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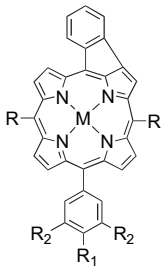

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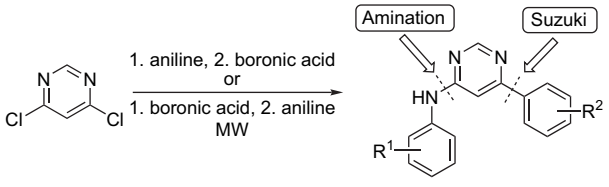

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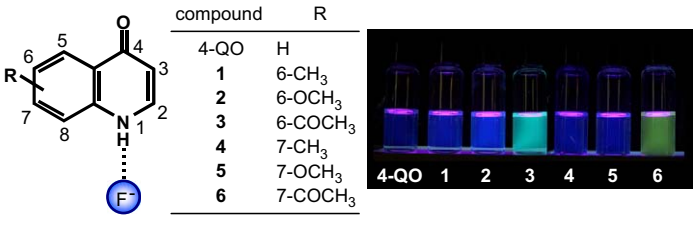

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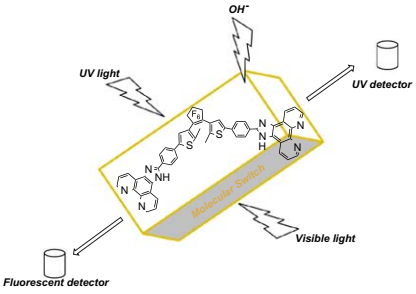

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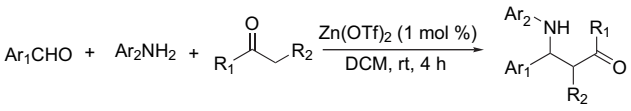

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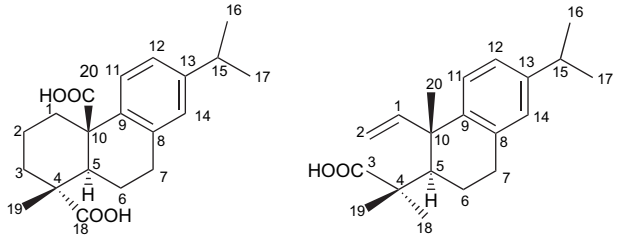

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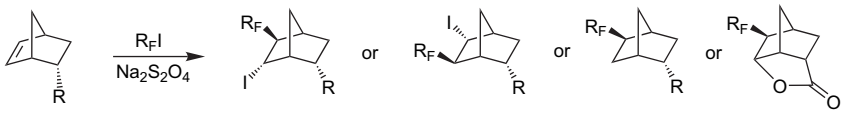

Sodium dithionite initiated free-radical addition of norbornene and its derivatives with polyfluoroalkyl iodides was investigated. In all the cases the addition of R_F was stereoselective at *exo*-position and the predominant configuration of products was trans. Norbornene with a high steric hindered group in the 2-*endo*-position gave 6-*exo*-R_F-5-*endo*-iodo adduct and deiodined product. Fluoroalkylation–lactonization occurred in the addition of norbornene-2-*endo*-carboxylic acid with R_FI to afford fluorinated γ-lactone products.

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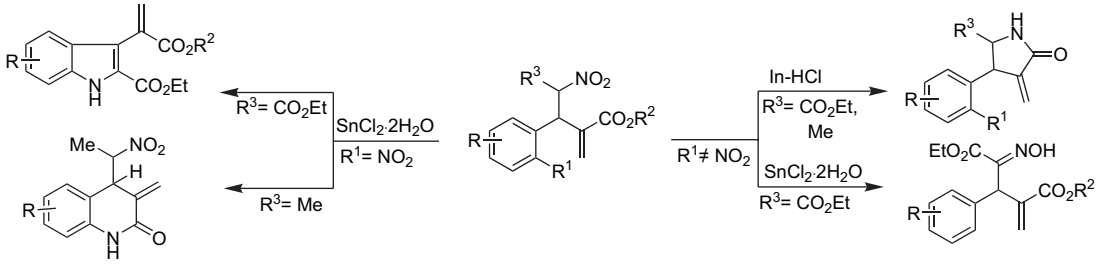

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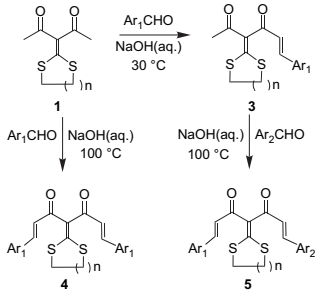

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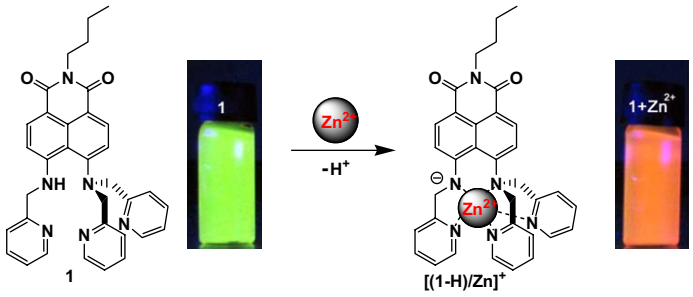

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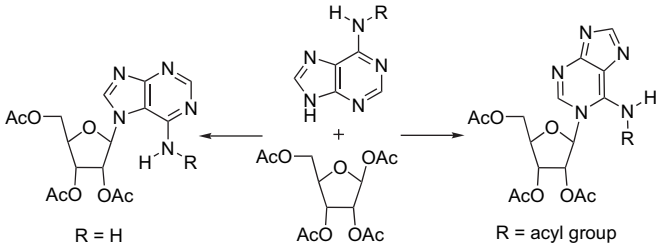

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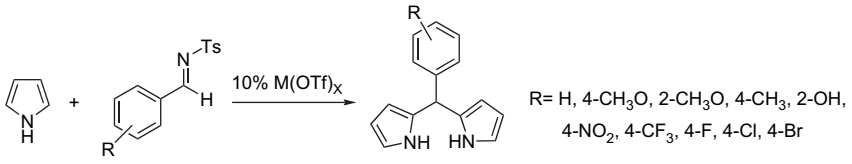

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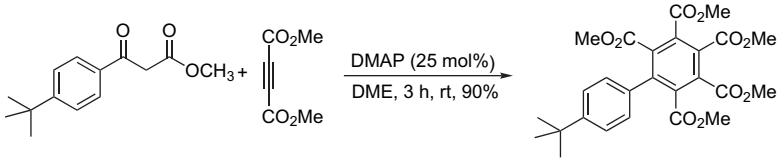

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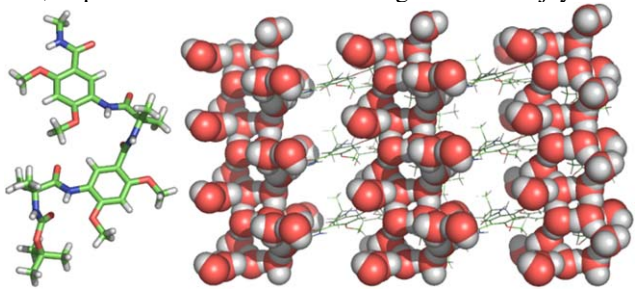

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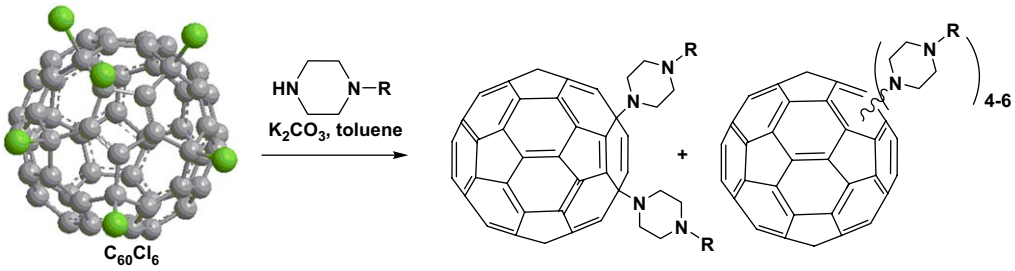

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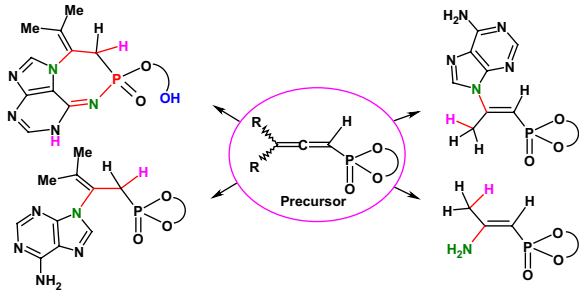

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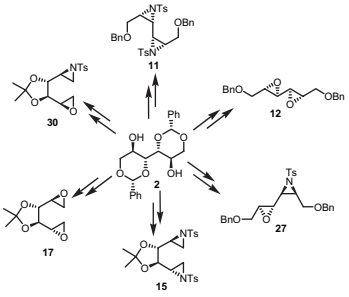

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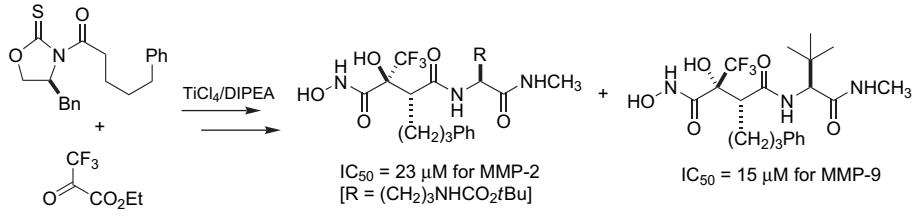

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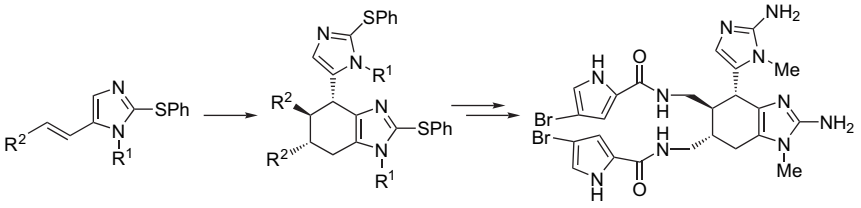

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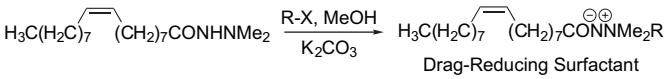

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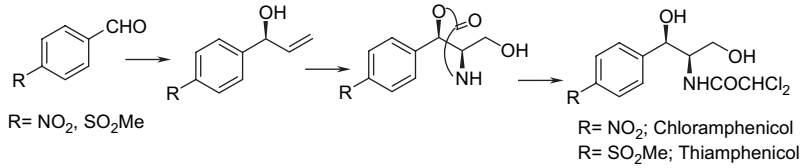

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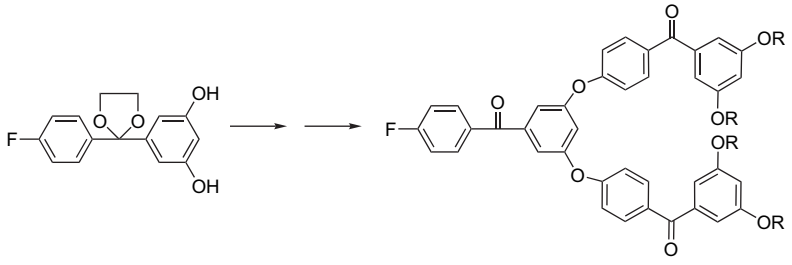

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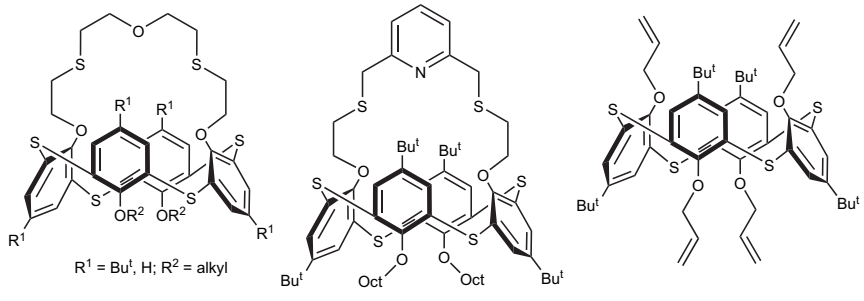

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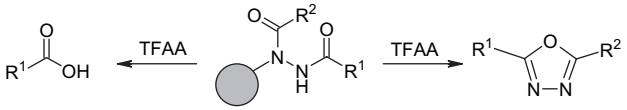

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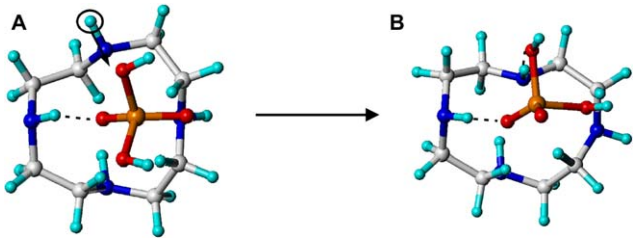

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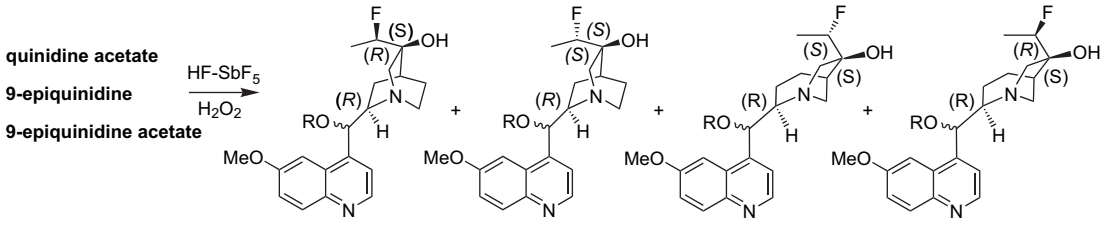

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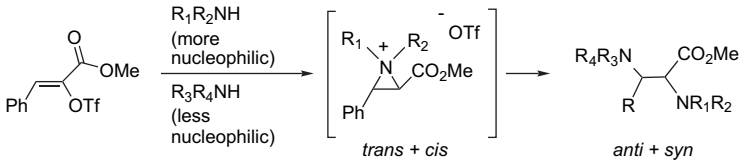

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Synthetic routes to porphyrins bearing fused rings

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1. Introduction

Since the early work of Fischer, porphyrin chemistry has evolved dramatically allowing many exotic macrocycles to be synthesised.[1] Few boundaries restrict the porphyrin chemist, as the field overlaps with organic, inorganic and physical chemistry, as well as with many areas of biology and medicine. Within this diversity of porphyrin chemistry, there has been much interest in the synthesis of porphyrins bearing fused rings, whether as extensions of the conjugated macrocycle or fused alicyclic ring systems. They have proved to be valuable research tools and a fruitful area for the development of synthetic methodology. These fused rings can affect porphyrins by altering their optical properties, both ground and excited state, coordination chemistry and redox behaviour, and it is this potential that has captured the attention of many scientists.

The formation of porphyrins with 'exocyclic' rings fused to the macrocycle can be achieved by a variety of reactions, which will be discussed further. Generally, porphyrins bearing fused rings can be divided into two categories. Namely those formed by intramolecular cyclisation reactions and those formed by intermolecular cyclisation reactions. An extensive discussion of methods for the formation of porphyrins with fused rings from non-porphyrin starting materials is outside the scope of this review and these will only be mentioned if they give access to starting materials for further modification of the fused rings. Finally, examples of the formation of arrays in which porphyrins are fused to one another and the use of porphyrins bearing fused rings to synthesise heterodimers will be covered briefly.

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2. Porphyrins with fused rings formed via intramolecular cyclisations

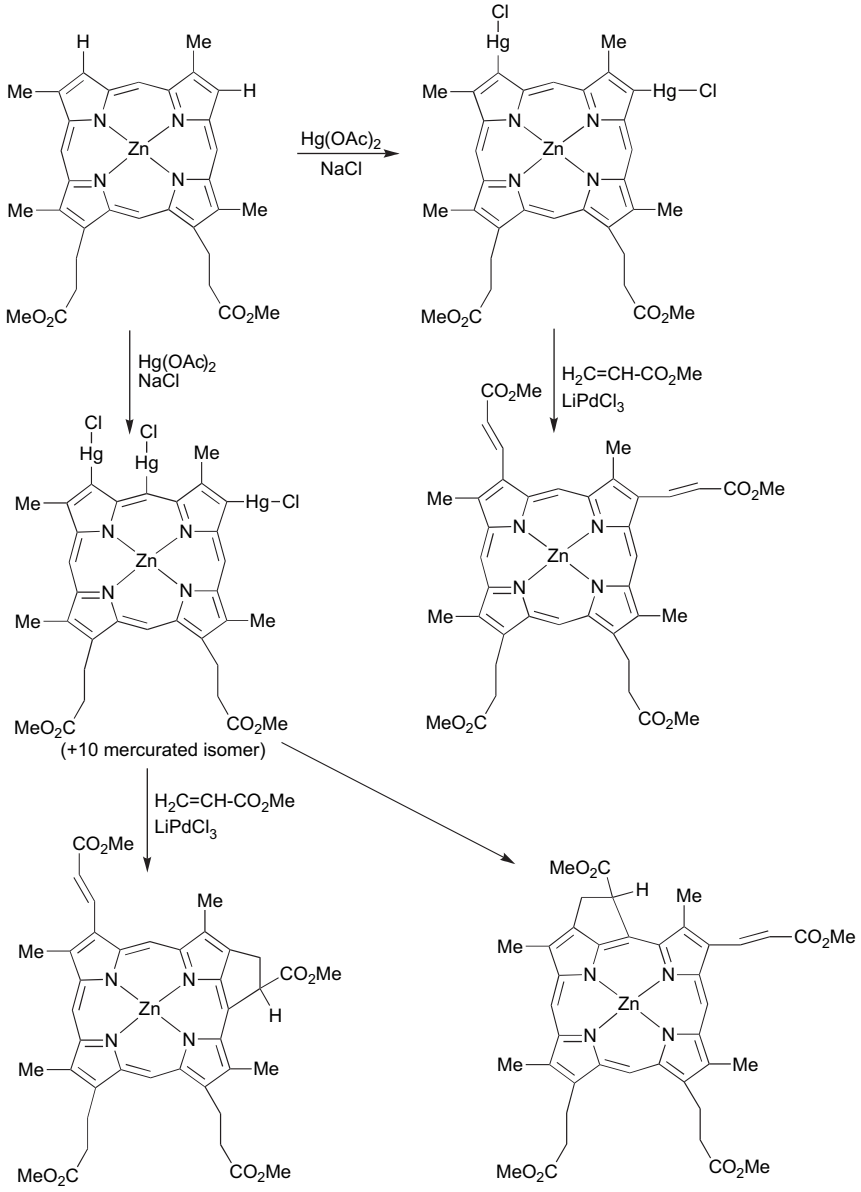
2.1. Metal-mediated cyclisations

In the 1980s, Smith et al. described a palladium-catalysed method that could be used to attach a number of unsaturated substituents directly to the periphery of mercurated porphyrins.[2–4] The first step was the mercuration of zinc(II) deuteroporphyrin IX dimethyl ester. Subsequent treatment with methyl acrylate and $LiPdCl_3$ gave the expected bis-acrylate, along with an unexpected by-product, which could be separated into two isomers (Scheme 1).

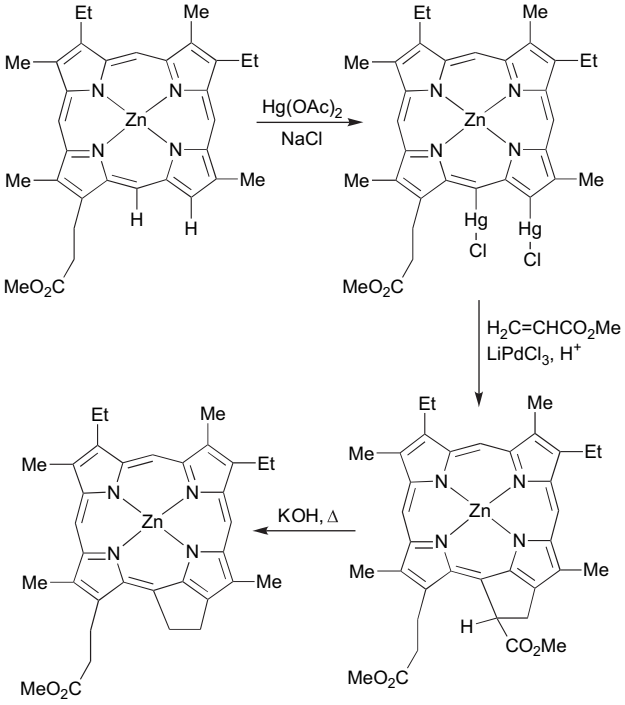
It was postulated that the bis-chloromercurated porphyrin product was contaminated with a tris-mercurated by-product in which mercuration had occurred at the 5- or 10-position. Subjecting these isomers to palladium-coupling conditions led to the formation of two products bearing fused five-membered exocyclic rings.[5] This synthetic method was then exploited to synthesise deoxyerythroetioporphyrin and deoxophylloerythrin methyl ester (Scheme 2).

Recently, Fox and Boyle[6] have developed a method for intramolecular cyclisation based on palladium-catalysed coupling of *meso*-(2-iodophenyl) porphyrins, which gives access to a variety of porphyrins in which the *meso*-phenyl rings are fused to adjacent β-positions (Scheme 3).

It is well documented that organozinc reagents can be easily prepared from organic bromides utilising metallic zinc.[7] Using this technique Chen et al.[8] discovered that treating 2-bromo-5,10,15,20-tetraphenylporphyrinatozinc with activated zinc metal[9] in DMSO at 60 °C for 30 min, resulted in the formation of a fused five-membered ring, similar to those accessed earlier by Fox and Boyle using intramolecular palladium coupling.



Scheme 1. Palladium-catalysed cross-couplings and cyclisations.



Scheme 2. Synthesis of deoxophylloerythrin methyl ester.

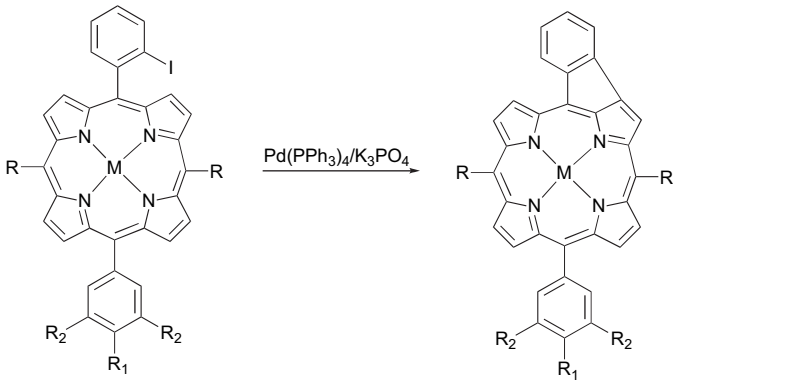
A further extension of this methodology led to the preparation and cyclisation of 2,3,12,13-tetrabromo-5,10,15,20-tetraphenylporphyrinatozinc (Scheme 4).

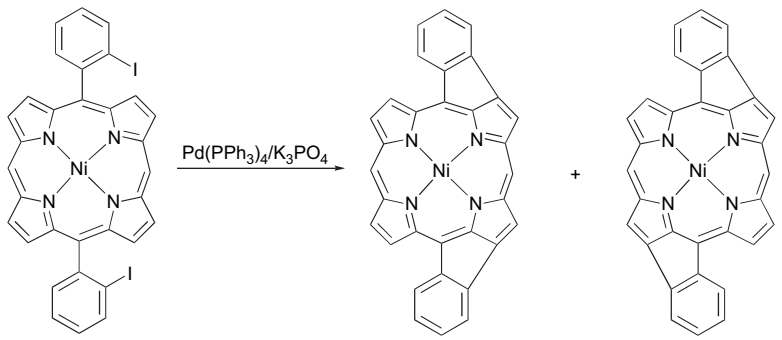
2.2. Acid- and base-catalysed intramolecular cyclisations

2.2.1. Naphthoporphyrins. Porphyrinoid systems with strong absorptions in the far red/near-infrared regions are of interest due to their potential applications, which range from sensors and novel optical materials[10] to the development of superior photosensitisers for photodynamic therapy.[11]

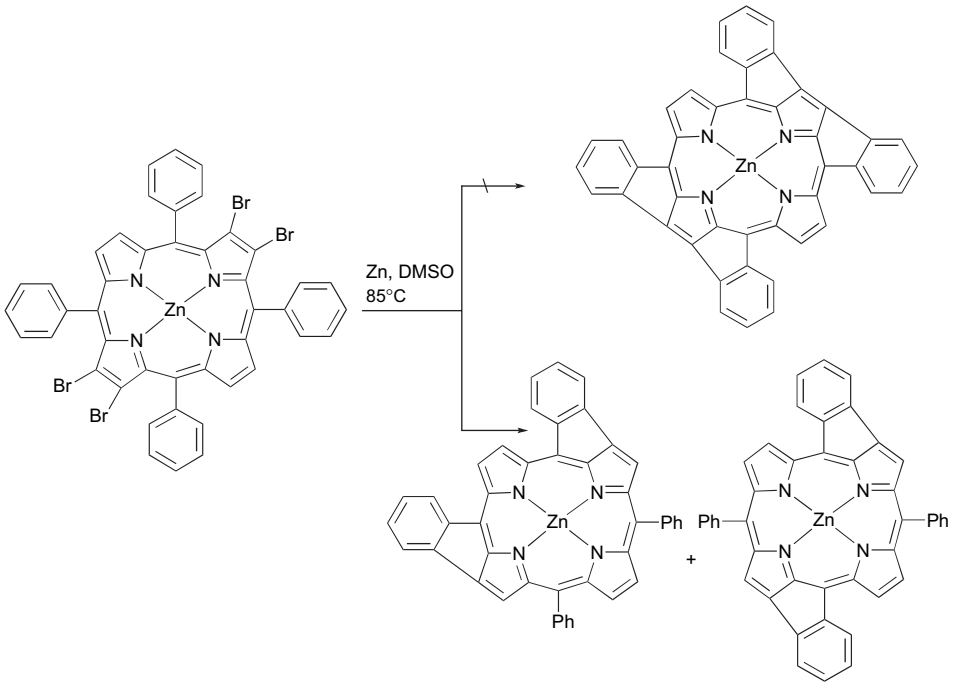
The synthesis of the so-called 'naphthoporphyrin' derivatives has been well documented in the literature by Callot, who used 2-formyl-5,10,15,20-tetraphenylporphyrinatocopper(II)[12] as an intermediate in an acid-catalysed condensation to yield oxonaphthoporphyrin.[13] In this reaction, the carbonyl carbon of the aldehyde group fuses to the *ortho* position of the adjacent phenyl group, producing, albeit in very low yield, an exocyclic six-membered ring containing a keto group (Scheme 5).

It was also found that substituted α-styryl-5,10,15,20-tetraphenylporphyrinatocobalt(III) could rearrange in the presence of low concentrations of acid to give the same naphthoporphyrin skeleton. The combination of air and TFA caused the cobalt(III)porphyrin to be oxidised to the corresponding π-cation radicals, which then suffered elimination followed by demetallation.[14] At low concentrations of acid, however, it was suggested that large amounts of starting material remained and reacted with either the cation radical or the α-styryl radical. The transfer of the styryl fragment

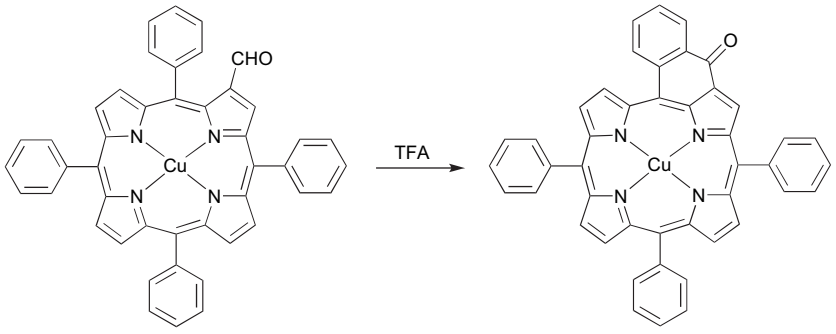




Scheme 3. Pd(0)-catalysed cyclisation of *meso*-(2-iodophenyl) porphyrins.



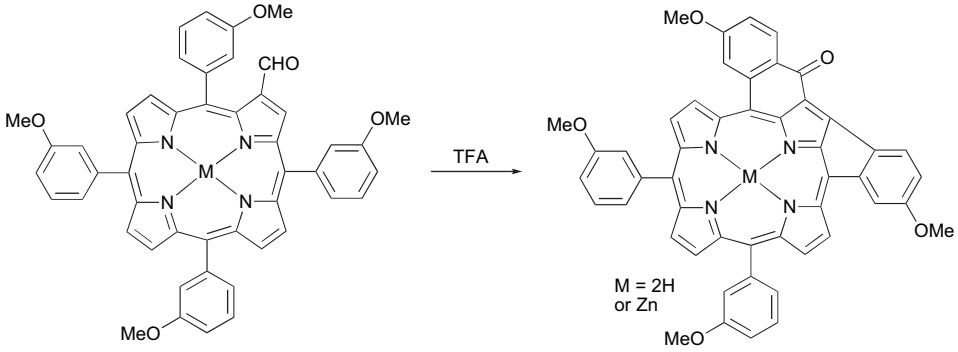
Scheme 4. Zinc-mediated intramolecular cyclisation of 2,3,12,13-tetrabromo-5,10,15,20-tetraphenylporphyrinatozinc.



Scheme 5. Callot's synthesis of an oxonaphthoporphyrin.

to the porphyrin β-position resulted in an olefinic intermediate, which underwent reaction with the adjacent phenyl group. In turn, the metal was lost, yielding a free-base naphthoporphyrin. The synthesis of these naphthoporphyrins provoked other studies into reactivity,[15] porphyrin oligomers,[16] and bis-acrylporphyrins with near-infrared absorbance.[17]

Much attention has been paid to naphthoporphyrin derivatives, due to their potential as photodynamic sensitisers. Dolphin et al.[18] synthesised a number of doubly cyclised derivatives (Scheme 6) that possessed enhanced absorptions in the far red region of the visible spectrum. This double cyclisation was attributed to electron-donating groups present on



Scheme 6. Synthesis of doubly cyclised naphthoporphyrin derivatives.

the *meta*-positions of the phenyl rings of the metallo-2-formyl-5,10,15,20-tetraphenylporphyrin starting material.

2.2.2. Purpurins. Purpurins are defined as tetrapyrrolic macrocycles containing a cyclopentyl ring fused to a reduced pyrrolic unit. They are formed by cyclisation of an appropriate side chain attached to the *meso*-position of the macrocycle, resulting in the formation of a five-membered ring. Like many porphyrins with modified optical properties, they received considerable interest as potential photodynamic sensitisers.[19]

Morgan et al.[19] presented results showing that *meso*-formylated etioporphyrinatonickel(II) could be converted into the corresponding purpurin in yields of up to 90%. This two-step procedure involved functional-group transformation of the aldehyde moiety into an unsaturated ester via a Wittig reaction and removal of the nickel, followed by the acid-catalysed cyclisation of the ester to form the five-membered ring and, hence, the purpurin (Scheme 7).

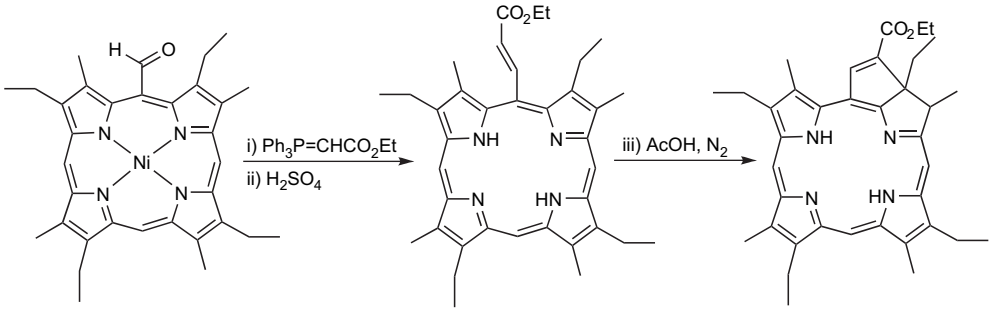
Gunter et al.[20] synthesised both type A and type B purpurins (Fig. 1) containing *meso*-phenyl substituents. Their findings were based on the theory that the purpurin yield was temperature dependent, e.g., purpurin B could be formed preferentially at higher temperatures.

By incorporating two vinylogous side chains, methods of synthesising doubly cyclised bacteriopurpurins have been investigated. Robinson[21] developed a new route to bacteriopurpurins from *meso*-substituted diacrylate octaalkylporphyrins (Scheme 8), and found that these compounds absorbed strongly in the region of 720–830 nm. Previously, Morgan et al.[19] had attempted to synthesise this class of compound via acidic catalysis. It was found, however, that the successful synthetic route required basic conditions, which resulted in the efficient cyclisation of *meso*-acrylate porphyrins to purpurins and bacteriopurpurins. Thus, 5,15-bis[β-(ethoxycarbonyl)vinyl]octaethylporphyrin was cyclised by refluxing in toluene/DBU for 6 h, producing two isomers of 5,15-octaethylbacteriopurpurin in 70% yield.

2.2.3. Benzochlorins. This class of compound is commonly synthesised by the acid-catalysed cyclisation of a corresponding metallo *meso*-(2-formylvinyl)porphyrin. Vicente and Smith[22] synthesised a series of porphyrins possessing 2-formylvinyl substituents by way of a modified Vilsmeier formylation developed by Inhoffen and co-workers.[23] Acid-promoted cyclisation of 2-formylvinyl porphyrins yielded a number of benzochlorins and benzobacteriochlorins. By incorporating two 2-formylvinyl groups into the porphyrin precursor, they were able to yield a mono-cyclised benzochlorin and a double-cyclised dibenzobacteriochlorin (Scheme 9). It was noted that, to achieve cyclisation, a divalent centrally chelated metal must be present.

Similar methods have been developed by Gunter and Robinson,[24] in an extension of previous work on purpurins.[20] Using the same 5,15-diphenylporphyrin skeleton, the group produced a number of 2-formylvinyl precursors and, in turn, synthesised the 5,15-diaryl-substituted benzochlorin derivatives (Scheme 10).

Other substituted benzochlorins have been synthesised and further modified by incorporating nonpolar side chains to increase the lipophilicity (Scheme 11).[25] Biologically, these



Scheme 7. Synthesis of etio purpurin.

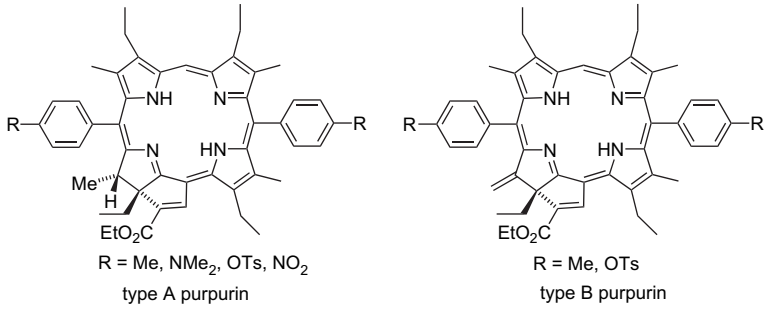
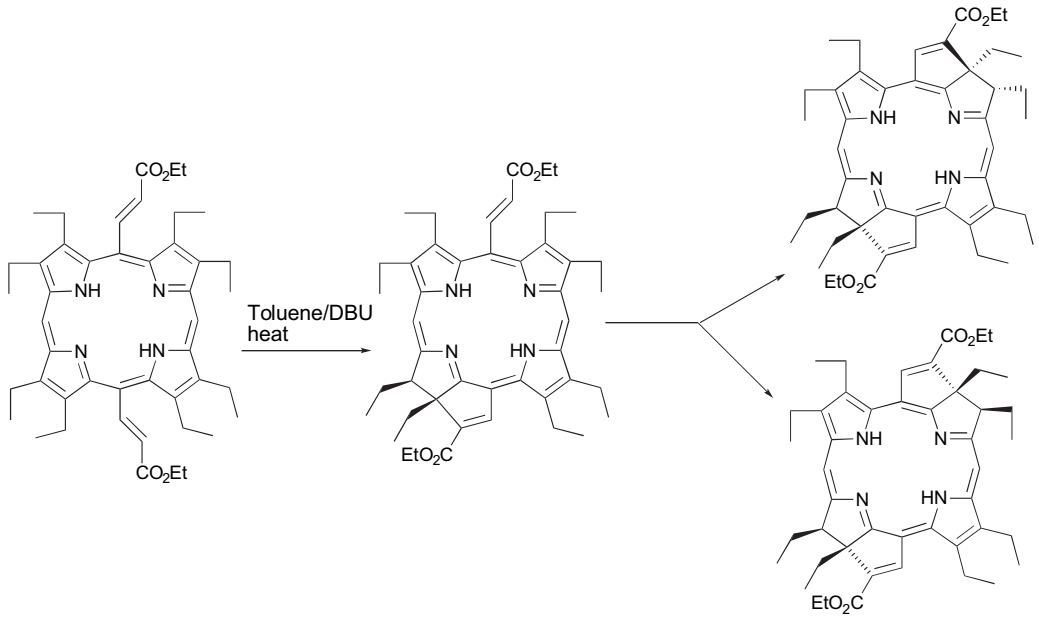
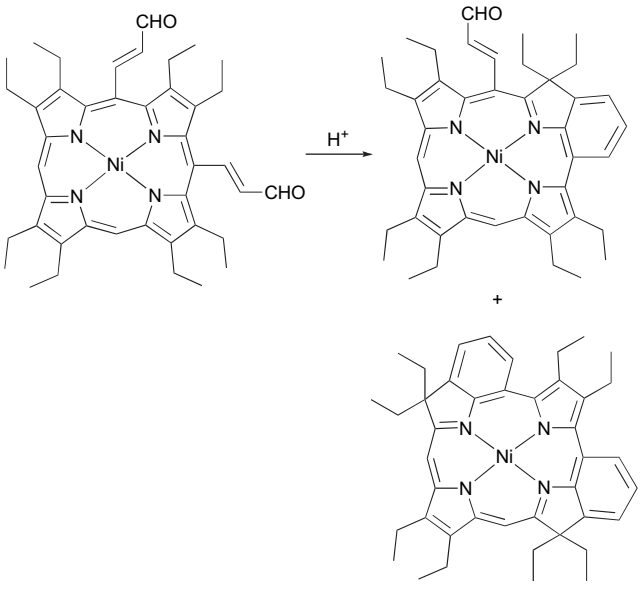


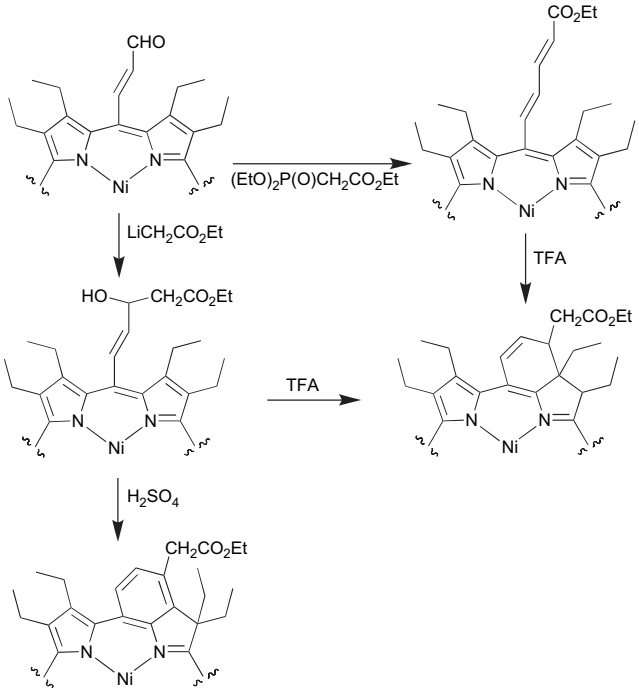
Figure 1. Types A and B purpurins.



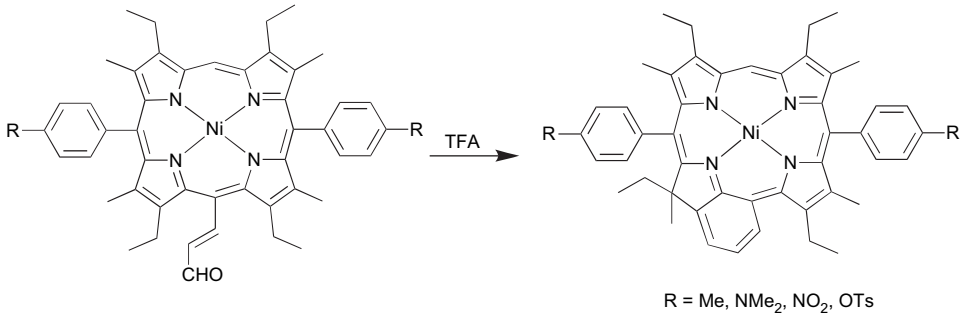
Scheme 8. Synthesis of 5,15-octaethylbacteriopurpurins.



Scheme 9. Synthesis of a benzochlorin and a dibenzobacteriochlorin.



Scheme 11. Preparation of lipophilic benzochlorins.



Scheme 10. Synthesis of 5,15-diphenyloctaalkylbenzochlorins.

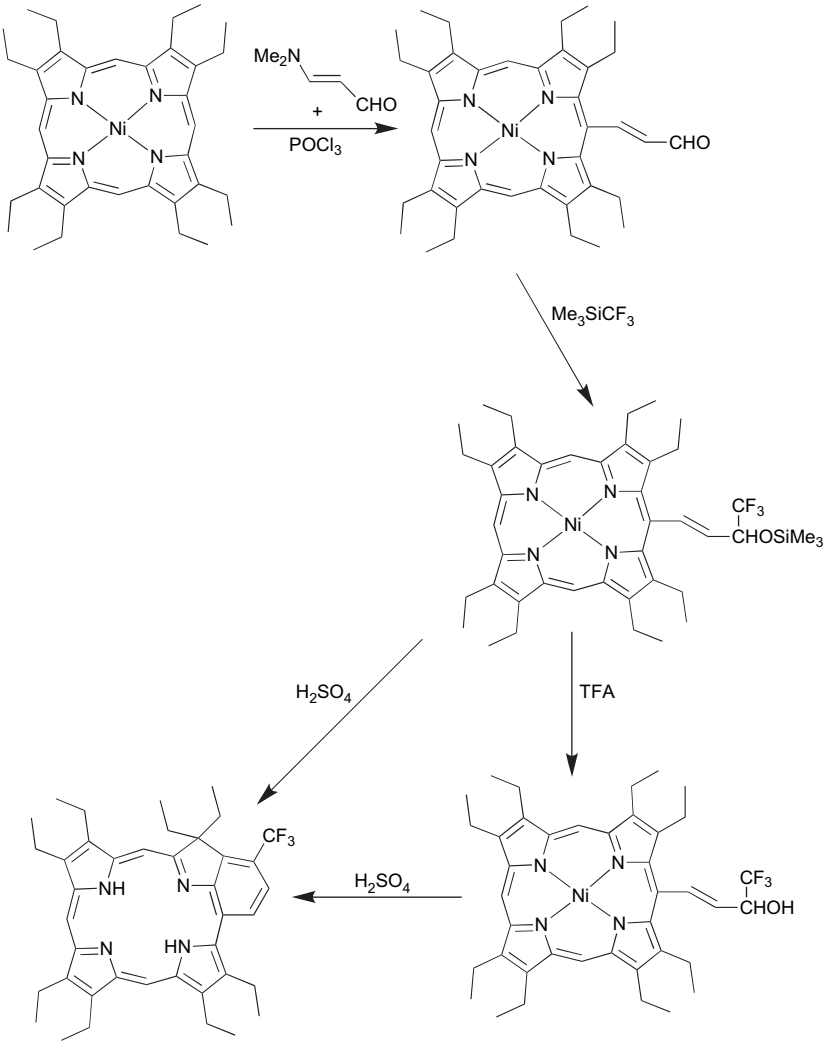
lipophilic benzochlorins were of great interest, and were produced in greater yield than the corresponding deuteroporphyrin derivatives.[22]

Many of the examples of benzochlorin synthesis are based on modification of octaethylporphyrin, as this compound is readily available commercially in both the free base and metallated forms, and is therefore a convenient starting material. Routes to fluorinated and non-fluorinated octaethylporphyrin-based benzochlorins have been developed by Pandey et al.[26] This work led to the synthesis of several benzochlorins with variable lipophilicity that were tested for their efficacy as drugs for photodynamic therapy. As with many of the examples discussed here, Vilsmeier formylation was initially used to attach a 2-formylvinyl group to one *meso*-position. The 2-formylvinyl side chain was then reacted with various fluorinated and non-fluorinated alkyl halides, yielding intermediates which, after acid-catalysed intramolecular cyclisation, generated the corresponding benzochlorins (Scheme 12).

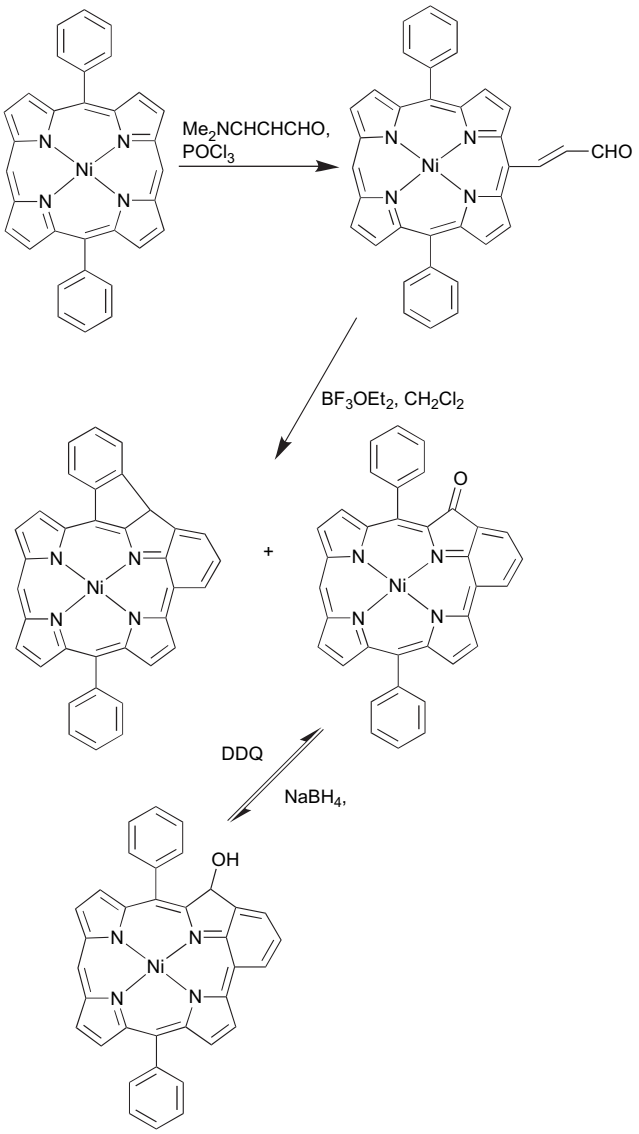
5,15-Diphenyloxobenzochlorins have been prepared by Boyle and Dolphin.[27] After vinylic formylation of 5,15-diphenylporphyrinatonickel(II), treatment with boron trifluoride etherate gave, unexpectedly, two products (Scheme 13), one of which was subsequently found to be an unusual multifused-ring benzochlorin.

2.2.4. Naphthochlorins. Until quite recently, the synthesis of naphthochlorins from octaalkylporphyrins had not been reported. Sengupta and Robinson[28,29] synthesised a number of *meso*-(2-hydroxymethylphenyl)octaalkyl-substituted porphyrins via methods developed by Johnson and Kay[30] and Grigg et al.,[31] and performed cyclisation reactions under acidic conditions. Interestingly, comparison of the octaethylnaphthochlorin with the octaethylbenzochlorin (Fig. 2) synthesised by Arnold et al.[32] revealed that the free base form of the naphthochlorin exhibited the greater long wavelength absorbance, but, conversely, when the metallated species were compared, the benzochlorin showed a greater bathochromic shift.

As mentioned above, the more common methods to access these molecules involve cyclisation of a vinylic group to yield the naphthochlorin. This method is facilitated by the ease with which the vinylic group can be formed from the corresponding formylporphyrins by way of the Wittig reaction.[12,32] Cavaleiro et al.[33] reported an intramolecular



Scheme 12. Synthesis of fluorinated benzochlorins.



Scheme 13. Synthesis of 5,15-diphenyl-7-oxobenzochlorins.

cyclisation of the Ni(II) complex of β-vinyl-5,10,15,20-tetraphenylporphyrins, resulting in naphthochlorins as the major products. In this case, treatment of 2-vinyl-5,10,15,20-tetraphenylporphyrins with dilute sulfuric acid did not afford the expected demetallated product, but, instead, the corresponding benzochlorins were formed in 60% yield (Scheme 14).

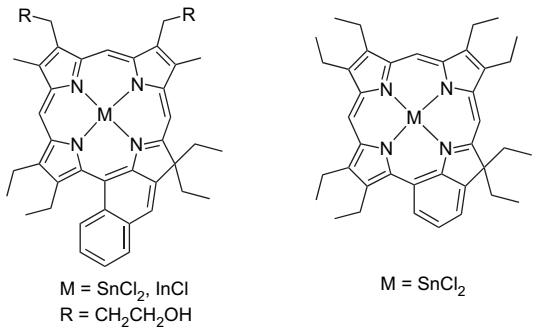


Figure 2. Synthesis of octaalkylbenzochlorins.

3. Porphyrins with fused rings formed via intermolecular reactions

3.1. Diels–Alder reactions

A versatile route to the synthesis of chlorins is the Diels–Alder reaction of vinylporphyrins with electron-deficient dienophiles,[34] and the same methodology can be applied to the synthesis of isobacteriochlorins and bacteriochlorins if divinylporphyrins are used.[35] Cavaleiro et al.[36] investigated [4+2] cycloadditions using the porphyrin exocyclic double bonds as the 2π-electron component. By heating 5,10,15,20-tetraphenyl porphyrin and an aromatic sulfone in trichlorobenzene for 7 h, a [4+2] cycloaddition reaction took place, yielding three products, a chlorin with a fused tetrahydronaphthalene ring (Scheme 15) as the major product, and two other naphthoporphyrins as the minor products.

3.2. Cycloaddition reactions

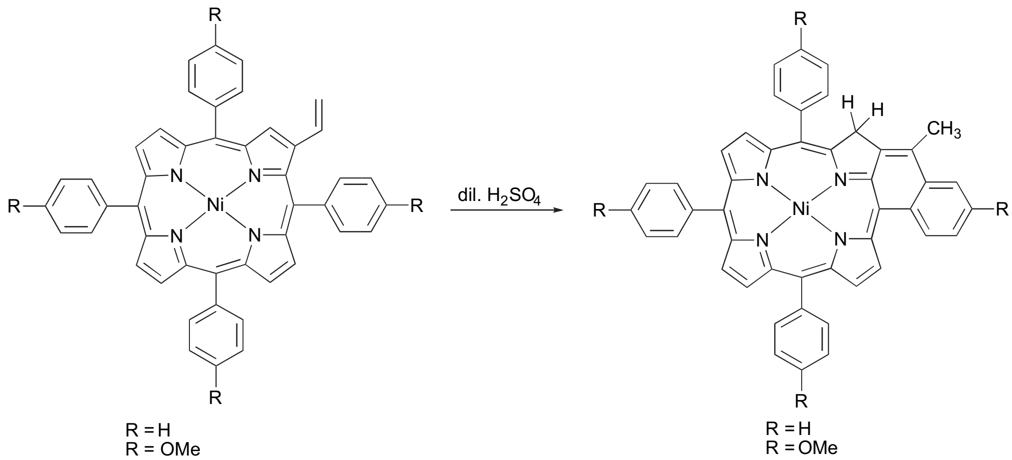
Azomethane ylides were reported by Cavaleiro et al.[37,38] to react with 5,10,15,20-tetraarylporphyrins as the dipolarophile in 1,3 cycloadditions, generating pyrrolidine-fused chlorins and bacteriochlorins in good yields (Scheme 16).

N-Protected pyrroles have been successfully used in a variety of [4+2] cycloaddition reactions with activated dienophiles, as described by Zhang and Trudell.[39] Smith et al.[40] synthesised β-fused pyrroloporphyrins from the Barton–Zard condensation[41] of metallo-2-nitro-5,10,15,20-tetraphenylporphyrins with isocyanoacetates. Studies on the cycloaddition reactions of β-fused metallopyrroloporphyrins with dimethyl acetylenedicarboxylate led to a synthetic route to benzoporphyrins and benzochlorins.[42] Interestingly, when synthesising benzoporphyrins by this route (Scheme 17), the Diels–Alder adduct was formed first, and then converted into the corresponding benzoporphyrin upon refluxing, conversion into the sole deaminated product (50–80% yield) occurring only after prolonged heating (overnight).

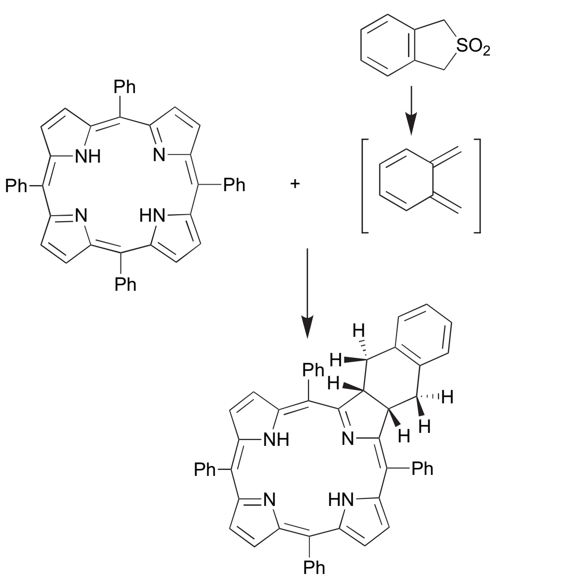
Mononitration of the corresponding benzoporphyrin and subsequent conjugate addition of malononitrile to the nitroalkene subunit of the benzoporphyrin in the presence of NaH in refluxing tetrahydrofuran[43] led to a β-fused benzochlorin as the major product (Fig. 3).

Similarly, as with *o*-quinodimethanes,[36] azomethine ylides[37] and nitrones,[43] it was found that sugar nitrones could be fused to porphyrin macrocycles. Carbohydrate derivatives of porphyrins have shown promise for applications in photodynamic therapy,[44] as these conjugates have demonstrated good water solubility and selectivity for cancer cells. By way of the 1,3-dipolar cycloaddition approach, Cavaleiro et al.[45] synthesised glyco derivatives of chlorins and bacteriochlorins by reacting several readily available sugar nitrones[46] with 5,10,15,20-tetra(pentafluorophenyl)porphyrin (Scheme 18).

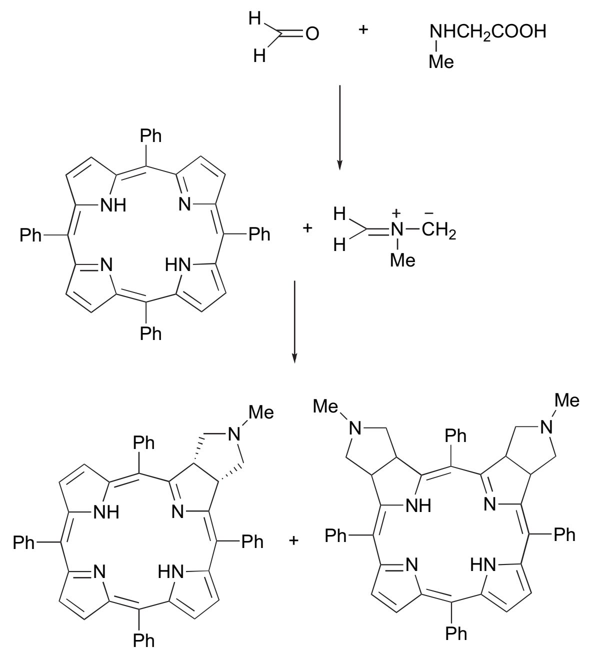
1,3-Dipolar [3+2] cycloaddition reactions are an effective method for the synthesis of five-membered heterocycles,[47] and these reactions have been successfully applied to



Scheme 14. Synthesis of naphthochlorins from 2-vinyl-5,10,15,20-tetraphenylporphyrins.



Scheme 15. 5,10,15,20-Tetraphenylporphyrin as a dienophile in the Diels–Alder reaction.



Scheme 16. Synthesis of pyrrolidine-fused chlorins and bacteriochlorins.

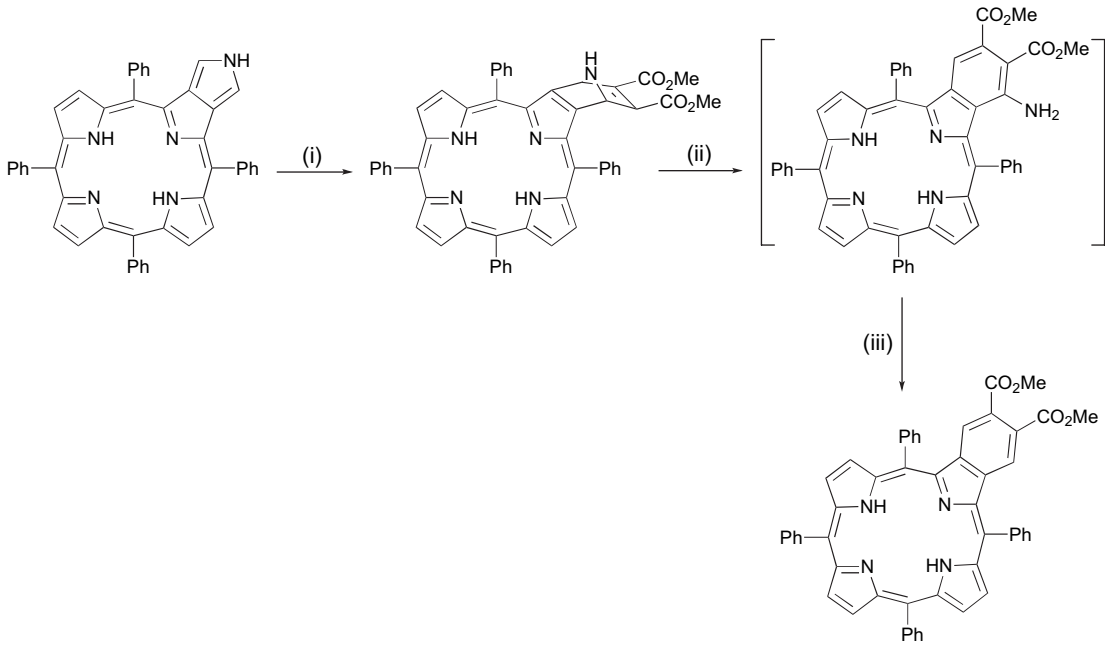
porphyrins by the group of Cavaleiro.[38] It has been noted that electron-deficient carbonyl ylides react with many dipolarophiles including aromatic systems.[48] More recently, non-stabilised carbonyl ylides have been shown to react with both electron-rich and electron-poor dipolarophiles.[49] Fleming and Dolphin[50] exploited these findings to devise a convenient route to chlorins via carbonyl ylides. On reacting 5,10,15,20-tetraphenylporphyrin with tetracyanoethylene oxide, the corresponding cycloadduct was produced in moderate yield (Scheme 19). It has been reported that the tetracyanoethylene oxide undergoes a first-order thermal electrocyclic ring opening to form the carbonyl ylide in refluxing toluene. The ylide then reacts via a 1,3-dipolar cycloaddition with the dipolarophile to yield a [3+2] adduct.[48]

Isoxazoline-fused chlorins have been synthesised as starting materials for further funtionalisation via chemical transformations of the isoxazoline ring by Li et al.[51] (Scheme 20).

The reaction of 5,10,15,20-tetra(4-chlorophenyl)porphyrin with an excess of 2,6-dichlorobenzonitrile oxide in benzene under reflux resulted in a mixture of three compounds. The chlorin was isolated as the major product in 53% yield. Interestingly, the reaction of porphyrins possessing electron-withdrawing aryl groups increased the yield, but porphyrins bearing electron-donating groups gave no cycloaddition adducts. This result obeyed the theory of reactivity of normal alkenes to nitrile oxide, whereby electron-withdrawing alkenes favour the cycloaddition reaction.[47]

3.3. Bergman cyclisation of porphyrin diynes

Only recently the Bergman cyclisation[52,53] has been applied to the synthesis of porphyrins bearing fused exocyclic rings.



Scheme 17. Synthesis of benzoporphyrins via [4+2] cycloaddition; reaction conditions: (i) dimethyl acetylenedicarboxylate, toluene, reflux; (ii) reflux overnight; (iii) continuous heating or reflux for 30 min in 1,2-trichlorobenzene.

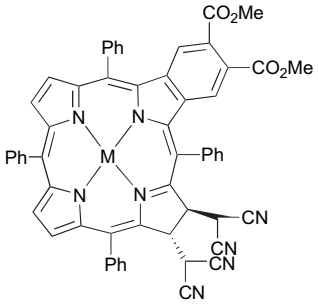
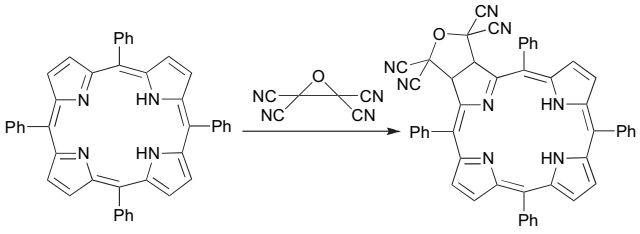


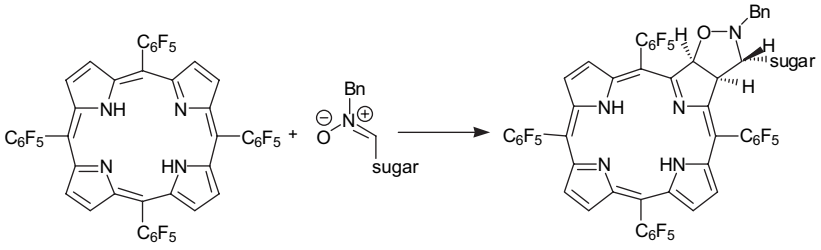
Figure 3. Benzochlorins generated by conjugate addition of malonitrile.



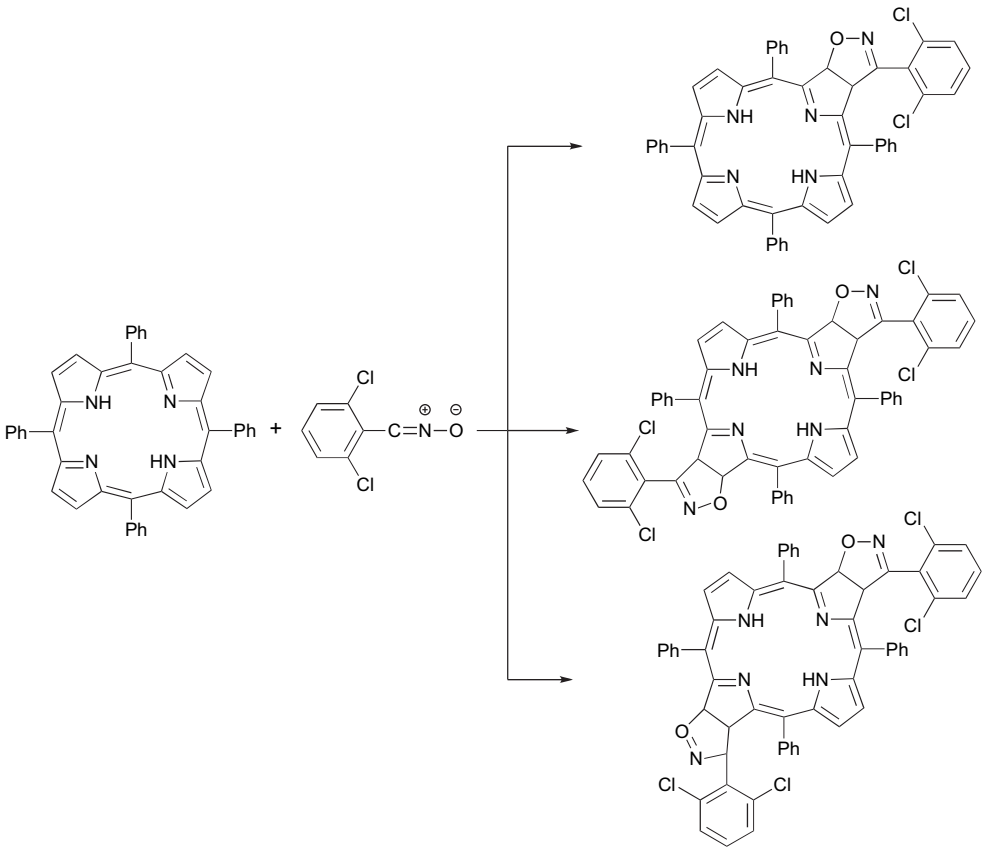
Scheme 19. 1,3-Dipolar cycloaddition of porphyrin and carbonyl ylide.

This method is described as a 'thermal benzoannulation' whereby the cyclisation of an enediyne is accomplished by heating the reaction mixture. The methodology was based on the realisation that two adjacent acetylenic moieties attached to the β-positions might behave in a similar fashion to components of an enediyne and cyclise under Bergman-type conditions. Smith et al.[54] proposed this theory and successfully demonstrated it experimentally. The first step in the synthesis involved a Pd(0)-catalysed cross-coupling[55] reaction with alkynyl-trimethylstannanes. In the second step the trimethylsilyl groups were cleaved, and then, finally, the porphyrin diyne was heated to reflux in cyclohexadiene/chlorobenzene at 190 °C to yield a picenoporphyrin. According to the literature, this was not the anticipated result, as only monobenzoporphyrin products were expected. In reality the reaction proceeded via a cascade tandem radical cyclisation to yield a multicarbocycle (Scheme 21).[54]

Zaleski et al.[56] discovered that this cascade tandem radical cyclisation could be performed at room temperature in the presence of DDQ. This indicated that the dehydrogenation step is rate limiting. To prevent the participation of *meso*-phenyl substituents in the reaction pathway, Spence et al.[57]

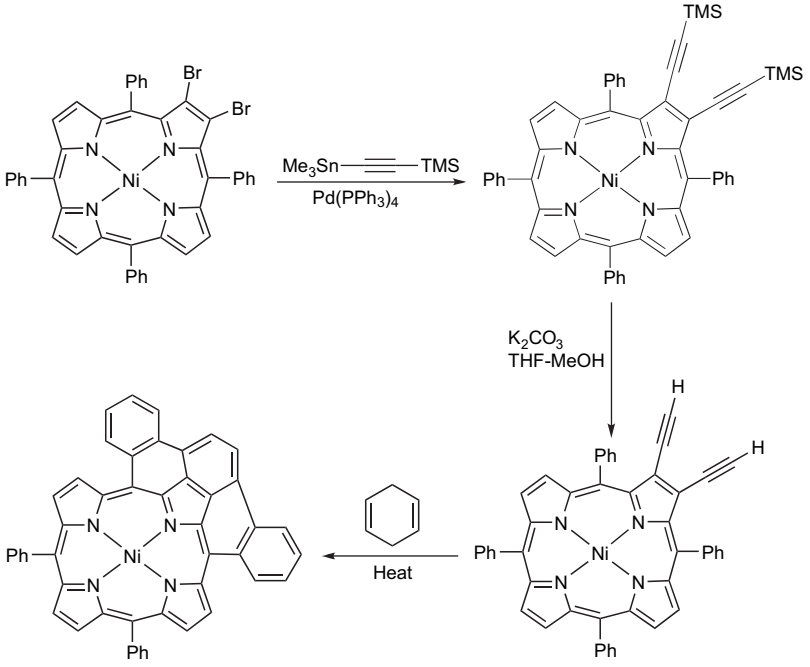


Scheme 18. Synthesis of glycoconjugated isoazolidine-fused chlorins.

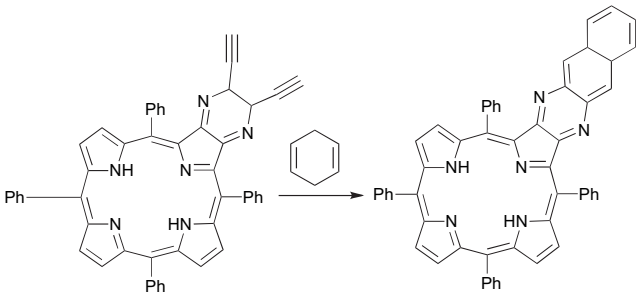


Scheme 20. Synthesis of isoxazoline-fused chlorins and bacteriochlorins.

prepared a porphyrin–enediyne that contained a conjugate quinoxaline spacer[58] between the enediyne core and the porphyrin macrocycle (Scheme 22). This spacer ensures that the enediyne is far enough away from the aromatic pathway of the macrocycle, thus suppressing tandem cyclisation to a picenoporphyrin.[54]



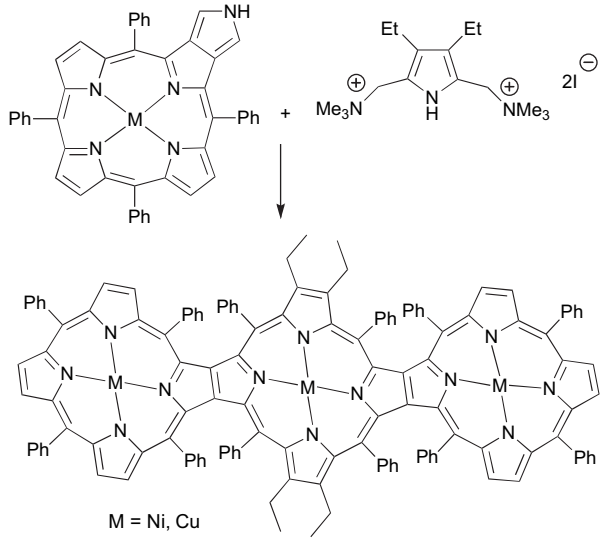
Scheme 21. Tandem radical cyclisation of 2,3-dialkynylporphyrins.



Scheme 22. Bergman cyclisation of porphyrin–enediyne.

4. Fused-ring systems incorporating multiple porphyrins

The syntheses of such covalently linked porphyrins have been investigated in order to examine their unique photoelectronic properties and potential applications as mimics of light harvesting in photosynthesis, and also as electron-transfer moieties in molecular wires.[59] Tetramerisation of pyrroloporphyrins is one possible way of producing cruciform porphyrins, but steric congestion undermines the viability and application of this method.[5] A synthesis of fully or directly fused oligoporphyrins that share a common extended π-electron system has been developed by Smith et al.[60] By reacting a nucleophilic, sterically hindered pyrrole with a pyrroloporphyrin, a porphyrin trimer was produced (Scheme 23).



Scheme 23. Synthesis of fused oligoporphyrins.

A cruciform pentamer was synthesised by Smith et al. [61] by acid-catalysed tetramerisation of a less sterically hindered 2*H*-dihydroisoindoloporphyrin. The pentamer (Scheme 24) contained two one-carbon linkages or 'spacers' between the pyrrolic rings and the porphyrin. The corresponding pyrroloporphyrin was synthesised via a [4+2] cycloaddition reaction of 1,1-sulfolano[3,4-*c*]pyrrole[36] and the *meso*-tetraarylporphyrin. This was then followed by acid-catalysed tetramerisation of the pyrroloporphyrin, and treatment of the pentamer with an excess of DDQ to give the fully conjugated pentamer.[61]

Recently, the properties of *meso–meso*-linked porphyrin arrays have been noted as possible photonic wires.[62–64] Osuka et al.[65] linked Cu(II)-porphyrins at both the *meso*- and β-positions with 2 equiv of tris(4-bromo-phenyl)aminium hexachloroantimonate (BA-HA) in C_6F_6 at room temperature for two days resulting in the triply linked diporphyrins in 62 and 6% yields (Fig. 4).

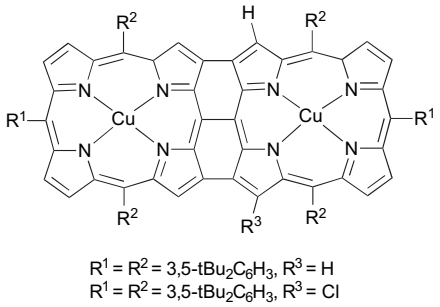
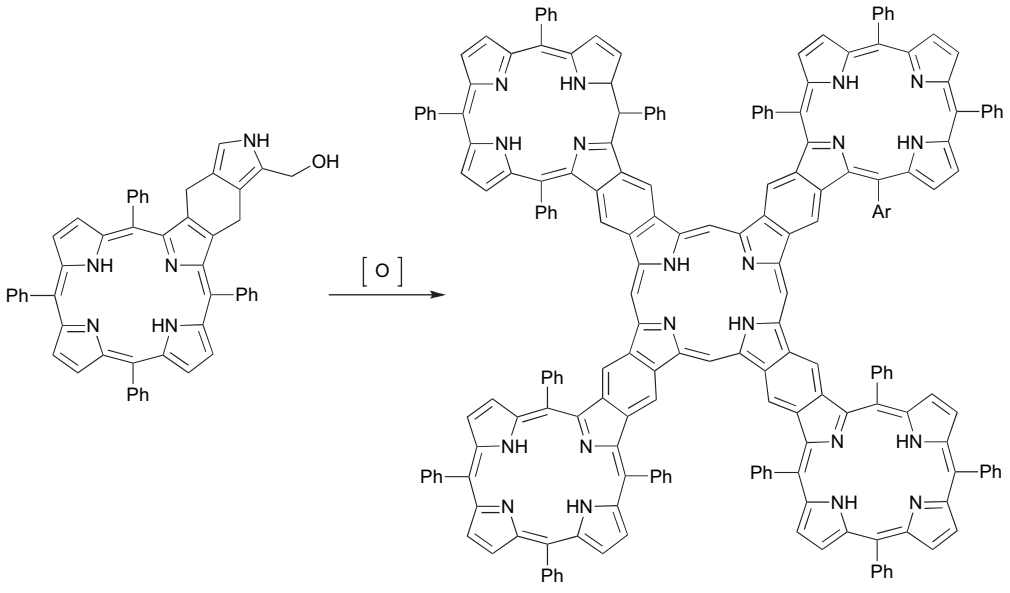


Figure 4. Triply fused diporphyrin.



Scheme 24. Synthesis of cruciform porphyrin pentamers.

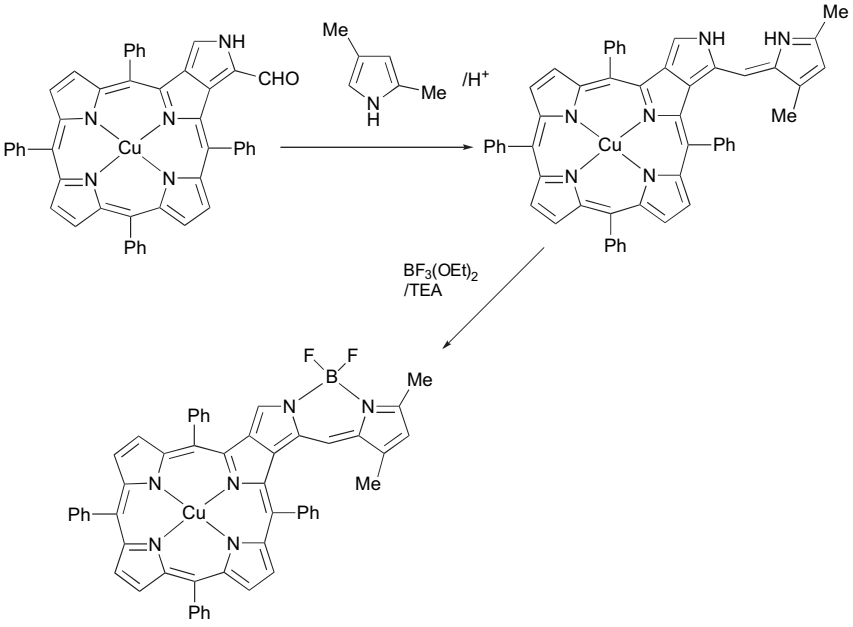
5. Use of porphyrins bearing fused rings to assemble heterodimeric systems

5.1. Fused porphyrin–BODIPY dyads

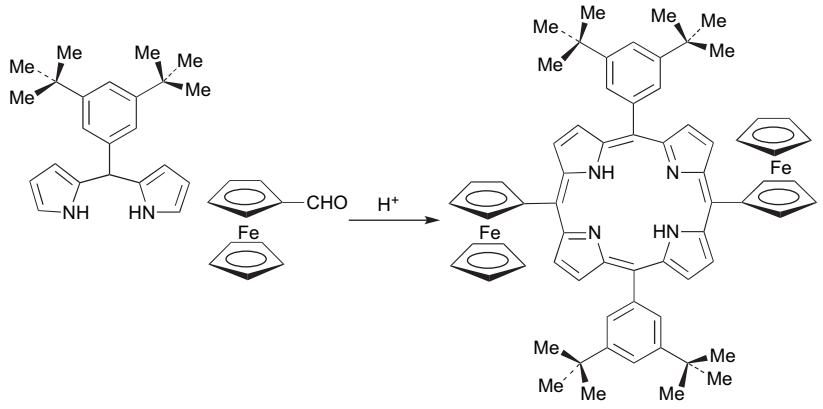
Fused porphyrin macrocycles are of great interest as potential molecular wires.[66–68] Smith's group had focused its attention on heterodyads, in which a porphyrin and another chromophore are fused through two neighbouring β-carbons, therefore giving rise to the extended conjugation of the aromatic π-system.[69] Among the different chromophores of interest, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY®) and related dyes had already been investigated for several applications.[70] In general, the pyrroloporphyrin[40] was used as the starting material in the synthesis of the fused BODIPY® and porphyrin moieties. The synthesis of CuTPP-BODIPY® began with the formylation of Cu-pyrroloporphyrin (Scheme 25).[71] The formylation of pyrroles is generally carried out by the Vilsmeier reaction, ($POCl_3$ and DMF), but the Vilsmeier reagents have been well documented as reacting with the β-positions of tetraarylporphyrins.[72] TFA and trimethyl orthoformate were used to selectively functionalise the pyrrole subunit.[73] The acid-catalysed condensation of formylpyrroloporphyrin gave dipyrromethenoporphyrin. Finally, treating the dipyrromethenoporphyrin with boron trifluoride etherate yielded the BODIPY® complex under basic conditions.[71]

5.2. Fused metallocenoporphyrins

In this final section, the synthesis of porphyrin/metallocene dyads will be discussed. The most commonly reported studies of porphyrin/metallocene dyads illustrate the metallocene part attached to the *meso*- or β-positions of the porphyrin through spacers,[74–82] or even directly through a central metal ion,[83] and the more uncommon direct linkages through a C–C bond at the *meso*-position have also been reported.[84,85] Smith et al. have synthesised a ferrocenylporphyrin via their previously reported work on Heck-type reactions and also via a 2+2 condensation (Scheme 26).



Scheme 25. Synthesis of CuTPP-BODIPY®.



Scheme 26. Synthesis of a 5,15-ferrocenylporphyrin.

Smith's group further investigated methods to synthesise the fused metallocenoporphyrins. Their aim was to synthesise the target compound (Fig. 5) via the corresponding tetrapropanoporphyrin.[86] The method used to obtain the precursors, however, had its limitations.[87]

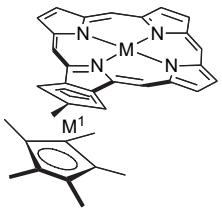
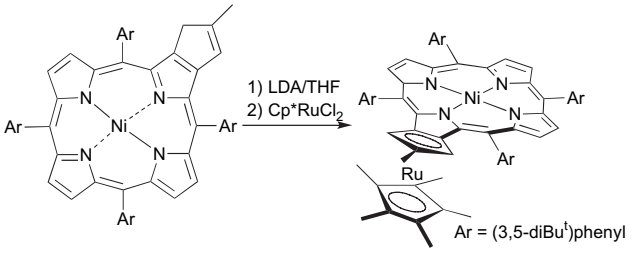


Figure 5. Fused metallocenoporphyrin.

After a consideration of the work by Holzapfel and van der Merwe,[88] Smith et al. subjected 2-nitro-5,10,15,20-tetra(3,5-di-*tert*-butylphenyl)porphyrinatonickel(II) to a palladium(0)-catalysed [3+2] cycloaddition with 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate, which gave the corresponding starting material. Formation of the anion by treatment with LDA and then addition of the Cp* resulted in the fused ruthenocenoporphyrin (Scheme 27).[69] Treatment of the methylcyclohexenylporphyrinatonickel(II) starting material with $FeCl_2$ yielded a bisporphyrinferrocene.[89,90]



Scheme 27. Synthesis of metallocenoporphyrins.

6. Conclusions

Reactions leading to porphyrins bearing fused rings have provided a wide range of novel and previously unknown macrocycles for study. The understanding of the spectroscopic, electrochemical and biological properties of porphyrin containing proteins and assemblies has thus been expanded at the fundamental level. On a practical level this has also led to the development of many new products, a particularly noteworthy example being the Diels–Alder adduct obtained from the reaction of protoporphyrin IX dimethyl ester with dimethyl acetylenedicarboxylate[91] followed by base-catalysed isomerisation and partial hydrolysis. The resulting chlorin bearing a six-membered ring fused to the A pyrrolic ring has now been developed into a successful drug for the photodynamic treatment of age related macular degeneration by QLT Inc. and Novartis. Under the trade name Visudyne® world-wide sales for 2005 were reported to be US$484.[92] In light of these intellectual and financial incentives it seems likely that this area of porphyrin synthetic chemistry will continue to be of great interest in the foreseeable future.

References and notes

1. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, CA, 2000; Vols. 1–20.
2. Smith, K. M.; Langry, K. C. *J. Org. Chem.* **1983**, *48*, 500.
3. Smith, K. M.; Langry, K. C.; Minnetian, O. M. *J. Org. Chem.* **1984**, *49*, 4602.
4. Morris, I. K.; Snow, K. M.; Smith, N. W.; Smith, K. M. *J. Org. Chem.* **1990**, *55*, 1231.
5. Vicente, M. G.; Smith, K. M. *J. Porphyrins Phthalocyanines* **2004**, *8*, 26.
6. Fox, S.; Boyle, R. W. *Chem. Commun.* **2004**, 1322.
7. Erdik, E. *Tetrahedron* **1987**, *43*, 2203.
8. Shen, D.-M.; Liu, C.; Chen, Q.-Y. *Chem. Commun.* **2005**, 4982.
9. Newman, M. S.; Arens, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946.
10. Fabian, J.; Nakazumi, H.; Matusuoka, M. *Chem. Rev.* **1992**, *92*, 1197.
11. Brown, S. B.; Truscott, T. G. *Chem. Br.* **1993**, *29*, 955.
12. Callot, H. J. *Tetrahedron* **1973**, *29*, 899.
13. Callot, H. J.; Schaeffer, E.; Cromer, R.; Metz, F. *Tetrahedron* **1990**, *46*, 5253.
14. Callot, H. J.; Metz, F. *J. Chem. Soc., Chem. Commun.* **1982**, 947.
15. Richeter, S.; Jeandon, C.; Ruppert, R.; Callot, H. J. *Tetrahedron Lett.* **2000**, *42*, 2103.
16. Richeter, S.; Jeandon, C.; Ruppert, R.; Callot, H. J. *Chem. Commun.* **2002**, 266.
17. Richeter, S.; Jeandon, C.; Kyritsakas, N.; Ruppert, R.; Callot, H. J. *J. Org. Chem.* **2003**, *68*, 9200.
18. Barloy, L.; Dolphin, D.; Dupre, D.; Wijesekera, T. P. *J. Org. Chem.* **1994**, *59*, 7976.
19. Morgan, A. R.; Rampersaud, A.; Garbo, G. M.; Keck, R. W.; Selman, S. H. *J. Med. Chem.* **1989**, 904.
20. Gunter, M. J.; Robinson, B. C. *Tetrahedron Lett.* **1990**, *31*, 285.
21. Robinson, B. C. *Tetrahedron* **2000**, *56*, 6005.
22. Vicente, M. G. H.; Smith, K. M. *J. Org. Chem.* **1991**, *56*, 4407.
23. Inhoffen, H. H.; Farlop, J. H.; Voigt, H.; Brochmann, H. *J. Org. Chem.* **1966**, *56*, 4407.
24. Gunter, M. J.; Robinson, B. C. *Tetrahedron* **1991**, *47*, 7868.
25. Kohil, D. H.; Morgan, A. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2175.
26. Li, G.; Graham, A.; Potter, W.; Grossman, Z. D.; Oseroff, A.; Dougherty, T. J.; Pandey, R. K. *J. Org. Chem.* **2001**, *66*, 1316.
27. Boyle, R. W.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1994**, 2463.
28. Sengupta, D.; Robinson, B. C. *Tetrahedron* **2002**, *58*, 8737.
29. Sengupta, D.; Robinson, B. C. *Tetrahedron* **2002**, *58*, 5497.
30. Johnson, A. W.; Kay, I. T. *J. Chem. Soc.* **1965**, 1620.
31. Grigg, R.; Johnson, A. W.; Kenyon, R.; Math, V. B.; Richardson, K. *J. Chem. Soc. C* **1969**, 176.
32. Arnold, D. P.; Gaete-Holmes, R.; Johnson, A. W.; Smith, A. R. P.; Williams, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1660.
33. Faustino, M. A.; Neves, M. G. P. S.; Vicente, M. G. H.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **1995**, *36*, 5977.
34. Callot, H. J.; Johnson, A. W.; Sweeney, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1424.
35. DiNello, R. K.; Dolphin, D. *J. Org. Chem.* **1980**, *45*, 5196.
36. Vicente, M. G. H.; Tome, A. C.; Walter, A.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **1997**, *38*, 3639.
37. Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *Chem. Commun.* **1999**, 1767.
38. Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Org. Chem.* **2005**, *70*, 2306.

39. Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189.
40. (a) Jaquinod, L.; Gros, C.; Olmstead, M. M.; Antolovich, M.; Smith, K. M. *Chem. Commun.* **1996**, 1475; (b) Gros, C. P.; Jaquinod, L.; Khong, R. G.; Olmstead, M. M.; Smith, K. M. *J. Porphyrins Phthalocyanines* **1997**, *1*, 201.
41. Barton, D. H. R.; Kervagoret, R. G.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587.
42. Vicente, M. G. H.; Jaquinod, L.; Khoury, R. G.; Madrona, A. Y.; Smith, K. M. *Tetrahedron Lett.* **1999**, *40*, 8763.
43. Shea, K. M.; Jaquinod, L.; Smith, K. M. *J. Org. Chem.* **1998**, *63*, 7013.
44. Pandey, R. K. *J. Porphyrins Phthalocyanines* **2000**, *4*, 368.
45. Silva, A. M. G.; Tome, A. C.; Neves, M. G. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Perrone, D.; Dondoni, A. *Tetrahedron Lett.* **2002**, *43*, 603.
46. Dondoni, A.; Franco, S.; Juniquera, F.; Merchain, F.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2537.
47. Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padawa, A., Ed.; Wiley Interscience: New York, NY, 1984.
48. Linn, N. J.; Benson, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 3657.
49. Hojo, M.; Aihara, H.; Sakata, K.; Hosomi, A. *J. Org. Chem.* **1997**, *62*, 8610.
50. Fleming, J.; Dolphin, D. *Tetrahedron Lett.* **2002**, *43*, 7281.
51. Li, X.; Zhuang, J.; Li, Y.; Liu, H.; Wang, S.; Zhu, D. *Tetrahedron Lett.* **2005**, *46*, 1555.
52. Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.
53. Lockhart, T. P.; Comita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082.
54. Aihara, H.; Jaquinod, L.; Nurco, D. J.; Smith, K. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3439.
55. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
56. Nath, M.; Huffman, J. C.; Zaleski, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 11484.
57. Spence, J. D.; Cline, E. D.; LLagostera, D. M.; O'Toole, P. S. *Chem. Commun.* **2004**, 180.
58. Crossley, M. J.; Burn, P. L. *J. Chem. Soc., Chem. Commun.* **1987**, 39.
59. (a) Norsten, T.; Branda, N. *Chem. Commun.* **1998**, 1257; (b) Warrener, R. N.; Johnson, M. R.; Gunter, M. J. *Synlett* **1998**, 593.
60. Jaquinod, L.; Siri, O.; Khoury, R. G.; Smith, K. M. *Chem. Commun.* **1998**, 1261.
61. Vicente, M. G. H.; Cancilla, M. T.; Lebrilla, C. B.; Smith, K. M. *Chem. Commun.* **1998**, 2355.
62. Osuka, A.; Shimidzu, H. *Angew. Chem., Int. Ed.* **1997**, *36*, 135.
63. Arantani, N.; Osuka, A.; Kim, Y. H.; Jeong, D. H.; Kim, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1458.
64. Ogawa, T.; Nishimoto, Y.; Yoshida, N.; Ono, N.; Osuka, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 176.
65. Tsuda, A.; Furuta, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2549.
66. Lu, T. X.; Reimers, J. R.; Crossley, M. J.; Hush, N. S. *J. Phys. Chem.* **1994**, *98*, 11878.
67. Reimers, J. R.; Lu, T. X.; Crossley, M. J.; Hush, N. S. *Chem. Phys. Lett.* **1996**, *256*, 353.
68. Reimers, J. R.; Hall, L. E.; Crossley, M. J.; Hush, N. S. *J. Phys. Chem.* **1999**, *103*, 4385.
69. Wang, H. J. H.; Jaquinod, L.; Nurco, D. J.; Vicente, M. G. H.; Smith, K. M. *Chem. Commun.* **2001**, 2646.
70. (a) Haugland, R. P.; Kang, H. C. U.S. Patent 4,774,339, 1998; (b) Molecular Probes Inc., Eugene, OR.
71. Kenyu, T.; Jaquinod, L.; Paolesse, R.; Nardis, S.; Di Natale, C.; Di Carlo, A.; Prodi, L.; Montalti, M.; Zaccheroni, N.; Smith, K. M. *Tetrahedron* **2004**, *60*, 1099.
72. Jaquinod, L. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, CA, 2000; Vol. 1, p 201.
73. Montforts, F.; Scheurich, G.; Meier, A.; Haake, G.; Hoper, F. *Tetrahedron Lett.* **1991**, *29*, 3477.
74. Imahori, H.; Yamada, H.; Nishimura, Y.; Yamazaki, I.; Sakata, Y. *J. Phys. Chem. B* **2000**, *104*, 2099.
75. Fujistuka, M.; Ito, O.; Imahori, H.; Yamada, K.; Yamada, H.; Sakata, Y. *Chem. Lett.* **1999**, 721.
76. Yanagida, M.; Kanai, T.; Zhang, X.; Kondo, T.; Uosaki, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2555.
77. Burrell, A. K.; Campbell, W. M.; Officer, D. L.; Scott, S. M.; Gordon, K. C.; McDonald, M. R. *J. Chem. Soc., Dalton Trans.* **1999**, 3349.
78. Wagner, R. W.; Brown, P. A.; Johnson, T. E.; Lindsey, J. S. *Chem. Commun.* **1999**, 1165.
79. Imahori, H.; Yamada, H.; Ozawa, S.; Ushida, K.; Sakata, Y. *Chem. Commun.* **1999**, 1165.
80. Imahori, H.; Norieda, H.; Yamada, H.; Nishimura, Y.; Yamazaki, I.; Sakata, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 100.
81. Rhee, S. W.; Na, Y. H.; Do, Y.; Kim, J. *Inorg. Chim. Acta* **2000**, *309*, 49.
82. Rhee, S. W.; Park, B. B.; Do, Y.; Kim, J. *Polyhedron* **2000**, *19*, 1961.
83. Maiya, G. B.; Barbe, J.-M.; Kadish, K. M. *Inorg. Chem.* **1989**, *28*, 2524.
84. Loim, N. M.; Abramova, N. V.; Sokolov, V. L. *Mendeleev Commun.* **1996**, 46.
85. Boyd, P. D. W.; Burrell, A. K.; Campbell, W. M.; Cocks, P. A.; Gordon, K. C.; Jameson, G. B.; Officer, D. L.; Zhao, Z. *Chem. Commun.* **1999**, 637.
86. Senge, M. O.; Vicente, M. G. H.; Parkin, S. R.; Hope, H.; Smith, K. M. *Z. Naturforsch., B: Chem. Sci.* **1992**, *23*, 1189.
87. Chang, C. K.; Sotiriou, C. *J. Org. Chem.* **1987**, *52*, 926.
88. Holzapfel, C. W.; van der Merwe, T. L. *Tetrahedron Lett.* **1996**, *37*, 2307.
89. Abraham, R. J.; Smith, K. M.; Goff, D. A.; Bobe, F. W. *J. Am. Chem. Soc.* **1985**, *107*, 1085.
90. Senge, M. O.; Gerzevske, K. R.; Vicente, M. G. H.; Forsyth, T. P.; Smith, K. M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 750.
91. Pangka, V. S.; Morgan, A. R.; Dolphin, D. *J. Org. Chem.* **1986**, *51*, 1094.
92. http://www.qltinc.com (13/07/2006).

Biographical sketch

Simon Fox was born in Beverley, UK. He graduated from the University of Hull with a B.Sc. (Hons) in Chemistry in 2002, after which he immediately started his Ph.D. under the supervision of Dr R. W. Boyle. During his time as a member of the Photomedicine and Photobiology group at the University of Hull, he investigated the synthesis of novel porphyrins bearing fused rings and related studies. He completed his doctoral thesis in 2005 and was awarded his Ph.D. in 2006.

Ross W. Boyle received his B.Sc. (Hons) in Chemistry and Ph.D. in Organic Chemistry from Paisley College of Technology under the supervision of Professor T. G. Truscott. Following this he spent six years in Canada, first as a postdoctoral research fellow in the MRC Group in Radiation Sciences, University of Sherbrooke with Professor J. E. van Lier, and then at the Department of Chemistry, University of British Columbia, working with Professor D. Dolphin. In 1996 he took up his first academic post as a Lecturer in Bioorganic Chemistry at University of Essex and in 2000 he moved to his current post of Reader in Biological Chemistry at Department of Chemistry, University of Hull. Research interests include porphyrin synthetic chemistry, photodynamic therapy and the application of light active molecules to image and modify biological systems.

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Efficient microwave-assisted synthesis of highly functionalized pyrimidine derivatives

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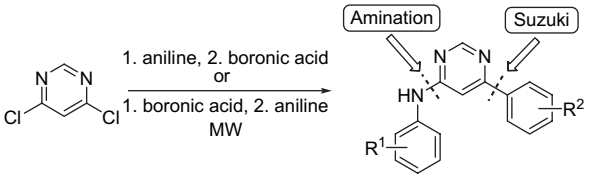
Abstract—A generally applicable one-pot procedure for the rapid, easy, and diverse asymmetric functionalization of pyrimidines was developed that requires minimum efforts for the purification of the final products. 4-Amino-6-aryl-substituted pyrimidines are prepared in good yields by combined microwave-assisted amination and Suzuki–Miyaura cross-coupling reactions. The acid-mediated amination reaction affords the products as easily separable salts in 30–40 min reaction time.

1. Introduction

The multiple diverse functionalization of heterocycles is of great importance in the synthesis of pharmacologically active compounds.[1] The formation of carbon–carbon, carbon—oxygen, and carbon–nitrogen bonds represent the most desirable and useful, but also the most challenging conversions in this respect. (Hetero)aryl–(hetero)aryl carbon–carbon bonds are well represented in drugs and can be synthesized conveniently by metal-catalyzed Suzuki–Miyaura, Stille, Kumada-Corriu, Negishi, or Hiyama cross-coupling reactions.[2] Correspondingly, efficient copper- and palladium-catalyzed carbon–nitrogen and carbon–oxygen bond forming processes, such as the Buchwald–Hartwig reaction, have been developed for the functionalization of aryl halides in the last decade.[2–5] A wide variety of catalytic processes for the functionalization of aromatic ring systems is therefore available. The application of metal-catalyzed reactions to the modification of heteroaromatic rings, however, is reported to a lesser extent.[3,4,6–8]

As part of our efforts in the synthesis of new effective protein kinase inhibitors, we focused on the preparation of pyrimidine derivatives.[9] The symmetrically disubstituted 4,6-dichloropyrimidine was derivatized by both an amino functionality and a (hetero)aryl moiety (Scheme 1).



Scheme 1. Difunctionalization of 4,6-dichloropyrimidine.

For the formation of the pyrimidine–(hetero)aryl C–C bond we used the Suzuki–Miyaura cross-coupling,[10] since a large number of diverse substituted boronic acids and esters are commercially available; additionally, they are stable even under demanding reaction conditions and they are of low toxicity. For the amination reaction, we explored several reaction conditions, ranging from nucleophilic substitution[11] to palladium- or copper-catalyzed reactions (see below). Taking advantage of the technique of microwave-assisted organic synthesis (MAOS),[12] we developed a generally applicable methodology for the rapid, easy, and diverse asymmetric functionalization of pyrimidines. Minimum efforts for the purification of the final products are required, which are available in a short reaction time, and without the requirement for special reaction conditions, such as inert gas or degassed solvents.

2. Result and discussion

The commercially available and symmetrically substituted 4,6-dichloropyrimidine was used as starting material for the preparation of new difunctionalized pyrimidines. In the first reaction step, one of the chlorine atoms is substituted either by an amine or by an (hetero)aryl moiety, yielding

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a monosubstituted chloropyrimidine derivative. This intermediate can subsequently be subjected to either Suzuki–Miyaura cross-coupling or amination, giving the final asymmetrically disubstituted products. We initially established separate protocols for amination and Suzuki–Miyaura-coupling reactions using 4,6-dichloropyrimidine. Subsequently, we performed three different sets of experiments. We first carried out the amination reaction, isolated the intermediate and did the Suzuki–Miyaura cross-coupling as the second step. In the next set of experiments we performed the cross-coupling reaction and subjected the isolated intermediates afterwards to amination. Finally, we simplified the methodology and carried out the cross-coupling and the amination reaction in a one-pot synthesis without isolation of the intermediates.

2.1. Acid- and base-mediated aminations

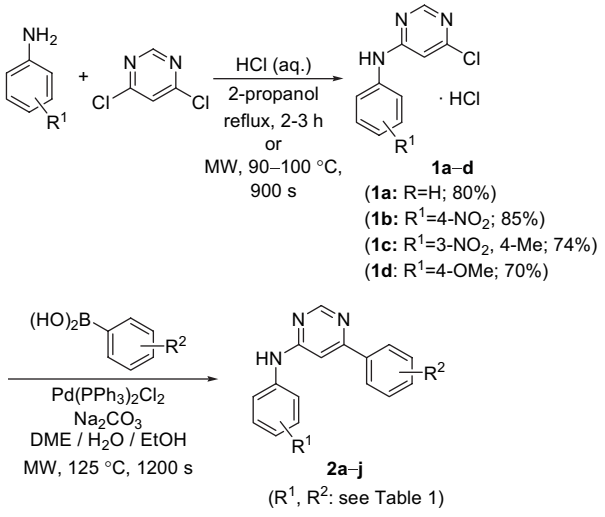
The amination of pyrimidine derivatives can be achieved via acid- or base-mediated nucleophilic substitution.[13–16] We therefore explored several reaction conditions in a model reaction between 4,6-dichloropyrimidine and aniline. These included acid- (aqueous hydrochloric acid) and base-mediated (Hunig's base (DIPEA), sodium hydride, sodium carbonate, caesium carbonate, potassium phosphate, sodium *tert*-butoxide), as well as copper- (copper(I) iodide, copper(I) iodide/*N*,*N*′-dimethylethylenediamine, copper(I) iodide/2,2,6,6-tetramethylhepta-3,5-dione, and copper(I) triflate)[17] and palladium-catalyzed[3,8,16,18] ($Pd(dppf)Cl_2$) reaction conditions at 100, 180 or 240 °C for 900 s in a microwave synthesizer. A number of different solvents, such as DMF, dioxane, methanol, ethanol, 2-propanol, and NMP or DME, were used. All base-mediated reactions showed product formation only at elevated temperatures with yields below 50%. The notable exception included the use of Hunig's base in NMP at 240 °C, yielding 60–70% of the amination product. Addition of any Cu-catalyst (20 mol %, sodium carbonate and DMF), and the $Pd(dppf)Cl_2$-catalyzed reaction (5 mol %, sodium *tert*-butoxide and dioxane) gave increased yields of up to 60–70%. However, all of the above conditions worked only at elevated temperatures with the drawback of considerable formation of the symmetrically disubstituted amination product as by-product, as well as the requirement for a subsequent work-up and isolation procedure. In marked contrast, the microwave-mediated amination worked very well with aqueous hydrochloric acid in 2-propanol[14] at moderate temperatures (100 °C), yielding the desired phenyl-(6-phenyl-pyrimidin-4-yl)-amine (**1a**) in more than 80% yield, even when only catalytic amounts of hydrochloric acid were used. The mono-amination product was formed almost exclusively, and only traces of the symmetrically disubstituted product were detected by LC–MS analysis. The product was isolated as the HCl-salt by filtration. Protonation of one of the nitrogen atoms of the dichloropyrimidine results in activation of the heteroaromatic system toward nucleophilic attack. The small amount of non-protonated amine in the equilibrium of mainly protonated amine and non-protonated species is a sufficient nucleophile, and the equilibrium is shifted toward the non-protonated amine as the reaction proceeds. Other strong acids, such as sulfuric acid or *p*-toluenesulfonic acid, worked similarly well. As an additional advantage, concentrated sulfuric acid does not contain water, which prevents formation of the hydroxy-substituted pyrimidine by-product in slow amination reactions by nucleophilic displacement of chlorine with water. In this respect, the use of 2-propanol as a solvent was beneficial over sterically less hindered methanol or ethanol, as only traces of isopropoxy-substituted by-products were observed.

2.2. Suzuki–Miyaura cross-coupling reactions

The Suzuki–Miyaura reaction of 4,6-dichloropyrimidine[7,15,19] was not optimized. Yields of 50–63% were obtained with a system containing $Pd(PPh_3)_2Cl_2$, sodium carbonate, and DME/ethanol/water under microwave irradiation at 125 °C for 1200 s.

2.3. Amination/Suzuki–Miyaura sequence

To explore the best sequence of the amination and the Suzuki–Miyaura reaction, we started with the amination reaction first (Scheme 2 and Table 1). A set of four different mono-aminated pyrimidines **1a–d** was synthesized in good yields (70–85%) using the previously established protocol for the acid-mediated reaction of 4,6-dichloropyrimidine. The amination reactions were carried out by heating to reflux for 2–3 h to allow the synthesis of larger quantities of **1a–d**. However, microwave irradiation (90–100 °C, 900 s) was equally successful in shorter reaction time. The products **1a–d** were isolated as HCl-salts by filtration. In the following step, the microwave-assisted Suzuki–Miyaura cross-coupling of **1a–d** with various substituted benzeneboronic acids gave access to products **2a–j** in good yields (60–99%; Table 1). Electron-withdrawing as well as electron-donating groups in the boronic acid coupling partner were well tolerated, even in the sterically problematic *ortho*-position.



Scheme 2. Amination of 4,6-dichloropyrimidine with aromatic amines and subsequent Suzuki–Miyaura cross-coupling.

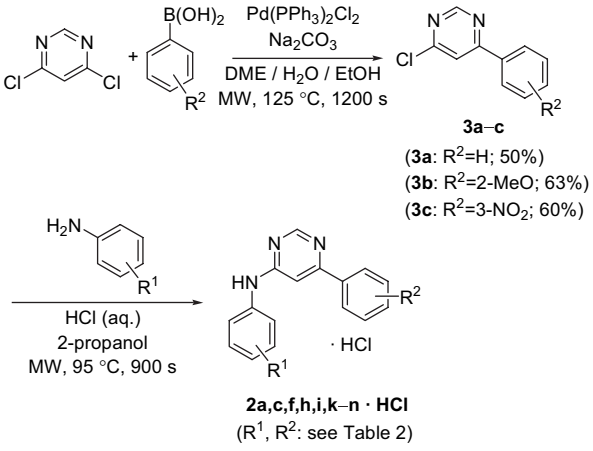
In the next experiment, we switched the order of the reaction sequence (Scheme 3 and Table 2). We initially synthesized three phenyl-substituted chloropyrimidines **3a–c** by Suzuki–Miyaura reaction of 4,6-dichloropyrimidine with the corresponding boronic acids under microwave-assisted conditions. Unfortunately, the coupling gave only moderate yields (50–63%). The subsequent amination step under acid-mediated microwave-assisted conditions usually gave the

Table 1. 4,6-Disubstituted pyrimidines **2a–j** produced via Scheme 2[a]

Entry	R^1	R^2	Isolated yield of 2nd step (%)	Overall yield (%)
1	H	H	87 (**2a**)	70
2	H	2-Me	99 (**2b**)	79
3	H	2-OMe	81 (**2c**)	65
4	H	2-COMe	81 (**2d**)	65
5	H	3-CH_2OH	85 (**2e**)	68
6	H	3-NO_2	93 (**2f**)	74
7	H	4-OMe	86 (**2g**)	69
8	4-OMe	H	79 (**2h**)	55
9	4-NO_2	H	60 (**2i**)	51
10	3-NO_2-4-Me	H	79 (**2j**)	58

[a] Typical procedure. First step: 10 mmol aromatic amine, 13 mmol 4,6-dichloropyrimidine, 15 mL 2-propanol, 1.5 mL concd HCl, reflux, 2.5 h; or 1 mmol aromatic amine, 1.3 mmol 4,6-dichloropyrimidine, 2 mL 2-propanol, 200–300 μL concd HCl, MW, 90–100 °C, 900 s. Second step: 1 mmol **1**, 1.25 mmol boronic acid, 3.5 equiv Na_2CO_3, 2 mol % $Pd(PPh_3)_2Cl_2$, 6 mL DME, 0.8 mL EtOH, 1.2 mL H_2O, MW, 125 °C, 1200 s.

final products **2a–j** as HCl-salts after filtration in moderate to good yields (55–96%). The amination reaction with electron-poor monosubstituted pyrimidines proceeds in slightly better yields than with electron-rich ones (Table 2, entries 3–5, 7, and 8).



Scheme 3. Suzuki–Miyaura cross-coupling of 4,6-dichloropyrimidine and subsequent amination with aromatic amines.

Table 2. 4,6-Disubstituted pyrimidines **2a–j** produced via Scheme 3[a]

Entry	R^1	R^2	Isolated yield for 2nd step (%)	Overall yield (%)
1	H	H	83 (**2a**·HCl)	42
2	2-Me	H	55 (**2k**)[b]	27
3	4-OMe	H	79 (**2h**·HCl)	40
4	4-NO_2	H	90 (**2i**·HCl)	45
5	4-COOMe	H	96 (**2l**·HCl)	48
6	H	2-OMe	66 (**2c**·HCl)	42
7	4-Br	2-OMe	86 (**2m**·HCl)	54
8	3-Br	3-NO_2	89 (**2n**·HCl)	53
9	H	3-NO_2	78 (**2f**·HCl)	47

[a] Typical procedure. First step: 8 mmol boronic acid, 9.6 mmol 4,6-dichloropyrimidine, 3 equiv Na_2CO_3, 2 mol % $Pd(PPh_3)_2Cl_2$, 15 mL DME, 2 mL EtOH, 3 mL H_2O, MW, 125 °C, 1200 s. Second step: 1 mmol **3**, 1.05 mmol aniline, 2 mL 2-propanol, 0.2 mL concd HCl, MW, 95 °C, 900 s.

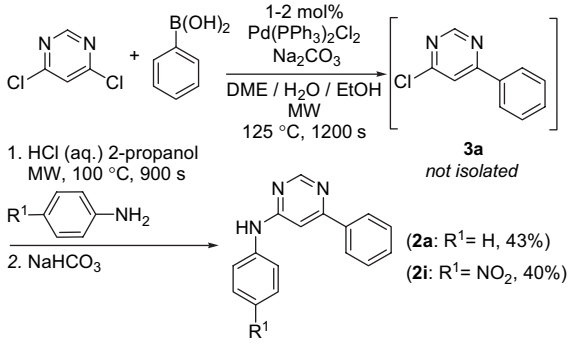
[b] Isolated as the free base by basic work-up and flash column chromatography.

The Suzuki/amination reaction sequence (Scheme 3) is preferable for aromatic amines that are more valuable or contain other reactive functionalities (such as a halogen, see Table 2, entries 7 and 8). The formation of undesirable side products in the Suzuki–Miyaura cross-coupling can thus be avoided by this sequence.

The principal flexibility of this methodology, which enabled the two reaction sequences to be performed in both directions, allowed the introduction of substituents on the aniline side or on the aryl side, which could subsequently be functionalized, for example, by metal-catalyzed cross-coupling reactions of the bromoaniline side-chain (Table 2, entries 7 and 8), or by subsequent reactions of the hydroxymethylene side-chain (Table 2, entry 5). This is an important requirement for the further modification of pyrimidine-based scaffolds as protein kinase inhibitors.

2.4. One-pot procedure

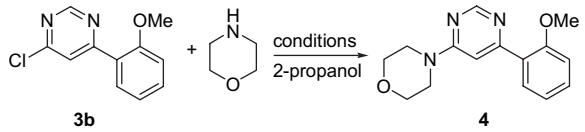
To demonstrate that the methodology can be simplified, we now conducted the sequence of Suzuki–Miyaura and subsequent amination reaction as a one-pot procedure. For that purpose, we used a simple model system consisting of benzeneboronic acid and aniline as well as *p*-nitroaniline as reactants. The reaction mixture was acidified and heated with the aromatic amine after an initial Suzuki–Miyaura cross-coupling (Scheme 4). The reaction sequence got completed in only 35 min under microwave irradiation. The products **2a** and **2i** were isolated in moderate yields after flash column chromatography (43% and 40%, respectively), which is comparable to the overall yields of the stepwise procedure (Table 2, entries 1 and 4).



Scheme 4. One-pot reaction of 4,6-dichloropyrimidine with benzene boronic acid and aromatic amines.

2.5. Amination with aliphatic amines

In order to extend the scope of the methodology, we performed the amination of the Suzuki–Miyaura product with aliphatic amines as the coupling partner (Scheme 5). The use of an excess of hydrochloric acid gave only traces of the desired amination product using **3b** and morpholine (Table 3, entry 1). This is in distinct contrast to the previously described reactions with aniline derivatives. Under the applied reaction conditions the aliphatic amine group is most likely quantitatively protonated due to its higher basicity, in contrast to an aromatic amino group. A nucleophilic substitution on the monosubstituted chloropyrimidine is therefore not possible.



Scheme 5. Amination with morpholine.

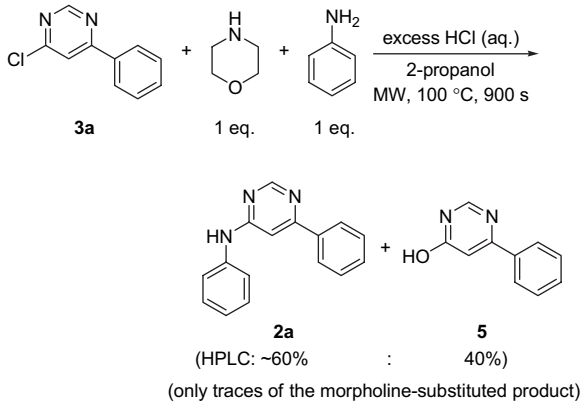
Table 3. Results of the synthesis of **4** produced via Scheme 5[a]

Entry	Acid/base	*T* [°C]	HPLC-yield of **4** (%)
1	3 equiv HCl	100	<2
2	~0.5 equiv HCl	100	50 (50% recov. SM)
3	—	115	80 (65% isolated yield)
4	2 equiv DIPEA	115	80

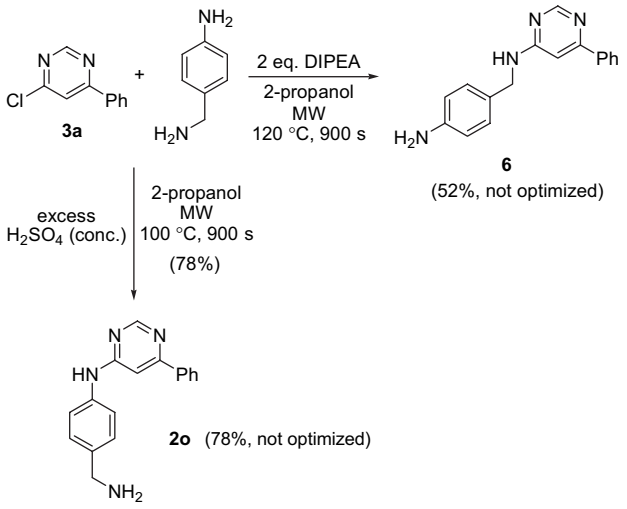
[a] Typical procedure: 1 mmol **3b**, 1.2 mmol morpholine, 3 mL 2-propanol, MW, 900 s.

The reaction results, however, in the formation of product **4** in low yields, when substoichiometrical amounts of hydrochloric acid are present (Table 3, entry 2), which is consistent with this explanation. The reaction was equally effective under relatively mild conditions, i.e., heating the mixture of starting materials without acid in the microwave synthesizer (Table 3, entry 3), or with additional Hunig's base (Table 3, entry 4). The aromatic amines react very slowly, if at all, under these basic conditions.

In a competition experiment of **3a** with aniline and morpholine under acidic conditions (Scheme 6), an estimated yield of 60% of the reaction product of **3a** with aniline was observed by HPLC analysis. Only traces of the morpholine-substituted product were detected by HPLC–MS analysis. The remaining 40% could be attributed to the by-product 6-phenyl-pyrimidin-4-ol (**5**) that is formed by nucleophilic attack of water at the chloropyrimidine. This difference in reactivity between the aromatic and the aliphatic amino groups was further exploited for the synthesis of different regioisomers by using 4-aminomethyl-phenylamine as a coupling partner that contains both an aliphatic and aromatic amino group (Scheme 7). The more nucleophilic benzylic amino group reacts with the pyrimidine under basic conditions (52% HPLC-yield of **6**), while the aromatic amino group added to the pyrimidine core under acidic conditions (78% HPLC-yield of **2o**).



Scheme 6. Competitive acid-mediated amination of 4-chloro-6-phenyl-pyrimidine (**3a**) with morpholine and aniline.



Scheme 7. Amination of 4-chloro-6-phenyl-pyrimidine (**3a**) with 4-aminomethyl-phenylamine.

3. Conclusion

We presented an efficient, flexible, and easy to perform two-step procedure for the synthesis of 4-amino-6-aryl-pyrimidines by the combined amination and Suzuki–Miyaura cross-coupling of 4,6-dichloropyrimidine. Either the Suzuki–Miyaura or the amination reaction was performed as the first step in the synthetic sequence. Using microwave-assisted organic synthesis, all reactions were completed in a short time. We could further demonstrate that the process is feasible as a one-pot procedure, thus simplifying the work-up procedure. The amination with aromatic amines under acidic conditions was straightforward and the products of this reaction were isolated by filtration of the HCl-salts. Aliphatic amines did not react under the applied acidic conditions, but a switch in reactivity from an aromatic to an aliphatic amino group was achieved by applying basic conditions. Extensive investigations to use this methodology for the general synthesis of highly functionalized amino-(hetero)aryl-heterocycles are currently underway in our laboratory.

4. Experimental

4.1. General

All reagents and solvents were used as purchased. The microwave-assisted reactions were carried out in a Personal Chemistry Emrys Optimizer instrument in sealed vials. Flash column chromatography was carried out on Merck silica gel 60 (0.040–0.063 mm), using cyclohexane (*c*Hex) and ethyl acetate (EtOAc) as eluents. The melting points are uncorrected and represent values obtained on recrystallized or chromatographically purified material. ^{1}H (200 MHz) and ^{13}C (66 MHz) NMR spectra were measured in $CDCl_3$ or DMSO-d_6 on a Varian Gemini 200 instrument. The chemical shifts δ are given in parts per million relative to $CHCl_3$ (δ (^{1}H)=7.26; δ (^{13}C)=77.0) in $CDCl_3$, and to DMSO-d_6 (δ (^{1}H)=2.49; δ (^{13}C)=39.7). HPLC–MS analyses were performed with a Waters 2795 Separation Module equipped with a Waters 2996 PDA detector and a Micromass ZQ

2000 mass detector (electrospray ionization with +ve/–ve switching). Standard LC–MS conditions are: Waters XTerra MS 5 μm C18, 3.0×50 mm at 35 °C; flow 0.8 mL/min, gradient 98% 1 mM aqueous ammonium acetate/2% acetonitrile to 100% acetonitrile over 7 min. HPLC purity is given as the mean value of the area under the peak curve at three different wavelengths (215, 254, and 310 nm). Elemental analyses were performed at the Leibniz-Institute for Organic Catalysis, Rostock, Germany, and at Mikroanalytisches Labor Pascher, Remagen–Bandorf, Germany. The purity of new compounds was assessed by ^{1}H NMR spectroscopy and HPLC or microanalysis.

4.2. General procedures

4.2.1. General method 1 (GM1): amination reaction. The aromatic amine (1.00 mmol) and the 4-chloropyrimidine derivative (0.95–1.30 mmol) were dissolved in 2 mL of 2-propanol. Concd HCl (37%, 200–300 μL) was added under stirring, and the mixture was heated in the microwave synthesizer at 95–100 °C for 900 s. The mixture was stored at 4 °C overnight. The precipitated product was filtered off, washed with a small amount of ice-cold 2-propanol, and dried in vacuum.

4.2.2. General method 2 (GM2): Suzuki–Miyaura cross-coupling reaction. The 4-chloropyrimidine derivative (1.00 mmol), the boronic acid (1.25 mmol), sodium carbonate (2.00–3.50 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol %) were suspended in a mixture of 6.0 mL of DME, 0.8 mL of EtOH, and 1.2 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=∼7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc mixtures) to afford the product.

4.2.3. General method 3 (GM3): one-pot Suzuki–Miyaura/amination reaction. The boronic acid (1.0 mmol), 4,6-dichloropyrimidine (1.1–1.2 mmol), sodium carbonate (3.0 mmol), and $Pd(PPh_3)_2Cl_2$ (1–2 mol %) were suspended in a mixture of 2.5–3.0 mL of DME, 0.4 mL of EtOH, and 0.5 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. 2-Propanol (1 mL) and the aromatic amine (1.1–1.3 mmol) were added, and the mixture was acidified with concd HCl (37%). The mixture was heated in the microwave synthesizer at 100 °C for 900 s. Satd aqueous $NaHCO_3$ was added, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc mixtures).

4.3. Synthesis of monosubstituted pyrimidines

4.3.1. (6-Chloro-pyrimidin-4-yl)-phenyl-amine hydrochloride (1a). Aniline (1.00 g, 10.7 mmol) and 4,6-dichloropyrimidine (2.07 g, 13.9 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1.5 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The off-white precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1a** (2.07 g, 80%). Off-white solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.92 (1H, s), 7.06 (1H, t, J=7.3 Hz), 7.28–7.39 (2H, m), 7.65 (2H, d, J=8.9 Hz), 8.46 (1H, s), 10.22 (1H, br s); ESIMS m/z=206/208 (MH^+).

4.3.2. (6-Chloro-pyrimidin-4-yl)-(4-nitro-phenyl)-amine hydrochloride (1b). 4-Nitroaniline (1.00 g, 7.2 mmol) and 4,6-dichloropyrimidine (1.40 g, 9.4 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1.5 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The yellow precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1b** (1.75 g, 85%). Yellow solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.98 (1H, s), 7.94 (2H, d, J=9.5 Hz), 8.24 (2H, d, J=9.5 Hz), 8.64 (1H, s), 10.54 (1H, br s); ESIMS m/z=251/253 (MH^+).

4.3.3. (6-Chloro-pyrimidin-4-yl)-(4-methyl-3-nitro-phenyl)-amine hydrochloride (1c). 4-Methyl-3-nitro-aniline (500 mg, 3.29 mmol) and 4,6-dichloropyrimidine (637 mg, 4.27 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The yellow-brown precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1c** (730 mg, 74%). Pale brown solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.46 (3H, s), 6.93 (1H, s), 7.45 (1H, d, J=8.3 Hz), 7.83 (1H, dd, J=8.3 Hz, J=2.2 Hz), 8.48 (1H, d, J=2.2 Hz), 8.55 (1H, s), 10.49 (1H, br s); ESIMS m/z=265/267 (MH^+).

4.3.4. (6-Chloro-pyrimidin-4-yl)-(4-methoxy-phenyl)-amine hydrochloride (1d). 4-Methoxyaniline (1.00 g, 8.1 mmol) and 4,6-dichloropyrimidine (1.57 g, 10.6 mmol, 1.3 equiv) were dissolved in 15 mL of 2-propanol. Concd HCl (37%, 1.5 mL) was added under stirring, and the mixture was heated under reflux for 2.5 h. The mixture was stored at 4 °C overnight. The slightly greenish precipitate was filtered off, washed with a small amount of cold 2-propanol, and dried in vacuum, to give **1d** (1.55 g, 70%). Pale green solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.74 (3H, s), 6.74 (1H, s), 6.94 (2H, d, J=8.7 Hz), 7.48 (2H, d, J=8.7 Hz), 8.39 (1H, s), 9.93 (1H, br s); ESIMS m/z=236/238 (MH^+).

4.3.5. 4-Chloro-6-phenyl-pyrimidine (3a). Benzeneboronic acid (1.00 g, 8.2 mmol), 4,6-dichloropyrimidine (1.47 g, 9.8 mmol, 1.2 equiv), sodium carbonate (2.61 g, 24.6 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (115 mg, 2 mol %) were suspended in a mixture of 15 mL of DME, 2 mL of EtOH, and 3 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=∼7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 20:1) to afford **3a** (0.78 g, 50%).

Colorless solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47–7.57 (3H, m), 7.74 (1H, s), 8.03–8.10 (2H, m), 9.03 (1H, s); ESIMS m/z=191/193 (MH^+).

4.3.6. 4-Chloro-6-(2-methoxy-phenyl)-pyrimidine (3b). 2-Methoxybenzeneboronic acid (1.20 g, 7.9 mmol), 4,6-dichloropyrimidine (1.41 g, 9.5 mmol, 1.2 equiv), sodium carbonate (2.51 g, 23.7 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (100 mg, 2 mol %) were suspended in a mixture of 15 mL of DME, 2 mL of EtOH, and 3 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1500 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=~7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 15:1–10:1) to afford **3b** (1.10 g, 63%). Colorless solid; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.91 (3H, s), 7.12 (1H, m), 7.23 (1H, d, J=8.4 Hz), 7.55 (1H, m), 7.98 (1H, d, J=7.9 Hz), 8.12 (1H, s), 9.09 (1H, s); ESIMS m/z= 221/223 (MH^+).

4.3.7. 4-Chloro-6-(3-nitro-phenyl)-pyrimidine (3c). 3-Nitrobenzeneboronic acid (1.00 g, 6.0 mmol), 4,6-dichloropyrimidine (1.07 g, 7.2 mmol, 1.2 equiv), sodium carbonate (1.91 g, 18.0 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (80 mg, 2 mol %) were suspended in a mixture of 15 mL of DME, 2 mL of EtOH, and 3 mL of water. The mixture was heated in the microwave synthesizer at 125 °C for 1200 s. Water was added, and the mixture was extracted three times with EtOAc. Satd aqueous NH_4Cl was added to the aqueous layer (pH=~7), and the mixture was extracted two more times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 10:1–3:1) to afford **3c** (0.85 g, 60%). Pale yellow solid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (1H, t, J=8.1 Hz), 7.85 (1H, d, J=1.5 Hz), 8.36–8.48 (2H, m), 8.95 (1H, t, J=2.3 Hz), 9.11 (1H, d, J=1.5 Hz); ESIMS m/z=236/238 (MH^+).

4.4. Synthesis of disubstituted pyrimidines

4.4.1. Phenyl-(6-phenyl-pyrimidin-4-yl)-amine (2a) and phenyl-(6-phenyl-pyrimidin-4-yl)-amine hydrochloride (2a·HCl). Method 1: following GM1, **3a** (100 mg, 0.525 mmol) and aniline (50 μL, 0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C in the microwave synthesizer. Cooling and filtration afforded **2a**·HCl (125 mg, 83%). Yellow solid; mp 258–259 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.18 (1H, t, J=7.2 Hz), 7.34 (1H, s), 7.37–7.48 (2H, m), 7.59–7.66 (3H, m), 7.71 (2H, d, J=7.6 Hz), 7.91–7.98 (2H, m), 8.87 (1H, s), 10.96 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.2, 121.7, 125.1, 127.2, 129.0, 129.3, 130.8, 132.1, 137.4, 153.4, 153.6, 161.5; ESIMS m/z=248 (MH^+); elemental analysis calcd for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97; N, 14.81. Found: C, 66.94; H, 5.18; N, 14.50.

Method 2: following GM2, **1a** (100 mg, 0.413 mmol), benzeneboronic acid (63 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water in the microwave synthesizer. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2a** (90 mg, 87%). Colorless solid; mp 185–186 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.03 (1H, t, J=7.3 Hz), 7.24 (1H, d, J=1.4 Hz), 7.35 (2H, t, J=7.3 Hz), 7.49–7.57 (3H, m), 7.72 (2H, d, J=7.3 Hz), 7.98–8.07 (2H, m), 8.72 (1H, d, J=1.4 Hz), 9.68 (1H, s); ^{13}C NMR (66 MHz, $CDCl_3$) δ 99.9, 122.3, 124.8, 126.9, 128.7, 129.5, 130.3, 137.4, 138.3, 158.8, 161.6, 163.7; HPLC purity 98%; ESIMS m/z=248 (MH^+), 246 ($M-H^-$).

Method 3: following GM3, benzeneboronic acid (120 mg, 0.98 mmol), 4,6-dichloropyrimidine (161 mg, 1.10 mmol, 1.1 equiv), sodium carbonate (313 mg, 3.00 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (7 mg, 1 mol %) were reacted in a mixture of 2.5 mL of DME, 0.4 mL of EtOH, and 0.5 mL of water in the microwave synthesizer. 2-Propanol (1.0 mL) and aniline (116 μL, 1.30 mmol) were added, the mixture was acidified with concd HCl (37%), and again reacted in the microwave synthesizer. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2a** (104 mg, 43%).

4.4.2. Phenyl-(6-*o*-tolyl-pyrimidin-4-yl)-amine (2b). Following GM2, **1a** (100 mg, 0.413 mmol), 2-methylbenzeneboronic acid (70 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in 3.0 mL DME, 0.4 mL EtOH, and 0.6 mL water. After neutralization with $NaHCO_3$, extraction of the organic layer with EtOAc, drying over Na_2SO_4, and evaporation, flash column chromatography (*c*Hex/EtOAc 5:1) afforded **2b** (107 mg, 99%). Colorless solid; mp 111–112 °C (MeCN/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.38 (3H, s), 6.86 (1H, s), 7.03 (1H, t, J=7.3 Hz), 7.25–7.46 (6H, m), 7.71 (2H, d, J=8.3 Hz), 8.69 (1H, s), 9.65 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 20.0, 106.1, 119.8, 122.4, 125.9, 128.7, 128.8, 129.0, 130.7, 135.4, 138.3, 139.6, 157.5, 160.3, 164.5; HPLC purity 98%; ESIMS m/z=262 (MH^+), 260 ($M-H^-$).

4.4.3. [6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine (2c) and [6-(2-methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine hydrochloride (2c·HCl). Method 1: following GM1, **3b** (70 mg, 0.32 mmol) and aniline (29 μL, 0.32 mmol) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Compound **2c**·HCl was isolated after filtration (66 mg, 66%). Yellow solid; mp 193–194 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.90 (3H, s), 7.12–7.36 (4H, m), 7.44 (2H, t, J=8.0 Hz), 7.55–7.75 (4H, m), 8.90 (1H, s), 11.25 (1H, br s); ^{13}C (66 MHz, DMSO-d_6) δ 55.9, 106.2, 112.3, 119.9, 120.9, 121.8, 125.1, 129.0, 130.2, 133.3, 137.4, 153.3, 154.6, 156.9, 161.2; ESIMS m/z= 278 (MH^+); elemental analysis calcd for $C_{17}H_{16}ClN_3O\cdot H_2O$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.62; H, 5.41; N, 12.55.

Method 2: following GM2, **1a** (100 mg, 0.413 mmol), 2-methoxybenzeneboronic acid (78 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of

3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 2:1) afforded **2c** (93 mg, 81%). Colorless solid; mp 139–140 °C (EtOAc/*c*Hex), ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.89 (3H, s), 6.96–7.21 (3H, m), 7.28–7.51 (4H, m), 7.72 (2H, d, J=8.0 Hz), 7.96 (1H, d, J=8.1 Hz), 8.70 (1H, s), 9.63 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 55.6, 106.9, 112.0, 119.7, 120.5, 122.2, 125.8, 128.7, 130.1, 131.1, 139.9, 157.4, 157.7, 159.4, 160.3; HPLC purity 97%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.4. 1-[2-(6-Phenylamino-pyrimidin-4-yl)-phenyl]-ethanone (2d). Following GM2, **1a** (100 mg, 0.413 mmol), 2-acetylbenzeneboronic acid (85 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 2:1) afforded **2d** (96 mg, 81%). Colorless solid; mp 129–130 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (3H, s), 6.99–7.10 (2H, m), 7.35 (2H, t, J=8.0 Hz), 7.54–7.75 (6H, m), 8.61 (1H, s), 9.78 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 30.3, 104.5, 120.0, 122.6, 127.3, 128.8, 129.5, 130.4, 136.6, 139.5, 141.4, 157.5, 160.7, 162.6, 202.7; HPLC purity 99%; ESIMS m/z=290 (MH^+), 288 ($M-H^-$).

4.4.5. [3-(6-Phenylamino-pyrimidin-4-yl)-phenyl]-methanol (2e). Following GM2, **1a** (100 mg, 0.413 mmol), 3-hydroxymethylbenzeneboronic acid (78 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 1:1–1:3) afforded **2e** (97 mg, 85%). Colorless solid; mp 161–162 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.60 (2H, d, J=6.0 Hz), 5.34 (1H, t, J=6.0 Hz), 7.03 (1H, t, J=7.2 Hz), 7.24–7.54 (5H, m), 7.73 (2H, d, J=8.0 Hz), 7.90 (1H, d, J=6.6 Hz), 8.03 (1H, s), 8.72 (1H, s), 9.69 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 62.7, 101.9, 119.7, 122.3, 124.3, 124.7, 128.3, 128.6, 128.8, 136.7, 139.8, 143.2, 158.2, 161.0, 161.2; HPLC purity 97%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.6. [6-(3-Nitro-phenyl)-pyrimidin-4-yl]-phenyl-amine (2f) and [6-(3-nitro-phenyl)-pyrimidin-4-yl]-phenyl-amine hydrochloride (2f·HCl). Method 1: following GM1, **3c** (150 mg, 0.637 mmol) and aniline (61 μL, 0.669 mmol, 1.05 equiv) were reacted in 1.5 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration gave **2f**·HCl (164 mg, 78%). Yellow solid; mp 276–277 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.13 (1H, t, J=7.8 Hz), 7.33–7.45 (3H, m), 7.72 (2H, d, J=8.0 Hz), 7.87 (1H, t, J=8.0 Hz), 8.35–8.45 (2H, m), 8.79 (1H, t, J=1.8 Hz), 8.86 (1H, s), 10.52 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.5, 120.8, 121.6, 123.9, 125.5, 129.0, 130.8, 133.1, 136.1, 138.5, 148.3, 155.7, 156.6, 161.2; ESIMS m/z=293 (MH^+); elemental analysis calcd for $C_{16}H_{13}ClN_4O_2$: C, 58.46; H, 3.99; N, 17.04. Found: C, 58.78; H, 4.02; N, 16.80.

Method 2: following GM2, **1a** (100 mg, 0.413 mmol), 3-nitrobenzeneboronic acid (86 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2f** (112 mg, 93%). Yellow solid; mp 156–157 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.05 (1H, t, J=7.3 Hz), 7.29–7.42 (3H, m), 7.72 (2H, d, J=8.8 Hz), 7.83 (1H, t, J=8.0 Hz), 8.25–8.48 (2H, m), 8.75 (1H, s), 8.80 (1H, s), 9.79 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 102.7, 119.9, 120.9, 122.6, 124.7, 128.8, 130.5, 132.4, 138.4, 139.5, 148.2, 158.4, 158.5, 161.0; HPLC purity 95%; ESIMS m/z=293 (MH^+), 291 ($M-H^-$).

4.4.7. [6-(4-Methoxy-phenyl)-pyrimidin-4-yl]-phenyl-amine (2g). Following GM2, **1a** (100 mg, 0.413 mmol), 4-methoxybenzeneboronic acid (78 mg, 0.516 mmol, 1.25 equiv), sodium carbonate (153 mg, 1.450 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (6 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1–3:1) afforded **2g** (99 mg, 86%). Colorless solid; mp 170–171 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.82 (3H, s), 6.96–7.12 (3H, m), 7.17 (1H, s), 7.34 (2H, t, J=8.1 Hz), 7.71 (2H, d, J=8.1 Hz), 7.99 (2H, d, J=8.8 Hz), 8.65 (1H, s), 9.63 (1H, br s); ^{13}C NMR (66 MHz, $CDCl_3$) δ 55.4, 98.5, 114.1, 122.4, 124.9, 128.4, 129.6, 129.7, 138.2, 158.7, 161.5, 161.6, 163.3; HPLC purity 99%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.8. (4-Methoxy-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2h) and (4-methoxy-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine hydrochloride (2h·HCl). Method 1: following GM1, **3a** (100 mg, 0.525 mmol) and *p*-anisidine (68 mg, 0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration and drying gave **2h**·HCl (130 mg, 79%). Yellow solid; mp 261–262 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.78 (3H, s), 7.01 (2H, d, J=9.0 Hz), 7.40 (1H, s), 7.57–7.69 (5H, m), 7.88–7.96 (2H, m), 8.85 (1H, s), 11.62 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 55.3, 102.7, 114.2, 123.6, 127.2, 129.3, 130.0, 130.5, 132.1, 152.7, 153.3, 156.8, 161.2; ESIMS m/z=278 (MH^+); elemental analysis calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39; found: C, 64.87; H, 5.23; N, 13.20.

Method 2: following GM2, **1d** (100 mg, 0.368 mmol), benzeneboronic acid (56 mg, 0.460 mmol, 1.25 equiv), sodium carbonate (136 mg, 1.290 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (5 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2h** (81 mg, 79%). Colorless solid; mp 152–153 °C (EtOH); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.74 (3H, s), 6.94 (2H, d, J=8.8 Hz), 7.12 (1H, s), 7.46–7.61 (5H, m), 7.95–8.04 (2H, m), 8.64 (1H, s), 9.50 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 55.1, 101.1, 114.0, 122.0, 126.3, 128.8, 130.2, 132.5, 137.0, 155.0, 158.3, 160.9, 161.1; HPLC purity 96%; ESIMS m/z=278 (MH^+), 276 ($M-H^-$).

4.4.9. (4-Nitro-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2i) and (4-nitro-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine hydrochloride (2i·HCl). Method 1: following GM1, **3a** (100 mg, 0.525 mmol) and 4-nitroaniline (76 mg,

0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration and drying afforded **2i**·HCl (155 mg, 90%). Yellow solid; mp 251–252 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.57–7.65 (4H, m), 7.97–8.12 (4H, m), 8.28 (2H, d, J=9.0 Hz), 8.97 (1H, s), 11.39 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 104.2, 119.5, 125.0, 126.9, 129.2, 131.4, 133.9, 141.7, 145.5, 156.2, 158.6, 161.0; ESIMS m/z=293 (MH^+); elemental analysis calcd for $C_{16}H_{13}ClN_4O_2$: C, 58.46; H, 3.99; N, 17.04. Found: C, 59.14; H, 4.06; N, 16.80.

Method 2: following GM2, **1b** (100 mg, 0.346 mmol), benzeneboronic acid (53 mg, 0.433 mmol, 1.25 equiv), sodium carbonate (128 mg, 1.210 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (5 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water at 125 °C for 2400 s. Flash column chromatography (*c*Hex/EtOAc 3:1) afforded **2i** (61 mg, 60%). Yellow solid; mp 218–219 °C (MeCN/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.39 (1H, s), 7.51–7.60 (3H, m), 7.98–8.12 (4H, m), 8.26 (2H, d, J=9.5 Hz), 8.88 (1H, s), 10.44 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.5, 118.4, 125.0, 126.5, 128.9, 130.6, 136.3, 140.8, 146.4, 158.0, 160.3, 161.9; HPLC purity 97%; ESIMS m/z=293 (MH^+), 291 ($M-H^-$).

Method 3: following GM3, benzeneboronic acid (100 mg, 0.82 mmol), 4,6-dichloropyrimidine (147 mg, 0.98 mmol, 1.2 equiv), sodium carbonate (304 mg, 2.46 mmol, 3.0 equiv), and $Pd(PPh_3)_2Cl_2$ (12 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.5 mL of water. 1 mL of 2-Propanol, and 4-nitroaniline (125 mg, 0.90 mmol, 1.1 equiv) were added, the mixture was acidified with concd HCl (37%), and again reacted in the microwave synthesizer. After neutralization with $NaHCO_3$, extraction of the organic layer with EtOAc, drying over Na_2SO_4 and evaporation, flash column chromatography (*c*Hex/EtOAc 3:1) afforded **2i** (96 mg, 40%).

4.4.10. (4-Methyl-3-nitro-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2j). Following GM2, **1c** (100 mg, 0.332 mmol), benzeneboronic acid (51 mg, 0.415 mmol, 1.25 equiv), sodium carbonate (123 mg, 1.16 mmol, 3.50 equiv), and $Pd(PPh_3)_2Cl_2$ (5 mg, 2 mol %) were reacted in a mixture of 3.0 mL of DME, 0.4 mL of EtOH, and 0.6 mL of water. Flash column chromatography (*c*Hex/EtOAc 4:1) afforded **2j** (80 mg, 79%). Yellow solid; mp 191–192 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.47 (3H, s), 7.25 (1H, s), 7.45 (1H, d, J=8.4 Hz), 7.49–7.58 (3H, m), 7.86 (1H, dd, J=2.2 Hz, J=8.4 Hz), 8.00–8.08 (2H, m), 8.59 (1H, d, J=2.2 Hz), 8.79 (1H, s), 10.06 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 19.0, 102.5, 114.3, 123.9, 125.7, 126.4, 128.9, 130.4, 133.0, 136.6, 138.9, 148.6, 158.1, 160.6, 161.4; HPLC purity 95%; ESIMS m/z=307 (MH^+), 305 ($M-H^-$).

4.4.11. (6-Phenyl-pyrimidin-4-yl)-*o*-tolyl-amine (2k). Following GM1, **3a** (100 mg, 0.525 mmol) and *o*-toluidine (59 μL, 0.551 mmol, 1.05 equiv) were reacted in 1 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Satd aqueous $NaHCO_3$ was added, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the crude product, which was purified by flash column chromatography (*c*Hex/EtOAc 3:1) to afford **2k** (75 mg, 55%). Colorless solid; mp 126–127 °C (EtOAc/*c*Hex); ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.24 (3H, s), 7.05–7.32 (4H, m), 7.45–7.55 (4H, m), 7.92–8.01 (2H, m), 8.58 (1H, s), 9.03 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 17.9, 100.2, 125.1, 125.2, 126.2, 126.3, 128.8, 130.2, 130.5, 130.6, 132.4, 136.9, 158.3, 161.3, 162.0; HPLC purity 99%; ESIMS m/z=262 (MH^+), 260 ($M-H^-$).

4.4.12. 4-(6-Phenyl-pyrimidin-4-ylamino)-benzoic acid methyl ester hydrochloride (2l·HCl). Following GM1, **3a** (73 mg, 0.383 mmol) and methyl 4-aminobenzoate (61 mg, 0.402 mmol, 1.05 equiv) were reacted in 800 μL of 2-propanol and 120 μL of concd HCl (37%) at 95 °C. Filtration and drying gave **2l**·HCl (125 mg, 96%). Slightly yellow solid; mp 270–272 °C (EtOH/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.84 (3H, s), 7.56–7.67 (4H, m), 7.91–8.04 (6H, m), 8.96 (1H, s), 11.50 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 51.9, 103.5, 119.4, 123.6, 126.8, 129.1, 130.3, 131.3, 134.2, 143.5, 156.4, 158.5, 161.0, 165.7; ESIMS m/z=306 (MH^+), 304 ($M-H^-$); elemental analysis calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 63.65; H, 4.70; N, 12.00.

4.4.13. (4-Bromo-phenyl)-[6-(2-methoxy-phenyl)-pyrimidin-4-yl]-amine hydrochloride (2m·HCl). Following GM1, **3b** (200 mg, 0.906 mmol) and 4-bromoaniline (156 mg, 0.906 mmol) were reacted in 2 mL of 2-propanol and 200 μL of concd HCl (37%) at 95 °C. Filtration and drying afforded **2m**·HCl (305 mg, 86%). Colorless solid; mp 248–249 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.90 (3H, s), 7.17 (1H, t, J=7.2 Hz), 7.28 (1H, d, J=7.9 Hz), 7.44 (1H, s), 7.56–7.77 (6H, m), 8.93 (1H, s), 11.56 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 56.0, 106.8, 112.4, 116.8, 119.7, 120.9, 123.4, 130.2, 131.8, 133.4, 137.0, 152.1, 153.3, 157.0, 161.1; ESIMS m/z=356/358 (MH^+), 354/356 ($M-H^-$); elemental analysis calcd for $C_{17}H_{15}BrClN_3O$: C, 52.00; H, 3.85; N, 10.70. Found: C, 51.84; H, 3.65; N, 10.60.

4.4.14. (3-Bromo-phenyl)-[6-(3-nitro-phenyl)-pyrimidin-4-yl]-amine hydrochloride (2n·HCl). Following GM1, **3c** (150 mg, 0.637 mmol) and 3-bromoaniline (73 μL, 0.669 mmol, 1.05 equiv) were reacted in 1.5 mL of 2-propanol and 150 μL of concd HCl (37%) at 95 °C. Filtration and drying afforded **2n**·HCl (230 mg, 89%). Yellow solid; mp 272–273 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.23–7.39 (2H, m), 7.52 (1H, s), 7.67 (1H, td, J=7.5 Hz, J=1.9 Hz), 7.88 (1H, t, J=8.0 Hz), 8.18 (1H, t, J=1.9 Hz), 8.37–8.45 (2H, m), 8.80 (1H, t, J=1.8 Hz), 8.90 (1H, s), 10.74 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 103.9, 118.9, 121.4, 121.6, 122.3, 125.4, 125.7, 130.7, 132.9, 136.5, 140.6, 148.2, 156.6, 157.1, 160.9, 161.0; ESIMS m/z=371/373 (MH^+), 369/371 ($M-H^-$); elemental analysis calcd for $C_{16}H_{12}BrClN_4O_2$: C, 47.14; H, 2.97; N, 13.74. Found: C, 47.29; H, 2.89; N, 13.90.

4.4.15. (4-Aminomethyl-phenyl)-(6-phenyl-pyrimidin-4-yl)-amine (2o). Following GM1, **3a** (84 mg, 0.441 mmol) and 4-aminobenzylamine (50 μL, 0.441 mmol) were reacted

in 2 mL of 2-propanol and 120 μL of concd H_2SO_4 (98%) at 100 °C for 900 s. The sulfate salt of **2o** was isolated after filtration. Satd aqueous $NaHCO_3$ solution was added (pH=8–9) to the solid, and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent afforded **2o** (95 mg, 78%). Slightly yellow solid; mp 153–155 °C (EtOAc); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.68 (2H, s), 7.21 (1H, s), 7.29 (2H, d, J=8.9 Hz), 7.47–7.57 (3H, m), 7.62 (2H, d, J=8.9 Hz), 7.96–8.05 (2H, m), 8.68 (1H, s), 9.64 (1H, br s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 45.1, 101.6, 119.8, 126.3, 127.5, 128.8, 130.2, 136.9, 137.8, 138.2, 158.3, 161.0, 161.0; HPLC purity 94%; ESIMS m/z=277 (MH^+), 275 ($M-H^-$).

4.4.16. 4-[6-(2-Methoxy-phenyl)-pyrimidin-4-yl]-morpholine hydrochloride (4). A suspension of **3b** (75 mg, 0.34 mmol) and morpholine (36 μL, 0.41 mmol, 1.2 equiv) in 1.0 mL of 2-propanol was heated in the microwave synthesizer at 115 °C for 900 s. Concd HCl (37%, 300 μL) was added. After storage at 4 °C overnight, the colorless precipitate was filtered, washed with cold 2-propanol, and dried to afford **4** (68 mg, 65%). Colorless solid; mp 231–232 °C (2-propanol/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.69–3.78 (4H, m), 3.86 (3H, s), 3.87–3.96 (4H, m), 7.16 (1H, t, J=7.8 Hz), 7.26 (1H, d, J=8.1 Hz), 7.34 (1H, s), 7.56–7.68 (2H, m), 8.83 (1H, s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 45.1, 55.9, 65.6, 102.6, 112.0, 119.5, 120.8, 130.7, 133.4, 151.2, 151.5, 156.7, 160.8; HPLC purity 98%; ESIMS m/z=272 (MH^+).

4.4.17. (4-Amino-benzyl)-(6-phenyl-pyrimidin-4-yl)-amine (6). Compound **3a** (50 mg, 0.262 mmol) and 4-aminobenzylamine (33 μL, 0.288 mmol, 1.1 equiv) were suspended in 1.5 mL of 2-propanol, treated with DIPEA (63 μL, 0.524 mmol, 2.0 equiv) and reacted at 120 °C for 900 s in the microwave synthesizer. The solvent was evaporated and the crude product purified by flash column chromatography (*c*Hex/EtOAc 1:1) to afford **6** (41 mg, 52%). Colorless solid; mp 156–157 °C (MeCN/H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.37 (2H, d, J=5.9 Hz), 4.97 (2H, s), 6.52 (2H, d, J=8.1 Hz), 6.95 (1H, s), 7.02 (2H, d, J=8.1 Hz), 7.43–7.54 (3H, m), 7.75 (1H, t, J=5.9 Hz), 7.91–8.03 (2H, m), 8.49 (1H, s); ^{13}C NMR (66 MHz, DMSO-d_6) δ 43.4, 100.7, 113.7, 125.9, 126.2, 128.3, 128.6, 129.9, 137.2, 147.6, 158.3, 159.8, 162.8; HPLC purity 99%; ESIMS m/z=277 (MH^+), 275 ($M-H^-$).

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References and notes

1. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003.
2. *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
3. Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968.
4. Stanetty, P.; Hattinger, G.; Schnuerch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 5215–5220.
5. (a) van der Heiden, M. R.; Frey, G. D.; Plenio, H. *Organometallics* **2004**, *23*, 3548–3551; (b) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775–2789; (c) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397–4400; (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209; (e) Hartwig, J. F. *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 107–168.
6. Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787–1789.
7. Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488.
8. Garnier, E.; Audoux, J.; Pasquinet, E.; Suzenet, F.; Poullain, D.; Lebret, B.; Guillaumet, G. *J. Org. Chem.* **2004**, *69*, 7809–7815.
9. For a review about pharmacologically active pyrimidines, especially protein kinase inhibitors, see: Fabbro, D.; Ruetz, S.; Buchdunger, E.; Cowan-Jacob, S.W.; Fendrich, G.; Liebetanz, J.; Mestan, J.; O'Reilly, T.; Traxler, P.; Chaudhuri, B.; Fretz, H.; Zimmermann, J.; Meyer, T.; Caravatti, G.; Furet, P.; Manley, P. W. *Pharmacol. Ther.* **2002**, *93*, 79–98.
10. Suzuki, A. *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 53–106; Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59.
11. (a) Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985–987; (b) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515–3517; (c) Parrot, I.; Ritter, G.; Wermuth, C. G.; Hibert, M. *Synlett* **2002**, 1123–1127; (d) Brown, G. R.; Foubister, A. J.; Roberts, C. A.; Wells, S. L.; Wood, R. *Tetrahedron Lett.* **2001**, *42*, 3917–3919; (e) Agarwal, N.; Raghuwanshi, S. K.; Upadhyay, D. N.; Shukla, P. K.; Ram, V. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 703–706; (f) El-Reedy, A. M.; Ali, A. S.; Ayyad, A. O. *J. Heterocycl. Chem.* **1989**, *26*, 313–316.
12. (a) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discov.* **2006**, *5*, 51–64; (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (c) Mavandadi, F.; Lidstrom, P. *Curr. Top. Med. Chem.* **2004**, *4*, 773–792; (d) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002; (e) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (f) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727; (g) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
13. (a) Bursavich, M. G.; Lombardi, S.; Gilbert, A. M. *Org. Lett.* **2005**, *7*, 4113–4116; (b) Beattie, J. F.; Breault, G. A.; Ellston, R. P. A.; Green, S.; Jewsbury, P. J.; Midgley, C. J.; Naven, R. T.; Minshull, C. A.; Pauptit, R. A.; Tucker, J. A.; Pease, J. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2955–2960; (c) Luo, G.; Chen, L.; Poindexter, G. S. *Tetrahedron Lett.* **2002**, *43*, 5739–5742; (d) Chorvat, R. J.; Bakthavatchalam, R.; Beck, J. P.; Gilligan, P. J.; Wilde, R. G.; Cocuzza, A. J.; Hobbs, F. W.; Cheeseman, R. S.; Curry, M.; Rescinito, J. P.; Krenitsky, P.; Chidester, D.; Yarem, J. A.; Klaczkiewicz, J. D.; Hodge, C. N.; Aldrich, P. E.; Wasserman, Z. R.; Fernandez, C. H.; Zaczek, R.; Fitzgerald, L. W.; Huang, S.-M.; Shen, H. L.; Wong, Y. N.; Chien, B. M.; Quon, C. Y.;

Arvanitis, A. *J. Med. Chem.* **1999**, *42*, 833–848; (e) Monge, A.; Martinez-Crespo, F. J.; Aranzazu Villanueva, M.; Font, M.; Santiageo, E.; Martinez de Irujo, J. J.; Alberdi, E.; Lopez-Unzu, M. J.; Cenarruzabeitia, E. *Arch. Pharm.* **1993**, *326*, 879–885; (f) Ram, V. J. *Arch. Pharm.* **1990**, *323*, 895–899; (g) De Angelis, G. G.; Hess, H. J. E. D.E. Patent 2165962, 1972; (h) Short, J. H. U.S. Patent 3,478,030, 1969.

14. Cumming, J. G.; McKenzie, C. L.; Bowden, S. G.; Campbell, D.; Masters, D. J.; Breed, J.; Jewsbury, P. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5389–5394.
15. (a) Gong, B.; Hong, F.; Kohm, C.; Jenkins, S.; Tulinsky, J.; Bhatt, R.; de Vries, P.; Singer, J. W.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2303–2308; (b) Cocuzza, A. J.; Chidester, D. R.; Culp, S.; Fitzgerald, L.; Gilligan, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1063–1066.
16. Angelo, M.; Ortwine, D.; Worth, D.; Werbel, L. M.; McCall, J. W. *J. Med. Chem.* **1983**, *26*, 1258–1267.
17. (a) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913–916; (b) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987–4990; (c) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669; (d) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623–1626; (e) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.
18. (a) Jensen, T. A.; Liang, X.; Tanner, D.; Skjaerbaek, N. *J. Org. Chem.* **2004**, *69*, 4936–4947; (b) Weigand, K.; Pelka, S. *Mol. Divers.* **2003**, *7*, 181–184; (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655; (d) Maes, B. U. W.; Loones, K. T. J.; Lemiere, G. L. F.; Dommisse, R. A. *Synlett* **2003**, 1822–1825; (e) Wang, T.; Magnin, D. R.; Hamann, L. G. *Org. Lett.* **2003**, *5*, 897–900; (f) Chida, N.; Suzuki, T.; Tanaka, S.; Yamada, I. *Tetrahedron Lett.* **1999**, *40*, 2573–2576; (g) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240–7241.
19. (a) Kasparec, J.; Adams, J. L.; Sisko, J.; Silva, D. J. *Tetrahedron Lett.* **2003**, *44*, 4567–4570; (b) Goodman, A. J.; Stanforth, S. P.; Tarbit, B. *Tetrahedron* **1999**, *55*, 15067–15070.

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Evaluation of a simple and novel fluorescent anion sensor, 4-quinolone, and modification of the emission color by substitutions based on molecular orbital calculations

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Abstract—4-Quinolone (4-QO) was evaluated as a simple and novel fluorescent anion sensor, and the modification of its emission color was carried out. The series of 4-QO derivatives having molecular orbitals with different energy levels was designed by substitutions at the 6 and 7 positions based on the molecular orbital calculations. All derivatives showed drastic fluorescence enhancements in the presence of F^- via the intramolecular charge transfer mechanism, and the successful modification of the emission color was achieved. The anion-induced emission colors of these derivatives as well as their binding affinities for F^- could be predicted by ab initio quantum chemical calculations, indicating that the present calculations are useful in designing new anion sensors.

1. Introduction

Anion sensing has been of great interest in biological and environmental sciences for several decades, and various fluorescent sensors have been developed for sensitive and simple detections.[1–3] As signaling mechanisms, photoinduced electron transfer,[4–9] intramolecular charge transfer (ICT),[10–18] excited-state proton transfer,[19,20] metal-to-ligand charge transfer,[21] excimer/exciplex formation,[22–24] and competitive binding[25–28] are reported. Particularly, ICT based on hydrogen bond formations between anions and NH or OH groups of the sensor molecules has been widely employed because of the simplicity and capability for multipoint interactions.

ICT fluorescent anion sensors can be classified into two types; one shows fluorescence quenching when binding to anions, and the other shows a fluorescence enhancement. For sensitive detection, the latter has the best advantages, nevertheless, only a few sensors of this type have so far been reported.[11,13,15] Therefore, the discovery and/or development of new ICT sensors of this type are strongly desired to establish a variety of methods for simple and sensitive anion sensing. In a previous study, we reported that some 4-quinolone (4-QO) derivatives are useful fluorophores with high fluorescence quantum efficiency and high stability in aqueous media.[29,30] We have been focusing on the discovery of new photophysical properties of these compounds, and found that 4-QO shows a drastic fluorescence enhancement via the ICT mechanism in the presence of anions. Herein, we now report for the first time the anion-induced changes in the absorption and fluorescence of 4-QO.

In addition, we have modified the emission color of 4-QO by the substitution based on molecular orbital calculations. The emission color of a sensor is of great importance for simple and selective detection, because it is often needed to avoid potential interferences by fluorescence impurities present in environmental and biological samples. Until now, several reported studies have focused on modifying the emission color of a sensor molecule based on substituent effects.[10,14,16,18] However, the introduction of substituents was in most cases still empirical, and theoretical methods based on molecular orbital calculations have scarcely been exploited in spite of the fact that various fluorescent compounds have recently been designed using computational calculations.[31–35] To the best of our knowledge, there have been no reports demonstrating the theoretical modification of the emission color using a sensor molecule that shows a fluorescence enhancement upon binding to anions via the ICT mechanism.

In the present paper, we report a simple and novel fluorescent anion sensor, 4-QO, that shows a drastic fluorescence enhancement via the ICT mechanism. By substitutions based on molecular orbital calculations, 4-QO derivatives **1–6** (Fig. 1) were designed in order to produce different emission

Keywords: Anion sensor; 4-Quinolone; Intramolecular charge transfer; Fluorescence; Molecular orbital calculation.
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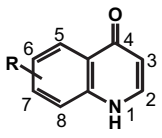

compound	R
4-QO	H
1	6-CH_3
2	6-OCH_3
3	6-$COCH_3$
4	7-CH_3
5	7-OCH_3
6	7-$COCH_3$

Figure 1. Structures of 4-QO derivatives.

colors from 4-QO. The binding affinities of these derivatives for anions were also considered using ab initio quantum chemical calculations.

2. Results and discussion

2.1. Anion response of 4-QO

The anion-induced changes in the absorption and fluorescence spectra of 4-QO were investigated using F^-, Cl^-, Br^-, HSO_4^-, AcO^-, and $H_2PO_4^-$ (as tetrabutylammonium salts). Figure 2 shows the absorption and fluorescence emission spectra in CH_3CN when titrated with F^-. The peak of the absorption spectrum was slightly red shifted from 330 to 338 nm and two isosbestic points at 332 and 299 nm were observed (Fig. 2a). In the fluorescence emission spectra, the intensity was drastically increased at 396 nm (Fig. 2b). With the titration of AcO^- and $H_2PO_4^-$ similar changes were observed, while the titrations of other anions caused no change in both spectra. This suggests that 4-QO forms complexes only with F^-, AcO^-, and $H_2PO_4^-$. This anion-selectivity is thought to be dictated by the anion basicity; F^-, AcO^-, and $H_2PO_4^-$ are stronger hydrogen acceptors than other tested anions. The Job plots for the complexation of 4-QO with anions obtained from the absorption titration experiments showed a 1:1 stoichiometry for F^- and 2:1 for AcO^-, while, more than two complex species were suggested to be present for $H_2PO_4^-$. To confirm the recognition mechanism of 4-QO for anions, a ^1H NMR titration experiment was carried out. The ^1H NMR spectrum of 4-QO in DMSO-d_6 showed a singlet signal for the NH proton at 11.70 ppm (Fig. 3a). Upon addition of 1.0 equiv F^-, the signal completely disappeared (Fig. 3b), which indicates hydrogen bond formation between the NH group of 4-QO and F^-. Ab initio quantum chemical calculations were performed, and the structure of the complex of 4-QO with F^- was optimized with B3LYP at the 6-31G(d) level. In the optimized structure, the distance between the NH proton and F^- is 1.009 Å, also indicating the presence of a hydrogen bond between these atoms. The negative charge of F^- calculated at the B3LYP/6-311+G(d,p) level using the optimized structure is −0.662; this means that a part of the negative charge is intramolecularly transferred from F^- to 4-QO. For a further confirmation, we synthesized 1-methyl-4-QO that has the CH_3 group at the recognition point, and investigated its anion response that is observed in the absorption and fluorescence emission spectra. With the addition of all anions tested, no change in both spectra was observed. These results clearly indicate that 4-QO recognizes anions via the NH group.

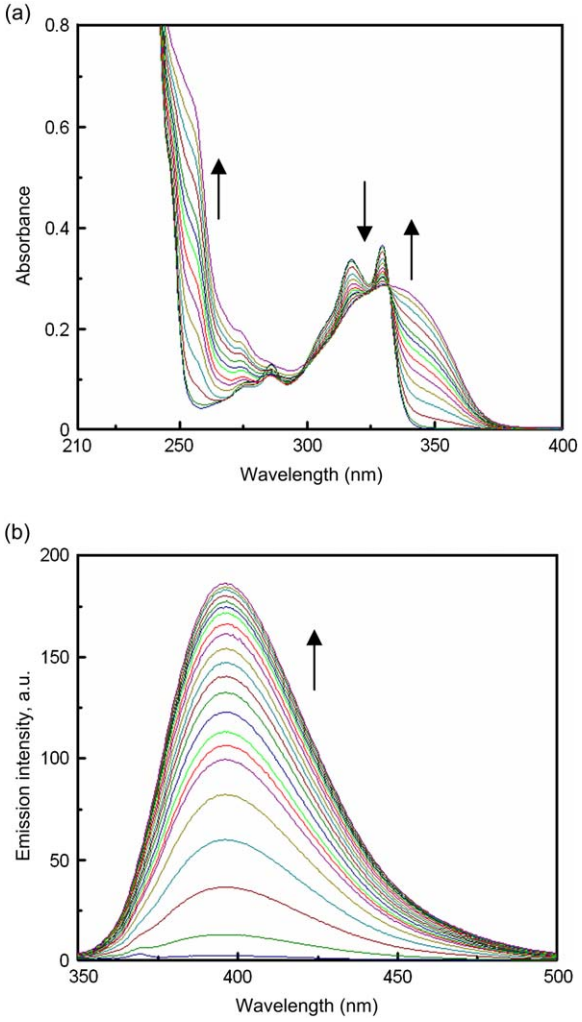

Figure 2. (a) Change in absorption spectra of 4-QO (30 μM in CH_3CN) upon the addition of F^- (0–0.3 mM); (b) change in fluorescence emission spectra of 4-QO (3 μM in CH_3CN) upon the addition of F^- (0–35 μM) with the excitation wavelength of 332 nm.

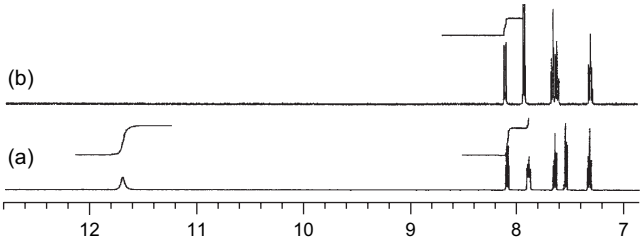

Figure 3. Partial ^1H NMR (500 MHz) spectra of 4-QO in DMSO-d_6 in (a) the absence, and (b) the presence of 1.0 equiv F^-.

2.2. Design of 4-QO derivatives as novel anion sensors using molecular orbital calculations

Adding electron-donating and/or -withdrawing groups to fluorophores is generally known to cause changes in their HOMO–LUMO gaps, and it is expected that not only a shift in the absorption wavelength, but also a shift in the emission wavelength would be induced. The complexes of 4-QO with anions emit the fluorescence at 396 nm, representing a violet-blue color. Therefore, as novel anion sensors showing

distinct visible emission colors, 4-QO derivatives having smaller HOMO–LUMO gaps than that of 4-QO in the complexes with anions would be desired; these derivatives are expected to have longer emission wavelengths. Concerning the synthesis of 4-QO derivatives, Gould–Jacobs reaction[36] is generally exploited. By utilizing this reaction, the introduction of various substituents at the 6 and/or 7 positions of 4-QO could be performed. From these points of views, we designed a series of 4-QO derivatives **1**–**6** for this study. The HOMO levels, LUMO levels, and HOMO–LUMO gaps of the complexes of **1**–**6** with F^- are summarized in Table 1. In this study, we selected F^- as the target anion because of the following reasons. F^- is one of the most attractive anions for its importance in dental care[37] and treatment of osteoporosis,[38] and most anion sensors are investigated for their responses to F^-. Therefore, by investigating the emission color modification using F^-, the obtained strategy could be expanded to various fluorescent anion sensors. In the F^- complexes, the HOMO–LUMO gaps of compounds **1**, **2**, **4**, and **5**, that have the electron-donating groups at the 6 or 7 positions, show energy gaps similar to that of 4-QO, while **3** and **6** that have electron-withdrawing groups show considerably smaller energy gaps than that of 4-QO. These calculation results imply that **3** and **6** are expected to have distinct absorption and fluorescence wavelengths from those of 4-QO.

Table 1. HOMO levels, LUMO levels, and HOMO−LUMO gaps of the F^- complexes of 4-QO derivatives

Compound	HOMO (eV)	LUMO (eV)	HOMO−LUMO gap (eV)
4-QO+F^-	−1.83	2.39	4.22
1+F^-	−1.78	2.43	4.21
2+F^-	−1.74	2.40	4.14
3+F^-	−2.36	1.18	3.54
4+F^-	−1.81	2.46	4.27
5+F^-	−1.83	2.20	4.03
6+F^-	−2.16	1.05	3.21

Data were obtained at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d).

2.3. Anion-induced changes in absorption and fluorescence of synthesized 4-QO derivatives

The designed 4-QO derivatives **1**–**6** were synthesized by Gould–Jacobs reaction, and their absorption and fluorescence properties have been investigated. All compounds showed changes in their absorption spectra upon the addition of F^-. The absorption spectra of **1**, **3**, and **6** in CH_3CN with the addition of F^- are shown in Figure 4. The results obtained for **2**, **4**, and **5** are very similar to that of **1**. These compounds (**1**, **2**, **4**, and **5**) showed the similar absorption changes to that of 4-QO (Fig. 2a); the absorption spectrum was slightly red shifted with some isosbestic points. On the other hand, compounds **3** and **6** showed the characteristic changes in absorption. In the absorption spectrum of compound **3**, the peak at 335 nm decreased, a new peak appeared at 395 nm, and three isosbestic points were observed at 351, 288, and 249 nm. In the spectrum of compound **6**, two new peaks at 389 and 337 nm and two isosbestic points at 370 and 346 nm appeared, and the absorbance at 347 nm decreased. Table 2 summarizes the wavelengths of the absorption

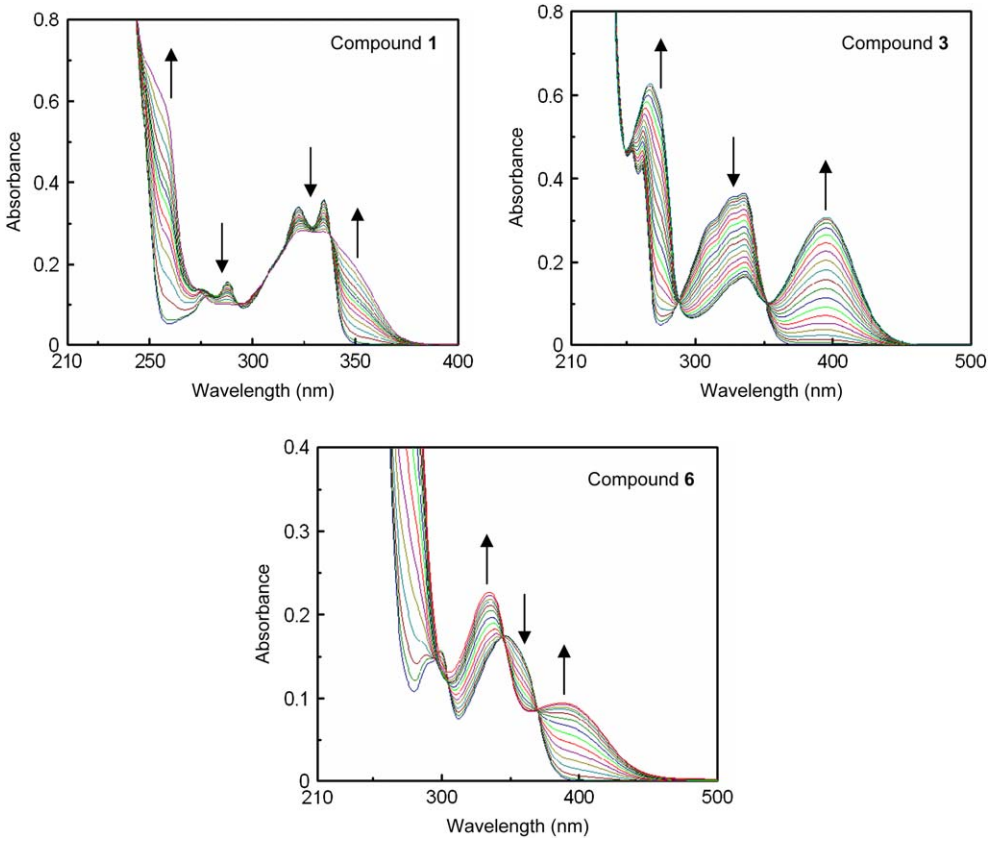

Figure 4. Changes in absorption spectra of **1**, **3**, and **6** (30 μM in CH_3CN) upon the addition of F^- (0–0.3 mM for **1**, 0–0.1 mM for **3**, and 0–0.2 mM for **6**).

Table 2. Absorption maxima of 4-QO derivatives and their F^- complexes

Compound	Absorption maximum (nm)[a]	Absorption maximum (nm)[b]
4-QO	338	330
1	336	335
2	344	345
3	395	335
4	337	328
5	340	322
6	389	347

[a] Values in the presence of F^-.
[b] Values in the absence of F^-.

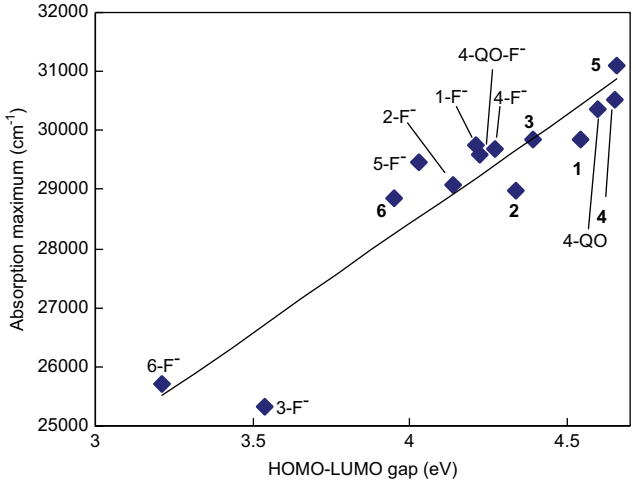

Figure 5. Correlation between the HOMO–LUMO gaps and the wavelengths of the absorption maxima of 4-QO derivatives and their F^- complexes.

maxima of the 4-QO derivatives in the F^- complexes, as well as their original absorption maxima in the absence of F^-. These values are in good agreement with the calculated HOMO–LUMO gaps (Fig. 5). This result indicates that the molecular orbital energies obtained by the quantum chemical calculations reflect the values from the experimental measurements, and the calculations performed in this study have a sufficient suitability for practical use.

Upon the addition of F^-, all compounds showed drastic fluorescence enhancements. Figure 6 shows the changes in the fluorescence emission spectra of **1**, **3**, and **6** in CH_3CN when titrated with F^-. Compounds **1**, **2**, **4**, and **5** emitted a fluorescence centered at almost the same wavelengths around 400 nm. Whereas **3** and **6**, that show considerably smaller HOMO–LUMO gaps than that of 4-QO in the F^- complexes, emitted a longer fluorescence centered at 492 and 542 nm, respectively. The emission colors of **1**, **2**, **4**, and **5** were violet-blue, being similar to that of 4-QO. On the other hand, the emission colors of **3** and **6** were green-blue and yellow-green (Fig. 7).

2.4. Association constants for 4-QO derivatives with F^-

The association constants for **1**–**6** with F^- obtained by Rose–Drago method using absorption spectroscopy[39] are summarized in Table 3. In comparison with 4-QO, compounds **1**, **2**, **4**, and **5** showed almost the same or a little lower binding affinities, while **3** and **6** showed notably higher affinities. This is empirically reasonable because the electron-withdrawing group of $COCH_3$ makes **3** and **6** strong electron acceptors by increasing the acidities of the NH protons. The structures of

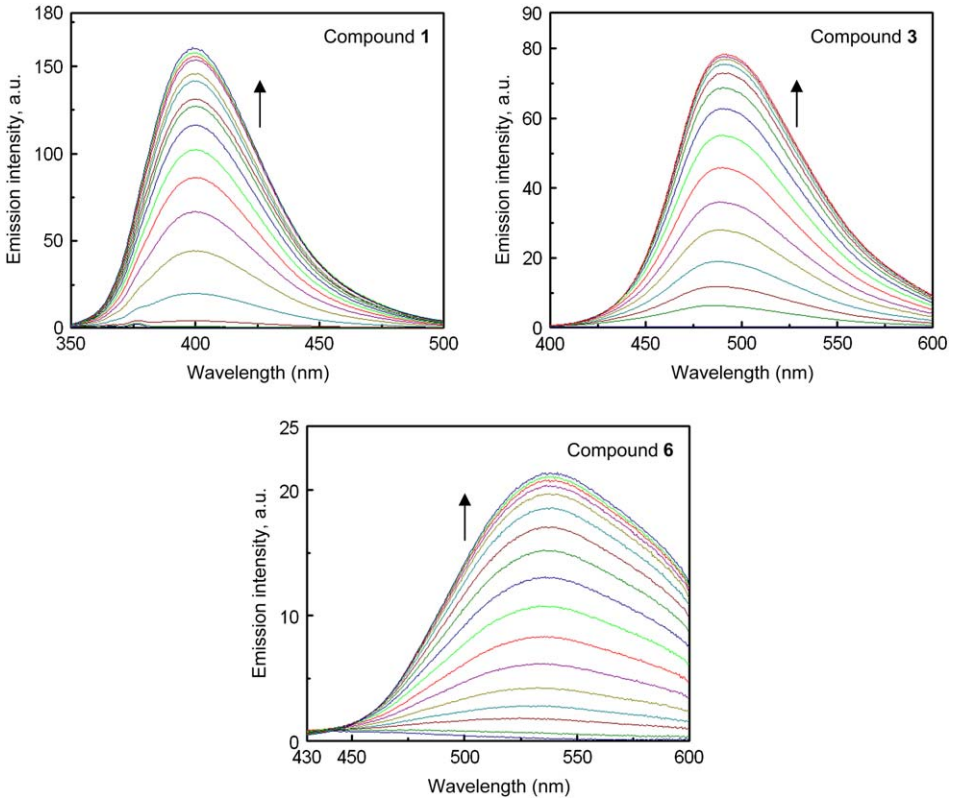

Figure 6. Changes in fluorescence emission spectra of **1**, **3**, and **6** (3 μM in CH_3CN) upon the addition of F^- (0–35 μM for **1**, 0–15 μM for **3**, and 0–18 μM for **6**) with the excitation wavelength of 338 nm for **1**, 351 nm for **3**, and 370 nm for **6**.

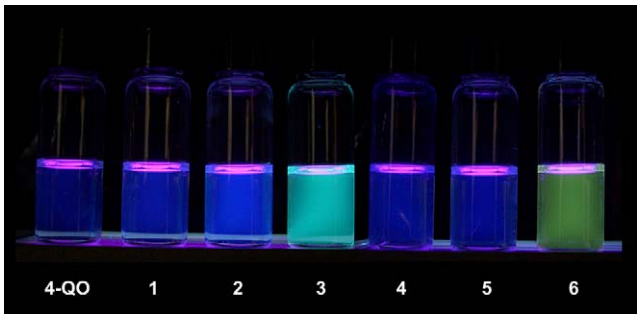

Figure 7. Emission colors of 4-QO derivatives (3 μM in CH_3CN) under UV light illumination (365 nm) in the presence of F^-.

Table 3. Association constants and binding energies for 4-QO derivatives with F^-, partial charges of F^-, and distances of NH···F^- in the F^- complexes

Compound	Association constant[a] (M^{-1})	Binding energy[b] (kcal/mol)	F^- charge[c]	NH···F^- distance (Å)
4-QO	$(6.2\pm2.3)\times10^3$	−55.8	−0.662	1.009
1	$(5.3\pm1.0)\times10^3$	−55.2	−0.663	1.009
2	$(1.9\pm0.8)\times10^3$	−55.2	−0.662	1.009
3	$(3.1\pm1.3)\times10^4$	−62.1	−0.654	1.000
4	$(5.5\pm1.1)\times10^3$	−54.6	−0.663	1.009
5	$(4.4\pm1.8)\times10^3$	−53.3	−0.661	1.008
6	$(1.3\pm0.6)\times10^4$	−59.6	−0.653	0.999

[a] Absorption titration experiments were carried out in CH_3CN at 293 K, and the errors in association constants were within 10%.
[b] Data were obtained at B3LYP/6-311+G(d,p)//B3LYP/6-31G(d).
[c] Charges were calculated with the natural population orbital analysis.

the F^- complexes of **1**–**6** optimized by ab initio quantum chemical calculations provide a detailed explanation of the magnitudes of the association constants. The calculated binding energies with F^- are −62.1 and −59.6 kcal/mol for **3** and **6**, respectively. These values indicate that the complexes are much more stable than other compounds having binding energies around −55 kcal/mol. In addition, the F^- complexes of **3** and **6** show smaller negative charges of F^- than those for other compounds by 0.007–0.010, indicating that the greater negative charge of F^- is transferred to 4-QO in the F^- complexes of **3** and **6**. The distances between the NH protons and F^- for **3** and **6** are 1 and 0.999 Å, respectively; these values are shorter than those for other compounds by 0.008–0.01 Å. These results indicate that the binding affinity for F^- could also be predicted by the binding energy calculations, negative charges of F^-, and the distances between the NH protons and F^- using the ab initio quantum chemical calculations.

3. Conclusions

We have presented a simple compound 4-QO as a valuable ICT fluorescent anion sensor. A series of 4-QO derivatives have been prepared as novel anion sensors, and revealed that not only the shift in the absorption wavelength, but also the shift in the emission color could be induced by lowering the HOMO–LUMO gap by substitutions based on molecular orbital calculations. In addition, the magnitudes of their association constants for F^- were well predicted using the ab initio quantum chemical calculations. The strategy demonstrated in the present work would be effective for the modifications of the absorption and emission properties, and the binding affinities of other ICT fluorescent anion sensors.

4. Experimental

4.1. General procedures

Commercially available materials were used without any additional purification. CH_3CN and DMSO used for the spectral studies were of spectroscopic grade, and all other solvents were of guaranteed reagent grade. 1-Methyl-4-QO was synthesized by methylation of 4-QO using CH_3I and K_2CO_3 in the general method. Compounds **1**–**6** were synthesized from aniline derivatives in four steps according to previously reported methods[40–42] with some modifications. The products were characterized by ^1H NMR, FABMS, and elemental analyses. The ^1H NMR spectra were recorded using a Varian Unity-500 spectrometer (500 MHz) in DMSO-d_6. Mass spectra were obtained using JEOL JMS 600 and JMS-SX102A mass spectrometers.

4.1.1. 1-Methyl-4-quinolone. Colorless blocks. Yield: 46.5%. Mp 152–153 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 3.80 (3H, s, CH_3–), 6.03 (1H, d, J=7.6 Hz, H-3), 7.39 (1H, m, H-6 or H-7), 7.64 (1H, d, J=8.5 Hz, H-5 or H-8), 7.74 (1H, m, H-6 or H-7), 7.95 (1H, d, J=7.8 Hz, H-2), 8.17 (1H, dd, J=1.4, 8.0 Hz, H-5 or H-8). HRMS (FAB): calcd for M+H, 160.0762; found, 160.0726.

4.1.2. 6-Methyl-4-quinolone (1). Colorless needles. Yield: 15.0%. Mp 240–241 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 2.39 (3H, s, CH_3–), 5.97 (1H, d, J=7.4 Hz, H-3), 7.27 (1H, dd, J=3.0, 8.9 Hz, H-7), 7.48–7.50 (2H, m, H-5, 8), 7.82 (1H, d, J=7.4 Hz, H-2), 11.62 (1H, br s, H-1). FABMS m/z=160.1 (M+H). Anal. Calcd for $C_{10}H_9NO\cdot H_2O$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.98; H, 6.18; N, 7.86.

4.1.3. 6-Methoxy-4-quinolone (2). Colorless needles. Yield: 15.8%. Mp 251–252 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 3.82 (3H, s, CH_3O–), 5.99 (1H, d, J=7.3 Hz, H-3), 7.27 (1H, dd, J=2.9, 9.0 Hz, H-7), 7.48–7.50 (2H, m, H-5, 8), 7.82 (1H, d, J=7.3 Hz, H-2), 11.70 (1H, br s, H-1). FABMS m/z=176.1 (M+H). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.16; H, 5.20; N, 8.03.

4.1.4. 6-Acetyl-4-quinolone (3). Orange plates. Yield: 25.1%. Mp>300 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 2.63 (3H, s, CH_3CO–), 6.11 (1H, d, J=7.4 Hz, H-3), 7.60 (1H, d, J=8.5 Hz, H-8), 7.94 (1H, d, J=7.4 Hz, H-2), 8.13 (1H, dd, J=2.2, 8.8 Hz, H-7), 8.66 (1H, d, J=2.2 Hz, H-5), 11.96 (1H, br s, H-1). FABMS m/z=188.2 (M+H). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.46; H, 4.88; N, 7.57.

4.1.5. 7-Methyl-4-quinolone (4). Colorless needles. Yield: 4.8%. Mp 232–233 °C. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 2.40 (3H, s, CH_3–), 5.96 (1H, d, J=7.3 Hz, H-3), 7.12 (1H, dd, J=1.0, 8.4 Hz, H-6), 7.28 (1H, s, H-8), 7.81 (1H, d, J=7.6 Hz, H-2), 7.95 (1H, d, J=8.2 Hz, H-5),

11.56 (1H, br s, H-1). FABMS *m*/*z*=160.1 (M+H). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.28; H, 5.71; N, 8.84.

4.1.6. 7-Methoxy-4-quinolone (5). Colorless needles. Yield: 6.9%. Mp 219–220 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 3.84 (3H, s, CH_3O–), 5.92 (1H, d, *J*=7.3 Hz, H-3), 6.88–6.90 (2H, m, H-5, 8), 7.78 (1H, d, *J*=7.3 Hz, H-2), 7.97 (2H, dd, *J*=0.9, 8.2 Hz, H-6), 11.48 (1H, br s, H-1). FABMS *m*/*z*=176.1 (M+H). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.43; H, 5.19; N, 7.96.

4.1.7. 7-Acetyl-4-quinolone (6). Colorless prisms. Yield: 4.5%. Mp 290–291 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 2.65 (3H, s, CH_3CO–), 6.09 (1H, d, *J*=7.3 Hz, H-3), 7.81 (1H, dd, *J*=1.5, 8.4 Hz, H-6), 7.99 (1H, d, *J*=7.6 Hz, H-2), 8.11 (1H, d, *J*=0.9 Hz, H-8), 8.17 (1H, d, *J*=8.5 Hz, H-5), 11.90 (1H, br s, H-1). FABMS *m*/*z*=188.1 (M+H). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.37; H, 4.91; N, 7.40.

4.2. Computational method

All calculations were carried out using Spartan'04(W). The geometry optimizations were performed with B3LYP at the 6-31G(d) level. The HOMO levels, LUMO levels, total energies, and atomic charges were estimated at single-point calculations (B3LYP/6-311+G(d,p)) using the geometries optimized at the B3LYP/6-31G(d) levels.

4.3. Absorption and fluorescence studies

The absorption and corrected fluorescence emission spectra were recorded using a JASCO V-530 UV–vis spectrophotometer and an F-6500 spectrofluorometer. All 4-QO derivatives were dissolved in DMSO at a 10 mM concentration. They were diluted to the appropriate concentrations with CH_3CN and used for the measurements. The titration experiments were performed by adding the anion solutions in CH_3CN to the solutions of the 4-QO derivatives. For estimation of the association constants, the absorbance data from the titration experiments were treated by Rose–Drago method.

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Supplementary data

Changes in absorption and fluorescence emission spectra of **2**, **4**, and **5** upon the addition of F^-, and Cartesian coordinates of the calculated structures are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.060.

References and notes

1. Martinez-Manez, R.; Sancenon, F. *Chem. Rev.* **2003**, *103*, 4419–4476.
2. Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 191–221.
3. Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486–516.
4. Kang, J.; Kim, H. S.; Jang, D. O. *Tetrahedron Lett.* **2005**, *46*, 6079–6082.
5. Gunnlaugsson, T.; Davis, A. P.; Hussey, G. M.; Tierney, J.; Glynn, M. *Org. Biomol. Chem.* **2004**, *2*, 1856–1863.
6. Gunnlaugsson, T.; Davis, A. P.; O'Brien, J. E.; Glynn, M. *Org. Lett.* **2002**, *4*, 2449–2452.
7. Kim, S. K.; Yoon, J. *Chem. Commun.* **2002**, 770–771.
8. Gunnlaugsson, T.; Davis, A. P.; Glynn, M. *Chem. Commun.* **2001**, 2556–2557.
9. Vance, D. H.; Czarnik, A. W. *J. Am. Chem. Soc.* **1994**, *116*, 9397–9398.
10. Aldakov, D.; Palacios, M. A.; Anzenbacher, P., Jr. *Chem. Mater.* **2005**, *17*, 5238–5241.
11. Curiel, D.; Cowley, A.; Beer, P. D. *Chem. Commun.* **2005**, 236–238.
12. Wen, Z.-C.; Jiang, Y.-B. *Tetrahedron* **2004**, *60*, 11109–11115.
13. Kovalchuk, A.; Bricks, J. L.; Reck, G.; Rurack, K.; Schulz, B.; Szumna, A.; Weibhoff, H. *Chem. Commun.* **2004**, 1946–1947.
14. Pohl, R.; Aldakov, D.; Kubat, P.; Jursikova, K.; Marquez, M.; Anzenbacher, P., Jr. *Chem. Commun.* **2004**, 1282–1283.
15. Xu, G.; Tarr, M. A. *Chem. Commun.* **2004**, 1050–1051.
16. Aldakov, D.; Anzenbacher, P., Jr. *Chem. Commun.* **2003**, 1394–1395.
17. Wu, F.-Y.; Jiang, Y.-B. *Chem. Phys. Lett.* **2002**, *355*, 438–444.
18. Black, C. B.; Andrioletti, B.; Try, A. C.; Ruiperez, C.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 10438–10439.
19. Zhang, X.; Guo, L.; Wu, F.-Y.; Jiang, Y.-B. *Org. Lett.* **2003**, *5*, 2667–2670.
20. Choi, K.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3912–3915.
21. Beer, P. D. *Acc. Chem. Res.* **1998**, *31*, 71–80.
22. Wu, J.-S.; Zhou, J.-H.; Wang, P.-F.; Zhang, X.-H.; Wu, S.-K. *Org. Lett.* **2005**, *7*, 2133–2136.
23. Nishizawa, S.; Kato, Y.; Teramae, N. *J. Am. Chem. Soc.* **1999**, *121*, 9463–9464.
24. Nishizawa, S.; Kaneda, H.; Uchida, T.; Teramae, N. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2325–2327.
25. Fabbrizzi, L.; Marcotte, N.; Stomeo, F.; Taglietti, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3811–3814.
26. Wiskur, S. L.; Ait-Haddou, H.; Lavigne, J. J.; Anslyn, E. V. *Acc. Chem. Res.* **2001**, *34*, 963–972.
27. Metzger, A.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649–652.
28. Niikura, K.; Metzger, A.; Anslyn, E. V. *J. Am. Chem. Soc.* **1998**, *120*, 8533–8534.
29. Hirano, J.; Hamase, K.; Fukuda, H.; Tomita, T.; Zaitsu, K. *J. Chromatogr., A* **2004**, *1059*, 225–231.
30. Hirano, J.; Hamase, K.; Akita, T.; Zaitsu, K. *Anal. Sci.* **2005**, *21*, x45–x46.
31. Wilson, J. N.; Bunz, U. H. F. *J. Am. Chem. Soc.* **2005**, *127*, 4124–4125.
32. Urano, Y.; Kamiya, M.; Kanda, K.; Ueno, T.; Hirose, K.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 4888–4894.
33. Gabe, Y.; Urano, Y.; Kikuchi, K.; Kojima, H.; Nagano, T. *J. Am. Chem. Soc.* **2004**, *126*, 3357–3367.

34. Shevyakov, S. V.; Li, H.; Muthyala, R.; Asato, A. E.; Croney, J. C.; Jameson, D. M.; Liu, R. S. H. *J. Phys. Chem. A* **2003**, *107*, 3295–3299.
35. Yamaguchi, S.; Shirasaka, T.; Akiyama, S.; Tamao, K. *J. Am. Chem. Soc.* **2002**, *124*, 8816–8817.
36. Gould, R. G., Jr.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890–2895.
37. Castioni, N. V.; Baehni, P. C.; Gurny, R. *Eur. J. Pharm. Biopharm.* **1998**, *45*, 101–111.
38. Kanis, J. A.; Sheffield, M. D. *Am. J. Med.* **1993**, *95*, S53–S61.
39. Rose, N. J.; Drago, R. S. *J. Am. Chem. Soc.* **1959**, *81*, 6138–6141.
40. Leyva, E.; Monreal, E.; Hernandez, A. *J. Fluorine Chem.* **1999**, *94*, 7–10.
41. Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358–1363.
42. Lin, A. J.; Loo, T. L. *J. Med. Chem.* **1978**, *21*, 268–272.

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Multi-state molecular switches based on dithienylperfluorocyclopentene and imidazo [4,5-*f*] [1,10] phenanthroline

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Abstract—Two novel diarylethene derivatives containing imidazo [4,5-*f*] [1,10] phenanthroline have been efficiently synthesized. These molecules are sensitive to both light and chemical stimuli. Under sequential alternating UV–vis light irradiation and alkali/acid treatment, distinct differences in NMR, UV–vis, and fluorescent spectra were observed. Taking advantage of the variations in visible absorption and fluorescence, a reversible four-state molecular switch with two optical outputs was realized by a single molecule.

1. Introduction

Molecular switches, which can be converted from one state to another by external stimuli such as light, electric field or chemical reaction, are becoming one of the most attractive fields in modern chemistry.[1–3] The use of photochromic compound as photon-mode switching system is considered to be a promising signaling mode for the molecular switches. In those systems, each isomer can represent either '*0*' or '*1*' of a digital binary code homologous to '*on*' and '*off*' states. Recently, the development of complex photochromic systems that integrate several switchable functions into a single molecule has attracted much attention because of the potential ability of such photochromic systems for applications in optical memory media and photonic devices.[4–7] Based on the reversible changes of the absorption and emission spectra of photochromic compounds under different external stimuli, the corresponding networks, including spiropyran,[8–17] diarylethene,[18] and some other complex systems[19–21] have been constructed. As a thermally irreversible system, diarylethenes may prove to be the most promising candidates for applications due to their good thermal stability and high fatigue resistance of both isomers. Irie et al. have reported that the digital switching of the fluorescence of diarylethene molecules can be controlled by irradiation with UV–vis light at the single-molecule level.[22] Tian et al. designed a single photochromic molecular switch with multi-optical outputs induced by light and chemical stimuli based on diarylethenes.[18,23] However, using only one photochromic diarylethene molecule to build a molecular switch with multi-optical outputs capable of building complex logic circuits is still a challenge. Moreover, the molecular switches, which can distinguish more than three kinds of states by digital output values, are rarely reported. In this report, we developed two novel photochromic diarylethene (**DAE**) molecules **1**·**2H** and **2**·**2H** containing imidazo [4,5-*f*] [1,10] phenanthroline (**IP**) moieties. In **1**·**2H**, **IP** and **DAE** moieties are directly linked to each other through a C–C σ bond without any intervening molecular bridge; whereas in the case of **2**·**2H**, a phenyl group connects the two moieties and mainly extends the conjugated system of **IP**. As we expected, both **1**·**2H** and **2**·**2H** were sensitive to both light irradiation and alkali simultaneously according to their structural characters, and gave multi-outputs of absorption and fluorescent emission signals (Scheme 1). Complex logic circuits were also built by using the single molecule based on the corresponding outputs.

2. Results and discussion

2.1. Synthesis of the diarylethene compounds

1·**2H** and **2**·**2H** were synthesized from 1,10-phenanthroline-5,6-dione and the corresponding aldehydes according to Scheme 2 in a good yield (70 and 80% for **1**·**2H** and **2**·**2H**, respectively). The molecular structures of these two compounds were confirmed by NMR spectroscopy and MALDI-TOF mass spectrometry, as well as by elemental analysis. Compared with **2**·**2H**, **1**·**2H** shows better solubility in methanol, ethanol, and DMSO.

Keywords: Molecular switches; Diarylethene; Fluorescence; Photochromism; Deprotonation.
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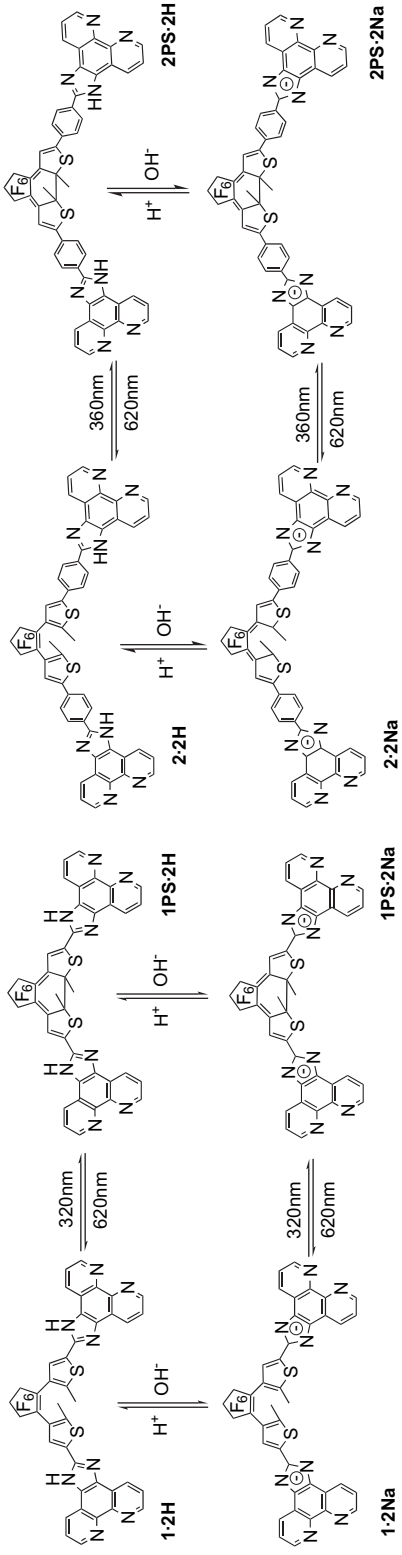


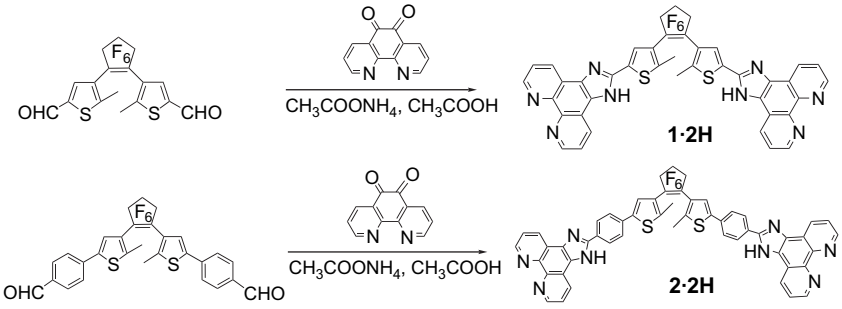
Scheme 1. The four states of **1** and **2** upon photochromism and deprotonation (**PS** is the abbreviation of photostationary state; **1**·**2Na**, **1PS**·**2Na**, and **2**·**2Na**, **2PS**·**2Na** are deprotonated isomers of **1**·**2H**, **1PS**·**2H**, and **2**·**2H**, **2PS**·**2H**, respectively).

2.2. NMR changes of 1·2H upon deprotonation by alkali

Deprotonation of the acidic imidazolyl N–H by addition of alkali changes the chemical shifts of the aryl protons of **1**·**2H**, which is revealed by the analysis of ^{1}H NMR spectra. Figure 1 displays the ^{1}H NMR spectral changes of **1**·**2H** in a DMSO-d_6 solution with titration of an NaOD solution. The ^{1}H NMR of **1**·**2H** exhibited an array of resonances corresponding to the aromatic protons in the molecule. The signal of NH in imidazolyl was not observed even prior to the addition of alkali. This may be due to fast proton exchange with water present in solution. Thienyl protons appear as a singlet at δ 8.04 (H1), and those for 2,8-positions of phenanthroline appear as multiplets centered at δ 7.80 (H3). A doublet at δ 8.80 with coupling constant of J=8.0 Hz is expected for H2 on phenanthroline. The other group of peaks at δ 9.03 should thus refer to H4 on phenanthroline. After adding NaOD into the DMSO-d_6 solution of **1**·**2H**, a clear upfield shift for H3 and H4 was observed. This is reasonable because the deprotonation enriches the electronic density of imidazolyl and leads to a higher shielding effect on these protons. The proton of H1 was incipiently upshifted and then shifted downfield while the amount of the base added was increased from 1 to 2 equiv. On the contrary, the signal for H2 was slowly shifted downfield. The different changes of the protons may be due to the anisotropic field effect of the anion to the π-system of phenanthroline. The resonances of the protons were constant after addition of more than 2 equiv of OH^-, which revealed a complete deprotonation of the imidazolyl. The altering chemical shift ($\Delta\delta$) of the protons for H1, H2, and H3 are -0.09, 0.08, and -0.08 ppm, respectively. The most significant change is that H4 on phenanthroline exhibited a significant upfield shift ($\Delta\delta$=-0.14 ppm), positing on the same signal position as H2. The NMR results indicate that the deprotonation promotes electron delocalization and averages the chemical environment of the protons on phenanthroline group of the molecule.[24]

2.3. Reversible absorption changes upon photochromism

The absorption spectra of both **1**·**2H** and **2**·**2H** show absorption bands only in the ultra violet range belonging to π–π^* transition (327 nm for **1**·**2H** and 343 nm for **2**·**2H**) (Fig. 2A and 2B). As expected, **1**·**2H** and **2**·**2H** showed reversible color and absorption spectral changes with the alternate irradiation of UV and visible lights (Scheme 1). Upon irradiation with light of 320 nm (360 nm for **2**·**2H**) within 5 min, the absorption at 598 nm (ε: 6100 dm^3 mol^{-1} cm^{-1}) and 612 nm (ε: 21,100 dm^3 mol^{-1} cm^{-1}) belonging to **1PS**·**2H** and **2PS**·**2H** (photostationary state), respectively, were observed accompanied with the deduction of the absorption bands in ultra violet range. Hence, the colorless solution of open-ring form became greenish blue due to the transformation of **1**·**2H** and **2**·**2H** by photocyclization into their closed-ring forms, with a quantum yields of 16 and 29%, respectively. The photocyclization conversion for **1**·**2H** and **2**·**2H** at photostationary state is 0.57 and 0.65, respectively. **1PS**·**2H** and **2PS**·**2H** were photochemically reverted to their open forms completely by 620 nm light irradiation with the quantum yields of 37 and 32%, respectively, and the greenish blue color disappeared. **2PS**·**2H** has a larger absorption efficiency and 14 nm red shift in visible range



Scheme 2. Synthesis procedures of **1·2H** and **2·2H**.

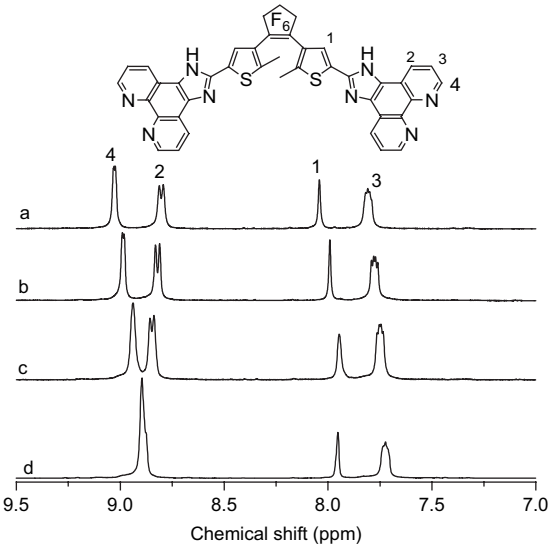


Figure 1. Partial ^{1}H NMR spectral changes of **1·2H** (2.5×10^{-2} mol/L) upon titration of NaOD (30%) at the equivalence of 0 (a), 0.6 (b), 1.0 (c), and 2.0 (d) of **1·2H** (400 MHz, DMSO-d_6 at 298 K).

compared with that of **1PS·2H**, showing a character of extended π-system. Both open and closed-ring forms of **1·2H**, **1PS·2H**, and **2·2H**, **2PS·2H** could be deprotonated to form **1·2Na**, **1PS·2Na**, and **2·2Na**, **2PS·2Na**, respectively, by adding alkali into their solutions. There is no appreciable difference in visible range of the absorption spectra between the corresponding protonated and deprotonated states in closed-ring forms of both molecules. This indicates that deprotonation has no notable effect on the ground state of closed **DAE** moiety in both molecules. The absorption band at UV region belonging to π–π* transition decreased a little in **1·2Na**, whereas this band decreases with an 8 nm red shift in **2·2Na**. The absorption spectra of **1·2H**, **1·2Na**, **2·2H**, **2·2Na**, and the corresponding photostationary states are shown in Figure 2C and 2D, respectively. The detailed quantitative data are given in Table 1.

2.4. Reversible fluorescent changes during photochromism and deprotonation

Generally, the open isomer of diarylethene emits fluorescence, while the fluorescence of closed-ring form is inactive. In the present work, **1·2H** and **2·2H** exhibited fluorescent changes during the process of photoisomerization as most of the diarylethene derivatives did.[25–40] The fluorescent emissions of **1·2H** and **2·2H** were at 516 and 510 nm with fluorescent quantum yields of 0.038 and 0.014, respectively (Table 2). The fluorescent lifetimes of **1·2H** and **2·2H** at 510 nm are 0.58 and 3.52 ns, respectively. To further understand the ascription of these emissions in **1·2H** and **2·2H**, the fluorescent properties of two model compounds of 2-methylthienyl-5-**IP** and *p*-bromophenyl-**IP** were investigated. These two compounds have fluorescent emissions at 436 and 438 nm, respectively. Comparing with the model compounds, the emission bands in **1·2H** and **2·2H** are red shifted about 70 nm, which indicates that the effect of the coupling of the **IP** substituent to the central **DAE** unit is much pronounced in fluorescence.[39] From careful comparison of the spectral shape of **1·2H** and **2·2H**, we observed much larger $W_{1/2}$ (peak width at half height) in the spectrum of **1·2H** (193 nm) than that of **2·2H** (106 nm), which reveals that the emission of **1·2H** may come from two sources. The inconspicuous shoulder peak at about 460 nm in **1·2H** accords with the characteristic local fluorescent emission of **IP**.[41,42] As expected, both the fluorescent emissions of **1·2H** and **2·2H** are quenched by photocyclization. The intensity of the emission in **2·2H** was quenched to ca. 7% of the original state upon irradiation with 360 nm UV light (Fig. 3A). However, the fluorescent intensity only decreased ca. 54% at its PS state in **1·2H** (Fig. 3B). The comparatively low photocyclization conversion and the existence of parallel configuration of **DAE** in **1·2H** may be the main cause for the unnotable fluorescent change induced by photo irradiation in **1·2H**. **2·2H** shows more significant fluorescent switch upon photochromism than that of **1·2H** because of the larger absorption efficiency and higher photocyclization conversion.

The deprotonation of imidazole in **1·2H** and **2·2H** also made significant emissive difference. The emission at 510 nm in **2·2H** decreased greatly with addition of alkali. The fluorescent Φ_F of **2·2Na** reduces to only 5% of that of **2·2H** (Fig. 4A). This efficient fluorescent quench is a result of photo induced electron transfer (PET) process[43] from deprotonated imidazole to **DAE** group because the deprotonation of imidazolyl group enhanced the electron density in **IP** group. It is interesting that the deprotonation process in **1·2H** resulted in a more complicate fluorescent change. The emission at 516 nm in **1·2H** decreased greatly with addition of alkali, and the shoulder peak at 460 nm emerged with fluorescent quantum yield of 0.025 in **1·2Na** (Fig. 4B). The emission spectra were no longer changed after more than 2 equiv of alkali were added in both **1·2H** and **2·2H**, consistent with ^{1}H NMR titration spectra. The lifetimes of both **1·2Na** and **2·2Na** at 510 nm are a little extended

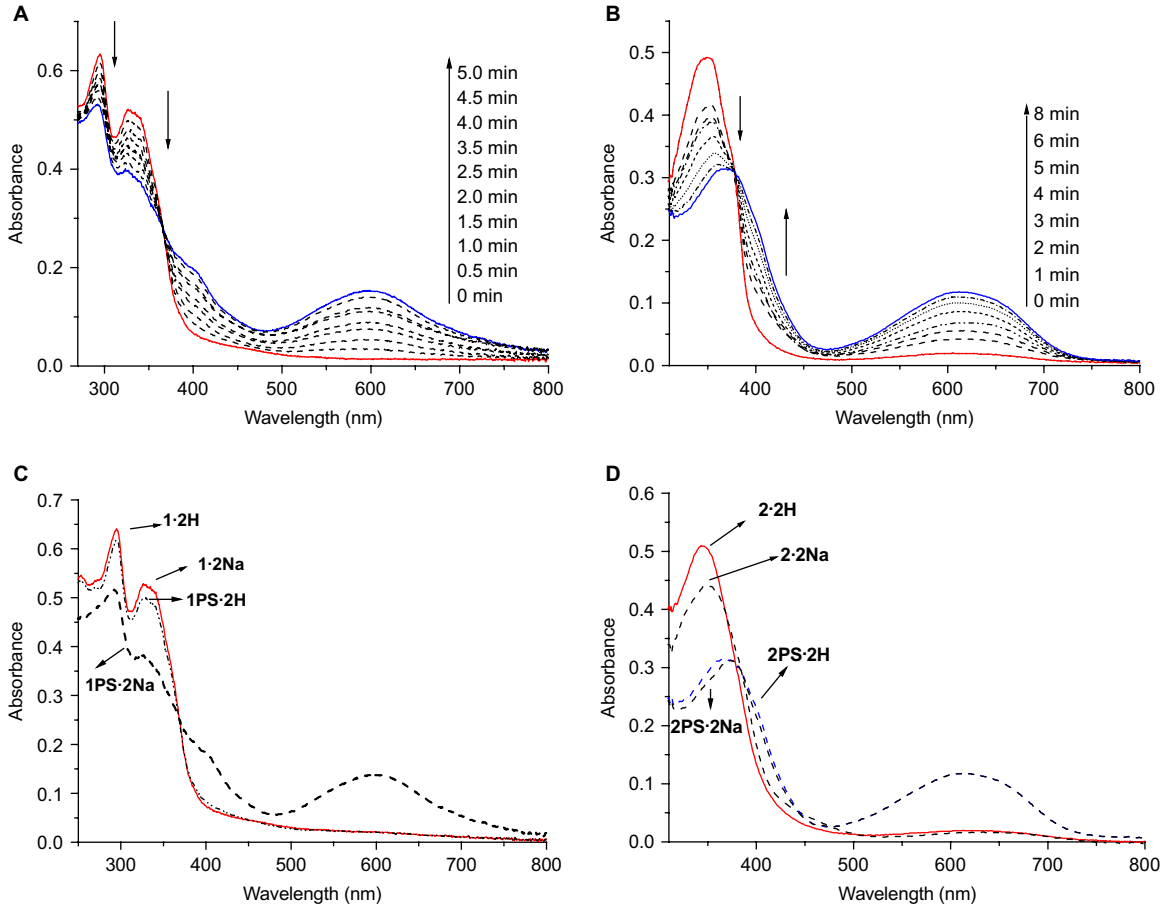


Figure 2. Absorption spectral changes upon irradiation of 320 nm for **1·2H** (A) and 360 nm for **2·2H** (B). Absorption spectra of **1** (C) and **2** (D) at the four states corresponding to Scheme 1. ([**1**]: 4.0×10^{-5} mol/L in methanol, [**2**]: 1.0×10^{-5} mol/L in methanol, 298 K, 2 equiv of the base was added for the corresponding deprotonated states).

Table 1. The quantitative data upon photochromism in **1** and **2**

Compound	λ_{max}^{abs}	ε ($dm^3\ mol^{-1}\ cm^{-1}$)	$\Phi_{o\rightarrow c}$ or $\Phi_{c\rightarrow o}$ [a]	Conversion (o→c) [b]
1·2H	327	14,000	0.16 (o→c)	0.57
1PS·2H	598	6100	0.29 (c→o)	1.00
1·2Na	327	13,400		
1PS·2Na	599	6100		
2·2H	343	68,000	0.29 (o→c)	0.65
2PS·2H	612	21,100	0.34 (c→o)	1.00
2·2Na	349	58,700		
2PS·2Na	612	21,100		

[a] Calculated from absorption spectral change.
[b] Obtained from the result of ^{1}H NMR.

Table 2. Fluorescent properties of **1** and **2**

Compound	λ_{max}^{F}	Φ_F [a]	τ (ns) (510 nm, λ_{ex}=370 nm)
1·2H	516	0.038	0.58
1·2Na	460	0.025	1.11
2·2H	510	0.014	3.52
2·2Na	550	<0.001	3.78

[a] $\Phi_F=\Phi_{ref}\ [(n^2A_{ref}I/n_{ref}^2AI_{ref})]$ (n, A, I denote the refractive index of solvent, the absorbance at the excitation wavelength, and the area of the corrected emission spectrum, respectively. Disulfate quinine was used as a reference (ref), Φ_{ref}=0.577).

comparing with that of **1·2H** and **2·2H** (Table 2). The behaviors of deprotonation-induced fluorescent spectral changes in **1PS·2H** and **2PS·2H** are similar to those of **1·2H** and **2·2H**, respectively.

The remarkably reversible emission quenching process by both photocyclization and deprotonation (Fig. 5A) makes **2·2H** a potential candidate for binary logic process as well as fluorescent switch and specific sensor on alkali. Moreover, both intensity and emission wavelengths of **1·2H** could be reversibly regulated by UV and visible lights, alkali and proton, respectively (Fig. 5B). This multi-output character of **1·2H** also makes it a possible candidate for binary logic process.

2.5. Multi-state molecular switches and logic circuit

The absorption and fluorescent changes of **2·2H** can be combined as a complicated molecular switch induced by three inputs: *I*1 (340 nm UV light), *I*2 (620 nm visible light), and *I*3 (alkali). Responding to these inputs, two corresponding optical outputs *O*1 (absorption difference ΔA at 610 nm by UV light irradiation) and *O*2 (emission variation ΔF_{510} at 510 nm) are produced. *O*1 is *on* in the case of $\Delta A>0.06$ (50% of that in photostationary state). When fluorescent intensity at 510 nm is quenched to half of the original height (**2·2H**), i.e. $\Delta F_{510}<0.5$, *O*2 is *off*, whereas *O*2 is *on* when

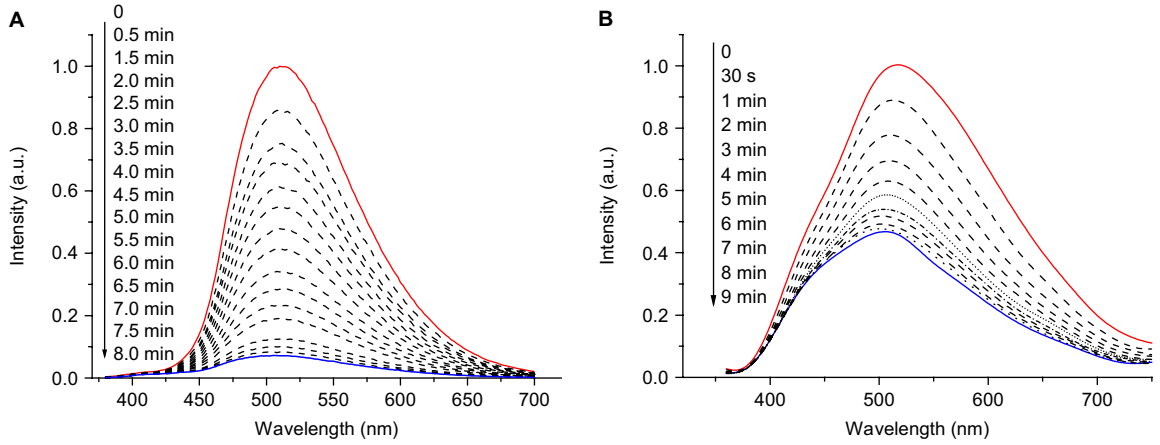


Figure 3. Fluorescent spectral changes of **2·2H** (A) and **1·2H** (B) upon irradiation of 360 and 320 nm light, respectively. ([**1**]: 4.0×10^{-5} mol/L in methanol, Ex: 320 nm; [**2**]: 1.0×10^{-5} mol/L in methanol, Ex: 360 nm, the fluorescent intensites of **1·2H** at 516 nm and **2·2H** at 510 nm were integrated to 1.0, for clear comparison. All the experiments are performed at room temperature.)

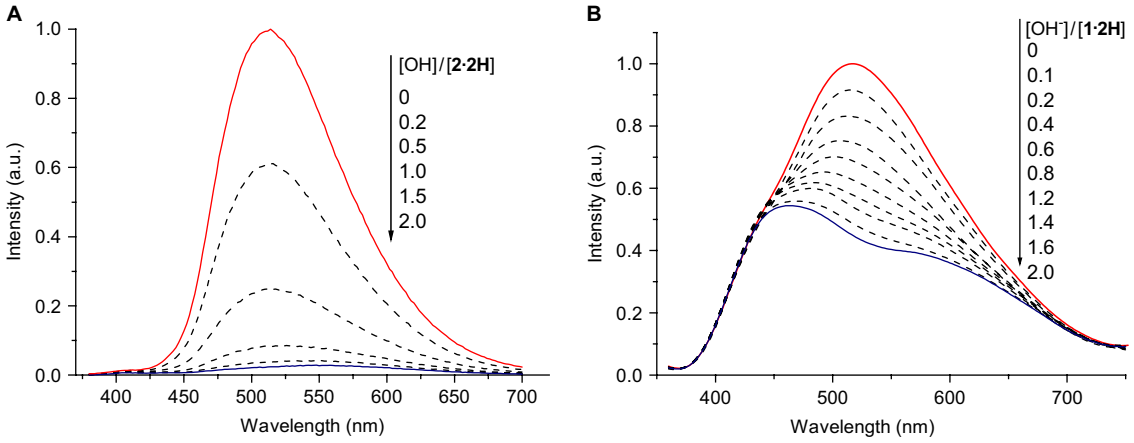


Figure 4. The emissive spectral changes during the deprotonation process of **2·2H** (A) and **1·2H** (B) upon titration of alkali equivalent to the corresponding molecule from 0 to 2.0 equiv (in the same condition as for Fig. 3).

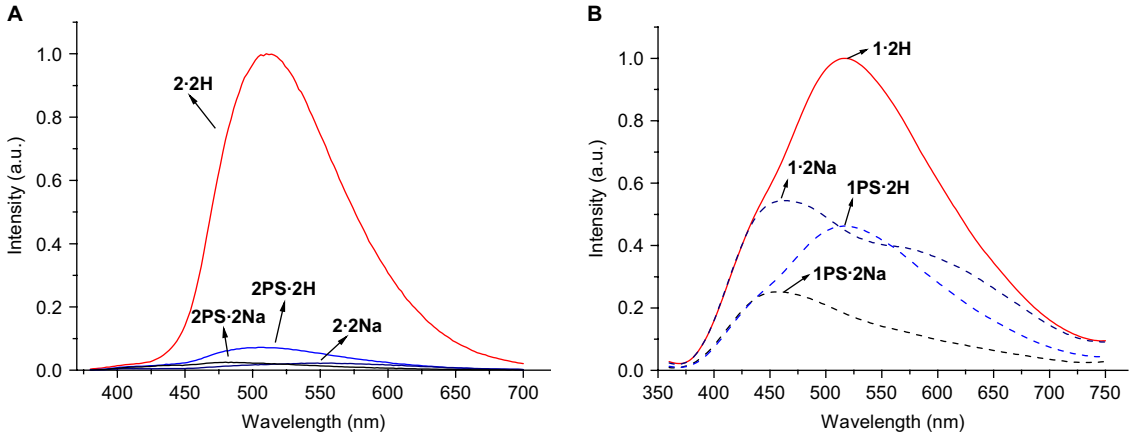


Figure 5. The fluorescent spectra of **1·2H** (A) and **2·2H** (B) at their four states corresponding to Scheme 1; for the conditions see Figure 3.

$\Delta F_{510}>0.5$. Each signal can be represented by a binary digit as either *on* or *off*. Therefore, the molecular switch reads a string of three binary inputs and writes a specific combination of two binary outputs (Table 3). Within that binary data, it is clear that the coloration ($O1=1$) and bleaching ($O1=0$) switch is dependent only on alternating UV–vis irradiation, while $I3$ gives no influence on $O1$. The low value of $I2$ (*off*) and high value of $I1$ (*on*) always tend to a high value of $O1$ (*on*). Upon simultaneous irradiation with UV and visible lights, absorption at 610 nm is in low value, indicating that

Table 3. Truth table for the communicating molecular switch in **2**

Inputs			Outputs	
*I*1	*I*2	*I*3	*O*1 (ΔA_{610})	*O*2 (ΔF_{510})
0	*0*	*0*	*0* (Low, <0.06)	*1* (High, >0.5)
0	*0*	*1*	*0*	*0* (Low, <0.5)
0	*1*	*0*	*0*	*1*
1	*0*	*0*	*1* (High, >0.06)	*0*
0	*1*	*1*	*0*	*0*
1	*0*	*1*	*1*	*0*
1	*1*	*0*	*0*	*1*
1	*1*	*1*	*0*	*0*

*I*1, *I*2, and *I*3 are the 340 nm UV light, 620 nm visible light, and alkali, respectively; *O*1, *O*2 are referred to the absorption and fluorescent difference at 610 and 510 nm, respectively.

*O*1 is *off* in this case. Thus the output *O*1 distinguishes the two kinds of states in the molecular switch, **2·2H** or **2·2Na**, *O*1=*0* and **2PS·2H** or **2PS·2Na**, *O*1=*1*. Therefore the input data *I*1, *I*2 are transduced into the output data *O*1 through an INHIBIT logic circuit by NOT and AND operators.[4] The other output *O*2 (ΔF_{510}) is varied along with *I*2 and *I*3 because the fluorescent intensity at 510 nm is quenched by both UV light and addition of alkali. Thus, *O*2 can be produced through a NOR operator by *I*1 or *I*3. Combining the output *O*1 and *O*2, the four states **2·2H**, **2PS·2H**, **2·2Na**, and **2PS·2Na** are addressed by three output strings *01*, *00*, and *10*, respectively, in the molecular switch.

3. Conclusion

In conclusion, we have obtained two multi-state diarylethenes (**1·2H** and **2·2H**) responsive to both light and chemical input, by utilizing the obviously different absorption and fluorescent emission under sequential alternating UV–vis irradiation and alkali/proton. The effective fluorescent quenching process upon both photochromism and deprotonation in **2·2H** provides a potential application in fluorescent switch or alkali sensor. Additionally, a reversible four-state molecular switch with two optical outputs is also realized in **2·2H**. This molecular level signal communication in the molecular switches is important for information storage and practical devices, even though the present systems still exihibit several limits such as working in solution media and long equilibrium time of deprotonation. The modification of the analogous molecules into soft materials such as gel or micro (nano) system may fulfill their practical application, especially in biological system. Moreover, phenanthroline group of these diarylethenes could coordinate with various metal ions to form metal complexes. These complexes would show more exciting characteristics on energy transfer and molecular switches. Further work is currently in progress toward the assembled soft materials and the coordinated systems of these diarylethenes.

4. Experimental

4.1. General

All starting materials were obtained from commercial supplies and used as received. Column chromatography was carried out on silica gel (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Mercuryplus-Varian instrument (400 MHz). Proton chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS). MALDI-TOF-MS was recorded on AXIMA-CFRPLVS mass spectroscopy instrument (Shimadzu). UV–vis spectra were recorded on UV–Vis 2550 spectroscope (Shimadzu). Fluorescent spectra were measured on Edinburgh Instruments (FLS 900). Time-resolved fluorescent decay was recorded on Edinburgh LifeSpec-ps with a PDL 800-B pulsed diode laser as excitation source. The UV and visible irradiations were carried out on a CHF-XM550W power system (China) by using suitable band-pass filter (Omega).

4.2. Synthesis

The aldehyde derivatives were synthesized according to references.[44,45] *1,2-Bis(5′-formyl-2′-methylthien-3′-yl)perfluorocyclopentene*: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K): δ 2.02 (s, 6H), 7.73 (s, 2H), 9.85 (s, 2H). *1,2-Bis[5′-(4-formylphenyl)-2′-methylthien-3′-yl]perfluorocyclopentene*: ^{1}H NMR ($CDCl_3$, 400 MHz, 298 K): δ 2.00 (s, 6H), 7.43 (s, 2H), 7.68–7.70 (d, J=8 Hz, 4H), 7.88–7.90 (d, J=8 Hz, 4H), 10.00 (s, 2H). *1,10-Phenanthroline-5,6-dione* was obtained according to previous report.[46] Mp 254–256. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.57–7.60 (q, $J1$=8.0 Hz, $J2$=4.8 Hz, 2H), 8.49–8.51 (d, J=8.0 Hz, 2H), 9.11–9.12 (d, J=4.8 Hz, 2H).

4.2.1. 1,2-Bis(5-(1*H*-imidazo [4,5-*f*] [1,10] phenanthroline-2-yl)-2-methylthien-3-yl)perfluorocyclopentene (1·2H). Acetic acid (15 mL) was added to a mixture of the aldehyde derivative (0.32 g, 0.75 mmol), 1,10-phenanthroline-5,6-dione (0.29 g, 1.4 mmol), and ammonium acetate (2.0 g, 26 mmol). The reaction mixture was stirred at reflux (80–90 °C) for 3 h. Then ice water was poured in, and a pale yellow solid of raw product was obtained by filtration. **1·2H** was recrystallized from ethanol as a pale yellow solid (yield: 70%). Mp>280 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 298 K): δ 1.89 (s, 6H), 7.80–7.82 (q, $J1$=8.0 Hz, $J2$=3.2 Hz, 4H), 8.04 (s, 2H), 8.80–8.82 (d, J=8.0 Hz, 4H), 9.03–9.04 (d, J=3.2 Hz, 4H). ^{13}C NMR (100 MHz, CD_3SOCD_3): δ 14.98, 116.60, 123.84, 125.28, 125.39, 130.19, 130.43, 133.06, 143.26, 144.13, 144.63, 145.52, 148.43, 148.56, 172.87. MALDI-TOF: m/z=805.1 $[M]^+$. Anal. Calcd for $C_{41}H_{22}F_6N_8S_2\cdot 4AcOH\cdot 2H_2O$: C, 54.54; H, 3.74; N, 10.38. Found: C, 54.96; H, 3.77; N, 9.91.

4.2.2. 1,2-Bis(5-(4-(1*H*-imidazo [4,5-*f*] [1,10] phenanthroline-2-yl) phenyl)-2-methylthien-3-yl)perfluorocyclopentene (2·2H). Raw product of **2·2H** was obtained by the same method as that of **1·2H**, and was purified by recrystallization from DMF–H_2O to give a pale yellow solid (yield: 80%). Mp>280 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 298 K): δ 1.89 (s, 6H), 7.69 (s, 2H), 7.79–7.82 (m, 4H), 7.87–7.89 (d, J=8.4 Hz, 4H), 8.31–8.33 (d, J=8.0 Hz, 4H), 8.91–8.93 (d, J=8.0 Hz, 4H), 9.01–9.02 (t, 4H). ^{13}C NMR (100 MHz, CD_3SOCD_3): δ 14.68, 122.00, 123.56, 125.79, 126.02, 127.37, 127.41, 128.01, 129.94, 130.26, 132.17, 133.68, 136.82, 141.81, 142.31, 144.02, 148.08, 150.40, 173.28. MALDI-TOF mass: m/z=957.2 $[M]^+$. Anal. Calcd for $C_{53}H_{30}F_6N_8S_2\cdot DMF\cdot 3H_2O$: C, 62.04; H, 4.00; N, 11.63. Found: C, 61.92; H, 4.08; N, 11.08.

Acknowledgements

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References and notes

1. Feringa, B. L. *Molecular Switches*; Wiley-VCH: Weinheim, 2001.
2. Irie, M. *Chem. Rev.* **2000**, *100*, 1685–1716.
3. Tian, H.; Yang, S. J. *Chem. Soc. Rev.* **2004**, *33*, 85–97.
4. Raymo, F. M. *Adv. Mater.* **2002**, *14*, 401–414.
5. de Silva, A. P.; Mcclenaghan, N. D. *Chem.—Eur. J.* **2004**, *10*, 574–586.
6. Szacilowski, K. *Chem.—Eur. J.* **2004**, *10*, 2520–2528.
7. Xiao, S.; Yi, T.; Li, F.; Huang, C. *Tetrahedron Lett.* **2005**, *46*, 9009–9012.
8. Raymo, F. M.; Giorgani, S. *J. Am. Chem. Soc.* **2001**, *123*, 4651–4652.
9. Raymo, F. M.; Giorgani, S. *Org. Lett.* **2001**, *3*, 1833–1836.
10. Raymo, F. M.; Giorgani, S. *Org. Lett.* **2001**, *3*, 3475–3478.
11. Raymo, F. M.; Giorgani, S. *J. Org. Chem.* **2003**, *68*, 4158–4169.
12. Raymo, F. M.; Giorgani, S. *J. Am. Chem. Soc.* **2002**, *124*, 2004–2007.
13. Guo, X.; Zhang, D.; Wang, T.; Zhu, D. *Chem. Commun.* **2003**, 914–915.
14. Guo, X.; Zhang, D.; Zhou, Y.; Zhu, D. *J. Org. Chem.* **2003**, *68*, 5681–5687.
15. Guo, X.; Zhang, D.; Zhang, G.; Zhu, D. *J. Phys. Chem. B* **2004**, *108*, 11942–11945.
16. Guo, X.; Zhang, D.; Zhu, D. *Adv. Mater.* **2004**, *16*, 125–129.
17. Zhou, Y.; Zhang, D.; Zhang, Y.; Tang, Y.; Zhu, D. *J. Org. Chem.* **2005**, *70*, 6164–6170.
18. Tian, H.; Qin, B.; Yao, R.; Zhao, X.; Yang, S. *Adv. Mater.* **2003**, *15*, 2104–2107.
19. Pina, F.; Roque, A.; Melo, M. J.; Maestri, M.; Belladelli, L.; Balzani, V. *Chem.—Eur. J.* **1998**, *4*, 1184–1191.
20. Cheng, P. N.; Chiang, P. T.; Chiu, S. H. *Chem. Commun.* **2005**, 1285–1287.
21. Qu, D. H.; Wang, Q. C.; Tian, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5296–5299.
22. Irie, M.; Fukaminato, T.; Sasaki, T.; Tamai, N.; Kawai, T. *Nature* **2002**, *420*, 759–760.
23. Luo, Q. F.; Li, X. C.; Jing, S. P.; Zhu, W. H.; Tian, H. *Chem. Lett.* **2003**, *32*, 1116–1117.
24. Liu, F.; Wang, K.; Bai, G.; Zhang, Y.; Gao, L. *Inorg. Chem.* **2004**, *43*, 1799–1806.
25. FernaÂndez-Acebes, A.; Lehn, J. M. *Chem.—Eur. J.* **1999**, *5*, 3285–3292.
26. FernaÂndez-Acebes, A.; Lehn, J. M. *Adv. Mater.* **1998**, *10*, 1519–1522.
27. Murguly, E.; Norsten, T. B.; Branda, N. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1752–1755.
28. Norsten, T. B.; Branda, N. R. *Adv. Mater.* **2001**, *13*, 347–349.
29. Chen, B.; Wang, M.; Wu, Y.; Tian, H. *Chem. Commun.* **2002**, 1060–1061.
30. Uchida, K.; Saito, M.; Murakami, A.; Nakamura, S.; Irie, M. *Adv. Mater.* **2003**, *15*, 121–125.
31. Chen, S. H.; Chen, H. M. P.; Geng, Y.; Jacobs, S. D.; Marshall, K. L.; Blanton, T. N. *Adv. Mater.* **2003**, *15*, 1061–1065.
32. Uchida, K.; Saito, M.; Murakami, A.; Kobayashi, T.; Nakamura, S.; Irie, M. *Chem.—Eur. J.* **2005**, *11*, 534–542.
33. Wigglesworth, T. J.; Branda, N. R. *Adv. Mater.* **2004**, *16*, 123–125.
34. Tian, H.; Chen, B.; Tu, H.; Mullen, K. *Adv. Mater.* **2002**, *14*, 918–923.
35. Lim, S. J.; An, B. K.; Jung, S. D.; Chung, M. A.; Park, S. Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 6346–6350.
36. Fukaminato, T.; Sasaki, T.; Kawai, T.; Tamai, N.; Irie, M. *J. Am. Chem. Soc.* **2004**, *126*, 14843–14849.
37. Frigoli, M.; Hehi, G. H. *Chem.—Eur. J.* **2004**, *10*, 5243–5250.
38. Yagi, K.; Soong, C. F.; Irie, M. *J. Org. Chem.* **2001**, *66*, 5419–5423.
39. Ern, J.; Bens, A. T.; Martin, H. D.; Mukamel, S.; Tretiak, S.; Tsyganenko, K.; Kuldova, K.; Trommsdorff, H. P.; Kryschi, C. *J. Phys. Chem. A* **2001**, *105*, 1741–1749.
40. Giordano, L.; Jovin, T. M.; Irie, M.; Jares-Erijman, A. E. *J. Am. Chem. Soc.* **2002**, *124*, 7481–7489.
41. Liu, Y.; Duan, Z. Y.; Zhang, H. Y.; Jiang, X. L.; Han, J. R. *J. Org. Chem.* **2005**, *70*, 1450–1455.
42. Mondal, J. A.; Ramakrishna, G.; Singh, A. K.; Ghosh, H. N.; Mariappan, M.; Maiya, B. G.; Mukherjee, T.; Palit, D. K. *J. Phys. Chem. A* **2004**, *108*, 7843–7852.
43. de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
44. Gilat, S. L.; Kawai, S. H.; Lehn, J. M. *Chem.—Eur. J.* **1995**, *1*, 275–284.
45. Yamamoto, S.; Matsuda, K.; Irie, M. *Chem.—Eur. J.* **2003**, *9*, 4878–4886.
46. Hiort, C.; Lincoln, P.; Norden, B. *J. Am. Chem. Soc.* **1993**, *115*, 3448–3454.

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Synthesis of β-amino carbonyl compounds via a $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds

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Abstract—A $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds was described. This one-pot three-component reaction afforded the corresponding β-amino carbonyl compounds, β-amino esters, and β-amino ketones in good to excellent yields. The reaction was also applied for the liquid-phase synthesis of β-amino carbonyl compound library using PEG as a support.

1. Introduction

β-Amino carbonyl compounds are useful building blocks for molecules with applications in pharmaceutical and material science.[1] β-Amino carbonyl moieties are found as structural units of a number of biologically active natural products.[2] The Mannich-type reactions are classical method for the synthesis of β-amino carbonyl compounds.[3] Lanthanide triflates as Lewis acids have been reported to be able to catalyze this kind of reactions.[4] High catalytic activity, low toxicity, and air tolerance make lanthanide triflates as attractive catalysts.[5] However, these catalysts suffer from some disadvantages such as requiring a large amount of Lewis acid (usually more than 10 mol %), a long reaction time, and/or atmosphere sensitive reagents. We report herein full details of a novel, rapid, and efficient three-component synthesis of β-amino esters via a $Zn(OTf)_2$-catalyzed cascade imino-formation/Mannich-type reaction of anilines with aromatic aldehydes and diethyl malonic ester,[6] and its extension to other kinds of β-amino carbonyl compounds as well as its applications in liquid-phase synthesis.

2. Results and discussion

In our initial experiments, we found that benzaldehydes **1**, anilines **2**, and diethyl malonic ester **3** in DCM were stirred in the presence of a catalytic amount (1 mol %) of $Zn(OTf)_2$ at room temperature for 4 h to give the corresponding β-amino esters **4**. As shown in Table 1, the three-component reaction of diethyl malonic ester with the electron-deficient anilines and the electron-deficient benzaldehydes afforded β-amino esters **4** in good to excellent yields (90–98%) (Table 1, entries 5–12). However, the electron-rich anilines and the electron-rich benzaldehydes gave lower (Table 1, entries 1–4) or poor yields (Table 1, entries 13 and 14).

These results promoted us to examine other carbonyl compounds. We then investigated the three-component condensation of anilines with benzaldehydes and cyclohexanone using $Zn(OTf)_2$ as a catalyst, and the results are summarized in Table 2. When 1 mol % $Zn(OTf)_2$ was used, β-amino ketones **6** were obtained as a mixture of *anti* and *syn* isomers. In this case, both the electron-rich and the electron-deficient benzaldehydes gave good to excellent yields (Table 2, entries 1–10), while the electron-deficient aniline almost did not work (Table 2, entry 11). The *anti* and *syn* isomers were identified by the coupling constants (*J*) of the vicinal protons adjacent to C═O and NH in their ^{1}H NMR spectra.[7] In general, the coupling constants for *anti* isomers are greater than that for *syn* isomers.[8] The ratio of the isomers was determined by integration of the corresponding peaks in ^{1}H NMR spectra. As shown in Table 2, high *anti* selectivity was obtained in our three-component reaction.

In connection with our researches on the liquid-phase synthesis using polyethylene glycol (PEG) as a support,[9] we performed this three-component reaction on PEG support. As shown in Scheme 1, the aldehyde was attached to PEG4000 by esterification of PEG with 4-formylbenzoic acid **7** in the presence of DCC and DMAP in anhydrous DCM at room temperature.[9h] The conversion of terminal hydroxyl groups on PEG was determined by ^{1}H NMR analysis to be quantitative. The resulting PEG-bound aldehyde **8** was then treated with various anilines **2** and carbonyl compounds **5** (Table 3,

Keywords: β-Amino esters; β-Amino ketones; Cascade reaction; Mannich reactions.
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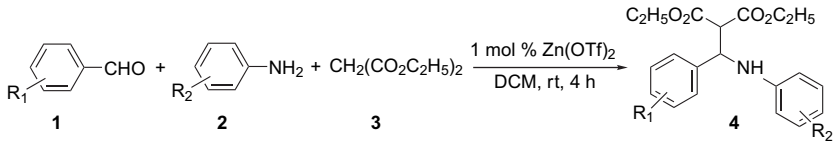
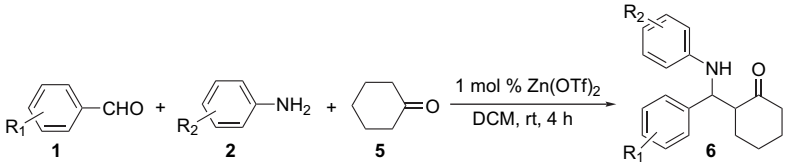
Table 1. Three-component reaction of benzaldehydes with anilines and diethyl malonic ester



Entry	R_1	R_2	Product	Yield (%)[a]
1	H	H	**4a**	50
2	2,6-Dichloro	2-CH_3	**4b**	50
3	2,6-Dichloro	4-OCH_3	**4c**	45
4	2,6-Dichloro	3-CH_3	**4d**	48
5	2-Cl	2-Cl	**4e**	88
6	2-Cl	4-Br	**4f**	92
7	3-NO_2	3-Cl	**4g**	96
8	2,6-Dichloro	4-Cl	**4h**	91
9	4-Br	4-Br	**4i**	95
10	2,6-Dichloro	3-Cl	**4j**	90
11	4-Br	4-Cl	**4k**	93
12	2,6-Dichloro	4-Br	**4l**	92
13	3,4-(OCH_2O)–	4-Cl	**4m**	5
14	3,4-(OCH_2O)–	4-OCH_3	**4n**	<1

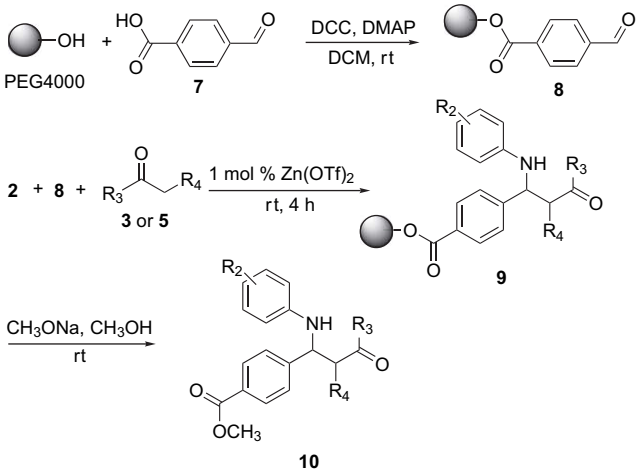
[a] Isolated yield.

Table 2. Three-component reaction of benzaldehydes with anilines and cyclohexanone



Entry	R_1	R_2	Product	Yield (%)[a]	*anti*/*syn*[b]
1	2,6-Dichloro	4-Br	**6a**	75	100:0
2	H	4-Br	**6b**	91	85:15
3	4-Cl	4-Cl	**6c**	98	97:3
4	4-Cl	4-Br	**6d**	95	100:0
5	3-NO_2	4-Cl	**6e**	96	75:25
6	4-NO_2	4-CH_3	**6f**	93	88:12
7	H	H	**6g**	93	90:10
8	H	3-Br	**6h**	85	74:26
9	4-OCH_3	4-Cl	**6i**	82	100:0
10	4-OCH_3	4-Br	**6j**	80	95:5
11	H	NO_2	**6k**	<1	—

[a] Isolated yield.
[b] Determined by ^{1}H NMR.



Scheme 1.

Table 3. The reaction of benzaldehyde with anilines and carbonyl compounds on PEG support

Entry	R_2	Carbonyl compounds	Product	Yield (%)[a]	Purity (%)[b]	*anti*/*syn*[c]
1	4-Br	**5**	**10a**	94	96	93:7
2	4-Cl	**5**	**10b**	97	99	100:0
3	3-Br	**5**	**10c**	92	93	85:15
4	3-Cl	**5**	**10d**	93	94	83:17
5	H	**5**	**10e**	91	90	71:29
6	3-CH_3	**5**	**10f**	88	89	88:12
7	4-OCH_3	**5**	**10g**	81	82	100:0
8	4-F	**5**	**10h**	99	95	89:11
9	4-NO_2	**5**	**10i**	<1	—	—
10	H	**3**	**10j**	90	89	—
11	4-Br	**3**	**10k**	98	98	—

[a] Yields refer to product cleaved from PEG.
[b] Purities were determined by HPLC analysis for the crude products.
[c] Determined by ^{1}H NMR.

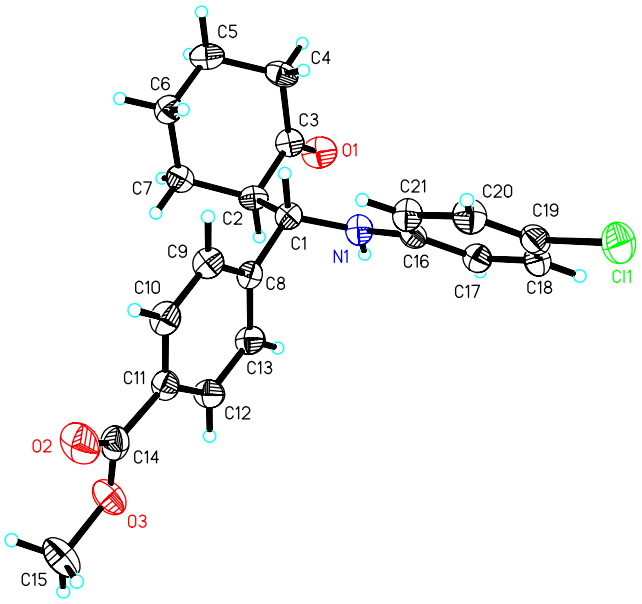


Figure 1. Crystal structure of compound **10b**.

entries 1–9) or **3** (Table 3, entries 10 and 11). Except the electron-deficient aniline (Table 3, entry 9), all reactions provided the corresponding crude products **10** in satisfactory yields (81–99%) with good purity (82–99%) as assessed by HPLC. In this case, high *anti* selectivity was also obtained. The *anti*-configuration of compound **10b** was unambiguously established by X-ray crystallographic analysis (Fig. 1).[10]

3. Conclusion

In summary, we have developed an efficient and general method for the synthesis of β-amino carbonyl compounds via $Zn(OTf)_2$-catalyzed cascade reaction of anilines with aromatic aldehydes and carbonyl compounds. The significant features of this procedure include: (a) facile operation; (b) cheap and readily available catalyst; (c) high yields; (d) reasonably good diastereoselectivities. Furthermore, this one-pot reaction was also applied for the liquid-phase synthesis of β-amino carbonyl compound library on PEG support and would be able to find its application in combinatorial chemistry.

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer 983 FT-IR spectrometer (KBr) and reported in reciprocal centimeters (cm^{-1}). Elemental analyses were recorded on a Carlo Erba 1110. ^1H and ^{13}C NMR spectra were obtained on a Bruker Advance DMX 500 instrument in $CDCl_3$ (TMS as internal standard). MS data were recorded on a Bruker Esquire 3000 plus instrument (ESI). HPLC analysis was carried out on an Agilent 1100 instrument (250×4.6 mm C18 column, gradient elution 80% MeOH and 20% H_2O, 0.8 ml/min, UV detection at λ 254 nm). Mp data were recorded on a YANACO apparatus.

4.2. General procedure for the synthesis of β-amino carbonyl compounds 4

A mixture of phenylamine (1 mmol), benzaldehyde (1 mmol), diethyl malonic ester (1 mmol), and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 4 h. After removal of the solvent in vacuum, the residue was purified by a flash column chromatography on silica gel with ethyl acetate–hexane (1:10) as eluent to afford pure β-amino carbonyl compound. Recrystallization from hexane–EtOAc gave crystalline product **4**.

4.2.1. Diethyl 2-(phenyl(phenylamino)methyl)malonate (4a). Colorless solid: mp 92–93 °C; IR (KBr) 3375, 1756, 1730, 1600, 1495, 1291 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.32 (m, 2H), 7.31–7.28 (m, 2H), 7.23–7.18 (m, 1H), 7.07–7.03 (m, 2H), 6.62–6.60 (m, 1H), 6.54–6.52 (m, 2H), 6.19 (t, J=10.8 Hz, 1H), 4.98 (d, J=11.0 Hz, 1H), 4.72 (d, J=10.7 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 4.00 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 166.6, 147.7, 141.9, 129.3, 128.7, 127.7, 127.4, 117.9, 114.3, 62.2, 61.9, 56.3, 53.8, 14.1, 13.9 ppm; MS (ESI) m/z ($[M+1]^+$) 342. Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.35; H, 6.79; N, 4.14.

4.2.2. Diethyl 2-((*o*-toluidino)(2,6-dichlorophenyl)-methyl)malonate (4b). Colorless solid: mp 85–86 °C; IR (KBr) 3398, 1721, 1598, 1531, 1352, 1269 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25–7.24 (m, 2H), 7.10–7.05 (m, 2H), 7.00–6.96 (m, 2H), 6.63 (d, J=7.3 Hz, 1H), 6.24 (t, J=11.0 Hz, 1H), 5.00 (d, J=11.1 Hz, 1H), 4.55 (d, J=10.7 Hz, 1H), 4.22–4.17 (m, 2H), 4.02–3.97 (m, 2H), 2.15 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 166.5, 144.2, 134.6, 130.4, 129.5, 127.3, 123.0, 118.3, 112.2, 62.1, 61.8, 56.4, 53.7, 17.7, 14.2, 13.9 ppm; MS (ESI) m/z ($[M+1]^+$) 424. Anal. Calcd for $C_{21}H_{23}Cl_2NO_4$: C, 59.44; H, 5.46; N, 3.30. Found: C, 59.45, H, 5.43, N, 3.37.

4.2.3. Diethyl 2-((2,6-dichlorophenyl)(4-methoxyphenyl-amino)methyl)malonate (4c). Colorless solid: mp 102–103 °C; IR (KBr) 3394, 1745, 1596, 1499 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25–7.23 (m, 2H), 7.09 (t, J=8.0 Hz, 1H), 6.79–6.78 (m, 2H), 6.72–6.70 (m, 2H), 6.11 (t, J=10.1 Hz, 1H), 4.70 (d, J=9.2 Hz, 1H), 4.50 (d, J=11.0 Hz, 1H), 4.30–4.22 (m, 2H), 4.02–3.97 (m, 2H), 3.70 (s, 3H), 1.28 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 166.5, 153.4, 140.1, 134.5, 130.2, 129.5, 129.1, 116.8, 114.8, 62.0, 61.7, 56.3, 53.8, 14.3, 13.9 ppm; MS (ESI) m/z ($[M+1]^+$) 440. Anal. Calcd for $C_{21}H_{23}Cl_2NO_5$: C, 57.28; H, 5.26; N, 3.18. Found: C, 57.25; H, 5.26; N, 3.17.

4.2.4. Diethyl 2-((*m*-toluidino)(2,6-dichlorophenyl)-methyl)malonate (4d). Colorless solid: mp 91–92 °C; IR (KBr) 3337, 1751, 1720, 1598, 1526, 1483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.24–7.21 (m, 2H), 7.07–6.98 (m, 2H), 6.63–6.61 (m, 2H), 6.52–6.50 (m, 1H), 6.18 (t, J=11.2 Hz, 1H), 4.88 (d, J=11.4 Hz, 1H), 4.82 (d, J=11.0 Hz, 1H), 4.23–4.20 (m, 2H), 4.01–3.96 (m, 2H), 2.22 (s, 3H), 1.24 (t, J=7.1 Hz, 3H), 1.04 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 166.4,

146.1, 139.8, 134.4, 129.5, 129.2, 120.0, 115.7, 111.9, 62.1, 61.8, 56.3, 54.2, 21.7, 14.2, 13.9 ppm; MS (ESI) *m/z* ([M+1]$^+$) 424. Anal. Calcd for $C_{21}H_{23}Cl_2NO_4$: C, 59.44; H, 5.46; N, 3.30. Found: C, 59.44; H, 5.48; N, 3.31.

4.2.5. Diethyl 2-((2-chlorophenyl)(2-chlorophenylamino)methyl)malonate (4e). Colorless solid: mp 80–81 °C; IR (KBr) 3339, 1752, 1720, 1598, 1483, 1297 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.35 (m, 2H), 7.23–7.15 (m, 3H), 7.00–6.96 (m, 1H), 6.57–6.56 (m, 1H), 6.41–6.40 (m, 1H), 6.41 (t, *J*=9.2 Hz, 1H), 4.70 (dd, *J*=4.3, 9.2 Hz, 1H), 4.22–4.09 (m, 5H), 1.20 (t, *J*=7.2 Hz, 3H), 1.17 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 167.2, 142.5, 136.1, 133.1, 130.0, 129.4, 129.3, 128.7, 127.9, 127.4, 120.0, 118.1, 112.2, 62.2, 61.8, 55.0, 54.1, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+1]$^+$) 410. Anal. Calcd for $C_{20}H_{21}Cl_2NO_4$: C, 58.55; H, 5.16; N, 3.41. Found: C, 58.52; H, 5.18; N, 3.41.

4.2.6. Diethyl 2-((4-bromophenylamino)(2-chlorophenyl)methyl)malonate (4f). Colorless solid: mp 106–107 °C; IR (KBr) 3394, 2981, 1745, 1569, 1499, 1375, 1250, 1178 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.32 (m, 2H), 7.21–7.15 (m, 4H), 6.41 (d, *J*=8.8 Hz, 2H), 5.80 (d, *J*=9.4 Hz, 1H), 5.50 (dd, *J*=4.3, 9.4 Hz, 1H), 4.24–4.02 (m, 5H), 1.20 (t, *J*=7.1 Hz, 3H), 1.11 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.5, 167.4, 145.4, 13.16, 133.1, 132.2, 132.1, 130.1, 129.4, 128.8, 127.4, 115.3, 115.2, 109.9, 62.3, 61.8, 54.6, 54.3, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 478. Anal. Calcd for $C_{20}H_{21}BrClNO_4$: C, 52.82; H, 4.65; N, 3.08. Found: C, 52.78; H, 4.67; N, 2.84.

4.2.7. Diethyl 2-((3-chlorophenylamino)(3-nitrophenyl)methyl)malonate (4g). Yellow solid: mp 99–100 °C; IR (KBr) 3398, 1721, 1598, 1531, 1352, 1269 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (s, 1H), 8.13–8.11 (m, 1H), 7.73 (t, *J*=7.8 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 6.66–6.64 (m, 1H), 6.57–6.56 (m, 1H), 6.47–6.46 (m, 1H), 6.44 (d, *J*=6.4 Hz, 1H), 5.56 (d, *J*=9.0 Hz, 1H), 5.28 (dd, *J*=5.4, 9.0 Hz, 1H), 4.19–4.08 (m, 4H), 3.91 (d, *J*=5.4 Hz, 1H), 1.19 (t, *J*=7.1 Hz, 3H), 1.11 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 166.8, 148.8, 147.3, 142.1, 135.3, 133.3, 130.5, 130.0, 123.2, 122.1, 118.7, 113.7, 122.1, 62.5, 62.2, 57.7, 56.5, 14.1, 14.0 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 444. Anal. Calcd for $C_{20}H_{21}ClN_2O_6$: C, 57.08; H, 5.03; N, 6.66. Found: C, 57.08; H, 4.90; N, 6.58.

4.2.8. Diethyl 2-((4-chlorophenylamino)(2,6-dichlorophenyl)methyl)malonate (4h). Colorless solid: mp 83–84 °C; IR (KBr) 3385, 1731, 1598, 1513, 1443 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.24 (m, 2H), 7.10–7.05 (m, 3H), 6.74 (d, *J*=8.8 Hz, 2H), 6.13 (d, *J*=11.1 Hz, 1H), 4.93 (d, *J*=11.3 Hz, 1H), 4.71 (d, *J*=10.8 Hz, 1H), 4.24 (q, *J*=7.2 Hz, 2H), 4.01 (q, *J*=7.2 Hz, 2H), 1.24 (t, *J*=7.1 Hz, 3H), 1.04 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 166.3, 144.8, 133.9, 129.7, 129.2, 123.8, 116.0, 62.2, 61.9, 56.1, 54.5, 14.3, 13.9 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 466. Anal. Calcd for $C_{20}H_{20}Cl_3NO_4$: C, 54.01; H, 4.53; N, 3.15. Found: C, 54.02; H, 4.55; N, 3.14.

4.2.9. Diethyl 2-((4-bromophenyl)(4-bromophenylamino)methyl)malonate (4i). Colorless solid: mp 107–108 °C; IR (KBr) 3348, 1721, 1599, 1530, 1355 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.5 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 7.16 (d, *J*=8.3 Hz, 2H), 6.44 (d, *J*=8.3 Hz, 2H), 5.42 (d, *J*=10.8 Hz, 1H), 5.21 (d, *J*=11.0 Hz, 1H), 4.17–4.09 (m, 4H), 3.83 (d, *J*=5.5 Hz, 1H), 1.18–1.14 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 167.1, 145.5, 138.6, 132.5, 132.2, 128.8, 122.0, 115.5, 110.1, 62.3, 62.0, 57.9, 55.8, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 522. Anal. Calcd for $C_{20}H_{21}Br_2NO_4$: C, 48.12; H, 4.24; N, 2.81. Found: C, 48.12; H, 4.26; N, 2.71.

4.2.10. Diethyl 2-((3-chlorophenylamino)(2,6-dichlorophenyl)methyl)malonate (4j). Colorless solid: mp 109–110 °C; IR (KBr) 3386, 1744, 1726, 1596, 1500, 1348, 1249 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.26 (m, 2H), 7.12 (t, *J*=8.0 Hz, 1H), 7.04 (t, *J*=8.1 Hz, 1H), 6.81 (t, *J*=2.0 Hz, 1H), 6.69–6.65 (m, 2H), 6.15 (d, *J*=11.1 Hz, 1H), 5.00 (d, *J*=11.2 Hz, 1H), 4.48 (d, *J*=10.8 Hz, 1H), 4.23–4.21 (m, 2H), 4.01–3.98 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H), 1.05 (t, *J*=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 166.2, 147.3, 135.1, 133.9, 130.4, 129.8, 119.0, 114.7, 112.8, 62.2, 61.9, 56.1, 54.1, 14.2, 13.9 ppm; MS (ESI) *m/z* ([M+1]$^+$) 444. Anal. Calcd for $C_{20}H_{20}Cl_3NO_4$: C, 54.01; H, 4.53; N, 3.15. Found: C, 54.00; H, 4.53; N, 3.13.

4.2.11. Diethyl 2-((4-bromophenyl)(4-chlorophenylamino)methyl)malonate (4k). Colorless solid: mp 88–89 °C; IR (KBr) 3379, 1753, 1729, 1597, 1560, 1485, 1288 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J*=8.4 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 2H), 7.04 (d, *J*=8.3 Hz, 2H), 6.49 (d, *J*=8.3 Hz, 2H), 5.40 (d, *J*=8.1 Hz, 1H), 5.12 (d, *J*=5.8 Hz, 1H), 4.12–4.07 (m, 4H), 3.83 (d, *J*=5.5 Hz, 1H), 1.18–1.14 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 167.1, 145.2, 138.7, 132.1, 129.3, 128.8, 123.0, 122.0, 115.1, 62.3, 62.0, 58.0, 56.9, 14.2, 14.1 ppm; MS (ESI) *m/z* ([M+1]$^+$) 454. Anal. Calcd for $C_{20}H_{21}BrClNO_4$: C, 52.82; H, 4.65; N, 3.08. Found: C, 52.85; H, 4.66; N, 3.04.

4.2.12. Diethyl 2-((4-bromophenylamino)(2,6-dichlorophenyl)methyl)malonate (4l). Colorless solid: mp 100–101 °C; IR (KBr) 3387, 1729, 1608, 1593, 1560, 1495 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25–7.24 (m, 2H), 7.21 (d, *J*=8.8 Hz, 2H), 7.12 (t, *J*=8.0 Hz, 1H), 6.70 (d, *J*=8.8 Hz, 2H), 6.13 (d, *J*=11.1 Hz, 1H), 4.94 (d, *J*=11.1 Hz, 1H), 4.47 (d, *J*=10.8 Hz, 1H), 4.47–4.44 (m, 2H), 4.01 (q, *J*=7.3 Hz, 2H), 1.24 (t, *J*=7.3 Hz, 3H), 1.04 (t, *J*=7.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 166.3, 145.2, 133.9, 132.1, 129.8, 116.5, 111.0, 62.2, 61.9, 56.1, 54.4, 14.3, 13.9 ppm; MS (ESI) *m/z* ([M+Na]$^+$) 510. Anal. Calcd for $C_{20}H_{20}BrCl_2NO_4$: C, 49.10; H, 4.12; N, 2.86. Found: C, 49.11; H, 4.10; N, 2.86.

4.3. General procedure for the synthesis of β-amino carbonyl compounds 6

A mixture of aniline (1 mmol), benzaldehyde (1 mmol), cyclohexanone (1.2 mmol), and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol) was stirred at room temperature for 4 h. After removal of the solvent in vacuum, the residue was purified by flash column chromatography on silica gel with ethyl acetate–hexane (1:16) as eluent to afford pure β-amino carbonyl compounds. Recrystallization from hexane–EtOAc afforded crystalline product **6**.

4.3.1. 2-((4-Bromophenylamino)(2,6-dichlorophenyl)-methyl)cyclohexanone (6a). Colorless solid: mp 128–129 °C; IR (KBr) 3362, 1704, 1596, 1519, 1489 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.22 (m, 2H), 7.17–7.15 (m, 2H), 7.10–7.07 (t, J=8.0 Hz, 1H), 6.60–6.57 (m, 2H), 5.78 (t, J=8.65 Hz, 1H), 4.68 (d, J=6.6 Hz, 1H), 3.30–3.25 (m, 1H), 2.50–2.41 (m, 2H), 1.96–1.92 (m, 2H), 1.85–1.82 (m, 1H), 1.69–1.68 (m, 1H), 1.61–1.59 (m, 1H), 1.42–1.41 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 211.0, 145.7, 135.1, 132.1, 130.7, 129.4, 128.9, 115.7, 110.0, 53.9, 53.7, 42.2, 31.0, 28.6, 24.4 ppm; MS (ESI) m/z ($[M+1]^+$) 426. Anal. Calcd for $C_{19}H_{18}BrCl_2NO$: C, 53.42; H, 4.25; N, 3.28. Found: C, 53.45; H, 4.26; N, 3.28.

4.3.2. 2-((4-Bromophenylamino)(phenyl)methyl)cyclohexanone (6b). Colorless solid: (*anti*/*syn*=85/15) mp 98–99 °C; IR (KBr) 3397, 1700, 1592, 1495, 1314 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.34–7.30 (m, 4H), 7.23–7.20 (m, 1H), 7.14–7.11 (m, 2H), 4.79 (s, 0.15H), 4.73 (s, 0.85H), 4.59 (s, 0.15H), 4.54 (d, J=6.8 Hz, 0.85H), 2.79–2.73 (m, 1H), 2.42–2.33 (m, 1H), 2.32–2.29 (m, 1H), 2.04–2.00 (m, 1H), 1.90–1.85 (m, 2H), 1.70–1.55 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 213.0, 146.7, 141.1, 132.0, 128.8, 127.7, 127.4, 115.5, 109.4, 57.7, 56.6, 42.2, 31.8, 28.2, 25.1; (minor isomer): δ 211.5, 146.5, 141.4, 131.9, 128.7, 127.6, 127.4, 115.9, 109.6, 58.4, 57.5, 42.6, 28.7, 27.1, 24.1 ppm; MS (ESI) m/z ($[M+1]^+$) 358. Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.70; H, 5.63; N, 3.94.

4.3.3. 2-((4-Chlorophenyl)(4-chlorophenylamino)-methyl)cyclohexanone (6c). Colorless solid: (*anti*/*syn*=97/3) mp 96–97 °C; IR (KBr) 3411, 1702, 1600, 1498, 1315 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.29–7.26 (m, 4H), 7.01 (d, J=8.8 Hz, 2H), 6.42 (d, J=8.8 Hz, 2H), 4.71 (s, 0.97H), 4.67 (s, 0.03H), 4.61 (s, 0.03H), 4.51 (d, J=5.7 Hz, 0.97H), 2.72–2.70 (m, 1H), 2.41–2.34 (m, 1H), 2.33–2.29 (m, 1H), 2.00–1.97 (m, 1H), 1.90–1.89 (m, 2H), 1.86–1.76 (m, 1H), 1.72–1.62 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.6, 145.8, 140.1, 133.2, 129.2, 128.9, 128.8, 122.6, 115.0, 58.0, 57.4, 42.4, 31.9, 28.1, 24.4; (minor isomer): δ 211.4, 145.8, 139.7, 133.2, 129.1, 128.9, 128.8, 122.6, 115.4, 57.3, 56.4, 42.6, 28.9, 27.1, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 348. Anal. Calcd for $C_{19}H_{19}Cl_2NO$: C, 65.53; H, 5.50; N, 4.02. Found: C, 65.59; H, 5.49; N, 4.01.

4.3.4. 2-((4-Bromophenylamino)(4-chlorophenyl)-methyl)cyclohexanone (6d). Colorless solid: mp 134–135 °C; IR (KBr) 3402, 1702, 1594, 1491, 1316 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.25 (m, 4H), 7.14 (d, J=8.8 Hz, 2H), 6.38 (d, J=8.8 Hz, 2H), 4.80 (s, 1H), 4.51 (d, J=4.8 Hz, 1H), 2.73–2.70 (m, 1H), 2.40–2.31 (m, 2H), 1.99–1.96 (m, 1H), 1.90–1.89 (m, 2H), 1.77–1.70 (m, 1H), 1.69–1.60 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6, 146.3, 140.1, 133.2, 132.1, 128.9, 128.8, 115.5, 109.7, 57.9, 57.4, 42.4, 32.0, 28.1, 24.4 ppm; MS (ESI) m/z ($[M+1]^+$) 392. Anal. Calcd for $C_{19}H_{19}BrClNO$: C, 58.11; H, 4.88; N, 3.57. Found: C, 58.16; H, 4.88; N, 3.58.

4.3.5. 2-((4-Chlorophenylamino)(3-nitrophenyl)methyl)-cyclohexanone (6e). Yellow solid: (*anti*/*syn*=75/25) mp 125–126 °C; IR (KBr) 3344, 1705, 1599, 1529, 1492, 1352 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 8.22 (d, J=9.3 Hz, 1H), 8.09 (m, 1H), 7.75 (t, J=6.0 Hz, 1H), 7.49–7.45 (m, 1H), 7.03 (d, J=8.7 Hz, 2H), 6.45 (d, J=8.7 Hz, 2H), 4.97 (d, J=7.6 Hz, 0.25H), 4.80 (d, J=6.4 Hz, 0.75H), 4.68 (d, J=6.6 Hz, 0.75H), 4.63 (d, J=7.0 Hz, 0.25H), 2.88–2.84 (m, 1H), 2.45–2.30 (m, 2H), 2.10–2.00 (m, 2H), 1.94–1.93 (m, 1H), 1.80–1.73 (m, 1H), 1.65–1.56 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.1, 148.6, 145.5, 144.2, 134.3, 129.7, 129.3, 122.9, 122.7, 122.6, 114.9, 58.2, 57.2, 42.6, 32.5, 28.1, 24.8; (minor isomer): δ 210.9, 148.6, 145.4, 143.8, 133.7, 129.6, 129.3, 123.2, 122.6, 122.4, 115.4, 57.4, 56.3, 42.8, 29.3, 27.2, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 359. Anal. Calcd for $C_{19}H_{19}ClN_2O_3$: C, 63.60; H, 5.34; N, 7.81. Found: C, 63.59; H, 5.34; N, 7.83.

4.3.6. 2-((4-Toluidino)(4-nitrophenyl)methyl)cyclohexanone (6f). Yellow solid: (*anti*/*syn*=88/12) mp 137–138 °C; IR (KBr) 3364, 1697, 1518, 1346 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 8.14 (d, J=8.7 Hz, 2H), 7.58 (d, J=8.7 Hz, 2H), 6.89 (d, J=8.1 Hz, 2H), 6.42 (d, J=8.1 Hz, 2H), 4.82 (s, 0.12H), 4.74 (s, 0.88H), 4.68 (s, 0.88H), 4.46 (m, 0.12H), 2.84–2.81 (m, 1H), 2.41–2.29 (m, 2H), 2.17 (s, 3H), 2.04–1.98 (m, 2H), 1.93–1.92 (m, 1H), 1.77–1.62 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.0, 150.3, 144.5, 130.0, 128.5, 127.6, 123.9, 113.9, 58.2, 57.3, 42.6, 32.1, 27.9, 24.7, 20.5; (minor isomer): δ 210.9, 149.9, 147.2, 129.9, 128.8, 127.8, 123.8, 114.5, 58.1, 56.5, 42.7, 29.2, 27.3, 25.2, 20.5 ppm; MS (ESI) m/z ($[M+1]^+$) 359. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.99; H, 6.55; N, 8.26.

4.3.7. 2-(Phenyl(phenylamino)methyl)cyclohexanone (6g). Colorless solid: (*anti*/*syn*=90/10) mp 115–116 °C; IR (KBr) 3330, 1702, 1602, 1497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.36–7.33 (m, 2H), 7.30–7.27 (m, 2H), 7.23–7.18 (m, 1H), 7.07–7.03 (m, 2H), 6.62–6.60 (m, 1H), 6.54–6.52 (m, 2H), 4.80 (s, 0.10H), 4.71 (s, 0.90H), 4.62 (d, J=7.0 Hz, 0.90H), 4.51 (s, 0.10H), 2.76–2.72 (m, 1H), 2.43–2.29 (m, 2H), 1.90–1.81 (m, 4H), 1.72–1.61 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 213.1, 147.4, 141.9, 129.3, 128.7, 127.5, 127.4, 117.7, 113.8, 58.2, 57.7, 42.0, 31.5, 28.1, 23.8; (minor isomer): δ 211.5, 147.7, 141.8, 129.2, 128.6, 127.7, 127.2, 117.9, 114.3, 57.4, 56.8, 42.6, 28.9, 27.2, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 280. Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.68; H, 7.49; N, 5.02.

4.3.8. 2-((3-Bromophenylamino)(phenyl)methyl)cyclohexanone (6h). Colorless solid: (*anti*/*syn*=74/26) mp 114–115 °C; IR (KBr) 3379, 1700, 1598, 1476 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (*anti*+*syn*): δ 7.35–7.29 (m, 4H), 7.25–7.21 (m, 1H), 6.89–6.87 (m, 1H), 6.73–6.67 (m, 2H), 6.44–6.42 (m, 1H), 4.80 (s, 0.74H), 4.76–4.74 (m, 0.26H), 4.65 (m, 0.26H), 4.54 (s, 0.74H), 2.78–2.75 (m, 1H), 2.42–2.29 (m, 2H), 2.04–2.02 (m, 1H), 1.90–1.86 (m, 2H), 1.71–1.57 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.9, 148.8, 141.3, 130.6, 128.8, 127.7, 127.3, 123.1, 120.5, 116.9, 112.4, 58.2, 57.5, 42.6, 31.8, 28.2, 24.1; (minor isomer): δ 211.4, 148.9, 141.0, 130.5, 128.7, 127.6, 127.4, 123.2, 120.6, 116.4, 112.7, 56.5, 57.3, 42.2, 28.8, 27.1, 25.0 ppm; MS (ESI) m/z ($[M+1]^+$) 358.

Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.70; H, 5.63; N, 3.91. Found: C, 63.70; H, 5.63; N, 3.94.

4.3.9. 2-((4-Chlorophenylamino)(4-methoxyphenyl)-methyl)cyclohexanone (6i). Colorless solid: mp 122–123 °C; IR (KBr) 3332, 1703, 1603, 1512, 1493, 1247 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J=8.7 Hz, 2H), 7.00 (d, J=8.9 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 6.44 (d, J=8.9 Hz, 2H), 4.69 (s, 1H), 4.50 (d, J=7.0 Hz, 1H), 3.76 (s, 3H), 2.69–2.68 (m, 1H), 2.42–2.38 (m, 1H), 2.43–2.32 (m, 1H), 1.93–1.81 (m, 4H), 1.68–1.63 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2, 158.9, 146.1, 133.3, 129.1, 128.5, 122.3, 115.0, 114.2, 57.9, 57.7, 55.4, 42.1, 31.6, 28.1, 23.9 ppm; MS (ESI) m/z ($[M+Na]^+$) 366. Anal. Calcd for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.94; H, 6.41; N, 4.06.

4.3.10. 2-((4-Bromophenylamino)(4-methoxyphenyl)-methyl)cyclohexanone (6j). Colorless solid: (*anti*/*syn*=95/5) mp 131–132 °C; IR (KBr) 3331, 1702, 1597, 1511, 1489, 1246 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J=8.6 Hz, 2H), 7.13 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.6 Hz, 2H), 6.40 (d, J=8.8 Hz, 2H), 4.71 (s, 0.95H), 4.64 (s, 0.05H), 4.50 (d, J=6.8 Hz, 0.95H), 4.49 (s, 0.05H), 3.76 (s, 3H), 2.71–2.68 (m, 1H), 2.42–2.38 (m, 1H), 2.34–2.32 (m, 1H), 1.94–1.80 (m, 4H), 1.68–1.63 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 213.2, 158.9, 146.5, 133.3, 131.9, 128.5, 115.5, 114.2, 109.4, 57.8, 57.7, 55.4, 42.1, 31.6, 28.1, 23.9; (minor isomer): δ 213.2, 158.9, 146.5, 133.3, 131.9, 128.8, 115.9, 114.0, 109.4, 57.8, 57.2, 56.6, 42.6, 29.0, 27.1, 25.0 ppm; MS (ESI) m/z ($[M+Na]^+$) 410. Anal. Calcd for $C_{20}H_{22}BrNO$: C, 61.86; H, 5.71; N, 3.61. Found: C, 61.84; H, 5.72; N, 3.65.

4.4. General procedure for the synthesis of β-amino carbonyl compounds 10

To the solution of PEG-bounded aldehyde **8** (2.0 g, 0.50 mmol) in DCM (10 ml) were added aniline (4 mmol), carbonyl compound (8 mmol), and $Zn(OTf)_2$ (3.6 mg, 0.01 mmol). The reaction mixture was stirred at room temperature for 4 h. Then Et_2O (40 ml) was added dropwise. The resulting polymer **9** as a precipitate was collected by filtration and then dissolved in methanol (5 ml). To the solution was added 0.1 N MeONa in methanol (5 ml). The mixture was stirred at room temperature for 5 h and then diluted with Et_2O (50 ml). After removing the precipitate by filtration, the filtrate was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. Removal of the solvent afforded the crude product **10**. Further purification of the crude product for structural analysis was performed by silica gel column chromatography (hexane–EtOAc, 10:1, v/v) and recrystallization from hexane–EtOAc.

4.4.1. Methyl 4-((4-bromophenylamino)(2-oxocyclohexyl)methyl)benzoate (10a). Colorless solid: (*anti*/*syn*=93/7) mp 145–146 °C; IR (KBr) 3371, 1724, 1703, 1590, 1496, 1284 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J=8.3 Hz, 2H), 7.43 (d, J=8.8 Hz, 2H), 7.14 (d, J=8.3 Hz, 2H), 6.39 (d, J=8.8 Hz, 2H), 4.87 (d, J=5.1 Hz, 0.93H), 4.78 (m, 0.07H), 4.62 (s, 0.07H), 4.59 (m, 0.93H), 3.88 (s, 3H), 2.80–2.78 (m, 1H), 2.41–2.38 (m, 1H), 2.34–2.32 (m, 1H), 1.91–1.90 (m, 3H), 1.71–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.0, 147.0, 146.3, 132.1, 130.1, 129.5, 127.5, 115.4, 109.7, 58.4, 57.3, 52.3, 42.5, 32.1, 28.1, 24.4; (minor isomer): δ 212.4, 167.0, 147.0, 146.3, 132.0, 130.0, 129.5, 127.8, 115.9, 109.7, 57.6, 55.4, 52.3, 42.6, 28.8, 27.2, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 416. Anal. Calcd for $C_{21}H_{22}BrNO_3$: C, 60.59; H, 5.33; N, 3.36. Found: C, 60.61; H, 5.27; N, 3.43.

4.4.2. Methyl 4-((4-chlorophenylamino)(2-oxocyclohexyl)methyl)benzoate (10b). Colorless solid: mp 133–134 °C; IR (KBr) 3348, 3312, 1713, 1712, 1701, 1491, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J=8.3 Hz, 2H), 7.43 (d, J=8.3 Hz, 2H), 7.01–7.00 (m, 2H), 6.43–6.40 (m, 2H), 4.85 (d, J=5.6 Hz, 1H), 4.60 (t, J=5.9 Hz, 1H), 3.88 (s, 3H), 2.80–2.78 (m, 1H), 2.40–2.32 (m, 2H), 2.00–1.98 (m, 1H), 1.91–1.89 (m, 2H), 1.76–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 167.0, 147.0, 145.8, 130.1, 129.5, 129.2, 127.5, 122.6, 114.9, 58.5, 57.3, 52.3, 42.5, 32.1, 28.1, 24.4 ppm; MS (ESI) m/z ($[M+1]^+$) 372. Anal. Calcd for $C_{21}H_{22}ClNO_3$: C, 67.83; H, 5.96; N, 3.77. Found: C, 67.84; H, 5.95; N, 3.86.

4.4.3. Methyl 4-((3-bromophenylamino)(2-oxocyclohexyl)methyl)benzoate (10c). Colorless solid: (*anti*/*syn*=85/15) mp 134–135 °C; IR (KBr) 3403, 1721, 1698, 1597, 1508, 1273 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.97 (m, 2H), 7.44–7.41 (m, 2H), 6.92–6.88 (m, 1H), 6.75–6.73 (m, 1H), 6.67–6.65 (m, 1H), 6.42–6.40 (m, 1H), 4.95 (d, J=7.4 Hz, 0.85H), 4.79 (m, 0.15H), 4.68 (m, 0.15H), 4.60 (t, J=6.6 Hz, 0.85H), 3.90 (s, 0.45H), 3.89 (s, 2.55H), 2.81–2.79 (m, 1H), 2.41–2.32 (m, 2H), 2.01–1.99 (m, 1H), 1.94–1.89 (m, 2H), 1.76–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.0, 148.6, 146.9, 130.7, 130.1, 129.5, 127.5, 123.3, 120.8, 116.4, 112.3, 58.2, 57.3, 52.3, 42.5, 32.2, 28.1, 24.5; (minor isomer): δ 211.0, 167.0, 148.6, 146.6, 130.6, 130.0, 129.5, 127.8, 123.2, 121.0, 117.0, 112.7, 57.4, 56.3, 52.3, 42.6, 28.9, 27.1, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 416. Anal. Calcd for $C_{21}H_{22}BrNO_3$: C, 60.59; H, 5.33; N, 3.36. Found: C, 60.53; H, 5.32; N, 3.41.

4.4.4. Methyl 4-((3-chlorophenylamino)(2-oxocyclohexyl)methyl)benzoate (10d). Colorless solid: (*anti*/*syn*=83/17) mp 137–138 °C; IR (KBr) 3403, 1721, 1700, 1600, 1272 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J=8.3 Hz, 2H), 7.44 (d, J=8.3 Hz, 2H), 6.97 (t, J=8.0 Hz, 1H), 6.60–6.59 (m, 1H), 6.50–6.48 (m, 1H), 6.38–6.37 (m, 1H), 4.96 (d, J=7.4 Hz, 0.83H), 4.80–4.79 (m, 0.13H), 4.70 (d, J=6.6 Hz, 0.17H), 4.61 (t, J=7.4 Hz, 0.83H), 3.90 (s, 0.51H), 3.89 (s, 2.49H), 2.81–2.79 (m, 1H), 2.41–2.32 (m, 2H), 2.02–1.99 (m, 1H), 1.93–1.89 (m, 2H), 1.77–1.69 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.0, 148.5, 146.9, 135.1, 130.3, 130.1, 129.5, 127.8, 117.9, 113.5, 112.0, 58.2, 57.3, 52.3, 42.5, 32.2, 28.1, 24.4; (minor isomer): δ 211.0, 167.0, 148.5, 146.6, 135.0, 130.3, 130.0, 129.5, 127.5, 118.1, 114.0, 112.4, 57.4, 56.3, 52.3, 42.6, 28.9, 21.1, 25.1 ppm; MS (ESI) m/z ($[M+1]^+$) 372. Anal. Calcd for $C_{21}H_{22}ClNO_3$: C, 60.83; H, 5.96; N, 3.77. Found: C, 60.83; H, 5.94; N, 3.80.

4.4.5. Methyl 4-((2-oxocyclohexyl)(phenylamino)-methyl)benzoate (10e). Colorless solid: (*anti*/*syn*=71/29)

mp 104–105 °C; IR (KBr) 3410, 1719, 1698, 1602, 1277 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97–7.95 (m, 2H), 7.45–7.43 (m, 2H), 7.07–7.04 (m, 2H), 6.66–6.62 (m, 1H), 6.52–6.50 (m, 2H), 4.83 (s, 0.29H), 4.78 (s, 0.71H), 4.67 (d, J=6.2 Hz, 0.71H), 4.54 (s, 0.29H), 3.87 (s, 3H), 2.81–2.77 (m, 1H), 2.43–2.29 (m, 2H), 2.04–2.03 (m, 1H), 1.96–1.89 (m, 2H), 1.72–1.58 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.4, 167.1, 147.5, 147.2, 130.0, 129.3, 129.2, 127.6, 118.0, 113.8, 58.1, 57.4, 52.2, 42.3, 31.8, 28.0, 24.3; (minor isomer): δ 211.1, 167.1, 147.4, 147.3, 129.9, 129.3, 129.2, 127.9, 118.2, 114.3, 57.5, 56.6, 52.2, 42.6, 28.9, 27.2, 25.1 ppm; MS (ESI) m/z ([M+1]$^+$) 338. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.75; H, 6.84; N, 4.22.

4.4.6. Methyl 4-((*m*-toluidino)(2-oxocyclohexyl)methyl)-benzoate (10f). Colorless solid: (*anti*/*syn*=88/12) mp 97–98 °C; IR (KBr) 3411, 1720, 1700, 1605, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.98 (m, 2H), 7.49–7.46 (m, 2H), 6.98 (d, J=7.8 Hz, 1H), 6.50–6.48 (m, 1H), 6.39 (s, 1H), 6.33–6.31 (m, 1H), 4.86 (br s, 1H), 4.85 (d, J=4.3 Hz, 0.12H), 4.68 (d, J=6.3 Hz, 0.88H), 3.90 (s, 3H), 2.83–2.80 (m, 1H), 2.45–2.40 (m, 1H), 2.36–2.34 (m, 1H), 2.20 (s, 3H), 1.99–1.90 (m, 3H), 1.79–1.68 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.5, 167.1, 147.5, 147.0, 139.1, 130.0, 129.2, 127.6, 119.1, 114.8, 110.8, 58.2, 57.3, 52.3, 42.3, 31.8, 28.1, 24.2; (minor isomer): δ 211.1, 167.2, 147.5, 147.3, 139.0, 129.9, 129.1, 127.8, 119.2, 115.2, 111.2, 57.4, 56.6, 52.3, 42.6, 28.9, 27.2, 25.1 ppm; MS (ESI) m/z ([M+1]$^+$) 352. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.20; H, 7.14; N, 4.02.

4.4.7. Methyl 4-((4-methoxyphenylamino)(2-oxocyclo-hexyl)methyl)benzoate (10g). Gray solid: mp 121–122 °C; IR (KBr) 3417, 1718, 1690, 1514, 1276 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J=8.1 Hz, 2H), 7.45 (d, J=8.1 Hz, 2H), 6.67 (d, J=8.8 Hz, 1H), 6.47 (d, J=8.8 Hz, 2H), 4.60 (d, J=6.6 Hz, 1H), 4.50 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 2.76–2.74 (m, 1H), 2.44–2.40 (m, 1H), 2.34–2.32 (m, 1H), 1.97–1.95 (m, 1H), 1.90–1.86 (m, 3H), 1.68–1.65 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 167.0, 152.4, 147.6, 141.2, 129.9, 129.2, 127.6, 115.3, 114.8, 59.0, 57.3, 55.7, 52.1, 42.1, 31.6, 27.9, 24.1 ppm; MS (ESI) m/z ([M+1]$^+$) 368. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.81; H, 6.86; N, 3.99.

4.4.8. Methyl 4-((4-fluorophenylamino)(2-oxocyclo-hexyl)methyl)benzoate (10h). Colorless solid: (*anti*/*syn*=92/8) mp 130–131 °C; IR (KBr) 3411, 1719, 1701, 1511, 1276 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00–7.98 (m, 2H), 7.46–7.43 (m, 2H), 6.78–6.74 (m, 2H), 6.44–6.42 (m, 2H), 4.80 (s, 0.8H), 4.68 (s, 0.92H), 4.58 (d, J=6.4 Hz, 1H), 3.88 (s, 3H), 2.77–2.75 (m, 1H), 2.43–2.39 (m, 1H), 2.36–2.33 (m, 1H), 2.20–1.97 (m, 1H), 1.89–1.87 (m, 2H), 1.78–1.66 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) (major isomer): δ 212.5, 167.0, 157.0 (d, J_{C-F}=234.5 Hz), 147.3, 143.6, 130.1, 129.4, 127.6, 115.9 (d, J_{C-F}=21.9 Hz), 114.9 (d, J_{C-F}=7.6 Hz), 59.0, 57.4, 52.3, 42.4, 31.9, 28.1, 24.4; (minor isomer): δ 211.2, 167.0, 157.0 (d, J_{C-F}=234.5 Hz), 147.3, 143.6, 130.0, 129.3, 127.8, 115.8 (d, J_{C-F}=22.1 Hz), 115.4 (d, J_{C-F}=7.5 Hz), 58.2, 56.6, 52.3, 42.6, 28.7 27.2, 25.1 ppm; MS (ESI) m/z ([M+1]$^+$) 356. Anal. Calcd for $C_{21}H_{22}FNO_3$: C, 70.97; H, 6.24; N, 3.94. Found: C, 70.96; H, 6.23; N, 3.98.

4.4.9. Diethyl 2-((4-(methoxycarbonyl)phenyl)(phenyl-amino)methyl)malonate (10j). Colorless solid: mp 105–106 °C; IR (KBr) 3398, 1751, 1720, 1700, 1605, 1271 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97–7.95 (m, 2H), 7.45–7.43 (m, 2H), 7.07–7.04 (m, 2H), 6.67–6.63 (m, 1H), 6.52–6.50 (m, 2H), 6.10 (t, J=11.0 Hz, 1H), 4.96 (d, J=11.1 Hz, 1H), 4.55 (d, J=10.7 Hz, 1H), 4.22–4.17 (m, 2H), 4.02–3.97 (m, 2H), 3.87 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.05 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 167.1, 166.5, 147.5, 147.2, 130.0, 129.3, 129.2, 127.6, 123.0, 118.0, 113.8, 62.1, 61.8, 56.4, 53.7, 52.3, 14.2, 13.9 ppm; MS (ESI) m/z ([M+1]$^+$) 400. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.16; H, 6.29; N, 3.50.

4.4.10. Diethyl 2-((4-bromophenylamino)(4-(methoxy-carbonyl)phenyl)methyl)malonate (10k). Colorless solid: mp 140–141 °C; IR (KBr) 3398, 1729, 1703, 1596, 1496, 1284 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J=8.4 Hz, 2H), 7.43 (d, J=8.7 Hz, 2H), 7.14 (d, J=8.4 Hz, 2H), 6.39 (d, J=8.7 Hz, 2H), 6.21 (t, J=11.2 Hz, 1H), 5.01 (d, J=11.3 Hz, 1H), 4.67 (d, J=10.8 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.01 (q, J=7.2 Hz, 2H), 3.88 (s, 3H), 1.24 (t, J=7.2 Hz, 3H), 1.06 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 167.5, 167.0, 166.5, 147.5, 147.0, 132.1, 130.1, 129.5, 127.5, 115.0, 110.0, 62.1, 61.8, 56.4, 53.7, 52.3, 14.2, 13.9 ppm; MS (ESI) m/z ([M+1]$^+$) 478. Anal. Calcd for $C_{22}H_{24}BrNO_6$: C, 55.24; H, 5.06; N, 2.93. Found C, 55.25; H, 5.06; N, 2.92.

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References and notes

1. (a) *Enantioselective Synthesis of β-Amino acids*; Juaristi, E., Ed.; Wiley-VCH: New York, NY, 1997; (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (c) Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998**, *41*, 973–980; (d) Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070.
2. (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44; (b) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97–99; (c) Kleinmann, E. F. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon: New York, NY, 1991; Vol. 2, Chapter 4.1; (d) Davis, F. A.; Szewczyk, J. M. *Tetrahedron Lett.* **1998**, *39*, 5951–5954.
3. (a) Schunk, S.; Enders, D. *Org. Lett.* **2001**, *3*, 3177–3180; (b) Fujita, T.; Nagasawa, H.; Uto, Y.; Hashimoto, T.; Asakawa,

Y.; Hori, H. *Org. Lett.* **2004**, *6*, 827–830; (c) Ishimaru, K.; Kojima, T. *Tetrahedron Lett.* **2003**, *44*, 5441–5444; (d) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, *68*, 8061–8064; (e) Evans, G. B.; Furneaux, R. H.; Tyler, P. C.; Schramm, V. L. *Org. Lett.* **2003**, *5*, 3639–3640; (f) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189–9192; (g) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904; (h) Wenzel, A. G.; Jacobern, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; (i) Müller, R.; Röttele, H.; Henke, H.; Waldmann, H. *Chem.—Eur. J.* **2000**, *6*, 2032–2043.

4. (a) Periasamy, M.; Suresh, S.; Ganesan, S. S. *Tetrahedron Lett.* **2005**, *46*, 5521–5524; (b) Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792–4796; (c) Komoto, I.; Kobayashi, S. *J. Org. Chem.* **2004**, *69*, 680–688; (d) Chung, W. J.; Omote, M.; Welch, J. T. *J. Org. Chem.* **2005**, *70*, 7784–7787; (e) Pandey, G.; Singh, R. P.; Garg, A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 2137–2140; (f) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1999**, 545–546; (g) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1995**, 233–234; (h) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143–145; (i) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395–3397.
5. Ollevier, T.; Nadeau, E. *J. Org. Chem.* **2004**, *69*, 9292–9295.
6. For a preliminary communication of a part of this work see: Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 1845–1847.
7. (a) Loh, T. P.; Liung, S. B. K. W.; Tan, K. L.; Wei, L. L. *Tetrahedron* **2000**, *56*, 3227–3237 and references cited therein; (b) Gennari, C.; Venturini, I.; Gislon, F.; Schimperma, G. *Tetrahedron Lett.* **1987**, *28*, 227–230; (c) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331–4334.
8. Ranu, B. C.; Samanta, S.; Guchhait, S. K. *Tetrahedron* **2002**, *58*, 983–988.
9. (a) Shang, Y. J.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 2247–2249; (b) Xia, M.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 7703–7705; (c) Shang, Y. J.; Shou, W. G.; Wang, Y. G. *Synlett* **2003**, 1064–1066; (d) Wang, Y. G.; Zhang, J.; Lin, X. F.; Ding, H. F. *Synlett* **2003**, 1467–1468; (e) Wang, Y. G.; Lin, X. F.; Cui, S. L. *Synlett* **2004**, 1175–1178; (f) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 530–536; (g) Cui, S. L.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2005**, *70*, 2866–2869; (h) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 3535–3540.
10. CCDC-615741 (**10b**) contains the supplementary crystallographic data for this paper. These can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/conts/retrieving.html (or CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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Two new abietane diterpenes from *Cordia latifolia*

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Abstract—Two new abietane diterpenes cordioic acid and cordifolic acid were isolated from the methanolic extract of *Cordia latifolia* stem bark. The structures of these diterpenes were elucidated using spectroscopic techniques. To the best of our knowledge, this is the first instance of isolation of diterpenoids from this source. Furthermore, cordifolic acid is a rare 2,3-*seco*-abietane suggestive of its biogenesis from 3-keto-analogue.

1. Introduction

Cordia latifolia (Boraginaceae) is a small deciduous tree growing nearly all over the Indo–Pak subcontinent. Practically every part of the tree is reported for its medicinal value in the indigenous system of medicine[1] and thus various groups of workers undertook studies on its chemical constituents and reported different classes of compounds, which include fatty acids,[2] sterols,[3] carbohydrate,[4–6] flavanone and flavanone glycosides,[7–11] triterpenoids and glycosides[12,13] and pyrrolizidine alkaloids.[14]

In the present study, two new abietane diterpenes cordioic acid (**1**) and cordifolic acid (**2**) were isolated from the methanolic extract of *C. latifolia* stem bark and their structures were determined by spectroscopic analysis.

2. Results and discussion

The molecular formula of compound **1** was established through HREIMS, which showed the molecular ion peak at *m/z* 330.1840 corresponding to the molecular formula $C_{20}H_{26}O_4$ (eight degrees of unsaturation). The IR spectrum displayed absorption bands attributable to carboxyl group (3100–2500 br, 1725 cm^{-1}), benzene ring (1599–1407 cm^{-1}, four peaks) and geminal methyls (1381 cm^{-1}). The ^1H NMR spectrum (Table 1) indicated the presence of an aromatic isopropyl moiety at δ 1.20 (6H, d, J=7.0 Hz), 2.80 (1H, septet, J=7.0 Hz), three aromatic protons at 7.14 (1H, d, J=8.1 Hz), 6.97 (1H, br d, J=8.1 Hz) and 6.86 (1H, br s) and one methyl singlet at δ 1.26 (3H, s).

The ^{13}C and DEPT NMR spectra (Table 1) suggested that **1** was a diterpenoid with a total of twenty carbons consisting of three methyls, five methylenes, five methines (including three aromatic CH) and seven quaternary carbons (including three aromatic and two carbonyl carbons). In the ^1H–^1H COSY spectrum, cross peaks between H-15 (δ 2.80) and the methyl protons at δ 1.20 (H-16, H-17) revealed that two methyls and one methine are part of an isopropyl group. The ^{13}C NMR spectrum further showed the presence of two carboxylic carbonyls at δ 183.3 and 183.4 and six aromatic carbons at δ 133.3 (C-8), 146.7 (C-9), 124.1 (C-11), 123.8 (C-12), 145.7 (C-13) and 126.9 (C-14). A detailed analysis of ^1H–^1H COSY, HMQC and HMBC spectra revealed that **1** is an abietane diterpenoid.[15,16] These structural features were supported by the HMBC spectrum in which cross peaks were observed for correlations between H-5 (δ 2.22) and C-3 (δ 36.7), C-4 (δ 47.3), C-6 (δ 21.7), C-7 (δ 29.9), C-9 (δ 146.7), C-10 (δ 51.4), C-18 (δ 183.3/183.4), C-19 (δ 16.2) and C-20 (δ 183.3/183.4) and between H-15 (δ 2.80) and C-12 (δ 123.8), C-13 (δ 145.7), C-14 (δ 126.9) and C-16/C-17 (δ 23.9) (Table 1). In the light of these observations the structure of compound **1** (Fig. 1) was established as abieta-8,11,13-trien-18,20-dioic acid. The assignments of proton and carbon nuclei are based on 2D NMR and compare well with the published values of similar partial structures,[15–17] which were also supportive for the carboxyl groups at C-4 and C-10. The values of C-4, C-5 and C-19 were particularly helpful in assigning the α disposition of the carboxyl group at C-4.[17]

The composition of **2** as $C_{20}H_{28}O_2$ (seven degrees of unsaturation) was evident from the molecular ion peak at *m/z* 300.2078 in the HREIMS spectrum. The IR spectrum displayed absorption bands attributable to carboxyl group (–O–H str., 3200–2500 cm^{-1} br; carbonyl str., 1720 cm^{-1}), benzene ring (1634–1459 cm^{-1}) and geminal methyls

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Table 1. ^{1}H and ^{13}C NMR data of compound **1** in $CDCl_3$[a]

Proton	δC[b]	δH[c,d]	^{1}H–^{1}H COSY	HMBC (H→C)
1	36.7	1.49–2.28 (m)	H-2	C-5, C-20
2	18.5	1.71, 1.82 (m)	H-1, H-3	C-1
3	37.9	1.49–2.28 (m)	H-2	—
4	47.3	—	—	—
5	44.6	2.22 (dd, 12.2, 2.5)	H-6	C-1, C-3, C-4, C-9, C-18
6	21.7	1.83, 1.85 (m)	H-5, H-7	C-5, C-7
7	29.9	2.65, 2.70 (m)	H-6	C-6, C-8
8	133.3	—	—	—
9	146.7	—	—	—
10	51.4	—	—	—
11	124.1	7.14 (d, 8.1)	H-12	C-8, C-12, C-13
12	123.8	6.97 (br d, 8.1)	H-11, H-14	C-9, C-11, C-13, C-14, C-15
13	145.7	—	—	—
14	126.9	6.86 (br s)	—	C-8, C-15
15	33.4	2.80 (septet, 7.0)	H-16, H-17	C-12, C-13, C-14, C-16/C-17
16	23.9	1.20 (d, 7.0)	H-15	C-13
17	23.9	1.20 (d, 7.0)	H-15	C-13
18	183.3[e]	—	—	—
19	16.2	1.26 (s)	—	C-3, C-4, C-5, C-18,
20	183.4[e]	—	—	—

[a] Assignments based on ^{1}H–^{1}H COSY, HMQC and HMBC experiments.
[b] Recorded at 125 MHz.
[c] Recorded at 500 MHz.
[d] Multiplicity and *J* values in hertz are given in parenthesis.
[e] Values may be interchanged.

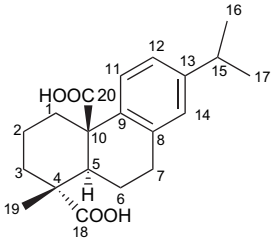

Figure 1. Structure of cordioic acid.

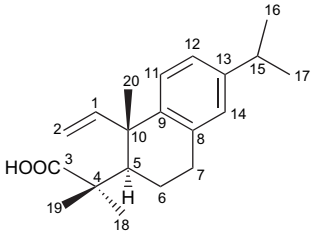

Figure 2. Structure of cordifolic acid (**2**).

(1383 cm^{-1}). The ^{1}H NMR spectrum revealed the resonances for a terminal double bond [δ 4.86 (1H, d, J=10.4 Hz), 4.83 (1H, d, J=17.2 Hz) and 5.68 (1H, dd, J=17.2, 10.4 Hz)], three aromatic protons [δ 7.08 (1H, d, J=8.1 Hz), 6.90 (1H, br d, J=8.0 Hz) and δ 6.79 (1H, br s)] suggestive of an *ortho–ortho* and *ortho–meta* coupled aromatic ring system, an isopropyl group [δ 1.13 (6H, d, J=6.8 Hz) and 2.73 (1H, septet, J=6.8 Hz)] and three methyl singlets [δ 1.10 (3H, s), 1.12 (3H, s) and 1.17 (3H, s)]. These proposals were supported by the ^{13}C NMR (broad band) DEPT spectra, which exhibited twenty carbons including five methyls, three methylenes (including one sp^2), six methines (including four sp^2) and six quaternary (including one carboxyl and three aromatic carbons).

Detailed analysis of the ^{1}H–^{1}H COSY and HMQC spectra of **2** demonstrated four structural units, three with correlated protons: –$CH(CH_3)_2$ (isopropyl), –^{5}CH–$^{6}CH_2$–$^{7}CH_2$–, $^{2}CH_2$=^{1}CH– and an *ortho–ortho*, *ortho–meta* coupled aromatic system as shown in Figure 2. These units were combined on the basis of heteronuclear multiple bond correlation (HMBC) (Table 2), which clarified the structure of **2** as 2,3-*seco*-abieta-1,8,11,13-tetraen-3-oic acid.

The stereochemistry of various centres was deduced from NOESY correlations, which were present between H-5/H-1, H-5/H-2, H-5/H-18 and H-19/H-20.

Compound **2** is a rare example of ring A *seco*-abietane derivative[18,19] and offers its interesting possible biogenesis through a Baeyer–Villiger oxidation of the 3-ketone followed by a fragmentation of the lactone to generate a carboxylic acid and an alkene.

3. Experimental

3.1. General experimental procedures

Column chromatography was carried out by using silica gel 60 (Merck Kieselgel 60, 70–230 mesh). TLC was taken on silica gel 60 PF_{254} (Merck); detection under UV lamp (λ_{max} 254, 366) and with I_2 spray. UV spectra were obtained using a Hitachi-U-3200 spectrophotometer. IR spectra were recorded on a Jasco A-302 spectrophotometer. NMR spectra were measured on Bruker AMX-500 spectrophotometer at 300 K. Mass spectra were obtained using Finnigan-Mat-311A spectrometer. Preparative HPLC was carried out on JAI LC-908W normal phase, column silica 12 nm, 20 cm× 250 nm, by using $CHCl_3$ as a mobile phase; loop was 3 ml; flow rate was 8.0 ml/min.

3.2. Plant material

The aerial parts of *C. latifolia* were collected from Karachi region during 2001 and identified by Mr. Jan-e-Alam,

Table 2. ^{1}H and ^{13}C NMR data of compound **2** in $CDCl_3$[a]

Proton	δC[b]	δH[c,d]	^{1}H–^{1}H COSY	HMBC (H→C)
1	147.2	5.68 (dd, 17.2, 10.4)	H-2	C-10, C-20
2a	112.6	4.86 (d, 10.4)	H-1	C-1, C-10
2b		4.83 (d, 17.2)		
3	181.5	—	—	—
4	47.0	—	—	—
5	48.8	1.85 (dd, 13.5, 3.0)	H-6	C-4, C-20
6	18.8	1.65, 1.70 (m)	H-5, H-7	—
7	29.6	2.62, 2.69 (m)	H-6	C-9
8	134.6	—	—	—
9	146.9	—	—	—
10	50.5	—	—	—
11	124.0	7.08 (d, 8.1)	H-12	C-9, C-12, C-13
12	123.7	6.90 (br d, 8.07)	H-11	C-9, C-11, C-14
13	145.6	—	—	—
14	126.7	6.79 (br s)	—	C-9, C-12
15	33.4	2.73 (septet, 6.8)	H-17	C-13
16/17	24.9	1.13 (d, 6.8)	H-15	C-13, C-15
18	29.3	1.17 (s)	—	C-3
19	23.8	1.10 (s)	—	C-3, C-4
20	16.8	1.12 (s)	—	C-1, C-9

[a] Assignments based on ^{1}H–^{1}H COSY, HMQC and HMBC experiment.
[b] Recorded at 125 MHz.
[c] Recorded at 500 MHz.
[d] Multiplicity and *J* values in hertz are given in parenthesis.

Department of Botany, University of Karachi. A voucher specimen (G.H. No. 68223) has been deposited in the herbarium of the same department. The bark of the stem was cut using hand chopper.

3.3. Extraction and isolation

The stem bark (5 kg) of *C. latifolia* was repeatedly (4×15 l) extracted with MeOH at room temperature. The combined methanolic extract was freed of the solvent in vacuo to a thick syrup, which was partitioned between EtOAc and H_2O. The EtOAc layer was washed with H_2O, dried (anhydrous Na_2SO_4) and evaporated under reduce pressure to give a gummy residue (400 g). It was divided into *n*-hexane soluble and insoluble fractions.

The *n*-hexane soluble fraction was extracted with 90% aq MeOH, which was extracted out with EtOAc after adding saline. The EtOAc phase was dried over Na_2SO_4 (anhydrous) and concentrated under vacuum. The residue left was divided into $CHCl_3$ soluble and insoluble fractions. The $CHCl_3$ soluble (100 g) fraction was subjected to gravity column chromatography (Merck Kieselgel 60, 70–230 mesh, 1500 g), which was eluted with $CHCl_3$, $CHCl_3$–MeOH in increasing order of polarity. As a result various fractions were obtained, which were combined on the basis of TLC to ultimately afford 37 fractions. Fraction 7 (50 mg) was purified over precoated silica gel 60 F_{254} aluminium sheets (20×10 cm; Merck) developed with *n*-hexane–EtOAc (7:3). Four bands were separated with the upper most band as the major component. It was further purified through HPLC to furnish compound **1** (12.0 mg) (JAI LC-908W, $CHCl_3$ as mobile phase, retention time 16 min). Fraction 19 (43.7 mg) was also purified over the same silica gel precoated sheets using *n*-hexane–EtOAc (7:3) solvent system affording three bands. Of these, the second band (27.4 mg) was further purified through HPLC to furnish **2** (15.2 mg) (JAI LC-908W, $CHCl_3$ as mobile phase, retention time 24 min).

3.4. Characteristics of each terpenoid

3.4.1. Cordioic acid (1). Amorphous solid; $[\alpha]_D^{27}$ +48.8 (*c* 0.15, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 288 (3.19), 266 (2.15) nm; IR (film) ν_{max} 3100–2500 br, 2927, 2858, 1725, 1599, 1527, 1449, 1407, 1381, 1275 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HREIMS *m/z* 330.1840 [M^+] (calcd for $C_{20}H_{26}O_4$, 330.1831).

3.4.2. Cordifolic acid (2). Amorphous solid; $[\alpha]_D^{27}$ +76.3 (*c* 0.25, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 290 (3.24), 267 (1.95) nm; IR (film) ν_{max} 3200–2500 br, 1634, 1601, 1459, 1383, 1277 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; HREIMS *m/z* 300.2078 [M^+] (calcd for $C_{20}H_{28}O_2$, 300.2089).

References and notes

1. Chopra, R. N.; Nayar, S. L.; Chopra, I. C. *Glossary of Indian Medicinal Plants*; C.S.I.R.: India, 1956; p 77.
2. Tiwari, R. D.; Srivastava, K. C.; Shukla, S.; Bajpai, R. K. *Planta Med.* **1967**, *15*, 240–244.
3. Tiwari, K. P.; Srivastava Smt, S. D. *Planta Med.* **1979**, *36*, 191–192.
4. Bhatty, M. K.; Shah, D. H.; Saeed, M. A.; Nasir, U. *Pak. J. Sci. Ind. Res.* **1978**, *21*, 162–163.
5. Ifzal, S. M.; Qureshi, A. *Pak. J. Sci. Ind. Res.* **1976**, *19*, 64–65.
6. Karawya, M. S.; Wassel, G. M.; Baghdadi, H. H.; Ammar, N. M. *Planta Med.* **1980**, *38*, 73–78.
7. Srivastava, S. K. *Indian J. Pharm. Sci.* **1980**, *42*, 95–96.
8. Chauhan, J. S.; Srivastava, S. K. *Indian J. Chem., Sect. B* **1977**, *15*, 760–761.
9. Srivastava, S. K.; Srivastava, S. D. *Phytochemistry* **1979**, *18*, 2058–2059.
10. Srivastava, S. K. *Indian Drugs* **1979**, *16*, 105–106.

11. Chauhan, J. S.; Srivastava, S. K.; Sultan, M. *Phytochemistry* **1978**, *17*, 334.
12. Chauhan, J. S.; Srivastava, S. K. *Phytochemistry* **1978**, *17*, 1005–1006.
13. Srivastava, S. K.; Srivastava, S. D.; Nigam, S. S. *J. Indian Chem. Soc.* **1983**, *60*, 202.
14. Wassel, G.; El-Menshawi, B.; Saeed, A.; Mahran, G.; El-Merzabani, M. *Pharmazie* **1987**, *42*, 709–711.
15. Levy, G. C. *Topics in Carbon-13 NMR Spectroscopy*; Wiley: New York, NY, London, Sydney, Toronto, 1976; Vol. 2.
16. Escudero, J.; Perez, L.; Rabanal, R. M.; Valverde, S. *Phytochemistry* **1983**, *22*, 585–587.
17. Chang, C. W. J.; Flament, I.; Matson, J. A.; Nishida, T.; Ohloff, G.; Wehrli, F. W.; Weinheimer, A. J. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: New York, NY, 1979; Vol. 36.
18. Charles, L.; Cantrell, S. L.; Richheimer, G. M.; Nicholas, B. K.; Schmidt, D.; Bailey, T. *J. Nat. Prod.* **2005**, *68*, 98–100.
19. Kuo-Chiou, H.; Jim-Min, F.; Shiachen, Y. *J. Nat. Prod.* **1995**, *58*, 1592–1595.

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Sodium dithionite initiated regio- and stereoselective radical addition of polyfluoroalkyl iodide with norbornene analogs

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Abstract—Sodium dithionite initiated free-radical addition of polyfluoroalkyl iodides (**2m–2s**) with norbornene **1a** and its derivatives, such as norbornene-2-carboxylates **1b** and **1c**, and norbornene-2-carboxylic acids **1d** and **1e** was investigated. In all the cases, the addition of R_F group was stereoselectively delivered at *exo*-position and the predominant configuration of products was trans. Under the similar condition, norbornene-2-carboxylic ethyl ester **1b** reacted with **2p** to give 6-*exo*-R_F-5-*endo*-iodo adduct **3bp** and 5-*exo*-R_F-6-*endo*-iodo adduct **5bp** in the ratio of 4:1. While **1c**, which has a heavy crowded group in the 2-*endo*-position, gave 6-*exo*-R_F-5-*endo*-iodo adduct **3cp** and polyfluoroalkylated product **4cp** retaining the trans-configuration and the *exo*-orientation of R_F group. The fluoroalkylation–lactonization reaction occurred in the reaction of norbornene-2-*endo*-carboxylic acids **1d** and **1e** with polyfluoroalkyl iodides to afford the corresponding fluoroalkylated γ-lactone products (**7dp–7ds**, and **7em–7er**). The configuration of the products was further confirmed by 2D NMR and X-ray diffraction analyses for the first time.

1. Introduction

The free-radical addition reaction of polyfluoroalkyl iodides with unsaturated compounds, such as olefins and alkynes, was an important method to prepare fluorinated compounds, which could usually be initiated by high temperature, UV, peroxide, metals, metal complexes, etc.[1] The reactions initiated by the sulfinatodehalogenated reagents, such as sodium dithionite, sodium disulfite, Rongalite, thiourea dioxide, and so on, have been extensively studied in our laboratory.[2] This reaction and its applications in industry have been described in many literatures,[3] however, the stereochemistry of this addition reaction, which played important roles in its theoretical chemistry and industrial utility, had seldom been mentioned. Accordingly, we had paid much attention to it and hoped to do some research in this aspect. Norbornene and its derivatives were usually chosen for the investigation of stereoselective addition of electrophiles at the double bond due to its special spatial structure,[4] however, the addition of norbornene analogs with polyfluoroalkyl iodides was examined in few cases in the literature. Brace investigated the reaction of norbornene and its symmetrical 2,3-dicarboxylic acid derivatives with polyfluoroalkyl iodides and pointed out that the configuration of the adducts was determined by the steric and electronic factor of the substrates and the reaction conditions,[5] therefore the high stereoselective addition might be reasonable by using the asymmetrical substrates under mild reaction conditions. Herein we investigated the regio- and stereoselectivity of the radical anion addition of polyfluoroalkyl iodides with norbornene and some asymmetrical derivatives initiated by sodium dithionite.

2. Results and discussion

2.1. The reaction of norbornene 1a with polyfluoroalkyl iodide

The reaction of norbornene **1a** with polyfluoroalkyl iodides was investigated at first. In the presence of sodium dithionite and sodium bicarbonate, the free-radical addition of R_FI (**2m–2q**) to norbornene **1a** occurred smoothly at room temperature in aqueous acetonitrile solution (CH_3CN–H_2O=3:1 (v/v)), after usual workup only trans-adduct with R_F at the *exo*-position (**3am–3aq**) was isolated in 63–91% yields by column chromatography (Scheme 1 and Table 1), which were consistent with the results reported by Brace.[5a,b] The heavy steric hindrance of R_F led to its attacking at the double bond from the *exo*-position of **1a** followed by the *endo*-oriented attack of iodine. By changing R_FI to uncrowded ethyl iododifluoroacetate (**2r**) the mixture of trans-adduct (**3ar**) and cis-adducts (**4ar**) was obtained in 87% overall yield in the ratio of 5:1 (Scheme 2). We had reported that the addition of **2r** with cyclopentene and cyclohexene gave only trans-adduct for the former and cis–trans mixture

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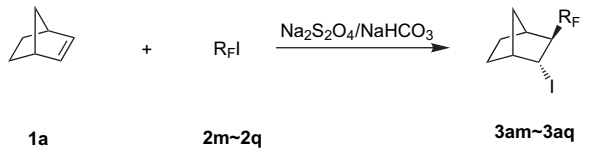


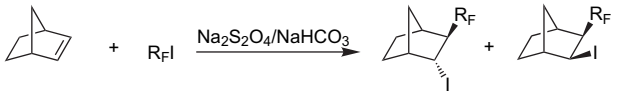
R_F = $Cl(CF_2)_n$ n=2, **m**; n=4, **p**; n=8, **q**
$F(CF_2)_n$ n=3, **n**; n=6; **s**
$(CF_3)_2CF$ **o**
CF_2CO_2E **r**

Scheme 1.

Table 1. Addition of norbornene with R_FI

Entry	Substrates	R_FI	Products	Configuration		Yields (%)
				R_F	R_F/I	
1	**1a**	**2m**	**3am**	*exo*	trans	78
2	**1a**	**2n**	**3an**	*exo*	trans	82
3	**1a**	**2o**	**3ao**	*exo*	trans	87
4	**1a**	**2p**	**3ap**	*exo*	trans	87
5	**1a**	**2q**	**3aq**	*exo*	trans	91
6	**1a**	**2r**	**3ar–4ar** (5:1)	*exo*	trans+cis	87

(1:1.6) for the latter under the similar condition.[6] It has been reported that different ratio of trans- and cis-adducts was obtained in the radical addition of ethyl bromoacetate with norbornene bearing various steric substituents.[5a,7] Therefore it can be speculated that the mode of addition depends heavily on the adding group and the structure of substrates in this reaction.



R_F = **r**: CF_2CO_2Et

Scheme 2.

The IR and ^1H NMR spectra were usually utilized to determine the configuration of adducts in the literatures,[5a,b] herein the stereo configuration of adducts was determined via 2D NMR spectrum. Compound **3ap** (Fig. 1) was taken as a typical example for the configuration analyses of compounds **3**. The assignment of the chemical shift in ^1H NMR was accomplished by the analysis of ^1H NMR, ^{13}C NMR, DEPT, HMBC, HMQC, etc. The observation of strong correlativity of H1–H2 and no obvious correlativity of H3–H4 in ^1H–^1H COSY combined with interaction of H2–H7s and no or weak interaction of H3–H7s in NOESY

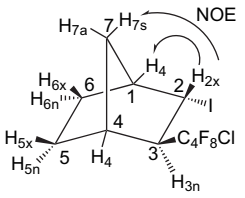


Figure 1.

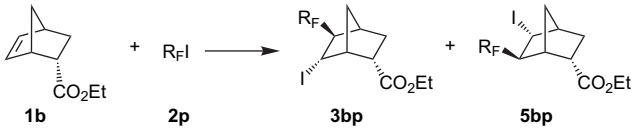
demonstrated its trans-configuration with R_F at *exo*-position and iodine atom at *endo*-position.

2.2. The reaction of 5-norbornene-2-*endo*-carboxylic acid ester 1b and 1c with R_FI

When **1b** reacted with **2p** under the same condition, two adducts **3bp** and **5bp** were obtained in the ratio of 4:1 (Table 2). Spectral data (1D and 2D NMR) showed that R_F was at the *exo*-position of C5 and iodine was at the *endo*-position of C6 of norbornene in **3bp** whereas R_F was at the *exo*-position of C5 and iodine was at the *endo*-position of C6 in **5bp** (Scheme 3).

Table 2. Addition of norbornene-2-*endo*-carboxylic ester with R_FI

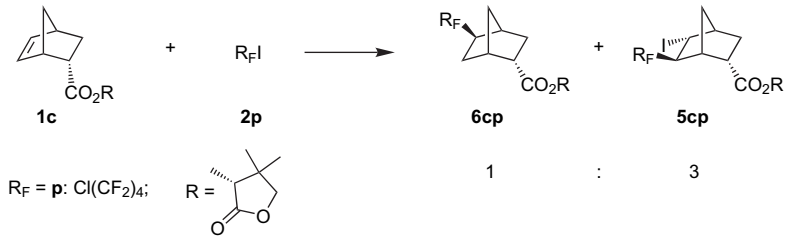
Entry	Substrates	R_FI	Products	Configuration		Overall yields (%)
				R_F	R_F/I	
1	**1b**	**2p**	**3bp–5bp** (4:1)	*exo*	trans	63
2	**1c**	**2p**	**6cp–5cp** (1:3)	*exo*	trans (**5cp**)	88



R_F = **p**: $Cl(CF_2)_4$

Scheme 3.

In order to examine steric hindrance effect, norbornene-2-*endo*-ester **1c**, bicyclo[2.2.1]hept-5-ene-2-carboxylic acid-4,4-dimethyl-2-oxo-tetrahydro-furan-3-yl ester, was allowed to react with **2p** (Scheme 4). Ester **1c** was synthesized via Diels–Alder addition of cyclopenta-1,3-diene with acrylic acid 4,4-dimethyl-2-oxotetrahydro-furan-3-yl ester, which was condensed from 3-hydroxy-4,4-dimethyl-dihydro-furan-2-one and acryl chloride.[10] The reaction of **1c** with **2p** proceeded at room temperature in the water and acetonitrile solution (v/v=1:1), two products (**5cp–6cp**=3:1) were isolated by column chromatography (eluent: PE–EA=30:1) in 88% overall yield (Table 2).



R_F = **p**: $Cl(CF_2)_4$;

Scheme 4.

Similar analyses of the spectral data (1D and 2D NMR) showed that **5cp** was a trans-adduct with R_F at the *exo*-position of C5 and iodine at the *endo*-position of C6 of norbornene, and **6cp** was the fluoroalkylated–deiodined product with R_F at the *exo*-position of C6 of norbornene, which was formed via the addition of H atom (from the solvent) to the C5 after the addition of R_F to *exo*-position of norbornene. To ascertain our deduction, the structure was further confirmed by the X-ray crystallography of **5cp** and **6cp** (Figs. 2 and 3).

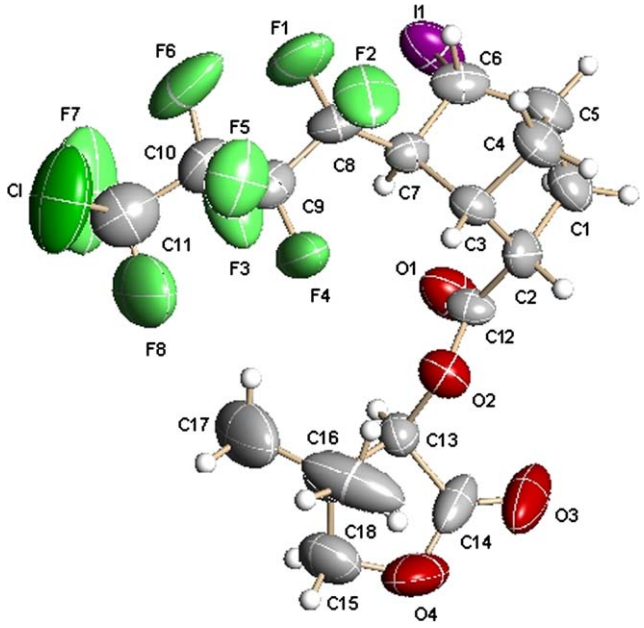


Figure 2. ORTEP of compound **5cp**.

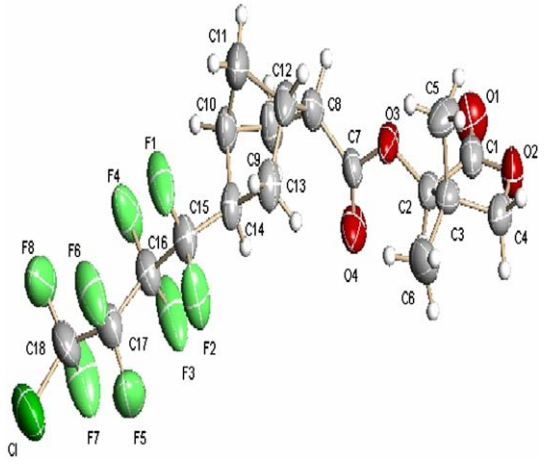


Figure 3. ORTEP of compound **6cp**.

It was observed from the crystallography of **6cp** that the 6-*endo*-position of norbornene had been filled with the crowded group (acrylic acid 4′,4′-dimethyl-2′-oxo-tetrahydro-furan-3′-yl ester) at 2-*endo*-position of norbornene, and the *exo*-position of the norbornene was crowded with great group C_4F_8Cl in the neighboring C3 and the 7-CH_2 group, which make it hard for the bulky iodine atom to approach the C6 from the *endo* or the *exo*-position of norbornene, however, the media H_2O molecule, which surrounded the free-radical intermediate could attack the C6 of norbornene to give compound **6cp**.

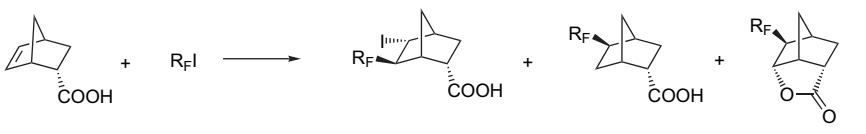
2.3. The reaction of norbornene-carboxylic acid 1d and 2-methyl-norbornene-carboxylic acid 1e with R_F

Besides the 6-*exo*-fluoroalkyl-5-*endo*-iodo adducts **5dp–5ds** and the fluoroalkylated compounds **6dp–6ds**, the addition of norbornene-2-*endo*-carboxylic acid **1d** with polyfluoroalkyl iodide gave the corresponding lactones **7dp–7ds** (Scheme 5 and Table 3). Similarly in all the cases R_F was added at *exo*-position of norbornene and iodine atom was added at *endo*-position. The lactone was produced via the iodolactonization of the intermediate adduct 5-*exo*-fluoroalkyl-6-*endo*-iodo-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid under the basic condition. The double peak at δ_H=4.95 ppm in ^{1}H NMR, the peak at δ_C=78.7 ppm in ^{13}C NMR, and ν=1780 cm^{-1} in IR revealed that there existed the latcone group in **7dp–7ds**. All the same configurations were confirmed by the analysis of COSY and NOESY spectra for **7dp–7ds**, **6dp–6ds**, and **5dp–5ds** and further by the crystallography of **5ds** (Fig. 4).

It is curious that there were no polyfluoroalkylated products formed except the 5-*exo*-R_F-latcone **7em–7ep** and the 6-*exo*-R_F-5-*endo*-adduct **5em–5ep** observed in the reaction of R_FI with **1e**, which have much similar structure with **1d** (Table 3 and Scheme 6). The ratio of **5em–5ep** and **7em–7ep** was from 2.1:1.0 to 0.9:1.0 with 50–72% overall yields. The crystallography of **5eo** (Fig. 5) and 2D NMR spectra were consistent with the trans-configuration of **5em–5ep** and **7em–7ep** with R_F at the *exo*-position of norbornene.

Table 3. Addition of norbornene-2-*endo*-carboxylic acid with R_FI

Entry	Substrate	R_FI	Product	Configuration		Yield (%)
				R_F	R_F/I	
1	**1d**	**2p**	**5dp–6dp–7dp** (1.0:1.1:0.8)	*exo*	trans (**5dp**)	70
2	**1d**	**2q**	**5dq–6dq–7dq** (1.0:1.5:0.3)	*exo*	trans (**5dq**)	52
3	**1d**	**2s**	**5ds–6ds–7ds** (1.0:1.1:0.8)	*exo*	trans (**5ds**)	58
4	**1e**	**2n**	**5en–7en** (1.0:1.0)	*exo*	trans (**5en**)	67
5	**1e**	**2o**	**5eo–7eo** (2.1:1.0)	*exo*	trans (**5eo**)	50
6	**1e**	**2p**	**5ep–7ep** (0.9:1.0)	*exo*	trans (**5ep**)	72



1d **2p, 2q, 2s** **5dp, 5dq, 5ds** **6dp, 6dq, 6ds** **7dp, 7dq, 7ds**

R_F = **p**: $Cl(CF_2)_4$; **q**: $Cl(CF_2)_8$; **s**: $F(CF_2)_6$

Scheme 5.

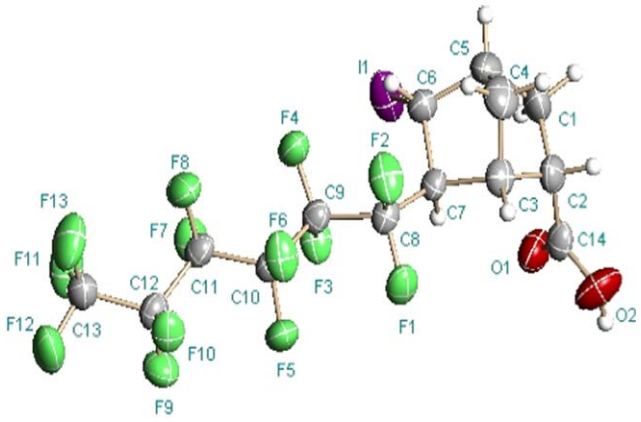
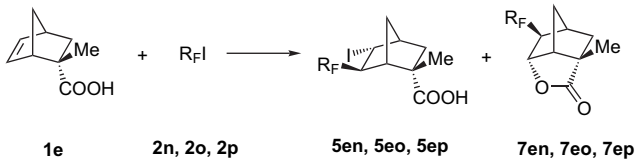


Figure 4. ORTEP of **5ds**.



1e **2n, 2o, 2p** **5en, 5eo, 5ep** **7en, 7eo, 7ep**

R_F = **n**: $F(CF_2)_3$; **o**: $(CF_3)_2CF$; **p**: $Cl(CF_2)_4$

Scheme 6.

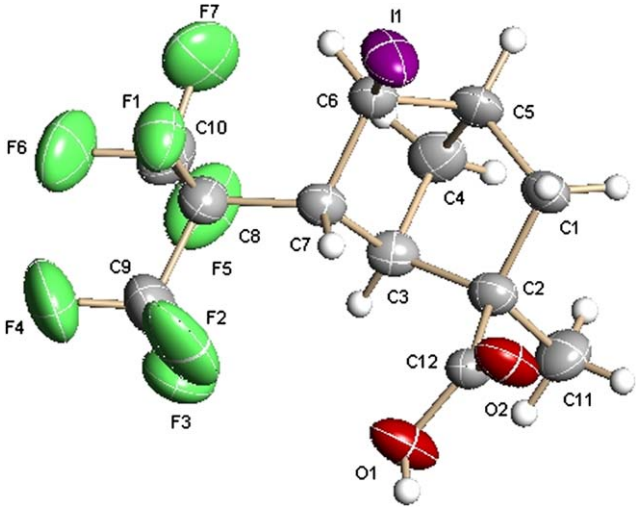
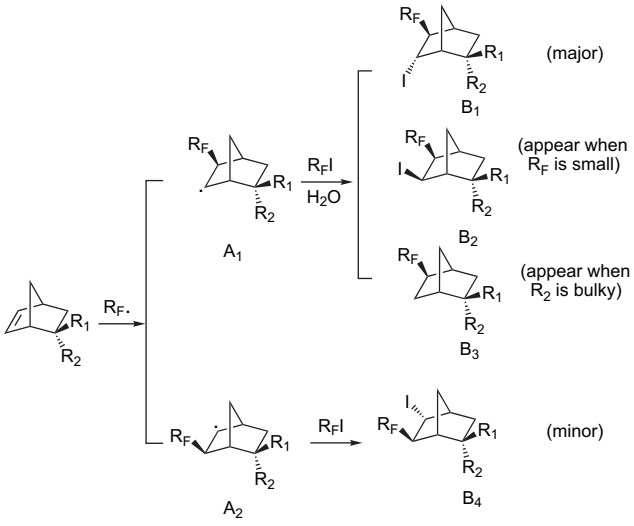


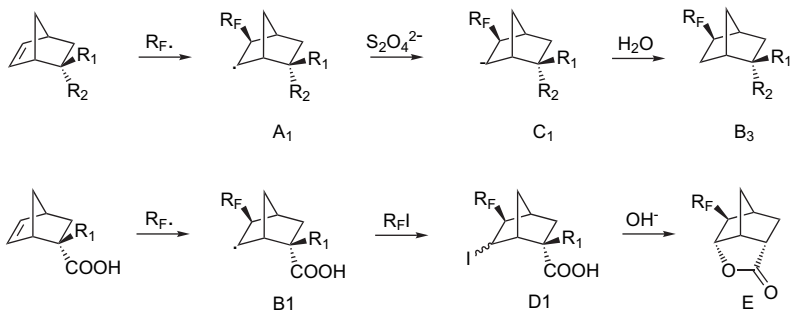
Figure 5. ORTEP of **5eo**.

2.4. Mechanism for the free-radical addition of norbornene and its 2-substituted derivatives with R_FI initiated by $Na_2S_2O_4$

According to the literatures,[3c,5] the supposed mechanism was described as following (Scheme 7): (1) R_F• was generated from R_FI under the initiation of $Na_2S_2O_4$, (2) 5-*exo*-R_F intermediates A_1 and 6-*exo*-R_F intermediate A_2 were produced by stereoselectively *exo*-oriented addition of R_F• to C=C of the norbornene and its derivatives, and (3) 5-*exo*-R_F-6-*endo*-iodo adduct B_1 was produced from the reaction of A_1 with R_FI and 6-*exo*-R_F-5-*endo*-iodo adduct B_2 was produced from the reaction of A_1 with R_FI. In this mechanism, the third step was the rate-determined step, which was influenced by steric and electronic effect of the substrate and adding group and played important roles in the configuration of the adducts. For the uncrowded R_FI (e.g., ICF_2COOEt), some cis-adducts were produced accompanying the trans-adducts and when the 2-*endo*-position was taken by bulky group, an anion C1 was obtained by transferring an electron to radical A1 from $S_2O_4^{2-}$, and then the hydrogenated product B_3 was obtained by the abstraction of proton from H_2O (Scheme 8). For norbornene-2-carboxylic acids **1d** and **1e**, the lactone E was obtained by base-catalyzed iodolactonization from the adduct D1 (Scheme 8).



Scheme 7. Mechanism proposed for this reaction.



Scheme 8. Mechanism proposed for the production of hydrogenated product and lactonizated product.

Generally we concluded that the free-radical addition reaction of norbornene and its 2-substituted derivatives with R_FI initiated by sodium dithionite was of high regio- and stereoselectivity with the addition of the R_F group to *exo*-position due to the narrow space of the *endo*-position of norbornene and its 2-*endo*-derivatives. The main products were of trans-configuration due to the heavily steric hindrance of the neighboring R_F group, which led to the predominant addition of iodine at the *endo*-position, and in some cases, the polyfluoroalkylated products were produced in concomitant with adducts. In the case of norbornene-2-*endo*-carboxylic acids, polyfluoroalkylated lactones were obtained from the polyfluoroalkylation–lactonization reaction of the adduct 5-*exo*-R_F-6-*endo*-iodobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid under the basic condition.

3. Experimental

3.1. General

Melting points were measured in WRS-1B digital melting point instrument. IR spectra were taken on a Nicolet FTIR 20sx IR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AC500 (500 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AC500 (500 MHz) spectrometer; chemical shifts are reported as $\delta_{CFCl_3}(\delta_{CFCl_3} = \delta_{TFA} - 76.8)$, negative for upfield shifts. Mass spectra were obtained on a Finnigan GC–MS 4021 spectrometer. X-ray data were measured at 293 K on a Bruker SMART CCD diffractometer with graphite monochromated Mok\α radiation. Column chromatography was performed using silica gel H, particle size was 10–40 μm.

3.2. Typical experimental procedure for the reaction of the norbornene 1a with R_FI

Norbornene (10 mmol) and polyfluoroalkyl iodide (12 mmol) were dissolved in the solution of water (10 mL) and acetonitrile (10 mL). Sodium dithionite (3.7 g) and sodium bicarbonate (1.85 g) were added to the solution. The mixture was stirred at ambient temperature for 6 h. When the reaction was accomplished, the mixture was treated with water (ca. 50 mL). The mixture was extracted with ether of 3×20 mL. The combined organic layers were washed with saturated brine and dried over anhydrous sodium sulfate. After the evaporation of ether, the crude product was purified by column chromatography (PE–EA=200:1) to give products **3am–3ar** and **4ar**.

3.2.1. 3-e*xo*-(2-Chloro-1,1,2,2-tetrafluoroethyl)-2-*endo*-iodobicyclo[2.2.1]heptane (3am). Oil. IR (film): ν_{max} 2980 (C–H), 1230 (C–F), 1150, 1080, 930, 800, 750, 640 (C–I) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24–1.26 (2H, m, H-7, H-5), 1.56–1.58 (2H, m, H-6, H-5), 1.62–1.67 (1H, m, H-7), 1.82–1.90 (1H, m, H-6), 2.20–2.32 (1H, m, H-3), 2.38 (1H, s, H-4), 2.42 (1H, s, H-1), 4.15–4.25 (1H, m, H-2); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −117.1 (2F, dd, *J*=385.8, 268.2 Hz, CF_2CF_2Cl), −69.3 (2F, dd, *J*=240.0, 174.1 Hz, CF_2Cl); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 27.3 (s, C-2), 28.2 (s, C-6), 30.4 (s, C-5), 35.6 (s, C-7), 38.8 (s, C-4), 45.4 (s, C-1), 56.0 (t, *J*=20 Hz, C-3), 115.5–118.0 (m, CF_2), 119.0–124.7 (m, CF_2Cl); HRMS calcd for $C_9H_{10}ClF_4I$: 355.9452, found: 355.9464.

3.2.2. 3-*exo*-(Heptfluoro-propyl)-2-*endo*-iodobicyclo-[2.2.1]heptane (3an). Oil. IR (film): ν_{max} 2980 (C–H), 1340, 1230 (C–F), 1180, 1110, 930, 740, 650 (C–I) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24–1.26 (2H, m, H-7, H-5), 1.56–1.60 (1H, m, H-6), 1.61–1.75 (2H, m, H-5, H-7), 1.80–1.90 (1H, m, H-6), 2.20–2.28 (1H, m, H-3), 2.36 (1H, s, H-4), 2.42 (1H, s, H-1), 4.20–4.26 (1H, m, H-2); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −126.1 (2F, s, CF_2CF_3), −119.1 (2F, dd, *J*=1411.5, 277.8 Hz, $CHCF_2$), −81.5 (3F, t, *J*=10.4 Hz, CF_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 24.8 (s, C-2), 26.4 (s, C-6), 28.7 (s, C-5), 34.0 (s, C-7), 36.8 (s, C-4), 43.6 (s, C-1), 54.5 (t, *J*=20.1 Hz, C-3), 106.0–120.5 (m, $CF_2CF_2CF_3$); HRMS calcd for $C_{10}H_{10}F_7I$: 389.9716, found: 389.9720.

3.2.3. 3-*exo*-(Heptfluoroisopropyl)-2-*endo*-iodo-bicyclo-[2.2.1]heptane (3ao). Oil. IR (film): ν_{max} 2980 (C–H), 1300, 1220 (C–F), 1150, 1030, 970, 740, 650 (C–I) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25–1.40 (2H, m, H-5, H-7), 1.62–1.75 (3H, m, H-5, H-6, H-7), 1.80–2.00 (1H, m, H-6), 2.25–2.31 (1H, m, H-3), 2.41 (1H, s, H-4), 2.43 (1H, s, H-1), 4.30–4.50 (1H, m, H-2), ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −75.8 (6F, d, *J*=682.2 Hz, $(CF_3)_2$), −76.4 (1F, m, CF); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.5 (s, C-2), 28.7 (s, C-6), 31.3 (s, C-5), 35.3 (s, C-7), 39.1 (s, C-4), 46.1 (s, C-1), 55.6 (d, *J*=18.9 HZ, C-3), 92.1 (dm, *J*=206.1, 30.8 Hz, CF), 121.7 (ddd, *J*=576.0, 288.0, 28.9 Hz, $(CF_3)_2$); HRMS calcd for $C_{10}H_{10}F_7I$: 389.9716, found: 389.9717.

3.2.4. 3-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-2-*endo*-iodo-bicyclo[2.2.1]heptane (3ap). Oil. IR (film): ν_{max} 2980 (C–H), 1230 (C–F), 1080, 760, 720, 640 (C–I) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20–1.40 (2H, m, H-5, H-7), 1.50–1.68 (1H, m, H-6), 1.80–1.92 (2H, m, H-5, H-7), 2.35–2.40 (1H, m, H-3), 2.44 (1H, s, H-4), 2.49 (1H, s, H-1), 4.31–4.35 (1H, m, H-2); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −120.9 (4F, m, CF_2CF_2), −118.8 (2F, m $CHCF_2$), −68.8 (2F, m, CF_2Cl); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 26.7 (s, C-2), 28.2 (s, C-6), 30.4 (s, C-5), 35.7 (s, C-7), 38.6 (s, C-4), 45.3 (s, C-1), 56.4 (t, *J*=20.1 Hz, C-3), 110.0–125.2 (m, $(CF_2)_4$); HRMS calcd for $C_{11}H_{10}ClF_8I$: 455.9388, found: 455.9407.

3.2.5. 3-*exo*-(8-Chloro-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-hexadecafluorooctyl)-2-*endo*-iodo-bicyclo[2.2.1]heptane (3aq). White solid. Mp: 56–57 °C; IR (film): ν_{max} 2980 (C–H), 1220 (C–F), 1150, 840, 770, 670, 650 (C–I) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31–1.33 (2H, m, H-7, H-5), 1.60–1.65 (1H, m, H-6), 1.68–1.72 (2H, m, H-5, H-7), 1.80–1.90 (1H, m, H-6), 2.35–2.38 (1H, m, H-3), 2.44 (1H, s, H-4), 2.49 (1H, s, H-1), 4.30–4.33 (1H, m, H-2); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −122.7 (6F, m, 3×CF_2), −122.2 (2F, m, CF_2), −121.8 (2F, m, CF_2), −121.1 (2F, m, CF_2), −118.2 (2F, dd, *J*=1270.4, 282.3 Hz, $CHCF_2$), −69.0 (2F, m, CF_2Cl); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 26.0 (s, C-2), 27.5 (s, C-6), 29.7 (s, C-5), 35.0 (s, C-7), 37.9 (s, C-4), 44.6 (s, C-1), 57.7 (t, *J*=20.1 Hz, C-3), 108.7–124.2 (m, $(CF_2)_8$); HRMS calcd for $C_{15}H_{10}ClF_{16}$ (M−I): 529.0216, found: 529.0222.

3.2.6. 3-*exo*-Difluoro-(2-*endo*-iodo-bicyclo[2.2.1]hept-3-yl)-acetic acid ethyl ester (3ar). Oil. IR (film): ν_{max} 2980, 2900, 1770 (s, ester), 1450, 1310, 1080, 850, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25–1.31 (1H, m, H-7, H-5), 1.38 (3H, t, J=7.1 Hz, CH_3), 1.60–1.62 (1H, m, H-6), 1.63–1.65 (1H, m, H-5), 1.68–1.70 (1H, m, H-7), 1.75–1.85 (1H, m, H-5), 2.20–2.30 (1H, m, H-2), 2.35 (1H, s, H-1), 2.47 (1H, s, H-4), 4.20–4.40 (1H, m, H-3), 4.37 (2H, q, J=7.1 Hz, OCH_2); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −116.2 (dd, $J_{F,F}$=253.8 Hz, $J_{F,H}$=18.8 Hz, 1F), −110.1 (dd, $J_{F,F}$=253.8 Hz, $J_{F,H}$=14.1 Hz, 1F); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.6 (s, CH_3), 27.9 (s, C-6), 27.9 (s, C-2), 30.6 (s, C-5), 35.6 (s, C-7), 38.0 (s, C-4), 45.6 (s, C-1), 58.3 (t, C-3), 63.9 (s, OCH_2), 116.2 (t, CF_2), 164.3 (t, C=O); HRMS calcd for $C_{11}H_{15}F_2IO_2$: 344.0085, found: 344.0080.

3.3. Typical experimental procedure for the reaction of the norbornene (1b and 1c) with R_FI

Norbornene derivative **1b** or **1c** (10 mmol) and polyfluoroalkyl iodide **2p** (12 mmol) were dissolved in the solution of water (10 mL) and acetonitrile (10 mL). Sodium dithionite (3.7 g) and sodium bicarbonate (1.85 g) were added to the solution. The mixture was stirred at ambient temperature for 6 h. When the reaction was accomplished, the mixture was treated with water (ca. 50 mL). The mixture was extracted with ether of 3×20 mL. The combined organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After the evaporation of ether, the crude product was purified by column chromatography (PE–EA=40:1 for **1b** and 30:1 for **1c**) to give products **3bp** and **5bp** for **1b** or **5cp** and **6cp** for **1c**.

3.3.1. Bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid ethyl ester (1b).[8,9] ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (3H, t, J=7.1 Hz, CH_3), 1.20–1.26 (1H, m, H-7), 1.40–1.45 (2H, m, H-7, H-2), 1.88–1.92 (1H, m, H-3), 2.90 (1H, s, H-4), 2.90–2.95 (1H, m, H-2), 3.21 (1H, s, H-1), 4.09 (2H, q, J=7.1 Hz, CH_3CH_2), 5.93 (1H, q, J=3 Hz, H-5), 6.19 (1H, q, J=3.0 Hz, H-6).

3.3.2. Bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid-4,4-dimethyl-2-oxotetrahydrofuran-3-yl ester (1c).[10] White solid. Mp: 116.5–117 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.15 (3H, s, CH_3-a), 1.18 (3H, s, CH_3-b), 1.33 (1H, d, J=8.2 Hz, H-7), 1.47 (1H, s, H-7), 1.49 (1H, m, H-3), 1.95 (1H, m, H-3), 2.96 (1H, s, H-4), 3.16 (1H, m, H-2), 3.27 (1H, m, H-1), 4.04 (2H, dd, J=20.7, 9.0 Hz, H-5′), 5.33 (1H, s, H-3′), 5.91 (1H, dd, J=5.6, 2.8 Hz, H-5), 6.26 (1H, dd, J=5.6, 3.1 Hz, H-6).

3.3.3. 5-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-6-*endo*-iodo-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid ethyl ester (3bp). White solid. Mp: 39–41 °C; IR (film): ν_{max} 2980, 1720, 1200, 1140, 720, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.33 (3H, t, J=7.2 Hz, CH_3), 1.39 (1H, d, J=10.8 Hz, H-7a), 1.75 (1H, d, J=10.8 Hz, H-7s), 1.90–1.95 (1H, m, H-3x), 2.01 (1H, ddd, J=13.2, 5.6, 2.6 Hz, H-3n), 2.60 (1H, br s, H-4), 2.63–2.65 (1H, m, H-5), 2.97–3.00 (1H, m, H-2), 3.04 (1H, br s H-1), 4.10–4.20 (1H, m, CH_2O), 4.10–4.20 (1H, m, H-6), 4.25–4.28 (1H, m, CH_2O); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −121.9 (4F, m, 2×CF_2), −119.1 (2F, dd, J=2583, 282.3 Hz, CF_2), −68.8 (2F, m, CF_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.6 (s, CH_3), 16.3 (s, C-6), 32.2 (s, C-3), 39.5 (s, C-7), 39.6 (s, C-4), 46.0 (s, C-2), 47.7 (s, C-1), 55.2 (t, C-5), 61.7 (s, C–O), 109.6–125.1 (m, $(CF_2)_4$), 173.2 (s, C=O); HRMS calcd for $C_{14}H_{14}F_8ClO_2I$: 527.9599, found: 527.9594.

3.3.4. 6-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-5-*endo*-iodo-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid ethyl ester (5bp). Oil. IR (film): ν_{max} 2980, 1730, 1200, 1100, 740, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (3H, t, J=7.1 Hz, CH_3), 1.45 (1H, d, J=10.9 Hz, H-7a), 1.82 (1H, d, J=10.9 Hz, H-7s), 1.90–1.95 (1H, m, H-3x), 2.29 (1H, ddd, J=13.6, 5.8, 2.6 Hz, H-3n), 2.54 (1H, br s H-4), 2.65–2.68 (1H, m, H-6), 2.74 (1H, br s H-1), 2.80–2.84 (1H, m, H-2), 4.15–4.20 (2H, m, CH_2O), 4.32–4.34 (1H, m, H-5); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −120.9 (2F, m, CF_2), −120.8 (2F, dd, J=376.4, 282.3 Hz, CF_2), −118.1 (2F, dd, J=1882, 282.3 Hz, CF_2), −68.8 (2F, m, CF_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.7 (s, CH_3), 25.2 (s, C-5), 30.5 (s, C-3), 37.8 (s, C-7), 42.2 (s, C-1), 45.8 (s, C-4), 46.5 (s, C-2), 51.4 (t, C-6), 61.6 (s, C–O), 109.9–125.4 (m, $(CF_2)_4$), 173.3 (s, C=O); HRMS calcd for $C_{14}H_{14}F_8ClO_2I$: 527.9599, found: 527.9605.

3.3.5. 6-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-5-*endo*-iodo-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid-4′,4′-dimethyl-2′-oxo-tetrahydrofuran-3′-yl ester (5cp). White solid. Mp: 98.1–98.4 °C; IR (KBr): ν_{max} 2990, 1800 (γ-lactone), 1750, 1380, 1240 (C–F), 1180, 1120, 1080, 840, 740, 650, 560 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.11 (3H, s, CH_3, H-6′s), 1.15 (3H, s, CH_3, H-6a), 1.51 (1H, d, J=10.9 Hz, H-7a), 1.89 (1H, d, J=11.0 Hz, H-7s), 2.00–2.12 (1H, m, H-3x), 2.35–2.40 (1H, m, H-3n), 2.58 (1H, s, H-4), 2.70–2.77 (1H, m, H-6), 2.80 (2H, s, H-1), 3.00–3.10 (1H, m, H-2), 4.03 (1H, d, J=9.0 Hz, H-5′s), 4.06 (1H, d, J=9.0 Hz, H-5′a), 4.32–4.35 (1H, m, H-5), 5.42 (1H, s, H-3′); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −120.8 (2F, m, CF_2), −120.3 (2F, m, CF_2), −117.5 (2F, m, CF_2), −68.9 (2F, m, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.4 (s, C-6′s), 23.2 (s, C-6′a), 24.9 (s, C-5), 30.8 (s, C-3), 38.1 (s, C-7), 40.7 (s, C-4′), 42.4 (s, C-1), 45.9 (s, C-4), 46.3 (s, C-2), 50.1 (t, C-6), 76.3 (s, C-3′), 76.9 (s, C-5′), 108.3–123.0 (m, $(CF_2)_4$), 172.4 (s, C-8), 172.6 (s, C-2′), HRMS calcd for $C_{18}H_{18}ClF_8O_4$ (M−I): 485.0766, found: 485.0765.

3.3.6. 5-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid-4,4-dimethyl-2-oxo-tetrahydrofuran-3-yl ester (6cp). White solid. Mp: 143.6–144.6 °C; IR (KBr): ν_{max} 2980, 1780 (γ-lactone), 1760, 1460, 1380, 1200 (C–F), 1150, 1100, 990, 720, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.12 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.44 (1H, d, J=10.3 Hz, H-7a), 1.60–1.65 (1H, m, H-6), 1.69 (1H, d, J=10.3 Hz, H-7s), 1.75–1.79 (2H, m, H-6, H-3n), 1.81 (1H, td, J=11.4, 4.2 Hz, H-3x), 2.35–2.38 (1H, m, H-5), 2.70 (2H, s, H-1, H-4), 3.04–3.10 (1H, m, H-2), 4.05 (1H, d, J=9.1 Hz, H-5′), 4.08 (1H, d, J=9.1 Hz, H-5′), 5.42 (1H, s, H-3′); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −121.5 (4F, m, 2×CF_2), −117.1 (2F, dd, J=1091.8, 272.9 Hz, CF_2), −68.8 (2F, m, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.7 (s, CH3, C-6′s), 23.8 (S, CH3, C-6′a), 27.9 (s, C-6), 33.6 (s, C-3),

38.2 (s, C-4), 39.4 (s, C-7), 40.6 (s, C-1), 40.9 (s, C-4′), 43.4 (t, C-5), 45.2 (s, C-2), 75.7 (s, C-3′), 76.8 (s, C-5′), 109.7–125.2 (m, $(CF_2)_4$), 172.9 (s, C-8), 173.9 (s, C-2′).

3.4. The addition of norbornene-2-*endo*-carboxylic acid (1d and 1e) with R_FI

Compound **1d** or **1e** (5 mmol) was dissolved in 2 N NaOH aqueous solution (5 mL). Acetonitrile (15 mL), R_FI (6 mmol), sodium dithionite (2.2 g), and sodium bicarbonate (1.70 g) were then added to the solution. After stirring for 5–8 h the mixture was treated with water (ca. 50 mL). The mixture was extracted with ether of 3×20 mL. The combined organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. After the evaporation of ether, the crude product was purified by column chromatography (PE–EA=20:1) to give products **7dp–7ds**, **5dp–5ds**, and **6dp–6ds** for **1d** or **5em–5ep** and **7em–7ep** for **1e**.

3.4.1. 6-*exo*-Tridecafluorohexyl-5-*endo*-iodo-bicyclo-[2.2.1]heptane-2-*endo*-carboxylic acid (5ds). White solid. Mp: 83.4–84.0 °C; IR (KBr): ν_{max} 2500–3500, 3000, 1720, 1420, 1240, 1210, 1180, 1150, 1060, 700, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (1H, d, J=10.9 Hz, H-7a), 1.84 (1H, d, J=11.0 Hz, H-7s), 1.98 (1H, tm, J=12.4, H-3x), 2.27 (1H, dm, J=13.7 Hz, H-3n), 2.56 (1H, s, H-4), 2.76 (1H, dt, J=24.5, 7.4 Hz, H-6), 2.77 (1H, s, H-1), 2.80–2.92 (1H, m, H-2), 4.30–4.35 (1H, m, H-5); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −127.2 (2F, m, CF_2), −123.8 (2F, m, CF_2), −122.8 (2F, m, CF_2), −121.7 (2F, m, CF_2), −119.9 (1F, d, J=277.3 Hz, CF), −116.3 (1F, d, J=282.0 Hz, CF), −81.8 (3F, m, CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.8 (s, C-5), 30.4 (s, C-7), 37.7 (s, C-3), 42.0 (s, C-4), 45.8 (s, C-1), 46.1 (s, C-2), 50.5 (t, J=20 Hz, C-6), 109.1–125.4 (m, $(CF_2)_6CF_3$), 178.6 (s, C=O, C-8); HRMS calcd for $C_{14}H_{10}F_{13}IO_2$: 583.9518, found: 583.9512.

3.4.2. 6-*exo*-Heptafluoropropyl-5-*endo*-iodo-2-*exo*-methyl-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (5en). White solid. Mp: 165–166 °C; IR (KBr): ν_{max} 2500–3500, 1700, 1220, 1100, 740, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (3H, s, H-9), 1.50–1.55 (1H, m, H-3n), 1.74 (2H, s, H-7), 2.47 (1H, s, H-1), 2.51 (1H, s, H-4), 2.55 (1H, dt, H-6), 2.60–2.72 (1H, m, H-3x), 4.20–4.35 (1H, m, H-5); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −125.9 (2F, dd, J=442.3, 291.7 Hz, CF_2), −118.6 (2F, dd, J=1757.3, 284.7 Hz, CF_2), −81.4 (3F, t, J=11.3 Hz, CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 23.6 (s, C-5), 26.9 (s, C-8), 34.3 (s, C-7), 38.8 (s, C-3), 45.8 (s, C-4), 47.3 (s, C-1), 51.4 (s, C-2), 52.5 (t, J=20 Hz, C-6), 107.9–120.7 (m, $CF_2CF_2CF_3$), 182.2 (s, C=O); HRMS calcd for $C_{12}H_{12}F_7IO_2$: 447.9770, found: 447.9775.

3.4.3. 6-*exo*-Heptafluoroisopropyl-5-*endo*-iodo-2-*exo*-methyl-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (5eo). White solid. Mp: 114.9–115.3 °C; IR (KBr): ν_{max} 2500–3500, 1700, 1280, 1220, 1160, 1100, 740, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (3H, s, H-9), 1.53 (1H, ddd, J=13.7 Hz, J=4.4, 1.8 Hz, H-3n), 1.74 (2H, dd, H-7), 2.51 (2H, s, H-4, H-1), 2.57 (1H, dd, J_{HF}=8.2 Hz, J=6.0 Hz, H-6), 2.76 (1H, dd, J=13.9, 2.2 Hz, H-3x), 4.45–4.50 (1H, m, H-5); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −73.7 (3F, m, CF_3), −72.4 (3F, m, CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 25.8 (s, C-5), 27.2 (s, C-9), 34.0 (s, C-7), 39.4 (s, C-3), 46.7 (s, C-4), 47.9 (s, C-1), 51.7 (d, J=19 Hz, C-6), 51.8 (s, C-2), 91.7–94.2 (m, CF), 120.3–122.9 (m, 2×CF_3), 181.3 (s, C=O); HRMS calcd for $C_{12}H_{12}F_7IO_2$: 447.9770, found: 447.9815.

3.4.4. 6-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-5-*endo*-iodo-2-*exo*-methyl-bicyclo[2.2.1]-heptane-2-*endo*-carboxylic acid (5ep). White solid. Mp: 173.7–174.1 °C; IR (KBr): ν_{max} 2500–3500 (OH), 1700, 1300, 1180, 1130, 720, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (3H, s, H-8), 1.53 (1H, dq, J=14, 2 Hz, H-3), 1.74 (2H, s, H-7), 2.47 (1H, s, H-1), 2.51 (1H, s, H-4), 2.55–2.60 (1H, m, H-6), 2.68 (1H, dd, J=14, 2 Hz, H-1), 4.30–4.34 (1H, m, H-5); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −120.8 (4F, m, 2×CF_2), −117.7 (2F, dd, J=1552.7, 282.3 Hz, CF_2), −68.9 (2F, m, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 23.2 (s, C-5), 26.2 (s, C-8), 36.6 (s, C-7), 38.2 (s, C-3), 45.2 (s, C-4), 46.6 (s, C-1), 50.6 (s, C-2), 52.1 (t, C-6), 107.4–124.5 (m, 4×CF_2), 180.8 (s, C=O); HRMS calcd for $C_{13}H_{12}ClF_8IO_2$: 513.9443, found: 513.9445.

3.4.5. 5-*exo*-(8-Chloro-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-hexadecafluorooctyl)-bicyclo-[2.2.1]heptane-2-*endo*-carboxylic acid (6dq). White solid. Mp: 96.6–96.8 °C; IR (KBr): ν_{max} 3000–3600 (OH), 2980, 1720, 1450, 1400, 1220, 1160, 1110, 740, 560 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (1H, d, J=10.0 Hz, H-7a), 1.68 (1H, d, J=10.8 Hz, H-7s), 1.73 (3H, m, H-6, H-3n), 1.80 (1H, td, J=11.6, 4.2 Hz, H-3x), 2.30–2.34 (1H, m, H-5), 2.68 (1H, d, J=3.2 Hz, H-4), 2.72 (1H, s, H-1), 2.90 (1H, dt, J=10.8, 4.4 Hz, H-2), 11.10 (1H, br s OH); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −122.8 (6F, s, 3×CF_2), −122.2 (4F, m, 2×CF_2), −121.1 (2F, s, CF_2), −118.2 (1F, d, J=277.3 Hz, CF), −115.7 (1F, d, J=277.3 Hz, CF),−69.0 (2F, t, J=13.6 Hz, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.9 (s, C-6), 33.5 (s, C-3), 38.3 (s, C-4), 39.5 (s, C-7), 40.5 (s, C-1), 43.4 (t, J=20 Hz, C-5), 45.1 (s, C-2), 109.7–122.4 (m, 8×CF_2), 180.5 (s, C=O); HRMS calcd for $C_{16}H_{11}ClF_{16}IO_2$: 574.0192, found: 574.0187.

3.4.6. 5-*exo*-Tridecafluorohexyl-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (6ds). Oil. IR (KBr): ν_{max} 2500–3500 (OH), 2980, 1710, 1420, 1300, 1240, 1200, 1160, 1060, 740, 700, 560 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (1H, d, J=10.0 Hz, H-7a), 1.68 (1H, d, J=10.4 Hz, H-7s), 1.70–1.75 (1H, m, H-6, H-3n), 1.80 (1H, td, J=11.6, 4.2 Hz, H-3x), 2.30–2.36 (1H, m, H-5), 2.68 (1H, d, J=3.2 Hz, H-4), 2.72 (1H, s, H-1), 2.90 (1H, dt, J=11.2, 4.2 Hz, H-2), 11.10 (1H, br s OH); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −127.3 (2F, s, CF_2), −123.9 (2F, s, CF_2), −123.2 (2F, s, CF_2), −122.4 (2F, s, CF_2), −118.3 (1F, dd, J=277.3, 14.1 Hz, CF), −115.9 (1F, s, J=282.0, 14.1 Hz, CF),−81.9 (3F, t, J=9.4 Hz, CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 27.9 (s, C-6), 33.5 (s, C-3), 38.3 (s, C-4), 39.5 (s, C-7), 40.5 (s, C-1), 43.5 (t, J=20 Hz, C-5), 45.2 (s, C-2), 106.7–121.7 (m, C_6F_{13}), 180.5 (s, C=O); HRMS calcd for $C_{14}H_{11}F_{13}IO_2$: 458.0551, found: 458.0559.

3.4.7. 2-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-4-oxa-tricyclo[4.2.1.0^{3,7}]nonan-5-one (7dp). White solid.

Mp: 39.3–40.8 °C; IR (KBr): ν_{max} 2990, 1780 (γ-lactone), 1350, 1220 (C–F), 1180, 1140, 1010, 840, 760, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.66 (1H, d, *J*=11.8 Hz, H-8a), 1.81 (1H, d, *J*=13.4 Hz, H-9n), 2.07 (1H, d, *J*=13.4 Hz, H-8s), 2.10–2.20 (1H, m, H-9x), 2.37 (1H, t, *J*=18.2 Hz, H-2), 2.65 (1H, dd, *J*=11.3, 4.6 Hz, H-6), 2.86 (1H, s, H-1), 3.29 (1H, t, *J*=4.6 Hz, H-7), 5.00 (1H, d, *J*=4.8 Hz, H-3); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −122.0 (2F, m, CF_2), −121.0 (2F, dd, *J*=818.8, 282.4 Hz, CF_2), −114.4 (2F, dd, *J*=889.4, 282.4 Hz, CF_2), −69.0 (2F, dd, *J*=282.4, 188.2 Hz, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 36.0 (s, C-8), 36.2 (s, C-9), 38.0 (s, C-1), 39.0 (s, C-6), 46.6 (s, C-7), 52.0 (t, *J*=20 Hz, C-2), 80.6 (s, C-3), 110.0–125.0 (m, $(CF_2)_4$), 180.2 (s, C-5); HRMS calcd for $C_{12}H_9ClF_8O_2$: 372.0320, found: 372.0201.

3.4.8. 2-*exo*-(8-Chloro-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-hexadecafluorooctyl)-4-oxa-tricyclo[4.2.1.0^{3,7}]nonan-5-one (7dq). White solid. Mp: 113.5–114.3 °C; IR (KBr): ν_{max} 3000, 1780 (γ-lactone), 1350, 1220 (C–F), 1150, 1020, 840, 650, 550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.66 (1H, d, *J*=11.7 Hz, H-8a), 1.81 (1H, d, *J*=13.5 Hz, H-9n), 2.09–2.20 (2H, m, H-8s, H-9x), 2.37 (1H, t, *J*=18.0 Hz, H-2), 2.66 (1H, dd, *J*=11.2, 4.6 Hz, H-6), 2.86 (1H, s, H-1), 3.29 (1H, t, *J*=4.5 Hz, H-7), 5.00 (1H, d, *J*=4.8 Hz, H-3); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −122.65 (6F, m, 3×CF_2), −122.40 (4F, m, 2×CF_2), −121.12 (2F, dd, *J*=818.8, 282.4 Hz, CF_2), −114.30 (2F, dd, *J*=889.4, 282.4 Hz, CF_2), −69.06 (2F, m, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 35.3 (s, C-8), 35.6 (s, C-9), 37.3 (s, C-1), 38.3 (s, C-6), 46.0 (s, C-7), 51.4 (t, *J*=20 Hz, C-2), 80.1 (s, C-3), 106.8–124.1 (m, $(CF_2)_8$), 179.5 (s, C-5); HRMS calcd for $C_{16}H_9ClF_{16}O_2$: 572.0036, found: 572.0036.

3.4.9. 2-*exo*-Tridecafluorohexyl-4-oxa-tricyclo[4.2.1.0^{3,7}]-nonan-5-one (7ds). White solid. Mp: 84.6–85.2 °C; IR (KBr): ν_{max} 3000, 1780 (γ-lactone), 1350, 1240, 1210 (C–F), 1150, 1050, 1020, 980, 700, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.66 (1H, d, *J*=11.7 Hz, H-8a), 1.81 (1H, d, *J*=13.4 Hz, H-9n), 2.08 (1H, d, *J*=12.4 Hz, H-8s), 2.12 (1H, dd, *J*=13.7 Hz, H-9x), 2.37 (1H, t, *J*=18.1 Hz, H-2), 2.66 (1H, dd, *J*=11.3, 4.6 Hz, H-6), 2.86 (1H, s, H-6), 3.29 (1H, t, *J*=4.5 Hz, H-7), 5.00 (1H, d, *J*=4.8 Hz, H-3); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −127.2 (2F, dd, *J*=413.6, 282.0 Hz, CF_2), −123.8 (2F, dd, *J*=310.2, 188.0 Hz, CF_2), −122.8 (4F, m, 2×CF_2), −114.3 (2F, dd, *J*=813.1, 282.0 Hz, CF_2), −81.8 (3F, m, CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 34.8 (s, C-8), 35.1 (s, C-9), 36.8 (s, C-1), 37.8 (s, C-6), 45.5 (s, C-7), 50.9 (t, *J*=20 Hz, C-2), 79.6 (s, C-3), 108.4–125.0 (m, $(CF_2)_5CF_3$), 179.0 (s, C-5); HRMS calcd for $C_{14}H_9F_{13}O_2$: 456.0395, found: 456.0397.

3.4.10. 2-*exo*-Heptafluoroisopropyl-6-*exo*-methyl-4-oxa-tricyclo[4.2.1.0^{3,7}]nonan-5-one (7en). White solid. Mp: 65.0–65.4 °C; IR (KBr): ν_{max} 2980, 1780 (γ-lactone), 1350, 1230 (C–F), 1120, 1020, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, s, H-10), 1.63 (1H, dd, *J*=13.5, 4.0 Hz, H-9x), 1.72 (1H, d, *J*=11.8 Hz, H-8s), 1.90 (1H, dd, *J*=13.5, 2.2 Hz, H-9n), 2.07 (1H, dd, *J*=11.8, 1.6 Hz, H-8x), 2.31 (1H, dd, *J*=19.3, 17.1 Hz, H-2), 2.82 (1H, s, H-1), 2.89 (1H, d, *J*=5.0 Hz, H-7), 4.95 (1H, d, *J*=5.0 Hz, H-3); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −127.0 (2F, dd, *J*=705.8, 282.3 Hz, CF_2), −115.2 (2F, dd, *J*=1176.3, 282.3 Hz, CF_2), −81.5 (3F, t, *J*=10.4 Hz, CF_3); ^{13}C NMR (125.8 HMz, $CDCl_3$): δ 20.6 (s, C-10), 35.2 (s, C-9), 38.8 (s, C-1), 43.6 (s, C-6), 44.2 (s, C-8), 51.3 (t, C-2), 51.9 (s, C-7), 78.8 (s, C-3), 111.9–133.8 (m, $CF_2CF_2CF_3$), 182.0 (s, C-5); HRMS calcd for $C_{12}H_{11}F_7O_2$: 320.0647, found: 320.0699.

3.4.11. 2-*exo*-Heptafluoroisopropyl-6-*exo*-methyl-4-oxa-tricyclo[4.2.1.0^{3,7}]nonan-5-one (7eo). White solid. Mp: 96.6–96.7 °C; IR (KBr): ν_{max} 2980, 1800 (γ-lactone), 1300, 1220 (C–F), 1120, 1020, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (3H, s, H-10), 1.64 (1H, dd, *J*=13.6, 4.2 Hz, H-9x), 1.74 (1H, d, *J*=11.8 Hz, H-8s), 1.90 (1H, dd, *J*=13.6, 2.2 Hz, H-9n), 1.98 (1H, d, *J*=11.7, 1.6 Hz, H-8x), 2.18 (1H, d, *J*=33.3 Hz, H-2), 2.78 (1H, s, H-1), 2.88 (1H, d, *J*=4.8 Hz, H-7), 5.00–5.10 (1H, m, H-3); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −77.0 (3F, m, CF_3), −73.9 (3F, m, CF_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.8 (s, C-10), 34.6 (s, C-9), 39.8 (s, C-1), 42.8 (s, C-6), 43.8 (s, C-8), 49.1 (d, C-2), 51.1 (s, C-7), 78.9 (s, C-3), 111.9–133.8 (m, $CF(CF_3)_2$), 181.4 (s, C-5); HRMS calcd for $C_{12}H_{11}F_7O_2$: 320.0647, found: 320.0666.

3.4.12. 2-*exo*-(4-Chloro-1,1,2,2,3,3,4,4-octafluorobutyl)-6-*exo*-methyl-4-oxa-tricyclo-[4.2.1.0^{3,7}]nonan-5-one (7ep). White solid. Mp: 58.3–58.4 °C; IR (KBr): ν_{max} 2990, 1780 (γ-lactone), 1350, 1200 (C–F), 1120, 1080, 840, 700, 640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, s, H-10), 1.63 (1H, dd, *J*=13.4, 4.0 Hz, H-8a), 1.72 (1H, d, *J*=11.8 Hz, H-9), 1.89 (1H, dd, *J*=13.4, 2.2 Hz, H-8), 2.07 (1H, dd, *J*=11.8, 1.7 Hz, H-9), 2.32 (1H, dd, *J*=20.3, 16.1 Hz, H-2), 2.82 (1H, s, H-1), 2.89 (1H, d, *J*=5.0 Hz, H-7), 4.95 (1H, d, *J*=5.0 Hz, H-3); ^{19}F NMR (470.5 MHz, $CDCl_3$): δ −122.1 (2F, m, CF_2), −120.9 (2F, dd, *J*=846.9, 291.7 Hz, CF_2), −114.3 (2F, dd, *J*=964.5, 272.9 Hz, CF_2), −69.0 (2F, dd, *J*=296.4, 178.8 Hz, $ClCF_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.0 (s, C-10), 34.5 (s, C-9), 38.2 (s, C-1), 42.9 (s, C-6), 43.5 (s, C-8), 51.1 (t, C-2), 51.6 (s, C-7), 78.3 (s, C-3), 107.4–124.4 (m, $(CF_2)_4$), 181.4 (s, C-5); HRMS calcd for $C_{13}H_{11}ClF_8O_2$: 386.0320, found: 386.0336.

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Supplementary data

^1H NMR, ^{19}F NMR, ^{13}C NMR, and 2D NMR spectra for some new compounds; crystallographic information files are in CIF format for **5eo**, **5cp**, **6cp**, and **5ds**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.042.

References and notes

1. (a) Tiers, G. D. V. *J. Am. Chem. Soc.* **1960**, *82*, 5513; (b) Masutani, T.; Yamamoto, A. JP 278874, 2001; (c) Chen, Q. Y.; Yang, Z. Y. *J. Fluorine Chem.* **1988**, *39*, 217–226;

(d) Davis, C. R.; Barton, D. J.; Yang, Z. Y. *J. Fluorine Chem.* **1995**, *70*, 135–140; (e) Maria, L.; Marcial, M. M.; Adelina, V. *Tetrahedron* **2002**, *58*, 4061–4065; (f) Andrew, E. F. *J. Org. Chem.* **1985**, *50*, 3269–3274.

2. (a) Huang, W. Y.; Huang, B. N.; Hu, C. M. *J. Fluorine Chem.* **1983**, *23*, 193–204; (b) Huang, W. Y.; Huang, B. N. *Acta Chim. Sin.* **1984**, *42*, 1106–1108; (c) Huang, W. Y.; Wang, W.; Huang, B. N. *Acta Chim. Sin.* **1986**, *44*, 178–184.
3. (a) Huang, W. Y.; Wu, F. H. *Isr. J. Chem.* **1999**, *39*, 167–170; (b) Huang, W. Y.; Wu, F. H. *J. Fluorine Chem.* **1988**, *92*, 85–87; (c) Wu, F. H.; Huang, W. Y. *Youji Huaxue* **1997**, *17*, 106–125; (d) Zur, C.; Miethchen, R. *Eur. J. Org. Chem.* **1998**, *3*, 531–539; (e) Liu, J. T.; Sui, G. D.; Chen, G.; Huang, W. Y. *J. Fluorine Chem.* **1999**, *93*, 49–51.
4. (a) Bondar, N. F.; Golubeva, M. B.; Isaenya, L. P.; Konopiya, N. A.; Kuzmitsky, B. B.; Lyukin, G. S. *Eur. J. Med. Chim. Ther.* **2004**, *39*, 389–396; (b) Varela, J. A.; Pena, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* **2001**, *15*, 2395–2398; (c) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460–3462.
5. (a) Brace, N. O. *J. Org. Chem.* **1962**, *27*, 3027–3033; (b) Brace, N. O. *J. Org. Chem.* **1979**, *44*, 1964–1971; (c) Brace, N. O. *J. Fluorine Chem.* **2003**, *123*, 237–248.
6. Xiao, F. H.; Wu, F. H.; Shen, Y. J.; Zhou, L. F. *J. Fluorine Chem.* **2003**, *126*, 63–67.
7. Davies, D. I. *J. Chem. Soc. C* **1969**, 1585–1590.
8. (a) Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *33*, 2418–2419; (b) Wu, Y. L.; Zhang, J. L. *Acta Chim. Sin.* **1982**, *40*, 157–163.
9. Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095–3098.
10. (a) Nooy, C. D. V.; Rondestvedt, C. S., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 3583–3586; (b) Whitesides, G. M.; Kendall, P. E. *J. Org. Chem.* **1972**, *37*, 3718–3725.

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Studies on the reduction of the nitro group in 3-aryl-2-methylene-4-nitro-alkanoates afforded by the Baylis–Hillman adducts: synthesis of 4-aryl-3-methylene-2-pyrrolidinones and 3-(1-alkoxycarbonyl-vinyl)-1*H*-indole-2-carboxylates☆

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Abstract—The formation of substituted 2-pyrrolidinones and indoles by the reduction of the secondary nitro group in appropriate 3-aryl-2-methylene-4-nitroalkanoates afforded by Baylis–Hillman chemistry via different reducing agents is described. The 3-aryl-2-methylene-4-nitroalkanoate obtained from S_N2 nucleophilic reaction between the acetate of Baylis–Hillman adducts and ethyl nitroacetate upon reduction with indium–HCl furnishes a mixture of cis and trans substituted phenyl-3-methylene-2-pyrrolidinones. In contrast, similar reductions of analogous substrates derived from nitroethane stereoselectively furnished only the trans substituted phenyl-3-methylene-2-pyrrolidinones. On the other hand the $SnCl_2\cdot 2H_2O$-promoted reductions of substrates derived from nitro ethylacetate give oxime derivatives while the ones obtained from nitroethane yield a mixture of *cis* and *trans* 4-aryl-3-methylene-2-pyrrolidinones. Alternatively, the $SnCl_2\cdot 2H_2O$-promoted reduction of substituted 2-nitrophenyl-2-methylene-alkanoate furnished from ethyl nitroacetate yield 3-(1-alkoxycarbonyl-vinyl)-1*H*-indole-2-carboxylate while indium-promoted reaction of this substrate leads to a complex mixture. Analogous reactions with $SnCl_2\cdot 2H_2O$ of substituted 2-nitrophenyl-2-methylene-alkanoate obtained from nitroethane yield 4-alkyl-3-methylene-2-quinolones in moderate yields.

1. Introduction

Nitrogen-heterocycles are structural units of several natural products and represent compounds of pharmacological significance. Their prevalence and medicinal utility perhaps are the major driving force for attracting organic and medicinal chemists to formulate their diverse syntheses via novel, convenient, and efficient methods. The propensity of the Baylis–Hillman reaction to afford products with multifunctional backbone, which could be tailored further, has found profound application toward the construction of an array of useful synthons, heterocycles, and natural products.[1] In order to expand the synthetic utility of this reaction, for the last couple of years our group has been involved in a program to carry out convenient and efficient syntheses of diverse heterocyclic systems utilizing the Baylis–Hillman chemistry.[2,3] Based on our previous work in this area and on the results reported by Janecki et al.[4] and Yus et al.[5] we reasoned that the 3-aryl-2-methylene-4-nitroalkanoates, obtained by S_N2 nucleophilic reaction of the acetate of the Baylis–Hillman products with nitroalkanes, should in principle offer opportunities for constructing highly substituted 3-methylene-2-pyrrolidinones provided the nitro group is chemoselectively reduced and the resulting amine could be made to undergo intramolecular cyclization. Recently, Kim and co-workers have reported the synthesis of 2-amino-2,3-dihydrobenzofuran derivatives via oxidation of similar nitro compounds afforded via S_N2' reaction of ethyl nitroacetate on the allyl bromides afforded by the Baylis–Hillman adducts.[6] In addition, several groups have accomplished the facile synthesis of different heterocyclic compounds employing nitro derivatives afforded via Baylis–Hillman adducts.[7,8] In order to investigate our envisaged strategy, we have carried out selective reduction of the nitro group in nitroalkanoates with In to afford the 4-aryl-3-methylene-2-pyrrolidinones in good yields. Interestingly, we have observed that reduction of the secondary nitro group via $SnCl_2\cdot 2H_2O$ in these compounds occurs only partially leading to the oxime derivatives. This unique observation has led us to formulate a simple synthesis of substituted indoles from the nitroalkanoates obtained from the Baylis–Hillman adducts of 2-nitrobenzaldehyde. The details of the results of our studies are described herein.

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Keywords: Baylis–Hillman; Nitroalkanoate; 2-Pyrrolidinone; 1*H*-Indole-2-carboxylate; Indium; $SnCl_2\cdot 2H_2O$.

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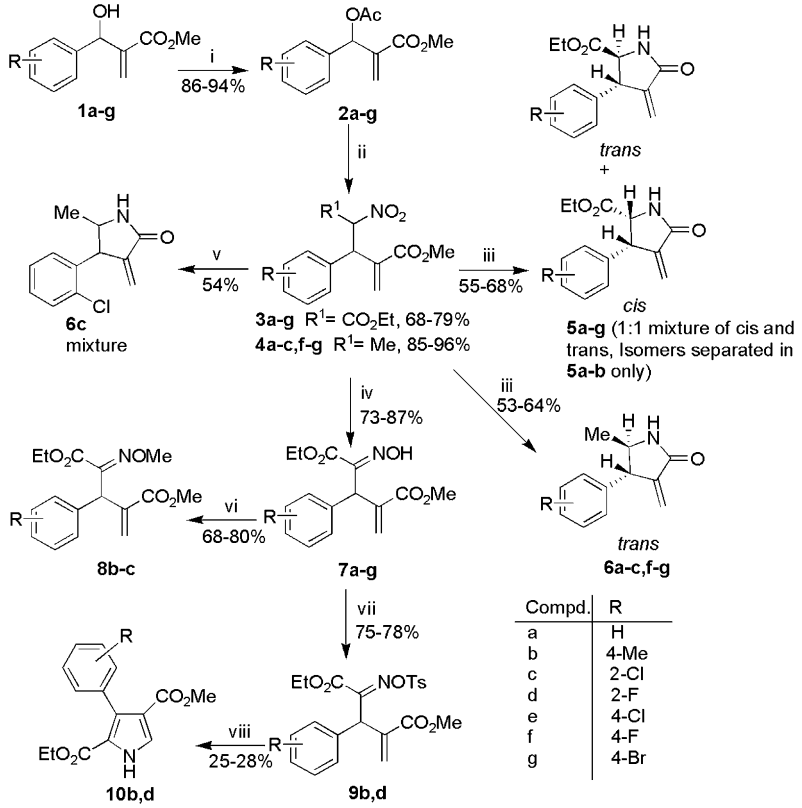
2. Results and discussion

The preparation of the starting materials in our synthetic sequence (Scheme 1), the acetates **2a–g**, was accomplished by acetylating Baylis–Hillman adducts **1a–g**, which in turn were afforded from substituted benzaldehydes following the literature procedure.[9] The S_N2 nucleophilic substitution of the acetate **2a–g** with ethyl nitroacetate in the presence of DABCO in a THF–water system yielded the nitroalkanoates **3a–g** in 4–6 h in 68–79% yields as diastereoisomeric mixtures. This observation is in contrast to the reactions carried out by Kim et al. who have reported the synthesis of similar derivatives after 2 days.[10] In the next step the products **3a–g** were subjected to chemoselective reduction of the nitro group without affecting the double bond. In a model reaction, the reduction of the nitro group of compound **3b** was examined with metallic In, Sn, Zn, and Fe in the presence of HCl or AcOH and $SnCl_2\cdot 2H_2O$.[11] The selection of these reagents was based on the fact that they are inexpensive, readily available, and do not require any elaborate reaction conditions. Results of our evaluation in this direction are illustrated in Table 1. The highest yield of the expected substituted 3-methylene-2-pyrrolidinone **4b** was achieved when the reaction was carried out in the presence of In using HCl in a THF–H_2O system at room temperature. Consequently all the substituted 3-methylene-2-pyrrolidinones **5a–g** were prepared by reducing the required nitro compound with In in the presence of aq HCl. In all cases these compounds were obtained as a mixture of cis and trans products. Our attempts to separate these diastereoisomers via silica gel column chromatography were successful with compounds **5a** and **5b**, whereas for compounds **5c–g** these could not be separated. The NOESY experiment of the polar isomer of compound **5b** indicated it to be the trans isomer.

Table 1. Results of optimization study for the synthesis of 4-aryl-3-methylene-2-pyrrolidinones

Entry	Metal/ metal salt	Condition	Product	Yield (%)
1	In	In/HCl in THF–H_2O for 2 h at rt	**5b**	64
2	Sn	Sn/HCl for 2 h at reflux	**5b**	42
3	Zn	Zn/HCl in EtOH for 24 h at rt	**5b**	39
4	Fe	Fe/AcOH for 2 h at rt	**5b**	45
5	$SnCl_2\cdot 2H_2O$	$SnCl_2\cdot 2H_2O$ in MeOH for 2 h at reflux	**7b**	78

However the reduction of compound **3b** with $SnCl_2\cdot 2H_2O$, instead of yielding the expected pyrrolidinone **5b**, gave the oxime **7b** (entry 5, Table 1). This was found to be the general course of reaction as substrates **3a–g** also furnished the corresponding oximes **7a–g** when subjected to the $SnCl_2$ reductive conditions. The spectroscopic data supported the structure assignments. Further support for the assigned structures of the oximes was made on the basis of an alternate synthesis. It is reported in the literature that the tin complexes generated from $SnCl_2\cdot 2H_2O$ in the presence of thiophenol and triethylamine reduces secondary aliphatic nitro compound to the corresponding oxime.[12] On the basis of this report, the compound **3a** was treated with $SnCl_2\cdot 2H_2O$, thiophenol, and triethylamine to yield a product, which was similar in all respect to the oxime **7a**. As would be expected,



Scheme 1. Reagents and conditions: (i) AcCl, Pyridine, CH_2Cl_2, rt, 3 h; (ii) DABCO, $R^1CH_2NO_2$, THF–H_2O, rt, 4–7 h; (iii) In, HCl, THF–H_2O, rt, 2 h; (iv) $SnCl_2\cdot 2H_2O$, MeOH, reflux, 1.5 h; (v) $SnCl_2\cdot 2H_2O$, MeOH, reflux, 24 h; (vi) MeI, Ag_2O, neat, reflux, 1 h; (vii) TsCl, Et_3N, CH_2Cl_2, rt, 3 h; and (viii) DBU, CH_2Cl_2, rt, 330 min.

the methylation of the oximes **7b**, **c** using methyl iodide in the presence of silver oxide furnished the methyl derivatives **8b**, **c**.[13] Although, the $SnCl_2\cdot 2H_2O$-promoted reduction of nitroalkenes to the corresponding oximes is documented,[14] the ability of $SnCl_2\cdot 2H_2O$ alone to transform the secondary aliphatic nitro compound to the oxime derivative is unreported.

The next phase of the study was aimed at determining the driving force responsible for the formation of the oximes. One possibility was the presence of the carboethoxy group on the α-carbon of the nitroalkane derivative as illustrated in Figure 1. In order to validate this concept experimentally, the S_N2 reaction of acetates **2a**–**c**, **f**, **g** with nitroethane in the presence of DABCO in a THF–H_2O system to afford products **4a**–**c**, **f**, **g** was accomplished. The nitro group in compound **4c** in the presence of $SnCl_2\cdot 2H_2O$ underwent reduction followed by cyclization to give 3-methylene-2-pyrrolidinones **6c** as a diastereoisomeric mixture, although the reaction took more than 24 h for completion. This supported our assumption that the presence of carboethoxy group was responsible for the formation of the oxime probably by the formation of an oximino intermediate. In order to establish that oxime was not the intermediate for the pyrrolidinone, in a model reaction the oxime **7c** was treated with $SnCl_2\cdot 2H_2O$ for more than 24 h. But this reaction failed indicating that the presence of the ester moiety stabilizes the oximes. Nevertheless, the reduction of the nitro group in compounds **4a**–**c**,**f**, **g** in the presence of In was complete in 2 h in a highly diastereoselective fashion to furnish the trans isomer of 4-aryl-5-methyl-3-methylene-2-pyrrolidinones **6a**–**c**, **f**, **g** exclusively in 53–64% yields.

Of particular relevance to **7**, it has been very recently reported that oximes obtained from α-aryl ketones can be transformed to indoles by an intermediate azirine in two steps.[15] In order to investigate such possibility with the oxime **7** generated during the present study, compounds **7b**, **d** were treated with tosyl chloride in the presence of triethylamine in dichloromethane at room temperature to yield the corresponding tosyl derivatives **9b**, **d**. Reaction of compounds **9b**, **d** with DBU in dichloromethane gave a complex mixture of products. The column chromatography of this mixture led to isolation of a pure product in low yield, the structure of which was established as substituted pyrroles **10a**, **d**. The formation of the pyrroles can be explained on the basis of the mechanism as shown in Figure 2.

Having demonstrated the utility of substrates such as **3a**–**g** and **4a**–**c**, **f**, **g** for the generation of the 3-methylene-2-pyrrolidinone system and oximes via selective reduction, we decided to explore the synthetic utility of similar substrates derived from 2-nitrophenyl benzaldehyde, such as **11a**–**c** (Scheme 2) for the following reasons. It is well established that the Baylis–Hillman derivatives obtained from 2-nitrobenzaldehyde and acrylates, upon reduction of the nitro moiety to amine invariably results in the formation of quinoline derivatives through an in situ intramolecular cyclization between the amino group on the phenyl ring and the ester group of the side chain.[16] However, in view of the findings of the present study, if compounds **11a**–**c** and **12** are reduced in the presence of $SnCl_2\cdot 2H_2O$, the aromatic nitro group will be chemoselectively reduced to an amino group, which will then compete for the two ester moieties for the intramolecular cyclization. Consequently compound **11a** was synthesized and reacted with $SnCl_2\cdot 2H_2O$ in methanol under reflux conditions. This reaction proceeded smoothly to be completed in 1.5 h to give a product, the structure of which was established as substituted 3-(1-methoxycarbonyl-vinyl)-1*H*-indole-2-carboxylic acid ethyl ester **14a** (Scheme 2). Subsequently other analogs **11b**, **c** and **12** were prepared and subjected to reaction with $SnCl_2\cdot 2H_2O$.

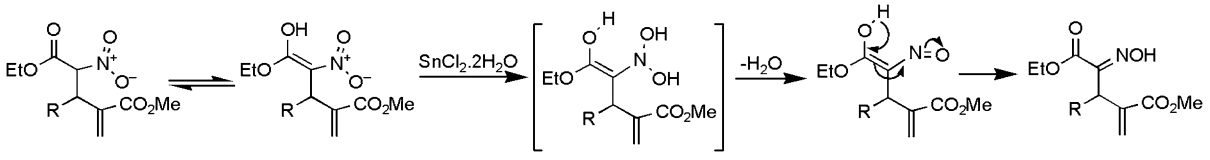


Figure 1. Mechanism for the formation of oximes.

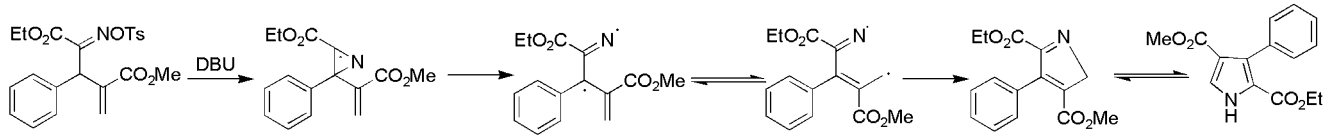
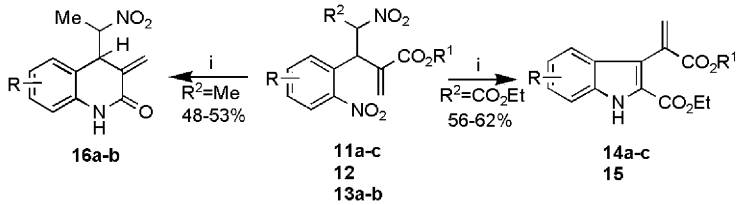


Figure 2. Mechanism for the formation of pyrroles.



Compd.	R	R^1
11a	H	Me
11b	3,4-OCH_2O	Me
11c	5-Cl	Me
12	H	Et
13a	H	Me
13b	5-Cl	Me

Scheme 2. Reagents and conditions: (i) $SnCl_2\cdot 2H_2O$, MeOH, reflux, 1.5–2 h.

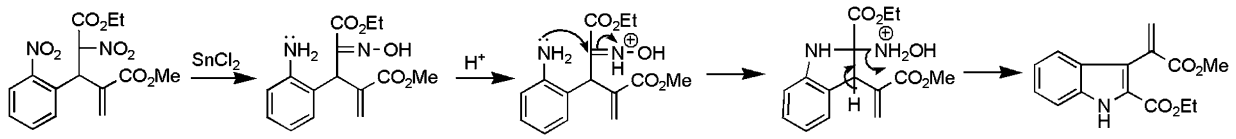


Figure 3. Mechanism for the formation of indole derivatives.

All these substrates afforded the respective indole derivatives **14b**, **c** and **15** indicating the general nature of this reaction and implying that this transformation invariably eliminates the aliphatic nitro group, presumably after reduction to the oxime. The expected mechanism for the formation of the indole derivative is shown in Figure 3. Unlike compounds **11** and **12**, compounds **13a**, **b** upon reduction in the presence of $SnCl_2 \cdot 2H_2O$ yielded the corresponding substituted 2-quinolones **16a**, **b** in 2 h in moderate yields. The formation of **16** was understandable since it has been previously observed that the aliphatic nitro group is reduced to an amino group only when the reaction is prolonged beyond 24 h. These results provoked us to evaluate the reactions of compounds **11** and **13a**, **b** with In in the presence of HCl in aqueous medium. However, this reaction led to a complex mixture, which could not be purified in all cases.

3. Conclusions

In summary, we demonstrated the scope of 3-aryl-2-methylene-4-nitroalkanoates obtained from the Baylis–Hillman chemistry for the generation of 4-aryl-3-methylene-2-pyrrolidinones and 3-(1-alkoxycarbonyl-vinyl)-1*H*-indole-2-carboxylates by the reduction of the secondary nitro group using different reducing conditions. The mechanistic details to account for the formation of different heterocyclic systems have also been proposed. All the synthetic achievements described herein were operationally simple and diversity oriented. We believe that the lactam and the indole derivatives described in this paper will serve as useful building blocks for the synthesis of compounds belonging to these classes.

4. Experimental

4.1. General

Melting points were recorded on a hot stage melting point apparatus and are uncorrected. The IR spectra were recorded on a FTIR spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on 200 MHz or 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded as FAB or LCMS having ES probe. The HRMS spectra were recorded as EIHRMS. All the solvents and chemicals were used as procured from the suppliers. The compounds **3a–g**, **4a–c**, **f**, **g**, **5c–g**, **11a–c**, **12**, **13a**, **b**, and **16a**, **b** were obtained as diastereoisomeric mixtures. All yields indicated herein are the isolated yields after column chromatography.

4.2. General procedure for the preparation of compounds 3a–g and 4a–c, f, g

To the stirred solution of appropriate compound from **2a–g** (1.0 equiv) in THF–H_2O (10 mL for approx. 1.5 g of compound, 50:50, v/v) was added DABCO (1.5 equiv) at room temperature and the reaction was allowed to continue for 20 min. Thereafter ethyl nitroacetate or nitroethane (1.2 equiv) was added to the reaction mixture and the reaction was allowed to proceed at room temperature for 4 h. The THF was removed from the reaction mixture via rotary evaporation and the residue was diluted with water (100 mL) and extracted with EtOAc (3×40 mL). The organic layers were pooled, washed with brine (50 mL), dried (anhyd Na_2SO_4), and evaporated to yield a residue, which was purified via silica gel chromatography employing hexane–EtOAc (80:20, v/v) to afford products as oils or solids.

4.2.1. 2-Methylene-4-nitro-3-phenylpentanedioic acid 5-ethyl ester 1-methyl ester (3a). Colorless oil 77% (1.0 g); ν_{max} (Neat) 1723 (CO_2Et), 1751 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.97 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.27 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.71 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.99 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.26 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.89 (d, 1H, J=12.0 Hz, CHAr), 4.95 (d, 1H, J=12.0 Hz, CHAr), 5.80 (s, 1H, =CH), 5.86 (s, 1H, =CH), 5.87 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.05 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.34 (s, 1H, =CH), 6.38 (s, 1H, =CH), 7.28–7.30 (m, 10H, 2×5ArH); mass (ES+) m/z 330.0 (M^++Na); Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.38; H, 5.76; N, 4.64.

4.2.2. 2-Methylene-4-nitro-3-*p*-tolylpentanedioic acid 5-ethyl ester 1-methyl ester (3b). Colorless oil 68% (1.4 g); ν_{max} (Neat) 1724 (CO_2Et), 1751 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.00 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.27 (t, 3H, J=7.1 Hz, CH_3CH_2), 2.30 (s, 6H, 2×$ArCH_3$), 3.70 (s, 3H, CO_2CH_3), 3.72 (s, 3H, CO_2CH_3), 4.01 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.25 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.85 (d, 1H, J=12.0 Hz, CHAr), 4.91 (d, 1H, J=12.0 Hz, CHAr), 5.79 (s, 1H, =CH), 5.83 (s, 1H, =CH), 5.82 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.02 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.32 (s, 1H, =CH), 6.35 (s, 1H, =CH), 7.08–7.22 (m, 8H, 2×4ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=13.9, 14.2, 21.4, 48.2, 48.6, 52.6, 63.3, 63.6, 90.1, 90.7, 125.6, 127.5, 128.2, 129.0, 129.9, 130.0, 132.2, 133.5, 138.3, 138.4, 139.0, 163.5, 163.7, 166.1; mass (ES+) m/z 344.0 (M^++Na); Anal. Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.48; H, 5.82; N, 4.26.

4.2.3. 3-(2-Chlorophenyl)-2-methylene-4-nitro-pentanedioic acid 5-ethyl ester 1-methyl ester (3c). Colorless oil 79% (2.5 g); ν_{max} (Neat) 1724 (CO_2Et), 1751 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.03 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.27 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.71 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.05 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.24 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.34 (d, 1H, J=12.1 Hz, CHAr), 5.40 (d, 1H, J=12.1 Hz, CHAr), 5.98 (s, 1H, =CH), 5.99 (s, 1H, =CH), 6.14

(d, 1H, J=12.1 Hz, $CHCO_2Et$), 6.31 (d, 1H, J=12.1 Hz, $CHCO_2Et$), 6.39 (s, 1H, =CH), 6.42 (s, 1H, =CH), 7.20–7.25 (m, 4H, ArH), 7.36–7.41 (m, 3H, ArH), 7.48–7.52 (m, 1H, ArH); mass (FAB+) m/z 342 (M^++1); Anal. Calcd for $C_{15}H_{16}ClNO_6$: C, 52.72; H, 4.72; N, 4.14. Found: C, 53.08; H, 4.93; N, 4.24.

4.2.4. 3-(2-Fluorophenyl)-2-methylene-4-nitro-pentanedioic acid 5-ethyl ester 1-methyl ester (3d). Colorless oil 73% (1.4 g from 1.5 g); ν_{max} (Neat) 1724 (CO_2Et), 1753 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.02 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.28 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.72 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 4.04 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.28 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.10–5.19 (m, 2H, CHAr), 5.92 (d, 1H, J=1.0 Hz, =CH), 5.95 (s, 1H, =CH), 6.08 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.23 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.38 (s, 1H, =CH), 6.41 (s, 1H, =CH), 7.03–7.39 (m, 8H, 2×4ArH); mass (ES+) m/z 326.4 (M^++1); Anal. Calcd for $C_{15}H_{16}FNO_6$: C, 55.38; H, 4.96; N, 4.31. Found: C, 55.89; H, 5.21; N, 4.52.

4.2.5. 3-(4-Chlorophenyl)-2-methylene-4-nitro-pentanedioic acid 5-ethyl ester 1-methyl ester (3e). Pale yellow solid 78% (1.23 g), mp 96–98 °C; ν_{max} (KBr) 1724 (CO_2Et), 1751 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.04 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.26 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.71 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.04 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.26 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.86 (d, 1H, J=12.1 Hz, CHAr), 4.91 (d, 1H, J=12.1 Hz, CHAr), 5.81 (s, 1H, =CH), 5.86 (s, 1H, =CH), 5.87 (d, 1H, J=12.1 Hz, $CHCO_2Et$), 6.02 (d, 1H, J=12.1 Hz, $CHCO_2Et$), 6.35 (s, 1H, =CH), 6.38 (s, 1H, =CH), 7.24–7.38 (m, 8H, 2×4ArH); mass (FAB+) m/z 342 (M^++1); Anal. Calcd for $C_{15}H_{16}ClNO_6$: C, 52.72; H, 4.72; N, 4.14. Found: C, 53.28; H, 4.54; N, 4.35.

4.2.6. 3-(4-Fluorophenyl)-2-methylene-4-nitro-pentanedioic acid 5-ethyl ester 1-methyl ester (3f). Pale yellow solid 72% (1.56 g), mp 82–84 °C; ν_{max} (KBr) 1723 (CO_2Et), 1750 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.00 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.27 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.72 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.03 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.26 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.85 (d, 1H, J=12.0 Hz, CHAr), 4.98 (d, 1H, J=12.0 Hz, CHAr), 5.80 (s, 1H, =CH), 5.86 (s, 1H, =CH), 5.87 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.01 (d, 1H, J=12.0 Hz, $CHCO_3Et$), 6.35 (s, 1H, =CH), 6.38 (s, 1H, =CH), 6.96–7.04 (m, 4H, 2×2ArH), 7.21–7.30 (m, 4H, 2×2ArH); mass (FAB+) m/z 326 (M^++1); Anal. Calcd for $C_{15}H_{16}FNO_6$: C, 55.38; H, 4.96; N, 4.31. Found: C, 55.98; H, 5.11; N, 4.52.

4.2.7. 3-(4-Bromophenyl)-2-methylene-4-nitro-pentanedioic acid 5-ethyl ester 1-methyl ester (3g). Colorless oil 72% (1.5 g); ν_{max} (Neat) 1721 (CO_2Et), 1750 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.04 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.26 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.71 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.05 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.26 (q, 2H, J=7.1 Hz, CH_2CH_3), 4.85 (d, 1H, J=12.0 Hz, CHAr), 4.89 (d, 1H, J=12.0 Hz, CHAr), 5.81 (s, 1H, =CH), 5.86 (s, 1H, =CH), 5.87 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.02 (d, 1H, J=12.0 Hz, $CHCO_2Et$), 6.34 (s, 1H, =CH), 6.38 (s, 1H, =CH), 7.14–7.22 (m, 4H, 2×2ArH), 7.42–7.57 (m, 4H, 2×2ArH); mass (ES+) m/z 386.2 (M^++1); Anal. Calcd for $C_{15}H_{16}BrNO_6$: C, 46.65; H, 4.18; N, 3.63. Found: C, 46.98; H, 4.25; N, 3.71.

4.2.8. 2-Methylene-4-nitro-3-phenylpentanoic acid methyl ester (4a). Colorless oil 96% (2.35 g); ν_{max} (Neat) 1721 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.40 (d, 3H, J=6.6 Hz, CH_3CH), 1.61 (d, 3H, J=6.6 Hz, CH_3CH), 3.73 (s, 6H, CO_2CH_3), 4.37 (d, 1H, J=12.0 Hz, CHAr), 4.44 (d, 1H, J=12.0 Hz, CHAr), 5.19–5.28 (m, 1H, $CHCH_3$), 5.42–5.60 (m, 1H, $CHCH_3$), 5.81 (s, 1H, =CH), 5.91 (d, 1H, J=1.8 Hz, =CH), 6.34 (s, 1H, =CH), 6.36 (s, 1H, =CH), 7.28–7.35 (m, 10H, 2×5ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=19.3, 19.5, 51.5, 52.5, 52.7, 85.5, 86.0, 125.2, 128.0, 128.2, 129.1, 129.4, 131.1, 137.8, 139.6, 139.9, 166.3, 166.6; mass (ES+) m/z 272.1 (M^++Na); Anal. Calcd for $C_{13}H_{15}F_3NO_5$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.97; H, 5.99; N, 5.53.

4.2.9. 2-(2-Nitro-1-*p*-tolylpropyl)-acrylic acid methyl ester (4b). Colorless oil 88% (0.73 g); ν_{max} (Neat) 1721 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.42 (d, 3H, J=6.0 Hz, CH_3CH), 1.62 (d, 3H, J=6.0 Hz, CH_3CH), 2.30 (s, 3H, $ArCH_3$), 2.34 (s, 3H, $ArCH_3$), 3.70 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 4.36 (d, 1H, J=12.0 Hz, CHAr), 4.43 (d, 1H, J=12.0 Hz, CHAr), 5.19–5.25 (m, 1H, $CHCH_3$), 5.44–5.50 (m, 1H, $CHCH_3$), 5.81 (s, 1H, =CH), 5.91 (d, 1H, J=3.0 Hz, =CH), 6.34 (s, 1H, =CH), 6.36 (s, 1H, =CH), 7.09–7.20 (m, 8H, 2×2ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=19.3, 19.5, 21.4, 51.2, 52.4, 52.5, 52.6, 85.6, 86.1, 125.0, 127.7, 128.3, 129.0, 130.1, 134.0, 134.8, 137.9, 138.1, 139.8, 140.0, 166.4, 166.7; mass (ES+) m/z 286.1 (M^++Na); Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.23; H, 6.89; N, 5.21.

4.2.10. 3-(2-Chlorophenyl)-2-methylene-4-nitro-pentanoic acid methyl ester (4c). Pale yellow oil 85% (1.8 g); ν_{max} (Neat) 1726 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.45 (d, 3H, J=6.6 Hz, CH_3CH), 1.63 (d, 3H, J=6.6 Hz, CH_3CH), 3.68 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 4.93 (d, 1H, J=11.0 Hz, CHAr), 5.08 (d, 1H, J=11.0 Hz, CHAr), 5.21–5.28 (m, 1H, $CHCH_3$), 5.64–5.73 (m, 1H, $CHCH_3$), 5.95 (s, 1H, =CH), 5.97 (s, 1H, =CH), 6.39 (s, 1H, =CH), 6.41 (s, 1H, =CH), 7.17–7.25 (m, 4H, 2×2ArH), 7.33–7.37 (m, 2H, 2×1ArH), 7.53–7.58 (m, 2H, 2×1ArH); mass (ES+) m/z 284.6 (M^++1); Anal. Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; N, 4.94. Found: C, 54.78; H, 5.08; N, 4.86.

4.2.11. 3-(4-Fluorophenyl)-2-methylene-4-nitro-pentanoic acid methyl ester (4f). Pale yellow oil 85% (1.5 g); ν_{max} (Neat) 1721 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.40 (d, 3H, J=6.6 Hz, CH_3CH), 1.61 (d, 3H, J=6.6 Hz, CH_3CH), 3.70 (s, 3H, CO_2CH_3), 3.74 (s, 3H, CO_2CH_3), 4.35 (d, 1H, J=11.2 Hz, CHAr), 4.43 (d, 1H, J=11.2 Hz, CHAr), 5.18–5.25 (m, 1H, $CHCH_3$), 5.40–5.49 (m, 1H, $CHCH_3$), 5.83 (s, 1H, =CH), 5.90 (s, 1H, =CH), 6.34 (s, 1H, =CH), 6.37 (s, 1H, =CH), 6.92–7.06 (m, 4H, 2×2ArH), 7.21–7.30 (m, 4H, 2×2ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=19.3, 19.5, 51.5, 52.5, 52.7, 85.5,

86.0, 125.2, 128.0, 128.2, 129.1, 129.4, 131.1, 137.8, 139.6, 139.9, 166.3, 166.6; mass (FAB+) *m/z* 268 (M^++1); Anal. Calcd for $C_{13}H_{14}FNO_4$: C, 58.42; H, 5.28; N, 5.24. Found: C, 58.01; H, 5.52; N, 5.20.

4.2.12. 3-(4-Bromophenyl)-2-methylene-4-nitro-pentanoic acid methyl ester (4g). Colorless oil 92% (2.4 g); ν_{max} (Neat) 1725 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.41 (d, 3H, *J*=6.6 Hz, C*H*$_3$CH), 1.61 (d, 3H, *J*=6.6 Hz, C*H*$_3$CH), 3.68 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 4.32 (d, 1H, *J*=11.5 Hz, CHAr), 4.41 (d, 1H, *J*=11.5 Hz, CHAr), 5.14–5.22 (m, 1H, C*H*CH$_3$), 5.41–5.47 (m, 1H, C*H*CH$_3$), 5.81 (s, 1H, =CH), 5.90 (s, 1H, =CH), 6.35 (s, 1H, =CH), 6.37 (s, 1H, =CH), 7.13–7.19 (m, 4H, 2×2ArH), 7.39–7.48 (m, 4H, 2×2ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=19.3, 19.4, 51.1, 52.4, 52.6, 52.8, 85.0, 85.7, 122.3, 125.6, 128.3, 130.1, 130.8, 132.3, 132.5, 136.1, 136.9, 139.1, 139.4, 166.1, 166.4; mass (FAB+) *m/z* 328 (M^++1); Anal. Calcd for $C_{13}H_{14}BrNO_4$: C, 47.58; H, 4.30; N, 4.27. Found: C, 46.71; H, 4.53; N, 4.41.

4.3. General procedure for the reduction of 3a–g and 4a–c, f, g with indium

To the stirred solution of appropriate compound from **3a–g** and **4a–c**, **f**, **g** (1.0 equiv) in THF–H_2O (5 mL for approx. 0.5 g of compound, 1:3, v/v) was added In powder (4.0 equiv) followed by 6 N HCl (6.0 equiv). The reaction was allowed to proceed at room temperature and was monitored via TLC. On completion, approximately 2 h, THF was evaporated and the pH of the residue was made alkaline with saturated $NaHCO_3$ solution. The solution was diluted with EtOAc and filtered through a bed of Celite. The filtrate was then extracted with EtOAc (3×25 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography over silica gel using hexane–EtOAc (30:70, v/v) to yield products **5a–g** and **6a–c**, **f**, **g**.

4.3.1. 4-Methylene-5-oxo-3-phenylpyrrolidine-2-carboxylic acid ethyl ester (5a)-(*cis*). Total yield 68% (0.54 g) as a white solid, mp 122–124 °C; ν_{max} (KBr) 1692 (CONH), 1746 (CO_2Et), 3400 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.27 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 4.18–4.27 (m, 4H, C*H*$_2$CH$_3$, CHAr and $CHCO_2Et$), 5.26 (s, 1H, =CH), 6.22 (s, 1H, =CH), 6.56 (s, 1H, NH), 7.29–7.38 (m, 5H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.5, 48.9, 61.9, 62.3, 119.8, 128.0, 128.4, 129.4, 141.7, 142.9, 170.1, 171.3; mass (ES+) *m/z* 246.1 (M^++1); HREIMS calculated for $C_{14}H_{15}NO_3$ 245.1052, found, 245.1052.

4.3.2. 4-Methylene-5-oxo-3-phenylpyrrolidine-2-carboxylic acid ethyl ester (5a)-(*trans*). Total yield 68% (0.54 g) as a white solid, mp 160–162 °C; ν_{max} (KBr) 1692 (CONH), 1738 (CO_2Et), 3445 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.83 (t, 3H, *J*=6.0 Hz, C*H*$_3$CH$_2$), 3.57–3.63 (m, 1H, CHAr), 3.75–3.81 (m, 1H, $CHCO_2Et$), 4.52–4.61 (m, 2H, C*H*$_2$CH$_3$), 5.33 (s, 1H, =CH), 6.26 (s, 1H, =CH), 6.76 (s, 1H, NH), 7.18–7.29 (m, 5H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=13.9, 48.2, 59.7, 61.6, 119.6, 128.2, 128.9, 129.4, 138.6, 142.3, 170.4, 171.4; mass (ES+) *m/z* 246.1 (M^++1); HREIMS calculated for $C_{14}H_{15}NO_3$ 245.1052, found, 245.1052.

4.3.3. 4-Methylene-5-oxo-3-*p*-tolylpyrrolidine-2-carboxylic acid ethyl ester (5b)-(*cis*). Total yield 64% (0.268 g) as a white solid, mp 123–125 °C; ν_{max} (KBr) 1695 (CONH), 1738 (CO_2Et), 3445 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.28 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 2.35 (s, 3H, ArCH$_3$), 4.15–4.27 (m, 4H, C*H*$_2$CH$_3$, CHAr and $CHCO_2Et$), 5.25 (d, 1H, *J*=1.8 Hz, =CH), 6.20 (d, 1H, *J*=2.6 Hz, =CH), 6.62 (s, 1H, NH), 7.17 (s, 4H, ArH); mass (FAB+) *m/z* 260 (M^++1); HREIMS calculated for $C_{15}H_{17}NO_3$ 259.1208, found, 259.1208.

4.3.4. 4-Methylene-5-oxo-3-*p*-tolylpyrrolidine-2-carboxylic acid ethyl ester (5b)-(*trans*). Total yield 64% (0.268 g) as a white solid, mp 162–164 °C; ν_{max} (KBr) 1695 (CONH), 1738 (CO_2Et), 3442 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.85 (t, 3H, *J*=7.3 Hz, C*H*$_3$CH$_2$), 2.30 (s, 3H, ArCH$_3$), 3.57–3.64 (m, 1H, CHAr), 3.74–3.77 (m, 1H, CHAr), 4.46–4.54 (m, 2H, C*H*$_2$CH$_3$), 5.29 (d, 1H, *J*=3.0 Hz, =CH), 6.22 (d, 1H, *J*=3.0 Hz, =CH), 6.57 (s, 1H, NH), 7.04–7.10 (m, 4H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=13.9, 21.4, 48.0, 59.8, 61.6, 119.4, 129.3, 129.5, 135.5, 137.9, 142.4, 170.4, 171.4; mass (FAB+) *m/z* 260 (M^++1); HREIMS calculated for $C_{15}H_{17}NO_3$ 259.1208, found, 259.1208.

4.3.5. 3-(2-Chlorophenyl)-4-methylene-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (5c). White solid 56% (0.37 g), mp 110–112 °C; ν_{max} (KBr) 1710 (CONH), 1728 (CO_2Et), 3412 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.82 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 1.27 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 3.49–3.62 (m, 1H, CH*H*CH$_3$), 3.67–3.79 (m, 1H, C*H*HCH$_3$), 4.17–4.31 (m, 2H, C*H*$_2$CH$_3$), 4.68 (d, 2H, *J*=9.0 Hz, 2×CHAr), 5.13 (d, 2H, *J*=9.0 Hz, 2×$CHCO_2Et$), 5.23 (s, 1H, =CH), 5.35 (s, 1H, =CH), 6.16 (d, 1H, *J*=2.4 Hz, =CH), 6.31 (d, 1H, *J*=2.6 Hz, =CH), 6.69 (br s, 2H, 2×1NH), 7.20–7.27 (m, 6H, 2×3ArH), 7.40–7.41 (m, 2H, 2×1ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=13.9, 14.4, 44.2, 46.1, 58.2, 60.5, 61.1, 62.4, 119.1, 119.7, 127.4, 127.9, 129.4, 129.7, 130.0, 130.3, 130.4, 134.2, 135.9, 138.8, 140.9, 142.1, 170.0, 170.4, 171.2; mass (ES+) *m/z* 280.1 (M^++1), 282.1 (M^++3); HREIMS calculated for $C_{14}H_{14}ClNO_3$ 279.0662, found, 279.0664.

4.3.6. 3-(2-Fluorophenyl)-4-methylene-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (5d). White solid 57% (0.12 g), mp 105–107 °C; ν_{max} (KBr) 1704 (CONH), 1743 (CO_2Et), 3332 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.85 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 1.29 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 3.48–3.61 (m, 2H, C*H*$_2$CH$_3$), 4.23–4.39 (m, 5H, C*H*$_2$CH$_3$, 2×CHAr and $CHCO_2Et$), 4.71–4.84 (m, 1H, $CHCO_2Et$), 5.28 (d, 1H, *J*=1.3 Hz, =CH), 5.36 (d, 1H, *J*=0.6 Hz, =CH), 6.20 (d, 1H, *J*=1.1 Hz, =CH), 6.38 (d, 1H, *J*=1.0 Hz, =CH), 7.04–7.30 (m, 8H, 2×4ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=13.9, 14.4, 40.0, 43.0, 58.8, 60.8, 61.7, 61.9, 115.3, 115.7, 116.1, 116.5, 119.7, 119.8, 124.7, 125.0, 125.1, 125.7, 129.8, 130.0, 130.2, 130.3, 138.9, 140.8, 142.0, 169.9, 170.2, 171.0, 171.5; mass (ES+) *m/z* 264.3 (M^++1); HREIMS calculated for $C_{14}H_{14}FNO_3$ 263.0958, found, 263.0954.

4.3.7. 3-(4-Chlorophenyl)-4-methylene-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (5e). White solid 61% (0.174 g), mp 106–108 °C; ν_{max} (KBr) 1713 (CONH),

1748 (CO_2Et), 3445 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.88 (t, 3H, J=7.2 Hz, CH_3CH_2), 1.29 (t, 3H, J=7.2 Hz, CH_3CH_2), 3.51–3.92 (m, 2H, 2×CHAr), 4.14–4.27 (m, 4H, 2×CH_2CH_3), 4.40–4.68 (m, 2H, 2×$CHCO_2Et$), 5.25 (d, 1H, J=1.9 Hz, =CH), 5.31 (d, 1H, J=1.6 Hz, =CH), 6.22 (d, 1H, J=2.9 Hz, =CH), 6.26 (d, 1H, J=2.6 Hz, =CH), 6.98 (s, 2H, 2×NH), 7.11–7.37 (m, 8H, 2×4ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.0, 14.5, 47.5, 48.2, 59.6, 61.8, 61.9, 62.6, 119.5, 120.1, 129.0, 129.6, 129.7, 129.8, 130.8, 133.9, 134.2, 137.1, 138.9, 140.0, 141.9, 142.6, 169.9, 170.1, 171.0, 171.3; mass (ES+) m/z 280.1 (M^++1); HREIMS calculated for $C_{14}H_{14}ClNO_3$ 279.0662, found, 279.0658.

4.3.8. 3-(4-Fluorophenyl)-4-methylene-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (5f). White solid 63% (0.315 g), mp 114–116 °C; ν_{max} (KBr) 1705 (CONH), 1743 (CO_2Et), 3214 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.21–1.39 (m, 6H, 2×CH_3CH_2), 3.70–3.98 (m, 2H, 2×CHAr), 4.05–4.38 (m, 6H, 2×CH_2CH_3 and 2×$CHCO_2Et$), 5.27–5.32 (m, 2H, 2×=CH), 6.23–6.28 (m, 2H, 2×=CH), 7.01–7.43 (m, 8H, 2×4ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.0, 14.5, 44.3, 45.8, 62.0, 62.6, 66.2, 67.9, 115.7, 116.1, 116.2, 116.7, 120.0, 120.3, 129.8, 130.0, 131.5, 131.7, 136.1, 139.2, 139.7, 142.0, 160.3, 164.7, 165.2, 168.2, 169.8; mass (FAB+) m/z 264 (M^++1); HREIMS calculated for $C_{14}H_{14}FNO_3$ 263.0958, found, 263.0958.

4.3.9. 3-(4-Bromophenyl)-4-methylene-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (5g). White solid 55% (0.21 g), mp 159–161 °C; ν_{max} (KBr) 1712 (CONH), 1750 (CO_2Et), 3430 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.88 (t, 3H, J=7.1 Hz, CH_3CH_2), 1.29 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.60–3.91 (m, 2H, 2×CHAr), 4.21–4.27 (m, 4H, 2×CH_2CH_3), 4.38–4.60 (m, 2H, 2×$CHCO_2Et$), 5.25 (d, 1H, J=2.0 Hz, =CH), 5.30 (d, 1H, J=1.7 Hz, =CH), 6.22 (d, 1H, J=2.9 Hz, =CH), 6.25 (d, 1H, J=2.5 Hz, =CH), 6.66 (br s, 2H, 2×NH), 7.06–7.57 (m, 8H, 2×4ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.0, 14.5, 47.5, 48.3, 59.4, 61.8, 62.4, 120.0, 122.0, 122.3, 130.2, 131.1, 131.5, 132.0, 132.5, 134.4, 137.7, 140.6, 141.9, 142.6, 170.2, 171.1, 171.9; mass (ES+) m/z 324.1 (M^++1), 326.1 (M^++3); HREIMS calculated for $C_{14}H_{14}BrNO_3$ 323.0157, found, 323.0155.

4.3.10. 5-Methyl-3-methylene-4-phenylpyrrolidin-2-one (6a). An off white solid 62% (0.144 g), mp 118–120 °C; ν_{max} (KBr) 1674 (CONH), 3413 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.45 (d, 3H, J=6.2 Hz, CH_3CH), 3.55–3.58 (m, 1H, CHAr), 3.82–3.88 (m, 1H, $CHCH_3$), 5.13 (d, 1H, J=2.4 Hz, =CH), 6.09 (d, 1H, J=3.0 Hz, =CH), 7.19 (m, 5H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=18.4, 51.2, 63.0, 117.8, 128.0, 128.8, 129.3, 140.4, 163.6; mass (ES+) 188.2 (M^++1); HREIMS calculated for $C_{12}H_{13}NO$ 187.0997, found, 187.0991.

4.3.11. 5-Methyl-3-methylene-4-*p*-tolylpyrrolidin-2-one (6b). Brown solid 60% (0.107 g), mp 155–157 °C; ν_{max} (KBr) 1686 (CONH), 3431 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.32 (d, 3H, J=6.0 Hz, CH_3CH), 2.35 (s, 3H, $ArCH_3$), 3.54 (d, 1H, J=2.7 Hz, CHAr), 3.68 (t, 1H, J=6.1 Hz, $CHCH_3$), 5.12 (s, 1H, =CH), 6.08 (d, 1H, J=2.7 Hz, =CH), 6.92 (s, 1H, NH), 7.11 (d, 2H, J=8.0 Hz, ArH), 7.17 (d, 2H, J=8.0 Hz, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=18.3, 21.4, 50.9, 62.9, 117.9, 128.7, 130.0, 137.3, 137.7, 163.8; mass (ES+) 188.2 (M^++1); HREIMS calculated for $C_{13}H_{15}NO$ 201.1155, found, 201.1148.

4.3.12. 4-(2-Chlorophenyl)-5-methyl-3-methylenepyrrolidin-2-one (6c). Brown solid 58% (0.09 g), mp 117–119 °C; ν_{max} (KBr) 1684 (CONH), 3433 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=0.76 (d, 3H, J=6.0 Hz, CH_3CH), 4.20–4.25 (m, 1H, CHAr), 4.85–4.90 (m, 1H, $CHCH_3$), 5.33 (d, 1H, J=3.0 Hz, =CH), 6.30 (d, 1H, J=3.0 Hz, =CH), 7.18–7.25 (m, 2H, ArH), 7.38–7.44 (m, 2H, ArH); mass (ES+) 222.1 (M^++1); HREIMS calculated for $C_{12}H_{12}ClNO$ 221.0607, found, 221.0606.

4.3.13. 4-(2-Chlorophenyl)-5-methyl-3-methylenepyrrolidin-2-one (6c) (diastereoisomeric mixture as obtained from reaction of $SnCl_2\cdot 2H_2O$). Brown solid 54% (0.13 g), mp 96–98 °C; ν_{max} (KBr) 1670 (CONH), 3415 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=0.77 (d, 3H, J=6.5 Hz, CH_3CH), 0.89 (d, 3H, J=6.5 Hz, CH_3CH), 3.60–3.65 (m, 1H, CHAr), 4.22–3.29 (m, 1H, CHAr), 4.35–4.39 (m, 1H, $CHCH_3$), 4.87–4.92 (m, 1H, $CHCH_3$), 5.26 (s, 1H, =CH), 5.37 (d, 1H, J=2.5 Hz, =CH), 6.14 (s, 1H, =CH), 6.34 (d, 1H, J=2.5 Hz, =CH), 6.96 (br s, 2H, 2×NH), 7.17–7.27 (m, 6H, 2×3ArH), 7.33–7.45 (m, 2H, 2×1ArH); mass (FAB+) 222 (M^++1); HREIMS calculated for $C_{12}H_{12}ClNO$ 221.0607, found, 221.0608.

4.3.14. 4-(4-Fluoro-phenyl)-5-methyl-3-methylenepyrrolidin-2-one (6f). White solid 53% (0.13 g), mp 162–164 °C; ν_{max} (KBr) 1667 (CONH), 3413 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.45 (d, 3H, J=6.2 Hz, CH_3CH), 3.54–3.57 (m, 1H, CHAr), 3.75–3.84 (m, 1H, $CHCH_3$), 5.12 (d, 1H, J=2.3 Hz, =CH), 6.08 (d, 1H, J=2.8 Hz, =CH), 6.99–7.08 (m, 2H, ArH), 7.14–7.21 (m, 2H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=18.3, 50.5, 63.1, 116.1, 116.5, 118.0, 130.2, 130.4, 131.4, 136.1, 141.8, 165.0; mass (ES+) m/z 206.1 (M^++1); HREIMS calculated for $C_{12}H_{12}FNO$ 205.0903, found, 205.0905.

4.3.15. 4-(4-Bromophenyl)-5-methyl-3-methylenepyrrolidin-2-one (6g). Yellow oil 64% (0.23 g); ν_{max} (Neat) 1688 (CONH), 3427 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.44 (d, 3H, J=6.2 Hz, CH_3CH), 3.53–3.58 (m, 1H, CHAr), 3.76–3.86 (m, 1H, $CHCH_3$), 5.13 (d, 1H, J=2.4 Hz, =CH), 6.07 (d, 1H, J=2.9 Hz, =CH), 7.08 (d, 2H, J=8.4 Hz, ArH), 7.48 (d, 2H, J=8.4 Hz, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=18.5, 51.2, 62.8, 117.9, 128.9, 130.2, 137.3, 137.9, 164.5; mass (ES+) m/z 266.0 (M^++1); HREIMS calculated for $C_{12}H_{12}BrNO$ 265.0102, found, 265.0108.

4.4. General procedure for reduction of compounds 3a–g with $SnCl_2\cdot 2H_2O$

To the solution of compounds from **3a–g** (1.0 equiv) in methanol (10 mL) was added $SnCl_2\cdot 2H_2O$ (5.0 equiv) and the reaction mixture was heated at reflux with stirring at 80 °C for 1.5 h in a nitrogen atmosphere. On completion, methanol was evaporated and the residue was made alkaline with saturated $NaHCO_3$ and then EtOAc (100 mL) was added. The suspension was passed through a bed of Celite

and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried (Na_2SO_4), and concentrated to afford a residue, which was purified by silica gel chromatography using hexane–EtOAc (90:10, v/v) or (20:80, v/v) as eluent to yield products **7a–g** as oils.

4.4.1. 2-Hydroxyimino-4-methylene-3-phenylpentanedioic acid 1-ethyl ester 5-methyl ester (7a). Pale yellow oil 73% (0.83 g); ν_{max} (Neat) 1630 (C=N), 1735 (CO_2Me and CO_2Et), 3425 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.26 (t, 3H, J=7.2 Hz, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.21 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.32 (d, 1H, J=2.1 Hz, =CH), 5.48 (s, 1H, CHAr), 6.35 (s, 1H, =CH), 7.31 (s, 5H, ArH), 9.20 (br s, 1H, OH); mass (ES+) m/z 291.9 (M^++1); HREIMS calculated for $C_{15}H_{17}NO_5$ 291.1107, found, 291.1110.

4.4.2. 2-Hydroxyimino-4-methylene-3-*p*-tolylpentanedioic acid 1-ethyl ester 5-methyl ester (7b). 78% (1.48 g); ν_{max} (Neat) 1631 (C=N), 1731 (CO_2Me and CO_2Et), 3425 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ=1.19–1.30 (m, 3H, CH_3CH_2), 2.33 (s, 3H, $ArCH_3$), 3.75 (s, 3H, CO_2CH_3), 4.07–4.28 (m, 2H, CH_2CH_3), 5.32 (d, 1H, J=1.2 Hz, =CH), 5.42 (s, 1H, CHAr), 6.33 (d, 1H, J=1.2 Hz, =CH), 7.13 (d, 2H, J=8.2 Hz, ArH), 7.20 (d, 2H, J=8.2 Hz, ArH), 9.20 (br s, 1H, OH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.2, 21.5, 45.1, 52.5, 62.2, 126.9, 129.8, 134.2, 137.4, 137.4, 140.4, 151.5, 163.6, 167.5; mass (FAB+) m/z 306 (M^++1); HREIMS calculated for $C_{16}H_{19}NO_5$ 305.1263, found, 305.1249.

4.4.3. 3-(2-Chlorophenyl)-2-hydroxyimino-4-methylenepentanedioic acid 1-ethyl ester 5-methyl ester (7c). Colorless oil 79% (0.45 g); ν_{max} (Neat) 1627 (C=N), 1726 (CO_2Et and CO_2Me), 3497 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.27–1.29 (m, 3H, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.11–4.28 (m, 2H, CH_2CH_3), 5.29 (s, 1H, =CH), 5.86 (s, 1H, CHAr), 6.40 (s, 1H, =CH), 7.20–7.34 (m, 3H, ArH), 7.38–7.41 (m, 1H, ArH), 9.21 (br s, 1H, OH); mass (FAB+) m/z 326 (M^++1); HREIMS calculated for $C_{15}H_{16}ClNO_5$ 325.0717, found, 325.0717.

4.4.4. 3-(2-Fluorophenyl)-2-hydroxyimino-4-methylenepentanedioic acid 1-ethyl ester 5-methyl ester (7d). Colorless oil 77% (0.73 g); ν_{max} (Neat) 1630 (C=N), 1724 (CO_2Et and CO_2Me), 3452 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.26 (t, 3H, J=7.0 Hz, CH_3CH_2), 3.76 (s, 3H, CO_2CH_3), 4.24 (q, 2H, J=7.0 Hz, CH_2CH_3), 5.31 (s, 1H, =CH), 5.77 (s, 1H, CHAr), 6.38 (s, 1H, =CH), 7.01–7.10 (m, 2H, ArH), 7.14–7.32 (m, 2H, ArH), 9.26 (br s, 1H, OH); mass (ES+) m/z 310.1 (M^++1); HREIMS calculated for $C_{15}H_{16}FNO_5$ 309.1013, found, 309.1015.

4.4.5. 3-(4-Chlorophenyl)-2-hydroxyimino-4-methylenepentanedioic acid 1-ethyl ester 5-methyl ester (7e). Colorless oil 75% (0.47 g); ν_{max} (Neat) 1627 (C=N), 1722 (CO_2Et and CO_2Me), 3341 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.26 (t, 3H, J=7.2 Hz, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.07–4.29 (m, 2H, CH_2CH_3), 5.33 (d, 1H, J=1.8 Hz, =CH), 5.45 (s, 1H, CHAr), 6.36 (d, 1H, J=1.6 Hz, =CH), 7.22–7.33 (m, 4H, ArH), 9.28 (br s, 1H, OH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.2, 44.8, 52.6, 62.4, 127.2, 129.2, 131.3, 133.7, 135.8, 139.7, 151.3, 163.3, 167.3; mass (FAB+) m/z 326; HREIMS calculated for $C_{15}H_{16}ClNO_5$ 325.0717, found, 325.0718.

4.4.6. 3-(4-Fluorophenyl)-2-hydroxyimino-4-methylenepentanedioic acid 1-ethyl ester 5-methyl ester (7f). Colorless oil 87% (0.24 g); ν_{max} (Neat) 1628 (C=N), 1722 (CO_2Et and CO_2Me), 3367 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.27 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.23 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.32 (d, 1H, J=1.6 Hz, =CH), 5.45 (s, 1H, CHAr), 6.35 (d, 1H, J=1.6 Hz, =CH), 6.97–7.09 (m, 2H, ArH), 7.29–7.33 (m, 2H, ArH), 9.35 (br s, 1H, OH); mass (ES+) m/z 310.0; HREIMS calculated for $C_{15}H_{16}FNO_5$ 309.1013, found, 309.1016.

4.4.7. 3-(4-Bromophenyl)-2-hydroxyimino-4-methylenepentanedioic acid 1-ethyl ester 5-methyl ester (7g). Pale yellow oil 73% (0.7 g from 1.0 g); ν_{max} (Neat) 1633 (C=N), 1722 (CO_2Et and CO_2Me), 3450 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.27 (t, 3H, J=7.2 Hz, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.23 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.34 (d, 1H, J=1.9 Hz, =CH), 5.43 (s, 1H, CHAr), 6.37 (d, 1H, J=1.6 Hz, =CH), 7.19 (d, 2H, J=8.4 Hz, ArH), 7.45 (d, 2H, J=8.4 Hz, ArH), 9.26 (br s, 1H, OH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.3, 44.8, 52.7, 62.4, 127.3, 131.7, 132.2, 141.8, 144.6, 152.2, 164.3, 166.7; mass (ES+) m/z 370.2 (M^++1); HREIMS calculated for $C_{15}H_{16}BrNO_5$ 369.0212, found, 369.0210.

4.5. Reaction of 3a with $Sn(SPh)_2$ complex

To a stirred solution of $SnCl_2\cdot 2H_2O$ (0.81 g, 3.61 mmol) in MeCN (5 mL), PhSH (1.12 mL, 12.1 mmol) and Et_3N (1.67 mL, 12.1 mmol) were added at room temperature. Subsequently a solution of compound **3a** (0.74 g, 2.25 mmol) in MeCN (2 mL) was added and the reaction was allowed to continue for 30 min. Thereafter, the reaction mixture was concentrated and the residue was purified by column chromatography over silica gel using hexane–EtOAc (90:10, v/v) as an eluent to give compound (0.42 g) (60%) **7a** as a pale yellow oil.

4.6. General procedure for the preparation of methyl derivatives 8b, c

To the flask charged with oxime **7b** or **7c** (1.0 equiv) and Ag_2O (1.0 equiv) was added MeI (5 mL for approx. 0.3 g substrate) with stirring at room temperature. After the initial exothermic reaction has subsided, the reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and filtered through a bed of Celite with the help of $CHCl_3$. The combined filtrates were evaporated and the residue was purified via silica gel column chromatography. Elution with hexane–EtOAc (90:10, v/v) gave pure **8b** or **8c**.

4.6.1. 2-Methoxyimino-4-methylene-3-*p*-tolylpentanedioic acid 1-ethyl ester 5-methyl ester (8b). Pale yellow oil 80% (0.25 g); ν_{max} (Neat) 1625 (C=N), 1735 (CO_2Me and CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.25 (t, 3H, J=7.1 Hz, CH_3CH_2), 2.32 (s, 3H, $ArCH_3$), 3.74 (s, 3H, CO_2CH_3), 3.98 (s, 3H, NCH_3), 4.23 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.32 (d, 1H, J=1.5 Hz, =CH), 5.39 (s, 1H, CHAr), 6.30 (s, 1H, =CH), 7.12 (s, 4H, ArH); mass

(FAB+) *m/z* 320 (M^++1); EIHRMS calculated for $C_{17}H_{21}NO_5$ 319.1420, found, 319.1421.

4.6.2. 3-(2-Chlorophenyl)-2-methoxyimino-4-methylene-pentanedioic acid 1-ethyl ester 5-methyl ester (8c). Colorless oil 68% (0.05 g); ν_{max} (Neat) 1627 (C=N), 1728 (CO_2Et and CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.24 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 3.74 (s, 3H, CO_2CH_3), 3.97 (s, 3H, NCH_3), 4.23 (q, 2H, *J*=7.1 Hz, CH$_2$CH$_3$), 5.29 (d, 1H, *J*=1.5 Hz, =CH), 5.80 (s, 1H, CHAr), 6.37 (s, 1H, =CH), 7.18–7.25 (m, 3H, ArH), 7.37–7.40 (m, 1H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.4, 43.4, 52.6, 62.3, 63.8, 127.3, 129.0, 130.0, 130.6, 134.7, 135.8, 138.2, 151.1, 163.4, 167.0; mass (FAB+) *m/z* 340 (M^++1); HREIMS calculated for $C_{16}H_{18}ClNO_5$ 339.0871, found, 339.0868.

4.7. General procedure for the preparation of tosyl derivatives 9b, d

To the stirred solution of appropriate oxime from **7b**, **d** (1.0 equiv) in dry dichloromethane (10 mL) was added Et_3N (1.5 mmol). The reaction mixture was brought to 0 °C via ice-bath and to it was added tosyl chloride (1.1 equiv) and the reaction was continued for 2 h at room temperature. Thereafter, the mixture was extracted with water and dichloromethane. The organic layer was separated, dried (Na_2SO_4), and evaporated to dryness to yield the crude product, which was purified by silica gel column chromatography using hexane–EtOAc (80:20, v/v) to yield pure products.

4.7.1. 2-Tosyloxyimino-4-methylene-3-*p*-tolylpentanedioic acid 1-ethyl ester 5-methyl ester (9b). Yellow oil 75% (0.61 g); ν_{max} (Neat) 1628 (C=N), 1732 (CO_2Et and CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.25 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 2.34 (s, 3H, ArCH$_3$), 2.44 (s, 3H, ArCH$_3$), 3.69 (s, 3H, CO_2CH_3), 4.17 (q, 2H, *J*=7.2 Hz, CH$_2$CH$_3$), 5.35 (two s merged, 2H, CHAr and =CH), 6.37 (s, 1H, =CH), 7.09 (s, 4H, ArH), 7.27 (d, 2H, *J*=8.0 Hz, ArH), 7.69 (d, 2H, *J*=8.0 Hz, ArH); mass (ES+) *m/z* 460.2 (M^++1); HREIMS calculated for $C_{23}H_{25}NO_7S$ 459.1352, found, 459.1364.

4.7.2. 3-(4-Fluorophenyl)-2-hydroxyimino-4-methylene pentanedioic acid 1-ethyl ester 5-methyl ester (9d). Yellow oil 78% (0.20 g); ν_{max} (Neat) 1630 (C=N), 1729 (CO_2Et and CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.23 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 2.45 (s, 3H, ArCH$_3$), 3.70 (s, 3H, CO_2CH_3), 4.20 (q, 2H, *J*=7.1 Hz, CH$_2$CH$_3$), 5.33 (two s merged, 2H, CHAr and =CH), 6.39 (d, 1H, *J*=1.3 Hz, =CH), 7.11–7.15 (m, 2H, ArH), 7.23–7.34 (m, 4H, ArH), 7.64–7.68 (m, 2H, ArH); mass (ES+) *m/z* 464.1 (M^++1); HREIMS calculated for $C_{22}H_{22}FNO_7S$ 463.1101, found, 463.1124.

4.8. General procedure for the reaction of 9b, d with DBU

To the stirred solution of appropriate tosyl derivatives from **9b**, **d** (1.0 mmol) in dry dichloromethane (5 mL), a solution of DBU (1.2 mmol) in dichloromethane (4.0 mL) was added dropwise at room temperature. After 30 min, organic layer was washed with water, dried (anhyd Na_2SO_4), and evaporated to furnish a residue, which was purified via silica gel column chromatography using hexane–EtOAc (85:15, v/v) to give the pyrroles in low yields.

4.8.1. 3-*p*-Tolyl-1*H*-pyrrole-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (10b). White solid 28% (0.11 g), mp 150–152 °C; ν_{max} (KBr) 1730 (CO_2Et and CO_2Me), 3429 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.37 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 2.40 (s, 3H, ArCH$_3$), 3.77 (s, 3H, CO_2CH_3), 4.33 (q, 2H, *J*=7.2 Hz, CH$_2$CH$_3$), 7.25 (d, 2H, *J*=7.8 Hz, ArH), 7.38 (d, 1H, *J*=2.8 Hz, =CH), 7.52 (d, 2H, *J*=7.8 Hz, ArH), 9.36 (s, 1H, NH); mass (FAB+) *m/z* 288 (M^++1); HREIMS calculated for $C_{16}H_{17}NO_4$ 287.1158, found, 287.1146.

4.8.2. 3-(4-Fluorophenyl)-1*H*-pyrrole-2,4-dicarboxylic acid 2-ethyl ester 4-methyl ester (10d). White solid 25% (0.023 g), mp 156–158 °C; ν_{max} (KBr) 1728 (CO_2Et and CO_2Me), 3441 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.38 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 3.77 (s, 3H, CO_2CH_3), 4.32 (q, 2H, *J*=7.2 Hz, CH$_2$CH$_3$), 7.10–7.18 (m, 2H, ArH), 7.38 (d, 1H, *J*=2.8 Hz, =CH), 7.59–7.65 (m, 2H, ArH), 9.38 (s, 1H, NH); mass (ES+) *m/z* 292.0 (M^++1); HREIMS calculated for $C_{15}H_{14}FNO_4$ 291.0907, found, 291.0919.

4.9. General procedure for the preparation of compounds 11a–c, 12, and 13a, b

The compounds **11a**–**c**, **12**, and **13a**, **b** were prepared following the procedure as described for compounds **3a**–**g** and the reactions were worked up after 1 h.

4.9.1. 2-Methylene-4-nitro-3-(2-nitrophenyl)-pentanedioic acid 5-ethyl ester 1-methyl ester (11a). An off white solid 72% (1.36 g), mp 116–118 °C; ν_{max} (KBr) 1721 (CO_2Et), 1755 (CO_2Me) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.07 (t, 3H, *J*=7.1 Hz, C*H*$_3$CH$_2$), 3.68 (s, 3H, CO_2CH_3), 4.09 (q, 2H, *J*=7.1 Hz, CH$_2$CH$_3$), 5.53 (d, 1H, *J*=11.5 Hz, CHAr), 5.99 (s, 1H, =CH), 6.08 (d, 1H, *J*=11.5 Hz, CHCO$_2$Et), 6.46 (s, 1H, =CH), 7.42–7.49 (m, 1H, ArH), 7.52–7.58 (m, 2H, ArH), 7.82–7.84 (d, 1H, *J*=7.6 Hz, ArH); ^{13}C NMR (50.632 MHz, $CDCl_3$) δ=13.8, 42.9, 52.8, 63.8, 89.3, 125.4, 128.5, 129.5, 130.1, 130.8, 133.2, 137.0, 150.5, 163.0, 165.7; mass (ES+) *m/z* 375.0 (M^++Na); HREIMS calculated for $C_{15}H_{16}N_2O_6$ 352.0907, found, 352.0909.

4.9.2. 2-Methylene-4-nitro-3-(6-nitrobenzo[1,3]dioxol-5-yl)-pentanedioic acid 5-ethyl ester 1-methyl ester (11b). Yellow solid 68% (0.42 g), mp 148–150 °C; ν_{max} (KBr) 1722 (CO_2Et), 1749 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.17 (t, 3H, *J*=7.2 Hz, C*H*$_3$CH$_2$), 3.71 (s, 3H, CO_2CH_3), 4.15 (q, 2H, *J*=7.2 Hz, CH$_2$CH$_3$), 5.63 (d, 1H, *J*=12.0 Hz, CHAr), 5.99 (d, 1H, *J*=12.0 Hz, CHCO$_2$Et), 6.02 (s, 1H, =CH), 6.12 (s, 2H, CH_2), 6.47 (s, 1H, =CH), 6.93 (s, 1H, ArH), 7.38 (s, 1H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.2, 42.8, 52.9, 63.9, 89.3, 103.7, 106.4, 109.3, 126.3, 128.4, 137.2, 144.7, 148.0, 151.8, 163.0, 165.8; mass (ES+) *m/z* 419.0 (M^++Na); HREIMS calculated for $C_{16}H_{16}N_2O_{10}$ 396.0805, found, 396.0806.

4.9.3. 3-(5-Chloro-2-nitro phenyl)-2-methylene-4-nitro-pentanedioic acid 5-ethyl ester 1-methyl ester (11c). Brown solid 75% (0.80 g), mp 130–132 °C; ν_{max} (KBr)

1725 (CO_2Et), 1750 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.12 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.70 (s, 3H, CO_2CH_3), 4.12 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.56 (d, 1H, J=11.6 Hz, CHAr), 6.00–6.06 (m, 2H, $CHCO_2Et$ and =CH), 6.49 (s, 1H, =CH), 7.39–7.44 (m, 1H, ArH), 7.52 (d, 1H, J=2.1 Hz, ArH), 7.83 (d, 1H, J=8.7 Hz, ArH); mass (ES+) m/z 409.0 (M^++Na); HREIMS calculated for $C_{15}H_{15}ClN_2O_8$ 386.0517, found, 386.0515.

4.9.4. 2-Methylene-4-nitro-3-(2-nitrophenyl)-pentanedioic acid diethyl ester (12). Yellow solid 71% (0.44 g), mp 90–92 °C; ν_{max} (KBr) 1728 (CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.03–1.30 (m, 6H, 2×CH_3CH_2), 4.03–4.28 (m, 4H, 2×CH_2CH_3), 5.52–5.59 (m, 2H, 2×CHAr), 5.96 (two s merged, 2H, =CH), 5.08 (d, 1H, J=11.5 Hz, $CHCO_2Et$), 6.29 (d, 1H, J=11.5 Hz, $CHCO_2Et$), 6.41 (s, 1H, =CH), 6.47 (s, 1H, =CH), 7.44–7.49 (m, 2H, 2×1ArH), 7.55–7.58 (m, 4H, 2×2ArH), 7.68–7.71 (m, 1H, ArH), 7.85 (d, 2H, J=7.8 Hz, ArH); mass (ES+) m/z 389.0 (M^++Na); HREIMS calculated for $C_{15}H_{16}N_2O_8$ 366.1063, found, 366.1059.

4.9.5. 2-Methylene-4-nitro-3-(2-nitrophenyl)-pentanoic acid methyl ester (13a). Brown solid 65% (0.58 g), mp 110–112 °C; ν_{max} (KBr) 1722 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.56 (d, 3H, J=6.6 Hz, CH_3CH), 1.63 (d, 3H, J=6.6 Hz, CH_3CH), 3.63 (s, 3H, CO_2CH_3), 3.75 (s, 3H, CO_2CH_3), 5.08 (d, 1H, J=11.0 Hz, CHAr), 5.21–5.35 (m, 2H, CHAr and $CHCO_2Et$), 5.64–5.68 (m, 1H, $CHCO_2Et$), 5.96 (s, 1H, =CH), 6.00 (s, 1H, =CH), 6.41 (two s merged, 2H, 2×=CH), 7.34–7.47 (m, 4H, 2×2ArH), 7.57 (t, 2H, J=7.2 Hz, 2×1ArH), 7.79 (t, 2H, J=7.2 Hz, 2×1ArH); mass (ES+) m/z 395.1 (M^++1); HREIMS calculated for $C_{15}H_{15}ClN_2O_8$ 294.0852, found, 294.0853.

4.9.6. 3-(5-Chloro-2-nitrophenyl)-2-methylene-4-nitropentanoic acid methyl ester (13b). Brown solid 66% (0.50 g), mp 104–106 °C; ν_{max} (KBr) 1724 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.57 (d, 3H, J=6.6 Hz, CH_3CH), 1.63 (d, 3H, J=6.6 Hz, CH_3CH), 3.65 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 5.06 (d, 1H, J=11.1 Hz, CHAr), 5.24–5.34 (m, 2H, CHAr and $CHCO_2Et$), 5.63–5.68 (m, 1H, $CHCO_2Et$), 5.99 (s, 1H, =CH), 6.04 (s, 1H, =CH), 6.45 (two s merged, 2H, 2×=CH), 7.30–7.31 (m, 2H, 2×1ArH), 7.38–7.44 (m, 2H, 2×1ArH), 7.76–7.83 (m, 2H, 2×1ArH); mass (ES+) m/z 329.1 (M^++1); HREIMS calculated for $C_{15}H_{15}ClN_2O_8$ 328.0462, found, 328.0458.

4.10. General procedure for the preparation of compounds 14a–c, 15, and 16a, b

To the solution of appropriate compounds from **11a–c**, **12**, and **13a**, **b** (1.0 equiv) in methanol (10 mL) was added $SnCl_2\cdot 2H_2O$ (10 equiv) and the reaction mixture was heated at reflux with stirring at 80 °C for 1 h in a nitrogen atmosphere. After completion, methanol was evaporated and the residue was made basic with saturated $NaHCO_3$ and taken up in EtOAc (100 mL). The suspension formed was filtered through a bed of Celite and the filtrate was partitioned in a separating funnel. The organic layer was separated, dried (Na_2SO_4), and concentrated to give a residue, which was purified by silica gel chromatography using hexane–EtOAc (80:20, v/v) as an eluent to yield the final products.

4.10.1. 3-(1-Methoxycarbonyl-vinyl)-1*H*-indole-2-carboxylic acid ethyl ester (14a). Yellow oil 56% (0.183 g); ν_{max} (Neat) 1723 (CO_2Et and CO_2Me), 3315 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.36 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.40 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.93 (s, 1H, =CH), 6.66 (s, 1H, =CH), 7.16–7.19 (m, 1H, ArH), 7.34–7.41 (m, 1H, ArH), 7.54–7.61 (m, 2H, ArH), 10.64 (s, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.4, 52.5, 61.7, 110.1, 114.2, 119.6, 120.9, 121.8, 126.4, 129.4, 133.3, 133.9, 164.3, 167.9; mass (ES+) m/z 274.0 (M^++1); HREIMS calculated for $C_{15}H_{15}NO_4$ 273.1001, found, 273.1004.

4.10.2. 3-(1-Methoxycarbonyl-vinyl)-5*H*-[1,3]dioxolo[4,5-*f*]indole-6-carboxylic acid ethyl ester (14b). Pale yellow solid 58% (0.093 g), mp 116–118 °C; ν_{max} (KBr) 1732 (CO_2Et and CO_2Me), 3308 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.23–1.36 (m, 3H, CH_3CH_2), 3.73 (s, 3H, CO_2CH_3), 4.31 (q, 2H, J=7.2 Hz, CH_2CH_3), 5.85 (t, 1H, J=2.8 Hz, =CH), 5.97 (s, 2H, CH_2), 6.60 (t, 1H, J=4.1 Hz, =CH), 6.85 (two s merged, 2H, ArH), 8.92 (s, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.6, 52.5, 62.5, 100.3, 102.7, 106.2, 115.3, 115.8, 120.4, 128.9, 136.9, 148.1, 151.6, 165.2, 168.3; mass (ES+) m/z 318.0 (M^++1), 340.1 (M^++Na); HREIMS calculated for $C_{16}H_{15}NO_6$ 317.0899, found, 317.0899.

4.10.3. 5-Chloro-3-(1-methoxycarbonyl-vinyl)-1*H*-indole-2-carboxylic acid ethyl ester (14c). Yellow oil 62% (0.103 g); ν_{max} (Neat) 1723 (CO_2Et and CO_2Me), 3372 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.36 (t, 3H, J=7.1 Hz, CH_3CH_2), 3.75 (s, 3H, CO_2CH_3), 4.40 (q, 2H, J=7.1 Hz, CH_2CH_3), 5.91 (s, 1H, =CH), 6.67 (s, 1H, =CH), 7.36 (s, 1H, ArH), 7.48–7.65 (m, 2H, ArH), 10.72 (s, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=13.8, 52.5, 61.8, 124.4, 125.6, 127.2, 130.6, 131.1, 131.4, 136.2, 141.7, 145.9, 165.2, 167.3; mass (ES+) m/z 308.0 (M^++1); HREIMS calculated for $C_{15}H_{14}ClNO_4$ 307.0611, found, 307.0612.

4.10.4. 3-(1-Ethoxycarbonyl-vinyl)-1*H*-indole-2-carboxylic acid ethyl ester (15). Brown solid 59% (0.10 g), mp 104–106 °C; ν_{max} (KBr) 1713 (CO_2Et), 3331 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.14–1.47 (m, 6H, 2×CH_3CH_2), 4.10–4.44 (m, 4H, 2×CH_2CH_3), 5.92 (s, 1H, =CH), 6.66 (s, 1H, =CH), 7.12–7.23 (m, 1H, ArH), 7.34–7.41 (m, 1H, ArH), 7.54–7.62 (m, 2H, ArH), 10.60 (s, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=14.4, 14.6, 61.4, 62.3, 110.1, 112.3, 114.2, 121.0, 121.7, 126.4, 129.1, 133.2, 134.2, 164.5, 167.7; mass (ES+) m/z 288.0 (M^++1); HREIMS calculated for $C_{16}H_{17}NO_4$ 287.1158, found, 287.1156.

4.10.5. 3-Methylene-4-(1-nitro-ethyl)-3,4-dihydro-1*H*-quinolin-2-one (16a). White solid 53% (0.062 g), mp 166–168 °C; ν_{max} (KBr) 1664 (CONH), 3218 (NH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.47 (d, 3H, J=4.7 Hz, CH_3CH), 1.50 (d, 3H, J=4.7 Hz, CH_3CH), 4.15 (d, 1H, J=7.6 Hz, CHAr), 4.23 (d, 1H, J=7.6 Hz, CHAr), 4.61–4.72 (m, 2H, 2×$CHCH_3$), 5.68 (two s merged, 2H,

2×=CH), 6.41 (s, 1H, =CH), 6.49 (s, 1H, =CH), 6.89–6.94 (m, 2H, 2×1ArH), 7.01–7.08 (m, 2H, 2×1ArH), 7.14–7.17 (m, 2H, 2×1ArH), 7.23–7.33 (m, 2H, 2×1ArH), 8.95 (s, 1H, NH), 9.10 (s, 1H, NH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ=19.3, 19.4, 51.2, 52.4, 85.6, 86.1, 124.9, 127.7, 128.3, 129.0, 129.8, 130.1, 134.0, 134.8, 137.9, 138.1, 139.8, 140.0, 166.4, 166.7; mass (FAB+) *m/z* 233 (M^++1); HREIMS calculated for $C_{12}H_{12}N_2O_3$ 232.0848, found, 232.0848.

4.10.6. 6-Chloro-3-methylene-4-(1-nitro-ethyl)-3,4-dihydro-1*H*-quinolin-2-one (16b). Pale yellow solid 48% (0.116 g), mp>250 °C; ν_{max} (KBr) 1672 (CONH), 3391 (NH) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.46 (d, 3H, *J*=4.6 Hz, C*H*$_3$CH), 1.52 (d, 3H, *J*=4.6 Hz, C*H*$_3$CH), 4.14 (d, 1H, *J*=7.8 Hz, CHAr), 4.22 (d, 1H, *J*=7.8 Hz, CHAr), 4.60–4.74 (m, 2H, 2×C*H*CH$_3$), 5.69 (two s merged, 2H, 2×=CH), 6.42 (s, 1H, =CH), 6.47 (s, 1H, =CH), 6.90–6.95 (m, 2H, 2×1ArH), 7.06–7.09 (m, 2H, 2×1ArH), 7.16–7.17 (m, 2H, 2×1ArH), 8.93 (s, 1H, NH), 9.08 (s, 1H, NH); mass (ES+) *m/z* 266.9 (M^++1), 289.0 (M^++Na); HREIMS calculated for $C_{13}H_{14}N_2O_3$ 266.0458, found, 266.0455.

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References and notes

1. (a) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–890; (b) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (c) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379–7382; (d) De Carvalho, G. P.; Silveira, E.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477–6481; (e) Kabalka, G. W.; Venkataiah, B. *Tetrahedron Lett.* **2005**, *46*, 7325–7328; (f) Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, *47*, 73–77; (g) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141–2145; (h) Seck, M.; Franck, X.; Seon-Meniel, B.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2006**, *47*, 4175–4180; (i) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3463–3466; (j) Kabalka, G. W.; Venkataiah, B.; Chen, C. *Tetrahedron Lett.* **2006**, *47*, 4187–4189; (k) Awad, L.; Demange, R.; Zhu, Y.-H.; Vogel, P. *Carbohydr. Res.* **2006**, web released 6th May; (l) Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. *Tetrahedron* **2006**, *62*, 4342–4348; (m) Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I.; Buffon, R. *Tetrahedron* **2006**, *62*, 4563–4572; (n) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052–4058.
2. (a) Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353–356; (b) Pathak, R.; Roy, A. K.; Batra, S. *Synlett* **2005**, 848–850; (c) Pathak, R.; Roy, A. K.; Kanojiya, S.; Batra, S. *Tetrahedron Lett.* **2005**, *46*, 5289–5292; (d) Pathak, R.; Batra, S. OCCB-2006, PN-102, CSIR–ACS conference at NCL, Pune, Jan 7–9, 2006.
3. Singh, V.; Batra, S. *Synthesis* **2006**, 63–72.
4. Blaszczyk, E.; Krawczyk, H.; Janecki, T. *Synlett* **2004**, 2685–2688.
5. Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376–3378.
6. Lee, K. Y.; Seo, J.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3913–3917.
7. (a) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621–1625; (b) Bauchet, R.; Le Rouille, E.; Foucad, A. *Bull. Soc. Chim. Fr.* **1991**, *128*, 267–271; (c) Chamakh, A.; M'hirsi, M.; Villieras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295–299.
8. (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–972; (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.
9. (a) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723–4725; (b) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276–281.
10. (a) Kim, M. K.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 657–658; (b) Lee, M. J.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1355–1358.
11. (a) For In: Lee, J. G.; Choi, K. I.; Kim, Y.; Kang, Y.; Cho, Y. S. *Synthesis* **2001**, 81–84; (b) For Sn: Vogel's Textbook of Practical Organic Chemistry, 5th ed.; Furniss, B. S., Hannaford, A. J., Smith, P. W. G., Tatchell, A. R., Eds.; Pearson Education: Singapore (Indian branch), 2004 (with permission from Longman group, UK); p 892; (c) For Zn: He, L.; Srikanth, G. S. C.; Castle, S. L. *J. Org. Chem.* **2005**, *70*, 8140–8147; (d) For Fe: see Ref. 7a.
12. Bartra, M.; Romea, P.; Felix, U.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587–594.
13. Roy, A. K.; Pathak, R.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, 1021–1027.
14. Kabalka, G. W.; Goudgaon, N. M. *Synth. Commun.* **1988**, *18*, 693–697.
15. Taber, D. F.; Tian, W. *J. Am. Chem. Soc.* **2006**, *128*, 1058–1059.
16. (a) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427–6430; (b) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343–345; (c) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385–390.

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Facile and clean synthesis of α-alkenoyl ketene-(*S*,*S*)-acetals via the aldol condensation reactions in water

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Abstract—The aldol condensation reactions of α,α-diacetyl ketene-(*S*,*S*)-acetals, **1a** and **1b**, with aromatic aldehydes **2** in the presence of NaOH in water have been investigated. At room temperature, the base-mediated condensations proceed smoothly to afford the corresponding mono-condensed products, α-alkenoyl ketene-(*S*,*S*)-acetals **3**, in high yields. At reflux temperature, the reactions produce high yields of symmetric double condensed α,α-dialkenoyl ketene-(*S*,*S*)-acetals **4** when 2 equiv of aldehyde are employed. Moreover, compounds **3** can condense with a different aldehyde to give unsymmetric double condensed α,α-dialkenoyl ketene-(*S*,*S*)-acetals **5**.

1. Introduction

The use of water as a solvent in organic chemistry was rediscovered in the 1980s in Breslow's work, which showed that hydrophobic effect could strongly enhance the rates of some organic reactions.[1] Organic reactions carried out in water, without the use of any organic solvent, can also be beneficial because water is an easily available, cheap, safe and environmentally benign solvent.[2] So far, extensive work has revealed that a variety of organic reactions including aldol reaction, allylation reaction, Diels–Alder reaction, Michael reaction, Mannich-type reaction and even dehydration reactions can be realized in water, especially in the presence of various catalysts such as inverse phase-transfer catalysts and surfactant-type Lewis or Bronsted acids.[3–5]

Very recently, we achieved a clean, facile and practical synthesis of α-oxo ketene-(*S*,*S*)-acetals based on the reaction of β-dicarbonyl compounds with carbon disulfide and alkyl bromide catalyzed by tetrabutylammonium bromide (TBAB) in the presence of potassium carbonate in water.[6] Indeed, our laboratory has also been engaging in the synthesis and application of α-oxo ketene-(*S*,*S*)-acetals.[7] During the course of our studies, we noted that α-alkenoyl ketene-(*S*,*S*)-acetals containing a dienone moiety showed promising structural features as novel organic intermediates for: (1) double Michael acceptors serving as five carbon 1,5-bielectrophilic species, (2) dense and flexible substitution patterns and (3) good leaving alkylthio groups that can be subjected to a nucleophilic vinyl substitution (S_NV) reaction. Consequently, we developed a novel synthetic strategy for the construction of highly substituted six-membered carbocycles and heterocycles, relying upon the utilization of α-alkenoyl ketene-(*S*,*S*)-acetals as a five carbon 1,5-bielectrophilic species in formal [5+1] annulations with various carbon, nitrogen and sulfur nucleophiles, respectively.[8] The important synthetic utility of such intermediates and our continuing interest in organic reactions in water prompted us to exploit the synthesis of novel α-alkenoyl ketene-(*S*,*S*)-acetals in aqueous media. In the present work, we wish to report our investigations on the aldol condensation reactions of α,α-diacetyl ketene-(*S*,*S*)-acetals with various selected aryl aldehydes affording a variety of novel α-alkenoyl ketene-(*S*,*S*)-acetals in water.

2. Results and discussion

The synthesis and application of α-oxo ketene-(*S*,*S*)-acetals have been reported elsewhere.[9] Following the procedure described in our previous work,[6] α,α-diacetyl ketene-(*S*,*S*)-acetals **1a** and **1b** were easily prepared from acetylacetone, carbon disulfide, 1,2-dibromoethane/1,3-dibromo propane catalyzed by TBAB in the presence of K_2CO_3 and water in nearly quantitative yields, respectively. Junjappa et al. and Pak et al. investigated the direct aldol condensation reactions of some α-acetyl ketene-(*S*,*S*)-acetals with aromatic aldehydes and described the synthetic utility of the condensed products.[10,11] Recently, Asokan and co-workers reported the preparation of bis(alkenoyl)ketene-(*S*,*S*)-acetals from **1a** and aldehydes in the presence of NaOEt in EtOH, and the stereoselective intramolecular [2+2] photocycloadditions of the title compounds.[12] In all these cases, the aldol condensation reactions were carried out in organic media in which strong bases, such as NaH and NaOEt, have been employed.

Keywords: Aldol condensation reactions; Aromatic aldehydes; α-Oxo ketene-(*S*,*S*)-acetals; Water.
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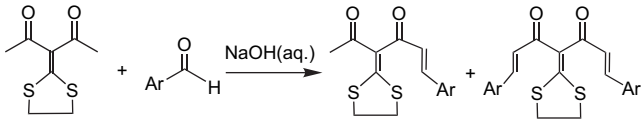
In the present work, the reaction of **1a** with 4-methoxybenzaldehyde **2a** (2 equiv) mediated by NaOH (3 equiv) at 20 °C in water was initially investigated. As indicated by TLC, a product was formed but the reaction proceeded sluggishly since some of the substrates could not be consumed even after prolonged reaction time. The reaction was stopped and a pure yellowish solid was obtained in 65% yield along with 30% recovery of the starting material **1a** after workup and column chromatography of the resulting reaction mixture (Table 1, entry 1). The only product was characterized as (*E*)-3-(1,3-dithiolan-2-ylidene)-6-(4-methoxyphenyl)hex-5-ene-2,4-dione **3aa**, a mono-condensed product, on the basis of its spectral and analytical data. Surprisingly, none of the desired double condensed product, (1*E*,6*E*)-4-(1,3-dithiolan-2-ylidene)-1,7-bis(4-methoxyphenyl)hepta-1,6-diene-3,5-dione **4aa**, could be detected in the reaction system. In a separate experiment, when **1a** and **2a** (2 equiv) were subjected to the similar conditions, namely in the presence of NaOH in ethanol at 20 °C, both **3aa** and **4aa** appeared simultaneously in the reaction system within 10 min. After 12 h, the reaction was complete, as indicated by TLC, affording **4aa** in 78% isolated yield, similar to that previously described in the literature.[12] The results reveal that the reaction media have great effect on the aldol condensations, and the clean conversion of **1a** into **3aa** in organic media is difficult.

The reactions of **1a** with **2a** were then carried out in water under various conditions to examine the reaction orientation and to optimize the yields (see Table 1). Table 1 clearly shows that the reaction temperature has a great effect on the test reactions based on the reaction time and yields. A complete conversion of **1a** could be realized at 30 °C within 20 h, which exclusively afforded compound **3aa** in 90% yield even when 2 equiv of **2a** were employed (entry 2, Table 1). With the increase of the reaction temperature, the reaction was significantly accelerated and led to the formation of **4aa** (entries 3–5, Table 1). At reflux temperature, the conversion of **1a** into **4aa** could be achieved within 4 h. It should be mentioned that much excess of base could result in a slightly lower yield of **4aa** for the formation of byproducts (entry 6, Table 1). Actually, 2.5 equiv of base were sufficient with the condensation reaction to give **4aa** (entry 7, Table 1). However, the excess of base or aldehyde **1a** did not have an obvious influence on the formation of **3aa** at low temperature (entries 8 and 9, Table 1). All the experiments have revealed that the condensation reaction can be controlled to exclusively produce **3aa** or **4aa** by simply varying the reaction temperature.

Table 1. The aldol condensation reactions of α,α-diacetyl ketene-(*S*,*S*)-acetal **1a** and 4-methoxybenzaldehyde **2a** in the presence of NaOH in water



1a **2a** (Ar = 4-MeOPh-) **3aa** **4aa**

Entry	Molar ratio[a]	Molar ratio[b]	*T* (°C)	Time (h)	Yield of **3aa** (%)[c]	Yield of **4aa** (%)[c]
1	2:1	3:1	20	20	65 (30)	0
2	2:1	3:1	30	20	90	0
3	2:1	3:1	50	15	78	9
4	2:1	3:1	70	10	62	24
5	2:1	3:1	100	4	0	80
6	2:1	5:1	100	4	0	75
7	2:1	5:2	100	4	0	82
8	1:1	3:1	30	20	90	0
9	1:1	3:2	30	20	91	0

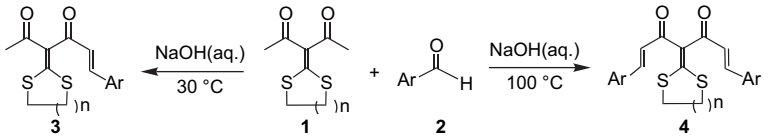
[a] Molar ratio for **2a**:**1a**.
[b] Molar ratio for NaOH:**1a**.
[c] Isolated yields, the value in bracket is recovery of **1a**.

Under the identical conditions as described in Table 1, entry 9, a range of reactions were performed on α,α-diacetyl ketene-(*S*,*S*)-acetals **1** with a variety of aromatic aldehydes **2**. Some of the results are summarized in Table 2 (entries 1–16). It is observed that all the reactions of aldehydes bearing electron-donating groups proceed smoothly under the mild basic conditions to afford the corresponding mono-condensed products **3aa**–**3bh** in high yields. It is noteworthy that these reactions are associated with very simple separation processes. In all cases, the product is a solid and deposits from the reaction system once formed. After the solid is collected, filtered and washed with water, the almost pure product is obtained. If necessary, the product can be easily purified further by flash chromatography (silica gel, diethyl ether–petroleum ether=1:4). However, the reaction of aldehyde **2i** bearing electron-withdrawing nitro group proceeded with difficulty since most of the substrates were not consumed even after a prolonged reaction time (entry 17, Table 2). In this case purification of the product had to be carried out by chromatography over silica gel.

Alternatively, a range of selected aldehydes **2** were subjected to the aldol condensation with compounds **1** under the identical conditions as described in Table 1, entry 7. Some of the results are also presented in Table 2 (entries 18–23). Within a short time, 4–5 h, all the reactions were complete affording the corresponding double condensed products **4aa**–**4af** in high yields. The results indicate that the mono-condensed products **3** can further react with aldehydes at high temperature, which suggests that compounds **3** might react with a second (different) aldehyde to generate unsymmetric double condensed α,α-dialkenoyl ketene-(*S*,*S*)-acetals **5** with different α-alkenoyl groups. This will enrich the versatility of the substituent patterns and make such intermediates even more useful, especially in library synthesis.

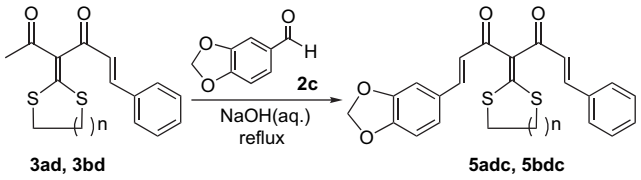
With many mono-condensed products **3** in hand, we next explored the possible transformations of these functionalities to prepare the unsymmetric double condensed α-alkenoyl ketene-(*S*,*S*)-acetals. Thus, two more experiments were carried out (Scheme 1). In one case, when **3ad** and benzo[*d*][1,3]-dioxole-5-carbaldehyde **2c** were subjected to the same aldol condensation under reflux temperature for 2 h, workup of the reaction mixture furnished a yellow product in 87% yield, which was characterized as (1*E*,6*E*)-1-(benzo[*d*][1,3]dioxol-5-yl)-4-(1,3-dithiolan-2-ylidene)-7-phenylhepta-1,6-diene-3,5-dione **5adc** on the basis of its spectral and analytical data. In another case, the reaction was performed on **3bd** and **2c** at reflux temperature for 2.5 h to give a yellow product, characterized as (1*E*,6*E*)-1-(benzo[*d*][1,3]dioxol-5-yl)-4-(1,3-dithian-2-ylidene)-7-phenylhepta-1,6-diene-3,5-dione **5bdc**, in 86% yield.

Table 2. The aldol condensation of α,α-diacetyl ketene-(*S*,*S*)-acetals **1a** and **1b** with aromatic aldehydes **2** in aqueous NaOH



Entry	Substrate **1**	*n*	Substrate **2**	Ar	*T* (°C)	Time (h)	Product **3** or **4**	Yield (%)[a]	Mp (°C)
1	**1a**	1	**2a**	4-MeOPh	30	20	**3aa**	91	156–158
2	**1b**	2	**2a**	4-MeOPh	30	20	**3ba**	90	138–140
3	**1a**	1	**2b**	4-MePh	30	18	**3ab**	92	114–116
4	**1b**	2	**2b**	4-MePh	30	19	**3bb**	93	119–121
5	**1a**	1	**2c**	3,4-OCH_2OPh	30	16	**3ac**	94	130–132
6	**1b**	2	**2c**	3,4-OCH_2OPh	30	17	**3bc**	92	141–142
7	**1a**	1	**2d**	Ph	30	21	**3ad**	92	108–109
8	**1b**	2	**2d**	Ph	30	22	**3bd**	90	116–118
9	**1a**	1	**2e**	PhCH=CH	30	24	**3ae**	86	118–120
10	**1b**	2	**2e**	PhCH=CH	30	24	**3be**	87	109–110
11	**1a**	1	**2f**	4-ClPh	30	23	**3af**	89	152–153
12	**1b**	2	**2f**	4-ClPh	30	24	**3bf**	90	135–137
13	**1a**	1	**2g**	4-NMe_2Ph	30	20	**3ag**	95	172–174
14	**1b**	2	**2g**	4-NMe_2Ph	30	21	**3bg**	93	129–131
15	**1a**	1	**2h**	2-Thioenyl	30	22	**3ah**	88	90–92
16	**1b**	2	**2h**	2-Thioenyl	30	23	**3bh**	91	101–103
17	**1a**	1	**2i**	4-NO_2Ph	30	48	**3ai**	24 (63)[b]	163–165
18	**1a**	1	**2a**	4-MeOPh	100	4	**4aa**	82	104–106
19	**1b**	2	**2a**	4-MeOPh	100	5	**4ba**	83	112–114
20	**1a**	1	**2b**	4-MePh	100	4	**4ab**	85	140–141
21	**1b**	2	**2b**	4-MePh	100	4	**4bb**	86	118–120
22	**1a**	1	**2d**	Ph	100	4	**4ad**	88	130–132
23	**1a**	1	**2f**	4-ClPh	100	4	**4af**	89	120–122

[a] Isolated yields for **3** and **4**.
[b] The value in bracket is recovery of **2i**.



Scheme 1. The reactions of benzo[*d*][1,3]dioxole-5-carbaldehyde **2c** with **3ad/3bd**.

3. Conclusion

In summary, we present here a facile, clean and practical protocol for the synthesis of α-alkenoyl ketene-(*S*,*S*)-acetals of types **3–5** via the aldol condensation of α,α-diacetyl ketene-(*S*,*S*)-acetals **1a** and **1b** with aromatic aldehydes **2** in the presence of NaOH in water. The simplicity of execution, mild conditions, high yields, ready availability of substrates and broad range of potential synthetic utility of the products, especially in relation to recent environmental concerns, make the protocol more attractive for academic research and practical applications. The scope of the aldol condensation and synthetic application of these intermediates of types **3–5** are under investigation in our laboratory.

4. Experimental

4.1. General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on an FTIR spectrophotometer in the range of 400–4000 cm^{-1}.

4.2. Typical procedure

Preparation of α-alkenoyl ketene-(*S*,*S*)-acetal **3aa**, via the aldol condensation reactions of α,α-diacyl ketene-(*S*,*S*)-acetal **1a** with aldehyde **2a**, is described as an example: to a 25 mL flask containing NaOH (3.0 mmol) in 10 mL water were added **1a** (2.0 mmol) and **2a** (2.0 mmol) under stirring. The mixture was stirred at 30 °C for about 20 h when the reaction was complete as indicated by TLC. The crude product was collected by filtration and washed with water. Further purification was carried out by flash chromatography over silica gel (eluent: diethyl ether–petroleum ether=1:4) to give pure product **3aa** as a yellowish solid (yield: 91%).

4.3. Selected data for compounds 3aa–3bh, 4aa–4af, 5adc and 5bdc

4.3.1. (*E*)-3-(1,3-Dithiolan-2-ylidene)-6-(4-methoxyphenyl)hex-5-ene-2,4-dione (3aa). Yellowish solid, mp 114–116 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.32 (s, 3H), 3.32–3.40 (m, 4H), 3.85 (s, 3H), 6.82 (d, 1H, *J*=16 Hz), 6.92 (d, 2H, *J*=8 Hz), 7.52 (d, 2H, *J*=8 Hz), 7.54 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=29.6, 37.0, 38.1, 55.7, 114.8, 124.3, 127.3, 127.9, 130.6, 145.4, 162.2, 172.2, 192.4, 193.6. IR (KBr, cm^{-1}): 2927, 2920, 1603, 1420, 1264, 1174, 1152, 1021, 870. Anal. Calcd for $C_{16}H_{16}O_3S_2$: C, 59.97; H, 5.03. Found: C, 60.06; H, 5.05.

4.3.2. (*E*)-3-(1,3-Dithian-2-ylidene)-6-(4-methoxyphenyl)hex-5-ene-2,4-dione (3ab). Yellowish solid, mp 119–121 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.21 (s, 3H), 2.19–2.27 (m, 2H), 2.92 (m, 4H), 3.84 (s, 3H), 6.75 (d, 1H, *J*=16 Hz), 6.91 (d, 2H, *J*=8 Hz), 7.48 (d, 1H, *J*=16 Hz), 7.50 (d, 2H, *J*=8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.4, 29.1, 29.7, 29.8, 55.7, 114.8, 125.2, 127.2, 130.7, 135.8, 145.7, 162.2, 164.7, 193.3, 193.5. IR (KBr, cm^{-1}): 3420, 2936, 1630, 1602, 1570, 1511, 1472, 1420, 1250, 1174, 1021. Anal. Calcd for $C_{17}H_{18}O_3S_2$: C, 61.05; H, 5.42. Found: C, 60.95; H, 5.45.

4.3.3. (*E*)-3-(1,3-Dithiolan-2-ylidene)-6-*p*-tolylhex-5-ene-2,4-dione (3ba). Yellowish solid, mp 156–158 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.33 (s, 3H), 2.39 (s, 3H), 3.33–3.39 (m, 4H), 6.90 (d, 1H, *J*=16 Hz), 7.22 (d, 2H, *J*=8 Hz), 7.46 (d, 2H, *J*=8 Hz), 7.56 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=21.8, 29.8, 37.0, 38.0, 125.6, 127.9, 128.8, 130.0, 131.9, 141.8, 145.4, 172.9, 192.1, 193.7. IR (KBr, cm^{-1}): 1626, 1582, 1565, 1418, 1323, 1245, 1178, 811. Anal. Calcd for $C_{16}H_{16}O_2S_2$: C, 63.13; H, 5.30. Found: C, 63.29; H, 5.34.

4.3.4. (*E*)-3-(1,3-Dithian-2-ylidene)-6-*p*-tolylhex-5-ene-2,4-dione (3bb). Yellowish solid, mp 138–140 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.21 (s, 3H), 2.22–2.26 (m, 2H), 2.38 (s, 3H), 2.92–2.96 (m, 4H), 6.84 (d, 1H, *J*=16 Hz), 7.21 (d, 2H, *J*=8 Hz), 7.46 (d, 2H, *J*=8 Hz), 7.50 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=21.4, 24.1, 28.8, 29.3, 29.5, 126.2, 128.5, 129.7, 131.6, 135.5, 141.5, 145.4, 192.9. IR (KBr, cm^{-1}): 3420, 2925, 1638, 1587, 1564, 1455, 1421, 1322, 1244, 1158, 980. Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.12; H, 5.70. Found: C, 64.32; H, 5.74.

4.3.5. (*E*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-3-(1,3-dithiolan-2-ylidene)hex-5-ene-2,4-dione (3ac). Yellowish solid, mp 130–132 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.32 (s, 3H), 3.34–3.38 (m, 4H), 6.03 (s, 2H), 6.77 (d, 1H, *J*=16 Hz), 6.83 (d, 1H, *J*=8 Hz), 7.05 (d, 1H, *J*=8 Hz), 7.07 (s, 1H), 7.50 (d, 1H, *J*=16 Hz) .^{13}C NMR ($CDCl_3$, 125 MHz): δ= 29.3, 36.7, 37.7, 101.6, 106.6, 108.6, 124.3, 125.3, 127.7, 128.8, 144.8, 148.4, 150.1, 172.4, 191.6, 193.3. IR (KBr, cm^{-1}): 3853, 3734, 1576, 1558, 1500, 1489, 1257, 1226, 1034. Anal. Calcd for $C_{16}H_{14}O_4S_2$: C, 57.47; H, 4.22. Found: C, 57.59; H, 4.26.

4.3.6. (*E*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-3-(1,3-dithian-2-ylidene)hex-5-ene-2,4-dione (3bc). Yellowish solid, mp 141–143 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.20 (s, 3H), 2.21–2.25 (m, 2H), 2.91–2.95 (m, 4H), 6.02 (s, 2H), 6.69 (d, 1H, *J*=16 Hz), 6.82 (d, 1H, *J*=8 Hz), 7.02 (d, 1H, *J*=8 Hz), 7.06 (s, 1H), 7.43 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.1, 28.8, 29.4, 29.5, 101.6, 106.6, 108.6, 125.2, 125.4, 128.7, 135.6, 145.1, 148.4, 150.1, 164.6, 192.7, 193.0. IR (KBr, cm^{-1}): 3446, 1623, 1502, 1480, 1449, 1358, 1253, 1214, 1034, 976. Anal. Calcd for $C_{17}H_{16}O_4S_2$: C, 58.60; H, 4.63. Found: C, 58.63; H, 4.61.

4.3.7. (*E*)-3-(1,3-Dithiolan-2-ylidene)-6-phenylhex-5-ene-2,4-dione (3ad). Yellowish solid, mp 108–110 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.33 (s, 3H), 3.33–3.39 (m, 4H), 6.95 (d, 1H, *J*=16 Hz), 7.39–7.41 (m, 3H), 7.50 (d, 2H, *J*=8 Hz), 7.58 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=29.8, 37.1, 38.0, 126.5, 128.6, 129.2, 131.1, 134.7, 144.1, 145.1, 173.8, 191.8, 193.7. IR (KBr, cm^{-1}): 3425, 3058, 2922, 1629, 1583, 1572, 1448, 1407, 1331, 1283, 1245, 1178, 982. Anal. Calcd for $C_{15}H_{14}O_2S_2$: C, 62.04; H, 4.86. Found: C, 61.93; H, 4.85.

4.3.8. (*E*)-3-(1,3-Dithian-2-ylidene)-6-phenylhex-5-ene-2,4-dione (3bd). Yellowish solid, mp 116–118 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.23 (s, 3H), 2.25–2.29 (m, 2H), 2.94 (m, 4H), 6.89 (d, 1H, *J*=16 Hz), 7.40–7.42 (m, 3H), 7.53 (d, 1H, *J*=16 Hz), 7.56 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.5, 29.2, 29.7, 29.9, 127.4, 128.8, 129.3, 131.2, 134.6, 135.8, 145.5, 165.5, 193.2, 193.3. IR (KBr, cm^{-1}): 1640, 1625, 1571, 1452, 1422, 1325, 1242, 1159, 977, 740. Anal. Calcd for $C_{16}H_{16}O_2S_2$: C, 63.13; H, 5.30. Found: C, 63.33; H, 5.31.

4.3.9. (5*E*,7*E*)-3-(1,3-Dithiolan-2-ylidene)-8-phenylocta-5,7-diene-2,4-dione (3ae). Yellowish solid, mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.32 (s, 3H), 3.34–3.38 (m, 4H), 6.49 (d, 1H, *J*=16 Hz), 6.96 (d, 1H, *J*= 8 Hz), 6.98 (s, 1H), 7.37–7.39 (m, 4H), 7.49 (d, 2H, *J*= 8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=29.8, 37.1, 38.0, 126.8, 127.7, 127.9, 129.1, 129.7, 129.8, 136.1, 142.6, 145.4, 173.1, 191.9, 193.8. IR (KBr, cm^{-1}): 3446, 1716, 1683, 1615, 1509, 1393, 1282, 1251, 1217, 1002. Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.53; H, 5.10. Found: C, 64.54; H, 5.13.

4.3.10. (5*E*,7*E*)-3-(1,3-Dithian-2-ylidene)-8-phenylocta-5,7-diene-2,4-dione (3be). Yellowish solid, mp 109–110 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.21 (s, 3H), 2.22–2.26 (m, 2H), 2.93 (m, 4H), 6.41 (d, 1H, *J*=16 Hz), 6.95 (d, 2H, *J*=8 Hz), 7.33–7.35 (m, 4H), 7.48 (d, 2H, *J*=8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.4, 29.1, 29.7, 29.9, 126.8, 127.7, 129.1, 129.7, 130.6, 135.8, 136.1, 142.6, 145.7, 165.0, 193.1, 193.4. IR (KBr, cm^{-1}): 1632, 1617, 1476. Anal. Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.53; H, 5.51.

4.3.11. (*E*)-6-(4-Chlorophenyl)-3-(1,3-dithiolan-2-ylidene)-hex-5-ene-2,4-dione (3af). Yellowish solid, mp 152–154 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.33 (s, 3H), 3.37–3.39 (m, 4H), 6.92 (d, 1H, *J*=16 Hz), 7.38 (d, 2H, *J*=8 Hz), 7.49 (d, 2H, *J*=8 Hz), 7.54 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=29.9, 37.1, 38.0, 126.9, 128.0, 129.6, 129.9, 133.2, 137.0, 143.4, 174.1, 191.2, 193.8. IR (KBr, cm^{-1}): 1623, 1572, 1490, 1405, 1379, 1182, 1087. Anal. Calcd for $C_{15}H_{13}ClO_2S_2$: C, 55.46; H, 4.03. Found: C, 55.62; H, 4.14.

4.3.12. (*E*)-6-(4-Chlorophenyl)-3-(1,3-dithian-2-ylidene)-hex-5-ene-2,4-dione (3bf). Yellowish solid, mp 135–137 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.22 (s, 3H), 2.26–2.30 (m, 2H), 2.93–2.95 (m, 4H), 6.84 (d, 1H, *J*=16 Hz), 7.37 (d, 2H, *J*=8 Hz), 7.47 (d, 2H, *J*=8 Hz), 7.49 (d, 1H, *J*=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.1, 28.9, 29.3, 29.6, 127.3, 129.2, 129.5, 132.8, 135.5, 136.7, 143.3, 165.2, 191.9, 193.2. IR (KBr, cm^{-1}): 1652, 1643, 1587, 1458, 1402, 1243, 1160, 1090. Anal. Calcd for $C_{16}H_{15}ClO_2S_2$: C, 56.71; H, 4.46. Found: C, 56.54; H, 4.50.

4.3.13. (*E*)-6-(4-(Dimethylamino)phenyl)-3-(1,3-dithiolan-2-ylidene)hex-5-ene-2,4-dione (3ag). Yellowish solid, mp 172–174 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.30

(s, 3H), 3.04 (s, 6H), 3.36–3.40 (m, 4H), 6.67 (d, 2H, J=8 Hz), 7.73 (d, 1H, J=16 Hz), 7.46 (d, 2H, J=8 Hz), 7.50 (d, 1H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=28.9, 36.5, 37.8, 39.9, 111.8, 121.3, 122.0, 127.9, 130.5, 146.6, 152.2, 169.7, 192.7, 193.0. IR (KBr, cm^{-1}): 1624, 1560, 1525, 1435, 1244, 1165, 1053. Anal. Calcd for $C_{17}H_{19}NO_2S_2$: C, 61.23; H, 5.74; N, 4.20. Found: C, 61.41; H, 5.79; N, 4.23.

4.3.14. (*E*)-6-(4-(Dimethylamino)phenyl)-3-(1,3-dithian-2-ylidene)hex-5-ene-2,4-dione (3bg). Yellowish solid, mp 129–131 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.20 (s, 3H), 2.21–2.25 (m, 2H), 2.88–2.92 (m, 4H), 3.04 (s, 6H), 6.66 (d, 2H, J=8 Hz), 6.69 (d, 1H, J=16 Hz), 7.45 (d, 1H, J=16 Hz), 7.46 (d, 2H, J=8 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.3, 29.0, 29.6, 40.4, 112.0, 122.0, 122.5, 130.9, 136.1, 147.4, 152.5, 163.5, 193.2, 194.1. IR (KBr, cm^{-1}): 3446, 1645, 1589, 1525, 1463, 1182, 1104, 978. Anal. Calcd for $C_{18}H_{21}NO_2S_2$: C, 62.21; H, 6.09; N, 4.03. Found: C, 62.34; H, 6.12; N, 4.11.

4.3.15. (*E*)-3-(1,3-Dithiolan-2-ylidene)-6-(thiophen-2-yl)-hex-5-ene-2,4-dione (3ah). Yellowish solid, mp 90–92 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.33 (s, 3H), 3.34–3.38 (m, 4H), 6.73 (d, 1H, J=16 Hz), 7.08 (dd, 1H, J_1=5 Hz, J_2=4 Hz), 7.32 (d, 1H, J=4 Hz), 7.44 (d, 1H, J=5 Hz), 7.72 (d, 1H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=29.7, 37.1, 38.1, 125.4, 127.9, 128.7, 129.8, 132.5, 137.6, 140.1, 173.3, 191.3, 193.6. IR (KBr, cm^{-1}): 3430, 1626, 1575, 1452, 1419, 1278, 1243, 1202, 1044, 718. Anal. Calcd for $C_{13}H_{12}O_2S_3$: C, 52.67; H, 4.08. Found: C, 52.75; H, 4.13.

4.3.16. (*E*)-3-(1,3-Dithian-2-ylidene)-6-(thiophen-2-yl)-hex-5-ene-2,4-dione (3bh). Yellowish solid, mp 101–103 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.22 (s, 3H), 2.23–2.27 (m, 2H), 2.93–2.95 (m, 4H), 6.66 (d, 1H, J=16 Hz), 7.08 (dd, 1H, J_1=5 Hz, J_2=4 Hz), 7.31 (d, 1H, J=4 Hz), 7.45 (d, 1H, J=5 Hz), 7.65 (d, 1H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.4, 29.2, 29.7, 29.8, 126.2, 128.7, 129.9, 132.5, 135.7, 137.9, 139.9, 165.4, 192.6, 193.3. IR (KBr, cm^{-1}): 3072, 2921, 1645, 1634, 1578, 1473, 1418, 1277, 1219, 1049, 986, 855. Anal. Calcd for $C_{14}H_{14}O_2S_3$: C, 54.16; H, 4.55. Found: C, 54.29; H, 4.51.

4.3.17. (*E*)-3-(1,3-Dithiolan-2-ylidene)-6-(4-nitrophenyl)-hex-5-ene-2,4-dione (3ai). Yellowish solid, mp 163–165 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.38 (s, 3H), 3.38–3.41 (m, 4H), 7.08 (d, 1H, J=16 Hz), 7.63 (d, 1H, J=16 Hz), 7.70 (d, 2H, J=8.5 Hz), 8.26 (d, 2H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=30.1, 37.2, 37.9, 124.8, 127.9, 129.1, 129.9, 140.9, 141.0, 148.8, 171.9, 189.7, 194.0. IR (KBr, cm^{-1}): 1632, 1577, 1562, 1407, 1348, 1265, 1187, 837. Anal. Calcd for $C_{15}H_{13}NO_4S_2$: C, 53.72; H, 3.91; N, 4.18. Found: C, 53.41; H, 4.03; N, 4.02.

4.3.18. (1*E*,6*E*)-4-(1,3-Dithiolan-2-ylidene)-1,7-bis(4-methoxyphenyl)hepta-1,6-diene-3,5-dione (4aa). Yellow solid, mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.38 (s, 4H), 3.81 (s, 6H), 6.85 (d, 4H, J=8 Hz), 6.88 (d, 2H, J=16 Hz), 7.45 (d, 4H, J=8 Hz), 7.68 (d, 2H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=37.5, 55.6, 113.6, 114.6, 123.9, 127.7, 129.3, 130.5, 143.9, 161.9, 188.3. IR (KBr, cm^{-1}): 1627, 1586, 1569, 1511, 1457, 1422, 1255, 1172, 1027, 828. Anal. Calcd for $C_{24}H_{22}O_4S_2$: C, 65.73; H, 5.06. Found: C, 65.87; H, 5.10.

4.3.19. (1*E*,6*E*)-4-(1,3-Dithian-2-ylidene)-1,7-bis(4-methoxyphenyl)hepta-1,6-diene-3,5-dione (4ba). Yellow solid, mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.25–2.29 (m, 2H), 2.94–2.96 (m, 4H), 3.80 (s, 6H), 6.75 (d, 2H, J=16 Hz), 6.85 (d, 4H, J=8 Hz), 7.45 (d, 4H, J=8 Hz), 7.60 (d, 2H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.8, 29.8, 55.7, 114.6, 124.2, 127.6, 130.6, 136.4, 144.7, 161.9, 167.8, 188.7. IR (KBr, cm^{-1}): 3626, 2928, 2837, 1772, 1563, 1509, 1383, 1250, 1150, 1028, 829. Anal. Calcd for $C_{25}H_{24}O_4S_2$: C, 66.34; H, 5.34. Found: C, 66.49; H, 5.31.

4.3.20. (1*E*,6*E*)-4-(1,3-Dithiolan-2-ylidene)-1,7-di-*p*-tolylhepta-1,6-diene-3,5-dione (4ab). Yellow solid, mp 101–103 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.38 (s, 3H), 3.29 (d, 2H), 3.70 (s, 2H), 6.78–6.79 (d, 2H, J=16 Hz), 7.19 (d, 4H), 7.43 (s, 4H), 7.75 (d, 2H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=21.8, 43.7, 43.9, 118.9, 119.9, 128.8, 129.9, 132.4, 141.3, 143.0, 179.8, 196.3. IR (KBr, cm^{-1}): 1624, 1586, 1457, 1422, 1255, 1176, 1027, 829. Anal. Calcd for $C_{24}H_{22}O_2S_2$: C, 70.90; H, 5.45. Found: C, 70.92; H, 5.49.

4.3.21. (1*E*,6*E*)-4-(1,3-Dithian-2-ylidene)-1,7-di-*p*-tolylhepta-1,6-diene-3,5-dione (4bb). Yellow solid, mp 112–114 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.27–2.29 (m, 2H), 2.34 (s, 3H), 2.94–2.96 (m, 4H), 6.83 (d, 2H, J=16 Hz), 7.14 (d, 2H, J=8 Hz), 7.39 (d, 4H, J=8 Hz), 7.62 (d, 2H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=21.8, 24.8, 29.8, 125.4, 128.8, 129.9, 132.1, 136.2, 141.4, 144.9, 168.7, 188.6. IR (KBr, cm^{-1}): 2917, 1632, 1586, 1420, 1298, 1151, 928, 815. Anal. Calcd for $C_{25}H_{24}O_2S_2$: C, 71.39; H, 5.75. Found: C, 71.56; H, 5.79.

4.3.22. (1*E*,6*E*)-4-(1,3-Dithiolan-2-ylidene)-1,7-diphenylhepta-1,6-diene-3,5-dione (4ad). Yellow solid, mp 130–132 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.37 (s, 4H), 6.93 (d, 2H, J=16 Hz), 7.27–7.30 (m, 2H), 7.29 (d, 4H, J=8 Hz), 7.38 (d, 4H, J=8 Hz), 7.62 (d, 2H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=38.0, 122.9, 123.4, 126.4, 128.0, 128.7, 135.2, 152.7, 183.8, 200.1. IR (KBr, cm^{-1}): 2920, 1637, 1539, 1390, 1211, 1171, 987, 929, 811. Anal. Calcd for $C_{22}H_{18}O_2S_2$: C, 69.81; H, 4.79. Found: C, 69.70; H, 4.68.

4.3.23. (1*E*,6*E*)-1,7-Bis(4-chlorophenyl)-4-(1,3-dithiolan-2-ylidene)hepta-1,6-diene-3,5-dione (4af). Yellow solid, mp 120–122 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.41 (s, 4H), 6.95 (d, 2H, J=16 Hz), 7.30 (d, 4H, J=8 Hz), 7.42 (d, 4H, J=8 Hz), 7.65 (d, 2H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=37.6, 126.5, 128.5, 129.5, 129.7, 133.4, 136.7, 142.5, 187.6, 201.3. IR (KBr, cm^{-1}): 2917, 1641, 1577, 1396, 1290, 1173, 930, 809. Anal. Calcd for $C_{22}H_{16}Cl_2O_2S_2$: C, 59.06; H, 3.60. Found: C, 58.98; H, 3.51.

4.3.24. (1*E*,6*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-4-(1,3-dithiolan-2-ylidene)-7-phenylhepta-1,6-diene-3,5-dione (5adc). Yellow solid, mp 166–168 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.40 (s, 4H), 5.97 (s, 2H), 6.77 (d, 1H, J=8 Hz), 6.83 (d, 1H, J=16 Hz), 7.00 (d, 1H, J=16 Hz),

7.01 (d, 1H, J=8 Hz), 7.34 (d, 1H, J=8 Hz), 7.50 (d, 2H, J=8 Hz), 7.63 (d, 1H, J=16 Hz), 7.70 (d, 1H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=37.5, 37.6, 101.8, 106.9, 108.9, 124.3, 125.4, 126.0, 128.2, 128.7, 129.2, 129.4, 130.7, 134.9, 143.9, 144.0, 148.6, 150.2, 187.9, 188.3. IR (KBr, cm^{-1}): 3734, 1635, 1590, 1559, 1447, 1251, 1034, 725. Anal. Calcd for $C_{23}H_{18}O_4S_2$: C, 65.38; H, 4.29. Found: C, 65.49; H, 4.25.

4.3.25. (1*E*,6*E*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-4-(1,3-dithian-2-ylidene)-7-phenylhepta-1,6-diene-3,5-dione (5bdc). Yellow solid, mp 148–150 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=2.25–2.29 (m, 2H), 2.94–2.96 (m, 4H), 5.98 (s, 2H), 6.77 (d, 1H, J=8 Hz), 6.84 (d, 1H, J=16 Hz), 7.01 (d, 1H, J=16 Hz), 7.02 (d, 1H, J=8 Hz), 7.51 (d, 2H, J=8 Hz), 7.64 (d, 1H, J=16 Hz), 7.71 (d, 1H, J=16 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=24.8, 29.7, 29.8, 101.8, 106.9, 108.9, 124.3, 125.4, 126.0, 128.2, 128.7, 129.2, 129.5, 130.7, 143.9, 144.0, 148.6, 150.2, 187.9, 188.3. IR (KBr, cm^{-1}): 3731, 3643, 2928, 1753, 1601, 1559, 1250, 1029, 721. Anal. Calcd for $C_{24}H_{20}O_4S_2$: C, 66.03; H, 4.62. Found: C, 65.99; H, 4.58.

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References and notes

1. (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817; (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (c) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471–478.
2. (a) *Aqueous-Phase Organometallic Catalysis. Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 1998; (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Thomson Science: Glawsgow, Scotland, 1998; (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, NY, 1997; (d) Kobayashi, S.; Manabe, K. *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vogtle, F., Eds.; Wiley-VCH: Weinheim, 2000; (e) *Clean Solvents: Alternative Media for Chemical Reactions and Processing*; Moens, L., Abraham, M., Eds.; ACS Symposium Series 819; American Chemical Society: Washington, DC, 2002.
3. (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (b) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305–317; (c) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439–452; (d) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209–217; (e) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725–2750; (f) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3165; (g) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2772.
4. (a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401–1402; (b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965–1967; (c) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101–10102; (d) Kobayashi, S.; Wakabayashi, T. *Tetrahedron Lett.* **1998**, *39*, 5389–5392.
5. (a) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *101*, 825–836; (b) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517–9525; (c) Rispens, T.; Engberts, J. B. F. N. *Org. Lett.* **2001**, *3*, 941–943; (d) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, 439–455.
6. Ouyang, Y.; Dong, D.; Yu, H.; Liang, Y.; Liu, Q. *Adv. Synth. Catal.* **2006**, *348*, 206–210.
7. (a) Liu, Q.; Che, G.; Yu, H.; Liu, Y.; Zhang, J.; Zhang, Q.; Dong, D. *J. Org. Chem.* **2003**, *68*, 9148–9150; (b) Sun, S.; Liu, Y.; Liu, Q.; Zhao, Y.; Dong, D. *Synlett* **2004**, 1731–1734; (c) Dong, D.; Liu, Y.; Zhao, Y.; Qi, Y.; Wang, Z.; Liu, Q. *Synthesis* **2005**, *1*, 85–91; (d) Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4535–4537; (e) Pan, W.; Dong, D.; Sun, S.; Liu, Q. *Synlett* **2006**, 1090–1094.
8. (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579; (b) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580–3582; (c) Bi, X.; Dong, D.; Li, Y.; Liu, Q.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 10886–10889; (d) Zhao, L.; Liang, F.; Bi, X.; Sun, S.; Liu, Q. *J. Org. Chem.* **2006**, *71*, 1094–1098.
9. For reviews on the synthesis and applications of α-oxo ketene-(*S*,*S*)-acetals, see: (a) Dieter, R. K. *Tetrahedron* **1986**, *42*, 3029–3096; (b) Tominaga, Y. *J. Heterocycl. Chem.* **1989**, *26*, 1167–1204; (c) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423–5506; (d) Kolb, M. *Synthesis* **1990**, 171–190; (e) Ila, H.; Junjappa, H.; Mohanta, P. K. *Progress in Heterocyclic Chemistry*; Gribble, G. H., Gilchrist, L. T., Eds.; Pergamon: Oxford, 2001; Vol. 13, Chapter 1, pp 1–24.
10. (a) Myrboh, B.; Asokan, C. V.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 50–51; (b) Asokan, C. V.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 163–165; (c) Asokan, C. V.; Balu, M. P.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 727–729.
11. Choi, E. B.; Youn, I. K.; Pak, C. S. *Synthesis* **1991**, 15–18.
12. Joseph, B. K.; Verghese, B.; Sudarsanakumar, C.; Deepa, S.; Viswam, D.; Chandran, P.; Asokan, C. V. *Chem. Commun.* **2002**, 736–737.

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Exploiting the deprotonation mechanism for the design of ratiometric and colorimetric Zn^{2+} fluorescent chemosensor with a large red-shift in emission

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Abstract—The design, synthesis, and photophysical evaluation of a new naphthalimide-based fluorescent chemosensor, *N*-butyl-4-[di-(2-picolyl)amino]-5-(2-picolyl)amino-1,8-naphthalimide (**1**), were described for the detection of Zn^{2+} in aqueous acetonitrile solution at pH 7.0. Probe **1** showed absorption at 451 nm and a strong fluorescence emission at 537 nm (Φ_F=0.33). The capture of Zn^{2+} by the receptor resulted in the deprotonation of the secondary amine conjugated to 1,8-naphthalimide so that the electron-donating ability of the N atom would be greatly enhanced; thus probe **1** showed a 56 nm red-shift in absorption (507 nm) and fluorescence spectra (593 nm, Φ_F=0.14), respectively, from which one could sense Zn^{2+} ratiometrically and colorimetrically. The deprotonated complex, [(**1**-H)/Zn]$^+$, was calculated at *m*/*z* 619.1800 and measured at *m*/*z* 618.9890. In contrast to these results, the emission of **1** was thoroughly quenched by Cu^{2+}, Co^{2+}, and Ni^{2+}. The addition of other metal ions such as Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Fe^{3+}, Mn^{2+}, Al^{3+}, Cd^{2+}, Hg^{2+}, Ag^+, and Pb^{2+} produced a nominal change in the optical properties of **1** due to their low affinity to probe **1**. This means that probe **1** has a very high fluorescent imaging selectivity to Zn^{2+} among metal ions.

1. Introduction

Chemosensors that convert molecular recognition into highly sensitive and easily detected signals have been actively investigated in recent years. A ratiometric and colorimetric fluorescent probes combine the sensitivity of fluorescence with the convenience and aesthetic appeal of a colorimetric assay.[1] In particular, ratiometric measurements have the important features that they permit signal rationing, and thus increase the dynamic range and provide built-in correction for environmental effects.[2]

The design of fluorescent probes for Zn^{2+} is actively investigated,[3] as this metal ion is a critical trace element, playing significant roles in biological processes such as regulators of enzymes,[4] structural cofactors in metalloproteins, neural signal transmission,[5] and gene expression.[6] It is also known that a disorder of zinc metabolism is closely associated with many severe neurological diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Guam ALS-Parkinsonism dementia, Parkinson's disease, hypoxia-ischemia, and epilepsy.[7] However, up to now, most of the Zn^{2+} fluorescent probes are intensity-responsive based on PET quenching mechanism.[8] Only a few ratiometric and colorimetric fluorescent probes for Zn^{2+} have been found in the literature. And still many efforts for a Zn^{2+} fluorescent probe should be made among the issues, such as easy synthesis, visible light excitation, large red-shift in emission for Zn^{2+} sensing, and no pH interference in the physiological pH range.

To carry out ratiometric measurements of Zn^{2+} and get quantitative readouts, various mechanisms, which can cause a large shift in emission or excitation spectra have been introduced into Zn^{2+} sensors such as excimer,[9] FRET,[10] ICT,[11] ESIPT,[12] two fluorophore approach,[13] conformational restriction,[14] time-resolved fluorescence techniques,[15] and self-assembly strategy.[16] Herein, we represent another new mechanism to design a ratiometric fluorescent probe for Zn^{2+} based on deprotonation mechanism.

The secondary amines conjugated to 1,8-naphthalimide could be deprotonated by Cu(II)[1c] or F^-,[17] and as a result, large red shifts in both absorption and fluorescence spectra were obtained, from which one could sense Cu^{2+} or F^- colorimetrically and ratiometrically. In addition, the

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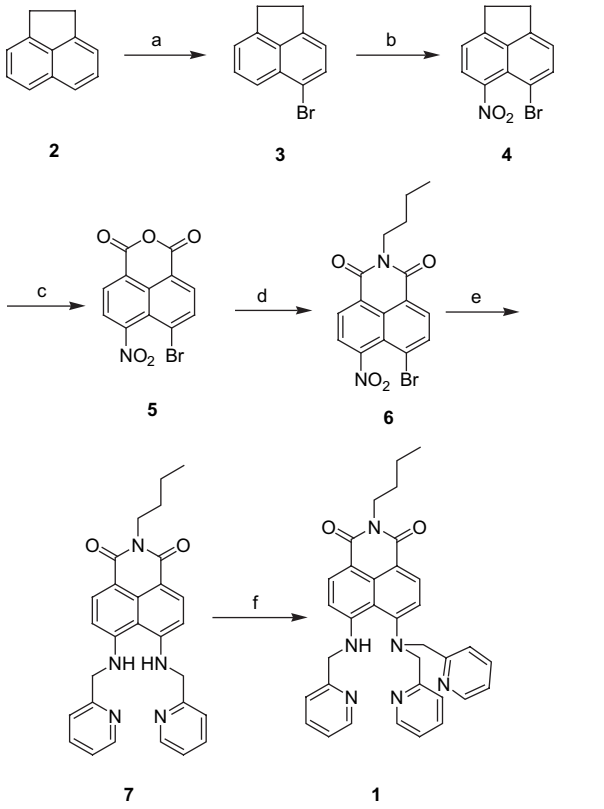
deprotonation of NH in amide or thiourea was believed to be the basis of F^- sensing in recent research.[18] Based on the same deprotonation mechanism, which should not be a privilege confined to Cu^{2+} or F^-, we introduced the well-known Zn^{2+} receptor tris(2-pyridylmethyl)-amine (TPA) into 1,8-naphthalimide fluorophore and easily obtained fluorescent probe **1**, *N*-butyl-4-[di-(2-picolyl)amino]-5-(2-picolyl)amino-1,8-naphthalimide. The capture of Zn^{2+} by the receptor resulted in the deprotonation of the secondary amine of **1**, which caused the ratiometric UV and fluorescence changes.

2. Results and discussions

2.1. Synthesis

The synthesis of **1** is shown in Scheme 1. The intermediate, compound **5**, was synthesized from acenaphthene following a literature procedure.[19] Compound **6** was prepared in 40.2% yield by the condensation of **5** with butylamine and was subsequently converted into compound **7**, which we have reported as a ratiometric Cu^{2+} fluorescent sensor,[1b] through reaction with 2-aminomethylpyridine. Probe **1** was easily synthesized by conjugating picolyl chloride and compound **7** in 56.5% yield.



Scheme 1. Synthesis of **1**. (a) NBS, DMF, room temperature, 82.4%; (b) fuming HNO_3, AcOH, 10–15 °C, 53.1%; (c) $Na_2Cr_2O_7 \cdot 2H_2O$, AcOH, reflux, 51.7%; (d) n-$C_4H_9NH_2$, C_2H_5OH, reflux, 40.2%; (e) 2-aminomethylpyridine, $CH_3OC_2H_4OH$, CH_3CN, reflux, 85%; (f) picolyl chloride, CH_3CN, K_2CO_3, N_2, reflux, 56.5%.

2.2. ESIMS analysis

Probe **1** showed absorption at 451 nm and a strong fluorescence emission at 537 nm in acetonitrile–water (80:20) solution. The capture of Zn^{2+} by the receptor resulted in the deprotonation of the secondary amine so that the electron-donating ability of the N atom conjugated to the naphthalene ring would be greatly enhanced; thus probe **1** showed large red shifts in absorption and fluorescence spectra. The ESIMS analysis revealed single-charged complex $[(\mathbf{1}\text{-H})/Zn]^+$ that is formed due to the interaction of **1** with 1 equiv of Zn^{2+} (Fig. 1). The $[(\mathbf{1}\text{-H})/Zn]^+$ complex was calculated at *m*/*z* 619.1800 and measured at *m*/*z* 618.9890. This indicated the formation of a **1**/Zn^{2+} adduct of 1:1 stoichiometry.

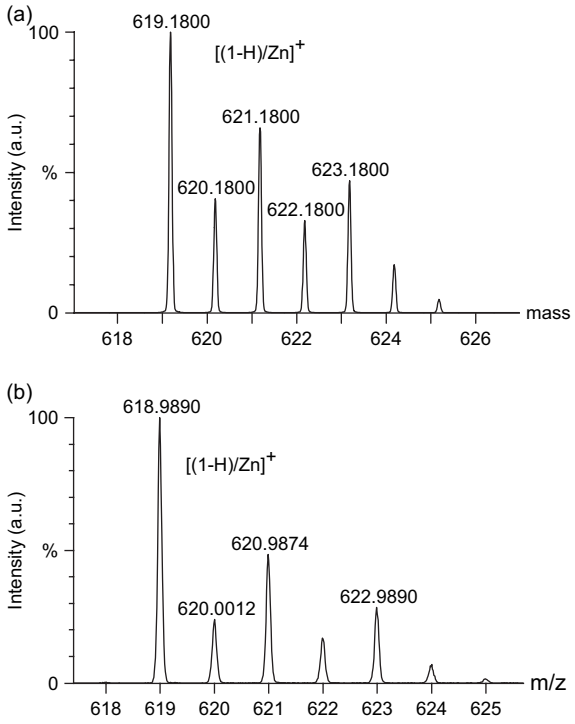


Figure 1. Electrospray mass spectrum of **1**-Zn sample in acetonitrile–water (80:20) solution at pH 7.0 maintained with HEPES buffer (50 mM). [**1**]=10 μM, $[Zn^{2+}]$=30 μM. (a) The calculated pattern of the most abundant complex $[(\mathbf{1}\text{-H})/Zn]^+$, $C_{34}H_{31}N_6O_2Zn$, *m*/*z*=619.1800. (b) The measured pattern of the most abundant complex $[(\mathbf{1}\text{-H})/Zn]^+$, $C_{34}H_{31}N_6O_2Zn$, *m*/*z*=618.9890.

2.3. The effect of pH

The influence of pH on the fluorescence of **1** was first determined by fluorescence titration in acetonitrile–water (80:20) solution (Fig. 2). The fluorescence of **1** at 537 nm remained unaffected between pH 13 and 4.21, and then gradually decreased from pH 4.21 to 1.77; below pH 1.77, no change in fluorescence was observed, leading to a sigmoid curve. Its pK_a value was 3.0. The fluorescence quenching was most likely caused by the photo-induced electron transfer (PET) from the fluorophore to protonated pyridine.[20] de Silva had found the similar phenomenon in the design of an 'off-on-off' fluorescent PET sensor.[21] The influence of pH on the deprotonation of **1** induced by Zn^{2+} was then investigated by means of the absorption and fluorescence measurements for a solution of 1 equiv of **1** and 2 equiv of Zn^{2+}. When 2 equiv of Zn^{2+} was added to an acidic solution of **1** (pH=2), the absorbance at 451 nm steadily decreased,

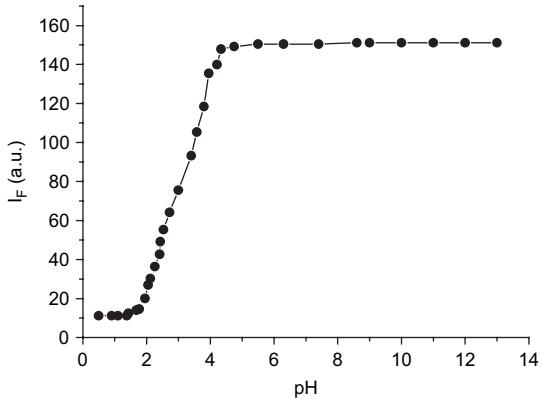


Figure 2. Influence of pH on the fluorescence of **1** in acetonitrile–water (80:20, v/v). Excitation wavelength is 470 nm. [**1**]=10 μM. The pH was modified by adding 75% $HClO_4$ or 10% $N^+(CH_3)_4OH^-$.

and a longer absorption band at 507 nm developed on titration with $N^+(CH_3)_4OH^-$ from pH 4.34 to 5.58 (Fig. 3a). The absorption *A* reached its limiting value between pH 5.58 and 8.3 after neutralization with the excess acid and on further addition of 1 equiv of base. The solution changed from primrose yellow to pink, in which [(**1**-H)/Zn]$^+$ became the dominant species. It was supposed that the three nitrogen atoms in pyridine rings and the deprotonated N^- played the role of ligands to coordinate Zn^{2+}. On addition of more bases, the absorbance at 507 nm lessened and the absorption band at 451 nm restored from pH 8.3 to 10.34. This response may be due to the stronger complexation of OH^- with Zn^{2+} than the complexation of the deprotonated N^- with Zn^{2+}. That means in strong basic conditions counter-reaction of deprotonation occurs, and OH^- becomes one ligand instead of N^-. Simultaneously, a native emission band of **1** centered at 537 nm and a red-shifted fluorescence emission band centered at 593 nm attributed to [(**1**-H)/Zn]$^+$ were in the ascendant alternately according to the above three pH windows similar to absorption spectra (Fig. 3b). The four plots of *A* versus pH and I_F versus pH all showed symmetrical bell-shaped curves centered at the same pH 7. Therefore, further and detailed studies were carried out in acetonitrile–water (80:20) solution at pH 7.0 maintained with HEPES buffer (50 mM). In our previous work,[1c] OH^- played the role of base to cooperate with Cu^{2+} to deprotonate the NH group conjugated to 1,8-naphthalimide, and then strong base would facilitate the deprotonation reaction much more. But in this case, OH^- primarily played the role of ligand, which, on the contrary, speeded the reverse reaction of deprotonation. Thus these four plots in Figure 3 show symmetrical shapes.

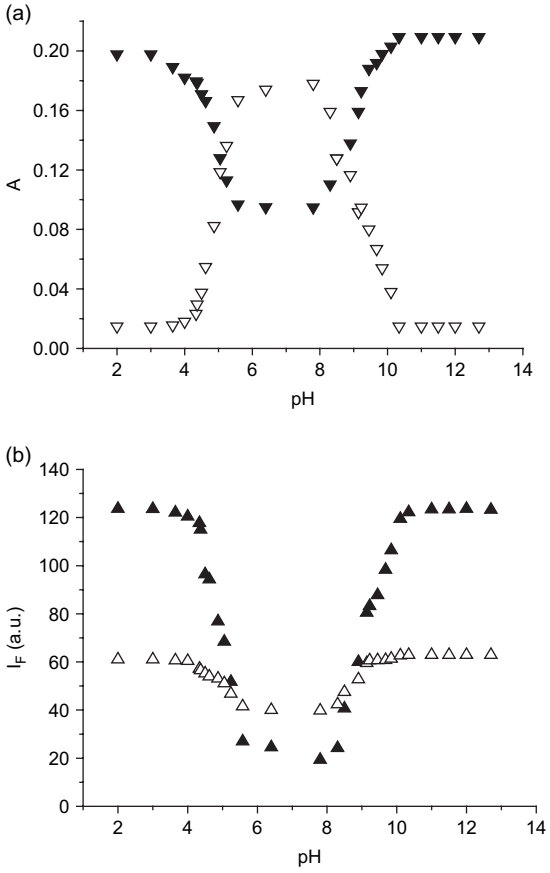


Figure 3. (a) Dependence of the absorbance of the band at 451 nm (▼) and 507 nm (▽) on pH for a solution of 1 equiv of **1** and 2 equiv of Zn^{2+} in acetonitrile–water (80:20, v/v). [**1**]=10 μM. (b) Dependence of the fluorescence intensity of the band centered at 537 nm (▲) and 593 nm (△) on pH for a solution of 1 equiv of **1** and 2 equiv of Zn^{2+} in acetonitrile–water (80:20, v/v). [**1**]=10 μM.

2.4. Recognition of metal cations

The changes in absorption spectra during the Zn^{2+} titration are shown in Figure 4. On addition of zinc ion to the solution of **1**, the absorption band at 451 nm decreased, and the other two bands at 309 and 507 nm occurred and increased prominently to their limiting values with isosbestic points at 382 and 470 nm, respectively. The emission spectra of **1** and its fluorescence titration with Zn^{2+} are displayed in Figure 5. When Zn^{2+} was added to the solution of **1**, a significant decrease in the 537 nm emission (Φ_F=0.33) and a large red-shifted emission band centered at 593 nm (ΔE_{em}=56 nm, Φ_F=0.14) were observed with a clear isoemissive point at 630 nm. The binding constant was calculated to be 6.76×10^5 using the method reported in our previous work.[1b] The absorption and fluorescence spectra of **1** titrated with Zn^{2+}, after adding 0.1 equiv of Zn^{2+} to the solution of **1** every time, were recorded in less than 30 s. If the interval was prolonged to 1 h, then the solution of **1** with 1 equiv of Zn^{2+}

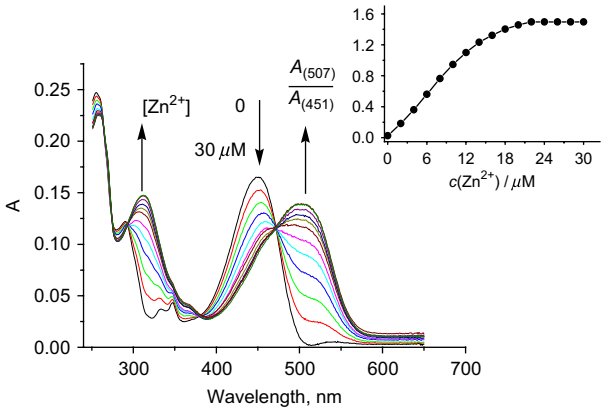


Figure 4. Dependence of the UV–vis absorption spectra of **1** on the concentration of Zn^{2+} in acetonitrile–water (80:20) solution at pH 7.0 maintained with HEPES buffer (50 mM). [**1**]=10 μM, [Zn^{2+}]=0–30 μM. Inset: ratiometric calibration curve A_{507}/A_{451} as a function of Zn^{2+} concentration.

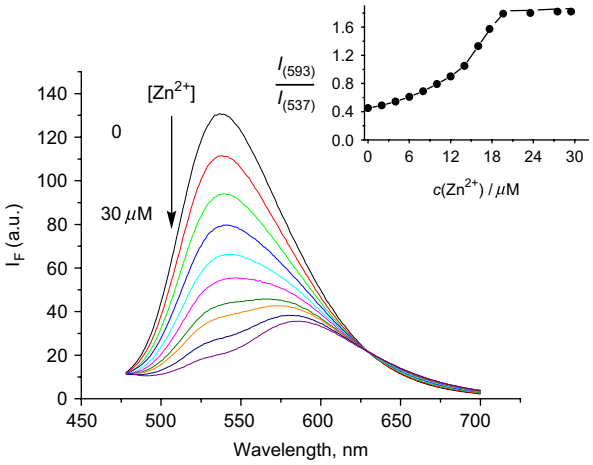


Figure 5. Fluorescent emission spectra of **1** in the presence of different concentrations of Zn^{2+} in acetonitrile–water (80:20) solution at pH 7.0 maintained with HEPES buffer (50 mM). Excitation wavelength was 470 nm. [**1**]=10 μM, [Zn^{2+}]=0–30 μM. Inset: ratiometric calibration curve I_{593}/I_{537} as a function of Zn^{2+} concentration.

displayed the same absorption and fluorescence spectra as the solution of **1** with 2 equiv of Zn^{2+}. The insets in Figures 4 and 5 indicated that 2 equiv of Zn^{2+} cooperating to react with 1 equiv of **1** could quickly reach the equilibrium in the formation of a (**1**-H)/Zn^{2+} complex of 1:1 stoichiometry on comparison with 1 equiv of Zn^{2+} with 1 equiv of **1**.

The titration of **1** with various metal ions was conducted to examine the selectivity. The addition of metal ions such as Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Fe^{3+}, Mn^{2+}, Al^{3+}, Cd^{2+}, Hg^{2+}, Ag^+, and Pb^{2+} produced a nominal change in the optical properties of **1** due to their low affinity to probe **1**. The addition of Cu^{2+}, Co^{2+}, and Ni^{2+} to the solution of **1** also can deprotonate probe **1** and change the solution color from primrose yellow to pink. However, in contrast with red-shifted emission induced by Zn^{2+}, the emission of **1** was thoroughly quenched by Cu^{2+}, Co^{2+}, and Ni^{2+} (Fig. 6). This means that probe **1** has a very high fluorescent imaging selectivity to Zn^{2+} (Fig. 7), although **1** does not show obvious binding discrimination among these four metal ions. This visible emission allows **1**+Zn^{2+} to be readily distinguished by naked eye (Fig. 8), and sensor **1** thus combines

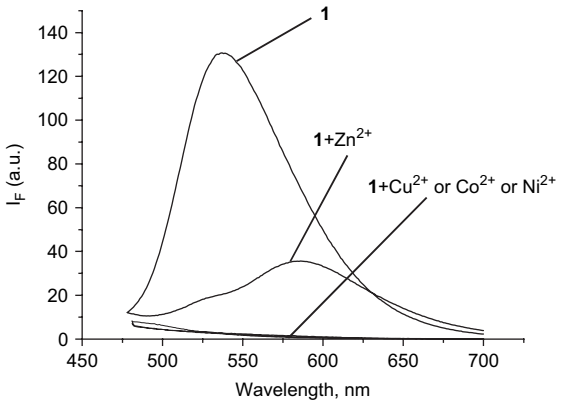


Figure 6. Fluorescent emission spectra of **1**, **1**+Zn^{2+}, and **1**+Cu^{2+} (or Co^{2+}, or Ni^{2+}). [**1**]=10 μM, [Zn^{2+}]=[Cu^{2+}]=[Co^{2+}]=[Ni^{2+}]=30 μM.

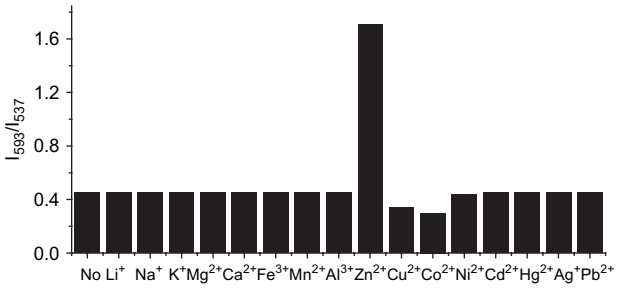


Figure 7. Fluorescence response of **1** to various metal ions in acetonitrile–water (80:20) solution at pH 7.0 maintained with HEPES buffer (50 mM). [**1**]=10 μM, and the concentration of each metal ion was 30 μM.

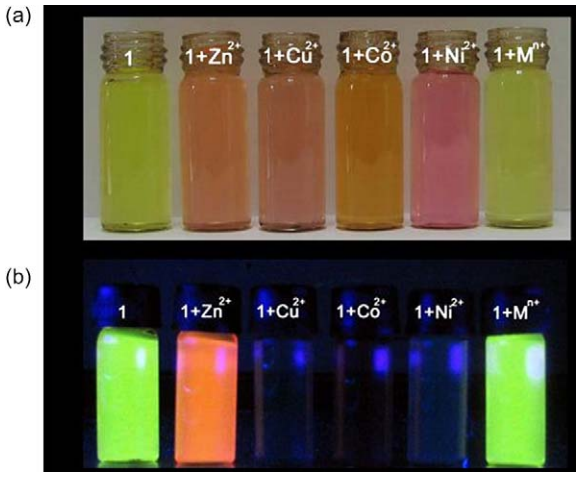


Figure 8. (a) Color change of compound **1** on addition of different metal ions. [**1**]=10 μM, [M]=30 μM. (b) Fluorescent emission observed from the solutions of **1** on addition of different metal ions. M^{n+} represents other metal ions including Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Fe^{3+}, Mn^{2+}, Al^{3+}, Cd^{2+}, Hg^{2+}, Ag^+, and Pb^{2+}. Excitation wavelength is 365 nm emitted from a portable fluorescent lamp.

the sensitivity of fluorescence with the convenience and aesthetic appeal of a colorimetric assay.[2a]

Additionally, to explore the effects of anionic counterions on the sensing behavior of **1** to metal ions, fluorescence responses of **1** to perchlorate, chloride, and nitrate salts with different cations were examined. The results were similar to that shown in Figures 4 and 5. There were no obvious changes in the fluorescence responses of **1** to $Zn(ClO_4)_2$, $ZnCl_2$, and $Zn(NO_3)_2$.

3. Conclusion

We have demonstrated that probe **1** displayed a colorimetric response with a large red-shift emission that was useful for the easy detection of Zn^{2+}. The change in solution color from primrose yellow to pink and the red-shifted fluorescence spectra from green to red were attributed to the deprotonation of the secondary amine conjugated to the naphthalene ring. Probe **1** for Zn^{2+} was developed from our former sensor[1b] for Cu^{2+} on the base of the same deprotonation mechanism. With the improvement of selectivity for HTM ion receptors, we believe that this design strategy would help to extend the development of ratiometric fluorescent probes for other HTM ions.

4. Experimental

4.1. General

All the solvents were of analytic grade and used as received. The solutions of metal ions were prepared from $LiClO_4 \cdot 3H_2O$, $NaClO_4$, $KClO_4$, $MgCl_2 \cdot 6H_2O$, $CaCl_2$, $Fe(NO_3)_3$, $Mn(ClO_4)_2 \cdot 6H_2O$, $Al(ClO_4)_3$, $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $ZnCl_2$, $CdCl_2 \cdot 2½H_2O$, $CuCl_2 \cdot 2H_2O$, $HgCl_2$, $AgNO_3$, $Pb(NO_3)_2$, respectively, and were dissolved in distilled water. ^1H NMR were measured on a Bruker AV-400 spectrometer with chemical shifts reported as parts per million (in $CDCl_3$/DMSO-d_6, TMS as internal standard). Mass spectra were measured on an HP 1100 LC-MS spectrometer. Melting points were determined by an X-6 micro-melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Nexus 770 spectrometer. All pH measurements were made with a Sartorius basic pH-Meter PB-20. Fluorescence spectra were determined on a Hitachi F-4500. Absorption spectra were determined on a PGENERAL TU-1901 UV–vis spectrophotometer. The fluorescence quantum yields (Φ_F) were estimated with *N*-butyl-4-butylamino-1,8-naphthalimide in absolute ethanol as a standard (Φ_F=0.81).[22]

4.2. Synthesis

4.2.1. *N*-Butyl-4-bromo-5-nitro-1,8-naphthalimide (6). To a solution of 200 mg (0.62 mmol) 4-bromo-5-nitro-1,8-naphthalic anhydride (**5**) in 20 mL ethanol was added dropwise 45 mg (0.62 mmol) butylamine in 6 mL ethanol. The mixture was then heated at reflux for 40 min and monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure. The crude product was then purified by column chromatography (SiO_2, $CHCl_3$) to give (**6**) as a white solid in 40.2% yield (94 mg). Mp: 175.8–176.2 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (t, J=7.2 Hz, 3H), 1.42–1.48 (m, J=7.2 Hz, 2H), 1.68–1.74 (m, J=7.2 Hz, 2H), 4.18 (t, J=7.2 Hz, 2H), 7.93 (d, J=8.0 Hz, 1H), 8.21 (d, J=8.0 Hz, 1H), 8.51 (d, J=8.0 Hz, 1H), 8.71 (d, J=8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.95, 20.49, 30.21, 40.92, 122.69, 123.72, 124.26, 125.99, 131.37, 132.49, 136.14, 162.21, 162.98. IR (KBr, cm^{-1}): 3057, 2963, 2935, 2912, 2860, 1706, 1568, 1541, 1230, 658, 586. HRMS (EI) calcd for $C_{16}H_{13}BrN_2O_4$ [M^+]: 376.0059, found: 376.0075.

4.2.2. *N*-Butyl-4,5-di[(2-picolyl)amino]-1,8-naphthalimide (7). 2-(Aminomethyl)pyridine (0.3 mL, 2.89 mmol) was added dropwise to a solution of 53 mg (0.141 mmol) *N*-butyl-4-bromo-5-nitro-1,8-naphthalimide (**6**) in 1.0 mL 2-methoxyethanol, and then the mixture was heated to reflux for 3 h and monitored by TLC. After the reaction was completed, the solution was cooled at room temperature to give yellow needle crystals. The product was filtered off, washed with 2-methoxyethanol, and then dried in air. The product was then purified by column chromatography (SiO_2, CH_2Cl_2/EtOAC, 2:1, v/v) to give **7** as a yellow powder in 85% yield (56 mg). Mp: 179.5–179.9 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J=7.6 Hz, 3H), 1.41–1.47 (m, J=7.6 Hz, 2H), 1.66–1.72 (m, J=7.6 Hz, 2H), 4.14 (t, J=7.6 Hz, 2H), 4.66 (s, 4H), 6.78 (d, J=8.4 Hz, 2H), 7.19 (t, J=7.2 Hz, 2H), 7.40 (d, J=7.6 Hz, 2H), 7.62 (S, N–H), 7.69 (t, J=7.2 Hz, 2H), 8.32 (d, J=8.4 Hz, 2H), 8.42 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.09, 20.65, 30.55, 39.97, 49.36, 105.98, 107.24, 112.38, 122.16, 122.77, 133.87, 137.24, 147.75, 149.06, 151.93, 156.31, 164.83. IR (KBr, cm^{-1}): 3328, 3043, 2953, 2869, 1673, 1633, 1592, 1541, 1508, 1310, 996. HRMS (ESI) calcd for $C_{28}H_{28}N_5O_2$ [MH^+]: 466.2243, found: 466.2247.

4.2.3. *N*-Butyl-4-[di-(2-picolyl)amino]-5-(2-picolyl)-amino-1,8-naphthalimide (1). To a solution of 200 mg (0.43 mmol) *N*-butyl-4,5-di[(pyridin-2-ylmethyl)amino]-1,8-naphthalimide (**7**) in 5 mL dry acetonitrile were added 57 mg (0.46 mmol) picolyl chloride and 150 mg K_2CO_3. The mixture was then heated at reflux for 2 h under nitrogen and monitored by TLC. After the reaction was completed, the solvent was removed under reduced pressure. The crude product was then purified by alumina column chromatography (CH_2Cl_2:MeOH=100:5) to give **1** as a yellow solid in 56.5% yield (135 mg). Mp: 133.6–134.9 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J=7.2 Hz, 3H), 1.39–1.45 (m, J=7.2 Hz, 2H), 1.64–1.70 (m, J=7.2 Hz, 2H), 4.12 (t, J=7.2 Hz, 2H), 4.54 (s, 4H), 4.93 (s, 2H), 6.61 (d, J=8.4 Hz, 1H), 7.09 (d, J=8.0 Hz, 2H), 7.12–7.17 (m, 3H), 7.22 (t, J=7.2 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.55 (t, J=7.6 Hz, 2H), 7.61 (d, J=7.6 Hz, 1H), 8.35 (d, J=8.4 Hz, 1H), 8.38 (d, J=8.4 Hz, 1H), 8.50 (d, J=4.8 Hz, 2H), 8.62 (d, J=4.4 Hz, 1H), 11.58 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.08, 20.63, 30.46, 40.01, 49.24, 59.64, 105.39, 109.17, 115.65, 119.24, 119.65, 121.16, 122.46, 122.78, 123.85, 131.52, 132.88, 134.75, 136.77, 137.03, 149.65, 152.65, 154.56, 156.33, 158.33, 164.48, 164.75. IR (KBr, cm^{-1}): 3435, 3182, 2954, 2869, 1679, 1638, 1578, 1541, 1433, 1397, 1356, 1317, 1240, 817, 750, 612. HRMS (ESI) calcd for $C_{34}H_{32}N_6O_2$ [MH^+]: 557.2665, found: 557.2662.

Acknowledgements

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Supplementary data

Spectroscopic data of **1** upon titration with Cu^{2+}, Co^{2+}, and Ni^{2+}. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.050.

References and notes

1. (a) Kubo, Y.; Yamamoto, M.; Ikeda, M.; Takeuchi, M.; Shinkai, S.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2036–2040; (b) Xu, Z.; Xiao, Y.; Qian, X.; Cui, J.; Cui, D. *Org. Lett.* **2005**, *7*, 889–892; (c) Xu, Z.; Qian, X.; Cui, J. *Org. Lett.* **2005**, *7*, 3029–3032.
2. (a) Mello, J. V.; Finney, N. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1536–1538; (b) Takakusa, H.; Kikuchi, K.; Urano, Y.; Sakamoto, S.; Yamaguchi, K.; Nagano, T. *J. Am. Chem. Soc.* **2002**, *124*, 1653–1657; (c) Choi, K.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3912–3915.

3. (a) Gee, K. R.; Zhou, Z.; Qian, W.; Kennedy, R. *J. Am. Chem. Soc.* **2002**, *124*, 776–778; (b) Gunnlaugsson, T.; Lee, T. C.; Parkesh, R. *Org. Biomol. Chem.* **2003**, *1*, 3265–3267; (c) Burdette, S. C.; Frederickson, C. J.; Bu, W.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 1778–1787; (d) Komatsu, K.; Kikuchi, K.; Kojima, H.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 10197–10204.
4. Berg, J. M.; Shi, Y. *Science* **1996**, *271*, 1081–1085.
5. Burdette, S. C.; Lippard, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3605–3610.
6. Andrews, G. K. *Biometals* **2001**, *14*, 223–237.
7. Cuajungco, M. P.; Lees, G. J. *Neurobiol. Dis.* **1997**, *4*, 137–169.
8. (a) See Refs. 3a,b; (b) Burdette, S. C.; Frederickson, C. J.; Bu, W.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 1778–1787; (c) Komatsu, K.; Kikuchi, K.; Kojima, H.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127*, 10197–10204.
9. Sclafani, J. A.; Maranto, M. T.; Sisk, T. M.; Arman, S. A. V. *Tetrahedron Lett.* **1996**, *37*, 2193–2196.
10. (a) Thompson, R. B.; Cramer, M. L.; Bozym, R. A.; Fierke, C. A. *J. Biomed. Opt.* **2002**, *7*, 555–560; (b) Bozym, R. A.; Thompson, R. B.; Stoddard, A. K.; Fierke, C. A. *ACS Chem. Biol.* **2006**, *1*, 103–111.
11. (a) Maruyama, S.; Kikuchi, K.; Hirano, T.; Urano, Y.; Nagano, T. *J. Am. Chem. Soc.* **2002**, *124*, 10650–10651; (b) Taki, M.; Wolford, J. L.; O'Halloran, T. V. *J. Am. Chem. Soc.* **2004**, *126*, 712–713; (c) Lim, N. C.; Schuster, J. V.; Porto, M. C.; Tanudra, M. A.; Yao, L.; Freake, H. C.; Bruckner, C. *Inorg. Chem.* **2005**, *44*, 2018–2030.
12. Henary, M. M.; Wu, Y.; Fahrni, C. J. *Chem.—Eur. J.* **2004**, *10*, 3015–3025.
13. Woodroofe, C. C.; Lippard, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 11458–11459.
14. Ajayaghosh, A.; Carol, P.; Sreejith, S. *J. Am. Chem. Soc.* **2005**, *127*, 14962–14963.
15. Royzen, M.; Durandin, A.; Young, V. G.; Geacintov, N. E.; Canary, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 3854–3855.
16. Wu, Z.; Zhang, Y.; Ma, J. S.; Yang, G. *Inorg. Chem.* **2006**, *45*, 3140–3142.
17. (a) Gunnlaugsson, T.; Kruger, P. E.; Lee, T. C.; Parkesh, R.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 6575–6578; (b) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Pfeffer, F. M.; Hussey, G. M. *Tetrahedron Lett.* **2003**, *44*, 8909–8913.
18. Boiocchi, M.; Boca, L. D.; Gómez, D. E.; Fabbrizzi, L.; Licchelli, M.; Monzani, E. *J. Am. Chem. Soc.* **2004**, *126*, 16507–16514.
19. Peters, A. T.; Behesti, Y. S. S. *J. Soc. Dyers Colour* **1989**, *105*, 29–35.
20. (a) de Silva, A. P.; Nimal Gunaratne, H. Q.; Lynch, P. L. M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 685–690; (b) Saeva, F. D. *J. Photochem. Photobiol., A: Chem.* **1994**, *78*, 201–204.
21. de Silva, A. P.; Nimal Gunaratne, H. Q.; McCoy, C. P. *Chem. Commun.* **1996**, 2399–2400.
22. Guo, X.; Qian, X.; Jia, L. *J. Am. Chem. Soc.* **2004**, *126*, 2272–2273.

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A reinvestigated mechanism of ribosylation of adenine under silylating conditions

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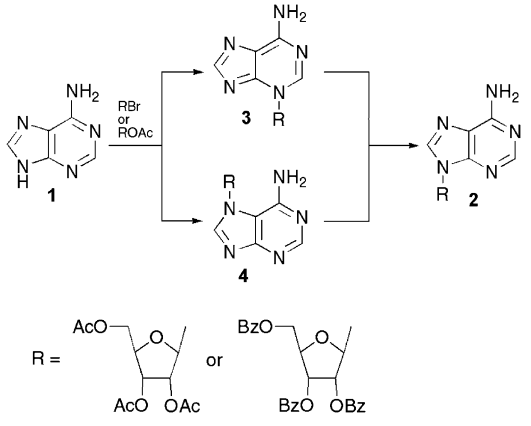
Abstract—The mechanism of chemical synthesis of adenosine has been reinvestigated. Depending on the reaction conditions and the presence of N^6-protecting groups, ribosylation of adenine proceeds via different kinetic products: 3-riboadenine in strongly acidic media, 7-ribosylated derivative in the silyl method, and 1-(β-D-ribofuranosyl)adenine when applying N^6-acyladenine and silylating conditions.

1. Introduction

It has been known for a century that ribosylation of adenine (**1**) in the presence of acidic catalysts gives 9-(β-D-ribofuranosyl)adenine, i.e., adenosine (**2**), one of the basic components of ribonucleic acids (Scheme 1). However, the literature data on the mechanism of ribosylation and the structure of a kinetically controlled product of ribosylation seem to be rather confusing. The first proposed mechanism[1] postulates an initial formation of 3-(β-D-ribofuranosyl)adenine (isoadenosine; **3**), and in fact, compounds of the type **3** have been isolated from reaction mixtures and their structures have been fully confirmed.[2,3] In line with that observation, the following sequence of events has been established: (i) initial ribosylation at N3, (ii) second ribosylation at N9 with the formation of 3,9-bis-ribosyladenine, and (iii) its decomposition to the stable 9-regioisomer (**2**). This mechanism has been extended for glycosylation reactions of all purine bases and may be found in every handbook on nucleoside chemistry. More recently, however, it has been shown that only N7 and N9 atoms can serve as glycosyl donors or acceptors in glycosylation and transglycosylation reactions in the guanine series.[4,5]



Scheme 1.

On the other hand, there are some literature reports on isolation of protected derivatives of 7-(β-D-ribofuranosyl)adenine (**4**) as kinetic products in the ribosylation of adenine.[6–10] The first synthesis of 7-riboadenine was presented in 1971: a direct coupling of bis(trimethylsilyl)-N^6-benzoyladenine and 1-bromo-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of $HgBr_2$ reportedly gave the 7-isomer, in addition to the predominant amount of N^6-benzoyladenosine.[6] Quite similar results were obtained when $SnCl_4$ was used as a catalyst.[7,8] More recently, it has been reported that glycosylation of persilylated N^6-benzoyladenine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose in the presence of trimethylsilyl triflate (TMSOTf) leads to a mixture of 7- and 9-regioisomers.[9] Interestingly, 7-riboadenine (**4**) can be formed not only under the Vorbrüggen's conditions[10] of ribosylation: compound **4** has been obtained in the fusion reaction of N^6-benzyladenine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose performed in nitrophenols, and the kinetic nature of the 7-regiosiomer has been demonstrated for the first time.[11] On the basis of those literature reports, we may assume that there is an alternative mechanism of ribosylation of adenine, different than the generally accepted 3→9

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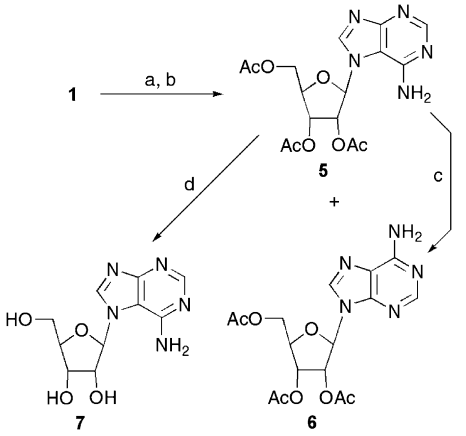
pathway of glycosylation. In this case, the kinetically controlled 7-regiosiomer of adenine would be transformed to adenosine (**2**) via a 7,9-bis-ribosyladenine intermediate, as it has been documented for 6-oxopurine bases: hypoxanthine[12] and guanine.[4,5,13]

2. Results and discussion

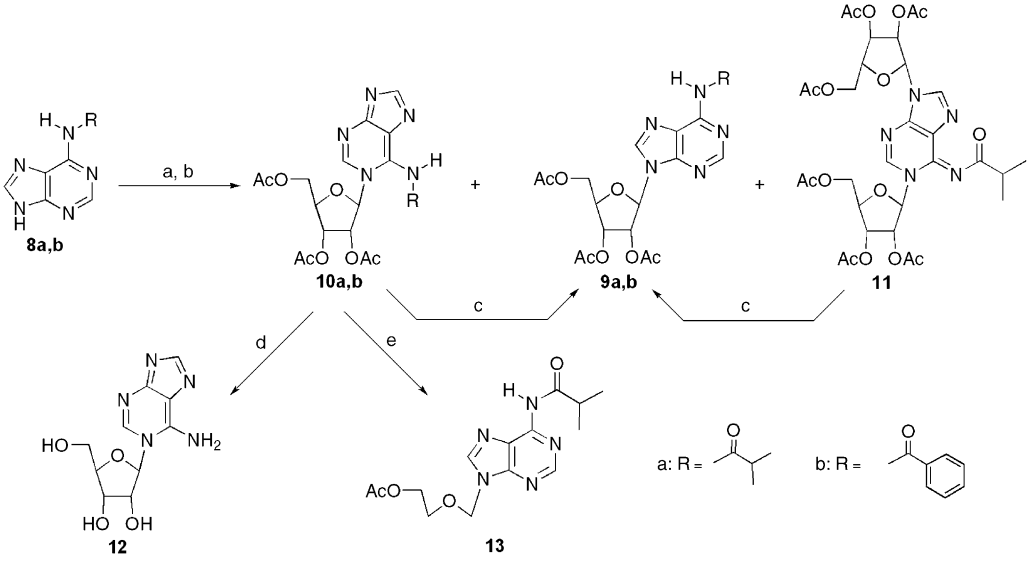
In the course of our systematic reinvestigation on mechanisms of the *N*-glycosylic bond formation, we performed a series of experiments to establish the factors responsible for either 3→9 or 7→9 mechanism in the ribosylation of adenine. This time we focused our attention on the silyl method, the most common synthetic procedure at present. Thus, adenine (**1**) was silylated with hexamethyldisilazane (HMDS) and then subjected to ribosylation with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of trimethylsilyl triflate (TMSOTf) (Scheme 2). After 80 min the reaction mixture contained 36% of the 7-isomer (**5**; isolated by column chromatography), along with a smaller amount (less than 10%) of triacetyladenosine (**6**). When heating was continued for a longer time, the 9-regioisomer **6** was the only remaining product. Similarly, the isolated product **5** could be quantitatively isomerized to **6** in the presence of *p*-toluenesulfonic acid on refluxing in chlorobenzene. This shows clearly that 7-riboadenine is a kinetic product in the ribosylation of adenine. Most probably, the 7→9 transglycosylation proceeds via a 7,9-bis-ribosyl intermediate, likewise in the guanine series, but the reaction equilibrium is totally shifted toward the 9-regioisomer (**6**). The product **5** was deprotected with aqueous ammonia in methanol to give 7-(β-D-ribofuranosyl)-adenine (**7**), identical in all respects with the sample obtained in the presence of $SnCl_4$.[7]



Scheme 2. Reagents and conditions: (a) $(NH_4)_2SO_4$, HMDS, reflux, 2.5 h; (b) CH_3CN, 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, TMSOTf, rt, 80 min; (c) *p*-TsOH, chlorobenzene, 150 °C, 2.5 h; and (d) 25% NH_4OH, MeOH, rt, 30 min.

Considering the above-mentioned result as well as the literature data,[6,7] we could expect a similar initial 7-ribosylation in the reaction of N^6-acylated derivatives of adenine, performed according to the Vorbrüggen's procedure. The reaction sequence is shown in Scheme 3. N^6-Isobutyryl (**8a**) and N^6-benzoyladenine (**8b**) were silylated with *N*,*O*-bis-trimethylsilylacetamide (BSA), and then subjected to ribosylation with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of TMSOTf. Surprisingly, the reaction gave, along with the 9-ribo products (**9a**,**b**), new products of the structure of 1-regioisomers (**10a**,**b**) in the yield of 33% and 30%, respectively. In addition, a careful chromatographic separation in the isobutyryl series allowed to isolate a minor reaction product, the 1,9-bis-ribosyl derivative **11** (5%). The deprotection of **10a** with methanolic ammonia gave 1-(β-D-ribofuranosyl)adenine (**12**), a new regioisomer of naturally occurring adenosine.

Compounds **10a**,**b** underwent isomerization to the respective 9-regioisomers (**9a**,**b**) after a prolonged reaction time, and this proves the kinetic nature of the 1-regioisomers of adenosine. Furthermore, the isolated N^6-isobutyryl derivative (**10a**) underwent an almost quantitative conversion to **9a** under transglycosylation conditions (refluxing in



Scheme 3. Reagents and conditions: (a) BSA/CH_3CN, Ar, 60 °C, 30 min; (b) 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, TMSOTf, 60–75 °C, 3 h; (c) *p*-TsOH, chlorobenzene, 60–150 °C, 10–150 min; (d) NH_3/MeOH, 25 °C, 24 h; and (e) $AcOCH_2CH_2OCH_2OAc$, *p*-TsOH, chlorobenzene, reflux, 4 h.

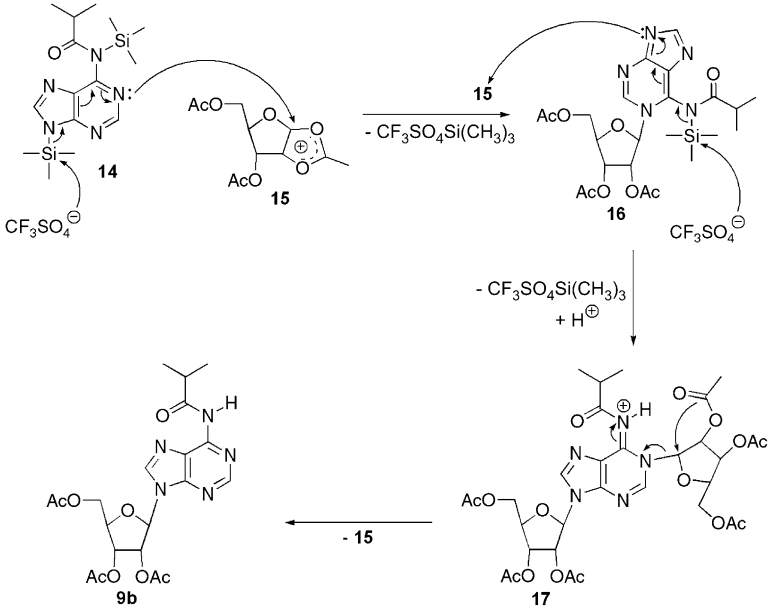
chlorobenzene in the presence of *p*-toluenesulfonic acid). Under the same conditions, the 1,9-bis-ribofuranosyl intermediate (**11**) was decomposed to a 6:1 mixture of the respective 9- and 1-regioisomers (**9a** and **10a**). Finally, the reaction of **10a** with 2-acetoxyethyl acetoxymethyl ether[14,15] resulted in the formation of acycloadenosine derivative **13**, and this is evidence for an intermolecular course of the 1→9 isomerization.

Taking into account these experimental facts, we can propose a new mechanism of the ribosylation in the N^6-acyl series (Scheme 4), shown here for the N^6-isobutyryl derivatives. In the first step, 9,N^6-bis-trimethylsilylated substrate (**14**) reacts with the acyloxonium sugar cation (**15**), generated from tetraacetylribose.[10] The position N9, an ultimate site of ribosylation, is already blocked by the TMS group. Therefore, the initial ribosylation may take place at any alternative site, e.g., N1, N3, or N7. As presented above, the N1-position is ribosylated first, perhaps due to a limited access to N7 in the presence of the two N^6-substituents, and this leads to the kinetically controlled 1-ribonucleoside **16** (isolated as a desilylated derivative **10a**). Compound **16** then undergoes an intermolecular transglycosylation to regain the thermodynamically preferred aromatic system, corresponding to the most stable N-9-H tautomer of adenine. Thus, a second ribosylation at N9 gives the 1,9-bis-ribosyl intermediate **11**, which after protonation (structure **17**) undergoes a decomposition to the final 9-regioisomer **9a**, with liberation of the acyloxonium cation **15**. The 1→9 isomerization is irreversible. It is worthy to note that quite a similar mechanism can be drawn for an isomeric structure of the bis-trimethylsilyl substrate **14**, in which the second TMS group would be attached not to N6, but to oxygen atom of the N^6-acyl substituent, as it has been proposed recently.[10] In that case, explanation of the observed regioselectivity would be even more convincing. Interestingly, the formation of 1-(β-D-ribofuranosyl)adenine as a possible kinetic intermediate has been anticipated by Vorbrüggen and Höfle,[16] but this has never been proved experimentally.

All compounds were fully characterized by the ^{1}H and ^{13}C NMR (1D & 2D, NOE) techniques and analytical methods. Table 1 presents the first comparison of ^{13}C NMR spectra of adenosine and all its regioisomers. In particular, the data for 7-riboadenine (**7**) are in good agreement with those published for related compounds.[17,18] Both isomeric nucleosides, 1- and 7-(β-D-ribofuranosyl)adenine (**12** and **7**, respectively) gave crystals suitable for X-ray diffraction and their crystal structures have been determined (Fig. 1).[19] In the crystals of **12**, there are two symmetry independent molecules, denoted A and B, showing no significant differences in their geometrical parameters. Interestingly, both regioisomeric nucleosides in their crystal structures adopt conformations, which enable the formation of a three-center intramolecular N–H···O hydrogen bond between the amino group of the base and O1′ and O5′ from the ribose moiety (Fig. 2). To form such a bond, the isomers must adopt different sugar conformations: 1-riboadenine (**12**) adopts an envelope C2′-*endo* form, while 7-riboadenosine (**7**) occurs in crystal as a C2′-*endo*-C1′-*exo* conformer.

3. Conclusion

The mechanism of ribosylation in the adenine series evidently depends on reaction conditions. While application of 1-halosugars in strongly acidic media favors the 3→9 pathway, the use of 1-*O*-acetylated sugars and Lewis acids in the silyl approach results in either 7→9 or 1→9 glycosylation sequence. In the latter method, a comparison of the data obtained in this work and those reported in the literature allows us to formulate some general rules, which may be useful in the synthesis of regioisomers of adenosine. The use of Lewis acid catalysts like $HgBr_2$[6] or $SnCl_4$[7,8] results in the formation of 7-(β-D-ribofuranosyl)adenine as



Scheme 4. A proposed mechanism for the 1→9 ribosylation pathway.

Table 1. Comparison of the ^{13}C NMR spectra of adenosine and its regioisomers (151 MHz, DMSO-d_6, TMS)

Compounds	C2	C4	C5	C6	C8	C1′	C2′	C3′	C4′	C5′
Adenosine	152.42	149.06	119.38	156.19	139.96	87.92	73.44	70.70	85.93	61.71
3-(β-D-Ribofuranosyl)adenine	143.53	147.14	120.68	155.69	151.28	94.95	72.12	71.01	87.82	61.85
7-(β-D-Ribofuranosyl)adenine (**7**)	152.61	160.69	110.05	151.49	144.41	89.18	74.82	68.78	86.16	60.32
1-(β-D-Ribofuranosyl)adenine (**12**)	140.43	148.58	118.88	154.42	150.53	92.14	72.66	69.82	86.19	60.43

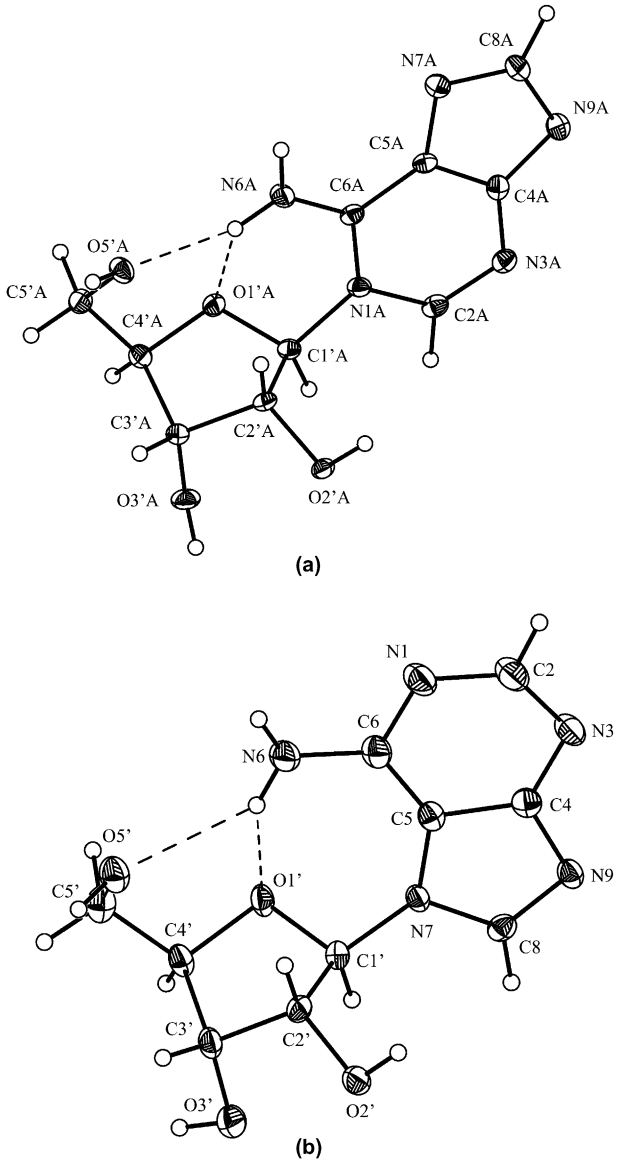


Figure 1. Ortep drawings of (a) **12**, molecule A, and (b) **7** at 50% probability level with atom numbering. Intramolecular hydrogen bonds are shown as dashed lines.

a kinetically controlled product, no matter whether the N^6-exocyclic amino group is protected or not. However, when the Vorbrüggen catalyst (TMSOTf) is applied, the presence of N^6-protection is crucial for the course of reaction: the ribosylation of persilylated derivatives of adenine without the N^6-acyl protection leads to the formation of 7-(β-D-ribofuranosyl)adenine, while N^6-acylated substrates are directly ribosylated in the position N1. To our knowledge, this is the first synthesis of the so far unknown 1-(β-D-ribofuranosyl) adenine, and that compound can now be obtained in a reasonable yield. The approach presented here should prove useful

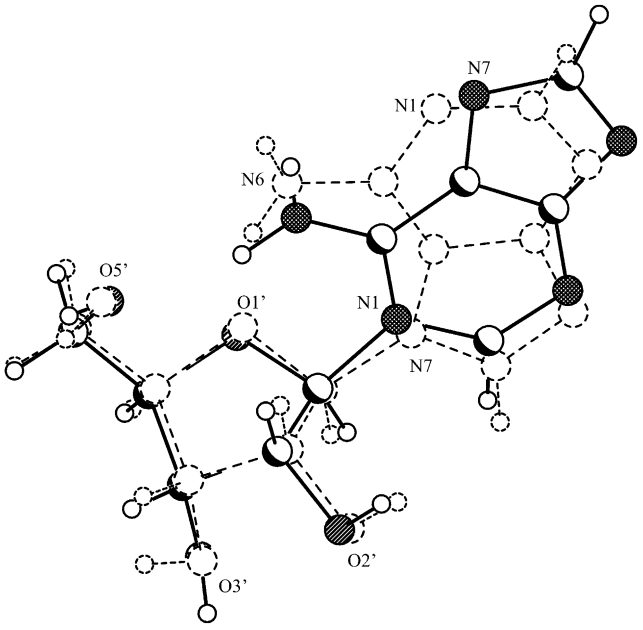


Figure 2. A superposition of the two isomers (**12** and **7**) in the conformations adopted in their crystal structures.

in the synthesis of related analogs of potential biological activity and in the study of base-pairing properties on the oligonucleotide level.

4. Experimental

4.1. General

3-(β-D-Ribofuranosyl)adenine for comparative study was obtained according to Leonard and Laursen.[2] N^6-Benzoyladenine (**8b**) was prepared according to the published procedure.[20] Melting points were determined on a Laboratory Devices Mel-Temp II micromelting points apparatus and are uncorrected. UV spectra were measured on a Beckman DU-65 spectrophotometer. The optical rotations were measured with a Perkin–Elmer 243B polarimeter. The infrared spectra were determined in KBr with a Bruker IFS 66v/s spectrophotometer. ^1H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Varian Unity 300 FT NMR 300 MHz spectrometer with tetramethylsilane as an internal standard, and chemical shifts are reported in δ-values (ppm). 2D ^1H and ^{13}C NMR (151 MHz) were recorded on a Bruker Avance 600 MHz spectrometer. The following NMR techniques were applied for structural assignment of the obtained compounds: COSY, HMQC, HMBC, TOCSY, and NOE. Mass spectra were taken on an AMD-604 spectrometer using the LSIMS technique (Cs^+, 12 keV; in NBA). Elemental analyses were performed on a Perkin–Elmer 240 Elemental Analyzer. TLC was conducted

on Merck silica gel F_{254} 60 plates using the following solvent systems (measured by volume): A, chloroform/methanol (9:1); B, toluene/ethanol (4:1); C, isopropanol/concd NH_4OH/water (7:1:2). For preparative short-column chromatography Merck TLC gel H 60 was used.

4.2. Crystal data

The diffraction data were collected at 130 K with a Kuma-CCD diffractometer, CrysAlis CCD, and CrysAlis RED. Version 1.171. Oxford Diffraction, using graphite monochromated Mo Kα radiation. The structures were solved by direct methods with the program SHELXS-97[21] and refined by full-matrix least-squares method on F2 with SHELXL-97.[22]

4.2.1. 7-(β-D-Ribofuranosyl)adenine 7 (CCDC 297135). $C_{10}H_{13}N_5O_4$, orthorhombic, space group $P2_12_12$, a=8.2006(7), b=17.8347(14), c=7.7064(7) Å, V=1346.04(19) Å^3, Z=4, d_x=1.575 g cm^{-3}, T=130 K. Data were collected for a crystal with dimensions 0.2×0.2×0.02 mm^3. Final R indices for 1021 reflections with $I>2\sigma(I)$ and 177 refined parameters are: R_1=0.0346, wR_2=0.0765 (R_1=0.0442, wR_2=0.0799 for all 1177 data).

4.2.2. 1-(β-D-Ribofuranosyl)adenine 12 (CCDC 297134). $C_{10}H_{13}N_5O_4$, monoclinic, space group $P2_1$, a=6.7737(4), b=16.7201(8), c=9.7134(4) Å, β=90.895(4)°, V=1099.98(10) Å^3, Z=4, d_x=1.614 g cm^{-3}, T=130 K. Data were collected for a crystal with dimensions 0.5×0.2×0.2 mm^3. Final R indices for 2232 reflections with $I>2\sigma(I)$ and 369 refined parameters are: R_1=0.0240, wR_2=0.0620 (R_1=0.0251, wR_2=0.0620 for all 2314 data).

4.3. 7-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)adenine (5) and 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)adenine (6)

To a stirred suspension of adenine (**1**; 200 mg, 1.48 mmol) in HMDS (6 mL) was added $(NH_4)_2SO_4$ (10 mg, 0.087 mmol) and the mixture was refluxed under argon for 2.5 h. The resulting solution was concentrated to an oil, dissolved in dry acetonitrile (6 mL), and treated with tetraacetylribose (470 mg, 1.47 mmol) and TMSOTf (267 μL, 1.47 mmol). After stirring at rt for 80 min, the reaction mixture was evaporated to a white solid foam. The products were isolated by SiO_2 column chromatography in a gradient of $CHCl_3$/MeOH (from 95:5 to 9:1) to give (in order of elution) the 9-isomer **6** (31 mg, 5.3%); R_f 0.48(A), 0.32(B) and the 7-isomer **5** (208 mg, 36%) as a solid foam: R_f 0.37(A), 0.10(B); λ_{max} (MeOH) 245 (sh), 274 nm; ^{1}H NMR ($CDCl_3$): 2.04, 2.10, 2.16 (3s, 3×3H), 4.36 (m, 3H), 5.47 (dd, 1H, J=4.5, 6.4 Hz), 5.59 (t, 1H, J=6.5 Hz), 5.70 (br s, 2H), 6.02 (d, 1H, J=6.6 Hz), 8.14 (s, 1H), 8.54 (s, 1H); ^{13}C NMR (DMSO-d_6): 20.11, 20.32, 20.39, 62.43, 68.74, 72.49, 79.65, 86.41, 110.19, 143.94, 151.30, 152.89, 160.43, 169.10, 169.48, 169.99; HRMS: calcd for $C_{16}H_{20}N_5O_7$ (M+H): m/z 394.1362, found: 394.1347.

4.4. 7-(β-D-Ribofuranosyl)adenine (7)

A solution of **5** (122 mg, 0.310 mmol) in methanol (4 mL) was treated with 25% NH_4OH (2 mL). After 30 min at rt the solvent was evaporated to obtain a white solid, which was crystallized from MeOH (60 mg, 72%): mp 207–210 °C (lit. 211–212[7] and 246[23]); R_f 0.57 (C; adenosine 0.65); $[\alpha]_D^{20}$ −93.6 (c 0.25, H_2O; lit. −100[7]); λ_{max} (MeOH) 245 (sh), 270 nm; ν_{max} 3500–2600 (br), 3443, 3345, 3246, 1636, 1593, 1561, 1520, 1489, 1447, 1408, 1303, 1116, 1057, 990, 881 cm^{-1}; ^{1}H NMR (DMSO-d_6): 3.68 (m, 2H), 3.99 (q, 1H, J=5.0 Hz), 4.07 (q, 1H, J=6.0 Hz), 4.12 (m, 1H), 5.31 (d, 1H, J=4.2 Hz), 5.36 (t, 1H, J=4.8 Hz), 5.62 (d, 1H, J=6.0 Hz), 5.82 (d, 1H, J=7.2 Hz), 6.99 (s, 2H), 8.22 (s, 1H), 8.52 (s, 1H). Anal. calcd for $C_{10}H_{13}N_5O_4$ (267.25): C, 44.94; H, 4.90; N, 26.21. Found: C, 44.86; H, 4.79; N, 26.17.

4.5. *N*^{6}-Isobutyryladenine (8a)

Adenine (6.7 g, 49.58 mmol) (vacuum dried) was stirred in isobutyric anhydride (160 mL) at 70 °C (oil bath temperature) for 4 h. TLC analysis showed the presence of two products, mono- and disubstituted ones. The mixture was then refluxed in absolute methanol (170 mL) until the disubstituted product was completely decomposed (2 h). The solvent was evaporated, and the resulting syrup was crystallized from ethanol. The product was recrystallized from boiling ethanol to give 9.15 g of white crystals (90%): mp 231–233 °C; R_f 0.38(A), 0.23(B); λ_{max} (MeOH) 281, 291 nm; ^{1}H NMR (DMSO-d_6): 1.17 (d, 6H, J=6.9 Hz), 2.92 (septet, 1H, J=6.9 Hz), 8.39 (s, 1H), 8.63 (s, 1H), 11.15 (s, 1H), 12.21 (s, 1H); HRMS: calcd for $C_9H_{12}N_5O$ (M+H): m/z 206.1041, found: 206.1032.

4.6. *N*^{6}-Isobutyryl-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)adenine (9a), *N*^{6}-isobutyryl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)adenine (10a), and *N*^{6}-isobutyryl-1,9-bis-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)adenine (11)

An anhydrous suspension of **8a** (0.90 g, 4.38 mmol) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (1.79 g, 5.63 mmol) in dry acetonitrile (20 mL) was washed with argon for 30 min, then BSA (1.64 g, 8.09 mmol) was added. The mixture was stirred at 75 °C for 30 min until a clear solution was obtained. TMSOTf (0.48 g, 2.11 mmol) was then added and the mixture was stirred at 75 °C for 3 h. After cooling down to rt the obtained solution was diluted with CH_2Cl_2 (180 mL) and extracted with cold saturated solution of $NaHCO_3$ (150 mL). The organic layer was dried over Na_2SO_4, evaporated to a yellow solid foam and then chromatographed on a SiO_2 column in a CH_3Cl/CH_3CN gradient (from 2:1 to 1:1) to give (in order of elution): compound **11**, an oil: 0.16 g, 5%; R_f 0.80(A), 0.50(B); $[\alpha]_D^{20}$ +20.7 (c 0.31, MeOH); λ_{max} (MeOH) 293 nm; ν_{max} 3600–2850 (br), 1755, 1685, 1629, 1547, 1531, 1508, 1464, 1430, 1374, 1229 (br), 1097, 1047, 1017, 904, 757 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.22, 1.24 (2d, 6H, J=6.9 Hz), 2.08, 2.09, 2.10, 2.12, 2.14, 2.20 (6s, 6×3H), 2.75 (septet, 1H, J=6.9 Hz), 4.41–4.45 (m, 6H), 5.33 (dd, 1H, J=5.4, 7.8 Hz), 5.60 (m, 2H), 5.88 (t, 1H, J=5.4 Hz), 6.03 (d, 1H, J=5.4 Hz), 6.27 (d, 1H, J=2.4 Hz), 7.81 (s, 1H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$): 18.97, 19.06, 20.21, 20.31, 20.35, 20.44, 20.49, 20.73, 37.41, 62.43, 62.76, 68.96, 69.88, 72.23, 72.42, 78.76, 79.54, 85.83, 90.04, 120.84, 139.87, 141.73, 143.35, 146.22, 169.13, 169.26, 169.40, 169.43, 170.23, 170.30, 187.60; HRMS: calcd for $C_{31}H_{40}N_5O_{15}$ (M+H): m/z 722.2521, found: 722.2538; the 9-isomer **9a**, an oil: 0.21 g, 10%; R_f 0.70(A), 0.46(B); λ_{max} (MeOH) 272 nm; the 1-isomer **10a**, a white

solid: 0.66 g, 33%; mp 159–161 °C (40% EtOH); R_f 0.54(A), 0.45(B); $[\alpha]_D^{20}$ +86.5 (*c* 0.27, MeOH); λ_{max} (MeOH) 313 nm; ν_{max} 3500–2850 (br), 1750, 1651, 1599, 1504, 1427, 1375, 1365, 1243, 1231, 1215, 1115, 1099, 1063, 1018 cm^{-1}; ^1H NMR ($CDCl_3$): 1.17 (d, 3H, *J*=7.0 Hz), 1.19 (d, 3H, *J*=7.0 Hz), 2.06, 2.18, 2.24 (3s, 3×3H), 2.65 (septet, 1H, *J*=7.0 Hz), 4.42 (dd, 1H, *J*=3.0, 12.6 Hz), 4.51–4.55 (m, 2H), 5.34 (dd, 1H, *J*=4.8, 8.4 Hz), 5.63 (d, 1H, *J*=4.8 Hz), 6.65 (s, 1H), 8.13 (s, 1H), 8.82 (s, 1H), 12.49 (br s, 1H); ^{13}C NMR ($CDCl_3$): 19.55, 19.84, 20.26, 20.30, 20.72, 39.51, 61.05, 67.67, 74.51, 78.86, 90.31, 114.27, 141.53, 142.17, 148.02, 157.05, 168.93, 169.20, 170.23, 188.87; HRMS: calcd for $C_{20}H_{26}N_5O_8$ (M+H): *m/z* 464.1781, found: 464.1809. Anal. calcd for $C_{20}H_{25}N_5O_8$ (463.45): C, 51.83; H, 5.44; N, 15.11. Found: C, 51.75; H, 5.23; N, 15.01.

4.7. N^6-Benzoyl-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)adenine (9b) and N^6-benzoyl-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)adenine (10b)

A similar experimental procedure as described for synthesis of **10a** was applied in the N^6-benzoyl series. Reaction of **8b** (0.60 g, 2.50 mmol), tetraacetylribose (0.955 g, 3.00 mmol), BSA (1.006 g, 4.90 mmol), and TMSOTf (0.280 g, 1.30 mmol) was carried out at 60 °C for 3 h to give, after chromatographic separation, the 9-isomer **9b**, an oil: 0.099 g, 8%; R_f 0.80(A), 0.50(B); λ_{max} (MeOH) 232, 280 nm, and the 1-isomer **10b**, an oil: 0.377 g, 30%; mp 202–205 °C (EtOH); R_f 0.62(A), 0.49(B); λ_{max} (MeOH) 228, 332 nm; ν_{max} 3600–2900 (br), 1749, 1745, 1641, 1599, 1557, 1500, 1487, 1423, 1373, 1315, 1287, 1230, 1118, 1095, 1058 cm^{-1}; ^1H NMR ($CDCl_3$): 2.07, 2.08, 2.25 (3s, 3×3H), 4.41–4.60 (m, 3H), 5.38 (dd, 1H, *J*=5.1, 8.1 Hz), 5.64 (dd, 1H, *J*=2.1, 5.1 Hz), 6.70 (d, 1H, *J*=2.1 Hz), 7.42 (m, 2H), 7.52 (m, 1H), 8.17 (s, 1H), 8.22 (m, 2H), 8.90 (s, 1H), 12.65 (br s, 1H); ^{13}C NMR ($CDCl_3$): 20.31, 20.41, 20.80, 61.26, 68.09, 74.90, 79.29, 89.93, 114.61, 128.03, 128.17, 129.75, 137.25, 141.95, 142.20, 148.81, 157.60, 168.88, 169.21, 170.24, 175.18; HRMS: calcd for $C_{23}H_{24}N_5O_8$ (M+H): *m/z* 498.1625, found: 498.1655.

4.8. 1-(β-D-Ribofuranosyl)adenine (12)

A solution of **10a** (0.222 g, 0.48 mmol) in saturated methanolic ammonia (10 mL) was stirred at 25 °C for 24 h. The solvent was evaporated to a white solid, which was stirred in $CHCl_3$/MeOH (1:1, 5 mL) for 2 h. The precipitate was filtered off to give 0.120 g (93%) of **12**. An analytical sample was crystallized from water, mp>178 °C (decomp.); R_f 0.53 (C); $[\alpha]_D^{20}$ −23.5 (*c* 0.14, H_2O); λ_{max} (MeOH) 228, 275 nm; ν_{max} 3550–2300 (br), 3407, 3339, 3189, 1679, 1623, 1561, 1557, 1476, 1450, 1358, 1310, 1117, 1071, 907, 863 cm^{-1}; ^1H NMR (D_2O): 4.04 (dd, 1H, *J*=3.6, 12.6 Hz), 4.07 (dd, 1H, *J*=2.4, 12.6 Hz), 4.49 (dd, 1H, *J*=3.6, 51 Hz), 4.79 (t, 1H, *J*=6.0 Hz), 6.15 (d, 1H, *J*=6.0 Hz), 8.21 (s, 1H), 8.60 (s, 1H). Anal. calcd for $C_{10}H_{13}N_5O_4$ (267.25): C, 44.94; H, 4.90; N, 26.21. Found: C, 44.74; H, 4.69; N, 26.15.

4.9. Transglycosylation reactions

4.9.1. N^6-Isobutyryl-9-[(2-acetoxyethoxy)methyl]adenine (13). An anhydrous solution of **10a** (150 mg, 0.32 mmol), 2-acetoxyethyl acetoxymethyl ether[14] (253 μL, 1.62 mmol), and *p*-toluenesulfonic acid monohydrate (6.2 mg, 0.032 mmol) in chlorobenzene (7.5 mL) was refluxed for 4 h. The solvent was removed in vacuo and the residue was subjected to SiO_2 column chromatography in a CH_3Cl/CH_3OH gradient (from 98:2 to 9:1) to yield **13** as an oil, 57 mg (55%); R_f 0.60(A), 0.34(B); λ_{max} (MeOH) 273 nm; ν_{max} 3400–2800 (br), 3262, 1736, 1729, 1721, 1686, 1605, 1589, 1580, 1454, 1266, 1237, 1220, 1050, 761 cm^{-1}; ^1H NMR (DMSO-d_6): 1.13 (d, 6H, *J*=6.9 Hz), 1.92 (s, 3H), 2.94 (septet, 1H, *J*=6.9 Hz), 3.74 (m, 2H), 4.07 (m, 2H), 5.68 (s, 2H), 8.61 (s, 1H), 8.68 (s, 1H), 10.67 (s, 1H); HRMS: calcd for $C_{14}H_{20}N_5O_4$ (M+H): *m/z* 322.1515, found: 322.1510.

4.9.2. Isomerization of 5 to 6. A suspension of protected 7-isomer **5** (4.2 mg, 0.01 mmol) and *p*-toluenesulfonic acid monohydrate (0.4 mg, 0.002 mmol) in chlorobenzene (0.4 mL) was stirred at 150 °C for 2.5 h to give a product identical with an authentic sample of **6** (>90%; TLC, ^1H NMR).

4.9.3. Isomerization of 10a to 9a. A sample of **10a** (6.0 mg, 0.013 mmol) was stirred with *p*-toluenesulfonic acid (0.25 mg, 0.0013 mmol) in chlorobenzene (1 mL) at 60 °C for 2 h. TLC analysis showed the formation of **9a** (ca. 90%), and traces of **8a**.

4.9.4. Decomposition of 11. A sample of 1,9-bis-ribofuranosyl derivative **11** (90.0 mg, 0.12 mmol) was refluxed with *p*-toluenesulfonic acid (2.2 mg, 0.012 mmol) in chlorobenzene (5 mL) for 10 min. After this time TLC analysis showed a mixture of **9a** and **10a** in a ratio 6:1, respectively. The structure of products was confirmed after their chromatographic separation (TLC, ^1H NMR, UV).

References and notes

1. Watanabe, K. A.; Hollenberg, D. H.; Fox, J. J. *J. Carbohydr. Nucl. Nucl.* **1974**, *1*, 1–37 and references cited therein.
2. Leonard, N. J.; Laursen, R. A. *Biochemistry* **1965**, *4*, 354–364.
3. Shimizu, B.; Miyaki, M. *Chem. Pharm. Bull.* **1970**, *18*, 732–740; *Chem. Pharm. Bull.* **1970**, *18*, 1446–1456.
4. Boryski, J. *Nucleosides Nucleotides* **1996**, *15*, 771–791 and references cited therein.
5. Boryski, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 649–652.
6. Ryan, K. J.; Acton, E. M.; Goodman, L. *J. Org. Chem.* **1971**, *36*, 2646–2657.
7. Akhrem, A. A.; Adarich, A. K.; Kulinkovich, N. L.; Mikhailopulo, I. A.; Posshasteva, E. B.; Timoshchuk, V. A. *Dokl. Akad. Nauk. SSSR* **1974**, *219*, 99–102.
8. Itoh, T.; Mizuno, Y. *Heterocycles* **1976**, *5*, 285–292.
9. Moyroud, E.; Strazewski, P. *Tetrahedron* **1999**, *55*, 1277–1284.
10. Vorbrüggen, H. *Acta Biochim. Polon.* **1996**, *43*, 25–36 and references cited therein.
11. Nakazaki, N.; Sekiya, M.; Yoshino, T.; Ishido, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3858–3863.
12. Dudycz, L. W.; Wright, G. E. *Nucleosides Nucleotides* **1984**, *3*, 33–44.
13. Manikowski, A.; Boryski, J. *Nucleosides Nucleotides* **1999**, *18*, 1057–1059.
14. Rosovsky, A.; Kim, S.-H.; Wick, M. *J. Med. Chem.* **1981**, *24*, 1177.

15. Framski, G.; Manikowski, A.; Zandecki, T.; Boryski, J. *Nucl. Acids Res. Suppl.* **2003**, *3*, 11–12.
16. Vorbrüggen, H.; Höfle, G. *Chem. Ber.* **1981**, *114*, 1256–1268.
17. Akhrem, A. A.; Mikhailopulo, I. A.; Abramov, A. F. *Org. Magn. Reson.* **1979**, *12*, 247–253.
18. Seela, F.; Winter, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 273–276.
19. Crystallographic data for compounds **12** and **7** have been deposited with Cambridge Crystallographic Data Centre (CCDC deposition numbers 297134 and 297135, respectively). Copies of the data can be obtained upon request from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk], quoting the deposition numbers.
20. Ness, N. K. *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W., Tipson, R. S., Eds.; Interscience: New York, NY, 1968; Vol. 1, pp 183–187.
21. Sheldrick, G. M. *SHELXL-97: Program for a Crystal Structure Solution*; University of Göttingen: Göttingen, Germany, 1997.
22. Sheldrick, G. M. *SHELXL-97: Program for the Refinement of a Crystal Structure from Diffraction Data*; University of Göttingen: Göttingen, Germany, 1997.
23. Montgomery, J. A.; Thomas, H. J. *J. Am. Chem. Soc.* **1965**, *87*, 5442–5447.

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A novel method for the synthesis of dipyrromethanes by metal triflate catalysis

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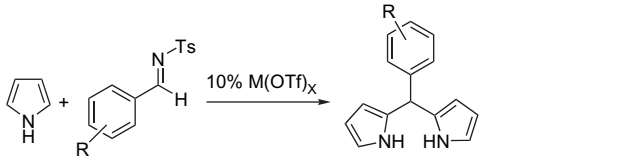
Abstract—5-Substituted dipyrromethanes were synthesized by the reaction of *N*-tosyl imines with excess pyrrole in the presence of metal triflates. Tripyrromethane and other oligomeric side products were not observed. High yields of 5-substituted dipyrromethanes were obtained for electron donating and withdrawing substituents by performing the reaction at two different temperatures. The new reaction procedure is simple and anhydrous conditions are not required.

1. Introduction

5-Substituted dipyrromethanes are important precursors for the synthesis of *meso*-substituted porphyrins, corroles, expanded and reduced porphyrins and related compounds such as dipyrrins, calixpyrroles and chlorins.[1] The first one-flask synthesis of dipyrromethanes was reported in 1994.[2] In the past decade, a number of methods have then been developed for the synthesis and purification of dipyrromethanes.[3] Almost all the methods consist of the condensation of an aldehyde and pyrrole in the presence of various acids such as $BF_3\cdot$etherate, trifluoroacetic acid (TFA), propionic acid and *p*-toluenesulfonic acid. These studies mostly afford moderate yields of *meso*-substituted dipyrromethanes. The yields are reduced due to the formation of oligomeric products, which make the purification of the dipyrromethanes from the reaction medium difficult.

Metal triflate catalyzed reactions are currently of great interest in organic chemistry. They have been used as water-stable and reuseable Lewis acids in several carbon–carbon bond forming reactions such as aldol, Michael, Diels–Alder and Friedel–Crafts acylation and alkylations.[4] Recently, we reported the metal triflate catalyzed addition of pyrroles to α,β-unsaturated esters.[5] We also examined the reactions of pyrrole with *N*-tosyl imines in the presence of catalytic amounts of metal triflates to obtain pyrrole-substituted sulfonamides.[6] In connection with this study, we report here a novel and an efficient method for preparing 5-substituted dipyrromethanes from the reaction of *N*-tosyl imines and excess pyrrole by using catalytic amounts of metal triflate (Scheme 1).



Scheme 1.

2. Results and discussion

Equimolar concentrations of pyrrole (**1**) and *N*-benzylidene-4-methylbenzenesulfonamide (**2a**) undergo a $Cu(OTf)_2$ catalyzed regioselective addition reaction in THF at rt to afford 4-methyl-*N*-(phenyl(1*H*-pyrrol-2-yl)methyl)benzenesulfonamide (**4a**). Increasing the molar ratio of pyrrole, to *N*-tosyl imine **2a**, to 2:1 gave **4a** in higher yield with the formation of 5-phenyldipyrromethane (**3a**) as a minor product.[6] After this examination, we focused on obtaining the 5-substituted dipyrromethane as the major product from the reaction of pyrrole and *N*-benzylidene-4-methylbenzenesulfonamide (**2a**). We performed the reaction of pyrrole with **2a** by using different pyrrole/*N*-tosyl imine ratios in the presence of copper triflate (10 mol %) at rt. Reactions with 10 and 20 equiv of pyrrole were carried out in THF, monitored with TLC and completed after 6 h, affording **3a**/**4a** with 34/37 and 40/32% yields, respectively (Scheme 2). When the reaction was performed with 40 equiv of pyrrole without solvent,

Keywords: Dipyrromethanes; Metal triflate; *N*-Tosyl imine; Pyrrole derivatives; Lewis acid catalysis.
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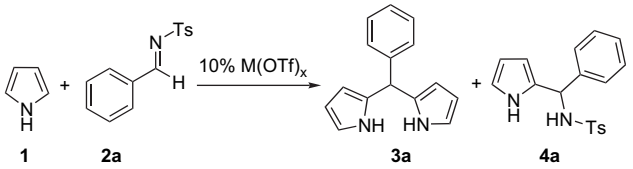
dipyrromethane was formed as the major product in 55% yield. Increasing the pyrrole equivalent did not obviously affect the yield of **3a**.



Scheme 2.

To investigate the effects of metal triflates, the reactions of pyrrole and *N*-benzylidene-4-methylbenzenesulfonamide (**2a**) were carried out in the presence of different metal triflates with excess pyrrole (40 equiv) at rt. Among all the metal triflates tested, $Gd(OTf)_3$ and $Cu(OTf)_2$ gave the highest yields of 5-phenyldipyrromethane (**3a**), 69 and 55%, respectively (Table 1).

Table 1. Effects of metal triflates on the synthesis of dipyrromethane **3a**[a]

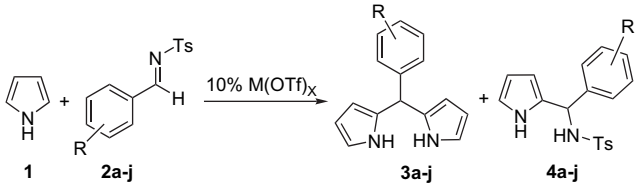
Entry	Catalyst	Yield (%)[b] **3a/4a**
1	$Cu(OTf)_2$	55/16
2	$Gd(OTf)_3$	69/20
3	$Yb(OTf)_3$	52/38
4	$Y(OTf)_3$	45/43
5	$La(OTf)_3$	34/53
6	$Zn(OTf)_2$	23/60
7	$Nd(OTf)_3$	14/72

[a] Reactions were carried out in excess pyrrole (40 equiv) as solvent at rt.
[b] Yield refers to pure product after column chromatography.

We continued to study the effect of substituents on the phenyl ring of the *N*-tosyl imines using $Cu(OTf)_2$ and $Gd(OTf)_3$ on the synthesis of 5-substituted dipyrromethanes. Reactions of *N*-tosyl imines (**2a–j**) and pyrrole with $Gd(OTf)_3$ catalyst gave 2-alkylated pyrrole sulfonamides (**4a–j**) in 10–85% yields and 5-substituted dipyrromethanes (**3a–j**) in 5–90% yields (Table 2). Similar results were obtained when $Cu(OTf)_2$ was used as the catalyst at rt; the corresponding pyrrole derivatives were obtained in 7–86% yields and dipyrromethanes in 5–85% yields. For both catalysts, formation of the products **3** and **4** is very sensitive to the nature of the substituents on *N*-tosyl imine. When the phenyl ring bears an electron donating substituent such as a methyl, hydroxy or methoxy, dipyrromethanes **3** are obtained in high yields (Table 2, entries 2–5). The reactions with electron withdrawing groups such as nitro, trifluoromethyl or halogens on the phenyl ring gave 5-substituted dipyrromethanes in lower yields at rt (Table 2, entries 6–10).

To improve the yields of dipyrromethane products having electron withdrawing substituents, reactions were carried out at 100 °C. It was observed that at high temperatures the yields of dipyrromethane products with electron withdrawing substituents and halogens increase dramatically (Table 2, entries 6–10). Dipyrromethanes with strongly electron withdrawing groups (nitro, trifluoromethyl) and halogens were synthesized in 68–79% yields with $Gd(OTf)_3$ and in 53–85% yields with $Cu(OTf)_2$. Despite this increase for electron withdrawing groups at 100 °C, yields for electron donating groups are lower. With this reaction protocol, we obtained high yields of dipyrromethanes for both types of

Table 2. Synthesis of 5-substituted dipyrromethanes by the reaction of pyrrole and different *N*-tosyl imines[a]



Entry	R	Catalyst $Gd(OTf)_3$ Yield (%)[b] **3/4**		Catalyst $Cu(OTf)_2$ Yield (%)[b] **3/4**		Compounds
		rt	100 °C	rt	100 °C	
1	H	69/20	65/17	55/16	48/10	**3a/4a**
2	4-CH_3O	83/10	64/15	85/8	45/19	**3b/4b**
3	2-CH_3O	71/17	61/21	55/20	48/35	**3c/4c**
4	4-CH_3	83/10	69/9	80/7	35/11	**3d/4d**
5	2-OH	90/—	44/—	77/—	27/—	**3e/4e**[c]
6	4-NO_2	5/85	79/8	7/78	72/9	**3f/4f**
7	4-CF_3	11/82	68/13	5/86	85/6	**3g/4g**
8	4-F	40/50	70/14	38/45	53/32	**3h/4h**
9	4-Cl	44/46	71/13	40/55	62/25	**3i/4i**
10	4-Br	20/71	74/12	38/53	74/14	**3j/4j**

[a] Reactions were carried out in excess pyrrole (40 equiv) as solvent.
[b] Yield refers to pure product after column chromatography.
[c] Addition product decomposed and could not be isolated by column chromatography.

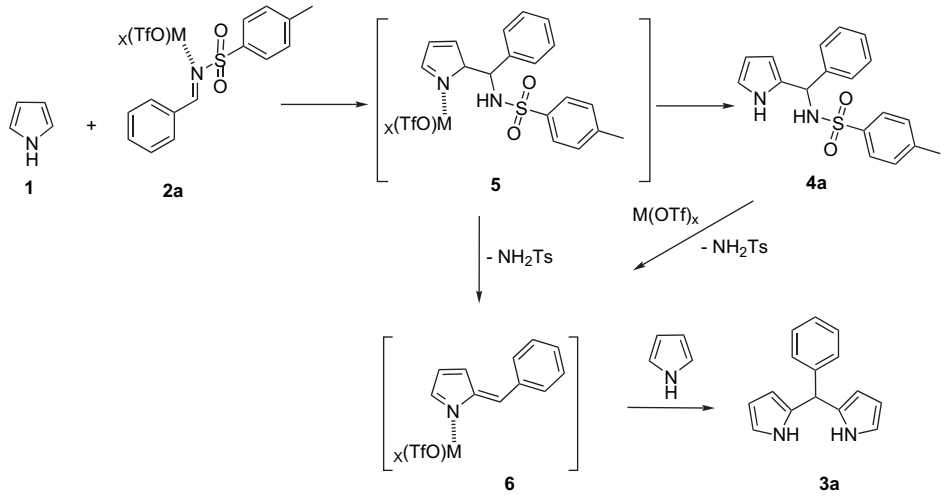
substituents only by performing the reaction at two different temperatures.

Structures of dipyrromethanes **3a–d**, **f**, **h–j** were confirmed by comparing their NMR spectra and melting points with those reported in literature.[2,7] Structures of **3e**, **g** and pyrrole derivatives **4a–j** were identified by ^1H NMR, ^{13}C NMR and elemental analysis. The position of the substituent was assigned by COSY spectra and by comparison of the ^1H NMR spectra with the known 2-alkylated pyrroles.[8]

The following reaction mechanism is proposed for the metal triflate catalyzed reaction of *N*-tosyl imine with pyrrole (Scheme 3). In the first step, *N*-tosyl imine is activated by the metal triflate. The addition of pyrrole to the activated imine complex affords structure **4a** through the intermediate **5**. Formation of dipyrromethane could be explained by the addition of a second pyrrole to the intermediate **6**, which is generated by the elimination of sulfonamide from intermediate **5** or compound **4a**. Structures like intermediate **6** are proposed by other researchers for the reaction of indole with imines, aldehydes and enones.[9] To support this proposed mechanism, the isolated product **4a** was reacted with excess pyrrole in the presence of metal triflate. Dipyrromethane was obtained as the main product after 6 h under the same conditions and *p*-toluenesulfonamide was isolated. The same reaction was performed without using the metal triflate and dipyrromethane formation was not observed. This examination shows that the metal triflate has a crucial role in the formation of dipyrromethane from **4a**.

3. Conclusion

In conclusion, a new and attractive synthetic method has been developed for the preparation of 5-substituted dipyrromethanes by the reaction of *N*-tosyl imine and pyrrole in the



Scheme 3.

presence of metal triflates. Tripyrromethane or any other oligomeric side products were not observed. The reaction procedure is simple and anhydrous conditions are not required. An advantage of this method is that high yields of 5-substituted dipyrromethanes with electron donating or withdrawing substituents can be obtained selectively only by tuning the reaction temperature.

4. Experimental

4.1. General

Commercially available reagents and solvents were used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using $SiMe_4$ as an internal reference with Bruker Ultrashield FT NMR spectrometer. IR spectra were determined on an Unicam Mattson 1000 FT IR spectrometer. Melting points were recorded on Gallenkamp melting-point apparatus and are uncorrected. Thin-layer chromatography was performed with 60F silica gel plates and flash column chromatography by use of silica gel 60 F_{254} (230–400 mesh). The spots were visualized with UV light (λ=254 nm). *N*-Tosyl imines (**2a**–**j**) are synthesized in high yields by the reaction of *p*-toluenesulfonamide and aldehydes in the presence of *p*-toluenesulfonic acid.

4.2. Synthesis of dipyrromethanes (3) and 2-substituted pyrrole sulfonamides (4)

N-Tosyl imine (1 mmol) was dissolved in excess pyrrole (40 mmol) and then metal triflate (0.1 mmol) was added to the reaction mixture at the temperature indicated in Table 2. The reaction was monitored with TLC and completed after 6 h. Metal triflate was removed from the reaction medium by subjecting the mixture to a short flash silica gel chromatography using ethyl acetate as an eluent. The eluent was removed under reduced pressure and the residue was purified by flash silica gel chromatography.

4.2.1. 5-Phenyldipyrromethane (3a).[7a] Pale yellow crystals; mp: 100–101 °C, lit.: 100–101 °C; R_f 0.60 (1:3 EtOAc/hexane); IR (KBr) 3449, 2951, 1630, 1510, 1410, 1293, 1225, 1048, 760, 703, 607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (s, 1H, *meso*H), 5.92 (br s, 2H, 2C3-H), 6.14 (dd, *J* 2.8, 5.9, 2H, 2C4-H), 6.68 (dd, *J* 2.6, 4.2, 2H, 2C5-H), 7.22–7.35 (m, 5H, Ar-H), 7.88 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.10, 107.45, 108.75, 117.12, 127.03, 128.51, 128.68, 132.36, 142.23.

4.2.2. 5-(4-Methoxyphenyl)dipyrromethane (3b).[7a] Pale yellow powder; mp: 98–99 °C, lit.: 99 °C; R_f 0.47 (1:3 EtOAc/hexane); IR (KBr) 3405, 2964, 2936, 1616, 1507, 1457, 1299, 1245, 1175, 1103, 1027, 965, 838, 774, 720, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 5.42 (s, 1H, *meso*H), 5.90–5.92 (m, 2H, 2C3-H), 6.14 (dd, *J* 2.8, 6.0, 2H, 2C4-H), 6.65–6.67 (m, 2H, 2C5-H), 6.85 (d, *J* 8.6, 2H, Ar-H), 7.14 (d, *J* 8.6, 2H, Ar-H), 7.82 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz): δ 43.21, 55.15, 107.27, 108.67, 114.03, 117.02, 129.44, 132.76, 134.29, 158.61.

4.2.3. 5-(2-Methoxyphenyl)dipyrromethane (3c).[7a] Pale yellow powder; mp: 114–115 °C, lit.: 115 °C; R_f 0.65 (1:3 EtOAc/hexane); IR (KBr) 3425, 1636, 1485, 1242, 1090, 1023, 966, 715, 555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 5.82 (s, 1H, *meso*H), 5.91 (br s, 2H, 2C3-H), 6.15 (d, *J* 2.5, 2H, 2C4-H), 6.63 (d, *J* 1.4, 2H, 2C5-H), 6.94–6.97 (m, 2H, Ar-H), 7.12 (d, *J* 6.8, 1H, Ar-H), 7.28 (t, *J* 7.8, 1H, Ar-H), 7.97 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.68, 55.74, 107.10, 108.70, 111.24, 116.67, 121.04, 128.07, 129.60, 131.14, 132.47, 156.73.

4.2.4. 5-(4-Methylphenyl)dipyrromethane (3d).[7b] Pale yellow crystals; mp: 110–111 °C, lit.: 110–111 °C; R_f 0.65 (1:3 EtOAc/hexane); IR (KBr) 3417, 2356, 1635, 1508, 1420, 1254, 1089, 1025, 964, 909, 790, 742, 509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 5.44 (s, 1H, *meso*H), 5.91 (br s, 2H, 2C3-H), 6.13 (dd, *J* 2.8, 5.9, 2H, 2C4-H), 6.66 (dd, *J* 2.6, 4.2, 2H, 2C5-H), 7.10–7.15 (m, 4H, Ar-H), 7.85 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.18, 43.72, 107.32, 108.74, 116.99, 128.42, 129.38, 132.57, 136.42, 139.25.

4.2.5. 5-(2-Hydroxyphenyl)dipyrromethane (3e). Light brown oil; R_f 0.32 (1:3 EtOAc/hexane); IR (KBr) 3418, 2072, 1635, 1493, 1451, 1330, 1255, 1085, 1023, 909, 790, 741, 529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.17

(br s, 1H, OH), 5.53 (s, 1H, *meso*H), 6.01 (br s, 2H, 2C3-H), 6.16 (dd, *J* 2.8, 5.9, 2H, 2C4-H), 6.70 (dd, *J* 2.6, 4.1, 2H, 2C5-H), 6.87–6.95 (m, 2H, Ar-H), 7.08–7.10 (m, 1H, Ar-H), 7.18–7.22 (m, 1H, Ar-H), 8.14 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.59, 107.22, 108.85, 117.89, 118.00, 121.63, 128.52, 128.81, 130.19, 130.78, 153.87. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.48; H, 6.03; N, 11.58.

4.2.6. 5-(4-Nitrophenyl)dipyrromethane (3f).[7a] Yellow powder; mp: 159–160 °C, lit.: 159–160 °C; R_f 0.48 (1:3 EtOAc/hexane); IR (KBr) 3394, 3359, 3101, 1595, 1512, 1348, 1114, 1027, 808, 735, 660, 568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (s, 1H, *meso*H), 5.88 (br s, 2H, 2C3-H), 6.18 (dd, *J* 2.8, 6.0, 2H, 2C4-H), 6.75 (dd, *J* 2.6, 4.2, 2H, 2C5-H), 7.39 (d, *J* 8.6, 2H, Ar-H), 7.98 (br s, 2H, 2N-H), 8.18 (d, *J* 8.8, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.87, 107.92, 108.95, 117.94, 123.80, 129.25, 130.76, 147.02, 149.66.

4.2.7. 5-(4-Trifluoromethylphenyl)dipyrromethane (3g). Yellow oil; R_f 0.47 (1:3 EtOAc/hexane); IR (KBr) 3448, 3401, 2980, 1618, 1416, 1326, 1164, 1124, 1067, 1019, 775, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (s, 1H, *meso*H), 5.91 (br s, 2H, 2C3-H), 6.20 (dd, *J* 2.8, 6.0, 2H, 2C4-H), 6.67–6.69 (m, 2H, 2C5-H), 7.35 (d, *J* 8.3, 2H, Ar-H), 7.63 (d, *J* 8.1, 2H, Ar-H), 7.82 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.78, 107.84, 108.82, 117.66, 124.16 (q, $^1J_{C-F}$ 270.3), 125.54 (q, $^3J_{C-F}$ 3.7), 128.75, 129.29 (q, $^2J_{C-F}$ 32.2), 131.50, 146.28. Anal. Calcd for $C_{16}H_{13}F_3N_2$: C, 66.20; H, 4.51; N, 9.65. Found: C, 66.07; H, 4.70; N, 9.59.

4.2.8. 5-(4-Fluorophenyl)dipyrromethane (3h).[7a] Light brown crystals; mp: 80–81 °C, lit.: 81 °C; R_f 0.53 (1:3 EtOAc/hexane); IR (KBr) 3410, 2928, 1610, 1498, 1451, 1285, 1175, 1103, 960, 764, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (s, 1H, *meso*H), 5.89 (br s, 2H, 2C3-H), 6.16 (dd, *J* 2.8, 5.8, 2H, 2C4-H), 6.66 (br s, 2H, 2C5-H), 7.00–7.05 (m, 2H, Ar-H), 7.16–7.20 (m, 2H, Ar-H), 7.81 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.28, 107.55, 108.79, 115.42 (d, $^2J_{C-F}$ 21.3), 117.34, 129.92 (d, $^3J_{C-F}$ 7.9), 132.24, 137.96 (d, $^4J_{C-F}$ 3.2), 161.85 (d, $^1J_{C-F}$ 244.5).

4.2.9. 5-(4-Chlorophenyl)dipyrromethane (3i).[7b] Pale yellow powder; mp: 112–113 °C, lit.: 112 °C; R_f 0.58 (1:3 EtOAc/hexane); IR (KBr) 3382, 2958, 2923, 2861, 1641, 1485, 1405, 1255, 1087, 1022, 767, 720, 550, 508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (s, 1H, *meso*H), 5.90 (br s, 2H, 2C3-H), 6.17 (dd, *J* 2.8, 5.8, 2H, 2C4-H), 6.66 (dd, *J* 2.6, 4.2, 2H, 2C5-H), 7.15 (d, *J* 8.4, 2H, Ar-H), 7.31 (d, *J* 8.4, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.35, 107.61, 108.75, 117.42, 128.70, 129.74, 131.88, 132.81, 140.69.

4.2.10. 5-(4-Bromophenyl)dipyrromethane (3j).[2] Pale yellow powder; mp: 122–123 °C, lit.: 125–125.5 °C; R_f 0.59 (1:3 EtOAc/hexane); IR (KBr) 3374, 3098, 2957, 2920, 2861, 1707, 1481, 1400, 1083, 1021, 765, 720, 643, 544, 503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41 (s, 1H, *meso*H), 5.90 (br s, 2H, 2C3-H), 6.16 (dd, *J* 2.8, 5.9, 2H, 2C4-H), 6.66 (dd, *J* 2.6, 4.2, 2H, 2C5-H), 7.10 (d, *J* 8.4, 2H, Ar-H), 7.46 (d, *J* 8.4, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.50, 107.65, 108.83, 117.44, 120.95, 130.17, 131.71, 131.77, 141.27.

4.2.11. 4-Methyl-*N*-(phenyl(1*H*-pyrrol-2-yl)methyl)-benzenesulfonamide (4a). White powder; mp: 132–133 °C; R_f 0.40 (1:3 EtOAc/hexane); IR (KBr): 3458, 2085, 1633, 1390, 1282, 1136, 1080, 1021, 689, 605, 531 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 5.57–5.60 (m, 2H, C3-H, CH), 5.85 (d, *J* 9.9, 1H, SO_2NH), 5.97 (dd, *J* 2.8, 6.0, 1H, C4-H), 6.65 (dd, *J* 2.5, 4.0, 1H, C5-H), 7.09–7.20 (m, 7H, Ar-H), 7.53 (d, *J* 8.3, 2H, Ar-H), 8.76 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.49, 55.78, 108.20, 118.57, 127.16, 127.38, 127.57, 128.35, 129.05, 129.29, 130.53, 137.47, 138.89, 142.87. Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58; S, 9.82. Found: C, 66.12; H, 5.63; N, 8.40; S, 9.73.

4.2.12. *N*-((4-Methoxyphenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (4b). Colourless viscous oil; R_f 0.30 (1:3 EtOAc/hexane); IR (KBr): 3516, 2072, 1636, 1507, 1243, 1169, 1027, 762, 715, 556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.50 (d, *J* 8.1, 1H, CH), 5.57–5.59 (m, 2H, SO_2NH, C3-H), 5.98 (dd, *J* 2.7, 6.0, 1H, C4-H), 6.67 (br s, 1H, C5-H), 6.70 (d, *J* 8.7, 2H, Ar-H), 7.02 (d, *J* 8.7, 2H, Ar-H), 7.14 (d, *J* 8.2, 2H, Ar-H), 7.55 (d, *J* 8.3, 2H, Ar-H), 7.84 (d, *J* 8.4, 2H, Ar-H), 8.72 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.55, 55.09, 55.53, 108.08, 108.19, 113.79, 118.51, 127.25, 128.04, 129.03, 130.90, 131.06, 137.54, 142.88, 159.19. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 64.25; H, 5.63; N, 7.88; S, 9.08.

4.2.13. *N*-((2-Methoxyphenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (4c). Light brown powder; mp: 132–133 °C; R_f 0.34 (1:3 EtOAc/hexane); IR (KBr): 3440, 2954, 2835, 1638, 1491, 1453, 1328, 1247, 1156, 1092, 1023, 909, 790, 743, 664, 549 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 5.51 (br s, 1H, C3-H), 5.64 (d, *J* 9.3, 1H, CH), 5.90 (d, *J* 9.1, 1H, SO_2NH), 5.97 (dd, *J* 2.8, 5.8, 1H, C4-H), 6.70 (dd, *J* 2.5, 4.1, 1H, C5-H), 6.73 (d, *J* 8.3, 1H, Ar-H), 6.81 (t, *J* 7.4, 1H, Ar-H), 7.00 (dd, *J* 1.6, 7.5, 1H, Ar-H), 7.09 (d, *J* 8.2, 2H, Ar-H), 7.16–7.21 (m, 1H, Ar-H), 7.55 (d, *J* 8.2, 2H, Ar-H), 8.72 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.55, 53.85, 55.45, 107.04, 108.26, 111.21, 118.01, 120.87, 126.82, 127.22, 129.09, 129.60, 130.55, 137.86, 142.55, 156.76. Anal. Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.02; H, 5.66; N, 7.86; S, 9.00. Found: C, 64.11; H, 5.81; N, 7.82; S, 8.75.

4.2.14. *N*-((1*H*-Pyrrol-2-yl)(*p*-tolyl)methyl)-4-methyl-benzenesulfonamide (4d). Light brown powder; mp: 96–97 °C; R_f 0.44 (1:3 EtOAc/hexane); IR (KBr): 3426, 2963, 2924, 2866, 2104, 1636, 1509, 1426, 1321, 1262, 1154, 1091, 1026, 910, 790, 722, 663, 563 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H, CH_3), 2.43 (s, 3H, SO_2Ph-CH_3), 5.52 (d, *J* 8.2, 1H, CH), 5.58 (br s, 1H, C3-H), 5.62 (d, *J* 8.0, 1H, SO_2NH), 5.98 (dd, *J* 2.8, 5.7, 1H, C4-H), 6.66 (br s, 1H, C5-H), 7.00–7.02 (m, 4H, Ar-H), 7.13 (d, *J* 8.1, 2H, Ar-H), 7.55 (d, *J* 8.2, 2H, Ar-H), 8.62 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.15, 21.53, 55.64, 108.13, 108.17, 118.51, 127.24,

127.37, 129.06, 129.31, 130.78, 135.98, 137.27, 137.55, 142.83. Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23; S, 9.42. Found: C, 66.90; H, 5.95; N, 8.20; S, 9.37.

4.2.15. 4-Methyl-*N*-((4-nitrophenyl)(1*H*-pyrrol-2-yl)-methyl)benzenesulfonamide (4f). Light brown powder; mp: 153–154 °C; R_f 0.34 (1:3 EtOAc/hexane); IR (KBr): 3419, 1716, 1636, 1512, 1412, 1337, 1255, 1150, 1089, 1014, 909, 791, 741, 688, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 5.29 (br s, 1H, SO_2NH), 5.52 (br s, 1H, C3-H), 5.70 (br s, 1H, CH), 6.02 (dd, *J* 2.8, 6.0, 1H, C4-H), 6.76 (dd, *J* 2.6, 4.0, 1H, C5-H), 7.20 (d, *J* 8.0, 2H, Ar-H), 7.37 (d, *J* 8.6, 2H, Ar-H), 7.60 (d, *J* 8.3, 2H, Ar-H), 8.10 (d, *J* 8.7, 2H, Ar-H), 8.56 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.93, 55.06, 108.69, 119.38, 123.54, 127.15, 128.16, 128.99, 129.56, 134.98, 137.06, 143.78, 145.64. Anal. Calcd for $C_{18}H_{17}N_3O_4S$: C, 58.21; H, 4.61; N, 11.31; S, 8.63. Found: C, 58.00; H, 4.68; N, 11.38; S, 8.51.

4.2.16. *N*-((1*H*-Pyrrol-2-yl)(4-(trifluoromethyl)phenyl)-methyl)-4-methylbenzenesulfonamide (4g). White powder; mp: 113–114 °C; R_f 0.38 (1:3 EtOAc/hexane); IR (KBr): 3382, 3272, 3107, 3061, 2926, 2867, 1918, 1802, 1612, 1489, 1422, 1325, 1160, 1125, 1063, 1026, 915, 850, 792, 732, 665, 660, 555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H, CH_3), 5.55 (br s, 1H, C3-H), 5.69 (d, *J* 8.6, 1H, CH), 6.00–6.03 (m, 2H, C4-H, SO_2NH), 6.69 (br s, 1H, C5-H), 7.07 (d, *J* 8.1, 2H, Ar-H), 7.24 (d, *J* 8.1, 2H, Ar-H), 7.39 (d, *J* 8.2, 2H, Ar-H), 7.47 (d, *J* 8.2, 2H, Ar-H), 8.86 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.32, 55.66, 108.36, 108.61, 119.15, 125.17 (q, $^3J_{C-F}$ 3.6), 127.05, 127.91, 129.39, 129.49, 129.90 (q, $^2J_{C-F}$ 32.2), 137.01, 142.49, 143.46. Anal. Calcd for $C_{19}H_{17}F_3N_2O_2S$: C, 57.86; H, 4.34; N, 7.10; S, 8.13. Found: C, 57.60; H, 4.32; N, 7.13; S, 7.99.

4.2.17. *N*-((4-Fluorophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (4h). Colourless viscous oil; R_f 0.37 (1:3 EtOAc/hexane); IR (KBr): 3423, 2978, 2922, 2870, 1640, 1505, 1429, 1322, 1223, 1154, 1092, 1029, 915, 844, 774, 722, 664, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H, CH_3), 5.54 (br s, 1H, C3-H), 5.57 (d, *J* 8.4, 1H, CH), 5.86 (d, *J* 8.4, 1H, SO_2NH), 5.98 (dd, *J* 2.7, 5.9, 1H, C4-H), 6.67 (dd, *J* 2.6, 4.1, 1H, C5-H), 6.84 (t, *J* 8.6, 2H, Ar-H), 7.07–7.13 (m, 4H, Ar-H), 7.52 (d, *J* 8.3, 2H, Ar-H), 8.77 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.50, 55.27, 108.25, 115.21 (d, $^2J_{C-F}$ 21.4), 118.81, 127.15, 129.10 (d, $^3J_{C-F}$ 8.1), 129.37, 130.31, 134.58 (d, $^4J_{C-F}$ 3.1), 137.35, 143.15, 162.21 (d, $^1J_{C-F}$ 245.7). Anal. Calcd for $C_{18}H_{17}FN_2O_2S$: C, 62.77; H, 4.98; N, 8.13; S, 9.31. Found: C, 62.40; H, 5.01; N, 8.05; S, 9.19.

4.2.18. *N*-((4-Chlorophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (4i). Brown powder; mp: 115–116 °C; R_f 0.43 (1:3 EtOAc/hexane); IR (KBr): 3448, 3405, 2965, 2922, 2863, 1636, 1332, 1155, 1087, 1022, 805, 721, 662, 561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 5.54–5.57 (m, 2H, C3-H, CH), 5.88 (d, *J* 8.5, 1H, SO_2NH), 5.98 (dd, *J* 2.7, 6.0, 1H, C4-H), 6.65–6.66 (m, 1H, C5-H), 7.05 (d, *J* 8.5, 2H, Ar-H), 7.11–7.13 (m, 4H, Ar-H), 7.49 (d, *J* 8.3, 2H, Ar-H), 8.79 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.53, 55.34, 108.27, 108.40, 118.91, 127.13, 128.44, 128.89, 129.40, 129.92, 133.60, 137.26, 137.32, 143.23. Anal. Calcd for $C_{18}H_{17}ClN_2O_2S$: C, 59.91; H, 4.75; N, 7.76; S, 8.89. Found: C, 59.67; H, 4.70; N, 7.82; S, 8.78.

4.2.19. *N*-((4-Bromophenyl)(1*H*-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (4j). Brown powder; mp: 116–117 °C; R_f 0.42 (1:3 EtOAc/hexane); IR (KBr): 3388, 3275, 2961, 2921, 2862, 2756, 1691, 1596, 1484, 1432, 1323, 1154, 1088, 1025, 807, 663, 559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 5.55–5.57 (m, 2H, C3-H, CH), 5.97–6.00 (m, 2H, SO_2NH, C4-H) 6.66 (dd, *J* 2.5, 4.0, 1H, C5-H), 6.98 (d, *J* 8.4, 2H, Ar-H), 7.10 (d, *J* 8.1, 2H, Ar-H), 7.26 (d, *J* 8.4, 2H, Ar-H), 7.47 (d, *J* 8.3, 2H, Ar-H), 8.83 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.55, 55.42, 108.27, 108.43, 118.94, 121.70, 127.11, 129.24, 129.41, 129.79, 131.38, 137.20, 137.77, 143.26. Anal. Calcd for $C_{18}H_{17}BrN_2O_2S$: C, 53.34; H, 4.23; N, 6.91; S, 7.91. Found: C, 53.67; H, 4.31; N, 6.84; S, 7.98.

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References and notes

1. (a) Pandey, R. K.; Jagerovic, N.; Ryan, M. J.; Dougherty, T. J.; Smith, K. M. *Tetrahedron* **1996**, *52*, 5349–5362; (b) Jasat, A.; Dolphin, D. *Chem. Rev.* **1997**, *97*, 2267–2340; (c) Gale, P. A.; Anzenbacher, P., Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57–102; (d) Sessler, J. L.; Camiolo, S.; Gale, P. A. *Coord. Chem. Rev.* **2003**, *240*, 17–55; (e) Wu, Y.-D.; Wang, D.-F.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739–3746; (f) Wagner, R. W.; Johnson, T. E.; Lindsey, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 11166–11180.
2. Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427–11440.
3. (a) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240–4250; (b) Nishino, N.; Wagner, R. W.; Lindsey, J. S. *J. Org. Chem.* **1996**, *61*, 7534–7544; (c) Casiraghi, G.; Cornia, M.; Zanardi, F.; Rassu, G.; Ragg, E.; Bortolini, R. *J. Org. Chem.* **1994**, *59*, 1801–1808; (d) Cornia, M.; Binacchi, S.; Del Soldato, T.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **1995**, *60*, 4964–4965; (e) Vigmond, S. J.; Chang, M. C.; Kallury, K. M. R.; Thompson, M. *Tetrahedron Lett.* **1994**, *35*, 2455–2458; (f) Casiraghi, G.; Cornia, M.; Rassu, G.; Del Sante, C.; Spanu, P. *Tetrahedron* **1992**, *48*, 5619–5628; (g) Boyle, R. W.; Xie, L. Y.; Dolphin, D. *Tetrahedron Lett.* **1994**, *35*, 5377–5380; (h) Nishino, N.; Wagner, R. W.; Lindsey, J. S. *J. Org. Chem.* **1996**, *61*, 7534–7544; (i) Setsune, J.; Hashimoto, M.; Shiozawa, K.; Hayakawa, J.; Ochi, T.; Masuda, R. *Tetrahedron* **1998**, *54*, 1407–1424; (j) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391–1396; (k) Wijesekera, T. P. *Can. J. Chem.* **1996**, *74*, 1868–1871.
4. (a) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302; (b) Kobayashi, S. *Eur. J.*

Org. Chem. **1999**, 15–27; (c) Kobayashi, S. *Synlett* **1994**, 689–701.
5. Unaleroglu, C.; Temelli, B.; Demir, A. S. *Synthesis* **2004**, *15*, 2574–2578.
6. Temelli, B.; Unaleroglu, C. *Tetrahedron Lett.* **2005**, *46*, 7941–7943.
7. (a) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391–1396; (b) Naik, R.; Joshi, P.; Kaiwar, S. P.; Deshpande, R. K. *Tetrahedron* **2003**, *59*, 2207–2213; (c) Chen, H.; Shao, X.-B.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2003**, *59*, 3505–3510; (d) Dubic, M.; Lhotak, P.; Kral, V.; Lang, K.; Stibar, I. *Tetrahedron Lett.* **1999**, *40*, 5949–5952.
8. (a) Kotsuki, H.; Nishiuchi, M.; Kobayashi, S.; Nishizawa, H. *J. Org. Chem.* **1990**, *55*, 2969–2972; (b) Jorapur, Y. R.; Lee, C.-H.; Chi, D. Y. *Org. Lett.* **2005**, *7*, 1231–1234.
9. (a) Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004**, *60*, 6679–6684; (b) Xie, W.; Bloomfield, K. M.; Jin, Y.; Dolney, N. Y.; Wang, P. G. *Synlett* **1999**, 498–500; (c) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. *Tetrahedron Lett.* **2004**, *45*, 3673–3676; (d) Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467–4470.

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DMAP catalyzed reaction of β-ketoesters and dimethyl acetylenedicarboxylate: efficient synthesis of polysubstituted benzenes and biaryls

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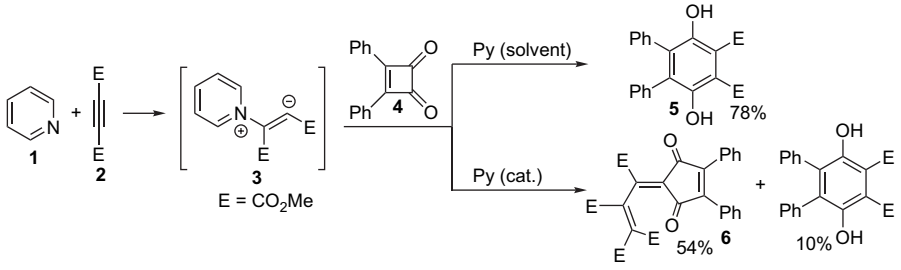
Abstract—A DMAP catalyzed tandem addition–cyclization–dehydration sequence involving dimethyl acetylenedicarboxylate and β-ketoesters leading to polysubstituted benzene/biaryl derivatives is presented.

1. Introduction

Benzene derivatives are uniquely important in organic chemistry. Not surprisingly therefore, the quest to develop efficient and versatile methods for the synthesis of substituted benzenes[1,2] has been a perennial theme in organic synthesis. The venerable Friedel–Crafts reaction[3] and the ortho-metallation strategy[4] can be used for introducing substituents into the benzene ring. The Reppe reaction,[5] the Vollhardt protocol,[6] the Diels–Alder strategy, and the Bergman cyclization[7] hold much promise for the synthesis of substituted benzenes. Biaryls are important as they constitute the core unit in many of the natural and synthetic compounds endowed with useful biological properties.[8] They are also useful as components in new organic materials like electroluminescent conjugated polymers,[9] semiconductors, and liquid crystals.[10] The Ullmann reaction,[11] the nucleophilic substitution reaction using organometallic aryls and activated arenes with electron withdrawing substituents,[12] the intramolecular transfer of aryl groups by a radical mechanism,[13] coupling reaction of various phenolic and non-phenolic aromatics by oxidation with di-*tert*-butyl peroxide (DTBP) or LTA[14] and nucleophilic addition of aryl organometallics to arynes[15] are good routes to biaryls.

In the course of our recent studies on the chemistry of zwitterionic species,[16] it was shown that interception of the zwitterion **3** with cyclobutene-1,2-diones provided selective access to either cyclopentenedione derivatives or hexa substituted benzene derivatives[17] depending on the amount of pyridine used (Scheme 1).

In the context of this interesting observation, it was surmised that the tandem addition of an enolate, generated from β-ketoesters by pyridine, to two molecules of acetylenic ester, if experimentally feasible, would generate a species, which



Scheme 1. Pyridine catalyzed reaction of DMAD with cyclobutene-1,2-diones.

Keywords: β-Ketoesters; DMAD; DMAP; Biaryl.
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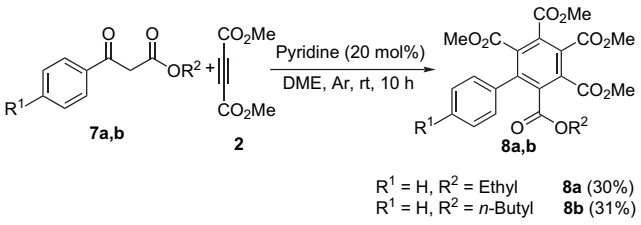
can transform into a hexatriene system well-disposed to undergo electrocyclization to afford a dihydrobenzene derivative, and the latter would undergo dehydration to deliver polysubstituted benzenes. The results of our studies validating the concept outlined above, leading to an unprecedented biaryl synthesis form the subject of this paper.

2. Results and discussion

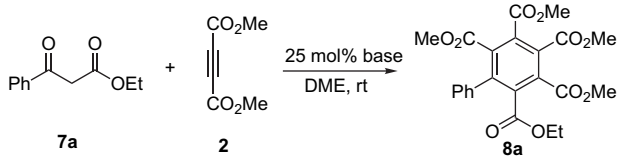
In the first instance, a solution of ethyl benzoyl acetate **7a** and dimethyl acetylenedicarboxylate (DMAD) **2** in DME was treated with 20 mol % pyridine at room temperature. The reaction afforded the fully substituted benzene derivative **8a** albeit in 30% yield (Scheme 2).



Scheme 2. Pyridine catalyzed reaction of DMAD with β-ketoesters.

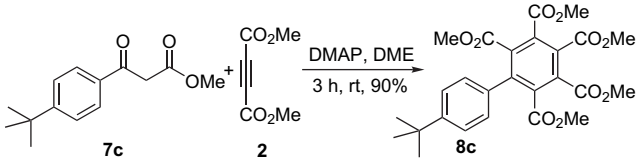
The enolate formation and subsequent annulation were investigated with different bases, and dimethyl aminopyridine (DMAP) was found to be the best catalyst for the transformation to biaryls; DABCO also gives comparable results, as summarized in Table 1.

Table 1. Optimization of reaction conditions



Entry	Base	Time (h)	DMAD (equiv)	Yield (%)
1	Pyridine	12	1	23
2	Pyridine	12	2.5	30
3	DABCO	3	2.5	90
4	DMAP	3	2.5	93
5	PPh_3	12	2.5	0
6	DBU	12	2.5	0
7	NaOMe	12	2.5	<10
8	NaH	12	2.5	<10

An illustrative example is the reaction of methyl-4-*tert*-butyl benzoyl acetate **7c** and DMAD in dry DME with 25 mol % of DMAP at room temperature under an argon atmosphere for 3 h affording the biphenyl derivative **8c** as a colorless crystalline solid in 90% yield (Scheme 3).



Scheme 3. DMAP catalyzed reaction of DMAD with β-ketoesters.

The product was characterized on the basis of spectroscopic data. In the IR spectrum, the ester carbonyl appeared at 1745 cm^{-1}. In the ^1H NMR spectrum, the carbomethoxy protons resonated at δ 3.89, 3.86, and 3.48. The ester carbonyls were discernible at δ 166.6, 166.0, and 165.5 in the ^{13}C NMR spectrum. Finally, the structure was unequivocally established by single crystal X-ray analysis (Fig. 1).[18]

The reaction was found to be general with various substituted β-ketoesters giving the substituted biaryls in excellent yields. The results are summarized in Table 2.

Mechanistically, the reaction can be interpreted as follows. The enolate generated by the deprotonation of β-ketoester adds to two molecules of DMAD in tandem, to furnish the

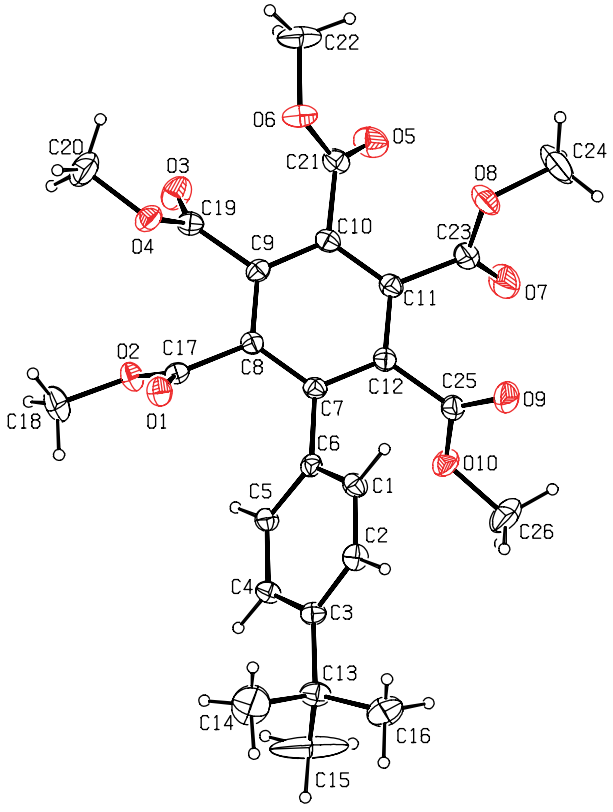
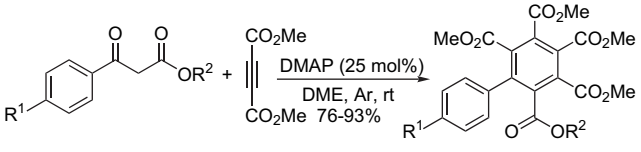
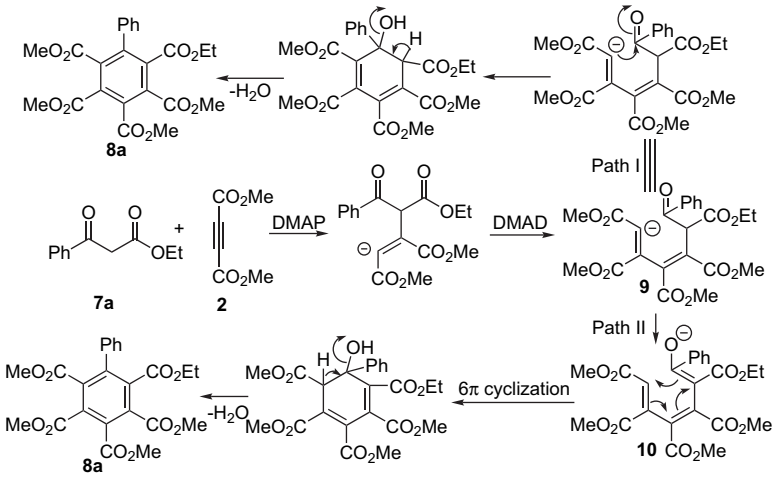


Figure 1. Single crystal X-ray structure of **8c**.

Table 2. DMAP catalyzed reaction of DMAD with various β-ketoesters



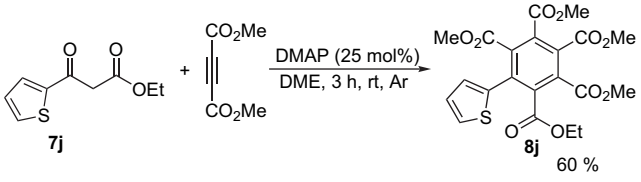
Entry	R^1	R^2	Product	Yield (%)
1	H	Ethyl	**8a**	93
2	H	*n*-Butyl	**8b**	86
3	Br	Methyl	**8d**	91
4	Br	*n*-Butyl	**8e**	85
5	F	*n*-Butyl	**8f**	86
6	F	Methyl	**8g**	88
7	CN	Methyl	**8h**	76
8	Ph	Methyl	**8i**	81



Scheme 4. Mechanistic rationalization.

vinyl anion **9**. Conceivably, this intermediate can transform into the product via two pathways. In path I, **9** undergo intramolecular addition of the vinylic anion to the benzoyl carbonyl followed by dehydration to afford **8a**. In pathway II, the enolate **10** generated from **9** by 1,5-proton transfer can undergo 6π-electrocyclization followed by dehydration to deliver **8a** (Scheme 4).

Thienyl substituted β-ketoester on treatment with DMAD in the presence of 25 mol % of DMAP also afforded the fully substituted benzene derivative in good yield (Scheme 5).



Scheme 5. Synthesis of fully substituted benzene derivative.

3. Conclusion

In conclusion, a new and an efficient protocol for the one pot synthesis of polysubstituted benzene/biaryl derivatives has been uncovered. The experimental simplicity and metal-free conditions of the synthesis are especially noteworthy.

4. Experimental

4.1. General

All reactions were conducted in oven-dried glassware sealed with rubber septa under a positive pressure of deoxygenated argon from a manifold. Solvents used for the experiments were distilled or dried as specified. Dimethyl acetylenedicarboxylate (DMAD), DMAP, and ethyl benzoyl acetate were purchased from Aldrich and used as received. The β-ketoesters used for our study are prepared from a known procedure.[19] All other reagents were purchased from local suppliers and used without purification. All reactions were monitored by TLC; visualization was effected with UV and/or by developing in iodine. Chromatography refers to open column chromatography on silica gel (100–200 mesh). Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Brücker DPX-300 MHz. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. IR spectra were recorded on Bomem MB series FT-IR spectrometer; absorbencies are reported in cm^{-1}. High-resolution mass spectra were obtained using Autospec M mass spectrometer. Elemental analyses were performed on a Perkin Elmer-2400 elemental analyzer.

4.2. General procedure for the synthesis of fully substituted benzene derivatives

To a stirred solution of β-ketoester (0.43 mmol) in anhydrous DME (10 mL) under an argon atmosphere was added DMAD (152 mg, 1.07 mmol) followed by DMAP (13 mg, 0.11 mmol). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, residue on silica gel column chromatography using 70:30 petroleum ether–ethyl acetate as eluent, to afford the respective product.

4.2.1. Compound 8a. Yield (221 mg, 93%). Colorless crystalline solid, mp 124–125 °C. IR (KBr) ν_{max}: 2955, 1738, 1571, 1443, 1412, 1328, 1251, 1219, 1096, 999 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.38–7.19 (m, 5H), 3.98–3.94 (m, 2H), 3.90 (s, 3H), 3.87 (s, 6H), 3.48 (s, 3H), 0.90 (uneven triplet, 3H, J_1=7.2 Hz, J_2=6.9 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.8, 165.7, 165.3, 165.2, 140.3, 136.6, 136.4, 135.9, 132.1, 131.4, 131.1, 128.4, 128.2, 127.9, 127.6, 66.9, 64.4, 61.7, 53.4, 52.9, 52.3. HRMS (EI): *m/z* calcd for $C_{23}H_{22}O_{10}$: 458.1213, found: 458.1238.

4.2.2. Compound 8b. Yield (153 mg, 86%). Colorless crystalline solid, mp 106–107 °C. IR (KBr) ν_{max}: 2959, 1748, 1738, 1439, 1346, 1243, 1218, 1135, 1094, 996 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33–7.21 (m, 5H), 3.89 (s, 3H), 3.86 (s, 6H), 3.48 (s, 3H), 1.24 (uneven triplet, 2H, J_1= 5.7 Hz, J_2=6.9 Hz), 1.13–1.06 (m, 2H), 0.85–0.77 (m, 5H).

^{13}C NMR ($CDCl_3$): δ 166.4, 166.1, 166.0, 165.5, 165.3, 140.3, 136.3, 136.6, 136.0, 132.2, 131.5, 130.2, 128.5, 128.3, 128.1, 65.6, 53.1, 52.6, 52.4, 51.8, 39.2, 30.3, 18.8. HRMS (EI): *m/z* calcd for $C_{25}H_{26}O_{10}$: 486.1526, found: 486.1468.

4.2.3. Compound 8c. Yield (192 mg, 90%). Colorless crystalline solid, mp 170 °C. IR (KBr) ν_{max}: 1745, 1610, 1568, 1512, 1442, 1352, 1251, 1182, 983 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.39 (d, 2H, J=5.4 Hz), 7.11 (d, 2H, J=8.4 Hz), 3.89 (s, 3H), 3.86 (s, 6H), 3.48 (s, 6H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 166.6, 166.0, 165.5, 151.6, 140.7, 136.8, 132.9, 131.3, 128.0, 125.1, 53.2, 53.1, 52.4, 34.7, 31.3. HRMS (FAB): *m/z* calcd (M^+) for $C_{26}H_{28}O_{10}$: 500.17, found: 500.36. The crystal structure for compound **8c** has been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 295899.

4.2.4. Compound 8d. Yield (184 mg, 91%). Colorless crystalline solid, mp 148–150 °C. IR (KBr) ν_{max}: 2953, 1742, 1732, 1542, 1440, 1221, 1001, 999 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H, J=8.4 Hz), 7.08 (d, 2H, J=8.1 Hz), 3.90 (s, 6H), 3.87 (s, 3H), 3.54 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.1, 165.8, 165.1, 139.2, 136.5, 134.7, 132.8, 131.4, 131.3, 130.0, 123.2, 53.3, 53.2, 52.7. Elemental analysis: Calcd for $C_{22}H_{19}BrO_{10}$, C, 50.50; H, 3.66. Found C, 50.82; H, 3.65.

4.2.5. Compound 8e. Yield (163 mg, 85%). Colorless crystalline solid, mp 123–125 °C. IR (KBr) ν_{max}: 2958, 1747, 1737, 1542, 1523, 1503, 1221, 1048, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.52 (d, 2H, J=8.4 Hz), 7.09 (d, 2H, J= 8.4 Hz), 3.92 (uneven triplet, 2H, J_1=6.6 Hz, J_2=9.0 Hz), 3.87 (s, 9H), 3.54 (s, 3H), 1.35–1.26 (m, 2H), 1.18–1.08 (m, 2H), 0.81 (uneven triplet, 3H, J_1=7.2 Hz, J_2=6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 166.1, 166.1, 165.8, 165.2, 139.0, 134.9, 131.4, 130.1, 123.2, 65.9, 53.2, 53.2, 53.1, 52.6, 30.1, 18.8. HRMS (FAB): For $C_{25}H_{25}BrO_{10}$: calcd ($M+Na^+$): 587.0529, found: 587.2785.

4.2.6. Compound 8f. Yield (190 mg, 86%). Colorless crystalline solid, mp 127–129 °C. IR (KBr) ν_{max}: 2958, 1747, 1732, 1537, 1513, 1455, 1216, 1102, 990 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.23–7.18 (m, 2H), 7.11–7.05 (m, 2H), 3.92 (uneven triplet, 2H, J_1=6.9 Hz, J_2=6.6 Hz), 3.87 (s, 3H), 3.83 (s, 6H), 3.53 (s, 3H), 1.37–1.26 (m, 2H), 1.19–1.10 (m, 2H), 0.82 (uneven triplet, 3H, J_1=7.2 Hz, J_2=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.9, 165.2, 164.5, 161.2 (aromatic carbon attached to fluorine), 136.8, 132.9, 132.6, 131.8, 131.8, 131.4, 131.2, 115.9, 115.4, 107.6, 105.4, 65.8, 53.4, 53.2, 53.2, 53.1, 30.4, 30.2, 18.8. HRMS (FAB): *m/z* calcd for $C_{25}H_{25}FO_{10}$: (M^+): 504.1432, found: 504.3005.

4.2.7. Compound 8g. Yield (200 mg, 88%). Colorless crystalline solid, mp 136–138 °C. IR (KBr) ν_{max}: 2958, 1742, 1737, 1542, 1513, 1450, 1226, 1052, 980 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.21–7.05 (m, 4H), 3.90 (s, 3H), 3.87 (s, 6H), 3.53 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.8, 165.2, 164.4, 161.1 (aromatic carbon attached to fluorine), 139.3, 136.8, 132.6, 131.6, 131.3, 130.2, 115.5, 115.2, 53.2, 53.1, 52.6. HRMS (EI): *m/z* calcd for $C_{22}H_{19}FO_{10}$: 462.0962, found: 462.0965.

4.2.8. Compound 8h. Yield (174 mg, 76%). Colorless crystalline solid, mp 144–146 °C. IR (KBr) ν_{max}: 2229, 1736, 1606, 1504, 1444, 1352, 1328, 1236, 1180, 930 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, 2H, J=8.1 Hz), 7.34 (d, 2H, J=8.4 Hz), 3.91 (s, 3H), 3.88 (s, 6H), 3.54 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 165.5, 165.4, 164.7, 140.5, 138.5, 135.9, 131.7, 131.4, 131.4, 130.2, 129.2, 112.7, 53.6, 53.2, 53.1. HRMS (EI): *m/z* calcd for $C_{23}H_{19}NO_{10}$: 469.1009, found: 469.1043.

4.2.9. Compound 8i. Yield (165 mg, 81%). Colorless crystalline solid, mp 184–186 °C. IR (KBr) ν_{max}: 1739, 1606, 1442, 1330, 1255, 1220, 1184, 983 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.65–7.61 (m, 4H), 7.45 (uneven triplet, 2H, J_1= 7.08 Hz, J_2=7.62 Hz), 7.43 (d, 2H, J=8.0 Hz), 7.34 (d, 1H, J=7.2 Hz), 3.86 (s, 9H), 3.52 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 166.5, 166.0, 165.4, 141.3, 140.3, 140.1, 136.7, 134.8, 132.4, 131.5, 130.2, 128.9, 128.0, 127.8, 126.8, 53.3, 53.2, 52.9. HRMS (EI): *m/z* calcd for $C_{28}H_{24}O_{10}$: 520.1369, found: 520.1105.

4.2.10. Compound 8j. Yield (143 mg, 60%). Colorless crystalline solid, mp 113–115 °C. IR (KBr) ν_{max}: 1739, 1722, 1571, 1448, 1359, 1321, 1259, 1180, 900 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, 1H, J=5.1 Hz), 7.06–7.01 (m, 2H), 4.06 (q, 2H, J_1=J_2=7.2 Hz), 3.89 (s, 3H), 3.87 (s, 6H), 3.51 (s, 3H), 1.05 (uneven triplet, 3H, J_1=6.9 Hz, J_2=7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2, 165.7, 165.6, 165.1, 165.1, 137.7, 131.1, 129.1, 127.6, 127.01, 62.0, 53.2, 53.2, 53.1, 52.7, 13.6. HRMS (EI): *m/z* calcd for $C_{21}H_{20}O_{10}S$: 464.0777, found: 464.0790.

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References and notes

1. Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.
2. (a) Sakakibara, T.; Tanaka, Y.; Yamasaki, S. *Chem. Lett.* **1986**, *5*, 797; (b) Sato, S.; Isobe, T.; Ushijima, T.; Nakamura, E. *Tetrahedron* **2005**, *61*, 11449; (c) Mohanakrishnan, A. K.; Prakash, C. *Synlett* **2005**, 2224.
3. (a) Eyley, S. C. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, NY, 1991; Vol. 2, p 707; (b) Heaney, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, NY, 1991; Vol. 2, p 733; (c) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, NY, 1973.
4. (a) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109; (b) Wittig, G.; Fuhrman, G. *Chem. Ber.* **1940**, *73*, 1197; (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
5. (a) Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104; (b) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925.
6. (a) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1; (b) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.
7. (a) Xi, C.; Chen, C.; Lin, J.; Hong, X. *Org. Lett.* **2005**, *7*, 347; (b) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.;

Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672; (c) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712; (d) Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143; (e) Jhones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660; (f) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25.

8. (a) Hassan, J.; Sèvignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gesser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.
9. Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 402.
10. Roncali, J. *Chem. Rev.* **1992**, *92*, 711.
11. Ullmann, F.; Bielecki. *J. Chem. Ber.* **1901**, *34*, 2174.
12. Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.
13. (a) Studer, A.; Bossart, M.; Vasella, T. *Org. Lett.* **2000**, *2*, 985; (b) Clive, D. L. J.; Kang, S. *Tetrahedron Lett.* **2000**, *41*, 1315.
14. Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331.
15. Huisgen, R.; Rist, H. *Justus Liebigs Ann. Chem.* **1955**, *594*, 137.
16. (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899; (b) Nair, V.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T.; Remadevi, B.; Menon, R. S.; Rath, N. P.; Srinivas, R. *Synthesis* **2003**, 1895; (c) Nair, V.; Pillai, A. N.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 1189.
17. Nair, V.; Pillai, A. N.; Beneesh, P. B.; Suresh, E. *Org. Lett.* **2005**, *7*, 4625.
18. The crystal structure for compound **8d** had been deposited at the Cambridge Crystallographic Data Center and allocated the reference no. CCDC 295899.
19. (a) Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488; (b) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

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A hybrid foldamer with unique architecture from conformationally constrained aliphatic–aromatic amino acid conjugate

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Abstract—In this paper, we describe the design and synthesis of a novel hybrid foldamer, derived from a conformationally constrained aliphatic–aromatic amino acid conjugate that adopts a well-defined, compact, three-dimensional structure, governed by a combined conformational restriction imposed by the individual amino acids from which the foldamer is composed. Conformational investigations confirmed the prevalence of a unique doubly bent conformation for the foldamer, in both solid and solution states, as evidenced from single crystal X-ray and 2D NOESY studies, respectively. The findings suggest that constrained aliphatic–aromatic amino acid conjugates offer new avenues for the de novo design of hybrid foldamers with distinctive structural architectures. Furthermore, the de novo design strategy disclosed herein has the potential for significantly augmenting the 'tool-box' of the modern day peptidomimetic chemist, as well as providing a novel approach to the field of rational design.

1. Introduction

Foldamers[1] as a class of conformationally ordered synthetic oligomers have been ushered into prominence primarily due to their enormous potential for the creation of unnatural oligomers that adopt discrete tertiary structures, just as biopolymers. The compact conformational features and their adjustable lengths mean that these synthetic oligomers may provide excellent starting points for the elaboration of protein mimics that might be difficult to design based on small-molecule scaffolds. Extensive investigations by several groups have resulted in the generation of a myriad of such synthetic oligomers with diverse backbone structures, conformations,[2] and functions.[3] Of late, increasing attention is being devoted to the design and development of hybrid foldamers with a view to expanding the conformational space available for foldamer design.[4–6] Of particular interest are α,β-hybrid peptides, reported by Gellman's group,[4] composed of alternately changing α- and β-amino acid constituents. NMR studies provided convincing hints for the formation of special helix types in this novel foldamer class.

2. Design principles

In an effort to augment the repertoire of conformational space available for foldamer design, we set out to generate novel foldamers, which contain conformationally constrained α-amino acid–aromatic amino acid-conjugated building blocks as subunits. In this article, we describe the design, synthesis, and conformational studies of a novel hybrid foldamer **3**, derived from regularly repeating α-aminoisobutyric acid (Aib) and 3-amino-4,6-dimethoxybenzoic acid (Adb) residues (Aib-Adb motif). We designed the Aib-Adb motif-based foldamer **3** anticipating that the corresponding oligomers would adopt a well-defined, compact, three-dimensional structure, governed by a combined conformational restriction imposed by both Aib and Adb residues (highlighted in blue and red bold bonds in **3**, Scheme 1). The achiral Aib residue is known to play a key role[7] in the conformational restriction of polypeptides due to its overwhelmingly constrained phi ($\phi\pm60°$) and psi ($\psi\pm30°$), while the backbone-rigidified aromatic amino acid residue Adb[8] is known to induce a crescent conformation in its oligomers via localized five- and six-membered ring hydrogen bonding interactions. Thus, we reasoned that hetero-oligomers made of Aib-Adb repeat motif should also display conformational rigidity. Structural studies (vide infra) indeed showed that the Aib-Adb dimer **3** folds into a well-defined, compact, three-dimensional structure, as evidenced from single crystal X-ray and 2D NOESY studies.

Keywords: Foldamer; Amino acids; Peptidomimetics; Conformation.
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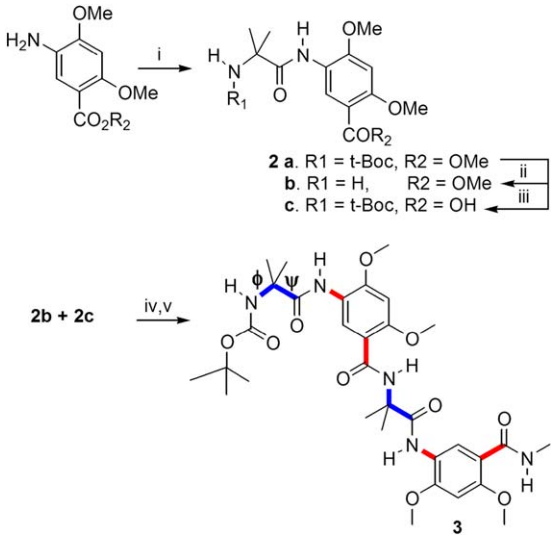
Most astonishingly, the crystal structure analysis revealed a fascinating arrangement of water clusters, in the crystal lattice, held by the backbone amide groups of the foldamer with a peculiar architecture. It is noteworthy that the understanding of three-dimensional structures of water clusters has profound implications in several areas ranging from water-mediated molecular self-assembly[9] to protein structure and function.[10] Furthermore, exploration of conformationally ordered synthetic oligomers that interact with water molecules may enable better understanding of the much debated issue of water interaction with Anti Freeze Proteins (AFPs) and Anti Freeze Glyco Proteins (AFGPs).[11]



Scheme 1. Synthesis of **3**: Reagents and conditions: (i) Boc-Aib-OH, DIPEA, TBTU, MeCN, rt, 6 h; (ii) dry HCl (gas), dioxane, rt, 5 min; (iii) 2 N LiOH, MeOH, rt, 12 h; (iv) DIPEA, TBTU, MeCN, rt, 8 h; (v) methanolic $MeNH_2$, 48 h, rt. *Note*: for aiding quick identification, the conformational restriction imposed by both Aib and Adb residues in **3** is highlighted in blue and red bold bonds, respectively.

3. Results and discussion

The Aib-Adb motif-based foldamer **3** was assembled from Boc-Aib-Adb-OMe building block **2a**, which in turn was synthesized by coupling the protected amino acids Aib and Adb using TBTU as a coupling agent (Scheme 1). However, attempts to synthesize higher oligomers using this 'segment doubling strategy' were unsuccessful, due to the formation of intractable mixture of products under various conditions.

The foldamer **3** crystallized from acetonitrile/water (90:10) in triclinic space group *P*-1. The unit cell contained two foldamers and 14 water molecules (Fig. 1).

Investigation of the crystal structure revealed that the intrinsically constrained Aib residues imposed a significant twist on the foldamer backbone, as expected, with ϕ and ψ torsion angles close to 60 and 30°, respectively, forcing the foldamer backbone to adopt a doubly bent conformation. It is interesting to compare the conformational propensities of the homo-oligomers made of the individual amino acids (Aib and Adb) and their hybrid oligomer **3**. Whereas the homo-oligomers of Aib and Adb have been reported to adopt 3_{10}-helical[12] and crescent architectures,[8] respectively, the hybrid foldamer

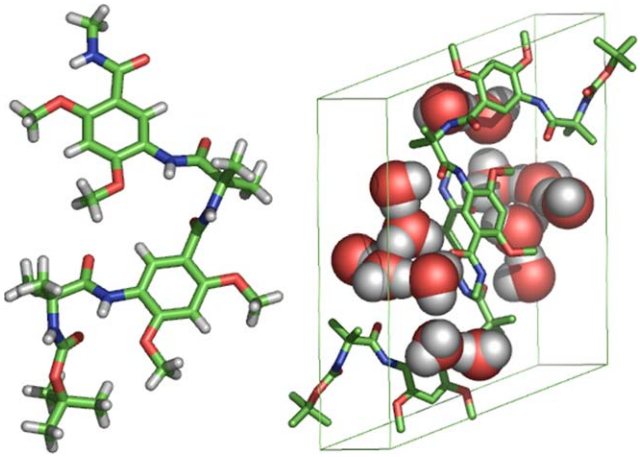


Figure 1. Crystal structure of the Aib-Adb motif-based foldamer **3**. Water molecules in the unit cell are represented in spheres, for aiding quick identification. Color coding: C green, H gray, N blue, O red.

3, containing alternately changing Aib and Adb residues, shows an entirely different structural architecture, a fact that clearly attests the importance of hybrid foldamer strategy[4] for augmenting the conformational space available for novel foldamer design.

Investigation of the crystal structure of **3** revealed the presence of water molecules embedded in the crystal lattice. A detailed analysis of the arrangement of water molecules revealed highly interesting features (Fig. 2).

There are mainly two types of water molecules discernible in the crystal lattice: the first type (colored red) forms a polymeric chain of water clusters and the second type (colored orange) bridges adjacent foldamer molecules as well as connects the foldamer to the water clusters, eventually forming a complex three-dimensional hydrogen bonded network. All the backbone carbonyl oxygens of the foldamer are involved in strong hydrogen bonding interactions with water molecules (O···O<3.0 Å).[13] However, only the Aib amide NHs (N3*H* and N5*H*) partake in interactions with water molecules, leaving the Adb amide NHs (N2*H* and N4*H*) and the methyl amide NH (N1*H*) to be satisfied with S(5)- and S(6)-type[14] hydrogen bonding interactions, respectively.

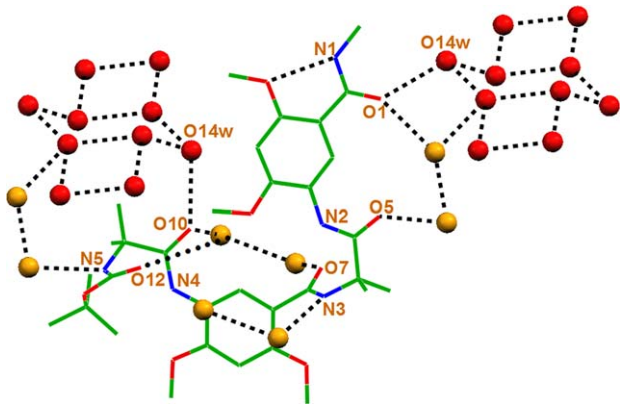


Figure 2. Crystal structure of Aib-Adb motif-based foldamer **3** showing interaction of the foldamer backbone with water molecules.

The water molecules, in pairs (colored orange), that bridge the backbone carbonyls of the adjacent residues donate two hydrogen bonds to the backbone carbonyl oxygens of the foldamer forming 12-membered ring hydrogen bonded network. Further, these *water pairs* accept hydrogen bonds (one each) from the Aib NHs of the adjacent foldamers. The backbone carbonyls O1 and O10 keep the parallel running water chains in place by hydrogen bonding with the water molecule ($O14_W$) that is part of the centrosymmetric six-membered water cluster. Interestingly, the same water molecule ($O14_W$) helps in building the hydrogen bonded three-dimensional network by donating a hydrogen bond to the carbonyl oxygens (O1 and O10) of another foldamer.

The infinite chain of water clusters has alternate four- and six-membered rings (oxygen atoms) sharing one edge. The oxygen atoms of the water molecules in four-membered rings assume square planar structure and the six-membered rings display a centrosymmetric chair conformation. The infinite chains of water clusters are held together by strong O_w–H$\cdots O_w$ hydrogen bonding interactions ($O_w\cdots O_w$=2.73–2.85 Å).[13] The supramolecular chains of water clusters are aligned parallel to each other (Fig. 3).

The folded structure is organized by the backbone H-bonds in solution state, as evidenced from the FTIR spectroscopy, a sensitive tool that is easily applicable for the detection of vibrational modes influenced by the presence of the H-bonds. In the N–H stretch region of **3**, the free N–H vibration, presumably due to the N-terminal Boc amide NH, appears as a weak signal at 3419 cm^{-1}, while intramolecular H-bonded N–H stretches give rise to a broad band in the region 3388 cm^{-1}. Another important source of information in IR spectra is the amide carbonyl region (1600–1700 cm^{-1}). The band at 1647 cm^{-1} can be ascribed to the H-bonded carbonyl in the backbone. Weaker H-bonds result in a slightly increased frequency. The band at 1683 cm^{-1} could be assigned to the N-terminal Boc carbonyl that is not taking part in intramolecular H-bonding.

Solution-state NMR studies (500 MHz) of the foldamer **3** in $CDCl_3$ strongly suggested the prevalence of a doubly bent conformation in solution state, similar to the one observed in the solid state, although the existence of water clusters in solution state could not be verified. One of the most characteristic NOE interactions that can be anticipated for a doubly bent conformation for **3**, as observed in the solid state, would be the NH versus NH dipolar couplings of the amide NHs of the adjacent Aib-Adb residues. Analysis of the 2D NOESY data (500 MHz, $CDCl_3$) indeed revealed the existence of NH versus NH dipolar couplings of the adjacent Aib-Adb residues (NH1/NH2 and NH3/NH4) as anticipated (Fig. 4). Furthermore, the characteristic NOE interactions between amide N*H* and the adjacent *O*-aryloxymethyls in **3** (NH2/OMe1, NH3/OMe2, NH4/OMe3, and NH5/OMe4) also strongly suggest their *syn* orientation, thereby making space for the S(5) and S(6)[14] type hydrogen bonded arrangement, a common feature in *O*-alkoxy arylamides.[8]

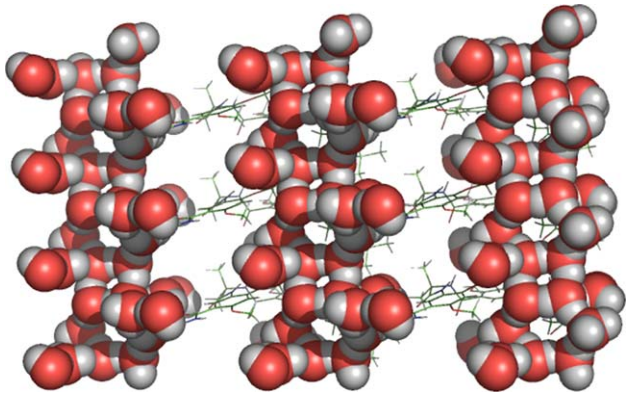


Figure 3. A view of the arrangement of polymeric chain of water clusters in the crystal lattice of **3**. For clarity, the polymeric chains of water clusters are represented in spheres and the foldamers in lines. Color coding: C green, H gray, N blue, O red.

4. Summary

In summary, we have designed and synthesized a novel constrained aliphatic–aromatic conjugated hybrid foldamer that adopts a well-defined, compact, three-dimensional architecture,[16] governed by a combined conformational restriction imposed by the individual amino acids from which it is composed. Conformational investigations confirmed the prevalence of a unique doubly bent conformation for **3**, in both solid and solution states, as evidenced from single crystal X-ray and 2D NOESY studies, respectively. The findings suggest that constrained aliphatic–aromatic amino acid conjugates offer new avenues for the de novo design of foldamers with distinctive structural architectures. The most striking feature of the present de novo designed foldamer is its remarkable ability to stabilize supramolecular polymeric chain of water clusters held together by strong hydrogen bonding interactions. We are currently probing the possibility of water cluster formation in related foldamers, as well as investigating the influence of substitution pattern in the aromatic nuclei on the structural architecture of the corresponding hybrid foldamer.

5. Experimental

5.1. General

Unless otherwise stated, all the chemicals and reagents were obtained commercially. Acetonitrile was dried by distilling over calcium hydride and kept it over 4 Å molecular sieves, prior to use. Chromatography was done on pre-coated silica gel plates (kieselgel $60F_{254}$, Merck). Column chromatographic purifications were done with 100–200 mesh silica gel. NMR spectra were recorded in $CDCl_3$ on Ac 200 MHz or DRX-500 MHz Bruker NMR spectrometers. All chemical shifts are reported in δ ppm downfield to TMS and peak multiplicities are reported as singlet (s), doublet (d), quartet (q), broad (br), broad singlet (br s) and multiplet (m). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd, Germany). IR spectra were recorded in Nujol or $CHCl_3$ using a Shimadzu FTIR-8400 spectrophotometer. Melting points were determined on a Buchi Melting Point B 540. MALDI-TOF mass spectra were obtained from Voyager-PE, Voyager DEPRO, and Voyager-DE STR Models. Single crystal

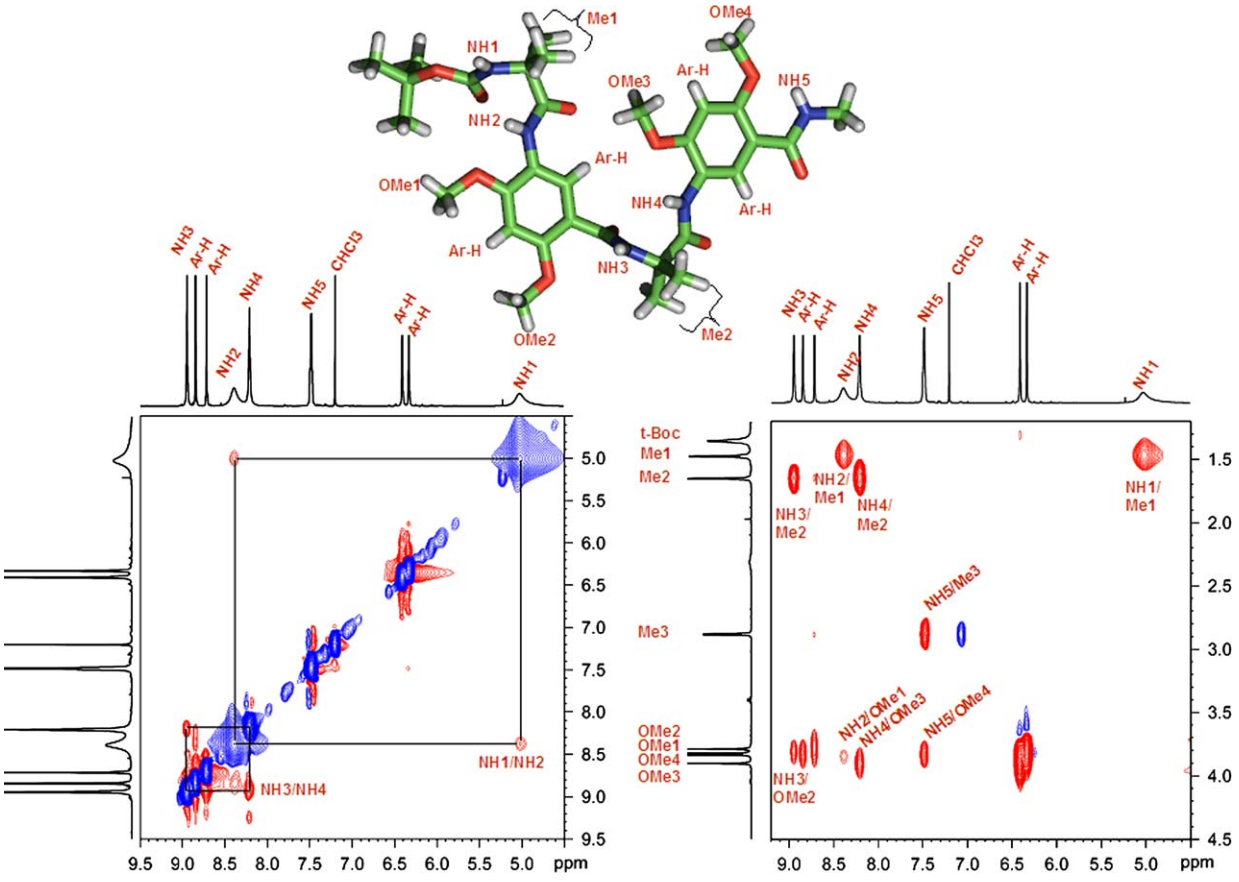


Figure 4. Partial 2D NOESY spectra of **3** (500 MHz, $CDCl_3$) showing characteristic NH1/NH2 and NH3/NH4 interactions (see also Supplementary data). For aiding interpretation of the 2D data, crystal structure of **3**[15] with selected labeled atoms is also shown.

X-ray data were collected on a *Bruker SMART APEX* CCD Area diffractometer with graphite monochromatized (Mo K_α=0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.

5.1.1. 5-(2-*tert*-Butoxycarbonylamino-2-methyl-propionylamino)-2,4-dimethoxy-benzoic acid methyl ester 2a. To an ice-cold stirred solution of the acid Boc-Aib-OH (5.70 g, 28.0 mmol, 1 equiv) and the aromatic amine **1** (5.33 g, 25.3 mmol, 0.9 equiv) in dry acetonitrile (30 mL) was added DIPEA (7.53 mL, 42.1 mmol, 1.5 equiv) followed by TBTU (12.61 g, 39.3 mmol, 1.4 equiv). The resulting mixture was stirred for 6 h at room temperature. The solvent was stripped off under reduced pressure and the residue was diluted with dichloromethane and washed sequentially with potassium hydrogen sulfate solution, saturated sodium bicarbonate, and water. Drying and concentration of the DCM extract under reduced pressure gave the crude product, which on column chromatography (50% EtOAc/Hexane) afforded the desired pure product **2a** (8 g, 72%). Mp 145 °C; IR ($CHCl_3$) ν (cm^{-1}): 3020, 1712, 1531, 1463, 1215, 754; ^1H NMR (500 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.58 (br s, 1H), 6.44 (s, 1H), 5.02 (br s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78 (s, 3H), 1.52 (s, 6H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 165.5, 157.8, 154.5, 152.6, 123.1, 120.4, 111.3, 95.5, 57.6, 56.4, 55.8, 51.5, 28.1, 25.7; MALDI-TOF Mass: 435.34 (M+K). Anal. Calcd for $C_{19}H_{28}N_2O_7$: C, 57.57; H, 7.07; N, 7.07. Found: C, 57.37; H, 7.03; N, 6.99.

5.1.2. 5-(2-Amino-2-methyl-propionylamino)-2,4-dimethoxy-benzoic acid methyl ester hydrochloride 2b. To an ice-cold stirred solution of the compound **2a** (0.5 g, 1.3 mmol) in dry dioxane (10 ml) was bubbled dry HCl gas for 5 min. Then dry ether (15 mL) was added to the reaction mixture, when the amine hydrochloride (**2b**) precipitated out as a white solid (0.37 g, 87%). The solid was filtered, washed with dry ether, dried, and used for the next reaction, without further purification.

5.1.3. 5-(2-*tert*-Butoxycarbonylamino-2-methyl-propionylamino)-2,4-dimethoxy-benzoic acid 2c. To a solution of compound **2a** (2.2 g, 5.6 mmol, 1 equiv) in methanol (15 mL) was added 2 M LiOH solution (11.08 mL, 22.2 mmol, 4 equiv). The reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness and diluted with distilled water, and acidified with saturated potassium hydrogen sulfate. Then the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic extracts were washed with brine. Drying and concentration of the organic layer, under reduced pressure, yielded the desired product **2c** (2.0 g, 94%), which was used for the next reaction, without further purification.

5.1.4. 1-(5-(1-(2,4-Dimethoxy-5-methylcarbonyl-phenylcarbamoyl)-1-methyl-ethylcarbamoyl)-2,4-dimethoxy-phenylcarbamoyl)-1-methyl-ethyl)-carbamic acid *tert*-butyl ester 3. To an ice-cold stirred solution of the acid **2c** (2.0 g, 5.2 mmol, 1 equiv) and amine **2b** (1.73 g, 5.23 mmol, 1 equiv) in dry acetonitrile (20 mL) was added DIPEA (2.3 mL, 13.0 mmol, 2.5 equiv) followed by TBTU (2.35 g, 7.3 mmol, 1.4 equiv). The resulting reaction mixture was stirred overnight at room temperature. The solvent was stripped off under reduced pressure; the residue was dissolved in dichloromethane (100 mL) and washed sequentially with potassium hydrogen sulfate solution, saturated sodium bicarbonate, and water. Drying and concentration in vacuum yielded the crude ester, which was directly used for the next amidation reaction, without further purification. The crude ester was taken in an RB flask containing saturated methanolic methylamine solution (25 mL) and stirred at room temperature for two days. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (5% methanol/ethyl acetate, R_f 0.4) to yield pure **3** (2.0 g, 69%), which could be crystallized from acetonitrile/water (90:10). Mp 212 °C; IR ($CHCl_3$) ν (cm^{-1}): 3419, 3388, 3018, 1683, 1647, 1610, 1517, 1215, 758; ^1H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.89 (s, 1H), 8.76 (s, 1H), 8.44 (br s, 1H), 8.26 (s, 1H), 7.53 (s, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 5.07 (br s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 2.93 (d, 3H, J=4.8 Hz), 1.70 (s, 6H), 1.52 (s, 6H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.5, 172.1, 165.7, 164.7, 154.6, 152.8, 152.4, 124.6, 124.0, 121.2, 121.1, 114.1, 113.8, 94.9, 94.8, 58.3, 57.5, 56.4, 56.2, 55.9, 28.1, 26.4, 25.5; MALDI-TOF Mass: 681.95 (M+Na). Anal. Calcd for $C_{32}H_{45}N_5O_{10}$: C, 58.27; H, 6.82; N, 10.62. Found: C, 58.15; H, 6.80; N, 10.59.

5.1.5. Crystal data for 3 $C_{32}H_{45}N_5O_{10}\cdot 7H_2O$. M=785.84. Colorless crystal, approximate size 0.56×0.27×0.05 mm, multi scan data acquisition, θ range=2.12–25.00°, triclinic, space group P-1, a=6.893 (15), b=15.55 (3), c=20.21 (4) Å, α=110.27 (5)°, β=93.77 (5)°, γ=93.37 (5)°, V=2019 (8) Å^3, Z=2, ρ_{calcd}=1.292 gcm^{-1}, T=297 (2), μ (Mo K_α)=0.105 mm^{-1}, 7052 reflections measured, 4044 unique [$I>2\sigma(I)$] reflections, 575 refined parameters, R value 0.0551, $wR2$=0.1244 (all data R=0.0916, $wR2$=0.01372). Crystallographic data of **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-289024. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.032.

References and notes

1. For reviews, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180; (b) Smith, M. D.; Fleet, G. W. J. *J. Peptide Sci.* **1999**, *5*, 425–441; (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011; (d) Schmuck, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2448–2452; (e) Sanford, A. R.; Yamato, K.; Yang, X.; Yuan, L.; Han, Y.; Gong, B. *Eur. J. Biochem.* **2004**, *271*, 1416–1425; (f) Huc, I. *Eur. J. Org. Chem.* **2004**, 17–29; (g) Licini, G.; Prins, L. J.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, 969–977.
2. For some selected recent examples, see: (a) Hunter, C. A.; Spitaleri, A.; Tomas, S. *Chem. Commun.* **2005**, 3691–3693; (b) Hang, F.; Bai, S.; Yap, G. P. A.; Tarwade, V.; Fox, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 10590–10599; (c) Huck, B. R.; Gellman, S. H. *J. Org. Chem.* **2005**, *70*, 3353–3362; (d) Goto, K.; Moore, J. S. *Org. Lett.* **2005**, *7*, 1683–1686; (e) Arunkumar, E.; Ajayaghosh, A.; Daub, J. *J. Am. Chem. Soc.* **2005**, *127*, 3156–3164; (f) Gabriel, G. J.; Sorey, S.; Iverson, B. L. *J. Am. Chem. Soc.* **2005**, *127*, 2637–2640; (g) Violette, A.; Averlant-Petit, M. C.; Semetey, V.; Hemmerlin, C.; Casimir, R.; Graff, R.; Marraud, M.; Briand, J. P.; Rognan, D.; Guichard, G. *J. Am. Chem. Soc.* **2005**, *127*, 2156–2164; (h) Chen, F.; Zhu, N. Y.; Yang, D. *J. Am. Chem. Soc.* **2004**, *126*, 15980–15981; (i) Farrera, S. J.; Zaccaro, L.; Vidal, D.; Salvatella, X.; Giralt, E.; Pons, M.; Albericio, F.; Royo, M. *J. Am. Chem. Soc.* **2004**, *126*, 6048–6057; (j) De, P. S.; Zorn, C.; Klein, C. D.; Zerbe, O.; Reiser, O. *Angew. Chem., Int. Ed.* **2004**, *43*, 511–514; (k) Baldauf, C.; Guenther, R.; Hofmann, H.-J. *Helv. Chim. Acta* **2003**, *86*, 2573–2588.
3. (a) Estroff, L. A.; Incarvito, C. D.; Hamilton, A. D. *J. Am. Chem. Soc.* **2004**, *126*, 2–3; (b) Sadowsky, J. D.; Schmitt, M. A.; Lee, H. S.; Umezawa, N.; Wang, S.; Tomita, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11966–11968; (c) Norgren, A. S.; Arvidsson, P. I. *Org. Biomol. Chem.* **2005**, *3*, 1359–1361; (d) Chang, K. J.; Kang, B. N.; Lee, M. H.; Jeong, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12214–12215.
4. Hayen, A.; Schmitt, M. A.; Ngassa, F. N.; Thomasson, K. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 505–510.
5. (a) Roy, R. S.; Karle, I. L.; Raghothama, S.; Balaram, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 16478–16482; (b) Sharma, G. V. M.; Nagendar, P.; Jayaprakash, P.; Krishna, P. R.; Ramakrishna, K. V. S.; Kunwar, A. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 5878–5882; (c) Baldauf, C.; Gunther, R.; Hofmann, H.-J. *J. Org. Chem.* **2006**, *71*, 1200–1208.
6. Cyclic peptides containing proline-aromatic amino acid units have been reported by Kubik et al., see: (a) Otto, S.; Kubik, S. *J. Am. Chem. Soc.* **2003**, *125*, 7804–7805; (b) Heinrichs, G.; Kubik, S.; Lacour, J.; Vial, L. *J. Org. Chem.* **2005**, *70*, 4498–4501.
7. α-Aminoisobutyric (Aib) residue is highly conformationally restricted, with allowed conformations lying largely in the region $\phi\pm$ 60°, $\psi\pm$30°, see: (a) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. *Biopolymers* **2001**, *60*, 396–419; (b) Kaul, R.; Balaram, P. *Bioorg. Med. Chem.* **1999**, *7*, 105–117.
8. Oligomers of aromatic amino acids and glycine that form self-assembled duplex with high association constant have been reported by Gong et al, see: (a) Zhu, J.; Parra, R. D.; Zeng, H.; Jankun, E. S.; Zeng, X. C.; Gong, B. *J. Am. Chem. Soc.* **2000**, *122*, 4219–4220; (b) Gong, B. *Chem.—Eur. J.* **2001**, *7*, 4336–4342.

9. (a) Barbour, L. J.; Orr, G. W.; Atwood, J. L. *Nature* **1998**, *393*, 671–673; (b) Barbour, L. J.; Orr, G. W.; Atwood, J. L. *Chem. Commun.* **2000**, 859–860; (c) Atwood, J. L.; Barbour, L. J.; Jerga, A.; Schottel, B. L. *Science* **2002**, *298*, 1000–1002; (d) Desiraju, G. R. *J. Chem. Soc., Chem. Commun.* **1991**, 426–428; (e) Magazu, S.; Migliardo, F.; Ramirez-Cuesta, A. J. *J. R. Soc. Interface* **2005**, *2*, 527–532.
10. Graether, S. P.; Kuiper, M. J.; Gagnes, S. M.; Walker, V. K.; Jia, Z.; Sykes, B. D.; Davies, P. L. *Nature* **2000**, *406*, 325–328.
11. For a review, see: Harding, M. M.; Anderberg, P. I.; Haymet, A. D. J. *Eur. J. Biochem.* **2003**, *270*, 1381–1392.
12. Aib homo-oligomers assume a regular (right- and left-handed) 3_{10}-helical structure (a series of type III/III′ β-bends), see: Ref. 7.
13. Vishweshwar, P.; Babu, N. J.; Nangia, A.; Mason, S. A.; Puschmann, H.; Mondal, R.; Howard, J. A. K. *J. Phys. Chem. A* **2004**, *108*, 9406–9416.
14. For an excellent account on the graph set analysis of H-bonded systems, see: Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.
15. This figure was generated using PyMOL molecular graphics system. W. L. DeLano, The PyMOL Molecular Graphics System. http://www.pymol.org (accessed 2004).
16. We have recently disclosed the compact, three-dimensional structural architecture of acrylamide oligomers forming protein β-sheet-like architecture, see: Amol, K.; Rajesh, R.; Rajamohanan, P. R.; Sanjayan, G. J. *Chem. Commun.* **2006**, 2756–2758.

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Reactions of chlorofullerene $C_{60}Cl_6$ with *N*-substituted piperazines

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Abstract—It was shown for the first time that reactions of C_{60} halides with aliphatic amines provide a facile route for the synthesis of aminofullerenes, valuable precursors for water-soluble cationic fullerene derivatives. Particularly, chlorofullerene $C_{60}Cl_6$ and *N*-substituted piperazines were investigated in this work. It was shown that substitution of chlorine atoms in $C_{60}Cl_6$ by amine groups is accompanied by partial elimination of addends from the fullerene cage that yields mixtures of di-, tetra- and, hexaaminofullerenes as the final products. Separation of these mixtures by column chromatography resulted in isolation of pure 1,4-diaminofullerenes; this procedure gives much higher and more reproducible yields of these compounds than direct oxidative photoaddition of secondary amines to C_{60}. ESI mass spectrometry and NMR spectroscopy data showed that hexaaminofullerene isomers are major components in inseparable mixtures of polyaddition products. Polyaminofullerenes were found to be readily soluble in aqueous acids; these solutions are unstable because of a facile substitution of protonated amine groups with hydroxyls. Nevertheless, the use of other amine substrates in the investigated reaction can potentially allow the preparation of more stable water-soluble cationic fullerene derivatives for biological studies.

1. Introduction

Halofullerenes are valuable substrates for preparation of novel fullerene derivatives by substitution of halogen atoms with appropriate organic groups. Chlorofullerene $C_{60}Cl_6$ is one of the most available [60]fullerene halides.[1] The symmetrical molecular structure as well as the low number of halogen addends allows for their selective substitution by various nucleophiles with formation of one or several major products. Thus, $C_{60}Cl_6$ undergoes Friedel–Crafts reaction with aromatics under Lewis acid catalysis to yield mainly $C_{60}Ar_5Cl$. Isolation of $C_{60}Ar_2$ and $C_{60}Ar_4$ compounds as side products points to the partial halogen elimination that competes with substitution.[2] Treatment of $C_{60}Cl_6$ with sodium alkoxides affords substitution products $C_{60}(OR)_5Cl$ (R=Me, Et), while reactions with less nucleophilic alcohols give mainly $C_{60}(OR)_2$ (R=Me, *i*Pr) through elimination of four chlorine atoms from the fullerene cage.[3] Reaction of the chlorofullerene with MeLi shows poor selectivity and yields mixtures of $C_{60}Me_6$, $C_{60}Me_5Cl$, $C_{60}Me_5O_2OH$, $C_{60}Me_5OOH$, etc.[4] Allyltrimethylsilane also reacts with $C_{60}Cl_6$ in the presence of $TiCl_4$ as a catalyst to give predominantly $C_{60}(CH_2CH{=}CH_2)_6$ and $C_{60}(CH_2CH{=}CH_2)_5Cl$ as a side product.[5]

Organic fullerene derivatives prepared from $C_{60}Cl_6$ possess all addends attached around one five-membered ring at the fullerene cage; this addition pathway cannot be achieved using commonly used cycloaddition reactions. Therefore, we considered $C_{60}Cl_6$ as a particularly valuable substrate for the preparation of water-soluble fullerene derivatives. There is a limited number of known derivatives of [60]fullerene that possess solubility in water above 1 mg/mL; most of them are represented by compounds bearing multiple addends (>5–6) that cover almost the whole fullerene surface.[6] Such fullerene derivatives cannot be applied as inhibitors of HIV-1 protease since its active center has good attraction to the hydrophobic [60]fullerene core.[7] Efficiencies of photosensitized generation of singlet oxygen (potential for photodynamic therapy of cancer) on the one hand, and quenching of radical species on the other (neuroprotection activity) also depend on the degree of distortion of the fullerene π-system in C_{60} derivatives.[8] Therefore, only a few water-soluble fullerene derivatives have potential to find some medicinal applications. Their syntheses usually require several steps and give relatively low overall product yields.[9] Replacement of 4–5–6 chlorine atoms in $C_{60}Cl_6$ with addends bearing masked ionic groups (–COO^-, –SO_3^-,

Keywords: Fullerene; Amines; C_{60}; $C_{60}Cl_6$; Nucleophilic substitution.
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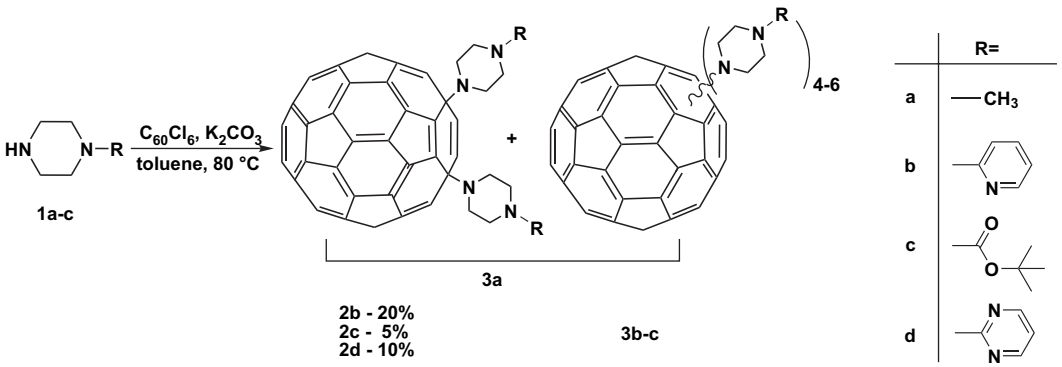

Scheme 1.

R_4N^+, etc.) can be considered as a superior approach to the synthesis of water-soluble fullerene derivatives.

It has been reported recently that cationic fullerene derivatives inhibit HIV and hepatitis C viruses quite efficiently and possess good antiproliferative and antibacterial activities.[10] Therefore, we address here the reaction of $C_{60}Cl_6$ with amines as a promising route to polyaminofullerenes and their water-soluble cationic derivatives.

2. Results and discussion

It was shown that $C_{60}Cl_6$ readily reacts with *N*-substituted piperazines **1a–d** with the formation of a mixture of products (Scheme 1).

Typically, hexachlorofullerene was dissolved in dry toluene at 80 °C, then rigorously dried potassium carbonate and the corresponding amine were added. The resulting mixture was stirred for 20 h at 80 °C and afterwards cooled down to room temperature.[†] All insoluble products were filtered off, while the filtrate was concentrated in vacuum to give brown solids that were washed with hexane and dried in air.

Mixtures of aminofullerenes were obtained in all syntheses as revealed by TLC and NMR spectroscopy. A crude product formed in the reaction of $C_{60}Cl_6$ with 1-methylpiperazine possesses an average composition of C_{60}(1-methylpiperazinyl)$_{4–5}$; this mixture could not be separated by column chromatography on silica because of almost irreversible absorption of the material at the stationary phase (due to strongly basic properties of amine residues). Addition of tertiary amines (triethylamine, pyridine) or acids (CF_3COOH, CH_3COOH) to the eluent ($CHCl_3$–methanol 2:1) resulted in elution of inseparable mixtures of partially hydrolyzed compounds with composition C_{60}(piperazinyl)$_x$(OH)$_y$. Electrospray mass spectrometry analysis (ESIMS) of a crude product with an average composition of C_{60}(1-methylpiperazinyl)$_{4–5}$ revealed intensive signals at *m*/*z*=819 (C_{60}(1-methylpiperazinyl)$_1^+$), 919 (C_{60}(1-methylpiperazinyl)$_2\cdot H^+$), 1017 (C_{60}(1-methylpiperazinyl)$_3^+$), and 1133 (C_{60}(1-methylpiperazinyl)$_4O\cdot H^+$). Less intensive peaks were observed at *m*/*z*=837 and 1035 due to C_{60}(1-methylpiperazinyl)$OH\cdot H^+$ and C_{60}(1-methylpiperazinyl)$_3OH\cdot H^+$, respectively. The later appeared most likely because of a partial hydrolysis of aminofullerenes (Fig. 1).

Application of the less basic piperazines **1b–d** bearing electron withdrawing groups allowed for separation of the crude reaction products using column chromatography on silica. In the course of separation, diaminofullerenes **2b–d** (toluene–methanol 125:1) were followed by distinct fraction that represented a mixture of polyaminofullerenes **3b–d**. Variation of the eluent composition and repeatable column chromatography did not result even in partial separation of components of **3b–d** presumably because of the strong similarity in their properties.

The composition and structure of **2b–d** was confirmed by chemical analysis data, ^1H and ^{13}C NMR spectrometry. The ^1H NMR spectrum of **2b** consists of two doublets and two triplets corresponding to pyridyl protons and a multiplet at

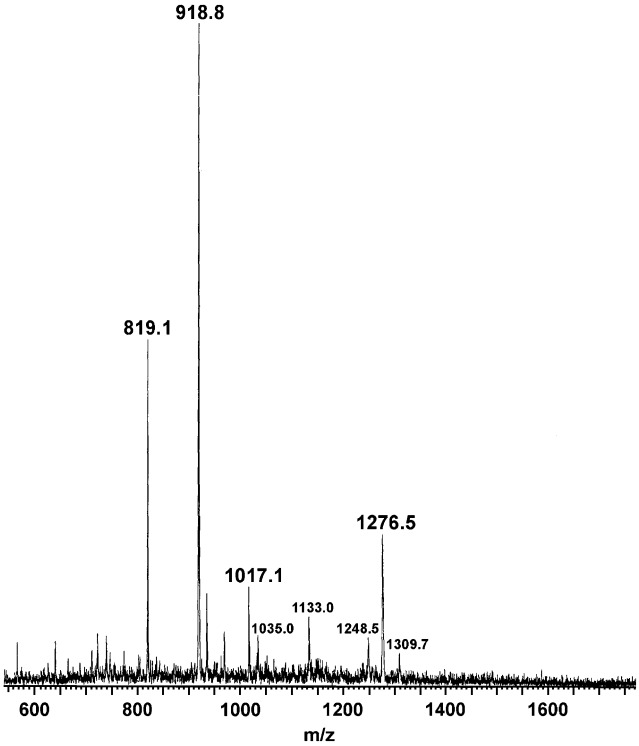

Figure 1. The ESIMS of the crude product formed in the reaction of $C_{60}Cl_6$ with *N*-methylpiperazine.

[†] If the reaction is conducted at room temperature, the result is essentially the same except for lower yields of **2b-d**.

3.8–4.0 ppm from the CH_2 protons of piperazine ring (Fig. 2). The ^{13}C NMR spectrum exhibited a signal at 73.5 ppm corresponding to the fullerene cage sp^3 carbon; 34 peaks of fullerene and pyridyl sp^2 carbons were detected in low field region (100–160 ppm) that prove unambiguously the C_s symmetry of the product corresponding to structure **2b**. Both ^1H and ^{13}C NMR spectra of **2C** and **2d** also correspond to the suggested structures. The UV–vis spectrum of **2b** exhibited a broad band at 445 nm typical for fullerene derivatives with 1,4-addition pathway.[11] Similar spectroscopic data were reported previously for 1,4-dimorpholinofullerene.[11]

It should be noted that although oxidative photochemical addition of secondary amines to parent C_{60} also yields 1,4-diaminofullerenes as minor products, their yields are lower than in our method based on $C_{60}Cl_6$ (0–8%).[11,12] Reactions of [60]fullerene with active amines such as piperazines **1a** and **1b** give mostly oxygen-containing tetraaminofullerenes $C_{60}[NR_2]_4O$ and other polyaddition products, while the corresponding 1,4-$C_{60}[NR_2]_2$ are not formed or form in very low yields (1–3%). Application of $C_{60}Cl_6$ as a substrate for preparation of 1,4-diaminofullerenes is also advantageous in the case of amines possessing labile functional groups. In particular, it is illustrated by the preparation of diaminofullerene **2c** reported here. This compound cannot be obtained directly in the reaction of [60]fullerene with *N*-(*tert*-butoxycarbonyl)piperazine because of degradation of this reagent even under mild photochemical conditions (irradiation from conventional 50 W incandescent light bulb) and formation of unsubstituted piperazine monoaddition product ($C_{60}N_2C_4H_8$).[12] Therefore, reaction of $C_{60}Cl_6$ with secondary amines can find useful application for preparation of some specific 1,4-diaminofullerenes under mild conditions. Compounds obtained here **2b** and **2c** possess chelating groups and can be used for construction of noncovalently linked donor–acceptor assembles with metalloporphyrins and formation of complexes with transition metals.

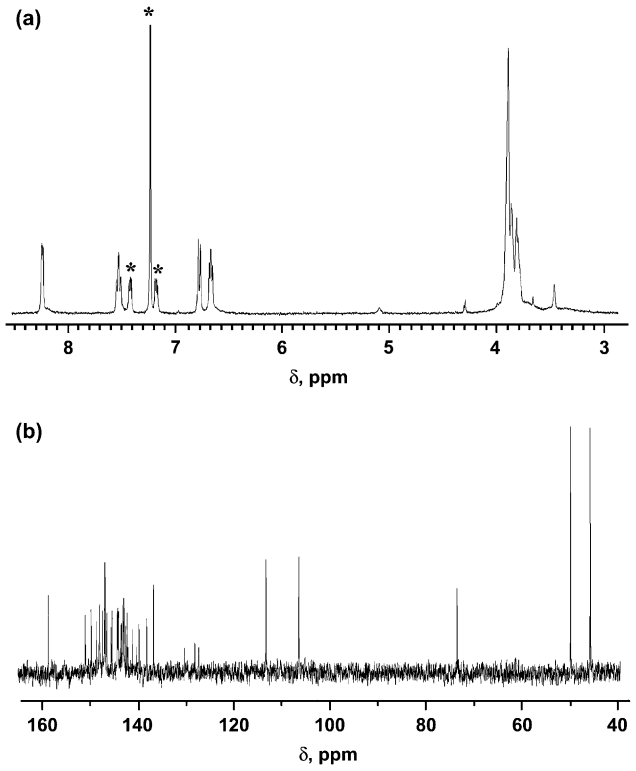

Figure 2. The ^1H and ^{13}C NMR spectra of **2b**. Symbol '*' denotes signals of residual $CHCl_3$ in $CDCl_3$ and 1,2-dichlorobenzene solvent impurities.

Another important feature of the investigated reaction is high-yield formation of polyaminofullerenes (ca. 60–70%) that most likely have all amine groups arranged at one hemisphere of the fullerene cage (like chlorine atoms in the starting $C_{60}Cl_6$). Thus, a mixture of polyaminofullerenes **3b** with average composition C_{60}(4-(2-pyridyl)piperazin-1-yl)$_{4.5}$ as determined from chemical analysis was characterized by ESI mass spectrometry. The most intensive peaks were observed at m/z=1693 and 847 amu, these correspond to molecular ions $[C_{60}(4\text{-}[2\text{-pyridyl}]piperazin\text{-}1\text{-}yl)_6\cdot H]^+$ and $[C_{60}(4\text{-}[2\text{-pyridyl}]piperazin\text{-}1\text{-}yl)_6\cdot 2H]^{2+}$, respectively. Surprisingly, signals of the corresponding tetraaminofullerenes were much less intensive. Both ^1H and ^{13}C NMR spectra of **3b** consisted of numerous partially overlapped peaks thus ruling out the possibility of high compositional and isomeric purity of **3b**.

As expected, polyaminofullerenes **3a**–**d** were readily soluble in organic and inorganic acids thus yielding the corresponding salts. Isolation of these salts by precipitating it by addition of acetone or acetonitrile or by concentration of these acidic solutions at room temperature and reduced pressure was challenged by competing solvolysis with exchange of amine groups with –OH or RCOO– residues. Thus, in contrast to the recently reported conversion of C_{60}[amine]$_4$O derivatives into water-soluble salts,[12] polyaminofullerenes **3a**–**d** give under the same conditions insoluble in water material. Nevertheless, we continue our investigations on $C_{60}Cl_6$ reactions with less bulky secondary and primary amines in order to obtain stable water-soluble cationic fullerene derivatives that can exhibit promising biological activities.

3. Conclusions

A reaction of $C_{60}Cl_6$ with amines was investigated for the first time. It was shown that it allows for superior preparation of 1,4-diaminofullerenes; the compounds reported here possess chelating pyridyl and pyrimidinyl groups and can potentially be utilized for construction of supramolecular assembles with metalloporphyrins and complexes with transition metals.

Isolated mixtures of polyaminofullerenes were characterized by ^1H and ^{13}C NMR and ESIMS; a peak for hexaaminated species $[C_{60}(NR_2)_6\cdot H]^+$ strongly dominated in the mass spectrum. The observed very high solubility of polyaminofullerenes in acidic media opens easy route for preparation of water-soluble fullerene derivatives, particularly, ones that can exhibit promising biological properties.

4. Experimental

4.1. Reagents and solvents

Chlorofullerene $C_{60}Cl_6$ was prepared by chlorination of C_{60} with ICl in 1,2-dichlorobenzene as described before.[13]

The solid $C_{60}Cl_6$ was obtained as a 1:1 solvate with 1,2-dichlorobenzene. Surprisingly, this 1,2-dichlorobenzene was observed as trace solvent impurity in the ^1H NMR spectra of some 1,4-diaminofullerenes (for instance, **2b**). Toluene for reactions of $C_{60}Cl_6$ with amines was distilled over metal sodium–benzophenone. All other reagents and solvents were purchased from Acros Organics and used as received.

4.2. General experimental procedure for reactions of $C_{60}Cl_6$ with *N*-substituted piperazines

Hexachlorofullerene (200 mg, 0,278 mmol) was dissolved in 100 mL of dry toluene under stirring at 80 °C within 3 h. Then vigorously dried potassium carbonate (5–10 g) was added to the hot chlorofullerene solution that was followed by dropwise addition of amine **1a–d** (2 mmol) dissolved in 40 mL of toluene. Resulting mixture was stirred for 20 h at 80 °C, afterwards cooled down to the room temperature. All insoluble products were filtered off, while the filtrate was concentrated in vacuum to give brown solids that were washed with hexane and dried in air.

To isolate **2b–d**, the crude product mixture was re-dissolved in toluene and then diluted by hexane to give 1:1 v/v solvent mixture. Resulting solution was filtered and poured at the top of silica gel column (silica gel purchased from Acros Organics, 30–75 μ, 90 Å). Very small amount of fullerene C_{60} (less than 1–2 mg, formed from $C_{60}Cl_6$ via loss of all chlorine atoms) was washed out from the column in the course of product deposition; following elution by toluene–methanol mixtures (toluene–MeOH 99.2:0.8 v/v) resulted in the fractions of diaminofullerenes **2b–d**. Increase in the methanol content in the solvent mixture (toluene–MeOH 98:2–97:3 v/v) resulted in elution of polyaminofullerenes **3b–d** as single fractions. Repeatable separation of **3b–d** on silica and alumina stationary phases using different solvent compositions did not result in any resolution of the components. The solutions of **2b–d** were concentrated at the rotary evaporator to the volume 10–15 mL; then hexane was added (40–50 mL) and the precipitate was collected by centrifugation and dried in air to afford compounds **2b–d** as brown solids in 5–20% yield.

4.2.1. Compound 2b. Found: C, 89.28; H, 2.77; N, 7.96. $C_{78}H_{24}N_6$ requires C, 89.64; H, 2.31; N, 8.04%; ν_{max} (KBr)=528, 729, 772, 940, 983, 1007, 1130, 1160, 1244, 1434, 1483, 1592, 2917 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.40–4.20 (16H, br m), 6.70 (2H, t, *J* 8.0 Hz), 6.81 (2H, d, *J* 8.8 Hz), 7.56 (2H, t, *J* 9.2 Hz), 8.27 (2H, d, *J* 3.7 Hz); δ_C (100 MHz, CS_2–C_6D_{12} 10:1) 45.8, 49.9, 73.5, 106.4, 113.3, 127.4, 128.2, 130.4, 136.8, 138.2, 139.8, 140.4, 141.1, 142.1, 142.3, 142.5, 143.0, 143.1, 143.2, 143.4, 143.5, 144.1, 144.2, 144.2, 144.3, 144.4, 145.4, 145.6, 146.5, 146.9, 147.0, 147.4, 148.0, 148.6, 149.8, 151.0, 158.7.

4.2.2. Compound 2c. Found: C, 85.74; H, 3.16; N, 5.07. $C_{78}H_{34}N_4O_4$ requires C, 85.86; H, 3.14; N, 5.13%; ν_{max} (KBr)=528, 1001, 1126, 1167, 1251, 1286, 1365, 1421, 1458, 1698, 1743, 2851, 2921 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.55 (18H, s), 3.60–3.90 (16H, br m); δ_C (150 MHz, CS_2–C_6D_{12} 10:1) 28.3, 30.1, 49.9, 73.4, 78.6, 138.2, 139.7, 140.4, 141.1, 142.1, 142.2, 142.5, 142.9, 143.0, 143.0, 143.1, 143.2, 143.4, 143.4, 143.6, 144.0, 144.1, 144.2, 144.3, 145.3, 145.6, 146.1, 146.5, 146.6, 146.7, 146.9, 147.0, 147.2, 148.6, 149.5, 150.7, 153.1.

4.2.3. Compound 2d. Found: C, 86.83; H, 2.45; N, 10.81. $C_{76}H_{22}N_8$ requires C, 87.18; H, 2.12; N, 10.70%; δ_H (400 MHz, $CDCl_3$) 3.72–4.07 (8H, br m), 4.22 (8H, br s), 6.56 (2H, t, *J* 4.8, 1.3 Hz), 8.39 (4H, dd, *J* 4.8, 1.6 Hz); δ_C (100 MHz, CS_2–C_6D_{12} 10:1) 44.3, 50.0, 73.6, 109.9, 138.2, 139.8, 140.4, 141.1, 142.1, 142.3, 142.5, 143.0, 143.1, 143.2, 143.4, 143.5, 143.7, 144.1, 144.2, 144.2, 144.3, 145.4, 145.6, 146.5, 146.9, 147.0, 147.3, 148.6, 149.8, 151.0, 157.1, 157.2, 157.3, 161.3.

4.2.4. Compound 3b. ν_{max} (KBr)=525, 732, 773, 943, 980, 1007, 1097, 1126, 1160, 1246, 1280, 1313, 1437, 1482, 1594, 2851, 2925 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.88–3.96 (br m, 16H), 6.50–6.70 (br m, 4H), 7.36–7.53 (br m, 2H), 8.09–8.33 (br m, 2H) ppm. ^1H, ^{13}C NMR, and ESIMS spectra are shown in Supporting data.

Acknowledgements

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Supplementary data

Supporting information available: spectral data for compounds **2c–d** and **3b**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.033.

References and notes

1. Birkett, P. R.; Avent, A. G.; Darwish, A. D.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *Chem. Commun.* **1993**, 1230–1231.
2. Birkett, P. B.; Avent, A. G.; Darwish, A.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *J. Chem. Soc. Perkin Trans. 2* **1997**, 457–461.
3. Avent, G.; Birkett, P. R.; Darwish, A. D.; Houlton, S. H.; Taylor, R.; Thomson, K. S. T.; Wei, X.-W. *J. Chem. Soc. Perkin Trans. 2* **2001**, 782–786.
4. Al-Matar, H.; Abdul-Sada, A. K.; Avent, A.; Fowler, P. W.; Hitchcock, P. B.; Rogers, K. M.; Taylor, R. *J. Chem. Soc. Perkin Trans. 2* **2002**, 53–58.
5. Abdul Sada, A.; Avent, A.; Birkett, P. R.; Kroto, H. W.; Taylor, R.; Walton, D. R. M. *J. Chem. Soc. Perkin Trans. 1* **1998**, 393–395.
6. Tagmatarchis, N.; Shinohara, H. *Mini Rev. Med. Chem.* **2001**, *1*, 339–348; Da Ros, T.; Prato, M. *Chem. Commun.* **1999**, 663–669.
7. Wilson, S. R. *Perspectives of Fullerene Nanotechnology*; Osawa, E., Ed.; Kluwer: Dordrecht–Boston–London, 2001; Zhu, Z.; Wilson, S. *Biochemistry* **2003**, *42*, 1326–1333.
8. Guldi, D. M.; Asmus, K.-D. *Radiation Physics and Chemistry* **1999**, *56*, 449–456; Bensasson, R. V.; Berberan-Santos, M. N.; Brettreich, M.; Frederiksen, J.; Göttinger, H.; Hirsch, A.; Land, E. J.; Leach, S.; McGarvey, D. J.; Schonberger, H.; Schroder, C. *Phys. Chem. Chem. Phys.* **2001**, *3*, 4679–4683.

9. Lamparth, I.; Hirsch, A. *Chem. Commun.* **1994**, 1727–1728; Brettreich, M.; Hirsch, A. *Tetrahedron Lett.* **1998**, *39*, 2731–2734.
10. Mashino, T.; Nishikawa, D.; Takanashi, K.; Usui, N.; Yamory, T.; Seki, M.; Endo, T.; Mochizuki, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4395–4397; Bosi, S.; Da Ros, T.; Spalluto, G.; Balzarini, J.; Prato, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4437–4440; Mashino, T.; Shimotohno, K.; Ikegami, N.; Nishikawa, D.; Okuda, K.; Takahashi, K.; Nakamura, S.; Mochizuki, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1107–1109.
11. Schick, G.; Kampe, K. D.; Hirsch, A. *Chem. Commun.* **1995**, 2023–2024.
12. Troshina, O. A.; Troshin, P. A.; Peregudov, A. S.; Kozlovski, V. I.; Lyubovskaya, R. N. *Chem.—Eur. J.* **2006**, *12*, 5569–5578.
13. Troshin, P. A.; Popkov, O.; Lyubovskaya, R. N. *Full. Nanot. Carb. Nanostruct.* **2003**, *11*, 163–182.

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Synthesis and utility of new amine/nucleobase addition products of allenylphosphonates

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Abstract—In the reaction of allenylphosphonates with amines/nucleobases, depending on the amine and the allenylphosphonate, either *Z*- or *E*-vinylphosphonate or allylphosphonate as a single isomer with a β-amino functionality was isolated. A simple route to phosphonates with a β-NH_2 group is developed by direct reaction with ammonia. In reactions with adenine, three different modes of reaction, with one of them involving an unusual cyclisation, are observed. The utility of (enamino)allyl phosphonate products thus obtained in the synthesis of (enamino)-1,3-butadienes via Horner–Wadsworth–Emmons (HWE) reaction is also demonstrated.

1. Introduction

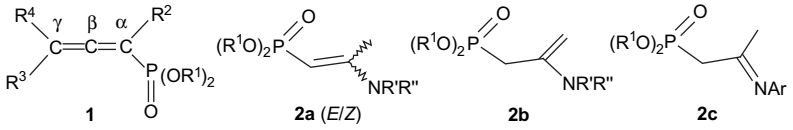
Allenes serve as potential precursors for a variety of molecules of industrial and biological importance.[1,2] Allenylphosphonates (phosphorylated allenes) **1** constitute a readily accessible family of allenes that can be used as versatile building blocks in organic chemistry.[3] One of their simplest reactions is amination leading to vinyl and/or allylphosphonates (**2a**–**b**); when aromatic amines are used, imine type of products (**2c**) are also possible.[4] It should be noted that the factors governing different modes of reactivity are not clear, but all of these (**2a**–**c**) upon reduction can lead to β-aminophosphonates that have a wide range of biological activity.[5] Compounds of type **2a** are well characterised but those of type **2b** are *not*. These latter compounds should be good precursors for Horner–Wadsworth–Emmons reactions. Among several synthetic routes for these β-aminophosphonates,[5c,6] one using enaminophosphonates is attractive because of the ease of preparation of the allenylphosphonate precursors. Also, if adenine, guanine, etc., are utilised as the amine components, it should be possible to obtain nucleobase-appended phosphonates that could be of biochemical interest (e.g., chemotherapy).[7] The reactive site in these nucleobases is another aspect on which details are unclear.

In addition to the above, enamines themselves are valuable intermediates in organic synthesis.[8] Unlike the thermodynamically unstable primary and secondary enamines, enaminophosphonates are relatively stable.[9] Thus amination of phosphorylated allenes constitutes a potential entry to stable enamines. Nonphosphorylated allenes undergo amination *mainly under catalytic conditions* to lead to the allylamines;[10] in particular, the phosphine catalysed reaction of azoles with allenes takes place at the terminal carbon.[10d]

In the above context and in continuation of our work on phosphonate/phosphorane chemistry,[11] we have explored the amination reactions of phosphorylated allenes.[12] Our results reveal an interesting array of products, not evident in earlier reports, in this apparently naive reaction. These results are reported here.

2. Results and discussion

In this paper, the following results are discussed in the same order: (i) synthesis and characterisation of (*E*)-*(enamino)-vinyl* phosphonates **4a**–**b** and *(enamino)allyl* phosphonates **5a**–**d**,[13] (ii) an extremely simple and straightforward route to the stable (*Z*)-β-enaminophosphonates **6**–**7**[6f] and (iii) first



1 2a (*E*/*Z*) 2b 2c

Keywords: Allenylphosphonates; Nucleobase; Enaminophosphonates; HWE reaction; Mitsunobu reaction; X-ray structure.
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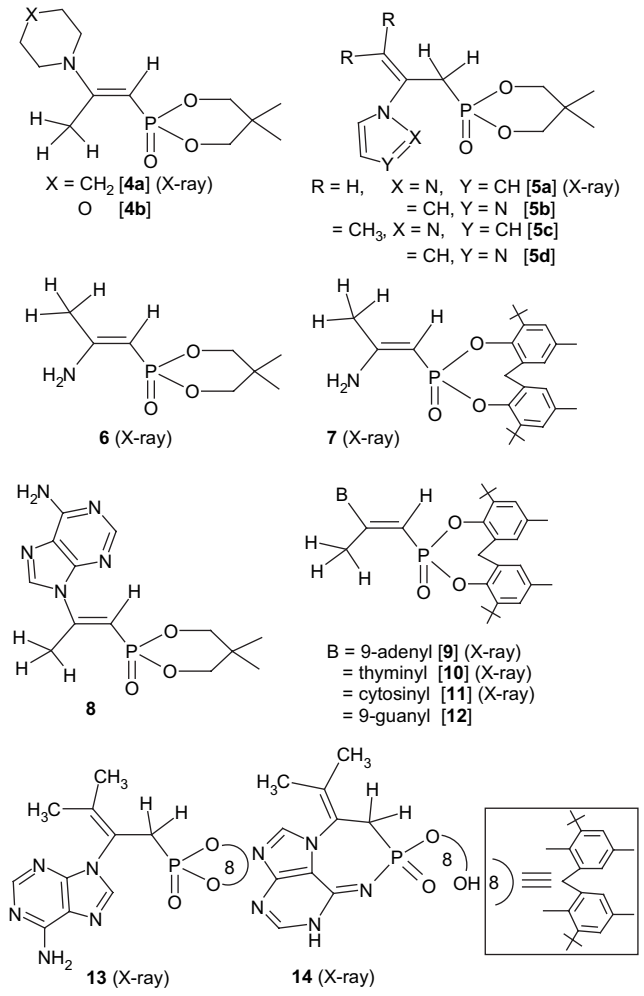


Chart 1.

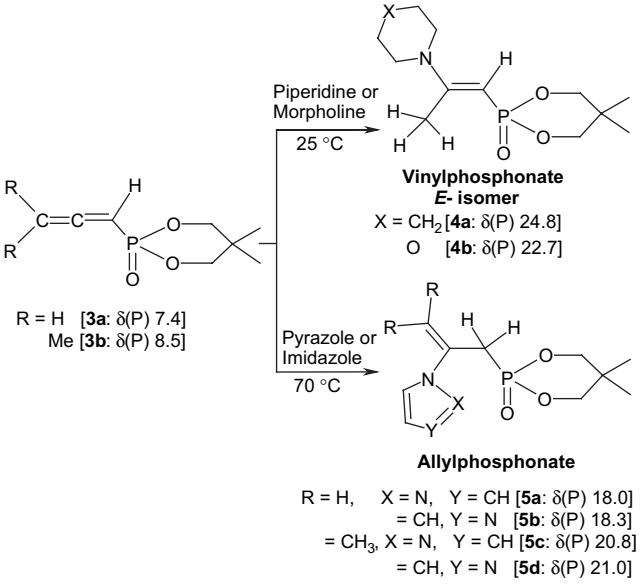
time isolation of nucleobase (adenine, thymine, cytosine and guanine) connected phosphonates **8–13** as *single* isomers,[14] and the unusual cyclisation product **14** with adenine residue. These compounds are shown in Chart 1.

Utility of the addition product of **3c** with *N*-methylethanolamine in the synthesis of adenyl-substituted phosphonates and of compounds **5b** and **5d** in the Horner–Wadsworth–Emmons (HWE) reaction leading to 1,3-butadienes is discussed later.

2.1. Reaction of allenes 3a–b with secondary amines—formation of (*E*)-*(enamino)vinyl* phosphonates 4a–b and *(enamino)allyl* phosphonates 5a–d

These reactions were conducted in methyl cyanide at 25 or 70 °C (Scheme 1). The yields are summarised in Table 1. Although it is reported in the literature that there is an equilibrium between the (enamino)vinyl phosphonate and the corresponding (enamino)allyl phosphonate as shown in Scheme 2,[3a] we did not find any evidence for the thermal conversion of **4a** (Chart 1, see Supplementary data for X-ray structure) to its (enamino)allyl form or of **5a** (Chart 1, see Supplementary data for X-ray structure) to its (enamino)-vinyl form. Even in the reaction mixture, only one compound, either **4** or **5**, was observed (^{31}P NMR) at 25 °C in both the cases. The amine adds to the central carbon in the reactions shown in Scheme 1. In contrast, it is important to note that phosphine catalysed addition of azoles to activated allenes takes place at the terminal carbon (Scheme 3).[10d] The *E* stereochemistry for **4a** observed here is different from *Z* stereochemistry observed for (Me)(NEt$_2$)C=C(F)[P(O)(OEt)]$_2$.[4b]

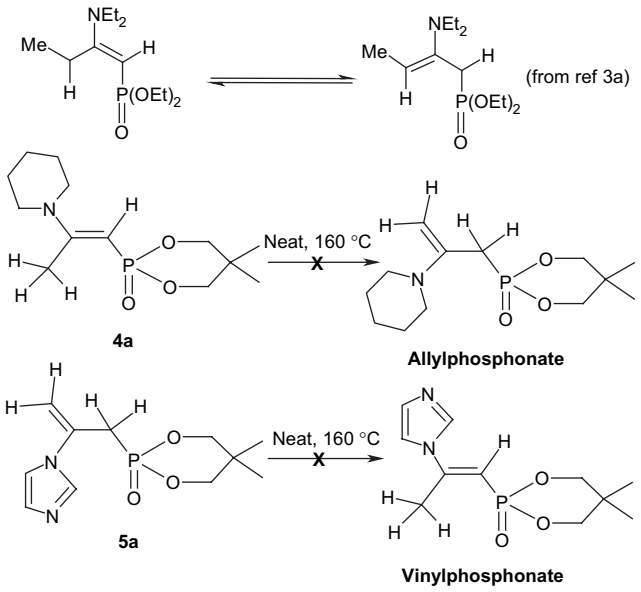
A preliminary theoretical study at B3LYP/6-31G* level using Gaussian '03 program package (see Supplementary



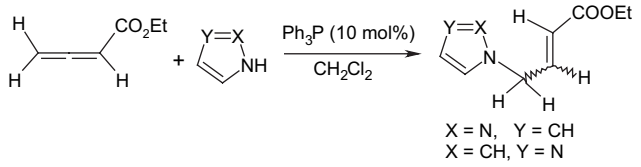
Scheme 1.

Table 1. Details on the reaction of phosphorylated allenes with amines/nucleoside bases

Entry	Allenylphosphonate	Amine, reaction conditions	Products	Yield (%)
1	**3a**	Piperidine, CH_3CN, rt	**4a**	100 (quantitative)
2	**3a**	Morpholine, CH_3CN, rt	**4b**	100 (quantitative)
3	**3a**	Pyrazole, CH_3CN, 70 °C	**5a**	80
4	**3a**	Imidazole, CH_3CN, 70 °C	**5b**	86
5	**3b**	Pyrazole, CH_3CN, 70 °C	**5c**	54
6	**3b**	Imidazole, CH_3CN, 70 °C	**5d**	62
7	**3a**	Ammonia, CH_3CN, rt	**6**	100 (quantitative)
8	**3c**	Ammonia, CH_3CN, rt	**7**	100 (quantitative)
9	**3a**	Adenine, DMF, K_2CO_3, rt	**8**	52
10	**3c**	Adenine, DMF, K_2CO_3, rt	**9**	70
11	**3c**	Thymine, DMF, K_2CO_3, rt	**10**	65
12	**3c**	Cytosine, DMF, K_2CO_3, rt	**11**	56
13	**3c**	Guanine, DMF, K_2CO_3, rt	**12**	68
14	**3d**	Adenine, DMF, K_2CO_3, rt	**13+14**	44+25
15	**3c**	*N*-methylethanolamine, CH_3CN, rt	**16**	100 (quantitative)



Scheme 2.

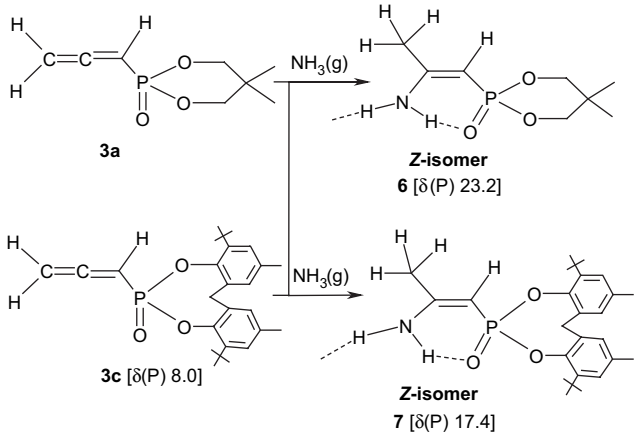


Scheme 3.

data for details) for **4a** and **5a** suggested that enamino(vinyl) form (type **4**) is more stable in the gas phase. However, it should be pointed out that gas phase stability could be different from that of the observed stability in solution/solid state. The main difference between compounds **4a** and **5a** is the presence of a saturated ring in the former and an unsaturated ring in the latter; to what extent this feature affects the stability of the vinyl and allyl forms is still not clear.

2.2. Reaction of allenes 3a and 3c with ammonia—formation of (*Z*)-*(enamino)vinyl* phosphonates 6–7

Compound **6** or **7** (quantitative yields) could be readily obtained after passing dry ammonia into a methyl cyanide solution of allene **3a** or **3c**, respectively (Scheme 4). For both



Scheme 4.

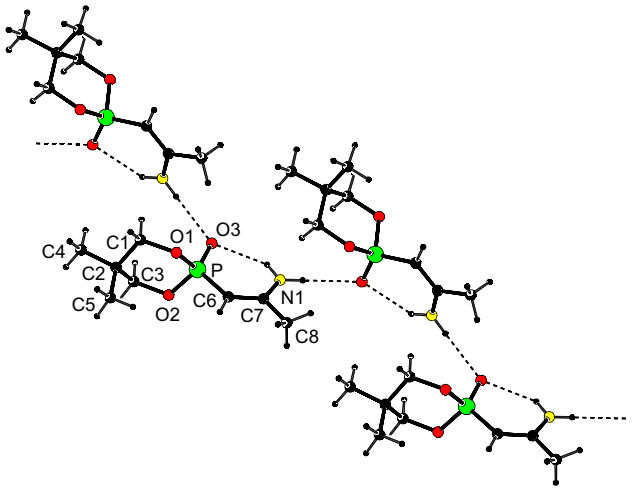
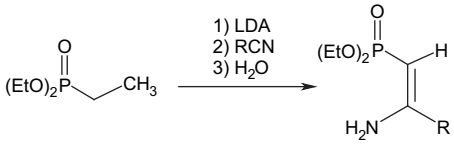


Figure 1. A PLATON drawing of **6** showing hydrogen bonding. P–C(6) 1.718(6) Å. Hydrogen bond parameters: N(1)–H(1)···O(3) 0.92(6), 2.23(5), 2.950(7) Å, 135(5)°; N(1)–H(2)···O(3′) 0.86(6), 2.34(6), 3.157(7) Å 160(6)°; N(1)–H(1)···O(1′) [not shown in the picture] 0.92(6), 2.70(6), 3.319(7) Å, 126(4)°.

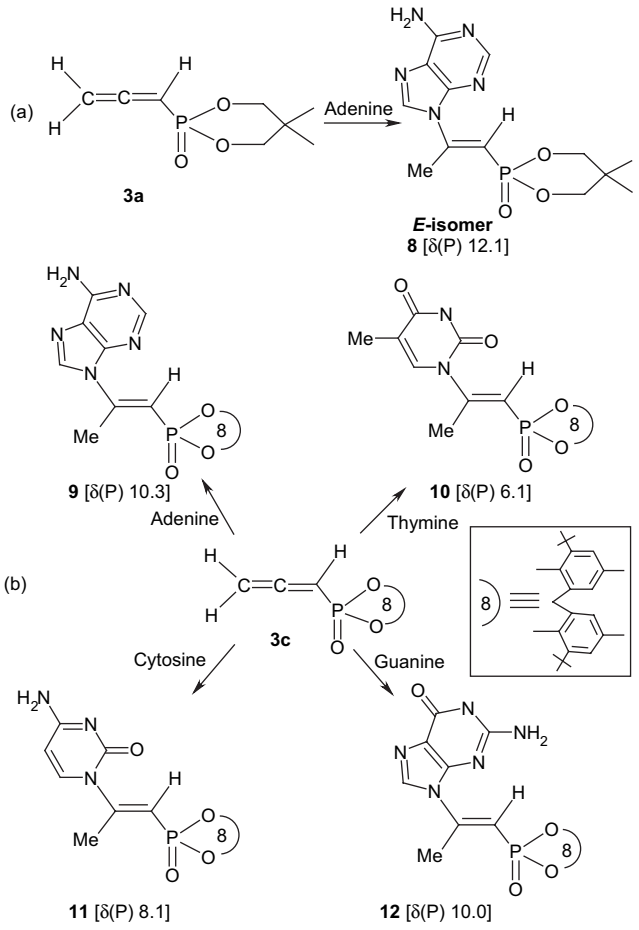
of these, the *Z* form (Fig. 1 for **6** and Supplementary data for the X-ray structure of **7**), and not the *E* form observed in **4a**–**b**, is favoured because of intramolecular hydrogen bonding involving the phosphoryl oxygen. Although intermolecular hydrogen bonding is also present, formation of hydrogen-bonded six-membered ring appears to have driven the structure towards the *Z* configuration in **6** and **7**. Previous reports have also suggested that the intramolecular hydrogen bonding leads to the *Z* form, but structural proof was not available.[6f] Our route also offers a viable alternative to the literature method (cf. Scheme 5) because of the ease of synthesis. The potentially reactive β-NH_2 group of **6**–**7** makes them attractive precursors for further investigations.[6c,6f]



Scheme 5.

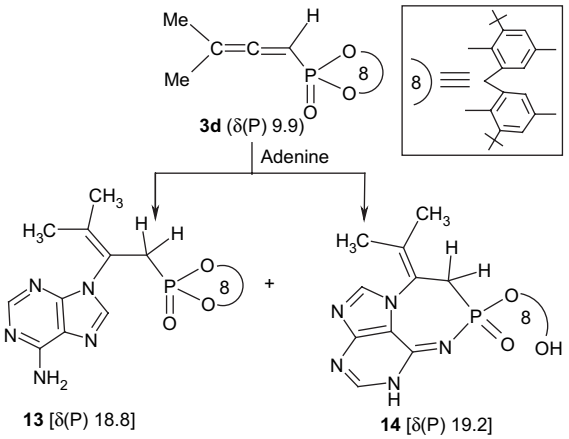
2.3. Reaction of allenylphosphonates with nucleobases—adenyl, thyminyl, cytosinyl and guanyl phosphonates 8–13 and the unusual cyclisation product 14

Reaction of allenes **3a** and **3c** with adenine in DMF at 25 °C afforded only the *E* isomer of the expected (enamino)vinyl phosphonates **8** and **9** (Scheme 6, see Supplementary data for X-ray structure). Details of the reaction conditions, yields, etc., are given in Scheme 6 and Table 1. Analogous reaction of **3c** with thymine, cytosine and guanine led to the (enamino)vinyl phosphonates **10**–**12** (Scheme 6, see Supplementary data for the X-ray structures).[15] To our knowledge, this is the first authentic report on the isolation of nucleobase-appended (enamino)vinyl phosphonates from the reaction of allenylphosphonates. Column chromatography was employed to separate the products from the unreacted allene/nucleobase. The other by-products were mainly the isomeric alkyne or the β-ketophosphonate formed due to hydrolysis of the allene.



Scheme 6.

In contrast to the formation of vinyl phosphonates **8**–**9** in the reaction of adenine with $=CH_2$ terminal allenes **3a** and **3c**, the allylphosphonate **13** (see Supplementary data for X-ray structure) and the novel cyclised product **14** (Scheme 7, Fig. 2) are obtained from the reaction of the $=CMe_2$ terminal allene **3d** with adenine. Compounds **13** and **14** could be readily separated from the same reaction mixture of the allene **3d** with adenine. The reactive centre in each of the nucleobases used in the present study (except in **14**) is



Scheme 7.

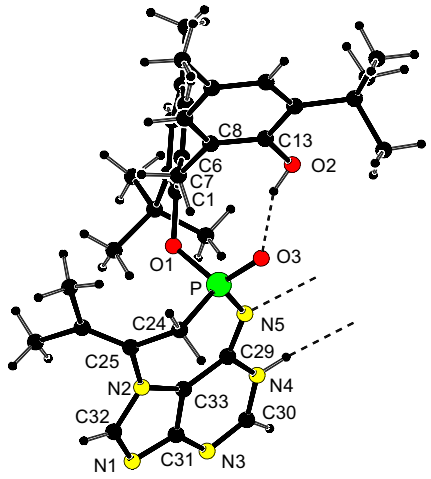
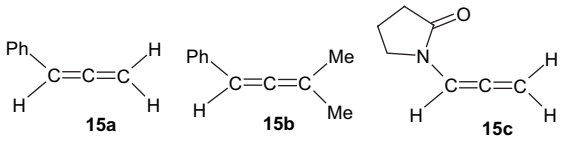
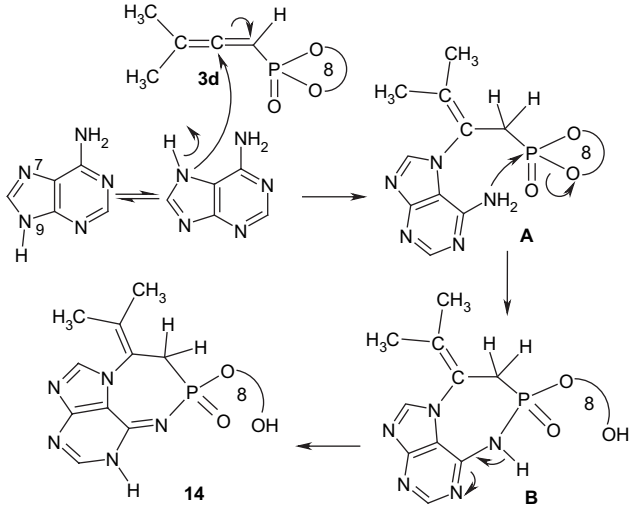


Figure 2. A PLATON drawing of **14**. Hatched lines represent hydrogen bonds. Selected distances: PN(5) 1.617(2), P–C(24) 1.798(2), N(5)–C(29) 1.315, N(2)–C(25) 1.436(3), N(4)–C(29) 1.374(3) Å.

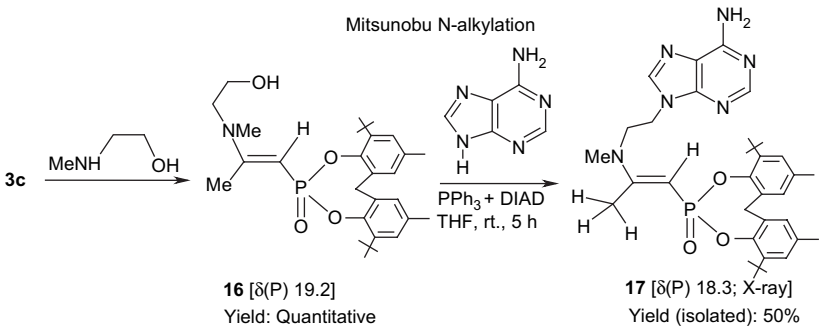
similar to that found in analogous reactions with terminal phosphorylated acetylenes, thus suggesting that they are the preferred sites of action.[7d] Under these conditions, traditional allenes **15a**–**c** did not react with adenine.



A plausible pathway for the formation of the unusual ring compound **14** is depicted in Scheme 8.[16] Here species **A** is the N(7) analogue of compound **13** [which is the N(9) derivative]. It should be noted that attack from N(7) of adenine is rather rare. Cyclisation involving the attack of the adenine–NH_2 at phosphorus leading to the seven-membered ring probably occurs via a pentacoordinated transition state, and to our knowledge, does not have precedence.



Scheme 8.



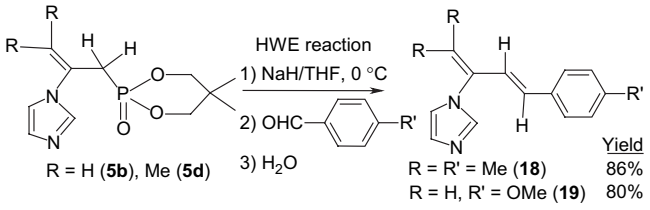
Scheme 9.

2.4. Reaction of *N*-methylethanolamine with 3c—use of the residual –OH group in the Mitsunobu coupling to adenine

Since secondary amines like piperidine and morpholine gave the vinyl phosphonates **4a**–**b**, we were interested in utilising this feature for inserting functionalised amines. As an example, by using *N*-methylethanolamine, we obtained product **16** in which the –OH group is intact. This residual –OH group undergoes facile Mitsunobu coupling with adenine to give the *N*-alkylated product **17** (Scheme 9), thus offering adenyl functionality at the ω-position of the phosphonate (see Supplementary data for X-ray structure).

2.5. Horner–Wadsworth–Emmons reaction of 5b and 5d with aldehydes

It can be noted that compounds **5a**–**d** possess a P–CH_2 group ideally suited for Horner–Wadsworth–Emmons reaction. Thus we have utilised **5b** and **5d** for the synthesis of substituted butadienes **18**–**19** (Scheme 10). To our knowledge, no other simpler route to such interesting butadienes with an enamine functionality is available in the literature.



Scheme 10.

3. Conclusion

In summary, the amination of allenylphosphonates, including those with nucleobases, takes place readily even in the absence of a transition metal catalyst leading to a single isomer of (enamino)vinyl or (enamino)allyl phosphonate while the allenes **15a**–**c** remained unreactive towards nitrogen nucleophiles. Unlike the equilibrium between the vinyl and allyl forms suggested in previous studies, only one form in each case was stable in the solution (^{31}P NMR evidence) as well as the solid state (X-ray). A very simple route to synthetically valuable β-NH_2 substituted phosphonates has been reported. New nucleobase-substituted phosphonates including a novel cyclisation product involving adenine, that could have potential biological activities, are highlighted. Utility of the products in HWE reaction as well as in the synthesis of remotely functionalized phosphonates via Mitsunobu N-alkylation is demonstrated.

4. Experimental

4.1. General

Chemicals were purified when required according to standard procedures.[17a] All reactions, unless stated otherwise, were performed in a dry nitrogen atmosphere. ^{1}H, ^{13}C and ^{31}P{H} NMR spectra were recorded using a 200 or a 400 MHz spectrometer in $CDCl_3$ (unless stated otherwise) with shifts referenced to $SiMe_4$ (δ=0) or 85% H_3PO_4 (δ=0). Infrared spectra were recorded on an FT/IR spectrometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Microanalyses were performed using a CHNS analyser. Mass spectra were recorded using a GCMS-QP2010 and LCMS 2010A.

Precursors 5,5-dimethyl-2-propa-1,2-dienyl-[1,3,2]dioxaphosphinane 2-oxide (**3a**) [δ_P 7.4] and 5,5-dimethyl-2-(3-methyl-buta-1,2-dienyl)-[1,3,2]dioxaphosphinane 2-oxide (**3b**) [δ_P 8.5] were prepared using a literature procedure;[12a] an analogous procedure was adapted for 4,8-di-*tert*-butyl-2,10-dimethyl-6-propa-1,2-dienyl-12*H*-5,7-dioxa-6-phospha-dibenzo[*a*,*d*]cyclooctene 6-oxide (**3c**) [δ_P 8.0] and 4,8-di-*tert*-butyl-2,10-dimethyl-6-(3-methyl-buta-1,2-dienyl)-12*H*-5,7-dioxa-6-phospha-dibenzo[*a*,*d*]cyclooctene 6-oxide (**3d**) [δ_P 9.9].[12b] Compounds propa-1,2-dienyl-benzene (**15a**), (3-methyl-buta-1,2-dienyl)-benzene (**15b**) and 1-propa-1,2-dienyl-pyrrolidin-2-one (**15c**) were prepared by known methods.[17b–c]

4.1.1. 1-[2-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-methyl-vinyl]-piperidine (4a). To a solution of allenylphosphonate **3a** (1.0 mmol) in dry methyl cyanide (10 mL), the amine (piperidine or morpholine) (1.0 mmol) was added via syringe at room temperature and the mixture was stirred for 4 h; the solution was concentrated in vacuo (to ca. 2.5 mL) and kept for crystallisation. Crystals were obtained after 24 h at 25 °C. Yield 0.27 g (100%); colourless needles; mp 74–76 °C [Found: C, 57.05; H, 8.69; N, 5.06. $C_{13}H_{24}NO_3P$ requires C, 57.13; H, 8.85; N, 5.12]; ν_{max} (KBr) 1576, 1441, 1416, 1236, 1057, 1011 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.23 (dd, J_{H-H}=4.7 Hz,

J_{H-P}=15.7 Hz, 2H, OCH_AH_B), 4.00 (d, J_{H-P}=8.8 Hz, 1H, PC*H*), 3.72 (dd, J_{H-H}=4.7 Hz, J_{H-P}=15.7 Hz, 2H, OCH_AH_B), 3.25 (br, 4H, $N(CH_2CH_2CH_2CH_2CH_2–)$), 2.29 (d, J_{H-P}=1.4 Hz, 3H, $C(N(CH_2)_4–)CH_3$), 1.59 (br, 6H, $C(NCH_2CH_2CH_2CH_2CH_2–)$), 1.14, 0.96 (2s, 6H, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 162.0 (d, J_{C-P}=21.7 Hz), 74.6, 74.5, 73.3 (d, J_{C-P}=217.4 Hz), 47.2, 32.3 (d, J_{C-P}=5.1 Hz), 25.2, 24.1, 21.9, 21.4, 18.1 (d, J_{C-P}=4.8 Hz); δ_P (80 MHz, $CDCl_3$) 24.8. X-ray structure was determined for this sample.

4.1.2. 4-[2-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-methyl-vinyl]-morpholine (4b). Yield 0.27 g (100%); white solid; mp 100–102 °C [Found: C, 52.27; H, 8.01; N, 5.08. $C_{12}H_{22}NO_4P$ requires C, 52.31; H, 8.06; N, 5.09]; ν_{max} (KBr) 1584, 1453, 1400, 1233, 1055, 997 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.09 (dd, J_{H-H}~2.0 Hz, J_{H-P}=10.8 Hz, 1H, OCH_AH_B), 4.00 (d, J_{H-P}=8.8 Hz, 1H, PC*H*), 3.63 (m, 6H, $N(CH_2CH_2OCH_2CH_2–)$), 3.13 (t, J_{H-H}= 5.0 Hz, 4H, $N(CH_2CH_2OCH_2CH_2–)$), 2.20 (d, J_{H-P}=2.0 Hz, 3H, $N(CH_2CH_2OCH_2CH_2–)CH_3$), 1.04, 0.90 (2s, 6H, $C(CH_3)_2$); δ_C (50 MHz, $CDCl_3$) 162.6 (d, J_{C-P}=20.5 Hz), 76.7 (d, J_{C-P}=214.0 Hz), 74.7, 66.2, 46.2, 32.4 (d, J_{C-P}= 4.4 Hz), 21.9, 21.4, 17.6 (d, J_{C-P}=3.8 Hz); δ_P (80 MHz, $CDCl_3$) 22.7.

4.1.3. 1-[1-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethyl)-vinyl]-1*H*-pyrazole (5a). To a solution of allenylphosphonate **3a** (1.88 g, 10.0 mmol) in dry methyl cyanide (20 mL), pyrazole (0.68 g, 10.0 mmol) was added and the reaction mixture heated under reflux (70 °C) for 14 h with continuous stirring. The solvent was removed under reduced pressure and the solid obtained was purified by column chromatography (silica gel, hexane–ethyl acetate). The product was crystallised from dichloromethane–hexane mixture (1:1). Yield 2.02 g (80%); colourless rectangular plates; mp 79–81 °C [Found: C, 51.46; H, 6.76; N, 10.73. $C_{11}H_{17}N_2O_3P$ requires C, 51.56; H, 6.69; N, 10.83]; ν_{max} (KBr) 1649, 1478, 1262, 1053, 1005 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.76 (d, J_{H-H}=2.0 Hz, 1H, pyrazolyl-*H*), 7.56 (br s, 1H, pyrazolyl-*H*), 6.32 (d, J_{H-H}=2.0 Hz, 1H, pyrazolyl-*H*), 5.36, 5.07 (2d, J_{H-H}=4.8 Hz, 2H, $=CH_2$), 3.75–4.02 (m, 4H, OCH_2), 3.45 (d, J_{H-P}=21.3 Hz, 2H, PCH_2), 1.04, 0.91 (2s, 6H, $C(CH_3)_2$); δ_C (50 MHz, $CDCl_3$) 142.0, 136.3 (d, J_{C-P}=10.4 Hz), 127.4, 107.3, 103.8 (d, J_{C-P}=9.7 Hz), 75.7, 75.6, 32.1 (d, J_{C-P}=5.5 Hz), 28.2 (d, J_{C-P}= 133.1 Hz), 21.4, 20.7; δ_P (80 MHz, $CDCl_3$) 18.0. X-ray structure was determined for this sample.

4.1.4. 1-[1-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethyl)-vinyl]-1*H*-imidazole (5b). The procedure was the same as that for **5a** using imidazole instead of pyrazole. Yield 1.58 g (86%); pale yellow solid; mp 69–71 °C [Found: C, 51.56; H, 6.72; N, 10.78. $C_{11}H_{17}O_3N_2P$ requires C, 51.56; H, 6.69; N, 10.83]; ν_{max} (KBr) 1647, 1489, 1269, 1059 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78, 7.21, 7.11 (3 br s, 3H, imidazolyl-*H*), 5.34, 5.22 (2d, J_{H-H}=5.2 Hz, 2H, $C=CH_2$), 4.26 (dd, J_{H-H}=4.8 Hz, J_{H-P}=11.1 Hz, 2H, OCH_AH_B), 3.75 (dd, J_{H-H}=4.8 Hz, J_{H-P}=12.1 Hz, 2H, OCH_AH_B), 3.18 (d, J_{H-P}=20.0 Hz, 2H, PCH_2), 1.07, 0.98 (2s, 6H, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 135.6, 133.3 (d, $^2J_{C-P}$=10.0 Hz), 130.0, 117.4, 108.2 (d, J_{C-P}=9.7 Hz), 75.5, 75.3, 32.5, 31.0 (d, J_{C-P}=137.0 Hz), 21.4, 21.2; δ_P (80 MHz, $CDCl_3$) 18.3.

4.1.5. 1-[1-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethyl)-2-methyl-propenyl]-1*H*-pyrazole (5c). This compound was obtained by using 10.5 mmol of the allene **3b** and following the same procedure as that for **5a**. Yield 1.37 g (54%); white solid; mp 102 °C [Found: C, 54.80; H, 7.49; N, 9.74. $C_{13}H_{21}O_3N_2P$ requires C, 54.92; H, 7.44; N, 9.85]; ν_{max} (KBr) 3108, 1721, 1672, 1643, 1510, 1285, 1065 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47, 7.39, 6.15 (3 br s, 3H, pyrazolyl-*H*), 3.79–3.73 (m, 2H, OCH_AH_B), 3.51–3.48 (m, 2H, OCH_AH_B), 3.17 (d, J_{H-P}=19.6 Hz, 2H, PCH_2), 1.83 (d, J_{H-P}=4.0 Hz, 3H, $C=C(CH_{3A})_2$), 1.48 (d, J_{H-P}=5.6 Hz, 3H, $C=C(CH_{3B})_2$), 0.93, 0.77 (2s, 6H, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 139.6, 134.0 (d, J_{C-P}= 11.6 Hz), 132.3, 123.7 (d, J_{C-P}=13.0 Hz), 75.7, 75.6, 32.2 (d, J_{C-P}=6.5 Hz), 27.7 (d, $^1J_{C-P}$=131.8 Hz), 21.4, 20.9, 20.4, 20.1; δ_P (160 MHz, $CDCl_3$) 20.8; LCMS: 285 $[M+1]^+$.

4.1.6. 1-[1-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-ylmethyl)-2-methyl-propenyl]-1*H*-imidazole (5d). This compound was obtained by using 10.5 mmol of the allene **3b** and following the same procedure as that for **5a**. Yield 1.58 g (62%); light brown solid; mp 78 °C [Found: C, 54.88; H, 7.38; N, 9.84. $C_{13}H_{21}O_3N_2P$ requires C, 54.92; H, 7.44; N, 9.85]; ν_{max} (KBr) 3106, 1684, 1489, 1263, 1063, 820 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.49, 7.26, 6.95 (3 br s, 3H, imidazolyl-*H*), 4.15–4.10 (m, 2H, OCH_AH_B), 3.67–3.60 (m, 2H, OCH_AH_B), 3.02 (d, J_{H-P}=21.0 Hz, 2H, PCH_2), 1.95 (d, J_{H-P}=4.6 Hz, 3H, $C=C(CH_{3A})_2$), 1.54 (d, J_{H-P}=6.1 Hz, 3H, $C=C(CH_{3B})_2$), 0.99, 1.02 (2s, 6H, $C(CH_3)_2$); δ_C (50 MHz, $CDCl_3$) 137.6, 136.4 (d, J_{C-P}=10.9 Hz), 128.9, 119.3, 119.8, 75.3, 75.1, 32.5 (d, J_{C-P}=6.0 Hz), 30.1 (d, J_{C-P}=135.8 Hz), 21.3, 20.5, 20.0; δ_P (80 MHz, $CDCl_3$) 21.0.

4.1.7. 2-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-methyl-vinylamine (6). To a solution of allenylphosphonate **3a** (1.0 mmol) in 5 mL dry methyl cyanide, an excess of a saturated solution of ammonia in dry methyl cyanide (20 mL) was added slowly at 0 °C with continuous stirring. After 15 min the reaction was brought to room temperature, continued the stirring for about 1 h. After removal of the solvent under reduced pressure, 3 mL of dry toluene was added to get the crystals at 0 °C after one day. However, direct passing of ammonia gas to the phosphorylated allene in toluene did not give the product.

Yield 0.20 g (100%); colourless needles; mp 82–84 °C [Found: C, 46.80; H, 7.87; N, 6.76. $C_8H_{16}O_3NP$ requires C, 46.83; H, 7.86; N, 6.83]; ν_{max} (KBr) 3409, 3322, 3239, 3202, 1647, 1576, 1429, 1219, 1059 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.00 (br s, 2H, NH_2), 4.24–4.28 (dd, J_{H-H}~2.3 Hz, J_{H-P}~9.4 Hz, 2H, OCH_2), 3.66–3.78 (m, 3H, OCH_2+PC*H*), 1.93 (s, 3H, CH_3), 1.17, 0.88 (2s, 6H, $C(CH_3)_2$); δ_C (50 MHz, $CDCl_3$) 163.0 (d, J_{C-P}=6.1 Hz), 74.2, 74.1, 69.9 (d, J_{C-P}= 201.3 Hz), 31.8 (d, J_{C-P}=5.0 Hz), 23.9 (d, J_{C-P}=21.5 Hz), 21.7, 21.0; δ_P (160 MHz, $CDCl_3$) 23.2. X-ray structure was determined for this sample.

4.1.8. 2-(4,8-Di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a*,*d*]cycloocten-6-yl)-1-methyl-vinylamine (7). The procedure was the same as that for **6** using **3c** and the same molar quantities. Yield 0.44 g (100%); colourless rectangular blocks; mp 130–132 °C [Found: C, 70.63; H, 8.12; N, 3.28. $C_{26}H_{36}O_3NP$ requires

C, 70.72; H, 8.22; N, 3.19]; ν_{max} (KBr) 3420, 3326, 3239, 3204, 1640, 1582, 1439, 1217, 1138 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.98–7.06 (2 br s, 4H, Ar-*H*), 4.40 (br s, 1H, $ArCH_AH_X$), 4.08 (d, J_{H-P}=14.8 Hz, 1H, PC*H*), 3.79(d, J_{H-H}=13.6 Hz, 1H, $ArCH_AH_X$), 2.27 (s, 6H, $ArCH_3$), 1.97, (s, 3H, CH_3), 1.38 (s, 18H, *t*-Bu-*H*); δ_C (50 MHz, $CDCl_3$) 160.7 (d, J_{C-P}=6.0 Hz), 147.2, 147.0, 140.8, 140.6, 133.5, 131.6, 129.4, 126.9, 73.7 (d, J_{C-P}=208.6 Hz), 36.1, 34.8, 30.8, 24.3 (d, J_{C-P}=23.0 Hz), 21.0; δ_P (160 MHz, $CDCl_3$) 17.4; GC–MS: 441 $[M]^+$. X-ray structure was determined for this sample.

4.2. Synthesis of nucleobase-appended phosphonates 8–14: representative procedure for 9

Method A: A mixture of adenine (0.191 g, 1.4 mmol), potassium *tert*-butoxide (0.157 g, 1.4 mmol) and catalytic amount of 18-crown–6 in dry methyl cyanide (80 mL) was stirred at room temperature for 30 min. Phosphorylated allene **3c** (0.191 g, 1.2 mmol) was then added all at once under a nitrogen atmosphere and the mixture stirred for overnight. The insolubles were filtered off and the solvent from the filtrate removed under reduced pressure. The residue was chromatographed on a silica gel column using ethyl acetate–hexane mixture as the eluent.

Method B: A mixture of adenine (0.191 g, 1.4 mmol) and potassium carbonate (0.195 g, 1.4 mmol) in dry DMF (70 mL) was stirred at room temperature for 15 min. Phosphorylated allene **3c** (0.50 g, 1.2 mmol) was then added all at once under a nitrogen atmosphere with stirring. Progress of the reaction was monitored by TLC. The solid was filtered off and the solvent was removed by vacuum distillation. The residue was chromatographed on a silica gel with ethyl acetate–hexane mixture.

Method B gave better yields than method A (using **3c**); this is what is given below and in Table 1. Crystals (compounds **9**, **10**, **11** and **13**) suitable for X-ray crystallography were obtained from methanol–methyl cyanide (~1:2) mixture.

4.2.1. 9-[2-(5,5-Dimethyl-2-oxo-2λ^5-[1,3,2]dioxaphosphinan-2-yl)-1-methyl-vinyl]-9*H*-purin-6-ylamine (8). Yield 0.20 g (52%); white solid; mp 270 °C [Found: C, 48.24; H, 5.51; N, 21.60. $C_{13}H_{18}O_3N_5P$ requires C, 48.30; H, 5.61; N, 21.66]; ν_{max} (KBr) 3304, 3152, 1671, 1642, 1605, 1564, 1476, 1238, 1057 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 8.40, 8.25 (2s, 2H, adenyl-*H*), 8.09 (br s, 2H, NH_2), 7.15 (d, J_{H-P}=12.0 Hz, 1H, PC*H*), 3.98–4.11 (multiplet, 4H, OCH_2), 2.72 (s, 3H, CH_3), 1.21, 0.96 (2s, 6H, $C(CH_3)_2$); Solubility was too low to record the ^{13}C NMR; δ_P (160 MHz, DMSO-d_6) 12.1. Crystals were obtained from dimethyl sulfoxide (not suitable for X-ray crystallography).

4.2.2. 9-[2-(4,8-Di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a*,*d*]cycloocten-6-yl)-1-methyl-vinyl]-9*H*-purin-6-ylamine (9). Yield 0.47 g (70%); colourless needles; mp 248–250 °C [Found: C, 66.58; H, 6.85; N, 12.65. $C_{31}H_{38}O_3N_5P$ requires C, 66.53; H, 6.84; N, 12.52]; ν_{max} (KBr) 3308, 3144, 1682, 1605, 1561, 1458, 1213, 1136 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.42 and 8.10 (2s, 2H, adenyl-*H*), 7.72 (d, J_{H-P}=12.0 Hz, 1H, PC*H*), 7.05 (s, 4H, Ar-*H*), 5.80 (br s, 2H, NH_2), 3.90–4.10 (br s, 2H, $ArCH_2$), 2.94 (d, J_{H-P}=2.9 Hz, 3H, CH_3), 2.29 (s, 6H, $ArCH_3$), 1.38 (s, 18H, *t*-Bu-*H*); δ_C (50 MHz, $CDCl_3$) 156.0, 153.7, 150.6, 147.5 (d, J_{C-P}=22.5 Hz), 146.1, 140.7, 140.6, 138.1, 134.4, 131.8, 129.5, 127.3, 120.8, 107.2 (d, J_{C-P}=209.8 Hz), 35.6, 34.8, 30.9, 21.0, 18.6; δ_P (160 MHz, $CDCl_3$) 10.3. X-ray structure was determined for this sample.

4.2.3. 1-[2-(4,8-Di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a*,*d*]cycloocten-6-yl)-1-methyl-vinyl]-5-methyl-1*H*-pyrimidine-2,4-dione (10). Yield 0.42 g (65%); colourless needles; mp 220 °C [Found: C, 67.53; H, 7.12; N, 5.19. $C_{31}H_{39}O_5N_2P$ requires C, 67.62; H, 7.14; N, 5.10]; ν_{max} (KBr) 3567 (br), 3206, 3075, 1699, 1458, 1260, 931 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.20 (br s, 1H, thyminyl-N*H*), 7.06 (br s, 4H, Ar-*H*), 6.91 (s, 1H, thyminyl-*H*), 6.01 (d, J_{H-P}=10.4 Hz, 1H, PC*H*), 4.06 (br s, 2H, $ArCH_2$), 2.64 (d, J_{H-P}=3.2 Hz, 3H, CH_3), 2.29 (s, 6H, $ArCH_3$), 1.97 (s, 3H, thyminyl-CH_3), 1.40 (s, 18H, *t*-Bu-*H*); δ_C (50 MHz, $CDCl_3$) 163.9, 148.7, 140.6, 134.8, 138.6, 131.8, 129.5, 127.5, 111.7, 115.9 (d, J_{C-P}= 202.5 Hz), 35.3, 34.9, 30.9, 29.7, 19.9; δ_P (80 MHz, $CDCl_3$) 6.1. X-ray structure was determined for this sample.

4.2.4. 4-Amino-1-[2-(4,8-di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a*,*d*]cycloocten-6-yl)-1-methyl-vinyl]-1*H*-pyrimidin-2-one (11). Yield 0.36 g (56%); colourless thick rectangular blocks; mp 200–205 °C [Found: C, 67.15; H, 7.15; N, 7.85. $C_{30}H_{38}O_4N_3P$ requires C, 67.26; H, 7.15; N, 7.85]; ν_{max} (KBr) 3370, 1651, 1508, 1385, 1211 cm^{-1}; δ_H (400 MHz, $CDCl_3$: DMSO-d_6) 7.20 (d, J_{H-P}=10.0 Hz, 1H, PC*H*), 7.09 (s, 4H, Ar-*H*), 6.06 (d, J_{H-H}=6.6 Hz, 1H, cytosinyl-*H*), 5.82 (d, J_{H-H}=6.4 Hz, 1H, cytosinyl-*H*), 4.07 (br s, 2H, $ArCH_2$), 2.63 (s, 3H, CH_3), 2.30 (s, 6H, $ArCH_3$), 1.40 (s, 18H, *t*-Bu-*H*); ^{13}C NMR spectrum was not clear due to lower solubility; δ_P (160 MHz, $CDCl_3$) 8.1. X-ray structure was determined for this sample.

4.2.5. 2-Amino-9-[2-(4,8-di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a*,*d*]cycloocten-6-yl)-1-methyl-vinyl]-1,9-dihydro-purin-6-one (12). Yield 0.46 g (68%); white solid; mp 268–274 °C [Found: C, 64.68; H, 6.63; N, 12.17. $C_{31}H_{38}O_4N_5P$ requires C, 64.68; H, 6.65; N, 12.17]; ν_{max} (KBr) 3393, 3308, 3196, 1703, 1640, 1599, 1211 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 12.30 (br s, 2H, NH_2), 7.90 (s, 1H, guanyl-*H*), 7.50 (d, J_{H-P}=19.5 Hz, 1H, PC*H*), 7.06 (br s, 4H, Ar-*H*), 6.50 (br s, 1H, N*H*), 4.07 (br s, 2H, $ArCH_2$), 2.86 (d, J_{H-P}=3.9 Hz, 3H, CH_3), 2.29 (s, 6H, $ArCH_3$), 1.29 (s, 18H, *t*-Bu-*H*); δ_C (100 MHz, DMSO-d_6) 157.0, 154.3, 151.8, 149.3 (d, J_{C-P}=22.0 Hz), 145.6, 140.9, 136.0, 134.5, 132.9, 129.7, 127.5, 118.6, 103.8 (d, J_{C-P}=202.0 Hz), 34.9, 34.2, 31.2, 21.0, 18.6 (d, J_{C-P}= 3.7 Hz); δ_P (160 MHz, $CDCl_3$) 10.0.

4.2.6. 9-[1-(4,8-Di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a*,*d*]cycloocten-6-yl-methyl)-2-methyl-propenyl]-9*H*-purin-6-ylamine (13). CH_3CN and 3-*tert*-butyl-5-[3-*tert*-butyl-5-(9-isopropylidene-7-oxo-5,7,8,9-tetrahydro-2,3,5,6,9a-pentaaza-7λ^5-phospha-benzo[*c*,*d*]azulen-7-yloxy)-2-methyl-benzyl]-4-methyl-phenol (14). Two products **13** and **14** were obtained in the reaction of **3d** with adenine following the same

procedure as that for **9** using the same molar quantities. The reaction mixture showed two peaks at δ 18.8 (ca. 80%) and 19.3 (ca. 20%) in the ^{31}P NMR.

Compound **13**: Yield 0.31 g (44%); colourless thin plates; mp 180–182 °C [Found (after drying): C, 67.33; H, 7.26; N, 11.86. $C_{33}H_{42}O_3N_5P$ requires C, 67.44; H, 7.20; N, 11.92]; ν_{max} (KBr) 3221, 3113, 3044, 1630, 1588, 1560, 1431, 1174 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.35 and 7.93 (2s, 2H, adenyl-*H*), 6.99 and 6.98 (2s, 4H, Ar-*H*), 5.58 (br s, 2H, N*H*$_2$), 3.90 (d and a broad signal, J_{H-C-P}=20.8 Hz, 3H, PC*H*$_2$ merged with peak due to 1H of ArC*H*$_A$H$_B$), 3.50 (br, 1H, ArC*H*$_2$), 2.24 (s, 6H, ArC*H*$_3$), 2.14 (d, J_{H-P}= 3.5 Hz, 3H, C(C*H*$_{3A}$)$_2$), 1.64 (s, 3H, C(C*H*$_{3B}$)$_2$), 1.25 (s, 18H, *t*-Bu-*H*); δ_C (100 MHz, $CDCl_3$) 155.5, 153.4, 150.1, 144.6, 144.5, 141.8, 140.9, 138.0, 137.8, 135.0, 132.8, 129.0, 127.6, 119.3, 119.1, 119.0, 34.7, 34.3, 31.3 (d, J_{C-P}= 146.6 Hz), 30.8, 21.2, 20.9, 20.3, 20.2; δ_P (160 MHz, $CDCl_3$) 18.8. X-ray structure was determined for this sample.

Compound **14**: Yield 0.17 g (25%); colourless diamond-like crystals; mp 196–198 °C [Found: C, 67.48; H, 7.22; N, 11.96. $C_{33}H_{42}O_3N_5P$ requires C, 67.44; H, 7.20; N, 11.92]; ν_{max} (KBr) 3335, 3177, 1669, 1595, 1456, 1238, 1196 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.01 and 7.93 (2s, 2H, adenyl-*H*), 7.26, 7.04, 6.93 (3s, 4H, Ar-*H*), 6.72, 6.48 (2 br s, 2H, N*H*+O*H*), 4.90 (br s, 1H, ArC*H*$_A$H$_X$), 3.67 (d, J_{H-P}=21.2 Hz, 2H, PC*H*), 3.20 (br s, 1H, ArCH$_A$*H*$_X$), 2.27 and 2.16 (2s, 6H, ArC*H*$_3$), 2.02 (d, J_{H-P}=4.8 Hz, 3H, =C(C*H*$_{3A}$)$_2$), 1.83 (d, J_{H-P}=6.0 Hz, 3H, =C(C*H*$_{3B}$)$_2$), 1.41, 1.20 (2s, 18H, *t*-Bu-*H*); δ_C (100 MHz, $CDCl_3$) 155.6, 145.6, 141.6, 135.2, 132.8, 128.0, 127.6, 126.3, 119.0, 34.8, 34.6 (d, J_{C-P}=167.3 Hz), 34.5, 31.5, 29.8, 21.2, 21.0, 20.9; δ_P (160 MHz, $CDCl_3$) 19.2. X-ray structure was determined for this sample.

4.2.7. 2-{[2-(4,8-Di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a,d*]cycloocten-6-yl)-1-methyl-vinyl]-methyl-amino}-ethanol (16). The procedure is similar to that of **4a** using the same molar quantities. Yield 0.49 g (100%); white solid; mp 198–202 °C [Found: C, 69.76; H, 8.19; N, 2.82. $C_{29}H_{42}O_4NP$ requires C, 69.71; H, 8.21; N, 2.80]; ν_{max} (KBr) 3457, 1570, 1456, 1238, 1132, 1032 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.01 (s, 4H, Ar-*H*), 4.30 (d, J_{H-P}=8.8 Hz, 1H, PC*H*), 3.96 (br s, 2H, ArC*H*$_2$), 3.73 (t, J_{H-H}=7.1 Hz, 2H, C*H*$_2$OH), 3.42 (t, J_{H-H}=7.1 Hz, 2H, NC*H*$_2$), 2.95 (s, 3H, C*H*$_3$), 2.44 (s, 3H, NC*H*$_3$), 2.27 (s, 6H, ArC*H*$_3$), 1.75 (br s, 1H, O*H*), 1.39 (s, 18H, *t*-Bu-*H*); δ_C (50 MHz, $CDCl_3$) 160.3 (d, J_{C-P}=23.5 Hz), 146.5, 140.8, 134.5, 133.5, 132.3, 129.3, 127.6, 126.9, 82.5 (d, J_{C-P}=226.0 Hz), 64.1, 60.1, 53.6, 35.7, 34.8, 30.8, 21.0, 18.2; δ_P (160 MHz, $CDCl_3$) 19.2.

4.2.8. 9-(2-{[2-(4,8-Di-*tert*-butyl-2,10-dimethyl-6-oxo-12*H*-5,7-dioxa-6λ^5-phospha-dibenzo[*a,d*]cycloocten-6-yl)-1-methyl-vinyl]-methyl-amino}-ethyl)-9*H*-purin-6-ylamine (17). To a stirred solution of **16** (0.632 g, 1.05 mmol), triphenylphosphine (0.332 g, 1.27 mmol) and adenine (0.142 g, 1.05 mmol) in dry THF (25 mL) at room temperature was added diethylazodicarboxylate dropwise (0.256 g, 1.27 mmol). The solution was then stirred at room temperature for 6 h, after which the volatile components were removed under reduced pressure and the residue was purified by chromatography (silica gel, in hexane–ethyl acetate) to give the pure product as a white solid. Crystals (**17**·2MeOH) were obtained after 48 h at 25 °C from methanol. Yield 0.37 g (50%); colourless plates; mp 248 °C [Found (after drying): C, 66.25; H, 7.34; N, 13.40. $C_{34}H_{45}O_3N_6P$ requires C, 66.21; H, 7.35; N, 13.36]; ν_{max} (KBr) 3459, 3297, 3129, 1649, 1574, 1439, 1236, 1128, 1026 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.37 and 7.63 (2s, 2H, adenyl-*H*), 7.02 (br s, 4H, Ar-*H*), 5.72 (br s, 2H, N*H*$_2$), 4.32 (br s, 3H, C*H*$_2$+ArC*H*$_A$H$_X$), 3.99 (br s, 1H, ArCH$_A$*H*$_X$), 3.74 (br s, 2H, NC*H*$_2$), 3.57 (d, J_{H-P}=23.3 Hz, 1H, PC*H*), 2.71 (s, 3H, C*H*$_3$), 2.35 (s, 3H, NC*H*$_3$), 2.26 (s, 6H, ArC*H*$_3$), 1.26–1.43 (multiplet, 18H, *t*-Bu-*H*); δ_C (100 MHz, $CDCl_3$) 159.0 (d, J_{C-P}=23.0 Hz), 155.7, 153.2, 149.9, 140.7, 140.4, 133.7, 132.3, 129.2, 127.8, 127.0, 111.6, 78.9 (d, J_{C-P}=231.0 Hz), 50.9, 41.4, 38.9, 34.8, 31.1, 30.8, 29.5, 21.0; δ_P (160 MHz, $CDCl_3$) δ 18.3; LCMS: 617 [M]$^+$ (after the loss of methanol solvent). X-ray structure was determined on this sample.

4.2.9. 1-[2-Methyl-1-(2-*p*-tolyl-vinyl)-propenyl]-1*H*-imidazole (18). To a suspension of sodium hydride (0.12 g, 4.8 mmol) in THF (10 mL), phosphonate **5b** (0.32 g, 1.2 mmol) in THF (20 mL) was added at 0 °C and the mixture stirred for 15 min. Then anisaldehyde (0.17 g, 1.2 mmol) in THF (10 mL) was added slowly (5 min), the mixture stirred for 4 h, quenched with water (20 mL) and extracted with ether (3×20 mL). The combined organic layer was washed with water, saturated brine solution, dried (Na_2SO_4) and the solvent evaporated to afford an oily material. This was purified by silica gel column chromatography using hexane–ethyl acetate mixture. Yield 0.23 g (86%); pale yellow liquid [Found: C, 80.52; H, 7.65; N, 11.68. $C_{16}H_{18}N_2$ requires C, 80.63; H, 7.61; N, 11.75]; ν_{max} (neat) 1709, 1640, 1609, 1510, 1248 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.45, 7.21 (2s, 2H, imidazolyl-*H*), 7.19 (s, 2H, Ar-*H*), 7.13 (d, J_{H-H}=15.7 Hz, 1H, C*H*$_A$=CH$_B$), 7.08 (d, J_{H-H}=7.8 Hz, 2H, Ar-*H*), 6.86 (s, 1H, imidazolyl-*H*), 5.78 (d, J_{H-H}=15.7 Hz, 1H, CH$_A$=C*H*$_B$), 2.30 (s, 3H, ArC*H*$_3$), 2.05 (s, 3H, C=C(C*H*$_{3A}$)$_2$), 1.57 (s, 3H, C=C(C*H*$_{3B}$)$_2$); δ_C (50 MHz, $CDCl_3$) 139.0, 134.4, 133.9, 130.3, 129.4, 129.1, 128.6, 126.5, 122.1, 120.5, 21.2, 20.63, 19.7; LCMS: 239 [M+1]$^+$.

4.2.10. 1-[3-(4-Methoxy-phenyl)-1-methylene-allyl]-1*H*-imidazole (19). The procedure was the same as that for **18** by starting with **5d** and using the same molar quantities. Yield 0.23 g (80%); pale yellow liquid [Found: C, 74.23; H, 6.21; N, 12.23. $C_{16}H_{18}ON_2$ requires C, 74.31; H, 6.24; N, 12.36]; ν_{max} (neat) 3119, 1740, 1682, 1603, 1512, 1254 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.68 (s, 1H, imidazolyl-*H*), 7.33 (d, J_{H-H}=8.8 Hz, 2H, Ar-*H*), 7.15 (s, 1H, imidazolyl-*H*), 7.10 (d, J_{H-H}=2.0 Hz, 1H, imidazolyl-*H*), 6.87 (d, J_{H-H}=8.8 Hz, 2H, Ar-*H*), 6.73 (d, J_{H-H}=15.6 Hz, 1H, C*H*$_A$=CH$_B$), 6.49 (d, J_{H-H}=15.6 Hz, 1H, CH$_A$=C*H*$_B$), 5.26, 5.17 (2s, 2H, C=C*H*$_2$), 3.82 (s, 3H, OC*H*$_3$); δ_C (50 MHz, $CDCl_3$) 160.3, 142.0, 137.0, 132.6, 129.3, 128.4, 122.1, 119.6, 114.4, 109.9, 55.4; LCMS: 227 [M+1]$^+$ (another peak at *m/e* 385 probably due to dimer minus imidazole was seen).

X-ray crystallography: Single crystal X-ray data were collected on an Enraf-Nonius MACH3 or on a Bruker

AXS-SMART diffractometer, using Mo Kα (λ=0.71073 Å) radiation. The structures were solved by direct methods and refined by full-matrix least squares method using standard procedures.[18] Absorption corrections were done using SADABS program, wherever applicable. In some cases, the terminal carbon atoms of the *tert*-butyl groups showed high thermals and hence were refined using a suitable disorder model. All nonhydrogen atoms were refined anisotropically; hydrogen atoms were fixed by geometry or located by a Difference Fourier and refined isotropically. Crystal data are available as Supplementary data as well as CIF files. CCDC reference numbers are 605830–605839.

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Supplementary data

Supplementary data (crystal data, PLATON drawings, CIF files and details of theoretical calculations) associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.034.

References and notes

1. Selected recent reviews: (a) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199; (b) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067; (c) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535; (d) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12; (e) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773; (f) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701; (g) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196; (h) Ma, S. *Chem. Rev.* **2005**, *105*, 2829; (i) Hammond, G. B. Functionalized Fluorinated Allenes. In *Fluorine-Containing Synthons*; Soloshonok, V., Ed.; ACS Publications Division and Oxford University Press: Washington, DC, 2005.
2. Some recent references: (a) Oh, C. H.; Ahn, T. W.; Raghava Reddy, V. *Chem. Commun.* **2003**, 2622; (b) Fleming, S. A.; Carroll, S. M.; Hirshi, J.; Liu, R.; Pace, J. L.; Redd, J. T. *Tetrahedron Lett.* **2004**, *45*, 3341; (c) Hopkins, C. D.; Malinakova, H. C. *Org. Lett.* **2004**, *6*, 2221; (d) Silvetri, M. A.; Bromfield, D. C.; Lepore, S. E. *J. Org. Chem.* **2005**, *70*, 8239; (e) Fu, C.; Ma, S. *Org. Lett.* **2005**, *7*, 1707; (f) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, Y. *Org. Lett.* **2005**, *7*, 1387; (g) Fu, C.; Chen, G.; Liu, X.; Ma, S. *Tetrahedron* **2005**, *61*, 7768; (h) Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977; (i) Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 3057; (j) Woodwar, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505.
3. (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, NY, 1984; pp 247–252; (b) Alabugin, I. V.; Brei, V. K. *Russ. Chem. Rev.* **1997**, *66*, 205; (c) Patois, C.; Richard, L.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1577.
4. (a) Palacios, F.; Aparicio, D.; García, J. *Tetrahedron* **1996**, *52*, 9609; (b) Zapata, A. J.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227; (c) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923.
5. (a) Kukhar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids-Chemistry and Biological Activity*; Wiley: Chichester, UK, 2000; Chapter 1; (b) Kafarski, P.; Lejczak, B. *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 301; (c) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.
6. Selected recent references: (a) Rulev, A. Yu.; Larina, L. I.; Voronkov, M. G. *Russ. J. Gen. Chem.* **2001**, *71*, 1891; (b) Panarina, A. E.; Dogadina, A. V.; Zakharov, V. I.; Ionin, B. I. *Tetrahedron Lett.* **2001**, *42*, 4365; (c) Palacios, F.; Pascual, S.; Oyarzabal, J.; de Retana, A. M. O. *Org. Lett.* **2002**, *4*, 769; (d) Palacios, F.; Aparicio, D.; de Retana, A. M. O.; de los Santos, J. M.; Gil, J. I.; de Munain, R. L. *Tetrahedron: Asymmetry* **2003**, *14*, 689; (e) Zhao, Y.; Jiang, N.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 8339; (f) Palacios, F.; de Retana, A. M. O.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767; (g) Xu, C.; Yuan, C. *Eur. J. Org. Chem.* **2004**, 4410.
7. For examples of nucleobase appended phosphonates and their biological activity see: (a) Holy, A. Synthesis and Biological Activity of Isopolar Acyclic Nucleotide Analogs. In *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier: Amsterdam, 2002; (b) Zídek, Z.; Potměšil, P.; Kmoníèieková, E.; Holý, A. *Eur. J. Pharmacol.* **2003**, *475*, 149; (c) Pérez-Pérez, M.-J.; Rozenski, J.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1995**, *60*, 1531; (d) Naesens, L.; Lenaerts, L.; Andrei, G.; Snoeck, R.; Van Beers, D.; Holy, A.; Balzarini, J.; De Clercq, E. *Antimicrob. Agents Chemother.* **2005**, *49*, 1010; (e) Wu, T.; Froeyen, M.; Kempeneers, V.; Pannecouque, C.; Wang, J.; Busson, R.; De Clercq, E.; Herdewijn, P. *J. Am. Chem. Soc.* **2005**, *127*, 5056; (f) De Clercq, E.; Balzarini, A. G.; Leyssen, P.; Naesens, L.; Neyts, J.; Pannecouque, C.; Snoeck, R.; Ying, C.; Hockova, D.; Holy, A. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 331; (g) Hocková, D.; Holý, A.; Masojidkova, G.; Andrei, R.; Snoeck, E.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2003**, *46*, 5064; (h) Lazrek, H. B.; Rochdi, A.; Khaider, H.; Barascut, J.-L.; Imbach, J.-L.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clercq, E. *Tetrahedron* **1998**, *54*, 3807.
8. *The Chemistry of Enamines*; Rappaport, Z., Ed.; Wiley: Chichester, UK, 1994.
9. Novak, B. M.; Cafmeyer, J. T. *J. Am. Chem. Soc.* **2001**, *123*, 11083.
10. Amination of nonphosphorylated allenes: (a) Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233; (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857; (c) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071; (d) Vineux, D.; Guillouzic, A.-F.; Cristau, H.-J. *Tetrahedron* **2006**, *62*, 3710.
11. (a) Muthiah, C.; Praveen Kumar, K.; Aruna Mani, C.; Kumara Swamy, K. C. *J. Org. Chem.* **2000**, *65*, 3733; (b) Praveen Kumar, K.; Muthiah, C.; Kumaraswamy, S.; Kumara Swamy, K. C. *Tetrahedron Lett.* **2001**, *42*, 3219; (c) Muthiah, C.; Senthil Kumar, K.; Vittal, J. J.; Kumara Swamy, K. C. *Synlett* **2002**, 1787; (d) Kumaraswamy, S.; Kommana, P.; Satish Kumar, N.; Kumara Swamy, K. C. *Chem. Commun.* **2002**, 40; (e) Balaraman, E.; Kumara Swamy, K. C. *Synthesis* **2004**, 3037; (f) Kumar, N. S.; Praveen Kumar, K.; Pavan Kumar, K. V. P.; Kommana, P.; Vittal, J. J.; Kumara Swamy, K. C. *J. Org. Chem.* **2004**, *69*, 1880; (g) Kumara Swamy, K. C.;

Kumaraswamy, S.; Senthil Kumar, K.; Muthiah, C. *Tetrahedron Lett.* **2005**, *46*, 3347; (h) Kumara Swamy, K. C.; Praveen Kumar, K.; Bhuvan Kumar, N. *J. Org. Chem.* **2006**, *71*, 1002; (i) Kumara Swamy, K. C.; Satish Kumar, N. *Acc. Chem. Res.* **2006**, *39*, 324.

12. Compounds **3a–b** are known; compounds **3c–d** were prepared similarly. See: (a) Patois, C.; Richard, L.; Savignac, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1577; (b) Satish Kumar, N. Ph.D. Thesis, University of Hyderabad, India, 2004.
13. Single crystal X-ray data were collected on a Bruker AXS SMART diffractometer using Mo Kα (λ=0.71073 Å) radiation. The structures were solved and refined by standard methods: (a) Sheldrick, G. M. *SADABS, Siemens Area Detector Absorption Correction*; University of Göttingen: Göttingen, Germany, 1996; (b) Sheldrick, G. M. *SHELXTL NT Crystal Structure Analysis Package, version 5.10*; Bruker AXS, Analytical X-ray System: Madison, WI, 1999.
14. (*Z*)- and (*E*)-α-Alkenyl phosphonates with nucleobases like adenine, guanine, thymine, etc., are prepared by reacting alkynyl phosphonates with nucleobase+KO-*t*-Bu+18-C-6 (Ref. 7h).
15. The allene **3a** also reacts, but **3c** yields more stable products.
16. For possible adenine-N(7)H tautomer depicted in Scheme 3, see: Shaw, G. Purines. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Potts, K. T. (Volume Editor); Pergamon: Oxford, UK, 1984; Vol. 5, Section 4.09, p 520.
17. (a) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, UK, 1986; (b) Brandsama, L. Synthesis of Acetylenes. In *Allenes and Cumulenes: Methods and Techniques*; Elsevier: Oxford, UK, 2004; pp 243; (c) Wei, L.-L.; Xiong, H.; Douglas, J. C.; Hsung, P. R. *Tetrahedron Lett.* **1999**, *40*, 6903.
18. (a) Sheldrick, G. M. *SADABS, Siemens Area Detector Absorption Correction*; University of Göttingen: Göttingen, Germany, 1996; (b) Sheldrick, G. M. *SHELXTL NT Crystal Structure Analysis Package, version 5.10*; Bruker AXS, Analytical X-ray System: Madison, WI, 1999.

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Synthesis of enantiopure bis-aziridines, bis-epoxides, and aziridino-epoxides from D-mannitol

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Abstract—A practical synthesis of enantiopure bis-aziridines **11** and **15**, bis-epoxides **12** and **17**, and aziridino-epoxides **27** and **30** is reported using inexpensive D-mannitol as the starting material. The key transformation involves the reductive cleavage of bis-benzylidene acetal **3** to form dimesylate **4**, which was further converted to monoazides and diazides followed by reduction, mesylation, and cyclization to furnish the required compounds in good yields.

1. Introduction

D-Mannitol is a naturally occurring inexpensive chiral building block used for the synthesis of many biologically active and pharmaceutically important natural products.[1,2] In general the bis-aziridines, bis-epoxides, and aziridino-epoxides derived from mannitol are key intermediates in the synthesis of various nitrogen, sulfur, and selenium heterocycles with potential biological activity.[4–8] Though Depezay et al.[3] reported the first synthesis of enantiopure 1,5-bis-aziridine and 1,5-bis-epoxide from D-mannitol in 1986, there are no alternate synthetic procedures available for the synthesis of chirally pure 1,5-bis-aziridines, 1,5-bis-epoxides, and 2,4-bis-epoxides. Additionally there are no reports on the synthesis of 2,4-bis-aziridines, 1,5-aziridino-epoxides, and 2,4-aziridino-epoxides from D-mannitol in the literature. The main problem with Depezay's procedure is the difficulty in the removal of triphenyl phosphine oxide byproduct. Herein, we report simple alternative procedures for the synthesis of optically pure 1,5-bis-aziridine, 1,5-bis-epoxide, 2,4-bis-aziridine, 2,4-bis-epoxide, 1,5-aziridino-epoxide, and 2,4-aziridino-epoxide starting from the same intermediate, bis-benzylidene acetal **2**, derived from D-mannitol.

2. Results and discussion

2.1. Synthesis of 2,4-bis-aziridine 11

The bis-benzylidene acetal **2**[9] derived from D-mannitol was converted to the dimesylate **3**[10] (Scheme 1; Fig. 1) in 71% yield in two steps. Using a procedure developed by Baskaran et al.,[11] a highly regio- and chemoselective reductive cleavage of bis-benzylidene acetal **3** with $BF_3\cdot Et_2O/Et_3SiH$ in dry CH_2Cl_2 furnished C_2-symmetric diol **4** (78%), which was then converted to the acetonide **5** in 80% yield. Nucleophilic substitution of the dimesylate **5** with NaN_3 afforded the corresponding diazide[11b] **6**, which was subjected to chemoselective reduction using Lindlar's catalyst to furnish the bis-amine **7**. Compound **7** was converted to the ditosylate **8** followed by deprotection using $FeCl_3\cdot 6H_2O$[12] in dry CH_2Cl_2 to give the diol **9**. Finally, mesylation of diol **9** and intramolecular cyclization using NaH in THF afforded enantiopure C_2-symmetric 2,4-bis-aziridine **11** in 23% overall yield from D-mannitol. The structure of compound **11**[13] was confirmed by single crystal X-ray analysis (Fig. 2).

2.2. Synthesis of 2,4-bis-epoxide 12

In order to synthesize the 2,4-bis-epoxide **12** from D-mannitol, dimesylate **4** was directly treated with NaH in THF. It underwent cyclization to afford the required enantiopure 2,4-bis-epoxide[14] **12** in 47% overall yield from D-mannitol (Scheme 2). Bis-epoxide **12** is a useful starting material for the synthesis of C_2-symmetric, diol-based HIV-1 protease inhibitors.[15]

2.3. Synthesis of 1,5-bis-aziridine 15

In order to synthesize the 1,5-bis-aziridine **15**, the intermediate ditosylate **8** (from Scheme 1) was subjected to hydrogenolysis (10% Pd/C, H_2, 1 atm, MeOH) to furnish diol **13** in 90% yield. Treatment of **13** with methane sulfonyl chloride followed by intramolecular cyclization using NaH in dry THF gave C_2-symmetric bis-aziridine[3] **15** in 24% overall yield from D-mannitol (Scheme 3).

Keywords: Bis-benzylidene acetal; Bis-aziridines; Bis-epoxides; Aziridino-epoxides.
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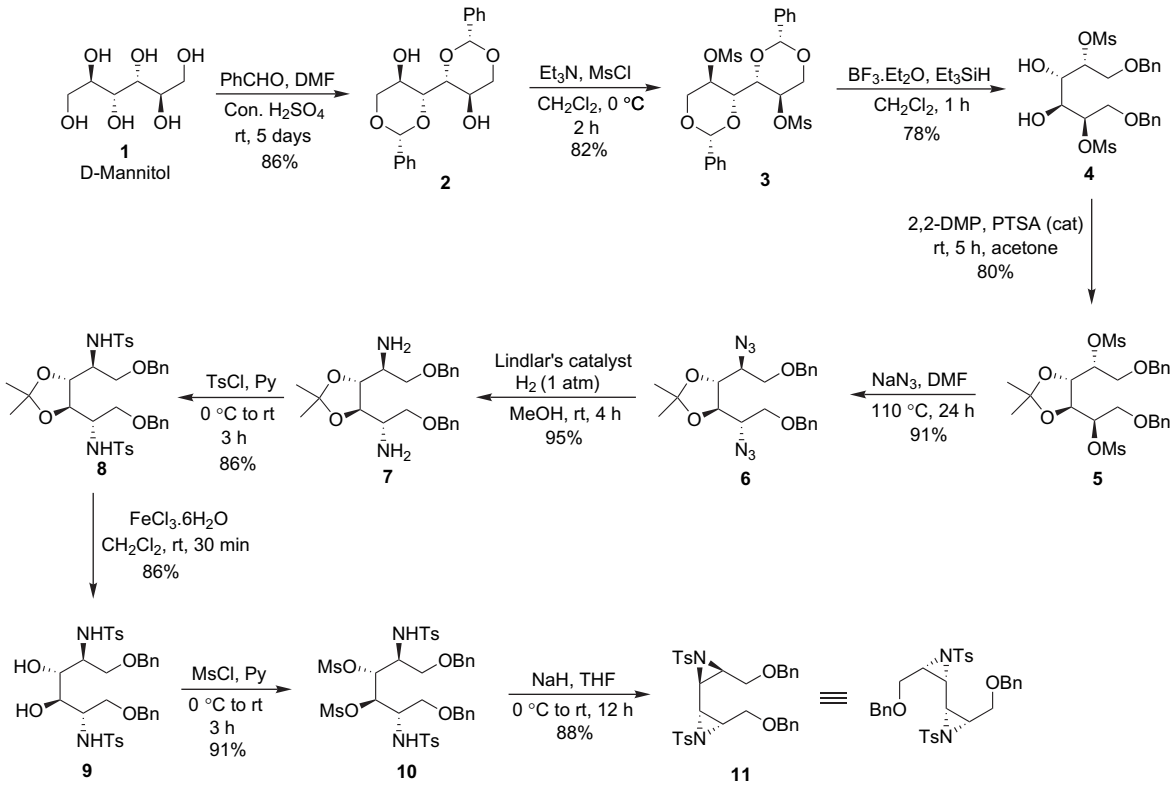


Scheme 1. Synthesis of C_2-symmetric *N*-tosyl-2,4-bis-aziridine **11**.

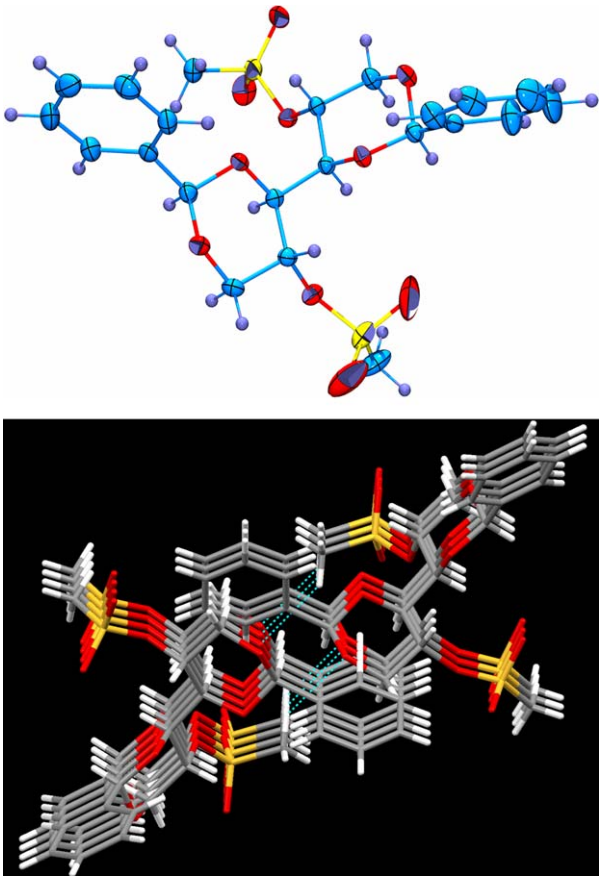


Figure 1. Solid state structure of compound **3** and C–H···O (C9–H9B···O: 2.485 Å; 140.08°) interactions that form chain like structure through '*b*' axis.

2.4. Synthesis of 1,5-bis-epoxide 17

The synthesis of 1,5-bis-epoxide **17** utilizes dimesylate **5** as the starting material, which upon hydrogenolysis (10% Pd/C, H_2, 1 atm, MeOH) afforded diol **16** in 86% yield. Subsequent intramolecular cyclization using NaH in THF gave the bis-epoxide[3] **17** in 32% overall yield from D-mannitol (Scheme 4). The bis-aziridine **15** and bis-epoxide **17** are the key intermediates in the synthesis of thiepane derivatives, which are potential glycosidase[7a] and HIV protease[8] inhibitors. The structure of bis-epoxide **17**[16] was confirmed by X-ray analysis (Fig. 3).

2.5. Synthesis of 2,4-aziridino-epoxide 27

In order to synthesize the aziridino-epoxide **27**, bis-benzylidene acetal **2** was reacted with 1 equiv TsCl in pyridine to furnish the monotosylate **18** in 62% yield. Compound **18** was converted to acetate **19**, which on reductive cleavage with $BF_3 \cdot Et_2O/Et_3SiH$ in dry CH_2Cl_2 gave the diol **20** in 78% yield. Next, diol **20** was protected as the corresponding acetonide **21**. Formation of the corresponding azide **22** and reduction using Lindlar's catalyst provided amine **23** in 91% yield. Amine **23** was converted to the tosylate **24**, which on hydrolysis resulted in the formation of diol **25**. Finally, diol **25** was converted into dimesylate **26** and intramolecular cyclization using NaOMe in MeOH afforded the 2,4-aziridino-epoxide **27** in 15% overall yield from D-mannitol (Scheme 5).

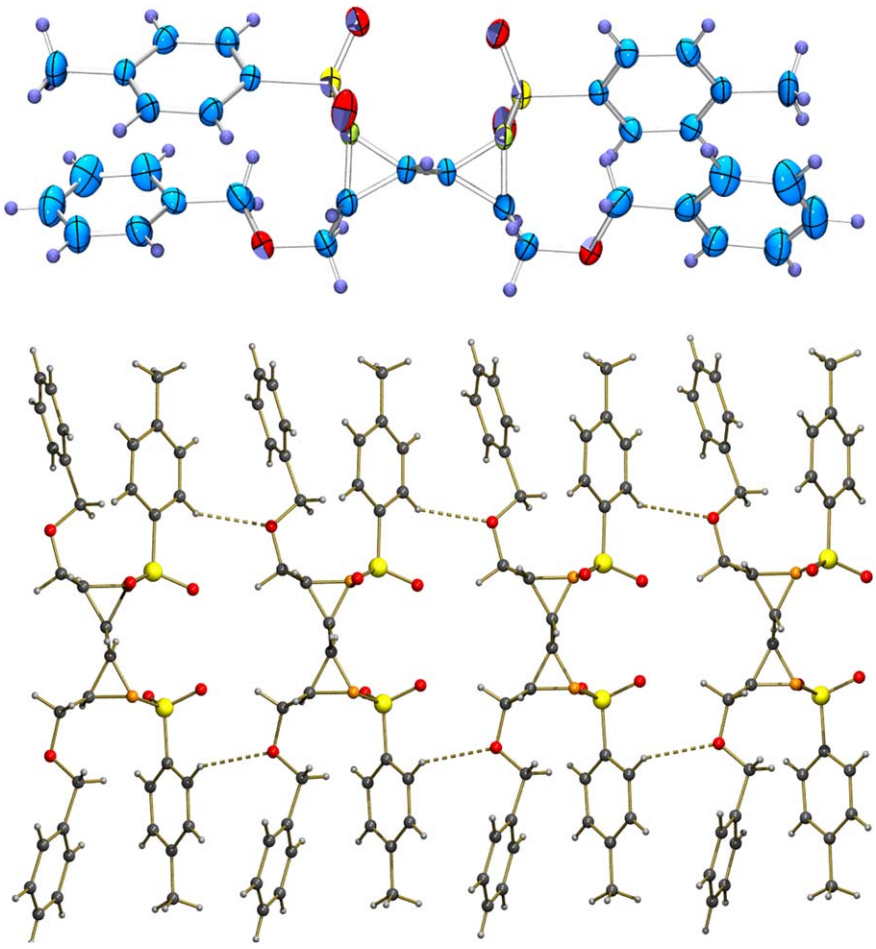
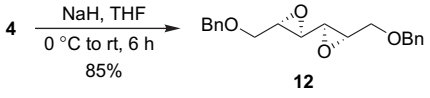
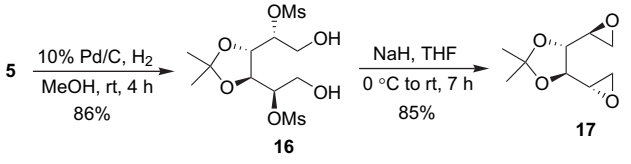


Figure 2. Solid state structure of compound **11** and C–H···O (C33–H33···O6: 2.570 Å; 137.44°) interactions that form chain like structure through '*a*' axis.



Scheme 2. Synthesis of C_2-symmetric 2,4-bis-epoxide **12**.



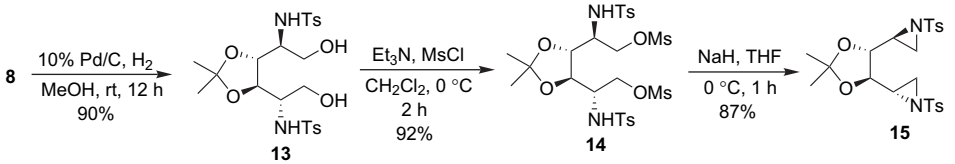
Scheme 4. Synthesis of C_2-symmetric 1,5-bis-epoxide **17**.

2.6. Synthesis of 1,5-aziridino-epoxide 30

To synthesize the unsymmetrical 1,5-aziridino-epoxide **30**, acetate **24** was subjected to hydrogenolysis (10% Pd/C, H_2, 1 atm, MeOH) to afford the diol **28** in 83% yield. Compound **28** on treatment with methane sulfonyl chloride gave the dimesylate **29**, which upon intramolecular cyclization using NaOMe in MeOH (0 °C, 1 h) furnished the 1,5-aziridino-epoxide **30** in 15% overall yield from D-mannitol (Scheme 6).

3. Conclusion

In conclusion, we have demonstrated here the development of simple but efficient synthesis of enantiopure bis-aziridines **11** and **15**, bis-epoxides **12** and **17**, and aziridino-epoxides **27** and **30** from readily available and inexpensive D-mannitol.



Scheme 3. Synthesis of C_2-symmetric 1,5-bis-aziridine **15**.

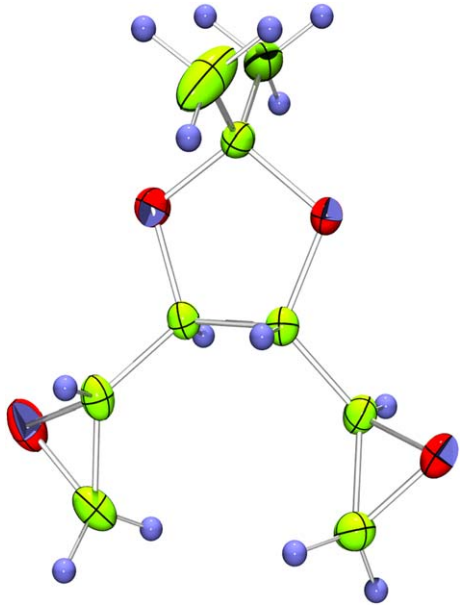


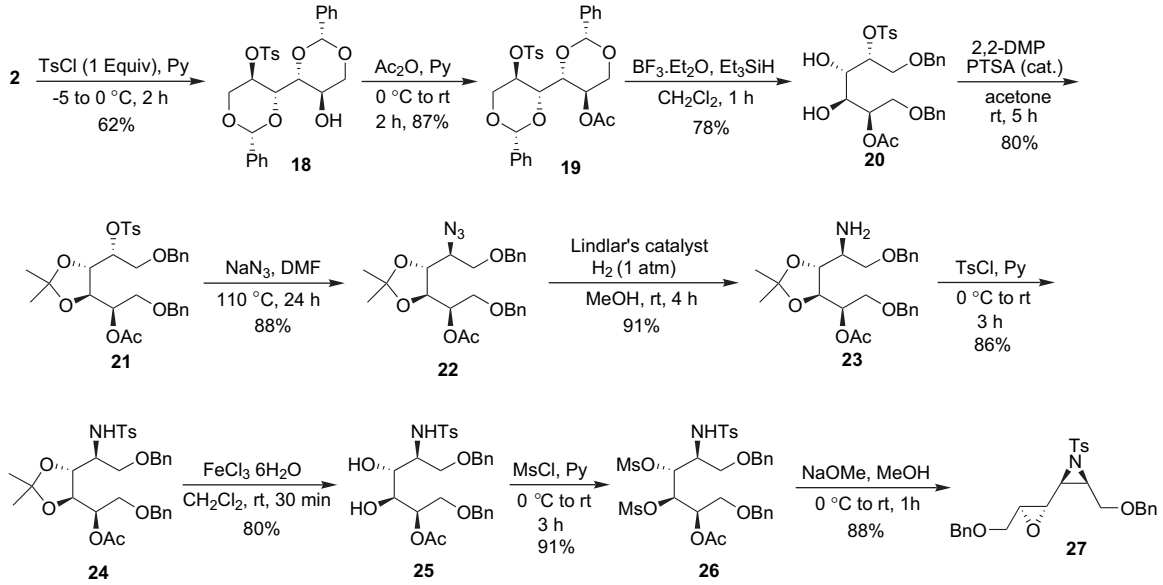
Figure 3. Solid state structure of compound **17**.

4. Experimental

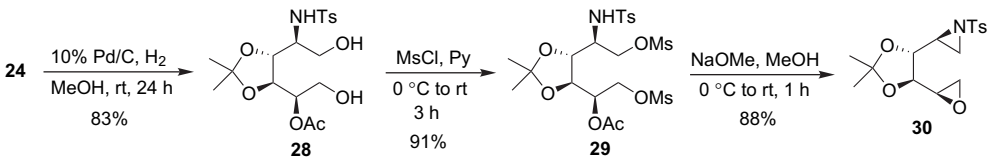
4.1. General methods

All reactions were carried out in oven-dried apparatus using dry solvents under anhydrous conditions. Commercial grade solvents were distilled and dried according to literature procedures. Analytical TLC was performed on commercial plates coated with silica gel GF_{254} (0.25 mm). Silica gel (230–400 mesh) was used for column chromatography. Melting points determined are uncorrected. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. NMR spectra were recorded on 300 or 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations explain the multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. IR spectra were recorded on a FTIR spectrometer.

4.1.1. (*S*)-2-(Benzyloxy)-1-((4*R*,5*R*)-5-((*S*)-2-(benzyloxy)-1-(tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-tosylethanamine 8. The azide **6** was synthesized from D-mannitol according to the literature procedure.[11] Lindlar's catalyst (0.115 g, 20 wt %) was added to the stirred solution of azide **6** (1 g, 2.2 mmol) in methanol (20 mL). The reaction flask was evacuated and flushed with H_2 gas. The resultant mixture was stirred under hydrogen atmosphere (balloon) at room temperature (28 °C) for 4 h. After completion of the reaction, the catalyst was filtered through a pad of Celite, washed with methanol (50 mL) and the filtrate was concentrated under reduced pressure. To the crude residue (0.84 g, 2.1 mmol) in pyridine (15 mL) at 0 °C was added tosyl chloride (0.88 g, 4.5 mmol) slowly. After 3 h stirring at room temperature, the reaction mixture was poured into ice cold solution of 1 M HCl and extracted with diethyl ether thrice (100 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave a yellow residue. The residue was purified



Scheme 5. Synthesis of 2,4-aziridino-epoxide **27**.



Scheme 6. Synthesis of 1,5-aziridino-epoxide **30**.

over silica gel (230–400 mesh) using 10–20% EtOAc in hexane solvent as eluent to afford pure compound **8** (1.28 g, 86%) as a colorless liquid. R_f=0.80 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ +16.00 (*c* 1.0, $CHCl_3$); IR (neat): 3281, 1328, 1160, 1092, 814, 738, 699, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.1 Hz, 2H), 7.32–7.26 (m, 3H), 7.17–7.13 (m, 4H), 4.87 (d, *J*=9.3 Hz, 1H), 4.29 (s, 2H), 4.05 (s, 1H), 3.69–3.62 (m, 1H), 3.39–3.29 (m, 2H), 2.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 138.1, 137.7, 129.4, 128.2, 127.6, 127.5, 127.1, 109.1, 76.7, 72.9, 70.5, 52.2, 26.9, 21.5; HRMS *m/z* calcd for $C_{37}H_{44}N_2O_8S_2$ [M+Na^+]: 731.2437; found: 731.2462.

4.1.2. (2*S*,3*R*,4*R*,5*S*)-1,6-Bis(benzyloxy)-2,5-bis(tosylamino)hexane-3,4-diol 9. To a solution of **8** (1 g, 1.41 mmol) in CH_2Cl_2 (20 mL) at room temperature was added $FeCl_3\cdot 6H_2O$[11] (1.33 g, 4.94 mmol). The resulting yellow to amber colored suspension was stirred for 30 min and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography of the resulting oil on silica gel (230–400 mesh) and elute with 20% EtOAc/hexanes yielded amino diol **9** (0.811 g, 86%). R_f=0.15 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −23.00 (*c* 1.0, $CHCl_3$); IR (neat): 3469, 3278, 1317, 1160, 813, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=8.1 Hz, 2H), 7.34–7.24 (m, 3H), 7.21–7.15 (m, 4H), 4.31 (dd, *J*=28.50, 12.0 Hz, 2H), 3.85 (s, 1H), 3.66 (t, *J*=4.2 Hz, 1H), 3.37 (dd, *J*=9.9, 4.5 Hz, 1H), 3.28 (dd, *J*=9.9, 5.4 Hz, 1H), 2.54 (br s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 137.8, 137.3, 129.5, 128.3, 127.7, 127.6, 126.9, 73.1, 70.9, 70.2, 53.4, 21.4; HRMS *m/z* calcd for $C_{34}H_{40}N_2O_8S_2$ [M+Na^+]: 691.2124; found: 691.2124.

4.1.3. (2*R*,3*S*,4*S*,5*R*)-1,6-Bis(benzyloxy)-3,4-bis((methylsulfonyl)methyl)-*N*2,*N*5-ditosylhexane-2,5-diamine 10. To a solution of diol **9** (0.80 g, 1.19 mmol) in dry CH_2Cl_2 (10 mL), pyridine (0.3 mL, 3.65 mmol) followed by mesyl chloride (0.24 mL, 2.98 mmol) were slowly added at 0 °C. The mixture was stirred at 20 °C for 3 h. The reaction mixture was diluted with Et_2O followed by washing with cold HCl (1 N). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) dimesylate **10** (0.923 g, 91%) as a colorless liquid. R_f=0.50 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ +18.00 (*c* 1.0, $CHCl_3$); IR (neat): 3280, 1454, 1334, 1162, 1091, 815, 738, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.1 Hz, 2H), 7.30–7.26 (m, 3H), 7.19 (d, *J*=8.1 Hz, 2H), 7.13–7.09 (m, 2H), 5.13 (d, *J*=9.9 Hz, 1H), 5.06 (d, *J*=6.0 Hz, 1H), 4.31 (d, *J*=11.7 Hz, 1H), 4.20 (d, *J*=11.7 Hz, 1H), 4.02–3.95 (m, 1H), 3.43 (dd, *J*=10.5, 2.1 Hz, 1H), 3.24 (s, 3H), 2.87 (dd, *J*=10.5, 3.9 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 137.2, 136.9, 129.9, 128.5, 127.9, 127.8, 126.9, 76.7, 73.2, 67.2, 53.7, 39.2, 21.5; HRMS *m/z* calcd for $C_{36}H_{44}N_2O_{12}S_4$ [M+Na^+]: 847.1675; found: 847.1695.

4.1.4. (2*R*,3*R*)-2-((Benzyloxy)methyl)-3-((2*R*,3*R*)-3-((benzyloxy)methyl)-1-tosylaziridin-2-yl)-1-tosylaziridine 11. To a solution of dimesylate **10** (0.90 g, 1.09 mmol) in dry THF (10 mL), NaH (0.08 g, 3.18 mmol) was slowly added at 0 °C. The mixture was stirred at 20 °C for 12 h, and then slowly water (1 mL) was added drop wise at 0 °C to quench the excess of NaH. The reaction mixture was diluted with water and extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) the bis-aziridine **11** (0.59 g, 88%) as a colorless solid. R_f=0.80 (EtOAc/hexanes, 1:1); mp: 121 °C; $[\alpha]_D^{27}$ +38.00 (*c* 1.0, $CHCl_3$); IR (neat): 1596, 1328, 1160, 1090, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.4 Hz, 2H), 7.35–7.17 (m, 7H), 4.39 (s, 2H), 3.67–3.57 (m, 2H), 3.08–2.99 (m, 1H), 2.89–2.84 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 137.5, 134.4, 129.6, 128.3, 127.9, 127.8, 127.6, 72.9, 66.4, 41.9, 39.3, 21.6; HRMS *m/z* calcd for $C_{34}H_{36}N_2O_6S_2$ [M+Na^+]: 655.1912; found: 655.1914.

4.1.5. (2*S*,3*R*)-2-((Benzyloxy)methyl)-3-((2*R*,3*S*)-3-((benzyloxy)methyl)oxiran-2-yl)oxirane 12. Bis-epoxide **12** (0.267 g, 85%) was synthesized from the dimesylate **4** (0.50 g, 0.97 mmol) as a colorless liquid by using the procedure described for compound **11** (see Section 4). R_f=0.80 (EtOAc/hexanes, 1:1); $[\alpha]_D^{27}$ +68.00 (*c* 1.0, $CHCl_3$); IR (neat): 1454, 1274, 1099, 892, 748, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.21 (m, 5H), 4.55 (dd, *J*=15.3, 12.0 Hz, 2H), 3.72 (dd, *J*=11.7, 3.0 Hz, 1H), 3.49 (dd, *J*=11.7, 5.1 Hz, 1H), 3.17–3.15 (m, 1H), 2.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 128.3, 127.6, 127.5, 73.1, 68.9, 54.4, 53.4; HRMS *m/z* calcd for $C_{20}H_{22}O_4$ [M+Na^+]: 349.1416; found: 349.1424.

4.1.6. (*S*)-2-((4*R*,5*R*)-5-((*S*)-1-(Tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-tosyl ethanamine 13. A solution of ditosylate **8** (0.50 g, 0.71 mmol) in MeOH (10 mL) was treated with H_2 over 10% Pd/C (0.05 mg) at atmospheric pressure for 12 h. The mixture was filtered through Celite and the solvent was evaporated in vacuo. The crude residue was purified by chromatography on silica gel (230–400 mesh) using 30–50% EtOAc in hexane solvent as eluent to afford pure compound **13** (0.336 g, 90%) as a colorless liquid. R_f=0.20 (EtOAc/hexanes, 7:3); $[\alpha]_D^{25}$ −42.00 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 3281, 1324, 1158, 816, 658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J*=8.1 Hz, 2H), 7.34 (d, *J*=8.1 Hz, 2H), 5.36 (d, *J*=9.3 Hz, 1H), 4.17 (s, 1H), 3.64 (dd, *J*=11.4, 2.7 Hz, 1H), 3.46–3.42 (m, 1H), 3.17–3.14 (m, 1H), 2.43 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 137.4, 129.9, 126.9, 109.7, 79.1, 63.9, 51.4, 26.9, 21.5; HRMS *m/z* calcd for $C_{23}H_{32}N_2O_8S_2$ [M+Na^+]: 551.1498; found: 551.1501.

4.1.7. (1*S*)-1-((4*S*,5*S*)-2,2-Dimethyl-5-(1*S*)-1-[(4-methylphenyl)sulfonyl]oxy-2-[(methylsulfonyl)oxy]ethyl-1,3-dioxolan-4-yl)-2-[(methylsulfonyl)oxy]ethyl 4-methyl-1-benzenesulfonate 14. The dimesylate **14** (0.358 g, 92%) was synthesized from the diol **13** (0.30 g, 0.57 mmol) as a colorless liquid by using the procedure described for compound **10** (see Section 4). R_f=0.20 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ −28 (*c* 1.0, $CHCl_3$); IR (neat): 3278, 1451, 1336, 1171, 1094, 821, 744, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 5.08 (d, *J*=9.6 Hz, 1H), 4.07–3.97 (m, 3H), 3.82–3.76 (m, 1H), 2.84 (s, 3H), 2.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$): δ 144.1, 137.5, 129.9, 127.0, 110.1, 75.1, 67.3, 50.7, 37.2, 26.8, 21.5; HRMS *m/z* calcd for $C_{25}H_{36}N_2O_{12}S_4$ [M+Na$^+$]: 707.1049; found: 707.1062.

4.1.8. (*S*)-2-((4*R*,5*R*)-2,2-Dimethyl-5-((*S*)-1-tosylaziridin-2-yl)-1,3-dioxolan-4-yl)-1-tosyl aziridine 15. The bis-aziridine **15** (0.22 g, 87%) was synthesized from the dimesylate **14** (0.35 g, 0.51 mmol) as a colorless solid by using the procedure described earlier for compound **11** (see Section 4). R_f=0.30 (EtOAc/hexanes, 2:8); mp: 68 °C; $[\alpha]_D^{27}$ −34.00 (*c* 1.0, $CHCl_3$); IR (neat): 1930, 1596, 1325, 1162, 678 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 3.83 (dd, *J*=2.7, 1.5 Hz, 1H), 2.77–2.73 (m, 1H), 2.60 (d, *J*=7.2 Hz, 1H), 2.45 (s, 3H), 2.38 (d, *J*=4.2 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 134.6, 129.8, 128.0, 110.4, 75.9, 37.8, 30.9, 26.6, 21.6; HRMS *m/z* calcd for $C_{23}H_{28}N_2O_6S_2$ [M+Na$^+$]: 515.1287; found: 515.1304.

4.1.9. (1*R*)-2-Hydroxy-1-((4*S*,5*S*)-5-(1*R*)-2-hydroxy-1-[(methylsulfonyl)oxy]ethyl-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl methanesulfonate 16. The diol **16** (0.175 g, 86%) was synthesized from the dimesylate **5** (0.30 g, 0.54 mmol) as a colorless liquid by using the procedure described earlier for compound **13**. R_f=0.20 (EtOAc/hexanes, 1:1); $[\alpha]_D^{25}$ +84.00 (*c* 1.0, $CHCl_3$); IR (neat): 3472, 1317, 1158, 814, 658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81–4.79 (m, 1H), 4.37 (dd, *J*=3.9, 1.5 Hz, 1H), 4.03 (dd, *J*=12.9, 3.3 Hz, 1H), 3.89 (dd, *J*=12.9, 6.0 Hz, 1H), 3.19 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 111.3, 82.0, 61.4, 38.7, 26.9; HRMS *m/z* calcd for $C_{11}H_{22}O_{10}S_2$ [M+Na$^+$]: 401.0552; found: 401.0546.

4.1.10. (4*R*,5*R*)-2,2-Dimethyl-4,5-di((*S*)-oxiran-2-yl)-1,3-dioxolane 17. The bis-epoxide **17** (0.063 g, 85%) was synthesized from the diol **16** (0.15 g, 0.40 mmol) as colorless crystals by using the procedure described for compound **11** (see Section 4). R_f=0.70 (EtOAc/hexanes, 3:7); mp: 74 °C; $[\alpha]_D^{27}$ −19.00 (*c* 1.0, $CHCl_3$); IR (neat): 1460, 1360, 1276, 1096, 890, 752, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (dd, *J*=3.3, 1.5 Hz, 1H), 3.10–3.06 (m, 1H), 2.85 (dd, *J*=5.4, 4.2 Hz, 1H), 2.75 (dd, *J*=5.4, 2.4 Hz, 1H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.7, 77.9, 51.1, 43.8, 26.6; HRMS *m/z* calcd for $C_9H_{14}O_4$ [M+Na$^+$]: 209.0790; found: 209.0798.

4.1.11. (2*R*,4*S*,5*R*)-4-((2*R*,4*R*,5*R*)-5-Hydroxy-2-phenyl-1,3-dioxan-4-yl)-2-phenyl-1,3-dioxan-5-yl-4-methylbenzenesulfonate 18. To a solution of diol **2** (3 g, 8.38 mmol) in dry pyridine (30 mL), tosyl chloride (1.75 g, 9.22 mmol) was slowly added at −5 °C. Then the reaction mixture was stirred for 2 h at 20 °C. The reaction mixture was diluted with Et_2O followed by washing with cold HCl (1 N). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) monotosylate **18** (2.66 g, 62%) as a colorless liquid. R_f=0.20 (EtOAc/hexanes, 4:6); $[\alpha]_D^{25}$ −22.00 (*c* 1.0, $CHCl_3$); IR (neat): 3464, 1338, 1154, 821, 660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=8.1 Hz, 2H), 7.45–7.31 (m, 10H), 7.09 (d, *J*=8.1 Hz, 2H), 5.48 (s, 1H), 4.96 (s, 1H), 4.82 (m, 1H), 4.41 (dd, *J*=11.1, 5.4 Hz, 1H), 4.26–4.16 (m, 2H), 4.03 (m, 1H), 3.82 (t, *J*=10.5 Hz, 1H), 3.61 (dd, *J*=9.3, 1.5 Hz, 1H), 3.47 (t, *J*=10.5 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 137.3, 136.8, 132.5, 129.9, 129.1, 128.8, 128.2, 127.9, 127.8, 126.2, 126.0, 101.3, 100.4, 77.3, 74.9, 71.0, 68.6, 67.2, 59.7, 21.5; HRMS *m/z* calcd for $C_{27}H_{28}O_8S$ [M+Na$^+$]: 535.1403; found: 535.1416.

4.1.12. (2*R*,3*S*,4*R*,5*R*)-5-Acetoxy-1,6-bis(benzyloxy)-3,4-dihydroxy-2-yl-4-methylbenzene sulfonate 20. To a solution of monotosylate **18** (2.5 g, 4.88 mmol) in dry pyridine (20 mL), Ac_2O (0.51 mL, 5.34 mmol) was slowly added at 0 °C. The reaction mixture was stirred at 20 °C for 2 h and it was diluted with Et_2O followed by washing with cold HCl (1 N). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated to afford crude acetate **19** (silica gel; EtOAc/hexanes, 80:20) as a colorless liquid, which was used in the next step without purification. To a crude solution of **19** in dry CH_2Cl_2 (40 mL) at 0 °C was added Et_3SiH (1.3 mL, 7.94 mmol) followed by $BF_3\cdot Et_2O$ (1.5 mL, 11.6 mmol). After stirring the reaction mixture at 0 °C for 1 h, it was quenched with saturated $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the product, which was purified by flash chromatography to give pure diol **20** (1.85 g, 68% overall yield). R_f=0.20 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −104.00 (*c* 1.0, $CHCl_3$); IR (neat): 3462, 1740, 1374, 1236, 1092, 736, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=8.1 Hz, 2H), 7.36–7.18 (m, 12H), 5.00 (q, *J*=4.2 Hz, 1H), 4.70 (q, *J*=3.9 Hz, 1H), 4.57 (dd, *J*=22.2, 12.0 Hz, 2H), 4.41 (s, 2H), 3.98 (d, *J*=8.4 Hz, 1H), 3.83 (d, *J*=7.8 Hz, 1H), 3.75 (d, *J*=4.5 Hz, 2H), 3.69 (dd, *J*=6.0, 4.2 Hz, 2H), 2.38 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 144.9, 137.7, 137.5, 133.4, 129.7, 128.4, 128.3, 127.9, 127.7, 127.6, 79.3, 73.4, 71.8, 68.7, 68.4, 68.1, 67.7, 21.6, 21.1; HRMS *m/z* calcd for $C_{29}H_{34}O_9S$ [M+Na$^+$]: 581.1821; found: 581.1833.

4.1.13. (*R*)-1-((4*S*,5*R*)-5-((*S*)-1-Azido-2-(benzyloxy)-ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(benzyloxy)-ethyl acetate 22. The diol **20** (1.8 g, 3.23 mmol) was dissolved in dry acetone (15 mL) and then treated with 2,2-dimethoxypropane (1.2 mL, 9.68 mmol) followed by a solution of *p*TSA in dry acetone (4 mL). The resultant mixture was allowed to stir for 5 h at room temperature. The mixture was then diluted with EtOAc (15 mL), washed with a saturated solution of $NaHCO_3$ (2×5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield a crude product, which was purified by flash chromatography to give pure acetonide **21** (1.53 g, 80% yield). A suspension of acetonide **21** (1.5 g, 2.54 mmol) and sodium azide (0.198 g, 3.05 mmol) in dry DMF (30 mL) was stirred at 110 °C for 24 h. After evaporation of DMF, 15 mL of water was added to the residue, which was then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and evaporated to give a syrupy liquid, which was purified by flash column chromatography to give pure azide **22** (1.05 g, 88%). R_f=0.80 (EtOAc/hexanes, 2:8); $[\alpha]_D^{25}$ +53.00 (*c* 1.0, $CHCl_3$); IR (neat): 2105, 1743, 1454, 1371, 1232, 1097, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 10H), 5.17–5.12 (m, 1H), 4.55

(d, J=5.1 Hz, 2H), 4.51 (d, J=3.0 Hz, 2H), 4.29 (dd, J=7.8, 5.2 Hz, 1H), 4.10 (dd, J=7.8, 2.7 Hz, 1H), 3.81–3.61 (m, 4H), 3.53–3.48 (m, 1H), 2.05 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 137.6, 137.5, 128.4, 128.3, 127.7, 127.6, 127.5, 110.4, 77.8, 76.1, 73.3, 73.2, 69.9, 68.4, 60.7, 26.9, 26.7, 20.9; HRMS m/z calcd for $C_{25}H_{31}N_3O_6$ [M+Na$^+$]: 492.2111; found: 492.2104.

4.1.14. (*R*)-2-(Benzyloxy)-1-((4*S*,5*R*)-5-((*S*)-2-(benzyloxy)-1-(tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate 24. The tosylate **24** (0.993 g, 78% overall yield) was synthesized from the azide **22** (1 g, 2.13 mmol) as a colorless liquid by using the procedure described for compound **8**. R_f=0.40 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −30.00 (c 1.0, $CHCl_3$); IR (neat): 3295, 1743, 1454, 1371, 1332, 1232, 1160, 1091, 815, 738, 698, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J=8.1 Hz, 2H), 7.32–7.25 (m, 10H), 7.17 (d, J=8.1 Hz, 2H), 5.20–5.15 (m, 1H), 4.98 (d, J=9.3 Hz, 1H), 4.52 (dd, J=18.6, 12.0 Hz, 2H), 4.32 (s, 2H), 4.25 (dd, J=8.1, 1.5 Hz, 1H), 3.86 (dd, J=8.1, 6.0 Hz, 1H), 3.65 (dd, J=11.4, 3.6 Hz, 2H), 3.48 (dd, J=11.4, 6.0 Hz, 1H), 3.40 (dd, J=9.3, 5.1 Hz, 1H), 3.33 (dd, J=17.1, 9.0 Hz, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 143.2, 137.9, 137.7, 137.6, 129.5, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 126.9, 109.6, 76.6, 75.9, 72.9, 72.8, 72.1, 69.9, 68.7, 52.6, 26.9, 26.7, 21.4, 20.9; HRMS m/z calcd for $C_{32}H_{39}NO_8S$ [M+Na$^+$]: 620.2294; found: 620.2267.

4.1.15. (2*R*,3*S*,4*R*,5*S*)-1,6-Bis(benzyloxy)-3,4-dihydroxy-5-(tosylamino)hexan-2-yl acetate 25. Diol **25** (0.672 g, 80%) was synthesized from acetonide **24** (0.90 g, 1.51 mmol) as a colorless liquid by using the procedure described for compound **9**. R_f=0.20 (EtOAc/hexanes, 4:8); $[\alpha]_D^{25}$ +21.00 (c 1.0, $CHCl_3$); IR (neat): 3502, 3272, 1733, 1454, 1240, 1160, 1093, 815, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J=8.1 Hz, 2H), 7.33–7.17 (m, 12H), 5.47 (d, J=6.9 Hz, 1H), 5.02–4.97 (m, 1H), 4.52 (d, J=3.6 Hz, 2H), 4.33 (s, 2H), 3.80–3.71 (m, 4H), 3.46 (d, J=7.2 Hz, 2H), 3.34–3.29 (m, 3H), 2.37 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 143.4, 137.6, 137.2, 136.9, 129.6, 128.4, 128.3, 127.8, 127.7, 127.6, 127.1, 73.3, 73.2, 72.2, 69.6, 68.7, 68.6, 68.5, 55.7, 21.5, 20.9; HRMS m/z calcd for $C_{29}H_{35}NO_8S$ [M+Na$^+$]: 580.1981; found: 580.1993.

4.1.16. (2*R*,3*S*,4*R*,5*S*)-1,6-Bis(benzyloxy)-3,4-dimethanesulfono-5-(tosylamino)hexan-2-yl acetate 26. The dimesylate **26** (0.70 g, 91%) was synthesized from the diol **25** (0.60 g, 1.08 mmol) as a colorless liquid by using the procedure described for compound **10**. R_f=0.40 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ +29.00 (c 1.0, $CHCl_3$); IR (neat): 3280, 1749, 1596, 1454, 1353, 1228, 1178, 1093, 954, 738, 700, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J=8.1 Hz, 2H), 7.30–7.24 (m, 8H), 7.21 (d, J=8.1 Hz, 2H), 7.08–7.04 (m, 2H), 5.49 (dd, J=7.8, 2.4 Hz, 1H), 5.33–5.26 (m, 2H), 5.18 (d, J=9.9 Hz, 1H), 4.55 (dd, J=13.8, 11.4 Hz, 2H), 4.07 (d, J=11.4 Hz, 1H), 3.95–3.88 (m, 2H), 3.84 (dd, J=10.2, 5.4 Hz, 1H), 3.69–3.62 (m, 1H), 3.23 (s, 3H), 3.09 (s, 3H), 2.95 (dd, J=9.9, 3.0 Hz, 1H), 2.67 (dd, J=9.9, 4.8 Hz, 1H), 2.41 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 143.9, 137.3, 136.8, 129.8, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 126.9, 79.6, 73.8, 73.3, 70.3, 68.4, 67.4, 52.6, 39.1, 38.2, 21.6, 20.8; HRMS m/z calcd for $C_{31}H_{39}NO_{12}S_3$ [M+Na$^+$]: 736.1532; found: 736.1533.

4.1.17. (2*R*,3*S*)-2-((Benzyloxy)methyl)-3-((2*S*,3*S*)-3-((benzyloxy)methyl)oxiran-2-yl)-1-tosyl aziridine 27. To a solution of dimesylate **26** (0.50 g, 0.70 mmol) in dry MeOH (10 mL), NaOMe (0.151 g, 2.8 mmol) was slowly added at 0 °C. The mixture was stirred at 20 °C for 1 h, and then MeOH was evaporated under reduced pressure. The reaction mixture was diluted with water and extracted with Et_2O (3×10 mL). The combined organic extract was dried (Na_2SO_4) and evaporated to afford after flash chromatography (silica gel; EtOAc/hexanes, 80:20) the aziridinoepoxide **27** (0.296 g, 88%) as a colorless liquid. R_f=0.80 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ +20.00 (c 1.0, CH_2Cl_2); IR (neat): 1361, 1336, 1176, 1162, 923, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, J=8.1 Hz, 2H), 7.33–7.18 (m, 12H), 4.50 (s, 2H), 4.43 (d, J=2.4 Hz, 2H), 3.70 (d, J=1.8 Hz, 1H), 3.68 (s, 1H), 3.65 (d, J=2.7 Hz, 1H), 3.44 (dd, J=11.7, 4.8 Hz, 1H), 3.17 (dd, J=11.7, 6.0 Hz, 1H), 3.07–3.04 (m, 1H), 2.99 (dd, J=7.2, 2.1 Hz, 1H), 2.91 (dd, J=7.2, 4.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 137.6, 134.5, 129.7, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 73.3, 73.0, 68.6, 66.7, 55.2, 50.7, 42.9, 41.8, 21.6; HRMS m/z calcd for $C_{27}H_{29}NO_5S$ [M+Na$^+$]: 502.1664; found: 502.1664.

4.1.18. (*R*)-2-Hydroxy-1-((4*S*,5*R*)-5-((*S*)-2-hydroxy-1-(tosylamino)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl acetate 28. The diol **28** (0.29 g, 83%) was synthesized from the tosylate **24** (0.50 g, 0.84 mmol) as a colorless liquid by using the hydrogenolysis procedure described earlier for compound **13**. R_f=0.40 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −16.00 (c 1.0, $CHCl_3$); IR (neat): 3523, 3297, 1739, 1598, 1454, 1367, 1243, 1176, 1093, 983, 815, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J=8.1 Hz, 2H), 7.32 (d, J=8.1 Hz, 2H), 5.17 (d, J=8.1 Hz, 1H), 4.28 (dd, J=9.9, 2.4 Hz, 1H), 3.99–3.88 (m, 5H), 3.72–3.68 (m, 2H), 2.43 (s, 3H), 2.12 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 143.9, 137.3, 129.8, 127.0, 109.7, 78.1, 74.9, 71.9, 68.8, 66.1, 51.9, 26.8, 21.6, 21.5, 20.7; HRMS m/z calcd for $C_{18}H_{27}NO_8S$ [M+Na$^+$]: 440.1355; found: 440.1362.

4.1.19. (1*R*)-2-Hydroxy-1-[(4*S*,5*R*)-5-((1*S*)-2-hydroxy-1-[(4-methylphenyl)sulfonyl]amino ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl acetate 29. The dimesylate **29** (0.312 g, 91%) was synthesized from the diol **28** (0.25 g, 0.60 mmol) as a colorless liquid by using the procedure described earlier for compound **10**. R_f=0.80 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −18.00 (c 1.0, $CHCl_3$); IR (neat): 3303, 1749, 1596, 1355, 1226, 1089, 970, 815 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, J=8.1 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 5.04 (d, J=9.6 Hz, 1H), 4.86–4.81 (m, 1H), 4.56 (dd, J=12.6, 2.1 Hz, 1H), 4.23 (dd, J=7.8, 1.2 Hz, 1H), 4.11–3.84 (m, 5H), 3.14 (s, 3H), 2.90 (s, 3H), 2.44 (s, 3H), 2.12 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 144.1, 137.5, 129.9, 127.1, 110.9, 79.0, 73.9, 67.4, 63.0, 51.9, 38.8, 37.2, 26.8, 26.6, 21.5, 20.7; HRMS m/z calcd for $C_{20}H_{31}NO_{12}S_3$ [M+Na$^+$]: 596.0906; found: 596.0922.

4.1.20. (*S*)-2-((4*R*,5*S*)-2,2-Dimethyl-5-((*R*)-oxiran-2-yl)-1,3-dioxolan-4-yl)-1-tosylaziridine 30. Dimesylate **29** was subjected to cyclization using the procedure described earlier for compound **27** to furnish aziridino-epoxide **30** (0.163 g, 80% overall yield). R_f=0.60 (EtOAc/hexanes, 3:7); $[\alpha]_D^{25}$ −59.00 (*c* 1.0, CH_2Cl_2); IR (neat): 1939, 1598, 1325, 1163, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 4.02 (dd, *J*=7.8, 3.9 Hz, 1H), 3.35 (t, *J*=7.8 Hz, 1H), 2.99–2.95 (m, 1H), 2.91–2.85 (m, 1H), 2.81 (dd, *J*=8.7, 5.1 Hz, 1H), 2.66 (d, *J*=7.5 Hz, 1H), 2.47–2.45 (m, 1H), 2.46 (s, 3H), 2.41 (d, *J*=4.8 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.7, 134.5, 129.7, 128.3, 110.8, 79.3, 76.6, 51.4, 45.9, 39.7, 30.4, 26.9, 26.4, 21.6; HRMS *m*/*z* calcd for $C_{16}H_{21}NO_5S$ [M+Na^+]: 362.1038; found: 362.1040.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.035.

References and notes

1. (a) Chandrasekar, M.; Chandra, K. L.; Singh, V. K. *J. Org. Chem.* **2003**, *68*, 4039–4045; (b) Chakraborty, T. K.; Srinivasu, P.; Kiran Kumar, S.; Kunwar, A. C. *J. Org. Chem.* **2002**, *67*, 2093–2100; (c) Lohray, B. B.; Baskaran, S.; Rao, B. S.; Reddy, B. Y.; Rao, I. N. *Tetrahedron Lett.* **1999**, *40*, 4855–4856; (d) Babjak, M.; Kapitan, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983–6985; (e) Poitout, L.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron Lett.* **1994**, *35*, 3293–3296.
2. (a) Chandrasekar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773–2775; (b) Chandrasekar, M.; Raina, S.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4969–4971; (c) Raina, S.; Singh, V. K. *Tetrahedron* **1996**, *52*, 4479–4484.
3. (a) Merrer, Y. L.; Dureault, A.; Gravier, C.; Languin, D. M.; Depezay, J. C. *Tetrahedron Lett.* **1985**, *26*, 319–322; (b) Dureault, C.; Greck, C.; Depezay, J. C. *Tetrahedron Lett.* **1986**, *27*, 4157–4160; (c) Merrer, Y. L.; Dureault, A.; Greck, C.; Languin, D. M.; Gravier, C.; Depezay, J. C. *Heterocycles* **1987**, *25*, 541–548.
4. (a) Wang, C. J. J.; Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, *24*, 585–621; (b) Angle, S. R.; Breitenbucher, J. G. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, The Netherlands, 1995; Vol. 16, pp 453–502; (c) Leclercq, S.; Daloze, D.; Braekman, J. C. *Org. Prep. Proced. Int.* **1996**, *28*, 501–543; (d) Nadin, A. *Contemp. Org. Synth.* **1997**, *4*, 387–414; (e) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633–640; (f) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781–1813.
5. (a) Szczepina, M. G.; Johnston, B. D.; Yuan, Y.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 12458–12469; (b) Fuzier, M.; Merrer, Y. L.; Depezay, J. C. *Tetrahedron Lett.* **1995**, *36*, 6443–6446.
6. (a) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 512–520; (b) Farr, R. A.; Holland, A. K.; Huber, E. W.; Peet, N. P.; Weintraub, P. M. *Tetrahedron* **1994**, *50*, 1033–1044; (c) Lohray, B. B.; Jayamma, Y.; Chatterjee, M. *J. Org. Chem.* **1995**, *60*, 5958–5960; (d) Morís-Varas, F.; Qian, X.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647–7652; (e) Qian, X. H.; Morís-Varas, F.; Fitzgerald, M. C.; Wong, C. H. *Bioorg. Med. Chem.* **1996**, *4*, 2055–2069; (f) Merrer, Y. L.; Poitout, L.; Depezay, J. C.; Dosbaa, I.; Geoffry, S.; Foglietti, M. J. *Bioorg. Med. Chem.* **1997**, *5*, 519–533; (g) Andreana, P. R.; Sanders, T.; Janczuk, A.; Warrick, J. I.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 6525–6528; (h) Joseph, C. C.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F. *Tetrahedron* **2002**, *58*, 6907–6911; (i) Tilekar, J. N.; Patil, N. T.; Jadhav, H. S.; Dhavale, D. D. *Tetrahedron* **2003**, *59*, 1873–1876; (j) Painter, G. F.; Elridge, P. J.; Falshaw, A. *Bioorg. Med. Chem.* **2004**, *12*, 225–232.
7. (a) Merrer, L. Y.; Fuzier, M.; Dosbaa, I.; Foglietti, M. J.; Depezay, J. C. *Tetrahedron* **1997**, *53*, 16731–16746; (b) Arcelli, A.; Cere, V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron: Asymmetry* **2002**, *13*, 191–196; (c) Arcelli, A.; Cere, V.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2001**, *57*, 3439–3444; (d) Cere, V.; Mantovani, G.; Peri, F.; Pollicino, S.; Ricci, A. *Tetrahedron* **2000**, *56*, 1225–1231; (e) Halila, S.; Benazza, M.; Demailly, G. *Tetrahedron Lett.* **2001**, *42*, 3307–3310; (f) Kuszmann, J.; Sohar, P. *Carbohydr. Res.* **1977**, *56*, 105–115; (g) Dureault, A.; Tranchepain, I.; Depezay, J. C. *J. Org. Chem.* **1989**, *54*, 5324–5330.
8. Kim, C. U.; McGee, L. R.; Krawczyk, S. H.; Harwood, E.; Harada, Y.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Cherrington, J. M.; Xiong, S. F.; Griffin, L.; Cundy, D. C.; Lee, A.; Yu, B.; Gulnik, S.; Erickson, J. W. *J. Med. Chem.* **1996**, *39*, 3431–3434.
9. (a) Baggett, N.; Stribblehill, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1123–1126; (b) Winn, C. L.; Goodman, J. M. *Tetrahedron Lett.* **2001**, *42*, 7091–7093.
10. Crystal data for compound **3**: structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P2_1/c$, cell parameters: a=11.256(4), b=9.278(4), c=12.614(5) Å, α=90.00°, β=112.461(6)°, γ=90.00°, V=1217.41 Å^3, Z=2, ρ_{calcd}=1.40 g cm^{-3}, $F(000)$=340, μ=0.272 mm^{-1}, λ=0.71073 Å. Total number l.s. parameters=309. $R1$=0.053 for 4240 $F_o>4\sigma(F_o)$ and 0.071 for all 8862 data. $wR2$=0.104, GOF=1.035, restrained GOF=1.035 for all data. (CCDC no. 612123).
11. (a) Aravind, A.; Baskaran, S. *Tetrahedron Lett.* **2005**, *46*, 743–745; (b) Aravind, A.; Subhendu, K.; Pratap, V.; Baskaran, S. *Tetrahedron Lett.* **2005**, *46*, 2965–2968; (c) Debenham, S. D.; Toone, E. J. *Tetrahedron: Asymmetry* **2000**, *11*, 385–387.
12. Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. L.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684–6686.
13. Crystal data for compound **11**: structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P2_1$, cell parameters: a=22.752(3), b=7.383(7), c=22.459(2) Å, α=90.00°, β=118.819(3)°,

γ=90.00°, V=3305.49 Å^3, Z=4, ρ_{calcd}=1.27 g cm^{-3}, $F(000)$=1336, μ=0.207 mm^{-1}, λ=0.71073 Å. Total number l.s. parameters=399. $R1$=0.049 for 5710 $F_o>4\sigma(F_o)$ and 0.060 for all 11973 data. $wR2$=0.107, GOF=1.134, restrained GOF=1.134 for all data. (CCDC no. 292270).

14. Lohray, B. B.; Vidya, B.; Chatterjee, M.; Jayamma, Y.; Prasuna, G. *Res. Chem. Intermed.* **1999**, *25*, 887–901.
15. Muhlman, A.; Classon, B.; Hallberg, A.; Samuelsson, B. *J. Med. Chem.* **2001**, *44*, 3402–3406.
16. Crystal data for compound **17**: structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on F^2 by using SHELXL-97. Crystal system: triclinic, space group: $P2_1$, cell parameters: a=5.434(6), b=11.272(9), c=8.406(9) Å, α=90.00°, β=105.842(2)°, γ=90.00°, V=495.35 Å^3, Z=2, ρ_{calcd}=1.25 g cm^{-3}, $F(000)$=200, μ=0.098 mm^{-1}, λ=0.71073 Å. Total number l.s. parameters=120. $R1$=0.045 for 1673 $F_o>4\sigma(F_o)$ and 0.060 for all 3523 data. $wR2$=0.085, GOF=1.079, restrained GOF=1.079 for all data. (CCDC no. 292059). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html.

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Stereochemically pure α-trifluoromethyl-malic hydroxamates: synthesis and evaluation as inhibitors of matrix metalloproteinases

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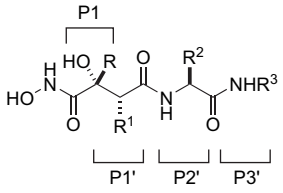
Abstract—The synthesis of trifluoromethyl (Tfm) analogs of known nanomolar matrix metalloproteinases (MMPs) inhibitors has been performed. The synthetic protocol is based on a moderately stereoselective aldol reaction of trifluoropyruvate with an *N*-acyl-oxazolidin-2-thione for the construction of the core α-Tfm-malic unit. Both the diastereomeric forms of the target α-Tfm-malic hydroxamates showed micromolar inhibitory potency toward MMP-2 and 9, according to zymographic tests, with a substantial drop with respect to the parent unfluorinated compounds. We also report some molecular modeling results, which provide a rationale for the experimental findings.

1. Introduction

Incorporation of fluorine into organic molecules is an effective strategy for improving and modifying their biological activity.[1] In particular, the trifluoromethyl group is recognized in medicinal chemistry as a substituent of distinctive qualities. It is, in fact, at the same time highly hydrophobic, electron rich, sterically demanding, moreover it can provide high in vivo stability, and is good mimic of several naturally occurring residues such as methyl, isopropyl, phenyl, etc.[2]

Matrix metalloproteinases (MMPs) are zinc (II)-dependent proteolytic enzymes involved in the degradation of the extracellular matrix.[3] More than 25 human MMPs have been identified so far. Loss in the regulation of their activity can result in the pathological destruction of connective tissue, a process associated with a number of severe diseases, such as cancer and arthritis. The inhibition of various MMPs has been envisaged as a strategy for the therapeutic intervention against such pathologies. To date, however, a number of drawbacks have hampered the successful exploitation of MMPs as pharmacological targets. In particular, the toxicity demonstrated by many MMPs' inhibitors in clinical trials has been ascribed to nonspecific inhibition. For example, recent work evidenced the importance of MMPs inhibitors sparing MMP-1, an enzyme thought to be responsible of the musculoskeletal side effect observed clinically with the broad-spectrum MMP inhibitor marimastat.[4]

Some years ago, Jacobson and co-workers described a new family of potent peptidomimetic hydroxamate inhibitors **A** (Fig. 1) of MMP-1, -3, and -9, bearing a quaternary α-methyl-alcoholic moiety at P1 position, and several different R^1 groups at P1′.[5] Interestingly, the other stereoisomers, including the epimers at the quaternary carbinol function, showed much lower activity, as the authors demonstrated that the hydroxamic binding function was moved away from the catalytic Zn^{2+} center. The crystal structure of the inhibitor **A** (R=CH_3) with MMP-3 (see Fig. 3) reveals several interesting features, including the presence of a hydrogen bond between the quaternary hydroxyl (H-bond donor) of **A** and the Glu-202 residue of the MMP-3 active site.[6]



A R = CH_3; **1** R = CF_3

Figure 1.

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Within the framework of a project aimed at studying the 'fluorine effect' in peptides and identifying selective fluorinated inhibitors of aspartic proteinases and MMPs,[8] we decided to explore the effect of the replacement of the quaternary α-methyl group in **A** with a trifluoromethyl (Tfm) group, with the hope of (1) increasing the affinity of the α-Tfm malic inhibitors with MMPs by reinforcing the α-OH hydrogen bonding, thanks to the increased acidity of the carbinolic function bearing the electron-withdrawing α-Tfm group; (2) improving the selectivity in favor of MMP-3 and -9 through the increased stereo-electronic demands of the Tfm group.

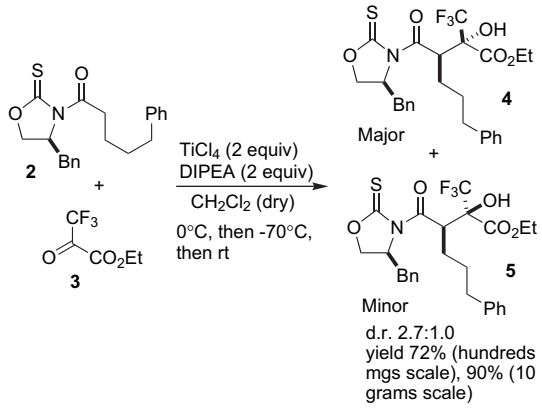
In this paper we describe in full detail the synthesis of the Tfm-analogs **1** (Fig. 1) of **A**, the effect of the replacement of the α-CH_3 group with a CF_3 on the inhibition of MMP-3 and 9, and an attempt to rationalize the experimental findings through molecular modeling.[9]

2. Results and discussion

2.1. Synthesis

We decided to concentrate our efforts on the substrates **1** having $R^1=(CH_2)_4Ph$, whose analogs **A** were reported to be very active. The α-Tfm-malic unit of **1** was recently obtained by our group via titanium (IV) catalyzed aldol reaction of trifluoropyruvic esters with enantiopure *N*-acyl oxazolidin-2-ones.[10] Although this reaction was per se satisfactory, the subsequent exocyclic cleavage of the oxazolidin-2-one auxiliary could not be performed, despite intensive efforts. We therefore decided to exploit the potential of oxazolidin-2-thiones,[11] whose cleavage has been reported to occur much more smoothly.[12]

The $TiCl_4$ catalyzed reaction of the *N*-acyl-oxazolidin-2-thione **2** (Scheme 1) with ethyl trifluoropyruvate **3** afforded the two diastereomeric adducts **4** and **5**, out of four possible, in low diastereomeric ratio. It is worth noting that the reaction features a favorable scale-up effect, affording ca. 70% yield on a hundred-milligram scale, and 90% on a ten-gram scale (the reaction was repeated many times on both scales). Several alternative conditions were explored, but no improvement in terms of diastereocontrol could be achieved. For example, with $Sn(OTf)_2/NEt_3$ and Bu_2BOTf/NEt_3 no reaction was observed, whereas LDA afforded a **4**:**5** ratio=2.6/1.0 (48% overall). However, the use of $TiCl_4$/(−)-sparteine produced a switch of diastereocontrol affording a 1.6:1.0 mixture in favor of **5**, in overall 74% yield. However, due to the cost of (−)-sparteine and the absence of a favorable scale-up effect, the $TiCl_4$/DIPEA system was always employed for conducting the reaction on a multigram scale.

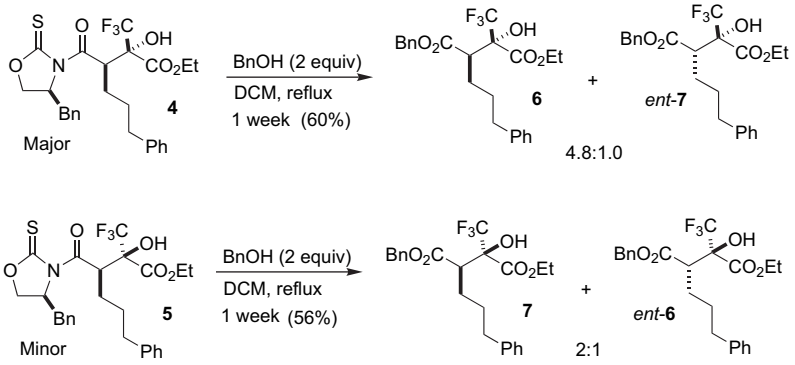


Scheme 1. The aldol reaction to form the α-Tfm-malic framework.

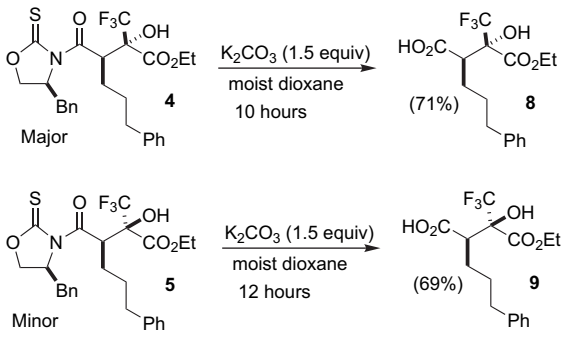
Cleavage of the oxazolidin-2-thione was found to be considerably more challenging than expected. In fact, under the standard conditions reported in the literature (BnOH, cat. DMAP, DCM, rt) the reaction on **4** was very slow,[12] affording modest conversion to the corresponding Bn-ester **6** (60%) after one week at reflux (Scheme 2), with partial (17%) α-epimerization to give *ent*-**7**. Even less effectively, the same reaction performed on **5** gave 56% yield of the diastereomeric Bn-ester **7**, containing 33% of the α-epimer *ent*-**6**. Although the unreacted starting materials **4** and **5** could be recovered unchanged in good yields, we felt that more efficient conditions were needed in order to complete the synthesis. Disappointingly, exploration of several different combinations of alcohols, solvents, and bases did not improve the situation.

However, we were glad to find that solid K_2CO_3 in moist dioxane (rt, 10–12 h) was able to produce directly the key carboxylic acid intermediates **8** and **9** (Scheme 3), from **4** and **5**, respectively, in satisfactory yields and with very low α-epimerization (2% for **8**, 9% for **9**).

In order to assess the stereochemistry of these compounds, the diastereomer **8** was coupled with L-Ala-$NH(CH_2)_2Ph$



Scheme 2. Attempted oxazolidin-2-thione cleavage with BnOH.



Scheme 3. Cleavage of the oxazolidin-2-thione auxiliary with K_2CO_3 in moist dioxane.

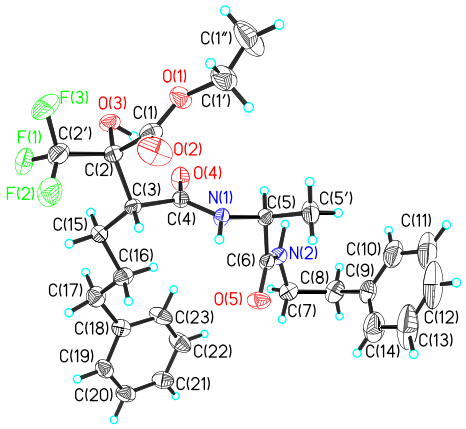
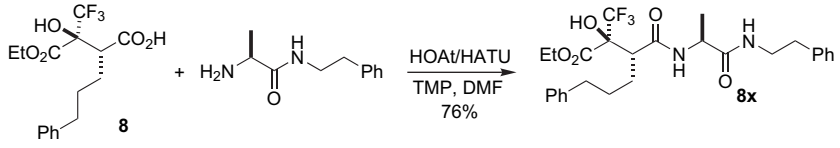


Figure 2. ORTEP view of **8x**.

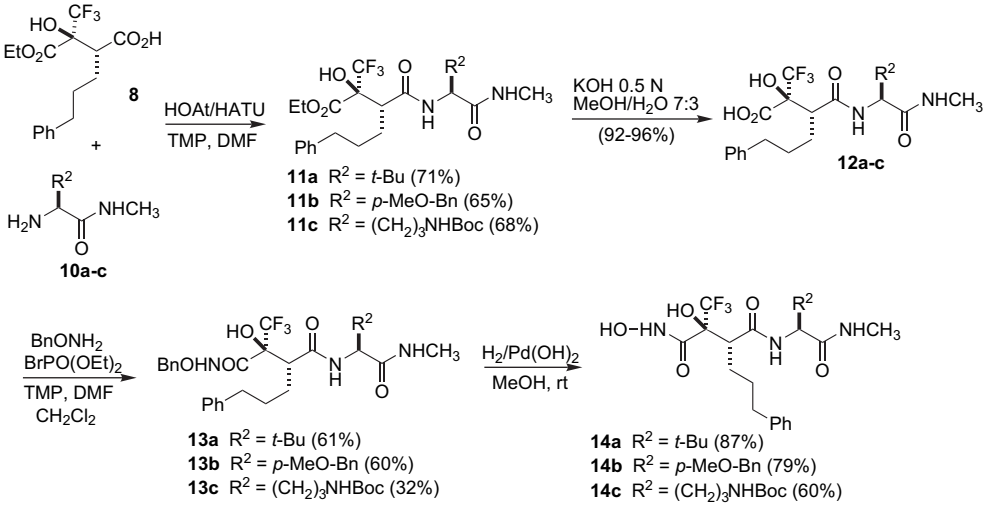
(Scheme 4), affording the crystalline dipeptide **8x**, whose structure was determined by X-ray diffraction (Fig. 2).[13]

Coupling of the acid **8** with α-amino acid amides **10a–c** was achieved in good yields with the HOAt/HATU system (Scheme 5).[14] The resulting peptidomimetic esters **11a–c** were submitted to saponification, affording the acids **12a–c** in high yields. The subsequent coupling of **12a–c** with *O*-Bn hydroxylamine proved to be extremely challenging, owing to the low reactivity and high steric hindrance of the carboxylic group bound the quaternary α-Tfm carbinolic center. A number of 'conventional' coupling agents for peptides[15] were tested (among them DCC/DMAP, EDC/HOBt, DIC/HOBt, HATU/HOAt, PyBroP/DIPEA) but no trace of the target *O*-Bn hydroxamates **13a–c** could be obtained. Finally, we found that freshly prepared $BrPO(OEt)_2$ was able to promote the coupling in reasonable yields (32–61%).[16] With **13a–c** in hand we addressed the final *O*-Bn cleavage by hydrogenolysis, that provided the hydroxamates **14a–c** in good yields.

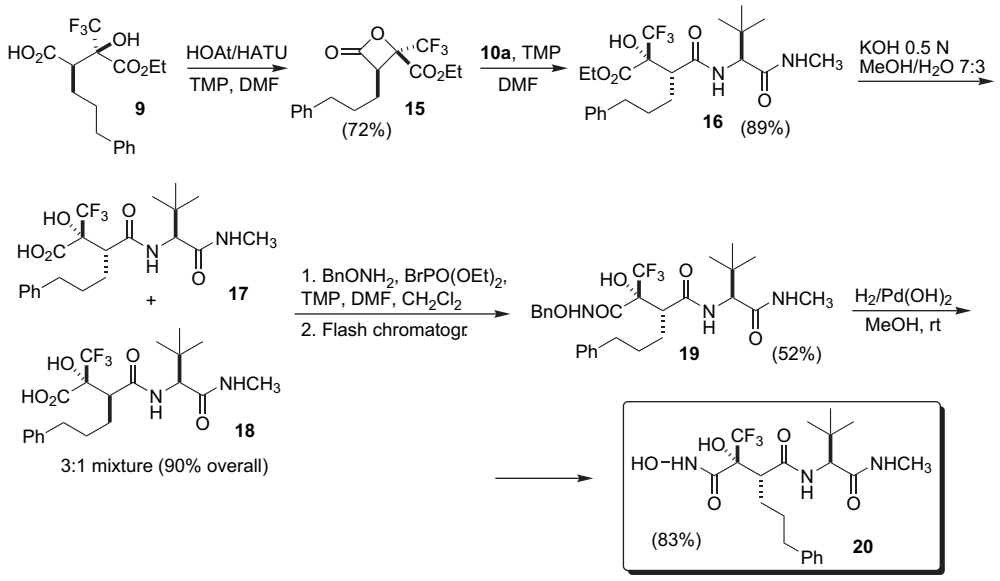
Since **14a–c** are the 'wrong' diastereomers with respect to **A**, we deemed it necessary to synthesize at least one analog having the correct stereochemistry, in order to have a complete set of biological data on the effect of the introduction of the Tfm group. However, a tailored synthetic protocol had to be developed ex-novo, because the minor diastereomer **9** (Scheme 6) featured a dramatically different reactivity in the key steps of the synthesis. First of all, we noticed that the coupling of **9** and **10a** with HATU/HOAt gave rise to relevant amounts of the β-lactone **15**, which had to be processed separately, besides the expected coupling product **16**. Thus, we decided to first prepare the intermediate **15** (72%), which could be purified by short flash chromatography (FC).



Scheme 4. Synthesis of the dipeptide **8x** for X-ray diffraction.



Scheme 5. Synthesis of the peptidomimetics **14** from the major diastereomer **8**.



Scheme 6. Synthesis of the target peptidomimetic **20** from the minor diastereomer **9**.

The latter was reacted with free **10a**, affording the desired molecule **16** in high yields.[17]

Saponification of the ester **16** occurred effectively, but disappointingly a partial epimerization of the [Ph(CH$_2$)$_3$]-stereocenter occurred, affording a 3:1 mixture of diastereomers **17** and **18** under optimized conditions. Since their chromatographic separation proved to be difficult, **17** and **18** were subjected together to coupling with BnONH$_2$ under the previously optimized conditions. The resulting diastereomeric *O*-Bn hydroxamates could be separated by FC, affording pure **19** (52%), that was hydrogenated to the target free hydroxamate **20** in 83% yield.

The hydroxamates **14a–c** and **20** were tested for their ability to inhibit MMP-2 and MMP-9 activity using zymographic analysis. The four hydroxamates inhibited, in a dose-dependent manner, the gelatinolytic bands at 92 and 72 kDa, corresponding respectively to pro-MMP-9 and pro-MMP-2 released in the conditioned medium by human melanoma cells WM983A. The IC$_{50}$ values (μM) portrayed in Table 1 show that diastereomers **14a–c** displayed low inhibitory activity, in line with the parent CH$_3$ compounds. Disappointingly, **20** showed a much lower activity than the exact CH$_3$-analog **A**, that was reported to be a low nanomolar inhibitor of MMP-9.

Table 1. IC$_{50}$ (μM) of the target Tfm-hydroxamates

Compound	MMP-2	MMP-9
14a	156	121
14b	407	84
14c	722	23
20	23	15

It is also worth noting that **14a** and **20** showed little selectivity, whereas **14b** and **14c** showed a better affinity for MMP-9, in comparison with MMP-2.

2.2. Simulations

In an attempt to explain the different activities of the hydrogenated (**A**) and the fluorinated (**1**) compounds, we first performed molecular dynamics (MD) simulations of a few protein-inhibitor complexes. The experimental X-ray structures[5] of the complexes of **1** with MMP-3 (Fig. 3) provided a very convenient starting point for these simulations. However we found that these simulations could not clearly discriminate between the different inhibitors, since both the hydrogenated and the fluorinated ligands remained coordinated to the active site within the time of the simulation. The likely reason for this failure is the limited time span, which could be explored by MD with current computer resources (a few nanoseconds). Therefore, instead of studying the whole protein–ligand complexes, we decided to factor the problem and investigate separately the effect of fluorination on (a) the coordinating strength of the hydroxamate group and (b) non-bonded interactions and the conformational equilibrium of the ligands.

The effect of fluorination on the coordinating strength of the ligands was investigated by ab initio B3LYP/6-31G* calculations on the reactants and products of the exchange reaction shown in Figure 4 (see Section 3). After energy minimization, we computed the net reaction energy as $\Delta E = E(\text{products}) - E(\text{reactants}) = +8.8$ kJ/mol. Therefore the replacement of –CH$_3$ by –CF$_3$ reduces the coordinating ability of the hydroxamate, presumably because of the electron-withdrawing effect of the latter.

Inspection of the conformation adopted by inhibitors **A** within the active site of MMP-3 reveals that the closest non-bonded contact formed by the methyl in P1 position is an intramolecular one, with the aromatic ring of the pseudo-tyrosine at the P2′ position (see Fig. 5). Replacement of this methyl by the more sterically demanding and electron-rich Tfm might produce a change in the intramolecular conformational equilibria of the ligand, affecting as a side

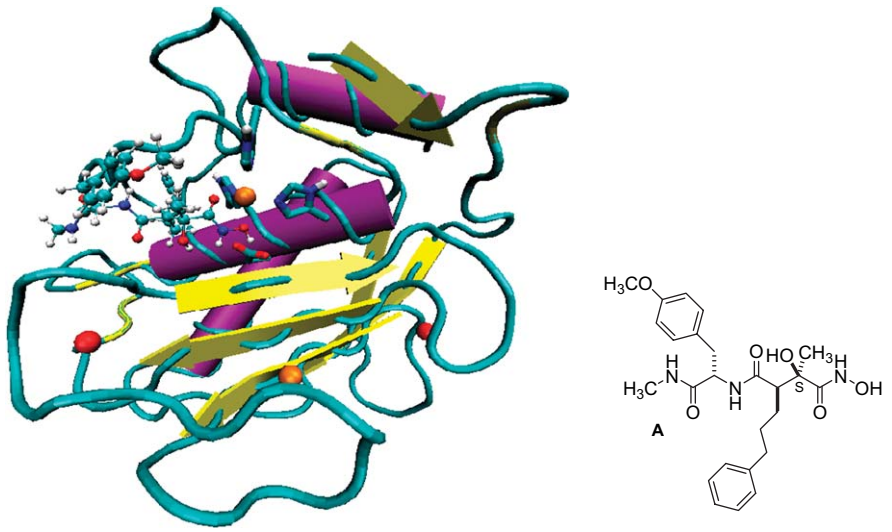


Figure 3. X-ray structure of the inhibitor **A** [R^1=$(CH_2)_3$Ph, R^2=4-CH_3O–$C_6H_4CH_2$, R^3=CH_3] bound to MMP-3 (courtesy of Bristol–Myers Squibb). The Zn^{2+} ion in the active site, the inhibitor, the three coordinating histidines, and the Glu-202 residue have been highlighted. Image produced with VMD.[7]

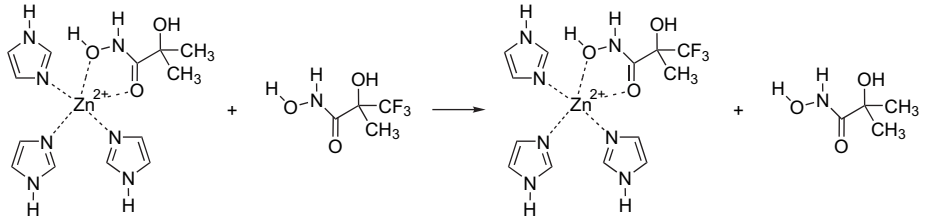


Figure 4. Exchange reaction between models of the hydrogenated and fluorinated ligands at the active site, investigated by ab initio calculations.

effect its ability to fit inside the protein active site. Therefore, we decided to carry out MD simulations of the inhibitors in water to test this hypothesis.

The analysis of a long (12 ns) MD simulation of the inhibitors in water (see Section 3 for details) produced very similar histograms for the populations of almost every torsion angle, indicating that they are mostly unaffected by fluorine substitution. However, we observed a certain difference in the populations of the C–C bond connecting the pseudo-tyrosine residue to the backbone (highlighted in yellow in Fig. 5). Therefore we decided to investigate further this point by computing the free energy profile of the molecules along this particular degree of freedom (see again Section 3). Figure 6 shows that the resulting torsion free energies are very similar, except for one important detail: the conformation at 300°, which is the one adopted by the inhibitor in the active site, is slightly destabilized by the introduction of the $–CF_3$ group. We identify this destabilization with the unfavorable interaction between the electron-rich Tfm and aromatic group. The lowest-energy conformation (by 2.5 kJ/mol) now corresponds to the state at 60°. As can be seen in Figure 5, this produces major change in the overall molecular shape.

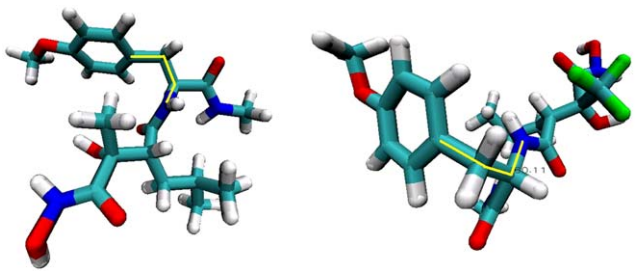


Figure 5. Minimum free energy conformations of **A** (left) and **1** (right), as obtained by MD simulations in water. With reference to Figure 1, R^1=$CH_2CH(CH_3)_2$, R^2=4-CH_3O–$C_6H_4CH_2$, R^3=CH_3. The conformation of **A** coincides with the experimental conformation within the active site. The broken yellow line indicates the torsion angle sampled in the free energy calculations. Images produced with VMD.[7]

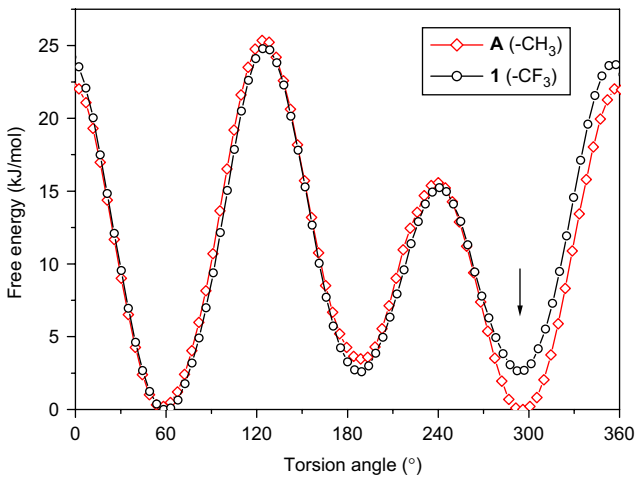


Figure 6. Free energy curves of **A** and **1** in water, corresponding to the torsion about the C–C bond connecting the pseudo-tyrosine residue to the backbone. The arrow indicates the conformation adopted inside the protein active site.

In summary, our molecular modeling study has allowed to identify two concurrent reasons for the reduced activity of the fluorinated inhibitors: (a) reduced coordinating strength of the neighboring hydroxamate group, and (b) the need of the fluorinated molecule to adopt within the binding site a conformation which does not coincide with its minimum-energy conformation in solution. Assuming additivity of these effects, we estimate that the overall binding energy of the fluorinated inhibitor to the active site is reduced by approximately 11.3 kJ/mol, compared to the original one. This results, at room temperature, in the reduction in the binding constant by two order of magnitude [$K_F/K_H = \exp\{-11.3/(0.00831 \times 298)\} = 0.010$]. This result roughly corresponds to the experimental observation.

3. Experimental

3.1. General details

Commercially available reagent-grade solvents were employed without purification. All reactions where an organic solvent was employed were performed under nitrogen atmosphere, after flame-drying of the glass apparatus. Melting points (mp) are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} Merck. Flash chromatographies (FC) were performed with silica gel 60 (60–200 μm, Merck). ^{1}H, ^{13}C, and ^{19}F NMR spectra were run at 250, 400 or 500 MHz. Chemical shifts are expressed in parts per million (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C=0.00), while C_6F_6 was used as external standard (δ_F −162.90) for ^{19}F.

3.2. Synthesis of aldol adducts 4 and 5

To a solution of *N*-acyl-oxazolidin-2-thione **2** (107 mg, 0.30 mmol) in dry CH_2Cl_2 (4 mL), cooled at 0 °C and under nitrogen atmosphere, a 1 M solution of $TiCl_4$ in toluene (600 μL, 0.60 mmol) was added. The solution was stirred for 5 min, then neat DIPEA (103 μL, 0.60 mmol) was added. The dark red solution of titanium enolate was stirred for 20 min at 0 °C, then cooled at −70 °C and neat ethyl trifluoropyruvate **3** (100 μL, 0.75 mmol) was added dropwise. The resulting mixture was stirred for 1 h at −70 °C, then warmed to rt. The reaction was quenched with a saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The collected organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by FC (*n*-Hex/EtOAc 9:1), affording 59 mg of **4**, 33 mg of **5**, and 21 mg of their mixture (72% overall yield).

Compound **4**: yellow oil; R_f 0.44 (EtOAc/*n*-Hex 2:8); $[\alpha]_D^{23}$ +88.9 (*c* 1.4, $CHCl_3$); FTIR (film) ν_{max}: 3462, 1748, 1691, 1348 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.48–7.00 (m, 10H), 6.11 (dd, *J*=7.3, 5.8 Hz, 1H), 4.76 (m, 1H), 4.44–4.14 (m, 4H), 4.11–4.00 (m, 1H), 3.23 (dd, *J*=13.1, 3.1 Hz, 1H), 2.71–2.49 (m, 3H), 2.12–1.94 (m, 2H), 1.89–1.51 (m, 2H), 1.31 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 184.5, 174.4, 168.3, 141.4, 134.9, 129.3, 129.1, 128.3, 127.5, 125.9, 123.0 (q, *J*=286.7 Hz), 78.6 (q, *J*=29.6 Hz), 69.7, 63.7, 60.5, 43.8, 37.1, 35.9, 28.4, 27.3, 13.9; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −75.4 (s, 3F); MS (DIS EI 70 eV) *m*/*z* (%): 524 [M+H$^+$] (36), 330 (62), 194 (100); HRMS *m*/*z* 523.1630 (calculated 523.1633, $C_{26}H_{28}F_3NO_5S$).

Compound **5**: yellow oil; R_f 0.36 (EtOAc/*n*-Hex 2:8); $[\alpha]_D^{23}$ +37.3 (*c* 1.6, $CHCl_3$); FTIR (film) ν_{max}: 3467, 1747, 1693, 1498 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.47–7.02 (m, 10H), 6.34 (dd, *J*=10.4, 3.7 Hz, 1H), 4.95 (m, 1H), 4.44–4.14 (m, 5H), 3.29 (dd, *J*=13.1 and 3.1 Hz, 1H), 2.67 (dd, *J*=13.1 and 10.4 Hz, 1H), 2.65–2.53 (m, 2H), 2.11–1.99 (m, 1H), 1.85–1.45 (m, 3H), 1.32 (t, *J*=6.9 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 184.7, 174.3, 167.1, 141.2, 134.9, 129.3, 129.0, 128.3, 127.5, 123.2 (q, *J*=288.5 Hz), 79.1 (q, *J*=29.6 Hz), 69.8, 63.7, 59.9, 42.7, 37.0, 35.0, 28.8, 28.3, 13.8; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −75.6 (s, 3F); MS (DIS EI 70 eV) *m*/*z* (%): 524 [M+H$^+$] (13), 330 (38), 194 (100).

3.3. Cleavage of the oxazolidin-2-thione

3.3.1. A—Cleavage with BnOH. General procedure. To a solution of **4** (102 mg, 0.19 mmol) in CH_2Cl_2 (5 mL), neat BnOH (40 μL, 0.38 mmol) and DMAP (4.2 mg, 0.038 mmol) were added. The solution was refluxed for one week. The solvent was removed in vacuo and the crude was purified by FC (*n*-Hex/EtOAc 9:1), affording 30 mg of **6**, 5 mg of *ent*-**7**, and 15 mg of their mixture (60% overall yield).

Compound **6**: colorless oil; R_f 0.25 (EtOAc/*n*-Hex 1:9); $[\alpha]_D^{23}$ +7.9 (*c* 0.9, $CHCl_3$); FTIR (film) ν_{max}: 3741, 1748, 1456 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.41–6.99 (m, 10H), 5.08 (s, 2H), 4.23–3.99 (m, 3H), 3.26 (dd, *J*=9.4, 4.5 Hz, 1H), 2.64–2.53 (m, 2H), 2.02–1.46 (m, 4H), 1.24 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.1, 168.9, 141.7, 134.9, 128.6, 128.5, 128.3, 123.1 (q, *J*=288.4 Hz), 78.1 (q, *J*=29.6 Hz), 67.1, 63.8, 47.7, 35.6, 29.2, 25.8, 13.6; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −75.1 (s, 3F); MS (DIS EI 70 eV) *m*/*z* (%): 439 [M+H$^+$] (54), 117 (78), 91 (100); HRMS *m*/*z* 438.1649 (calculated 438.1647, $C_{23}H_{25}F_3O_5$).

Compound **7**: colorless oil; R_f 0.20 (EtOAc/*n*-Hex 1:9); $[\alpha]_D^{23}$ −3.8 (*c* 1.4, $CHCl_3$); FTIR (film) ν_{max}: 3467, 1746, 1456 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.29–6.99 (m, 10H), 5.21 (d, *J*=12.0 Hz, 1H), 5.11 (d, *J*=12.0 Hz, 1H), 4.47 (s, 1H), 4.35–4.20 (m, 2H), 3.21 (dd, *J*=11.7, 3.4 Hz, 1H), 2.56 (m, 2H), 2.07–1.87 (m, 1H), 1.65–1.29 (m, 3H), 1.24 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.9, 167.2, 141.2, 134.9, 128.6, 128.3, 128.2, 125.9, 123.1 (q, *J*=288.5 Hz), 78.5 (q, *J*=27.7 Hz), 67.4, 63.7, 46.9, 35.1, 28.6, 27.1, 13.8; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −76.9 (s, 3F); MS (DIS EI 70 eV) *m*/*z* (%): 439 [M+H$^+$] (59), 421 (100).

3.3.2. B—Cleavage with K_2CO_3. General procedure. To a solution of **4** (91 mg, 0.17 mmol) in moist dioxane (2 mL), K_2CO_3 (70 mg, 0.51 mmol) was added. The resulting mixture was stirred for 10 h. The solvent was removed in vacuo and the crude was dissolved in EtOAc. A 1 M solution of HCl was added until pH 1–2 was reached. The layers were separated and the aqueous phase was extracted with EtOAc. The collected organic phases were dried over anhydrous

Na_2SO_4, filtered and the solvent was removed in vacuo to give 42 mg of **8** (71% yield).

Compound **8**: colorless oil; R_f 0.48 ($CHCl_3$/MeOH 8:2); $[\alpha]_D^{23}$ +16.5 (*c* 1.4, MeOH); FTIR (film) ν_{max}: 3466.6, 1732.9, 1454.5 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 7.29–7.05 (m, 5H), 4.25 (q, *J*=7.5 Hz, 2H), 3.13 (m, 1H), 2.71–2.53 (m, 2H), 1.95–1.52 (m, 4H), 1.27 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 177.0, 168.9, 141.5, 128.3, 128.2, 125.9, 122.9 (q, *J*=288.5 Hz), 77.9 (q, *J*=29.6 Hz), 64.2, 47.8, 35.6, 29.2, 25.7, 13.6; ^{19}F NMR (235.5 MHz, CD_3OD) δ: −75.6 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 349 [M+H$^+$] (65), 330 (60), 91 (100); HRMS *m/z* 348.1200 (calculated 348.1198, $C_{16}H_{19}F_3O_5$).

Compound **9**: colorless oil; R_f 0.46 ($CHCl_3$/MeOH 8:2); $[\alpha]_D^{23}$ +11.9 (*c* 0.9, MeOH); FTIR (film) ν_{max}: 3476, 1748, 1454 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 7.28–7.09 (m, 5H), 4.29–4.15 (m, 2H), 3.05 (dd, *J*=11.7, 3.2 Hz, 1H), 2.61 (dt, *J*=7.2, 2.0 Hz, 2H), 1.97–1.85 (m, 1H), 1.76–1.59 (m, 2H), 1.44–1.32 (m, 1H), 1.21 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 174.8, 168.7, 141.8, 129.4, 126.9, 124.8 (q, *J*=282.6 Hz), 80.4 (q, *J*=27.7 Hz), 64.1, 49.2, 36.2, 30.2, 27.8, 14.2; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −74.1 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 349 [M+H$^+$] (5), 330 (18), 159 (40), 91 (100).

3.4. Synthesis of peptidomimetics esters 11a–c and 8x. General procedure

To a solution of **8** (198 mg, 0.57 mmol) and **10a** (98 mg, 0.68 mmol) in dry DMF (5 mL), HOAt (77 mg, 0.57 mmol), HATU (217 mg, 0.57 mmol), and TMP (150 μL, 1.14 mmol) were added. The solution was stirred for 2 h, then diluted with H_2O. The resulting mixture was extracted with Et_2O and the organic phase was washed with a 1 M solution of HCl and with brine. After drying over anhydrous Na_2SO_4, and filtration, the solvent was removed in vacuo, and the residue was purified by FC (*n*-Hex/EtOAc 6:4) to give 192 mg of **11a** (71% yield), as a white solid: R_f 0.67 (EtOAc/*n*-Hex 6:4); $[\alpha]_D^{23}$ +4.5 (*c* 1.8, $CHCl_3$); FTIR (microscope) ν_{max}: 3307, 1754, 1647, 1535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.19 (m, 2H), 7.18–7.07 (m, 3H), 6.70 (br d, *J*=9.3 Hz, 1H), 6.03, (br s, 1H), 4.92 (br s, 1H), 4.33–4.17 (m, 2H), 4.14 (d, *J*=9.3 Hz, 1H), 3.08 (dd, *J*=9.3, 5.9 Hz, 1H), 2.72 (d, *J*=4.6 Hz, 3H), 2.70–2.52 (m, 2H), 1.93–1.79 (m, 2H), 1.61 (m, 2H), 1.27 (t, *J*=7.2 Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 171.5, 170.5, 168.7, 141.5, 128.4, 128.2, 125.9, 122.9 (q, *J*= 285.9 Hz), 78.9 (q, *J*=28.9 Hz), 63.6, 60.8, 49.1, 35.7, 34.5, 28.7, 26.6, 26.4, 26.1, 13.8; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −74.5 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 474 [M$^+$] (8), 416 (18), 86 (100); HRMS *m/z* 474.2340 (calculated 474.2333, $C_{23}H_{33}F_3N_2O_5$).

Compound **11b**: white solid; R_f 0.42 (EtOAc/*n*-Hex 6:4); $[\alpha]_D^{23}$ +2.9 (*c* 1.2, in $CHCl_3$); FTIR (microscope) ν_{max}: 3300, 1745, 1650, 1517.1 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.29–7.21 (m, 2H), 7.19–7.00 (m, 6H), 6.79 (d, *J*=8.8 Hz, 2H), 6.68 (br d, *J*=7.7 Hz, 1H), 5.80 (br s, 1H), 4.47 (q, *J*=7.2 Hz, 1H), 4.33–4.19 (m, 2H), 3.72 (s, 3H), 3.04 (dd, *J*=10.9, 4.4 Hz, 1H), 2.90 (dd, *J*=13.7, 7.2 Hz, 1H), 2.88 (dd, *J*=13.7, 7.2 Hz, 1H), 2.67 (d, *J*=4.9 Hz, 3H), 2.63–2.46 (m, 2H), 1.86–1.65 (m, 2H), 1.52–1.39 (m, 2H), 1.28 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 171.2, 170.7, 169.2, 158.8, 141.5, 130.1, 128.4, 128.3, 128.2, 125.9, 122.8 (q, *J*=287.5 Hz), 114.3, 78.5 (q, *J*=29.3 Hz), 64.0, 55.2, 54.8, 49.3, 37.3, 35.5, 28.6, 26.2, 13.8; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −74.3 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 539 [M+H$^+$] (34), 191 (100); HRMS *m/z* 538.2281 (calculated 538.2282, $C_{27}H_{33}F_3N_2O_6$).

Compound **11c**: white solid; R_f 0.19 (AcOEt/*n*-Hex 1:1); $[\alpha]_D^{23}$ +13.9 (*c* 0.84, $CHCl_3$); FTIR (microscope) ν_{max}: 3284, 1750, 1639, 1531 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.43 (br s, 1H), 7.35–7.08 (m, 5H), 7.02 (br s, 1H), 5.01 (br s, 1H), 4.59 (br s, 1H), 4.38–4.19 (m, 2H), 3.46–3.25 (m, 1H), 3.18 (dd, *J*=10.8, 4.2 Hz, 1H), 3.13–2.95 (m, 1H), 2.74 (d, *J*=4.4 Hz, 3H), 2.69–2.54 (m, 2H), 2.03–1.70 (m, 4H), 1.69–1.56 (m, 2H), 1.46 (s, 9H), 1.31 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.9, 171.6, 168.8, 156.7, 141.5, 128.4, 128.2, 125.7, 122.9 (q, *J*=286.7 Hz), 78.9 (q, *J*=29.6 Hz), 63.2, 48.3, 35.5, 28.6, 28.3, 25.9, 13.7; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −74.2 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 576 [M+H$^+$] (20), 474 (30), 430 (60), 57 (100); HRMS *m/z* 575.2811 (calculated 575.2808, $C_{27}H_{40}F_3N_3O_7$).

Compound **8x**: white solid; R_f 0.29 (AcOEt/*n*-Hex 4:6); $[\alpha]_D^{23}$ −10.4 (*c* 1.2, $CHCl_3$); mp=93–97 °C (EtOAc/*n*-Hex); FTIR (microscope) ν_{max}: 3280, 1752, 1641, 1533.5 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.37–7.11 (m, 10H), 6.53 (d, *J*=7.9 Hz, 1H), 5.96 (br t, *J*=5.3 Hz, 1H), 4.36–4.22 (m, 3H), 3.59–3.43 (m, 2H), 3.04 (dd, *J*=11.2, 5.3 Hz, 1H), 3.87–2.77 (m, 2H), 2.73–2.57 (m, 2H), 1.94–1.82 (m, 2H), 1.79–1.68 (br s, 1H), 1.67–1.57 (m, 2H), 1.33 (t, *J*=7.2 Hz, 3H), 1.27 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.4, 170.7, 168.8, 141.5, 138.4, 128.7, 128.6, 128.3, 128.2, 126.5, 125.9, 123.0 (q, *J*=286.7 Hz), 78.6 (q, *J*=29.5 Hz), 63.6, 48.7, 40.7, 35.5, 35.3, 28.7, 25.8, 18.4, 13.8; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −73.8 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 576 [M+H$^+$] (20), 474 (30), 430 (60), 57 (100). Anal. Calcd for $C_{27}H_{33}F_3N_2O_5$: C, 62.06; H, 6.37; N, 5.36. Found: C, 61.98; H, 6.44; N, 5.31.

3.5. Synthesis of acids 12a–c. General procedure

To a solution of **11a** (123 mg, 0.26 mmol) in a MeOH/H_2O 7:3 mixture (5 mL), a 0.5 M aqueous solution of KOH (1.00 mL, 0.52 mmol) was added. The reaction was stirred for 2 h, then the MeOH was removed in vacuo. A 1 M solution of HCl was added until pH 1–2 was reached, and the reaction mixture was extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to give 111 mg of **12a** (96% yield), as a white solid: R_f 0.54 ($CHCl_3$/MeOH 7:3); $[\alpha]_D^{23}$ +1.3 (*c* 1.2, MeOH); FTIR (microscope) ν_{max}: 3453, 1749, 1654, 1488 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 7.30–7.06 (m, 5H), 4.19 (s, 1H), 3.23 (dd, *J*=10.3, 4.7 Hz, 1H), 2.64 (s, 4H), 2.59–2.50 (m, 1H), 1.85–1.74 (m, 2H), 1.68–1.51 (m, 2H), 0.97 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 174.1, 172.6, 170.8, 141.5, 128.4, 128.2, 125.9, 122.9 (q, *J*=285.9 Hz), 78.9 (q, *J*=28.9 Hz), 63.6, 35.7, 34.5, 28.7, 26.6, 26.4, 26.1, 13.8; ^{19}F NMR (250 MHz, CD_3OD) δ: −74.5 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 447 [M+H$^+$]

(8), 388 (20), 91 (40), 86 (100); HRMS *m/z* 446.2018 (calculated 446.2021, $C_{21}H_{29}F_3N_2O_5$).

Compound **12b**: white solid; R_f 0.45 ($CHCl_3$/MeOH 7:3); $[\alpha]_D^{23}$ +4.2 (*c* 0.3, MeOH); FTIR (microscope) ν_{max}: 3371, 1743, 1654, 1434 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 7.29–7.19 (m, 2H), 7.17–7.03 (m, 5H), 6.81 (d, *J*=8.9 Hz, 2H), 4.51 (t, *J*=7.2 Hz, 1H), 3.70 (s, 3H), 3.06–2.98 (m, 2H), 2.86 (dd, *J*=14.1, 7.9 Hz, 1H), 2.64 (s, 3H), 2.61–2.41 (m, 2H), 1.79–1.60 (m, 2H), 1.48–1.36 (m, 2H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 173.6, 170.6, 169.9, 158.9, 141.2, 130.2, 128.4, 128.3, 127.6, 126.0, 123.0 (q, *J*=284.7 Hz), 114.3, 77.6 (q, *J*=28.9 Hz), 55.8, 55.3, 48.1, 37.7, 35.2, 28.4, 27.4, 26.2; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −72.5 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 511 [M+H$^+$] (15), 209 (20), 191 (100); HRMS *m/z* 510.1965 (calculated 510.1970, $C_{25}H_{29}F_3N_2O_6$).

Compound **12c**: white solid; R_f 0.27 ($CHCl_3$/MeOH 8:2); $[\alpha]_D^{23}$ −1.9 (*c* 1.1, MeOH); FTIR (microscope) ν_{max}: 3302, 1746, 1656, 1522 cm^{-1}; ^1H NMR (250 MHz, CD_3OD) δ: 7.30–7.07 (m, 5H), 4.38–4.25 (m, 1H), 3.16–2.98 (m, 3H), 2.68 (s, 3H), 2.65–2.48 (m, 2H), 1.89–1.55 (m, 8H), 1.42 (s, 9H); ^{13}C NMR (62.9 MHz, CD_3OD) δ: 174.9, 171.8, 159.5, 144.1, 130.4, 130.2, 127.7, 125.8 (q, *J*=286.7 Hz), 80.7 (q, *J*=29.6 Hz), 62.4, 55.2, 41.5, 37.4, 31.1, 29.7, 28.6, 28.3, 27.2; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −72.5 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 548 [M+H$^+$] (5), 430 (60), 41 (100); HRMS *m/z* 547.2499 (calculated 547.2496, $C_{25}H_{36}F_3N_3O_7$).

3.6. Synthesis of lactone 15

To a solution of **9** (50 mg, 0.14 mmol) in DMF (2 mL), HOAt (20 mg, 0.15 mmol), HATU (57 mg, 0.15 mmol), and TMP (37 μL, 0.28 mmol) were added. The solution was stirred for 2 h, then diluted with H_2O. The resulting mixture was extracted with Et_2O and the organic phase was washed with a 1 M solution of HCl and with brine. After drying over anhydrous Na_2SO_4, and filtration, the solvent was removed in vacuo, and the residue was purified by FC (*n*-Hex/(*i*Pr)$_2$O 9:1) to give 33 mg of **15** (72% yield) as a colorless oil: R_f 0.55 (EtOAc/*n*-Hex 1:9); $[\alpha]_D^{23}$ +6.8 (*c* 0.8, $CHCl_3$); FTIR (film) ν_{max}: 1870, 1752, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.09 (m, 5H), 4.31 (q, *J*=7.2 Hz, 2H), 3.99 (m, 1H), 2.73–2.58 (m, 2H), 1.90–1.69 (m, 4H), 1.30 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 165.5, 162.4, 140.7, 128.6, 128.4, 121.9 (q, *J*=281.4 Hz), 76.5 (q, *J*=33.7 Hz), 63.6, 58.0, 35.2, 28.1, 24.8, 13.9; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −77.1 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 330 [M$^+$] (17), 159 (40), 104 (100); HRMS *m/z* 330.1079 (calculated 330.1074, $C_{16}H_{17}F_3O_4$).

3.7. Synthesis of peptidomimetic ester 16

To a solution of **15** (139 mg, 0.42 mmol) and **10a** (121 mg, 0.84 mmol) in DMF (5 mL), TMP (111 μL, 0.84 mmol) was added. The solution was stirred for 6 h, then diluted with H_2O. The resulting mixture was extracted with Et_2O and the organic phase was washed with a 1 M solution of HCl, then with brine. After drying over anhydrous Na_2SO_4 and filtration, the solvent was removed in vacuo, and the residue was purified by FC (*n*-Hex/EtOAc 7:3) to give 177 mg of **16** (89% yield) as a colorless oil: R_f 0.61 (EtOAc/*n*-Hex 1:1); $[\alpha]_D^{23}$ −0.5 (*c* 1.1, MeOH); FTIR (film) ν_{max}: 3317, 1750, 1654, 1545 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 7.27–7.05 (m, 5H), 4.24–4.19 (m, 3H), 3.17 (dd, *J*=11.4, 3.5 Hz, 1H), 2.65 (s, 3H), 2.47–2.54 (m, 2H), 1.96–1.74 (m, 1H), 1.59 (m, 2H), 1.38–1.28 (m, 1H), 1.22 (t, *J*=6.9 Hz, 3H), 0.98 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 173.9, 172.7, 168.4, 142.9, 129.5, 129.3, 126.9, 125.1 (q, *J*=287.9 Hz), 80.5 (q, *J*=28.1 Hz), 64.0, 62.1, 47.9, 36.3, 35.2, 29.6, 29.1, 27.1, 25.9, 14.2; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −73.9 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 475 [M+H$^+$] (28), 416 (20), 86 (100); HRMS *m/z* 474.2330 (calculated 474.2333, $C_{23}H_{33}F_3N_2O_5$).

3.8. Synthesis of acids 17 and 18

To a solution of **16** (278 mg, 0.59 mmol) in a MeOH/H_2O 7:3 mixture (5 mL), a 0.5 M aqueous solution of KOH (3.5 mL, 1.77 mmol) was added. The reaction was stirred for 20 h, then the MeOH was removed in vacuo. A 1 M solution of HCl was added until pH 1–2 was reached, and the reaction mixture was extracted with EtOAc. The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to give 237 mg of a mixture of **17** and **18** (90% overall yield) as a white solid: R_f 0.37 ($CHCl_3$/MeOH 8:2); $[\alpha]_D^{23}$ −3.9 (*c* 0.8, MeOH); FTIR (microscope) ν_{max}: 3450, 1748, 1656, 1544 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 7.28–7.08 (m, 5H), 4.19 (s, 1H), 3.23–3.16 (m, 1H), 2.71 (s, 3H), 2.68–2.50 (m, 2H), 1.89–1.53 (m, 4H), 0.97 (s, 9H); ^{13}C NMR (62.9 MHz, CD_3OD) δ: 175.0, 172.3, 169.1, 143.0, 129.3, 126.6, 125.2 (q, *J*=286.6 Hz), 79.8 (q, *J*=27.3 Hz), 62.2, 36.5, 35.9, 35.1, 30.6, 29.9, 26.9, 26.0; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −72.9 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 447 [M+H$^+$] (25), 388 (30), 91 (40), 86 (100).

3.9. Synthesis of peptidomimetics 13a–c and 19. General procedure

To a solution of **12a** (58 mg, 0.13 mmol) in a CH_2Cl_2/DMF 2:1 mixture (3 mL), cooled at 0 °C, a solution of $BrPO(OEt)_2$ (35 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) and neat TMP (34 μL, 0.26 mmol) were added dropwise. The resulting solution was stirred for 45 min at 0 °C, then a solution of $BnONH_2$ (32 mg, 0.26 mmol) in CH_2Cl_2 (0.5 mL) and neat TMP (34 μL, 0.26 mmol) were added. The reaction was allowed to warm to rt and stirred for 5 h. The solvent was removed in vacuo and the crude material was dissolved in a EtOAc/Et_2O 1:1 mixture. The resulting mixture was washed with a 1 M solution of HCl and with brine, then the organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified by FC (*n*-Hex/EtOAc 6:4) to give 44 mg of **13a** (61% yield) as a white solid: R_f 0.26 (EtOAc/*n*-Hex 3:7); $[\alpha]_D^{23}$ −23.9 (*c* 1.9, $CHCl_3$); FTIR (microscope) ν_{max}: 3228, 1692, 1646, 1537 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.02 (br s, 1H), 7.46–6.96 (m, 11H), 5.84 (d, *J*=4.6 Hz, 1H), 5.69 (br s, 1H), 4.86 (s, 2H), 4.14 (d, *J*=9.6 Hz, 1H), 3.10 (dd, *J*=10.8, 3.9 Hz, 1H), 2.67 (d, *J*=4.6 Hz, 3H), 2.60–2.43 (m, 2H), 1.81–1.61 (m, 2H),1.58–1.39 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 172.9, 170.2, 163.8, 141.5, 134.8, 129.2, 128.8, 128.6, 128.3, 125.9, 123.2 (q, *J*=286.7 Hz), 78.3, 77.8 (q, *J*=28.9 Hz),

61.3, 48.2, 35.4, 34.5, 28.5, 27.1, 26.5, 26.0; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −76.4 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 552 [M+H$^+$] (12), 370 (19), 91 (99), 86 (100); HRMS *m/z* 551.2599 (calculated 551.2598, $C_{28}H_{36}F_3N_3O_5$).

Compound **13b**: white solid; R_f 0.44 (EtOAc/*n*-Hex 1:1); $[\alpha]_D^{23}$ −14.8 (*c* 1.6, $CHCl_3$); FTIR (microscope) ν_{max}: 3245, 1657, 1567, 1423 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.39 (br s, 1H), 7.48–7.02 (m, 13H), 6.84 (d, *J*=8.6 Hz, 2H), 5.49 (br s, 1H), 5.28 (br s, 1H), 4.93 (d, *J*=12.4 Hz, 1H), 4.87 (d, *J*=12.4 Hz, 1H), 4.06 (m, 1H), 3.77 (s, 3H), 3.05–2.93 (m, 2H), 2.81 (dd, *J*=13.7, 9.2 Hz, 1H), 2.60 (d, *J*=4.8 Hz, 3H), 2.58–2.47 (m, 2H), 1.82–1.57 (m, 2H), 1.55–1.43 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 172.6, 170.3, 163.5, 158.9, 141.5, 134.8, 130.3, 129.3, 128.9, 128.6, 128.4, 128.3, 128.2, 125.9, 123.1 (q, *J*=287.1 Hz), 114.3, 78.4 (q, *J*=27.8 Hz), 55.6, 55.3, 48.4, 37.6, 35.5, 28.8, 26.9, 26.2; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −76.9 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 616 [M+H$^+$] (18), 191 (100); HRMS *m/z* 615.2551 (calculated 615.2547, $C_{32}H_{36}F_3N_3O_6$).

Compound **13c**: white solid; R_f 0.24 (EtOAc/*n*-Hex 1:1); $[\alpha]_D^{23}$ −27.4 (*c* 1.9, $CHCl_3$); FTIR (microscope) ν_{max}: 3368, 1688, 1653, 1412 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.29 (br s, 1H), 7.68 (br s, 1H), 7.48–7.04 (m, 10H), 6.55 (br s, 1H), 5.61 (br s, 1H), 4.91 (m, 2H), 4.57 (br s, 1H), 4.12 (m, 1H), 3.23 (m, 1H), 3.09 (m, 1H), 2.97 (m, 1H), 2.73 (s, 3H), 2.63–2.49 (m, 2H), 1.71–1.55 (m, 7H), 1.47 (s, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 172.9, 171.6, 163.9, 156.8, 141.5, 134.5, 129.2, 128.5, 128.2, 125.8, 123.2 (q, *J*=288.5 Hz), 79.2, 77.5, 77.1 (q, *J*=28.5 Hz), 51.8, 47.3, 38.7, 35.2, 29.6, 29.3, 28.5, 28.3, 25.9, 25.8; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −76.3 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 653 [M+H$^+$] (5), 553 (40), 91 (100); HRMS *m/z* 652.3078 (calculated 652.3073, $C_{32}H_{43}F_3N_4O_7$).

Compound **19**: white solid; R_f 0.30 (EtOAc/*n*-Hex 1:1); $[\alpha]_D^{23}$ +11.7 (*c* 0.9, $CHCl_3$); FTIR (microscope): ν_{max}=3379, 1687, 1650, 1535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, *J*=8.6 Hz, 1H), 7.43–7.05 (m, 11H), 6.07 (br s, 1H), 6.01 (d, *J*=4.1 Hz, 1H), 4.81 (d, *J*=10.6 Hz, 1H), 4.75 (d, *J*=10.6 Hz, 1H), 4.05 (d, *J*=8.9 Hz, 1H), 3.01 (dd, *J*=11.3, 3.4 Hz, 1H), 2.56 (m, 5H), 2.02–1.50 (m, 4H), 0.99 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 170.3, 169.7, 168.1, 141.4, 134.6, 129.3, 128.9, 128.6, 128.4, 128.3, 126.0, 123.1 (q, *J*=287.1 Hz), 79.2 (q, *J*=27.7 Hz), 78.5, 62.2, 44.2, 35.6, 34.6, 29.7, 28.9, 26.7, 26.1; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −74.3 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 552 [M+H$^+$] (100).

3.10. Synthesis of hydroxamates 14a–c and 20. General procedure

To a solution of **13a** (50 mg, 0.09 mmol) in MeOH (5 mL), a catalytic amount of $Pd(OH)_2$/C was added and the reaction mixture was vigorously stirred under hydrogen atmosphere at rt for 1 h. The palladium powder was filtered over a Celite pad and the residue was washed with MeOH. The solvent was removed in vacuo and the residue was purified by FC ($CHCl_3$/MeOH 97:3), affording 36 mg of **14a** (87% yield), as a white solid: R_f 0.44 (EtOAc/*n*-Hex 1:1); $[\alpha]_D^{23}$ −29.6 (*c* 1.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.26–7.09 (m, 5H), 4.20 (s, 1H), 3.28 (m, 1H), 2.62 (s, 4H), 2.58–2.48 (m, 1H), 1.81–1.71 (m, 2H), 1.68–1.46 (m, 2H), 0.97 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 175.2, 173.6, 166.9, 144.1, 130.2, 130.1, 127.7, 125.8 (q, *J*=287.6 Hz), 80.5 (q, *J*=28.1 Hz), 64.9, 39.2, 37.5, 36.0, 30.8, 28.9, 28.0, 26.7; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −73.0 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 462 [M+H$^+$] (10), 91 (30), 86 (100); HRMS *m/z* 461.2131 (calculated 461.2130, $C_{21}H_{30}F_3N_3O_5$).

Compound **14b**: white solid; R_f 0.31 (EtOAc/*n*-Hex 7:3); $[\alpha]_D^{23}$ −17.4 (*c* 0.9, MeOH); FTIR (microscope): ν_{max}=3215, 1654, 1546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27–7.06 (m, 7H), 6.85 (d, *J*=8.7 Hz, 2H), 4.48 (t, *J*=7.4 Hz, 1H), 3.71 (s, 3H), 3.08 (dd, *J*=10.4, 4.1 Hz, 1H), 2.99 (dd, *J*=13.9, 7.7 Hz, 1H), 2.88 (dd, *J*=13.9, 7.4 Hz, 1H), 2.59 (s, 3H), 2.57–2.46 (m, 2H), 1.74–1.64 (m, 2H), 1.54–1.43 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 174.4, 173.9, 166.6, 160.7, 143.7, 131.8, 130.7, 129.9, 129.8, 127.4, 125.5 (q, *J*=285.9 Hz), 115.5, 80.1 (q, *J*=27.1 Hz), 57.2, 56.2, 38.6, 37.1, 30.9, 30.4, 28.3, 26.7; ^{19}F NMR (235.3 MHz, $CDCl_3$) δ: −73.4 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 526 [M+H$^+$] (5), 191 (100); HRMS *m/z* 525.2082 (calculated 525.2079, $C_{25}H_{30}F_3N_3O_6$).

Compound **14c**: white solid; R_f 0.22 (EtOAc/*n*-Hex 7:3); $[\alpha]_D^{23}$ −25.2 (*c* 1.9, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.28–7.07 (m, 5H), 4.38–4.27 (m, 1H), 3.20 (dd, *J*=10.9, 3.7 Hz, 1H), 3.11–2.96 (m, 2H), 2.66 (s, 3H), 2.64–2.51 (m, 2H), 1.85–1.55 (m, 6H), 1.47 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (62.9 MHz, CD_3OD) δ: 174.7, 174.4, 166.7, 158.8, 143.5, 129.7, 129.6, 127.1, 124.4 (q, *J*=286.7 Hz), 80.1, 79.7 (q, *J*=29.6 Hz), 62.4, 54.4, 40.9, 36.8, 30.5, 30.3, 29.1, 27.7, 27.4, 26.5; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −72.9 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 563 [M+H$^+$] (5), 114 (45), 91 (100); HRMS *m/z* 562.2600 (calculated 562.2605, $C_{25}H_{37}F_3N_4O_7$).

Compound **20**: white solid; R_f 0.24 (EtOAc/*n*-Hex 7:3); $[\alpha]_D^{23}$ +1.8 (*c* 0.9, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ: 7.29–7.07 (m, 5H), 4.15 (s, 1H), 2.86 (dd, *J*=11.4, 3.0 Hz, 1H), 2.70 (s, 3H), 2.69–2.62 (m, 2H), 2.61–1.51 (m, 4H), 0.97 (s, 9H); ^{13}C NMR (100.6 MHz, CD_3OD) δ: 172.4, 170.2, 168.3, 142.9, 129.4, 129.3, 126.8, 124.9 (q, *J*=286.7 Hz), 79.7 (q, *J*=26.9 Hz), 63.2, 46.7, 36.5, 35.5, 30.1, 27.4, 27.2, 26.1; ^{19}F NMR (235.3 MHz, CD_3OD) δ: −73.5 (s, 3F); MS (DIS EI 70 eV) *m/z* (%): 462 [M+H$^+$] (8), 446 (18), 99 (40), 86 (100).

3.11. X-ray structure analysis of 8x

A colorless crystal with approximate dimensions 0.25×0.3×0.4 mm was used. Hexagonal, space group $P6_5$, *a*=13.038(1), *b*=13.038(1), *c*=28.066(4) Å, *V*=4131.7(7) Å^3, *Z*=6, D_c=1.260 g cm^{-3}, μ=0.844 mm^{-1}, Bruker P4 diffractometer with graphite monochromated Cu Kα radiation (λ=1.54179 Å), $\omega/2\theta$ scan technique, room temperature, a total of reflections 6037 (2541 unique, R_{int}=0.072) collected up to 2θ=134.0°. The structure was solved by direct methods[18] and refined[19] against F^2, the amide and the hydroxyl hydrogen atoms were determined from Fourier difference maps and refined, as the other H atoms, in riding mode.

R_1=0.0414 (R_w=0.098) for 1952 observed reflections [$I \geq 2\sigma(I)$], 336 parameters refined, R_1=0.0585 (R_w=0.1074) for all data, goodness of fit=1.012, residual electron density of 0.164 and −0.118 e Å^{-3}. The value of the Flack index[20] is 0.0(3) for space group $P6_5$ and 0.2(3) for space group $P6_1$. Although hardly significant it points to the correct enantiomer that can be readily identified since L-alanine was used in the synthesis of **8x**.

3.12. Biological assays

3.12.1. Zymographic analysis. Tfm-hydroxamates **14a–c** and **20** were dissolved in EtOH to yield 10^{-1} M stock and further diluted in test solutions. Subconfluents human melanoma cells WM983A were incubated in serum free medium for 24 h. The conditioned medium containing pro-MMP-9 and pro-MMP-2 was then analyzed by zymography. Samples in 70 mM Tris–HCl pH 6.8, 10% glycerol, 2% SDS, and 0.01% bromophenol blue were applied to SDS–polyacrylamide (8%) gels co-polymerized with 1 mg/mL gelatin. After electrophoresis, gels were washed three times for 20 min with 2.5% Triton X-100 at room temperature and incubated overnight in 50 mM Tris–HCI, pH 7.5, 5 mM $CaCl_2$, 150 mM NaCl, and 0.02% Brij-35 at 37 °C in the presence or not of Tfm-hydroxamates. Gels were then stained with 0.5% Coomassie blue in 25% methanol and 10% acetic acid, and destained in the same solution without Coomassie blue. Gel images were acquired with a Duoscan T1200 scanner (AGFA), and the levels of MMPs were quantified by the Image-Pro Plus 4.1 program. The results were expressed in arbitrary units (IOD) and the IC_{50} was calculated.

3.13. Molecular modeling

Ab initio quantum chemical calculations on the active site models were performed using hybrid density functional theory (HDFT) at the B3LYP/6-31G* level,[21] using the GAMESS-USA program.[22] Geometries were fully optimized in vacuo, without any restraints.

Molecular dynamics simulations of the inhibitors were performed with the DYNAMO program[23] using a hybrid QM/MM description. Inhibitors **A** and **1** [R^1=$CH_2CH(CH_3)_2$, R^2=4-CH_3O–$C_6H_4CH_2$, R^3=CH_3] were fully solvated in a large box of water molecules and simulated in the NVT ensemble at 300 K for over 10 ns. The PM3 semiempirical method[24] was used to describe the hydroxamate and the neighboring P1 group (including –CH_3 or –CF_3) of the inhibitors. This was done in order to avoid any parametrization of these non-standard functional groups. The TIP3P water model and the OPLS-AA force field were used to describe the remaining atoms.[25] The interface between the MM and QM regions of the inhibitors was treated by the link-atom method.[23] The PM3 method including the recent re-parametrization for Zn by Merz and co-workers[24c] was used also to describe the protein active site (Zn^{2+} ion and the three hystidine rings) in our MD simulations of the protein-inhibitor complexes. The conformational free energy profiles (or potential of mean force) of the inhibitors in water were computed by umbrella sampling and subsequent WHAM analysis.[26] In particular, we applied harmonic restraints on one torsion angle, centered at values spaced by 30° [force constant 0.035 kJ/(mol deg^2), 1 ns MD simulations for each harmonic window].

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.036

References and notes

1. *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Books; American Chemical Society: Washington, DC, 1996.
2. Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, NY, 1994.
3. (a) Coussens, L. M.; Fingleton, B.; Matrisian, L. M. *Science* **2002**, *295*, 2387–2392; (b) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735–2776; (c) Bode, W.; Huber, R. *Biochim. Biophys. Acta* **2000**, *1477*, 241–252; (d) Giavazzi, R.; Taraboletti, G. *Crit. Rev. Oncol. Hematol.* **2001**, *37*, 53–60.
4. Becker, D. P.; DeCrescenzo, G.; Freskos, J.; Getman, D. P.; Hockerman, S. L.; Li, M.; Mehta, P.; Munie, G. E.; Swearingen, C. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2723–2725.
5. (a) Jacobson, I. C.; Reddy, P. G.; Wasserman, Z. R.; Hardman, K. D.; Covington, M. B.; Arner, E. C.; Copeland, R. A.; Decicco, C. P.; Magolda, R. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 837–842; (b) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263–8266.
6. However, it should be noted that the hydrogen bond involving the quaternary OH and the Glu-202 of MMP-3 is not present in the X-ray structure of the complex with the **A** analog having R^1=$CH_2CH(CH_3)_2$.
7. Humphrey, W.; Dalke, A.; Schulten, K. *J. Mol. Graphics* **1996**, *14*, 33–38.
8. Zanda, M. *New J. Chem.* **2004**, *28*, 1401–1411.
9. For a communication on this work see: Sani, M.; Belotti, D.; Giavazzi, R.; Panzeri, W.; Volonterio, A.; Zanda, M. *Tetrahedron Lett.* **2004**, *45*, 1611–1615.
10. Zucca, C.; Bravo, P.; Malpezzi, L.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2002**, *114*, 215–223.
11. (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902; (b) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591–594 and references therein; (c) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.—Eur. J.* **2002**, *8*, 37–44.

12. Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197–4198.
13. CCDC 601635 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposi@ccdc.cam.ac.uk).
14. Carpino, L. A.; El Faham, A. *J. Org. Chem.* **1995**, *60*, 3561–3564 and references therein.
15. Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2266.
16. (a) Gorecka, A.; Leplawy, M.; Zabrocki, J.; Zwierzak, A. *Synthesis* **1978**, 474–476. Contrary to the statement of these authors, $BrPO(OEt)_2$ undergoes rapid decomposition even at 4 °C, therefore it must be used within 1–2 h from its preparation. Our results are in agreement with an earlier report: (b) Goldwhite, H.; Saunders, B. C. *J. Chem. Soc.* **1955**, 3564.
17. For the addition of amine nucleophiles to β-lactones see: Nelson, S. G.; Spencer, K. L.; Cheung, W. S.; Mamie, S. J. *Tetrahedron* **2002**, *58*, 7081–7091.
18. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G. P.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
19. Sheldrick, G. M. *SHELXL-97. Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.
20. Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881.
21. (a) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, NY, 1986; (b) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, 2000.
22. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
23. (a) Field, M. J. *A Practical Introduction to the Simulation of Molecular Systems*; Cambridge University Press: Cambridge, 1999; (b) Field, M. J.; Albe, M.; Bret, C.; Proust-De Martin, F.; Thomas, A. *J. Comput. Chem.* **2000**, *21*, 1088–1100.
24. (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220; (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221–264; (c) Brothers, E. N.; Suarez, D.; Deerfield, D. W., II; Merz, K. M., Jr. *J. Comput. Chem.* **2004**, *25*, 1677–1692.
25. Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, *115*, 11225–11235.
26. Roux, B. *Comput. Phys. Commun.* **1995**, *91*, 275–282.

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Homonuclear Diels–Alder dimerization of 5-ethenyl-2-phenylsulfanyl-1*H*-imidazoles and its application to synthesis of 12,12′-dimethylageliferin

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Abstract—Homonuclear Diels–Alder dimerization of various 5-ethenyl-2-phenylsulfanyl-1*H*-imidazoles provided a novel highly regio- and stereoselective route to the preparation of multifunctionalized 4,5,6,7-tetrahydrobenzimidazoles, which is the basic skeleton of ageliferin, a biologically active pyrrole-imidazole marine alkaloid. The reaction was applied to the synthesis of 12,12′-dimethylageliferin.

1. Introduction

Recently, many types of biologically active pyrrole-imidazole alkaloids have been isolated from marine lives such as sponges, and they have become an important focus of scientific attention.[1,2] In 1990, ageliferins **1**–**3** were isolated from *Agelas* sponges and found to have various biological properties such as actomyosin ATPase,[3] antiviral, antibacterial,[4] and several other interesting activities.[5] The structural skeleton of **1**–**3** in Figure 1 has been considered to be biochemically synthesized through [4π+2π] cycloaddition[1b,3,4] of the simplest pyrrole-imidazole alkaloids, oroidin **4**[6] or/and hymenidin **5**.[7] We have investigated the total synthesis of several biologically active imidazole marine alkaloids,[8] and at this time our attention was focused on the asymmetric total synthesis of ageliferins via a biomimetic synthetic route. In this paper, we would like to present a highly regio- and stereoselective homonuclear Diels–Alder (DA) dimerization of various 5-ethenyl-2-phenylsulfanyl-1*H*-imidazoles **8**, **9**, and the first synthesis of a 12,12′-dimethyl derivative of ageliferin **22**.[9] In 2004, Baran and co-workers reported the total synthesis of **1** by microwave heating of sceptrin,[10] a pyrrole-imidazole alkaloid.[11]

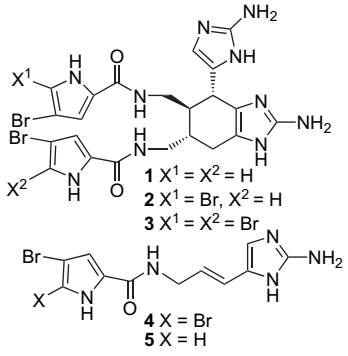

Figure 1.

2. Results and discussion

To examine the reactivity of 5(4)-ethenylimidazoles under thermal reaction conditions, various DA dimerization precursors, **8a**–**c** and **9a**–**f**, were prepared from 1,2-disubstituted imidazoles **6** as shown in Scheme 1.[12] Formylimidazoles **7** were prepared through 5-lithioimidazoles[13] and then converted to vinylimidazoles, **8a**–**c**, by Wittig reaction. *E*-Acrylates **9a**–**e** were prepared from **7** by applying Horner–Wadsworth–Emmons reaction.[14] The amide **9f** was obtained from the ester **9a**.

The result of DA dimerization of **8a**–**c** and **9a**–**f** is summarized in Table 1. The desired homonuclear DA dimerization of **8a**–**c** and **9a**,**b** proceeded successfully (entries 1–5). Although there have been several examples of intermolecular DA reactions of 4- or 5-ethenylimidazole derivatives as the diene component with active dienophiles such as *N*-phenylmaleimide or 4-phenyl-1,2,4-triazoline-3,5-dione,[15,16] homonuclear DA dimerization of imidazole derivatives has not been developed.

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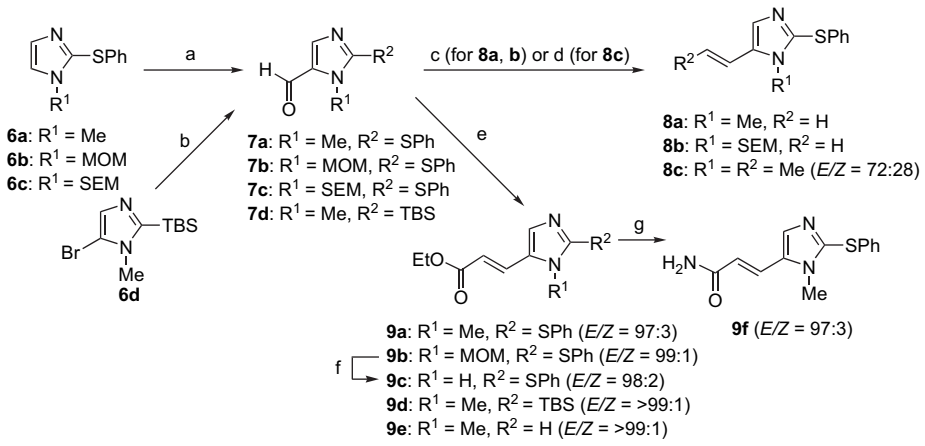
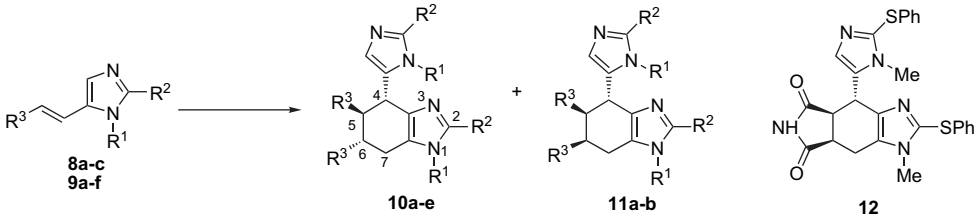


Scheme 1. Reagents and conditions: (a) LTMP, DMF, THF, DME, −78 °C, 98% (**7a**), 83% (**7b**), 95% (**7c**); (b) *n*-BuLi, DMF, THF, −78 °C, 58%; (c) *n*-BuLi, $Ph_3P^+MeBr^-$, THF, 0 °C to rt, 90% (**8a**), 77% (**8b**); (d) PhLi, $Ph_3P^+EtBr^-$, AcOH, *t*-BuOK, THF, Et_2O, −66 °C to rt, 92% (**8c**); (e) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, MeCN, rt, 99% (**9a**), 100% (**9b**), 86% (**9d**); (f) 10% HCl aq, EtOH, 60 °C, 71% (from **9b**); (g) NH_3, MeOH, rt, 59% (from **9a**).

Table 1. DA dimerization of the alkenyl imidazoles **8** and **9**



Entry	Starting Compd	Reaction condition[a]	Reaction time (h)	R^1	R^2	R^3	Yield (**10**+**11** or **12**) (%)[b]	Ratio (**10**/**11** or **12**)[c]	Product(s)
1	**8a**	A	30	Me	SPh	H	92	—	**10a**
2	**8b**	B	30	SEM	SPh	H	36	—	**10b**
3	**8c**	B	75	Me	SPh	Me	42	1:0	**10c**
4	**9a**	A	30	Me	SPh	CO_2Et	55	50:1	**10d/11a**
5	**9b**	C	60	MOM	SPh	CO_2Et	14[d]	4:1	**10e/11b**
6	**9c**	D	60	H	SPh	CO_2Et	0[e]	—	—
7	**9d**	D	60	Me	TBS	CO_2Et	0[e]	—	—
8	**9e**	D	60	Me	H	CO_2Et	0[d]	—	—
9	**9f**	D	30	Me	SPh	$CONH_2$	59	1:1.2	**10f/12**

[a] Reaction conditions: (A) refluxed in xylene at 140 °C; (B) neat in sealed tube at 150 °C; (C) neat in sealed tube at 100 °C; (D) neat in sealed tube at 120 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Starting material was mainly recovered.
[e] Decomposed.

Fortunately, we found that the plane and stereo structure of the major products **10c–e** were consistent with those of ageliferins.[17] Especially, the DA dimerization of **9a** proceeded in regio- and stereoselective fashion to give the multifunctionalized 4,5,6,7-tetrahydrobenzimidazole **10d** in 54% yield (entry 4). On the other hand, the reaction of **9c–e** gave no DA product (entries 6–8); this result shows that the presence of the alkyl group at the 1-position and the phenylsulfanyl group at the 2-position of the imidazole ring might be important for the DA dimerization of 5-ethenylimidazoles. The amide **9f** provided the DA dimerized product in relatively good yield (59%); however, the structure of the major product was imide **12** and unfortunately the undesired 5,6-*cis*-substituted 4,5,6,7-tetrahydrobenzimidazole.

We calculated the LUMO and HOMO energies and orbital coefficients of 5-[(2-methoxycarbonyl)ethenyl]-1-methyl-2-phenylsulfanyl-1*H*-imidazole **9g** as a model substrate using the MOPAC PM3 semiempirical method (Fig. 2, Table 2).[18] These results indicated that the ethyl acrylate **9a** might also react as both diene (C_4–C_5–C_6–C_7) and dienophile (C_6–C_7) in the homonuclear [4π+2π] cycloaddition to produce the desired product **10d**.

Next, we planned the synthesis of **16a**,**b** starting from diester **10d** as model compounds of the ageliferin analogue (Scheme 2). The diol **13** was obtained by $LiAlH_4$ reduction of the diester **10d** in 98% yield. Introduction of the nitrogen function into the side chain of the 5- and 6-position of the 4,5,6,7-tetrahydrobenzimidazole nucleus was achieved by Mitsunobu reaction, combination of DEAD, PPh_3, and phthalimide, to give the imide **14**. Removal of the phenylsulfanyl groups of **14** by desulfurization with a combination of $NiCl_2$ and $NaBH_4$[19] gave the 2,2′-unsubstituted derivative **15**

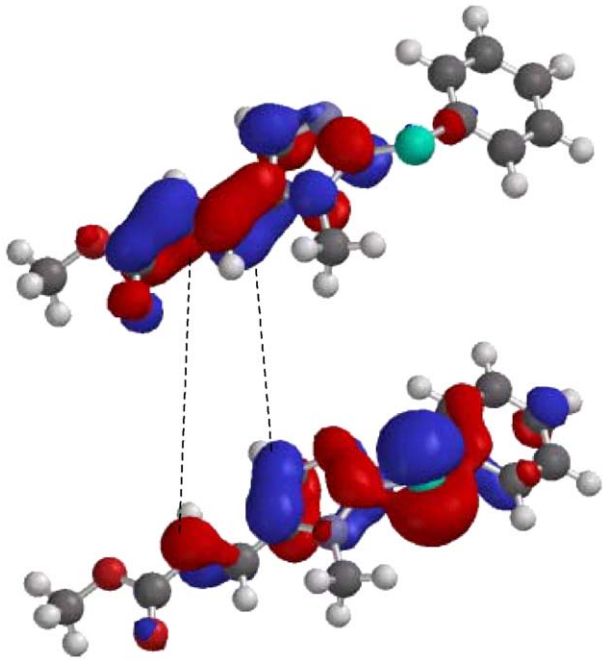


Figure 2. Approach of the LUMO (upper) to HOMO (lower) orbital of the methyl ester **9g**.

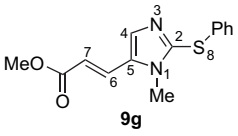
in 62% yield. Two-step conversion of **14** and **15** afforded the pyrrole-imidazole dimers **16a** and **b** in 49 and 72% yields, respectively.

Encouraged by this result, we then planned the synthesis of 12,12′-dimethylageliferin **24** (Scheme 3). The hydroxyl groups of **13** were protected by the TBDPS group to give the silyl ether **17** in 99% yield and the stereo structure of **17** was further confirmed by X-ray crystallographic analysis as shown in Figure 3.[20] After removal of the phenylsulfanyl groups of **17** by desulfurization with $NiCl_2$ and $NaBH_4$, introduction of azide groups into the 2- and 2′-position of the imidazole nucleus of **18** was achieved by lithiation with *sec*-BuLi followed by treatment with trisyl azide[21] to give the diazide **19** in 39% overall yield from **17**. The diazide **19** was hydrogenated over 5% Pd/C, and the resulting primary amino groups were protected with benzaldehyde to afford the diimine **20** followed by the removal of TBDPS groups by the action of CsF to give the diol **21** (42% in three steps). After several examinations for introduction of a nitrogen function by a substitution reaction of **21**, we found that the diazide compound **22** was obtained in excellent yield (95%) by the combination of DEAD, PPh_3, and DPPA.[22] The diazide **22** was converted to the corresponding diamine by selective reduction with PPh_3 in the presence of H_2O,[23] and then the diamine was acylated with 4-bromo-2-(trichloroacetyl)pyrrole[24] to give the protected ageliferin analogue **23** (21% yield in two steps). Finally, hydrolysis of the imino groups of **23** with dilute hydrochloric acid gave 12,12′-dimethylageliferin dihydrochloride **24** as powder.

3. Conclusion

We have successfully developed a convenient and efficient preparation method for the highly functionalized 4,5,6,7-tetrahydrobenzimidazole derivatives by novel homonuclear DA dimerization reactions of 5-alkenyl imidazoles with high regio- and stereoselectivity. And the method could be applied to the first synthesis of an ageliferin derivative **24**. We are currently investigating the scope of this reaction with various

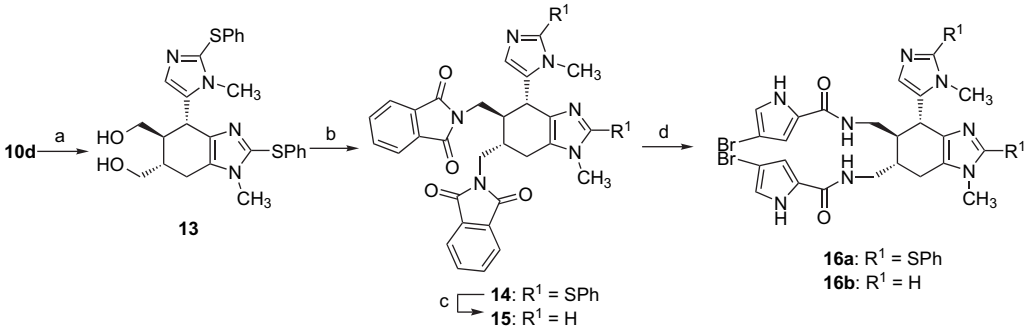
Table 2. The LUMO and HOMO energies and orbital coefficients of **9g**



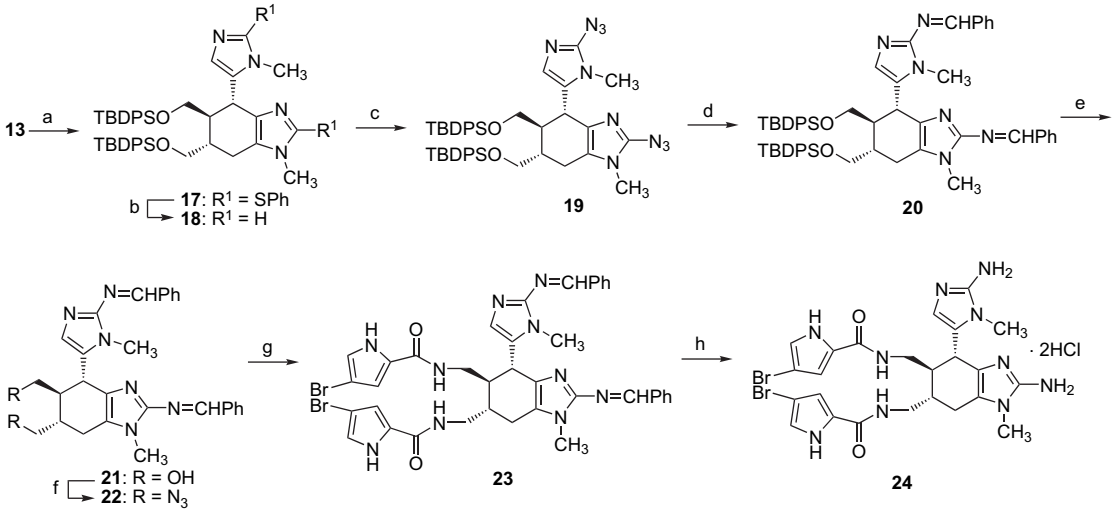
9g

	Energy (eV)	Coefficients of π-orbital at the atom positions							
		1[a]	2	3	4	5	6	7	8
LUMO	−0.9008	0.35	−0.34	0.08	0.31	−0.28	**−0.45**	**0.44**	0.12
HOMO	−8.7552	0.10	0.33	0.21	**−0.27**	−0.37	0.10	**0.27**	−0.49

[a] Position number.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, rt, 98%; (b) DEAD, PPh_3, phthalimide, THF, 0 °C–rt, 63%; (c) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, THF, MeOH, 0 °C–rt, 62%; (d) NH_2NH_2, 70 °C, then K_2CO_3, 4-bromo-2-(trichloroacetyl)pyrrole, DMAc, rt, 49% (**16a**), 72% (**16b**).



Scheme 3. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 99%; (b) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, THF, MeOH, 0 °C–rt, 70%; (c) *sec*-BuLi, trisyl azide, THF, DME, −40 °C to rt, 55%; (d) H_2, Pd/C, AcOEt, rt, then PhCHO, PhMe, reflux, 50%; (e) CsF, DMF, 100 °C, 83%; (f) DEAD, PPh_3, $(PhO)_2P(O)N_3$, THF, rt, 95%; (g) PPh_3, THF, H_2O, rt, then K_2CO_3, 4-bromo-2-(trichloroacetyl)pyrrole, DMAc, rt, 21%; (h) 0.5 M HCl aq, EtOH, rt, 76%.

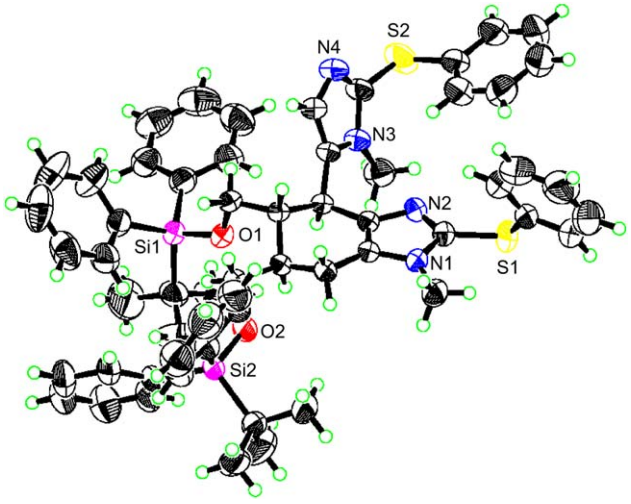


Figure 3. ORTEP plot of **17**.

imidazole substitution patterns and the asymmetric total synthesis of ageliferins (**1–3**) and their analogues.

4. Experimental

4.1. General

Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. IR spectra were taken with Shimadzu IR-435 spectrophotometer. NMR (^1H, ^{13}C) spectra were measured on Varian UNITY INOVA 400NB (^1H: 400 MHz, ^{13}C: 100 MHz) and the chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane as the internal standard (^1H) or referenced of solvent peak (^{13}C). MS and HRMS were measured on JEOL JMS BU-20 (EI) or JEOL JMS-SX 102A QQ (FAB) spectrometer. Silica gel (Merck Art. 7737) was used for column chromatography.

4.1.1. General procedure for 5-formylimidazoles (7a–c), synthesis of 5-formyl-1-methyl-2-phenylsulfanyl-1*H*-imidazole (7a) as an example. *n*-BuLi (1.6 M in *n*-hexane, 49.3 mL, 78.8 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (TMP) (13.3 mL, 78.8 mmol) in THF (50 mL) and DME (50 mL) under N_2 at −78 °C. After stirring for 30 min at the same temperature, a solution of **6a**[12a] (10.00 g, 52.56 mmol) in THF (50 mL) was added to the reaction mixture and the whole was stirred for 1 h at −78 °C. Then, DMF (6.10 mL, 78.8 mmol) was slowly added to the reaction mixture and the whole was stirred for 4 h at ambient temperature. H_2O (10 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (100 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a crystalline residue, which was purified by recrystallization from AcOEt/*n*-hexane to give **7a** as yellow needles (11.184 g, 98%); mp 57–58 °C; ^1H NMR ($CDCl_3$): δ 3.91 (3H, s, NCH_3), 7.32–7.42 (5H, m, Ph), 7.78 (1H, s, 4-H), 9.66 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 33.3, 128.4, 129.5, 130.1, 131.5, 133.2, 143.4, 149.6, 178.4; IR ($CHCl_3$): ν_{max} 2961, 2807, 1664, 1457, 1325, 1154, 1079 cm^{-1}; MS (EI): *m/z* 218 (M^+, 100), 190 (24), 148 (19), 136 (13), 121 (33), 109 (20), 91 (59), 77 (27); HRMS (EI) *m/z* 218.0509 (M^+) (requires $C_{11}H_{10}N_2OS$: 218.0514). Found: C, 60.29; H, 4.59; N, 12.73; $C_{11}H_{10}N_2OS$ requires C, 60.53; H, 4.62; N, 12.83.

4.1.2. 5-Formyl-1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazole (7b). Starting with **6b**[12b] (5.507 g, 25.00 mmol), *n*-BuLi (23.4 mL, 37.5 mmol), TMP (6.33 mL, 37.5 mmol), DMF (2.90 mL, 37.5 mmol), THF (48 mL), and DME (24 mL), **7b** was purified by column chromatography (AcOEt/*n*-hexane=1/3) and isolated as a yellow viscous oil (5.127 g, 83%); ^1H NMR ($CDCl_3$): δ 3.36 (3H, s, OCH_3), 5.78 (2H, s, NCH_2O), 7.38–7.55 (5H, m, Ph), 7.77 (1H, s, 4-H), 9.67 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 56.5, 75.5, 129.06, 129.13, 129.5, 132.85, 132.92, 144.2, 152.3, 178.2; IR ($CHCl_3$): ν_{max} 2972, 2807, 1663, 1473, 1439, 1333, 1149, 1116 cm^{-1}; MS (EI): *m/z* 248 (M^+, 100), 233 (31), 217 (43), 205 (72), 139 (33), 121 (82), 109 (31), 91 (41),

77 (43), 65 (29), 51 (37). HRMS (EI) *m/z* 248.0617 (M^+) (requires $C_{12}H_{12}N_2O_2S$: 248.0619).

4.1.3. 5-Formyl-1-1-[2-(trimethylsilyl)ethoxymethyl]-2-phenylsulfanyl-1*H*-imidazole (7c).[12e] Starting with **6c**[12c] (0.581 g, 1.90 mmol), *n*-BuLi (1.78 mL, 2.85 mmol), TMP (0.48 mL, 2.85 mmol), DMF (0.22 mL, 2.85 mmol), THF (3.6 mL), and DME (1.8 mL), **7c** was purified by column chromatography (AcOEt/*n*-hexane=1/3) and isolated as a yellow viscous oil (0.604 g, 95%); ^{1}H NMR ($CDCl_3$): δ −0.02 (9H, s, $SiMe_3$), 0.91 (2H, t, J=8.2 Hz, CH_2CH_2Si), 3.59 (2H, t, J=8.2 Hz, CH_2CH_2Si), 5.81 (2H, s, NCH_2O), 7.36–7.40 (3H, m, Ph), 7.52–7.54 (2H, m, Ph), 7.76 (1H, s, 4-H), 9.66 (1H, s, CHO).

4.1.4. 2-*tert*-Butyldimethylsilyl-5-formyl-1-methyl-1*H*-imidazole (7d). *n*-BuLi (3.13 mL, 5.00 mmol) was added to a stirred solution of **6d**[12d] (1.376 g, 5.00 mmol) in THF (5 mL) under N_2 at −78 °C. After stirring for 20 min at the same temperature, DMF (0.39 mL, 5.00 mmol) was added to the reaction mixture and the whole was stirred for 2 h at ambient temperature. H_2O (3 mL) was added to the mixture and after evaporation of the solvent the products were extracted with Et_2O (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/3) to give **7d** as a yellow viscous oil (652 mg, 58%); ^{1}H NMR ($CDCl_3$): δ 0.44 (6H, s, $SiMe_2$), 0.98 (9H, s, CMe_3), 4.02 (3H, s, NMe), 7.89 (1H, s, 4-H), 9.77 (1H, s, CHO); ^{13}C NMR ($CDCl_3$): δ −4.9, 17.7, 26.4, 34.8, 133.4, 144.5, 159.2, 179.1; IR ($CHCl_3$): ν_{max} 2934, 2830, 1667, 1459, 1250, 1145, 837, 808 cm^{-1}; MS (EI): *m/z* 224 (M^+, 3), 209 (8), 167 (100), 140 (12), 113 (3); HRMS (EI) *m/z* 224.1340 (M^+) (requires $C_{11}H_{20}N_2OSi$: 224.1345).

4.1.5. General procedure for 5-ethenylimidazoles (8a,b), synthesis of 1-methyl-2-phenylsulfanyl-5-ethenyl-1*H*-imidazole (8a) as an example. *n*-BuLi (3.13 mL, 5.00 mmol) was added to a stirred solution of methyltriphenylphosphonium bromide (1.79 g, 5.00 mmol) in THF (3 mL) under N_2 at 0 °C. After stirring for 1 h at the same temperature, a solution of **7a** (218 mg, 1.00 mmol) in THF (2 mL) was added to the reaction mixture and the whole was stirred for 6.5 h at ambient temperature. H_2O (3 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt) and recrystallized from AcOEt/*n*-hexane to give **8a** as yellow needles (195 mg, 90%); mp 59–62 °C; ^{1}H NMR ($CDCl_3$): δ 3.60 (3H, s, NCH_3), 5.30 (1H, dd, J=1.1, 11.4 Hz, C=C*H*H), 5.66 (1H, dd, J=1.1, 17.6 Hz, C=CH*H*), 6.48 (1H, ddd, J=0.7, 11.4, 17.6 Hz, *H*C=CH_2), 7.13–7.20 (3H, m, ArH), 7.23–7.28 (2H, m, ArH), 7.35 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 31.6, 115.7, 123.2, 126.6, 127.9, 128.0, 129.2, 134.4, 134.8, 138.5; IR ($CHCl_3$): ν_{max} 2960, 1722, 1473, 1440, 1389, 1243, 1213, 1041 cm^{-1}; MS (EI): *m/z* 216 (M^+, 100), 183 (14), 91 (20), 80 (12), 68 (10); HRMS (EI) *m/z* 216.0714 (M^+) (requires $C_{12}H_{12}N_2S$: 216.0721). Found: C, 66.65; H, 5.65; N, 12.75; $C_{12}H_{12}N_2S$ requires C, 66.63; H, 5.59; N, 12.95.

4.1.6. 1-[2-(Trimethylsilyl)ethoxymethyl]-2-phenylsulfanyl-5-ethenyl-1*H*-imidazole (8b). Starting with **7c** (600 mg, 1.79 mmol), *n*-BuLi (5.59 mL, 8.95 mmol), methyltriphenylphosphonium bromide (3.20 g, 8.95 mmol), and THF (9 mL), **8b** was purified by column chromatography (AcOEt/*n*-hexane=1/1) and isolated as a yellow viscous oil (459 mg, 77%); ^{1}H NMR ($CDCl_3$): δ −0.07 (9H, s, $SiMe_3$), 0.82 (2H, t, J=8.2 Hz, CH_2CH_2Si), 3.40 (2H, t, J=8.2 Hz, CH_2CH_2Si), 5.32 (1H, dd, J=1.1, 11.4 Hz, C=C*H*H), 5.43 (2H, s, NCH_2O), 5.72 (1H, dd, J=1.1, 17.8 Hz, C=CH*H*), 6.64 (1H, ddd, J=0.7, 11.4, 17.8 Hz, *H*C=CH_2), 7.16–7.28 (5H, m, Ph), 7.38 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ −1.5, 17.4, 66.1, 73.3, 116.1, 123.1, 126.8, 128.1, 128.4, 129.2, 134.4, 134.7, 138.9; IR ($CHCl_3$): ν_{max} 2935, 1246, 1172, 1088, 856, 834 cm^{-1}; MS (EI): *m/z* 332 (M^+, 31), 237 (23), 259 (26), 73 (100); HRMS (EI) *m/z* 332.1378 (M^+) (requires $C_{17}H_{24}N_2OSSi$: 332.1379).

4.1.7. 1-Methyl-2-phenylsulfanyl-5-(1-propenyl)-1*H*-imidazole (8c). PhLi (0.97 M in Et_2O/cyclohexane, 27.6 mL, 26.8 mmol) was added to a stirred solution of ethyltriphenylphosphonium bromide (9.95 g, 26.8 mmol) in THF (22.5 mL) and Et_2O (15 mL) under N_2 at 0 °C. The reaction mixture was cooled to −70 °C, and a solution of **7a** (2.925 mg, 13.40 mmol) in THF (15 mL) and Et_2O (12 mL) was added to it. Then, PhLi (13.8 mL, 13.4 mmol) was added to the mixture at −40 °C and the reaction temperature was elevated to −20 °C. AcOH (0.77 mL, 13.4 mmol) and *t*-BuOK (2.26 g, 20.1 mmol) were added to the reaction mixture and the whole was stirred for 2 h at ambient temperature. H_2O (3 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (30 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/1) to give **8c** (*E*/*Z*=72/28) as a yellow viscous oil (2.919 g, 95%). *E*-**8c**: ^{1}H NMR ($CDCl_3$): δ 1.89 (3H, t, J=2.8 Hz, C=CH*Me*), 3.56 (3H, s, NCH_3), 6.10–6.13 (1H, m, C=C*H*Me), 6.14–6.16 (1H, m, C*H*=CHMe), 7.11–7.27 (6H, m, Ph and 4-H); ^{13}C NMR ($CDCl_3$) δ: 18.7, 31.3, 117.4, 126.3, 126.7, 127.6, 128.6, 129.1, 134.6, 135.2, 137.1; IR ($CHCl_3$): ν_{max} 2934, 1579, 1474, 1478, 1395, 1097 cm^{-1}; MS (EI): *m/z* 230 (M^+, 100), 215 (52), 197 (11), 91 (13), 80 (15); HRMS (EI) *m/z* 230.0875 (M^+) (requires $C_{13}H_{14}N_2S$: 230.0878).

4.1.8. General procedure for 5-ethenylimidazoles (9a,b,d), synthesis of 5-[(2-ethoxycarbonyl)ethenyl]-1-methyl-2-phenylsulfanyl-1*H*-imidazole (9a) as an example. DBU (11.3 mL, 75.6 mmol) was added to a stirred solution of LiCl (3.20 g, 75.6 mmol) and triethyl phosphonoacetate (15.0 mL, 75.6 mmol) in CH_3CN (250 mL) under N_2 at 0 °C. After stirring for 10 min at the same temperature, **7a** (11.000 g, 50.39 mmol) was added to the reaction mixture and the whole was stirred for 5 h at ambient temperature. H_2O (10 mL) was added to the mixture and after evaporation of the solvent the products were extracted with AcOEt (100 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a crystalline residue, which was purified by recrystallization from AcOEt/*n*-hexane to give **9a** (*E*/*Z*=97/3) as colorless needles (14.083 g, 97%); mp 64–66 °C. *E*-**9a**: ^{1}H NMR ($CDCl_3$): δ 1.33 (3H, t, J=7.1 Hz, CH_2CH_3), 3.69 (3H, s, NCH_3), 4.26 (2H, q,

J=7.1 Hz, CH_2CH$_3$), 6.31 (1H, d, J=15.9 Hz, C=CHCO), 7.13–7.20 (5H, m, Ph), 7.48 (1H, dd, J=0.5, 15.9 Hz, CH=CHCO), 7.58 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 14.3, 32.0, 60.7, 117.2, 127.2, 129.0, 129.4, 129.5, 131.5, 132.2, 133.4, 142.5, 166.7; IR ($CHCl_3$): ν_{max} 2964, 1699, 1630, 1441, 1303, 1276, 1178, 1155 cm^{-1}; MS (EI): m/z 288 (M$^+$, 100), 259 (31), 243 (15), 215 (87), 121 (15), 109 (16), 91 (30), 80 (16), 65 (8), 51 (10); HRMS (EI) m/z 288.0930 (M$^+$) (requires $C_{15}H_{16}N_2O_2S$: 288.0932). Found: C, 62.66; H, 5.65; N, 9.69; $C_{15}H_{16}N_2O_2S$ requires C, 62.48; H, 5.59; N, 9.71.

4.1.9. 5-[(2-Ethoxycarbonyl)ethenyl]-1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazole (9b). Starting with **7b** (4.924 g, 19.83 mmol), DBU (4.4 mL, 29.7 mmol), LiCl (1.26 g, 29.7 mmol), triethyl phosphonoacetate (5.9 mL, 29.7 mmol), and CH_3CN (100 mL), **9b** was purified by column chromatography (AcOEt/*n*-hexane=1/3) and recrystallized from AcOEt/*n*-hexane as colorless needles (6.301 g, 100%, *E*/*Z*=99/1); mp 71–73 °C. *E*-**9b**: ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, J=7.1 Hz, CH_2CH_3), 3.22 (3H, s, OMe), 4.25 (q, 2H, J=7.1 Hz, CH_2CH$_3$), 5.47 (2H, s, NCH$_2$), 6.37 (1H, d, J=16.1 Hz, C=CHCO), 7.22–7.32 (5H, m, Ph), 7.58 (1H, dd, J=0.6, 15.9 Hz, CH=CHCO), 7.58 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 14.2, 56.1, 60.6, 75.1, 118.1, 127.5, 129.0, 129.3, 129.4, 131.4, 132.8, 132.9, 143.3, 166.6; IR ($CHCl_3$): ν_{max} 2961, 1699, 1629, 1477, 1366, 1303, 1182, 1148, 1110 cm^{-1}; MS (EI): m/z 318 (M$^+$, 100), 275 (20), 227 (26), 121 (20), 91 (14); HRMS (EI) m/z 318.1027 (M$^+$) (requires $C_{16}H_{18}N_2O_3S$: 318.1038). Found: C, 60.11; H, 5.80; N, 8.71; $C_{16}H_{18}N_2O_3S$ requires C, 60.36; H, 5.70; N, 8.80.

4.1.10. 2-*tert*-Butyldimethylsilyl-5-(2-ethoxycarbonylethenyl)-1-methyl-1*H*-imidazole (9d). Starting with **7d** (449 mg, 2.00 mmol), DBU (0.45 mL, 3.00 mmol), LiCl (127 mg, 3.00 mmol), triethyl phosphonoacetate (0.60 mL, 3.00 mmol), and CH_3CN (15 mL), **9d** was purified by column chromatography (AcOEt/*n*-hexane=1/1) and isolated as a yellow viscous oil (507 mg, 86%, *E*/*Z*=99/1). *E*-**9d**: ^{1}H NMR ($CDCl_3$): δ 0.33 (6H, s, SiMe$_2$), 0.87 (9H, s, CMe$_3$), 1.23 (3H, t, J=7.1 Hz, CH_2CH_3), 3.67 (3H, s, NMe), 4.14 (2H, q, J=7.1 Hz, CH_2CH$_3$), 6.20 (1H, d, J=15.9 Hz, C=CHCO), 7.46 (1H, d, J=15.9 Hz, CH=CHCO), 7.54 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ −4.8, 14.2, 17.7, 26.4, 32.9, 60.4, 116.2, 129.6, 131.0, 132.8, 154.4, 167.0; IR ($CHCl_3$): ν_{max} 2928, 1694, 1627, 1303, 1271, 1250, 1201, 1147 cm^{-1}; MS (EI): m/z 294 (M$^+$, 11), 279 (5), 249 (7), 237 (100), 165 (37), 135 (6), 113 (10), 75 (41), 59 (8); HRMS (EI) m/z 294.1764 (M$^+$) (requires $C_{15}H_{26}N_2O_2Si$: 294.1763).

4.1.11. 4-[(2-Ethoxycarbonyl)ethenyl]-2-phenylsulfanyl-1*H*-imidazole (9c). A solution of **9b** (200 mg, 0.63 mmol) in HCl aq (10%, 3 mL) and EtOH (3 mL) was heated at 60 °C for 2 h. The reaction mixture was basified by adding K_2CO_3 and the products were extracted with AcOEt (10 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt) to give **9c** as a yellow viscous oil (122 mg, 71%). *E*-**9c**: ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, J=7.1 Hz, CH_2CH_3), 4.18 (2H, q, J=7.1 Hz, CH_2CH$_3$), 6.34 (1H, d, J=15.9 Hz, C=CHCO), 7.14 (1H, s, 5-H), 7.15–7.22 (5H, m, Ph), 7.46 (1H, d, J=15.9 Hz, CH=CHCO), 11.99 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.2, 60.4, 116.2, 126.0, 127.5, 129.3, 129.9, 132.9, 133.7, 136.1, 141.3, 167.4; IR ($CHCl_3$): ν_{max} 3115, 3013, 2832, 1689, 1635, 1472, 1295, 1255, 1170, 972 cm^{-1}; MS (EI): m/z 274 (M$^+$, 100), 227 (47), 201 (40), 109 (19), 66 (10); HRMS (EI) m/z 274.0775 (M$^+$) (requires $C_{14}H_{14}N_2O_2S$: 274.0776).

4.1.12. 5-[(2-Carbamoyl)ethenyl]-1-methyl-2-phenylsulfanyl-1*H*-imidazole (9f). A solution of **9a** (507 mg, 1.76 mmol) in MeOH (3 mL, saturated with NH_3 gas) was stirred for 3 days at room temperature. After evaporation of the solvent, a crystalline residue was purified by recrystallization from MeOH to give **9f** as colorless prisms (270 mg, 59%); mp 142–145 °C. *E*-**9f**: ^{1}H NMR ($CDCl_3$): δ 3.66 (3H, s, NMe), 5.99 (1H, br s, NH$_2$), 6.15 (1H, br s, NH$_2$), 6.41 (1H, d, J=15.4 Hz, C=CHCO), 7.15–7.30 (5H, m, Ph), 7.47 (1H, d, J=15.4 Hz, CH=CHCO), 7.54 (1H, s, 4-H); ^{13}C NMR ($CDCl_3$): δ 31.8, 119.1, 127.2, 127.4, 128.8, 129.4, 130.9, 131.9, 133.5, 141.7, 167.3; IR ($CHCl_3$): ν_{max} 3291, 2971, 1672, 1627, 1594, 1443, 1399, 1345, 1288 cm^{-1}; MS (EI): m/z 259 (M$^+$, 100), 241 (6), 215 (40), 150 (10), 121 (12), 109 (8), 91 (17), 80 (12), 66 (7), 51 (7); HRMS (EI) m/z 259.0783 (M$^+$) (requires $C_{13}H_{13}N_3OS$: 259.0779). Found: C, 59.97; H, 5.24; N, 15.95; $C_{13}H_{13}N_3OS$ requires C, 60.21; H, 5.05; N, 16.20.

4.1.13. General procedure for 5-ethenylimidazoles (10–12), synthesis of 1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10a) as an example (condition A in Table 1). A solution of **8a** (50 mg, 0.23 mmol) in xylene (1 mL) was refluxed under N_2 for 30 h. After evaporation of the solvent, the crystalline residue was purified by preparative TLC (PTLC) (AcOEt/*n*-hexane=1/1) to give **10a** as a yellow amorphous (46 mg, 92%); ^{1}H NMR ($CDCl_3$): δ 1.83–2.02 (3H, m, 6-CH$_2$ and 5-H), 2.04–2.13 (1H, m, 5-H), 2.51–2.65 (2H, m, 7-CH$_2$), 3.50 (3H, s, NMe), 3.66 (3H, s, NMe), 4.10 (1H, t, J=4.4 Hz, 4-H), 6.73 (1H, d, J=0.5 Hz, 4′-H), 7.10–7.29 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 19.6, 21.1, 29.2, 30.9, 31.5, 32.1, 126.1, 126.4, 127.4, 127.7, 128.6, 129.1, 129.2, 130.8, 135.3, 135.6, 135.9, 136.9, 137.1, 137.9; IR ($CHCl_3$): ν_{max} 2925, 1474, 1439, 1174, 1092 cm^{-1}; MS (EI): m/z 432 (M$^+$, 100), 417 (3), 404 (5), 374 (11), 355 (7), 341 (46), 323 (10), 295 (14), 243 (10), 110 (7), 91 (5); HRMS (EI) m/z 432.1436 (M$^+$) (requires $C_{24}H_{24}N_4S_2$: 432.1442).

4.1.14. 2-Phenylsulfanyl-4-{2-phenylsulfanyl-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-imidazol-5-yl}-4,5,6,7-tetrahydro-1*H*-benzimidazole (10b). Starting with **8b** (33 mg, 0.10 mmol) by the reaction condition B, **10b** was isolated as a colorless viscous oil (12 mg, 36%); ^{1}H NMR ($CDCl_3$): δ −0.09 (9H, s, SiMe$_3$), −0.06 (s, 9H, SiMe$_3$), 0.80 (4H, m, 2×CH$_2$CH_2Si), 1.82–1.88 (2H, m, 6-CH$_2$), 2.17–2.27 (2H, m, 5-CH$_2$), 2.61–2.70 (2H, m, 7-CH$_2$), 3.31–3.42 (4H, m, 2×CH_2CH$_2$Si), 4.18 (1H, br t, J=5.3 Hz, 4-H), 5.22, 5.28 (1H each, each d, J=10.6 Hz, NCH$_2$), 5.30, 5.35 (1H each, each d, J=10.6 Hz, NCH$_2$), 6.91 (1H, d, J=0.7 Hz, 4′-H), 7.10–7.26 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ −1.5, −1.4, 17.7, 17.8, 19.9, 21.3, 30.1, 34.6, 66.1, 66.2, 73.3, 75.4, 122.3, 126.2, 126.3, 127.3, 127.5, 128.3, 129.1, 129.2, 135.7, 135.8, 136.0, 136.4, 139.4, 146.8;

IR ($CHCl_3$): ν_{max} 2930, 1244, 1220, 1170, 1086, 1023, 856, 834 cm^{-1}; MS (EI): *m/z* 664 (M^+, 100), 563 (15), 555 (25), 548 (21), 534 (11), 490 (13), 429 (10), 355 (9), 277 (6), 110 (25), 73 (46); HRMS (EI) *m/z* 664.2771 (M^+) (requires $C_{34}H_{48}N_4O_2S_2Si_2$: 664.2757).

4.1.15. (4*R,5*R**,6*R**)-1,5,6-Trimethyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10c).** Starting with **8c** (23 mg, 0.10 mmol) by the reaction condition B, **10c** was isolated as a yellow viscous oil (10 mg, 43%); ^1H NMR ($CDCl_3$): δ 1.02 (3H, d, J=6.4 Hz, 5-Me), 1.16 (3H, d, J=6.4 Hz, 6-Me), 1.66–1.84 (2H, m, 5- and 6-H), 2.31 (1H, ddd, J=2.4, 10.4, 15.9 Hz, 7-H), 2.66 (1H, ddd, J=1.1, 5.1, 15.9 Hz, 7-H), 3.46 (3H, s, NMe), 3.52 (3H, s, NMe), 3.69 (1H, br d, J=10.1 Hz, 4-H), 7.00 (1H, s, 4′-H), 7.02–7.26 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 17.1, 19.9, 30.0, 30.9, 32.1, 35.7, 41.1, 41.2, 125.8, 126.3, 126.8, 127.7, 128.9, 129.1×2, 129.2, 135.3, 135.9, 136.1, 136.7, 136.8, 138.1; IR ($CHCl_3$): ν_{max} 3044, 1579, 1474, 1447, 1371, 1092 cm^{-1}; MS (EI): *m/z* 460 (M^+, 73), 445 (8), 404 (48), 369 (15), 327 (9), 295 (100), 230 (10), 202 (10), 150 (8), 109 (9), 91 (10), 77 (9); HRMS (EI) *m/z* 460.1764 (M^+) (requires $C_{26}H_{28}N_4S_2$: 460.1755).

4.1.16. (4*R,5*S**,6*S**)-5,6-Bis(ethoxycarbonyl)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10d) and (4*R**,5*S**,6*R**)-5,6-bis(ethoxycarbonyl)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (11a).** Starting with **9a** (29 mg, 0.10 mmol) by the reaction condition A, a mixture of **10d** and **11a** (16 mg, 55%, **10d/11a**=50/1) was obtained and **10d** was isolated from the second fraction as a yellow amorphous and **11a** was isolated from the first fraction as a yellow viscous oil. Compound **10d**; ^1H NMR ($CDCl_3$): δ 1.15 (3H, t, J=7.1 Hz, CH_2CH_3), 1.20 (3H, t, J=7.1 Hz, CH_2CH_3), 2.94–3.04 (2H, m, 7-CH_2), 3.25–3.39 (2H, m, 5- and 6-H), 3.51 (3H, s, NMe), 3.57 (3H, s, NMe), 3.96–4.14 (4H, m, 2×CH_2CH_3), 4.49 (1H, br d, J=8.2 Hz, 4-H), 6.86 (1H, s, 4′-H), 7.09–7.24 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 13.95, 14.01, 22.9, 31.2, 31.9, 35.9, 41.8, 47.8, 61.2, 61.4, 126.1, 126.6, 127.3, 127.6, 128.0, 129.1, 129.2, 129.7, 133.8, 134.6, 135.4, 135.5, 137.7, 137.8, 172.3, 172.6; IR ($CHCl_3$): ν_{max} 3017, 1725, 1474, 1447, 1368, 1266, 1229, 1177, 1091, 1032 cm^{-1}; MS (EI): *m/z* 576 (M^+, 100), 531 (7), 503 (93), 429 (20), 404 (47), 295 (61), 241 (12), 191 (9), 150 (8), 110 (12), 91 (12), 77 (12); HRMS (EI) *m/z* 576.1859 (M^+) (requires $C_{30}H_{32}N_4O_4S_2$: 576.1865). Compound **11a**: ^1H NMR ($CDCl_3$): δ 1.22 (3H, t, J=7.1 Hz, CH_2CH_3), 1.27 (3H, t, J=7.1 Hz, CH_2CH_3), 2.99 (1H, dd, J=5.0, 14.5 Hz, 7-H), 3.06–3.11 (1H, m, 6-H), 3.16 (1H, ddd, J=0.9, 10.4, 14.7 Hz, 7-H), 3.37 (1H, dd, J=2.0, 2.9 Hz, 5-H), 3.54 (3H, s, NMe), 3.75 (3H, s, NMe), 4.10–4.25 (4H, m, 2×CH_2CH_3), 4.71 (1H, br t, J=0.8 Hz, 4-H), 6.55 (1H, d, J=0.6 Hz, 4′-H), 7.10–7.29 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.1, 20.8, 31.1, 31.3, 34.2, 36.9, 46.1, 61.2, 61.3, 126.5, 126.6, 127.81, 127.87, 129.19, 129.25, 129.27, 129.6, 134.2, 134.66, 134.68, 136.4, 137.8, 138.4, 170.9, 172.3; IR ($CHCl_3$): ν_{max} 2949, 1723, 1579, 1474, 1446, 1367, 1264, 1022 cm^{-1}; MS (EI): *m/z* 576 (M^+, 81), 503 (100), 429 (26), 404 (25), 295 (51), 241 (14), 217 (10), 191 (19), 110 (18), 91 (14), 77 (10), 57 (8); HRMS (EI) *m/z* 576.1866 (M^+) (requires $C_{30}H_{32}N_4O_4S_2$: 576.1865).

4.1.17. (4*R,5*S**,6*S**)-5,6-Bis(ethoxycarbonyl)-1-methoxymethyl-4-(1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10e) and (4*R**,5*S**,6*R**)-5,6-bis(ethoxycarbonyl)-1-methoxymethyl-4-(1-methoxymethyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (11b).** Starting with **9b** (57 mg, 0.18 mmol) by the reaction condition C, a mixture of **10e** and **11b** (8 mg, 14%, **10e/11b**=4/1) was obtained by PTLC ($CHCl_3$/MeOH=20/1) and **10e** was isolated from the second fraction as a yellow viscous oil and **11b** was isolated from the first fraction as a yellow viscous oil. Compound **10e**: ^1H NMR ($CDCl_3$): δ 1.16 (3H, t, J=7.1 Hz, CH_2CH_3), 1.20 (3H, t, J=7.1 Hz, CH_2CH_3), 3.05 (2H, dd, J=1.3, 7.5 Hz, 7-CH_2), 3.14 (3H, s, OMe), 3.19 (3H, s, OMe), 3.30–3.36 (1H, m, 6-H), 3.59 (1H, dd, J=8.4, 9.2 Hz, 5-H), 3.96–4.15 (4H, m, 2×CH_2CH_3), 4.67 (1H, d, J=8.4 Hz, 4-H), 5.19 (1H, br s, NC*H*H), 5.28 and 5.33 (1H each, each d, J=10.8 Hz, NCH_2O), 5.61 (1H, br d, J=10.8 Hz, NCH*H*), 6.93 (1H, s, 4′-H), 7.11–7.23 (10H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 14.0, 14.1, 22.7, 35.4, 41.8, 47.4, 55.7, 56.0, 61.1, 61.3, 75.3, 75.7, 126.5, 126.9, 127.7, 127.9, 128.3, 129.18, 129.22, 130.5, 134.0, 134.6, 135.1, 136.2, 138.4, 139.0, 172.4, 172.7; MS (EI): *m/z* 636 (M^+, 100), 621 (20), 604 (91), 591 (50), 563 (43), 531 (30), 513 (13), 485 (27), 441 (12), 413 (23), 323 (9), 239 (8), 121 (9), 91 (7); HRMS (EI) *m/z* 636.2079 (M^+) (requires $C_{32}H_{36}N_4O_6S_2$: 636.2076). Compound **11b**: ^1H NMR ($CDCl_3$): δ 1.19 (3H, t, J=7.1 Hz, CH_2CH_3), 1.25 (3H, t, J=7.1 Hz, CH_2CH_3), 3.04–3.19 (3H, m, 6-H and 7-CH_2), 3.14 (3H, s, OMe), 3.33 (3H, s, OMe), 3.81 (1H, br t, J=2.2 Hz, 5-H), 4.09–4.24 (4H, m, 2×CH_2CH_3), 4.85 (1H, br t, J=0.9 Hz, 4-H), 5.30 and 5.35 (1H each, each d, J=10.6 Hz, NCH_2O), 5.51 and 5.57 (1H each, each d, J=11.1 Hz, NCH_2O), 6.55 (1H, s, 4′-H), 7.15–7.38 (10H, m, Ph).

4.1.18. (4*R,5*S**,6*S**)-5,6-Dicarbamoyl-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (10f) and (4*R**,5*S**,6*S**)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole-5,6-dicarboxamide (12).** Starting with **9f** (52 mg, 0.20 mmol) by the reaction condition D, **10f** was isolated from the second fraction as a yellow viscous oil (14 mg, 27%) and **12** was isolated from the first fraction as a yellow viscous oil (16 mg, 32%). Compound **10f**: ^1H NMR (CD_3OD): δ 2.94–2.98 (2H, m, 7-CH_2), 3.02 (1H, t, J=10.8 Hz, 5-H), 3.13 (1H, dt, J=5.9, 10.8 Hz, 6-H), 3.53 (3H, s, NMe), 3.56 (3H, s, NMe), 4.43 (1H, d, J=10.4 Hz, 4-H), 6.99 (1H, s, 4′-H), 7.06–7.28 (10H, m, Ph); ^{13}C NMR (CD_3OD): δ 18.2, 25.7, 31.7, 32.6, 37.3, 45.4, 115.3, 127.5, 128.0, 128.2, 129.1×2, 130.5, 130.6, 134.1, 135.9, 136.4, 137.7, 138.7, 141.6, 176.8, 177.5; IR (KBr): ν_{max} 3316, 3199, 2905, 1667, 1630, 1591, 1450 cm^{-1}; HRMS (FAB) *m/z* 519.1629 $(M+H)^+$ (requires $C_{26}H_{27}N_6O_2S_2$: 519.1637). Compound **12**: ^1H NMR ($CDCl_3$): δ 2.97 (1H, dd, J=7.4, 16.0 Hz, 7-H), 3.27 (1H, dd, J=1.4, 16.0 Hz, 7-H), 3.50 (3H, s, NCH_3), 3.52–3.62 (2H, m, 5- and 6-H), 3.80 (3H, s, NCH_3), 4.80 (1H, br s, 4-H), 6.71 (1H, d, J=0.6 Hz, 4′-H), 7.06–7.28 (10H, m, Ph), 8.51 (1H, br s, NH); ^{13}C NMR

($CDCl_3$): δ 20.6, 31.3, 31.9, 33.1, 40.5, 46.5, 126.1, 126.8, 126.9, 127.4, 128.1, 128.2, 129.3, 129.4, 134.3×2, 135.5, 135.8, 137.8, 156.5, 177.2, 178.6; IR ($CHCl_3$): ν_{max} 3126, 2928, 1776, 1714, 1578, 1473, 1437, 1347 cm^{-1}; MS (EI): *m/z* 501 (M^+, 100), 429 (10), 404 (27), 295 (27), 142 (25), 110 (16), 77 (6); HRMS (EI) *m/z* 501.1289 (M^+) (requires $C_{26}H_{23}N_5O_2S_2$: 501.1293).

4.1.19. (4*R,5*R**,6*S**)-5,6-Bis(hydroxymethyl)-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (13).** Lithium aluminum hydride (602 mg, 15.9 mmol) was added to a stirred solution of **10d** (3.000 g, 5.20 mmol) in THF (30 mL) under N_2 at 0 °C. After stirring for 21 min at ambient temperature, saturated $NaHCO_3$ aq (20 mL) was added to the mixture and after evaporation of the solvent the products were extracted with $CHCl_3$ (100 mL×3). The organic layer was dried over Na_2SO_4 and evaporated to give a crystalline residue, which was purified by recrystallization from EtOH/Et_2O to give **13** as colorless powder (2.522 g, 98%); mp 119–123 °C; ^1H NMR (DMSO-d_6): δ 1.93–2.00 (1H, m, 5-H), 2.07–2.15 (1H, m, 6-H), 2.59 (1H, ddd, *J*=2.0, 10.1, 16.3 Hz, 7-H), 2.74 (1H, dd, *J*=5.5, 15.6 Hz, 7-H), 3.30–3.35 (1H, m, C*H*$_2$OH), 3.48 (3H, s, NMe), 3.55 (3H, s, NMe), 3.62–3.65 (3H, m, C*H*$_2$OH), 4.15 (1H, br d, *J*=9.3 Hz, 4-H), 4.65 (1H, t, *J*=5.0 Hz, OH), 4.70 (1H, t, *J*=5.0 Hz, OH), 6.83 (1H, s, 4′-H), 6.97–7.28 (10H, m, Ph); ^{13}C NMR (DMSO-d_6): δ 23.3, 30.8, 31.7, 33.5, 37.3, 42.4, 58.9, 62.4, 126.0, 126.1, 126.3, 126.7, 128.1, 129.35, 129.40, 130.0, 133.9, 134.7, 135.6, 135.9, 137.3, 137.7; IR (KBr): ν_{max} 3371, 2874, 1474, 1448, 1386, 736 cm^{-1}; MS (EI): *m/z* 492 (M^+, 62), 461 (29), 404 (49), 295 (100), 241 (20), 191 (11), 150 (12), 109 (15), 77 (19), 51 (7); HRMS (EI) *m/z* 492.1667 (M^+) (requires $C_{26}H_{28}N_4O_2S_2$: 492.1653). Found: C, 63.11; H, 5.84; N, 11.16; $C_{26}H_{28}N_4O_2S_2$ requires C, 63.39; H, 5.73; N, 11.37.

4.1.20. (4*R,5*R**,6*S**)-5,6-Bis[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (14).** DEAD (40% in toluene, 1.28 mL, 2.94 mmol) was added to a stirred solution of **13** (181 mg, 0.37 mmol), triphenylphosphine (771 mg, 2.94 mmol), and phthalimide (433 mg, 2.94 mmol) in THF (2 mL) under N_2 at 0 °C. The reaction mixture was stirred for 18 h at ambient temperature. HCl aq (10%, 1 mL) was added to the mixture and the aqueous phase was washed with AcOEt (10 mL×2), basified by K_2CO_3, and extracted with AcOEt (10 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/1) and recrystallization from AcOEt/*n*-hexane gave **14** as colorless needles (174 mg, 63%); mp 124–125 °C; ^1H NMR ($CDCl_3$): δ 2.30–2.35 (1H, m, 6-H), 2.58 (1H, dd, *J*=3.3, 16.5 Hz, 7-H), 2.73–2.78 (1H, m, 5-H), 2.95 (1H, dd, *J*=5.7, 16.5 Hz, 7-H), 3.23 (1H, dd, *J*=2.7, 13.8 Hz, NCH_2), 3.56 (3H, s, NMe), 3.79 (3H, s, NMe), 3.86 (1H, dd, *J*=5.3, 14.1 Hz, NCH_2), 3.94 (1H, dd, *J*=9.8, 14.1 Hz, NCH_2), 3.97 (1H, dd, *J*=11.0, 13.8 Hz, NCH_2), 4.10 (1H, d, *J*=1.5 Hz, 4-H), 6.76 (1H, d, *J*=0.9 Hz, 4′-H), 7.01–7.31 (10H, m, Ar), 7.67–7.84 (8H, m, Ar); ^{13}C NMR ($CDCl_3$): δ 20.8, 31.2, 31.6, 35.0, 35.2, 41.1×2, 41.2, 123.3, 123.4, 126.1, 126.4, 127.4, 127.6, 128.1, 129.2×2, 129.3, 131.6, 131.7, 133.7, 134.1, 134.3, 135.3×2, 136.9, 137.65, 137.69, 168.3, 168.5; IR ($CHCl_3$): ν_{max} 2919, 1708, 1375, 1354, 1174, 1092 cm^{-1}; MS (EI): *m/z* 750 (M^+, 14), 590 (100), 429 (21), 403 (6), 295 (16), 254 (9), 181 (13), 131 (15), 110 (38), 91 (14), 69 (42), 57 (19); HRMS (EI) *m/z* 750.2069 (M^+) (requires $C_{42}H_{34}N_6O_4S_2$: 750.2083). Found: C, 66.73; H, 4.82; N, 10.81; $C_{42}H_{34}N_6O_4S_2\cdot 1/3H_2O$ requires C, 66.65; H, 4.62; N, 11.10.

4.1.21. General procedure for 15 and 18 by desulfurization, synthesis of (4*R,5*R**,6*S**)-5,6-bis[(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)methyl]-1-methyl-4-(1-methyl-1*H*-imidazol-5-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (15) as an example.** $NaBH_4$ (45 mg, 1.18 mmol) was added to a stirred solution of **14** (45 mg, 0.060 mmol) and $NiCl_2\cdot 6H_2O$ (21 mg, 0.89 mmol) in THF (2 mL) and MeOH (6 mL) under N_2 at 0 °C. The reaction mixture was stirred for 1 h at ambient temperature. HCl aq (36%, 2 mL) was added to the mixture and the whole was stirred for 10 min and was basified by 28% NH_3 aq. The products were extracted with AcOEt (20 mL×5). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH=5/1) to give **15** as a colorless amorphous (20 mg, 62%); ^1H NMR (CD_3OD): δ 2.38–2.46 (1H, m, 6-H), 2.55 (1H, dd, *J*=3.6, 16.4 Hz, 7-H), 2.72–2.78 (1H, m, 5-H), 2.90 (1H, dd, *J*=5.8, 16.6 Hz, 7-H), 3.23 (1H, dd, *J*=3.6, 13.8 Hz, NCH_2), 3.60 (3H, s, NMe), 3.79 (3H, s, NMe), 3.81–3.89 (3H, m, NCH_2), 4.06 (1H, br s, 4-H), 6.44 (1H, s, 4′-H), 7.54 (1H, s, 2′-H), 7.62 (1H, s, 2-H), 7.71–7.80 (8H, m, Ar). ^{13}C NMR (CD_3OD): δ 30.1, 31.5, 32.4, 34.9, 36.3, 41.8, 41.9, 42.3, 124.1, 124.2, 126.4, 127.1, 128.2, 128.5, 130.5, 133.1, 135.4, 135.5, 138.9, 139.3, 169.87, 169.93; IR (KBr): ν_{max} 3365, 2908, 1763, 1702, 1395, 1357, 715 cm^{-1}; MS (EI): *m/z* 534 (M^+, 12), 374 (100), 213 (11), 187 (21), 160 (12), 132 (9), 104 (7), 77 (7); HRMS (EI) *m/z* 534.2027 (M^+) (requires $C_{30}H_{26}N_6O_4$: 534.2015).

4.1.22. General procedure for pyrrole-imidazole dimmers (16a,b), synthesis of (4*R,5*R**,6*S**)-5,6-bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (16a) as an example.** A solution of **14** (57 mg, 0.08 mmol) in hydrazine monohydrate (3 mL) was heated at 70 °C under N_2 for 9 h. After evaporation of the solvent, the residue was dissolved in DMAc (3 mL). 4-Bromo-2-(trichloroacetyl)pyrrole[24] (177 mg, 0.61 mmol) and K_2CO_3 (84 mg, 0.61 mmol) were added to the reaction mixture and the whole was stirred for 3 h at room temperature. After evaporation of the solvent, H_2O (1 mL) was added and the products were extracted with $CHCl_3$ (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography ($CHCl_3$/MeOH=10/1) to give **16a** as a yellow amorphous (31 mg, 49%); ^1H NMR (CD_3OD): δ 2.35–2.43 (2H, m, 5- and 6-H), 2.61 (1H, dd, *J*=4.5, 16.5 Hz, 7-H), 2.84 (1H, dd, *J*=5.2, 16.4 Hz, 7-H), 3.29–3.34 (2H, m, NCH_2), 3.39 (1H, dd, *J*=5.9, 14.1 Hz, NCH_2), 3.53 (3H, s, NMe), 3.55 (3H, s, NMe), 3.66 (1H, dd, *J*=4.8, 14.1 Hz, NCH_2), 4.08 (1H, d, *J*=4.6 Hz, 4-H), 6.76 (1H, d, *J*=1.5 Hz, pyrrole), 6.82 (1H, d, *J*=1.5 Hz, pyrrole), 6.83 (1H, s, 4′-H), 6.90 (1H, d, *J*=1.5 Hz, pyrrole), 6.91 (1H, d, *J*=1.6 Hz,

pyrrole), 7.04–7.25 (m, 10H, Ph); ^{13}C NMR (CD_3OD): δ 23.0, 31.6, 32.5, 35.7, 37.8, 41.9, 43.0, 43.6, 97.5, 97.6, 113.3, 113.7, 114.1, 122.9, 123.1, 127.3, 127.4, 127.6, 127.9, 128.4, 128.8, 129.7, 130.5×2, 131.1, 135.7, 136.1, 136.3, 138.4, 139.0, 162.7, 162.8; IR (KBr): ν_{max} 3392, 2973, 1629, 1577, 1449, 1380, 1318, 919 cm^{-1}; HRMS (FAB) *m/z* 833.0703 (M+H)$^+$ (requires $C_{36}H_{35}Br_2N_8O_2S_2$: 833.0691).

4.1.23. (4*R,5*R**,6*S**)-5,6-Bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4-(1-methyl-1*H*-imidazol-5-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (16b).** Starting with **15** (49 mg, 0.09 mmol), hydrazine monohydrate (3 mL), DMAc (3 mL), 4-bromo-2-(trichloroacetyl)-pyrrole[24] (213 mg, 0.73 mmol), and K_2CO_3 (101 mg, 0.73 mmol), **16b** was purified by column chromatography ($CHCl_3$/MeOH=5/1) and isolated as a colorless amorphous (41 mg, 72%); ^{1}H NMR (CD_3OD): δ 2.29–2.36 (2H, m, 5- and 6-H), 2.57 (1H, dd, *J*=4.6, 16.7 Hz, 7-H), 2.82 (1H, dd, *J*=4.2, 13.6 Hz, 7-H), 3.34–3.40 (3H, m, NCH_2), 3.55 (3H, s, NMe), 3.57 (3H, s, NMe), 3.65 (1H, dd, *J*=4.0, 13.9 Hz, NCH_2), 3.98 (1H, d, *J*=4.2 Hz, 4-H), 6.61 (1H, s, 4′-H), 6.77 (1H, d, *J*=1.5 Hz, pyrrole), 6.84 (1H, d, *J*=1.6 Hz, pyrrole), 6.91 (1H, d, *J*=1.6 Hz, pyrrole), 6.93 (1H, d, *J*=1.5 Hz, pyrrole), 7.50 (2H, s, 2- and 2′-H); ^{13}C NMR (CD_3OD): δ 21.3, 31.4, 32.2, 35.5, 38.4, 41.8, 43.4, 43.5, 97.47, 97.54, 113.3, 113.7, 122.9, 123.0, 126.7, 127.40, 127.43, 128.1, 134.7, 135.1, 138.5, 139.4, 162.7, 162.8; IR (KBr): ν_{max} 3371, 3262, 2937, 1723, 1622, 1271, 1119 cm^{-1}; HRMS (FAB) *m/z* 617.0627 (M+H)$^+$ (requires $C_{24}H_{27}Br_2N_8O_2$: 617.0624).

4.1.24. (4*R,5*R**,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)-methyl]-1-methyl-4-(1-methyl-2-phenylsulfanyl-1*H*-imidazol-5-yl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (17).** TBDPSCl (2.54 mL, 9.76 mmol) was added to a solution of **12** (2.186 g, 4.44 mmol) and imidazole (1.51 g, 22.19 mmol) in DMF (5 mL). After stirring for 7 h at room temperature, saturated $NaHCO_3$ aq (3 mL) was added to the reaction mixture and the products were extracted with Et_2O (20 mL×2). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (AcOEt/*n*-hexane=1/3) to give **17** as a colorless amorphous (4.261 g, 99%); ^{1}H NMR ($CDCl_3$): δ 0.99 (9H, s, CMe_3), 1.02 (9H, s, CMe_3), 2.17–2.23 (1H, m, 5- or 6-H), 2.39–2.47 (1H, m, 5- or 6-H), 2.55 (2H, br d, *J*=6.6 Hz, 7-CH_2), 3.40 (3H, s, NMe), 3.46 (3H, s, NMe), 3.69–3.84 (4H, m, 2×OCH_2), 4.31 (1H, br d, *J*=6.2 Hz, 4-H), 6.65 (1H, s, 4′-H), 7.01–7.42 (22H, m, Ph), 7.44–7.61 (8H, m, Ph); ^{13}C NMR ($CDCl_3$) δ: 19.28, 19.32, 23.0, 26.9×2, 30.8, 31.8, 33.6, 37.4, 42.0, 62.2, 65.1, 125.8, 126.4, 126.8, 127.7, 127.9, 128.6, 128.9, 129.10, 129.13, 129.69, 129.74, 129.8, 133.07, 133.12, 133.4, 133.5, 135.2, 135.4, 135.51, 135.53, 135.9, 136.3, 136.6, 136.8, 136.9; IR ($CHCl_3$): ν_{max} 2916, 1467, 1437, 1100 cm^{-1}; HRMS (FAB) *m/z* 969.4097 (M+H)$^+$ (requires $C_{58}H_{65}N_4O_2S_2Si_2$: 969.4087).

4.1.25. (4*R,5*R**,6*S**)-5,6-Bis[(*tert*-butyldiphenylsiloxy)-methyl]-1-methyl-4-(1-methyl-1*H*-imidazol-5-yl)-4,5,6,7-tetrahydro-1*H*-benzimidazole (18).** Starting with **17** (485 mg, 0.50 mmol), $NiCl_2\cdot 6H_2O$ (1.663 g, 7.00 mmol), $NaBH_4$ (794 mg, 21.00 mmol), THF (15 mL), and MeOH (45 mL), **18** was purified by PTLC ($CHCl_3$/MeOH=20/1) and isolated as a colorless amorphous (263 mg, 70%); ^{1}H NMR ($CDCl_3$): δ 0.99 (9H, s, CMe_3), 1.04 (9H, s, CMe_3), 2.11 (1H, br t, *J*=9.9 Hz, 5-H), 2.38–2.47 (1H, m, 6-H), 2.53 (1H, dd, *J*=1.8, 15.4 Hz, 7-H), 2.60 (1H, dd, *J*=5.9, 15.2 Hz, 7-H), 3.44 (3H, s, NMe), 3.46 (3H, s, NMe), 3.76 (2H, d, *J*=2.6 Hz, 5-CH_2O), 3.84 (1H, dd, *J*=4.9, 10.3 Hz, 6-CH_2O), 3.88 (1H, dd, *J*=3.3, 10.4 Hz, 6-CH_2O), 4.24 (1H, br d, *J*=9.7 Hz, 4-H), 6.55 (1H, s, 4′-H), 7.19–7.55 (18H, m, Ph), 7.57–7.62 (4H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 19.28, 19.30, 22.7, 26.7, 26.9, 30.8, 31.8, 32.6, 37.5, 42.2, 61.3, 65.0, 125.0, 126.4, 127.56, 127.59, 127.62, 129.6, 129.7, 132.7, 133.19, 133.22, 133.4, 133.6, 135.4, 135.5, 135.6, 136.4, 136.7, 137.8; IR (KBr): ν_{max} 3339, 2908, 1498, 1466, 1445, 1105, 820 cm^{-1}; MS (EI): *m/z* 752 (M$^+$, 53), 695 (8), 483 (100), 319 (7), 263 (10), 213 (17), 159 (9), 135 (33), 95 (10), 57 (6); HRMS (EI) *m/z* 752.3941 (M$^+$) (requires $C_{46}H_{56}N_4O_2Si_2$: 752.3941).

4.1.26. (4*R,5*R**,6*S**)-2-Azido-4-(2-azido-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(*tert*-butyldiphenylsiloxy)methyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (19).** *sec*-BuLi (1.0 M in cyclohexane, 3.4 mL, 3.4 mmol) was added to a stirred solution of **18** (855 mg, 1.14 mmol) in THF (6 mL) and DME (6 mL) under N_2 at −40 °C. After stirring for 10 min at the same temperature, trisyl azide (738 mg, 2.39 mmol) was added to the reaction mixture and the whole was stirred for 30 min at −40 °C. H_2O (1 mL) was added to the mixture and after evaporation of the solvent the products were extracted with $CHCl_3$ (20 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give a crystalline residue, which was purified by column chromatography ($CHCl_3$/MeOH=50/1) to give **19** as a yellow amorphous (521 mg, 55%); ^{1}H NMR ($CDCl_3$): δ 0.99 (9H, s, CMe_3), 1.02 (9H, s, CMe_3), 2.11–2.17 (1H, m, 5-H), 2.34–2.40 (1H, m, 6-H), 2.45–2.48 (2H, m, 7-CH_2), 3.21 (3H, s, NMe), 3.23 (3H, s, NMe), 3.72 (2H, d, *J*=2.6 Hz, 5-CH_2O), 3.78 (1H, dd, *J*=5.9, 10.3 Hz, 6-CH_2O), 3.83 (1H, dd, *J*=3.9, 10.2 Hz, 6-CH_2O), 4.07 (1H, br d, *J*=8.6 Hz, 4-H), 6.35 (1H, d, *J*=0.5 Hz, 4′-H), 7.24–7.44 (12H, m, Ph), 7.46–7.49 (4H, m, Ph), 7.56–7.59 (4H, m, Ph); IR ($CHCl_3$): ν_{max} 2933, 2126, 1482, 1108 cm^{-1}; HRMS (FAB) *m/z* 835.4042 (M+H)$^+$ (requires $C_{46}H_{55}N_{10}O_2Si_2$: 835.4048).

4.1.27. (4*R,5*R**,6*S**)-2-Benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(*tert*-butyldiphenylsiloxy)methyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (20).** A mixture of **19** (142 mg, 0.17 mmol) and Pd/C (10%, 100 mg) in AcOEt (3 mL) was stirred under H_2 (1 atm) for 12 h at room temperature. Pd/C was removed by filtration, the filtrate was evaporated, and the residue was dissolved in toluene (1 mL). Benzaldehyde (0.04 mL, 0.42 mmol) was added to the mixture and the whole was refluxed for 8 h. After evaporation of the solvent, the residue was purified by column chromatography (AcOEt/*n*-hexane=1/3) to give **20** as a yellow amorphous (81 mg, 50%); ^{1}H NMR ($CDCl_3$): δ 1.02 (9H, s, CMe_3), 1.03 (9H, s, CMe_3), 2.26–2.32 (1H, m, 5-H), 2.42–2.51 (1H, m, 6-H), 2.63 (2H, d, *J*=7.0 Hz, 7-CH_2), 3.61 (3H, s, NMe), 3.63 (3H, s, NMe), 3.78–3.85 (4H, m, 2×CH_2O), 4.34 (1H, d, *J*=8.2 Hz, 4-H), 6.54 (1H, s, 4′-H), 7.23–7.61 (26H, m, Ph), 7.89–7.96 (4H, m, Ph), 9.09 (1H, s, NC*H*Ph), 9.19 (1H, s, NC*H*Ph); ^{13}C NMR ($CDCl_3$): δ 19.31, 19.34, 22.6, 26.9, 27.0, 28.8, 29.8, 33.4, 37.4, 42.1, 62.3, 65.2, 125.75,

125.81, 127.6, 128.6, 128.7, 128.81, 128.83, 129.65, 129.68, 129.70, 131.19, 131.22, 133.2, 133.4, 133.5, 133.7, 134.0, 135.50, 135.58, 135.60, 136.3, 136.4, 149.4, 150.0, 158.1, 158.2; IR ($CHCl_3$): ν_{max} 2910, 1606, 1468, 1423, 1108 cm^{-1}; HRMS (FAB) *m/z* 959.4860 $(M+H)^+$ (requires $C_{60}H_{67}N_6O_2Si_2$: 959.4864).

4.1.28. (4*R,5*R**,6*S**)-2-Benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis(hydroxymethyl)-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (21).** CsF (16 mg, 0.11 mmol) was added to a solution of **20** (10 mg, 0.01 mmol) in DMF (0.1 mL) and the whole was stirred at 80 °C for 9 h. After evaporation of the solvent, the residue was purified by PTLC ($CHCl_3$/MeOH=5/1) and recrystallization from MeOH gave **21** as yellow powder (4 mg, 83%); mp 273–274 °C; ^1H NMR ($CDCl_3$, CD_3OD): δ 1.99–2.05 (1H, m, 5-H), 2.26 (1H, ddd, *J*=4.8, 9.5, 14.5 Hz, 6-H), 2.67–2.82 (2H, m, 7-CH_2), 3.59 (1H, dd, *J*=3.7, 11.5 Hz, CH_2O), 3.69 (3H, s, NMe), 3.71 (3H, s, NMe), 3.77–3.87 (3H, m, CH_2O), 4.20 (1H, d, *J*=9.3 Hz, 4-H), 6.77 (1H, s, 4′-H), 7.42–7.53 (6H, m, Ph), 7.83–7.98 (4H, m, Ph), 8.94 (1H, s, NC*H*Ph), 9.04 (1H, s, NC*H*Ph); ^{13}C NMR ($CDCl_3$, CD_3OD): δ 22.6, 28.3, 29.2, 33.3, 37.8, 44.6, 60.0, 63.6, 125.0, 126.1, 128.18, 128.22, 128.36, 128.42, 131.2, 131.3, 133.1, 133.2, 135.5×2, 149.1, 149.4, 158.8, 159.0; IR ($CHCl_3$): ν_{max} 2909, 1722, 1369, 1239, 1209, 1041 cm^{-1}; HRMS (FAB) *m/z* 483.2513 $(M+H)^+$ (requires $C_{28}H_{31}N_6O_2$: 483.2508). Found: C, 69.46; H, 6.41; N, 17.24; $C_{28}H_{30}N_6O_2$ requires C, 69.69; H, 6.27; N, 17.41.

4.1.29. (4*R,5*R**,6*S**)-5,6-Bis(azidomethyl)-2-benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (22).** DEAD (40% in toluene, 0.18 mL, 0.42 mmol) was added to a stirred solution of **21** (48 mg, 0.10 mmol), triphenylphosphine (107 mg, 0.41 mmol), and DPPA (0.107 mL, 0.50 mmol) in THF (1 mL) under N_2 at 0 °C. After stirring for 1.5 h, the solvent was evaporated and saturated $NaHCO_3$ aq (1 mL) was added to the residue, the products were extracted with $CHCl_3$ (10 mL×3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give an oily residue, which was purified by PTLC (AcOEt) to give **22** as a yellow amorphous (50 mg, 95%); ^1H NMR ($CDCl_3$): δ 2.13–2.19 (1H, m, 5- or 6-H), 2.27–2.36 (1H, m, 5- or 6-H), 2.69 (1H, ddd, *J*=1.8, 9.0, 15.9 Hz, 7-H), 2.77 (1H, ddd, *J*=1.1, 5.7, 16.1 Hz, 7-H), 3.58–3.65 (4H, m, 2×CH_2N_3), 3.67 (3H, s, NMe), 3.70 (3H, s, NMe), 4.17 (1H, d, *J*=8.4 Hz, 4-H), 6.81 (1H, s, 4′-H), 7.39–7.58 (6H, m, Ph), 7.88–7.97 (4H, m, Ph), 9.08 (1H, s, NC*H*Ph), 9.23 (1H, s, NC*H*Ph); ^{13}C NMR ($CDCl_3$): δ 23.8, 29.0, 30.0, 34.7, 35.9, 41.2, 51.0, 54.1, 125.5, 126.3, 128.6, 128.7, 128.87, 128.92, 131.4, 131.5, 131.9, 133.4, 136.0, 136.1, 149.9, 150.6, 158.9, 159.0; IR ($CHCl_3$): ν_{max} 2916, 2089, 1476, 1420, 1266, 961 cm^{-1}; MS (EI): *m/z* 532 (M^+, 63), 504 (17), 490 (21), 419 (50), 394 (39), 292 (31), 250 (60), 236 (100), 170 (31), 145 (29), 94 (59), 77 (46); HRMS (EI) *m/z* 532.2573 (M^+) (requires $C_{28}H_{28}N_{12}$: 532.2559).

4.1.30. (4*R,5*R**,6*S**)-2-Benzylidenamino-4-(2-benzylidenamino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (23).** Triphenylphosphine (56 mg, 0.21 mmol) and 1 drop of H_2O were added to a stirred solution of **22** (50 mg, 0.09 mmol) in THF (0.5 mL) and the whole was stirred for 1.5 h at room temperature. After evaporation of the solvent, the residue was dissolved in DMAc (0.5 mL). 4-Bromo-2-(trichloroacetyl)pyrrole[24] (164 mg, 0.56 mmol) and K_2CO_3 (78 mg, 0.56 mmol) were added to the reaction mixture and the whole was stirred for 3 h at room temperature. K_2CO_3 was removed by filtration and the filtrate was evaporated to give an oily residue, which was purified by PTLC ($CHCl_3$/MeOH=10/1) to give **23** as a yellow amorphous (16 mg, 21%); ^1H NMR (CD_3OD): δ 2.37–2.42 (1H, m, 5- or 6-H), 2.46–2.52 (1H, m, 5- or 6-H), 2.66 (1H, dd, *J*=6.0, 17.2 Hz, 7-H), 2.89–2.94 (1H, m, 7-H), 3.42–3.47 (3H, m, NCH_2), 3.65–3.71 (1H, m, NCH_2), 3.68 (3H, s, NMe), 3.70 (3H, s, NMe), 4.06 (1H, br d, *J*=5.3 Hz, 4-H), 6.70 (1H, s, 4′-H), 6.77 (1H, d, *J*=1.5 Hz, pyrrole), 6.81 (1H, d, *J*=1.5 Hz, pyrrole), 6.86 (1H, d, *J*=1.5 Hz, pyrrole), 6.90 (1H, d, *J*=1.5 Hz, pyrrole), 7.43–7.53 (6H, m, Ph), 7.89–7.95 (4H, m, Ph), 8.94 (2H, s, NC*H*Ph); ^{13}C NMR (CD_3OD): δ 21.3, 29.5, 30.3, 35.5, 37.8, 38.4, 42.9, 43.4, 97.5×2, 113.3, 113.6, 122.9, 123.0, 127.3, 127.4, 127.5, 129.88, 129.93, 129.97, 130.08, 130.17, 130.21, 132.9, 133.1, 135.4, 137.36, 137.40, 151.2×2, 160.9×2, 162.7, 162.8; IR (KBr): ν_{max} 3340, 2903, 1617, 1583, 1317 cm^{-1}; HRMS (FAB) *m/z* 823.1465 $(M+H)^+$ (requires $C_{38}H_{37}Br_2N_{10}O_2$: 823.1468).

4.1.31. (4*R,5*R**,6*S**)-2-Amino-4-(2-amino-1-methyl-1*H*-imidazol-5-yl)-5,6-bis[(4-bromo-1*H*-pyrrol-2-yl)-carbonylaminomethyl]-1-methyl-4,5,6,7-tetrahydro-1*H*-benzimidazole (24) (12,12′-dimethylageliferin).** A solution of **23** (6 mg, 0.007 mmol) in EtOH (0.5 mL) and HCl (0.5 M, 0.5 mL) was stirred for 30 min at room temperature. After evaporation of the solvent, the residue was washed with AcOEt (10 mL) and dried to give **24** as a yellow amorphous (4 mg, 76%); ^1H NMR (CD_3OD): δ 2.37–2.44 (1H, m, 5- or 6-H), 2.44–2.50 (1H, m, 5- or 6-H), 2.55 (1H, br d, *J*=17.0 Hz, 7-H), 2.75 (1H, dd, *J*=17.0, 5.0 Hz, 7-H), 3.406 (3H, s, NMe), 3.414 (3H, s, NMe), 3.42–3.49 (2H, m, NCH_2), 3.56 (1H, dd, *J*=9.5, 5.1 Hz, NCH_2), 3.67 (1H, dd, *J*=9.5, 4.2 Hz, NCH_2), 3.95 (1H, br s, 4-H), 6.73 (1H, br s, 4′-H), 6.83 (1H, d, *J*=1.5 Hz, pyrrole), 6.90 (1H, d, *J*=1.5 Hz, pyrrole), 6.92 (1H, d, *J*=1.5 Hz, pyrrole), 6.95 (1H, d, *J*=1.5 Hz, pyrrole); IR (KBr): ν_{max} 3285, 2993, 1659, 1634 cm^{-1}; HRMS (FAB) *m/z* 647.0839 $(M+H)^+$ (requires $C_{24}H_{29}Br_2N_{10}O_2$: 647.0842).

4.2. X-ray crystallography

4.2.1. Compound 17. *Crystal data*: $C_{58}H_{64}N_4O_2S_2Si_2$, *M*=969.46, triclinic, *a*=14.419(7), *b*=14.670(3), *c*=13.487(5) Å, α=101.91(2)°, β=102.32(4)°, γ=82.14(2)°; *V*=2714(1) Å^3; *Z*=2, μ(Cu Kα)=16.53 cm^{-1}; *T*=296 K; *R*1=0.075 for 8620 observations, space group *P*-1(#2).

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References and notes

1. For reviews, see: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753; (b) Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237; (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 417.
2. (a) Jacquot, D. E. N.; Zoellinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295; (b) Travert, N.; Martin, M.-T.; Bourguet-Kondracki, M.-L.; Al-Mourabit, A. *Tetrahedron Lett.* **2005**, *46*, 249; (c) Lindel, T.; Breckle, G.; Hochgürtel, M.; Volk, C.; Grube, A.; Köck, M. *Tetrahedron Lett.* **2004**, *45*, 8149; (d) Travert, N.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2004**, *126*, 10252; (e) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623; (f) Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett.* **2002**, *4*, 2645; (g) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060; (h) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699; (i) Wiese, K. J.; Yakushijin, K.; Horne, D. A. *Tetrahedron Lett.* **2002**, *43*, 5135; (j) Fresneda, P. M.; Molina, P.; Sanz, M. A. *Tetrahedron Lett.* **2001**, *42*, 851; (k) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574.
3. Kobayashi, J.; Tsuda, M.; Murayama, T.; Nakamura, H.; Ohizumi, Y.; Ishibashi, M.; Iwamura, M.; Ohta, T.; Nozoe, S. *Tetrahedron* **1990**, *46*, 5579.
4. Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G., Jr.; Rittechof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965.
5. (a) Assmann, M.; Lichte, E.; Pawlik, J. R.; Köck, M. *Mar. Ecol.: Prog. Ser.* **2000**, *207*, 255; (b) Eder, C.; Proksch, P.; Wray, V.; van Soest, R. W. M.; Ferdinandus, E.; Pattisina, L. A.; Sudarsono. *J. Nat. Prod.* **1999**, *62*, 1295; (c) Vassas, A.; Bourdy, G.; Paillard, J. J.; Lavayre, J.; Païs, M.; Quirion, J. C.; Debitus, C. *Planta Med.* **1996**, *62*, 28.
6. Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *J. Chem. Soc., Chem. Commun.* **1971**, 1129.
7. Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176.
8. (a) Nakamura, S.; Kawasaki, I.; Yamashita, M.; Ohta, S. *Heterocycles* **2003**, *60*, 583; (b) Nakamura, S.; Kawasaki, I.; Kunimura, M.; Matsui, M.; Noma, Y.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1061; (c) Kawasaki, I.; Nakamura, S.; Yanagitani, S.; Kakuno, A.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3095; (d) Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. *Heterocycles* **2000**, *53*, 1939; (e) Ohta, S.; Tsuno, N.; Maeda, K.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I. *Tetrahedron Lett.* **2000**, *41*, 4623; (f) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887; (g) Kawasaki, I.; Taguchi, N.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1997**, *45*, 1393; (h) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull.* **1996**, *44*, 1831; (i) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycl. Commun.* **1996**, *2*, 189; (j) Kawasaki, I.; Taguchi, N.; Yoneda, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1996**, *43*, 1375; (k) Kawasaki, I.; Taguchi, N.; Yamamoto, T.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 8251; (l) Kawasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085.
9. Kawasaki, I.; Sakaguchi, N.; Fukushima, N.; Fujioka, N.; Nikaido, F.; Yamashita, M.; Ohta, S. *Tetrahedron Lett.* **2002**, *43*, 4377.
10. (a) Baran, P. S.; O'Malley, D. P.; Mitsos, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 249; (b) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674.
11. Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772.
12. Compound **6a** (a), **6b** (b), **6c** (c), **6d** (d), **7c** (e), and **9e** (f) were known compounds. See: (a) Ohta, S.; Yamamoto, T.; Kawasaki, I.; Yamashita, M.; Katsuma, H.; Nasako, R.; Kobayashi, K.; Ogawa, K. *Chem. Pharm. Bull.* **1992**, *40*, 2681; (b) Tang, C. C.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918; (c) Nakamura, S.; Tsuno, N.; Yamashita, M.; Kawasaki, I.; Ohta, S.; Ohishi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 429; (d) Azami, H.; Barrett, D.; Tanaka, A.; Sasaki, H.; Matsuda, K.; Sakurai, M.; Matsumoto, Y.; Tawara, S.; Chiba, T.; Sakane, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1409; (e) Lipshutz, B. H.; Huff, B.; Hagen, W. T. *Tetrahedron Lett.* **1988**, *29*, 3411; (f) Sakamoto, T.; Nagata, H.; Kondo, Y.; Shiraiwa, M.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 823.
13. Ohta, S.; Yamamoto, T.; Kawasaki, I.; Yamashita, M.; Nagashima, Y.; Yoshikawa, T. *Chem. Pharm. Bull.* **1994**, *42*, 821.
14. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1995**, *36*, 8251.
15. (a) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319; (b) Deghati, P. Y. F.; Wanner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1998**, *39*, 4561; (c) Walters, M. A.; Lee, M. D. *Tetrahedron Lett.* **1994**, *35*, 8307.
16. Intramolecular DA reaction of 4-vinylimidazoles was reported, Ref. 2e.
17. The structure of **10a** was confirmed by HMBC experiment, and the regio- and stereochemistry of **10c–d** and **11a** were determined by HMBC and NOESY experiments.
18. Hehre, W. J. *SPARTAN, version 2.0*; Wavefunction: Irvine, CA, 1999.
19. Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993**, *58*, 2407.
20. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited at the Cambridge Crystallographic Data Centre as a supplementary number CCDC 616563. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
21. Lindel, T.; Hochgürtel, M. *J. Org. Chem.* **2000**, *65*, 2806.
22. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.
23. Knouzi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr.* **1985**, 815.
24. Bélanger, P. *Tetrahedron Lett.* **1979**, 2505.

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Synthesis of aminimides derived from oleic acid: a new family of drag-reducing surfactants

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Abstract—Large-scale syntheses of aminimide surfactants that serve as low temperature drag-reducing agents in ethylene glycol–water mixtures are described. Preliminary drag reduction results are presented and the susceptibility of the surfactants to methanolysis is discussed.

1. Introduction

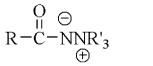
Addition of small amounts of materials to turbulent flow systems can reduce the pressure drop over a range of turbulent flow rates. This phenomenon is called drag reduction (DR).[1] Surfactant DR additives are of interest because they can be used to save pumping energy in district cooling systems wherein fluids are circulated through a closed loop (for example in buildings in large airports, urban districts, college campuses, and in hotel complexes). Such systems are widely used in the US and in Japan.

Surfactants constitute one family of DR additive.[2] These materials have the advantage over polymeric DR additives that they can recover from mechanical degradation by self-assembling into micelle structures responsible for DR.[3] Though cationic surfactants have been widely studied as DR additives and are effective, they are not easily biodegradable and could be an environmental hazard in case of a spill or leak into a stream, river or lake. Therefore, more easily biodegraded zwitterionic surfactants are of interest for use as drag-reducing additives. Aminimides derived from fatty acids (**1**) (Fig. 1) constitute a family of zwitterionic surfactants that have been used as detergents and adhesives, but never evaluated as DR additives.[4] We have examined the use of these materials as DR additives with some success in ethylene glycol (EG)–water. This article describes scaleable procedures for the preparation of these materials, presents preliminary results of DR studies in EG–water, and describes stability studies that reveal some new chemistry of aminimides.

2. Synthesis of aminimides

Aminimides derived from carboxylic acids have been prepared by two principle methods: (1) alkylation of the basic nitrogen of acylhydrazides[5] and (2) acylation of trialkylammonium amides with appropriate carboxylic acid derivatives.[6] The former method was used in what appears to be the first preparation of an aminimide surfactant[7] and the latter method has been used to prepare aminimides derived from fatty acids as long ago as 1972.[8] Our studies adopted the former method because it seemed to have the greatest flexibility for the preparation of a series of aminimides and it also seemed the most amenable to scale-up using simple laboratory equipment.

Scheme 1 outlines the preparation of seven aminimides based on a simple two-reaction sequence. Thus, treatment of commercially available oleoyl chloride (**2**) with slightly over 1 equiv of *N*,*N*-dimethylhydrazine in the presence of



1 R = fatty acid chain

Figure 1. Structure of aminimide surfactants.

Keywords: Aminimides; *N*-Acylhydrazides; District cooling; Drag reduction; Methanolysis.
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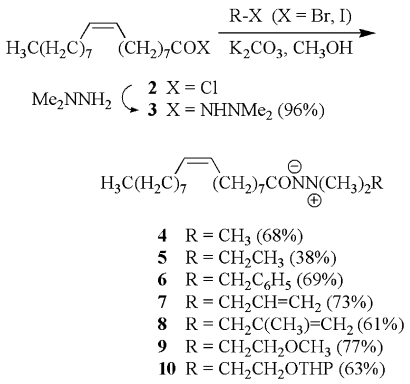
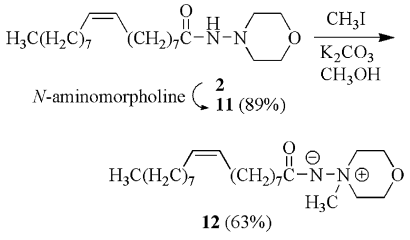


Scheme 1. Synthesis of aminimides **4**–**10**.

triethylamine provided *N*-acylhydrazide **3** in 96% yield after filtration through alumina to remove traces of amine salts. Treatment of **3** with a suitable alkyl halide in the presence of potassium carbonate using methanol as the solvent provided aminimides **4**–**10** in good yields after purification by chromatography over silica gel. Iodomethane was used for the synthesis of **4** while alkyl bromides were used for aminimides **5**–**10**. The yields are shown in parentheses in Scheme 1. These procedures were used to prepare multi-gram quantities of all aminimides shown in Scheme 1 (see Section 7). Scheme 2 describes the synthesis of an aminimide based on *N*-acylhydrazide **11**, prepared in 89% yield by reaction of oleoyl chloride with commercially available *N*-aminomorpholine. Alkylation of **11** with iodomethane provided aminimide **12** in 63% yield (Scheme 2).



Scheme 2. Synthesis of surfactant **12**.

Whereas the use of alkyl iodides and bromides provided materials that were pure enough for drag reduction studies, the aminimides derived from iodomethane (**4** and **12**) were usually more yellow in appearance than those derived from bromides. We suspected that this color was associated with iodine or traces of iodide that might be present in the products. Thus, for the synthesis of **4** we also examined dimethyl sulfate as the alkylating agent. This provided material that was less colored and did not become more yellow over time.

3. Characterization of *N*-acylhydrazides and aminimides

N-Acylhydrazides **3** and **11** exhibited isomerism characteristic of such compounds.[9] For example, the ^{1}H NMR spectrum of **3** exhibited two NH signals as broad singlets at δ 8.1 (minor isomer) and 8.7 (major isomer) in DMSO-d_6. In addition, two triplets were observed for the α-methylene ($CH_2C{=}O$) at δ 1.9 (major isomer) and 2.3 (minor isomer) and two singlets were observed for the $N(CH_3)_2$ groups at δ 2.41 (minor isomer) and 2.43 (major isomer). The ^{13}C NMR spectrum of **3** (DMSO-d_6) also showed two signals for the C=O groups at δ 174.3 and 169.4 and two signals for the $N(CH_3)_2$ groups at δ 47.7 and 46.2. The major and minor isomers appeared in a 62:38 ratio (based on integration of NH or $CH_2C{=}O$ signals in ^{1}H NMR spectrum). The major isomer was assigned *E*-geometry about the amide NC bond based on NOE experiments that established the proximal relationship between the NH and $CH_2C{=}O$ groups. The NMR spectra of **3** in $CDCl_3$ also showed the aforementioned geometrical isomerism. *N*-Acylhydrazide **11** exhibited similar spectroscopic behavior to **3**.

The spectroscopic behavior of aminimides **4**–**10** and **12** was more straightforward. All of these compounds exhibited the typical C=O stretch at approximately 1575 cm^{-1}.[4,10] Table 1 shows the average chemical shifts of seven ^{13}C NMR signals (C=O, C=C, NCH_3, allylic CH_2's, α-CH_2 relative to C=O, β-CH_2 relative to C=O, and terminal CH_3) and six ^{1}H NMR signals (CH=CH, NCH_3, $CH_2C{=}O$, $CH_2C{=}$, $CH_2CH_2C{=}O$, and terminal CH_3) observed for the eight aminimides prepared in this study. The assignments were based on chemical shift values and were supported by ^{1}H–^{13}C COSY experiments on aminimide **4** and selected DEPT experiments. These signals provide a signature for oleic acid derived aminimides. Appropriate signals unique to each aminimide, resulting from the different alkyl groups introduced in the *N*-acylhydrazide, were also observed in each case. Finally, the elemental composition of the aminimides was supported by HRMS (electrospray ionization).

All of the aforementioned aminimides were isolated as oils. A selection of these materials (**4**, **6**–**9**, **12**) exhibited hydrogen and nitrogen combustion analyses in accord with their elemental compositions. All of these compounds, however, gave combustion analyses that were slightly low in carbon. The IR spectra of all aminimides showed the presence of some water (approximately 3380 cm^{-1}). Karl Fischer titration indicated that the water content ranged from 1 to 6% by weight depending on the preparation. Spectral data, however, indicated that the materials prepared by the aforementioned procedures were pure enough for use in DR studies (see Supplementary data).

Table 1. Selected spectral data from aminimides

Spectrum	Observed	Signal
IR[a]	C=O stretch	1575
^{13}C NMR[b]	*C*=O	176.7
	*C*H=*C*H	129.7, 129.8
	N*C*H_3	53.7
	CH_2C=O	36.5
	CH_2CH=CH*C*H_2	27.10, 27.15
	CH_2CH_2C=O	26.7
	R–*C*H_3[c]	14.0
^{1}H NMR[b]	C*H*=C*H*	5.3
	NCH_3	3.3
	CH_2C=O	2.0
	CH_2CH=CHCH_2	1.95
	CH_2CH_2C=O	1.55
	R–CH_3[c]	0.8

[a] cm^{-1}.
[b] Parts per million from TMS in $CDCl_3$.
[c] From oleoyl group.

4. Drag reduction studies

4.1. Drag reduction measurement procedures

Drag reduction experiments were performed in a circulation flow system. The schematic is shown in Figure 2. The test section was a 2.18 m long stainless steel tube with a diameter of 10.9 mm. Two 4-gallon stainless steel surge tanks were installed to dampen pressure fluctuations in the loop. Other sections of the system were composed of all stainless steel parts and ½-inch tubing. Fluid temperatures at the inlet and outlet of the test section were measured by K-type thermocouples. A 2 kW heater, connected to a Variac, supplied the heat for high temperature runs. Pressure drops were measured by a Validyne differential pressure transducer. Flow rates were measured with a Rosemount Series 8700 magnetic flow meter. The system was equipped with a PolyScience chilling unit (Model KR-60A) to remove heat from the test system. The cooling temperature was controlled by a thermo-regulator (ranging from −30 to +30 °C, ±1%). The lowest temperature attainable in the test system was about −7 °C.

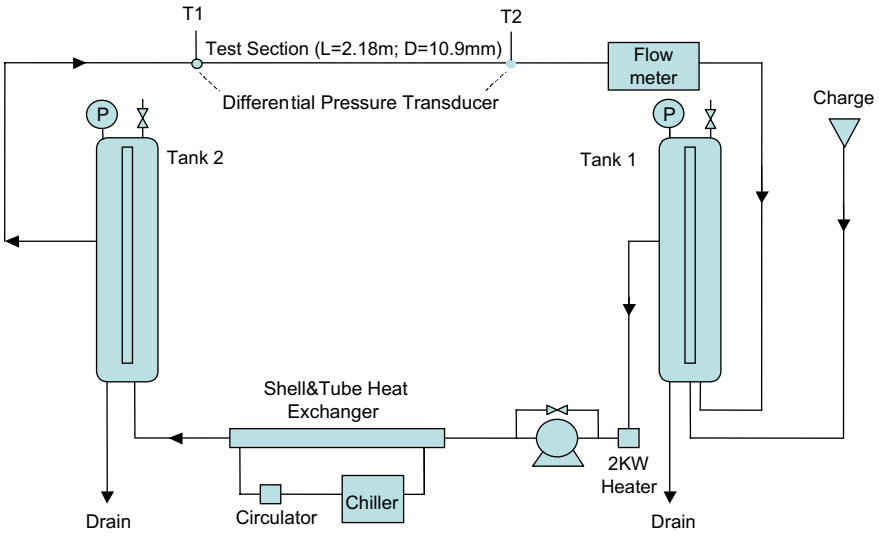


Figure 2. Schematic of drag reduction measurement flow loop.

Drag reduction in turbulent flow was determined from comparisons of measured pressure gradients ($\Delta P/L$) for the solution with additives and the pure solvent $(\Delta P/L)_S$ at the same flow rate. Drag reductions at different temperatures were calculated from the following equation over a Reynolds number range of 3×10^3–3×10^5:

$$\%\,\mathrm{DR} = \frac{(\Delta P/L)_S - (\Delta P/L)}{(\Delta P/L)_S} \times 100$$

4.2. Screening of surfactant DR candidates

Since approximately 30 g of surfactant was needed for drag reduction measurements in the recirculation system, screening of small surfactant samples were needed to focus on the most promising aminimides. For screening, approximately 60 mL of surfactant solution was stirred in a beaker by a magnetic stirrer. After the stirrer is stopped, the solution slows down in the direction of the swirling motion. Then, if it is viscoelastic, it will swirl in the opposite direction. The shorter the time between stopping the stirrer and the start of the back-swirl (swirl decay time), the greater the viscoelasticity. Although some non-viscoelastic surfactant systems have been observed with DR effectiveness, most surfactant DR additives are viscoelastic and have a distinct swirl decay time. To the best of our knowledge, a non-drag reducing but viscoelastic surfactant system in its dilute regime has never been reported. Therefore, this method was applied to screen small samples of the synthesized surfactants to select the most promising ones for preparing larger samples for drag reduction measurements.

4.3. Drag reduction results

On the basis of the aforementioned swirl test, and with the objective of testing a variety of structural types, aminimides **4**, **9**, and **12** were selected for evaluation as DR additives. These studies were conducted in the circulation flow system described in Section 4.1 over a Reynolds number range of 3×10^3–3×10^5 in 20% ethylene glycol–80% water. The behavior of DR additives in 20% EG–water is of special interest because its useful operating temperature range in district cooling systems (−5 to +15 °C) is twice the temperature range available in water (+5 to +15 °C), thus reducing the mass flow requirements by about half.

Table 2 documents the maximum % drag reduction at two temperatures in 20% EG–water. The aminimide surfactants clearly behave as good DR additives over a potentially useful range of temperatures in district cooling systems. The apparatus used to obtain the results shown in Table 2 holds a volume of about 30 L of fluid. Evaluation of aminimide **4** in a 1000-L system indicates that it remains a good DR additive

Table 2. Drag reduction of aminimide surfactants in 20% ethylene glycol–80% water at selected temperatures

[Surfactant]	Temperature (°C)	Max % drag reduction
[**4**]=6 mM	20	80
[**4**]=6 mM	−5	64
[**9**]=6 mM	20	72
[**9**]=6 mM	−1	67
[**12**]=6 mM	20	81
[**12**]=6 mM	−5	83

at even lower concentrations (% DR at 25 and −5 °C=59 and 47%, respectively, at 50 ppm).[11] Finally, cryo-TEM evaluation of 20% EG–water solutions of **4** indicated the presence of thread-like micelles at −5 °C.[12] It is generally believed that such micelles are an indication that a given surfactant will behave as an effective DR additive. Additional details of DR studies of these aminimides are reported elsewhere.[13]

4.4. Comparisons with commercial zwitterionics

DR results of three commercial zwitterionic surfactants in 20% ethylene glycol–80% water solvents are shown in Table 3 for comparison with the results in Table 2.[14] DR0206 (Akzo Nobel) has 20% myristylamidopropylbetaine, 10% rapeseedamidopropylbetaine, and 5% sodium alkylbenzenesulfonate (C_{10}–C_{13}). It was not DR effective in 20% EG–water alone but showed DR above 50% with the addition of 145 mM $NaNO_2$. Chemoxide OL (Chemron) is largely *N*,*N*-dimethyloleoylamine oxide. No DR effectiveness was observed for 5 mM (~2000 ppm) solutions of Chemoxide OL in 20% EG–water unless $NaNO_2$ was added. Results with 5 mM Chemoxide OL+10 mM $NaNO_2$ are shown in Table 3. Chembetaine OL (Chemron) is composed of oleyl betaine and was used with the addition of sodium dodecylbenzenesulfonate (SDBS) as a DR additive. The results of 4.8 mM Chembetaine OL+1.2 mM SDBS+6 mM $NaNO_2$ are also shown in Table 3. Thus, the aminimides evaluated in Table 2 compare very favorably with several commercially available surfactants used as DR additives.

Table 3. Drag reduction of selected commercial zwitterionic surfactant systems in 20% ethylene glycol–80% water at selected temperatures

Surfactant	Temperature (°C)	Max % drag reduction
DR0206 (9 mM)–$NaNO_2$ (145 mM)	15	45
DR0206 (9 mM)–$NaNO_2$ (145 mM)	2	52
Chemoxide OL (5 mM)–$NaNO_2$ (10 mM)	20	69
Chemoxide OL (5 mM)–$NaNO_2$ (10 mM)	5	57
Chembetaine OL (4.8 mM)–SDBS (1.2 mM)–$NaNO_2$ (6 mM)	20	0
Chembetaine OL (4.8 mM)–SDBS (1.2 mM)–$NaNO_2$ (6 mM)	−4	8

5. Stability studies

District cooling systems normally operate at basic pH's to minimize corrosion in the pipes. Nonetheless, the stability of aminimide surfactants under DR conditions was a matter of concern. This concern was in part prompted by the

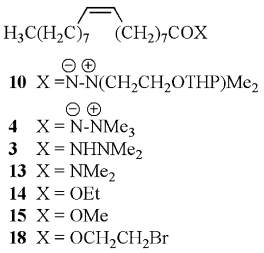
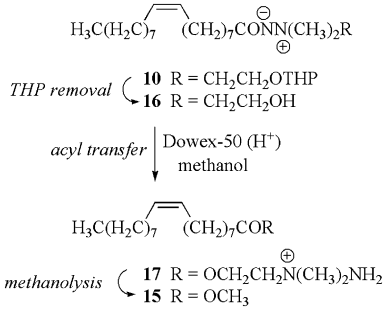


Figure 3. Selected oleic acid derivatives.

observation that attempts to remove the tetrahydropyranyl acetal group of **10** using methanol and Dowex-50 (H^+) at room temperature for 6.25 h led to methanolysis of the aminimide with formation of methyl oleate (**15**) in 66% yield (Fig. 3). These concerns were eliminated when it was shown that aminimide **4** could be recovered unchanged from a 20% EG–water solution that had been used in DR studies and stored for periods up to one month. Nonetheless, the behavior of **10** led us to evaluate the stability of aminimide **4**, and other oleic acid derivatives, under the aforementioned methanolysis conditions. In contrast to **10**, aminimide **4** did not undergo methanolysis under the aforementioned conditions. Instead, it was adsorbed on the Dowex-50 resin, presumably by protonation of the acylated nitrogen to form an ionic complex.[15] Warming the mixture at 70 °C, however, resulted in gradual production of methyl oleate (**15**) and after 24 h **15** could be isolated in 70% yield. For the purpose of comparison, acylhydrazine **3**, *N*,*N*-dimethyloleamide (**13**), and ethyl oleate (**14**) were also treated with Dowex-50 in methanol at 70 °C for 24 h. Whereas acylhydrazide **3** gave a 94% yield of methyl oleate under these conditions, amide **13** was recovered unchanged and ethyl oleate (**14**) was converted to a 62:38 mixture of the methyl and ethyl esters **15** and **14**, respectively. Therefore, under the acidic conditions described above, the relative rates of methanolysis of a series of carboxylic acid derivatives qualitatively appear to be amides<<<esters<aminimides~*N*-acylhydrazides.

The facile methanolysis of aminimide **10** can be explained (in part) by neighboring group participation (Scheme 3). Initial methanolysis of the THP ether would afford **16**. Intramolecular acyl transfer from nitrogen to oxygen would provide ester **17** and methanolysis of **17** would then provide the observed product **15**.



Scheme 3. Methanolysis of aminimide **10**.

Supporting evidence for this supposition follows. On one occasion it was found that treatment of **10** with $CuCl_2$

dihydrate in methanol at reflux for several hours provided a compound whose spectral data were consistent with those of ester **17** (or its conjugate base). Critical ^{1}H and ^{13}C NMR chemical shifts of **17** were consistent with those observed for methyl oleate (**15**) and not with those observed for aminimides. For example, the α-$CH_2C{=}O$ signal appears at δ 2.4 in the ^{1}H NMR spectrum of the presumed **17**. This signal appears at δ 2.35 in esters **14** and **15**, and at δ 2.0 for typical aminimides. The Cu(II)-mediated methanolysis, however, was difficult to reproduce. Therefore, an independent synthesis of **17** was undertaken to confirm the structure assignment and to see if **17** was kinetically competent to be an intermediate in the Dowex-50 mediated conversion of **10** to **15**. Treatment of oleoyl chloride (**2**) with 2-bromoethanol provided ester **18** (Fig. 3) in 94% yield. Reaction of **18** with *N*,*N*-dimethylhydrazine in tetrahydrofuran gave **17** (97%) with ^{1}H and ^{13}C NMR spectra identical to the material obtained from the Cu(II)-mediated methanolysis experiment.[16] In addition, the structure assignment of **17** was supported by the presence of ester (1740 cm^{-1}) and amine (3150 and 3210 cm^{-1}) stretching frequencies in its IR spectrum. Finally, when **17** was subjected to the methanolysis conditions used with aminimide **10** (methanol, Dowex-50, room temperature, 6.25 h), methyl oleate (**15**) was obtained in 77% yield. These experiments support the mechanistic hypothesis set forth in Scheme 3. The ease with which aminimides **4** and **10** and ester **17** undergo methanolysis is notable. A comparison of their rates of hydrolysis with a variety of acylating agents, including choline derivatives, will be reported in due course.[17]

6. Summary

This article describes the large-scale synthesis of aminimide surfactants that show promise as DR additives in 20% ethylene glycol–80% water. Procedures have been reported that are amenable to the synthesis of the quantities of material needed for large-scale DR experiments.[18] Stability studies reveal that standard aminimide surfactants are slightly more susceptible to methanolysis than esters under one set of acidic conditions. It has also been shown that one *N*-hydroxyethyl substituted aminimide undergoes methanolysis at faster rate than standard aminimides due (in part) to neighboring group participation.

7. Experimental

7.1. General experimental procedures

Solvents were purchased from commercial sources and used without purification. All reagents were purchased from commercial sources and not purified prior to use unless stated otherwise. Dowex-50WX8-100 was purchased from Aldrich Chemical Company and was used without purification or acid/base washing. Chromatography was conducted over silica gel. NMR spectra are reported in δ units from external tetramethylsilane. Copies of all spectra, including ^{13}C expansions, DEPT, and NOE experiments, are provided as Supplementary data. Combustion analytical data are reported as Supplementary data (for **4**, **6–9**, and **12**) along with adjustments for the presence of water, determined by Karl Fischer titration.[19]

7.1.1. *N*-Acylhydrazide 3. A three-neck flask equipped with a mechanical stirrer was charged with 220 g (0.73 mol) of freshly distilled oleoyl chloride in 1.0 L of toluene. The flask was cooled to 5 °C using an ice water bath and 68 mL (52.6 g, 0.88 mol) of 1,1-dimethylhydrazine was carefully added using a pressure equalizing addition funnel. The reaction was stirred for an additional 5 min and 123 mL (88.5 g, 0.88 mol) of triethylamine was added. The cold bath was removed and the reaction was stirred at room temperature for 24 h. The resulting heterogeneous mixture was filtered and the precipitate was rinsed with 200 mL of benzene. The combined filtrates were concentrated in vacuo to afford 234 g (97%) of crude **3** as a yellow liquid suitable for use in the next reaction. On one occasion when the reaction was performed on a 0.37 mol scale, the crude product was purified by chromatography over 800 g of neutral alumina (eluted with 1:1 ethyl acetate–hexanes) to give 114 g (96%) of acylhydrazide **3** as a pale yellow liquid: IR (neat) 3194, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.5–1.7 (m, 2H, CH_2CH_2CO), 1.8–2.1 (m, 4H, $H_2CC{=}$), 2.3–2.6 (m, 8H, CH_3N, CH_2CO), 5.2–5.4 (m, 2H, CH=CH), 6.1–6.2 (1H, NH, isomer 1), 6.2–6.3 (1H, NH, isomer 2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.0, 22.6, 24.8, 27.1, 29.06, 29.11, 29.15, 29.25, 29.39, 29.45, 29.63, 29.7, 31.84, 31.92, 47.5, 48.6, 129.6, 129.8, 171.0 (isomer 1), 176.0 (isomer 2); HRMS (ESI) calcd for $C_{20}H_{40}N_2O+H^+$: *m*/*z* 325.3219, found: *m*/*z* 325.3216.

7.1.2. Aminimide 4. To a one-neck round bottom flask equipped with a football shaped stir bar and a condenser fitted with a calcium chloride drying tube were added 132.9 g (0.41 mol) of *N*-acylhydrazide **3**, 300 mL of methanol, 135.8 g (0.98 mol) of potassium carbonate, and 76.6 mL (174.7 g, 1.23 mol) of methyl iodide. The mixture was warmed under reflux for 24 h, cooled to room temperature, and 300 mL of dichloromethane was added. The solution was filtered and the filtrate was concentrated in vacuo. The crude product was chromatographed over 600 g of silica gel (eluted with ethyl acetate followed by 1:1 ethyl acetate–methanol) to give 94 g (68%) of the aminimide **4** as a pale yellow oil: IR (CCl_4) 1577 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.3 (m, 20H), 1.4–1.6 (m, 2H, CH_2CH_2CO), 1.8–2.0 (m, 6H, CH_2CO, $CH_2CH{=}$), 3.3 (s, 9H, CH_3N), 5.2–5.3 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 22.6 (t), 26.7 (t, C_β), 27.15 (t, C8 or C11), 27.18 (t, C11 or C8), 29.40 (t), 29.46 (t), 29.49 (t), 29.72 (t), 31.8 (t), 36.6 (t, C_α), 55.4 (q, NMe), 129.80 (d), 129.85 (d), 177.0 (s) (four aliphatic carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{21}H_{40}N_2ONa$: *m*/*z* 361.3189, found: *m*/*z* 361.3200.

7.1.3. Aminimide 5. A mixture of 15.0 g (46.3 mmol) of *N*-acylhydrazide **3**, 50 mL of methanol, 15.3 g (0.11 mol) of potassium carbonate, and 28.0 mL (41.8 g, 0.37 mol) of ethyl bromide was warmed at 70 °C for 48 h, cooled to room temperature, and 60 mL of dichloromethane was added. The solution was filtered and the filtrate was concentrated in vacuo. The crude product was purified by chromatography over 150 g of silica gel (eluted with ethyl acetate followed by 9:1 ethyl acetate–methanol) to give 6.1 g (38%) of the aminimide **5** as a colorless oil: IR (CCl_4) 1578 cm^{-1}; ^{1}H NMR

($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.3 (m, 21H), 1.5 (m, 2H, CH_2CH$_2$CO), 1.95 (m, 4H, CH_2C=), 2.0 (t, J=7 Hz, 2H, CH_2CO), 3.3 (s, 6H, CH_3N), 3.7 (q, J=7.5 Hz, 2H, CH_2N), 5.2–5.3 (m, 2H, CH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.9, 13.9, 22.5, 26.7, 26.99, 27.02, 29.1, 29.25, 29.30, 29.40, 29.56, 29.58, 31.7, 36.3, 52.8 (NCH_3), 60.3, 129.62, 129.70, 176.4 (two carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{22}H_{42}N_2O$+H$^+$: m/z 353.3532, found: m/z 353.3521.

7.1.4. Aminimide 6. A mixture of 15.0 g (46.3 mmol) of *N*-acylhydrazide **3**, 50 mL of methanol, 15.3 g (0.11 mol) of potassium carbonate, and 13.8 mL (19.8 g, 115.8 mmol) of benzyl bromide was warmed overnight at 60 °C for 48 h, cooled to room temperature, and 60 mL of dichloromethane was added. The solution was filtered and the filtrate was concentrated in vacuo. The crude product was chromatographed over 150 g of silica gel (eluted with ethyl acetate followed by 9:1 ethyl acetate–hexanes) to give 10.5 g (55%) of the aminimide **6** as a colorless oil: IR (CCl_4) 1573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.3 (m, 20H), 1.4–1.6 (m, 2H, CH_2CH$_2$CO), 1.95 (m, 6H, CH_2CO, CH_2C=), 3.3 (s, 6H, CH_3N), 4.9 (s, 2H, CH_2N), 5.2–5.3 (m, 2H, CH=CH), 7.3–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.6, 26.7, 27.18, 27.21, 29.27, 29.45, 29.48, 29.6, 29.75, 29.77, 31.9, 36.8, 52.8 (NCH_3), 67.7 (NCH_2), 128.74, 129.8, 129.9, 132.4, 176.9 (two aromatic and two aliphatic carbons were not observed due to overlap of signals); HRMS (ESI) calcd for $C_{27}H_{46}N_2ONa$: m/z 437.3508, found: m/z 437.3513.

7.1.5. Aminimide 7. A mixture of 15.0 g (46.3 mmol) of *N*-acylhydrazide **3**, 50 mL of methanol, 15.3 g (0.18 mol) of potassium carbonate, and 7.8 mL (11.2 g, 92.6 mol) of allyl bromide was warmed at 60 °C for 24 h, cooled to room temperature, and 60 mL of dichloromethane was added. The solution was filtered and the filtrate was concentrated in vacuo. The crude product was chromatographed over 150 g of silica gel (eluted with ethyl acetate followed by 20:1 ethyl acetate–methanol) to give 11.6 g (69%) of the aminimide **7** as a colorless oil: IR (CCl_4) 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.3 (m, 20H), 1.5 (m, 2H, CH_2CH$_2$CO), 1.95 (m, 6H, CH_2CO and CH_2C=), 3.2 (s, 6H, CH_3N), 4.3 (d, J=7.5 Hz, 2H, CH_2N), 5.2–5.3 (m, 2H, CH=CH), 5.4–5.5 (m, 2H, =CH_2), 5.9–6.1 (m, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 22.5, 26.6, 27.02, 27.05, 29.1, 29.27, 29.33, 29.42, 29.59, 29.61, 31.7, 36.4, 52.8 (NCH_3), 67.3 (NCH_2), 125.0, 127.4, 129.65, 129.73, 176.6 (two aliphatic carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{23}H_{44}N_2ONa$: m/z 365.3532, found: m/z 365.3532.

7.1.6. Aminimide 8. A mixture of 10.0 g (30.9 mmol) of *N*-acylhydrazide **3**, 40 mL of methanol, 10.3 g (74.2 mmol) of potassium carbonate, and 14.1 mL (18.7 g, 139.1 mol) of 3-bromo-2-methylpropene was warmed at 70 °C for 48 h, cooled to room temperature, and 60 mL of dichloromethane was added. The solution was filtered and the filtrate was concentrated in vacuo. The crude product was chromatographed over 120 g of silica gel (eluted with ethyl acetate followed by 7:3 ethyl acetate–methanol) to give 8.5 g (73%) of the aminimide **8** as a colorless oil: IR (CCl_4) 1576 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.3 (m, 20H), 1.55 (m, 2H, CH_2CH$_2$CO), 1.9–2.0 (m, 9H, CH_3C=, CH_2C=O, CH_2C=), 3.3 (s, 6H, CH_3N), 4.4 (s, 2H, CH_2N), 5.1 (s, 2H, =CH_2), 5.2–5.3 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 22.4 (t), 22.8 (q), 26.3 (t), 26.90 (t), 26.93 (t), 29.01 (t), 29.16 (t), 29.22 (t), 29.38 (t), 29.48 (t), 29.50 (t), 31.6 (t), 36.5 (t), 53.4 (q, NCH_3), 69.4 (t, NCH_2), 123.3 (t), 129.5 (d), 129.6 (d), 136.6 (s), 176.5 (s) (two aliphatic carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{24}H_{46}N_2ONa$: m/z 401.3508, found: m/z 401.3513.

7.1.7. Aminimide 9. To a one-neck round bottom flask equipped with a football shaped stir bar and a condenser fitted with a calcium chloride drying tube were added 70 g (0.22 mol) of the *N*-acylhydrazide **3**, 200 mL of absolute ethanol, 72.8 g (0.53 mol) of potassium carbonate, and 61.2 g (0.44 mol) of 2-bromoethyl methyl ether. The mixture was warmed under reflux for four days, cooled to room temperature, 200 mL of dichloromethane was added, and the heterogeneous mixture was filtered. The filtrate was concentrated in vacuo and the crude product was purified by chromatography over 300 g of silica gel (eluted with ethyl acetate followed by 4:1 ethyl acetate–methanol) to give 51.5 g (61%) of the aminimide **9** as a pale yellow oil: IR (CCl_4) 1573 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.5 (quintet, J=7 Hz, 2H, CH_2CH$_2$CO), 1.9–2.1 (m, 6H, CH_2CO, CH_2C=), 3.20–3.23 (two s, 9H, CH_3O, CH_3N), 3.6–3.7 (m, 2H), 3.9–4.0 (m, 2H), 5.27 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.6, 26.7, 27.1, 27.18, 29.24, 29.38, 29.44, 29.53, 29.7, 29.74, 31.8, 36.4, 55.0, 58.7, 64.1, 67.0, 129.77, 129.83, 176.6 (two aliphatic carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{23}H_{46}N_2O_2Na$: m/z 405.3424, found: m/z 405.3451.

7.1.8. Aminimide 10. To a one-neck round bottom flask equipped with a football shaped stir bar and a condenser fitted with a calcium chloride drying tube were added 6.8 g (0.021 mol) *N*-acylhydrazide **3**, 150 mL of absolute ethanol, 6.9 g (0.05 mol) of potassium carbonate, and 9.1 g (44 mmol) of the tetrahydropyranyl ether of 2-bromoethanol.[20] The mixture was warmed under reflux for five days, cooled to room temperature, 80 mL of dichloromethane was added, and the mixture was filtered. The filtrate was concentrated in vacuo and the crude product was purified by chromatography over 120 g of silica (eluted with ethyl acetate followed by 4:1 ethyl acetate–methanol) to afford 7 g (77%) of the aminimide **10** as a pale yellow oil: IR (CCl_4) 1574 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.4–1.6 (m, 6H), 1.6–1.8 (m, 2H), 1.8–2.0 (m, 6H), 3.30 and 3.35 (two s, 6H, CH_3N), 3.45 (m, 1H), 3.75 (m, 2H), 3.85 (m, 1H), 4.0 (m, 2H), 4.55 (m, 1H, OCHO), 5.3 (m, 2H, CH=); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 19.5, 22.5, 25.1, 26.8, 27.09, 27.13, 29.19, 29.35, 29.39, 29.53, 29.66, 29.69, 30.4, 31.8, 36.5, 54.5, 54.9, 62.11, 62.7, 64.2, 99.2, 129.7, 129.8, 176.7 (one aliphatic carbon was not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{27}H_{52}N_2O_2$+H$^+$: m/z 453.4056, found: m/z 452.4048.

7.1.9. *N*-Acylhydrazide 11. A one-neck round bottom flask equipped with a football shaped stir bar and an addition funnel was charged with 25 g (0.24 mol) of *N*-aminomorpholine and 350 mL of benzene. The addition funnel was charged with 80 g (0.22 mol) of oleoyl chloride (85% solution) and the acid chloride was added dropwise to the hydrazine at 5 °C over a period of 25 min. Upon completion of the addition, 150 mL of benzene was added, the cold bath was removed, and the heterogeneous reaction mixture was stirred for 24 h at room temperature. The resulting mixture was filtered and the filter cake was rinsed with 80 mL of benzene. The combined filtrates were concentrated in vacuo to afford 71.4 g (89%) of acylhydrazide **11** as a yellow solid, suitable for use in subsequent reactions without further purification: mp 87–88 °C; IR (neat) 3250, 3196, 1649 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.3 (m, 20H), 1.4–1.6 (m, 2H, CH_2CH_2CO), 1.8–2.0 (m, 5H), 2.3 (t, J=7.5 Hz, 1H), 2.4–2.9 (m, 4H), 3.4–3.8 (m, 4H), 5.2–5.3 (m, 2H), 7.0–7.1 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, diagnostic signals) δ 55.4 and 56.6 (CH_2N of geometrical isomers), 66.1 and 66.2 (CH_2O of geometrical isomers), 170.4 and 176.4 (C=O of geometrical isomers); HRMS (ESI) calcd for $C_{22}H_{42}N_2O_2Na$: m/z 389.3144, found: m/z 389.3139.

7.1.10. Aminimide 12. To a one-neck round bottom flask equipped with a football shaped stir bar and a condenser fitted with a calcium chloride drying tube were added 35.5 g (97 mmol) of *N*-acylhydrazide **11**, 120 mL of methanol, 32 g (23 mmol) of potassium carbonate, and 41.3 g (29 mmol) of methyl iodide. The mixture was warmed under reflux for 24 h, cooled to room temperature, 100 mL of dichloromethane was added, and the mixture was filtered. The filtrate was concentrated in vacuo and the residual crude product was purified by chromatography over 250 g of silica gel (eluted with ethyl acetate followed by methanol) to give 23 g (63%) of the aminimide **12** as a yellow semi-solid: IR (CCl_4) 1577 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.5 (quintet, J=7 Hz, 2H, CH_2CH_2CO), 1.9–2.0 (m, 4H, CH_2C=), 2.1 (t, J=7 Hz, 2H, CH_2CO), 3.1 (td, J=7, 1.2 Hz, 2H), 3.4 (s, 3H, CH_3N), 3.7 (d, J=12 Hz, 2H), 4.2 (t, J=12 Hz, 2H), 4.3 (d, J=12 Hz, 2H), 5.23 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.6, 26.8, 27.19, 27.2, 29.3, 29.4, 29.5, 29.60, 29.67, 29.75, 29.77, 31.8, 36.9, 53.4 (NCH_3), 61.6, 62.2, 129.85, 129.86, 176.9 (one carbon was not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{23}H_{44}N_2O_2Na$: m/z 403.3281, found: m/z 403.3294.

7.1.11. Methanolysis of aminimide 10. A mixture of 200 mg (0.44 mmol) of aminimide **10**, 10 mL of methanol, and 400 mg of acidic Dowex-50WX8-100 was stirred at room temperature for 12 h. The mixture was filtered and the filtrate was concentrated in vacuo to afford 120 mg (92% yield) of pure methyl oleate (**15**): ^1H NMR ($CDCl_3$, 400 MHz) δ 0.8 (t, J=7.5 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.6 (quintet, J=7 Hz, 2H, CH_2CH_2CO), 2.0 (m, 4H, CH_2C=), 2.3 (t, J=7 Hz, 2H, CH_2CO), 3.6 (s, 3H, CH_3O), 5.3 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 22.7 (t), 24.9 (t), 27.1 (t), 27.2 (t), 29.07 (t), 29.11 (t), 29.13 (t), 29.3 (t), 29.5 (t), 29.67 (t), 29.75 (t), 31.9 (t), 34.1 (t), 51.4 (q), 129.7 (d), 129.9 (d), 174.2 (s) (the signal at δ 29.3 represents two carbons based on intensity).

7.1.12. Methanolysis of *N*-acylhydrazide 3. A mixture of 200 mg (0.61 mmol) of *N*-acylhydrazide **3**, 10 mL of methanol, and 400 mg of acidic Dowex-50WX8-100 was stirred at 70 °C (oil bath temperature) for 24 h. The mixture was filtered and the filtrate was concentrated in vacuo to afford 170 mg (94%) of methyl oleate (**15**).

7.1.13. Methanolysis of aminimide 4. A mixture of 200 mg (0.59 mmol) of aminimide **4**, 10 mL of methanol, and 400 mg of acidic Dowex-50WX8-100 was stirred at 70 °C (oil bath temperature) for 24 h. The mixture was filtered and the filtrate was concentrated in vacuo and the residue was purified by chromatography over 15 g of silica gel (eluted with 7:3 hexane–ethyl acetate) to afford 120 mg (70%) of methyl oleate (**15**).

7.1.14. Attempted methanolysis of amide 13. A mixture of 200 mg (0.66 mmol) of amide **14**,[21] 10 mL of methanol, and 400 mg of acidic Dowex-50WX8-100 was stirred at 70 °C (oil bath temperature) for 24 h. The mixture was filtered and the filtrate was concentrated in vacuo to afford 190 mg (95%) of unchanged amide **13**.

7.1.15. Methanolysis of ethyl oleate (14). A mixture of 200 mg (0.65 mmol) of ethyl oleate (**14**), 10 mL of methanol, and 400 mg of acidic Dowex-50WX8-100 was stirred at 70 °C (oil bath temperature) for 12 h. The mixture was filtered and the filtrate was concentrated in vacuo to afford 200 mg of a 62:38 mixture of methyl oleate and ethyl oleate, respectively. When the reaction was analyzed after 5.5 h and four days, the ratios of methyl:ethyl esters were 11:89 and 96:4, respectively.

7.1.16. 2-Bromoethyl oleate (18). To a solution of 2.0 g (6.6 mmol) of oleoyl chloride in 50 mL of benzene were added sequentially 0.87 g (0.49 mL, 6.93 mmol) of 2-bromoethanol and 1.33 g (1.8 mL, 13.2 mmol) of triethylamine via syringe. The mixture was stirred at room temperature for 15 h, filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography over 60 g of silica (eluted with hexanes–ethyl acetate, 95:5) to give 2.42 g (94%) of ester **18** as yellow oil: IR (neat) 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.8 (t, J=7 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.5–1.7 (m, 2H, CH_2CH_2CO), 1.8–2.0 (m, 4H, CH_2C=), 2.3 (t, J=7.3 Hz, 2H, CH_2CO), 3.5 (t, J=7.3 Hz, 2H, CH_2Br), 4.4 (t, J=7.3 Hz, 2H, CH_2O), 5.2–5.3 (m, 2H, CH=); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.1, 22.6, 24.8, 27.1, 27.1, 28.7, 29.0, 29.1, 29.3, 29.5, 29.6, 29.7, 31.8, 34.0, 63.5, 129.6, 129.9, 173.2 (two carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{20}H_{37}O_2{}^{79}BrNa$: m/z 411.1875, found: m/z 411.1862.

7.1.17. Ester 17. To a solution of 0.3 g (0.77 mmol) of bromide **18** in 1.5 mL of tetrahydrofuran was added 0.29 g (0.36 mL, 4.77 mmol) of 1,1-dimethylhydrazine in one portion. The mixture was stirred in a sealed tube with warming at 60 °C (oil bath temperature) for 5.5 h. The reaction was allowed to cool to room temperature and the solvent and excess 1,1-dimethylhydrazine were removed in vacuo to give

0.34 g (97%) of ester **17** as a yellow gel: IR (neat) 3214, 3111, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.8 (t, J=7 Hz, 3H, CH_3), 1.1–1.4 (m, 20H), 1.5–1.7 (m, 2H, CH_2CH_2CO), 1.8–2.0 (m, 4H, CH_2C=), 2.3 (t, J=7.3 Hz, 2H, CH_2CO), 3.6 (s, 6H, CH_3N), 4.0–4.1 (m, 2H, CH_2O or CH_2N), 4.5–4.6 (m, 2H, CH_2N or CH_2O), 5.2–5.3 (m, 2H, CH=); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 14.0, 22.5, 24.5, 27.0, 27.1, 28.96, 29.04, 29.13, 29.34, 29.54, 29.57, 31.7, 33.9, 56.9, 57.5, 67.5, 129.5, 129.8, 172.8 (two carbons were not observed due to suspected overlap of signals around δ 29); HRMS (ESI) calcd for $C_{22}H_{45}N_2O_2$: m/z 369.3481, found: m/z 369.3477. This material contained traces of contamination by both ^1H and ^{13}C NMR spectroscopies (see Supplementary data).

7.1.18. Methanolysis of aminimide 10. To a solution of 100 mg (0.22 mmol) of aminimide **10** in 5.0 mL of methanol was added 200 mg of Dowex-50X8-100 in one portion. The mixture was stirred at room temperature for 6.25 h, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography over 20 g of silica gel (eluted with hexanes–ethyl acetate, 90:10) to give 42 mg (66%) of the methyl oleate (**15**) as a pale yellow liquid.

7.1.19. Methanolysis of ester 17. To a solution of 49 mg (0.11 mmol) of ester **17** in 2.5 mL of methanol was added 100 mg of Dowex-50X8-100 in one portion. The mixture was stirred at room temperature for 6.25 h, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography over 15 g of silica gel (eluted with hexanes–ethyl acetate, 90:10) to give 25 mg (77%) of the methyl oleate (**15**) as a pale yellow liquid. ^1H NMR analysis prior to chromatography indicated a 95:5 mixture of **15** and **17**, respectively.

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Supplementary data

Selected experimental procedures, analytical data, and copies of ^1H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.023.

References and notes

1. Mysels, K. J. U.S. Patent No. 2,492,173, 1949; Mysels, K. J. *Chem. Eng. Prog. Symp. Ser.* **1971**, *67*, 45; Toms, B. A. *Phys. Fluids* **1977**, *20*, 53; Nadolink, R. H.; Haigh, W. W. *Appl. Mech. Rev.* **1995**, *48*, 351; Zakin, J. L.; Qi, Y.; Zhang, Y. *Encyclopedia of Chemical Processing*; Lee, S., Ed.; Taylor & Francis: New York, NY, 2005; pp 767–785.
2. Zakin, J. L.; Lu, B.; Bewersdorff. *Rev. Chem. Eng.* **1998**, *37*, 528.
3. Myska, J.; Zakin, J. L. *Ind. Eng. Chem. Res.* **1997**, *36*, 5483; Zheng, Y.; Lin, Z.; Zakin, J. L.; Talmon, Y.; Davis, H. T.; Scriven, L. E. *J. Phys. Chem. B* **2000**, *104*, 5263.
4. For a review of aminimide chemistry see: McKillip, W. J.; Sedor, E. A.; Culbertson, B. M.; Wawzonek, S. *Chem. Rev.* **1973**, *73*, 255.
5. Hinman, R. L.; Flores, M. C. *J. Org. Chem.* **1959**, *24*, 660; McKillip, W. J.; Clemens, L. M.; Haugland, R. *Can. J. Chem.* **1967**, *45*, 2613.
6. Schiessl, H. W.; Appel, R. *J. Org. Chem.* **1966**, *31*, 3851; McKillip, W. J.; Slagel, R. C. *Can. J. Chem.* **1967**, *45*, 2619.
7. Berry, R. W. H.; Brocklehurst, P. *J. Chem. Soc.* **1964**, 2264.
8. Freis, R. E.; Grimm, R. A.; McKillip, W. J. *J. Am. Oil Chem. Soc.* **1972**, *42*, 111.
9. Dewar, M. J. S.; Jennings, W. B. *J. Am. Chem. Soc.* **1973**, *95*, 1562; Green, D. V. S.; Hillier, I. H.; Morris, G. A.; Gensmante, N.; Payling, D. W.; Robinson, D. H. *J. Mol. Struct. (Theochem)* **1991**, *251*, 173.
10. Wawzonek, S.; Paschke, E. E. *J. Org. Chem.* **1971**, *36*, 1474.
11. Details of these drag reduction experiments, conducted in the Kawaguchi laboratories, will be reported elsewhere.
12. For a description of the cryo-TEM procedures (Talmon laboratories), see: Zhang, Y.; Schmidt, J.; Talmon, Y.; Zakin, J. L. *J. Colloid Interface Sci.* **2005**, *286*, 696. Details will be reported elsewhere.
13. Zhang, Y.; Oba, G.; Hart, D. J.; Kesselman, E.; Talmon, Y.; Zakin, J. L. *Proceedings of the 4th Pacific Rim Conference on Rheology*; Shanghai, China, August 7–11, 2005. Zhang, Y. Correlations among surfactant drag reduction, additive chemical structures, rheological properties and microstructures in water and water/co-solvent systems. Ph.D. Dissertation, The Ohio State University, 2005.
14. Although the focus of this research is zwitterionic surfactants, we have also studied cationic surfactants as DR additives in 20% EG–80% water. For example, we have reported that a combination of EO12 (5 mM) and sodium salicylate (12.5 M) exhibits maximum % DRs of 60 and 58% at 20 and 0 °C, respectively.[12] To our knowledge there have been very few studies of drag-reducing agents in EG–water. These studies all employ zwitterionic or zwitterionic/anionic surfactant mixtures. For an amine oxide, $CH_3(CH_2)_7(CH{=}CH)$–$(CH_7)_8N(CH_2CH_2OH)_2O$, see: Haruki, N.; Inaba, H.; Horibe, A.; Tanaka, S. *Netsu Bussei* **2005**, *19*, 67 [CAN:143:250274]; For a patent that describes combinations of ammonium carboxylates [such as $CH_3(CH_2)_{17}N(CH_3)_2CH_2CO_2$] with dodecylbenzenesulfonates, monoalkyl sulfates, and related surfactants, see: Hellsten, M.; Oskarsson, H. World Intellectual Property Organization. WO 02/059228 A1 [CAN:137:142495].
15. This observation suggests that Dowex-50 might be used to sequester aminimides from DR solvent systems. Indeed, in a single experiment we have shown that 400 mg of Dowex-50 (H^+) will sequester at least 90% of **4** from 100 mL of a 6 mM solution of the aminimide in 20% EG–80% water. A pK_a of 5.3 has been reported for an aminimide derived from decanoic acid.[7]
16. For the selective N-alkylation of 1,1-dimethylhydrazine, see: Koenig, K. H.; Zeeh, B. *Chem. Ber.* **1970**, *103*, 2052.
17. For choline ester hydrolysis experiments of relevance to this study, see: Fellman, J. H.; Fujita, T. S. *Biochim. Biophys. Acta* **1963**, *71*, 701; Kunz, H.; Buchholz, M. *Chem. Ber.*

1979, *112*, 2145. It is notable that **10**, **14**, and **17** are stable to methanol (rt, 6.25 h) in the absence of Dowex-50. In addition, ethyl oleate (**14**) was recovered unchanged from treatment with Dowex-50 in methanol at rt for 4 h.

18. The procedures described herein were used to prepare over 1 kg of **4** for use in DR studies in a 1000-L flow system.[11]
19. We thank Dr. Chad Bennett at Schering–Plough Research Institute for conducting Karl Fischer titrations. For previous reports of the hygroscopic nature of aminimides, see: Wawzonek, S.; Yeakey, E. *J. Am. Chem. Soc.* **1960**, *82*, 5718.
20. Solas, D.; Wolinsky, J. *J. Org. Chem.* **1983**, *48*, 1988.
21. Liu, H.-J.; Chan, W. H.; Lee, S. P. *Synth. Commun.* **1979**, *9*, 31.

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A short enantioselective synthesis of (−)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation

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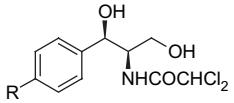
Abstract—An efficient enantioselective synthesis of (−)-chloramphenicol (**1**) and (+)-thiamphenicol (**2**) is described. These antibiotics have been synthesized from commercially available 4-nitrobenzaldehyde and 4-(methylthio)benzaldehyde, respectively, using tethered aminohydroxylation and Sharpless asymmetric epoxidation as the chirality inducing steps.

1. Introduction

(−)-Chloramphenicol **1** and (+)-thiamphenicol **2** (Fig. 1) are broad-spectrum antibiotics with a range of biological activities.[1] The antibiotic chloramphenicol is active only in its D-*threo* configuration and is especially effective in the treatment of typhus, dysentery and ocular bacterial infections.[2] (+)-Thiamphenicol **2**, a synthetic analogue of chloramphenicol **1**, is bacteriostatic for both Gram-positive and Gram-negative aerobes and for some anaerobes.[3] Owing to their potential biological activity, a number of syntheses have been described.[4–7]



R= NO_2; (-)-Chloramphenicol, **1**

R= SO_2Me; (+)-Thiamphenicol, **2**

Figure 1.

Sharpless asymmetric epoxidation has previously been used for the syntheses of **1** and **2**.[5c,d,j,7c,e] In one of these reports, the authors made use of a *Z*-cinnamyl alcohol for which the asymmetric epoxidation required a long reaction time.[5c] Further, in some cases, the use of *E*-cinnamyl alcohol resulted in the increase of the number of steps.[5d,7c,e] In another report, the use of Sharpless asymmetric epoxidation under kinetic resolution conditions required expensive, unnatural (−)-diisopropyl tartrate [(−)-DIPT].[5j] However, we are able to replace the unnatural (−)-diisopropyl tartrate with naturally occurring and cheaply available (+)-diisopropyl tartrate for the enantioselective syntheses of **1** and **2**.

The tethered aminohydroxylation (TA),[8] an intramolecular asymmetric aminohydroxylation of alkenes, has become a reliable method in recent years for achieving excellent levels of *syn* selectivity while providing at the same time complete control over the regio- and chemoselectivity of the oxidation. We describe herein a new, short approach for the stereoselective synthesis of (−)-chloramphenicol **1** and (+)-thiamphenicol **2** by employing two key reactions, namely, Sharpless asymmetric epoxidation[11] and the tethered aminohydroxylation.[8]

2. Result and discussion

Our synthesis of (−)-chloramphenicol **1** (Scheme 1) starts with the reaction of 4-nitrobenzaldehyde **3a** with divinylzinc[9] to give 1-(4-nitrophenyl)allyl alcohol **4a** in 68% yield. Allylic alcohol **4a** was then subjected to Sharpless asymmetric epoxidation under kinetic resolution conditions[10] using the naturally occurring (+)-diisopropyl tartrate [(+)-DIPT] to furnish the corresponding chiral allylic alcohol, 1-(***S***)-4-(nitrophenyl)-2-propen-1-ol **6a**, in 44% chemical yield and 98% ee (optical purity was determined by ^{1}H NMR analysis of the corresponding Mosher's ester **10a**, see Section 4 for details) along with the corresponding epoxide **7a** in 49% yield. Both chiral alcohol **6a** and epoxide **7a** could be easily separated by column chromatographic purification. Alcohol **6a** was then treated with trichloroacetyl isocyanate[11] in CH_2Cl_2 to give the corresponding isocyanate, which on treatment with K_2CO_3 and methanol in the presence of H_2O gave the carbamate **8a** in 90% yield.

The carbamate **8a** thus obtained was converted into the oxazolidinone **9a** by a tethered aminohydroxylation protocol[8b]

Keywords: Asymmetric synthesis; Asymmetric epoxidation; Kinetic resolution; Tethered aminohydroxylation.
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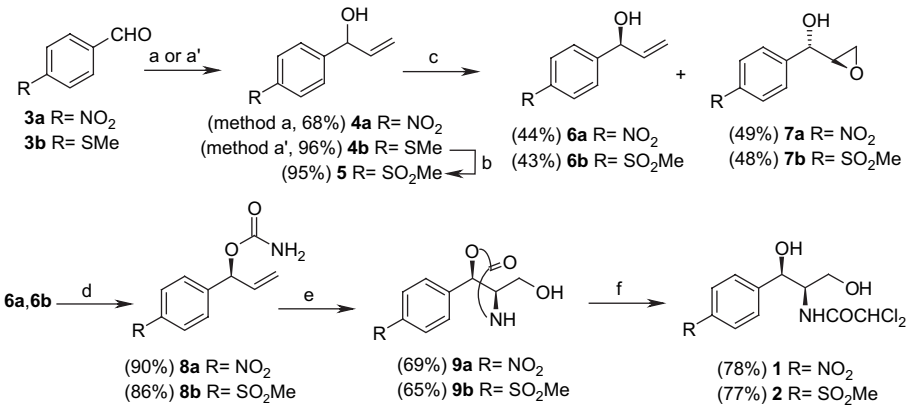

Scheme 1. Reagents and conditions: (a) divinylzinc, THF, Et_2O, −78–25 °C, 10 h; (a′) vinylmagnesium bromide, THF, 0–25 °C, 2 h; (b) oxone, THF/MeOH/H_2O (1:1:1), 0–25 °C, 30 min, 95%; (c) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −20 °C, 14–24 h; (d) (i) trichloroacetyl isocyanate, CH_2Cl_2, 0–25 °C, 2 h; (ii) K_2CO_3, MeOH, H_2O, 0–25 °C, 18 h; (e) $K_2Os(OH)_4O_2$, *t*-BuOCl, NaOH, EtN-*i*-Pr_2, *n*-PrOH/H_2O (1:1), 25 °C, 3 h; (f) (i) 1 N NaOH, MeOH, 25 °C, overnight; (ii) methyl dichloroacetate, 90 °C, 3 h.

using *tert*-butyl hypochlorite as the oxidant in the presence of potassium osmate, 0.08 M NaOH, diisopropyl ethylamine and propan-1-ol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **9a** as a single isomer with complete regiocontrol and excellent *syn* selectivity (*syn*:*anti*>20:1, determined by ^{1}H NMR analysis) giving 69% yield. The compound **9a** was then hydrolyzed using 1 N NaOH in methanol[5h] to furnish the crude aminoalcohol, which was then taken in methyl dichloroacetate[4a,5h] and heated at 90 °C for 3 h to give (−)-chloramphenicol **1** in 78% yield. $[\alpha]_D^{25}$ −25.4 (*c* 1, EtOAc) [lit.[12] $[\alpha]_D^{23}$ −25.5 (*c* 1, EtOAc)]. The spectral data of **1** was in complete agreement with the reported values.[1b]

The same strategy was extended to the synthesis of (+)-thiamphenicol **2** (Scheme 1). Commercially available 4-(methylthio)benzaldehyde **3b** was converted to the allyl alcohol **4b** using vinylmagnesium bromide in THF.[5j] The thioether **4b** was then oxidized using oxone[13] to give the corresponding sulfonyl ester **5** in 95% yield. Allyl alcohol **5** was then subjected to Sharpless asymmetric epoxidation[10] using (+)-diisopropyl tartrate under kinetic resolution conditions to furnish the chiral alcohol **6b** in 43% yield and 98% ee (the optical purity was determined by ^{1}H NMR analysis of the corresponding Mosher's ester **10b**, see Section 4 for details) along with the epoxide **7b**. Both alcohol **6b** and epoxide **7b** could be easily separated by column chromatography. The carbamate **8b** obtained from **6b** under the same experimental conditions[11] as explained earlier was converted into the oxazolidinone **9b** using tethered aminohydroxylation.[8b] The desired isomer of the oxazolidinone **9b** was obtained with high stereoselectivity (*syn*:*anti*>20:1, determined by ^{1}H NMR analysis) giving 65% yield. Finally, the hydrolysis of **9b** with 1 N NaOH in methanol[5h] followed by the treatment with methyl dichloroacetate[4a,5h] gave the final product thiamphenicol **2** in 77% yield. $[\alpha]_D^{25}$ +12.7 (*c* 1, EtOH) [lit.[3] $[\alpha]_D^{25}$ +12.9 (*c* 1, EtOH)]. The spectral data of **2** was in complete agreement with the reported values.[5j,14]

3. Conclusion

In conclusion, we have achieved an efficient synthesis of (−)-chloramphenicol (overall yield 29%, 98% ee) and (+)-thiamphenicol (overall yield 34%, 98% ee) using tethered aminohydroxylation and Sharpless asymmetric epoxidation as the two key chirality inducing steps. The major advantages of this work are the use of naturally occurring (+)-DIPT for the kinetic resolution and the use of tethered aminohydroxylation for the induction of second chiral centre in the molecule in a highly diastereoselective fashion (dr=98:2).

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures before use;[15] petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV-200, AV-400 and BRX-500 NMR spectrometers, respectively. Elemental analysis was carried on a Carlo Erba CHNS-O analyzer.

4.2. 1-(4-Nitrophenyl)-2-propen-1-ol (4a)

To a stirred solution of vinylmagnesium bromide [prepared from vinyl bromide (8.49 g, 79.4 mmol) and magnesium (1.93 g, 79.4 mmol)] in THF (90 mL), freshly fused $ZnCl_2$ (5.40 g, 39.7 mmol) dissolved in THF (30 mL) was added at 0 °C under nitrogen atmosphere. This solution was stirred at 55 °C for 18 h, after which it was cooled to 10 °C and dry ether (150 mL) was added and stirred for 10 min. The reaction mixture was allowed to settle for 30 min. The supernatant liquid was transferred through a canula to another flask. This solution was allowed to cool to −78 °C, then 4-nitrobenzaldehyde **3a** (1.5 g, 9.92 mmol) in THF (20 mL) was added over a period of 15 min. The reaction mixture was allowed to warm to room temperature and stirring continued for 10 h. The reaction mixture was then quenched at −20 °C by the addition of aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic fractions collected and washed with water and brine solution, then dried over Na_2SO_4 and

concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford compound **4a** (1.21 g, 68%) as a pale yellow amorphous solid. Mp: 48–49 °C; IR ($CHCl_3$) ν_{max} 3433, 2858, 1606, 1519, 1348, 1217, 1108, 1041, 989, 854, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (d, J=8.8 Hz, 2H), 7.56 (d, J=8.5 Hz, 2H), 5.91–6.05 (m, 1H), 5.25–5.45 (m, 3H), 2.04 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 147.1, 139.1, 126.9, 123.5, 116.6, 74.4. Anal. Calcd for $C_9H_9NO_3$ (179.18): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.45; H, 5.09; N, 7.94%.

4.3. 1-(*S*)-(4-Nitrophenyl)-2-propen-1-ol (6a)

To a stirred suspension of powdered 4 Å molecular sieves (1.5 g) in dry CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (1.27 g, 4.47 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to −20 °C and (+)-diisopropyl tartrate (1.25 g, 5.36 mmol) was added and stirred for 10 min, after which allyl alcohol **4a** (0.8 g, 4.5 mmol) dissolved in CH_2Cl_2 (20 mL) was added and stirred at −20 °C for 30 min. To the above solution *tert*-butyl hydroperoxide (0.22 g, 2.5 mmol) dissolved in toluene was added and stirred at −20 °C for 14 h. After completion of half of the reaction (monitored by TLC), the reaction mixture was quenched with 10% aqueous solution of tartaric acid (25 mL), after which stirring was continued for 1 h at −20 °C and 2 h at room temperature. The organic layer was separated, washed with water and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was diluted with ether (75 mL) and stirred with 1 M NaOH (25 mL) for 1 h at 0 °C. The organic layer was then separated, washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford compound **6a** (0.35 g, 44%) as a pale yellow amorphous solid. Mp: 48–49 °C; $[\alpha]_D^{25}$ +41.3 (c 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3433, 2858, 1606, 1519, 1348, 1217, 1108, 1041, 989, 854, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (d, J=8.8 Hz, 2H), 7.56 (d, J=8.5 Hz, 2H), 5.91–6.05 (m, 1H), 5.25–5.45 (m, 3H), 2.04 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 147.1, 139.1, 126.9, 123.5, 116.6, 74.4. Anal. Calcd for $C_9H_9NO_3$ (179.18): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.45; H, 5.09; N, 7.94%.

4.4. (1*R*,2*S*)-1-(4-Nitrophenyl)oxiranemethanol (7a)

White amorphous solid. Mp: 74–75 °C; $[\alpha]_D^{25}$ +60.8 (c 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.23 (d, J=9.0 Hz, 2H), 7.57 (d, J=9.0 Hz, 2H), 5.01 (br d, J=3.0 Hz, 1H), 3.20 (ddd, J=2.6, 3.0, 4.2 Hz, 1H), 2.88 (dd, J=2.6, 4.9 Hz, 1H), 2.72 (dd, J=4.2, 4.9 Hz, 1H), 2.45 (br s, 1H).

4.5. Preparation of Mosher's ester of 1-(*S*)-(4-nitrophenyl)-2-propen-1-ol (10a)

A two-neck 10 mL flask with septum was charged with (44 mg, 0.21 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of alcohol **6a** (32 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over Na_2SO_4 and then concentrated under reduced pressure to give Mosher's ester of the alcohol (53 mg, 70%) as a thick syrup. $[\alpha]_D^{25}$ +39.5 (c 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015, 957, 911, 735, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, J=9 Hz, 2H), 7.32–7.53 (m, 7H), 6.48 (d, J=6.6 Hz, 1H), 5.90–6.06 (m, 1H), 5.36–5.47 (m, 2H), 3.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.27, 147.98, 144.53, 134.09, 133.87, 132.04, 129.79, 128.45, 127.68, 127.24, 123.86, 119.95, 77.06, 55.56. Anal. Calcd for $C_{19}H_{16}F_3NO_5$ (395.10): C, 57.72; H, 4.08; F, 14.42; N, 3.54. Found: C, 57.94; H, 3.82; F, 14.68; N, 3.21.

4.6. 1-(*S*)-(4-Nitrophenyl)allyl carbamate (8a)

To a stirred solution of alcohol **6a** (0.45 g, 2.5 mmol) in dichloromethane (12 mL) at 0 °C was added dropwise trichloroacetyl isocyanate (0.36 mL, 3 mmol). The resulting solution was stirred for 2 h and then concentrated in vacuo. The residue was diluted with MeOH (13 mL), cooled to 0 °C and a solution of potassium carbonate (1.04 g, 7.5 mmol) in H_2O (2.4 mL) was added. The resulting suspension was stirred at 0 °C for 2 h, then at room temperature for 16 h. The reaction was concentrated in vacuo, diluted with H_2O (50 mL) and brine (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography using petroleum ether/EtOAc (6:4) to give **8a** (0.5 g, 90%) as a pale yellow crystalline solid. Mp: 101 °C; $[\alpha]_D^{25}$ +12.39 (c 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3471, 3280, 3178, 1724, 1620, 1514, 1386, 1346, 1328, 1215, 925, 854, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.23 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.7 Hz, 2H), 6.23 (d, J=6 Hz, 1H), 5.89–6.06 (m, 1H), 5.35 (t, J=7.3 Hz, 2H), 4.86 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5, 147.5, 146.3, 135.2, 127.5, 123.7, 118.2, 75.7. Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222.22): C, 54.05; H, 4.54; N, 12.62. Found: C, 54.16; H, 4.50; N, 12.61%.

4.7. (5*R*,6*R*)-4-(Hydroxymethyl)-5-(4-nitrophenyl)-2-oxazolidinone (9a)

A fresh aqueous solution of sodium hydroxide (0.08 M, 0.9 equiv) was prepared. All but a few drops of this were added in one portion to a stirred solution of the allylic carbamate (0.222 g, 1 mmol) in propan-1-ol (12 mL). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.114 mL, 1 mmol) was added. The mixture was again allowed to stir for 5 min. To this was added diisopropyl ethylamine (5 mol %) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (4 mol %) in the remainder of the sodium hydroxide solution made earlier. The reaction was monitored by TLC and halted when

no further change was detected. The reaction was quenched by the addition of sodium sulfite (500 mg), and allowed to stir for 30 min. The mixture was extracted with ethyl acetate (2×50 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica using petroleum ether/EtOAc (4:6) to give **9a** (0.16 g, 69%) as a gum. $[\alpha]_D^{25}$ −4.08 (*c* 1.1, EtOH); IR ($CHCl_3$) ν_{max} 3351, 2944, 2832, 2523, 1755, 1607, 1527, 1450, 1416, 1351, 1112, 666 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.33 (d, *J*=8.3 Hz, 2H), 7.75 (d, *J*=8.7 Hz, 2H), 6.96 (s, 1H), 5.61 (m, 1H), 4.49 (s, 1H), 3.81 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.3, 148.6, 148.3, 127.3, 124.4, 78.6, 63.7, 62.1. Anal. Calcd for $C_{10}H_{10}N_2O_5$ (238.22): C, 50.42; H, 4.23; N, 11.77. Found: C, 50.36; H, 4.36; N, 11.86%.

4.8. (1*R*,2*R*)-2-(Dichloroacetamido)-1-(4-nitrophenyl)-1,3-propanediol (1)

A solution of 1 N NaOH was made in methanol. The above solution (10 mL) was added to **9a** (0.95 g, 0.4 mmol) and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuum. The crude compound was taken in methyl dichloroacetate (2 mL) and heated at 90 °C for 3 h. The excess ester was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/EtOAc (3:7) to give the product **1** (0.1 g, 78%) as a white amorphous solid. Mp: 151–152 °C [lit.[11] 149.7–150.7 °C]; $[\alpha]_D^{25}$ −24.9 (*c* 1, EtOAc) [lit.[11] $[\alpha]_D^{23}$ −25.5 (*c* 1, EtOAc)]; IR ($CHCl_3$) ν_{max} 3420, 3020, 2929, 1686, 1604, 1523, 1454, 1403, 1348, 1216, 1049, 850 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, *J*=9 Hz, 1H), 8.15 (d, *J*=8.3 Hz, 2H), 7.58 (d, *J*=8.5 Hz, 2H), 6.47 (s, 1H), 6.04 (br s, 1H), 4.83–5.05 (m, 2H), 3.90–3.95 (m, 1H), 3.56–3.61 (m, 1H), 3.33–3.40 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.3, 150.1, 147.3, 128.2, 123.2, 70.6, 66.6, 61.6, 56.9. Anal. Calcd for $C_{11}H_{12}Cl_2N_2O_5$ (323.15): C, 40.89; H, 3.74; Cl, 21.94; N, 8.68. Found: C, 40.93; H, 3.82; Cl, 21.89; N, 8.66%.

4.9. 1-(4-Methylsulfanylphenyl)-2-propen-1-ol (4b)

To a stirred suspension of Mg (7.1 g, 296 mmol) in THF (75 mL), vinyl bromide (15.82 g, 147.81 mmol) in THF (45 mL) was added at 0 °C under nitrogen atmosphere over a period of 15 min and continued stirring at room temperature for a further 30 min. The reaction mixture was cooled to 0 °C and 4-(methylthio)benzaldehyde **3b** (7.5 g, 49.26 mmol) dissolved in THF (75 mL) was added over a period of 10 min. After the addition was completed, the reaction mixture was allowed to return to room temperature and stirring continued for another 2 h. The reaction mixture was quenched by the addition of aqueous ammonium chloride and extracted with ethyl acetate (3×100 mL). The combined organic fractions were collected and washed with water and brine solution, then dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford compound **4b** (8.5 g, 96%) as a thick syrup; IR ($CHCl_3$) ν_{max} 3398, 3078, 2981, 2920, 1639, 1598, 1492, 1431, 1404, 1219, 1093, 989, 927, 815 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H), 5.95–6.11 (m, 1H), 5.17–5.39 (m, 3H), 2.48 (s, 3H), 1.97 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.9, 139.4, 137.5, 126.7, 126.5, 114.9, 74.6, 15.74. Anal. Calcd for $C_{10}H_{12}OS$ (180.27): C, 66.63; H, 6.71; S, 17.79. Found: C, 66.79; H, 6.89; S, 17.68%.

4.10. 1-(4-Methylsulfonylphenyl)-2-propen-1-ol (5)

To a vigorously stirred solution of sulfide **4b** (3.78 g, 21 mmol) in THF (20 mL), MeOH (20 mL) and H_2O (20 mL) at 0 °C was added oxone (36 g, 59 mmol) portionwise. After 5 min at 0 °C, the white suspension was warmed to room temperature and stirred for 30 min. The reaction was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3×100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to give sulfone **5** (4.25 g, 95%) as a white amorphous solid. Mp: 56.5–57.5 °C; IR ($CHCl_3$) ν_{max} 3481, 3020, 2927, 2360, 1639, 1598, 1407, 1303, 1149, 1087, 958, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.2 Hz, 2H), 5.99 (m, 1H), 5.23–5.43 (m, 3H), 3.03 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.0, 139.3, 139.1, 127.3, 127.1, 116.2, 74.34, 44.39. Anal. Calcd for $C_{10}H_{12}O_3S$ (212.27): C, 56.58; H, 5.69; S, 15.11. Found: C, 56.69; H, 5.76; S, 15.23%.

4.11. 1-(*S*)-(4-Methylsulfonylphenyl)-2-propen-1-ol (6b)

To a stirred suspension of powdered 4 Å molecular sieves (7 g) in dry CH_2Cl_2 (75 mL), $Ti(O^iPr)_4$ (3.12 g, 11 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to −20 °C and (+)-diisopropyl tartrate (3.1 g, 13.2 mmol) was added and stirred for 10 min, after which allyl alcohol **5** (2.3 g, 11 mmol) dissolved in CH_2Cl_2 (60 mL) was added and stirred at −20 °C for about 30 min. To the above solution *tert*-butyl hydroperoxide (0.59 g, 6.6 mmol) dissolved in toluene was added and stirred at −20 °C for about 24 h. After completion of half of the reaction (monitored by TLC), the reaction mixture was quenched with 10% aqueous solution of tartaric acid (80 mL), after which stirring was continued for 1 h at −20 °C and 2 h at room temperature. The organic layer was separated, washed with water and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with ether (250 mL) and stirred with 1 M NaOH (100 mL) for about 1 h at 0 °C. The organic layer was then separated, washed with brine solution, dried over Na_2SO_4 and then concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to afford compound **6b** (1 g, 43%) as white amorphous solid. Mp: 56.5–57.5 °C; $[\alpha]_D^{25}$ +28.38 (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3481, 3020, 2927, 2360, 1639, 1598, 1407, 1303, 1149, 1087, 958, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.2 Hz, 2H), 5.99 (m, 1H), 5.23–5.43 (m, 3H), 3.03 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.0, 139.3, 139.1, 127.3, 127.1, 116.2, 74.34, 44.39. Anal. Calcd for $C_{10}H_{12}O_3S$ (212.27): C, 56.58; H, 5.69; S, 15.11. Found: C, 56.55; H, 5.61; S, 15.26%.

4.12. (1*R*,2*S*)-1-(4-Methylsulfonylphenyl)oxirane-methanol (7b)

Thick syrup. $[\alpha]_D^{25}$ +47.3 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.3 Hz, 2H), 7.59 (d, *J*=8.3 Hz, 2H), 4.96 (br d, *J*=3.0 Hz, 1H), 3.19 (m, 1H), 3.02 (s, 3H), 2.88 (dd, *J*=3.0, 5.2 Hz, 1H), 2.73 (dd, *J*=3.7, 5.2 Hz, 1H), 2.50 (br s, 1H).

4.13. Preparation of Mosher's ester of 1-(*S*)-(4-methylsulfonylphenyl)-2-propen-1-ol (10b)

A two-neck 10 mL flask with septum was charged with (44 mg, 0.21 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of alcohol **6b** (38 mg, 0.179 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over Na_2SO_4 and then concentrated under reduced pressure to get Mosher's ester of the alcohol (53 mg, 70%) as a thick syrup. $[\alpha]_D^{25}$ +42.5 (*c* 0.4, MeOH); IR ($CHCl_3$) ν_{max} 3156, 3069, 2951, 2930, 2851, 2255, 1754, 1644, 1601, 1496, 1452, 1410, 1318, 1243, 1154, 1016, 957, 910, 737, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (d, *J*=8.5 Hz, 2H), 7.35–7.45 (m, 7H), 6.48 (d, *J*=6.5 Hz, 1H), 5.89–6.06 (m, 1H), 5.35–5.47 (m, 2H), 3.55 (s, 3H), 3.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.33, 147.44, 143.67, 140.73, 134.17, 131.99, 129.77, 128.43, 127.78, 127.24, 119.84, 77.31, 55.55, 44.44. Anal. Calcd for $C_{20}H_{19}F_3O_5S$ (428.42): C, 56.07; H, 4.47; F, 13.30; S, 7.48. Found: C, 57.24; H, 4.24; F, 13.06; S, 7.71.

4.14. 1-(*S*)-(4-(Methylsulfonyl)phenyl)allyl carbamate (8b)

To a stirred solution of alcohol **6b** (1 g, 4.7 mmol) in dichloromethane (23 mL) at 0 °C was added dropwise trichloroacetyl isocyanate (0.71 mL, 5.64 mmol). The resulting solution was stirred for 2 h and then concentrated in vacuo. The residue was diluted with MeOH (25 mL), cooled to 0 °C and a solution of potassium carbonate (1.95 g, 14.1 mmol) in H_2O (5 mL) was added. The resulting suspension was stirred at 0 °C for 2 h, then at room temperature for 16 h. The reaction was concentrated in vacuo, diluted with H_2O (50 mL) and brine (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography using petroleum ether/EtOAc (4:6) to give **8b** (0.99 g, 86%) as a white crystalline solid. Mp: 159 °C; $[\alpha]_D^{25}$ −10.23 (*c* 1, MeOH); IR (neat) ν_{max} 3421, 3265, 2906, 1720, 1608, 1406, 1379, 1298, 1145, 1041, 947, 769 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, *J*=7.8 Hz, 2H), 7.58 (d, *J*=7.8 Hz, 2H), 6.84 (s, 1H), 6.61 (s, 1H), 6.10 (d, *J*=5.5 Hz, 1H), 5.97–6.04 (m, 1H), 5.32 (d, *J*=16.9 Hz, 1H), 5.22 (d, *J*=10.1 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 155.7, 146.1, 140.2, 136.9, 127.5, 127.4, 117.0, 74.5, 43.7. Anal. Calcd for $C_{11}H_{13}NO_4S$ (255.30): C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.79; H, 5.27; N, 5.40; S, 12.49%.

4.15. (5*R*,6*R*)-4-(Hydroxymethyl)-5-(4-(methylsulfonyl)phenyl)-2-oxazolidinone (9b)

A fresh aqueous solution of sodium hydroxide (0.08 M, 0.9 equiv) was prepared. All but a few drops of this were added in one portion to a stirred solution of the allylic carbamate (0.76 g, 3 mmol) in propan-1-ol (30 mL). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.4 mL, 3 mmol) was added. The mixture was again allowed to stir for 5 min. To this was added diisopropyl ethylamine (5 mol %) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (4 mol %) in the remainder of the sodium hydroxide solution made earlier. The reaction was monitored by TLC and halted when no further change was detected. The reaction was quenched by the addition of sodium sulfite (1.5 g), and allowed to stir for 30 min. The mixture was extracted with ethyl acetate (2×50 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica using petroleum ether/EtOAc (2:8) to give **9b** (0.53 g, 65%) as a pale yellow amorphous solid. Mp: 152 °C; $[\alpha]_D^{25}$ +9.74 (*c* 1.16, MeOH); IR (neat) ν_{max} 3259, 3020, 2929, 2399, 2360, 1716, 1602, 1407, 1299, 1215, 1149, 1089, 1026, 954, 769 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.98 (d, *J*=8.5 Hz, 2H), 7.95 (br s, 1H), 7.62 (d, *J*=8.3 Hz, 2H), 5.45 (d, *J*=3.9 Hz, 1H), 5.20 (t, *J*=5.3 Hz, 1H), 3.46–3.59 (m, 3H), 3.22 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.1, 146.0, 140.8, 127.8, 126.6, 77.8, 62.6, 61.3, 43.7. Anal. Calcd for $C_{11}H_{13}NO_5S$ (271.30): C, 48.69; H, 4.83; N, 5.17; S, 11.82. Found: C, 48.62; H, 4.94; N, 5.23; S, 11.76%.

4.16. (1*R*,2*R*)-2-(Dichloroacetamido)-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol (2)

A solution of 1 N NaOH was made in methanol. The above solution (10 mL) was added to **9b** (0.14 g, 0.4 mmol) and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuum. The crude compound was taken in methyl dichloroacetate (2 mL) and heated at 90 °C for 3 h. The excess ester was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/EtOAc (1:9) to give the product **2** (0.11 g, 77%) as a white amorphous solid. Mp: 164–165 °C [lit.[2] 164.3–166.3 °C]; $[\alpha]_D^{25}$ +12.5 (*c* 1, EtOH) [lit.[2] $[\alpha]_D^{25}$ +12.9 (*c* 1, EtOH)]; IR (neat) ν_{max} 3481, 3407, 3242, 3082, 3020, 2925, 1699, 1562, 1406, 1282, 1215, 1145, 1033, 906, 806, 767 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.93 (d, *J*=8.5 Hz, 2H), 7.71 (d, *J*=8.2 Hz, 2H), 7.70 (d, *J*=8.2 Hz, 1H), 6.41 (s, 1H), 5.31 (d, *J*=2.4 Hz, 1H), 5.27 (d, *J*=3.8 Hz, 1H) 4.28 (t, *J*=4.7 Hz, 1H), 4.10–4.20 (m, 1H), 3.77–3.89 (m, 1H), 3.63–3.72 (m, 1H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.42, 149.59, 140.95, 127.85,

127.77, 71.21, 67.51, 62.08, 57.99, 44.34. Anal. Calcd for $C_{12}H_{15}Cl_2NO_5S$ (356.23): C, 40.46; H, 4.24; Cl, 19.9; N, 3.93, S, 9.0. Found: C, 40.59; H, 4.38; Cl, 19.85; N, 4.05; S, 8.96%.

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References and notes

1. (a) Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Josylyn, D. A.; Burkholder, P. R. *Science* **1947**, *106*, 417; (b) Al-Badr, A. A.; El-Obeid, H. A. *Chloramphenicol*; Florey, K., Ed.; Analytical Profiles of Drug Substances; Academic: Orlando, 1986; Vol. 15, p 701.
2. Gillet, A. D.; Abdel-Monem, M. M. *J. Med. Chem.* **1973**, *16*, 992 and the references cited therein.
3. Cutler, R. A.; Stenger, R. J.; Suter, C. M. *J. Am. Chem. Soc.* **1952**, *74*, 5475.
4. For racemic syntheses of chloramphenicol: (a) Controulis, J.; Rebstock, M. C.; Crooks, H. M., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 2463; (b) Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 2469; (c) Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 2473; (d) Ehrhart, G.; Siedel, W.; Nahm, H. *Chem. Ber.* **1957**, *90*, 2088; (e) Horak, V.; Moezie, F.; Klein, R. F. X.; Giordano, C. *Synthesis* **1984**, 839; (f) Hazra, B. G.; Pore, V. S.; Maybhate, S. P. *Synth. Commun.* **1997**, *27*, 1857.
5. For chiral syntheses of chloramphenicol: (a) Chenevert, R.; Thiboutot, S. *Synthesis* **1989**, 444; (b) Schollkopf, U.; Beulshausen, T. *Liebigs Ann. Chem.* **1989**, 223; (c) Rao, A. V. R.; Rao, S. P.; Bhanu, M. N. *J. Chem. Soc., Chem. Commun.* **1992**, 859; (d) Lou, B.-L.; Zhang, Y.-Z.; Dai, L.-X. *Chem. Ind.* **1993**, *7*, 249; (e) Easton, C. J.; Hutton, C. A.; Merrett, M. C.; Tiekink, E. R. T. *Tetrahedron* **1996**, *52*, 7025; (f) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 8503; (g) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **2000**, *41*, 2765; (h) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett.* **2000**, *41*, 5553; (i) Loncaric, C.; Wul, W. D. *Org. Lett.* **2001**, *3*, 3675; (j) Bhaskar, G.; Kumar, V. S.; Rao, B. V. *Tetrahedron: Asymmetry* **2004**, *15*, 1279; (k) Boruwa, J.; Borah, J. C.; Gogoi, S.; Barua, N. C. *Tetrahedron Lett.* **2005**, *46*, 1743.
6. For racemic syntheses of thiamphenicol: (a) McCombie, S. W.; Nagabhushan, T. L. *Tetrahedron Lett.* **1987**, *28*, 5395; (b) Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. *Tetrahedron Lett.* **1988**, *29*, 5561.
7. For chiral syntheses of thiamphenicol: (a) Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. *J. Org. Chem.* **1991**, *56*, 6114; (b) Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525; (c) Wu, G.-Z.; Tormos, W. I. PTC Int. Appl. WO 94/14764, 1994 (to Schering); (d) Gennari, C.; Pain, G. *Tetrahedron Lett.* **1996**, *37*, 3747; (e) Wu, G.-Z.; Schumacher, D. P.; Tormos, W.; Clark, J. E.; Murphy, B. L. *J. Org. Chem.* **1997**, *62*, 2996; (f) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909; (g) Kaptein, B.; Dooren, T. J. G. M. V.; Boesten, W. H. J.; Sonke, T.; Duchateau, A. L. L.; Broxterman, Q. B.; Kamphuis, J. *Org. Process Res. Dev.* **1998**, *2*, 10; (h) See Ref. 5j.
8. (a) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934; (b) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583.
9. Bartocha, B.; Kaesz, H. D.; Stone, F. G. A. *Z. Naturforsch.* **1959**, *14b*, 352; *Chem. Abstr.* **1960**, *54*, 1272h.
10. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; (b) Martin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
11. Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2005**, *7*, 1275.
12. Bartz, Q. R. *J. Biol. Chem.* **1948**, *172*, 445.
13. Voight, E. A.; Roethle, P. A.; Burke, S. D. *J. Org. Chem.* **2004**, *69*, 4534.
14. Zolek, T.; Paradowska, K.; Krajewska, D.; Rozanski, A.; Wawer, I. *J. Mol. Struct.* **2003**, *646*, 141.
15. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, UK, 1996.

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A convergent route to poly(phenyl ketone ether) dendrons

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Abstract—A series of poly(phenyl ketone) dendrons have been constructed using a convergent strategy. An aryl fluoro-substituent is deactivated towards nucleophilic substitution by protection of a para-ketone as an acetal. This allows coupling to an activated aryl fluoride. Subsequent deprotection of the acetyl group then activates the first fluoro-substituent and allows the next generation of the dendron to be added. The synthesis of higher generations is complicated by a scrambling reaction, which lowers the yields.

1. Introduction

Ever since their realisation in the 1980s,[1] dendrimers have been widely studied due to their unique properties.[2] The exterior or interior can be decorated with functional groups for applications such as encapsulation,[3] light harvesting,[4] catalysis[5] or electroluminescence.[6] Most dendrimers are constructed using flexible linkers, as their chemistry and processing tend to be easier. However, in certain applications where structural integrity is important, rigid branches may prove important. Examples of rigid dendrimers include those based on branched phenylenes[7] and phenylacetylenes.[8] While dendrimers have been the focus of research in the past, more recently dendrons have proved their importance in their own right as solubilising and rigidifying modifiers for polymers.[9]

There are two distinct routes for dendrimer/dendron synthesis, namely the divergent or convergent step-wise growth methods. The divergent method of dendrimer synthesis involves the build up of successive layers of protected, polyfunctional monomers starting from a central core. Several addition/activating steps are carried out until the desired dendrimer size is obtained. An increasing number of chain end monomers at the periphery is produced as the dendrimer is built up. An example of this is the synthesis of poly(amidoamine) PAMAM Starburst dendrimers,[1c,d] where ammonia acts as the core molecule. As successive generations are built up it gets increasingly difficult to obtain high yielding reactions and the maximum size of the dendrimer is limited due to the level of steric crowding at the surface. Another problem is in the purification at each generation, as any single defect in the dendrimer makes only a small difference to its properties.

The convergent method on the other hand differs in the fact that the synthesis starts from the periphery monomer units and works inwards to form dendrons or 'wedges'. These wedges (once the desired size is obtained) can be attached to a polyfunctional core to form the dendrimer. The convergent method has the advantage in the fact that in each step there are only two reactions (i.e., two monomers/dendrons in the *n*th generation couple to the appropriate functionality of the monomer unit in the $(n-1)$th generation) and the number of reaction sites does not increase with increasing size of the dendrimer, unlike in the divergent approach. However, if the dendrons become too big, reactivity may become impaired due to the large amount of crowding that develops near the focal point.

We were interested in the possible use of dendrimers and dendrons as high glass transition temperature (T_g) cross-linkers and polymer modifiers. For these purposes, the exterior needed to be decorated with (protected) phenolic groups, and the branching linkers needed to be thermally and oxidatively stable. The high T_g was hoped to be afforded by the use of rigid branching units. While the T_g of un-cross-linked dendrimers seems to be determined by the outer surface functionality as much by the nature of the branching linkages,[10] no studies have been made on cross-linked materials. The diaryl ketone linkage was chosen as being suitable as the T_g of linear poly(phenyl ketones) ranges from 150 to 220 °C.[11] There are two main routes known for the synthesis of polyphenyl ketone dendrimers. The first was a convergent route, which used an oxidative step to activate the fluorophenyl group towards further nucleophilic substitution (Scheme 1a).[12] This was ruled out in the present case for two reasons. The branching units in our case were ethers, which may activate the phenyl unit towards oxidation. As

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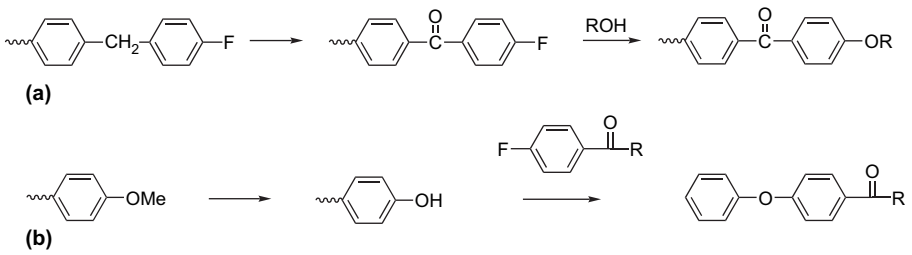


Scheme 1.

well, the oxidation may prove less selective or lower yielding as the size of the dendrimer increases. The second divergent method used the deprotection of methoxy phenyl ethers with BBr_3 or $AlCl_3$ to expose new phenoxy-groups (Scheme 1b).[13]

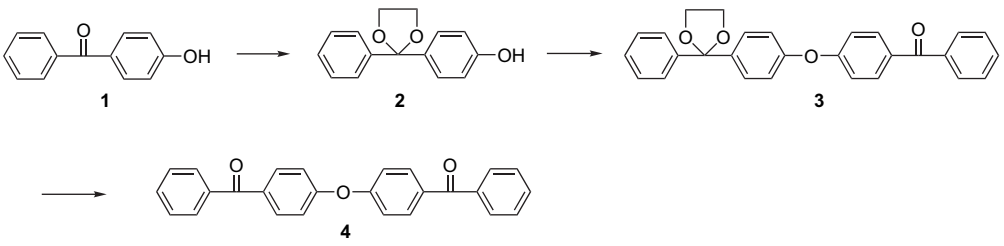
Dendrimers normally use a protection–deprotection scheme in order to selectively couple units together. The most obvious protection chemistry for the aromatic ketones would appear to be the use of cyclic acetals, which can be cleanly deprotected under mildly acidic conditions. Cyclic acetals have been used to protect fluorophenyl ketones in the synthesis of pharmaceutical derivatives, though in these instances the acetal groups were used to protect the ketone than to control the activation of the fluoro-substituent as here.[14] They have also been used to functionalise the carbonyl groups of poly(phenyl ketones) to give improved solubility over the parent polymer.[15] In that particular case, though, the acetal groups were added after the nucleophilic polymerisation step.

2. Results

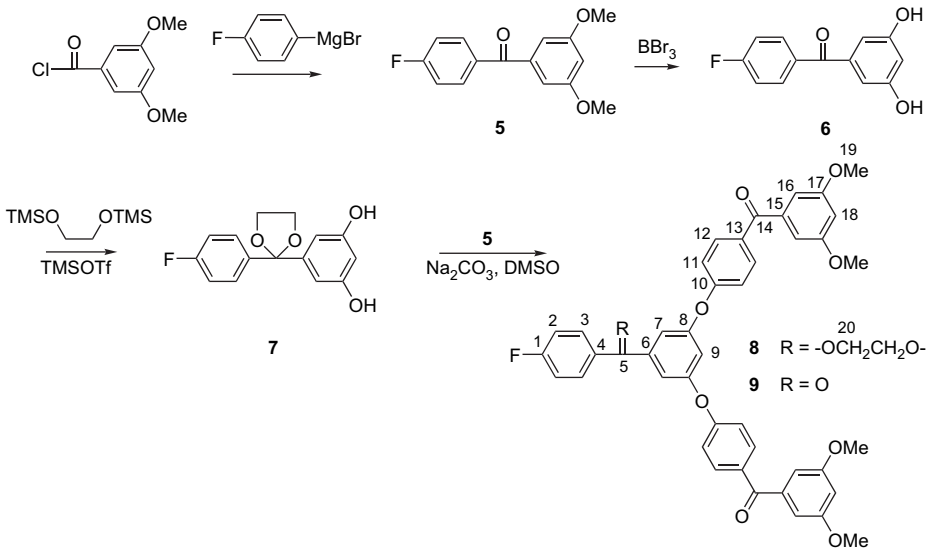
We were unsure whether a simple acetal could withstand the high temperatures and polar solvents usually used in aromatic nucleophilic substitutions. To this end, some model chemistry was undertaken in order to prove the concept. Formation of an acetal of 4-hydroxyphenyl ketone **1** was attempted under standard conditions (ethylene glycol, acid, azeotropic removal of water), but even after 5 days, only starting material could be recovered. It was possibly due to that the phenolic group was interfering in the reaction. Diaryl ketones appear difficult to protect with acetal groups at the best of times and prolonged reaction times (5 days or more) have often been employed.[15] A milder literature procedure to protect aromatic ketones involving 1,2-bis(trimethylsiloxy)ethane was then tried.[16] This reaction, which requires the use of a catalyst, trimethylsilyl trifluoromethanesulfonate, went in reasonable yield (71%) after only 3 h, the remainder being the starting material (Scheme 2). The unprotected phenolic group did not appear to interfere in the reaction. The protected ketone **2** was then reacted with 4-fluorophenyl phenyl ketone **3** using sodium carbonate as base at 160 °C to give **6** in 81% isolated yield without any apparent side products (Scheme 2). The reaction appeared clean, with no other products isolated. Gratifyingly, the cyclic acetal showed no signs of instability at those temperatures and conditions. Deprotection was cleanly performed by heating in acetone in the presence of an acid catalyst to give diketone **4** in 93% yield from **3**. Our work would seem to be the first to directly protect an activated arylfluorine group via the use of acetal protection chemistry.

The key dihydroxyketone **6** was prepared in two steps from the reaction of 4-fluorophenyl magnesium chloride with 3,5-dimethoxybenzoyl chloride to give **5**, followed by deprotection of the methoxy groups with BBr_3 (Scheme 3). The diol **6** was then protected with 1,2-bis(trimethylsiloxy)ethane. The resulting product **7**, isolated in 70% yield, proved only moderately stable and decomposed upon standing after a week. Undoubtedly, the presence of the mildly acidic phenolic protons was catalysing the attack on the acetal functionality. However, **7** could be kept indefinitely in solution (in THF) if stored over sodium carbonate. In practise, the compound was used immediately after preparation and purification.

The reaction between 4-fluoro-3′,5′-dihydroxybenzophenone and **7** proceeded in 73% yield to give a waxy amorphous solid **8**. Sodium carbonate was used as a base, as it has been reported that the use of potassium carbonate can catalyse transetherification reactions in similar systems.[17] This is because the bi-product, potassium fluoride, is soluble in DMSO solvent and can attack the existing diphenyl ketone ether structures, whereas sodium fluoride is insoluble. While this is of little consequence when producing polymers, in the present case any transetherification will produce scrambling of the dendrimer leading to defects in the structures. We looked at DMF as an alternative solvent. However, at high temperatures needed for the coupling, we found some



Scheme 2.



Scheme 3. Synthesis of generation one dendron **9**.

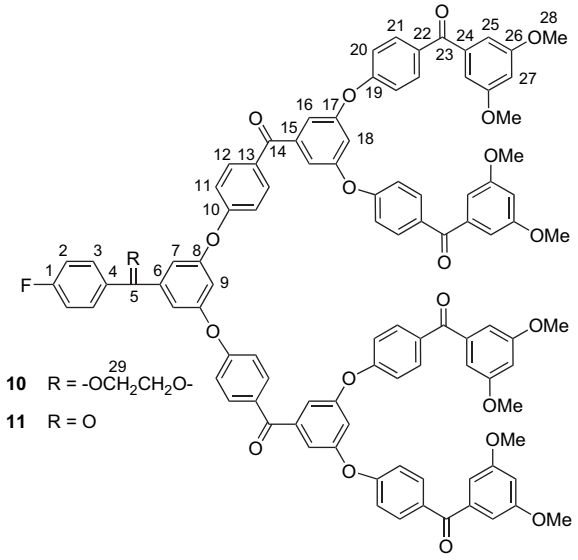
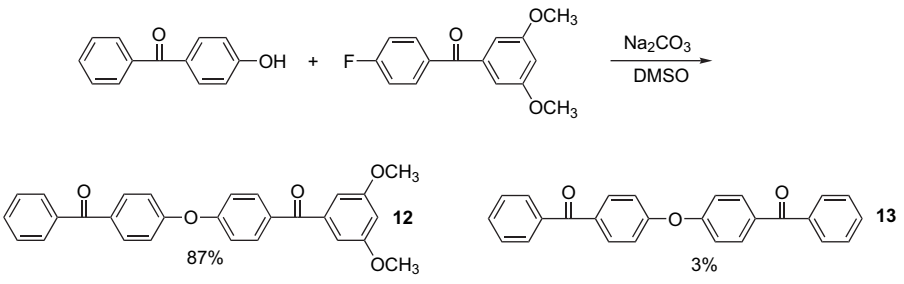


Figure 1. Structure and atom numbering of dendrons **10** and **11**.

substitution of fluoride with dimethylamine had occurred. This side-product, probably arose via decomposition of the solvent under the basic conditions.

The NMR of **8** showed that the acetal ring survived during the reaction and work-up. Again, the reaction appeared clean with only one product seen on TLC analysis and isolated. Compound **8** was deprotected cleanly to give the first generation product **9**. Coupling of **9** with **7** under identical conditions as before gave the protected second generation wedge **10** in a reduced yield of 48% (Fig. 1). Unlike previous couplings, several other compounds could be seen under TLC analysis, suggesting that the reaction was not quite as clean as hoped. Deprotection as before gave **11** in 83% yield as an amorphous white solid. While the deprotection was very clean by TLC analysis, some of the compounds appeared to irreversibly bind to the silica column, perhaps accounting for the less than quantitative yields.

Attempted preparation of the third generation wedge produced a complex mixture that couldn't be purified further. It was obvious that side reactions were competing with the desired coupling reactions. In order to determine the possible cause, a model study was performed. Coupling of 4-hydroxybenzophenone with **1**, under conditions used previously, gave an isolated yield of 87% of the expected product **12**, along with 3% of the side-product **13**. The side-product was clearly being produced by the attack of phenoxide on the product (Scheme 4). Transetherification in benzophenone derivatives has been noted before,[17] and we were unable to find any different conditions (temperature, solvents or base) to eliminate the formation of this side-product. It appears that the rate difference in the nucleophilic aromatic substitution between an aryl fluoride and aryl phenyl ether



Scheme 4. Model coupling reaction.

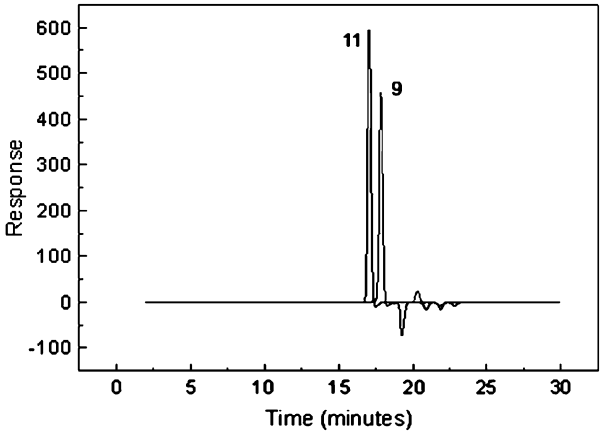


Figure 2. Size exclusion chromatographs of dendrons **9** and **11**.

may be fairly insensitive to conditions. Three percent transetherification is of minor consequence in the formation of lower generation dendrimers. However, by the time a generation three product is required, there are six times more potentially reactive aryl ether sites than fluoride sites in the starting material. Added to this is the strong possibility that the terminal fluoride group may have lower reactivity than expected due to steric crowding at the apex of the dendron. The net result appears to be the scrambling of dendrimeric structure at high generation, which appears to be a limitation in the use of a nucleophilic route to higher poly(phenyl ether) structures at present.

The purity of the generations one and two wedges was checked for any scrambling. The ^{1}H and ^{13}C NMR spectra of both products were very clean, and all the carbons could be accounted for, with no extra peaks. The carbon and proton spectra were fully assigned by use of model compounds and peak intensities. Gel permeation chromatography of the generations one and two structures showed a monodisperse product (polydispersity$<$1.05) (Fig. 2), and mass spectral analysis (ESI) showed no higher molecular weight products. The dendrimers were all amorphous, waxy materials, perhaps suggesting a low T_g for the un-cross-linked material. DSC measurements did not reveal an obvious glass transition point, perhaps due to the variety of the structural elements present.

3. Conclusions

Protection of an aryl fluoride towards nucleophilic substitution can be achieved via acetylisation of a *para*-ketone substituent. The best reagent for the protection was found to be trimethylsilyl trifluoromethanesulfonate. Deprotection can be achieved under mild acidic conditions to activate the fluoro-group. This protection–deprotection strategy allows the formation of phenyl ketone denritic wedges and possibly dendrimers to be constructed in a convergent fashion. A generation two dendritic wedge was ultimately constructed. This method works well for lower generations, but transetherification produces scrambling at higher generation that limits the utility of this method at this time for larger structures until more selective reaction conditions are found.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded using Bruker DPX-250 (250 MHz), DPX-400 (400 MHz) and DPX-500 (500 MHz) using the indicated deuterated solvent. Chemical shifts (δ in parts per million) are quoted relative to residual proton signals in chloroform where δ ($CHCl_3$)=7.26. Signal multiplets are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer. The samples were prepared as KBr discs or as thin films on NaCl plates as an oil. Microanalysis was performed by the University Chemical Laboratory Microanalytical Department. Melting points were determined using a Gallenkamp melting point apparatus and are not corrected. Flash chromatography was carried out on Merck Silica Gel 60. Thin layer chromatography (TLC) was carried out on a pre-coated 0.2 mm Merck 60 F_{254} silica plates, visualised by either UV light (366 nm) or potassium permanganate oxidation. Size exclusion chromatography was carried out using 3 Polymer Laboratories PL Gel mixed C (cross-linked polystyrene/divinylbenzene) columns, chloroform solvent, flow rate 1 mL/min and at 30 °C.

4.1.1. 4-(2-Phenyl-[1,3]dioxolan-2-yl)-phenol (2). To a solution of 4-hydroxybenzophenone **1** (0.60 g, 3.0 mmol) in dry DCM (15 mL), at 0 °C under nitrogen, was added 1,2-bis(trimethylsilyloxy)ethane (1.40 mL, 6.1 mmol). The mixture was left for 30 min under nitrogen and then trimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.3 mmol) was added under nitrogen. After 30 min the temperature was raised to room temperature for 5 h. Pyridine (0.1 mL) was added to the mixture and then it was placed into water (40 mL) and extracted with ethyl acetate (3×30 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography on silica gel, using 82:18 hexane/ethyl acetate yielded 0.52 g (71%) of a white solid, **2**; R_f (hexane/ethyl acetate 1:1) 0.85; mp 107–109 °C; IR (KBr) 3100–3000, 2900, 1590, 1555, 1500, 1250, 1180 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.49 (d, 2H, H-3, $^{3}J_{HH}$=8.0 Hz), 7.37–7.25 (m, 5H, aromatic), 6.74 (d, 2H, H-8, $^{3}J_{HH}$=9.0 Hz), 4.93 (s, 1H, OH), 4.04 (m, 4H, H-10); *m/z* (ESI) 265.08 [M+Na^+. $C_{15}H_{14}O_3Na$ requires M+Na, 265.08406]; *m/z* (ESI) 265.1 (M+Na^+, 100%), 243.1 (23%); found C, 74.0%; H, 5.8%. $C_{15}H_{14}O_3$ requires C, 74.4%; H, 5.8%.

4.1.2. Phenyl-4-{[4-(2-phenyl-[1,3]dioxolan-2-yl)-phenoxy]-phenyl}-methanone (3). To a solution of compound **2** (0.50 g, 2.1 mmol) and 4-fluorobenzophenone (0.46 g, 2.1 mmol) in dry DMSO (20 mL) was added Na_2CO_3 (0.22 g, 2.1 mmol). The mixture was heated to 160 °C for 24 h and then cooled to room temperature. Water (40 mL) was then added and the mixture was extracted with ethyl acetate (3×30 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Recrystallisation from hexane/ether yielded 0.72 g (84%) of a white solid, **3**; R_f (hexane/ethyl acetate 1:1) 0.69; mp 119–121 °C; IR (KBr) 3050, 2900, 1660, 1590, 1310, 1250, 1180, 1080 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.79 (d, 2H,

H-16, $^3J_{HH}$=7.0 Hz), 7.76 (d, 2H, H-12, $^3J_{HH}$=7.0 Hz), 7.58–7.50 (m, 4H, aromatic), 7.45 (t, 2H, H-2, $^3J_{HH}$= 8.0 Hz), 7.36–7.27 (m, 4H, aromatic), 7.04 (d, 2H, H-8, $^3J_{HH}$=7.0 Hz), 7.01 (d, 2H, H-11, $^3J_{HH}$=7.0 Hz), 4.07 (m, 4H, H-19, H-20); ^{13}C NMR (100 MHz) δ ($CDCl_3$) 195.5, 161.3, 155.4, 141.9, 138.4, 137.9, 132.4, 132.1, 132.0, 129.8, 128.2, 128.2, 128.1, 126.1, 119.6, 117.3, 109.1, 64.9; *m/z* (EI) 422.15206 [M^+. $C_{28}H_{22}O_4$ requires M, 422.15181]; *m/z* (EI) 422.2 (M^+, 40%), 345.1 (100%), 149.1 (57%), 68.9 (38%); found C, 79.6%; H, 5.3%. $C_{28}H_{22}O_4$ requires C, 79.4%; H, 5.3%.

4.1.3. Bis-(4-benzoylphenyl) ether (4). To a solution of **3** (0.50 g, 1.2 mmol) in acetone (15 mL) was added *p*-toluenesulfonic acid (0.33 g, 1.2 mmol). The mixture was heated at 50 °C for 3 h and then placed in water (30 mL). The mixture was then extracted with ethyl acetate (3×30 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Recrystallisation from ethanol yielded 0.42 g (93%) of a white solid, **4**; R_f (hexane/ethyl acetate 1:1) 0.72; mp 162–164 °C (lit.[18] mp 163–165 °C); IR (KBr) 3030, 1650, 1600, 1500, 1320, 1290, 1170 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.87 (d, 4H, H-7, $^3J_{HH}$=9.0 Hz), 7.79 (d, 4H, H-3, $^3J_{HH}$=7.0 Hz), 7.58 (t, 2H, H-1, $^3J_{HH}$=7.5 Hz), 7.48 (t, 4H, H-2, $^3J_{HH}$=7.5 Hz), 7.14 (d, 4H, H-8, $^3J_{HH}$=9.0 Hz); *m/z* (EI) 378.12547 [M^+. $C_{26}H_{18}O_3$ requires M, 378.12559]; *m/z* (EI) 378.1 (M^+, 98%), 301.1 (100%), 68.9 (97%); found C, 82.3%; H, 4.8%. $C_{26}H_{18}O_3$ requires C, 82.5%; H, 4.8%.

4.1.4. 5-(2-Phenyl-[1,3]dioxolan-2-yl)-benzene-1,3-diol (7). To a solution of 4-fluoro-3′,5′-dihydroxybenzophenone[10c] **6** (1.10 g, 4.7 mmol) in dry ether (15 mL), at 0 °C under nitrogen, was added 1,2-bis(trimethylsilyloxy)-ethane (1.40 mL, 6.1 mmol). The mixture was left for 30 min under nitrogen and then trimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.3 mmol) and trifluoroacetic acid (two drops) were added. After 30 min, the temperature was raised to room temperature for 5 h. Pyridine (0.1 mL) was added to the mixture and, after 30 min, water (40 mL) was added. The mixture was extracted with ethyl acetate (3× 30 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography on silica gel using 60:40 hexane/ethyl acetate yielded a waxy solid. The waxy solid was stirred in DCM where upon a precipitate was formed. The precipitate was filtered and the filtrate was concentrated in vacuo to yield 0.93 g (70%) of a waxy solid, **7**; R_f (hexane/ethyl acetate 1:1) 0.40; IR (KBr) 3100–3000, 2900, 1720, 1600, 1650, 1510, 1500, 1420, 1225, 1180 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.45 (dd, 2H, H-3, $^3J_{HH}$=9.0 Hz, $^4J_{HF}$=9.0 Hz), 6.98 (t, 2H, H-2, $^3J_{HH}$=$^4J_{HF}$=9.0 Hz), 6.54 (d, 2H, H-7, $^4J_{HH}$=2.5 Hz), 6.26 (d, 1H, H-9, $^4J_{HH}$=2.5 Hz), 5.00–4.85 (s, 2H, OH), 4.04 (m, 4H, H-10, H-11); *m/z* (EI) 276.1 (M^+, 38%), 181.1 (45%), 167.1 (54%), 123.0 (54%), 95 (71%), 68.9 (100%); found C, 65.3%; H, 4.1%. $C_{15}H_{13}O_4F$ requires C, 65.2%; H, 4.7%.

4.1.5. First generation protected poly(ether ketone) dendron (8). 4-Fluoro-3′,5′-dimethoxybenzophenone[18] **5** (0.44 g, 1.6 mmol) and **7** (0.11 g, 0.8 mmol) were dissolved in dry DMSO (10 mL) and Na_2CO_3 (0.20 g) was added. The mixture was heated to 160 °C for 24 h and then cooled to room temperature. The solvent was evaporated and column chromatography on silica gel using 73:27 hexane/ethyl acetate yielded 0.43 g (72%) of a waxy solid, **8**; R_f (hexane/ethyl acetate 1:1) 0.60; IR (KBr) 2900, 1725, 1600, 1505, 1480, 1380, 1160, 1100 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.81 (d, 4H, H-12, $^3J_{HH}$=8.8 Hz), 7.45 (m, 2H, H-3), 7.09–6.08 (m, 8H, H-7, H-2, H-11), 6.87 (d, 4H, H-16, $^3J_{HH}$=2.3 Hz), 6.71 (t, 1H, H-9, $^4J_{HH}$=2.3 Hz), 6.65 (t, 2H, H-18, $^4J_{HH}$=2.3 Hz), 4.05 (m, 4H, H-20), 3.82 (s, 12H, H-19); ^{13}C NMR (100 MHz) δ ($CDCl_3$) 195.0 (C14), 162.6 (d, J_{CF}=246 Hz, C1), 160.6 (C17, C10), 156.9 (C8), 146.4 (C6), 137.8 (C4), 132.5 (C12), 132.5 (C13), 127.8 (d, J_{CF}=9 Hz, C3), 117.9 (C11), 115.3 (d, J_{CF}=21 Hz, C2), 113.4 (C7), 110.8 (C9), 108.3 (C5), 107.7 (C16), 104.5 (C18), 65.1 (C20), 55.6 (C19); *m/z* (ESI) 779.22780 [M+Na^+. $C_{45}H_{37}O_{10}F$ requires M+Na, 779.22685]; *m/z* (ESI) 779.23 (M+Na^+, 100%); found C, 71.9%; H, 4.8%. $C_{45}H_{37}O_{10}F$ requires C, 71.5%; H, 4.9%.

4.1.6. Deprotected first generation poly(ether ketone) dendron (9). To the methoxy terminated poly(ether ketone) dendron **8** (0.27 g, 0.35 mmol) in acetone (10 mL) was added *p*-toluenesulfonic acid (0.2 g). The mixture was heated at 50 °C for 3 h and then placed in water (30 mL). The mixture was then extracted with ethyl acetate (3×30 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography on silica gel using 75:25 hexane/ethyl acetate yielded 0.21 g (83%) of a waxy solid, **9**; R_f (hexane/ethyl acetate 1:1) 0.67; IR (KBr) 3000, 2810, 1725, 1655, 1600, 1505, 1480, 1280, 1170, 1080 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.85 (m, 6H, H-3, H-12), 7.27 (d, 2H, H-7, $^4J_{HH}$=2.0 Hz), 7.16 (t, 2H, H-2, $^3J_{HH}$=$^3J_{HF}$=8.5 Hz), 7.09 (d, 4H, H-11, $^3J_{HH}$=8.5 Hz), 7.03 (t, 1H, H-9, $^4J_{HH}$=2.0 Hz), 6.87 (d, 4H, H-16, $^4J_{HH}$=2.5 Hz), 6.65 (t, 2H, H-18, $^4J_{HH}$=2.5 Hz), 3.82 (s, 12H, H-19); ^{13}C NMR (100 MHz) δ ($CDCl_3$) 194.9 (C14), 193.2 (C5), 165.5 (d, J_{CF}=254 Hz, C1), 160.6 (C17), 160.0 (C8), 157.4 (C10), 140.7 (C6), 139.5 (C15), 133.0 (C13), 132.9 (d, J_{CF}=3 Hz, C4), 132.7 (d, J_{CF}=9 Hz, C3), 132.6 (C12), 117.9 (C11), 116.2 (C7), 115.7 (d, J_{CF}=24 Hz, C2), 114.6 (C9), 107.7 (C16), 104.5 (C18), 55.6 (C19); *m/z* (EI) 735.20008 [M+Na^+. $C_{43}H_{33}O_9F$ requires M+Na, 735.20063]; *m/z* (ESI) 735.20 (M+Na^+, 30%), 306.1 (100%); found C, 72.7%; H, 5.2%. $C_{43}H_{33}O_9F$ requires C, 72.5%; H, 5.0%.

4.1.7. Second generation protected poly(ether ketone) dendron (10). Protected dendron **9** (0.20 g, 0.275 mmol) and diol **7** (0.038 g, 0.14 mmol) were dissolved in dry DMSO (7 mL) and Na_2CO_3 (0.12 g) was added. The mixture was heated to 160 °C for 24 h and then cooled to room temperature. Column chromatography on silica gel using 55:45 hexane/ethyl acetate yielded 0.11 g (48%) of a waxy solid, **10**; R_f (hexane/ethyl acetate 1:1) 0.52; IR (KBr) 3000, 2900, 1725, 1650, 1600, 1505, 1480, 1380, 1160, 1100, 1080 cm^{-1}; ^{1}H NMR (400 MHz) δ ($CDCl_3$) 7.87–7.79 (2d, 12H, H-12, H-21, $^3J_{HH}$=8.5 Hz), 7.43 (t, 2H, H-2, $^3J_{HH}$=$^3J_{HF}$=9.0 Hz), 7.26 (m, 4H, aromatic), 7.15–6.95 (m, 16H, aromatic), 6.87 (d, 8H, H-25, $^3J_{HH}$=2.0 Hz), 6.70 (m, 3H, H-18, H-9), 6.65 (t, 4H, H-27, $^4J_{HH}$=2.0 Hz), 4.03 (m, 4H, H-29, H-30), 3.80, (s, 24H, H-28); ^{13}C NMR (100 MHz) δ ($CDCl_3$) 194.9 (C23), 193.3 (C14), 164.6 (d, J_{C-F}= 151 Hz, C1), 161.4 (C10), 161.1 (C26), 160.6 (C19), 157.2

(C17), 156.7 (C8), 146.5 (C6), 141.0 (C15), 139.4 (C24), 132.9 (C22), 132.6 (C21), 132.5 (C12), 131.9 (C4), 131.5 (C13), 127.8 (d, J_{CF}=8 Hz, C3), 118.0 (C20), 117.6 (C11), 116.3 (C16), 115.2 (d, J_{CF}=21 Hz, C2), 114.4 (C7), 113.6 (C18), 111.1 (C9), 108.3 (C5), 107.7 (C25), 104.5 (C27), 65.1 (C29), 55.6 (C28); found C, 73.2%; H, 4.4%. $C_{101}H_{77}O_{22}F$ requires C, 73.0%; H, 4.7%.

4.1.8. Second generation deprotected poly(ether ketone) dendron (11). To the methoxy terminated poly(ether ketone) dendron **10** (0.11 g, 0.056 mmol) in acetone (10 mL) was added *p*-toluenesulfonic acid (0.1 g). The mixture was heated at 50 °C for 3 h and then placed in water (20 mL). The mixture was then extracted with ethyl acetate (3× 20 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography on silica gel using 57:43 hexane/ethyl acetate yielded 0.09 g (80%) of a waxy solid, **11**; R_f (hexane/ethyl acetate 1:1) 0.54; IR (KBr) 2900, 1725, 1700, 1690, 1650, 1600, 1505, 1480, 1280, 1235, 1155, 1080 cm^{-1}; ^1H NMR (400 MHz) δ ($CDCl_3$) 7.85 (m, 14H, H-3, H-12, H-21), 7.27–7.23 (m, 7H, aromatic), 7.15–7.00 (m, 16H, aromatic), 6.87 (d, 8H, H-25, $^3J_{HH}$=2.3 Hz), 6.64 (t, 4H, H-27, $^4J_{HH}$=2.3 Hz), 3.80 (s, 24H, H-28); ^{13}C NMR (100 MHz) δ ($CDCl_3$) 194.9 (C23), 193.2 (C14), 193.0 (C5), 160.6 (C26), 160.5 (C10), 160.1 (C19), 157.3 (C17), 157.1 (C8), 140.9 (C15), 140.8 (C6), 139.5 (C24), 133.0 (C22), 132.7 (C21+C12+C3), 132.6 (C4), 132.1 (C13), 118.0 (C11), 117.9 (C20), 116.5 (C7), 116.4 (C16), 115.7 (d, J_{CF}=18 Hz), 114.8 (C9), 114.5 (C18), 107.7 (C25), 104.5 (C27), 55.6 (C28); SEC (THF) M_w 1210, PD 1.05; found C, 73.0%; H, 5.3%. $C_{99}H_{73}O_8F$ requires C, 73.4%; H, 4.8%.

4.1.9. {4-[4-(3,5-Dimethoxy-benzoyl)-phenoxy]-phenyl}-phenyl-methanone (12). To a solution of 4-fluoro-3′,5′-dimethoxybenzophenone **5** (0.20 g, 0.7 mmol) and 4-hydroxybenzophenone (0.15 g, 0.8 mmol) in anhydrous DMSO (20 mL) was added Na_2CO_3 (0.81 g, 0.8 mmol). The mixture was heated to 160 °C under nitrogen for 24 h and then cooled to room temperature. The mixture was then added to water (40 mL) and extracted with ethyl acetate (3×40 mL). The combined extracts were then dried over magnesium sulfate, filtered and concentrated in vacuo. Column chromatography on silica gel using 90:10 hexane/ethyl acetate yielded 0.30 g (89%) of product as a waxy solid, **12**; R_f (hexane/ethyl acetate 1:1) 0.82; IR (KBr) 2950, 2360, 1710, 1660, 1590, 1510, 1460, 1110 cm^{-1}; ^1H NMR (400 MHz) δ ($CDCl_3$) 7.87 (d, 2H, H-3, $^3J_{HH}$=9.0 Hz), 7.85 (d, 2H, H-7, $^3J_{HH}$=9.0 Hz), 7.78 (d, 2H, H-3, $^3J_{HH}$= 7.0 Hz), 7.58 (t, 1H, H-1, $^3J_{HH}$=7.5 Hz), 7.48 (t, 2H, H-2, $^3J_{HH}$=7.5 Hz), 7.12 (m, 4H, H-8, H-11), 6.90 (d, 2H, H-16, $^4J_{HH}$=2.5 Hz), 6.66 (t, 1H, H-18, $^4J_{HH}$=2.5 Hz), 3.82 (s, 6H, H-19); ^{13}C NMR (100 MHz) δ ($CDCl_3$) 195.4, 195.0 (C5, C14), 160.6 (C17), 159.9, 159.8 (C9, C10), 139.5 (C15), 137.7 (C4), 133.5, 133.1 (C6, C13), 132.5, 132.5 (C7, C12), 132.3 (C1), 131.9, (C3), 129.8, 128.3 (C2), 118.6, 118.5 (C8, C11), 107.8 (C16), 104.5 (C18), 55.6 (C19); *m/z* (EI) 438.14734 [M^+. $C_{28}H_{22}O_5$ requires M, 438.14673]; *m/z* (EI) 438.1 (30%), 301.1 (20%), 119.0 (80%), 68.8 (100%); found C, 77.1%; H, 5.7%. $C_{28}H_{22}O_5$ requires C, 76.7%; H, 5.1%.

Column chromatography using 85:15 hexane/ethyl acetate and crystallisation from ether/hexane yielded 0.009 g (3%) of a white solid, **4**.

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References and notes

1. (a) Denkewalter, R. G.; Kolc, J. F.; Lukasavage, W. J. U.S. Patent 4,410,688, 1983; (b) Newkombe, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003–2004; (c) Tomalia, D. A. B.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* **1985**, *17*, 117–132; (d) Tomalia, D. A. B.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Macromolecules* **1986**, *19*, 2466–2468; (e) Padias, A. B.; Hall, H. K.; Tomalia, D. A.; McConnell, J. R. *J. Org. Chem.* **1987**, *52*, 5305–5312.
2. (a) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons; Concepts, Synthesis and Applications*; Wiley-VCH: Weinheim, 2001; (b) *Topics in Current Chemistry, Vol. 197, Dendrimers*; Vögtle, F., Ed.; Springer: Berlin, 1998; and *Vol. 210, Dendrimers II*, Springer: Berlin, 2000; (c) *Dendrimers and Other Dendritic Polymers*; Fréchet, J. M. J., Donald, A., Tomalia, D. A., Eds.; Wiley: Chichester, UK, 2001.
3. Jansen, J. F. G. A.; De Brabander Vandenberg, E. M. M.; Meijer, E. W. *Science* **1994**, *266*, 1226–1229.
4. (a) Stewart, G. M.; Fox, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 4354–4360; (b) Balzani, V.; Campagna, S.; Denti, G.; Juris, A.; Serroni, S.; Venturi, M. *Coord. Chem. Rev.* **1994**, *132*, 1–13.
5. (a) Evans, D. J.; Kanagasooriam, A.; Williams, A.; Pryce, R. J. *J. Mol. Catal.* **1993**, *85*, 21–32; (b) Brunner, H.; Altmann, S. *Chem. Ber.* **1994**, *127*, 2285–2296.
6. Wang, P. W.; Liu, Y. J.; Devadoss, C.; Bharathi, P.; Moore, J. S. *Adv. Mater.* **1996**, *8*, 237–241.
7. (a) Morgenroth, F.; Ruether, E.; Mullen, K. *Angew. Chem., Int. Ed.* **1997**, *36*, 631–634; (b) Miller, T. M.; Neenan, T. X. *Chem. Mater.* **1990**, *2*, 346–649.
8. Xu, Z.; Moore, J. S. *Acta Polym.* **1994**, *45*, 83–87.
9. (a) Stewart, G. M.; Fox, M. A. *Chem. Mater.* **1998**, *10*, 860–863; (b) Jakubiak, R.; Bao, Z.; Rothberg, L. *Synth. Met.* **2000**, *114*, 61–64; (c) Malenfant, P. R. L.; Fréchet, J. M. J. *Macromolecules* **2000**, *33*, 3634–3640; (d) Shu, L. J.; Schafer, T.; Schluter, A. D. *Macromolecules* **2000**, *33*, 4321–4328.
10. (a) Hawker, C. J.; Fréchet, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2459–2469; (b) Wooley, K. L.; Hawker, C. J.; Lee, R.; Fréchet, J. M. J. *Polym. J.* **1994**, *26*, 187–197; (c) Chu, R.; Hawker, C. J. *Polym. Bull.* **1993**, *30*, 265–272; (d) Kim, Y. H.; Webster, O. W. *Macromolecules* **1992**, *25*, 5561–5572; (e) Miller, T. M.; Neenan, T. X.; Zayas, R.; Blair, H. E. *J. Am. Chem. Soc.* **1992**, *114*, 1018–1025.
11. *Polymer Handbook*, 4th ed.; Brandrup, J., Immergut, E. H., Grulke, E. A., Eds.; Wiley: New York, NY, 1999.
12. Abramov, M. A.; Shukla, R.; Amabilino, D. B.; Dehaen, W. *J. Org. Chem.* **2002**, *67*, 1004–1007.
13. Morikawa, A.; Kakimoto, M.; Imai, Y. *Macromolecules* **1993**, *26*, 6324–6329.

14. (a) For examples, see: Bolos, J.; Gubert, S.; Anglada, L.; Planas, J. M.; Burgarolas, C. *J. Med. Chem.* **1996**, *15*, 2962–2970; (b) Ravina, E.; Fueyo, J.; Masaguer, C. F.; Negreira, J.; Cid, J. *Chem. Pharm. Bull.* **1996**, *44*, 534–541.
15. Kelsey, D. R.; Robeson, L. M.; Clendinning, R. A. *Macromolecules* **1987**, *20*, 1204–1212.
16. Lucas, P.; Mehdi, N. E.; Ho, H. A.; Belanger, D.; Breau, L. *Synthesis* **2000**, *9*, 1253–1258.
17. Colquhoun, H. M.; Dudman, C. C.; Blundell, D. J.; Bunn, A.; Macenzie, P. D.; McGrail, P. T.; Williams, D. J. *Macromolecules* **1993**, *26*, 107–111.
18. Fukawa, I.; Tanabe, T.; Dozona, T. *J. Chem. Soc., Perkin Trans. 2* **1992**, 377–382.

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Functionalized thiacalix- and calix[4]arene-based Ag^+ ionophores: synthesis and comparative NMR study

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Abstract—Thiacalix[4]arene ionophores comprised of cyclic or linear *O*,*S*,*N* ligating and/or π-coordinate groups on the lower rim were synthesized and their Ag^+ binding was studied by ^1H NMR methods in comparison with the respective known and novel calix[4]arene counterparts. Calix[4](*O*,*S*,*N*)crowns were found stronger binders than the π-coordinate molecules and thiacalixarene ionophores were generally superior to calixarenes. This study helped to develop silver ion-selective electrodes working in the subnanomolar region.

1. Introduction

Over the last two decades, considerable efforts have been devoted to the design and synthesis of calixarene (CA)-based ionophores and a number of functionalized derivatives have been applied as extractants and sensors in analytical and separation chemistry.[1,2] In fact, many calixarenes containing pendant ether, ester, amide and ketonic groups, in addition to calix(mono- and biscrowns) have been used as neutral carriers in ion-selective electrodes (ISE) exhibiting selective responses to main group metal ions, such as Na^+, K^+ and Cs^+.[3–14] Transition metal ion (Ag^+, Hg^{2+}, Pb^{2+} etc.) selective receptors are less prevalent in calixarene chemistry,[15–19] but recently Zhang's group has published a series of Ag^+ ionophores comprised of sulfur, selenium, nitrogen and phosphorus atoms in the ligating groups attached to the lower rim.[20–26] The binding ability of these ligands is based alike on the preferred interaction between the soft donor atoms (S, Se, N) and the soft Ag^+ ion. At the same time, some recent works have demonstrated that a π-system can be suitable binding site for soft cations via π-cation interaction[27] and in fact, a π-coordinate tetraallyloxy-CA was already utilized in the development of a calixarene-based Ag^+ ISE.[28] Although thiacalix[4]arenes (TCA) have received growing interest since their discovery in 1997,[29] so far the synthesis and application of the respective thiacalixarene ionophores have remained unexplored. The investigation of cation extraction ability of the parent TCA revealed that it efficiently extracts a number of transition metal ions without any selectivity at pH 7.5.[30,31] Obviously, similar to calix[4]arenes, appropriate functionalization on the lower rim is required to achieve cation selectivities of practical value. Probably, synthetic difficulties aroused on the regio- and stereoselective functionalization of TCA have prevented an extended research in this field.[32] In fact, only a few thiacalix[4]crown-6 ethers (**I**) have been reported to display Cs^+ selectivity in extraction experiments[33,34] and utilized as neutral carriers in ISEs.[35,36] Besides, the selective cation extraction ability of 24,26-bis(3-hydroxypropoxy)-*p*-*tert*-butyl-TCA (Ag^+)[31] and 24,25,26,27-tetrakis(diethylcarbamoylmethoxy)-*p*-*tert*-butyl-TCA (Pb^{2+})[37] are worth mentioning.

Seeking a selective method for the distal dialkylation and ring closure of TCA, we have recently recognized that the Mitsunobu reaction is an extremely simple, efficient and mild method to diametrically alkylate and cyclize TCA with alcohols and diols.[38–40]

In this way, we have prepared a series of thiacalix[4](*O*,*S*,*N*-crown-5)ethers[40] and herein our studies with selected derivatives, completed by new molecules containing known soft ligating functions, are reported. For comparison, the respective calixarene counterparts including known and new ionophores were synthesized and their Ag^+ sensing was also investigated by ^1H NMR under similar conditions. Our final goal was to find TCA ligands for developing silver ISEs

Keywords: Thiacalix[4]arenes; Calix[4]arenes; Calix[4]crowns; Ag^+ complexation; NMR.
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possessing high stability and sensitivity in the subnanomolar region without the drawbacks of the known sensors. The electroanalytical evaluation of ISEs fabricated from our best ligands has been published elsewhere.[41]

2. Results and discussion

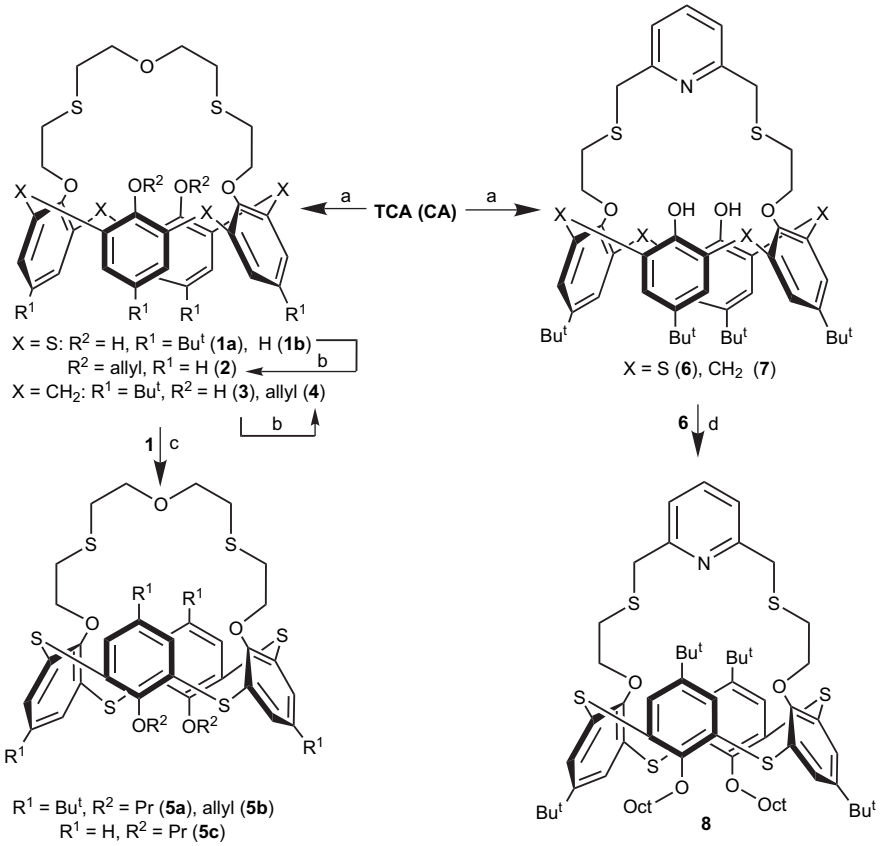
The potential silver sensing ligands are surveyed in Schemes 1 and 2. The selection of molecules requires some comments. A number of thiacrown ethers were designed as neutral carriers for Ag^+ ISEs.[1d] However, the binding of Ag^+ with the crown-ring sulfur atoms is strong, often causing slow metal ion exchange equilibrium in the membrane interface, which results in slow sensor response and poor selectivity. These disadvantages and the alkali- and alkaline earth metal ion interference were expected to be eliminated by designing calix[4](*O*,*S*,*N*-crown-5) ethers (cone **1**–**4**, **6**, **7** and 1,3-alt **5** and **8**), where the calixarene skeleton and the conformation were varied (Scheme 1).

Podands **9** and **10**, containing the same 1,3-benzothiazole binding site attached to different calixarenes in distal position through a spacer, represent the flexible version of receptors that may have advantages over rigid ionophores. The π–cation interaction of soft Ag^+ is relatively weak, but quite selective, thereby providing another way of sensing.[28] Therefore, it seemed to be promising to test the binding ability of ligands **11**–**16** (including **14** as reference[28]), where the number of π-donor allyl groups, the calixarene scaffold and the conformation were varied (Scheme 2).

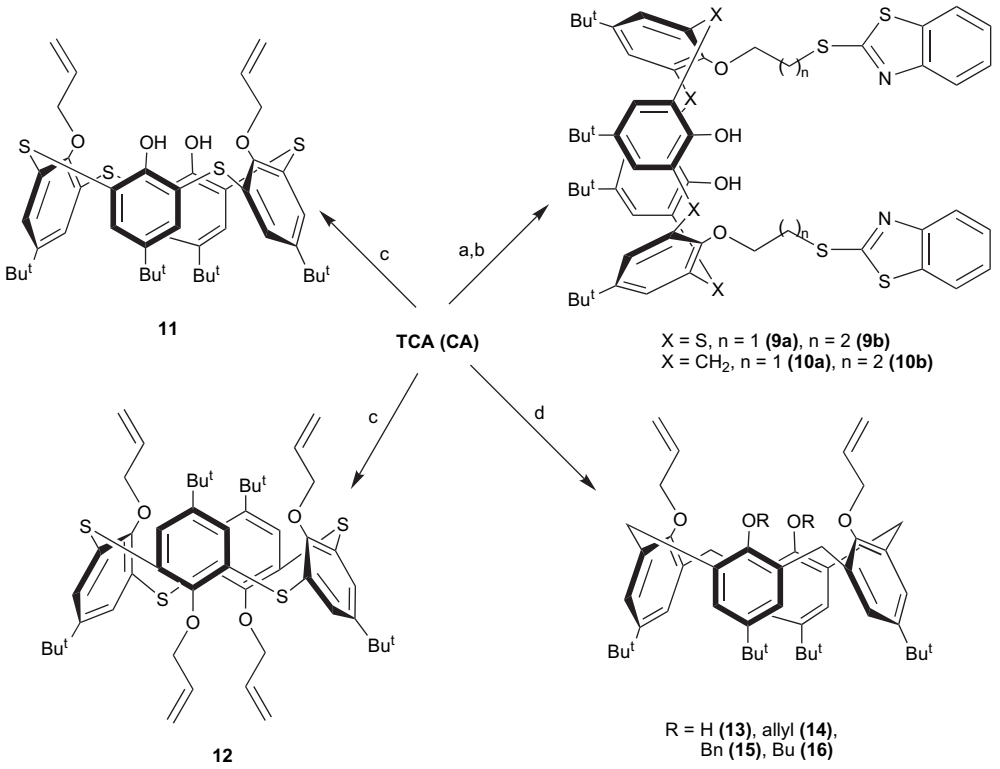
2.1. Synthesis

Thiacalix[4](*O*,*S*,*N*-crown-5)ethers **1a**, **6** and **8** were described by us[40] and the analogous **1b**, **3** and **7** were prepared similarly by the Mitsunobu cyclization of TCA or *p*-Bu^{t}CA with diols using triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) coupling agents.

The O-alkylation of **1b** and **3** was performed with allylbromide under PTC conditions (50% aq NaOH/$Bu_4N^+Br^-$)[42] to afford cone **2** and **4**, and with PrI or allylbromide/Cs_2CO_3 to give 1,3-alt **5a**–**c**. Bis(1,3-benzothiazol-2-yl)-CA derivatives **10a**,**b** were described by Zhang using the weak base-promoted S-alkylation of 2-mercapto-1,3-benzothiazole with 25,27-bis(bromoalkoxy)-*p*-*tert*-butylcalix[4]-arene.[23,25] The TCA analogue **9a** was obtained by slight modification of the literature method developed for **10a**,**b**[23] but this procedure failed to give **9b**. Instead, the Mitsunobu alkylation of *p*-Bu^t-TCA with 2-(3-hydroxypropylthio)-1,3-benzothiazole led to success. The π-coordinate allyloxy-TCA ligands **11** and **12** were obtained by our regio- and conformation-selective alkylation of TCA with allylalcohol under Mitsunobu condition,[38] while 25,27-diallyloxy-CA **13** was prepared as described earlier.[43] Tetrasubstituted CA ionophores **14**–**16** were synthesized by our PTC alkylation method of CA with allylbromide (**14**), and



Scheme 1. Survey and synthesis of calix[4]crown ionophores to be tested for Ag^+ sensing. Reagents and conditions: (a) diol, TPP/DEAD, toluene, rt (**1a**,**b**, **3**, **6**, **7**); (b) **1b** or **3**, allylbromide, aq NaOH, PTC (**2**, **4**); (c) allylbromide or PrI, Cs_2CO_3, MeCN, 80 °C (**5a**–**c**); (d) OctOH, TPP/DEAD, toluene, 80 °C.



Scheme 2. Survey and synthesis of open-chain calix[4]arene ionophores to be tested for Ag^+ sensing. Reagents and conditions: (a1) (i) *p*-Bu^t-TCA, 2-bromoethanol, TPP/DEAD, toluene, rt; (ii) 2-mercapto-1,3-benzothiazole, $NaHCO_3$, MeCN, 80 °C (**9a**); (a2) (i) *p*-Bu^t-CA, 1,2-dibromoethane, K_2CO_3, MeCN, 80 °C; (ii) 2-mercapto-1,3-benzothiazole, $NaHCO_3$, aq THF (**10a**,**b**); (b) *p*-Bu^t-TCA, 2-(3-hydroxypropylthio)-1,3-benzothiazole, TPP/DEAD, toluene, rt (**9b**); (c) allylalcohol, TPP/DEAD, toluene, rt (**11**) or 80 °C (**12**); (d1) *p*-Bu^t-CA, allylbromide, K_2CO_3, acetone, 56 °C (**13**); (d2) *p*-Bu^t-CA, allylbromide, aq NaOH, PTC (**14**); (d3) **13**, aq NaOH, PTC, BnBr (**15**) or BuBr (**16**).

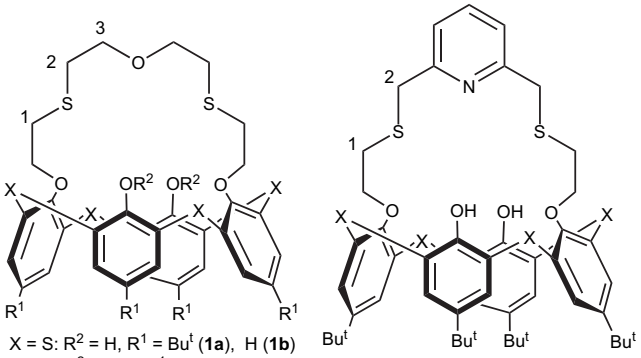
by that of **13** with BnBr (**15**) or BuBr (**16**)[42] (Schemes 1 and 2).

2.2. Investigation of Ag^+ binding by ^{1}H NMR methods

Among ionophores only calix[4]arene derivatives **10a**,**b** and **14** were applied to fabricate silver ISEs,[23,25,28] therefore, they served as references in the NMR measurements of TCA ligands. Our aim was to recognize the dominant binding sites and events by comparing the respective ^{1}H chemical shift differences. Stability constants were not calculated, although they are useful but not indispensable to estimate the binding affinities (in ISE experiments these data are significantly affected by the membrane composition[44]). The NMR measurements were performed with equimolar quantity of $AgClO_4$ (excess of Ag^+ did not change the spectra) in $CDCl_3$ (TCA) or $CDCl_3$–CD_3OD=4:1 (CA) solvents at 25 °C and the chemical shift differences ($\Delta\delta=\delta$ (in the presence of Ag^+)$-\delta$ (metal free)) are summarized in Tables 1–4.

The spectral changes of ligands **1a**–**4** clearly show that the SCH_2 protons exhibit the largest $\Delta\delta$ values suggesting that the soft sulfur atoms are primarily involved in complexation. The central hard oxygen atom also takes part in binding but, as expected, to a lesser extent. The allyl groups of **2** and **4** are assumed not to be involved in binding (little $\Delta\delta$ values as compared to those in Table 4). In the pyridinocrown derivative **6** the central sp^2 nitrogen together with the sulfur atoms efficiently coordinates the silver ion as reflected by the significant downfield shifts of the heteroaromatic *m*- and *p*-protons (0.28, 0.34) and the SCH_2 protons as well. In contrast, the three-point ligation involving the sp^2 nitrogen in the CA counterpart **7** is suppressed (PyH 0.03*m*, 0.05*p* ppm), similar to the respective OS_2 ligand **3** (Table 1).

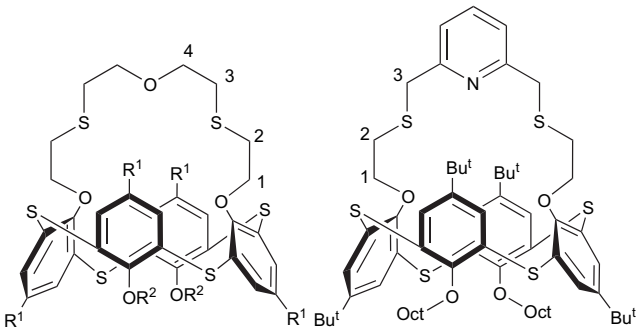
Table 1. Chemical shift differences ($\Delta\delta$, ppm) of cone thiacalix- and calix[4]crowns **1a**, **2**–**4**, **6** and **7** upon addition of $AgClO_4$ ([L]/[Ag^+]=1:1)



L	CH_2-3	SCH_2-1,2	PyH	=CH	$=CH_2$
1a[a]	0.39	0.51, 0.67	—	—	—
2	0.15	0.19, 0.18	—	0.19	0.06*t*, 0.19*c*
3	0.03	0.27, 0.17	—	—	—
4	0.16	0.41, 0.16	—	0.04	0.03*t*, 0.12*c*
6	—	0.36, 0.65	0.28*m*, 0.34*p*	—	—
7	—	0.22, 0.17	0.03*m*, 0.05*p*	—	—

[a] Ligand **1b** did not give well-resolved signals on exposure to Ag^+.

Table 2. Chemical shift differences ($\Delta\delta$, ppm) of 1,3-alt thiacalix[4]crowns **5a–c** and **8** upon addition of $AgClO_4$ ([L]/[Ag^+]=1:1)



R^1 = Bu^t, R^2 = Pr (**5a**), allyl (**5b**)
R^1 = H, R^2 = Pr (**5c**)

8

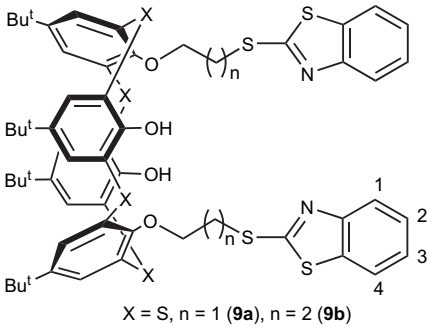
L	OCH_2-1	OCH_2-4	SCH_2-2,3	PyH
5a	0.53	0.16	0.84, 0.54	—
5b[a,b]	0.44	0.17	0.78, 0.56	—
5c	0.46	0.17	1.02, 0.63	—
8	0.47	—	0.79, 0.61	0.35*m*, 0.27*p*

[a] =CH −0.01.
[b] $=CH_2$ 0.10 (*cis*), 0.05 (*trans*).

The bulky *p*-Bu^t groups of 1,3-alt **5a**,**b** and **8** do not prevent the Ag^+ ion from accessing the crown ring, where it is bound analogously to the cone TCA ligands **1a** and **6**. The significant increase in the $\Delta\delta$ values of the SCH_2 protons of **5** and **8** (Table 2) as compared with those of cone **1**–**4** (Table 1) reveals that the 1,3-alt conformation is superior to the cone for binding, meanwhile the coordination power of the central oxygen and nitrogen atoms is kept.

The ^1H NMR titration of ligands **5a** with $AgClO_4$ demonstrates that the SCH_2-2,3 signals are gradually broadening and coalesce at ligand/Ag^+=0.5 ratio. Increasing further the Ag^+ ratio, the signal was enhanced reaching the final point at 1:1 stoichiometry. A similar phenomenon appears with the OCH_2-4 signal, while the PrO group, being far from the binding site, is lesser affected. The involvement

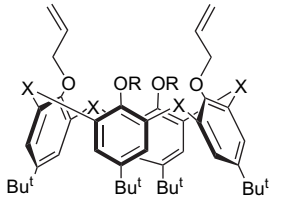
Table 3. Chemical shift differences ($\Delta\delta$, ppm) of open-chain thiacalix- and calix[4]arenes **9**–**11** upon addition of $AgClO_4$ ([L]/[Ag^+]=1:1, $CDCl_3$, 25 °C)



X = S, n = 1 (**9a**), n = 2 (**9b**)
X = CH_2, n = 1 (**10a**), n = 2 (**10b**)

L	BtH-1	BtH-2	BtH-3	BtH-4
9a	0.17	0.13	0.16	0.09
9b	0.42	0.12	0.13	0.06
10a	0.19	0.23	0.25	0.20
10b	0.35	0.25	0.21	0.18

Table 4. Chemical shift differences ($\Delta\delta$, ppm) of open-chain thiacalix- and calix[4]arenes **11**, **13**, **14**–**16** upon addition of $AgClO_4$ ([L]/[Ag^+]=1:1, $CDCl_3$, 25 °C)



X = S, R = H (**11**)
X = CH_2, R = H (**13**), allyl (**14**), Bn (**15**), Bu (**16**)

L	=CH	$=CH_2$ *cis*	$=CH_2$ *trans*	BnH
11	0.45	0.38	0.27	—
13	0.34	0.21	0.12	—
14	0.27 (0.26)[28]	0.48 (0.51)[28]	0.56 (0.62)[28]	—
15	0.11	0.02	0.27	0.28*o*,*p*, 0.09*m*
16	0.32	0.66	0.68	—

of two phenol-etheric oxygen atoms (OCH_2-1), as part of the crown ring, in ligation is possible but not sure, since the large downfield shifts of $ArOCH_2$ protons (0.53 ppm for **5a**) may originate from a complexation-induced conformational distortion of the calixarene skeleton (Fig. 1).

On the basis of data shown in Tables 1 and 2, we concluded that the 1,3-alt crowned TCA ligands **5** and **8** can sense the silver ion more efficiently than the respective cone TCA or CA counterparts **1**–**4**, **6** and **7**.

The largest upfield shifts of ligands **9** and **10** were measured for the benzothiazole aromatic protons (BtH) as shown in Table 3. In fact, the benzothiazole rings constitute the binding site, but in TCA compounds **9** they seem not to form a sandwich-like complex with Ag^+, only a two-point ligation occurs with the primary donor nitrogen atoms, where the cation is located in the plane of the aromatic rings. In this case the sulfur atoms do not play considerable role in complexation as reflected by the small $\Delta\delta$ values of BtH-4=0.06–0.09 ppm. The longer chain in ligand **9b** is more flexible than the shorter one in **9a**, thereby it provides a more favourable steric arrangement of the ligating site for binding, which

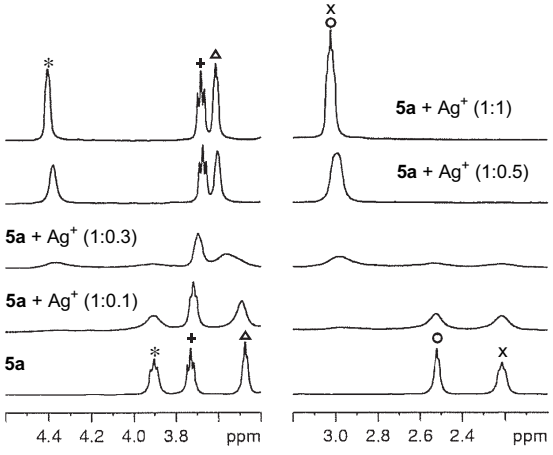


Figure 1. ^1H NMR titration of **5a** with $AgClO_4$ in $CDCl_3$ (labelled protons: SCH_2-2$^{\times}$, 3$^{\bigcirc}$; OCH_2-4$^{\triangle}$, (Pr)OCH_2^+, OCH_2-1*).

is shown by the larger downfield shift of the BtH-1 protons (0.42 vs 0.17 ppm). A similar result was obtained with the CA ligands **10a**,**b**, where again **10b** coordinates Ag^+ more strongly than **10a** (BtH-1 0.35 vs 0.19 ppm). It is notable, however, that in the latter ionophores the benzothiazole sulfur atom acts as an assistant donor besides the primary donor nitrogen providing a four-point ligation by the two benzothiazole rings (BtH-4 0.2, 0.18 ppm). Recent comprehensive ISE membrane experiments and X-ray studies with CA ligands **10** and related molecules[23] give strong evidences for this complexation pattern.

Diallyloxy-TCA ligand **11**, in contrast to the allyl derivatives of crowns **2**, **4** and **5b**, exhibits significant downfield shifts of the CH=CH_2 protons indicating a powerful π–cation interaction. Similar or larger $\Delta\delta$ values were measured for the CA ligands **13**, **14** and **16** containing two or four allyloxy groups. Diallyloxy-dibenzyloxy derivative **15**, however, behaves quite differently, here the Ag^+ ion is probably bound by the π-system of two parallel benzyl groups (*o*- and *p*-BnH 0.28 ppm) and the allyl groups are not involved in ligation. The measured small downfield shifts of the =CH and =CH_2 protons cannot stem from complexation, as only the trans proton of the terminal =CH_2 group is shifted due to the anisotropy caused by the ring current of benzyl groups (Table 4).

The behaviour of 1,3-alt tetraallyloxy-TCA **12** is worth discussing in detail. NMR titration did not indicate notable spectral changes referring to complexation up to 1 equiv $AgClO_4$. When **12** was exposed to a large quantity of Ag^+, however, the originally 1,3-alt conformation gradually changed and after 24 h, ca. 15% of 1,3-alt (free) and 85% of partial cone (complexed) ligands were detected (Fig. 2).

The structure elucidation using APT, COSY, HMQC, HMBC and ROESY methods was based on the unambiguous assignment of allyl protons (Table 5).

The partial cone conformer of **12**-Ag^+ complex contains three *syn* (**I** and **II**) and one *anti* (**III**) allyl groups. It would be reasonable to assume the involvement of the *syn* allyl groups in binding, but this process should be reflected by

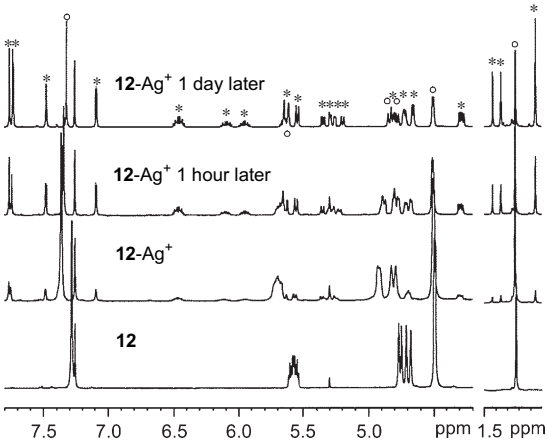


Figure 2. Time-dependent partial ^{1}H NMR spectra of **12** on exposure to 5 equiv Ag^+ in $CDCl_3$ (labelled protons: 1,3-alt-○ and paco* conformation; $CHCl_3$: 7.25 ppm).

Table 5. Allyl proton shifts of 1,3-alt **12**-Ag^+ complex

	OCH_2	=CH	=CH_2 *cis*	=CH_2 *trans*
I *syn*	4.70	5.99	5.38	5.29
II *syn*[a]	4.30, 4.77	6.49	5.55	5.62
III *anti*	4.62	6.05	5.14	5.18
12 (free)	4.49	5.58	4.76	4.69

[a] Two distal allyl groups.

downfield shifts. In contrast, the measured chemical shifts of the complex actually fell in the region of the uncomplexed allyl groups located in cone conformation. The *anti* (**III**) allyl group, however, shows significant downfield shifts ($\Delta\delta$ =CH 0.5, =CH_2 0.4 ppm) suggesting that the silver ion is probably located in the calixarene cavity surrounded by *syn* phenyl rings with two bridging sulfur donor atoms that can sufficiently stabilize the thiophil cation with the assistance of the *anti* allyl group (Fig. 3).

Since the 1,3-alt conformation of free **12** is stable, the binding process as a whole is assumed to take place through at least two consecutive equilibria. First, it starts with a weak coordination of Ag^+ of the 1,3-alt conformer followed by a slow conformational change to paco resulting in the thermodynamically more stable complex.

Simultaneously with the binding studies, ligands 1,3-alt **5a**, **8** and cone **14** (as reference[28])–**16** were selected for ISE screening experiments.[41] Though a poor binder, ligand **12** was also included to affirm (or to disprove) our expectation under quite different conditions. The potentiometric selectivity coefficients were determined in PVC membranes containing *o*NPOE plasticizer, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate lipophilic anion additive and the ionophores. We have found that ISEs based on π-coordinate ligands **14**–**16** are significantly less sensitive and selective towards a series of cations than crowns **5a** and **8**. Ligands **15** and **16** exhibited similar or slightly better characteristics of Ag^+ sensing than the reference **14**[28] as supported by the NMR binding studies. Ligand **12** proved to be inferior in respect of selectivity and responses affirming the result of NMR studies.

ISEs fabricated from **5a** and **8** were chosen for further evaluation and we established that both have excellent electroanalytical characteristics including high selectivities over a number of relevant cations (selected data are given

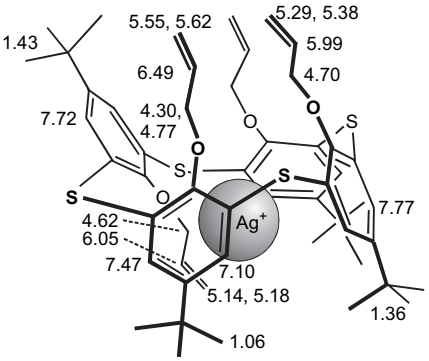


Figure 3. Proposed structure of **12**-Ag^+ complex based on ^{1}H NMR measurements.

Table 6. Potentiometric selectivity coefficients, log $K_{Ag/M}$

L	H^+	Na^+	K^+	Mg^{2+}	Ca^{2+}	Cu^{2+}	Pb^{2+}
5a	−10.2	−10.3	−8.4	−11.4	−11.3	−11.1	−10.4
CAb[a]	−8.9	−9.0	−8.4	−10.1	−10.2	−9.0	−8.7

[a] So far the best calix[4]arene-based Ag^+ ISE containing 25,27-bis(2-methylthioethoxy)-*p*-Bu^t-CA sensing ligand.[16]

in Table 6). For practical use, **5a** is superior to **8** (due to proton interference of the basic nitrogen) and it has the lowest detection limit of sensing yet measured.[41,45]

3. Conclusions

A series of cone- and 1,3-alt thiacalix[4]arene-based ionophores comprised of distal *O*,*S*,*N*-crown-5 bridges and soft open-chained ligating functions, respectively, were synthesized and investigated as Ag^+ sensing ligands in comparison with known and new calix[4]arene counterparts. The complexation was detected in solution by ^{1}H NMR measurements and evaluated by comparing the characteristic $\Delta\delta$ values of groups involved in binding. In summary, we concluded that crowned 1,3-alt TCA ligands OS_2-**5** and S_2N-**8** exhibit much stronger binding with Ag^+ than the cone counterparts irrespective of the calixarene skeleton. Ligands 1,3-alt **5a**, **8**, **12** and cone **14** (as reference)–**16** were selected as promising candidates for potentiometric ISE membrane screening experiments. Comprehensive electroanalytical evaluation revealed[41] that the π-coordinate ligands were significantly less sensitive and selective over a series of cations than crowns **5a** and **8**. To the best of our knowledge, the ISE based on **5a** has the lowest detection limit in Ag^+ sensing that has been measured until now.

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 500/125 MHz on a Bruker Avance DRX-500 spectrometer. FAB mass spectra were taken on a Finnigan MAT 8430 spectrometer (ion source temperature: 25 °C, matrix: *m*-nitrobenzyl alcohol, gas: xenon, accelerating voltage: 9 kV). Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were of reagent grade and used without further purification. DEAD[46] (Caution! DEAD may explode if exposed to shock, friction or heating) and ligands **1a**, **5a**, **8**,[40] **10a**,**b**,[23] **13**,[43] **14**–**16**[42] were synthesized as described in the literature.

4.2. General procedure for the synthesis of calix[4](O_3S_2-crown-5)ethers (1b, 3 and 7)

To the stirred mixture of thiacalix[4]arene (0.5 g, 1 mmol for **1b**) or *p*-*tert*-butylcalix[4]arene (0.65 g, 1 mmol for **3** and **7**), TPP (0.8 g, 3 mmol), 3,9-dioxa-6-thia-undecane-1,11-diol (for **1b** and **3**) or 2,6-bis(1-hydroxy-3-thiabutyl)pyridine (for **7**) (1.5 mmol each) in 20 ml toluene, a 40% toluene solution of DEAD (1.3 ml, 3 mmol) was added at room temperature and allowed to react for 1 h (**1b** and **3**) or refluxed (**7**). The solvent was then removed under reduced pressure and the residue was triturated with MeOH to free from by-products. Thereafter, the insoluble part was purified by chromatography on silica with hexane–EtOAc=8:2 eluent to give white solids.

4.2.1. Compound 1b. Yield: 95%, mp 127–129 °C; ^{1}H NMR δ 7.64 (d, 4H, *J*=7.5, Ar*H*), 7.54 (s, 4H, O*H*), 6.87 (d, 4H, *J*=7.5, Ar*H*), 6.84 (t, 2H, *J*=7.5, Ar*H*), 6.53 (t, 2H, *J*=7.5, Ar*H*), 4.71 (t, 4H, *J*=7.0, ArOCH_2), 3.80 (t, 4H, *J*=5.5, OCH_2), 3.34 (t, 4H, *J*=7.0, SCH_2), 2.99 (t, 4H, *J*=5.5, SCH_2); ^{13}C NMR δ 158.2, 158.0, 136.9, 135.2, 130.0, 125.5, 123.1, 119.8 (Ar), 74.8, 71.7 (O*C*H$_2$), 32.4, 34.2 (S*C*H$_2$); FABMS *m*/*z*: 688.2 [M+H]$^+$. Anal. Calcd for $C_{32}H_{30}O_5S_6$ (686.04): C, 55.95; H, 4.40; S, 28.01. Found: C, 55.69; H, 4.35; S, 27.67%.

4.2.2. Compound 3. Yield: 40%, mp 221–224 °C; ^{1}H NMR δ 7.07 (s, 4+2H, Ar*H*, O*H*), 6.76 (s, 2H, Ar*H*), 4.37 (d, 4H, *J*=13.0, ArCH_2Ar), 4.19 (t, 4H, *J*=6.3, OCH_2), 3.86 (t, 4H, *J*=5.8, OCH_2), 3.33 (t, 4H, *J*=6.3, SCH_2), 3.31 (d, 4H, *J*=13.0, ArCH_2Ar), 3.04 (t, 4H, *J*=5.8, SCH_2), 1.26 (s, 18H, C(CH_3)$_3$), 1.04 (s, 18H, C(CH_3)$_3$); ^{13}C NMR δ 150.8, 150.1, 147.1, 132.6, 128.1, 125.7, 125.3 (Ar), 76.8, 72.5 (O*C*H$_2$), 34.1, 34.0 (*C*(CH$_3$)$_3$), 33.1, 32.8 (S*C*H$_2$), 31.9, 31.2 (*C*H$_3$), 31.9 (Ar*C*H$_2$Ar); FABMS *m*/*z*: 841.2 [M+H]$^+$. Anal. Calcd for $C_{52}H_{70}O_5S_2$ (839.24): C, 74.42; H, 8.41; S, 7.62. Found: C, 74.08; H, 8.49; S, 7.48%.

4.2.3. Compound 7. Yield: 37%, mp 234–237 °C; ^{1}H NMR δ 7.89 (s, 2H, O*H*), 7.76 (t, 1H, *J*=7.5, Ar*H*), 7.39 (d, 2H, *J*=7.5, Ar*H*), 7.03 (s, 4H, Ar*H*), 7.02 (s, 4H, Ar*H*), 4.29 (d, 4H, *J*=13.0, ArCH_2Ar), 4.17 (t, 4H, *J*=7.5, OCH_2), 4.03 (s, 4H, SCH_2), 3.35 (d, 4H, *J*=13.0, ArCH_2Ar), 3.26 (t, 4H, *J*=7.5, SCH_2), 1.19 (s, 18H, C(CH_3)$_3$), 1.06 (s, 18H, C(CH_3)$_3$); ^{13}C NMR δ 158.7, 150.6, 150.1, 147.4, 141.9, 138.1, 133.3, 128.1, 126.0, 125.4, 121.5 (Ar), 75.7 (O*C*H$_2$), 38.8, 30.8 (S*C*H$_2$), 34.3, 34.0 (*C*(CH$_3$)$_3$), 32.5 (Ar*C*H$_2$Ar), 31.9, 31.3 (*C*H$_3$); FABMS *m*/*z*: 874.2 [M+H]$^+$. Anal. Calcd for $C_{55}H_{69}NO_4S_2$ (872.27): C, 75.73; H, 7.97; S, 7.34. Found: C, 75.28; H, 8.03; S, 7.27%.

4.3. General procedure for the cone-selective allylation of 1b and 3

The same method was used as described for the PTC alkylation of calix[4]arenes.[42] Thus, ligands **1b** or **3** (0.5 mmol), allylbromide (2.5 mmol), 50% aqueous NaOH (1 ml) and TBAB catalyst (0.05 g) in toluene (10 ml) were refluxed for 6 h under vigorous stirring to give **2** and **4** as white solids (purified by chromatography on silica with hexane–EtOAc=8:2 eluent).

4.3.1. Compound 2. Yield: 52%, mp 147–148 °C; ^{1}H NMR δ 7.62 (d, 4H, *J*=8.0, Ar*H*), 7.04 (t, 2H, *J*=8.0, Ar*H*), 6.34 (t, 2H, Ar*H*), 6.32 (d, 4H, Ar*H*), 6.17 (m, 2H, =C*H*), 5.42 (d, 2H, *J*=17.0, =CH_2 *trans*), 5.28 (d, 2H, *J*=10.0, =CH$_2$ *cis*), 4.51 (t, 4H, *J*=7.5, ArOCH_2), 4.44 (d, 4H, *J*=5.5, OCH_2), 3.78 (t, 4H, *J*=6.0, OCH_2), 3.05 (t, 4H, *J*=7.5, SCH_2), 2.84 (t, 4H, *J*=6.0, SCH_2); ^{13}C NMR δ 160.6, 157.3, 136.8, 133.5, 132.1, 131.6, 124.8, 123.3 (Ar), 133.9, 118.7 (allyl), 77.6, 72.9, 71.2 (O*C*H$_2$), 32.0, 30.7 (S*C*H$_2$); FABMS *m*/*z*: 768 [M+H]$^+$. Anal. Calcd for $C_{38}H_{38}O_5S_6$

(766.10): C, 59.50; H, 4.99; S, 25.08. Found: C, 59.28; H, 5.03; S, 24.89%.

4.3.2. Compound 4. Yield: 78%, mp 214–217 °C; ^{1}H NMR δ 7.12 (s, 4H, Ar*H*), 6.45 (s, 4H, Ar*H*), 6.35 (m, 2H, =C*H*), 5.42 (d, 2H, *J*=17.0, =CH_2 *trans*), 5.32 (d, 2H, *J*=10.0, =CH_2 *cis*), 4.37 (d, 4H, *J*=12.5, ArCH_2Ar), 4.26 (d, 4H, *J*=6.5, OCH_2), 4.21 (t, 4H, *J*=6.5, ArOCH_2), 3.81 (t, 4H, *J*=6.0, OCH_2), 3.27 (t, 4H, *J*=6.5, SCH_2), 3.15 (d, 4H, *J*=12.5, ArCH_2Ar), 2.83 (t, 4H, *J*=6.0, SCH_2), 1.34 (s, 18H, C(CH_3)$_3$), 0.81 (s, 18H, C(CH_3)$_3$); ^{13}C NMR δ 153.7, 151.9, 145.3, 144.4, 135.6, 131.8, 125.5, 124.5 (Ar), 135.2, 118.3 (allyl), 77.0, 73.8, 71.9 (OCH_2), 34.1, 33.6 (*C*(CH$_3$)$_3$), 31.7, 31.1 (*C*H$_3$), 31.5 (ArCH_2Ar), 31.4, 31.3 (SCH_2); FABMS *m*/*z*: 921.4 [M+H]$^+$. Anal. Calcd for $C_{58}H_{78}O_5S_2$ (919.37): C, 75.77; H, 8.55; S, 6.96. Found: C, 75.31; H, 8.62; S, 6.88%.

4.4. General procedure for the 1,3-alt-selective alkylation of 1b

The same method was used as described for the preparation of **5a**.[40] Thus, **1b** (1 mmol) was treated with allylbromide or PrI (5 mmol), Cs_2CO_3 (8 mmol) in MeCN (20 ml) under reflux for 12 h to give **5b**,**c** as white solids.

4.4.1. Compound 5b. Yield: 93%, mp 280–282 °C; ^{1}H NMR δ 7.34 (s, 4H, Ar*H*), 7.25 (s, 4H, Ar*H*), 5.39 (m, 2H, =C*H*), 4.66 (dd, 2H, *J*=10.5, 1.5, =CH_2 *cis*), 4.62 (dd, 2H, *J*=12.5, 1.5, =CH_2 *trans*), 4.39 (d, 4H, *J*=3.5, OCH_2), 3.95 (t, 4H, *J*=8.0, ArOCH_2), 3.47 (t, 4H, *J*=5.0, OCH_2), 2.50 (t, 4H, *J*=5.0, SCH_2), 2.29 (t, 4H, *J*=7.5, SCH_2), 1.35 (s, 18H, C(CH_3)$_3$), 1.22 (s, 18H, C(CH_3)$_3$); ^{13}C NMR δ 156.8, 156.3, 146.5, 146.0, 133.8, 128.7, 128.5, 127.5, 126.6 (Ar), 133.8, 115.6 (allyl), 74.1, 69.2, 68.2 (OCH_2), 34.6, 34.4 (*C*(CH$_3$)$_3$), 33.8, 33.3 (SCH_2), 31.7, 31.5 (C(*C*H$_3$)$_3$); FABMS *m*/*z*: 992.4 [M+H]$^+$. Anal. Calcd for $C_{54}H_{70}O_5S_6$ (990.35): C, 65.41; H, 7.12; S, 19.40. Found: C, 65.19; H, 7.06; S, 19.23%.

4.4.2. Compound 5c. Yield: 60%, mp 199–200 °C; ^{1}H NMR δ 7.42 (d, 4H, *J*=7.5, Ar*H*), 7.31 (d, 4H, *J*=8.0, Ar*H*), 6.93 (t, 2H, *J*=8.0, Ar*H*), 6.89 (t, 2H, *J*=7.5, Ar*H*), 3.94 (t, 4H, *J*=8.5, ArOCH_2), 3.86 (t, 4H, *J*=7.0, ArOCH_2), 3.62 (t, 4H, *J*=5.0, OCH_2), 2.62 (t, 4H, *J*=5.0, SCH_2), 2.15 (t, 4H, *J*=8.0, SCH_2), 1.14 (m, 4H, CH_2), 0.59 (t, 6H, *J*=7.0, CH_3); ^{13}C NMR δ 160.1, 158.6, 131.3, 130.6, 128.9, 128.8, 123.5, 123.4 (Ar), 73.7, 70.7, 67.7 (OCH_2), 33.6, 32.5 (SCH_2), 22.5 (CH_2), 10.3 (CH_3); FABMS *m*/*z*: 771.14 [M+H]$^+$. Anal. Calcd for $C_{38}H_{42}O_5S_6$ (770.14): C, 59.19; H, 5.49; S, 24.95. Found: C, 59.28; H, 5.42; S, 24.69%.

4.5. Synthesis of 25,27-bis[1,3-benzothiazole-2-(1-thioalkoxy)]-*p*-Bu^{t}TCA (9a,b)

Ligand **9a** was prepared according to literature analogy by the $NaHCO_3$ promoted alkylation of 2-mercapto-1,3-benzothiazole with 25,27-bis(2-bromoethoxy)-*p*-Bu^{t}TCA[38] changing the solvent from aqueous THF[23] to boiling MeCN. Ligand **9b** was synthesized by the Mitsunobu alkylation of *p*-Bu^{t}TCA (0.72 g, 1 mmol) with 2-(3-hydroxypropylthio)-1,3-benzothiazole (0.56 g, 2.5 mmol) using TPP/DEAD (3 mmol) coupling agents following the procedure described in Section 4.2. The crude product was purified by recrystallization from EtOAc–hexane.

4.5.1. Compound 9a. Yield: 52%, mp 148–150 °C; ^{1}H NMR δ 7.82 (d, 2H, *J*=8.0, Ar*H*), 7.79 (s, 2H, O*H*), 7.68 (d, 2H, *J*=8.0, Ar*H*), 7.66 (s, 4H, Ar*H*), 7.36 (t, 2H, *J*=8.0, Ar*H*), 7.24 (t, 2H, *J*=8.0, Ar*H*), 6.95 (s, 4H, Ar*H*), 4.95 (t, 4H, *J*=6.0, ArOCH_2), 4.02 (t, 4H, *J*=6.0, SCH_2), 1.34 (s, 18H, C(CH_3)$_3$), 0.79 (s, 18H, C(CH_3)$_3$); ^{13}C NMR δ 166.6, 156.0, 155.9, 153.4, 148.4, 143.0, 135.7, 134.6, 133.0, 129.2, 126.1, 124.3, 122.3, 121.8, 121.1 (Ar), 73.3 (OCH_2), 34.4, 34.2 (*C*(CH$_3$)$_3$), 33.4 (SCH_2), 31.7, 31.0 (C(*C*H$_3$)$_3$); FABMS *m*/*z*: 1108.2 [M+H]$^+$. Anal. Calcd for $C_{58}H_{62}N_2O_4S_8$ (1106.25): C, 62.89; H, 5.64; N, 2.53; S, 23.16. Found: C, 62.57; H, 5.70; N, 2.49; S, 23.05%.

4.5.2. Compound 9b. Yield: 63%, mp 154–156 °C; ^{1}H NMR δ 7.90 (s, 2H, O*H*), 7.83 (d, 2H, *J*=8.0, Ar*H*), 7.68 (d, 2H, *J*=8.0, Ar*H*), 7.66 (s, 4H, Ar*H*), 7.34 (t, 2H, *J*=8.0, Ar*H*), 7.22 (t, 2H, *J*=8.0, Ar*H*), 7.00 (s, 4H, Ar*H*), 4.67 (t, 4H, *J*=6.5, ArOCH_2), 3.76 (t, 4H, *J*=6.5, SCH_2), 2.53 (quint., 4H, *J*=6.5, CH_2), 1.34 (s, 18H, C(CH_3)$_3$), 0.82 (s, 18H, C(CH_3)$_3$); ^{13}C NMR δ 167.3, 156.3, 156.0, 153.6, 148.4, 143.0, 135.5, 134.6, 133.3, 129.1, 126.1, 124.2, 122.2, 121.8, 121.1 (Ar), 74.0 (OCH_2), 34.4, 34.3 (*C*(CH$_3$)$_3$), 31.7, 31.0 (C(*C*H$_3$)$_3$), 30.7 (SCH_2), 30.3 (CH_2); FABMS *m*/*z*: 1136.3 [M+H]$^+$. Anal. Calcd for $C_{60}H_{66}N_2O_4S_8$ (1134.28): C, 63.45; H, 5.86; N, 2.47; O, 5.64; S, 22.59. Found: C, 63.11; H, 5.83; N, 2.43; S, 22.34%.

4.6. Synthesis of 25,27-diallyloxy- and 25,26,27,28-tetraallyloxy-*p*-Bu^{t}TCA (11 and 12)

To the stirred mixture of *p*-*tert*-butylthiacalix[4]arene (0.72 g, 1 mmol), TPP (0.8 g, 3 mmol for **11** and 1.6 g, 6 mmol for **12**), allylalcohol (0.13 g, 2.2 mmol for **11** and 0.58 g, 10 mmol for **12**) in 20 ml toluene, a 40% toluene solution of DEAD (1.3 ml, 3 mmol for **11** and 2.6 ml, 6 mmol for **12**) was added at room temperature and allowed to react for 0.5 h (**11**) or refluxed for 12 h (**12**). The solvent was then removed under reduced pressure and the residue was triturated with hot acetone (20 ml) and filtered to give white solid in essentially pure form.

4.6.1. Compound 11. Yield: 85%, mp 222–224 °C; ^{1}H NMR δ 7.87 (s, 2H, O*H*), 7.66 (s, 4H, Ar*H*), 6.97 (s, 4H, Ar*H*), 6.32 (m, 2H, =C*H*), 5.55 (d, 2H, *J*=17.0, =CH_2 *trans*), 5.37 (d, 2H, *J*=10.0, =CH_2 *cis*), 5.01 (d, 4H, *J*=5.5, OCH_2), 1.33 (s, 36H, C(CH_3)$_3$), 0.80 (s, 36H, C(CH_3)$_3$); ^{13}C NMR δ 156.2, 156.0, 148.2, 142.8, 134.6, 133.0, 129.3, 122.3 (Ar), 133.6, 118.9 (allyl), 76.6 (OCH_2), 34.4, 34.2 (*C*(CH$_3$)$_3$), 31.8, 31.0 (C(*C*H$_3$)$_3$); FABMS *m*/*z* (%): 801 [M+H]$^+$. Anal. Calcd for $C_{46}H_{56}O_4S_4$ (800.31): C, 68.96; H, 7.05; S, 16.01. Found: C, 69.16; H, 6.98; S, 16.18%.

4.6.2. Compound 12. Yield: 90%, mp 245–247 °C; ^{1}H NMR δ 7.28 (s, 8H, Ar*H*), 5.58 (m, 4H, =C*H*), 4.76 (d, 2H, *J*=10.5, =CH_2 *cis*), 4.69 (d, 2H, *J*=17.5, =CH_2 *trans*), 4.49 (d, 2H, *J*=4.0, OCH_2), 1.22 (s, 36H, C(CH_3)$_3$); ^{13}C NMR δ 156.9, 145.8, 129.4, 128.5 (Ar), 133.9, 115.6 (allyl), 69.4 (OCH_2), 34.4 (*C*(CH$_3$)$_3$), 31.5 (C(*C*H$_3$)$_3$); FABMS *m*/*z* (%): 882.4 [M+H]$^+$. Anal. Calcd for $C_{52}H_{64}O_4S_4$ (880.37): C,

70.84; H, 7.32; S, 14.55. Found: C, 70.47; H, 7.36; S, 14.39%.

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References and notes

1. See recent reviews: (a) Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. *Calixarenes 2001*; Asfari, M., Boehmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 2001; p 312, 365, 385, 407; (b) Ludwig, R. *Fresenius' J. Anal. Chem.* **2000**, 103; (c) Gale, P. A. *Coord. Chem. Rev.* **2001**, *213*, 79; (d) Bühlmann, B.; Pretsch, E.; Bakker, E. *Chem. Rev.* **1998**, *98*, 1593.
2. Thuéry, P.; Nierlich, M.; Lamare, V.; Dozol, J.-F.; Asfari, Z.; Vicens, J. *J. Incl. Phenom. Macrocycl. Chem.* **2000**, *36*, 375.
3. Kimura, K.; Miura, T.; Matsuo, M.; Shono, T. *Anal. Chem.* **1990**, *62*, 1510.
4. Cunningham, K.; Svehla, G.; Harris, S. J.; Mc Kervey, M. A. *Anal. Proc.* **1991**, *28*, 294.
5. Brazozka, Z.; Lammerink, B.; Reinhoudt, D. N.; Ghidini, E.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1037.
6. Metzger, E.; Aeschimann, R.; Egli, M.; Suter, G.; Dohner, R.; Ammann, D.; Dobler, M.; Simon, W. *Helv. Chim. Acta* **1986**, *69*, 1821.
7. Schaller, U.; Bakker, E.; Spichiger, U. E.; Pretsch, E. *Anal. Chem.* **1994**, *66*, 391.
8. Chen, L.; Ju, H.; Zeng, X.; He, X.; Zhang, Z. Z. *Anal. Chim. Acta* **2001**, *447*, 41.
9. Pérez-Jiménez, C.; Escriche, L.; Casbo, J. *Anal. Chim. Acta* **1998**, *371*, 155.
10. Ohki, A.; Maeda, S.; Lu, J. P.; Bartsch, R. A. *Anal. Chem.* **1994**, *66*, 1743.
11. Kimura, K.; Yano, H.; Kitazawa, S.; Shono, T. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1945.
12. Cadogan, F.; Kane, P.; Mc Kervey, M. A.; Diamond, D. *Anal. Chem.* **1999**, *71*, 5544.
13. Kim, J. S.; Suh, I. H.; Kim, J. K.; Cho, M. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2307.
14. Lamare, V.; Dozol, J.-F.; Fuangswasdi, S.; Arnaud-Neu, F.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 271.
15. O'Conner, K. M.; Svehla, G.; Harris, S. J.; Mc Kervey, M. A. *Anal. Proc.* **1993**, *30*, 137.
16. (a) Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, D.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573; (b) Malinowska, E.; Brzozka, Z.; Kasiura, K.; Egberink, R. J. M.; Reinhoudt, D. N. *Anal. Chim. Acta* **1994**, *298*, 245.
17. Lai, M. T.; Shih, J. S. *Analyst* **1986**, *111*, 891.
18. Srivastava, S. K.; Gupta, V. K.; Jain, S. *Anal. Chem.* **1996**, *68*, 1272.
19. Kim, S. J.; Ohki, A.; Ueki, R.; Ishizuka, T.; Shimotashiro, T.; Maeda, S. *Talanta* **1999**, *48*, 705.
20. Zeng, X.; Weng, L.; Chen, L.; Leng, X.; Ju, H.; He, X.; Zhang, Z. Z. *J. Chem. Soc., Perkin Trans. 2* **2001**, 545.
21. Zeng, X.; Han, X.; Chen, L.; Li, Q.; Xu, F.; He, X.; Zhang, Z. Z. *J. Chem. Soc., Perkin Trans. 2* **2002**, 796.
22. Zeng, X.; Han, L.; Chen, L.; Li, Q.; Xu, F.; He, X.; Zhang, Z. Z. *Tetrahedron Lett.* **2002**, *43*, 131.
23. Zeng, X.; Weng, L.; Chen, L.; Xu, F.; Li, Q.; Leng, X.; He, X.; Zhang, Z. Z. *Tetrahedron* **2002**, *58*, 2647.
24. Chen, L.; Ju, H.; Zeng, X.; He, X.; Zhang, Z. Z. *Anal. Chim. Acta* **2001**, *437*, 191.
25. Chen, L.; Zeng, X.; He, X.; Zhang, Z. Z. *Fresenius' J. Anal. Chem.* **2000**, *367*, 535.
26. Zeng, X.; Sun, H.; Chen, L.; Leng, X.; Xu, F.; Li, Q.; He, X.; Zhang, W.; Zhang, Z. Z. *Org. Biomol. Chem.* **2003**, 1073.
27. (a) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303; (b) Xu, F.; Weng, L.; Sun, L.; Zhang, Z. Z.; Zhou, Z. *Organometallics* **2000**, *19*, 2658; (c) Xu, F.; Li, Q.; Wu, L.; Li, Z.; Leng, X.; Zeng, X.; Chow, Y.; Zhang, Z. Z. *Organometallics* **2003**, *22*, 633; (d) Ikeda, A.; Shinkai, S. *J. Am. Chem. Soc.* **1994**, *116*, 3102; (e) Inokuchi, F.; Miyahara, Y.; Inazu, T.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1364.
28. Kimura, K.; Yayima, S.; Tatsumu, K.; Yokoyama, M.; Oue, M. *Anal. Chem.* **2000**, *72*, 5290.
29. Kumagai, H.; Hasegawa, M.; Miyanari, S.; Sugawa, Y.; Sato, Y.; Hori, T.; Ueda, S.; Kamiyama, H.; Miyano, S. *Tetrahedron Lett.* **1997**, *38*, 3971.
30. Iki, N.; Morohashi, N.; Narumi, F.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1597.
31. Ha, X.; Pan, Z.; Wang, L.; Shi, X. *Spectrochim. Acta, Part A* **2003**, *59*, 2419.
32. Lhotak, P. *Eur. J. Org. Chem.* **2004**, 1675.
33. Grün, A.; Csokai, V.; Parlagh, Gy.; Bitter, I. *Tetrahedron Lett.* **2002**, *43*, 4153.
34. Csokai, V.; Grün, A.; Parlagh, Gy.; Bitter, I. *Tetrahedron Lett.* **2002**, *43*, 7627.
35. Kim, C. Y.; Li, H.; Kwang, J.; Li, S. H.; Lim, H. B.; Kim, J. S. *Talanta* **2004**, *64*, 975.
36. Bereczki, R.; Csokai, V.; Grün, A.; Bitter, I.; Tóth, K. *Anal. Chim. Acta* **2006**, *569*, 42.
37. Bouhroum, S.; Arnaud-Neu, F.; Asfari, Z.; Vicens, J. *Supramol. Chem.* **2005**, *17*, 629.
38. Bitter, I.; Csokai, V. *Tetrahedron Lett.* **2003**, *44*, 2261.
39. Csokai, V.; Grün, A.; Bitter, I. *Tetrahedron Lett.* **2003**, *44*, 4681.
40. Csokai, V.; Bitter, I. *Supramol. Chem.* **2004**, *16*, 611.
41. Szigeti, Zs.; Malon, A.; Vigassy, T.; Csokai, V.; Grün, A.; Wygladacz, K.; Ye, Nan; Xu, Chao; Bitter, I.; Rathore, R.; Bakker, E.; Pretsch, E. *Anal. Chim. Acta* **2006**, *572*, 1.
42. Bitter, I.; Grün, A.; Ágai, B.; Tőke, L. *Tetrahedron* **1995**, *51*, 7835.
43. Van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639.
44. For complex formation constants (log β) measured in PVC (*o*NPOE), see Ref. 41.
45. Malon, A.; Vigassy, T.; Bakker, E.; Pretsch, E. *J. Am. Chem. Soc.* **2006**, *128* (published in Web 06/07/2006).
46. Kauer, J. C. *Org. Synth. Coll. Vol. IV* **1963**, 411.

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1,3,4-Oxadiazole formation as traceless release in solid phase organic synthesis

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Abstract—Oxadiazoles were generated upon a dehydrative cyclization reaction with 2-acyl hydrazides bound to the polymeric support via one of their N atoms using TFAA as a dehydration agent.

1. Introduction

Oxadiazoles are important structural components in many pharmaceuticals and agrochemicals[1] due to their topology and electronic properties.[2] The most common synthesis of 1,3,4-oxadiazoles is the dehydration of 2-acyl hydrazides.[3]

Recent synthesis methodologies making use of solid-support-bound reagents[4] may be highly useful to adapt oxadiazole formation to parallel chemistry. Two reports on the synthesis of oxadiazoles on solid supports have addressed this subject.[5] Herein we report the development of a method producing libraries of oxadiazoles in an array format with minimal manipulations and independent of the solubility of starting materials or intermediates.

By analogy to our solid-phase-mediated synthesis of oxazoles,[6] we investigated the possibility of synthesizing oxadiazoles from 2-acyl hydrazides covalently attached to a solid phase via a nitrogen atom, *directly* involved in the oxadiazole formation. Such a process would require a linker between the oxadiazole and the polymeric support, which could be cleaved concomitantly with the dehydrative cyclization, merely leaving a lone electron pair on the product as a 'trace'. To our knowledge, oxadiazole formations involving *N*1-alkylated 2-acyl hydrazides have not yet been reported.

2. Results and discussion

The choice of the linker is essential for our proposed process (Scheme 1). We intended to use an acid labile linker, which would readily eliminate a polymer-bound cation upon cyclization of a support-bound 2-acyl hydrazide. Among the commonly used linkers, which may provide such a stabilized cation, we considered trityl (**VI**), MAMP (**VII**), and *o*-methoxybenzyl[7] (**VIII**). Preliminary attempts to synthesize 2-acyl hydrazides on trityl and MAMP resins had failed owing to steric constraints imposed by the linker. The rigidity of the 2-acyl hydrazides may be another factor, impeding access of reagents and solvents, thus complicating oxadiazole formation. Therefore, we focused on an *o*-methoxybenzyl linker attached to the polystyrene resin via a flexible 4-butyryloxy spacer (**VIII**).

Firstly, our process involved the attachment of the 2-acyl hydrazides (**2a**–**e**) onto a polystyrene support via a flexible 4(4-formyl-3-methoxyphenoxy)butyryl linker **1**. Then, the support-bound acyl hydrazones (**3a**–**e**) were reduced to hydrazides (**4a**–**e**) using commercial borane–pyridine complex.[8] The latter reagent gave reproducibly clean, quantitative reductions without any precipitation. Subsequent acylation of hydrazides **4a**–**e** afforded 2-acyl hydrazides **6a**–**q**. Since monitoring these intermediates by cleavage with TFA gave low recovery and complex mixtures, the support-bound hydrazones **3a**–**e** and hydrazides **4a**–**e** were analyzed by IR and MAS ^{1}H NMR. The use of DMF-d_7 was essential for the MAS ^{1}H NMR analysis, since it assured sufficient swelling of the resin, and narrow NMR signals (including NH) facilitating spectral interpretation. Mono-acylation was required in order to avoid the formation of symmetrically substituted oxadiazoles, bearing only R^2 groups. Where carboxylic acids R^2–CO_2H were utilized as precursors, mono-acylations were performed with isopropoxy carbonyl-based mixed anhydrides[9] or symmetrical anhydrides, readily synthesized from carboxylic acids and ethoxy acetylene.[10] Alternatively, when acylchlorides were utilized, preferably they were converted to pentafluorophenyl esters, producing

Keywords: Cyclative release; Traceless linker; Dehydration; TFAA; Transacylation.
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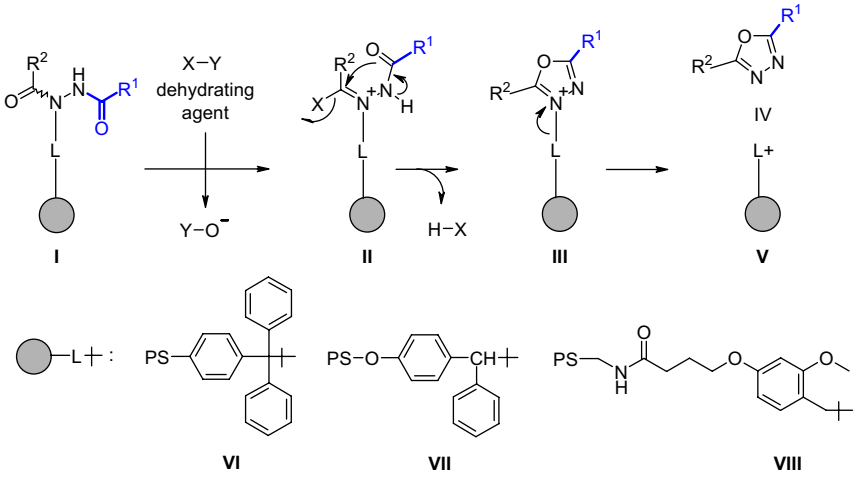
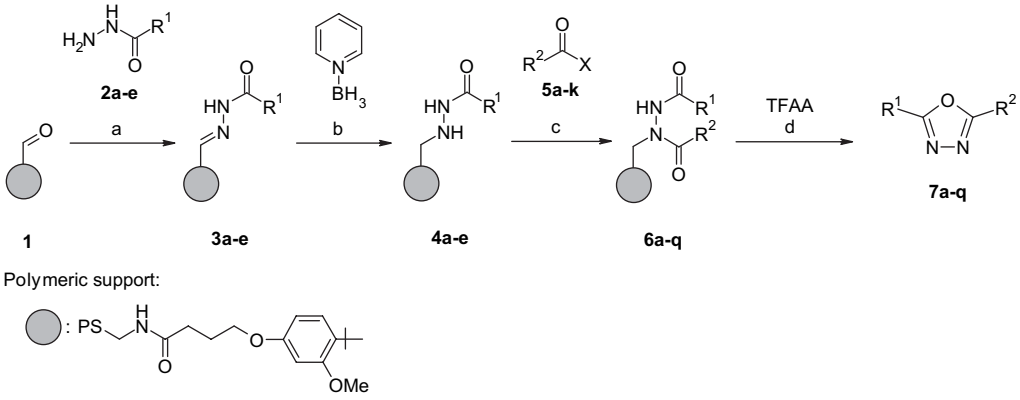


Scheme 1. Proposed oxadiazole formation on solid phase via cyclative release. PS: polystyrene; L: linker.



Scheme 2. Reagents and conditions: (a) 1.5 equiv **2a**–**e**, 1 equiv HOAc, CH_2Cl_2, 24 h, rt; (b) CH_2Cl_2–HOAc–pyridine·BH_3 (85:10:5, v/v/v), 8 h, rt; (c) 11 equiv anhydrides or pentafluorophenyl esters, NMI, CH_2Cl_2, 2 days, rt; (d) (i) TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v), 5 h, rt; (ii) evaporation; (iii) MeOH, DOWEX1-X2 (carbonate form), 3 h, rt.

only mono-acylation products.[11] Additionally, we observed that the base was also crucial for the acylations. DIPEA (Hünig's base), TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or NMM (*N*-methylmorpholine) gave multiple acylations with hydrazides bearing CH-acidic carbons. NMI (*N*-methyl imidazole) appeared to be the base of choice, being a powerful, yet not too basic acylation catalyst. Finally, dehydrative, cyclative release of the oxadiazoles **7a**–**q** from the polymeric support was performed using volatile TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v) (Scheme 2).

The cyclizations were completed in less than 5 h. Prolonged or multiple TFAA treatments did not afford higher yields. The crude cleavage products were treated briefly with DOWEX1-X2 (carbonate form) and gave products of acceptable purity for biological screens (Table 1).

2.1. Mechanistic aspects

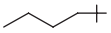
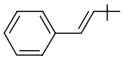
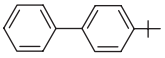
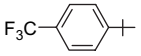
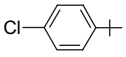
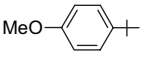
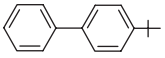
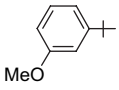
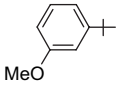
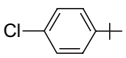
The oxadiazole formations were performed with TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v) unless specified otherwise. Under these conditions, three processes were found to occur:

2.1.1 oxadiazole formation on resin,
2.1.2 deacylation of R^1COOH versus cyclization,
2.1.3 sequestration of support-bound species by the resin.

2.1.1. Oxadiazole formation on resin. Scheme 3 shows the TFAA-mediated dehydration of immobilized 2-acyl hydrazides. The TFAA-mediated dehydration of resin-bound diacylhydrazides occurred without dissociation of the 2-acyl hydrazides from the solid support as evidenced by the fact that product mixtures were different from those obtained in solution phase under identical conditions. Specifically, the dehydration of immobilized 2-acyl hydrazide **6a** with TFAA liberated only **7a** and **11a**. Alternatively, the TFAA treatment of compound **8a** in solution phase generated products **7a**, **11a**, and **14** (Scheme 4). In fact, trifluoromethylated oxadiazoles, such as **14**, were never observed in either of our oxadiazole formations involving support-bound 2-acyl hydrazides, or in that involving the *N*-benzylated 2-acyl hydrazide **18** (Scheme 9).

Furthermore, the acidity of CH_2Cl_2–TFA (95:5, v/v) in the absence of dehydrating agents was found to be insufficient to liberate hydrazide **8a** from resin **6a**.

Table 1

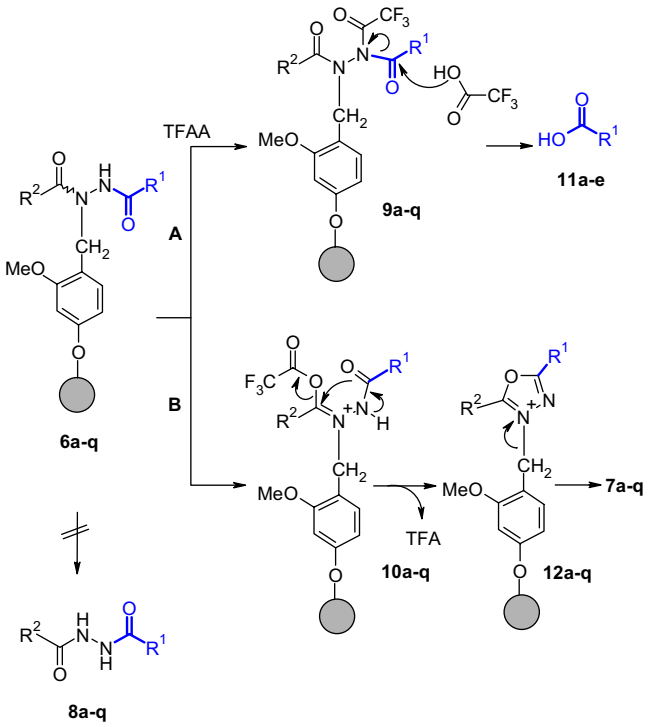
Entry	Polymer supported hydrazides	R^1	Acylation method[a]	R^2	R^2COX	Diacyl-hydrazine	Oxadiazoles[b]	Yield[c]	Purity[d]
1	**4a**		A		**5a**	**6a**	**7a**	48	92.5
2	**4a**		B		**5b**	**6ab**	**7b**	63	94.6
3	**4a**		A		**5c**	**6c**	**7c**	69	96.6
4	**4a**		B		**5d**	**6d**	**7d**	11	89.8
5	**4a**		B		**5e**	**6e**	**7e**	29	93.5
6	**4a**		**C**		**5f**	**6f**	**7f**	35	96.8
7	**4a**		D		**5g**	**6g**	**7g**	22	100
8	**4a**		D		**5h**	**6h**	**7h**	30	100
9	**4a**		D		**5i**	**6i**	**7i**	40	87.9
10	**4a**		D		**5j**	**6j**	**7j**	25	79.5
11	**4a**		D		**5k**	**6k**	**7k**	15	80.0
12	**4b**		A		**5a**	**6ba**	**7b**	31	87.2
13	**4b**		D		**5h**	**6l**	**7l**	22	85.1
14	**4c**		A		**5a**	**6m**	**7m**	32	92.3
15	**4c**		C		**5f**	**6n**	**7n**	7	91.8
16	**4d**		A		**5a**	**6o**	**7o**	49	87.1
17	**4d**		D		**5i**	**6p**	**7p**	15	79.8
18	**4e**		A		**5a**	**6q**	**7q**	31	88.4

[a] Acylation methods: A: $(R^3CO)_2O$ (0.5 M, 11 equiv), CH_2Cl_2, NMI (0.5 M, 11 equiv), rt 48 h; B: R^3CO_2H (0.5 M, 11 equiv), CH_2Cl_2, NMI (0.025 M, 0.5 equiv), ethoxyacetylene (0.5 M, 11 equiv), rt 48 h; C: (a) R^3CO_2H (0.5 M, 11 equiv), CH_2Cl_2, NMI (1 M, 22 equiv), *i*PrOCOCl (0.5 M, 11 equiv), rt 30 min, (b) addition to resin, rt 48 h; D: (a) R^3COCl (0.5 M, 11 equiv), CH_2Cl_2, NMI (1 M, 22 equiv), pentafluorophenol (PFP) (0.5 M, 11 equiv), rt 30 min, (b) addition to resin, rt 48 h.

[b] All cyclative cleavages were performed using TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v), 5 h, rt.

[c] Isolated yields based on the manufacturer's specification of loading of the initial aldehyde resin (i.e., over four consecutive steps). The crude cyclization product mixture was treated for 3 h with DOWEX1-X2 (carbonate form) before it was isolated and the yields determined by weight.

[d] The purity of the isolated products was determined by integration of the product peak analytical HPLC trace at 220 nm.



Scheme 3. TFAA-mediated dehydration of solid phase bound 2-acyl hydrazides.

Recent reports on the synthesis of oxadiazolinium salts by analogous dehydration reactions[12] strongly suggest the intermediacy of a support-bound oxadiazolinium species like **12a** (Scheme 3, path B).

The difference in the reaction mechanism between dehydrations in solution and on solid phase is supported by the different impact of the reaction solvent on the product compositions. In solution phase, the ratio of **7a**/**14** was highly solvent dependent (Table 4). On solid phase, the dehydration cocktail had little influence on the product composition. In solution phase, compounds **14** could only have been liberated upon fragmentation of a *N*-trifluoroacylated intermediate, such as **13** (Scheme 4, path A′).

2.1.2. Deacylation R^2COOH versus cyclization. The liberation of acyl groups, such as **11a**, also occurred from a resin-bound species. Here again, resin involvement was evident, since only the acyl groups β to the support-link R^1CO_2H, such as **11a**, were released from the resin (Table 2, Scheme 3, path A). The absence of deacylation in the dehydration reactions using $SOCl_2$ (Table 3) supported the role of a trifluoroacetylated intermediate, such as **9a** (Scheme 3, path A). The deacylation site was determined in a study using the following support-bound hydrazides (Table 2).

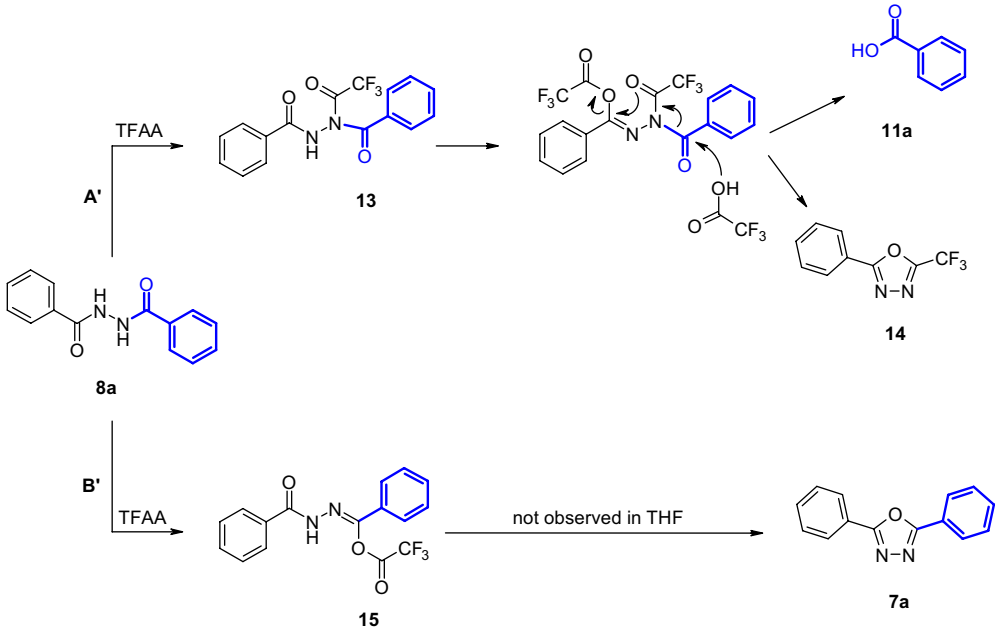
We obtained further evidence for the proposed transacylation step[13] (Scheme 3, path A, Scheme 4, path A′) through a solution phase model reaction. When treating benzohydrazide (**2a**) with excess TFAA, we obtained benzoate (**11a**),

Table 2

Entry	Hydrazide resin starting material	Resin-bound 2-acyl hydrazide	Desired oxadiazole (yield %)[a]		Co-isolated acid R^1CO_2H (yield %)[a]	
1	**4a**	**6a**	**7a**	(32.6)	**11a**	(62.2)
2	**4c**	**6m**	**7m**	(68.3)	**11c**	(19.8)
3	**4d**	**6o**	**7o**	(42.5)	**11d**	(41.4)
4	**4e**	**6q**	**7q**	(23.5)	**11e**	(51.6)
5	**4a**	**6d**	**7d**	(37.4)	**11a**	(33.1)

Deacylation of the acyl group 'β' to the support link R^1 during oxadiazole formations on solid support using TFAA–CH_2Cl_2 (1:4, v/v). The acids stemming from R^2 were not observed.

[a] The yields were based on the integration of the product peak in the HPLC trace of the purified product at 220 nm.



Scheme 4. TFAA-mediated oxadiazole formations in solution phase.

Table 3. $SOCl_2$-mediated oxadiazole formations

Entry	Hydrazide resin starting material	Resin-bound acyl hydrazide	Desired oxadiazole (yield %)[a]		Formed hydrazide (major side product)		
					(yield %)[a]		ESI-MS *m/z* $(M+H)^+$
1	**4a**	**6a**	**7a**	(50.4)	**8a**	(16.8)	241
2	**4b**	**6b**	**7b**	nd[b]	—	nd[b]	—
3	**4c**	**6m**	**7m**	(44.7)	**8m**	(13.2)	259
4	**4d**	**6o**	**7o**	(47.8)	**8o**	(11.8)	271
5	**4e**	**6q**	**7q**	(32.2)	**8q**	(22.4)	247

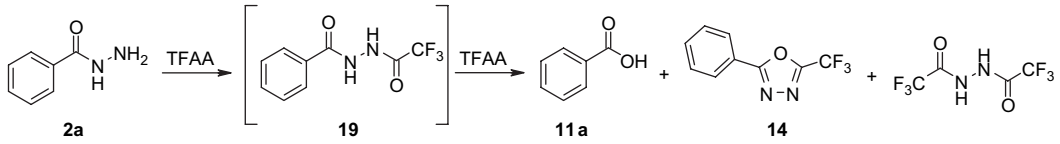
Oxadiazole formation in $SOCl_2$–CH_2Cl_2–DMF (100:400:1, v/v/v), rt, 15.5 h (126 equiv $SOCl_2$). Deacylation of the acyl group 'β' to the support link R^1 was not observed. Compounds **8a–s** were not observed in TFAA-mediated cyclizations.

[a] The yields were based on the integration of the product peak in the HPLC trace of the crude reaction mixture at 220 nm.

[b] Complex mixture.

and the *O*-trifluoroacetates **X** and **XI**. The calculations were performed using B3LYP[16] density functions with a 6-31G* basis set starting from the MMFF conformer. Among the four hydrazide conformers, the MMFF force field favored **IXa**, **IXc**, and **IXd** while **IXb** was converted into **IXc** upon the optimization. On the bases of earlier calculations and X-ray structures of related compounds,[14,15] conformer **IXc** would clearly be favored. **IXa**, is an 'unusual' conformer with a non-planar amide bond, and is probably an artifact of the calculations.

The calculations suggested the conformers **IXc** (EZ) or **IXd** (EE) to be attacked on the carbonyl functions next to R^2 by dehydrating agents due to the co-localization of their HOMOs and negative charge. Scheme 7 represents a mechanistic pathway elaborating upon the discussions of Scheme 3, considering the results of the MO calculations. The resulting cationic Vilsmeier–Haack intermediate **XI** (Scheme 7)



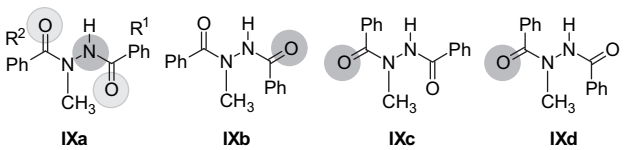
Scheme 5.

oxadiazole **14**, and 2,2,2-trifluoro-*N*′-(trifluoroacetyl) acetohydrazide (Scheme 5).

Unlike with dehydrations involving TFAA, $SOCl_2$-mediated oxadiazole formations were *not* accompanied by deacylation. However, these sluggish reactions yielded oxadiazoles and hydrazides **8a–q** with $M=(M_{oxadiazole}+18)$ (Table 3). Since, $SOCl_2$ is unable to form a stable N-adduct with hydrazides, we deduced N-trifluoroacetylation to be the reason for the deacylation.

A problem with TFAA-mediated oxadiazole formations was the competition with deacylation. In order to gain further insight in the reaction mechanisms, we performed MO calculations on model structures resembling the support-bound intermediates. Based on crystal structures of *N*2-acyl hydrazides[14] and steric bulk imposed by the linker, we assumed the secondary amide to be predominantly in the *Z*-configuration, while the tertiary amide with the support link was assumed to be *E* or *Z*. It is likely that in the support-bound hydrazides, the CO–N–N–CO dihedral angles are near 90° in their lowest energy conformations and the rotation about the N–N bond is hindered ($E_a \approx 19$ kcal/mol).[15]

We performed MO calculations on simplified model hydrazides **IXa** (ZZ), **IXb** (ZE), **IXc** (EZ), **IXd** (EE) (Scheme 6)

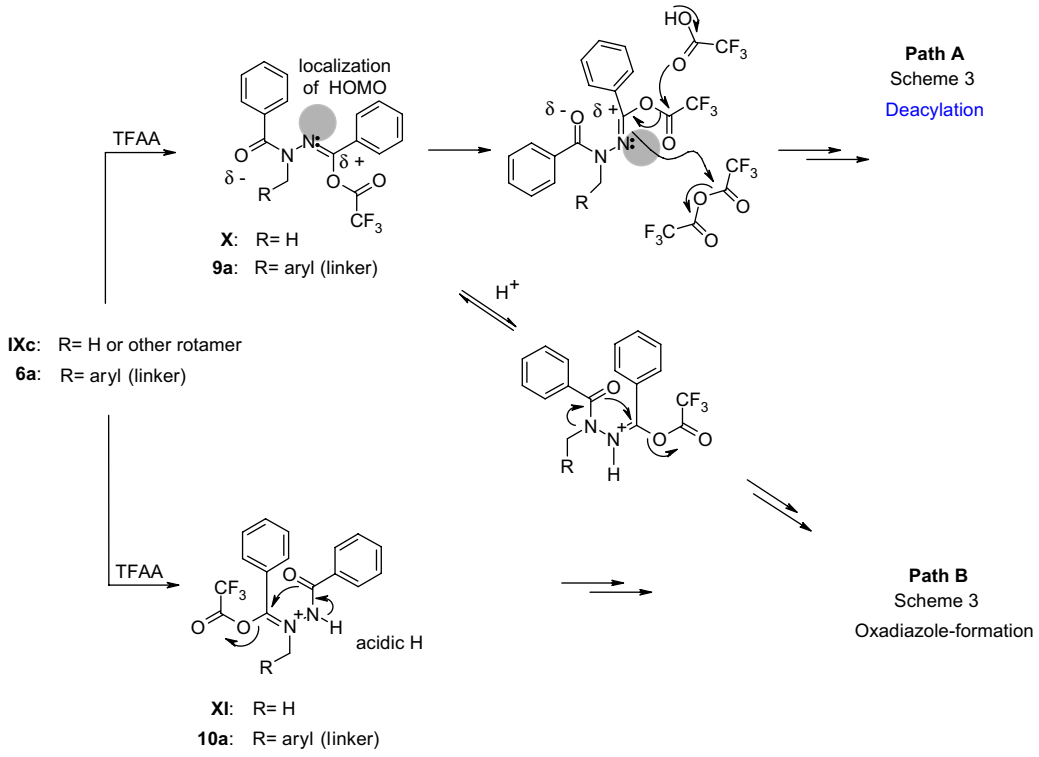


Scheme 6. Structures of the model compounds **IXa–d**. The highlighted atoms indicate the localization of the HOMO.

would initiate oxadiazole formation (as seen in path B, Scheme 3). In turn, an attack of TFAA on the carbonyl functions next to R^1 would lead to the intermediate **X**. This intermediate may not only be a precursor for oxadiazole formation (Scheme 7), but also may initiate deacylation according to path A in Scheme 3. Our calculations suggested the highlighted N atom of **X** to be its most nucleophilic moiety (Schemes 6 and 7). It also may be trifluoroacetylated, initiating path A in Scheme 3. Addition of TFA, as in our preferred cyclization cocktail, may in fact 'protect' the intermediate **X** from N-acylation and promote oxadiazole formation. Indeed, adding TFA to the cyclization cocktail resulted in slightly higher yields.

On the resin, the dehydrating agent TFAA may either attack the more nucleophilic carbonyl function or the more accessible one. It remained difficult to ascertain the influence of the hydrazide conformation on this attack. Attempts to use various NMR methods to determine the conformation of resin-bound hydrazides, such as **6a**, and model compound **18** were unsuccessful.

To support the reaction mechanism on the solid phase (Scheme 3), we also attempted to analyze the chemical species remaining on the polymer after the oxadiazole formation. Unfortunately, the structure of the resins was modified by the TFAA treatment, rendering it impossible to obtain MAS NMR spectra of the remaining resin-bound chemical entities. However, we performed elemental analysis on the resins affording **7a** or **7b** *after* the TFAA treatment. The measured N content of 2.5% was significantly higher than the calculated 1.2% required for the one resin-bound nitrogen, being part of the spacer (Scheme 3). Thus, about 50% of the originally support-bound hydrazide was not involved in oxadiazole formation,



Scheme 7. The expected reactivities of the model structures **IXc**, **X**, and **XI**, corresponded to the proposed intermediates **6a**, **9a**, and **10a**. The highlighted atoms indicate the localization of the HOMO.

and its nitrogen remained on the resin, as suggested by Scheme 3.

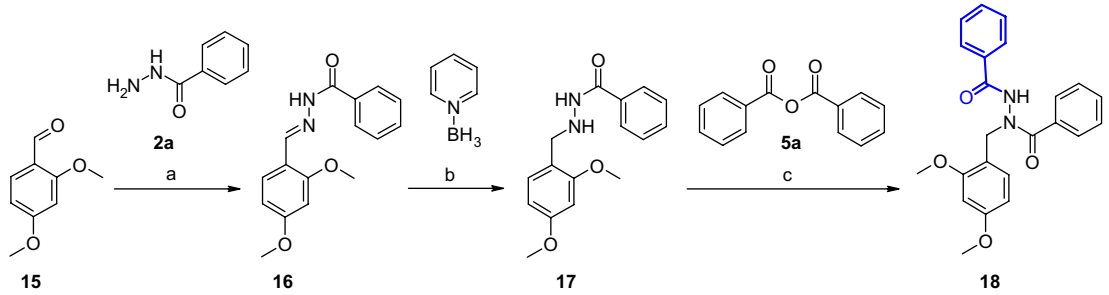
Finally, compound **18**, synthesized according to Scheme 8, served as our model for the transformations undergone by the resin-bound hydrazide **6a** during the TFAA treatment.

Fortunately, solution-phase oxadiazole formation using model compound **18** (Scheme 9) afforded the products suggested by reaction pathways A and B in Scheme 3.

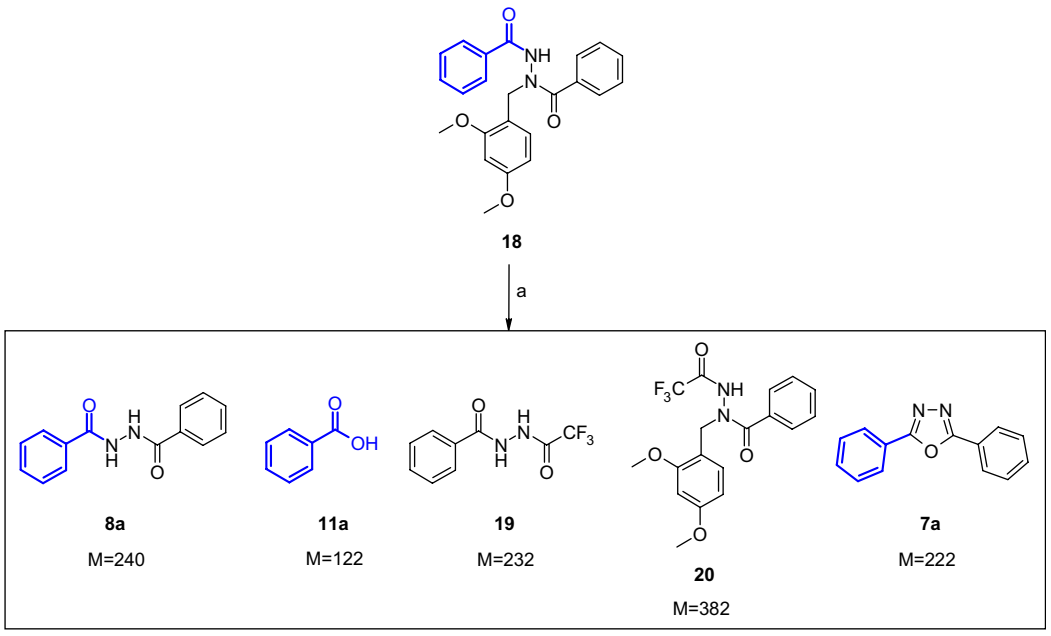
Thus, TFAA treatment of compound **18** gave the desired product **7a**. The side products **11a**, **19**[17] ($(M-H)^-$=231), and **20** ($(M+H)^+$=383, $M-H)^-$=381) resulted from the deacylation according to the mechanism in Scheme 3. The deacylation mechanism was further supported by the fact that in the HPLC trace of the reaction mixture at 220 nm, the integration of the peak of **11a** amounted to that of peaks **19** and **20** together. Unlike in TFAA-mediated oxadiazole formations on solid support, we also observed some dibenzoylation of **18**, giving **8a**.

Many lipophilic, high-molecular-weight compounds (M>700), and a white solid, a degradation product of **20**, insoluble in DMSO, DMF, CH_3OH, and water, were observed. Conversely, from the solid phase synthesis, side products **19**, **20**, the several lipophilic side products and the 'white solid' did not elute from the resin, even after repeated TFAA treatment. They remained tightly bound to the support lowering the overall recovery of isolated products. This sequestration by the polymeric support will be discussed in Section 2.1.3.

We also examined the influence of solvents on the outcome of the TFAA-mediated oxadiazole formations. Encouraged by dramatically different **7a**/**14** ratios in solution phase reactions (Table 4), we hoped to find solvents that could suppress the deacylation effectively on solid phase.



Scheme 8. Reagents and conditions: (a) HOAc, CH_2Cl_2, 24 h, rt; (b) CH_2Cl_2–HOAc (9:1, v/v), 3 h, rt; (c) NMI, CH_2Cl_2, 3 days, rt.



Scheme 9. Reagents and conditions: (a) TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v), 3 h, rt.

Unfortunately, on the solid support, the formation of **7a** could not be improved dramatically by changing reaction solvents.

The reason for the dramatic solvent dependence in TFAA-mediated solution-phase oxadiazole formations is not understood. Our calculations suggested the oxadiazole formation to be a largely charge driven process. In our hands reactions in toluene and THF were much slower than reactions in CH_2Cl_2, which solubilizes ionic intermediates much better. For instance, in the reaction in toluene (Table 4, entry 5) only 3% of the starting material was converted **7a**. The *N*-trifluoroacetyl derivative **19** failed to cyclize at all.

Reaction cocktails containing TFA or ethylene glycol gave broad ^{19}F NMR signals indicating rapid trans-trifluoroacetylation. These cocktails influenced the **7a/14** ratios in solution dramatically, but gave relatively modest effects on solid support. Unfortunately, the influence of the solvent can only be exploited for the reactions on solid phase within limits restricted by use of certain volatile solvents, permitting swelling of the resin and facile product isolation.

Table 4. Solvent influence on oxadiazole formation

Entry	Conditions	Solution phase:ratio[a] **7a**:**14**	Solid phase:isolated yield of **7a**
1	TFAA–THF (1:4)	Only **14**	n.d.
2	TFAA–THF (1:4)+5% TFA	Only **14**	n.d.
3	TFAA–DCM (1:4)+0.1% ethylene glycol	1:7.3	30.2
4	TFAA–DCM (1:4)+5% TFA	64:1	47.9
5	TFAA–toluene (1:4)	Only **7a**[b]	n.d.

[a] The ratio was determined by HPLC/MS at 254 nm after 48 h.
[b] After 48 h HPLC/MS at 220 nm indicated only 3% conversion to **7a**, main products: **8a** (12%), benzoyl hydrazide (41%), and **19** (5%).

2.1.3. Sequestration of support-bound species by the resin. The mass of all isolated products in our oxadiazole formations amounted to less than that was expected, based on the previously discussed pathways A and B (Scheme 3). In our solution phase model, the formation of the uncharacterized 'insoluble white solid' gave additional evidence of a third, 'sequestration pathway'. The latter is independent of TFAA, but mediated by acids. Thus, pre-incubation of resin **6q** with 5% TFA in CH_2Cl_2, prior to addition of TFAA, had an impact on the mass of isolated products (recovery) and on their purity (Fig. 1).

The purity of the isolated products was determined by integration of the product peak of their analytical HPLC traces at 220 nm. The product mixtures contained two components **7q** and **11e**.

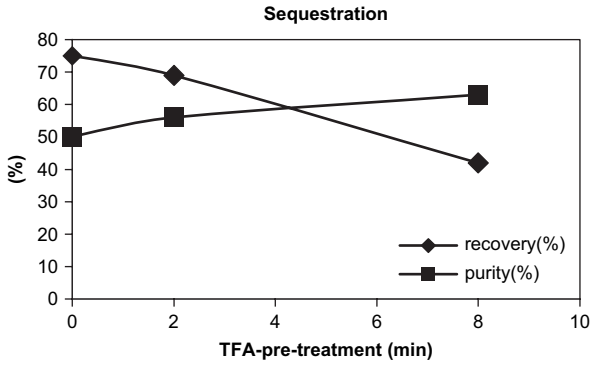


Figure 1. Sequestration of support-bound oxadiazole precursors upon action of TFA on support **6q** for various time periods. Subsequent oxadiazole formation was performed for 5 h in TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v). The recovery was determined by the following equation:

$$\text{recovery}[\%] = \frac{\text{gross isolated mass}}{\text{theoret. yield of oxadiazole}} \times 100.$$

Some dehydrating conditions promote the sequestration of the hydrazide more than others. For support **6a** sequestration follows the order: TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v)<$SOCl_2$–CH_2Cl_2 (25:75, v/v), rt≈$SOCl_2$–$CHCl_3$ (25:75, v/v) 60 °C,<$BF_3\cdot OEt_2$–$CHCl_3$ (1:9, v/v) 60 °C. In the latter case, no oxadiazole could be recovered from the resin. Slow addition of TFAA to a suspension of resin **6q** in CH_2Cl_2 to afford a solution of TFAA–CH_2Cl_2 (20:80, v/v) within 10 h also led to complete sequestration of all products. Though the mechanism of sequestration is not known, it certainly competed with deacylation and oxadiazole formation. Thus, the conditions for oxadiazole formation in Table 1 represent a compromise between purity of the crude desired product and its recovery.

3. Limits

The TFAA-mediated cyclizations were not successful for ureas and thioureas stemming from R^2–NCS or R^2NCO and R^2 bearing aromatic nitro-groups, or α-keto-groups. Chloromethyl oxadiazoles were identified in crude reaction mixtures involving chloroacetylated support-bound hydrazides, but did not survive the methanolic DOWEX-workup due to methoxylation.

4. Conclusion

We have studied the possibility of applying an acid labile linker as a leaving group in the synthesis of 1,3,4-oxadiazoles on solid phase. We also elucidated the role of TFAA in such processes, demonstrating its diverse reactivity. Many oxadiazoles have been obtained in purities suitable for our chemical collection without HPLC purification. In the underlying cyclizations, the linker is really traceless, leaving only an electron pair on the released substrate. Our process of few manipulations makes use of widely available and cheap commercial reagents. However, in order to obtain high isolated yields, other dehydrating conditions and different support linkers would be of need. The dehydrating volatile agent 'TFAA' also imposed some limitations regarding side reactions on choice of building blocks (for instance incompatibility with nitro-groups). In the case of the oxadiazole formation, we have demonstrated the role of the polymeric support in mediating a reaction pathway on solid phase differing from that in solution. The newly discovered reactivity of *N*-benzylated *N′*-acyl hydrazides may be exploitable for other applications.

5. Experimental

5.1. General

4(4-Formyl-3-methoxyphenoxy)butyryl resin was purchased from Calbiochem-Novabiochem AG, Weidenmattweg 4, CH-4448 Laeufelfingen, Switzerland. All solvents and reagents were purchased from Sigma–Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233, USA and Dr. Theodor Schuchardt & Company, Edward-Buchner Strasse 14-20, D-85662 Hohenbrunn, Germany. All other solvents and reagents were purchased from Aldrich.

5.1.1. Parallel reactions. Parallel reactions on solid supports were performed in Mettler Bohdan Miniblock: Mettler-Toledo Bohdan Inc., 562 Bunker Court, Vernon Hills, IL 60610 USA.

For the reactions performed on beads, quantitative loading of the resin-bound starting material was assumed. Large excess of reagents was generally applied to assure pseudo-first-order kinetics.

5.1.2. HPLC. HPLC/MS was performed on a Waters XTerra RP18 (4.6×50 mm, 3.5 μm) column using a Waters 2790 HPLC system equipped with a 996 Waters PDA detector and a Micromass mod. ZQ single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Mobile phase A: NH_4OAc (5 mM buffer with HOAc, pH 5.5)–CH_3CN (95:5, v/v); mobile phase B: H_2O–CH_3CN (5:95, v/v). A linear gradient was run from 10 to 90% B in 8 min, hold 90% B 2 min. UV detection at 220 and 254 nm. Flow rate: 1 mL/min; injection volume: 10 μL. Full scan, mass range from 100 to 800 amu. Capillary voltage: 2.5 kV; source temperature: 120 °C; cone voltage: 10 V. Retention times are given in minutes at 220 or 254 nm.

5.1.3. Exact mass. Exact mass data ESI(+) were obtained on a Waters Q-T of Ultima directly connected with micro HPLC 1100 Agilent as previously described.[18]

A reserpine solution 250 pg/μL (about 100 counts/s) was used as a reference compound for TOF Lock Mass correction ($[M+H]^+$ ion 609.2806 *m/z*).

5.1.4. NMR. NMR experiments were performed on two different instruments; chemical shifts were referenced with respect to the residual solvent signals.

^1H NMR spectra were recorded in DMSO-d_6 at a constant temperature of 25 °C on a Varian INOVA 500 spectrometer operating at 499.7 MHz for ^1H. The instrument was equipped with a *Z*-axis gradient triple resonance ^1H {$^{13}C/^{15}N$} PFG ID cold probe.

5.1.4.1. Magic angle spinning NMR. ^1H MAS NMR was performed in DMF-d_7 on a Varian INOVA 500 spectrometer operating at 500.25 MHz for ^1H equipped with a gHX Nano-Probe ($^1H\{^{31}P–^{15}N\}$).

5.1.5. MO calculations. MO calculations were performed using the 'Titan' molecular modeling program by Wavefunctions, Inc. 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA and Schroedinger, Inc. 1500 SW First Avenue, Suite 1180, Portland, OR 97201, USA.

5.2. Hydrazones bound on 4(4-formyl-3-methoxyphenoxy)butyryl resin

To 3-methoxy-benzaldehyde-resin (**1**) (2000 mg, loading 0.86 mmol/g), suspended in CH_2Cl_2 (20 mL), HOAc (1.58 mmol, 100 μL, 0.98 equiv), were added hydrazides

2a–e (1.5 equiv). The slurries were agitated for 18 h at rt, then washed successively with alternating washes of 3× (a) CH_2Cl_2, (b) dioxane; 3× (a) CH_2Cl_2, (b) EtOEt then with 3×EtOEt. The resins were dried in vacuo and analyzed by IR and NMR.

Note: The elemental analysis of resins is not very exact, due to residual solvent. It is an approximation of the loading. All following NMR experiments revealed quantitative conversion.

5.2.1. Resin 3a. IR (powder): 3025, 2972, 2920, 2850, 1645, 1601, 1546, 1503, 1492, 1451, 1420, 1352, 1308, 1272, 1200, 1163, 1115, 1074, 1028, 976, 909, 873, 834, 795, 757, 696 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 11.86 (1H, NH, hydrazone), 8.90 (1H, CH═N, hydrazone), 8.09 (2H, benzoyl), 7.96 (1H, linker), 7.41–7.57 (3H, benzoyl), 6.67, 6.62 (2H, linker), 4.38 (2H, –NH–CH_2– spacer), 4.10 (2H, –CH_2–O– spacer), 3.83 (3H, Me, linker), 2.49 (2H, –$COCH_2$– spacer), 2.11 (2H, –CH_2– spacer); determination of loading by elemental analysis: N: 3.86%, 0.91 mmol/g.

5.2.2. Resin 3b. IR (powder): 3058, 3025, 2924, 1651, 1601, 1549, 1493, 1452, 1420, 1372, 1309, 1272, 1199, 1163, 1113, 1029, 974, 905, 833, 755, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 11.53, 11.12 (1H, NH, hydrazone), 8.47, 8.62 (1H, CH═N, hydrazone), 7.90, 7.84 (1H, linker), 7.16–7.45 (5H, phenyl), 6.67–6.70 (2H, linker), 4.39 (2H, NH–CH_2– spacer), 4.10 (2H, –CH_2–O– spacer), 4.06, 3.63 (2H, CH_2), 3.81 (3H, Me, linker), 2.49 (2H, CO–CH_2–O– spacer), 2.12 (2H, –CH_2– spacer); determination of loading by elemental analysis: N: 3.83%, 0.91 mmol/g.

5.2.3. Resin 3c. IR (powder): 305, 2972, 2925, 2851, 1647, 1600, 1586, 1549, 1503, 1493, 1452, 1420, 1359, 1310, 1270, 1200, 1163, 1114, 1029, 961, 907, 817, 799, 748, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 12.41, 11.88 (1H, NH, hydrazone), 9.14, 8.88 (1H, CH═N, hydrazone), 7.94, 7.87, 7.55, 7.37 (5H, 4H: 3-fluoro benzoyl, 1H: linker), 6.69, 6.63 (2H, linker), 4.39 (2H, –NH–CH_2– spacer), 4.10 (2H, –CH_2–O– spacer), 3.84 (3H, Me, linker), 2.49 (2H, –$COCH_2$– spacer), 2.11 (2H, –CH_2– spacer); determination of loading by elemental analysis: N: 3.67%, 0.89 mmol/g; F: 2.03%, 1.07 mmol/g.

5.2.4. Resin 3d. IR (powder): 3057, 3025, 2923, 1645, 1599, 1544, 1491, 1451, 1420, 1357, 1273, 1199, 1163, 1114, 1030, 973, 908, 972, 804, 747, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 12.38, 11.82 (1H, NH, hydrazone), 9.06, 8.88 (1H, CH═N, hydrazone), 7.94 (1H, linker), 7.66, 7.41, 7.12 (4H, 3-methoxybenzoyl), 6.58–6.69 (2H, linker), 4.38 (2H, –NH–CH_2– spacer), 4.10 (2H, –CH_2–O– spacer), 3.82 (6H, 3H: Me, linker, 3H: Me, 3-methoxybenzoyl), 2.49 (2H, –$COCH_2$– spacer), 2.11 (2H, –CH_2– spacer).

5.2.5. Resin 3e. IR (powder): 3034, 2922, 1641, 1600, 1550, 1505, 1551, 1493, 1451, 1417, 1377, 1309, 1272, 1223, 1200, 1163, 1113, 1030, 975, 908, 826, 756, 732, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 11.88, 11.56 (1H, NH, hydrazone), 8.82, 8.60 (1H, CH═N, hydrazone), 8.17, 7.85 (1H, H3, thienyl), 8.06, 7.80 (1H, 1H: H5, thienyl), 8.06, 7.93 (1H, linker), 7.17 (1H, H4, thienyl), 6.55–6.73 (2H, linker), 4.39 (2H, –NH–CH_2– spacer), 4.12 (2H, –CH_2–O– spacer), 3.84 (3H, Me, linker), 2.49 (2H, –$COCH_2$– spacer), 2.13 (2H, –CH_2– spacer); determination of loading by elemental analysis: N: 3.74%, 0.89 mmol/g, S: 2.31%, 0.79 mmol/g.

5.3. Reduction of resin-bound hydrazones 3a–e to hydrazides 4a–e

Hydrazone resins **3a–e** (1000 mg, loading 0.86 mmol/g) were suspended in 10 mL of (CH_2Cl_2–HOAc–pyridine·BH_3 (85:10:5, v/v/v) and agitated for 8 h at rt. The reaction mixtures were washed successively with alternating washes of 3× (a) DMF, (b) CH_2Cl_2; 3× (a) MeOH, (b) CH_2Cl_2; 3× (a) CH_2Cl_2, (b) EtOEt and 3×EtOEt. The resins were dried in vacuo and analyzed by IR and NMR. All following NMR experiments revealed quantitative conversion.

5.3.1. Resin 4a. IR (powder): 1651, 1611, 1506, 1493, 1419, 1284, 1263, 1198, 1160, 1131, 1028, 970, 901, 821, 757, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 9.97–10.27 (1H, –CO–N*H*–NH–), 7.85–8.03 (2H, *o*-CH, benzoyl), 7.32–7.58 (1H, *p*-CH, benzoyl), 7.03–7.29m (1H, linker), 7.03–7.28 (2H, *m*-CH, benzoyl), 6.54–6.65 (1H, linker), 6.42–6.51 (1H, linker), 4.23–4.53 (2H, –N–CH_2– spacer), 3.9–4.12 (4H, –CH_2–O–, –CH_2–NH–NH– linker), 2.36–2.55 (2H, –$COCH_2$– spacer), 2.03–2.07 (2H, –CH_2– spacer).

5.3.2. Resin 4b. IR (powder): 1662, 1647, 1613, 1506, 1493, 1451, 1419, 1286, 1262, 1197, 1160, 1132, 1031, 971, 829, 756, 679 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 9.44–9.86 (1H, –CO–N*H*–NH–), 6.82–7.52 (6H, 5H: phenyl, 1H: linker), 6.53–6.60 (1H, 1H, linker), 6.43–6.49 (1H, linker), 4.22–4.50 (2H, –N–CH_2– spacer), 3.45–3.49 (2H, CH_2, benzyl), 3.98–4.13 (4H, –CH_2–O–), 3.83–3.93 (2H, –N–CH_2– spacer), 3.68–3.81 (5H, Me linker, –CH_2–NH–NH– linker), 2.41–2.59 (2H, –$COCH_2$– spacer), 2.06–2.18 (2H, –CH_2– spacer).

5.3.3. Resin 4c. IR (powder): 2920, 1647, 1612, 1585, 1493, 1451, 1420, 1286, 1269, 1199, 1160, 1130, 1030, 972, 942, 888, 820, 795, 754, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 9.92–10.52 (1H, –CO–N*H*–NH–), 7.76–7.85 (1H, 3-fluorophenyl), 7.68–7.76 (1H, 3-fluorophenyl), 7.16–7.34 (2H, 1H: 3-fluorophenyl, 1H: linker), 6.52–6.64 (1H, linker), 6.41–6.50 (1H, linker), 4.22–4.53 (2H, –N–CH_2– spacer), (2H, –CH_2–NH–NH– linker, –CH_2–NH–NH– linker), 3.91–4.16 (4H, –CH_2–O–, N–CH_2– spacer), 3.61–3.96 (3H, Me, linker), 2.29–2.61 (2H, –$COCH_2$– spacer), 1.99–2.22 (2H, –CH_2– spacer).

5.3.4. Resin 4d. IR (powder): 1653, 1607, 1582, 1539, 1506, 1492, 1451, 1421, 1284, 1198, 1160, 1132, 1119, 1033, 972, 835, 793, 756, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 9.92–10.33 (1H, –CO–N*H*–NH–), 7.48–7.59 (2H, 3-methoxybenzoyl), 7.29–7.41 (1H, 1H: 3-methoxybenzoyl), 7.21–7.27 (1H, linker), 7.00–7.13 (1H, 3-methoxybenzoyl), 6.53–6.63 (1H, linker), 6.41–6.52 (1H, linker), 4.15–4.52 (2H, –N–CH_2– spacer), 3.92–4.07 (2H, –CH_2–O–), 3.90–4.09 (2H, –CO–NH–NH–CH_2–), 3.67–3.85 (6H, 3H: Me methoxybenzoyl, 3H: Me, linker), 2.41–2.53 (2H, –$COCH_2$– spacer), 2.04–2.17 (2H, –CH_2– spacer).

5.3.5. Resin 4e. IR (powder): 1652, 1613, 1539, 1505, 1493, 1451, 1417, 1286, 1198, 1160, 1127, 1028, 968, 908, 821, 756, 697 cm^{-1}; ^1H MAS NMR (500 MHz, DMF-d_7) δ 9.97–10.26 (1H, –CO–N*H*–NH–), 7.81–7.90 (1H, H5 thienyl), 7.62–7.73 (1H, H3 thienyl), 7.19–7.29 (1H, linker), 7.04–7.15 (1H, H4 thienyl), 6.55–6.63 (1H, linker), 6.43–6.52 (1H, linker), 4.23–4.50 (2H, –N–CH_2– spacer), 3.92–4.12 (4H, 2H: –CH_2–NH–NH– linker, 2H: –$COCH_2$– spacer), 3.66–3.84 (3H, Me, linker), 2.40–2.56 (2H, –$COCH_2$– spacer), 2.09 (2H, –CH_2– spacer).

5.4. Acyl hydrazides

The acyl hydrazides have been isolated as side products during the $SOCl_2$-mediated oxadiazole formation (Table 3). Their mass spectrum and HPLC retention time match that of the reference compounds synthesized in the following way.

5.5. Representative procedure: *N′*-benzoylbenzohydrazide (8a)

To a suspension of benzohydrazide (2 mmol, 272 mg) in CH_2Cl_2, DIEA (2.5 mmol, 424 μL) was added benzoyl chloride (2.1 mmol, 243 μL). A massive precipitation was observed immediately. After 3 h at rt the solid was filtered off and washed with CH_2Cl_2. The white solid was dried in vacuo and analyzed. Yield: 458 mg, 95.3%.

5.5.1. *N′*-Benzoylbenzohydrazide (8a). ^1H NMR (500 MHz, DMSO-d_6) δ 10.50 (2H, s, NH), 7.94 (4H, m, H2, H6 phenyl), 7.62 (2H, m, H4 phenyl), 7.54 (4H, m, H3, H5 phenyl). HRMS *m/z* calcd for $C_{14}H_{12}N_2O_2$: 241.0971 $(M+H)^+$, found 241.0983.

5.5.2. *N′*-Benzoyl-3-fluorobenzohydrazide (8m). ^1H NMR (500 MHz, DMSO-d_6) δ 10.56 (2H, s, NH), 7.93 (2H, m, H2, H6 phenyl), 7.74–7.81 (m, 2H, H2, H6 3-fluorophenyl), 7.61 (2H, m, H4 phenyl, H5 3-fluorophenyl), 7.54 (2H, m, H3, H5 phenyl), 7.51 (1H, m, H4 3-fluorophenyl).

5.5.3. *N′*-Benzoyl-3-methoxybenzohydrazide (8o).[19] ^1H NMR (500 MHz, DMSO-d_6) δ 10.50 (2H, s, NH), 7.94 (2H, m, H2, H6 phenyl), 7.61 (m, 1H, H4 phenyl), 7.38–7.57 (m, 5H, H4, H5, H6 3-methoxyphenyl, H3, H5 phenyl), 7.19 (1H, m, H2 3-methoxyphenyl), 3.82, 3.84 (3H, 2s, Me).

5.5.4. *N′*-Benzoylthiophene-2-carbohydrazide (8q). ^1H NMR (500 MHz, DMSO-d_6) δ 10.50 (2H, s, NH), 7.94 (4H, m, H2, H6 phenyl, H3, H5 thienyl), 7.54 (3H, m, H3, H4, H5 phenyl), 7.23 (1H, m, H4 thienyl), HRMS *m/z* calcd for $C_{12}H_{10}N_2O_2S$: 247.0536 $(M+H)^+$, found 247.0546.

5.6. Solution-phase synthesis of 2-phenyl-5-(trifluoromethyl)-1,3,4-oxadiazole (14)

To **8a** (220 mg, 0.5 mmol) was added a solution of THF–TFAA (4:1, v/v) (5 mL). The reaction mixture became homogeneous after 5 min, though the TLC of an aliquot of the hydrolyzed reaction mixture did not indicate any conversion. The reaction mixture was stirred at rt for another 3 days. The TLC of the reaction mixture then revealed complete conversion into two products. CH_2Cl_2–MeOH (9:1, v/v) R_f: 0.78, 0.38. The reaction mixture was poured on ice and was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, the salts were removed, and the crude product was chromatographed on silica using CH_2Cl_2–MeOH (95:5, v/v).

The high R_f product (105 mg, 97.6%) was **14**. ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–8.13 (2H, d, H2, H6 phenyl), 7.53–7.66 (3H, m, H3, H4, H5 phenyl), (ESI-MS) *m/z*: 215.0 $(M+H)^+$, 232.1 $(M+NH_4)^+$. The low R_f product was benzoic acid **11a**: (ESI-MS) 121.1 $(M-H)^-$.

5.7. Acylated resins

On-bead acylations were performed in Bohdan Miniblocks® on 50 mg of reduced resins (**4a–e**) per reactor. To this amount of resin was then added 2 mL of an acylating solution.

The following solutions were used:

A: To a reactor was added 2 mL of a solution of $(R^2CO)_2O$ (0.5 M), NMI (0.5 M) in CH_2Cl_2.

B: To a reactor were added R^2CO_2H (1 mmol), *N*-methyl imidazole (0.025 mmol), CH_2Cl_2 (2 mL), and ethoxyacetylene (1 mmol as solution in hexane, quantity based on the titer).

C: In an oven dried glass vial, covered with a septum was made a solution (or suspension) of R^2CO_2H (1 M) in CH_2Cl_2 to which was added 2 M equiv of *N*-methyl imidazole. The resulting solution was cooled to 0 °C, and 1 M equiv of isopropyl chloroformate was added as 1 M solution in toluene. The resulting reagent was allowed to come to rt within 30 min and was then added (2 mL per each reactor) to the corresponding reactors in the Miniblock using a syringe.

D: In an oven dried glass vial closed with a septum a solution of pentafluorophenol (PFP) (0.5 M, 1 equiv) and *N*-methyl imidazole (1 M, 2 equiv) in CH_2Cl_2 was prepared. To the resulting solution 1 M equiv (based on PFP) of R^2COCl was added at 0 °C. The resulting solution was allowed to come to rt within 30 min and was then added (2 mL per each reactor) to the corresponding reactors in the Miniblock using a syringe.

The resins were agitated in an orbital shaker for 48 h and were washed using 3×DMF (2 mL) and 1×DMF–H_2O–NEt_3 (4:1:1, v/v/v) (2 mL), followed by alternating washes with 3× (a) DMF (2 mL), (b) CH_2Cl_2 (2 mL); 3× (a) MeOH (2 mL), (b) CH_2Cl_2 (2 mL); 3× (a) CH_2Cl_2 (2 mL), (b) Et_2O (2 mL); 3×Et_2O.

The resins were dried in vacuo for 5 h prior to the cyclative oxadiazole formation.

The following resins were analyzed on solid phase. (Attempted cleavage of the acylated resins with TFA gave complex mixtures, which could not be used for analysis of the resin.) All following NMR experiments revealed quantitative conversion!

5.7.1. Resin 6a. ^1H MAS NMR (500 MHz, DMF-d_7) δ 10.93 (1H, –CO–N*H*–), 7.69 (4H, H2, H6 benzoyl), 7.42 (1H, H4

benzoyl on *tert* amide), 7.31 (1H, H6 linker), 7.12 (5H, H3, H4, H5 benzoyl on primary amide, H3, H5 on secondary amide), 6.59 (1H, H3 linker), 6.51 (1H, H5 linker), 5.51, 4.42 (2H, CH_2, linker), 4.05 (2H, –CH_2–O– spacer), 3.73, 3.64 (3H, Me, linker), 2.47 (2H, –$COCH_2$– spacer), 2.09 (2H, –CH_2– spacer).

5.7.2. Resin 6ba. ^{1}H MAS NMR (500 MHz, DMF-d_7) δ 10.57 (1H, –CO–N*H*–), 7.54 (2H, H2, H6 benzoyl), 7.15–7.39 (6H, H3, H4, H5 benzoyl, H6, linker), 6.91 (2H, H2, H6 benzyl), 6.64 (1H, H3 linker), 6.52 (1H, H5, linker), 5.43, 4.32 (2H, CH_2, linker), 4.09 (2H, –CH_2–O– spacer), 3.77, 3.74 (3H, Me, linker), 2.50 (2H, –$COCH_2$– spacer), 2.13 (2H, –CH_2– spacer).

5.7.3. Resin 6m. ^{1}H MAS NMR (500 MHz, DMF-d_7) δ 11.05 (1H, –CO–N*H*–), 7.69 (2H, H2, H6 benzoyl), 7.56 (1H, H6 3-fluorophenyl), 7.44 (2H, H2, H4 3-fluorophenyl), 7.16–7.34 (2H, 1H: 3-fluorophenyl, H6: linker), 6.61 (1H, H3, linker), 6.54 (1H, H5 linker), 5.50, 4.44 (2H, CH_2 linker), 4.07 (2H, –CH_2–O–, N–CH_2– spacer), 3.66 (3H, Me, linker), 2.49 (2H, –$COCH_2$– spacer), 2.11 (2H, –CH_2– spacer).

5.7.4. Resin 6o. ^{1}H MAS NMR (500 MHz, DMF-d_7) δ 10.91 (1H, –CO–N*H*–), 7.69 (2H, H2, H5 benzoyl), 7.31 (5H, H5, H6 3-methoxybenzoyl, H3, H4, H5 benzoyl, H6 linker), 7.21 (1H, H2 3-methoxybenzoyl), 7.03 (1H, H4 3-methoxybenzoyl), 6.60 (1H, H3, linker), 6.52 (1H, H5 linker), 5.49, 4.41 (2H, CH_2 linker), 4.05 (2H, –CH_2–O), 3.73, 3.70 (3H, Me 3-methoxybenzoyl), 3.66 (3H, Me linker), 2.46 (2H, –$COCH_2$– spacer), 2.04–2.17 (2H, –CH_2– spacer).

5.7.5. Resin 6q. ^{1}H MAS NMR (500 MHz, DMF-d_7) δ 10.95 (1H, –CO–N*H*–), 7.65 (3H, H5 thienyl, H2, H6 benzoyl), 7.27 (1H, H6 linker), 7.01 (1H, H4 thienyl), 6.57 (1H, H3 linker), 6.49 (1H, H5 linker), 5.44, 4.37 (2H, CH_2 linker), 4.03 (2H, –O–CH_2 spacer), 3.60 (3H, Me linker), 2.44 (2H, –$COCH_2$– spacer), 2.07 (2H, –CH_2– spacer).

5.8. Oxadiazole formation on solid phase

The acylated resins were treated with a solution of TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v) (2 mL per reactor) for 5 h at rt. The reaction mixture was drained and the resin was washed with TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v) (1 mL per reactor). The effluent was collected and toluene (1 mL per reaction) was added prior to the evaporation of the reaction mixtures. This toluene addition prevents buildup of TFA and TFAA during the evaporation process, which may lead to side reactions when acids with a –CH_2(C=O)OH– motif are used. The dried reaction mixtures were weighed and analyzed by HPLC/MS to obtain the crude yields. The crude, dried down reaction mixtures were dissolved in MeOH (3 mL each). The resulting solutions were transferred into another Miniblock containing reactors filled with DOWEX1-X2 (carbonate form) (50 mg per reaction). The methanolic solutions of the crude products were agitated for another 3 h prior to filtration and a wash of the DOWEX with methanol (1 mL). The filtrates were analyzed by HPLC/MS for purity and evaporated to white powders or crystals to obtain the isolated yields.

5.9. Analysis of what remained on the resin

Resins **6a** and **6b** were washed after the oxadiazole formation and isolation of the products as follows: 5× with CH_2Cl_2 (2 mL) followed by alternating washes with 3× (a) MeOH (2 mL), (b) CH_2Cl_2 (2 mL); 3× (a) CH_2Cl_2 (2 mL), (b) Et_2O (2 mL); 3×Et_2O. The resins were dried in vacuo for 5 h prior to submission to elemental analysis or ^{1}H MAS NMR (see text, Section 2.1.2).

5.10. Oxadiazoles

5.10.1. 2,5-Diphenyl-1,3,4-oxadiazole (7a). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.15–8.18 (4H, m, H2, H6 phenyl), 7.63–7.71 (6H, m, H3, H4, H5 phenyl). UV: (λ_{max}) 278 nm; HRMS *m*/*z* calcd for $C_{14}H_{10}N_2O$: 223.0866 $(M+H)^+$, found: 223.0865; HPLC retention time: 6.27 min.

5.10.2. 2-Benzyl-5-phenyl-1,3,4-oxadiazole (7b). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96–7.99 (2H, m, H2, H6 phenyl), 7.57–7.66 (3H, m, H3, H4, H5 phenyl), 7.37–7.42 (4H, m, H2, H3, H5, H6 *phenyl*-methyl), 7.29–7.35 (1H, m, H4 *phenyl*-methyl), 4.38 (2H, br s, CH_2, phenyl-methyl). UV: (λ_{max}) 251 nm; HRMS *m*/*z* calcd for $C_{15}H_{12}N_2O$: 237.1022 $(M+H)^+$, found: 237.1032; HPLC retention time: 5.94 min.

5.10.3. 2-Butyl-5-phenyl-1,3,4-oxadiazole (7c). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98–8.01 (2H, m, H2, H6 phenyl), 7.59–7.64 (3H, m, H3, H4, H5 phenyl), 2.95 (2H, t, J=8 Hz, α-CH_2, *n*-Bu), 1.77 (2H, m, β-CH_2, *n*-Bu), 1.42 (2H, m, γ-CH_2, *n*-Bu), 0.94 (3H, t, J=8 Hz, Me, *n*-Bu). UV: (λ_{max}) 248 nm, MS (CI) *m*/*z* (relative intensity) 203 ([M+H] 100%), HMRS *m*/*z* calcd for $C_{12}H_{14}N_2O$: 203.1179 $(M+H)^+$, found: 203.1180; HPLC retention time: 5.96 min.

5.10.4. 2-Phenyl-5-[(*E*)-2-phenylvinyl]-1,3,4-oxadiazole (7d). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11–8.14 (2H, m, H2, H6 phenyl), 7.81–7.84 (2H, m, H2, H6 phenyl of cinnamyl), 7.80 (1H, d, J=17 Hz, –*H*C=CH–Ph, cinnamyl), 7.61–7.71 (3H, m, H3, H4, H5 phenyl), 7.42–7.51 (3H, m, H3, H4, H5 phenyl of cinnamyl), 7.41 (1H, d, J=17 Hz, –HC=C*H*–Ph, cinnamyl). UV: 253.9, 313.2 nm, HMRS calcd for $C_{16}H_{12}N_2O$: 249.1022 $(M+H)^+$, found: 249.1011; HPLC retention time: 6.82 min.

5.10.5. 2-(2-Methylphenyl)-5-phenyl-1,3,4-oxadiazole (7e). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13–8.17 (2H, m, H4, H6 2-methyl phenyl), 8.1 (1H, dd, J=8 Hz, J'=1 Hz, H3 2-methyl phenyl), 7.64–7.70 (3H, m, H2, H6 phenyl, H5 2-methyl phenyl), 7.56 (1H, m, H4 phenyl), 7.41–7.52 (2H, m, H3, H5 phenyl), 2.72 (3H, s, Me). UV: (λ_{max}) 281.1 nm, HRMS *m*/*z* calcd for $C_{15}H_{12}N_2O$: 237.1022 $(M+H)^+$, found: 237.1012; HPLC retention time: 6.91 min.

5.10.6. 2-Biphenyl-4-yl-5-phenyl-1,3,4-oxadiazole (7f). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (2H, d, J=9 Hz, H2, H6 4-phenyl *phenyl*), 8.17–8.20 (2H, m, H2, H6 phenyl), 7.97 (2H, d, J=9 Hz, H3, H5 4-phenyl *phenyl*), 7.80–7.83 (2H, m, H2′, H6′ 4-*phenyl* phenyl), 7.64–7.69 (3H, m, H3, H4, H5 phenyl), 7.55 (2H, t, J=7 Hz, H3′, H5′ 4-phenyl phenyl), 7.46 (1H, t, J=7 Hz, H4′ 4-phenyl phenyl). UV: (λ_{max}) 301.3 nm, HRMS *m*/*z* calcd for $C_{20}H_{14}N_2O$:

299.1179 $(M+H)^+$, found: 299.1171; HPLC retention time: 8.07 min.

5.10.7. 2-Phenyl-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazole (7g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.37 (2H, d, J=9 Hz, H2, H6 trifluoromethyl phenyl), 8.19 (2H, dd, J=8, J'=2 Hz, H2, H6 phenyl), 7.80 (m, 3H, H3, H4, H5 phenyl). UV: (λ_{max}) 282.3 nm, HRMS m/z calcd for $C_{15}H_9F_3N_2O$: 291.0740 $(M+H)^+$, found: 291.0744; HPLC retention time: 7.38 min.

5.10.8. 2-(2-Furyl)-5-phenyl-1,3,4-oxadiazole (7h). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08–8.11 (3H, m, H2, H6 phenyl, H3 furyl), 7.62–7.71 (3H, m, H3, H4, H5 phenyl), 7.48 (1H, dd, J=4 Hz, J'=1 Hz, H5 furyl), 6.85 (1H, m, H4, furyl). UV: (λ_{max}) 238.6, 293 nm, HRMS m/z calcd for $C_{12}H_8N_2O_2$: 213.0658 $(M+H)^+$, found: 213.0668; HPLC retention time: 5.32 min.

5.10.9. 2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (7i). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.17 (4H, m, H2, H6 phenyl, H2, H6 4-chlorophenyl), 7.75 (2H, m, H3, H5 4-chlorophenyl), 7.67 (3H, m, H3, H4, H5 phenyl). UV: (λ_{max}) 287.4 nm, HRMS m/z calcd for $C_{14}H_9ClN_2O$: 257.0476 $(M+H)^+$, found: 257.0468; HPLC retention time: 7.12 min.

5.10.10. 2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (7j). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13–8.15 (2H, m, H2, H6 phenyl), 8.10 (2H, d, J=8 Hz, H3, H5 4-methoxyphenyl), 7.61–7.68 (m, 3H, H3, H4, H5 phenyl), 7.20 (2H, d, J=8 Hz, H3, H5 4-methoxyphenyl), 3.89 (3H, s, Me). UV: (λ_{max}) 243.3, 294.2 nm, HRMS m/z calcd for $C_{15}H_{12}N_2O_2$: 253.0971 $(M+H)^+$, found: 253.0972; HPLC retention time: 6.31 min.

5.10.11. 2-(1-Naphthyl)-5-phenyl-1,3,4-oxadiazole (7k). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (1H, d, J=9 Hz, H2 naphthyl), 8.43 (1H, d, J=7 Hz, H8 naphthyl), 8.26 (1H, d, J=7 Hz, H5 naphthyl), 8.21 (2H, m, H2, H6 phenyl), 8.13 (1H, J=9 Hz, H4 naphthyl), 7.65–7.83 (m, 6H (H3, H4, H5 phenyl, H3, H6, H7 naphthyl). UV: (λ_{max}) 222.1, 263.4, 313.2 nm, HRMS m/z calcd for $C_{18}H_{12}N_2O$: 273.1022 $(M+H)^+$, found: 273.1010; HPLC retention time: 7.72 min.

5.10.12. 2-Benzyl-5-(2-furyl)-1,3,4-oxadiazole (7l). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03 (1H, m, H5 furyl), 7.29–7.41 (6H, m, phenyl, H3 furyl), 6.78 (1H, m, H4 furyl), 4.36 (2H, s, CH_2–Ph). UV: (λ_{max}) 266.9 nm. MS (CI) m/z (relative intensity) 227 ($[M+H]^+$ 100%), HPLC retention time: 5.97 min.

5.10.13. 2-(3-Fluorophenyl)-5-phenyl-1,3,4-oxadiazole (7m). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (2H, m, H2, H6 phenyl), 8.01 (1H, m, H6 3-fluorophenyl), 7.99 (1H, m, H2 3-fluorophenyl), 7.64–7.74 (4H, m, H3, H4, H5 phenyl, H5 3-fluorophenyl), 7.55 (1H, t of m, J=9 Hz, H4 3-fluorophenyl). UV: (λ_{max}) 280 nm, HRMS m/z calcd for $C_{14}H_9FN_2O$: 241.0772 $(M+H)^+$, found: 241.0762; HPLC retention time: 6.55 min.

5.10.14. 2-Biphenyl-4-yl-5-(3-fluorophenyl)-1,3,4-oxadiazole (7n). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (2H, d, J=9 Hz, H2, H6 4-phenyl-*phenyl*), 8.04 (1H, m, H5 3-fluorophenyl), 8.00 (1H, m, H2 3-fluorophenyl), 7.97 (2H, d, 9 Hz, H3, H5 4-phenyl-*phenyl*), 7.82 (2H, d, J=8 Hz, H2′, H6′ 4-*phenyl*-phenyl), 7.72 (1H, m, H5 3-fluorophenyl), 7.53–7.57 (3H, m, H4 3-fluorophenyl, H3′, H5′ 4-*phenyl*-phenyl), 7.47 (1H, t, J=7 Hz, H4′ 4-*phenyl*-phenyl). UV: (λ_{max}) 302.5 nm, HRMS m/z calcd for $C_{20}H_{13}FN_2O$: 317.1085 $(M+H)^+$, found: 317.1088; HPLC retention time: 8.27 min.

5.10.15. 2-(3-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (7o). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (2H, m, H2, H6 phenyl), 7.74 (1H, d of m, J=8 Hz, H6 3-methoxyphenyl), 7.67 (4H, m, H2 3-methoxyphenyl, H3, H4, H5 phenyl), 7.58 (1H, t, J=8 Hz, H5, 3-methoxyphenyl), 7.25 (1H, dd, J=8 Hz, J'=1 Hz, H4, 3-methoxyphenyl), 3.9 (3H, s, Me). UV: (λ_{max}) 280, 313 nm; HRMS m/z calcd for $C_{15}H_{12}N_2O_2$: 253.0971 $(M+H)^+$, found: 253.0962; HPLC retention time: 6.49 min.

5.10.16. 2-(4-Chlorophenyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (7p). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (2H, m, J=9 Hz, H2, H6 4-chlorophenyl), 7.72 (1H, m, H6 3-methoxyphenyl), 7.72 (2H, d, J=9 Hz, H3, H5 4-chlorophenyl), 7.65 (1H, m, H2 3-methoxyphenyl), 7.56 (1H, t, J=8 Hz, H5 3-methoxyphenyl), 7.24 (1H, dd, J=8 Hz, J'=1 Hz, H4, 3-methoxyphenyl), 3.89 (3H, s, Me). UV: (λ_{max}) 236–242 nm (plateau), 283 nm; HRMS m/z calcd for $C_{15}H_{11}ClN_2O_2$: 287.0582 $(M+H)^+$, found: 287.0568; HPLC retention time: 7.03 min.

5.10.17. 2-Phenyl-5-(2-thienyl)-1,3,4-oxadiazole (7q). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (2H, m, H2, H6 phenyl); 7.98 (2H, m, H3, H5 thienyl), 7.62–7.7 (3H, m, H3, H4, H5 phenyl), 7.36 (1H, m, H4 thienyl). UV: (λ_{max}) 300.7 nm, HRMS m/z calcd for $C_{12}H_8N_2OS$: 229.0430 $(M+H)^+$, found: 229.0425; HPLC retention time: 5.95 min.

5.11. Trans-trifluoroacetylation: reaction of 2a with TFAA

Benzohydrazide **2a** (0.367 mmol, 50 mg) was treated with TFAA–CH_2Cl_2 (1:4, v/v) (2 mL) for 14 h at rt. A white precipitate formed, which was found to be 2,2,2-trifluoro-*N*′-(trifluoroacetyl)acetohydrazide upon comparison with an authentic sample prepared according to Ref. 6a. The crude reaction mixture was taken up in MeCN–H_2O (4:1, v/v) and subjected to HPLC/MS. The HPLC trace indicated the formation of three products, benzoic acid (**11a**), 2-phenyl-5-(trifluoromethyl)-1,3,4-oxadiazole (**14**), and 2,2,2-trifluoro-*N*′-(trifluoroacetyl)acetohydrazide.[6a] The peaks were compared with authentic samples by UV, MS, retention time, and co-injection.

5.12. Synthesis of 'solution phase model compound 18' (Scheme 8)

5.12.1. 2,4-Dimethoxybenzaldehyde benzoylhydrazone (16). 2,4-Dimethoxybenzaldehyde (**15**) (2 mmol, 272.3 mg), benzoylhydrazone (**2a**) (2 mmol, 332.3 mg) were stirred in CH_2Cl_2 (10 mL) containing HOAc (10 μL) for 24 h at rt. The resulting precipitation was completed upon addition of EtOEt (30 mL). The product was filtered and washed with EtOEt. Yield: 510.4 mg (89.8%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (1H, br s, NH hydrazone), 8.73 (1H, s, CH hydrazone), 7.92 (2H, d, J=7 Hz, H2, H6 phenyl), 7.82 (1H, d, J=9 Hz, H6 2,4-dimethoxyphenyl), 7.57–7.62 (1H, t, J=7 Hz, H4 benzoyl), 7.49–7.56 (2H, dd, J=7 Hz, H3, H5 benzoyl), 6.63–6.69 (2H, m, H3, H5 2,4-dimethoxyphenyl), 3.88 (3H, s, Me), 3.85 (3H, s, Me); HRMS *m/z* calcd for $C_{16}H_{16}N_2O_3$: 285.1234 $(M+H)^+$, found: 285.1230.

5.12.2. *N′*-(2,4-Dimethoxybenzyl)benzohydrazide (17). To **16** (800 mg, 2.81 mmol) dissolved in CH_2Cl_2–HOAc (4:1, v/v) was added a complex of borane and pyridine (465 mg, 5 mmol). After 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with aqueous NaOH (0.5 M). The organic phase was dried over Na_2SO_4, the salts were then removed and the products evaporated to dryness. The borane adduct of **17** was removed from the crude product by chromatography on SiO_2 using CH_2Cl_2. The desired product was eluted with CH_2Cl_2–MeOH (9:1, v/v). Yield: 701 mg (86.9%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.05 (1H, br d, J=7 Hz, NH), 7.79 (2H, d, J=7 Hz, H2, H6 benzoyl), 7.53 (1H, t, J=7 Hz, H4 benzoyl), 7.45 (2H, t, J=7 Hz, H3, H5 benzoyl), 7.21 (1H, d, J=8 Hz, H6 2,4-dimethoxybenzyl), 6.55 (1H, d, J=2 Hz, H3 2,4-dimethoxybenzyl), 6.49 (1H, dd, J=8 Hz, J'=2 Hz, H5 2,4-dimethoxybenzyl), 5.36 (1H, q, J=6 Hz, N′H), 3.89 (2H, d, J=6 Hz, CH_2 2,4-dimethoxybenzyl), 3.80 (3H, s, Me), 3.76 (3H, s, Me); HRMS *m/z* calcd for $C_{16}H_{18}N_2O_3$: 287.1390 $(M+H)^+$, found: 287.1401.

5.12.3. *N′*-Benzoyl-*N*-(2,4-dimethoxybenzyl) benzohydrazide (18). To **17** (117 mg, 0.41 mmol) dissolved in CH_2Cl_2 (5 mL) were added benzoic anhydride (**5a**) (276 mg, 1.22 mmol) and *N*-methyl imidazole (120 μL). After three days at rt the reaction mixture was extracted successively twice with 20% aqueous HOAc, then twice with satd aqueous Na_2CO_3, and with brine. The organic phase was dried over Na_2SO_4, then absorbed onto a Celite®-plug followed by chromatography on silica with EtOAc–hexane (1:1, v/v). Yield: 113.3 mg (70.7%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.78 (1H, br s, NH), 7.55–7.56 (4H, H2, H6 benzoyl, one conformer), 7.45–7.53, 7.33–7.45 (overlapping signals of various conformers, benzoyl), 7.25 (1H, d, J=7.3 Hz, H6 2,4-dimethoxybenzyl), 6.57 (1H, d, J=2 Hz, H3 2,4-dimethoxybenzyl), 6.54 (1H, J=8 Hz, J'=2 Hz, H5 2,4-dimethoxybenzyl), 5.26, 4.33 (2H, 2d, J=14 Hz, AB-system, br, CH_2 2,4-dimethoxybenzyl), 3.76 (3H, s, Me), 3.67 (3H, s, Me); ^{13}C NMR obtained by indirect detection (gradient HSQC and gradient HMBC spectra see Supplementary data) δ 171.9, 165.8, 160.3, 158.5, 131.9, 131.8, 131.3, 129.8, 128.3, 127.6, 127.3, 127.2, 104.4, 98.3, 55.5, 55.3, 44.9. HRMS *m/z* calcd for $C_{23}H_{22}N_2O_4$: 391.1651 $(M+H)^+$, found: 391.1652.

5.13. Oxadiazole formation in solution from 18 (Scheme 9)

Compound **18** (90 mg, 0.23 mmol) was treated with TFAA–CH_2Cl_2–TFA (20:75:5, v/v/v) 10 mL for 3 h at rt. An aliquot of 100 μL was taken, evaporated to dryness, and taken up in DMSO. The white solid was filtered off and the filtrate injected into the HPLC/MS system. All major peaks were compared with authentic samples by UV, MS, retention time, and co-injection.

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Supplementary data

Printout of MO calculations, gradient HSQC and gradient HMBS spectra of compound **18**; HPLC traces of oxadiazole formation on solid phase and with solution phase model **18**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.08.016.

References and notes

1. For instance, recent publications: (a) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 816–819; (b) Quadrelli, P.; Scrocchi, R.; Piccanello, A.; Pierluigi, C. *J. Comb. Chem.* **2005**, *7*, 887–892; (c) Lin, X.; Cui, S.; Wang, Y. Faming Zhuanli Shenqing Gongkai Shuomingshu 2003, 10 pp; CODEN: CNXXEV CN 1445219 A 20031001 Patent written in Chinese. Application: CN 2003-116520 20030417; (d) Severinsen, R.; Kilburn, J. P.; Lau, J. F. *Tetrahedron* **2005**, *61*, 5565–5575; (e) Hennies, H.-H.; Sundermann, C.; Buschmann, H.; Sundermann, B. PCT Int. Appl. 2004, 49 pp; CODEN: PIXXD2 WO 2004024725; (f) Zou, X.-J.; Lai, L.-H.; Jin, Gui-Y.; Zhang, Z.-X. *J. Agric. Food Chem.* **2002**, *50*, 3757–3760.
2. (a) Sauer, W. H. B.; Schwarz, M. K. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987–1003; (b) Polanski, J.; Jarzembek, Krystyna; Lysiak, V. *Acta Pol. Pharm.* **2000**, *57*, 80–81.
3. Recent syntheses of 1,3,4-oxadiazoles from 2-acyl hydrazides: (a) Kosmrli, J.; Kocevar, M.; Polanc, S. *Synlett* **1996**, 652–654; (b) Park, Y.-D.; Kim, J.-J.; Chung, H.-A.; Kweon, D.-H.; Cho, S.-D.; Lee, S.-G.; Yoon, Y.-J. *Synthesis* **2003**, 560–564; (c) Huang, W.; Hou, X.; Li, C.; He, B. *Lizi Jiaohuan Yu Xifu* **1998**, *14*, 171–174.
4. Brown, B. J.; Clemens, I. R.; Neesom, J. K. *Synlett* **2000**, 131–133.
5. (a) Kilburn, J. P.; Lau, J.; Jones, C. F. *Tetrahedron Lett.* **2001**, *43*, 2583–2586; (b) Pauvannan, K.; Hale, R.; Sedehi, D.; Chen, T. *Tetrahedron* **2001**, *57*, 9677–9682.
6. (a) Young, J. A.; Durrell, W. S.; Dresdner, R. D. *J. Am. Chem. Soc.* **1962**, *84*, 2105–2109; (b) Earlier reports on analogous solid phase Robinson–Gabriel synthesis of oxazoles: Pulici, M.; Quartieri, F.; Felder, E. R. *J. Comb. Chem.* **2005**, *7*, 463–473; (c) TFAA-mediated Bischler–Napieralski synthesis of isoquinolines: Nagubandi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165–177.
7. Liley, M. J.; Johnson, T.; Gibson, S. E. *J. Org. Chem.* **2006**, *71*, 1322–1329.
8. (a) Kikugawa, Y.; Kawase, M. *Synth. Commun.* **1979**, *9*, 49–52. The mildness of this reducing agent allows it to be used even with proteins; (b) Wong, W. S. D.; Osuga, D. T.; Feeney, R. E. *Anal. Biochem.* **1984**, *139*, 58–67; Analogous complexes have been reported to give reductions with hydrazides:

(c) Miyamura, T.; Egashira, T.; Sano, M.; Bendiak, B. K.; Kato, I. PCT Int. Appl. 2002, 42 pp; CODEN: PIXXD2 WO 2002012254 A1 20020214; Application: WO 2001-JP6524 20010730. Priority: JP 2000-234508 20000802. CAN 136:184050 AN 2002:123019; (d) Perdicchila, D.; Licandro, E.; Maiorana, S.; Baldoli, C.; Giannini, C. *Tetrahedron* **2003**, *59*, 7733–7742.

9. (a) Bouget, K.; Aubin, S.; Delcros, J.-G.; Arlot-Bonnemains, Y.; Baudy-Floc'h, M. *Bioorg. Med. Chem.* **2003**, 4881–4889; (b) Dugave, C.; Demange, L. *Lett. Pept. Sci.* **2003**, *10*, 1–9; (c) Hidaka, K.; Kimura, T.; Hayashi, Y.; McDaniel, K. F.; Dekhtyar, T.; Colletti, L.; Kiso, Y. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 93–96; Guide-Jampel, E.; Chalecki, Z.; Bassir, M.; Gelo-Pujic, M. *Tetrahedron* **1996**, *52*, 4397–4402.
10. Eglington, G.; Jones, R. H.; Shaw, B. L.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1860–1865.
11. Zhao, H.; Burke, T. R. *Tetrahedron* **1997**, *53*, 4219–4230.
12. Oxadiazolinium-intermediates like proposed **12a–q** have been reported earlier, for instance: Molina, P.; Tarraga, A.; Espinoas, A. *Synthesis* **1988**, 690–693.
13. A similar transacylation followed by oxadiazole formation was described by: Hassan, M. A.; Mohamad, M. M.; Shiba, S. A.; Abou-El-Regal, M. K.; Ali, A. K. *J. Saudi Chem. Soc.* **2003**, *3*, 389–396.
14. (a) Hiller, W. *Z. Kristallogr.* **1996**, *211*, 747–749; (b) Rodiou, D. C.; Kokkou, S. C.; Rentzeperis, P. J. *Acta Crystallogr., Sect. B* **1981**, *37*, 989–991; (c) Raj, S. S. S.; Yamin, B. M.; Boshaala, A. M. A.; Tarafder, M. T. H.; Crouse, K. A.; Fun, H.-K. *Acta Crystallogr., Sect. C* **2000**, *56*, 1011–1012.
15. Reynolds, C.; Hormann, R. E. *J. Am. Chem. Soc.* **1996**, *118*, 9395–9401 and references therein.
16. (a) Samdal, S.; Mollendal, H. *J. Phys. Chem. A.* **2003**, *107*, 8845–8850; (b) Chakravorty, S.; Reynolds, C. H. *J. Mol. Graphics Modell.* **1999**, *17*, 315–324.
17. Wang, Z. Y. U.S. Pat. Appl. Publ. 2003; 15 pp; CODEN: USXXCO US 2003010963 A1 20030116 CAN 138:114780 AN 2003:42708.
18. Colombo, M.; Riccardi-Sirtori, F.; Rizzo, V. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 511–517.
19. Grekov, A. P.; Shvaika, O. P. *Zh. Obshch. Khim.* **1960**, *30*, 3802–3806.

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Structure, intramolecular flexibility, and complexation of aza crown ethers to anions $H_2PO_4^-$ and HSO_4^- in nonprotic solvents

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Abstract—Both the structure and intramolecular flexibility of a series of aza crown ethers were studied by experimental NMR and theoretical molecular modeling. The stoichiometries of complexation to the anions $H_2PO_4^-$ and HSO_4^- and resulting complex stabilities were determined by experimental NMR (^1H, ^{31}P) titration and, in addition, the structure and mobility changes of the aza crown ethers upon complexation were also examined.

1. Introduction

The use of aza crowns for anion complexation is a long standing classic of supramolecular chemistry, starting with the early papers of Hosseini and Lehn.[1] A number of reviews of this research have been published.[2] Aza crown ethers due to their nitrogen lone pairs and N–H moieties are potentially able to complex both cations and anions, dependent on the pH value of aqueous solution. This kind of research is still popular because of the continuing search for useful sensor systems.

Just recently two papers were published studying not only the ability of this kind of compounds for their complexation to Cu^{2+}, Hg^{2+}, and Ni^{2+},[3] but also dealing, at the same time, with the ability of certain aza crowns to coordinate to certain anions in aqueous solution.[4] Although a number of X-ray structures of the complexes have been reported,[5] only limited information is available on the conformation of both aza crown ether hosts and their complexes in solution: Novak and Potts[6] have determined by photoelectron spectroscopy the cavity width of 12-tetraaza crown-4 ether (**1**) and 14-tetraaza crown-4 ether (**4**); Ranganathan et al.[7] detailed the vicinal H,H couplings of 12-tetraaza crown-4 ether (**1**) with respect to the preferred conformation of the compound and found that *synclinal* N–C–C–N fragments were well preorganized for complexation. At the same time, Bultinck et al.[8] ab initio MO calculated at the HF level the latter compound and confirmed the *synclinal* N–C–C–N conformations and, in addition, determined that hydrogen bonding plays only a minor role in stabilizing the ground state geometry of 14-tetraaza crown-4 ether (**4**) and its analogs in solution. Rather than hydrogen bonding, it is the electrostatic repulsions of the N-lone pairs that are determinate for the global minima states.

In addition to the aforementioned tetraaza crown ethers, we have synthesized a series of analogs (Scheme 1) and studied both experimentally by NMR and theoretically by molecular modeling with respect to their preferred conformers. The flexibility of both the free entities and when complexed to the anions $H_2PO_4^-$ and HSO_4^- was also evaluated as was the stoichiometry and stability of the complexes.

2. Results and discussion

2.1. NMR spectra

The ^1H and ^{13}C NMR spectra of the compounds were consistent with the structures presented in Scheme 1 and the nuclei absorb in the ranges expected (see Tables 1 and 2). From both ^1H and ^{13}C NMR spectra, due to the number of observed lines, it can be concluded that the compounds are symmetric on the NMR timescale although lines in both spectra were somewhat broadened and thus restricted interconversion of the macrocyclic rings or some other slow process in the compounds is inferred.

2.2. Complexation study

In order to test the complexational behavior of the di-, tri-, and tetraaza crown ethers **1**–**10** to anions, NMR titration experiments with the salts $H_2PO_4^-{}^+N(n\text{-Bu})_4$ and $HSO_4^-{}^+N(n\text{-Bu})_4$ were performed in $CDCl_3$. Both the ^1H

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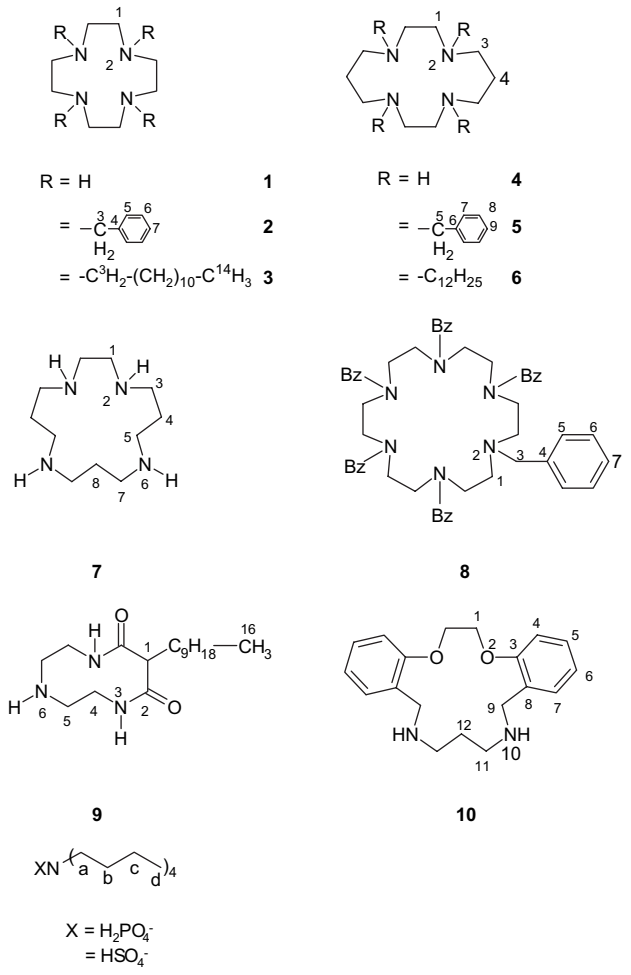

Scheme 1. Compounds studied.

and ^{13}C chemical shifts of the various nuclei were followed with increasing addition of the anions and, in case of the phosphate titration, the ^{31}P NMR was also recorded.[9] With increasing amounts of anion, both the ^{1}H and ^{13}C chemical shifts of the macrocyclic ring atoms as well as those of the R substituents were shifted, and thus complexation was evident. The same conclusion was drawn from the behavior of the ^{31}P chemical shifts in the case of phosphate anion. The stoichiometry of the complexes was determined from Job's plots,[10] e.g., Figure 1 illustrates the titration of **9** with $H_2PO_4^-{}^+N(n\text{-}Bu)_4$ following the ^{1}H chemical shift changes of several protons as well as of the ^{31}P signal of the added salt.

With respect to the stoichiometry of the complexes, the following results were obtained: (i) complexes between dioxa,diaza crown ether **10** and $H_2PO_4^-$ and between hexaaza crown ether **8** and HSO_4^- do not form at all, (ii) the unsubstituted tetraaza crown ethers **1** and **4** form 1:2 complexes with phosphate, due to dimerization of $H_2PO_4^-$ by hydrogen bonding in the less polar solvent $CDCl_3$,[11] (iii) 1:1 complexation occurs in the case of **2**, **3**, and **5**–**9** with $H_2PO_4^-$, and (iv) all of the crown ethers studied, except for **8**, form 1:1 complexes with HSO_4^-. The stability constants of the complexes are presented in Table 3 and lie in the range 1.21–4.91 for log *K*. Similar values were obtained by Martell et al.[12] for the coordination of $H_2PO_4^-$ with dioxa,hexaaza macrocycles in aqueous solution. The lowest complexation for $H_2PO_4^-$ and HSO_4^- was obtained for **3**; obviously, due to the long fatty acid tails the macrocyclic ring system is sterically hindered and thus limits anion complexation. The *N*-unsubstituted tetraaza crown ethers **1**, **4**, and **7** are the most useful for complexing the selected anions as complexation constants of log $K>3$ were obtained. If complexation of the aza crown ethers is compared with respect to both their ring size and substitution, the following orders are obtained: with respect to ring size, **1**>**4** and **2**>**5**; and with respect to substitution, R=H>R=benzyl>R=alkyl. The lowest tendency for complexation was observed for **3** and **6** due to the previously mentioned steric hindrance; the less flexible benzyl substituents in **2** and **5**, however, allow easier approach of the anions to the host cavity for successful complexation.

2.3. Structural information from ^{1}H and ^{13}C NMR spectra

Structural information was limited due to fast ring interconversion at ambient temperature and, further, the symmetry of the aza crown ethers.

2.3.1. *J* information. The weighted averages of the participating *synclinal*, *anticlinal* and *antiperiplanar* conformations change with increasing steric hindrance (cf. Table 4) and thus changes in the $^{3}J_{H,H}$ values, when measurable, imply variations in the dihedral angles N–C–C–C. For **4** (an unsubstituted aza crown), the optimal conformer is *synclinal*, but in **5**, and even more so in **6**, this dihedral angle changes evermore to the *anticlinal* conformation due to the steric hindrance of the R substituents. Similar $^{3}J_{H,H}$ values were obtained for both the free and the complexed crown ethers, and so obviously complexation does not very much change the conformational equilibria of the host compounds (as far as it could be concluded from weighted averages in $^{3}J_{H,H}$)—thus, **4** and **7** seem to be already in free state well organized for complexation.

2.3.2. Spatial information. Only limited NOE spatial information was obtained for **2**, **5**, and **8** (NOE contacts were not observed in the NOESY/ROESY spectra obtained for **1**, **3**, **4**, **6**, **7**, and **9**). NOEs between the NCH_2 and *ortho* phenyl protons were observed, however, this is without structural implication. The situation improves slightly in **10** where NOEs between H-1···H-4, H-7···H-9, and H-9···H-11 were observed and thus some dihedral angles can be excluded: NOE (H-1···H-4) indicates the *antiperiplanar* or *anticlinal* conformation of C_1–O_2–C_3–C_7; NOE (H-7···H-9) is representative for *synclinal* or *anticlinal* conformation of C_7–C_8–C_9–N_{10} (*synperiplanar* arrangement precludes NOEs and the *antiperiplanar* conformer is sterically prevented); and NOE (H-9···H-11) provides an indication of the geometry of the C_8–C_9–N_{10}–C_{11} and O_2–C_1–$C_{1'}$–$O_{2'}$ systems. Only if the C–C–N–C moiety is in a *synclinal* arrangement the two protons H-9 and H-11 can remain within a measurable NOE distance for each orientation of the other C–C–N–C dihedral angle. Finally, O_2–C_1–$C_{1'}$–$O_{2'}$ must be in a *synclinal* or *anticlinal* orientation as an *antiperiplanar* orientation would bring H-1 near to H-2, an NOE contact, which was not detected.

Of note, intermolecular NOEs were also measured between host protons and those of the $^{+}N(n\text{-}Bu)_4$ ammonium cation.

Table 1. ^{1}H NMR chemical shifts (δ/ppm) of the aza crown ethers **1–10** and differential values upon complexation to $H_2PO_4^-$ and HSO_4^- anions

Compound	H-1	N(2)H	H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	H-12	H-13	H-14	H-15	H-16
1	2.65	2.56		—	—	—	—	—	—	—	—	—	—	—	—	—
1···$H_2PO_4^-$	−0.13															
1···HSO_4^-	+0.03															
2	2.68		3.43		7.36	7.25	7.19									
2···$H_2PO_4^-$	−0.02		−0.01		−0.01	−0.01	+0.01									
2···HSO_4^-	+0.06		+0.03		+0.03	+0.07	+0.12									
3	3.51		2.30	1.64	1.27									0.89		
3···$H_2PO_4^-$	−0.06		−0.02	−0.01	−0.02									−0.01		
3···HSO_4^-	−0.12		+0.08	+0.07	+0.09									+0.09		
4	2.66	3.35	2.73	1.7												
4···$H_2PO_4^-$	−0.16		−0.06	−0.04												
4···HSO_4^-	−0.39	−0.45	+0.01	+0.02												
5	2.59		2.49	1.73	3.42		7.29	7.24	7.18							
5···$H_2PO_4^-$	−0.06		−0.04	−0.15	−0.05		−0.09	−0.07	−0.07							
5···HSO_4^-	+0.03		+0.03	+0.02	+0.03		+0.07	+0.02	±0							
6	2.65		2.88	1.40	2.32	1.26										0.88
6···$H_2PO_4^-$	−0.02		+0.04	+0.05	+0.01	−0.03										−0.03
6···HSO_4^-	±0		+0.05	+0.08	+0.04	±0										+0.11
7	2.67	2.97	2.71	1.67	2.71	2.97	2.71	1.70								
7···$H_2PO_4^-$	−0.12		−0.06	−0.02	−0.06		−0.06	−0.05								
7···HSO_4^-	+0.16		+0.12	+0.15	+0.12		+0.12	+0.12								
8	3.13		3.42		7.06	7.34	7.41									
8···$H_2PO_4^-$	−0.05		+0.19		−0.05	−0.14	−0.03									
8···HSO_4^-	[a]															
9	4.19		1.83	3.32	2.76	1.83	1.83	1.24								0.87
9···$H_2PO_4^-$	−0.44		−0.08	+0.27	+0.13	−0.08	−0.08	+0.01								−0.01
9···HSO_4^-	−0.49		−0.07	+0.23	+0.34	−0.07	−0.07	−0.02								±0
10	4.39			6.92	6.89	7.29	7.20		3.75	1.91	2.64	1.75				
10···$H_2PO_4^-$	[a]															
10···HSO_4^-	−0.04			+0.30	+0.32	+0.01	+0.08		+0.17		+0.09	−0.11				

[a] No coordination observed.

Obviously, not only the anion, but also the cation (as a salt pair) forms part of the complexes. Similar suggestions have been made by Valiyaveettil et al.[11] when studying the phosphate complexation of open-chain polyaza ethylene compounds. Actually, evidence for the existence of such complete complexes was implied by ESIMS measurements.[13]

2.4. Flexibility information from T_1 measurements

Spin–lattice relaxation times T_1 of certain aza crown ether protons were measured in order to confirm the interaction of the aza crown ethers with the two different anions (cf. Table 5). As expected, with increasing amounts of the two different anions in solution, the T_1s were reduced in value. This is due to complexation in reducing the intramolecular flexibility of the aza crown ethers.[14]

The T_1s of the NCH_2 protons of the ammonium cations were also measured (see Table 6), and these values proved to be very interesting since the cations are not directly involved in aza crown ether···anion complexation. In the case of the *N*-unsubstituted tetraaza crowns **1**, **4**, and **7**, the T_1s increased in value leading to the conclusion that as the anion complexes with the aza crown ethers, ammonium cations are less strongly bound to the anion (as ion pairs) and their flexibility therefore increases. In the remaining aza crowns **2**, **3**, **5**, **6**, and **8–10**, complexation to the anion was only minor or non-existent, therefore no effect on the T_1 values of the ammonium cation protons was expected and they should remain constant. However, they were observed to decrease in value and the only conclusion from this result is that obviously the long fatty acid chains attached to the aza crown ethers and the *n*-butyl chains of the ammonium cation become arranged along each other due to hydrophobic interactions and thereby the flexibility of the ammonium cation is reduced and subsequently the T_1 values decrease as well.

2.5. Variable temperature ^{1}H and ^{13}C NMR spectroscopy

Since some signals of the aza crown ethers in both the ^{1}H and ^{13}C NMR spectra were already broadened at ambient temperature, deconvolution was thus expected at lower temperatures and the aza crown solutions, both free as well as complexed to phosphate and sulfate, were examined accordingly. However, only in case of **10** this was successful. This dioxa,diaza crown ether contains some rigid units, which reduce the flexibility of the macrocyclic 15-membered ring system (vide supra) and from following the line width of H-1 and H-9, the free energy of interconversion of the 15-membered ring could be calculated to be 9.2–9.3 kcal/mol, in excellent agreement with values obtained for similar crown ethers.[15]

The ring interconversion of the remaining aza crown ethers **1–9** could not be frozen within the temperature range of the present NMR equipment when observing ^{1}H NMR spectra.

Table 2. ^{13}C NMR chemical shifts (δ/ppm) of the aza crown ethers **1–10** and differential values upon complexation to $H_2PO_4^-$ and HSO_4^- anions

Compound	C-1	N-2/C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16
1	46.5															
1···$H_2PO_4^-$	−0.9															
1···HSO_4^-	+0.5															
2	53.0		60.1	140.1	128.9	128.0	126.6									
2···$H_2PO_4^-$	−0.4		−0.5	+0.6	−0.1	−0.1	−0.1									
2···HSO_4^-	+0.3		+0.6	−11.0	+1.3	+2.2	+2.2									
3	49.9		31.9	29.6	25.3	22.7[a]								14.1		
3···$H_2PO_4^-$	−0.6		±0	+0.1	−0.1	±0										
3···HSO_4^-	−0.2		+0.1	+0.2	±0	±0										
4	50.8		49.3	29.3												
4···$H_2PO_4^-$	−1.6		+1.3	±0												
4···HSO_4^-	−1.5		+1.4	+1.4												
5	50.8		51.9	24.4	59.6	140.6	129.8	128.6	127.6							
5···$H_2PO_4^-$	−0.4		−0.5	−0.3	−0.2	−0.6	−0.9	−0.6	−1.0							
5···HSO_4^-	+0.5		+0.5	+0.2	+0.7	+0.3	+0.1	+1.0	+0.1							
6	62.0		56.2	31.9	32.2	14.1	29.6	28.0	23.4[a]							
6···$H_2PO_4^-$	−0.6		+2.3	+1.6	−0.4	−0.1	+1.2	−0.8	±0							
6···HSO_4^-	−2.2		−1.8	+0.2	−0.3	±0	+1.4	−0.7	±0							
7	49.5		49.8	28.8	50.4		51.3	29.2								
7···$H_2PO_4^-$	−0.5		−0.8	±0	−0.6		−1.2	+0.1								
7···HSO_4^-	+1.8		+0.4	+2.1	+0.2		±0	+0.9								
8	48.5		59.5	139.1	129.8	128.5	132.8									
8···$H_2PO_4^-$	−0.2		−1.9	−0.4	−0.7	−1.2	−2.5									
8···HSO_4^-	[b]															
9	61.5	171.1		39.2	47.8		29.6, 14.1	29.3	22.7[a]							
9···$H_2PO_4^-$	−2.4	−0.7					+0.1	+0.1	±0	±0						
9···HSO_4^-	−1.7	−0.6					+0.1	+1.4	+0.8	+0.1						
10	65.7		158.2	110.1	120.6	128.5	131.2	158.2	51.6		47.8	29.0				
10···$H_2PO_4^-$	[b]															
10···HSO_4^-	−0.2		+0.8	+0.1	±0	+0.8	+0.9	+0.8	+1.6		+0.8	−3.5				

[a] Not further assigned.
[b] No coordination observed.

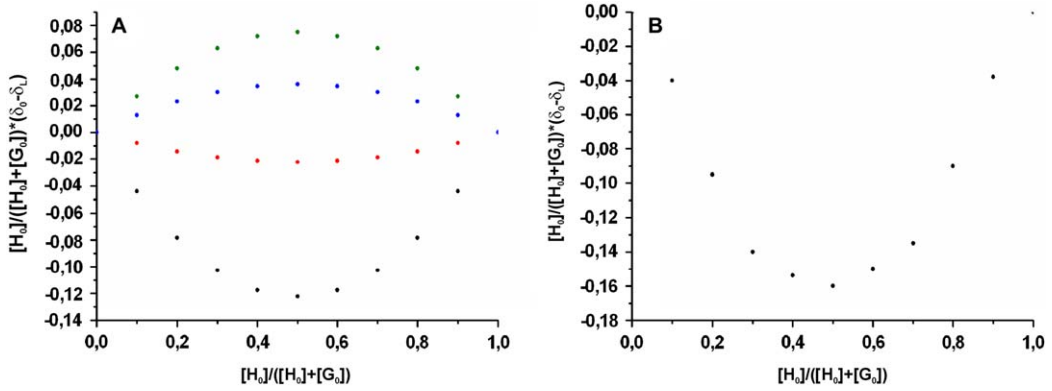

Figure 1. Job plots of the titration of **9** with $H_2PO_4^-$: (A) ^1H NMR and (B) ^{31}P NMR chemical shift variations; from the plot of the two parameters the anion-to-ligand ratio of the complexes was inferred by the value of the *x*-coordinate at the plot azimuth.

Table 3. Stability constants and stoichiometry of the complexes of **1–10** (log *K*) with $H_2PO_4^-$ and HSO_4^- anions

Complex	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
With $H_2PO_4^-$	4.67	2.52	1.68	3.40	2.18	2.08	3.30	2.19	4.91	[a]
	1:2	1:1	1:1	1:2	1:1	1:1	1:1	1:1	1:1	—
With HSO_4^-	3.53	2.31	1.21	3.23	2.55	2.17	3.89	[a]	4.40	2.83
	1:1	1:1	1:1	1:1	1:1	1:1	1:1	—	1:1	1:1

[a] No coordination observed.

Table 4. $^3J_{H,H}$ coupling constants (Hz) in free aza crown ethers **4–7** and **10** and in their complexes with $H_2PO_4^-$ and HSO_4^- anions

Compound	Free	With $H_2PO_4^-$	With HSO_4^-
4	5.5	5.0	5.5
5	7.0	7.0	7.0
6	8.5	8.5	8.0
7	5.0	5.0	5.0
10	5.5	[a]	5.5

[a] No coordination observed.

Table 5. Spin–lattice relaxation times T_1 (s) of the H-1 protons in aza crown ethers **1–10** and differential values in their complexes with $H_2PO_4^-$ and HSO_4^- anions

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Free crown	1.1	0.4	0.35	1.0	0.4	0.3	0.9	0.4	0.6	0.7
$+H_2PO_4^-$	−0.2	−0.05	−0.1	−0.1	−0.1	−0.05	−0.05	−0.05	−0.1	[a]
$+HSO_4^-$	−0.1	−0.05	−0.05	−0.1	−0.1	−0.05	−0.1	[a]	−0.1	−0.1

[a] No coordination observed.

Table 6. Spin–lattice relaxation times T_1 (s) of the NCH_2 protons of the ammonium cations and differential values upon complexation to aza crown ethers **1–10**

Compound	Free	Complexed									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
TBAHP[a]	0.2	+0.15	−0.1	−0.1	+0.1	−0.05	−0.05	+0.1	−0.15	−0.1	[b]
TBAHS[c]	0.25	+0.1	−0.1	−0.05	+0.05	−0.1	−0.05	+0.05	[b]	−0.1	−0.15

[a] Tetra-*n*-butyl ammonium hydrogen phosphate.
[b] No coordination observed.
[c] Tetra-*n*-butyl ammonium sulfate.

The signals broadened and split into overlapping, very wide absorptions on going down to 190 K but, due to these difficulties, barriers to ring interconversions could not be determined. For example, in Figure 2 the temperature dependence of the ^{1}H NMR spectrum of **2** is depicted.

Since the signal disparities in the corresponding ^{13}C spectra after deconvolution are generally larger than in the ^{1}H spectra and thus coalescence temperatures are usually higher,[14] the temperature dependence of the ^{13}C NMR signals was also examined, but again without success (cf. also Fig. 2). Even at 170 K the resonances did not decoalescence and only became more broadened. Thus, the line broadening as obtained must be, at least partly, assigned to the obviously complicated T_2 relaxational behavior of the aza crowns studied.[15b] The same result was obtained for the corresponding complexes and thus supports the aforementioned conclusion. The inherent broad width of the ^{1}H NMR signal lines also precluded the extraction of precise J information for conformational analysis and thus the accompanying molecular modeling study was necessary in order to overcome the deficiencies regarding the adopted conformations.

2.6. Molecular modeling of aza crown ethers 1–10 and their complexes

In order to assess the conformational behavior of **1–10**, the steric hindrance of the coordinating anions and the mechanism of complexation of the aza crown ethers and their anion complexes were also studied theoretically in detail.

The modeling study was started by random search calculations to estimate the conformational equilibria in solution. For each crown ether, 10^5 cycles were calculated and up to

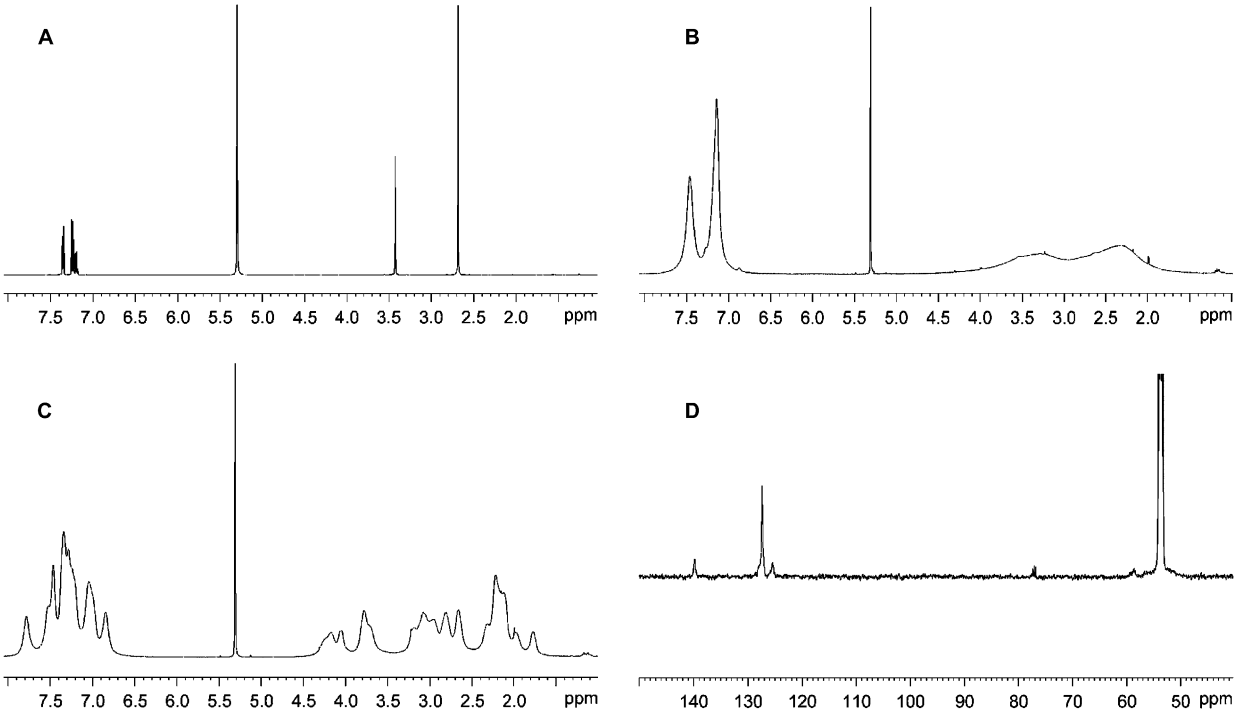

Figure 2. Temperature dependence of the NMR spectra of aza crown ether **2**: (A) ^{1}H at 298 K, (B) ^{1}H at 190 K, (C) ^{1}H at 170 K, and (D) ^{13}C at 170 K.

three torsional angles in the macrocyclic ring were varied *per* cycle and the obtained geometries were optimized by force field calculations. Conformations within 3 kcal/mol of the global minimum structure were stored in a data bank. However, in order to save CPU time the following simplifications were introduced: *N*-alkyl chains were substituted by *N*-methyl and the effect of the fatty acid tails was studied later by molecular dynamic simulations (vide infra); benzyl substituents were substituted by hydrogen but their effect later considered by grid search calculations and thus correct conformations of the benzyl substituted aza crowns could be obtained (vide infra).

The conformers obtained by the random search calculations were then continuum solvent geometry optimized by the PM3 method. Aza crown ethers **1** and **4** have already been ab initio MO studied by Bultinck et al.[8] and they were included into the present study in order to estimate the quality of the present semiempirical calculations.

As a result of this theoretical study, a large number of conformations were obtained within a relatively narrow energy window of 3 kcal/mol, though only the global minima structures of the various crowns were continuum solvent geometry optimized and collected in Table 7. Even if there is a number of different conformations for each aza crown ether studied, some really informative trends with respect to their ground state structures and complexational behavior can be construed:

(i) If the aza crown ethers are *N*-unsubstituted (**1**, **4**, **7**, and **9**), the macrocyclic ring with respect to the N–C–C–N dihedral angle is *synclinal* in orientation. This result is in complete agreement with both the theoretical studies of Wolf et al.[16] and Bultinck et al.[8]

(ii) If the aza crown ethers are *N*-substituted with the strong sterically hindering fatty acid tails or benzyl substituents, the corresponding N–C–C–N dihedral angles change from *synclinal* orientations to *antiperiplanar* and are seldom in *synclinal* or *anticlinal* orientations.

(iii) Adjacent C–N–C–C dihedral angles remain in a *synclinal* orientation, in good agreement with the NOE study of crown ether **10**.

(iv) The N–C–C–C torsional angles are in *synclinal* conformations, in agreement with experimental information (cf. **4** and **7**). The same *N*-substituent steric effect, as mentioned previously, is observed: N–C–C–C torsional angles change then to *antiperiplanar* conformations.

(v) Due to experimental data in the case of **10** ($^3J_{H_{11},H_{12}}$=5.5 Hz, no NOE between H-1 and H-11), the global minimum is validated: both the N–C–C–C and O–C–C–O torsion angles are *synclinal*, though *anticlinal* but not *antiperiplanar* conformations are also possible. In good agreement with the experiment results are the *anticlinal* C=C–C–N and C–O–C=C *antiperiplanar* conformations. The global minimum structure of dioxa,diaza crown ether **10** is presented in Figure 3.

2.7. Steric *N*-substituent effect on the conformation of the macrocyclic ring

Within this context, firstly, grid search calculations of the benzyl substituted aza crown ethers were processed. All

Table 7. Dihedral angles of the global minima structures of the aza crown ethers **1–10** as obtained by PM3 energy optimization

Compound	$NCCN^I$	CCN^IC	CN^ICC	N^ICCN^{II}	$CCN^{II}C$	$CN^{II}CC$	$N^{II}CCN^{III}$	$CCN^{III}C$	$CN^{III}CC$	$N^{III}CCN$	CCNC	CNCC
1	129	−79	142	−79	−85	73	68	−167	69	86	−83	−82
2	78	−97	−59	168	−69	−60	162	−57	−68	147	−155	64
3	165	−79	82	−152	62	69	−164	137	−88	120	−93	−60

Compound	NCCC	$CCCN^I$	CCN^IC^I	$CN^IC^IC^I$	$N^IC^IC^IN^{II}$	$C^IC^IN^{II}C^{II}$	$C^IN^{II}C^{II}C^{II}$	$N^{II}C^{II}C^{II}C^{II}$	$C^{II}C^{II}C^{II}N^{III}$	$C^{II}C^{II}N^{III}C^{III}$	$C^{II}N^{III}C^{III}C^{III}$	$N^{III}C^{III}C^{III}N$	$C^{III}C^{III}NC$	$C^{III}NCC$
4	−90	180	−137	55	66	−154	112	−168	83	91	−68	−77	172	−69
5	−179	−100	75	−160	76	68	−161	−170	−97	41	−95	−170	−80	−73
6	−159	−177	−67	84	−170	73	59	−177	148	−65	159	−110	−56	93
7	81	76	172	176	−80	79	63	−167	180	−78	−67	177	−69	−87

Compound		$NCCN^I$	CCN^IC	CN^ICC	N^ICCN^{II}	$CCN^{II}C$	$CN^{II}CC$	$N^{II}CCN^{III}$	$CCN^{III}C$	$CN^{III}CC$	$N^{III}CCN^{IV}$	$CCN^{IV}C$	$CN^{IV}CC$	$N^{IV}CCN^{V}$	$CCN^{V}C$	$CN^{V}CC$	$N^{V}CCN$	CCNC	CNCC
8	0.00	84	−86	168	−148	−63	179	−158	−57	139	−55	52	143	92	33	131	−159	−103	66
9	0.00	−147	60	48	−147	122	−62	99	−144	60	64	−123	74	159	−166	−85	84	−127	177

Compound		O^IC^ICO	C^ICCO	COCC	OCCC	CCCN	CCNC	CNCC	$NCCC^I$	CCC^IN^I	$CC^IN^IC^I$	$C^IN^IC^IC^I$	$N^IC^IC^IC^I$	$C^IC^IC^IO^I$	$C^IC^IO^IC^I$	$C^IC^IO^IC$
10	0.00	−59	−78	121	−8	103	−82	−53	−68	171	−71	115	118	1	168	−78

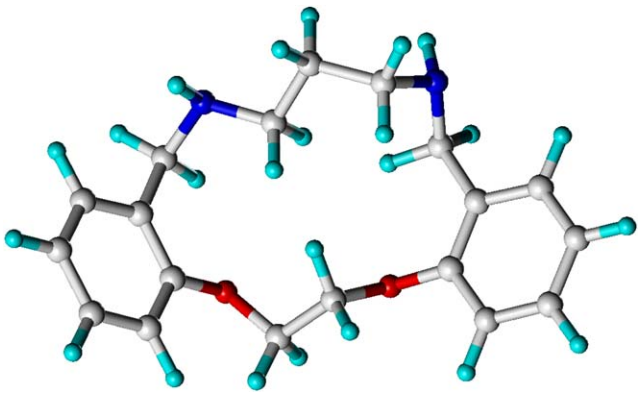

Figure 3. Global minimum structure of crown ether **10**.

the torsional angles C–N–C–C_{ar} and N–C–C_{ar}–C_{ar} were varied systematically in 30° steps and the structures thus obtained were energetically optimized. Comparing the resulting structures and their energies, it was clear that those conformations with *N*-benzyl substituents oriented exocyclically were the most stable ones. Thus, an *N*-benzyl substituent does not shield the aza crown cavity completely but allows the opportunity for anion complexation, and this is available from both sides of the macrocycle (cf. Fig. 4).

In order to consider the much more flexible fatty acid tails, molecular dynamic simulations were employed. For **3**, **6**, and **9**, the global minima structures from random search calculations were applied substituted with the corresponding *N*-alkyl chains (C-12 in the case of **3** and **6** but C-10 in the case of **9**). During 1 ns, the substituents were allowed to move freely at 300 K, the aza crown ether skeleton, however, was structurally fixed. The results are not surprising: the fatty acid tails sterically shield the macrocyclic ring cavity (cf. Fig. 5) to a great extent and thereby prevent the opportunity of the anions to approach for complexation. By contrast, the single $C_{10}H_{21}$ alkyl chains in aza crown ether **9** are unable to cover the whole macrocyclic ring cavity (cf. Fig. 6). They can partly cover one side of the cavity, but only one and thus from the opposite side the approach of the anion is possible and hence complexation with adequate complex stability results (vide supra).

2.8. Host–guest interaction in the $H_2PO_4^-$ and HSO_4^- complexes

Various models concerning the present host–guest interactions have been published. Lu et al.[17] consider the number and strength of potential hydrogen bondings as the fundamental criterion for successful complexation—complex stability increases if aza crown ethers are protonated.[15] Albelda et al.,[18] on the other hand, suggest that $H_2PO_4^-$ should be sufficiently acidic to protonate nitrogen atoms (the corresponding ^{15}N chemical shifts are strongly deshielded by complexation) and complex to the aza crown ethers via

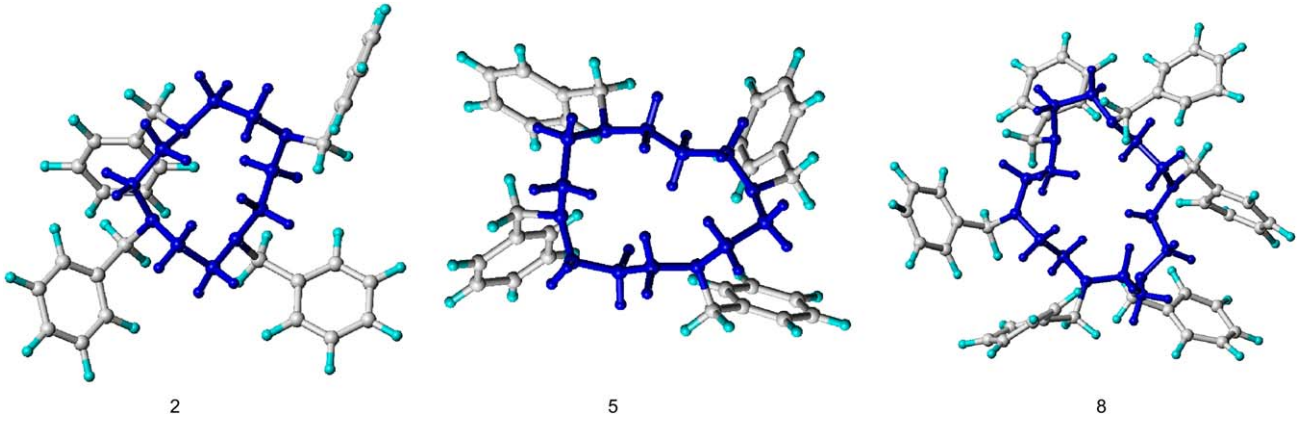

Figure 4. Preferred ground state conformations of aza crown ethers **2**, **5**, and **8**.

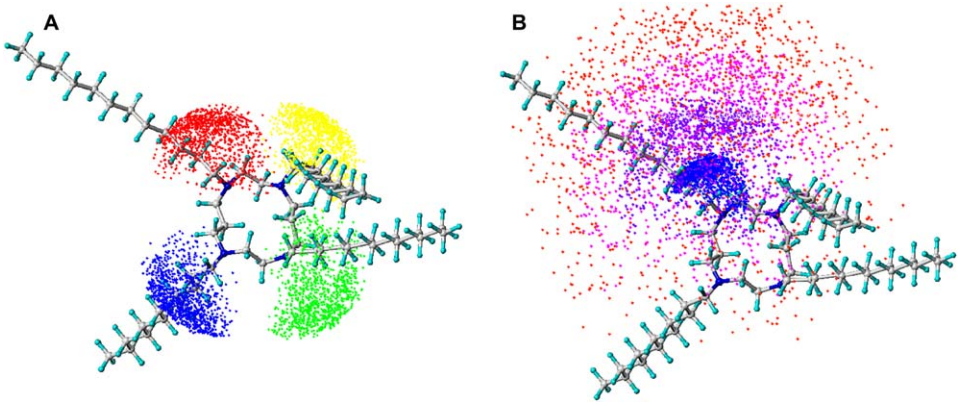

Figure 5. Spatial extension of fatty acid tails in crown ether **6**; possible positions of C-8 (A) and mobility of the alkyl chain (B).

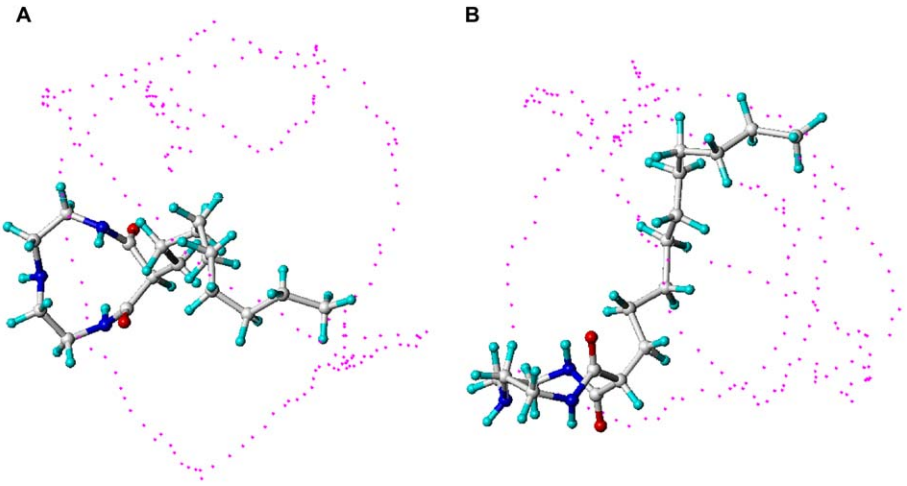

Figure 6. Mobility of the single alkyl chain of crown ether **9** illustrated from two different directions (A and B).

electrostatic interactions. And finally, Beer and Gale[19] consider that the charged anions can complex to the neutral aza crown ethers via dipole–ion interactions.

Firstly, hydrogen bonding was examined: the anions $H_2PO_4^-$ and HSO_4^- were positioned near to the cavity (P═O and S═O moieties, respectively, in the direction of the cavity) of the NH aza crown ethers **1**, **4**, **7**, **9**, and **10** and then PM3 geometry was optimized. The following trend was evident: P═O and NH of the aza crown ether form hydrogen bonds (cf. Fig. 7 for aza crown ether **1**) and the macrocyclic ring changes its conformation in order to enable as many of these hydrogen bonds as possible, at the same time, the anion occupies the most favorable position possible. However, the aza crown cavity cannot completely host the entire anion as has been observed for 20-membered rings[18] because of the smaller ring sizes in **1**–**10**. If the aza crown ethers studied are *N*-substituted (**2**, **3**, **5**, **6**, and **8**) then the former interaction (hydrogen bonding), however, is excluded.

In order to study possible N-protonation of the ligand by the anion, the relevant ligands were monoprotonated and a HPO_4^{2-} species was positioned near to the cavity and this geometry was then optimized. The result of this approach is obvious (cf. Fig. 8 for N-protonation of $\mathbf{3}H^+$—instead of the long alkyl chains only R=Me was considered): the NH proton left the crown ether moiety and transferred back to the oxygen of the anion, but at the same time the anion approached the aza crown macrocyclic ring system to complete the complexation. Certainly hydrogen bonding could not be identified in these cases as a major source of stabilization and therefore dipolar-ion interaction was deemed to be the major source.

As the other mode for complex formation, dipole–ion interactions were further considered. On the Connolly surface[20] of the aza crown ethers (generated by SYBYL)[21] surrounded by the solvent, the electrostatic potential[22] of the aza crown ethers was projected and the anion positioned near the positive charge region (cf. Fig. 9 for aza crown ether 2—instead of benzyl only R=Me was considered). Geometry optimization resulted in the following: N–C–C–N dihedral angles changed completely to *antiperiplanar* positions and the NCH_2 groups pointed to the inside of the macrocyclic ring system. Both P═O and S═O anion moieties also pointed to the same direction but the N-lone pairs are positioned away from the anion, obviously in order to minimize the repulsion of anion negative charges and N-lone pairs. In the case of this kind of conformation, already present in the starting structures, nothing changes during the energy minimization of the complexes. During the approach of the anion, the electron density of the phosphate/sulfate protons is shifted to other parts of the anion; the electrostatic potential of the aza crown near to the P═O/S═O bonds demonstrates the large positive range of the aza crown ethers in this respect (cf. the red area of Fig. 9).

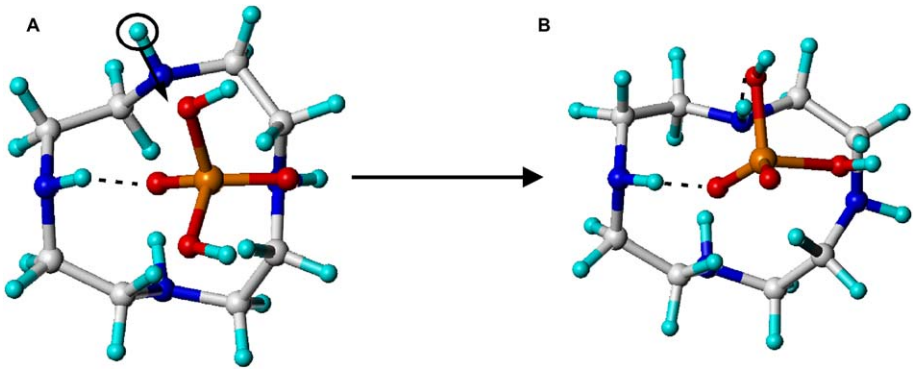

Figure 7. PM3 optimized geometry of the host–guest complex $\mathbf{1}\cdots H_2PO_4^-$ (A) before and (B) after optimization.

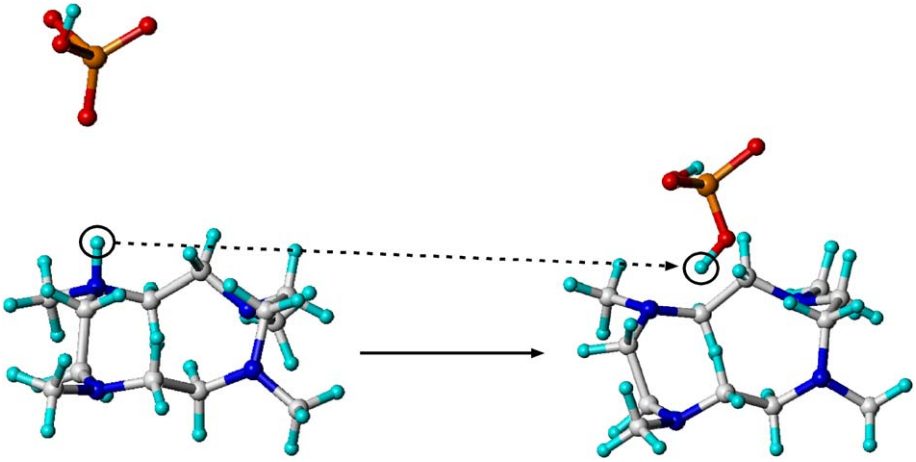

Figure 8. PM3 energy optimization of the $\mathbf{3}H^{+}\cdots HPO_4^{2-}$ complex—instead of the long alkyl chain only R=Me was considered.

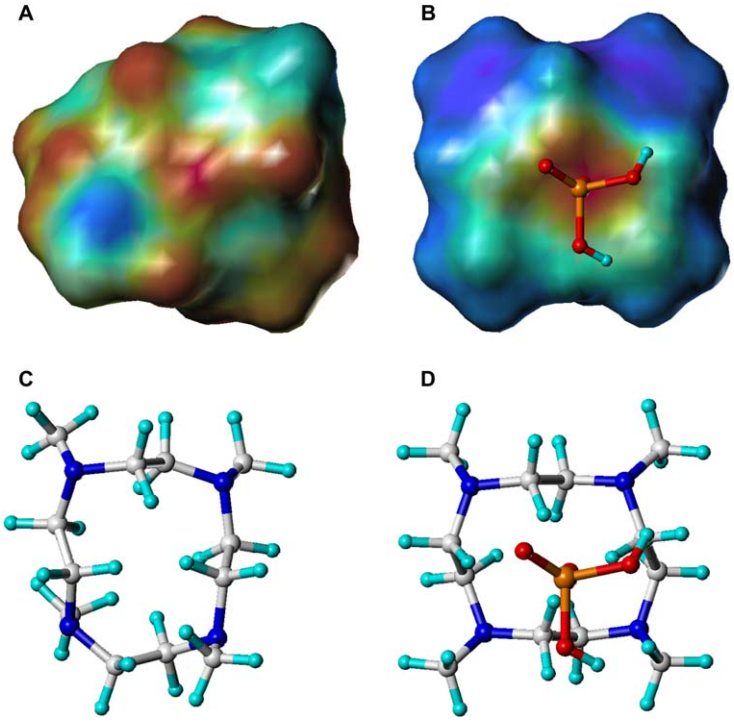

Figure 9. Electrostatic potential of **2** without (A) and with $H_2PO_4^-$ (B); in addition conformations of **2** without (C) and with $H_2PO_4^-$ (D) are given—instead of benzyl only R=Me was considered.

3. Conclusions

From the detailed NMR study of a series of aza crown ethers **1**–**10** both the stoichiometry and complex stability constants with the anions $H_2PO_4^-$ and HSO_4^- were obtained. The aza crown ethers generally form 1:1 complexes but the complex stability proved to be strongly dependent on the sterically hindering effect of the *N*-substituents if present. At the same time, the flexibility of **1**–**10** is reduced upon complexation.

Although structural *J* and spatial NOE information from NMR were very limited except in the case of **10**, the data were still able to be included as constraints in the accompanying molecular modeling study. As the major results of the modeling study it was determined that:

(i) *N*-Unsubstituted aza crown ethers prefer stable *endo* orientations of the donor atoms; if benzyl or alkyl substituents are present, due to their steric effects, donor atoms change *synclinal* to *antiperiplanar* orientations of N–C–C–N moieties.

(ii) *N*-Unsubstituted aza crown ethers form hydrogen bonds NH···O=S(O=P) to the corresponding anions; thereby, the geometry of the macrocyclic ring system changes in order to maximize the number and possibilities of this hydrogen bonding.

(iii) Complexation of aza crown ethers and anions in *N*-substituted compounds proceeds via dipole–ion interactions. Due to impossible H-bonding [cf. (ii)] and due to steric hindrance of complexation by the *N*-substituents, the stability constants of the corresponding complexes drop accordingly.

It has been proved by study that detailed structural information about crown ethers in solution can be obtained (both in free and complexed state) not only as an substantial alternative to X-ray studies in the solid state but also as the only information if no useful crystals could be obtained.

4. Experimental

4.1. Syntheses

The di-, tri-, and tetraaza crown ethers **1**–**9** and the mixed dioxa,diaza crown ether **10** were synthesized according to literature procedures collected in Ref. 23. The reaction products were purified by column chromatography and both the structure and purity of the compounds were determined by ^{1}H and ^{13}C NMR spectroscopy and accurate mass measurements by ESIMS. The salts $H_2PO_4^-{}^+N(n\text{-}Bu)_4$ and $HSO_4^-{}^+N(n\text{-}Bu)_4$ for the complexation studies were purchased from Aldrich and NMR solvents from Chemotrade; all were used without further purification.

4.2. NMR spectroscopy

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 500 or 300 NMR spectrometers using 5 mm probes operating at 500 and 300 MHz for ^{1}H, and 125 and 75 MHz for ^{13}C. For all measurements, $CDCl_3$ (for lower temperatures CD_2Cl_2) was employed as the solvent using TMS as an internal reference (=0 ppm for both nuclei). ^{31}P NMR spectra were calibrated externally (capillary) with 85% H_3PO_4 (=0 ppm). Signal assignment was performed at 298 K and utilized standard Bruker pulse sequences (^{1}H, ^{13}C, ^{31}P, COSY, HMQC, and HMBC).

For ^{1}H NMR spectra, the digital resolution was set to 16 data points per hertz and to 1.6 data points per hertz for ^{13}C spectra. For 2D NOESY experiments, an optimal value for the mixing time τ_m was assessed as 400 ms. To avoid confusion arising from spin diffusion, 2D ROESY spectra were also recorded for comparison and also utilized mixing times of 400 ms. For both NOESY and ROESY experiments as well as the T_1 measurements, paramagnetic oxygen was displaced from the NMR solutions by ultrasonification for 30 min under argon prior to measurement. T_1 values were measured using the inversion recovery pulse sequence with a total of 16 different delay times. T_1 values were calculated using standard Bruker software and are reported with an uncertainty of 50 ms. Vicinal ^{1}H–^{1}H coupling constants were measured using the JRESQF pulse sequence where the spectral widths were set to 4125 and 40 Hz for the f_2 and f_1 dimensions, respectively, with digital resolutions of 4 and 0.2 Hz.

For the determination of the barriers to ring interconversion ($\Delta G^{\neq}$), the rate constants k_c at the coalescence temperatures T_c were calculated from the chemical sift difference $\Delta\nu$ of the respective peaks extrapolated to T_c using the Gutowski–Holm method ($k_c=2.22\times\Delta\nu$).[24] Inserting the resulting rate constants into the Eyring equation [$\Delta G^{\neq}=19.14\times T_c\times(10.32+\log(T_c/k_c)$] provided values of $\Delta G^{\neq}$. Coalescence temperatures are reported with an uncertainty of 1 K.

Titration experiments were conducted using the continuous variation method[25] as follows: stock solutions of the salts $H_2PO_4^-{}^+N(n\text{-}Bu)_4$ and $HSO_4^-{}^+N(n\text{-}Bu)_4$ and compounds **1**–**10** were, for ease of convenience, made to the same concentration (3.3×10^{-4} M) to facilitate a simple procedure whereby the sum of the concentrations of the ligands and the anions were maintained as a constant during the course of the titration. The ^{1}H NMR spectra of the free ligands were first recorded and then the concentration of the ligand was decreased successively whilst the concentration of the anion was increased accordingly (e.g., from **1**:$H_2PO_4^-{}^+N(n\text{-}Bu)_4$ or $HSO_4^-{}^+N(n\text{-}Bu)_4$=9:1 to 8:2…1:9, etc.).

4.3. Molecular modeling

Random search simulations were performed using the program *SYBYL*[21] with the Tripos force field[26] and consisted of 100,000 cycles. All torsional angles within the ring were allowed to vary randomly and no constraints were applied. After each cycle, the optimized conformation was stored if the heat of formation was within 3 kcal/mol of the lowest calculated heat of formation. The simulation was terminated prematurely if all so obtained conformations had been counted at least five times. This ensured that the global minimum was found with a confidence in excess of 95%.

Geometry optimizations were performed using the semiempirical method PM3.[27] The SCRF/SCIPCM (self-consistent reaction field/self-consistent isodensity polarized continuum model)[28] method were used to consider the solvent effect; the dielectric constant of chloroform (ε=4.8) was applied. Calculations were performed on IRIS-INDIGO XS24 or SGI O2 workstations or on PCs with Pentium 1 processors.

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References and notes

1. Hosseini, M. W.; Lehn, J.-M. *Helv. Chim. Acta* **1987**, *70*, 1312.
2. (a) Mertes, M. P.; Mertes, K. B. *Acc. Chem. Res.* **1990**, *23*, 413; (b) *Supramolecular Chemistry of Anions*; Bianchi, A., Bowman-James, K., Garcia-España, E., Eds.; VCH: Weinheim, 1997; (c) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609; (d) Shestakova, A. K.; Chertkov, V. A.; Schneider, H. J.; Lysenko, K. A. *Org. Lett.* **2001**, *3*, 325 and references therein.
3. (a) Xavier, C.; Paulo, A.; Domingos, A.; Santos, I. *Eur. J. Inorg. Chem.* **2004**, *2*, 243; (b) Subat, M.; Borovik, A.; König, B. *J. Am. Chem. Soc.* **2004**, *126*, 3185.
4. Chupakhin, O. N.; Itsikson, N. A.; Morzherin, Y. Y.; Charushin, V. N. *Heterocycles* **2005**, *66*, 689.
5. Llinares, J. M.; Powell, D.; Bowman-James, K. *Coord. Chem. Rev.* **2003**, *240*, 57.
6. Novak, I.; Potts, A. W. *J. Org. Chem.* **1996**, *61*, 786.
7. Ranganathan, R. S.; Pillai, R. K.; Raju, N.; Fan, H.; Nguyen, N.; Tweedle, M. F.; Desreux, J. F.; Jaques, V. *Inorg. Chem.* **2002**, *41*, 4846.

8. Bultinck, P.; van Alsenoy, C.; Goeminne, A.; van de Vondel, D. *J. Phys. Chem. A* **2000**, *140*, 11801.
9. Andres, A.; Arago, J.; Bencini, A.; Bianchi, A.; Domenech, A.; Fusi, V.; Garcia-Espania, E.; Paoletti, P.; Ramirez, J. A. *Inorg. Chem.* **1993**, *32*, 3418.
10. (a) Job, P. *Comp. Rend.* **1925**, *180*, 928; (b) Job, P. *Ann. Chim. Phys.* **1928**, *9*, 113.
11. Valiyaveettil, S.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 900.
12. Martell, A. E.; Motekaitis, R. J.; Lu, Q.; Nation, D. A. *Polyhedron* **1999**, *18*, 3203.
13. Starke, I.; Kleinpeter, E, unpublished results.
14. Pihlaja, K.; Kleinpeter, E. *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis*; Marchand, A. P., Ed.; Methods in Stereochemical Analysis; VCH: New York, NY, 1994; p 207.
15. (a) Holzberger, A.; Holdt, H.-J.; Kleinpeter, E. *Org. Biomol. Chem.* **2004**, *2*, 1691; (b) Holzberger, A.; Holdt, H.-J.; Kleinpeter, E. *J. Phys. Org. Chem.* **2004**, *17*, 257; (c) Holzberger, A.; Kleinpeter, E. *Magn. Reson. Chem.* **2004**, *42*, 589; (d) Kleinpeter, E.; Grotjahn, M.; Klika, K. D.; Drexler, H.-J.; Holdt, H.-J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 988; (e) Kleinpeter, E. *J. Prakt. Chem.* **1991**, *333*, 817.
16. Wolf, R. E.; Hartmann, J. A. R.; Storey, J. M. E.; Foxman, B. M.; Cooper, S. R. *J. Am. Chem. Soc.* **1987**, *109*, 4328.
17. Lu, Q.; Motakaitis, R. J.; Reibenspies, J. J.; Martell, A. E. *Inorg. Chem.* **1995**, *34*, 4958.
18. Albelda, M. T.; Burguete, M. I.; Frias, J. C.; Garcie-Espana, E.; Luis, S. V.; Miravet, J. F.; Querol, M. *J. Org. Chem.* **2001**, *66*, 7505.
19. Beer, P. D.; Gale, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 486.
20. (a) Connolly, M. L. *Science* **1983**, *221*, 709; (b) Connolly, M. L. *J. Appl. Crystallogr.* **1983**, *16*, 548.
21. (a) SYBYL Molecular Modeling Software, Version 6.8. Tripos: St. Louis, MO, 2003; (b) SYBYL Molecular Modeling Software. *Force Field Manual*, Version 6.8. Tripos: St. Louis, MO, 2003; pp 92–93; (c) SYBYL Molecular Modeling Software. *Molecular Spreadsheet Manual*, Version 6.8. Tripos: St. Louis, MO, 2003; pp 199–202; (d) SYBYL Molecular Modeling Software. *Graphics Manual*, Version 6.8. Tripos: St. Louis, MO, 2003; pp 199–202.
22. Gilson, M.; Sharp, K.; Honig, B. *J. Comput. Chem.* **1987**, *9*, 327.
23. Gokel, G. W. *Crown Ethers and Cryptands*; Stoddart, J. F., Ed.; Monographs in Supramolecular Chemistry; The Royal Society of Chemistry: Cambridge, 1991.
24. Gutowski, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.
25. (a) Shibata, Y.; Inouye, B.; Nakatsuka, Y. *Nippon Kagaku Kaishi* **1921**, *42*, 983; (b) Tsuchida, R. *Bull. Chem. Soc. Jpn.* **1935**, *10*, 27.
26. Clark, M.; Cramer, R. D., III; van Opdenbosch, N. *J. Comput. Chem.* **1989**, *10*, 982.
27. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
28. Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.

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Synthesis of fluorhydrins by reaction of quinidine acetate, epiquinidine, and its acetate in superacid

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Abstract—In HF–SbF_5, with or without H_2O_2, a source of 'OH^+' equivalent, quinidine **1a** yields three ethers, the preferred conformation of the substrate favoring the observed cyclization. Under similar conditions, quinidine acetate **1b**, epiquinidine **2a**, and its acetate **2b** give fluorhydrins with or without rearrangement in different amounts according to the nature of the substrate and the acidity. At low acidity, epiquinidine **2a** yields selectively a sole nonrearranged fluorhydrin **10a**. Quinidine acetate **1b**, at high acidity, yields only rearranged fluorhydrins **8b** and **9b**.

1. Introduction

Cinchona alkaloids quinine and quinidine have been used, respectively, as antimalarial and antiarrhythmic drugs.[1] Moreover, the special structure of these alkaloids has attracted much attention as chiral catalysts in asymmetric reactions.[2] We have previously reported that the reactivity of *Cinchona* alkaloids (quinine and quinidine) in superacid is dramatically modified when compared to what is observed in conventional acids.[3] In our search for new derivatives, we have studied the reactivity of quinidine derivatives in HF–SbF_5 in the presence of hydrogen peroxide H_2O_2, source of 'OH^+' equivalent in the reaction conditions.[4]

1.1. Reaction of quinidine 1a, epiquinidine 2a, and acetates 1b and 2b

1.1.1. Results. In the presence of hydrogen peroxide, quinidine **1a** yielded three ethers **3**, **4**, and **5** already obtained in HF–SbF_5. Compounds **3** and **4** have been previously prepared from **1a** in H_2SO_4 and isomer **5** from $\Delta^{3,10}$-isoquinidine in the presence of HBr (Fig. 1).[5]

In the same conditions, all other substrates have given fluorhydrins with or without rearrangement in different amounts, according to the nature of the substrate and the acidity (Table 1). The influence of acidity on the yields of the different products should be pointed out, starting from compounds **1b** and **2a**:

- compound **1b** at high acidity (HF–SbF_5 molar ratio 1:1) yields only rearranged fluorhydrins **8b** and **9b**.
- compound **2a** at low acidity (HF–SbF_5 molar ratio 2:1) gives the sole nonrearranged fluorhydrin **10a**.

1.2. Structure determination

1.2.1. Nonrearranged compounds 6b and 7b. The mass spectra of compounds **6b** and **7b** have shown that the molecular weight $[M+H]^+$ (403 g mol^{-1}) implies the formal addition of FOH. These compounds have spectroscopic properties (^1H and ^{13}C NMR data) very close to those exhibited by fluorhydrins obtained in quinine or epiquinine series.[6] Whereas the quinoline moiety appears not to be modified when compared to compound **1b**, changes are observed in the upper part with the disappearance of the vinylic protons and the presence of a CH_3–CHF group. A NOESY interaction is observed between H-10, H-2A, and H-7A implying that the two compounds have the same configuration at C-3 and only differ in configuration at C-10. The value close to 0 Hz of fluorine coupling with carbon C-4 is in agreement with *R* configuration of carbon C-10 in compound **7b**, and consequently with *S* configuration for compound **6b** (Fig. 2).[7]

The structure of compound **6b** has been confirmed by X-ray analysis (Fig. 3). It should be pointed out that a *gauche* effect is in operation for this compound (X-ray and in solution).

The sole compound **10a**, obtained at low acidity, has been identified by NMR after inversion of configuration at C-9 and acetylation to yield compound **6b**.

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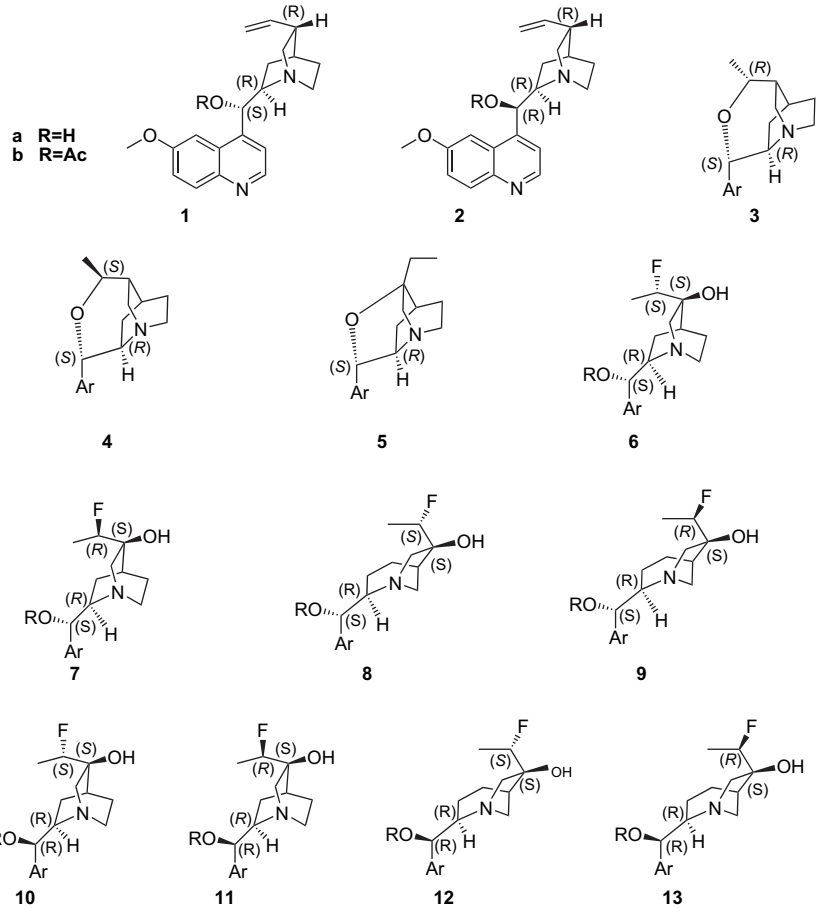


Figure 1.

Table 1. Reactivity of quinidine, epiquinidine, and their acetates in HF–SbF_5

Entry	Substrate	HF–SbF_5 (molar ratio)	Products (yield %)
1	**12a**	7:1 or 18:5	**14** (40)+**15** (15)+**16** (15)
2	**12b**	7:1	**17b** (21)+**18b** (3)+**19b** (10)+**20b** (12)
3	**12b**	18:5	**19b** (23)+**20b** (28)
4	**13a**	7:1	**21a** (33)
5	**13a**	18:5	**21a** (25)+**22a** (3)+**23a** (10)+**24a** (15)
6	**13b**	7:1	**21b** (20)+**22b** (3)+**23b** (11)+**24b** (15)
7	**13b**	18:5	**21b** (20)+**22b** (3)+**23b** (11)+**24b** (15)

Reaction conditions: HF–SbF_5, 3 min, −35 °C.

Compounds **11a** and **11b** have been obtained in too small amount (≅3%), not perfectly pure, and consequently, could not be analyzed. Their structures are proposed by analogy with the quinidine acetate reaction.

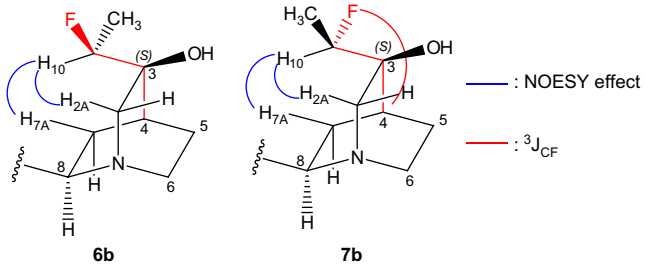


Figure 2.

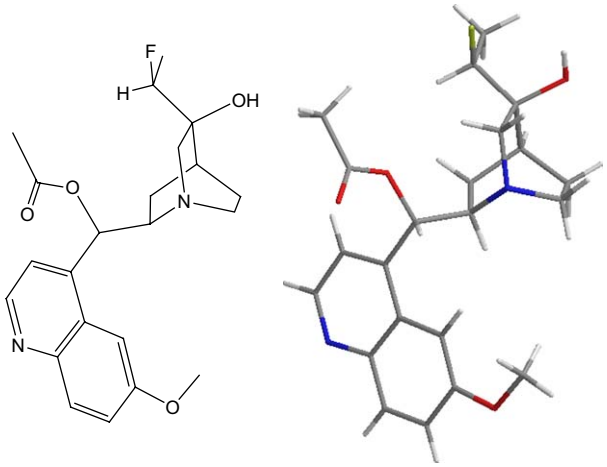


Figure 3. Compound **6b**, X-ray analysis.

1.2.2. Rearranged compounds 8b and 9b. The mass spectra of compound **8b** and **9b** have shown that the molecular weight $[M+H]^+$ (403 g mol^{-1}) implies the formal addition of FOH. In ^1H and ^{13}C NMR spectra the quinoline moiety appeared not to be modified when compared to the starting compound **1b**. Significant changes were observed in quinuclidine moiety:

- Disappearance of a vinylic group and presence of a CH_3–CHF group bonded to a quaternary carbon. For

example, in ^{1}H NMR, the CH_3–CHF group of compound **8b** is characterized by a doublet of quadruplets at 5.02 ppm (J_1=46.7 Hz and J_2=6.3 Hz) for C10–H and a doublet of doublets at 1.49 ppm (J_1=24.9 Hz and J_2=6.3 Hz) for the methyl group.
- Secondary C-6 carbon is identifiable by ^{1}H and ^{13}C resonances. One of the hydrogen atoms at C-6 carbon is coupled with the hydrogen atom on the tertiary C-5 carbon at 44.3 ppm. This is in agreement with an azabicyclo[3,2,1]octane with a CH_3–CHF group. Analogous rearrangement has been previously obtained with quinidine acetate in HF–SbF_5 in the presence of chloride ion.[3c]

In compounds **8b** and **9b** *exo* H-2 and *endo* H-2 respectively, have been identified by NMR experiments (W coupling) (Fig. 4).

In both compounds, NOESY interactions between *endo* H-2 and H-10 imply that the two compounds **8b** and **9b** have the same configuration at C-3 and only differ in configuration at C-10. This configuration has been determined by NMR as previously carried out for compounds **6b** and **7b**.

The structure **8b** has been confirmed by X-ray analysis (Fig. 5). It should be pointed out that a *gauche* effect is in operation for this compound (X-ray analysis and in solution).

The structure of compounds **12a** and **13a** has been determined similarly.

Deacetylation of compounds **10b**, **11b**, and **13b** yields compounds **10a**, **12a**, and **13a**.

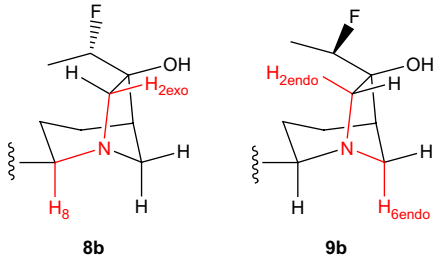


Figure 4.

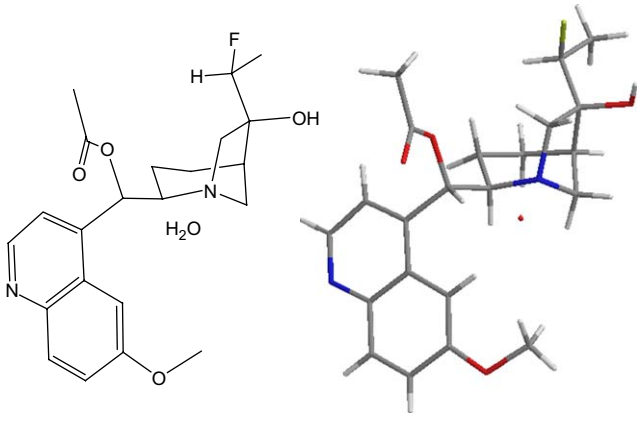


Figure 5. Compound **8b**, X-ray analysis.

1.3. Reaction mechanism

1.3.1. Formation of compounds 6b and 7b. Formation of fluorhydrins **6b** and **7b** can be accounted for by a mechanism similar to that postulated in quinine series.[6] The higher stereoselectivity in quinidine series results in the steric hindrance of the quinoline moiety, favoring an '*anti*' attack of the double bond by the equivalent 'OH$^+$' electrophile. Furthermore, the structure of the major compound **6b** implies that the electrophile reacted on the (*Z*)-isomer of the C3–C10 double bond. This is in agreement with the previous results obtained by Portlock et al. in equilibrating conditions showing that the (*Z*)-isomer is the more stable one.[8]

A similar process can be accounted for the formation of compounds **10a**, **10b**, **11a**, and **11b**.

1.3.2. Formation of compounds 8b and 9b. Formation of fluorhydrins **8b** and **9b** is a result of a rearrangement, which can be accounted for by a mechanism similar to that postulated in *gem*-difluorination of quinidine acetate.[3c] The proposed mechanism is outlined on Scheme 1.

- Pathway **a** implies a rearrangement involving several 1,3-hydride shifts and a carbon shift (C3–C4) to yield ion **K**, another 1,3-hydride shift leading to ion **L**.
- Pathway **b** implies the protonated cyclopropane **N**, which can directly lead to ion **L**.

Deprotonation of ion **L** can give ion **M** with a double bond (Z or *E*) C3–C10. An *exo* attack of this double bond by the electrophile 'OH$^+$' leads to the precursors of compounds **8b** and **9b**.

It should be pointed out that compounds **8b** and **9b** are formed with similar yields, implying close stabilities of the *Z* or *E* precursors.

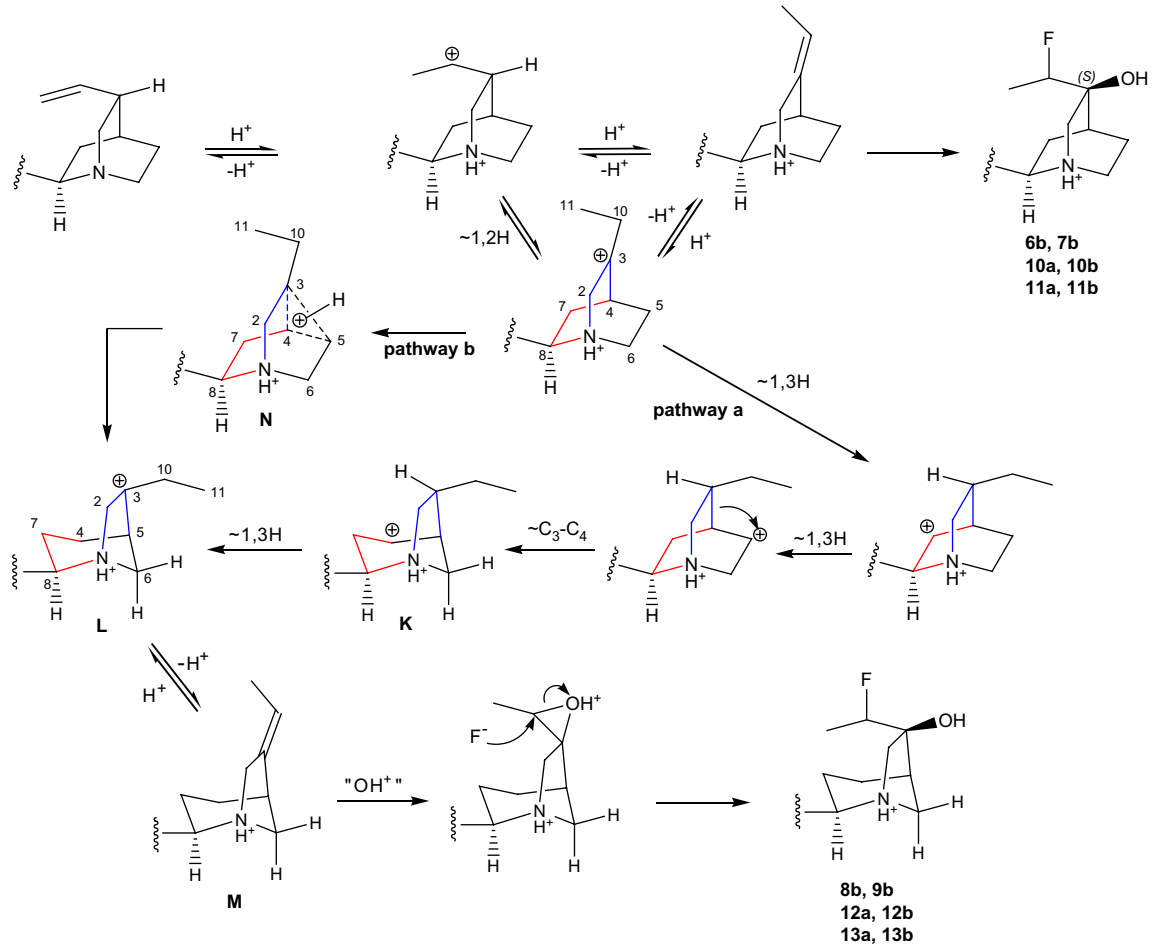
1.3.3. Comparison of the reactivity of substrates. For quinidine **1a**, the more stable conformation is favorable to cyclization with formation of ethers. Whatever the acidity is, this cyclization is no more possible with the corresponding acetate, and the reaction yields fluorhydrins. Furthermore, in the reaction of acetate **1b** at higher acidity, the repulsive interaction of carboxyl group and carbocation at C-3 or C-10 favors the observed rearrangement (Fig. 6).

For epiquinidine **2a**, at low acidity, the hydroxyl group is not protonated (diprotonation of the quinoline moiety and N protonation of the quinuclidyl ring disfavoring the protonation of the hydroxyl group at C-9). No rearrangement is observed since the conformation of the substrate minimizes repulsive and steric interactions.

At higher acidity, the hydroxyl is probably protonated and the repulsive interaction between the hydroxyl at C-9 and ion at C-3 or C-10 favors the rearrangement.

Geometry optimizations were carried out with Chem 3D by applying the PM3 semi-empirical methods in MOPAC (Fig. 7).

It should be pointed out that no oxidation is observed at the benzylic position. The oxidation would imply formation of



Scheme 1.

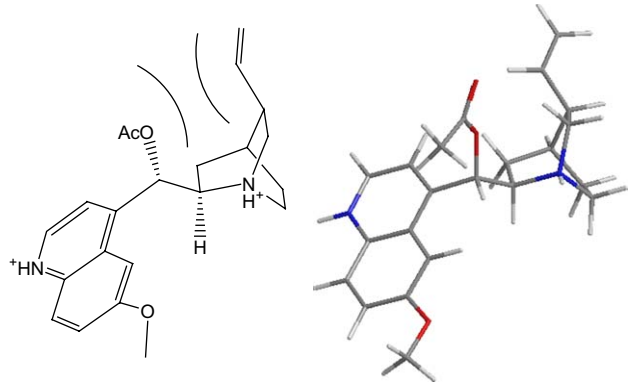


Figure 6. Preferred conformation of protonated quinidine derivatives.

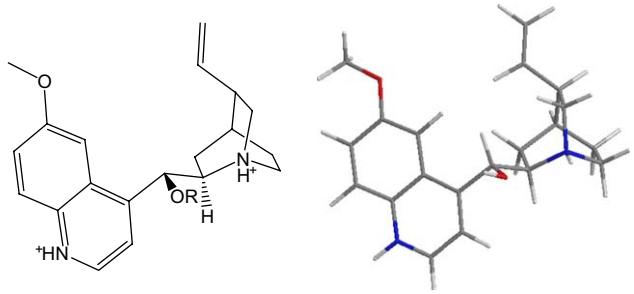


Figure 7. Preferred conformation of protonated epiquinidine derivatives.

the corresponding carbenium ion, which is disfavored by the protonation of both quinoline moiety and nitrogen quinuclidyl group.

2. Conclusion

In the presence of hydrogen peroxide, source of 'OH^+' equivalent, quinidine **1a** cyclizes to ethers, previously obtained in usual acidic conditions. However, all other substrates **1b**, **2a**, and **2b** yield fluorhydrins, with or without rearrangement pointed out the importance of the configuration and the nature of the functional group at C-9. The rearrangement of the quinuclidine moiety and the different reactivities of the substrates, according to the acidity, are probably the result of steric and repulsive interactions.

We have synthesized new fluorhydrins, which can have biological or catalytic activities, confirming the interest of superacids in organic chemistry.

3. Experimental

3.1. General method

The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen

fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Reactions performed in superacid were carried out in a sealed Teflon® flask with a magnetic stirrer. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out in anhydrous conditions leads to the same results as expected).

Yields refer to isolated pure products. ^{1}H and ^{13}C NMR were recorded on a 300 MHz Bruker spectrometer using $CDCl_3$ as solvent and TMS as internal standard.

Melting points were determined in a capillary tube and are uncorrected.

High-resolution mass spectra were performed on a Micromass ZABSpec TOF by the Centre Regional de Mesures Physiques de l'Ouest, Université Rennes.

All separations were done under flash-chromatography conditions on silica gel (15–40 μm).

Crystals of dimensions, 0.32×0.24×0.18 (**6b**) and 0.40×0.30×0.10 (**8b**) mm^3, were mounted with Paratone-N oil (Hampton Research) coating and immediately placed in a nitrogen cold stream.

X-ray intensity data were collected at 100 K on a Bruker-Nonius X8-APEX2 CCD area-detector diffractometer using Mo Kα radiation (λ=0.71073 Å).

Three sets of narrow data frames (20 s per frame) were collected at different values of θ, for 3 initial values of ω using 0.5° increments of ω for **6b**.

Four sets of narrow data frames (20 s per frame) were collected at different values of θ, for 3 and 1 initial values of θ and ω, respectively, using 0.5° increments of θ or ω for **8b**. Data reductions were accomplished using APEX2 V1.0-8.[9] The substantial redundancy in data allowed a semi-empirical absorption correction (APEX2 V1.0-8) to be applied, on the basis of multiple measurements of equivalent reflections. The structures were solved by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^9 data using SHELXTL V6.14.[10] Hydrogen atoms were included in calculated positions and allowed to ride on their parent atoms.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 602650 for **6b** and CCDC 602651 for **8b**.

Geometry optimizations were executed with Chem 3D by applying the PM3 semi-empirical methods in MOPAC.

3.2. General procedure in superacidic media

To a mixture of $HF–SbF_5$ (7:1 or 18:5 molar ratio) and 80% H_2O_2 (3 equiv), maintained at −35 °C was added quinidine derivative. The mixture was magnetically stirred at the same temperature for 3 min. The reaction mixture was then neutralized with water–ice–Na_2CO_3, and worked up by usual manner. Products were isolated by column chromatography and preparative TLC over SiO_2.

3.3. Reaction on quinidine acetate 1b

After reaction of quinidine acetate **1b** (500 mg, 1.37 mmol) with $HF–SbF_5$ 7:1 (A) or 18:5 (B) (molar ratio), following the general procedure, compounds **6b** (A: 21%, 115 mg), **7b** (A: 3%, 16 mg), **8b** (A: 10%, 55 mg; B: 28%, 154 mg), and **9b** (A: 12%, 66 mg; B: 23%, 126 mg) were isolated as white solids after preparative TLC eluted with the mixture CH_2Cl_2–MeOH–NH_3: 97/2/1 (v/v/v).

3.3.1. Compound 6b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.72 (1H, d, J=4.6 Hz, H-2′), 8.02 (1H, d, J=9.2 Hz, H-8′), 7.44 (1H, d, J=2.7 Hz, H-5′), 7.40 (1H, dd, J=9.2, 2.7 Hz, H-7′), 7.26 (1H, d, J=4.6 Hz, H-3′), 6.82 (1H, br d, J=3.9 Hz, H-9), 5.10 (1H, dq, J=46.4, 6.4 Hz, H-10), 4.0 (3H, s, OMe), 3.65 (1H, br d, J=15.0 Hz, H-2), 3.33 (1H, m, H-8), 3.00 (2H, m, H-6), 2.90 (1H, br d, J=15.0 Hz, H-2), 2.20 (3H, s, CH_3COO), 2.16 (1H, m, H-5), 1.96 (1H, m, H-4), 1.85 (1H, m, H-7), 1.54 (1H, m, H-7), 1.42 (3H, dd, J=25.0, 6.3 Hz, H-11), 1.32 (1H, m, H-5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3 (COO), 158.5 (C-6′), 147.1 (C-2′), 144.6 (C-9′), 142.4 (C-4′), 131.8 (C-8′), 126.4 (C-10′), 122.5 (C-7′), 117.7 (C-3′), 101.0 (C-5′), 94.5 (d, J=166.3 Hz, C-10), 72.6 (C-9), 71.7 (d, J=19.2 Hz, C-3), 57.3 (OCH_3), 56.9 (d, J=5.5 Hz, C-2), 56.2 (C-8), 49.5 (C-6), 29.2 (d, J=5.5 Hz, C-4), 23.5 (C-7), 21.1 (CH_3COO), 19.9 (C-5), 14.8 (d, J=23.6 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −181.0 (m).

ESIMS: 403.2037 $[M+H]^+$ (calculated for $C_{22}H_{28}N_2O_4F$, 403.2033), 425.1854 $[M+Na]^+$ (calculated for $C_{22}H_{28}N_2O_4FNa$, 425.18526), 441.1591 $[M+K]^+$ (calculated for $C_{22}H_{28}N_2O_4FK$, 441.15919). $[\alpha]_D^{20}$ 5.9 (c 0.34, CH_2Cl_2). Mp: 82 °C (CH_2Cl_2–hexane (20/80, v/v)).

Crystal color: colorless prisms, chemical formula $C_{22}H_{27}FN_2O_4$, molecular weight M=402.46, crystal system: orthorhombic, a=9.8074 (8) Å, b=13.262 (2) Å, c=15.520 (2) Å, volume of unit cell V=2018.5 (4) $Å^3$; Z=4; total reflections collected: 9608; independent reflections: 3285 ($2987 F_o > 4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 59.94° (99.5% coverage). Number of variables: 266; R_1=0.0367, wR_2=0.0958, S=1.031; highest residual electron density 0.352 $eÅ^{-3}$.

3.3.2. Compound 7b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, d, J=4.5 Hz, H-2′), 8.03 (1H, d, J=9.1 Hz, H-8′), 7.40 (1H, dd, J=9.1, 2.6 Hz, H-7′), 7.31 (1H, d, J=2.6 Hz, H-5′), 7.29 (1H, d, J=4.5 Hz, H-3′), 6.46 (1H, d, J=5.8 Hz, H-9), 5.03 (1H, dq, J=47.4, 6.3 Hz, H-10), 3.95 (3H, s, OMe), 3.26 (1H, m, H-8), 2.89 (2H, m, H-6), 2.83 (1H, br d, J=14.4 Hz, H-2), 2.55 (1H, br d, J=14.4 Hz, H-2), 2.17 (1H, m, H-4), 2.16 (3H, s, CH_3COO), 1.94 (1H, m, H-5), 1.80 (1H, m, H-7), 1.60 (1H, m, H-7), 1.37 (3H, dd, J=24.8, 6.3 Hz, H-11), 1.28 (1H, m, H-5).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1 (COO), 158.5 (C-6′), 147.8 (C-2′), 145.0 (C-9′), 143.5 (C-4′), 132.3 (C-8′), 127.0 (C-10′), 118.5 (C-7′), 122.4 (C-3′), 101.5 (C-5′), 90.5 (d, J=170.1 Hz, C-10), 74.4 (C-9), 73.0 (d, J=18.8 Hz, C-3), 56.0 (OCH_3), 53.5 (d, J=4.4 Hz, C-2), 57.7 (C-8), 50.0 (C-6), 29.4 (s, C-4), 24.8 (C-7), 21.5 (CH_3COO), 21.5 (C-5), 14.2 (d, J=23.4 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −183.9 (m).

3.3.3. Compound 8b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.71 (1H, d, J=4.4 Hz, H-2′), 8.02 (1H, d, J=9.0 Hz, H-8′), 7.53 (1H, d, J=2.6 Hz, H-5′), 7.40 (1H, dd, J=9.2, 2.6 Hz, H-7′), 7.24 (1H, d, J=4.6 Hz, H-3′), 6.85 (1H, br d, J=3.3 Hz, H-9), 5.02 (1H, dq, J=46.7, 6.3 Hz, H-10), 4.04 (3H, s, OMe), 3.96 (1H, br d, J=15.0 Hz, H-2), 3.86 (1H, br d, J=11.7 Hz, H-6), 3.52 (1H, m, H-8), 3.36 (1H, br d, J=15.0 Hz, H-2), 2.86 (1H, br d, J=11.1 Hz, H-6), 2.19 (3H, s, CH_3COO), 2.13 (2H, m, H-4), 1.99 (1H, m, H-7), 1.64 (1H, m, H-5), 1.64 (1H, m, H-7), 1.49 (3H, dd, J=24.9, 6.3 Hz, H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.0 (COO), 158.7 (C-6′), 146.9 (C-2′), 144.6 (C-9′), 141.9 (C-4′), 131.7 (C-8′), 126.4 (C-10′), 122.8 (C-7′), 117.9 (C-3′), 101.1 (C-5′), 91.2 (d, J=168.0 Hz, C-10), 82.1 (d, J=18.7 Hz, C-3), 72.6 (C-9), 64.5 (C-8), 61.5 (C-6), 59.4 (br d, C-2), 56.6 (OCH_3), 43.1 (d, J=6.0 Hz, C-5), 23.4 (C-4), 21.1 (CH_3COO), 18.9 (C-7), 16.0 (d, J=23.1 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −185.7 (m).

ESIMS: 403.2029 $[M+H]^+$ (calculated for $C_{22}H_{28}N_2O_4F$, 403.2033), 425.1868 $[M+Na]^+$ (calculated for $C_{22}H_{28}N_2O_4FNa$, 425.18526). $[\alpha]_D^{20}$ −4.2 (c 0.236, CH_2Cl_2). Mp: 84 °C (CH_2Cl_2–hexane (20/80, v/v)).

Crystal color: colorless prisms, chemical formula $C_{22}H_{27.5}FN_2O_{4.25}$, molecular weight M=406.96, crystal system: orthorhombic, a=11.2381 (9) Å, b=13.577 (1) Å, c=13.671 (2) Å, volume of unit cell V=2085.8 (3) Å^3. Z=4; total reflections collected: 43445; independent reflections: 3399 ($3197F_o>4\sigma(F_o)$); data were collected up to a $2\theta_{max}$ value of 60° (100% coverage). Number of variables: 275; R_1=0.0531, wR_2=0.1463, S=1.103; highest residual electron density 0.734 eÅ^{-3}.

3.3.4. Compound 9b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.71 (1H, d, J=4.6 Hz, H-2′), 8.02 (1H, d, J=9.2 Hz, H-8′), 7.44 (1H, d, J=2.4 Hz, H-5′), 7.39 (1H, dd, J=9.2, 2.7 Hz, H-7′), 7.25 (1H, d, J=4.6 Hz, H-3′), 6.60 (1H, br d, J=3.2 Hz, H-9), 5.10 (1H, dq, J=46.8, 6.4 Hz, H-10), 4.00 (3H, s, OMe), 3.63 (1H, br d, J=10.2 Hz, H-6), 3.43 (1H, m, H-8), 3.36 (1H, br d, J=13.9 Hz, H-2), 3.04 (1H, br d, J=13.9 Hz, H-2), 2.76 (1H, br d, J=11.1 Hz, H-6), 2.17 (3H, s, CH_3COO), 2.15 (1H, m, H-5), 1.92 (1H, m, H-4), 1.86 (1H, m, H-7), 1.66 (1H, m, H-4), 1.61 (1H, m, H-7), 1.49 (3H, dd, J=24.4, 6.3 Hz, H-11).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.3 (COO), 158.4 (C-6′), 147.1 (C-2′), 144.6 (C-9′), 142.5 (C-4′), 131.8 (C-8′), 126.5 (C-10′), 122.3 (C-7′), 118.3 (C-3′), 101.1 (C-5′), 89.7 (d, J=170.7 Hz, C-10), 82.8 (d, J=19.2 Hz, C-3), 73.6 (C-9), 64.9 (C-8), 61.5 (C-6), 56.6 (d, J=4.9 Hz, C-2), 56.2 (OCH_3), 44.3 (s, C-5), 24.0 (C-4), 21.1 (CH_3COO), 19.0 (C-7), 15.7 (d, J=23.1 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −184.5 (m).

ESIMS: 403.2030 $[M+H]^+$ (calculated for $C_{22}H_{28}N_2O_4F$, 403.2033), 425.1821 $[M+Na]^+$ (calculated for $C_{22}H_{28}N_2O_4FNa$, 425.18526). $[\alpha]_D^{20}$ −18.9 (c 0.09, CH_2Cl_2). Mp: 95 °C (CH_2Cl_2–hexane (20/80, v/v)).

3.4. Reaction on epiquinidine 2a

After the reaction of epiquinidine **2a** (400 mg, 1.24 mmol) with HF–SbF_5 7:1 (A) or 18:5 (B) (molar ratio), following the general procedure, compounds **10a** (A: 33%, 148 mg; B: 23%, 103 mg), **11a** (B: 3%, 10 mg), **12a** (B: 10%, 44 mg), and **13a** (B: 15%, 67 mg) were obtained as colorless oils after preparative TLC eluted with the mixture CH_2Cl_2–MeOH–NH_3: 96/3/1 (v/v/v).

3.4.1. Compound 10a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.75 (1H, d, J=4.5 Hz, H-2′), 8.04 (1H, d, J=9.3 Hz, H-8′), 7.60 (1H, d, J=2.6 Hz, H-5′), 7.43 (1H, d, J=4.5 Hz, H-3′), 7.39 (1H, dd, J=9.3, 2.6 Hz, H-7′), 4.99 (1H, d, J=10.1 Hz, H-9), 4.91 (1H, dq, J=46.9, 6.4 Hz, H-10), 3.95 (3H, s, OMe), 3.44 (1H, d, J=15.0 Hz, H-2_a), 3.13 (1H, m, H-6_b), 3.09 (1H, m, H-8), 2.98 (1H, m, H-6_a), 2.76 (1H, d, J=15.0 Hz, H-2_b), 2.05 (1H, m, H-7), 1.77 (1H, m, H-4), 1.35 (3H, dd, J=25.0, 6.4 Hz, H-11), 1.19 (2H, m, H-5), 1.19 (1H, m, H-7).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.0 (C-6′), 147.9 (C-2′), 145.3 (C-9′), 144.4 (C-4′), 132.2 (C-8′), 128.4 (C-10′), 122.1 (C-7′), 120.5 (C-3′), 102.4 (C-5′), 95.6 (d, J=167.0 Hz, C-10), 71.2 (C-9), 72.7 (d, J=18.7 Hz, C-3), 60.7 (C-8), 55.8 (OCH_3), 55.6 (d, J=4.4 Hz, C-2), 49.3 (C-6), 29.9 (d, J=4.4 Hz, C-4), 25.9 (C-5), 21.5 (C-7), 15.3 (d, J=23.2 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −189.4 (m).

ESIMS: 361.1932 $[M+H]^+$ (calculated for $C_{20}H_{25}N_2O_3F$, 19275), 383.1742 $[M+Na]^+$ (calculated for $C_{20}H_{25}N_2O_3FNa$, 383.17469), 399.1462 $[M+K]^+$ (calculated for $C_{20}H_{25}N_2O_3FK$, 399.14863). $[\alpha]_D^{20}$ 16.47 (c 0.17, CH_2Cl_2).

3.4.2. Compound 12a. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, d, J=4.5 Hz, H-2′), 8.02 (1H, d, J=9.2 Hz, H-8′), 7.55 (1H, d, J=2.6 Hz, H-5′), 7.43 (1H, d, J=4.3 Hz, H-3′), 7.37 (1H, dd, J=9.2, 2.6 Hz, H-7′), 4.96 (1H, dq, J=46.4, 6.3 Hz, H-10), 4.85 (1H, d, J=9.7 Hz, H-9), 3.95 (3H, s, OMe), 3.51 (1H, d, J=14.2 Hz, H-2_a), 3.62 (1H, d, J=11.4 Hz, H-6_b), 3.06 (1H, m, H-8), 2.91 (1H, d, J=14.2 Hz, H-2_b), 2.78 (1H, d, J=11.4 Hz, H-6_a), 1.87 (1H, m, H-4), 1.44 (3H, dd, J=25.0, 6.3 Hz, H-11), 1.35 (1H, m, H-5), 1.24 (1H, m, H-7), 1.24 (1H, m, H-5), 0.92 (1H, m, H-7).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.5 (C-6′), 147.7 (C-2′), 144.7 (C-9′), 144.2 (C-4′), 131.7 (C-8′), 127.7 (C-10′), 121.3 (C-7′), 120.1 (C-3′), 102.5 (C-5′), 91.8 (d, J=164.3 Hz, C-10), 82.7 (d, J=18.8 Hz, C-3), 72.2 (C-9),

68.6 (C-8), 60.6 (C-6), 59.4 (C-2), 55.6 (OCH_3), 43.3 (d, J=5.3 Hz, C-5), 24.1 (C-4), 21.8 (C-7), 16.2 (d, J=23.3 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −185.8 (m).

ESIMS: 361.1923 $[M+H]^+$ (calculated for $C_{20}H_{26}N_2O_3F$, 361.19275), 383.1748 $[M+Na]^+$ (calculated for $C_{20}H_{25}N_2O_3FNa$, 383.17469). $[\alpha]_D^{20}$ −6.92 (c 0.13, CH_2Cl_2).

3.4.3. Compound 13a. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.67 (1H, d, J=4.5 Hz, H-2′), 7.97 (1H, d, J=9.2 Hz, H-8′), 7.50 (1H, d, J=2.7 Hz, H-5′), 7.33 (1H, d, J=4.5 Hz, H-3′), 7.31 (1H, dd, J=9.2, 2.7 Hz, H-7′), 4.95 (1H, dq, J=46.7, 6.3 Hz, H-10), 4.70 (1H, br d, J=9.7 Hz, H-9), 3.93 (3H, s, OMe), 3.55 (1H, d, J=11.4 Hz, H-6_b), 3.03 (1H, m, H-8), 2.91 (1H, d, J=14.1 Hz, H-2_a), 2.77 (1H, d, J=11.4 Hz, H-6_a), 2.73 (1H, d, J=14.1 Hz, H-2_b), 1.98 (2H, m, H-4), 1.64 (1H, m, H-5), 1.41 (3H, dd, J=24.5, 6.3 Hz, H-11), 1.18 (1H, m, H-7), 0.83 (1H, m, H-7).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.8 (C-6′), 148.0 (C-2′), 145.1 (C-9′), 144.7 (C-4′), 132.1 (C-8′), 128.1 (C-10′), 121.5 (C-7′), 120.6 (C-3′), 103.2 (C-5′), 89.9 (d, J=169.0 Hz, C-10), 83.5 (d, J=19.4 Hz, C-3), 73.1 (C-9), 68.6 (C-8), 60.9 (C-6), 55.0 (d, J=4.6 Hz, C-2), 55.9 (OCH_3), 45.7 (s, C-5), 24.8 (C-4), 21.6 (C-7), 16.1 (d, J=23.3 Hz, C11).

^{19}F NMR ($CDCl_3$, 282 MHz): −181.3 (m).

ESIMS: 361.1926 $[M+H]^+$ (calculated for $C_{20}H_{26}N_2O_3F$, 361.19275). $[\alpha]_D^{20}$ 9.38 (c 0.16, CH_2Cl_2).

3.5. Hydrolysis of compounds 10b, 11b, 12b, and 13b

Compounds **10b**, **11b**, **12b**, and **13b** were treated with K_2CO_3 (1.2 equiv) in a solution of MeOH–H_2O (7/93, v/v). After being stirred for 2 h, the residue was diluted with AcOEt, washed, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give compounds **10a**, **11a**, **12a**, and **13a** as colorless oils (90%).

References and notes

1. (a) Verpoorte, R.; Schripsema, J.; Der Leer, T. V. *Cinchona Alkaloids in the Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Academic: San Diego, 1988; Vol. 34, pp 331–398; (b) Bruneton, J. *Pharmacognosie, Phytochimie, Plantes médicinales*; Lavoisier: Paris, 1987.
2. For recent and selected reports, see: (a) Margitfalvi, J. L.; Hegedus, M.; Tfirst, E. *Tetrahedron: Asymmetry* **1996**, *7*, 571–580; (b) Augustine, R. L.; Tanielyan, S. K. *J. Mol. Catal. A: Chem.* **1996**, *112*, 93–104; (c) Wang, G. Z.; Mallat, T.; Baiker, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2133–2140; (d) Blaser, H. U.; Jalett, H. P.; Lottenbach, W.; Studer, M. *J. Am. Chem. Soc.* **2000**, *122*, 12675–12682; (e) Bartok, M.; Sutyinszki, M.; Felföldi, K.; Szollosi, G. *Chem. Commun.* **2002**, 1130–1131; (f) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728–10729; (g) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867–1869; (h) Shibata, N.; Suzuki, E.; Asachi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001–7009; (i) Corey, E. J.; Lotto, G. I. *Tetrahedron Lett.* **1990**, *31*, 2665–2668; (j) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.; Kwong, H. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226–12227; (k) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291; (l) Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S. *Tetrahedron: Asymmetry* **1996**, *7*, 648–654; (m) Chen, Y.; Tian, S. K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543; (n) Baudequin, C.; Loubassou, J. F.; Plaquevent, J. C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122*, 189–193; (o) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Toupet, L.; Roques, N. *Tetrahedron Lett.* **2001**, *42*, 1867–1869; (p) Goodman, L. S.; Gilman, A. G. *The Pharmacological Basis of Therapeutics*, 7th ed.; McMillan: New York, NY, 1985; 756–1041; (q) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291–3294 and references cited therein.
3. (a) Thibaudeau, S.; Violeau, B.; Martin-Mingot, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2002**, *43*, 8773–8775; (b) Debarge, S.; Thibaudeau, S.; Violeau, B.; Martin-Mingot, A.; Jouannetaud, M. P.; Jacquesy, J. C.; Cousson, A. *Tetrahedron* **2005**, *61*, 2065–2073; (c) Debarge, S.; Violeau, B.; Jouannetaud, M. P.; Jacquesy, J. C.; Cousson, A. *Tetrahedron* **2006**, *61*, 2065–2073; (d) Vancik, H.; Percac, K.; Sunko, D. E. *J. Am. Chem. Soc.* **1990**, *112*, 7418–7419; (e) Culmann, J. C.; Simon, M.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1098–1100.
4. (a) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley Interscience: New York, NY, 1985; (b) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Vidal, Y. *Tetrahedron* **1990**, *46*, 815–826; (c) Jacquesy, J. C.; Berrier, C.; Gesson, J. P.; Jouannetaud, M. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 658–664; (d) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Lafitte, C.; Vidal, Y.; Zunino, F.; Fahy, J.; Duflos, A. *Tetrahedron* **1998**, *54*, 13761–13770; (e) Duflos, A.; Redoules, F.; Fahy, J.; Jacquesy, J. C.; Jouannetaud, M. P. *J. Nat. Prod.* **2001**, *64*, 193–195.
5. Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495–3512.
6. Chagnault, V.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2006**, *47*, 5723–5726.
7. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987; p 205.
8. Portlock, D.; Naskar, D.; West, L.; Seibel, W.; Gu, T.; Krauss, H.; Sean Peng, X.; Dybas, P.; Soyke, E.; Ashon, S.; Burton, J. *Tetrahedron Lett.* **2003**, *44*, 5365–5368.
9. *APEX2 Version 1.0-8*; Bruker AXS: Madison, WI, 2003.
10. *SHELXTL Version 6.14*; Bruker AXS: Madison, WI, 2001.

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Reaction of vinyl triflates of α-keto esters and imides with secondary amines: synthesis of α,β-diamino carboxylic acid derivatives through aziridinium ions

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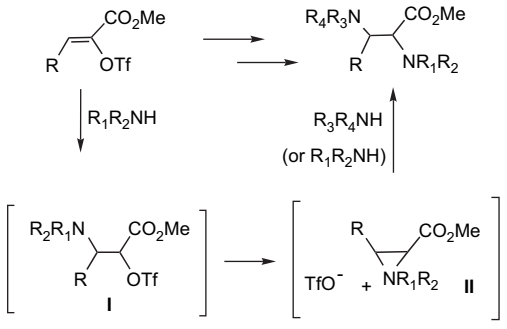
Abstract—Reaction between secondary amines and vinyl triflates of α-keto esters and imides under solvent-free condition provides a ready access to α,β-diamino carboxylates.

1. Introduction

Tandem (also described as domino or cascade) reactions, which permit complex molecules to be constructed in a one-pot assembly, are an important topic in organic synthesis.[1] Vinyl triflates of α-keto acid derivatives, which contain three contiguous electrophilic centres, are therefore very promising substrates in this field. However, it is rather surprising to note that this readily available class of compounds remains unexplored.[2] We have recently started investigating their potential in a series of tandem reactions and showed their effectiveness in this area.[3,4] We notably demonstrated that such molecules are highly reactive with primary amines to provide a reliable access to aziridine carboxylates[4,5] through an overall aza-MIRC (Michael intramolecular ring closure) process.[6] The logical progression in terms of substitution pattern now called for the addition of secondary amines which, through sequential conjugate addition–intramolecular nucleophilic substitution, should provide an unprecedented route towards aziridinium ions (type **II**, Scheme 1).[7] The latter, which are recognized as very reactive transient electrophilic intermediates,[8] are expected to be ring opened during their formation by a second equivalent of amine to provide α,β-diamino carboxylic acid derivatives (Scheme 1).[9]



Scheme 1.

Herein are reported preliminary results establishing that this path can be accomplished offering a new route to α,β-diamino carboxylic esters through an unusual aziridinium ion formation mode.

2. Results and discussion

2.1. Reaction of the vinyl triflates with 2 equiv of a single secondary amine

In a first series of experiments, the cinnamate derivative **1** (R=Ph in Scheme 1) was reacted with various secondary amines in neat conditions. These solvent-free conditions were selected to overcome the intrinsic low reactivity of cinnamate acceptors towards aza-nucleophiles.[4] Amines were used in excess to ensure homogeneous reaction conditions with this crystalline substrate (Table 1). Once formed, the intermediate **I** (Scheme 1) was expected to evolve spontaneously into an aziridinium ion **II** owing to the very high electrophilic character of the Cα atom bearing the triflate and ester functionalities. Accordingly, the reactions were carried out at room temperature unless otherwise indicated. Since α,β-primary diamino carboxylic acids would be particularly useful final products, both diallylamine and dibenzylamine were examined as synthetic ammonia equivalents.

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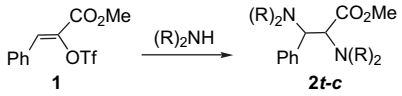
Table 1. Reaction of vinyl triflate **1** with secondary amines



1 **2t-c**

Runs[a]	Amine	Time	Products *t–c* (yields %)[b]		Yields (%)[b]
1	$(Me)_2NH$[10]	24 h	**2a*t*** (38)[c]	**2a*c*** (51)	
2	$(Me)_2NH$[d]	30 min	**2a*t*** (39)[c]	**2a*t*** (50)	
3[e]	$(Et)_2NH$	4 d	**2b*t*** (33)	**2b*c*** (20)[c]	53[c]
4[f]	$(Allyl)_2NH$	7 d	**2c*t*/2c*c*** 2:1 59(73)[g,h]		
5[f]	$(Bn)_2NH$	7 d	No reaction		
6	Morpholine	1 h	**2e*t*** (61)	**2e*c*** (23)[i]	84
7	Pyrrolidine	1 h	**2f*t*** (51)	**2f*c*** (18)[c]	
8	Piperidine	1 h	**2g*t*** (70)	**2g*c*** (30)[i]	100

[a] Unless otherwise indicated, the reactions were conducted at room temperature.
[b] Isolated yields.
[c] The stereochemistry of **2a*t***, **2b*t*** and **2f*t*** was determined by spectroscopic correlation (see Section 2.3).
[d] An aqueous solution (50%) was used.
[e] Enamine **3b** was isolated in 11% yield.
[f] The reaction was stirred at 40 °C for 7 days.
[g] Yield in brackets based on recovered starting triflate.
[h] Enamine **3c** was isolated in 14% yield.
[i] The stereochemistry of **2e*t*** and **2g*t*** was determined by chemical correlation using the Sharpless method[8c,d] (see Section 2.3).

Of the acyclic amines tested (runs 1–5), only dimethylamine, rapidly and cleanly provided the expected diamino adducts **2a*t*–*c*** in a 1:1.3 ratio (run 1).[10] More interestingly, even aqueous $(Me)_2NH$ could be used, affording a prompt reaction with an identical stereochemical profile (run 2).[11]

The lack of stereoselectivity obtained in this reaction was similar to that previously observed in cases of aziridine syntheses, and suggests a non stereoselective protonation of the enolate formed after the conjugate addition of the amine.[4] The reaction of diethylamine (run 3) was slow and provided the expected diamino esters **2b*t*–*c*** (1.4:1 ratio) in moderate yield, contaminated by side-products (TLC monitoring) among them the enamine **3b** (stereochemistry not determined) (Fig. 1). Type **3** enamines are common impurities in this type of chemistry.[12] An even slower but more selective reaction took place with diallylamine, affording, after 1 week the stereomeric mixture of inseparable diamino esters **2c*t*–*c*** (2.3:1 ratio) in correct yield along with the enamine **3c** as a unique impurity (run 4).

On the other hand, no trace of addition product of dibenzylamine could be detected even after prolonged heating. This first set of experiments clearly shows that the reaction strongly depends on steric effects.

As expected, the less sterically demanding and more nucleophilic cyclic amines reacted equally well as dimethylamine, giving a stereomeric mixture of all separable diamines **2e*t*–g*t*** of *anti* stereochemistry[11] and **2e*c*–g*c*** of *syn* stereochemistry[11] (runs 6–8) with a *anti*/*syn* ratio ranging from

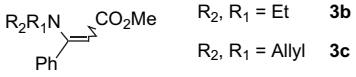
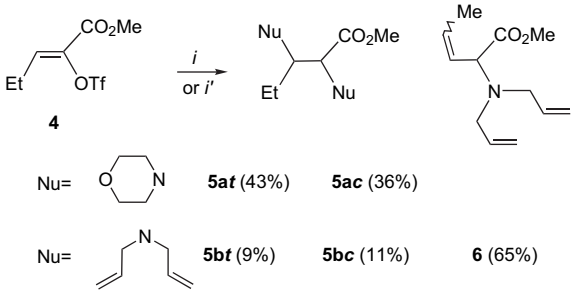


Figure 1. Structure of the enamines **3b** and **c** obtained as side-products through this work.

2.3:1 to 2.8:1. The successful set of results depicted in runs 1, 2 and 6–8 compares favourably with similar reactions carried out on methyl cinnamate itself, and is testament of the powerful role served by the triflate group to accelerate the ordinarily slow uncatalyzed 1,4-additions of the weak Michael donor secondary amines.

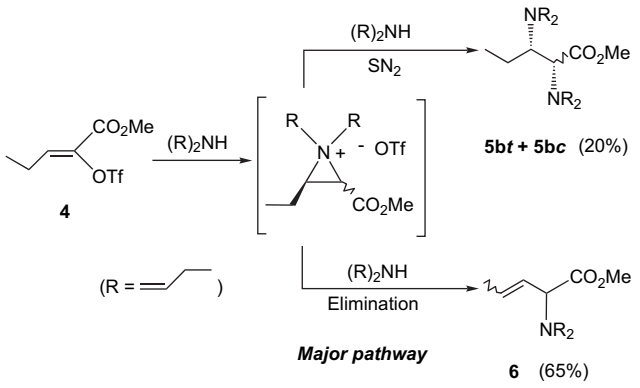
Overall, the low reactivity of the acyclic hindered amines towards the cinnamate derivative **1** provides a severe limit for the reaction. In terms of reactivity, conjugate acceptors substituted by an alkyl group at the β-position ordinarily outperform their β-aryl analogues in the 1,4-addition reactions of amines. Therefore, we next evaluated the β-ethyl vinyl triflate **4** as a prototypic more electrophilic candidate for this aza-MIRC process (Scheme 2).



Scheme 2. (*i*) Morpholine (3.5 equiv), rt, 5 min; (*i'*) Diallylamine (3.5 equiv), rt, 8 h (not optimized).

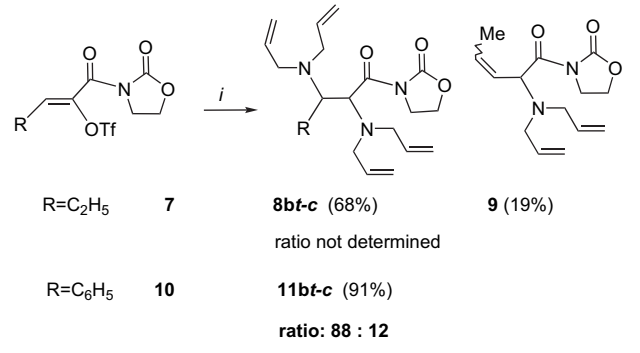
Since compound **4** is an oil, a minimum amount of the amines (3.5 equiv) was used. Substrate **4** actually turned out to be exceedingly responsive towards both cyclic and acyclic amines, as proven first by its reaction with morpholine, which readily gave the separable desired dimorpholino esters **5a*t*–*c*** in 80% yield and almost no diastereoselectivity. The vinyl triflate **4** also disappeared rapidly upon reaction with diallylamine, to afford separable adducts **5b*t*** and **5b*c*** in only 20% yield (Scheme 2). In this case, the major product was the allylic α-amino ester **6**, obtained as a sole geometrical isomer *Z* or *E*, the stereochemistry of which could not be determined due to interference in the ^1H NMR spectrum between the vinylic protons at C3 and C4 and the vinylic hydrogen atoms of the diallylamine moiety. Carrying out the reaction at 60 °C did not change the reaction profile, with similar yields of **5b*t*–*c*** and **6** being obtained. This disappointing result markedly contrasts with a set of examples recently published by Zhu and co-workers[13] describing the highly α-selective and generally efficient-opening of an *N*,*N*-dibenzyl aziridinium salt derived from serine methyl ester by a range of nucleophiles, including the sterically demanding and poorly nucleophilic *N*,*N*-dibenzyl amine.[14] In line with Zhu's results, it should be postulated that the diamines **5a*t*–*c*** and **5b*t*–*c*** obtained herein originate from an α-regioselective aziridinium opening, which is the inverse to the β-selectivity expected for the reactions involving the cinnamate derivative **1**.[15] Overall, this result supports the occurrence of an aziridinium pathway (Scheme 1), the opening of which, either in the cis or trans form, is retarded at the expense of a less sterically demanding elimination process leading to compound **6** (Scheme 3).

The result of the reaction between **4** and diallylamine clearly reveals that a more generally acceptable solution must be



Scheme 3.

found for an efficient aza-MIRC reaction of acyclic secondary amines towards vinyl triflates derived from α-keto acids. This prompted us to examine the use of unsaturated imides as more electrophilic substrates.[16] Hence, imides **7** and **10** were prepared in three steps (a. LiOH, b. $(COCl)_2$/cat DMF then c. *N*-lithium salt of oxazolidin-2-one) from the methyl esters **1** and **4** and their reaction with diallylamine was evaluated (Scheme 4). Conjugate addition to imide **7** was immediately rewarded by yield enhancement (68% yield for **8b*t*–*c*** as an inseparable mixture vs 20% yield for **5b*t*–*c***). Hence, the formation of the allylic α-amino acid derivative **9** (one geometrical isomer, analogous to the product **6**) was reduced from 65% (Scheme 2) to 19%. Reaction of the cinnamoyl derivative **10** with diallylamine provided additional insight into the beneficial impact of an imide acceptor. In this case, the reaction rate was enhanced by at least a seven-fold factor (in comparison with the reaction of **1**), affording an inseparable mixture of diamino imides **11b*t*–*c*** in high yield and with an increased diastereomeric ratio of 88:12 (see for comparison Table 1, run 3).



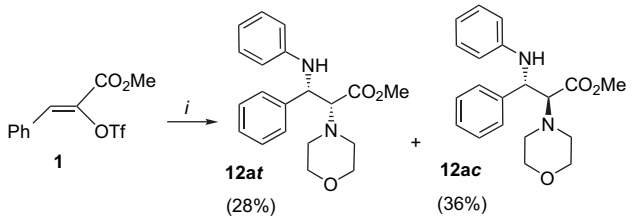
Scheme 4. (*i*) Diallylamine (3.5 equiv), rt, 1 h for **7**, 24 h (unoptimized) for **10**.

The diamino compounds so obtained could, in principle, have been obtained by direct intermolecular S_N2 substitution of the triflate group in the β-amino α-triflyloxy carbonyl intermediate **I** (Scheme 1) without the need to invoke an aziridinium ion. Owing to the above-mentioned very high electrophilic character expected for the α-carbon in type **I** intermediate, in conjunction with the comments relative to Scheme 3 and with several recent publications in the area of diamine synthesis from vicinal *N*,*N*-dialkylamino alcohols, wherein the contribution of aziridinium forms was clearly demonstrated,[13,17] it is likely that aziridiniums are the active intermediates in the chemistry exposed herein. Moreover, the replacement of the methoxy carbonyl group in the cinnamate derivative **1** by the more activating imide function in compound **10** questions about the influence of such an imide group on the regioselectivity of the aziridinium opening process (α- vs β-), which is known to be highly β-selective in the ester series.[15]

2.2. Reaction of the vinyl triflates 1 and 10 with two amines of different nucleophilicities

In order to expand the scope of the present methodology, we sought to develop conditions by which the aziridinium **II** (Scheme 1) could be continuously trapped by a second nucleophile (Nu_2) weaker than the first reactive amine (Nu_1).

A model reaction was investigated by which morpholine (3 equiv) was added to a solution of substrate **1** in aniline (30 equiv). A very slow reaction took place at room temperature[18] to afford the easily separable diastereomers **12a*t*** (less polar, *syn*)[11] and **12a*c*** (more polar, *anti*)[11] in 64% yield, along with the dianilino adduct (not shown) in 8% yield (Scheme 5). Although the formation of this dianilino adduct is, in the present case, anecdotic, it reveals that the aniline derivatives behave as secondary amines rather than as primary ones, an interesting feature that could potentially be exploited to expand the scope of the chemistry practiced herein.

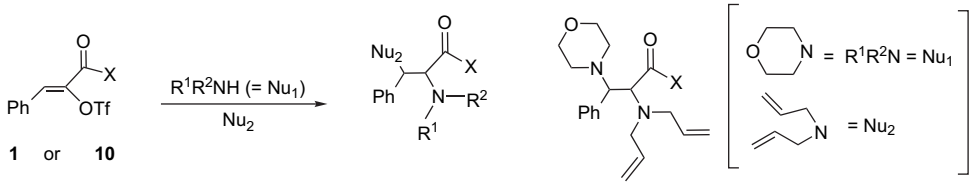


Scheme 5. (*i*) Aniline (30 equiv), morpholine (3 equiv), rt, 168 h.

The structure of **12a*t*–*c*** could be tentatively assigned by means of ^1H and ^{13}C NMR spectroscopies, which shows that one molecule each of morpholine and aniline has been incorporated in both cases. Regiochemistry was confirmed by GC/MS analysis as the fragment ion $[C_6H_5CHNHC_6H_5]^+$ was clearly observed for both diastereomers. *These results strongly support an aziridinium mechanism* since direct intermolecular displacement of the triflate group by aniline in type **I** intermediate (Scheme 1) should have led to the formation of the opposite regioisomer. Moreover, this result corroborates with recent literature precedents, which have revealed high levels of regiocontrol in openings of unsymmetrical benzyl aziridinium ions.[15]

These solvent-free conditions were effective across a series of combination of good and weak amine donors (R_1R_2NH and Nu_2, respectively) to give the crossed diamines in the 31–65% range of yields (Table 2). Combined with aniline, piperidine and pyrrolidine displayed quite higher reactivity than morpholine (2 h vs 7 days), and the outcome of their reactions was improved at 40 °C (runs 2 and 3). Generally, a virtually perfect regiocontrol did occur, favouring products of types **12** and **14** resulting from an opening of the aziridinium at the benzylic position (runs 1–4 and 6).[15] Use of diallylamine as the weak nucleophile in combination with

Table 2. Reactions of vinyl triflates **1** and **10** with two amines of different nucleophilicities



12a*t*c-12e*t*c (X = OMe) **13b** (X = OMe, 6%)

14a*t*c-14b*t*c (X = Oxazolidinone) **15b** (X = Oxazolidinone, 11%)[g]

Runs	X	R^1R^2NH (equiv)	Nu_2 (equiv)	Conditions	Products (yields %)[a]		*anti*/*syn*
1[b]	OMe	Morpholine (3)	Aniline (30)	168 h, 20 °C	**12a*t*** (28)	**12a*c*** (36)	56/44[h]
2[c]	OMe	Piperidine (2)	Aniline (30)	2 h, 40 °C	**12b*t*** (27)[d]	**12b*c*** (32)	54/46[h]
3[c]	OMe	Pyrrolidine (2)	Aniline (30)	2 h, 40 °C	**12c*t*** (46)	**12c*c*** (19)	30/70[i]
4[c]	OMe	Morpholine (1.5)	^{t}BuNH$_2$ (30)	30 min, 20 °C	**12d*t*/12d*c*** 1:2 (31)[e]		66/33[h]
5[c]	OMe	Morpholine (1.5)	Diallylamine (30)	24 h, 40 °C	**12e*t*/12e*c*** 1:1 (41)[f]		[j]
6[c]	Oxazolidinone	Morpholine (2)	Aniline (10)	1 h, 20 °C	**14a*t*** (43)	**14a*c*** (8)	16/84[k]
7[c]	Oxazolidinone	Morpholine (2)	Diallylamine (10)	1 h, 20 °C	**14b*t*** (28)	**14b*c*** (10)[g]	[j]

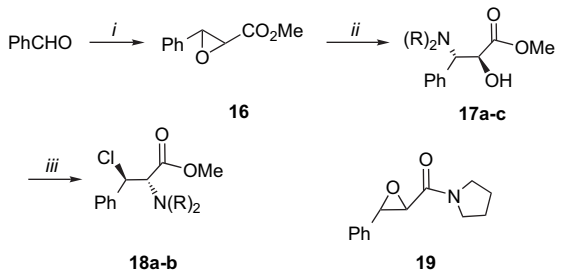
[a] Isolated yields.
[b] When the reaction was carried out at 40 °C, no acceleration was observed and **12a*t*** and **12a*c*** were isolated in 12 and 22% yields, respectively.
[c] Time not optimized.
[d] A pure sample of the less polar adduct **12b*t*** could not be secured due to contamination by the *anti* dipiperidino ester **2g*t***. A similar reaction profile was observed carrying out the reaction at rt.
[e] The adducts were not separable. Moreover, stereomeric aziridine carboxylates and dimorpholino esters **2e*t*–*c*** were also isolated in 25 and 28% yields, respectively.
[f] The regioisomer **13b** (one stereomer, stereochemistry not determined) was isolated in 6% yield.
[g] The regioisomers **15b*t*** and **15b*c*** (stereochemistry not determined) were isolated in 8 and 3% yields, respectively.
[h] Stereochemistry determined by chemical correlation using the Sharpless method[8c,d] (see Table 3 and comments thereof).
[i] Stereochemistry determined by spectroscopic correlation (see Table 3 and comments thereof).
[j] Stereochemistry not determined.
[k] Stereochemistry determined by chemical correlation using the Sharpless method[8c,d] after methanolysis (see Scheme 8 and comments thereof).

morpholine made exception to this rule, with the expected adducts **12e*t*–*c*** and **14b*t*–*c*** being accompanied by low amounts of regioisomers **13** and **15** (runs 5 and 7). This observation compares with the previous Chuang–Sharpless reports and supports the evidence that the nature of the nucleophile is a key parameter in the regiochemical outcome of type **II** aziridinium (Scheme 1) opening.[8c,d] When the imide **10** (X=oxazolidinone) was processed, yields similar to those exhibited in the ester series were observed whereas stereoselectivity was improved (as also previously observed in the case of using only one amine: Scheme 4) and, perhaps more interestingly, its sense reversed (runs 6 and 7 vs runs 1 and 2). The presence of intense peaks for the fragments ions $[C_6H_5CHNHC_6H_5]^+$ and $[C_6H_5CHN(C_3H_5)_2]^+$ in the GC/MS spectra of the major isomers **14a*t*–*c*** and **14b*t*–*c*** accounts for a usual β-selective aziridinium opening pathway, and furthermore proves that the functional group interconversions at the carbonyl moiety is less influential than the amine structure with respect to the regiochemical outcome of aziridinium opening.

Even if closer inspection of the reaction conditions is further needed to maximize the yield of the desired products in these crossed reactions, we have shown for the first time that addition of two different amines to the double bond of activated vinyl triflates is possible through an original pathway including aziridinium ion formation followed by in situ opening by a second amine.

2.3. Stereochemical determination

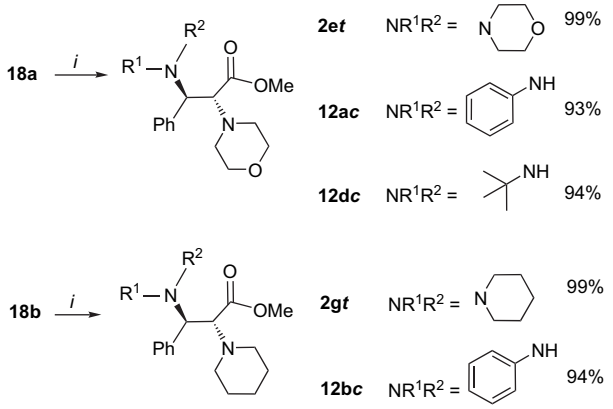
The last part of this work was aimed at determining the stereochemistry of the diamino carboxylic acid derivatives obtained in a stereochemically pure form throughout this study. Several attempts to obtain crystals suitable for X-ray crystallography from diamines **2e*t*–*g*t**, **12a*t*–*c*t** failed. Therefore, we elected to use a sequence recently implemented by Sharpless and Chuang to synthesize *anti* 2,3-diamino ethyl esters from ethyl glycidate.[8c,d] Methyl glycidic ester **16** was synthesized in 48% yield (not optimized) by a Darzens' reaction between α-chloro methyl acetate and benzaldehyde promoted by NaH (Scheme 6). In agreement with the Chuang and Sharpless results, compound **16** was efficiently transformed in two steps into the aziridinium reservoirs **18a** ($N(R)_2$=morpholine) and **18b** ($N(R)_2$=piperidine) as depicted in Scheme 6. The use of pyrrolidine as the amine component was less satisfactory, affording in the oxirane ring opening step the desired amino alcohol **17c** in a disappointing 26% yield after flash-chromatography on silica



Scheme 6. (*i*) α-Chloro methyl acetate (1 equiv), NaH (1 equiv), THF, 0 °C, 1 h, 48% yield; (*ii*) $(R)_2NH$ (1 equiv), MeOH, reflux, 12 h, $(R)_2=(CH_2CH_2)_2O$ **17a** (74%), $(R)_2=(CH_2)_5$ **17b** (78%), $(R)_2=(CH_2)_4$ **17c** (26%); (*iii*) MsCl (1.05 equiv), NEt_3 (1.05 equiv), CH_2Cl_2, 0 °C to rt, 3 h, $(R)_2=(CH_2CH_2)_2O$ **18a** (94%), $(R)_2=(CH_2)_5$ **18b** (96%), $(R)_2=N(CH_2)_4$ **19** (90%).

gel. An even worse result was obtained during the mesylation protocol aimed at producing the required 3-chloro-2-pyrrolidino methyl ester **18c**. The latter was indeed not formed and the oxiranyl *N*-pyrrolidino carboxamide **19** was isolated instead in 90% yield.

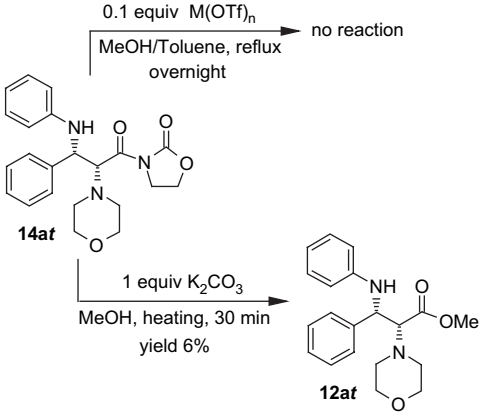
With the stereochemically pure (*anti*) aziridinium ion reservoirs **18a** and **18b** in hand, the stage was now set for the stereochemical establishments. In line with the Chuang–Sharpless results, subjection of **18a** and **18b** to the appropriate amines under optimal conditions (1 equiv each of the amine and K_2CO_3 in refluxing acetonitrile) gave in all cases examined a single product in nearly quantitative yields (Scheme 7). The comparison of the physical and analytical data of the diamino esters so obtained (R_f, mp, ^{1}H NMR spectra) with those obtained through our aza-MIRC approach (Table 3, lines 1 and 2 and 6–8) led to the following conclusions.



Scheme 7. (*i*) K_2CO_3 (1 equiv), R^1R^2NH (1.1 equiv), CH_3CN, reflux, 3 h.

When the cinnamate triflate **1** is processed by 2 equiv of the same amine, the diamino ester with the *anti* stereochemistry is produced as the less polar isomer and, correspondingly, the diamino ester with the *syn* stereochemistry is formed as the more polar isomer. In stark contrast, in the cases of using two different amines, the diamine with the *anti* stereochemistry is formed as the more polar isomer. Key data ascertaining these stereochemical establishments, including R_f values, melting points and chemical shifts in ^{1}H NMR spectroscopy for the MeO group in the case of adducts bearing two identical amino groups (lines 1–5),[19] are provided in Table 3.

To complete this study on the stereochemical outcome of the crossed reactions, we verified whether the rationale applied to the methyl ester series would be also effective in the imide series. To this end, attempts to transform **14a*t*–*c*** into their methyl ester analogues using a recent $Cu(OTf)_2$-catalyzed methanolysis procedure[20] left the substrates untouched (Scheme 8). Processing other metal triflate catalysts (Yb, Sn, Sc) also failed to give the expected esters **12a**. After a considerable number of trials, we found that, when treated with K_2CO_3 (1 equiv) in refluxing dry methanol the less polar (major) oxazolidinone adduct **14a*t*** was totally consumed within 30 min to give several products among them the less polar methyl ester **12a*t*** was isolated in a disappointingly low 6% yield (Scheme 8) and proved to be identical in all respects (R_f, mp, ^{1}H and ^{13}C NMR) with the *syn* adduct **12a*t*** previously characterized. No trace of the diastereoisomer **12a*c*** could be detected. Provided that no epimerization has taken place at the enolizable position, this experiment demonstrates that the stereochemistry of the crossed imide adducts correlates well with that of the corresponding methyl esters, that is, the less polar adduct **14a*t*** is the *syn* isomer and the more polar one **14a*c*** is the *anti* isomer.



Scheme 8.

3. Conclusion

To summarize, we have shown that vinyl triflates of α-keto esters and imides react with secondary amines in solvent-free conditions to provide α,β-diamino carboxylates in good yields, yet modest stereoselectivity through the probable occurrence of an aziridinium ion. This reaction involves an unprecedented aza-MIRC process leading to an aziridinium ion, which is opened in situ by a second equivalent of amine. We have also demonstrated that introduction of two amines of markedly different nucleophilicities may be possible.

4. Experimental

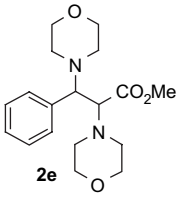
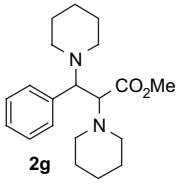
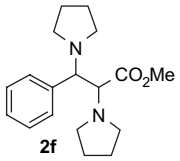
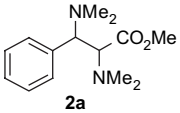
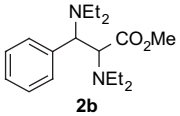
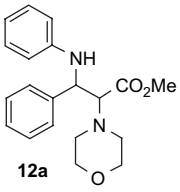
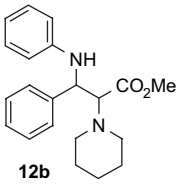
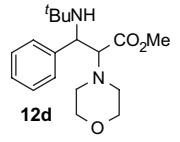
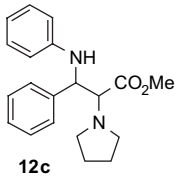
4.1. General

^{1}H and ^{13}C NMR spectra were recorded, respectively, at 200 and 50 MHz. The infrared spectra were recorded on a Perkin–Elmer FT-IR paragon 1000 spectrometer. Thin-layer chromatographies (TLC) were performed with aluminium plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230–400 mesh) was used for flash-chromatography separations. Gas chromatography/mass spectrometry (GC/MS) was performed with a GC apparatus equipped with a 12 m capillary column, at 90 °C for 2 min, then 10 °C min^{-1} up to 290 °C. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France.

4.2. Formation of the vinyl triflates 1, 4, 7 and 10

The preparation and analytical data of the methoxy carbonyls vinyl triflates **1** and **4** were reported recently.[4]

Table 3. Stereochemical establishments for the diamines originating from the methyl cinnamate-derived vinyl triflate **1**

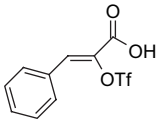
Structure	Stereochemistry	R_f	Mp (°C)	δ MeO[a]
 **2e**	Chuang–Sharpless	0.60[b]	162	3.76
	Aza-MIRC *t anti*	*0.60*	*160–165*	*3.76*
	Aza-MIRC *c*	0.41	100	3.38
 **2g**	Chuang–Sharpless	0.55[c]	102	3.84
	Aza-MIRC *t anti*	*0.55*	*101–103*	*3.84*
	Aza-MIRC *c*	0.38	123–125	3.36
 **2f**	Aza-MIRC *t anti*	*0.68*[d]		*3.69*
	Aza-MIRC *c*	0.37		3.29
 **2a**	Aza-MIRC *t anti*	*0.44*[e]		*3.75*
	Aza-MIRC *c*	0.12		3.38
 **2b**	Aza-MIRC *t anti*	*0.65*[c]		*3.65*
	Aza-MIRC *c*	0.34		3.43
 **12a**	Chuang–Sharpless	0.22[c]	117	3.41
	Aza-MIRC *t*	0.33	135–136	3.52
	Aza-MIRC *c anti*	*0.22*	*116–118*	*3.41*
 **12b**	Chuang–Sharpless	0.43[c]	183	3.40
	Aza-MIRC *t*	0.58	[f]	3.49
	Aza-MIRC *c anti*	*0.43*	*183–184*	*3.40*
 **12d**	Chuang–Sharpless	0.30[c]		3.70
	Aza-MIRC *t*[g]	0.32		3.63
	Aza-MIRC *c anti*	*0.30*		*3.70*
 **12c**	Aza-MIRC *t*	0.60[c]		
	Aza-MIRC *c anti*	*0.42*		

[a] Values in parts per million corresponding to the chemical shift in ^{1}H NMR spectroscopy.
[b] Eluent: cyclohexane/EtOAc 4:6.
[c] Eluent: cyclohexane/EtOAc 8:2.
[d] Eluent: cyclohexane/EtOAc 6:4.
[e] Eluent: cyclohexane/EtOAc 5:5.
[f] No melting point is given due to contamination of the less polar stereomer **12b*t*** by the dipiperidino adduct **2g*t***.
[g] The two stereomers **12d*t*–*c*** were not separated. However, their ratio could be evaluated by ^{1}H NMR spectroscopy (**12dc**/**12d*t***=2:1).

4.2.1. General procedures for the preparation of the imides triflates 7 and 10.

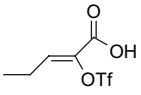
4.2.1.1. Saponification. A solution of anhydrous LiOH (3 equiv) in water (15 ml) was added dropwise over 30 min at 0 °C to a solution of the methyl ester **1** or **4** (1 g) in THF (15 ml). At the end of the addition, the reaction was stirred for an additional period of 15 min at 0 °C. The cryogenic bath was removed and the stirring was pursued for 10 min. An aqueous solution of sodium hydrogen carbonate (10%) was added, the two phases were decanted and the aqueous layer was extracted rapidly three times with ether. The aqueous phase was carefully acidified using 6 M hydrochloric acid, saturated with sodium chloride and extracted three times with dichloromethane. After two washings with brine, drying over magnesium sulfate and evaporation of the solvent, the crystals were dried under high vacuum and used directly without purification.

4.2.1.1.1. (Z)-3-Phenyl-2-trifluoromethylsulfonyloxy propenoic acid.



Yield 60–70%. Pale green solid, mp 104 °C (decomposition); IR (ν, cm^{-1}, $CHCl_3$) 1712; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45–7.55 (m, 3H), 7.65–7.75 (m, 3H), 12 (COOH, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 108.7 (CF_3), 115.1 (CF_3), 121.5 (CF_3), 127.9 (CF_3), 129, 129.4, 130.9, 131.8, 133.7, 133.8, 134.2, 138.2, 166.5.

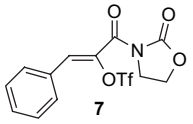
4.2.1.1.2. (Z)-2-Trifluoromethylsulfonyloxy pentenoic acid.



Yield 81%. White solid; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (t, J=7.8 Hz, 3H), 2.41 (quint, J=7.8 Hz, 2H), 6.91 (t, J=7.8 Hz, 1H).

4.2.1.2. Imide formation. To a solution of the above carboxylic acids (1 equiv) in dry dichloromethane (2 ml $mmol^{-1}$) were added dropwise under an argon atmosphere oxalyl chloride (2 equiv) and DMF (one drop). After stirring for 1 h, the volatiles were carefully evaporated and dry tetrahydrofuran (5 mP) was added under argon to the acid chloride. This solution was kept at −80 °C. In the same time, to a solution of 2-oxazolidinone (1.05 equiv) in dry THF (2 ml $mmol^{-1}$) was added under an argon atmosphere at −80 °C a commercially available solution of *n*-butyllithium 1.6 M in hexane (1.05 equiv per substrate equiv). After stirring for 30 min, this solution was added dropwise at −80 °C to the solution of the acid chloride. After stirring for 1 h, water and ethyl ether (5 ml $mmol^{-1}$) and solid NaCl were added until saturation of the aqueous phase. After decantation, the aqueous layer was extracted three times with ethyl ether (5 ml $mmol^{-1}$). The organic layer was dried over magnesium sulfate and concentrated to afford a crude product, which was purified by flash-chromatography.

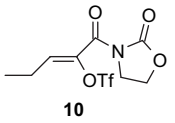
*4.2.1.2.1. (Z)-3-Phenyl-2-trifluoromethanesulfonyloxy propenoic N-oxazolidin-2-one carboxamide (**7**).*



7

Yield 50%. White solid, mp 112 °C; IR (ν, cm^{-1}, $CHCl_3$) 1794.2, 1587.3; ^1H NMR (200 MHz, $CDCl_3$) δ 4.09 (t, J=7.8 Hz, 2H), 4.52 (t, J=7.8 Hz, 2H), 7.09 (s, 1H), 7.4–7.48 (m, 3H), 7.6–7.7 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 43.3, 62.9, 108.7 (CF_3), 115.1 (CF_3), 121.5 (CF_3), 127.9 (CF_3), 128.9, 129.6, 130.7, 131.2, 136.4, 152.1, 162.3; LRMS *m/z* 365 (M^+, 5), 232 (45), 204 (64), 105 (45), 89 (Base). Anal. Calcd for $C_{13}H_{10}NO_6F_3S$ (365.28): C, 42.74; H, 2.76; N, 3.83. Found: C, 42.57; H, 2.98; N, 3.70.

*4.2.1.2.2. (Z)-2-Trifluoromethylsulfonyloxy pentenoic N-oxazolidin-2-one carboxamide (**10**).*



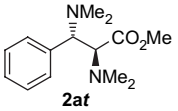
10

Yield 45%. White solid, mp 43 °C; IR (ν, cm^{-1}, $CHCl_3$) 1797.0, 1698.2; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (t, J=7.8 Hz, 3H), 2.39 (quint, J=7.8 Hz, 2H), 4.03 (t, J=7.8 Hz, 2H), 4.46 (t, J=7.8 Hz, 2H), 6.39 (t, J=7.8 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 12.2, 19.9, 43.3, 62.7, 112.1 (CF_3), 116.3 (CF_3), 120.6 (CF_3), 124.8 (CF_3), 137.2, 137.6, 149.0, 161.6; LRMS *m/z* 231 (M^+−96, 2), 184 (32), 114 (29), 88 (67), 69 (Base). Anal. Calcd for $C_9H_{10}NO_6F_3S$ (317.24): C, 34.07; H, 3.17; N, 4.41. Found: C, 34.27; H, 3.09; N, 4.26.

4.3. General procedure for the reaction of amines with the alkoxymethyl vinyl triflates 1 and 4

To 100 mg of the triflate was added in one portion 1 ml of the amine. The mixture was magnetically stirred for 1 h, the excess of solvent was removed under vacuum and the residue was purified by flash-column chromatography, eluting with cyclohexane/EtOAc.

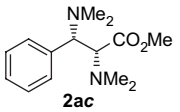
4.3.1. Methyl 2,3-bis-dimethylamino-3-phenyl propanoate (2a). The reaction gave two diastereomers but only the less polar diamino adduct **2a*t*** could be recovered. Eluent used for the flash-column chromatography: cyclohexane/EtOAc 60:40 to EtOAc.



2a*t*

Less polar isomer **2a*t***, R_f=0.44 (cyclohexane/EtOAc 50:50). White solid; yield 31 mg, 38%; mp 101–103 °C; IR (ν, cm^{-1}, $CHCl_3$) 1725.7; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.05 (s, 6H), 2.20 (s, 6H), 3.75 (s, 3H), 3.85 (d, J=11.7 Hz, 1H), 3.99 (d, J=11.7 Hz, 1H), 7.06–7.19 (m, 2H), 7.21–7.41 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 41.2, 41.3, 50.8, 67.5, 67.7, 127.3, 127.6, 129.5,

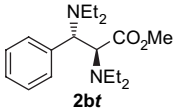
171.5; LRMS *m/z* 205 (M^+-45, <1), 191 (9), 134 (Base). Anal. Calcd for $C_{14}H_{22}O_2N_2$ (250.34): C, 67.17; H, 8.86; N, 11.19. Found: C, 67.27; H, 8.93; N, 11.06.



2ac

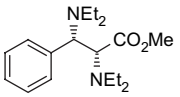
More polar isomer **2ac**, R_f=0.12 (cyclohexane/EtOAc 50:50). White solid; yield 41 mg, 51%; mp 57 °C; IR (*ν*, cm^{-1}, $CHCl_3$) 1725.7; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) *δ* 2.19 (s, 6H), 2.46 (s, 6H), 3.38 (s, 3H), 3.92 (d, *J*=11.7 Hz, 1H), 4.03 (d, *J*=11.7 Hz, 1H), 7.12–7.18 (m, 2H), 7.25–7.39 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) *δ* 40.7, 41.4, 50.5, 66.0, 67.3, 127.6, 127.7, 129.5, 132.7, 169.6; LRMS *m/z* 206 (M^+-44, 1), 191 (6), 134 (Base). Anal. Calcd for $C_{14}H_{22}O_2N_2$ (250.34): C, 67.17; H, 8.86; N, 11.19. Found: C, 67.09; H, 8.95; N, 11.13.

4.3.2. Methyl 2,3-bis-diethylamino-3-phenyl propanoate (2b). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20.



2bt

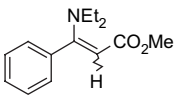
Less polar diastereomer **2bt**, R_f=0.65. Colourless oil; yield 33 mg, 33%; IR (*ν*, cm^{-1}, $CHCl_3$) 1725.7; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) *δ* 0.75 (t, *J*=7.0 Hz, 6H), 0.96 (t, *J*=7.0 Hz, 6H), 1.90–2.12 (m, 2H), 2.20–2.40 (m, 2H), 2.49–2.79 (m, 4H), 3.69 (s, 3H), 4.02 (d, *J*=11.7 Hz, 1H), 4.24 (d, *J*=11.7 Hz, 1H), 7.08–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) *δ* 13.6, 14.0, 44.1, 44.2, 50.5, 63.1, 64.2, 126.7, 127.3, 129.7, 135.5, 173.2; LRMS *m/z* 247 (M^+-59, 2), 175 (2), 162 (80), 91 (Base). Anal. Calcd for $C_{18}H_{30}O_2N_2$ (306.45): C, 70.54; H, 9.86; N, 9.14. Found: C, 70.30; H, 9.99; N, 9.26.



2bc

More polar diastereomer **2bc**, R_f=0.34. Colourless oil; yield 20 mg, 20%; IR (*ν*, cm^{-1}, $CHCl_3$) 1725.7; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) *δ* 1.03 or 1.09 (t, *J*=7.0 Hz, 12H), 2.03–2.19 (m, 2H), 2.29–2.46 (m, 2H), 2.58–2.76 (m, 2H), 2.80–2.99 (m, 2H), 3.43 (s, 3H), 4.02 (d, *J*=10.9 Hz, 1H), 4.25 (d, *J*=10.9 Hz, 1H), 7.12–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) *δ* 13.9, 13.9, 43.2, 44.0, 50.5, 61.5, 64.0, 127.1, 127.8, 128.3, 129.1, 137.2, 172.0; LRMS *m/z* 247 (M^+-59, 2), 175 (2), 162 (80), 91 (Base). Anal. Calcd for $C_{18}H_{30}O_2N_2$ (306.45): C, 70.54; H, 9.86; N, 9.14. Found: C, 70.71; H, 9.97; N, 9.41.

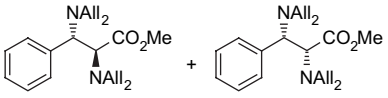
4.3.3. Methyl 3-diethylamino-3-phenyl propenoate (3b).



3b

R_f=0.36. Yellow oil (contaminated by **2bc**); yield 12 mg, 11% (estimated by ^1H NMR spectroscopy); ^1H NMR (200 MHz, $CDCl_3$) *δ* 1.03 or 1.09 (t, *J*=7.0 Hz, 6H), 3.05–3.20 (m, 2H), 3.34 (s, 3H), 4.80 (s, 1H), 7.10–7.20 (m, 3H), 7.35–7.45 (m, 2H).

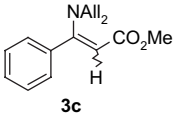
4.3.4. Methyl 2,3-bis-diallylamino-3-phenyl propanoate (2c). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20. Stereomeric adducts **2ct** and **2cc** were obtained as an inseparable mixture in an approximative 2.3:1 ratio. R_f=0.57.



2ct **2cc**

Colourless oil; yield 69 mg, 59%; IR (*ν*, cm^{-1}, $CHCl_3$) 1728.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) *δ* 2.40–2.56 (2dd, *J*=8.6 Hz, 14.1 Hz, 2H, *diast.* 1+*diast.* 2), 2.75–2.95 (2dd, *J*=8.6 Hz, 14.1 Hz, 2H, *diast.* 1+*diast.* 2), 3.2–3.4 (m, 6H, *diast.* 1+*diast.* 2), 3.35 (s, 3H, *diast.* 1), 3.49–3.59 (m, 6H, *diast.* 1+*diast.* 2), 3.73 (s, 3H, *diast.* 2), 4.10 (d, *J*=11.7 Hz, 1H, *diast.* 1), 4.14 (d, *J*=11.7 Hz, 1H, *diast.* 2), 4.28 (d, *J*=11.7 Hz, 1H, *diast.* 1), 4.33 (d, *J*=11.7 Hz, 1H, *diast.* 2), 4.9–5.3 (m, 8H, *diast.* 1+*diast.* 2), 5.2–5.5 (m, 1H, *diast.* 1+*diast.* 2), 5.6–6.0 (m, 3H, *diast.* 1+*diast.* 2), 7.05–7.19 (m, 2H, *diast.* 1+*diast.* 2), 7.22–7.36 (m, 3H, *diast.* 1+*diast.* 2); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) *δ* 50.6, 52.5, 53, 53.3, 53.3, 60.6, 61.8, 62.4, 62.8, 116.8, 116.9, 117, 117.3, 127, 127.4, 127.5, 127.9, 129.3, 129.8, 134.1, 135.4, 136.2, 136.8, 137.3, 137.4, 171.4, 172.6.

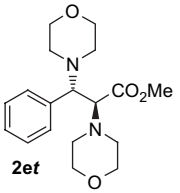
4.3.5. Methyl 3-diallylamino-3-phenyl propenoate (3c).



3c

R_f=0.26. Yellow oil; yield 10 mg, 14%; IR (*ν*, cm^{-1}, $CHCl_3$) 1725.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) *δ* 3.43 (s, 3H), 3.7–3.8 (m, 4H), 4.89 (s, 1H), 5.10–5.30 (m, 4H), 5.60–5.85 (m, 2H), 7.15–7.25 (m, 2H), 7.35–7.45 (m, 3H); LRMS *m/z* 258 (M^++1, 3), 257 (M^+, 27), 226 (22), 216 (33), 186 (Base).

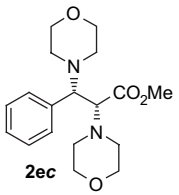
4.3.6. Methyl 2,3-dimorpholino-3-phenyl propanoate (2e). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 40:60.



2et

Less polar diastereomer **2et**, R_f=0.60. White solid; yield 33 mg, 61%; mp 160–63 °C; IR (*ν*, cm^{-1}, $CHCl_3$) 1728.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) *δ* 2.10–2.26 (m, 2H), 2.39–2.65 (m, 6H), 3.19–3.36 (m, 2H), 3.36–3.48 (m, 2H), 3.51–3.59 (m, 4H), 3.76 (s, 3H), 3.85 (d, *J*=11.7 Hz, 1H),

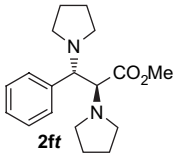
4.02 (d, J=11.7 Hz, 1H), 7.05–7.12 (m, 2H), 7.25–7.36 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 49.6, 49.9, 50.9, 67.1, 67.4, 67.7, 67.8, 127.4, 127.6, 129.2, 133.1, 171.5; LRMS m/z 275 (M^+-59, 5), 176 (Base). Anal. Calcd for $C_{18}H_{26}O_4N_2$ (334.42): C, 64.65; H, 8.08; N, 8.37. Found: C, 64.89; H, 8.29; N, 8.26.



2ec

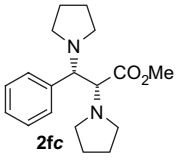
More polar diastereomer **2ec**, R_f=0.41. Yellow solid; yield 12 mg, 23%; mp 100 °C; IR (ν, cm^{-1}, $CHCl_3$) 1731.1 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.34–2.60 (m, 4H), 2.68–2.90 (m, 4H), 3.38 (s, 3H), 3.60–3.75 (m, 8H), 3.87 (d, J=11.7 Hz, 1H), 4.05 (d, J=11.7 Hz, 1H), 7.07–7.17 (m, 2H), 7.23–7.35 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 49.2, 49.7, 51.0, 66.0, 67.2, 67.5, 67.7, 127.9, 128.0, 129.1, 134.2, 170.0; LRMS m/z 275 (M^+-59, 5), 176 (Base). Anal. Calcd for $C_{18}H_{26}O_4N_2$ (334.42): C, 64.65; H, 8.08; N, 8.37. Found: C, 64.71; H, 8.16; N, 8.31.

4.3.7. Methyl 2,3-dipyrrolidino-3-phenyl propanoate (2f). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 60:40.



2ft

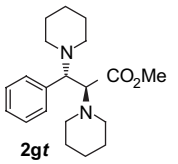
Less polar diastereomer **2ft**, R_f=0.68. Yellow solid; yield 25 mg, 51%; mp 99–102 °C; IR (ν, cm^{-1}, $CHCl_3$) 1725.7; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.35–1.62 (m, 8H), 2.19–2.56 (m, 6H), 2.57–2.74 (m, 2H), 3.69 (s, 3H), 4.06 (d, J=11.7 Hz, 1H), 4.24 (d, J=11.7 Hz, 1H), 7.09–7.20 (m, 2H), 7.21–7.36 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 22.7, 23.4, 47.9, 49.1, 50.9, 65.1, 66.5, 127.0, 127.4, 129.6, 134.2, 172.8; 243 (M^+-59, 3), 160 (Base). Anal. Calcd for $C_{18}H_{26}O_2N_2$ (302.42): C, 71.49; H, 8.66; N, 9.26. Found: C, 71.62; H, 8.81; N, 9.13.



2fc

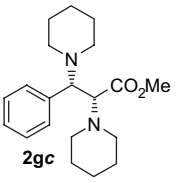
More polar diastereomer **2fc**, R_f=0.37. White solid; yield 9 mg, 18%; mp 78–81 °C; IR (ν, cm^{-1}, $CHCl_3$) 1725.4; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.52–1.80 (m, 8H), 2.33–245 (m, 2H), 2.55–2.92 (m, 6H), 3.29 (s, 3H), 3.88 (d, J=9.4 Hz, 1H), 3.98 (d, J=9.4 Hz, 1H), 7.10–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 22.9, 23.5, 49.7, 50.6, 51.1, 67.4, 68.4, 127.4, 127.7, 129.2, 170.6; LRMS m/z 243 (M^+-59, 3), 160 (Base). Anal. Calcd for $C_{18}H_{26}O_2N_2$ (302.42): C, 71.49; H, 8.66; N, 9.26. Found: C, 71.73; H, 8.52; N, 9.11.

4.3.8. Methyl 2,3-dipiperidino-3-phenyl propanoate (2g). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20.



2gt

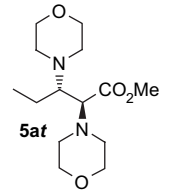
Less polar diastereomer **2gt**, R_f=0.55. White solid; yield 40 mg, 70%; mp 101–103 °C; IR (ν, cm^{-1}, $CHCl_3$) 1726.9; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.97–1.54 (m, 12H, piperidine), 1.97–2.18 (m, 2H), 2.31–2.58 (m, 6H), 3.72 (s, 3H), 3.84 (d, J=11.7 Hz, 1H), 4.02 (d, J=11.7 Hz, 1H), 7.02–7.17 (m, 2H), 7.18–7.35 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 24.5, 26.3, 26.8, 50.5, 50.6, 51.0, 68.4, 68.6, 126.7, 127.2, 129.4, 134.4, 172.3; LRMS m/z 243 (M^+-31, 4), 174 (Base). Anal. Calcd for $C_{20}H_{30}O_2N_2$ (330.47): C, 72.69; H, 8.15; N, 8.47. Found: C, 72.53; H, 8.06; N, 8.44.



2gc

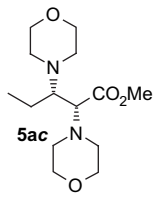
More polar diastereomer **2gc**, R_f=0.38. White solid; yield 18 mg, 30%; mp 123–125 °C; IR (ν, cm^{-1}, $CHCl_3$) 1731.9; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.20–1.62 (m, 12H), 2.20–2.52 (m, 4H), 2.60–2.80 (m, 4H), 3.36 (s, 3H), 3.84 (d, J=11.7 Hz, 1H), 4.03 (d, J=11.7 Hz, 1H), 7.08–7.15 (m, 2H), 7.19–7.31 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 24.7, 24.9, 26.7, 26.9, 50.1, 50.5, 50.6, 66.7, 67.9, 127.2, 127.7, 129.1, 135.5, 171.0; LRMS m/z 243 (M^+-31, 4), 174 (Base). Anal. Calcd for $C_{20}H_{30}O_2N_2$ (330.47): C, 72.69; H, 8.15; N, 8.47. Found: C, 72.93; H, 8.38; N, 8.57.

4.3.9. Methyl 2,3-dimorpholino pentanoate (5a). Only the less polar diastereoisomer could be isolated in pure form. Eluent used for the flash-column chromatography: cyclohexane/EtOAc 60:40.



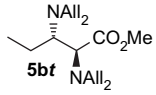
5at

Less polar diastereomer **5at**, R_f=0.40. White solid; yield 44 mg, 43%; mp 109 °C; IR (ν, cm^{-1}, $CHCl_3$) 1691.1; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.0 (t, J=7.8 Hz, 3H), 1.30–1.80 (m, 2H), 2.42–2.60 (m, 6H), 2.64–2.89 (m, 3H), 3.09 (d, J=10.9 Hz, 1H), 3.42–3.70 (m, 8H), 3.67 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.2, 20.6, 49.8, 50.2, 50.6, 63.8, 67.4, 67.9, 71.2, 171.5; LRMS m/z 227 (M^+-59, 20), 128 (Base). Anal. Calcd for $C_{14}H_{26}O_4N_2$ (286.37): C, 58.72; H, 9.15; N, 9.78. Found: C, 58.83; H, 9.07; N, 9.54.

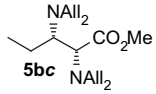


More polar diastereomer **5ac**, R_f=0.34 (contaminated by the first diastereomer). Orange solid; yield 21 mg, 36%; mp 69–70 °C; IR (ν, cm^{-1}, $CHCl_3$) 1725.7; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.91 (t, J=7.8 Hz, 3H), 1.30–1.80 (m, 2H), 2.47–2.60 (m, 6H), 2.7–2.96 (m, 3H), 3.18 (d, J=9.4 Hz, 1H), 3.42–3.70 (m, 8H), 3.67 (s, 3H).

4.3.10. Methyl 2,3-bis-diallylamino pentanoate (5b). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 95:05.

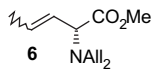


Less polar diastereomer **5b*t***, R_f=0.40. Yellow oil; yield 10 mg, 9%; IR (ν, cm^{-1}, $CHCl_3$) 1725.7; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.95 (t, J=7.04 Hz, 3H), 1.32–1.76 (m, 2H), 2.70–3.50 (m, 10H), 3.64 (s, 3H), 4.98–5.22 (m, 8H), 5.53–5.83 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 13.1, 21.1, 50.4, 53.6, 54.0, 59.6, 66.2, 116.0, 117.0, 136.4, 137.8, 172.5; LRMS *m/z* 247 (M−59, 6), 138 (Base). Anal. Calcd for $C_{18}H_{30}O_2N_2$ (306.45): C, 70.54; H, 9.86; N, 8.47. Found: C, 70.83; H, 10.13; N, 8.24.



More polar diastereomer **5b*c***, R_f=0.28. Yellow oil; yield 12 mg, 11%; IR (ν, cm^{-1}, $CHCl_3$) 1722.9; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.88 (t, J=7.04 Hz, 3H), 0.92–1.80 (m, 2H), 2.70–3.55 (m, 10H), 3.64 (s, 3H), 4.94–5.30 (m, 8H), 5.54–5.91 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 12.1, 23.0, 50.7, 52.9, 53.8, 58.0, 64.8, 115.7, 117.5, 136.4, 138.5, 172.0; LRMS *m/z* 247 (M−59, 6), 138 (Base). Anal. Calcd for $C_{18}H_{30}O_2N_2$ (306.45): C, 70.54; H, 9.86; N, 8.47. Found: C, 70.64; H, 10.00; N, 8.39.

4.3.11. Methyl 2-diallylamino pent-3-enoate (6).

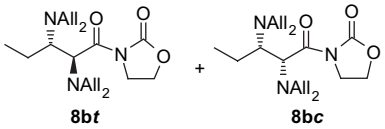


R_f=0.14. Yellow oil; yield 46 mg, 65%; IR (ν, cm^{-1}, $CHCl_3$) 1731.1; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.71 (d, J=6.3 Hz, 3H), 3.08–3.3 (d, J=6.3 Hz, 4H), 3.68 (s, 3H), 3.91 (d, J=7.8 Hz, 1H), 5.05–5.22 (m, 4H), 5.42–5.90 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 18.0, 51.6, 53.5, 65.7, 117.7, 125.6, 131.2, 135.6, 172.9; LRMS *m/z* 209 (M^+, 1), 182 (6), 150 (Base). Anal. Calcd for $C_{12}H_{19}O_2N$ (209.29): C, 68.86; H, 9.15; N, 6.69. Found: C, 68.77; H, 9.19; N, 6.81.

4.4. General procedure for the reaction of diallylamine with the oxazolidinone vinyl triflates 7 and 10

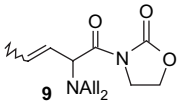
To 100 mg of the triflate was added in one portion 4 equiv of diallylamine (0.15 ml for the reaction with triflate **7**, 0.13 ml for the reaction with triflate **10**). The mixture was magnetically stirred for 5 h (case of triflate **7**) or for 20 h (case of triflate **10**) and directly purified by flash-column chromatography, eluting with cyclohexane/EtOAc 60:40.

4.4.1. 2,3-Bis-diallylamino pentanoic *N*-oxazolidin-2-one carboxamide (8b). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 60:40. Stereomeric adducts **8b*t*** and **8b*c*** were obtained as an inseparable mixture in a nearly 1.5:1 ratio. R_f=0.53.



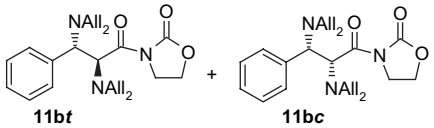
Colourless oil; yield 63 mg, 68%; IR (ν, cm^{-1}, $CHCl_3$) 1690.0, 1775.0 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.87 (t, J=7.04 Hz, 3H, *diast.* 1), 0.99 (t, J=7.04 Hz, 3H, *diast.* 2), 0.9–1.1 (m, 1H, *diast.* 2), 1.35–1.50 (m, 1H, *diast.* 2), 1.50–1.75 (m, 2H, *diast.* 1), 2.89–3.57 (m, 10H, *diast.* 1+*diast.* 2), 3.97 (t, J=8.6 Hz, 2H, *diast.* 1+*diast.* 2), 4.32 (t, J=8.6 Hz, 2H, *diast.* 1), 4.34 (t, J=8.6 Hz, 2H, *diast.* 2), 4.95–5.3 (m, 8H, *diast.* 1+*diast.* 2), 5.51–5.96 (m, 4H, *diast.* 1+*diast.* 2); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 12.1, 13.4, 20.9, 22.2, 42.3 (2), 52.9, 53.2, 53.5, 53.9, 58.6, 60.3, 61.5, 61.7, 61.8, 62.6, 115.6 (2), 116.4, 116.9, 136.1, 136.2, 137.2, 138.5, 153.3, 153.5, 173.2, 173.8.

4.4.2. (*Z* or *E*)-2-Diallylamino pent-3-enoic *N*-oxazolidin-2-one carboxamide (9).



R_f=0.34. Yellow oil; yield 13 mg, 23%; IR (ν, cm^{-1}, $CHCl_3$) 1698.2, 1780.5; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.72 (d, J=6.3 Hz, 3H), 2.89–3.40 (m, 4H), 3.98 (t, J=7.8 Hz, 2H), 4.37 (t, J=7.8 Hz, 2H), 5.05–5.25 (m, 4H), 5.31 (d, J=7.8 Hz, 1H), 5.46–5.95 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 18.2, 42.6, 53.9, 62.0, 62.8, 117.5, 124.8, 135.7, 152.7, 174.9; LRMS *m/z* 264 (M^+, <1), 223 (6), 150 (Base). Anal. Calcd for $C_{14}H_{20}O_3N_2$ (264.32): C, 63.61; H, 7.62; N, 10.60. Found: C, 63.68; H, 7.70; N, 10.43.

4.4.3. 2,3-Bis-diallylamino-3-phenyl propanoic *N*-oxazolidin-2-one carboxamide (11b). Stereomeric adducts **11b*t*** and **11b*c*** were obtained as an inseparable mixture in a nearly 7:1 ratio. Eluent used for the flash-column chromatography: cyclohexane/EtOAc 70:30. R_f=0.5.

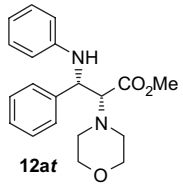


Colourless oil; yield 91 mg, 91%; IR (ν, cm^{-1}, $CHCl_3$) 1692.7, 1775.0; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.4 (dd, J=7.8 Hz, 14.8 Hz, 2H, *diast.* 2), 2.62 (dd, J=8.6 Hz, 14.1 Hz, 2H, *diast.* 1), 3.30–3.8 (m, 8H, *diast.* 1+*diast.* 2), 3.91–4.25 (m, 1H, *diast.* 1+*diast.* 2), 4.3–4.5 (m, 1H, *diast.* 1+*diast.* 2), 4.4 (d, J=10.9 Hz, 1H, *diast.* 1+*diast.* 2), 5.05–5.25 (m, 8H, *diast.* 1+*diast.* 2), 5.7 (d, J=10.9 Hz, 1H, *diast.* 1+*diast.* 2), 5.8–6 (m, 4H, *diast.* 1+*diast.* 2); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 42.3, 52.9, 53.2, 59.7, 61.5, 62.0, 116.1, 116.2 (*diast. min.*), 116.3 (*diast. min.*), 117.0, 127.4, 127.5 (*diast. min.*), 127.8, 129.6, 130.0 (*diast. min.*), 135.1, 136.0 (*diast. min.*), 136.9 (*diast. min.*), 137.2, 152.8, 172.8.

4.5. Crossed reactions of two different amines with vinyl triflate 1

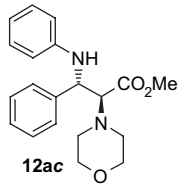
4.5.1. General procedure. To 100 mg of the triflate **1** were successively added in one portion 30 equiv of the less nucleophilic amine (0.88 ml aniline or 1 ml *tert*-butylamine or 1.19 ml diallylamine) and the more nucleophilic amine: morpholine (3 equiv, 89 µl), piperidine (2 equiv, 73 µl), pyrrolidine (2 equiv, 53 µl) (cases of aniline and *tert*-butylamine), or morpholine (1.5 equiv, 44 µl) (case of diallylamine). The mixture was stirred at the temperature indicated in Table 2 until total disappearance of the starting material (TLC monitoring). The excess of the less nucleophilic amine was removed under vacuum and the crude mixture was directly purified by flash-column chromatography, eluting with cyclohexane/EtOAc.

4.5.1.1. Methyl 3-anilino-2-morpholino-3-phenyl propanoate (12a). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20.



12a*t*

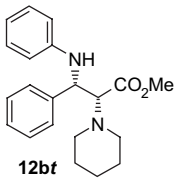
Less polar diastereomer **12a*t***, R_f=0.33. Yellow solid; yield 28 mg, 28%; mp 135–136 °C; IR (ν, cm^{-1}, $CHCl_3$) 1731.3; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.50–2.75 (m, 4H), 3.32 (d, J=10.9 Hz, 1H), 3.52 (s, 3H), 3.59–3.82 (m, 4H), 4.49 (d, J=10.9 Hz, 1H), 5.34 (s, 1H, NH), 6.51 (d, J=8.6 Hz, 2H), 6.66 (t, J=7.04 Hz, 1H), 7.05 (t, J=8.6 Hz, 2H), 7.20–7.35 (m, 3H), 7.40–7.48 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 49.5, 51.1, 56.0, 67.4, 73.6, 113.9, 118.0, 127.4, 127.8, 128.7, 129.1, 140.7, 147.8, 169.0; LRMS m/z 340 (M^+, 10), 281 (35), 180 (Base). Anal. Calcd for $C_{20}H_{24}O_3N_2$ (340.42): C, 70.56; H, 7.10; N, 8.23. Found: C, 70.64; H, 7.25; N, 8.15.



12ac

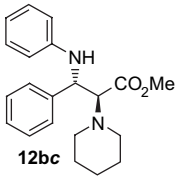
More polar diastereomer **12a*c***, R_f=0.22. White solid; yield 35 mg, 35%; mp 116–118 °C; IR (ν, cm^{-1}, $CHCl_3$) 1736.9; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.42–2.68 (m, 4H), 3.31 (d, J=6.3 Hz, 1H), 3.41 (s, 3H), 3.61–3.72 (t, J=4.7 Hz, 4H), 4.72 (d, J=6.3 Hz, 1H), 6.51 (d, J=8.6 Hz, 2H), 6.63 (t, J=7.0 Hz, 1H), 7.07 (dd, J=7.0 Hz, 8.6 Hz, 2H), 7.20–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 51.1, 51.4, 56.4, 66.8, 74.0, 113.3, 117.5, 126.6, 127.6, 128.5, 129.1, 139.5, 146.9, 170.8; LRMS m/z 340 (M^+, 10), 281 (35); 180 (Base). Anal. Calcd for $C_{20}H_{24}O_3N_2$ (340.42): C, 70.56; H, 7.10; N, 8.23. Found: C, 70.71; H, 7.28; N, 8.11.

4.5.1.2. Methyl 3-anilino-2-piperidino-3-phenyl propanoate (12b). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20.



12b*t*

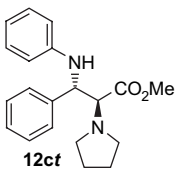
Less polar diastereomer **12b*t*** (contaminated by the dipiperidino compound **2g*t***; **12b*t*/2g*t***=1:0.66 deduced from the ^1H NMR spectrum), R_f=0.58. Yellow solid; yield 48 mg (29 mg **12b*t***, 19 mg **2g*t***), 27%; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.35–1.78 (m, 6H), 2.38–2.57 (m, 4H), 3.26 (d, J=10.2 Hz, 1H), 3.49 (s, 3H), 4.45 (d, J=10.2 Hz, 1H), 5.5 (s, 1H, NH), 6.49 (d, J=7.8 Hz, 2H), 6.62 (t, J=7.0 Hz, 1H), 7.0–7.15 (m, 2H), 7.20–7.35 (m, 3H), 7.41 (d, J=7.0 Hz, 2H).



12bc

More polar diastereomer **12b*c***, R_f=0.43. White solid; yield 35 mg, 32%; mp 183–184 °C; IR (ν, cm^{-1}, $CHCl_3$) 1731.1; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.35–1.78 (m, 6H), 2.38–2.57 (m, 4H), 3.26 (d, J=6.2 Hz, 1H), 3.40 (s, 3H), 4.70 (d, J=6.2 Hz, 1H), 5.2 (s, 1H, NH), 6.51 (d, J=7.0 Hz, 2H), 6.66 (t, J=7.0 Hz, 1H), 7.05 (t, J=7.0 Hz, 2H), 7.20–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 24.3, 25.9, 51.2, 51.9, 56.6, 74.6, 113.4, 117.3, 126.8, 127.4, 128.4, 129.0, 140.0, 146.2, 171.4; LRMS m/z 194 (M^+−156, 1); 182 (Base). Anal. Calcd for $C_{21}H_{26}O_2N_2$ (338.46): C, 74.52; H, 7.74; N, 8.27. Found: C, 74.41; H, 7.88; N, 8.11.

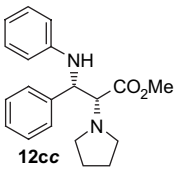
4.5.1.3. Methyl 3-anilino-2-pyrrolidino-3-phenyl propanoate (12c). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20.



12c*t*

Less polar diastereomer **12c*t***, R_f=0.60. White solid; yield 48 mg, 46%; mp 134–135 °C; IR (ν, cm^{-1}, $CHCl_3$) 1725.7; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.72–1.85 (m, 4H), 2.60–2.75 (m, 2H), 2.80–2.97 (m, 2H), 3.48 (s, 3H), 3.65

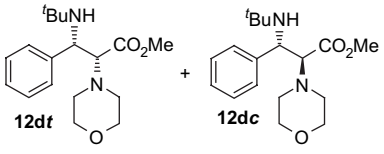
(d, J=10.2 Hz, 1H), 4.49 (d, J=10.2 Hz, 1H), 5.0 (s, 1H, NH), 6.54 (d, J=8.6 Hz, 2H), 6.66 (t, J=7.0 Hz, 1H), 7.06 (dd, J=7.0 Hz, 8.6 Hz, 2H), 7.18–7.38 (m, 3H), 7.46 (d, J=7.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 23.5, 48.2, 50.9, 58.1, 69.5, 114.0, 117.7, 127.3, 127.6, 128.5, 128.9, 141.1, 148.1, 170.1; LRMS m/z 194 (M^+-130, 1), 182 (Base). Anal. Calcd for $C_{20}H_{24}O_2N_2$ (324.42): C, 74.04; H, 7.45; N, 8.63. Found: C, 73.94; H, 7.52; N, 8.55.



12cc

More polar diastereomer **12cc**, R_f=0.42. Pale yellow oil; yield 18 mg, 17%; IR (ν, cm^{-1}, $CHCl_3$) 1736.9; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.75–1.90 (m, 4H), 2.55–2.72 (m, 4H), 3.28 (d, J=4.7 Hz, 1H), 3.42 (s, 3H), 4.65 (d, J=4.7 Hz, 1H), 5.45 (br, 1H, NH), 6.53 (d, J=7.8 Hz, 2H), 6.65 (t, J=7.8 Hz, 1H), 7.08 (t, J=7.0 Hz, 2H), 7.23–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 23.2, 51.4, 51.8, 58.8, 73.6, 113.2, 117.1, 126.5, 127.5, 128.5, 129.0, 139.8, 147.4, 171.4; LRMS m/z 194 (M^+-130, 1), 182 (Base). Anal. Calcd for $C_{20}H_{24}O_2N_2$ (324.42): C, 74.04; H, 7.45; N, 8.63. Found: C, 74.09; H, 7.48; N, 8.39.

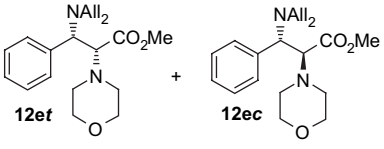
4.5.1.4. Methyl 3-*tert*-butylamino-2-morpholino-3-phenyl propanoate (12d). The stereomeric adducts **12d*t*** and **12d*c*** were obtained as an inseparable mixture in an approximative 1:2 ratio. Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20.



12dt **12dc**

R_f=0.32. White solid; yield 33 mg, 31%; IR (ν, cm^{-1}, $CHCl_3$) 1728.4; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 0.81 (s, 9H, *diast. min.*), 0.85 (s, 9H, *diast. maj.*), 2.05–2.5 (m, 4H, *diast. min.*+*diast. maj.*), 3.11 (d, J=10.9 Hz, 1H, *diast. min.*), 3.25–3.35 (m, 4H, *diast. min.*), 3.40–3.50 (m, 4H, *diast. maj.*), 3.55 (d, J=10.9 Hz, 1H, *diast. maj.*), 3.63 (s, 3H, *diast. min.*), 3.70 (s, 3H, *diast. maj.*), 3.98 (d, J=10.9 Hz, 1H, *diast. maj.*), 4.04 (d, J=10.9 Hz, 1H, *diast. min.*), 7.20–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 29.1 and 30.3, 49.9 and 50.3, 50.8 and 51.7, 55.9 and 57.3, 67.4 and 67.5, 73.0 and 75.3, 126.7, 127.1, 127.7, 127.9, 128.0, 128.6, 129.4, 133.0, 171.0 and 177.0; LRMS m/z 248 (M^+-72, 1), 106 (Base).

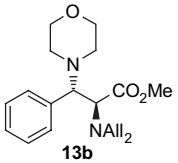
4.5.1.5. Methyl 3-diallylamino-2-morpholino-3-phenyl propanoate (12e). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 80:20. Stereomeric adducts **12e*t*** and **12e*c*** were obtained as an inseparable mixture of diastereomers in a nearly 1:1 ratio.



12et **12ec**

R_f=0.40. White solid; yield 44 mg, 41%; mp 108 °C; IR (ν, cm^{-1}, $CHCl_3$) 1728.4; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.40–2.92 (m, 6H, *diast.* 1+*diast.* 2), 3.22–3.5 (m, 4H, *diast.* 1+*diast.* 2), 3.42 (s, 3H, *diast.* 1), 3.71–3.78 (m, 2H, *diast.* 1+*diast.* 2), 3.78 (s, 3H, *diast.* 2), 3.89 (d, J=11.7 Hz, 1H, *diast.* 1), 3.93 (d, J=11.7 Hz, 1H, *diast.* 2), 4.31 (d, J=11.7 Hz, 1H, *diast.* 1), 4.36 (d, J=11.7 Hz, 1H, *diast.* 2), 5.10–5.25 (m, 4H), 5.62–5.95 (m, 2H), 7.15–7.25 (m, 2H), 7.30–7.42 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 49.7 (CH_2), 50.8 (CH_3), 52.7 (CH_2), 53.4 (CH_2), 60.3 (CH), 60.6 (CH), 67.2 (CH_2), 67.6 (CH_2), 116.9 (CH_2), 127.1 (CH), 127.5 (CH), 127.6 (CH), 128.0 (CH), 129.2 (CH), 129.4 (CH), 137.1 (CH), 137.4 (CH), 170.0 (C=O), 171.3 (C=O); LRMS m/z 285 (M^+-59, 8), 186 (92). Anal. Calcd for $C_{20}H_{28}O_3N_2$ (344.46): C, 69.74; H, 8.19; N, 8.13. Found: C, 69.69; H, 8.25; N, 8.21.

4.5.1.6. Methyl 2-diallylamino-3-morpholino-3-phenyl propanoate (13b). This product was obtained as a single stereomer.



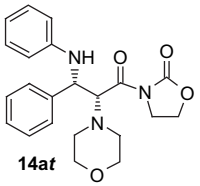
13b

R_f=0.45. Colourless oil; yield 6 mg, 6%; IR (ν, cm^{-1}, $CHCl_3$) 1695.5, 1777.8; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.28–2.52 (m, 4H), 2.93 (dd, J=7.05 Hz, 14.1 Hz, 2H), 3.37 (s, 3H), 3.45–3.75 (m, 6H), 4.01 (d, J=11.7 Hz, 1H), 4.10 (d, J=11.7 Hz, 1H), 5.05–5.3 (m, 4H), 5.75–5.95 (m, 2H), 7.08–7.19 (m, 2H), 7.23–7.38 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 49.4, 50.8, 53.3, 62.0, 67.2, 67.4, 117.1, 127.7, 127.9, 129.2, 136.8, 171.3; LRMS m/z 285 (10, M^+-59, 2), 176 (Base). Anal. Calcd for $C_{20}H_{28}O_3N_2$ (344.46): C, 69.74; H, 8.19; N, 8.13. Found: C, 69.86; H, 8.33; N, 7.96.

4.6. Crossed reactions of two different amines with vinyl triflate 10

4.6.1. General procedure. To a mixture of 10 equiv of the less nucleophilic amine (0.25 ml aniline or 0.33 ml diallylamine) and 2 equiv of the more nucleophilic amine (48 µl morpholine) was added 100 mg of the triflate in one portion. The mixture was stirred for 3 h, the residual less nucleophilic amine was removed under vacuum and the crude mixture directly purified by flash-column chromatography, eluting with cyclohexane/EtOAc.

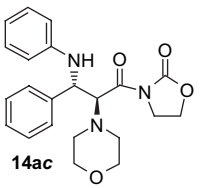
4.6.1.1. 3-Anilino-2-morpholino-3-phenyl pentanoic *N*-oxazolidin-2-one carboxamide (14a). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 40:60.



14at

Less polar diastereomer **14a*t***, R_f=0.36. White solid; yield 46 mg, 43%; mp 170–173 °C; IR (ν, cm^{-1}, $CHCl_3$)

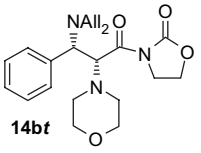
1783.3; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.57–2.88 (m, 4H), 3.43–4.27 (m, 6H), 4.38–4.59 (d+t, J_d=10.2 Hz, J_t=7.4 Hz, 3H), 5.22 (d, J=10.2 Hz, 1H), 5.22 (s, 1H, NH), 6.52 (d, J=8.6 Hz, 2H), 6.60–6.8 (m, 1H), 7.05 (t, J=8.6 Hz, 2H), 7.20–7.35 (m, 3H), 7.40–7.48 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 42.2, 47.8, 49.3, 57.0, 61.7, 62.8, 67.5, 67.6, 113.1, 113.9, 118.0, 118.1, 127.8, 127.9, 128.5, 129.0, 129.3, 140.0, 147.9, 152.7, 170.3; LRMS *m*/*z* 213 (M^+−182, 3), 182 (Base). Anal. Calcd for $C_{22}H_{25}O_4N_3$ (395.46): C, 66.82; H, 6.37; N, 10.62. Found: C, 66.89; H, 6.43; N, 10.38.



14a*c*

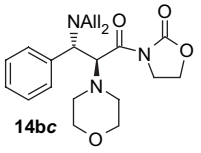
More polar diastereomer **14a*c***, R_f=0.31.Yellow solid; yield 8 mg, 8%; mp 170 °C; IR (ν, cm^{-1}, $CHCl_3$) 1777.8; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.51–2.78 (m, 4H), 3.37–3.74 (m, 5H), 3.74–4.0 (m, 2H), 4.12–4.33 (m, 1H), 4.83 (d, J=7.8 Hz, 1H), 5.16 (d, J=7.8 Hz, 1H), 6.54 (d, J=7.8 Hz, 2H), 6.64 (t, J=7.8 Hz, 1H), 7.07 (t, J=7.8 Hz, 2H), 7.16–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 42.5, 50.6, 57.0, 61.9, 67.0, 67.8, 113.8, 117.8, 126.9, 127.6, 128.5, 129.1, 139.7, 146.7, 173.3, 181.5; LRMS *m*/*z* 213 (M^+−182, 3), 182 (Base).

4.6.1.2. 3-Diallylamino-2-morpholino-3-phenyl pentanoic *N*-oxazolidin-2-one carboxamide (14b). Eluent used for the flash-column chromatography: cyclohexane/EtOAc 50:50.



14b*t*

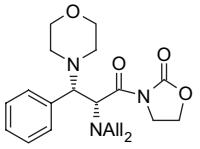
Less polar diastereomer **14b*t***, R_f=0.30. Colourless oil; yield 30 mg, 28%; IR (ν, cm^{-1}, $CHCl_3$) 1775.0, 1695.5; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.65 (dd, J=8.6 Hz, 13.3 Hz, 2H), 2.85–3.0 (m, 3.5H), 3.4–3.65 (m, 3.5H), 3.65–3.80 (m, 3.5H), 3.80–3.95 (m, 1H), 4.02–4.35 (m, 2.5H), 4.44 (d, J=11.7 Hz, 1H), 5.1–5.3 (m, 4H), 5.69 (d, J=11.7 Hz, 1H), 5.80–6.05 (m, 2H), 7.15–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.1, 49.5, 52.9, 60.6, 61.6, 61.9, 67.8, 117.2, 127.4, 128, 129.3, 129.7, 135.0, 137.0, 153.3, 170.1; LRMS *m*/*z* 287 (M^++2−114, 2), 186 (Base). Anal. Calcd for $C_{22}H_{29}O_4N_3$ (399.49): C, 66.14; H, 7.31; N, 10.52. Found: C, 66.28; H, 7.49; N, 10.28.



14b*c*

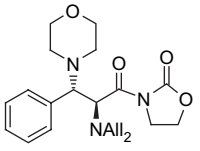
More polar diastereomer **14b*c***, R_f=0.14. Yellow oil; yield 11 mg, 10%; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.6 (dd, J=8.6 Hz, 14.1 Hz, 2H), 2.85–2.95 (m, 3H), 3.4–3.9 (m, 7H), 4.03–4.15 (m, 1H), 4.19–4.32 (m, 1H), 4.4 (d, J=11.7 Hz, 1H), 5.05–5.3 (m, 4H), 5.65 (d, J=11.7 Hz, 1H), 5.7–5.95 (m, 2H), 7.15–7.45 (m, 5H); LRMS *m*/*z* 287 (M^++2−114, 2), 186 (Base).

4.6.1.3. 2-Diallylamino-3-morpholino-3-phenyl pentanoic *N*-oxazolidin-2-one carboxamide (15).



15b*t*

Less polar diastereomer **15b*t***, R_f=0.51. Colourless oil; yield 8 mg, 8%; IR (ν, cm^{-1}, $CHCl_3$) 1725.7; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.28–2.42 (m, 2H), 2.5–2.65 (m, 2H), 3.30–3.80 (m, 10H), 3.9–4.4 (m, 2H), 4.2 (d, J=11.7 Hz, 1H), 5.1–5.3 (m, 4H), 5.67 (d, J=11.7 Hz, 1H), 5.75–5.98 (m, 2H), 7.1–7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 42.4, 49.7, 53.6, 61.7, 67.2, 68.0, 77.2, 116.3, 127.8, 128.0, 128.6, 129.3, 137.2, 153.0, 170.2; LRMS *m*/*z* 223 (M^+−176, 1), 176 (Base).



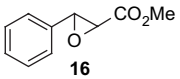
15b*c*

More polar diastereomer **15b*c***, R_f=0.34. Colourless oil; yield 3 mg, 3%; IR (ν, cm^{-1}, $CHCl_3$) 1775.04, 1695.48; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.35–2.52 (m, 4H), 2.55–2.7 (m, 2H), 3.12–3.35 (m, 6H), 4.0–4.1 (m, 2H), 4.3–4.42 (m, 2H), 4.35 (d, J=12.5 Hz, 1H), 5.0–5.15 (m, 4H), 5.5–5.7 (m, 2H), 5.67 (d, J=12.5 Hz, 1H), 7.12–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 42.4, 49.5, 53.4, 61.3, 61.8, 62.2, 67.3, 116.3, 127.2, 127.6, 129.7, 134.0, 136.8, 153.0, 171.7; LRMS *m*/*z* 223 (M^+−176, 10), 176 (Base).

4.7. Stereochemical determinations

4.7.1. Stereochemical determination of diamine carboxylates.

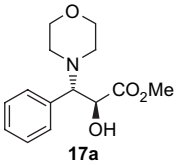
4.7.1.1. Methyl 3-phenyl glycidate (16). To a solution of benzaldehyde (10.6 g, 100 mmol) and methyl chloro acetate (10.86 g, 100 mmol) in dry tetrahydrofuran (200 ml) was added NaH (4 g, 100 mmol, 60% in suspension in oil) by small portions at 0 °C. After stirring for 1 h, the solution was quenched with an aqueous solution of 0.5 M HCl (100 ml). Ether (100 ml) was added, the aqueous layer was extracted three times with ether (30 ml) and the combined organic layers were dried over $MgSO_4$. After concentration under vacuum, the crude mixture was purified by flash-column chromatography, eluting with cyclohexane/EtOAc 80:20 (R_f=0.18), to afford the title compound as a colourless oil (8.1 g, 48% yield).



16

^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 3.51 (d, J=1.6 Hz, 1H), 3.82 (s, 3H), 4.08 (d, J=1.6 Hz, 1H), 7.20–7.40 (m, 5H).

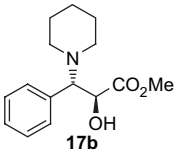
4.7.1.2. Methyl 2-hydroxy-3-morpholino-3-phenylpropanoate (17a). The title compound was synthesized using the Sharpless protocol[8c,d] (epoxy ester **16** 4.6 g, 25.84 mmol, morpholine 2.26 ml, 25.84 mmol, methanol 25 ml). Recrystallization of the crude product from ether gave the pure regioisomer **17a** (5 g, 74%) as a colourless crystalline solid.



17a

Mp 96 °C; R_f=0.18 (cyclohexane/EtOAc 6:4); IR (ν, cm^{-1}, $CHCl_3$) 1739.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.38–2.65 (m, 4H+OH), 3.57 (d, J=3.9 Hz, 1H), 3.62 (s, 3H), 3.73 (t, J=4.7 Hz, 4H), 4.79 (d, J=3.9 Hz, 1H), 7.30–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 51.5, 52.2, 67.0, 70.1, 72.3, 128.2, 128.3, 129.0, 135.5, 173.1; LRMS m/z 206 (M^+-59, 2), 176 (Base). Anal. Calcd for $C_{14}H_{19}O_4N$ (265.31): C, 63.38; H, 7.21; N, 5.28. Found: C, 63.33; H, 7.34; N, 5.24.

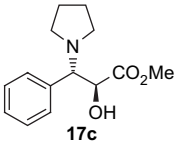
4.7.1.3. Methyl 2-hydroxy-3-piperidino-3-phenylpropanoate (17b). The title compound was synthesized using the Sharpless protocol[8c,d] (epoxy ester **16** 3 g, 16.85 mmol, piperidine 1.75 ml, 17.69 mmol, methanol 19 ml). Purification of the crude product by flash-column chromatography, eluting with cyclohexane/EtOAc 5:5 gave the pure regioisomer **17b** as the major compound (3.5 g, 78%) as a colourless crystalline solid (the other regioisomer was also isolated (188 mg, 4%).



17b

Mp 88 °C; R_f=0.32 (cyclohexane/EtOAc 5:5); IR (ν, cm^{-1}, $CHCl_3$) 1739.4; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.32–1.70 (m, 6H), 1.6 (br s, 1H), 2.35–2.5 (m, 4H), 3.58 (s, 3H), 3.59 (d, J=5.5 Hz, 1H), 4.81 (d, J=5.5 Hz, 1H), 7.29–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.3, 26.1, 51.9, 52.0, 70.7, 72.5, 127.9, 128.1, 129.0, 136.1, 173.3; LRMS m/z 204 (M^+-59, 5), 174 (Base). Anal. Calcd for $C_{15}H_{21}O_3N$ (263.34): C, 68.41; H, 8.03; N, 5.32. Found: C, 68.48; H, 7.99; N, 5.35.

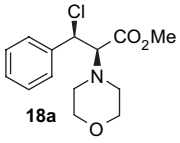
4.7.1.4. Methyl 2-hydroxy-3-pyrrolidino-3-phenylpropanoate (17c). The title compound was synthesized using the Sharpless protocol[8c,d] (epoxy ester **16** 3.5 g, 19.74 mmol, pyrrolidine 1.73 ml, 20.73 mmol, methanol 20 ml). Purification of the crude product by flash-column chromatography, eluting with cyclohexane/EtOAc 3:7 to 0:10 gave the epoxide amide **19** (600 mg, 13%) and the desired pure regioisomer **17c** (1.3 g, 26%) as colourless crystalline solids.



17c

Mp 84 °C; R_f=0.16 (cyclohexane/EtOAc 2:8); IR (ν, cm^{-1}, $CHCl_3$) 1646.1; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.75–1.85 (br s, 1H+m, 4H), 2.45–2.6 (m, 2H), 2.62–2.76 (m, 2H), 3.56 (d, J=3.1 Hz, 1H), 3.58 (s, 3H), 4.72 (d, J=3.1 Hz, 1H), 7.24–7.39 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4, 52.1, 52.8, 72.3, 72.4, 128.0, 128.1, 128.6, 137.4, 172.5; LRMS m/z 218 (M^+-31, 2), 82 (Base). Anal. Calcd for $C_{14}H_{19}O_3N$ (249.31): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.72; H, 7.79; N, 5.57.

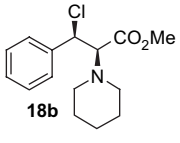
4.7.1.5. Methyl 3-chloro-2-morpholino-3-phenylpropanoate (18a). The title compound was synthesized using the Sharpless protocol[8c,d] (amino alcohol **17a** 4.24 g, 16 mmol, triethylamine 2.45 ml, 17.6 mmol, methanesulfonyl chloride 1.36 ml, 17.6 mmol, dichloromethane 16 ml). After stirring for 3 h, the ammonium mesylate was removed by treating the solution on a plug of silica gel, eluting with ether. Concentration under vacuum afforded **18a** (4.41 g, 97%, colourless crystalline solid) as a regioisomeric 3:1 mixture.



18a

Mp 112–113 °C; R_f=0.57 (cyclohexane/EtOAc 6:4); IR (ν, cm^{-1}, $CHCl_3$) 1733.9; ^1H NMR (200 MHz, $CDCl_3$, 25 °C) δ 2.25–2.72 (m, 4H, two regioisomers), 3.28–3.45 (m, 4H, major regioisomer), 3.28–3.45 (m, 4H, major regioisomer), 3.55–3.62 (m, 4H, minor regioisomer), 3.74 (d, J=10.9 Hz, 1H, major regioisomer), 3.84 (s, 3H, two regioisomers), 4.08 (d, J=10.9 Hz, 1H, minor regioisomer), 4.78 (d, J=10.9 Hz, 1H, minor regioisomer), 5.16 (d, J=10.9 Hz, 1H, major regioisomer), 7.30–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.1, 51.6, 52.7 (minor), 55.3 (minor), 59.1, 61.9 (minor), 67.0, 67.2 (minor), 72.2 (minor), 73.6, 127.8, 128.2 (minor), 128.3 (minor), 128.4, 128.6, 128.9 (minor), 138.4, 169.2; LRMS m/z 224 (M^+-59, 16), 158 (Base). Anal. Calcd for $C_{14}H_{18}O_3NCl$ (283.75): C, 59.26; H, 6.39; N, 4.94. Found: C, 59.33; H, 6.41; N, 5.01.

4.7.1.6. Methyl 3-chloro-2-piperidino-3-phenylpropanoate (18b). The title compound was synthesized using the Sharpless protocol[8c,d] (amino alcohol **17b** 2.48 g, 9.43 mmol, triethylamine 1.44 ml, 10.37 mmol, methanesulfonyl chloride 802 µl, 10.37 mmol, dichloromethane 10 ml). After stirring for 3 h, the ammonium mesylate was removed by treating the solution on a plug of silica gel, eluting with ether. Concentration under vacuum afforded the pure regioisomer **18b** (2.53 g, 96%) as a colourless crystalline solid. In contrast to its morpholino analogue **18a**, compound **18b** decomposes on standing at room temperature and therefore must be stored in the freezer at −20 °C. At this temperature, **18b** is indefinitely quite stable.

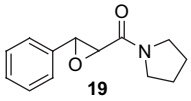


18b

Mp 88 °C; R_f=0.69 (cyclohexane/EtOAc 8:2); IR (ν, cm^{-1}, $CHCl_3$) 1731.1; ^1H NMR (200 MHz, $CDCl_3$, 25 °C)

δ 1.1–1.3 (br s, 1H+m, 6H), 2.20–2.35 (m, 2H), 2.50–2.65 (m, 2H), 3.71 (d, *J*=11 Hz, 1H), 3.83 (s, 3H), 5.17 (d, *J*=11 Hz, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.2, 26.2, 51.1, 51.3, 59.6, 74.2, 127.9, 128.2, 128.3, 138.9, 169.7; LRMS *m/z* 246 (M^+−35, 2), 156 (Base). Anal. Calcd for $C_{15}H_{20}O_2NCl$ (281.78): C, 63.94; H, 7.15; N, 4.97. Found: C, 63.90; H, 7.21; N, 4.91.

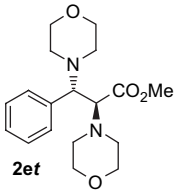
4.7.1.7. *trans*-2,3-Epoxy-3-phenyl-propenoic *N*,*N*-pyrrolidinylcarboxamide (19). The title compound was obtained instead of the expected chloro amine **18c** using the Sharpless protocol[8c,d] (amino alcohol **17c** 1.3 g, 5.22 mmol, triethylamine 800 µl, 5.74 mmol, methanesulfonyl chloride 444 µl, 5.74 mmol, dichloromethane 5 ml). After stirring for 3 h, the ammonium mesylate was removed by filtering the solution on a plug of silica gel, eluting with ether. Concentration under vacuum afforded the pure compound **19** (1.02 g, 90%) as a colourless crystalline solid.



19

Mp 56 °C; R_f=0.25 (cyclohexane/EtOAc 3:7); IR (*ν*, cm^{-1}, $CHCl_3$) 1739.4; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ 1.85–2.15 (m, 4H), 2.52–3.75 (m, 4H), 3.57 (d, *J*=1.6 Hz, 1H), 4.15 (d, *J*=1.6 Hz, 1H), 7.32–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.3, 51.9, 52.6, 72.2, 125.6, 127.5, 127.9, 135.7, 172.4; LRMS *m/z* 217 (M^+, 7), 82 (Base). Anal. Calcd for $C_{13}H_{15}O_2N$ (217.76): C, 71.86; H, 6.96; N, 6.44. Found: C, 72.0; H, 6.91; N, 6.31.

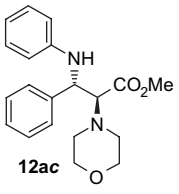
4.7.1.8. Methyl 2,3-dimorpholino-3-phenyl propanoate (2e*t*).



2e*t*

The title compound was synthesized using the Sharpless protocol[8c,d] (amino chloride **18a** 284 mg, 1 mmol, K_2CO_3 138 mg, 1 mmol, morpholine 96 µl, 1.1 mmol, acetonitrile 2 ml). The pure compound **2e** so obtained (331 mg, 99%) gave analytical data identical in all respects with those described for the less polar product **2e*t*** obtained by our aza-MIRC methodology.

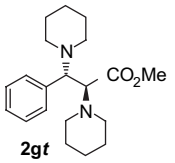
4.7.1.9. Methyl 3-anilino-2-morpholino-3-phenyl propanoate (12a*c*).



12ac

The title compound was synthesized using the Sharpless protocol[8c,d] (amino chloride **18a** 284 mg, 1 mmol, K_2CO_3 138 mg, 1 mmol, aniline 100 µl, 1.1 mmol, acetonitrile 2 ml). The pure compound **12a** so obtained (316 mg, 93%) gave analytical data identical in all respects with those described for the more polar product **12a*c*** obtained by our aza-MIRC methodology.

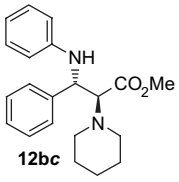
4.7.1.10. Methyl 2,3-dipiperidino-3-phenyl propanoate (2g*t*).



2g*t*

The title compound was synthesized using the Sharpless protocol[8c,d] (amino chloride **18b** 282 mg, 1 mmol, K_2CO_3 138 mg, 1 mmol, morpholine 109 µl, 1.1 mmol, acetonitrile 2 ml). The pure compound **2g** so obtained (327 mg, 99%) gave analytical data identical in all respects with those described for the less polar product **2g*t*** obtained by our aza-MIRC methodology.

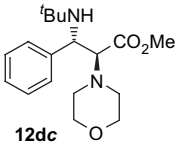
4.7.1.11. Methyl 3-anilino-2-piperidino-3-phenyl propanoate (12b*c*).



12bc

The title compound was synthesized using the Sharpless protocol[8c,d] (amino chloride **18b** 282 mg, 1 mmol, K_2CO_3 138 mg, 1 mmol, aniline 100 µl, 1.1 mmol, acetonitrile 2 ml). The pure compound **12b** so obtained (317 mg, 94%) gave analytical data identical in all respects with those described for the more polar product **12b*c*** obtained by our aza-MIRC methodology.

4.7.1.12. Methyl 3-*tert*-butylamino-2-morpholino-3-phenyl propanoate (12d*c*).



12dc

The title compound was synthesized using the Sharpless protocol[8c,d] (amino chloride **18a** 284 mg, 1 mmol, K_2CO_3 138 mg, 1 mmol, *tert*-butylamine 114 µl, 1.1 mmol, acetonitrile 2 ml). The ^{1}H NMR spectrum of the pure compound **12d** so obtained (300 mg, 94%, mp 90 °C) exhibited signals identical to those of the major stereomer in the adduct **12d*t*–*c*** obtained by our aza-MIRC methodology. ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.4, 50.3, 50.8, 51.3, 55.9, 67.2, 75.4, 126.7, 127.1, 128.0, 133.0, 171.0. Anal. Calcd for $C_{18}H_{28}O_3N_2$ (320.43): C, 67.47; H, 8.82; N, 8.74. Found: C, 67.64; H, 8.95; N, 8.85.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.085.

References and notes

1. For recent reviews on tandem reactions, see: (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957; (d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (e) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (f) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619; (g) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143.
2. To the best of our knowledge, only a few examples of use of this class of compounds, each dealing with Pd-catalyzed coupling reactions, have been reported. See: (a) Beccalli, E. M.; Gelmi, M. L.; Marchesini, A. *Tetrahedron* **1998**, *54*, 6909; (b) Beccalli, E. M.; Clerici, F. L.; Marchesini, A. *Tetrahedron* **2000**, *56*, 2699; (c) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 3105; (d) Siegel, K.; Brückner, R. *Chem.—Eur. J.* **1998**, *4*, 1116; (e) Kalwinsh, I.; Metten, K.; Brückner, R. *Heterocycles* **1995**, *40*, 939.
3. Dalla, V.; Decroix, B. *Tetrahedron Lett.* **2002**, *43*, 1657.
4. Tranchant, M. J.; Dalla, V.; Jabin, I.; Decroix, B. *Tetrahedron* **2002**, *58*, 8425.
5. See also: (a) de Saint-Fuscien, C.; Tarrade, A.; Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **2000**, *41*, 6393; (b) Tarrade, A.; Dauban, P.; Dodd, R. H. *J. Org. Chem.* **2003**, *68*, 9521.
6. For some recent developments in the aza-MIRC chemistry: (a) For the use of α,β-unsaturated carbonyl derivatives α-substituted by a leaving group. See Ref. 5 and references therein; (b) For the use of *N*-alkoxy amines, see: Cardillo, G.; Gentilucci, L.; De Matteis, V. *J. Org. Chem.* **2002**, *67*, 5957 and Ref. 8 cited therein; (c) For the use of nosyloxycarbamates, see: Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A. *Tetrahedron* **1998**, *54*, 6169; Fioravanti, S.; Pellacani, L.; Morreale, S.; Tardella, P. A. *Synthesis* **2001**, 1975; Fioravanti, S.; Pellacani, L.; Morreale, S.; Tardella, P. A. *J. Org. Chem.* **2002**, *67*, 4972.
7. Recently, a comparable but inverse approach for accessing transient aziridinium ions, based on sequential alkylation followed by aza-Michael addition of N–H aziridine to electron-deficient 6-iodo alkynes, has been published. Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545.
8. For some recent leading references in the chemistry of aziridinium ions, see: (a) de Sousa, S. E.; O'Brien, P.; Ploumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483; (b) O'Brien, P.; Towers, T. D. *J. Org. Chem.* **2002**, *67*, 304; (c) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 1435; (d) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555; (e) Liu, K.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511; (f) Rayner, C. M. *Synlett* **1997**, 11; (g) Graham, M. A.; Wadsworth, A. H.; Zahid, A.; Rayner, C. M. *Org. Biomol. Chem.* **2003**, *1*, 834; (h) Couty, F.; Evano, G.; Prim, D. *Tetrahedron Lett.* **2005**, *46*, 2253.
9. For the utility of α,β-diamino acids and esters, see the following reviews: (a) Lucet, D.; Le Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580; (b) Viso, A.; Fernandez de le Pradilla, R.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
10. In the course of related work aimed at developing these reactions in solution, we discovered that dissolving compound **1** in freshly distilled DMF which had been refluxed overnight on potassium hydroxide produced a smooth reaction leading to the α,β-diamino adducts **2a*t*–*c***. Applying this procedure to an *m*-nitro aryl analogue of **1** as the vinyl triflate component even gave a spontaneous and exothermic reaction furnishing the stereomeric diamino adducts within few minutes. This technique may be considered as a valuable water-free source of dimethylamine.
11. Letters *t* and *c* referred to the less and more polar diastereomers, respectively. The stereochemical attribution of these adducts has been made by chemical correlation using the Sharpless methodology[8c,d] (details are included in Section 2.3 at the end of the manuscript).
12. The formation of type **3** enamines was a major problem encountered during the development of similar reactions in solution. After screening various solvents, it was found that reaction could be conducted efficiently in DME, enamine formation being reduced to a great extent. Dalla, V.; Tranchant, M. J., unpublished results.
13. Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183.
14. Diallylamine is expected to be a higher nucleophile than dibenzylamine. This seems to be confirmed by the results in Table 1, runs 4 and 5.
15. For previous studies documenting the highly regioselective opening of benzylic aziridinium salts, see: (a) Refs. 8a–d and 8h of the present article; (b) Dieter, K. R.; Deo, N.; Lagu, B.; Dieter, L. W. *J. Org. Chem.* **1992**, *57*, 1663; (c) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670; (d) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585; (e) Rossiter, B. E.; Miao, G. *J. Org. Chem.* **1995**, *60*, 8424; (f) Saravanan, P.; Bisai, A.; Baktharanan, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693; (g) Andrews, D. R.; Dahanukar, V. H.; Eckert, J. M.; Gala, D.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A. *Tetrahedron Lett.* **2002**, *43*, 6121.
16. See Ref. 6b.
17. For representative example, see Refs. 8a–d (especially Ref. 8b) of the present manuscript and references cited therein.
18. No substantial enhancement of the reaction rate was observed at 40 °C, these conditions actually compromising the reaction profile, with notable formation of increased quantities of dimorpholino adducts **2e*t*–*c***.
19. Unfortunately, no NMR correlations were found for the crossed diamino esters and therefore no conclusive evidence could be drawn for the overall series (Table 3, case of **12c**, last line). Also, the NMR correlation did not match the diamines **5a–b*t*–*c*** derived from the β-ethyl vinyl triflate **4** (see Scheme 2), the stereochemistry of which, therefore, could not be determined.
20. Orita, A.; Nagano, Y.; Hirano, J.; Otera, J. *Synlett* **2001**, 637.