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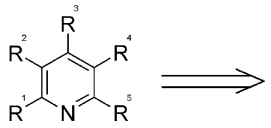
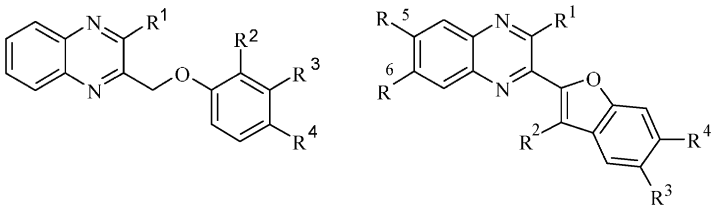
Contents

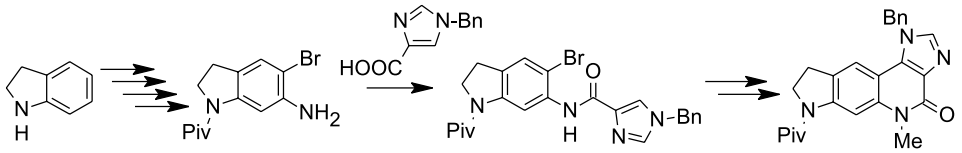
REPORT

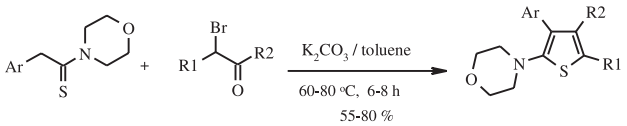


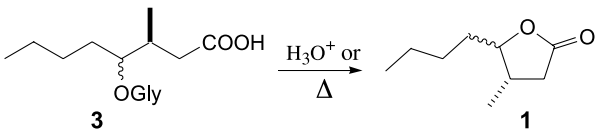
The syntheses of substituted pyridines are reviewed, organised by the nature of the disconnection of the ring.

ARTICLES

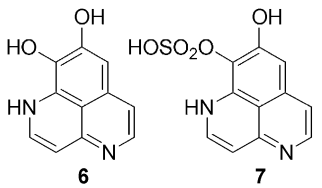




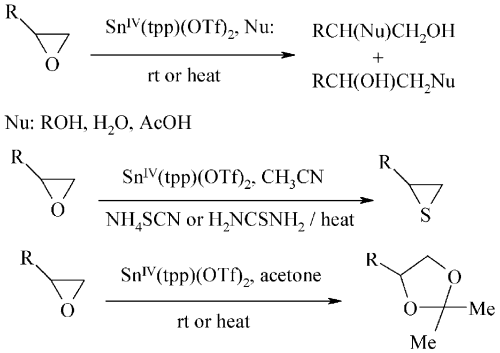


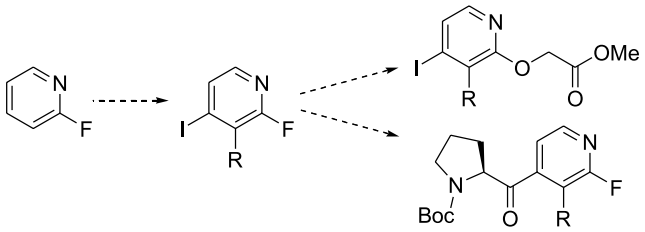


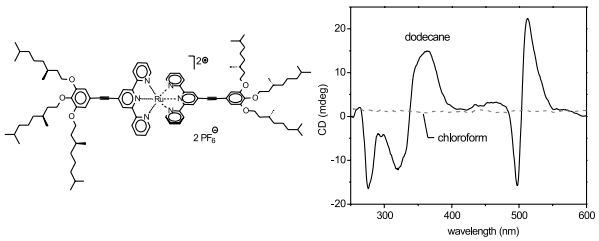
A series of glycosides **3** has been prepared. Both the straight glucoside and its galloylglucose derivative have each been shown to produce oak lactone **1** under acidic and pyrolytic conditions.



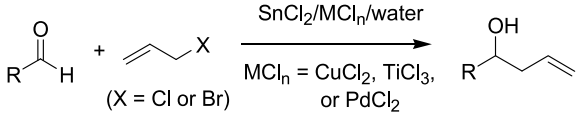
The new electron deficient tin(IV) tetraphenylporphyrinato trifluoromethanesulfonate, [Sn^{IV}(tpp)$(OTf)_2$], was used as an efficient catalyst for the alcoholysis, hydrolysis, and acetolysis of epoxides. Conversion of epoxides to thiiranes and acetonides were also performed efficiently in the presence of this catalyst.

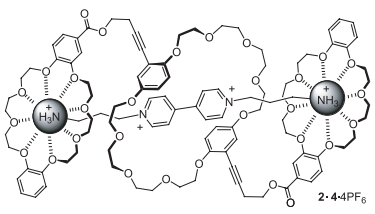


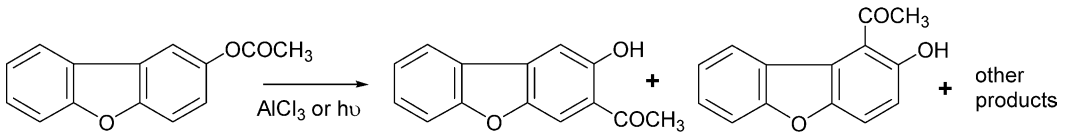


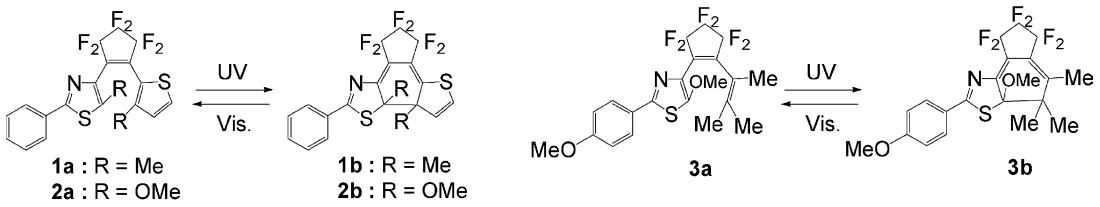


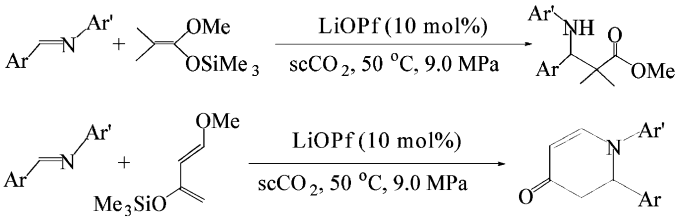
Chiral and achiral terpyridine ligands were complexed with ruthenium(II) ions, which resulted in the case of the chiral terpyridine ligand in the formation of chiral aggregates, as studied by CD-spectroscopy.



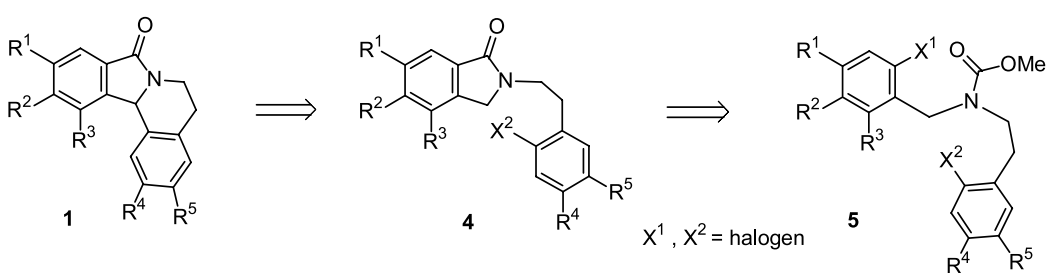


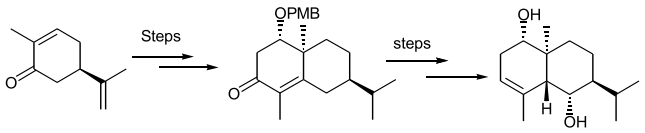


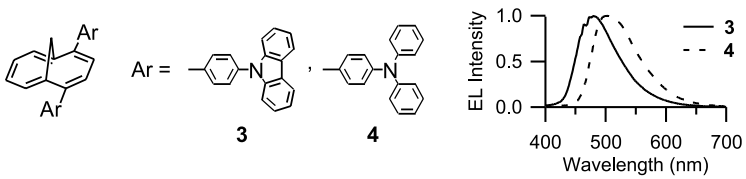


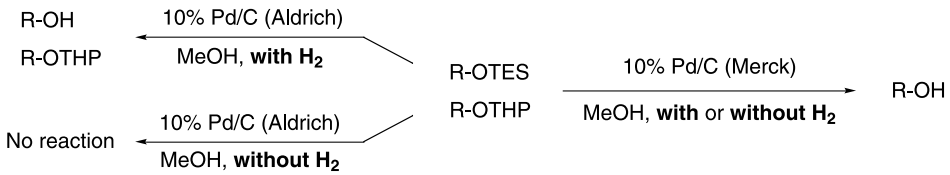


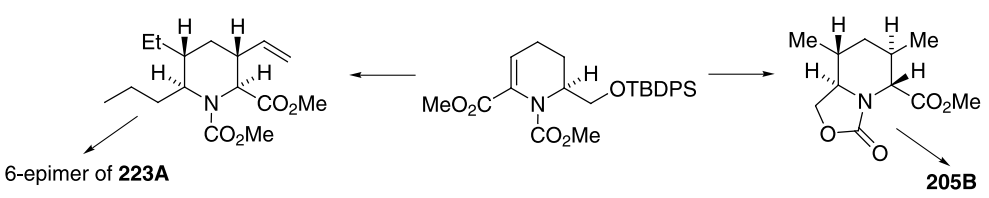
The Mannich-type reaction of imines with (1-methoxy-2-methylpropenyloxy)trimethylsilane and aza-Diels–Alder reaction of imines with Danishefsky's diene can be carried out in $scCO_2$ in the presence of lithium heptadecafluorooctanesulfonate.

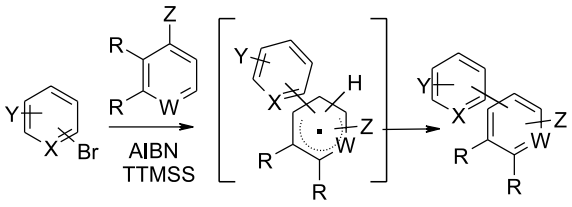


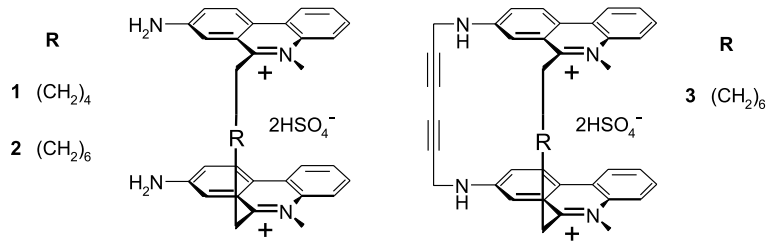












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De novo synthesis of substituted pyridines

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Contents

Fundamental as a building block of nature and the chemical industry, pyridine is presented in this review in terms of its history, key applications and de novo synthesis of the ring.

1. History of pyridine

Names often give fascinating insights into what they describe and in the case of pyridine, we learn of its history and nature: 'pyr' is Greek for fire and 'idine' is a suffix used at one time for all aromatic bases. Pyridine bases were first obtained from the pyrolysis of bone by the condensation of simple aldehydes and ketones with ammonia, which are thought to be formed from the decomposition of glycerol and nitrogenous material in bone oil under these conditions.[1]

Anderson isolated the first pyridine base, picoline, from bone oil in 1846, but the correct structure of pyridine was not proposed until Körner (1869) and Dewar (1871) independently formulated a mono-aza-analogue of benzene.[1–4]

With this understanding of the structure of pyridine, synthetic routes appeared from the latter half of the 19th century starting with Ramsay in 1876,[5] although pyridine derivatives were of little commercial importance for decades and required quantities could be obtained from

Keywords: Pyridine synthesis; Review; Combinatorial; Solution-phase; Solid-phase.

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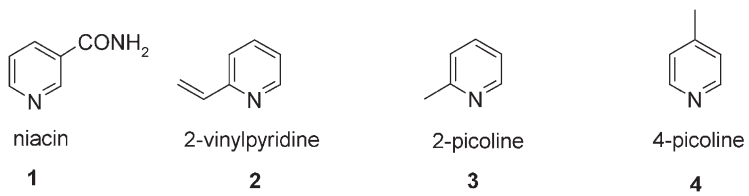
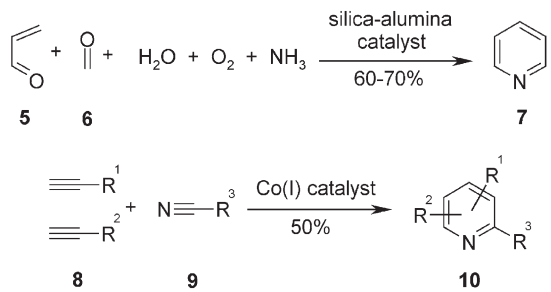


Scheme 1.

coal tar distillation. Pyridines came to prominence in the 1930s with the recognition of the importance of niacin **1** (Scheme 1) for the prevention of dermatitis and dementia. In the 1940s a new major application was discovered for 2-vinylpyridine **2** as a constituent in latex that promoted the binding of rubber to tyre cord. Demand for 2-picoline **3** for latex production outstretched its availability from coal tar sources and so researchers at Reilly industries developed an industrial synthesis of 2- and 4-picolines **3**, **4** (Scheme 1) by vapour phase catalytic reactions. The demand for pyridine and its derivatives has further increased over the last 50 years by the discovery of many bioactive pyridine-containing compounds by several companies.[6]

Modern commercial methods for the production of pyridine **7** rely on gas-phase high-temperature condensation reactions similar to those developed at Reilly industries. Crotonaldehyde **5**, formaldehyde **6**, steam, air and ammonia over a silica–alumina catalyst react to give pyridine **7** in 60–70% yield. Alkylpyridines **10** are manufactured using acetylenes **8** and nitriles **9** over a cobalt catalyst in around 50% yield (Scheme 2).



Scheme 2.

2. Key applications

Since the middle of the last century, pyridine has assumed an important role in our understanding of the chemistry of biological systems. It plays a key role catalysing both biological and chemical systems. In many enzymes of living organisms it is the prosthetic pyridine nucleotide **11** (NADP) that is involved in various oxidation–reduction processes.[7] Other evidence of the potent activity of pyridine in biological systems is its presence in the important vitamins niacin **1** and pyridoxine **12** (vitamin B_6) and also in highly toxic alkaloids such as nicotine **13** (Scheme 3).[8]

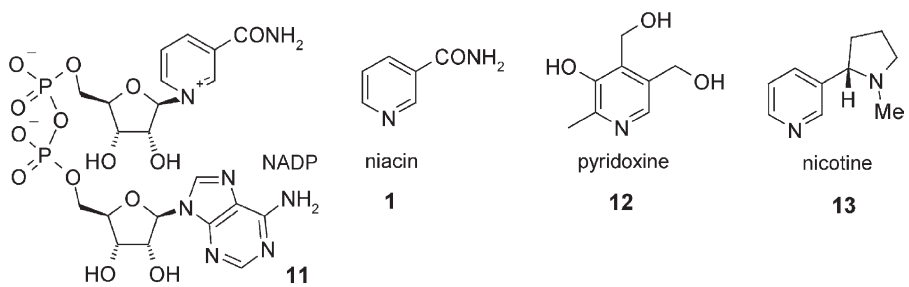
In the pharmaceutical industry, pyridine forms the nucleus of over 7000 existing drugs.[9,10] Some of these drugs **14**–**21** and their applications are shown in Scheme 4.[8,11–15]

The pyridine ring is also ubiquitous in agrochemicals.[16] Some of these chemicals **22**–**31** and their applications are shown in Scheme 5.[16–18]

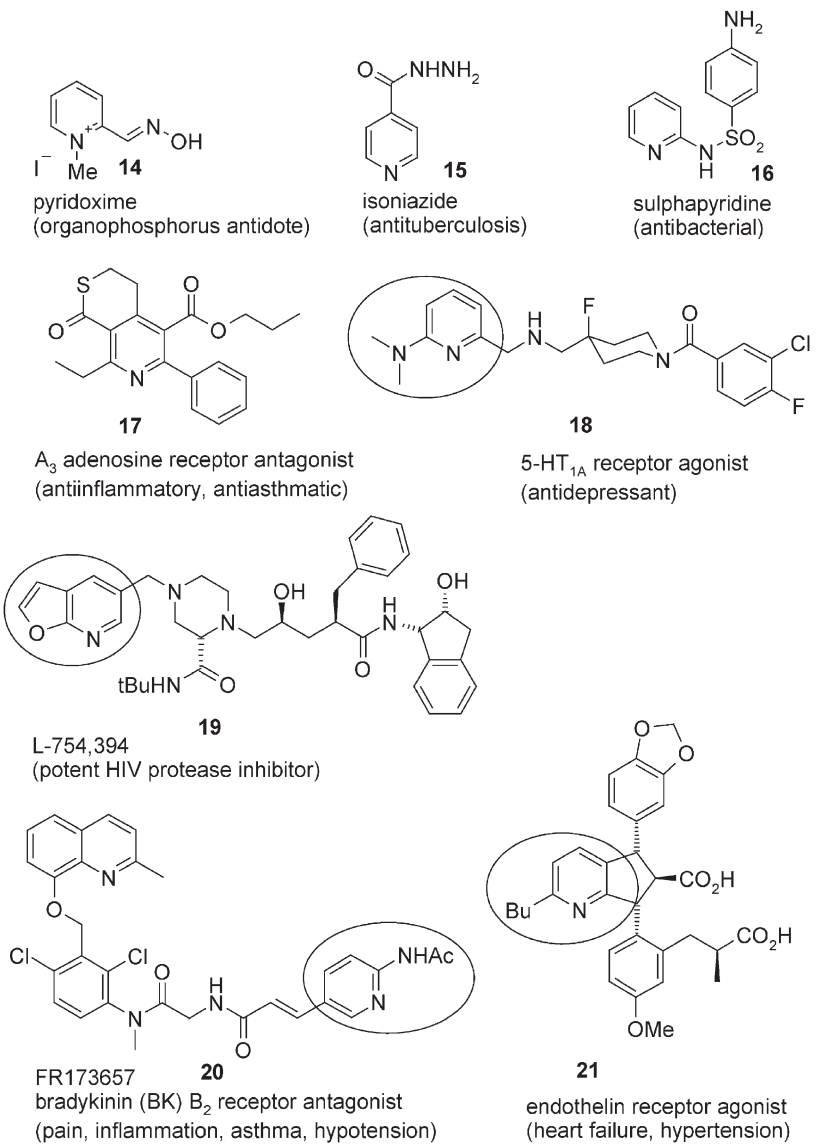
In addition to these important biological applications, pyridine is also of great utility in preparative organic chemistry (Scheme 6), for example, DMAP **32**, which is used in demanding process-scale acylation reactions and in the activation of carboxylic acids without racemisation of a sensitive chiral α-functionality. An axially chiral analogue of DMAP **33** has been developed to carry out enantioselective acylation, a reaction formerly dependent on the use of enzymes.[6]

Within synthetic organic chemistry, pyridines are extensively utilised in coordination chemistry: bipyridines such as **34** and terpyridines such as **37** have an excellent ability to complex various metal ions, including ruthenium, zinc and copper. These functional ligands have found a multitude of applications in highly sensitive analytical reagents, sensor systems, enantioselective synthesis, luminescent agents for labelled peptide synthesis and building blocks for supramolecular chemistry.[19]

Other applications of pyridines include vinylpyridine polymers such as **36**, used industrially as acid scavengers, supports for oxidising and reducing agents and as materials for chemical separations. *N*-Alkylpyridinium salts such as **35** are ionic liquids, which can dissolve organic and inorganic compounds and are highly polar but non-coordinating. They can replace water in 2-phase systems since they are immiscible with organic solvents and they are



Scheme 3.



Scheme 4.

non-volatile and can therefore be used in high-vacuum systems. *N*-Alkylpyridinium salts **35** therefore, have potential in 'green' industrial applications especially as they can even dissolve spent nuclear fuels.[6]

A quotation from Moody and co-workers in their paper on a Bohlmann-Rahtz route to functionalised pyridines[20] forms a fitting conclusion to this section:

'The wide-ranging biological activity associated with many pyridine derivatives, both naturally occurring and synthetic, ensures that the synthesis of this important ring system remains a topic of current interest.'

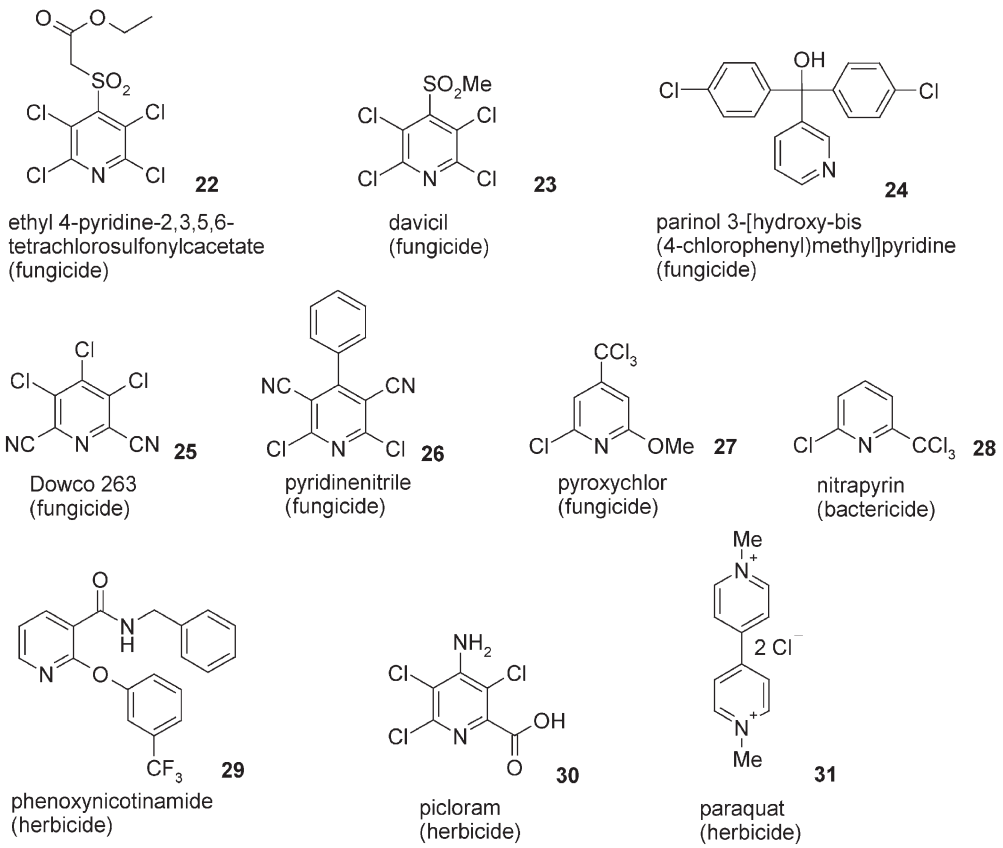
3. Pyridine synthesis

For more than a century, many diverse methods have been developed to synthesise pyridines with new substitution patterns around the ring. The greatest access to diverse substitution naturally comes with disconnection of the ring into a maximum number of fragments, which should be readily available for the method to be of general value. In Section 3.1, the most common methods for the synthesis of small pyridine libraries in solution will be discussed and these are grouped according to the nature of the ring-disconnection, for example:

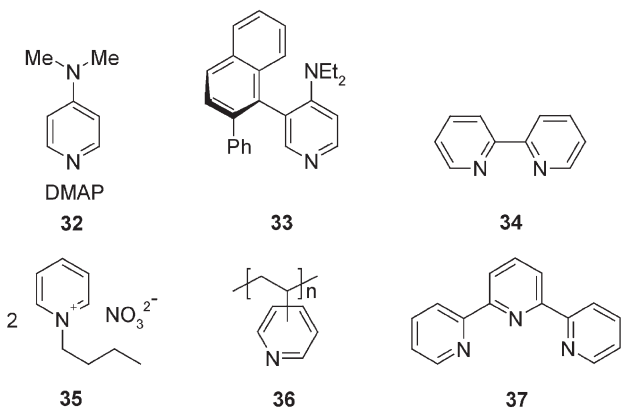
[5+1]

[5+1] means that the ring can be divided into two parts, one with five ring atoms and one with one ring atom and the diagram above shows the exact disconnection.

In Section 3.2, the solution-phase combinatorial methods for pyridine synthesis are reviewed, followed in Section 3.3, by the solid-phase combinatorial methods for pyridine synthesis.



Scheme 5.

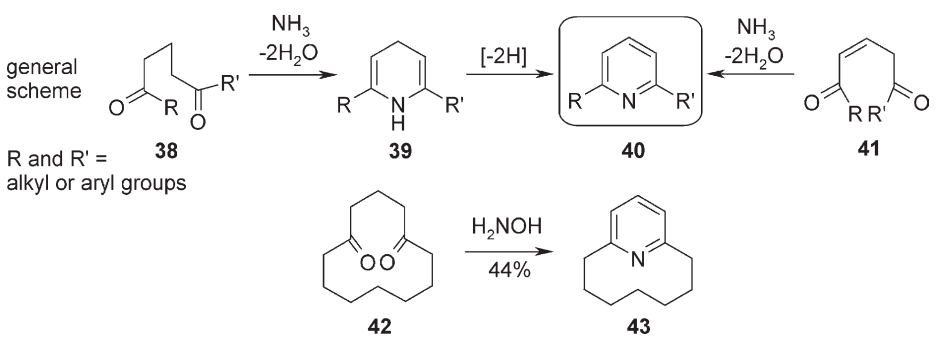


Scheme 6.

3.1. Solution-phase strategies for substituted pyridine synthesis

3.1.1. [5+1].

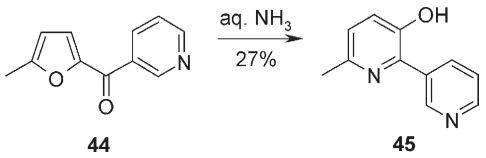
The disconnection shown above requires a nitrogen derivative and a five-carbon fragment, usually a 1,5-dicarbonyl (Scheme 7).[21] When a 1,5-diketone **38** reacts with ammonia, 2 equiv. of water are lost to produce a 1,4-dihydropyridine **39**, which can be easily oxidised to the aromatic heterocycle **40** (nitric acid is commonly used).



Scheme 7.

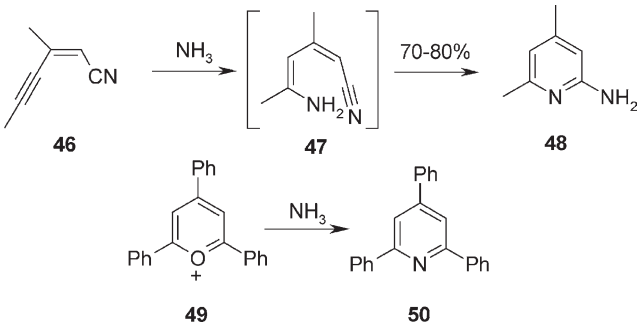
1,5-Dicarbonyl systems can be accessed by Michael addition of enolate to enone or by ozonolysis of cyclopentenes.[8] To avoid an additional oxidation step, 1,5-diketones **42** can react with hydroxylamine to form the pyridine **43** directly in 44% yield, as in the example shown, by Nozaki and co-workers in 1969,[1,22] or unsaturated 1,5-dicarbonyls **41** can be used. This is the most simple and reliable route to pyridines **40**, although the availability of the 1,5-dicarbonyls **38** can be a problem.

The 2-acylfuran **44** has been used as a 1,5-dicarbonyl equivalent by Chubb and co-workers in 2001, affording the substituted pyridine **45** with a hydroxyl group at the 3-position in low yield (27%) on reaction with ammonia at high temperature and pressure (Scheme 8). The 2-acylfuran **44** is readily available from the reaction of the 2-lithiofuran and the α-substituted nitrile, which provides an alternative method for the synthesis of aryl-substituted pyridines, such as **45**, to the standard palladium-catalysed Stille or Suzuki biaryl couplings, but the yields are low.[23]



44 **45**

Scheme 8.



46 **47** **48**

49 **50**

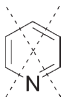
Scheme 9.

In other examples (Scheme 9),[1,24] 1,6-addition of ammonia to the conjugated nitriles **46** by Perveev and Koshmina in 1968 gives the 2-aminopyridine **48** via **47** in good yield (70–80%) and pyrylium salts, for example, **49**, are efficiently converted into the 2,4,6-trisubstituted pyridine **50**, as shown by Balaban in 1969.[25] The general usefulness of these methods is restricted by a limited range of readily available starting materials.

[5+1]

An example of the unusual disconnection shown above by Katritzky and co-workers in 1999 is illustrated in Scheme 10. The pyridine **55** is prepared by the reaction of a Vilsmeier-type reagent **54** with a dienamine **53**, which is easily synthesised from ketones such as **51** and β-aminocrotononitrile **52**. The nicotinonitrile-like pyridine derivatives, such as **55**, are in high demand for many applications and this work represents the first generally applicable and regioselective synthesis.[26]

3.1.2. [2+2+1+1].

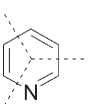


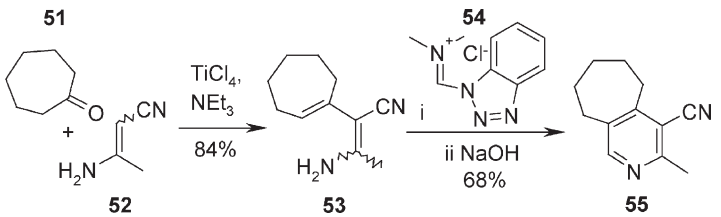
The Scheme above shows the signature disconnection for the classical Hantzsch synthesis, first published by Hantzsch in 1882.[27] Symmetrical pyridines **60** are normally generated via this method, by the interaction of ammonia, an aldehyde **57** and 2 equiv. of a 1,3-dicarbonyl compound **56** (via **58**) as shown in Scheme 11. Analogous to the method illustrated in Scheme 7, pyridines are only obtained after the oxidation of the 1,4-dihydropyridine **59**. Unsymmetrical pyridines can be synthesised by making the enone separately in an aldol condensation, followed by reaction with an enamine.[8] The Hantzsch synthesis is very important for the synthesis of 2,3,4,5,6-substituted pyridines, but is commonly limited to carboxyl substituents at the 3- and 5-positions and an aryl substituent at the 4-position (Scheme 11).[28] Despite this strategic limitation, the Hantzsch synthesis has been of huge synthetic significance for over a century.

A selection of Hantzsch-inspired strategies is now given. The first, by Hegde and co-workers in 1987 (Scheme 12), requires an aryl substituent at the pyridine 4-position for the synthesis of the tetrapyridine **61**.[29]

In the second example, Alvarez-Insua and co-workers in 1970 used malononitrile **62** as the reactive methylene component to create the pyridine **63** (Scheme 13).[30]

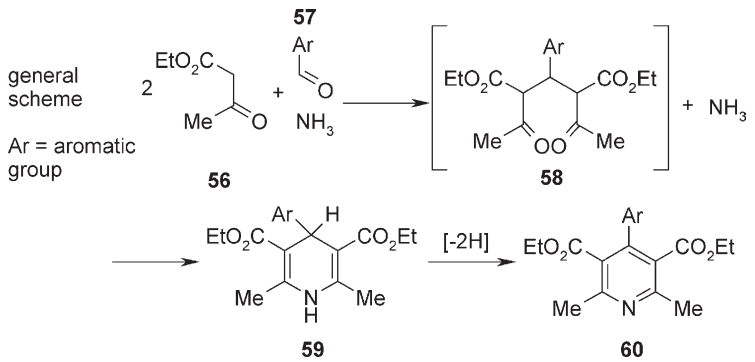
3.1.3. [2+2+2].



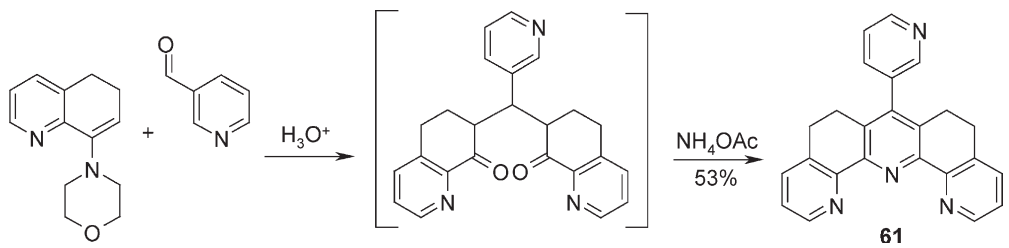


52 **53** **55**

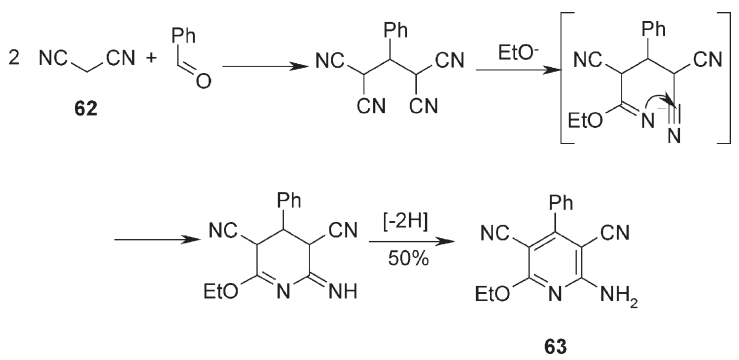
Scheme 10.



Scheme 11.

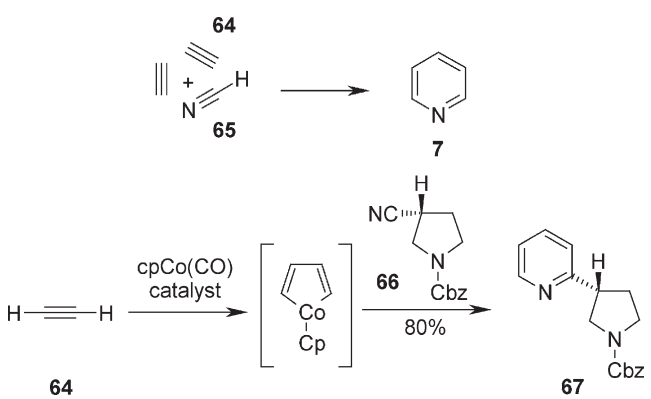


Scheme 12.



Scheme 13.

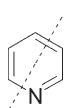
The original laboratory preparation of pyridine **7** by Ramsay in 1876 was carried out via the disconnection shown above, by passing acetylene **64** and hydrogen cyanide **65** through a red-hot tube.[31] This process has been superseded by a modern cobalt(I)-catalysed variant which is a highly commercially valuable route to alkylpyridines **67**, involving the cyclisation of alkyl(aryl)alkynes and nitriles **66** to give mixtures of 2,4- and 2,5-substituted products, in addition to trisubstituted benzenes, as shown by Chelucci and co-workers in 1990 (Scheme 14).[32] By using mixtures of unsymmetrical alkynes, a great variety of substitution patterns can be generated.



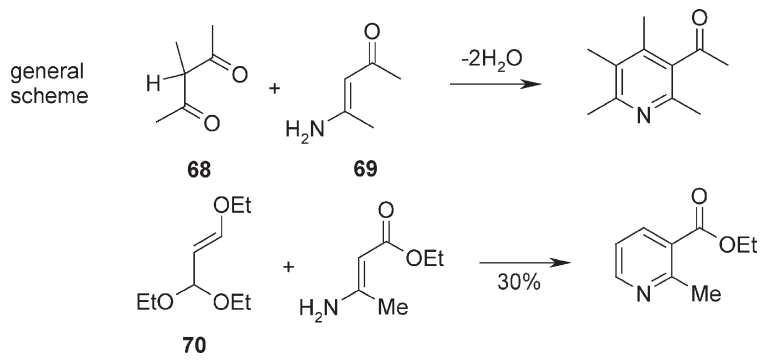
Scheme 14.

The major advantage of this route is the three-way disconnection of the pyridine ring into three readily variable two-atom fragments. This is the most powerful method for creating large numbers of differentially substituted pyridines, with the downside being the difficulty of separating large numbers of very similar molecules, as illustrated later by Scheme 36 in the solution-phase combinatorial methods section.

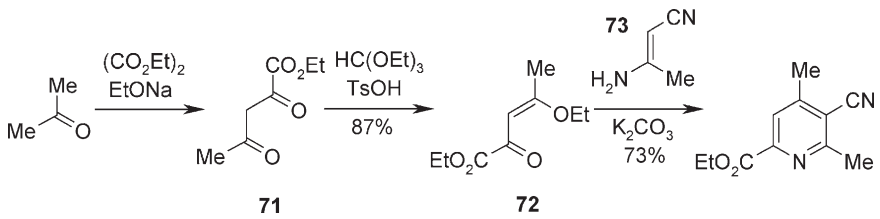
3.1.4. [3+3].



The reaction of 1,3-dicarbonyl compounds **68** and 3-amino-enones **69** or -nitriles is one of the most versatile and useful,



Scheme 15.

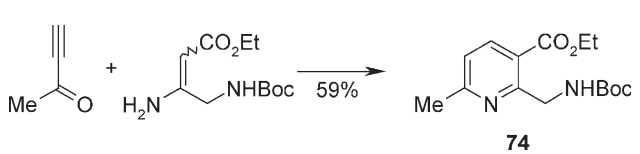


Scheme 16.

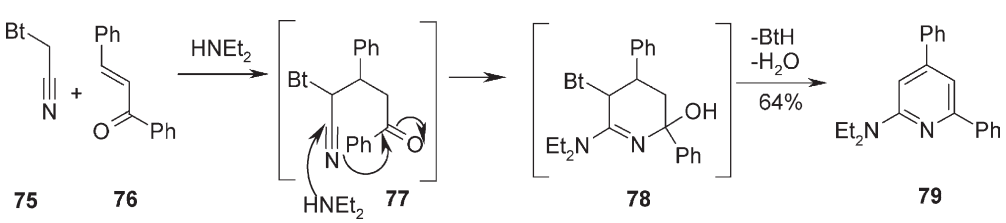
since it allows the construction of unsymmetrically substituted pyridines from relatively simple precursors (Scheme 15). 3-Aminoenones and acrylates of the type **69** are readily available from the reaction of ammonia with 1,3-diketones or 1,3-ketoesters. 1,3-Dialdehyde equivalents can also be used, but only in the form of their acetal enol ethers **70**.[8]

Variations of the [3+3]-based routes to pyridines include the Guareschi synthesis, where the 1,3-ketoester **71** combines with triethyl orthoformate to give an ester enol ether **72**, before (Michael) addition of a 3-amino-nitrile **73**, by Henecke in 1949 (Scheme 16),[8,33] and the versatile, but little used, Bohlman-Rahtz route to pyridines, which forms a fully unsaturated pyridine **74** directly, as demonstrated by Moody and co-workers in 2003 (Scheme 17).[20]

Further innovation with the [3+3] disconnection strategy came from Katritzky and co-workers in 1997, who employed α-benzotriazole nitriles **75** as nucleophiles for Michael addition onto α,β-unsaturated carbonyls **76**, as shown in Scheme 18. Nucleophilic attack onto the nitrile **77** by a secondary amine then initiates condensation followed by aromatisation, via **78**, to yield the desired 2,4,6-substituted pyridine **79** in good yield (64%).[34]

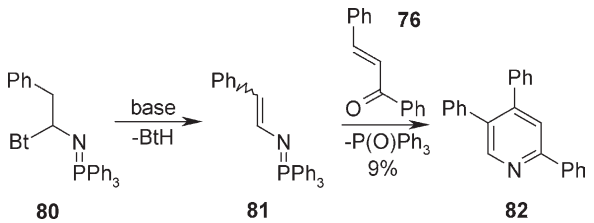


Scheme 17.



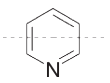
Scheme 18.

More unusual still are the cyclisations between enones **76** and iminophosphoranes **81** (prepared from the benzotriazole-substituted precursor **80**) developed in 1999 by Katritzky and co-workers, in which the enones react via pyrylium salts (Scheme 19) to give pyridines **82**, but the yields are low (9%).[28]

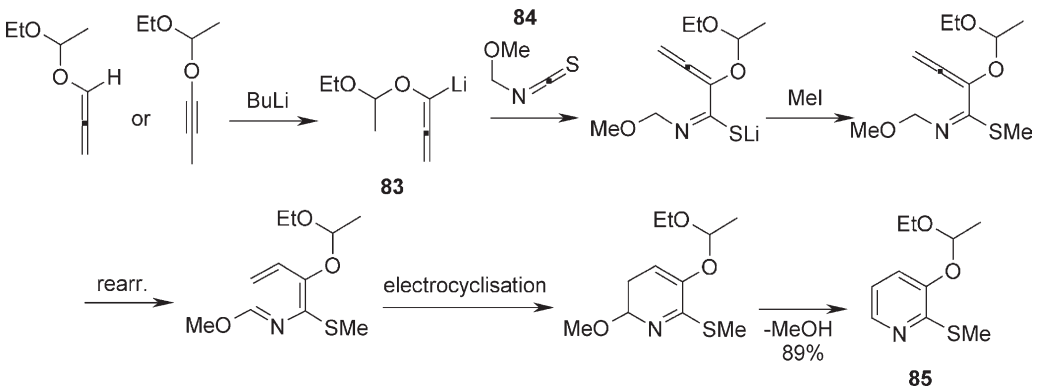


Scheme 19.

[3+3]



One recent and novel version of the unusual disconnection shown above and developed by Brandsma and co-workers in 2002 is the reaction of lithiated allenes and alkynes **83** with methoxymethyl isocyanate **84**, giving pyridines **85**



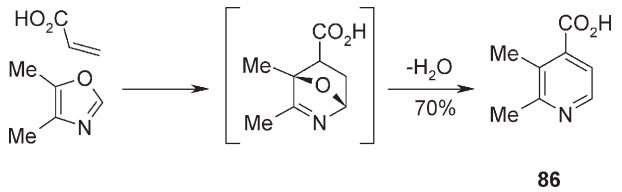
Scheme 20.

with limited substitution patterns in excellent yield (89%) (Scheme 20).[35]

3.1.5. [4+2].

The first of the [4+2] disconnections to be discussed in this review is the addition of a dienophile to an oxazole by Kondrat'eva and Huan in 1965, where the subsequent extrusion of the oxazole oxygen gives the target pyridine **86** in good yield (70%) (Scheme 21).[8,36]

Similarly, 1,2,4-triazines **87** undergo inverse-type Diels–Alder reactions with electron-rich and angle-strained



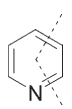
Scheme 21.

dienophiles such as **88** to give pyridine derivatives **89**, after extrusion of molecular nitrogen, in 64–90% yield, as shown by Sauer and co-workers in 1998 (Scheme 22).[37]

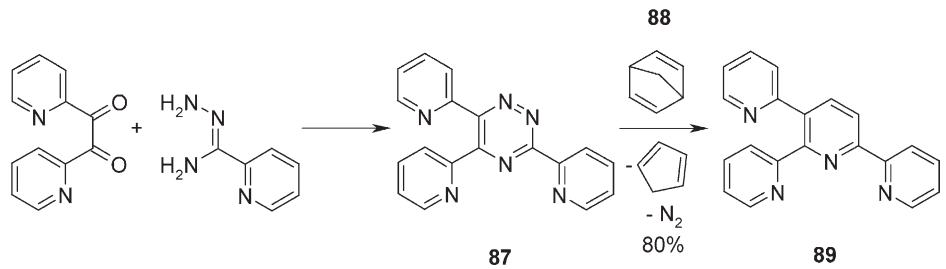
An unusual and selective [4+2] example involves the cycloaddition of unsaturated imines **91** with enamines **92** (Scheme 23). In the example illustrated, iminophosphoranes **90** undergo an aza-Wittig reaction to give the *N*-vinyl-carbodiimide **91**, which acts as a diene, as shown by Nitta and co-workers in 1991, to give pyridines **93**, in yields ranging from 9–41%.[38]

The final example of this [4+2] disconnection, shown in Scheme 24, was reported by Smith and Lenoir in 2000 and is an innovative radical annulation reaction of vinyl isonitriles **95** and iodoalkynes **94** to give the cyclopenta-fused pyridines **97** via **96** in varying yields (20–72%).[39]

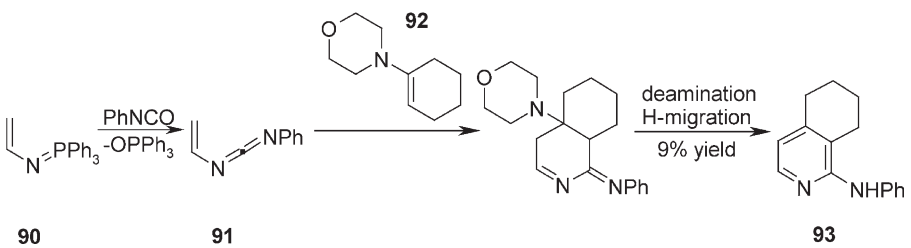
[4+2]



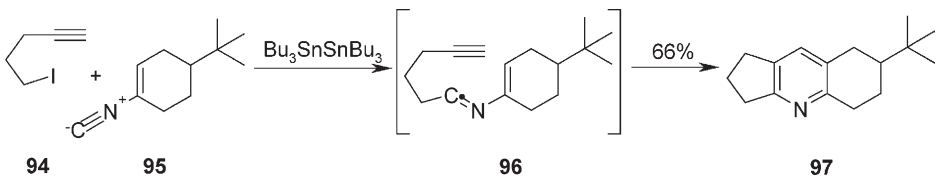
With the [4+2] disconnection shown above, we again encounter Diels–Alder chemistry with a creative example



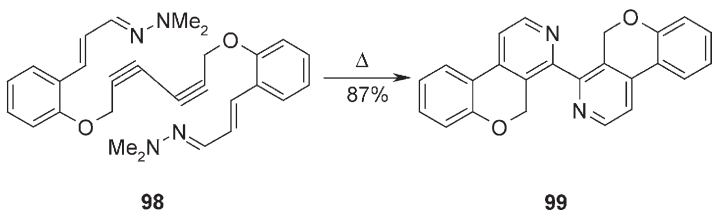
Scheme 22.



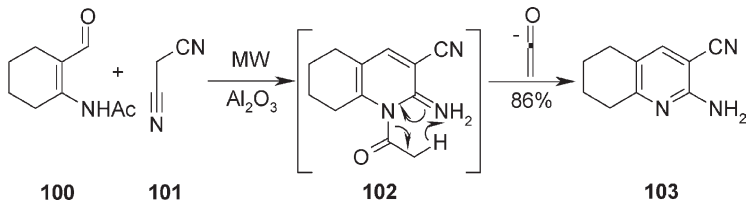
Scheme 23.



Scheme 24.



Scheme 25.

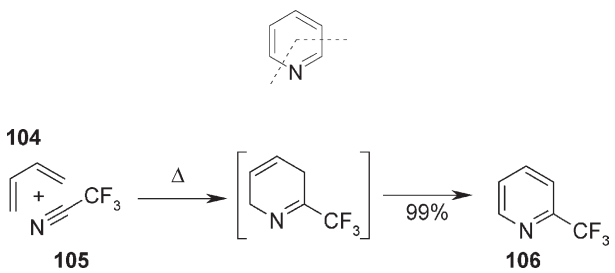


Scheme 26.

reported by Moody and co-workers in 1999. The double Diels–Alder reaction of α,β-unsaturated hydrazones **98** delivers bipyridines **99** in one step with varying yields (20–87%) (Scheme 25). The diyne function in **98** is created in excellent yield by a Glaser–Eglinton coupling of the terminal acetylene.[40]

In the second example, by Boruah and co-workers in 2000, pyridines **103** are formed in very good yields (81–88%) via **102** from the condensation of β-formyl enamides **100** with cyanomethylenes **101** under microwave radiation, catalysed by alumina (Scheme 26).[41]

[4+2]



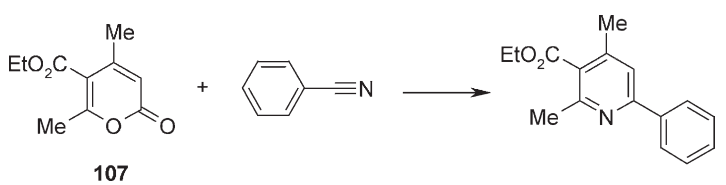
Scheme 27.

The [4+2] disconnection shown above also lends itself to Diels–Alder reactions, as illustrated by the reaction of 1,3-dienes **104** with nitriles **105** by Janz and Monaghan in 1964 (Scheme 27), giving moderate to excellent yields of pyridines **106** (99%). High temperatures (~400 °C) are necessary, except in reactions involving the most electrophilic of nitriles, for example, RSO_2CN.[1,42]

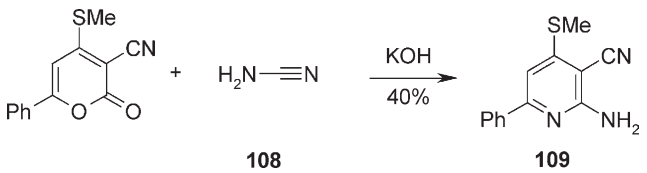
Pyrones such as **107** can be an attractive replacement for the 1,3-dienes **104** in the Diels–Alder reaction, as shown by Jaworski and Kwiatkowski in 1970 (Scheme 28),[1,43] and they have the potential to act as electrophiles towards amines **108** to form pyridines **109** in low yield (40%) by an alternative mechanism, as shown by Goel and co-workers in 2003 (Scheme 29).[7]

3.1.6. [3+2+1]. The [3+2+1] disconnection is the most frequently employed pyridine disconnection and often produces 2,4,6-trisubstituted pyridines.

[3+2+1]



Scheme 28.



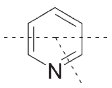
Scheme 29.

A common method which utilises the [3+2+1] disconnection is the base-promoted Michael addition of α-substituted ketones **111** with α,β-unsaturated compounds **110** which forms a 1,5-dicarbonyl intermediate **112**. The efficiency of the pyridine synthesis depends on the leaving group ability of the α-substituent (X) during the aromatisation process (Scheme 30). When the substituent X is a pyridinium, quinolinium or picolinium salt, the reaction is called the Kröhnke synthesis, which can yield a variety of poly-substituted pyridines **114** via **113**. Substitution is limited at the 5-position, however, as such salts of the type X with an extra α-substituent are unstable to strongly basic media and at the 2-position where phenyl seems to work best.[28]

A mild variation of the [3+2+1] disconnection by Konno and co-workers in 1986 reverses the reactivity α,β-unsaturated carbonyl compounds **115** (Scheme 31). An α,β-unsaturated carbonyl compound **115** undergoes Michael attack by thiophenol, followed by aldol condensation with a ketone **116**, to form a new α,β-unsaturated carbonyl **117**. The pyridine **119** is synthesised in 49–60% yield overall via a 1,5-dicarbonyl intermediate **118** using a Pummerer reaction and subsequent ammonolysis.[44]

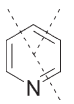
Another example is a recently published process route by Davies and co-workers in 2000 (Scheme 32) to a COX-2-specific inhibitor **122** (antiinflammatory). This novel annulation of the ketone **120**, the vinamidinium species **121** and ammonia gives the desired pyridine **122** in an excellent yield of 97%.[45,46]

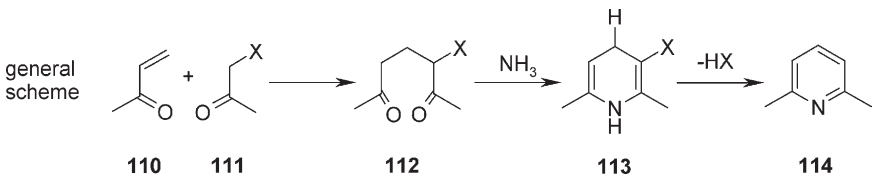
[3+2+1]



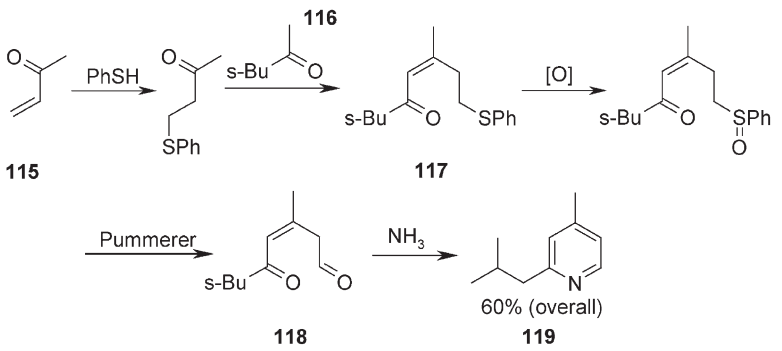
One novel pyridine synthesis utilising the disconnection shown above by Bates and co-workers in 1980 involves the reaction of the 2-methyleneallyl dianion **123** with nitriles **124** (Scheme 33). The yield of pyridine **125** is excellent (85%) when 2 equiv. of benzonitrile **124** are used.[47]

[3+2+1]

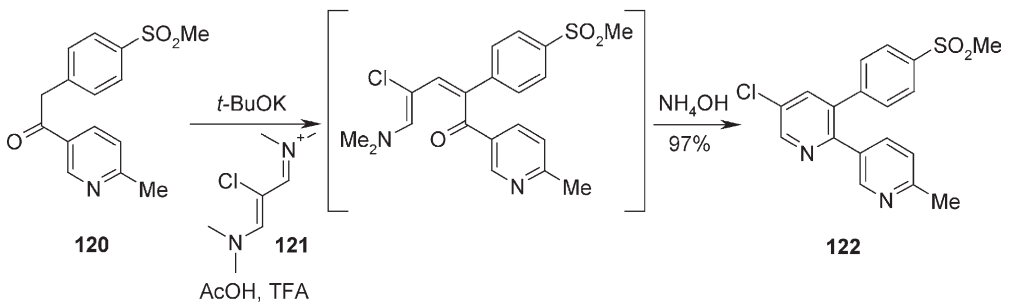




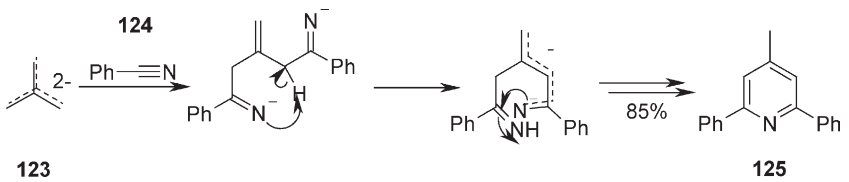
Scheme 30.



Scheme 31.



Scheme 32.



Scheme 33.

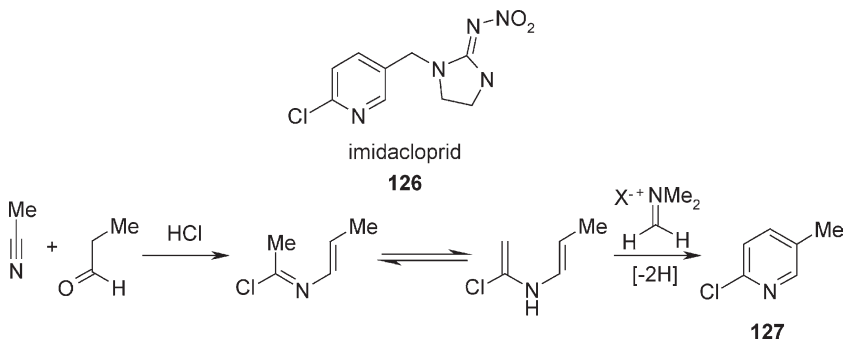
Scriven and Murugan from Reilly Industries published in 2000 an interesting version of the disconnection approach shown above to gain access to a valuable 2-chloro-5-methyl pyridine **127** (the yield was not given) for the synthesis of the insecticide imidacloprid **126** (Scheme 34).[48]

3.2. Solution-phase combinatorial strategies for substituted pyridine synthesis

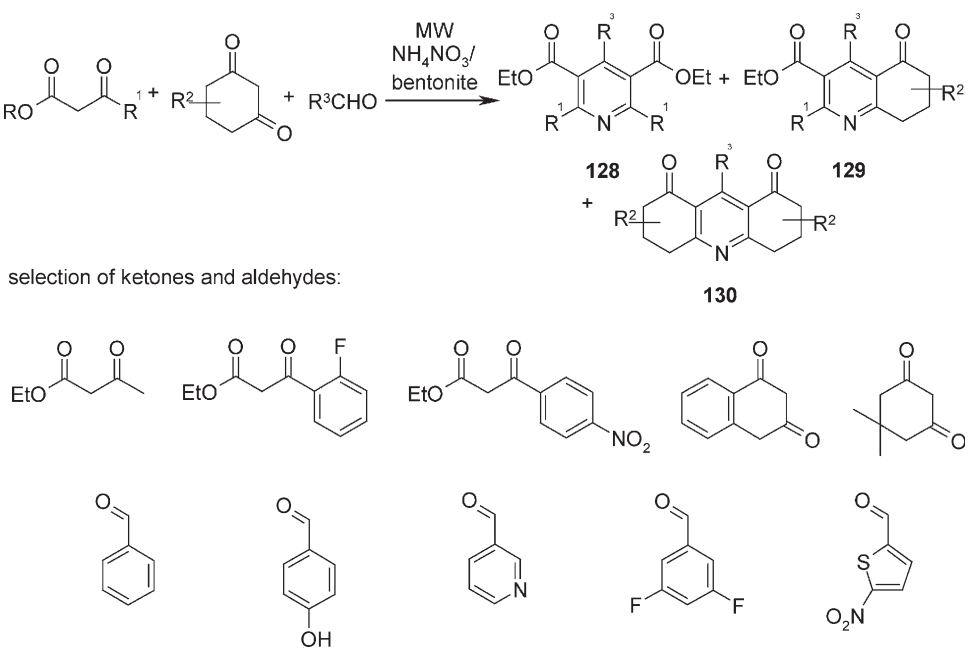
Combinatorial chemistry techniques have gained widespread support in recent decades in medicinal chemistry for lead discovery and optimisation from the production of large numbers of compounds for biological screening. The combinatorial approach has also recently received attention from topics outside medicinal chemistry, such as materials science and catalysis.[49] A measure of the impact of combinatorial technologies in recent times is that the value of new synthetic methodology (especially heterocycle synthesis) has become linked to its suitability for adaptation to these technologies.

Much work has been done in the area of combinatorial pyridine synthesis, yet only a small fraction is in the public domain due to commercial interests. In Section 3.2 of this review, many the fundamental pyridine syntheses discussed in the previous section will be illustrated in a combinatorial context.

The examples of solution-phase combinatorial synthesis show that large compound libraries can be created very efficiently, despite being limited to one step.

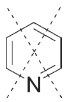


Scheme 34.



Scheme 35.

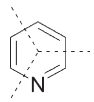
3.2.1. [2+2+1+1].



Khmelnitsky and co-workers demonstrated in 1998 the first practical application of microwave-assisted combinatorial synthesis (MICROCOS) in a Hantzsch pyridine synthesis (Scheme 35).[50] Microwave-assisted organic synthesis (MAOS) offers some interesting advantages over standard techniques such as greatly reduced reaction times and solvent-free synthesis. A solution of the reactants in a volatile solvent was impregnated into bentonite clay, the solvent was evaporated and the clay was irradiated by microwaves. Ammonium nitrate was also present as the source of ammonia and oxidant (nitric acid). The reactions are described as solution-phase as the reactants are non-covalently bound to a solid.

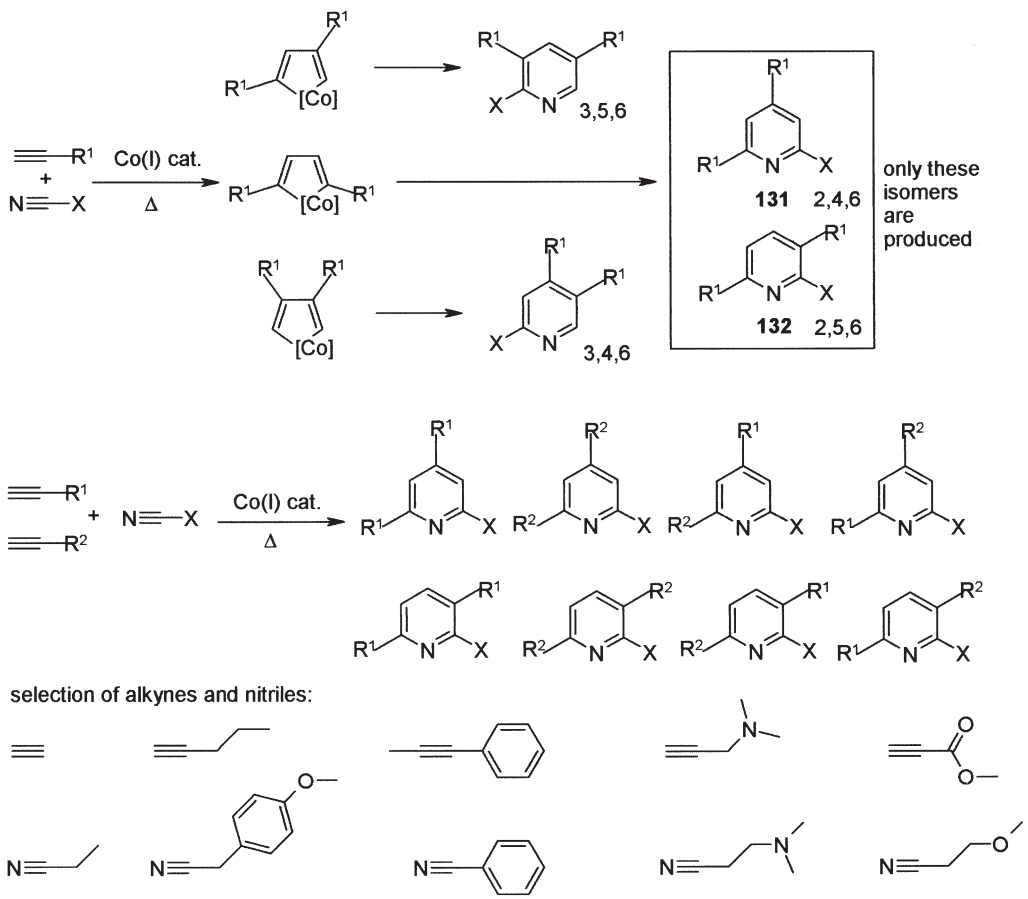
The library was constructed from 12 aldehydes and eight 1,3-dicarbonyl compounds giving all of the expected 96 nonsymmetrical pyridines **128**–**130** and 70 out of 108 symmetrical pyridines with an HPLC product purity of at least 70% (the yields are not given). The products are, however, limited to the traditional Hantzsch substitution pattern, with carbonyl substituents at the 3- and 5-positions and an aryl substituent at the 4-position.

3.2.2. [2+2+2].



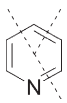
The cobalt(I)-catalysed pyridine synthesis illustrated in Scheme 14 has also been modified by Brandli and Ward in 2000 to create a library of 2,4,6- and 2,5,6-trisubstituted pyridines **131** and **132** (Scheme 36).[51] [$CpCo(CO)_2$] was chosen as the catalyst, since it gave low yields of alkyne trimerisation products (carbocycles) and rigorous anaerobic conditions were not required. The addition of a carbon monoxide scavenger (morpholine *N*-oxide or trimethylamine *N*-oxide) allowed a decrease in the reaction temperature from 185 to ca. 85 °C. Purification was effected using an acidic cationic-exchange resin to give essentially pure (by GC) mixtures of pyridines in ca. 50% overall yield.

The 14 alkyne and ten nitrile building blocks used could theoretically produce 3920 pyridines, but, in practice, a full complement of regioisomers was not observed in every case. This work illustrates the power of three-component condensations to rapidly generate very large-diversity mixtures, although a major drawback in this example is the production of inseparable regioisomeric mixtures that complicate the analytical and biological evaluation.



Scheme 36.

3.2.3. [3+2+1].



An outstanding example of a versatile pyridine synthesis was published by Powers and co-workers of ArQule in 1998, who produced around 9000 2,3,4,6-tertrasubstituted pyridines using an automated parallel synthesis (Scheme 37).[52] The use of varied dinucleophiles afforded over 74,000 individual enone derivatives **133**, in nine combinatorial arrays. First, a 1280-member chalcone array was prepared from 32 acetophenones and 40 aldehydes, with an average purity of 96% by HPLC. These compounds were then reacted with the enamines **134**–**136** in refluxing ethanol to give the pyridines **137**–**139** in moderate yields, with an average purity of greater than 85% by HPLC.

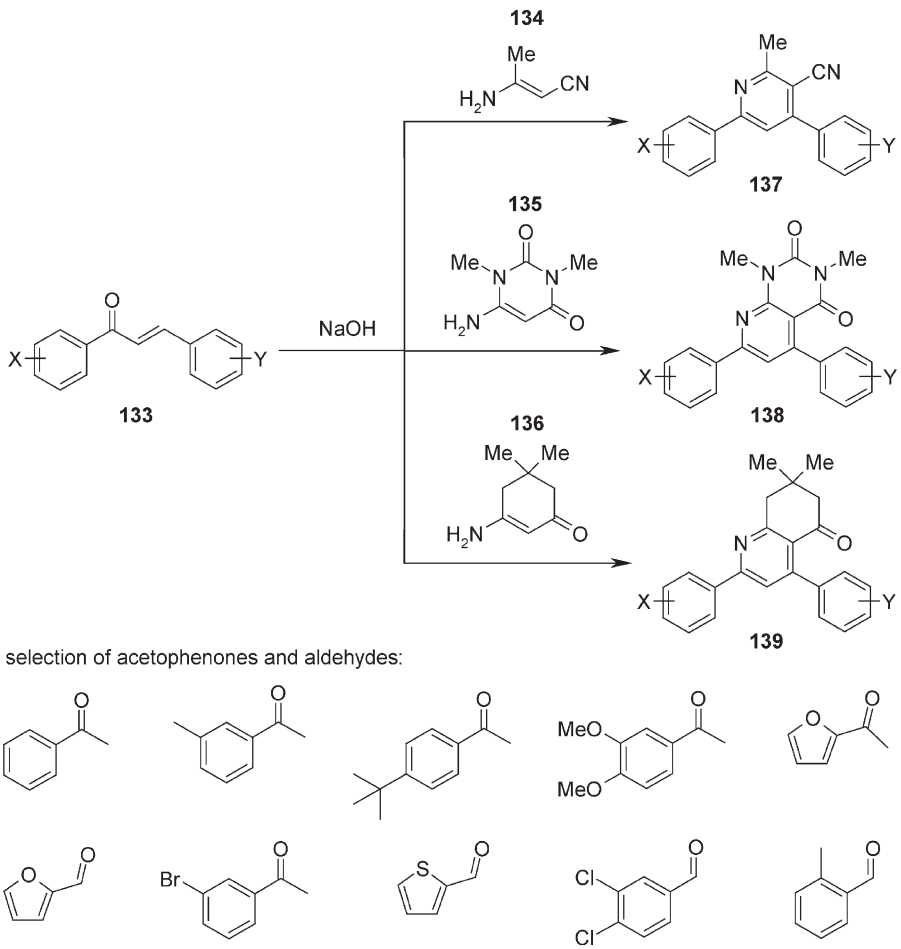
3.3. Solid-phase combinatorial strategies for substituted pyridine synthesis

Solid-phase chemistry is an effective tool for preparing large numbers of compounds in a highly pure form. It offers several advantages (and disadvantages) over the traditional solution-phase chemistry, some of which are given below:

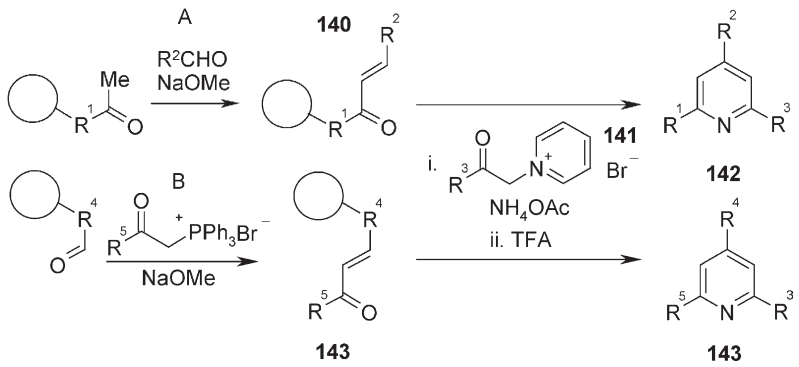
- Simple purification by washing
- Products of high purity
- Possibility of 'split and mix'
- Large excesses of reagents can be used to force reactions to completion
- Reactants are isolated from each other, giving a dilution effect
- Characterisation and reaction monitoring are more difficult
- Reaction conditions, solvents and temperatures are more limited
- Two extra steps: attachment to and detachment from solid-phase

The examples of solid-phase synthesis which follow are based on a very narrow cross-section of pyridine methodology and so give a limited range of substitution patterns. All of the examples feature ester or phenol points of attachment to the solid-phase linker. The examples included do, however, have the intrinsic diversity of involving at least three separate components. Ellingboe and co-workers in their paper on 'solid-phase synthesis of 2,4,6-trisubstituted pyridines' in 1999 made a pertinent comment on pyridine diversity:

'to prepare a combinatorial library of pyridines with a high degree of potential diversity and wide utility for drug discovery using solid-phase techniques, it is important to design a pyridine synthesis in which at least three components can be independently and readily varied.'[53]



Scheme 37.

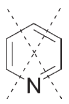


Scheme 38.

Table 1. Selected results for pyridine synthesis

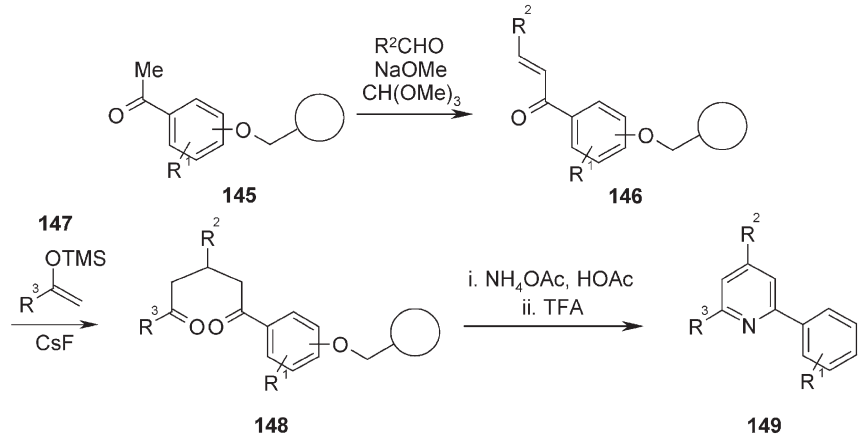
Entry	$R^{1/5}$	$R^{2/4}$	R^3	Path	Purity (%) (HPLC)	Yield (%)
1	4-OH–C_6H_4–	4-NO_2–C_6H_4–	4-F–C_6H_4–	A	89	78
2	4-Cl–C_6H_4–	3-($CONH_2$)–C_6H_4–	C_6H_5–	B	97	78
3	4-Cl–C_6H_4–	3-OH–C_6H_4–	C_6H_5–	B	96	72
4	2-Pyridyl–	4-OH-3,5-$(MeO)_2$–C_6H_2–	2-Pyridyl-	B	85	69
5	2-OH–C_6H_4–	4-MeO–C_6H_4–	2-Pyridyl-	A	91	71

3.3.1. [2+2+1+1].



Jung and co-workers in 1999 reported a three-step solid-phase pyridine synthesis (Scheme 38).[49] They successfully adapted the Kröhnke synthesis to solid-phase with the Michael addition of α-pyridinium aryl ketones **141** to resin-bound enones **140**, followed by cyclisation with ammonium acetate and cleavage with TFA to give the 2,4,6-trisubstituted pyridines **142** and **144** in solution. Enones **140** and **143** attached to the resin at different positions were used and synthesised by the two methods shown in Scheme 38 (Knoevenagel condensation A, Wittig reaction B). This chemistry was used to make 18 different pyridine rings with purity of 77% or greater and good yields (68–85%) (Table 1).

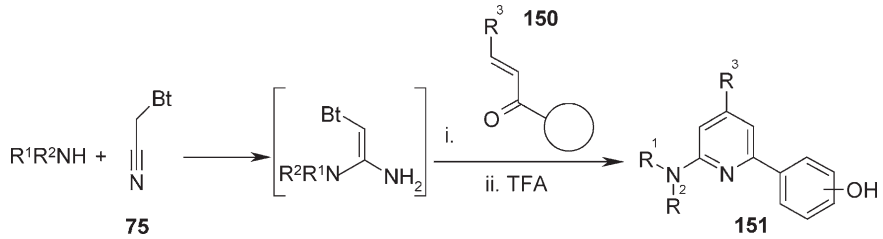
The solid-phase Hantzsch synthesis of pyridine by Ellingboe and co-workers in 1999 involves a similar method, but employs the trimethylsilyl enol nucleophiles **147** and oxidation in air after cyclisation with ammonium acetate (Scheme 39).[53] The enone **146** is formed by a Claisen–Schmidt reaction of aldehyde with the resin-bound



Scheme 39.

Table 2. Selected results for pyridine synthesis

Entry	Phenol	R^2	R^3	Purity (%) (HPLC)	Yield (%)
1	2-OH–C_6H_4–	3,4-F–C_6H_3–	4-Cl–C_6H_4–	70	62
2	2-OH–C_6H_4–	3,4-F–C_6H_3–	2-Naphthyl-	57	46
3	2-OH-5-F–C_6H_4–	4-C_6H_5–C_6H_4–	4-Pyridyl-	56	51
4	2-OH-5-F–C_6H_4–	Cyclohexyl-	2-Furyl-	55	32
5	3-OH–C_6H_4–	4-C_6H_5–C_6H_4–	2-Naphthyl-	50	34



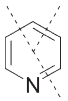
Scheme 40.

Table 3. Selected results for pyridine synthesis

Entry	R^1	R^2	R^3	Purity (%) (HPLC)
1	$-(CH_2)_4-$		4-Me–C_6H_4–	95
2	$-CH_2CH{=}CH_2$	H	4-Me–C_6H_4–	90
3	$-(CH_2)_2-O-(CH_2)_2-$		4-OMe–C_6H_4–	76
4	$CH_2CH_2CO_2H$	H	Ph	85
5	*cyclo*-C_5H_9	H	4-Me–C_6H_4–	90

β-ketoester **145** in this case and, after cyclisation of **148**, the 2,4,6-trisubstituted pyridines **149** are cleaved with TFA. A small 10-member compound array was prepared, giving a crude product purity in the 21–81% range with yields from 19–62% after purification (Table 2).

3.3.2. [3+2+1].



All of the strategies demonstrating the disconnection shown above involve the reaction of enones with enamines and they have been ordered by the position of attachment of the enone to the solid-phase.

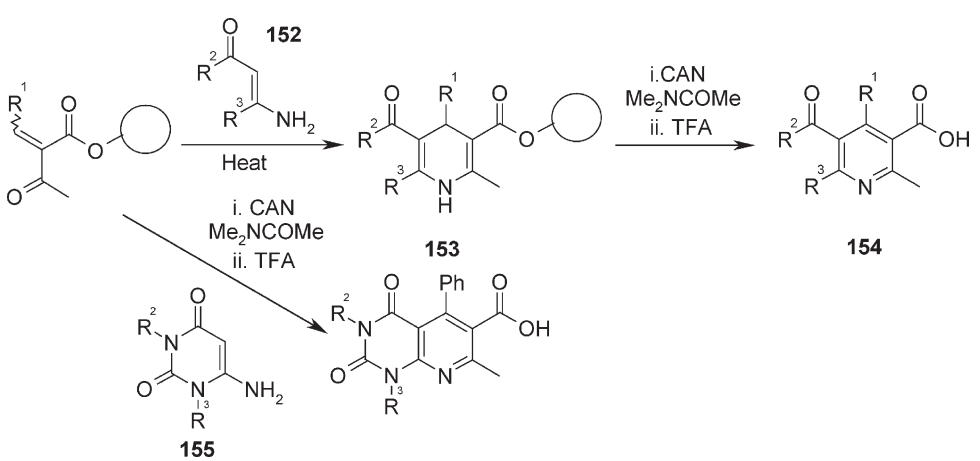
3.3.2.1. 1-Position of enone attached to solid-phase. A new protocol for the preparation of the resin-bound enones **150**, some of the most common building blocks for the assembly of heterocyclic rings, was developed by Katritzky and co-workers in 2000 through a modified Mitsunobu reaction between Wang resin and hydroxyacetophenones, followed by condensations with aryl aldehydes (Scheme 40).[54] Using α-benzotriazole amidines **75** as dinucleophiles, a collection of ten 2-(di)alkylaminopyridines **151**, with additional substituents at the 4- and 6-positions were synthesised with a 75–95% purity with a typical yield of 90%, which compares well with the other methods reviewed (Table 3).

3.3.2.2. 2-Position of enone attached to solid-phase. The most referenced work on the solid-phase synthesis of pyridine is that of Gordeev and co-workers in 1996 (Scheme 41). The Knoevenagel synthesis of the resin-bound enones **140** (by Jung and co-workers) illustrated in Scheme 38 above is similar to that published by Gordeev and co-workers three years previously. Instead of α-pyridinium arylketones **141** as nucleophiles, the latter group used enamino–esters and -ketones **152** to form 1,4-dihydropyridines **153** that underwent CAN oxidation and TFA cleavage to yield typical Hantzsch 2,3,4,5,6-pentasubstituted pyridines **154**. The HPLC purity of the 20 crude pyridines synthesised was generally above 90%, with a typical yield of 91% (Table 4). It should be noted that 6-aminouracil **155** does not react with the enone in solution-phase chemistry, illustrating the possibility of driving difficult reactions to completion on a solid support by using an excess of reagents in solution.[55]

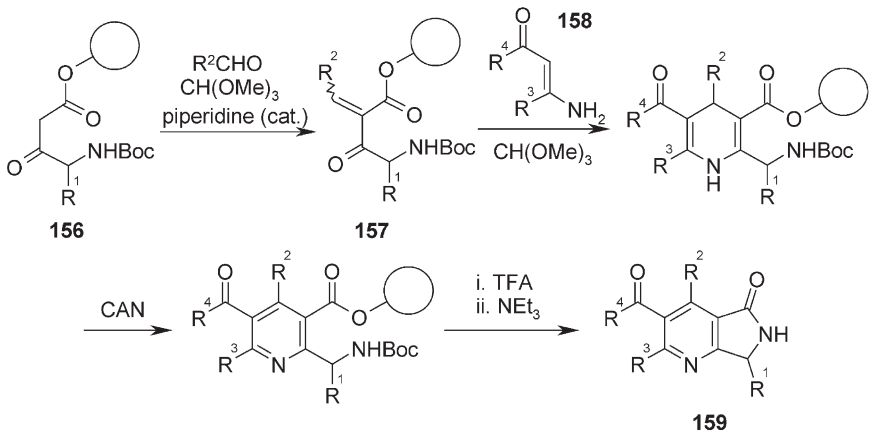
Bhandari and co-workers in 1999 published a very similar synthesis of pyrrolo[3,4-*b*]pyridines **159** that was used to

Table 4. Selected results for pyridine synthesis

Entry	Compound	R^1	R^2	R^3	Purity (%) (HPLC)
1	**247**	Ph(^{13}C)	MeO	Me	80
2	**247**	2-Naphthyl	MeO	Me	98
3	**247**	4-Pyridyl-	*i*-PrO	Me	90
4	**249**	Ph	Et	Et	98
5	**249**	Ph	H	Allyl	100



Scheme 41.



Scheme 42.

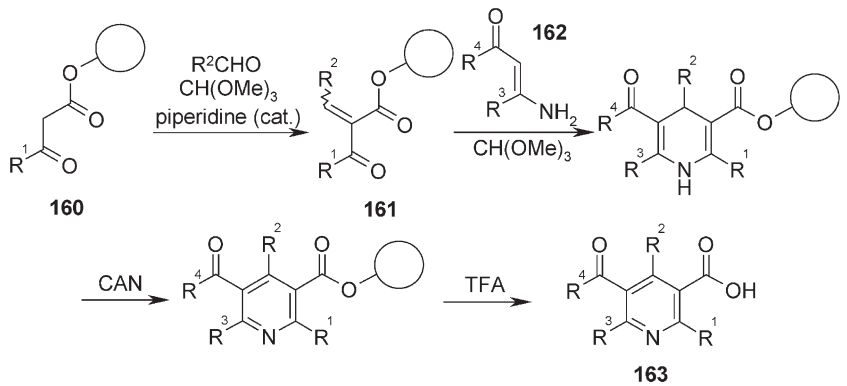
Table 5. Selected results for pyridine synthesis

Entry	R^1	R^2	R^3	R^4	Purity (%) (HPLC)	Yield (%)
1	Bn	Ph	Me	OMe	95	33
2	*s*-Bu	4-CO_2CH_3–C_6H_4–	Me	OEt	98	41
3	Bn	4-Ph–C_6H_4–	*n*-Pr	OEt	95	39
4	Bn	3,4-Cl–C_6H_3–	Me	Me	90	20
5	4-OH–$C_6H_4CH_2$–	4-OBn–C_6H_4–	*n*-Pr	OEt	90	27

produce a combinatorial library of ~5000 compounds (Scheme 42).[56] Starting from the solid-supported β-ketoesters **156**, the enones **157** were produced by Knoevenagel condensation with aromatic aldehydes and these underwent reaction with a variety of electron-deficient enamines **158** (including enamino esters, enamino amides, enamino ketones and enamino nitriles). After CAN oxidation and deprotection of the amine function, the desired pyrrolo[3,4-*b*]pyridines **159** were obtained via cyclorelease in the presence of triethylamine. The yields of the Hantzsch 2,3,4,5,6-substitution products **159** were modest (20–50%), but the purities were excellent (>90% by HPLC) (Table 5).

Bhandari and co-workers also used enones attached to a solid-phase at the 2-position **161** in 1999 to synthesise the highly functionalised bipyridines **163** (Scheme 43).[57] A library of 500 bipyridines with purities of 70–98% and yields of 28–84% was generated by split/pool synthesis from five β-ketoesters **160**, ten aldehydes and ten electron-deficient enamines **162** (Table 6).

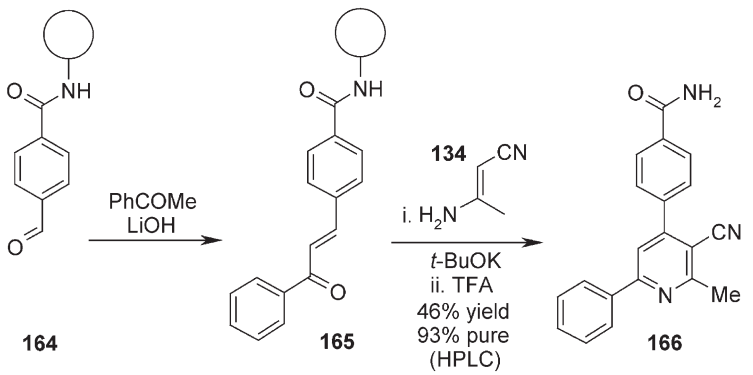
3.3.2.3. 3-Position of enone attached to solid-phase. The value of enones **165** was further demonstrated by Marzinzik and co-workers in 1998 as intermediates for the combinatorial assembly of four different templates (pyrimidines, dihydropyrimidinones, pyridines and pyrazoles) on



Scheme 43.

Table 6. Selected results for pyridine synthesis

Entry	R^1	R^2	R^3	R^4	Purity (%) (HPLC)	Yield (%)
1	5-OMe-2-Pyridyl-	Ph	Me	OMe	95	31
2	5-Cl-2-Pyridyl-	4-Ph–C_6H_4–	Me	OMe	90	84
3	Me	Ph	2-Pyridyl-	O*t*-Bu	85	79
4	Me	2-Thiophene	2-Pyridyl-	OEt	76	47
5	5-Cl-2-Pyridyl-	4-Ph–C_6H_4–	5-Me-2-Pyridyl-	OEt	70	48



Scheme 44.

the solid-phase (Scheme 44).[58] In this Hantzsch-type pyridine synthesis, a 2,4,5,6-tetrasubstituted pyridine **166** was prepared in 46% yield with a purity of 93% starting from a solid-supported aldehyde **164**. The enones **165** were then produced via Wittig and Claisen–Schmidt methods, by reacting with the α-cyano enamine **134** to form the pyridine ring that was subsequently cleaved by treatment with TFA.

4. Conclusion

The spectrum of syntheses included in Section 3.1 shows a high degree of diversity and flexibility, yet there seems to be no truly general method for the synthesis of substituted pyridines. For each pyridine desired, the number, nature and pattern of substituents will dictate the suitability of each strategy. There are many creative and practical methods, however, every one being incompatible with certain functional groups and each synthesis must be carefully planned. To conclude, there is a continuing need to generate new and improved methods for pyridine synthesis.

The most efficient methods from Section 3.1, giving the most diverse ranges of pyridines, are represented in the solution-phase combinatorial chemistry literature in Section 3.2 and each has been used to generate a massive diversity in one single step. Other methods from Section 3.1 may become more practical through the use of new solid-phase reagents.

The domain of solid-phase chemistry shows great promise for the synthesis of many compound types, especially peptides and heterocycles. In the area of pyridine synthesis, the examples discussed in Section 3.3 demonstrate that solid-phase is a powerful medium, but it is striking that the range of chemistry published on solid-phase pyridine synthesis is so limited, probably because of the results having remained in the private domain. Despite their varying points of attachment to solid-support and library size, the published syntheses are all very similar, involving enones which either react with enamines or ketones and an ammonia source. With such a narrow band of precedent in the literature, there is a need for other complementary methods.

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Biographical sketch

Gavin D. Henry was born in 1978 in Belfast, Northern Ireland. He received his M.Sci. in 2000 from Imperial College London, during the course of which he spent one year in the group of Professor Pierre Sinaÿ at Ecole Normale Supérieure, Paris, he also had industrial placements at SmithKline Beecham (US) and Chiroscience (UK) and earned the Merck Prize for research in organic chemistry. He completed his PhD thesis in 2004, under the guidance of Professor Donald Craig at Imperial College London, on a new synthetic route to substituted pyridines and its application to natural product synthesis.

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Quinoxalines. Part 13: Synthesis and mass spectrometric study of aryloxymethylquinoxalines and benzo[*b*]furylquinoxalines☆,☆☆,★

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Abstract—A series of new aryloxymethylquinoxalines, benzo[*b*]- and naphtho[2,1-*b*]furylquinoxalines, possessing potential biological activity, was prepared, characterized by IR and NMR spectroscopy and their electron ionization (EI) mass spectra studied in detail. The aryloxymethylquinoxalines were obtained by reacting halogenomethylquinoxalines with bifunctional *O*-nucleophiles. The benzo[*b*]-furylquinoxalines and naphtho[2,1-*b*]furylquinoxalines were prepared via two routes, which differed in the order of the two cyclization steps involved in the syntheses. The composition of the ions obtained by EI mass spectrometry were determined by accurate mass measurements and the fragmentation pathways clarified by B/E linked scans and collision induced dissociation. The mass spectrometric behaviour of the compounds studied as to the possible loss of OH˙ radicals proved to be very characteristic.

1. Introduction

In our previous report the mass spectrometric fragmentation of differently substituted aryl- and heteroaryloxymethyl-quinoxalines was discussed.[1] In this paper, both the syntheses and the mass spectral fragmentation of several new aryloxymethylquinoxalines, benzo[*b*]- and naphtho[2,1-*b*]-furylquinoxalines **3a**–**11c** and **16a**–**22c** will be reported (cf. Scheme 1a and b). Their mass spectra did not exhibit the $[M-RCN]^+$ peaks, previously reported as typical of quinoxalines;[2] in contrast, the presence of the $[M-OH]^+$ ions, depending on the substitution pattern of the aryl moiety, was observed. The fragmentation pattern involving aryl migration to the methyl group in position 3 of the quinoxaline ring system, described in our earlier study,[1] was observed in the present case as well.

The structures of the compounds synthesized were established by IR and NMR. Their EI and ESI/CID (MS/MS) mass spectra deserve a special discussion because they proved to be sensitive to a number of structural factors including the substitution pattern in positions 2 and 3 of the quinoxaline ring.

2. Results and discussion

2.1. Syntheses

The chemistry of quinoxaline and its derivatives attracts continuous attention as a consequence of the potential biological activity of this class of compounds. Recently, we published a new synthetic route to pyrazolo[3,4-*b*]quinoxalines.[3] Continuing this research, in the present study, the syntheses of several new aryloxymethyl-, benzo[*b*]-, and naphtho[2,1-*b*]-quinoxalines will be reported. Compound **4** (cf. Scheme 1a), for instance, was found to be a useful intermediate for the preparation of the substituted phenoxy acetic acid derivatives. This group of compounds has been patented as inhibitors of the arachidonic acid metabolism.[4] The 'quizalofop-P' (cf. Scheme 2) and related compounds are hormone weedkillers. The 'quizalofop-P' is a selective systemic herbicide, which is used for post-emergence control of annual and perennial grass weeds in broad-leaved crops, applied as a mixture with other herbicides in amounts of 150 g/ha.[5–8] The benzo[*b*]- and naphtho[2,1-*b*]quinoxalines are chemically similar to the aryloxymethylquinoxalines

☆ Part 12, see Ref. 3.

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★ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.05.064

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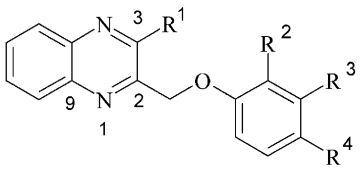
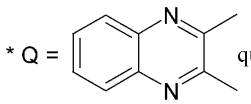


Comp.- No.	R^1	R^2	R^3	R^4
3a	CH_3	OCH_2-Q-CH_3*		
3b	CH_3		OCH_2-Q-CH_3*	
3c	CH_3			OCH_2-Q-CH_3*
3d	C_6H_5			OCH_2-Q-C_6H_5*
4a	CH_3	OH		
4b	CH_3		OH	
4c	CH_3			OH
6a	CH_3	$OCOC_6H_5$		
6b	CH_3		$OCOC_6H_5$	
6c	CH_3			$OCOC_6H_5$
8a	CH_3			$OCH_2COOCH_2CH_3$
8b	CH_3			OCH_2COOH
9a	CH_3			$OCH(CH_3)COOCH_3$
9b	CH_3			$OCH(CH_3)COOH$
11a	CH_3	CH_2OH		
11b	CH_3			CH_2OH
11c	CH_3	OCH_3		CH_2OH



Scheme 1a.

and some of their derivatives, and have been proved to be biologically active. The unsubstituted compound **16a** (cf. Scheme 1b) was used, for instance, in the chlorella test and was found by a factor of 10 more active than the known herbicide di-nitro(*ortho*)cresole DNOC.[9]

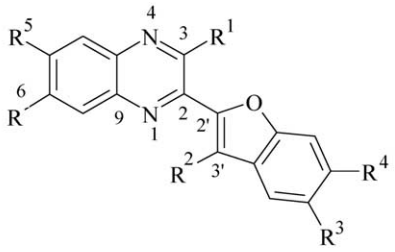
The reaction of dihydroxy benzenes (**2**) with halomethylquinoxaline **1** (in a molar ratio 1:2) afforded the aryloxymethylquinoxalines **3** (cf. Scheme 3); if the molar ratio was 1:1, a mixture of **2**, **3** and the monoether **4** was obtained. To protect one of the hydroxy groups, **2a**–**c** were reacted with benzoyl chloride; if the reaction was carried out at room temperature, the monobenzoyl products **5** were obtained in 90% yield.[10] These monohydroxy derivatives **5a**–**c** reacted with halomethyl compounds **1a**,**b** in 2-butanone solution in the presence of anhydrous powdered potassium carbonate when heated under reflux for several hours, giving the corresponding aryloxymethylquinoxalines **6a**–**c**. The latter could be easily converted back to the corresponding phenol derivatives **4a**–**c** by alkaline hydrolysis.

The *para*-disubstituted derivative **4c** reacted with bromoacetic acid ethylester (**7a**) or with 2-bromopropionic acid methylester (**7b**) in the presence of K_2CO_3 and gave the corresponding esters **8a** and **8b** as depicted in Scheme 4 in 60–65% yields. Compounds **8a**, **8b** were further converted to their potassium salts by heating in ethanolic KOH and subsequently to the corresponding free carboxylic acids **9a**, **9b** by acidifying the solution with acetic acid.

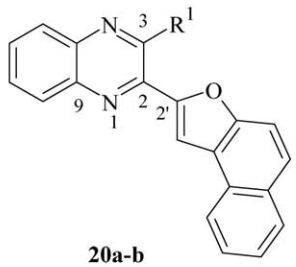
The *o*- and *p*-hydroxy benzyl alcohols **10a**–**c** reacted with **1a** and KOH in a molar ratio of ca. 1:1:1 affording the aryloxymethylquinoxalines **11a**–**c** (cf. Scheme 5).

The benzo[*b*]furylquinoxalines **16**, **20** and **22** (cf. Scheme 1b), which behave chemically very similar to the aryloxymethylquinoxalines, were synthesized along two routes which differ in the sequence of the two ring closures involved in the procedures. In the first procedure, the initial step was cyclization of salicylaldehydes **12a**–**c** with bromo- or chloroacetone to yield the corresponding 2-acetylbenzo[*b*]furanes **13a**–**c**;[11] these were oxidized with SeO_2 to give the glyoxals **14a**–**c** which, without isolation, were cyclized with 1,2-phenylene diamines **15a**–**c** to the quinoxalines **16a**–**g** (cf. Scheme 6).

In the second procedure, the ring closure to the benzofuran ring happened after the cyclization step of the quinoxaline ring system (cf. Scheme 7). Precursors for this second type of syntheses are halogenomethylquinoxalines already



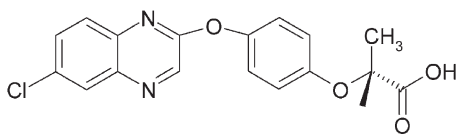
16 a-s , 22 a-c



20a-b

Compound No.	R^1	R^2	R^3	R^4	R^5	R^6
16a						
16b					Cl	Cl
16c					CH_3	CH_3
16d			Cl			
16e			Cl		Cl	Cl
16f			Cl		CH_3	CH_3
16g			Br			
16h	CH_3					
16i	CH_3		Cl			
16j	CH_3		Br			
16k	CH_3	CH_3				
16l	CH_3	C_6H_5		OCH_3		
16m		$OCOCH_3$				
16n	CH_3	$OCOCH_3$				
16o	CH_3	$OCOC_6H_5$				
16p	C_6H_5					
16q	C_6H_5	$OCOCH_3$				
16r	C_6H_5	$OCOC_6H_5$				
16s	4-Cl-C_6H_4					
20a	CH_3					
20b	C_6H_5					
22a	benzofuryl					
22b	benzofuryl				Cl	
22c	benzofuryl				CH_3	CH_3

Scheme 1b.



quizalofop-P

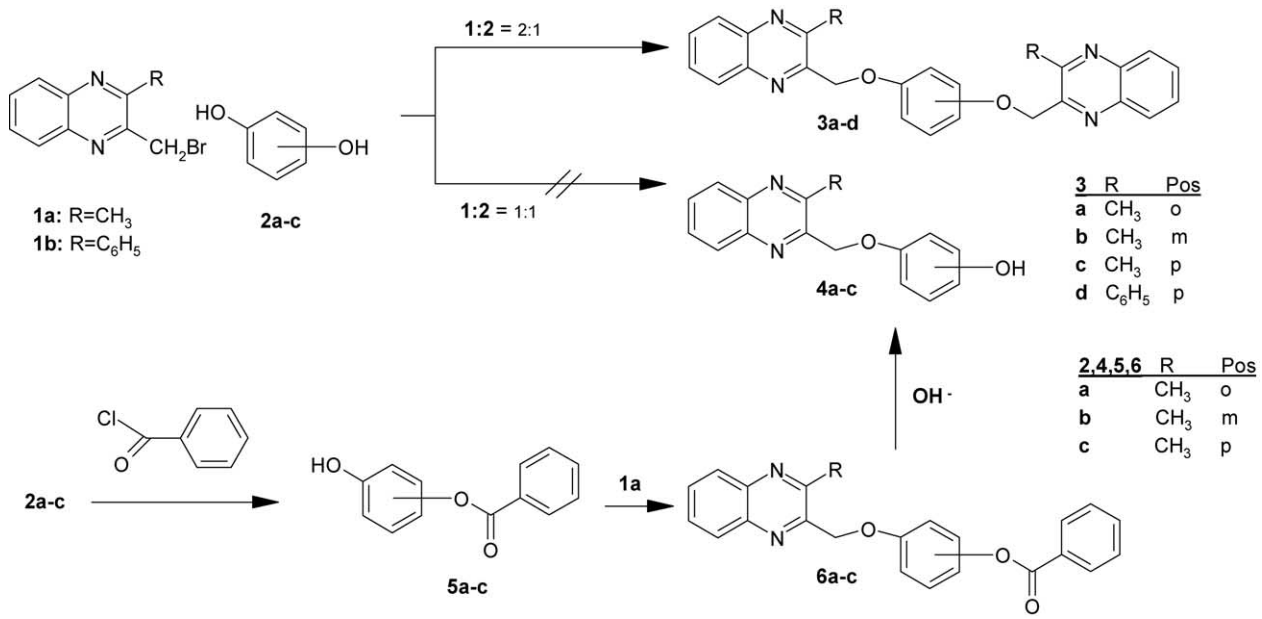
(R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionic acid

Scheme 2.

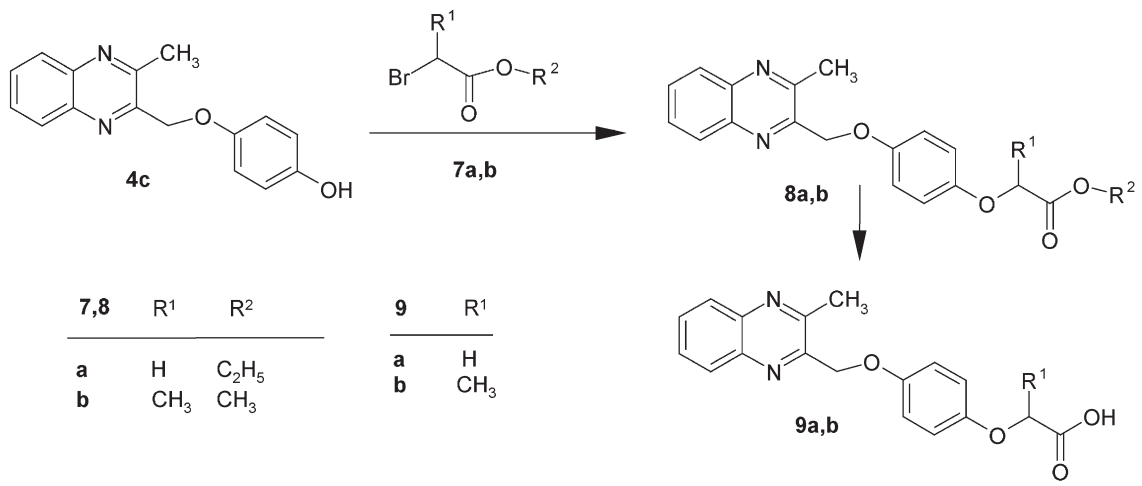
known: 2-(chloromethyl)quinoxaline **1g**,[12] 2-(bromomethyl)-3-methylquinoxaline **1a**[13] and 2-(bromomethyl)-3-phenylquinoxaline **1b**, respectively.[14] 2-(Bromomethyl)-3-(4-chlorophenyl)quinoxaline **1c** was synthesized from 4-chloropropiophenone by converting it into the isonitroso compound using ethyl nitrite. The isonitroso compound was hydrolyzed into the 1,2-diketone by steam distillation from a sulfuric acid solution; this compound was treated with bromine in boiling chloroform to afford the 1-(4-chlorophenyl)-3-bromopropan-1,2-dione, which was used further without isolation. Finally, the latter compound reacted exothermically with 1,2-phenylene diamine leading to 2-(bromomethyl)-3-(4-chlorophenyl)quinoxaline **1c**.

The CH_2Hal group in **1a**–**g** is highly reactive because of the electron-withdrawing activity of both the halogen atoms and the quinoxaline ring. Hence nucleophilic attack on this carbon atom can easily take place by the phenolate anion, which was obtained by addition of an equimolar amount of KOH. This nucleophilic substitution of the halogen by the phenolate led to the aryloxymethylquinoxalines **17**, **19** and **21** (cf. Scheme 7). Since these new ether derivatives possess an adequately active carbonyl group in the neighbourhood of the ether bond (in *ortho*-position of the phenyl moiety), addition of a second equivalent of KOH enforces the cyclization to the benzo[*b*]furane system.

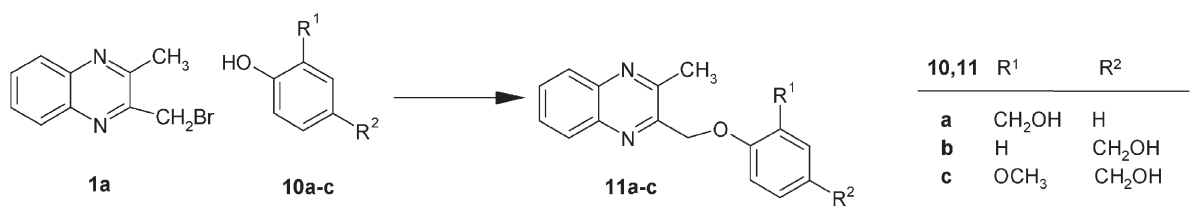
As phenolate precursors, salicylic aldehydes **12a**–**c**, 2-hydroxy-naphthalen-1-carbaldehyde **18** and 2-hydroxyketones **12d**, **12e** were used;[15] yields for the final benzo[*b*]furylquinoxalines were between 80–90%.



Scheme 3.



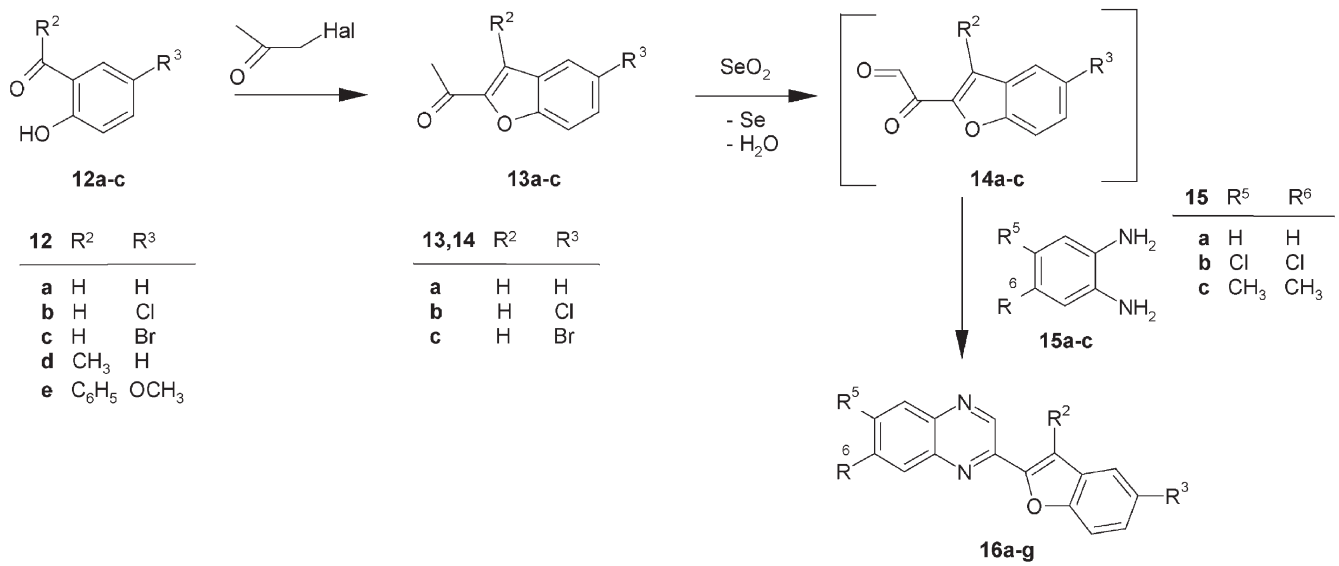
Scheme 4.



Scheme 5.

2.2. Mass spectrometry

2.2.1. Aryloxymethylquinoxalines. The main peaks of the low resolution 70 eV EI mass spectra of the compounds studied (cf. Scheme 1a and b) are listed in Table 1a of Supplementary Material. The EI mass spectra of compounds **3a–c**, **6a–b**, **8a**, and **9a** are dominated by rearrangement processes. This kind of skeletal rearrangements involving aryl migrations have been invoked to explain the fragmentation modes of different types of compounds and have been described in detail.[16–22] The corresponding aryl migration can be revealed from the spectra of the compounds **6a**, **6c**, **8a** and **9a** which leads to weak ions at *m/z* 211 ($C_{14}H_{11}O_2$) and *m/z* 193 ($C_{11}H_{13}O_3$) for **8a** and **9a**, respectively. The

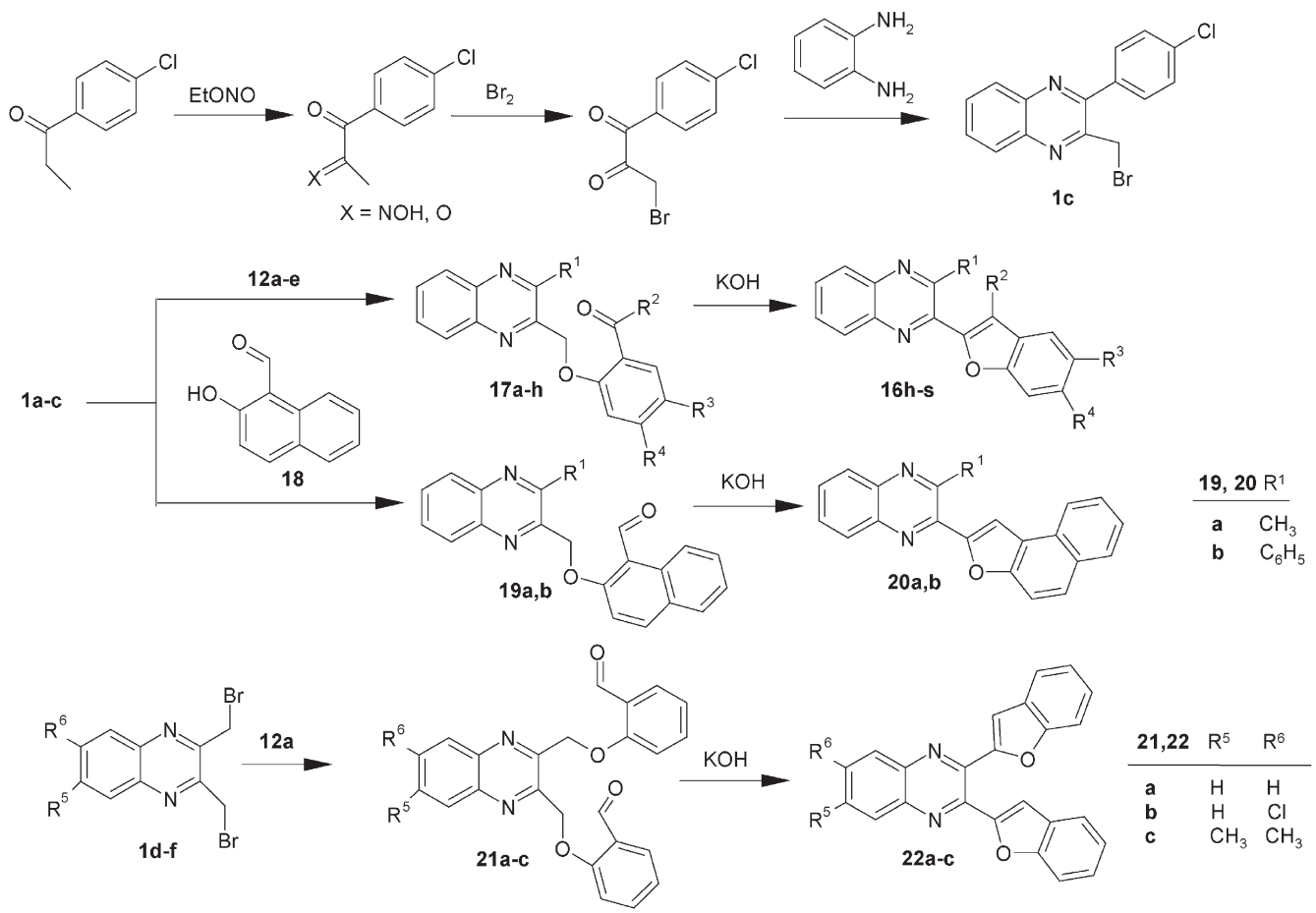


12	R^2	R^3
a	H	H
b	H	Cl
c	H	Br
d	CH_3	H
e	C_6H_5	OCH_3

13,14	R^2	R^3
a	H	H
b	H	Cl
c	H	Br

15	R^5	R^6
a	H	H
b	Cl	Cl
c	CH_3	CH_3

Scheme 6.



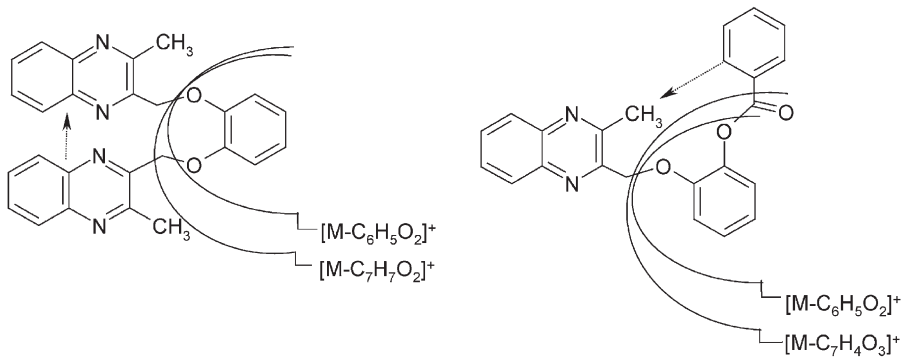
19, 20	R^1
a	CH_3
b	C_6H_5

21,22	R^5	R^6
a	H	H
b	H	Cl
c	CH_3	CH_3

Scheme 7.

presence of these fragment ions together with their accurate masses (cf. Table 2a in Supplementary Material) reveals that the aryl substituent migrates to the methyl group at position 3 of the quinoxaline ring system (cf. Scheme 8). Previously,[1] the aryl migrations in aryloxymethyl quinoxalines were found to be favoured by electron donating substituents in the migrating aryl group; accordingly, in the cases of compounds **4a–c**, **8b**, **9b**, and **11a–c** no aryl migration was observed.

In **3a–c**, **6a** and **6c** the relatively abundant ions $[M-C_6H_5O_2]^+$ and $[M-C_7H_7O_2]^+$ (and the ions $[M-C_6H_5O_2]^+$ and $[M-C_7H_4O_3]^+$ for **6a** and **6c**, respectively) prove a skeletal rearrangement to occur. This



Scheme 8.

is also the case for compound **3d** (with Ph on position 3); the ejection of the aroyl system was observed but only to a very small extent (*m/z* 437, ~1% relative abundance—RA). The key step of the aroyl loss from compounds **3a**–**c** when compared to **6a** and **6c** should involve the rearrangement of the corresponding molecular ions in two different ways. The elimination of the aroyl group from compounds **6a** and **6c** can be rationalized with an aryl migration which occurs to the methyl group at position 3 (R^1=CH_3), as described in Scheme 8. The location of the phenyl substituents is very important for the relative abundance of the resulting ions $[M-C_6H_5O_2]^+$ or $[M-C_7H_4O_3]^+$. The mass spectrum of **6a** exhibits the strongest loss of $C_6H_5O_2$ radical ($[M-C_6H_5O_2]^+$ ca. 61% RA), while for **6c** the RA of the corresponding ion was only 2%. In the mass spectrum of compound **6b** the ions $[M-C_6H_5O_2]^+$ or $[M-C_7H_4O_3]^+$ could not be observed at all, thus no aryl migration takes place (cf. Scheme 8).

However, the observation of the relatively abundant ions $[M-C_6H_5O_2]^+$ and $[M-C_7H_7O_2]^+$ in the EI mass spectra of **3a**-**c** should result from another rearrangement process. In order to get deeper insight into the mechanism of these fragmentations we also recorded the mass spectra of **6a**,**c**, **8a**,**b** and **11b** (beside **3a**–**c**), generated by positive electrospray ionization (ESI). The corresponding $[M+H]^+$ ions were used as precursor ions and their CID fragmentations were studied. The main results of the MS/MS measurements are depicted in Table 3a. In compounds **6a** and **6c**, the EI fragmentations, however, differ clearly from those of the ESI mass spectra since the $[M-C_6H_5O_2]^+$ or $[M-C_7H_4O_3]^+$ ions (RA of the latter being 60% under EI conditions) were not found at all.

Interestingly, only the CID spectra of compounds **3a**–**c** correspond exactly to the EI mass spectra and the ions *m/z* 314 and 299 to the loss of the aroyl group. Obviously, the aryl migration is induced exclusively by electron ionization, while the same rearrangement in compounds **3a**–**c** occurs also under the soft ESI conditions.

2.2.2. Benzo[*b*]- and naphtho[2,1-*b*]furyl quinoxalines. The highly conjugated nature of compounds **16a**–**s**, **20a**,**b** and **22a**–**c** (depicted in Scheme 1b) is reflected in the stability of their molecular ions (cf. Table 1b in Supplementary Material; RA 100% except for compounds **16k** and **16m**–**r**). The loss of HCN and RCN from the molecular ions and the formation of the $[M-CHO]^+$ ions from the benzofuran ring unit were reported in similar compounds.[2] Surprisingly, the ester derivatives **16m**–**o**, **16q** and **16r** did not show the $[M-RCN]^+$ peaks like the aryloxymethylquinoxalines mentioned above. Comparison of the spectra of compounds **16a**, **16h**, **16p** and **22a** with cases where R^1=H, CH_3, Ph or benzofuryl show that the fragmentation patterns are quite similar for these compounds (cf. Tables 1b and 2b in Supplementary Material). Different substituents (CH_3, Cl, and Br) at different positions R^3, R^4, R^5, R^6 (compared to compounds **16b**–**g**, **16i**–**j**) did not influence the fragmentation behaviour.[23]

The relative abundance of the $[M-OH]^+$ ions in the MS/MS spectra proved to be very characteristic for the compounds studied: In case of the benzo[*b*]furylquinoxalines, the replacement of the methyl group in position 3 of the quinoxaline moiety by phenyl or benzofuryl modifies significantly the loss of OH˙ radicals from the molecular ions compared with the corresponding aryloxymethylquinoxalines. In addition for determining the structure–fragmentation relationship of these compounds, the main mass spectrometric fragmentation patterns of some

Table 3a. Characteristic fragment ions of compounds **3a**, **6a**, **8a** and **8b** as proved by collision induced decomposition of the selected precursor ion from ESI positive spectra

No. of compound		Results from the CID-spectra *m/z*
3a	MS from *m/z* 423	314$[M-C_6H_5O_2]^+$, 299$[M-C_7H_7O_2]^+$, 265$[M-C_{10}H_9N_2]^+$, 249$[M-C_{10}H_9N_2O]^+$, 157$[M-C_{16}H_{13}N_2O_2]^+$
6a	MS from *m/z* 371	353$[M-OH]^+$, 249$[M-C_7H_5O_2]^+$, 197$[M-C_{10}H_9N_2O]^+$, 157$[M-C_{13}H_8O_3]^+$, 105$[M-C_{16}H_{13}N_2O_2]^+$
8a	MS from *m/z* 353	337$[M-CH_3]^+$, 335$[M-OH]^+$, 279$[M-COOCH_2CH_3]^+$, 266$[M-CH_2COOCH_2CH_3]^+$, 249$[M-OCH_2COOCH_2CH_3]^+$ 157$[M-C_{10}H_{10}O_4]^+$
8b	MS from *m/z* 325	310$[M-CH_3]^+$, 307$[M-OH]^+$, 279$[M-COOH]^+$, 266$[M-CH_2COOH]^+$, 249$[M-OCH_2COOH]^+$, 157$[M-C_8H_7O_4]^+$

Table 3b. Characteristic fragment ions of compounds **16p**, **16s**, **20a**–**b**, **22a** as proved by linked scan measurements

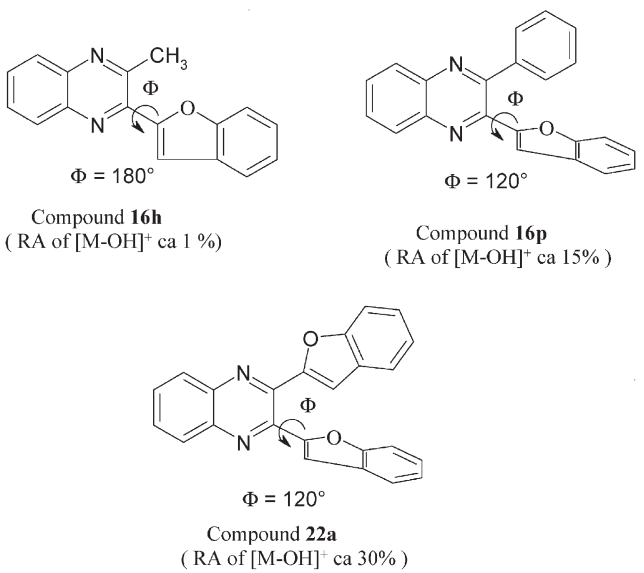
No of compound		Result of the linked scans *m/z*
16p	B/E from *m/z* 322	305[M−OH]$^+$, 293[M−CHO]$^+$, 245[M−Ph]$^{+\cdot}$, 219[M−PhCN]$^{+\cdot}$
	B/E from *m/z* 293	266[M−HCO−HCN]$^+$, 190[M−HCO−PhCN]$^+$
16s	B/E from *m/z* 356	339[M−OH]$^+$, 328[M−CO]$^+$, 321[M−Cl]$^+$, 219[M−PhCNCl]$^{+\cdot}$, 213[M−143]$^+$
	B/E from *m/z* 339	304[M−OH−Cl]$^+$
20a	B/E from *m/z* 310	393[M−OH]$^+$, 281[M−CHO]$^+$, 269[M−CH_3CN]$^{+\cdot}$
20b	B/E from *m/z* 372	355[M−OH]$^+$, 343[M−CHO]$^+$, 269[M−PhCN]$^{+\cdot}$, 205[M−naphthofuryl]$^+$
22a	B/E from *m/z* 362	345[M−OH]$^+$, 334[M−CO]$^+$
	B/E from *m/z* 345	316[F−CHO]$^+$

characteristic compounds were analyzed as a function of the substituents at positions 2 and 3 of the quinoxaline moiety.

2.2.3. Influence of the substituents (H, CH_3, and Ar) at position 3 on the loss of OH$^\cdot$ radical from the aryloxymethylquinoxalines, as compared to the benzo-[*b*]- and naphtho[2,1-*b*]furyl quinoxalines. The aryloxymethyl quinoxalines with hydrogen or methyl at position 3 of the quinoxaline moiety (R^1=H or CH_3) exhibit [M−OH]$^+$ and [M−CHO]$^+$ ions as the main rearrangement products. In contrast the mass spectra of the 2-benzo[*b*]furyl quinoxalines having hydrogen or methyl at position 3 did not exhibit these peaks at all or only in a very small abundance (RA<3%). However, with Ph or benzofuryl at position 1 the mass spectra exhibit the strongest loss of OH$^\cdot$ radical (RA of [M−OH]$^+$ ions 5–30%). Metastable data from B/E scan confirm the formation of these ions directly from [M]$^{+\cdot}$ (depicted in Table 3b).[24]

Previous investigations based on NMR spectroscopy show that the conformation of the 2-benzo[*b*]furyl quinoxalines is flexible about the C(2)–C(2′) bond. If there are substituents in the 3,3′-positions, the free rotation was proved to be sterically hindered and the two heteroaromatic moieties are twisted (cf. Scheme 9).[25] Obviously in the case of the benzo[*b*]- and naphtho[2,1-*b*]furyl type quinoxalines, the torsional angle ϕ (interannular π-conjugation between the π-deficient quinoxaline ring system and the π-rich benzo[*b*]furyl substituent at position 2) play the most important role as to the RA of the [M−OH]$^+$ peaks (cf. Scheme 9). The benzofuryl quinoxalines with hydrogen or methyl at position 3 are well conjugated (ϕ=180°). If the torsional angle ϕ between the quinoxaline ring system and the attached benzofuryl/naphthofuryl system is 180°, a complete delocalisation of the π-electrons and a full interannular conjugation will be possible and nearly no loss of OH$^\cdot$ radical occurs. Torsional twist from 180° in case of compounds **16p**, **16s**, **20b**, **22a**–**22c** (R^1=Ph, ClC_6H_4 or benzofuryl), however, disturbs the interannular π-conjugation and the compounds lose easily the OH$^\cdot$ radical (RA of [M−OH]$^+$ ions 15–28%).

The aryl migration discussed for the aryloxymethyl quinoxalines is not observed in the mass spectra of the benzo[*b*]-, and naphtho[2,1-*b*]furyl quinoxalines.



Scheme 9.

3. Conclusions

A large variety of aryloxymethylquinoxalines, benzo[*b*]- and naphtho[2,1-*b*]furyl quinoxalines possessing potential biological activities were prepared and studied by IR, NMR, and MS.

The aryloxymethylquinoxalines were prepared by reacting halomethylquinoxalines with different substituted monohydroxy- or dihydroxy compounds. Several of the aryloxymethylquinoxalines consist of building blocks of the known herbicide *quizalofop*. The benzo[*b*]furyl quinoxalines were prepared with two methods, which differ in the order of cyclization. In the first approach, acetyl-substituted benzo[*b*]furanes **13** were used as starting material, which was oxidized with SeO_2; the resulting glyoxals were cyclized with 1,2-phenylene diamine into the quinoxaline without isolation of the glyoxals. In the second procedure, halomethyl-substituted quinoxalines were reacted with aromatic 2-hydroxy carbonyl compounds after addition of one equivalent of base to obtain the aryloxymethylquinoxalines and then adding another equivalent of base to carry out the cyclization to the benzo[*b*]furyl quinoxalines. These two step syntheses can be conveniently carried out in one pot.

Detailed analysis of the mass spectra of the quinoxaline derivatives, thus obtained, allows the following conclusions to be drawn. Generally, the fragmentation pathways of the molecular ions depend on the substituents on position 2 of the quinoxaline moiety. The mass spectra of the variously substituted derivatives resemble very much each other. The

aryloxymethylquinoxalines did not exhibit the loss of HCN and RCN, although the spectra of the corresponding benzo[*b*]- and naphtho[2,1-*b*]furyl quinoxalines exhibit the $[M-HCN]^{+\cdot}$ and $[M-RCN]^{+\cdot}$ ions. The aryloxymethylquinoxalines with methyl in position 3 of the quinoxaline ring moiety exhibit $[M-OH]^{+}$ ions as the main aryl migration/rearrangement products. The corresponding benzo[*b*]furyl quinoxalines with R^1=H, CH_3 do not lose the $OH^{\cdot}$ radical or do so only in very low amounts (RA 1–3%). In contrast, the benzo[*b*]- and naphtho[2,1-*b*]furyl quinoxalines with a phenyl or benzofuryl group at position 3 exhibit the strongest loss of $OH^{\cdot}$ (RA 15–28%). The π-conjugation between the quinoxaline moiety and the benzo[*b*]- or naphtho[2,1-*b*]furyl substituents play the most important role as to the RA of the $[M-OH]^{+}$ peaks.

If position 3′ of the benzofuryl ring contains an ester group the main fragmentation of the molecular ion is due to an elimination of the ester radical and no $[M-RCN]^{+\cdot}$ ions are observed. The quinoxalines with benzo[*b*]furyl and naphtho[2,1-*b*]furyl groups undergo ring cleavage at the carbon nitrogen bond N(1)–C(9) due to the opening of the quinoxaline ring, but in the mass spectra of the aryloxymethylquinoxalines no such fragments occur.

4. Experimental

Melting points were determined on a Boetius micro hotstage microscope. The IR spectra were recorded with a Perkin–Elmer FTIR 1600 spectrometer (cm^{-1}). The NMR spectra were acquired with a Bruker NMR ARX 300 spectrometer. The ^1H and ^{13}C chemical shifts are given in the δ scale (ppm) downfield from tetramethylsilane (TMS) as internal standard.

4.1. Mass spectrometry

The low resolution EI mass spectra were obtained using a Thermo Finnigan SSQ710 instrument (Finnigan, San Jose, CA, USA) with an electron energy of 70 eV, and source temperatures between 430 and 470 K, using a direct insertion probe. Elemental compositions were determined by accurate mass measurement within an average accuracy of ca 3×10^{-4} au, at a resolution of 10.000–12.000 (10% valley) with a VG Zabspec instrument using the peak matching technique and a Micromass GC-TOF_{micro} mass spectrometer (Micromass, Wythenshawe, UK) with standard deviation <5 ppm. Perfluorokerosene (PFK) was used as reference compound in both cases. Metastable ion spectra (B/E and B^2/E linked scans; MIKES) were recorded using the VG ZABspec.

The ESI and CID spectra were recorded using a Micromass Q-TOF_{micro} mass spectrometer in positive electrospray mode. All samples were injected (10–15 μl/min) with a Harvard syringe pump. The capillary voltage was set to 2.8 kV, with a cone voltage between 25–35 V. The source temperature was 80 °C and the desolvation temperature 150 °C. The cone and desolvation gases (nitrogen) were delivered at 50 and 360 l h^{-1} respectively. For MS/MS after selection of the appropriate precursor ion, argon was used as the collision gas (~5×10^{-5} mbar) and the gas cell was maintained between 15 and 20 eV.

4.2. Syntheses of the compounds

Compounds **17a–h**, **19a**,**b** and **21a–c** were characterized by hr-MS or $^1H/^{13}C$ NMR spectroscopy (IR data are given generally); they were reacted into the final products **16** and **20** immediately. In cases, where hr-MS data are not given in the procedures, they are collected in Tables 2a and b in the Supplementary Material.

2-(Bromomethyl)-3-(4-chlorophenyl)quinoxaline (**1c**). Step 1. 1-(4-Chlorophenyl)-2-hydroxyiminopropan-1-on (CAUTION! To breath in ethylnitrite causes dizziness. Use fumehood.) The generator for the ethylnitrite consists of a two-necked flask and a dropping funnel. A solution of HCl (725 mmol, ca. 60 ml), EtOH (375 mmol, 17.25 g, 22 ml) and water (140 ml) are added to a $NaNO_2$ solution (725 mmol, 50 g) in EtOH (350 mmol, 16.1 g, 20.5 ml) and water (140 ml). The resulting gaseous ethylnitrite reacts with a solution of 4′-chloropropiophenone (650 mmol, 110 g) in EtOH (2 mol, 92 g, 117 ml) in a 500 ml three-necked flask equipped with a cooler, thermometer and a gas inlet. At the beginning of the reaction, the propiophenone solution was acidified with 5 ml conc. HCl and heated to 50 °C. The reaction time took place in 4 h. After intensive cooling the product crystallized in 61% yield and it was recrystallized from aqueous ethanol, mp 116–117 °C.

Step 2. 1-(4-Chlorophenyl)propan-1,2-dione. After steam distillation of a mixture of 1-(4-chlorophenyl)-2-hydroxyiminopropan-1-one (400 mmol, 79 g) and 1 M sulfuric acid (550 ml), the diketone was extracted with dichloromethane from 4 l of the distillate. The product was dried on sodium sulfate and filtered. After removing the solvent the oil was isolated in 88% yield by cooling in a refrigerator; mp 22–23 °C.

Steps 3 and 4. 1-(4-Chlorophenyl)-3-bromo-propan-1,2-dione and 2-(Bromomethyl)-3-(4-chlorophenyl)-quinoxaline (**1c**). (CAUTION! Halodiketones are lacrimatory!) A solution of bromine (350 mmol, 55.93 g) in chloroform (200 ml) was added to a boiling solution of 1-(4-chlorophenyl)propan-1,2-dione (350 mmol, 63.91 g) in chloroform (100 ml). The addition was carried out in ca 30 min. The mixture was heated under reflux for 30 min and washed after cooling four times with 150 ml ice water. Then a solution of *o*-phenylene-diamine (350 mmol, 37.8 g) in chloroform (500 ml, 50 °C) was added slowly to 3-bromo-1,2-dione (exothermic reaction!). The mixture was heated under reflux for 20 min, dried on $CaCl_2$ and filtered. The solvent was removed in vacuo. After washing with a little amount of cold methanol, the product was filtered by suction and recrystallized from 1-butanone, yield 58%, mp 175–177 °C.

4.2.1. General procedure for the synthesis of the compounds 3a, 3c, and 3d. The diol **2** (10 mmol, 1.1 g), dissolved in 50 ml EtOH under argon, was mixed with a KOH solution (20 mmol, 1.12 g) in 50 ml EtOH and a solution of the 3-substituted 2-(bromomethyl)quinoxaline

(20 mmol) in EtOH by stirring under argon. The mixture was refluxed for 2 h, concentrated in vacuo and kept in a refrigerator overnight. The solid was collected by filtration, washed with water and recrystallized.

o-Phenylene-bis[oxymethylen(3-methyl-quinoxalin-2-yl)] (**3a**). This compound[26,27] was obtained from **1a** (4.75 g, dissolved in 130 ml EtOH) and **2a** in 77% yield as pale beige needles, mp 176–178 °C (1-butanol); IR: 3060, 3040, 2955, 2930, 2825, 1590, 1515, 1500, 1455, 1400, 1370, 1350, 1325, 1290, 1250, 1200, 1155, 1120, 1050, 1025, 1005, 930, 950, 900, 840, 810, 750, 730, 680, 660, 605, 590, 555, 520, 480, 455, 425; ^{1}H NMR ($CDCl_3$): δ 8.02–7.96, 7.71–7.66 (m, 8H, quin), 7.15–7.13, 6.97–6.94 (m, 4H, phen.), 5.38 (s, 4H, $2CH_2$), 2.82 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 153.9, 150.3, 148.5, 141.7, 140.3 (5×2 quart. C), 130.0, 129.0, 129.0, 128.2, 122.1, 114.9 (6×2 tert. C), 71.7 ($2CH_2$), 22.2 ($2CH_3$). Anal. Calcd for $C_{26}H_{22}N_4O_2$ (422.49 g/mol): C, 73.92; H, 5.25; N, 13.26. Found: C, 73.79; H, 5.43; N, 13.07.

p-Phenylene-bis[oxymethylen-(3-methyl-quinoxalin-2-yl)] (**3c**). This compound [26,27] was obtained from **1a** (4.75 g, dissolved in 130 ml EtOH) and **2c** in 73% yield as colorless needles, mp 214.5–215.5 °C (from DMF); IR: 3046, 2932, 2874, 1854, 1610, 1566, 1588, 1488, 1460, 1434, 1372, 1354, 1324, 1288, 1265, 1232, 1164, 1130, 1114, 1036, 958, 904, 822, 786, 758, 696, 688, 612, 554, 522, 448; ^{1}H NMR ($CDCl_3$): δ 8.10–8.02, 7.78–7.69 (m, 8H, quin), 7.01 (s, 4H, phen), 5.33 (s, 4H, $2CH_2$), 2.87 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 153.9, 153.1, 150.1, 141.7, 140.3 (5×2 quart. C), 130.2, 129.2, 129.0, 128.2, 115.9 (6×2 tert. C), 71.2, ($2CH_2$), 22.2 ($2CH_3$). Anal. Calcd for $C_{26}H_{22}N_4O_2$ (422.49 g/mol): C, 73.92; H, 5.25; N, 13.26. Found: C, 73.70; H, 5.36; N, 13.47.

p-Phenylene-bis[oxymethylen(3-phenyl-quinoxalin-2-yl)] (**3d**). This compound was obtained from **1b** (6.00 g, in 500 ml EtOH) and **2c** in 54% yield as beige prisms, mp 200–202 °C (pyridine); IR: 3062, 2943, 1550, 1504, 1219, 842, 820, 767, 702; ^{1}H NMR ($CDCl_3$): δ 8.64–8.61, 8.22–8.17 (m, 8H, 2×4H in the condensed benzo-cycle), 7.83–7.26 (m, 10H, 2×phenyl), 6.84 (s, 4H, 1,4 subst phen −5.26 (s, 4H, $2\times CH_2$); ^{13}C NMR ($CDCl_3$): δ 155.0, 153.0, 149.0, 141.9, 141.3, 138.1, 135.9, 135.9, 130.6, 130.0, 129.3, 129.3 (12 quart. C), 149.8 (4), 129.2 (2), 129.0 (4), 128.6 (4), 123.7 (4), 116.0 (4), (22 tert. C), 70.6 ($2CH_2$).

hr-MS: *m*/*z* Calcd for $C_{36}H_{26}N_4O_2^+$: 546.2056 found. 546.2009.

4.2.2. General procedure for the synthesis of compounds (3b, 6a–c). In the case of monohydroxy phenols, 20 mmol, in case of diols 10 mmol were applied. A mixture of the hydroxy-compound, 2-(bromomethyl)-3-methyl-quinoxaline (20 mmol, 4.75 g) and anhydrous potassium carbonate (30 mmol, 4.15 g) in 2-butanone (100 ml) was heated under argon at reflux for 5 h with vigorous stirring. Inorganic salts were separated by filtering the boiling solution. The residue was washed two times with hot 2-butanone (30 ml). The filtrates were combined and the solvent removed. The resulting oil crystallized by mixing with EtOH (10 ml) and the product was purified by recrystallization.

m-Phenylene-bis[oxymethylen(3-methyl-quinoxalin-2-yl)] (**3b**). This compound[26,27] was obtained from resorcinol (**2b**) (10 mmol, 1.10 g) and **1a** in 32% yield as pale rosa, nearly colorless needles, mp 148–151 °C (octane); IR: 3030, 2930, 2870, 1600, 1490, 1455, 1430, 1400, 1365, 1350, 1325, 1280, 1205, 1185, 1165, 1150, 1130, 1045, 985, 955, 930, 900, 825, 745, 630, 605, 595, 440; ^{1}H NMR ($CDCl_3$): δ 8.08–8.00, 7.74–7.65 (m, 8H, quin), 7.23–7.18, 6.83–6.82, 6.72–6.68 (m, 4H, phen), 5.34 (s, 4H, $2CH_2$), 2.83 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 159.4, 153.7, 150.1, 141.6, 140.3 (5×2 quart. C), 130.1, 129.1, 128.9, 128.1, 107.7, 102.2 (6×2 tert. C), 70.5 ($2CH_2$), 22.2 ($2CH_3$). Anal. Calcd for $C_{26}H_{22}N_4O_2$ (422.49 g/mol): C, 73.92; H, 5.25; N, 13.26. Found: C, 73.72; H, 5.54; N, 13.51.

2-(3-Methylquinoxalin-2-ylmethoxy)phenyl benzoate (**6a**). This compound was obtained from 2-hydroxyphenyl benzoate (**5a**) (20 mmol, 4.28 g) and **1a** (20 mmol, 4.74 g) in 59% yield as colorless needles, mp 153–155 °C; IR: 3068, 1728, 1604, 1500, 1454, 1380, 1306, 1284, 1252, 1178, 1110, 1082, 1064, 1026, 1010, 906, 854, 832, 792, 764, 754, 718, 676, 612, 580, 424; ^{1}H NMR ($CDCl_3$): δ 8.15–8.12, 7.96–7.94 (m, 4H, quin), 7.66–6.99 (m, 9H, phen, *o*-phenylene), 5.39 (s, 2H, CH_2), 2.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.7, 153.9, 149.9, 141.6, 140.2 (8 quart. C), 133.4, 130.1, 129.1, 129.0, 128.4, 128.1, 126.9, 123.2, 121.7, 114.3 (13 tert. C), 71.4 (CH_2), 22.0 (CH_3). hr-MS: Calcd for $C_{23}H_{18}N_2O_3^+$: 370.1317, found 370.1300.

3-(3-Methylquinoxalin-2-ylmethoxy)phenyl benzoate (**6b**). This compound was obtained from 3-hydroxyphenyl benzoate (**5b**) (20 mmol, 4.28 g) and **1a** (20 mmol, 4.74 g) in 72% yield as light brown needles, mp 85–87 °C; IR: 3082, 2874, 1732, 1598, 1488, 1452, 1372, 1356, 1314, 1272, 1246, 1168, 1138, 1078, 1064, 1046, 1024, 998, 930, 892, 868, 826, 776, 762, 734, 706, 690, 678, 614, 694, 436, 420; ^{1}H NMR ($CDCl_3$): δ 8.19–8.16, 8.08–8. 01, 7.72–6.86 (m, 13H, phen, 5.36 (s, 2H, CH_2), 2.86 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 164.8, 159.1, 153.7, 151.8, 149.9, 141.8, 140.3, 129.3 (8 quart. C), 133.5, 130.1, 130.0, 130.0, 129.9, 129.1, 129.0, 128.4, 128.4, 128.2, 114.7, 112.3, 108.7 (13 tert. C), 70.7 (CH_2), 22.1 (CH_3).

hr-MS: Calcd for $C_{23}H_{18}N_2O_3^+$: 370.1317, found 370.1304.

4-(3-Methylquinoxalin-2-ylmethoxy)phenyl benzoate (**6c**). This compound was obtained from 4-hydroxyphenyl benzoate (**5c**) (20 mmol, 4.28 g) and **1a** (20 mmol, 4.74 g) in 51% yield as colorless needles, mp 157–158 °C; IR: 3060, 2936, 1872, 1738, 1600, 1566, 1506, 1400, 1460, 1450, 1372, 1358, 1314, 1272, 1248, 1198, 1168, 1132, 1104, 1082, 1062, 1026, 1014, 1002, 934, 904, 866, 814, 788, 764, 736, 702, 682, 672, 614, 580, 540, 526, 470, 428; ^{1}H NMR ($CDCl_3$): δ 8.19–8.03 (m, 4H, quin), 7.73–7.45, 7.14–7.09, phen, 5.37 (s, 2H, CH_2), 2.87 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 165.3, 156.0, 153.8, 150.2, 144.9, 141.8, 140.4, 133.5 (8 quart. C), 130.2, 130.0, 130.0, 129.4, 129.1, 129.0, 128.4, 128.4, 128.3, 122.5, 122.5, 115.5, 115.5 (13 tert. C), 71.0 (CH_2), 22.2 (CH_3).

hr-MS: Calcd for $C_{23}H_{18}N_2O_3^+$: 370.1304, found 370.1317.

4.2.3. General procedure for the synthesis of phenols 4 from the benzoates 6. The solution of the appropriate benzoate **6** (10 mmol, 3.70 g) in hot ethanol was treated with a 2.5 N aqueous potassium hydroxide (10 ml, 25 mmol). The mixture was heated at reflux for 15 min. After the addition of acetic acid (25 mmol, 1.5 g) the solution was concentrated in vacuo. The resulting mixture was kept in a refrigerator overnight and the precipitate was collected by suction filtration, washed with aqueous solution of sodium hydrogen carbonate and with water. The crude product was purified by recrystallization.

2-(3-Methyl-quinoxalin-2-ylmethoxy)phenol (**4a**). This compound was obtained from **6a** in 75% yield as pale beige, nearly colorless prisms, mp 164–165 °C (EtOH); IR: 3052, 2937, 1596, 1570, 1500, 1464, 1430, 1376, 1358, 1330, 1300, 1266, 1206, 1132, 1110, 1028, 1010, 910, 852, 832, 786, 758, 736, 680, 618, 540, 450; ^{1}H NMR ($CDCl_3$): δ 9.57 (s, 1H, OH), 7.98–7.91, 7.71–7.66 (m, 4H, quin), 7.12–6.85 (m, 4H, phen), 5.32 (s, 2H, CH_2), 2.62 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 151.7, 150.4, 148.5, 147.3, 141.4, 139.3 (6 quart. C), 130.2, 129.6, 128.2, 128.1, 124.2, 120.0, 117.4, 116.9 (8 tert. C), 72.6 (CH_2), 21.5 (CH_3).

hr-MS: Calcd for $C_{16}H_{14}N_2O_2^+$: 266.1055, found 266.1059.

3-(3-Methyl-quinoxalin-2-ylmethoxy)phenol (**4b**). This compound was obtained from **6b** in 71% yield as beige prisms, mp 190–192 °C (1-propanol); IR: 3400–2250 (br), 3068, 2957, 2734, 2608, 1598, 1508, 1494, 1462, 1372, 1312, 1290, 1246, 1210, 1184, 1146, 1074, 1054, 1010, 944, 912, 862, 824, 774, 686, 668, 618, 532, 484, 458, 438, 422; ^{1}H NMR (DMSO): δ 9.58 (s, 1H, OH), 8.12–8.04, 7.88–7.80 (m, 4H, quin), 7.15–7.10, 6.58–6.44 (m, 4H, phen), 5.40 (s, 2H, CH_2), 2.80 (s, 3H, CH_3); ^{13}C NMR (DMSO): δ 159.5, 158.7, 154.1, 151.1, 141.2, 139.8 (6 quart. C), 130.3, 130.1, 129.5, 128.8, 128.2, 108.6, 105.5, 102.3 (8 tert. C), 69.8 (CH_2), 22.0 (CH_3).

hr-MS: Calcd for $C_{16}H_{14}N_2O_2^+$: 266.1055, found 266.1060.

4-(3-Methyl-quinoxalin-2-ylmethoxy)phenol (**4c**). This compound was obtained from **6c** in 82% yield as colorless prisms, mp 206–209 °C (1-butanol); IR: 3500–2250 (br), 3168, 3059, 2882, 2360, 1734, 1616, 1572, 1514, 1492, 1452, 1374, 1318, 1262, 1228, 1156, 1124, 1102, 1084, 1006, 924, 878, 852, 828, 770, 736, 710, 680, 616, 762, 538, 516, 426; ^{1}H NMR (DMSO): δ 9.06 (s, 1H, OH), 8.06–8.00, 7.83–7.74 (m, 4H, quin), 6.94–6.91, 6.72–6.69 (m, 4H, phen), 5.38 (s, 2H, CH_2), 2.77 (s, 3H, CH_3); ^{13}C NMR (DMSO): δ 154.1, 151.8, 151.4, 151.1, 141.2, 139.8 (6 quart. C), 130.2, 129.4, 128.7, 128.1, 116.1, 116.1, 115.8, 115.8 (8 tert. C), 70.7 (CH_2), 22.0 (CH_3).

hr-MS: Calcd for $C_{16}H_{14}N_2O_2^+$: 266.1055, found 266.1055.

4.2.4. General procedure for the synthesis of compounds 8a and 8b. A mixture of **4c** (20 mmol, 5.32 g), 2-bromo-alkanoic acid alkyl ester (24 mmol) and powdered anhydrous potassium carbonate (29 mmol, 4.01 g) in 2-butanone (400 ml) was heated at reflux for 5 h by vigorous stirring. Inorganic salts were separated by filtering the boiling solution. The residue was washed two times with hot 2-butanone. The filtrates were combined and the solvent was removed totally. The resulting oil crystallized by mixing with ice-cold alcohol (10 ml).

Ethyl 2-[4-(3-methyl-quinoxalin-2-ylmethoxy)phenoxy]-acetate (**8a**). This compound was obtained from ethyl bromacetate (4.01 g) in 62% yield as colorless columns, mp 91–93 °C (EtOH); IR: 3060, 2984, 2912, 1750, 1612, 1594, 1566, 1508, 1474, 1462, 1436, 1406, 1382, 1374, 1356, 1326, 1308, 1234, 1178, 1162, 1128, 1108, 1090, 1036, 1018, 962, 906, 858, 832, 816, 792, 766, 680, 612, 576, 540, 524, 458, 426; ^{1}H NMR ($CDCl_3$): δ 8.08–8.00, 7.73–7.69 (m, 4H, quin), 6.99, 6.86 (dd, 4H, *p*-subst.phen), 5.31 (s, 2H, CH_2O), 4.56 (s, 2H, acetate-CH_2O), 4.26 (q, J=7.1 Hz, 2H, ethyl-CH_2O), 2.85 (s, 3H, 3-CH_3), 1.27 (t, J=7.1 Hz, 3H, ethyl-CH_3); ^{13}C NMR ($CDCl_3$): δ 168.5, 153.4, 152.7, 152.0, 150.0, 141.3, 140.0 (7 quart.C), 129.6, 128.6, 128.5, 127.8 (4 tert. C), 115.3 (4 tert. C), 71.0, 65.6, 60.7 (3 sec. C), 21.8 (3-CH_3), 13.6 (ester-CH_3).

hr-MS: Calcd for $C_{20}H_{20}N_2O_4^+$: 352.1423, found 352.1404.

Methyl 2-[4-(3-methyl-quinoxalin-2-ylmethoxy)phenoxy]-propionate (**8b**). This compound was obtained from methyl 2-bromopropionate (4.01 g) in 63% yield as colorless columns, mp 90–91 °C; IR: 3066, 2996, 2950, 1740, 1598, 1568, 1508, 1458, 1434, 1372, 1326, 1306, 1222, 160, 1130, 1110, 1050, 1032, 1010, 982, 946, 906, 860, 822, 786, 762, 706, 680, 614, 522, 420; ^{1}H NMR ($CDCl_3$): δ 8.08–8.00, 7.73–7.69 (2m, 4H, quin), 6.98–6.96, 6.85–6.82 (dd, 4H, *p*-subst phen), 5.31 (s, 2H, CH_2O), 4.67 (q, J=6.8 Hz, 3.74 (s, 3H, OCH_3), 2.84 (s, 3H, 3-CH_3), 1.57 (d, J=6.8 Hz, 3H, ^{13}C NMR ($CDCl_3$): δ 172.7 (C=O), 153.8, 153.1, 152.1, 150.4, 141.7, 140.3 (6 quart. C), 130.0, 129.0, 128.9, 128.2 (4 tert. C), 116.3 (2 tert. C), 115.8 (2 tert.), 73.2, 71.1 (2 sec. C), 52.2 (OCH_3), 22.2 (3-CH_3), 18.5 (2-CH_3).

hr-MS: Calcd for $C_{18}H_{16}N_2O_4^+$: 324.1110, found 324.1108.

4.2.5. A procedure for preparing compounds 9a, 9b. The ethanolic solution of the esters **8a**, **8b** (10 mmol [3.52 g] in 50 ml EtOH) was mixed with the ethanolic KOH (11 mmol [0.62 g] in 50 ml EtOH). The mixture was heated at reflux for 15 min. The potassium salt, precipitating from the boiling solution, was filtered by suction under cooling to room temperature. The potassium salt—yield nearly quantitative—was dissolved in water (50 ml). This solution was treated with aquous acetic acid (20 mmol [1.2 g] AcOH, 12 ml H_2O). The resulting acids **9a/9b**, first often colloidally dissolved, were separated in crystallic form by inoculation and/or stirring and keeping in the refrigerator overnight. The product in question was separated by filtration, washed with water (50 ml) and recrystallized.

4-(3-Methylquinoxalin-2-ylmethoxy)phenyloxyacetic acid (**9a**). This compound was obtained from **8a** in 78% yield as colorless crystals, mp 157 °C (dec.) (EtOH); IR: 3062, 2936, 2518, 1724, 1598, 1574, 1500, 1464, 1448, 1382, 1364, 1328, 1306, 1268, 1238, 1198, 1164, 1132, 1108, 1076, 1030, 1012, 968, 910, 882, 860, 840, 818, 800, 778, 764, 704690, 670, 636, 620, 582, 520, 482, 426; ^{1}H NMR (DMSO): δ 8.07–8.03, 7.84–7.79 (m, 4H, quin), 5.39 (s,

2H, CH_2O), 4.66 (s, 2H, CH_2O), 3.9 (br., s, 1H, COOH, 2.80 (s, 3H, CH_3); ^{13}C NMR (DMSO): δ 170.5 (C═O), 154.1, 152.7, 152.4, 151.2, (4 tert. C), 141.2, 139.9 (2 each tert. C), 130.3, 129.4, 128.8, 128.2 (4 tert. C), 115.9, 115.5 (je 2 tert.C), 70.5, 65.1 (2 sec. C), 22.0 (CH_3).

hr-MS: Calcd for $C_{20}H_{20}N_2O_4^+$: 352.1423, found 352.1368.

2-[4-(3-Methyl-quinoxalin-2-ylmethoxy)phenyloxy]propionic acid (**9b**). This compound was obtained from **8b** in 63% yield as colorless crystals, mp 146 °C (dec.)(50% EtOH); IR: 2926, 1732, 1568, 1508, 1462, 1376, 1330, 1288, 1228, 1166, 1134, 1102, 1040, 952, 908, 816, 784, 770, 756, 728, 684, 614, 558, 522, 460, 424; ^1H NMR (DMSO): δ 7.88–7.82, 7.65–7.56 (m, 4H, quin), 6.86–6.89, 6.67–6.64 (dd, 4H, phen), 5.17, (s, 2H, CH_2O), 4.53 (q, J=6.7 Hz, 1H, alpha-CH), 2.58 (s, 3H, 3-CH_3), 2.30 (s, 1H, COOH), 1.29 (d, J=6.7 Hz, 3H, α-CCH_3); ^{13}C NMR (DMSO): δ 173.5 (C═O), 154.1, 152.6, 152.1, 151.2, 141.2, 139.8 (6 quart. C), 130.3, 129.4, 128.8, 128.2 (4 tert. C), 151.9 (4 tert. C), 72.2 (O–CH), 70.5 (OC–H_2), 22.0 (3-CH_3), 18.5 (CH_3).

hr-MS: Calcd. for $C_{19}H_{18}N_2O_4^+$: 338.1267, found 338.1263.

4.2.6. General procedure for the synthesis of compounds 11a–c. To the solution of a hydroxybenzyl alcohol (22 mmol) in EtOH (50 ml) was first added ethanolic KOH solution (21 mmol, 1.18 g in 50 ml EtOH) and thereafter a solution of 2-(bromomethyl)-3-methylquinoxaline (20 mmol, 4.74 g) in warm EtOH (120 ml) under stirring. The mixture was heated at reflux for 2 h. KBr crystallized during this time was filtered off from the boiling solution. After the addition of water (40 ml), the EtOH was evaporated in vacuo. The residue was kept in the refrigerator overnight. The solid product was collected by filtration, washed with 50% aqueous ethanol and recrystallized.

2-(3-Methylquinoxalin-2-ylmethoxy)benzyl alcohol (**11a**). This compound was obtained from 2-hydroxybenzyl alcohol (2.73 g) in 86% yield as colorless needles, mp 119–121 °C (EtOH); IR: 3286, 3182, 3062, 2920, 2882, 1602, 1588, 1568, 1490, 1454, 1434, 1402, 1370, 1326, 1282, 1240, 1162, 1132, 1112, 1038, 1008, 930, 906, 848, 824, 772, 758, 712, 682, 614, 598, 490, 434, ^1H NMR ($CDCl_3$): δ 8.05–7.95, 7.69–7.65, 7.32–7.23, 7.04–6.94 (m, 8H, quin, phen.), 5.38 (s, 2H, CH_2O), 4.76 (s, 2H, CH_2OH), 2.70 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 156.4, 152.2, 150.2, 141.5, 140.1 (5 quart. C), 130.3, 130.1, 129.3, 129.1, 128.8, 128.6, 128.1, 121.5, 111.7 (9 tert. C), 68.7, 61.7 (2 sec. C), 21.8 (CH_3).

hr-MS: Calcd for $C_{17}H_{16}N_2O_2^+$: 280.1212, found 280.1199.

4-(3-Methylquinoxalin-2-ylmethoxy)benzyl alcohol (**11b**). This compound was obtained from 4-hydroxybenzyl alcohol (2.73 g) in 59% yield as colorless needles, mp 149–151.5 °C (EtOH); IR: 3368, 3044, 2920, 2868, 1606, 1584, 1510, 1492, 1464, 1438, 1404, 1370, 1328, 1292, 1246, 1172, 1130, 1114, 1034, 1004, 906, 874, 852, 834, 798, 782, 762, 738, 700, 680, 614, 586, 550, 512, 488, 460, 434; ^1H NMR (DMSO): δ 7.89–7.82, 7.63–7.59 (m, 4H, quin), 7.08, 6.88 (dd, 4H, subst. phen.), 5.23 (s, 2H, CH_2O), 4.26 (s, 2H, CH_2OH), 3.5 (br., s, 1H, OH,), 2.59 (s, 3H, CH_3); ^{13}C NMR (DMSO): δ 157.2, 154.0, 151.1, 141.2, 139.8, 135.3 (6 quart.C), 130.3, 129.4, 128.8, 128.2, 128.1, 128.1, 114.6, 114.6 (8 tert.C), 69.9, 62.6 (2CH_2), 22.0 (CH_3).

hr-MS: Calcd for $C_{17}H_{16}N_2O_2^+$: 280.1212, found 280.1218.

3-Methoxy-4-(3-methylquinoxalin-2-ylmethoxy)benzyl alcohol (**11c**). This compound was obtained from 4-hydroxy-3-methoxybenzyl alcohol (3.39 g) in 72% yield as colorless needles, mp 159–160 °C (toluene); IR: 3388, 3046, 2994, 2942, 2872, 1594, 1568, 1514, 1466, 1422, 1376, 1328, 1260, 1234, 1162, 1136, 1030, 908, 846, 826, 802, 764, 740, 680, 642, 616, 550, 442; ^1H NMR (DMSO): δ 8.06–8.00, 7.83–7.75 (m, 4H, quin), 7.08, (d, 1H, *o*-phen), 6.96 (s, 1H, phen), 6.82 (d, 1H, *o*-phen), 5.37 (s, 2H, CH_2O), 5.15 (t, J=5.6 Hz, 1H,OH), 4.42 (d, J=5.6 Hz, 2H, CH_2OH), 3.73 (s, 3H, CH_3O), 2.80 (s, 3H, 3-CH_3); ^{13}C NMR (DMSO): δ 154.4, 151.2, 149.3, 146.3, 141.2, 139.8, 136.5 (7 quart.C), 130.3, 129.4, 128.8, 128.1, 118.6, 114.5, 110.9 (7 tert.C), 71.2 (CH_2), 62.8 (CH_2), 55.5 (OCH_3), 21.9 (3-CH_3).

hr-MS: Calcd for $C_{18}H_{18}N_2O_3^+$: 310.1317, found 310.1307.

4.2.7. General procedure for the synthesis of compounds 16a–g. The solution of SeO_2 (20 mmol, 2.22 g) in aqueous dioxane (19 ml dioxane and 1 ml water) was added to the solution of an acetyl compound **13a-c** (20 mmol) in dioxane (30 ml). The mixture was heated at reflux for 2–3 h, while the acetyl group was oxidized into the glyoxalyl group, selen was precipitated and the mixture became dark. The precipitate was filtered off from the boiling mixture and washed with hot dioxane (25 ml). The dioxane solutions were combined and mixed with a solution of an appropriate 1,2-phenylenediamine **15a-c** (20 mmol) in dioxane (25 ml). The resulting mixture was heated at reflux for 2 h again, concentrated in vacuo and kept at room temperature overnight. The product was collected by filtration, washed with icecold MeOH and with water and recrystallized.

2-(Benzo[*b*]fur-2-yl)quinoxaline (**16a**). This compound[13,14] was obtained from 3.20 g **13a** and 2.16 g **15a** in 64% yield as pale yellow prisms, mp 174–175 °C (1-butanol); IR: 3115, 3060, 1590, 1540, 1305, 1255, 920, 765, 750, 745, 690; ^1H and ^{13}C NMR-data.[28]

hr-MS: *m/z* Calcd. for $C_{16}H_{10}N_2O$: 246.0799, found 246.0793.

2-(Benzo[*b*]fur-2-yl)-6,7-dichloroquinoxaline (**16b**). This compound was obtained from 3.20 g **13a** and 3.54 g **15b** in 58% yield as colorless needles, mp 206–208 °C (1-pentanol); IR 3098, 1932, 1750, 1602, 1576, 1536, 1456, 1392, 1348, 1308, 1286, 1260, 1184, 1144, 1106, 1052, 962, 932, 920, 906, 882, 852, 822, 784, 750, 688, 680, 658, 624, 608, 558, 494, 424; ^1H NMR ($CDCl_3$): δ 9.40, 8.27, 8.21 (s, 3H-quin.), δ 7.32–7.46 and δ 7.64–7.73 (m, 4H-benzf.), ^{13}C NMR ($CDCl_3$): δ 128.6, 134.8, 135.8, 141.4, 140.8, 145.2, 152.7, 156.4 (8 quart.C), 109.3, 112.4, 122.6, 124.3, 127.2, 129.9, 130.3, 143.9 (8 tert.C).

hr-MS: *m/z* Calcd. for $C_{16}H_8Cl_2N_2O$: 314.0014, found 314.0010.

2-(Benzo[*b*]fur-2-yl)-6,7-dimethylquinoxaline (**16c**). This compound was obtained from 3.20 g **13a** and 2.72 g **15c** in 42% yield as yellow prisms, mp 184–185 °C (cyclohexane); IR 3050, 2972, 2916, 1930, 1748, 1626, 1590, 1538, 1486, 1448, 1360, 1310, 1294, 1260, 1210, 1178, 1156, 1144, 1110, 1048, 1026, 1002, 970, 920, 910, 882, 868, 810, 792, 742, 694, 648, 628, 610, 514, 488, 426; ^{1}H NMR($CDCl_3$): δ 9.27, 7.89, 7.81 (s, 3H-quin.), δ 7.58–7.68 and 7.27–7.41 (m, 5H-benzf.), ^{13}C NMR ($CDCl_3$): δ 140.6, 140.7, 141.0, 141.2, 141.5, 143.0, 153.2, 155.7 (8 quart.C), 107.0, 111.8, 121.8, 123.5, 125.9, 128.2, 128.4, 128.5 (8 tert.C), 20.3 ($2CH_3$).

hr-MS: *m/z* Calcd for $C_{18}H_{14}N_2O$: 274.1106, found 274.1101.

2-(5-Chlorobenzo[*b*]fur-2-yl)quinoxaline (**16d**). This compound was obtained from 3.89 g **13b** and 2.16 g **15a** in 57% yield as colorless needles, mp 200–204 °C (nonane); IR 3068, 3028, 1612, 1582, 1546, 1486, 1466, 1446, 1410, 1366, 1348, 1328, 1292, 1266, 1240, 1206, 1168, 1132, 1054, 958, 926, 908, 876, 864, 826, 812, 760, 696, 628, 612, 582, 436, 410; ^{1}HNMR($CDCl_3$): δ 9.31 (s 1H-quin.), δ 8.08–8.15 and 7.72–7.81 (m, 4H-quin.), δ 7.31–7.58 and 7.57–7.63 (m, 4H-benzf.), ^{13}C NMR ($CDCl_3$): δ 129.58, 141.9, 142.1, 142.3, 143.4, 154.1, 154.3 (7 quart.C), 107.0, 112.9, 121.4, 126.4, 129.27, 129.31, 129.45, 130.1, 130.7 (9 tert.C).

hr-MS: *m/z* Calcd for $C_{16}H_9ClN_2O$: 280.0403, found 280.0398.

2-(5-Chlorobenzo[*b*]fur-2-yl)-6,7-dichloroquinoxaline (**16e**). This compound was obtained from 3.89 g **13b** and 3.54 g **15b** in 56% yield as colorless needles, mp 256–257 °C (dioxane); IR 3086, 1734, 1598, 1576, 1538, 1492, 1392, 1324, 1288, 1262, 1208, 1180, 1156, 1108, 1054, 966, 930, 918, 900, 874, 802, 736, 698, 680, 660, 622, 578, 558, 496, 426; ^{1}H NMR($CDCl_3$): δ 9.40, 8.29, 8.25 (s, 3H-quin.), δ 7.70–7.57 and 7.26–7.41 (m, 5H-benzf.); ^{13}C NMR ($CDCl_3$/CH_3OH, 315K): δ 108.1, 112.6, 121.4, 126.7, 129.5, 129.6, 143.1 (7 tert.C), δ 130.5, 134.6, 135.4, 140.4, 140.7, 144.3, 148.3, 153.2, 154.1 (9 quart. C).

hr-MS: *m/z* Calcd for $C_{16}H_7Cl_3N_2O$: 347.9624, found 347.9611.

2-(5-Chlorobenzo[*b*]fur-2-yl)-6,7-dimethylquinoxaline (**16f**). This compound was obtained from 3.89 g **13b** and 2.72 g **15c** in 45% yield as yellow prisms, mp 221–222 °C (nonane); IR 3098, 2976, 2948, 1854, 1726, 1624, 1580, 1536, 1484, 1444, 1362, 1328, 1294, 1282, 1262, 1208, 1178, 1156, 1110, 1054, 1022, 1002, 970, 920, 900, 866, 800, 760, 736, 696, 626, 578, 516, 488, 460, 426; ^{1}H NMR($CDCl_3$): δ 9.31, 7.91, 7.86 (s, 3H-quin.) δ 7.66–7.55 and 7.36–7.35 (m, 4H-benzf.), δ 2.52 (s $2CH_3$), ^{13}C NMR($CDCl_3$): δ 129.2, 129.8, 141.1, 141.4, 154.1, 156.2 (6 quart.C), 106.4, 112.9, 121.4, 126.2, 128.4, 128.5 (6 tert.C), 20.4 ($2CH_3$).

hr-MS: *m/z* Calcd for $C_{18}H_{13}ClN_2O$: 308.0716, found 308.0707.

2-(5-Bromobenzo[*b*]fur-2-yl)quinoxaline (**16g**). This compound was obtained from 4.78 g **13c** and 2.16 g **15a** in 34% yield as reddish-brown crystals, mp 200–204 °C (nonane); IR 3068, 3018, 1890, 1732, 1610, 1578, 1540, 1484, 1438, 1406, 1364, 1346, 1324, 1290, 1262, 1204, 1158, 1126, 1046, 960, 924, 868, 810, 762, 696, 670, 626, 608, 576, 558, 524, 458, 426, 412; ^{1}H NMR($CDCl_3$): δ 9.40 (s 1H-quin.) δ 8.24–8.10 (m, 2H-quin.) δ 7.83–7.76 and 7.61–7.79 (m, 6H-quin and benzf.), ^{13}C NMR ($CDCl_3$): δ 116.8, 141.9, 142.2, 142.3, 143.5, 154.2, 154.5 (7 quart.C), 106.9, 113.4, 124.5, 129.1, 129.3, 129.5, 130.2, 130.3, 130.8 (9 tert.C).

hr-MS: *m/z* Calcd for $C_{16}H_9BrN_2O$: 323.9898, found 323.9885.

4.2.8. General procedure for the synthesis of compounds 16a,h–j,l,p,s, 20a,b from compounds 17a–h, 19a,b, respectively. The respective compound (**17a–h**, **19a**,**b**) was dissolved in EtOH under heating and then mixed with the equimolar amount of ethanolic KOH. The mixture was heated at reflux for 2–3 h, concentrated in vacuo, water added and the mixture was kept in the refrigerator overnight, the product was collected by filtration, washed with water and with icecold MeOH and purified by recrystalization.

2-(Benzo[*b*]fur-2-yl)quinoxaline (**16a**).[28] This compound was obtained from the compound **17a** in 62% yield.

2-(Benzo[*b*]fur-2-yl)-3-methylquinoxaline (**16h**). This compound was obtained from the compound **17b** in 92% yield as pale yellow needles, mp 142–143.5 °C (EtOH); IR 3055, 3200, 2992, 1570, 1535, 1480, 1430, 1390, 1375, 1330, 1315, 1240, 1195, 1150, 1130, 1010, 920, 980, 830, 815, 745, 760, 750, 710, 630, 605, 560, 530, 420; ^{1}H and ^{13}C NMR.[28]

hr-MS: *m/z* Calcd for $C_{17}H_{12}N_2O$: 260.0950, found 260.0959.

2-(5-Chlorobenzo[*b*]fur-2-yl)-3-methylquinoxaline (**16i**). This compound was obtained from the compound **17c** in 92% yield as pale yellow needles, mp 157–159 °C (PrOH); IR 3060, 1535, 1480, 1430, 1375, 1335, 1320, 1245, 1190, 1150, 1130, 1050, 1005, 950, 925, 890, 855, 820, 800, 775, 755, 715, 700, 690, 605, 450, 420; ^{1}H NMR($CDCl_3$): δ 8.15–7.96 and 7.76–7.67 (m, 4H-quin.), δ 7.63 (d, 1H-benzf.) δ 7.54–7.30 (m, 3H-benzf.), δ 3.12 (s CH_3); ^{13}C NMR ($CDCl_3$): δ 129.1, 129.6, 140.6, 141.0, 143.4, 151.4, 153.7, 154.9 (8 quart.C), 109.3, 112.8, 121.2, 126.1, 128.3, 129.0, 129.4, 130.3 (8 tert.C), 25.0 (CH_3).

hr-MS: *m/z* Calcd for $C_{17}H_{11}ClN_2O$: 294.0560, found 294.0548.

2-(5-Bromobenzo[*b*]fur-2-yl)-3-methylquinoxaline (**16j**). This compound was obtained from the compound **17d** in 86% yield as pale yellow needles, mp 167–168.5 °C (propanol); IR 3066, 2924, 1720, 1632, 1606, 1572, 1556, 1542, 1480, 1452, 1428, 1372, 1338, 1320, 1244, 1190, 1152, 1134, 1118, 1046, 1024, 1012, 960, 926, 900, 862, 826, 806, 780, 762, 720, 704, 674, 638, 610, 582, 568, 450, 426; ^{1}H NMR ($CDCl_3$): δ 8.14–7.99 and 7.76–7.71

(m, 4H-quin), δ 7.81–7.80 and 7.52–7.45 (m, 4H benzf.), δ 3.07 (s CH_3); ^{13}C NMR ($CDCl_3$): δ 116.54, 130.1, 140.6, 141.1, 143.4, 151.4, 154.1, 154.8 (8 quart.C), 108.9, 113.3, 124.4, 128.4, 128.8, 129.2, 129.6, 130.4 (8 tert.C), 25.0 (CH_3); HR-MS: *m/z* Calcd for $C_{17}H_{11}BrN_2O$: 338.0055, found 338.0052.

2-(6-Methoxy-3-phenylbenzo[*b*]fur-2-yl)-3-methylquinoxaline (**16l**). This compound was obtained from the compound **17f** in 73% yield as yellow needles, mp 115–117 °C (EtOH); IR 3050, 2970, 2940, 2840, 1615, 1500, 1485, 1450, 1440, 1400, 1365, 1340, 1320, 1300, 1280, 1190, 1150, 1130, 1105, 1075, 1050, 1020, 1000, 960, 940, 920, 855, 820, 755, 745, 725, 700, 665, 630, 600, 580, 565, 550, 540, 430; ^1H and ^{13}C NMR and elemental analysis data see Ref. 28.

2-(Benzo[*b*]fur-2-yl)-3-phenylquinoxaline (**16p**). This compound was obtained from the compound **17g** in 84% yield as yellow needles, mp 160–161 °C (EtOH); IR 3056, 1952, 1772, 1686, 1612, 1560, 1478, 1460, 1444, 1398, 1356, 1312, 1216, 1222, 1198, 1186, 1138, 1060, 1028, 990, 928, 880, 822, 804, 758, 700, 656, 614, 564, 538, 512, 428; ^1H and ^{13}C NMR-data.[28]

hr-MS: Calcd for $C_{22}H_{14}N_2O^+$: 322.1106, found 322.1104.

2-(Benzo[*b*]fur-2-yl)-3-(4-chlorophenyl)quinoxaline (**16s**). This compound was obtained from the compound **17h** in 83% yield as yellow needles, mp 192–193 °C (EtOH); IR 3062, 3037, 1936, 1897, 1857, 1777, 1668, 1639, 1612, 1594, 1559, 1537, 1492, 1477, 1459, 1397, 1354, 1315, 1261, 1218, 1198, 1170, 1134, 1092, 1057, 990, 960, 928, 882, 836, 824, 807, 764, 748, 719, 658, 617, 590, 552, 539, 515, 485, 458, 446, 429; ^1H NMR($CDCl_3$): δ 8.28–8.12 and 7.83–7.79 (m, 4H-quin.), δ 7.62–6.49 and δ 6.79 (m and s 10H benzf. and phen); ^{13}C NMR ($CDCl_3$): δ 127.8, 135.6, 137.6, 140.8, 141.0, 143.0, 151.8, 152.5, 155.3 (9 quart.C), 110.7, 111.9, 121.9, 123.4, 126.1, 128.9, 129.2, 129.3, 130.5, 130.6, 130.7 (11 tert.C).

hr-MS: Calcd for $C_{22}H_{13}N_2OCl^+$: 356.0716, found 356.0694.

2-Methyl-3-(naphtho[2,1-*b*]fur-2-yl)quinoxaline (**20a**). This compound[25] was obtained from the compound **19a** in 89% yield as yellow needles, mp 184–185 °C (toluene); IR 3050, 1580, 1570, 1510, 1470, 1435., 1370, 1330, 1300, 1245, 1215, 1200, 1145, 1120, 1070, 1025, 1010, 985, 950, 915, 860, 820, 795, 770, 750, 740, 710, 630, 605, 570, 550, 505, 465, 445; ^1H NMR ($CDCl_3$): δ 8.20–8.17 and δ 8.14–8.11 and 8.02–7.97 and 7.93–7.90 (m, 4H-quin.), δ 7.79–7.67 and 7.62–7.40 (m, 6 H-naphth.) δ 3.11 (s CH_3); ^{13}C NMR ($CDCl_3$): δ 123.7, 127.7, 130.5, 140.6, 140.7, 143.8, 153.1, 153.4, 151.3 (9 quart.C), 108.9, 112.5, 123.4, 124.9, 126.7, 127.1, 128.3, 128.8, 129.0, 129.5, 129.8 (11 tert.C), 25.3 (CH_3).

hr-MS: Calcd for $C_{21}H_{14}N_2O^+$: 310.1106, found 310.1111.

2-(Naphtho[2,1-*b*]fur-2-yl)-3-phenylquinoxaline (**20b**). This compound[29,30] was obtained from the compound **19b** in 80% yield as yellow needles, mp 187.5–188.5 °C (toluene); IR 3050, 1630, 1585, 1545, 1475, 1445, 1400, 1350, 1215, 1170, 1135, 1085, 1060, 1025, 990, 925, 855, 800, 780, 750, 700, 610, 590, 550, 520, 490, 420; ^1H NMR($CDCl_3$): δ 8.29–8.26 and 8.16 and 8.12 (m for 2H-quin.), δ 7.90–7.40 (m, 13H-quin. and naphth.), δ 7.05 (m 1H-phen); ^{13}C NMR ($CDCl_3$): δ 123.5, 127.7, 129.3, 139.3, 140.1, 141.1, 143.2, 152.0, 153.0, 153.3 (10 quart.C), 109.8, 112.6, 123.1, 124.9, 126.7, 127.3, 127.71, 128.8, 128.9, 129.2, 130.27, 130.4 (12 tert.C).

hr-MS: Calcd for $C_{26}H_{16}N_2O^+$: 372.1263, found 372.1247.

4.2.9. General procedure for the synthesis of compounds 16h,k,l, 20a,b from compounds 1a,b and 12a–e, 18 (examples for a one-pot-method). The procedure is the same as above for the synthesis of compounds **17** and **19** with one exception—after heating at reflux, another equivalent of base (KOH or EtONa), dissolved in EtOH, was added and the mixture was then heated further at reflux for 2 h.

2-(Benzo[*b*]fur-2-yl)-3-methylquinoxaline (**16h**).[28] This compound was obtained from the reaction of compound **1a** with **12a** in ethanolic KOH in 82% yield.

2-(3-Methylbenzo[*b*]fur-2-yl)-3-methylquinoxaline (**16k**).[28] This compound was obtained from the reaction of compound **1a** with **12d** and in ethanolic EtONa in 58% yield as pale yellow needles, mp 117–118 °C (EtOH); IR 3050, 2970, 2910, 1575, 1530, 1475, 1425, 1395, 1370, 1330, 1310, 1270, 1240, 1190, 1125, 1100, 1060, 990, 920, 900, 875, 750, 740, 715, 690, 620, 600, 590, 515, 450, 420; ^1H, ^{13}C NMR and elemental analysis data see Ref. 15.

2-(6-Methoxy-3-phenylbenzo[*b*]fur-2-yl)-3-methylquinoxaline (**16l**).[29] This compound was obtained from the reaction of compound **1a** with **12e** in ethanolic KOH in 61% yield; ^1H and ^{13}C NMR and elemental analysis data see Ref. 15.

2-Methyl-3-(naphtho[2,1-*b*]fur-2-yl)quinoxaline (**20a**). This compound[30] was obtained from the reaction of compound **1a** with **18** in ethanolic KOH in 61% yield.

2-(Naphtho[2,1-*b*]fur-2-yl)-3-phenylquinoxaline (**20b**). This compound[21] was obtained from the reaction of compound **1b** with **18** in ethanolic KOH in 80% yield.

General procedure for preparing compounds **17** and **19**. Equimolar amounts of an *o*-hydroxy carbonyl compound (**12a-e**, **18**), a strong base (KOH or EtONa) and of 2-(halomethyl) compound (**1a-c**, **1g**) were dissolved in ethanol under heating and mixed in this sequence. The mixture was heated at reflux for 2 h and then concentrated in vacuo. It was often expedient to add little water at the end to precipitate the product and to dissolve the KBr formed. The mixture was cooled and kept in the refrigerator. Next day, the solid was separated by filtering by suction and purified by recrystalization.

2-(Quinoxalin-2-ylmethoxy)benzaldehyde (**17a**). This compound was obtained from the reaction of 2-(chloromethyl)-quinoxaline (**1g**) with compound **12a** in 15% yield as

colorless needles, mp 117.5–118.5 °C (heptane); IR 3072, 2920, 2854, 2752, 1924, 1668, 1600, 1554, 1490, 1446, 1414, 1378, 1308, 1282, 1234, 1202, 1124, 1106, 1058, 972, 910, 846, 816, 758, 648, 600, 532, 498, 448, 410. Anal. Calcld for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60; Found: C, 72.55; H, 4.56; N, 10.45.

2-(3-Methylquinoxalin-2-ylmethoxy)benzaldehyde (**17b**). This compound was obtained from the reaction of compound **1a** with compound **12a** in 89% yield as colorless crystals, mp 129–131 (EtOH); IR 3060, 2950, 2875, 2775, 1690, 1600, 1580, 1560, 1480, 1460, 1430, 1400, 1375, 1350, 1295, 1255, 1220, 1200, 1165, 1130, 1100, 1045, 1025, 1000, 980, 900, 840, 810, 775, 755, 665, 645, 610, 565, 520, 475, 440, 405. Anal. Calcld for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.06; Found: C, 73.52; H, 5.16; N, 9.87.

5-Chloro-2-(3-methylquinoxalin-2-ylmethoxy)benzaldehyde (**17c**). This compound was obtained from the reaction of compound **1a** with compound **12b** in 46% yield as colorless needles, mp 152–153 °C (toluene); IR 3040, 3000, 2970, 2945, 2880, 1690, 1595, 1485, 1455, 1405, 1390, 1365, 1325, 1265, 1230, 1200, 1180, 1125, 1020, 1000, 900, 890, 840, 805, 765, 750, 705, 680, 650, 610, 530, 435. Anal. Calcld for $C_{17}H_{13}Cl\ N_2O_2$: C, 65.29; H, 4.19; N, 8.96; Found: C, 64.98; H, 4.30; N, 8.78.

5-Bromo-2-(3-methylquinoxalin-2-ylmethoxy)benzaldehyde (**17d**). This compound was obtained from the reaction of compound **1a** with compound **12c** in 83% yield as colorless needles, mp 160–161 °C (EtOH); IR 3040, 3000, 2945, 2880, 1690, 1590, 1510, 1485, 1465, 1425, 1400, 1390, 1370, 1325, 1260, 1230, 1200, 1185, 1110, 1020, 1000, 915, 890, 880, 830, 800, 765, 745, 680, 630, 610, 515, 435. Anal. Calcld for $C_{17}H_{13}BrN_2O_2$: C, 57.16; H, 3.67; N, 7.84; Found C, 57.15; H, 3.77; N, 7.88.

2-(3-Methylquinoxalin-2-ylmethoxy)acetophenone (**17e**). This compound was obtained from the reaction of compound **1a** with compound **12d** in 35% yield as pale yellow crystals, mp 102–103 °C (heptane); IR 3060, 3030, 3000, 2925, 2885, 1665, 1595, 1485, 1455, 1405, 1375, 1360, 1325, 1290, 1240, 1170, 1165, 1125, 1065, 1045, 1025, 1000, 915, 900, 850, 820, 775, 765, 710, 675, 600, 590, 525, 435. Anal. Calcld for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58; Found: C, 74.29; H, 5.62; N, 9.44.

4-Methoxy-2-(3-methylquinoxalin-2-ylmethoxy)benzophenone (**17f**). This compound was obtained from the reaction of compound **1a** with compound **12e** in 63% yield as colorless needles, mp 127–128 °C (CCl_4); IR 3000, 2975, 2945, 2835, 1610, 1575, 1545, 1495, 1480, 1440, 1400, 1365, 1335, 1320, 1300, 1280, 1185, 1150, 1120, 1100, 1075, 1045, 1015, 995, 960, 935, 915, 900, 865, 840, 815, 760, 740, 720, 695, 660, 625, 600, 575, 560, 550, 530, 430. Anal. Calcld for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29; Found: C, 74.85; H, 5.08; N, 7.42.

2-(3-Phenylquinoxalin-2-ylmethoxy)benzaldehyde (**17g**). This compound was obtained from the reaction of compound **1b** with compound **12a** in 77% yield as colorless crystals, mp 121.5–122.5 °C (BuOH); IR 3070, 2948, 2870, 2766, 1958, 1690, 1598, 1542, 1482, 1454, 1400, 1378, 1365, 1320, 1284, 1238, 1188, 1156, 1132, 1098, 1078, 1040, 1012, 930, 904, 860, 832, 812, 874, 762, 716, 700, 648, 622, 602, 572, 554, 474, 440. Anal. Calcld for $C_{22}H_{16}N_2O_2$: C, 77.63; H, 4.74; N, 8.23; Found: C, 77.69; H, 4.81; N, 8.48.

2-(3-[4-Chlorophenyl]quinoxalin-2-ylmethoxy)benzaldehyde (**17h**). This compound was obtained from the reaction of compound **1c** with compound **12a** in 74% yield as colorless crystals, mp 167–168 °C (EtOH), IR 3066, 3041, 2957, 2932, 2862, 2758, 1907, 1686, 1597, 1546, 1481, 1455, 1398, 1382, 1356, 1284, 1230, 1193, 1160, 1125, 1093, 1043, 1031, 1015, 1000, 961, 902, 860, 840, 798, 763, 730, 703, 651, 633, 616, 601, 592, 564, 530, 501, 485, 459, 442. Anal. Calcld for $C_{22}H_{15}ClN_2O_2$: C, 70.50; H, 4.03; N, 7.47; Found: C, 70.28; H, 3.87; N, 7.22.

2-(3-Methylquinoxalin-2-ylmethoxy)naphthalen-1-carbaldehyde (**19a**). This compound was obtained from the reaction of compound **1a** with compound **18** in 67% yield as colorless crystals, mp 175–177 °C (toluene, 2-ethoxyethanol); IR 3054, 2992, 2943, 2803, 1911, 1828, 1658, 1618, 1589, 1511, 1493, 1498, 1434, 1418, 1399, 1368, 1344, 1300, 1265, 1230, 1180, 1160, 1144, 1063, 1027, 1005, 950, 913, 858, 820, 765, 707, 665, 637, 615, 597, 555, 520, 506, 438, 416. Anal. Calcld for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53; Found: C, 76.78; H, 5.21; N, 8.26.

2-(3-Phenylquinoxalin-2-ylmethoxy)naphthalen-1-carbaldehyde (**19b**). This compound was obtained from the reaction of compound **1b** with compound **18** in 72% yield as colorless crystals, mp 148–150 °C (toluene); IR 3050, 2925, 2885, 1650, 1610, 1585, 1560, 1500, 1480, 1455, 1435, 1365, 1345, 1320, 1285, 1220, 1160, 1150, 1120, 1085, 1050, 1025, 1000, 905, 855, 810, 760, 750, 710, 700, 670, 640, 615, 600, 560, 500. Anal. Calcld for $C_{26}H_{18}N_2O_2$: C, 79.98; H, 4.65; N, 7.17; Found: C, 80.34; H, 4.78; N, 6.93.

4.2.10. General procedure for the synthesis of compounds 21a–c. KOH solution (55 mmol, 3.08 g) in hot EtOH (150 ml) was mixed with salicylic aldehyde (60 mmol, 7.33 g). The resulting phenolate solution was poured into the solution of the 2,3-bis(bromomethyl)-quinoxaline **1d**, **1e** or **1f** (25 mmol) in hot EtOH while stirring. The mixture was heated at reflux for 3 h. The KBr precipitate was removed by filtering from the boiling mixture and washed with boiling EtOH (50 ml). The ethanolic washings were combined with the reaction solution. After adding 20 ml of water the solution was concentrated in vacuo and kept in the refrigerator overnight. The crystalized product was collected and recrystallized.

2,2′-Quinoxalin-2″,3″-diylmethoxydibenzaldehyde (**21a**). This compound was obtained from the reaction of **1d** with **12a** in ethanolic KOH in 62% yield as colorless needles (ethanol), mp 150–151 °C; IR: 3070, 3010, 2896, 2774, 1978, 1684, 1600, 1582, 1478, 1458, 1404, 1356, 1202, 1242, 1220, 1200, 1164, 1126, 1102, 1042, 1012, 990, 908, 866, 834, 804, 754, 696, 648, 612, 598, 564, 528, 478, 444, 418; ^{1}H NMR ($CDCl_3$): δ 10.32 (s, 2H, 2CHO), 8.16–7.00 (m, 12H, 2H-4, H-5, H-6, H-7; H-5′, H-6′, H-7′, H-8′), 5.70

(s, 4H, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 188.9 (2CHO), 160.2, 149.8, 141.3, 125.1 (4×2 quart. C); 135.9, 130.9, 129.3, 129.1, 121.5, 112.9 (6×2 tert. C); 70.6 ($2CH_2$).

2,2′-(6″-Chloroquinoxalin-2″,3″-diyl)methoxydibenzaldehyde (**21b**). This compound was obtained from the reaction of **1e** with **12a** in ethanolic KOH in 54% yield as colorless needles (ethanol), mp 115–117 °C; IR: 3073, 2860, 2736, 1688, 1600, 1481, 1457, 1400, 1286, 1231, 1192, 1184, 1125, 1103, 1066, 1045, 1014, 942, 873, 834, 753, 646, 584, 489, 437; ^1H NMR ($CDCl_3$): δ 10.30 (s, 2H, 2CHO), 8.12–7.01 (m, 11H, 2H-2, H-3, H-4, H-5; H-5′, H-6′, H-8′), 5.68 (s, 4H, $2CH_2$); ^{13}C NMR ($CDCl_3$): δ 188.9 (2CHO); 160.1, 160.0, 150.9, 150.0, 141.6 (2), 139.8 (2), 136.8 (9 quart.C); 135.9 (2), 131.9, 130.3, 129.5, 128.4, 125.0, 121.6 (2), 112.9 (2) (11 tert.C); 70.4 ($2CH_2$).

2,2′-(6″,7″-Dimethylquinoxalin-2″,3″-diyl)methoxydibenzaldehyde (**21c**). This compound was obtained from the reaction of **1f** with **12a** in ethanolic KOH in 76% yield as colorless needles (ethanol), mp 153–154 °C; IR: 3074, 2975, 2863, 2765, 1684, 1600, 1559, 1482, 1458, 1402, 1360, 1291, 1244, 1223, 1200, 1162, 1103, 1046, 1013, 986, 873, 833, 754, 649, 583, 528, 439; ^1H NMR ($CDCl_3$): δ 10.34 (s, 2H, 2CHO); 7.89 (s, 2H, H-5′, H-8′), 7.80–7.01 (m, 8H, 2H-2, H-3, H-4, H-5), 2.53 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 188.9 (2CHO); 160.3, 148.7, 141.7, 140.3, 125.0 (5×2 quart.C); 135.9, 129.1, 128.1, 121.4, 113.0 (5×2 tert.C); 70.6 ($2CH_2$); 20.3 ($2CH_3$).

4.2.11. General procedure for the synthesis of compounds 22a–c. The dialdehyde (**21a**,**b** or **c**) (10 mmol) was dissolved in boiling ethanol, mixed with ethanolic solution of potassium hydroxide (25 mmol) and heated at reflux for 2 h. The resulting mixture was kept in a refrigerator overnight. The solid product was collected by filtering by suction and recrystallized.

2,3-Bis(benzo[*b*]fur-2-yl)quinoxaline (**22a**). This compound was obtained from the dialdehyde **21a** in 64% yield as pale yellow needles (toluene), mp 226–227 °C; IR: 3116, 3064, 3038, 2364, 1926, 1888, 1856, 1774, 1666, 1614, 1600, 1560, 1534, 1478, 1452, 1394, 1358, 1314, 1254, 1236, 1196, 1162, 1138, 1108, 1060, 1004, 974, 924, 884, 850, 824, 812, 776, 736, 690, 654, 634, 612, 570, 536, 508, 490, 460, 418; ^1H NMR ($CDCl_3$): δ 8.24–8.18, 7.92–7.66 (m, 4H, H-5, H-6, H-7, H-8), 7.62 (d, J=7.8 Hz, 2H, H-4′(2) or H-7′(2)), 7.55 (d, J=7.9 Hz, 2H, H-7′(2) or H-4′(2)), 7.35 (t, J=8.0 Hz, 2H, H-6′(2) or H-5′(2)), 7.28 (t, J=8.0 Hz, 2H, H-5′(2) or H-6′(2)); ^{13}C NMR ($CDCl_3$): δ 155.4, 152.5, 143.0, 140.9, 128.2 (5×2 quart.C), 130.9, 129.3, 125.9, 123.4, 121.9, 111.9, 109.5 (7×2 quart. C).

hr-MS: Calcd for $C_{24}H_{14}N_2O_2^+$: 362.1055, found 362.1046.

2,3-Bis(benzo[*b*]fur-2-yl)-6-chloroquinoxaline (**22b**). This compound was obtained from the dialdehyde **21b** in 72% yield as pale yellow needles (toluene), mp 198–199 °C; IR: 3386, 3065, 2925, 1935, 1596, 1558, 1531, 1474, 1452, 1397, 1349, 1320, 1257, 1193, 1168, 1144, 1109, 1064, 1005, 933, 884, 830, 790, 748, 697, 650, 612, 579, 506, 423; ^1H NMR ($CDCl_3$): δ 8.20–8.12 (m, 2H-quin.), δ 7.62–7.20 (m, 10H-benzf., 1H-quin.); ^{13}C NMR ($CDCl_3$): δ 155.5, 155.4, 152.2, 143.7, 143.0, 141.2 (2), 139.4 (2), 136.9 (2) (11 quart.C); 131.9, 130.5, 128.2, 128.1, 126.2, 126.1, 123.5, 122.2, 122.0, 111.9 (2), 110.1, 110.0 (13 tert.C).

hr-MS: Calcd for $C_{24}H_{13}N_2O_2Cl^+$: 396.0666, found 396.0668.

2,3-Bis(benzo[*b*]fur-2-yl)-6,7-dimethylquinoxaline (**22c**). This compound was obtained from the dialdehyde **21c** in 67% yield as pale yellow needles (toluene), mp 185–186.5 °C; IR: 3393, 3061, 3038, 2980, 2919, 2366, 2343, 1945, 1782, 1683, 1561, 1544, 1478, 1451, 1417, 1350, 1326, 1309, 1256, 1229, 1204, 1161, 1144, 1111, 1060, 1023, 1000, 932, 907, 881, 820, 786, 751, 682, 655, 631, 612, 569, 492, 428; ^1H NMR ($CDCl_3$): δ 7.93 (s, 2H, H-5, H-8), 7.59 (d, J=8.4 Hz, 2H, H-4′(2) or H-7′(2)), 7.49 (d, J=8.7 Hz, 2H, H-7′ or H-4′(2)), 7.32 (t, J=8.0 Hz, 2H, H-6′(2) or H-5′(2)), 7.24 (t, J=8.0 Hz, 2H, H-5′(2) or H-6′(2)); 7.11 (s, 2H, H-3′(2)); 2.48 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$): δ 155.2, 152.8., 142.0, 141.8, 139.9, 128.3 (6×2 quart.C); 128.3, 125.5, 123.2, 121.7, 111.7, 108.9 (6×2 tert.C); 20.4 ($2CH_3$).

hr-MS: Calcd for $C_{26}H_{18}N_2O^+$: 390.1368, found 390.1375.

5. Supporting information available

Tables 1a and b. Relative abundance (RA/%) of the most important fragment ions of the aryloxymethyl quinoxalines **3**, **4**, **6**, **8**, **9**, **11**, **16**, **20** and **22**. Tables 2a and b. Elemental compositions and accurate masses for diagnostic ions of compounds **3**, **4**, **6**, **8**, **9**, **11**, **16**, **20** and **22**. This material is available online alongside the electronic version of the article in Elsevier web products including ScienceDirect: http://www. Sciencedirect.com.

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Synthesis of 1-benzyl-8,9-dihydroimidazo[4,5-*c*]pyrrolo[3,2-*g*]-quinolin-4(5*H*)-one via palladium-catalyzed intramolecular arylation

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Abstract—The synthesis of a novel tetracyclic structure, 8,9-dihydroimidazo[4,5-*c*]pyrrolo[3,2-*g*]quinolin-4(5*H*)-one, has been achieved by a convergent pathway. Coupling of the weakly nucleophilic hindered aromatic amine with 1-benzylimidazole-4-carboxylic acid, **7**, afforded the corresponding amide **9** using a DCP/DMF complex; subsequent Heck-type arylation leading to desired tetracyclic molecule imidazo[4,5-*c*]-pyrrolo[3,2-*g*]quinolin-4(5*H*)-one.

1. Introduction

Heterocycles with a plane structure have attracted considerable interest in pharmaceutical research due to their therapeutic potentialities; in the field of anticancer agents, several drugs have been designed because their structure allowed DNA intercalation and/or interaction with topoisomerases.[1,2] Such molecules display a wide range of chemical structure but among them we can distinguish several compounds with a plane arc-shaped structure like ellipticine[3] and intoplicine,[4] which are long-known topoisomerase II inhibitors (Fig. 1). Due to multidrug-resistance phenomena, the search for new active structures is still a challenge. Interestingly, amiloride (Fig. 1), a drug used as diuretic, acts also as a topoisomerase II inhibitor.[6] This activity has been strongly correlated with the ability of the molecule to adopt a plane arc-shaped conformation. A similar structure has been observed in other cytotoxic compounds like grossularines,[7,8] but unfortunately, the authors did not investigate their action against topoisomerases (Fig. 1). Therefore, we were interested in the synthesis of a new tetracyclic structure inspired from ellipticine, amiloride and grossularines: imidazo[4,5-*c*]-pyrrolo[3,2-*g*] quinolinone (Fig. 2).

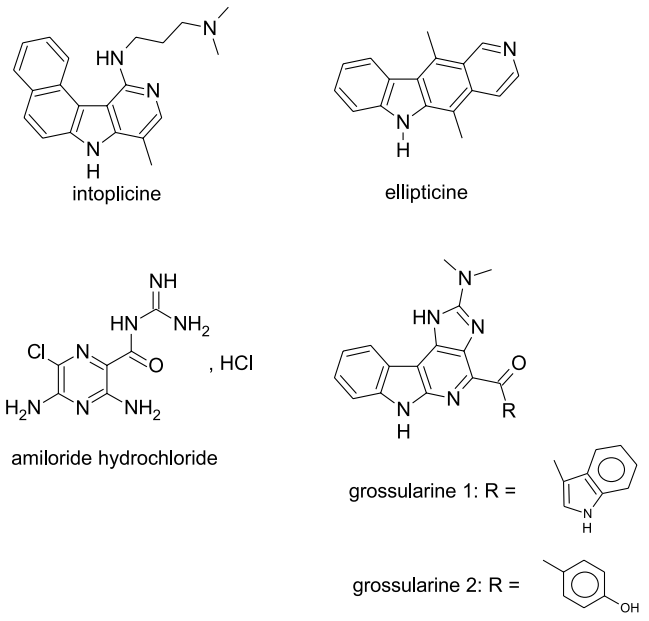

Figure 1. Topoisomerase-II inhibitors.

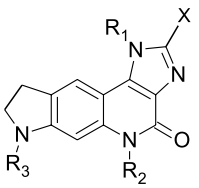

Figure 2. Imidazo[4,5-*c*]pyrrolo[3,2-*g*]quinolines.

Keywords: Amide coupling; DCP/DMF complex; Palladium-catalyzed intramolecular arylation; 8,9-Dihydroimidazo[4,5-*c*]pyrrolo[3,2-*g*]-quinolin-4(5*H*)-one.
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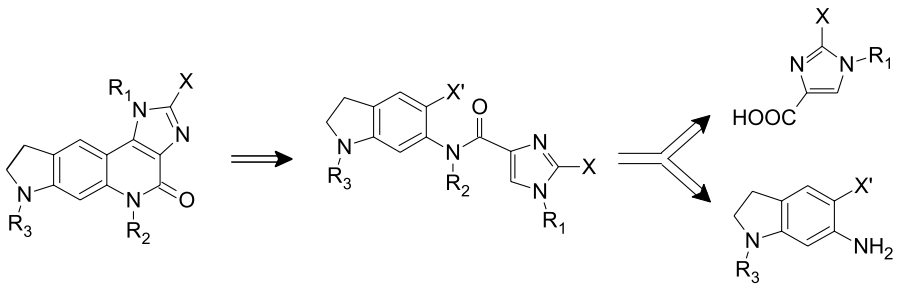
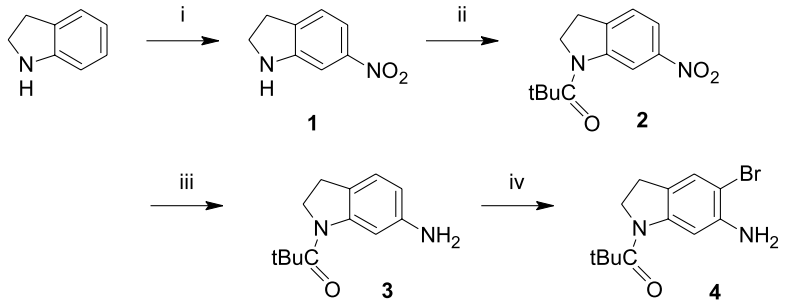


Scheme 1. Retrosynthetic pathways for 8,9-dihydroimidazo[4,5-*c*]pyrrolo[3,2-*g*]quinolin-4(5*H*)-one synthesis.



Scheme 2. (i) KNO_3, H_2SO_4; (ii) *t*BuCOCl, Et_3N, DCE, 0 °C, 4 h; (iii) H_2, Raney Ni, THF, rt, 24 h.

In this communication, we wish to report the first synthesis of this new tetracyclic structure.

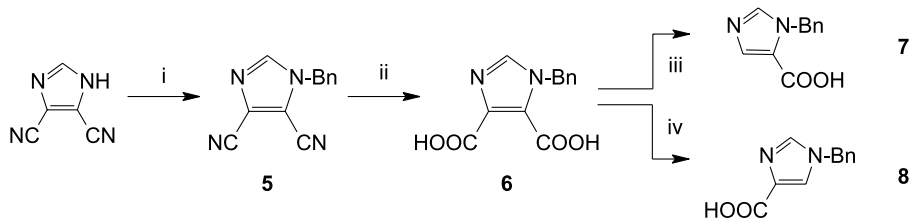
2. Results and discussion

A convergent synthesis has been selected for the preparation of such molecules, the key-steps of this pathway being the coupling of an aminoindoline derivative with a protected imidazole-4-carboxylic acid, and a palladium-catalyzed cyclization on the amide (Scheme 1).

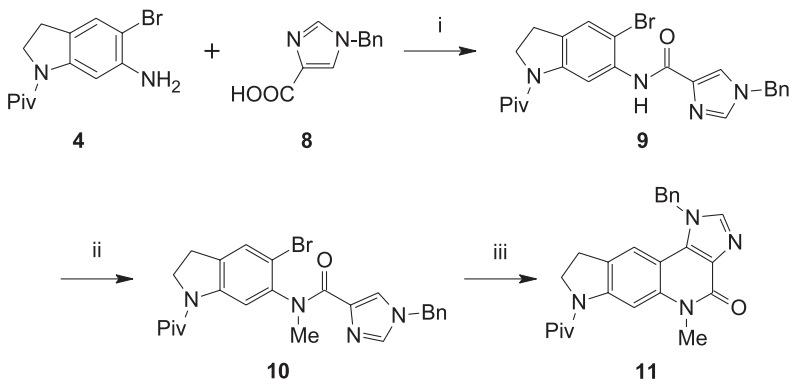
First, the synthesis of the indoline moiety[4] was performed by nitration of indoline according to Teventev et al.[5] in concentrated sulphuric acid affording 6-nitroindoline **1** in a 95% yield (Scheme 2). The intracyclic nitrogen atom of the pyrroline ring was then protected by a pivaloyl group, using pivaloyl chloride and triethylamine in 1,2-dichloroethane, providing 6-nitro-1-pivaloylindoline **2** in a 95% yield. Reduction of the nitro group by catalytic hydrogenation using Raney nickel as catalyst, led to 6-amino-1-pivaloyl-indoline **3** in a quantitative yield. Bromination of compound **3**, with bromine in acetic acid, afforded 6-amino-5-bromo-1-pivaloylindoline **4** as the sole product in 91% yield.

The synthesis of the imidazole moiety has been achieved starting from the commercially available 4,5-dicyano-imidazole in analogy with O'Connell's method[7] (Scheme 3). 4,5-Dicyanoimidazole was alkylated with benzyl chloride in the presence of sodium hydride in *N*,*N*-dimethylformamide to afford compound **5** in 81% yield. Nitrile functions of **5** were then hydrolyzed into diacid **6** with 94% yield. Compound **6** can then be selectively decarboxylated at the 5-position to 1-benzylimidazole-4-carboxylic acid **8** by refluxing for 4 h in *N*,*N*-dimethyl-acetamide at 165 °C in 80% yield, whereas decarboxylation occurred at the 4-position when heated in acetic anhydride at 100 °C to give **7** in almost quantitative yield.

Coupling of the indoline moiety with the imidazole residue was achieved using a complex of phenyl dichlorophosphate and *N*,*N*-dimethylformamide. This complex was first described by Cramer and Winter in 1961 as an efficient phosphorylation agent,[9] and was used by Garcia et al. to activate acids as mixed anhydrides of carboxylic and phosphoric acids in the synthesis of esters.[10] We have been able to couple sterically hindered aromatic amines with strongly deactivated carboxylic acids in stoichiometric amounts at room temperature with good yields thanks to this complex.[11] This complex revealed to be non expensive and easy to prepare. In addition, its use afforded amide **9** from amine **4** and acid **7** in 77% yield (Scheme 4). Amidic nitrogen in compound **9** was then methylated to afford compound **10** in 59% yield. Compound **11** with the desired



Scheme 3. (i) NaH, DMF, $PhCH_2Cl$; (ii) NaOH 10 M; (iii) Ac_2O, 100 °C; (iv) DMA, 165 °C.



Scheme 4. (i) DCP, DMF, pyridine, CH_2Cl_2, rt, 2 h; (ii) NaH, MeI, DMF; (iii) $Pd(OAc)_2$ (cat.), PPh_3 (cat.), K_2CO_3, DMA, 170 °C.

tetracyclic structure was obtained, via palladium-catalyzed intramolecular cyclization, in 28% yield with a catalytic system consisting of palladium acetate and triphenylphosphine when heating at 170 °C in *N*,*N*-dimethylacetamide in the presence of potassium carbonate.

3. Summary

We reported the synthesis of imidazo[4,5-*c*]pyrrolo[3,2-*g*]-quinolin-4(5*H*)-ones by a convergent pathway. Key step involved amide coupling with a DCP/DMF complex, non expensive and easy-to-prepare reagent which revealed efficient, and Heck-type arylation. The scope of use of this coupling agent is currently under way and will be soon reported elsewhere. This novel tetracyclic structure may prove to be of great interest in different therapeutic areas, especially as anticancer agent.

4. Experimental

4.1. General

4.1.1. 6-Nitroindoline (1). A solution of potassium nitrate (7.17 g, 70.9 mmol) was added at 0 °C to a solution of indoline (6 g, 50.2 mmol) in concentrated sulfuric acid (40 mL). After stirring 75 min at room temperature, the solution was poured into ice–water (400 mL) and pH was brought to 4 with 10 N sodium hydroxide. Basification was pursued until precipitation stopped. The solution was extracted with dichloromethane (300 mL), washed with water (200 mL), dried over sodium sulfate, filtered, evaporated to give **1** (7.88 g, 95%). The solid was recrystallized from diethyl ether/hexane. Mp 67–68 °C. (lit.[5] 67 °C, ligroin) IR (KBr, cm^{-1}): 3415, 1511. ^1H NMR ($CDCl_3$, 250 MHz) δ 3.10 (t, 2H, $^3J_{HH}$=8.4 Hz), 3.68 (t, 2H, $^3J_{HH}$=8.4 Hz), 3.92 (s, 1H); 7.13 (d, 1H, $^3J_{HH}$=7.9 Hz), 7.35 (d, 1H, $^4J_{HH}$=2.1 Hz), 7.54 (dd, 1H, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=2.1 Hz). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 29.9, 48.0, 102.8, 114.1, 124.2, 136.9, 148.2, 152.5. MS (+ESI): *m*/*z*: 165 [MH^+].

4.1.2. 6-Nitro-*N*-pivaloylindoline (2). Triethylamine (8.2 mL, 59 mmol) was added to a solution of **1** (3.86 g, 23.5 mmol) in 1,2-dichloroethane. Pivaloyl chloride (4.4 mL, 36 mmol) was added at 0 °C. After stirring 4 h at 30 °C, the solution was poured into 0.3 M chlorhydric acid (200 mL), extracted with dichloromethane (200 mL), washed with water (100 mL), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography over silicagel eluting with dichloromethane to give **2** (5.56 g, 95%). Mp 138 °C. IR (KBr, cm^{-1}): 1646, 1519, 1347. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.38 (s, 9H), 3.24 (t, 2H, $^3J_{HH}$=8.1 Hz), 4.35 (t, 2H, $^3J_{HH}$=8.1 Hz), 7.28 (d, 1H, $^3J_{HH}$=8.2 Hz), 7.88 (dd, 1H, $^3J_{HH}$=8.2 Hz, $^4J_{HH}$=2.1 Hz), 9.04 (d, 1H, $^4J_{HH}$=2.1 Hz). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 27.6, 29.2, 40.3, 49.9, 113.2, 119.1, 124.1, 138.1, 145.7, 147.7, 177.1. MS (+ESI): *m*/*z*: 249 [MH^+].

4.1.3. 6-Amino-*N*-pivaloylindoline (3). A solution of **2** (2.01 g, 8.10 mmol) in THF (50 mL) was placed in a Parr apparatus for hydrogenation. Raney nickel (1 g) rinsed with ethanol and THF was added. The suspension was stirred overnight under 150 psi of hydrogen at room temperature and then filtered over celite, rinsed with THF, dried over calcium chloride, filtered and evaporated to give **3** (1.77 g, 99%). Mp 126–127 °C. IR (KBr, cm^{-1}): 3433, 3390, 1630, 1332, 1201. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.37 (s, 9H), 3.03 (t, 2H, $^3J_{HH}$=7.9 Hz), 3.61 (large s, 2H), 4.21 (t, 2H, $^3J_{HH}$=7.9 Hz), 6.37 (dd, 1H, $^3J_{HH}$=7.9 Hz, $^4J_{HH}$=2.1 Hz), 6.95 (d, 1H, $^3J_{HH}$=7.9 Hz), 7.73 (d, 1H, $^4J_{HH}$=2.1 Hz). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 27.5, 28.4, 40.2, 50.0, 105.2, 110.1, 120.5, 124.3, 145.6, 145.9, 176.6. MS (+ESI): *m*/*z*: 219 [MH^+].

4.1.4. 6-Amino-5-bromo-*N*-pivaloylindoline (4). To a solution of **3** (5 g, 22.9 mmol) in acetic acid (277 mL), bromine (1.41 mL, 27.5 mmol) was added drop-by-drop. After stirring 1 h at room temperature, the solution was poured into water (250 mL), extracted with dichloromethane (150 mL), dried over sodium sulfate, filtered and evaporated. The crude mixture was purified by column chromatography over silicagel eluting with dichloromethane and then with a 97/3 mixture of dichloromethane and ethanol to give **4** (6.19 g, 91%). Mp 163–164 °C. IR (KBr, cm^{-1}): 3455, 3342, 1627, 648. ^1H NMR ($CDCl_3$, 250 MHz) δ 1.37 (s, 9H), 3.04 (td, 2H, $^3J_{HH}$=8.1 Hz, $^4J_{HH}$=0.9 Hz), 4.00 (large s, 2H), 4.21 (t, 2H, $^3J_{HH}$=8.1 Hz), 7.19 (large s, 1H), 7.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 27.6, 28.2, 40.2, 50.0, 102.7, 106.1, 122.0, 127.3, 143.1, 145.0, 176.6. MS (+ESI): *m*/*z*: 297, 299 [MH^+].

4.1.5. *N*-Benzyl-4,5-dicyanoimidazole (5). To a solution of 4,5-dicyanoimidazole (8.90 g, 75.4 mmol) in DMF

(100 mL), a 60% suspension in mineral oil of sodium hydride (3.62 g, 90.4 mmol) was added under a nitrogen atmosphere at 0 °C. The solution was stirred at room temperature until gas evolution stopped. Benzyl chloride (10.4 mL, 90.4 mmol) was then added at 0 °C and the solution was stirred 12 h at room temperature, evaporated to dryness, solubilized in dichloromethane (200 mL), washed with water (3×200 mL), dried over sodium sulfate, filtered and evaporated to afford **5** (12.7 g, 81%). Mp 124–125 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.28 (s, 2H), 7.68 (s, 1H), 7.27–7.47 (m, 5H). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 50.6, 111.8, 112.3, 108.4, 121.9, 127.8, 128.6, 129.0, 134.4, 143.5. MS (+ESI): *m*/*z*: 209 [MH^+].

4.1.6. *N*-Benzylimidazole-4,5-dicarboxylic acid (6). Compound **5** (19.3 g, 92.7 mmol) was refluxed in a 6 M sodium hydroxide solution (250 mL, 1.5 mol) during 2 h. The hot solution was filtered and washed with a solution of 3 M chlorhydric acid (1.1 L). The filtrate was cooled and filtered to get **6** (21.5 g, 94%). Mp 217–218 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 5.83 (s, 2H), 7.32–7.43 (m, 5H), 9.36 (s, 1H). ^{13}C NMR (DMSO-d_6, 250 MHz) δ 50.9, 125.9, 128.0, 128.6, 135.8, 137.1, 138.5, 158.8, 159.5. MS (+ESI): *m*/*z*: 247 [MH^+].

4.1.7. *N*-Benzylimidazole-4-carboxylic acid (7). Carboxylic acid **6** (1.00 g, 4.06 mmol) was placed in acetic anhydride (30 mL) and heated at 100 °C during 25 min. The solution was evaporated. The residue was suspended in ethanol, filtered and recrystallized in ethanol to afford **7** (0.81 g, 99%). Mp 254–255 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 5.58 (s, 2H), 7.17–7.40 (m, 5H), 7.67 (d, 1H, $^4J_{HH}$=0.9 Hz), 8.13 (d, 1H, $^4J_{HH}$=0.9 Hz), 12.9 (large s, 1H). ^{13}C NMR (DMSO-d_6, 250 MHz) δ 48.7, 126.9, 128.0, 128.8, 137.0, 137.7, 143.0, 161.0. MS (+ESI): *m*/*z*: 203 [MH^+].

4.1.8. *N*-Benzylimidazole-5-carboxylic acid (8). Compound **6** (1.00 g, 4.06 mmol) was placed in *N*,*N*-dimethylacetamide (15 mL) and heated at 165 °C during 4 h. The solution was evaporated. The residue was recrystallized in ethanol to afford **8** (0.66 g, 80%). Mp 221–222 °C. ^{1}H NMR (DMSO-d_6, 250 MHz) δ 5.28 (s, 2H), 7.34–7.44 (m, 5H), 7.93 (d, 1H, $^4J_{HH}$=1.2 Hz), 7.96 (d, 1H, $^4J_{HH}$=1.2 Hz), 12.2 (large s, 1H). ^{13}C NMR (DMSO-d_6, 250 MHz) δ 49.8, 125.9, 127.7, 127.9, 128.7, 133.4, 137.1, 138.5, 163.5. MS (+ESI): *m*/*z*: 203 [MH^+].

4.1.9. *N*-(5-Bromo-1-pivaloylindolin-6-yl)-(1-benzylimidazol-4-yl)carboxamide (9). To DMF (0.29 mL, 3.76 mmol), phenyl dichlorophosphate (0.37 mL, 2.47 mmol) was added at 0 °C and stirred for 5 min. Then dichloromethane (15 mL) and **7** (0.4 g, 1.98 mmol) were added. Solution was stirred for 10 min and pyridine (0.64 mL, 7.9 mmol) was added. Solution was stirred for 10 min and **4** (0.705 g, 2.37 mmol) was added. After stirring 4 h at room temperature, the mixture was poured into water (30 mL), extracted with dichloromethane (3×50 mL), evaporated and purified by column chromatography over silica eluting with a 95:5 mixture of dichloromethane and ethanol to give **9** (0.735 g, 77%). Mp 203–204 °C. IR (KBr, cm^{-1}): 3352, 1684, 1642, 656. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.33 (s, 9H), 3.06 (t, 2H, $^3J_{HH}$=8.1 Hz), 4.21 (t, 2H, $^3J_{HH}$=8.1 Hz), 5.16 (s, 2H), 7.18–7.22 (m, 2H), 7.33–7.42 (m, 4H), 7.52 (d, 1H, $^4J_{HH}$=1.2 Hz), 7.63 (d, 1H, $^4J_{HH}$=1.2 Hz), 9.22 (s, 1H), 9.31 (s, 1H). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 27.6, 28.5, 40.1, 49.9, 51.3, 107.6, 112.4, 122.9, 127.1, 127.5, 127.9, 128.4, 129.0, 134.6, 135.1, 136.8, 137.5, 144.7, 159.8, 176.1. MS (+ESI): *m*/*z*: 481, 483 [MH^+].

4.1.10. *N*-(5-Bromo-1-pivaloylindolin-6-yl)-*N*-methyl-(1-benzylimidazol-4-yl)carboxamide (10). A 60% suspension in mineral oil of sodium hydride (0.099 g, 2.5 mmol) was added at 0 °C to a solution of **9** (0.79 g, 1.64 mmol) in DMF (20 mL) under nitrogen atmosphere. The reaction mixture was then stirred at room temperature until gas evolution stopped. Methyl iodide (0.123 mL, 1.97 mmol) was then added at 0 °C. The mixture was stirred 12 h at room temperature, evaporated to dryness, solubilized in dichloromethane (30 mL), washed with water (3×20 mL), dried over sodium sulfate, filtered and evaporated to afford **10** (0.482 g, 59%). Mp 98–100 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.35 (s, 9H), 3.13 (m, 2H), 3.32 (s, 3H), 4.25 (m, 2H), 4.95–4.97 (m, 2H), 6.78–6.82 (m, 1H), 7.00–7.05 (m, 2H), 7.20–7.45 (m, 5H), 8.21 (s, 1H). MS (+ESI): *m*/*z*: 495, 497 [MH^+].

4.1.11. 1-Benzyl-5-methyl-7-pivaloyl-8,9-dihydroimidazo[4,5-*c*]pyrrolo[3,2-*g*]quinolin-4-(5*H*)one (11). Under an nitrogen atmosphere, palladium acetate (17.2 mg, 0.08 mmol), potassium carbonate (0.212 g, 1.53 mmol), triphenylphosphine (40.2 mg, 0.15 mmol) were added to a solution of **10** (0.38 g, 0.77 mmol) in 15 mL of *N*,*N*-dimethylacetamide. After 3 freeze/pump/thaw cycles, the mixture was stirred at 170 °C during 24 h. It was then evaporated to dryness under reduced pressure. Dichloromethane (150 mL) was added, the organic phase was washed with 0.5 M sodium hydroxide (100 mL) and with a saturated solution of sodium chloride (50 mL), dried over sodium sulfate, filtered and evaporated. The residue was purified by column chromatography over silicagel eluting with a 90:10 mixture of dichloromethane and ethanol to give **11** (0.088 g, 28%). Mp >300 °C. IR (KBr, cm^{-1}): 1640, 1665. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.40 (s, 9H), 3.08 (t, 2H, $^3J_{HH}$=8.0 Hz), 3.84 (s, 3H), 4.29 (t, 2H, $^3J_{HH}$=8.0 Hz), 5.65 (s, 2H), 7.08–7.15 (m, 2H), 7.30–7.40 (m, 3H), 7.42 (s, 1H), 7.76 (s, 1H), 8.54 (s, 1H). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 27.6, 28.4, 30.2, 40.5, 50.1, 50.9, 105.5, 108.7, 116.6, 125.4, 126.2, 128.4, 129.3, 131.8, 132.6, 134.8, 138.3, 142.4, 145.3, 158.2, 177.3. MS (+ESI): *m*/*z*: 415 [MH^+].

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An efficient and facile one-step synthesis of highly substituted thiophenes

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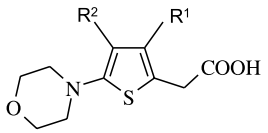
Abstract—An efficient one-step method for the synthesis of fully substituted thiophenes, from thiomorpholides and α-halo ketones, was developed. A mechanism has also been proposed for the course of reaction.

1. Introduction

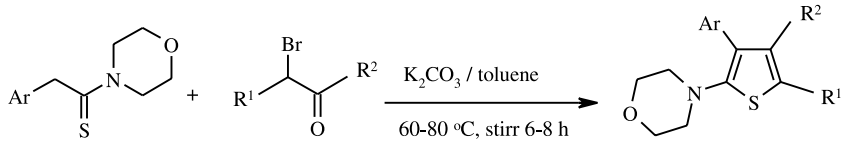
The synthesis of highly substituted thiophenes has attracted a great deal of interest over the years due to their presence in natural products,[1] as new conducting polymers[2] and isosteric replacement for phenyl group in medicinal chemistry.[3] Our interest in this class of compound was based on their use as novel anti-inflammatory and analgesic drugs having general formula (A).



(A)

However, the synthesis of highly substituted thiophenes is restricted by the lack of enough available methods to construct the desired ring bearing functionality in a controlled fashion. The most convenient method for preparing thiophenes with a high degree of functionality is by the Gewald method in which elemental sulfur is reacted with an activated acetonitrile and an aldehyde, ketone or 1,3-dicarbonyl compound in the presence of a base (equimolar quantities of each).[4] A modification of the Gewald method has been reported in which an alkoxyacetone is reacted with ethylcyanoacetate, sulfur, and morpholine producing 5-alkoxy thiophene derivatives in poor yields (19–39%).[5]

Thioamides have been used as useful synthons in the synthesis of heterocycles.[6] Thiazole derivatives are produced by the reaction of primary and/or secondary thioamides with α-haloketones. But, in contrast to the primary and secondary thioamides, the nitrogen atom of



1 a-i **2 a-i** **3 a-i**

55-80 %

a: Ar= phenyl, R^1= H, R^2= 4-bromophenyl
b: Ar= 4-chlorophenyl, R^1= H, R^2= 4-bromophenyl
c: Ar= 4-biphenyl, R^1= H, R^2= 4-bromophenyl
d: Ar= 2-naphthyl, R^1= H, R^2= 4 -bromophenyl
e: Ar= phenyl, R^1= phenyl, R^2= phenyl
f: Ar= 4-chlorophenyl, R_1= phenyl, R_2= phenyl
g: Ar= 2-naphthyl, R^1=phenyl, R^2= phenyl
h: Ar= 4-methoxyphenyl, R^1= phenyl, R^2= phenyl
i : Ar= phenyl, R^1=methyl, R^2=H

Scheme 1.

Keywords: Substituted thiophenes.
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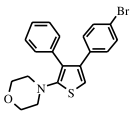
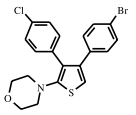
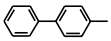
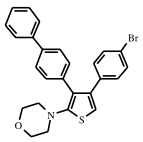
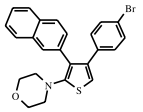
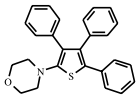
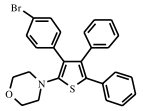
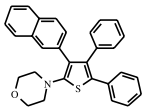
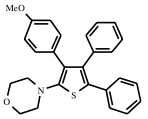
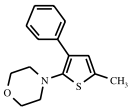
Table 1. Constraction of highly substituted thiophenes using thiomorpholides

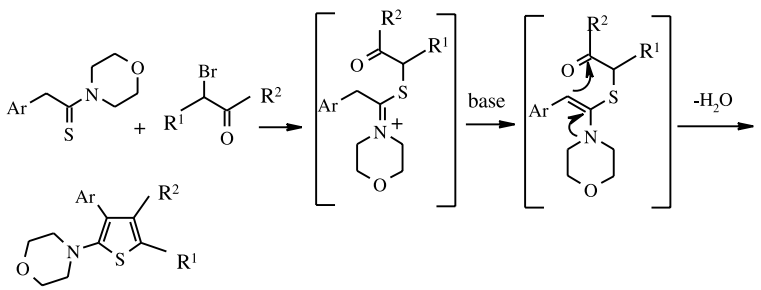
Entry	Ar	R^1	R^2	Product	Reaction time (h)	Temperature	Isolated yield (%)	Mp (°)
1		H			7	70	75	178
2		H			8	80	58	145
3		H			7	75	60	153
4		H			7	85	63	158
5					6.5	75	80	208
6					7	80	55	214
7					8	85	62	243
8					7	75	69	196
9		$-CH_3$	H		6	70	70	105

tertiary thioamides could not take part in heterocyclization. However, the tertiary thioamides having an activated methylene group could react with α-halocarbonyl compounds in the presence of a base leading to the synthesis of 2-aminothiophene derivatives. For example, tertiary thioacetamides in benzene react with α-bromoketones in the presence of DBU yielding 2-amino-3-nitrothiophenes.[7] These reactions are restricted to the tertiary nitro thioacetamides as starting materials. Earlier we have reported a simple microwave-induced method for the preparation of thiomorpholides including aryl thioacetomorpholides.[8] The availability of such thiomorpholides provided a unique opportunity of examining their synthetic utility. We were especially intrigued by the possibility of their use in the synthesis of thiophene containing heterocyclic compounds especially aryl acetic acids. We hoped that such compounds would exhibit interesting analgesic and anti-inflammatory properties. As a preliminary result, recently we have reported a versatile one-pot synthesis of trisubstituted thiophenes from thiomorpholides via S-Claisen rearrangement.[9] In continuation of our research in this area and aiming to find new biologically active heterocyclic compounds, such as 2-aminothiophene derivatives, here we report our results on the reaction of aromatic thioacetomorpholides with α-bromoketones (Scheme 1).

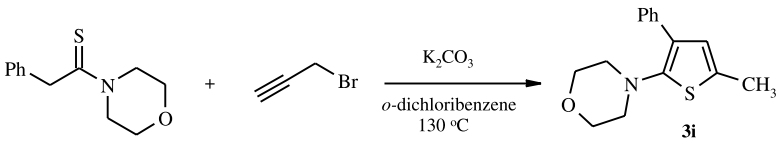
When the thiomorpholide **1** was treated with α-bromoketone **2** in toluene and stirred for 6–8 h at 60–80 °C in the presence of anhydrous K_2CO_3, the highly substituted thiophenes were obtained in good yields. Several examples have been investigated and Table 1 summarizes our results along with the melting points of the compounds.

A mechanism is proposed for the reaction course and shown in Scheme 2. Thiomorpholide undergoes first an *S*-alkylation with α-haloketone, then subsequent treatment with base leading to cyclization and formation of thiophene ring with water elimination.

For confirming the proposed mechanism, one of the model compounds (**3i**) was prepared by a reaction pathway for



Scheme 2.

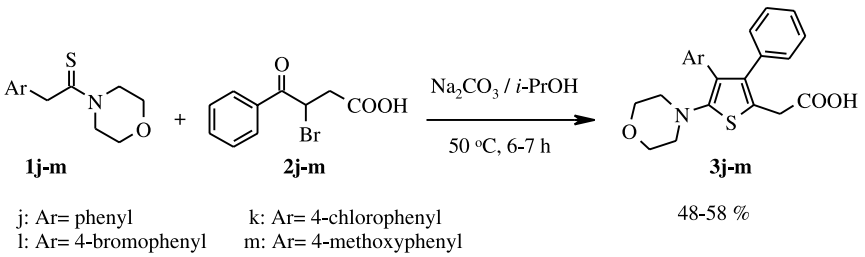


Scheme 3.

which the mechanism was known (Scheme 3).[9,10] Both reactions gave the same compound with fixed substitutes in thiophene ring.

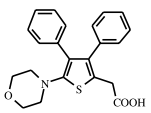
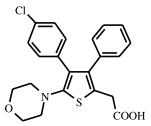
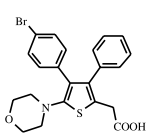
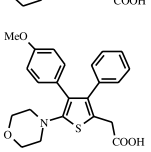
In order to obtain new aryl acetic acid derivatives, it was also found that the thiomorpholides could react with functionalized α-haloketones such as β-bromo-β-benzoyl propionic acid to give fully substituted thiophenes in one step and good chemical yields (Scheme 4). Table 2 resumes our results.

Surprisingly this reaction proceeded more conveniently in a polar solvent such as isopropanol in the presence of anhydrous Na_2CO_3 as base compared to the toluene/K_2CO_3 system. In toluene, the reaction proceeded sluggishly with low yield. These new aryl acetic acid



Scheme 4.

Table 2. One-step synthesis of thiophene acetic acid derivatives

Entry	Ar	Product	Reaction time (h)	Temprature	Isolated yield (%)	Mp (°)
1			6	65	58	172
2			7	65	52	228
3			7	60	50	190
4			6	55	48	185

derivatives have promising analgesic and anti-inflammatory effect.

In conclusion we have developed a new general efficient and simple method for the preparation of highly substituted thiophenes. The generality of the method has been demonstrated by the successful conversion of twelve substrates into tri or tetra substituted morpholino thiophenes in good yields. The base is rather cheap and readily available in all chemistry laboratories. The method was easily extended to the synthesis of thiophenes (see Table 2) bearing an acetic acid unit at position 5. These materials especially 2-morpholino-5-acetic acid substituted thiophenes have the potential to be used as analgesic and anti-inflammatory drugs. The methodology described here seems to be the simplest one for the one-step synthesis of these compounds.

2. Experimental

The compounds gave satisfactory all spectroscopic data. FT IR spectra were recorded as KBr pellets on a Nicolet spectrometer (Magna 550). A Bruker (DRX-500 Avance) NMR was used to record the ^{1}H NMR spectra. All ^{1}H NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were determined on a Büchi B540 apparatus.

2.1. General procedure for the one-pot preparation of compounds (a–i)

To a stirred solution of thiomorpholide (4 mmol) in toluene (5 ml), anhydrous K_2CO_3 (0.552 g, 4 mmol) was added. Then a solution of bromoketone (4 mmol) in toluene (~3 ml) was added dropwise over 10 min. The reaction mixture was heated at 75 °C for about 7 h. The solvent was evaporated to half volume. After cooling a precipitate was appeared. The precipitate was filtered and crystallized from a suitable solvent.

2.2. General procedure for the one-pot preparation of compounds (j–l)

To a stirred solution of thiomorpholide (4 mmol) in 2-propanol (3 ml), β-bromo-β-benzoyl propionic acid (4 mmol) was added. Then reaction mixture was heated to 70 °C for about 1 h. Then, anhydrous Na_2CO_3 (0.212 g, 2 mmol) was added and stirred overnight. The solvent was removed under vacuum and the residue was dissolved in ether (20 ml), washed with 2×5 ml NaOH (5%). The aqueous solution was acidified with HCl (5%) and extracted with diethyl ether. The solvent was evaporated and the solid residue was recrystallized from ethanol.

2.3. Spectroscopic data for compounds (3a–3m)

Compound **3a**: white powder (EtOH), mp: 178 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.33 (d, J=8.2 Hz, 2H), 7.29 (d, J=9.4 Hz, 2H), 7.27 (t, J=5.4 Hz, 1H), 7.23 (t, J=5.4 Hz, 2H), 6.96 (d, J=8.2 Hz, 2H), 6.86 (s, 1H), 3.67 (t, J=4.3 Hz, 4H), 2.87 (t, J=4.3 Hz, 4H); IR (KBr) 3100, 2915, 1645, 1500, 1123, 830 (cm^{-1}).

Compound **3b**: white powder (EtOH), mp: 145 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.36 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.18 (d, J=8.5 Hz, 2H), 6.95 (d, J=8.4 Hz, 2H), 6.87 (s, 1H), 3.68 (t, J=4.6 Hz, 4H), 2.86 (t, J=4.6 Hz, 4H); IR (KBr) 3050, 2953, 1584, 1500, 1123, 830 (cm^{-1}).

Compound **3c**: light yellow crystals (EtOH), mp: 153 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.65 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.0 Hz, 2H), 7.46 (t, J=7.6 Hz, 2H), 7.36 (t, J=8.1 Hz, 1H), 7.34 (d, J=8.1 Hz, 2H2), 7.31 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.2 Hz, 2H), 6.88 (s, 1H), 3.70 (t, J=4.4 Hz, 4H), 2.91 (t, J=4.5 Hz, 4H); IR (KBr) 3060, 2845, 1638, 1500, 1123, 830 (cm^{-1}).

Compound **3d**: yellow powder (EtOH), mp: 157 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.83 (d, J=7.3 Hz, 1H), 7.77, (d, J=8.5 Hz, 1H), 7.72 (d, J=8.5 Hz, 1H), 7.70 (s, 1H), 7.45–7.50 (m, 2H), 7.41 (d, d, J=8.4, 1.5 Hz, 1H), 7.29 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 6.90 (s, 1H), 3,64 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3110, 2950, 1610, 1445, 1123, 700 (cm^{-1}).

Compound **3e**: white powder (EtOH), mp: 208 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.13–7.24 (m, 13H), 6.96 (d, d, J=7.4, 1.8 Hz, 2H), 3.61 (t, J=4.6 Hz, 4H), 2.88 (t, J=4.6 Hz, 4H); IR (KBr) 3090, 2970, 1620, 1500, 1123, 700 (cm^{-1}).

Compound **3f**: yellow powder (EtOH), mp: 214 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.14–7.23 (m, 8H), 7.10 (d, J=8.7 Hz, 2H), 6.97 (d, d, J=7.3, 2 Hz, 2H), 6.79 (d, J=8.7 Hz, 2H), 3.62 (t, J=4.6 Hz, 4H), 2.89 (t, J=4.6 Hz, 4H); IR (KBr) 3120, 2845, 1600, 1507, 1123, 753 (cm^{-1}).

Compound **3g**: light yellow powder (EtOH), mp: 243 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.75 (d, J=7.7 Hz, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.58 (s, 1H), 7.40–7.43 (m, 2H), 7.38 (d, J=8.5 Hz, 1H), 7.13–7.23 (m, 5H), 7.07–7.11 (m, 3H), 6.96 (d, J=6.5 Hz, 2H), 3.64 (t, J=4.4 Hz, 4H), 2.93 (t, J=4.4 Hz, 4H); IR (KBr) 3097, 2807, 1607, 1500, 1253, 836 (cm^{-1}).

Compound **3h**: light yellow crystals (EtOH), mp: 196 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.1–7.18 (m, 8H), 7.06 (d, J=8.6 Hz, 2H), 6.93 9m, 2H), 6.71 (d, J=8.6 Hz, 2H), 3.79 (s, 3H), 3.69 (t, J=4.4 Hz, 4H), 2.94 (t, J=4.5 Hz, 4H); IR (KBr) 3090, 2856, 1597, 1502, 1125, 830 (cm^{-1}).

Compound **3i**: white crystals (EtOH), mp: 105 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 7.79 (d, J=7.7 Hz, 2H), 7.41 (t, J=7.7 Hz, 2H), 7.27 (t, J=7.6 Hz, 1H), 6.79 (s, 1H), 3.81 (t, J=4.6 Hz, 4H), 2.97 (t, J=4.6 Hz, 4H), 2.48 (s, 3H); IR (KBr) 2964, 2907, 2860, 1643, 1505, 1117, 837 (cm^{-1}).

Compound **3j**: white powder (EtOH), mp: 172 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 9.45 (s, 1H), 7.24 (m, 3H), 7.11–7.19 (m, 5H), 7.05 (m, 2H), 3.72 (s, 2H), 3.67 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3738, 3050, 2923, 1707, 1446, 1253, 759 (cm^{-1}).

Compound **3k**: light yellow powder (EtOH), mp: 228 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) 9.52 (s, 1H), 7.26 (m, 3H), 7.15 (d, J=8.5 Hz, 2H), 7.1 (d, J=8.5 Hz, 2H), 7.02–7.04 (m, 2H),

3.71 (s, 2H), 3.68 (t, J=4.4 Hz, 4H), 2.88 (t, J=4.4 Hz, 4H); IR (KBr) 3610, 3110, 2961, 1710, 1446, 1262, 707 (cm^{-1}).

Compound **3l**: light yellow crystals (EtOH), mp: 190 °C, ^1H NMR ($CDCl_3$, 500 MHz) 9.58 (s, 1H), 7.25 (m, 3H), 7.08 (d, J=8.6 Hz, 2H), 7.05 (m, 2H), 6.72 (d, J=8.6 Hz, 2H), 3.79 (s, 2H), 3.68 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3446, 2923, 1692, 1592, 1261, 769 (cm^{-1}).

Compound **3m**: yellow crystals (EtOH), mp:185 °C, ^1H NMR ($CDCl_3$, 500 MHz) 9.50 (s, 1H), 7.22–7.27 (m, 3H), 7.08 (d, J=8.7 Hz, 2H), 7.05 (d, J=7.7 Hz, 2H), 6.72 (d, J=8.7 Hz, 2H), 3.77 (s, 3H), 3.71 (s, 2H), 3.68 (t, J=4.5 Hz, 4H), 2.89 (t, J=4.5 Hz, 4H); IR (KBr) 3455, 2937, 1702, 1595, 1257, 748 (cm^{-1}).

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Precursors to oak lactone. Part 2: Synthesis, separation and cleavage of several β-D-glucopyranosides of 3-methyl-4-hydroxyoctanoic acid☆

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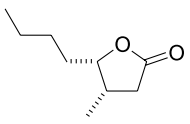
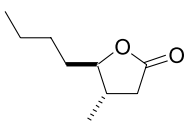
Abstract—The β-D-glucopyranosides of all four stereoisomers of 3-methyl-4-hydroxyoctanoic acid have been prepared. The (3*S*,4*S*) and (3*R*,4*R*) species were prepared from *cis*-5-*n*-butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone (*cis*-oak lactone) by a process involving ring-opening with base and protection of the carboxyl function as its benzyl ester. The glucose unit was introduced by a modified Koenigs–Knorr procedure. A different strategy was necessary for synthesis of the (3*S*,4*R*) and (3*R*,4*S*) compounds. This was based on the reductive ring-opening of *trans*-oak lactone and subsequent protection of the primary alcohol as its *t*-butyldiphenylsilyl ether. Separation of the individual glucosides was effected by preparative thin layer chromatography. Those corresponding to the nature-identical isomers of oak lactone have been shown to produce oak lactone under both acidic hydrolysis and pyrolysis conditions. The galloyl-β-D-glucoside of the *cis*-species, obtained as a natural isolate from the wood of *Platycarya strobilacea*, was also found to produce *cis*-oak lactone upon both acid hydrolysis and pyrolysis. Both the nature-identical (4*S*,5*S*) *cis*-oak lactone and its non-natural (4*R*,5*R*) enantiomer have been prepared from their corresponding glycosides and their aroma thresholds in white wine were determined to be 23 and 82 μg/L (ppb) respectively. The aroma threshold of the nature-identical isomer in a red wine was 46 μg/L.

1. Introduction

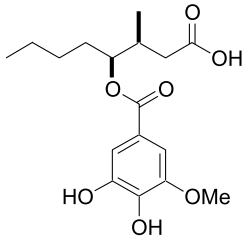
It has long been recognised that the use of oak barrels as vessels for the fermentation and/or maturation of wine can impart favourable sensory characteristics to the beverage. Some 200 oak derived volatile compounds have been identified in wines or spirits that have been so treated,[1] and there are doubtless others awaiting isolation and



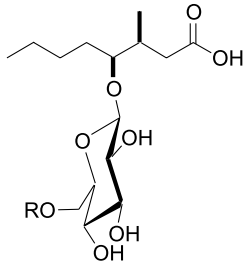
cis-**1**



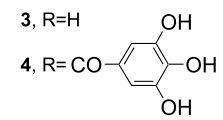
trans-**1**



2



3, R=H



☆ For Part 1, see Ref. 12.

Keywords: Oak lactone; Glycosides; Hydrolysis; Pyrolysis; β-Glucosidase; Aroma thresholds.
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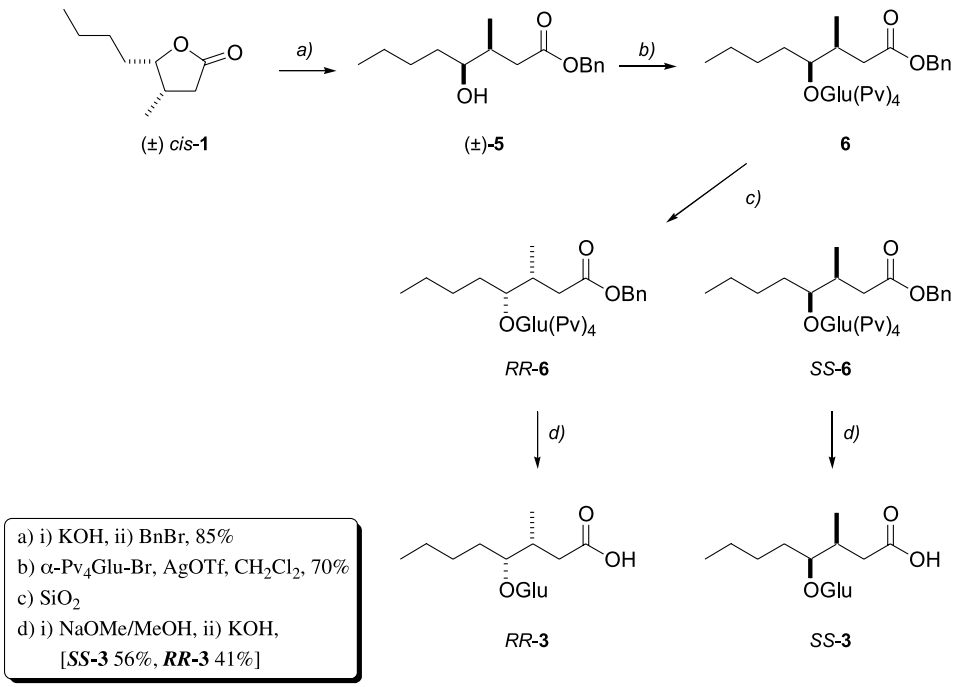
identification. Of these, the most important are considered to be the (4*S*,5*S*) *cis*- and (4*S*,5*R*) *trans*-isomers of 5-*n*-butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone **1**, also known as 'oak lactone' or 'whisky lactone'.[2] These were first identified by Suomalainen and Nykänen[3,4] after an earlier study had incorrectly assigned their structure (tentatively) as a branched δ-nonalactone.[5] Of the two, the *cis*-isomer is considered to be the more important in sensory terms, having a reported aroma threshold for the racemate of 92 μg/L (ppb) in white wine, whereas the aroma threshold for the racemic *trans*-isomer has been reported as 460 ppb in the same medium.[6] Up to now, no thresholds of the naturally occurring isomers in wine have been reported. Aroma descriptors for both isomers include 'coconut', 'citrus' and 'vanilla'.[2,7] A study by a Japanese group has shown a moderate correlation between the presence of oak lactones and the perceived quality of whiskey samples.[8] A recent sensory study showed a positive correlation between the concentration of the *cis*-isomer and the aroma intensity of the 'coconut' descriptor in Chardonnay wine.[9] Similar correlations between this isomer and the aroma intensity of coconut, 'vanilla' and 'berry' were found in Cabernet Sauvignon wines.

Despite their importance to the aroma and flavour of alcoholic beverages, the origin of these compounds remains unclear. *cis*- and *trans*-Oak lactone are already present in green oakwood, but additional quantities of these compounds can be generated in the wood during the drying (seasoning) and coopering processes,[2] in model wine oak extracts heated to 50 °C,[10] and even in the injector block of a gas chromatograph during analysis of oak extracts.[7] Such observations suggest the presence of at least one precursor form of oak lactone in oakwood; to date the literature has provided only three possible candidates. Otsuka et al.[11] isolated, from oakwood powder, a compound to which they assigned the structure **2**. This assignment was based on degradation studies with analysis by tlc, and while the proposed structure was consistent with the observed data, the evidence was not conclusive. Recently, we synthesised an authentic sample of **2** from *cis*-oak lactone and demonstrated that this original structural assignment was erroneous.[12] The second and third potential precursors, **3** and **4**, were isolated from the wood of *P. strobilacea*, a member of the walnut (Juglandaceae) family of trees by Tanaka and Kuono.[13] Compound **4** has subsequently been found in a sample of oakwood.[14] Both **3** and **4** are characterised by the presence of the β-D-glucopyranosyl moiety at C_4 of the open chain form of *cis*-oak lactone, with 4 being further substituted at the 6′ position with the galloyl group. Hydrolysis of both compounds in strong acid produced the expected (4*S*,5*S*) *cis*-oak lactone. To date, no potential precursor to *trans*-oak lactone has been isolated, nor indeed proposed.

2. Results and discussion

2.1. Synthesis of glycosides 3

The two diastereomeric *cis*-glucosides were prepared as shown in Scheme 1. Ring opening of racemic *cis*-oak lactone with potassium hydroxide and subsequent trapping of the carboxylate with benzyl bromide gave the benzyl esters **5**, which were successfully converted into their corresponding β-D-glucopyranosides **6** via a modified Koenigs–Knorr procedure.[15] We chose to employ the tetrapivaloylated bromoglucose as the reagent for the introduction of the carbohydrate unit as we have found, in keeping with earlier reports,[16] that this species produces essentially none of the α-anomer. In contrast, the corresponding tetraacetate often yields significant amounts (ca. 10%) of this isomer. After separation of the protected glucosides **6** was effected via preparative tlc,



Scheme 1.

Table 1. Measured and reported specific rotations for all four isomers of oak lactone

Isomer	$[\alpha]_D$,[a] this study	$[\alpha]_D$,[a] lit.[b]
cis (4*S*,5*S*)[c]	−74	−78
cis (4*R*,5*R*)	+79	+76
trans (4*S*,5*R*)[c]	+100	+96
trans (4*R*,5*S*)	−97	−95

[a] Measured as a solution in methanol.
[b] Ref. 23.
[c] Nature-identical isomer.

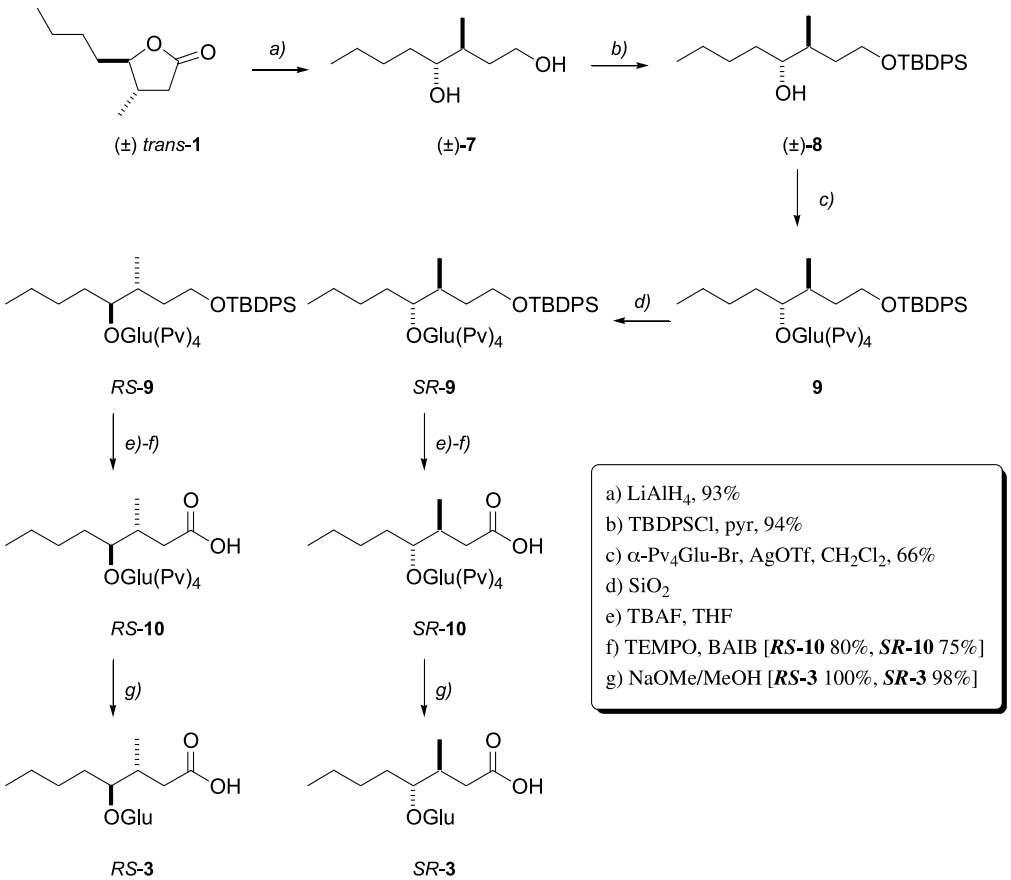
depivaloylation gave the (3*R*,4*R*) and (3*S*,4*S*) isomers of **3**. The stereochemistry of each isomer was assigned based on the results of either of two experiments: strong acid hydrolysis of the glycosylated acid **3** derived from the higher-eluting isomer (on tlc) of **6** produced oak lactone which had a measured specific rotation (in methanol) of $[\alpha]_D=-74$. The other lower-eluting isomer produced oak lactone whose specific rotation was $[\alpha]_D=+79$. Based on the data collected in Table 1, the higher-eluting isomer of **6** is assigned the (3*S*,4*S*) absolute stereochemistry, with the lower-eluting isomer assigned the (3*R*,4*R*) absolute stereochemistry. Quite independently, the stereochemistry of each was also assigned based on the results of chiral GC–MS (Cyclosil B column). A solution of racemic *cis*-oak lactone showed two peaks, with retention times of 14.57 and 14.62 min (Table 2). That the first of these peaks was due to the nature-identical (4*S*,5*S*) isomer was confirmed by analysis of a sample of *cis*-oak lactone obtained from a natural oak extract. Finally, the major synthetic oak lactones produced by hydrolysis of the glucosides **3** also revealed the higher eluting isomer of **6** to have the (3*S*,4*S*) configuration. Further details of the minor oak lactone isomers in the hydrolysates are discussed in the following section.

Table 2. Retention times on chiral GC (Cyclosil B column) of racemic, natural and synthetic isomers of oak lactone

Isomer	Retention times[a] (Cyclosil B)	
Racemic *cis*	14.57	14.62
Natural *cis*	14.57	—
1st *cis* isomer	14.57	—
2nd *cis* isomer	—	14.62
Racemic *trans*	13.93	14.12
Natural *trans*	13.93	—
1st *trans* isomer	—	14.12
2nd *trans* isomer	13.93	—

[a] Minutes.

In the case of the *trans* species, an alternative strategy was required due to problems in both the isolation and handling of the analogous benzyl ester. Although the desired ester could be prepared (as evidenced by NMR), attempts at isolation by chromatography resulted in recovery of only relactonised *trans*-oak lactone. When an attempt was made to glycosylate the crude benzyl ester, the only recovered products were *trans*-oak lactone and the *O*-β-D-glucopyranoside of benzyl alcohol.[16] This rapid lactonisation of the *trans*-isomer, relative to the *cis*-isomer has been found to be a general feature of these two compounds, and a



Scheme 2.

comprehensive kinetic investigation into the chemistry of the aglycone components of both *cis*- and *trans*-**3** has been completed.[17]

The alternative strategy (Scheme 2) employed was based on an earlier synthesis we had reported of the putative oak lactone precursor **2**.[12] Reduction of racemic *trans*-oak lactone with $LiAlH_4$ followed by selective protection of the primary alcohol function gave **8** which, as before, was successfully glycosylated and separated into the two diastereomers of **9**. Removal of the silyl group followed by oxidation and depivaloylation furnished the two *trans*-diastereomers of **3**. As was the case for the two *cis*-glycosides, the stereochemistry of the two *trans*-glycosides was assigned based on both the specific rotations of the two isomers of *trans*-oak lactone produced after cleavage of the sugar moiety in **3**, as well as chiral GC–MS analysis of the derived lactones (Tables 1 and 2, respectively). In this case, the lower-eluting isomer (on tlc) of **9** ultimately provided the nature-identical *trans*-oak lactone, and is therefore assigned (3*S*,4*R*) absolute stereochemistry, while the first-eluting isomer of **9** is assigned (3*R*,4*S*) absolute stereochemistry.

2.2. Chiral GC–MS analysis of oak lactones in hydrolysates

Although NMR spectroscopy indicated that each of the synthetic β-D-glucosides was of high purity, chiral GC–MS analysis gave a more detailed indication of the stereochemical purity of the glycoconjugates, and the oak lactones formed by their hydrolyses. Furthermore, before determining the aroma impact of the individual oak lactone stereoisomers, it was desirable to know the precise composition of the solutions under investigation. Additionally, these data were important in interpreting the results of the hydrolysis and pyrolysis experiments.

Accordingly, solutions of each of the nature-identical oak lactone stereoisomers produced by both strong acid and enzyme hydrolysis of the corresponding β-D-glucosides **3** were examined by chiral GC–MS (Cyclosil B column) and the results are collected in Table 3. That the acid hydrolysis conditions could influence the relative proportion of oak lactone isomers was established by analysis of the acid hydrolysate of the galloyl-β-D-glucoside **4**. This compound was a natural isolate and is therefore expected to be stereochemically pure; this was confirmed by both NMR spectroscopy and, importantly, chiral GC–MS analysis of the enzyme hydrolysate. However, chiral GC–MS analysis of oak lactone from the acid hydrolysate indicated only 92% purity, with 8% of the (4*S*,5*R*) *trans* isomer present. Therefore, we conclude that the newly formed (4*S*,5*R*) *trans*-oak lactone is an artefact of strong acid hydrolysis, indicating the potential for acid-catalysed epimerisation at C_4 under these conditions.

Table 3. Purity (%) of glycosides **3** or **4**, and of oak lactones obtained from hydrolysis of **3** or **4**, as determined by NMR spectrosopy or chiral GC–MS analysis

Sample	Analysis	*SR-trans*	*RS-trans*	*SS-cis*	*RR-cis*
3*S*,4*S*-(**4**)[a]	NMR	—	—	100	—
Enzyme hydrolysate	GC–MS	—	—	100	—
Acid hydrolysate	GC–MS	8	—	92	—
3*S*,4*S*-(**3**)	NMR	—	5	95	—
Enzyme hydrolysate	GC–MS	—	14	86	—
Acid hydrolysate	GC–MS	4	6	90	—
3*S*,4*R*-(**3**)	NMR	94	6	—	—
Enzyme hydrolysate	GC–MS	87	9	2	2
Acid hydrolysate	GC–MS	85	9	3	3

[a] Natural isolate obtained from the wood of *P. strobilacea*.

^{1}H NMR spectroscopy of the (3*S*,4*S*) *cis*-β-D-glucoside **3** indicated it to be 95% pure, with 5% of the (3*R*,4*S*) *trans* isomer present, but neither the (3*S*,4*R*) *trans* nor (3*R*,4*R*) *cis* isomers were present in detectable quantities. This last point was confirmed by enzymatic cleavage of the sugar unit and inspection of the product mixture. The proportion of (4*R*,5*S*) *trans*-oak lactone in the enzyme hydrolysate (14%) is higher than that detected by NMR in the original glucoside, and may reflect some stereoselectivity of the β-glucosidase towards the (3*R*,4*S*) glucoside **3**. Analysis of the strong acid hydrolysate confirmed the absence of the (4*R*,5*R*) *cis* isomer of oak lactone, as well as the presence of 6% of the (4*R*,5*S*) *trans* isomer. However, it also showed the presence of the (4*S*,5*R*) *trans* isomer (4%). As with the hydrolysis of **4**, this isomer of *trans*-oak lactone is presumed to arise from epimerisation at C_4 of the (3*S*,4*S*) glucoside. The other component of this hydrolysate, namely the (4*R*,5*S*) isomer of *trans*-oak lactone appears to be the expected hydrolysis product of the minor component in the original glucoside sample. Given that epimerisation takes place to convert (a small proportion of) *cis*-glucoside into *trans*-oak lactone, one might expect to see the converse taking place. The fact that this hydrolysate contained no detectable *RR cis*-oak lactone may simply reflect the detection limits of the instrument, or alternatively, it may be a manifestation of the thermodynamic preference for formation of the *trans* isomer relative to the *cis*.[17]

Similar considerations of the strong acid and enzyme hydrolysates of the (3*S*,4*R*) *trans*-β-D-glucoside **3** suggested that this diastereomer was of slightly lower purity, approximately 85–90%, with 9% of the (3*R*,4*S*) isomer, as well as smaller amounts (~2–3%) of each of the (3*S*,4*S*) and (3*R*,4*R*) isomers. Although neither the (3*S*,4*S*) nor the (3*R*,4*R*) isomers could be detected by NMR spectroscopy, it is probable that the limited sensitivity of NMR spectroscopy could have impeded their detection at these low concentrations. Their presence in the enzyme hydrolysate is strongly supportive of this.

2.3. Hydrolytic and pyrolytic behaviour of glucosides 3

Although the glucosides **3** present themselves prima facie as candidates for the generation of natural oak lactone, their provenance in oak wood has yet to be established. Their detection in sub-mg/kg amounts by HPLC, unlike that of **4**, is likely to be hampered by the absence of a suitable chromophore.[14] However, it is worth reiterating that (3*S*,4*S*)-**3** has previously been isolated and identified in walnut. Thus, we were keen to investigate the behaviour towards both acidic media (approximating barrel maturation) and pyrolysis (approximating the toasting undergone during cooperage) of the isomers of **3** with absolute

stereochemistry corresponding to the natural isomers of oak lactone. In addition to the glucosides prepared for this study, we also investigated the behaviour of the galloyl-β-D-glucoside **4**.

Table 4 contains quantified amounts of oak lactone produced hydrolytically, and shows that after 48 days at pH 3.0 and 100 °C, the hydrolyses of both the (3*S*,4*S*) and (3*S*,4*R*) isomers of **3** were greater than 90% complete. At the lower temperature (45 °C), no more than trace quantities of oak lactones were produced by either isomer over this time. This is perhaps not surprising as previous studies within our laboratories have shown that hydrolysis of glycosides under mild conditions is extremely slow except where the glycoside is attached at an activated hydroxyl position.[18] Under the same higher temperature conditions, the hydrolysis of the galloyl substituted glycoside **4** was only approximately 20% complete after 35 days. In the case of **4**, the expected *cis*-oak lactone is accompanied by approximately 8% of the *trans*-isomer, produced by epimerisation under the acidic conditions employed, as discussed above. This minor epimerisation is also observed in the hydrolysis of the (3*S*,4*S*) isomer of **3**. Of the 10% *trans* produced, approximately half can be attributed to an impurity in the original glucoside, and the remainder to epimerisation. In contrast, the small proportion of *cis*-oak lactone in the hydrolysate of (3*S*,4*R*)-**3** is likely to arise mostly from impurities in the glucoside, rather than by epimerisation (see Table 3). In this case, lack of epimerisation can be attributed to the thermodynamic stability of the *trans* compared to the *cis* isomer.

Table 4. Quantified amounts of oak lactone produced by the hydrolysis of **3** and **4**, at pH 3.0

Isomer	Temperature (°C)	Time (days)	Total **1**[a]
(3*S*,4*S*)-**3**	45	8	1.1 (0.2)
		48	1.6 (0.3)
(3*S*,4*S*)-**3**	100	8	171.2 (31)
		48	516.2 (93)
		cis:*trans*	90: 10
(3*S*,4*R*)-**3**	45	8	n.d.
		48	n.d.
(3*S*,4*R*)-**3**	100	8	158.0 (28)
		48	521.6 (94)
		cis:*trans*	6: 94
(3*S*,4*S*)-**4**	45	5	n.d.
		35	n.d.
(3*S*,4*S*)-**4**	100	5	17.6 (3)
		35	106.8 (20)
		cis:*trans*	92: 8

[a] μg oak lactone; mean value from two replicates. Values were in agreement to ca. 2%; values in parentheses represent the percentage of oak lactone formed relative to the theoretical maximum.

The pyrolysis of both **3** and **4** was investigated by adsorbing the desired compound onto oakwood powder, and then subjecting the whole to conditions which were expected to closely mimic barrel toasting temperatures.[19] The oakwood for this experiment was chosen for its intrinsically low levels of oak lactone, even after toasting. In contrast to their hydrolytic behaviour, the pyrolysis of all three glycosides resulted in reasonably rapid formation of significant amounts of the oak lactones, (20–30% conversion, Table 5) again with epimerisation of *cis* to *trans* being more important than the converse.

Table 5. Quantified amounts of oak lactone produced in the pyrolysis of **3** and **4**

Isomer	*cis*-**1**[a]	*trans*-**1**[a]	Yield[b]
Control untoasted	n.d.	n.d.	—
Control toasted	0.2	0.1	–
(3*S*,4*S*)-**3** toasted	60.0	7.1	29
cis:*trans*	89	11	
(3*S*,4*R*)-**3** toasted	4.0	55.4	26
cis:*trans*	6	94	
(3*S*,4*S*)-**4** toasted	36.9	2.0	15
cis:*trans*	5	95	

[a] (μg/g wood); mean value from three replicates. Values were in agreement to ca. 2%.
[b] Yield defined as the percentage of total oak lactone produced relative to the theoretical maximum.

2.4. Sensory evaluation of (4*S*,5*S*)-*cis*-1 and (4*R*,5*R*)-*cis*-1

In order to satisfactorily assess the aroma impact of the individual stereoisomers of **1**, it is necessary to know the precise composition of the solution under investigation. Accordingly, solutions of each of the four isomers of **1** produced were examined by chiral GC–MS (Cyclosil B column) with the results collected in Table 6. While no one of the solutions is 'pure' in the literal meaning of the word, they are each strongly enriched in their respective isomer. Given that the reported threshold for racemic *cis*-oak lactone (92 ppb in white wine) is much lower than the reported threshold for racemic *trans*-oak lactone (460 ppb) in the same medium, it is apparent that small amounts of *trans*-isomer in the solution of predominantly *cis*-oak lactone would be expected to have little impact on the sensory properties of the solution. Conversely, however, small amounts of the more potent *cis*-isomer in the predominantly *trans*-solution would be problematic. Consequently, sensory analysis was limited to the *cis*-enriched solutions.

Table 6. Chiral GC–MS analysis of the composition of oak lactones produced by strong acid hydrolysis of **3**

Sample	*SR-trans*	*RS-trans*	*SS-cis*	*RR-cis*
SS-cis	4	6	90	—
RR-cis	5	7	4	84
SR-trans	85	9	3	3
RS-trans	2	96	1	1

A duo–trio test[20] was conducted to establish whether or not there was a perceptible difference in aroma impact between the two *cis*-enriched solutions; a young (<12 months old) neutral, dry white wine (2002 South Australian Chenin Blanc) was spiked with either (4*S*,5*S*)-*cis*-**1** or (4*R*,5*R*)-*cis*-**1** (161.7 μg/L) and presented to a panel of 25 judges, 20 of whom correctly identified the sample which differed from the reference. These data show that the two *cis*-isomers are significantly different (at the 99% confidence level). Furthermore, they bring into question the wisdom of conducting sensory impact studies using racemic *cis*-**1**.

The aroma detection thresholds[21] of solutions of each of the *cis* isomers of **1** were determined in the same neutral white wine. The aroma detection threshold for the solution enriched in (4*S*,5*S*)-*cis*-**1** (90% pure) was calculated to be 23 μg/L. The best estimate threshold for each panellist was the geometric mean of the highest concentration missed and the next higher concentration tested. The group threshold was calculated as the geometric mean of the individual best estimate thresholds. The distributions of best-estimate thresholds for individual panellists are shown in Figure 1. Informal descriptors used by the panel to describe this isomer included: 'fruity', 'coconut', 'woody', 'caramel', 'buttery', and 'vanilla'. The aroma detection threshold for the solution rich in the non-natural isomer, (4*R*,5*R*)-*cis*-**1** (84% pure) was similarly calculated to be 82 μg/L, with informal descriptors including 'lime', citrus, 'honey', 'coconut', 'vanilla', 'burnt apple' and 'cinnamon'. Finally, the aroma detection threshold of the solution rich in (4*S*,5*S*)-*cis*-**1** was determined in red wine to be 46 μg/L, with similar informal descriptors to those from the white wine study.

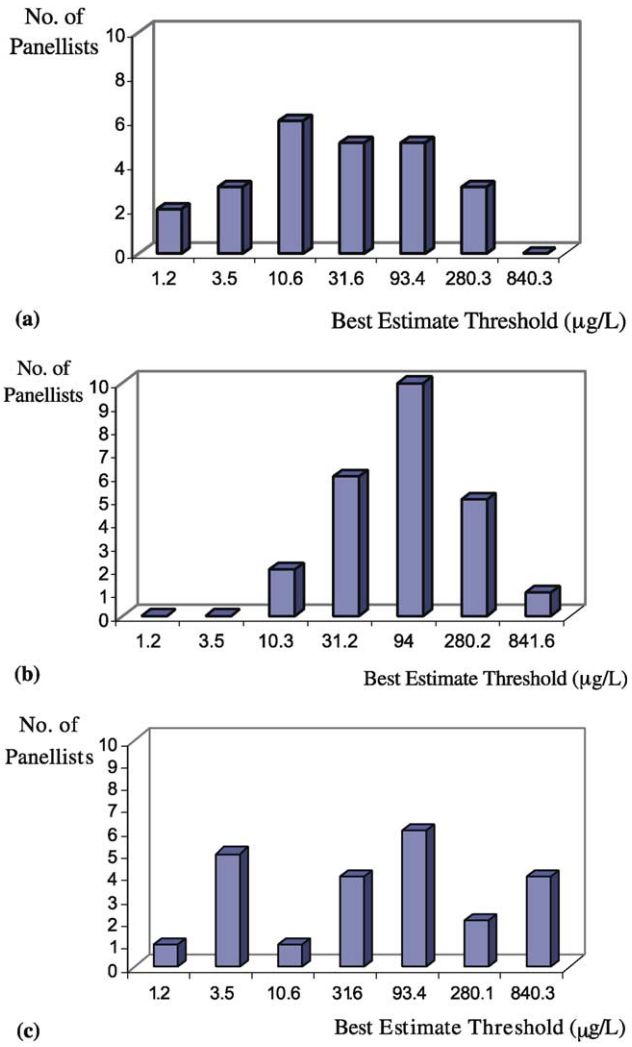


Figure 1. Histograms showing best estimate threshold distributions for (a) (4*S*,5*S*)-*cis*-**1** in white wine, (b) (4*R*,5*R*)-*cis*-**1** in white wine, and (c) (4*S*,5*S*)-*cis*-**1** in red wine.

3. Conclusions

Hydrolytic studies at wine pH have shown that the simple or substituted glucosides **3** and **4** are not likely to be significant sources of oak lactones during barrel maturation of wines unless microorganisms with β-glucosidase activity are present. Such derivatives cannot explain the observation[10] that oak lactone concentration in pH 3 oak extracts can increase after the oak is removed from soaking. In contrast, such compounds are likely to be important sources of additional oak lactone formed during barrel manufacture and toasting.

4. Experimental

4.1. General

Chemicals were purchased from Sigma-Aldrich. Commercial oak lactone (50:50) was fractionated by spinning band column distillation to give pure fractions of both the *cis*- and *trans*-isomers. All solvents used were HPLC grade from OmniSolv and HiPerSolv. Column chromatography was performed using silica gel 60 (230–400 mesh) from Merck. Preparative thin layer chromatography was performed using glass-backed silica gel 60 plates (20×20 cm) from Merck. All organic solvent solutions were dried over anhydrous sodium sulfate before being filtered. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini spectrometer at operating frequencies of 300 and 75.5 MHz, respectively. Mass spectra were recorded on a Hewlett–Packard (HP) 6890 gas chromatograph fitted with liquid HP 6890 series injector and coupled to a HP 5973 mass spectrometer. Optical rotations were measured with a PolAAr 21 polarimeter. Microanalyses were performed at Microanalytical Services, University of Otago, New Zealand. Oak lactone was quantified by the SIDA method reported previously.[7]

4.1.1. (3*R*,4*R*) and (3*S*,4*S*) Benzyl 3-methyl-4-hydroxyoctanoate (±5). To a solution of *cis*-oak lactone (1.10 g, 7.05 mmol) in methanol (30 mL) was added potassium hydroxide (400 mg, 7.05 mmol) and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated and the residue dissolved in DMF (30 mL). To this solution was added benzyl bromide (840 μL, 7.07 mmol) and the reaction mixture stirred at room temperature for 16 h. The solution was diluted with water (10 mL) and extracted with ether (3×20 mL). The combined organics were washed with water (2×20 mL), dried and concentrated. The resulting oil was purified by column chromatography (20% ethyl acetate in hexane) to give a colourless oil (1.59 g, 85%). [Found: C, 72.7; H 9.2. $C_{16}H_{24}O_3$ requires C, 72.69; H 9.15%]; δ_H ($CDCl_3$) 7.40–7.25 (5H, m, Ar*H*), 5.12 (2H, s, CH_2Ar), 3.55 (1H, m, H_4), 2.53 (1H, dd, J=15.2, 6.6 Hz, H_{2a}), 2.29 (1H, dd, J=15.2, 7.6 Hz, H_{2b}), 2.28 (1H, m, H_3), 1.44–1.24 (6H, m, $H_{5,6,7}$), 0.92 (3H, d, J=6.9 Hz, H_9), 0.89 (3H, t, J=7.2 Hz, H_8); δ_C ($CDCl_3$) 173.4, 135.9, 128.5, 128.2, 126.9, 74.2, 66.2, 38.4, 35.4, 33.8, 28.4, 22.7, 14.0 13.6; ESI-MS (80% MeOH) 287.2 ($M+Na^+$).

4.1.2. (3*R*,4*R*) and (3*S*,4*S*) Benzyl 3-methyl-4-*O*-(2′,3′,4′,6′-tetrapivaloyl-β-D-glucopyranosyl) octanoate (6).

2,3,4,5-Tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide, prepared according to Kunz et al.[16] (3.5 g, 6.04 mmol) was added to a solution of (±**5**) (1.6 g, 6.01 mmol) in dichloromethane (25 mL) containing silver triflate (1.6 g, 6.23 mmol) and 2,6-lutidine (700 μL, 6.04 mmol). The reaction mixture was stirred at room temperature in the dark for 16 h before being quenched with saturated sodium bicarbonate solution and extracted with dichloromethane (2×15 mL). The combined organic extracts were washed with brine (25 mL), dried and concentrated. The crude product was purified by column chromatography eluting with 10% ethyl acetate in hexane to give a colourless resin (3.2 g, 70%). [Found: C, 66.3; H 9.0. $C_{42}H_{66}O_{12}$ requires C, 66.12; H 8.72%]; A solution of this diastereomeric mixture in dichloromethane was loaded onto preparative tlc plates (20 cm×20 cm, Silica 60) and eluted two or three times (as required) with dichloromethane. The plates were visualised under UV light, the fractions of interest removed and extracted with 80% dichloromethane in methanol (2×50 mL) and methanol (2×50 mL).

Compound (3*S*,4*S*)-**6**. δ_H ($CDCl_3$) 7.45–7.29 (5H, m, Ar*H*), 5.25 (1H, dd, *J*=9.3, 9.3 Hz, $H_{3'}$), 5.15 (1H, d, *J*=12.0 Hz, CH_2Ar), 5.08 (1H, dd, *J*=9.3, 9.3 Hz, $H_{4'}$), 5.06 (1H, d, *J*=12.0 Hz, CH_2Ar), 5.01 (1H, dd, *J*=9.3, 7.8 Hz, $H_{2'}$), 4.52 (1H, d, *J*=7.8 Hz, $H_{1'}$), 4.18 (1H, dd, *J*=12.3, 1.8 Hz, $H_{6a'}$), 3.92 (1H, dd, *J*=12.3, 5.4 Hz, $H_{6b'}$), 3.56–3.34 (2H, m, $H_{4,5'}$), 2.52–2.14 (3H, m, $H_{2,3}$), 1.54–1.20 (6H, m, $H_{5,6,7}$), 1.21, 1.15, 1.11, 1.10 (36H, 4s, C*Me*$_3$), 0.90–0.80 (6H, m, $H_{8,9}$); δ_C ($CDCl_3$) 178.0, 177.2, 176.5, 176.4, 172.7, 135.9, 128.6, 128.4, 128.3, 99.8, 80.7, 72.8, 71.9, 71.8, 68.2, 66.1, 61.9, 38.8, 38.7, 38.7, 38.6, 37.2, 33.0, 31.2, 27.8, 27.3, 27.2, 27.1, 27.1, 22.6, 14.4, 13.9; ESI-MS (80% MeOH) 785.6 ($M+Na^+$).

Compound (3*R*,4*R*)-**6**. δ_H ($CDCl_3$) 7.42–7.28 (5H, m, Ar*H*), 5.29 (1H, dd, *J*=9.2, 9.5 Hz, $H_{3'}$), 5.16 (1H, d, *J*=12.3 Hz, CH_2Ar), 5.11 (1H, dd, *J*=9.5, 10.0 Hz, $H_{4'}$), 5.02 (1H, d, *J*=12.3 Hz, CH_2Ar), 4.99 (1H, dd, *J*=9.2, 7.9 Hz, $H_{2'}$), 4.55 (1H, d, *J*=7.9 Hz, $H_{1'}$), 4.18 (1H, dd, *J*=12.1, 1.8 Hz, $H_{6a'}$), 3.94 (1H, dd, *J*=12.1, 4.9 Hz, $H_{6b'}$), 3.68–3.56 (2H, m, $H_{4,5'}$), 2.57 (1H, dd, *J*=15.3, 4.8 Hz, H_{2a}), 2.22 (1H, dd, *J*=15.3, 8.4 Hz, H_{2b}), 2.16 (1H, m, H_3), 1.54–1.20 (6H, m, $H_{5,6,7}$), 1.17, 1.13, 1.13, 1.09 (36H, 4s, C*Me*$_3$), 0.88 (3H, t, *J*=6.8 Hz, H_8), 0.82 (3H, d, *J*=6.6 Hz, H_9); δ_C ($CDCl_3$) 177.9, 177.1, 176.3, 176.3, 173.2, 136.1, 128.4, 128.1, 128.0, 98.9, 80.3, 72.4, 71.9, 71.5, 68.0, 65.9, 61.7, 38.8, 38.7, 38.7, 38.7, 38.0, 32.7, 31.2, 28.1, 27.1, 27.1, 27.0, 27.0, 22.8, 13.9, 13.1.; ESI-MS (80% MeOH) 785.6 ($M+Na^+$).

4.2. General procedure for depivaloylation of *cis*-glycosides (6)

Sodium metal (130 mg, 5.6 mmol) was dissolved in methanol (5 mL) and the resulting solution was added to a solution of (3*R*,4*R* and 3*S*,4*S*) **6** (337.5 mg, 0.44 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was then stirred for a further 30 min in the presence of acidified Amberlite IRC-50 (H) ion exchange resin. The reaction mixture was filtered, concentrated in vacuo to remove methyl pivalate, and the residue obtained dissolved in water (10 mL). Potassium hydroxide (194.6 mg, 3.48 mmol) was added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was acidified to pH 3 with 10% hydrochloric acid solution and extracted with ether (10 mL). The crude aqueous glycoside solution was then purified by chromatography on XAD-2 resin to give a colourless resin (106.1 mg, 71%).

4.2.1. (3*S*,4*S*) 3-Methyl-4-*O*-β-D-glucopyranosyloctanoic acid (3). The free glycoside (33.5 mg, 56%) was obtained from (3*S*,4*S*)-**6** (135.5 mg, 0.18 mmol) as described above, $[\alpha]_D$=−29.8 (*c* 0.67, CH_3OH), lit.[13] $[\alpha]_D$=−23; δ_H (CD_3OD) 4.31 (1H, d, *J*=7.8 Hz, $H_{1'}$), 3.82 (1H, dd, *J*=11.8, 2.2 Hz, $H_{6a'}$), 3.67 (1H, dd, *J*=11.8, 5.2 Hz, $H_{6b'}$), 3.63 (1H, m, H_4), 3.40–3.18 (3H, m, $H_{3',4',5'}$), 3.16 (1H, dd, *J*=9.0, 7.8 Hz, $H_{2'}$), 2.62 (1H, dd, *J*=14.6, 4.8 Hz, H_{2a}), 2.27 (1H, m, H_3), 2.15 (1H, dd, *J*=14.6, 8.6 Hz, H_{2b}), 1.62–1.24 (6H, m, $H_{5,6,7}$), 0.95 (3H, d, *J*=6.6 Hz, H_9), 0.91 (3H, t, *J*=7.1 Hz, H_8); δ_C (CD_3OD) 178.5, 104.9, 84.3, 79.0, 78.5, 76.3, 72.6, 63.7, 38.9, 35.1, 32.9, 30.0, 24.6, 16.0, 15.3; ESI-MS (80% MeOH) 359.4 ($M+Na^+$).

4.2.2. (3*R*,4*R*) 3-Methyl-4-*O*-β-D-glucopyranosyloctanoic acid (3). The free glycoside (22.7 mg, 41%) was obtained from (3*R*,4*R*)-**6** (154.4 mg, 0.20 mmol) as described above, $[\alpha]_D$=−16.4 (*c* 0.55, CH_3OH); δ_H (CD_3OD) 4.26 (1H, d, *J*=7.7 Hz, $H_{1'}$), 3.85 (1H, dd, *J*=12.6, 1.9 Hz, $H_{6a'}$), 3.72–3.58 (2H, m, $H_{6b',4}$), 3.40–3.20 (3H, m, $H_{3',4',5'}$), 3.15 (1H, dd, *J*=9.1, 7.7 Hz, $H_{2'}$), 2.66 (1H, dd, *J*=15.1, 6.8 Hz, H_{2a}), 2.26 (1H, m, H_3), 2.12 (1H, dd, *J*=15.1, 7.6 Hz, H_{2b}), 1.62–1.22 (6H, m, $H_{5,6,7}$), 0.95–0.89 (6H, m, $H_{8,9}$); δ_C (CD_3OD) 178.8, 104.9, 83.9, 79.0, 78.6, 76.2, 72.6, 63.9, 39.5, 35.5, 33.0, 30.1, 24.7, 15.4, 15.3; ESI-MS (80% MeOH) 359.4 ($M+Na^+$).

4.2.3. (3*R*,4*S*) and (3*S*,4*R*) 3-Methyloctan-1,4-diol (±7). LAH (540 mg, 14.2 mmol) was added to a cooled solution of *trans*-oak-lactone (2.0 g, 12.82 mmol) in anhydrous THF (40 mL). The reaction mixture was then heated at reflux overnight before being quenched by addition of acetone (5.0 mL) followed by addition of a solution of sodium hydroxide (1.0 M, 4.0 mL) and saturated sodium sulfate. The resulting solids were removed by filtration and the filtrate concentrated and coevaporated with CH_3CN (3×10 mL) to give the product (1.91 g, 93%) as a colourless oil. δ_H ($CDCl_3$) 3.80–3.58 (2H, m, H_1), 3.43 (1H, m, H_4), 1.75–1.25 (9H, m, $H_{2,3,5,6,7}$), 0.94 (3H, d, *J*=6.6 Hz, H_9), 0.90 (3H, d, *J*=7.2 Hz, H_8); δ_C ($CDCl_3$) 75.9, 60.5, 36.3, 35.2, 34.1, 28.0, 22.8, 16.5, 14.0.

4.2.4. (3*R*,4*S*) and (3*S*,4*R*) 1-*t*-Butyldiphenylsilyloxy-3-methyloctan-4-ol (±8). TBDPSCl (4.22 g, 15 mmol) and (±**7**) (2.2 g, 13.75 mmol) in pyridine (40 mL) were stirred at room temperature for 72 h, after which time the solvent was removed. The residue was diluted with dichloromethane (100 mL) and washed with saturated copper sulfate solution (100 mL), saturated sodium bicarbonate solution (100 mL) and water (100 mL). The organic phase was then dried and concentrated to give a pale yellow oil, which was purified by column chromatography (100% dichloromethane) to give a colourless oil (5.17 g, 94%). [Found: C, 75.6; H, 9.6. $C_{25}H_{38}O_2Si$ requires C, 75.32; H 9.61%]; δ_H ($CDCl_3$) 7.75–7.65 (4H, m, Ar*H*), 7.47–7.36 (6H, m, Ar*H*),

3.80–3.62 (2H, m, H_1), 3.45 (1H, m, H_4), 1.80–1.25 (9H, m, $H_{2,3,5,6,7}$), 1.09 (9H, s, *t*Bu), 0.93 (3H, t, J=6.0 Hz, H_8), 0.89 (3H, d, J=6.6 Hz, H_9); δ_C ($CDCl_3$) 135.6, 133.5, 129.6, 127.6, 75.7, 62.0, 35.9, 34.5, 33.8, 28.2, 26.8, 22.8, 19.1, 16.2, 14.1.

4.2.5. (3*R*,4*S*) and (3*S*,4*R*) 1-*t*-Butyldiphenylsilyloxy-3-methyl-4-*O*-(2′,3′,4′,6′-tetrapivaloyl-β-D-glucopyranosyl)octane (9). The alcohol (±**8**) (2.83 g, 7.1 mmol) was glycosylated in an identical manner to that described above for the *cis*-species, using 2,3,4,5-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (4.11 g, 7.1 mmol), silver triflate (1.824 g, 7.1 mmol) and 2,6-lutidine (820 μL, 7.1 mmol). The crude product was purified by column chromatography (10% ethyl acetate in hexane) to give a colourless resin (4.2 g, 66%). [Found: C, 68.5; H 9.2. $C_{51}H_{80}O_{11}Si$ requires C, 68.27; H 8.99%]; The individual glycoside diastereomers were separated in an identical manner to that described for **6**.

Compound (3*R*,4*S*)-**9**. δ_H ($CDCl_3$) 7.68–7.62 (4H, m, Ar*H*), 7.48–7.35 (6H, m, Ar*H*), 5.26 (1H, dd, J=9.3, 9.3 Hz, $H_{3'}$), 5.10 (1H, dd, J=9.3, 9.3 Hz, $H_{4'}$), 5.01 (1H, dd, J=9.3, 7.8 Hz, $H_{2'}$), 4.50 (1H, d, J=7.8 Hz, $H_{1'}$), 4.18 (1H, dd, J=12.0, 1.8 Hz, $H_{6a'}$), 3.93 (1H, dd, J=12.0, 5.1 Hz, $H_{6b'}$), 3.72–3.44 (4H, m, $H_{1,4,5'}$), 1.58–1.48 (1H, m, H_3), 1.48–1.20 (8H, m, $H_{2,5,6,7}$), 1.20, 1.14, 1.14, 1.11 (36H, 4s, COCMe_3), 1.06 (9H, s, SiCMe_3), 0.84 (3H, t, J=6.9 Hz, H_8), 0.79 (3H, d, J=6.9 Hz, H_9). δ_C ($CDCl_3$) 178.0, 177.2, 176.4, 176.3, 135.5, 134.0, 129.7, 127.7, 99.4, 82.1, 72.9, 71.8, 71.6, 68.1, 61.8, 61.8, 38.8, 38.7, 38.7, 35.2, 32.0, 29.2, 27.9, 27.3, 27.2, 27.0, 27.0, 26.9, 22.6, 14.5, 14.0; ESI-MS (80% MeOH) 919.8 ($M+Na^+$).

Compound (3*S*,4*R*)-**9**. δ_H ($CDCl_3$) 7.68–7.62 (4H, m, Ar*H*), 7.44–7.33 (6H, m, Ar*H*), 5.29 (1H, dd, J=9.6, 9.3 Hz, $H_{3'}$), 5.07 (1H, dd, J=9.9, 9.6 Hz, $H_{4'}$), 4.99 (1H, dd, J=9.3, 7.8 Hz, $H_{2'}$), 4.56 (1H, d, J=7.8 Hz, $H_{1'}$), 4.21 (1H, dd, J=12.3, 1.8 Hz, $H_{6a'}$), 3.92 (1H, dd, J=12.3, 6.0 Hz, $H_{6b'}$), 3.76–3.58 (3H, m, $H_{1,5'}$), 3.48 (1H, m, H_4), 1.90–1.20 (9H, m, $H_{2,3,5,6,7}$), 1.18, 1.14, 1.14, 1.11 (36H, 4s, COCMe_3), 1.03 (9H, s, SiCMe_3), 0.88 (3H, t, J=6.6 Hz, H_8), 0.82 (3H, d, J=6.6 Hz, H_9); δ_C ($CDCl_3$) 178.0, 177.2, 176.5, 176.3, 135.5, 134.0, 129.5, 127.6, 99.0, 82.6, 72.6, 71.9, 71.6, 68.3, 62.2, 62.0, 38.8, 38.7, 38.7, 33.7, 32.3, 30.4, 28.2, 27.2, 27.2, 27.1, 27.0, 26.9, 22.9, 15.8, 14.0; ESI-MS (80% MeOH) 919.8 ($M+Na^+$).

4.3. General procedure for deprotection and oxidation of 9

TBAF (230 mg, 0.72 mmol) was added to a solution of (3*R*,4*S*) and (3*S*,4*R*)-**9** (540 mg, 0.6 mmol) in THF (20 mL) and stirred at room temperature for 16 h during which time the solution became yellow in colour. The solvent was evaporated and the residue dissolved in ethyl acetate (30 mL) and washed with saturated sodium bicarbonate solution (10 mL), 5% citric acid solution (10 mL) and water (2×10 mL). The organic phases were dried and concentrated and the crude product was purified by column chromatography (10% ethyl acetate in hexane) to give (3*R*,4*S*) and (3*S*,4*R*) 3-methyl-4-*O*-(2′,3′,4′,6′-tetrapivaloyl-β-D-glucopyranosyl)octan-1-ol as a colourless oil (230 mg, 87%). [Found: C 63.9; H 9.3. $C_{35}H_{62}O_{11}$ requires C, 63.80; H 9.48%]. To this mixture (159 mg, 0.241 mmol) was added TEMPO (50 mg, 0.32 mmol) and BAIB (200 mg, 0.6 mmol) in acetonitrile (2 mL) and water (3 mL).[22] After stirring at room temperature for 48 h, the reaction mixture was extracted with ethyl acetate (2×30 mL) and the extracts washed with 5% citric acid solution (15 mL) and water (15 mL), before being dried and concentrated to give an orange oil. The crude product was purified by column chromatography (2% methanol in dichloromethane) to give (3*R*,4*S*) and (3*S*,4*R*) 3-methyl-4-*O*-(2′,3′,4′,6′-tetrapivaloyl-β-D-glucopyranosyl)octanoic acid (**10**) as a pale yellow resin (132 mg, 81%).

4.3.1. (3*R*,4*S*) 3-Methyl-4-*O*-(2′,3′,4′,6′-tetrapivaloyl-β-D-glucopyranosyl)octanoic acid (10). Conversion of (3*R*,4*S*)-**9** (144.0 mg, 0.16 mmol) into the acid (3*R*,4*S*)-**10** was accomplished as outlined above to give a colourless oil (87.0 mg, 80%); δ_H ($CDCl_3$) 5.31 (1H, dd, J=9.4, 9.0 Hz, $H_{3'}$), 5.11 (1H, dd, J=9.8, 9.4 Hz, $H_{4'}$), 5.03 (1H, dd, J=9.4, 7.8 Hz, $H_{2'}$), 4.61 (1H, d, J=7.8 Hz, $H_{1'}$), 4.22 (1H, br d, J=12.2 Hz, $H_{6a'}$), 3.97 (1H, dd, J=12.2, 5.3 Hz, $H_{6b'}$), 3.66 (1H, m, $H_{5'}$), 3.50 (1H, m, H_4), 2.6–2.46 (1H, m, H_{2a}), 2.18–1.96 (2H, m, $H_{2b,3}$), 1.50–1.10 (6H, m, $H_{5,6,7}$) 1.20, 1.15, 1.14, 1.10 (36H, 4s, CMe_3), 0.91 (3H, d, J=6.3 Hz, H_9), 0.85 (3H, t, J=7.1 Hz, H_8); ESI-MS (80% MeOH) 695.4 ($M+Na^+$).

4.3.2. (3*S*,4*R*) 3-Methyl-4-*O*-(2′,3′,4′,6′-tetrapivaloyl-β-D-glucopyranosyl)octanoic acid (10). (3*S*,4*R*)-**9** (202.2 mg, 0.23 mmol) was treated as outlined above to give the acid (3*S*,4*R*)-**10** as a colourless oil (113.9 mg, 75%); δ_H ($CDCl_3$): 5.29 (1H, dd, J=9.5, 9.5 Hz, $H_{3'}$), 5.09 (1H, dd, J=9.5, 9.3 Hz, $H_{4'}$), 4.98 (1H, dd, J=9.5, 7.9 Hz, $H_{2'}$), 4.57 (1H, d, J=7.9 Hz, $H_{1'}$), 4.23 (1H, br d, J=12.0, $H_{6a'}$), 3.94 (1H, dd, J=12.0, 5.5 Hz, $H_{6b'}$), 3.66 (1H, m, $H_{5'}$), 3.47 (1H, m, H_4), 2.42–2.32 (1H, m, H_{2a}), 2.24–1.95 (2H, m, $H_{2b,3}$), 1.50–1.10 (6H, m, $H_{5,6,7}$), 1.19, 1.12, 1.12, 1.08 (36H, 4s, CMe_3), 0.94 (3H, d, J=6.5 Hz, H_9), 0.87 (3H, t, J=6.7 Hz, H_8); ESI-MS (80% MeOH) 695.4 ($M+Na^+$).

4.3.3. (3*R*,4*S*) 3-Methyl-4-*O*-β-D-glucopyranosyloctanoic acid (3). Protected glycoside (3*R*,4*S*)-**10** (87.0 mg, 0.13 mmol) was converted into the free glycoside according to the procedure outlined above, but omitting the second KOH step, to give (3*R*,4*S*)-**3** (43.5 mg, 100%); δ_H (CD_3OD): 4.33 (1H, d, J=7.7 Hz, $H_{1'}$), 3.85 (1H, dd, J=11.7, 2.4 Hz, $H_{6a'}$), 3.69 (1H, dd, J=11.7, 5.2 Hz, $H_{6b'}$) 3.57 (1H, app. q, H_4), 3.39–3.16 (4H, m, $H_{2',3',4',5'}$), 2.54 (1H, dd, J=14.6, 4.6 Hz, H_{2a}), 2.26 (1H, m, H_3), 2.14 (1H, dd, J=14.6, 8.8 Hz, H_{2b}), 1.62–1.24 (6H, m, $H_{5,6,7}$), 0.99 (3H, d, J=6.7 Hz, H_9), 0.92 (3H, t, J=7.2 Hz, H_8); δ_C (CD_3OD): 178.4, 105.0, 85.0, 79.0, 78.5, 76.2, 72.6, 63.7, 39.3, 35.4, 32.9, 29.1, 24.6, 16.8, 15.3; ESI-MS (80% MeOH) 359.4 ($M+Na^+$); $[\alpha]_D$=−15.5 (*c* 0.52, CH_3OH).

4.3.4. (3*S*,4*R*) 3-Methyl-4-*O*-β-D-glucopyranosyloctanoic acid (3). Protected glycoside (3*S*,4*R*)-**10** (113.9 mg, 0.17 mmol) was converted into the free glycoside according to the procedure outlined above, to give (3*S*,4*R*)-**3** (55.9 mg, 98%); δ_H (CD_3OD): 4.30 (1H, d, J=7.7 Hz, $H_{1'}$), 3.86 (1H, dd, J=11.8, 2.2 Hz, $H_{6a'}$), 3.68 (1H, dd, J=11.8, 5.3 Hz, $H_{6b'}$) 3.58 (1H, app. q, H_4), 3.40–3.14 (4H, m, $H_{2',3',4',5'}$), 2.59 (1H, dd, J=15.3, 5.0 Hz, H_{2a}), 2.24 (1H, m, H_3), 2.10

(1H, dd, J=15.3, 8.5 Hz, H_{2b}), 1.60–1.24 (6H, m, $H_{5,6,7}$), 0.97 (3H, d, J=6.8 Hz, H_9), 0.94 (3H, t, J=7.2 Hz, H_8); δ_C (CD_3OD): 178.8, 104.3, 83.8, 78.9, 78.6, 76.1, 72.6, 63.8, 39.7, 35.9, 32.3, 28.8, 24.9, 17.9, 15.3; ESI-MS (80% MeOH) 359.4 ($M+Na^+$); $[\alpha]_D$=−21.3 (c 0.7, CH_3OH).

4.4. General procedure for strong acid hydrolysis of glycosides 3 to oak lactone (1)

(3*R*,4*S*)-**3** (36.3 mg, 0.11 mmol) was dissolved in water (9 mL), concentrated sulfuric acid (1 mL) and dioxane (1 mL) and refluxed for 16 h. The cooled mixture was extracted with ether (2×10 mL), washed with water (10 mL), dried and concentrated. The resulting oil was purified by column chromatography (20% ether in pentane) to give (4*R*,5*S*)-*trans*-**1** as a colourless oil (8.5 mg, 62%): $[\alpha]_D$=−97 (c 0.34, CH_3OH), lit.[23] $[\alpha]_D$=−95.

(4*S*,5*R*)-*trans*-**1** was prepared as above (17.1 mg, 78%) $[\alpha]_D$=+100 (c 0.48, CH_3OH), lit.[23] $[\alpha]_D$=+96.

(4*S*,5*S*)-*cis*-**1** was prepared as above (10.5 mg, 60%) $[\alpha]_D$=−74 (c 0.42, CH_3OH), lit.[23] $[\alpha]_D$=−78.

(4*R*,5*R*)-*cis*-**1** was prepared as above (12.1 mg, 63%) $[\alpha]_D$=+79 (c 0.50, CH_3OH), lit.[23] $[\alpha]_D$=+76.

4.5. Aroma detection thresholds of (4*S*,5*S*)-*cis*-1 and (4*R*,5*R*)-*cis*-1

The aroma threshold of (4*S*,5*S*)-*cis*-**1** in a young (<12 months old) neutral dry white wine (2002 South Australian Chenin blanc) was determined according to the American Society for Testing and Materials (ASTM) method E 679, using 24 judges. The judges were of European origin, aged between 20 and 50, with similar numbers of males and females. The white wine had a free sulfur dioxide content of 24 mg/L. Wines were presented (as part of a triangle test) in ascending order of (4*S*,5*S*)-*cis*-**1** concentration, at 2.0, 6.1, 18.5, 53.9, 161.7 and 485.1 μg/L. Panellists smelt, but did not taste the samples. Those who could detect the spiked wines at all of these concentrations were then tested at lower concentrations; conversely, those who could not detect the spike at any of the concentrations were tested at higher concentrations. The aroma threshold of (4*R*,5*R*)-*cis*-oak lactone was determined in the above manner. The aroma threshold of (4*S*,5*S*)-*cis*-**1** was also determined in a young (2002 South Australian Shiraz) red wine, as described above.

4.6. Mild acid hydrolysis of glycosides (3*S*,4*S*)-3, (3*S*,4*R*)-3 and (3*S*,4*S*)-4

A solution of the required glycoside was prepared by dissolving either **3** (1.2 mg) or **4**[13] (1.7 mg) in water (1000 mL containing 10% EtOH) buffered to pH 3.0 by saturating a solution with potassium hydrogen tartarate, and adjusting the pH with 10% aqueous tartaric acid solution. Portions (7 mL) of the solutions were sealed in glass ampoules and heated at the temperatures and times indicated in Table 2. The ampoules were then opened and analysed for oak lactone content as described by Pollnitz et al.[7]

4.7. Enzyme hydrolysis of glycosides (3*S*,4*S*)-3, (3*S*,4*R*)-3 and (3*S*,4*S*)-4

To a solution of the required glycoside (~20 mg) in pH 5.0 buffer solution (9 mL) was added either AR2000 enzyme (~30 mg) or almond emulsion β-glucosidase enzyme (~30 mg), and warmed at 30 °C for 48 h. The reaction mixture was acidified to pH 1.0 with 10% hydrochloric acid, allowed to stand overnight, and then extracted with ether (2×25 mL). The combined ether extracts were dried and concentrated. A small portion was dissolved in dichloromethane (approx. 1 ppm) and analysed by chiral GC–MS.

4.7.1. Pyrolysis of glycosides (3*S*,4*S*)-3, (3*S*,4*R*)-3 and (3*S*,4*S*)-4. To a sample of powdered oakwood (1 g) in a large glass ampoule (50 mL) was added a solution of either glycoside **3** (500 μg in EtOH, 100 μL) or glycoside 4[13] (800 μg in EtOH, 100 μL). The ampoules were sealed and heated at 235 °C for 30 min (equivalent to a heavy toasting). The ampoules were then opened and extracted with model wine (20 mL) for 72 h, prior to analysis for oak lactone content.[7]

4.7.2. GC–MS chiral analysis. Samples of oak lactone produced by strong acid hydrolysis of the various glycosides, **3** or **4**, dissolved in dichloromethane were analysed with a Hewlett–Packard (HP) 6890 gas chromatograph fitted with liquid HP 6890 series injector and coupled to a HP 5973 mass spectrometer. The liquid injector was operated in fast liquid injection mode with a 10 μL syringe (SGE, Australia) fitted. The gas chromatograph was fitted with an approx. 30 m×0.25 mm J and W fused silica capillary column Cyclosil-B, 0.25 μm film thickness. The carrier gas was helium (BOC gases, Ultra High Purity), flow rate 1.2 mL/min. The oven temperature was started at 50 °C, held at this temperature for 1 min, then increased to 220 °C at 10 °C/min and held at this temperature for 10 min. The injector was held at 220 °C and the transfer line at 240 °C. The sample volume injected was 2 μL and the splitter, at 42:1, was opened after 36 s. Fast injection was done in pulse splitless mode with an inlet pressure of 25.0 psi maintained until splitting. The glass liner (Agilent Technologies) was borosilicate glass with a plug of resilanised glass wool (2–4 mm) at the tapered end to the column. Positive ion electron impact spectra at 70 eV were recorded in the range m/z 35–350 for scan runs. All solvents were Mallinckrodt nanopure grade, and verified for purity by GC–MS prior to use.

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Alkaloids from marine organisms. Part 8: Isolation of bisdemethylaaptamine and bisdemethylaaptamine-9-*O*-sulfate from an Indonesian *Aaptos* sp. marine sponge☆

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Abstract—Bisdemethylaaptamine (**6**), a proposed biosynthetic precursor of the aaptamines has been isolated from an *Aaptos* sp. marine sponge harvested off the Indonesian coast, and its identity confirmed by comparison of its spectral data with that of synthetic material. Bisdemethylaaptamine-9-*O*-sulfate (**7**) was also isolated from the same source. This is the first report of a sulfated aaptamine.

1. Introduction

Marine sponges of the genus, *Aaptos* have been found to be a rich, although not exclusive, source of a group of 1*H*-benzo[*d*,*e*][1,6]-naphthyridine alkaloids known collectively as aaptamines that have interesting biological activities.[1] Five aaptamines, aaptamine (**1**),[2] 9-demethylaaptamine (**2**),[3] 9-demethyloxyaaptamine (**3**),[3] isoaaptamine (**4**)[4] and 4-*N*-methylaaptamine (**5**)[5] have so far been identified in *Aaptos* sp. Their structures are shown in Figure 1 where it can be seen that all contain at least one methyl group on nitrogen or oxygen. In a previous paper[1] it was proposed that bisdemethylaaptamine (**6**) was a possible biosynthetic precursor for these alkaloids and a concise synthesis of **6** based on a biomimetic approach was reported. This earlier work has led us to investigate whether **6** could be detected in marine sponges of the *Aaptos* genus.

2. Results

Methanolic extracts of *Aaptos* sp sponges harvested near Bunaken Island, North Sulawesi, Indonesia were profiled by reverse phase HPLC (C18, 12–22% acetonitrile in 0.1% trifluoroacetic acid in water over 30 min). The chromatogram was dominated by three peaks at 17.5, 24.0 and 25.4 min. Isolation by semi-preparative HPLC and comparison of their ^{1}H, ^{13}C NMR and mass spectral properties with those in the literature,[2–4] showed these three peaks to be due to 9-demethylaaptamine[3], isoaaptamine[4] and aaptamine,[2] respectively. In addition the chromatogram contained two small peaks at 15.3 and 16.0 min that possessed similar UV spectral properties to the other three, less polar aaptamines.

The peak at 16.0 min had an identical retention time and UV spectrum to that of synthetic **6** and gave a symmetrical peak when co-injected with the latter. Isolation of the 16.0 min eluter by semi-preparative HPLC and examination of its ^{1}H, ^{13}C NMR and mass spectral properties showed it to be identical with synthetic bisdemethylaaptamine **6** trifluoroacetate.[1] To the best of our knowledge, this is the first instance of bisdemethylaaptamine being isolated as a natural product.

When collected from the analytical HPLC column in the mobile phase (approximately 15% acetonitrile in 0.1% trifluoroacetic acid in water) and heated at 90 °C for 4 h, the peak at 15.3 min which we designated as compound **7** converted cleanly to **6** (monitoring by HPLC analysis). However, **6** when treated under the same conditions remained unchanged.

☆ For Part 7, see Ref. 1.

Keywords: *Aaptos*; Bisdemethylaaptamine; Sulfated aaptamines.
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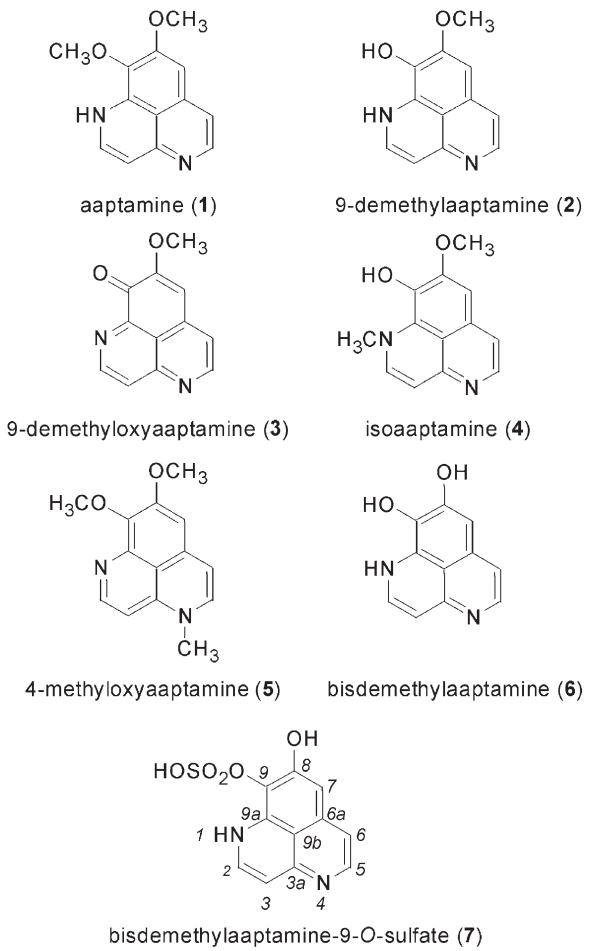

Figure 1. Naturally isolated 1*H*-benzo[*d*,*e*][1,6]naphthyridine alkaloids.

The NMR data for **6** and **7** are shown in Table 1. The ^{1}H NMR spectrum of **7** indicates that its non-exchangeable protons are in a similar aromatic environment to those of **6**, that is, there are two sets of *ortho*-coupled protons and one further proton that is a singlet. This connectivity was confirmed by COSY, HMBC and NOE measurements. There are also two NH protons present in the ^{1}H NMR spectrum of **7** as the trifluoroacetate salt. The most striking difference between the two compounds is that in **7** there is only one OH proton. Since **7** converts irreversibly to **6** on heating in dilute acid, this suggests that in **7**, one of the hydroxyl hydrogens must be replaced by an acid-labile functional group.

Table 1 also indicates that **7** contains eleven carbons that, like the hydrogens, are in a similar environment to **6**. The greatest differences in the ^{13}C NMR shifts between **6** and **7** occur however, in the oxygen-containing aromatic ring. In **7**, C-9 shows an upfield shift of nearly 5 ppm, while the *ortho* carbons, 8, 9a and *para* carbon, 6a are shifted downfield by nearly the same amount. These carbon shifts are indicative of an electron withdrawing group attached to the phenol oxygen, and strongly suggest that it is located at C-9 and not C-8.

ESI-MS in negative ion mode for **7** gave a strong peak at 279 amu, while in positive ion mode a (sodiated) peak at 303 amu was observed. This indicates that **7** has a molecular weight of 280. The difference of 80 mass units between **7** and **6** suggests that the acid-labile functional group at C-9 could either be sulfate (an increment of SO_3), or phosphate (an increment of PO_3H). The IR spectrum in KBr of **7** showed two strong absorptions at 1052 and 1206 cm^{-1} that were not present in the IR spectrum of **6**. These can be attributed to the C–O–S and S=O stretching frequencies respectively of a phenol sulfate.[6] The ^{13}C NMR shift differences in the oxygen-containing ring observed between **7** and **6**, match those in both magnitude and sign for the *ipso*, *ortho*, *meta* and *para* carbon shifts between phenol sulfates and phenols.[6] Thus, the structure of **7** is confirmed as bisdemethylaaptamine-9-*O*-sulfate. This is the first report of a naturally occurring sulfated aaptamine, and is to the best of our knowledge, a new compound.

3. Conclusions

We have isolated two new aaptamines, bisdemethylaaptamine

Table 1. NMR data for bisdemethylaaptamine (**6**) and bisdemethylaaptamine-9-*O*-sulfate (**7**)[a] as monotrifluoroacetate salts

6×TFA								**7**×TFA								
Position	δH	Signal	*J* (Hz)	δC	HMBC			δH	Signal	*J* (Hz)	δC	HMBC			NOE	ΔC
					^{2}J	^{3}J	^{4}J					^{2}J	^{3}J	^{4}J		
1	11.92	d	5.6		9a	3, 9b		11.79	s						2	
2	7.70	t	6.5	141.8	3	3a, 9a		7.82	d	7.0	141.8	3	3a, 9a		1, 3	0.0
3	6.21	d	7.0	97.4				6.35	d	7.5	98.3		9b		2, 4	0.9
3a				150.0							149.5					−0.5
4	12.30	s				5, 9b		12.30	s						3, 5	
5	7.17	dd	7.1, 4.4	127.3		3a, 6a		7.32	d	7.0	129.8		3a, 6a		4, 6	2.5
6	6.70	d	7.3	112.4	5	9b	3a	6.76	d	7.0	111.9		7, 9b		5	−0.5
6a				128.2							133.2					5.0
7	6.82	s		104.2	8	6, 9, 9b	3a, 5	6.80	s		105.5		6, 9, 9b			1.3
8				151.3							156.1					4.8
9				129.2							124.4					−4.8
9a				130.0							135.0					5.0
9b				116.1							115.8					−0.3
OH	9.88	s						10.24	s							
OH	11.29	s														

[a] Solvent d_6-DMSO. NMR field strengths: **6**, ^{1}H 500 MHz, ^{13}C 176.1 MHz. **7**, ^{1}H 500 MHz, ^{13}C 125 MHz.

6, and bisdemethylaaptamine-9-*O*-sulfate **7** from an *Aaptos* sp. marine sponge.

The identification of **7** indicates that there may be two pathways in the biosynthesis of the aaptamines. In one pathway, **7** is biosynthetically methylated to give 9-demethylaaptamine and isoaaptamine as their 9-*O*-sulfates. The sulfate group is then removed possibly by enzymatic hydrolysis to give **2** and **4**. In the second pathway, the *O*-sulfate group is removed prior to methylation which would then give rise to **1** and **5**. We have not detected any other *O*-sulfates in the crude methanolic extract of *Aaptos* sp. however.

We are attempting to synthesize **7** in order to investigate its biological properties further. We also plan to investigate whether **7** can be methylated to the five known aaptamines **1**–**5**. As mentioned in the previous paper,[1] however, **6** continues to defy our attempts to successfully methylate it to produce the aaptamines.

4. Experimental

4.1. General

AR or HPLC grade solvents were used exclusively in this work Evaporation was carried out using a rotary evaporator equipped with a cold finger condenser cooled by acetone–dry ice, and with the water bath temperature maintained at 35 °C.

Analytical HPLC was carried out on an Alltech Apollo 5 μm, C18 250×4.6 mm column held at 40 °C connected to a Hewlett–Packard 1090 liquid chromatograph with an on-board auto-sampler and diode array detector monitoring at 254 nm. Instrument control and data acquisition were provided by Hewlett–Packard ChemStation version 7.0 software. Semi-preparative HPLC was carried out on a YMC Pack 5 μm, ODS-AQ 250×20 mm column at ambient temperature connected to a Waters gradient system consisting of two Waters 510 pumps, Rheodyne 7125 injector with 2.0 mL sample loop, and a Waters 481 UV–visible detector monitoring at 254 nm. Instrument control and data acquisition were provided by Waters Maxima software. For analytical HPLC a linear gradient of 12–32% acetonitrile containing 0.1% TFA was run over 30 min at 1 mL/min. For semi-preparative HPLC the mobile phase was held at 10% acetonitrile containing 0.1% TFA for 20 min to elute **6** and **7**. It was then ramped to 30% TFA over 20 min to elute **1**, **2** and **4**. 100 mg of crude methanolic extract were injected each time for semi-preparative HPLC with a flow rate of 10 mL/min being held throughout.

Compounds were dissolved in d_6-DMSO for NMR measurements and chemical shifts are expressed relative to TMS as internal reference. ^{1}H and ^{13}C NMR spectra for **6** were recorded on a Bruker DRX 500 instrument with a TXI CryoProbe or a Bruker DRX 700 spectrometer, respectively. ^{1}H and ^{13}C NMR spectra for **7** were recorded on a Varian Mercury 300 or INOVA 500 spectrometer. Due to the small quantity of **7** isolated, a ^{1}H–^{13}C nanoprobe was used for its 2D NMR measurements.

ESI-MS were recorded on a VG Quatro II mass spectrometer. The high-resolution ESI measurement was made on a Bruker Apex III FT ICR mass spectrometer with a 4.7 T superconducting magnet operating in positive ion mode.

UV/Vis spectra were obtained in HPLC mobile phase by the diode array detector interfaced with the analytical HPLC instrument. IR spectra were obtained in approximately 1% dispersions in KBr.

4.2. Isolation of aaptamines

The *Aaptos* sp sponge was harvested off the coast of Bunaken Island, North Sulawesi, Indonesia in April 2000. A voucher specimen has been deposited at the National Institute of Oceanology, Indonesian Institute of Sciences, Jln. Pasir Putih I, Ancol Timur, Jakarta 14430, Indonesia. Following harvesting, 4 kg of the sponge was immediately macerated with ethanol to give, after evaporation, 638 g of material. 200 g of this ethanol extract was dissolved in 100:1 methanol–acetic acid and extracted with hexane to remove lipids. The middle layer was separated and evaporated to give 80 g of a dark brown gum with a fishy odor. Ten grams of this gum was dissolved in water containing 0.1% trifluoroacetic acid and filtered. Portions of the filtrate corresponding to 100 mg of the gum were separated by semi-preparative HPLC as described above. The HPLC fractions were evaporated to dryness and dried further under high vacuum prior to NMR and MS analysis. The quantities of material isolated below are those obtained from 100 mg of the gum.

4.2.1. 8-Methoxy-9-hydroxy-1*H*-benzo[*d*,*e*][1,6]naphthyridin-4-ium monotrifluoroacetate (9-demethylaaptamin-4-ium monotrifluoroacetate, 2 as monotrifluoroacetate salt). 6.8 mg, yellow solid, mp 207–210 °C (decomp). UV/Vis λ_{max} (log ε) 410 (3.24), 365 (3.38), 315 (3.29), 269 (3.85), 248 (4.05) nm. IR 3420, 1679, 1555, 1466, 1324, 1201, 1129 cm^{-1}. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.97 (s, 3H), 6.22 (d, J=6.3 Hz, 1H), 6.80 (d, J=6.6 Hz, 1H), 7.10 (s, 1H), 7.24 (dd, J=7.2, 4.8 Hz, 1H), 7.73 (t, J=6.6 Hz, 1H), 10.12 (br. s, 1H), 11.96 (br. d, J=4.8 Hz, 1H), 12.25 (br. s, 1H). ^{13}C (75 MHz, d_6-DMSO) δ 56.4, 97.4, 100.6, 112.9, 116.7, 127.9, 128.3, 129.1, 129.8, 142.1, 150.1, 152.1). ESI-MS (+) ion mode m/z 215 [M+H]. The NMR spectral data matched that previously reported.[3]

4.2.2. 1-*N*-Methyl-8-methoxy-9-hydroxy-1*H*-benzo[*d*,*e*]-[1,6]naphthyridin-4-ium monotrifluoroacetate (isoaaptamin-4-ium monotrifluoroacetate, 4 as monotrifluoroacetate salt). 21.6 mg, yellow solid, mp 190–192 °C (decomp). UV/Vis λ_{max} (log ε) 412 (3.63), 367 (3.50), 320 (3.62), 270 (4.13), 248 (4.25) nm. IR 3095, 1675, 1649, 1604, 1532, 1466, 1302, 1198, 1125 cm^{-1}. ^{1}H NMR (300 MHz, d_6-DMSO) δ 3.95 (s, 3H), 4.03 (s, 3H), 6.16 (d, J=7.2 Hz, 1H), 6.78 (d, J=7.2 Hz, 1H), 7.13 (s, 1H), 7.24 (d, J=6.6 Hz, 1H), 7.71 (d, J=7.5 Hz, 1H), 9.48 (br. s, 1H), 12.46 (br. s, 1H). ^{13}C (75 MHz, d_6-DMSO) δ 46.0, 56.6, 97.4, 101.5, 113.2, 118.1, 127.9, 129.3, 132.3, 149.1, 149.3, 153.6. ESI-MS (+) ion mode m/z 229 [M+H]. The NMR spectral data matched that previously reported.[4]

4.2.3. 8,9-Dimethoxy-1*H*-benzo[*d*,*e*][1,6]naphthyridin-4-ium monotrifluoroacetate (aaptamin-4-ium monotrifluoroacetate, 1 as monotrifluoroacetate salt). 22.8 mg, yellow solid, mp 170–171 °C. UV/Vis λ_{max} (log ε) 382 (3.67), 312 (3.56), 256 (4.25), 238 (4.23), 217 (4.22) nm. IR 2950, 1683, 1654, 1608, 1549, 1468, 1331, 1200, 1178, 1116 cm^{-1}. ^1H NMR (300 MHz, d_6-DMSO) δ 3.80 (s, 3H), 3.97 (s, 3H), 6.37 (d, J=6.9 Hz, 1H), 6.86 (d, J=7.2 Hz, 1H), 7.11 (s, 1H), 7.40 (dd, J=7.2, 4.2 Hz, 1H), 7.84 (t, J=6.9 Hz, 1H), 12.27 (br. d, J=5.4 Hz, 1H), 12.68 (br. s, 1H). ^{13}C (75 MHz, d_6-DMSO) δ 56.5, 60.4, 98.1, 101.0, 112.7, 116.3, 129.9, 131.4, 132.6, 133.7, 142.0, 149.7, 156.9. ESI-MS (+) ion mode *m*/*z* 229 [M+H]. The NMR spectral data matched that previously reported.[2]

4.2.4. 8,9-Dihydroxy-1*H*-benzo[*d*,*e*][1,6]naphthyridin-4-ium monotrifluoroacetate, (bisdemethylaaptamin-4-ium monotrifluoroacetate, 6 as monotrifluoroacetate salt). 0.9 mg, yellow solid UV/Vis λ_{max} (log ε) 402 (3.58), 363 (3.67), 313 (3.63), 267 (4.19), 241 (4.43) nm. IR 3531, 3169, 2892, 1660, 1611, 1575, 1439, 1401, 1340, 1234, 1192, 1133, 1095, 940, 853, 801, 722, 643 cm^{-1}, NMR, see Table 1. ESI-MS (+) ion mode *m*/*z* 223 [M+Na].

4.2.5. 8-Hydroxy-9-sulfoxy-1*H*-benzo[*d*,*e*][1,6]naphthyridin-4-ium monotrifluoroacetate (bisdemethylaaptamin-4-ium monotrifluoroacetate-9-*O*-sulfate, 7 as monotrifluoroacetate salt). 0.3 mg, pale yellow solid UV/Vis λ_{max} (log ε) 373 (3.63), 310 (3.49), 257 (4.18), 236 (4.12), 216 (4.14) nm. IR 3286, 2937, 1734, 1657, 1616, 1561, 1450, 1257, 1206, 1172, 1052, 946, 842, 724, 644 cm^{-1}. NMR, see Table 1. ESI-MS (+) ion mode *m*/*z* 303 [M+Na], 223 [M+Na−SO_3]; (−) ion mode 279 [M−H]. HR-ESI-MS (+) for [M+H] 281.02301, $C_{11}H_9N_2O_5S$ requires 281.02322, $C_{11}H_{10}N_2O_5P$ requires 281.03274.

Acknowledgements

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Tetrahedron

Rapid and efficient ring opening of epoxides catalyzed by a new electron deficient tin(IV) porphyrin

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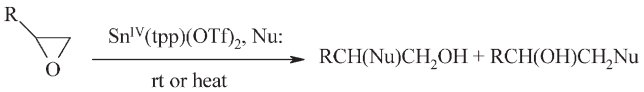
Abstract—The new electron deficient tin(IV) tetraphenylporphyrinato trifluoromethanesulfonate, [Sn^{IV}(tpp)$(OTf)_2$], was used as an efficient catalyst for the alcoholysis, hydrolysis and acetolysis of epoxides. Conversion of epoxides to thiiranes and acetonides were also performed efficiently in the presence of this catalyst.

1. Introduction

Epoxides are important and versatile synthetic intermediates in organic synthesis.[1] Epoxides can be opened under a variety of conditions, although the most practical and widely employed strategy for the synthesis of 1,2-bifunctional compounds is via nucleophilic ring-opening using a Lewis acid or a strong base.[2] Under the reported conditions, these reactions have limited applicability in modern organic synthesis. In most of the epoxide ring-opening reactions under acidic conditions, the formation of a mixture of regio-isomers and polymerization is observed. Some of the reported catalysts suffer from disadvantages such as high acidity, the non-catalytic nature of the reagents, long reaction times and inconvenient handling procedures.[3] Therefore, the introduction of new methods for the nucleophilic ring-opening of epoxides, which work under mild conditions, are still in demand and are important in synthetic organic chemistry. A number of methods using Lewis acids and one-electron transfer catalysts have been also reported for the ring-opening reactions of epoxides with different nucleophiles.[4]

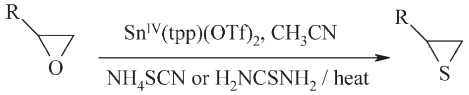
The successful applications of metalloporphyrins as Lewis acid catalysts[5] prompted us to explore the potential of electron-deficient metalloporphyrins as catalysts for the nucleophilic ring-opening of epoxides.

We found that the newly synthesized Sn^{IV}(tpp)$(CF_3SO_3)_2$ can act as an efficient catalyst for the alcoholysis, hydrolysis, acetolysis and for the conversion of epoxides to thiiranes with ammonium thiocyanate and thiourea, and also for the preparation of acetonides from epoxides and acetone (Schemes 1–3).

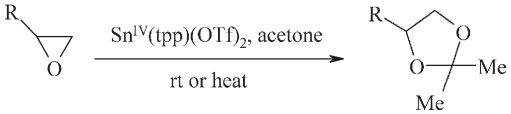


Nu: ROH, H_2O, AcOH

Scheme 1.



Scheme 2.



Scheme 3.

2. Results and discussions

2.1. Alcoholysis, hydrolysis and acetolysis of epoxides catalyzed by Sn^{IV}(tpp)$(OTf)_2$

The alcoholysis of various epoxides such as cyclohexene and styrene oxides, (chloromethyl)oxirane, allyl oxiranylmethyl ether, isopropyl oxiranylmethyl ether and 1,2-epoxyoctane as examples of aliphatic, alicyclic, activated and deactivated epoxides, were performed with primary,

Keywords: Electron deficient metallporphyrin; Ring opening; Epoxide.
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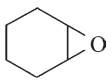
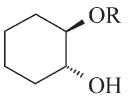
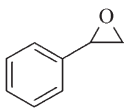
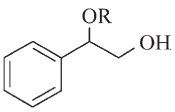
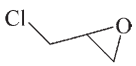
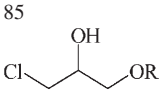
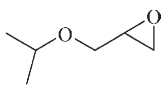
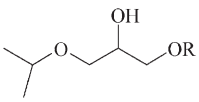
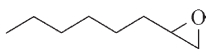
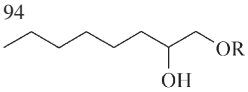
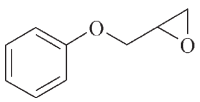
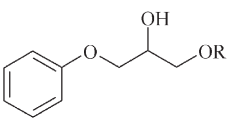
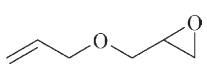
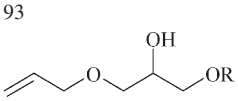
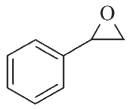
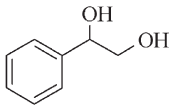
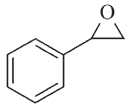
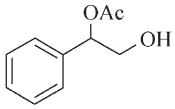
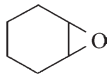
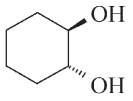
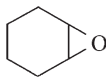
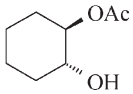
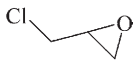
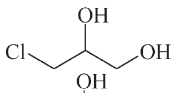
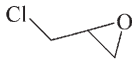
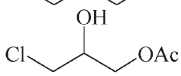
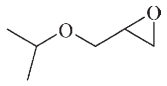
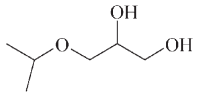
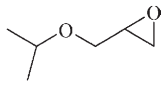
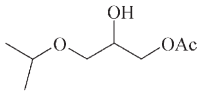
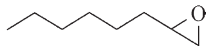
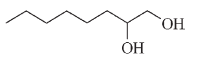
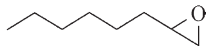
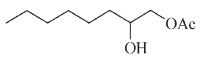
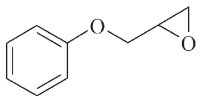
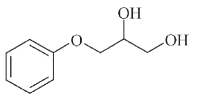
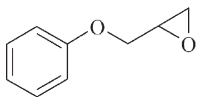
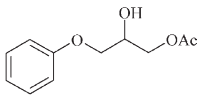
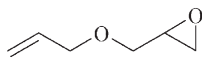
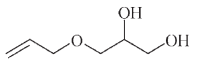
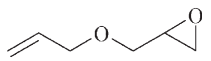
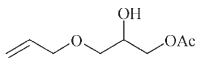
Table 1. Alcoholysis of various epoxides catalyzed by Sn(IV)(tpp)$(OTf)_2$[a]

Entry	Epoxide	R-OH/condition	Time (min)	Product/yield[b,c]	Bp (°C/Torr) or n_D^{25}	
					Found	Reported[4g,j,8,9]
						
1		R=CH_3/rt	10	99	108–111/65	107–110/65
2		R=C_2H_5/rt	20	99	82–85/15	81–85/15
3		R=*n*-Pr/reflux	5	99	94–97/14	95–97/14
4		R=*i*-Pr/reflux	10	99	90–93/18	90–92/18
5		R=*t*-Bu/reflux	10	98	90–92/15	87–91/14
						
6		R=CH_3/rt	5	99	74–76/0.7	75/0.7
7		R=C_2H_5/rt	5	99	1.5146	1.5144
8		R=*n*-Pr/reflux	5	99	1.5109	1.5106
9		R=*i*-Pr/reflux	5	98	1.5074	1.5075
10		R=*t*-Bu/reflux	5	85	1.5129	1.5130
						
11		R=CH_3/reflux	60	94	98–100/9	104/10
12		R=C_2H_5/reflux	60	94	103–106/10	105–108/10
13		R=*n*-Pr/reflux	60	93	1.4382	1.4390
14		R=*i*-Pr/reflux	60	92	107–110/10	108–110/10
15		R=*t*-Bu/reflux	60	90	1.4436	1.4435
						
16		R=CH_3/reflux	20	99	202–204	200–203
17		R=C_2H_5/reflux	20	99	207–209	208
18		R=*n*-Pr/reflux	25	99	1.4290	1.4294
19		R=*i*-Pr/reflux	30	98	1.4199	1.4196
20		R=*t*-Bu/reflux	60	94	1.4050	1.4054
						
21		R=CH_3/rt	25	99	85–87/6	84–86/6
22		R=C_2H_5/reflux	10	99	127–130/11	128–130/11
23		R=*n*-Pr/reflux	15	99	1.4315	1.4318
24		R=*i*-Pr/reflux	20	98	1.4326	1.4328
25		R=*t*-Bu/reflux	75	95	1.4410	1.4413
						
26		R=CH_3/reflux	5	99	120–123/3	121–123/3
27		R=C_2H_5/reflux	20	99	1.5147	1.5145
28		R=*n*-Pr/reflux	25	95	1.5043	1.5042
29		R=*i*-Pr/reflux	40	93	1.4974	1.4973
30		R=*t*-Bu/reflux	45	93	1.4951	1.4949
						
31		R=CH_3/reflux	20	99	1.4462	1.4460
32		R=C_2H_5/reflux	20	99	1.4370	1.4373
33		R=*n*-Pr/reflux	25	99	1.4383	1.4380
34		R=*i*-Pr/reflux	30	98	1.4366	1.4363
35		R=*t*-Bu/reflux	50	97	1.4584	1.4581

[a] Epoxide (1 mmol), alcohol (5 mL), catalyst (1.9 mol%).
[b] All products were identified by comparison of their physical and spectral data with those of authentic samples.
[c] Yields refer to isolated products.

Table 2. Hydrolysis and acetolysis of various epoxides catalyzed by Sn(IV)(tpp)$(OTf)_2$[a]

Entry	Epoxide	Solvent	Time (min)/condition	Product[b]	Yield[c]	Mp, bp (°C/Torr) or n_D^{25}	
						Found	Reported[4g,j,8,9]
1		H_2O/CH_3CN	15/Reflux		98	65–68	65–67
2		CH_3CO_2H	5/rt		92	163–165/15	163–170/15
3		H_2O/CH_3CN	35/rt		93	104–105	104
4		CH_3CO_2H	10/rt		99	1.5416	1.5418
5		H_2O/CH_3CN	140/Reflux		99	119–122/18	117–120/18
6		CH_3CO_2H	40/Reflux		99	1.4753	1.4755
7		H_2O/CH_3CN	120/Reflux		99	150–152/9	151–152/9
8		CH_3CO_2H	10/Reflux		99	1.4186	1.4183
9		H_2O/CH_3CN	40/Reflux		95	130–134/10	131–134/10
10		CH_3CO_2H	55/rt		90	1.4160	1.4162
11		H_2O/CH_3CN	130/Reflux		99	200–202/22	146/149/0.6
12		CH_3CO_2H	35/Reflux		99	174–177/10	175/10
13		H_2O/CH_3CN	100/Reflux		96	1.5580	1.5583
14		CH_3CO_2H	15/Reflux		99	1.4379	1.4381

[a] Epoxide (1 mmol), catalyst (1.9 mol%).
[b] All products were identified by comparison of their physical and spectral data with those of authentic samples.
[c] Yields refer to isolated products.

secondary and tertiary alcohols, affording the corresponding β-alkoxy alcohols in high yields (Table 1). The reactions in the case of cyclohexene oxide were stereoselective, and the only *trans* products were obtained (entries 1–5). In the case of unsymmetrical epoxides, the reactions are regioselective with an attack of the nucleophile (alcohol) on the less substituted oxirane carbon to yield the anti Markovnikov type products (entries 11–35). The only exception is given by styrene oxide, in which the reactions occur on the more substituted carbon; Markovnikov type products were obtained (entries 6–10).

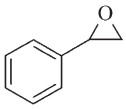
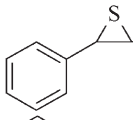
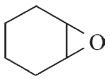
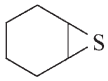
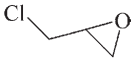
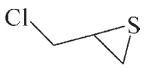
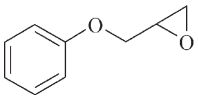
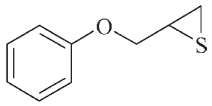
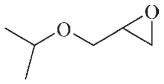
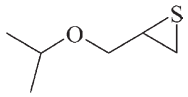
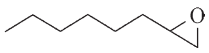
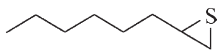
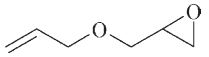
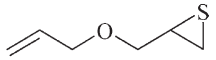
The reaction of these epoxides with acetic acid in the presence of catalytic amounts (0.019 mol equiv.) of $Sn^{IV}(tpp)(OTf)_2$ occurred in the same manner as the alcohols, high yields of the corresponding β-acetoxy alcohols were obtained (Table 2).

Hydrolysis of the epoxides was also performed in the presence of this catalyst in aqueous acetonitrile; the corresponding diols were obtained in high yields (Table 2).

2.2. Conversion of epoxides to thiiranes catalyzed by $Sn^{IV}(tpp)(OTf)_2$

Conversion of epoxides to thiiranes with NH_4SCN and

Table 3. Conversion of epoxides to thiiranes catalyzed by $Sn^{IV}(tpp)(OTf)_2$ in refluxing acetonitrile[a]

Entry	Epoxide	Yield% (t/min)[b]		Product[c]	Bp (°C)/Torr	
		NH_4SCN	NH_2CSNH_2		Found	Reported
1		99(20)	98(60)		84–85/5	85–86/5[7g]
2		99(20)	99(40)		53–54/7	54–55/7[7g]
3		99(25)	96(90)		59–60/30	60–61/30[7g]
4		99(20)	98(30)		104–105/7	103–104/7[7g]
5		99(30)	97(40)		55–56/11	54/11[13]
6		99(40)	98(90)		83–84/5	83/5[14]
7		98(25)	98(45)		77–78/8	78–79/8[15]

[a] Epoxide (1 mmol), NH_4SCN or H_2NCSNH_2 (2 mmol), acetonitrile (5 mL), catalyst (1.9 mol%).
[b] Yields refer to isolated products.
[c] All products were identified by comparison of their physical and spectral data with those of authentic samples.

thiourea in the presence of a suitable catalyst[6,7] is important in organic chemistry. Reaction of different aliphatic and cyclic epoxides including those electron-withdrawing substituents with NH_4SCN and thiourea were performed in refluxing acetonitrile and in the presence of 0.019 mol equiv. of $Sn^{IV}(tpp)(OTf)_2$. Table 3 summarizes the results obtained for conversion of different epoxides to their corresponding thiiranes.

The effects of other solvents such as acetone, dichloromethane, chloroform and carbon tetrachloride were also investigated. Compared to acetonitrile solvent, the reaction times were longer and the yields of thiiranes were lower in all of the other solvents.

2.3. Conversion of epoxides to acetonides catalyzed by $Sn^{IV}(tpp)(OTf)_2$

1,3-Dioxolanes are widely used as protecting groups for diols[10] with special application for carbohydrate and steroid chemistry. In addition they are very suitable derivatives of diols for GC, GLC and mass spectrometry.[11] Direct conversion of an epoxide into 1,3-dioxolane instead of adding water to form diol with subsequent elimination in the presence of acetone has been studied with relatively few reagents.[12]

Due to the importance of the direct synthesis of acetonides from epoxides and acetone, the ring-opening reaction of various epoxides with acetone was also studied. Reactions of different aliphatic and cyclic epoxides including those electron-withdrawing substituents were performed in refluxing acetone (except for cyclohexene and styrene oxide) and in the presence of only 0.019 mol equiv. of $Sn^{IV}(tpp)(OTf)_2$. The results are shown in Table 4.

3. Conclusion

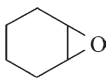
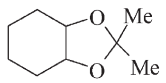
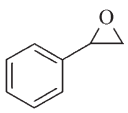
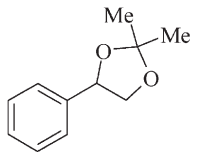
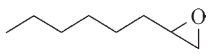
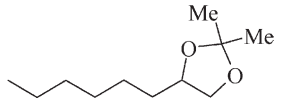
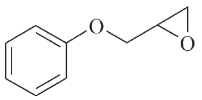
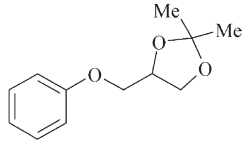
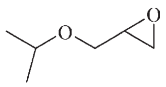
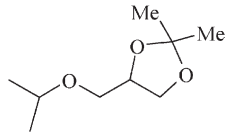
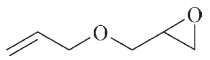
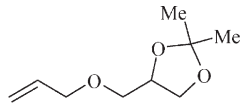
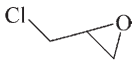
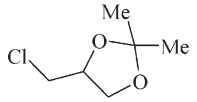
Although metalloporphyrins are widely used as redox catalysts, there have been few studies on their catalytic activity as Lewis acids. In this report we have demonstrated that the tin(IV) tetraphenylporphyrinato trifluoromethanesulfonate, $Sn^{IV}(tpp)(OTf)_2$, which is a stable Sn(IV) compound, can be considered as a mild Lewis acid for efficient and catalytic ring-opening reactions of epoxides with different nucleophiles under both solvolytic and non-solvolytic reaction conditions. In addition, in the presence of this catalyst, efficient conversion of epoxides to their corresponding thiiranes and acetonides is also possible. Further works on the synthetic applications of this tin(IV) porphyrin are in progress.

4. Experimental

4.1. General considerations

All chemicals used were of reagent grade. The tetraphenylporphyrin was prepared and metallated according to the literature.[16,17] All yields refer to isolated products. Products were characterised by comparison of their physical data, IR and NMR with those of authentic samples. ^1H NMR spectra were obtained with a Brucker AW 80 (80 MHz) spectrometer. GLC analyse were performed on a Shimadzu

Table 4. Conversion of epoxides to acetonide catalyzed by $Sn^{IV}(tpp)(OTf)_2$ in refluxing acetone[a]

Entry	Epoxide	Time (h)	Yield (%)[b]	Product
1	 **1a**	0.5[c]	90	 **2a**
2	 **1b**	0.4[c]	94	 **2b**
3	 **1c**	3.5	94	 **2c**
4	 **1d**	4	90	 **2d**
5	 **1e**	2.5	98	 **2e**
6	 **1f**	3	91	 **2f**
7	 **1g**	3	88	 **2g**

[a] Epoxide (1 mmol), acetone (5 mL), catalyst (1.9 mol%).
[b] Yields refer to isolated products.
[c] These reactions carried out at room temperature.

GC-16A instrument. Infrared spectra were recorded on a Philips PU-9716 or Shimadzu IR-4350 spectrophotometers.

4.1.1. Preparation of tin(IV) tetraphenyporphyrinato trifluoromethanesulfonate, $Sn^{IV}(tpp)(OTf)_2$. To a solution of $Sn(tpp)Cl_2$ (1.03 g, 1 mmol) in 100 mL of THF, at 55 °C, $AgCF_3SO_3$ (0.54 g, 2 mmol) was added. The solution was stirred at 55 °C for 30 min. The AgCl precipitate was filtered through a 0.45 μM filter. The resulting solution was evaporated at room temperature. The $Sn^{IV}(tpp)(OTf)_2$ then extracted with CH_2Cl_2. The $Sn^{IV}(tpp)(OTf)_2$ crystals obtained by evaporation of solvent at room temperature. Visible spectrum: 420 (Soret), 556, 595, 629 nm; ν_{max} ($CHCl_3$): 1029, 1170, 1230, 1293 cm^{-1} (belong to SO_3 groups and porphyrin ring); CHN analyses: Calcd C, 53.68; H, 2.72; N, 5.45; found: C, 54.35; H, 2.8; N, 5.35.

4.1.2. Reaction of epoxides with alcohols and acetic acid. General procedure. $Sn^{IV}(tpp)(OTf)_2$ (20 mg, 0.019 mmol) was added to a solution of epoxide (1 mmol) in appropriate alcohol or acetic acid (5 mL). The mixture was stirred for the specified time and at the appropriate temperature according to Tables 1 and 2. The progress of the reaction was monitored by GLC. After completion of reaction, the mixture was passed through a silica gel column (1:1 hexane–ethyl acetate) to remove the catalyst. The eluate was concentrated under reduced pressure and chromatographed on silica gel column to give the pure product in 85–99% yields.

4.2. Reaction of epoxides in aqueous acetonitrile. General procedure

To a solution of epoxide (1 mmol) in an equal mixture of CH_3CN/H_2O (5 mL) was added $Sn^{IV}(tpp)(OTf)_2$ (20 mg, 0.019 mmol). The mixture was stirred for the specified time at reflux conditions according to Table 2. The progress of the reaction was monitored by GLC. After completion of the reaction, the mixture was passed through a silica gel column (8:1 CCl_4/methanol) to remove the catalyst. The elute was

concentrated under reduced pressure and chromatographed on silica gel column to give the pure product in 93–99% yields.

4.3. General procedure for conversion of epoxides to thiiranes with NH_4SCN or H_2NCSNH_2

In a round-bottomed flask (25 mL) equipped with a condenser and a magnetic stirrer, a solution of epoxide (1 mmol) in acetonitrile (5 mL) was prepared. Ammonium thiocyanate or thiourea (2 mmol) and Sn(IV)(tpp)$(OTf)_2$ (20 mg, 0.019 mmol) was added to this solution and the reaction mixture was stirred magnetically under reflux conditions. After completion of the reaction (monitored by GLC), the mixture was directly passed through a short column of silica-gel (1:1 hexane–ethyl acetate) to remove the catalyst. Evaporation of the solvent followed by chromatography on a short column of silica gel gave pure thiirane; yield 96–99%.

4.4. General procedure for conversion of epoxides to 1,3-dioxolanes

In a round-bottomed flask (25 mL) equipped with a condenser and a magnetic stirrer, a solution of epoxide (1 mmol) in acetone (5 mL) was prepared. Sn(IV)(tpp)$(OTf)_2$ (20 mg, 0.019 mmol) was added to this solution and the reaction mixture was stirred magnetically under reflux conditions or room temperature. The reaction progress was monitored by GLC. After completion of the reaction, the mixture was directly passed through a short column of silica-gel (1:1 hexane–ethyl acetate) to remove the catalyst. The elute was evaporated under reduced pressure and the crude product was obtained in a quantitative yield. Distillation of product under reduced pressure resulted in the corresponding 1,3-dioxolane in 88–98% yields.

4.4.1. Physical and spectral data for 1,3-dioxolanes. *Compound* **2a**: n_D^{20}=1.4465 (lit.[18a] n_D^{20}=1.448); ^{1}H NMR($CDCl_3$) δ: 4.34–4.05(2H, m), 2.58–2.07(4H, m), 1.35(6H, s), 1.24–1.00(4H, m); IR(neat): 2980, 2930, 2870, 1440, 1355, 1260, 1180, 1080, 960, 885, 835, 780 cm^{-1}.

Compound **2b**: n_D^{20}=1.5270 (lit.[18b] n_D^{20}=1.5273); ^{1}H NMR($CDCl_3$) δ: 7.25 (5H, s), 5.00(1H, dd, J=8 Hz), 4.23(1H, dd, J=7 Hz), 3.62(1H, dd, J=6 Hz), 1.48(3H, s), 1.40(3H, s); IR(neat): 3036, 2990, 2870, 1600, 1495, 1450, 1365, 1230, 1150, 1055, 945, 850, 755, 700 cm^{-1}.

Compound **2c**: n_D^{20}=1.2495; ^{1}H NMR($CDCl_3$) δ: 4.20–3.31(3H, m), 1.72–1.13(16H, m), 0.82(3H, t, J=7 Hz); IR(neat): 2970, 2915, 2860, 1460, 1375, 1250, 1160, 1050, 950, 850, 730 cm^{-1}.

Compound **2d**: mp 63 °C (lit.[18c] mp 64–65 °C); ^{1}H NMR($CDCl_3$) δ: 7.47–6.72(5H, m), 4.65–3.64(5H, m), 1.42(3H, s), 1.30(3H, s); IR(KBr): 3070, 2990, 2920, 1600, 1585, 1490, 1445, 1344, 1240, 1210, 1170, 1035, 910, 810, 747 cm^{-1}.

Compound **2e**: n_D^{20}=1.4170 (lit.[18d] n_D^{20}=1.4168); ^{1}H NMR($CDCl_3$) δ: 4.37–3.30(6H, m), 1.37(3H, s), 1.27(3H, s), 1.15(6H, d, J=6 Hz); IR(neat): 2970, 2930, 2870, 1460, 1380, 1365, 1260, 1125, 1070, 1030, 920, 850, 735 cm^{-1}.

Compound **2f**: n_D^{20}=1.4318 (lit.[18e] n_D^{20}=1.4320); ^{1}H NMR($CDCl_3$) δ: 5.95–4.70(3H, m), 4.35–3.32(7H, m), 1.33(3H, s), 1.25(3H, s); IR(neat): 3050, 3000, 2920, 2850, 1455, 1360, 1320, 1250, 1090, 920, 840, 755 cm^{-1}.

Compound **2g**: n_D^{15}=1.4359 (lit.[18f] n_D^{15}=1.4357); ^{1}H NMR($CDCl_3$) δ: 4.34–3.12(5H, m), 1.32(3H, s), 1.21(3H, s); IR(neat): 2960, 2900, 2860, 1450, 1375, 1250, 1165, 1080, 1025, 935, 870, 740 cm^{-1}.

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A synthetic approach to 2,3,4-substituted pyridines useful as scaffolds for tripeptidomimetics

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Abstract—The synthesis of 2,3,4-substituted pyridine derivatives useful as scaffolds in the development of peptidomimetics is described. The use of a variety of electrophiles in a halogen-dance reaction to produce 3-alkyl-2-fluoro-4-iodo-pyridine derivatives as 'functionalized scaffolds' and the possibility to differentiate between the reactivities of the two halogen handles have been explored. Coupling of amino acid derivatives in the 4-position of the pyridine was found to proceed efficiently by conversion of iodo-pyridine to a Grignard derivative, which was allowed to react with a protected amino aldehyde. Substitution of fluorine in the 2-position of the pyridine was found to be facile with alkoxide nucleophiles, whereas amines were much less reactive.

1. Introduction

Peptides are known to influence many vital physiological processes and thereby they constitute important lead compounds in medicinal chemistry research. However, poor pharmacokinetic properties such as low oral bioavailability and rapid enzymatic degradation make most peptides unsuitable as drugs. In addition, the conformational flexibility of peptides may reduce the receptor selectivity. These problems can be addressed by the design and synthesis of small rigid molecules known as peptidomimetics. In the interaction between a peptide and its receptor or enzyme, the peptide backbone serves as a scaffold which positions important amino acid side chains in defined spatial positions. One approach towards the development of peptidomimetics is to find rigid and physiologically stable structures that can replace the peptide backbone, i.e. providing a molecular framework to which the recognition elements can be anchored and correctly presented for the target structure.[1,2]

We have for some time been interested in the development of a general scaffold useful in mimetics of biologically active tripeptides or tripeptide sequences. A computer based design proposed a trisubstituted pyridine ring as a scaffold to which appropriate amino acids and side chain moieties should be attached in the 2-, 3- and 4-positions (Fig. 1). The suggested scaffold provides a rigid framework with a well defined geometry due to the aromaticity of the pyridine ring. There are no remaining amide bonds in the peptidomimetic; a feature that is desirable when developing new bioactive compounds. The nitrogen atom of the pyridine ring is positioned to mimic the electrostatics of the carbonyl oxygen of the original amide bond between the second and third residues of a tripeptide (Fig. 1). The middle amino acid of the tripeptide sequence is represented by the pyridine ring, which carries a side chain equivalent in position 3. The *N*-terminal amino acid moiety is attached to the 4-position of the pyridine ring via a carbonyl group, and the *C*-terminal amino acid moiety is attached to the 2-position via an amino or ether bridge. Here we report our findings towards the development of a facile synthetic strategy to produce these compounds. A main goal has been to allow the use of derivatives of the natural amino acids as building blocks,

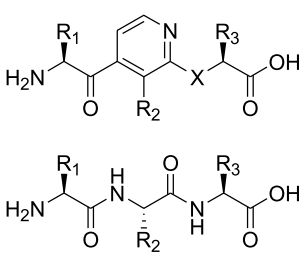

Figure 1. The proposed pyridine based tripeptidomimetic scaffold compared with a general tripeptide. R_1-R_3 are amino acid side-chains, X=NH or O.

Keywords: Peptidomimetic; Pyridine; Scaffold; Grignard reaction; Halogen-dance.

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thereby obtaining the correct stereochemistry of peptides and providing ready access to a variety of different tripeptidomimetic sequences.

2. Results and discussion

2.1. Retrosynthetic analysis

The synthetic strategy was based on an appropriately substituted pyridine derivative that should allow selective synthetic manipulations in one position without disturbing the others. This requirement was fulfilled by the 3-alkyl-2-fluoro-4-iodopyridine scaffold **1** (the 'functionalized scaffold'), as shown in the retrosynthetic analysis (Fig. 2). A fluorine atom activates the 2-position for nucleophilic substitution. For example, α-amino or α-hydroxy acid derivatives with an appropriately protected carboxylic acid functionality could be used as nucleophiles. The iodine in the 4-position of the pyridine ring could be envisioned to be useful in metal catalyzed coupling reactions with amino acid derivatives such as Weinreb's amides, amino acid chlorides or amino aldehydes. Thus, this synthetic strategy allows the use of natural amino acids as reagents for the substituents in the 2- and 4-positions of the pyridine scaffold. The side chain equivalent in the 3-position is attached by alkylation with an electrophile, which might limit the possibilities of making functionalized scaffolds corresponding to all natural amino acids. Regardless of this limitation, use of the functionalized pyridine scaffold with its two halogen handles with different reactivities seemed like a promising approach for preparation of tripeptidomimetics.

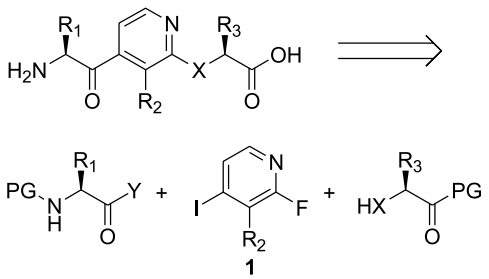


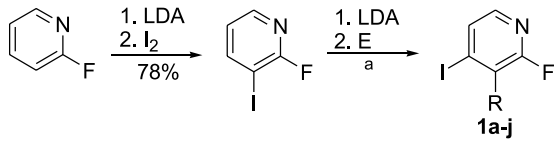
Figure 2. Retrosynthetic analysis of the tripeptidomimetic. R_1-R_3 are amino acid side-chains, X=NH or O, Y=N(OMe)(Me), Cl or H.

2.2. Synthesis of the functionalized scaffold

The functionalized scaffold **1** was obtained in two steps starting from commercially available 2-fluoropyridine according to the procedure by Queguiner.[3] 2-Fluoro-3-iodopyridine was synthesized from 2-fluoropyridine in 78% yield by reaction with LDA followed by addition of I_2 (Table 1).[4] In the following step, treatment with LDA is associated with a phenomenon commonly referred to as a 'halogen dance', whereby iodine migrates to the 4-position and the subsequently added electrophile is attached to the 3-position of the pyridine ring. The alkylating agents that are used should mimic the side chain of the middle amino acid of a tripeptide sequence.

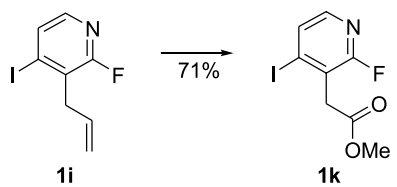
In addition to the previously reported compounds **1a**[3] and **1b**,[3] which in our application correspond to glycine (R=H) and alanine (R=Me), side chain equivalents of phenylalanine (R=Bn), leucine (R=isobutylene), threonine (R=$CH(OH)CH_3$) and the methyl ester of aspartic acid (R=CH_2COOMe) have successfully been introduced (Table 1 and Scheme 1). Treatment of the lithiated scaffold with benzyl bromide smoothly introduced a benzyl substituent thus producing the functionalized scaffold **1c**, corresponding to the phenylalanine side chain, in 71% yield. The direct introduction of an isobutyl group to afford the leucine mimetic **1d** proved unsuccessful using isobutyl bromide or isobutyl iodide as electrophiles, with or without the addition of TMEDA. However, when using isobutyric aldehyde, the expected alcohol **1e** was afforded in 96% yield. Removal of the hydroxyl group either directly or after modification to the tosylate[5] was not successful. Attempted catalytic hydrogenation in the presence of acid[6] or reduction with a variety of reagents (Et_3SiH/TFA, $NaBH_4$/TFA-AcOH,[7] HCOOH/triflic acid,[8] $NaCNBH_3/BF_3{\cdot}Et_2O$,[9] $LiAlH_4$[10] at various temperatures or $LiEt_3BH{\cdot}THF$[11]) either resulted in the isolation of unreacted starting material, or the deiodinated starting material, or gave esters formed from reactions of the alcohol with the different acids present. In one case, after refluxing the tosylate in toluene with DBU,[12] the elimination product was isolated in 55% yield. These findings indicated that the removal of the hydroxyl group would require several steps with possibilities of side reactions such as deiodination and this approach was therefore abandoned. Instead, the introduction of an isobutyl

Table 1. Introduction of substituents at the 3-position in the pyridine template



Entry	Electrophile	R-group	Product	Yield (%)
1	H_2O	H	**1a**	80
2	MeI	Me	**1b**	89
3	BnBr	Bn	**1c**	71
4	Isobutyl halide	Isobutyl	**1d**	~0[b]
5	Isobutyric aldehyde	$Me_2CHCH(OH)$	**1e**	96
6	Methallyl bromide	Isobutylene	**1f**	93
7	Acetaldehyde	MeCH(OH)	**1g**	51
8	Ethyl bromoacetate	CH_2COOEt	**1h**	13[c]
9	Allyl bromide	Allyl	**1i**	87
10	Ethyl acrylate	CH_2CH_2COOEt	**1j**	~0

[a]Reaction conditions: 2-fluoro-3-iodopyridine was reacted with LDA in THF at −78 °C for 1 h before the electrophile was added as a solution in THF.
[b] Isobutyl bromide and isobutyl iodide with or without TMEDA at −78 °C to −30 °C were used as electrophiles.
[c] See Scheme 1 for synthesis of the corresponding methyl ester.

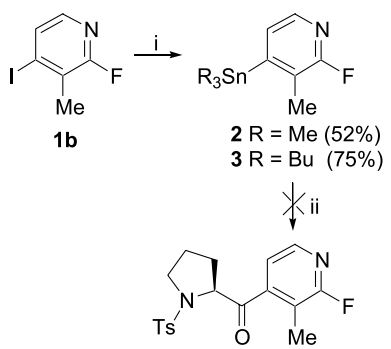


Scheme 1. Reagents and conditions: O_3, NaOH in MeOH, CH_2Cl_2, −78 °C, 15 min.

equivalent was performed by using 2-methyl-2-propenyl bromide as electrophile. Thereby a methallyl group was successfully introduced to afford **1f** in 93% yield. Since catalytic hydrogenation resulted in extensive deiodination of **1e**, no attempts to reduce the double bond at this stage were made. The hydrogenation is however not expected to be problematic after substitution of the iodine has been accomplished. The side chain corresponding to threonine was introduced by using acetaldehyde as electrophile to afford **1g** in 51% yield. The ester **1h**, corresponding to an aspartic acid residue, was isolated in only 13% yield after reaction with ethyl bromoacetate. To improve the yield, the desired product was instead synthesized in a two-step procedure; first an allyl group was introduced by using allyl bromide as electrophile to afford **1i** in 87% yield. The allyl group was then treated with ozone and methanolic sodium hydroxide in dichloromethane to afford the methyl ester **1k** in 71% yield (Scheme 1).[13] Attempts to introduce the side chain corresponding to glutamic acid by using ethyl acrylate as electrophile to afford **1j** were unsuccessful. However, the allyl substituent in **1i** could be useful as precursor for side chain equivalents of asparagine (via ester **1k**), glutamine and glutamate (via the primary alcohol). In subsequent studies of the reactivities of fluorine and iodine at the 2- and 4-positions of the functionalized scaffold, the methyl derivative **1b** was used.

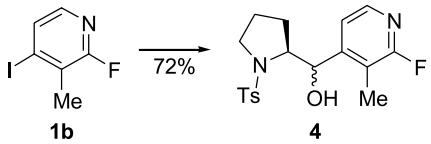
2.3. Introduction of the N-terminal amino acid moiety

The next step to explore was the possibility of introducing an amino acid moiety in the 4-position of the pyridine ring where the functionalized scaffold carries an iodine handle. The first approach was to perform the coupling via the corresponding tin derivative in a palladium catalyzed Stille cross-coupling reaction with an amino acid chloride.[14–16] Although this is a thoroughly explored reaction also for pyridine derivatives,[17–19] to our knowledge only one example of a Stille coupling with amino acid chlorides has previously been reported.[20] The trialkyl tin derivatives **2** and **3** were synthesized by reaction of **1b** with BuLi in THF at −78 °C followed by the addition of trialkyl tin chloride (Scheme 2). A test reaction between **2** and 3-phenyl-propionyl chloride succeeded at the first attempt using $Pd(PPh_3)_4$ as catalyst and CuI as additive producing the desired product in approximately 40% yield. Considerable effort was thereafter made to use amino acid chlorides such as Ts-Pro-COCl, Fmoc-Phe-COCl or Eoc-Phe-COCl in similar couplings. However, although a range of Pd-catalysts [$Pd(PPh_3)_4$, $Pd(OAc)_2$, $(PPh_3)_2PdCl_2$, $Pd_2(dba)_3$], ligands [dppf, dppe, $P(t\text{-}Bu)_3$, $AsPh_3$], co-catalysts and additives [CuI, CuCl, CuO, LiCl], solvents [benzene, DMSO, $CHCl_3$, DMF] and reaction temperatures [25, 60 and 80 °C] were explored, the desired coupling reaction between the pyridine scaffold and an amino acid chloride was never realized.



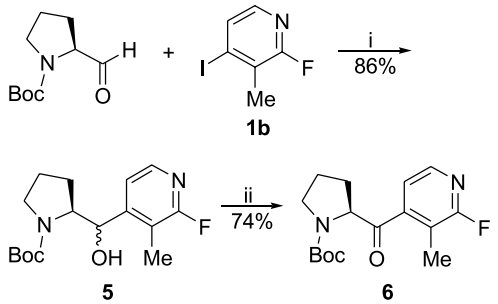
Scheme 2. Reagents and conditions: (i) (1) BuLi, THF, −78 °C, 1 h; (2) R_3SnCl, −78 °C, 1–1.5 h. (ii) Ts-ProCOCl, Pd-catalyst, co-catalyst, additive, solvent and temperature were varied as specified in the text.

The disappointing results from the Stille reactions led us to investigate the reactivity of the 4-lithiated scaffold. It was found that the Weinreb's amide of Eoc-protected phenylalanine could be coupled to **1b** by using 2 equiv. of BuLi in the presence of TMEDA. The use of TMEDA was found to be required but even so, the yield was only around 10%. An aldehyde, Ts-Pro-CHO,[21,22] showed higher reactivity and coupling under the same conditions, and by using 2 equiv. of the pyridine derivative, the reaction proceeded in approximately 60% yield. Finally, a pyridine Grignard derivative proved to be excellent for the coupling reaction in the 4-position of the pyridine.[23] Reaction of 1 equiv. of **1b** with *i*PrMgCl in THF at room temperature followed by the addition of Ts-Pro-CHO afforded the desired product **4** in 72% yield (Scheme 3). The reaction proceeded very cleanly and no additional purification was needed after work-up by extraction. ^{13}C NMR spectra of the crude product show signals for CH–OH at δ 71.26 and 71.22, respectively, which indicates that the two diastereomers were formed in equal amounts.



Scheme 3. Reagents and conditions: (1) *i*PrMgCl, THF, rt, 1.5 h; (2) Ts-Pro-CHO, rt, o.n.

Encouraged by these results, use of a Boc-protected amino aldehyde instead of the tosyl protected one was also attempted. It was found that the reaction proceeded nicely with Boc-Pro-CHO‡ providing **5** in 86% yield with a diastereomeric ratio of 1:3 according to ^1H NMR analysis. To afford the desired amino acid moiety in the 4-position, alcohol **5** was oxidized using Dess–Martin periodinane to give ketone **6** in 74% yield (Scheme 4). The optical purity of



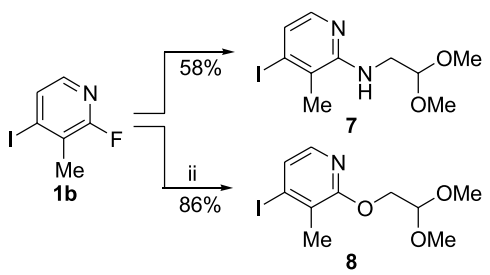
Scheme 4. Reagents and conditions: (i) (1) *i*PrMgCl, THF, rt, 1 h; (2) Boc-Pro-CHO, rt, o.n. (ii) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h.

‡ Boc-Pro-CHO was synthesized according to Ref. 22 or obtained commercially from Aldrich.

6 was confirmed by chiral HPLC analysis on a Pirkle Covalent (S,S)-Whelk-O 1 10/100 Krom Fec column using dichloromethane–isopropanol–heptane (48:4:48) as eluent. A single peak was observed in the chromatogram for **6** which was compared to a chromatogram obtained from the racemate.[§]

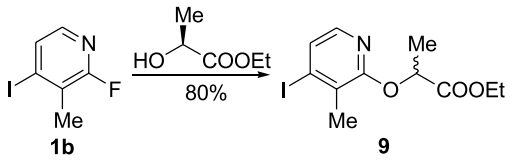
2.4. Introduction of the C-terminal amino acid moiety

The introduction of amino acid equivalents in the 2-position of the functionalized scaffold by nucleophilic substitution of fluorine was thereafter investigated. At first, the reactivity of nitrogen versus oxygen nucleophiles was compared using glycine aldehyde dimethyl acetal and the corresponding alcohol analogue (Scheme 5). It was found that the amine required quite harsh reaction conditions; the substitution was performed using the amino acetal as solvent at 140 °C. The reaction was stopped after 4.5 h when a byproduct was detected by TLC and the product **7** was isolated in 58% yield. The byproduct was isolated in 4% yield and found to be the 4-substituted derivative, i.e. the 4-iodo group had been substituted instead of the fluorine atom.[¶] The glycolaldehyde dimethylacetal was tested and found to react considerably faster than the amino analogue; after deprotonation by NaH the substitution went smoothly at room temperature in THF and the expected product **8** was isolated in 86% yield. The poor reactivity of amino acid analogues under these conditions was confirmed by a test reaction with the amino acid glycine in DMF. After 20 h at 140 °C the starting material was still intact according to TLC analysis.



Scheme 5. Reagents and conditions: (i) glycine aldehyde dimethyl acetal, 140 °C, 4.5 h. (ii) glycol aldehyde dimethyl acetal, NaH, THF, rt, o.n.

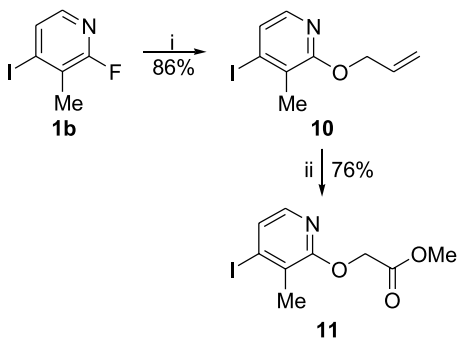
The above findings indicated that considerable problems would probably be experienced using regular amino acids as nucleophiles in the substitution at the 2-position of the scaffold. In addition, the conversion of the acetal functionality of **8** into an aldehyde or ester was unsuccessful although several different reaction conditions were explored [CrO_3/AcOH,[24] Oxone®/wet Al_2O_3,[25] trichloroisocyanuric acid,[26] AcOH/H_2O,[27] wet SiO_2/oxalic acid or H_2SO_4,[28,29] Amberlite® IR-120,[30] formic acid,[31] Amberlyst® 15,[30] $TiCl_4$/LiI,[32] *p*TsOH,[33] $BF_3{\cdot}Et_2O$/LiI,[34] ozone[35]]. The synthesis of derivatives with an ether bridge between the pyridine ring and the amino acid residue in the 2-position was therefore further explored. It was found that L-ethyl lactate could be used as nucleophile after deprotonation



Scheme 6. Reagents and conditions: NaH, THF, rt to 60 °C, o.n.

with NaH in a 0.2 M solution in THF (higher concentration caused problems with polymerization) at 60 °C (Scheme 6). It was important not to have an excess of NaH, since that resulted in deiodination of the starting material. However, even though the ether **9** was isolated in a satisfactory 80% yield, it was found both by chiral HPLC analysis and by measurement of optical rotation that the optical activity of the product was lost under these reaction conditions. To examine whether the racemization of the product was caused by the excess of nucleophile, 1 equiv. of L- and D-methyl lactate, respectively, were reacted with **1b** using KH as base. Chiral HPLC analysis (MTBE–heptane 5:95) showed that even when the reaction was stopped after 30 min at room temperature (before complete consumption of the starting material), the product was almost completely racemized (er 56:44).

It was not possible to use the ethyl ester of glycolic acid as a nucleophile together with NaH due to problems with polymerization. This was not unexpected as there is less steric hindrance in the glycolate compared to the lactate. Another route for the introduction of a glycolate ester was therefore employed. Use of allyl alcohol together with NaH in THF allowed a smooth reaction to take place at room temperature and the allyl ether **10** was isolated in 86% yield. The methyl ester **11** could then be afforded from the alkene in 76% yield by treatment with ozone and NaOH/MeOH in CH_2Cl_2 (Scheme 7).



Scheme 7. Reagents and conditions: (i) Allyl alcohol, NaH, THF, rt, 0.5 h. (ii) O_3, NaOH in MeOH, CH_2Cl_2, −78 °C, 1.5 h.

3. Conclusion

We have developed a synthetic strategy towards trisubstituted pyridine derivatives based on a functionalized scaffold that provides the possibility of selective manipulation of one position without disturbing the others. Efficient introduction of substituents in the 3- and 4-positions of the pyridine scaffold has been accomplished, whereas more work is needed to provide access to chiral amino acid derived nucleophiles suitable for substitution in the 2-position.

[§] The racemate was produced by treatment of **6** with DBU in refluxing THF.

[¶] According to ^1H NMR and ^{19}F NMR analysis.

4. Experimental

4.1. General data

THF was distilled from potassium/sodium. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 (399.53 MHz) or a JEOL Eclipse 400 (399.78 MHz) spectrometer using residual peak of solvent as internal reference; $CDCl_3$ [$CHCl_3$ δ_H 7.26, $CDCl_3$ δ_C 77.0]. TLC analysis was performed on Silica Gel F_{254} (Merck) and detection was carried out by examination under UV light and staining with phosphomolybdic acid. Flash column chromatography was performed on Silica Gel (Matrex, 60 Å, 35–70 μm, Grace Amicon). Chiral HPLC chromatography was performed on a Pirkle Covalent (S,S)-Whelk-O 1 10/100 Krom Fec column. After work-up, all organic phases were dried with $MgSO_4$. All new compounds were determined to be >95% pure by ^{1}H NMR and ^{13}C NMR spectroscopy. For the synthesis of compounds **1a** and **1b** see Ref. 3.

4.2. General procedure for the synthesis of 2-fluoro-4-iodo-3-substituted pyridine derivatives

LDA was prepared by the addition of diisopropylamine (0.63 mL, 4.48 mmol) to freshly distilled THF (10 mL) in a dry two-necked round bottomed flask kept under nitrogen atmosphere. The solution was cooled to −78 °C before 1.6 M *n*-BuLi in hexane (2.80 mL, 4.48 mmol) was added and the resulting clear, colorless solution was stirred for 15 min. 2-Fluoro-3-iodopyridine (1.00 g, 4.48 mmol) was added as a solution in THF (2 mL) whereby the reaction immediately turned bright yellow. The mixture was stirred for 1 h at −78 °C before the electrophile (4.48 mmol) was added with syringe (neat or as a solution in THF). After the indicated reaction times (see below), the mixture was quenched by the addition of H_2O and extracted into Et_2O. The pooled organic phases were washed with brine, dried and evaporated to yield the crude product.

4.2.1. 3-Benzyl-2-fluoro-4-iodo-pyridine (1c). LDA (20 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (18 mmol) as described above. After the addition of benzyl bromide (2.4 mL, 20 mmol), the reaction was allowed to reach room temperature while stirred over night. Work-up as described above afforded a crude product which was purified by flash chromatography (EtOAc–heptane 1:10) to yield **1c** (4.0 g, 71%) as a yellow oil; δ ^{1}H NMR ($CDCl_3$) 7.75–7.71 (m, 1H), 7.67–7.63 (m, 1H), 7.33–7.20 (m, 5H), 4.19 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 160.68 (d, J_{C-F}=242.2 Hz), 145.63 (d, J_{C-F}=16.2 Hz), 137.26, 132.69 (d, J_{C-F}=4.4 Hz), 128.53 (4 C:s), 127.12 (d, J_{C-F}=32.3), 126.68, 114.88 (d, J_{C-F}=4.0 Hz), 38.63; IR (neat) 2360 (w), 1579, 1544, 1441, 1394 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_9FIN$ $(M+H)^+$ 313.9842, found 313.9845.

4.2.2. 1-(2-Fluoro-4-iodo-pyridin-3-yl)-2-methyl-propan-1-ol (1e). LDA (4.48 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (4.48 mmol) as described above. After the addition of isobutyraldehyde (0.41 mL, 4.48 mmol), the reaction was stirred for 2 h at −78 °C. Work-up as described above afforded a crude product which was purified by flash chromatography (EtOAc–heptane 1:10 then 1:5) to yield **1e** (1.27 g, 96%) as a non-viscous, colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, 1H, *J*=5.3 Hz), 7.58 (d, 1H, *J*=5.3 Hz), 4.56 (d, 1H, *J*=9.1 Hz), 3.03 (br s, 1H), 2.24 (m, 1H), 1.11 (d, 3H, *J*=6.7 Hz), 0.75 (d, 3H, *J*=6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 159.61 (d, J_{C-F}=244.5 Hz), 145.75 (d, J_{C-F}=16.8 Hz), 132.94 (d, J_{C-F}=4.0 Hz), 128.65 (d, J_{C-F}=27.6 Hz), 113.01 (d, J_{C-F}=5.4 Hz), 81.36 (d, J_{C-F}=3.7 Hz), 33.66 (d, J_{C-F}=2.7 Hz), 19.20, 18.97; IR (CH_2Cl_2 cast) 3389 (br), 3083 (w), 2961, 2871, 1581, 1539, 1444, 1401 cm^{-1}; HRMS (EI+) calcd for $C_9H_{11}FINO$ $(M)^+$ 294.9869, found 294.9871.

4.2.3. 2-Fluoro-4-iodo-3-(2-methyl-allyl)-pyridine (1f). LDA (4.48 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (4.48 mmol) as described above. After the addition of 3-bromo-2-methyl-1-propene (0.47 mL, 4.48 mmol), the reaction was stirred for 2 h at −78 °C and then for 2.5 h at −45 °C. Work-up as described above afforded 1.22 g of a yellow-brown clear light crude oil. Purification by distillation at reduced pressure afforded **1f** (1.15 g, 93%) as a non-viscous, colorless oil, which solidified upon standing: mp 38–40 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, 1H, *J*=5.2 Hz, 0.7 Hz), 7.60 (d, 1H, *J*=5.2 Hz), 4.80 (m, 1H), 4.41 (m, 1H), 3.44 (s, 2H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.52 (d, J_{C-F}=242.5 Hz), 145.42 (d, J_{C-F}=15.8 Hz), 140.60, 132.46 (d, J_{C-F}=4.4 Hz), 125.86 (d, J_{C-F}=32.3 Hz), 115.13 (d, J_{C-F}=4.4 Hz), 112.09, 40.60 (d, J_{C-F}=1.3 Hz), 22.90; IR (CH_2Cl_2 cast) 3082 (w), 2974 (w), 1581, 1547, 1444, 1403 cm^{-1}; HRMS (CI) calcd for $C_9H_{10}FIN$ $(M+H)^+$ 277.9842, found 277.9837. Anal. calcd for C_9H_9FIN: C, 39.1; H, 3.3; N, 5.1. Found: C, 39.3; H, 3.4; N, 5.2.

4.2.4. 1-(2-Fluoro-4-iodo-pyridin-3-yl)-ethanol (1g). LDA (0.49 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (0.45 mmol) as described above. After the addition of acetaldehyde (0.028 mL, 0.49 mmol), the reaction was stirred for 2 h at −78 °C. Work-up as described above afforded a crude oil which was purified by flash chromatography (EtOAc–heptane 1:5) to yield **1g** (62 mg, 51%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, *J*=5.2 Hz), 7.64 (d, 1H, *J*=5.2 Hz), 5.16 (q, 1H, *J*=6.7 Hz), 1.59 (dd, 3H, *J*=6.7, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 159.99 (d, J_{C-F}=242.9 Hz), 146.14 (d, J_{C-F}=17.2 Hz), 132.97 (d, J_{C-F}=4.4 Hz), 129.72 (d, J_{C-F}=27.3 Hz), 110.97 (d, J_{C-F}=5.4 Hz), 72.92 (d, J_{C-F}=2.7 Hz), 22.23 (d, J_{C-F}=2.4 Hz); IR (CH_2Cl_2 cast) 3360 (br), 3084 (w), 2976, 2929, 1580, 1546, 1443, 1402 cm^{-1}; HRMS (FAB+) calcd for C_7H_8FINO $(M+H)^+$ 267.9635, found 267.9641.

4.2.5. 3-Allyl-2-fluoro-4-iodo-pyridine (1i). LDA (4.93 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (4.48 mmol) as described above. After the addition of allyl bromide (0.43 mL, 4.93 mmol), the reaction was allowed to reach room temperature over night. Work-up as described above afforded a brown crude oil which was purified by distillation under reduced pressure to afford **1i** (1.03 g, 87%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1H, *J*=5.2 Hz), 7.62 (d, 1H, *J*=5.2 Hz), 5.86 (ddt, 1H, *J*=16.6, 10.2, 6.2 Hz), 5.15–5.07 (m, 2H), 3.55 (app dq, 2H, *J*=6.2, 1.4 Hz); ^{13}C NMR ($CDCl_3$) δ 160.46 (d, J_{C-F}=242.8 Hz), 145.46 (d, J_{C-F}=15.8 Hz), 132.51 (d,

J_{C-F}=4.7 Hz), 132.46, 125.98 (d, J_{C-F}=32.3 Hz), 117.19, 114.25 (d, J_{C-F}=4.4 Hz), 37.20 (d, J_{C-F}=1.4 Hz); IR (CH_2Cl_2 cast) 3303 (w), 3081, 2981, 2921, 1639, 1580, 1544, 1444, 1401 cm^{-1}; HRMS (FAB+) calcd for C_8H_8FIN $(M+H)^+$ 263.9685, found 263.9697.

4.2.6. Methyl 2-(2-fluoro-4-iodo-pyridin-3-yl)-acetate (1k). The allyl derivative **1i** (24 mg, 0.091 mmol) was dissolved in CH_2Cl_2 (2 mL). NaOH (0.46 mmol) was added as a 2.5 M solution in MeOH and the reaction was cooled to −78 °C, whereafter ozone was passed through the solution which immediately turned orange. After 15 min, the solution turned blue and the ozone generator was switched off to allow oxygen to pass through the reaction mixture until the color disappeared. After addition of H_2O–Et_2O (1:1, 2 mL) the reaction was allowed to reach room temperature. The mixture was extracted into Et_2O, the combined organic phases were washed with brine, dried and evaporated to afford a crude oil which was purified by flash chromatography (EtOAc–heptane 1:9) to yield **1k** (19 mg, 71%) as a white solid; ^1H NMR ($CDCl_3$) δ 7.78 (d, 1H, J=5.2 Hz), 7.65 (d, 1H, J=5.2 Hz), 3.87 (s, 2H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.05, 160.64 (d, J_{C-F}= 243.5 Hz), 146.52 (d, J_{C-F}=15.8 Hz), 132.39 (d, J_{C-F}= 4.0 Hz), 121.65 (d, J_{C-F}=32.7 Hz), 115.16, 52.52, 38.70; IR (CH_2Cl_2 cast) 2951 (w), 1737 (s), 1584, 1540, 1435, 1399 cm^{-1}; HRMS (FAB+) calcd for $C_8H_8FINO_2$ $(M+H)^+$ 295.9584, found 295.9579.

4.3. 2-Fluoro-3-methyl-4-trimethylstannyl-pyridine (2)

The pyridine derivative **1b** (3.1 g, 13 mmol) was dissolved in THF (30 mL) and the solution was cooled to −78 °C. BuLi (1.6 M, 9.1 mL) was added dropwise and the reaction was stirred for 1 h before trimethyl tin chloride (2.9 g, 14 mmol) was added as a solution in THF (15 mL). The reaction was stirred for 1 h before it was allowed to reach room temperature. H_2O was added and the mixture was extracted into Et_2O, dried and evaporated to yield a crude yellowish oil which was purified by sublimation under vacuum to collect most of the starting material as crystals, followed by flash chromatography (CH_2Cl_2–MeOH–hexane 8:1:10) of the remaining oil to afford **2** (1.9 g, 52%) as an oil; ^1H NMR ($CDCl_3$) δ 7.95 (d, 1H, J=4.9 Hz), 7.17 (dd, 1H, J=4.9, 2.6 Hz), 2.33 (d, 3H, J=1.5 Hz), 0.38 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 161.73 (d, J_{C-F}=243.5 Hz), 159.44, 143.42 (d, J_{C-F}=12.5 Hz), 128.25 (d, J_{C-F}= 4.0 Hz), 125.51 (d, J_{C-F}=26.9 Hz), 16.91 (d, J_{C-F}= 1.7 Hz), −8.72 (3 C:s); HRMS (FAB+) calcd for $C_9H_{15}FNSn$ $(M+H)^+$ 276.0211, found 276.0215.

4.4. 2-Fluoro-3-methyl-4-tributylstannyl-pyridine (3)

The pyridine derivative **1b** (2.2 g, 8.0 mmol) was dissolved in THF (30 mL) and the solution was cooled to −78 °C. BuLi (1.6 M, 5.5 mL) was added and the reaction was stirred for 1 h before tributyl tin chloride (2.2 mL, 8.8 mmol) was added. The reaction was stirred for 1.5 h before it was quenched with H_2O (50 mL) and allowed to reach room temperature. The mixture was extracted into Et_2O, dried and evaporated to yield a crude semi-solid which was purified by flash chromatography (Et_2O–hexane 1:19) to afford **3** (2.4 g, 75%) as a non-viscous, colorless oil; ^1H NMR ($CDCl_3$) δ 7.93 (d, 1H, J=4.7 Hz), 7.15 (dd, 1H, J=4.7, 2.6 Hz), 2.30 (d, 3H, J=1.6 Hz), 1.56–1.45 (m, 6H), 1.32 (sextet, 6H, J=7.3 Hz), 1.16–1.09 (m, 6H), 0.88 (t, 9H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 161.78 (d, J_{C-F}= 243.5 Hz), 160.01 (d, J_{C-F}=1.0 Hz), 143.29 (d, J_{C-F}= 12.5 Hz), 128.89 (d, J_{C-F}=4.0 Hz), 125.62 (d, J_{C-F}= 26.6 Hz), 28.95 (3 C:s), 27.92 (3 C:s), 17.25 (d, J_{C-F}= 1.7 Hz), 13.56 (3 C:s), 10.29 (3 C:s); HRMS (FAB+) calcd for $C_{18}H_{33}FNSn$ $(M+H)^+$ 402.1619, found 402.1624.

4.5. 1-(2-Fluoro-3-methyl-pyridin-4-yl)-1-[(*S*)-1-(*p*-toluylsulfonyl)-pyrrolidin-2-yl]methanol (4)

The pyridine derivative **1b** (100 mg, 0.42 mmol) was dissolved in freshly distilled THF (1 mL) and kept under nitrogen atmosphere. Isopropyl magnesium chloride (0.21 mL, 0.42 mmol, 2.0 M in THF) was added with syringe. A white precipitate was formed immediately. After 1.5 h, Ts-Pro-CHO (0.11 g, 0.42 mmol) was added with syringe as a solution in THF (1 mL). The reaction mixture turned clear and was stirred at room temperature over night before it was quenched by the addition of H_2O (2 mL). The mixture was extracted into CH_2Cl_2, dried and evaporated to yield **4** (111 mg, 72%) as a solid with dr 1:1 according to ^{13}C NMR analysis; δ ^1H NMR ($CDCl_3$) 7.96 (d, 1H, J=5.2 Hz), 7.67 (d, 2H, J=8.3 Hz), 7.38 (d, 1H, J=5.2 Hz), 7.28 (d, 2H, J=8.3 Hz), 5.55 (d, 1H, J=2.0 Hz), 3.85 (br s, 1H), 3.66–3.60 (m, 1H), 3.48–3.40 (m, 1H), 3.34–3.26 (m, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 1.91–1.78 (m, 2H), 1.28–1.11 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 162.04 (d, J_{C-F}= 236.8 Hz), 153.34 (d, J_{C-F}=5.4 Hz), 144.02 (d, J_{C-F}= 15.2 Hz), 143.85, 133.67, 129.78 (2 C:s), 127.30 (2 C:s), 119.00 (d, J_{C-F}=3.7 Hz), 116.06 (d, J_{C-F}=31.7 Hz), 71.26 (CH–OH), 71.22 (CH–OH), 62.94, 50.34, 24.84, 24.71, 21.35, 10.54; IR (CH_2Cl_2 cast) 3297 (br), 2953, 2872, 1611, 1567, 1453, 1410, 1344, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{22}FN_2O_3S$ $(M+H)^+$ 365.1335, found 365.1333.

4.6. 1-((*S*)-1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-1-[(2-fluoro-3-methyl-pyridin-4-yl)]-methanol (5)

The pyridine derivative **1b** (100 mg, 0.42 mmol) was dissolved in freshly distilled THF (1 mL) and kept under nitrogen atmosphere. Isopropyl magnesium chloride (0.21 mL, 0.42 mmol, 2.0 M in THF) was added with syringe. A white precipitate was formed immediately. After 1 h, Boc-Pro-CHO (84 mg, 0.42 mmol) was added as a solution in THF (0.5 mL). The reaction mixture turned clear and was stirred at room temperature over night before it was quenched by the addition of H_2O. The mixture was extracted into Et_2O, the combined organic phases were washed with brine, dried and evaporated to yield a crude yellow oil (dr 1:3 according to ^1H NMR analysis). Purification by flash chromatography (EtOAc–heptane 1:3 then 1:1) afforded the diastereomeric alcohols of **5** (113 mg, 86% combined yield) as a colorless oil. Partial separation allowed the isolation of respective pure isomer for characterization: *Major isomer* $[\alpha]_D$=−14.2 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.99 (s, 1H), 7.26 (s, 1H), 4.84 (d, 1H, J=7.9 Hz), 4.18–4.09 (m, 1H), 3.50–3.23 (m, 2H), 2.26 (s, 3H), 1.83–1.57 (m, 3H), 1.47 (s, 9H), 1.38–1.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 162.24 (d, J_{C-F}=237.1), 158.23, 154.46 (d, J_{C-F}=4.7 Hz), 144.32 (d, J_{C-F}=

15.5 Hz), 120.17, 117.41 (d, J_{C-F}=31.7 Hz), 81.16, 74.12. 63.55, 47.64, 28.31 (3 C:s), 28.09, 24.02, 10.83; IR (CH_2Cl_2 cast) 3372 (br), 3054 (w), 2977, 2934, 2886, 2360, 2341, 1682, 1404 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{24}FN_2O_3$ $(M+H)^+$ 311.1771, found 311.1768. *Minor isomer* $[\alpha]_D$=−34.8 (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.33 (s, 1H), 5.41 (s, 1H), 4.27–3.89 (m, 1H), 3.71–3.01 (m, 3H), 2.31 (s, 3H), 1.99–1.56 (m, 4H), 1.52–1.48 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 162.16 (d, J_{C-F}=237.8 Hz), 155.85 (br), 153.86, 143.93 (d, J_{C-F}=12.1 Hz), 119.46, 116.42 (br), 80.49, 70.27, 61.21 (br), 48.09, 28.52 (3 C:s), 25.76, 24.05, 10.94; IR (CH_2Cl_2 cast) 3371 (br), 2978, 2921, 2889, 2358, 2339, 1692, 1403 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{24}FN_2O_3$ $(M+H)^+$ 311.1771, found 311.1773.

4.7. (*S*)-4-(1-*tert*-Butoxycarbonylpyrrolidin-2-oyl)-2-fluoro-3-methyl-pyridine (6)

The diastereomeric mixture of **5** (30 mg, 0.097 mmol) was dissolved in dry CH_2Cl_2 (1 mL). Dess–Martin periodinane (0.41 mL, 0.19 mmol) was added as a 15% wt solution in CH_2Cl_2. The reaction was stirred for 3 h at room temperature before it was quenched with $Na_2S_2O_3$ (0.28 g, 1.13 mmol) dissolved in $NaHCO_3$ (aq. sat.). The mixture was extracted into Et_2O, the combined organic phases were washed with $NaHCO_3$ (aq. sat.) and brine, dried and evaporated to yield **6** (22 mg, 74%) as an oil: $[\alpha]_D$=−3.5 (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) δ major [minor] rotamer (ratio 3:2) 8.11 [8.16] (d, 1H, *J*=5.1 Hz), 7.40 [7.27] (d, 1H, *J*=5.1 Hz), 4.94–4.85 (m, 1H), 3.71–3.39 (m, 2H), 2.31 (s, 3H), 2.23–2.11 (m, 1H), 2.03–1.76 (m, 3H), 1.44 [1.38] (s, 9H); ^{13}C NMR ($CDCl_3$) δ major [minor] rotamer (ratio 3:2) 202.39 [200.69], 162.72 [162.87] (d, J_{C-F}=239.8 Hz), 154.48 [153.52], 149.32 [148.47], 144.68 [144.94] (d, J_{C-F}=14.8 Hz), 119.09 [118.85], 118.40 [118.08], 80.13 [80.42], 63.85, 46.82 [46.67], 28.82 [29.37], 28.33 (3 C:s), 24.32 [23.11], 11.35 [11.54]; IR (CH_2Cl_2 cast) 3038 (w), 2977, 2934, 2882, 1693, 1602, 1556, 1402 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{22}FN_2O_3$ $(M+H)^+$ 309.1614, found 309.1617. Chiral HPLC using CH_2Cl_2–*i*PrOH–heptane (48:4:48) as eluent, retention time 5.1 min.

The racemate of **6** was produced by treating **6** (2 mg, 6.5 μmol) with DBU (10 μL, 65 μmol) in refluxing THF for 7 h: Chiral HPLC using CH_2Cl_2–*i*PrOH–heptane (48:4:48) as eluent, retention time 4.3 and 5.1 min, respectively.

4.8. 2-(2,2-Dimethoxyethylamino)-4-iodo-3-methyl-pyridine (7)

The pyridine derivative **1b** (0.10 g, 0.42 mmol) was dissolved in glycine aldehyde dimethyl acetal (0.23 mL, 2.1 mmol) and heated to 140 °C. After 1.5 h, more amine (0.23 mL, 2.1 mmol) was added. The reaction was stopped after 4.5 h when the formation of a by-product was detected by TLC. After cooling, the mixture was diluted with CH_2Cl_2 (5 mL) and washed with 0.05 M HCl, H_2O and brine. The organic phase was dried and evaporated to yield a brown solid which was purified by flash chromatography (CH_2Cl_2–MeOH–hexane 5:1:20) to afford **7** (79 mg, 58%) as a white semi-solid; δ ^1H NMR ($CDCl_3$) 7.55 (d, 1H, *J*=5.3 Hz), 7.03 (d, 1H, *J*=5.3 Hz), 4.77–4.55 (m, 1H), 4.52 (t, 1H, *J*=5.5 Hz), 3.59 (app t, 2H, *J*=5.5 Hz), 3.41 (s, 6H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.72, 145.34, 123.65, 120.12, 111.87, 102.80, 54.25 (2 C:s), 43.31, 21.80; IR (CH_2Cl_2 cast) 3399 (w), 2978 (w), 2936 (w), 2360, 2340, 1691, 1567, 1398 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{16}IN_2O_2$ $(M+H)^+$ 323.0257, found 323.0232.

4.9. 2-(2,2-Dimethoxy-ethoxy)-4-iodo-3-methyl-pyridine (8)

Glycol aldehyde dimethyl acetal (1.1 g, 10 mmol) was dissolved in THF (2.5 mL) and NaH (0.25 g, 5.8 mmol, 55% in mineral oil) was added carefully. After the gas evolution ceased, the pyridine derivative **1b** (0.50 g, 2.1 mmol) was added as a solution in THF (2.5 mL). The reaction was stirred over night before it was quenched by the addition of H_2O and extracted into CH_2Cl_2. The combined organic phases were dried and evaporated to yield a crude oil which was purified by flash chromatography (EtOAc–heptane 1:10) to afford **8** (0.59 g, 86%) as a non-viscous, colorless oil; ^1H NMR ($CDCl_3$) δ 7.56 (d, 1H, *J*=5.3 Hz), 7.29 (d, 1H, *J*=5.3 Hz), 4.75 (t, 1H, *J*=5.4 Hz), 4.34 (d, 2H, *J*=5.4 Hz), 3.43 (s, 6H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.39, 143.85, 127.66, 125.17, 112.89, 101.74, 65.34, 53.89 (2 C:s), 20.60; IR (CH_2Cl_2 cast) 3042 (w), 2952, 2831, 1563, 1445, 1411, 1386, 1135, 1077 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{15}INO_3$ $(M+H)^+$ 324.0097, found 324.0099.

4.10. (*R*,*S*)-Ethyl 2-(4-Iodo-3-methyl-pyridin-2-yloxy)-propanoate (9)

L-Ethyl lactate (2.5 g, 21 mmol) was dissolved in THF (100 mL) and 55% NaH in mineral oil (0.46 g, 10 mmol) was added carefully. The reaction was allowed to stir until the gas evolution ceased (almost 2 h) and the solution was clear with no solid particles before the pyridine derivative **1b** (1.0 g, 4.2 mmol) was added as a solution in THF (15 mL). The reaction was heated to 60 °C and allowed to stir over night before it was cooled to room temperature, quenched with H_2O and extracted into Et_2O. The combined organic phases were washed with brine, dried and evaporated to yield a crude oil which was purified by flash chromatography (CH_2Cl_2–MeOH–heptane 5:1:50) to afford the racemate **9** (1.1 g, 80%) as a non-viscous, colorless oil; δ ^1H NMR ($CDCl_3$) 7.49 (d, 1H, *J*=5.3 Hz), 7.27 (d, 1H, *J*=5.3 Hz), 5.23 (q, 1H, *J*=7.0 Hz), 4.17 (q, 2H, *J*=7.1 Hz), 2.37 (s, 3H), 1.59 (d, 3H, *J*=7.0 Hz), 1.22 (t, 3H, *J*=7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.15, 159.64, 143.55, 127.83, 124.87, 112.98, 70.36, 60.78, 20.45, 17.53, 14.03; IR (CH_2Cl_2 cast) 3044 (w), 2984, 2938, 1752, 1561, 1402, 1177, 1098 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{15}INO_3$ $(M+H)^+$ 336.0097, found 336.0092.

4.11. 2-Allyloxy-4-iodo-3-methyl-pyridine (10)

Allyl alcohol (0.50 mL, 7.4 mmol) was dissolved in THF (4 mL) and NaH (0.14 g, 3.6 mmol, 60% in mineral oil) was added carefully. After the gas evolution ceased the pyridine derivative **1b** (0.35 g, 1.5 mmol) was added as a solution in THF (2 mL). The reaction was allowed to stir at room temperature for 0.5 h before it was quenched with H_2O and extracted into EtOAc. The combined organic phases were washed with brine, dried and evaporated to yield a crude product which was purified by flash chromatography

(EtOAc–heptane 1:20) to afford **10** (0.35 g, 86%) as a colorless oil; δ ^{1}H NMR ($CDCl_3$) 7.57 (d, 1H, J=5.3 Hz), 7.28 (d, 1H, J=5.3 Hz), 6.08 (ddt, 1H, J=17.2, 10.4, 5.2 Hz), 5.38 (ddt, 1H, J=17.2, 1.6, 1.6 Hz), 5.23 (ddt, 1H, J=10.4, 1.6, 1.6 Hz), 4.82 (ddd, 2H, J=5.2, 1.6, 1.6 Hz), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.51, 143.86, 133.42, 127.35, 125.08, 116.94, 112.76, 66.86, 20.60; IR (CH_2Cl_2 cast) 3080 (w), 2988 (w), 2936, 1563, 1401, 1334, 1259, 1175, 1007 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{11}INO$ $(M+H)^+$ 275.9885, found 275.9883.

4.12. Methyl (4-iodo-3-methyl-pyridin-2-yloxy)-acetate (11)

The pyridine derivative **10** (52 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (2 mL) and NaOH in MeOH (2.5 M, 0.40 mL) was added. The solution was cooled to −78 °C before ozone was bubbled through. The reaction turned dark-yellow immediately and the color disappeared gradually until it was clear and colorless with a yellow precipitate after 80 min. The ozone generator was switched off after another 10 min when the reaction turned blue and O_2 was allowed to pass through until the solution was colorless. H_2O–Et_2O (1:1, 2 mL) was added and the mixture was allowed to reach room temperature. Additional H_2O was added and the reaction mixture was extracted into Et_2O. The combined organic phases were washed with brine, dried and evaporated to yield **11** (44 mg, 76%) as an oil; δ ^{1}H NMR ($CDCl_3$) 7.53 (d, 1H, J=5.3 Hz), 7.32 (d, 1H, J=5.3 Hz), 4.88 (s, 2H), 3.75 (s, 3H), 2.39 (s, 3H); δ ^{13}C NMR ($CDCl_3$) 169.61, 159.53, 143.65, 128.26, 125.11, 113.22, 62.74, 51.98, 20.49; IR (CH_2Cl_2 cast) 2998 (w), 2951, 1762, 1567, 1428, 1397, 1215, 1175, 1073 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{11}INO_3$ $(M+H)^+$ 307.9784, found 307.9792.

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Synthesis and optical properties of (a)chiral terpyridine–ruthenium complexes

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Abstract—Chiral terpyridine ligands have been synthesized and characterized. By applying Ru(III)/Ru(II) chemistry, symmetrical as well as asymmetrical bis-terpyridine ruthenium(II) complexes were obtained. These materials were fully characterized and their optical properties investigated. While the chiral metal complexes revealed no Cotton effect in good solvents such as chloroform, CD-measurements in dodecane showed an effect in both ligand and MLCT regions, suggesting chirality transfer from the lateral alkyl chains to the complex core. This behavior points to the formation of supramolecular aggregates in dodecane. Furthermore, the analogous achiral ligand and its corresponding ruthenium(II) complexes were prepared.

1. Introduction

Supramolecular chemistry,[1] especially the self-assembly of functional molecules into nanostructures, is of special interest concerning potential applications in novel kinds of molecular devices. Non-covalent interactions such as hydrogen-bonding,[2] $\pi-\pi$-interaction[3] or metal coordination[4‡] are utilized to form various types of aggregates. Chiral non-covalently aggregated systems are a special class of nanostructures. Among the recent examples are dimers of ureido-triazines carrying chiral trialkoxybenzene chains, formed by self-complementary quadruple hydrogen bonding, which subsequently assembled to helical columnar aggregates in apolar solvents like dodecane.[5]

For coordination chemistry, terpyridines are of special interest due to their ability of forming stable complexes with many transition metal ions. Such complexes possess interesting photophysical, electrochemical and photochemical properties[6,7] and they allow the construction of extended supramolecular architectures. A few attempts to obtain chiral terpyridine complexes have already been achieved.[8,9] However, in most of these systems, the chiral groups were directly connected to the aromatic pyridine rings by fused terpene or pinene rings. In this way, distorted terpyridine moieties were obtained leading therefore to chiral distorted metal complexes. In addition, attempts have been undertaken to introduce chirality into moieties, which are connected via a single bond to the terpyridine.[10] However, transfer of chiral information to the complex core was minimal.

In our approach, the chirality is located in the lateral alkyl chains of a 4′-phenylethynyl substituted terpyridine.[11] In this contribution we describe the synthesis of the chiral and the achiral terpyridine ligands and the subsequent formation of corresponding symmetric and asymmetric ruthenium(II) complexes as well as the study of their supramolecular helical aggregation behavior (for a preliminary communication see Ref. [11]).

2. Results and discussion

In order to introduce chirality into terpyridine metal complexes, which have the ability to form aggregates in non-polar solvents, a phenylethyne bearing chiral alkyl side chains[12] (**1**) was reacted with 4′-bromo-2,2′:6′,2″-terpyridine

Keywords: CD-spectroscopy; Ruthenium; Supramolecular chemistry; Terpyridine complex.
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‡ It has to be mentioned that metal coordination bonds, also depending on the metal ion used, possess a certain covalent character.

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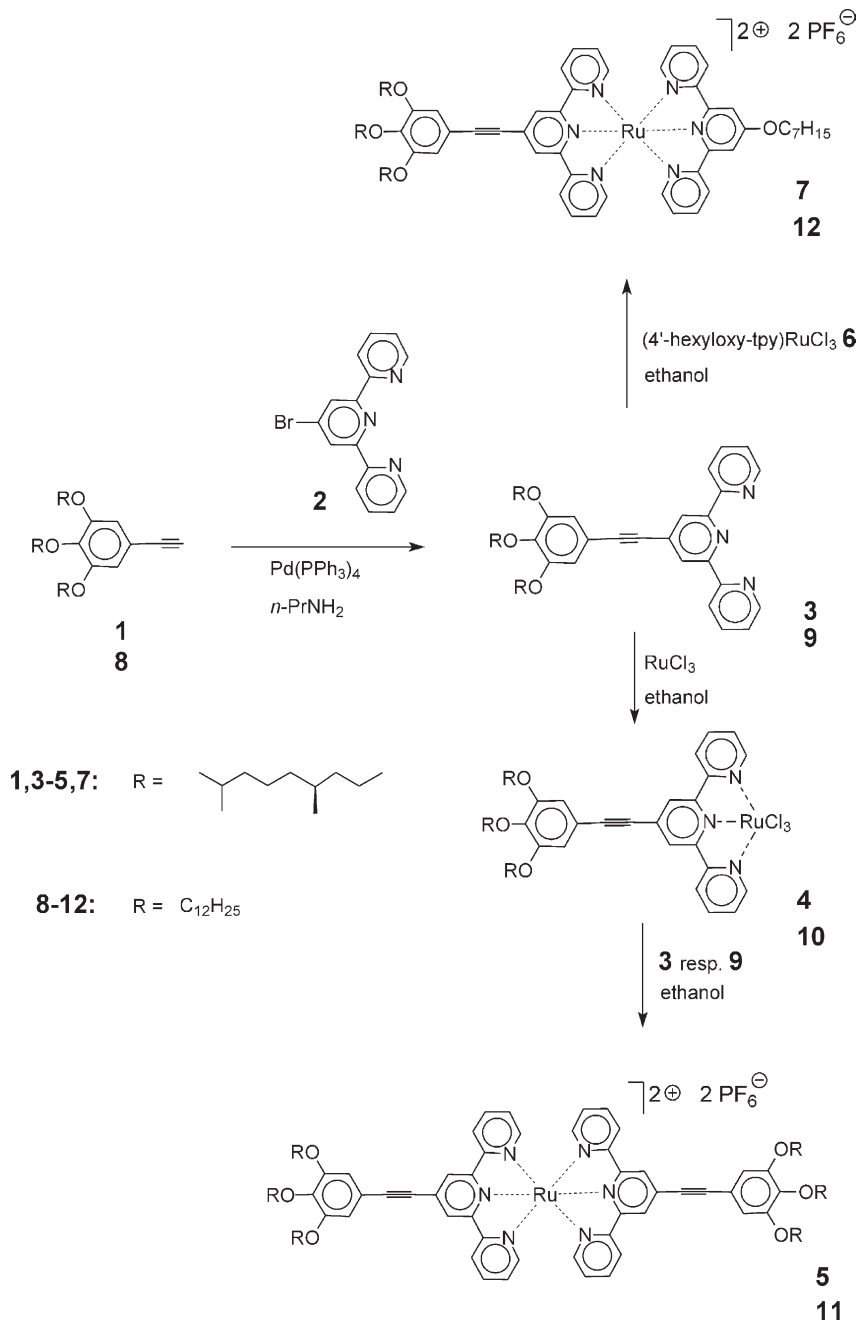

Scheme 1. Schematic representation of the synthesis of the ruthenium(II) complexes **5**, **7**, **11** and **12**.

2 utilizing the Sonogashira cross-coupling reaction[13] (Scheme 1). The resulting compound 4′-[3,4,5-tris-(3,7-dimethyl-octyloxy)-phenylethynyl]-2,2′:6′,2″-terpyridine (**3**) was purified by column chromatography (alumina) and characterized by NMR, UV–vis, MALDI-TOF-MS and elemental analysis. Subsequently, the corresponding ruthenium(II)-complex was synthesized. Ruthenium(II) was chosen due to the high stability and the interesting photophysical properties of such complexes. The complexation reaction was performed in two steps: first, the ruthenium(III) monocomplex **4** was obtained as intermediate by reacting ligand **3** with $RuCl_3$ by precipitation. In the second step, another equivalent of **3** was applied under reductive conditions (refluxing ethanol containing *N*-ethylmorpholine). Compound **5** was precipitated in water (after exchange of the counterions by addition of NH_4PF_6) and subsequently purified by preparative size exclusion on a Bio-Beads SX-1 column.

Application of the ruthenium(III/II) chemistry leads in a directed way in the same type of reaction as described for **5** to asymmetric terpyridine complexes. For this purpose, the Ru(III)-mono-complex of heptylterpyridine **6**[14] was reacted with compound **3**, yielding the asymmetric complex **7** under the same conditions as described above. The complex was purified by recrystallization from acetonitrile/diethyl ether. Using the same synthesis strategy as for compound **5** and **7**, analogous symmetric and asymmetric complexes (**11** and **12**) were prepared, where the chiral alkyl chains were replaced by achiral

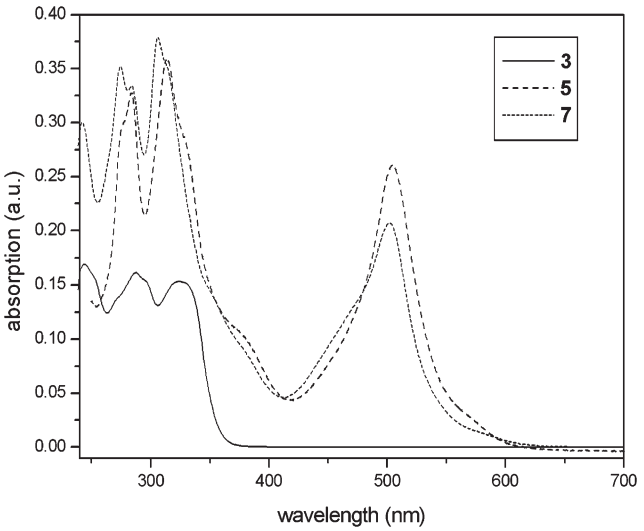

Figure 1. UV–vis spectra of **3**, **5** and **7** (in chloroform).

dodecyl-groups (see also Refs. [12,15] for tris-dodecyl-oxy phenylacetylenes).

The UV–vis absorption spectra of the complexes **5**, **7**, **11** and **12** revealed intense absorption bands between 270 and 300 nm, which derived from the ligand-centered $\pi-\pi^*$ transitions associated with the electrons of the aromatic systems. The bathochromic shift of these bands confirms for all cases the successful complex formation. Moreover, metal to ligand charge transfer (MLCT) transitions were observed for the ruthenium(II) complexes at around 500 nm (Fig. 1).

The successful formation of the complexes could also be shown by ^{1}H NMR spectroscopy (Fig. 2). The signals for the aromatic protons of the terpyridine moieties and the phenyl ring were detected between 7 and 9 ppm. The most characteristic evidence for the formation of bis-terpyridine ruthenium(II) complexes is the upfield shift of the peaks for the 6,6″-protons when comparing the spectra of the ligands with the corresponding complexes. The OCH_2-signals could be found at 4–4.5 ppm and the aliphatic resonances were

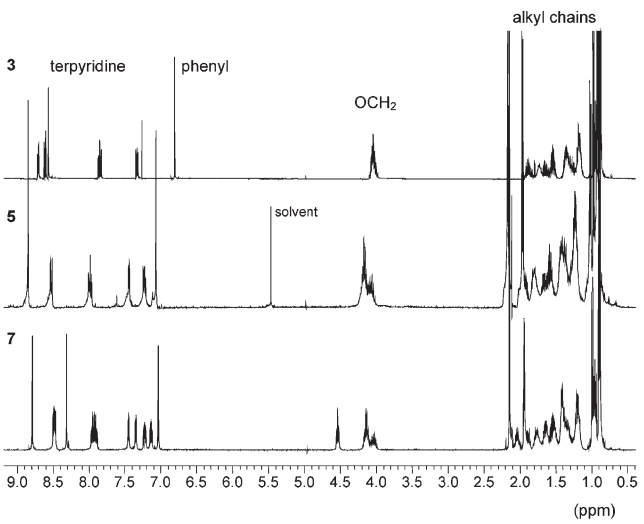

Figure 2. ^{1}H NMR spectra of ligand **3** (in chloroform) and the complexes **5** and **7** (in acetonitrile).

observed at highest field between 0.8 and 2.3 ppm. Utilizing ^{1}H,^{1}H-COSY-NMR spectroscopy, the pattern of the asymmetric complexes could be interpreted and the signals assigned (see Fig. 3 and Section 3). MALDI-TOF mass spectrometry is an excellent tool for proving the existence of such complexes.[16] With this technique it is possible to detect the unfragmented complex cations (beside fragments and matrix adducts).[17] Also ion pairs of the cation with one PF_6-counterion were detected for **5** and **7** (Fig. 4). All observed species carry the charge +1, which is usually found for this type of complexes.[18] Furthermore, in electrospray-mass spectrometry both the singly as well as the doubly charged species were observed.

In order to investigate the chiral characteristics of the ligand as well as the complexes, UV–vis and circular dichroism (CD) measurements were performed. In acetonitrile and in chloroform no CD effect was found, suggesting that both the ligand and the complexes are molecularly dissolved and therefore no transfer of chiral information to the metal-ligand core exists.

In the bulk the ligands and their metal complexes show no liquid-crystalline behavior since they have well defined melting point. To study the formation of chiral aggregates in solution, dodecane as a less good solvent for the terpyridine metal complexes was employed in order to stimulate aggregation of the complexes.[5] UV–vis spectroscopy of **5** in dodecane revealed a small shift of the absorption bands from 505 nm (chloroform) to 502 nm (dodecane). CD spectroscopy was performed on the ligand **3** as well as on the ruthenium(II) complexes **5** and **7**. In the case of the free ligand, no Cotton effect was observed, corresponding to an absence of aggregation processes. In contrast, the complexes showed a strong CD effect (Fig. 5). The effect appeared at the absorption bands of the ligand as well as the MLCT-bands. This suggests that the chirality of the side-chains is transferred to the metal center, inducing chirality into the whole complex. Due to the aggregation, the geometry of the ligand coordinated to the metal center is distorted in a chiral fashion. Such a behavior of a CD effect initiated by aggregation, involving metal centers, has been found recently in helical platinum 'wires'.[19] In the case of the symmetric complex **5**, a bisignate CD effect was found: At the maxima of the UV–vis absorption bands, the CD signals are changing from positive to negative values, with positive values at higher and negative values at lower wavelengths than the absorption maxima. This behavior indicates an exciton coupling and suggests the presence of right-handed helical aggregates for the complex **5**.[19,20] On the other hand, complex **7** possesses only one chiral ligand and furthermore lacks one moiety that is able to undergo stacking. Therefore, chiral aggregates of a different architecture can be expected, as shown by the different (non-bisignate) CD spectrum of compound **7**, where no exciton coupling was found. In addition, a different UV–vis behavior was observed: a small shift of the MLCT-band from 502 nm (in chloroform) to 504 (dodecane) was found.

CD spectroscopy at higher temperatures (up to 110 °C) revealed only a minor decrease of the intensity of the CD signal (Fig. 6), showing that the aggregates of complexes **5** and **7** are stable even at elevated temperatures. The stepwise

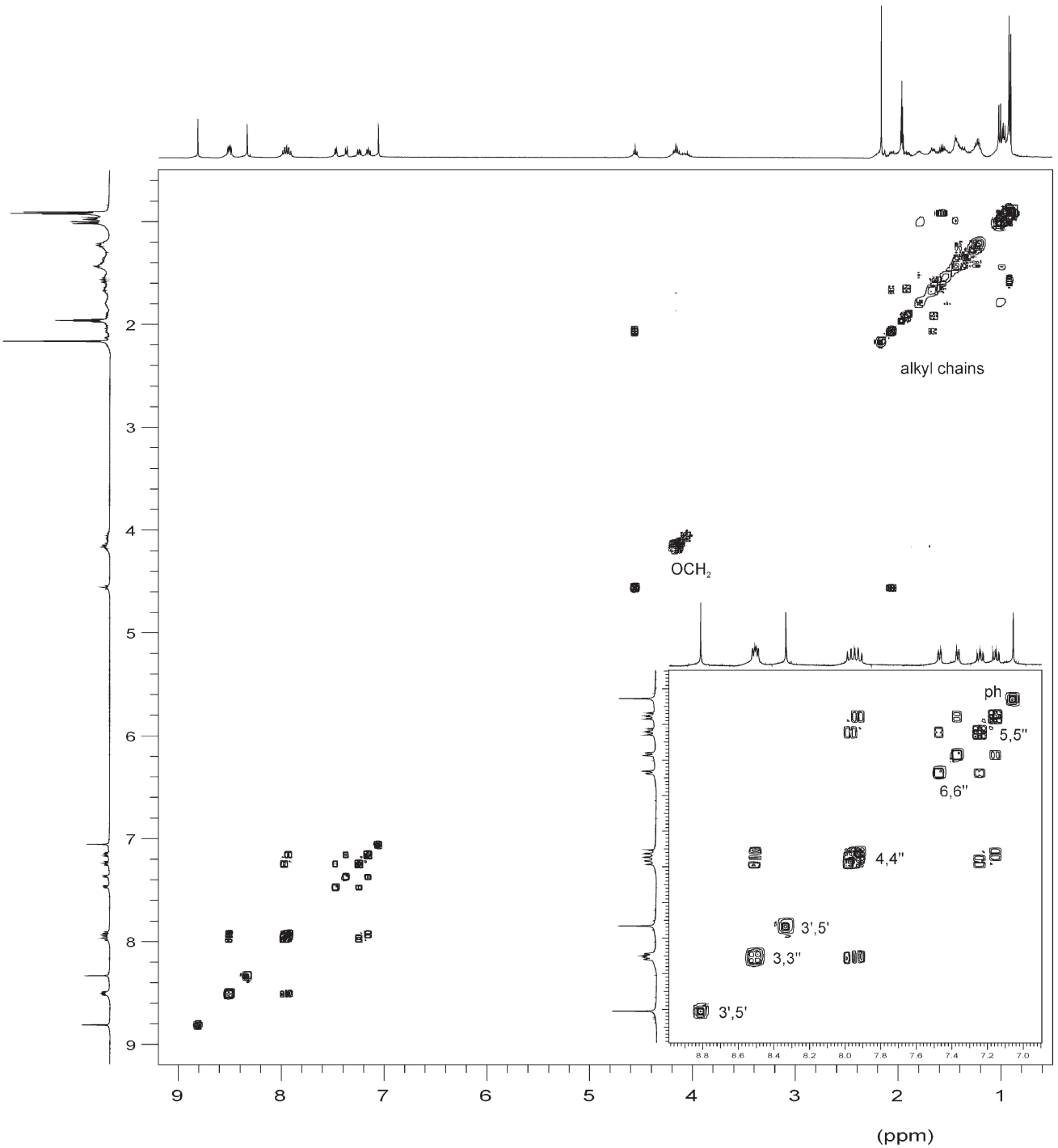

Figure 3. ^{1}H-COSY-NMR spectrum of complex **7** (in acetonitrile).

addition of chloroform to the dodecane solution resulted in a stepwise decrease of the CD effect (Fig. 7). This indicates a subsequent break-up of the aggregates upon chloroform addition.

The corresponding achiral complexes **11** and **12** did not reveal any CD effect. In order to investigate if a similar aggregation is taking place, the absorption spectra of both complexes were recorded in dodecane. Similar absorption spectra as in the case of **5** and **7** were obtained, suggesting the same aggregation behavior for both chiral and achiral metal complexes (Fig. 8). These results provide the evidence that the chirality is indeed induced exclusively by the chiral side chains and that the chirality is transferred to the complex moiety, caused by aggregation of the metal complexes.

3. Experimental

3.1. Materials and instrumentation

Basic chemicals were obtained from Sigma-Aldrich. The acetylenes **1** and **8** have been synthesized as described

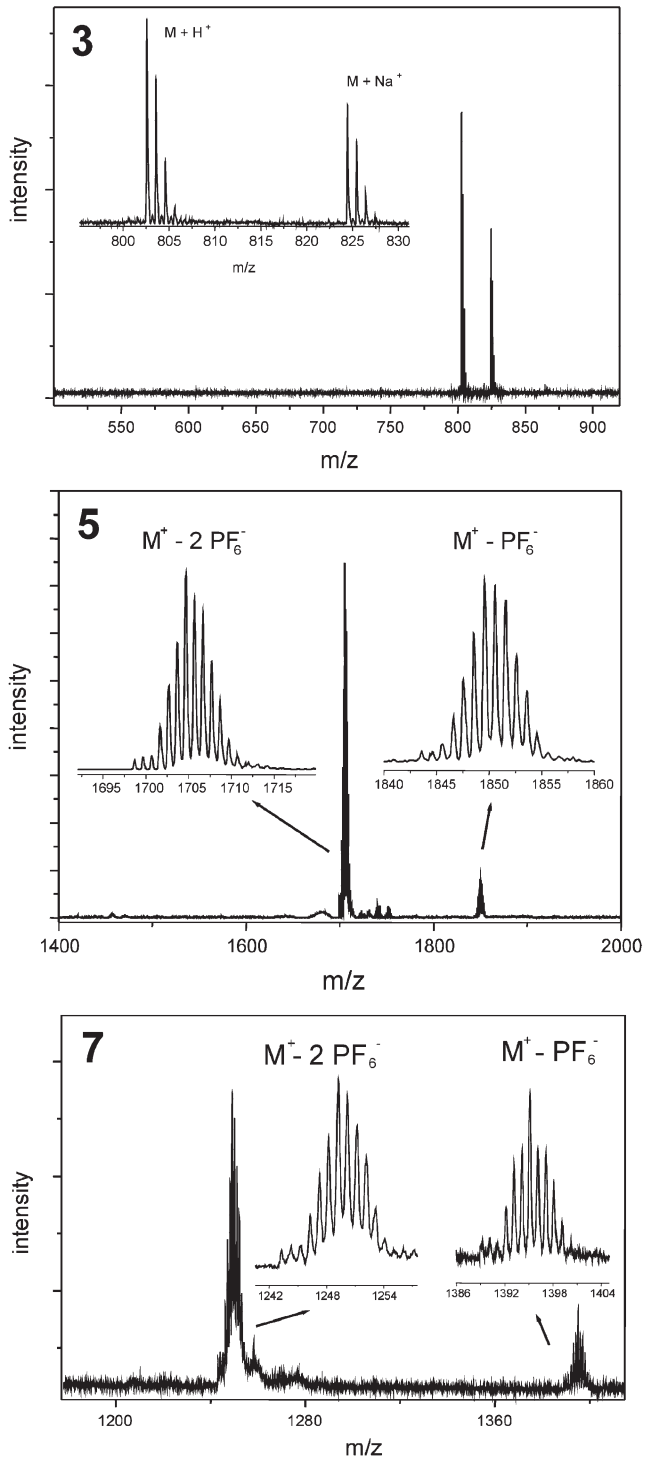

Figure 4. MALDI-TOF-MS of ligand **3** and the complexes **5** and **7** (matrix: dithranol).

elsewhere.[12] Preparative size exclusion chromatography was carried out on BioBeads SX1 columns (CH_2Cl_2). NMR spectra were measured on a Varian Mercury 400 and a Varian Gemini 300 NMR spectrometer. The chemical shifts were calibrated to the residual solvent peaks or TMS. UV–vis spectra were recorded on a Perkin Elmer Lamda-45 spectrophotometer (1 cm cuvettes) and CD-measurements on a Jasco J600 CD-machine. Temperature-dependent CD-spectra were recorded from −10 to 100 °C in steps of 10 °C. MALDI-TOF mass spectra were recorded on a BioSystems Perseptive Voyager 2000 instrument using dithranol as matrix. DSC investigations were performed on a Perkin Elmer Pyris-1 DSC system with a heating rate of 40 K/min (T_g).

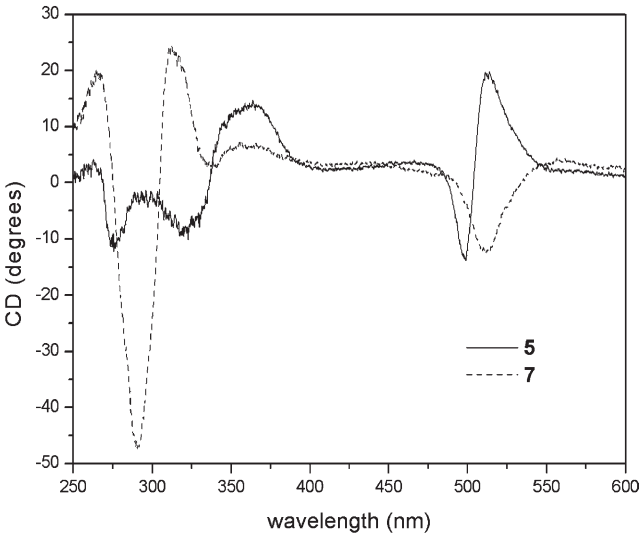

Figure 5. CD spectrum of **5** and **7** (in dodecane at room temperature).

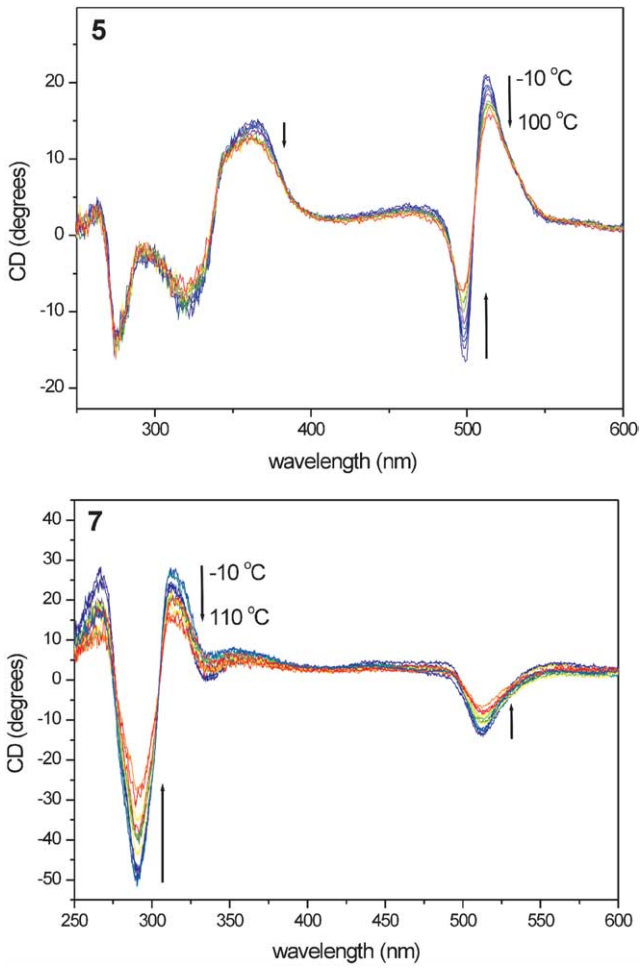

Figure 6. Temperature dependant (−10–110 °C) CD measurements of **5** and **7** (dodecane), showing a decrease in the intensity of the CD-signal (arrow).

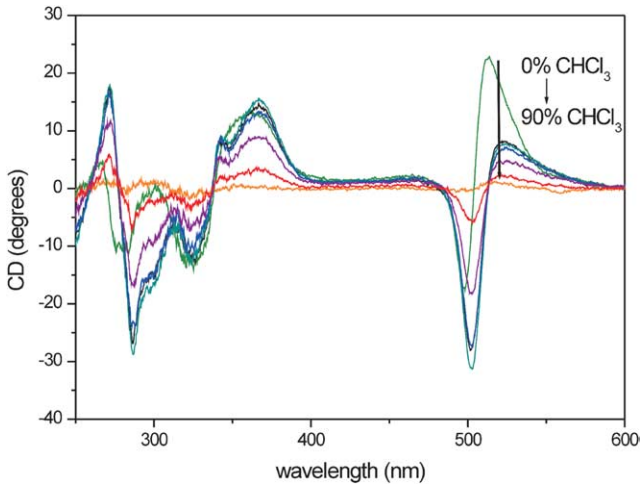

Figure 7. Solvent dependant CD measurements of **5** (dodecane→chloroform).

3.1.1. 4′-[3,4,5-Tris-(3,7-dimethyl-octyloxy)-phenylethynyl]-2,2′:6′,2″-terpyridine 3. 250 mg (0.801 mmol) of 4′-bromo-2,2′:6′,2″-terpyridine **2** and 250 mg (0.438 mmol) of the acetylene **1** were dissolved in degassed *n*-$PrNH_2$, and $Pd(PPh_3)_4$ (6 mol%) was added. After heating up to 65 °C for 40 h the solvent was evaporated under vacuum and the product was purified through column chromatography using an alumina column and a 50:50 mixture of dichloromethane/hexane as eluent. Yield: 260 mg (74%).

Elemental analysis: Found: C, 79.39; H, 9.30; N, 5.05%. $C_{53}H_{75}N_3O_3$ requires C, 79.35; H, 9.42; N, 5.24%.

UV–vis (acetonitrile): λ_{max}/nm (ε/l mol^{-1} cm^{-1})=238 (27700), 285 (25400), 320 (23700).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=0.88 (18H, d, J=6.59 Hz, 7-CH_3), 0.94 (3H, d, J=6.59 Hz, 3-$CH_{3(para\text{-chain})}$), 0.97 (6H, d, J=6.59 Hz, $CH_{3(meta\text{-chains})}$), 1.18 (10H, m, CH_2), 1.35 (10H, m, CH_2), 1.54 (4H, m, CH_2), 1.64 (2H, m, CH_2), 1.73 (3H, m, CH), 1.88 (3H, m, CH), 4.04 (6H, m, OCH_2), 6.81 (2H, s, H_{phenyl}), 7.33 (2H, ddd, J=5.86, 4.39, 1.47 Hz, $H_{5,5''}$), 7.85 (2H, ddd, J=8.06, 8.06, 1.47 Hz, $H_{4,4''}$), 8.56 (2H, s, $H_{3',5'}$), 8.61 (2H, dd, J=8.06, 1.47 Hz, $H_{3,3''}$), 8.71 (2H, d, J=6.59 Hz, $H_{6,6''}$).

^{13}C NMR (100 MHz, $CHCl_3$): δ (ppm)=155.6, 155.4, 153.0, 149.1, 139.6, 136.9, 133.5, 123.9, 122.7, 121.2, 116.8, 110.3 (aromatic), 94.4, 86.4 (alkyne), 71.8, 67.4 (OCH_2), 39.3, 39.2, 37.5, 37.3, 37.0 (CH_2), 29.8, 29.6, 28.0 (CH), 24.7 (CH_2), 22.6, 22.7, 19.6 (CH_3).

MALDI-TOF-MS: m/z=802.59 $[M+H]^+$, 824.56 $[M+Na]^+$.

3.1.2. [4′-[3,4,5-Tris-(3,7-dimethyl-octyloxy)-phenylethynyl]-2,2′:6′,2″-terpyridine)] ruthenium(III) chloride 4. 126 mg (0.157 mmol) of 4′-[3,4,5-(tris-(3,7-dimethyl-octyloxy)-phenylethynyl]-2,2′:6′,2″-terpyridine **3** was mixed with 207 mg of $RuCl_3 \times H_2O$ in ethanol. The suspension was heated to 65 °C for 4 h. A brown precipitate occurred which was collected by filtration and washed with ethanol. The compound was used without further purification or characterization. Yield: 143 mg (91%).

3.1.3. Bis-[4′-[3,4,5-tris(3,7-dimethyl-octyloxy)-phenylethynyl]-2,2′:6′,2″-terpyridine] ruthenium(II) hexafluorophosphate 5. 32 mg (0.040 mmol) of **3** and 40 mg (0.040 mmol) of **4** were mixed in ethanol and 30 μL of *N*-ethylmorpholine were added. The mixture was heated up to 70 °C for 4 h. After cooling to room temperature ammoniumhexafluorophosphate (in ethanol) was added. The compound was precipitated by adding water and evaporating the ethanol. A dark red solid was obtained, which was filtrated and further purified by size exclusion chromatography on a Bio-Beads SX1 column. Yield: 65.4 mg (82%).

Elemental analysis: Found: C, 63.07; H, 7.24; N, 4.17%. $C_{106}H_{150}N_6O_6RuP_2F_{12}$ requires C, 63.23; H, 7.61; N, 4.07%.

UV–vis (acetonitrile): λ_{max}/nm (ε/l mol^{-1} cm^{-1})=282 (66200), 314 (65200), 501 (45300).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 0.88 (27H, dd, J=6.59, 2.20 Hz, CH_3), 0.96 (12H, t, J=6.59 Hz, CH_3), 1.18 (10H, m, CH_2), 1.35 (10H, m, CH_2), 1.54 (4H, m, CH_2), 1.62 (2H, m, CH_2), 1.73 (3H, m, CH), 1.89 (3H, m, CH), 4.10 (6H, m, OCH_2), 7.00 (2H, s, H_{phenyl}), 7.21 (2H, d, J=6.59 Hz, $H_{5,5''}$), 7.31 (2H, d, J=5.86 Hz, $H_{6,6''}$), 7.85 (2H,

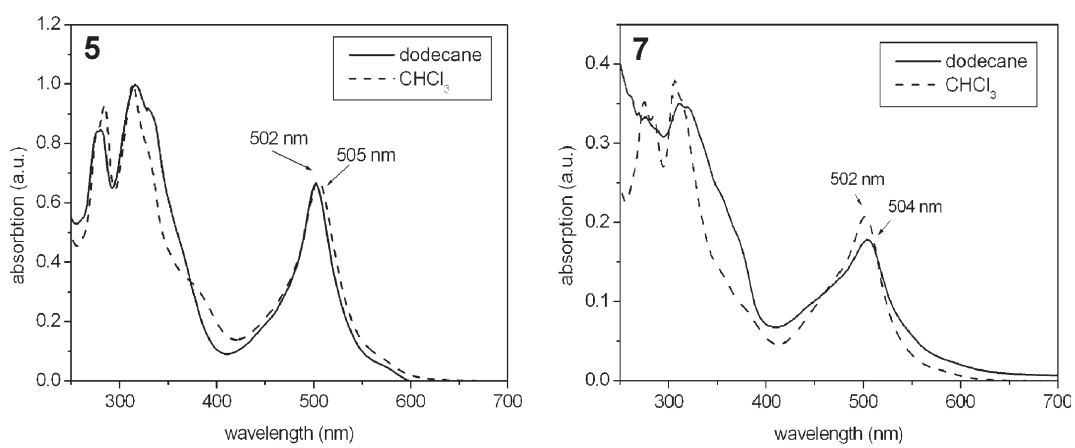

Figure 8. UV–vis spectra of the complexes **5** (right) and **7** (left) in dodecane and chloroform, respectively.

dd, J=7.23, 7.23 Hz, $H_{4,4''}$), 8.38 (2H, d, J=8.06 Hz, $H_{3,3''}$), 8.65 (2H, s, $H_{3',5'}$).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm)=158.4, 156.0, 154.2, 153.5, 141.1, 139.1, 131.4, 128.5, 125.9, 125.4, 116.7, 111.4 (aromatic), 98.6, 86.1 (alkyne), 72.4, 68.2 (OCH_2), 40.0, 39.9, 38.1, 38.0, 37.9, 37.1 (CH_2), 30.5, 30.4, 28.7 (CH), 25.5, 25.4 (CH_2), 22.9, 22.8, 20.0, 19.8 (CH_3).

ESI-MS: m/z=852.73 $[M-2PF_6]^{2+}$, 1850.7 $[M-PF_6]^+$.

MALDI-TOF-MS: m/z=1704.69 $[M-2PF_6]^+$, 1849.75 $[M-PF_6]^+$.

DSC: T_m=115.2 °C.

3.1.4. (4′-Heptyloxy-2,2′:6′,2″-terpyridine) ruthenium-(III) trichloride 6. This compound was prepared as described in Ref. [14] by reacting 1-bromoheptane with pyridone in DMF and subsequently treating the product with $RuCl_3{\times}H_2O$, followed by isolation of the product by filtration. This compound was used without further characterization.

3.1.5. (4′-[3,4,5-Tris-(3,7-dimethyl-octyloxy)-phenylethynyl]-2,2′:6′,2″-terpyridine) (4′-heptyloxy-2,2′:6′,2″-terpyridine) ruthenium(II) hexafluorophosphate 7. The compound was prepared following the procedure for **5**. In this case a precipitate was obtained after the addition of NH_4PF_6 solution which was collected by filtration, washed with 50 mL of ethanol/water (50:50) and recrystallized from acetonitrile/diethyl ether. 36 mg (0.046 mmol) **3**, 24.6 (0.046 mmol) **6**. Yield: 53 mg (72%). This complex, however, was not readily soluble in dodecane. Therefore a solution in chloroform was mixed with dodecane and the chloroform was subsequently removed by evaporation. The obtained solution was used for the UV–vis and CD investigations.

Elemental analysis: Found: C, 58.84; H, 6.35; N, 5.25%. $C_{75}H_{100}N_6O_6RuP_2F_{12}$ requires C, 58.47; H, 6.54; N, 5.45%.

UV–vis (acetonitrile): λ_{max}/nm (ε/l mol^{-1} cm^{-1})=241 (61000), 273 (66300), 304 (68800), 502 (34100).

^{1}H NMR (400 MHz, CD_3CN): δ (ppm)=0.89 (18H, d, J=6.59 Hz, CH_3), 0.95 (6H, m, CH_3), 0.99 (6H, d, J=6.59 Hz, CH_3), 1.20 (10H, m, CH_2), 1.37 (14H, m, CH_2), 1.53 (6H, m, CH_2), 1.63 (4H, m, CH_2), 1.76 (2H, m, CH_2), 1.90 (3H, m, CH), 2.04 (3H, m, CH), 4.05 (2H, m, OCH_2), 4.13 (4H, m, OCH_2), 4.53 (2H, t, J=6.59 Hz, $OCH_{2(heptyl)}$), 7.03 (2H, s, H_{phenyl}), 7.13 (2H, ddd, J=7.32, 7.32, 1.46 Hz, $H_{5,5''}$), 7.21, (2H, ddd, J=7.32, 7.32, 1.46 Hz, $H_{5,5''}$), 7.35 (2H, d, J=5.13 Hz, $H_{6,6''}$), 7.45 (2H, d, J=5.13 Hz, $H_{6,6''}$), 7.90 (2H, ddd, J=8.06, 8.06, 1.46 Hz, $H_{4,4''}$), 7.94 (2H, ddd, J=8.06, 8.06, 1.46 Hz, $H_{4,4''}$), 8.31 (2H, s, $H_{3',5'}$), 8.48 (2H, d, J=8.06 Hz, $H_{3,3''}$), 8.49 (2H, d, J=8.06 Hz, $H_{3,3''}$), 8.79 (2H, s, $H_{3',5'}$).

^{13}C NMR (100 MHz, CD_3CN): δ (ppm)=178.9, 166.9, 158.3, 156.1, 153.6, 153.0, 152.6, 140.4, 138.3, 138.2, 127.9, 127.6, 125.1, 124.7, 124.6, 116.7, 111.3, 110.7, 98.6, 85.6 (alkyne), 71.7 ($OCH_{2(para\text{-chain})}$), 70.7 ($OCH_{2(heptyl)}$), 67.5 ($OCH_{2(meta\text{-chains})}$), 39.4, 39.4, 37.4, 37.35, 37.3, 36.4 (CH_2), 31.8, 29.8 ($CH_{(heptyl)}$), 29.7, 28.9, 28.0 (CH), 24.8, 25.4 (CH_2), 22.6 (3-$CH_{3(para\text{-chain})}$), 22.2 (3-$CH_{3(meta\text{-chains})}$), 19.3 (7-$CH_{3(para\text{-chain})}$), 19.1 (7-$CH_{3(meta\text{-chains})}$), 13.7 ($CH_{3heptyl}$).

MALDI-TOF-MS: m/z=1249.23 $[M-2PF_6]^+$, 1395.15 $[M-PF_6]^+$.

ESI-MS: m/z=623.0 $[M-2PF_6]^{2+}$, 1393.8 $[M-PF_6]^+$.

3.1.6. 4′-(3,4,5-Tris-dodecyl-phenylethynyl)-2,2′:6′,2″-terpyridine 9. The reactions were performed in the same way as described before. 500 mg (0.76 mmol) **8**, 217 mg (0.70 mmol) 4′-bromo-2,2′:6′,2″-terpyridine **2** and 53 mg (6 mol%) $Pd(PPh_3)_4$. Yield: 530 mg (85%).

Elemental analysis: Found: C, 79.63; H, 9.96; N, 4.56%. $C_{59}H_{87}N_3O_3$ requires C, 79.95; H, 9.89; N, 4.74%.

UV–vis (acetonitrile): λ_{max}/nm (ε/l mol^{-1} cm^{-1})=238 (27700), 285 (25400), 320 (23700).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=0.88 (9H, m, CH_3), 1.27 (49H, m, CH_2), 1.49 (6H, m, CH_2), 1.78 and 1.82 (6H, m, CH_2), 4.00 (6H, m, OCH_2), 6.78 (2H, s, H_{phenyl}), 7.30 (2H, ddd, J=5.86, 4.39, 1.47 Hz, $H_{5,5''}$), 7.82 (2H, ddd, J=8.06, 8.06, 1.47 Hz, $H_{4,4''}$), 8.55 (2H, s, $H_{3',5'}$), 8.59 (2H, dd, J=8.06, 1.47 Hz, $H_{3,3''}$), 8.69 (2H, d, J=6.59 Hz, $H_{6,6''}$).

^{13}C NMR (100 MHz, $CHCl_3$): δ (ppm)=155.6, 155.4, 153.0, 149.0, 139.6, 136.7, 133.4, 123.9, 122.6, 121.1, 116.7, 110.3 (aromatic), 94.3, 86.4 (alkyne), 73.5 ($OCH_{2(para\text{-chain})}$), 69.1 ($OCH_{2(meta\text{-chains})}$), 31.9, 30.3, 29.7, 29.6, 29.4, 29.33, 29.28, 26.0 (CH_2), 22.6 (CH_2CH_3), 14.1 (CH_3).

MALDI-TOF-MS: m/z=886.73 $[M+H]^+$, 908.85 $[M+Na]^+$.

3.1.7. [4′-(3,4,5-Tris-dodecyl-phenylethynyl)-2,2′:6′,2″-terpyridine)] ruthenium(III) chloride 10. This compound has been prepared in the same manner as compound **4** and used without further characterization. 82 mg (0.093 mmol) **9**, 130 mg (0.63 mmol) $RuCl_3{\times}H_2O$. Yield: 99.7 mg (98%). The compound was used without further purification or characterization.

3.1.8. Bis-[4′-(3,4,5-tris-dodecyl-phenylethynyl)-2,2′:6′,2″-terpyridine)] ruthenium(II) hexafluorophosphate 11. The compound was prepared following the procedure for **5**. 50 mg (0.045 mmol) **10**, 40 mg (0.045 mmol) **9**. Yield: 61 mg (62%).

Elemental analysis: Found: C, 64.91; H, 8.03; N, 3.84%. $C_{118}H_{174}N_6O_6RuP_2F_{12}$ +1 H_2O requires C, 64.96; H, 8.13; N, 3.85%.

UV–vis (acetonitrile): λ_{max}/nm (ε/l mol^{-1} cm^{-1})=282 (66200), 314 (65200), 501 (45300).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 0.89 (9H, m, CH_3), 1.27 (58H, m, CH_2), 1.50 and 1.57 (10H, m, CH_2), 1.77 and

1.84 (6H, m, CH_2), 4.05 (6H, m, OCH_2), 6.98 (2H, s, H_{phenyl}), 7.21 (2H, t, J=6.59 Hz, $H_{5,5''}$), 7.32 (2H, d, J=5.13 Hz, $H_{6,6''}$), 7.85 (2H, dd, J=7.23, 7.23 Hz, $H_{4,4''}$), 8.37 (2H, d, J=8.06 Hz, $H_{3,3''}$), 8.64 (2H, s, $H_{3',5'}$).

^{13}C NMR (100 MHz, $CHCl_3$): δ (ppm)=157.1, 154.6, 153.1, 152.0, 140.3, 138.3, 131.9, 124.7, 128.2, 125.1, 115.7, 110.8 (aromatic), 99.8, 85.4 (alkyne), 73.6 ($OCH_{2(para\text{-chain})}$), 69.2 ($OCH_{2(meta\text{-chains})}$), 31.9, 30.3, 29.7, 29.6, 29.4, 29.3, 26.14, 26.07 (CH_2), 22.7 (CH_2CH_3), 14.1 (CH_3).

MALDI-TOF-MS: m/z=1872.52 $[M-2PF_6]^+$, 2017.38 $[M-PF_6]^+$.

3.1.9. [4′-(3,4,5-Tris-dodecyl-phenylethynyl)-2,2′:6′,2″-terpyridine][4′-heptyloxy-2,2′:6′,2″-terpyridine] ruthenium(II) hexafluorophosphate 12. The compound was prepared following the procedure for **7**. 25 mg (0.028 mmol) **9**, 16 mg (0.028 mmol) **6**. Yield: 29 mg (63%). Dodecane solutions were obtained in a similar procedure as for **7**.

UV–vis (acetonitrile): λ_{max}/nm (ε/l mol^{-1} cm^{-1})=241 (61000), 273 (66300), 304 (68800), 502 (34100).

^{1}H NMR (400 MHz, CD_3CN): δ (ppm)=0.88 (9H, m, CH_3), 0.96 (3H, t, J=6.86 Hz, $CH_{3heptyl}$), 1.11 (22H, m, CH_2), 1.29 (54H, m, CH_2), 1.42 (8H, m, CH_2), 1.52 (8H, m, CH_2), 1.66 (4H, m, CH_2), 1.82 (6H, m, CH_2), 3.98 (2H, t, J=6.59 Hz, OCH_2), 4.08 (4H, t, J=6.04 Hz, OCH_2), 4.53 (2H, t, J=6.59 Hz, OCH_2), 7.01 (2H, s, H_{phenyl}), 7.13 (2H, d, J=7.32, 7.32, 1.46 Hz, $H_{5,5''}$), 7.22, (2H, ddd, J=7.32, 7.32, 1.46 Hz, $H_{5,5''}$), 7.35 (2H, d, J=5.13 Hz, $H_{6,6''}$), 7.45 (2H, d, J=5.13 Hz, $H_{6,6''}$), 7.90 (2H, ddd, J=8.06, 8.06, 1.46 Hz, $H_{4,4''}$), 7.94 (2H, ddd, J=8.06, 8.06, 1.46 Hz, $H_{4,4''}$), 8.31 (2H, s, $H_{3',5'}$), 8.48 (2H, d, J=8.06 Hz, $H_{3,3''}$), 8.49 (2H, d, J=8.06 Hz, $H_{3,3''}$), 8.78 (2H, s, $H_{3',5'}$).

MALDI-TOF-MS: m/z=1335.02 $[M-2PF_6]^+$, 1480.00 $[M-PF_6]^+$.

4. Conclusion

We have synthesized and characterized functional terpyridines bearing a chiral as well as an achiral alkyl group, respectively. Their corresponding symmetric and asymmetric ruthenium(II) complexes were obtained and fully characterized. The formation of chiral aggregates was studied by CD-spectroscopy, giving evidence of chiral aggregates in dodecane, which are stable up to 110 °C. Whereas the symmetric complex shows a bisignate CD-effect, suggesting the formation of helical aggregates, a different kind of aggregate was found for the asymmetric complexes. Future investigations will include the visualization of the chiral aggregates by imaging techniques such as AFM or TEM and attempts to design complexes with thermotropic liquid-crystalline behavior.

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$SnCl_2$-mediated carbonyl allylation in fully aqueous media

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Abstract—Systematic studies were performed on $SnCl_2$-mediated carbonyl allylation reaction between aldehydes and allyl halides in fully aqueous media. Totally three valuable reaction systems were discovered, which were $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, and $SnCl_2/PdCl_2$. They all provided good to excellent yields in the allylation of aliphatic and aromatic aldehydes under very mild and convenient conditions. $SnCl_2$, by itself, was also found to be effective for the allylation reaction when allyl bromide was employed. However, the $SnCl_2$-only reaction could only tolerate very small amount of water as the solvent. The $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, and $SnCl_2/PdCl_2$-mediated reactions exhibited good regioselectivity favoring the γ-adduct when cinnamyl halides were employed as the allylation reagent. The same reactions with cinnamyl halides also showed good diastereoselectivity favoring the *anti*-product. Mechanistic studies using proton NMR techniques suggested that the additive (i.e., $CuCl_2$, $TiCl_3$, $PdCl_2$) could accelerate the formation of allyltin intermediate, but this step was shown not to be the most important for the allylation. Thus we proposed that the Lewis acid catalysis effect exerted by the additive was the main reason for the observed reactivity enhancement.

1. Introduction

Carbonyl allylation is a highly important synthetic transformation in organic and pharmaceutical chemistry, because the homoallylic alcohol product is a versatile subunit in synthesis that can easily be converted to a number of other useful functions.[1] Until now, many methods have been developed to accomplish carbonyl allylation, which usually involve the synthesis of a certain allylic organometallic reagent and the addition of the organometallic reagent to the carbonyl compound in anhydrous organic solvents. However, because of the high reactivity and moisture-sensitivity of most allylic organometallic reagents, this synthetic approach is neither operationally simple nor safe to scale up.

An alternative and attractive approach to achieve carbonyl allylation is to use the Barbier reaction,[2] which refers to the metal-mediated coupling between a carbonyl compound and an organic halide in a one-pot fashion. Operational simplicity is an obvious advantage of the Barbier reaction, because no reaction intermediate needs to be isolated. Moreover, it was found recently that the Barbier reaction could be conducted in partially or even fully aqueous media.[3] This 'surprising' discovery attracts considerable attention because of the increasing public interest in Green Chemistry.[4]

So far, numerous metals have been reported to be effective in mediating the aqueous Barbier reaction. Examples include aluminum,[5] magnesium,[6] manganese,[7] indium,[8] antimony,[9] bismuth,[10] lead,[11] gallium,[12] zinc,[13] and tin.[14] Although good yields can often be obtained in these reactions, the use of zero-valent metals unavoidably causes some operational problems. For instance, it is often difficult to stir the reaction mixture when a large amount of metal is used. Metal oxide or hydroxide precipitation on the surface of metal may slow or stop the reaction, so that organic co-solvent or ultrasonic radiation has to be utilized in some of the above reactions. Furthermore, some zero-valent metals are too reactive and significant byproducts (e.g., pinacol reaction product, carbonyl reduction product, and Wurtz reaction product) can be produced in the reaction.

We thought that water-soluble reductive metal salts such as $SnCl_2$, if applicable to the aqueous Barbier reaction, might solve some of the above problems associated with the zero-valent metals. Thus we recently investigated the possible use of $SnCl_2$ in aqueous Barbier reaction. We found that a combination of $SnCl_2$ and Cu could efficiently mediate the aqueous carbonyl allylation reactions.[15] We also found that $TiCl_3$ could dramatically catalyze the $SnCl_2$-mediated carbonyl allylation reactions in fully aqueous media.[16] It is worth mentioning that Roy et al. recently found that SnO/Cu_2O and $SnCl_2/CuCl_2$ could also mediate the carbonyl allylation reactions.[17] However, in their reactions the use of organic co-solvent such as THF was necessary. Furthermore, Samoshin[18] and Yuan[19] reported very recently that $SnCl_2$/KI and $SnCl_2$/untrasonication could mediate the carbonyl allylation reactions in water.

Keywords: Allylation; $SnCl_2$; Aqueous medium; Green chemistry; Barbier reaction.
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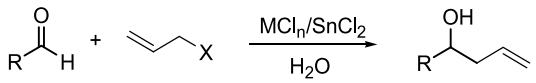
All the above findings suggest that $SnCl_2$-mediated allylation in aqueous media might be developed into a valuable reaction for organic synthesis. However, a lot of details about this reaction still remain poorly understood at present. For instance, the mechanism of the reaction is not fully clear and the role of the additive (e.g., Cu, $TiCl_3$) in the reaction is quite ambiguous. Secondly, the scope of the reaction has not been adequately studied and the reaction condition may require more optimization. Thirdly, most studies reported so far only put emphasis on un-substituted allyl halides, while the regio- and diastereo-chemistry associated with substituted allyl halides has received little attention.

In the present paper we wish to report some new findings concerning the aqueous $SnCl_2$-mediated carbonyl allylation reactions. We screened many Lewis acid additives for the reaction and we studied the role of the additive in the reaction. For the Lewis acid additives that were found to be effective, we optimized the reaction conditions and investigated the scope of the reaction. We also studied the allylation reactions involving cinnamyl halides, where some interesting regio- and diastereo-selectivities were observed. Furthermore, we performed some NMR studies on the reaction intermediates, from which we obtained some novel insights into the reaction mechanism.

2. $SnCl_2/MCl_n$-mediated carbonyl allylation

In the previous studies Cu, $CuCl_2$, Cu_2O, and $TiCl_3$ additives were found to be able to catalyze the $SnCl_2$-mediated carbonyl allylation reactions in water.[15–19] Herein, we examined a variety of water-soluble metal chlorides as the additive for the aqueous $SnCl_2$-mediated allylation reaction (Scheme 1). It is worth mentioning that we did not examine the water-insoluble Lewis acids, because the water-insoluble Lewis acids (usually solids) might cause serious operational trouble for large scale reactions.



Scheme 1.

Our results (Table 1) show that $TiCl_3$, $CuCl_2$, and $PdCl_2$ can effectively catalyze the $SnCl_2$-mediated allylation reaction (yields >95%). $LaCl_3$, $CrCl_3$, $MnCl_2$, $FeCl_2$, $CoCl_2$, and $NiCl_2$ show some but fairly low catalytic effects (yields= 6–40%). Other Lewis acids, for example, $MgCl_2$, $ZnCl_2$, $CdCl_2$, $InCl_3$, $PbCl_2$, and $BiCl_3$ exhibit almost no effects as very little product can be detected.

Interestingly, the trend of the catalytic activities of different Lewis acids in our allylation reaction is not fully consistent with that observed by Kobayashi et al. in their aqueous aldol reactions.[20] In their cases, Ln(III), Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II) were found to afford the desired aldol adduct in high yields in aqueous solvents, whereas Pd(II) was found to be much less active. In our aqueous allylation reaction, however, $PdCl_2$ is found to be the most effective. Moreover, we found that Ti(III) could be used as an interesting water-compatible Lewis acid. This application of Ti(III) has received very little attention before.

Table 1. Carbonyl allylation between benzaldehyde and allyl bromide mediated by $SnCl_2/MCl_n$[a]

Entry	MCl_n[a]	Yield (%)[b]
1	$MgCl_2$	Trace
2	$LaCl_3$	6
3	$TiCl_3$	99
4	$CrCl_3$	22
5	$MnCl_2$	27
6	$FeCl_2$	32
7	$CoCl_2$	40
8	$NiCl_2$	27
9	$PdCl_2$	99
10	$CuCl_2$	95
11	$ZnCl_2$	Trace
12	$CdCl_2$	Trace
13	$InCl_3$	Trace
14	$PbCl_2$	Trace
15	$BiCl_3$	Trace

[a] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of allyl bromide, 10 mmol of $SnCl_2$, 5 mmol of MCl_n (for $PdCl_2$ this amount is reduced to 0.5 mmol), 25 mL of water.
[b] Yields were calculated using ^1H NMR (300 MHz) after the reaction was stirred for 24 h.

Using the $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, and $SnCl_2/PdCl_2$ methods we examined the scope of the aqueous allylation reactions (Table 2). It is found that both aliphatic and aromatic aldehydes can be efficiently allylated using any one of these three methods. Using allyl bromide as the allylation reagent the reaction yields are mostly over 90%. The yields are slightly lower (>80%) when allyl chloride is used in the reaction.

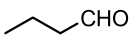
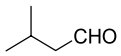
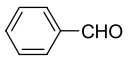
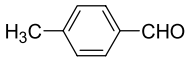
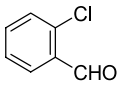
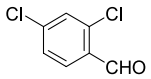
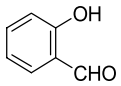
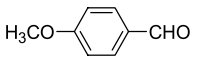
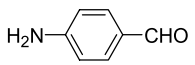
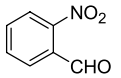
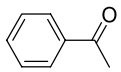
It is worth noting that 2-nitrobenzyldehyde (entry 10 in Table 2) cannot be effectively allylated using $SnCl_2/TiCl_3$, because the NO_2 group is considerably reduced in the reaction. Similar NO_2 reduction problem was noted before in many zero-valent metal mediated carbonyl allylation reactions.[5–14] Nevertheless, $SnCl_2/CuCl_2$ and $SnCl_2/PdCl_2$ do not have this problem as their allylation yields for 2-nitrobenzaldehyde are about 80–90%.

In comparison with aldehydes, neither aliphatic nor aromatic ketones can be efficiently allylated using any one of the three methods (entries 11 and 12 in Table 2). In particular, when the $SnCl_2/PdCl_2$ method is employed and allyl chloride is used as the allylation reagent, only trace amount of allylation product can be detected for both the aliphatic and aromatic ketones. Therefore, one can use the $SnCl_2/PdCl_2$ method to selectively allylate aldehyde groups in the presence of ketone groups.

3. $SnCl_2$-mediated carbonyl allylation

Yuan et al. reported very recently that $SnCl_2$ can mediate aqueous carbonyl allylation reactions under ultrasonic condition without using any other additive.[19] This report immediately called upon our attention as we were interested in the role of the additive in the allylation reaction. Thus we carefully studied the aqueous allylation reactions using $SnCl_2$ alone.

Table 2. Carbonyl allylation mediated by $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, $SnCl_2/PdCl_2$, and $SnCl_2$

Entry	Substrates	X[a]	Yield (%)[b]			
			$SnCl_2/CuCl_2$[c]	$SnCl_2/TiCl_3$[c]	$SnCl_2/PdCl_2$[c]	$SnCl_2$ only[d]
1		Br	92	95	92[b]	85
		Cl	85	88	90	21
2		Br	95	98	99	95
		Cl	90	94	99	25
3		Br	96	99	99	99
		Cl	98	99	99	51
4		Br	93	99	99	99
		Cl	90	91	99	36
5		Br	91	99	99	75
		Cl	87	99	99	25
6		Br	96	99	99	87
		Cl	88	93	99	22
7		Br	94	90	99	92
		Cl	83	85	90	41
8		Br	92	93	94	87
		Cl	79	90	92	30
9		Br	90	96	80	65
		Cl	84	96	95	15
10		Br	88	51	88	49
		Cl	79	Trace	80	Trace
11		Br	43	25	Trace	Trace
		Cl	41	17	Trace	Trace
12		Br	23	9	17	Trace
		Cl	11	Trace	Trace	Trace

[a] X indicates whether the allylation reagent is allyl bromide (X=Br) or allyl chloride (X=Cl).
[b] All the reactions were run for 24 h at room temperature.
[c] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of allyl bromide, 10 mmol of $SnCl_2$, 5 mmol of MCl_n (for $PdCl_2$ this amount is reduced to 0.5 mmol), 25 mL of water.
[d] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of allyl bromide, 10 mmol of $SnCl_2$, 2–5 mL of water.

We found that $SnCl_2$ indeed could mediate the carbonyl allylation reactions in water without using any additive (Table 2). However, only allyl bromide can be used in these reactions as allyl chloride provides very poor yields. Moreover, we observed a very interesting water effect on $SnCl_2$-mediated allylation reactions (Fig. 1).

As shown in Figure 1, the yield of the aqueous $SnCl_2$-mediated carbonyl allylation reaction is highly sensitive to the amount of water used in the reaction. When less than 30 equiv. of water (compared to $SnCl_2$) is used in the reaction, the allylation yield is over 98%. When 55 equiv. of water is used, the yield drops to 75%. When over 100 equiv. of water is used, the yield is lower than 10%. Therefore, the key for the $SnCl_2$-mediated allylation reaction without any additive is to use very little amount of water. That is, for 1 g of $SnCl_2$ one can only add less than 3 g of water as solvent. Indeed, in Yuan's work only 10 mL of water was used as solvent for a reaction involving 3.8 g of $SnCl_2$ (20 mmol).[19]

Interestingly, the dramatic water effect on the $SnCl_2$-mediated allylation reaction is not exhibited by the $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, or $SnCl_2/PdCl_2$-mediated reactions (Fig. 1). For these three reactions, increasing the amount of water from 30 equiv. to over 200 equiv. only reduces the allylation yield from 99% to about 94%. Therefore, $CuCl_2$, $TiCl_3$, and $PdCl_2$ truly have some positive effects on the $SnCl_2$-mediated allylation reactions. The positive effects of $CuCl_2$, $TiCl_3$, and $PdCl_2$ are also revealed by the fact that allyl chloride can be successfully used in these allylation reactions.

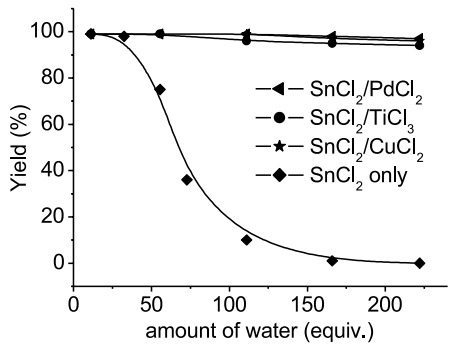
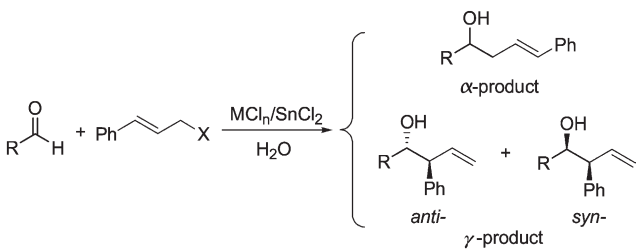


Figure 1. Yields of benzaldehyde allylation mediated by $SnCl_2$ and $MCl_x/SnCl_2$ in different amount of water.

It is possible that $SnCl_2$ serves as the Lewis acid catalyst in the allylation reaction mediated by $SnCl_2$ alone. However, the fact that only a strictly limited amount of water can be used indicates that $SnCl_2$ is not as effective as $CuCl_2$, $TiCl_3$, or $PdCl_2$. Furthermore, there is one serious operational problem associated with the $SnCl_2$-mediated allylation reaction without using any additive. That is, so little amount of water can be used in the process that the reaction mixture may become too dense to deal with. In comparison, the $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, and $SnCl_2/PdCl_2$ reactions are much easier to stir.

4. Regio- and diastereo-selectivity

In order to investigate the regio- and diastereo-selectivities of the allylation reactions, we used cinnamyl and crotyl halides as the allylation reagent. The allylation reactions involving cinnamyl halides can provide both α-adduct and γ-adduct. The γ-adduct can be either *anti*- or *syn*-product (Scheme 2).



Scheme 2.

It is found that $SnCl_2$, by itself, cannot effectively mediate the allylation reaction in water when cinnamyl chloride is used as reactant. Thus $CuCl_2$, $TiCl_3$, or $PdCl_2$ catalyst has to be added to induce the reaction. The yields under these conditions are usually 80–90%. On the other hand, when cinnamyl bromide is used as reactant, $SnCl_2$ is capable of mediating the aqueous allylation reaction by itself, although in this case a strictly limited amount of water can be used in the reaction. The yields under this condition are around 70–80%. Adding $CuCl_2$, $TiCl_3$, or $PdCl_2$ catalyst increases the yields to 80–95%. It is worth noting that by utilizing $CuCl_2$, $TiCl_3$, or $PdCl_2$ as catalyst, we do not need to restrict the amount of water to be used.

Fairly good regioselectivities are observed for the $SnCl_2/CuCl_2$, $SnCl_2/TiCl_3$, or $SnCl_2/PdCl_2$-mediated allylation reactions, in which the γ-adduct is obtained as the favored isomer. For most cases, the ratio between the γ- and α-adduct is over 95:5. This type of regioselectivity has been well known in literature.

On the other hand, when $SnCl_2$ is used for the allylation reaction without any additive, we observed a significant amount of α-adduct so that the ratio between the γ- and α-adduct decreases to about 60:40. Similar observations about the α-adducts have been reported recently by Loh et al.[21] They proposed that the metal salts formed from the metal-mediated allylation can catalyze the γ-adduct to undergo a bond cleavage to generate the parent aldehyde in situ followed by a concerted rearrangement, perhaps a retroene reaction followed by a 2-oxonia[3,3]-sigmatropic rearrangement to furnish the α-adduct.

Loh et al. found that the α-adduct became important only when very little amount of water was used as solvent.[21] This indicates that the proposed rearrangement may only occur in a highly concentrated solution of metal salts. In our $SnCl_2$-mediated allylation without any additive, we had to use very little water as solvent. Thus the α-adduct observed in the present work may also be explained by Loh's mechanism (Table 3).

The diastereoselectivity of the allylation reaction (i.e., *anti*- vs. *syn*-product) can be studied using both proton NMR and GC–MS techniques.[22] It is found in the present study that the $SnCl_2$-mediated allylation reaction always exhibits the *anti*-selectivity with or without $CuCl_2$, $TiCl_3$, or $PdCl_2$ catalyst for both cinnamyl halides and crotyl bromide (Table 4). The same *anti*-selectivity was also observed before by Masuyama et al.[22] and Roy et al.[17]

5. Mechanism

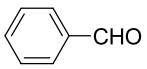
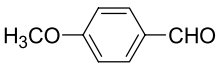
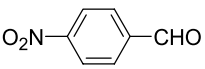
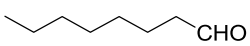
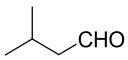
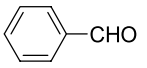
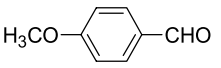
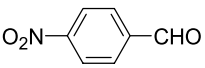
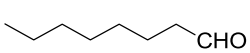
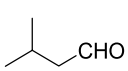
A possible (and crude) mechanism for the $SnCl_2$-mediated allylation reaction is shown in Scheme 3. What remains unclear is the role of $CuCl_2$, $TiCl_3$, or $PdCl_2$ in the reaction. Do they catalyze the first step (umpolung of the allyl species) or the second step (allylation)?

A number of proton NMR experiments were conducted to investigate the first step of the allylation reaction. In the first series of experiments, we mixed $SnCl_2$ (2 mmol) and allyl bromide (1.5 mmol) in 3 mL of D_2O. After the reaction was run for 6 h, we observed a new peak in ^1H NMR corresponding to an allyltin species (δ=2.5 ppm, doublet, J ($^{119}Sn-H$)=155 Hz.) (Fig. 2A). Comparing this new peak with the peak for allyl bromide (δ=4.1 ppm), we determined that the yield of the allyltin species was 57%.

Then we added $PdCl_2$ (0.1 mmol) into the above mixture, and continued the reaction for 18 h. The NMR spectrum of the new mixture (Fig. 2B) is almost identical to that shown in A. This experiment demonstrates that the allyltin species can form without the help of $PdCl_2$. Addition of $PdCl_2$ does not change the nature and yield of the allyltin species, either.

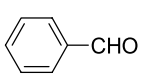
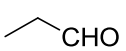
Since the allylation reaction mediated by $SnCl_2$ without any

Table 3. The reactions of cinnamyl halides and aldehydes mediated by $SnCl_2$, $CuCl_2/SnCl_2$, $TiCl_3/SnCl_2$ and $PdCl_2/SnCl_2$

Entry	Condition	Substrates	X[a]	Yield (%)	γ:α[b]	*anti*:*syn*[b]
1	$SnCl_2/CuCl_2$[c]		Cl	88	99:1	90:10
2	$SnCl_2/TiCl_3$[c]			89	98:2	83:17
3	$SnCl_2/PdCl_2$[c]			85	98:2	85:15
4	$SnCl_2/CuCl_2$		Cl	80	94:6	67:33
5	$SnCl_2/TiCl_3$			83	95:5	90:10
6	$SnCl_2/PdCl_2$			91	89:11	75:25
7	$SnCl_2/CuCl_2$		Cl	75	99:1	83:17
8[d]	$SnCl_2/TiCl_3$			—	—	—
9	$SnCl_2/PdCl_2$			93	93:7	89:11
10	$SnCl_2/CuCl_2$		Cl	90	99:1	88:12
11	$SnCl_2/TiCl_3$			94	88:12	75:25
12	$SnCl_2/PdCl_2$			94	97:3	90:10
13	$SnCl_2/CuCl_2$		Cl	81	93:7	75:25
14	$SnCl_2/TiCl_3$			89	95:5	80:20
15	$SnCl_2/PdCl_2$			88	98:2	62:38
16	$SnCl_2$ only[d]		Br	87	85:15	91:9
17	$SnCl_2/CuCl_2$			86	99:1	89:11
18	$SnCl_2/TiCl_3$			93	90:10	87:13
19	$SnCl_2/PdCl_2$			80	99:1	83:17
20	$SnCl_2$ only		Br	71	58:42	62:38
21	$SnCl_2/CuCl_2$			84	98:2	84:16
22	$SnCl_2/TiCl_3$			87	96:4	83:17
23	$SnCl_2/PdCl_2$			92	97:3	75:25
24	$SnCl_2$ only		Br	70	55:45	91:9
25	$SnCl_2/CuCl_2$			77	90:10	96:4
26	$SnCl_2/TiCl_3$			—	—	—
27	$SnCl_2/PdCl_2$			85	94:6	85:15
28	$SnCl_2$ only		Br	81	56:44	85:15
29	$SnCl_2/CuCl_2$			92	87:13	77:23
30	$SnCl_2/TiCl_3$			95	96:4	82:18
31	$SnCl_2/PdCl_2$			92	99:1	86:14
32	$SnCl_2$ only		Br	79	75:25	68:32
33	$SnCl_2/CuCl_2$			87	95:5	78:22
34	$SnCl_2/TiCl_3$			84	96:4	77:23
35	$SnCl_2/PdCl_2$			82	94:6	81:19

[a] X indicates whether the allylation reagent is cinnamyl bromide (X=Br) or cinnamyl chloride (X=Cl). All the reactions were run for 24 h at room temperature.
[b] Determined using GC–MS and 300 MHz ^{1}H NMR.
[c] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of cinnamyl bromide, 10 mmol of $SnCl_2$, 10 mmol of MCl_n (for $PdCl_2$ this amount is reduced to 0.5 mmol), 25 mL of water.
[d] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of cinnamyl chloride or bromide, 10 mmol of $SnCl_2$, 2 mL of water.

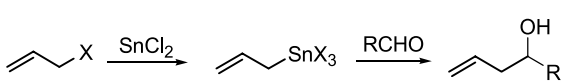
Table 4. The reactions of crotyl bromide and aldehydes mediated by $SnCl_2$, $CuCl_2/SnCl_2$, $TiCl_3/SnCl_2$ and $PdCl_2/SnCl_2$[a]

Entry	Condition	Substrates	X	Yield (%)	γ:α[b]	*anti*:*syn*[b]
1	$SnCl_2$ only[c]		Br	97	95:5	91:9
2	$SnCl_2/CuCl_2$[d]			98	99:1	94:6
3	$SnCl_2/TiCl_3$[d]			99	99:1	93:7
4	$SnCl_2/PdCl_2$[d]			99	99:1	96:4
5	$SnCl_2$ only		Br	68	78:22	62:38
6	$SnCl_2/CuCl_2$			81	82:18	66:34
7	$SnCl_2/TiCl_3$			82	80:20	71:29
8	$SnCl_2/PdCl_2$			88	84:16	69:31

[a] All the reactions were run for 24 h at room temperature.
[b] Determined using GC–MS and 300 MHz ^{1}H NMR.
[c] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of crotyl bromide, 10 mmol of $SnCl_2$, 10 mmol of MCl_n (for $PdCl_2$ this amount is reduced to 0.5 mmol), 25 mL of water.
[d] Reaction condition: 5 mmol of benzaldehyde, 10 mmol of crotyl bromide, 10 mmol of $SnCl_2$, 2 mL of water.

additive has a strong restriction on the amount of water that can be used, we also studied the water effect of the allyltin intermediate formation. We added 10 mmol of $SnCl_2$ and 7.5 mmol of allyl bromide in 3 mL of D_2O. The proton NMR of this reaction mixture (Fig. 2C) is very similar to that in Figure 2A or B. Therefore, the yield of the allyltin species is not dependent on the amount of water as the solvent.

The next question is whether or not the additive increases the rate of allyltin formation. Therefore, we monitored the appearance of the NMR peak at 2.5 ppm in the first 6 h of



Scheme 3.

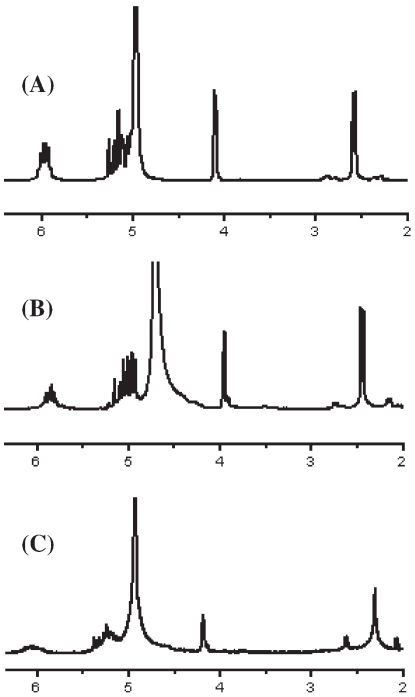


Figure 2. ^{1}H NMR spectra in D_2O (3 mL) for: (A) $SnCl_2$ (2 mmol)/allyl bromide (1.5 mmol), standing for 6 h; (B) the same mixture as in A with 0.1 mmol of $PdCl_2$ added after 6 h, standing for extra 18 h; (C) $SnCl_2$ (10 mmol)/allyl bromide (7.5 mmol), standing for 24 h.

the reaction (Fig. 3). It was found that $PdCl_2$ and $CuCl_2$ indeed could accelerate the formation of the allytin species. Nevertheless, the yield of the allyltin species is always ca. 60% with or without the additive. The maximum yield of the allyltin species can also be achieved in 6 h with or without the additive.

The above experiments show some effects of the additive on the formation of the allyltin intermediate. However, none of the above experimental findings can be used to explain the following observation. That is, without appropriate additive carbonyl allylation reaction does not occur even after 24 h (Table 1), although it is expected that the allyltin intermediate is adequately produced in 6 h.

Thus we have to propose that more important catalytic effects (presumably Lewis acid catalysis) should be exerted by the additives in the allylation step (Scheme 4). There are two possible structures for the transition state. The first is an acyclic one as proposed by Koreeda and Tanaka.[23] They reported that carbonyl allylation by (*E*)-cinnamyltributyltin or (*E*)-cinnamyltriphenyltin catalyzed by $BF_3{\cdot}Et_2O$ in CH_2Cl_2 also exhibited *anti*-diastereoselectivity.[23] The second one, which is more popular, involves a cyclic six-membered ring structure.[1]

Currently we are not certain about which transition state structure is correct. More detailed experiments need to designed and conducted. Meanwhile theoretical studies are required to compare the energies of all the possible transition states. These studies are undergoing at the moment in our lab and we will report the results in due course.

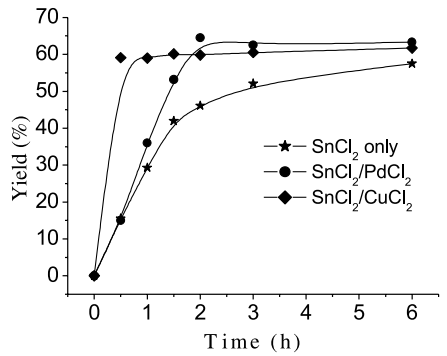
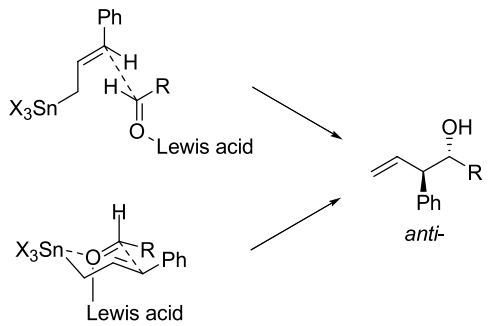


Figure 3. Yields of the allyltin species with or without additive in the first 6 h of the reaction. Conditions: $SnCl_2$ (2 mmol), allyl bromide (1.5 mmol), D_2O (3 mL), $CuCl_2$ (when applicable, 1 mmol), $PdCl_2$ (when applicable, 0.1 mmol).



Scheme 4.

6. Conclusion

In the present paper we reported our systematic studies on $SnCl_2$-mediated carbonyl allylation reaction between aldehydes and allyl halides in fully aqueous media. Totally three valuable reaction systems were found, which were $SnCl_2$/$CuCl_2$, $SnCl_2$/$TiCl_3$, and $SnCl_2$/$PdCl_2$. They all provided good to excellent yields in the allylation of aliphatic and aromatic aldehydes under very mild and convenient conditions. $SnCl_2$, by itself, was also found to be effective for the allylation reaction when allyl bromide was employed. However, the $SnCl_2$-only reaction could only tolerate very small amount of water as the solvent.

The reactions exhibited good regioselectivity favoring the γ-adduct when cinnamyl halides were employed as the allylation reagent. The same reactions with cinnamyl halides also showed good diastereoselectivity favoring the *anti*-product. Mechanistic studies using NMR techniques suggested that the additive (i.e., $CuCl_2$, $TiCl_3$, $PdCl_2$) could accelerate the formation of allyltin intermediate, but this step was shown not to be the most important. Thus we proposed that the Lewis acid catalysis effect exerted by the additive was the main reason for the observed reactivity enhancement.

7. Experimental

All the reactions were carried out in air. ^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 or 400 MHz)

instrument using TMS as internal standard and $CDCl_3$ or D_2O as solvent. IR spectra were recorded on an FT/IR/410 JASCO instrument. GC–MS was recorded on a TRACE GC–MS instrument.

The yields reported in Tables 1 and 3 were determined using the ^1H NMR method. We obtained the ^1H NMR spectrum of the crude product from extraction. We integrated the peaks for the aldehyde C–H proton ($\delta\approx10$) of the starting material and for the allylic C–H proton ($\delta\approx4.8$) of the homoallylic alcohol product. Since the aldehyde and homoallylic alcohol in these cases are not volatile and they can be fully extracted into the organic layer, we consider this method to be accurate and convenient for yield determination.

The yields reported in Table 2 were determined as the isolation yields. The α:γ ratio in Table 3 were determined using ^1H NMR peak areas for the allylic C–H protons of the homoallylic alcohol products ($\delta\approx2.5$ for α and $\delta\approx3.4$ for γ). The *anti*:*syn* ratio in Table 3 were determined using the GC–MS method.

7.1. Typical procedure of $SnCl_2$ and $MCl_x/SnCl_2$-mediated carbonyl allylation

To a mixture of carbonyl compound (10 mmol) and allyl halide (15 mmol) in water, $SnCl_2$ (20 mmol) and certain catalyst were added (for the detailed amount of water and catalyst please see Tables 1–3). The mixture was vigorously stirred at room temperature for approximately 3 h. The mixture was extracted with ether (3×30 mL). The combined organic layers were washed by water (2×20 mL). Then the organic layer was dried over anhydrous $MgSO_4$ and was filtered and evaporated. The residue, for most cases, afforded the corresponding homoallylic alcohols of sufficient purity as judged by TLC and 300 MHz ^1H NMR without the need for further purification. If necessary, purification was performed by flash column chromatography (silica gel: 60–120 mesh; eluent: ethyl acetate–petroleum, 1/5 v/v). The products in Table 2 are known compounds. Some products in Table 3 are new compounds and listed below.

7.1.1. 1,2-Diphenyl-but-3-en-1-ol. IR (neat, cm^{-1}) 3422, 3078, 3029, 2930, 1643, 1600, 1496, 1450, 744, 699. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 7.35–7.05 (m, 10H), 6.25 (m, 1H), 5.30 (q, J=8.73 Hz, 2H), 4.85 (m, 1H), 3.55 (t, J=8.21 Hz, 1H), 2.30 (br, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) δ 141.8, 140.6, 140.3, 137.9, 137.7, 128.8, 128.7, 128.4, 127.9, 127.7, 127.4, 127.1, 126.7, 126.6, 118.5, 117.2, 77.5, 77.2, 59.2, 58.5. HRMS (EI) *m*/*z* calcd for $C_{16}H_{16}O$ 224.1201. Found 224.1252. GC (column temp.=250 °C) t_R=8.51 (*anti*), 10.60 (*syn*).

7.1.2. 1-(4-Methoxy-phenyl)-2-phenyl-but-3-en-1-ol. IR (neat, cm^{-1}) 3441, 3029, 2906, 1635, 1611, 1585, 1513, 1453, 1248, 701, 676. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26–7.00 (m, 7H), 6.73 (d, J=11.49 Hz, 2H), 6.25 (m, 1H), 5.26 (m, 2H), 4.80 (d, J=12.0 Hz, 1H), 3.74 (s, 3H), 3.52 (m, 1H), 2.25 (br, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 158.8, 140.4, 138.3, 137.9, 134.2, 134.1, 132.1, 128.9, 128.7, 128.0, 127.9, 127.2, 126.6, 126.5, 118.3, 117.3, 116.2, 115.2, 113.7, 113.5, 113.4, 75.5, 74.5, 59.4, 58.6, 55.4, 55.3. HRMS (EI) *m*/*z* calcd for $C_{17}H_{18}O_2$ 254.3280. Found 254.3252. GC (column temp.=250 °C) t_R=10.86 (*anti*), 11.06 (*syn*).

7.1.3. 1-(4-Nitro-phenyl)-2-phenyl-but-3-en-1-ol. IR (neat, cm^{-1}) 3422, 3080, 3028, 1637, 1601, 1518, 1493, 1452, 1346, 759, 700. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.05 (d, J=7.90 Hz, 2H), 7.30–7.18 (m, 5H), 7.04 (d, J=7.40 Hz, 2H), 6.25 (m, 1H), 5.34 (m, 2H), 4.94 (d, J=7.76 Hz, 1H), 3.50 (t, J=8.54 Hz, 1H), 1.60 (br, 1H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) (*anti*) 149.4, 139.7, 137.0, 128.8, 128.3, 127.6, 127.3, 123.2, 119.5, 76.5, 59.5. HRMS (EI) *m*/*z* calcd for $C_{16}H_{15}NO_3$ 269.2994. Found 269.2911. GC (column temp.=250 °C) t_R=13.12 (*anti*), 13.32 (*syn*).

7.1.4. 3-Phenyl-undec-1-en-4-ol: (*anti*). IR (neat, cm^{-1}) 3380, 3060, 1600. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 7.41–7.19 (m, 5H), 6.12 (m, 1H), 5.22 (q, J=7.0 Hz, 2H), 3.80 (m, 1H), 3.25 (t, J=8.13 Hz, 1H), 1.78(br, 1H), 1.48–1.21 (m, 12H), 0.88 (t, J=6.6 Hz 3H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) (*anti*) δ 142.0, 138.5, 128.5, 128.4, 126.6, 126.1, 117.2, 74.0, 57.1, 34.6, 31.7, 29.6, 29.5, 25.7, 22.6, 14.0. HRMS (EI) *m*/*z* calcd for $C_{17}H_{26}O$ 246.3918. Found 246.3930. GC (column temp.=250 °C) t_R=8.99 (*anti*), 9.09 (*syn*).

7.1.5. 6-Methyl-3-phenyl-hept-1-en-4-ol: (*anti*). IR (neat, cm^{-1}) 3421, 3078, 3025, 2985, 1640, 1600, 1495, 1450, 1000, 744, 699. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 7.41–7.19 (m, 5H), 6.05 (m, 1H), 5.18 (q, J=7.0 Hz, 2H), 3.87 (m, 1H), 3.20 (t, J=8.03 Hz, 1H), 1.80 (br, 1H), 1.32 (m, 2H), 1.11 (m, 1H), 0.87 (d, J=5.23 Hz, 6H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm) (*anti*) 141.9, 138.4, 128.8, 128.3, 126.7, 117.7, 72.1, 57.9, 43.9, 24.5, 23.8, 21.6. HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O$ 204.3114. Found 204.3158. GC (column temp.=250 °C) t_R=5.39 (*anti*), 5.54 (*syn*).

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Highly stable pseudo[2]rotaxanes co-driven by crown ether–ammonium and donor–acceptor interactions

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Abstract—Bis-*p*-phenylene-34-crown-10 derivatives **1** and **2**, bearing one and two dibenzo[24]crown-8 units, respectively, and 4,4′-dipyridinium derivatives of **3**·3PF_6 and of **4**·4PF_6, bearing one and two ammonium groups, respectively, have been synthesized from readily available starting materials. ^{1}H NMR and UV–vis studies reveal that in polar acetonitrile **1** binds **3**·3PF_6 to produce pseudo[2]rotaxane **1**·**3**·3PF_6 by making use of one donor–acceptor and one electrostatic interaction, whereas **2** binds **4**·4PF_6 to form pseudo[2]rotaxane **2**·**4**·4PF_6 through one donor–acceptor and two electrostatic interactions. The association constants of the two pseudorotaxanes have been determined by the UV–vis titration method to be 9.1 ($\pm$1.0)$\times10^3$ M^{-1} and 6.5 ($\pm$0.7)$\times10^5$ M^{-1}, respectively. The high stability of the new pseudo[2]rotaxanes has been ascribed to the cooperative interaction of the two different non-covalent forces.

1. Introduction

Pseudorotaxanes are non-interlocked counterparts of rotaxanes, in which a linear molecule interpenetrates the cavities of one or more macrocyclic molecules to form inclusion complexes.[1] This kind of structurally unique complexes are not only important precursors or 'intermediates' for the formation of a large number of rotaxanes and catenanes,[2] but also have been used as new models for mimicking photosynthetic centers and photo-tuned molecular devices.[3,4] Recently, several stable pseudorotaxanes have also been utilized to assemble nano-sized functional materials.[5]

Development of efficient approaches for improving or regulating the stability of pseudorotaxanes is of great importance for their future applications in materials science and further functionalizations. The stability of a pseudorotaxane can be remarkably affected by many factors, including the structures of its linear and cyclic components, solvent and temperature. Nevertheless, the non-covalent force between the components obviously plays the most important role.[6,7] Most pseudorotaxanes reported yet make use of a single non-covalent interaction, such as hydrogen bonding, electrostatic interaction, solvophobic interaction, and metal-ligand coordination, as the driving force to induce their formation. In principle, increase in the number of the binding sites should be able to improve the stability of a pseudorotaxane. However, this seemingly simple approach will need to modify the cyclic component, which is usually a daunting work due to the inherent difficulty in the synthesis of marcocyclic compounds.[8,9] Previously, we have demonstrated that introducing two different non-covalent interactions into a pseudorotaxane architecture could significantly increase its stability compared to similar supramolecular systems driven by single non-covalent interaction.[10] Similar approaches have also been utilized to assemble a number of other interlocked supramolecules.[11,12] In this paper, we report that complexation between dibenzo[24]crown-8 and ammonium and donor–acceptor interaction between electron rich bis-*p*-phenylene-34-crown-10 and electron deficient 4,4′-dipyridinium could interact cooperatively to generate a new series of highly stable pseudo[2]rotaxanes in polar acetonitrile.[13,14]

2. Results and discussion

Compounds **1** and **2** have been designed as the ring components, in which one bis-*p*-phenylene-34-crown-10 unit is connected with one and two dibenzo[24]crown-8 units, respectively, whereas cationic compounds **3**·3PF_6 and **4**·4PF_6 have been used as linear components, in which the electron deficient 4,4′-dipyridinium unit is linked with additional alkyl ammonium chains.[15] Instead of using the smaller dibenzo[18]crown-6 unit which possesses an even stronger binding ability towards ammonium or alkylammonium,[16] we had chosen to use the dibenzo[24]-crown-8 unit for complexing alkylammonium, since this

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larger crown ether can allow the interpenetration of a secondary ammonium through its cavity and we logically viewed this work as a first step towards the development of new generation of pseudo[*n*]rotaxanes and [*n*]rotaxanes ($n \geq 3$) (Chart 1).[13]

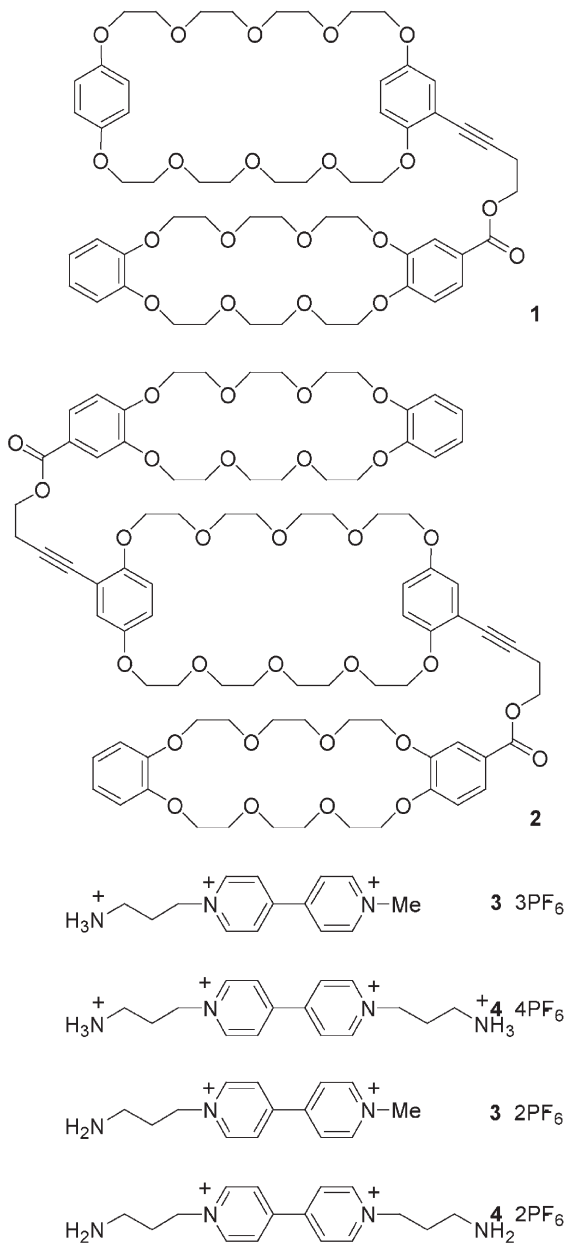
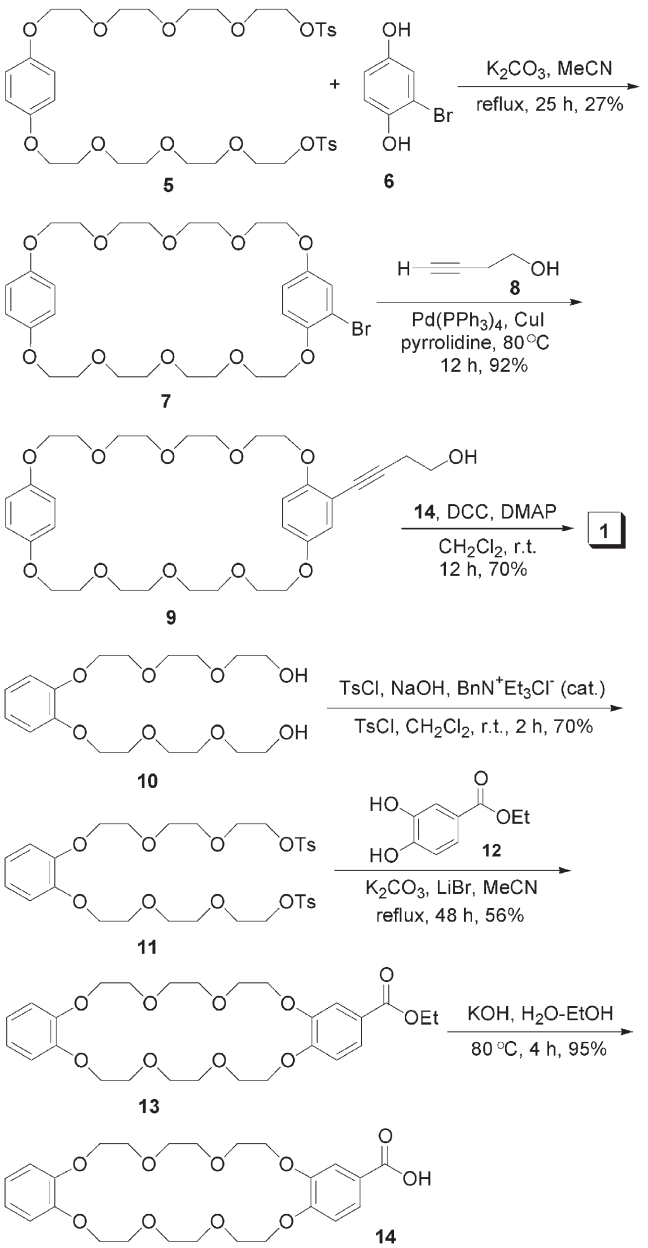


Chart 1.

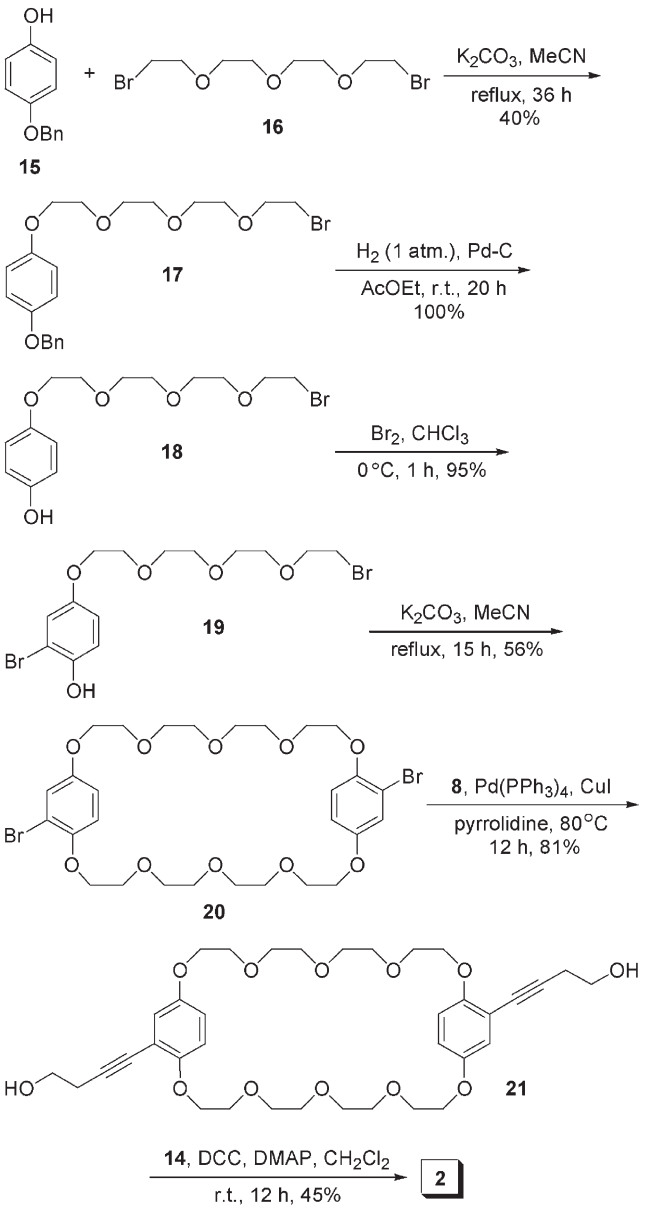
The synthesis of compound **1** is provided in Scheme 1. Macrocycle **7** was first prepared from the reaction of **5** and **6** according to a method we develop previously.[10] The palladium-catalyzed coupling reaction of **7** with compound **8** in hot pyrrolidine produced compound **9** in 92% yield. Treatment of **9** with crown ether **14** in dichloromethane with dicyclohexyl carbodiimide (DCC) as condensing reagent afforded macrocycle **1** in 70% yield. The synthesis of **14** started from diol **10**. Thus, treatment of **10** with tosyl chloride in dichloromethane first afforded **11** in 70% yield. The latter was then reacted with compound **12** in refluxing



Scheme 1.

acetonitrile in the presence of potassium carbonate to produce crown ether **13** in 56% yield. Finally, hydrolysis of **13** with potassium hydroxide in hot water and ethanol afford **14** in 95% yield.

For the synthesis of compound **2**, bromide **17** was first prepared from the reaction of phenol **15** and excessive amount of dibromide **16** in refluxing acetonitrile. Then, **17** was hydrogenated in the presence of Pd–C in ethyl acetate to give **18** in quantitative yield. Compound **18** was then selectively converted into phenol **19** in 95% yield. Self-macrocyclization of **19** in the presence of potassium carbonate in refluxing acetonitrile produced **20** in 56% yield. This compound was then treated with excessive amount of diol **8** with palladium(0) as catalyst to afford diol **21**. Finally, **21** was reacted with acid **14** with DCC as a coupling reagent to give **2** in 45% yield (Scheme 2).



Scheme 2.

The syntheses of ionic molecules **3**·3PF_6 and **4**·4PF_6 are shown in Scheme 3. Thus, treatment of compound **22** with bromide **23** in hot DMF produced tricationic compound **3**·3PF_6 after purification and anionic exchange with NH_4PF_6. In a similar way, dipyridyl **24** was reacted with **23** in hot DMF to yield compound **4**·4PF_6 after purification and anionic exchange. For the sake of comparison, compounds **3**·2PF_6 and **4**·2PF_6 were also prepared based on reported methods.[17,18]

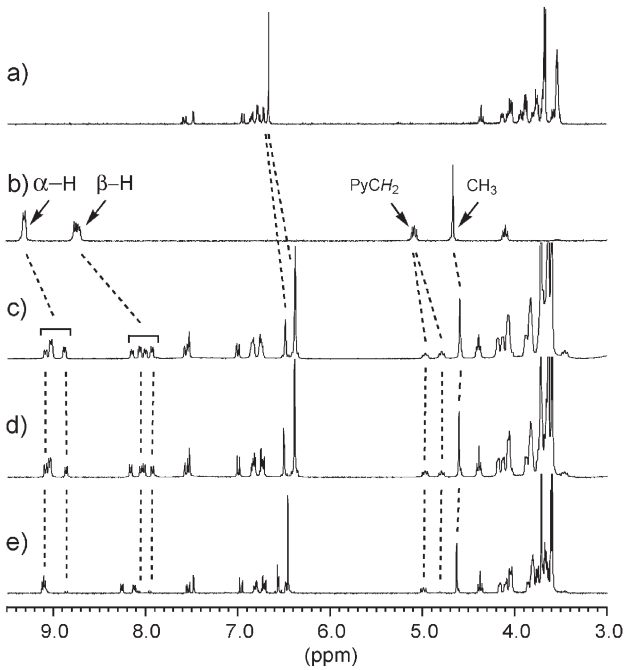
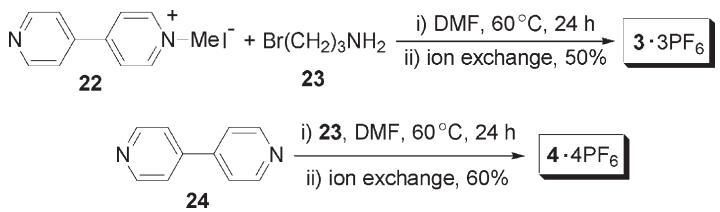
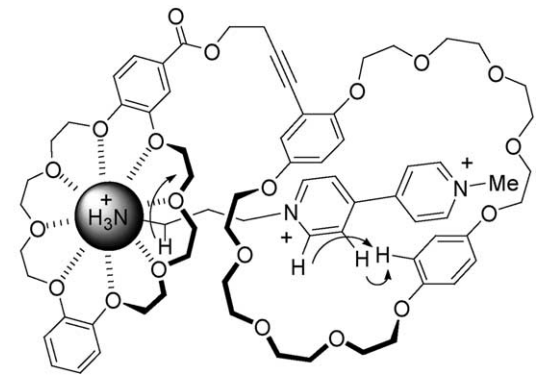


Figure 1. Partial ^{1}H NMR (400 MHz) of (a) **1** (20 mM), (b) **3**·3PF_6 (20 mM), (c) **1**+**3**·3PF_6 (1:1, 20 mM), (d) **1**+**3**·3PF_6 (1:1, 3 mM), and (e) **1**+**3**·3PF_6 (1:1, 0.5 mM) in MeCN-d_3 at 25 °C.

Adding 1 equiv. of **1** to the solution of 1 equiv. of **3**·3PF_6 in MeCN-d_3 caused the signals of **3**·3PF_6 to shift upfield substantially, as shown in Figure 1. The signals of the aromatic protons of the bis-*p*-phenylene-34-crown-10 unit of **1** also moved upfield significantly. 2D-NOESY ^{1}H NMR experiments also revealed intermolecular NOE connections of moderate strength, which are shown in Chart 2 (vide infra). In addition, the 1:1 solution of the two compounds in acetonitrile also displayed a charger-transfer absorbance band at λ_{max}=435 nm in the UV–vis spectrum. All these observations indicate that stacking between the electron deficient and rich aromatic units occurred as a result of the intermolecular donor–acceptor interaction.[19] The α- and β-H signals of the pyridine units, which produced two sets of signals in pure **3**·2PF_6 as a result of its unsymmetric structure, were further split into four sets of signals (Fig. 1c). The signals had been assigned based on the 2D-NOESY ^{1}H NMR experiments. Adding triethylamine (5 equiv.) to the 1:1 solution induced the signals to combine to produce two sets of signals, while two sets of signals were also observed in the ^{1}H NMR spectrum of the 1:1 mixture of **1** and **3**·2PF_6 in MeCN-d_3. Therefore, the above splitting can be reasonably attributed to the formation of two isomeric complexes **1**·**3**·3PF_6 (A) and **1**·**3**·3PF_6 (B) as a result of the different orientation of the dibenzo[24]crown-8 relative to its bis-*p*-phenylene-34-crown-10 unit (Chart 2), although



Scheme 3.



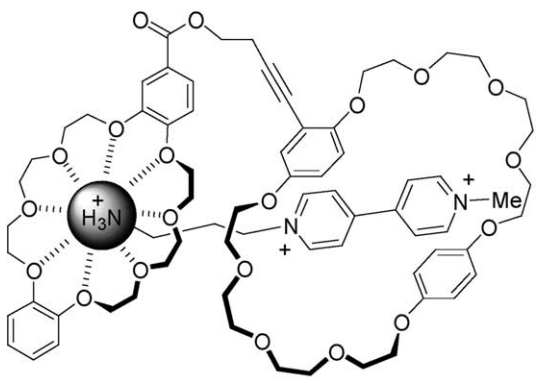


Chart 2.

we are not able to differentiate between them at the present stage.

Increasing the temperature of the 1:1 solution from 25 to 75 °C did not induce the split signals to coalescence or to shift upfield or downfield greatly, indicating that the binding was strong and the exchanging processes between the two isomers was slow on the NMR time scale even at increased temperature. Reducing the temperature of the solution to −20 °C either had no important influence on the relative ratio of the two sets of signals. Interestingly, reducing the solution concentration from 60 to 0.5 mM could lead to one set of the signals to decrease significantly (Fig. 1c–e), which implied that one of the isomers was converted to another one at lowered concentration.

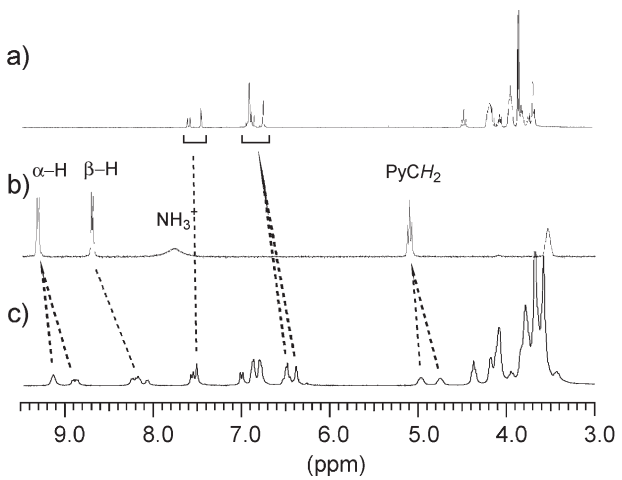


Figure 2. Partial ^{1}H NMR (400 MHz) spectrum of (a) **2** (20 mM), (b) **4**·4PF$_6$ (20 mM), and (c) **2**+**4**·4PF$_6$ (1:1, 20 mM) in MeCN-d_3 at 25 °C.

Mixing the same equiv. of **2** and **4**·4PF$_6$ in MeCN-d_3 also induced the ^{1}H NMR signals of both compounds to shift substantially, indicative of the formation of complex **2**·**4**·4PF$_6$. As shown in Figure 2, the pyridine α- and β-H and the pyridine-linking CH_2 signals of **4**·4PF$_6$ moved upfield significantly and split into several sets of signals. Partial aromatic proton signals of **2** also shifted upfield. This result is similar to that observed for **1** in the mixture of **1** and **3**·3PF$_6$. The peaks had also been referred to with the 2D-NOESY ^{1}H NMR experiments, which also revealed intermolecular NOE connections (Chart 3, vide infra). The UV–vis spectrum of the solution also displayed a strong charge-transfer absorbance band (λ_{max}=456 nm) due to the intermolecular complexing interaction (Fig. 3, vide infra).

As observed for the mixture of **1** and **3**·3PF$_6$, the ^{1}H NMR splitting of the pyridine proton signals of **4**·4PF$_6$ in the mixture solution might be generated as a result of the different orientation of the peripheral dibenzo[24]crown-8 relative to the central bis-*p*-phenylene-34-crown-10 unit of **2**. In principle, there was also another possibility: the two ammoniums of **4**·4PF$_6$ bound the two dibenzo[24]crown-8 units, respectively, while its central dipyridinium unit did not thread through the cavity of the bis-*p*-phenylene-34-crown-10 unit of **2**. However, this possibility could be ruled out due to the following results. First, it was reported that the binding ability of the dibenzo[24]crown-8 unit towards alkylammonium is very weak (K_{assoc}=ca. 50 M^{-1} in MeCN-d_3).[20] Secondly, adding excessive amount of **2** to the 1:1 mixture solution did not impose notable influence on the ratio of the split pyridine signals of **4**·4PF$_6$. Finally, as shown in Figure 2, all the split signals of the pyridine unit of **4**·4PF$_6$ shifted upfield remarkably (0.15–0.55 ppm), which is obviously impossible for an uncomplexed and unthreaded dipyridinium unit. In principle, there are three possible isomers (*trans*–*trans*, *trans*–*cis*, and *cis*–*cis*) for complexes **2**·**4**·4PF$_6$, depending on the different orientation of the two dibenzo[24]crown-8 units of **2** relative to its bis-*p*-phenylene-34-crown-10 unit. As an example, one of the three isomeric complexes is shown in Chart 3.

The complicated splitting pattern and the lowered resolution at lower concentration of the ^{1}H NMR spectra of both complexes made it impossible to utilize the ^{1}H NMR titration or dilution method to quantitatively study their binding stability.[21] Therefore, UV–vis titration experiments were carried out at fixed concentration of **1** or **2** by observing the change of the charge-transfer absorbance with the increase in the ionic component for both complexes in acetonitrile.[22] Association constants of 9.1 (±1.0)×10^3 M^{-1} (ΔG=5.40 kcal/mol) and 6.5 (±0.7)×10^5 M^{-1} (ΔG=7.8 kcal/mol) were obtained by a linear regression of the titration data according to a 1:1 binding mode.[23] As an example, the plot of the charge-transfer absorbance change of the solution of **2** and **4**·4PF$_6$ with the addition of the latter is presented in Figure 3. By utilizing the ^{1}H NMR dilution method,[24] the association constants of **1**·**3**·2PF$_6$, **2**·**4**·2PF$_6$, and the complex between

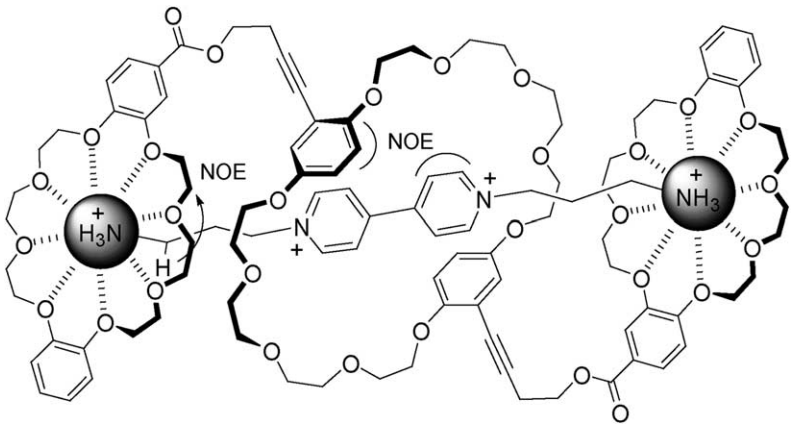


Chart 3. One of three possible **2**·**4**·4PF_6 isomers.

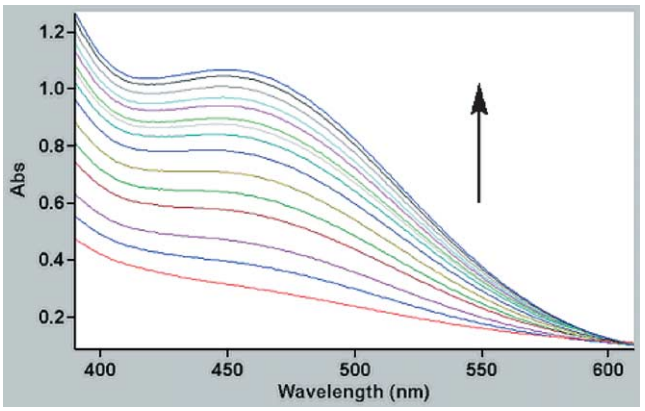


Figure 3. The plot of the charge-transfer absorption change of the solution of **2** (3.3 mM) in acetonitrile with the addition of **4**·4PF_6 from 0.5 to 60 mM.

13 and $^{+}NH_3C_3H_7$-*n* PF_6^- in MeCN-d_3 were also determined to be ca. 200, 190, and 34 M^{-1} (ΔG=3.1, 3.1, and 2.1 kcal/mol), respectively. Comparing the stabilities of the complexes reveals that pronounced cooperative interaction exists between the two non-covalent forces to drive the formation of pseudo[2]rotaxane **1**·**3**·3PF_6, **2**·**4**·4PF_6.

3. Conclusion

In summary, we have reported the self-assembly and characterizations of two new pseudo[2]rotaxanes in acetonitrile from two new macrocyclic polyethers based on the donor–acceptor interaction between the electron rich bis-*p*-phenylene-34-crown-10 unit and the electron deficient 4,4-dipyridinium unit and the electrostatic interaction between the dibenzo[24]crown-8 unit and alkylammonium. The pseudo[2]rotaxanes exist as stable conformational isomers as a result of the different orientation of the dibenzo[24]-crown-8 unit relative to the bis-*p*-phenylene-34-crown-10 in the macrocyclic polyethers. These new supramolecular architectures display high stability in polar acetonitrile due to the cooperative effect of the two different non-covalent forces. Future work will be focused on the construction of new generation of [*n*]rotaxanes (n>2) with covalently connected ring components.

4. Experimental

4.1. General methods

Melting points are uncorrected. All reactions were carried out under an atmosphere of nitrogen. The ^{1}H NMR spectra were recorded on 400 or 300 MHz spectrometers in the indicated solvents. Chemical shifts are expressed in parts per million (δ) using residual solvent protons as internal standards. Chloroform (δ 7.26 ppm) was used as an internal standard for chloroform-*d*. Elemental analysis was carried out at the SIOC Analytical Center. Unless otherwise indicated, all commercially available materials were used as received. All solvents were dried before use following standard procedures. Compounds **5**,[25] **6**,[26] **7**,[10] **10**,[27] **15**,[28] and **16**[29] were prepared according to reported methods.

4.1.1. 1,4,7,13,20,23,26,29,32-Decaoxa-15-(4-hydroxy-but-1-ynyl)[13,13]paracyclophane (9). To a stirred solution of compound **7** (0.10 g, 0.22 mmol), $Pd(PPh_3)_4$ (83 mg, 0.07 mmol), and cupric iodide (10 mg) in pyrrolidine (5.0 mL) was added a solution of 3-butyl-1-ol **8** (0.1 mL) in pyrrolidine (1.5 mL). The mixture was stirred at 80 C for 12 h and then concentrated in vacuo. The resulting residue was triturated with dichloromethane (50 mL) and the organic phase washed with hydrochloric acid (1 N, 5 mL), water (5 mL), brine (5 mL), and dried over sodium sulfate. Upon removal of the solvent under reduced pressure, the crude product was subjected to column chromatography (EtOAc/MeOH 40:1) to give compound **9** as a colorless oil (0.13 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=6.92 (d, J=3.0 Hz, 1H), 6.81–6.75 (m, 5H), 6.70 (d, J=9.0 Hz, 1H), 4.08–3.65 (m, 34H), 2.69 (t, J=5.4 Hz, 2H). HRMS MS (EI): *m*/*z* 605.2956. Calcd for $C_{32}H_{44}O_{11}$: 605.2960.

4.1.2. Compound 1. A suspension of compounds **7** (0.30 g, 0.50 mmol) and **13** (0.25 g, 0.50 mmol) in dichloromethane (5 mL) was stirred for 30 min in an ice-bath. A solution of DCC (0.12 g, 0.60 mmol) and DMAP (0.01 g) in dichloromethane (2 mL) was added. The mixture was stirred for 1 h at room temperature and dichloromethane (20 mL) was added. The organic phase was washed with hydrochloric acid (2 M, 20 mL), saturated $NaHCO_3$ solution (20 mL), water (20 mL×2), brine (20 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the resulting residue was purified by column chromatography (AcOEt/

MeOH 15:1) to afford compound **1** as a colorless oil (0.38 g, 70%). ^{1}H NMR (acetone-d_6, 300 MHz): δ=7.68 (d, d, J_1=2.4 Hz, J_2=9.0 Hz, 1H), 7.56 (d, J=1.5 Hz, 1H), 7.33 (d, J=9.0 Hz, 1H), 6.97–6.94 (m, 2H), 6.91–6.86 (m, 3H), 6.83–6.81 (m, 2H), 6.77–6.75 (m, 4H), 4.46 (t, J=7.0 Hz, 4H), 4.24–4.18 (m, 2H), 4.12–4.05 (m, 6H), 3.96–3.91 (m, 8H), 3.84–3.81 (m, 8H), 3.77–3.76 (m, 16H), 3.70–3.63 (m, 16H), 2.93 (t, J=7.0 Hz, 2H). MS (ESI): *m*/*z* 1079 $[M+H]^+$. Anal. Calcd for $C_{57}H_{74}O_{20}$: C, 63.44; H, 6.91. Found: C, 63.07; H, 7.02.

4.1.3. 1,2-Bis[2-[2-[2-(2-tosyloxyethoxy)-ethoxy]-ethoxy]-benzene (11).[30] To a stirred solution of compound **10** (9.00 g, 24.0 mmol), tosyl chloride (11.5 g, 60.0 mmol), and Et_3NBn^+ Cl^- (0.45 g, 1.90 mmol) in dichloromethane (200 mL) was added aqueous sodium hydroxide solution (30%, 36 mL). The mixture was then stirred vigorously at room temperature for 3 h. The organic phase was separated, and washed with dilute sodium carbonate, water, brine, and dried over sodium sulfate. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography (CH_2Cl_2/MeOH 200:1) to obtain compound **11** as an oily solid (13.50 g, 82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, J=8.4 Hz, 4H), 7.33 (d, J=8.4 Hz, 4H), 6.91(m, 4H), 4.16–4.12 (m, 8H), 3.84–3.80 (m, 4H), 3.70–3.66 (m, 8H), 3.61–3.59 (m, 4H), 2.43 (s, 6H). MS (EI): *m*/*z* 683 $[M+H]^+$.

4.1.4. Ethyl 6,7,9,10,12,13,20,21,23,24,6,27-dodecahydrodibenzo[*b*,*n*][1,4,7,10,13,16,19,22]octaoxacyclotetracosine-2-carboxylate (13). A suspension of **11** (6.14 g, 9.00 mmol) and potassium carbonate (5.04 g, 36.0 mmol) in acetonitrile (450 mL) was stirred at room temperature for 20 min. Then, a solution of **12** (1.62 g, 9.00 mmol) in acetonitrile (50 mL) was added. The mixture was heated under reflux for 48 h and the solid then concentrated under reduced pressure. The resulting residue was triturated with dichloromethane (200 mL). The organic phase was washed with dilute hydrochloric acid, water, brine, and dried over sodium sulfate. Upon removal of the solvent, the oily residue was purified with column chromatography (CH_2Cl_2/MeOH 99:1) to produce gave compound **13** as an oily solid (2.62 g, 56%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.65 (d, d, J_1=1.8 Hz, J_2=8.7 Hz, 1H), 7.54 (d, J=1.8 Hz, 1H), 6.83–6.89 (m, 5H), 4.34 (q, J=7.2 Hz, 2H), 4.13–4.24 (m, 8H), 3.90–3.98 (m, 8H), 3.79–3.86 (m, 8H), 1.38 (t, J=6.9 Hz, 3H). MS (EI): *m*/*z* 520 $[M]^+$. Anal. Calcd for $C_{27}H_{36}O_{10}$: C, 62.36; H, 6.98. Found: C, 62.05; H, 6.78.

4.1.5. 2,5,8,11,18,21,24,27-Octaoxa-tricyclo[26.4.0.0^{12,17}]-dotriaconta-1(28),12,14,16,29,31-hexaene-14-carboxylic acid (14). To a solution of **13** (1.00 g, 2.00 mmol) in ethanol (15 mL) was added aqueous potassium hydroxide solution (4 N, 3 mL). The solution was then heated under reflux for 12 h. Upon cooling to room temperature, hydrochloric acid was added to pH=4. The solution was concentrated in vacuo and the resulting residue was washed with water thoroughly and dried. The resulting white solid was recrystallyzed from ethanol to give compound **14** (0.85 g, 95%) as a white solid. Mp 184–186° [182–183 °C[31]]. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.72 (d, d, J_1=1.5 Hz, J_2=8.4 Hz, 1H), 7.56 (d, J=2.1 Hz, 1H), 6.89–6.86 (m, 5H), 4.21–4.15 (m, 8H), 3.95–3.85 (m, 16H). MS (EI): *m*/*z* 492 $[M]^+$.

4.1.6. 4-[2-[2-[2-(2-Bromo-ethoxy)-ethoxy]-ethoxy]-ethoxy]-phenyl benzyl ether (17). A mixture of **15** (5.70 g, 28.0 mmol), **16** (45.0 g, 0.14 mol), and potassium carbonate (7.00 g, 70.0 mmol) in dry acetone (200 mL) was stirred at room temperature for 1 h and then under reflux for another 36 h. Upon cooling to room temperature, the solid was filtered and washed with chloroform. The filtrate was concentrated under reduced pressure and the resulting residue was taken up by ether (300 mL). The organic phase was then washed with dilute sodium carbonate solution (2 N), water, brine, and dried over sodium sulfate. After the solvent was removed in vacuo, the crude product was purified by column chromatography (petroleum ether/AcOEt 6:1) to afford the desired product as a white solid (5.00 g, 40%). ^{1}H NMR ($CDCl_3$): δ=7.45–7.32 (m, 5H), 6.92–6.83 (m, 4H), 5.01 (s, 2H), 4.10–4.07 (m, 2H), 3.85–3.68 (m, 12H), 3.47 (t, J=6.0 Hz, 2H). MS (EI): *m*/*z* 438 $[M]^+$. Anal. Calcd for $C_{21}H_{27}BrO_5$: C, 57.41; H, 6.19. Found: C, 57.64; H, 6.15.

4.1.7. 4-[2-[2-(2-Propoxy-ethoxy)-ethoxy]-ethoxy]phenol (18). A suspension of compound **17** (23.0 g, 44.0 mmol) and Pd–C (10%, 2.00 g) in ethyl acetate (400 mL) was stirred at room temperature under 1 atom of hydrogen gas for 8 h. The solid was then removed by filtration through celite. The filtrate was evaporated under reduced pressure and the resulting residue purified by column chromatography (CH_2Cl_2/AcOEt 30:1) to afford compound **18** as a colorless oil (15.0 g, 98%). ^{1}H NMR ($CDCl_3$, 300 Hz): δ=6.74 (d, J=1.2 Hz, 4H), 5.58 (s, 1H), 4.03–4.00 (m, 2H), 3.83–3.77 (m, 4H), 3.75–3.67 (m, 8H), 3.44 (t, J=6.0 Hz, 2H). MS (EI): *m*/*z* 348 $[M]^+$. Anal. Calcd for $C_{14}H_{21}BrO_5$: C, 48.15; H, 6.06. Found: C, 48.02; H, 5.92.

4.1.8. 2-Bromo-4-[2-[2-[2-(2-bromo-ethoxy)-ethoxy]-ethoxy]-ethoxy]phenol (19). To a solution of compound **18** (10.8 g, 31.0 mmol) in dichloromethane (100 mL), cooled in an ice bath, was added dropwise a solution of bromine (1.7 mL, 31.0 mmol) in dichloromethane (50 mL) within 30 min. The mixture was stirred at 0 °C for 1 h. Then, aqueous $NaHSO_3$ solution (5%, 100 mL) was added. Stirring was continued until the mixture became colorless. The organic phase was washed with water (50 mL×2), brine (50 mL), and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude produce was purified by flash chromatography (AcOEt/petroleum ether 1:4) to produce compound **19** as a colorless oil (12.5 g, 95%). ^{1}H NMR ($CDCl_3$): δ=7.03 (d, J=3.0 Hz, 1H), 6.92 (d, J=9.0 Hz, 1H), 6.92 (d, d, J_1=3.0 Hz, J_2=9.0 Hz, 1H), 5.44 (s, 1H), 4.06–4.03 (m, 2H), 3.84–3.78 (m, 4H), 3.74–3.68 (m, 8H), 3.46 (t, J=6.0 Hz, 2H). HRMS (EI) Calcd for $C_{14}H_{20}Br_2O_5$: 425.9676. Found: 448.9576 $[M+Na]^+$.

4.1.9. 1,4,7,13,20,23,26,29,32-Decaoxa-15,34-dibromo-[13,13]paracyclophane (20). A suspension of phenol **19** (0.85 g, 2.00 mmol) and potassium carbonate (1.40 g, 10.0 mmol) in acetonitrile (80 mL) was heated under reflux for 24 h and then cooled to room temperature. The solid was filtered off and the filtrate was concentrated under reduced pressure. The resulting residue was triturated in 100 mL of

dichloromethane and the organic phase was washed with dilute sodium carbonate solution, water, brine, and dried over sodium sulfate. Upon removal of the solvent in vacuo, the crude produce was purified by column chromatography (CH_2Cl_2/AcOEt 2:1) to afford compound **20** as a white solid (0.38 g, 56%). Mp 104–106 °C. ^{1}H NMR ($CDCl_3$): δ=7.08 (d, J=3.0 Hz, 2H), 6.78 (d, J=9.0 Hz, 2H), 6.73 (d, d, J_1=9.0 Hz, J_2=3.0 Hz, 2H), 4.04–4.07 (m, 4H), 3.99–3.96 (m, 4H), 3.88–3.85 (m, 4H), 3.83–3.80 (m, 4H), 3.78–3.75 (m, 4H), 3.70–3.64 (m, 12H). MS (EI): m/z 694 $[M]^+$. Anal. Calcd for $C_{28}H_{38}Br_2O_{10}$: C, 48.43; H, 5.52. Found: C, 48.44; H, 5.51.

4.1.10. 1,4,7,13,20,23,26,29,32-Decaoxa-15,34-di(4-hydroxy-but-1-ynyl)[13,13]paracyclophane (21). This compound was prepared as a white solid (81%) from the reaction of **8** and **19** according to the method described for **9**. Mp 72–74 °C. ^{1}H NMR ($CDCl_3$): δ=6.87 (d, J=3.0 Hz, 2H), 6.66 (d, J=9.0 Hz, 2H), 6.75 (d, d, J_1=9.0 Hz, J_2=3.0 Hz, 2H), 4.05–4.02 (m, 4H), 3.96–3.94 (m, 4H), 3.88–3.85 (m, 4H), 3.82–3.70 (m, 12H), 3.69–3.68 (m, 12H), 3.01 (br, 2H), 2.66 (t, J=6.0 Hz, 4H). MS (EI): m/z 672 $[M]^+$. Anal. Calcd for $C_{36}H_{48}O_{12}$: C, 64.28; H, 7.19. Found: C, 63.96; H, 6.80.

4.1.11. Cyclophane 2. This compound was prepared as a white solid (45%) from the reaction of **14** (2 equiv.) and **21** according to the method described for **1**. Mp 92–94 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ=7.67 (d, d, J_1=2.4 Hz, J_2=9.0 Hz, 2H), 7.57 (d, J=2.4 Hz, 2H), 6.91–6.82 (m, 12H), 6.72 (d, J=2.4 Hz, 4H), 4.45 (t, J=7.2 Hz, 4H), 4.19–4.14 (m, 16H), 4.04 (m, 4H), 3.96–3.91 (m, 20H), 3.85–3.79 (m, 24H), 3.74–3.66 (m, 16H), 2.88 (t, J=7.5 Hz, 4H). HRMS (MALDI-tof): Calcd for $C_{86}H_{108}O_{30}$: 1621.6192. Found: 1643.6818, $[M+Na]^+$.

4.1.12. 1-Methyl-[4,4′]bipyridylium iodide (22·I). A solution of 4,4′-dipyridyl (1.80 g, 11.0 mmol) and methyl iodide (0.80 mL, 14.0 mmol) in dichloromethane was stirred at reflux for 2 h. After the mixture was cooled to room temperature, the solid was filtered and washed with ethyl acetate thoroughly, the crude product was recrystallyzed from methanol to give the desired compound as a yellow solid (2.86g, 95%). Mp >248 °C (244 °C, lit.[32]). ^{1}H NMR (DMSO-d_6, 300 MHz): δ=9.14 (d, J=6.6 Hz, 2H), 8.87 (d, J=6.0 Hz, 2H), 8.62 (d, J=6.6 Hz, 2H), 8.04 (d, J=6.0 Hz, 2H), 4.38 (s, 3H). MS (ESI): m/z 171 $[M-I]^+$.

4.1.13. 3-(1′-Methyl-4,4′-bipyridinium)propylammonium tris(hexafluorophosphate) (3·3PF$_6$). A suspension of the compound **22**·I (1.30 g, 4.80 mmol) and 3-bromopropylamine hydro bromide **23** (1.30 g, 5.50 mmol) in DMF (25 mL) was stirred at 60 °C for 24 h. After the mixture was cooled to room temperature, the solid was filtered, washed with methanol and ether thoroughly, and then dissolved in water (ca. 5 mL). Then, a saturated aqueous ammonium hexfluorophosphate was added dropwise to the above solution until no precipitate was generated. The precipitate was filtered and washed with cold water. After recrystallization from methanol, the desired product was obtained as a pale yellow solid (1.50 g, 50%). Mp >250 °C. ^{1}H NMR (acetone-d_6, 300 MHz): δ=9.41 (d, J=6.6 Hz, 2H), 9.35 (d, J=6.9 Hz, 2H), 8.84 (d, J=6.9 Hz, 2H), 8.82 (d, 2H, J=6.6 Hz), 5.19 (t, J=7.5 Hz, 2H), 4.74 (s, 3H), 3.62 (t, J=6.9 Hz, 2H,), 2.86 (m, 2H). MS (ESI): m/z 542 $[M-2PF_6^-]^{2+}$. Anal. Calcd for $C_{14}H_{20}F_{18}N_3P_4$: C, 22.48; H, 3.14; N, 6.55. Found: C, 22.39; H, 3.14; N, 6.24.

4.1.14. Compound 4·4PF$_6$. The compound was prepared as a yellowish solid (60%) from the reaction of **22** and **23** (2.2 equiv.) according to the method described for **3**·3PF$_6$. Mp >255 °C (decom.). ^{1}H NMR (acetone-d_6, 300 MHz): δ=9.36 (d, J=7.0 Hz, 4H), 8.87 (d, J=7.0 Hz, 4H), 5.15–5.10 (t, J=7.5 Hz, 4H), 3.53–3.54 (m, 4H), 2.80–2.75 (m, 4H). MS (ESI): m/z 417 $[M-3PF_6^-]^{3+}$. Calcd for $C_{16}H_{26}F_{24}N_4P_4$: C, 22.50; H, 3.07; N, 6.56. Found: C, 22.64; H, 3.20; N, 6.51.

4.2. Binding studies

For UV–vis absorption titration experiments, 2.5 mL of the mixture solution in acetonitrile with the fixed [**1**] or [**2**] and the changing concentration of the ionic components was placed in a cuvette and the UV–vis absorption spectra were sequentially recorded (15–20 samples). The values of the absorbance at the fixed wavelength were used. Origin 6.0 software was used to fit the data to a 1:1 binding isotherm: $\Delta A=(\Delta A_{max}/[H])\times\{0.5[G]+0.5([H]+K_d)-0.5[[G]^2+(2[G](K_d-[H])+(K_d+[H])^2)^{1/2}]\}$, where [G] is the concentration of the changing component (**3**·3PF$_6$ or **4**·4PF$_6$), [H] is the fixed concentration of the macrocycle (**1** or **2**), and $K_d=(K_{assoc})^{-1}$. For the ^{1}H NMR dilution study, the following equation was used to fit the 1:1 binding isotherm: $\Delta\delta=\delta-\delta_0=\Delta\delta_{max}\{1+(0.5/K_{assoc}[H])-[(0.5/K_{assoc}[H])^2+1/K_{assoc}[H]]^{1/2}\}$, where δ=chemical shift of the probe signal in monomer/complex mixture, δ_0=chemical shift of the probe signal in monomer.[24] Association constants reported are the average values of two experiments.

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Fries rearrangement of dibenzofuran-2-yl ethanoate under photochemical and Lewis-acid-catalysed conditions

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Abstract—The Fries rearrangement of dibenzofuran-2-yl ethanoate as a route to *o*-hydroxyacetyldibenzofurans has been investigated, both under thermal Lewis-acid catalysed and non-catalysed photochemical conditions. The reactions were examined theoretically at semi-empirical (PM3 and ZINDO/S) and density functional theory (DFT) levels. The correct selection of reaction conditions provides viable preparative routes to *ortho*-acylated hydroxydibenzofurans.

1. Introduction

Following previous work regarding the preparation of benzopsoralen analogues,[1] the synthesis of derivatives containing an acetyl group in position 4 of the pyranone ring was examined. This required the synthesis of acetyl-substituted hydroxydibenzofurans, and the readily available dibenzofuran-2-ol (**1**) was chosen as the starting material, as its acetyl ester **2** should undergo Fries rearrangement and potentially afford derivatives of this type (Fig. 1).

The Fries rearrangement of benzene derivatives is well known and can be induced either thermally or photochemically.[2,3] The thermal Fries reaction involves the formation of a solvent caged ion pair,[4] whereas the photoreaction occurs via radical intermediates.[2,5] In the latter case, electronic excitation is followed by homolytic cleavage to yield aryloxy and acyl radical pairs,[6] and calculations indicate that this involves the excited singlet state.[7] The photo-Fries rearrangement was first observed by Anderson and Reese, in 1960.[8] In both processes, the resulting pairs of ions or radicals are restrained by the solvent cage, until they combine to form rearrangement products. This can involve reformation of the original ester or formation of several isomeric ketone intermediates. Alternatively, the reactive species can diffuse apart to give other products.

In the present work, the photochemical and the Lewis acid catalysed thermal Fries rearrangements of **2** under a variety of conditions have been investigated and the results compared with theoretical predictions.

2. Experimental results

The synthesis of dibenzofuran-2-yl ethanoate (**2**) was obtained in almost quantitative yield (98% yield) by reaction of dibenzofuran-2-ol (**1**) with diethylmalonate, in pyridine.[9]

The acid catalysed experiments were conducted either without solvent or in dichloromethane solution, using $AlCl_3$ or $TiCl_4$ as Lewis acids, at various temperatures.

The photo-Fries reactions were carried out by sealing solutions of the dibenzofuran (solvents: ethanol, cyclohexane, dichloromethane and acetonitrile) in quartz tubes and exposing them for the appropriate length of time to the radiation from a 16 W low-pressure mercury lamp (principal emission at 254 nm). The main products (Fig. 1) were isolated by column chromatography and characterized by ^{1}H NMR, UV, IR and elemental analysis.

The product yields for both the dark and photochemical reactions were estimated by separation of the products by column chromatography or by high performance liquid chromatography (HPLC), using a silica column (Fig. 2). In order to estimate the yields for the main products by HPLC

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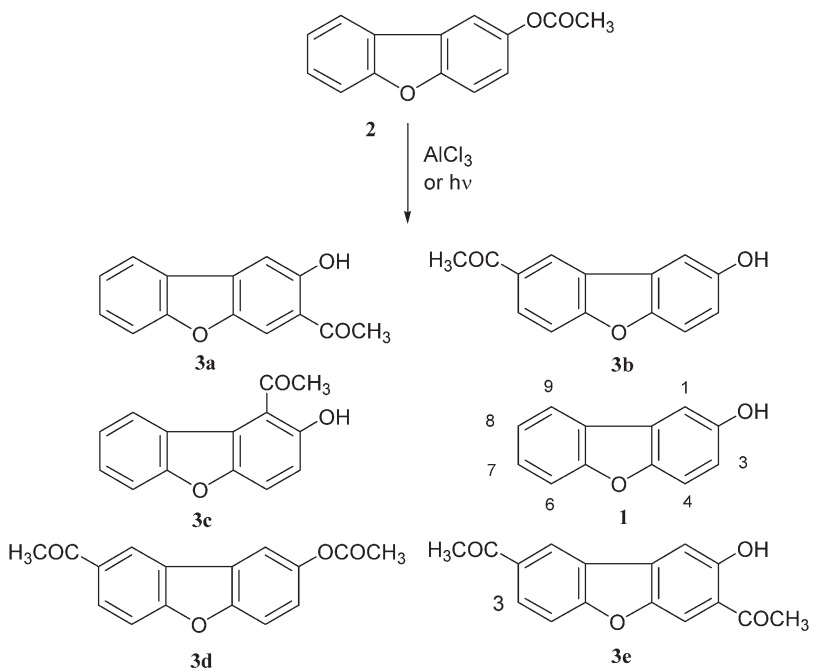

Figure 1. Products obtained in the Fries rearrangements.

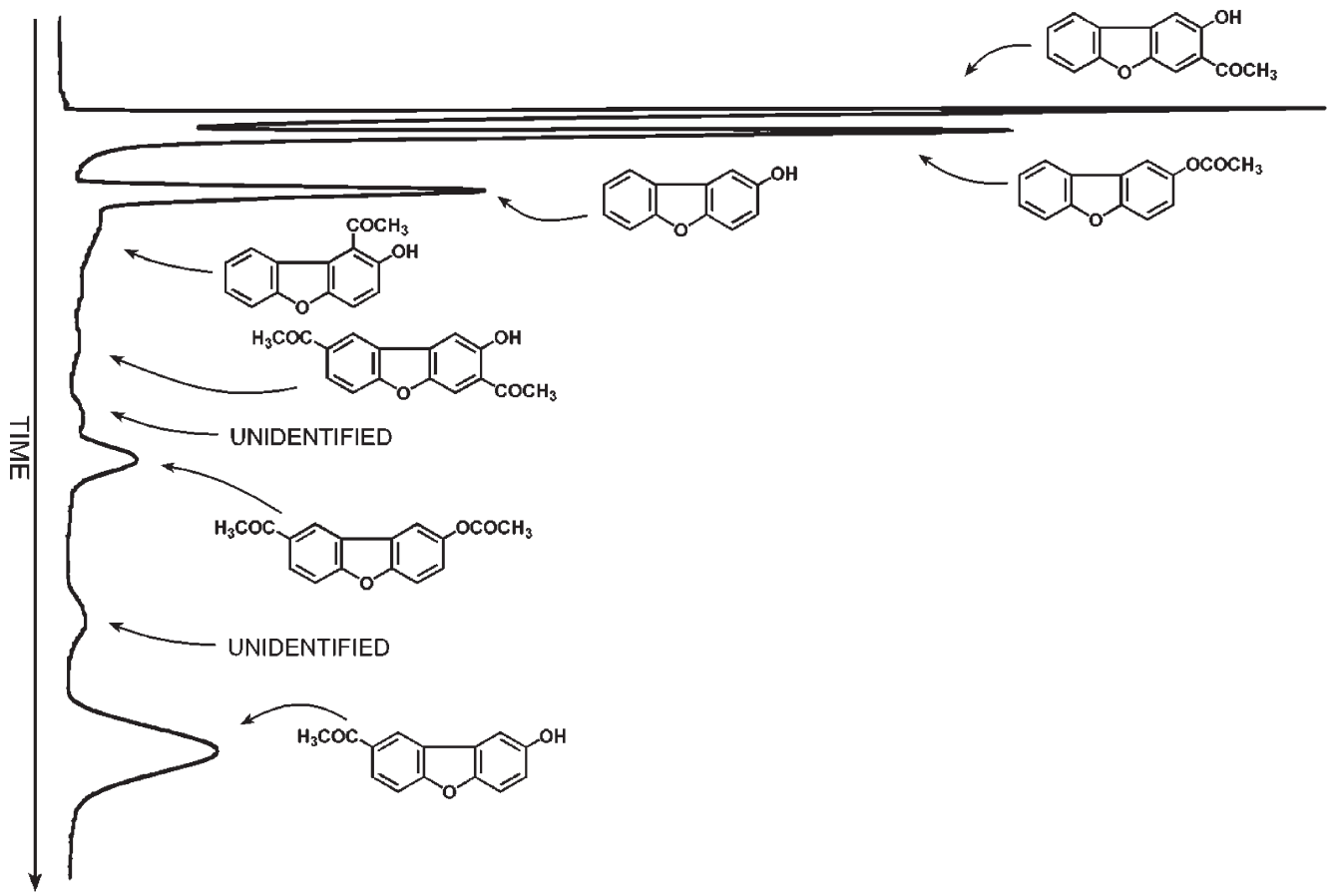

Figure 2. HPLC chromatogram from experiment 4 (see Table 1). Conditions: Column: LichroCART (5 μm, silica 60). Dimensions: 25 cm×4 mm. Mobile phase: AcOEt/hexane 20:80. Flow rate: 1.6 ml/min. Detector: UV absorption (290 nm, 0.64 AUFs). Sample volume: 5 μl.

Table 1. Products obtained from the catalysed Fries rearrangement of **2** under various experimental conditions

Exp.	Conditions	Product/Yield (%)						
		2	**3a**	**3b**	**3c**	**3d**	**3e**	**1**
1	$2AlCl_3$, CH_2Cl_2, 7 days, 20 °C	94	0	0	0	0	0	2
2	$2AlCl_3$, CH_2Cl_2, 30 min, reflux	9	4	0	0	4	0	0
3	$2TiCl_4$, CH_2Cl_2, 3 h, reflux[a]	64	0	0	0	0	0	27
4	$2AlCl_3$, 130 °C, 15 min	17	31	28	3	7	1	10
5	$2AlCl_3$, 130 °C→150 °C, 15 min	19	27	16	3	4	0	11

[a] Yield obtained by column chromatography.

Table 2. Products obtained from the photo-Fries rearrangement of **2** in different solvents

Solvent	Yield, %				Reaction time, min
	2	**3a**	**3c**	**1**	
Dichloromethane	5	19	41	10	300
Cyclohexane	11	21	32	2	1260
Ethanol	13	20[a]	27	12	300
Acetonitrile	37	12[b]	16	12	135

[a] 22% for 540 min of reaction.
[b] 14% for 210 min of reaction.

analysis, external calibration was used with solutions of pure reference compounds and the peak height was plotted as a function of the concentration of each compound (peak areas were less useful and difficult to quantify due to the overlap of peaks).

2.1. Dark reactions

Solutions of dibenzofuran-2-yl ethanoate in dichloromethane containing aluminium chloride or titanium chloride as catalyst showed no significant rearrangement reaction, either at room temperature or at reflux temperature (Table 1, experiments 1–3). In some instances a high level of decomposition of the reactant occurred (e.g. experiment 2). However, when a mixture of reactant and catalyst with no solvent was heated for a short period of time (15 min), rearrangement took place readily, and the main products, apart from the phenol (**1**), formed by hydrolysis, were 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**) and 8-hydroxydibenzofuran-2-yl methyl ketone (**3b**) (see Table 1, experiments 4 and 5). Only traces of 2-hydroxydibenzofuran-1-yl methyl ketone (**3c**) were observed. Other products were also obtained and two were identified as 8-acetyldibenzofuran-2-yl ethanoate (**3d**) and 8-hydroxydibenzofuran-2,7-diyl dimethyl diketone (**3e**).

2.2. Photochemical reactions

The photochemical Fries reaction proved to be more efficient than the thermal acid-catalysed process. In contrast to the thermal reaction, the photochemical process showed that the two rearrangement products were 2-hydroxydibenzofuran-1-yl methyl ketone (**3c**) and 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**), with **3c** always present in higher proportion (Table 2). Yields were dependent on solvent and/or reaction time.

The best results were obtained in dichloromethane (41% of **3c** and 19% of **3a**) after 300 min exposure. Roughly similar yields were obtained in ethanol and cyclohexane, but it was noteworthy that significantly longer irradiation time was needed in the latter solvent (Table 2). The reaction was inefficient in acetonitrile and yields of **3a** and **3c** were low. There was a tendency for the primary photoproducts to undergo secondary reactions with increased irradiation time. A similar trend was also observed in dichloromethane and ethanol, but not in cyclohexane. In all cases, the analysis of the products by HPLC showed formation of species with lower retention times than **3a** or **3c** and, in dichloromethane, also some species with higher retention times.

The formation of the rearrangement product **3a** as a function of time in these different solvents is shown in Figure 3. The

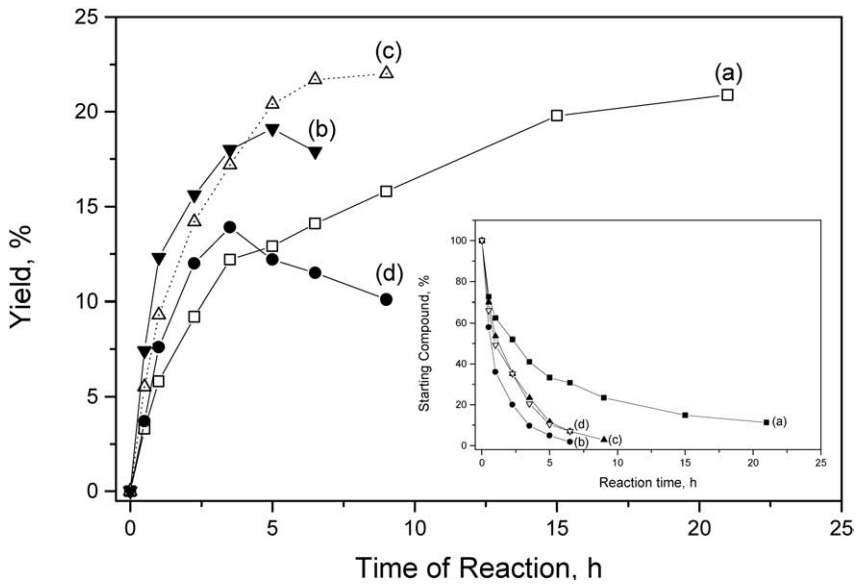

Figure 3. Photo-formation of 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**), in different solvents: (a) cyclohexane, (b) dichloromethane, (c) ethanol, (d) acetonitrile. In detail: consumption of dibenzofuran-2-yl ethanoate (**2**) in the photochemical reaction, using different solvents: (a) acetonitrile, (b) ethanol, (c) cyclohexane, (d) dichloromethane.

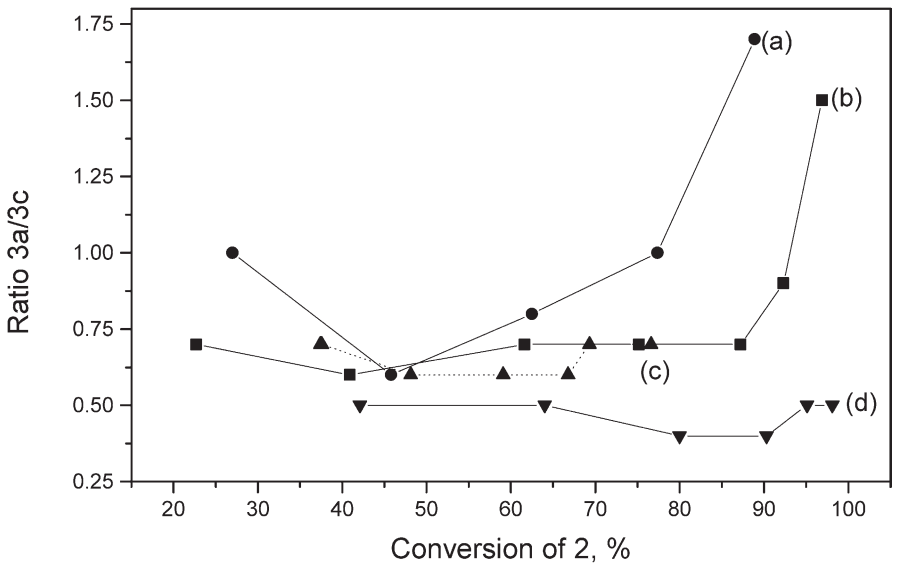

Figure 4. Ratios **3a/3c** as a function of the conversion of **2**.

detail in Figure 3 shows the parallel percentage decrease in concentration of the starting material **2** with time. The highest rate of disappearance of dibenzofuran-2-yl ethanoate (**2**) occurred in dichloromethane, and the lowest rate in cyclohexane. It can be seen from Figure 3 that photodecomposition of **3a** becomes evident after varying irradiation times, depending on the solvent, and is most pronounced in acetonitrile (after ca. 3 h), whereas in cyclohexane formation of **3a** is still increasing after 20 h.

Similar results were also observed for formation of **3c**, but its tendency to undergo photodecomposition was higher. As the sum of the amounts of **3a**, **3c** and unreacted **2** do not reach 100%, it can be concluded that other species that were not identified, are formed.

The variation of the ratios **3a/3c** as a function of the conversion of **2** is shown in Figure 4. The ratio is below unity and it is approximately constant throughout each reaction until a relatively high conversion of **2** has been reached, when the ratio increases sharply. This can be attributed principally to the fact that **3c** decomposes faster than **3a** towards the end of the reaction.

In order to study the effect of the concentration of starting material on the formation of the reaction products, ethanolic solutions of **2** of three different concentrations (1×10^{-3}, 2×10^{-3}, and 5×10^{-3} mol dm^{-3}) were irradiated, and the percent formation of **3a** determined as a function of irradiation time. The results are shown in Figure 5. It can be seen that for more dilute solutions, decomposition starts earlier and consequently the yield decreases. However, the maximum yield obtained is only 22%.

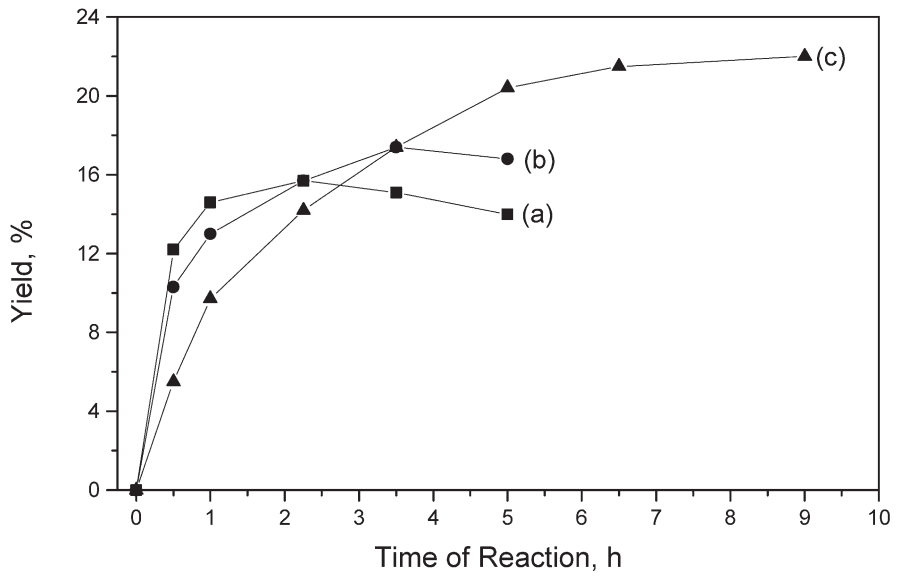

Figure 5. Effect of the dibenzofuran-2-yl ethanoate (**2**) concentration on the photo-formation of 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**) in ethanol: (a) 1×10^{-3} mol dm^{-3}, (b) 2×10^{-3} mol dm^{-3}, (c) 5×10^{-3} mol dm^{-3}.

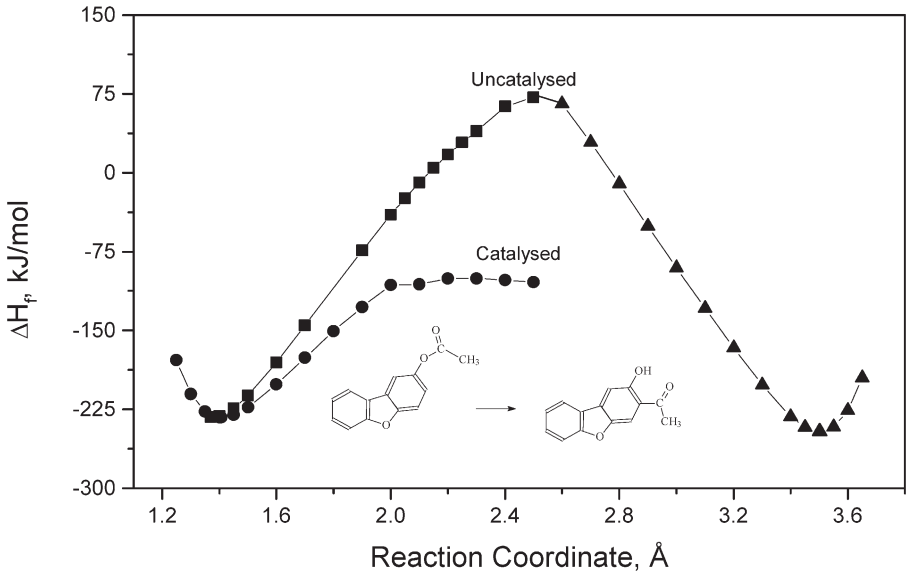

Figure 6. Reaction coordinates, calculated using PM3, considering the formation of 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**), for the catalysed and uncatalysed reactions.

3. Discussion

3.1. Dark reaction

The reaction coordinates for the production of 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**), calculated using PM3 for the catalysed reaction and for the hypothetical non-catalysed reaction are shown in Figure 6. The reaction coordinate is the distance between the oxygen atom of dibenzofuran-2-yl ethanoate and the acylium cation as the transition state is approached. For the uncatalysed reaction the coordinate of the reaction is shown until the bond is formed in **3a**. The reaction coordinate for the catalysed reaction ($AlCl_3$) is the bond distance of $O-(CO)CH_3$ until reaching the transition state. Comparing ΔH_F calculated values for the transition state, a decrease of 172 kJ/mol for the catalysed reaction is indicated. As expected, the activation energy needed for the catalysed reaction is lower. The transition state indicated by the maximum of the uncatalysed curve can be considered to represent the ion pair formed between the acylium cation and the dibenzofuranoxide anion, and similarly, the maximum of the catalysed curve can be considered to represent the complex formed between the dibenzofuranoxide anion and the Lewis' acid. The activation energy for the uncatalysed reaction was calculated to be 306 kJ/mol, whereas for the catalysed reaction the corresponding value was 135 kJ/mol, some 56% lower.

The best practical conditions to effect the thermal rearrangement involves the use of a Lewis acid in combination with heat. The use of a catalyst in refluxing dichloromethane did not result in any significant rearrangement as the boiling point of the solvent (40 °C) was too low to reach an appropriate reaction temperature, and only decomposition of the starting material was observed. It is noteworthy that the complex formed between $AlCl_3$ and **2** virtually eliminates the formation of the compound **3c**.

As the ions will possess limited mobility, there will be high tendency for the ion pair to undergo recombination, so regenerating the starting material **2** and preventing rearrangement. This can be overcome by an increase in the reaction temperature, which will tend to displace the transition state (ion pair) in the direction of the products. The concentration of the starting material is also an important parameter, as high concentrations will favour the formation of intermolecular recombination products.

Significant amounts of dibenzofuran-2-ol (**1**) could also be isolated in these Lewis acid catalysed reactions, and this can be ascribed to protonation of the dibenzofuranoxide anion after displacement of the acylium cation. Considering positions in the dibenzofuran ring system that might be attacked by the acylium ion, in an intramolecular process the distance between the acylium cation and that position will play an important role. If one considers the dibenzofuranoxide anion, the positions potentially most susceptible to electrophilic attack by the acylium cation may be predicted from the charge densities on the carbon atoms at those positions. Calculated charge densities are shown in Figure 7.

It can be seen that, on this basis, all the unsubstituted carbon atoms in the dibenzofuranoxide anion have the potential to undergo intramolecular acylation, but only products arising from attack at positions 1, 3 and 8 were isolated. Other minor products formed were due to intermolecular reactions, as in the case of 8-acetyldibenzofuran-2-yl ethanoate (**3d**) and 8-hydroxydibenzofuran-2,7-diyl dimethyl diketone (**3e**) and other compounds in small amounts.

The non-reactivity of position 4 may be attributed to the fact that 4 is *meta* to the phenoxide group and as with all electrophilic substitution reactions of phenols and phenolate anions, this position will be much less reactive than the two *ortho* positions 1 and 3 on simple resonance grounds. Similar resonance considerations, may explain why there is no reaction in position 7 and 9 in spite of their charge densities. Thus positions 7 and 9 are *meta* to the furan

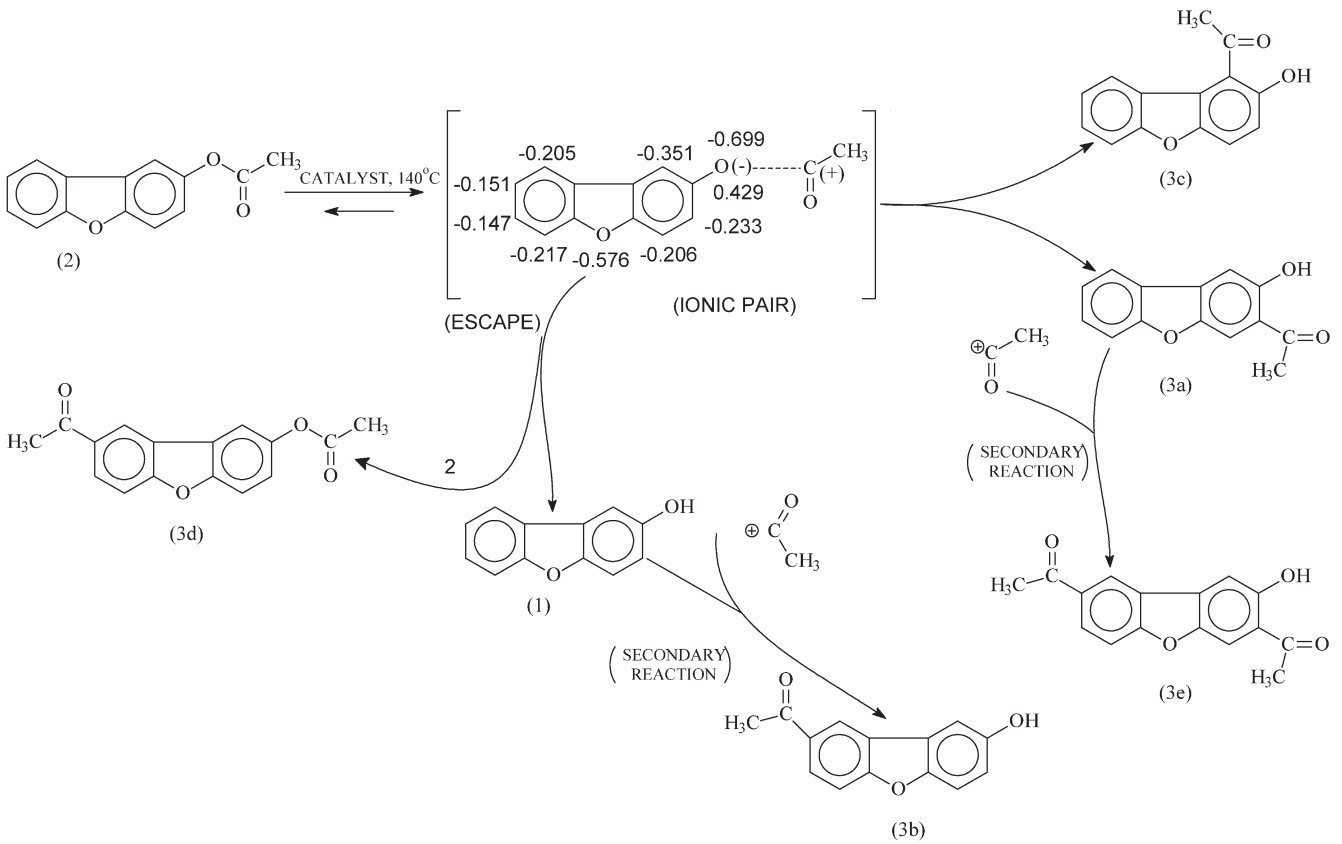

Figure 7. Reaction pathways for the Lewis acid-catalysed Fries reaction of dibenzofuran-2-yl ethanoate (**2**). Total atomic charges over the dibenzofuranoxide anion, estimated using DFT calculation (B3LYP/6-31G*), are also shown.

oxygen atom. In the case of position 9 there is also the likelihood of steric inhibition, due the proximity of the Lewis acid moiety. On charge density grounds and their favourable *ortho* or *para* orientation with respect to the furan oxygen, one would expect positions 6 and 8 to be both appreciably reactive to acylation, and yet only the product arising from reaction at position 8 can be detected. Again this may be a steric effect, the furan oxygen making *ortho* attack at position 6 less favourable.

Of the two dominant rearrangement products **3a** and **3c**, the former is by far the most favoured (Table 1), even though the 1-position has a calculated negative charge density about 1.5 times higher than for position 3. This is surprising, as simple electrophilic substitution reactions of 2-hydroxydibenzofuran (e.g. diazo coupling, nitration, bromination) normally strongly favour 1-substitution. This may be due to a steric effect. The Lewis acid moiety at position 2 will exert a large steric effect, so inhibiting reaction at positions 1 and 3. However, position 1 will be additionally hindered to attack because of the proximity of the hydrogen atom in the 9 position of the second benzene ring.

In the most successful reaction (no solvent; $AlCl_3$ catalyst; 130 °C—experiment 4, Table 1), 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**) was the major product.

An estimate of the equilibrium distance between the dibenzofuranoxide and acylium ions in the ion pair in the transition state gave a value of around 2.51 Å. The estimated distance between the nearest reaction centres (positions 1 and 3) and the cation is, respectively, 3.88 and 4.58 Å. The formation of the compound 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**) must occur through electrophilic substitution of the acylium cation in the 3-position followed by proton transfer to oxygen. A summary of the reaction

Table 3. Calculated ΔH_f values (PM3) for **2** and its various reaction products from the Fries reaction

Compound	ΔH_f, kJ/mol	Observation[a]
Dibenzofuran-2-yl ethanoate (**2**)	−232.74	Starting reagent
2-hydroxydibenzofuran-3-yl methyl ketone (**3a**)	−250.11	Major product
8-hydroxydibenzofuran-2-yl methyl ketone (**3b**)	−255.02	Results from the escape of the cation
2-hydroxydibenzofuran-1-yl methyl ketone (**3c**)	−245.31	Traces
8-acetyldibenzofuran-2-yl ethanoate (**3d**)	−406.72	Results from the escape of the cation (intermolecular rearrangement)
8-hydroxydibenzofuran-2,7-diyl dimethyl diketone (**3e**)	− 422.42	From secondary reaction (traces)
Dibenzofuran-2-ol (**1**)	−81.26	Results from the loss of the acylium cation

[a] Applies to the dark reactions.

sequences taking place in the non-photochemical Lewis acid—catalysed reaction of dibenzofuran-2-yl ethanoate (**2**) is shown in Figure 7.

The calculated standard enthalpies of formation for the isolated compounds, are listed in Table 3 and shows that the products **3a**, **3b** and **3c** are thermodynamically more stable than the starting material, **2**, as would be expected.

3.2. Photochemical rearrangement

In contrast to the catalysed dark reaction in which, reaction at position 1 is inhibited by the catalyst, the photochemical rearrangement has no such inhibition and reaction at this position is preferred. This must be due, at least in part, to its higher electronic charge density compared to position 3 (see Fig. 7). The most efficient reaction occurred with dichloromethane as the solvent, when the product **3c** was isolated in 41% yield after 300 min exposure to UV light (Table 2).

The product distributions obtained in ethanol and cyclohexane showed slightly lower yields. In both solvents the maximum yield of **3c** was around 30%. However, the reaction time, in cyclohexane, needed to reach this yield was about 4.2 times longer than in ethanol. Despite the longer irradiation period needed to reach a yield of **3c** in cyclohexane comparable to that obtained in ethanol after 300 min, secondary reactions of **3a**, **3c**, and even **2**, were less prevalent than in other solvents. As solvent polarity increases, there is an increasing tendency to form other products, including secondary photoproducts from **3a** and (especially) from **3c** (Figs. 3 and 4). This can be explained in terms of increased stabilization of the radical species in more polar solvents, thus favouring the formation of rearrangement products within the solvent cage.[6] Furthermore, the additional stabilization of the dibenzofuranoxy radical, in a polar solvent will increase the probability of this radical escaping from the solvent cage and undergoing hydrogen abstraction to give **1**. As can be seen (Table 2), polar solvents favour this diffusion product. This is in marked contrast to Plank's observations,[10] in which he noted that polar solvents such as methanol favoured radical rearrangement, whereas non-polar solvents favoured radical migration followed by hydrogen abstraction.

It is well accepted that the photo-Fries reaction proceeds through radical pairs, formed by excitation of the starting material to a $S_1(n,\pi^*)$ state and subsequent homolytic cleavage of the C–O bond.[6,11] Our theoretical calculations confirm the n,π^* character of the S_1 state of **2**. DFT-TD, PM3 and ZINDO/S calculations (these last two at a configuration interaction level), show that this electronic transition arises from an overlap of excited states involving the carbonyl group and the dibenzofuran ring. As expected, the TD-DFT calculations furnished a more quantitative description of the electronic transitions, presenting an absorption line at 295 nm for the $S_0 \rightarrow S_1$ transition for the isolated molecule, very near to the estimated maximum for this transition observed in ethyl acetate (Fig. 8).

The five lines presented in Figure 8 correspond to the first five electronic transitions for **2**, and the band corresponding to the $S_0 \rightarrow S_1$ transition appears as a shoulder in the experimental spectrum, overlapped by the band corresponding to the $S_0 \rightarrow S_2$ transition. The relatively low calculated oscillator strength (0.18 for the isolated molecule) is consistent with the $n \rightarrow \pi^*$ character of this transition.

4. Conclusions

The Fries rearrangement of dibenzofuran-2-yl ethanoate (**2**) as a route to *o*-hydroxyacetyldibenzofurans has been investigated, both under thermal Lewis-acid ($AlCl_3$ and $TiCl_4$) catalysed and non-catalysed photochemical conditions. Reaction products have been isolated and characterized, and the effects of temperature, solvent, type of acid, concentration and time on product distributions have been investigated.

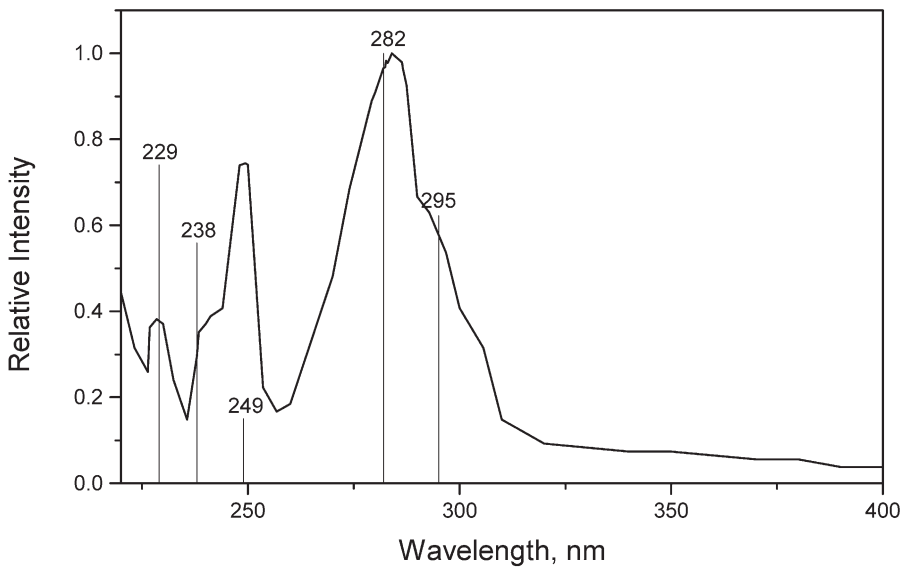

Figure 8. UV–Vis spectrum of dibenzofuran-2-yl ethanoate (**2**) in ethyl acetate (1×10^{-5} mol dm^{-3}). Vertical lines represent calculated electronic transitions for the isolated molecule (TD-DFT).

The efficiency of the Lewis-acid catalysed Fries reaction is critically dependent on choice of reaction conditions. The reaction proceeds best at temperatures above about 130 °C, and in the absence of solvent. The principal rearrangement products are 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**) and 8-hydroxydibenzofuran-2-yl methyl ketone (**3b**). The formation of **3a** possibly occurs by a concerted intramolecular mechanism, mediated by the Lewis' acid, whereas formation of **3b** can still be regarded as intramolecular, but will involve discrete separation of the acylium cation from the complexed dibenzofuranoxide anion within the solvent cage. Minor products are also observed where the separated acylium ion takes part in intermolecular reactions. Steric effects caused by the association between the catalyst and the aryloxy group help explain why 2-hydroxydibenzofuran-1-yl methyl ketone (**3c**) is not formed as the dominant product. A theoretical evaluation of the reaction coordinate, using the PM3 method, shows that the activation energy for rearrangement is about 306 and 135 kJ/mol for the uncatalysed and catalysed processes.

For the photo-Fries reaction, the major products are 2-hydroxydibenzofuran-1-yl methyl ketone (**3c**) and 2-hydroxydibenzofuran-3-yl methyl ketone (**3a**), with **3c** generally dominating. The yields of products in the photochemical reaction are very sensitive to solvent polarity and, as occurs with the dark reaction, the experimental data show that there is a competition between intramolecular and intermolecular mechanisms. The best preparative results were obtained for very low polarity solvents. Photo-rearrangement is also particularly slow in cyclohexane, suggesting that polar solvents favour homolytic cleavage of the ester to give the radical pair.

5. Experimental

5.1. Syntheses

Light petroleum refers to solvent boiling in the range 40–60 °C. Column chromatography (CC) was performed on Merck silica gel 60 (230–400 mesh). Melting points were determined on a Gallenkamp apparatus and are uncorrected. Ultraviolet spectra were recorded in ethyl acetate on a HITACHI 2000 and data are presented in λ_{max} (nm), log ε ($mol^{-1}\,dm^3\,cm^{-1}$). Infrared spectra were recorded on a Diffus-IR Bomem MB-Series FTIR spectrometer in cm^{-1}. ^1H NMR spectra were obtained on a Varian Unity Plus at 300 MHz and the assignments were based on irradiation experiments. The solvent was $CDCl_3$ (if not stated otherwise) and δ is in ppm, relative to internal $SiMe_4$. Elemental analyses were carried out with a LECO CHNS-932.

5.1.1. Dibenzofuran-2-yl ethanoate (2). A mixture of dibenzofuran-2-ol (**1**) (2.78 g, 15.1 mmol), pyridine (25 ml) and acetic anhydride (7.1 ml, 75.3 mmol) was refluxed for 3 h. Crushed ice (100 g) was added and the mixture was stirred until a formation of a beige precipitate is observed. The mixture was filtered and the solid was recrystallized from ethanol.

Dibenzofuran-2-yl ethanoate (**2**) was obtained as colourless crystals (3.35 g, 94%); mp: 113.5–114.5 °C (ethanol) (lit.[12] 115–116 °C, *n*-propanol). UV: 284, (4.30). IR (Nujol): 1755 (C═O), 1224, 1158, 1112, 929, 892, 834, 745, 724. ^1H NMR: 7.91 (1H, br d, J=7.8 Hz, H-9); 7.69 (1H, d, J=2.7 Hz, H-1); 7.58 (1H, br d, J=8.1 Hz, H-6), 7.56 (1H, d, J=9.0 Hz, H-4); 7.49 (1H, dt, J=1.5, 7.8 Hz, H-7); 7.35 (1H, dt, J=0.9, 7.5 Hz, H-8); 7.17 (1H, dd, J=2.4, 8.7 Hz, H-3); 2.37 (3H, s, CH_3). Anal. calcd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46%. Found: C, 74.04; H, 4.68%.

5.2. Lewis-acid catalysed reaction

A. With solvent. To a solution of dibenzofuran-2-yl ethanoate (**2**) (0.23 g, 1.0 mmol) in dichloromethane (10 ml) was added the Lewis acid (2.0 mmol of $AlCl_3$, solid, or $TiCl_4$, 1 mol dm^{-3}, in CH_2Cl_2). The mixture was stirred at room temperature or refluxed. Hydrochloric acid (2 M) and crushed ice were added and the mixture was stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (3×25 ml) and the combined organic extracts were dried ($MgSO_4$). The solvent was evaporated and a solid was obtained. A solution of the final solid, in ethyl acetate, was prepared and diluted to a known volume for HPLC analysis.

B. Without solvent. A mixture of dibenzofuran-2-yl ethanoate (**2**) (0.45 g, 2.0 mmol) and $AlCl_3$ (0.53 g, 4.0 mmol) was heated under argon for 15 min, at the temperature indicated in Table 1. After cooling, crushed ice and conc. HCl (5.0 ml) were added. The resulting mixture was stirred for 15 min and extracted with diethyl ether (3×30 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. A solution of the final solid, in ethyl acetate, was prepared and diluted for analysis by HPLC.

The remaining solids of several experiments were combined and submitted to column chromatography (silica, ethyl acetate/light petroleum ether, 4–60%).

5.2.1. 2-Hydroxydibenzofuran-3-yl methyl ketone (3a). The title compound was the first compound eluted and was obtained as intense yellow crystals, mp: 170.0–172.0 °C (ethanol) (lit.[12] 168–169 °C, ethanol/*n*-propanol/water). UV: 365 (3.71), 315 (4.44), 280 (4.01). IR (KBr): 1650, 1631 (strong, C═O), 1609, 1590, 1459, 1426, 1370, 1328, 1218, 865, 817, 749, 660. ^1H NMR: 12.25 (1H, s, OH); 7.95 (1H, br d, J=7.8 Hz, H-9); 7.90 (1H, s, H-4); 7.57–7.53 (1H, m, H-7); 7.48 (1H, s, H-1); 7.41–7.31 (2H, m, H-6 and H-8); 2.74 (3H, s, CH_3). Anal. calcd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46%. Found: C, 74.09; H, 4.70%.

5.2.2. Dibenzofuran-2-yl ethanoate (2). The second compound eluted was obtained as colourless crystals; mp and spectroscopic data were identical to those of an authentic sample of 2.

5.2.3. Dibenzofuran-2-ol (1). The third compound eluted was obtained as beige crystals; mp: 133.5–134.5 °C (lit.[13] 134 °C, ethanol) UV: 324 (3.73), 290 (4.19). IR (KBr): 3272 (OH), 1600, 1482, 1447, 1361, 1334, 1308, 1282, 1214, 1191, 1168, 1150, 1017, 869, 842, 801, 743. ^1H NMR: 7.89 (1H, br d, J=7.5 Hz, H-9); 7.55 (1H, br d, J=8.1 Hz, H-6);

7.46 (1H, dt, *J*=1.2, 8.2 Hz, H-7); 7.44 (1H, d, *J*=9 Hz, H-4); 7.38 (1H, d, *J*=2.4 Hz, H-1); 7.32 (1H, dt, *J*=1.2, 7.8 Hz, H-8); 6.97 (1H, dd, *J*=2.4, 8.7 Hz, H-3); 5.01 (1H, br s, OH).

5.2.4. 2-Hydroxydibenzofuran-1-yl methyl ketone (3c). The fourth compound eluted was obtained as pale yellow crystals, mp: 154.5–155.5 °C (ethanol/hexane) (lit.[12] 105–110 °C). UV: 302 (4.02). IR (KBr): 3177 (OH), 1654 (C═O), 1592, 1454, 1432, 1368, 1277, 1263, 1079, 889, 809, 739, 730. ^{1}H NMR: 11.25 (1H, s, OH); 8.03 (1H, br d, *J*=8.4 Hz, H-9); 7.69 (1H, d, *J*=9.0 Hz, H-4); 7.62 (1H, br d, *J*=8.4 Hz, H-6); 7.51 (1H, dt, *J*=1.2, 7.2 Hz, H-7); 7.36 (1H, dt, *J*=1.2, 8.4 Hz, H-8); 7.12 (1H, d, *J*=9.0 Hz, H-3); 2.91 (3H, s, CH_3). Anal. calcd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46%. Found: C, 74.52; H, 4.81%.

5.2.5. 8-Hydroxydibenzofuran-2,7-diyl dimethyl diketone (3e). The fifth compound eluted was obtained as yellow crystals, mp: 224.5–226.0 °C (ethanol). UV: 365 (3.70), 275 (4.67). IR (KBr): 1679 (C═O), 1651, 1628 (strong, C═O), 1423, 1359, 1324, 1239, 1213, 1128, 944, 823, 785. ^{1}H NMR: 12.27 (1H, s, OH), 8.57 (1H, d, *J*=2.1 Hz, H-1); 8.20 (1H, dd, *J*=1.8, 8.7 Hz, H-3); 7.94 (1H, s, H-6); 7.60 (1H, d, *J*=8.7 Hz, H-4); 7.54 (1H, s, H-9); 2.76 (3H, s, 3-$COCH_3$ or 9-$COCH_3$); 2.73 (3H, s, 9-$COCH_3$ or 3-$COCH_3$). Anal. calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.52%. Found: C, 71.71; H, 4.67%.

5.2.6. 8-Acetyldibenzofuran-2-yl ethanoate (3d). The sixth compound eluted was obtained as yellow crystals, mp: 145.0–147.0 °C (ethyl acetate/hexane). UV: 292 (4.04), 249 (4.52). IR (Nujol): 1745 (C═O), 1672 (C═O), 1634, 1596, 1287, 1245, 1216, 1155, 1015, 904, 823, 807. ^{1}H NMR: 8.52 (1H, d, *J*=1.2 Hz, H-9); 8.12 (1H, dd, *J*=2.1, 8.7 Hz, H-7); 7.73 (1H, d, *J*=2.4 Hz, H-1) 7.59 (1H, d, *J*=8.4 Hz, H-6); 7.57 (1H, d, *J*=8.7 Hz, H-4); 7.22 (1H, dd, *J*=2.4, 9.0 Hz, H-3); 2.71 (3H, s, $COCH_3$); 2.38 (3H, s, $OCOCH_3$). Anal. calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.52%. Found: C, 71.61; H, 4.75%.

5.2.7. 8-Hydroxydibenzofuran-2-yl methyl ketone (3b). The last compound to be eluted was obtained as brownish yellow crystals, mp: 223.5–225.5 °C (ethyl acetate/hexane). UV: 326 (3.70), 248 (4.62). IR (Nujol): 3193 (OH), 1660 (C═O) 1596, 1580, 1304, 1286, 1263, 1185, 1169, 1113, 1019, 864, 824, 723. ^{1}H NMR (d_6-acetone): 8.73 (1H, d, *J*=2.1 Hz, H-1); 8.62 (1H, br s, OH); 8.18 (1H, dd, *J*=1.8, 9.0 Hz, H-3); 7.68 (1H, d, *J*=9.0 Hz, H-4); 7.64 (1H, d, *J*=2.4 Hz, H-9); 7.54 (1H, d, *J*=9.0 Hz, H-6); 7.11 (1H, dd, *J*=2.4, 9.0 Hz, H-7); 2.72 (3H, s, CH_3). Anal. calcd for $C_{14}H_{10}O_3$: C, 74.31; H, 4.46%. Found: C, 74.32; H, 4.50%.

5.3. Photochemical experiments

The photochemical experiments were conducted using a 16 W low-pressure mercury lamp (emission at 254 nm) positioned in the center of a merry-go-round set-up (Annular Photoreactor, Model APQ 40—PhotoChemical Reactors Limited). Solutions of dibenzofuran-2-yl ethanoate (**2**) (5.0×10^{-3} mol dm^{-3}), in the appropriate solvent, were sealed in stoppered quartz tubes (23 ml, 1 cm diameter), and placed at 4 cm from the lamp. The samples were rotated about throughout the irradiation period. Samples (0.5 ml) of the solutions were withdrawn at different photolysis times for HPLC analysis, until the concentration of the main products started to decrease after reaching a maximum value.

In order to study the effect of concentration, several ethanolic solutions of **2** of different concentrations (5.0×10^{-3} mol dm^{-3}, 2.0×10^{-3} mol dm^{-3} and 1.0×10^{-3} mol dm^{-3}) were also irradiated.

5.4. HPLC analyses

High performance liquid chromatography (HPLC) analyses of the reaction mixtures were carried out using a JASCO PU-980 pump with a RHEODYNE—7725i (20 μl) loop valve, a JASCO UV-975 UV–Vis variable wavelength detector, without scanning capability, and a Shimadzu C-R6A Chromatopac recorder. The column was a Merck LichroCART, 250×4 mm^2 (Lichrospher Si 60, 5 μm). The analyses were conducted at constant flow rate (1.6 ml/min), with monitoring at λ=290 nm and with 0.64 AUFs. All the samples were prepared in ethyl acetate and 5 μl aliquots were injected for each analysis. The standards were obtained by column chromatography and solutions of different concentrations were prepared in order to obtain an external calibration from peak height plotted as a function of the concentration for each compound. The mobile phase was a mixture of ethyl acetate/hexane of analytical grade, in the proportion 20:80.

5.5. Theoretical calculations

The quantum-mechanical calculations were carried out at the semi-empirical (PM3 and ZINDO/S) and density functional theory (DFT) levels. The DFT B3LYP method was employed, using a Gaussian basis-function (6-31G*), to refine the structure of the compound dibenzofuran-2-yl ethanoate (**2**) after its modelling using the PM3 method (UHF calculation, gradient 0.1000 kcal/Å mol, Polak-Ribiere optimization algorithm)[14] and to evaluate the charge distribution in the ground state of the 2-dibenzofuranoxide anion and radical.

The Berny analytical gradient was used in the optimization using DFT. The requested convergence limit on RMS density matrix was 1×10^{-8} and the threshold values for the maximum force and the maximum displacement were 0.000450 and 0.001800 au, respectively.

Using time-dependent DFT calculations (B3LYP/6-31G*), the electronic spectrum of the compound dibenzofuran-2-yl ethanoate (**2**) was predicted[15] and compared with experiment.

The reaction coordinates for the formation of the principal product of the dark—Fries reaction under the catalysed and the uncatalysed conditions were calculated using PM3.[16] PM3 was also used to estimate the standard ΔH_f for the starting reagent and all isolated products.

The methods used are available in HYPERCHEM 5.11 Pro,[14] AMPAC 6.56 PC[16] and GAUSSIAN 98W,[15] suites of programs, installed in PC-compatible computers.

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Synthesis and photochromic properties of novel yellow developing photochromic compounds

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Abstract—Two 1-thiazolyl-2-thienylcyclopentene derivatives, **1a** and **2a**, and a 1-thiazolyl-2-vinylcyclopentene derivative **3a** have been synthesized in an attempt to obtain photochromic compounds which change the color from colorless to yellow, and have low photocycloreversion quantum yields and high absorption coefficients of the colored isomers. All of these compounds underwent reversible photochromic reactions. Compounds **1a** and **2a** in toluene solutions changed the color upon 313 nm light irradiation from colorless to orange and pink, in which absorption maxima were observed at 494 nm (ε=10,000 M^{-1} cm^{-1}) and 525 nm (ε=8500 M^{-1} cm^{-1}), respectively. On the other hand, the colorless toluene solution of **3a** turned yellow upon irradiation with 313 nm light, in which the absorption maximum was observed at 416 nm (ε=17,100 M^{-1} cm^{-1}). The photocyclization/cycloreversion quantum yields of **3** were 0.19 and 0.0014, respectively. The conversion from the open- to the closed-ring isomer of **3** in the photostationary state under irradiation with 313 nm light was close to 100%.

1. Introduction

Photochromic compounds have attracted much attention because of their potential ability for optical memory, photo-optical switching and display devices.[1,2] Among them diarylethenes with heterocyclic aryl groups, such as thiophene or benzothiophene groups, are the most promising candidates for the applications[3–8] because of their fatigue resistant and thermally irreversible photochromic performance.[9,10] For the application to a full color display it is indispensable to prepare red and yellow developing diarylethene derivatives. Several attempts have been conducted to shift the absorption maximum of the closed-ring isomer to shorter wavelengths by introduction of thiazole rings as the aryl group. When the thiophene rings of 1,2-bis(2-methyl-5-phenyl-3-thienyl)perfluorocyclopentenes[11] are replaced with thiazole rings, the absorption maximum of the closed-ring isomer shifts from 575 nm (blue) to 525 nm (red).[12,13] Another approach to further shift the absorption band to shorter wavelength (yellow) is to attach the thiophene rings to the ethene moiety at the 2-position.[13–15] Very recently, oxazolylfulgides and 2,3-bis(2,3,5-trimethyl-3-thienyl)maleic imidine have been reported as yellow photochromic dyes.[16,17] These colored isomers are, however, photochemically unstable and the photocycloreversion quantum yields are rather high. For a full color display it is strongly desired to develop yellow photochromic compounds which have low photocycloreversion quantum yields and thermal stability at room temperature. In previous papers, we showed that introduction of alkoxy groups at the reactive carbons of diarylethene derivatives remarkably suppresses the photocycloreversion quantum yields.[6,12,18] Furthermore, the rational correlations between the substitution and the photocycloreversion quantum yields have been demonstrated based on an ab initio MO calculation.[19] In this study, we have synthesized two 1-thiazolyl-2-thienylcyclopentene derivatives **1a** and **2a**, and a 1-thiazolyl-2-vinylcyclopentene derivative **3a** having methoxy substituents to obtain yellow photochromic compounds having a low photocycloreversion quantum yield (Scheme 1).

2. Results and discussion

2.1. Synthesis and photochromic properties of 1-thiazolyl-2-thienylcyclopentene derivatives

4-Thiazolyl[12,13] and 2-thienyl[14,15] chromophores were chosen as the aryl groups of diarylethenes to shift the absorption maxima of the closed-ring isomers to shorter

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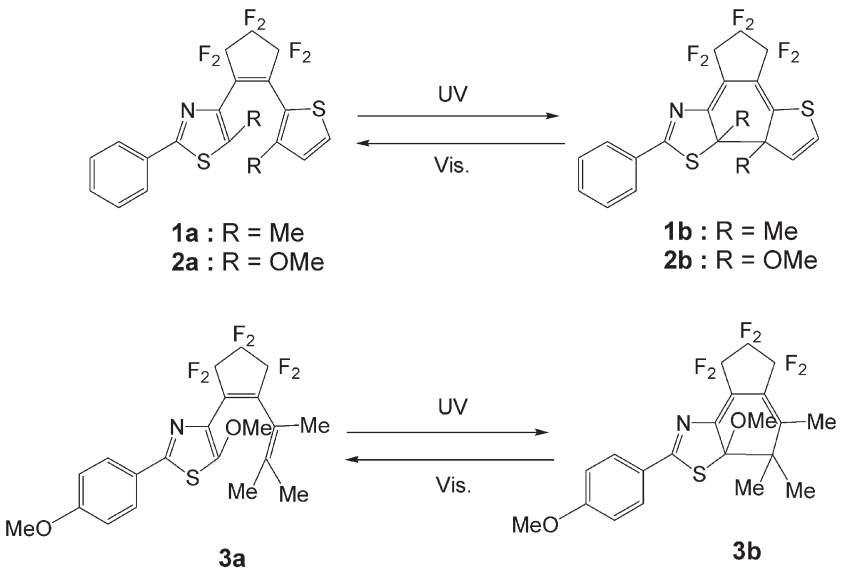
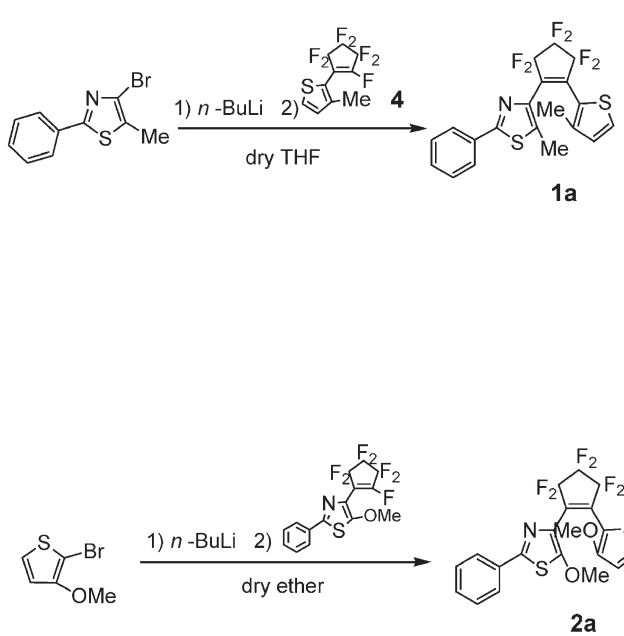


Scheme 1.

wavelengths. In order to reduce the photocycloreversion quantum yield, methoxy substituents were introduced at the reactive carbons. According to the above molecular design principle, compounds **1a** and **2a** were constructed. Compound **1a** was synthesized by the reaction of 4-bromo-5-methyl-2-phenylthiazole[12] with 1-(3-methyl-2-thienyl)octafluorocyclopentene (**4**) by bromine-lithium exchange followed by nucleophilic displacement of fluoride. A colorless solid was obtained in 14% yield. **2a** was synthesized by the reaction of 2-bromo-3-methoxythiophene[20] with 1-(5-methoxy-2-phenyl-4-thiazolyl)octafluorocyclopentene[12] in dry ether as a colorless solid. Both compounds were purified by column chromatography (hexane/AcOEt) and characterized by ^{1}H NMR spectroscopy, MS, and elemental analysis. (Scheme 2).

Figure 1 shows the absorption spectral change of **1** (3.3×10^{-5} M) in toluene by UV irradiation. Upon irradiation with 313 nm light, the colorless solution turned orange, in which a visible absorption band was observed at 494 nm (ε=10,000 M^{-1} cm^{-1}). The orange color is due to the closed-ring isomer **1b**. When the orange solution was irradiated with visible light (λ>440 nm), the spectrum readily returned back to the original one. The colored isomer was stable in the dark at room temperature and could be isolated by high performance liquid chromatography (HPLC, ethyl acetate/hexane=1/9 as the eluent). The structure of **1b** was analyzed with ^{1}H NMR spectroscopy, MS, and elemental analysis. All data agreed well with the closed-ring isomer **1b**. The conversion from **1a** to **1b** in the photostationary state under irradiation with 313 nm light was 69%.



Scheme 2.

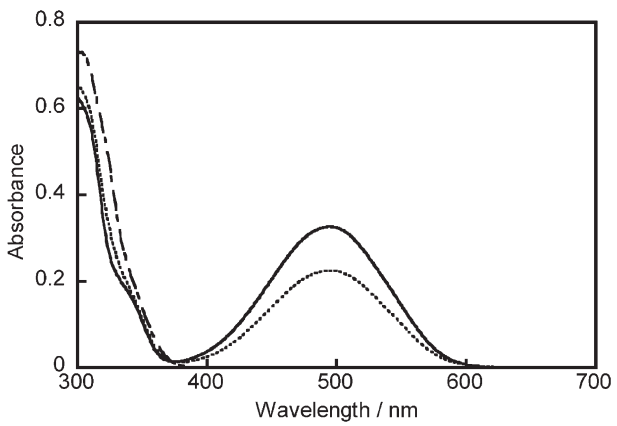


Figure 1. Absorption spectra of compound **1** (3.3×10^{-5} M) in toluene: (dashed line) open-ring isomer **1a**, (solid line) closed-ring isomer **1b**, and (dotted line) in the photostationary state under irradiation with 313 nm light.

Figure 2 shows the absorption spectral changes of **2** (2.4×10^{-5} M) in toluene by UV irradiation. The absorption maximum of the photogenerated closed-ring isomer **2b** was observed at 525 nm. The absorption maximum is 31 nm longer than that of **1b** (494 nm). The pink color is due to the closed-ring form **2b** and bleached by irradiation with visible

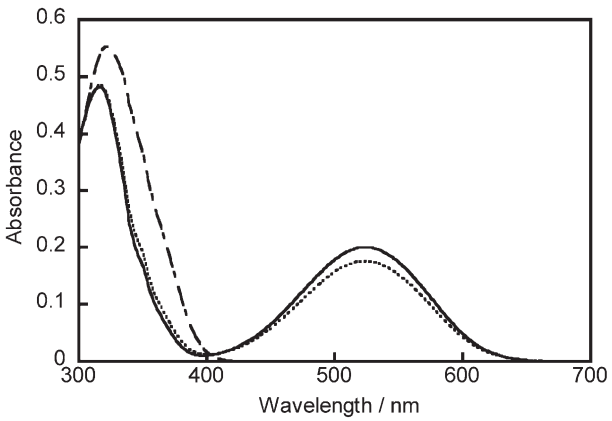


Figure 2. Absorption spectra of compound **2** (2.4×10^{-5} M) in toluene: (dashed line) open-ring isomer **2a**, (solid line) closed-ring isomer **2b**, and (dotted line) in the photostationary state under irradiation with 313 nm light.

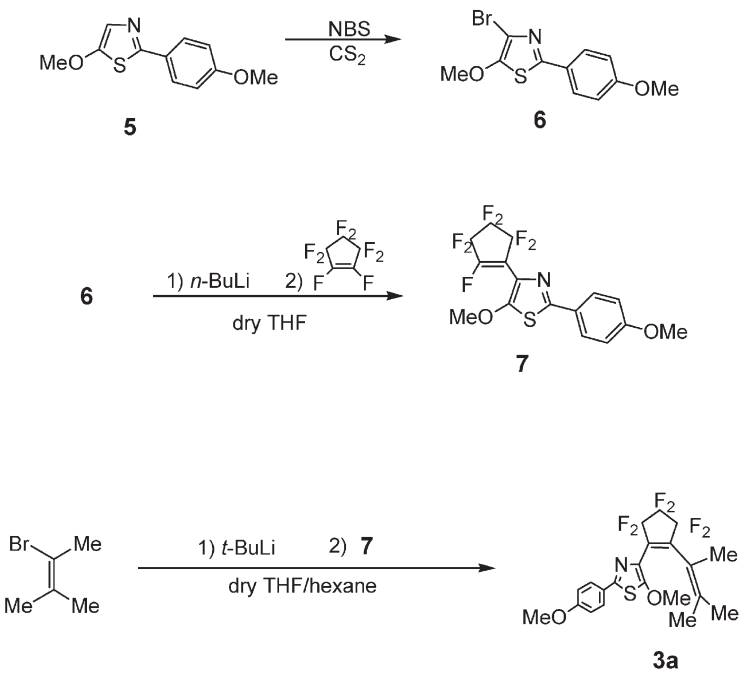
light ($\lambda>440$ nm). The structure of isolated colored product was analyzed by ^{1}H NMR spectroscopy, MS, and elemental analysis. All data agreed well with the closed-ring isomer **2b**. The photobleaching rate of **2b** was slower than that of **1b**. The absorption coefficient of **2b** is 8500 M^{-1} cm^{-1}, which is less than that of **1b**. The conversion from the open-ring to the closed-ring isomer by irradiation with 313 nm was 89%.

The photocyclization/cycloreversion quantum yields were measured in toluene at 25 °C. The photocyclization quantum yields of **1a** and **2a** were determined to be 0.36 and 0.26, respectively. The methoxy substitution scarcely affected the cyclization reaction. On the other hand, the photocycloreversion quantum yield was strongly suppressed by the methoxy substituents. The photocycloreversion quantum yield of **2b** (0.012) was decreased as much as 10 times in comparison with that of **1b** (0.12). The hypsochromic shifts of **1b** and **2b** are not large enough to exhibit yellow color. Therefore, the 2-thiophene group[14,15] was replaced with an ethylene unit to further shift the absorption band of the closed-ring isomer to shorter wavelengths.

2.2. Synthesis and photochromic properties of a 1-thiazolyl-2-vinylcyclopentene derivative

Recently, novel photochromic compounds having a thiophene and a 2-butene or stryl unit have been reported by Branda et al. [21] and Yokoyama et al.[22,23] The colorless solutions of these compounds turned to yellow by irradiation with UV light. The absorption maximum of the closed-ring isomer of 1-(1,2-dimethylpropenyl)-2-(2-methyl-5-phenyl-3-thienyl)perfluorocyclopentene (**8**) is reported to be 450 nm in dichloromethane.[21] When the thiophene ring is replaced with a thiazole ring, the absorption maximum of the closed-ring isomer is expected to shift to a wavelength shorter 450 nm. In other words, the closed-ring isomer would not give yellow color. In order to obtain yellow colored closed-ring isomer, it is required to introduce substituents[24,25] which shift the band to longer wavelengths. We designed a derivative **3a**, which has methoxy substituents at the *para*-position of the phenyl ring and 5-position of the thiazole ring. Both methoxy substituents are effective to induce bathochromic shift.[6,12,18,24] The methoxy group at the 5-position is also known to decrease the photocycloreversion quantum yield. The synthesis was performed according to Scheme 3. 5-Methoxy-2-(4-methoxyphenyl)thiazole **5** was obtained from *N*-(4-methoxybenzoyl) glycine methyl ester as a yellow solid in 80% yield. Compound **3a** was synthesized by the coupling reaction of **7** and 2-bromo-3-methyl-2-butene,[26] and was purified by HPLC. The structures of all compounds were confirmed by ^{1}H NMR, mass spectroscopy, and elemental analysis.

Figure 3 shows the absorption spectral change of **3** (2.5×10^{-5} M) in toluene by irradiation with UV light. The



Scheme 3.

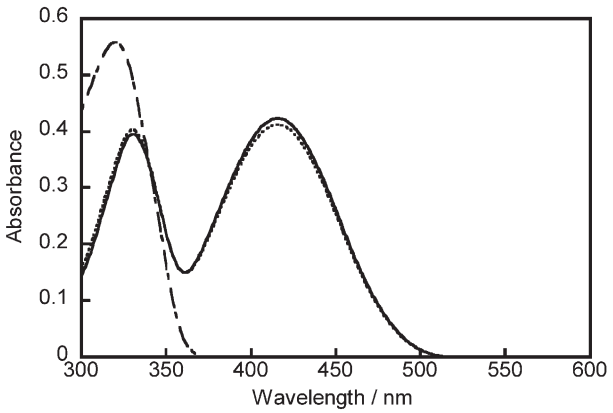


Figure 3. Absorption spectra of compound **3** (2.5×10^{-5} M) in toluene: (dashed line) open-ring isomer **3a**, (solid line) closed-ring isomer **3b**, and (dotted line) in the photostationary state under irradiation with 313 nm light.

spectrum of the isolated colored isomer is also shown in Figure 3. Upon irradiation with 313 nm light the colorless toluene solution of **3a** slowly turned yellow, in which absorption maxima were observed at 330 and 416 nm. It should be noted that any photochemical side product was not observed by HPLC analysis. The photostationary spectrum is almost the same as the colored isomer, indicating a high conversion from the colorless to the colored isomers by irradiation with 313 nm light. The yellow colored solution slowly returned back to the initial colorless solution upon prolonged irradiation with visible light. The colored isomer was stable in the dark at room temperature and could be isolated by HPLC (silica gel; ethyl acetate/hexane=2/8 as the eluent). The molecular characteristics of the yellow colored isomer was examined by ^{1}H NMR, mass spectrum, and elemental analysis. All analysis data agreed with that of the closed-ring isomer **3b**.

The cyclization quantum yield (313 nm) was determined to be 0.19. The quantum yield is slightly smaller than the values of **1a** and **2a**. On the other hand, the cycloreversion quantum yield was remarkably suppressed to 0.0014. Although the photocyclization/cycloreversion quantum yields of (**8**) are not reported, the conversion from the open- to the closed-ring isomer with 365 nm light at the photostationary state is reported to be 64%.[21] The low conversion suggests that the photocycloreversion quantum yield is rather high in comparison with **3**, in which the conversion as high as 100% is observed. The photocyclization and photocycloreversion quantum yields of **1**, **2** and **3** are summarized in Table 1. The photocycloreversion quantum yield of **3b** is 10 times smaller than that of **2b**.

Figure 4 shows the colors of the closed-ring isomers **1b**, **2b** and **3b** in toluene. The absorption band of **3b** (416 nm) showed hypochromic shift in compared with those of **1b**

Table 1. Absorption maxima and coefficients of the open- and closed-ring isomers of compounds **1**, **2**, and **3**, and the quantum yields in toluene

	λ max/nm (ε/M^{-1} cm^{-1})	$\Phi_{a\rightarrow b}$		λ max/nm (ε/M^{-1} cm^{-1})	$\Phi_{b\rightarrow a}$	Conversion (313 nm)
1a	302 (22300)	0.36 (300 nm)	**1b**	494 (10000)	1.2×10^{-1}(492 nm)	0.69
2a	321 (23000)	0.26 (313 nm)	**2b**	525 (8500)	1.2×10^{-2}(525 nm)	0.89
3a	320 (22500)	0.19 (313 nm)	**3b**	416 (17100)	1.4×10^{-3}(416 nm)	0.97

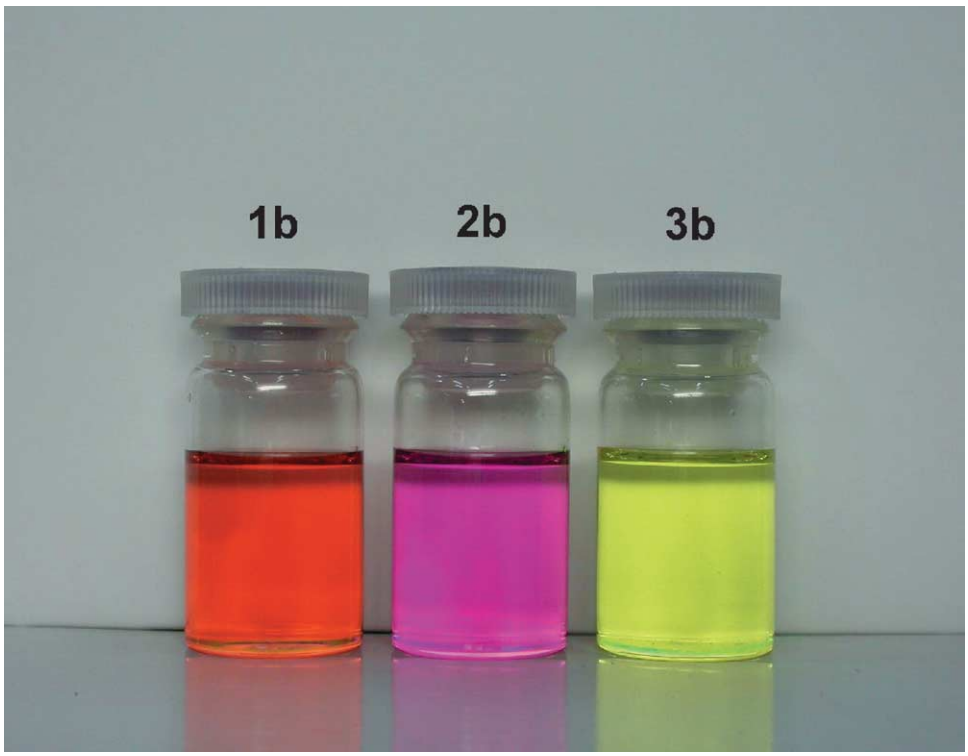


Figure 4. Toluene solutions of compounds **1**, **2**, and **3** under irradiation with 313 nm: orange (**1b**), pink (**2b**), and yellow colors (**3b**).

(494 nm) and **2b** (525 nm). This is ascribed to shorter π-conjugation length of **3b** in comparison with **1b** and **2b**. More interestingly, the absorption coefficient of **3b** is 17,100 M^{-1} cm^{-1}, which is much larger than that of **1b** (10,000 M^{-1} cm^{-1}) and **2b** (8500 M^{-1} cm^{-1}). The value, is also much larger than the absorption coefficients of the closed-ring isomers of yellow developing diarylethenes,[7] such as 1,2-bis(3-methyl-2-thienyl)perfluorocyclopentene (6870 M^{-1} cm^{-1} at 432 nm in 3-methylpentane),[27] 1,2-bis(3,5-dimethyl-2-thienyl)perfluorocyclopentene (5800 M^{-1} cm^{-1} at 425 nm in hexane),[14,28,29] 1,2-bis(3-methyl-5-phenyl-2-thienyl)perfluorocyclopentene (5250 M^{-1} cm^{-1} at 438 nm in hexane),[14,28,29] 1,2-bis(2,4-dimethyl-5-thiazolyl)perfluorocyclopentene (7000 M^{-1} cm^{-1} at 390 nm in hexane)[13] and 1,2-bis(2-methyl-4-phenyl-5-thiazolyl)perfluorocyclopentene (7000 M^{-1} cm^{-1} at 406 nm in hexane)[13]. The large absorption coefficient of **3b** is due to the methoxy group at the *para*-position of the phenyl ring.[24]

3. Conclusion

New photochromic compounds **1a**, **2a** and **3a** were synthesized in an attempt to obtain yellow developing photochromic compounds with low photocycloreversion quantum yields and large absorption coefficients of the closed-ring isomers. The toluene solution of **3a** turned yellow by irradiation with 313 nm, showing an absorption maximum at 416 nm (ε=17,100 M^{-1} cm^{-1}). The absorption coefficient of the closed-ring isomer **3b** was much larger than those of **1b** and **2b**. The photocyclization/cycloreversion quantum yields of **3** were determined to be 0.19 and 0.0014, respectively. Compound **3** is a useful candidate as a yellow photochromic dye.

4. Experimental

HPLC was performed on a Hitachi L-7100 liquid chromatography coupled with a Hitachi L-7400 spectrophotometeric detector. ^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument. Mass spectra were measured with a Shimadzu GCMS-QP5050A gas chromatography-mass spectrometer. Absorption spectra were measured on a Hitachi U-3500 absorption spectrophotometer. Photoirradiation was carried out using an Ushio 500 W superhigh-pressure mercury lamp or an Ushio 500 W xenon lamp. Monochromatic light was isolated by passing the light through a cut off filter (UV-27) and monochromator (Ritsu MC-10N). The quantum yields were determined by comparing the reaction rate of the photochromic compounds in toluene against furyl fulgide in toluene.[30,31] The samples were not degassed. The quantum yield measurement was carried out three times and average values were adopted as the quantum yields.

4.1. Compound data

4.1.1. 1-(5-Methyl-2-phenyl-4-thiazolyl)-2-(3-methyl-2-thienyl)perfluorocyclopentene (1a). To a stirring solution of 4-bromo-5-methyl-2-methylthiazole[12] (524 mg, 2.10 mmol) in dry THF (6 mL) was slowly added 1.6 M *n*-BuLi in hexane (1.30 mL, 2.20 mmol) at −80 °C under argon atmosphere. After the mixture had been stirred for 15 min at −80 °C, compound **4** (540 mg, 1.90 mmol) in dry THF (2 mL) was added. The reaction mixture was further stirred at −80 °C for 2 h, and then distilled water was added. The product was extracted with ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane=1/9) and HPLC (ethyl acetate/hexane=1/9) to afford to 130 mg (14%) of **1a** as colorless needles: mp 107–108 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.80 (s, 3H), 1.98 (s, 3H), 6.86 (d, *J*=5.0 Hz, 1H), 7.44 (m, 5H), 7.88 (m, 2H). MS (*m*/*z*) 445 (M^+). Anal. Found: C, 53.96; H, 2.85; N, 3.00%. Calcd for $C_{20}H_{13}F_6NS_2$: C, 53.93; H, 2.94; N, 3.14%.

4.1.2. Closed-ring isomer for 1a (1b). Compound **1b** was isolated as an orange solid by passing a photostationary solution containing **1a** and **1b** thorough HPLC (ethyl acetate/hexane=1/9): ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.68 (s, 3H), 1.81 (s, 3H), 5.73 (d, *J*=6.0 Hz, 1H), 6.24 (d, *J*=6.0 Hz, 1H), 7.42–7.62 (m, 3H), 7.85–8.05 (m, 2H). MS (*m*/*z*) 445 (M^+). Anal. Found: C, 53.93; H, 2.95; N, 3.18%. Calcd for $C_{20}H_{13}F_6NS_2$: C, 53.93; H, 2.94; N, 3.14%.

4.1.3. 1-(5-Methoxy-2-phenyl-4-thiazolyl)-2-(3-methoxy-2-thienyl)perfluorocyclopentene (2a). To a stirring solution of 2-bromo-3-methoxythiophene[20] (500 mg, 2.6 mmol) in dry ether (25 mL) was slowly added 1.6 M *n*-BuLi in hexane (1.6 mL, 2.7 mmol) at −80 °C under argon atmosphere. After the mixture had been stirred for 15 min at −80 °C, 1-(5-methoxy-2-phenyl-4-thiazolyl)perfluorocyclopentene[12] (1.0 g, 2.8 mmol) in dry ether (10 mL) was added. The reaction mixture was further stirred at −80 °C for 1 h, and then distilled water was added. The product was extracted with diethyl ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane=2/8) and HPLC (ethyl acetate/hexane=2/8) to afford to 50 mg (4%) of **2a** as colorless plates: mp 133–134 °C. ^{1}H NMR ($CDCl_3$, 200 MHz). δ=3.59 (s, 3H), 3.81 (s, 3H), 6.80 (d, *J*=5.6 Hz, 2H), 7.35–7.50 (m, 5H), 7.70–7.80 (m, 2H). MS (*m*/*z*) 447 (M^+). Anal. Found: C, 50.58; H, 2.85; N, 3.10%. Calcd for $C_{20}H_{13}F_6NO_2S_2$: C, 50.31; H, 2.74; N, 2.93%.

4.1.4. Closed-ring isomer for 2a (2b). Compound **2b** was isolated as a red solid by passing a photostationary solution containing **2a** and **2b** thorough HPLC (ethyl acetate/hexane=2/8): ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.67 (s, 3H), 1.75 (s, 3H), 2.39 (s, 3H), 7.34–7.16 (m, 5H), 7.42–7.34 (m, 3H), 7.85–7.76 (m, 2H). MS (*m*/*z*) 447 (M^+). Anal. Found: C, 50.57; H, 2.76; N, 3.18%. Calcd for $C_{20}H_{13}F_6NO_2S_2$: C, 50.31; H, 2.74; N, 2.93%.

4.1.5. 1-[5-Methoxy-2-(4-methoxyphenyl)-4-thiazolyl]-2-(1,2-dimethylpropenyl)perfluoro-cyclopentene (3a). To a stirring solution of 2-bromo-3-methyl-2-butene[26] (210 mg, 1.4 mmol) in a mixed solvent of anhydrous hexane (13 mL) and THF (13 mL) was slowly added 1.5 M *t*-BuLi in heptane (1.1 mL, 1.7 mmol) at −80 °C under argon atmosphere. After the mixture had been stirred for 40 min at −80 °C, compound **7** (250 mg, 0.61 mmol) in a mixed solvent of anhydrous hexane (2.5 mL) and THF (2.5 mL)

was added. The reaction mixture was further stirred at −80 °C for 1 h, and the reaction was allowed to slowly warm to room temperature and stirred there for 1 h. The reaction was quenched with distilled water. The product was extracted with ether, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane=3/7) and HPLC (ethyl acetate/hexane=2/8) to afford to 15 mg (5%) of **3a** as colorless needles: mp 93–94 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.49 (s, 3H), 1.75 (s, 3H), 1.93 (s, 3H), 3.86 (s, 3H), 4.01 (s, 3H), 6.93 (d, J=9.0 Hz, 2H), 7.71 (d, J=9.0 Hz, 2H). MS (*m*/*z*) 463 (M^+). Anal. Found: C, 54.30; H, 4.20; N, 3.18%. Calcd for $C_{21}H_{19}F_6NO_2S_2$: C, 54.42; H, 4.13; N, 3.02%.

4.1.6. Closed-ring isomer for 3a (3b). Compound **3b** was isolated as a yellow solid by passing a photostationary solution containing **3a** and **3b** thorough HPLC (ethyl acetate/hexane=3/7): ^{1}H NMR ($CDCl_3$, 200 MHz): δ=1.20 (s, 3H), 1.44 (s, 3H), 2.04 (s, 3H), 3.16 (s, 3H), 3.90 (s, 3H), 6.97 (d, J=9.0 Hz, 2H), 8.01 (d, J=9.0 Hz, 2H). MS (*m*/*z*) 463 (M^+). Anal. Found: C, 54.40; H, 4.10; N, 2.80%. Calcd for $C_{21}H_{19}F_6NO_2S_2$: C, 54.42; H, 4.13; N, 3.02%.

4.1.7. 1-(3-Methyl-2-thienyl)perfluorocyclopentene (4). To a solution of 2-bromo-3-methylthiophene (5.0 g, 28 mmol) in dry ether (60 mL) was added slowly 1.6 M *n*-BuLi in hexane (18 mL, 29 mmol) at −80 °C under argon atmosphere. After the mixture was stirred for 30 min at −80 °C, perfluorocyclopentene (3.8 mL, 28 mmol) in dry ether (2 mL) was added. The reaction mixture was further stirred at −80 °C for 1 h and then distilled water was added. The product was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane) to afford 5.8 g (71%) of **4** as colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.29 (d, J=3.4 Hz, 1H), 6.99 (d, J=5.2 Hz, 1H), 7.53 (d, J=5.2 Hz, 1H). MS (*m*/*z*) 290 (M^+). Anal. Found: C, 41.42; H, 1.76%. Calcd for $C_{10}H_5F_7S$: C, 41.39, H, 1.74%.

4.1.8. 5-Methoxy-2-(4-methoxyphenyl)thiazole (5). *N*-(4-methoxybenzoyl) glycine methyl ester[32,33] (10.0 g, 52 mmol) and phosphorus pentasulfide (10 g, 52 mmol) were rapidly added to dry chloroform (15 mL), and the mixture solution was stirred at 80 °C under argon atmosphere. After stirring for 1 h, white precipitate was deposited in the mixture solution. Then the mixture was refluxed for 24 h under argon atmosphere. The reaction mixture was poured in aqueous NaOH water, and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane=3/7) to afford 8 g (80%) of **5** as a yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.84 (s, 3H), 3.94 (s, 3H), 6.92 (d, J=9.0 Hz, 2H), 7.06 (s, 1H), 7.73 (d, J=9.0 Hz, 2H). MS (*m*/*z*) 221 (M^+). Anal. Found: C, 59.91; H, 5.25; N, 6.41%. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33%.

4.1.9. 4-Bromo-5-methoxy-2-(4-methoxyphenyl)thiazole (6). *N*-bromosuccinimide (5.5 g, 31 mmol) was added to a stirred solution of **5** (6.9 g, 31.0 mmol) in dry chloroform (140 mL). The mixture was stirred at −80 °C for 1 h and room temperature for 1 h and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane=3/7) to afford 7.5 g (80%) of **6** as colorless crystals: mp 102–103 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.85 (s, 3H), 4.02 (s, 3H), 6.93 (d, J=9.0 Hz, 2H), 7.75 (d, J=9.0 Hz, 2H). MS (*m*/*z*) 300 (M^+). Anal. Found: C, 44.21; H, 3.41; N, 4.63%. Calcd for $C_{11}H_{10}NO_2SBr$: C, 44.01; H, 3.36; N, 4.67%.

4.1.10. 1-[5-Methoxy-2-(4-methoxyphenyl)-4-thiazolyl]-perfluorocyclopentene (7). To a solution of **7** (1 g, 3.33 mmol) in dry THF (40 mL) was added slowly 1.6 M *n*-BuLi in hexane (2.0 mL, 3.2 mmol) at −80 °C under argon atmosphere. After the mixture was stirred for 15 min at −78 °C, perfluorocyclopentene (0.50 mL, 2.34 mmol) in dry THF (2 mL) was added. The reaction mixture was further stirred at −78 °C for 1 h and then distilled water was added. The product was extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/hexane=3/7) to afford 870 mg (67%) of **7** as colorless needles: mp 77–78 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.86 (s, 3H), 4.10 (s, 3H), 6.95 (d, J=8.8 Hz, 2H), 7.78 (d, J=8.8 Hz, 2H). MS (*m*/*z*) 413 (M^+). Anal. Found: C, 46.27; H, 2.63; N, 3.65%. Calcd for $C_{16}H_{10}NO_2SF_7$: C, 46.50; H, 2.44; N, 3.39%.

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Lithium heptadecafluorooctanesulfonate catalyzed Mannich-type and aza-Diels–Alder reactions in supercritical carbon dioxide

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Abstract—The Mannich-type reaction of imines with (1-methoxy-2-methylpropenyloxy)trimethylsilane and aza-Diels–Alder reaction of imines with Danishefsky's diene can be carried out in $scCO_2$ in the presence of lithium heptadecafluorooctanesulfonate which offer a way to synthesize β-amino carbonyl compounds and nitrogen-containing six-membered ring compounds under environmentally benign conditions.

1. Introduction

Green chemistry provides challenges and opportunities to those who practice chemistry in industry and academic research.[1–5] Of those suitable alternatives to conventional solvents ionic liquids,[6] perfluorinated hydrocarbons,[7] water,[8] and supercritical carbon dioxide ($scCO_2$)[9–11] have been widely investigated. Several advantages which include inexpensiveness, non-flammability, its environmentally benign nature and its ready separability from products make $scCO_2$ an attractive solvent for organic reactions. Above the critical temperature and pressure, (T_c=31 °C, P_c=7.4 MPa) CO_2 has gas-like viscosity and liquid-like density. These moderate critical conditions allow for safe commercial and laboratory operating conditions. Indeed, a great variety of metal-catalyzed reactions have been carried out in $scCO_2$.[10–19]

Mannich-type and aza-Diels–Alder reactions are useful synthetic methods to prepare various β-amino carbonyl compounds[20] and nitrogen-containing six-membered ring compounds,[21] which constitute a broad spectrum of natural products, biologically active compounds, and other functional materials. Recently, Kobayashi and co-workers have developed Mannich-type reactions in water using a hydrophobic polymer-supported sulfonic acid catalyst and alkaline salt-catalyzed aza-Diels–Alder reactions of Danishefsky's diene with imines in water under neutral conditions.[22] In order to explore an alternative environmentally benign condition for these two reactions, we attempted to carry out these reactions in $scCO_2$ in the presence of alkaline salt or other metal catalysts. Herein, we wish to report the lithium heptadecafluorooctanesulfonate-catalyzed Mannich-type and aza-Diels–Alder reactions of imines in $scCO_2$ under mild conditions.

2. Results and discussion

We initially chose various alkali metal salts as catalyst (10 mol%) to promote Mannich-type reaction of benzylidene(phenyl)amine **1a** (0.30 mmol, 54 mg) with (1-methoxy-2-methylpropenyloxy)trimethylsilane (0.45 mmol, 90 μL) at 50 °C and under 10 MPa in $scCO_2$. The results are listed in Table 1. The reaction proceeded smoothly to give desired adduct **2a** in moderate to high yields in the presence of alkali metal salts such as LiOTf (CF_3SO_3Li), LiOPf ($C_8F_{17}SO_3Li$), NaOTf (CF_3SO_3Na), NaOPf ($C_8F_{17}SO_3Na$) and KOPf ($C_8F_{17}SO_3K$) (Table 1, entries 1–4 and 6). On the other hand, KOTf (CF_3SO_3K), CsOTf (CF_3SO_3Cs) and CsOPf ($C_8F_{17}SO_3Cs$) performed poorly (Table 1, entries 5, 7 and 8). The best result was obtained with LiOTf (Table 1, entry 2). In general alkali metal salts derived from a long chain perfluorinated sulfonic acid severed as effective promoters for this Mannich-type reaction in $scCO_2$. This is because a long perfluorinated alkyl chain can allow the $scCO_2$ reaction system become an effective homogenous phase, namely, this catalyst is soluble in $scCO_2$. Through the high pressure glass window placed in $scCO_2$ reaction vessel, we confirmed that the LiOPf ($C_8F_{17}SO_3Li$), **1a** and (1-methoxy-2-methylpropenyloxy)-

Keywords: Mannich-type reaction; Aza-Diels–Alder reaction; Imines; (1-Methoxy-2-methylpropenyloxy)trimethylsilane; Danishefsky's diene; Supercritical carbon dioxide; Lithium heptadecafluorooctanesulfonate; Environmentally benign conditions.
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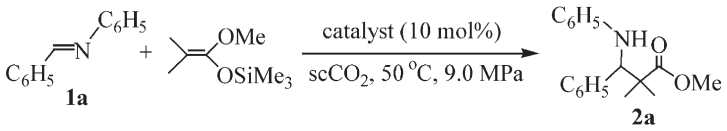
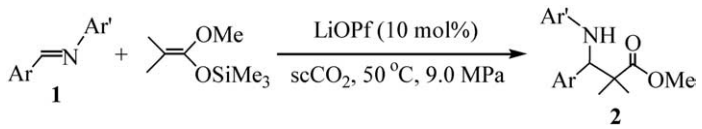
Table 1. The alkali metal salt catalyzed-Mannich-type reaction in $scCO_2$



Entry	Catalyst	Time (h)	**2a**, Yields (%)[a]
1	LiOTf	10	59
2	LiOPf	10	93
3	NaOTf	10	54
4	NaOPf	10	88
5	KOTf	10	6
6	KOPf	10	83
7	CsOTf	10	Trace
8	CsOPf	10	21

LiOPf=$C_8F_{17}SO_3Li$.
[a] Isolated yield.

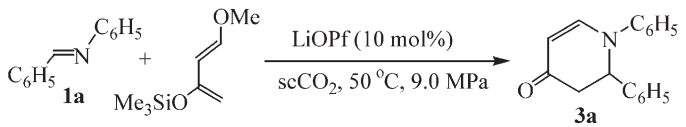
Table 2. LiOPf catalyzed-Mannich-type reaction in $scCO_2$



Entry	Ar	Ar′	Time (h)	**2**, Yields (%)[a]
1	C_6H_5	*m*-$CF_3C_6H_4$	10	**2b**, 85
2	*p*-$MeOC_6H_4$	C_6H_5	10	**2c**, 66
3	*p*-$NO_2C_6H_4$	C_6H_5	10	**2d**, 83
4	*p*-ClC_6H_4	C_6H_5	10	**2e**, 60
5	C_6H_5	*m*-FC_6H_4	10	**2f**, 52

[a] Isolated yield.

Table 3. Alkali and lanthanide metal salts catalyzed-aza-Diels–Alder reaction in $scCO_2$



Entry	Catalyst	Time (h)	**3a**, Yields (%)[a]
1	—	10	—[b]
2	LiOTf	10	80
3	LiOPf	10	88
4	NaOPf	10	78
5	KOPf	10	32
6	$Sc(OTf)_3$	10	64
7	$Yb(OTf)_3$	10	40
8	$Yb(OPf)_3$	10	45

[a] Isolated yield.
[b] No reaction.

trimethylsilane are completely dissolved in $scCO_2$ to form a homogeneous reaction system.

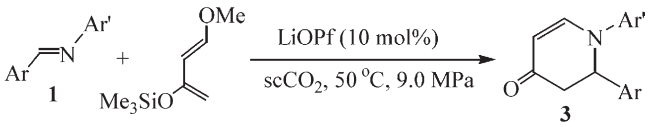
Under the optimized reaction conditions, we then examined this Mannich-type reaction of various imines with (1-methoxy-2-methylpropenyloxy)trimethylsilane in the presence of LiOPf (10 mol%) in $scCO_2$. The results are summarized in Table 2. As can be seen from Table 2, the desired adducts **2** can be obtained in good yields (Table 2, entries 1–5).

Turning our attention to aza-Diels–Alder reactions in $scCO_2$ we noted the reaction of Danishefsky's diene with imines had been conducted previously in methanol, ethanol, DMF, and THF in the absence of any catalyst.[23] Thus, we first examined the aza-Diels–Alder reaction of Danishefsky's diene (0.45 mmol, 77.4 mg) with benzylidene(phenyl)amine **1a** (0.3 mmol, 54 mg) in the absence of any catalyst and found no reaction occurred in $scCO_2$ (Table 3, entry 1). We believe that this is because $scCO_2$ is a non-polar solvent similar to alkanes which are ineffective to

promote aza-Diels–Alder reaction of Danishefsky's diene with imines in contrast to polar organic solvents. However, we found that using LiOTf, LiOPf, or NaOPf as catalysts, this type of aza-Diels–Alder reaction proceeded smoothly to give the corresponding aza-Diels–Alder adduct **3a** in good yields. KOPf did not efficiently catalyze this reaction under the same conditions. The results are listed in Table 3 (entries 2–5). The lanthanide triflates such as $Sc(OTf)_3$ or $Yb(OTf)_3$ and $Yb(OPf)_3$ did not efficiently catalyze this reaction in $scCO_2$ (9.0 MPa) as those of LiOPf, or NaOPf (Table 3, entries 6–8), although using $Sc(OPf)_3$ as a catalyst under higher pressure of $scCO_2$ (10 MPa), this reaction could proceed smoothly to give the adduct in high yield.[17d] LiOPf appeared to be the catalyst of choice in our study.

Under the optimized reaction conditions, we then examined the aza-Diels–Alder reaction of Danishefsky's diene with various imines in $scCO_2$. The results are summarized in Table 4. As can be seen from Table 4, the corresponding nitrogen-containing six-membered ring compounds **3** can be obtained in good yields (Table 4, entries 1–5).

Table 4. LiOPf catalyzed-aza-Diels–Alder reaction in $scCO_2$



Entry	Ar	Ar′	Time (h)	**3**, Yields (%)[a]
1	C_6H_5	*m*-$CF_3C_6H_4$	10	**3b**, 72
2	*p*-$MeOC_6H_4$	C_6H_5	10	**3c**, 75
3	*p*-$NO_2C_6H_4$	C_6H_5	10	**3d**, 80
4	*p*-ClC_6H_4	C_6H_5	10	**3e**, 84
5	C_6H_5	*m*-FC_6H_4	10	**3f**, 70

LiOPf=$C_8F_{17}SO_3Li$.
[a] Isolated yield.

In conclusion, Mannich-type reaction of imines with (1-methoxy-2-methylpropenyloxy)trimethylsilane and the aza-Diels–Alder reaction of Danishefsky's diene with imines take place in $scCO_2$ in the presence of LiOPf ($C_8F_{17}SO_3Li$) under relatively milder conditions (9.0 MPa).[24] This finding offers an access to the formation of β-amino carbonyl compounds[20] and nitrogen-containing six-membered ring compounds under environmentally benign conditions by means of a CO_2-philic catalyst LiOPf ($C_8F_{17}SO_3Li$) and the use of hazardous organic solvents for these reactions can be avoided. Further investigations to develop other types of reactions in $scCO_2$ or modified $scCO_2$ are now in progress.

3. Experimental

3.1. General methods

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded by EI methods, and HRMS was measured on a Finnigan MA^+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. All solid compounds reported in this paper gave satisfactory CHN microanalyses. Reagents obtained commercially were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. $C_8F_{17}SO_3H$ was purchased from TCI (Tokyo Kasei, H0781).

3.2. General procedure for the Mannich-type reaction of imine 1 with (1-methoxy-2-methylpropenyloxy)-trimethylsilane and aza-Diels–Alder reaction of imine 1 with Danishefsky's diene in the presence of LiOPf in $scCO_2$

Imine **1a** (54 mg, 0.30 mmol), (1-methoxy-2-methyl-propenyloxy) trimethylsilane (90 μL, 0.45 mmol) or Danishefsky's diene (90 μL, 0.45 mmol), and LiOPf (15 mg, 10 mol%) were placed in a stainless high pressure reaction vessel of $scCO_2$. The reaction was performed at 50 °C, 9 MPa for 10 h under CO_2 pressure. After the CO_2 pressure was released, the residue was washed with water and extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by passing through a silica gel column (hexane/ethyl acetate=1/4 as an eluent) to afford the products **2a** and **3a** as oily or solid compound.

3.2.1. 2,2-Dimethyl-3-phenyl-3-phenylaminopropionic acid methyl ester 2a. A white solid, 79 mg, yield 93%; this is a known compound. Its ^1H NMR spectroscopic data are in consistent with those reported in literature.[25]

^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, s, CH_3), 1.27 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 4.49 (1H, s, CH), 4.79 (1H, s, NH), 6.49 (2H, dd, *J*=1.2, 8.7 Hz, ArH), 6.59 (1H, t, *J*=7.5 Hz, ArH), 7.04 (2H, dd, *J*=7.5, 8.7 Hz, ArH), 7.17–7.29 (5H, m, ArH).

3.2.2. 2,2-Dimethyl-3-phenyl-3-(3-trifluoromethylphenyl-amino)propionic acid methyl ester 2b. A white solid, 89 mg, yield 85%. Mp 108–110 °C; IR ($CHCl_3$) ν 1714, 1616, 1519, 1495, 1437, 1266, 1124, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (3H, s, CH_3), 1.30 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 4.46 (1H, s, CH), 5.14 (1H, s, NH), 6.60 (1H, d, *J*=8.1 Hz, ArH), 6.72 (1H, s, ArH), 6.82 (1H, d, *J*=8.1 Hz, ArH), 7.11 (1H, t, *J*=8.1 Hz, ArH), 7.21–7.33 (5H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 25.0, 47.1, 52.4, 64.7, 110.0 (q, *J*=4.1 Hz), 114.1 (q, *J*=4.2 Hz), 116.2, 117.7 (q, *J*=277.5 Hz), 127.9, 128.4, 128.5, 129.7, 129.9 (q, *J*=10.1 Hz), 138.7, 147.3, 177.1; MS (EI) *m/z* 351 (M^+, 2.16), 250 (M^+-101, 100), 172 (M^+-179, 11.97), 145 (M^+-206, 15.63). Anal. calcd for $C_{19}H_{20}F_3NO_2$ requires C, 64.95; H, 5.74; N, 3.99. Found: C, 65.06; H, 5.88; N, 3.95%.

3.2.3. 2,2-Dimethyl-3-(4-methoxyphenyl)-3-phenyl-aminopropionic acid methyl ester 2c. A yellowish oil, 61 mg, yield 66%; IR ($CHCl_3$) ν 1727, 1603, 1510, 1265, 1178, 1034 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (3H, s, CH_3), 1.25 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.44 (1H, s, CH), 4.74 (1H, s, NH), 6.49 (2H, d, *J*=8.4 Hz, ArH), 6.59 (1H, t, *J*=7.4 Hz, ArH), 6.81 (2H, d, *J*=8.7 Hz, ArH), 7.04 (2H, dd, *J*=7.4 Hz, 8.4 Hz, ArH),

7.18 (2H, d, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 24.7, 47.4, 52.3, 55.4, 64.0, 113.6, 113.7, 117.4, 129.2, 129.5, 131.4, 147.2, 159.1, 177.3; MS (EI) m/z 313 (M^+, 3.08), 212 (M^+-101, 100), 168 (M^+-145, 6.10), 104 (M^+-209, 15.95), 77(M^+-236, 14.87); HRMS (MALDI) calcd for $C_{19}H_{24}O_3N$ (M^++H) requires 314.1756. Found: 314.1751.

3.2.4. 2,2-Dimethyl-3-(4-nitrophenyl)-3-phenylamino-propionic acid methyl ester 2d. A yellow solid, 81 mg, yield 83%; mp 103–105 °C; IR ($CHCl_3$) ν 1728, 1603, 1507, 1523, 1438, 1266, 1139, 853 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (3H, s, CH_3), 1.32 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 4.57 (1H, d, J=7.1 Hz, CH), 4.90 (1H, d, J=7.1 Hz, NH), 6.45 (2H, d, J=8.6 Hz, ArH), 6.64 (1H, t, J=7.5 Hz, ArH), 7.06 (2H, dd, J=7.5 Hz, 8.6 Hz, ArH), 7.49 (2H, d, J=8.9 Hz, ArH), 8.16 (2H, d, J=8.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 24.5, 46.8, 52.3, 64.2, 113.3, 118.0, 123.3, 129.1, 129.2, 146.1, 147.4, 147.5, 176.2; MS (EI) m/z 328 (M^+, 5.74), 227 (M^+-101, 100), 181 (M^+-147, 37.21), 168 (M^+-160, 8.99), 77 (M^+-251, 19.42). Anal. calcd for $C_{18}H_{20}N_2O_4$ requires C, 65.84; H, 6.14. N, 8.53. Found: C, 65.99; H, 6.14; N, 8.44%.

3.2.5. 2,2-Dimethyl-3-(4-chlorophenyl)-3-phenylamino-propionic acid methyl ester 2e. A white solid, 54 mg, yield 60%; mp 108–110 °C; IR ($CHCl_3$) ν 1732, 1613, 1510, 1533, 1442, 1149, 873 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (3H, s, CH_3), 1.27 (3H, s, CH_3), 3.65 (3H, s, OCH_3), 4.45 (1H, s, CH), 4.79 (1H, s, NH), 6.46 (2H, dd, J=1.0, 8.8 Hz, ArH), 6.62 (1H, t, J=7.4 Hz, ArH), 7.05 (2H, dd, J=7.4, 8.8 Hz, ArH), 7.20–7.28 (4H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 24.4, 46.9, 52.1, 65.8, 113.3, 117.5, 128.2, 129.0, 129.6, 133.2, 137.9, 146.6, 176.7; MS (EI) m/z 317 (M^+, 4.63), 216 (M^+-101, 100), 180 (M^+-137, 4.27), 104 (M^+-213, 13.22), 77 (M^+-240, 19.37). Anal. calcd for $C_{18}H_{20}ClNO_2$ requires C, 68.03; H, 6.34; N, 4.41. Found: C, 68.26; H, 6.33; N, 4.40%.

3.2.6. 2,2-Dimethyl-3-phenyl-3-(3-fluorophenylamino)-propionic acid methyl ester 2f. A white solid (47 mg, 52%); mp 89–91 °C; IR ($CHCl_3$) ν 1727, 1591, 1493, 1265, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (3H, s, CH_3), 1.28 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 4.41 (1H, d, J=7.3 Hz, CH), 5.02 (1H, d, J=7.3 Hz, NH), 6.15 (1H, dt, J=2.8 Hz, 11.8 Hz, ArH), 6.25–6.31 (2H, m, ArH), 6.96 (1H, dd, J=8.1 Hz, 15.0 Hz, ArH), 7.23–7.29 (5H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 24.9, 47.1, 52.3, 64.8, 100.3 (d, J=25.5 Hz), 104.0 (d, J=22.1 Hz), 109.5 (d, J=2.4 Hz), 127.9, 128.4 (d, J=3.6 Hz), 130.2, 130.3, 139.0, 149.0 (d, J=11.0 Hz), 164.1 (d, J=254.7 Hz), 177.1; MS (EI) m/z 301 (M^+, 3.40), 200 (M^+-101, 100), 122 (M^+-179, 21.75), 95 (M^+-206, 20.93), 77 (M^+-224, 9.22). Anal. calcd for $C_{18}H_{20}FNO_2$ requires C, 71.74; H, 6.69; N, 4.65. Found: C, 71.80; H, 6.40; N, 4.53%.

3.2.7. 1,2-Diphenyl-2,3-dihydro-1*H*-pyridin-4-one 3a. A white solid (66 mg, 88%); this is a known compound. Its ^{1}H NMR spectroscopic data are in consistent with those reported in literature.[26]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.79 (1H, ddd, J=1.2, 3.3, 16.4 Hz, CH), 3.31 (1H, dd, J=6.6, 16.4 Hz, CH), 5.26–5.31 (2H, m, CH_2), 7.00–7.05 (2H, m, ArH), 7.08–7.14 (1H, m, ArH), 7.25–7.33 (7H, m, ArH), 7.68 (1H, dd, J=1.2, 7.8 Hz, CH).

3.2.8. 2-Phenyl-1-(3-trifluoromethylphenyl)-2,3-dihydro-1*H*-pyridin-4-one 3b. A colorless oil (68 mg, 72%); IR ($CHCl_3$) ν 1653, 1589, 1497, 1336 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.84 (1H, ddd, J=1.3, 3.3, 16.5 Hz, CH), 3.30 (1H, dd, J=7.0, 16.4 Hz, CH), 5.28–5.31 (1H, m, CH_2), 5.36 (1H, dd, J=0.8, 8.0 Hz, CH_2), 7.13–7.41 (9H, m, ArH), 7.67 (1H, dd, J=0.8, 7.9 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.5, 61.7, 104.3, 115.1 (q, J=3.9 Hz), 120.7 (q, J=3.9 Hz), 121.3, 123.5 (q, J=271.3 Hz), 126.0, 128.1, 129.1, 129.1, 130.2, 131.9 (q, J=33.9 Hz), 137.2, 145.0, 147.3, 190.2; MS (EI) m/z 317 (M^+, 84.57), 240 (M^+-77, 95.26), 185 (M^+-132, 100), 77 (M^+-240, 6.25); HRMS (MALDI) calcd for $C_{18}H_{15}OF_3N$ (M^++H) requires 318.1106. Found: 318.1100.

3.2.9. 2-(4-Methoxyphenyl)-1-phenyl-2,3-dihydro-1*H*-pyridin-4-one 3c. A yellowish oil (63 mg, 75%); this is a known compound. Its ^{1}H NMR spectroscopic data are in consistent with those reported in the literature.[23] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.76 (1H, ddd, J=1.0, 3.3, 16.3 Hz, CH), 3.26 (1H, dd, J=6.9, 16.3 Hz, CH), 3.78 (3H, s, OCH_3), 5.24 (1H, dd, J=3.3, 7.1 Hz, CH_2), 5.28 (1H, dd, J=1.0, 7.1 Hz, CH_2), 6.84 (2H, d, J=2.1, 6.6 Hz, ArH), 7.01–7.33 (7H, m, ArH), 7.64 (1H, dd, J=1.0, 7.8 Hz, CH).

3.2.10. 2-(4-Nitrophenyl)-1-phenyl-2,3-dihydro-1*H*-pyridin-4-one 3d. A yellow solid (71 mg, 80%); this is a known compound. Its ^{1}H NMR spectroscopic data are in consistent with those reported in the literature.[23] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.78 (1H, dd, J=2.9, 16.2 Hz, CH), 3.37 (1H, dd, J=7.3, 16.2 Hz, CH), 5.34 (1H, d, J=7.9 Hz, CH_2), 5.39 (1H, dd, J=2.8, 7.9 Hz, CH_2), 6.99 (2H, d, J=7.8 Hz, ArH), 7.15 (1H, t, J=7.4 Hz, ArH), 7.33 (2H, dd, J=7.4, 7.8 Hz, ArH), 7.47 (2H, d, J=8.5 Hz, ArH), 7.70 (1H, d, J=7.7 Hz, CH), 8.21 (2H, d, J=8.5 Hz, ArH); MS (EI) m/z 294 (M^+, 100), 172 (M^+-122, 29.9), 145 (M^+-149, 81.07), 117 (M^+-177, 67.36), 77 (M^+-217, 25.47).

3.2.11. 2-(4-Chlorophenyl)-1-phenyl-2,3-dihydro-1*H*-pyridin-4-one 3e. A white solid (72 mg, 84%); this is a known compound. Its ^{1}H NMR spectroscopic data are in consistent with those reported in the literature.[23] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.75 (1H, ddd, J=1.0, 3.4, 16.5 Hz, CH), 3.30 (1H, dd, J=6.9, 16.5 Hz, CH), 5.26 (1H, dd, J=3.3, 7.6 Hz, CH_2), 5.29 (1H, dd, J=1.2, 9.1 Hz, CH_2), 7.00 (2H, d, J=7.7 Hz, ArH), 7.10–7.34 (7H, m, ArH), 7.65 (1H, dd, J=1.0, 7.6 Hz, CH); MS (EI) m/z 283 (M^+, 98.03), 172 (M^+-111, 100), 145 (M^+-138, 95.68), 117 (M^+-166, 81.18), 77 (M^+-206, 33.47).

3.2.12. 1-(3-Fluorophenyl)-2-phenyl-2,3-dihydro-1*H*-pyridin-4-one 3f. A colorless oil (55 mg, 70%). IR ($CHCl_3$) ν 1653, 1591, 1494, 1366 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (1H, ddd, J=1.1 Hz, 2.9 Hz, 16.4 Hz, CH), 3.31 (1H, dd, J=6.9, 16.4 Hz, CH), 5.27 (1H, dd, J=2.6, 7.1 Hz, CH_2), 5.32 (1H, dd, J=0.8, 7.1 Hz, CH_2), 6.70–6.75 (1H, m, ArH), 6.78–6.82 (2H, m, ArH), 7.20–7.35 (6H, m, ArH), 7.66 (1H, dd, J=1.1, 7.9 Hz, CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.4, 61.5, 103.6, 105.6 (d,

J=21.2 Hz), 110.9 (d, J=21.2 Hz), 113.6 (d, J=3.4 Hz), 125.9, 127.9, 130.8 (d, J=9.5 Hz), 137.3, 146.1 (d, J=10.0 Hz), 147.3, 163.2 (d, J=256.4 Hz),190.2; MS (EI) m/z 267 (M^+, 65.81), 190 (M^+-77, 49.22), 163 (M^+-104, 52.31), 135 (M^+-132, 100), 95 (M^+-172, 52.69); HRMS (MALDI) calcd for $C_{17}H_{15}OFN$ (M^++H) requires 268.1138. found: 268.1132.

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A new approach to isoindoloisoquinolinones. A simple synthesis of nuevamine

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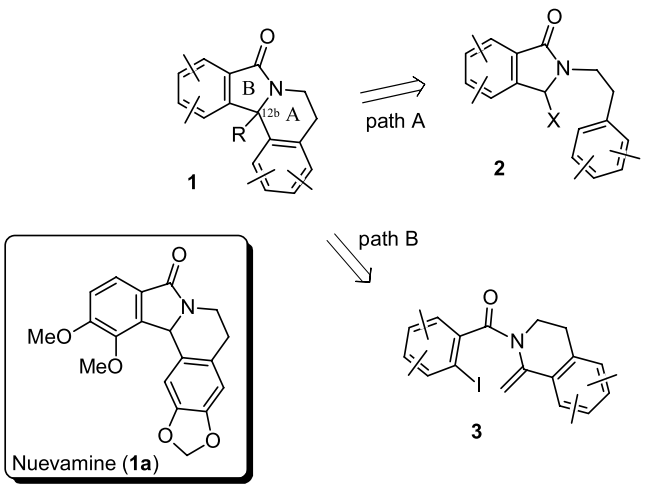
Abstract—A convenient and versatile short step synthesis of isoindoloisoquinolinones, illustrated by the total synthesis of the alkaloid nuevamine **1a**, is described. The tetracyclic lactam compounds were obtained by a tactical combination of the Parham procedure for the elaboration of the isoindolinone template and an aryne-mediated cyclization giving rise to the nitrogen containing six-membered heteroring unit.

1. Introduction

Members of the plant family *Berberidaceae* are known to produce an array of unusual isoquinoline alkaloids. Their study is facilitated by the fact that relatively large amounts of these plants can be collected. This therefore makes conceivable the study of minor alkaloids present, that is, those available only in small amounts, which often afford an insight into the catabolic pathways for the principal alkaloids. This is notably the case of isoindolo[1,2-*a*]-isoquinolinones **1**, a class of tetracyclic lactams which are interesting due to the real and potential biological activities of many of their derivatives.[1] The eminent example nuevamine **1a** has been isolated from *Berberis darwinii* Hook, gathered in southern Chile, in the vicinity of Cuidad Osorno.[2] This alkaloid occupies a special place since it was the first recognized isoindoloisoquinolinone reported from natural sources. Initially, its structure was erroneously assigned but later revision led unambiguously to structure **1a**.[3] Two main general approaches to the synthesis of isoindolo[1,2-*a*]isoquinolinones have been reported so far. They differ in the type of the annulation process and in the heteroring unit embedded in the alkaloid skeleton, formed in the last step. Thus, creation of ring A has been generally achieved by intramolecular cyclization of *N*-acyliminium ions derived from α-substituted isoindolinone derivatives **2** (Retrosynthetic Scheme 1, path A) and a closer analysis of the literature reveals that improvement and modification of this synthetic approach has been confined to the development of new precursors of the acyliminium species.



Scheme 1.

Thus, intramolecular amidoarylation as the key ring-forming step has been ensured from α-hydroxy (X=OH)[4] and α-alkoxy (X=OMe)[5] lactamic precursors by treatment with a wide variety of Lewis acid catalysts such as scandium and copper triflates,[5c,d] $SnCl_4$,[5e] TMSOTf,[5c] $BF_3{\cdot}OEt_2$,[5e,f] $TiCl_4$,[5b] and trifluoroacetic acid.[4,5a] An original structural modification recently developed by Katritzky led to the generation of the *N*-acyliminium cation by loss of a benzotriazolyl anion upon treatment of **2** (X=benzotriazolyl) with $TiCl_4$.[6] An alternative synthetic tactic has been also proposed by Sotomayor in which the intermediate *N*-acyliminium species was generated from a preformed

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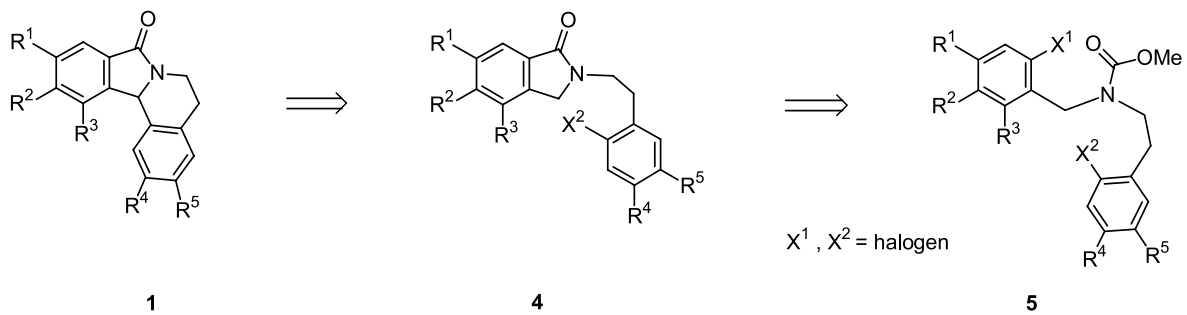
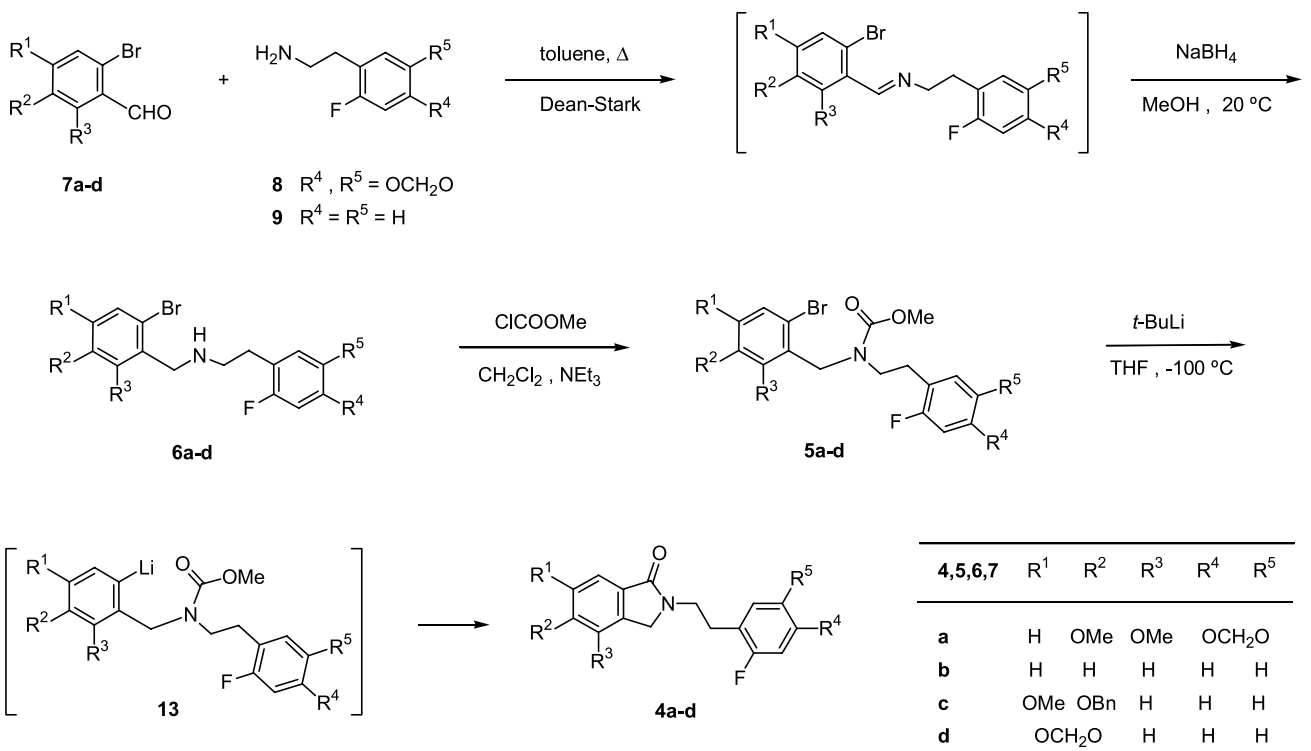
annulated model **1** (R=OH).[7] This skilful approach allowed intermolecular α-amidoalkylation, giving access to a wide variety of C-12b substituted nuevamine-type alkaloids. However, probably due to difficulties associated with the elaboration of the starting compounds and particularly the absolute necessity of having an unsymmetrically disubstituted isoindolinone parent compound available, most of these syntheses have only been claimed to give access to the nuevamine skeleton. Isoindoloisoquinolinones have been also accessed by ring B formation performed by intramolecular Heck cyclization of aromatic enamides **3** (Scheme 1, path B). In this annulation process the 6-*endo-trig* cyclization often competes with the 5-*exo-trig* cyclization but this problem has been circumvented by the addition of a hydride source which favors the regio-controlled formation of the five-membered ring product.[8] Unfortunately, all models elaborated by this technique are inevitably alkylated at the C-12b position and this precludes the synthesis of unsubstituted models such as the alkaloid nuevamine. Some more confidential methods based upon the phosphoric acid cyclization of β-phenylethylaminophthalide[9] or by a combination of the Pictet–Spengler reaction with Pd-catalyzed carbonylation applied to (2-iodobenzylidene)-phenethylamine derivatives[10] have been also used occasionally for the assemblage of the isoindoloisoquinolinone framework. Consequently, the elegant synthetic approach reported by Castedo et al.[3] which allowed the unambiguous assignment of the structure of the alkaloid nuevamine can arguably be deemed to be the sole total synthesis to date of this natural product.

2. Results and discussion

In continuation of our investigation into the synthesis of alkaloids with an isoindolinone ring system as the main structural subunit[11] we herein wish to disclose an alternative, efficient and tactically new approach to isoindoloisoquinolinones illustrated by the total synthesis of the alkaloid nuevamine isolated as a racemate from Chilean barberries. Our strategy, which is depicted in retrosynthetic Scheme 2, is based on the use of 2-arylethylisoindolinones **4** as key



Scheme 2.

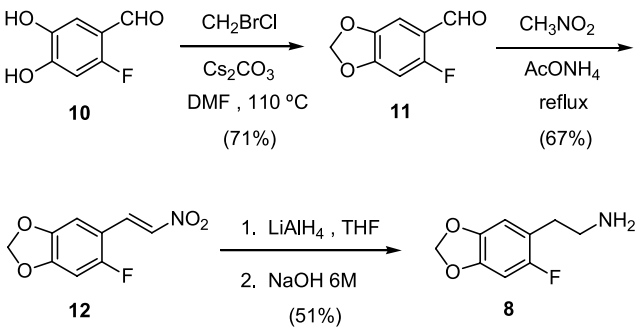


4,5,6,7	R^1	R^2	R^3	R^4	R^5
a	H	OMe	OMe	OCH_2O	
b	H	H	H	H	H
c	OMe	OBn	H	H	H
d	OCH_2O		H	H	H

Scheme 3.

intermediates. These lactams were obtained by Parham-type cyclization induced by aromatic lithiation of the halogenodiarylalkylamine **5** with a carbamate function acting as the internal electrophile.[12] Aryne-mediated cyclization induced by basic treatment of the primarily annulated compounds **4** then should complete the synthesis of the target isoindoloisoquinolinones **1**. A contentious issue in the elaboration of the starting compounds was judging the proper choice for the halogen atoms X^1, X^2 connected to the environmentally different aromatic units of **5**. Critical to the success of the strategy was the incorporation of a halogen atom X^1 liable to cause the aromatic metallation–cyclization sequence leading to **4** by a metal–halogen exchange, while sparing the second halogen atom X^2. In contrast X^2 should allow and, if feasible, facilitate the mandatory aryne formation for the ultimate annulation step. Since it has been clearly established that metal–halogen exchange occurs preferentially with aryl bromides and iodides, whereas arylfluorides and chlorides do not normally react with organolithium compounds but undergo instead *ortho*-metallation and aryne formation afterwards[13] we embarked on the synthesis of the diversely halogenated carbamates **5a–d** (Scheme 3).

The first facet of the synthesis was the elaboration of the halogenated diarylalkylamines **6a–d**. These compounds were readily obtained by a reductive amination process involving the bromobenzaldehyde derivatives **7a–d** and the appropriate fluorinated arylethylamines **8**, **9**. Initially, the aromatic fluorinated amine **8** was obtained by the three step sequence depicted in Scheme 4 which involves the double reduction of the nitrostyrene derivative **12** deriving from the fluorocarboxaldehyde derivative **11**.



Scheme 4.

The compound **11** was readily accessible by linking the vicinal hydrophenolic functions of the parent compound **10** (Scheme 4).

Treatment of amines **6a–d** with methyl chloroformate delivered the carbamates **5a–d** in excellent yields (73–91%). To ensure the formation of the lithiated intermediate **13** a THF solution of the appropriate arylbromide was treated with 1.1 equiv. of *t*-BuLi at −100 °C in THF. The intramolecular ring closure was instantaneous as demonstrated by the isolation solely of the annulated compounds **4a–d** upon aqueous work-up (Table 1).

Table 1. Yields for compounds **6a–d**, **5a–d** and **4a–d** produced via Scheme 3

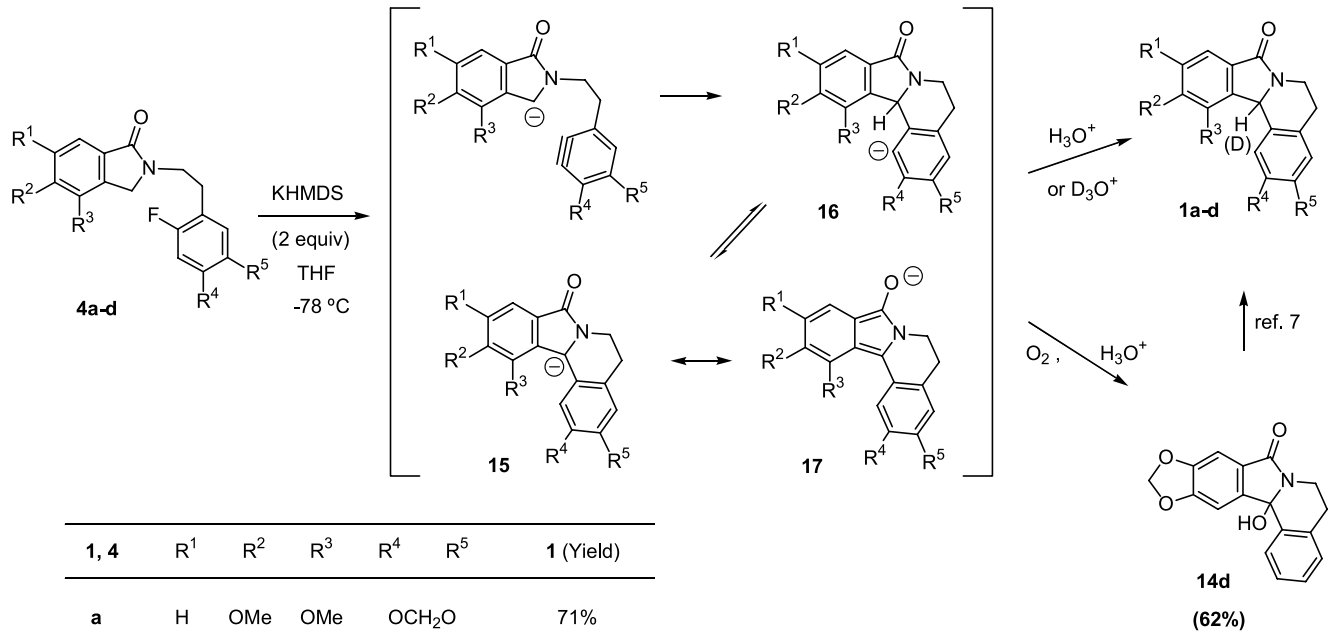
	6 (%)	**5** (%)	**4** (%)
a	94	78	68
b	86	91	72
c	97	76	64
d	95	73	62

The concept of the subsequent generation of the six-membered heteroring unit embedded in the isoindoloisoquinolinone skeleton originated from the following premises: (i) isoindolinones have been easily metalated at the benzylic position of the lactam unit thus allowing the connection of a range of electrophiles at the 3-position of the heteroring system;[14] (ii) arylfluorides are good candidates for the generation of arynes[13,15a] and the anion–aryne cyclization processes, particularly those involving nitrogen-bearing nucleophiles and carbanions, occupy a place of choice in the arsenal of alkaloid synthesis tactics.[15b] Compounds **4b–d** were then treated with KHMDS [potassium bis(trimethylsilyl)amide] (2.2 equiv.) in the presence of 18-crown-6 at −78 °C in THF and gratifyingly classical work-up delivered single compounds which were unambiguously identified as the annulated isoindolinones **1b–d**. Performing this reaction sequence with the appropriate open model **4a** led straightforwardly to the target natural product nuevamine **1a** with a very satisfactory yield (38% over last three steps).

It is worth noting that reactions must be preferably carried out after careful degassing of the solution since quite significant amounts of products which were hydroxylated at C-12b, as exemplified by the formation of **14d**, were obtained in reactions performed in non-deoxygenated solutions (Scheme 5). The formation of this α-hydroxylactam may tentatively be explained by capture of the carbanionic species **15** by oxygen. Intermediate **15** would be formed by a prototropy of **16**, attributable to a greater stabilization of the bibenzylic carbanionic species which can further adopt the *o*-quinodimethane structure **17**. The fact that acidic work-up with D_3O^+ led to the exclusive incorporation of deuterium on the bibenzylic C-12b position as exemplified by the formation of **1a**(D) corroborates this hypothesis. However, this reaction was not really detrimental to the elaboration of the desired compounds **1a–d** since the hemiaminal compounds (e.g., **14d**) can be almost quantitatively converted into the dehydroxylated models (e.g., **1d**)[7] and can also serve for the introduction of substituents at C-12b.[7]

3. Conclusion

In summary, we have identified a novel and flexible synthetic approach to isoindoloisoquinolinones. In only two key synthetic steps from easily accessible precursors we have prepared the isoindolinone template by reliance on the Parham procedure and the creation of the isoquinoline ring system by an aryne-mediated cyclization process. The total synthesis of the alkaloid nuevamine emphasizes the versatility and regiospecificity of this new conceptual approach and we believe that this work demonstrates a general new methodology for the preparation of similar structurally modified isoindoloisoquinolinone alkaloids.



1, 4	R^1	R^2	R^3	R^4	R^5	1 (Yield)
a	H	OMe	OMe	OCH_2O		71%
b	H	H	H	H	H	73%
c	OMe	OBn	H	H	H	77%
d	OCH_2O		H	H	H	69%

Scheme 5.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μ; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert–Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 and 75 MHz, for ^1H and ^{13}C respectively). For ^1H, ^{13}C NMR, $CDCl_3$ was used as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

The bromobenzaldehyde derivatives **7a**[16,17] and **7c**[18,19] were synthesized according to literature methods.

4.2. Synthesis of 2-(6-fluorobenzo[1,3]dioxol-5-yl)-ethylamine (8)

2-Fluoro-4,5-dihydroxybenzaldehyde **10** was obtained from 4-fluoroveratrole by sequential formylation[20] and demethylation.[21]

4.2.1. 6-Fluorobenzo[1,3]dioxole-5-carbaldehyde (6-fluoropiperonal, 11). Bromochloromethane (2.61 g, 20.2 mmol) was added, under Ar, to a stirred suspension of 2-fluoro-4,5-dihydroxybenzaldehyde **10** (2.10 g, 13.4 mmol) and cesium carbonate (6.57 g, 20.2 mmol) in anhydrous DMF (20 mL) and the resulting mixture was heated at 110 °C for 3 h. After cooling to room temperature the mixture was filtered through a pad of Celite® which was subsequently washed with EtOAc (50 mL). Water (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The organic layers were combined, washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent left a residue, which was purified by flash column chromatography with hexanes/AcOEt (50:50) as eluent. Yield 1.60 g (71%); mp 72–73 °C; ^1H NMR (δ) 6.05 (s, 2H, OCH_2O), 6.61 (d, J_{HF}=9.8 Hz, 1H, aromatic H), 7.19 (d, J_{HF}=5.4 Hz, 1H, aromatic H), 10.15 (s, 1H, CHO); ^{13}C NMR (δ) 97.9 (d, J_{CF}=29 Hz), 102.9, 104.9 (d, J_{CF}=3 Hz), 117.9 (d, J_{CF}=8 Hz), 144.8 (d, J_{CF}=1 Hz), 154.0 (d, J_{CF}=15 Hz), 162.5 (d, J_{CF}=252 Hz), 185.4 (d, J_{CF}=8 Hz). Anal. Calcd for $C_8H_5O_3F$ (168.1): C, 57.15; H, 3.00%. Found: C, 57.35; H, 2.94%.

4.2.2. 5-Fluoro-6-(2-nitrovinyl)-benzo[1,3]dioxole (12). A solution of 6-fluorobenzo[1,3]dioxole-5-carbaldehyde (1.45 g, 8.6 mmol), $AcONH_4$ (0.15 g, mmol) in nitromethane (CH_3NO_2, 6.5 mL) was refluxed for 5 h. After cooling, the yellow precipitate was filtered and washed with MeOH (20 mL) to afford yellow crystals. Yield 1.12 g, (67%); mp 143–144 °C; ^1H NMR (δ) 6.07 (s, 2H, OCH_2O), 6.68 (d, J_{HF}=9.8 Hz, 1H, aromatic H), 6.87 (d, J_{HF}=5.9 Hz, 1H, aromatic H), 7.55 (d, J=13.7 Hz, 1H, CH=), 8.03 (d, J=13.7 Hz, 1H, CH=); ^{13}C NMR (δ) 98.7 (d, J_{CF}=30 Hz), 102.9, 106.8 (d, J_{CF}=4 Hz), 110.6 (d, J_{CF}=13 Hz), 132.2 (d, J_{CF}=3 Hz), 137.0 (d, J_{CF}=9 Hz), 144.9, 152.1 (d, J_{CF}=15 Hz), 158.5 (d, J_{CF}=250 Hz). Anal. Calcd for $C_9H_6FNO_4$ (211.1): C, 51.20; H, 2.86; N, 6.63%. Found: C, 51.02; H, 3.01; N, 6.55%.

4.2.3. 2-(6-Fluorobenzo[1,3]dioxol-5-yl)ethylamine (8). A solution of the nitro derivative **12** (2.00 g, 10.3 mmol) in dry THF (15 mL) was added dropwise, under Ar, to an ice cooled suspension of lithium aluminum hydride ($LiAlH_4$, 3.89 g, 102.6 mmol) in dry THF (50 mL). The mixture was stirred at 0 °C for 2 h and then refluxed overnight. The suspension was cooled to 0 °C and the excess of $LiAlH_4$ was quenched with 6 M aqueous sodium hydroxide (50 mL). The precipitate was filtered off and extracted with boiling THF for 1 h, then filtered and washed with Et_2O (50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After evaporation of the solvent the residue was purified by flash column chromatography with AcOEt/Et_3N (90:10) as eluent. Yield 0.96 g (51%); oil; ^1H NMR (δ_H) 1.76 (br s, 2H, NH_2), 2.73 (t, J=7.1 Hz, 2H, CH_2), 3.23 (t, J=7.1 Hz, 2H, CH_2), 5.79 (s, 2H, OCH_2O), 6.43 (d, J_{HF}=8.8 Hz, 1H, aromatic H), 6.54 (d, J_{HF}=5.6 Hz, 1H, aromatic H); ^{13}C NMR (δ_C) 29.2, 51.9, 97.7 (d, J_{CF}= 31 Hz), 101.5, 109.6 (d, J_{CF}=6 Hz), 119.0 (d, J_{CF}=14 Hz), 143.3 (d, J_{CF}=2 Hz), 146.2 (d, J_{CF}=14 Hz), 155.6 (d, J_{CF}=237 Hz). Anal. Calcd for $C_9H_{10}FNO_2$ (183.2): C, 59.01; H, 5.50; N, 7.65%. Found: C, 59.23; H, 5.40; N, 7.77%.

4.3. General procedure for the synthesis of the amines 6a–d

A solution of the [2-(2-fluorophenyl)ethyl]amine derivative **8** or **9** (10 mmol) and the appropriate bromobenzaldehyde derivative **7a–d** (10 mmol) in toluene (40 mL) was refluxed for 3 h in a Dean–Stark apparatus. After removal of toluene in vacuo the *N*-benzylidene-[2-(2-fluorophenyl)ethyl]-amine derivative was used directly in the next step without further purification. $NaBH_4$ (20 mmol, 0.76 g) was added portionwise to a solution of the previously obtained Schiff base in MeOH (50 mL) at room temperature. The mixture was stirred at room temperature for 1 h and the solvent was removed under vacuo. The crude mixture was dissolved in dichloromethane (50 mL), washed with saturated aqueous NH_4Cl solution (30 mL) and then brine (30 mL). The organic solution was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude oily amines **6a–d** were purified by flash column chromatography with AcOEt/hexanes/NEt_3 (80:10:10) as eluent.

4.3.1. (6-Bromo-2,3-dimethoxybenzyl)-[2-(6-fluorobenzo[1,3]dioxol-5-yl)ethyl]amine (6a). Yield 3.78 g, (94%), oil; ^1H NMR (δ) 1.70 (br s, 1H, NH), 2.68–2.77 (m, 4H, 2×CH_2), 3.79 (s, 6H, 2×CH_3), 3.92 (s, 2H, CH_2), 5.86 (s, 2H, OCH_2O), 6.50 (d, J_{HF}=9.0 Hz, 1H, aromatic H), 6.60 (d, J_{HF}=6.1 Hz, 1H, aromatic H), 6.67 (d, J= 8.8 Hz, 1H, aromatic H), 7.19 (d, J=8.8 Hz, 1H, aromatic H); ^{13}C NMR (δ) 29.4 (d, J_{CF}=2 Hz), 47.6, 48.7, 55.8, 61.1, 97.8 (d, J_{CF}=31 Hz), 101.5, 112.5 (d, J_{CF}=6 Hz), 112.5, 115.4, 118.7 (d, J_{CF}=19 Hz), 127.8, 133.6, 143.4 (d, J_{CF}= 2 Hz), 146.2 (d, J_{CF}=14 Hz), 148.6, 152.2, 155.6 (d, J_{CF}=236 Hz). Anal. Calcd for $C_{18}H_{19}BrFNO_4$ (412.3): C, 52.44; H, 4.65; N, 3.40%. Found: C, 52.56; H, 4.78; N, 3.17%.

4.3.2. (2-Bromobenzyl)-[2-(2-fluorophenyl)ethyl]amine (6b). Yield 2.65 g (86%); oil; ^1H NMR (δ) 1.57 (br s, 1H, NH), 2.91 (s, 4H, 2×CH_2), 3.90 (s, 2H, CH_2), 6.99–7.13 (m, 3H, aromatic H), 7.15–7.29 (m, 3H, aromatic H), 7.37 (d, J=7.6 Hz, 1H, aromatic H), 7.53 (d, J=7.8 Hz, 1H, aromatic H); ^{13}C NMR (δ) 29.8 (d, J_{CF}=2 Hz), 49.1 (d, J_{CF}=1 Hz), 53.5, 115.3 (d, J_{CF}=22 Hz), 124.0 (d, J_{CF}= 4 Hz), 124.0, 126.9 (d, J_{CF}=16 Hz), 127.4, 127.9 (d, J_{CF}= 8 Hz), 128.5, 130.2, 131.0 (d, J_{CF}=5 Hz), 132.8, 139.3, 161.3 (d, J_{CF}=243 Hz). Anal. Calcd for $C_{15}H_{15}BrFN$ (308.2): C, 58.46; H, 4.91; N, 4.54%. Found: C, 58.21; H, 5.14; N, 4.41%.

4.3.3. (5-Benzyloxy-2-bromo-4-methoxybenzyl)-[2-(2-fluorophenyl)ethyl]amine (6c). Yield 4.31 g (97%); oil; ^1H NMR (δ) 1.56 (br s, 1H, NH), 2.81 (s, 4H, 2×CH_2), 3.76 (s, 2H, CH_2), 3.85 (s, 3H, CH_3), 5.10 (s, 2H, CH_2), 6.93 (s, 1H, aromatic H), 6.98–7.07 (m, 3H, aromatic H), 7.16–7.21 (m, 2H, aromatic H), 7.25–7.36 (m, 3H, aromatic H), 7.42 (d, J=7.1 Hz, 2H, aromatic H); ^{13}C NMR (δ) 29.7 (d, J_{CF}= 2 Hz), 48.8, 53.0, 56.3, 71.1, 114.2, 115.3 (d, J_{CF}=22 Hz), 115.6, 116.1, 124.0 (d, J_{CF}=4 Hz), 126.9 (d, J_{CF}=16 Hz), 127.4, 127.9 (d, J_{CF}=8 Hz), 128.0, 128.6, 130.9 (d, J_{CF}= 5 Hz), 131.3, 136.8, 147.4, 149.2, 161.3 (d, J_{CF}=243 Hz). Anal. Calcd for $C_{23}H_{23}BrFNO_2$ (444.35): C, 62.17; H, 5.22; N, 3.15%. Found: C, 62.23; H, 5.30; N, 3.29%.

4.3.4. (6-Bromobenzo[1,3]dioxol-5-ylmethyl)-[2-(2-fluorophenyl)ethyl]amine (6d). Yield 3.34 g (95%); oil; ^1H NMR (δ) 1.54 (br s, 1H, NH), 2.86 (s, 4H, 2×CH_2), 3.77 (s, 2H, CH_2), 5.94 (s, 2H, CH_2), 6.86 (s, 1H, aromatic H), 6.96 (s, 1H, aromatic H), 7.02–7.08 (m, 2H, aromatic H), 7.14–7.25 (m, 2H, aromatic H); ^{13}C NMR (δ_C) 29.8 (d, J_{CF}=2 Hz), 48.9 (d, J_{CF}=1 Hz), 53.4, 101.6, 110.0, 112.7, 114.0, 115.3 (d, J_{CF}=22 Hz), 124.0 (d, J_{CF}=4 Hz), 126.8 (d, J_{CF}=16 Hz), 127.9 (d, J_{C-F}=8 Hz), 131.0 (d, J_{CF}=5 Hz), 132.5, 147.3, 147.4, 161.3 (d, J_{CF}=243 Hz). Anal. Calcd for $C_{16}H_{15}BrFNO_2$ (352.2): C, 54.56; H, 4.29; N, 3.98%. Found: C, 54.23; H, 4.51; N, 4.19%.

4.4. General procedure for the synthesis of the carbamic acid methyl esters 5a–d

Methyl chloroformate (0.99 g, 10.5 mmol) was added dropwise at 0 °C to a stirred solution of the secondary amine **6a–d** (7.0 mmol) and NEt_3 (1.42 g, 14.0 mmol) in CH_2Cl_2 (40 mL). The mixture was allowed to warm to room temperature and then stirred for an additional 3 h. The mixture was washed with water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to left an oily residue which was purified by flash column chromatography with AcOEt/hexanes (40:60) as eluent.

4.4.1. (6-Bromo-2,3-dimethoxybenzyl)-[2-(6-fluorobenzo-[1,3]dioxol-5-yl)ethyl]carbamic acid methyl ester (5a). Yield 2.57 g (78%); oil; ^1H NMR (δ, mixture of two rotational isomers 2:3) 2.52–2.64 (m, 2H, CH_2), 3.12–3.23 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 3.76 (s, 6H, 2×CH_3), 4.61 and 4.68 (2×s, together 2H, CH_2), 5.81 (s, 2H, OCH_2O), 6.41 (d, J_{HF}=8.6 Hz, 1H, aromatic H), 6.59 (d, J_{HF}=7.3 Hz, 1H, aromatic H), 6.70 (d, J=8.8 Hz, 1H, aromatic H), 7.18 (d, J=8.8 Hz, 1H, aromatic H); ^{13}C NMR (δ, mixture of two rotational isomers) 28.0 (d, J_{CF}=2 Hz), 45.0, 45.4, 52.5, 55.9, 60.8, 97.6 (d, J_{CF}=30 Hz), 101.5, 109.4 (d, J_{CF}= 5 Hz), 113.4, 115.8, 117.6 (d, J_{CF}=15 Hz), 127.9, 130.1,

143.3 (d, J_{CF}=2 Hz), 146.3 (d, J_{CF}=14 Hz), 149.5, 152.3, 155.6 (d, J_{CF}=237 Hz), 156.6. Anal. Calcd for $C_{20}H_{21}BrFNO_6$ (470.3): C, 51.08; H, 4.50; N, 2.98%. Found: C, 51.27; H, 4.32; N, 2.84%.

4.4.2. (2-Bromobenzyl)-[2-(2-fluorophenyl)ethyl]carbamic acid methyl ester (5b). Yield 2.33 g (91%); oil; ^{1}H NMR (δ) (δ, mixture of two rotational isomers 4:5) 2.86–2.94 (m, 2H, CH_2), 3.44–3.50 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 4.46 and 4.57 (2×s, together 2H, CH_2), 6.96–7.25 (m, 7H, aromatic H), 7.51 (d, J=7.8 Hz, 1H, aromatic H); ^{13}C NMR (δ_C), (δ, mixture of two rotational isomers A and B) 27.7 (A), 28.3 (B), 46.9 (B), 47.9 (A), 50.6 (B), 50.9 (A), 52.8, 115.3 (d, J_{CF}=22 Hz), 122.9 (A), 123.4 (B), 124.1 (d, J_{CF}=4 Hz), 125.7 (d, J_{C-F}=16 Hz), 127.6 (B), 127.9 (A), 128.3 (d, J_{CF}=8 Hz), 128.8 (two peaks overlapping), 129.1, 131.2 (d, J_{CF}=5 Hz), 132.8, 136.8, 156.8 (A), 157.2 (B), 161.3 (d, J_{CF}=244 Hz). Anal. Calcd for $C_{17}H_{17}BrFNO_2$ (366.2): C, 55.75; H, 4.68; N, 3.82%. Found: C, 55.65; H, 4.49; N, 4.13%.

4.4.3. (5-Benzyloxy-2-bromo-4-methoxybenzyl)-[2-(2-fluorophenyl)ethyl]carbamic acid methyl ester (5c). Yield 2.67 g (76%); mp 54–55 °C (from hexane–toluene); ^{1}H NMR (δ, mixture of two rotational isomers 4:5) 2.70–2.85 (m, 2H, CH_2), 3.22–3.34 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.33 and 4.46 (2×s, together 2H, CH_2), 5.10 (s, 2H, OCH_2O), 6.62 and 6.84 (2×s, together 1H, s, aromatic H), 6.96–7.25 (m, 6H, aromatic H), 7.29–7.37 (m, 4H, aromatic H); ^{13}C NMR (δ_C, mixture of two rotational isomers) 29.7, 46.4, 49.8, 52.7, 56.3, 71.1, 113.9, 115.2 (d, J_{CF}=22 Hz), 115.8, 116.1, 124.0 (d, J_{CF}=4 Hz), 125.8 (d, J_{CF}=16 Hz), 127.4, 127.9, 128.2 (d, J_{CF}=8 Hz), 128.6, 128.9, 131.2 (d, J_{CF}=5 Hz), 136.6, 147.6, 149.5, 157.2, 161.3 (d, J_{CF}=244 Hz). Anal. Calcd for $C_{25}H_{25}BrFNO_4$ (502.4): C, 59.77; H, 5.02; N, 2.79%. Found: C, 59.92; H, 5.11; N, 3.02%.

4.4.4. (6-Bromobenzo[1,3]dioxol-5-ylmethyl)-[2-(2-fluorophenyl)ethyl]carbamic acid methyl ester (5d). Yield 2.09 g (73%); mp 76–78 °C (from hexane–toluene); ^{1}H NMR (δ_H, mixture of two rotational isomers 2:3) 2.80–2.89 (m, 2H, CH_2), 3.36–3.44 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 4.34 and 4.44 (2×s, together 2H, CH_2), 5.91 (s, 2H, OCH_2O), 6.60 and 6.75 (2×s, together 1H, aromatic H), 6.93 (s, 1H, aromatic H), 6.96–7.09 (m, 2H, aromatic H), 7.18–7.25 (m, 2H, aromatic H); ^{13}C NMR (δ_C, mixture of two rotational isomers A and B) 27.6 (A), 28.2 (B), 46.7 (B), 47.6 (A), 50.2 (B), 50.5 (A), 52.8, 101.8, 108.1 (A), 109.0 (B), 112.5 (B), 112.7 (A), 113.3 (A), 113.6 (B), 115.2 (d, J_{CF}=22 Hz), 124.1 (d, J_{CF}=4 Hz), 125.7 (d, J_{CF}=16 Hz), 128.2 (d, J_{CF}=8 Hz), 130.0 (A), 130.1 (B), 131.2 (d, J_{CF}=5 Hz), 147.7, 156.6 (A), 157.2 (B), 161.3 (d, J_{CF}=244 Hz). Anal. Calcd for $C_{18}H_{17}BrFNO_4$ (410.2): C, 52.70; H, 4.18; N, 3.41%. Found: C, 52.61; H, 4.04; N, 3.31%.

4.5. General procedure for the synthesis of the isoindolinones 4a–d

A solution of *t*-BuLi (2.5 mL, 1.7 M in pentane, 4.25 mmol) was added dropwise by syringe at −100 °C under Ar to a solution of carbamate **5a–d** (3.86 mmol) in dry THF (50 mL). The reaction mixture was allowed to warm to 0 °C over a period of 30 min followed by addition of saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (30 mL), extracted with Et_2O (2×25 mL) and the combined organic layers were dried (Na_2SO_4). Evaporation of solvent in vacuo left a solid residue which was purified by flash column chromatography with AcOEt/hexanes (60:40) as eluent. Isoindolinones **4a–d** were finally purified by recrystallization from hexane–toluene.

4.5.1. 2-[2-(6-Fluorobenzo[1,3]dioxol-5-yl)ethyl]-4,5-dimethoxy-2,3-dihydro-isoindol-1-one (4a). Yield 942 mg (68%); mp 161–162 °C; ^{1}H NMR (δ) 2.89 (t, J=6.8 Hz, 2H, CH_2), 3.76 (t, J=6.8 Hz, 2H, CH_2), 3.90 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 5.91 (s, 2H, OCH_2O), 6.55 (d, J_{HF}=9.0 Hz, 1H, aromatic H), 6.65 (d, J_{HF}=6.4 Hz, 1H, aromatic H), 6.99 (d, J=8.3 Hz, 1H, aromatic H), 7.52 (d, J=8.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 28.0, 42.9, 48.1, 56.2, 60.3, 97.9 (d, J_{CF}=31 Hz), 101.7, 109.3 (d, J_{CF}=5 Hz), 112.7, 117.2 (d, J_{CF}=18 Hz), 119.5, 126.3, 133.2, 143.4, 143.7, 146.7 (d, J_{CF}=14 Hz), 154.6, 155.7 (d, J_{CF}=236 Hz), 168.1. Anal. Calcd for $C_{19}H_{18}FNO_5$ (359.4): C, 63.51; H, 5.05; N, 3.90%. Found: C, 63.44; H, 4.84; N, 4.17%.

4.5.2. 2-[2-(2-Fluorophenyl)ethyl]-2,3-dihydro-isoindol-1-one (4b). Yield 707 mg (72%); mp 116–118 °C; ^{1}H NMR (δ) 3.02 (t, J=7.3 Hz, 2H, CH_2), 3.86 (d, J=7.3 Hz, 2H, CH_2), 4.25 (s, 2H, CH_2), 6.98–7.05 (m, 2H, aromatic H), 7.15–7.25 (m, 2H, aromatic H), 7.36–7.52 (m, 3H, aromatic H), 7.82 (d, J=7.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 28.3 (d, J_{CF}=2 Hz), 42.73 (d, J_{CF}=1 Hz), 50.5, 115.3 (d, J_{CF}=22 Hz), 122.6 123.6, 124.3 (d, J_{CF}=4 Hz), 125.6 (d, J_{CF}=16 Hz), 128.0, 128.4 (d, J_{CF}=8 Hz), 131.1 (d, J_{CF}=5 Hz), 131.2, 132.8, 141.2, 161.3 (d, J_{CF}=244 Hz), 168.5. Anal. Calcd for $C_{16}H_{14}FNO$ (255.3): C, 75.28; H, 5.53; N, 5.49%. Found: C, 75.48; H, 5.79; N, 5.27%.

4.5.3. 5-Benzyloxy-2-[2-(2-fluorophenyl)ethyl]-6-methoxy-2,3-dihydro-isoindol-1-one (4c). Yield 966 mg (64%); mp 123–124 °C; ^{1}H NMR (δ) 2.97 (t, J=7.1 Hz, 2H, CH_2), 3.80 (t, J=7.1 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 5.15 (s, 2H, OCH_2O), 6.84 (s, 1H, aromatic H), 6.95–7.03 (m, 2H, aromatic H), 7.13–7.22 (m, 2H, aromatic H), 7.28–7.37 (m, 6H, aromatic H); ^{13}C NMR (δ) 28.3 (d, J_{CF}=2 Hz), 42.7, 50.0, 56.2, 71.1, 105.7, 107.3, 115.3 (d, J_{CF}=22 Hz), 124.2 (d, J_{CF}=4 Hz), 125.5, 125.7 (d, J_{CF}=16 Hz), 127.2, 1281, 128.3 (d, J_{CF}=8 Hz), 128.7, 131.0 (d, J_{CF}=5 Hz), 134.4, 136.4, 150.2, 151.5, 161.2 (d, J_{CF}=243 Hz), 168.7. Anal. Calcd for $C_{24}H_{22}FNO_3$ (377.4): C, 73.64; H, 5.66; N, 3.58%. Found: C, 73.51; H, 5.75; N, 3.84%.

4.5.4. 6-[2-(2-Fluorophenyl)ethyl]-6,7-dihydro-[1,3]dioxolo[4,5-*f*]-isoindol-5-one (4d). Yield 716 mg (62%); mp 104–105 °C; ^{1}H NMR (δ) 3.00 (t, J=7.1 Hz, 2H, CH_2), 3.81 (t, J=7.1 Hz, 2H, CH_2), 4.12 (s, 2H, CH_2), 6.02 (s, 2H, OCH_2O), 6.77 (s, 1H, aromatic H), 6.98–7.05 (m, 2H, aromatic H), 7.16–7.26 (m, 3H, aromatic H); ^{13}C NMR (δ) 28.4 (d, J_{CF}=2 Hz), 42.8, 50.2, 101.8, 103.0, 103.4, 115.3 (d, J_{CF}=2 Hz), 124.3 (d, J_{CF}=4 Hz), 125.7 (d, J_{CF}=16 Hz), 126.7, 128.4 (d, J_{CF}=8 Hz), 131.1 (d, J_{CF}=5 Hz), 136.5, 148.2, 151.1, 161.3 (d, J_{CF}=243 Hz), 168.1. Anal. Calcd for $C_{17}H_{14}FNO_3$ (299.3): C, 68.22; H, 4.71; N, 4.68%. Found: C, 68.03; H, 4.94; N, 4.65%.

4.6. General procedure for the generation of isoquinoline skeleton of the compounds 1a–d by intramolecular ring closure

A solution of isoindolinone **4a–d** (1.04 mmol) and 18-crown-6 (600 mg, 2.28 mmol) in dry THF (50 mL) was carefully degassed by three freeze–thaw cycles and stirred at −78 °C under dry deoxygenated Ar. Then a solution of KHMDS (4.6 mL, 0.5 M in toluene, 2.28 mmol) was added dropwise. The mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature within 2 h. Aqueous NH_4Cl solution (10%, 5 mL) was added and after dilution with water (30 mL) the mixture was extracted with Et_2O (2×25 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated in vacuo to left **1a–d** as solids which were purified by flash column chromatography with Et_2O as eluent.

4.6.1. 5,12b-Dihydro-6*H*-11,12-dimethoxy-1,3-dioxolo-[4,5-*g*]isoindolo[1,2a]isoquinolin-8-one (Nuevamine, 1a). Yield 250 mg (71%); mp 210–211 °C (lit.[2] 212 °C); ^{1}H NMR (δ) 2.85 (dt, J_{gem}=15.4 Hz, J=6.1 Hz, 1H, CH_2), 3.00 (dt, J_{gem}=15.4 Hz, J=6.1 Hz, 1H, CH_2), 3.57 (dt, J_{gem}=12.5 Hz, J=6.1 Hz, 1H, CH_2), 3.96 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 3.94–4.02 (m, 1H, CH_2), 5.61 (s, 1H, NCH), 5.87 (d, J_{gem}=17.9 Hz, 1H, OCH_2O), 5.88 (d, J_{gem}=17.9 Hz, 1H, OCH_2O), 6.65 (s, 1H, aromatic H), 7.05 (d, J=8.3 Hz, 1H, aromatic H), 7.28 (s, 1H, aromatic H), 7.57 (d, J=8.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 28.9, 38.9, 56.3, 58.5, 60.5, 101.0, 107.5, 108.4, 113.3, 119.8, 126.4, 128.2, 128.8, 136.0, 144.4, 146.5, 146.8, 155.6, 167.9.

4.6.2. 5,12b-Dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (1b). Yield 178 mg (73%); mp 114–116 °C (lit.[6] 114–116 °C).

4.6.3. 11-Benzyloxy-10-methoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (1c). Yield 297 mg (77%); mp 147–149 °C; ^{1}H NMR (δ) 2.78 (ddd, J_{gem}=15.6 Hz, J=4.6, 4.9 Hz, 1H, CH_2), 2.94 (ddd, J_{gem}=15.7 Hz, J=6.4, 9.0 Hz, 1H, CH_2), 3.36–3.48 (m, 1H, CH_2), 3.87 (s, 3H, CH_3), 4.25 (ddd, J_{gem}=12.9 Hz, ^3J=4.9, 6.4 Hz, 1H, CH_2), 5.23 (d, J_{gem}=12.4 Hz, 1H, OCH_2), 5.33 (d, J_{gem}=12.4 Hz, 1H, OCH_2), 5.40 (s, 1H, NCH), 7.10–7.46 (m, 11H, aromatic H); ^{13}C NMR (δ) 29.3, 34.8, 56.2, 58.6, 71.3, 105.7, 109.0, 124.8, 125.6 (two peaks overlapping), 126.6, 127.3, 128.1, 128.7, 129.1, 134.6, 134.8, 136.5, 137.3, 150.6, 151.2, 168.3. Anal. Calcd for $C_{24}H_{21}NO_3$ (371.4): C, 77.61; H, 5.70; N, 3.77%. Found: C, 77.77; H, 5.83; N, 3.97%.

4.6.4. 5,6,8,13b-Tetrahydro[1,3]dioxolo[4′,5′:5,6]isoindolo[1,2-*a*]isoquinolin-8-one (1d). Yield 200 mg (69%); mp 170–172 °C; ^{1}H NMR (δ) 2.82 (ddd, J_{gem}=15.7 Hz, J=4.5, 4.9 Hz, 1H, CH_2), 3.01 (ddd, J_{gem}=15.7 Hz, J=5.7, 9.3 Hz, 1H, CH_2), 3.41 (ddd, J_{gem}=12.9 Hz, J=4.5, 9.3 Hz, 1H, CH_2), 4.35 (ddd, J_{gem}=12.9 Hz, J=4.9, 5.7 Hz, 1H, CH_2), 5.51 (s, 1H, NCH), 6.03 (d, J_{gem}=11.8 Hz, 1H, OCH_2O), 6.035 (d, J_{gem}=11.8 Hz, 1H, OCH_2O), 7.15–7.28 (m, 5H, aromatic H), 7.51 (d, J=7.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 29.4, 38.4, 58.8, 102.1, 103.4, 103.9, 125.1, 126.7, 126.9, 127.4, 129.3, 134.4, 134.8, 139.8, 148.5, 151.4, 167.8. Anal. Calcd for $C_{17}H_{13}NO_3$ (279.3): C, 73.11; H, 4.69; N, 5.01%. Found: C, 73.08; H, 4.80; N, 4.87%.

4.6.5. 13b-Hydroxy-5,6,8,13b-tetrahydro[1,3]dioxolo[4′,5′:5,6]isoindolo[1,2-*a*]isoquinolin-8-one (14d). Yield 190 mg (62%); mp 189–190 °C; ^{1}H NMR (δ_H, DMSO d_6) 2.77–2.83 (m, 2H, CH_2), 3.36 (dt, J_{gem}=12.7 Hz, J=8.1 Hz, 1H, CH_2), 4.12–4.19 (m, 1H, CH_2), 6.10 (s, 1H, OCH_2O), 6.16 (s, 1H, OCH_2O), 6.95 (br s, 1H, OH), 7.05 (s, 1H, aromatic H), 7.11–7.27 (m, 3H, aromatic H), 7.73 (s, 1H, aromatic H), 8.00 (d, J=7.8 Hz, 1H, aromatic H); ^{13}C NMR (δ_C, DMSO d_6) 28.8, 34.6, 85.1, 101.9, 102.2, 104.5, 124.3, 126.4, 127.7, 128.1, 128.9, 134.2, 137.6, 144.4, 148.5, 151.4, 165.9. Anal. Calcd for $C_{17}H_{13}NO_4$ (295.3): C, 69.15, 4.44; N, 4.74%. Found: C, 69.22; H, 4.25; N, 4.89%.

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A novel approach for introduction of C-1 oxygenated group on decalin skeleton: first asymmetric total synthesis of 1α,6α-dihydroxy-eudesm-3-ene

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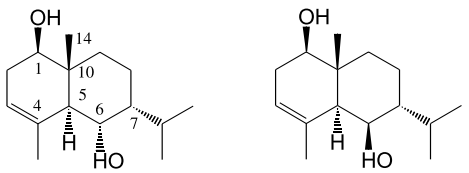
Abstract—This paper describes a novel approach for introduction of C-1 hydroxy on decalin ring system starting from (−)-carvone. Utilizing the substrate controlled Mukaiyama aldol reaction and alkaline cyclization as key steps, the C-1 oxygenated decalin eudesmane skeleton **2′** and its four isomers were synthesized efficiently. What's more, X-ray structural analysis confirmed sufficiently that something was wrong about the structure of natural product: 1β,6β-dihydroxy-7-*epi*-eudesm-3-ene as reported by the literature.

1. Introduction

Although considerable efforts have been devoted to the total synthesis of eudesmane and agarofuran sesquiterpenoids over the past decades, introduction of C-1 oxygenated group on decalin skeleton still represents a significant challenge for synthetic chemist.[1] To our knowledge, many C-1 oxygenated decalin of eudesmane and agarofuran sesquiterpenoids have been isolated in recent years,[2] but there was few report on total synthesis of them. In connection with our ongoing studies on the total synthesis of bioactive sesquiterpenoids,[3–5] we intended to explore a new strategy for the introduction of an oxygenated functional group at the C-1 position in the decalin ring system.

2. Result and discussion

Compounds **1** and **2** (Fig. 1) were first isolated in 1997 from the leaves of *Pluchea dioscoridis*, the structures were confirmed to be 1β,6α-dihydroxy-7-*epi*-eudesm-3-ene and it's C-6 epimer.[6] They both had an oxygenated group in C-1 position. Our first attempt was to synthesize the aimed compounds **1′** and **2′** (the enantiomner of **1** and **2**). Surprisingly, when we accomplished the aimed compounds **1′** and **2′**, we found that the spectral data of two compounds were inconsistent with the literature.



1 **2**

Figure 1.

The total synthesis of compounds **1′** and **2′** is detailed in Scheme 1. Compound **7** could be readily prepared from commercially available (−)-carvone by catalytic hydrogenation and refluxing with *tert*-butyldimethylsilyl chloride (TBSCl) in *N*,*N*-dimethylformamide. After refluxing for 2 days, the silyl enol ether **7** was obtained in 90% yield and the selectivity of thermodynamic and kinetic silyl enol ethers was up to 20:1 when the solvent was tripled the amount of the literature procedure.[7] However, for our substrate, the literature procedure gave less than 10% yield of **7** and we found that high temperature (about 140 °C) was essential for good yield. Mukaiyama aldol reaction[8] of aldehyde **6** and **7** successfully introduced C-1 oxygenated group to give **8** and **9** (2:1 in ratio) which were both key optical intermediates for the synthesis of natural occurring compounds. The stereochemistry of methyl group was determined as α by NOESY due to the steric bulk of the *tert*-butyldimethylsilyl group. After the hydroxy of **8** was protected with *p*-methoxybenzyl group and deprotection of benzoyl group, the resulting compound was oxidized with PCC to afford aldehyde keto **11**.

Keywords: Asymmetric synthesis; C-1 oxygenated; Eudesmane; X-ray structural analysis; Wrong structure.
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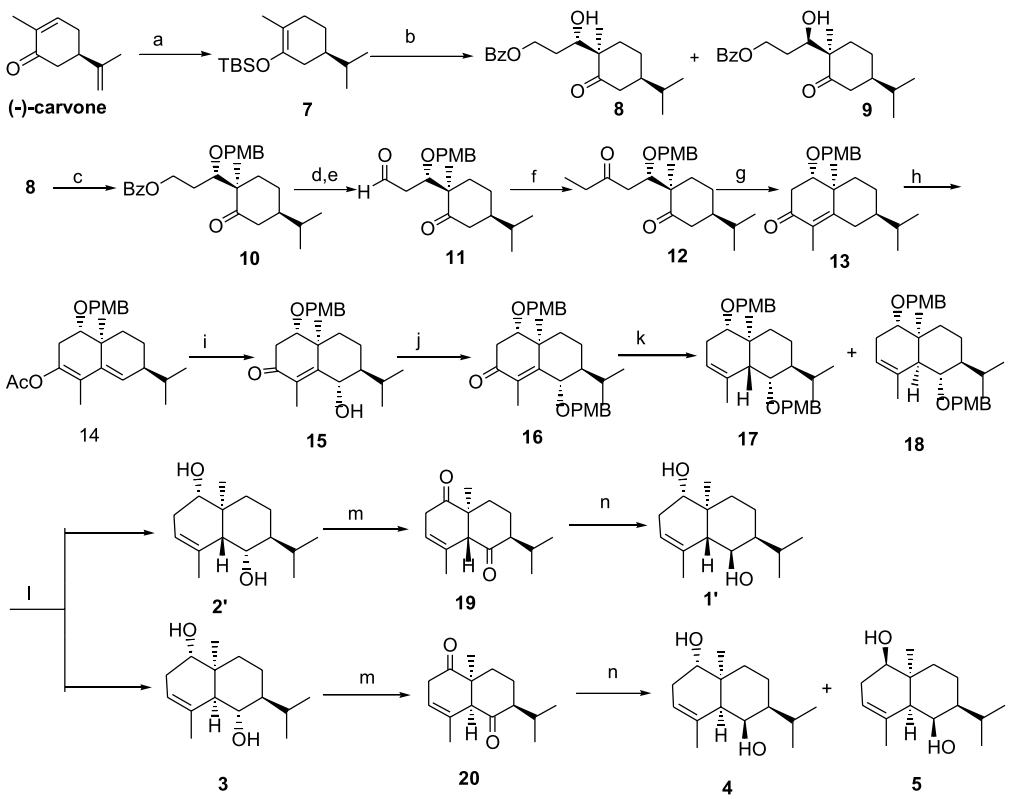

Scheme 1. Reagents and conditions: (a) pd/C/H_2, EtOH; then TBSCl/Et_3N, DMF, reflux 2 days, 90%; (b) **6** ($BzOCH_2CH_2CHO$)/$TiCl_4$, CH_2Cl_2, 60%; (c) PMBOC(=NH)CCl_3, *p*-TsOH, CH_2Cl_2, 85%; (d) 2% NaOH, MeOH, 96%; (e) PCC, Py, CH_2Cl_2, 80%; (f) −78 °C, EtMgBr, THF, 75%; PCC, Py, CH_2Cl_2, 90%; (g) 0.2% NaOMe/MeOH, 98%; MsCl, NEt_3, 89%; (h) AcCl, Ac_2O, DMAP, NaOAc,82%; (i) *m*-CPBA, CH_2Cl_2, 83%; (j) PMBOC(=NH)CCl_3, *p*-TsOH, CH_2Cl_2, 82%; (k) $TsNHNH_2$/HOAc, $NaBH_4$, 80%; (l) DDQ,CH_2Cl_2–H_2O, 87%; (m) Dess–Martin reagent, CH_2Cl_2, 92%; (n) $NaBH_4$/MeOH, 80–90%.

The diketo **12**, obtained by the highly selective reaction of EtMgBr and aldehyde keto **11** at −78 °C and subsequent PCC oxidation, was cyclized and dehydrated under condition of 0.2% CH_3ONa/CH_3OH and $MsCl/NEt_3$ respectively.[9] We have tried many other conditions, such as 10% KOH/MeOH[10] refluxing, NaOMe/MeOH[11] refluxing and TsOH/benzene refluxing, but none of them turned out to be ideal. That is, under such conditions, either the yield is rather low or the product is unwanted (obtaining compound **21**, Fig. 2). Refluxing enone **13** in AcCl and Ac_2O (2:1 in ratio) with the addition of sodium acetate (2 equiv.) to prevent eliminating of C-1 oxygenated group afforded **14**.[12] Oxidation of **14** with 3-chloroperoxybenzoic acid and subsequent deacetylation under acidity condition gave the alcohol **15**. The reaction went on in a highly stereoselective way to give 100% (*S*)-alcohol, which could be deduced from the coupling constants ($J_{6,7}$=2.4 Hz), and also proved by the X-ray structure analysis. The protection of alcohol **15** with *p*-methoxybenzyl group afforded **16**. The reaction of **16** with $TsNHNH_2$ in acetic acid for 10 h followed by addition of $NaBH_4$ generated compounds **17** and **18**,[13] which couldn't be separated by silica gel chromatography. Deprotection of *p*-methoxybenzyl group with DDQ in CH_2Cl_2–H_2O (18:1)[14] afforded **2′** and **3** (1:4 in ratio), which could be easily separated. Oxidation of diol **2′** with Dess–Martin reagent and subsequent reduction with $NaBH_4$ gave diol **1′**. Similarly, we got diol **4** and **5** (6:1 in ratio) from **3**.

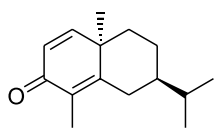

Figure 2.

Unfortunately, the spectral data of **1′** and **2′** were inconsistent with those of **1** and **2** in literature. Based on the inevitability of the reaction (from **16** to **17** and **18**), only one chiral carbon (C-5) was introduced and two compounds were generated. Obviously, they must be epimers of C-5, **17** was *trans*-fused-ring and **18** was *cis*-fused-ring. However, it was difficult to determine which one was the *trans*-fused-ring from the spectral data of ^1H NMR and ^{13}C NMR. For this reason, a single crystal X-ray structural analysis of the compound **3** (relatively more in amount) was performed to confirm the absolute configuration (Fig. 3). Thus, the configuration of **2′** was determined as the just right compound we anticipated. The configurations of compounds **1′**, **4** and **5** could be elucidated according to the stereoselectivity of the reaction and the spectral data of the compounds. However, none of the five isomers was consistent with the two compounds in literature.

What's wrong with the compounds **1** and **2**? In literature, the configuration of compound **1** was determined by the coupling constants ($J_{5,6}$=9.5 Hz, $J_{6,7}$=5 Hz), which were in agreement with an (axial–axial and axial–equatorial) pattern for these protons. So the configuration was assigned as 5α,6α,7β (H). The conclusion seemed plausible. Those configurations were also proved by the NOE 1D. It couldn't

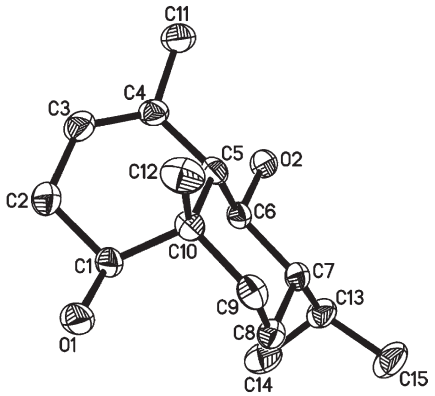

Figure 3. Molecular structure of **3** (CCDC 220322).

be denied that the result of NOE 1D was a very important factor to determine the configuration of the compound, but it could not be the sole evidence.

3. Conclusion

In summary, a novel approach for introduction of C-1 oxygenated group on decalin skeleton was exemplified in synthesis of 1α,6α-dihydroxy-eudesm-3-ene and its four isomers. The strategy is of great potential for the divergent synthesis of complex polyhydroxylated eudesmane and agarofuran sesquiterpenoids. The application of the established method to the further synthesis of a number of C-1 oxygenated natural products is under active investigation.

4. Experimental

4.1. General

IR spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 or Varian Mercury Plus-300 spectrometer in $CDCl_3$ using TMS as an internal reference, and *J* values were given in Hertz. Mass spectra were determined on a HP5988A spectrometer by direct inlet at 70 eV. Optical rotation measurements were carried out on a Perkin–Elmer 141 polarimeter. Flash chromatography was performed on silica gel, with petroleum ether (PE) and diethyl ether (Et) mixtures as eluent.

4.1.1. *tert*-Butyl-(5β-isopropyl-2-methyl-cyclohex-1-enyloxy)-dimethyl-silane (7). A mixture of (−)-carvone (9 g) and 10% Pd/C (900 mg) in EtOH 20 mL was stirred under hydrogen for 30 h and the mixture was filtered through a celite gel, which without further purification, was taken in dry DMF (250 mL) and treated with NEt_3 (24 mL, 3 equiv.) and TBSCl (13.1 g, 1.5 equiv.). The resulting mixture was refluxed for 2 days before it was extracted with petroleum ether and dried over $MgSO_4$. After chromatographic purification, the silyl enol ether **7** (14.4 g) was obtained, yielding 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.87–1.00 (m, 15H, $C(CH_3)_3$ and $CH(CH_3)_2$), 1.02–1.19 (m, 2H), 1.32–1.50(m, 2H), 1.57 (s, 3H, CH_3), 1.65–1.75 (m, 2H), 1.76–2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.7, −3.4, 16.4, 18.4, 19.9, 20.2, 25.9, 26.7, 30.7, 32.4, 34.3, 41.9, 111.4, 143.0.

4.1.2. 2β-(3-Benzyloxy-1α(β)-hydroxy-propyl)-5β-isopropyl-2α-methyl-cyclohexanone 8 (9). A mixture of aldehyde **6** (900 mg, 5 mmol) and silyl enol ether **7** (1.33 g, 5 mmol) in 5 mL CH_2Cl_2 was added dropwise to $TiCl_4$ (0.5 mL, 5 mmol) in 20 mL dry CH_2Cl_2 under argon at −78 °C. The mixture was allowed to warm up to −40 °C, stirred for 2 h and quenched with aqueous sodium carbonate at −40 °C then to room temperature. The mixture was extracted with ether and washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. After chromatographic purification, 332 mg of **9** (yellow oil) and 670 mg of pure **8** (white crystal, mp 84–86 °C) were obtained, yielding 60%. Compound **8** $[\alpha]_D^{25}$=+21° (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J*=4.1 Hz, Me), 0.83 (d, 3H, *J*=4.1 Hz, Me), 1.05 (s, 3H, Me), 1.34–1.49 (m, 2H), 1.62–1.74 (m, 4H), 2.14–2.19 (m, 1H), 2.24–2.28 (m, 1H), 2.39–2.44 (dd, 1H, *J*=4.4, 14 Hz), 2.55 (d, 1H, *J*=5.8 Hz), 4.15–4.19 (m, 1H, CHOH), 4.40–4.45 (m, 1H, OCH_2), 4.56–4.62 (m, 1H, OCH_2), 7.43 (t, 2H, *J*=7.9 Hz, Ar), 7.55–7.57 (t, 1H, *J*=7.6 Hz, Ar), 8.01–8.03 (d, 2H, *J*=8.4 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.5, 19.6, 23.5, 30.8, 31.2, 32.9, 42.9, 45.2, 53.1, 62.3, 68.9, 128.4, 129.5, 130.1, 133.1, 166.9, 216.0; MS *m/z* (%): 314 ($M-H_2O$, 0.6), 192 (5), 154 (50), 122 (14), 111 (10), 105 (100), 77 (41), 69 (17), 55 (20), 41 (21); IR (film, cm^{-1}) ν_{max}=3476, 2959, 2931, 1718, 1689, 1272, 1121, 1099, 1070, 974, 710. Compound **9** $[\alpha]_D^{25}$=+55° (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, 3H, *J*=5.1 Hz, Me), 0.84 (d, 3H, *J*=5.1 Hz, Me), 1.06 (s, 3H, Me), 1.46–1.49 (m, 2H), 1.58–1.70 (m, 4H), 1.86–1.89 (m, 2H), 2.40–2.43 (m, 2H), 4.20 (dd, 1H, *J*=8.1, 1 Hz, CHOH), 4.49–4.60 (m, 2H, $BzOCH_2$), 7.42–7.45 (m, 2H, Ar), 7.55–7.58 (m, 1H, Ar), 8.01–8.06 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.5, 23.7, 25.6, 30.2, 31.5, 34.9, 42.0, 45.2, 52.2, 62.3, 70.6, 128.3, 129.6, 133.0, 166.7, 216.2.

4.1.3. 2β-[3-Benzyloxy-1α-(4-methoxy-benzyloxy)-propyl]-5β-isopropyl-2α-methyl-cyclohexanone (10). *p*-TsOH (25 mg) was added to alcohol **8** (1.66 g, 5 mmol) in 5 mL dry CH_2Cl_2 under argon. The mixture was cooled to 0 °C, then 2, 2, 2-trichloro-acetimidic acid 4-methoxy-benzyl ester (1.7 g, 6 mmol) in 2 mL dry CH_2Cl_2 was added, the mixture was allowed to warm up to room temperature and stirred for 24 h. The crude was directly chromatographed on silica gel to afford a colorless oil **10** (1.92 g, 85%). $[\alpha]_D^{25}$=+16.5° (*c* 3.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, 3H, *J*=3.6 Hz, Me), 0.76 (d, 3H, *J*=3.9 Hz, Me), 0.96 (s, 3H, Me), 1.25–1.27 (m, 1H), 1.41–1.60 (m, 4H), 1.75–1.80 (m, 2H), 2.06–2.10 (m, 2H), 2.22–2.28 (m, 2H), 3.68 (s, 3H, OMe), 4.04 (d, 1H, *J*=9.6 Hz, $CHOCH_2$), 4.28–4.32 (m, 2H, OCH_2), 4.52 (s, 2H, OCH_2Ar), 6.75 (d, 2H, *J*=8.4 Hz, Ar), 7.17 (d, 2H, *J*=8.4 Hz, Ar), 7.35 (t, 2H, *J*=7.5 Hz, Ar), 7.49 (t, 1H, *J*=7.5 Hz, Ar), 7.94 (d, 2H, *J*=8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.2, 19.4, 23.9, 30.7, 32.3, 34.6, 43.3, 45.6, 53.9, 55.1, 62.0, 74.7, 75.7, 113.7, 128.4, 130.0, 130.1, 133.0, 159.2, 166.2, 214.9; MS *m/z* (%): 452 (M^+, 0.8), 316 (10), 194 (17), 179 (7), 151 (9), 137 (10), 121 (100), 77 (17), 41 (7); IR (film, cm^{-1}) ν_{max}=2958, 2871, 1718, 1611, 1513, 1456, 1273, 1250, 1176, 1112, 1074, 1033, 823.

4.1.4. 3-(4β-Isopropyl-1α-methyl-2-oxo-cyclohexyl)-3α-(4-methoxy-benzyloxy)-propionaldehyde (11). To a solution of ketone **10** (1.8 g, 4 mmol) in 5 mL MeOH was added 2% NaOH/MeOH (20 mL) at 0 °C and stirred for 3 h. Then MeOH was evaporated under a reduced pressure, diluted with ether, washed with water, brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_2Cl_2 (20 mL) and treated with PCC (1.7 g, 8 mmol), pyridine (0.64 mL, 8 mmol) and SiO_2 (2.4 g). The resulting suspension mixture was stirred over night at room temperature and diluted with ether. The mixture was filtered through a silica gel. The solvent was removed and the residue was purified by chromatography to furnish yellow oil (1.06 g, 77%). $[\alpha]_D^{25}=+100°$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 6H, *J*=6.3 Hz, Me), 0.93 (s, 3H, Me), 1.17–1.31 (m, 2H), 1.40–1.52 (m, 2H), 2.01–2.09 (m, 1H), 2.20–2.27 (m, 2H), 2.27–2.39 (m, 1H), 2.59–2.68 (m, 1H), 3.73 (s, 3H, OMe), 4.33 (d, 1H, *J*=11.1 Hz, OCH_2Ar), 4.40 (dd, 1H, *J*=3.6, 7.2 Hz, $CHOCH_2$), 4.49 (d, 1H, *J*=10.8 Hz, OCH_2Ar), 6.81 (d, 2H, *J*=14.7 Hz, Ar), 7.18 (d, 2H, *J*=14.7 Hz, Ar), 9.73 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.4, 19.6, 23.8, 32.3, 34.3, 43. 6, 45.5, 45.9, 53.5, 55.3, 72.5, 72.8, 113.8, 129.7, 130.0, 159.3, 200.7, 215.1; MS *m*/*z* (%): 346 (M^+, 0.4), 210 (2), 173 (14), 167 (11), 137 (24), 121 (100), 55 (13), 41 (23); IR (film, cm^{-1}) ν_{max}=2957, 2871, 1722, 1702, 1612, 1514, 1462, 1249, 1176, 1081, 1034, 823.

4.1.5. 5β-Isopropyl-2β-[1α-(4-methoxy-benzyloxy)-3-oxo-pentyl]-2α-methyl-cyclohexanone (12). To a solution of aldehyde **11** (1.2 g, 3.46 mmol) in dry THF (5 mL) under argon atmosphere was added dropwise EtMgBr (8 mL, 4 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min and quenched with aqueous ammonium chloride. The resulting mixture was extracted with ether and washed successively with sodium hydrogencarbonate and brine, and dried over $MgSO_4$. The solvent was removed in vacuum to give the crude product, which without further purification, was taken in CH_2Cl_2 (20 mL) and treated with PCC (1.48 g, 7 mmol), pyridine (0.5 mL, 7 mmol) and SiO_2 (2.22 g). The resulting suspension mixture was stirred for 2 days at room temperature and diluted with ether. The mixture was filtered through a silica gel. The solvent was removed and the residue was purified by chromatography to furnish yellow oil **12** (880 mg, 68%). $[\alpha]_D^{25}=+62°$ (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, 6H, *J*=1.8 Hz, Me), 0.92 (s, 3H, Me), 0.96 (t, 3H, *J*=7.2 Hz, Me), 1.14–1.21 (m, 2H), 1.43–1.50 (m, 4H), 2.09–2.13 (m, 1H), 2.18–2.34 (m, 2H), 2.30 (q, 2H, *J*=7.5Hz, CH_2), 2.55–2.63 (m, 1H), 3.73 (s, 3H, OMe), 4.33 (d, 1H, *J*=11.1 Hz, OCH_2Ar), 4.45 (m, 2H, OCH_2Ar and $CHOCH_2$), 6.81 (d, 2H, *J*=8.7 Hz, Ar), 7.18 (d, 2H, *J*=8.7 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.6, 17.1, 19.4, 19.5, 23.8, 32.5, 35.0, 36.9, 43.6, 44.0, 46.0, 53.7, 55.2, 72.8, 73.3, 113.7, 129.5, 131.9, 159.2, 210.0, 215.3; MS *m*/*z* (%): 374 (M^+, 0.3), 238 (10), 202 (12), 167 (36), 121 (100), 57 (13); IR (film, cm^{-1}) ν_{max}=2958, 2938, 2872, 1702, 1603, 1513, 1460, 1250, 1161, 1035, 830.

4.1.6. 1α-(4-Methoxy-benzyloxy)-10-*epi*-eudesm-4 (5)-en-3-one (13). To a solution of diketone **12** (500 mg, 1.34 mmol) in dry MeOH 10 mL was added NaOMe (20 mg) under argon at 0 °C. Then the mixture was allowed to warm up to room temperature and stirred for 2 h. The solution was evaporated to dryness in vacuum and the residue was diluted with ether, washed with 5% HCl, sodium hydrogencarbonate, brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_2Cl_2 (5 mL) and treated with NEt_3 (1.8 mL) and MsCl (1.2 mL). The resulting mixture was stirred for 8 h at room temperature and diluted with ether, washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Purification by flash chromatography gave white crystal **13** (415 mg, 87%, mp 116–118 °C). $[\alpha]_D^{25}=+11°$ (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, 3H, *J*=6.4 Hz, Me), 0.85 (d, 3H, *J*=6.4 Hz, Me), 1.18 (s, 3H, Me), 1.26–1.29 (m, 1H), 1.37–1.38 (m, 1H), 1.41–1.46 (m, 2H), 1.60–1.64 (m, 1H), 1.70 (s, 3H, Me), 1.71–1.74 (m, 1H), 2.16–2.21 (m, 1H), 2.39–2.46 (m, 1H), 2.68–2.75 (m, 2H), 3.45 (dd, 1H, *J*=4.8, 12.8 Hz, $CHOCH_2$), 3.73 (s, 3H, OMe), 4.31 (d, 1H, *J*=11.6 Hz, OCH_2Ar), 4.45 (d, 1H, *J*=11.6 Hz, OCH_2Ar), 6.81 (d, 2H, *J*=11.2 Hz, Ar), 7.19 (d, 2H, *J*=11.2 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 18.2, 20.3, 21.6, 23.4, 28.6, 30.2, 32.5, 39.2, 41.7, 41.8, 55.2, 71.0, 79.8, 113.7, 129.1, 129.8, 130.5, 159.1, 162.8, 197.4; MS *m*/*z* (‰): 356 (M^+, 0.5), 235 (32), 220 (15), 192 (12), 163 (4), 135 (26), 121(1000), 110 (19), 91 (47), 77(57), 43 (55); IR (film, cm^{-1}) ν_{max}=2966, 2889, 1658, 1608, 1512, 1459, 1348, 1309, 1246, 1072, 822.

4.1.7. 1α-(4-Methoxy-benzyloxy)-10-*epi*-eudesm-3-aceyloxy-3 (4), 5 (6)-dien (14). To a solution of enone **13** (350 mg, 0.98 mmol) in Ac_2O (1 mL) was added NaOAc (500 mg), DMAP (10 mg) and AcCl (2 mL) and stirred at 0 °C for 2 min. The resulting mixture was heated to reflux and stirred for 20 min. The reaction was then cooled to 0 °C and diluted with ether before NEt_3 (10 mL) and water (2 mL) was added. The resulting mixture was stirred for a further 0.5 h prior to extraction with ether. The organic phase was washed with water, 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel afforded compound **14** (320 mg, 82%). $[\alpha]_D^{25}=+141°$ (*c* 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=5.1 Hz, Me), 0.92 (d, 3H, *J*=5.1 Hz, Me), 0.98 (s, 3H, Me), 1.29–1.36 (m, 1H), 1.54–1.63 (m, 2H), 1.65 (s, 3H, Me), 1.78–1.83 (m, 1H), 1.91–1.95 (m, 1H), 2.05–2.08 (m, 1H), 2.19 (s, 3H, Me), 2.38–2.42 (m, 1H), 2.52–2.58 (m, 1H), 3.35–3.38 (m, 1H, $CHOCH_2$), 3.80 (s, 3H, OMe), 4.38 (d, 1H, *J*=8.7 Hz, OCH_2Ar), 4.55 (d, 1H, *J*=8.7 Hz, OCH_2Ar), 5.70 (d, 1H, *J*=3.6 Hz, CH=), 6.86 (d, 2H, *J*=6.3 Hz, Ar), 7.25 (d, 2H, *J*=6.3 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 17.5, 20.3, 20.7, 20.8, 31.1, 31.4, 32.9, 37.9, 40.7, 55.3, 71.0, 80.8, 113.7, 113.8, 120.5, 126.7, 129.0, 131.1, 139.5, 141.0, 159.0, 169.0; MS *m*/*z* (‰): 398 (M^+, 2.6), 356 (11), 313 (46), 235 (20), 193 (29), 175 (39), 161 (11), 135 (73), 121 (1000), 107 (24), 91 (44), 77 (56), 43 (145); IR (film, cm^{-1}) ν_{max}=2954, 2870, 1752, 1513, 1366, 1246, 1212, 1173, 1096, 1035, 822.

4.1.8. 1α-(4-Methoxy-benzyloxy)-10-*epi*-eudesm-4 (5)-en-6α-hydroxy-3-one (15). To a solution of **14** (520 mg, 1.3 mmol) in CH_2Cl_2 (15 mL) was added *m*-CPBA (387 mg, 70%, 1.56 mmol) and stirred for 24 h at room temperature. Then saturated aqueous $Na_2S_2O_3$ (5 mL) was

added and stirred for 5 min before extraction. The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil. Flash column chromatography on silica gel yielded alcohol **15** (400 mg, 83%). $[\alpha]_D^{25}=+53°$ (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=6.4 Hz, Me), 0.96 (d, 3H, *J*=6.4 Hz, Me), 1.24–1.38 (m, 2H), 1.39 (s, 3H, Me), 1.41–1.48 (m, 2H), 1.51–1.58 (m, 1H), 1.85 (s, 3H, Me), 1.98–2.04 (m, 1H), 2.56 (dd, 1H, *J*=12.8, 16.8 Hz), 2.82 (dd, 1H, *J*=4.8, 16.8 Hz), 3.50 (dd, 1H, *J*=4.8, 12.8 Hz, $CHOCH_2$), 3.81 (s, 3H, OMe), 4.39 (d, 1H, *J*=11.2 Hz, OCH_2Ar), 4.57 (d, 1H, *J*=11.2 Hz, OCH_2Ar), 4.96 (d, 1H, *J*=2.4 Hz, CHOH), 6.88 (d, 2H, *J*=8.8 Hz, Ar), 7.26 (d, 2H, *J*=8.8 Hz, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 18.0, 20.3, 20.6, 21.7, 27.0, 31.4, 39.5, 40.7, 48.2, 55.3, 69.5, 71.0, 80.0, 113.7, 129.1, 130.4, 133.2, 159.2, 159.5, 198.5; MS *m/z* (‰): 372 (M^+, 0.4), 354 (0.2), 251 (3), 234 (26), 191 (37), 165 (34), 121 (1000), 107(20), 91 (33), 77 (43), 43 (84); IR (film, cm^{-1}) ν_{max}=3438, 2954, 2872, 1662, 1612, 1513, 1461, 1248, 1175, 1081, 1036, 1005, 820.

4.1.9. 1α,6α-Di-(4-methoxy-benzyloxy)-10-*epi*-eudesm-4 (5)-en-3-one (16). To a mixture of alcohol **15** (400 mg, 1.08 mmol) and *p*-TsOH (8 mg) in dry CH_2Cl_2 (5 mL) was added dropwise 2,2,2-trichloro-acetimidic acid 4-methoxy-benzyl ester (456 mg, 1.61 mmol) in CH_2Cl_2 (2 mL) under argon at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 24 h. The crude was directly chromatographyed on silica gel and afforded colorless oil **16** (434 mg, 82%). $[\alpha]_D^{25}=+21°$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, 3H, *J*=6.8 Hz, Me), 0.88 (d, 3H, *J*=6.8 Hz, Me), 1.17–1.31 (m, 2H), 1.38 (s, 3H, Me), 1.50–1.55 (m, 1H), 1.61–1.71 (m, 1H), 1.72 (s, 3H, Me), 1.79–1.95 (m, 2H), 2.60 (dd, 1H, *J*=16.8, 12.8 Hz), 2.83 (dd, 1H, *J*=4.8, 12.8 Hz), 3.53 (dd, 1H, *J*=4.8, 12.8 Hz, $CHOCH_2$), 3.80 (s, 6H, OMe), 4.25 (d, 1H, *J*=7.2 Hz, OCH_2Ar), 4.38–4.41 (m, 2H, OCH_2Ar and $CHOCH_2$), 4.43–4.59 (m, 2H, OCH_2Ar), 6.86–6.89 (m, 4H, Ar), 7.24–7.27 (m, 4H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 19.1, 19.8, 20.2, 21.6, 27.4, 31.3, 39.3, 41.4, 47.7, 55.2, 69.5, 71.1, 76.0, 79.1, 113.7, 128.8, 129.1, 130.4, 130.6, 134.4, 157.8, 159.0, 159.1, 198.5; MS *m/z* (‰): 492 (M^+, 1), 463 (1), 371 (1.6), 235 (10), 191 (10), 177 (2), 121 (1000), 91 (22), 77 (35), 43 (16); IR (film, cm^{-1}) ν_{max}=2952, 2870, 1669, 1612, 1513, 1461, 1248, 1174, 1080, 1038, 821.

4.1.10. 1α,6α-Dihydroxy-5β(α)-*H*−10-*epi*-eudesm-3 (4)-ene 2′ (3). To a solution of **16** (150 mg, 0.3 mmol) in acetic acid (1.5 mL) was added $TsNHNH_2$ (57 mg, 0.45 mmol) and stirred for 10 h at room temperature. Then $NaBH_4$ (342 mg, 9 mmol) was added in batches during 0.5 h. The resulting mixture was diluted with ether and washed successively with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil. Flash column chromatography on silica gel afforded compound **17** and **18** (117 mg, 80%), which without further purification, was taken in 5 mL $CH_2Cl_2{\cdot}H_2O$ (18:1), and treated with DDQ (82 mg, 0.36 mmol) at 0 °C and stirred for 3 h before it was quenched by saturated aqueous $NaHCO_3$ (1 mL) at 0 °C. After stirring for a further 15 min, the reaction mixture was extraction with ether. The organic phase was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Evaporation of the solvent followed by flash column chromatography on silica gel afforded colorless oil **2′** (10 mg, 17.4%) and white crystal **3** (40 mg, 70%, mp 140–142 °C). Compound **2′** $[\alpha]_D^{26}=-28°$ (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J*=4 Hz, 3H, Me), 0.96 (d, *J*=4 Hz, 3H, Me), 1.05 (s, 3H, Me), 1.17–1.24 (m, 1H), 1.31–1.34 (m, 1H), 1.57–1.66 (m, 4H), 1.80 (s, 3H, Me), 1.94–2.00 (m, 1H), 2.02 (s, br, 1H), 2.26–2.30 (m, 1H), 3.51 (dd, *J*=10.2, 6.4 Hz, 1H, CHOH), 4.25 (s, br, 1H, CHOH), 5.42 (s, br, 1H, CH═); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 20.3, 20.3, 21.4, 21.7, 26.9, 30.1, 32.3, 37.3, 45.0, 48.0, 69.5, 76.7, 122.1, 133.6; MS *m/z* 238 (M^+, 0.5%), 220 (7), 205 (5), 202 (5), 177 (6), 159 (15), 135 (11), 123 (22), 107 (72), 93 (36), 83 (85), 69 (51), 43 (100); IR (film, cm^{-1}) ν_{max}=3272.3, 2951.7, 2887.9, 1456.1, 1427.3, 1367.5, 1289.2, 1048.5, 1028.0, 989.0, 828.3, 804.2. Compound **3** $[\alpha]_D^{26}=+31°$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, *J*=6.4 Hz, 3H, Me), 0.85 (s, 3H, Me), 0.94 (d, *J*=6.4 Hz, 3H, Me), 1.09–1.12 (m, 1H), 1.26–1.27 (m, 1H), 1.30–1.37 (m, 1H), 1.46–1.47 (m, 1H), 1.63–1.65(d, *J*=14 Hz, 1H), 1.89 (s, 3H, Me), 1.90–1.95 (m, 1H), 2.03–2.06 (m, 1H), 2.07–2.17 (m, 1H), 2.49–2.53 (m, 1H), 3.46 (d, *J*=9 Hz, 1H, CHOH), 4.02 (t, *J*=8 Hz, 1H, CHOH), 5.34 (s, br, 1H, CH═); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 18.0, 20.2, 21.0, 25.9, 26.3, 33.3, 33.9, 38.9, 51.1, 57.3, 65.9, 75.9, 120.4, 137.0; MS *m/z* 238 (M^+, 1%), 220 (7), 205 (6), 202 (3), 177 (7), 159 (10), 123 (31), 107 (92), 93 (33), 83 (15), 69 (30), 43 (100).

4.1.11. 1α,6β-Dihydroxy-5β-*H*-10-*epi*-eudesm-3 (4)-ene (1′). To a solution of **2′** (5 mg) in CH_2Cl_2 (2 mL) was added Dess–Martin regent (10 mg) at 0 °C and stirred for 8 h before it was quenched by saturated aqueous $Na_2S_2O_3$ (1 mL) at 0 °C. After stirring for a further 15 min, the reaction mixture was extraction with ether. The organic phase was washed with water, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_3OH (2 mL) and treated with $NaBH_4$ (10 mg). The resulting mixture was stirred for 1 h at room temperature and diluted with ether, washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Purification by flash chromatography gave colorless oil **1′** (4 mg, 80%). $[\alpha]_D^{26}=-21°$ (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H, Me), 0.95 (d, *J*=6.8 Hz, 3H, Me), 0.97(d, *J*=6.4 Hz, 3H, Me), 1.26–1.30 (m, 1H), 1.42–1.43 (m, 1H), 1.45–1.55 (m, 2H), 1.64–1.69 (m, 2H), 1.71 (s, 3H, Me), 1.93–1.95 (m, 1H), 2.02–2.03 (m, 1H), 2.12–2.13 (m, 1H), 2.40–2.44 (m, 1H), 3.98 (s, br, 1H, CHOH), 4.44 (t, *J*=8.6 Hz, 1H, CHOH), 5.57 (s, br, 1H, CH═); MS *m/z* 238 (M^+, 1.8%), 220 (57), 205 (45), 202 (5), 177 (25), 159 (17), 135 (13), 123 (47), 107 (66), 93 (25), 84 (100), 69 (21), 43 (47); IR (film, cm^{-1}) ν_{max}=3368, 2957, 2928, 2851, 1456, 1372, 1275, 1154, 1072, 1049, 1025, 835.

4.1.12. 1α(β),6β-Dihydroxy-5α-*H*-10-*epi*-eudesm-3 (4)-ene 4 (5). To a solution of **3** (30 mg) in CH_2Cl_2 (4 mL) was added Dess–Martin regent (60 mg) at 0 °C and stirred for 14 h before it was quenched by saturated aqueous $Na_2S_2O_3$ (2 mL) at 0 °C. After stirring for a further 15 min, the reaction mixture was extraction with ether. The organic phase was washed with water, saturated aqueous $NaHCO_3$

and brine, dried over $MgSO_4$. Evaporation of the solvent in vacuum gave the crude product, which without further purification, was taken in CH_3OH (4 mL) and treated with $NaBH_4$ (50 mg). The resulting mixture was stirred for 1 h at room temperature and diluted with ether, washed with 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Purification by flash chromatography gave white crystal **4** (18 mg, 60%, mp 174–176 °C) and gave colorless oil **5** (3 mg, 10%). Compound **4** $[\alpha]_D^{26}=+8°$ (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H, Me), 0.90 (d, *J*=6.4 Hz, 3H, Me), 0.94 (d, *J*=6.8 Hz, 3H, Me), 1.29–1.37 (m, 2H), 1.56–1.58 (m, 2H), 1.59–1.71(m, 2H), 1.77 (s, 3H, Me), 1.84–1.90 (m, 1H), 2.03–2.08 (m, 1H), 2.37–2.44 (m, 1H), 3.41 (d, *J*=4.2 Hz, 1H, CHOH), 4.12 (s, br, 1H, CHOH), 5.47 (s, br, 1H, CH═); MS *m/z* 238 (M^+, 0.7%), 220 (29), 205 (6), 202 (5), 177 (6), 159 (23), 135 (7), 123 (20), 107 (100), 93 (24), 81 (20), 69 (24), 43 (81); IR (film, cm^{-1}) ν_{max}=3360, 2955, 2916, 2854, 1447, 1372, 1301, 1148, 1062, 854, 788. Compound **5** $[\alpha]_D^{26}=+18°$ (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H, Me), 0.95 (d, *J*=6.8 Hz, 3H, Me), 0.97 (d, *J*=6.8 Hz, 3H, Me), 1.19–1.23 (m, 2H), 1.31–1.61 (m, 2H), 1.63–1.69 (m, 1H), 1.71 (s, 3H, Me), 1.75 (s, br, 1H), 1.87–1.94 (m, 1H), 2.07–2.18 (m, 1H), 2.44–2.50 (m, 1H), 3.98 (s, br, 1H, CHOH), 4.44 (s, br, 1H, CHOH), 5.56 (s, br, 1H, CH═); MS *m/z* 238 (M^+, 1.3%), 220 (74), 205 (63), 202 (1.6), 177 (32), 159 (21), 136 (26), 123 (50), 107 (85), 93 (34), 84 (59), 69 (28), 43 (100); IR (film, cm^{-1}) ν_{max}=3351, 2929, 1444, 1372, 1231, 1150, 1069, 1046, 1024, 829.

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Disubstituted 1,6-methano[10]annulene derivatives for use in organic light-emitting diodes

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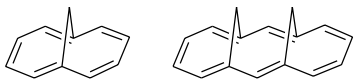
Abstract—Bis(carbazolylphenyl) and bis(diphenylaminophenyl) derivatives of 1,6-methano[10]annulene, which is luminescent material and contains seven-membered rings, are synthesized. The bis(phenylcarbazole) derivative **3** have high melting point and glass transition temperature. Electroluminescence characteristics of organic light-emitting diodes using these methano[10]annulenes were investigated.

1. Introduction

Organic light-emitting diodes (OLEDs) are one of the most promising next-generation full-color flat panel displays alternative to liquid crystal-based devices.[1] For the purpose of practical use, OLEDs researches have several unsolved problems such as an operational stability of the devices, color shift after operation, and so on. A part of these problems could be solved by modification of organic compounds, which have high melting points, high glass transition temperatures, and high electrochemical stability. In the field of OLEDs, luminescent materials in the emitting layer consists of five- or six-membered rings such as thiophenes, oxazoles, oxadiazoles, benzenes, pyridines. On the other hand, to our knowledge, no compounds constructed by seven- or more-membered rings except porphyrins[2] are investigated as luminescent materials for OLEDs. We envisage that good luminescent materials for OLEDs are present in these compounds. The bridged-annulenes such as 1,6-methano[10]annulene (**1**) and *syn*-1,6:8,13-bismethano[14]annulene (**2**), which contain seven- or eight-membered rings, are known as fluorescent materials.[3] However, the melting points of these materials are low for using in OLEDs (**1**; 28–29 °C, **2**; 116 °C).[4,5] Therefore, we synthesized these aryl derivatives to raise the melting points, because aryl groups (phenyl, *p*-tolyl, *p*-anisyl, and 2-thienyl) are known to raise the melting point of **1**.[6] We choose carbazolylphenyl and diphenylaminophenyl groups as the aryl substituents, because these groups have bulky structures and are commonly used for luminescent materials in OLEDs. Here we report on the synthesis and electroluminescence (EL) characteristics of 2,5-bis{4-(carbazol-9-yl)phenyl}- (**3**) and 2,5-bis(4-diphenylaminophenyl)-1,6-methano[10]annulene (**4**) (Chart 1).



1 **2**

Chart 1.

2. Results and discussions

2.1. Synthesis

Target molecules were synthesized from 1,6-diacetylcyclohepta-1,3,5-triene (**5**)[7] by the reported pathway.[6] The reaction of **5** with 9-(4-iodophenyl)carbazole[8] and 4-iodotriphenylamine[9] in the presence of butyllithium gave the diols **6** and **7**. The dehydration, cyclization, and oxidation of diols were carried out by a one-flask procedure. The treatment of **6** and **7** with a catalytic amount of pyridinium *p*-toluenesulfonate (*p*-TsOH·Py) in refluxing benzene for 24 h gave dihydro-1,6-methano[10]annulenes (Scheme 1). Then, an equimolar amount of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) was added to this reaction solution; this resulting mixture was refluxed for an additional 1.5–2 h. The solvent was evaporated and the residue was chromatographed with ethyl acetate/hexane as an eluent to gave methano[10]annulenes **3** and **4** in 58 and 38% yield based on **6** and **7**, respectively.

2.2. Properties

Compounds **3** and **4** were fully characterized on the basis of

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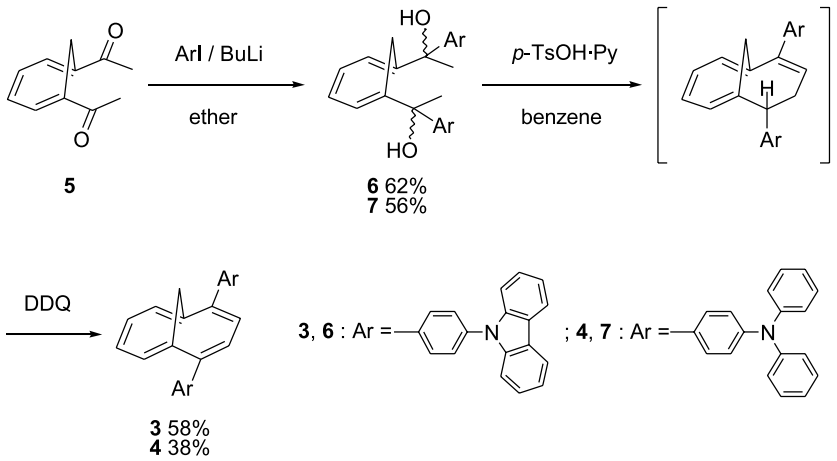

Scheme 1.

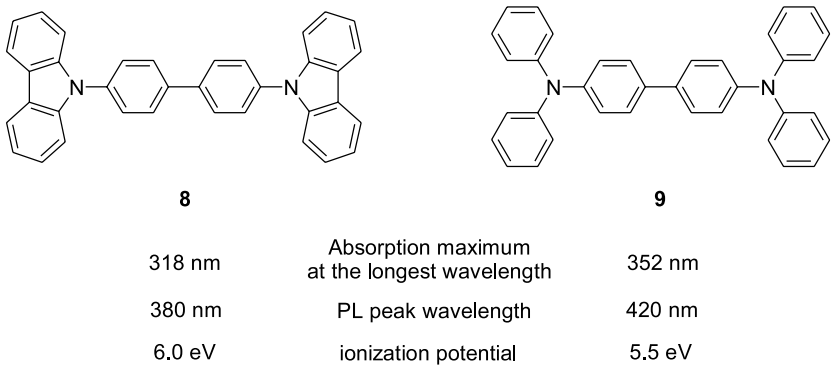

Figure 1. Absorption maxima at the longest wavelength, PL peak wavelengths, and ionization potentials of **8** and **9**.

IR, UV–vis, mass spectral data as well as elemental analyses. In the ^{1}H NMR spectrum, the chemical shift of methylene protons were observed in a similar range of 2,5-diaryl 1,6-methano[10]annulenes (**3**; δ=−0.17 and 0.35, **4**; δ=−0.33 and 0.25).[6] The melting points of **3** and **4** are >300 and 145 °C, respectively, and in particular the bis(phenylcarbazole) derivative **3** has a high glass transition temperature of 179 °C. However, the glass transition temperature of **4** is not observed. As we expected, bulky aryl groups raise the melting point of **1**. The high melting point and glass transition temperature of **3** compared with **4** may be attributable to the difference of rigidity between the two substituents. The absorption maxima at the longest wavelength of **3** and **4** in neat thin films (100 nm) on quartz substrates are observed at 370 and 396 nm, respectively, which are almost identical to those in solution. These peaks are observed at shorter-wavelength region than that of **1** (399 nm)[3,6] and are observed at longer-wavelength region than those of **8** and **9**, which are dimer of phenylcarbazol and triphenylamine (Fig. 1).[10] The similar effects of aryl substituents on absorption spectra have already been observed.[6] On the absorption spectra, we assume that the aryl-substituted seven-membered ring part of diaryl derivatives of **1** act as the dimethylenecycloheptadiene structure A (Chart 2) because of conjugation between the diene part and the aryl groups. The photoluminescence (PL) spectra of **3** and **4** of thin films on quartz have peaks at 488 and 510 nm, respectively, and Stokes shifts of each material are about 115 nm (Fig. 2). These Stokes shifts are larger than that of **1** (ca. 40 nm), **8** (62 nm), and **9** (68 nm).[3,10] This finding might reflect that the distinction of structures between ground state and excited state of **3** and **4** are larger than those of **1**, **8** and **9**.

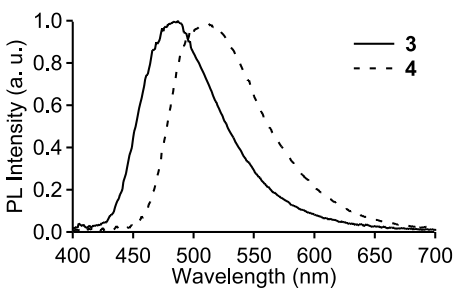

Figure 2. PL spectra of **3** and **4** of neat thin films (thickness: 100 nm; on irradiation with 254 nm light).

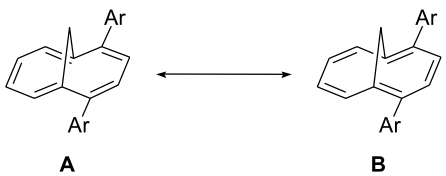

Chart 2.

The ionization potentials and the electron affinities of 1,6-methano[10]annulenes are obtained as follows: ionization potential: **3** (5.9 eV) and **4** (5.5 eV), electron affinity: **3** (3.1 eV) and **4** (2.8 eV). The ionization potentials are

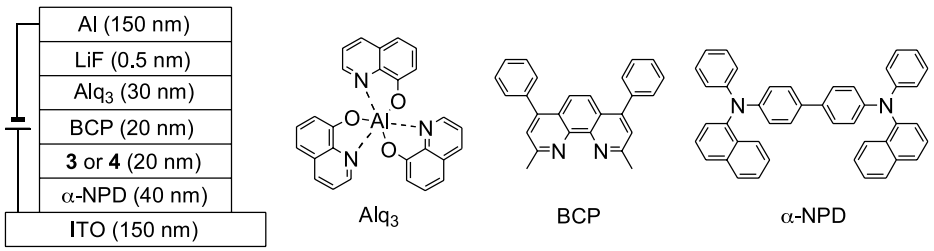

Figure 3. The OLED structure and molecular structures of α-NPD, BCP, and Alq_3.

measured using UV photoelectron spectrometer (Riken-Keiki AC-2). The electron affinities are calculated by subtracting the optical band gaps from ionization potentials. The ionization potentials of **3** and **4** are similar to those of **8** (6.0 eV) and **9** (5.5 eV), respectively.[11,12] We assume that the ionization potentials of **3** and **4** are affected by aryl substituents rather than by 1,6-methano[10]annulene moiety.

2.3. The OLEDs properties

To investigate the EL properties of **3** and **4**, the OLEDs were fabricated by high-vacuum (10^{-7}–10^{-6} Torr) thermal evaporation (Fig. 3). The devices have EL peaks at 479 and 503 nm, respectively (Fig. 4). The profiles of EL spectra are nearly identical to those of PL spectra. This finding evidenced that **3** and **4** act as luminescent materials in OLEDs. The Commission Internationale de l'Eclairage (CIE) coordinates are estimated to be x=0.17, y=0.30 (**3**, light-blue) and x=0.25, y=0.52 (**4**, green), respectively. The spectra and CIE coordinates are independent of current densities.

Figure 5 displays the plot of luminance as a function of voltage. The maximum luminances of **3** and **4** devices are

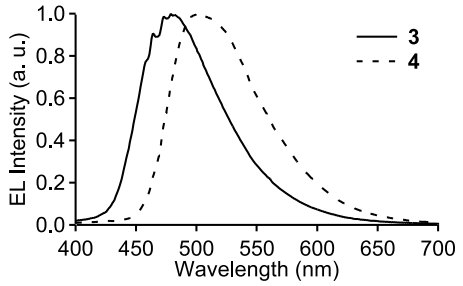

Figure 4. EL spectra of OLEDs using **3** and **4** as the emitting layer at 11 mA/cm^2.

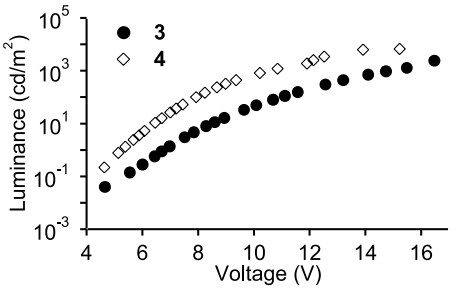

Figure 5. Plot of luminance versus voltage of the OLEDs using **3** and **4** as the emitting layer.

2410 cd/m^2 at 220 mA/cm^2 and 6420 cd/m^2 at 330 mA/cm^2, respectively. The external quantum efficiencies at 400 cd/m^2 are 0.8% (**3**) and 1.4% (**4**), respectively. Figure 6 shows the current density–voltage (J–V) characteristics. The current density at a given bias voltage for **4** device is higher than that for **3** device. We assume that ionization potential of **4** is smaller than that of **3**, facilitating injection of holes from α-NPD (as hole transporting layer, ionization potential: 5.7 eV). We suppose that the facilitation of hole injection from α-NPD to **4** plays an important role in the maximum luminance and the external quantum efficiency.

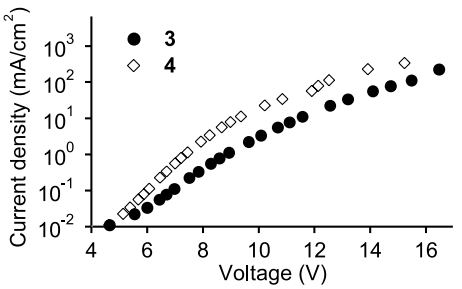

Figure 6. Plot of current density versus voltage of the OLEDs using **3** and **4** as the emitting layer.

3. Summary

In summary, we have synthesized 2,5-bis{4-(carbazol-9-yl)phenyl}- (**3**) and 2,5-bis(4-diphenylaminophenyl)-1,6-methano[10]annulene (**4**), which contain seven-membered ring and new luminescent materials for OLEDs, from 1,6-diacetylcyclohepta-1,3,5-triene (**5**) in three steps. In particular, the bis(phenylcarbazole) derivative **3** has high melting point (>300 °C) and high glass transition temperature (179 °C), which are favorable properties for OLEDs. The EL spectra of the OLEDs using **3** and **4** as the emitting layer have maxima at a wavelength of 479 (light-blue light) and 503 (green light) nm, respectively. These finding suggest utility and possibility of 1,6-methano[10]annulene derivatives as luminescent materials for OLEDs. Further studies concerning synthesis and EL properties of other derivertives of **1** and 1,4-disubstituted naphtalenes to compare with **3** and **4** are under way.

4. Experimental

4.1. General

The melting points were measured with a Perkin–Elmer DSC-7 and uncorrected. IR spectra were recorded on a

Nicolet FT-IR Avatar360. Absorption spectra were measured on a Hitachi-330. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded in a $CDCl_3$ solution with tetramethylsilane as an internal standard on a JNM-LA500. Mass spectra were measured on a JEOL JMS-700 at an ionization energy of 70 eV. Column chromatography was performed with Merck Kieselgel 60 Art 7734. THF was purified just before use by distillation from sodium-benzophenone ketyl.

4.2. Preparation of diols (6 and 7) from diacetylcyclo-heptatriene 5. General procedure

A solution of 1.59 M butyllithium in hexane (7.9 mL) was added to a solution of 9-(4-iodophenyl)-carbzole or 4-iodotriphenylamine (11.0 mmol) in THF (20 mL) at −78 °C. The mixture was stirred at −78 °C for 0.5 h, and then a solution of diacetylcycloheptatriene **5** (5.00 mmol) in THF (20 mL) was added to the mixture at the same temperature. After stirring at rt for 3 h, the reaction mixture was poured into water (400 mL) and extracted with ethyl ether (3×100 mL). The combined organic layer was washed with brine (200 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (SiO_2, ethyl acetate/hexane) to give diols **6** (*dl*-**6**::*meso*-**6**=4:5) or **7**. The diols were used in the next reaction without further purification. Diols *dl*-**7** and *meso*-**7** could not be separated.

4.2.1. *dl*-1,6-Bis{4-(carbazol-9-yl)-α-hydroxy-α-methyl-benzyl}cyclohepta-1,3,5-triene (*dl*-6). Colorless needles; mp 152 °C; IR (KBr) ν_{max} 3371m, 3044w, 2976w, 2928w, 1599m, 1512s, 1479m, 1452s, 1362m, 1334m, 1316m, 1230s, 1171w, 1119w, 1071w, 914m, 838m, 749s, 723s, 628m cm^{-1}; ^{1}H NMR δ= 1.88 (s, 6H), 2.64 (s, 2H), 4.03 (s, 2H), 6.09 (m, 2H), 6.56 (dd, *J*=3.7, 2.8 Hz, 2H), 7.29 (tm, *J*=6.7 Hz, 4H), 7.41 (tm, *J*=7.0 Hz, 4H), 7.46 (dm, *J*= 7.9 Hz, 4H), 7.57 (dt, *J*=8.6, 2.0 Hz, 4H), 7.76 (dt, *J*=8.6, 2.1 Hz, 4H), 8.16 (dm, *J*=7.7 Hz, 4H); ^{13}C NMR δ=29.1, 29.8, 77.6, 109.8, 119.3, 120.3, 123.0, 123.4, 125.9, 126.7, 127.6, 130.1, 136.6, 140.8, 143.1, 146.2; MS *m*/*z* 662 (M^+, 4), 644 (M^+-H_2O, 9), 626 (M^+-2H_2O, 99), 612 (12), 445 (7), 383 (8), 358 (19), 313 (14), 286 (15), 268 (99), 241 (83), 189 (12), 166 (100), 140 (16), 115 (10), 91 (5). Anal. found: C, 85.20; H, 6.15; N, 3.94%. Calcd for $C_{47}H_{38}N_2O_2$: C, 85.17; H, 5.78; N, 4.23%.

4.2.2. *meso*-1,6-Bis{4-(carbazol-9-yl)-α-hydroxy-α-methylbenzyl}cyclohepta-1,3,5-triene (*meso*-6). Colorless needles; mp 164 °C; IR (KBr) ν_{max} 3339m, 3044w, 2976w, 2927w, 1599m, 1512s, 1479m, 1452s, 1362m, 1334m, 1316m, 1230s, 1170m, 1119w, 1098w, 1078w, 1017m, 926m, 838m, 748s, 723s, 627m cm^{-1}; ^{1}H NMR δ=1.81 (d, *J*=13.7 Hz, 1H), 1.85 (s, 6H), 2.74 (d, *J*=13.5 Hz, 1H), 4.35 (s, 2H), 6.48 (m, 2H), 6.67 (dd, *J*=3.7, 2.5 Hz, 2H), 7.22 (td, *J*=7.0, 1.2 Hz, 4H), 7.25 (td, *J*=7.5, 1.2 Hz, 4H), 7.35 (dm, *J*=7.7 Hz, 4H), 7.51 (dt, *J*=8.9, 2.1 Hz, 4H), 7.71 (dt, *J*= 8.6, 2.3 Hz, 4H), 8.11 (dm, *J*=7.3 Hz, 4H); ^{13}C NMR δ=30.0, 30.5, 77.4, 109.7, 119.9, 120.2, 122.0, 123.3, 125.9, 126.67, 126.73, 130.3, 136.4, 140.8, 142.7, 145.9; MS *m*/*z* 662 (M^+, 3), 644 (M^+-H_2O, 9), 626 (M^+-2H_2O, 100), 612 (14), 445 (6), 383 (8), 358 (19), 313 (15), 268 (84), 241 (64), 189 (11), 166 (91), 140 (14), 115 (9), 91 (4). Anal. found: C, 84.70; H, 6.03; N, 3.98%. Calcd for $C_{47}H_{38}N_2O_2{\cdot}0.2H_2O$: C, 84.71; H, 5.81; N, 4.20%.

4.3. Preparation of disubstituted 1,6-methano[10]-annulenes (3 and 4) from the diol (6 and 7). General procedure

A solution of diol **6** or **7** (2.00 mmol) and *p*-TsOH·Py (25.1 mg, 0.100 mmol) in benzene (15 mL) was refluxed for 24 h. Then, DDQ (454 mg, 2.00 mmol) was added to the reaction mixture, which was refluxed for 1.5–2 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by chromatography (SiO2, ethyl acetate/hexane) to gave **3** and **4**.

4.3.1. 2,5-Bis{4-(carbazol-9-yl)phenyl}-1,6-methano[10]-annulenes (3). Pale yellow needles; mp >300 °C; IR (KBr) ν_{max} 3037w, 2949w, 1599m, 1507s, 1478m, 1450s, 1361w, 1334m, 1315m, 1228s, 1169w, 1118w, 1016w, 1001w, 914w, 840w, 820m, 747s, 722s, 627w, 565w cm^{-1}; ^{1}H NMR δ=−0.17 (d, *J*=9.5 Hz, 1H), 0.35 (d, *J*=9.5 Hz, 1H), 7.33 (m, 6H), 7.43 (s, 2H), 7.46 (tm, *J*=7.7 Hz, 4H), 7.56 (d, *J*=8.2 Hz, 4H), 7.71 (m, 2H), 7.71 (d, *J*=8.2 Hz, 4H), 8.07 (dm, *J*=8.6 Hz, 4H), 8.18 (d, *J*=7.6 Hz, 4H); ^{13}C NMR δ= 36.0, 109.9, 116.7, 120.1, 120.4, 123.5, 126.0, 126.2, 127.0, 128.9, 129.0, 132.2, 137.3, 138.9, 140.8, 142.5; UV/vis (cyclohexane) λ_{max} 224sh (log ε=4.85) nm, 238 (4.95), 257sh (4.63), 273sh (4.57), 282sh (4.63), 285 (4.63), 292 (4.67), 328 (4.21), 341 (4.32), 366 (4.33); MS *m*/*z* 624 (M^+, 100), 610 (16), 457 (10), 369 (7), 312 (21), 241 (30), 215 (26), 166 (43). Anal. found: C, 89.12; H, 5.49; N, 4.17%. Calcd for $C_{47}H_{32}N_2{\cdot}0.5H_2O$: C, 89.07; H, 5.25; N, 4.42%.

4.3.2. 2,5-Bis(4-diphenylaminophenyl)-1,6-methano[10]-annulene (4). Pale yellow needles; mp 145 °C; IR (KBr) ν_{max} 3032w, 1591s, 1492s, 1449w, 1315m, 1274s, 1191w, 1177w, 814m, 751m, 694s cm^{-1}; ^{1}H NMR δ=−0.33 (d, *J*=9.2 Hz, 1H), 0.25 (d, *J*=9.2 Hz, 1H), 7.05 (t, *J*=7.3 Hz, 4H), 7.15 (d, *J*=8.6 Hz, 4H), 7.17 (d, *J*=8.0 Hz, 8H), 7.20 (s, 2H), 7.21 (dd, *J*=5.8, 2.4 Hz, 2H), 7.29 (t, *J*=7.8 Hz, 8H), 7.58 (dd, *J*=5.7, 2.6 Hz, 2H), 7.67 (d, *J*=8.5 Hz, 4H); ^{13}C NMR δ=36.0, 117.2, 123.07, 123.13, 124.6, 125.2, 128.2, 128.8, 129.3, 131.5, 134.2, 142.3, 147.4, 147.6; UV/vis (cyclohexane) λ_{max} 209sh (log ε=5.07) nm, 225sh (4.59), 252sh (4.41), 273sh (4.58), 302 (4.68), 353sh (4.31), 391 (4.57); MS *m*/*z* 628 (M^+, 100), 614 (5), 459 (5), 384 (5), 314 (14), 291 (8), 256 (9), 215 (11), 167 (20). Anal. found: C, 88.95; H, 5.88; N, 4.27%. Calcd for $C_{47}H_{36}N_2{\cdot}0.33H_2O$: C, 88.93; H, 5.82; N, 4.41%.

4.4. OLED fabrication

The OLED structure employed in this study is shown in the inset of Figure 3. Organic layers were fabricated by high-vacuum (10^{-7}–10^{-6} Torr) thermal evaporation onto a glass substrate precoated with an ITO layer with a sheet resistance of 10 Ω/square. Prior to use, the ITO was degreased with solvents and cleaned in UV-ozone chamber before loading into the evaporation system. A 40 nm-thick of α-NPD as the hole transporting layer, a 20 nm-thick of **3** or **4** as the emitting layer, a 20 nm-thick of BCP as the hole blocking layer, a 30 nm-thick of Alq_3 as the electron transporting layer, a 0.5 nm-thick of LiF as the electron injection layer,

and a 150 nm-thick of aluminum metal as a cathode were deposited on the substrate. Devices were encapsulated under nitrogen in a glass-to-glass epoxy sealed package.

Acknowledgements

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Tetrahedron

Unexpected deprotection of silyl and THP ethers induced by serious disparity in the quality of Pd/C catalysts and elucidation of the mechanism

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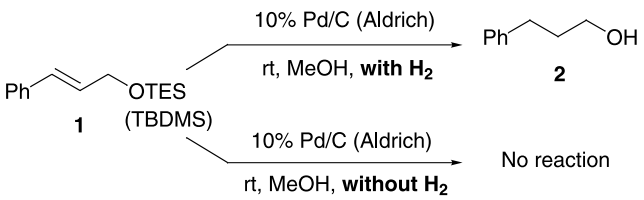
Abstract—Commercial Pd/C catalysts show different catalytic activity toward the deprotection of silyl and THP ethers. The Pd/C purchased from Merck and ACROS exhibits marked tendency to cleave these protective groups unexpectedly without hydrogen conditions although Aldrich's Pd/C (20,569-9) is inactive in the absence of hydrogen. It was proved that the Pd/C disparity toward the deprotection of TES and THP ethers results from residual acids and/or palladium chloride in the production process of Pd/Cs. Although a TES ether cleavage reaction in the absence of hydrogen and a THP ether cleavage reaction in the presence of hydrogen using 10% Pd/C were recently published, we could conclude they were only an acid-catalyzed solvolysis, the acid being released from the catalyst. Hydrogen is essential for the actual 10% Pd/C-catalyzed cleavage of TES ethers and THP ethers which must be stable under the true Pd/C-catalyzed hydrogenation conditions.

1. Introduction

Silyl and THP (tetrahydropyranyl) ethers are extensively used protective groups for alcohols in synthetic chemistry because of its low cost, efficiency of preparation, stability under the intended reaction conditions and easy and selective removal.[1] A variety of methods for the selective deprotection of their protective groups have been developed including treatment with fluoride ion,[1] acid,[1] hydride[2,3] and palladium catalyst.[4] As a rule, protective groups must be stable under the intended reaction conditions as the unexpected removal of protective groups would cause serious damage to a synthetic process. On the other hand, catalytic hydrogenation is one of the most useful and widely applicable methods for the reduction of chemical substances, and has been applied in numerous synthetic processes in laboratories and industries. Hydrogenation using Pd/C as catalyst has many advantages such as stability of the catalyst, ease of removal from the reaction mixture, a wide range of applicable reaction conditions and high catalytic activity.[5] Although many preparative methods of Pd/C catalysts have been reported,[5] there have been some reports suggesting several distinctive features among Pd/C catalysts prepared by different methods[5] or purchased from different suppliers[6] to date.

Recently, we have reported TBDMS (*tert*-butyldimethylsilyl) and TES (triethylsilyl) ethers are frequently cleaved under hydrogenation conditions using 10% Pd/C (Aldrich product number 20,569-9) in MeOH at room temperature under hydrogen atmosphere (balloon),[7] although these silyl ethers were entirely intact without hydrogen atmosphere (under air or Ar) (Scheme 1).[7]



Scheme 1.

In contrast, Rotulo-Sims and Prunet have reported, during the review of our manuscript,[7c] a simple deprotection method of TES ether using 10% Pd/C in MeOH or 95% EtOH at room temperature in the absence of hydrogen atmosphere (Scheme 2).[8] Their data are apparently in conflict with our conclusion. In a preliminary communication,[9] we have suggested the cleavage of TES ethers in the absence of hydrogen conditions should be interpreted as an acid-catalyzed solvolysis. Herein, we provide a detailed discussion regarding the unreliability of the Pd/C-catalyzed cleavage of TES ethers in the absence of hydrogen conditions reported by Prunet et al. and further disclose

Keywords: Palladium on carbon; Hydrogenation; Silyl ether; Acidity.
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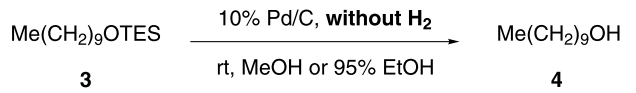
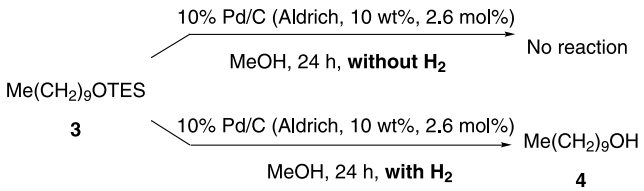


Scheme 2.

Pd/C catalysts exhibit remarkable supplier-dependent difference in the property and quality (acidity).

2. Results and discussion

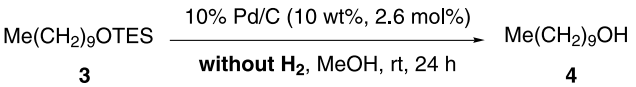
In our initial investigations, the reproducibility of Prunet's results using triethylsilyloxydecane (**3**) which was employed as a substrate in their paper[8] and 10% Pd/C (Aldrich) as a catalyst was reevaluated. The silyl group (**3**) has been recovered quantitatively in the absence of hydrogen even after 24 h, whereas quite ready cleavage of the TES ether under a hydrogen atmosphere (our conditions[7c]) was observed (Scheme 3). Consequently, reproducibility of Prunet's deprotection method[8] is quite poor. From these results it occurred to us that certain disparity in the property of various commercial 10% Pd/C catalysts might have caused the serious conflicting results. It is obvious that Prunet et al. have used 10% Pd/C catalyst obtained from a different supplier[10] from ours (Aldrich, 20,569-9).



Scheme 3.

Next, we investigated catalyst activity of various commercial 10% Pd/C toward the deprotection of TES ether (**3**) in the absence of hydrogen (Table 1). Most commercial Pd/C, except for Aldrich's catalyst (entry 2), showed catalyst activity at room temperature toward the cleavage of TES ether in varying degrees, albeit without hydrogen (entries 3–9). Especially, 10% Pd/C purchased from Merck and ACROS cleaved the TES ether (**3**) completely within an hour as well as in Prunet's report[8] (entries 8 and 9).

Table 1. Cleavage of the TES ether (**3**) using 10% Pd/C purchased from various suppliers in the absence of hydrogen

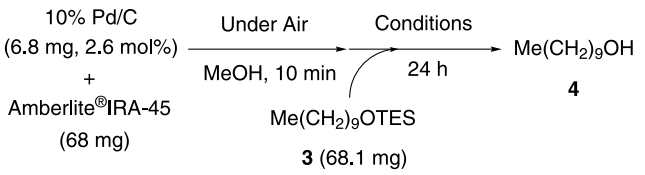


Entry	10% Pd/C[a]	**3**:**4**[b]
1	None	100:0
2	Aldrich (20,569-9)	100:0[c]
3	WAKO (163-15272)	87:13
4	N. E. ChemCat (dry)	78:22
5	Nakalai (25928-84)	75:25
6	Kishida (400-59095)	59:41
7	Engelhard C3645[d]	40:60
8	ACROS (19503-0100)	0:100[e]
9	Merck (807104-0010)	0:100[f]

[a] Supplier's product number is indicated in parentheses.
[b] Determined by ^{1}H NMR.
[c] The reproducibility of the data was confirmed in experiments using different lots of the Pd/C (Lot. AI 05401JS and Lot. KA 13921CA).
[d] This catalyst was purchased from Aldrich (Aldrich product number 52,088-8).
[e] The reaction was completed in approximately 1 h.
[f] The reaction was completed within 1 h.

Our attention next turned to the mechanism of the deprotection of the TES group of **3** using 10% Pd/C as a catalyst dispensing with hydrogen. In view of these undesirable results, we believed that the cleavage reaction of TES ethers with 10% Pd/C without hydrogen conditions was promoted by the contaminated acid in the Pd/C catalysts although Prunet asserted strongly that the cleavage was Pd-catalyzed reaction.[8] In general, palladium chloride in concentrated hydrochloric acid solution is used for the preparation of Pd/C catalysts as a starting material. The palladium chloride is held by adsorption on heavy metal-free activated charcoal and reduced using a suitable reductant.[5] So it may be contaminated by a trace amount of retained hydrochloric acid, and/or residual $PdCl_2$ by the incomplete reduction during the production process even after being washed repeatedly with distilled water.[5] In order to elucidate the deprotection mechanism we examined the cleavage reaction of the TES ether (**3**) in the presence of a basic gel-type resin, Amberlite®IRA-45, as an acid scavenger (Table 2). 10% Pd/C (Merck or Aldrich) was stirred with Amberlite®IRA-45 in MeOH under air for 10 min and then the reaction mixture was stirred with the TES ether (**3**) under air or hydrogen atmosphere. Pre-treatment with Amberlite®IRA-45 under air conditions resulted in no cleavage of TES ether (**3**) without hydrogen conditions with either catalyst (Merck and Aldrich, entries 1 and 3) while the TES ether (**3**) was completely cleaved under hydrogen conditions without any depression of the catalyst activities toward the cleavage of TES ethers even with coexisting Amberlite®IRA-45 (entries 2 and 4).

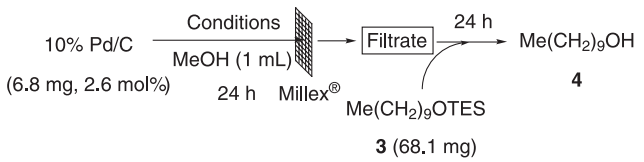
Table 2. Cleavage of the TES ether (**3**) in the presence of Amberlite®IRA-45



Entry	10% Pd/C	Conditions	**3**:**4**
1	Merck	Air	100:0
2	Merck	H_2	0:100
3	Aldrich	Air	100:0
4	Aldrich	H_2	0:100

We then investigated whether the TES cleavage reaction in the absence of hydrogen conditions[8] is certainly a palladium-catalyzed (mediated) reaction or only an acid-catalyzed solvolysis (Table 3). 10% Pd/C (Merck) in MeOH was stirred under various conditions for 24 h and then the catalyst was removed by filtration using a membrane filter (Millipore, Millex®-LG, 0.20 μm). TES ether (**3**) was stirred in the resulting filtrate for 24 h (entries 1–6). In the filtrate stirred with 10% Pd/C (Merck) under air atmosphere, 59% cleavage of the TES protective group

Table 3. Cleavage of the TES ether (**3**) in the filtrate



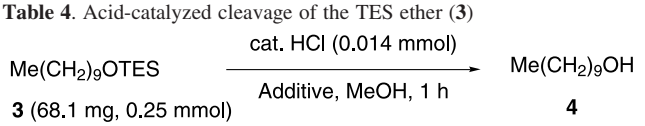
Entry	10% Pd/C	Conditions	**3**:**4**[a]
1	Merck	Air	59:41[b]
2	Merck	Air+Amberlite®IRA-45	100:0
3	Merck	Sonication	50:50[c]
4	Merck	Sonication+Amberlite®IRA-45	100:0
5	Merck	H_2	37:63[c]
6	Merck	H_2+Amberlite®IRA-45	100:0
7	Aldrich	Air	100:0
8	Aldrich	Sonication	100:0
9	Aldrich	H_2	100:0

[a] Determined by ^{1}H NMR.
[b] Average of 6 times.
[c] Average of 4 times.

was observed on the average of 6 experiments (entry 1). The deprotection was slightly enhanced by the pre-treatment of 10% Pd/C (Merck) under sonication or hydrogen conditions (entries 3 and 5). Since the cleavage rates of the filtrates were enhanced under sonication or hydrogen conditions, the retained acids may be driven away from the fine pores of the charcoal[11] and/or residual $PdCl_2$ by the incomplete reduction during the production process may be reduced by hydrogen.[6] This deprotection reaction was depressed completely by the addition of Amberlite®IRA-45 into the pretreatment suspension of Pd/C in MeOH (entries 2, 4 and 6). On the other hand, TES was not cleaved at all in the filtrate stirred with 10% Pd/C (Aldrich) even under sonication and hydrogen conditions (entries 7–9). These results strongly suggest that the cleavage of TES ether using Merck's 10% Pd/C without hydrogen conditions[8] is only an acid-catalyzed methanolysis.

Further, the acid-catalyzed methanolysis of **3** in the presence of non-stoichiometric hydrochloric acid (0.06 equiv. against the substrate) resulted in 87% loss of the TES protective group of **3** within 1 h without hydrogen (Table 4, entry 1). The addition of Aldrich's 10% Pd/C which possesses no TES-cleaving activity under neutral non-hydrogen conditions, to the above acid-catalyzed reaction conditions was examined (entry 2). The cleavage of the TES ether was slightly enhanced (98%) although the addition of activated carbon (Norit®SX3) or Pd-black resulted in no acceleration of the cleavage (entries 3 and 4).

Table 4. Acid-catalyzed cleavage of the TES ether (**3**)



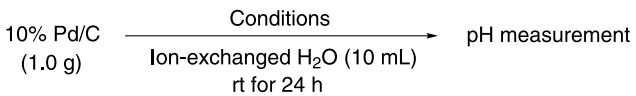
Entry	Additive	**3**:**4**[a]
1	None	13:87
2	10% Pd/C (Aldrich, 6.8 mg, 2.6 mol%)	2:98
3	Norit®SX3 (6.8 mg)	22:78
4	Pd-black (Kishida, 0.7 mg, 2.6 mol%)	37:63

[a] Determined by ^{1}H NMR.

In addition, we determined the pH of aqueous suspension of commercial 10% Pd/C catalysts after stirring at room temperature for 24 h using pH meter (Table 5). The suspension of 10% Pd/C catalysts purchased from Merck and ACROS, having a quite high TES-cleaving tendency, indicates a quite acidic property (entries 6–10). Under sonication conditions, the acidity of the suspension was slightly enhanced (compare entries 8 and 9) as well as an enhancement of TES cleavage activity in the filtrate (Table 3, entries 1 and 3). Surprisingly, the suspension of Merck's Pd/C recorded pH<3 under the H_2 atmosphere (entry 10) while Aldrich's Pd/C indicates a rather slightly basic to neutral range (entries 1–3), compared with the pH value of ion-exchanged water (ca. 6.0, entry 11).[12,13] These results also strongly indicate Merck's Pd/C includes significant amounts of residual $PdCl_2$ together with acids. Recently, we reported the smooth reduction of $Pd(OAc)_2$ to zero valent palladium by MeOH as a reductant at room temperature.[14] Consequently, the residual $PdCl_2$ in Merck's Pd/C should be smoothly reduced during the TES cleavage reaction in MeOH or 95% EtOH without hydrogen conditions (Scheme 2)[8] and a certain amount of hydrogen chloride should be generated.[15] Acidity of the slurry of commercial 10% Pd/Cs increases in the following order, Aldrich<Kishida<ACROS<Merck. These results are approximately parallel to the order of the catalyst activity of 10% Pd/Cs toward the cleavage of TES ether (**3**) without hydrogen conditions (compare Tables 1 and 5).

Since the unexpected loss of other acidic-sensitive protective groups from the mother molecule would cause extensive damage to a multi-step synthetic process, the

Table 5. Comparison of acidity of commercial 10% Pd/C

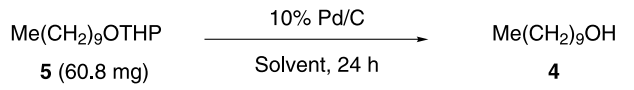


Entry	10% Pd/C	Conditions	pH[a]	Temperature (°C)
1	Aldrich	Air	6.28	24.6
			6.34	24.5
2		Sonication	6.17	25.1
			6.19	25.1
3		H_2	5.91	26.5
			5.98	26.2
4	Kishida	Air	5.97	23.0
			6.00	23.0
5		H_2	5.38	23.3
			5.36	22.6
6	ACROS	Air	5.75	24.8
			5.82	24.8
7		H_2	3.34	25.0
			3.38	24.6
8	Merck	Air	4.82	24.3
			4.79	24.2
9		Sonication	4.67	25.1
			4.63	25.0
10		H_2	2.96	26.5
			2.88	26.1
11	Ion-exchanged H_2O[b]		5.92	23.5
			5.99	23.5

[a] The pH measurements were carried out on a Horiba D-21 pH meter.
[b] Ion-exchanged H_2O indicates slightly acidic pH by the dissolved atmospheric CO_2.

acid-catalyzed solvolysis of THP ether (**5**) was also examined with 10 wt% (2.3 mol%) of 10% Pd/C at room temperature in MeOH. Table 6 summarizes the stability of THP ether (**5**) in the presence of a commercial 10% Pd/C. Although no cleavage of the THP ether (**5**) occurred in the presence and absence of hydrogen conditions when Aldrich's Pd/C was used as a catalyst (Table 6, entries 1–4), partial deprotection (**5**:**4**=56:44) of the THP ether (**5**) under atmospheric air conditions (entry 9) and complete cleavage under hydrogen conditions (entry 10) occurred by the use of 10 wt% (2.3 mol%) of Merck's Pd/C. Without hydrogen Pd/C (Engelhard) has no cleaving activity (entries 5 and 7), whereas under hydrogenation conditions the THP ether (**5**) was cleaved (entries 6 and 8). Further, while no cleavage of the THP protective group of **5** occurred with Engelhard's 10% Pd/C (Engelhard code C3645) without hydrogen conditions (entries 5 and 7), the deprotection was observed under hydrogen atmosphere and the deprotection ratio was increased with increasing the amount of the catalyst (entries 6 and 8).

Table 6. Cleavage of the THP ether (**5**) in the presence of 10% Pd/C



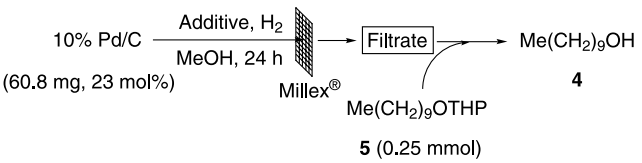
Entry	10% Pd/C	Loading wt% (mol%)	Solvent (mL)	Condition	**5**:**4**[a]
1	Aldrich[b]	10 (2.3)	MeOH (1 mL)	Air	100:0
2		10 (2.3)	MeOH (1 mL)	H_2	100:0
3		100 (23)	EtOH (10 mL)	Air	100:0
4		100 (23)	EtOH (10 mL)	H_2	100:0
5	Engelhard[c]	10 (2.3)	MeOH (1 mL)	Air	100:0
6		10 (2.3)	MeOH (1 mL)	H_2	58:42
7		100 (23)	EtOH (10 mL)	Air	100:0
8		100 (23)	EtOH (10 mL)	H_2	0:100
9	Merck[d]	10 (2.3)	MeOH (1 mL)	Air	56:44
10		10 (2.3)	MeOH (1 mL)	H_2	0:100

[a] Determined by ^{1}H NMR.
[b] Aldrich product number; 20,569-9.
[c] This catalyst was purchased from Aldrich (Aldrich product number; 52,088-8, Engelhard code C3645).
[d] Merck product number; 807104-0010.

To confirm whether the deprotection of the THP ether (**5**) with Merck or Engelhard's 10% Pd/C is due to the contaminated acids or not, we examined the cleavage of the THP ether (**5**) in the filtrate after pre-stirring of the suspension of 10% Pd/C catalyst in MeOH (Table 7). After stirring the suspension of 10% Pd/C (Merck or Engelhard) for 24 h, significant cleavage of the THP protective group of **5** was observed in the Pd/C-free filtrate (entries 2 and 4). In contrast, when the suspension of 10% Pd/C (Merck or Engelhard) was stirred in the presence of Amberlite®IRA-45, the cleavage was completely depressed (entries 3 and 5). Needless to say, THP-cleavage did not proceed in the filtrate of the stirred suspension of Aldrich's Pd/C (entry 1).

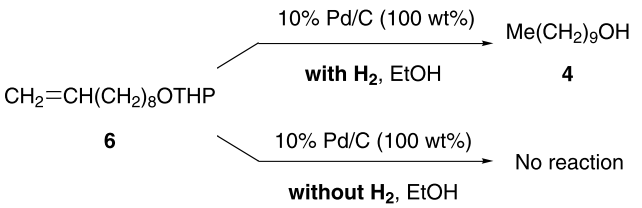
Kaisalo and Hase previously reported[6] the cleavage of the THP protective group of **6** under hydrogenation conditions using an equal amount (100 wt%) to the substrate of Aldrich's Pd/C-catalyzed in EtOH (Scheme 4). In contrast to their report, no reproducibility of their results was

Table 7. Cleavage of the THP ether (**5**) in the filtrate



Entry	10% Pd/C	Additive	**5**:**4**[a]
1	Aldrich[b]	None	100:0
2	Engelhard[c]	None	25:75
3		Amberlite®IRA-45	100:0
4	Merck[d]	None	8:92
5		Amberlite®IRA-45	100:0

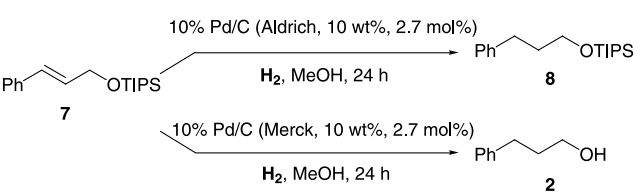
[a] Determined by ^{1}H NMR.
[b] Aldrich product number; 20,569-9.
[c] This catalyst was purchased from Aldrich (Aldrich product number; 52,088-8, Engelhard code C3645).
[d] Merck product number; 807104-0010.



Scheme 4.

indicated in our study using 10% Pd/C (Aldrich product number 20,569-9) (Table 6, entry 4). Since two kinds of dry 10% Pd/C [Aldrich product numbers, 20,569-9 and 52,088-8 (Engelhard code C3645)] are inserted in an Aldrich catalog, it is contemplated that the different kinds of dry 10% Pd/C (52,088-8) described as 10% Pd/C (Engelhard) in this paper was used in their paper[6] (Table 6, entries 6 and 8). It is obvious that their cleavage of the THP protective group of **6** also is only an acid-catalyzed ethanolysis and THP protective groups must be stable under the true Pd/C-catalyzed hydrogenation conditions.

Finally, we investigated the stability of TIPS (triisopropylsilyl) group under the hydrogenation conditions using acidic (Merck) and neutral (Aldrich) 10% Pd/C. The selective hydrogenation of the olefin functionality of 1-triisopropylsilyloxy-3-phenyl-2-propene (**7**) was achieved with Aldrich's 10% Pd/C under ambient hydrogen pressure, although the deprotection of the TIPS protective group and the hydrogenation of the olefin proceeded simultaneously with acidic Merck's 10% Pd/C catalyst (Scheme 5). It should be noted that the TIPS protective group which is more stable than the TBDMS or the TES ethers is also frequently used as a protective group of hydroxyl groups in organic synthetic chemistry and it seems likely that the



Scheme 5.

acidity of commercial Pd/C catalysts results in a variety of serious problems including unexpected deprotection of acid somewhat sensitive protective groups.

3. Conclusion

We have disclosed some commercial 10% Pd/C are quite acidic and exhibit marked tendency to cleave silyl and THP ethers unexpectedly without hydrogen conditions. It was clearly proved that the deprotection methods of TES ethers in the absence of hydrogen reported by Prunet et al.[8] and THP ethers in the presence of hydrogen reported by Kaisalo et al.[6] are not palladium-catalyzed reaction and only an acid, released from the catalysts, catalyzed solvolysis and hydrogen is absolutely essential for the real 10% Pd/C-catalyzed cleavage of TES (silyl) ethers. THP ethers must be stable under the true Pd/C-catalyzed hydrogenation conditions. Furthermore, we have also demonstrated commercial Pd/C catalysts exhibit remarkable supplier-dependent disparity in the property and quality. Since the unexpected loss of protective groups would cause serious damage to a synthetic process, especially in multi-step synthesis of complex natural products, therefore, when a Pd/C catalyst is used in an article, the name of the supplier and the product number of the catalyst must be clarified to avoid wasted efforts in the organic chemistry community. It is noteworthy that 10% Pd/C of Aldrich (20,569-9) is a quite safe, nearly neutral and useful hydrogenation catalyst. According to all of the results indicated in this paper, the 10% Pd/C (Aldrich)-catalyzed TES cleavage mechanism under hydrogen conditions[7c] can involve a direct hydrogenolysis of the silyl group or a true palladium-catalyzed methanolysis by the 10% Pd/C activated by hydrogen.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz). Chemical shifts (δ) are given in ppm relative to residual solvent or tetramethylsilane as an internal standard. Low and high-resolution mass spectra were taken on a JEOL JMS-SX 102 machine. The pH measurements were carried out on a Horiba D-21 pH meter that was calibrated before each set of measurements. Methylene chloride was distillated from CaH_2. Methanol for HPLC (Wako Pure Chemical Industries, Ltd.) was used without further purification. Ethanol, dehydrated (Wako Pure Chemical Industries, Ltd.) was used without purification. Amberlite®IRA-45 (basic gel-type resin) was used after washing with water and methanol. All reagents were commercially available and used without purification. All new compounds were further characterized by HRMS. Compounds known in the literature were characterized by comparison of their ^{1}H NMR data with the previously reported data.

4.1.1. Preparation of triethylsilyloxydecane (3).[16] To a solution of 1-decanol (**4**) (1.58 g, 10 mmol) in dichloromethane (20 mL) at room temperature was added triethylamine (1.7 mL, 12 mmol) and DMAP (224.3 mg, 2 mmol) followed by triethylsilyl chloride (2.0 mL, 12 mmol). The mixture was stirred for 8 h at room temperature. Methanol (1 mL) was added to quench the excess amount of triethylsilyl chloride, and after 30 min a saturated aqueous NH_4Cl solution (20 mL) was added to the mixture. The aqueous layer was extracted with ether (20 mL×3), then the combined organic layer was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel elution with hexane to afford 2.61 g (96%) of triethylsilyloxydecane (**3**) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 3.59 (t, J=6.8 Hz, 2H), 1.55–1.51 (m, 2H), 1.28–1.26 (m, 14H), 0.96 (t, J=8.1 Hz, 9H), 0.88 (t, J=6.8 Hz, 3H), 0.60 (q, J=7.8 Hz, 6H). ^{13}C NMR ($CDCL_3$): δ 63.0, 32.9, 31.9, 29.6, 29.6, 29.5, 29.3, 25.8, 22.7, 14.1, 6.8, 4.4. MS (FAB, NBA) m/z 273 (M^++H, 18%), 271 (17), 243 (40). HRMS (FAB, NBA) calcd for $C_{16}H_{37}OSi$ (M^++H) 273.2614. Found 273.2610.

4.1.2. General procedure for cleavage of the TES ether (1) accompanying hydrogenation of the olefin using 10% Pd/C (Aldrich; 20,569-9) in the presence of hydrogen (Scheme 1).[7] After two vacuum/H_2 cycles to remove air from the reaction tube, a stirred mixture of the substrate (0.25 mmol), 10% Pd/C (Aldrich product number 20,569-9; 10 wt% of the substrate) in methanol (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm), and the filtrate was concentrated in vacuo to afford 35 mg (100%) of 3-phenyl-1-propanol (**2**) as a colorless oil.

4.1.3. General procedure for cleavage of the TES ether (3) using 10% Pd/C purchased from various suppliers in the absence of hydrogen (Table 1). To a solution of triethylsilyloxydecane (**3**) (68.1 mg, 0.25 mmol) in methanol (1 mL) was added 10% Pd/C (6.8 mg, 10 wt% of the substrate) and then stirred at room temperature for 24 h. The solution was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm), and MeOH was removed in vacuo. The ratio of the substrate (**3**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.4. General procedure for cleavage of the TES ether (3) in the presence of Amberlite®IRA-45 (Table 2). A suspension of 10% Pd/C (6.8 mg, 10 wt% of the substrate) and Amberlite®IRA-45 (68 mg) in methanol (1 mL) was stirred at room temperature for 10 min. After two vacuum/H_2 or Ar cycles to remove air from the reaction tube, triethylsilyloxydecane (**3**) was added to the mixture and then stirred at room temperature for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated in vacuo. The ratio of the substrate (**3**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.5. General procedure for cleavage of the TES ether (3) in the filtrate (Table 3, part 1, entries 1–4, 7 and 8). A suspension of 10% Pd/C (6.8 mg, 10 wt% of the substrate) [and Amberlite®IRA-45 (68 mg)] in methanol (1 mL) was stirred for 24 h (under sonication). The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LG,

0.20 μm). Triethylsilyloxydecane (**3**) was added to the filtrate and then stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure. The ratio of the substrate (**3**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.6. General procedure for cleavage of the TES ether (3) in the filtrate (Table 3, part 2, entries 5, 6 and 9). After two vacuum/H_2 cycles to remove air from the reaction tube, [a suspension of the Amberlite®IRA-45 (68 mg) and] 10% Pd/C (6.8 mg, 10 wt% of the substrate) in methanol (1 mL) was stirred under hydrogen atmosphere at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The solution was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm). Triethylsilyloxydecane (**3**) was added to the filtrate and then stirred under air at room temperature for 24 h. The solution was concentrated under reduced pressure. The ratio of the substrate (**3**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.7. General procedure for acid catalyzed cleavage of the TES ether (3) (Table 4). To a mixture of hydrogen chloride (10 μL of 5% HCl in MeOH, 0.014 mmol) with an additive indicated in Table 4 in methanol (1 mL) was added triethylsilyloxydecane (**3**) (68.1 mg, 0.25 mmol) and stirred at room temperature for 24 h. [The solution was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm)] The solution (or filtrate) was concentrated under reduced pressure. The ratio of the substrate (**3**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.8. General procedure for the pH measurement of the suspension of commercial 10% Pd/C (Table 5). A suspension of 10% Pd/C (1.0 g) in 10 mL of methanol was stirred at room temperature under each condition for 24 h. The pH of the slurry was measured by Horiba D-21 pH meter that was calibrated before each set of measurements.

4.1.9. Preparation of 2-tetrahydropyranyl-1-decanyl ether (5).[17] To an ice-cold solution of 1-decanol (**4**) (1.58 g, 10 mmol) and dihydropyrane (3.7 mL, 40 mmol) in dry dichloromethane (10 mL) was added *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.1 mmol). The mixture was stirred at 0 °C for 10 min, the ice bath was removed, and the solution was stirred at room temperature for 1.5 h. The mixture was partitioned between ether (20 mL) and brine (20 mL). The organic layer was washed with saturated sodium carbonate solution (20 mL), water (40 mL) and brine (20 mL×2), dried with anhydrous Na_2SO_4, and evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel elution with hexane/ether 20:1 to afford 2.30 g (95%) of 2-tetrahydropyranyl-1-decanyl ether (**5**) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 4.58 (t, *J*=3.4 Hz, 1H), 3.90–3.85 (m, 1H), 3.76–3.70 (m, 1H), 3.53–3.47 (m, 1H), 3.41–3.35 (m, 1H), 1.87–1.79 (m, 1H), 1.75–1.69 (m, 1H), 1.63–1.49 (m, 6H), 1.35–1.26 (m, 14H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C NMR ($CDCL_3$): δ 98.8, 67.7, 62.3, 31.9, 30.8, 29.7, 29.6, 29.5, 29.3, 26.2, 25.5, 22.6, 19.7, 14.1. MS (FAB, NBA) *m/z* 243 (M^++H, 40%), 241 (32), 238 (23). HRMS (FAB, NBA) Calcd for $C_{15}H_{31}O_2$ (M^++H) 243.2317. Found 243.2324.

4.1.10. General procedure for cleavage of the THP ether (5) using commercial 10% Pd/C in the absence of hydrogen (Table 6, part 1, entries 1, 3, 5, 7 and 9). A mixture of the THP ether (**5**) (60.6 mg, 0.25 mmol) and 10% Pd/C (6.1 or 60.8 mg) in methanol (1 mL) or ethanol (10 mL) was stirred at room temperature for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm or -LH, 0.45 μm), and the solvent was removed in vacuo. The ratio of the substrate (**5**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.11. General procedure for cleavage of the THP ether (5) using 10% Pd/C in the presence of hydrogen (Table 6, part 2, entries 2, 4, 6, 8 and 10). After two vacuum/H_2 cycles to remove air from the reaction tube, a stirred mixture of the 2-tetrahydropyranyl-1-decanyl ether (**5**) (60.6 mg, 0.25 mmol) and 10% Pd/C (6.1 or 60.8 mg) in methanol (1 mL) or ethanol (10 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm or -LH, 0.45 μm), and the filtrate was concentrated in vacuo. The ratio of the substrate (**5**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.12. General procedure for cleavage of the THP ether (5) in the filtrate (Table 7). After two vacuum/H_2 cycles to remove air from the reaction tube, a suspension of [the Amberlite®IRA-45 (61 mg) and] 10% Pd/C (60.8 mg, 100 wt% of the substrate) in methanol (1 mL) was stirred under hydrogen atmosphere at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LH, 0.45 μm). 2-Tetrahydropyranyl-1-decanyl ether (**5**) was added to the filtrate and then stirred under air at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure. The ratio of the substrate (**5**) and 1-decanol (**4**) was confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

4.1.13. Preparation of 1-triisopropylsilyloxy-3-phenyl-2-propene (7).[18] To a solution of cinnamylalcohol (671 mg, 5 mmol) and imidazole (408 mg, 6 mmol) in dichloromethane (20 mL) at room temperature was added triisopropylsilyl chloride (1.16 g, 6 mmol). The mixture was stirred at room temperature for 24 h. Methanol (1 mL) was then added to quench the excess of triisopropylsilyl chloride, and after 30 min a saturated aqueous NH_4Cl solution (20 mL) was added. The aqueous layer was extracted with ether (20 mL×3) and the combined the organic layer was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel elution with hexane to afford 593 mg (41%) of 1-triisopropylsilyloxy-3-phenyl-2-propene (**7**) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.42–7.24 (m, 5H), 6.67 (d, *J*=15.6 Hz, 1H), 6.34 (dt, *J*=15.6, 4.9 Hz, 1H), 4.46 (dd,

J=4.9 Hz, 1.5 Hz, 2H), 1.21–1.12 (m, 3H and 18H). ^{13}C NMR ($CDCl_3$): δ 137.3, 129.4, 129.0, 128.5, 127.2, 126.4, 63.9, 18.0, 12.1. MS (EI) m/z 290.5 (M^+, 20%), 248 (21), 247 (100), 117 (47), 115 (15). HRMS (EI) calcd for $C_{18}H_{30}OSi$ (M^+) 290.2066. Found 290.2057.

4.1.14. General procedure for investigation of the stability of the TIPS ether (7) (Scheme 5). After two vacuum/H_2 cycles to remove air from the reaction tube, a stirred mixture of 1-triisopropylsilyloxy-3-phenyl-2-propene (**7**) (72.6 mg, 0.25 mmol) and 10% Pd/C (Aldrich or Merck, 7.3 mg, 10 wt% of the substrate) in methanol (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LG, 0.20 μm) and the filtrate was concentrated in vacuo. The quantitative conversion of the substrate (**7**) into 1-triisopropylsilyloxy-3-phenyl-2-propane (**8**) or 3-phenylpropanol (**2**) was confirmed by ^1H NMR in $CDCl_3$. 3-Phenylpropanol (**2**) agreed with the analytical data of commercially available sample.

4.1.14.1. 1-Triisopropylsilyloxy-3-phenylpropane (8). 93% Yield as a colorless oil. ^1H NMR ($CDCl_3$): δ 7.29–7.17 (m, 5H), 3.71 (t, J=6.1 Hz, 2H), 2.71 (t, J=7.8 Hz, 2H), 1.89–1.82 (m, 2H), 1.12–1.04 (m, 3H and 18H). ^{13}C NMR ($CDCL_3$): δ 142.4, 128.5, 128.2, 125.6, 62.6, 34.7, 32.1, 18.0, 12.0, 11.8. MS (EI) m/z 249 ($M^+-C_3H_7$, 100%). HRMS (EI) calcd for $C_{15}H_{25}OSi$ ($M^+-C_3H_7$) 249.1675. Found 249.1667.

References and notes

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Entry	10% Pd/C[a]	Pd content (%)
1	Merck (807104-0010, Lot: S23284 835)	8.7
2	ACROS (19503-0100, Lot: A012028901)	8.5
3	Kishida (400-59095, Lot: F26175K)	8.2
4	Aldrich (20,569-9, Lot: KA 13921CA)	9.2

[a] Supplier's product and Lot numbers are indicated in parentheses.

13. A milky precipitate was formed by addition of one drop of 0.1 mol/L silver nitrate ($AgNO_3$) solution to the filtrate of the pH-determined suspension (ca. 2 mL) in Table 5. The amount of the precipitate was increased with the drop in pH. Consequently, the cause of the high acidity of the 10% Pd/C purchased from Merck or ACROS is contamination of HCl and $PdCl_2$.
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Stereodivergent synthesis of the 2,3,5,6-tetrasubstituted piperidine ring system: an application to the synthesis of alkaloids 223A and 205B from poison frogs

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Abstract—Stereodivergent synthesis of the 2,3,5,6-tetrasubstituted piperidine ring system has been achieved by sequential stereocontrolled Michael-type conjugate addition reaction of appropriate enaminoesters. This methodology has been applied to the total syntheses of the poison frog alkaloids **223A** and **205B**. The relative stereochemistry of natural **223A** at the 6-position was revised, and the absolute stereochemistry of natural **205B** was determined by the present synthesis.

1. Introduction

Alkaloids containing a piperidine ring are abundant in nature. 2,6-Disubstituted piperidine ring systems especially, are a major structural element found in these natural products.[1] Many of these alkaloids exhibit intriguing biological activities. Accordingly, numerous efforts to construct this heterocycle have been reported to date.[2] The 2,3,5,6-tetrasubstituted piperidine system, which is found in some natural products, is generally more difficult to synthesize and few general methods exist to control the relative stereochemistry of the four substituents. As part of a program aimed at developing syntheses of biologically active alkaloids,[3] we present here a full account of the stereodivergent construction of two 2,3,5,6-tetrasubstituted piperidine ring systems.[4]

Our basic strategy for the stereodivergent construction of the 2,3,5,6-tetrasubstituted piperidine ring core is shown in Figure 1. The strategy involves the sequential use of Michael-type conjugate addition reaction to an enaminoester. The stereodiversity is a consequence of using an acyclic or cyclic carbamate functionality to provide total conformational control of the substrate in the second addition reaction.

2. Results and discussion

The synthesis of a 3,5-*cis*-type 2,3,5,6-tetrasubstituted piperidine core started with known amide **1**.[5] Treatment of **1** with *n*-BuLi and $ClCO_2Me$ provided methyl carbamate **2**, which was converted in high yield to enoltriflate **3** using

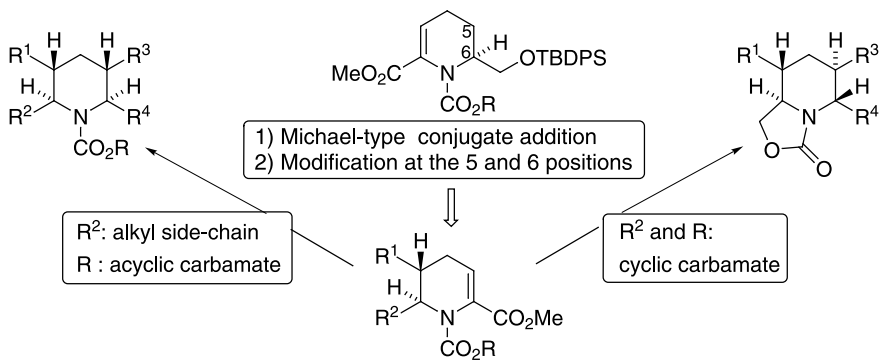

Figure 1.

Keywords: Alkaloids; Comins' triflating agent; Piperidones.
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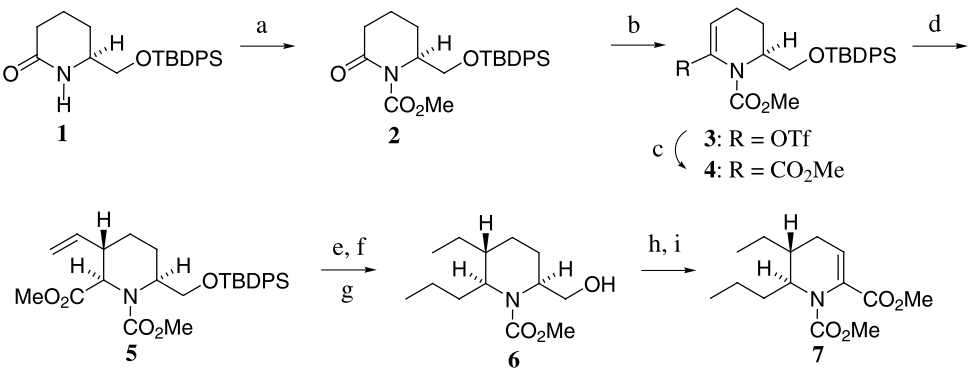


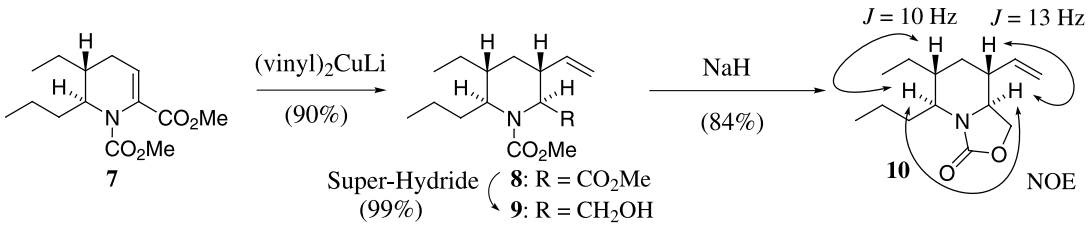
Scheme 1. (a) *n*-BuLi, $ClCO_2Me$ (98%); (b) LiHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent) (96%); (c) CO, $Pd(Pl_3P)_4$, Et_3N, MeOH (88%); (d) $(vinyl)_2CuLi$ (96%); (e) Supper-Hydride (96%); (f) Swern ox. then *n*-BuLi, $EtP^+Ph_3Br^-$ (79%); (g) 5% Pd–C, H_2 then TBAF (77%); (h) swern ox. then $NaClO_2$ then CH_2N_2 (90%); (i) LiHMDS, PhSeCl (77%).

Comins' triflating agent.[6] Palladium-catalyzed CO insertion reaction in the presence of MeOH[7] gave rise to enaminoester **4**. The first Michael-type conjugate addition reaction[8] to **4** proceeded smoothly to afford the adduct **5** as a single isomer. For the key, second Michael-type conjugate addition reaction of divinyllithium cuprate, the adduct **5** was transformed into the second enaminoester **7** via the alcohol **6** as shown in Scheme 1.

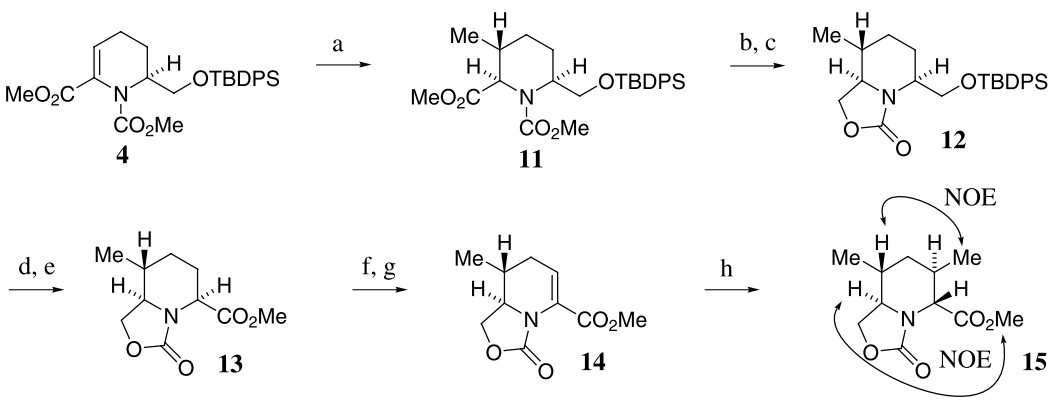
With the requisite enaminoester **7** in hand, we next investigated the second and key conjugate addition reaction. Accordingly, treatment of **7** with divinyllithium cuprate provided the tetrasubstituted piperidine **8**, again as a single isomer. The expected 3,5-*cis*-stereochemistry of **8** was confirmed by the coupling constants indicated and an NOE experiment on the corresponding oxazolizinone derivative **10**, prepared via the alcohol **9** as shown in Scheme 2.

From the synthesis of **205B** we required the cyclic enaminoester **14**. The previously obtained enaminoester **4** was converted to the trisubstituted piperidine **11** using our original Michael-type conjugate addition reaction, which was transformed into the oxazolizinone **12**. Removal of the silyl protecting group and a two-step oxidation of the resulting alcohol followed by esterification with diazomethane provided the methyl ester **13**. This ester was converted to **14** using the protocol developed by Matsumura et al.[9] The key, second Michael-type conjugate addition reaction of **14** proceeded smoothly to give rise to the tetrasubstituted piperidine **15** in high yield and as a single isomer. The 3,5-*trans*-stereochemistry of **15** was confirmed by the NOE experiment, whose results are shown in Scheme 3.

The observed, remarkable stereoselectivity of the conjugate addition reactions of **7** and **14** can be rationalized by the stereoelectronic effect[10] and is also consistent with Cieplak's hypothesis,[11] both illustrated in Figure 2.



Scheme 2.



Scheme 3. (a) $(Me)_2CuLi$ (98%); (b) Super-Hydride (92%); (c) NaH (99%); (d) TBAF (99%); (e) Swern ox. then $NaClO_2$ then CH_2N_2 (86%); (f) LiHMDS, PhSSPh (99%); (g) *m*-CPBA, 2,6-lutidine (85%); (h) $(Me)_2CuLi$ (93%).

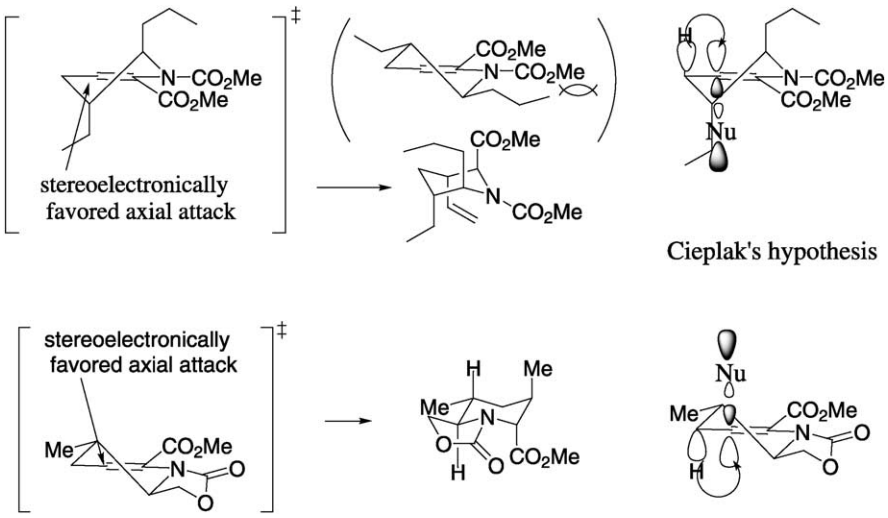
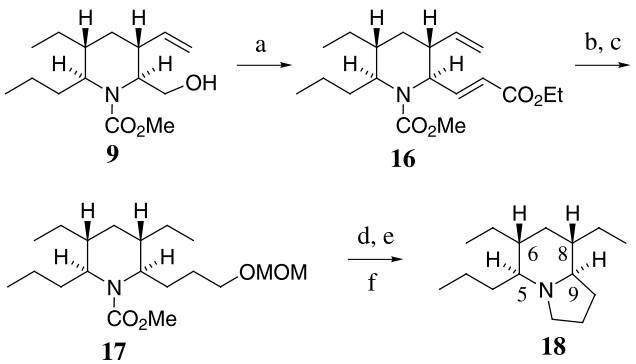


Figure 2.

Thus, we achieved the stereodivergent synthesis of the 2,3,5,6-tetrasubstituted piperidine ring core with complete stereoselection. To illustrate the efficacy of our protocol for the construction of tetrasubstituted piperidines, syntheses of poison frog alkaloids **223A** and **205B** were undertaken. Alkaloid **223A** was isolated from a skin extract of a Panamanian population of the frog *Dendrobates pumilio* Schmidt (Dendrobatidae) in 1997, and it was the first member of a new trialkyl-substituted indolizidine class of amphibian alkaloids to be characterized.[12] In a preliminary report, the configuration of the ethyl group at C-6 position was revised.[4] The tetrasubstituted piperidine **9** was converted to the unsaturated ester **16**, whose double bonds were hydrogenated over Pd–C. Reduction of the ester moiety with Super-Hydride followed by protection of the resulting alcohol with MOMCl in the presence of Hünig's base provided the MOM ether **17**. Finally, removal of the methoxycarbonyl and MOM groups, followed by indolizidine cyclization of the intermediate propyl bromide furnished the desired indolizidine **18** (Scheme 4).



Scheme 4. (a) Swern ox. then $(EtO)_2P(O)CH_2CO_2Et$, NaH (96%); (b) 10% Pd–C, H_2, then Super-Hydride (89%); (c) MOMCl, Hünig's base (86%); (d) *n*-PrSLi, HMPA; (e) c. HCl, MeOH; (f) CBr_4, Ph_3P, Et_3N (52%).

The ^1H and ^{13}C NMR and IR spectra of **18** were not identical with those for the natural product, nor was the GC retention time. The close similarity of the Bohlmann bands in the vapor phase FTIR spectra of **18** and natural **223A** indicated the same 5,9-*Z* configuration for both compounds. In ^1H NMR spectra, our synthetic DCl salt of **18** showed a nicely separated quartet-like signal at δ 1.01 with a *J* of 12.5 Hz for the H-7 axial proton. This observation means that the quartet-like signal with three large and approximately equal couplings for the H-7 axial proton must include two *trans*-diaxial vicinal couplings with H-6 and H-8 protons and one geminal coupling with the H-7 equatorial proton, and thus both ethyl-substituents at the 6- and 8-positions should be of the equatorial orientation as shown in Figure 3. A quartet at this chemical shift was not seen in the natural material. On the other hand, the H-5 proton in **18** and natural **223A** was a doublet of triplet with *J* values of 11, 2.5 and 11, 4.7 Hz, respectively, in the ^1H NMR spectrum. We now conclude the hindered rotation at C-5 in the C-6 epimer **30** of proposed structure for natural **223A** (**18**) leads to a large (11-Hz J_{5-10}) coupling and does not reflect an originally assumed *trans*-diaxial J_{5-6} coupling.

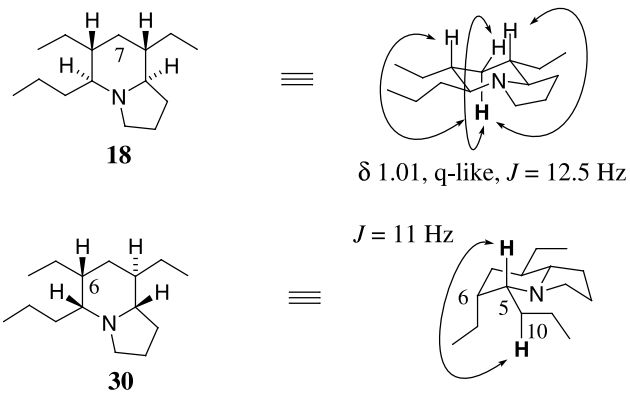
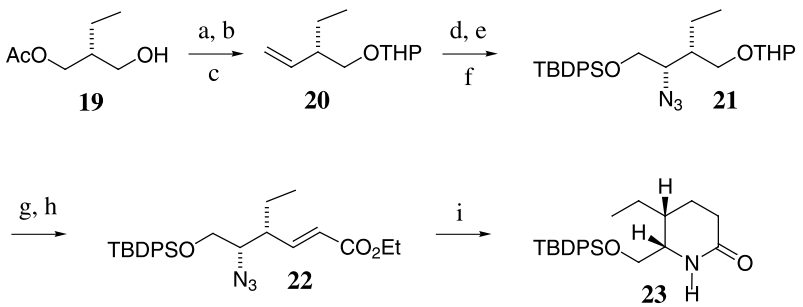
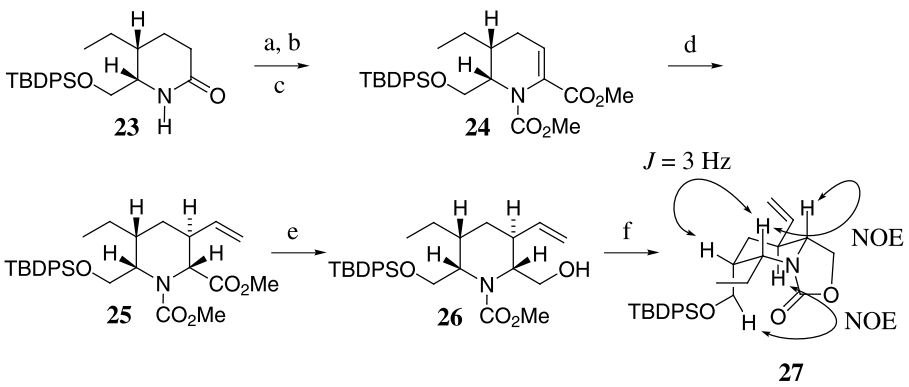


Figure 3.

Therefore, we commenced the synthesis of the 6-epimer (**30**) of initially proposed structure for **223A**. For the synthesis of **30**, we needed the *cis*-substituted piperidone **23**. Synthesis of **23** began with the known 2*R* mono-acetate **19**,[13] which was converted to the olefin **20**. A $(DHQD)_2$-PYR ligand-induced AD reaction[14] of **20** followed by protection of the primary hydroxyl group gave the secondary alcohol, which was transformed into the azide **21** via the mesylate. Removal of the THP protecting group



Scheme 5. (a) DHP, PPTS; (b) K_2CO_3, MeOH; (c) Swern ox then $PH_3P^+CH_3Br^-$, *n*-BuLi (76%); (d) AD-mix β-$(DHQD)_2PYR$ ligand (80%); (e) TBDPSCl, Et_3N, DMAP (98%); (f) MsCl, Et_3N then NaN_3 (83%); (g) PPTS, EtOH; (h) Swern ox then NaH, $(EtO)_2P(O)CH_2CO_2Et$ (88%); (i) 10% Pd–C, H_2 (73%).



Scheme 6. (a) *n*-BuLi, $ClCO_2Me$ (97%); (b) LiHMDS, Comins' reagent (97%); (c) CO, $Pd(Ph_3P)_4$, Et_3N, MeOH (75%); (d) $(vinyl)_2CuLi$ (95%); (e) Super-Hydride (96%); (f) NaH (94%).

with PPTS, and Swern oxidation followed by the Horner–Emmons reaction provided the unsaturated ester **22**. Hydrogenation of **22** over Pd–C under medium pressure gave rise to desired piperidone **23** (Scheme 5).

This piperidone was transformed into the enaminoester **24** in the same manner as the synthesis of **4**. The key Michael-type conjugate addition reaction to **24** was achieved by treatment of **24** with divinyllithium cuprate to give the 3,5-*trans*-adduct **25** as a single isomer. The stereochemistry of **25** was determined to be that of the desired intermediate for the synthesis of **30** by the coupling constant indicated and the NOE cross peaks of the oxazolidinone **27** derived from the alcohol **26** as shown in Scheme 6.

Stereoselectivity of this conjugate addition reaction can also be explained as shown in Figure 4. Attack of the vinyl anion is preferred from the stereoelectronically favored β-axial orientation on the conformation **24-A** to form **25**. The alternative conformation **24-B** is unlikely due to $A^{(1,3)}$ strain.[15]

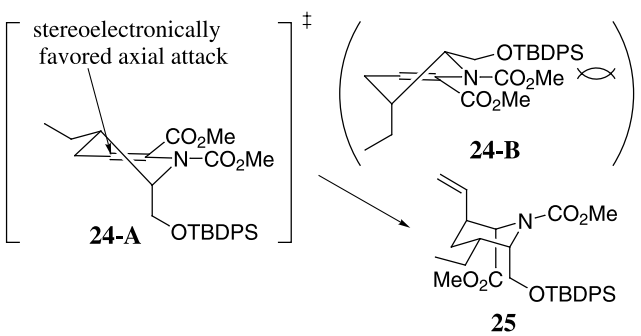
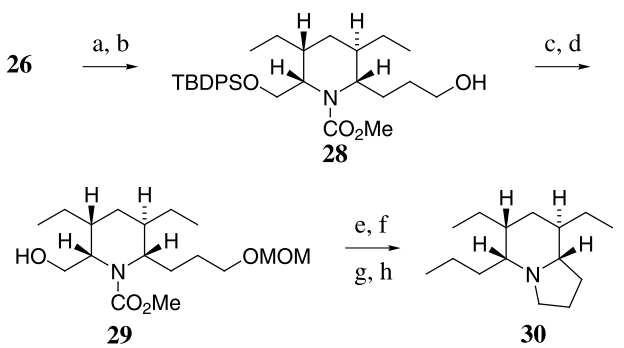


Figure 4.

The alcohol **26** was converted to the 2-carbon-homologated alcohol **28**. Protection of the hydroxyl group in **28** followed by removal of the silyl group provided the alcohol **29**. After carbon-chain elongation of **29** at the α-position, a three-step indolizidine cyclization reaction gave rise to indolizidine **30**,[16] whose spectral data were completely in accord with those for natural **223A** (Scheme 7).

Thus the structure of natural **223A** was revised to **30**,[4] and the relative stereochemistry of this natural product was



Scheme 7. (a) Swern ox. then $(EtO)_2P(O)CH_2CO_2Et$, NaH (92%); (b) 10% Pd–C, H_2 then Super-Hydride (98%); (c) MOMCl, Hünig base (89%); (d) TBAF (79%); (e) Swern ox. then *n*-BuLi, $EtP^+Ph_3Br^-$ (83%); (f) 10% Pd–C, H_2; (g) *n*-PrSLi, HMPA then c. HCl, MeOH; (h) CBr_4, Ph_3P, Et_3N (51%).

determined to be $5R^*,6R^*,8R^*,9S^*$ by the present synthesis.

Alkaloid **205B**, isolated from skin extracts of the Panamanian frog *Dendrobates pumilio*, possesses an unusual and unique 8b-azaacenaphthylene ring system.[17] In addition to this unique structure, the alkaloid contains five asymmetric centers in its compact, fourteen-carbon-atom tricycle. The structure of alkaloid **205B** was first reported to be **A**, and recently revised to be **B** based on FTIR, NMR, and MS spectral data.[18] At present, no synthesis of this alkaloid has been reported, and the absolute stereochemistry is still unknown (Fig. 5).

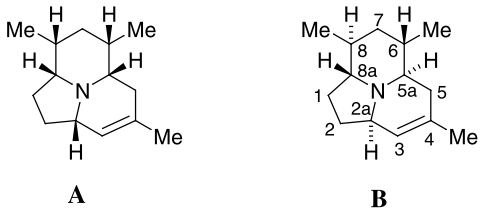


Figure 5.

We applied our tetrasubstituted piperidine synthesis illustrated in Figure 1 to the synthesis of alkaloid **205B**. The side chain on the 6-position of **15** was homologated by the Arndt–Eistert sequence to afford the ester **31**, which was converted to methyl ketone **33** via Weinreb's amide[19] **32** in good yield. After protection of the carbonyl group in **33**, the oxazolizinone ring was hydrolyzed by treatment with 2 M KOH in *i*-PrOH at 120 °C in a sealed tube followed by protection of the resulting amino alcohol with Boc_2O in the presence of NaOH to give rise to **34**. Swern oxidation of **34** followed by the Horner–Emmons reaction of the resulting aldehyde yielded the unsaturated ester **35**. Hydrogenation of the double bond in **35** and reduction of the ester moiety with DIBAL provided the aldehyde, which was subjected to an intramolecular Mannich-type cyclization reaction by treatment with *p*TsOH to provide the tricyclic ketone **36** along with its acetal **37** (Scheme 8).

The stereochemical outcome of this cyclization can be explained as depicted in Figure 6.

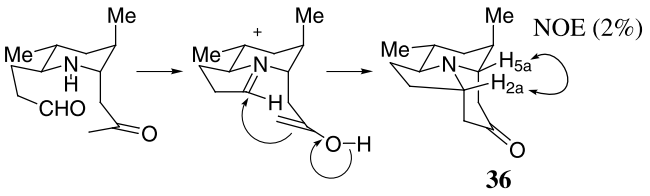
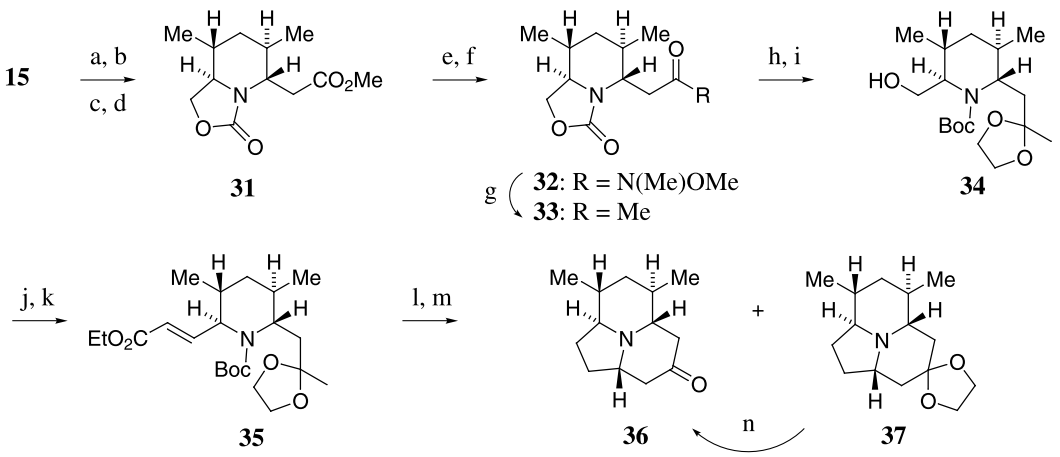


Figure 6.

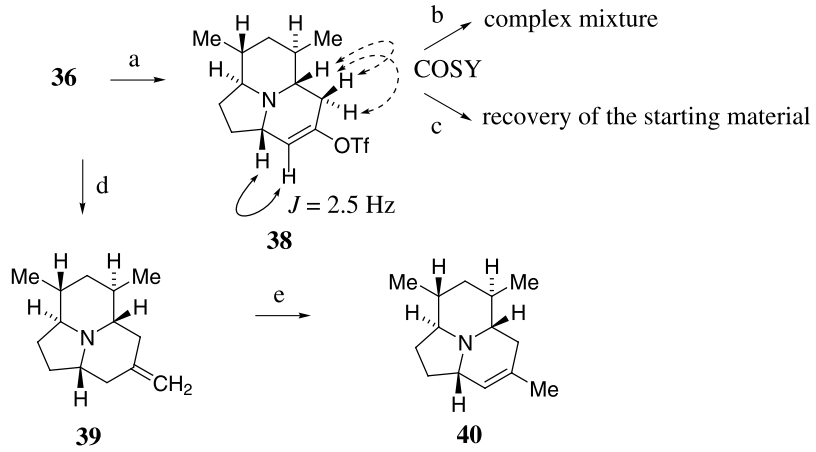
Regioselective enolization of the ketone precursor to **36** in the presence of a chiral lithium amide base was performed to give the enol triflate as a 3:1 mixture of regioisomers, and major product **38** resulted in 54% yield. The tricyclic ketone **38** was confirmed to have the desired stereochemistry as shown in Scheme 9. Attempts to convert **38** into final product **40** under the Takai and Nozaki's protocol[20] or McMurry's reaction conditions[21] led only to a complex mixture or recovered starting material, respectively. On the other hand, the acid-catalyzed isomerization of the exo-olefin **39**, derived from **36** by Wittig olefination was quite effective,[22] and led to the desired endo-olefin **40** in 63% yield. The spectroscopic data of **40** were identical with those for the natural product. The absolute sterochemistry of natural **205B** was unambiguously determined to be an antipode of our synthetic **40** by comparison of optical rotations.

3. Conclusion

In summary, we have succeeded in stereodivergent syntheses of two 2,3,5,6-tetrasubstituted piperidine ring systems with complete stereoselection by sequential use of Michael-type conjugate addition reaction to enaminoesters. Using this methodology, we completed the first total synthesis of the alkaloids **223A** and **205B** both of which possess the above tetrasubstituted piperidine ring structural element. The original structure for alkaloid **223A** has been



Scheme 8. (a) LiOH, MeOH–H_2O; (b) $ClCO_2Et$, Et_3N: (c) CH_2N_2; (d) $PhCO_2Ag$, Et_3N, MeOH (71%); (e) LiOH, MeOH–H_2O; (f) 1,1′-carbonyldiimidazole then E_3tN, (MeO)MeNH·HCl (98%); (g) MeMgBr (73%); (h) ethylene glycol *p*-TsOH (86%); (i) 2 M KOH in *i*-PrOH, 120 °C then Boc_2O, NaOH (74%); (j) Swern ox.; (k) $(EtO)_2P(O)CH_2CO_2Et$, NaH (74%); (l) 10% Pd–C, H_2 then DIBAL; (m) *p*-TsOH, benzene–acetone (**36**; 62%, **37**; 15%); *n*-TsOH, acetone (80%).



Scheme 9. (a) *R*-(*R**, *R**)-(+)-bis(α-methylbenzyl)amine, *n*-BuLi then Comins' reagent (54%); (b) $Pd(Ph_3P)_4$, Me_3Al; (c) $(Me)_2CuLi$; (d) $MeP^+Ph_3I^-$, *n*-BuLi (84%); (e) *p*-TsOH, benzene, reflux (63%).

revised to **30**, and the absolute stereochemistry of **205B** was determined to be 2a*R*,5a*R*,6*S*,8*S*,8a*R* by the present total synthesis.

4. Experimental

4.1. General

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on a Varian Gemini 300 or Unity Plus 500 spectrometer. ^1H NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q=methyl, t=methylene, d=methyne, and s=quaternary carbons. Infrared spectra (IR) were measured with a Perkin–Elmer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (No 7734-5B) or (No 9385). Elemental analysis were performed by the micro analytical laboratory of this University.

4.1.1. Methyl (6*S*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-6-oxopiperidine-1-carboxylate (2). To a stirred solution of **1** (1.85 g, 5.40 mmol) in THF (22 mL) was added a solution of *n*-BuLi (1.6 m in hexane, 3.5 mL, 5.54 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. To the reaction mixture was added $ClCO_2Me$ (0.43 mL, 5.54 mmol) at −78 °C, and then the reaction mixture was warmed to 0 °C for 2 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (50 mL×1, 15 mL×2). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=30:1–20:1) to give **2** (2.10 g, 98%) as a colorless solid (mp 97–102 °C).

IR (KBr) 2958, 1718, 1113 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (9H, s), 1.69–1.75 (1H, m), 1.86–1.99 (2H, m), 2.12–2.17 (1H, m), 2.49–2.52 (2H, m), 3.72–3.76 (2H, m), 3.76 (3H, s), 4.41–4.44 (1H, m), 7.37–7.45 (6H, m), 7.63–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 17.44 (t), 18.96 (s), 24.18 (t), 26.63 (q), 34.64 (t), 53.52 (q), 56.16 (d), 64.10 (t), 127.60 (d), 129.65 and 129.68 (each d), 132.63 and 132.81 (each s), 135.36 and 135.42 (each d), 154.69 (s), 171.69 (s); MS: 425 (M^+), 115 (100); HRMS: Calcd for $C_{24}H_{31}NO_4Si$ 425.2022. Found 425.2006. Anal. Calcd for $C_{24}H_{31}NO_4Si$ C, 67.73; H, 7.34; N, 3.29. Found C, 67.73; H, 7.39; N, 3.32; $[\alpha]_D^{26}$=41.6 (*c* 5.67, $CHCl_3$).

4.1.2. Mehtyl (6*S*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-6-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylate (3). To a stirred solution of hexamethyldisilazane (1.5 mL, 6.97 mmol) in THF (5 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 4.4 mL, 6.97 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To a stirred solution of **2** (2.47 g, 5.81 mmol) in THF (15 mL) was added a solution of LiHMDS prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the above reaction mixture was added a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]5-chloropyridine (Comins' reagent) (97%, 2.73 g, 6.97 mmol) in THF (6 mL) at −78 °C, and the resulting mixture was warned to −40 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow solid, which was chromatographed on SiO_2 (60 g, hexane:acetone=100:1–50:1) to give **3** (3.0 g, 96%) as a colorless oil.

IR (neat) 2962, 1733, 1423, 1213, 1114 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (9H, s), 1.69–1.76 (1H, m), 1.91–2.04 (2H, br m), 2.13–2.19 (1H, m), 3.57 (2H, dd, *J*=10.2, 8.1 Hz), 3.79 (3H, s), 4.64–4.68 (1H, m), 5.17 (1H, t,

J=3.8 Hz), 7.37–7.46 (6H, m), 7.63–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 19.09 (t), 19.29 (s), 22.22 (t), 26.81 (q), 53.69 (q), 55.63 (d), 60.79 (t), 106.05 (d), 127.63 (d), 129.69 (d), 133.06 and 133.11 (each s), 135.42 and 135.44 (each d), 138.05 (s), 154.69 (s); MS: 557 (M^+), 422 (100); HRMS: Calcd for $C_{25}H_{30}F_3NO_6Si$ 557.1515. Found 557.1518; $[\alpha]_D^{26}$=−18.8 (*c* 1.57, $CHCl_3$).

4.1.3. Dimethyl (*S*)-(−)-6-(*tert*-butyldiphenylsilyloxymethyl)-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylate (4). To a stirred solution of the above **3** (5.30 g, 9.52 mmol) in DMF (25 mL) was added $Pd(Ph_3P)_4$ (550 mg, 0.48 mmol), and the resulting mixture was stirred at room temperature under CO balloon pressure for 30 min. To the reaction mixture were added Et_3N (5.3 mL, 38.1 mmol) and MeOH (15.4 mL, 381.0 mmol), and then the reaction mixture was stirred at 70 °C under CO balloon pressure for 15 h. After cooling, the reaction mixture was diluted with H_2O (100 mL) and brine (25 mL), and the aqueous mixture was extracted with Et_2O (50 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (80 g, hexane:acetone=50:1–30:1) to give **4** (3.91 g, 88%) as a colorless oil.

IR (neat) 2968, 1732, 1652, 1240 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (9H, s), 1.77–1.85 (1H, m), 1.91–1.99 (1H, br m), 2.04–2.16 (2H, m), 3.52 (1H, dd, J=10.2, 8.5 Hz), 3.70 (3H, s), 3.71 (3H, s), 3.77 (1H, dd, J=10.2, 6.3 Hz), 4.55 (1H, br), 5.96 (1H, t, J=3.5 Hz), 7.37–7.45 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 19.43 (t), 19.55 (s), 22.48 (t), 26.95 (q), 52.16 (q), 52.69 (d), 53.30 (q), 61.39 (t), 121.98 (s), 127.72 (d), 129.72 and 129.75 (each d), 130.59 (s), 133.31 and 133.41 (each s), 135.58 (d), 154.52 (s), 165.49 (s); MS: 467 (M^+, 100); HRMS: Calcd for $C_{26}H_{33}NO_5Si$ 467.2128. Found 467.2134; $[\alpha]_D^{26}$=−53.3 (*c* 1.33, $CHCl_3$).

4.1.4. Dimethyl (2*R*,3*S*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-3-vinylpiperidine-1,2-dicarboxylate (5). To a stirred suspension of CuI (1.71 g, 9.00 mmol) in Et_2O (15 mL) was added a solution of vinyl lithium, prepared from tetravinyltin (0.37 mL, 4.50 mmol) and MeLi (1.0 M in Et_2O, 18 mL, 18.0 mmol) in Et_2O (15 mL) at 0 °C for 30 min, at −78 °C, and the resulting suspension was warmed to −35 °C for 20 min. The resulting suspension was re-cooled to −78 °C, and a solution of **4** (1.05 g, 2.25 mmol) in Et_2O (5 mL) was added to the resulting suspension. The reaction mixture was warmed to −30 °C for 1 h, and the reaction was quenched with satd. NH_4Cl (aq.). The aqueous mixture was diluted with CH_2Cl_2 (100 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=40:1–30:1) to give **5** (1.07 g, 96%) as a colorless oil.

IR (neat) 3071, 2935, 2890, 1750, 1705, 1113 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (9H, s), 1.41–1.43 (1H, m), 1.59 (1H, br), 1.74–1.81 (1H, br m), 1.85–1.88 (1H, m), 3.00 (1H, br), 3.45 (3H, s), 3.65 (3H, s), 3.67–3.70 (1H, m), 4.28 (1H, br), 4.78 (1H, br), 5.09–5.30 (2H, m), 5.81–5.88 (1H, m), 7.36–7.44 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 18.68 (t), 19.56 (s), 21.03 (t), 27.15(q), 37.06 (d), 52.27 (d), 52.34 (q), 53.19 (q), 56.05 (d), 62.34 (t), 115.56 (t), 127.74 (d), 129.72 (d), 133.76 (s), 135.63 (d), 138.91 (d), 157.63 (s), 172.66 (s); MS: 495 (M^+); HRMS: Calcd for $C_{28}H_{37}NO_5Si$ 495.2441. Found 495.2464; $[\alpha]_D^{26}$=+2.1 (*c* 1.57, $CHCl_3$).

4.1.5. Methyl (2*R*,3*S*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxymethyl-3-vinylpiperidine-1-carboxylate. To a stirred solution of **5** (2.0 g, 4.04 mmol) in THF (15 mL) was added Super-Hydride (1 M in THF, 8.9 mL, 8.9 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×6). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=30:1–6:1) to give an alcohol (1.8 g, 96%) as a colorless oil.

IR (neat) 3449, 3070, 2937, 2862, 1679 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (9H, s), 1.26–1.39 (2H, m), 1.63–1.70 (1H, m), 1.79–1.86 (1H, br m), 2.35 (1H, br), 2.96 (1H, br), 3.55–3.69 (4H, m), 3.67 (3H, br s), 4.25–4.29 (1H, m), 4.39 (1H, br), 5.06–5.12 (2H, m), 5.79–5.86 (1H, m), 7.39–7.46 (6H, m), 7.66–7.72 (4H, m); ^{13}C NMR (125 MHz) δ 19.03 (s), 19.95 (t), 21.27 (t), 26.67 and 26.72 (each q), 36.70 (d), 50.83 (d), 52.72 (q), 56.14 (d), 64.43 (t), 64.88 (t), 115.05 (t), 127.67 and 127.70 (each d), 129.74 (d), 132.93 and 133.02 (each s), 135.44 and 135.49 (each d), 140.18 (d), 157.97 (s); MS: 410 (M^+−57), 378 (100); HRMS: Calcd for $C_{23}H_{28}NO_4Si$ 410.1787. Found 410.1807; $[\alpha]_D^{26}$=+19.7 (*c* 1.53, $CHCl_3$).

4.1.6. Methyl (2*S*,3*S*,6*S*)-(−)-6-(*tert*-butyldiphenylsilyloxymethyl)-2-propenyl-3-vinylpiperidine-1-carboxylate. To a stirred solution of $(COCl)_2$ (0.24 mL, 2.77 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.38 mL, 5.43 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of the alcohol prepared above (857 mg, 1.84 mmol) in CH_2Cl_2 (4 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (1.1 mL, 7.98 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $EtP^+Ph_3Br^-$ (2.73 g, 7.35 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 4 mL, 6.4 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the solution was added a solution of the above oil in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=100:1–80:1) to give an olefin (691 mg, 79% in 2 steps) as a colorless oil.

IR (neat) 3070, 2938, 2860, 1697 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (9H, s), 1.33–1.38 (1H, m), 1.67 (3H, t-like, J=6.8 Hz), 1.69–1.75 (2H, br m), 1.81–1.88 (1H, m), 2.19 (1H, br), 3.58–3.69 (2H, m), 3.63 (3H, br s), 4.35 (1H, m), 4.90 (1H, d-like, J=9.4 Hz), 5.05–5.10 (2H, m), 5.29–5.33 (1H, m), 5.38–5.43 (1H, m), 5.85–5.91 (1H, m), 7.38–7.45 (6H, m), 7.67–7.68 (4H, m); ^{13}C NMR (125 MHz) δ 13.02 (q), 19.18 (s), 19.47 (t), 20.73 (t), 26.78 (q), 41.73 (d), 51.01 (d), 51.71 (d), 52.46 (q), 64.35 (t), 114.70 (t), 127.62 (d), 129.62 (d), 131.10 (d), 133.50 and 133.64 (each s), 135.56 and 135.59 (each d), 140.22 (d), 156.81 (s); MS: 420 (M^+-57), 423 (100); HRMS: Calcd for $C_{25}H_{30}NO_3Si$ 420.1995. Found 420.2017; $[\alpha]_D^{26}=-64.5$ (c 2.09, $CHCl_3$).

4.1.7. Methyl (2*S*,3*R*,6*S*)-(−)-3-ethyl-6-hydroxymethyl-2-propylpiperidine-1-carboxylate (6). To a solution of the above olefin (704 mg, 1.48 mmol) in EtOAc (15 mL) was added 5% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 48 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (10 mL) was added a solution of TBAF (1 M in THF, 1.9 mL, 1.9 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×8). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=20:1–7:1) to give **6** (276 mg, 77% in 2 steps) as a colorless oil.

IR (neat) 3447, 2956, 2872, 2672 cm^{-1}; ^1H NMR (500 MHz) δ 0.87–0.91 (6H, m), 1.23–1.59 (9H, br m), 1.71–1.81 (2H, m), 2.94 (1H, br), 3.57–3.64 (2H, m), 3.68 (3H, s), 3.92 (1H, br), 4.25 (1H, br); ^{13}C NMR (125 MHz) δ 11.96 (q), 13.98 (q), 19.92 (t), 20.15 (t), 25.73 (t), 37.93 (d), 38.87 (t), 52.67 (q), 52.89 (d), 54.46 (d), 52.46 (q), 65.77 (t), 158.85 (s); MS: 243 (M^+), 131 (100); HRMS: Calcd for $C_{13}H_{25}NO_3$ 243.1833. Found 243.1821; $[\alpha]_D^{26}=-21.8$ (c 1.05, $CHCl_3$).

4.1.8. Dimethyl (2*S*,5*R*,6*S*)-(−)-5-ethyl-6-propylpiperidine-1,2-dicarboxylate. To a stirred solution of $(COCl)_2$ (0.53 mL, 6.12 mmol) in CH_2Cl_2 (12 mL) was added DMSO (0.88 mL, 12.38 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **6** (1 g, 4.12 mmol) in CH_2Cl_2 (9 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (2.6 mL, 18.47 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH_2PO_4 (4.9 g, 40.83 mmol), 2-methyl-2-butene (8.8 mL, 82.5 mmol), and the above oil in t-BuOH (20 mL) was added a solution of $NaClO_2$ (80%, 2.7 g, 24.3 mmol) in H_2O (8 mL), and the resulting suspension was stirred at room temperature for 45 min. The reaction was quenched with satd. $NaHSO_3$ (aq.) and 10% HCl at 0 °C, and the aqueous mixture was extracted with EtOAc (15 mL×10). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in EtOAc (20 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (40 g, hexane:acetone=20:1) to give a methyl ester (1.008 g, 90% in 3 steps) as a colorless oil.

IR (neat) 2957, 2872, 1740, 1701 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (6H, t-like, J=6.8 Hz), 1.24–1.42 (7H, br m), 1.46–1.52 (1H, m), 1.71–1.87 (2H, m), 1.96 (1H, br), 3.66 (3H, s), 3.69 (3H, br s), 3.88–4.05 (1H, br), 4.63 and 4.84 (1H, br); ^{13}C NMR (125 MHz) δ 11.87 (q), 13.86 (q), 19.91 (t), 20.31 (t), 25.02 (t), 36.19 (t), 37.75 (d), 51.92 (q), 52.72 (q), 54.79 (d), 157.80 (s), 173.24 (s); MS: 271 (M^+), 228 (100); HRMS: Calcd for $C_{14}H_{25}NO_4$ 271.1784. Found 271.1816; $[\alpha]_D^{26}=-65.1$ (c 2.17, $CHCl_3$).

4.1.9. Dimethyl (5*R*,6*S*)-(+)-5-ethyl-6-propyl-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylate (7). To a stirred solution of hexamethyldisilazane (0.32 mL, 1.5 mmol) in THF (3 mL) was added a solution of n-BuLi (1.6 M in hexane, 0.94 mL, 1.5 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To a stirred solution of the above methyl ester (271 mg, 1 mmol) in THF (2 mL) was added a solution of LiHMDS prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To a stirred solution of PhSeCl (610 mg, 3 mmol) in THF (5 mL) was added a solution of Li enolate prepared above at −78 °C, and the resulting suspension was stirred at room temperature for 20 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (30 g, hexane:acetone=40:1–35:1) to give **7** (207 mg, 77%) as a colorless oil.

IR (neat) 2958, 2874, 1708, 1646 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 and 0.93 (each 3H, each t, J=7.2 Hz), 1.17–1.34 (4H, br m), 1.42–1.51 (3H, m), 1.99 (1H, dd, J=19.2, 3.9 Hz), 2.27 (1H, ddd, J=19.2, 7.3, 3.9 Hz), 3.70 (3H, br s), 3.76 (3H, s), 4.26 (1H, br), 5.97 (1H, t, J=3.9 Hz); ^{13}C NMR (125 MHz) δ 11.91 (q), 14.02 (q), 19.30 (t), 25.12 and 26.20 (each t), 33.04 (t), 36.30 (t), 37.99 and 38.66 (each d), 52.10 (q), 53.07 (q), 55.29 (d), 121.05 (d), 129.05 and 129.28 (each s), 155.49 (s), 165.40 (s); MS: 269 (M^+, 100); HRMS: Calcd for $C_{14}H_{23}NO_4$ 269.1627. Found 269.1604; $[\alpha]_D^{26}=+63.4$ (c 0.68, $CHCl_3$).

4.1.10. Dimethyl (2*S*,3*R*,5*R*,6*S*)-(−)-5-ethyl-6-propyl-3-vinylpiperidine-1,2-dicarboxylate (8). To a stirred suspension of CuI (622 mg, 3.27 mmol) in Et_2O (5 mL) was added a solution of vinyl lithium, prepared from tetravinyltin (0.31 mL, 1.63 mmol) and MeLi (1.01 M in Et_2O, 6.5 mL, 6.6 mmol) in Et_2O (3 mL) at 0 °C for 30 min, at −78 °C, and the resulting suspension was warmed to −35 °C for 20 min. The resulting suspension was re-cooled to −78 °C, and a solution of **7** (176 mg, 0.65 mmol) in Et_2O (4 mL) was added to the resulting suspension. The reaction mixture was warmed to 0 °C for 1 h, and the reaction was quenched with

satd. NH_4Cl (aq.). The aqueous mixture was diluted with CH_2Cl_2 (50 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=70:1–40:1) to give **8** (174 mg, 90%) as a colorless oil.

IR (neat) 2957, 2873, 1747, 1702 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 and 0.89 (each 3H, each t, J=7.3 Hz), 0.96 (1H, q, J=12 Hz), 1.24–1.46 (6H, br m), 1.62–1.70 (1H, m), 1.70–1.77 (1H, m), 2.64 (1H, q-like, J=8 Hz), 3.67 (3H, s), 3.69 (3H, s), 3.92 (1H, br), 4.29 (1H, br), 5.00–5.08 (2H, m), 5.71–5.78 (1H, m); ^{13}C NMR (125 MHz) δ 11.31 (q), 13.98 (q), 19.86 (t), 29.56 (t), 31.76 (t), 39.68 (d), 40.50 (t), 40.86 (d), 51.73 (q), 52.81 (q), 55.40 (d), 59.78 (d), 115.31 (t), 139.95 (d), 157.35 (s), 173.20 (s); MS: 254 (M^+-43, 100); HRMS: Calcd for $C_{13}H_{20}NO_4$ ($M^+-C_3H_7$) 254.1392. Found 254.1353; $[\alpha]_D^{26}=-65.9$ (c 0.91, $CHCl_3$).

4.1.11. Methyl (2*S*,3*R*,5*R*,6*S*)-(−)-5-ethyl-2-hydroxymethyl-6-propyl-3-vinylpiperidine-1-carboxylate (9). To a stirred solution of **8** (45 mg, 0.15 mmol) in THF (1 mL) was added a solution of Super-Hydride (1 M in THF, 0.4 mL, 0.4 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=30:1–15:1) to give **9** (41 mg, 99%) as a colorless oil.

IR (neat) 3456, 3078, 2958, 2873, 1672 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 and 0.92 (each 3H, each t, J=7.3 Hz), 1.00 (1H, q, J=10.7 Hz), 1.28–1.47 (6H, br m), 1.53–1.59 (1H, m), 1.62–1.66 (2H, m), 2.12 (1H, br q-like, J=9.8 Hz), 3.54–3.59 (1H, m), 3.71 (3H, s), 3.72–3.85 (1H, br), 3.97 (2H, br), 5.03–5.29 (2H, m), 5.69 (1H, ddd, J=17.1, 9.8, 8.1 Hz); ^{13}C NMR (125 MHz) δ 11.22 (q), 13.88 (q), 19.65 (t), 29.56 (t), 32.50 (t), 40.51 (d), 41.63 (t), 41.74 (d), 52.98 (q), 55.65 (d), 60.40 (d), 67.09 (t), 115.63 (t), 141.02 (d); MS: 238 (M^+-31), 117 (100); HRMS: Calcd for $C_{14}H_{24}NO_2$ (M^+-MeO), 238.1808. Found 238.1792; $[\alpha]_D^{26}=-93.4$ (c 1.86, $CHCl_3$).

4.1.12. (5*S*,6*R*,8*R*,9*S*)-(−)-6-Ethyl-5-propyl-8-vinylhexahydrooxazolo[3,4-*a*]pyridin-3-one (10). To a stirred solution of **9** (41 mg, 0.15 mmol) in THF (1 mL) was added NaH (60%, 7.9 mg, 0.20 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with 10% AcOH, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=20:1) to give **10** (30.3 mg, 84%) as a colorless oil.

IR (neat) 3078, 2962, 2872, 1751 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t, J=7.5 Hz), 0.93 (3H, t, J=7.3 Hz), 1.06–1.16 (2H, m), 1.26–1.33 (1H, br m), 1.51 (1H, qm, J=11.5 Hz), 1.54–1.62 (2H, m), 1.73–1.80 (1H, m), 1.97 (1H, dt, J=13, 3.5 Hz), 2.17 (1H, qm, J=11 Hz), 2.21–2.29 (1H, m), 2.82 (1H, td, J=10, 3.5 Hz), 3.24 (1H, ddd, J=13, 7, 3 Hz), 3.96 (1H, dd, J=8, 3 Hz), 4.16 (1H, dd, J=8, 7 Hz), 5.10–5.14 (2H, m), 5.52 (1H, ddd, J=16.5, 10, 8 Hz); ^{13}C NMR (125 MHz) δ 10.20 (q), 14.01 (q), 19.49 (t), 24.19 (t), 29.34 (t), 35.98 (t), 39.97 (d), 44.78 (d), 61.16 (d), 61.20 (d), 64.87 (t), 117.44 (t), 137.61 (d), 155.82 (s); MS: 237 (M^+, 100); HRMS: Calcd for $C_{14}H_{23}NO_2$, 237.1728. Found 237.1740; $[\alpha]_D^{26}=-31.9$ (c 1.52, $CHCl_3$).

4.1.13. Dimethyl (2*R*,3*R*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-3-methylpiperidine-1,2-dicarboxylate (11). To a stirred suspension of CuI (5.95 g, 31.25 mmol) in Et_2O (20 mL) was added a solution of MeLi (1.14 M in Et_2O, 55 mL, 62.5 mmol) at −78 °C, and the resulting suspension was stirred at −78 to −35 °C for 20 min. The resulting solution was cooled to −78 °C, and a solution of **4** (2.92 g, 6.25 mmol) in Et_2O (10 mL) was added to the above reaction mixture at −78 °C. The temperature was gradually raised to −35 °C, and then the reaction was quenched with satd. NH_4Cl (aq.). The reaction mixture was diluted with CH_2Cl_2, and the insoluble material was removed through a celite pad. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2. The filtrate and organic layers were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (60 g, hexane:acetone=30:1–20:1) to give **11** (2.96 g, 98%) as a colorless oil.

IR (neat) 2955, 1861, 1708 cm^{-1}; ^1H NMR (500 MHz) δ 1.05 (9H, s), 1.07 (3H, d, J=6.8 Hz), 1.18–1.25 (1H, m), 1.54–1.57 (1H, br), 1.81–1.85 (2H, m), 2.45 (1H, br), 3.45 (3H, s), 3.49 (1H, t-like, J=9.9 Hz), 3.65 (3H, s), 3.68 (1H, dd, J=9.9, 4.3 Hz), 4.28 (1H, br), 4.44 (1H, br), 7.35–7.44 (6H, m), 7.64–7.68 (4H, m); ^{13}C NMR (125 MHz) δ 17.98 (q), 18.13 (t), 19.19 (s), 21.87 (t), 26.78 (q), 28.02 (d), 51.77 (q), 52.06 (d), 52.80 (q), 58.48 (d), 127.53 and 127.56 (each d), 129.53 and 129.54 (each d), 133.58 and 133.63 (each s), 135.47 (d), 157.36 (s), 172.82 (s); MS: 483 (M^+), 426 (100); HRMS: Calcd for $C_{23}H_{28}NO_5Si$ ($M^+-C_4H_9$) 426.1736. Found 426.1744; $[\alpha]_D^{26}=+13.6$ (c 5.12, $CHCl_3$).

4.1.14. Methyl (2*R*,3*R*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxymethyl-3-methylpiperidine-1-carboxylate. To a stirred solution of **11** (2.96 g, 6.13 mmol) in THF (15 mL) was added a solution of Super-Hydride (1 M in THF, 13.5 mL, 13.48 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2. The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (45 g, hexane:acetone=30:1–6:1) to give an alcohol (2.58 g, 92%) as a colorless oil.

IR (neat) 3450, 3070, 2956, 1680 cm^{-1}; ^1H NMR (500 MHz) δ 1.04 (9H, s), 1.05 (3H, d, J=7.7 Hz), 1.15–1.18 (1H, m), 1.43 (1H, br), 1.58–1.64 (1H, m), 1.78–1.90 (2H, m), 2.99 (1H, br), 3.53–3.64 (4H, m), 3.67 (3H, s), 4.01–4.04 (1H, m), 4.39 (1H, br), 7.37–7.46 (6H, m), 7.66–7.72 (4H, m); ^{13}C NMR (125 MHz) δ 18.98 (q), 19.14 (s), 19.49 (t), 22.37 (t), 26.63 (q), 27.28 (d), 50.81 (d), 52.63 (q), 58.79 (d), 64.89 (t), 127.62 and 127.65 (each d), 129.68 and

129.69 (each d), 133.03 (s), 135.39 and 135.45 (each d), 158.32 (s); MS: 398, 366 (100); HRMS: Calcd for $C_{22}H_{28}NO_4Si$ ($M^+-C_4H_9$) 398.1787. Found 398.1787; $[\alpha]_D^{26}=+19.8$ (*c* 1.89, $CHCl_3$).

4.1.15. (5*S*,8*R*,9*R*)-(−)-5-(*tert*-Butyldiphenylsilyloxymethyl)-8-methylhexahydrooxazolo[3,4-*a*]pyridin-3-one (12). To a stirred solution of the above alcohol (493 mg, 1.08 mmol) in THF (8 mL) was added NaH (60%, 48 mg, 1.19 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with 10% AcOH (aq.), and the aqueous mixture was extracted with CH_2Cl_2. The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1–15:1) to give **12** (456 mg, 99%) as a colorless solid (mp 81–83 °C).

IR (KBr) 2958, 2859, 1751, 757 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, d, *J*=6.4 Hz), 1.03 (9H, s), 1.11–1.20 (1H, m), 1.41–1.48 (2H, m), 1.90 (1H, dq, *J*=13.7, 3.4 Hz), 2.07 (1H, dq, *J*=13.4, 3.4 Hz), 3.12–3.20 (2H, m), 3.89 (1H, dd, *J*=8.6, 7.3 Hz), 4.18 (1H, dd, *J*=10.2, 8.1 Hz), 4.33 (1H, dd, *J*=8.6, 7.7 Hz), 4.48 (1H, dd, *J*=10.2, 4.3 Hz), 7.36–7.43 (6H, m), 7.66–7.69 (4H, m); ^{13}C NMR (125 MHz) δ 16.87 (q), 19.14 (s), 26.75 (q), 28.39 (t), 31.72 (t), 35.09 (t), 56.93 (d), 62.38 (d), 63.16 (t), 66.64 (t), 127.48 (d), 129.45 (d), 133.38 and 133.50 (each s), 135.40 and 135.46 (each d), 156.20 (s); MS: 366 (100); HRMS: Calcd for $C_{21}H_{24}NO_3Si$ ($M^+-C_4H_9$) 366.1526. Found 366.1526. Anal. Calcd for C25H33NO3Si C, 70.88; H, 7.85; N, 3.31. Found C, 70.71; H, 7.92; N, 3.39; $[\alpha]_D^{26}=-43.5$ (*c* 1.46, $CHCl_3$).

4.1.16. (5*S*,8*R*,9*R*)-(−)-5-Hydroxymethyl-8-methylhexahydrooxazolo[3,4-*a*]pyridin-3-one. To a stirred solution of **12** (1.49 g, 3.51 mmol) in THF (20 mL) was added a solution of TBAF (1 M in THF, 4.6 mL, 4.6 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$. The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (18 g, hexane:acetone=10:1–4:1) to give an alcohol (648 mg, 99%) as a colorless oil.

IR (neat) 3420, 2930, 2875, 1723 cm^{-1}; ^1H NMR (500 MHz) δ 0.78–0.83 (3H, m), 1.06–1.16 (1H, m), 1.26–1.37 (2H, m), 1.51–1.57 (1H, m), 1.76–1.82 (1H, m), 3.04–3.13 (1H, m), 3.13–3.21 (1H, m), 3.66–3.71 (1H, m), 3.73–3.84 (1H, m), 3.86–3.91 (1H, m), 4.37–4.41 (1H, m), 4.57–4.62 (1H, m); ^{13}C NMR (125 MHz) δ 16.52 (q), 27.46 (t), 31.40 (t), 35.70 (d), 58.44 (d), 62.02 (d), 63.23 (t), 67.52 (t), 157.40 (s); MS: 185 (M^+), 155 (100); HRMS: Calcd for $C_9H_{15}NO_3$ 185.1052. Found 185.1050; $[\alpha]_D^{26}=-39.7$ (*c* 1.32, $CHCl_3$).

4.1.17. Methyl (5*S*,8*R*,9*R*)-(−)-8-methyl-3-oxohexahydrooxazolo[3,4-*a*]pyridine-5-carboxylate (13). To a stirred solution of $(COCl)_2$ (0.65 mL, 7.47 mmol) in CH_2Cl_2 (10 mL) was added DMSO (1.1 mL, 15.41 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 5 min. To the mixture was added a solution of the above alcohol (923 mg, 4.99 mmol) in CH_2Cl_2 (5 mL) via canule at −78 °C, and then stirring was continued for 30 min. To the reaction mixture was added Et_3N (3.1 mL, 22.62 mmol) at −78 °C, and the temperature was gradually raised to 0 °C. The reaction mixture was diluted with Et_2O and water, and the organic layer was separated. The aqueous layer was extracted with Et_2O and the organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the above oil in *t*-BuOH (21 mL) were added $NaHPO_4$ (5.9 g, 49.17 mmol) and 2-methyl-2-butene (21 mL, 192.92 mmol) at room temperature, and then a solution of $NaClO_2$ (80%, 3.3 g, 29.18 mmol) in water (8 mL) was added dropwise to the reaction mixture at 0 °C. The resulting suspension was stirred at room temperature for 30 min, and the reaction was quenched with satd. $NaHSO_3$ (aq.) at 0 °C. To the mixture was added 10% HCl (aq.), and the aqueous mixture was saturated with NaCl. The aqueous mixture was extracted with EtOAc, and the organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used direcly in the next step.

To a stirred solution of the above pale yellow oil in EtOAc (10 mL) was added a solution of CH_2N_2 in Et_2O (10 mL) at 0 °C, and then the resulting solution was stirred at room temparature for 23 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (40 g, hexane:acetone=15:1–12:1) to give **13** (1.06 g, 86% in 2 steps) as a colorless solid (mp 74–76 °C).

IR (KBr) 2960, 2932, 1762, 1205 cm^{-1}; ^1H NMR (500 MHz) δ 0.90 (3H, d, *J*=6.4 Hz), 1.13 (1H, qd, *J*=12.8, 3.4 Hz), 1.54–1.60 (1H, m), 1.71–1.80 (1H, m), 1.88–1.98 (2H, m), 3.14–3.20 (1H, m), 3.67 (1H, dd, *J*=11, 3.5 Hz), 3.77 (3H, s), 3.95 (1H, t-like, *J*=8.5 Hz), 4.41 (1H, t-like, *J*=8.5 Hz); ^{13}C NMR (125 MHz) δ 16.88 (q), 27.70 (t), 30.66 (t), 34.08 (d), 52.44 (q), 55.82 (d), 61.40 (d), 67.97 (t), 156.79 (s), 170.36 (s); MS: 213 (M^+), 211 (100); HRMS: Calcd for $C_{10}H_{15}NO_4$ 213.0101. Found 213.0991; $[\alpha]_D^{26}=-96.7$ (*c* 1.08, $CHCl_3$).

4.1.18. Methyl (8*R*,9*R*)-(−)-8-methyl-3-oxo-5-phenylsulfanylhexahydrooxazolo[3,4-*a*]pyridine-5-carboxylate. To a stirred solution of hexamethyldisilazane (1.01 mL, 4.73 mmol) in THF (6 mL) was added *n*-BuLi (1 M in hexane, 3.0 mL, 4.73 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. To a stirred solution of **7** (871 mg, 4.09 mmol) in THF (6 mL) was added a solution of LiHMDS in THF prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the reaction mixture was added a solution of $(PhS)_2$ in THF (4 mL) via canule at −78 °C, and the temperature was gradually raised to 0 °C. The volatiles were removed and the residue was chromatographed on SiO_2 (50 g, hexane:acetone=10:1) to give a phenylthio ether (1.3 g, 99%) as a colorless oil.

IR (neat) 2956, 1762, 1269, 1202, 758 cm^{-1}; ^1H NMR (500 MHz) δ 0.94 (3H, d, *J*=6.4 Hz), 1.52–1.59 (1H, m), 1.65–1.73 (2H, m), 1.87 (1H, dt-like, *J*=14.5, 3 Hz), 2.05–2.11 (1H, m), 3.65–3.70 (1H, m), 3.74 (3H, s), 3.88 (1H, t-like, *J*=8.5 Hz), 4.40 (1H, t-like, *J*=8.5 Hz), 7.25–7.29 (2H, m), 7.31–7.33 (1H, m), 7.66–7.68 (2H, m); ^{13}C NMR (125 MHz) δ 16.74 (q), 27.93 (t), 32.82 (t), 34.59 (d), 53.08 (q), 57.42 (d), 67.96 (t), 71.98 (s), 128.57 (d), 129.25 (s),

129.57 (d), 137.10 (d), 155.17 (s), 169.56 (s); MS: 321 (M^+), 213 (100); HRMS: Calcd for $C_{16}H_{19}NO_4S$ 321.1035. Found 321.1038; $[\alpha]_D^{26}=-13.3$ (*c* 1.38, $CHCl_3$).

4.1.19. Methyl (8*R*,9*R*)-(−)-8-methyl-3-oxo-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridine-5-carboxylate (14). To a stirred solution of the above phenylthio ether (160 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (0.15 mL, 1.29 mmol), and then *m*CPBA (65%, 320 mg, 1.20 mmol) was added to the resulting mixture in four portions in 15 min interval at room temperature. The reaction was quenched with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ (aq.), and the aqueous mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layer and extracts were combined, washed with brine, 10% HCl, and brine, successively, dried and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=10:1) to give **14** (89 mg, 85%) as a colorless solid (mp 101–103 °C).

IR (KBr) 2989, 2956, 1763, 1730, 1411, 1249, 1214 cm^{-1}; ^1H NMR (500 MHz) δ 1.01 (3H, d, *J*=6.4 Hz), 1.85–1.87 (1H, m), 1.89–1.96 (1H, m), 2.48 (1H, dt, *J*=19.7, 5.1 Hz), 3.39–3.44 (1H, m), 3.83 (3H, s), 4.23 (1H, dd, *J*=9.0, 3.0 Hz), 4.55 (1H, t-like, *J*=8.5 Hz), 6.25 (1H, dd, *J*=4.9, 2.8 Hz); ^{13}C NMR (125 MHz) δ 16.43 (q), 30.64 (d), 31.42 (t), 52.44 (q), 57.98 (d), 123.56 (d), 154.76 (s), 163.25 (s); MS:211 (M^+); HRMS: Calcd for $C_{10}H_{13}NO_4$ 211.0844. Found 211.0870; $[\alpha]_D^{26}=-34.4$ (*c* 0.46, $CHCl_3$).

4.1.20. Methyl (5*R*,6*R*,8*R*,9*R*)-(−)-6,8-dimethyl-3-oxo-hexahydrooxazolo[3,4-*a*]pyridine-5-carboxylate (15). To a stirred suspension of CuI (744 mg, 3.91 mmol) in Et_2O (25 mL) was added a solution of MeLi (1.18 M in Et_2O, 6.6 mL, 7.82 mmol) at −78 °C, and the reaction mixture was warmed to −35 °C for 30 min. To a solution of **14** (165 mg, 0.78 mmol) in Et_2O (70 mL) was added a solution of $(Me)_2CuLi$, prepared above, at −78 °C, and the reaction mixture was warmed to −10 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was diluted with CH_2Cl_2 (300 mL). The resulting suspension was filtered, and the filtrate was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2), and the filtrate and organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=14:1) to give **15** (165 mg, 93%) as a colorless oil.

IR (neat) 2961, 1748, 1420, 1272, 1243 cm^{-1}; ^1H NMR (500 MHz) δ 0.84 (3H, d, *J*=6.4 Hz), 1.13 (3H, d, *J*=7.3 Hz), 1.28 (1H, td, *J*=13, 4.3 Hz), 1.53 (1H, dt, *J*=14, 3 Hz), 1.65–1.72 (1H, m), 2.49–2.51 (1H, m), 3.59 (1H, dt, *J*=10, 8 Hz), 3.74 (3H, s), 3.97 (1H, t-like, *J*=8.5 Hz), 4.26 (1H, br), 4.52 (1H, t-like, *J*=8.5 Hz); ^{13}C NMR (125 MHz) δ 17.18 (q), 18.17 (q), 29.51 (d), 29.73 (d), 34.82 (t), 52.39 (q), 57.21 (d), 57.67 (d), 68.12 (t), 157.68 (s), 170.97 (s); MS: 227 (M^+), 169 (100); HRMS: Calcd for $C_{11}H_{17}NO_4$ 227.1158. Found 227.1168; $[\alpha]_D^{26}=-36.4$ (*c* 0.96, $CHCl_3$).

4.1.21. Methyl (2*S*,3*R*,5*R*,6*S*)-(−)-2-(2-ethoxycarbonyl-vinyl)-5-ethyl-6-propyl-3-vinylpiperidine-1-carboxylate (16). To a stirred solution of $(COCl)_2$ (0.11 mL, 1.26 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.18 mL, 2.52 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **9** (150 mg, 0.56 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.52 mL, 3.78 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 25 mg, 0.61 mmol) in THF (2 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.12 mL, 0.59 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. To the reaction mixture was added a slolution of the above oil in THF (4 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (12 g, hexane:acetone=80:1) to give **16** (181 mg, 96%) as a colorless oil.

IR (neat) 3078, 2958, 2873, 1697 cm^{-1}; ^1H NMR (500 MHz) δ 0.86–0.92 (6H, m), 1.00 (1H, q, *J*=11.1 Hz), 1.25 (3H, t, *J*=7.3 Hz), 1.29–1.45 (7H, br m), 1.51–1.58 (1H, m), 1.68–1.72 (1H, m), 2.30 (1H, q-like, *J*=11.1 Hz), 3.67 (3H, s), 4.16 (2H, q, *J*=7.3 Hz), 4.18 (1H, br), 5.03–5.07 (2H, m), 5.59–5.66 (1H, m), 5.79–5.87 (1H, m), 6.77 (1H, dd, *J*=15.8, 6.9 Hz); ^{13}C NMR (125 MHz) δ 11.20 (q), 13.80 (q), 14.15 (q), 19.76 (t), 29.70 (t), 32.23 (t), 41.17 (t), 41.51 (d), 41.82 (d), 52.69 (q), 55.37 (d), 58.29 (d), 60.35 (t), 116.19 (t), 122.33 (d), 139.72 (d), 147.09 (d), 157.17 (s), 166.42 (s); MS: 337 (M^+), 294 (100); HRMS: Calcd for $C_{19}H_{31}NO_4$, 337.2253. Found 337.2231; $[\alpha]_D^{26}=-42.1$ (*c* 1.08, $CHCl_3$).

4.1.22. Methyl (2*R*,3*S*,5*R*,6*S*)-(−)-3,5-diethyl-2-(3-hydroxypropyl)-6-propylpiperidine-1-carboxylate. To a solution of **16** (200 mg, 0.59 mmol) in EtOAc (10 mL) was added 5% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 72 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above in THF (8 mL) was added a solution of Super-Hydride (1 M in THF, 1.3 mL, 1.3 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=30:1–8:1) to give an alcohol (157 mg, 89%) as a colorless oil.

IR (neat) 3448, 2957, 2872, 1674 cm^{-1}; ^1H NMR (500 MHz) δ 0.63 (1H, q-like, *J*=11.1 Hz), 0.86–0.89 (9H, m), 1.18–1.66 (15H, br m), 2.60 (1H, br), 3.59–3.65 (2H, br), 3.63 (3H, s), 3.76 (1H, br), 3.92 (1H, br); ^{13}C NMR (125 MHz) δ 11.46 (q), 14.02 (q), 20.09 (t), 28.45 (t), 28.82

(t), 29.73 (t), 30.60 (t), 34.41 (t), 40.46 (t), 42.12 (d), 52.43 (q), 55.23 (d), 56.74 (d), 62.70 (t), 158.40 (s); MS: 299 (M^+), 256 (100); HRMS: Calcd for $C_{17}H_{33}NO_3$, 299.2460. Found 299.2459; $[\alpha]_D^{26}=-7.2$ (*c* 3.00, $CHCl_3$).

4.1.23. Methyl (2*R*,3*S*,5*R*,6*S*)-(+)-3,5-diethyl-2-(3-methoxymethoxypropyl)-6-propylpiperidine-1-carboxylate (17). To a stirred solution of the above alcohol (217 mg, 0.73 mmol) in $CHCl_3$ (5 mL) were added MOMCl (0.22 mL, 2.9 mmol) and Hünig base (0.56 mL, 3.19 mmol), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated and the residue was chromatographed on SiO_2 (15 g, hexane:acetone=30:1) to give **17** (215 mg, 86%) as a colorless oil.

IR (neat) 2955, 2873, 1693, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 0.60 (1H, q-like, *J*=8.8 Hz), 0.83–0.86 (9H, m), 1.19–1.62 (15H, br m), 3.30 (3H, br s), 3.46 (2H, br), 3.60 (3H, br s), 3.71 (1H, br), 3.91 (1H, br), 4.55 (2H, br s); ^{13}C NMR (125 MHz) δ 11.42 (q), 14.00 (q), 20.10 (t), 27.17 (t), 28.60 (t), 30.60 (t), 34.38 (t), 40.21 (t), 42.08 (d), 52.22 (q), 54.91 (q), 56.76 (d), 67.52 (t), 96.20 (t), 158.13 (s); MS: 343 (M^+), 300 (100); HRMS: Calcd for $C_{19}H_{37}NO_4$, 343.2721. Found 343.2709; $[\alpha]_D^{26}=+0.126$ (*c* 6.28, $CHCl_3$).

4.1.24. (5*S*,6*R*,8*S*,9*R*)-(+)-6,8-Diethyl-5-propyloctahydroindolizine (18). To a stirred solution of *n*-PrSLi, prepared from *n*-PrSH (0.11 mL, 1.17 mmol) and *n*-BuLi (1.6 M in hexane, 0.69 mL, 1.13 mmol) in HMPA (0.5 mL) at 0 °C for 30 min. To the reaction mixture was added a solution of **17** (40 mg, 0.17 mmol) in THF (2 mL) at 0 °C, and the resulting solution was stirred at room temperature for 48 h. The reaction was quenched with NH_3 (aq.), and the aqueous mixture was extracted with Et_2O (5 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (4 mL) was added c. HCl (3 drops), and the resulting mixture was refluxed for 1 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (5 mL×8). The organic extracts were combined, dried over K_2CO_3, and evaporated to give colorless oil, which was used directly in the next step.

Carbontetrabromide (55 mg, 0.16 mmol) and Ph_3P (46 mg, 0.17 mmol) were added to a solution of the above oil in CH_2Cl_2 (1 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture was added Et_3N (0.26 mL, 1.87 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 10 min. The solvent was evaporated, and the residue was extracted with *n*-pentane (5 mL×5). The organic extracts were combined and evaporated to give colorless solid, which was chromatographed on SiO_2 (7 g, hexane:acetone:Et_3N=50:1:5 drops) to give **18** (14 mg, 52%) as a pale yellow oil.

IR (neat) 2959, 2872, 2778, 1461, 1379, 1324, 1247, 1172, 934, 901, 733 cm^{-1}; ^1H NMR (500 MHz) δ 0.61 (1H, q-like, *J*=12 Hz), 0.89 (9H, t, *J*=7 Hz), 1.07 (2H, m), 1.20–1.80 (13H, br m), 1.93 (3H, br dt-like, *J*=13, 3.5 Hz), 3.18 (1H, br); ^{13}C NMR (75 MHz) δ 11.08 (q), 14.76 (q), 18.00 (t), 20.71 (t), 24.71 (t), 26.03 (t), 28.80 (t), 32.98 (t), 35.23 (t), 39.94 (d), 52.06 (t), 67.49 (d); MS: 223 (M^+), 190 (100); $[\alpha]_D^{26}=+60.4$ (*c* 0.25, $CHCl_3$).

DCl salt. ^1H NMR (500 MHz, D_2O) δ 0.84–0.91 (9H, m), 1.01 (1H, q-like, *J*=12.5 Hz), 1.23 (3H, m), 1.39 (1H, m), 1.55 (3H, br m), 1.65 (2H, m), 1.75 (2H, m), 1.94 (1H, quint-like, *J*=11 Hz), 2.05 (2H, dm, *J*=14 Hz), 2.33 (1H, m), 2.89 (1H, dt-like, *J*=12, 2.5 Hz), 2.93 (1H, m), 3.03 (1H, q-like, *J*=10 Hz), 3.65 (1H, td-like, *J*=10, 3 Hz); ^{13}C NMR (75 MHz, D_2O) δ 9.79 (q), 9.99 (q), 13.79 (q), 16.49 (t), 19.45 (t), 23.74 (t), 25.13 (t), 27.12 (t), 30.15 (t), 33.20 (t), 38.53 (d), 40.21 (d), 51.42 (t), 67.89 (d), 71.87 (d); $[\alpha]_D^{26}=+17.2$ (*c* 0.3, $CHCl_3$).

4.1.25. (2*S*)-2-(2-Ethylbut-3-enyloxy)tetrahydropyran (20). To a stirred solution of (2*R*)-2-(hydroxymethyl)butyl acetate (**19**, 730 mg, 5 mmol) in CH_2Cl_2 (5 mL) were added 3,4-dihydro-2*H*-pyran (0.55 mL, 6 mmol) and PPTS (251 mg, 1 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with satd $NaHCO_3$ (a), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (5 mL) was added solid K_2CO_3 (414 mg, 3 mmol) at 0 °C, and the resulting suspension was stirred at room temperature for 3 h. The reaction was quenched with 10% AcOH, and the aqueous mixture was extracted with $CHCl_3$ (10 mL×6). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of $(COCl)_2$ (0.65 mL, 7.5 mmol) in CH_2Cl_2 (7 mL) was added DMSO (1.06 mL, 15.0 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of the above oil in CH_2Cl_2 (6 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (3.1 mL, 22.5 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $MeP^+Ph_3Br^-$ (8.08 g, 20.0 mmol) in THF (20 mL) was added a solution of *n*-BuLi (1.6 M ih hexane, 12 mL, 19.0 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the solution was added a solution of the above oil in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (25 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=100:1–80:1) to give **20** (695 mg, 76% in 4 steps) as a colorless oil.

^1H NMR (500 MHz) δ 0.88 (3H, t, *J*=7.3 Hz), 1.22–1.35 (1H, m), 1.46–1.62 (5H, br m), 1.69 (1H, m), 1.80 (1H, m),

2.22 (1H, br), 3.31 (1H, m), 3.50 (1H, br), 3.68 (1H, m), 3.80 (1H, m), 4.59 (1H, br), 5.07 (2H, m), 5.63 (1H, m).

4.1.26. (2*R*,3*R*)-3-(Tetrahydropyran-2-yloxymethyl)-pentane-1,2-diol. To a stirred solution of **20** (690 mg, 3.75 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) was added AD-mix β (4 g), prepared from $(DHQD)_2PYR$ (0.5 g), $K_2OsO_4{\cdot}2H_2O$ (40.5 mg), $K_3Fe(CN)_6$ (54.7 g), and K_2CO_3 (22.9 g), at 0 °C, and the resulting suspension was stirred at 0 °C for 24 h. The reaction was quenched with Na_2SO_3 (4 g), and the reaction mixture was extracted with EtOAc (20 mL×5). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=10:1–4:1) to give a diol (654 mg, 80%) as a colorless oil.

IR (neat) 3405, 2940, 2877, 1124 cm^{-1}; ^1H NMR (500 MHz) δ 0.91–0.94 (3H, m), 1.31–1.78 (9H, br m), 2.22 and 2.28 (1H, each br), 3.46–3.65 (3H, m), 3.66–3.72 (3H, m), 3.78 (1H, br), 3.82–3.93 (2H, br m), 4.52 and 4.57 (1H, each br), 3.91 (1H, br); ^{13}C NMR (125 MHz) δ 11.60 and 11.61 (each q), 19.37 and 19.76 (each t), 21.22 and 21.43 (each t), 25.13 (t), 30.41 and 30.55 (each t), 42.13 and 42.27 (each d), 62.38 and 62.99 (each t), 65.11 (t), 67.74 and 68.15 (each t), 73.61 and 73.59 (each d), 98.88 and 99.74 (each d).

4.1.27. (2*R*,3*R*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(tetrahydropyran-2-yloxymethyl)-pentan-2-ol. To a stirred solution of the above diol (590 mg, 2.71 mmol) in CH_2Cl_2 (5 mL) were added TBDPSCl (0.8 mL, 2.98 mmol), Et_3N (0.5 mL, 3.52 mmol), and DMAP (70 mg, 0.54 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated and the redisue was chromatographed on SiO_2 (30 g, hexane:acetone=50:1–30:1) to give a silyl ether (1.21 g, 98%) as a colorless oil.

IR (neat) 3486, 3069, 2935, 2864, 1113 cm^{-1}; ^1H NMR (500 MHz) δ 0.95 and 0.96 (3H, each t, each J=7.7 Hz), 1.06 (9H, s), 1.42–1.76 (9H, br m), 3.01–3.05 (1H, m), 3.44–3.52 (2H, m), 3.72–3.95 (5H, br m), 4.52 (1H, br), 7.40–7.46 (6H, m), 7.69–7.72 (4H, m); ^{13}C NMR (125 MHz) δ 11.62 and 11.76 (each q), 19.12 and 19.14 (each t), 19.32 (s), 21.02 and 21.08 (each t), 25.24 and 25.27 (each t), 26.77 (q), 30.38 and 30.41 (each t), 41.57 (d), 61.77 and 61.82 (each t), 66.33 (t), 66.97 (t), 73.18 and 73.24 (each d), 98.55 and 99.12 (each d), 127.61 (d), 129.61 and 129.62 (each d), 133.27 and 133.28 (each s), 135.47 (d).

4.1.28. (2*S*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(tetrahydropyran-2-yloxymethyl)pentan-2-azide (21). To a stirred solution of the above silyl ether (1.49 g, 3.27 mmol) in CH_2Cl_2 (4 mL) were added MsCl (0.28 mL) and Et_3N (0.68 mL) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in DMF (10 mL) was added NaN_3 (2.1 g, 32.65 mmol), and the resulting suspension was stirred at 80 °C for 15 h. After cooling, the insoluble material was filtered, washed with CH_2Cl_2, and filtrate was evaporated to give pale yellow oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=50:1–40:1) to give **21** (1.3 g, 83%) as a colorless oil.

IR (neat) 3070, 2936, 2098, 1112, 1032 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 and 0.90 (3H, each t, each J=7.3 Hz), 1.10 (9H, s), 1.44–1.75 (9H, br m), 3.22–3.29 (1H, m), 3.44–3.52 (1H, m), 3.66–3.83 (5H, br m), 4.46 and 4.51 (1H, each br), 7.39–7.47 (6H, m), 7.70–7.74 (4H, m); ^{13}C NMR (125 MHz) δ 11.82 and 11.91 (each q), 19.06 and 19.14 (each t), 19.42 (s), 20.09 and 20.26 (each t), 25.35 and 25.38 (each t), 26.66 (q), 30.45 and 30.49 (each t), 41.26 and 41.32 (each d), 61.76 and 62.22 (each t), 65.49 and 65.55 (each d), 65.68 (t), 66.19 (t), 66.83 (t), 98.32 and 99.35 (each d), 127.70 (d), 129.70 and 129.72 (each d), 133.03 and 133.14 (each s), 135.58 and 135.60 (each d).

4.1.29. Ethyl (4*R*,5*S*)-5-azide-6-(*tert*-butyldiphenylsilyloxy)-4-ethyl-2-hexenoate (22). To a stirred solution of **21** (1.1 g, 2.29 mmol) in EtOH (5 mL) was added PPTS (115 mg, 0.46 mmol), and the reaction mixture was stirred at 60 °C for 2 h. After cooling, the reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of $(COCl)_2$ (0.3 mL, 3.43 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.5 mL, 6.86 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of the above alcohol in CH_2Cl_2 (8 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (1.4 mL, 10.29 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 100 mg, 2.52 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.5 mL, 2.52 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. To the reaction mixture was added a solution of the above aldehyde in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=80:1) to give **22** (935 mg, 88% in 3 steps) as a colorless oil.

IR (neat) 3070, 2962, 2934, 2861, 1720, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 0.84–0.92 (3H, m), 1.11 (9H, s), 1.31 (3H, t, J=6.0 Hz), 1.33–1.40 (1H, m), 1.69–1.77 (1H, m), 2.30–2.44 (1H, m), 3.36–3.40 (1H, m), 3.56–3.74 (1H, m), 3.78–3.81 (1H, m), 4.21 (2H, q, J=6.0 Hz),5.83 (1H, d, J=15.4 Hz), 6.63 (1H, dd, J=15.4, 7.7 Hz), 7.40–7.48 (6H, m), 7.69–7.73 (4H, m); ^{13}C NMR (125 MHz) δ 11.35 (q), 14.17 (q), 19.00 (s), 23.36 (t), 26.62 (q), 44.97 (d), 60.28 (t),

65.37 (t), 66.12 (d), 123.73 (d), 127.71 and 127.75 (each d), 129.78 and 129.80 (each d), 132.64 and 132.66 (each s), 135.47 and 135.50 (each d), 139.33 (d), 147.35 (d), 165.79 (s).

4.1.30. (5*R*,6*S*)-(+)-6-(*tert*-Butyldiphenylsilyloxymethyl)-5-ethylpiperidin-2-one (23). To a solution of **22** (3.88 g, 8.34 mmol) in EtOAc (100 mL) was added 10% Pd–C (800 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 4 atm for 72 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was chromatographed on SiO_2 (80 g, hexane:acetone=40:1–8:1) to give **23** (2.4 g, 73%) as a colorless oil.

IR (neat) 3402, 3206, 2933, 1666, 1108 cm^{-1}; ^1H NMR (500 MHz) δ 0.81 (3H, t, J=7.5 Hz), 1.05 (9H, s), 1.17–1.26 (2H, m), 1.66–1.70 (2H, m), 1.72–1.76 (1H, m), 2.30–2.39 (2H, m), 3.53–3.57 (1H, m), 3.58 (1H, t-like, J=9 Hz), 3.63 (1H, dd, J=9, 3 Hz), 6.20 (1H, br), 7.37–7.46 (6H, m), 7.62–7.65 (4H, m); ^{13}C NMR (125 MHz) δ 11.57 (q), 19.05 (s), 21.19 (t), 23.00 (t), 26.73 (q), 29.48 (t), 35.73 (d), 56.78 (d), 64.42 (t), 127.79 and 127.81 (each d), 129.85 and 129.88 (each d), 132.79 (s), 135.44 and 135.46 (each d), 171.89 (s); MS: 338 (M^+-57), 199 (100); HRMS: Calcd for $C_{20}H_{24}NO_2Si$ ($M^+-C_4H_9$) 338.1577. Found 338.1592; $[\alpha]_D^{26}$=+28.2 (*c* 2.94, $CHCl_3$).

4.1.31. Methyl (2*S*,3*R*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-ethyl-6-oxopiperidine-1-carboxylate. To a stirred solution of **23** (1.7 g, 4.30 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 3.0 mL, 4.80 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the reaction mixture was added $ClCO_2Me$ (0.5 mL, 6.33 mmol) at −78 °C, and the resulting mixture was warmed to 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=20:1–15:1) to give an imide (1.88 g, 97%) as a colorless oil.

IR (neat) 3069, 3049, 2957, 2883, 2860, 1774, 1719, 1108 cm^{-1}; ^1H NMR (300 MHz) δ 0.93 (3H, t, J=7.4 Hz), 1.02 (9H, s), 1.23–1.44 (2H, m), 1.81–1.88 (2H, m), 1.99–2.06 (1H, m), 2.49–2.70 (2H, m), 3.73 (1H, dd, J=11, 3.3 Hz), 3.80 (3H, s), 3.83 (1H, dd, J=11, 4.4 Hz), 4.28 (1H, br), 7.35–7.47 (6H, m), 7.61–7.68 (4H, m); ^{13}C NMR (75 MHz) δ 12.02 (q), 18.96 (s), 24.53 (t), 25.68 (t), 26.71 (q), 34.38 (t), 39.11 (d), 53.69 (q), 59.25 (d), 61.48 (t), 127.55 and 127.58 (each d), 129.62 (d), 132.08 and 132.63 (each s), 135.41 and 135.52 (each d), 154.82 (s), 171.78 (s); MS: 396 (M^+-57), 84 (100); HRMS: Calcd for $C_{22}H_{26}NO_4Si$ ($M^+-C_4H_9$) 396.1631. Found 396.1631; $[\alpha]_D^{26}$=−34.9 (*c* 3.38, $CHCl_3$).

4.1.32. Methyl (2*S*,3*R*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-ethyl-6-trifluoromethanesulfonyl-oxy-3,4-dihydro-2*H*-pyridine-1-carboxylate. To a stirred solution of hexamethyldisilazane (1.03 mL, 4.87 mmol) in THF (8 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 3.03 mL, 4.86 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To a stirred solution of the above imide (1.84 g, 4.06 mmol) in THF (10 mL) was added a solution of LiHMDS prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the above reaction mixture was added a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]5-chloropyridine (Comins' reagent) (97%, 1.96 g, 4.85 mmol) in THF (6 mL) at −78 °C, and the resulting mixture was warned to −45 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow solid, which was chromatographed on SiO_2 (40 g, hexane:acetone=50:1–40:1) to give an enol triflate (2.3 g, 97%) as a colorless oil.

IR (neat) 3070, 2959, 2933, 2887, 2860, 1733, 1684, 1213, 1111 cm^{-1}; ^1H NMR (300 MHz) δ 0.83 (3H, t, J=7.4 Hz), 1.06 (9H, s), 1.13–1.30 (2H, m), 1.60–1.81 (2H, m), 2.32 (1H, dm, J=16.4 Hz), 3.57–3.63 (1H, m), 3.71–3.78 (1H, m), 3.85 (3H, s), 4.61–4.67 (1H, m), 5.23 (1H, t, J=3.4 Hz), 7.38–7.48 (6H, m), 7.67–7.75 (4H, m); ^{13}C NMR (75 MHz) δ 11.89 (q), 19.11 (s), 25.44 (t), 26.49 (t), 26.59 (q), 37.62 (d), 53.46 (q), 59.25 (d), 58.43 (t), 59.75 (d), 105.51 (d), 127.51 and 127.56 (each d), 129.52 and 129.60 (each d), 133.09 and 133.14 (each s), 135.42 and 135.51 (each d), 138.13 (s), 153.80 (s); MS: 528 (M^+-57), 308 (100); HRMS: Calcd for $C_{23}H_{25}NO_6F_3SiS$ ($M^+-C_4H_9$) 528.1124. Found 528.1115; $[\alpha]_D^{26}$=−43.8 (*c* 5.73, $CHCl_3$).

4.1.33. Dimethyl (5*R*,6*S*)-(−)-6-(*tert*-butyldiphenylsilyloxymethyl)-5-ethyl-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylate (24). To a stirred solution of the above enol triflate (2.3 g, 3.93 mmol) in DMF (15 mL) was added $Pd(Ph_3P)_4$ (230 mg, 0.20 mmol), and the resulting mixture was stirred at room temperature under CO balloon pressure for 30 min. To the reaction mixture were added Et_3N (2.2 mL, 15.73 mmol) and MeOH (6.4 mL, 157.26 mmol), and then the reaction mixture was stirred at 70 °C under CO balloon pressure for 14 h. After cooling, the reaction mixture was diluted with H_2O (50 mL) and brine (10 mL), and the aqueous mixture was extracted with Et_2O (50 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=40:1–20:1) to give **24** (1.46 g, 75%) as a colorless oil.

IR (neat) 3048, 2955, 2882, 2859, 1919, 1650 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t, J=7.5 Hz), 1.04 (9H, s), 1.18–1.32 (2H, m), 1.66–1.72 (1H, m), 1.82–1.86 (1H, m), 2.27–2.33 (1H, m), 3.59–3.71 (2H, m), 3.74 (3H, s), 3.75 (3H, s), 4.54 (1H, br), 6.01 (1H, br), 7.36–7.45 (6H, m), 7.66–7.73 (4H, m); ^{13}C NMR (125 MHz) δ 11.80 (q), 19.14 (s), 26.02 (t), 26.55 (q), 27.43 (t), 37.51 (d), 51.89 (q), 53.04 (q), 56.29 (d), 59.14 (t), 121.34 (d), 127.43 and 127.46 (each d), 129.41 and 129.47 (each d), 133.28 (s), 133.26 (s), 135.44 and 135.47 (each d), 154.42 (s), 165.58 (s); MS: 438 (M^+-57), 68 (100); HRMS: Calcd for $C_{24}H_{28}NO_5Si$ ($M^+-C_4H_9$) 438.1736. Found 438.1741; $[\alpha]_D^{26}$=−47.1 (*c* 4.22, $CHCl_3$).

4.1.34. Dimethyl (2*R*,3*S*,5*R*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-5-ethyl-3-vinylpiperidine-1,2-dicarboxylate (25). To a stirred suspension of CuI (2.69 g,

14.14 mmol) in Et_2O (15 mL) was added a solution of vinyl lithium, (prepared from tetravinyltin (1.2 mL, 7.07 mmol) and MeLi (1.0 M in Et_2O, 28 mL, 28.0 mmol) in Et_2O (10 mL) at 0 °C for 30 min), at −78 °C, and the resulting suspension was warmed to −35 °C for 20 min. The resulting suspension was re-cooled to −78 °C, and a solution of **24** (1.4 g, 2.82 mmol) in Et_2O (8 mL) was added to the resulting suspension. The reaction mixture was warmed to −20 °C for 1 h, and the reaction was quenched with satd. NH_4Cl (aq.). The aqueous mixture was diluted with CH_2Cl_2 (100 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=50:1–30:1) to give **25** (1.41 g, 95%) as a colorless oil.

IR (neat) 3070, 2954, 2860, 1704, 1112 cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (3H, t-like, J=7 Hz), 1.05 (9H, s), 1.11–1.18 (1H, m), 1.36 (1H, quint-like, J=7.2 Hz), 1.52 (1H, d-like, J=13.7 Hz), 1.64 (1H, td, J=13.2, 4.7 Hz), 1.72–1.77 (1H, m), 3.09 (1H, br), 3.45 (3H, s), 3.63 (2H, d, J=6.8 Hz), 3.70 (3H, br s), 4.40 (1H, br), 4.98 (1H, br), 5.07–5.13 (2H, m), 5.79–5.85 (1H, m), 7.36–7.45 (6H, m), 7.68–7.69 (4H, br); ^{13}C NMR (75 MHz) δ 11.91 (q), 19.21 (s), 25.70 (t), 26.83 (q), 27.81 (t), 34.63 (d), 36.99 (d), 52.00 (q), 52.97 (q), 54.80 (d), 61.18 (t), 115.07 (t), 127.46 (d), 129.49 (d), 133.34 and 133.39 (each s), 135.42 (d), 139.15 (d), 156.91 (s), 172.52 (s); MS: 466 (M^+-57, 100); HRMS: Calcd for $C_{26}H_{32}NO_5Si$ ($M^+-C_4H_9$) 466.2050. Found 466.2035; $[\alpha]_D^{26}$=+26.6 (*c* 5.52, $CHCl_3$).

4.1.35. Methyl (2*S*,3*R*,5*S*,6*R*)-(+)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-ethyl-6-hydroxymethyl-5-vinylpiperidine-1-carboxylate (26). To a stirred solution of **25** (1.38 g, 2.64 mmol) in THF (15 mL) was added a solution of Super-Hydride (1 M in THF, 6 mL, 6.0 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×6). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=40:1–15:1) to give **26** (1.26 g, 96%) as a colorless oil.

IR (neat) 3459, 3071, 2957, 2932, 1692, 1111 cm^{-1}; ^1H NMR (500 MHz) δ 0.53 and 0.64 (3H, br), 0.90–0.99 (2H, br), 1.02 (9H, s), 1.40–1.44 (1H, br), 1.56 (1H, td, J=13.7, 4.7 Hz), 1.71–1.77 (1H, br), 2.30 and 2.41 (1H, br), 3.61–3.91 (8H, br), 4.44–4.69 (2H, br), 5.00–5.14 (2H, m), 5.83–5.90 (1H, m), 7.39–7.46 (6H, m), 7.65–7.88 (4H, m); ^{13}C NMR (75 MHz) δ 11.04 (q), 18.95 (s), 25.11 (t), 26.65 (q), 27.43 (t), 33.67 (d), 36.62 (d), 52.81 (q), 54.61 (d), 61.95 (t), 64.36 (t), 114.75 (t), 127.58 and 127.69 (each d), 129.68 and 129.78 (each d), 132.66 (s), 135.21 (d), 140.12 (d), 157.90 (s); MS: 438 (M^+-57), 407 (100); HRMS: Calcd for $C_{25}H_{32}NO_4Si$ ($M^+-C_4H_9$) 438.2101. Found 438.2099; $[\alpha]_D^{26}$=+22.7 (*c* 2.37, $CHCl_3$).

4.1.36. (5*S*,6*R*,8*R*,9*R*)-(−)-5-(*tert*-Butyldiphenylsilyloxymethyl)-6-ethyl-8-vinyl-hexahydrooxazolo[3,4-*a*]pyridin-3-one (27). To a stirred solution of **26** (50 mg, 0.10 mmol) in THF (0.5 mL) was added NaH (60%, 4.8 mg, 0.12 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with 10% AcOH, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=40:1–25:1) to give **27** (44 mg, 94%) as a colorless oil.

IR (neat) 3070, 2958, 2933, 1753, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (3H, t, J=7.4 Hz), 1.09 (9H, s), 1.25–1.32 (1H, m), 1.41 (1H, ddd, J=15, 12, 5 Hz), 1.49–1.57 (1H, m), 2.01–2.05 (2H, m), 2.27 (1H, ddd, J=12, 10, 5 Hz), 3.35 (1H, ddd, J=10.5, 8.5, 5 Hz), 3.42 (1H, ddd, J=8.5, 5.5, 3 Hz), 3.94 (1H, dd, J=8.5, 5 Hz), 4.25 (1H, t, J=8.5 Hz), 4.32 (1H, dd, J=10.5, 8.5 Hz), 4.35 (1H, dd, J=10.5, 5.5 Hz), 5.05–5.16 (2H, m), 5.48–5.55 (1H, m), 7.37–7.45 (6H, m), 7.65–7.73 (4H, m); ^{13}C NMR (75 MHz) δ 11.89 (q), 18.25 (t), 19.34 (s), 26.99 (q), 32.81 (t), 35.42 (d), 40.53 (d), 59.77 (d), 60.11 (d), 60.42 (t), 66.44 (t), 117.09 (t), 127.55 (d), 129.55 (d), 133.35 and 133.42 (each s), 135.41 and 135.44 (each d), 137.46 (d), 156.38 (s); MS: 406 (M^+-57, 100); HRMS: Calcd for $C_{24}H_{28}NO_3Si$ ($M^+-C_4H_9$) 406.1839. Found 406.1841; $[\alpha]_D^{26}$=−32.8 (*c* 2.03, $CHCl_3$).

4.1.37. Methyl (2*S*,3*R*,5*S*,6*R*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,5-diethyl-6-(2-ethoxycarbonylvinyl)-piperidine-1-carboxylate. To a stirred solution of $(COCl)_2$ (0.26 mL, 3.03 mmol) in CH_2Cl_2 (8 mL) was added DMSO (0.43 mL, 6.06 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **26** (1.0 g, 2.02 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (1.26 mL, 9.09 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 90 mg, 2.22 mmol) in THF (10 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.44 mL, 2.22 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. To the reaction mixture was added a solution of the above oil in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (30 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=80:1–40:1) to give an α,β-unsaturated ester (1.05 g, 92%) as a colorless oil.

IR (neat) 3070, 2957, 2932, 1703, 1111 cm^{-1}; ^1H NMR (500 MHz) δ 0.62 (3H, br t-like, J=7 Hz), 0.95 (2H, quint-like, J=7.5 Hz), 1.07 (9H, s), 1.20 (3H, t, J=7.5 Hz), 1.44 (1H, d-like, J=14 Hz), 1.60 (1H, td, J=13, 4.7 Hz), 1.76 (1H, br), 2.71 (1H, br), 3.49 (1H, dd, J=11, 5.2 Hz), 3.64–3.76 (5H, br m), 4.10–4.24 (2H, m), 4.40–4.65 (1H, br), 5.09–5.28 (2H, m), 5.88–5.94 (1H, m), 6.16 (1H, d-like, J=16 Hz), 7.26 (1H, d-like, J=16 Hz), 7.36–7.45 (6H, m), 7.67–7.81 (4H, m); ^{13}C NMR (75 MHz) δ 11.30 (q), 14.27

(q), 19.01 (s), 25.29 (t), 26.71 (q), 27.46 (t), 33.70 (d), 39.16 (d), 52.81 (q), 53.41 (d), 54.32 (d), 60.16 (t), 60.37 (t), 115.15 (t), 121.36 (d), 129.42 and 129.50 (each d), 133.35 (s), 135.38 (d), 139.62 (d), 149.26 (d), 157.15 (s), 166.12 (s); MS: 506 (M^+-57), 69 (100); HRMS: Calcd for $C_{29}H_{36}NO_5Si$ ($M^+-C_4H_9$) 506.2363. Found 506.2363; $[\alpha]_D^{26}=-10.8$ (*c* 4.43, $CHCl_3$).

4.1.38. Methyl (2*S*,3*R*,5*R*,6*S*)-(+)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,5-diethyl-6-(3-hydroxypropyl)piperidine-1-carboxylate (28). To a solution of the above α,β-unsaturated ester (1.0 g, 1.78 mmol) in EtOAc (30 mL) was added 5% Pd–C (100 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 72 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above in THF (12 mL) was added a solution of Super-Hydride (1 M in THF, 4.0 mL, 4.0 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=40:1–12:1) to give **28** (913 mg, 98%) as a colorless oil.

IR (neat) 3448, 2998, 2962, 2839, 1738, 1240 cm^{-1}; ^1H NMR (500 MHz) δ 0.76–0.95 (6H, m), 1.04 (9H, s), 1.15–1.86 (11H, br m), 1.98–2.23 (1H, br), 2.72 (1H, br), 3.58–3.71 (4H, br m), 3.62 (3H, s), 3.91–4.08 (1H, br), 4.41–4.45 (1H, br), 7.39–7.41 (6H, m), 7.63–7.69 (4H, m); ^{13}C NMR (75 MHz) δ 11.89 (q), 12.38 and 12.54 (each q), 19.16 (s), 22.67 (t), 25.53 (t), 25.71 (t), 26.78 (q), 29.53 (t), 31.16 (t), 33.51 (d), 33.67 (d), 52.59 (q), 53.54 (d), 54.74 (d), 59.25 (t), 61.99 (t), 127.50 and 127.56 (each d), 129.49 and 129.58 (each d), 133.21 and 133.35 (each s), 135.33 and 135.41 (each d), 158.23 (s); MS: 468 (M^+-57), 256 (100); HRMS: Calcd for $C_{27}H_{38}NO_4Si$ ($M^+-C_4H_9$) 468.2570. Found 468.2568; $[\alpha]_D^{26}=+10.6$ (*c* 1.57, $CHCl_3$).

4.1.39. Methyl (2*S*,3*R*,5*R*,6*S*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,5-diethyl-6-(3-methoxymethoxypropyl)piperidine-1-carboxylate. To a stirred soultion of **28** (913 mg, 1.74 mmol) in $CHCl_3$ (12 mL) were added MOMCl (0.52 mL, 6.96 mmol) and Hünig base (1.4 mL, 7.66 mmol), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated and the residue was chromatographed on SiO_2 (25 g, hexane:acetone=40:1) to a MOM ether (878 mg, 89%) as a colorless oil.

IR (neat) 2932, 1692, 1111 cm^{-1}; ^1H NMR (500 MHz) δ 0.73 and 0.79 (3H, each t, each *J*=7.3 Hz), 0.90 (3H, t-like, *J*=7.3 Hz), 1.02 (9H, s), 1.14–1.77 (12H, br m), 3.30 (3H, s), 3.41–3.45 (1H, m), 3.49–3.58 (1H, m), 3.64 (3H, s), 3.61–3.69 (2H, m), 3.93 and 4.12 (1H, m), 4.42 and 4.68 (1H, m), 4.57 (2H, s), 7.37–7.44 (6H, m), 7.67–7.78 (4H, m); ^{13}C NMR (75 MHz) δ 11.70 and 11.86 (each q), 12.36 and 12.48 (each q), 19.09 (s), 25.47 (t), 25.66 (t), 26.70 (q), 27.81 (t), 31.81 (t), 33.41 and 33.77 (each d), 37.59 and 38.01 (each d), 52.39 (q), 54.38 (d), 54.75 (d), 54.98 (q), 62.12 (t), 67.70 (t), 96.27 (t), 127.43 and 127.48 (each d), 129.41 (d), 133.27 and 133.37 (each s), 135.28 and 135.33 (each d), 157.53 (s); MS: 512 (M^+-57, 100); HRMS: Calcd for $C_{29}H_{42}NO_5Si$ ($M^+-C_4H_9$) 512.2832. Found 512.2829; $[\alpha]_D^{26}=-0.98$ (*c* 3.37, $CHCl_3$).

4.1.40. Methyl (2*S*,3*R*,5*R*,6*S*)-(+)-3,5-diethyl-2-hydroxymethyl-6-(3-methoxymethoxypropyl)-piperidine-1-carboxylate (29). To a stirred solution of the above MOM ether (240 mg, 0.42 mmol) in THF (8 mL) was added a solution of TBAF (1 M in THF, 1.5 mL, 1.5 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1–6:1) to give **29** (110 mg, 79%) as a colorless oil.

IR (neat) 3461, 2955, 2878, 1680, 1114, 1042 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (3H, t-like, *J*=7.3 Hz), 0.90 (3H, t, *J*=7.2 Hz), 1.12 (1H, m), 1.22–1.38 (2H, m), 11.40–1.59 (3H, m), 1.61–1.72 (5H, m), 2.17 (1H, br), 2.46 (1H, br), 3.32 (3H, s), 3.50 (2H, m), 3.57–3.66 (1H, m), 3.67 (3H, s), 3.69–3.76 (1H, br), 3.93–4.14 (1H, br), 4.31–4.46 (1H, br), 4.58 (2H, s); ^{13}C NMR (75 MHz) δ 11.93 (q), 12.30 (q), 25.29 (t), 25.50 (t), 27.43 (t), 32.15 (t), 33.28 (d), 37.94 (d), 52.84 (q), 54.43 (d), 55.11 (q), 55.21 (d), 62.12 (t), 67.47 (t), 96.25 (t), 159.39 (s); MS: 330 (M^+-1), 300 (100); HRMS: Calcd for $C_{17}H_{32}NO_5$ (M^+-H) 330.2279. Found 330.2291; $[\alpha]_D^{26}=+3.6$ (*c* 4.85, $CHCl_3$).

4.1.41. Methyl (2*S*,3*R*,5*R*,6*S*)-(+)-3,5-diethyl-2-(3-methoxymethoxypropyl)-6-propenylpiperidine-1-carboxylate. To a stirred solution of $(COCl)_2$ (0.12 mL, 1.41 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.2 mL, 2.82 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **29** (311 mg, 0.94 mmol) in CH_2Cl_2 (4 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.58 mL, 4.23 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $EtP^+Ph_3Br^-$ (1.7 g, 4.70 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M ih hexane, 2.6 mL, 4.22 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the solution was added a solution of the above oil in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=100:1–30:1) to give an olefin (266 mg, 83% in 2 steps) as a colorless oil.

IR (neat) 2929, 1693 cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (3H, t, *J*=7.3 Hz), 0.86 (3H, m), 1.01–1.08 (1H, m), 1.09–1.15 (1H, m), 1.22–1.74 (12H, br m), 1.77 (1H, d-like,

J=6 Hz), 3.31 (3H, s), 3.44–3.48 (2H, br), 3.63 and 3.66 (3H, each s), 3.94 and 4.27 (1H, each br), 4.56 (2H, s), 4.93 and 5.11 (1H, each br), 5.48 (1H, q-like, J=9.4 Hz), 5.54 (1H, br); ^{13}C NMR (75 MHz) δ 11.44 (q), 12.38 (q), 13.19 and 13.63 (each q), 25.37 and 25.42 (each t), 25.76 (t), 26.99 and 27.20 (each t), 32.60 (t), 34.14 (d), 38.07 and 38.65 (each d), 49.96 (d), 52.38 (q), 54.15 (d), 55.01 (q), 67.54 (t), 96.17 (t), 126.28 and 126.51 (each d), 127.37 and 128.42 (each d), 156.83 (s); MS: 341 (M^+), 239 (100); HRMS: Calcd for $C_{19}H_{35}NO_4$ 341.2564. Found 341.2583; $[\alpha]_D^{26}$=+34.7 (c 1.50, $CHCl_3$).

4.1.42. (5*R*,6*R*,8*R*,9*S*)-(−)-6,8-Diethyl-5-propyloctahydroindolizine (30). To a solution of the above olefin (120 mg, 0.35 mmol) in EtOAc (12 mL) was added 5% Pd–C (100 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 84 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of *n*-PrSLi, prepared from *n*-PrSH (0.32 mL, 3.50 mmol) and *n*-BuLi (1.6 M in hexane, 2.1 mL, 3.33 mmol) in HMPA (3 mL) at 0 °C for 30 min. To the reaction mixture was added a solution of the above oil in THF (3 mL) at 0 °C, and the resulting solution was stirred at room temperature for 60 h. The reaction was quenched with NH_3 (aq.), and the aqueous mixture was extracted with Et_2O (10 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (10 mL) was added c. HCl (8 drops), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 mL×8). The organic extracts were combined, dried over K_2CO_3, and evaporated to give colorless oil, which was used directly in the next step.

Carbontetrabromide (163 mg, 0.49 mmol) and Ph_3P (138 mg, 0.53 mmol) were added to a solution of the above oil in CH_2Cl_2 (6 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture was added Et_3N (0.77 mL, 5.60 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min. The solvent was evaporated, and the residue was extracted with *n*-pentane (10 mL×5). The organic extracts were combined and evaporated to give colorless solid, which was chromatographed on SiO_2 (15 g, hexane:acetone:Et_3N=50:1:5 drops) to give **30** (40 mg, 51%) as a pale yellow oil.

IR (neat) 2958, 2874, 2776, 1460, 1378, 1316, 1180, 1112, 928, 888 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, t, J=7.5 Hz), 0.87 (3H, t, J=7.5 Hz), 0.91 (3H, t, J=7 Hz), 0.97–1.06 (1H, m), 1.13–1.21 (1H, m), 1.21–1.52 (11H, br m), 1.55–1.62 (1H, m), 1.70–1.77 (1H, m), 1.86 (1H, q, J=9 Hz), 1.86–1.92 (1H, m), 1.94 (1H, dt, J=13, 3 Hz), 1.95–1.99 (1H, m), 3.12 (1H, td, J=8, 2 Hz); ^{13}C NMR (75 MHz) δ 11.23 (q), 12.56 (q), 14.68 (q), 18.45 (t), 19.17 (t), 20.49 (t), 26.00 (t), 29.29 (t), 32.49 (t), 33.51 (t), 37.28 (d), 37.86 (d), 52.13 (t), 66.82 (d), 71.34 (d); MS: 223 (M^+, 100); $[\alpha]_D^{26}$=−100.9 (c 1.76, $CHCl_3$).

DCl salt. ^{1}H NMR (500 MHz, D_2O) δ 0.83–0.89 (9H, m), 1.10–1.23 (4H, m), 1.32–1.39 (1H, m), 1.42–1.51 (2H, br m), 1.53–1.62 (3H, m), 1.66–1.74 (1H, m), 1.85–2.01 (3H, m), 2.07 (1H, dm, J=13.5 Hz), 2.27–2.34 (1H, m), 2.85 (1H, td-like, J=11, 6 Hz), 2.94 (1H, q-like, J=10 Hz), 3.14 (1H, dm, J=11 Hz), 3.58 (1H, tm, J=10 Hz); ^{13}C NMR (75 MHz, D_2O) δ 9.47 (q), 11.10 (q), 12.77 (q), 16.57 (t), 17.35 (t), 18.27 (t), 24.06 (t), 26.39 (t), 29.43 (t), 29.48 (t), 34.92 (d), 35.00 (d), 51.08 (t), 66.13 (d), 71.82 (d); $[\alpha]_D^{26}$=−40.9 (c 0.25, $CHCl_3$).

4.1.43. Methyl (5*S*,6*R*,8*R*,9*R*)-(−)-(6,8-dimethyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)acetate (31). To a stirred solution of **15** (211 mg, 0.93 mmol) in MeOH (3 mL) and H_2O (1 mL) was added LiOH·H_2O (84 mg, 1.99 mmol), and the resulting solution was refluxed for 2 h. After cooling, the MeOH was evaporated, and the aqueous residue was acidified with 10% HCl and saturated with NaCl. The aqueous layer was extracted with EtOAc (10 mL×7), and the organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (8 mL) were added $ClCO_2Et$ (0.15 mL, 1.56 mmol) and Et_3N (0.23 mL, 1.66 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The insoluble material was filtered off, and the filtrate was evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in Et_2O (15 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the resulting mixture was stirred at room temperature for 19 h. The solvent was evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (10 mL) were added $PhCO_2Ag$ (48 mg, 0.21 mmol) and Et_3N (0.3 mL, 2.17 mmol) at 0 °C, and the resulting suspension was stirred in the dark at room temperature for 27 h. The insoluble material was filtered, and the filtrate was evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=14:1) to give **31** (160 mg, 71% in 4 steps) as a colorless oil.

IR (neat) 2960, 2923, 1750 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.85 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=7.3 Hz), 1.42–1.53 (2H, m), 1.64–1.70 (1H, m), 1.84–1.89 (1H, m), 2.53 (1H, dd, J=14.5, 7.7 Hz), 2.61 (1H, dd, J=14.5, 8.2 Hz), 3.28–3.34 (1H, m), 3.66 (3H, s), 3.95 (1H, dd, J=8.5, 6.4 Hz), 4.09 (1H, t-like, J=7.9 Hz), 4.41 (1H, t-like, J=8.5 Hz); ^{13}C NMR (125 MHz) δ 17.25 (q), 18.56 (q), 29.95 (d), 30.85 (d), 33.46 (t), 36.15 (t), 51.70 (d), 51.94 (q), 56.32 (d), 67.34 (t), 157.16 (s), 170.96 (s); MS: 241 (M^+), 197 (100); HRMS: Calcd for $C_{12}H_{19}NO_4$ 241.1314. Found 241.1312; $[\alpha]_D^{26}$=−37.7 (c 1.01, $CHCl_3$).

4.1.44. (5*S*,6*R*,8*R*,9*R*)-(−)-2-(6,8-Dimethyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)-*N*-methoxy-*N*-methylacetamide (32). To a stirred solution of **31** (267 mg, 1.11 mmol) in MeOH (3 mL) and H_2O (1 mL) was added LiOH·H_2O (94 mg, 2.22 mmol), and the resulting solution was refluxed for 1 h. After cooling, the MeOH was

evaporated, and the aqueous residue was acidified with 10% HCl and saturated with NaCl. The aqueous layer was extracted with EtOAc (10 mL×8), and the organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (5 mL) was added 1,1′-carbonyldiimidazole (234 mg, 1.44 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 30 min. To the reaction mixture were added Me(MeO)NH·HCl (141 mg, 1.44 mmol) and Et_3N (0.2 mL, 1.44 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h. The solvent was evaporated and the rsidue was chromatographed on SiO_2 (15 g, hexane:acetone=10:1–4:1) to give **32** (292 mg, 98%) as a colorless oil.

IR (neat) 2961, 2926, 1746, 1656, 1416 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (3H, d, J=6.4 Hz), 1.09 (3H, d, J=7.3 Hz), 1.49–1.50 (2H, m), 1.64–1.68 (1H, m), 1.93–1.95 (1H, m), 2.62 (1H, dd, J=13.7, 7.6 Hz), 2.73 (1H, dd, J=13.7, 7.7 Hz), 3.15 (3H, s), 3.39 (1H, q-like, J=8.1 Hz), 3.72 (3H, s), 3.92 (1H, t-like, J=7.3 Hz), 4.10 (1H, t-like, J=7.2 Hz), 4.42 (1H, t-like, J=7.3 Hz; ^{13}C NMR (125 MHz) δ 17.26 (q), 18.65 (q), 30.07 (d), 30.74 (d), 32.14 (q), 33.56 (t), 34.31 (t), 51.36 (d), 56.60 (d), 61.41 (d), 67.52 (t), 157.27 (s), 171.23 (s); MS: 270 (M^+), HRMS: Calcd for $C_{13}H_{22}N_2O_4$ 270.1578. Found 270.1563; $[\alpha]_D^{26}$=−53.3 (c 1.28, $CHCl_3$).

4.1.45. (5*S*,6*R*,8*R*,9*R*)-(−)-6,8-Dimethyl-5-(2-oxopropyl)-hexahydrooxazolo[3,4-*a*]pyridin-3-one (33). To a stirred solution of **32** (51 mg, 0.19 mmol) in THF (2 mL) was added a solution of MeMgBr (0.9 m in THF, 0.31 mL, 0.28 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=10:1–7:1) to give **33** (31 mg, 73%) as a colorless solid (mp 53–56 °C).

IR (KBr) 2962, 1748 cm^{-1}; ^1H NMR (500 MHz) δ 0.83 (3H, d, J=6.4 Hz), 1.07 (3H, d, J=7.3 Hz), 1.40–1.50 (2H, m), 1.62–1.69 (1H, m), 1.82–1.84 (1H, br), 2.13 (3H, s), 2.63 (1H, dd, J=15.4, 7.6 Hz), 2.68 (1H, dd, J=15.4, 7.7 Hz), 3.23–3.28 (1H, m), 3.95 (1H, dd, J=8.5, 6.4 Hz), 4.12 (1H, t-like, J=7.7 Hz), 4.36 (1H, dd, J=8.5, 6.4 Hz); ^{13}C NMR (125 MHz) δ 17.22 (q), 18.52 (q), 29.68 (q), 29.77 (d), 30.86 (d), 33.40 (t), 45.30 (t), 50.99 (d), 56.41 (d), 67.25 (t), 157.24 (s), 206.19 (s); MS: 225 (M^+), 182 (100); HRMS: Calcd for $C_{12}H_{19}NO_3$ 225.1364. Found 225.1364; $[\alpha]_D^{26}$=−13.9 (c 1.48, $CHCl_3$).

4.1.46. (5*S*,6*R*,8*R*,9*R*)-(−)-6,8-Dimethyl-5-(2-methyl-[1,3]dioxolan-2-ylmethyl)hexahydrooxazolo[3,4-*a*]pyridin-3-one. To a stirred solution of **33** (161 mg, 0.72 mmol) in benzene (15 mL) were added p-TsOH·H_2O (30 mg, 0.16 mmol) and ethyleneglycol (0.3 mL, 5.39 mmol), and the reaction mixture was refluxed using Dean–Stark apparatus for 18 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.) and the organic layer was separated. The aqueous layer was extracted with benzene (10 mL×3), and the organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=10:1–7:1) to give an acetal (166 mg, 86%) as a colorless solid (mp 82–84 °C).

IR (KBr) 2961, 2922, 1740, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=7.3 Hz), 1.33 (3H, s), 1.45–1.47 (2H, m), 1.63–1.69 (1H, m), 1.76 (1H, dd, J=14.5, 4.7 Hz), 1.83–1.88 (1H, m), 2.06 (1H, dd, J=14.5, 9 Hz), 3.28–3.33 (1H, m), 3.87–3.99 (6H, m), 4.36 (1H, t-like, J=8.5 Hz); ^{13}C NMR (125 MHz) δ 17.35 (q), 18.34 (q), 23.76 (q), 30.16 (d), 32.20 (d), 33.75 (t), 39.65 (t), 50.72 (d), 56.25 (d), 64.26 (t), 66.91 (t), 109.03 (s), 157.09 (s); MS: 269 (M^+), 254 (100); HRMS: Calcd for $C_{14}H_{23}NO_4$ 269.1627. Found 269.1641. Anal. Calcd for C14H23NO4 C, 62.43; H, 8.61; N, 5.20. Found C, 62.59; H, 8.67; N, 5.14; $[\alpha]_D^{26}$=−20.4 (c 1.59, $CHCl_3$).

4.1.47. 2-Methyl-2-propyl (2*R*,3*R*,5*R*,6*S*)-(+)-2-hydroxymethyl-3,5-dimethyl-6-(2-methyl-[1,3]dioxolan-2-ylmethyl)piperidine-1-carboxylate (34). A solution of 2 M KOH in i-PrOH (50 mL) was added to the above acetal (1.9 g, 7.06 mmol), and the resulting mixture was heated at 120 °C in the sealed tube for 2 days. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. The aqueous mixture was extracted with $CHCl_3$ (20 mL×10), and the organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in H_2O (24 mL) and dioxane (48 mL) were added NaOH (950 mg, 23.75 mmol) and Boc_2O (4.8 g, 21.99 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 18 h. The aqueous layer was extracted with $CHCl_3$ (10 mL×5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=20:1) to give **34** (1.8 g, 74% in 2 steps) as a colorless oil.

IR (neat) 3425, 2963, 2928, 1669 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (3H, d, J=6.4 Hz), 0.98 (3H, d, J=6.8 Hz), 1.33 (3H, s), 1.38–1.42 (2H, br), 1.44 (9H, s), 1.72 (1H, br), 1.76 (1H, dd, J=14.5, 4.1 Hz), 2.00–2.16 (2H, br), 2.83 (1H, br), 3.89 (2H, br), 3.92 (4H, m), 4.19 (1H, br), 5.29 (1H, br); ^{13}C NMR (125 MHz) δ 18.34 (q), 18.95 (q), 23.88 (q), 26.58 (d), 28.37 (q), 33.42 (d), 36.36 (t), 41.79 (t), 55.75 (d), 60.60 (t), 61.31 (d), 64.31 (t), 64.51 (t), 79.92 (s), 109.53 (s), 157.60 (s); MS: 343 (M^+), 212 (100); HRMS: Calcd for $C_{18}H_{33}NO_5$ 343.2357. Found 343.2345; $[\alpha]_D^{26}$=+22.8 (c 9.84, $CHCl_3$).

4.1.48. (2*R*,3*R*,5*R*,6*S*)-(+)-2-Methyl-2-propyl 2(2-ethoxycarbonylvinyl)-3,5-dimethyl-6-(2-methyl-[1,3]-dioxolan-2-ylmethyl)piperidine-1-carboxylate (35). To a stirred solution of $(COCl)_2$ (0.7 mL, 8.06 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1.2 mL, 17.0 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **12** (1.8 g, 5.25 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine

(3.3 mL, 23.92 mmol) was added to the reaction mixture at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 330 mg, 8.05 mmol) in THF (20 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (1.6 mL, 7.87 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To the mixture was added a solution of the above aldehyde in THF (9 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=20:1) to give **35** (2.16 g, 73% in 2 steps) as a colorless oil.

IR (neat) 2972, 2929, 2881, 1716, 1690 cm^{-1}; ^1H NMR (500 MHz) δ 0.81 (3H, d, J=6.4 Hz), 0.98 (3H, d, J=6.8 Hz), 1.26 (3H, t, J=7.2 Hz), 1.33 (3H, s), 1.35–1.42 (1H, m), 1.40 (9H, s), 1.80–1.86 (4H, m), 2.14–2.18 (1H, m), 3.46 (1H, t-like, J=8.5 Hz), 3.88–3.95 (5H, m), 4.18 (2H, q, J=7.2 Hz), 5.80 (1H, d, J=15.8 Hz), 7.10 (1H, dd, J=15.8, 7.7 Hz); ^{13}C NMR (125 MHz) δ 14.18 (q), 18.67 (q), 18.85 (q), 23.82 (q), 28.28 (q), 29.28 (d), 31.70 (d), 35.36 (t), 39.46 (t), 55.18 (d), 60.06 (t), 64.24 (t), 64.34 (t), 79.87 (s), 109.32 (s), 120.12 (d), 148.59 (d), 155.75 (s), 166.58 (s); MS: 411 (M^+), 253 (100); HRMS: Calcd for $C_{22}H_{37}NO_6$ 411.2619. Found 411.2932; $[\alpha]_D^{26}$=+37.0 (*c* 1.39, $CHCl_3$).

4.1.49. (2a*S*,5a*S*,6*R*,8*R*,8a*S*)-(+)-6,8-Dimethyldecahydropyrrolo[2,1,5-de]quinolizin-4-one (14) and its acetal (36). To a stirred solution of **35** (165 mg, 0.40 mmol) in EtOAc (20 mL) was added 10% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 45 h. The catalyst was removed by filtration and the filtrate was evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (2 mL) was added a solution of DIBAL (0.93 M in hexane, 0.43 mL, 0.4 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. The reaction was quenched with MeOH (1 mL) and satd. Rochelle solution in H_2O (1 mL). The organic layer was seperated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in benzene (24 mL) and acetone (4 mL) was added p-TsOH·H_2O (228 mg, 1.2 mmol), and the reaction mixture was heated at reflux using Dean–Stark apparatus for 5 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×5), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=30:1–15:1) to give **36** (52 mg, 62% in 3 steps) as a colorless solid (mp 57–58 °C) and its acetal **37** (15 mg, 15% in 3 steps) as a pale yellow oil.

Ketone **36**. IR (KBr) 2959, 2920, 2867, 1707 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (3H, d, J=6.3 Hz), 1.18 (3H, d, J=7 Hz), 1.38–1.53 (4H, m), 1.63 (1H, m), 1.75 (1H, m), 2.02–2.08 (2H, m), 2.13–2.20 (2H, m), 2.29 (1H, dd, J=13.5, 11 Hz), 2.58 (1H, td, J=10, 6.4 Hz), 2.64 (1H, t, J=13 Hz), 3.08 (1H, dt, J=12, 2.5 Hz), 3.39 (1H, m); ^{13}C NMR (125 MHz) δ 18.74 (q), 20.42 (q), 28.88 (t), 29.00 (t), 32.13 (d), 33.23 (d), 35.68 (t), 42.67 (t), 45.14 (t), 59.59 (d), 61.05 (d), 61.55 (d), 210.34 (s); MS: 207 (M^+), 91 (100); HRMS: Calcd for $C_{13}H_{21}NO$ 207.1622. Found 207.1642; $[\alpha]_D^{26}$=+27.1 (*c* 2.29, $CHCl_3$).

Acetal **37**. IR (neat) 2951, 2921, 2878, 1152 cm^{-1}; ^1H NMR (500 MHz) δ 0.84 (3H, d, J=6.4 Hz), 1.15 (3H, d, J=7.3 Hz), 1.27–1.39 (5H, m), 1.42–1.44 (1H, m), 1.51–1.56 (2H, m), 1.68 (1H, br), 1.83 (1H, t, J=12.8 Hz), 1.94 (1H, m), 2.04 (1H, m), 2.44 (1H, m), 3.00 (1H, d-like, J=12.7 Hz), 3.26 (1H, m), 3.96 (4H, s-like); ^{13}C NMR (125 MHz) δ 18.82 (q), 20.42 (q), 28.07 (t), 28.95 (t), 32.18 (d), 32.93 (d), 34.19 (t), 36.36 (t), 36.57 (t), 57.33 (d), 57.73 (d), 58.96 (d), 63.83 (t), 64.41 (t), 109.17 (s); MS: 251 (M^+), 250 (100); HRMS: Calcd for $C_{15}H_{25}NO_2$ 251.1884. Found 251.1889; $[\alpha]_D^{26}$=−4.6 (*c* 1.48, $CHCl_3$).

Deprotection of **37** with acid. To a stirred solution of **37** (179 mg, 0.71 mmol) in acetone (20 mL) was added p-TsOH·H_2O (1 g, 5.71 mmol), and the reaction mixture was heated at reflux for 20 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1–15:1) to give **36** (118 mg, 80%) as a colorless solid, whose spectral data were identical with those of the authentic sample.

4.1.50. (2a*S*,5a*S*,6*R*,8*R*,8a*R*)-(−)-6,8-Dimethyl-2,2a,5,5a,6,7,8,8a-octahydro-1*H*-pyrrolo[2,1,5-de]-quinolizin-4-yl trifluoromethanesulfonate (38). To a stirred solution of *R*-(*R**,*R**)-(+)-bis(α-methylbenzyl)amine (110 mg, 0.49 mmol) in THF (1 mL) was added *n*-BuLi (1.6 M in hexane, 0.3 mL, 0.49 mmol) at 0 °C, and the resulting solution was stirred at 0 ° C for 30 min. To the above solution was added a solution of **36** (66 mg, 0.32 mmol) in THF (2 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the reaction mixture was added a solution of 2[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridie (Comins' reagent) (194 mg, 0.49 mmol) at −78 °C, and the reaction mixture was warmed to −40 °C for 30 min. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=150:1) to give **38** (58 mg, 54%) as a colorless oil.

IR (neat) 2947, 2926, 2875, 1283 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, d, J=6.4 Hz), 1.20 (3H, d, J=7.3 Hz), 1.34–1.46 (4H, m), 1.52 (1H, m), 1.78 (1H, m), 1.99 (2H, m), 2.10 (1H, td, J=10, 5 Hz), 2.20 (1H, m),

2.59 (1H, m), 3.11 (1H, dd, J=11, 5 Hz), 3.99 (1H, dd-like, J=7, 2.5 Hz), 5.62 (1H, t-like, J=2.5 Hz); ^{13}C NMR (125 MHz) δ 18.77 (q), 20.03 (q), 26.65 (t), 27.86 (t), 29.19 (t), 32.22 (d), 35.19 (t), 57.23 (d), 57.46 (d), 60.79 (d), 100.57 (s), 121.95 (d), 144.71 (s); MS: 339 (M^+), 69 (100); HRMS: Calcd for $C_{14}H_{20}F_3NO_3S$ 339.1115. Found 339.1137; $[\alpha]_D^{26}$=−13.8 (*c* 1.84, $CHCl_3$).

4.1.51. (2a*S*,5a*S*,6*R*,8*R*,8a*S*)-(+)-3,5-Dimethyl-7-methylenedecahydropyrrolo[2,1,5-de]quinolizine (39). To a stirred suspension of $MeP^+Ph_3Br^-$ (1.22 g, 3.01 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in hexane, 1.65 mL, 2.63 mmol) at 0 °C, and the resulting yellow suspension was stirred at 0 °C for 15 min. To the suspension was added a solution of **36** (78 mg, 0.38 mmol) in THF (2 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 21 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×4). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=100:1) to give **39** (65 mg, 84%) as a colorless oil.

IR (neat) 3070, 2954, 2927, 2791 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, d, J=6.9 Hz), 1.14 (3H, d, J=7.3 Hz), 1.34–1.38 (4H, m), 1.54 (1H, m), 1.74 (1H, br), 1.85 (1H, d, J=11.5 Hz), 1.96–2.07 (4H, m), 2.32 (1H, t, J=12.4 Hz), 2.59 (1H, q-like, J=6.9 Hz), 2.74 (1H, dm, J=12.4 Hz), 3.05 (1H, br), 4.66 (2H, br); ^{13}C NMR (125 MHz) δ 18.79 (q), 20.49 (q), 28.54 (t), 29.11 (t), 32.31 (d), 33.25 (d), 35.13 (t), 36.52 (t), 37.60 (t), 59.45 (d), 61.58 (d), 61.92 (d), 106.48 (t), 148.42 (s); MS: 205 (M^+), 150 (100); HRMS: Calcd for $C_{14}H_{23}N$ 205.1829. Found 205.1844; $[\alpha]_D^{26}$=+12.4 (*c* 3.01, $CHCl_3$).

4.1.52. (2a*S*,5a*S*,6*R*,8*R*,8a*S*)-(+)-3,5,7-Trimethyl-2,2a,3,4,5,5a,6,8a-octahydro-1*H*-pyrrolo[2,1,5-de]-quinolizidine (205B, 40). To a stirred solution of **39** (60 mg, 0.29 mmol) in benzene (6 mL) was added *p*-TsOH·H_2O (167 mg, 0.88 mmol), and the reaction mixture was heated at reflux for 24 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.), and the organic layer was separated. The aqueous layer was extracted with Et_2O (10 mL×4), the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=100:1) to give **40** (38 mg, 63%) as a pale yellow oil.

IR (neat) 2956, 2905, 2790, 1660, 1458, 1375, 1317, 1216, 1169 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, d, J=6.4 Hz), 1.19 (3H, d, J=7.3 Hz), 1.27–1.52 (6H, br m), 1.64 (3H, s), 1.72 (1H, m), 1.92 (1H, m), 2.12–2.18 (3H, m), 3.00 (1H, dd, J=11.2, 4.5 Hz), 3.80 (1H, br), 5.20 (1H, br); ^{13}C NMR (125 MHz) δ 18.83 (q), 20.19 (q), 23.56 (q), 28.35 (t), 28.38 (t), 29.22 (t), 32.44 (d), 32.55 (d), 35.42 (d), 56.49 (d), 58.04 (d), 60.46 (d), 125.52 (d), 129.52 (d); MS: 205 (M^+), 71 (100); HRMS: Calcd for $C_{14}H_{23}N$ 205.1829. Found 205.1828; $[\alpha]_D^{26}$=+8.1 (*c* 1.05, $CHCl_3$).

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22. Calculations were performed by using the B3LYP method in Gaussian98 with the 6-31+G** basis set. The desired isomer **40** is more stable than the other by 2.01 kcal/mol^{-1}.

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Synthesis of carbo- and heterobiaryls by intermolecular radical addition of aryl bromides onto aromatic solvents

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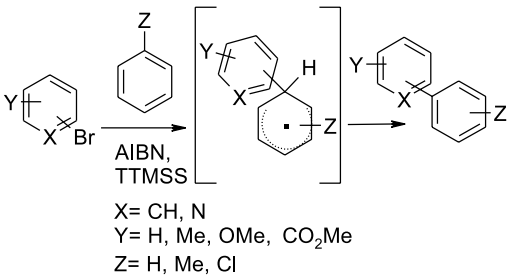
Abstract—Tris(trimethylsilyl)silane (TTMSS) and azabisisobutyronitrile (AIBN) promoted the intermolecular arylation of aryl and heteroaryl bromides onto aromatic solvents under thermal conditions via a radical pathway.

1. Introduction

Biaryls (Ar^1-Ar^2) and related systems, such as heterobiaryls and arylheterocyclic compounds have found numerous applications in several fields: as advanced materials, biologically active molecules, chelating agents or metal ligands.[1–3] Consequently, a wide variety of synthetic methods have been developed for their preparation, with palladium cross-coupling reactions currently being the most popular choice.[1,4] Additional methods reported for the preparation of biaryls include some examples involving arylation of arenes through radical mechanisms. Intramolecular radical additions, of aryl radicals to benzene[5] or heterocyclic rings,[6] under reductive conditions, followed by rearomatisation, have been reported. In this context, intramolecular arylations, by *ipso* substitution of suitable sulfonyl,[7] phosphinate,[8] silyl[9] or benzylic ether[10] derivatives, also under reductive conditions, have been widely reported for the preparation of both biaryls and arylheterocyclic derivatives. On the other hand, the intermolecular version of the radical arylation has been scarcely explored. At the start of the present project, only radical approaches based on photochemical arylation of arenes, among other oxidative conditions, have been described.[11] Our group recently reported a simple method for the preparation of aryl compounds,[12] based on thermal intermolecular radical addition of aryl or heteroaryl radicals onto benzene (Scheme 1). The process takes place under reductive conditions, using the corresponding aryl bromides as starting material and AIBN/TTMSS (azobis-isobutyronitrile/tris(trimethylsilyl)silane) as initiator for the radical process. The intermolecular radical addition of *ortho*-functionalized aryl iodides to benzene has recently been applied by Crich and Sannigrahi in an elegant approach to functionalised tetrahydrobenzofuranes.[13]



Scheme 1.

In this paper, the results on the intermolecular addition of aryl (and heteroaryl) radicals onto arenes and heteroarenes are described. During the study, scope and limitations of the process were evaluated, by varying the radical acceptor (usually the solvent) and the aryl radical donor.

2. Results and discussion

2.1. Variations on the radical acceptor

In a preceding communication[12] we reported phenylation of 2-bromopyridine **1a** (Scheme 2, Z=H; Table 1, entry 1). The best results were obtained by slow addition (8 h) of a solution of TTMSS (2 equiv.), AIBN (2 equiv.) and 2-bromopyridine (1 equiv.) in 5 mL of benzene, into an additional 10 mL of benzene (Method A), to supply 2-phenylpyridine **2a** in 41% yield. Similar results were obtained from 3-bromopyridine **1b**, which gave

Keywords: Aryl bromides; Arylation; Biaryls; Radicals and radical reaction; Tris(trimethylsilyl)silane (TTMSS).
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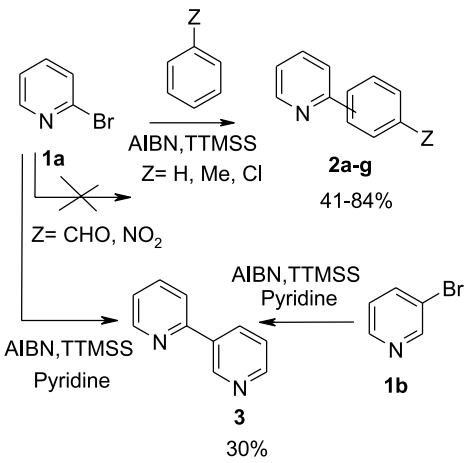
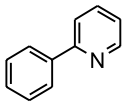
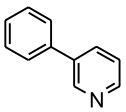
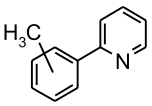
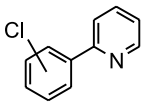
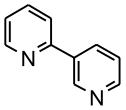
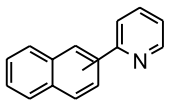
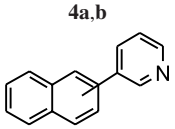


Scheme 2.

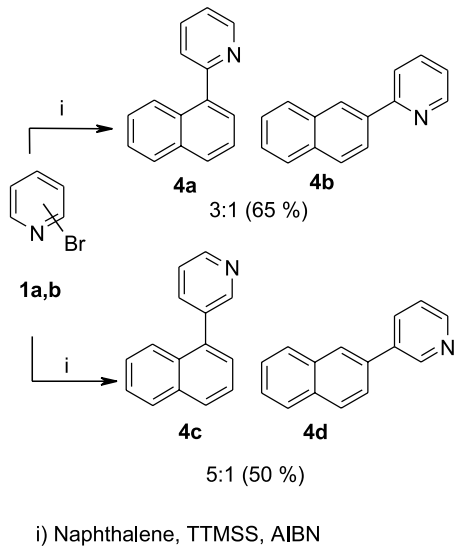
3-phenylpyridine **2b** in 74% yield (Table 1, entry 2). Attempts to extend the scope of the process were carried out using toluene (Scheme 2, Z=Me; Table 1, entry 3) and chlorobenzene (Scheme 2, Z=Cl; Table 1, entry 4) as aromatic solvents. In these cases, the best results were obtained using chlorobenzene, an electron-poor substrate, which produced a mixture of the 2-phenylpyridines (13:0:1 of the *o*/*m*/*p* isomers) with an overall yield of 84%. The use of toluene led to a mixture of the corresponding 2-tolylpyridines (2:1:1 of the *o*/*m*/*p* isomers) in 61% overall yield. As the best results were obtained using chlorobenzene, other electron-deficient solvents were also tested, such as benzaldehyde (Scheme 2, Z=CHO; Table 1, entry 5) or nitrobenzene (Scheme 2, Z=NO_2; Table 1, entry 6): but no arylated products were detected.

Pyridine, another electron-deficient substrate was also tested. Thus, when the process was carried out using 2-bromopyridine **1a** as a source of the 2-pyridyl radical, and pyridine as the solvent, 2,3′-bipyridine **3**, was isolated, in a

Table 1. Variations of the (radical acceptor) solvent

Entry	Starting material	Solvent	Biaryl comp.	Ratio	Yield (%)[a]	Method
1	**1a**	Ph-H	 **2a**	—	41	A
2	**1b**	Ph-H	 **2b**	—	74	A
3	**1a**	Ph-Me	 **2c–e**	*o*/*m*/*p* 2:1:1	61	A
4	**1a**	Ph-Cl	 **2f**,**g**	*o*/*m*/*p* 13:0:1	84	A
5	**1a**	Ph-CHO	—	—	—	A
6	**1a**	Ph-NO_2	—	—	—	A
7	**1a**	Pyr	 **3**	—	30	A
8	**1b**	Pyr	**3**	—	30	A
9	**1a**	$C_{10}H_8$	 **4a**,**b**	α:β 3:1	61	B
10	**1b**	$C_{10}H_8$	 **4c**,**d**	α:β 5:1	50	B

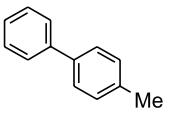
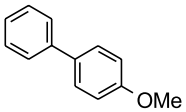
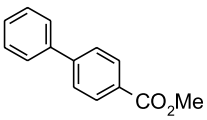
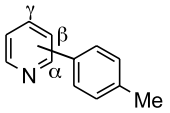
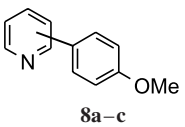
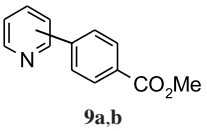
[a] Yields refer to isolated pure product. All the compounds were identified by spectroscopic and literature data. Method A: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding pyridyl bromide **1** (1 equiv.) in the solvent (5 mL) added into an additional 10 mL of the corresponding solvent during 8 h, 80 °C, 24 h. Method B: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding pyridyl bromide **1** in MeCN (5 mL) added over naphthalene (55 equiv.) during 4 h, 80 °C, 24 h.



Scheme 3.

30% yield (Scheme 2; Table 1, entry 7). Surprisingly, the same process using 3-bromopyridine **1b** as the starting material, also yielded 2,3′-bipyridine **3**, again in 30% yield, and only traces of the alternative isomeric compound (Scheme 2; Table 1, entry 8). In general, one would expect that the regioselectivity of the process mainly depends on the electrophilicity or nucleophilicity of both, radical and acceptor, as well as on polar effects and orbital control. As far as the character of attacking radicals is concerned, it is now recognized that heteroaryl species with a carbon radical adjacent to the heteroatom behave as electrophiles, with the electrophilicity interpreted in terms of the inductive effect of the ring heteroatom.[11a,b] In all examples discussed, the 2-pyridyl radical would act as an electrophile, thus attacking either substituted benzenes or pyridine when they are both acceptor and solvent. Almost all substituents stabilize radicals, and so, substituted benzenes, including toluene and chlorobenzene, usually react faster than benzene itself. Furthermore, most substituted benzenes show some preference for *ortho*/*para* attack, because attack at these sites gives the more stable intermediates.[14] Moreover, in the case of chlorobenzene, the mesomeric π-donor character of the chloro-substituent must be taken into consideration. In a

Table 2. Variations on the radical

Entry	Starting material	Biaryl compound	Ratio α:β:γ	Yield (%)[a]	Method
1	**5a**	 **6a**	—	51	A
2	**5b**	 **6b**	—	50	A
3	**5c**	 **6c**	—	52	A
4	**5a**	 **2e**,**7**	—	—	A
5	**5a**	**2e**,**7**	4:1:0	10	C
6	**5b**	 **8a**–**c**	4:1:1	30	A
7	**5b**	**8a**–**c**	10:1:4	72	C
8	**5c**	 **9a**,**b**	2:1:0	15	A
9	**5c**	**9a**–**c**	2:1:0.1	20	C

[a] Yields refer to isolated pure product. All the compounds were identified by spectroscopic and literature data. Method A: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding aryl bromide **5** (1 equiv.) in the solvent (5 mL) added into an additional 10 mL of solvent during 8 h, 80 °C, 24 h. Method C: TTMSS (2 equiv.), AIBN (2 equiv.), the corresponding pyridyl bromide **5** (1 equiv.) in pyridine (5 mL) added over additional 10 mL of pyridine and 2.5 mL of acetic acid during 8 h, 80 °C, 24 h.

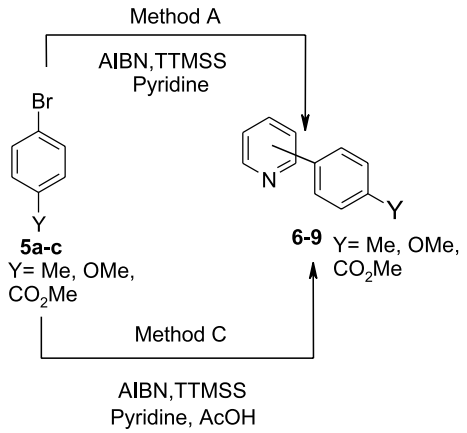
similar way, when the solvent is pyridine, the 2-pyridyl radical would behave as an electrophile, thus attacking at the 3-position, a situation in agreement with other photochemical arylations described previously.[11a] In contrast, the 3-pyridyl radical, which is comparatively nucleophilic, would attack preferentially at the 2-position of the pyridine acceptor.

Several attempts were undertaken to make the radical more π-deficient (e.g., using 2-bromopyridine-*N*-oxide instead of 2-bromopyridine) or to increase the electrophilicity of the solvent (e.g., using thiophene instead of pyridine). However, these approaches did not generate any satisfactory results.

Other aromatic solvents were also tested. Reaction of the 2-pyridyl radical, obtained from 2-bromopyridine **1a** on naphthalene, using a modified experimental method (Method B) (see Table 1 and Section 4) produced a 3:1 mixture of α/β naphthyl derivatives **4a**,**b** in 61% yield (Scheme 3; Table 1, entry 9). Similarly, 3-bromopyridine **1b**, produced a 5:1 mixture of α/β 3-(naphthyl)pyridines **4c**,**d** (Scheme 3; Table 1, entry 10). The regioselectivity of the radical attack is clearly as one would expect, considering orbital control, because of the symmetry of the system and in agreement with the regioselectivity reported for other radical arylations.[14,15]

2.2. Variations on the aryl radical

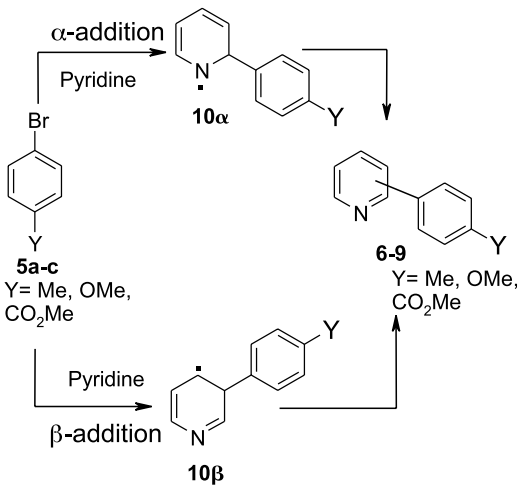
It is an axiom in radical chemistry that the π-system in an aryl radical should have little or no effect on its reactivity, since the unpaired electron would be placed on the σ-skeleton.[16,17] On this assumption, additional experiments were carried out using 4-methylphenyl, 4-methoxyphenyl, and 4-methoxycarbonylphenylbromides **5a**–**c** as sources of aryl radicals. In a previous communication[12] we reported these arylations using benzene as solvent, which yielded compounds **6a**–**c** (50–52%) essentially yielding the same results for both, heterocyclic and carbocyclic radicals. The experimental results are summarized in Table 2 (Entries 1–3) and in Section 4. The same process, but using pyridine as solvent, is outlined in Scheme 4 and Table 2. The slow addition (8 h) of a solution of TTMSS (2 equiv.), AIBN (2 equiv.) and 1-bromo-4-methyl benzene **5a** (1 equiv.) in pyridine to an additional 10 mL of pyridine at 80 °C, with the mixture kept at 80 °C for a further 16 h, did not generate any detectable biaryl (Table 2, entry 4). When the same conditions were applied to 1-bromo-4-methoxy-benzene **5b** as the starting material, biaryls **8a**–**c** were isolated in 30% yield (4:1:1 of the α:β:γ isomers) (Table 2, entry 6). The same process, when applied from 4-bromo benzoic acid methyl ester **5c**, yielded 15% of biaryls **9a**,**b** (2:1:0 of the α:β:γ isomers) (Table 2, entry 8). The experimental results seem to suggest that all radical species used in this particular type of reaction behave as relatively nucleophilic, with the ring substituents, however, exerting some effect on the reactivity of such radicals. The lack of reactivity for compound **5a** and the higher percentage of α-substitution on pyridine in the other cases could, tentatively, be explained by considering the following two classes of factors:



Scheme 4.

(a) A relatively nucleophilic radical has a higher energy SOMO and will react faster with molecules having a low-energy LUMO.[14,18,19]

(b) For unprotonated pyridines, the reactivity and selectivity on the homolytic phenylation appears to be mainly governed by the stability of the intermediate radical adduct **10**[20] (Scheme 5), with regioselectivity being α>β for both the more and the less nucleophilic radical (i.e., radicals derived from **5b** and **5c**, respectively). Since there is no radical π-stabilizing effect by aryl substituents, a relatively weak inductive effect could be exerted by the relatively π-excessive or π-deficient aryl substrate (intermediate **10α**,**β**, where Y=OMe or CO_2Me, respectively),[19] whereas the absence of such effect in **5a** should prevent the progress of the reaction.



Scheme 5.

Presumably, the radical arylation on protonated heteroaromatic bases will be more important, where the dominant SOMO/LUMO interaction may well be stronger. So in the case of unsubstituted pyridinium cation, reaction at the α- and at the γ-positions is predicted according to theory.[19,20] Bearing these factors in mind, and in accordance with the work of Minisci[20–22] and Togo,[23,24] the reaction was performed in an acidic medium. Thus, in protonated pyridines, in which polarity is strongly increased, the polar effect would play a significant role in determining both

reactivity and regioselectivity (Table 2).[20] Protonated heteroarenes are π-deficient substrates, which react with nucleophilic radicals with high regioselectivity, and the rate of radical addition correlated with nucleophilicity of the attacking radical (derived from **5a** and **5b**, entries 5 and 7, respectively), whereas the reaction with the less nucleophilic radical (derived from **5c**, entry 9) is scarcely affected with regard to reactivity and regioselectivity.

3. Conclusion

As a conclusion, a simple method of synthesis of biaryl compounds has been developed, based on the intermolecular radical addition of aryl or heteroaryl radicals onto an aromatic solvent. The method is very efficient when the aromatic solvent is benzene, but in general, occurs in low yields on other arenes. Experimental results seem to suggest that most aryl radicals, are nucleophilic to some extent, with aryl substituents modulating the reactivity through their electronic effect on the π-aryl system.

4. Experimental

4.1. General

All experiments were carried out under dry argon atmosphere. Toluene and benzene were distilled from sodium under dry argon. Chlorobenzene was distilled from calcium chloride, under dry argon. Pyridine was distilled from potassium hydroxide pellets under dry argon. Acetonitrile was distilled from phosphorus pentoxide under dry argon. Naphthalene was crystallized from ethanol. All chemicals were purchased from Aldrich Chemical company and were used without purification. ^{1}H and ^{13}C were recorded on a Varian UNITY 300 MHz or a VARIAN UNITY PLUS 500 MHz spectrometers. Mass spectra were recorded on a VG AutoSec (Micromass Instrument).

4.2. General procedure. Method A

A solution of TTMSS (498 mg, 2 mmol), AIBN (328 mg, 2 mmol), and the corresponding bromide **1a**,**b** or **5a**–**c** (1 mmol) in 5 mL of the suitable solvent, was dropwise added with a syringe pump along 8 h, to 10 mL of the same solvent, stirred at 80 °C (bath temperature). Stirring was maintained at the same temperature for 24 h, and full consumption of starting material was observed (TLC analysis). The pale yellow solution was concentrated in vacuo, providing a crude mixture that was purified using flash chromatography to yield the corresponding biaryl compound.

4.3. Method B

A solution of TTMSS (498 mg, 2 mmol), AIBN (328 mg, 2 mmol) and the corresponding bromide **1a**,**b** (1 mmol, 158 mg) in 5 mL of MeCN, was dropwise added with a syringe pump over 4 h, to 7 g (55 mmol) of naphthalene, stirred at 80 °C (bath temperature). Stirring was maintained at the same temperature for 24 h, and full consumption of **1** was observed (TLC analysis). The solution was concentrated, providing a crude mixture, which was separated by flash chromatography (silicagel, hexanes/ethyl acetate (80:20)), yielding the pure compounds.

4.4. Method C

A solution of TTMSS (498 mg, 2 mmol), AIBN (328 mg, 2 mmol), and the corresponding bromide **5a**–**c** (1 mmol) in 5 mL of pyridine, was dropwise added with a syringe pump over 8 h, to 10 mL of pyridine and 5 mL of acetic acid, stirred at 80 °C (bath temperature). Stirring was maintained at the same temperature for 24 h, then the solution was made basic with potassium carbonate and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness. The residue was purified using flash chromatography to yield the corresponding compounds **7**–**9**.

4.5. Preparation of arylpyridines 2a–g and bipyridine 3

4.5.1. 2-Phenylpyridine 2a.[25] The general procedure (Method A) using **1a** (158 mg) as bromide and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (90/10)), a colorless liquid (63.5 mg, 41%). This product was identical to an authentic sample obtained from Aldrich. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (td, 1H, J=4.7, 1.4 Hz), 8.01 (dd, 2H, J=8.4, 1.6 Hz), 7.69 (m, 2H), 7.45 (m, 3H), 7.19 (dd, 1H, J=8.8, 4.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 149.4, 139.2, 136.5, 128.8, 128.5, 126.7, 121.8, 120.3.

4.5.2. 3-Phenylpyridine 2b.[25,26] The general procedure (Method A) using **1b** as bromide (158 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (80:20)), a colorless liquid (115 mg, 74%). The product was identical to an authentic sample obtained from Aldrich. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (dd, 1H, J=2.6, 0.9 Hz), 8.57 (dd, 1H, J=4.9, 1.6 Hz), 7.85 (ddd, 1H, J=7.7, 2.6, 1.6 Hz), 7.56 (dd, 2H, J=8.2, 1.4 Hz), 7.45 (m, 3H), 7.34 (ddd, 1H, J=7.7, 4.9, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 148.2, 137.7, 136.4, 134.2, 128.9, 127.9, 127.0, 123.3.

4.5.3. 2-(2′-Methylphenyl)pyridine 2c,[27,28] **2-(3′-methylphenyl)pyridine 2d**[27,28] **and 2-(4′-methylphenyl)pyridine 2e.**[11a,27,29] The general procedure (Method A) using **1a** as bromide (158 mg) and toluene as solvent, gave a mixture of products (*o*/*m*/*p*, 2:1:1). After separation by flash chromatography (silicagel, dichloromethane/ethyl acetate (100:2.5)), pure compounds **2c**, **2d** and **2e** were obtained. Yield 61% (50.5 mg of **2c** (R_f=0.35), 27 mg of **2d** (R_f=0.41) and 25.5 mg of **2e** (R_f=0.40)). **2c** Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, 1H, J=4.8, 1.8, 1.0 Hz), 7.72 (dt, 1H, J=7.7, 1.8 Hz), 7.37 (td, 1H, J=7.7, 1.0 Hz), 7.36 (m, 1H), 7.27 (m, 3H), 7.22 (ddd, 1H, J=7.7, 4.8, 1.0 Hz), 2.34 (s, 3H). **2d** Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (ddd, 1H, J=4.8, 1.5, 1.0 Hz), 7.82 (bs, 1H), 7.73 (dt, 1H, J=8.0, 1.5 Hz), 7.70 (m, 2H), 7.34 (t, 1H, J=7.6 Hz), 7.21 (m, 1H), 7.20 (ddd, 1H, J=8.0, 4.8, 1.9 Hz) 2.42 (s, 3H). **2e** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, J=4.4 Hz), 7.86 (d, 2H, J=8.1 Hz), 7.70 (m, 2H), 7.26 (d, 2H, J=8.1 Hz), 7.20 (m,

1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 149.3, 138.6, 136.4, 136.3, 129.2, 126.5, 121.5, 120.0, 21.0.

4.5.4. 2-(2′-Chlorophenyl)pyridine 2f[27,28] and 2-(4′-chlorophenyl)pyridine 2g.[27] The general procedure (Method A) using **1a** as bromide (158 mg) and chlorobenzene as solvent, gave a mixture of products (*o*/*m*/*p*, 13:0:1). After separation by flash chromatography (silicagel, hexanes/ethyl acetate (90:10)), pure compounds **2f** and **2g** were obtained. Yield 84% (148 mg of **2f** (R_f=0.35) and 11.5 mg of **2g** (R_f=0.45)). **2f** Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (ddd, 1H, *J*=5.0, 1.7, 1.1 Hz), 7.75 (dt, 1H, *J*=8.7, 1.7 Hz), 7.63 (td, 1H, *J*=7.7, 1.1 Hz), 7.57 (m, 1H), 7.46 (m, 1H), 7.33 (m, 2H), 7.27 (ddd, 1H, *J*=7.7, 5.0, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 149.5, 139.2, 135.8, 132.1, 131.5, 130.0, 129.4, 127.0, 124.8, 122.3. **2g** Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, *J*=4.5 Hz), 7.93 (d, 2H, *J*=8.6 Hz), 7.75 (dt, 1H, *J*=7.2, 1.6 Hz), 7.69 (bd, 1H, *J*=7.2 Hz), 7.44 (d, 2H, *J*=8.6 Hz), 7.24 (ddd, 1H, *J*=7.2, 4.5, 1.6 Hz).

4.5.5. 2,3′-Bipyridinyl 3.[25,30] The general procedure (Method A) using **1a** (158 mg) as bromide and pyridine as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (30:70), R_f=0.21) 47 mg, 30% yield of bipyridine **3** as a colorless oil. Identical results were obtained from **1b** (158 mg) and only traces were detected of other isomeric bipyridines. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (dd, 1H, *J*=2.2, 0.7 Hz), 8.71 (d, 1H, *J*=4.6 Hz), 8.64 (dd, 1H, *J*=4.7, 1.7 Hz), 8.31 (ddd, 1H, *J*=8.2, 2.2, 1.7 Hz), 7.77 (m, 2H), 7.40 (ddd, 1H, *J*=8.2, 4.7, 0.7 Hz), 7.26 (ddd, 1H, *J*=7.8, 4.6, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 150.1, 149.9, 148.2, 137.1, 134.4, 123.7, 122.9, 120.7; MS (EI, 70 eV) *m*/*z* (relative intensity) 156 (M^+, 100), 155 (M^+-1, 72), 130 (22), 78 (14).

4.6. Preparation of naphthylpyridines 4a–d

4.6.1. 2-Naphthalen-1-yl-pyridine 4a[31] and 2-naphthalen-2-yl-pyridine 4b.[31] The general procedure (Method B) using **1a** (158 mg) as starting bromide gave, after flash chromatography, 61% yield (α/β 3:1) of 2-naphthalenyl-pyridines **4a**,**b**, (94 mg of **4a** (R_f=0.56) and 30 mg of **4b** (R_f=0.58). **4a**: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (dd, 1H, *J*=4.8, 1.7 Hz), 8.08 (dd, 1H, *J*=7.1, 2.9 Hz), 7.91 (d, 2H, *J*=8.1), 7.82 (dt, 1H, *J*=7.7, 1.7 Hz), 7.56 (m, 5H), 7.33 (ddd, 1H, *J*=7.7, 4.8, 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 149.7, 138.7, 136.5, 134.2, 131.4, 129.0, 128.5, 127.6, 126.6, 126.0, 125.8, 125.4, 125.2, 122.1. MS (EI, 70 eV) *m*/*z* (relative intensity) 205 (M+, 39), 204 (100), 176 (9), 126 (2). **4b**: yellow solid; mp 77–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, 1H, *J*=4.2 Hz), 8.49 (s, 1H), 8.14 (dd, 1H, *J*=8.6, 1.5 Hz), 7.90 (m, 4H), 7.80 (td, 1H, *J*=7.5, 1.8 Hz), 7.50 (m, 2H), 7.26 (dd, 1H, *J*=7.5, 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 149.7, 136.7, 133.5, 133.4, 128.6, 128.3, 127.6, 126.4, 126.2, 124.5, 122.1, 120.7; MS (EI, 70 eV) *m*/*z* (relative intensity) 205 (M^+, 100), 204 (66), 176 (16), 126 (8).

4.6.2. 3-Naphthalen-1-yl-pyridine 4c[32] and 3-naphthalen-2-yl-pyridine 4d.[31] The general procedure (Method B) using **1b** (158 mg) as starting bromide gave, after flash chromatography 50% (α/β 5:1) of 3-Naphthalenyl-pyridines **4c**,**d**, (85.5 mg of **4c** (R_f=0.35) and 17 mg of **4d** (R_f=0.23). **4c**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 1H, *J*=2.2 Hz), 8.67 (dd, 1H, *J*=4.9, 1.6 Hz), 7.92 (m, 2H), 7.82 (m, 2H), 7.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 148.4, 137.4, 136.2, 133.8, 131.5, 128.5, 128.4, 127.4, 126.5, 126.1, 125.3, 125.2, 123.1; HPLC-MS (CI) [M^++1]=206.1. **4d**: white solid, mp 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, 1H, *J*=1.6 Hz), 8.60 (dd, 1H, *J*=4.8, 1.6 Hz), 8.06 (s, 1H), 8.03 (td, 1H, *J*=8.1, 1.6 Hz), 7.90 (m, 3H), 7.71 (dd, 1H, *J*=8.5, 2.0 Hz), 7.53 (m, 2H), 7.40 (dd, 1H, *J*=8.1, 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 148.4, 135.0, 134.5, 133.5, 132.8, 128.8. 128.1, 127.6, 126.5, 126.3, 126.1, 124.9, 123.5; MS (CI, 70 eV) *m*/*z* (relative intensity) 206 (M^++1, 100), 159 (5).

4.7. Preparation of biphenyl compounds 6a–c and arylpyridines 7–9

4.7.1. 4-Methylbiphenyl 6a.[33,34] The general procedure (Method A) using **5a** as bromide (171 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (95:5)), a white solid, mp 46–47 °C (85.5 mg, 51%). ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (dd, 2H, *J*=8.3, 1.2 Hz), 7.50 (d, 2H, *J*=8.1 Hz), 7.42 (t, 2H, *J*=8.3 Hz), 7.31 (td, 1H, *J*=8.3, 1.2 Hz) 7.25 (d, 2H, *J*=8.1 Hz), 2.39 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 142.4, 139.6, 138.1, 130.4, 129.7, 127.9, 127.8, 127.7, 21.1.

4.7.2. 4-Methoxybiphenyl 6b.[33,35] The general procedure (Method A) using **5b** as bromide (187 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (95:5)), a white solid, mp 86–87 °C (92 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 4H), 7.43 (t, 2H, *J*=7.5 Hz), 7.32 (tt, 1H, *J*=7.5, 1.2 Hz) 6.99 (d, 2H, *J*=8.8 Hz), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.3.

4.7.3. Biphenyl 4-carboxylic acid methyl ester 6c.[34,36] The general procedure (Method A) using **5c** as bromide (215 mg) and benzene as solvent gave, after flash chromatography (silicagel, hexanes/ethyl acetate (95:5)), a white solid, mp 116–117 °C (110 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J*=8.4 Hz), 7.59 (d, 2H, *J*=8.4 Hz), 7.56 (dd, 2H, *J*=7.4, 1.3 Hz); 7.44 (dd, 2H, *J*=7.4, 7.2 Hz), 7.33 (tt, 1H, *J*=7.2, 1.3 Hz) 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 145.5, 139.9, 130.0, 128.8, 128.6, 128.1, 127.2, 126.9, 52.0.

4.7.4. 2-(4′-Methylphenyl)pyridine 2e[11a,27,29] and 3-(4′-methylphenyl)pyridine 7.[11a] The general procedure (Method A) using **5a** (171 mg) as starting bromide and pyridine as solvent did not generate any biaryl compound. The same process, using Method C gave, after separation by flash chromatography (silicagel, hexanes/ethyl acetate (80:20)), 10% yield of 4′-methylphenyl)pyridines (α/β/γ 4:1:0). **2e** (13.5 mg, R_f=0.80) colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, *J*=4.4 Hz), 7.86 (d, 2H, *J*=8.1 Hz), 7.70 (m, 2H), 7.26 (d, 2H, *J*=8.1 Hz), 7.20 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 149.3, 138.6, 136.4, 136.3, 129.2, 126.5, 121.5, 120.0, 21.0; MS (EI, 70 eV) *m*/*z* (relative intensity) 169 (M^+, 100), 168 (59, M^++1), 154 (9), 51 (20). **7** (4 mg, R_f=0.53) colorless

oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, 1H, J=2.3 Hz), 8.55 (dd, 1H, J=4.6, 1.5 Hz), 7.85 (ddd, 1H, J=7.81, 2.3, 1.5 Hz), 7.48 (d, 2H, J=8.2 Hz), 7.35 (m, 1H), 7.30 (d, 2H, J=8.2 Hz), 2.42 (s, 3H); MS (EI, 70 eV) m/z (relative intensity) 169 (M^+, 83), 110 (100), 80 (30).

4.7.5. 2-(4′-Methoxyphenyl)pyridine 8a,[11a,27] 3-(4′-methoxyphenyl)pyridine 8b[11a] and 4-(4′-methoxyphenyl)pyridine 8c.[37] The general procedure (Method A) using **5b** (187 mg) as starting bromide and pyridine as solvent gave, after separation by flash chromatography (silicagel, hexanes/ethyl acetate (70:30)), 30% yield of methoxyphenylpyridines **8a–c** (α/β/γ 4:1:1). The same process, using Method C gave 72% yield of methoxyphenylpyridines **8a–c** (α/β/γ 10:1:4). **8a** (37 mg from Method A or 92.5 mg from Method B) (R_f=0.80) colorless plates, mp 53–54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (dd, 1H, J=4.7, 1.8 Hz), 7.95 (d, 2H, J=7.9 Hz), 7.72 (ddd, 1H, J=8.0, 6.9, 1.8 Hz), 7.66 (dd, 1H, J=8.0, 1.5 Hz), 7.16 (ddd, 1H, J=6.9, 4.7, 1.5 Hz), 6.98 (d, 2H, J=7.9 Hz), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 156.9, 149.3, 136.7, 131.7, 128.1, 121.3, 119.9, 114.0, 55.3; MS (EI, 70 eV) m/z (relative intensity) 185 (M^+, 100), 170 (36), 142 (45), 141 (31), 84 (14). **8b** (9 mg from Method A or 9 mg from Method C) (R_f=0.35) colorless plates, mp 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H, J=1.8 Hz), 8.53 (dd, 1H, J=4.7, 1.4 Hz), 7.83 (ddd, 1H, J=8.1, 1.8, 1.4 Hz), 7.51 (d, 2H, J=8.8 Hz), 7.33 (ddd, 1H, J=8.1, 4.7, 0.7 Hz), 7.01 (d, 2H, J=8.8 Hz), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 148.0, 147.9, 136.2, 133.8, 130.2, 128.2, 123.4, 114.5, 55.3; MS (EI, 70 eV) m/z (relative intensity) 185 (M^+, 100), 170 (54), 142 (52), 115 (30). **8c** (9 mg from Method A or 30 mg from Method C) (R_f=0.22), white solid, mp 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd, 2H, J=4.6, 1.6 Hz), 7.60 (d, 2H, J=9 Hz), 7.51 (dd, 2H, J=4.6, 1.6 Hz), 7.01 (d, 2H, J=9 Hz), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 150.3, 148.1, 130.5, 128.3, 121.3, 114.8, 55.6; MS (EI, 70 eV) m/z (relative intensity) 185 (M^+, 100), 170 (34), 142 (42),115 (32), 86 (51), 84 (75).

4.7.6. 4-Pyridin-2-yl-benzoic acid methyl ester 9a,[11a,27] 4-pyridin-3-yl-benzoic acid methyl ester 9b[11a] and 4-pyridin-4-yl-benzoic acid methyl ester 9c.[38] The general procedure (Method A) using **5c** (215 mg) as starting bromide and pyridine as solvent gave, after separation by flash chromatography (silicagel, hexanes/ethyl acetate (70:30)), 15% yield of **9a**,**b** (α/β/γ 2:1:0). The same process, using Method B gave 20% yield of 4-pyridin benzoic acid methyl esters **9a–c** (α/β/γ 2:1:0.1). **9a** (21 mg from Method A or 29 mg from Method C) (R_f=0.60) colorless plates, mp 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, 1H, J=4.7, 1.3 Hz), 8.13 (d, 2H, J=8.7 Hz), 8.11 (d, 2H, J=8.7 Hz), 7.77 (m, 2H), 7.27 (dd, 1H, J=8.9, 4.7 Hz), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 156.1, 149.8, 143.4, 136.9, 130.3, 129.9, 126.7, 122.8, 120.9, 52.1; MS (EI, 70 eV) m/z (relative intensity) 213 (M^+, 58), 182 (100), 154 (47), 127 (24). **9b** (11 mg from Method A or 15 mg from Method C) (R_f=0.40), white solid, mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, 1H, J=1.7 Hz), 8.63 (dd, 1H, J=4.8, 1.7 Hz), 8.14 (d, 2H, J=8.4 Hz), 7.91 (td, 1H, J=7.8, 1.7 Hz), 7.65 (d, 2H, J=8.4 Hz), 7.40 (dd, 1H, J=7.8, 4.8 Hz), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 149.1, 148.2, 142.1, 135.5, 134.4, 130.3, 129.7, 127.0, 123.6, 52.1; MS (EI, 70 eV) m/z (relative intensity) 213 (M^+, 68), 182 (100), 154 (27), 127 (21).

9c (1 mg from Method C) (R_f=0.15) white solid, mp 103–105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, 2H, J=4.2 Hz), 8.15 (d, 2H, J=8.4 Hz, 7.70 (d, 2H, J=8.4 Hz), 7.54 (d, 2H, J=4.2 Hz), 3.94 (s, 3H); MS (EI, 70 eV) m/z (relative intensity) 213 (M^+, 95), 182 (100), 154 (56), 127 (66), 80 (48).

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Interactions of acyclic and cyclic bis-phenanthridinium derivatives with ss- and ds-polynucleotides☆,☆☆

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Abstract—The acyclic bis-phenanthridinium ligands **1**, **2** and the cyclic analogue **3** bind to ss-RNA by bis-intercalation. Due to it's shorter linker **1** exhibits mono-intercalative binding to ds-polynucleotides, while a mixed mode of binding with **2** is shown to strongly dependent on the base composition and tertiary structure of ds-DNA and RNA. The cyclic analogue **3** binds to ds-polynucleotides by non-intercalative mode. Comparing the ss-/ds-polynucleotide selectivity obtained for **3** and previously reported for 3,8-linked bis-phenanthridinium analogues, it is clear that the more rigid structure and sterically more restricted cleft of the latter could better distinguish ss- from ds-polynucleotide regions.

1. Introduction

It is known that a number of powerful antibiotics and antitumor drugs base their biological activity on intercalation into DNA/RNA of a living cell.[1,2] Bis-intercalation, in which two aromatic units of a ligand stack between two separate base pairs, has undergone intensive research in the last few decades in view of increased affinity towards DNA/RNA, slower dissociation rates and greater sequence specificity. Thus, bisintercalators could hold much promise relative to monointercalators.[1,3] Nevertheless, studies were mostly restricted to some naturally occurring bis-intercalative antibiotics and antitumor agents like echinomycin, triostin A and luzopeptins.[4–6] Bis-acridinium derivatives, in which two large aromatic units are separated by flexible linkers, are the best-studied group among synthetic bis-intercalators; the influence of the linker properties and position of their attachment on the aromatic moiety being investigated in details by numerous methods.[3] In the case of bis-phenanthridinium derivatives, the analogues of well known ethidium bromide, such detailed systematic study was done to a much lesser extent.[3] However, those studied showed intriguing properties making them useful for assaying nanogram quantities of DNA, some showed strong (10-fold) RNA preference and other exceptionally high (5000-fold) preference for binding to poly(dA)–poly(dT) over polyA–polydT and 5-fold preference for poly(dG–dC)$_2$ over *ct*-DNA.[3] Also, it was reported that the rigidity of the linking chain of bifunctional intercalators in the ditercalinium series was critical for antitumor activity.[7] Here we report on the interactions of the flexible acyclic and rigid cyclic bis-phenanthridinium derivatives with ss- and ds-RNA and DNA. The acyclic derivatives **1** and **2** differ in linker length, allowing insertion of one (**1**) or two nucleobases (**2**) between aromatic units. Bis-intercalation[3] into doublestranded polynucleotides however is not expected for **1** in view of the 'neighbour exclusion principle', but could be possible for **2**. The aromatic units of **3**, a cyclic analogue of **2**, are due to more rigid structure not intramoleculary self-stacked in aqueous solution.[8] The cleft between the aromatic units of **3** is well defined by distance (allowing insertion of one or two adjacent nucleobases of polynucleotide) and by the position of two linkers at the arenes offering for larger substrates like polynucleotides a site of access. Contrary to acyclic analogues, the derivative **3** does not have primary NH_2 groups, which can also interact with polynucleotides.[9] As reported previously,[8] self-stacking does not hamper insertion of aromatic substrates between aromatic units, the same

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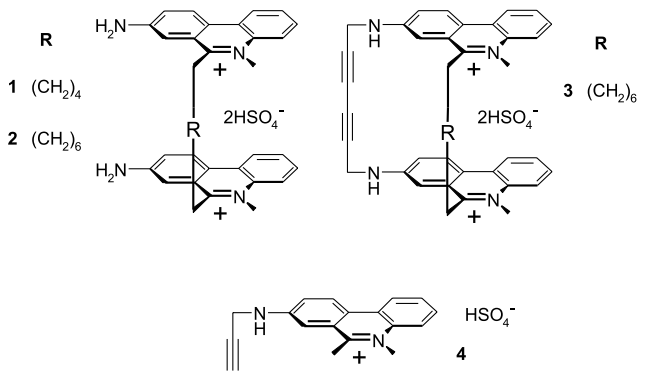

Chart 1. Studied acyclic **1**, **2** and cyclic **3** bis-phenanthridinium derivatives and the previously studied 'monomer' **4**.

holds for **1** and **2** as for the not self-stacked **3**, which all form very stable complexes with nucleotides ($K_s \approx 10^5$ dm^{-3} mol^{-1}) (Chart 1).

2. Materials and methods

Polynucleotides were purchased from Sigma and Aldrich and used without further purification by dissolving in the respective buffer. Their concentration was determined spectroscopically[10] as the concentration of phosphates. The compounds **1**–**3** were prepared and their properties determined previously.[8,11] Electronic absorption spectra were recorded on a Varian Cary 1 spectrometer using quartz cuvettes (1 cm). Absorbance of **1**–**3** is linearly dependent on concentration up to $c=5\times10^{-5}$ mol dm^{-3}, indicating that there is no significant intermolecular stacking which should give rise to hypochromicity effects. Fluorescence spectra were recorded on a Perkin–Elmer LS 50 fluorimeter in quartz cuvettes (1 cm). In fluorimetric titrations excitation wavelengths of 320 and 420 nm (**1**, **2**); 430 nm (**3**) were used and changes of emission were monitored at 540 nm (**1**, **2**); 550 nm (**3**). The stability constants (K_s) and [bound **1**–**3**]/[polynucleotide phosphate] ratio (n) were calculated according to the Scatchard equation[12,13] by non-linear least-square fitting.[10] Values for K_s and n given in Table 1 all have satisfying correlation coefficients (>0.99). Due to previously observed slow kinetics of macrocyclic bis-acridinium analogues[14], all titrations were done in a way that solution of **1**–**3** was mixed with increasing concentrations of polynucleotide in separate vessels, left to equilibrate for 2 h (in dark; room temperature) and then emissions were recorded for each vessel starting from lower to higher c (polynucleotide). The use of NMR techniques was hampered by low solubility of the complexes of **1**–**3** with nucleotides and polynucleotides even upon addition of up to 80% DMSO. Thermal melting curves for DNA, RNA and their complexes were determined as previously described[10,11] by following the absorption change at 260 nm as a function of temperature. The absorbance of the ligands was subtracted from every curve, and the absorbance scale was normalised. T_m values are the midpoints of the transition curves, determined from the maximum of the first derivative or graphically by a tangent method.[15] ΔT_m values were calculated subtracting T_m of the free nucleic acid from T_m of complex. Every ΔT_m value here reported was the average of at least two measurements, the error in ΔT_m is ±0.5 °C. Viscometric titrations were conducted in an Ubbelohde micro viscometer (Schott) according to previously described procedure[10] with modification that aliquots of DMSO stock solutions of studied ligands were added and obtained viscometry data corrected for DMSO content (final content not exceeding 5% of the total volume). Under the chosen conditions for the measurements (pH=6.2/6.25), all compounds **1**–**3** carry two positive charges since the amino functions on the aromatic units (pK_s=3–4) are not protonated.

Table 1. Fluorescence emission changes Int[a] of **1**–**3** induced by binding of polynucleotides at excess of polynucleotide binding sites over ligand (low ratios r)

	1	2	3
PolyA	2.5	2.7	2.6
PolyG	10	9	2.6
PolyU	8[b]	4	2.2
PolyG–polyC	6	5	0.9
PolyA–polyU	17	16[b]	8
PolydA–polydT	34	17	16[b]

[a] Int=$I_0/I_{complex}$(calculated for 100% complexation) at emission λ_{max}=540 nm (**1**, **2**) or λ_{max}=550 nm (**3**) induced by complex formation.
[b] $I_{complex}$ estimated by extrapolation of titration curve.

3. Interactions of 1–3 with polynucleotides

3.1. UV/Vis titrations

Addition of any ds- or ss-polynucleotide to buffered solution of **1**–**3** ($c=1-3\times10^{-5}$ mol dm^{-3}) at ratio r [(**1**–**3**)/(polynucleotide)]>0.1 induced precipitation. However, at ratio $r\leq0.1$ no precipitation of **1** and **2** was observed, making possible monitoring of the changes in UV/Vis spectra upon addition of polynucleotide. Addition of the double stranded (*ct*-DNA, polyA–polyU) and single stranded (polyA) polynucleotides induced very similar changes in UV/Vis spectra of **1** and **2**, namely a strong hypochromic effect (21–26%) and bathochromic shifts (21–30 nm). Further additions of the mentioned polynucleotides (r=0.05 and lower) did not produce any additional spectral changes (Fig. 1) suggesting that at

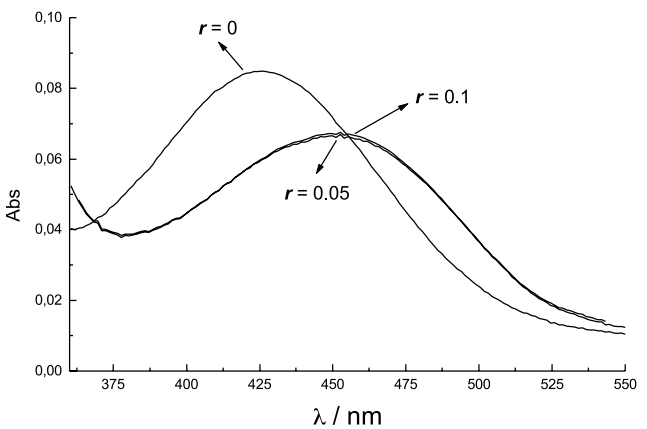

Figure 1. UV/Vis spectra of **2** ($c=2\times10^{-5}$ mol dm^{-3}) and complex **2**/polyA at different ratios r=[**2**]/[polyA], pH=6.2, Na cacodylate buffer, 0.02 M, (I=0.02 M).

$r \approx 0.1$, compounds **1** and **2** are completely bound to the polynucleotide. According to that one can estimate Scatchard[12] ratio [(bound compound)/(polynucleotide)] $n \approx 0.1 \pm 0.05$.

In UV/Vis titrations of 'monomer' **4** with polynucleotides similar changes in spectra (38% hypochromism, 21 nm bathochromic shift) were observed as for **1** and **2**. Binding constants K_s and ratios n of **4** with polynucleotides determined previously[16] are in good accordance with results found for ethidium bromide (**EB**) complexes with single stranded[17] and double stranded[18,19] polynucleotides.

3.2. Fluorimetric titrations

Due to the much lower concentration of **1**–**3** in fluorimetric titrations ($c=2-4\times10^{-6}$ mol dm^{-3}), no precipitation was observed upon addition of polynucleotides[20]. Addition of ss-polynucleotides at $r>0.8$ quenched fluorescence of **1**–**3** (Fig. 2) and induced bathochromic shift by 15 nm. Further addition of polynucleotide ($r=0.8-0.001$) yielded an increase of fluorescence (Fig. 2) and a hypsochromic shift of 10 nm. It is interesting to note that in the titration range where fluorescence was increased, much longer incubation time for equilibration was needed (1–2 h) than in the part where fluorescence quenching was observed (1–5 min). Similar changes of fluorescence were noticed upon addition of ds-polynucleotides to **1**–**3** but with different 'break point' between quenching and increase. As shown in Figure 3, the 'break point' for ss-polynucleotides occurs at $r=0.7-0.9$ and for ds-polynucleotides at $r=0.22-0.35$.

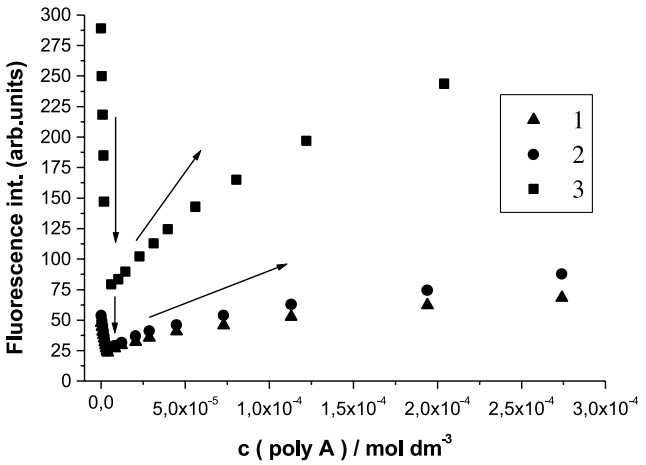

Figure 2. Fluorimetric titration of **1**, **2** (λ_{exc}=422 nm; λ_{em}=550 nm) and **3** (λ_{exc}=440 nm; λ_{em}=531 nm), $c=3\times10^{-6}$ mol dm^{-3} with polyA, pH=6.2, Na cacodylate buffer, 0.02 M, (I=0.02 M).

The mentioned r values correspond to theoretically expected values for saturation of intercalative binding sites. The results of UV/Vis and especially fluorimetric experiments suggest that **1**–**3** form at least two different types of complexes with polynucleotides, one being dominant at excess of compound over intercalation binding sites ($r>0.9$ for ss- and $r>0.3$ for ds-polynucleotides) and the other prevailing at reversed ratio. At large excess of most of the polynucleotides, the fluorescence increase of acyclic **1** and **2** was much more pronounced compared to

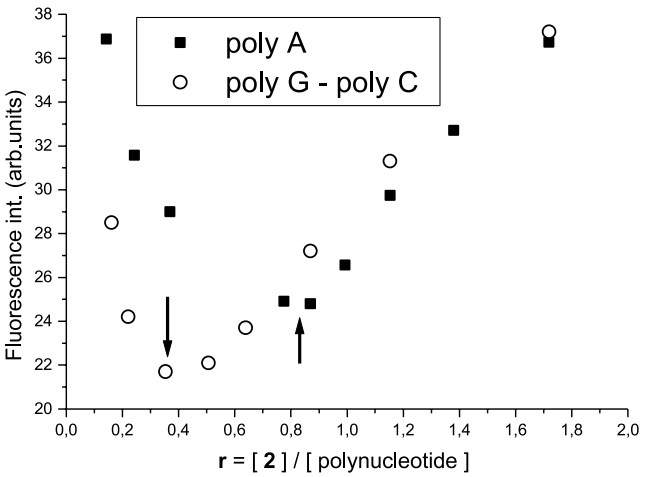

Figure 3. Fluorimetric titration of **2** (λ_{exc}=422 nm; λ_{em}=550 nm), $c=3\times10^{-6}$ mol dm^{-3} with polyA (■) and polyG–polyC (○), pH=6.2, Na cacodylate buffer; 0.02 M, (I=0.02 M).

cyclic analogue **3** (Table 1). It was previously found that intramolecular stacking of flexible **1** and **2** in water resulted in strong quenching of their fluorescence compared to **3** due to the rigid structure and therefore unstacked conformation of the latter.[8] Fluorescence increase of **3**/polynucleotide complex at high excess of polynucleotide can be explained with similar mechanism as reported for **EB**, monomer **4** and other rigid bis-phenanthridinium analogues.[16] Formation of an intercalative complex with polynucleotide should disrupt intramolecular interactions in **1** and **2** and combined with the aforementioned mechanism proposed for **3**[16] should result in stronger increase of their fluorescence compared to **3**.

3.3. Stability of polynucleotide complexes with 1–3

A steep and almost linear decrease of fluorescence intensity (Fig. 2) under conditions of ligand molecule excess over intercalation binding sites points towards a high cumulative binding constant (K_s). At such ratios ($r>0.9$ for ss- and $r>0.3$ for ds-polynucleotides, respectively) it is well known for most intercalating agents that additional, non-intercalative binding of intercalator self-associates is contributing to a cumulative binding constant.[17,21–23] Some of the previously described bis-acridinium and phenanthridinium analogues at $r>n$ also bind to polynucleotides by non-intercalative mode, where the interactions of self-stacked bis-intercalator associates on the outer surface of polynucleotide (acting as polyelectrolyte) seem to play an important role.[3] Due to more binding modes of **1**–**3** with obviously high cumulative affinity toward polynucleotides it was not possible to calculate binding constants K_s for ratios $r>n$. For macrocyclic porphyrin derivative (**Pbiph**) exhibiting similar fluorescence quenching and increase as observed for **1**–**3**, binding constants K_s were calculated only for titration data taken at the large excess of the binding sites[24] ($r \ll 0.1$). Under such conditions it was assumed that molecules of the studied compound bind independently on isolated sites on the polynucleotide. Therefore, stability constants (K_s) were calculated by non-linear fitting according to Scatchard equation for the equilibrium:

$$(\text{Pbiph, polynucleotide})_{\text{aggregates}} \overset{\text{polynucleotide}}{\rightleftharpoons} \times (\text{Pbiph, polynucleotide})_{\text{isolated}}$$

Following the same idea (large excess of binding sites, r=0.1–0.001, Fig. 2), we calculated K_s and n values for (**1**–**3**)/polynucleotide complexes (Table 2).

Table 2. Binding constants (log K_s) and ratios n ([bound compound]/[polynucleotide phosphate]) calculated according to fluorimetric titrations[a] of **1**–**3** with polynucleotides, pH=6.2, Na cacodylate buffer, 0.02 M (I=0.02 M)

	1		**2**		**3**	
	n	log K_s	n	log K_s	n	log K_s
PolyA	0.1	4.2	0.1	3.8	0.1[b]	4.1[b]
PolyG	0.15	5.3	0.1	5.8	0.09	5.4
PolyU	0.1	3.7	0.1	4.1	0.1	4.2
PolyG–polyC	0.01[b]	6.5[b]	0.01[b]	6.3[b]	0.05[b]	6.5[b]
PolyA–polyU	0.1	5.7	0.1[c]	8[c]	0.12	5.3
PolydA–polydT	0.15	5.2	0.32	5.7	[c]	[c]

[a] Accuracy of n±30%, consequently varying values log K_s±0.5.
[b] Calculated for n values estimated in UV/Vis experiments.
[c] Systematic deviation of experimental data from best-fitted Scatchard isotherm allowed only estimation of cumulative binding constant.

Contrary to most of the intercalators (e.g., 'monomer' **4**[16] and ethidium bromide[17,25]), **1**–**3** exhibit similar affinities toward polyA and polyU. The same behaviour was observed for **1**–**3**/nucleotide complexes[8] and was explained by only partial insertion of purinic nucleobase into the sterically restricted space between phenanthridinium units. he order of magnitude higher K_s value found for polyG compared to other ss-polynucleotides can be explained by the peculiar properties of the polymer, which forms a number of self-aggregated structures in water.[26] Although **1**–**3** exhibit similar affinity toward ss-polynucleotides, this does not apply to their interactions with double stranded DNA and RNA. Hexamethylene derivative **1** and octamethylene derivative **2** bind similarly to polyG–polyC but significantly different to polyA–polyU and polydA–polydT (Table 2), the different linker length being obviously responsible for that. Affinity of **1** towards all studied ds-polynucleotides points to the intercalative binding mode being dominant at excess of intercalation binding sites, with ratios n being in good agreement with those estimated from UV/Vis experiments. Interactions of **2** significantly depend on the type of ds-polynucleotide. Systematic deviation of experimental data from the best fitted Scatchard isotherm in the case of **2** /polyA–polyU titration and the ratio n=0.32 found for **2** /polydA–polydT titrations too high for only intercalation point to additional non-intercalative interactions, even at this high excess of intercalation sites at $r \ll 0.1$, or to mixed binding mode of **2**. At higher ionic strength (I=0.12 mol dm^{-3}) stronger affinity and lower n values (0.22) of **2**/polydA–polydT complex were found, surprisingly opposite to the affinity dependence on the ionic strength commonly found for classical intercalators.[22] However, for some bis-phenanthridinium derivatives, it was reported that mixed mono- and bis-intercalative modes at low ionic strength change to the dominantly bis-intercalative modes at high ionic strength.[27] Results obtained for cyclic derivative **3** binding to polyA–polyU and polyG–polyC are similar to **1**, and the constant for **3** and polyA–polyU is also similar to that of the monomer **4**. Systematic deviation of experimental data from best fitted Scatchard isotherm in the case of **3**/polydA–polydT titration points toward different additionally stabilizing types of interactions.

3.4. CD experiments

To clarify the results of fluorimetric titrations of **1**–**3** with ss-polynucleotides, influence of **1**–**3** addition on CD spectra of ss-polynucleotides was studied, polyG chosen as the representative. Addition of **1**–**3** to polyG significantly decreases CD spectra of polynucleotide (Supplementary data) pointing to distortion of helicity upon binding and therefore loss of chirality.[28,29] More pronounced effect induced by **1** than by **2** and **3** can be easily attributed to the shorter linker between aromatic units of **1**, consequently inducing more pronounced distortion of helical structure of polyG. This finding suggests involvement of both aromatic units in complex formation, possibly due to the formation of a bis-intercalative complex of **1**–**3** with polyG.

3.5. Melting transition experiments

Monomer **4** showed lower ΔT_m values (Table 3) compared to **EB** possibly due to the additional interactions of the primary amino substituents[30–32] of **EB**. Monomer **4** is exhibiting RNA preference, as found for **EB**[31] or pyrenium monointercalators,[10] independent of the ratio r. Melting transitions were typically monophasic as found for most of the intercalators.[16] Melting curves of all polynucleotides in the presence of **1** and **2** at ratios r=0.05–0.2 at I=0.01 M are found to be strongly biphasic (Table 3). This observation coincides with the breakpoint of emission change observed at these values of ratio r in fluorimetric titrations (Fig. 2). The high ΔT_m values of **1** and **2** are close to those of known bisintercalators.[33,34] There is almost no difference between

Table 3. ΔT_m-Values (°C) and RD-ratios[a] (ΔT_m (RNA)/ΔT_m (DNA)) of **1**, **2**, **3** and **4** with *ct*-DNA, polydA–polydT and polyA–polyU at pH=6.25; I=0.01 M (MES buffer, 0.01 M)

	r=	0.05	0.1	0.2	0.3
1	*ct* DNA	2.3/>35[b,c]	4.9/>36[b,c]	>33[b]	>33[b]
	dAdT	3.3/34.2[c]	6.3/39.4[c]	—/45.3[c]	—/45.9[c]
	AU	5.5/21.6[c]	—/21.6[c]	—/21.5[c]	16.6
	RD[a]	0.6	0.5	0.5	0.4
2	*ct* DNA	3.2/>36[b,c]	8.3/>36[b,c]	>32[b]	>36[b]
	DAdT	3.9/36.6[c]	8.6/41.3[c]	—/42.5[c]	—/43.5[c]
	AU	4.1/20.3[c]	8.3/20.7[c]	—/20.7[c]	17.8
	RD[a]	0.6	0.5	0.5	0.4
3	*ct* DNA	2.9/—[b,c]	5.7/—[b,c]	14.3	14.3
	DAdT	2.3/28.4[c]	4.8/29.3[c]	25.6	25.6
	AU	2.9	3.5	3.9	4.3
	RD[a]	0.1	0.12	0.15	0.17
4	*ct* DNA	4.3	6.0	9.2	11.9
	DAdT	0.8	1.5	2.6	3.5
	AU	1.9	3.6	6.1	8.4
	RD	2.4	2.4	2.3	2.4

r=mol ligand/nucleic acid phosphates.
[a] Only the second transition ΔT_m values of biphasic curves was used for calculation.
[b] Not possible to determine due to the lack of melting midpoint.
[c] Biphasic melting curve, values for both melting midpoints given when possible.

ΔT_m values of **1** and **2** for all polynucleotides at $r \geq 0.05$ (I=0.01 M). It should be noted that the RNA/DNA preference is reversed compared to monomer **4**, with **1** and **2** showing the same small, 2-fold preference toward polydA–polydT, which is too small to appear in the binding constants of **1**. There is virtually no difference between the values found for *ct*-DNA and polydA–polydT, pointing toward similar stabilisation of dA–dT and dG–dC rich sequences of DNA, as found for some diacridines.[35,36]

The cyclic derivative **3** stabilises studied polynucleotides significantly differently from both, acyclic bis-phenanthridinium analogues **1** and **2** and monomer **4**. Compounds **1** and **2** show significantly higher ΔT_m values for *ct*-DNA and polydA–polydT than the dimer **3** with substituted amino functions. DNA preference with **3** is strongly pronounced, polyA–polyU being stabilised at higher ratios for only half of the value found for monomer **4** and much less than found for **1** and **2**. Also, opposite to **1** and **2** there is a small but negligible 2-fold difference in stabilisation of *ct*-DNA and polydA–polydT, in favour of the latter (Table 3). Opposite to a bisintercalating macrocyclic diacridine,[14,37,38] the cyclic dimer **3** shows a large increase of ΔT_m value towards its monomer **4** with polydA–polydT, but much less for the mixed sequence *ct*-DNA.

At higher ionic strength (I=0.12 mol dm^{-3}) (Table 4) the hexamethylene derivative **1** stabilised polynucleotides less than at lower ionic strength, due to the competitive stabilisation of double helix by Na^+ cations.[22] Melting curves were no longer biphasic, possibly due to the very small total change at which it was not possible to distinguish two transition midpoints. Contrary to **1**, ΔT_m values found for octamethylene derivative **2** are strongly dependent on the type of the polynucleotide. Opposite to the monophasic profiles of polydA–poydT with **1**, melting curves of polydA–polydT/**2** complex were at all ratios clearly triphasic, pointing to a quite complex system of bound species (and additionally stabilizing processes) which even at high ionic strength gave dramatic cumulative stabilisation of this polynucleotide compared to **1** and most of the other bis-intercalator molecules.[3] Surprisingly, **2** stabilised *ct*-DNA much less; ΔT_m values are comparable to those of **1**, melting curves being monophasic for both compounds. A very high cumulative affinity of **2** towards polydA–polydT could explain the low influence of increased ionic strength on stabilisation of a double strand.

Table 4. ΔT_m-Values (°C) of **1** and **2** with *ct*-DNA, polydA–polydT and polyA–polyU at pH=6.25, I=0.11 M (MES buffer, 0.01 M+0.1 M NaCl)

	r=	0.1	0.2	0.3
1	*ct* DNA	6.1	9.6	>13[a]
	dAdT	3.7	5.9	10.1
	AU	1.9/(>32) [a,b]	1.7/(>33) [a,b]	[a]
2	*ct*-DNA	6.9	10.6	12.5
	dAdT	4.2/(13.8)/21.5[c]	5.3/(14.2)/24.4[c]	9.1/(17.9)/>26.7[c]
	AU	1.2/(24.0)[b]	1.0/(28.7)[b]	[a]

[a] Not possible to determine due to the lack of melting midpoint.
[b] Strong absorbance increase after first transition.
[c] Triphasic melting curve, after de- and renaturation biphasic.

3.6. Viscometric measurements

The α-value with monomer **4** is in good agreement with the one reported for **EB**.[3,10,31] α-Values found for **1** and **2** are also in the range of monointercalation. Comparison of the viscosity results found for **1** and **2** agree with the behaviour of bifunctional 9-aminoacridine compounds linked via the amino nitrogens by methylene chains of various lengths but in general too short for bisintercalation.[3,39] Four or even five methylene groups together with the two nitrogens attached to the acridine ring are not sufficient in length to allow bis-intercalation, even if only one base pair is included in the intercalation site,[39] the same holds for high ionic strength (I=0.11 M).[40] A similar behaviour can be assumed for the hexamethylene derivative **1**. Drugs which are known to act as bis-intercalators usually possess longer spacer,[14,37] with a minimum distance of ca. 7 Å[41] or in the case of flexible chains the equivalent of octamethylene spacer of **2**.[39] Nevertheless, according to the low α value bis-intercalation of **2** with *ct*-DNA seems to be hindered, possibly due to its substituents.[42] Since cyclic diacridines cannot bind as mono-intercalators[43–46] which can be also assumed for analogue **3**, the observed value α=0.2 suggests non-intercalative binding. However, bis-intercalative binding of **3** at low $r \leq 0.025$ combined with severe kinking of double helix or mixed with non-intercalative binding (α=0.75) cannot be excluded for *ct*-DNA (Table 5).[3]

Table 5. Viscometric α-values of compounds **1**–**4** with *ct*-DNA at pH=6.25, I=0.01 M (MES buffer, 0.01 M)[a]

Ligand	**1**	**2**	**3**	**4**
α-Value[b]	0.85	1.05	0.75/0.2[c]	0.9

[a] Aliquots of DMSO stock solutions of studied ligands were added and obtained viscometry data corrected for DMSO content (final content not exceeding 5% of the total volume).
[b] $\alpha = 1/r\,(L/L_0 - 1)$.
[c] $r \leq 0.025$: α=0.75; $r > 0.025$; α=0.2.

4. Discussion of results

The results of UV/Vis, fluorimetric and CD experiments lead to the conclusion that **1**–**3** at high excess of ss-polynucleotides form stable intercalative complexes where a nucleobase is inserted between aromatic units. Additional binding present at opposite dye/polynucleotide ratios ($r > 0.9$) is probably due to non-intercalative, electrostatic interaction of self-aggregated **1**–**3** at the negatively charged polynucleotide backbone. Therefore, the **1**–**3**/polynucleotide complexes formed at high ratios r are of lower solubility in water, possibly due to the partial neutralisation of the charge and self-aggregation of **1**–**3**.

Binding of **1**–**3** to ds-polynucleotides reveals a much more complex situation. Fluorimetric titrations and viscosity experiments support mono-intercalation as the dominant binding mode for all **1**/ds-polynucleotide complexes at low ratios r. This conclusion is in accordance with results reported for bis-acridinium derivatives possessing linker of similar length.[3,39] However, high ΔT_m values found for **1**/ds-polynucleotide complexes point toward additional interactions of the non-intercalating phenanthridinium unit, which additionally stabilizes the double helix.

The octamethylene linker of **2** could allow bis-intercalative binding to ds-polynucleotides, possibly obeying the 'neighbour exclusion' principle.[47,48] Although the viscometric α-value with *ct*-DNA points toward mono-intercalation, bis-intercalation with severe kinking of double helix cannot be excluded. However, fluorimetric and melting experiments of **2**/ds-polynucleotide complexes revealed a strong dependence of binding on base pair composition, type of ds-helix and ionic strength. It has been reported previously that even at high ionic strength (I=0.7 M) the ethidium bromide dimer bis-intercalates by covering 5.7 base pairs (corresponds to the value of n=0.09) when the ratio r was low, but that with a decreasing number of available intercalation sites the binding mode changed and the drug mono-intercalated (corresponds to the value of n=0.17).[27] One can also presume that the aggregates of **2** formed close to the saturation of polynucleotide have an important influence on binding even at large excess of intercalation sites, contrary to the situation with **1**. Due to the obvious overlap of different binding modes at all experimental conditions in some cases only an estimation of cumulative binding constant was possible.

The cyclic derivative **3**, due to the more rigid structure compared to acyclic analogue **2**, cannot bind to ds-polynucleotides by monointercalation.[43] Therefore, it was not surprising that viscometric results, especially at r>0.025, and the dramatic difference in melting transition results found with dA–dT and A–U polynucleotides, respectively, upon addition of **3** (Table 3) strongly support a dominant non-intercalative binding mode. Since it has been shown that polydA–polydT[31,49] and to some extent polyA–polyU possess a significantly more lipophilic minor groove suitable for the binding of aggregates than polyG–polyC, and since the amino-group of guanine in GC-rich sequences hinders groove-binding, dominating minor groove binding with **3** seems plausible. Comparison of ss-/ds-polynucleotide preference previously reported for 3,8-linked bis-phenanthridinium analogues[16] and found for **3** stressed the importance of steric factors in polynucleotide binding.

Another significant point is that the RNA/DNA ds-helix stabilisation ratio (RD at e.g., r=0.2, Table 3) changed in the sequence **4** (RD=2.3)>**1**, **2** (RD=0.5)>**3** (RD=0.15). The monomer **4** shows RNA-preference like ethidium bromide, and the ethidium bromide dimer was found to bind ten times more tightly to *t*RNA than to DNA.[50] The examined dimers **1**–**3** changed to a DNA-preference (RD<1) compared to these monointercalators because of stronger stabilization increase in binding to polydA–polydT than to polyA–polyU (Table 3). In the case of **3**, there is no increase or decrease in ΔT_m towards the monomer **4** found in the stabilization of polyA–polyU.

5. Conclusions

The results presented in this work have stressed the importance of linker length and rigidity interplay in interactions of bis-phenanthridinium derivatives and polynucleotides. The cyclic derivative **3** distinguishes ss- and ds-polynucleotides by binding mode, which makes it interesting for interactions with specific single stranded regions and abasic sites in some naturally occurring RNA.[51–53] Comparing the ss-polynucleotide/ds-polynucleotide selectivity obtained with **3** and the previously reported selectivity with 3,8-linked bis-phenanthridinium analogues,[16] it is clear that a more rigid structure and a steric control of the cleft accessibility by the position of linkage offers an advantage in ss-polynucleotide over ds-polynucleotide selection.

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Corrigendum

Corrigendum to "Synthesis of (+)-zeylenone from shikimic acid" [Tetrahedron 60 (2004) 3689]☆

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