–157 (q, $^2J_{C,F}=36$ Hz, CF_3CO), 167.36 (ester), 170.97 (ester) and 193.31 (ketone).

3.1.7. Reduction of methyl (2*S*)-5-[(2*S*)-1-benzyl-2-*tert*-butoxycarbonyl-5-pyrrolidinylidenyl]-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate 18. Trifluoroacetic acid (0.97 ml, 13 mmol) and 10% palladium on activated carbon (2.30 g, 75% by weight) were added to a solution of methyl (2*S*)-5-[(2*S*)-1-benzyl-2-*tert*-butoxycarbonyl-5-pyrrolidinylidenyl]-4-oxo-2-(2,2,2-trifluoroacetamido)-pentanoate **18** (3.081 g, 6.18 mmol) in methanol (150 ml). The suspension was hydrogenated at 60 psi for 50 h in a Parr pressure reactor. The reaction vessel was repressurised as necessary. The mixture was filtered through Celite® and the filtrate was adjusted to pH 7 by addition of 2 M aqueous sodium hydroxide. The solvents were removed in vacuo and the residual oil was dissolved in dichloromethane (60 ml). The solution was washed with water (20 ml) and the aqueous layer was further extracted with dichloromethane (2×20 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo to yield a yellow oil which was purified by column chromatography on silica gel, eluting with ethyl acetate. This provided methyl (2*S*)-5-[(2*S*,5*S*)-2-*tert*-butoxycarbonyl-5-pyrrolidinyl]-2-(2,2,2-trifluoroacetamido)-pentanoate **19** as an amber oil (1.36 g, 56%); $[\alpha]_D^{28}=+8.53$ (*c* 1, $CHCl_3$); *m/z* [EI] Found: 397.194013 ($[M+H]^+$). [$C_{17}H_{27}N_2O_5F_3+H$] requires 397.195032; *m/z* [+ve FAB (3-NBA)] 397 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 3326 (NH) and 1724 (ester); δ_H (360 MHz, C^2HCl_3) 1.16–1.27 (2H, m, H-7), 1.45 (9H, s, $C(CH_3)_3$), 1.54–1.57 (2H, m, H-4), 1.82–2.08 (6H, m, H-3, H-6+H-8), 2.60 (>1H, br s, NH, exchanges

in ^2H_2O), 3.01 (1H, br s, H-9), 3.62 (1H, dd, $J=4.9$, 9.2 Hz, H-5), 3.77 (3H, s, OCH_3), 4.55 (1H, br s, H-2) and 7.75 (1H, br s, NH, exchanges in ^2H_2O); δ_C (75.5 MHz, $^2H_6$-benzene) 23.18 (C-4), 28.05 ($C(CH_3)_3$), 30.72 and 31.02 (C-6 and C-7), 32.35 (C-3), 34.70 (C-8), 52.19 (OCH_3), 53.53 (C-9), 59.49 (C-5), 60.78 (C-2), 80.92 ($OC(CH_3)_3$), 171.59 (ester) and 174.64 (ester).

On one occasion repetition of the hydrogenation using identical quantities and conditions to those outlined above, gave a second product after purification by column chromatography. The second compound, *tert*-butyl (3*S*,6*S*,8*S*,10*S*)-8-hydroxy-6-(2,2,2-trifluoroacetylamino)-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **22** was collected as a yellow crystalline solid (17% yield); mp 141–143 °C; $[\alpha]_D^{28}=+14.57$ (*c* 1, $CHCl_3$). (Found: C 50.8, H 6.1, N 7.3. $C_{16}H_{23}N_2O_5F_3$ requires C 50.5, H 6.1, N 7.4%); *m/z* [+ve electrospray] 381 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3407 (OH), 1733 (ester) and 1656 (amide); δ_H (250 MHz, C^2HCl_3) 1.48 (9H, s, $C(CH_3)_3$), 1.67–1.90 (3H, m, H-2 and H-7A), 2.04–2.19 (3H, m, H-1B and H-9), 2.25–2.40 (2H, m, H-1A and H-7B), 2.57 (1H, br s, OH, exchanges in ^2H_2O), 3.77–3.88 (1H, td, $J=7$ Hz, $J_{10,1A}=10$ Hz, H-10), 4.03–4.17 (1H, tt, $J_{8,9B/7B}=4$ Hz, $J_{8,9A/7A}=11$ Hz, H-8), 4.38 (1H, dd, $J_{6,NH}=6$ Hz, $J_{6,7}=11$ Hz, H-6), 4.55 (1H, t, $J_{3,2}=6$ Hz, H-3) and 7.99 (1H, d, $J_{NH,6}=6$ Hz, NH, exchanges in ^2H_2O); δ_C (100.5 MHz, C^2HCl_3) 27.77 (C-1), 27.93 ($C(CH_3)_3$), 32.66 (C-2), 38.57 (C-9), 42.52 (C-7), 49.13 (C-10), 54.64 (C-6), 61.51 (C-3), 69.68 (C-8), 82.05 ($OC(CH_3)_3$), 111–120 (q, $^1J_{C,F}=287.8$ Hz, CF_3), 156.0–156.5 (q, $^2J_{C,F}=37.4$ Hz, $COCF_3$), 168.16 (ester) and 170.40 (amide).

3.1.8. *tert*-Butyl (3*S*,6*S*,10*S*)-6-(2,2,2-trifluoroacetylamino)-5-oxo-octahydro-1*H*-pyrrolo [1,2-*a*]azepine-3-carboxylate (8). Methyl (2*S*)-5-[(2*S*,5*S*)-2-*tert*-butoxycarbonyl-5-pyrrolidinyl]-2-(2,2,2-trifluoroacetamido)-pentanoate **19** (1.30 g, 3.29 mmol) was dissolved in anhydrous diethyl ether (70 ml) under nitrogen. The solution was cooled to 0 °C and *tert*-butyl magnesium chloride in diethyl ether (ca. 2 M, 8.3 ml, 16.4 mmol) was added via syringe over a period of 30 min. A white precipitate instantly formed. The mixture was stirred at 0 °C for 2 h, the ice bath was removed and the solution was stirred overnight at room temperature. Saturated aqueous ammonium chloride (40 ml) was added and the aqueous layer was diluted with water until all of the precipitate had dissolved. The solution was extracted with diethyl ether (2×40 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo to give a yellow oil, which was purified by column chromatography on silica gel, eluting with cyclohexane–ethyl acetate (2:1). *tert*-Butyl (3*S*,6*S*,10*S*)-6-(2,2,2-trifluoroacetylamino)-5-oxo-octahydro-1*H*-pyrrolo [1,2-*a*]azepine-3-carboxylate **8** was collected as a yellow crystalline solid (338 mg, 29%); mp 127–129 °C; $[\alpha]_D^{32}=-20.6$ (*c* 1, $CHCl_3$). (Found: C 52.7; H 6.3; 7.6. $C_{16}H_{23}N_2O_4F_3$ requires C 52.7; H 6.4; N 7.7%); *m/z* [EI] Found 365.169228 ($[M+H]^+$). $[C_{16}H_{23}N_2O_4F_3+H]$ requires 365.168817; *m/z* [+ve electrospray] 387 ($[M+Na]^+$) and 365 ($[M+H]^+$); ν_{max} (KBr)/cm^{-1} 3343 (NH), 1734 (ester), 1700 and 1661 (amide); δ_H (300 MHz, C^2HCl_3) 1.42 (9H, s, $C(CH_3)_3$), 1.52–1.82 (5H, m, H-1B, H-9, H-8B, H-7B), 1.87–2.08 (4H, m, H-2, H-8A, H-7A), 2.19 (1H, dt, $J_{1A,2/10}=7.3$ Hz, $J_{1A,1B}=12.5$ Hz, H-1A), 3.76 (1H, dd, $J_{10,1A}=7.3$ Hz, $J=16.7$ Hz, H-10), 4.35 (1H, m, $J_{6,7B}=5.7$ Hz, $J_{6,7A}=10.5$ Hz, H-6), 4.48 (1H, t, $J_{3,2}=5.8$ Hz, H-3) and 7.88 (1H, br s, NH exchanges in ^2H_2O); δ_C (75.5 MHz, C^2HCl_3) 27.81 and 28.19 (C-1 and C-8), 28.41 ($C(CH_3)_3$), 30.51 (C-9), 33.22 (C-2), 34.51 (C-7), 54.23 (C-6), 59.75 (C-10), 61.91 (C-3), 82.25 ($OC(CH_3)_3$), 169.78 and 171.08 (2×C=O).

3.1.9. *tert*-Butyl (3*S*,6*S*,10*S*)-6-amino-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (23). A suspension of *tert*-butyl (3*S*,6*S*,10*S*)-6-(2,2,2-trifluoroacetylamino)-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **8** (158 mg, 0.434 mmol) and potassium carbonate (310 mg, 2.25 mmol) in methanol–water (12:1, 13 ml) was heated at reflux for 2 h. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (30 ml) and water (20 ml) was added. The aqueous layer was extracted with a further two portions of dichloromethane (30 ml). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed in vacuo to yield *t*-butyl (3*S*,6*S*,10*S*)-6-amino-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **23** as a yellow oil (100 mg, 86%); $[\alpha]_D^{23}=-80.76$ (*c* 1.01, CH_2Cl_2); *m/z* [+ve electrospray] Found: 268.178708 ($[M]^+$). $C_{14}H_{24}N_2O_3$ requires 268.178693; *m/z* [+ve thermospray] 269 ($[M+H]^+$); ν_{max} (diffuse reflectance)/cm^{-1} 3362 (NH), 1737 (ester) and 1657 (amide); δ_H (300 MHz, C^2HCl_3) 1.46 (9H, s, $C(CH_3)_3$), 1.55–1.80 (5H, m, H-1B, H-9B, H-8B, H-7), 1.87 (1H, br, H-9A), 1.96–2.02 (3H, m, H-2 and H-8A), 2.20 (1H, td, $J_{1A,10/2}=7.0$ Hz, $J_{1A,1B}=12.0$ Hz, H-1A), 2.29 (2H, br s, NH, exchanges in ^2H_2O), 3.46 (1H, br s, H-6), 3.75 (1H, dd, $J_{10,1A}=7.0$ Hz, $J=15.2$ Hz, H-10) and 4.49–4.54 (1H, t, $J_{3,2}=5.5$ Hz, H-3); δ_C (62.9 MHz, C^2HCl_3) 27.67 and 28.19 (C-1 and C-8), 28.02 ($C(CH_3)_3$), 29.70 (C-9), 33.07 (C-2), 34.58 (C-7), 55.16 (C-6), 58.69 (C-10), 61.51 (C-3), 81.26 ($OC(CH_3)_3$), 171.45 and 174.89 (2×C=O).

3.1.10. *tert*-Butyl (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (24). *tert*-Butyl (3*S*,6*S*,10*S*)-6-amino-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*] azepine-3-carboxylate **23** (100 mg, 0.373 mmol) and 9-fluorenylmethoxycarbonyl-(2*S*)-valine (127 mg, 0.373 mmol) were dissolved in dry dimethylformamide (7 ml) under nitrogen. 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (120 mg, 0.373 mmol) and diisopropylethylamine (0.065 ml, 0.373 mmol) were added and the solution was stirred overnight at room temperature. The solvent was removed in vacuo at 30 °C. The residue was dissolved in ethyl acetate (40 ml) and washed with 5% aqueous citric acid (2×15 ml), 5% aqueous sodium hydrogen carbonate (2×15 ml) and brine (2×15 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give a yellow oil which was purified by column chromatography on silica gel, eluting with methanol–dichloromethane (3:97) to give *tert*-butyl (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo [1,2-*a*]azepine-3-carboxylate **24** as a white solid (176 mg, 80%); mp 129–131 °C; $[\alpha]_D^{25}=-24.40$ (*c* 1.08, $CHCl_3$); *m/z* [electrospray] Found: 590.322190 ($[M+H]^+$). $[C_{34}H_{43}N_3O_6+H]$ requires 590.323012; ν_{max} (diffuse

reflectance)/cm^{-1} 3314 (NH), 1725 (ester) and 1638 (amide); δ_H (300 MHz, C^2HCl_3) 0.85 (6H, t, $J_{\beta,\beta\text{-Me}}$= 7.3 Hz, 2×β-Me), 1.38 (9H, s, C(CH_3)$_3$), 1.44–1.99 (>9H, m, H-2, H-1B, H-9, H-8 and H-7), 2.04–2.15 (2H, m, H-1A+H-β), 3.72 (1H, m, H-10), 4.04 (1H, dd, $J_{\alpha,\beta}$= 7.0 Hz, $J_{\alpha,NH}$=8.6 Hz, H-α), 4.14 (1H, t, $J_{6,7}$=7.0 Hz, H-6), 4.34–4.39 (3H, m, CH_2CH-fluorenenyl), 4.44 (1H, t, $J_{3,2}$=5.6 Hz, H-3), 5.53 (1H, d, $J_{NH,\alpha}$=8.6 Hz, NH exchanges in ^2H_2O) and 7.19–7.68 (8H, m, aromatics); δ_C (62.9 MHz, C^2HCl_3) 17.58 (β-Me), 27.46 and 27.65 (C-1 and C-8), 27.92 (C(CH_3)$_3$), 31.07, 32.78 and 34.14 (C-2, C-9 and C-7), 47.13 (C-α), 53.31 (C-β), 59.17 (C-6), 60.01 (C-10), 61.23 (C-3), 66.94 (Fmoc-CH_2), 81.52 (OC(CH$_3$)$_3$), 119.85–127.56, 141.20 and 143.89 (aromatics) and 170.50–170.83 (4×C=O).

3.1.11. (3*S*,6*S*,10*S*)-6-[(2*S*)-9-Fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (25). *tert*-Butyl (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **24** (375 mg, 0.634 mmol) was dissolved in dichloromethane (12 ml). Trifluoroacetic acid (4 ml) was added and the solution was stirred for 4 h at room temperature, during which time the yellow solution turned brown. The solvents were removed in vacuo to yield a brown oil which was washed with diethyl ether (4×10 ml). Removal of the solvents in vacuo followed by drying in vacuo yielded (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **25** as a yellow solid (379 mg, >quantitative); mp 131–132 °C; $[\alpha]_D^{26}=-69.57$ (*c* 0.465, $CHCl_3$); *m/z* [+ve electrospray] Found: 551.287467 ($[M+NH_4]^+$). [$C_{30}H_{35}N_3O_6+NH_4$] requires 551.286960; ν_{max} (KBr)/cm^{-1} 2927 (acid), 1719 (acid) and 1637 (amide); δ_H (250 MHz, C^2HCl_3/$C^2H_3O^2H$) 0.88 (6H, t, $J_{\beta\text{-Me},\beta}$=7.2 Hz, β-Me), 1.53–2.23 (11H, m, H-2, H-1, H-9, H-8, H-7 and H-β), 3.80 (1H, m, H-10), 4.01 (1H, m, H-α), 4.25–4.43 (4H, m, H-6 and CH_2CH-fluorenenyl), 4.55 (1H, dd, $J_{3,2B}$=4.2 Hz, $J_{3,2A}$=6.9 Hz, H-3), 5.82 (1H, d, *J*= 8 Hz, NH) and 7.21–7.72 (8H, m, aromatics); δ_C (75.5 MHz, C^2HCl_3) 14.59 and 18.23 (β-Me), 27.67 and 27.81 (C-1 and C-8), 30.12, 31.23, 33.34 and 34.35 (C-β, C-2, C-9 and C-7), 47.47 (C-α), 59.91 and 60.82 and 61.14 (C-6, C-10 and C-3), 67.78 (Fmoc-CH_2), 120.38–128.14, 141.61 and 144.26 (aromatics) and 157.09–170.83 (4×C=O).

3.1.12. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (26). (3*S*,6*S*,10*S*)-6-[(2*S*)-9-Fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*] azepine-3-carboxylate **25** (379 mg, 0.711 mmol) was dissolved in dichloromethane (25 ml). Diphenyldiazomethane (205 mg, 1.67 mmol)[24] was added via pipette. The pale brown solution turned red and there was some effervescence which quickly subsided. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo to yield a red oil which was purified by column chromatography on silica gel, eluting with petroleum ether–ethyl acetate (1:1) to give diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*] azepine-3-carboxylate **26** as a yellow oil (316 mg, 64%); $[\alpha]_D^{30}=-32.46$ (*c* 1, $CHCl_3$); *m/z* [+ve electrospray] Found: 717.364916 ($[M+NH_4]^+$)]. [$C_{43}H_{45}N_3O_6+NH_4$] requires 717.365211; *m/z* [+ve electrospray] 717 ([M+ $NH_4]^+$)] and 700 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 3309 (NH), 1720 (ester) and 1637 (amide); δ_H (300 MHz, C^2HCl_3) 0.85 (3H, d, $J_{\beta\text{-MeA},\beta}$=6.9 Hz, β-Me$_A$), 0.88 (3H, d, $J_{\beta\text{-MeB},\beta}$= 6.8 Hz, β-Me$_B$), 1.35–2.26 (11H, m, H-2, H-1, H-9, H-8, H-7+H-β), 3.75 (1H, m, H-10), 4.01–4.08 (1H, q, $J_{\alpha,\beta}$= 7.1 Hz, H-α), 4.13–4.39 (4H, m, H-6 and CH_2CH-fluorenenyl), 4.73 (1H, t, $J_{3,2}$=5.5 Hz, H-3), 5.42 (1H, d, *J*=8.7 Hz, NH), 6.79 (1H, s, OCHAr$_2$) and 7.18–7.69 (19H, m, NH+aromatics); δ_C (75.5 MHz, C^2HCl_3) 18.09 and 19.63 (β-Me), 27.93 (C-1 and C-8), 30.13, 31.43, 33.27 and 34.53 (C-β, C-2, C-9 and C-7), 47.62 (C-α), 59.63 and 60.57 and 61.02 (C-6, C-10 and C-3), 67.47 (Fmoc-CH_2), 78.44 (OCHAr$_2$), 120.38–129.01 and 139.88–144.69 (aromatics) and 156.70–171.27 (4×C=O).

3.1.13. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-amino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (27). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-9-fluorenylmethoxycarbonylamino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **26** (310 mg, 0.44 mmol) was dissolved in dry dimethylformamide (6 ml). Piperidine (1.2 ml, 20% by volume) was added and the solution was stirred at room temperature under nitrogen for 2.5 h. The solvent was removed in vacuo at <50 °C to yield a white solid which was purified by column chromatography on silica gel, eluting with a gradient of methanol–dichloromethane (1:99 to 5:95). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-amino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*] azepine-3-carboxylate **27** was collected as a yellow foam (182 mg, 87%); $[\alpha]_D^{30}=-16.18$ (*c* 1, $CHCl_3$); *m/z* [+ve electrospray] Found: 478.271527 ($[M+H]^+$). [$C_{28}H_{35}N_3O_4+H$] requires 478.270582; *m/z* [+ve electrospray] 955 ($[2M+H]^+$) and 478 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 3368 (NH), 1744 (ester) and 1640 (amide); δ_H (300 MHz, C^2HCl_3) 0.79 (3H, d, $J_{\beta\text{-MeA},\beta}$=6.9 Hz, β-Me$_A$), 0.92 (3H, d, $J_{\beta\text{-MeB},\beta}$=6.9 Hz, β-Me$_B$), 1.40–2.03 (>9H, m, H-2, H-1B, H-9, H-7, H-8), 2.10–2.20 (2H, m, H-β and H-1A), 2.28 (2H, br s, NH, exchanges in ^2H_2O), 3.21 (1H, br d, $J_{\alpha,\beta}$=3.9 Hz, H-α), 3.78 (1H, m, H-10), 4.41 (1H, br dd, *J*=6.5, 10.4 Hz, H-6), 4.73 (1H, dd, $J_{3,2B}$=4.0 Hz, $J_{3,2A}$= 7.6 Hz, H-3), 6.81 (1H, s, OCHAr$_2$), 7.19–7.94 (10H, m, aromatics) and 8.14 (1H, d, *J*=6.5 Hz, NH, exchanges in ^2H_2O); δ_C (75.5 MHz, C^2HCl_3) 16.87 and 19.97 (CH(CH_3)$_2$), 27.91 and 28.00 (C-1 and C-8), 31.58 (C-β), 31.65, 33.31 and 34.62 (C-2, C-9 and C-7), 53.49 (C-α), 59.55, 60.60 and 61.03 (C-6, C-10 and C-3), 78.30 (OCHAr$_2$), 126.30–129.45, 139.92 and 140.24 (aromatics) and 171.37–173.40 (3×C=O).

3.1.14. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((2*S*)-2-(9*H*)-fluoren-9-ylmethoxycarbonylamino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (28). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-amino-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **27** (170 mg, 0.356 mmol) and 4-*tert*-butyl *N*-9-fluorenylmethoxycarbonyl-(2*S*)-aspartate (161 mg, 0.392 mmol) were dissolved in dry dimethylformamide

(10 ml). 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (126 mg, 0.392 mmol) and diisopropylethylamine (0.068 ml, 0.392 mmol) were added and the solution was stirred under nitrogen at room temperature overnight. The solvent was removed in vacuo at <50 °C and the resulting oil was dissolved in dichloromethane and washed with 5% aqueous citric acid, 5% aqueous sodium hydrogen carbonate and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel, eluting with methanol–dichloromethane (3:97) to yield diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((2*S*)-2-(9*H*)-fluoren-9-ylmethoxycarbonylamino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **28** as a white powder (274 mg, 88%); $[\alpha]_D^{28} = -14.74$ (*c* 1, $CHCl_3$); *m/z* [+ve electrospray] Found: 888.455720 ($[M+NH_4]^+$). [$C_{51}H_{58}N_4O_9+NH_4$] requires 888.454754; *m/z* [+ve electrospray] 909 ($[M+K]^+$), 893 ($[M+Na]^+$) and 871 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 1729 (ester) and 1646 (amide); δ_H (300 MHz, C^2HCl_3) 0.93–0.98 (6H, t, $J_{\beta\text{-Me},\beta}=6.8$ Hz, β-Me, 1.46 (9H, s, $C(CH_3)_3$), 1.54–2.26 (11H, m, H-2, H-1, H-9, H-7, H-8+H-β), 2.73 (1H, dd, $J_{\beta'A,\alpha'}=6.7$ Hz, $J_{\beta'A,\beta'B}=17.4$ Hz, H-β'_A), 2.97 (1H, dd, $J_{\beta'B,\alpha'}=4.1$ Hz, $J_{\beta'B,\beta'A}=17.4$ Hz, H-β'_B), 3.82 (1H, m, *J*=9.4 Hz, H-10), 4.26 (1H, q, $J_{\alpha,\beta}=7.2$ Hz, H-α), 4.32 (1H, dd, $J_{6,NH}=5.6$ Hz, $J_{6,7}=8.2$ Hz, H-6), 4.42 (3H, br d, *J*=7.2 Hz, C*H*$_2$C*H*-fluorenenyl), 4.60 (1H, br s, H-3), 4.80 (1H, t, $J_{\alpha',\beta'}=5.2$ Hz, H-α′), 6.12 (1H, d, *J*=8.4 Hz, NH, exchanges in ^2H_2O), 6.89 (1H, s, $OCHAr_2$), 7.16 (1H, d, $J_{NH,6}=5.6$ Hz, NH, exchanges in ^2H_2O), 7.25–7.80 (18H, m, aromatics); δ_C (62.9 MHz, C^2HCl_3) 17.56 and 19.17 (β-Me), 27.42 (C-1 and C-8), 27.91 (C(*C*H$_3$)$_3$), 30.93 (C-β′ and C-β), 31.15, 32.76 and 37.41 (C-2, C-9 and C-7), 47.02 (C-α′), 53.27 (C-α), 58.62, 59.08 and 60.41 (C-6, C-10 and C-3), 67.25 (Fmoc*C*H$_2$), 76.49 (Fmoc-*C*H), 77.93 ($OCHAr_2$), 81.78 (O*C*(CH$_3$)$_3$), 119.90–128.49, 139.40 and 143.76 (aromatics) and 155.97–171.44 (6×C=O).

3.1.15. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((2*S*)-2-amino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (29). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((2*S*)-2-(9*H*)-fluoren-9-ylmethoxycarbonylamino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **28** (250 mg, 0.287 mmol) was dissolved in dry dimethylformamide (5 ml). Piperidine (1 ml, 20% by volume) was added and the solution was stirred at room temperature under nitrogen for 2 h. The solvent was removed in vacuo (<40 °C) and the residual oil was purified by column chromatography on silica gel, eluting with a gradient of methanol–dichloromethane (1:99–5:95). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((2*S*)-2-amino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **29** was collected as a white oily foam (152 mg, 82%); $[\alpha]_D^{28} = -42.91$ (*c* 1, $CHCl_3$); *m/z* [+ve FAB (PEGH/NOBA)] Found: 649.364583 ($[M+H]^+$). [$C_{36}H_{48}N_4O_7+H$] requires 649.360125; ν_{max} (film)/cm^{-1} 1727 (ester) and 1639 (amide); δ_H (250 MHz, $C^2HCl_3/C^2H_3O^2H$) 0.91 (6H, t, $J_{\beta\text{-Me},\beta}=7$ Hz, β-Me), 1.44 (9H, s, $C(CH_3)_3$), 1.47–2.27 (~11H, m, H-2, H-1, H-9, H-7, H-8 and H-β), 2.57 (1H, dd, $J_{\beta'A',\alpha'}=8$ Hz, $J_{\beta'A',\beta'B}=17$ Hz, H-β'_A), 2.81 (1H, dd, $J_{\beta'B,\alpha'}=4$ Hz, $J_{\beta'B,\beta'A}=17$ Hz, H-β'_B), 3.73 (1H, dd, $J_{\alpha',\beta'B}=4$ Hz, $J_{\alpha',\beta'A}=8$ Hz, H-α′), 3.83 (1H, br dd, *J*=8, 17 Hz, H-10), 4.23 (1H, dd, $J_{\alpha,\beta}=6$ Hz, $J_{\alpha,NH}=11$ Hz, H-α), 4.40 (1H, dd, *J*=7, 10 Hz, H-6), 4.76 (1H, dd, $J_{3,2B}=5$ Hz, $J_{3,2A}=7$ Hz, H-3), 6.84 (1H, s, $OCHAr_2$), 7.25–7.35 (10H, m, aromatics), 7.43 (1H, d, *J*=6 Hz, NH) and 8.00 (<1H, d, *J*=8 Hz, NH); δ_C (62.9 MHz, C^2HCl_3) 17.62 and 19.27 (2×β-Me), 27.44 (C-1 and C-8), 28.03 (C(*C*H$_3$)$_3$), 31.04 (C-β′ and C-β), 32.79, 34.09 and 39.87 (C-2, C-9 and C-7), 52.09 (C-α′), 53.28 (C-α), 58.26 (C-6), 59.13 (C-10), 60.53 (C-3), 77.92 (O*C*H(Ph)$_2$), 81.27 (O*C*(CH$_3$)$_3$), 128.98–128.47, 139.43 and 139.70 (aromatics) and 169.98–173.07 (5×C=O).

3.1.16. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-(9*H*)-fluor-9-enylmethoxycarbonylamino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (30). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((2*S*)-2-amino-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **29** (180 mg, 0.277 mmol) and 9-fluorenylmethoxycarbonyl-(2*S*)-leucine (108 mg, 0.305 mmol) were dissolved in dry dimethylformamide (3 ml). 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (98 mg, 0.305 mmol) and diisopropylethylamine (0.054 ml, 0.305 mmol) dissolved in dimethylformamide (1 ml) were added and the solution was stirred under nitrogen at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in dichloromethane and washed with 5% aqueous citric acid, followed by 5% aqueous sodium hydrogen carbonate and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give an oil which was purified by column chromatography on silica gel, eluting with methanol–dichloromethane (3:97). This yielded diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-(9*H*)-fluor-9-enylmethoxycarbonylamino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **30** as a white foam (223 mg, 82%); $[\alpha]_D^{29} = -30.65$ (*c* 1, $CHCl_3$); *m/z* [+ve FAB (3-NBA)] 983 ($[M]^+$); ν_{max} (film)/cm^{-1} 3301 (NH), 1723 (ester) and 1637 (amide); δ_H (300 MHz, C^2HCl_3) 0.80–0.85 (12H, m, β-Me+γ″-Me), 1.32 (9H, s, $C(CH_3)_3$), 1.40–1.99 (12H, m, H-2, H-1B, H-9, H-7, H-8, H-β″+H-γ″), 2.04–2.14 (2H, m, $J_{1A,10}=7.1$ Hz, H-1A and H-β), 2.58 (1H, dd, $J_{\beta'A,\beta'B}=17.0$ Hz, $J_{\beta A',\alpha'}=7.0$ Hz, H-β'_A), 2.74 (1H, dd, $J_{\beta'B,\beta'A}=17.0$ Hz, $J_{\beta B',\alpha'}=3.7$ Hz, H-β'_B), 3.70 (1H, br dd, *J*=7.1, 16.8 Hz, H-10), 4.13 (1H, t, $J_{6,7}=6.9$ Hz, H-6), 4.22–4.37 (5H, m, *J*=7.0 Hz, H-α, H-α″ and C*H*$_2$C*H*-fluorenenyl), 4.73 (2H, br dd, H-3 and H-α′), 5.35 (1H, d, *J*=7.9 Hz, NH, exchanges in ^2H_2O), 6.78 (1H, s, $OCHAr_2$), and 7.19–7.69 (21H, m, aromatics+3×NH, 3 protons exchange with ^2H_2O); δ_C (75.5 MHz, C^2HCl_3) 18.13, 19.67, 22.25 and 23.40 (β-Me+γ″-Me), 25.14 (C-γ″), 27.86–27.93 (C-1, C-8 and C-β′), 28.37 (C(*C*H$_3$)$_3$), 31.50, 33.25, 34.57 and 39.41 (C-2, C-9, C-7 and C-β), 42.29 (C-β″), 47.57, 53.60 and 53.70 (C-α, C-α′ and C-α″), 59.04, 59.53 and 60.92 (C-3, C-10 and C-6), 67.45 (Fmoc-*C*H$_2$), 78.32 (O*C*HAr_2), 82.28 (O*C*(CH$_3$)$_3$), 120.37–128.99 and 139.90–144.35 (aromatics) and 156.56–172.59 (7×C=O).

3.1.17. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-amino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (31). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-(9*H*)-fluor-9-enylmethoxycarbonylamino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **30** (200 mg, 0.203 mmol) was dissolved in dry dimethylformamide (6 ml). Piperidine (20% by volume, 1.2 ml) was added and the solution was stirred at room temperature under nitrogen for 2 h. The solvent was removed in vacuo at 40 °C. The residual oil was purified by column chromatography on silica gel, eluting with a gradient from pure dichloromethane to dichloromethane–methanol (95:5). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-amino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **31** was collected as a foam (137 mg, 88%); $[\alpha]_D^{27} = -41.12$ (*c* 0.98, $CHCl_3$); *m/z* [+ve FAB (PEGNa/NOBA)] Found: 762.445100 ($[M+H]^+$). $[C_{42}H_{59}N_5O_8+H]$ requires 762.444190; *m/z* [+ve FAB (3-NBA)] 762 ($[M+H]^+$); ν_{max} (film)/cm^{-1} 1735 (ester) and 1636 (amide); δ_H (250 MHz, C^2HCl_3) 0.89–0.97 (12H, m, β-Me+γ″-Me), 1.20 (9H, s, $C(CH_3)_3$), 1.51–2.25 (14H, m, H-2, H-1, H-9, H-7, H-8, H-β″+H-γ″+H-β), 2.50 (<2H, br s, NH_2, exchanges in ^2H_2O), 2.71 (1H, dd, $J_{\beta'A,\beta'B}$ 16.9 Hz, $J_{\beta'A,\alpha'}$=6.5 Hz, H-β′$_A$), 2.88 (1H, dd, $J_{\beta'B,\beta'A}$=16.9 Hz, $J_{\beta'B,\alpha'}$=5.2 Hz, H-β′$_B$), 3.50 (1H, m, H-α″), 3.80 (1H, br q, *J*=9.7 Hz, H-10), 4.25 (1H, dd, $J_{6,7}$=5.2 Hz, $J_{6,NH}$=8.1 Hz, H-6), 4.40 (1H, dd, *J*=6.0, 10.2 Hz, H-α), 4.77 (2H, br dd, H-3 and H-α′), 6.87 (1H, s, $OCHAr_2$), 7.20 (1H, d, *J*=6.0 Hz, NH, exchanges in ^2H_2O), 7.24–7.38 (11H, m, aromatics+NH, 1 proton exchanges in ^2H_2O) and 8.40 (1H, d, $J_{NH,6}$=8.1 Hz, NH, exchanges in ^2H_2O); δ_C (62.9 MHz, C^2HCl_3) 17.69, 19.22, 21.45 and 23.18 (β-Me+γ″-Me), 24.72 (C-γ″), 27.40 (C-1 and C-8), 27.94 ($C(CH_3)_3$), 30.89 (C-β+C-β′), 32.79, 34.10 and 36.92 (C-2, C-9 and C-7), 43.42 (C-β″), 53.23 and 53.38 (C-α and C-α′), 58.79, 59.10 and 60.51 (C-6, C-10 and C-3), 77.89 ($OCHAr_2$), 81.54 ($OC(CH_3)_3$), 126.95–128.48, 139.43 and 139.68 (aromatics) and 169.66–175.23 (6×C=O).

3.1.18. Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((((2*S*)-2-(((2*S*)-2-(2-carbobenzyloxyaminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (32). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-(((2*S*)-2-((2*S*)-2-amino-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **31** (109 mg, 0.143 mmol) and *N*-carbobenzyloxyglycine (33 mg, 0.158 mmol) were dissolved in dry dimethylformamide (5 ml). 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (51 mg, 0.158 mmol) and diisopropylethylamine (0.028 ml, 0.158 mmol) were added and the solution was stirred under nitrogen at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in dichloromethane and washed with 5% aqueous citric acid, followed by 5% aqueous sodium hydrogen carbonate and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo to give an oil which was purified by column chromatography on silica gel, eluting with methanol–dichloromethane (3:97). This gave diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((((2*S*)-2-(((2*S*)-2-(2-carbobenzyloxyaminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **32** as a white powder (110 mg, 81%); $[\alpha]_D^{30} = -29.68$ (*c* 1, $CHCl_3$); ν_{max} (film)/cm^{-1} 3276 (NH), 1730 (ester) and 1630 (amide); *m/z* [+ve FAB (3-NBA)] 975 ($[M+Na]^+$) and 953 ($[M+H]^+$); δ_H (250 MHz, 318 K, C^2HCl_3) 0.89–0.96 (12H, m, β-Me+γ″-Me), 1.41 (9H, s, $C(CH_3)_3$), 1.47–2.01 (>12H, m, H-2, H-1B, H-9, H-7, H-8, H-β″+H-γ″), 2.15 (2H, m, H-1A and H-β), 2.72 (1H, dd, $J_{\beta'A,\beta'B}$=16.6 Hz, $J_{\beta'A,\alpha'}$=6.8 Hz, H-β′$_A$), 2.84 (1H, dd, $J_{\beta'B,\beta'A}$=16.6 Hz, $J_{\beta'B,\alpha'}$=5.7 Hz, H-β′$_B$), 3.72–3.92 (3H, m, H-10 and H-α‴), 4.40 (2H, m, H-α and H-α‴), 4.61–4.78 (1H, m, *J*=5.4 Hz, H-6), 4.83 (2H, m, H-3 and H-α′), 5.12 (2H, d, *J*=5.4 Hz, $OCH_2C_6H_5$), 5.81 (1H, br s, NH, exchanges in ^2H_2O), 6.85 (1H, s, $OCHAr_2$), 7.00 (1H, d, *J*=6.6 Hz, NH, exchanges in ^2H_2O), 7.30–7.38 (15H, m, aromatics) and 7.63 (1H, d, *J*=7.7 Hz, NH, exchanges in ^2H_2O); δ_C (75.5 MHz, C^2HCl_3) 18.37, 19.64, 23.18 and 25.22 (β-Me+γ″-Me), 23.18 (C-γ″), 27.84 (C-1 and C-8), 28.36 ($C(CH_3)_3$), 31.53 (C-β), 31.75 (C-β″), 33.51, 34.53, and 38.29 (C-2, C-9 and C-7), 39.4 (C-β″), 42.30 (C-β′), 44.80 (C-α‴), 52.02 (C-α‴), 53.64 (C-α), 58.82, 59.27 and 60.73 (C-3, C-10 and C-6), 67.32 (OCH_2Ph), 78.31 ($OCHAr_2$), 81.71 ($OC(CH_3)_3$), 126.27–128.99, 136.92, 139.88 and 140.21 (aromatics) and 157.16–172.49 (8×C=O).

3.1.19. (3*S*,6*S*,10*S*)-6-[((((2*S*)-2-(((2*S*)-2-(((2*S*)-2-(2-Aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (33). Diphenylmethyl (3*S*,6*S*,10*S*)-6-[(2*S*)-2-((((2*S*)-2-(((2*S*)-2-(2-carbobenzyloxyaminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **32** (56 mg, 0.056 mmol) was dissolved in a 1:1 mixture of methanol and THF (6 ml). 10% Palladium on activated carbon (6 mg) was added and the reaction mixture was hydrogenated at atmospheric pressure for 4 h, at room temperature. The suspension was filtered through fine filter paper and the solvent was removed in vacuo to yield (3*S*,6*S*,10*S*)-6-[((((2*S*)-2-(((2*S*)-2-(((2*S*)-2-(2-aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **33** as a white solid (38 mg, 92%); $[\alpha]_D^{30} = -77.62$ (*c* 0.5, MeOH); *m/z* [+ve FAB (3-NBA)] 675 ($[M+Na]^+$), ν_{max} (film)/cm^{-1} 1723 (ester), 1710 (acid) 1639 (amide) and 1545 (amide); δ_H (300 MHz, $C^2H_3O^2H$) 0.83 (12H, t, *J*=6.8 Hz, β-Me+γ″-Me), 1.33 (9H, s, $C(CH_3)_3$), 1.48–2.07 (14H, m, H-2, H-1, H-9, H-7, H-8, H-β+H-β″+H-γ″), 2.53–2.90 (2H, m, H-β′), 3.37–3.62 (3H, m, H-10 and H-α‴), 3.79 and 4.13 (2H, m, H-α and H-α″), 4.34 (2H, m, H-6 and H-α′) and 4.63 (1H, m, H-3); δ_C (75.5 MHz, $C^2H_3O^2H$) 17.30, 18.59, 22.16 and 24.63 (β-Me+γ″-Me), 20.81 (C-γ″), 27.09 ($C(CH_3)_3$), 27.67 and 28.20 (C-1 and C-8), 30.99 (C-β), 30.41 (C-β″), 30.75, 32.87 and 33.87 (C-2, C-9 and C-7), 36.60 (C-β′), 40.89 (C-α‴), 48.27 (C-α), 52.23 (C-α″), 53.51 (C-α′), 59.33, 59.69 and 63.73

(C-3, C-10 and C-6), 81.22 ($OC(CH_3)_3$) and 126.05–171.36 (6×C=O).

3.1.20. (3*S*,6*S*,10*S*)-3,6-Cyclo-[glycyl-(2*S*)-leucyl-(4-*tert*-butyl (2*S*)-aspartyl)-(2*S*)-valylamino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine (34). (3*S*,6*S*,10*S*)-6-[((((2*S*)-2-(((2*S*)-2-(((2*S*)-2-(2-Aminoacetamido)-4-methylpentanamido)-4-*tert*-butoxycarbonylpropanamido)-3-methylbutanamido]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **33** (21 mg, 0.032 mmol) was dissolved in dry dimethylformamide (40 ml). 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (62 mg, 0.193 mmol) and dimethylaminopyridine (28 mg, 0.225 mmol) were added and the solution was stirred under nitrogen at room temperature for 28 h. An aliquot (1 ml) was removed from the reaction mixture and the solvent was removed in vacuo. FAB mass spectrometry showed no sign of any starting material and intense ions were observed for DMAP and the coupling reagents. $[M+Na]^+$ for (3*S*,6*S*,10*S*)-3,6-cyclo-[glycyl-(2*S*)-leucyl-(4-*tert*-butyl (2*S*)-aspartyl)-(2*S*)-valylamino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine **34** was also present at *m/z* 657. The solvent was removed in vacuo (<40 °C) and the residue was dissolved in dichloromethane and washed with 5% aqueous sodium hydrogen carbonate (2×15 ml) and brine (2×15 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. Attempts at purification by column chromatography and preparative HPLC were unsuccessful and so (3*S*,6*S*,10*S*)-3,6-cyclo-[glycyl-(2*S*)-leucyl-(*4-tert*-butyl (2*S*)-aspartyl)-(2*S*)-valylamino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine **34** was used directly in the next step without purification or analysis.

3.1.21. (3*S*,6*S*,10*S*)-3,6-Cyclo-[glycyl-(2*S*)-leucyl-(2*S*)-aspartyl-(2*S*)-valylamino]-5-oxo-octahydro-1*H*-pyrrolo [1,2-*a*]azepine (35). A solution of triethylsilane (0.15 ml) and trifluoroacetic acid (3 ml) was added to the crude (3*S*,6*S*,10*S*)-3,6-cyclo-[glycyl-(2*S*)-leucyl-(4-*tert*-butyl (2*S*)-aspartyl)-(2*S*)-valylamino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine **34** (13 mg, 0.0198 mmol) at 0 °C. The mixture was stirred under nitrogen at this temperature for 20 min, warmed to room temperature and stirred for a further 2 h. The solvents were removed in vacuo to yield a brown oil which was washed with diethyl ether (4×10 ml). Removal of the solvents in vacuo followed by drying in vacuo yielded a pale brown solid. The crude product was purified using preparative HPLC using a Supelcosil LC-ABZ+Plus column (10 cm, 21.2 mm diameter). The solvent gradient started at 100% H_2O (+0.1% TFA) and went to 95% CH_3CN (+0.05% TFA) over 17.5 min, then continued at 95% CH_3CN (+0.05% TFA) for 10 min. The retention time of the required compound was 15.5–16.0 min. The sample was obtained as a very fine glassy solid from freeze drying the combined fractions of multiple HPLC runs to give (3*S*,6*S*,10*S*)-3,6-cyclo-[glycyl-(2*S*)-leucyl-(2*S*)-aspartyl-(2*S*)-valylamino]-5-oxo-octahydro-1*H*-pyrrolo[1,2-*a*]azepine **35**; *m/z* [+ve electrospray] 579 ($[M+H]^+$); *m/z* [−ve electrospray] 577 ($[M-H]^+$); δ_H (750 MHz, H_2O: ^2H_2O (9:1) 0.77, 0.84 (6H, 2×s, β-Me), 0.83, 0.89 (6H, 2×s, γ″-Me), 1.39 (2H, m, H-9), 1.42, 1.75 (2H, 2×m, H-β″), 1.50 (1H, m, H-γ″), 1.61 (3H, m, H-7+H-1A), 1.67 (1H, m, H-1B), 1.88 (2H, m, H-8) 1.94, 2.10 (2H, 2×m, H-2), 2.36, 2.40 (2H, 2×m, H-β), 2.81, 2.91 (2H, 2×m, H-β′), 3.62, 4.01 (2H, 2×m, H-α‴), 4.35 (1H, m, H-α), 4.45 (1H, m, H-6), 4.47 (1H, m, H-3), 4.48 (1H, m, C-10) 4.53 (1H, m, H-α′), 4.78 (1H, m, H-α″), 7.24 (1H, d, $J_{\alpha,NH}$=9.5 Hz, α-NH), 7.53 (1H, d, $J_{6,NH}$=5.6 Hz, 6-NH), 8.40 (1H, d, $J_{NH,\alpha''}$=9.0 Hz, α″-NH), 8.58 (1H, d, $J_{NH,\alpha'}$=5.5 Hz, α′-NH) and 8.68 (1H, q, $J_{\alpha''',NH}$=5.4, 7.0 Hz, α‴-NH). ROESY data (200 ms mixing time—loosely characterised as strong (s), medium (m) or weak (w)). Intra-residue α/NH—Glyα (m/w), Glyα′ (s); Asp (m/w); Val (s); Leu (under H_2O peak. Intra-residue NH/βH-Asp (β&β′) (m); Leu-β (s); Val (m); also intra-residue α/β cross-peak for Val and sequential NH/NH (*i*, *i*+1) cross peaks for Asp/Val. The ^1H–^1H COSY spectrum is included as supplementary material.

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References and notes

1. Part of this work has been published as a preliminary communication in: Davies, D. E.; Doyle, P. M.; Farrant, R. D.; Hill, R. D.; Hitchcock, P. B.; Sanderson, P. N.; Young, D. W. *Tetrahedron Lett.* **2003**, *44*, 8887–8891.
2. Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1–109.
3. Smith, J. A.; Pease, L. G. *CRC Crit. Rev. Biochem.* **1980**, *8*, 315–399.
4. Nagai, U.; Sato, K. *Tetrahedron Lett.* **1985**, *26*, 647–650.
5. Sato, K.; Nagai, U. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1231–1234.
6. Nagai, U.; Sato, K.; Nakamura, R.; Kato, R. *Tetrahedron* **1993**, *49*, 3577–3592.
7. Wisskirchen, F. M.; Doyle, P. M.; Gough, S. L.; Harris, C. J.; Marshall, I. *Br. J. Pharm.* **1999**, *126*, 1163–1170.
8. Osano, Y. T.; Nagai, U.; Matsuzaki, T. *Anal. Sci.* **1989**, *5*, 625–626. The data are available from the Cambridge Crystallographic Data Centre, Cambridge, code number SEYZUR.
9. Doyle, P. M.; Harris, C. J.; Moody, C. M.; Sadler, P. J.; Sims, M.; Thornton, J. M.; Uppenbrink, J.; Viles, J. H. *Int. J. Peptide Protein Res.* **1996**, *47*, 427–436.
10. Berry, J. M.; Doyle, P. M.; Young, D. W. *Tetrahedron* **2004**, *60*, preceding paper. doi:10.1016/j.tet.2004.09.036.
11. Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Brown, B.; Ryono, D. E.; Bird, J. E.; Asaad, M. M.; Schaeffer, T. R.; Trippodo, N. C. *J. Med. Chem.* **1996**, *39*, 494–502.
12. Belvisi, L.; Bernardi, A.; Checchia, A.; Manzoni, L.; Potenza, D.; Scolastico, C.; Castorina, M.; Cupelli, A.; Giannini, G.; Carminati, P.; Pisano, C. *Org. Lett.* **2001**, *3*, 1001–1004.
13. Cornille, F.; Slomczynska, U.; Smythe, M. L.; Beusen, D. D.;

Moeller, K. D.; Marshall, G. R. *J. Am. Chem. Soc.* **1995**, *117*, 909–917.
14. Haubner, R.; Finsinger, D.; Kessler, H. *Angew. Chem. Int. Ed.* **1997**, *36*, 1374–1389.
15. Weygand, F.; Klinke, P.; Eigen, I. *Chem. Ber.* **1957**, *90*, 1896–1905.
16. Gani, D.; Young, D. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2393–2398.
17. First prepared by August, R. A. D. Phil Thesis, Sussex, 1987.
18. Andersen, T. P.; Rasmussen, P. B.; Thomsen, I.; Lawesson, S.-O.; Jørgensen, P.; Lindhardt, P. *Annalen* **1986**, 269–279.
19. Shiosaki, K. In Heathcock, C. H., Ed.; Comprehensive Organic Synthesis, Trost, B.; Fleming, I., Series Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 865–892.
20. Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc*. **1984**, *106*, 4539–4547.
21. Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1990**, *55*, 1711–1721.
22. Wilmot, C. M.; Thornton, J. M. *J. Mol. Biol.* **1998**, *203*, 221–232.
23. Takishi, I. *Tetrahedron* **2003**, *59*, 3527–3536.
24. Smith, L. I.; Howard, K. L. In *Organic Syntheses*; Horning E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 135.