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Tetrahedron

Tetrahedron Vol. 61, No. 52, 2005

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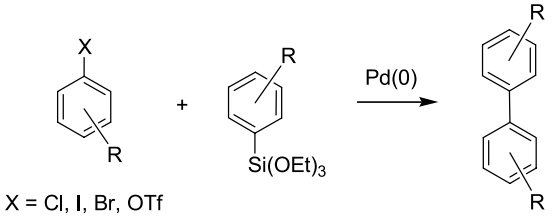

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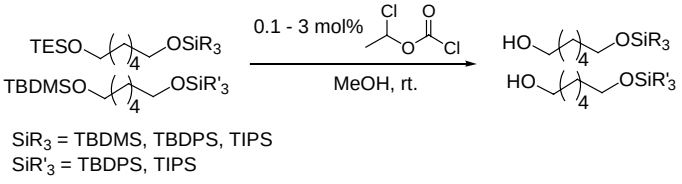

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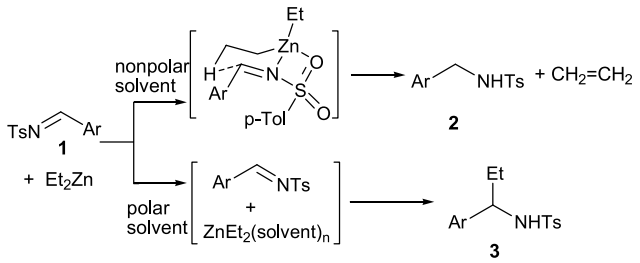

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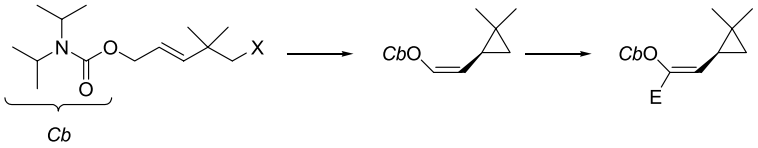

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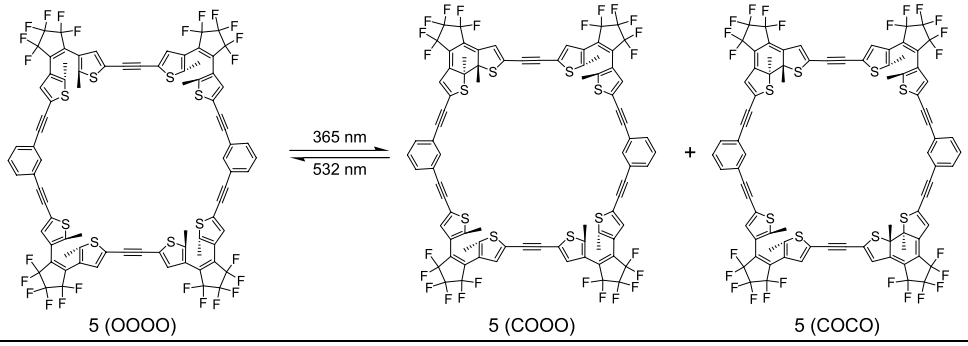

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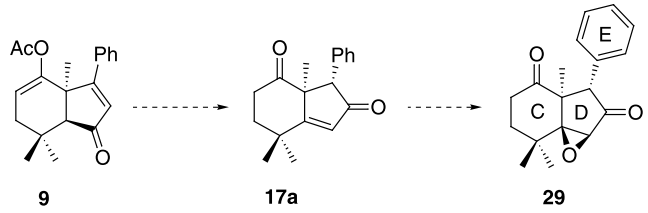

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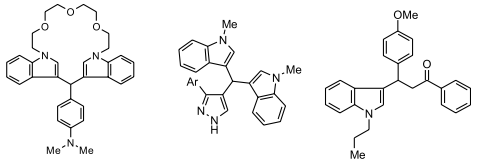

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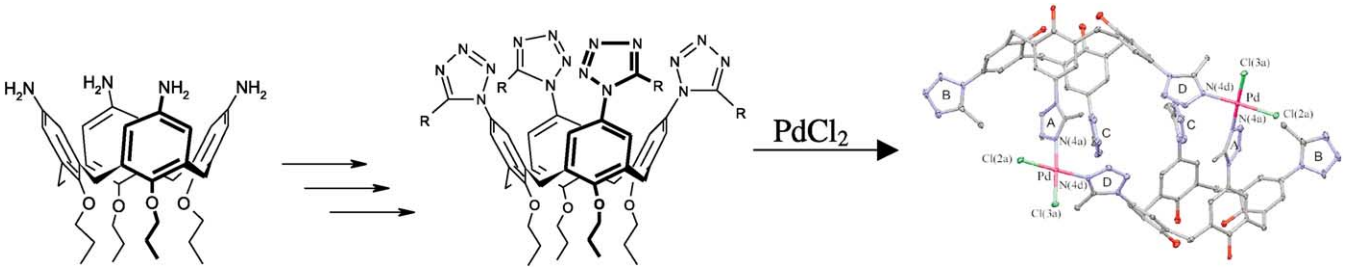

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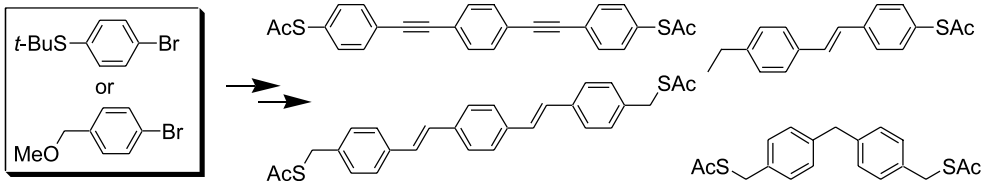

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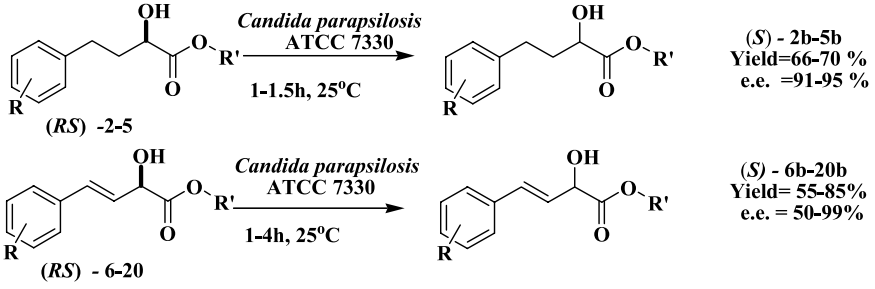

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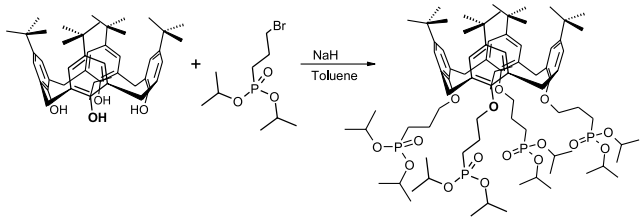

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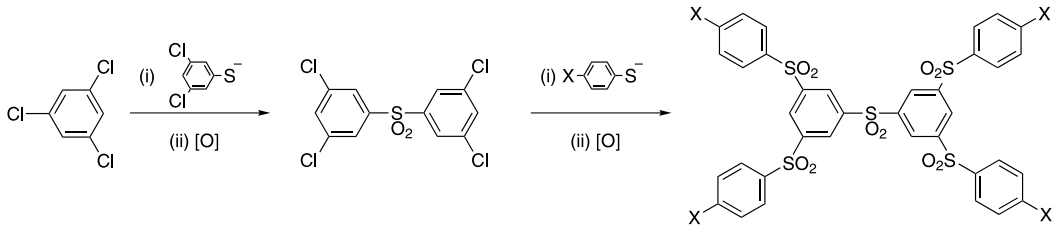

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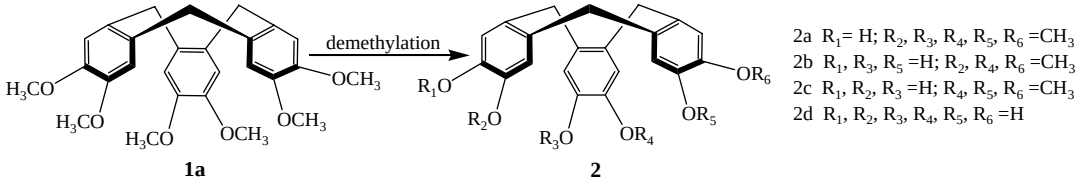

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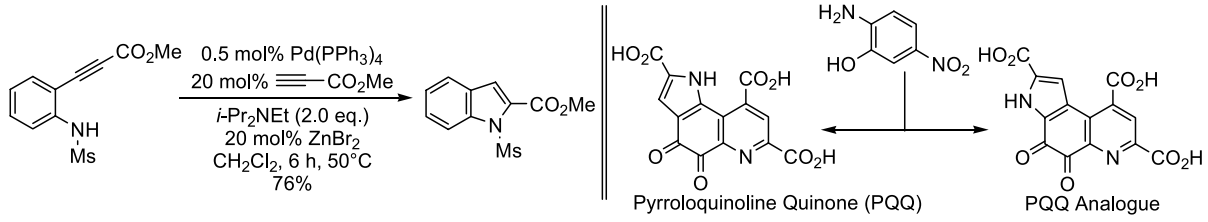

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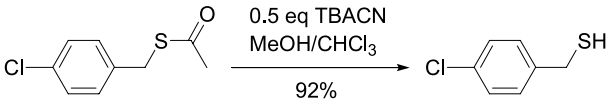

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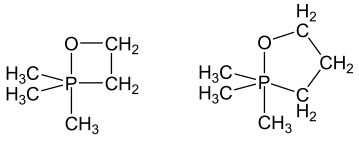
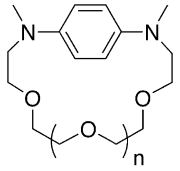


The first ab initio calculations, using scaled DFT and EMPI methods, of the ^{31}P NMR chemical shift of phosphoranes have given satisfactory values with a root-mean-square-error of 15–20 ppm from experimental shifts. The calculations are useful in predicting shifts for new compounds. Of special interest are calculations for the cyclic compounds illustrated above. The shifts are δ −97.7 and δ −89.8, respectively, and are quite unlike shifts around δ +19 reported for some P-phenyl derivatives purported to have the five-membered ring system. These shifts suggest instead 4-coordinate (phosphonium) phosphorus.

Wurster's crownophanes: an alternate topology for *para*-phenylenediamine-based macrocycles **pp 12350–12357**
John W. Sibert,* Greg R. Hundt, Andrew L. Sargent* and Vincent Lynch



Herein, we describe the synthesis and properties of Wurster's crownophanes. These electrochemically active macrocycles can be viewed as cyclophane/crown ether hybrid structures and represent an alternate architecture for the incorporation of phenylenediamine into a macrocyclic framework. The largest member studied showed an affinity for alkaline earth metal cations and ammonium.

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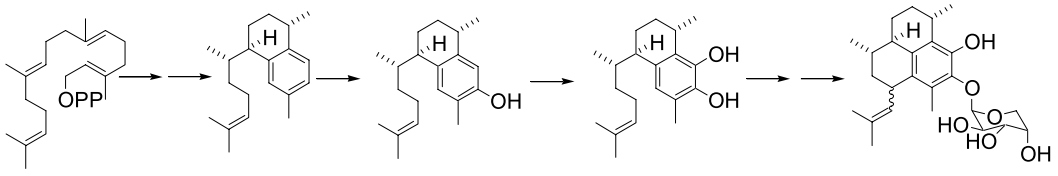

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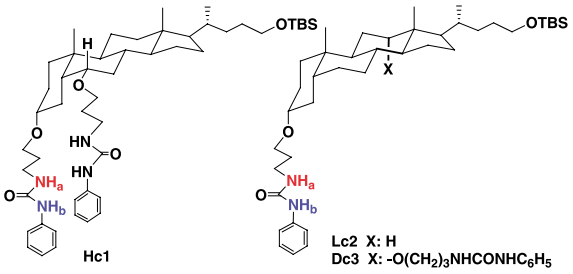

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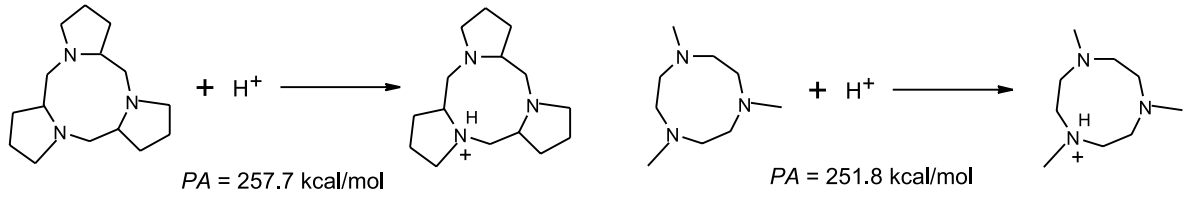

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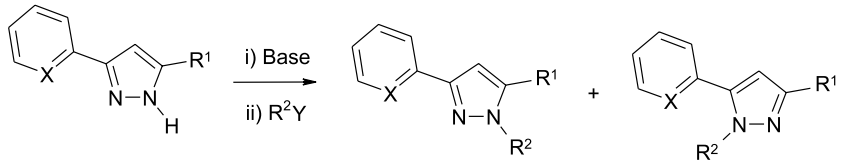

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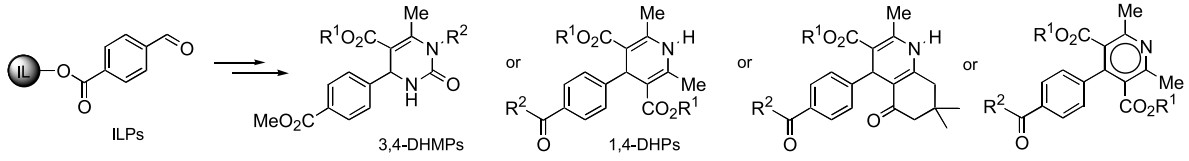

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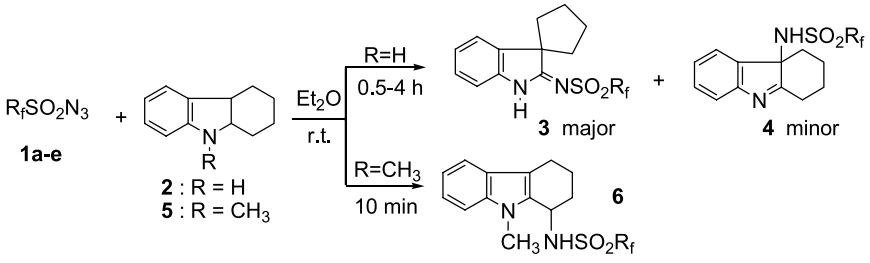

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ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 12201–12225

Tetrahedron report number 744

Recent advances in siloxane-based aryl–aryl coupling reactions: focus on heteroaromatic systems

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Received 16 August 2005

Available online 8 September 2005

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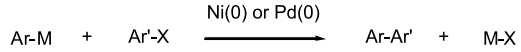
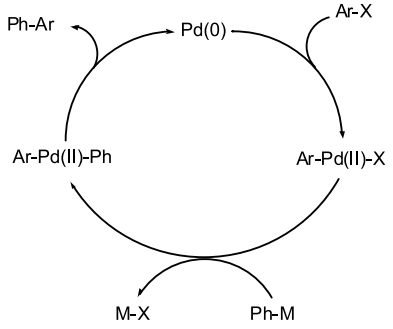
1. Introduction

The efficient formation of carbon–carbon bonds is among the most crucial transformations in synthetic chemistry. The palladium-catalyzed aryl–aryl cross-coupling reaction is one such route to these bond formations, and structurally complex products may be obtained in one step by reaction of a nucleophilic organometallic species with an electrophile, such as an aryl halide (Scheme 1). The reaction, typically, is catalyzed by group VIII transition metals, with nickel and palladium as the two metals most frequently employed as catalysts in cross-coupling reactions.[1]



Scheme 1.

Traditional methods that have been employed to accomplish this transformation include the Stille[1–6] and Suzuki[3,5,7–10] reactions. The accepted catalytic cycle for these reactions, which employ Pd(0) as the catalyst, centers around a standard oxidative addition/transmetallation/reductive elimination sequence of steps (Scheme 2).[9]



Scheme 2.

Keywords: Cross-coupling; Aryl siloxane; Palladium-catalyzed.
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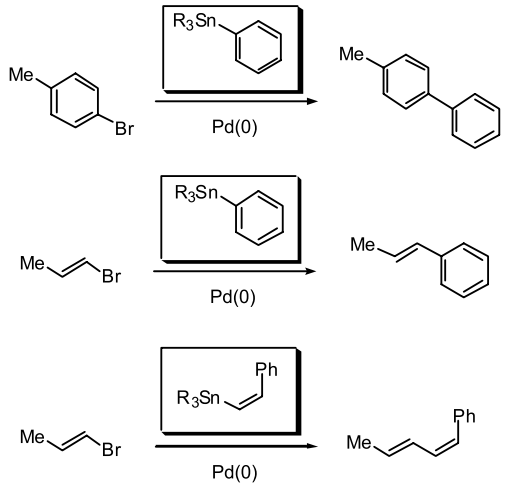
doi:10.1016/j.tet.2005.08.057

1.1. Stille coupling

The Stille reaction has found widespread use in organic synthesis, as it is well suited for the formation of unsymmetrical biaryls. This palladium-catalyzed process utilizes either an aryl halide or a sulfonate as the electrophilic component of the reaction.[1,4] The distinguishing feature of the Stille reaction is the nucleophilic organostannane that is utilized in the coupling (Scheme 3).

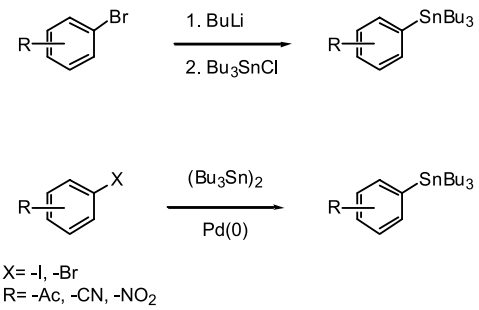


Scheme 3.

The stannane typically contains a single transferable group, most often aryl, heteroaryl, benzyl, allyl, alkenyl, or alkynyl. The remaining groups directly bound to tin transfer at a rate that essentially renders them non-transferable. These non-transferable groups are typically alkyl groups such as methyl or butyl.[2]

The most common route to the synthesis of organostannanes involves treatment of trialkyltin chlorides with organolithium or organomagnesium reagents.[1,2] When an incompatibility with organic functional groups arises, hexaalkyldistannanes may be cross coupled with organic electrophiles using transition-metal catalysts such as Pd(0) (Scheme 4).[1,2]

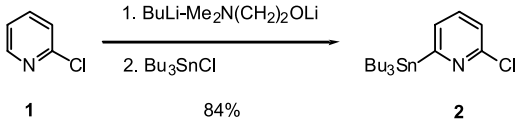
The Stille reaction has gained prominence due to the widespread availability of organostannanes. Additionally, the air- and moisture-stability of organostannanes leads to convenience in purification and storage of these reagents.[1,5] The compatibility of stannanes toward a wide variety of



Scheme 4.

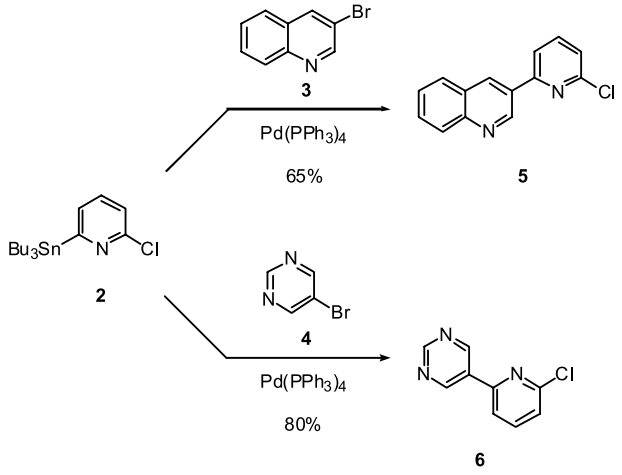
organic functional groups makes the use of tedious protecting-group strategies unnecessary.[2] The mild reaction conditions employed during couplings are reflected in the frequent use of Stille couplings among the final steps of complex natural-product syntheses.[2]

Recent work by Fort et al. highlights the power of the Stille methodology, specifically involving couplings of heteroaryl substrates.[11] In this research, a unique lithiation using lithium 2-dimethylamino-ethoxide superbase (BuLi–LiDMAE) is performed on 2-chloropyridine (**1**). Trapping with tributyltin chloride affords the Stille reagent **2** in high yield (Scheme 5).[11]



Scheme 5.

With the heteroaromatic stannane **2** in hand, Stille couplings to various heteroaryl halides were then attempted. In the presence of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), both 3-bromoquinoline (**3**) and 5-bromopyrimidine (**4**) afforded the cross-coupled products **5** and **6** in good yield (Scheme 6).[11]



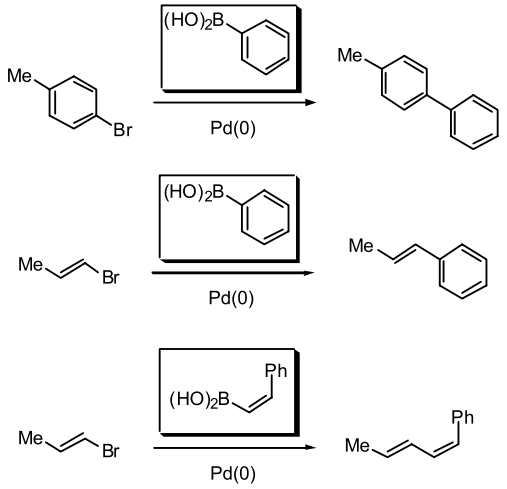
Scheme 6.

The Stille coupling is a powerful route to the formation of biaryls. However, there are areas in which the Stille coupling is problematic. The chief limitation of the Stille reaction lies in the high toxicity of the tin reagents employed in the coupling.[12,13] Further complicating this fact is the subsequent difficulty in removing the tin byproducts from the desired coupled product.[2]

1.2. Suzuki coupling

While the Stille reaction performs in a general fashion, frequently affording coupled products in high yield, it has largely been supplanted by the Suzuki reaction. The distinguishing feature of the Suzuki reaction is the use of boronic acids or esters as the nucleophilic partner in the

coupling (Scheme 7). Thus, the negative issues associated with the use of tin reagents in the Stille coupling are eliminated through the use of relatively benign organoboron compounds.[5] Like the Stille reaction, the Suzuki reaction tolerates aryl iodides, bromides, chlorides, and sulfonates as the electrophile.[7–9]

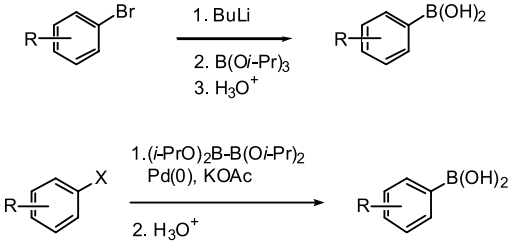


Scheme 7.

In addition to the non-toxic nature of boronic acids and the resulting boron-containing byproducts from the coupling reaction, organoboron reagents exhibit good thermal stability. Boronic acids are also stable to air and moisture, which allows couplings to occur in aqueous medium while exposed to the atmosphere.[5] However, the synthesis of arylboronic acids is somewhat more problematic than the synthesis of arylstannanes.

The synthesis of arylboronic acids for use in Suzuki couplings is generally accomplished in the same fashion as the synthesis of Stille reagents. Arylboronic acids or esters may be synthesized by reacting organolithium or organomagnesium compounds with trialkyl borates (Scheme 8).[7–9] Acid hydrolysis then gives the arylboronic acid. In contrast to the preparation of the corresponding tin reagent where chloride is the only leaving group, multiple additions to boron may occur as additional alkoxy groups are displaced. In cases where this approach fails, aryl halides may be cross coupled with (alkoxy)diboron reagents in good yield (Scheme 8).[7,9]

Recent examples have demonstrated the utility of the Suzuki reaction in couplings involving heteroaromatic substrates. Work by Yang and Martin included the coupling



Scheme 8.

of 5-indoleboronic acid (**7**) with 1-bromo-4-fluorobenzene (**8**), (Scheme 9),[14] and the coupled product **9** was obtained in high yield. Later work by Carrera and Sheppard accomplished a similar coupling by reversing the roles of the two coupling partners. In this case, 7-bromoindole (**10**) was synthesized and subsequently coupled with 4-fluorophenylboronic acid (**11**) to give the coupled product **12** (Scheme 9).[15]

2. Silicon-based coupling

Recently, alternative routes to biaryl couplings utilizing silicon-based reagents have gained increased attention. Like boronic acids, silicon reagents exhibit low toxicity relative to their tin counterparts.[16] While certain boronic acids sometimes exhibit limited stability and are difficult to prepare, silicon reagents may be prepared by a variety of methods. Unlike boronic acids, silicon-based reagents are stable to most reaction conditions employed in synthetic chemistry.[16]

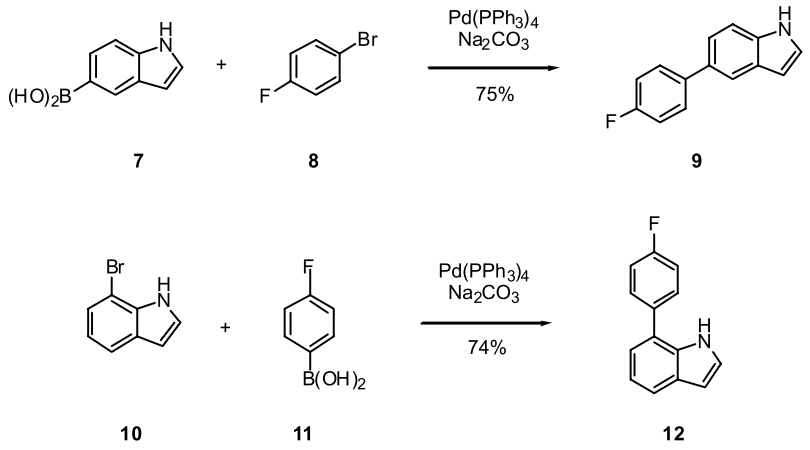
Results from Hiyama, Denmark, our lab, and others have shown palladium-catalyzed, fluoride-promoted reactions of silicon derivatives to be viable alternatives to the Stille and Suzuki coupling methodologies.[5,16–40] The commonly accepted mechanism, initially proposed by Hiyama and Hatanaka, involves three steps (Scheme 10).[41]

The first step involves oxidative addition of the aryl halide to the palladium(0) complex. In the second step, transmetallation of the arylpalladium complex with the anionic arylsilicate occurs. Finally, the cross-coupled product is produced and the palladium(0) catalyst regenerated through reductive elimination of the bis(aryl)palladium(II) species.

The key intermediate to the process, and the distinguishing feature of silicon-based couplings, is the pentacoordinate arylsilicate anion.[42] This species is formed by treatment of the corresponding tetracoordinate silane with an activating anion, typically fluoride (Scheme 11).

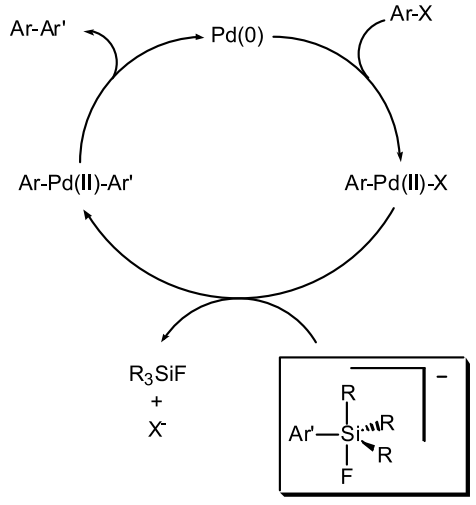
It is notable that experimental evidence shows pentacoordinate silicates to be much more reactive than the corresponding tetracoordinate silane.[42] These results are supported by calculations, which show the positive charge on the central silicon atom to be maintained, or even increased, by coordination of the fifth ligand.[43,44] This holds true, even with the addition of anionic ligands such as fluoride, hydroxide, or hydride.[42] The residual positive charge on silicon, in addition to a lengthening of the silicon–ligand bonds, accounts for the higher reactivity of the pentacoordinate silicon species.[42]

Our initial interest in the palladium-catalyzed formation of unsymmetrical biaryls began with the discovery that tetrabutylammonium triphenyldifluorosilicate (TBAT, **13**) would cross couple with aryl iodides and aryl triflates (Table 1).[34] In this study, various electrophiles were shown to cross couple in excellent yield when reacted with TBAT in the presence of a palladium catalyst. Substituents could be electron withdrawing (Table 1, entries 1–3) or electron donating (Table 1, entries 4–7). Additionally, these initial

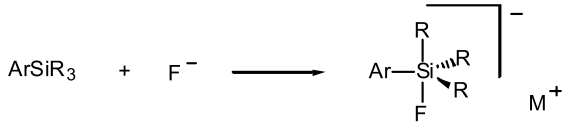


7 8 9 10 11 12

Scheme 9.



Scheme 10.



Scheme 11.

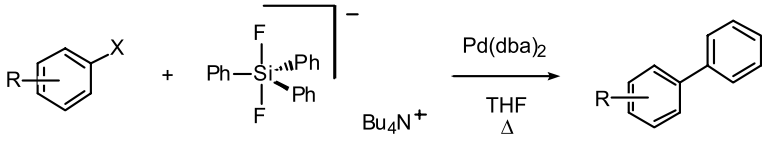
results showed that coupling would occur regardless of the substituent position on the aryl iodide (Table 1, entries 4–6).

Several limitations of the TBAT cross-coupling methodology become apparent upon closer study of these results. First, the catalyst employed only allows for efficient cross coupling between aryl iodides and aryl triflates. Furthermore, aryl triflates must bear electron-withdrawing substituents in order for the couplings to proceed in high yield. An additional shortcoming was discovered when studies conducted in our laboratory indicated that only two of the three available phenyl groups on TBAT could be transferred in the couplings.[45]

In order to improve upon these shortcomings, studies were initiated utilizing phenyltrimethoxysilane as the precursor to the arylation agent in the cross-coupling reactions. When treated with an activator such as tetrabutylammonium fluoride (TBAF), a pentacoordinate silicate **14** is presumably formed in situ (Scheme 12).[35,36,38] This intermediate is then available to function in a similar fashion to the preformed hypercoordinate salt TBAT in palladium-catalyzed cross couplings.

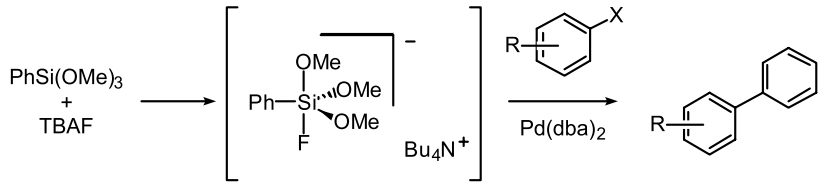
Initial studies demonstrated that the coupling outlined in Scheme 12 worked efficiently, affording the coupled product in high yield when aryl iodides were employed as

Table 1. Palladium-catalyzed cross-coupling of aryl iodides and triflates with TBAT



13

Entry	R	X	Yield (%)
1	4-Ac	I	87
2	4-Ac	OTf	73
3	4-NO_2	OTf	73
4	4-Me	I	64
5	3-Me	I	68
6	2-Me	I	90
7	4-OMe	I	88

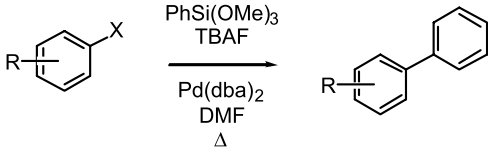


14

Scheme 12.

the electrophile (Table 2, entries 1–4).[36] Once again, aryl bromides gave the coupled product in poor yield, except in cases where electron-withdrawing substituents were present (Table 2, entries 5–7). This result suggested that the problem with aryl bromide activation was the oxidative addition step of the catalytic cycle. It was proposed that this problem could be remedied through the use of a more aggressive catalyst.

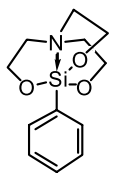
Table 2. Palladium-catalyzed siloxane couplings of aryl iodides and bromides



Entry	R	X	Yield (%)
1	4-Ac	I	58
2	4-Me	I	90
3	4-OMe	I	54
4	4-Cl	I	78
5	4-Ac	Br	78
6	4-Me	Br	0
7	4-OMe	Br	0

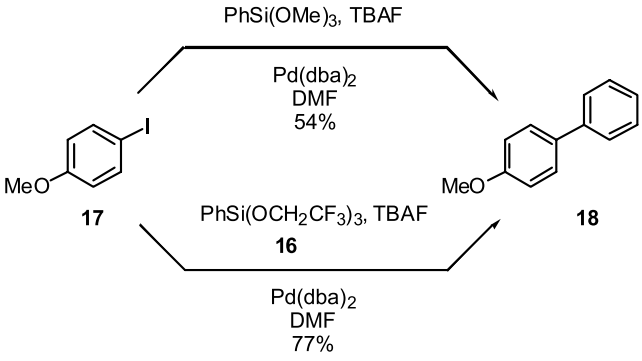
Notable, however, is the ability of the catalyst to discriminate between the Ar–Cl and Ar–I bonds. The result of a coupling between phenyltrimethoxysilane and 1-chloro-4-iodobenzene indicates exclusive oxidative addition into the Ar–I bond, giving 4-chlorobiphenyl in 78% yield (entry 4). No 4-iodobiphenyl was obtained in this reaction.

Two other results of note were produced by this study. While aryl triflates were found to effectively cross couple when TBAT was employed as the phenylating agent, the coupling failed when phenyltrimethoxysilane was employed. The exclusive product isolated after the attempted siloxane coupling of various triflates was the hydrolyzed triflate.[46] Studies are currently underway in which cross coupling of aryl triflates occurs in good yield using phenylsilatrane (**15**).[47] The synthesis of various arylsilatranes, as well as studies involving their use in palladium-catalyzed cross couplings, is also underway.



15

A second important contribution from these studies utilizing siloxanes in couplings involved the reactivity of the siloxane. In some cases, cross couplings with phenyltrimethoxysilane proceed slowly and in low yield. It was found that utilization of phenyltris(2,2,2-trifluoroethoxy) silane (**16**) aided coupling by increasing both the rate of reaction and the yield of product (Scheme 13).[36] Specifically, the use of siloxane **16** in the cross coupling of 4-iodoanisole (**17**) resulted in a marked increase in the yield of the coupled product **18** versus couplings employing phenyltrimethoxysilane.



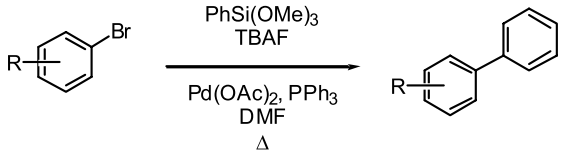
Scheme 13.

Presumably, increasing the electron-withdrawing character of the alkoxy groups directly bound to silicon better facilitates the formation of the reactive hypervalent intermediate. This effect has been well documented in the formation of other penta- and hexacoordinate silicates.[48] This, in turn, improves the efficiency of the transmetallation step in the catalytic cycle, as a higher concentration of the reactive intermediate is present in the reaction mixture.

While siloxane couplings with aryl iodides had been shown to proceed efficiently, couplings with aryl bromides and chlorides had proven to be problematic.[36] Therefore, studies were undertaken to extend the methodology to include these less-reactive aryl halides. By changing the palladium catalyst to palladium(II) acetate ($Pd(OAc)_2$) and including a phosphine ligand such as triphenylphosphine (PPh_3) or tri-*o*-tolylphosphine ($P(o\text{-tol})_3$), aryl bromides were shown to cross couple in excellent yield (Table 3).[35] This catalyst–ligand combination has been shown to be a convenient method for the in situ generation of Pd(0).[49]

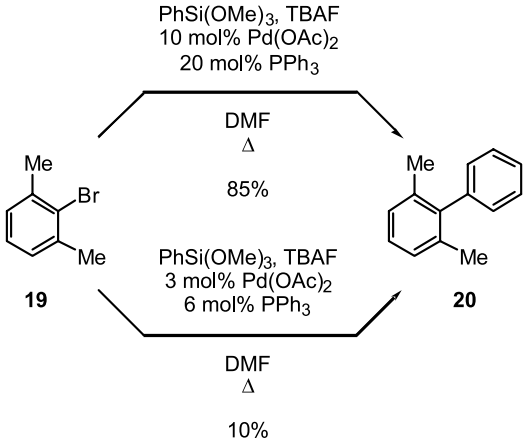
The presence of both electron-withdrawing and electron-donating groups was tolerated in couplings employing these conditions (Table 3, entries 1 and 3). Further studies indicated that the catalyst loading could be decreased to as

Table 3. Palladium-catalyzed siloxane couplings of aryl bromides



Entry	R	Yield (%)
1	4-Ac	86
2	4-Me	82
3	4-OMe	74

little as 3 mol% for unhindered substrates, rather than the typically-employed 10 mol%. For sterically hindered aryl bromides such as 2-bromo-*m*-xylene (**19**), catalyst loadings of 10 mol% were necessary to facilitate couplings in high yield (Scheme 14).[35] By employing 10 mol% of the catalyst, the coupled product **20** could be obtained in high yield.

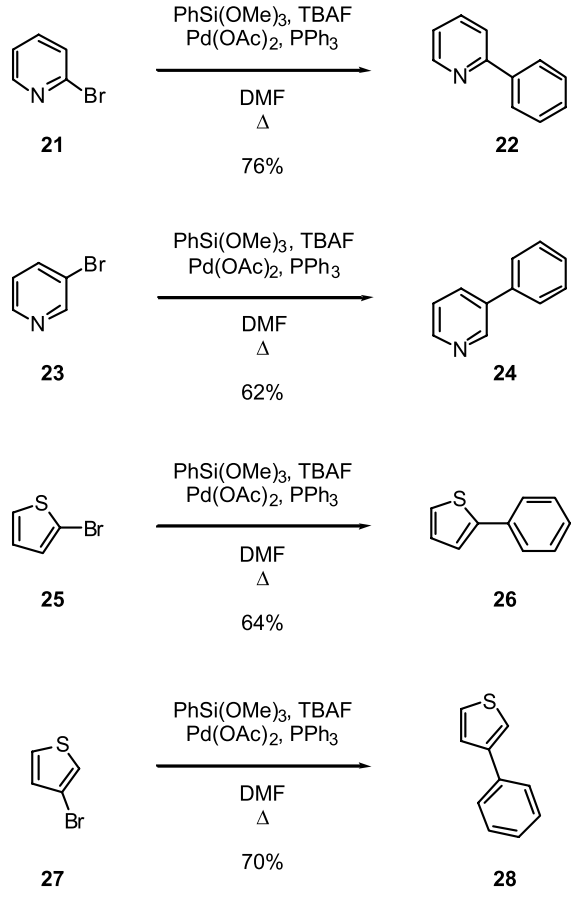


Scheme 14.

In addition to allowing for couplings of simple aryl bromides, this catalyst–ligand combination was shown to allow for couplings of simple heteroaryl bromides. Both 2-bromopyridine (**21**) and 3-bromopyridine (**23**), as well as 2-bromothiophene (**25**) and 3-bromothiophene (**27**), were shown to give the coupled products (**22**, **24**, **26**, **28**, respectively), in good yields (Scheme 15).[35]

The final result of note from this study involved the successful coupling of aryl chlorides. It had been shown that aryl chlorides coupled in poor yield using the $Pd(OAc)_2/PPh_3$ catalyst–ligand combination, even when electron-withdrawing substituents were present on the aryl chloride. The best yield was obtained in couplings with 4-chloroacetophenone (**29**), which gave the coupled product **30** in only 29% yield (Scheme 16). With electron-donating groups present on the aryl ring, the couplings failed completely.

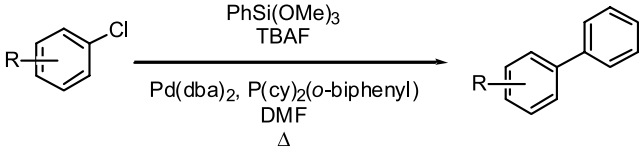
It was found that the use of 2-(dicyclohexylphosphino) biphenyl ($P(cy)_2$(*o*-biphenyl), **31**) allowed aryl chlorides to successfully couple in the siloxane methodology (Table 4). Phosphine ligands **31** and **32** were developed by Buchwald



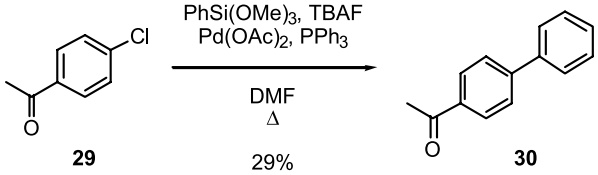
Scheme 15.

et al. and successfully employed in Suzuki couplings of aryl chlorides.[50,51] Siloxane couplings with aryl chlorides tolerated the presence of both electron-withdrawing (Table 4, entry 1) and electron-donating (Table 4, entry 3) substituents.[35]

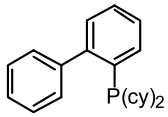
Table 4. Palladium-catalyzed siloxane couplings of aryl chlorides



Entry	R	Yield (%)
1	4-Ac	47
2	4-Me	63
3	4-OMe	71



Scheme 16.



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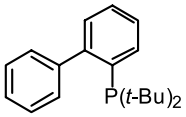
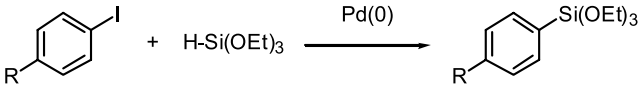


32

3. Synthesis of siloxanes

Like the corresponding preparations of Stille and Suzuki reagents, the synthesis of siloxanes falls into one of two categories. The first, treatment of an aryl Grignard or aryllithium reagent with a silicon electrophile, has traditionally been limited by low yields, as well as by the nature of the substituents present on the arene, for example, electrophilic functional groups such as esters and ketones will not tolerate these reaction conditions.[52]

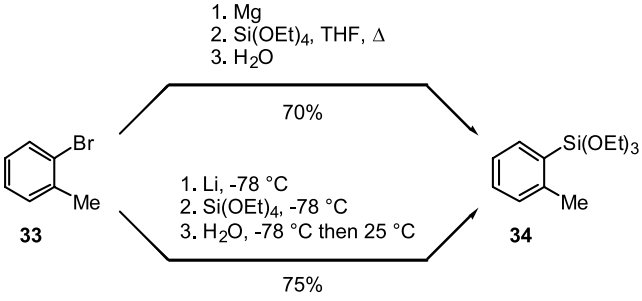
The second method involves silylation of aryl iodides by triethoxysilane ($(EtO)_3SiH$) in the presence of a palladium catalyst (Scheme 17).[52,53] This method suffers from the limitation of requiring electron-rich aryl iodides. The reaction fails, or gives low yields, when *ortho*- or *meta*-substituted aryl iodides are employed. Additionally, aryl bromides are generally unreactive under these conditions.[52,53]



Scheme 17.

In an effort to develop efficient and general syntheses of arylsiloxanes, studies were initiated using both Grignard and silylation chemistry for the synthesis of simple substituted siloxanes. As a result of these investigations, two complementary methods to accomplish these goals were developed. One route involved the formation of aryl Grignard or aryllithium reagents from aryl bromides (Scheme 18).[54] This method excels at forming siloxanes bearing *ortho*-substituents, such as 2-bromotoluene (**33**). Siloxane **34** is formed in high yield utilizing either an organolithium or Grignard reagent.[54]

In general, both metallation pathways to *ortho*-substituted siloxanes work well. The trend in reactivity observed is that the organolithium reagents are more reactive than the corresponding Grignard reagents.[54] However, this method



Scheme 18.

fails for aryl halides bearing electrophilic substituents (i.e., esters and ketones). An additional limitation is overaddition of the organometallic reagent to silicon, displacing more than one ethoxy group.[54] The study revealed, however, that strict control of the reaction temperature suppressed the formation of di- and tri-arylated siloxanes. A wide range of substituted siloxanes were synthesized using Grignard or organolithium reagents (Figs. 1 and 2).

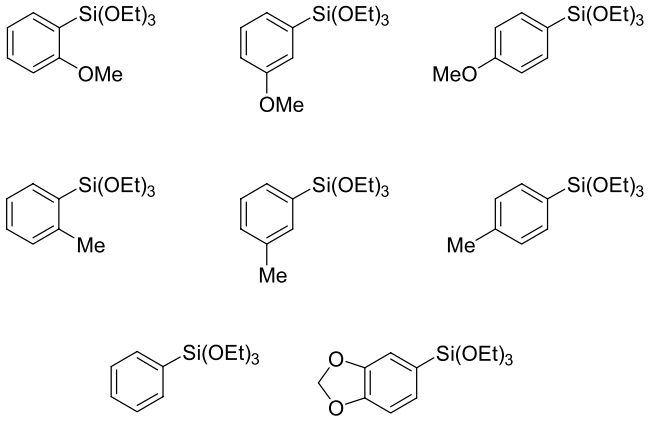


Figure 1. Siloxanes synthesized using both Grignard and lithium reagents.

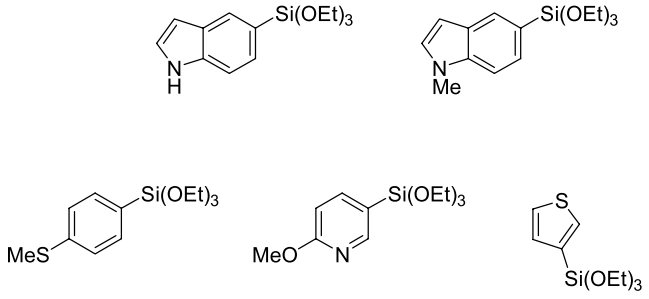
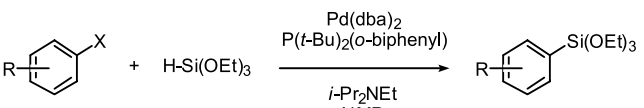


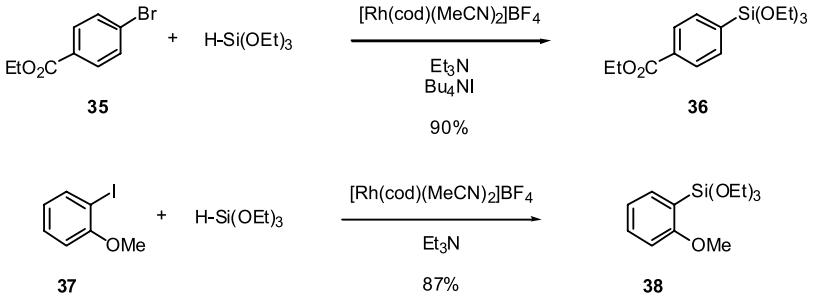
Figure 2. Siloxanes synthesized using lithium reagents.

The nucleophilic displacement approach discussed above works well in many cases; a second route, the palladium-catalyzed silylation approach, offers the advantage of tolerating a larger range of functional groups.[52] Unfortunately, good yields are obtained only when electron-rich aryl iodides and bromides are used (Table 5). In the case of the electron-rich 4-iodoanisole (Table 5, entry 1) and 4-bromoanisole (Table 5, entry 2), good yields of the substituted siloxane are obtained. The yield drops off

Table 5. Palladium-catalyzed silylation of aryl halides



Entry	X	R	Yield (%)
1	I	4-OMe	86
2	Br	4-OMe	68
3	Br	3-OMe	25
4	Br	2-OMe	0
5	I	4-OH	70
6	I	4-Ac	24



Scheme 19.

appreciably in the silylation of 3-bromoanisole (Table 5, entry 3). In contrast to the good yields obtained via metallation chemistry for 2-bromotoluene, 2-bromoanisole fails to give any product using silylation chemistry (Table 5, entry 4). Notable is the ability of the silylation chemistry to afford the corresponding substituted siloxane from 4-iodophenol (Table 5, entry 5) and 4-iodoacetophenone (Table 5, entry 6). Neither of these substrates are amenable to the reaction conditions employed in the strongly nucleophilic metallation approach.

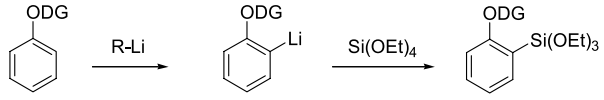
While the silylation method developed in our laboratories works well, it suffers from the limitation of requiring *para*- or *meta*-substitution on electron-rich arenes. Similar chemistry recently developed by Masuda et al. addresses these issues.[55] This silylation of aryl halides employs a rhodium catalyst and, allows for the preparation of an even wider range of substituted siloxanes (Scheme 19).[55] These conditions will activate substrates bearing electron-withdrawing substituents such as the ester **35**, as well as those that possess *ortho*-substitution, such as 2-iodoanisole (**37**).

More recent studies on the formation of arylsiloxanes for use in cross-coupling reactions have focused on employing directed *ortho*-metalation as a means to form aryllithium reagents.[56] A number of *ortho*-directing groups were employed in this study, which produced a range of *ortho*-substituted siloxanes suitable for use in palladium-catalyzed coupling reactions (Table 6).

In general, it was found that tetraethyl orthosilicate was an acceptable electrophile in the reaction. A survey of several other silicon electrophiles suggested that triethoxysilyl triflate was an alternate reagent that offered an increased yield of the arylsiloxane in several cases.[56]

A wide range of simple aryl halides has previously been shown to effectively participate in palladium-catalyzed cross-coupling reactions with siloxanes. The goal of this research was to expand the scope of the siloxane methodology to include couplings of substrates that traditionally have been difficult to cross couple using Suzuki methodology, particularly heteroaryl substrates. In turn, these studies will serve to explore the scope and limitations of siloxane couplings for use in natural product syntheses.

Table 6. Synthesis of aryl(triethoxy)silanes via orthometallation



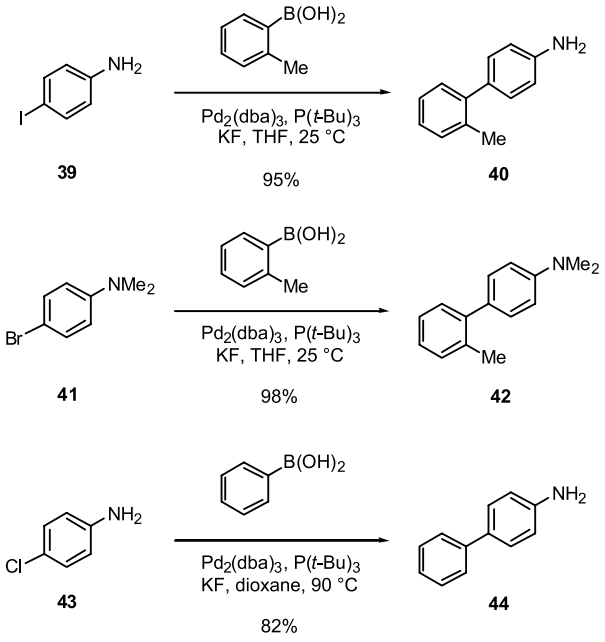
Entry	Product	Yield
1	OMe	62
2	OMOM	61
3	$OC(O)NEt_2$	57
4	NHC(O)*t*-Bu	63
5	NHBoc	61

4. Formation of heteroaromatic biaryls

Palladium-catalyzed cross couplings utilizing hypercoordinate siloxanes have been shown to tolerate a wide range of aryl halides. Substituents may be electron donating, electron withdrawing, or neutral.[35,36,38] One class of compounds not investigated in these preliminary studies are derivatives of aniline. While there exist numerous examples of haloanilines being utilized in Suzuki couplings, reports of couplings using the Stille methodology are limited.

A recent study reporting Suzuki couplings of aniline derivatives was conducted by Fu and co-workers.[57] In this work, tri-*t*-butylphosphine ($P(t\text{-}Bu)_3$) is utilized as a ligand, allowing for the activation of aryl chlorides in Suzuki couplings. It is assumed that the electron-donating character of the alkyl groups on the phosphine, as well as its steric bulk, results in a more facile oxidative addition of palladium into the aryl halide.[58] Prior work utilizing aryl chlorides in Suzuki couplings required strongly electron-withdrawing substituents on the aryl chloride.[57]

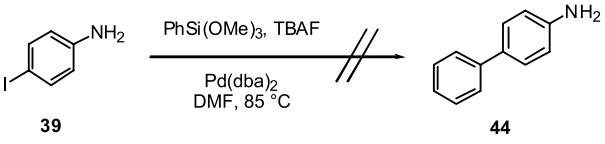
Results from the coupling of 4-iodoaniline (**39**), 4-bromo-*N*,*N*-dimethylaniline (**41**), and 4-chloroaniline (**43**) show that excellent yields are obtained using $Pd_2(dba)_3$ and $P(t\text{-}Bu)_3$ as the catalyst–ligand combination (Scheme 20). More vigorous reaction conditions were required for the reaction involving 4-chloroaniline. This follows the typical order of reactivity for aryl halides ($I > Br \gg Cl$).[59] The coupled products **40**, **42**, and **44** are obtained in excellent yield. The significance of this work is that it extends the Suzuki methodology to aryl chlorides, which are attractive due to their low cost and ready availability.[7] A limitation of this methodology is the required use of $P(t\text{-}Bu)_3$, which is unstable in air and moisture and readily oxidized. As a consequence, this reactive liquid phosphine is most easily handled as a 0.2 M solution in hexane.[60]



Scheme 20.

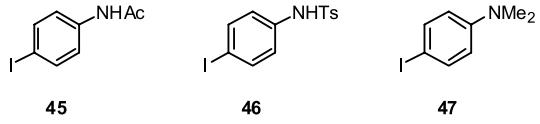
4.1. Initial studies

For our studies, 4-iodoaniline (**39**) was selected as the initial electrophilic coupling partner for investigation in the hypervalent siloxane methodology. The reaction was first attempted using the general conditions developed for couplings of aryl iodides (Scheme 21).[34,36] Unfortunately, these conditions did not result in the formation of coupled product **44**. Only unreacted starting material was recovered.



Scheme 21.

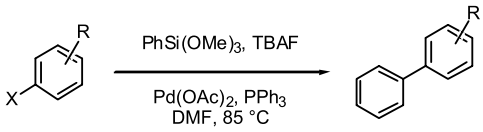
Concerned that the free amine was interfering with the catalytic cycle,[61,62] *N*-protected iodoanilines **45**–**47** were prepared. Subjecting **45**–**47** to the above conditions did not result in the formation of the desired coupled product. Once again, unreacted starting material was recovered.



The results from these attempted couplings suggest that a more aggressive catalyst system might yield favorable results. To this end, the catalyst–ligand combination of $Pd(OAc)_2/PPh_3$ was employed. This system has been previously shown to allow for efficient siloxane cross couplings of aryl bromides.[35]

In the first attempted coupling of iodoaniline **39** utilizing this more aggressive catalyst system, the coupled product was obtained in 95% yield (Table 7, entry 1). Similar results

Table 7. Results of cross couplings of aryl iodides and bromides



Entry	R	X	Yield (%)
1	4-NH_2	I	95
2	4-NH_2	Br	90
3	4-NMe_2	I	69
4	4-NMe_2	Br	70
5	4-NHAc	I	70
6	4-NHAc	Br	77
7	4-NHTs	I	65
8	4-NHTs	Br	72
9	3-NH_2	I	75
10	2-NH_2	I	82
11	4-OH	Br	66
12	2-NO_2	I	58

were obtained using 4-bromoaniline as the electrophile (Table 7, entry 2). Application of this methodology to aryl bromides is of interest, given the unfavorable cost and limited stability of aryl iodides.[7]

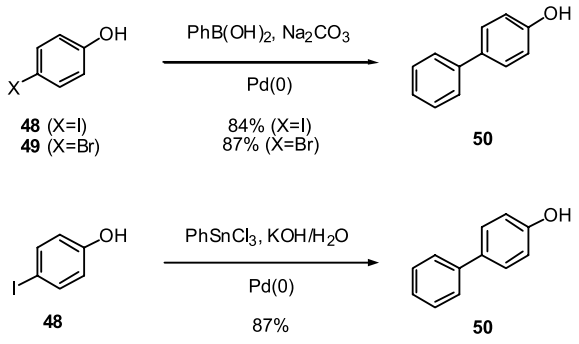
Similar results were obtained utilizing *N*-protected iodoanilines **45**–**47**, as well as the corresponding bromoanilines. Both *N*,*N*-dimethyl-4-iodoaniline and *N*,*N*-dimethyl-4-bromoaniline afforded the coupled product in good yield (Table 7, entries 3 and 4). Additionally, the 4-iodo- and 4-bromoacetamides and sulfonamides (Table 7, entries 5–8) gave the coupled products in a similarly good yield.

These results demonstrate that *para*-substituted anilines do tolerate the conditions utilized in siloxane couplings. The next compounds of interest were *ortho*- and *meta*-substituted iodoanilines. These substrates were chosen to investigate effects involving the substitution pattern on the aromatic aniline. The results of this study demonstrate that only a small decrease in yield is observed in going from *para*- to *meta*- to *ortho*-substitution (Table 7, entries 1, 9, and 10).

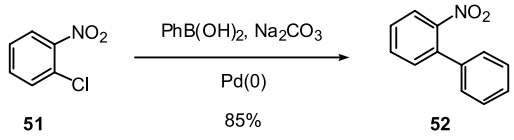
Two final substrates of interest in these initial studies include 4-bromophenol and 2-iodonitrobenzene (Table 7, entries 11 and 12). Both substrates gave the coupled products in good yield. Several examples exist in the literature involving Suzuki and Stille couplings of these and similar substrates. Both 4-iodophenol[63] (**48**) and 4-bromophenol[64] (**49**) have been successfully utilized in aqueous Suzuki couplings, while 4-iodophenol has been shown to couple under Stille conditions.[65] These Stille and Suzuki couplings proceeded to give biaryl **50** in good yield (Scheme 22).

Recently, Shen accomplished the Suzuki coupling of 2-chloronitrobenzene (**51**) in 85% yield (Scheme 23).[66] Coupling of this aryl chloride using Suzuki methodology to give **52** occurs readily, presumably due to the presence of the strongly electron-withdrawing nitro-substituent on the aromatic ring.

While numerous aryl halides have been utilized in siloxane



Scheme 22.



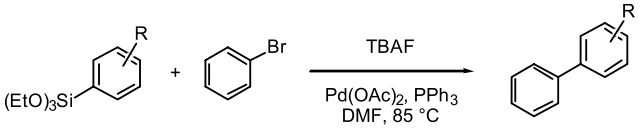
Scheme 23.

cross couplings, relatively few substituted arylsiloxanes have been employed in these couplings.[37] As a consequence, it was decided to investigate couplings involving simple *para*-, *meta*-, and *ortho*-substituted arylsiloxanes (Table 8). These siloxanes were synthesized either via Grignard chemistry[54] or using a modified procedure of Masuda.[52] Both routes to substituted siloxanes are discussed in detail elsewhere.[67]

The results from this study involving simple substituted arylsiloxanes demonstrate that there is no significant decrease in yield among the *ortho*-, *meta*-, and *para*-methyl-substituted arylsiloxanes. In this series, the yield ranged from 90% for couplings with the *para*-methyl siloxane to 80% for couplings with the *ortho*-methyl siloxane (Table 8, entries 1–3). This small variance in yield may occur due to increased steric crowding present in the *ortho*-substituted siloxane.

A more interesting result is obtained in the methoxy-substituted arylsiloxane series. Coupling with bromobenzene utilizing the *para*- and *meta*-methoxy-substituted siloxanes resulted in the formation of the coupled product in 80 and 75% yields, respectively, (Table 8, entries 4 and 5). However, when the coupling was attempted with the *ortho*-methoxy-substituted siloxane, only 10% of the coupled product was obtained (Table 8, entry 6). Similar results were obtained when utilizing the methoxy-substituted series of siloxanes in couplings with allylic benzoates.[68]

Table 8. Couplings utilizing simple *ortho*-, *meta*- and *para*-substituted arylsiloxanes



Entry	R	$Pd(OAc)_2$ (equiv)	PPh_3 (equiv)	Yield (%)
1	4-Me	0.1	0.2	90
2	3-Me	0.1	0.2	85
3	2-Me	0.1	0.2	80
4	4-OMe	0.1	0.2	80
5	3-OMe	0.1	0.2	75
6	2-OMe	0.1	0.2	10
7	2-OMe	0.5	1	70
8	$4\text{-}NH_2$	0.1	0.2	75
9	4-NHAc	0.1	0.2	70
10	$4\text{-}NMe_2$	0.1	0.2	80

In an attempt to determine the cause of this unexpected result, several additional experiments were conducted. The first experiment involved looking at the ^{29}Si NMR spectrum of the methoxy-substituted siloxanes. This experiment was conducted to determine if the *ortho*-methoxy group was coordinating with the silicon atom in the tetracoordinate species, resulting in the presence of a hypercoordinate silicon species in a similar fashion to the dative bond found in phenylsilatrane (Fig. 3).[48] It is well documented that, when silicon becomes hypercoordinate, a significant upfield shift in its ^{29}Si signal is observed.[69] For example, the ^{29}Si chemical shift of tetracoordinate triphenylsilyl fluoride is 3.3 ppm.[70] Addition of tetrabutylammonium fluoride results in the formation of pentacoordinate TBAT (**13**), which exhibits a ^{29}Si chemical shift of -106.3 ppm.[71]

Both the *para*- and *ortho*-substituted siloxanes were studied. The chemical shift for the *para*-substituted siloxane, where the possibility of intramolecular coordination does not exist, was determined to be -57.0 ppm. The *ortho*-substituted siloxane showed a similar chemical shift of -57.5 ppm. This experiment suggested that the methoxy group in the *ortho*-substituted siloxane did not form a dative bond with the silicon atom.[45] However, this experiment did not rule out the possibility of such a dative bond in the hypervalent system that would form as a result of fluoride anion addition to the siloxane.

A second experiment involved mixing each siloxane with an equimolar amount of TBAF. In this series of experiments, each mixture was stirred overnight and the reaction mixture was analyzed by GC. In the case of the *para*- and *meta*-methoxy siloxanes, only the unreacted siloxane was found in the mixture. In the case of the *ortho*-methoxy siloxane, the only compound present in the mixture was anisole.[68] Subsequent investigation showed that the *ortho*-methoxy siloxane underwent this protodesilylation reaction within 10 min of mixing with fluoride anion.[68]

With this knowledge in hand, the coupling of the *ortho*-methoxy siloxane was attempted with 0.5 equiv of palladium, in an attempt to markedly increase the rate of formation of the product. Under these conditions of high catalyst loading, the coupled product was obtained in 70% yield, with the reaction being complete in 5 min (Table 8, entry 7).

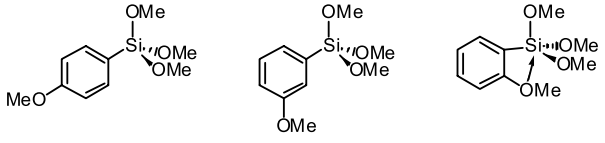


Figure 3. Proposed effect of substituent position in siloxanes.

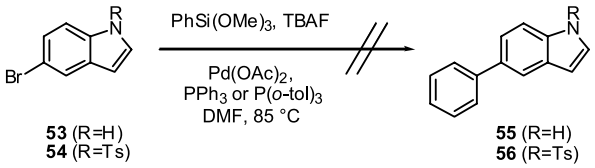
The inability of the siloxane methodology to tolerate the presence of the methoxy group at the *ortho* position without the presence of a non-catalytic amount of the palladium catalyst is a potential drawback of this methodology. However, one may arrive at the same product by utilizing an *ortho*-substituted haloanisole in conjunction with phenyltrimethoxysilane. Studies involving siloxanes with other heteroatoms at the *ortho*-position, as well as siloxanes bearing *ortho*-substituents that may be subsequently converted into a methoxy group, are under way. Studies involving the coupling of *ortho*-methoxy-substituted siloxanes in solutions of high concentration, by reducing the amount of solvent used in the reaction, are currently under way. This would have the net effect of increasing the concentration of the active palladium catalyst without employing high catalyst loadings.

The final results from this study involve couplings using aniline-based siloxanes. Each of the three *para*-substituted siloxanes gave the coupled product in high yield (Table 8, entries 8–10).

Having expanded the scope of siloxane couplings to include anilines, phenols, nitrobenzenes, and simple substituted siloxanes, it was desired to investigate couplings involving more complex heteroaromatic substrates. Previous work involving siloxane couplings of bromopyridines and bromothiophenes resulted in the formation of the coupled products in good yield (Scheme 15).[35] Additionally, there exist numerous examples of Suzuki[5,7–9] and Stille[1,2] couplings of heteroaromatic substrates.

4.2. Indole substrates

The first substrate investigated was 5-bromoindole (**53**). Efficient formation of 5-arylated indoles is useful, as they may later be readily converted into tryptamines and tetrahydropyridylindoles that are of biological interest.[72] Unfortunately, the first attempts at coupling bromoindole **53** using typical conditions for the siloxane coupling of aryl bromides were unsuccessful (Scheme 24).



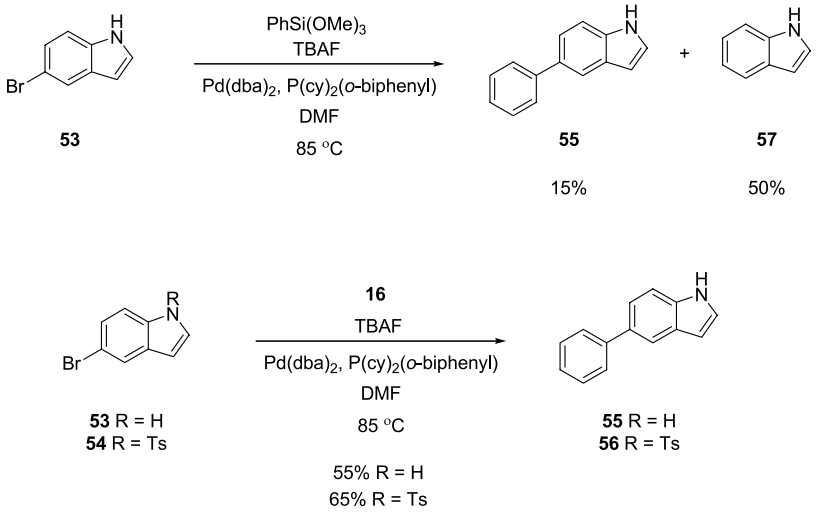
Scheme 24.

As was the case with aniline couplings, it was postulated that the free nitrogen atom in the indole could be interfering with the catalytic cycle. Therefore, the sulfonated indole **54** was prepared[73] and subjected to the coupling conditions. In a similar fashion, only unreacted bromoindole **54** was recovered (Scheme 24). The use of P(*o*-tol)$_3$, a more hindered phosphine, which is thought to facilitate oxidative addition,[74] did not alter the negative results.

The results of these failed coupling experiments once again suggested the need to employ a more aggressive catalyst system. The previously employed catalyst–ligand system of Pd(dba)$_2$/P(cy)$_2$(*o*-biphenyl) had been shown to allow for couplings of relatively unreactive aryl chlorides in both the siloxane[36] and Suzuki[50,51] methodology.

When this catalyst system was employed, an interesting result was obtained (Scheme 25). In addition to obtaining a small amount of the coupled indole **55**, a significant amount of indole (**57**) was obtained as a byproduct.

This result suggested that a competing reaction pathway might be in operation, possibly involving the participation of DMF.[75,76] However, employing 1-methyl-2-pyrrolidinone (NMP) in this coupling, rather than DMF, also results in the formation of the product of protodesilylation. Studies involving the effect of water on the formation of this byproduct are currently under way. In an attempt to speed up the desired cross coupling pathway, the use of phenyltris(2,2,2-trifluoroethoxy)silane (**16**)[77] was investigated. Previous work has shown siloxane **16** to both increase yield and decrease reaction time versus couplings utilizing phenyltrimethoxysilane in most cases.[36] Thus, this siloxane was employed in the coupling of **53** (Scheme 25).



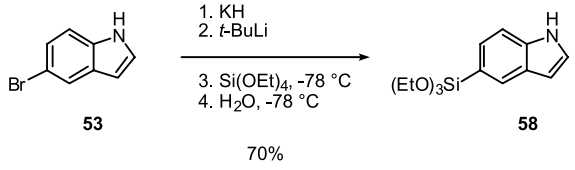
Scheme 25.

As expected, the use of siloxane **16** resulted in an increased yield of the coupled product **54**. In addition to observing a 55% yield of the coupled product, no unreacted starting material was recovered from the reaction. Only a trace amount of indole was obtained as a byproduct. Additionally, couplings utilizing the sulfonated indole **54** with siloxane **16** resulted in the production of the coupled product **56** in 65% yield (Scheme 25).

Having shown that the siloxane methodology would tolerate bromoindoles **53** and **54** as substrates in coupling reactions, it was postulated that the coupled indole **55** could also be synthesized by the reaction of bromobenzene and the 5-indolylsiloxane. To date, there exist no reports of palladium-catalyzed cross couplings involving heteroaryl-silicon reagents.[3]

To accomplish this goal, a synthesis of the heteroaryl siloxane had to be developed. Based on previous work by Martin and co-workers,[78] it was proposed that the siloxane could be prepared via trapping of a 5-lithio-1-potassioindole intermediate. This procedure has been utilized to prepare both indole-5-boronic acid and 5-(trimethylstannyl)indole in 44 and 37% yield, respectively.[78]

Accordingly, 5-bromoindole (**53**) was first treated with potassium hydride (KH). This step is necessary to prevent metallation at C-2 and to maintain solubility of the organolithium species.[79] The potassioindole intermediate was then subjected to halogen–metal exchange using *tert*-butyllithium (*t*-BuLi). The resulting intermediate was then trapped with tetraethyl orthosilicate ($Si(OEt)_4$) to afford 5-(triethoxysilyl)indole (**58**) in 70% yield (Scheme 26).

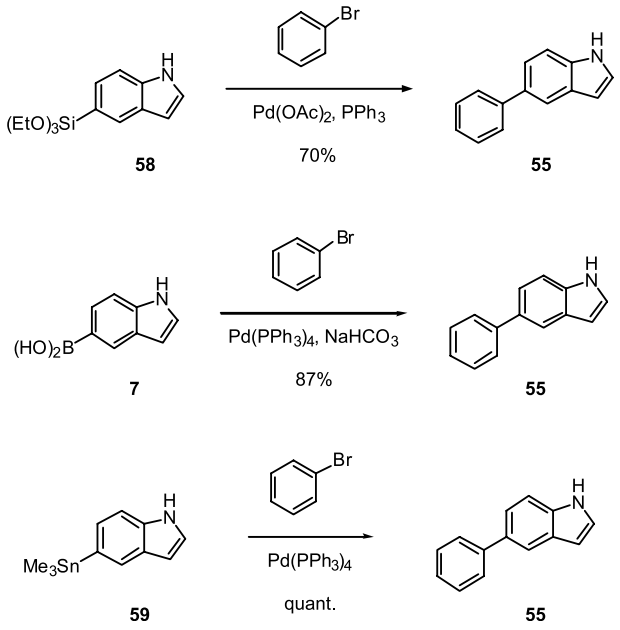


Scheme 26.

With heteroarylsilicon reagent **58** in hand, its coupling with bromobenzene could be attempted. Previous work utilizing 5-indoleboronic acid (**7**) and corresponding stannane **59** resulted in couplings in 87% and quantitative yield, respectively, (Scheme 27).[14,78]

As both the boronic acid and stannane couple in excellent yield, a comparison of the siloxane methodology was undertaken. Using the general conditions for coupling of aryl bromides, the coupling of siloxane **58** with bromobenzene was attempted (Scheme 27). The coupling proceeded in good yield, cleanly producing the coupled indole **55** in 70% yield.

While the siloxane coupling proceeded in lower yield than the Suzuki and Stille couplings, an advantage of the siloxane methodology is that the preparation of the indole siloxane proceeded in much higher yield than the preparation of either the corresponding boronic acid or stannane. Consequently, the overall yield of the two steps is higher in the



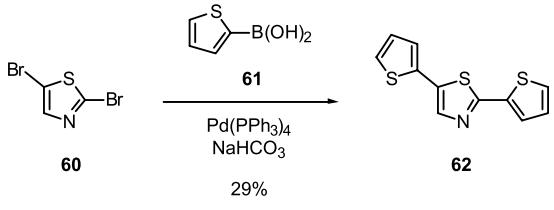
Scheme 27.

siloxane methodology than in either the Stille or Suzuki coupling.

4.3. Thiazole and pyrazole substrates

Following the successful coupling of 5-bromoindole (**53**), attention shifted toward couplings of compounds with two heteroatoms, including bromothiazoles and bromopyrazoles. Reports of successful palladium-catalyzed couplings of halopyrazoles and halothiazoles are rare.[3,80–82]

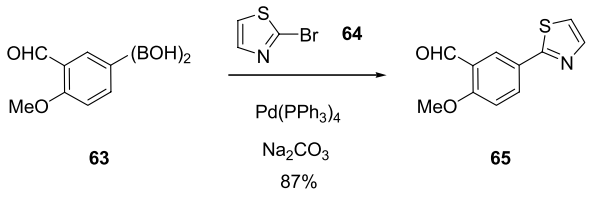
In one such study, an attempt to prepare 2-thiazole boronic acid failed.[80] However, some success was attained using dibromothiazole **60** as an electrophilic coupling partner with 2-thiophene boronic acid (**61**), (Scheme 28).[80] Unfortunately, this synthesis was limited in that the yield of the coupled product **62** was low, and attempts to use 3-thiophene boronic acid in the coupling failed.



Scheme 28.

Later work by Armour and co-workers utilized a Suzuki coupling between 3-formyl-4-methoxyphenyl boronic acid (**63**) and 2-bromothiazole (**64**) to afford the coupled product **65** in 87% yield (Scheme 29).[81] Compound **65** was then used as an intermediate in the synthesis of an orally bioavailable NK_1 receptor antagonist.

Thiazoles have been more extensively utilized in Stille couplings due to the relative ease of synthesis of stannylthiazoles. This is a notable advantage of the Stille



Scheme 29.

methodology over Suzuki couplings when working with thiazoles. Specifically, Dondoni and co-workers were able to prepare 2-, 4-, and 5-trimethylstannylthiazoles (Fig. 4).[82] All three stannanes were prepared in yields exceeding 60%. These and other substituted stannylthiazoles have been utilized in a number of palladium-catalyzed cross couplings with various aryl halides.[3]

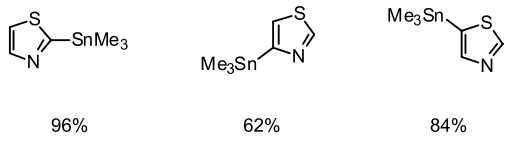
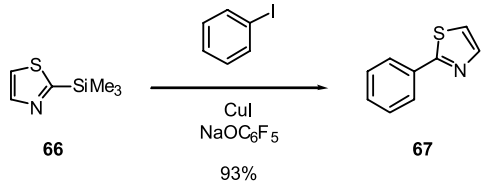


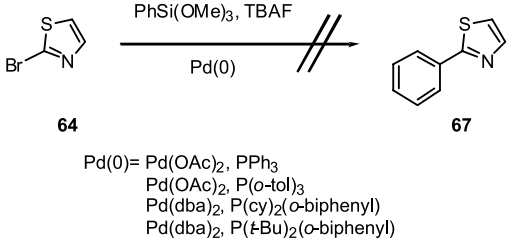
Figure 4. Yields of prepared trimethylstannylthiazoles.

Additionally, Hosomi and co-workers successfully prepared 2-trimethylsilylthiazole (**66**).[83] Subsequent work showed that **66** would cross couple with iodobenzene in the presence of a copper(I) salt (Scheme 30).[83] A downfall of this procedure is the non-catalytic nature of the reaction, which requires a stoichiometric amount of the copper salt.



Scheme 30.

While the preparation of thiazolesiloxanes was not attempted, several couplings involving 2-bromothiazole (**64**) were attempted (Scheme 31). Utilization of numerous palladium catalyst–phosphine ligand combinations did not result in the formation of the coupled product **67**. Unreacted starting material was obtained in most cases. Attempts at utilizing the more reactive siloxane **16** or preformed hypervalent silicate TBAT (**13**) did not alter this negative result.



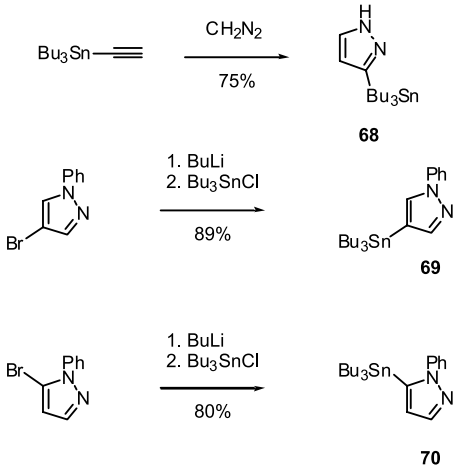
Scheme 31.

Similarly, few examples of palladium-catalyzed aryl couplings involving pyrazoles have been reported. Concise syntheses of arylpyrazoles are attractive, as their synthesis typically involves a multistep sequence, which ultimately places limitations on the functionalities of the aryl moiety.[84–87]

Several successful palladium-catalyzed couplings involving pyrazoles have been reported in the literature.[88–92] An advantage of the Stille over the Suzuki methodology is the ability to prepare stannylated pyrazoles in high yield. The tin reagents may then be utilized in couplings with other aryl halides. This route to coupled pyrazoles is not accessible via Suzuki methodology, as the corresponding boronic acids cannot be prepared.[91]

The first reported attempt of a palladium-catalyzed coupling of a pyrazole was by Stavenuiter et al. in 1987.[88] In a general study involving cross couplings of phenylboronic acid with various heteroaryl halides, an attempt was made to utilize 4-iodopyrazole as a substrate. This initial attempt failed, and the authors attributed the failure to insufficient aromatic character of the pyrazole ring.[88]

Successful coupling of pyrazoles was achieved by Yamanaka and co-workers, when a series of 3-, 4-, and 5-tributylstannylpyrazoles was prepared (**68–70**), (Scheme 32).[89] The 3-tributylstannylpyrazoles were prepared via 1,3-dipolar cycloaddition, while the 4- and 5-tributylstannylpyrazoles were prepared by stannylation of the corresponding lithiopyrazole.[89] Each synthesis proceeded in excellent yield.

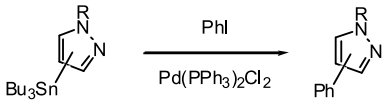


Scheme 32.

Stannanes **68–70** were then utilized in palladium-catalyzed cross couplings with iodobenzene, though with moderate success. While **68** and **69** coupled in 59 and 49% yield, respectively, (Table 9, entries 1 and 2), **70** failed to afford the coupled product (Table 9, entry 3).[89]

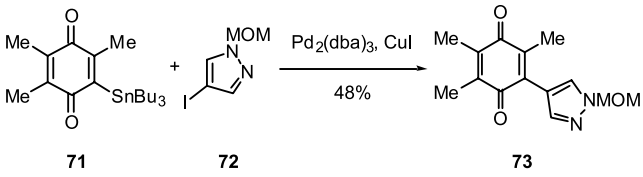
Subsequent work by Liebeskind and Riesinger utilized a different strategy to arrive at the coupled pyrazole products.[90] In this work, a coupled product originating from a halopyrazole was prepared. The synthesis utilized stannylquinone **71** and MOM-protected iodopyrazole **72** in

Table 9. Stille couplings of stannylpyrazoles



Entry	Stannane	R	Yield (%)
1	3-$SnBu_3$	H	59
2	4-$SnBu_3$	Ph	49
3	5-$SnBu_3$	Ph	0

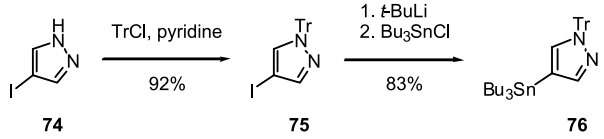
the presence of a palladium-copper co-catalyst to afford the coupled product **73** (Scheme 33).[90] As was the case in previous pyrazole couplings, a low yield of the coupled product was obtained.



71 72 73

Scheme 33.

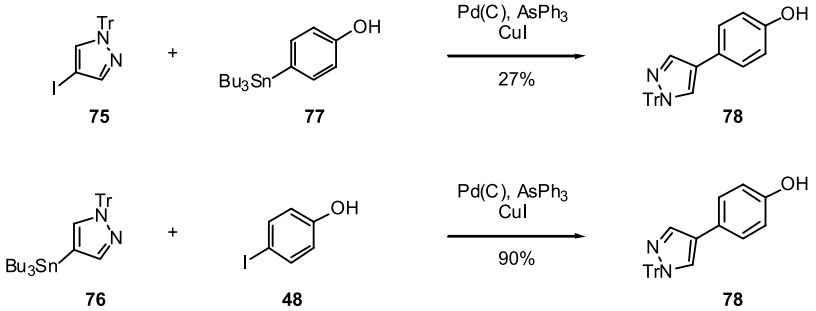
These few examples of pyrazole couplings influenced Pardo et al. to develop a general method for the palladium-catalyzed preparation of 4-arylpyrazoles.[91] These researchers began by preparing *N*-trityl-4-halopyrazoles such as **75** from **74** (Scheme 34). Generation of the lithiopyrazole followed by quenching with tributyltin chloride resulted in the formation of the stannylpyrazole **76** in 83% yield. Lower yields were obtained when the corresponding bromopyrazole was used.[91]



74 75 76

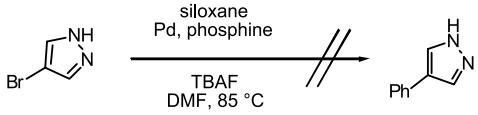
Scheme 34.

Having prepared the stannylpyrazole **76**, the authors were able to compare the yields of arylpyrazoles obtained from couplings involving both stannylpyrazoles and iodopyrazoles. The optimized catalyst, Pd(C)/CuI/Ph_3As, was determined to afford arylpyrazoles in a general fashion, in yields ranging from 0 to 90% (Scheme 35).[91] Much higher yields of the coupled product **78** were obtained when



Scheme 35.

Table 10. Attempted couplings of 4-bromopyrazole



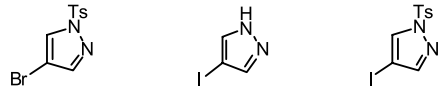
Entry	Siloxane	Pd	Phosphine
1	$PhSi(OMe)_3$	$Pd(OAc)_2$	PPh_3
2	$PhSi(OMe)_3$	$Pd(OAc)_2$	P(*o*-tol)$_3$
3	$PhSi(OMe)_3$	$Pd(dba)_2$	P(cy)$_2$(*o*-biphenyl)
4	$PhSi(OMe)_3$	$Pd(dba)_2$	P(*t*-Bu)$_2$(*o*-biphenyl)
5	$PhSi(OCH_2CF_3)_3$	$Pd(dba)_2$	P(cy)$_2$(*o*-biphenyl)
6	TBAT	$Pd(dba)_2$	P(cy)$_2$(*o*-biphenyl)

utilizing the stannylpyrazole **76** rather than the corresponding iodopyrazole **75**.[91]

Our goal was to improve on the existing Stille and Suzuki couplings of halopyrazoles, given recent the improvements made with regard to phosphine ligands.[5] The first attempted coupling employed phenyltrimethoxysilane with the commercially available 4-bromopyrazole (Table 10). Despite employing a wide variety of palladium catalysts and phosphine ligands, the reactions afforded only recovery of unreacted starting material.

The use of traditional phosphines such as PPh_3 and P(*o*-tol)$_3$ did not afford the coupled product (Table 10, entries 1 and 2). Use of the Buchwald ligands **31** and **32** did not alter this negative result (Table 10, entries 3 and 4), nor did the use of siloxane **16** or preformed hypercoordinate salt TBAT (Table 10, entries 5 and 6).

Following unsuccessful attempts at coupling the unprotected pyrazole, protection of the azole nitrogen was carried out. Sulfonated bromopyrazole **79** was prepared[93] and utilized in the series of coupling reactions highlighted in Table 10. Once again, these conditions did not result in the formation of the desired product, with unreacted starting material being recovered in each case.



79 80 81

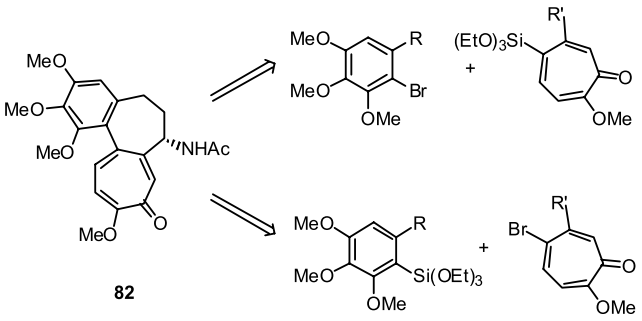
Final attempts at coupling into the pyrazole system were undertaken utilizing 4-iodopyrazole (**80**). This species was utilized due to the presumption that it would be more

reactive, following the general series I > Br ≫ Cl. Unfortunately, the unprotected iodopyrazole **80** did not afford the coupled product when subjected to the series of conditions outlined in Table 10. Utilization of the sulfonated iodopyrazole **81**[93] did not allow for the formation of the coupled product.

The failure of the pyrazole derivatives to afford the coupled product can most likely be attributed to the choice of the protecting groups employed in the above experiments. Previous work has shown halopyrazole couplings to be extremely sensitive to the protection strategy employed on the azole nitrogen. To date, the most sucessful couplings have employed either MOM protection[90] or installation of a trityl group.[91]

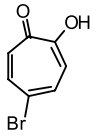
4.4. Application to natural product synthesis

At this point, the focus shifted toward couplings that could be utilized in the synthesis of natural products. The first such system investigated was a coupling that would result in the formation of a critical bond in the synthesis of the anticancer compound colchicine (**82**).[94,95] This bond-forming reaction would occur between a tropolone derivative and a tetrasubstituted aryl bromide or arylsiloxane (Scheme 36).



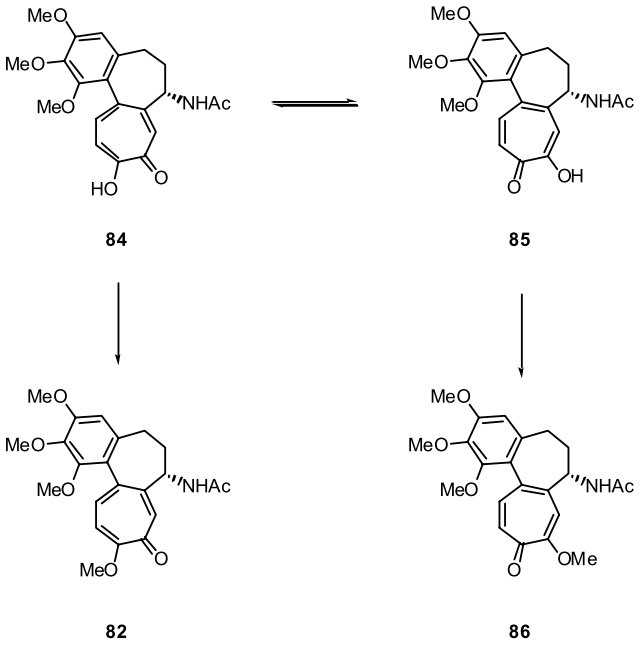
Scheme 36.

Colchicine can be considered a biaryl derivative of benzene and tropolone. Because the siloxane methodology has yet to be used in the cross-couplings of tropolones, the focus was placed on couplings involving this class of compounds. Initial studies were carried out on a model system, which was chosen to be 5-bromotropolone (**83**).



83

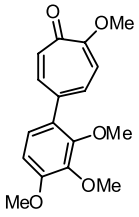
Several total syntheses of colchicine exist in the literature.[96–106] A major downfall of many of these syntheses is that they proceed through colchiceine (**84**). Tautomerization of **84** leads, via **85**, to the formation of isocolchicine (**86**). Consequently, there exists a lack of regiocontrol in the final steps, resulting in the production of equal amounts of colchicine (**82**) and isocolchicine (**86**) (Scheme 37).[97]



Scheme 37.

Our proposed synthesis using the siloxane methodology would offer several advantages over these syntheses. First, the regiochemistry would be set early in the synthesis, which would minimize the loss of valuable intermediates. Second, numerous substitution patterns on the two halves of the coupled piece could be synthesized and coupled under similar reaction conditions. This would allow for easy assembly of colchicine derivatives in a combinatorial fashion.

Interest in short routes to aryltropolones has grown since Fitzgerald reported that 5-(2,3,4-trimethoxyphenyl)tropolone methyl ether (**87**) retains the potent antimitotic properties of colchicine.[107] Therefore, it is of interest to study tropolone couplings for this purpose, as well as for use in the total synthesis of colchicine.



87

The first step in the attempted synthesis of colchicine is testing the siloxane coupling methodology for compatibility with halotropolones. The model system chosen for this task was 5-bromotropolone. It was chosen both for its ready availability, and the fact that its two tautomers are equivalent (Fig. 5). If the unprotected tropolone were to be utilized in cross couplings, the resulting coupled product from each tautomer would be identical.

Couplings of 5-bromotropolones have been successfully accomplished using both Stille and Suzuki couplings. Banwell and co-workers first utilized bromotropolones in

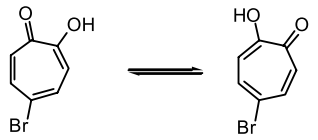
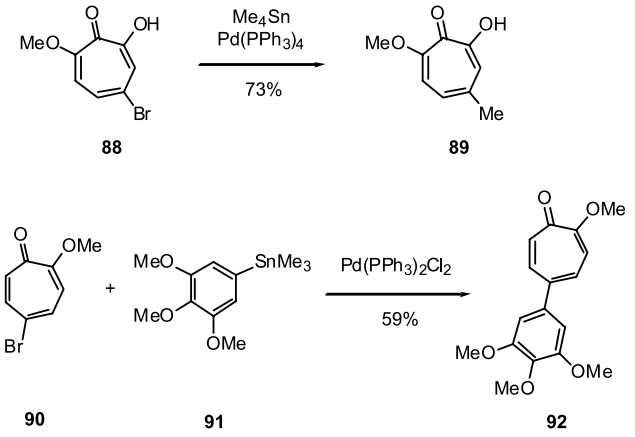


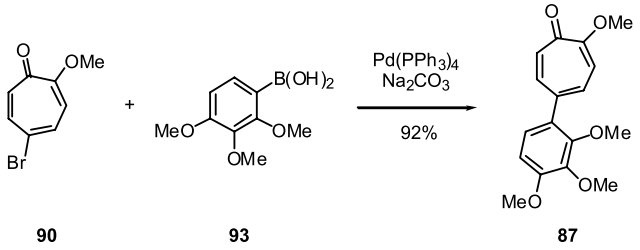
Figure 5. Tautomers of 5-bromotropolone.

palladium-catalyzed couplings with organostannanes and arylboronic acids.[108] In this work, organostannanes were used in the alkylations and arylations of bromotropolones **88** and **90** (Scheme 38). A range of coupled products were obtained, although 5-(2,3,4-trimethoxyphenyl)tropolone methyl ether (**87**) proved elusive. Arylated tropolone **87** is the biaryl portion of the carbon skeleton comprising colchicine.



Scheme 38.

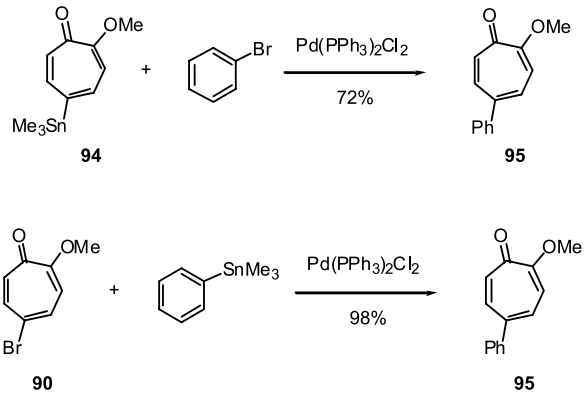
Similar success was achieved in couplings with boronic acids. Additionally, where the Stille methodology failed in the preparation of arylated tropolone **87**, the Suzuki methodology allowed its preparation in excellent yield (Scheme 39).[108] The authors conclude that the Suzuki methodology is clearly superior for use in preparing sterically demanding bicyclic colchicine analogs.



Scheme 39.

Subsequent work by Banwell and co-workers focused on the synthesis of stannylated tropolones and their use in palladium-catalyzed cross-coupling reactions (Scheme 40).[109] This work provided the coupled products, although frequently in lower yield than in the previous work involving boronic acid couplings.

It was our intent to show that siloxane couplings would occur in the tropolone system. The siloxane methodology



Scheme 40.

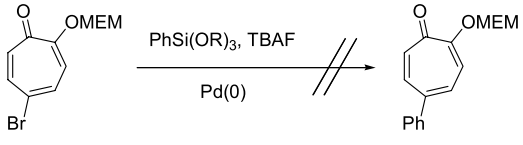
would circumvent problems associated with the use of toxic tin reagents.[2] While stannylated tropolones have been prepared and utilized in palladium-catalyzed couplings, boronic acids incorporating the tropolone moiety have not been synthesized.

To test our methodology, 5-bromotropolone was synthesized using previously established protocols.[110,111] Prior to its use in the siloxane coupling reaction, it was deemed imperative to protect the alcohol functionality of the tropolone. This protection step is necessary to allow for chromatographic purification of the arylated product.[112] Both MOM and MEM groups have been successfully employed in palladium-catalyzed couplings of siloxanes.[45] Correspondingly, the tropolone was protected utilizing standard conditions for the introduction of a MEM group[113] to give the tropolone ether **96**.

Following protection, couplings utilizing the MEM-protected tropolone **96** were investigated. In all but a few cases, the unreacted starting material was recovered. When heated at high temperatures ($>100\ ^{\circ}C$) in DMF or dioxane for a period of several days, decomposition of the starting bromide was observed. The conditions that were employed in these attempted couplings are summarized in Table 11.

As was the case in the attempted couplings of halopyrazoles, traditional phosphines such as PPh_3 and P(*o*-tol)$_3$ in conjunction with $Pd(OAc)_2$ failed to afford the coupled tropolone (Table 11, entries 1 and 2). The use of siloxane **16**,

Table 11. Coupling attempts of MEM-protected 5-bromotropolone **96**

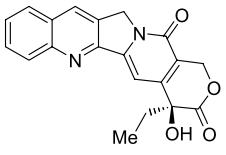


Entry	Pd	Phosphine	R	Solvent
1	$Pd(OAc)_2$	PPh_3	Me	DMF
2	$Pd(OAc)_2$	P(*o*-tol)$_3$	Me	DMF
3	$Pd(OAc)_2$	PPh_3	CH_2CF_3	DMF
4	$Pd(dba)_2$	P(cy)$_2$(*o*-biphenyl)	Me	DMF
5	$Pd(dba)_2$	P(*t*-Bu)$_2$(*o*-biphenyl)	Me	DMF
6	$Pd(PPh_3)_4$	—	Me	Dioxane
7	$PdCl_2(PPh_3)_2$	—	Me	Dioxane

as well as the Buchwald phosphine ligands **31** and **32**, did not alter these negative results (Table 11, entries 3–5). Utilization of tetrakis(triphenylphosphine)palladium(0) or dichlorobis(triphenylphosphine)palladium(II), two catalysts successfully employed in the Stille and Suzuki couplings of bromotropolone derivatives, also failed to give the coupled product (Table 11, entries 6 and 7).

Failure of the bromotropolone derivatives to afford the coupled product could be attributed to the dilute reaction conditions employed in the attempted couplings. Most efforts at coupling were made with the MEM-protected bromotropolone. The results from these experiments suggest that oxidative addition did not occur, as the unreacted starting material was isolated from the attempted reactions. The methoxy-protected tropolone has been shown to couple using the Stille and Suzuki methodologies,[108] which suggests that siloxane coupling should also give the coupled product using both the MEM- and methoxy-protected substrates. Reactions employing a higher catalyst loading, or run at higher concentration, might afford the coupled product.

A second natural product of interest for synthesis using a siloxane coupling as the key bond-forming reaction is camptothecin (**97**), as well as the related compound, mappicine (**98**).[94,114,115] The siloxane coupling methodology would afford a simple route to the synthesis of these two compounds, and varying the two coupling partners in the reaction would allow a simple route to various analogs of the two compounds.



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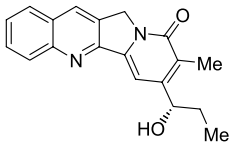
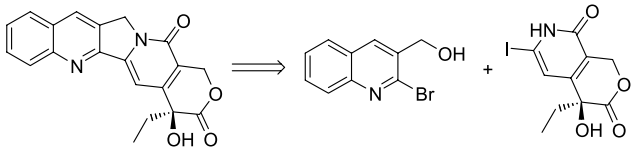


98

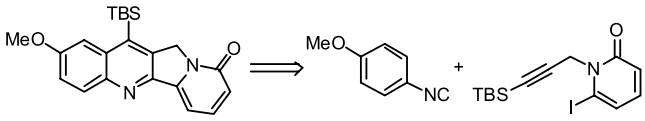
Several syntheses of camptothecin and camptothecin-like compounds have been published.[116] The most notable contributions have been those from Comins et al.[117–120] and Curran et al.[121–126] The short, practical route developed by Comins and co-workers utilized an N-alkylation reaction, followed by an intramolecular Heck reaction to connect the A,B and D,E ring fragments (Scheme 41).[120]



97

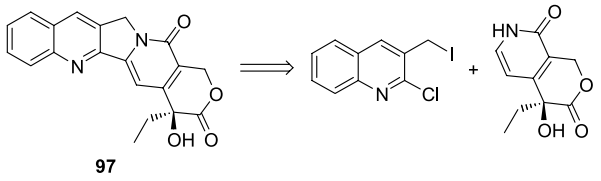
Scheme 41.

The Curran group synthesis utilized a palladium-promoted cascade reaction to form the general carbon framework of the camptothecin-related molecules (Scheme 42).[121] This method was an improvement on Curran's earlier work, which relied on stoichiometric amounts of tin reagents to initiate the radical cascade reaction.[116]



Scheme 42.

In our retrosynthesis of camptothecin (**97**), one synthon may ultimately be obtained from 2-bromoquinoline (Scheme 43). Either fragment may then be utilized as the electrophile or converted into the corresponding siloxane. Due to the challenges present in previous couplings employing structurally similar bromoindoles and bromopyridines, initial studies based on couplings of simple bromoquinolines were designed.

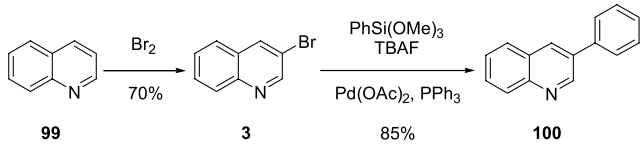


97

Scheme 43.

The first heteroaromatic system to be investigated was 3-bromoquinoline (**3**), which was easily obtained through reaction of quinoline (**99**) with bromine (Scheme 44).[127] This compound has been successfully coupled using Suzuki methodology in yields ranging from 40–90%.[88,128–130] Additionally, 3-iodoquinoline has been cross coupled by Hiyama et al. with alkylphenyldifluorosilanes in good yield.[131]

Siloxane coupling of 3-bromoquinoline (**3**) was then attempted. Using typical conditions for the cross coupling of aryl bromides, 3-phenylquinoline (**100**) was obtained from 3-bromoquinoline **3** in 85% yield (Scheme 44). This coupling proceeded in yields comparable to those obtained in prior Suzuki couplings.[88,128–130]

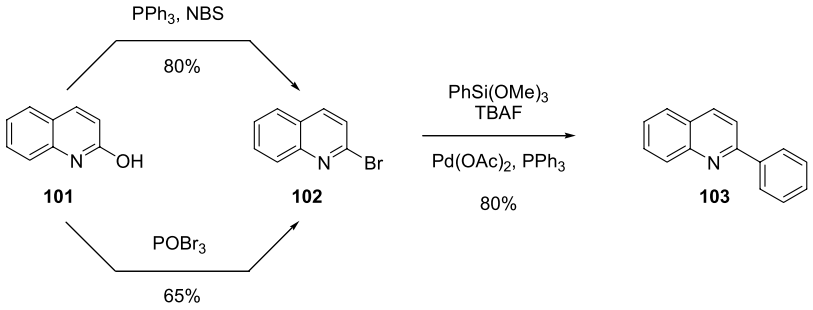


99 **3** **100**

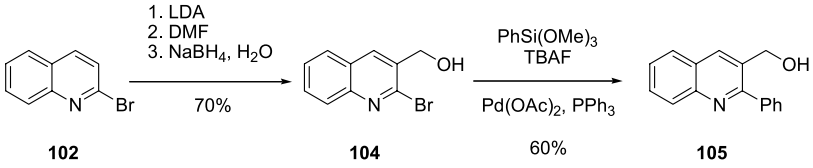
Scheme 44.

One potential advantage of the siloxane over the Suzuki methodology would be the ability to easily synthesize quinoline siloxanes, allowing quinoline to function as either the electrophilic or the nucleophilic coupling partner. Initial attempts to prepare the siloxane from 3-bromoquinoline using modified hydrosilylation[52,53] and organolithium[54] chemistry were unsuccessful.

Having demonstrated the successful coupling of phenyltrimethoxysilane with bromoquinoline **3**, the coupling reaction was investigated using 2-bromoquinoline (**102**). The proposed camptothecin synthesis would depend on the successful coupling of a 3-substituted 2-bromoquinoline derivative. The synthesis of 2-bromoquinoline (**102**) was



Scheme 45.



Scheme 46.

achieved by treatment of 2-hydroxyquinoline (**101**) with either PPh_3/NBS[132] or $POBr_3$ (Scheme 45).[133]

Subsequent coupling with phenyltrimethoxysilane could then be investigated. Using conditions identical to those utilized in the 3-bromoquinoline coupling, 2-phenyquinoline (**103**) was obtained in 80% yield (Scheme 45). While the yields obtained in both bromoquinoline couplings were comparable, it is notable that 2-bromoquinoline required more time to completely react than did 3-bromoquinoline. This observation suggests the possibility of control of sequential couplings in dibromoquinoline systems, as well as other heterodibromides.[134]

While this coupling suggested that siloxane couplings are a viable route toward the synthesis of camptothecin (**97**), a functionalized 2-bromoquinoline would be necessary to ultimately carry out the synthesis. The necessary quinoline piece in the retrosynthesis was thus, prepared by C-3 lithiation of **102** followed by trapping of the lithioquinoline with DMF (Scheme 46).[119] Subsequent reductive work-up resulted in the formation of the functionalized bromoquinoline **104** in 70% yield. Quinoline **104** was then utilized in palladium-catalyzed siloxane coupling with phenyltrimethoxysilane to afford the coupled product **105** in 60% yield (Scheme 46).

Initial studies involving the coupling of bromoquinolines suggested that they are less problematic than bromoindoles in siloxane couplings, behaving more like bromopyridines. An important result obtained in this study centered on the slower rate of coupling observed for 2-bromoquinoline (**102**) versus 3-bromoquinoline (**3**). The coupling also tolerated additional functionality on the quinoline system, as in the case of the coupling of substituted bromoquinoline **104**.

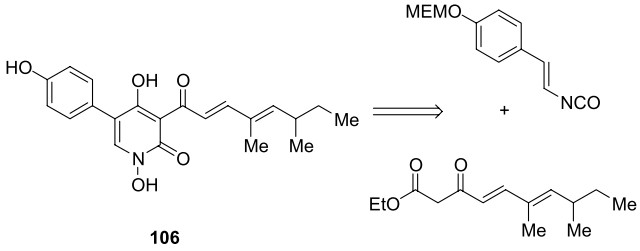
The final natural product of interest was tenellin (**106**), a fungal metabolite elaborated by *Beauveria bassiana* Vuill.[135] Few syntheses of this compound, which contains an unusually substituted 2-pyridone ring, have been reported.[136–138] One such synthesis by Rigby and Qabar utilizes a vinyl isocyanate as a key building block (Scheme 47).[138]

In our retrosynthesis, a substituted methoxypyridine would be one of the critical synthons (Scheme 48). We selected 5-bromo-2-methoxypyridine (**108**) to test the siloxane methodology for potential use in a tenellin synthesis. Pyridine **108** is attractive to study, as it is readily available via bromination of the commercially available 2-methoxypyridine (**107**) (Scheme 49).[139]

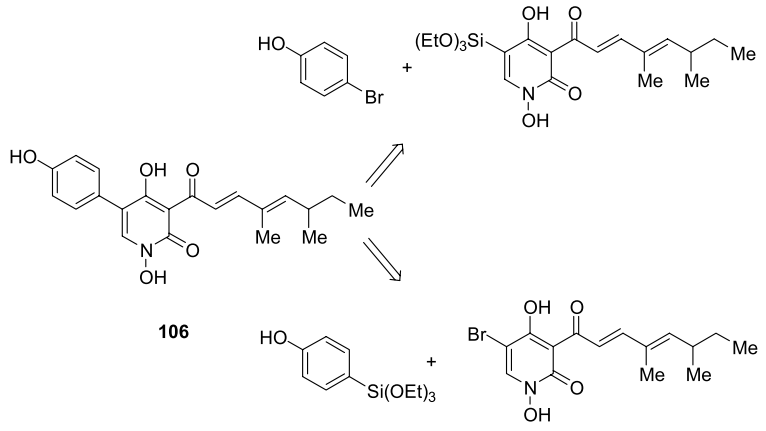
Our interest in pyridine **108** was twofold. First, its use as a model system for the key coupling in a future synthesis of tenellin was of interest. Second, previous attempts to synthesize pyridyl siloxanes had failed. Attempts to utilize both silylation chemistry and Grignard chemistry in the preparation of pyridyl siloxanes were unsuccessful.[52,67]

With 5-bromo-2-methoxypyridine (**108**) in hand, attempts to synthesize the coupled products incorporating this heteroaryl subunit could be made. Prior to these coupling attempts, the synthesis of the corresponding siloxane was attempted. The route selected to obtain this siloxane was the metallation approach.

Treatment of **108** with butyllithium, followed by electrophilic trapping with $Si(OEt)_4$ and an H_2O quench, resulted in formation of siloxane **109** in 25% yield (Scheme 50). The apparent high reactivity of the organolithium intermediate



Scheme 47.

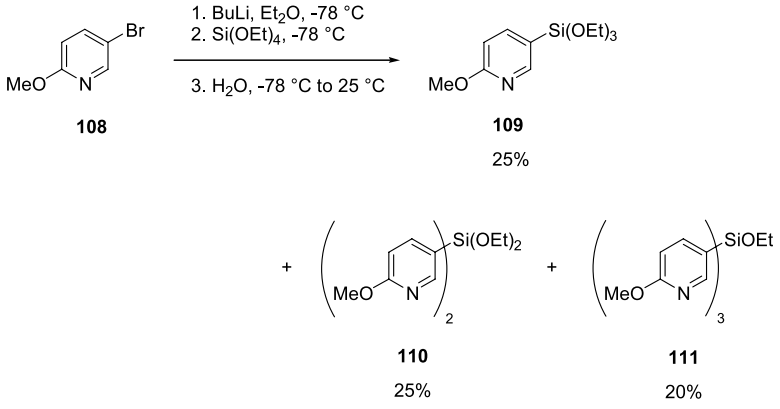


106

Scheme 48.

107 **108**

Scheme 49.



108 **109** 25%

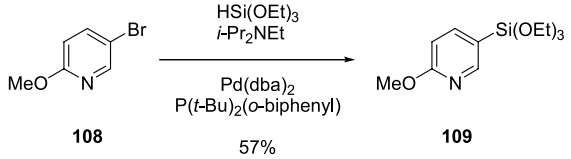
110 25% **111** 20%

Scheme 50.

also resulted in production of the products of di- and tri-addition, **110** and **111**, respectively.

These three products were obtained in an approximate 1:1:1 ratio. While the products were isolated and characterized in the study, this crude reaction mixture has also been shown to effectively cross couple without purification.[45] It should be noted that the monoaryl siloxane **109** may be prepared in higher yield utilizing the silylation approach outlined in Scheme 51.[52]

Having synthesized both bromopyridine **108** and siloxane **109**, couplings were then attempted. This study demonstrated that the methoxypyridine portion of the coupled product could originate from either the siloxane or the aryl halide (Scheme 52). In both couplings, heterobiaryl **112** was obtained in high yield. This result demonstrates the versatility of the siloxane coupling reaction, as the coupled product may be efficiently prepared using either route.



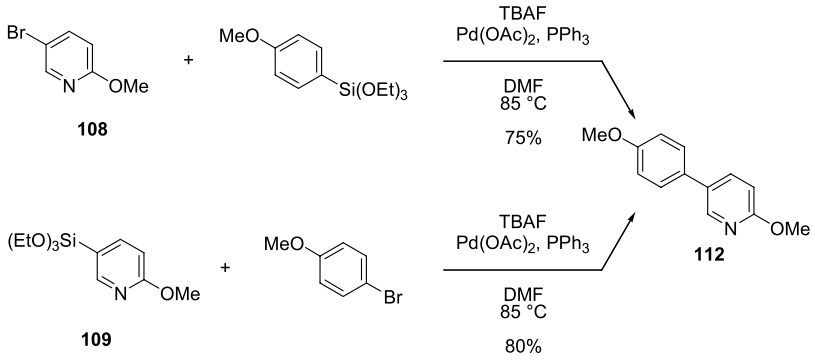
108 **109**

Scheme 51.

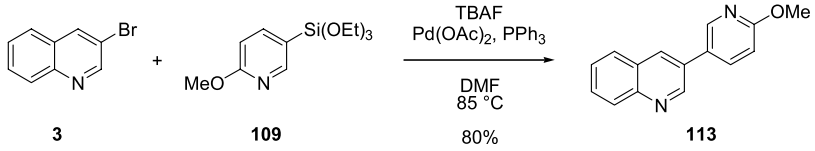
Of significance is that the coupled product **112** represents the formation of the biaryl portion of tenellin (**106**) in one step. This suggests a possible fast and efficient route to tenellin in which the siloxane and aryl halide may comprise either aryl half of the molecule.

An additional coupling employing heteroaryl siloxane **109** was also attempted. The purpose of this coupling was to utilize both a heteroaryl siloxane and a heteroaryl halide. Once again, typical coupling conditions previously employed in aryl bromide couplings allowed for cross coupling to occur between methoxypyridyl siloxane **109** and 3-bromoquinoline (**3**) (Scheme 53). The resulting coupled product **113**, which is comprised of two heteroaryl pieces, was obtained in excellent yield.

Similar pyridines have been utilized in palladium-catalyzed arylations. The most successful and general route is via Stille couplings. In one example, Kelly et al. utilized a similar substituted methoxypyridine in a synthesis of micrococcinic acid.[140] In this work, metal–halogen



Scheme 52.



Scheme 53.

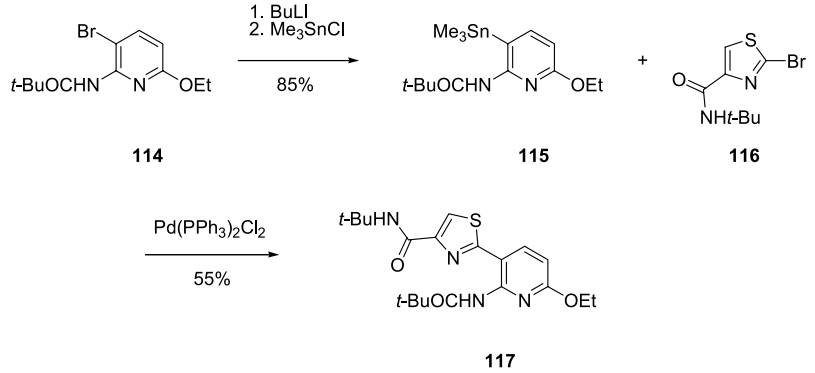
exchange was utilized to prepare 2-ethoxypyridylstannane **115** from **114** in 85% yield (Scheme 54). Stannane **115** was then coupled to bromopyrazole **116** to afford the coupled product **117** in 55% yield.[140]

A second example of the utilization of the Stille methodology in the formation of biaryls in the 2-alkoxypyridine system was contributed by Dehmlow and Veretenov.[141] In this study, stannanes were used in the formation of unsymmetrically and symmetrically structured dihydroxybipyridines. Formation of symmetrical heterobiaryl **119** from **118** occurred in 72% yield (Scheme 55).[141]

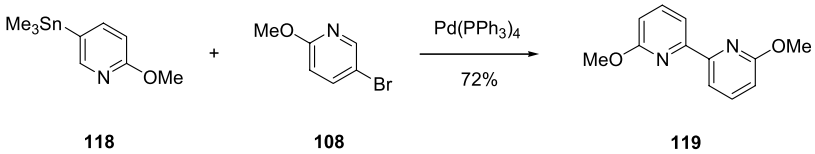
The use of boronic acids in analogous couplings has been more limited. One study by Thompson and co-workers utilized couplings of pyridylboronic acid **121** to highly functionalized bromopyridine **120**, though only 22% of the coupled product **122** was obtained (Scheme 56).[142] In general, these researchers found that the use of ferrocene-ligated palladium catalysts were superior to the more commonly used palladium catalysts.

Lindström later utilized boronic acid couplings to efficiently synthesize precursors to a common food carcinogen.[143] In this study, functionalized bromopyridine **123** was coupled to several different arylboronic acids, all in good yield (Table 12, entries 1–3).

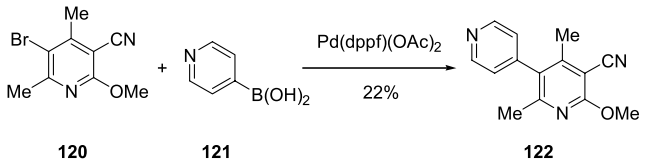
Siloxanes have also been shown to be effective in couplings involving complex bromopyridine derivatives. In preliminary work toward the synthesis of the antitumor antibiotics, streptonigrin, and lavendamycin, hypercoordinate siloxanes



Scheme 54.



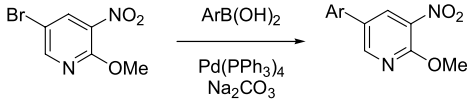
Scheme 55.



120 121 122

Scheme 56.

Table 12. Suzuki couplings with 5-bromo-2-methoxy-3-nitropyridine (**123**)



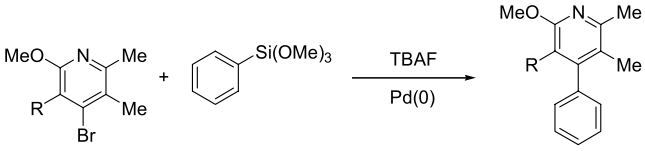
123

Entry	Ar	Yield (%)
1	Ph	80
2	4-MeC_6H_4	70
3	3-$NO_2C_6H_4$	62

were utilized to synthesize a series of highly substituted arylpyridines.[144]

The results of this study provided an insight into the streric and electronic effects of couplings in highly functionalized bromopyridine systems. The steric limitations of these systems were tested by synthesizing the bromopyridines **124–126**. The results from couplings utilizing phenyltrimethoxysilane demonstrated that the coupling would tolerate the sterically demanding *ortho*,*ortho*′ substitution in the bromopyridine (Scheme 57). This demanding substitution pattern is present in the coupling step of the proposed synthesis of the natural products.

The results from the study also showed that electronics, specifically at C-3 of the bromopyridine, played an important role in the coupling reaction. While the coupled product was obtained in the presence of a nitro group at C-3, the reaction afforded no product when the corresponding aminopyridine was employed (Scheme 57).



124, R = Me 89%
125, R = NO_2 36%
126, R = NH_2 0%

Scheme 57.

5. Conclusions

Palladium-catalyzed cross couplings utilizing hypervalent siloxanes have been shown to be a viable alternative to Stille and Suzuki couplings. To date, a large number of simple aryl halides have been shown to afford the coupled product in good to excellent yield. In addition, the methodology has been successfully employed in cross couplings of heteroaryl halides. Due to the low toxicity of the silicon reagents relative to their tin counterparts, siloxane coupling is an attractive alternative to Stille couplings. Furthermore, the stability of siloxanes to chromatography and distillation, as well as the general routes to their synthesis, distinguish siloxane couplings from Suzuki couplings.

Of note is the general and predictable nature of palladium-catalyzed siloxane couplings compared to Suzuki couplings. While Suzuki couplings generally give the coupled products in high yield, the individual reactions are often highly dependent on the reaction conditions employed. In general, aryl iodides couple in high yield in the siloxane methodology when $Pd(dba)_2$ is employed as the catalyst. The exception to this trend is the derivatives of aniline, which couple effectively using $Pd(OAc)_2$ and PPh_3 as the catalyst system. Both aryl and heteroaryl bromides couple efficiently using $Pd(OAc)_2$ and PPh_3 as the catalyst–ligand system, while aryl chlorides afford good yields of the coupled product employing $Pd(dba)_2$ and phosphine ligand **31** as the catalyst system. The reaction performs consistently using DMF as the reaction solvent, and TBAF as the activator.

The large number of aryl and heteroaryl halides that participate in siloxane couplings, as well as the ability to synthesize and subsequently couple aryl and heteroaryl siloxanes, makes the palladium-catalyzed siloxane coupling reaction a powerful method for the formation of functionalized biaryls. Initial results investigating this reaction in key bond-forming reactions in the synthesis of several natural products are promising, and the full results will be reported in due course.

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Biographical sketch

Christopher J. Handy obtained his BS in 1994 from the University of North Carolina. He began his graduate career at the University of Maryland in the group of Philip DeShong. His studies included aryl siloxane-coupling of heteroaromatic systems and NMR studies of hypercoordinate silicates, which led to his PhD in 2002. He then worked as a postdoc at the National Institutes of Health under the direction of Donald Jerina. He is currently a Chemical Analyst at the National Security Administration.

William T. McElroy received his BS in 1995 from Muhlenberg College. He began his graduate studies in 2000 at the University of Maryland working with Philip DeShong. His thesis research concerns the application of siloxane-based cross-coupling strategies to the synthesis of the anticancer agent streptonigrin.

Amy S. Manoso received her BA from the University of Virginia in 1994. She started her graduate studies at the University of Maryland later that year in the laboratory of Philip DeShong. She then moved back to Maryland and worked as an Organic Chemistry Lecturer. She completed her PhD in 2004, which focused on the development of new methodology for the synthesis of aryl siloxanes.

W. Michael Seganish was born in Baltimore, Maryland, USA. He received his BS in 2001 from the University of Maryland working under the direction of Dr. Daniel Evans, where he worked on the design of chiral bis-sulfoxide ligands. He continued his studies at the University of Maryland under the supervision of Professor Philip DeShong, where he is currently completing his PhD, the focus of which is the application of arylsiloxane coupling methodology to the total synthesis of natural products.

Philip DeShong received degrees at the University of Texas, Austin (BS, with Royston Roberts and Philip Stotter) and the Massachusetts Institute of Technology (Sc D, with George Büchi), respectively. After postdoctoral studies with Duilio Arigoni at the ETH, Zürich and Christopher Walsh at MIT, he joined the faculty at the Pennsylvania State University as an Assistant Professor. In 1987, he moved to the University of Maryland where he currently holds appointments in the Chemistry and the Bioengineering programs. He is also a member of the University of Maryland Nanotechnology Center. His research interests over the years have included development of new synthetic methods, particularly organometallic methods, synthesis of biologically active substances, and mechanistic organometallic chemistry. In recent years, his research interests have broadened to include a variety of silicon-based technologies for organic synthesis and surface functionalization.

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Tetrahedron 61 (2005) 12227–12237

Efficient chemoselective deprotection of silyl ethers using catalytic 1-chloroethyl chloroformate in methanol

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Received 14 July 2005; revised 14 October 2005; accepted 17 October 2005

Available online 11 November 2005

Abstract—Fast and chemoselective desilylation of silyl-protected alcohols was achieved using a catalytic amount of 1-chloroethyl chloroformate in methanol. With a minimal amount of 1-chloroethyl chloroformate as the source for anhydrous HCl, extremely efficient cleavage of silyl ethers of primary and secondary alcohols was accomplished, and chemoselective deprotection of one silyl ether in the presence of another silyl or other acid-labile group was possible through controlling the amount of the chloroformate and reaction time.

1. Introduction

Trialkylsilyl-groups have been widely used as hydroxyl-protecting agents in organic synthesis[1] due to easy installation,[1c,2] stability to most reaction conditions and selectivity in cleavage reactions. Cleavage of the silyl ethers can be effected either using acidic conditions or a fluoride source. However, cleavage using a fluoride ion is often associated with poor selectivity in the case of compounds having two different siloxy groups and unwanted side reactions such as silyl migration.[3] Furthermore, use of excess tetrabutylammonium fluoride (TBAF),[4] one of the most commonly employed deprotection reagents, often requires extensive chromatography for the removal of remaining tetrabutylammonium (TBA) salt. Alternatives to the fluoride ion include acidic or basic conditions,[5] Lewis acid catalysts including transition metals,[5] oxidative or reductive methods,[6] and catalytic hydrogenation.[7]

During our investigation on the desilylation of various silyl ethers, we have encountered fast cleavage of silyl ethers with an extremely small amount of 1-chloroethyl chloroformate (CEC) in methanol: triethylsilyl (TES) ethers were cleaved completely in as short as 1 min with 0.01 mol% 1-chloroethyl chloroformate. It is of particular note that 1-chloroethyl chloroformate, which is often utilized as dealkylating agent of tertiary amines,[8] can readily generate hydrochloric acid in alcoholic media at rt, and this anhydrous HCl-catalyzed desilylation in methanol is considerably faster than the previously reported acidic hydrolyses of silyl ethers in aqueous alcoholic solvents.[9] Two reports exist on the rate of aq HCl-mediated hydrolysis of silyl ethers. When more than 0.31 equiv of 1% HCl in 95% aq MeOH was employed for the hydrolysis of *n*-hexyl *tert*-butyldiphenylsilyl (TBDPS) ether, the half-life of desilylation was 225 min.[9a] The half-life of *n*-butyl TBDPS ether hydrolysis was 244 min with 1% HCl in 95% aq EtOH.[9b] In our case, however, the half-life of *n*-hexyl TBDPS ether cleavage was about 20 min when 0.155 equiv of CEC in methanol (equivalent to 0.31 equiv HCl) was employed.[10]

2. Results and discussion

In general, anhydrous HCl can be generated from a chloride source such as thionyl chloride in alcoholic solvents. Though this protocol is conveniently applicable to desilylation, use of thionyl chloride exhibited lower chemoselectivity in the deprotection of triethylsily group in the presence of a *tert*-butyldimethylsilyl group as shown in Table 1 (entries 1–3). With 0.1 mol% of thionyl chloride in methanol, there appeared already a significant amount of diol even after 90 s. On the other hand, employment of CEC (0.1 mol%) ensured unusually high level of chemoselectivity (entry 5). Even with 0.2 mol% CEC, mono-desilylated product was formed in 93% yield (entry 4). Upon reaction with methanol, it is expected to yield one equivalent of HCl and more slowly another equivalent producing CO_2 and volatile acetaldehyde dimethyl acetal, which can be later removed by simple evaporation. This slow and sequential generation of HCl from CEC may be critical for the observed chemoselectivity, contrary to the rapid generation of HCl from thionyl chloride.[11] Commercially

Keywords: 1-Chloroethyl chloroformate; Desilylation; Silyl ethers; Chemoselective; Catalytic.
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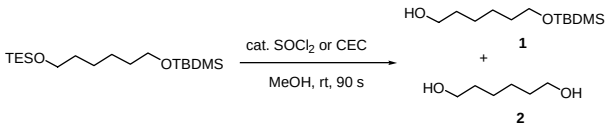
doi:10.1016/j.tet.2005.10.043

Table 1. Results of TES removal in presence of TBDMS group using thionyl chloride or CEC

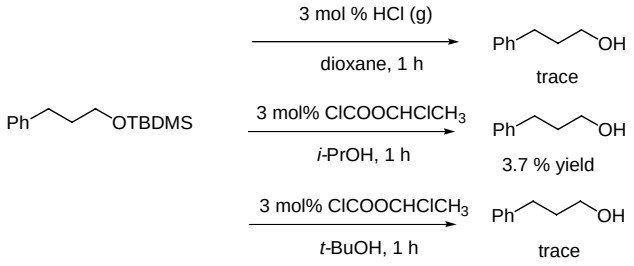


Entry	HCl source	mol%	Yield of **1**[a]	Yield of **2**[a]
1	$SOCl_2$	0.2	58	38
2	$SOCl_2$	0.1	68	19
3	$SOCl_2$	0.05	83	6
4	CEC	0.2	93	5
5	CEC	0.1	95	3

[a] Yields of isolated alcohols.

available methanolic HCl solution (1.25 M) was also examined for the selective TES-removal. In this case, it was difficult to determine optimal amounts of the HCl in methanol due to extremely high reactivity, and when carefully controlled amounts of methanolic HCl was employed, selective removal of TES in the presence of the TBDMS did take place, however the chemoselectivity of mono-desilylation was always inferior to that obtained with CEC.[12] Since the in situ generated hydrogen halides offer many advantages,[13] we investigated the scope of this new protocol.

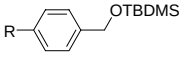
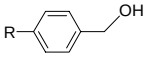
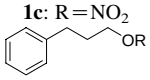
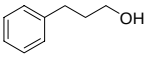
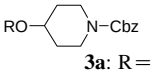
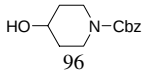
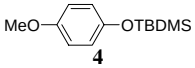
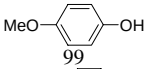
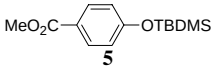
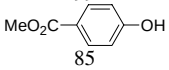
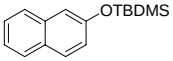
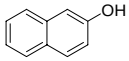
First, it was found that the selection of methanol as a solvent was critical to the observed reactivity of this reaction (Scheme 1). When desilylation of 3-phenyl-1-propyl TBDMS ether was carried out using 3 mol% anhydrous hydrochloric acid in methanol, the cleavage of silyl ether proceeded in less than 3 min giving 98% yield of the alcohol, whereas in 1,4-dioxane the alcohol production was minimal after 1 h. This strongly indicates that the nucleophilic methanol was required for the desilylation, thus ruling out the possibility of silyl cation species as a possible intermediate.[14] When *i*-PrOH or *t*-BuOH was used instead of methanol with 3 mol% of CEC, the reaction was very slow; only 3.7% yield and trace of products, respectively, were obtained after 1 h.



Scheme 1. Desilylation using various solvents. Yields of isolated alcohols.

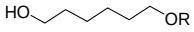
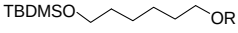
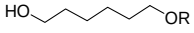
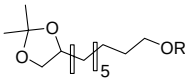
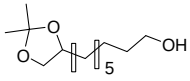
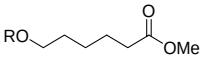
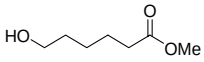
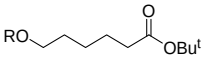
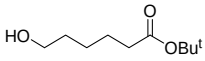
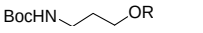
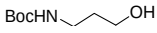
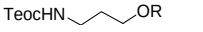
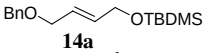
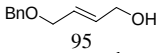
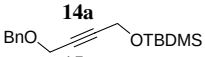
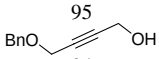
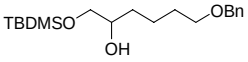
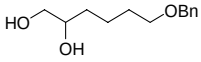
Then we examined the deprotection of various silyl ethers using CEC in methanol (Table 2). First, it was found that the rate of the silyl ether cleavage depends highly upon the Lewis basicity of the alcohol oxygen (entry 1), indicating that the protonation on the silyl oxygen is connected to the reaction rate. As can be seen in Table 2, fast deprotection of TES, TBDMS, and TIPS ethers of primary (entries 2a–c) and secondary alcohols (entries 3a and 3b) was observed with 0.1∼5 mol% of CEC in methanol at rt. Even TBDPS-protected alcohols (entries 2d and 3c) were cleaved efficiently using increased amount (8 and 30 mol%, respectively) of CEC at longer reaction time. This difference in reactivity could be the basis for chemoselective desilylation of compounds having two different siloxy groups. (vide infra). Cleavage of aryl silyl ethers was relatively slower than that of the aliphatic alcohols (entries 4–6), and the rate was again directly related to the electronic properties of the ring substituents, electron-donating methoxy group being more activating than the methoxy-carbonyl (entries 4 and 5).

Table 2. Desilylation of primary, secondary and aryl silyl ethers in methanol

Entry	Silyl ether	Chloroformate amount, reaction time	Product and yield (%)[a]
1			
	1a: R=OMe	3 mol%, <5 min	95
	1b: R=Me	3 mol%, <5 min	97
	1c: R=NO_2	3 mol%, 2.5 h	91
2			
	2a: R=TES	0.1 mol%, <2 min	95
	2b: R=TBDMS	3 mol%, <5 min	98
	2c: R=TIPS	5 mol%, 1.5 h	95
	2d: R=TBDPS	8 mol%, 3 h	94
3			
	3a: R=TES	0.2 mol%, <2 min	96
	3b: R=TBDMS	5 mol%, 30 min	97
	3c: R=TBDPS	30 mol%, 7 h	89
4	 **4**	5 mol%, 4 h	 99
5	 **5**	10 mol%, 65 h	 85
6	 **6**	5 mol%, 20 h	 98

[a] Yields of isolated alcohols.

Table 3. Chemoselective desilylation of various compounds having two different siloxy groups and silyl ethers possessing acid-labile functionalities

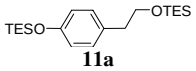
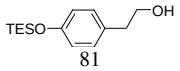
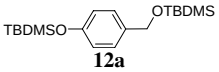
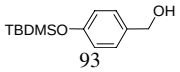
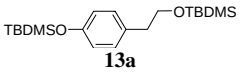
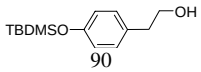
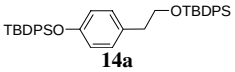
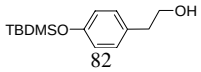
Entry	Silyl ether	Reaction conditions	Product and yield (%)[a]
1			
	7a: R=TBDMS	0.1 mol%, <2 min	R=TBDMS, 95
	7b: R=TIPS	0.1 mol%, <2 min	T=TIPS, 97
	7c: R=TBDPS	0.1 mol%, <2 min	R=TBDPS, 98
	7d: R=THP	0.1 mol%, <2 min	R=THP, 97
	7e: R=Trt	0.1 mol%, <2 min	R=Trt, 98
	7f: R=MOM	0.1 mol%, <2 min	R=MOM, 96
	7 g: R=MEM	0.1 mol%, <2 min	R=MEM, 94
	7 h: R=Ts	0.2 mol%, 15 min	R=Ts, 97
2			
	8a: R=TIPS	1 mol%, 15 min	R=TIPS, 86
	8b: R=TBDPS	3 mol%, <7 min	R=TBDPS, 92
	8c: R=MOM	3 mol%, <7 min	R=MOM, 95
	8d: R=MEM	3 mol%, <7 min	R=MEM, 92
	8e: R=Ts	3 mol%, <7 min	R=Ts, 96
3			
	9a: R=TES	0.2 mol%, 1.5 min	93
4			
	10a: R=TBDMS	3 mol%, <7 min	97
	10b: R=TBDPS	8 mol%, 3.5 h	93
5			
	11a: R=TBDMS	3 mol%, <7 min	92
	11b: R=TBDPS	8 mol%, 3.5 h	88
6			
	12a: R=TBDMS	3 mol%, 25 min	97
	12b: R=TBDPS	8 mol%, 5.5 h	75
7			
	13a: R=TBDMS	3 mol%, 15 min	93
	13b: R=TBDPS	8 mol%, 5.5 h	89
8		3 mol%, 8 min	
	14a		95
9		3 mol%, 10 min	
	15a		84
10		3 mol%, 7 min	
	16a		90

[a] Yields of isolated alcohols.

Encouraged by the above results, selective desilylation of compounds having two different siloxy groups and silyl ethers possessing other acid-sensitive groups was investigated extensively (Table 3). Not many reports exist on preferential cleavage of TES group in presence of TBDMS group.[5i,6c,15,16] In our case, however, TES ether (**7a**) was cleaved cleanly in preference to TBDMS group within 2 min with only 0.1 mol% of CEC, furnishing the desired product in 86% yield. In presence of TIPS or TBDPS ethers (**7b** and **7c**), selective deprotection of TES was achieved in excellent yields. When other acid sensitive hydroxyl-protecting groups, such as THP (**7d**), Trt (**7e**), MOM (**7f**), MEM (**7g**), isopropylidene (**9a**), and tosyl (**7h**) groups were present at other hydroxyl functionalities, all of them survived the TES removal conditions using 0.1∼0.2 mol% CEC. Selective deprotection of TBDMS group was also achieved successfully in presence of TIPS (**8a**), TBDPS (**8b**), MOM (**8c**), MEM (**8d**), Ts (**8e**), and Bn (**14a** and **15a**) groups using 3 mol% of CEC (entry 2). Other acid-sensitive groups such as methyl and *t*-butyl esters (**10a**, **10b**, **11a**, and **11b**) survived the TBDMS and TBDPS removal conditions (entries 4 and 5). Acid-sensitive amine protecting groups, that is, Boc (entry 6) and Cbz (entry 3, Table 2) were also stable under these conditions, and all silyl ethers including TBDPS were preferentially removed. It is noteworthy that Teoc group, a fluoride-sensitive amine protecting moiety, also remained intact under TBDMS and TBDPS cleavage conditions (entry 7). When allylic and propargylic TBDMS ethers were tested, neither migration of the silyl group nor reaction on the unsaturated bond was detected (entries 8 and 9). In the case of a monosilylated vicinal diol, no 1,2-migration of the primary silyl group to the secondary alcohol was observed (entry 10).

Chemoselective desilylation of disilyl ethers of aryl and alkyl alcohols was also tested (Table 4). Generally removal of alkyl silyl ethers is faster than aryl silyl ethers in acidic media,[5a–d] and the reverse is true under basic conditions.[5a,e] Additionally, removal of alkyl silyl ethers is faster than aryl silyl ethers even under neutral hydrogenation condition.[17] In our case, the silyl ethers of aliphatic alcohols were also removed selectively leaving phenolic silyl ethers in

Table 4. Chemoselective desilylation of various aryloxysilyl and alkoxysilyl groups

Entry	Silyl ether	Condition	Productivity and yield (%)[a]
1	 **11a**	0.01 mol%, 1 min	 81
2	 **12a**	5 mol%, 8 min	 93
3	 **13a**	3 mol%, 8 min	 90
4	 **14a**	8 mol%, 5.5 h	 82

[a] Yields of isolated alcohols.

excellent yields. Furthermore, not only di-TBDMS (entries 2 and 3) but also di-TES (entry 1) and di-TBDPS ethers (entry 4) showed reasonable chemoselectivity, yielding 81 and 82% yields, respectively, of the mono-desilylated products.[5f,18] It is noteworthy that the aliphatic TES removal of 2-(4-hydroxyphenyl)ethyl alcohol was extremely fast, taking only 45 s.

Based upon the observed experimental results, a plausible catalytic cycle is presented, which involves the methanolysis of silyl ether catalyzed by HCl, and continuous regeneration of the acid (Fig. 1). The isolation of TBDPSOMe in over 90% yields from the reaction starting from a TBDPS ether strongly supports this catalytic cycle.

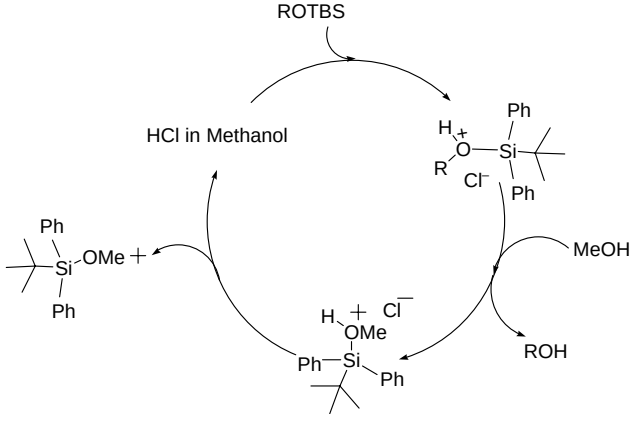


Figure 1. Plausible catalytic cycle for silyl ether cleavage.

3. Conclusion

A facile, convenient and mild desilylation method was developed using 1-chloroethyl chloroformate in methanol. This new method utilizes only a minute amount of 1-chloroethyl chloroformate. No by-products are formed that require complicated chromatographic purification; only short filtration through silica gel suffices to provide pure products. By controlling the amount of the chloroformate and reaction time, chemoselective desilylation was accomplished in presence of bulkier silyl groups and other acid-sensitive alcohol protecting groups.

4. Experimental

4.1. General

All reactions were carried out under nitrogen atmosphere in dried solvents. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on Bruker AM-300 instruments. Chemical shifts were reported in ppm (δ units) downfield of Me_4Si (TMS) as the internal standards, or residual $CHCl_3$. High-resolution mass (HRMS) were obtained on JEOL JMS 600 mass spectrometer. Methylene chloride (CH_2Cl_2) was dried from refluxing with CaH_2; methanol (MeOH), 1-chloroethyl chloroformate, and other commercially available materials were purchased from supplier and used without further purification. All reactions as well as column chromatography were monitored routinely by thin-layer chromatography, which is performed with aluminum backed silica gel plates coated with a 0.2 mm thickness of silica gel 60 F_{254} (Merck). Column chromatography was performed with indicated eluting conditions on silica gel (Merck. 7734 or 9385 Kiesel gel 60).

4.2. General procedure for the preparation of silyl ethers from corresponding alcohols

To a magnetically stirred solution of the alcohol (1.00 mmol) in dry CH_2Cl_2 or DMF (3 mL) was added imidazole (2.00 mmol) and trialkylsilyl chloride (1.10 mmol) sequentially. After starting material disappeared on TLC, brine was poured into reaction mixture. The organic layer was washed with brine (2.0 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography with indicated eluting solvent.

4.2.1. *tert*-Butyl-(4-methoxybenzyloxy)dimethylsilane (1a).[19a] (Eluted with *n*-hexane/EtOAc=30:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.88 (m, 2H), 4.68 (s, 2H), 3.81 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 133.6, 127.5, 113.6, 64.7, 55.3, 26.0, 18.4, −5.2.

4.2.2. *tert*-Butyl-(4-methylbenzyloxy)dimethylsilane (1b).[19b] (Eluted with *n*-hexane/EtOAc=30:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.88

(m, 2H), 4.68 (s, 2H), 3.81 (s, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.4, 129.3, 127.2, 65.1, 21.3, 18.7, −4.9.

4.2.3. *tert*-Butyl-(4-nitrobenzyloxy)dimethylsilane (1c).[19c] (Eluted with *n*-hexane/EtOAc=10:1, yellowish oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J=9.0 Hz, 2H), 7.49 (d, J=8.7 Hz, 2H), 4.83 (s, 2H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 147.4, 130.4, 128.4, 64.2, 24.5, 18.6, −4.3.

4.2.4. 1-Triethylsilyloxy-3-phenylpropane (2a).[7b] (Eluted with *n*-hexane/EtOAc=30:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.15 (m, 5H), 3.64 (t, J=6.4 Hz, 2H), 2.68 (t, 2H), 1.89–1.82 (m, 2H), 0.96 (t, J=8.0 Hz, 9H), 0.60 (q, J=8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 128.8, 128.7, 126.3, 62.5, 34.5, 32.1, 7.3, 5.3.

4.2.5. 1-*tert*-Butyldimethylsilyloxy-3-phenylpropane (2b).[7b] (Eluted with *n*-hexane/EtOAc=30:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J=1.5, 7.8 Hz, 4H), 7.44–7.15 (m, 1H), 3.69 (t, J=6.4 Hz, 2H), 2.72 (t, J=7.8 Hz, 2H), 0.60 (q, J=8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 129.0, 128.8, 126.2, 62.8, 35.0, 32.6, 26.5, 18.8, −4.8.

4.2.6. 1-Triisopropylsilyloxy-3-phenylpropane (2c).[17b] (Eluted with *n*-hexane/EtOAc=30:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.17 (m, 5H), 3.71 (t, J=6.1 Hz, 2H), 2.71 (t, J=7.8 Hz, 2H), 1.89–1.82 (m, 2H), 1.12–1.04 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 128.5, 128.2, 126.2, 62.6, 34.7, 32.1, 18.0, 12.5.

4.2.7. 1-*tert*-Butyldiphenylsilyloxy-3-phenylpropane (2d).[7b] (Eluted with *n*-hexane/EtOAc=30:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, J=1.5, 7.8 Hz, 4H), 7.44–7.15 (m, 16H), 3.69 (t, J=6.4 Hz, 2H), 2.72 (t, J=7.8 Hz, 2H), 1.91–1.84 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 136.2, 134.6, 130.2, 129.1, 128.9, 128.3, 126.3, 62.6, 34.7, 32.1, 18.0, 12.0, 11.8.

4.2.8. 4-(Methoxyphenoxy)-*tert*-butyldimethylsilane (4).[19d] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 4H), 3.74 (s, 3H), 0.96 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 149.8, 121.1, 114.9, 55.9, 26.2, 18.6, −4.1.

4.2.9. Methyl 4-(*tert*-butyldimethylsilyloxy)benzoate (5).[19e] (Eluted with *n*-hexane/EtOAc=7:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J=8.6 Hz, 2H), 3.86 (s, 3H), 0.98 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 160.4, 131.9, 123.6, 120.2, 52.1, 25.9, 18.6, −4.1.

4.2.10. 2-(Naphthalenyloxy)-*tert*-butyldimethylsilane. (6).[19c] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J=8.1 Hz, 1H), 7.72 (d, J=9.0 Hz, 1H), 7.68 (d, J=8.7 Hz, 1H), 7.38 (t, J=7.0 Hz, 1H), 7.30 (t, J=7.0 Hz), 7.19 (d, J=2.4 Hz, 1H), 7.07 (dd, J=3.2 Hz, J=8.7 Hz, 1H), 1.02 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 135.3, 135.2, 129.9, 128.2, 127.3, 126.7, 124.3, 122.6, 115.5, 26.3, 18.8, −3.7.

4.2.11. 1-(Triethylsilyloxy)-4-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-butane (9a). (Eluted with *n*-hexane/EtOAc=15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14–4.05 (m, 2H), 3.72 (t, J=6.4 Hz, 2H), 3.50 (m, 1H), 1.76–1.26 (m, 13H), 0.97–0.93 (m, 9H), 0.61–0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 76.6, 69.9, 63.3, 33.7, 33.0, 27.4, 26.1, 7.2, 4.8; HRMS (CI) Calcd for $C_{26}H_{39}O_3Si$ $[M+H]^+$, 289.2158, found 289.2154.

4.2.12. Methyl 6-(*tert*-butyldimethylsilyloxy)hexanoate (10a).[19f] (Eluted with *n*-hexane/EtOAc=15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.59 (t, J=6.4 Hz, 2H), 2.30 (t, J=8.0 Hz, 2H), 1.63 (quint, J=6.4 Hz, 2H), 1.31–1.39 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 63.1, 51.6, 34.3, 32.7, 26.2, 25.6, 25.0, 28.5, −5.1.

4.2.13. Methyl 6-(*tert*-butyldiphenylsilyloxy)hexanoate (10b).[19g] (Eluted with *n*-hexane/EtOAc=15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.30 (m, 10H), 3.66 (s, 3H), 3.69–3.61 (m, 2H), 2.29 (t, J=7.5 Hz, 2H), 1.69–1.30 (m, 6H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 136.0, 134.6, 130.0, 128.0, 63.1, 51.6, 34.3, 32.7, 26.2, 25.6, 17.9, 12.0.

4.2.14. *tert*-Butyl 6-(*tert*-butyldimethylsilyloxy)hexanoate (11a).[19h] (Eluted with *n*-hexane/EtOAc=15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, J=6.4 Hz, 2H), 2.20 (t, J=7.1 Hz, 2H), 1.61–1.33 (m, 6H), 1.44 (s, 9H), 0.90 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 79.9, 61.2, 35.4, 32.2, 28.0, 26.0, 25.2, 24.7, 18.3, −5.0.

4.2.15. *tert*-Butyl 6-(*tert*-butyldiphenylsilyloxy)hexanoate (11b). (Eluted with *n*-hexane/EtOAc=15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.44–7.34 (m, 6H), 3.65 (t, J=6.3 Hz, 2H), 2.19 (t, J=7.2 Hz, 2H), 1.62–1.35 (m, 6H), 1.44 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 135.8, 134.5, 130.0, 128.2, 79.7, 61.2, 35.4, 32.2, 28.0, 25.9, 25.2, 24.8, 18.5; HRMS (CI) Calcd for $C_{26}H_{39}O_3Si$ $[M+H]^+$, 427.2668, found 427.2665.

4.2.16. *N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)propylamine (12a).[19i] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (br, 1H), 3.64 (t, J=6.0 Hz, 2H), 3.16 (t, J=6.5 Hz, 2H), 1.80–1.60 (m, 2H), 1.44 (s, 9H), 0.92 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 62.6, 39.6, 32.3, 28.8, 26.3, 18.5, −4.3.

4.2.17. *N*-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldiphenylsilyloxy)propylamine (12b).[19j] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.68 (m, 4H), 7.47–7.39 (m, 6H), 5.09 (br, 1H), 3.77 (t, J=6.0 Hz, 2H), 3.34–3.30 (m, 2H), 1.79–1.72 (m, 2H), 1.46 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 135.9, 133.8, 130.2, 128.2, 78.8, 63.2, 39.2, 32.5, 28.9, 27.4, 19.6.

4.2.18. (*E*)-1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)-oxy]-2-butene (14a).[19k] (Eluted with *n*-hexane/EtOAc = 15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H), 5.81–5.66 (s, 2H), 4.52 (s, 2H), 4.28–4.27 (m, 2H), 4.14–4.12 (m, 2H), 0.96 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 133.3, 128.8, 128.1, 128.0, 127.2, 72.6, 66.2, 60.0, 26.4, 18.7, −4.7.

4.2.19. 1-(Benzyloxy)-4-[(*tert*-butyldimethylsilyl)oxy]-2-butyne (15a).[19l] (Eluted with *n*-hexane/EtOAc = 15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 4.64 (s, 2H), 4.42 (s, 2H), 4.24 (s, 2H), 0.98 (s, 6H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.9, 128.7, 128.3, 127.4, 85.7, 81.2, 72.1, 57.8, 52.2, 26.1, 18.7, −4.7.

4.2.20. 6-(Benzyloxy)-1-[(*tert*-butyldimenylsilyl)oxy]-2-hexanol (16a).[19m] (Eluted with *n*-hexane/EtOAc = 5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 4.48 (s, 2H), 3.7–3.3 (m, 5H), 3.2 (br, 2H), 1.7–1.3 (m, 6H), 0.97 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 129.4, 128.8, 128.6, 72.6, 70.6, 67.2, 33.4, 30.0, 26.2, 22.6, 18.8, −4.9.

4.3. General procedure for preparing 4-(trialkylsilyloxy)-piperidine-1-carboxylic acid benzyl ester

To a magnetically stirred solution of 4-hydroxypiperidine (1 mmol) and Et_3N (1.5 mmol) in dry CH_2Cl_2 (3 mL) was added benzyl chloroformate (1.2 mmol) dropwise at 0 °C. After 20 min, the reaction mixture was allowed to warm to rt, and stirred for 2 h. It was washed with brine (2 mL), and the organic layer was dried over $MgSO_4$, filtered, and concentrated. Resulting residue was dissolved in CH_2Cl_2 (3 mL) and imidazole (1.5 mmol) and trialkylsilyl chloride (1.1 mmol) were added and the mixture stirred for 3 h. After starting material disappeared on TLC, brine (5 mL) was poured into the reaction mixture. The organic layer was washed with brine (2 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (eluted with *n*-hexane/EtOAc = 4:1).

4.3.1. 4-(Triethylsilyl)piperidine-1-carboxylic acid benzyl ester (3a). (Eluted with *n*-hexane/EtOAc = 4:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 5.19 (s, 2H), 3.91–3.86 (m, 1H), 3.82–3.74 (m, 2H), 3.35–3.27 (m, 2H), 1.74 (m, 2H), 1.54–1.52 (m, 2H), 1.00–0.96 (m, 9H), 0.66–0.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 135.3, 135.2, 129.9, 128.2, 127.3, 126.7, 124.3, 122.6, 115.5, 26.3, 18.8, −3.7; HRMS (CI) Calcd for $C_{19}H_{32}NO_3Si$ $[M+H]^+$, 350.2151, found 350.2156.

4.3.2. 4-(*tert*-Butyldimethylsilyloxy)piperidine-1-carboxylic acid benzyl ester (3b).[20] (Eluted with *n*-hexane/EtOAc = 4:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5H), 5.12 (s, 2H), 3.91–3.89 (m, 1H), 3.70–3.62 (m, 2H), 3.42–3.35 (m, 2H), 1.70 (m, 2H), 1.52 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 137.4, 128.9, 128.3, 67.3, 41.0, 34.5, 26.2, 18.5, −4.3.

4.3.3. 4-(*tert*-Butyldiphenylsilyloxy)piperidine-1-carboxylic acid benzyl ester (3c). (Eluted with *n*-hexane/EtOAc = 4:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.45–7.29 (m, 11H), 5.11 (s, 2H), 3.93 (m, 1H), 3.73–3.65 (m, 2H), 3.34–3.26 (m, 2H), 1.57 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 137.4, 136.4, 136.2, 135.4, 134.6, 130.3, 129.9, 129.0, 128.4, 128.3, 128.2, 128.1, 68.3, 67.5, 41.2, 34.3, 27.5, 19.7; HRMS (CI) Calcd for $C_{29}H_{36}NO_3Si$ $[M+H]^+$, 474.2464, found 474.2462.

4.3.4. Procedure for the preparation of *N*-[2′-(trimethylsilyl)ethoxycarbonyl]-3-(*tert*-butyldimethyl-silyloxy) propylamine (13a). To a magnetically stirred solution of (trimethylsilyl)ethanol (0.19 mL, 1.30 mmol) in dry CH_2Cl_2 (10 mL) were added triethylamine (0.90 mL, 6.51 mmol) and *N*,*N*′-(disuccinimidyl)carbonate (500 mg, 1.95 mmol) sequentially. After 2 h, 3-aminopropanol (0.12 mL, 1.56 mmol) was added, and the mixture was stirred for additional 2 h. Brine (20 mL) was poured into the reaction mixture, and organic layer was washed with brine (80 mL) three times, separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (*n*-hexane/EtOAc = 1:2) gave pure Teoc-protected alcohol. (0.21 g, 51%). 3-[2′-(Trimethylsilyl)ethoxycarbonyl)-amino-1-propanol was dissolved in CH_2Cl_2 (6 mL). To the solution imidazole (150 mg, 1.92 mmol) and *tert*-butyldimethylsilyl chloride (140 mg, 0.96 mmol) were added and the mixture stirred for 3 h. After the starting material disappeared on TLC, brine (50 mL) was poured into the reaction mixture. The organic layer was washed with brine (50 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc = 12:1) to yield **13a** as a colorless oil. (7.4 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.13 (br, 1H), 4.12–4.07 (m, 2H), 3.69–3.65 (m, 2H), 3.26–3.22 (m, 2H), 1.71–1.63 (m, 2H), 0.92–0.83 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 63.0, 62.3, 39.7, 32.5, 27.2, 26.3, 18.6, −1.1, −4.1; HRMS (CI) Calcd for $C_{15}H_{36}NO_3Si_2$ $[M+H]^+$, 334.2234, found 334.2234.

4.3.5. *N*-[2′-(Trimethylsilyl)ethoxycarbonyl]-3-(*tert*-butyldiphenylsilyloxy)propylamine (13b). (Eluted with *n*-hexane/EtOAc = 15:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.68 (m, 4H), 7.45–7.37 (m, 6H), 5.07 (br, 1H), 4.10 (t, J = 8.3 Hz, 2H), 3.70 (t, J = 6.6 Hz, 2H), 3.31–3.26 (m, 2H), 1.71 (quint, J = 6.6 Hz, 2H), 1.04 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 136.1, 133.9, 130.2, 128.2, 63.2, 62.9, 39.4, 32.4, 27.3, 27.1, 19.5, 18.2, −1.0; HRMS (CI) Calcd for $C_{25}H_{40}NO_3Si_2$ $[M+H]^+$, 458.2547, found 458.2547.

4.3.6. Preparation of 1-(*tert*-butyldimethylsilyloxy)-6-(triethylsilyloxy)-hexane (7a) (a representative procedure for the preparation of compounds having two different silyloxy groups). To a magnetically stirred solution of 1,6-hexanediol (10.0 g, 84.6 mmol) in dry CH_2Cl_2 (60 mL) and DMF (30 mL) were added imidazole (2.9 g, 42.3 mmol) and triethylsilyl chloride (4.80 mL, 28.2 mmol) sequentially. After 5 h, brine (50 mL) was poured into reaction mixture. The organic layer was washed with brine (80 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography

(*n*-hexane/EtOAc = 5:1) gave pure mono-silyl ether. (5.2 g, 78%). 6-(Triethylsilyloxy)hexanol was dissolved in CH_2Cl_2 (60 mL). To the solution were added midazole (2.30 g, 33.2 mmol) and *tert*-butyldimethylsilyl chloride (3.70 g, 24.6 mmol) and the mixture stirred for 3 h. After the starting material disappeared on TLC, brine (50 mL) was poured into reaction mixture. The organic layer was washed with brine (50 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc = 25:1) to yield **7a** as a colorless oil. (7.40 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58–3.54 (m, 4H), 1.52–1.46 (m, 4H), 1.32–1.27 (m, 4H), 0.97–0.90 (m, 9H), 0.86 (s, 9H), 0.60–0.52 (m, 6H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.6, 33.3, 26.4, 26.1, 18.8, 7.2, 4.8, −4.9; HRMS (CI) Calcd for $C_{18}H_{43}O_2Si_2$ $[M+H]^+$, 347.2802, found 347.2800.

4.3.7. 1-(Triethylsilyloxy)-6-(triisopropylsilyloxy)-hexane (7b). (Eluted with *n*-hexane/EtOAc = 25:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, J = 6.6 Hz, 2H), 3.62 (t, J = 6.7 Hz, 2H), 1.58–1.54 (m, 4H), 1.38–1.36 (m, 4H), 1.10–1.05 (m, 21H), 1.00–0.98 (m, 9H), 0.65–0.57 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.7, 63.4, 33.4, 33.2, 26.1, 26.0, 18.4, 12.4, 7.2, 4.8; HRMS (CI) Calcd for $C_{21}H_{49}O_2Si_2$ $[M+H]^+$, 389.3271, found 389.3271.

4.3.8. 1-(*tert*-Butyldiphenylsilyloxy)-6-(triethylsilyloxy)-hexane (7c). (Eluted with *n*-hexane/EtOAc = 25:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.66 (4H, m), 7.39–7.36 (6H, m), 3.68–3.56 (4H, m), 1.61–1.50 (4H, m), 1.37–1.30 (4H, m), 1.05 (9H, s), 0.98–0.93 (9H, m), 0.63–0.55 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 134.6, 129.9, 128.0, 64.4, 63.3, 33.3, 33.0, 27.3, 26.1, 19.7, 7.2, 4.9; HRMS (CI) Calcd for $C_{28}H_{47}O_2Si_2$ $[M+H]^+$, 471.3115, found 471.3117.

4.3.9. 1-(*tert*-Butyldimethylsilyloxy)-6-(triisopropyl silyloxy)hexane (8a).[21a] (Eluted with *n*-hexane/EtOAc = 25:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (2H, J = 6.5 Hz, t), 3.56 (2H, J = 6.5 Hz, t), 1.52–1.46 (4H, m), 1.31–1.29 (4H, m), 1.02 (21H, m), 0.85 (9H, s), 0.03 (6H,s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.8, 63.6, 26.4, 26.0, 18.8, 18.4, 12.4, −4.9.

4.3.10. 1-(*tert*-Butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)hexane (8b).[21b] (Eluted with *n*-hexane/EtOAc = 25:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.43–7.36 (m, 6H), 3.66 (t, J = 6.3 Hz, 2H), 3.59 (t, J = 6.3 Hz, 2H), 1.60–1.49 (m, 4H), 1.37–1.30 (m, 4H), 1.05 (s, 9H), 0.90 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 134.6, 130.0, 128.0, 64.4, 63.7, 33.3, 33.1, 27.4, 26.5, 26.1, 26.0, 19.7, 18.8, −4.8.

4.4. Preparation and spectroscopic data of silyl ethers possessing other acid-sensitive functional groups

4.4.1. Preparation of 1-(triethylsilyloxy)-6-(tetrahydro-2*H*-2′-pyranyloxy)hexane (7d). To a magnetically stirred solution of 1,6-hexanediol (10.0 g, 84.6 mmol) in dry CH_2Cl_2 (60 mL) and DMF (30 mL) were added 3, 4-dihydro-2*H*-pyran (3.1 mL, 33.8 mmol) and pyridinium *p*-toluenesulfonate (850 mg, 3.38 mmol) sequentially. After 3 h, satd aq $NaHCO_3$ solution (50 mL) was poured into the reaction mixture and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (*n*-hexane/EtOAc = 15:1) gave pure mono-tetrahydropyranyl ether (4.8 g, 70%). 6-(Tetrahydro-2*H*-2′-pyranyloxy)-1-hexanol was dissolved in CH_2Cl_2 (60 mL), and to the solution were added imidazole (2.4 g, 35.6 mmol), and chlorotriethylsilane (3.9 g, 26.1 mmol) and the mixture stirred for 3 h. After the starting material disappeared on TLC, brine (60 mL) was poured into the reaction mixture and the organic layer was washed with brine (50 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc = 20:1) to yield **7d** as a colorless oil. (7.1 g, 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58–4.56 (m, 1H), 3.91–3.85 (m, 1H), 3.75–3.69 (m, 1H), 3.60 (t, J = 6.6 Hz, 2H), 3.51–3.50 (m, 1H), 3.42–3.37 (m, 1H), 1.84–1.69 (m, 2H), 1.63–1.54 (m, 8H), 1.38–1.36 (m, 4H), 0.98–0.93 (m, 9H), 0.63–0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.2, 68.0, 63.3, 62.7, 33.3, 31.2, 30.1, 26.5, 26.1, 25.9, 20.1, 7.2, 4.8; HRMS (CI) Calcd for $C_{17}H_{37}O_3Si$ $[M+H]^+$, 317.2512, found 317.2513.

4.4.2. Preparation of 1-(triethylsilyloxy)-6-(triphenylmethyloxy)hexane (7e). To a magnetically stirred solution of 1,6-hexanediol (10 g, 84.6 mmol) in dry CH_2Cl_2 (70 mL) and DMF (30 mL) were added diisopropylethylamine (4.9 mL, 56.4 mmol) and triphenylmethoxymethyl chloride (3.9 g, 28.2 mmol) sequentially. After 3 h, brine (50 mL) was poured into reaction mixture, organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (*n*-hexane/EtOAc = 5:1) gave pure mono-Trt ether. (1.9 g, 37%). The product, 6-(triphenylmethyloxy)-1-hexanol was dissolved in CH_2Cl_2 (18 mL) and to the solution were added imidazole (540 mg, 7.91 mmol), and chlorotriethylsilane (0.97 mL, 5.8 mmol). The mixture was stirred for 3 h. After the starting material disappeared on TLC, brine (10 mL) was poured to the reaction mixture. The organic layer was washed with brine (10 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc = 25:1) to yield **7e** as a colorless oil. (2.4 g, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.43 (m, 6H), 7.28–7.16 (m, 9H), 3.58 (t, J = 6.6 Hz, 2H), 3.05 (t, J = 6.6 Hz, 2H), 1.65–1.60 (m, 2H), 1.54–1.49 (m, 2H), 1.41–1.27 (m, 4H), 0.98–0.93 (m, 9H), 0.63–0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 129.5, 128.2, 127.3, 86.8, 64.1, 63.4, 33.4, 30.6, 26.7, 26.3, 7.3, 4.9; HRMS (CI) Calcd for $C_{31}H_{43}O_2Si$ $[M+H]^+$, 475.3012, found 475.3008.

4.4.3. Preparation of 1-(triethylsilyloxy)-6-(methoxymethoxy)hexane (7f). To a magnetically stirred solution of 1,6-hexanediol (6.0 g, 51.3 mmol) in dry CH_2Cl_2 (70 mL) and DMF (30 mL) were added diisopropylethylamine (5.9 mL, 34.2 mmol) and methoxymethyl chloride (1.3 mL, 17.1 mmol) sequentially. After 3 h, brine (70 mL) was poured into the reaction mixture, and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (*n*-hexane/EtOAc = 2:1) gave pure mono-MOM ether. (2.4 g, 88%). To a solution of 6-(methoxymethyl)-1-hexanol in CH_2Cl_2 (50 mL) were added imidazole (2 g, 15.0 mmol) and chlorotriethylsilane

(2.56 mL, 7.5 mmol) and the mixture stirred for 3 h. After the starting material disappeared on TLC, brine (40 mL) was poured into the reaction mixture. The organic layer was washed with brine (40 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc=10:1) to yield **7f** as a colorless oil. (1.8 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 3.60 (t, J=6.6 Hz, 2H), 3.52 (t, J=6.6 Hz, 2H), 3.36 (s, 3H), 1.63–1.54 (m, 4H), 1.38–1.36 (m, 4H), 0.98–0.93 (m, 9H), 0.63–0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.7, 68.1, 63.3, 55.4, 33.2, 30.1, 26.5, 26.1, 7.2, 4.8; HRMS (CI) Calcd for $C_{14}H_{33}O_3Si$ $[M+H]^+$, 277.2199, found 277.2192.

4.4.4. 1-(*tert*-Butyldimethylsilyloxy)-6-(methoxy methoxy)-hexane (8c).[22a] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2H), 3.58 (t, J=6.6 Hz, 2H), 3.49 (t, J=6.6 Hz, 2H), 3.33 (s, 3H), 1.60–1.48 (m, 4H), 1.35–1.32 (m, 4H), 0.86 (m, 9H), 0.02 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.8, 68.1, 63.6, 55.4, 33.2, 30.1, 26.4, 26.3, 26.0, 18.7, −4.9.

4.4.5. Preparation of 1-(triethylsilyloxy)-6-(methoxyethoxymethoxy)-hexane (7g). To a magnetically stirred solution of 1,6-hexanediol (5.3 g, 44.7 mmol) in dry CH_2Cl_2 (70 mL) and DMF (30 mL) were added diisopropylethylamine (5.2 mL, 29.8 mmol) and MEM chloride (1.7 mL, 14.9 mmol) sequentially. After 3 h, brine (70 mL) was poured into the reaction mixture and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (*n*-hexane/EtOAc=1:2) gave pure mono-MEM ether (1.7 g, 57%). To a solution of 6-(methoxyethoxymethyl)-1-hexanol in CH_2Cl_2 (25 mL) were added imidazole (1.2 g, 16.9 mmol), and chlorotriethylsilane (1.42 mL, 8.4 mmol) and the mixture stirred for 3 h. After the starting material disappeared on TLC, brine (20 mL) was poured into reaction mixture. The organic layer was washed with brine (20 mL) twice, separated, dried over $MgSO_4$, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc=8:1) to yield **7g** as a colorless oil. (2.1 g, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.71 (s, 2H), 3.71–3.68 (m, 2H), 3.62–3.54 (m, 6H), 3.40 (s, 3H), 1.62–1.51 (m, 4H), 1.37–1.35 (m, 4H), 0.98–0.93 (m, 9H), 0.63–0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.8, 72.2, 68.3, 67.0, 63.2, 59.4, 33.2, 30.1, 26.4, 26.1, 6.99, 4.78; HRMS (CI) Calcd for $C_{16}H_{37}O_4Si$ $[M+H]^+$, 321.2461, found 321.2464.

4.4.6. 1-(*tert*-Butyldimethylsilyloxy)-6-(methoxyethoxymethoxy)-hexane (8d).[22b] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (s, 2H), 3.58 (t, J=6.6 Hz, 2H), 3.49 (t, J=6.6 Hz, 2H), 3.33 (s, 3H), 1.60–1.48 (m, 4H), 1.35–1.32 (m, 4H), 0.87 (m, 9H), 0.01 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.8, 72.2, 68.3, 67.0, 63.2, 59.4, 33.2, 30.1, 26.4, 26.1, 18.7, −4.9.

4.4.7. Preparation of toluene-4-sulfonic acid 6-(triethylsilyloxy)-hexyl ester (7h). To a magnetically stirred solution of 1,6-hexanediol (5.0 g, 42.3 mmol) in dry CH_2Cl_2 (70 mL) and DMF (30 mL) were added imidazole (2.88 g, 42.3 mmol), and chlorotriethylsilane (3.56 mL, 21.2 mmol) sequentially and the mixture stirred for 3 h. After 3 h, brine (70 mL) was poured into the reaction mixture and the organic layer was separated, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (*n*-hexane/EtOAc=5:1) gave pure mono-triethylsilyl ether. (4.0 g, 81%). To a solution of 6-(triethylsilyloxy)-1-hexanol (800 mg, 3.44 mmol) in CH_2Cl_2 (12 mL) were added triethylamine (0.72 mL, 5.16 mmol), and *p*-toluenesulfonyl chloride (660 mg, 3.44 mmol) and the mixture stirred for 3 h. After the starting material disappeared on TLC, brine (10 mL) was poured into reaction mixture. The organic layer was washed with brine (10 mL) twice, separated, dried over MgSO4, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc=10:1) to yield **7h** as a colorless oil. (1.0 g, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.76 (m, 2H), 7.35–7.32 (m, 2H), 4.01 (t, J=7.2 Hz, 2H), 3.56 (t, J=6.6 Hz, 2H), 2.40 (s, 3H), 1.66–1.59 (m, 2H), 1.49–1.43 (m, 2H), 1.31–1.26 (m, 4H), 0.99–0.92 (m, 9H), 0.62–0.54 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 133.5, 130.2, 128.2, 71.0, 62.9, 33.0, 29.2, 25.6, 21.9, 6.2, 4.7; HRMS (CI) Calcd for $C_{19}H_{35}O_4SiS$ $[M+H]^+$, 387.2025, found 387.2026.

4.4.8. Toluene-4-sulfonic acid 6-(*tert*-butyldimethylsilyloxy)hexyl ester (8e).[22c] (Eluted with *n*-hexane/EtOAc=10:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.76 (m, 2H), 7.49–7.46 (m, 2H), 3.98 (t, J=7.2 Hz, 2H), 3.55 (t, J=6.6 Hz, 2H), 2.37 (s, 3H), 1.65–1.58 (m, 2H), 1.44–1.40 (m, 2H), 1.27–1.25 (m, 4H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 133.5, 130.2, 128.2, 71.0, 63.3, 33.0, 29.2, 27.0, 26.3, 25.6, 25.6, 22.0, 18.7, −4.9.

4.4.9. Preparation of 1-(triethylsilyloxy)-4-(ethylsilyloxyethyl)-benzene (11a)[23d] **(a representative procedure for the preparation of compounds having two same silyloxy groups)** To a magnetically stirred solution of an alcohol (1 mmol) in dry CH_2Cl_2 (3 mL) or DMF (3 mL) were added imidazole (2.5 mmol) and triethylsilyl chloride (2.2 mmol) sequentially. After the starting material disappeared on TLC, brine (2 mL) was poured into reaction mixture. The organic layer was washed with brine (2 mL) twice, separated, dried over MgSO4, filtered, and concentrated. Resulting residue was further purified by flash chromatography (*n*-hexane/EtOAc=25:1) to yield **11a** as a colorless oil. (97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–7.03 (d, J=8.3 Hz, 2H), 6.77–6.74 (d, J=8.3 Hz, 2H), 3.76 (t, J=7.2 Hz, 2H), 2.76 (t, J=7.2 Hz, 2H), 1.02–0.89 (m, 18H), 0.76–0.51 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 131.8, 130.2, 119.6, 64.6, 38.9, 6.74, 6.62, 4.95, 4.37.

4.4.10. 1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)benzene (11b).[19c] (Eluted with *n*-hexane/EtOAc=25:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J=8.4 Hz, 2H), 6.79 (d, J=6.79 Hz, 2H), 4.66 (s, 2H), 0.98 (s, 9H), 0.93 (s, 9H), 0.18 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 132.3, 129.9, 120.3, 64.6, 25.7, 25.6, 18.4, 18.2, −4.4, −5.3.

4.4.11. 1-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyl dimethylsilyloxyethyl)benzene (11c).[5j] (Eluted with *n*-hexane/EtOAc=25:1, colorless oil); ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.04 (d, J=6.5 Hz, 2H), 6.74 (d, J=6.6 Hz, 2H), 3.76 (t, J=7.0 Hz, 2H), 2.74 (t, J=7.0 Hz, 2H), 0.97 (s, 9H), 0.86 (s, 9H), 0.16 (s, 6H), −0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 132.6, 130.4, 120.2, 65.2, 39.2, 26.3, 26.1, 18.6, 18.4, −4.1, −5.0.

4.4.12. 1-(*tert*-Butyldiphenylsilyloxy)-4-(*tert*-butyldiphethylsilyloxyethyl)benzene (11d).[5f] (Eluted with *n*-hexane/EtOAc=25:1, colorless sticky oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.69 (m, 4H), 7.57–7.54 (m, 4H), 7.36–7.31 (m, 12H), 6.87–6.85 (m, 2H), 6.67–6.64 (m, 2H), 3.75 (t, J=7.0 Hz, 2H), 2.71 (t, J=7.0 Hz, 2H), 1.08 (s, 9H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 136.0, 135.9, 133.5, 131.9, 130.3, 130.2, 129.9, 128.1, 128.0, 126.3, 119.7, 65.6, 38.8, 27.2, 26.9, 19.9, 19.5.

4.5. Representative procedure for the cleavage of silyl ether

To a magnetically stirred solution of starting material (silyl ether) (1 mmol) in methanol (1 mL), was added indicated amount of 1-chloroethyl chloroformate dropwise at rt. The mixture was stirred at rt until the starting material disappeared on TLC, then the reaction was quenched by addition of satd aq $NaHCO_3$ solution (3 mL), and the mixture was extracted with ethyl ether (4 mL×2). The organic layer was dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was filtered through a short silica gel column and the corresponding alcohol was obtained in pure form.

4.5.1. 4-Hydroxypiperidine-1-carboxylic acid benzyl ester (Table 2, entry 3).[23a] (Eluted with *n*-hexane/EtOAc=1:2, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 5.09 (s, 2H), 3.88–3.72 (m, 4H), 3.12–3.03 (m, 2H), 1.87–1.78 (m, 2H), 1.46–1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 137.0, 128.9, 128.6, 128.2, 67.6, 67.2, 41.9, 34.2.

4.5.2. 6-(*tert*-Butyldimethylsilyloxy)-1-hexanol (Table 3, entries 1 and 2).[23b] (Eluted with *n*-hexane/EtOAc=5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81–3.57 (m, 4H), 1.82 (br, 1H), 1.56–1.44 (m, 4H), 1.41–1.31 (m, 4H), 0.90 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.4, 63.2, 32.8, 31.5, 25.9, 22.5, 18.5, 14.0, −5.3.

4.5.3. 6-(Triisopropylsilyloxy)-1-hexanol (Table 3, entries 1 and 2).[23c] (Eluted with *n*-hexane/EtOAc=5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (t, J=6.6 Hz, 2H), 3.54 (t, J=6.6 Hz, 2H), 1.95 (br, 1H), 1.60–1.55 (m, 4H), 1.52–1.36 (m, 4H), 1.16–1.08 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.7, 63.0, 33.4, 33.2, 26.0, 25.9, 18.4, 12.4.

4.5.4. 6-(*tert*-Butyldiphenylsilyloxy)-1-hexanol (Table 3, entries 1 and 2).[23c] (Eluted with *n*-hexane/EtOAc=5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4H), 745–7.31 (m, 6H), 3.67 (t, J=6.6 Hz, 2H), 3.61 (t, J=6.6 Hz, 2H), 1.65–1.50 (m, 4H), 1.46–1.30 (m, 4H), 1.25 (br, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 133.8, 129.4, 127.5, 63.7, 62.2, 32.3, 32.2, 26.7, 25.4, 25.3, 19.1.

4.5.5. 6-(Tetrahydro-2*H*-2-pyranyloxy)-1-hexanol (Table 3, entry 1).[23d] (Eluted with *n*-hexane/EtOAc=5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 1H), 3.88 (m, 2H), 3.53–3.34 (m, 4H), 1.92–1.34 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.2, 68.0, 63.3, 62.7, 33.3, 31.2, 30.1, 26.5, 26.1, 25.9, 20.1.

4.5.6. 6-(Triphenylmethyloxy)-1-hexanol (Table 3, entry 1).[23e] (Eluted with *n*-hexane/EtOAc=5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.43 (m, 6H), 7.28–7.15 (m, 9H), 3.58 (t, J=6.0 Hz, 2H), 3.17 (t, J=6.5 Hz, 2H), 1.65–1.60 (m, 2H), 1.54–1.49 (m, 3H), 1.45–1.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 129.7, 128.1, 127.5, 85.8, 65.1, 63.4, 33.4, 30.6, 26.7, 26.2.

4.5.7. 6-(Methoxymethoxy)-1-hexanol (Table 3, entries 1 and 2).[23f] (Eluted with *n*-hexane/EtOAc=2:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 3.63 (t, J=6.6 Hz, 2H), 3.54 (t, J=6.3 Hz, 2H), 3.36 (s, 3H), 3.14 (br, 1H), 1.62–1.56 (m, 4H), 1.50–1.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.2, 67.6, 62.6, 55.0, 32.5, 29.5, 25.9, 25.5.

4.5.8. 6-(Methoxyethoxymethoxy)-1-hexanol (Table 3, entries 1 and 2).[23d] (Eluted with *n*-hexane/EtOAc=1:2, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.69 (s, 2H), 3.66–3.61 (t, J=6.0 Hz, 2H), 3.56–3.44 (m, 6H), 3.40 (s, 3H), 2.53 (br, 1H), 1.62–1.54 (m, 4H), 1.40–1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.7, 72.1, 68.2, 67.0, 62.9, 59.3, 32.9, 29.9, 26.3, 25.9.

4.5.9. Toluene-4-sulfonic acid 6-hydroxyhexyl ester (Table 3, entries 1 and 2).[23] (Eluted with *n*-hexane/EtOAc=2:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2H), 7.37–7.34 (m, 2H), 4.04–3.98 (m, 2H), 3.59–3.53 (m, 2H), 2.54 (s, 1H), 2.45 (s, 3H), 1.66–1.60 (m, 2H), 1.55–1.46 (m, 2H), 1.38–1.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 133.28, 130.3, 128.2, 71.1, 62.8, 32.7, 29.1, 25.5, 22.0.

4.5.10. 4-(2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl)-butanol (Table 3, entry 3).[23h] (Eluted with *n*-hexane/EtOAc=7:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10–4.00 (m, 2H), 3.73 (t, J=6.5 Hz, 2H), 3.50 (m, 1H), 2.18 (br, 1H), 1.62–1.31 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.8, 76.4, 69.7, 63.3, 33.7, 33.0, 27.4, 26.1.

4.5.11. Methyl 6-hydroxyhexanoate (Table 3, entry 4).[23i] (Eluted with *n*-hexane/EtOAc=2:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.64 (m, 2H), 3.01 (br, 1H), 2.34 (t, J=7.2 Hz, 2H), 1.66 (q, J=7.4 Hz, 2H), 1.59 (q, J=7.0 Hz, 2H), 1.45–1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 62.5, 51.9, 34.1, 32.5, 25.8, 25.0.

4.5.12. *tert*-Butyl 6-hydroxyhexanoate (Table 3, entry 5).[19h] (Eluted with *n*-hexane/EtOAc=4:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, J=6.6 Hz, 2H), 2.37 (br, 1H), 2.23 (t, J=7.4 Hz, 2H), 1.66–1.53 (m, 4H), 1.46 (s, 9H), 1.48–1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 79.8, 61.4, 35.4, 32.2, 28.0, 25.2, 24.7.

4.5.13. *N*-[(*tert*-Butyloxycarbonyl)]-3-amino-1-propanol (Table 3, entry 6).[23j] (Eluted with *n*-hexane/EtOAc=1:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (br, 1H),

3.79 (br, 1H), 3.65 (m, 2H), 3.26–3.24 (m, 2H), 1.69–1.66 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 79.8, 59.6, 37.5, 33.0, 28.7.

4.5.14. *N*-[(2′-Trimethylsilylethyl)oxy]-3-amino-1-propanol (Table 3, entry 7). (Eluted with *n*-hexane/EtOAc = 1:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (br, 1H), 4.11 (t, J = 8.4 Hz, 2H), 3.63 (m, 2H), 3.31–3.25 (m, 3H), 2.42 (br, 1H), 1.66 (quint, J = 6.6 Hz, 2H), 0.94 (t, J = 8.4 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 63.6, 59.7, 37.9, 33.0, 18.1, −1.1; HRMS (CI) Calcd for $C_9H_{22}NO_3Si$ $[M+H]^+$, 220.1369, found 220.1371.

4.5.15. (*E*)-4-(Benzyloxy)-2-buten-1-ol (Table 3, entry 8).[23k] (Eluted with *n*-hexane/EtOAc = 2:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.81–5.66 (m, 2H), 4.54 (s, 2H), 4.28–4.27 (m, 2H), 4.14–4.12 (m, 2H), 2.24 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 132.3, 128.3, 127.7, 127.5, 72.6, 70.3, 62.7.

4.5.16. 4-(Benzyloxy)-2-butyn-1-ol (Table 3, entry 9).[23l] (Eluted with *n*-hexane/EtOAc = 2:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.61 (s, 2H), 4.23 (d, 2H), 4.09 (m, 2H), 1.68 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 128.4, 128.1, 127.9, 86.3, 81.7, 71.6, 71.4, 57.4.

4.5.17. 6-(Benzyloxy)-1,2-hexanediol (Table 3, entry 10).[23m] (Eluted with *n*-hexane/EtOAc = 5:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 4.48 (s, 2H), 3.76–3.31 (m, 5H), 3.24 (br, 2H), 1.75–1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 129.4, 128.8, 128.6, 72.6, 70.6, 67.2, 33.4, 30.0, 26.2, 22.6.

4.5.18. 2-[4′-(Triethylsilyloxy)phenyl]ethanol (Table 4, entry 1).[22d] (Eluted with *n*-hexane/EtOAc = 6:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–7.04 (m, 2H), 6.81–6.77 (m, 2H), 3.76 (t, J = 6.6 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H), 2.04 (br, 1H), 1.02–0.97 (m, 9H), 0.77–0.69 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 131.5, 130.3, 120.4, 64.1, 38.8, 7.0, 5.4.

4.5.19. 4-(*tert*-Butyldimethylsilyloxy)benzyl alcohol (Table 4, entry 2).[19c] (Eluted with *n*-hexane/EtOAc = 6:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.84 (m, 2H), 4.60 (s, 2H), 1.74 (br, 1H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 132.3, 129.9, 120.3, 64.6, 25.6, 18.4, −4.0.

4.5.20. 2-[4′-(*tert*-Butyldimethylsilyloxy)phenyl]ethanol (Table 4, entry 3).[23n] (Eluted with *n*-hexane/EtOAc = 6:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.06 (m, 2H), 6.81–6.77 (m, 2H), 3.58 (t, J = 6.6 Hz, 2H), 2.80–2.76 (t, J = 6.6 Hz, 2H), 2.10 (s, 1H), 1.00 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 131.5, 130.3, 120.5, 64.1, 38.8, 26.1, 18.6, −4.0.

4.5.21. 2-[4′-(*tert*-Butyldiphenylsilyloxy)phenyl]ethanol (Table 4, entry 4).[23o] (Eluted with *n*-hexane/EtOAc = 6:1, colorless oil); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.70 (m, 4H), 7.41–7.33 (m, 6H), 6.94–6.91 (m, 2H), 6.72–6.69 (m, 2H), 3.77–3.71 (m, 2H), 2.74–2.68 (m, 2H), 1.47 (br, 1H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 136.0, 133.4, 131.1, 130.3, 128.2, 126.3, 120.2, 64.1, 38.7, 27.0, 20.0.

Acknowledgements

Generous financial support from the Korea Research Fund (2004-015-C00273) is gratefully acknowledged.

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11. We examined the selective TES cleavage over TBDMS with lower amount of thionyl chloride (0.01, 0.02, 0.025 mol%), and the results were still less desirable than those obtained with 1-chloroethyl chloroformate (83–89% yield vs 93–95%, respectively).
12. Per suggestion from one of the reviewers, commercially available 1.25 M HCl in methanol (Fluka) was examined in

the desilylation. By employing varying amounts of HCl in methanol from 0.025, 0.05, 0.1, to 0.2 mol%, we obtained mono-desilylated alcohol (Table 1, **1**) in 85, 89, 86, and 76% yields, respectively, along with diols. These yields were 8–21% lower than those obtained with CEC. When a very small amount (~0.01 mol%) of methanolic HCl was employed, the yield of TES removal was less than 6%, and most starting material was recovered. We also carried out selective TBDMS removal over TIPS with **8a** with varying amount of HCl, and yields were 73–83%, which are again lower than those obtained with CEC.

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The effect of coordination on the reaction of *N*-tosyl imines with diethylzinc

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Received 26 August 2005; revised 20 September 2005; accepted 23 September 2005

Available online 21 October 2005

Abstract—The effect of coordination on the reaction of *N*-tosyl imines and diethylzinc was studied in detail. It showed that there was strong coordination between *N*-tosyl imine and diethylzinc. Due to this coordination, *N*-tosyl imines could be reduced directly through the β-H transferring mechanism by diethylzinc in nonpolar solvents to afford the corresponding secondary amines in excellent yields at mild conditions. The coordination of diethylzinc and *N*-tosyl imine was hindered by reacting in polar solvents or adding TMEDA to the reaction, it afforded ethylating product partially or exclusively.

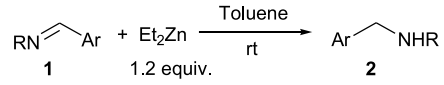
1. Introduction

The reduction of imines to amines is an important transformation in organic chemistry. Most of the methods involve borohydride reagents or transition metal hydrogenation catalysts;[1] Few general methods employing main group Lewis acid catalysts have appeared.[2] Imines also could be reduced by Grignard reagents bearing β-H. Thies et al. have observed that *N*-benzylidene-*N*-butylimine could be partially reduced to amines by *i*-PrMgI during the addition reaction.[3] Davis et al. have also found that *N*-sulfinylimine could be slightly reduced to amines by *n*-BuMgCl during the addition reaction.[4] Crowe et al. have even reported that, in the presence of a catalytic amount of Cp_2TiCl_2, *n*-BuMgCl could be used as the reductive reagent in the reduction of imine.[5]

Diethylzinc has been widely applied in organic synthesis, such as addition to aldehydes,[6] ketones[7] and imines,[1a] radical addition as chain-transfer agent[2b,8] and catalytic enantioselective reduction of ketones as the precatalyst.[9]

Though diethylzinc could reduce benzaldehyde to afford benzyl alcohol as the byproduct in the addition reaction to benzaldehyde,[10] there are also a few reports about the reduction of imines by diethylzinc during the enantioselective addition to the imines.[11]

Table 1. Reduction of imines by diethylzinc in toluene



Entry	Ar	R	Time (h)	Yield[a] of **2** (%)
1	**1a**, Ph	Ts	1	**2a**, 98
2	**1b**, 4-$MeOC_6H_4$		1	**2b**, 96
3	**1c**, 2-$MeOC_6H_4$		1	**2c**, quant.
4	**1d**, 4-MeC_6H_4		2	**2d**, 71
5	**1e**, 4-ClC_6H_4		1	**2e**, 98
6	**1f**, 1-$C_{10}H_7$		5	**2f**, 70
7	**1g**, Ph	Ms	1	**2g**, 86
8	**1h**, Ph	$P(O)Ph_2$	24	—
9	**1i**, Ph	Ph	24	—
10	**1j**, Ph	2-$MeOC_6H_4$	24	—

[a] Isolated yield.

Various imines were allowed to react with diethylzinc in toluene at rt, the results were summarized in Table 1. All *N*-tosyl imines afforded the corresponding reduction products with good to excellent yields exclusively (entry 1–7, Table 1) while there was no reductive or addition reaction product under the same conditions in the case of *N*-aryl aldimines and *N*-phosphinylimine (entry 8–10, Table 1). For *N*-phosphinylimine had the similar structure to *N*-tosyl imine, it was possible due to the bond length differences between *N*-tosyl-imine and *N*-phosphinylimine.

The effect of solvents on the reaction of *N*-tosyl imine and diethylzinc was studied. The results were shown in Table 2. It turned out that solvents had strong effect on the reaction.

Keywords: *N*-Tosyl imines; Diethylzinc; Reduction; Ethylation; Solvent effect; Coordination.
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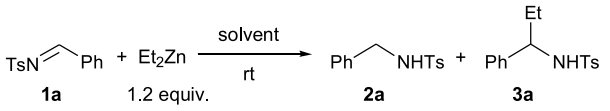
doi:10.1016/j.tet.2005.09.111

Table 2. Effect of the solvents



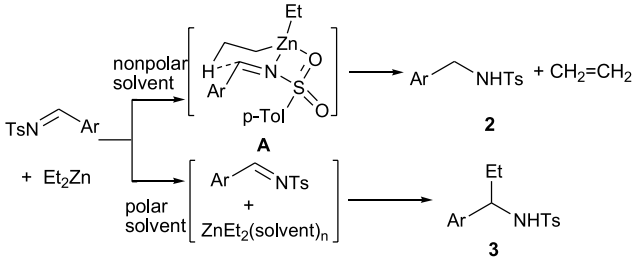
Entry	Solvent	Time (h)	**2a**[a] (%)	**3a**[a](%)
1	Hexane	3	92	—
2	Toluene	1	98	—
3	THF	6	27	40
4	Et_2O	6	65	14
5	CH_3CN	6	51	18
6	CH_2Cl_2	6	85	14

[a] Isolated yield.

It was found that *N*-tosyl imine **1a** could be readily reduced by diethylzinc at very mild conditions in nonpolar solvents (entry 1–2, Table 2). Though the *N*-tosyl imine **1a** and the corresponding reduction product **2a** were almost insoluble in hexane, the reduction reaction still proceeded smoothly (entry 1, Table 2). The reaction phenomenon in toluene was especially interesting. Those *N*-tosyl imines could not be dissolved in toluene completely under the reaction conditions (entry 1–7, Table 1). After diethylzinc was added into the mixture, the turbid mixture became clear. About 30 min later, white precipitates came out in company with a releasing gas which was trapped by liquid N_2 and proved to be ethylene by GC–MS.

But in polar solvents, ethylating product was also found in the reaction along with reduction product (entry 3–6, Table 2).

According to the reaction phenomenon and results, we proposed the reaction of *N*-tosyl imines and diethylzinc in different solvents may proceed as Scheme 1.

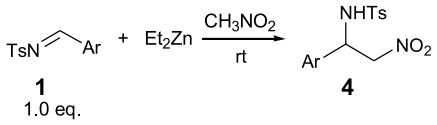


Scheme 1.

In nonpolar solvent diethylzinc and the *N*-tosyl imine brought out a zinc specie with the presumed structure **A**, then the β-hydrogen atom of the ethyl group was transferred to the C=N double bond with release of ethylene, therefore the reduction product **2** was formed. The product **2** was obtained exclusively in toluene and hexane.

On the contrary, the polar solvent such as THF, which could coordinate predominately with diethylzinc and activate diethylzinc in some extent, led to the addition reaction. As a result, the addition product **3** became the main product (entry 3, Table 2). When weaker coordination solvent such as Et_2O was used, it was still predominated by the reduction reaction was still the (entry 4, Table 2).

Table 3. Nitro-Mannich reaction in CH_3NO_2

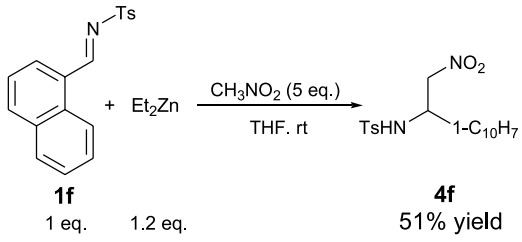


Entry	Ar	Amount of Et_2Zn (equiv)	Time (h)	Yield[a] of 4 (%)
1	**1a**, Ph	1.2	6	**4a**, 73
2		0.5	18	**4a**, 62
3		0.2	24	**4a**, 25
4	**1b**, 4-$MeOC_6H_4$	1.2	6	**4b**, 86
5	**1c**, 2-$MeOC_6H_4$		6	**4c**, 59
6	**1d**, 4-MeC_6H_4		6	**4d**, 79
7	**1e**, 4-ClC_6H_4		6	**4e**, 75
9	**1f**, 1-$C_{10}H_7$		12	**4f**, 50[b]

[a] Isolated yield.
[b] 47% Reduction product **2f** was isolated.

The coordination between *N*-tosyl imine and diethylzinc was shown more obviously in nitro-Mannich reaction when CH_3NO_2 was used as the reaction solvent (Table 3). In those reaction, it was found that dialkylzinc could only promote but not catalyze the nitro-Mannich reaction either in CH_3NO_2 (entry 1–3, Table 3) or in other solvents such as toluene, hexane, CH_2Cl_2, Et_2O and THF, while even Et_3N (20 mol%) could catalyze the nitro-Mannich reaction of *N*-tosyl imine with a yield of 74%.[12]

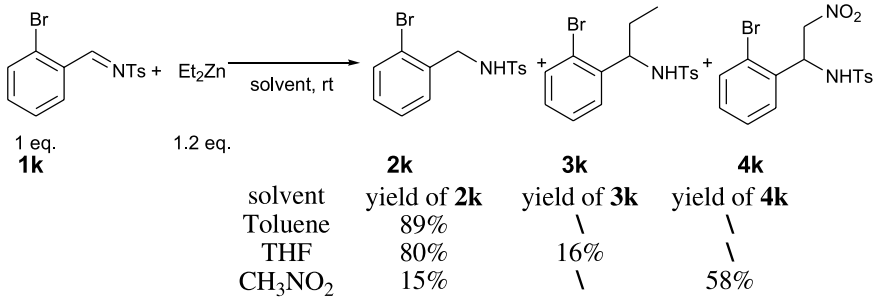
Interestingly, when imine **1f** and diethylzinc were reacted in CH_3NO_2, the product ratio between **4f** (nitro-Mannich adduct) and **2f** (reduction product) was almost 1:1 (entry 9, Table 3). We thought it might be caused by the steric effect, which suppressed the nitro-Mannich reaction. If a stronger coordination ligand was added to break the coordination between imine **1f** and diethylzinc, it would reduce the amount of reduction product. Indeed, when this reaction was taken place in THF, no reduction product was detected other than 51% nitro-Mannich addition product **4f** (Scheme 2). These were all in accordance with the β-H transferring mechanism also.



Scheme 2.

This could be confirmed by the results of another steric hindered imine **1k** (Scheme 3). Similar to the imine **1f**, it took much longer time, 12 h, for imine **1k** to be reduced in toluene than other imines **1a**–**1e** and the reduction product **2k** was also isolated with 15% yield when imine **1k** and diethylzinc was reacted in CH_3NO_2. Unlike imine **1a**, the reduction product **2k** was the major one when it was reacted in THF.

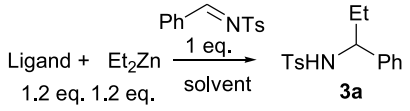
The coordination effects could be proven by following experiments more clearly. Diethylzinc with an equiv of

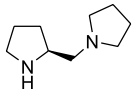


solvent	yield of **2k**	yield of **3k**	yield of **4k**
Toluene	89%	\	\
THF	80%	16%	\
CH_3NO_2	15%	\	58%

Scheme 3.

TMEDA (tetramethyl ethylene diamine) or (*S*)-1,2′-methylenedipyrrolidine, which could prevent the coordination of diethylzinc with *N*-tosyl imine, were stirred for 30 min at rt, and then 1 equiv of *N*-tosyl imine was added to the reaction mixture. It was found all gave ethylating product in good yield without detection of the reduction product in NMR whether in THF or toluene. In the case of the chiral ligand (*S*)-1,2′-methylenedipyrrolidine, it gave 98% yield with 77% ee in toluene (Scheme 4).



Solvent	Ligand	Temp.	Yield(%)
THF	Me_2N ⟋⟍ NMe_2	rt	69
Toluene	Me_2N ⟋⟍ NMe_2	rt	83
Toluene		-78°	98(77%ee)

Scheme 4.

In conclusion, we studied the effect of solvents on the reaction of *N*-tosyl imines and diethylzinc in detail and found there was strong coordination between *N*-tosyl imine and diethylzinc. The *N*-tosyl imines were reduced directly by diethylzinc in nonpolar solvents to give corresponding secondary amines in good to excellent yields through the β-H transferring mechanism. The coordination of diethylzinc and *N*-tosyl imine was hindered by using the polar solvents or addition of TMEDA or (*S*)-1,2′-methylenedipyrrolidine to the reaction, it afforded ethylating product partially or exclusively. This coordination could be used in the further study.

2. Experimental

2.1. General

All reactions were performed under a nitrogen atmosphere using oven-dried glassware. Unless otherwise stated, all reagents were employed as received. Solvents were distilled on CaH_2 or Na/benzophenon. NMR spectrums were made on BRUCKER AMX-300 for proton. IR spectra were obtained on a Shimadzu IR-440 infrared spectrophotometer. Mass spectra were determined on a Finnigan 8230 mass spectrometer. Elemental analyses were performed on a Foss-Heraeus Vario EL instrument.

2.1.1. General procedure (for reduction of Imine 1a–1k by diethylzinc). Under N_2 atmosphere, imine **1a** (260 mg, 1 mmol) was dissolved in 5 mL toluene at rt. Diethylzinc (1.2 mL, 1 M in hexane) was syringed into the solution. The turbid mixture soon became clear in 5 min. After about 30 min, white precipitates came out while bubbling. When no gas was released, the reaction was treated with 1 M HCl, 15 mL ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum to give a white solid **2a**, *N*-Benzyl-4-methylbenzenesulfonamide (254 mg, 98% yield), no need for further purification. Mp 111.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.69 (d, J=8.25 Hz, 2H), 7.26–7.12 (m, 7H), 4.64 (t, J=6.1 Hz, 1H), 4.05 (d, J=6.1 Hz, 2H), 2.37 (s, 3H); IR (KBr): ν=3271, 1599, 1381, 1163 cm^{-1}; MS (*m*/*z*) 262, 135. Anal. Calcld for $C_{14}H_{15}NO_2S$: C: 64.34, H: 5.79, N: 5.38, S: 12.27. Found: C: 64.62, H: 5.78, N: 5.23, S: 12.42.

2.1.2. *N*-(4-Methoxybenzyl)-4-methylbenzenesulfonamide 2b. The product was obtained according to the general procedure, isolated as a white solid in quantitative yield. Mp 116.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.76 (d, J=7.63 Hz, 2H), 7.31 (d, J=7.73 Hz, 2H), 7.10 (d, J=7.91 Hz, 2H), 6.80 (d, J=7.86 Hz, 2H), 4.63 (br s, 1H), 4.05 (d, J=3.34 Hz, 2H), 3.77 (s, 3H), 2.44 (s, 3H); IR (KBr): ν=3253, 1612, 1381, 1160 cm^{-1}; MS (*m*/*z*) 291, 135. Anal. Calcld for $C_{15}H_{17}NO_3S$: C: 61.83, H: 5.88, N: 4.81, S: 11.01. Found: C: 61.57, H: 5.76, N: 4.81, S: 11.29.

2.1.3. *N*-(2-Methoxybenzyl)-4-methylbenzenesulfonamide 2c. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetate ethyl=5:1) and isolated as a pale oil in 96% yield; ^{1}H NMR (300 MHz,$CDCl_3$, 25 °C, TMS): δ=7.58 (d, J=8.20 Hz, 2H), 7.12–7.09 (m, 3H), 6.98 (t, J=7.4 Hz, 1H), 6.72 (t, J=7.4 Hz, 1H), 6.64 (d, J=8.2 Hz, 1H), 5.13 (t, J=6.4 Hz, 1H), 4.05 (d, J=6.4 Hz, 2H), 3.64 (s, 3H), 2.37 (s, 3H); IR (KBr): ν=3362, 1599, 1381, 1162 cm^{-1}; MS (*m*/*z*) 291, 136; HRMS: Calcld for $C_{15}H_{17}NO_3S$: 291.0929, found: 291.0956.

2.1.4. 4-Methyl-*N*-(4-methylbenzyl)benzenesulfonamide 2d. The product was obtained according to the general

procedure, purified by silica gel chromatography (petroleum ether/acetate ethyl=5:1) and isolated as a white solid in 71% yield. Mp 86.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.76 (d, J=8.23 Hz, 2H), 7.30 (d, J=8.10 Hz, 2H), 7.08 (s, 4H), 4.69 (t, J=5.93 Hz, 1H), 4.07 (d, J=5.93 Hz, 2H), 2.44 (s, 3H), 2.33 (s, 3H); IR (KBr): ν=3250, 1598, 1378, 1167 cm^{-1}; MS (*m/z*) 274, 120. Anal. Calcld for $C_{15}H_{17}NO_2S$: C: 65.45, H: 6.18, N: 5.09, S: 11.64. Found: C: 65.27, H: 6.17, N: 5.22, S: 11.38.

2.1.5. *N*-(4-Chlorobenzyl)-4-methylbenzenesulfonamide 2e. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetate ethyl=5:1) and isolated as a white solid in 70% yield. Mp 101.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.71 (d, J=8.3 Hz, 2H), 7.27 (d, J=8.10 Hz, 2H), 7.21 (d, J=8.5 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H), 5.17 (t, J=6.2 Hz, 1H), 4.07 (d, J=6.4 Hz, 2H),2.43 (s, 3H); IR (KBr): ν=3330, 1597, 1392, 1157 cm^{-1}; MS (*m/z*) 296, 140. Anal. Calcld for $C_{14}H_{14}ClNO_2S$: C: 56.85, H: 4.47, N: 4.74, S: 10.84. Found: C: 56.95, H: 4.61, N: 4.61, S: 11.12.

2.1.6. 4-Methyl-*N*-(naphthalen-1-ylmethyl)benzenesulfonamide 2f. The product was obtained according to the general procedure, isolated as a white solid in 98% yield. Mp 151.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.81–7.61 (m, 5H), 7.40–7.39 (m, 2H), 7.24–7.17 (m, 4H), 4.61 (t, J=5.7 Hz, 1H), 4.46 (d, J=5.7 Hz, 2H), 2.35 (s, 3H); IR (KBr): ν=3330, 1597, 1392, 1157 cm^{-1}; MS (*m/z*) 311, 154. Anal. Calcld for $C_{18}H_{17}NO_2S$: C: 69.43, H: 5.50, N: 4.50, S: 10.30. Found: C: 69.38, H: 5.50, N: 4.37, S: 10.35.

2.1.7. *N*-(2-Bromobenzyl)-4-methylbenzenesulfonamide 2k. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetate ethyl=5:1) and isolated as a white solid in 70% yield. Mp 73.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.71 (d, J=8.1 Hz, 2H), 7.46 (d, J=7.8 Hz, 1H), 7.32–7.08 (m, 6H), 4.97 (t, J=6.3 Hz, 1H), 4.23 (d, J=6.3 Hz, 2H), 2.41 (s, 3H); IR (KBr): ν=3258, 1597, 1438,1392, 1155 cm^{-1}; MS (*m/z*) 342, 340, 260, 184. Anal. Calcld for $C_{14}H_{14}BrNO_2S$: C: 49.42, H: 4.15, N: 4.12. Found: C: 49.32, H: 4.07, N: 3.96.

2.2. General procedure (for reaction between diethylzinc and *N*-tosyl imine 1a and 1k in THF)

Under N_2 atmosphere, imine **1a** (1 mmol) was dissolved in 5 mL THF at rt. Diethylzinc (1.2 mL, 1 M in hexane) was syringed into the mixture. After about 6 h, the reaction was treated with 1 M HCl, 30 mL ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum and purified by silica gel chromatography.

2.2.1. 4-Methyl-*N*-(1-phenylpropyl)benzenesulfonamide 3a. The product was obtained according to the general procedure, purified by silica gel chromatography(petroleum ether/acetate ethyl=5:1) and isolated as a white solid **3a** in 40% yield along with **2a** in 27% yield. Mp 109–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.54 (d, J=8.33 Hz, 2H), 7.32–6.99 (m,7H), 5.09 (d, J=7.29 Hz, 1H), 4.22–4.15 (m, 1H), 2.35 (s, 3H), 1.86–1.64 (m, 2H), 0.78 (t, J=7.39 Hz, 3H); IR (KBr): ν=3059, 1598, 1368, 1130 cm^{-1}; MS (*m/z*) 289, 260, 91. Anal. Calcld for $C_{16}H_{19}NO_2S$: C: 66.40, H: 6.62, N: 4.84, S: 11.08. Found: C: 66.46, H: 6.64, N: 4.68, S: 11.26.

2.2.2. *N*-(1-(2-Bromophenyl)propyl)-4-methylbenzenesulfonamide 3k. According to the general procedure, purified by silica gel chromatography(petroleum ether/acetate ethyl=5:1) and isolated a mixture of **3k** in 16% yield and **2k** in 80% yield which were hard to separate. The pure **3k** was obtained by following: Diethylzinc (1.2 mL, 1 M in hexane) and TMEDA were stirred in THF at rt for 1 h. Imine **1k**(1 mmol) was added into the reaction mixture. After 10 h, the reaction was treated with 1 M HCl, 30 mL ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum and purified by silica gel chromatography(petroleum ether/acetone=6:1) to a white solid **3k** in 89% yield. Mp 131.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.63–7.61 (m, 2H), 7.36–7.32 (m, 1H), 7.18–6.93 (m, 5H), 5.93 (d, J=7.8 Hz, 1H), 4.70 (d, J=7.2 Hz, 1H), 2.32 (s, 3H), 1.76–1.66 (m, 2H), 0.84 (t, J=7.5 Hz, 3H); IR (KBr): ν=3273, 1438, 1335, 1159 cm^{-1}; MS (*m/z*) 370, 368, 155. Anal. Calcld for $C_{16}H_{18}BrNO_2S$: C: 52.18, H: 4.93, N: 3.80. Found: C: 52.29, H: 5.11, N: 3.76.

2.3. General procedure (for Nitro-Mannich reaction of Imine 1a–1k in CH_3NO_2)

Under N_2 atmosphere, imine **1** (1 mmol) was dissolved in 5 mL CH_3NO_2 at rt. Diethylzinc (1.2 mL, 1 M in hexane) was syringed into the mixture solution. After about 24 h, the reaction was treated with 1 M HCl, 20 mL ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum and purified by silica gel chromatography.

2.3.1. 4-Methyl-*N*-(2-nitro-1-phenylethyl)benzenesulfonamide 4a. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 70% yield. Mp 155–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.65 (d, J=8.3 Hz, 2H), 7.27–7.24 (m, 5H), 7.10 (d, J=8.3 Hz, 2H), 5.50 (d, J=7.57 Hz, 1H), 5.03–4.96 (m, 1H), 4.84 (d-d, J=13.08, 6.64 Hz, 1H), 4.66 (d-d, J=13.07, 6.34 Hz, 1H), 2.40 (s, 3H); IR (KBr): ν=3426, 1550, 1380, 1167 cm^{-1}; MS (*m/z*) 274, 260, 91. Anal. Calcld for $C_{15}H_{16}N_2O_4S$: C: 56.24, H: 5.03, N: 8.74, S: 10.00. Found: C: 56.50, H: 4.95, N: 8.82, S: 10.15.

2.3.2. *N*-(1-(4-Methoxyphenyl)-2-nitroethyl)-4-methylbenzenesulfonamide 4b. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 86% yield. Mp 142.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.64 (d, J=8.2 Hz, 2H), 7.24 (d, J=8.0 Hz, 2H), 7.00 (d, J=8.62 Hz, 2H), 6.76 (d, J=8.62 Hz, 2H), 5.43 (d, J=6.92 Hz, 1H), 4.93–4.89 (m, 1H), 4.83 (d-d, J=12.83, 6.67 Hz, 1H), 4.64 (d-d, J=12.71, 6.57 Hz, 1H), 3.76 (s, 3H), 2.41 (s, 3H); IR (KBr): ν=3255, 1615, 1380, 1163 cm^{-1}; MS (*m/z*) 350, 91. Anal.

Calcld for $C_{16}H_{18}N_2O_5S$: C: 54.85, H: 5.18, N: 7.99, S: 9.15. Found: C: 54.88, H: 5.31, N: 7.89, S: 9.29.

2.3.3. *N*-(1-(2-Methoxyphenyl)-2-nitroethyl)-4-methylbenzenesulfonamide 4c. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 59% yield. Mp 142.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.56 (d, J=8.3 Hz, 2H), 7.21–7.16 (m, 1H), 7.10 (d, J=8.0 Hz, 2H), 6.95–6.93 (m, 1H), 6.78–6.72 (m, 2H), 6.00 (br s, 1H), 5.1 (br s, 1H), 4.81 (d-d, J=12.60, 7.5 Hz, 1H), 4.64 (d-d, J=12.60, 6.70 Hz, 1H), 3.80 (s, 3H), 2.33 (s, 3H); IR (KBr): ν=3289, 1601, 1368, 1159 cm^{-1}; MS (*m*/*z*) 354, 91. Anal. Calcld for $C_{16}H_{18}N_2O_5S$: C: 54.85, H: 5.18, N: 7.99, S: 9.15. Found: C: 54.99, H: 5.02, N: 8.12, S: 9.44.

2.3.4. 4-Methyl-*N*-(2-nitro-1-p-tolylethyl)benzenesulfonamide 4d. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 79% yield. Mp 192.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.67 (d, J=8.2 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 7.01 (d, J=7.9 Hz, 2H), 6.98 (d, J=6.9 Hz, 2H), 5.24 (d, J=7.1 Hz, 1H), 4.92 (q, J=6.7 Hz, 1H), 4.84 (d-d, J=13.0, 6.4 Hz, 1H), 4.67 (d-d, J=12.9, 6.7 Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H); IR (KBr): ν=3248, 1552, 1378, 1167 cm^{-1}; MS (*m*/*z*) 335, 91. Anal. Calcld for $C_{16}H_{18}N_2O_4S$: C: 57.47, H: 5.43, N: 8.38, S: 9.59. Found: C: 57.49, H: 5.50, N: 8.33, S: 9.36.

2.3.5. *N*-(1-(4-Chlorophenyl)-2-nitroethyl)-4-methylbenzenesulfonamide 4e. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 75% yield. Mp 193.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ=7.41 (d, J=8.1 Hz, 2H), 7.16–7.08 (m, 6H), 5.04–4.99 (m, 1H), 4.68 (d, J=7.5 Hz, 2H), 2.34 (s, 3H); IR (KBr): ν=3242, 1599, 1380, 1168 cm^{-1}; MS (*m*/*z*) 355, 91. Anal. Calcld for $C_{15}H_{15}ClN_2O_4S$: C: 50.85, H: 4.26, N: 7.90, S: 9.04. Found: C: 51.04, H: 4.12, N: 7.97, S: 9.33.

2.3.6. 4-Methyl-*N*-(1-(naphthalen-1-yl)-2-nitroethyl)benzenesulfonamide 4f. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 50% yield along with **2f** in 47% yield. Mp 164.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.84–7.74 (m, 3H), 7.57–7.26 (m, 6H), 7.08 (d, J=7.99 Hz, 2H), 5.88–5.86 (m, 1H), 5.74 (d, J=7.28 Hz, 1H), 4.99 (d-d, J=13.14, 7.35 Hz, 1H), 4.64 (d-d, J=13.14, 5.94 Hz, 1H), 2.33 (s, 3H); IR (KBr): ν=3359, 1597, 1402, 1157 cm^{-1}; MS (*m*/*z*) 350, 154. Anal. Calcld for $C_{19}H_{18}N_2O_4S$: C: 61.61 H: 4.90, N: 7.56, S: 8.65. Found: C: 61.62, H: 4.92, N: 7.47, S: 8.75.

2.3.7. *N*-(1-(2-Bromophenyl)-2-nitroethyl)-4-methylbenzenesulfonamide 4k. The product was obtained according to the general procedure, purified by silica gel chromatography (petroleum ether/acetone=4:1) and isolated as a white solid in 58% yield along with **2k** in 15% yield. Mp 137.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.61 (d, J=7.8 Hz, 2H), 7.44 (d, J=7.8 Hz, 1H), 7.26–7.06 (m, 5H), 6.21 (d, J=8.7 Hz, 1H), 5.52–5.45 (m, 1H), 4.78–4.64 (m, 2H), 2.35 (s, 3H); IR (KBr): ν=3244, 1554, 1341, 1158 cm^{-1}; MS (*m*/*z*) 340, 338, 319, 91. Anal. Calcld for $C_{15}H_{15}BrN_2O_4S$: C: 45.12 H: 3.79, N: 7.02. Found: C: 45.01, H: 3.95, N: 7.04.

2.4. General procedure (for nitro-Mannich reaction of Imine 1f in THF)

Under N_2 atmosphere, imine **1a** (1 mmol) was dissolved in 5 mL THF and 5 equiv CH_3NO_2 at rt for 10 min. Diethylzinc (1.2 mL, 1 M in hexane) was syringed into the solution. After about 12 h, the reaction mixture was treated with 1 M HCl, 30 mL of ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum and purified by silica gel chromatography (petroleum ether/acetone=4:1) and **4f** was isolated as a white solid **4f** in 51% yield.

Procedure (for the ethylating reaction of imine **1a** *with TMEDA (Scheme 4))*. Diethylzinc (1.2 mL, 1 M in hexane) and TMEDA were stirred in THF at rt for 1 h. Imine **1a** (1 mmol) was added. After 10 h, the reaction was treated with 1 M HCl, 30 mL of ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum and purified by silica gel chromatography(petroleum ether/acetate ethyl=5:1) to give **3a** as a white solid in 69% yield.

Procedure (for the ethylating reaction of Imine **1a** *with (S)-1,2′-methylenedipyrrolidine (Scheme 4))*. Diethylzinc (1.2 mL, 1 M in hexane) and (*S*)-1,2′-methylenedipyrrolidine were stirred in toluene at −78 °C for 1 h. Imine **1a** (1 mmol) was added. After 10 h, the reaction was treated with 1 M HCl, 30 mL of ethyl acetate was added, washed with water and brine, dried over Na_2SO_4, evaporated in vacuum and purified by silica gel chromatography (petroleum ether/acetate ethyl=5:1) to afford an optical **3a** in 98% yield and 77% ee (determined by HPLC analysis on a chiralcel OD column with ^{i}PrOH/hexane=20/80 as the eluent).

Acknowledgements

Financial supports from the National Natural Sciences Foundation of China and the State Key Project of Basic Research (Project 973, No. G2000048007) are gratefully acknowledged.

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Asymmetric synthesis of (2-carbamoyloxy-1-alkenyl)cyclopropanes by intramolecular cycloalkylation

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Received 12 August 2005; revised 22 September 2005; accepted 22 September 2005

Available online 25 October 2005

Abstract—Enantioenriched, diastereomerically pure (2-carbamoyloxy-1-alkenyl)cyclopropanes **22** are easily prepared via deprotonation of different allyl carbamates with *n*-butyllithium and (−)-sparteine (**4**). The mechanism of the cyclization reaction was determined and several substituted (*S*)-configured vinylcyclopropanes **32** were synthesized by two different methods. The configurational stability of the intermediate lithiated allyl carbamates and the half-time of epimerization were investigated in a series of silylation experiments, achieving up to 90% ee in the kinetically controlled enantiotopos-differentiating deprotonation.

1. Introduction

Cyclopropanes bearing simple functionalities are endowed with a large spectrum of biological properties ranging from insecticidal to pharmaceutical activities.[1] The preparation of the enantioenriched, functionalized cyclopropane ring is often a key step in the total synthesis.[2] The research in the area of diastereo- and enantioselective cyclopropanations was largely focused on the modification of allylic alcohols through carbenoid intermediates as in Simmon–Smith chemistry.[3,4] We had developed a novel intramolecular cyclization reaction for the synthesis of enantioenriched cyclopropanes starting from alkyl carbamates (Scheme 1).[5] After *pro*-H_S-atom abstraction of the 1,3-alkanediyl dicarbamate **1**, the lithiated, configurationally stable lithium compound **2** cyclizes in an intramolecular 1,3-cycloelimination reaction to the enantioenriched cyclopropanes **3**/*ent*-**3** in good yields with high enantioselectivities of up to >95% ee. Here, the 2,2,4,4-tetramethyl-1,3-oxazolidine-3-carbonyl group (*Cby*O) enhances the kinetic acidity of the α-protons in the deprotonation step and fixes the lithium cation in the α-position by chelation.[6] The cyclization step requires assistance of Lewis acid, which determines the stereochemical course of the cycloalkylation. From further investigations it is known that removal of the *pro*-H_S-atom by *n*-butyllithium/(−)-sparteine (**4**) is kinetically favoured for *O*-alkyl carbamates[7] as well as for *O*-alkenyl carbamates.[8]

Cycloalkylation reactions of allyllithium species,[9,10] which lead to enantioenriched divinylcyclopentenes[11] or cyclononadienes,[12] are based on a stereoselective *pro*-H_S-atom abstraction by *n*-butyllithium and (−)-sparteine (**4**) in the α-position of suitable functionalized allyl carbamates. The (*S*)-configured allyllithium intermediates are, in contrast to lithiated alkyl carbamates, configurationally unstable, even at −90 °C, but due to high reaction rates of the intramolecular allylic cycloalkylation reactions, 5- and 9-membered rings are formed with enantiomeric excesses of up to 80%.[11,12]

According to the above mentioned principle, the (−)-sparteine-mediated deprotonation of 2-pentenyl carbamates, bearing a leaving group in the 5-position, followed by an intramolecular vinylogous cycloalkylation should lead to optically active (2-carbamoyloxyethenyl)cyclopropanes (Scheme 5). As possible leaving groups in the ω-position of the allyl carbamate, we investigated silyloxy (**10**), chloride (**17a**), bromide (**17b**), iodide (**13**), and tosyloxy (**12**).[13]

2. Results and discussion

2.1. Synthesis of allyl carbamates

The carbamates **10**, **12**, and **13** were prepared from 2,2-dimethylpropan-1,3-diol (**5**). After monoprotection of **5** with TBSCl and oxidation to the corresponding aldehyde **7**, it was subjected to a Horner–Wadsworth–Emmons chain elongation (Scheme 2).[14] The ester **8** was reduced to the

Keywords: Asymmetric synthesis; Carbanions; (−)-Sparteine; Small ring systems; Cyclization; Vinyllithium derivatives.
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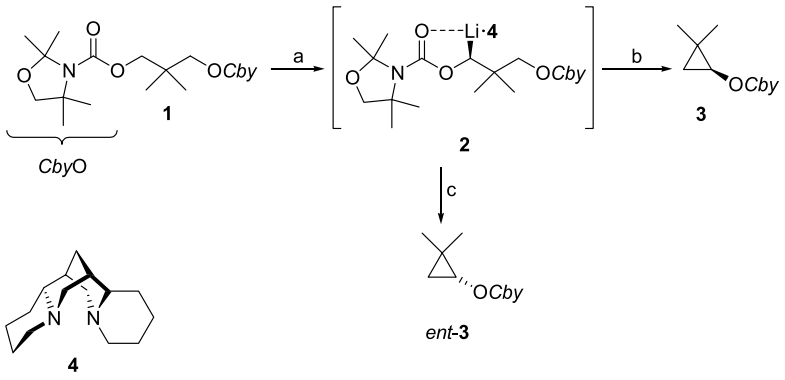
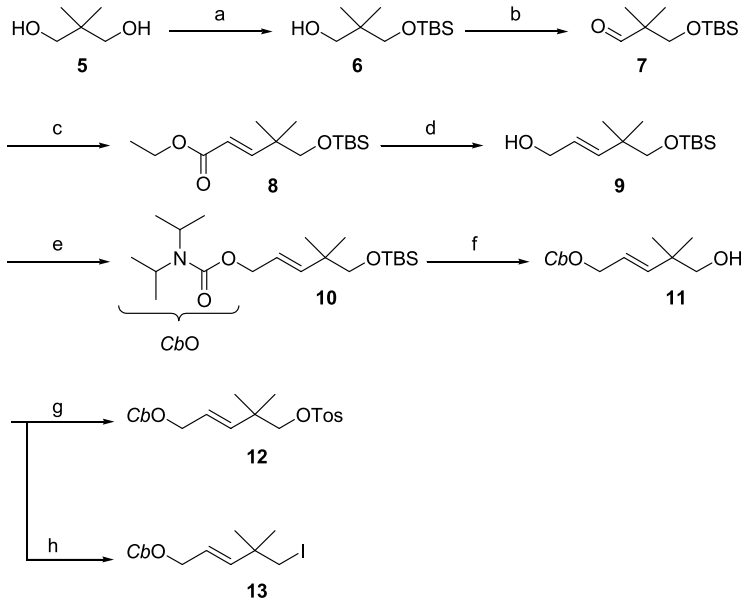
doi:10.1016/j.tet.2005.09.110



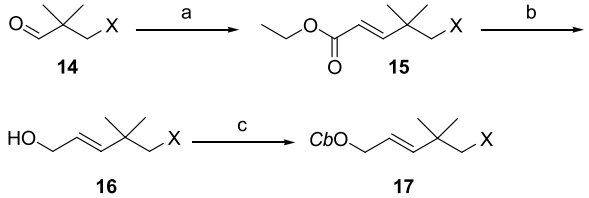
Scheme 1. Reagents and conditions. (a) *sec*BuLi, (−)-sparteine, Et_2O, −78 °C; (b) $TiCl_4$, 42%, >95% ee; (c) TMSCl, 95%, >95% ee.



Scheme 2. Reagents and conditions. (a) TBSCl, DMAP, NEt_3, THF, 88%; (b) $(COCl)_2$, DMSO, NEt_3, −78 °C, 90%; (c) NaH, $EtOOCCH_2P(O)(OEt)_2$, Et_2O, 86%; (d) DIBAL-H, toluene, −78 °C, 90%; (e) *N*,*N*-diisopropylcarbamoyl chloride, pyridine, 90 °C, 70%; (f) TBAF, Et_2O, 93%; (g) TosCl, pyridine, DMAP, 73%; (h) I_2, PPh_3, pyridine, benzene, 36%.

allylic alcohol **9** using DIBAL-H at −78 °C. Carbamoylation of **9** with *N*,*N*-diisopropylcarbamoyl chloride in pyridine furnished the carbamate **10** in 43% overall yield. Complete diastereomerical purity was confirmed by GC-analysis. The cyclization precursors **12** and **13** were obtained in a conventional two-step sequence starting from **10**.

The halides **17a** (X=Cl) and **17b** (X=Br) are easily prepared in a three-step sequence starting from the known aldehydes **14** (Scheme 3).[15] After a Horner–Wadsworth–

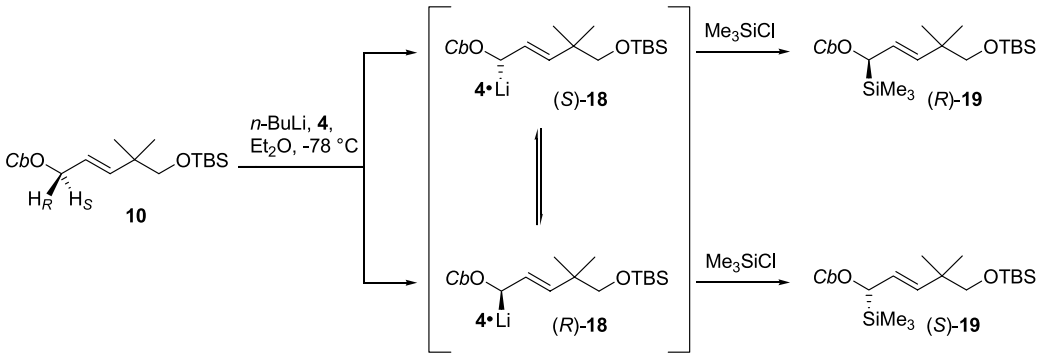


Scheme 3. Reagents and conditions. **14a**, **15a**, **16a**, **17a**: X=Cl; **14b**, **15b**, **16b**, **17b**: X=Br; (a) NaH, $EtOOCCH_2P(O)(OEt)_2$, Et_2O, **15a**: 86%, **15b**: 89%; (b) DIBAL-H, toluene, −78 °C, **16a**, **16b**: 68%; (c) *N*,*N*-diisopropylcarbamoyl chloride, pyridine, 90 °C, **17a**: 74%, **17b**: 80%.

Emmons chain elongation of the aldehyde **14** with triethyl phosphonoacetate, the resulting esters **15** were reduced to the alcohols **16** with DIBAL-H at −78 °C. The diastereomerically pure allyl carbamates **17** were obtained after treatment of **16** with *N*,*N*-diisopropylcarbamoyl chloride in good overall yields. The (*E*)-geometry of the double bond was confirmed by the ^1H NMR coupling constants of the olefinic protons (**17a**, $^3J_{2,3}=15.8$ Hz; **17b**, $^3J_{2,3}=15.8$ Hz).

2.2. Deprotonation and silylation reactions

In a series of deprotonation experiments of the silyloxy compound **10** with *n*-butyllithium/(−)-sparteine (**4**), the stereochemical efficiency of the kinetically controlled deprotonation and the degree of configurational stability of the generated lithium-species were investigated (Scheme 4). The silylation reactions with chlorotrimethylsilane are known to proceed rapidly with lithiated allyl carbamates.[8] They react with high α-regioselectivity under inversion of configuration.[8b,16] With the information in hand that *n*-butyllithium/(−)-sparteine (**4**) removes the *pro*-H_S-atom of *O*-2-alkenyl carbamates we can predict the stereochemical outcome of the silylation reactions.



Scheme 4. For yields and ee values, see Table 1.

The enantiotopos-differentiating deprotonation of allyl carbamates with *n*-butyllithium/(−)-sparteine (**4**) leads to a (*S*)-configured lithium complex, which reacts under inversion of configuration with chlorotrimethylsilane to yield the (*R*)-configured silane **19**. The enantiomeric ratio of a silylated carbamate roughly reflects the diasteromeric ratio of the lithiated intermediates, although kinetic resolution originating from different reactivities of the diastereomers may cause some error. Time-dependent silylation reactions provide information on the configurational stability of the lithiated allyl carbamate. Deprotonation of the carbamate **10** with *n*-butyllithium in the presence of the achiral diamine *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at −78 °C in diethyl ether furnished the α-lithiated allyl carbamate, but no further cyclization to the vinylcyclopropane **22** was observed.

For an in situ silylation reaction, the carbamate **10** was deprotonated with *n*-butyllithium/(−)-sparteine (**4**) in the presence of chlorotrimethylsilane (Table 1, entry 2). The α-silylated carbamate (*R*)-**19** was isolated in 21% yield with an enantiomeric ratio of 95:5. The (*E*)-double bond geometry was determined with a 2D ^{1}H, ^{13}C-GHSQC NMR-experiment (without ^{13}C-decoupling during the acquisition phase).[17] The $^{3}J_{2,3}$ coupling constant of 16.4 Hz from the measurement of the ^{13}C-satellites of H-2 and H-3 verified the geometry of the double bond. The enantiomeric ratios were determined by GC on a chiral β-Dex™ 120 column, by comparison with the corresponding racemate (entry 1). Additionally 35% of the starting material **10** was recovered. The value of 90% ee reflects the minimal efficiency of the kinetically controlled enantiotopos-differentiating deprotonation. The initial ratio of the lithiated intermediates (*S*)-**18**/(*R*)-**18** is therefore at least 95:5. Longer deprotonation times show a dramatically decrease of the enantiomeric ratio of (*R*)-**19**. After a deprotonation time of 5 min (*R*)-**19** was obtained in 77% yield, but with only 20% ee (entry 3). The thermodynamic equilibrium of the lithiated species (*S*)-**18**/(*R*)-**18** is achieved after 10–30 min with resulting of 8–9% ee in the α-silylated carbamate (*R*)-**19** (entry 4 and 5).

In summary, the enantiotopos-differentiating deprotonation of allyl carbamates proceed in highly stereoselective manner but the epimeric (−)-sparteine/allyllithium-complexes **18** are configurationally labile. The half-times for the epimerization are of the magnitude of 3–4 min at −78 °C in diethyl ether.

2.3. Cyclization reactions

Our investigations started with the ω-chloro-substituted carbamate **17a** as cyclization precursor. The reaction was carried out by precomplexation of **4** and *n*-butyllithium for 15 min in diethyl ether at −78 °C followed by slow addition of the carbamate solution. The vinylcyclopropane (*S*,*Z*)-**22** was furnished in 90% yield with an enantiomeric excess of up to 57% (Table 2, entry 2). The cycloalkylation reaction proceeds via the *endo*-conformation of **21** to form the (*Z*)-configured double bond (Scheme 5). The (*Z*)-configuration of the double bond was confirmed by the coupling constant of the olefinic protons in the ^{1}H NMR ($^{3}J_{\text{H-1,H-2}}$=6.4 Hz). In the cyclization reactions at least two equivalents of *n*-butyllithium were required. This is due to the high acidity of the formed vinylic proton at the C-1 position in the cyclopropane **22**. Quantitative removal of one allylic proton is therefore just possible when using at least two equivalents of *n*-butyllithium. Additional cyclization experiments were performed in different solvents, yielding the vinylcyclopropane **22** in good yields of up to 80%, but with moderate enantiomeric excesses.

Table 1. Lithiation and silylation of allyl carbamate **10**

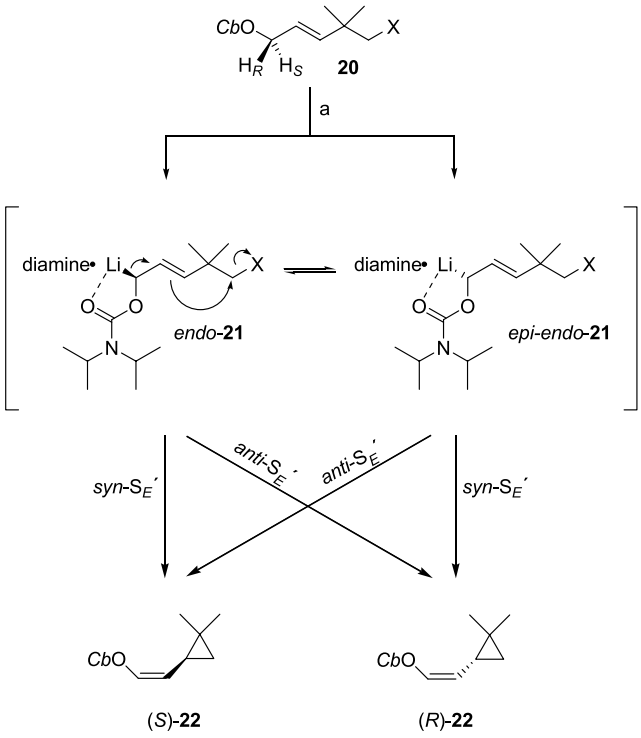
Entry	Diamine	Deprotonation [min]	Yield (*S*)-**19** [%]	% ee[a]	$[\alpha]_D^{20b}$
1	TMEDA	30	65	—	—
2	(−)-Sparteine	0[c]	21[d]	90	+5.5
3	(−)-Sparteine	5	77	20	+1.2
4	(−)-Sparteine	10	90	9	+0.6
5	(−)-Sparteine	30	52	8	+0.5

[a] Enantiomeric excesses were determined by chiral GC (column: β-Dex™ 120).
[b] c=0.72–1.11, CH_2Cl_2.
[c] In situ experiment.
[d] Additionally 35% of **10** were isolated.

Table 2. Synthesis of vinylcyclopropane **22**

Entry	Starting material	Solvent	*T* [°C]	Diamine	Yield **22** [%]	ee [%][a]	Configuration
1	**17a**	Et_2O	−78	TMEDA	75	—	*rac*
2	**17a**	Et_2O	−78	(−)-Sparteine	90	57	*S*
3	**17a**	Toluene	−78	(−)-Sparteine	51	46	*S*
4	**17a**	THF	−78	(−)-Sparteine	75	<1	*S*
5	**17a**	*t*BuOMe	−78	(−)-Sparteine	65	40	*S*
6	**17a**	*n*-Pentane	−78	(−)-Sparteine	80	34	*S*
7	**17a**	Et_2O	−78	(−)-**23**	0	—	—
8	**17a**	Et_2O	−78	(*R*,*R*)-**24**	30	12	*R*
9	**17a**	Et_2O	−78	(*S*,*S*)-**25**	41	29	*R*
10	**17a**	Et_2O	0	(−)-Sparteine	47	32	*S*
11	**17a**	Et_2O	−85	(−)-Sparteine	53	49	*S*
12	**17a**	Et_2O	−116	(−)-Sparteine	21	19	*S*
13	**17b**	Et_2O	−78	(−)-Sparteine	79	38	*S*
14	**17b**	Toluene	−78	(−)-Sparteine	60	20	*S*
15	**17b**	THF	−78	(−)-Sparteine	63	9	*S*
16	**13**	Et_2O	−78	(−)-Sparteine	22	6	*S*
17	**13**	Toluene	−78	(−)-Sparteine	35	2	*S*
18	**13**	THF	−78	(−)-Sparteine	0[b]	—	—
19	**12**	Et_2O	−78	(−)-Sparteine	78	27	*S*

[a] Shift experiment with $Eu(hfc)_3$.
[b] Decomposition takes place.



Scheme 5. For specific reaction conditions, yields and ee values see Table 2. (a) *n*-BuLi, diamine (X=Cl, Br, I, OTos).

The influence of different chiral diamines, (−)-α-isosparteine (**23**), (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane (**24**)[18] and (4*S*)-2,2′-(1-ethylpropylidene)bis[4-(1-methylethyl)-4,5-dihydrooxazole (**25**),[19] were also investigated in the cyclization reaction (Fig. 1), but lower ee's (up to 29%) were achieved. As expected from earlier work, (−)-α-isosparteine (**23**) (entry 7) is not able to support the deprotonation of the allyl carbamate **20**.[20] Interestingly, the enantiomeric vinylcyclopropane (*R*,*Z*)-**22** was obtained when using the chiral diamines (*R*,*R*)-**24** or (*S*,*S*)-**25** (entry 8 and 9).

Applying lower reaction temperatures (−116 °C, entry 12), the yield (21%) and the ee (16%) are reduced, but the same is true for higher temperatures (0 °C, entry 10): 41% yield and 32% ee. This may origin from the fact that three reaction steps (deprotonation, epimerization and cycloalkylation) with different, unpredictable temperature dependence of the stereoselectivity are involved (see below). Lower enantioselectivity is also recorded for the ω-bromo-(**17b**), ω-iodo-(**13**), and ω-tosyloxy-allyl carbamate (**12**) (entry 13–19). When the deprotonations were carried out in THF as the solvent (entry 4 and 15) essentially racemic product **22** was obtained. As we noticed in another case, THF displaces (−)-sparteine (**4**) from the lithium base.[21] In the cyclization reaction of the ω-iodo carbamate **13**, decomposition and side reactions were detected, but it is remarkable, that the ω-iodo substituent survives (at least in part) in the presence of a strong lithium base.

The knowledge of the absolute configuration of **22** is required to understand the mechanistical pathway of the asymmetric cycloalkylation reaction. The absolute configuration was determined by treatment of (*S*)-**22** with an excess of $NaIO_4$ and 10 mol% $RuCl_3 \cdot H_2O$ yielding the known (−)-(*R*)-2,2-dimethylcyclopropane carboxylic acid (*R*)-**26** in quantitative yield (Scheme 6).[22] Comparison of the optical rotation with the reported data confirms the absolute configuration of (*S*)-**22**.[23]

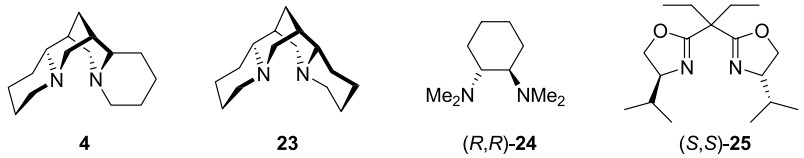
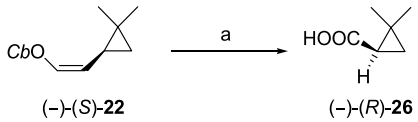


Figure 1. Used diamines.

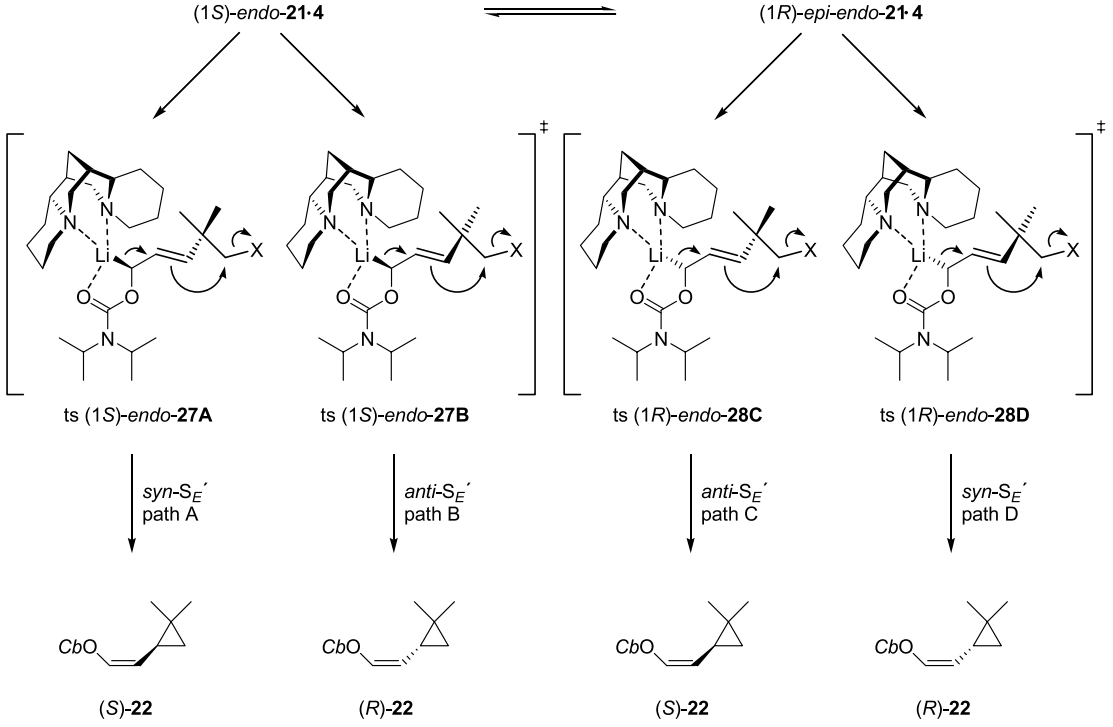


Scheme 6. Reagents and conditions. (a) $NaIO_4$, $RuCl_3 \cdot H_2O$, CCl_4, CH_3CN, H_2O, quant.

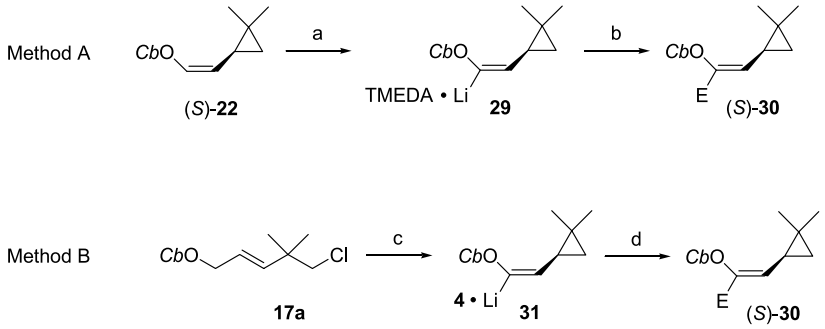
(*S*)-**22** can be either formed from (1*S*)-*endo*-**21**·**4** in a *syn*-S_E' substitution via pathway A or from the (1*R*)-epimer *epi-endo*-**21**·**4** in an *anti*-S_E' process via pathway C (Scheme 7). Since we observed *anti*-S_E' reactions in several vinylogous cycloalkylations of lithiated allyl carbamates pathway C cannot be excluded.[11,12] Path C requires that the rates of epimerization and cycloalkylation are of similar magnitude and that the *anti*-S_E' reaction of (1*R*)-*endo*-**28** proceeds slightly more rapidly than the *syn*-S_E' reaction of (1*S*)-*endo*-**27**. As the consequence of a dynamic kinetic resolution, the enantiomeric ratio of (*S*)-**22**/(*R*)-**22** is greatly influenced by slight changes in the relative rates of epimerization and the cycloalkylation reaction.[24] The strong dependence of ee-values from the solvent, the leaving group, and the temperature (Table 2) support the assumption of a dynamic kinetic resolution.

2.4. Synthesis of side-chain substituted vinylcyclopropanes

The α-position of the vinyl carbamate **22** can be further substituted via deprotonation without racemization of the stereogenic centre and with complete retention of the double bond geometry.[25] The configurational stability of (*S*)-**22** was examined by deprotonation with *n*-butyllithium in the presence of TMEDA at −78 °C in diethyl ether and reprotonation after 4 h. No racemization of the recovered (*S*)-**22** was observed. Several electrophiles were used for trapping the generated vinyllithium species (EX = CH_3I, $(CH_3)_3SnCl$, TMSCl, TIPSCl and TBSCl). The resulting substituted 1-alkenylcyclopropanes (*S*)-**30** were obtained in yields of up to 71% as single diastereomers (Scheme 8, Table 3, Method A). In case of sterically demanding electrophiles (TIPSCl and TBSCl) incomplete conversion of



Scheme 7. Possible competing reaction pathways.



Scheme 8. Reagents and conditions. For EX see Table 3. (a) 1. *n*-BuLi, TMEDA, Et_2O, −78 °C; (b) EX; (c) 1. *n*-BuLi, (−)-sparteine, Et_2O, −78 °C; (d) EX.

Table 3. Synthesis of functionalized vinylcyclopropanes **28**

Entry	Compund (% ee)	Method	Product	EX	E	Yield [%]	ee [%]	$[\alpha]_D^{20a}$
1	(*S*)-**22** (51)	A	(*S*)-**30a**	CH_3I	CH_3	32	51	−31.4
2	**17a**	B	(*S*)-**30a**	CH_3I	CH_3	64	46	−28.3
3	(*S*)-**22** (51)	A	(*S*)-**30b**	$(CH_3)_3SnCl$	$(CH_3)_3Sn$	71	51	−4.9
4	**17a**	B	(*S*)-**30b**	$(CH_3)_3SnCl$	$(CH_3)_3Sn$	65	48	−4.6
5	(*S*)-**22** (57)	A	(*S*)-**30c**	TMSCl	TMS	66	57	−24.6
6	**17a**	B	(*S*)-**30c**	TMSCl	TMS	79	57	−24.6
7	**22**	A	**30d**	TIPSCl	TIPS	36[b]	*rac*	—
8	**22**	A	**30e**	TBSCl	TBDMS	0[c]	—	—

[a] $c=0.13$–0.53, CH_2Cl_2.
[b] In addition 20% **22** was isolated.
[c] Starting material recovered.

the lithium species was observed due to the slow reaction rate of these electrophiles.

The α-substituted vinylcyclopropanes (*S*)-**30** are also accessible by a one-pot cyclization-substitution reaction starting from **17a**. After formation of (*S*)-**22**, as described above, the vinylic proton at C-1 is abstracted with a second equivalent of *n*-butyllithium (Scheme 8, Method B). The resulting lithiated vinylcyclopropane **31** subsequently was reacted with the above mentioned electrophiles. The resulting α-substituted 1-alkenylcyclopropanes (*S*)-**30** again were obtained in good yields of up to 79% over two steps and with enantiomeric excesses in the range of 46–57%, comparable to those of method A.

3. Conclusion

The enantiotopos-differentiating deprotonation of ω-substituted 2-pentenyl carbamates by *n*-butyllithium/(−)-sparteine (**4**) proceeds in a highly stereoselective manner but the epimeric (−)-sparteine/allyllithium-complexes are configurative labile. Presumably, the lithium species **21** underwent a dynamic kinetic resolution to form in an *anti*-S_E' reaction the (*Z*)-configured enantioenriched vinylcyclopropane (*S*)-**22** with up to 57% ee, which can be further substituted with electrophiles.

4. Experimental

4.1. General

All solvents were dried and purified prior to use. Unless otherwise specified, materials were obtained from commercial sources and used without purification. Diethyl ether and toluene were distilled over sodium benzophenone ketyl, THF over potassium benzophenone ketyl and CH_2Cl_2 was distilled over CaH_2. Pyridine was distilled over KOH and stored over molecular sieve (3 Å). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA), TMSCl and NEt_3 were distilled from powdered calcium hydride and stored under argon. All reactions were performed under argon atmosphere in flame-dried glassware. Flash column chromatography (FCC) was performed on Merck 60 silica gel, 0.040–0.063 mm, and monitored by thin layer chromatography (TLC) on Merck 60 F_{254} silica gel. Melting points: Gallenkamp MFB 595 (uncorrected values). IR: Nicolet 5 DXC. MS: Finnigan MAT 8230 (EI); Micromass Quattro LCZ (ESI), Micromass MAT 8200 (GC-TOF/HRMS). Optical rotations: Perkin-Elmer 341 polarimeter. NMR: Bruker ARX 300, AM 360, AMX 400 or Varian Associated Unity Plus 600; spectra from solutions in $CDCl_3$ ($\delta_C=77.0$ ppm) are calibrated relative to residual content of $CHCl_3$ ($\delta_H=7.24$ ppm) or $SiMe_4$ ($\delta_H=0.0$ ppm). Elemental analyses: Heraeus CHN-O-Rapid or Elementar Analysensysteme Vario EL III. GC: Agilent 6890, 30 m×0.32 mm HP 5, 1.5 mL×min^{-1} H_2 start at 50 °C/10 °C×min^{-1} 20 min at 270 °C; Hewlett–Packard 6890, cyclodextrins from Supelco (30 m×0.32 mm) or Machery–Nagel (25 m×0.2 mm), 100 kPa pre-column pressure N_2, isothermal runs.

4.1.1. 3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpropan-1-ol (6). Triethylamine (2.40 g, 23.5 mmol, 3.5 equiv) and DMAP (50 mg, 2 mol%) were added to a solution of 2,2-dimethylpropan-1,3-diol (2.10 g, 20.1 mmol, 3.0 equiv) in THF (10 mL). After 30 min, *tert*-butyldimethylsilyl chloride (1.00 g, 6.7 mmol, 1.0 equiv), dissolved in THF (5 mL), was added and the reaction mixture was stirred for 12 h at room temperature. Solvent was evaporated under vacuum and the residue was taken up with diethyl ether (10 mL) and 5% acetic acid (10 mL). The aqueous phase was separated and extracted with diethyl ether (3×25 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL) and dried over $MgSO_4$. The solvents were evaporated under vacuum. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:3) yielding **6** (1.31 g, 5.9 mmol, 88%) as colourless liquid. ^1H NMR (300 MHz, $CDCl_3$): $\delta=0.07$ (s, 6H, OSi–CH_3), 0.88 (s, 6H, 2-CH_3), 0.90 (s, 9H, OSi–$C(CH_3)_3$), 2.68 (t, $^3J_{1,OH}=5.8$ Hz, 1H, OH), 3.45 (d, $^3J_{1,OH}=5.8$ Hz, 2H, H-1), 3.46 (s, 2H, H-3).[14a]

4.1.2. 3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethylpropanal (7). To a solution of $(COCl)_2$ (300 mg, 2.4 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL) was carefully added DMSO (380 mg, 4.8 mmol, 2.4 equiv) at −78 °C. After 30 min, **6** (436 mg, 2.0 mmol, 1.0 equiv), dissolved in CH_2Cl_2 (10 mL), was injected and the reaction mixture was stirred for 1 h. Triethylamine (1.0 g, 10.0 mmol, 5.0 equiv) was added and after 1 h the reaction mixture was warmed to room temperature. For workup, water (10 mL) was added. The phases were separated and the aqueous phase extracted with diethyl ether (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated under vacuum. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:1) yielding **7** (388 mg, 1.8 mmol, 90%) as a colourless liquid. ^1H NMR (300 MHz,

$CDCl_3$): δ=0.00 (s, 6H, OSi–CH_3), 0.84 (s, 9H, OSi–$C(CH_3)_3$), 1.00 (s, 6H, 2-CH_3); 3.60 (s, 2H, H-3), 9.53 (s, 1H, H-1).[14b]

4.1.3. (*E*)-5-(*tert*-Butyldimethylsilyloxy)-4,4-dimethylpent-2-enoic acid ethyl ester (8). Sodium hydride (60% in mineral oil, 108 mg, 2.7 mmol 1.5 equiv) was suspended in Et_2O (30 mL) and cooled down to 0 °C. Triethyl phosphonoacetate (837 mg, 4.6 mmol, 2.5 equiv) was added slowly and then the reaction mixture was refluxed for 60 min. The solution was cooled to 0 °C, **7** (389 mg, 1.8 mmol, 1.0 equiv), dissolved in Et_2O (10 mL) was injected and the mixture was stirred 3 h at room temperature. For workup, water (20 mL) was added. The aqueous phase was separated and extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated under vacuum. The residue was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:10) affording **8** (442 mg, 1.5 mmol, 86%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.00 (s, 6H, OSi–CH_3), 0.87 (s, 9H, OSi–$C(CH_3)_3$), 1.01 (s, 6H, 4-CH_3), 1.26 (t, $^3J_{CH3,CH2}$= 7.0 Hz, 3H, CH_3), 3.34 (s, 2H, H-5), 4.16 (q, $^3J_{CH3,CH2}$= 7.0 Hz, 2H, CH_2), 5.75 (d, $^3J_{2,3}$=16.0 Hz, 1H, H-3), 6.95 (d, $^3J_{2,3}$=16.0 Hz, 1H, H-2).[14c]

4.1.4. (*E*)-5-(*tert*-Butyldimethylsilyloxy)-4,4-dimethylpent-2-en-1-ol (9). 8 (3.98 g, 13.9 mmol, 1.0 equiv) was dissolved in toluene (50 mL) and the solution was cooled down to −78 °C. DIBAL-H (1.0 M in THF, 32.0 mL, 32.0 mmol, 2.3 equiv) was injected and the solution was stirred for 3 h. Water (5.5 mL) was added at −78 °C, the reaction mixture was warmed to room temperature and stirred for additional 1 h. 20 mL of diethyl ether was added and after 0.5 h the mixture was filtered through 1–2 cm bed of silica washing through with diethyl ether. The extracts were dried over $MgSO_4$, evaporated and the crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:3) to give **9** (3.06 g, 12.5 mmol, 90%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.00 (s, 6H, OSi–CH_3), 0.87 (s, 9H, OSi–$C(CH_3)_3$), 0.95 (s, 6H, 4-CH_3), 3.26 (s, 2H, H-5), 4.07 (d, $^3J_{1,2}$=5.4 Hz, 2H, H-1), 5.61 (dt, $^3J_{2,3}$=15.4 Hz, $^3J_{1,2}$=5.4 Hz, 1H, H-2), 6.95 (dd, $^3J_{2,3}$= 15.4 Hz, $^4J_{1,3}$=0.7 Hz, 1H, H-3).[14c]

4.1.5. (*E*)-*N*,*N*-Diisopropylcarbamic acid (5-(*tert*-butyldimethylsilyloxy)-4,4-dimethylpent-2-enyl) ester (10). *N*,*N*-diisopropylcarbamoyl chloride (7.0 g, 42.8 mmol, 4.0 equiv) and **9** (2.6 g, 10.7 mmol, 1.0 equiv) were heated in pyridine (5.5 mL) at 90 °C for 18 h. The reaction mixture was cooled down to room temperature and poured onto a mixture of ice (50 g), 2 N HCl (10 mL) and diethyl ether (30 mL). The aqueous phase was separated and extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (10 mL) and dried over $MgSO_4$. The solvents were evaporated under vacuum. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:10) yielding **10** (2.7 g, 7.4 mmol, 70%) as a colourless liquid. R_F=0.54 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.00 (s, 6H, OSi–CH_3), 0.87 (s, 9H, OSi–$C(CH_3)_3$), 0.97 (s, 6H, 4-CH_3), 1.20 (d, $^3J_{NCH(CH3)2\text{-}NCH(CH3)2}$=6.7 Hz, 6H, $NCH(CH_3)_2$), 3.28 (s, 2H, H-5), 3.88 (bs, 2H, $NCH(CH_3)_2$), 4.53 (d, $^3J_{1,2}$=6.1 Hz, 2H, H-1), 5.56 (dt, $^3J_{1,2}$=6.1 Hz, $^3J_{2,3}$=15.9 Hz, 1H, H-2), 5.73 (td, $^3J_{2,3}$= 15.9 Hz, $^4J_{H\text{-}1,H\text{-}3}$=1.1 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=−5.1 (CH_3, $OSiCH_3$), 20.4 (C_q, OSiC), 21.4 (CH_3, $NCH(CH_3)_2$), 24.2 (CH_3, 4-CH_3), 26.3 (CH_3, $OSiC(CH_3)_3$), 38.6 (C_q, C4), 46.3 (CH, $NCH(CH_3)_2$), 66.0 (CH_2, C1), 72.2 (CH_2, C5), 122.6 (CH, C3), 142.3 (CH, C2), 193.3 (CO). MS (70 eV): *m*/*z*=371, 356, 314, 290, 260, 243, 202, 160, 128, 86 (100), 75. IR (film)=2965, 2930, 2862 ν (C_{aliph}–H), 1694 ν (C=O), 1471, 1367, 1312, 1254, 1223, 1104, 1049, 977, 836, 775, 668 cm^{-1}. $C_{20}H_{41}NO_3Si$ (371.63): calcd C 64.70, H 11.04, N 3.77, found C 64.56, H 11.21, N 3.85.

4.1.6. (*E*)-*N*,*N*-Diisopropylcarbamic acid (5-hydroxy-4,4-dimethylpent-2-enyl) ester (11). TBAF (1.0 M in THF, 5.4 mL, 5.4 mmol, 3.0 equiv) was added to a solution of **10** (667 mg, 1.8 mmol, 1.0 equiv) in diethyl ether (10 mL). The reaction mixture was stirred for 72 h at room temperature. Water (10 mL) was added, the aqueous phase was separated, extracted with diethyl ether (3×10 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:5) to give **11** (429 mg, 1.7 mmol, 93%) as a colourless liquid. R_F=0.06 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.03 (s, 6H, 4-CH_3), 1.21 (d, $^3J_{NCH(CH3)2,NCH(CH3)2}$=7.0 Hz, 12H, $NCH(CH_3)_2$), 1.55 (bs, 1H, OH), 3.33 (s, 2H, H-5), 3.90 (bs, 2H, $NCH(CH_3)_2$), 4.57 (d, $^3J_{1,2}$=5.1 Hz, 2H, H-1), 5.63 (m, 2H, H-2/H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0 (CH_3,$NCH(CH_3)_2$), 23.6 (CH_3, 4-CH_3), 38.4 (C_q, C4), 45.9 (CH, $NCH(CH_3)_2$), 65.2 (CH_2, C1), 71.5 (CH_2, C5), 124.4 (CH, C3), 140.9 (CH, C2), 155.5 (CO). MS (70 eV): *m*/*z*=257, 242, 226, 198, 155, 129, 128, 95, 86 (100). IR (film)=3465 ν (OH), 2978, 2937, 2873 ν (C_{aliph}–H), 1684 ν (C=O), 1447, 1371, 1311, 1218, 1164, 1084, 957, 772 cm^{-1}. $C_{14}H_{27}NO_3$ (257.37): calcd C 65.33, H 10.57, N 5.44, found C 65.33, H 10.66, N 5.24.

4.1.7. (*E*)-Toluene-4-sulfonic acid [5-(*N*,*N*-diisopropylcarbamoyloxy)-2,2-dimethylpent-3-enyl] ester (12). Compound **11** (711 mg, 2.8 mmol, 1.0 equiv) was dissolved in pyridine (10 mL) and cooled down to 0 °C. DMAP (50 mg, cat) and toluene-4-sulfonic acid chloride (686 mg, 3.6 mmol, 1.3 equiv) were added and the reaction mixture was warmed to room temperature overnight. After addition of saturated NaCl solution (20 mL), 2 N HCl (20 mL), and diethyl ether (20 mL) the aqueous phase was separated and extracted with diethyl ether (3×20 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (15 mL) and dried over $MgSO_4$. The solvents were evaporated under vacuum. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:3) to give **12** (830 mg, 2.0 mmol, 73%) as a colourless liquid. R_F=0.78 (Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.02 (s, 6H, 2-CH_3), 1.20 (d, $^3J_{NCH(CH3)2,NCH(CH3)2}$=7.0 Hz, 12H, $NCH(CH_3)_2$), 2.45 (s, 3H, $C_6H_4CH_3$), 3.12 (s, 2H, H-5), 3.73 (s, 2H, H-1), 3.89 (bs, 2H, $NCH(CH_3)_2$), 4.49 (m, 2H, H-5), 5.57 (m, 2H, H-3/H-4), 7.34 (d, $^3J_{o\text{-}Ph,m\text{-}Ph}$=4.2 Hz, 2H, *o*-Ph), 7.77 (d, $^3J_{o\text{-}Ph,m\text{-}Ph}$=4.2 Hz, 2H, *m*-Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0 (CH_3, $NCH(CH_3)_2$), 21.6 (CH_3, $C_6H_4CH_3$), 23.9 (CH_3, 2-CH_3), 30.9 (C_q, C2), 45.8 (CH, $NCH(CH_3)_2$), 64.9 (CH_2, C5), 76.8 (CH_2, C1), 124.3,

127.9, 129.8, 133.1 (CH and C_q, C4/*o*-Ph/*m*-Ph/*p*-Ph), 138.5 (CH, C3), 144.7 (C_q, *i*-Ph), 155.3 (CO). MS (70 eV): *m/z*= 411, 396, 352, 256, 226, 155, 128, 95 (100), 91, 86, 67. IR (film)=2939, 2920, 2853 ν (C_{aliph}–H), 1669 ν (C=O), 1424, 1350, 1309, 1292, 1159, 1083, 1034, 958, 834, 761 cm^{-1}. $C_{21}H_{33}NO_5S$ (411.56): calcd C 61.29, H 8.08, N 3.40, found C 61.36, H 7.99, N 3.27.

4.1.8. (*E*)-*N*,*N*-Diisopropylcarbamic acid (5-iodo-4,4-dimethylpent-2-enyl) ester (13). Compound **11** (108 mg, 0.42 mmol, 1.0 equiv), triphenylphosphine (235 mg, 0.89 mmol, 2.1 equiv) and iodine (106 mg, 0.84 mmol, 2.0 equiv) were suspended in mixture of benzene (1.0 mL) and pyridine (0.3 mL). The reaction mixture was heated for 24 h under reflux. After cooling to room temperature, *n*-pentane (5 mL) was added and the mixture was filtered through 1–2 cm bed of silica washing with diethyl ether. The solvents were evaporated under vacuum. After FCC on silica gel (diethyl ether/*n*-pentane 1:15) **13** (55 mg, 0.15 mmol, 36%) was obtained as colourless liquid. R_F= 0.51 (PE/Et_2O, 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ=1.17 (s, 6H, 4-CH_3), 1.21 (d, $^3J_{NCH(CH3)2,NCH(CH3)2}$=7.3 Hz, 12H, NCH($CH_3$)$_2$), 3.16 (s, 2H, H-5), 3.92 (bd, 2H, NCH(CH_3)$_2$), 4.57 (dd, $^3J_{1,2}$=6.1 Hz, $^4J_{1,3}$=1.0 Hz, 2H, H-1), 5.59 (td, $^3J_{1,2}$=6.1 Hz, $^3J_{2,3}$=15.7 Hz, 1H, H-2), 5.70 (td, $^3J_{2,3}$=15.7 Hz, $^4J_{1,3}$=1.0 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0 (CH_3, NCH(CH_3)$_2$), 22.3 (CH_2, C5), 26.9 (CH_3, 4-CH_3), 36.1 (C_q, C4), 45.9 (CH, NCH(CH_3)$_2$), 64.9 (CH_2, C1), 123.6 (CH, C3), 140.2 (CH, C2), 155.4 (CO). MS (70 eV): *m/z*=367, 352, 308, 240, 223, 212, 181, 146, 128, 95 (100), 86. IR (film)=2947, 2930, 2911 ν (C_{aliph}–H), 1673 ν (C=O), 1425, 1360, 1299, 1208, 1147, 1125, 1038, 964, 877, 760 cm^{-1}. $C_{14}H_{26}INO_2$ (367.27): calcd C 45.78, H 7.14, N 3.81, found C 45.75, H 7.14, N 3.69.

4.1.9. (*E*)-5-Chloro-4,4-dimethylpent-2-enoic acid ethyl ester (15a). Sodium hydride (60% in mineral oil, 1.5 g, 37.5 mmol 1.5 equiv), triethyl phosphonoacetate (14.0 g, 62.5 mmol, 2.5 equiv), and 3-chloro-2,2-dimethylpropanal (3.0 g, 33.3 mmol, 1.0 equiv) were treated in Et_2O (100 mL) in the same manner as described for compound **8**. Purification by FCC on silica gel (diethyl ether/*n*-pentane 1:10) yielded **15a** (5.4 g, 28.6 mmol, 86%) as a colourless liquid. R_F=0.51 (PE/Et_2O, 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ=1.19 (s, 6H, 4-CH_3), 1.30 (t, ^3J=7.4 Hz, 3H, OCH_2CH_3), 3.43 (s, 2H, H-5), 4.21 (q, ^3J=7.4 Hz, 2H, OCH_2CH_3), 5.84 (d, $^3J_{2,3}$=16.3 Hz, 1H, H-2), 6.92 (d, $^3J_{2,3}$=16.3 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2 (CH_3, OCH_2CH_3), 24.5 (CH_3, 4-CH_3), 38.6 (C_q, C4), 53.8 (CH_2, C5), 60.4 (CH_2, OCH_2CH_3), 120.0 (CH, C3), 153.4 (CH, C2), 166.6 (C_q, C1). MS (70 eV): *m/z*=190, 175, 155, 145, 141 (100), 127, 113, 95, 81, 67. IR (film)= 2976, 2908, 2876 ν (C_{aliph}–H), 1716 ν (C=O), 1652, 1467, 1367, 1309, 1179, 1041, 977, 917, 746 cm^{-1}. $C_9H_{15}ClO_2$ (190.67): calcd C 56.58, H 7.93, found C 56.73, H 7.84.

4.1.10. (*E*)-5-Chloro-4,4-dimethylpent-2-en-1-ol (16a). Compound **15a** (10.96 g, 57.5 mmol, 1.0 equiv), DIBAL-H (1.0 M in *n*-hexane, 133.0 mL, 133.0 mmol, 2.3 equiv) were treated in toluene (150 mL) in the same manner as described for compound **9**. The crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:3) to give **16a** (7.26 g, 48.9 mmol, 85%) as a colourless liquid. R_F=0.09 (PE/Et_2O, 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (s, 6H, 4-CH_3), 1.44 (bs, 1H, O-H), 3.37 (s, 2H, H-5), 4.13 (m, 2H, H-1); 5.68 (m, 2H, H-2/H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.0 (CH_3, 4-CH_3), 37.4 (C_q, C4), 55.2 (CH_2, C5), 65.8 (CH_2, C1), 127.6 (CH, C2), 138.2 (CH, C3). MS (70 eV): *m/z*=148, 130, 117, 113, 112, 99, 97, 94, 82, 81, 77, 71, 57 (100). IR (film)=3347 ν (O-H), 2967, 2948, 2871 ν (C_{aliph}–H), 1565, 1471, 1384, 1361, 1293, 1084, 1022, 977, 900, 730 cm^{-1}. $C_7H_{13}ClO$ (148.63): calcd C 56.57, H 8.82, found C 56.52, H 8.93.

4.1.11. (*E*)-*N*,*N*-Diisopropylcarbamic acid (5-chloro-4,4-dimethylpent-2-enyl) ester (17a). *N*,*N*-Diisopropylcarbamoyl chloride (2.48 g, 15.2 mmol, 4.0 equiv), **16a** (0.51 g, 3.4 mmol, 1.0 equiv) were heated in pyridine (2.5 mL) at 90 °C for 18 h and then treated in the same manner as described for compound **10**. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:10) yielding **17a** (0.70 g, 2.5 mmol, 74%) as a colourless liquid, which starts crystallizing after some days. Mp= 38 °C, (PE/Et_2O). R_F=0.48 (PE/Et_2O, 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ=1.13 (s, 6H, 4-CH_3), 1.21 (d, $^3J_{NCH(CH3)2,N-H(CH3)2}$=6.8 Hz, 12H, NCH($CH_3$)$_2$), 3.37 (s, 2H, H-5), 3.90 (bs, 2H, NCH(CH_3)$_2$), 4.57 (dd, $^3J_{H\text{-}1,H\text{-}2}$= 5.8 Hz, $^4J_{H\text{-}1,H\text{-}3}$=1.3 Hz, 2H, H-1), 5.63 (td, $^3J_{H\text{-}1,H\text{-}2}$= 5.8 Hz, $^3J_{H\text{-}2,H\text{-}3}$=15.8 Hz, 1H, H-2), 5.74 (td, $^3J_{H\text{-}2,H\text{-}3}$= 15.8 Hz, $^4J_{H\text{-}1,H\text{-}3}$=1.3 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.8 (CH_3, NCH(CH_3)$_2$), 26.7 (CH_3, 4-CH_3), 39.5 (C_q, C-4), 47.7 (CH, NCH(CH_3)$_2$), 56.9 (CH_2, C-1), 66.7 (CH_2, C-5), 125.6 (CH, C-3), 141.7 (CH, C-2), 157.7 (CO). MS (70 eV): *m/z*=275, 260, 226, 216, 144, 128, 95, 86 (100), 55. IR (film)=2979, 2931, 2876 ν (C_{aliph}–H), 1705 ν (C=O), 1441, 1371, 1310, 1216, 1160, 1050, 972, 771, 738 cm^{-1}. $C_{14}H_{26}ClNO_2$ (275.82): calcd C 60.97, H 9.50, N 5.08, found C 61.32, H 9.38, N 5.04.

4.1.12. (*E*)-5-Bromo-4,4-dimethylpent-2-enoic acid ethyl ester (15b). Sodium hydride (60% in mineral oil, 3.4 g, 85.3 mmol 1.5 equiv), triethyl phosphonoacetate (31.8 g, 142.1 mmol, 2.5 equiv), and 3-bromo-2,2-dimethylpropanal (9.4 g, 56.8 mmol, 1.0 equiv) were treated in Et_2O (150 mL) in the same manner as described for compound **8**. Purification by FCC on silica gel (diethyl ether/*n*-pentane 1:10) yielded **15b** (11.8 g, 50.4 mmol, 89%) as a colourless liquid. R_F=0.51 (PE/Et_2O, 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ=1.22 (s, 6H, 4-CH_3), 1.31 (t, ^3J=7.2 Hz, 3H, OCH_2CH_3), 3.34 (s, 2H, H-5), 4.21 (q, ^3J=7.2 Hz, 2H, OCH_2CH_3), 5.83 (d, $^3J_{2,3}$=16.0 Hz, 1H, H-2), 6.91 (d, $^3J_{2,3}$=16.0 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 14.2 (CH_3, OCH_2CH_3), 25.3 (CH_3, 4-CH_3), 37.9 (C_q, C4), 43.7 (CH_2, C5), 60.5 (CH_2, OCH_2CH_3), 120.0 (CH, C3), 153.6 (CH, C2), 166.6 (C_q, C1). MS (70 eV): *m/z*=236, 234, 221, 219, 191, 189, 155, 141 (100), 127, 113, 95, 81, 67, 55. IR (film)=2964, 2945, 2812 ν (C_{aliph}–H), 1707 ν (C=O), 1641, 1450, 1358, 1296, 1258, 1232, 1164, 1031 cm^{-1}. $C_9H_{15}BrO_2$ (235,12): calcd C 45.98, H 6.43, found C 45.94, H 6.59.

4.1.13. (*E*)-5-Bromo-4,4-dimethylpent-2-en-1-ol (16b). Compound **15b** (10.0 g, 42.5 mmol, 1.0 equiv) and DIBAL-H (1.0 M in *n*-hexane, 103.0 mL, 103.0 mmol, 2.3 equiv) were treated in toluene (150 mL) in the same

manner as described for compound **9**. The crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:3) to give **16b** (5.6 g, 29.0 mmol, 68%) as a colourless liquid. R_F=0.09 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.16 (s, 6H, 4-CH_3), 1.52 (bs, 1H, OH), 3.30 (s, 2H, H-5), 4.14 (m, 2H, H-1); 5.67 (m, 2H, H-2/H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=25.8 (CH_3, 4-CH_3), 37.0 (C_q, C4), 45.7 (CH_2, C5), 63.6 (CH_2, C1), 127.6 (CH, C2), 138.3 (CH, C3). IR (film)=3340 ν (OH), 2941, 2908, 2848 ν (C_{aliph}–H), 1471, 1440, 1369, 1351, 1232, 1192, 1083, 961, 900, 649 cm^{-1}. $C_7H_{13}BrO$ (193.08): calcd C 43.54, H 6.79, found C 43.37, H 6.91.

4.1.14. (*E*)-*N*,*N*-Diisopropylcarbamic acid (5-bromo-4,4-dimethylpent-2-enyl) ester (17b). *N*,*N*-diisopropylcarbamoyl chloride (14.5 g, 88.4 mmol, 4.3 equiv), **16b** (4.0 g, 20.7 mmol, 1.0 equiv) were heated in pyridine (15 mL) at 90 °C for 18 h and then treated in the same manner as described for compound **10**. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:3) yielding **17b** (5.3 g, 16.5 mmol, 80%) as a colourless solid. Mp=46 °C, (PE/Et_2O). R_F=0.42 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.16 (s, 6H, 4-CH_3), 1.21 (d, $^3J_{NCH(CH3)2,NCH(CH3)2}$=6.9 Hz, 12H, $NCH(CH_3)_2$), 3.30 (s, 2H, H-5), 3.91 (bs, 2H, $NCH(CH_3)_2$), 4.58 (dd, $^3J_{H\text{-}1,H\text{-}2}$=5.9 Hz, $^4J_{H\text{-}1,H\text{-}3}$=1.1 Hz, 2H, H-1), 5.62 (td, $^3J_{H\text{-}1,H\text{-}2}$=5.9 Hz, $^3J_{H\text{-}2,H\text{-}3}$=15.8 Hz, 1H, H-2), 5.73 (td, $^3J_{H\text{-}2,H\text{-}3}$=15.8 Hz, $^4J_{H\text{-}1,H\text{-}3}$=1.1 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.1 (CH_3, $NCH(CH_3)_2$), 25.7 (CH_3, 4-CH_3), 37.1 (C_q, C-4), 45.5 (CH_2, C-5), 45.8 (CH, $NCH(CH_3)_2$), 64.9 (CH_2, C-1), 123.9 (CH, C-3), 140.0 (CH, C-2), 155.2 (CO). MS-ESI (1.25 kV): *m*/*z*=344 [{MBr^{81}+Na}$^+$]; 342 [{MBr^{79}+Na}$^+$]. IR (KBr)=3087–2726 ν (C_{aliph}–H), 1646 ν (C=O), 1404, 1334, 1280, 1188, 1113, 1020, 944, 871, 749, 623, 590, 549, 494 cm^{-1}. $C_{14}H_{26}BrNO_2$ (320.27): calcd C 52.50, H 8.18, N 4.37, found C 52.89, H 8.30, N 4.33.

4.1.15. (*R*)-(*E*)-*N*,*N*-Diisopropylcarbamic acid (5-(*tert*-butyldimethylsilyloxy)-4,4-dimethyl-1-trimethylsilylpent-2-enyl) ester (19). *General procedure for silylation of carbamate* **10**. The diamine (0.77 mmol, 1.4 equiv) was dissolved in diethyl ether (2 mL), cooled down to −78 °C, and *n*-butyllithium (1.6 M in *n*-hexane, 0.38 mL, 0.61 mmol, 1.1 equiv) was added dropwise. After 15 min, **10** (200 mg, 0.54 mmol, 1.0 equiv) was injected and after additional 2–30 min (see Table 1) freshly distilled trimethylsilyl chloride (117 mg, 1.08 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 3 h at −78 °C, methanol (1 mL) and water (1 mL) were added and then the mixture was warmed up to room temperature. The mixture was diluted with diethyl ether (40 mL) and dried over $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:15) yielding **19** as colourless liquid.

In situ silylation of carbamate **10**. Freshly distilled trimethylsilyl chloride (117 mg, 1.08 mmol, 2.0 equiv), **10** (200 mg, 0.54 mmol, 1.0 equiv) and (−)-sparteine (180 mg, 0.77 mmol, 1.4 equiv) were dissolved in diethyl ether (2 mL) and cooled down to −78 °C. *n*-Butyllithium (1.6 M in *n*-hexane, 0.38 mL, 0.61 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 3 h at −78 °C. Methanol (1 mL) and water (1 mL) were added and then the mixture was warmed up to room temperature. The mixture was diluted with diethyl ether (40 mL) and dried over $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:15) yielding **19** as colourless liquid.

R_F=0.58 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=−0.09 (s, 9H, Si–CH_3), 0.0 (s, 6H, OSi–CH_3), 0.84 (s, 9H, OSi–C(CH_3)$_3$), 0.84 (s, 6H, 4-CH_3); 1.17 (d, $^3J_{NCH(CH3)2\text{-}NCH(CH3)2}$=8.2 Hz, 6H, $NCH(CH_3)_2$), 3.22 (s, 2H, H-5), 3.87 (bs, 2H, $NCH(CH_3)_2$), 5.06 (m, 1H, H-1), 5.73 (m, $^3J_{2,3}$=16.4 Hz, 2H, H-2/H-3).[15] ^{13}C NMR (75 MHz, $CDCl_3$): δ=−4.8 (CH_3, $OSiCH_3$), −2.8 (CH_3, $SiCH_3$), 18.3 (C_q, OSiC), 21.3 (CH_3, $NCH(CH_3)_2$), 24.1 (CH_3, 4-CH_3), 24.5 (CH_3, 4-CH_3), 25.9 (CH_3, OSiC(CH_3)$_3$), 38.1 (C_q, C4), 45.9 (CH, $NCH(CH_3)_2$), 70.3 (CH, C1), 72.1 (CH_2, C5), 124.6 (CH, C3), 135.7 (CH, C2), 155.6 (CO). MS (70 eV): *m*/*z*=443, 428, 386, 298, 244, 216, 202, 172, 128, 86, 73 (100). IR (film)=2961, 2934, 2864 ν (C_{aliph}–H), 1700 ν (C=O), 1473, 1439, 1370, 1294, 1248, 1223, 1104, 973, 840, 779, 671 cm^{-1}. HRMS (ESI): $C_{23}H_{49}NO_3Si_2$ [M+Na$^+$] calcd 466.3143; found 466.3159 (purity >98% ^{1}H NMR). $[\alpha]_D^{20}$=+5.5 (*c*=1.11, CH_2Cl_2), at 90% ee (er=95:5).

4.1.16. (*Z*)-*N*,*N*-Diisopropylcarbamic acid [2-(2,2-dimethylcyclopropyl)vinyl] ester (22). *General procedure for cyclization of carbamates*:. The diamine (2.0 equiv) was dissolved (2–3 mL/mmol carbamate, see Table 2) and cooled down to the temperature as stated in Table 2. *n*-Butyllithium (1.6 M in *n*-hexane, 2.0 equiv) was added slowly and after 15 min the carbamate (2–3 mL/mmol carbamate, see Table 2) was injected. After 3 h, the reaction was quenched at −78 °C with ethanol (1 mL/mmol carbamate) and water (1 mL/mmol carbamate). The reaction mixture was warmed up to room temperature. The aqueous phase was separated and extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated under vacuum. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:15) yielding **22** as colourless liquid. R_F=0.38 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.29 (t, $^3J_{H\text{-}1',H\text{-}3'trans}$=5.3 Hz, $^2J_{H\text{-}3'a,H\text{-}3'b}$=5.3 Hz, 1H, H-3′*trans*), 0.73 (dd, $^3J_{H\text{-}1',H\text{-}3'cis}$=8.6 Hz, $^2J_{H\text{-}3'a,H\text{-}3'b}$=5.3 Hz, 1H, H-3′*cis*), 1.06 (s, 3H, 2′-CH_3), 1.10 (s, 3H, 2′-CH_3), 1.27 (d, $^3J_{NCH(CH3)2,NCH(CH3)2}$=5.9 Hz, 12H, $NCH(CH_3)_2$), 1.52 (dddd, $^3J_{H\text{-}2,H\text{-}1'}$=8.6 Hz, $^3J_{H\text{-}1',H\text{-}3'cis}$=8.6 Hz, $^3J_{H\text{-}1',H\text{-}3'trans}$=5.3 Hz, $^4J_{H\text{-}1,H\text{-}1'}$=1.0 Hz, 1H, H-1′), 3.97 (bd, 2H, $NCH(CH_3)_2$), 4.45 (dd, $^3J_{H\text{-}1,H\text{-}2}$=6.4 Hz, $^3J_{H\text{-}2,H\text{-}1'}$=8.6 Hz, 1H, H-2), 7.08 (dd, $^3J_{H\text{-}1,H\text{-}2}$=6.4 Hz, $^4J_{H\text{-}1,H\text{-}1'}$=1.0 Hz, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ=17.0 (C_q, C2′), 19.8 (CH_3, $NCH(CH_3)_2$), 21.3 (CH_2, C3′), 24.5 (CH, C1′), 25.7 (CH_3, 2′-CH_3), 44.6 (CH, $NCH(CH_3)_2$), 110.2 (CH, C2), 134.8 (CH, C1), 153.2 (CO). MS (70 eV): *m*/*z*=239, 224, 195, 144, 128, 97, 86 (100). IR (film)=2973, 2943, 2872 ν (C_{aliph}–H), 1714 ν (C=O), 1666, 1442, 1373, 1314, 1285, 1135, 1080, 907, 857, 762 cm^{-1}. $C_{14}H_{25}NO_2$ (239.35): calcd C 70.25, H 10.53, N 5.85, found C 70.18, H 10.61, N 5.67. $[\alpha]_D^{20}$=−39.8 (*c*=0.58, CH_2Cl_2), at 49% ee

(er=75.5:24.5). Shift experiment with 150% Eu(hfc)$_3$ in C_6D_6. $\Delta\delta$[2′-CH_3 at $\delta=1.06$]=0.02, signal of major enantiomer appears at lower field.

General procedure for α-substitution of **22** (*Method A*). **22** (1.0 equiv) was dissolved in diethyl ether (5 mL/mmol carbamate) and cooled down to −78 °C. TMEDA (1.3 equiv) and *n*-butyllithium (1.6 M in *n*-hexane, 1.3 equiv) were injected and the solution was stirred for 1 h at −78 °C. The electrophile (2.0–3.0 equiv) was added and after 4 h of stirring the reaction mixture was quenched at −78 °C with ethanol (1 mL/mmol carbamate) and water (1 mL/mmol carbamate). The reaction mixture was warmed up to room temperature. The aqueous phase was separated and extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated under vacuum. The crude product was subjected to FCC on silica gel (diethyl ether/*n*-pentane 1:15) yielding the pure cyclopropane.

General procedure for cyclization and α-substitution of **17a** (*Method B*). (−)-Sparteine (2.0–2.2 equiv) was dissolved in diethyl ether (3 mL/mmol carbamate) and cooled down to −78 °C. *n*-Butyllithium (1.6 M in *n*-hexane, 2.0–2.2 equiv) was added slowly and after 15 min a solution of **17a** (1.0 equiv) in diethyl ether (3 mL/mmol carbamate). After the mixture was stirred for 3 h at −78 °C, the electrophile (3.0 equiv) was added and the stirring was continued for additional 3 h. The reaction mixture was quenched at −78 °C with ethanol (1 mL/mmol carbamate) and water (1 mL/mmol carbamate). The reaction mixture was warmed up to room temperature, the aqueous phase was separated and extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated under vacuum. The crude product was purified by FCC on silica gel (diethyl ether/*n*-pentane 1:15) yielding the pure α-functionalized cyclopropane.

4.1.17. (*Z*)-*N*,*N*-Diisopropylcarbamic acid [2-(2,2-dimethylcyclopropyl)-1-methylvinyl] ester (30a). *Method A.* (*S*)-**22** (50 mg, 0.21 mmol, 1.0 equiv, 51% ee), TMEDA (32 mg, 0.27 mmol, 1.3 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.17 mL, 0.27 mmol, 1.3 equiv), and methyl iodide (89 mg, 0.63 mmol, 3.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method A. Purification by FCC yielded (*S*)-**30a** (17 mg, 0.07 mmol, 32%) as colourless liquid.

Method B. **17a** (100 mg, 0.36 mmol, 1.0 equiv), (−)-sparteine (187 mg, 0.79 mmol, 2.2 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.50 mL, 0.79 mmol, 2.2 equiv), and methyl iodide (155 mg, 1.09 mmol, 3.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method B. FCC of the crude product yielded (*S*)-**30a** (59 mg, 0.23 mmol, 64%, 46% ee) as colourless liquid and **17a** (12 mg, 0.09 mmol, 12%).

R_F=0.48 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.24$ (t, $^3J_{\text{H-1}',\text{H-3}'trans}=4.7$ Hz, $^2J_{\text{H-3}'cis,\text{H-3}'trans}=4.7$ Hz, 1H, H-3′*trans*), 0.65 (dd, $^3J_{\text{H-1}',\text{H-3}'cis}=8.5$ Hz, $^2J_{\text{H-3}'cis,\text{H-3}'trans}=4.7$ Hz, 1H, H-3′*cis*), 1.04 (s, 3H, 2′-CH_3), 1.05 (s, 3H, 2′-CH_3), 1.26 (d, $^3J_{\text{NCH(CH3)2,NCH(CH3)2}}=7.0$ Hz, 12H, NCH(CH_3)$_2$), 1.59 (bs, 1H, H-1′), 1.91 (s, 3H, 1-CH_3), 3.96 (bd, 2H, NCH(CH_3)$_2$), 4.67 (dd, $^3J_{\text{H-1}',\text{H-2}}=8.7$ Hz, $^4J_{\text{1-CH3,H-2}}=1.1$ Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=17.8$ (C_q, C-2′), 20.7 (CH_3, NCH(CH_3)$_2$), 20.0, 21.0 (CH, CH_2, C-1′/C-3′), 22.1 (CH_3, 1-CH_3), 26.9 (CH_3, 2′-CH_3), 45.7 (CH, NCH(CH_3)$_2$), 116.7 (CH, C-2), 145.9 (C_q, C-1), 153.3 (CO). MS (70 eV): *m*/*z*=253, 213, 188, 144, 128 (100), 111, 86. IR (film)=2978, 2948, 2875 ν (C_{aliph}–H), 1707 ν (C=O), 1436, 1372, 1331, 1304, 1272, 1249, 1214, 1188, 1150, 1082, 1047, 1012, 907, 764 cm^{-1}. $C_{15}H_{27}NO_2$ (253.38): calcd C 71.10, H 10.74, N 5.53, found C 70.77, H 10.90, N 5.37. $[\alpha]_D^{20}=-28.3$ (*c*=0.53, CH_2Cl_2), at 46% ee (er=73:26).

4.1.18. (*Z*)-*N*,*N*-Diisopropylcarbamic acid [2-(2,2-dimethylcyclopropyl)-1-trimethylstannylvinyl] ester (30b). *Method A.* (*S*)-**22** (50 mg, 0.21 mmol, 1.0 equiv, 57% ee), TMEDA (32 mg, 0.27 mmol, 1.3 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.17 mL, 0.27 mmol, 1.3 equiv), and trimethyltin chloride (1.0 M in *n*-hexane, 0.42 mL, 0.42 mmol, 2.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method A. Purification by FCC yielded (*S*)-**30b** (60 mg, 0.15 mmol, 71%) as colourless liquid.

Method B. **17a** (100 mg, 0.36 mmol, 1.0 equiv), (−)-sparteine (170 mg, 0.72 mmol, 2.0 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.45 mL, 0.72 mmol, 2.0 equiv), and trimethyltin chloride (1.0 M in *n*-hexane, 1.09 mL, 1.09 mmol, 3.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method B. The crude product was purified by FCC and (*S*)-**30b** (95 mg, 0.24 mmol, 65, 48% ee) was obtained as colourless liquid.

R_F=0.70 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 0.10 (s, 9H, $SnCH_3$), 0.28 (t, $^3J_{\text{H-1}',\text{H-3}'trans}=5.1$ Hz, $^2J_{\text{H-3}'cis,\text{H-3}'trans}=5.1$ Hz, 1H, H-3′*trans*), 0.70 (dd, $^3J_{\text{H-1}',\text{H-3}'cis}=8.6$ Hz, $^2J_{\text{H-3}'cis,\text{H-3}'trans}=5.1$ Hz, 1H, H-3′*cis*), 1.05 (s, 3H, 2′-CH_3), 1.06 (s, 3H, 2′-CH_3), 1.23 (bs, 12H, NCH(CH_3)$_2$), 1.67 (ddd, $^3J_{\text{H-1}',\text{H-3}'cis}=8.6$ Hz, $^3J_{\text{H-1}',\text{H-3}'trans}=5.1$ Hz, $^3J_{\text{H-1}',\text{H-2}}=9.1$ Hz, 1H, H-1′), 3.94 (bd, 2H, NCH(CH_3)$_2$), 4.56 (d, $^3J_{\text{H-1}',\text{H-2}}=9.1$ Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=-6.3$ (CH_3, $SnCH_3$), 18.6 (C_q, C-2′), 20.9 (CH, C-1′), 21.5 (CH_3, NCH(CH_3)$_2$), 22.9 (CH_2, C-3′), 27.0 (CH_3, 2′-CH_3), 45.6 (CH, NCH(CH_3)$_2$), 124.8 (CH, C-2), 155.6 (C_q, C-1), 157.7 (CO). MS (70 eV): *m*/*z*=388, 294, 263, 164, 128, 86 (100), 58. IR (film)= 2974, 2944, 2876 ν (C_{aliph}-H), 1690 ν (C=O), 1438, 1373, 1334, 1313, 1270, 1217, 1157, 1139, 1064, 769 cm^{-1}. $C_{17}H_{33}NO_2Sn$ (403.15): calcd C 50.77, H 8.27, N 3.48, found C 51.17, H 8.40, N 3.53. $[\alpha]_D^{20}=-4.9$ (*c*=0.39, CH_2Cl_2), at 51% ee (er=75.5:24.5).

4.1.19. (*Z*)-*N*,*N*-Diisopropylcarbamic acid [2-(2,2-dimethylcyclopropyl)-1-trimethylsilylvinyl] ester (30c). *Method A.* (*S*)-**22** (50 mg, 0.21 mmol, 1.0 equiv, 57% ee), TMEDA (32 mg, 0.27 mmol, 1.3 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.17 mL, 0.27 mmol, 1.3 equiv), and trimethylsilyl chloride (45 mg, 0.42 mmol, 2.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method A. Purification by FCC yielded (*S*)-**30c** (43 mg, 0.14 mmol, 66%) as colourless liquid.

Method B. **17a** (100 mg, 0.36 mmol, 1.0 equiv), (−)-sparteine (170 mg, 0.72 mmol, 2.0 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.45 mL, 0.72 mmol, 2.0 equiv), and trimethylsilyl chloride (118 mg, 1.09 mmol, 3.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method B. FCC of the crude product yielded (*S*)-**30c** (89 mg, 0.29 mmol, 79%, 57% ee) as colourless liquid.

R_F=0.71 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.10 (s, 9H, $SiCH_3$), 0.30 (t, $^3J_{H\text{-}1',H\text{-}3'trans}$=5.0 Hz, $^2J_{H\text{-}3'cis,H\text{-}3'trans}$=5.0 Hz, 1H, H-3′*trans*), 0.70 (dd, $^3J_{H\text{-}1',H\text{-}3'cis}$=8.5 Hz, $^2J_{H\text{-}3'cis,H\text{-}3'trans}$=5.0 Hz, 1H, H-3′*cis*), 1.03 (s, 3H, 2′-CH_3), 1.04 (s, 3H, 2′-CH_3), 1.22 (d, $^3J_{NCH(CH3)2,NCH(CH3)2}$=7.0 Hz, 12H, N–$CH(CH_3)_2$), 1.48 (ddd, $^3J_{H\text{-}1',H\text{-}3'cis}$=8.5 Hz, $^3J_{H\text{-}1',H\text{-}3'trans}$=5.0 Hz, $^3J_{H\text{-}1',H\text{-}2}$=9.0 Hz, 1H, H-1′), 3.92 (bd, 2H, $NCH(CH_3)_2$), 4.98 (d, $^3J_{H\text{-}1',H\text{-}2}$=9.0 Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=−0.8 (CH_3, $SiCH_3$), 20.9 (C_q, C-2′), 20.5, 21.5 (CH_3, $NCH(CH_3)_2$), 22.3, 23.1 (CH, CH_2, C-1′/C-3′), 27.0 (CH_3 2′-CH_3), 45.8, 46.2 (CH, $NCH(CH_3)_2$), 130.3 (CH, C-2), 154.2 (C_q, C-1), 155.2 (CO). MS (70 eV): *m*/*z*=311, 296, 216, 202, 169, 128, 86 (100), 73. IR (film)=2972, 2901, 2873 ν (C_{aliph}-H), 1704 ν (C=O), 1438, 1368, 1327, 1273, 1214, 1157, 1134, 1070, 843, 771 cm^{-1}. $C_{17}H_{33}NO_2Si$ (311.53): calcd C 65.54, H 10.68, N 4.49, found C 65.44, H 10.96, N 4.54. $[\alpha]_D^{20}$=−24.6 (*c*=0.13, CH_2Cl_2), at 57% ee (er=78.5:21.5).

4.1.20. (*Z*)-*N*,*N*-Diisopropylcarbamic acid [2-(2,2-dimethylcyclopropyl)-1-triisopropylsilylvinyl] ester (*rac*-30d). *Method A.* *rac*-**22** (50 mg, 0.21 mmol, 1.0 equiv), TMEDA (32 mg, 0.27 mmol, 1.3 equiv), *n*-butyllithium (1.6 M in *n*-hexane, 0.17 mL, 0.27 mmol, 1.3 equiv), and triisopropylsilyl chloride (61 mg, 0.42 mmol, 2.0 equiv), dissolved in diethyl ether (2 mL), were treated according to Method A. Purification by FCC yielded *rac*-**22** (10 mg, 0.04 mmol, 20%) and *rac*-**30d** (30 mg, 0.08 mmol, 36%) as colourless liquid.

R_F=0.74 (PE/Et_2O, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.34 (t, $^2J_{H\text{-}3'cis,H\text{-}3'trans}$=5.1 Hz, $^3J_{H\text{-}1',H\text{-}3'trans}$=5.1 Hz, 1H, H-3′*trans*), 0.71 (dd, $^2J_{H\text{-}3'cis,H\text{-}3'trans}$=5.1 Hz, $^3J_{H\text{-}1',H\text{-}3'cis}$=8.4 Hz, 1H, H-3′*cis*), 1.00–1.11 (m, 27H, 2′-CH_3/$SiCH(CH_3)_2$/$SiCH(CH_3)_2$), 1.21 (bs, 12H, $NCH(CH_3)_2$), 1.30 (ddd, $^3J_{H\text{-}1',H\text{-}3'cis}$=8.4 Hz, $^3J_{H\text{-}1',H\text{-}3'trans}$=5.1 Hz, $^3J_{H\text{-}1',H\text{-}2}$=8.9 Hz, 1H, H-1′), 3.91 (bd, 2H, $NCH(CH_3)_2$), 5.12 (d, $^3J_{H\text{-}1',H\text{-}2}$=8.9 Hz, 1H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=−0.0 (CH, $SiCH(CH_3)_2$); 11.1 (CH_3, $SiCH(CH_3)_2$); 19.2 (C_q, C-2′); 21.2 (CH, C-1′); 20.4, 21.4 (CH_3, $NCH(CH_3)_2$); 23.2 (CH_2, C-3′); 27.0 (CH_3, 2′-CH_3); 45.8, 46.3 (CH, $NCH(CH_3)_2$); 135.4 (CH, C-2); 151.3 (C_q, C-1); 152.8 (CO). GC-TOF: *m*/*z*=352, 258, 216, 153, 144, 128, 111, 86 (100), 59, 43. IR (film)=2963, 2941, 2891, 2867 ν (C_{aliph}-H), 1704 ν (C=O), 1624, 1465, 1424, 1378, 1367, 1315, 1267, 1215, 1154, 1135, 1096, 1059, 1017, 883, 753 cm^{-1}. $C_{23}H_{45}NO_2Si$ (395.69): calcd C 69.81, H 11.46, N 3.54, found C 69.52, H 11.39, N 3.49.

4.1.21. (−)-(*R*)-2,2-Dimethylcyclopropane carboxylic acid (26). $NaIO_4$ (1.78 g, 8.32 mmol, 20.0 equiv) and $RuCl_3 \cdot H_2O$ (10 mg, 0.04 mmol, 0.1 equiv) were suspended in CCl_4 (2.0 mL), water (3.2 mL), and acetonitrile (2.0 mL). The suspension was stirred for 30 min at room temperature and (*S*)-**22** (100 mg, 0.42 mmol, 1.0 equiv, 38% ee) was added. After 48 h, the reaction mixture was filtered and the residue was washed with CH_2Cl_2 (3×5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents evaporated under vacuum. The carboxylic acid **26** (48 mg, 0.42 mmol, quant.) was used without further purification. $[\alpha]_D^{20}$=−20 (*c*=0.19, $CHCl_3$, purity 80–90%).[22]

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 424) and the Fonds der Chemischen Industrie. We thank Mrs. U. Allebrod for her skilful experimental assistance.

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Synthesis and photochromic reactivity of macromolecules incorporating four dithienylethene units

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Received 11 August 2005; revised 21 September 2005; accepted 22 September 2005

Available online 25 October 2005

Abstract—Two macrocycles bearing four dithienylethene units were synthesized. Upon irradiation of the macrocycles **5** and **6** with ultraviolet light, only one or two photo-induced cyclization reaction occurs. Each isomers were isolated and analyzed by ^{1}H NMR spectrum. The quantum yield of **5** and **6** are 0.58 and 0.64, respectively. The high value is due to the presence of enforced antiparallel conformation in the macrocycles **5** and **6**.

1. Introduction

The conformationally rigid and shape-persistent supramolecules of nanometer size have attracted much interest because of their potential in host–guest systems,[1] fluorescence ion sensor,[2] self-aggregation,[3] organometallic coordination,[4] and liquid crystal.[5] The design of geometrically well-defined supramolecules will play an important role because the incorporation of orientationally-controlled functional units into molecules can be utilized as the encoding of information.[6] The combination of the self-assembly and photochromic unit promises to be useful in optical technological devices.[7] Photochromic 1,2-diarylethene is very suitable for this purpose, due to the remarkable thermal stability and high fatigue resistance.[8] The open-ring isomer of diarylethene has two conformations—antiparallel and parallel—in equal amounts. The conrotatory cyclization can proceed only from the antiparallel conformation. Therefore, the cyclization quantum yield cannot exceed 50% in solution. To achieve high quantum yield, it is required to increase the population of the antiparallel conformers. Thus, diarylethene—backbone photochromic polymer,[9] multi-dithienylethene arrays,[10] and diarylethene in the crystal lattice[11] showed a high cyclization quantum yield due to the geometrical restriction. In a recent development, new dithienylethene based mono- and multi-substituted phthalocyanine and tetraazaporphyrin hybrids have been introduced in the form of a macrocyclic photochromic system.[12] We envisioned that the strategic placement of diarylethene units within a macrocyclic framework would achieve high quantum yield because the macromolecule has the enforced antiparallel conformation of the diarylethene units. We now describe (i) the synthesis of macromolecules having diarylethene units; (ii) their photochromic reactivities; (iii) the isolation of photocyclized products.

2. Results and discussion

Our strategy for the synthesis of macrocycles is to incorporate the diarylethene units within a macrocyclic framework. New macromolecules **5** and **6** are conveniently synthesized in four steps from the 1,2-bis[2-methyl-5-bromo-3-thienyl]perfluorocyclopentene. The palladium-catalyzed cross-coupling of 1,3-diethynylbenzene with **1** afforded **2** in 53% yield. The Sonogashira coupling of **2** with 2.2 equiv of trimethylsilylacetylene followed by basic hydrolysis yielded **4**. Our synthesis of macrocycles **5** and **6** was prepared by the cross-coupling reaction of **2** with **4** and coupling reaction[13] of the dialkyne **4** with *trans*-$Pt(PEt_3)_2Cl_2$, respectively (Scheme 1). Spectroscopic data for **5** is completely consistent with its proposed structures. Four resonances at 2.07, 2.06, 1.96, and 1.95 ppm in the ^{1}H NMR spectrum and two peaks at 15.6 and 14.5 ppm in ^{13}C NMR spectrum of **5** for the methyl group are observed. The

Keywords: Photoswitch; Macrocycle; Diarylethene; High quantum yield.
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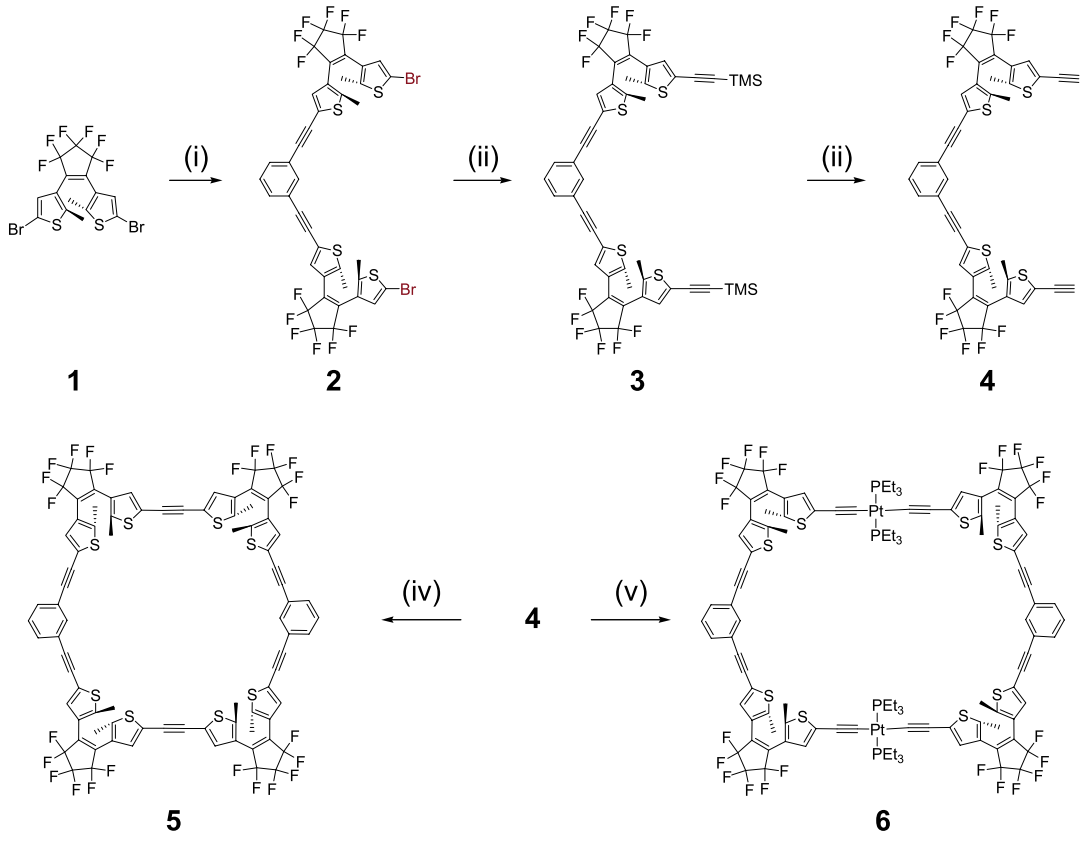
doi:10.1016/j.tet.2005.09.099



Scheme 1. Reagents and conditions: (i) 1,3-diethynylbenzene, $Pd(PPh_3)_4$, CuI in NEt_3; (ii) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI in NEt_3; (iii) KOH in MeOH and THF, then H_2O; (iv) **2**+**4**, $Pd(PPh_3)_2Cl_2$, P(*o*-tolyl)$_3$, CuI in NEt_3; (v) **4**, *trans*-$Pt(PEt_3)_2Cl_2$, CuCl in Et_2NH.

mass spectrum of **5** showed a molecular ion at *m/z* 1760. Compound **6** was characterized by ^1H, ^{13}C, and ^{31}P NMR, mass spectroscopy, and elemental analysis. The initial indication of the macromolecule **6** stemmed for the observation of an ion in the mass spectrum at *m/z* 2637. Three peaks in the ^1H NMR spectrum (1.96, 1.95, and 1.85 ppm) and four peaks at 16.5, 15.1, 9.7, and 8.7 ppm in the ^{13}C NMR spectrum of **6** proved that a macrocycle is formed in **6**. The ^{31}P NMR spectrum of **6** shows a singlet at 5.84 ppm with a small coupling constant of $^1J_{PtP}$ (2348 Hz), which is consistent with the trans configuration of **6**.[13]

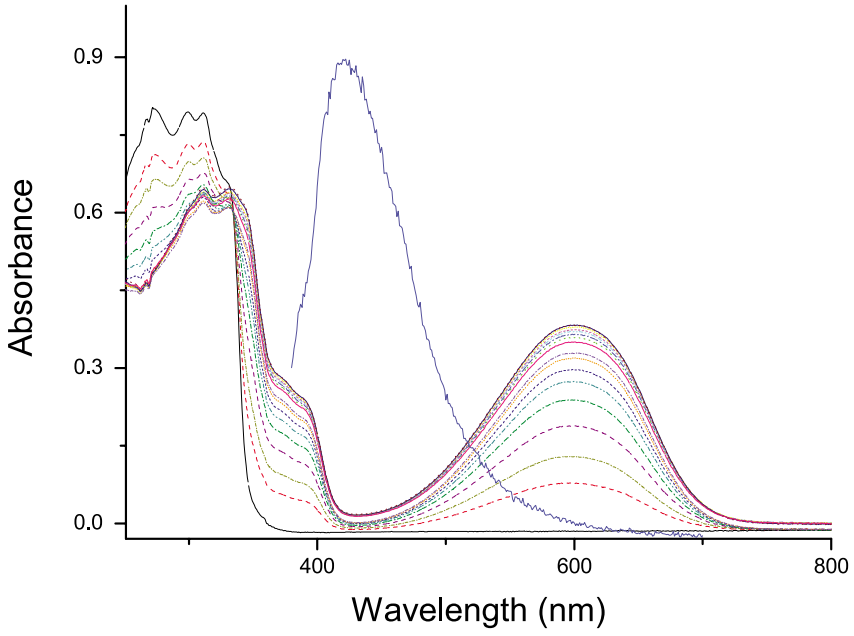


Figure 1. Absorption spectral change of **3** in chloroform upon irradiation with 325 nm light (- - -). Total irradiation periods are 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 150, 200, and 300 s. Steady-state fluorescence spectrum of the **3** (OO) (—) (excitation at 360 nm).

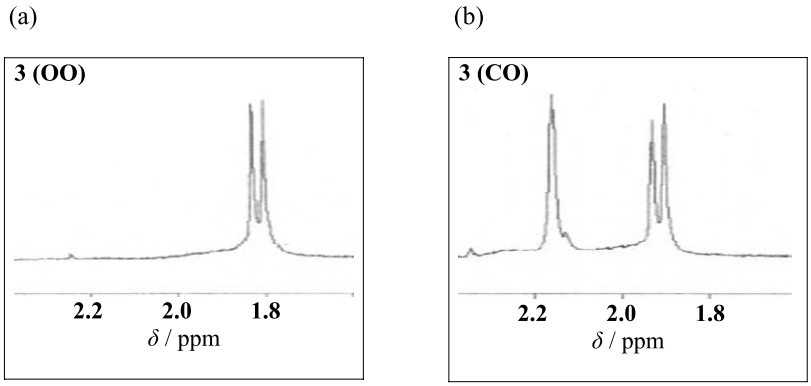
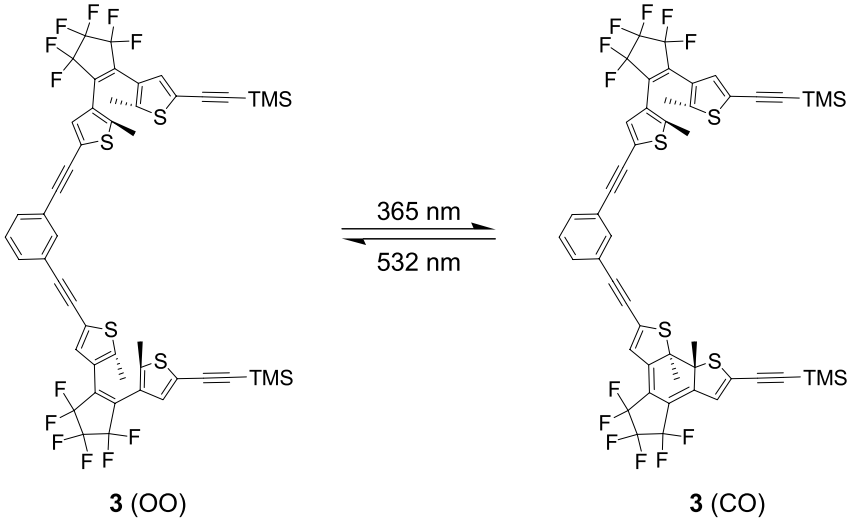


Figure 2. ^{1}H NMR methyl signals of (a) the **3** (OO) dimer; and (b) the **3** (CO) dimer.

Figure 1 shows a typical absorption spectral change of **3** in chloroform upon ultraviolet light irradiation. Irradiation of chloroform solution of **3** at 325 nm light resulted in an immediate increase in the absorption intensity at 600 nm. After visible light irradiation ($\lambda > 532$ nm) for 6 h, the colored solution was completely bleached. In the first 120 s of irradiation, an absorption band centered at 600 nm grows in as **3** is converted from the colourless-open form **3** (OO) to the blue-closed form **3** (CO). The presence of an isosbestic point at 334 nm indicates that **3** (OO) is cleanly converted to a second unique photocyclized product. The closed-ring isomer **3** (CO) was isolated from the blue colored solution by HPLC. The photogenerated ring-closed form **3** (CO) was stable at room temperature. Figure 2 shows the ^{1}H NMR spectrum of methyl protons of **3** in $CDCl_3$ before photoirradiation and in the ring-closed form, respectively. In the ^{1}H NMR spectrum of **3** (OO), two methyl resonances were observed at 1.83 and 1.80 ppm. In the blue isomer **3** (CO), one distinct new band was appeared at 2.16 ppm, together with two singlets at 1.93 and 1.88 ppm, which are slightly down-field shifted to those of **3** (OO). The integral ratio of the two signals was 1:1, which indicates that the colored isomer is a C– dimer. Another key feature in the ^{1}H NMR spectrum of **3** (CO) is the presence of four thienyl signals at 7.24, 7.22, 6.47, and 6.41 ppm. The two new resonances at 6.47 and 6.41 ppm are significantly up-field shifted as would be expected for the ring-closed isomer. Such an up-field shift was observed in covalently linked double 1,2-dithienylethenes.[10a] The dissymmetric nature of the photogenerated product indicates that only one of the thienyl units has cyclized to form **3** (CO) (Scheme 2). The fluorescence band of **3** (OO) ($\lambda = 420$ nm) shows a substantial spectral overlap with the absorption band of **3** (CO), and the Förster excitation energy transfer can take place from the photogenerated **3** (OO) to the colored form **3** (CO). Accordingly, the cyclization reaction of another open-ring form cannot take place. A similar result has been observed in the thienylethene dimer.[10]

Figure 3 shows the absorption spectral change of the macromolecule **5** in chloroform by photoirradiation. Upon irradiation with 325 nm light, the colourless solution of the open-ring isomer **5** (OOOO) with the absorption maximum at 313 nm turned blue, in which characteristic absorption maximum was observed at 602 nm. Upon visible ($\lambda > 532$ nm) light irradiation, the blue color was completely bleached.

The photogenerated products were analyzed with HPLC chromatograph (silica gel column, eluent: hexane/ethyl acetate 4:1). When monitored at the isosbestic point of 338 nm, three peaks were observed. The first peak isomer had the absorption maximum at 610 nm, while the absorption maximum of the second peak isomer was shifted



Scheme 2. The photochromic reactivity of **3**.

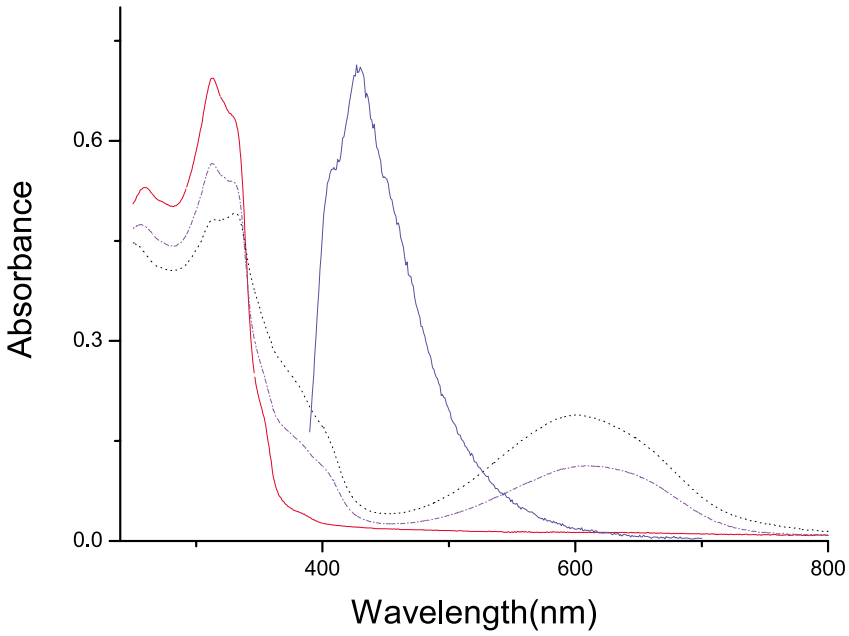


Figure 3. Absorption spectra of **5** (OOOO) (—), **5**(COOO) (– · – · –), and **5**(COCO) (- - -) in the photostaionary state under irradiation with 325 nm light, and fluorescence spectrum of **5** (OOOO) (—) in chloroform.

to 602 nm. The three isomers were isolated and analyzed by ^{1}H NMR. Figure 4 shows the ^{1}H NMR spectra of methyl protons of **5** in $CDCl_3$ before photoirradiation and in the ring-closed forms. The methyl protons of the first peak isomer show seven resonances at 2.18, 2.16, 2.07, 2.05, 1.96, 1.94, and 1.92 ppm. The first two signals at 2.18 and 2.16 ppm are assigned to the methyl protons of the closed-ring form. Other five signals are ascribed to the open-ring form. A characteristic feature in the ^{1}H NMR spectrum includes four singlets at 7.17, 7.13, 7.09, and 6.48 ppm in the region of thienyl protons. The new signal at 6.48 ppm is assigned to the proton of closed-ring thienyl unit. This indicates that the first peak isomer is due to the isomer having one closed-ring form **5** (COOO) (Scheme 3). The methyl protons of the second peak isomer show five resonances at 2.17, 2.07, 2.05, 1.97, and 1.95 ppm. The signal at 2.17 ppm is assigned to the protons of the closed-ring form. The integral ratio of a signal at 2.17 ppm with

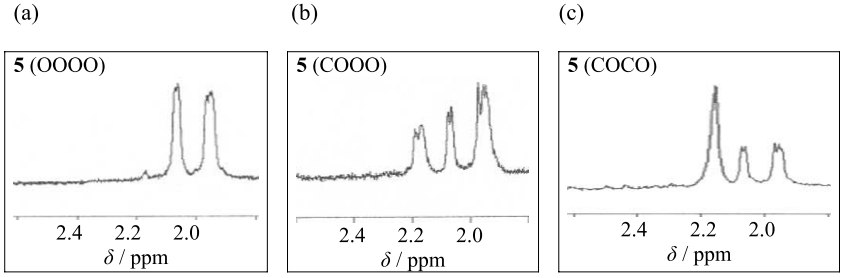
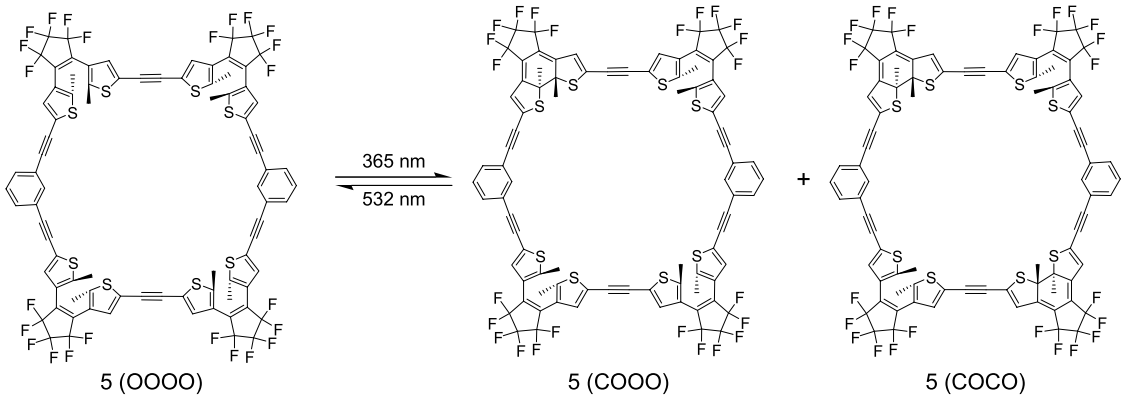
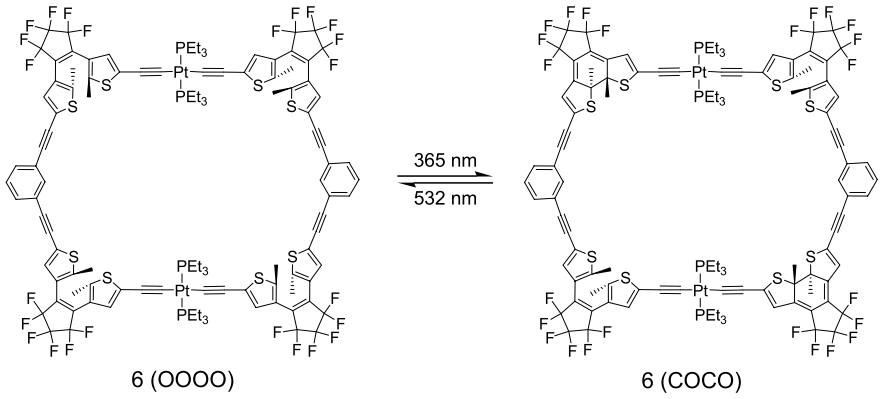


Figure 4. ^{1}H NMR methyl signals of the (a) **5** (OOOO); (b) **5** (COOO); and (c) **5** (COCO).



Scheme 3. The photochromic reactivity of **5**.



Scheme 4. The photochromic reactivity of **6**.

other signals is approximately 1:1. In addition, there are four distinct bands at 7.13, 7.09, 6.72, and 6.52 ppm in the thienyl region, in which the signals at 6.72 and 6.52 ppm is assigned to the closed-ring thienyl units. This indicates that two closed-ring form units are included in the macromolecule **5** (COCO). The methyl protons of the third peak isomer are identical to those of the open-ring form isomer **5** (OOOO). Excitation of **5** (OOOO) at 315 nm results in light emission with a maximum at 430 nm. Due to the spectral overlap of the fluorescence peak of **5** (OOOO) and absorption peak of **5** (COCO), followed by the Förster excitation energy transfer, the second peak isomer has the **5** (COCO) form. Such excited energy transfer is considered to prohibit the formation of further closed-ring form (Scheme 4).

Figure 5 shows the absorption spectra of **6** in chloroform before photoirradiation and in the photostationary state under irradiation with 325 nm light. Irradiation of chloroform solution of **6** at 325 nm light resulted in an immediate increase in the absorption intensity at 628 nm. The absorption maximum shifts to longer wavelength by 26 nm in comparison with **5**. Upon exposure of the dark blue solution to the visible light ($\lambda > 532$ nm) for 3 min, the colored solution was completely bleached. In the photostationary state, 88% of **6** is converted into the closed form. The closed-ring isomer **6** (COCO) is stable and isolated from the blue colored solution by HPLC. Figure 6 shows the ^{1}H NMR spectra of methyl protons of **6** in $CDCl_3$ before photoirradiation and in the ring-closed form. Before photoirradiation, three resonances are observed at 1.96, 1.95, and 1.85 ppm. In the ring-closed form, one new resonance appears at 2.14 ppm along with a decrease of the intensity of the three resonances. The strong one resonance at 2.14 ppm is assigned to the methyl protons of the closed form. No side reaction was detected from the ^{1}H NMR spectra.

The quantum yield of this macromolecules **5** and **6** are measured using 1,2-bis(2-methyl-3-thienyl)perfluorocyclopentene (TF_6) as a reference.[14] The cyclization quantum yield of **5** from the all open-ring form **5** (OOOO) to the **5** (COOO) isomer and form **5** (COOO) to the **5** (COCO) isomer was determined to be 0.33 and 0.25, respectively.

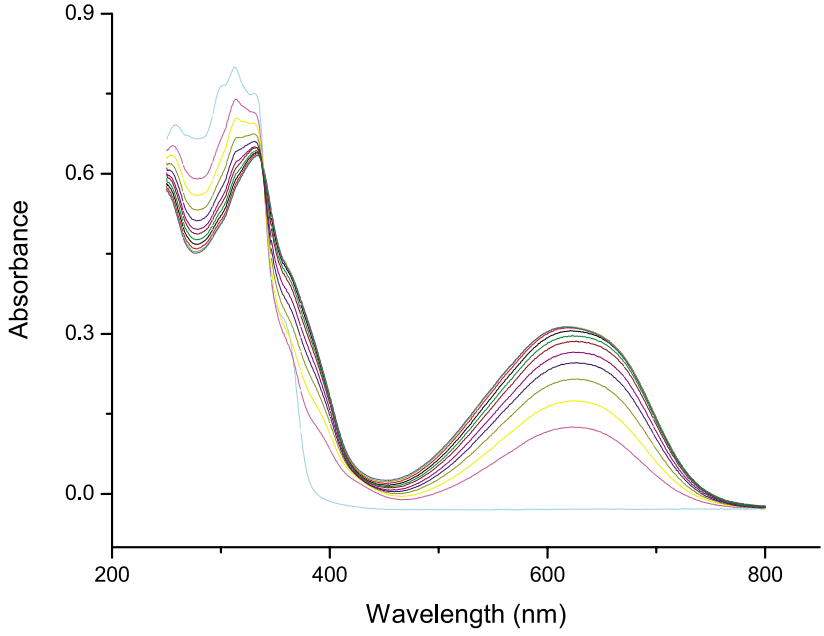


Figure 5. Absorption spectral change of **6** in chloroform upon irradiation with 325 nm light. Total irradiation periods are 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 and 150 s.

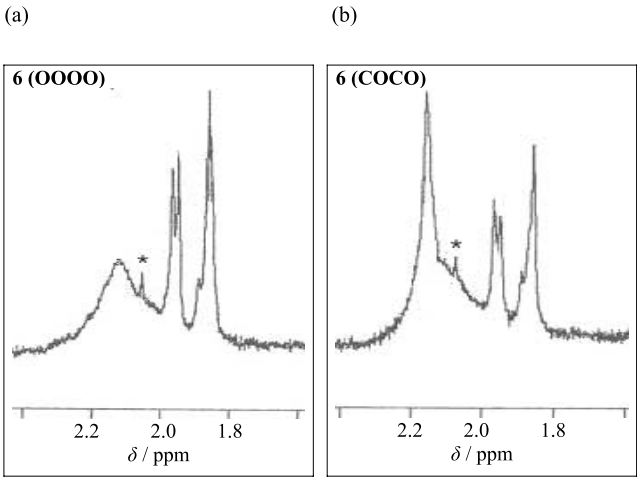


Figure 6. ^{1}H NMR methyl signals of the (a) **6** (OOOO); and (b) **6** (COCO). The asterisk denotes unidentified impurity.

The total cyclization quantum yield is 0.58, which is much higher than that of tetra-dithienylethene array.[10d] The coloration quantum yield of **6** was determined to be 0.64. The high value is due to the presence of enforced antiparallel conformation in the macromolecule **5**. The cycloreversion quantum yield of the **5** (COCO) and **6** (COCO) was measured to be 4.8×10^{-3} and 9.4×10^{-3}, respectively.

In order to obtain the geometrical configuration and characteristic features of the electronic structure, molecular orbital calculation of **5** was performed with the semi-empirical AM1. The optimized calculations show that two of four diarylethene units have different configurations. The HOMO is delocalized over the π-conjugated system via the 1,3-diethynylbenzene through two dithienylethene array. Examination of the HOMO and LUMO of **5** indicates that photoexcitation results in a net charge transfer from the π-conjugated system to the dithienylethene array (Fig. 7).

In summary, we have prepared two macromolecules incorporating four dithienylethene units. Upon irradiation of **5** and **6** with ultraviolet light, only one or two photo-induced cyclization reaction occurs. Each isomers were isolated and analyzed by ^{1}H NMR spectrum. The quantum yield of **5** and **6** are 0.58 and 0.64, respectively. The high value is due to the presence of enforced antiparallel conformation in the macrocycles **5** and **6**.

3. Experimental

All reactions were carried out under an argon atmosphere. Solvents were distilled from appropriate reagents. Perfluorocyclopenthene was purchased from Fluorochem. 1,3-Diethynylbenzene[15] and 1,2-bis[2-methyl-5-bromo-3-thienyl]perfluorocyclopentene[16] were synthesized using a modified procedure of previous references. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer. The absorption and photoluminescence spectra were recorded on a Perkin–Elmer Lambda 2S UV–vis spectrometer and a Perkin LS fluorescence spectrometer, respectively. The fluorescence quantum yields using 9,10-diphenylanthracene as the standard were determined by the dilution method.[17]

3.1. Determination of quantum yields

The quantum yields of photochromic ring-cyclizaiton of **5** and **6** were determined form the absorption change at λ_{max} in UV spectra upon excitation with UV-light for the ring-closure reaction and visible light for the ring-opening reaction. The molar extinction coefficients of **5** and **6** are $3.11\times10^{4}\,M^{-1}\,cm^{-1}$ [**5** (OOOO)], $2.60\times10^{4}\,M^{-1}\,cm^{-1}$ [**5** (COOO)], $2.33\times10^{4}\,M^{-1}\,cm^{-1}$ [**5** (COCO)], $3.00\times10^{4}\,M^{-1}\,cm^{-1}$ [**6** (OOOO)], $2.46\times10^{4}\,M^{-1}\,cm^{-1}$ [**6** (COCO)]. Then, the quantum yield was determined according to the method described in Ref. 14.

3.1.1. Compound 2. A mixture of 1,2-bis[2-methyl-5-bromo-3-thienyl]perfluoro-cyclopentene (9.28 g, 17.6 mmol), 1,3-diethynylbenzene (0.7 g, 5.5 mmol), $Pd(PPh_3)_4$ (1.0 g, 1 mmol), and CuI (0.1 g, 0.5 mmol) was vacuum-dried and added NEt_3 (40 ml). The solution was refluxed for 12 h and then evacuated to dryness. The product **2** was purified by chromatography on a silica gel column (1:10 methylene chloride/hexane, $R_f=0.3$) to afford **2** (2.99 g) in 53% yield. Mp: 205 °C. ^{1}H NMR ($CDCl_3$): δ

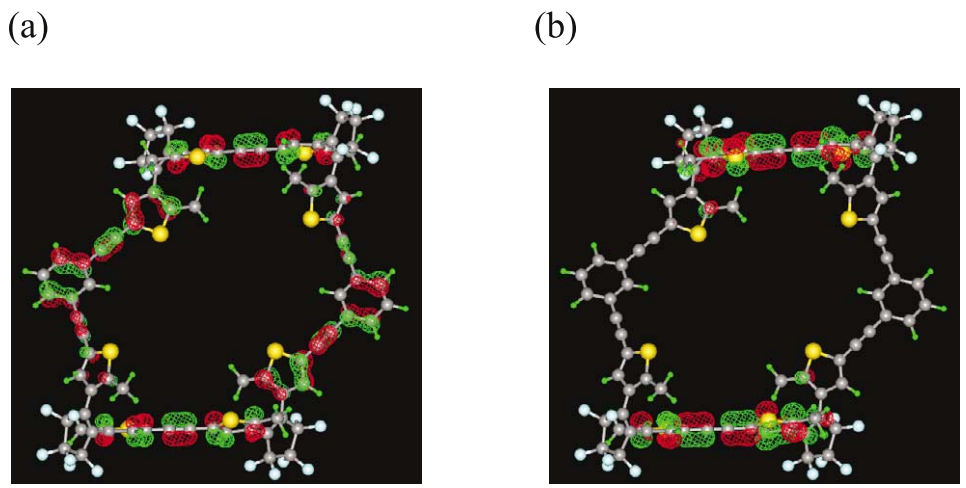


Figure 7. Representation of (a) HOMO; and (b) LUMO of **5** based on semi-empirical AM1.

7.64 (s, 1H), 7.45 (d, 2H, $J=8.40$ Hz), 7.33 (t, 1H, $J=8.40$ Hz), 7.23 (s, 2H), 7.02 (s, 2H), 1.98 (s, 6H), 1.88 (s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.4, 143.7, 143.5, 134.1, 131.8, 131.3, 129.9, 128.6, 125.3, 124.9, 123.0, 121.6, 155.9, 110.2, 93.0, 82.3, 14.9, 14.6. MS: *m/z* 1013 [M^+]. Anal. Calcd for $C_{40}H_{20}Br_2F_{12}S_4$: C, 47.26; H, 1.98. Found: C, 47.02; H, 1.90.

3.1.2. Compound 3. A mixture of **2** (1.0 g, 1 mmol), $Pd(PPh_3)_4$ (0.06 g, 0.05 mmol), and CuI (0.01 g, 0.5 mmol) was vacuum-dried and added NEt_3 (40 ml) and trimethylsilylacetylene (0.31 ml, 2.2 mmol). The solution was refluxed for 12 h and then evacuated to dryness. The pure product **3** was obtained by chromatography on a silica gel column (1:10 methylene chloride/hexane, $R_f=0.4$) to afford **3** in 81% yield. Mp: 164 °C. ^1H NMR ($CDCl_3$): δ 7.58 (s, 1H), 7.35 (d, 2H, $J=8.1$ Hz), 7.24 (t, 1H, $J=8.1$ Hz), 7.14 (s, 2H), 7.12 (s, 2H), 1.83 (s, 6H), 1.80 (s, 6H). 0.14 (s, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.8, 143.5, 136.2, 132.7, 132.2, 131.6, 131.2, 125.0, 124.6, 123.1, 121.9, 121.5, 116.0, 111.0, 100.2, 96.3, 93.0, 82.0, 17.6, 17.2, −0.7. MS: *m/z* 1050 [M^+]. Anal. Calcd for $C_{50}H_{38}F_{12}S_4Si_2$: C, 57.13; H, 3.64. Found: C, 56.82; H, 3.52.

3.1.3. Compound 4. Compound **3** (1.0 g, 0.95 mmol) and KOH (0.01 g) were dissolved in THF (20 ml) and MeOH (20 ml) and then added H_2O (10 ml). The solution was stirred for 12 h and evacuated to dryness. The pure product **4** was obtained by chromatography on a silica gel column (1:10 methylene chloride/hexane, $R_f=0.2$) to afford **4** (0.73 g) in 81% yield. Mp: 151 °C. ^1H NMR ($CDCl_3$): δ 7.65 (s, 1H), 7.46 (d, 2H, $J=8.4$ Hz), 7.34 (t, 1H, $J=8.1$ Hz), 7.26 (s, 2H), 7.24 (s, 2H), 3.36 (s, 2H), 1.92 (s, 12H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.7, 143.8, 136.2, 133.2, 132.3, 132.0, 130.8, 124.9, 123.0, 121.6, 120.8, 119.1, 116.0, 111.2, 100.4, 95.4, 93.1, 82.3, 16.2. MS: *m/z* 906 [M^+]. Anal. Calcd for $C_{44}H_{22}F_{12}S_4$: C, 58.27; H, 2.45. Found: C, 58.01; H, 2.32.

3.1.4. Compound 5. A mixture of **2** (0.28 g, 0.28 mmol), **4** (0.25 g, 0.28 mmol), $Pd(PPh_3)_4$ (0.003 g), and CuI (0.0005 g) was vacuum-dried and added NEt_3 (60 ml). The solution was refluxed for 12 h and then evacuated to dryness. The product **5** was separated by chromatography on a silica gel column (1:2 methylene chloride/hexane) to afford **5** in 9% yield. ^1H NMR ($CDCl_3$): δ 7.65 (s, 2H), 7.45 (d, 4H, $J=7.3$ Hz), 7.34 (t, 2H, $J=7.3$ Hz), 7.19 (s, 2H), 7.17 (s, 2H), 7.12 (s, 2H), 7.09 (s, 2H), 2.07 (s, 6H), 2.06 (s, 6H), 1.96 (s, 6H), 1.95 (s, 6H). $^{13}C\{^1H\}$NMR ($CDCl_3$): δ 148.0, 146.9, 144.3, 143.8, 136.4, 134.2, 133.3, 131.6, 129.2, 125.0, 123.0, 121.7, 121.1, 116.5, 111.5, 93.1, 86.0, 82.3, 15.6, 14.5. MS: *m/z* 1760 [M^+]. Anal. Calcd for $C_{84}H_{40}F_{24}S_8$: C, 57.27; H, 2.29. Found: C, 57.01; H, 2.20.

3.1.5. Compound 6. A mixture of **4** (0.45 g, 0.50 mmol), *trans*-$Pt(PEt_3)_2Cl_2$ in Et_2NH (50 ml) was added CuCl (0.001 g). The solution was stirred for 12 h and then evacuated to dryness. The product **6** was purified with chromatography on a silica gel column (1:3 methylene chloride/hexane) to give **6** in 27% yield. ^1H NMR ($CDCl_3$): δ 7.65 (s, 2H), 7.46 (d, 4H, $J=7.2$ Hz), 7.34 (t, 2H, $J=7.2$ Hz), 7.16 (s, 2H), 7.14 (s, 2H), 7.05 (s, 2H), 6.76 (s. 2H), 2.22–2.05 (m, 24H), 1.96 (s, 6H), 1.95 (s, 6H), 1.85 (s, 12H), 1.19 (t, 36H, $J=8.4$ Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.9, 143.9, 139.3, 131.5, 129.4, 127.8, 125.4, 124.1, 123.1, 121.1, 116.1, 115.0, 111.4, 108.2, 100.7, 92.8, 92.1, 82.5, 24.6, 16.5, 15.1, 9.7, 8.7, 4.8. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 5.84 (s, $J=2348$ Hz). MS: *m/z* 2673 [M^+]. Anal. Calcd for $C_{112}H_{100}F_{24}P_4S_8Pt_2$: C, 50.33; H, 3.77. Found: C, 50.18; H, 3.69.

3.1.6. Closed-ring isomer of 3 (CO). ^1H NMR ($CDCl_3$): δ 7.64 (s, 1H), 7.46 (d, 2H, $J=9.0$ Hz), 7.36 (t, 1H, $J=9.0$ Hz), 7.24 (s, 1H), 7.22 (s, 1H), 6.47 (s, 1H), 6.41 (s, 1H), 2.16 (s, 6H), 1.93 (s, 3H), 1.88 (s, 3H). 0.24 (s, 18H).

3.1.7. Closed-ring isomer of 5 (COOO). ^1H NMR ($CDCl_3$): δ 7.65 (s, 2H), 7.45 (d, 4H, $J=7.2$ Hz), 7.34 (t, 2H, $J=7.2$ Hz), 7.17 (s, 2H), 7.13 (s, 2H), 7.09 (s, 2H), 6.48 (s, 2H), 2.18 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.96 (s, 3H), 1.94 (s, 6H), 1.92 (s, 3H).

3.1.8. Closed-ring isomer of 5 (COCO). ^1H NMR ($CDCl_3$): δ 7.65 (s, 2H), 7.45 (d, 4H, $J=7.2$ Hz), 7.36 (t, 2H, $J=7.2$ Hz), 7.13 (s, 2H), 7.09 (s, 2H), 6.72 (s, 2H), 6.52 (s, 2H), 2.17 (s, 12H), 2.07 (s, 3H), 2.05 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H).

3.1.9. Closed-ring isomer of 6 (COCO). ^1H NMR ($CDCl_3$): δ 7.65 (s, 2H), 7.46 (d, 4H, $J=7.2$ Hz), 7.32 (t, 2H, $J=7.2$ Hz), 7.17 (s, 2H), 7.08 (s, 2H), 6.76 (s, 2H), 6.54 (s, 2H), 2.14 (s, 12H), 1.96 (s, 3H), 1.95 (s, 3H), 1.85 (s, 6H).

Acknowledgements

This work was supported by the KOSEF through National Research Laboratory (NRL 2005) program awarded to J.K.

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Synthesis of the insect antifeedant CDE molecular fragment of 12-ketoepoxyazadiradione and related compounds

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Received 22 July 2005; revised 22 September 2005; accepted 22 September 2005

Available online 25 October 2005

Abstract—A diastereoselective synthesis of the model insect antifeedant **29** a CDE molecular fragment of 12-ketoepoxyazadiradione has been achieved in ten steps from indenone **9** in 44% overall yield. Several of the compounds obtained along the synthesis related to model compound **29** show significant antifeedant activity against *Spodoptera littoralis* and *Spodoptera frugiperda*.

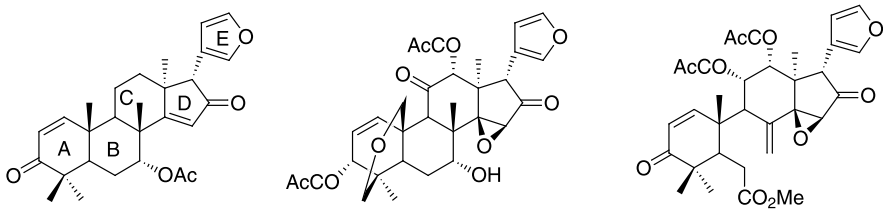
1. Introduction

In a previous paper we described the synthesis of model insect antifeedants related to azadiradione with the aim of finding simple analogues with similar biological activity that of the archetype.[1] Recently, we have developed a new procedure based on construction of the pentagonal D ring of limonoids by the cationic electrocyclization of dienones; the method can be adapted by tuning the vicinal function to the synthesis of the CDE structural fragments of limonoids with an oxygenated function at the C-11/C-12 position.[2] Certain limonoids with this functionality are among the most active of this family of naturally occurring compounds[3] (Fig. 1). The oxygenated functions confer these compounds better water solubility and lower volatility. We have also replaced the furan ring by a phenyl ring in order to avoid the extreme chemical sensitivity of the former. All these changes are directed to SAR studies.[4]

The present work details the synthesis of **29** and related compounds, and reports their antifeedant activity against *Spodoptera littoralis* and *Spodoptera frugiperda*. The synthetic approach to the diketone **29** involves 10 steps from the unsaturated ketone **9** (overall yield 44%), and allows the preparation of reasonable medium-scale quantities. The strategy for the preparation of **29** is outlined in Scheme 1.

2. Results and discussion

Synthesis of the indane model **29** was achieved through two parallel routes, starting from dienone **1** and enone enol



Azadiradione Sendanin Toonacilin

Figure 1.

Keywords: Limonoids; Antifeedant; Azadiradione; Diastereoselective synthesis.
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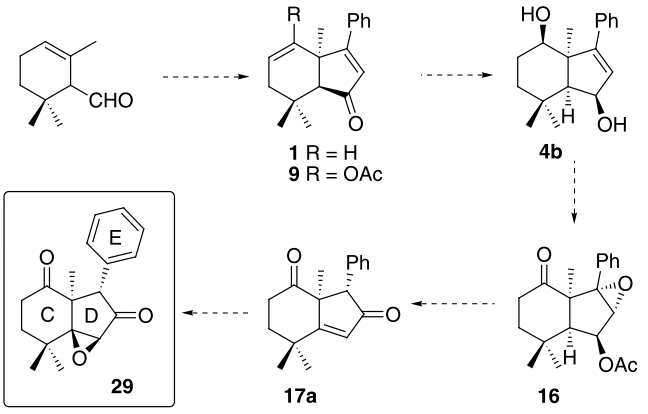
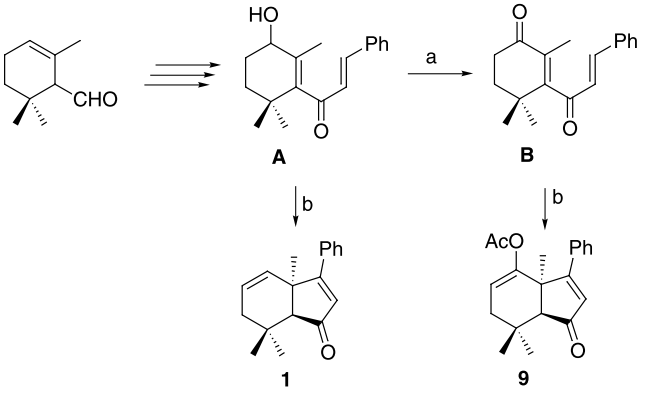
doi:10.1016/j.tet.2005.09.109



Scheme 1.

acetate **9**. Both starting materials are readily available from α-cyclocitral through hydroxy dienone **A** and diendione **B**, respectively, by the Nazarov reaction in good yield. (Scheme 2).[2e]



Scheme 2. Reaction conditions: (a) PCC, CH_2Cl_2; (b) 10^{-1} M $HClO_4$–1 M Ac_2O.

The first approach to **29** started with the epoxidation of dienone **1**, which is expected to be chemoselective on the isolated double bond. The major epoxide **2** (68%) resulted from *exo* attack on the unconjugated double bond of **1**. Unfortunately, this product was a poor intermediate since cleavage of its oxirane ring with LAH was very difficult. A complicated mixture resulted with only a trace amount of the diol **4a** (Scheme 3).

Additionally treatment of the minor epoxyketone **3** with LAH smoothly afforded diol **4b**, in good yield.[5] Cleavage of the oxirane ring in both epoxides, **2** and **3**, could be explained through the conformers **2A**, **2B** and **3A**. A *trans*-diaxial ring-opening with LAH of **2A** seemed very difficult as it is an *endo* neopentylic position that would be attacked. The conformer **2B** was also troublesome. In contrast, the oxirane opening through **3A** was, as expected from the Fig. 2, very easy. The parallel reduction of the carbonyl group of ketones **2** and **3** is exo selective in both compound.

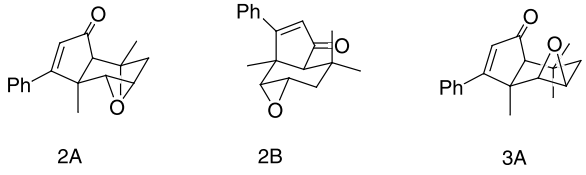
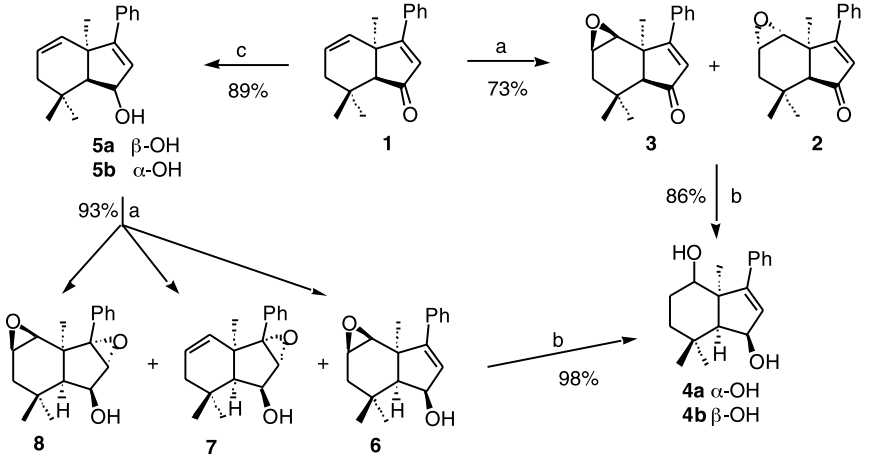


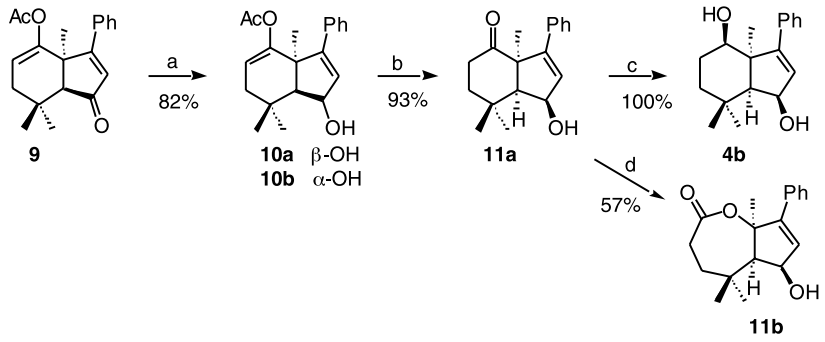
Figure 2.

By changing the order of events in the sequence from dienone **1** we obtained better results, and diol **4b**, a key intermediate in our limonoid model synthesis, was achieved in three steps. First, reduction of **1** with $NaBH_4/CeCl_3$[6] afforded alcohol **5a** as the major product (82%) through *exo* attack of hydride. Subsequent treatment of **5a** with *m*CPBA gave the required epoxide **6** in 76% yield together with two other products: diepoxide **8** (14%) and unsaturated epoxyalcohol **7** (3%). It is interesting to note the chemo- and stereoselectivity observed in the epoxidation reaction of **5a** to **6**, which is clearly driven by the *endo* hydroxyl group. After reduction of the *endo* epoxy alcohol **6** with LAH, diol **4b** was obtained quantitatively.

The second route to the diol **4b** started from ketoester **9**[2e] and comprises three steps. First, *exo*-stereoselective reduction with tandem $NaBH_4/CeCl_3$ to **10**, then, saponification with KOH to **11a** and third, *exo*-reduction with LAH in ether to **4b**[7]. The overall yield of the sequence was 70% (Scheme 4).



Scheme 3. Reaction conditions: (a) *m*-CPBA, CH_2Cl_2; (b) $LiAlH_4$, THF, reflux; (c) $NaBH_4$–$CeCl_3 \cdot 7H_2O$, MeOH.



Scheme 4. Reaction conditions: (a) $NaBH_4$–$CeCl_3 \cdot 7H_2O$; (b) KOH–$_2$O, MeOH; (c) $LiAlH_4$, ether, 0 °C; (d) *m*-CPBA, CH_2Cl_2.

From the unsaturated diol **4b** there are two routes to **17a**, both passing through the epoxydiol **12**, which was obtained quantitatively by *exo* reaction of **4b** with *m*-CPBA. The apparently short route to epoxy diketone **17a** was problematic. The first step involved the rearrangement of epoxydiol **12**, carried out with pTsOH in toluene at reflux,[2a–d] and afforded besides the expected hydroxy enone **13** (31%),[5] a CDE molecular fragment of 12-hydroxyazadiradione, the oxyketone **14** (45%). It was observed that the product ratio was time dependent, such that the proportion of the hydroxyenone **13** increased at the expense of the oxyketone **14**. Treatment of the isolated oxyketone **14** with pTsOH at reflux in toluene for 7 h afforded only the hydroxy enone **13**, although in low yield (31%) (Scheme 5).

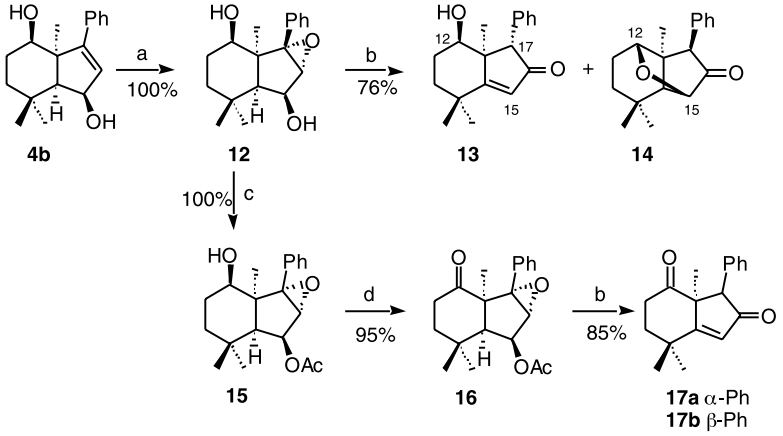
In order to increase the overall yield, we converted the 12-hydroxy group of epoxydiol **12** into a ketone group in order to prevent the formation of the ether bond between the C-12 and C-15. The best way to accomplish this transformation was found to be selective protection of the C-15 hydroxyl group as an acetate. Thus epoxy ester **16** was obtained in almost quantitative yield, by acetylation of the C-15 hydroxyl group of **12**, followed by Dess–Martin oxidation of the C-12 hydroxyl group of **15**.

Rearrangement of epoxide **16** was carried out as usual[2a–d] to afforded the expected diketone **17a** in 73% yield,[5] together with the C-17 epimer **17b** in 12% yield.

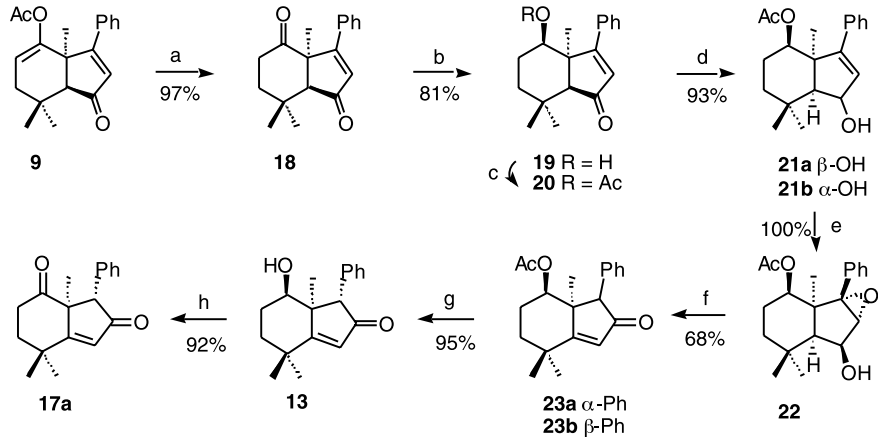
An alternative route to diketone **17a** started from ketoacetate **9**,[2e] using a synthetic sequence of eight steps (Scheme 6). Acid hydrolysis of **9** afforded diketone **18** that, by reduction with $NaBH_4$, molar ratio 1/6, at 5 °C to **19**, followed by slow acetylation catalyzed by DMPA, afforded ketoester **20**. Stereoselective *exo* reduction of **20** was carried out with $NaBH_4/CeCl_3 \cdot 7H_2O$[6] to give alcohol **21a**[5] (85%). Epoxidation of **21a** with *m*CPBA was also completely *exo* stereoselective to afford epoxide **22**, which after treatment with pTsOH provided the enone **23a**[5] as the main product (63%). Two other products were obtained: the α-17 epimer **23b** (5%), and the position isomer **20** (19%). Finally, hydrolysis of ester **23a**, followed by oxidation afforded dienone **17a** in 37% overall yield.

The last step expected in the synthesis of epoxydione **29**, was problematic. Attempts to epoxidize the unsaturated diketone **17a** with hydrogen peroxide in alkaline medium gave as the main product the ketoester **24**, after treatment of the crude product with diazomethane. Treatment of **17a** with sodium hydroxide alone in methanol, followed by acidification and addition of diazomethane, gave only **24** in 90% yield. This is a very interesting retro-Claisen reaction[8] that could possibly be applied to the synthesis of C-*seco* limonoids, and deserves further study. A feasible explanation for the C ring cleavage is given in Scheme 7. The structure of **24** was determined by spectroscopic data and H–C correlations.[5]

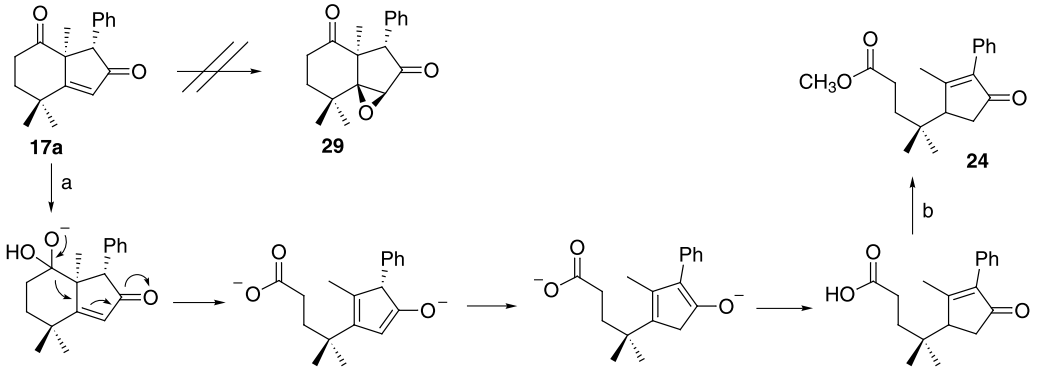
After we failed to achieve the direct epoxidation of **17a**, we followed a longer way, which necessarily passed through the reduction of the enone to the corresponding allylic



Scheme 5. Reaction conditions: (a) *m*-CPBA, CH_2Cl_2; (b) *p*-TsOH, toluene, reflux; (c) Ac_2O, pyr, DMAP; (d) Dess–Martin, CH_2Cl_2.



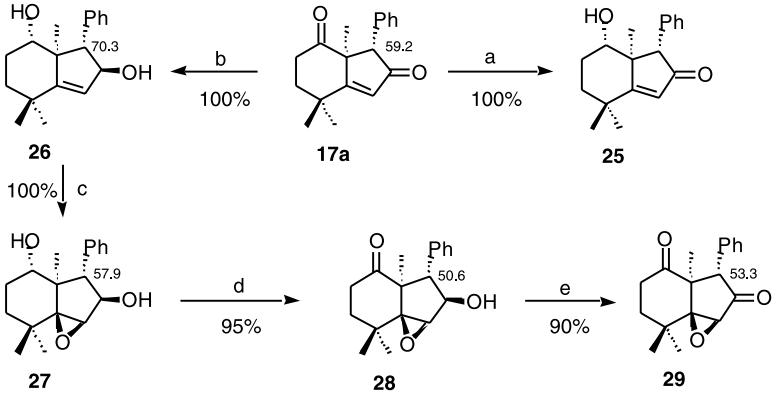
Scheme 6. Reaction conditions: (a) 6 M HCl, MeOH; (b) $NaBH_4$, MeOH; (c) Ac_2O, pyr, DMAP; (d) $NaBH_4$–$CeCl_3 \cdot 7H_2O$, MeOH; (e) *m*-CPBA, CH_2Cl_2; (f) *p*-TsOH·H_2O, toluene; (g) KOH–$_2$O, MeOH; (h) Dess–Martin, CH_2Cl_2.



Scheme 7. Reaction conditions: (a) (i) 6 M NaOH, MeOH; (ii) 2 M HCl; (b) CH_2N_2, ether.

alcohol. Despite this, the roundabout route allowed us to collect interesting new products for SAR insect antifeedant studies. Reduction of diketone **17a** with LAH in ether at 0 °C gave hydroxy ketone **25** quantitatively.[9] When, the reduction was carried out at room temperature, diol **26** was obtained as the only product in quantitative amounts. The hydroxy enone **25** is the C-12 epimer of the above compound **13**; both are CDE molecular fragments of 12-hydroxy azadiradione. The orientation of the allylic hydroxyl group of **26** has been assigned based on our long experience with similar compounds (Scheme 8).[1]

Through the *syn* effect, the allylic C-15 hydroxyl group directs stereospecific epoxidation with mCPBA to afford epoxydiol **27** in 100% yield.[1] By Dess–Martin oxidation of diol **27**, ketone **28** was obtained in excellent yield in a short time period (30 min). When the oxidation was prolonged to 24 h, diketone **29** was obtained in 90% yield. This final



Scheme 8. Reaction conditions: (a) $LiAlH_4$, ether, 0 °C; (b) $LiAlH_4$, ether, rt; (c) *m*-CPBA, CH_2Cl_2; (d) Dess–Martin, CH_2Cl_2; 30 min; (e) Dess–Martin, CH_2Cl_2, 24 h.

compound obtained is our target compound, a CDE molecular fragment of 12-oxo-14,15-epoxy azadiradione.

3. Biological results

Larvae of the African leafworms *S. littoralis* and *S. frugiperda* were used to assess the antifeedant activity of our molecular fragments.[10] In the series related to azadiradione, the racemic 12-oxygenated fragments **13**, **17a**, **23a**, **25** and **29** were found to be more active than the C-12 deoxygenated enantiopures archetypes azadiradione and epoxyazadiradione.

The antifeedant activity is influenced by the hydroxyl group orientation in C-12, see **13** and **25**. The acetate **23a** is more active than the corresponding alcohol **13**, against *Spodoptera litoralis*. The 'epoxides', **29** and **27**, are more active than the 'alkenes', **17a** and **26**. All compounds marked with asterisk have a significant antifeedant activity (Table 1).

Table 1. Antifeedant index of the test compounds in choice bioassays

	Antifeedant index at 100 ppm	
	Spodoptera littoralis	*Spodoptera frugiperda*
Azadiradione	1 (11.3)	—
Epoxyazadiradione	22 (19.1)	—
13	8 (2.7)	34 (5.8)*
17a	16 (15.9)	21 (4.7)
23a	28 (4.7)*	23 (5.4)
25	14 (5.9)	4 (8.2)
26	12 (6.9)	21 (4.8)
27	26 (5.9)*	24 (4.9)
28	27 (5.6)*	26 (2.5)*
29	27 (6.4)*	29 (1.6)*

* Antifeedant index $=[(C-T)/(C+T)]\%$ of test compounds in choice biassay with glass fibre discs control (C) versus treatment (T) ($n=20$).

4. Experimental

4.1. General methods

When required, all solvents and reagents were purified by standard techniques. Reactions were monitored by TLC on silica 60 F245. Organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure with the aid of a rotary evaporator. Column chromatographyc was performed on silica gel 60 (0.040–0.063 mm).

4.1.1. Epoxidation of 1 with *m*-CPBA. To a stirred solution of **1** (800 mg, 3.17 mmol) in CH_2Cl_2 (56 mL) was added *m*-CPBA (552 mg, 3.20 mmol). The reaction mixture was stirred under argon at room temperature for 23 h. Then, Na_2SO_3 (5%) was added, and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (10%) and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–AcOEt (90/10) furnished 3,3,6a-trimethyl-6-phenyl-1a,2,3,3a,6,6a,6b-hexahydro-1-oxacyclopropa[*e*]inden-4-one **2** (576 mg, 2.16 mmol, 68%), as a white solid, mp 102–104 °C. IR, ν: 2924, 1686, 766, 700 cm^{-1}. ^1H NMR $CDCl_3$, δ: 0.76 (3H, s), 1.17 (3H, s), 1.66 (3H, s), 1.90 (1H, s), 3.21 (1H, m), 3.46 (1H, d, $J=2$ Hz), 6.21 (1H, s) 7.43–7.59 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 24.3, 28.2, 28.6, 34.1, 39.6, 46.0, 53.1, 53.5, 64.2, 127.8 (2C), 128.6 (2C), 129.6, 130.0, 133.8, 179.2, 208.5 ppm. MS EI, *m/z* (relative intensity): 268 (M^+, 3), 250 (6), 235 (15), 172 (100), 115 (39), 91 (35), 77 (45), 55 (41). Anal. Calcd For $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.61; H, 7.57.

Eluting with hexane–AcOEt (85/15) furnished 3,3,6a-trimethyl-6-phenyl-1a,2,3,3a,6,6a,6b-hexahydro-1-oxacyclopropa[*e*]inden-4-one **3** (72 mg, 0.027 mmol, 9%), as a white solid, mp 128–130 °C. IR, ν: 2924, 1686, 766 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.09 (3H, s), 1.17 (3H, s), 1.37 (3H, s), 1.86 (1H, s), 3.23 (1H, d, $J=4$ Hz), 3.45 (1H, m), 6.14 (1H, s) 7.41–7.60 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 26.0, 28.0, 31.8, 33.5, 36.6, 46.6, 54.6, 54.9, 61.9, 127.8 (2C), 128.6 (2C), 129.5, 130.7, 134.6, 179.4, 208.5 ppm. MS EI, *m/z* (relative intensity): 250 (M^+-18, 4), 235 (8), 172 (100), 107 (33), 91 (27), 77 (27), 55 (23). Anal. Calcd For $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.79; H, 7.63.

4.1.2. 3a,7,7-Trimethyl-3-phenyl-3a,4,5,6,7,7a-hexhydro-1*H*-1,4-diol 4b. $LiAlH_4$ (14 mg, 0.38 mmol) was added to a solution of the epoxy ketone **3** (72 mg, 0.27 mmol) in THF (10 ml). The reaction mixture was vigorously stirred at reflux under argon for 3 h, after which it was quenched with $Na_2SO_4\cdot 10H_2O$. The resulting mixture was filtered, and then the filtrate was evaporated under reduced pressure to afford a crude residue, which was purified by flash chromatography. Eluting with pentane–Et_2O (85/15) furnished diol **4b** (62 mg, 0.23 mmol, 86%) as a white solid, mp 122–124 °C. IR $CHCl_3$, ν: 3297, 2928, 764 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.08 (3H, s), 1.15 (3H, s), 1.26 (3H, s), 1.58 (1H, d, $J=5.5$ Hz), 3.98 (1H, 11 m), 4.49 (1H, m), 6.07 (1H, d, $J=3$ Hz), 7.25–7.30 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 24.5, 26.2, 28.4, 29.8, 31.2, 32.1, 52.0, 58.1, 69.6, 75.1, 127.3 (2C), 128.2 (3C), 132.2, 137.2, 153.6 ppm. MS EI, *m/z* (relative intensity): 254 (M^+-18, 33), 239 (3), 236 (3), 197 (50), 156 (26), 115 (25), 91 (28), 81 (100), 55 (47). Anal. Calcd For $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.57; H, 8.92.

4.1.3. Reduction of 1 with $NaBH_4/CeCl_3$. To a solution of the ketone **1** (160 mg, 0.63 mmol) in MeOH (16 mL) at 0 °C, was added $CeCl_3\cdot 7H_2O$ (0.25 g, 0.69 mmol) and $NaBH_4$ (0.12 g, 3.15 mmol). The reaction mixture was stirred at 0 °C under argon for 3 h and after adding acetone, concentrated. The residue was treated with brine and Et_2O, stirring 30 min. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–ethyl acetate (90/10) furnished 3a,7,7-trimethyl-3-phenyl-3a,6,7,7a-tetrahydro-1*H*-inden-1-ol **5a** (132 g, 0.51 mmol, 82%) as a pale yellow oil. IR $CHCl_3$, ν: 3430, 2955, 764, 698 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.14 (3H, s), 1.20 (3H, s), 1.30 (3H, s), 4.70 (1H, m), 5.63 (1H, m), 5.68 (1H, d, $J=3$ Hz), 5.99 (1H, m), 7.32–7.35 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 26.2, 28.4, 32.1,

32.3, 37.5, 49.5, 58.8, 77.3, 124.7, 127.4, 128.0 (2C), 128.3 (2C), 128.6, 131.9, 137.2, 156.2 ppm. MS EI, *m/z* (relative intensity): 254 (M^+, 5), 236 (73), 221 (100), 193 (44), 165 (45), 129 (54), 115 (48), 91 (64), 77 (60). HRMS (EI): 245.1669 (M^+, $C_{18}H_{22}O$), calcd 254.1671.

Eluting with hexane–ethyl acetate (80/20) furnished α-alcohol **5b** (11 mg, 0.04 mmol, 7%), as a white solid, mp 64–66 °C. IR $CHCl_3$, *ν*: 3381, 2959, 758, 700 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.12 (6H, s), 1.30 (3H, s), 1.80 (1H, d, $J=5.7$ Hz), 4.75 (1H, dd, $J_1=2$ Hz, $J_2=5.7$ Hz), 5.58 (1H, m), 5.62 (1H, d, $J=2$ Hz), 5.75 (1H, m), 7.26–7.32 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 27.9, 28.3, 29.0, 31.5, 35.8, 50.8, 65.0, 76.9, 123.2, 127.0, 127.6 (2C), 128.0 (2C), 129.0, 132.3, 136.6, 153.5 ppm. MS EI, *m/z* (relative intensity): 254 (M^+, 13), 239 (15), 236 (29), 221 (51), 165 (30), 143 (30), 131 (100), 91 (52), 77 (36). Anal. Calcd For $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.59; H, 8.67.

4.1.4. Epoxidation of 5a with *m*-CPBA. To a stirred solution of **5a** (73 mg, 0.29 mmol) in CH_2Cl_2 (4 mL) was added *m*-CPBA (69 mg, 0.40 mmol). The reaction mixture was stirred under argon at room temperature for 1 h. Then, Na_2SO_3 (5%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (10%) and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography.

Eluting with hexane–AcOEt (95/5) furnished 3,3,6a-trimethyl-6-phenyl-1a,3,3a,4,6a,6b-hexahydro-2*H*-1-oxa-cyclopropa[*e*]inden-4-ol **6** (59 mg, 0.22 mmol, 76%), as a yellow oil. IR, *ν*: 3412, 2924, 752 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.08 (3H, s), 1.20 (3H, s), 1.27 (3H, s), 3.21 (1H, d, $J=4$ Hz), 3.51 (1H, m), 4.43 (1H, m), 5.99 (1H, d, $J=3$ Hz), 7.30–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 23.8, 28.1, 30.9, 33.5, 34.5, 47.7, 56.0, 56.8, 57.4, 75.3, 127.3, 128.0 (2C), 128.1 (2C), 132.3, 137.1, 152.4 ppm. HRMS (EI): 270.1651 (M^+, $C_{18}H_{22}O_2$), calcd 270.1620.

The second fraction (12 mg, 0.04 mmol, 14%) which as a white solid, was identified as diepoxide **8**, mp 102–104 °C. ^1H NMR $CDCl_3$, *δ*: 1.00 (3H, s), 1.17 (3H, s), 1.30 (3H, s), 2.76 (1H, d, $J=4$ Hz), 3.44 (1H, m), 3.88 (1H, d, $J=12$ Hz), 4.20 (1H, dd, $J_1=5$ Hz, $J_2=12$ Hz), 7.35–7.60 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 19.6, 29.3, 30.0, 33.5, 34.2, 43.4, 53.6, 55.3, 56.7, 65.4, 72.4, 72.9, 128.0 (2C), 128.1, 128.8 (2C), 134.2 ppm. Anal. Calcd For $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.77; H, 7.61.

Eluting with hexane–AcOEt (90/10) furnished 1b,5,5-trimethyl-1a-phenyl-1a,1b,5,5a,6,6a-hexahydro-4*H*-1-oxa-cyclopropa[*a*]inden-6-ol **7** (2 mg, 0.007 mmol, 3%), as a yellow oil. IR, *ν*: 3459, 2924, 785 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.07 (3H, s), 1.25 (6H, s), 3.46 (1H, br s), 4.45 (1H, m), 5.40 (1H, m), 5.80 (1H, m), 7.36 (5H, s) ppm. HRMS (EI): 270.1633 (M^+, $C_{18}H_{22}O_2$), calcd 270.1620.

4.1.5. Reduction of 6 with $LiAlH_4$. $LiAlH_4$ (8.3 mg, 0.22 mmol) was added to a solution of the epoxy alcohol **4b** (43 mg, 0.16 mmol) in THF (6 ml). The reaction mixture was vigorously stirred at reflux under argon for 2.5 h, after which it was quenched with $Na_2SO_4\cdot 10H_2O$. The resulting mixture was filtered, and then the filtrate was evaporated under reduced pressure to afford unsaturated diol **4b** (42 mg, 0.15 mmol, 98%).

4.1.6. 1-Hydroxy-3a,7,7-trimethyl-3-phenyl-3a,6,7,7a-tetrahydro-1*H*-inden-4-yl acetate 10. To a solution of **9** (1.70 g, 5.49 mmol) in MeOH (137 mL) at 0 °C, was added $CeCl_3\cdot 7H_2O$ (2.25 g, 6.04 mmol) and $NaBH_4$ (1.04 g, 27.5 mmol). The reaction mixture was stirred at 0 °C under argon for 2 h and after adding acetone, concentrated. The residue was treated with brine and Et_2O, stirring 30 min. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (75/25) furnished **10a** (1.30 g, 4.17 mmol, 76%) as a white solid, mp 88–90 °C. IR $CHCl_3$, *ν*: 3393, 2924, 1746, 762, 702 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.25 (3H, s), 1.32 (3H, s), 1.53 (3H, s), 1.55 (3H, s), 4.64 (1H, m), 5.19 (1H, dd, $J_1=3$ Hz, $J_2=5.5$ Hz), 5.95 (1H, d, $J=3$ Hz), 7.28–7.34 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 20.2, 24.1, 27.9, 32.1, 32.6, 37.5, 51.5, 61.4, 76.4, 114.4, 127.2, 127.7 (2C), 128.4 (2C), 132.1, 137.9, 149.5, 153.9, 169.5 ppm. Anal. Calcd For $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.92; H, 7.65.

Eluting with hexane–Et_2O (70/30) furnished **10b** (103 mg, 0.33 mmol, 6%), as a colourless oil. IR, *ν*: 3451, 2920, 1744, 764 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.19 (3H, s), 1.43 (3H, s), 1.52 (6H, s), 4.80 (1H, m), 5.25 (1H, m), 5.66 (1H, d, $J=2.0$ Hz), 7.20–7.30 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 20.3, 25.1, 28.9, 29.4, 32.1, 35.6, 53.5, 67.4, 76.4, 112.4, 127.0, 127.2 (2C), 127.5 (2C), 132.6, 138.2, 150.4, 151.7, 168.8 ppm. HRMS (EI): 312.1759 (M^+, $C_{20}H_{24}O_3$), calcd 312.1725.

4.1.7. 1-Hydroxy-3a,7,7-trimethyl-3-phenyl-1,3a,5,6,7,7a-hexa-hydro-inden-4-one 11a. To a stirred solution of **10a** (1.18 g, 3.78 mmol) in EtOH (9.8 mL) were added 5 M KOH (1.7 mL). The reaction mixture was stirred at room temperature under argon for 15 min and then concentrated to afford a residue, which was dissolved in H_2O and extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded a white solid identified as **11a** (950 mg, 3.52 mmol, 93%), mp 88–90 °C. IR $CHCl_3$, *ν*: 3385, 2961, 1692, 764 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.28 (3H, s), 1.35 (3H, s), 1.44 (3H, s), 1.98 (1H, dd, $J_1=2$ Hz, $J_2=5.0$ Hz), 4.65 (1H, t, $J=3.5$ Hz), 6.19 (1H, d, $J=3.5$ Hz), 7.24–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 22.9, 27.8, 31.2, 33.0, 36.1, 39.8, 61.1, 66.5, 75.6, 127.6, 128.0 (2C), 128.7 (2C), 130.3, 136.0, 155.0, 218.0 ppm. MS EI, *m/z* (relative intensity): 270 (M^+, 26), 255 (4), 197 (98), 156 (100), 115 (30), 97 (50), 69 (62), 55 (41). Anal. Calcd For $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.15; H, 8.27.

4.1.8. 6-Hydroxy-5,5,8a-trimethyl-8-phenyl-3,4,5,5a,6,8a-hexahydro-cyclopenta-[*b*]oxepin-2-one 11b. To a stirred solution of **11a** (18 mg, 67 μmol) in CH_2Cl_2 (0.5 mL) was added *m*-CPBA (13 mg, 74 μmol). The reaction mixture was stirred under argon at room temperature for 90 min.

Then, Na_2SO_3 (5%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (10%) and brine. Removal of the solvent afforded a white solid identified as **11b** (11 mg, 38 μmol, 57%), mp 116–118 °C. IR $CHCl_3$,*ν*: 3466, 2959, 1726, 756, 700 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.30–2.40 (4H, m), 2.50–3.00 (2H, m), 1.31 (3H, s), 1.33 (3H, s), 1.63 (3H, s), 4.95 (1H, m), 6.23 (1H, d, $J=3.0$ Hz), 7.30–7.60 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 28.7, 30.9, 31.7, 32.7, 34.5, 35.8, 60.9, 75.8, 91.9, 128.1 (2C), 128.3 (2C), 128.9, 132.1, 134.0, 150.4, 174.7 ppm. Anal. Calcd For $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.89; H, 7.57.

4.1.9. 3a,7,7-Trimethyl-3-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1,4-diol 4b. $LiAlH_4$ (63 mg, 1.65 mmol) was added to a solution of the ketone **11a** (888 mg, 3.29 mmol) in dry ethyl ether (39 mL) cooled to 0 °C. The reaction mixture was vigorously stirred under argon for 30 min, after which it was quenched with $Na_2SO_4\cdot 10H_2O$. The resulting mixture was filtered, and then the filtrate was evaporated under reduced pressure to afford a white solid identified as diol **4b** (894 mg, 3.29 mmol, 100%).

4.1.10. 1b,5,5-Trimethyl-1a-phenyl-octahydro-1-oxa-cyclopropa[*a*]indene-2,6-diol 12. To a stirred solution of **4b** (814 mg, 2.99 mmol) in CH_2Cl_2 (19 mL) was added *m*-CPBA (567 mg, 3.29 mmol). The reaction mixture was stirred under argon at room temperature for 3 h and 30 min. Then, Na_2SO_3 (5%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (10%) and brine. Removal of the solvent afforded **12** (860 mg, 2.99 mmol, 100%), as a white solid, mp 172–174 °C. IR nujol, *ν*: 3295, 2924, 664 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.05 (3H, s), 1.23 (3H, s), 1.25 (3H, s), 1.58 (1H, d, $J=5.2$ Hz), 3.50 (2H, m), 4.23 (1H, m), 7.29–7.67 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 20.7, 26.3, 29.5, 30.0, 31.1, 31.6, 46.9, 52.2, 64.0, 69.5, 72.2, 72.6, 127.7 (2C), 127.9, 129.6 (2C), 134.7 ppm. Anal. Calcd For $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.62; H, 8.32.

4.1.11. Reaction of 12 with *p*-toluenesulphonic acid. A solution of **12** (150 mg, 0.52 mmol) in toluene (7.8 mL) was added to p-TsOH$\cdot H_2O$ (10 mg, 52 μmol). The reaction mixture was stirred under argon at reflux for 10 min. Then, the mixture was cooled to room temperature and then an aqueous solution of 5% $NaHCO_3$ was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (80/20) furnished oxyketone **14** (63 mg, 0.23 mmol, 45%), as a solid which decomposed at 200 °C. IR nujol, *ν*: 2926, 1755, 752, 702 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.09 (3H, s), 1.15 (3H, s), 1.29 (3H, s), 1.62 (1H, s), 3.17 (1H, s), 3.87 (1H, d, $J=5.0$ Hz), 4.26 (1H, s), 7.10–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 15.9, 24.2, 29.2, 32.0, 32.4, 33.2, 49.6, 57.2, 64.2, 75.1, 82.0, 127.4, 128.5 (2C), 130.5 (2C), 133.6, 205.0 ppm. MS EI, *m/z* (relative intensity): 270 (M^+, 33), 252 (37), 237 (40), 213 (79), 209 (59), 115 (64), 91 (100), 77 (58), 55 (70).

Eluting with hexane–Et_2O (50/50) furnished 4-hydroxy-3a,7,7-trimethyl-3-phenyl-3,3a,4,5,6,7-hexahydro-inden-2-one **13** (44 mg, 0.16 mmol, 31%), as a colourless solid (CH_2Cl_2/pentane), mp 144–146 °C. IR nujol, *ν*: 3287, 2928, 1682, 760, 698 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 0.89 (3H, s), 1.28 (6H, s), 3.79 (1H, m), 4.57 (1H, s), 6.06 (1H, s), 7.13–7.32 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 25.0, 26.0, 28.1, 30.9, 33.0, 35.5, 53.2, 58.9, 70.7, 126.8, 127.3, 128.2 (2C), 130.4 (2C), 136.4, 189.1, 207.8 ppm. SM EI, *m/z* (relative intensity): 270 (M^+, 51), 252 (43), 237 (30), 213 (62), 207 (22), 115 (67), 91 (100), 73 (86), 55 (97). Anal. Calcd For $C_{18}H_{22}O_2$: C, 79.94; H, 8.20. Found: C, 79.99; H, 8.27.

4.1.12. 2-Hydroxy-1b,5,5-trimethyl-1a-phenyl-octahydro-1-oxa-cyclopropa[*a*]inden-6-yl acetate 15. To a solution of **12** (500 mg, 1.74 mmol) in pyridine (0.98 mL, 12 mmol) was added Ac_2O (0.98 mL, 10 mmol) and DMAP (21 mg, 0.17 mmol). The reaction mixture was stirred at room temperature under argon for 1 h and then diluted with Et_2O and poured into ice-water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed $NaHCO_3$ (5%) and brine. Removal of the solvent afforded **15** (573 mg, 1.74 mmol, 100%), as a colourless solid, mp (*t*-BuOMe/hexane) 132–134 °C. IR $CHCl_3$, *ν*: 3557, 2938, 1755, 754, 700 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.00 (3H, s), 1.00–1.90 (5H, m), 1.09 (3H, s), 1.22 (3H, s), 2.22 (3H, s), 3.45 (1H, m), 3.52 (1H, s), 3.70 (1H, m), 5.41 (1H, d, $J=5.5$ Hz), 7.25–7.40 (3H, m), 7.70–7.80 (2H, m) ppm. ^{13}C RMN $CDCl_3$, *δ*: 21.4 (2C), 25.7, 29.5, 30.0, 30.9, 31.5, 48.0, 50.2, 61.8, 69.3, 73.0, 76.3, 127.7 (2C), 128.0, 129.7 (2C), 133.9, 168.7 ppm. MS EI, *m/z* (relative intensity): 315 (M^+-15, 2), 252 (30), 221 (54), 196 (65), 105 (100), 91 (73), 77 (62). Anal. Calcd For $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.83; H, 7.85.

4.1.13. 1b,5,5-Trimethyl-2-oxo-1a-phenyl-octahydro-1-oxa-cyclopropa[*a*]inden-6-yl acetate 16. To a stirred suspension of Dess–Martin (634 mg, 1.50 mmol) in CH_2Cl_2 (6 mL), was added a solution of the alcohol **15** (450 mg, 1.36 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was vigorously stirred at room temperature under argon for 5 h. Then, 1 M $NaHCO_3$ and 0.125 M $Na_2S_2O_3$ was added and the mixture was stirred for 30 min at room temperature. The organic layer was separated, and the aqueous phase was extracted whit ether. The combined organic extracts were washed with brine. Removal of the solvent afforded **16** (423 mg, 1.29 mmol, 95%) as a colourless solid, mp 141–143 °C. IR $CHCl_3$, *ν*: 2926, 1748, 1713, 754, 700 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 1.04 (3H, s), 1.29 (3H, s), 1.61 (3H, s), 1.70 (1H, m), 2.10 (3H, s), 2,10–2.35 (3H, m), 2.65–2.85 (2H, m), 3.65 (1H, s), 5.39 (1H, d, $J=4.1$ Hz), 7.25–7.50 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 20.5, 21.1, 29.1, 31.3, 31.7, 36.0, 38.4, 55.9, 57.0, 61.2, 70.6, 75.5, 127.3 (2C), 128.0, 129.7 (2C), 134.8, 170.0, 212.6 ppm. MS IE, *m/z* (relative intensity): 328 (M^+, 2), 285 (6), 268 (22), 172 (56), 105 (100), 91 (63), 77 (51), 55 (79). Anal. Calcd For $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.72; H, 7.21.

4.1.14. Reaction of 16 with *p*-toluenesulphonic acid. A solution of **16** (350 mg, 1.07 mmol) in toluene (16 mL) was

added to *p*-TsOH·H_2O (21 mg, 0.11 mmol). The reaction mixture was stirred under argon at reflux for 1 h and 20 min. Then, the mixture was cooled to room temperature and then an aqueous solution of 5% $NaHCO_3$ was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–Et_2O (80/20) furnished 3a,7,7-trimethyl-3-phenyl-3,3a,6,7-tetrahydro-5*H*-indene-2,4-dione **17a** (209 mg, 0.78 mmol, 73%), as a colourless solid, mp 122–124 °C. IR $CHCl_3$, δ: 2924, 2870, 1699, 725, 704 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.10 (3H, s), 1.33 (H, s), 1.44 (3H, s), 1.80 (1H, ddd, $J_1=5.0$ Hz, $J_2=7.8$ Hz, $J_3=14$ Hz), 2.15 (1H, ddd, $J_1=5.0$ Hz, $J_2=9.4$ Hz, $J_3=14$ Hz), 2.40 (1H, ddd, $J_1=5.0$ Hz, $J_2=9.4$ Hz, $J_3=17$ Hz), 2.77 (1H, ddd, $J_1=5.0$ Hz, $J_2=7.8$ Hz, $J_3=17$ Hz), 4.27 (1H, s), 6.11 (1H, s), 7.20–7.35 (5H, m) ppm. ^{13}C NMR $CDCl_3$, ν: 24.2, 29.2, 30.0, 35.5 (2C), 36.0, 59.2, 62.0, 127.0, 128.1 (3C), 131.1 (2C), 135.8, 188.1, 206.2, 211.0 ppm. SM EI, *m/z* (relative intensity): 268 (M^+, 13), 253 (5), 169 (52), 115 (86), 91 (79), 77 (84), 55 (100). HRMS (EI): 268.1476 (M^+, $C_{18}H_{20}O_2$), calcd 268.1463. Anal. Calcd For $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.60.

Eluting with hexane–Et_2O (75/25) furnished 3a,7,7-trimethyl-3-phenyl-3,3a,6,7-tetrahdro-5*H*-indene-2,4-dione **17b** (35 mg, 0.13 mmol, 12%), as a colourless oil. IR, ν: 2963, 2870, 1728, 1694, 766, 708 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.46 (3H, s), 1.50 (3H, s), 1.63 (3H, s), 1.78–2.52 (4H, m), 3.55 (1H, s), 6.21 (1H, s), 6.90–7.05 (2H, m), 7.15–7.30 (3H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 30.0, 30.3, 30.9, 34.1, 35.3, 38.4, 61.8, 66.1, 127.4 (3C), 128.3, 128.7 (2C), 137.8, 191.3, 205.5, 209.4 ppm. SM EI, *m/z* (relative intensity): 268 (M^+, 54), 253 (19), 225 (31), 207 (46), 169 (100), 91 (41), 55 (47). HRMS (EI): exp. 268.1449 (M^+, $C_{18}H_{20}O_2$), calcd 268.1463.

4.1.15. 3a,7,7-Trimethyl-3-phenyl-5,6,7,7a-tetrahydro-3a*H*-indeno-1,4-dione 18. To a solution of **9** (2.00 g, 6.45 mmol) in MeOH (110 mL) was added 6 M HCl (4.5 mL). The reaction mixture was stirred under argon at room temperature for 48 h. Removal of the solvent, the residue was treated with brine and Et_2O and water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with 5% Na_2CO_3 and brine. Removal of the solvent afforded a crude product, which was purified by flash chromatography. Eluting with hexane/AcOEt 95:5 furnished **18** (1.67 g, 6.26 mmol, 97%), as a colourless solid, mp 70–72 °C. IR $CHCl_3$, ν: 2932, 2874, 1699, 762, 696 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.09 (3H, s), 1.12 (3H, s), 1.55 (3H, s), 1.70 (1H, m), 1.98 (1H, m), 2.33 (1H, d, $J=1.6$ Hz), 2.28–2.62 (2H, m), 6.56 (1H, s), 7.35–7.60 (5H, m) ppm. ^{13}C NMR $CHCl_3$, δ: 24.9, 26.4, 29.0, 34.3, 34.6, 35.9, 59.7, 68.9, 128.2 (2C); 128.8 (2C), 130.5, 131.2, 133.4, 175.3, 207.0, 213.5 ppm. MS EI, *m/z* (relative intensity): 268 (M^+, 20), 213 (100), 199 (35), 184 (34), 91 (24), 77 (28), 55 (31). Anal. Calcd For $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.41; H, 7.55.

4.1.16. 4-Hydroxy-3a,7,7-trimethyl-3-phenyl-3a,4,5,6,7,7a-hexahydro-inden-1-one 19. To a solution of **18** (1.60 g, 5.97 mmol) in MeOH (300 mL) at 5 °C, was added $NaBH_4$ (1.36 g, 35.8 mmol). The reaction mixture was stirred under argon for 8 h and after adding acetone, concentrated. The residue was treated with brine and Et_2O, stirring 30 min. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–AcOEt (85/15) furnished **19** (1.30 g, 4.83 mmol, 81%) as a white solid, mp 140–142 °C. IR nujol, ν: 3339, 2926, 2857, 1674, 762, 692 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.00–2.10 (5H, m), 1.15 (3H, s), 1.36 (3H, s), 1.40 (3H, s), 2.04 (1H, s), 4.18 (1H, dd, $J_1=3.3$ Hz, $J_2=6.3$ Hz), 6.26 (1H, s), 7.35–7.50 (5H, m) ppm. 13C NMR $CDCl_3$, δ: 25.3, 26.4, 27.6, 31.5, 32.3, 33.1, 52.6, 62.6, 70.9, 127.6 (2C), 128.7 (2C), 129.3, 133.0, 135.4, 175.9, 206.3 ppm. SM EI, *m/z* (relative intensity): 270 (M+, 4), 252 (6), 213 (14), 172 (100), 99 (33), 81 (81), 77 (25), 55 (38). Anal. Calcd For $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.19; H, 8.17.

4.1.17. 3a,7,7-Trimethyl-1-oxo-3-phenyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl acetate 20. To a solution of **19** (1.20 g, 4.44 mmol) in pyridine (2.5 mL, 31.1 mmol) was added Ac_2O (2.5 mL, 26.6 mmol) and DMAP (54 mg, 0.44 mmol). The reaction mixture was stirred at room temperature under argon for 24 h and then diluted with Et_2O and poured into ice-water. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed $NaHCO_3$ (5%) and brine. Removal of the solvent afforded **20** (573 mg, 1.74 mmol, 100%), as a colourless solid, mp (*t*-BuOMe/hexane) 70–71 °C. IR $CHCl_3$, ν: 2947, 1738, 1697, 768, 698 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.20 (3H, s), 1.20–2.10 (4H, m), 1.26 (3H, s), 1.43 (3H, s), 1.75 (3H, s), 2.10 (1H, s), 5.29 (1H, t, $J=4.0$ Hz), 6.22 (1H, s), 7.30–7.45 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 20.8, 24.1, 26.4 (2C); 32.3, 32.7, 33.0, 50.4, 63.1, 73.0, 127.3 (2C), 128.6 (2C), 129.2, 132.0, 135.3, 169.5, 176.0, 206.7 ppm. SM EI, *m/z* (relative intensity): 312 (M^+, 1), 252 (9), 172 (28), 108 (14), 81 (24), 55 (12), 43 (100). Anal. Calcd For $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.73; H, 7.67.

4.1.18. 1-Hydroxy-3a,7,7-trimethyl-3-fenil-3a,4,5,6,7,7a-hexahydro-1*H*-inden-4-yl acetate 21a. To a solution of **20** (1.30 g, 4.16 mmol) in MeOH (208 mL) at 0 °C, was added $CeCl_3 \cdot 7H_2O$ (1.70 g, 4.58 mmol) and $NaBH_4$ (790 g, 20.8 mmol). The reaction mixture was stirred at 0 °C under argon for 3 h and 30 min after adding acetone, concentrated. The residue was treated with brine and Et_2O, stirring 30 min. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–AcOEt (95/5) furnished **21b** (104 mg, 0.33 mmol, 8%), as a colourless oil. IR, ν: 3549, 2934, 2866, 1746, 766, 698 cm^{-1}. ^1H NMR $CDCl_3$, δ: 1.10–2.00 (5H, m), 1.13 (3H, s), 1.23 (3H, s), 1.32 (3H, s), 2.02 (3H, s), 2.75 (1H, d, $J=12$ Hz), 4.52 (1H, ddd, $J_1=2.9$ Hz, $J_2=5.3$ Hz, $J_3=12$ Hz), 5.30 (1H, m), 6.13 (1H, d, $J=2.9$ Hz), 7.10–7.20 (2H, m), 7.25–7.40 (3H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 21.2, 23.5, 25.0, 28.2, 30.6, 31.2, 32.2,

50.1, 58.1, 127.3 (2C), 127.5, 128.4 (2C), 132.0, 136.8, 153.1, 168.7 ppm. SM EI, *m/z* (relative intensity) 314 (M^+, 1), 296 (8), 254 (10), 236 (20), 221 (100), 184 (37), 165 (39), 129 (40), 115 (40), 91 (64), 55 (46).

Eluting with hexane–AcOEt (80/20) furnished **21a** (1.11 g, 3.53 mmol, 85%) as a colourless oil. IR, *ν*: 3395, 2957, 2874, 1730, 1248, 760, 700 cm^{-1}. ^1H RMN $CDCl_3$, *δ*: 1.13 (3H, s), 1.18 (3H, s), 1.25 (3H, s), 1.60–1.90 (5H, m), 1.94 (3H, s), 4.80 (1H, dd, $J_1=1.5$ Hz, $J_2=8.3$ Hz), 5.88 (1H, d, $J=1.5$ Hz), 7.10–7.35 (5H, m) ppm. ^{13}C RMN $CDCl_3$, *δ*: 21.3, 22.4, 24.7, 29.6, 30.2, 31.4, 31.9, 51.5, 65.5, 73.1, 76.9, 127.2, 127.5 (2C), 128.2 (2C), 133.5, 136.7, 149.2, 169.8 ppm. SM EI, *m/z* (relative intensity): 314 (M^+, 2), 296 (6), 254 (24), 221 (98), 184 (100), 131 (72), 81 (88), 77 (51), 55 (71). HRMS (EI): 314.1860 (M^+, $C_{20}H_{26}O_3$), calcd 314.1882.

4.1.19. 6-Hydroxy-1b,5,5-trimethyl-1a-phenyl-octahydro-1-oxa-cyclopropa[*a*]inden-2-yl acetate 22. To a stirred solution of **21a** (1.00 g, 3.18 mmol) in CH_2Cl_2 (20 mL) was added *m*-CPBA (604 mg, 3.50 mmol). The reaction mixture was stirred under argon at room temperature for 3 h and 30 min. Then, Na_2SO_3 (5%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (10%) and brine. Removal of the solvent afforded **22** (1.05 g, 3.18 mmol, 100%), as a white solid, mp 106–107 °C. IR nujol, *ν*: 3312, 2924, 1736, 754, 704 cm^{-1}. ^1H RMN $CDCl_3$, *δ*: 1.08 (3H, s), 1.10 (1H, m), 1.12 (3H, s), 1.36 (3H, s), 1.40 (1H, m), 1.50 (1H, m), 1.65 (1H, m), 1.80 (1H, m), 2.14 (3H, s), 3.76 (1H, s), 4.33 (1H, d, $J=8.4$ Hz), 4.39 (1H, m), 7.29 (5H, s) ppm. ^{13}C RMN $CDCl_3$, *δ*: 20.0, 21.7, 21.8, 30.0, 30.6, 30.8 (2C), 47.1, 54.7, 65.4, 69.5, 74.0, 74.5, 128.1 (2C), 128.5, 128.8 (2C), 133.6, 169.2 ppm. MS EI, *m/z* (relative intensity): 330 (M^+, 1), 296 (2), 270 (12), 221 (26), 105 (100), 91 (69), 77 (50), 55 (46). Anal. Calcd For $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.95; H, 8.05.

4.1.20. Reaction of 22 with *p*-toluenesulphonic acid. A solution of **22** (500 mg, 1.51 mmol) in toluene (23 mL) was added to *p*-TsOH·H_2O (29 mg, 0.15 mmol). The reaction mixture was stirred under argon at reflux for 4 h. Then, the mixture was cooled to room temperature and then an aqueous solution of 5% $NaHCO_3$ was added to quench the reaction. The organic layer was separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography. Eluting with hexane–AcOEt (90/10) furnished **20** (90 mg, 0.29 mmol, 19%). Eluting with hexane–AcOEt (90/10) furnished 3a,7,7-trimethyl-2-oxo-3-phenyl-2,3a,4,5,6,7-hexahydro-3*H*-inden-4-yl acetate **23a** (296 mg, 0.95 mmol, 63%), as a colourless solid (CH_2Cl_2/pentane), mp 167–169 °C. IR nujol, *ν*: 2961, 2870, 1738, 1703, 760, 700 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 0.95 (3H, s), 1.30 (6H, s), 1.50 (1H, m), 1.75–1.95 (2H, m), 2.10 (1H, m), 2.15 (3H, s), 3.99 (1H, s), 4.99 (1H, m), 6.09 (1H, s), 7.00 (2H, m), 7.20–7.35 (2H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 21.1, 22.9, 24.9, 28.2, 31.0, 33.9, 33.5, 51.5, 59.3, 73.6, 121.1, 127.3, 128.4 (2C), 130.3 (2C), 135.6, 170.0, 188.1, 206.2 ppm. MS EI, *m/z* (relative intensity): 312 (M^+, 25), 270 (9), 252 (36), 237 (100), 209 (84), 115 (41), 77 (38), 55 (40). Anal. Calcd For $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.41; H, 7.69.

Eluting with hexane–AcOEt (80/20) furnished 3a,7,7-trimethyl-2-oxo-3-phenyl-2,3a,4,5,6,7-hexahydro-3*H*-inden-4-yl acetate **23b** (24 mg, 77 μmol, 5%). IR $CHCl_3$, *ν*: 2926, 2870, 1738, 1703, 758, 702 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 0.80–1.90 (4H, m), 1.05 (3H, s), 1.30 (3H, s), 1.56 (3H, s), 1.97 (3H, s), 3.66 (1H, s), 5.00 (1H, m), 6.10 (1H, s), 7.00 (2H, m), 7.30 (3H, m). HRMS (EI): 312.1796 (M^+, $C_{20}H_{24}O_3$), calcd 312.1725.

4.1.21. 4-Hydroxy-3a,7,7-trimethyl-3-phenyl-3,3a,4,5,6,7-hexahydro-inden-2-one 13. To a solution of **23a** (250 mg, 0.80 mmol) in EtOH (2 ml) was added a 5 M aqueous solution of KOH (0.4 ml). The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure. To the residue were added H_2O and Et_2O. The organic layer was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were washed with brine. Removal of the solvent afforded **13** (205 mg, 0.76 mmol, 95%).

4.1.22. 3a,7,7-Trimethyl-3-phenyl-3,3a,6,7-tetrahydro-5*H*-indene-2,4-dione 17a. To a stirred suspension of Dess–Martin (393 mg, 0.93 mmol) in CH_2Cl_2 (2 mL), was added a solution of the hydroxy ketone **13** (125 mg, 0.46 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was vigorously stirred at room temperature under argon for 20 h. Then, 1 M $NaHCO_3$ and 0.125 M $Na_2S_2O_3$ was added and the mixture were stirred for 30 min at room temperature. The organic layer was separated, and the aqueous phase was extracted whit ether. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude product, which was purified by flash chromatography. Eluting with hexane–ether (80/20) furnished **17a** (113 mg, 0.42 mmol, 92%) as a white solid.

4.1.23. Methyl 4-methyl-4-(2-methyl-4-oxo-3-phenyl-cyclopent-2-enyl)-pentanoate 24. To a solution of **17a** (25 mg, 93 μmol) in MeOH (0.25 ml) was added a 6 M aqueous solution of NaOH (42 μL). The mixture was stirred at room temperature for 10 min and then concentrated under reduced pressure. To the residue were added H_2O and Et_2O. The organic layer was separated and the aqueous phase was acidified with 2 N HCl and extracted with Et_2O. The combined organic extract were washed with brine and concentrated. The residue was dissolved in Et_2O and then was added dropwise a solution of CH_2N_2 in Et_2O until the release of nitrogen stopped. Removal of the solvent afforded a crude product, which was purified by flash chromatography. Eluting with hexane–Et_2O (60/40) afforded **24** (26 mg, 90%) as a white solid, mp (*t*BuOMe/hexane) 96–98 °C. IR $CHCl_3$, *ν*: 2957, 1730, 1692, 754, 700 cm^{-1}. ^1H NMR $CDCl_3$, *δ*: 0.98 (3H, s), 1.06 (3H, s), 1.70 (2H, m), 2.20 (3H, s), 2.30–2.65 (4H, m), 2.80 (1H, m), 3.68 (3H, s), 7.20–7.50 (5H, m) ppm. ^{13}C NMR $CDCl_3$, *δ*: 20.3, 24.9, 25.8, 29.3, 35.8, 36.7, 39.5, 51.6, 52.2, 127.8, 128.2 (2C), 129.4 (2C), 131.8, 143.8, 172.5, 174.0, 205.7 ppm. MS EI, *m/z* (relative intensity): 300 (M^+, 41), 285 (27), 172 (48), 129 (100), 115 (50), 97 (63),

72 (25). Anal. Calcd For $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.28; H, 7.93.

4.1.24. 4-Hydroxy-3a,7,7-trimethyl-3-phenyl-3,3a,4,5,6,7-hexahydro-inden-2-one 25. $LiAlH_4$ (2 mg, 38 μmol) was added to a solution of the unsaturated diketone **17a** (20 mg, 75 μmol) in dry ethyl ether (0.9 mL) cooled to 0 °C. The reaction mixture was vigorously stirred under argon for 10 min, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was filtered, and then the filtrate was evaporated under reduced pressure to afforded **25** (20 mg, 75 μmol, 100%), as a white solid, mp (*t*-BuOMe/hexane) 142–144 °C. IR $CHCl_3$, ν: 3432, 2938, 1690, 762, 729, 698 cm^{-1}. ^1H NMR $CDCl_3$, δ: 0.80–2.00 (5H, m), 0.92 (3H, s), 1.26 (3H, s), 1.27 (3H, s), 3.73 (1H, s), 3.76 (1H, dd, $J_1=4.6$ Hz, $J_2=11$ Hz), 6.07 (1H, s), 7.10–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 18.2, 26.8, 27.9, 30.8, 35.7, 38.3, 53.8, 67.5, 80.5, 127.0, 127.4, 128.2 (2C), 130.9 (2C), 137.0, 190.7, 207.5 ppm. MS EI, *m/z* (relative intensity): 270 (M^+, 20), 254 (20), 205 (100), 91 (40). Anal. Calcd For $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.57; H, 8.29.

4.1.25. 3a,7,7-Trimetyl-3-phenyl-3,3a,4,5,6,7-hexahydro-2*H*-indeno-2,4-diol 26. $LiAlH_4$ (11 mg, 0.30 mmol) was added to a solution of the ketone **17a** (80 mg, 0.30 mmol) in dry ethyl ether (3.6 mL). The reaction mixture was vigorously stirred under argon at room temperature for 10 min, after which it was quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting mixture was filtered, and then the filtrate was evaporated under reduced pressure to afforded **26** (81 mg, 0.30 mmol, 100%), as a colourless oil. IR $CHCl_3$, ν: 3412, 2932, 2870, 1690, 760, 702 cm^{-1}. ^1H NMR $CDCl_3$, δ: 0.80–1.80 (6H, m), 0.94 (3H, s), 1.11 (3H, s), 1.15 (3H, s), 3.05 (1H, d, $J=8.6$ Hz), 3.80 (1H, m), 5.14 (1H, dd, $J_1=1.3$ Hz, $J_2=8.6$ Hz), 5.55 (1H, d, $J=5.5$ Hz), 7.15–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 16.4, 27.3, 27.9, 30.4, 38.1, 38.6, 53.8, 70.3, 79.2, 81.5, 125.2, 127.5, 128.6 (2C), 129.3 (2C), 139.1 158.4 ppm. HRMS (EI): 272.1805 (M^+, $C_{18}H_{24}O_2$), calcd 272.1776.

4.1.26. 2,4-Dihydroxy-3a,7,7-trimethyl-3-phenyl-hexahydro-1-oxa-cyclopropa[*c*]indene 27. To a stirred solution of **26** (70 mg, 0.26 mmol) in CH_2Cl_2 (1.6 mL) was added *m*-CPBA (50 mg, 0.29 mmol). The reaction mixture was stirred under argon at room temperature for 30 min. Then, Na_2SO_3 (5%) was added and the resulting heterogeneous mixture was vigorously stirred for 15 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with $NaHCO_3$ (10%) and brine. Removal of the solvent afforded a crude product, which was purified by flash chromatography. Eluting with hexane–AcOEt (80/20) afforded **27** (74 mg, 0.26 mmol, 100%), as a colourless oil. IR, ν: 3422, 2930, 2870, 760, 708 cm^{-1}. ^1H NMR $CDCl_3$, δ: 0.80–1.80 (6H, m), 0.83 (3H, s), 0.92 (3H, s), 1.18 (3H, s), 3.01 (1H, d, $J=9.1$ Hz), 3.58 (1H, s), 4.11 (1H, m), 4.50 (1H, d, $J=9.1$ Hz), 7.20–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 14.2, 25.2, 26.8, 27.8, 32.8, 36.5, 48.4, 57.9, 59.2, 73.2, 75.0, 76.8, 127.3, 128.7 (2C), 130.1 (2C), 137.5 ppm. HRMS (EI): 288.1797 (M^+, $C_{18}H_{24}O_3$), calcd 288.1725.

4.1.27. 2-Hydroxy-3a,7,7-trimethyl-3-phenyl-hexahydro-1-oxa-cyclopropa[*c*]inden-4-one 28. To a stirred suspensionof Dess–Martin (59 mg, 0.14 mmol) in CH_2Cl_2 (0.6 mL), was added a solution of the diol **27** (20 mg, 69 μmol) in CH_2Cl_2 (0.25 mL). The reaction mixture was vigorously stirred at room temperature under argon for 30 min. Then, 1 M $NaHCO_3$ and 0.125 M $Na_2S_2O_3$ was added and the mixture was stirred for 30 min at room temperature. The organic layer was separated, and the aqueous phase was extracted whit ether. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude product, which was purified by flash chromatography. Eluting with hexane–ether (65/35) furnished **28** (19 mg, 66 μmol, 95%) as a colourless oil. ^1H NMR $CDCl_3$, δ: 0.94 (3H, s), 1.06 (3H, s), 1.34 (3H, s), 2.00 (2H, m), 2.60 (2H, m), 3.26 (1H, d, $J=9.1$ Hz), 3.64 (1H, s), 4.60 (1H, d, $J=9.1$ Hz), 7.20–7.50 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 18.9, 26.3, 27.4, 32.5, 36.3, 36.4, 50.6, 56.3, 59.2, 72.9, 74.6, 126.8, 128.1 (2C), 130.6 (2C), 136.1, 212.2 ppm. MS EI, *m/z* (relative intensity): 286 (M^+, 15), 271 (1), 268 (1), 138 (55), 96 (100). HRMS (EI): 286.1531 (M^+, $C_{18}H_{22}O_3$), calcd 286.1569.

4.1.28. 3a,7,7-Trimethyl-3-phenyl-tetrahydro-1-oxa-cyclopropa[c]indeno-2,4-dione 29. To a stirred suspension of Dess–Martin (76 mg, 0.18 mmol) in CH_2Cl_2 (0.4 mL), was added a solution of the diol **27** (25 mg, 89 μmol) in CH_2Cl_2 (0.32 mL). The reaction mixture was vigorously stirred at room temperature under argon for 24 h. Then, 1 M $NaHCO_3$ and 0.125 M $Na_2S_2O_3$ was added and the mixture ware stirred for 30 min at room temperature. The organic layer was separated, and the aqueous phase was extracted whit ether. The combined organic extracts were washed with brine. Removal of the solvent afforded a crude product, which was purified by flash chromatography. Eluting with hexane–ether (80/20) furnished **29** (22 mg, 78 μmol, 90%) as a white solid, mp 154–156 °C. ^1H NMR $CDCl_3$, δ: 0.98 (3H, s), 1.13 (3H, s), 1.39 (3H, s), 2.10 (2H, m), 2.65 (2H, m), 3.51 (1H, s), 4.34 (1H, s), 7.30–7.40 (5H, m) ppm. ^{13}C NMR $CDCl_3$, δ: 19.8, 26.0, 27.5, 33.0, 36.0, 36.1, 53.5, 55.6, 56.8, 74.6, 127.2, 127.8 (2C), 131.9 (2C), 132.7, 207.7, 210.7 ppm. MS EI, *m/z* (relative intensity): 284 (M^+, 30), 269 (9), 211 (81), 91 (100), 77 (44), 55 (79). Anal. Calcd For $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.83; H, 7.37.

Acknowledgements

Financial support for this work from the Ministerio de Educación y Ciencia of Spain PB 98-0251 and the Junta de Castilla y León SA 24/00B is gratefully acknowledged. We also thank the Ministerio de Educación y Ciencia for the fellowship to E.M.M.N and R.R.C; and Dr A. Lithgow for performing ^{13}C NMR and H– correlations experiments.

Supplementary Data

^1H, ^{13}C, H– correlations spectra and NOE for compounds. **4b**, **13**, **14**, **17a**, **21a**, **24**, **25**, **26**, **27**, **28**, **29**.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.09.109

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A mild, efficient and improved protocol for the synthesis of novel indolyl crown ethers, di(indolyl)pyrazolyl methanes and 3-alkylated indoles using $H_4[Si(W_3O_{10})_3]$

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Received 18 July 2005; revised 30 August 2005; accepted 22 September 2005

Available online 27 October 2005

Abstract—Efficient electrophilic substitution reactions of indoles with various aldehydes proceed smoothly in acetonitrile using heteropoly acid ($H_4[Si(W_3O_{10})_3]$) to afford the corresponding new indolyl crown ethers and di(indolyl)pyrazolyl methanes. $H_4[Si(W_3O_{10})_3]$ is also found to catalyze the Michael addition of indoles to α,β-unsaturated compounds for the synthesis of 3-alkylated indoles.

1. Introduction

The synthesis and the reactions of indoles have received much interest for over a century because a number of their derivatives occur in nature and possess a variety of biological activities.[1] Pyrazole derivatives have been found to have anticancer,[2] antiviral[3] and antihyperglycemic activity.[4] Our efforts here are to synthesize the di(indolyl)-pyrazolyl methanes which might exert high antimicrobial activity.[5] Crown ethers are heteromacrocycles in which the framework is typically comprised of repeating ethylene oxy[–(CH_2CH_2O)–] units. Nitrogen and sulfur commonly replace oxygen in this framework leading to a great variety of compounds that have been used in molecular recognition studies and supramolecular chemistry.[6] Alkali metal cation–π interactions have recently received considerable attention due to their biological importance.[7]

The electrophilic substitution reactions of indoles with aromatic aldehydes afford corresponding bis(indolyl)-methanes. Lewis acids,[8] protic acids,[9] ionic liquids,[10] iodine,[11] clays,[12] LPDE,[13] amberlyst-15[14] and $RE(PFO)_3$[15] are known to promote these reactions. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required because the acids are trapped by nitrogen.[16]

The 3-position of indole is the preferred site for the electrophilic substitution reactions, 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[17] A simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of either protic[18] or Lewis acids.[19] However, the acid catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerization or polymerization. Many of these procedures involve strongly acidic conditions, expensive reagents and long reaction times, give low yields of the products and involve cumbersome experimental product isolation procedures. The lanthanide triflates and gold catalysts[20] though less acidic are rather expensive which limits their use in large scale synthesis. For this reason, cheaper acid catalysts that secure catalytic activity, low toxicity, moisture and air tolerance are desirable. In this paper, we wish to introduce $H_4[Si(W_3O_{10})_3]$ as mild, highly efficient moisture tolerant catalyst for the preparation of indole derivatives under mild conditions.

Heteropolyacids are remarkable catalysts that are used in both homogenous and heterogeneous conditions. Their application as acid catalysts has been already reviewed.[21] $H_4[Si(W_3O_{10})_3]$ is a solid heteropolyacid that has been used

Keywords: Indolyl crown ether; Di(indolyl)pyrazolyl methanes; Michael addition; 3-Alkylated indoles.
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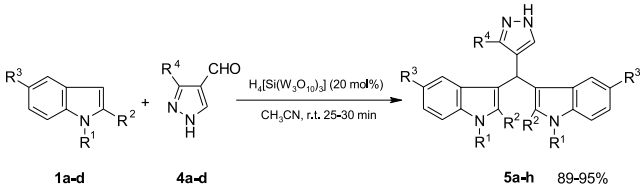
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.108

for the synthesis of trioxanes,[22] polymerization and for estimating nicotine and radioactive cesium in some derivatives.[23] Its efficiency as an acid catalyst in condensation and Michael addition in indoles is explored in this report.

2. Results and discussion

Di(indolyl)pyrazolylmethanes have been synthesized via $H_4[Si(W_3O_{10})_3]$ catalyzed condensation of indole (2 equiv) and pyrazolyl aldehydes (1 equiv). The reaction is facile and is complete within 30 min at room temperature. The method reported is favorable as good yields (89–95%) are obtained (Scheme 1). The procedure finds easy applicability because of the solubility of $H_4[Si(W_3O_{10})_3]$ in acetonitrile.



Scheme 1.

The catalytic activity of $H_4[Si(W_3O_{10})_3]$ is found to vary with different solvents (Table 1). The reaction of indole **1** with pyrazolyl aldehyde **4a** using $H_4[Si(W_3O_{10})_3]$ (20 mol%) as a catalyst was chosen as a model for optimization. Acetonitrile was found to give maximum yield followed by THF. The catalyst was found to be only mildly effective in dichloromethane. The effect of different ionic liquids on the $H_4[Si(W_3O_{10})_3]$ (20 mol%) catalyzed reaction was also examined. Butyl methyl imidazolium chloride [bmim][Cl] was found to be better than the other ionic liquids, but it could not compete with the effectiveness of the catalyst in acetonitrile.

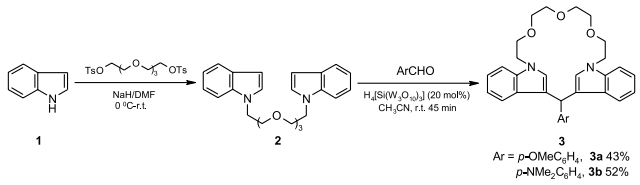
Table 1. Effect of solvent on the conversion to di(indolyl)pyrazolyl methane (**5a**)

Entry	Solvents	Time (min)	Yield (%)[a]
a	EtOH	60	75
b	THF	60	87
c	CH_2Cl_2	60	20
d	CH_3CN	25	95
e	[pmim][Br]	60	56
f	[ppy][Br]	60	41
g	[bmim][Cl]	60	72

[a] Isolated yields.

New indolyl crown ethers have been synthesized (Scheme 2) via $H_4[Si(W_3O_{10})_3]$ (20 mol%) catalyzed condensation of indole **2** (1 equiv) and aldehyde (1 equiv) under mild conditions. The reaction is facile and complete within 45 min at room temperature. The structure of **3a**[24] was further confirmed by single crystal X-ray crystallography (Fig. 1).

The efficacy of Lewis acids, such as CuI, $ZnCl_2$, $FeCl_3$, $CeCl_3$ and $InCl_3$ in acetonitrile was studied for the synthesis of di(indolyl)pyrazolylmethane **5a**. In comparison,



Scheme 2.

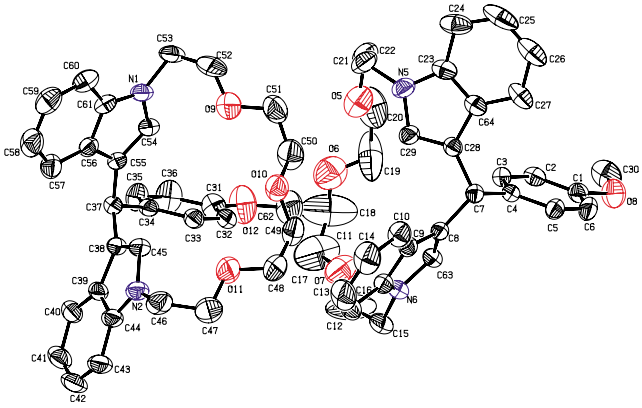


Figure 1. X-ray crystal structure of **3a**.

$H_4[Si(W_3O_{10})_3]$ was found to be an excellent acid catalyst in terms of conversion and reaction time (Table 2).

The maximum yield was 95% for **5a**. In fact, all the pyrazolyl aldehyde condensed with indoles giving di(indolyl)pyrazolylmethanes **5a–h** in high yields (89–95%). The catalytic activity of $H_4[Si(W_3O_{10})_3]$ was explored for the Michael addition of indole with α,β-unsaturated carbonyl compounds (Scheme 3). Methyl vinyl ketone reacted with indole and 2-methyl indole in the presence of a catalytic amount of $H_4[Si(W_3O_{10})_3]$ to give the 3-alkylated indoles (**7a**, **7c**) in excellent yields (Table 3).

The reaction was found to proceed smoothly at ambient temperature with high selectivity. Other electron deficient olefins like phenyl vinyl ketone **6b** afforded the product in good yield (87%). The same reaction was attempted with β-nitro styrene **6d** with indole in the presence of $H_4[Si(W_3O_{10})_3]$. The corresponding 3-alkylated indole **7f** was obtained in 90% yield without any side reactions thereby emphasizing the mild catalytic activity of $H_4[Si(W_3O_{10})_3]$.

The reactions were clean and the products were obtained in high yields (85–93%) without the formation of any side products such as dimers or trimers, which are normally observed under the influence of strong acids. Furthermore, no aqueous work-up was required after completion of the reaction. The reaction mixture was directly charged into a column after removing the solvent under vacuum.

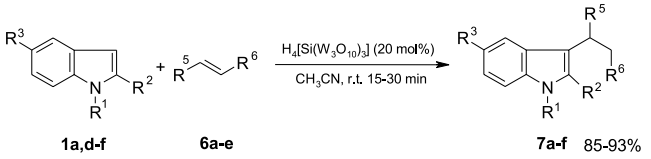
3. Conclusions

In conclusion, we report $H_4[Si(W_3O_{10})_3]$ as a highly efficient catalyst for the synthesis of new indolyl crown ethers, di(indolyl)pyrazolylmethanes and Michael addition

Table 2. $H_4[Si(W_3O_{10})_3]$ catalyzed synthesis of di(indolyl)pyrazolyl methanes[a]

Entry	Substituents				Time (min)	Yield (%)[b]
	R^1	R^2	R^3	R^4		
a	H	H	H	C_6H_5 **5a**	25	95
b	H	H	H	*m*-$OMeC_6H_4$ **5b**	30	94
c	H	H	H	*p*-$OMeC_6H_4$ **5c**	30	91
d	H	H	H	*p*-ClC_6H_4 **5d**	25	90
e	H	Me	H	C_6H_5 **5e**	30	93
f	H	H	OMe	C_6H_5 **5f**	30	89
g	Me	H	H	C_6H_5 **5g**	30	94
h	Me	H	H	*p*-ClC_6H_5 **5h**	30	91

[a] All products were characterized by IR, NMR and mass spectra.
[b] Isolated yields after purification.



Scheme 3.

Table 3. $H_4[Si(W_3O_{10})_3]$ catalyzed synthesis of 3-alkylated indoles[a]

Entry	Substituents					Product	Time (min)	Yield (%)[b]
	R^1	R^2	R^3	R^5	R^6			
a	H	H	H	H	COMe **6a**	**7a**	15	85
b	H	H	H	H	COPh **6b**	**7b**	15	87
c	H	Me	H	H	COMe **6a**	**7c**	10	91
d	H	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7d**	25	89
e	Me	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7e**	15	93
f	H	H	H	Ph	NO_2 **6d**	**7f**	15	90
g	*n*-Pr	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7g**	20	92
h	*n*-Bu	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7h**	15	90
i	H	H	OH	Ph	NO_2 **6d**	**7i**	25	90
j	H	H	H	CO_2Me	NO_2 **6e**	**7j**	20	93

[a] All products were characterized by IR, NMR and mass spectra.
[b] Isolated yields after purification.

of indoles with α,β-unsaturated carbonyl compounds. The reactions were successfully carried out in the presence of a catalytic amount of $H_4[Si(W_3O_{10})_3]$ in acetonitrile. $H_4[Si(W_3O_{10})_3]$ offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, and high yields of products. This simple experimental procedure, offers an alternative route to the synthesis of biologically active indole derivatives.

4. Experimental

4.1. General

Melting points were recorded on a CONCORD melting point apparatus and are uncorrected. Analytical TLC was performed on precoated sheets of silica gel G of 0.25 mm thickness containing PF254 indicator (Merck, Darmstadt). $H_4[Si(W_3O_{10})_3]$ was purchased from Sisco Research Lab, India and used as such. Column chromatography was performed with silica gel (100–200 mesh, s.d fine). Mass spectra were recorded on JEOL-JMS DX 303HF mass spectrometer. IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. NMR spectra were obtained on a JEOL ECA-500 MHz spectrometer. NMR was recorded at 500 MHz in $CDCl_3$ and DMSO-d_6 and the chemical shifts are given in δ. X-ray diffraction data were made on a Bruker SMART CCD area detector with monochromated Mo Kα radiation.

4.1.1. 1-[2-(2-{2-[2-(1*H*-Indol-1-yl)ethoxy]ethoxy}ethoxy)-ethyl]-1*H*-indole (2). Indole **1a** (500 mg, 4.27 mmol) was added to a suspension of NaH (60% in oil, 256 mg, 6.41 mmol washed with dry *n*-hexane [3×10 mL] by syringe) in dry DMF (30 mL), was stirred at 0 °C under nitrogen atmosphere. After the evolution of hydrogen gas had ceased, a dry DMF (10 mL) solution of tetraethylene glycol ditosylate (1.07 g, 2.14 mmol) was added dropwise to the suspension with stirring for 50 min at room temperature. After the reaction was complete, the organic solution was filtered and evaporated in vacuum, extracted with EtOAc (3×20 mL) washed with water, the brine then dried over anhydrous Na_2SO_4 and purified by column chromatography (Merck, 100–200 mesh, EtOAc–hexane, 2:8) to afford the pure product **2** in 85% yield (1.42 g) as a light yellow oil; [Found: C, 73.41; H, 7.15; N, 7.12. $C_{24}H_{28}N_2O_3$ requires C, 73.44; H, 7.19; N, 7.14%]; ν_{max} (neat) 3301, 1610, 1464, 1101, 754 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70 (2H, d, J=8.0 Hz, ind *H*), 7.40 (2H, d, J=9.1 Hz, ind *H*), 7.27 (2H, t, J=7.4 Hz, ind *H*), 7.21 (2H, t, J=3.4 Hz, ind *H*), 7.17 (2H, t, J=7.4 Hz, C=C*H*N), 6.55 (2H, d, J=2.9 Hz, C*H*=CHN), 4.30 (4H, t, J=5.7 Hz, CH_2N), 3.79 (4H, t, J=5.7 Hz, OCH_2CH_2N), 3.53–3.49 (8H, m, OCH_2-CH_2O); δ_C (125 MHz, $CDCl_3$) 136.2, 128.8, 128.7, 121.6,

121.1, 119.5, 109.5, 101.3, 70.9, 70.7, 70.3, 46.3; *m/z* 392 (M^+).

4.2. Typical experimental procedure 3

A mixture of indole **2** (510 mg, 1.30 mmol), 4-(dimethylamino)benzaldehyde (194 mg, 1.30 mmol) and $H_4[Si(W_3O_{10})_3]$ (20 mol%) in acetonitrile (10 mL) was stirred at room temperature for 45 min. After complete conversion, as indicated by TLC, the reaction mixture was concentrated in vacuum, and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 3:7) to afford the pure product **3b** in 52% yield (354 mg).

4.2.1. 3-[1-[2-(2-{2-[2-(1*H*-Indolyl-1-yl)ethoxy]ethoxy}-ethoxy)ethyl](4-methoxyphenyl)methyl]-1*H*-indole (3a). Orange crystal (280 mg, 43%), mp 140–142 °C; [Found: C, 75.25; H, 6.68; N, 5.51. $C_{32}H_{34}N_2O_4$ requires C, 75.27; H, 6.71; N, 5.49%]; ν_{max} (KBr) 2865, 1609, 1465, 1350, 1103, 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42 (2H, d, $J=8.4$ Hz, ind *H*), 7.31 (2H, d, $J=7.6$ Hz, ind *H*), 7.28 (2H, d, $J=8.4$ Hz, Ph), 7.19 (2H, t, $J=7.6$ Hz, ind *H*), 7.01 (2H, t, $J=7.6$ Hz, ind *H*), 6.85 (2H, d, $J=8.4$ Hz, Ph), 6.75 (2H, s, C═C*H*N), 5.87 (1H, s, Ar_3CH), 4.27–4.23 (2H, m, CH_2N), 4.15–4.12 (2H, m, CH_2N), 3.81 (3H, s, OCH_3), 3.74–3.66 (4H, m, OCH_2), 3.46–3.43 (2H, m, OCH_2), 3.37–3.30 (6H, m, OCH_2CH_2O); δ_C (125 MHz, $CDCl_3$) 157.9, 136.8, 136.7, 129.8, 129.7, 128.6, 127.7, 121.3, 120.1, 118.8, 113.6, 109.1, 72.0, 71.1, 70.0, 55.3, 46.3, 39.1; *m/z* 510 (M^+); λ_{max} (UV, MeOH) 309.6 nm.

4.2.2. 3-[1-[2-(2-{2-[2-(1*H*-Indolyl-1-yl)ethoxy]ethoxy}-ethoxy)ethyl](4-*N*,*N*-dimethylaminophenyl)methyl]-1*H*-indole (3b). Pink crystal (354 mg, 52%), mp 162–164 °C; [Found: C, 75.65; H, 7.11; N, 7.99. $C_{33}H_{37}N_3O_3$ requires C, 75.69; H, 7.12; N, 8.02%]; ν_{max} (KBr) 2865, 1611, 1517, 1466, 1350, 1123, 729 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.41 (2H, d, $J=8.0$ Hz, ind *H*), 7.29 (2H, d, $J=8.6$ Hz, Ph), 7.21–7.14 (4H, m, ind *H*), 6.98 (2H, t, $J=7.4$ Hz, ind *H*), 6.74 (2H, s, C═C*H*N), 6.70 (2H, d, $J=8.6$ Hz, ind *H*), 5.81 (1H, s, Ar_3CH), 4.27–4.20 (2H, m, CH_2N), 4.15–4.09 (2H, m, CH_2N), 3.73–3.64 (4H, m, OCH_2CH_2N), 3.45–3.40 (2H, m, OCH_2), 3.35–3.25 (6H, m, OCH_2CH_2O), 2.92 (6H, s, $N(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 156.3. 136.6, 129.4, 128.5, 127.8, 121.1, 120.3, 119.2, 118.6, 112.9, 109.0, 105.4, 72.0, 71.1, 70.0, 55.7, 46.3, 41.0; *m/z* 523 (M^+); λ_{max} (UV, MeOH) 309.0 nm.

4.3. Typical experimental procedure 5

A mixture of indole **1a** (200 mg, 1.71 mmol), 3-phenyl-1*H*-pyrazole-4-carbaldehyde **4a** (147 mg, 0.85 mmol) and $H_4[Si(W_3O_{10})_3]$ (20 mol%) in acetonitrile (10 mL) was stirred at room temperature for 25 min. After complete conversion, as indicated by TLC, the solvent was evaporated under vacuum and the product purified by column chromatography on silica gel (100–200 mesh, EtOAc–hexane, 3:7). The product obtained was analyzed and the yield was found to be (630 mg, 95%). The same procedure was followed for all the reactions (Table 2).

4.3.1. 3-[1*H*-Indol-3-yl(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5a). Light orange solid (630 mg, 95%), mp 206 °C; [Found: C, 80.38; H, 5.16; N, 14.40. requires $C_{26}H_{20}N_4$ C, 80.39; H, 5.19; N, 14.42%]; ν_{max} (KBr) 3410, 3048, 1627, 1462, 1420, 1339, 1095, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.52 (1H, br s, pyr N*H*), 10.78 (2H, s, ind N*H*), 7.56 (2H, d, $J=7.6$ Hz), 7.44 (1H, s, pyr C═C*H*N), 7.35–7.27 (5H, m, Ph), 7.17 (2H, d, $J=7.6$ Hz, ind *H*), 6.99 (2H, t, $J=7.6$ Hz, ind *H*), 6.86 (2H, s, ind C═C*H*N), 6.81 (2H, t, $J=7.7$ Hz, ind *H*), 5.83 (1H, s, Ar_3CH); δ_C (125 MHz, DMSO-d_6) 170.9, 137.2, 134.3, 132.4, 129.2, 127.9, 126.8, 123.9, 121.4, 119.3, 118.8, 114.3, 112.1, 111.2, 56.6, 30.2; *m/z* 388 (M^+).

4.3.2. 3-[1*H*-Indol-3-yl(3-(3-methoxyphenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5b). Orange solid (672 mg, 94%), mp 202–204 °C; [Found: C, 77.45; H, 5.32; N, 13.36. $C_{27}H_{22}N_4O$ requires C, 77.49; H, 5.30; N, 13.39%]; ν_{max} (KBr) 3418, 3037, 1620, 1462, 1431, 1250, 1088, 1037, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.80 (1H, br s, pyr N*H*), 10.76 (2H, s, ind N*H*), 7.31 (2H, d, $J=8.4$ Hz, Ph), 7.27 (1H, s, pyr C═C*H*N), 7.24–7.17 (4H, m, Ph and ind *H*), 7.03 (1H, s, Ph), 7.00 (3H, t, $J=7.6$ Hz, ind *H*), 6.85 (2H, s, ind C═C*H*N), 6.81 (2H, t, $J=7.7$ Hz, ind *H*), 5.83 (1H, s, Ar_3CH), 3.37 (3H, s, OCH_3); δ_C (125 MHz, DMSO-d_6) 159.7, 137.2, 130.1, 129.4, 126.9, 125.3, 123.9, 122.0, 121.4, 119.9, 119.4, 119.1, 118.7, 116.2, 114.0, 112.6, 112.0, 55.0, 30.4; *m/z* 418 (M^+).

4.3.3. 3-[1*H*-Indol-3-yl(3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5c). Brown solid (650 mg, 91%), mp 207–209 °C; [Found: C, 77.46; H, 5.28; N, 13.41. $C_{27}H_{22}N_4O$ requires C, 77.49; H, 5.30; N, 13.39%]; ν_{max} (KBr) 3414, 3034, 1612, 1427, 1415, 1338, 1238, 1088, 1018, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.83 (1H, br s, pyr N*H*), 10.80 (2H, s, ind N*H*), 7.50 (2H, d, $J=8.0$ Hz, Ph), 7.42 (1H, s, pyr C═C*H*N), 7.32 (2H, t, $J=7.6$ Hz, ind *H*), 7.20 (2H, d, $J=7.7$ Hz, ind *H*), 7.02 (2H, t, $J=7.6$ Hz, Ph), 6.91 (2H, t, $J=7.6$ Hz, ind *H*), 6.88 (2H, s, ind C═C*H*N), 6.85 (2H, t, $J=7.7$ Hz, ind H), 5.83 (1H, s, Ar_3CH), 3.73 (3H, s, OCH_3); δ_C (125 MHz, DMSO-d_6) 162.8, 159.1, 137.2, 130.2, 128.9, 126.9, 123.8, 121.3, 119.4, 119.2, 118.6, 114.5, 112.5, 111.9, 110.0, 55.5, 30.2; *m/z* 418 (M^+).

4.3.4. 3-[1*H*-Indol-3-yl(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5d). Orange solid (649 mg, 90%), mp 227–228 °C; [Found: C, 73.80; H, 4.53; N, 13.19. $C_{26}H_{19}ClN_4$ requires C, 73.84; H, 4.53; N, 13.25%]; ν_{max} (KBr) 3417, 1623, 1454, 1416, 1099, 737 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.85 (1H, br s, pyr N*H*), 10.80 (2H, s, ind N*H*), 7.61 (2H, d, $J=8.2$ Hz, Ph), 7.39 (3H, t, $J=7.6$ Hz, Ph), 7.35 (1H, t, $J=7.6$ Hz, ind *H*), 7.34 (1H, s, pyr C═C*H*N), 7.22 (2H, d, $J=8.0$ Hz, ind *H*), 7.03 (2H, t, $J=7.7$ Hz, ind *H*), 6.88 (2H, s, ind C═C*H*N), 6.85 (2H, t, $J=7.6$ Hz, ind *H*), 5.86 (1H, s, Ar_3CH); δ_C (125 MHz, DMSO-d_6) 160.1, 137.2, 134.4, 128.7, 126.6, 126.2, 124.0, 121.1, 119.5, 118.5, 116.6, 116.1, 115.9, 111.8, 109.2, 33.5; *m/z* 422 (M^+).

4.3.5. 2-Methyl-3-[(2-methyl-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5e). Brownish orange solid (591 mg, 93%), mp 194–196 °C; [Found: C, 80.71; H, 5.80; N, 13.42. $C_{28}H_{24}N_4$ requires C, 80.74; H,

5.81; N, 13.45%]; ν_{max} (KBr) 3422, 3298, 1656, 1472, 1113, 1042, 756 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.75 (1H, br s, pyr N*H*), 10.64 (2H, s, ind N*H*), 7.50 (2H, d, J=7.6 Hz, Ph), 7.23 (3H, t, J=6.9 Hz, Ph), 7.17 (2H, d, J=7.6 Hz, ind *H*), 7.14 (1H, s, pyr C=C*H*N), 6.92 (2H, d, J=7.6 Hz, ind *H*), 6.86 (2H, t, J=7.6 Hz, ind *H*), 6.68 (2H, t, J=7.6 Hz, ind *H*), 5.78 (1H, s, Ar_3CH), 2.04 (6H, s, CH_3); δ_C (125 MHz, DMSO-d_6) 170.8, 160.9, 135.5, 131.9, 128.9, 128.6, 127.3, 121.5, 120.1, 118.7, 118.5, 113.4, 112.5, 111.8, 110.9, 60.3, 30.3; *m/z* 416 (M^+).

4.3.6. 5-Methoxy-3-[(5-methoxy-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5f). Orange solid (615 mg, 90%), mp 118–120 °C; [Found: C, 74.94; H, 5.33; N, 12.48. $C_{28}H_{24}N_4O_2$ requires C, 74.98; H, 5.39; N, 12.49%]; ν_{max} (KBr) 3417, 3300, 1620, 1482, 1211, 1054, 772 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.70 (1H, br s, pyr N*H*), 10.59 (2H, s, ind N*H*), 7.54 (2H, d, J=7.6 Hz, Ph), 7.34 (2H, t, J=6.9 Hz, Ph), 7.27 (1H, t, J=7.6 Hz, Ph), 7.21 (1H, s, pyr C=C*H*N), 7.19 (2H, s, ind *H*), 6.85 (2H, s, ind C=C*H*N), 6.65 (2H, dd, J=2.3, 8.4 Hz, ind *H*), 6.57 (2H, s, ind *H*), 5.67 (1H, s, Ar_3CH), 3.51 (6H, s, OCH_3); δ_C (125 MHz, DMSO-d_6) 170.5, 153.1, 135.6, 130.6, 130.0, 129.4, 129.1, 127.9, 127.3, 124.5, 121.6, 118.7, 112.6, 111.0, 101.6, 55.7, 30.3; *m/z* 448 (M^+).

4.3.7. 1-Methyl-3-[(1-methyl-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5g). Brown solid (561 mg, 94%), mp 142 °C; [Found: C, 80.72; H, 5.78; N, 13.44. $C_{28}H_{24}N_4$ requires C, 80.74; H, 5.81; N, 13.45%]; ν_{max} (KBr) 3432, 3059, 2926, 1616, 1473, 1329, 1097, 1013, 740 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.84 (1H, br s, pyr N*H*), 7.55 (2H, d, J=8.4 Hz, Ph), 7.35 (2H, d, J=8.5 Hz, Ph), 7.33 (3H, d, J=3.9 Hz, Ph and ind *H*), 7.31 (1H, s, pyr C=C*H*N), 7.18 (2H, d, J=7.6 Hz, ind *H*), 7.05 (2H, t, J=7.6 Hz, ind *H*), 6.85 (2H, t, J=7.6 Hz, ind *H*), 6.83 (2H, s, C=C*H*N), 5.80 (1H, s, Ar_3CH), 3.64 (6H, s, CH_3); δ_C (125 MHz, DMSO-d_6) 164.2, 149.4, 137.6, 132.2, 129.4, 129.1, 128.3, 127.1, 122.1, 121.5, 119.5, 118.9, 118.2, 116.5, 110.2, 32.8, 29.9; *m/z* 416 (M^+).

4.3.8. 1-Methyl-3-[(1-methyl-1*H*-indol-3-yl)(3-(4-chloro phenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5h). Orange solid (625 mg, 91%), mp 138 °C; [Found: C, 74.56; H, 5.11; N, 12.39. $C_{28}H_{23}ClN_4$ requires C, 74.57; H, 5.14; N, 12.42%]; ν_{max} (KBr) 3431, 3056, 2928, 1617, 1470, 1326, 1097, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.85 (1H, br s, pyr N*H*), 7.54 (2H, d, J=8.4 Hz, Ph), 7.35 (2H, d, J=8.5 Hz, Ph), 7.33 (2H, d, J=7.6 Hz, ind *H*), 7.31 (1H, s, pyr C=C*H*N), 7.18 (2H, d, J=8.5 Hz, ind *H*), 7.05 (2H, t, J=7.7 Hz, ind *H*), 6.85 (2H, t, J=7.6 Hz, ind *H*), 6.82 (2H, s, ind C=C*H*N), 5.79 (1H, s, Ar_3CH), 3.64 (6H, s, CH_3); δ_C (125 MHz, DMSO-d_6) 161.5, 152.1, 129.4, 129.1, 128.3, 127.1, 122.1, 121.5, 119.5, 118.9, 118.2, 117.1, 115.2, 111.1, 110.2, 89.7, 32.1; *m/z* 450 (M^+).

4.4. Typical experimental procedure 7

To a mixture of 1-propyl indole (200 mg, 1.26 mmol) and (2*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **4g** (299 mg, 1.26 mmol) in acetonitrile (10 mL), $H_4[Si(W_3O_{10})_3]$ (20 mol%) was added and the reaction stirred for 20 min at room temperature. After complete conversion, as indicated by TLC, the solvent was evaporated under vacuum and the product purified by column chromatography on silica gel (100–200 mesh, EtOAc–hexane, 2:8) and the product was obtained (458 mg, 92% yield, Table 3).

4.4.1. 4-(1*H*-Indol-3-yl)butan-2-one (7a).[19a] Light brown solid (272 mg, 85%), mp 70–72 °C; [Found: 76.95; H, 7.02; N, 7.45. $C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%]; ν_{max} (KBr) 3409, 2928, 1709, 1165, 1067, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ind N*H*), 7.38 (1H, d, J=7.6 Hz, ind *H*), 7.28 (1H, d, J=7.6 Hz, ind *H*), 7.17 (1H, t, J=7.1 Hz, ind *H*), 7.10 (1H, t, J=7.0 Hz, ind *H*), 7.02 (1H, s, C=C*H*N), 3.05 (2H, t, J=6.8 Hz, ind CH_2), 2.80 (2H, t, J=6.8 Hz, CH_2C=O), 2.13 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 201.9, 136.7, 128.7, 126.4, 122.1, 121.5, 119.4, 118.5, 111.4, 110.8, 39.5, 8.9; *m/z* 187 (M^+).

4.4.2. 3-(1*H*-Indol-3-yl)-1-phenylpropan-1-one (7b).[19a] Brown solid (370 mg, 87%), mp 126–127 °C; [Found: C, 82.94; H, 6.03; N, 5.59. $C_{17}H_{15}NO$ requires C, 82.90; H, 6.06; N, 5.62%]; ν_{max} (KBr) 3410, 3055, 2928, 1683, 1335, 1205, 1097, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.05 (1H, s, ind N*H*), 7.64–7.53 (2H, m, ind *H*), 7.48–7.32 (5H, m, Ph), 7.19–7.05 (3H, m, ind *H*), 3.51 (2H, t, J=7.6 Hz, ind CH_2), 3.26 (2H, t, J=7.6 Hz, CH_2C=O); δ_C (125 MHz, $CDCl_3$) 201.0, 138.2, 136.2, 132.9, 128.6, 128.1, 126.8, 121.9, 121.5, 118.9, 118.4, 111.7, 110.8, 39.5, 19.9; *m/z* 249 (M^+).

4.4.3. 4-(2-Methyl-1*H*-indol-3-yl)butan-2-one (7c).[19a] Colorless oil (313 mg, 91%); [Found: C, 77.55; H, 5.57; N, 6.92. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51; N, 6.96%]; ν_{max} (neat) 3415, 3028, 1714, 1457, 1371, 1226, 1035, 748 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ind N*H*), 7.35 (1H, d, J=7.1 Hz, ind *H*), 7.15 (1H, t, J=7.1 Hz, ind *H*), 7.10 (1H, t, J=7.0 Hz, ind *H*), 6.95 (1H, d, J=2.1 Hz, ind *H*), 3.05 (2H, t, J=6.8 Hz), 2.80 (2H, t, J=6.8 Hz, CH_2C=O), 2.41 (3H, s, CH_3C=O), 2.13 (3H, s, ind CH_3); δ_C (125 MHz, $CDCl_3$) 201.8, 136.2, 128.5, 126.4, 123.9, 121.6, 119.7, 118.9, 110.4, 78.3, 38.5, 19.7, 12.4; *m/z* 201 (M^+).

4.4.4. 3-(1*H*-Indol-3-yl)-3-(4-methoxy phenyl)-1-phenyl propan-1-one (7d). Brown solid (540 mg, 89%), mp 128–130 °C; [Found: C, 81.07; H, 5.93; N, 3.95. $C_{24}H_{21}NO_2$ requires C, 81.10; H, 5.96; N, 3.94%]; ν_{max} (KBr) 3425, 3300, 2925, 1675, 1508, 1465, 1035, 739 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.09 (1H, s, ind N*H*), 7.95 (2H, d, J=7.5 Hz, Ph), 7.55 (1H, t, J=7.5 Hz, Ph), 7.45–7.41 (3H, m, Ph), 7.28 (3H, dd, J=2.3, 10.9 Hz, Ph), 7.16 (1H, t, J=8.0 Hz, ind *H*), 7.05 (1H, t, J=6.9 Hz, ind *H*), 6.93 (1H, s, C=C*H*N), 6.82 (2H, d, J=11.4 Hz, Ph), 5.06 (1H, t, J=6.9 Hz, Ar_2CH), 3.79–3.74 (2H, m, CH_2), 3.73 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 199.9, 158.1, 137.3, 136.8, 136.5, 133.2, 128.9, 128.7, 128.3, 126.7, 122.2, 121.5, 119.7, 119.6, 119.5, 113.9, 111.4, 55.3, 45.5, 37.6; *m/z* 355 (M^+).

4.4.5. 3-(1-Methyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7e). Brown solid (523 mg, 93%), mp 112 °C; [Found: C, 81.25; H, 6.24; N, 3.81. $C_{25}H_{23}NO_2$ requires C, 81.27; H, 6.27; N, 3.79%]; ν_{max} (KBr) 3420, 3302, 2925, 1505, 1035, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$)

7.95 (2H, d, J=7.6 Hz, Ph), 7.54 (1H, t, J=6.9 Hz, Ph), 7.47–7.42 (3H, m, Ph), 7.28 (3H, t, J=8.6 Hz, Ph), 7.20 (2H, t, J=7.4 Hz, ind *H*), 7.03 (1H, s, C=C*H*N), 6.83 (2H, t, J=8.5 Hz, ind *H*), 5.04 (1H, t, J=6.9 Hz, Ar_2CH), 3.82–3.78 (2H, dd, J=6.3, 16.6 Hz, CH_2), 3.75 (3H, s, OCH_3), 3.72 (3H, s, NCH_3); δ_C (125 MHz, $CDCl_3$) 198.9, 158.0, 137.5, 137.3, 136.6, 133.1, 128.9, 128.7, 128.2, 127.1, 126.3, 121.8, 120.4, 119.7, 118.9, 118.3, 113.9, 109.3, 55.3, 45.5, 37.6; *m/z* 369 (M^+).

4.4.6. 3-(2-Nitro-1-phenylethyl)-1*H*-indole (7f).[19a] Colorless oil (409 mg, 90%); [Found: C, 72.11; H, 5.27; N, 10.54. $C_{16}H_{14}N_2O_2$ requires C, 72.17; H, 5.30; N, 10.58%]; ν_{max} (neat): 3417, 3030, 2925, 1456, 1223, 1015, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ind N*H*), 7.42 (1H, d, J=7.6 Hz, Ph), 7.33–7.24 (6H, m, Ph and ind *H*), 7.21 (1H, t, J=7.6 Hz, ind *H*), 7.08 (1H, t, J=7.6 Hz, ind *H*), 6.97 (1H, d, J=2.5 Hz, ind *H*), 5.20 (1H, t, J=7.6 Hz, Ar_2CH), 4.81 (2H, m, CH_2); δ_C (125 MHz, $CDCl_3$) 139.2, 136.5, 128.9, 127.6, 127.4, 125.9, 123.4, 121.6, 119.8, 118.8, 114.1, 111.4, 79.4, 40.9; *m/z* 266 (M^+).

4.4.7. 3-(1-Propyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7g). Brown oil (459 mg, 92%); [Found: C, 81.53; H, 6.84; N, 3.50. $C_{27}H_{27}NO_2$ requires C, 81.58; H, 6.85; N, 3.52%]; ν_{max} (neat) 3425, 3300, 2925, 1504, 1463, 1035, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.13 (2H, d, J=8.0 Hz, Ph), 8.11 (1H, d, J=8.1 Hz, Ph), 7.74 (1H, d, J=8.1 Hz, Ph), 7.61–7.45 (5H, m, Ph), 7.38 (1H, t, J=7.4 Hz, ind *H*), 7.24 (1H, t, J=7.4 Hz, ind *H*), 7.15 (1H, s, C=C*H*N), 7.00 (2H, d, J=8.5 Hz, ind *H*), 5.34 (1H, s, Ar_2CH), 4.06 (2H, t, J=6.9 Hz, CH_2N), 3.99 (2H, dd, J=6.3, 20.6 Hz, CH_2C=O), 3.80 (3H, s, OCH_3), 1.95–1.88 (2H, m, CH_2), 1.02 (3H, t, J=7.4 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 199.0, 158.4, 137.6, 137.1, 137.0, 133.3, 129.2, 128.9, 128.4, 127.6, 125.7, 121.9, 120.1, 118.3, 119.1, 114.2, 109.9, 55.3, 48.1, 45.8, 37.9, 23.8, 11.8; *m/z* 397 (M^+).

4.4.8. 3-(1-Butyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7h). Brown oil (442 mg, 93%); [Found: C, 81.69; H, 7.12; N, 3.41. $C_{28}H_{29}NO_2$ requires C, 81.72; H, 7.10; N, 3.40%]; ν_{max} (neat) 3420, 3307, 2922, 1675, 1465, 1037, 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.08 (2H, d, J=8.0 Hz, Ph), 7.76 (2H, d, J=8.0 Hz, Ph), 7.64–7.47 (5H, m, Ph), 7.39 (1H, d, J=7.6 Hz, ind *H*), 7.25 (2H, t, J=7.4 Hz, Ph), 7.17 (1H, d, J=6.9 Hz, ind *H*), 7.03 (1H, s, C=C*H*N), 5.05 (1H, s, Ar_2CH), 4.07 (2H, t, J=7.6 Hz, NCH_2), 4.01–3.95 (2H, m, CH_2C=O), 3.82 (3H, s, OCH_3), 1.97–1.85 (4H, m, CH_2), 0.89 (3H, t, J=7.6 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 199.9, 159.0, 137.2, 136.6, 133.2, 129.2, 128.7, 128.2, 127.6, 126.3, 121.8, 120.4, 119.7, 119.5, 119.1, 118.3, 113.7, 110.4, 55.3, 48.1, 45.8, 38.0, 24.0, 11.8; *m/z* 411 (M^+).

4.4.9. 3-(2-Nitro-1-phenylethyl)-1*H*-indol-5-ol (7i). Brown solid (319 mg, 90%), mp 124 °C; [Found: C, 68.01; H, 4.95; N, 9.88. $C_{16}H_{14}N_2O_3$ requires C, 68.07; H, 5.00; N, 9.92%]; ν_{max} (KBr) 3406, 3030, 1745, 1376, 1035, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.05 (1H, s, ind N*H*), 7.32–7.20 (5H, m), 7.18 (1H, d, J=8.4 Hz), 6.98 (1H, d, J=2.6 Hz), 6.83–6.73 (2H, m), 5.11–4.80 (4H, m); δ_C (125 MHz, $CDCl_3$) 155.6, 148.7, 134.4, 132.9, 132.5, 127.4, 124.8, 124.1, 117.1, 108.1, 104.8, 102.3, 85.0, 37.5; *m/z* 282 (M^+).

4.4.10. Methyl-2-(1*H*-indol-3-yl)-3-nitropropanoate (7j). Light yellow oil (335 mg, 90%); [Found: C, 58.00; H, 4.85; N, 11.27. $C_{12}H_{12}N_2O_4$ requires C, 58.06; H, 4.87; N, 11.29%]; ν_{max} (neat) 3409, 3035, 1747, 1374, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.02 (1H, s, ind N*H*), 7.64 (1H, d, J=8.4 Hz), 7.40–7.35 (1H, m), 7.32–7.13 (3H, m), 5.28–5.19 (1H, m), 4.81–4.60 (2H, m, CH_2), 3.73 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 172.0, 136.4, 125.9, 123.3, 123.1, 120.6, 118.7, 111.9, 76.3, 53.0, 39.1; *m/z* 248 (M^+).

Acknowledgements

R.M. thanks Dr. R. Sridhar-National University of Singapore and E. Ramesh—University of Madras for their help.

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Tetrahedron 61 (2005) 12282–12287
Tetrahedron

Tetrazolecalix[4]arenes as new ligands for palladium(II)

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Received 7 July 2005; revised 31 August 2005; accepted 22 September 2005

Available online 19 October 2005

Abstract—The synthesis of new calix[4]arenes bearing two or four tetrazole liganting groups at the upper rim is decribed. The structures of tetrakis-tetrazolecalix[4]arene and its palladium dichloride (2:2) complex are examined by X-ray crystallography.

1. Introduction

Calixarenes[1] decorated with donor functional groups are suitable platforms for design of polynuclear complexes of transition metals.[2] Due to the spatial proximity of coordinated metal cations to the bowl-shaped molecular cavity, which is able to include organic molecules of complementary size and geometry, these complexes can behave as homogeneous catalysts combining the metallocomplex and supramolecular functions.[3] Recently, methods of anchoring for calixarenes onto silicagel surface have been developed, thus making calixarene metallocomplexes potentially useful in heterogeneous catalysis.[4]

Catalytic systems including calixarene metal complexes demonstrate wide applicability. It was shown that niobium oxocomplexes of calixarenes catalyze the transformation of molecular nitrogen to nitride.[5] Palladium-bis-pyrazolylcalixarene complex effectively catalyzes the Suzuki cross-coupling reaction of chlorotoluene.[6] Copper and zinc complexes of calixarene derivatives functionalized with pyridine and imidazole catalyze, like metalloenzymes, esterification and transesterification of phosphates.[7]

Calixarenes are potential ligands for the development of chiral metallocomplex catalysts.[8] It was shown that achiral *p-tert*-butylcalix[4]arene promotes the enantioselective allylation of aldehydes catalyzed by Zr-BINOL system.[9] Optically active diphosphine metallocomplexes obtained from inherently chiral calixarenes show high catalytic activity and enantioselectivity in alkylation and hydrogenation reactions due to the chiral macrocyclic skeleton, which can transfer chiral information to the catalytic centre.[10]

In this paper, we present the synthesis of bis- and tetrakis-tetrazole derivatives of calix[4]arene (**5**, **10**) and the results of structural investigation of macrocycle **10** and its complex with palladium dichloride **11**. To the best of our knowledge, tetrazoles have not been investigated as a ligand function of calixarene, though they demonstrate ability to bind cations of transition metals.[11]

2. Results and discussion

Attempts to insert tetrazole residues onto the upper rim of the calix[4]arene macrocycle by the reaction of 1*H*-phenyl and 1*H*-benzyltetrazole with tetrakis-chloromethyltetrapropoxycalixarene[12] show that the alkylation is not regioselective and the mixture of 1*N*-substitued and 2*N*-substitued tetrazole derivatives is formed. As the modular approach is unsuitable, tetrazole groups were inserted by a synthetic sequence starting from diaminodipropoxycalix[4]arene **1** and tetraaminotetrapropoxycalix[4]arene **6** in the cone conformation.

Calixarene **5** with two distal tetrazole rings was obtained according to Scheme 1. Acylation of diamine **1** by *p*-chlorobenzoylchloride leads to the formation of amide **2**. Diamide **2** was converted to the corresponding bis-imydoylchloride **3** by reaction with phosphorus pentachloride. The active chlorine atoms of **3** were replaced by azide groups in refluxing trimethylsilylazide with a catalytic

Keywords: Calixarenes; Tetrazole; Metallocomplexes; Transition metals; Stereochemistry; X-ray analysis.
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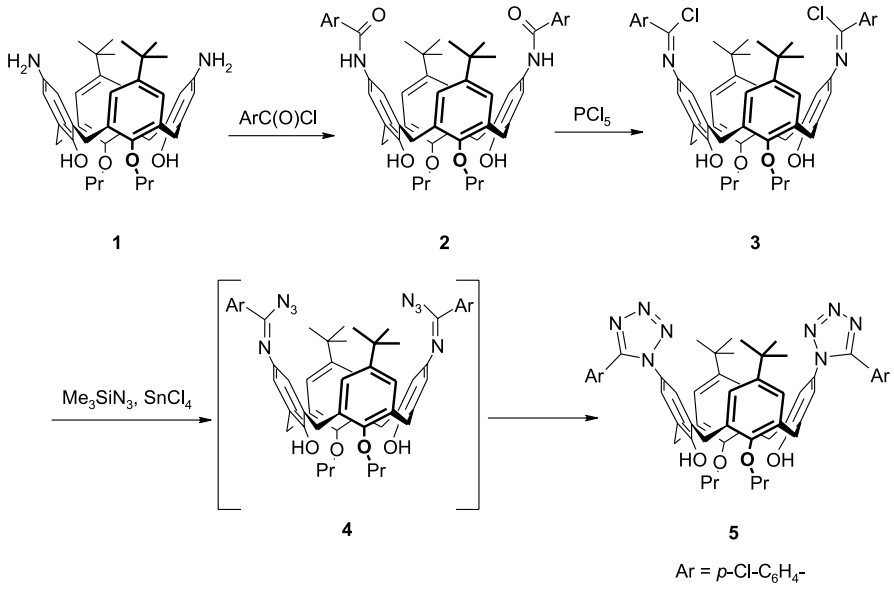
doi:10.1016/j.tet.2005.09.107



Scheme 1.

amount of $SnCl_4$. The resulting bis-azide **4** was thermodynamically unstable and spontaneously isomerized into bis-tetrazole **5**.

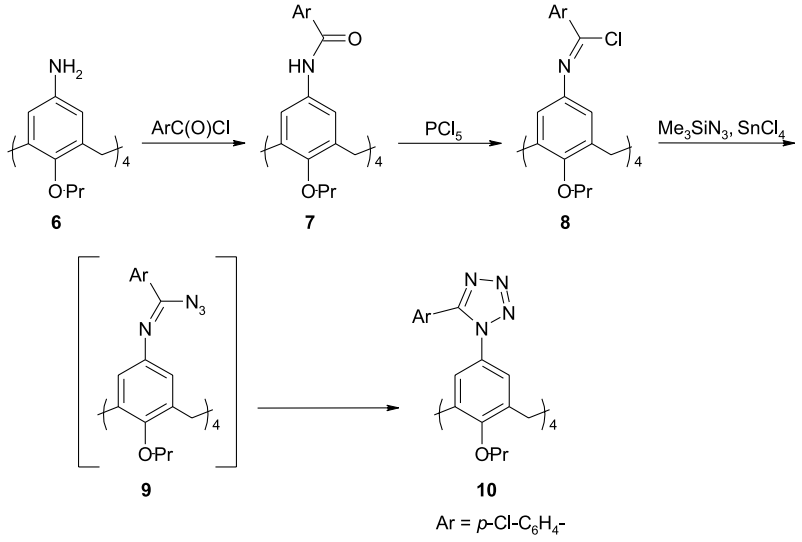
Like other 25,27-dialkoxycalixarenes[13], bis-tetrazolecalixarene **5** adopts, in solutions, a pinched cone conformation, stabilized by the network of two intramolecular OH···OPr hydrogen bonds. This conclusion is confirmed by the 0.79 ppm difference between axial and equatorial protons of the macrocyclic methylene groups[14] (two doublets of AB spin system with $^2J_{HH} \approx 13$ Hz are presented in the ^{1}H NMR spectra) and the downfield shift of OH hydrogens at 8.72 ppm caused by the formation of the hydrogen bonds.[13]

Calixarene **10** containing four tetrazole groups at the upper rim of the macrocycle was obtained analogously via the transformation of tetraamine **6** into corresponding amide **7**, imidoylchloride **8**, azide **9** and then tetrazolecalixarene **10** (Scheme 2)

The difference of 1.36 ppm in chemical shifts between the axial and equatorial hydrogen atoms of the macrocycle methylene groups in ^{1}H NMR spectra of tetrapropoxycalixarene **10** is significantly larger than that for dipropoxycalixarene **5**. Such a feature can be explained by rapid (on the NMR scale time) mutual exchange of two equal pinched cone conformations in calixarene **10**, which equilibrate through the regular cone conformation.[14a]

Similar in solution, in the solid state molecule **10** adopts the pinched cone conformation (Fig. 1). Two opposite phenolic rings (A and C) are nearly orthogonal to the mean plane formed by the four methylene groups of the macrocycle and are slightly tilted inside the cavity. At the same time, the phenolic rings B and D are inclined outside the cavity of the macrocycle (Table 1).

The tetrazole rings are rotated relative to the corresponding phenol rings by angles ranging from 22.0 to 88.8 degrees



Scheme 2.

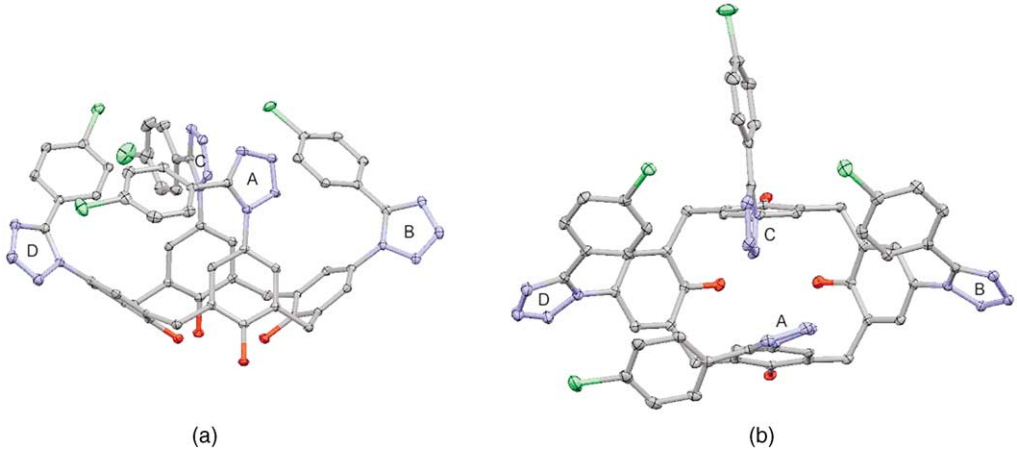


Figure 1. Side (a) and top (b) views of the molecule of calixarene **10** at 30% probability ellipsoid level. The disordered propyl groups at the lower rim, solvent molecules and all hydrogen atoms are omitted for clarity.

and are also essentially non-coplanar with their *p*-chlorophenyl substituents (Table 1). The large deviations of the aromatic fragments from coplanarity indicate the lack of conjugation in the molecule. This means that the geometry of the upper rim of the macrocycle is determined mainly by intramolecular steric repulsions because any strong intermolecular interactions in the crystal lattice of **10** are absent and the shortest contacts between non-hydrogen atoms of different molecules exceed 3.3 Å. Three of the four propyl groups at lower rim of calixarene **10** are disordered.

The rotational freedom of the tetrazole fragments relative to the phenolic rings allow to believe that compound **10** can adopt a conformation with the orientation of the tetrazole units suitable for the formation of metal complexes. However, the attempts to prepare the copper and nickel complexes via reaction of this ligand with the corresponding metal perchlorate salts failed. Apparently, this is due to the relatively low donating ability of the nitrogen atoms of tetrazole rings, insufficient to form coordination bonds with 3d metals. At the same time, the salt of 4d metal ion, K_2PdCl_4, in acetonitrile solution readily forms the palladium(II) complex **11**, which has the composition (**10**·$PdCl_2$) (see Section 3).

Structural data revealed a dimeric structure for the complex **11** (Fig. 2). Each ligand is coordinated to the palladium in a bis-monodentate manner through nitrogen atoms at the 4 position of proximal tetrazole rings.[15] In this case both calixarene ligands become inherently chiral (ABCC

Table 1. The angles (deg) between some mean planes in tetrazolecalixarene **10** and its palladium(II) complex **11**

Phenol or tetrazole ring	Mean plane of four methylene groups–phenol ring		Tetrazole ring–phenol ring		Tetrazole ring–chlorophenyl ring	
	10	**11**	**10**	**11**	**10**	**11**
A	76.3	76.7	22.0	33.4	53.6	73.7
B	141.0	146.3	48.0	54.1	38.4	32.6
C	94.9	85.8	88.8	69.2	8.9	13.5
D	146.9	134.0	54.8	55.4	30.1	39.6

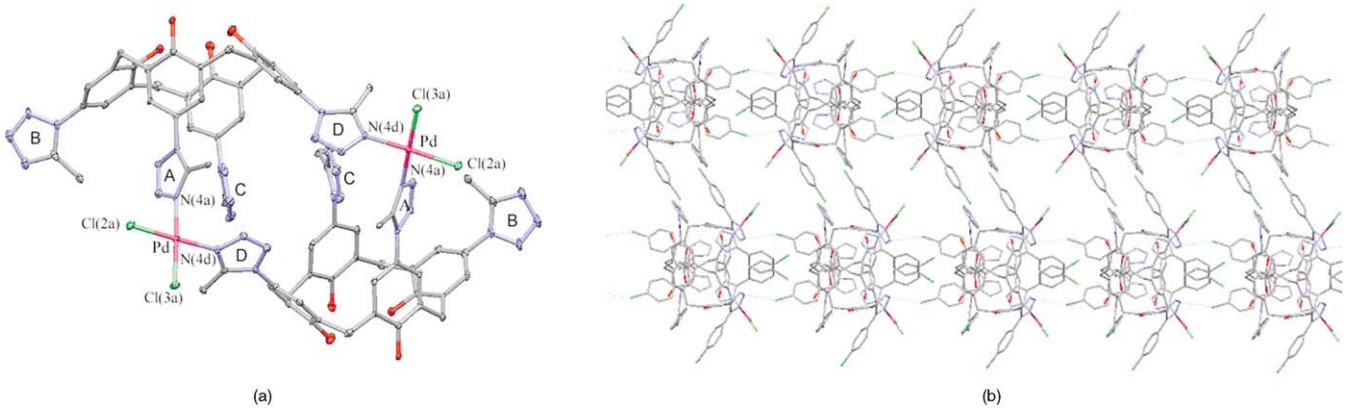


Figure 2. (a) View of complex **11** with 30% probability ellipsoid level. Propyl groups, chlorophenyl rings (except of carbon atoms connected to tetrazoles) and all hydrogen atoms are omitted for clarity. (b) The rods formed by the complex running along the *b* axis (intermolecular contacts are shown as blue dotted lines).

substitution type[8]) and since the halves of the molecule are related via a mirror symmetry operation, the complex as a whole has racemic structure. The four-coordinate Pd(II) ion has a distorted square-planar *cis*-N_2Cl_2 coordination environment. The average deviation of the atoms from PdN_2Cl_2 mean plane equals to 0.39 Å. The Pd–N coordination bonds (2.036(6) and 2.014(7) Å) lie in the ranges typical for these kinds of interatomic donor–acceptor distances (cf. with average value 2.03 Å[16]), but, surprisingly, the Pd–Cl bonds (2.271(2) and 2.276(2) Å) are essentially shorter (cf. with 2.42 Å[16]). Interestingly, all the angles around the central Pd atoms are close to 90° changing from 88.4 to 90.8°.

The comparison of the angles between different mean planes in **10** and **11** testifies to insignificant changes of the conformation of the macrocycle in the complex as compared to the non-coordinated ligand (for the overlay see Fig. 3). This can therefore be considered as a degree of pre-organization of the ligand, which permits easy formation of complex **11** with 2:2 Pd-to-ligand stoichoimetry.

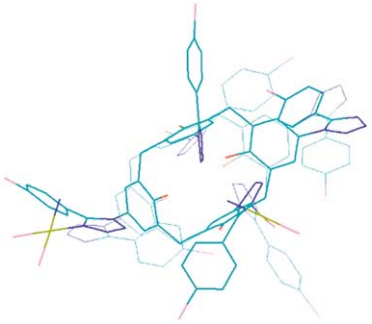


Figure 3. Overlay of the calixarene molecules in ligand **10** and palladium complex **11** (bold lines).

As in the previous case, strong intermolecular interactions are absent in the crystal lattice of **11**. Only relatively weak contacts between chlorine atoms of the aromatic substituents C and nitrogen atoms of tetrazole ring D (3.247(2) Å) leading to the formation of nanosized rods with the dimensions ca. 20 Å (Fig. 2b) are noteworthy.

In conclusion, the first synthsesis of bowl shaped tetrazolecalix[4]arene ligands for palladium(II) has been devised. The utility of the compounds for design of self-assembled cage structures possessing transition metal cations as linkers was demonstrated.

3. Experimental

3.1. General

All procedures for the synthesis of **5** and **10** were carried out in anhydrous solvents under a dry atmosphere. ^{1}H NMR spectra were recorded on 'Varian-300' spectrometer at 300 MHz (TMS as internal standard). Diaminocalix[4]arene **1**[17] and tetraaminocalix[4]arene **6**[17b] were synthesized according to literature procedures.

3.1.1. 5,17-Di(4-chlorophenylcarboxamido)-11,23-di-*tert*-butyl-25,27-dipropoxy-26,28-dihydroxycalix[4]arene (2). A solution of diaminocalixarene **1** (650 mg, 1 mmol) in toluene (10 ml) was added to a stirred solution of *p*-chlorobenzoylchloride (385 mg, 2.2 mmol) in toluene (10 ml). The reaction mixture was further stirred with reflux for 12 h. The product was filtered off from the cooled mixture and recrystallized from toluene. Yield 70%, mp 243–245 °C. White powder. ^{1}H NMR ($CDCl_3$): δ 8.27 (2H, s, OH), 7.77 (4H, d, J=8.9 Hz, C(O)ArH, *ortho*), 7.53 (2H, br s, NH), 7.45 (4H, d, J=8.9 Hz, C(O)ArH *meta*), 7.31 and 6.96 (8H, two s, ArH) 4.32 (4H, d, J=13.3 Hz, $ArCH_{ax}Ar$), 3.97 (4H, t, J=6.6 Hz, O–CH_2–CH_2–CH_3), 3.38 (4H, d, J=13.3 Hz, $ArCH_{eq}Ar$), 2.09 (4H, m, O–CH_2–CH_2–CH_3), 1.26 (6H, t, J=7.4 Hz, O–CH_2–CH_2–CH_3) 1.09 (18H, s, *t*-Bu). Anal. Calcd for $C_{56}H_{60}Cl_2N_2O_6$: C 72.47%, H 6.53%, N 3.02% Cl 7.64%. Found: C 72.32%, H 6.62%, N 3.18%, Cl 7.84%.

3.1.2. 5,17-Di(1-chloro-1-(4-chlorophenyl)methylidene-amino)-11,23-di-*tert*-butyl-25,27-dipropoxy-26,28-dihydroxycalix[4]arene 3. A mixture of amidocalixarene **2** (280 mg, 0.3 mmol) and phosphorus pentachloride (130 mg, 0.605 mmol) was refluxed in dry benzene (15 ml) for 14 h. A small amount of precipitate was filtered off. After the solvent and phosphorus oxychloride were removed in vacuo pure imidoylchloride **3** was obtained. Yield 92%. Yellow-brown moisture sensitive solid. ^{1}H NMR ($CDCl_3$): δ 8.10 (4H, d, J=8.4 Hz, C(O)ArH, *ortho*), 8.04 (2H, s, OH), 7.94 and 6.89 (8H, two s, Ar*H*) 7.45 (4H, d, J=8.4 Hz, C(O)ArH *meta*), 4.31 (4H, d, J=13.2 Hz, $ArCH_{ax}Ar$), 3.96 (4H, t, J=6.1 Hz, O–CH_2–CH_2–CH_3), 3.38 (4H, d, J=13.2 Hz, $ArCH_{eq}Ar$), 2.04 (4H, m, O–CH_2–CH_2–CH_3), 1.28 (6H, t, J=7.2 Hz, O–CH_2–CH_2–CH_3) 1.01 (18H, s, *t*-Bu)

3.1.3. 5,17-Di(5-(4-chlorophenyl)-1*H*-1,2,3,4-tetrazol-1-yl)-11,23-di-*tert*-butyl-25,27-dipropoxy-26,28-dihydroxy-calix[4]arene 5. To a boiled suspension of imidoylchloride **3** (190 mg, 0.2 mmol) in trimethylsilylazide (4 ml), 2 drops of $SnCl_4$ were added. The mixture was refluxed for 14 h (the reaction was followed by TLC). Mixture was cooled and precipitate was filtered off. Recrystalization from aceto-nitrile gave pure tetrazolecalixarene **5**. Yield 40%, mp 248–250 °C. Colorless crystals. ^{1}H NMR ($CDCl_3$): δ 8.72 (2H, s, OH) 7.55 (4H, d, J=8.5 Hz, C(O)ArH, *ortho*), 7.33 (4H, d, J=8.5 Hz, C(O)ArH, *meta*), 7.15 and 6.77 (8H, two s, ArH), 4.29 (4H, d, J=13.2 Hz, $ArCH_{ax}Ar$), 3.97 (4H, t, J=6.3 Hz, O–CH_2–CH_2–CH_3), 3.40 (4H, d, J=13.2 Hz, $ArCH_{eq}Ar$), 2.05 (4H, m, O–CH_2–CH_2–CH_3), 1.31 (6H, t, J=7.4 Hz, O–CH_2–CH_2–CH_3) 0.96 (18H, s, *t*-Bu). Anal. Calcd for $C_{56}H_{58}Cl_2N_8O_4$: C 67.95%, H 5.78%, N 11.46%, Cl 7.25%. Found: C 67.47%, H 6.12%, N 11.59%, Cl 7.63%.

3.1.4. 5,11,17,23-Tetra(4-chlorophenylcarboxamido)-25,26,27,28-tetrapropoxycalix[4]arene 7. This was obtained in a similar manner to compound **2** by the reaction of *p*-chlorobenzoylchloride (385 mg, 2 mmol) with tetra-aminocalixarene **6** (325 mg, 0.5 mmol) in toluene (35 ml). Analytically pure product precipitated from the reaction mixture. Yield 90%, mp 220–222 °C. Colorless crystals. ^{1}H NMR (DMSO-d_6): δ 9.93 (4H, s, NH), 7.82 (8H, d, J=8.5 Hz, C(O)ArH *ortho*), 7.47 (8H, d, J=8.5 Hz, C(O)ArH

meta), 7.21 (8H, s, ArH), 4.42 (4H, d, $J=13.0$ Hz, $ArCH_{ax}Ar$), 3.86 (8H, t, $J=7.5$ Hz, O–CH_2–CH_2–CH_3), 3.22 (4H, d, $J=13.0$ Hz, $ArCH_{eq}Ar$), 1.95 (8H, m, O–CH_2–CH_2–CH_3), 0.99 (12H, t, $J=7.3$ Hz, O–CH_2–CH_2–CH_3). Anal. Calcd $C_{68}H_{64}Cl_4N_4O_8$: C 67.66%, H 5.35%, N 4.64% Cl 11.75%. Found: C 67.82%, H 5.70%, N 4.89% Cl 11.67%.

3.1.5. 5,11,17,23-Tetra(1-chloro-1-(4-chlorophenyl)-methylideneamino)-25,26,27,28- tetrapropoxycalix[4]arene 8. This was obtained in a similar manner to compound **3** by the reaction of tetraamide **7** (360 mg, 0.3 mmol) with phosphorus pentachloride (250 mg, 1.21 mmol) in dry benzene (15 ml). Yield 85%. Yellow-brown moisture sensitive solid. ^{1}H NMR ($CDCl_3$): δ 7.86 (8H, d, $J=8.7$ Hz, C(O)ArH *ortho*), 7.27 (8H, d, $J=8.7$ Hz, C(O)ArH *meta*), 6.64 (8H, s, ArH), 4.51 (4H, d, $J=13.0$ Hz, $ArCH_{ax}Ar$), 3.93 (8H, t, $J=7.5$ Hz, O–CH_2–CH_2–CH_3), 3.25 (4H, d, $J=13.0$ Hz, $ArCH_{eq}Ar$), 2.03 (8H, m, O–CH_2–CH_2–CH_3), 1.04 (12H, t, $J=7.5$ Hz, O–CH_2–CH_2–CH_3).

3.1.6. 5,11,17,23-Tetra(5-(4-chlorophenyl)-1*H*-1,2,3,4-tetrazol-1-yl)-25,26,27,28-tetrapropoxycalix[4]arene 10. This was obtained in a similar manner to compound **5** by boiling imidoylchloride **8** (260 mg, 0,2 mmol) in trimethylsilylazide (4 ml) with catalytic amount of $SnCl_4$. Yield 55%, mp 198–200 °C (CH_3CN). Colorless solid. ^{1}H NMR ($CDCl_3$): δ 7.44 (8H, d, $J=8.4$ Hz, C(O)ArH *ortho*), 7,25 (8H, d, $J=8.4$ Hz, C(O)ArH *meta*), 6.69 (8H, s, ArH), 4.52 (4H, d, $J=13.8$ Hz, $ArCH_{ax}Ar$), 3.97 (8H, t, $J=7.5$ Hz, O–CH_2–CH_2–CH_3), 2.83 (4H, d, $J=13.8$ Hz, $ArCH_{eq}Ar$), 1.96 (8H, m, O–CH_2–CH_2–CH_3), 1.04 (12H, t, $J=7.4$ Hz, O–CH_2–CH_2–CH_3) Anal. Calcd for $C_{68}H_{60}Cl_4N_{16}O_4$: C 62.48%, H 4.63%, N 17.14%, Cl 10.80%. Found: C 62.30%, H 5.10%, N 16.70%, Cl 10.98%.

Single crystals of **10**·$2CH_3CN$ H_2O were obtained by slow crystallization from acetonitrile.

3.1.7. Bis-{((5,11,17,23-tetra(5-(4-chlorophenyl)-1*H*-1,2,3,4-tetrazol-1-yl)-25,26,27,28-tetrapropoxycalix[4]-arene)palladium dichloride}tris(acetonitrile) solvate 11. An aqueous solution (0.5 ml) of K_2PdCl_4 (25 mg, 0.08 mmol) was added under stirring to ligand **10** (50 mg, 0.04 mmol) dissolved in acetonitrile–chloroform (10:1 v/v) mixture (11 ml). The stirring was continued for 2 h and the solution was left for 3 days. The precipitate was filtered off, washed with cold acetonitrile and ethanol and dried in air. Yield 65%. Yellow microcrystalline solid. Anal. Calcd for $C_{142}H_{129}Cl_{12}N_{35}O_8Pd_2$: C 55.16%, H 4.21%, N 15.85%. Found: C 55.51%, H 3.98%, N 16.10%. Single crystals suitable for X-ray analysis was obtained by slow evaporation of solution obtained after filtration of first microcrystalline portion of complex **11**.

3.2. X-ray investigation

3.2.1. Crystal data for 10. $C_{68}H_{60}Cl_4N_{16}O_4$·$2CH_3CN$ H_2O Mr=1389.24; colorless, crystal size 0.70×0.50×0.25 mm, monoclinic $P2_1/c$, $a=16.4178(3)$ Å, $b=16.9687(3)$ Å, $c=25.4646(3)$ Å, $\beta=98.477(1)°$, $V=7017.0(2)$ Å^3, $Z=4$, $\rho_{calcd}=1.321$ g/cm^3; $2\theta_{max}=49.4°$. Intensity data were collected at 100(2) K on a Nonius KappaCCD diffractometer using Mo Kα radiation ($\lambda=0.71073$ Å). Lorentz and polarization corrections were applied and diffracted data were not corrected for absorption.[18] Structure was solved and refined using SHELXS-97[19] and SHELXL-97[19], respectively. Hydrogen atoms were calculated to their idealized positions and were refined as riding atoms. Three propyl groups of the calixarene are disordered over two sites (0.65/0.35, 0.84/0.16 and 0.54/0.46 occupancy factors, respectively). Two molecules of acetonitrile were located; one molecule is disordered over two positions (0.65/0.35). The final values of *R*-factors are $R_1=0.055$ for 9706 reflections [$I>2\sigma(I)$] and 0.073 for all 11909 data; final *wR* was 0.111. Residual electron density was between 0.939 and -0.782 eÅ^{-3}. The crystallographic data for this structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 276500.

3.2.2. Crystal data for complex 11. $C_{136}H_{120}Cl_{12}N_{32}O_8Pd_2$·$3CH_3CN$: Mr=3092.09; yellow, crystal size 0.40×0.23×0.05 mm, monoclinic $C2/c$, $a=43.710(2)$ Å, $b=14.0345(4)$ Å, $c=31.713(1)$ Å, $\beta=128.889(1)°$, $V=15143(1)$ Å^3, $Z=8$, $\rho_{calcd}=1.410$ g/cm^3; $2\theta_{max}=40.8°$. Intensity data were collected at 100(2) K on a Nonius KappaCCD diffractometer using Mo Kα radiation ($\lambda=0.71073$ Å). Lorentz and polarization corrections were applied and diffracted data were not corrected for absorption.[18] Structure was solved and refined using SHELXS-97[19] and SHELXL-97[19] respectively. Hydrogen atoms were calculated to their idealized positions and were refined as riding atoms. The final values of *R*-factors are $R_1=0.080$ for 6248 reflections [$I>2\sigma(I)$] and 0.104 for all 7435 data; final *wR* was 0.1264. Residual electron density was between 0.477 and -0.494 eÅ^{-3}. The crystallographic data for this structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 276501.

Acknowledgements

This research was supported by the National Academy of Sciences of Ukraine (Grant 5A/4-B) and the Polish Ministry of Science and Information Society Technologies (Grant 4 T09A 068 25).

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Tetrahedron

Synthetic protocols and building blocks for molecular electronics

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Received 29 June 2005; revised 6 September 2005; accepted 22 September 2005

Available online 19 October 2005

Abstract—Simple and readily accessible aryl bromides are useful building blocks for thiol end-capped molecular wires. Thus, 4-bromophenyl *tert*-butyl sulfide and 1-bromo-4-(methoxymethyl)benzene serve as precursors for a variety of oligo(phenylenevinylene) and oligo(phenyleneethynylene) wires via efficient synthetic transformations as presented in this paper.

1. Introduction

The development of molecular wires for molecular electronics has attracted immense interest in recent years.[1] Thus, molecules are designed to interconnect molecular devices, such as single electron transistors, electron turnstiles, molecular switches, and chemical sensors. Especially sp^2-carbon based molecular wires have been intensely targeted due to their conducting properties. Compared to semiconductors such as silicon, it is possible to fabricate much smaller and better defined carbon based nanodevices. Much work has focused on thiol-terminated conjugated π-systems, such as oligo(phenylenevinylene)s (OPVs),[2] oligo(phenyleneethynylene)s (OPEs),[3] and oligothiophenes.[4]

Some of us have recently developed several new procedures for the synthesis and applications of OPVs[5] that have been found to exhibit some of the best conducting properties.[6] In order to utilize a molecular wire in a device, it has to be placed between electrodes. One method is direct evaporation of the molecular wire into a nanogap.[2a] However, manufacture of stable devices with wires fixed between electrodes requires 'molecular alligator clips'. Adhesion to gold electrodes can be accomplished with terminal end-groups such as thiols.[2b]

It is important to establish how small changes in molecular structure will affect the single molecule conductivity. Parameters to vary are the nature of the wire (choice of conjugated π-system, alternating π- and σ-systems, non-covalent junctions, etc.), the wire length, the number of electrode attachment sites and the nature of these. Figure 1 shows schematically five important classes of molecular wires (**A**–**E**) with protected thiol end-groups.[7] The acetyl group has found general applicability as a thiol protecting

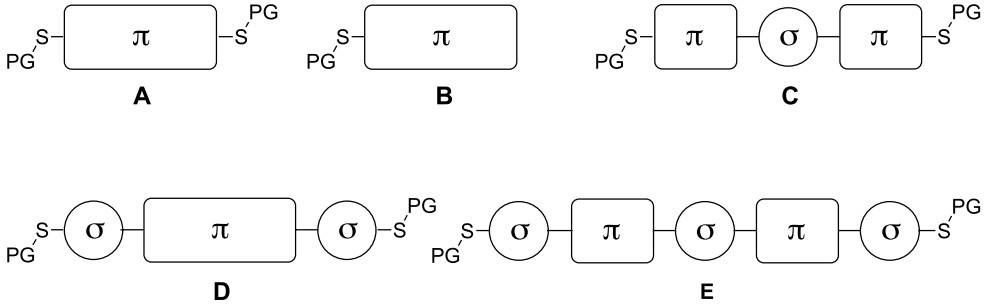

Figure 1. Schematic representation of five classes of molecular wires (**A**–**E**). PG = thiol protecting group.

Keywords: Molecular electronics; Oligo(phenylenevinylene)s; Oligo(phenyleneethynylene)s; Aryl thiols.
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doi:10.1016/j.tet.2005.09.106

group (PG), since it is readily cleaved in situ under mild basic conditions.[2b]

In this paper we present synthetic protocols for wires of type **A**, **B**, **D**, and **E**. Thus, we have developed: (i) a new synthesis of OPE3 with terminal acetylthio groups (class **A**) via a *tert*-butylthio precursor, a procedure that may be generalized to related molecules, (ii) new synthetic procedures for molecular wires where the conjugation is disrupted by methylene bridges (classes **D** and **E**), and (iii) efficient synthesis of unsymmetrical OPVs (class **B**).

In our previous synthesis of thiol end-capped molecular OPV wires,[5] we adopted an approach where the aryl thiol functionality was introduced as the *t*-Bu sulfide at the beginning of the synthetic sequence via the building block 4-bromophenyl *tert*-butyl sulfide (**1**) and maintained through the subsequent steps owing to the resistance of *t*-Bu-S-Ar to both strongly basic and acidic conditions. In a final step, the *t*-BuS group was converted into the AcS moiety by means of AcCl/BBr_3.[8] We became interested to employ the same approach to prepare acetyl-protected OPEs, providing an alternative procedure to that of Tour and co-workers.[9] It deserves mention that the lability of the acetyl protecting group has stimulated the exploitation of other protecting groups as well. Thus, recently Bryce and co-workers[10] successfully utilized cyanoethyl as a thiolate protecting group.

Disruption of the conjugated system or changes in the conjugation pathway may lead to significant changes in the tunnelling mechanism of the molecules inserted between metal electrodes.[2b,11] Several examples where the conjugation is broken within the wire (class **C**) have been reported by Tour and co-workers.[9] Synthetic methods for two-terminal wires where the conjugation is instead broken between the intact wire and the thiol end-caps are less common. To our knowledge, only one example of a two-terminal class **D** OPV3 (with –OBu substitution at the central phenylene) has been reported in the literature with a focus on the current-voltage characteristics rather than the synthesis.[12,13]

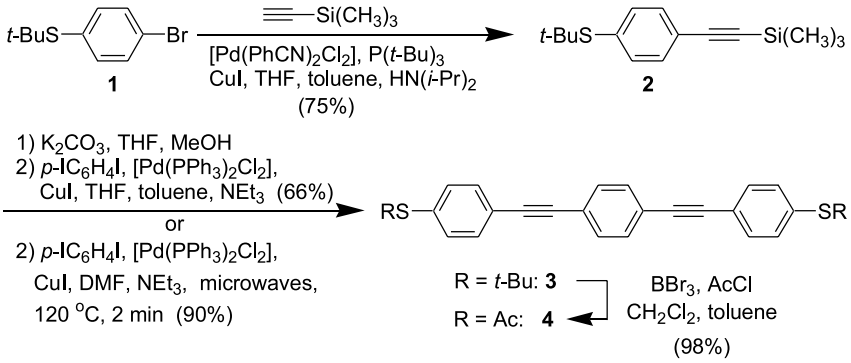
The next logical step in synthetic manipulations towards functional wires is further development of molecules having isolated aromatic units (π-islands) between thiols, again applying methylene spacers as isolating units between individual islands (class **E**).

Finally, we report the synthesis of unsymmetrical OPVs of class **B**. Highly ordered self-assembled monolayers (SAMs) of such molecules on electrode surfaces are interesting with respect to mediating electron transfer across the interfacial barrier represented by the monolayer.[4a,14]

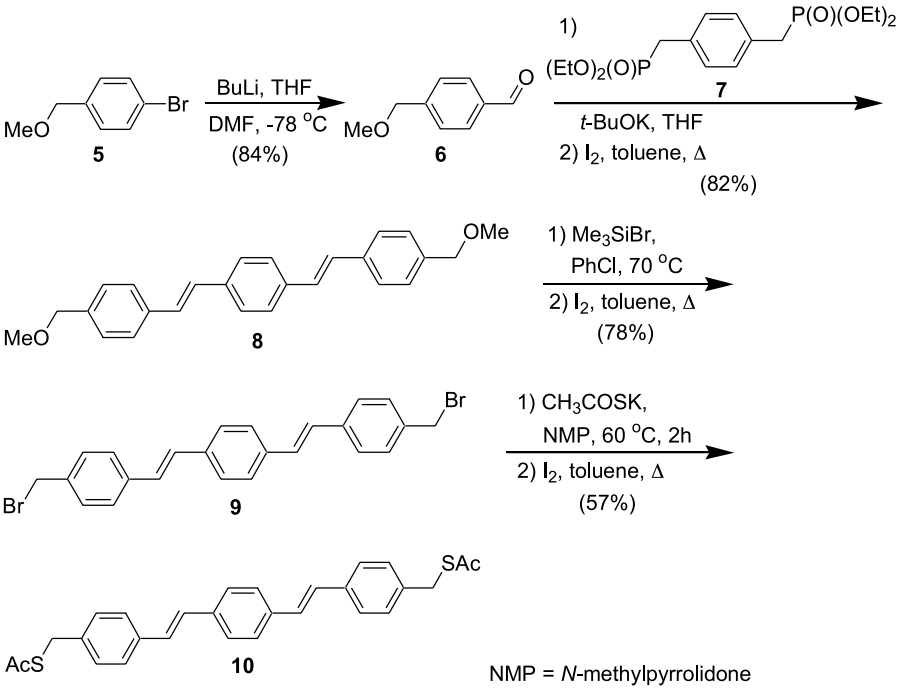
2. Results and discussion

The synthesis of SAc end-capped OPE3 proceeds according to Scheme 1. First, bromide **1** was subjected to a Pd-catalyzed cross-coupling with trimethylsilylacetylene, employing the [$Pd(PhCN)_2Cl_2$]/P(*t*-Bu)$_3$/CuI catalyst system. Hundertmark et al.[15] have shown that this system allows room temperature Sonogashira coupling[16] of aryl bromides with a wide variety of terminal acetylenes. Indeed, we managed to obtain **2** under these conditions in a yield of 75%.[17] This same compound was previously prepared by Mayor et al.[18] from the more reactive, but less accessible, 4-iodophenyl *tert*-butyl sulfide. After silyl deprotection using K_2CO_3 in THF/MeOH, **2** was subjected to a two-fold cross-coupling with 1,4-diiodobenzene, which afforded the OPE3 **3** in 66% yield. The yield was increased significantly, however, by employing microwave heating at 120 °C for 5 min, which gave **3** in 90%. This OPE was finally converted quantitatively into the acetyl-protected wire **4** by means of AcCl/BBr_3.

An AcS-CH_2 end-capped OPV3 was prepared according to Scheme 2. The synthesis starts from 1-bromo-4-(methoxymethyl)benzene **5**[19] (that we conveniently prepared from 4-bromobenzylbromide by treatment with sodium methoxide). Compound **5** was treated with butyllithium and DMF, which provided aldehyde **6**. Several procedures are available in the literature for synthesis of **6**,[20] but since the existing procedures involve either carcinogenic compounds,[20a] long reaction times (several days for one reaction),[20b] or a starting material not readily available,[20c] the present procedure is more convenient. The aldehyde was subsequently coupled with tetraethyl 1,4-xylylenediphosphonate **7**[21] in a typical Horner–Wadsworth–Emmons (HWE) reaction[22] upon treatment with potassium *tert*-butoxide. Treatment of the product with iodine in toluene provided the pure all-*trans* OPV3 **8**. Demasking this new wire with bromotrimethylsilane gave the dibromide **9** that was subsequently treated with potassium thioacetate to give the protected thiomethyl wire **10**.

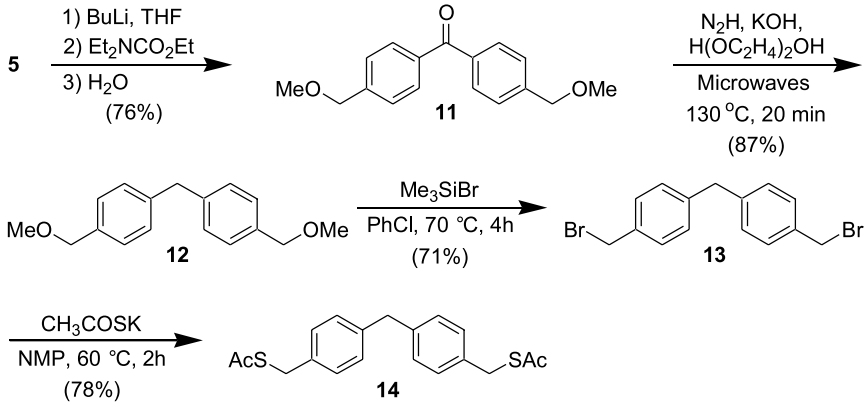


Scheme 1.

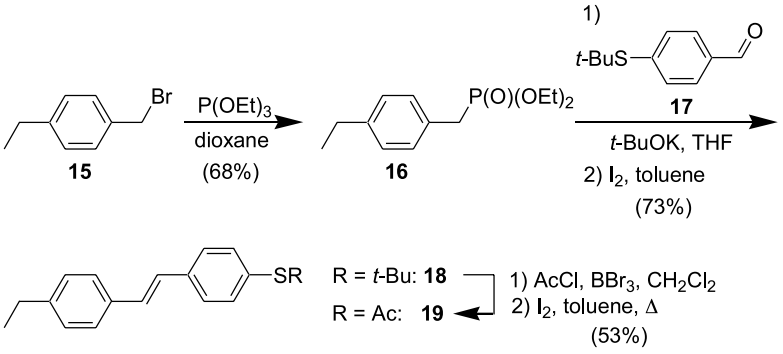


Scheme 2.

Synthesis of bis[4-(*S*-acetylthiomethyl)phenyl]methane (**14**) was carried out according to Scheme 3. First, Br/Li-exchange on **5** with butyllithium followed by reaction of the lithium reagent with ethyl *N*,*N*-diethylcarbamate[23] gave the ketone **11**. Subjecting **11** to a microwave-assisted Huang–Minlon modification[24] of the Wolff–Kishner procedure produced **12** containing a central methylene unit. Demasking the methoxymethyl functionalities by means of bromotrimethylsilane gave the dibromide **13**[25] that was treated with potassium thioacetate to provide the acetyl-protected wire **14** with three methylene bridges.



Scheme 3.



Scheme 4.

An unsymmetrical OPV wire was prepared in analogy to our previous two-terminal OPV synthesis (Scheme 4).[5a] The bromide **15**,[26] prepared from the corresponding alcohol,[27] was first converted to the phosphonate **16**. A HWE reaction between **16** and aldehyde **17** (obtained from **1**[5]) gave, after iodine-induced isomerization, the *trans*-stilbene **18**. Finally, the *tert*-butyl group was converted into an acetyl group to provide **19**.

3. Conclusion

In conclusion, we have devised efficient protocols for the synthesis of a selection of wires for molecular electronics applications. The protocols are both simple and reliable and may allow future synthesis of more complex systems. The successful development of molecular electronics and the establishment of structure-property relationships is strongly dependent on such synthetic advances.

4. Experimental

4.1. General experimental procedures

Thin-layer chromatography (TLC) was carried out using aluminium sheets pre-coated with silica gel 60F (Merck 5554). Column chromatography was carried out using silica gel 60F (Merck 9385, 0.040–0.063 mm). For microwave-assisted reactions, a CEM925110 Discover microwave oven was employed. Melting points were determined on a Büchi melting point apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian instrument. Samples were prepared using $CDCl_3$ purchased from Cambridge Isotope Labs. Electron impact ionisation mass spectrometry (EI-MS) was performed on a Varian MAT 311A. Fast atom bombardment (FAB) spectra were ontained on a Jeol JMS-HX 110 Tandem Mass Spectrometer in the positive ion mode using 3-nitrobenzyl alcohol (NBA) as matrix. Gas chromatography–Mass spectrometry (GC–MS) was performed on a HP5890 Series II plus gas chromatograph coupled with a HP5972 Series Mass analyzer. Microanalyses were performed at the Microanalytical Laboratory at the Department of Chemistry, University of Copenhagen.

4.1.1. 1-*tert*-Butylthio-4-trimethylsilylethynylbenzene (2). $[Pd(PhCN)_2Cl_2]$ (0.04 g, 0.104 mmol) and CuI (0.005 g, 0.026 mmol) were dissolved in dry and argon-degassed THF (2.5 mL) and toluene (2.5 mL) and stirred under a flow of argon for 10 min. Then $HN(i\text{-}Pr)_2$ (1 mL) and $P(t\text{-}Bu)_3$ (10% in hexane, 0.63 mL) were added followed by 1-bromo-4-(*tert*-butylthio)benzene **1** (1.25 g, 5 mmol) and trimethylsilylacetylene (0.85 g, 8.7 mmol). The dark solution was heated to 50 °C for 2 h. The reaction was stopped by pouring the reaction mixture onto H_2O (100 mL) and extracting with diethyl ether (3×100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to a yellow oil. Column chromatography (SiO_2, heptane) afforded **2** (994 mg, 75%) as a semi-crystalline oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.25 (s, 9H), 1.27 (s, 9H), 7.43 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 0.1, 31.0, 46.4, 96.0, 104.4, 123.4, 131.8, 133.5, 137.1. MS (EI) (%): *m*/*z* 262 (M^+, 36%), 206 (60%), 191 (100%). HR-MS (EI): *m*/*z* 262.1207 (M^+, calcd for $C_{15}H_{22}SSi$ 262.1211).

4.1.2. 4.1.2. Desilylation of 2. To a solution of **2** (0.335 g, 1.28 mmol) in MeOH (40 mL) and THF (7 mL) was added K_2CO_3 (0.190 g, 1.37 mmol), and the mixture was stirred for 45 min at room temperature. Then it was poured into water (200 mL) and extracted with diethyl ether (3×100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to an orange oil of 1-*tert*-butylthio-4-ethynylbenzene that can be cross-coupled without further purification. A pure sample (semi-crystalline oil) can be obtained by column chromatography (SiO_2, heptane/EtOAc gradual increase from 1:0 to 50:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 9H), 3.19 (s, 1H), 7.45 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9, 46.1, 78.6, 83.1, 123.4, 131.6, 131.8, 138.9. MS (GC): *m*/*z* 190 (M^+).

4.1.3. 1,4-Bis(4-*tert*-butylthiophenylethynyl)benzene (3). *Procedure (i)*. Compound **2** (0.307 g, 1.17 mmol) was desilylated according to the procedure described above. $[Pd(PPh_3)_2Cl_2]$ (0.020 g, 0.03 mmol) and CuI (0.010 g, 0.05 mmol) were dissolved in dry and argon-degassed THF (3.5 mL), toluene (3.5 mL), and NEt_3 (3 mL). The mixture was stirred under a flow of argon for about 30 min, whereupon the desilylated **2** and 1,4-diiodobenzene (0.126 g, 0.383 mmol) were added. The solution turned black immediately. After 30 min of stirring under argon, a white precipitate had formed. After 2 h the mixture was poured onto aqueous NH_4Cl and extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo until the precipitation of a white precipitate. Cooling on ice provided further precipitation, and the solid was filtered and washed with cold diethyl ether. The crude product was recrystallized from hot diethyl ether to afford **3** (115 mg, 66%) as a white powder. *Procedure (ii)*. Compound **2** (0.131 g, 0.50 mmol) was desilylated according to the procedure described above. $[Pd(PPh_3)_2Cl_2]$ (9.5 mg, 0.014 mmol) and CuI (5 mg, 0.026 mmol) were dissolved in dry and argon-degassed DMF (2 mL) and NEt_3 (1 mL). The mixture was stirred under a flow of argon for about 10 min and then transferred to a heavy-walled reaction vessel (sealed with a teflon septum), containing the desilylated **2** and 1,4-diiodobenzene (0.072 g, 0.22 mmol). The solution turned black immediately. The mixture was heated in a microwave oven (ramp time: 2 min, temperature: 120 °C, hold time: 5 min, pressure: 1.5 bar). After cooling to room temperature, the mixture was evaporated to dryness and purified by column chromatography (SiO_2, heptane). After recrystallization from hot heptane, the product **3** (90.5 mg, 90%) was obtained as a white powder. Mp 205–207 °C. Sublimation temperature 170 °C at 2×10^{-2} mbar. IR(KBr): ν (cm^{-1}) 2951, 2927, 2860, 1920, 1799, 1736, 1670, 1586, 1506, 1466, 1397, 1366, 1300, 1263, 1160, 1101, 1015, 833, 730, 535. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 18H), 7.51 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): 31.3, 46.8, 90.8, 91.1,

123.3, 123.6, 131.8, 131.8, 133.8, 137.5. HR-MS (FAB): *m/z* 454.1793 (M^+, calcd for $C_{30}H_{30}S_2$ 454.1789).

4.1.4. 1,4-Bis(4-acetylthiophenylethynyl)benzene (4). OPE3 **3** (0.100 g, 0.220 mmol) was dissolved in CH_2Cl_2 (10 mL) and toluene (10 mL). Then acetyl chloride (2 mL) and boron tribromide (1 M in CH_2Cl_2, 4 mL, 4 mmol) were added while stirring. The reaction was stirred for 3 h under inert atmosphere and then poured onto ice and extracted with CH_2Cl_2 (4×100 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography (SiO_2, heptane/EtOAc gradual increase from 10:1 to 0:1) to afford **4** as an off-white powder (96 mg, 98%). Mp 188–189 °C. IR(KBr): ν (cm^{-1}) 2922, 2852, 1916, 1696, 1591, 1513, 1480, 1422, 1407, 1396, 1354, 1304, 1269, 1117, 1013, 964, 873, 824, 695, 621, 542, 508. UV–vis ($CHCl_3$): λ_{max} (nm) (ε (M^{-1} cm^{-1})) 318 (sh, 50400), 332 (61800), 350 (sh, 38300). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 6H), 7.41 (d, J=7.8 Hz, 4H), 7.52 (s, 4H), 7.56 (d, J=7.8 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3, 90.6, 90.7, 123.0, 124.2, 128.3, 131.6, 132.2, 134.2, 199.4. HR-MS (FAB): *m/z* 426.0728 (M^+, calcd for $C_{26}H_{18}O_2S_2$ 426.0748).

4.1.5. 1-Bromo-4-(methoxymethyl)benzene (5). To a slurry of 4-bromobenzylbromide (37.5 g, 150 mmol) in MeOH (100 mL) was added NaOMe (25% in MeOH, 35.7 g, 0.165 mmol). The resulting reaction mixture was refluxed for 2 h under nitrogen and poured into water (350 mL) and extracted with pentane (3×50 mL). The pooled organic extracts were filtered through basic alumina (10 g) and evaporated. Bulb-to-bulb distillation (0.5 mmHg, air bath 100 °C) gave **5** (25.1 g, 83%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (s, 3H), 4.40 (s, 2H), 7.20 (d, J=8.2 Hz, 2H), 7.47 (d, J=8.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.0, 73.7, 121.3, 129.1, 131.3, 137.1. MS (EI, 70 eV) (%): *m/z* 202 (M^+, 15), 171 (37), 157 (5), 121 (100).

4.1.6. 4-(Methoxymethyl)benzaldehyde (6). Compound **5** (10.05 g, 50 mmol) was added dropwise under an argon atmosphere to a solution of butyllithium (2.5 M in hexanes, 20 mL, 50 mmol) in THF (50 mL) cooled in a dry ice/acetone bath. The reaction mixture was stirred at −78 °C for 15 min, then DMF (10 mL) was added in one portion, and stirring was maintained at room temperature for 30 min. The clear reaction mixture was poured into H_2O (200 mL) and extracted with pentane (3×50 mL). The combined organic layers were washed with H_2O (30 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg). Distillation at 77–79 °C (0.40–0.45 mmHg) in a column-free standard Claisen equipment gave **6** (6.28 g, 84%) as a colorless liquid. Purity >98% (GC–MS). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 3H), 4.50 (s, 2H), 7.46 (d, J=7.9 Hz, 2H), 7.83 (d, J=7.9 Hz, 2H), 9.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.3, 73.7, 127.5, 129.7, 135.6, 145.2, 191.8. MS (EI, 70 eV) (%): *m/z* 150 (M^+, 40), 135 (100), 121 (71). HR-MS (EI): *m/z* 150.0699 (M^+, calcd for $C_9H_{10}O_2$ 150.0681).

4.1.7. (*E*,*E*)-1,4-Bis[4-(methoxymethyl)styryl]benzene (8). To a solution of **6** (3.00 g, 20 mmol) and tetraethyl 1,4-xylylenediphosphonate **7** (3.78 g, 10 mmol) in THF (80 mL) cooled in an ice bath was added *t*-BuOK (2.47 g, 22 mmol) in small portions during a period of 10 min. The reaction mixture was further stirred at room temperature for 6 h under nitrogen and then poured into water (300 mL). A yellow material was filtered off, washed with H_2O, and dried in a vacuum oven (120 °C, 1 mmHg). The product was dissolved in the minimum amount of a boiling solution containing iodine in toluene (0.1 mM). Reflux was maintained for 12 h. By slow cooling at room temperature, the pure *trans*-stilbene **8** (3.05 g, 82%) precipitated as yellow crystals. Mp 259–260 °C. IR(KBr): ν (cm^{-1}) 3021, 2985, 2923, 2891, 2821, 2066, 1914, 1693, 1650, 1632, 1610, 1567, 1518, 1456, 1423, 1381, 1336, 1322, 1306, 1278, 1209, 1196, 1112, 1017, 970, 949, 927, 830, 803, 781, 713, 601, 549. Anal. Calcd for $C_{26}H_{26}O_2$: C, 84.29; H, 7.07. Found: C, 84.45; H, 7.06. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40 (s, 6H), 4.47 (s, 4H), 7.12 (s, 4H), 7.33 (d, J=8.1 Hz, 4H), 7.50 (s, 4H), 7.51 (d, J=8.1 Hz, 4H). Crystals not soluble enough for ^{13}C NMR. MS (EI, 70 eV) (%): *m/z* 370 (M^+, 100), 354 (10), 339 (17).

4.1.8. (*E*,*E*)-1,4-Bis[4-(bromomethyl)styryl]benzene (9). To a slurry of **8** (0.74 g, 2 mmol) in chlorobenzene (15 mL) was added bromotrimethylsilane (0.70 g, 4.6 mmol) and the resulting slurry was stirred at 75 °C for 4 h under nitrogen. The grey slurry was poured into MeOH (150 mL), and a yellow powder was filtered off. The product was dissolved in the minimum amount of a boiling solution containing iodine in toluene (0.1 mM). Reflux was maintained for 12 h. By slow cooling at room temperature, the product **9** (0.73 g, 78%) precipitated as yellow crystals. Mp >280 °C. Anal. Calcd for $C_{24}H_{20}Br_2$: C, 61.56; H, 4.31. Found: C, 61.20; H, 4.21. Crystals not soluble enough for NMR. MS (EI, 70 eV) (%): *m/z* 468 (M^+, 63), 389 (100), 308 (26).

4.1.9. (*E*,*E*)-1,4-Bis[4-(*S*-acetylthiomethyl)styryl]benzene (10). A slurry of **9** (0.23 g, 0.5 mmol) and potassium thioacetate (0.14 g, 1.2 mmol) in NMP (15 mL) was heated at 60 °C for 2 h. The clear solution was poured into ice (200 g). Filtration and separation on silica gel 60F (30 g) by means of CH_2Cl_2 gave yellow crystalline material which was dissolved in the minimum amount of a boiling solution containing iodine in toluene (0.1 mM). Reflux was maintained for 12 h. By slow cooling at room temperature, the product **10** (0.13 g, 57%) precipitated as light-yellow plates. Mp 257–258 °C. Anal. Calcd for $C_{28}H_{26}O_2S_2$: C, 73.33; H, 5.71; S, 13.98. Found: C, 73.32; H, 5.70; S, 13.84. IR(KBr): ν (cm^{-1}) 3015, 2909, 1910, 1698, 1654, 1604, 1515, 1422, 1352, 1335, 1141, 1099, 1015, 961, 947, 889, 833, 779, 751, 701, 633, 570, 546, 540. UV–vis ($CHCl_3$): λ_{max} (nm) (ε (M^{-1} cm^{-1})) 350 (sh, 61100), 362 (68700), 383 (sh, 43800). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H), 4.13 (s, 4H), 7.08 (s, 4H), 7.28 (d, J=8.2 Hz, 4H), 7.45 (d, J=8.2 Hz, 4H), 7.49 (s, 4H). Crystals not soluble enough for ^{13}C NMR. MS (EI, 70 eV) (%): *m/z* 458 (M^+, 100), 415 (11), 383 (72), 339 (14).

4.1.10. 4,4′-Bis(methoxymethyl)benzophenone (11). Compound **5** (10.05 g, 50 mmol) was added dropwise under an argon atmosphere to a solution of butyllithium (2.5 M in hexanes, 20 mL, 50 mmol) in THF (50 mL) cooled in a dry ice/acetone bath. After stirring the reaction mixture at −8 °C for 15 min, ethyl *N*,*N*-diethylcarbamate

(3.63 g, 25 mmol) was added during a 10 min period in a dropwise fashion. After stirring the reaction mixture at −78 °C for an additional 15 min, H_2O (10 mL) was added dropwise, and the reaction mixture was poured into H_2O (300 mL) and extracted with pentane (3×50 mL). The combined organic layers were washed with H_2O (30 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg). Bulb-to-bulb distillation (0.05 mmHg, air bath 200 °C) afforded **11** (5.14 g, 76%) as a colorless liquid that crystallized into white crystals upon standing. Mp 45–46 °C. Purity >98% (GC–MS). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.95; H, 6.72. IR(KBr): ν (cm^{-1}) 3037, 3000, 2982, 2926, 2893, 2861, 2824, 2732, 2069, 1934, 1824, 1733, 1651, 1609, 1571, 1510, 1469, 1455, 1409, 1379, 1310, 1277, 1211, 1195, 1175, 1148, 1104, 1017, 972, 928, 854, 841, 819, 754, 681, 629, 487, 474, 436. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (s, 6H), 4.48 (s, 4H), 7.40 (d, J=8.2 Hz, 4H), 7.74 (d, J=8.2 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.1, 73.7, 126.8, 129.8, 136.5, 142.7, 195.7. MS (EI, 70 eV) (%): *m/z* 270 (M^+, 25), 255 (4), 225 (7), 210 (34), 195 (7), 180 (18), 165 (18), 149 (100).

4.1.11. 4,4′-Bis(methoxymethyl)diphenylmethane (12). A slurry of ketone **11** (1.08 g, 4 mmol), KOH (1.35 g, 24 mmol), and hydrazine monohydrate (0.30 g, 6 mmol) in diethylene glycol (25 mL) was stirred at room temperature for 10 min in order to become homogeneous and then heated in a microwave oven for 20 min at 130 °C under the influence of 20 W microwaves. The clear colorless solution was poured into H_2O (200 mL) and extracted with pentane (3×50 mL). The combined organic layers were washed with H_2O (30 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation (30 °C, 20 mmHg). Bulb-to-bulb distillation (0.05 mmHg, air bath 200 °C) afforded **12** (0.89 g, 87%) as a colorless liquid. Purity >98% (GC–MS). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.78; H, 7.66. IR(KBr): ν (cm^{-1}) 3050, 3010, 2983, 2925, 2894, 2852, 2820, 2736, 1912, 1803, 1721, 1656, 1612, 1577, 1512, 1450, 1417, 1381, 1364, 1304, 1278, 1193, 1155, 1099, 1021, 967, 919, 857, 806, 754, 616, 579, 485. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38 (s, 6H), 3.98 (s, 2H), 4.43 (s, 4H), 7.17 (d, J=8.1 Hz, 4H), 7.26 (d, J=8.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.2, 57.9, 74.4, 127.9, 128.8, 135.8, 140.4. MS (EI, 70 eV) (%): *m/z* 256 (M^+, 47), 225 (19), 211 (26), 179 (42), 121 (100).

4.1.12. 4,4′-Bis(bromomethyl)diphenylmethane (13). To a mixture of **12** (0.51 g, 2 mmol) and chlorobenzene (10 mL) was added bromotrimethylsilane (0.67 g, 4.4 mmol). The resulting yellow slurry was stirred at 75 °C for 4 h under nitrogen and poured into H_2O (100 mL). The phases were separated, and the aqueous phase was further extracted with toluene (2×20 mL). The combined organic extracts were filtered through silica gel 60F (10 g) by means of CH_2Cl_2–pentane (1/9). Evaporation afforded **13** (0.89 g, 87%) as white crystals. Mp 146–147 °C (lit.:[25] 151.5–153.5 °C). Anal. Calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.99. Found: C, 51.18; H, 3.92. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 2H), 4.48 (s, 4H), 7.15 (d, J=8.1 Hz, 4H), 7.32 (d, J=8.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.3, 41.2, 129.1, 129.2, 135.6, 141.0. MS (EI, 70 eV) (%): *m/z* 354 (M^+, 5), 275 (100), 194 (100).

4.1.13. 4,4′-Bis(*S*-acetylthiomethyl)diphenylmethane (14). A slurry of dibromide **13** (0.35 g, 1 mmol) and potassium thioacetate (0.25 g, 2.2 mmol) in NMP (10 mL) was heated at 60 °C for 2 h. The clear colorless solution was poured into ice (100 g) and extracted with Et_2O (3× 20 mL). The combined organic layers were washed with H_2O (30 mL) and evaporated. Separation on silica gel 60F (20 g) by means of CH_2Cl_2 gave a white crystalline material upon evaporation. Recrystallization from heptane afforded **14** (0.27 g, 78%) as white needles. Mp 90–91 °C. Anal. Calcd for $C_{19}H_{20}O_2S_2$: C, 66.25; H, 5.85; S, 18.65. Found: C, 66.25; H, 5.84; S, 18.69. IR(KBr): ν (cm^{-1}) 3045, 3002, 2920, 2832, 1912, 1693, 1510, 1431, 1411, 1359, 1241, 1130, 1098, 1023, 1000, 964, 914, 866, 839, 823, 774, 728, 718, 687, 626, 568, 541, 513, 475. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 6H), 3.90 (s, 2H), 4.08 (s, 4H), 7.09 (d, J=6.3 Hz, 4H), 7.19 (d, J=6.3 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.2, 33.0, 41.1, 128.8, 129.0, 135.2, 139.9, 195.0. MS (EI, 70 eV) (%): *m/z* 344 (M^+, 21), 301 (8), 269 (100).

4.1.14. Diethyl 4-ethylbenzylphosphonate (16). A solution of bromide **15** (4.36 g, 22 mmol) and triethylphosphite (5 g, 30 mmol) in dioxane (40 mL) was refluxed under nitrogen for 12 h. The solvent was evaporated in vacuo, and bulb-to-bulb distillation (0.1 mbar, air bath 180 °C) gave the phosphonate **16** (3.8 g, 68%) as a colorless liquid. Anal. Calcd for $C_{13}H_{21}O_3P$: C, 60.93; H, 8.26. Found: C, 60.51; H, 8.69. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J=7.2 Hz, 3H), 1.24 (t, J=7.2 Hz, 6H), 2.62 (q, J=7.2 Hz, 2H), 3.23 (d, J=21 Hz, 2H), 4.01 (q, J=7.2 Hz, 4H), 7.13 (d, J=8.1 Hz, 2H), 7.22 (d, J=8.2, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 15.4, 16.2 (d, J=6 Hz), 28.3, 33.1 (d, J=138 Hz), 61.7 (d, J=7 Hz), 127.8 (d, J=3 Hz), 128.0 (d, J=3 Hz), 129.5 (d, J=3 Hz), 142.6 (d, J=3 Hz). MS–S (EI) (%): *m/z* 256 (M^+, 100).

4.1.15. *Trans*-4-*tert*-butylthio-4′-ethylstilbene (18). A solution of phosphonate **16** (0.77 g, 3 mmol) and aldehyde **17** (0.58 g, 3 mmol) in freshly distilled THF (50 mL) was cooled to 0 °C, and potassium *tert*-butoxide (0.37 g, 3.3 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and poured into water. The white crystalline precipitate was filtered off and dried in vacuo. Recrystallization and isomerization to the *trans* compound was achieved by refluxing the compound for 6 h in toluene (5 mL) containing iodine (0.1 mM), thus affording **18** (0.65 g, 73%). Mp 90.3–91.6 °C. Anal. Calcd for $C_{20}H_{24}S$: C, 81.02; H, 8.16; S, 10.82. Found: C, 80.55; H, 8.40; S, 10.51. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J=7.2 Hz, 3H), 1.30 (s, 9H), 2.62 (q, J=7.2 Hz, 2H), 7.04 (d, J= 16 Hz, 1H), 7.14 (d, J=16 Hz, 1H), 7.20 (d, J=7.7 Hz, 2H), 7.42–7.53 (m, 6H). ^{13}C (62.9 MHz, $CDCl_3$) δ 15.4, 28.6, 30.9, 46.1, 126.2, 126.5, 126.9, 128.1, 129.5, 131.6, 134.5, 137.6, 137.9, 144.1. MS (FAB): *m/z* 296 (M^+).

4.1.16. *Trans*-4-acetylthio-4′-ethylstilbene (19). To a solution of **18** (0.33 g, 1.1 mmol) and acetyl chloride (1 mL) in CH_2Cl_2 (20 mL) was added BBr_3 (1.5 mmol, 1 M in CH_2Cl_2). The black solution was stirred under

nitrogen for 2 h and poured into ice/water (100 mL). The precipitate was purified using coloumn chromatography (SiO_2, CH_2Cl_2). The product containing fraction was recrystallized and isomerized to the *trans* compound by refluxing the compound for 6 h in toluene (5 mL) containing iodine (0.1 mM). The product **19** precipitated as white crystals (170 mg, 53%). Mp 98.5–101.3 °C. Anal. Calcd for $C_{15}H_{18}OS$: C, 76.56; H, 6.42; S, 11.35. Found: C, 76.44; H, 6.26; S, 11.24. IR(KBr): ν (cm^{-1}) 3019, 2961, 2928, 2870, 1911, 1704, 1587, 1508, 1455, 1411, 1350, 1179, 1121, 1008, 963, 831, 681, 617, 546. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, $J=7.2$ Hz, 3H), 2.42 (s, 3H) 2.62 (q, $J=7.2$ Hz, 2H), 7.05 (d, $J=17$ Hz, 1H), 7.14 (d, $J=17$ Hz, 1H), 7.21 (d, $J=8.7$ Hz, 2H), 7.39 (d, $J=8.7$ Hz, 2H) 7.45 (d, $J=8.7$ Hz, 2H), 7.54 (d, $J=8.7$ Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 15.4, 28.6, 30.1, 126.4, 127.6, 126.9, 128.2, 130.1, 134.3, 134.6, 138.7, 144.3, 194.1; One signal overlapping. MS (EI) (%): *m/z* 282 (M^+, 55), 240 (100), 225 (25).

Acknowledgements

This research was supported by EC FP6 funding (contract no. FP6-2004-IST-003673, CANEL). This publication reflects the views of the authors and not necessarily those of the EC. The Community is not liable for any use that may be made of the information contained herein. Moreover, the Danish Technical Research Council (STVF, grant # 26-01-0033) is gratefully acknowledged. We thank Niels V. Holst for recording UV–vis spectra.

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Deracemisation of aryl substituted α-hydroxy esters using *Candida parapsilosis* ATCC 7330: effect of substrate structure and mechanism

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Received 29 June 2005; revised 2 September 2005; accepted 22 September 2005

Available online 25 October 2005

Abstract—*Candida parapsilosis* ATCC 7330 was found to be an efficient biocatalyst for the deracemisation of aryl α-hydroxy esters (65–85% yield and 90–99% ee). A variety of aryl and aryl substituted α-hydroxy esters were synthesized to reflect steric and electronic effects on biocatalytic deracemisation. The mechanism of this biocatalytic deracemisation was found to be stereoinversion.

1. Introduction

Optically pure α-hydroxy esters are important building blocks for the asymmetric synthesis of a wide variety of bioactive molecules.[1] In particular, enantiomerically pure 2-hydroxy-4-phenylbutanoic acid/ester is an important pharmaceutical intermediate, which finds widespread use in the synthesis of drugs like anti-hypertensives and ACE inhibitors.[2] Several methods, chemical[3,4] and enzymatic[5] have been reported for the synthesis of aryl α-hydroxy esters. Biocatalytic preparation of optically pure α-hydroxy esters by lipase mediated resolution of racemic α-hydroxy esters[6,7] and biocatalytic asymmetric reduction of α-oxo esters[8] is known. Enzymatic resolution can result in a maximum theoretical yield of only 50% for each enantiomer. In order to increase the yield of one enantiomer beyond 50%, the starting racemate can be deracemised. Deracemisation is a method by which a single enantiomer is obtained from a racemic mixture.[9] Preparation of enantiomerically pure compounds by dynamic kinetic resolution is one method for deracemisation.[10,11] Backvall et al. reported enzymatic resolution in combination with metal-catalysed racemisation of α-hydroxy esters.[12] Biocatalytic deracemisation of α-hydroxy acids and secondary alcohols can employ either whole cells or isolated enzymes.[13–20] Racemic mandelic acid was deracemised using a two enzyme system[13] and (*R*)-3-pentyn-2-ol was obtained from the corresponding racemic alcohol by the use of *Nocardia fusca*.[14] Arylethanols were deracemised using *Geotrichum candidum*[15,16] and *Sphingomonas pausimobilis*.[17] Plant cell cultures were used for the deracemisation of various aromatic alcohols.[18] 1,2-Diols were deracemised using *Corynosporium cassiicola* DSM 6247520[19] and (*S*)-1,2-pentanediol was produced from the racemic 1,2-diol using *Candida parapsilosis*.[20] We have used *C. parapsilosis* ATCC 7330 successfully to deracemise 2-hydroxy-4-phenylbutanoic esters,[21] which are versatile chiral synthons given the fact that they have a –COOR' functional group in addition to the –OH group. The only other α-hydroxy acid/ester studied as a substrate for biocatalytic deracemisation so far is mandelic acid and its derivatives, and this was achieved using a two-enzyme system.[13] To study the scope of *C. parapsilosis* ATCC 7330 as a general biocatalyst for the deracemisation of α-hydroxy esters, different types of α-hydroxy esters were synthesized for this study. Methods reported in the literature were modified to prepare 2-hydroxy-4-arylbutanoic and but-3-enoic esters with a view to increase the number of functional groups in the substrates and study the selectivity of this biocatalytic reaction. This paper reports the modifications made for the synthesis of the racemic substrates, their separation using chiral HPLC, deracemisation and the mechanism of deracemisation by *C. parapsilosis* ATCC 7330 to give optically pure α-hydroxy esters.

2. Results and discussion

2.1. Synthesis of substrates

During our attempts to synthesise racemic α-hydroxy esters, which were used as substrates for biocatalytic

Keywords: Deracemisation; Chiral HPLC; *Candida parapsilosis* ATCC 7330; Stereoinversion; Alpha hydroxy esters.
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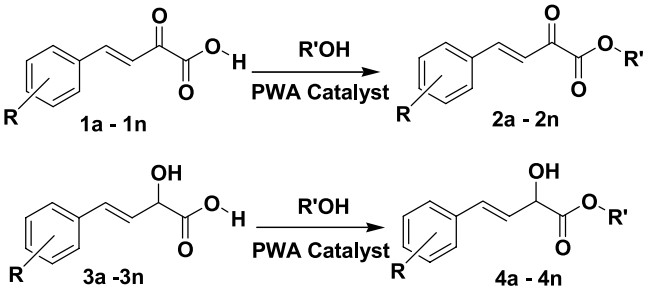
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.104

deracemisation, methods were developed by modifications to the available literature to give the great advantage of reduced reaction times and high yields of the target esters. Thus, the modifications mainly include the use of microwave irradiation for the synthesis and the use of phosphotungstic acid—a solid acid for esterification.

2.2. Esterification of 2-oxo-4-arylbut-3-anoic acid and 2-hydroxy-4-arylbut-3-enoic acid using phosphotungstic acid

Use of diazomethane for esterification is known for the preparation of α-oxo esters[22a] but these reactions require careful handling and dry conditions. α-Hydroxy esters can be prepared by Grignard reaction, which also requires stringent conditions and expensive reagents.[22b] Both these problems were overcome by employing a suitable catalyst viz. a heteropoly acid, which has been reported for a number of esterification reactions.[23]

The main reason for employing a heteropoly acid in esterification reactions is its Keggin structure, which helps in the controlled release of protons.[23] Heteropoly acids act as solid catalysts for both homogeneous and heterogeneous reactions due to their high acid strength and high thermal stability. These catalysts can be recovered after the reactions and reused for multiple cycles without loss in activity. Phosphotungstic acid—a heteropoly acid was used for esterifying various 2-oxo-4-arylbut-3-enoic acids (**1a**–**1n**) and 2-hydroxy-4-arylbut-3-enoic acids (**3a**–**3n**) with different alcohols. The reaction was carried out using a Dean–Stark apparatus in dry toluene at 90 °C for 6–10 h (Scheme 1). The yields of the final 2-oxo esters (**2a**–**2n**) and 2-hydroxy esters (**4a**–**4n**) ranged from 50–85 and 63–80%, respectively (Table 1).



Scheme 1.

2.3. Synthesis of alkyl 2-hydroxy-3-arylpropionates

Alkyl 2-hydroxy-3-arylpropionates have been prepared by various methods.[24a–h] The most common methods are reduction of α-keto esters,[24a,b] hydrolysis of α-halo esters,[24c] rearrangement of α-keto acetals,[24d] oxidation of ketene silyl acetals,[24e] ring opening of epoxy esters with subsequent reduction of the resulting iodohydrins[24f,g] and regioselective deoxygenation of cyclic thionocarbonates of 2,3-dihydroxy esters.[23h] The main drawback in the reported methods is the difficulty in obtaining starting materials.[24d–h]

The preparation of 2-hydroxy-3-arylpropanoic esters as reported by Dalla et al.,[25] utilizes azalactones, which are convenient starting materials, but the reaction takes 4–24 h and results in low yields of the target esters. Azalactones can be obtained by microwave irradiation of hippuric acid as the starting material.[26] The second step, that is, hydrolysis of the azalactones, gives α-keto acids[27] from which the target α-hydroxy esters can be obtained by two different methods—(i) reduction of the α-keto-enol acid using Zn–Hg metal[27] followed by esterification and (ii) esterification of the α-keto-enol acid followed by reduction of the corresponding α-keto ester using sodium borohydride.[25] Both these methods have disadvantages—the first uses toxic metals while the second method lacks chemoselectivity, that is, the reduction of the ester and keto groups, which results in the diol. In our approach, the synthesis of various substituted 2-hydroxy-4-phenylpropionic esters using azalactones (**1a**–**1k**) resulted in good yields of the product (73–86%). Briefly, the procedure involves treating a mixture of aldehydes with *N*-acetyl glycine in the presence of sodium acetate and acetic anhydride under microwave irradiation using a domestic microwave oven. The major advantage of this method is the short reaction time of 3–5 min. Reduction of the keto-enol of the acid using sodium borohydride in alkaline medium at 5–10 °C for 1–2 h results in the formation of the corresponding saturated α-hydroxy acid (**3a**–**e** and **3h**) in good yields (68–87%). The α-hydroxy acids thus obtained were treated with alcohols in the presence of phosphotungstic acid metal catalyst in toluene at 90 °C for 6–10 h to give the corresponding esters (**4a**–**e** and **4h**) (Scheme 2) in good yields (73–86%) (Table 2).

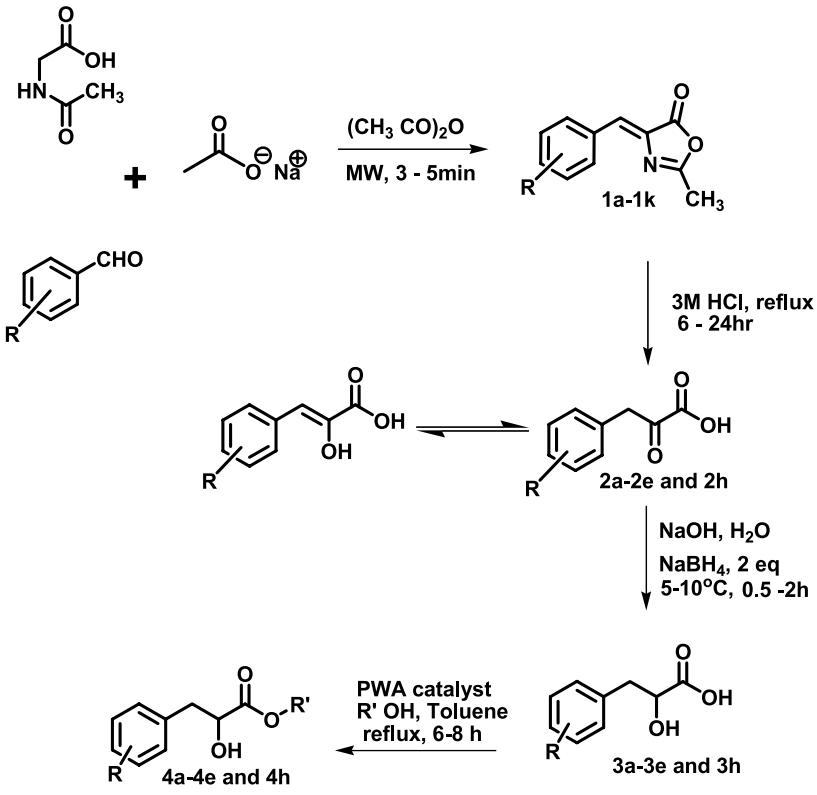
Table 1. Esterification of 2-oxo-4-arylbut-3-enoic acids (**1a**–**1n**) and 2-hydroxy-4-arylbut-3-enoic acids (**3a**–**3n**) using phosphotungstic acid as catalyst

R	R^1		Yield (%)		Yield (%)
H	Me	**2a**	75	**4a**	80
H	Et	**2b**	77	**4b**	78
p-Cl	Me	**2c**	81	**4c**	75
p-Cl	Et	**2d**	78	**4d**	73
p-Me	Me	**2e**	85	**4e**	70
p-Me	Et	**2f**	81	**4f**	73
o-Cl	Me	**2g**	64	**4g**	71
o-Cl	Et	**2h**	63	**4h**	65
m-NO_2	Me	**2i**	68	**4g**	75
m-NO_2	Et	**2j**	67	**4j**	77
2,4-DiCl	Me	**2k**	69	**4k**	75
2,4-DiCl	Et	**2l**	75	**4l**	79
2,5-DiOMe	Me	**2m**	55	**4m**	63
2,5-DiOMe	Et	**2n**	50	**4n**	64

3. Separation of racemic α-hydroxy esters by chiral HPLC

3.1. Direct separation

All the racemic α-hydroxy esters synthesized for biocatalytic deracemisation were resolved on a chiral column using HPLC. The direct separation of enantiomers using a chiral stationary phase (CSP) by high-performance liquid chromatography (HPLC) is a powerful, versatile and convenient method.[28] Solutions of racemic α-hydroxy esters (1 mg ml^{-1}) were prepared in the eluent for the separations.



Scheme 2.

Table 2. Synthesis of alkyl 2-hydroxy-3-arylpropionates

S. no.	R	Time (min)	Yield (%) **1**	R^1	Yield (%) **3**	Yield (%) **4**
a	H	4	92	Et	85	86
b	*p*-Cl	4	94	Me	82	83
c	2,4-DiCl	5	65	Me	68	79
d	*o*-NO_2	3	85	Me	75	75
e	*m*-NO_2	3	93	Me	79	73
f	*p*-NO_2	3	95	—	—	—
g	*p*-$OCOCH_3$	4	84	—	—	—
h	*p*-Me	4	90	Et	87	85
i	2,5-DiOMe	5	60	—	—	—
j	*o*-OMe	5	65	—	—	—
k	1-Naphthyl[a]	5	60	—	—	—

[a] Aryl, 1-naphthyl.

The chiral columns used in this study for the direct separation of racemic α-hydroxy acid esters (**3a**–**3v**) (Table 3) (Fig. 1) were cellulose tris(3,5-dimethylphenylcarbamate) (Chiralcel OD-H) column and cellulose tris(4-methylbenzoate) (Chiralcel OJ-H) column.

Twenty two racemic α-hydroxy esters were resolved by chiral HPLC. Compounds **3a**, **3b**, **3i**, **3j′**, **3m**, **3o**, **3p**, **3s**, **3u** and **3v** on OD-H, **3c**, **3d**, **3e**, **3f**, **3g**, **3g′**, **3h**, **3j**, **3k**, **3l**, **3n**, **3q** and **3t** on OJ-H (Table 4). The retention factor (k'), separation factor (α) and resolution (R_s) of every solute was regulated over a wide range by the addition of 2-propanol. Enantiomeric separation of **3a**–**3v** was achieved by varying the composition of hexane/isopropanol in the range 99:1–93:7. Increasing the concentration of 2-propanol in the mobile phase decreased the retention times (e.g., **3g** and **3g′**) and the column behaved as a normal-phase column. Compounds (**3c**–**3p**) are resolved for the first time in detail with complete optimization.

As can be inferred from Table 4, the OJ-H column gave good separation of unsaturated *p*-substituted; 2,4- and 2,5-substituted 2-hydroxy-4-arylbut-3-enoates (**3c**–**3f**, **3g**–**h**, **3l** and **3m**), whereas for *meta*-substituted 2-hydroxy-4-arylbut-3-enoates (**3m** and **3o**), OD-H column proved to be better. For unsubstituted saturated 2-hydroxy-4-arylbutanoates (**3q**–**3t**), and 2-hydroxy-3-arylpropanoates (**3u**–**3v**), *ortho*-substituted 2-hydroxy-4-arylbut-3-enoates (**3a**–**b** and **3j**), enantiomeric separation was achieved on both OJ-H and OD-H columns (Table 4). In all the cases, base line separation was achieved with good separation factors ($\alpha > 1$).

3.2. Effect of polar modifiers

In order to study the effect of polarity of the eluent on separation of racemic 2-hydroxy esters, hexane was used with either 2-propanol or ethanol as polar modifiers. Both, CSPs of cellulose derivatives and the polar modifier (alcohols) have the ability to form hydrogen bonds.[29]

Table 3. Ethyl and methyl esters of racemic 2-hydroxy-4-arylbut-3-enoic acids (**1**–**16**), 2-hydroxy-4-arylbutanoic acids (**17**–**20**) and 2-hydroxy-3-arylpropanoic acids (**21**–**22**)

S. no.	C. no.[a]	R	R′
1	3a	H	CH_3
2	3b	H	CH_2CH_3
3	3c	*p*-Cl	CH_2CH_3
4	3d	*p*-Cl	CH_3
5	3e	*p*-Me	CH_3
6	3f	*p*-Me	CH_2CH_3
7,7a	3g,3g′	2,4-Di Cl	CH_3
8	3h	2,4-Di Cl	CH_2CH_3
9,9a	3i,3i′	*o*-Cl	CH_3
10,10a	3j,3j′	*o*-Cl	CH_2CH_3
11	3k	1-Naphthyl	CH_3
12	3l	2,5-OMe	CH_2CH_3
13	3m	*m*-NO_2	CH_2CH_3
14	3n	2,5-OMe	CH_3
15	3o	*m*-NO_2	CH_3
16	3p	*p*-Cl[b]	$CH_2C_6H_5$
17	3q	*p*-Cl	CH_2CH_3
18	3r	*p*-Cl	CH_3
19	3s	*p*-Me	CH_3
20	3t	*p*-Me	CH_2CH_3
21	3u	H[b]	CH_2CH_3
22	3v	*p*-Me	CH_2CH_3

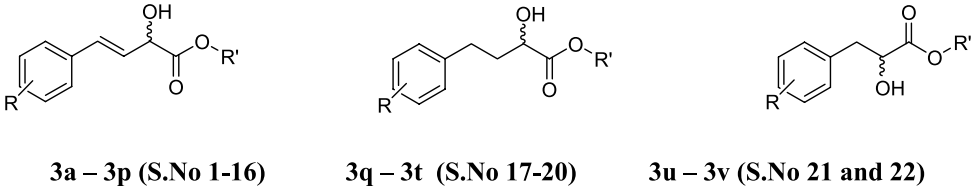
[a] Compound number.
[b] Acylated on hydroxy functional group.

Competition takes place between the analyte and alcohol for the chiral sites of the CSP. The enantiomeric separation of **3b**, **3c** and **3e** on OD-H and OJ-H columns with hexane/alcohol (ethanol or isopropanol) (98:2) as the mobile phase eluent showed the following results. Good enantiomeric separation for compound **3b** was achieved on the OD-H column while compounds **3c** and **3f** were resolved on the OJ-H column. Isopropanol improved the separation factor (α) for all three compounds **3b**, **3c** and **3f** when separated on Chiralcel OD-H and/or OJ-H columns. This can be clearly understood from the considerable decrease in retention time of the analyte when ethanol was used as polar modifier as compared to 2-propanol, on OD-H and OJ-H columns. Enantiomeric resolution (α) was higher for isopropanol ($\alpha > 1$) than for ethanol ($\alpha \sim 1$ or < 1). This improvement in resolution as the size of the alcohol is increased at constant composition of mobile phase has been attributed to the decrease in the capacity of larger alcohols to compete for hydrogen bonding sites because of steric hindrance.[30]

4. Deracemization of various aryl α-hydroxy esters by the whole cells of *C. parapsilosis* ATCC 7330

4.1. Substrate specificity

The fact that deracemisation can theoretically deliver 100%



3a – 3p (S.No 1-16) **3q – 3t (S.No 17-20)** **3u – 3v (S.No 21 and 22)**

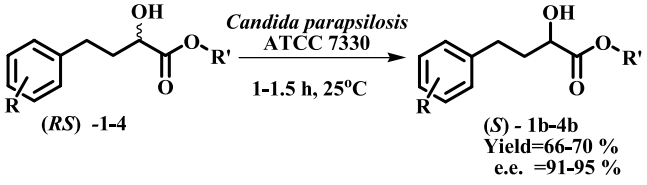
Figure 1. Ethyl and methyl esters of racemic 2-hydroxy esters.

Table 4. Retention factors (k' and k''), separation factor (α) and resolutions (R_s) of racemic α-hydroxy esters (**3a**–**3v**)

S.No	C. no.[a]	Column used	Hex: IPA (ml/min)	α	R_s	k'	k''
1	3a	OD-H	98:2; 1 ml	1.38	5.02	7.02	9.67
2	3b	OD-H	98:2; 1 ml	1.37	4.72	5.04	6.91
3	3c	OJ-H	98:2; 1 ml	1.15	2.75	6.57	7.58
4	3d	OJ-H	98:2; 1 ml	1.20	4.07	11.14	13.37
5	3e	OJ-H	98:2; 1 ml	1.11	2.36	11.53	12.82
6	3f	OJ-H	98:2; 1 ml	1.12	2.11	7.14	7.92
7	3g	OJ-H	96:4; 1 ml	1.12	1.95	3.76	4.19
7a	3g′	OJ-H	98:2; 1 ml	1.13	2.13	9.154	10.2
8	3h	OJ-H	96:4; 1 ml	1.10	1.26	2.29	2.51
9	3i	OD-H	98:2; 0.5 ml	1.90	7.36	5.59	10.62
9a	3i′	OD-H	99:1; 0.5 ml	1.92	9.84	8.07	15.52
10	3j	OJ-H	98:2; 1 ml	1.22	2.76	6.27	7.59
10a	3j′	OD-H	99:1; 1 ml	1.94	11.21	6.20	12.03
11	3k	OJ-H	98:2; 1 ml	1.40	2.08	7.92	11.08
12	3l	OJ-H	95:5; 1 ml	1.22	3.01	10.68	12.98
13	3m	OD-H	93:7; 0.5 ml	1.09	1.32	9.41	10.21
14	3n	OJ-H	95:5; 1 ml	1.16	3.64	13.17	15.22
15	3o	OD-H	95:5; 1 ml	1.08	1.52	7.28	7.83
16	3p	OD-H	95:5; 1 ml	1.38	3.88	4.79	6.62
17	3q	OJ-H	96:4; 0.5 ml	1.32	3.50	3.42	4.51
18	3r	OJ-H	96:4; 0.5 ml	1.39	3.92	4.85	6.75
19	3s	OD-H	98:2; 1 ml	1.11	1.90	7.71	8.55
20	3t	OJ-H	98:2; 1 ml	1.10	1.68	4.27	4.64
21	3u	OD-H	95:5; 1 ml	1.15	1.56	0.86	0.99
22	3v	OD-H	98:2; 1 ml	1.20	2.16	1.69	2.08

[a] C. no., Compound number.

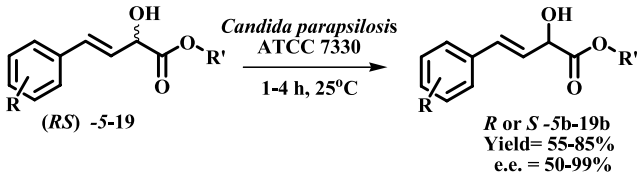
yield and >99% ee of one enantiomer from a racemate makes it a very important strategy to prepare chiral synthons. We have earlier reported the deracemisation of racemic ethyl 2-hydroxy-4-phenylbutanoate into the corresponding optically pure (*S*)-2-hydroxy ester by whole cells of *C. parapsilosis* ATCC 7330.[21] In the present study, the substrate tolerance (wrt electronic and steric effects of the aryl substituents) of this biocatalyst was studied. Deracemisation of substituted *p*-chloro and *p*-methyl esters by the whole cells of *C. parapsilosis* ATCC 7330 resulted in the optically pure (*S*)-enantiomers in good yields (66–70%) and high ee's of 91–95% (Scheme 3, Table 5). The time of the reaction was 1.5 h. Introduction of a chloro-substituent at the *para* position in the aromatic ring of 2-hydroxy-4-phenylbutanoic methyl and ethyl esters (**1–4**) gave slightly lower chemical yields (68–69%) as well as ee (93–95%) as compared to the corresponding unsubstituted substrate. Presence of electron donating groups such as *para* methyl (**3–4**, Scheme 3) also gave slightly less chemical yield (66–70%) than for unsubstituted α-hydroxy ester.[21] The ee was slightly lower (91–93%). Incubation times of these reactions were also 1.5 h.



Scheme 3.

For the unsaturated compounds **5b** and **6b**, chemical and optical yields were 74–75 and 98–99%, respectively. The time of the reaction was 1.5 h. *C. parapsilosis* ATCC 7330 was found to deracemise aryl substituted (*E*)-2-hydroxy-4-arylbut-3-enoic esters that have electron withdrawing or electron donating substituents at the *ortho*, *para* and *meta* positions in the aromatic ring (**7b–13b**) (Scheme 4, Table 6) with slightly lower chemical yields (65–70%) and optical purity ranging from (52–99% ee) as compared to unsubstituted α-hydroxy esters. Optical rotation was measured for **5b** and compared with the value reported in literature[31] while for compounds **6b**, **7b** and **11b**; optical rotations were measured after hydrogenation and compared with those reported in the literature.[32] For compounds **7b**, **9b–10b** and **12–17b** optical rotations are reported here for the first time. When the reaction was carried out with di-substituted compounds such as 2,4-dichloro and 2,5-dimethoxy compounds (**14–17**), the ee and chemical yield of the reaction dropped to 50–65 and 52–72%, respectively.

Substrate molecules possessing two substituents, one at the



Scheme 4.

ortho position and the other one at the *para* position on the aromatic ring yielded lower chemical and optical yields of the final product (**14b–17b**) as compared to monosubstituted substrates (**5–13**) possibly due to steric reasons. The polar substrates (**14–17**) do seem to lend themselves to the action of other enzymes resulting in lower yield of the product. The benzyl ester of 2-hydroxy-4-(*p*-chlorophenyl)but-3-enoic acid (**19**) and the methyl ester of 2-hydroxy-4-(1-naphthyl)but-3-enoic acid (**18**) were not deracemised by *C. parapsilosis* ATCC 7330. The reason for this could also be steric due to the bulky groups present in these two esters, that is, benzyl ester group in the former case and the 1-naphthyl group in the latter case. Incubation of these two reactions was extended to 4 h at 25 °C without any resulting deracemisation.

4.2. Deracemisation of racemic 2-hydroxy-3-arylpropanoic esters (20a–22a) by the whole cells of *C. parapsilosis* ATCC 7330

Deracemisation of racemic 2-hydroxy-3-arylpropanoic esters (**20a–22a**) resulted in the formation of (*S*)-2-hydroxy-3-propanoic esters (**20b–22b**) (Table 7) using *C. parapsilosis* ATCC 7330. At the end of 1 h, only 15% ee was obtained. The reaction was prolonged to 4 h, which resulted in 62–70% chemical yield and 34–60% ee (Scheme 5). In essence it seems that 2-hydroxy 4-phenylbutanoic ethyl ester is the substrate, which gives the highest yield and ee of the deracemised (*S*)-product. Mandelates are also deracemised but propionates are not.

5. Mechanistic studies

The deracemisation of various racemic aryl α-hydroxy esters (**1b–13b**) to the corresponding *S*-isomer was achieved by using the whole cells of *C. parapsilosis* ATCC 7330 in good chemical yields (65–85%) and with high ee (92–99%) (Tables 5–7). There were few exceptions viz. **14b–17b** and **20b–22b** for which the chemical yields were 55–70% and ee were 50–65% as discussed. Significantly, all the deracemisation reactions irrespective of the substitution in the aryl group, chain length and ester group resulted exclusively in the formation of '*S*' isomer. The mechanism of the deracemisation of α-hydroxy esters can be explained in two different ways (i) abstraction of the α-methine proton via enolisation

Table 5. Deracemisation of α-hydroxy esters (**1a–4a**) by the whole cells of *C. parapsilosis* ATCC 7330

Entry	R	R^1	ee (%)	Yield (%)	Time (h)	$[\alpha]_D^{27}$	Lit. value	Abs config.
1b	*p*-Cl	Me	95	69	1.5	+22.2 (*c* 0.57 $CHCl_3$)	Nr	*S*
2b	*p*-Cl	Et	93	68	1.5	+17.4 (*c* 1 $CHCl_3$)	−18.6 (*c* 1.02 $CHCl_3$)[a]	*S*
3b	*p*-Me	Me	91	66	1.5	+28.8 (1.05 $CHCl_3$)	Nr	—
4b	*p*-Me	Et	93	70	1.5	+18 (*c* 0.6 $CHCl_3$)	Nr	*S*

[a] Ref. 32.

(Scheme 6) or a redox mechanism (stereoinversion) mediated by oxidoreductases (Scheme 7). The choice of ethyl mandelate (**23**) for the mechanistic study using *C. parapsilosis* ATCC 7330 was based on the easy availability of (*R*)- and (*S*)-ethyl mandelates in sufficient amounts to carry out experiments to elucidate the mechanism of deracemisation. There are only two reports in the literature for deracemisation of racemic mandelic acid.[33,34] It is important to note that neither of these reports has made use of microbial whole cells to bring about the reaction in one pot.

Stereoinversion seemed the most plausible mechanism for the deracemisation of α-hydroxy esters as is seen in other secondary alcohols.[35,36] In order to verify that the mechanism of deracemisation of racemic α-hydroxy esters proceeds through stereoinversion, the following experiments were performed. Optically pure antipodes of ethyl mandelate [(*R*)-**23a** and (*S*)-**23b**] were also employed in these experiments.

5.1. Stereoinversion of (*R*)-ethyl mandelate (23a) using whole cells of *C. parapsilosis* ATCC 7330

Stereoinversion of (*R*)-ethyl mandelate **23a** to the (*S*)-ethyl mandelate **23b** is to be expected in order to obtain the (*S*)-enantiomer in high ee and yield. Incubation of (*R*)-ethyl mandelate with whole cells of *C. parapsilosis* ATCC 7330 resulted in complete conversion to the (*S*)-enantiomer (99% ee). The reaction was carried out for 1 h at 25 °C (Scheme 8).

Table 6. Deracemisation of (*E*)-2-hydroxy-4-arylbut-3-enoic esters (**5a–19a**) by *C. parapsilosis* ATCC 7330

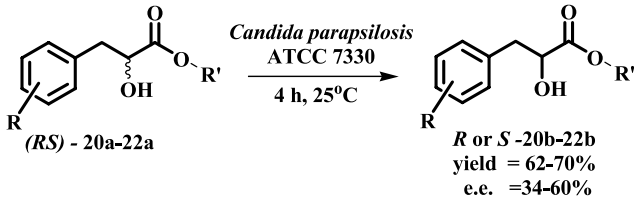
Entry	R	R^1	ee (%)	Yield (%)	Time (h)	$[\alpha]_D^{27}$	Lit. value	Abs config.
5b	H	Me	98	74	1.5	+67.1 (*c* 1 $CHCl_3$)	−67.7 (*c* 1 $CHCl_3$)[a]	*S*
6b	H	Et	99	75	1.5	+21.3 (*c* 1.1 $CHCl_3$)[b]	−21.3 (*c* 1.1 $CHCl_3$)[c]	*S*
7b	*p*-Cl	Me	98	69	1.5	+55.4 (*c* 1.25 $CHCl_3$)	Nr	*S*
8b	*p*-Cl	Et	98	65	1.5	+18.9 (*c* 1 $CHCl_3$)[b]	−18.6 (*c* 1.02 $CHCl_3$)[c]	*S*
9b	*p*-Me	Me	92	70	2	+50.5 (*c* 1.1 $CHCl_3$)	Nr	—
10b	*p*-Me	Et	90	68	2	+40.2 (*c* 1.2 $CHCl_3$)	Nr	*S*
11b	*o*-Cl	Et	95	68	2	+13 (*c* 0.75 $CHCl_3$)[b]	−12.4 (*c* 0.70 $CHCl_3$)[c]	*S*
12b	*m*-NO_2	Et	95	70	1.5	+46 (*c* 0.51 $CHCl_3$)	Nr	—
13b	*m*-NO_2	Me	93	69	1.5	+55 (*c* 0.63 $CHCl_3$)	Nr	—
14b	2,4-DiCl	Me	50	70	4	+15 (*c* 0.75 $CHCl_3$)	Nr	—
15b	2,4-DiCl	Et	54	72	4	+11 (*c* 1.1 $CHCl_3$)	Nr	—
16b	2,5-DiOMe	Me	53	55	4	+13 (*c* 1.3 $CHCl_3$)	Nr	—
17b	2,5-DiOMe	Et	65	52	4	+9 (*c* 1.1 $CHCl_3$)	Nr	—
18b[d]	1-Naphthyl	Me	10	75	4	—	—	—
19b	*p*-Cl	CH_2 Ph	03	93	4	—	—	—

Nr, not reported.
[a] Ref. 31.
[b] Optical rotation was taken after hydrogenation.
[c] Ref. 32.
[d] Aryl, 1-naphthyl.

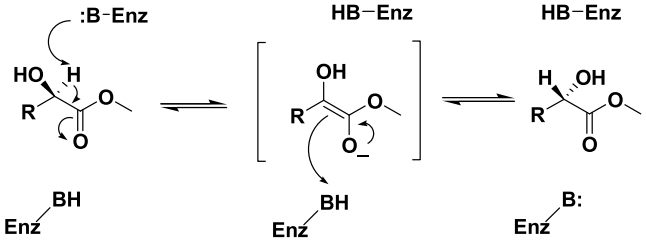
Table 7. Deracemisation of 2-hydroxy-4-arylpropanoic esters (**20a–22a**) by the whole cells of *C. parapsilosis* ATCC 7330

Product	R	R^1	Time (h)	ee (%)	Yield (%)	Abs config.
20b	H	Et	4	60	70	*S*
21b	2,4-DiCl	Me	4	34	65	Nr
22b	*p*-Me	Et	4	45	62	*S*

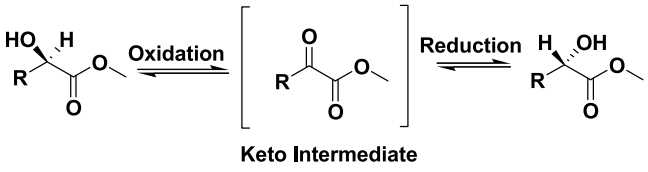
Nr, not reported.



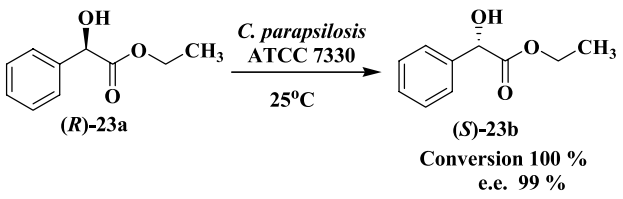
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

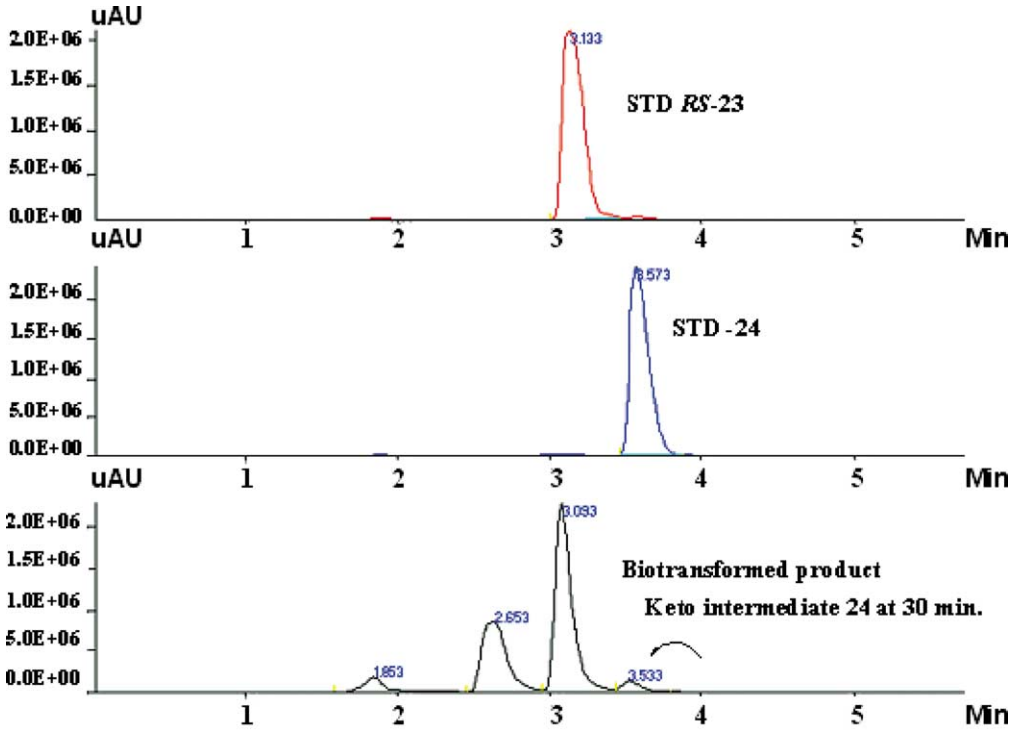


Figure 2. HPLC chromatogram of stereoinversion of *RS*-**23a** using *C. parapsilosis* ATCC 7330.

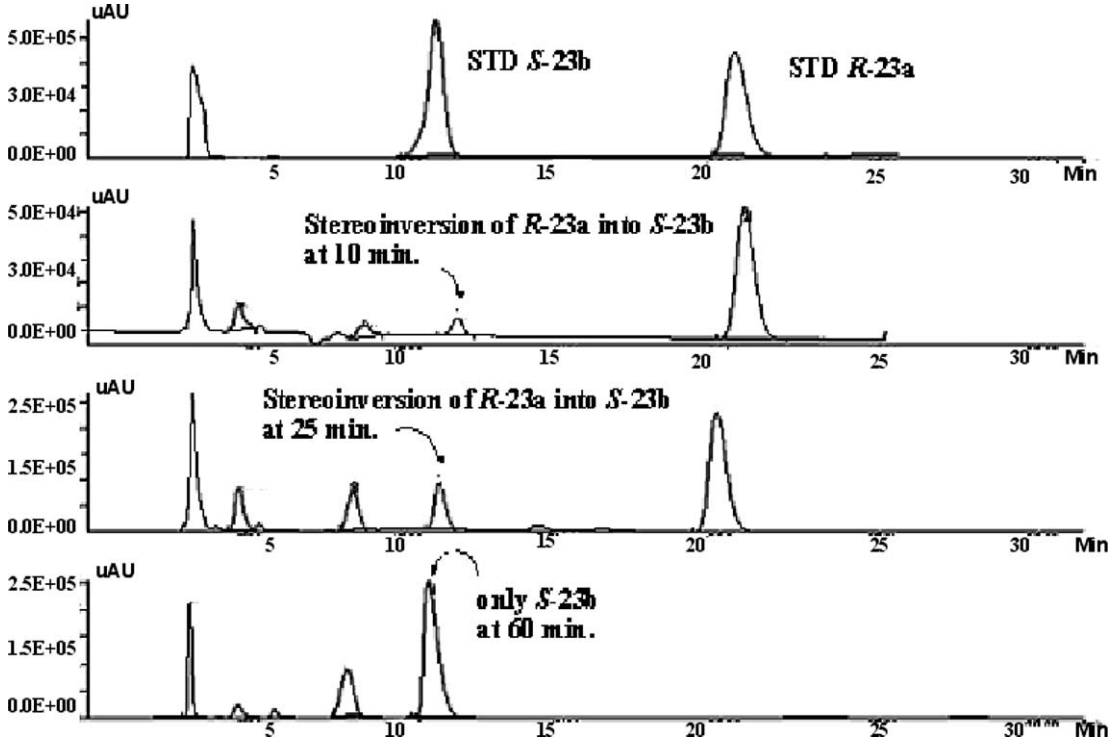
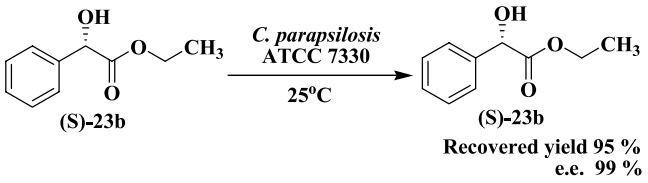


Figure 3. HPLC chromatogram of stereoinversion of *R*-**23a** into *S*-**23b** using *C. parapsilosis* ATCC 7330.

Having established that the (*R*)-enantiomer (*R*-**23a**) is converted to the (*S*)-enantiomer (*S*-**23b**), the time course of the above reaction was determined in order to trap any intermediate, which may be formed. Aliquots of reaction mixture were monitored by HPLC on a Sil C-18 column. The formation of a keto intermediate was detected at 30 min (Fig. 2). The conversion of the *R*-**23a** to the *S*-**23b** was followed by HPLC (Fig. 3) using a Chiralcel OD-H column.

Incubation of (*S*)-**23b** with *C.parapsilosis* ATCC 7330 gave unchanged starting material (*S*)-**23b** in 95% yield and 99% ee (Scheme 9) which was confirmed by chiral HPLC (Fig. 4) using a Chiralcel OD-H column.



Scheme 9.

5.2. Asymmetric reduction of ethyl benzoylformate (24)

Since the keto intermediate was detected during the stereoinversion of the (*R*)-**23a** isomer to (*S*)-**23b**, the reduction of this keto intermediate (**24**) viz. ethyl benzoyl formate prepared synthetically was attempted using *C. parapsilosis* ATCC 7330.

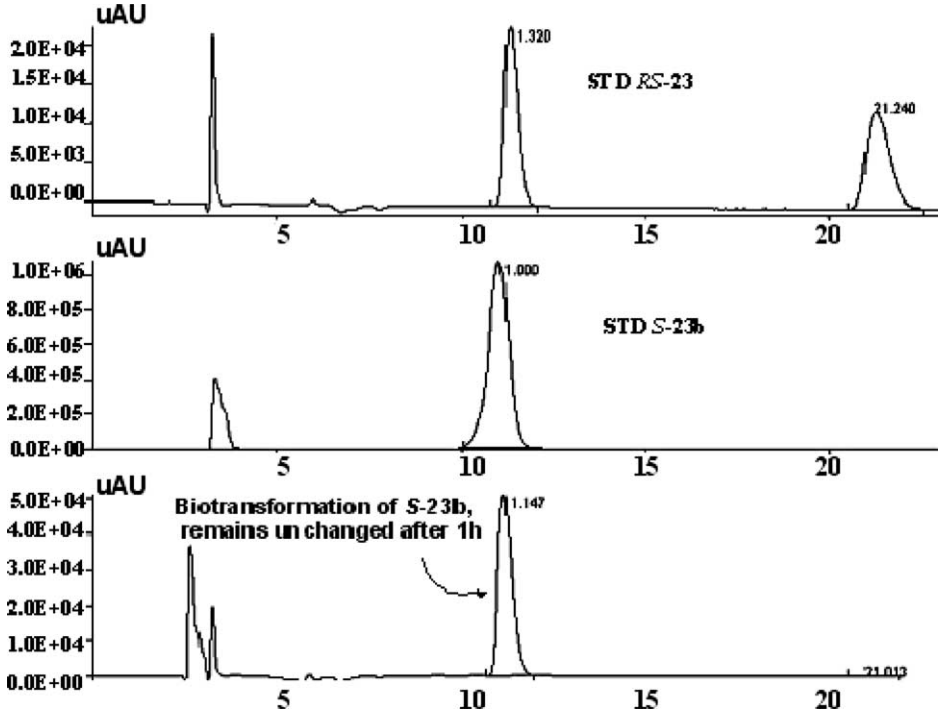


Figure 4. HPLC chromatogram of biotransformation of *S*-**23b** after 1 h using *C. parapsilosis* ATCC 7330.

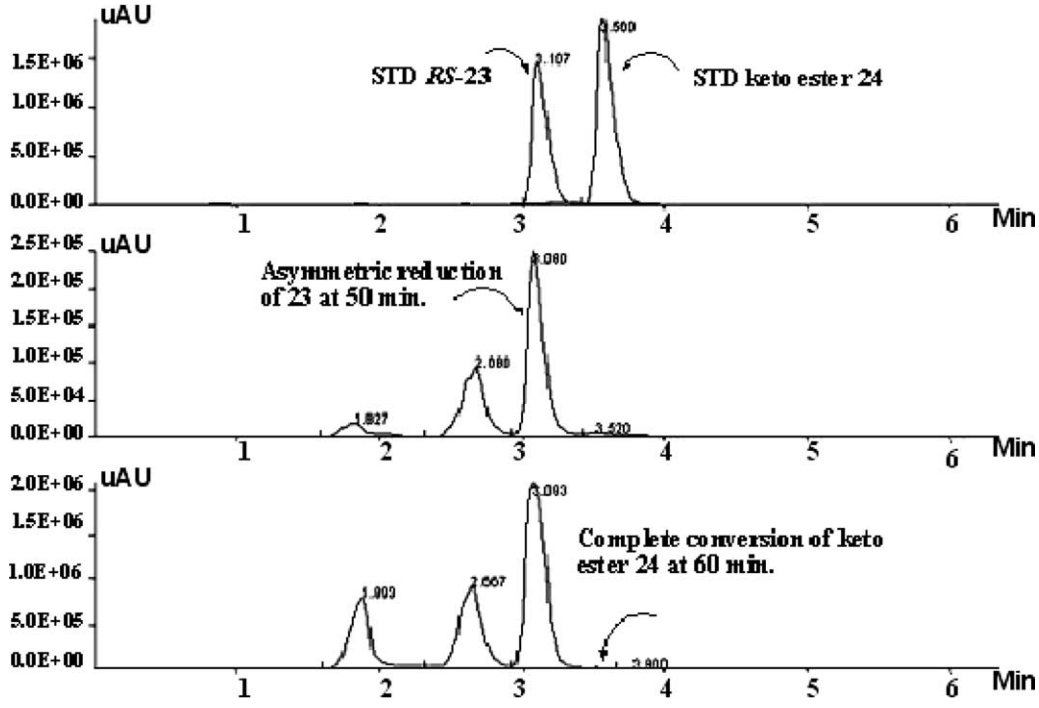
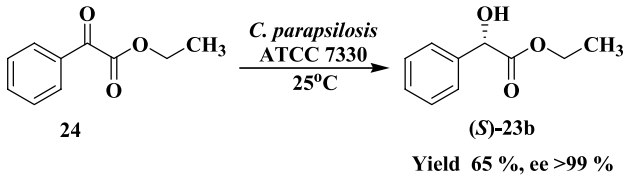


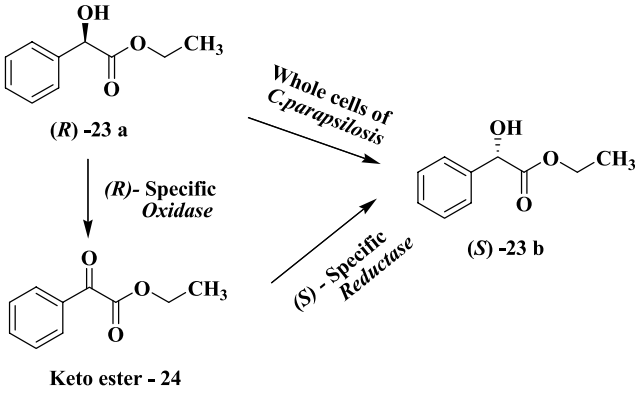
Figure 5. HPLC chromatogram of asymmetric reduction of keto ester **24** using *C. parapsilosis* ATCC 7330.

The reduction of ethyl benzoylformate (**24**) to the expected product ethyl mandelate (**23b**) was monitored by HPLC on a Sil-C18 column (Fig. 5). The absolute configuration of ethyl mandelate thus obtained was established by comparing with standard using HPLC details of which are given in Section 7.4.2. (*S*)-ethyl mandelate (**23b**) was obtained in 65% chemical yield and 99% ee (Scheme 10).



Scheme 10.

In addition to the above experiments, appropriate controls were also carried out. The control experiments were (a) only cells of *C. parapsilosis* ATCC 7330 and (b) only substrate [i.e., (*RS*)-**23**, (*R*)-**23a** and (*S*)-**23b**] under identical conditions as done for the experiments 5.1 and 5.2. These experiments confirmed that (*R*,*S*)-ethyl mandelate is deracemised by *C. parapsilosis* ATCC 7330 to (*S*)-ethyl mandelate possibly by a combination of two enzymes, (*R*)-specific oxidase and (*S*)-specific reductases (Scheme 11). Given this mechanism, the observation that propionates are not deracemised by *C. parapsilosis* ATCC 7330 may be attributed to the preponderance (50–80%) of the enol form in the unsubstituted, *p*-methyl and 2,4-diCl arylpropionic α-keto esters, which cannot be substrates for the (*S*)-specific reductases.



Scheme 11.

6. Conclusion

A series of racemic aryl and aryl substituted α-hydroxy esters were synthesized by modifying known literature methods to obtain good yields. The racemic esters synthesized were resolved by chiral HPLC on chiral columns OD-H and OJ-H using hexane and IPA as eluents. Subsequently, the racemic aryl α-hydroxy esters sythesised were deracemised by the whole cells of *C. parapsilosis* ATCC 7330 to give the corresponding optically pure (*S*)-hydroxy esters in good yields (65–85%) and ee (90–99%). To elucidate the mechanism of deracemisation, a detailed study was carried out on deracemisation of mandelic ester and was found to involve two different enzymatic reactions viz. oxidation of one of the antipodes by an (*R*)-oxidase to the keto intermediate followed by its subsequent reduction by a (*S*)-specific reductase enzyme.

7. Experimental

7.1. General methods

HPLC analysis was done on a Jasco PU-1580 liquid chromatograph equipped with a manual injector (20 μl) and a PDA detector. The columns used were Chiralcel OD-H and Chiralcel OJ-H (Daicel, 4.6×250 mm). The enantiomeric excesses (% ee) of **1b**–**23b** were determined by HPLC analysis. The eluent used was hexane–isopropanol (98/2) at a flow rate of 1 ml min^{-1} and the absorbance monitored using a PDA detector at 254 nm. Optical rotations were determined on a Jasco Dip 370 digital polarimeter. TLC was done on Kieselger 60F 254 aluminium sheets (Merck 1.05554).

7.2. Synthesis of substrates

7.2.1. Preparation of alkyl (*E*)-2-oxo-4-arylbut-3-enoates (2a–2n). *Typical reaction procedure of compound* **2d**. Esterification of 2-oxo-4-(*p*-chlorophenyl)but-3-enoic acid (5 mmol, 950 mg) was carried out with ethanol (5 ml) in the presence of phosphotungstic acid (95 mg) as catalyst in dry toluene (10 ml) for 8 h at 95 °C. After esterification was complete, toluene and excess ethanol were removed. Compound **2d** was obtained as a yellow colour solid in 78% yield (850 mg, 3.9 mmol) after column purification using hexane–ethyl acetate (95/5) as eluent.

The same procedure was followed for compounds (**2a–c** and **2e–1n**) (Scheme 1, Table 1).

7.2.2. Preparation of alkyl (*E*)-2-hydroxy-4-arylbut-3-enoates (4a–4n). *Typical reaction procedure of compound* **4d**. Esterification of 2-hydroxy-4-(*p*-chlorophenyl)but-3-enoic acid (**3** R=*p*-Cl) (5 mmol, 960 mg) was carried out with ethanol (5 ml) in the presence of phosphotungstic acid as catalyst (96 mg) in dry toluene (10 ml) for 9 h at 95 °C. After esterification, toluene and excess ethanol were removed by evaporation. Upon column purification, compound **4d** was obtained as a white solid in 73% yield (803 mg, 3.65 mmol).

The same procedure was followed for the rest of the compounds (**4a–c** and **4e–4n**) and the yields ranged from 44–85% (Table 1, Scheme 1).

7.2.3. Preparation of alkyl 2-hydroxy-3-arylpropanoates (4a–f,h). *Typical reaction procedure for compound p-methyl benzylidine-2-methyl oxazol (4H)-5-ones* (**1h**). A mixture of *N*-acetyl glycine (10 mmol, 1.15 g) and *p*-methylbenzaldehyde (10 mmol, 1.19 g) in acetic anhydride (40 mmol, 4.0 g) was taken in a 100 ml Erlenmeyer conical flask. The conical flask containing the reaction mixture was uniformly mixed using a vortex mixer and then the reaction mixture was irradiated using a microwave oven for 4 min. On cooling, the reaction solidified. The residue was washed with ethanol/water 50:50 mixture and dried

under vaccum. The product (**1h**) was obtained in 90% yield (8.9 mmol, 1.57 g) as a pale yellow solid. Compounds **1a–g** and **1i–k** were prepared by following the procedure described above for compound **1h** (Scheme 2) and the yields obtained are given in Table 2.

Typical reaction procedure for compound (**3h**). The sodium salt of (*p*-methylphenyl)pyruvic acid **2h** (10 mmol, 2 g) in water (2 ml) was cooled to 5–10 °C and sodium borohydride (15 mmol, 540 mg) was added portionwise. The reaction mixture was stirred for 2 h at 5–10 °C. A foamy white precipitate appeared upon neutralization with dil HCl, which was extracted with ethyl acetate (4×20 ml). The combined layers of ethyl acetate were dried over anhydrous sodium sulfate and on evaporation of solvent, resulted in the hydroxy acid (**3h**) as a colourless liquid in 87% yield (8.7 mmol, 1.566 g). Compounds **3a–e** were also prepared by the method described above for compound **3h** (Scheme 2) and the yields obtained are given in Table 2.

Typical reaction procedure for compound **4h**. Esterification of 2-hydroxy-3-(*p*-methylphenyl)propanoic acid (**3h**) (5 mmol, 900 mg) was carried out with ethanol (5 ml) in the presence of phosphotungstic acid (90 mg) as catalyst in dry toluene (10 ml) for 6 h at 95 °C. After completion of reaction, toluene and excess ethanol were removed to afford compound **4h** as a colourless liquid in 85% yield (884 mg, 4.376 mmol) after column purification using hexane and ethyl acetate (95:5) as the mobile phase eluent. Compounds **4a–e** were prepared by following the procedure described above for compound **4h** (Scheme 2) and the yields obtained are given in Table 2.

7.3. Deracemisation of α-hydroxy esters

7.3.1. Culture medium of the microorganism. The yeast, *C. parapsilosis* (ATCC 7330) was grown in YMB medium (60 ml) in 250 ml Erlenmeyer flasks. The flasks were incubated at 25 °C with a shaking speed of 200 rpm for 40 h. The cells were pelleted down by centrifugation at 3214×*g* for 15 min, washed with distilled water and used for the biotransformation reaction.

7.3.2. Typical procedure for biotransformation of 1 using free cells of *C. parapsilosis* ATCC 7330. To a 500 ml conical flask containing 30 g of pelleted *C. parapsilosis* ATCC 7330 cells suspended in sterile distilled water, 300 mg (1.41 mmol) of methyl 2-hydroxy-4-(*p*-chlorophenyl) butanoate (**1**) dissolved in 7.5 ml of ethanol was added. The total volume of the reaction mixture was made up to 100 ml by adding sterile distilled water. The reaction was carried out in a water bath shaker at 150 rpm and 25 °C for 1.5 h. After incubation, the reaction mixture was centrifuged at 5000 rpm for 10 min. The product formed was isolated using ethyl acetate (3×40 ml) and the organic layer dried over anhydrous sodium sulfate. The solvent was removed by evaporation and **1b** was obtained as a pale yellow solid after purification by silica gel column chromatography using hexane–ethyl acetate (98/2) as a mobile phase eluent. The product was characterized by ^{1}H and ^{13}C NMR (400 MHz) spectroscopy. The ee was found to be 95% as determined using HPLC on a Chiralcel OJ-H column [hexane–isopropanol (96/4)]. The yield of the isolated product, methyl (*S*)-2-hydroxy-4-(*p*-chlorophenyl)butanoate (**1b**), was 69% (207 mg, 0.97 mmol).

7.4. Mechanistic studies

7.4.1. Stereoinversion of 23a using whole cells of *C. parapsilosis* ATCC 7330. To a test tube containing 0.3 g of pelleted *C. parapsilosis* ATCC 7330 cells suspended in sterile distilled water, 1.5 mg of **23a** dissolved in 40 μl of ethanol was added. The total volume of the reaction mixture was made up to 1 ml by adding sterile distilled water. The reaction was carried out in a water bath shaker at 150 rpm and 25 °C for 1 h. After incubation, the reaction mixture was centrifuged at 5000 rpm for 10 min. The product formed was isolated using ethyl acetate (3×40 ml) and the organic layer dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the ee was found to be 99% as determined using HPLC on a Chiralcel OD-H column [hexane–isopropanol (99/1)].

The same procedure was adapted for compound **23b**.

7.4.2. Asymmetric reduction of 24 using whole cells of *C. parapsilosis* ATCC 7330. To a 500 ml conical flask containing 30 g of pelleted *C. parapsilosis* ATCC 7330 cells suspended in sterile distilled water, 150 mg (0.842 mmol) of **24** dissolved in 3.6 ml of ethanol was added. The total volume of the reaction mixture was made up to 100 ml by adding sterile distilled water. The reaction was carried out in a water bath shaker at 150 rpm and 25 °C for 1 h. After incubation, the reaction mixture was centrifuged at 5000 rpm for 10 min. The product formed was isolated using ethyl acetate (3×40 ml) and the organic layer dried over anhydrous sodium sulfate. The solvent was removed by evaporation and **23b** was obtained as a low melting solid after purification by silica gel column chromatography using hexane–ethyl acetate (98/2) as a mobile phase eluent. The product was characterized by ^{1}H and ^{13}C NMR (400 MHz) spectroscopy. The ee was found to be 99% as determined using HPLC on a Chiralcel OD-H column [hexane–isopropanol (98/2)]. The yield of the isolated product, (*S*)-ethyl mandelate **23b** was 65% (98 mg, 0.64 mmol). The absolute configuration of (*S*)-enantiomer **23b** was confirmed by comparing with standards (*RS*)-**23**, (*R*)-**23a** and (*S*)-**23b** using Chiral HPLC on a Chiralcel OD-H column [hexane–isopropanol (98/2)]. The retention times of (*R*)-**23a** and (*S*)-**23b** were 20.41 and 10.99 min, respectively.

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Lower rim substituted *tert*-butylcalix[4]arenes. Part 8: Calix[4]arenes with dialkoxyphosphoryl functions. Synthesis and complexing properties☆

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Received 3 June 2005; revised 2 September 2005; accepted 22 September 2005

Available online 20 October 2005

Abstract—New compounds: 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(3-diisopropoxyphosphorylpropoxy)calix[4]arene (**1**) and 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(3-methoxyethoxyphosphorylpropoxy)calix[4]arene (**2**) were synthesized and their ionophoric properties in ion-selective membrane electrodes were studied in comparison with already described by us 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(3-diethoxyphophorylpropoxy)calix[4]arene (**3**). Complexes of **1** with calcium(II), lanthanum(III), europium(III) and gadolinium(III) nitrates were prepared in direct reaction of the ligand and appropriate metal salts. They were characterized by spectral data (IR, UV/Vis, luminescence, NMR, ESI-MS) and elemental analysis. The similarity in complexing behavior of the (dialkoxyphosphoryl)propoxy-calix[4]arenes toward calcium and some lanthanides was observed.

1. Introduction

Calix[4]arenes with a variety of substituents at the lower rim pendant arms are known as selective complexing agents for many different cations.[1] For the last few years substituents with a phosphine oxide moiety have been introduced to the calix[4]arene structure and interesting complexing properties of such compounds have been found.[2–6] Among such calix[4]arene derivatives are: carbamoyl methyl phosphine oxide (CMPO) selective for trivalent lanthanides,[2] phosphorylated calix[4]arenes selective for bioactive and hazardous ions or molecules,[3,4] calix[4]arenes with diaryl phosphine oxide functionalities used as extractive agents and carriers for silver ions[5] and with dialkyl phosphine oxides showing complexing properties toward potassium and calcium ions.[6] Molecular dynamic simulation of the lanthanide inclusion complexes of *t*-butyl-calix[4]arenes substituted by four CH_2–$P(O)Ph_2$ arms has given the idea of the nature and structure of the extracted neutral complexes.[7]

We present here the synthesis and properties of new calix[4]arene derivatives functionalized at the narrow rim by four arms with (dialkoxyphosphoryl)alkyl groups (**1** and **2**). These tetra-substituted phosphonate derivatives behave as calcium(II)-selective ionophores in ion-selective PVC-membrane electrodes (Ca-ISE) similarly to compound **3** described by us[8] and to calix[4]arene substituted with tetraphosphine.[9] The di-substituted calix[4]-phosphonates described by us earlier are not so highly selective and in ISE they behave as ionophores for potassium and rubidium ions.[10]

Because of the similarity in ionic radii, coordination chemistry and binding behaviour between the lanthanide(III) cations and alkaline earth metal cations and the remarkable multitude of spectroscopic and magnetic properties, lanthanides have been broadly used as presumed isomorphous replacement for calcium and to a lesser degree, other biometals.[11–18] They serve as informative spectroscopic probes of metal binding sites of macromolecules of biological interest, particularly for calcium in biomembranes. They are utilized as markers to trace the movement and deposition of calcium in tissues and have been used in investigating the role of calcium in muscle and nerve activity. The latest suggestions of possible future employment of lanthanides as therapeutic agents in

☆ For part VII see ref. 28

Keywords: Calix[4]arenes; Synthesis; Complexes; Calcium; Lanthanides; Ca^{2+}-selective membrane electrodes; Selectivity coefficients.
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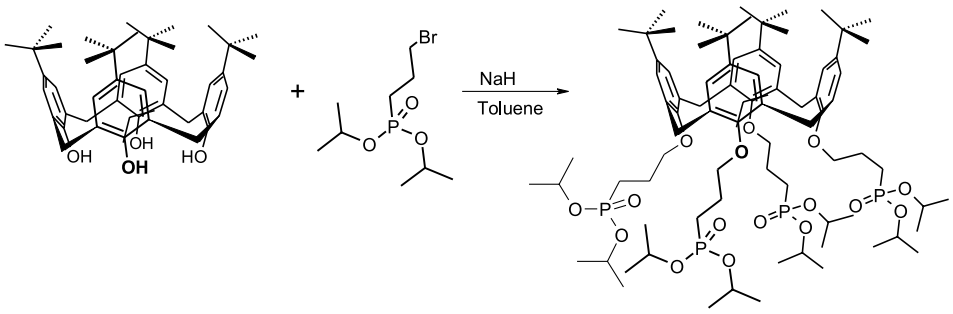
doi:10.1016/j.tet.2005.09.102



1 (68 %)

Scheme 1. Synthesis of compound **1**.

the treatment of inflammation, arthritis and atherosclerosis are based on the ability of lanthanide ions to antagonize the calcium-dependent processes. It seemed therefore, to be of interest for us to compare the complexing ability of new calix[4]arene receptors toward the calcium ion and lanthanides.

2. Results and discussion

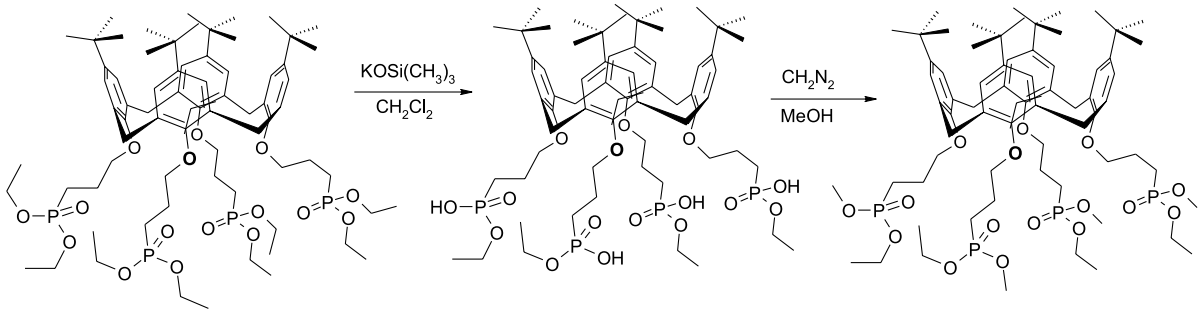
Calix[4]arene **1** was synthesized according to the route shown in Scheme 1, in the same manner as compound **3** already published.[8] The synthesis of compound **2** was carried out starting from compound **3** by hydrolysis of the diester groups to monoesters using $KOSi(CH_3)_3$.[19] Base-mediated hydrolysis of the four dialkyl phosphonate groups in calix[4]arene to their monoalkyl phosphonic acid would require drastic conditions (high pH and long heating time). We found that treatment of calix[4]arene-phosphonates with potassium trimethylsilanolate in CH_2Cl_2 affords tetra monoalkyl phosphonates with high purity in good yield. Reaction was then carried out with diazomethane in MeOH.[20] The product, calix[4]arene with four methyl ethyl phosphonate groups, was formed with high yield (Scheme 2).

Calix[4]arenes in *cone* conformation substituted at the lower rim with four arms having a P═O moiety have previously proved to be interesting ligands for calcium ion sensing.[8,9] In alkoxyphosphorylated compounds **1**–**3**, four arms with P═O groups appear to form a cavity suitable for coordination of Ca^{2+} and some lanthanides.

The ionophoric properties of the new compounds **1** and **2** were studied by using them as the active material in electrochemical sensors, ion-selective membrane electrodes (ISE).[8,9,21,22] Electrode membranes with three different plasticizers were made and compared: bis-butylhexylsebacate (BEHS) (electrodes 1 and 4), *o*-nitrophenyloctylether (NPOE) (electrodes 2 and 5) and bis(butyl-pentyl)adipate BBPA (electrodes 3 and 6). We studied complexation behavior of the compounds **1** and **2** toward alkali metal ions, alkali earth cations, some transition metal ions Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and tetramethylammonium (TMA^+) ions. Electrodes 1–6 generated very stable potentials. Both compounds **1** and **2**, similarly to compound **3**,[8] are highly calcium selective, irrespective of the used plasticizer. However, the membranes plasticized with NPOE show the best properties: Nernstian slope of 29.8–26.4 mV and high selectivity. The electrodes show linear characteristics within a wide concentration range: 10^{-1}–10^{-6} M (PVC/NPOE membranes) and slightly worse 10^{-1}–10^{-5} M for PVC/BEHS membrane electrodes 1 and 4.

The characteristics of the studied electrodes 1–6 and ions of preference are presented in Table 1. In Figure 1 typical calibration curves are presented for the electrodes 2 (ligand **1**) and 5 (ligand **2**) with (NPOE) and in Figure 2 for electrodes 1 and 4 with BEHS.

Selectivity is one of the most important characteristics of a sensor. The following selectivity pattern was observed: $Li^+ > Ca^{2+} > Na^+ > TMA^+ > K^+$, Rb^+, Cs^+ and among divalent cations: $Ca^{2+} > Zn^{2+} > Cu^{2+} > Sr^{2+} > Mg^{2+} >$



3 **(60 %)** **2 (100 %)**

Scheme 2. Synthesis of compound **2**.

Table 1. Characteristics of the studied electrodes 1–6

Electrode number	Ionophore (2.2%)	Lipophilic salt KTpClPB (0.27%)	Plastisizer (65%)	PVC (32.5%)	Ion a_i	Slope S (mV)	Linear range $-\log a_i$
1	**1**	+	BEHS	+	Li^+, Ca^{2+}, Zn^{2+}	50.3, 26.1, 25.1	3.2–1.0, 5.0–1.0, 3.2–1.0
2	**1**	+	NPOE	+	Li^+, Ca^{2+}, Zn^{2+}	50.0, 29.8, 25.0	3.2–1.0, 6.3–1.0, 3.0–1.0
3	**1**	+	BBPA	+	Li^+, Ca^{2+}, Zn^{2+}	50.0, 25.2, 25.6	3.2–1.0, 5.8–1.0, 4.2–1.0
4	**2**	+	BEHS	+	Ca^{2+}, Zn^{2+}	25.6, 27.5	5.0–1.0, 3.0–1.0
5	**2**	+	NPOE	+	Ca^{2+}, Zn^{2+}	26.4, 25.0	6.0–1.0, 3.0–1.0
6	**2**	+	BBPA	+	Ca^{2+}, Zn^{2+}	25.1, 25.3	5.0–1.0, 4.5–1.0

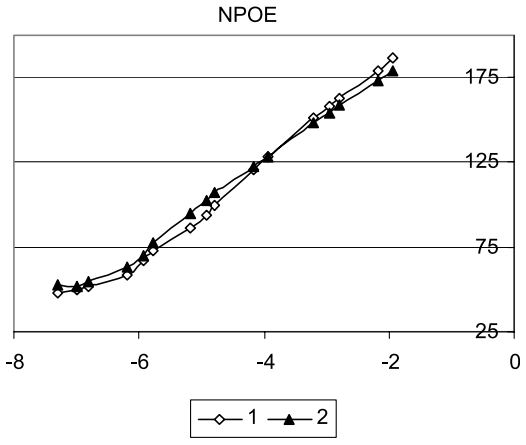


Figure 1. Characteristics for Ca^{2+}-selective electrodes 2 and 5, with ionophores **1** and **2** in PVC/NPOE membrane.

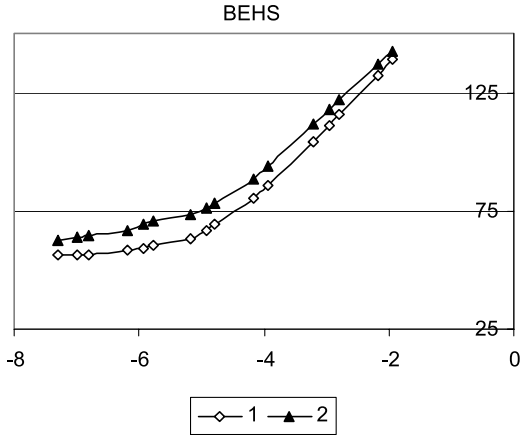


Figure 2. Characteristics for Ca^{2+}-selective electrodes 1 and 4 with ionophores **1** and **2** in PVC/BEHS membrane.

$Ni^{2+} > Cd^{2+}$. Selectivity was determined by the separate solution method (SSM).[23] The calculated selectivity coefficients for electrodes 1–6 based on ligands **1** and **2** are shown as their logarithmic values in Diagram 1a, b.

In solutions of rather high lithium concentration (10^{-3}–10^{-1} M) electrodes 1–6 show near-Nernstian characteristics for Li^+. We also found selectivity coefficient values favouring lithium ($\log K^{pot}_{Ca,Li} = +1.5$) but this is not of practical importance, because of the narrow linear range of the electrode characteristic. The second ion of preference for the electrodes is Zn^{2+} and the selectivity coefficient values as $\log K^{pot}_{Ca,Zn} = -1.5$.

In order to investigate the binding properties toward metal centers, new calix[4]arene ligand **1** was allowed to react with 1 equiv of calcium(II), lanthanum(III), europium(III) or gadolinium(III) nitrate. The complexes are yellow, air stable solids, soluble in methanol and chloroform. The formulations of these complexes as $[Ca(NO_3)(\mathbf{1})][Ca(NO_3)_3]\cdot 4CH_3OH\cdot 7H_2O$ $[La(NO_3)_3(\mathbf{1})]\cdot CH_3OH\cdot 6H_2O$, $[Eu(NO_3)_3(\mathbf{1})]\cdot CH_3OH$ and $[Gd(NO_3)_3(\mathbf{1})]\cdot 6CH_3OH\cdot 10H_2O$ follow from IR, UV/Vis, ES-MS, ^1H and ^{31}P NMR spectral data and elemental analysis.

To elucidate the coordination mode of this calix[4]arene, spectral characterization of the complexes was performed with reference to the free ligand. The IR spectroscopic data are consistent with a coordination taking place through P=O groups of the ligand. P=O stretching frequency observed as a strong band at 1207 cm^{-1} in the free ligand is shifted ($\Delta\nu = 11$–$26\ cm^{-1}$) to lower frequencies upon complexation as expected from reducing the electron density on the oxygen atom due to coordination with metal cations. The shifts of the other P vibrations are difficult to determine since the calix[4]arene modes fall in the same region. In the spectra of the complexes, additional bands of medium intensity occur in the 553–543 cm^{-1} region and may be assigned to the metal–oxygen vibration. The IR spectra clearly demonstrate the presence of coordinated nitrates. The profile and magnitude of splitting (163–188 cm^{-1}) of the bands associated with asymmetric nitrate vibrations is typical of the bidentate chelating behavior of nitrate counterions. The broad diffuse band of medium intensity centered at 3446–3422 cm^{-1} is assigned to the symmetric and antisymmetric O– stretching mode of water molecules.

Further evidence for the coordination of the P=O groups and for the stability of the complexes in solution arises from the comparison of the ^1H and ^{31}P NMR spectra of calix[4]arene ligand and its diamagnetic complexes. The ^1H NMR spectrum of the lanthanum complex displays a downfield shift of the protons in close vicinity to the P=O groups (see Section 3). The characteristic AB spin pattern of the non equivalent axial and equatorial protons of the Ar–CH_2–Ar methylene bridges remains intact after complex formation providing evidence that the calix[4]arene ligand **1** retains the cone conformation in the complex. The ^{31}P NMR shifts are also affected by the complexation. The ^{31}P NMR spectra of the calcium and lantanum nitrate complexes of **1** show a single shifted resonance ($\Delta\delta = 3.22$ ppm for La and 2.43 ppm for Ca, relative to the free ligand) consistent with all four P=O moieties coordinating to the metal.

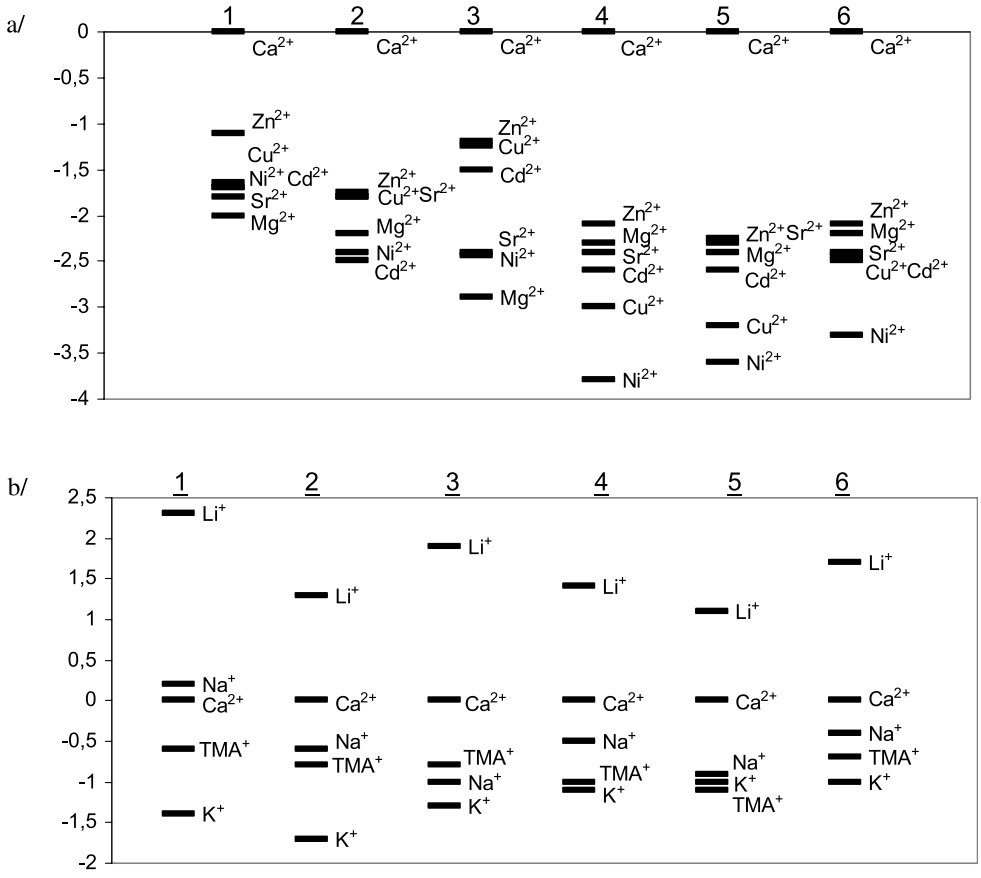


Diagram 1. Potentiometric selectivity coefficients as log $K^{pot}_{Ca,J}$ determined by the separate solution method (SSM) for the membrane electrodes 1–6; for clarity: a/J = divalent cations tested; b/J = alkali metal and tetramethylammonium ions.

The electronic spectra of the ligand and its complexes in methanol show similar features containing three absorption bands with maxima at 232.5, 277.5 and 282.5 nm for the free ligand and 229.0–238.5, 275.5–276.0 and 281.5 for the complexes attributable to intraligand $\pi\rightarrow\pi^*$ transition slightly affected by metal–ligand interaction. The luminescence spectrum of the europium complex of **1** supports complex formation showing medium and intense lines at $\lambda_{em}=592$ and 620 nm associated with $^5D_o\rightarrow{}^7F_1$ and $^5D_o\rightarrow{}^7F_2$ transition.

In order to reveal the molecular complexity, ESI-MS spectra have been recorded in both positive and negative modes. As a mild method, electrospray ionization mass spectroscopy has been proven to be particularly suitable for large, noncovalent species with high molecular masses. The ESI spectra display peaks corresponding to ligand **1** coordinated to the appropriate metal ion with the loss of nitrate anions. All the spectra exhibit peaks assigned to the species containing one metal ion coordinated to one molecule of the ligand. The ESI spectrum of the calcium complex shows an additional prominent feature, namely a major peak at a mass corresponding to the $Ca(NO_3)_3^-$ anion.

Elemental analyses are consistent with the formation of compounds with a 1:1 metal/ligand stoichiometry for lanthanide ions, while a compound with a 2:1 metal/ligand stoichiometric ratio was isolated with a calcium ion. The IR spectra (vide supra) reveal the presence of coordinated nitrate counterions.

Interestingly, we have found the same 2:1 metal/ligand stoichiometry in calcium(II) and lanthanum(III) nitrate complexes with calix[4]arene ligand **3**, obtained in similar experimental conditions and formulated as $[Ca(NO_3)(\mathbf{3})][Ca(NO_3)_3]\cdot 4H_2O$ and $[La(NO_3)_2(\mathbf{3})][La(NO_3)_4]\cdot 12H_2O$ on the basis of spectral and analytical data. The ESI mass spectra exhibit the peaks at $m/z=1463.2$ and 1623.0 consistent with the $[Ca(NO_3)(\mathbf{3})]^+$ and $[La(NO_3)_2(\mathbf{3})]^+$ species, respectively, containing one metal ion coordinated to one molecule of the ligand. The ESI spectra run in the negative mode show major peaks at $m/z=226.0$ and 387.0 corresponding to the $Ca(NO_3)_3^-$ and $La(NO_3)_4^-$ anions, respectively. These results along with the known tendency of calcium and lanthanide ions to form stable polynitrato anionic species allow us to assume that the complexes of calix[4]arene **1** and **3** with calcium and lanthanide ions contain the cationic complex with ligand coordinated to the metal ion in the 1:1 ratio and, in some cases, polyanionic species with the inorganic anion coordinated to the metal ion which balances the charge of the complex cation. Molecular model analysis and references to the known structures of related substituted calix[4]arenes[24–27] reveal that the new calix[4]arene ligands functionalized with phosphonoyl goups are capable of encapsulating calcium or lanthanide ions in the pseudo-cavity that is spatially

defined by the oxygen atoms of the four P═O groups located in the pendant arms. There does not appear to be enough space to accommodate a second metal ion into this cavity. Saturation of the high coordination number typical of calcium and lanthanides is achieved by the incorporation of the bidentate chelating nitrate groups in the coordination environment. The similar chelating behaviour of the alkoxyphosphorylated *tert*-butylcalix[4]arenes toward calcium and lanthanide ions seems to be an important observation in view of the use of the lanthanides as a presumed isomorphous replacement for calcium for potential biochemical and medical applications.

3. Experimental

3.1. General

The ^{1}H and ^{31}P NMR spectra were recorded on a Varian 500 MHz spectrometer. Mass spectra (MALDI TOF techniques) were obtained on a Bruker BIFLEX 3 mass spectrometer. Electrospray mass spectra were determined in methanol using a Waters Micromass ZQ spectrometer. IR spectra were recorded using KBr pellets in the 4000–400 cm^{-1} on a Perkin-Elmer 580 spectrophotometer. The electronic absorption spectra were measured on a Shimadzu UV 2401 PC spectrometer in methanol. The luminescence spectrum for the europium complex of **1** in methanol was recorded using a Perkin-Elmer MPF-3 spectrofluorometer with the excitation wavelength of 394 nm. Microanalyses were obtained using a Carlo Erba Instruments CHNS-O EA1108—Elemental Analyzer and an Elementar Vario III microanalyzer. The organic reagents and solvents were reagent grade. Both the structure and purity of the compounds were confirmed by NMR, mass spectra and elemental analysis. Hydrated lanthanide(III) nitrates were prepared by dissolving the 99.99% oxide (Fluka) in a slight excess of nitric acids. The solutions were evaporated and the precipitates were recrystallized from methanol. Calcium nitrate (Merck) was used as received.

3.1.1. Synthesis of 1. 5,11,17,23-tetra-*tert*-Butyl-25,26,27,28-tetrakis(3-disopropoxyphosphorylpropoxy) calix[4]arene (**1**) was prepared according to the procedure published earlier for compound **3**[8] (see Scheme 1). Yield of waxy semisolid 68%. R_f=0.3 in $CHCl_3$: CH_3OH 10:1.

$C_{80}H_{132}O_{16}P_4$ (**1**): 1473.76 MS (MALDI TOF) *m/z* 1474.0; 1496.0 [M+Na^+], 1512.0 [M+K^+]; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.06 (s, 36H, *t*-But), 1.30 (m, 48H, 8CH(CH_3)$_2$), 1.75 (m, 8H, 4CH_2), 2.15 (m, 8H, 4P-CH_2), 3.16 (d, AB $^{2}J_{H,H}$=12.6 Hz, 4H, ArCH_2Ar eq), 3.98 (m, 8H, ArOCH_2), 4.33 (d, AB $^{2}J_{H,H}$=12.6 Hz, 4H, ArCH_2Ar), 4.68 (m, 8H, PCH(CH_3)$_2$), 6.72 (s, 8H, ArH); ^{31}P NMR ($CDCl_3$) δ (ppm): 31.15; IR (film) (ν cm^{-1}): 3454, 1467, 1386, 1207, 1110, 989; EA Calcd for ($C_{80}H_{132}O_{16}P_4\cdot CH_3OH$): C, 64.63; H, 9.03; Found: C, 64.60; H, 8.79.

3.1.2. Synthesis of 2 (see Scheme 2). *Synthesis of 5,11,17,23-tetra-tert*-butyl-25,26,27,28-tetrakis(3-ethoxyhydroxyphosphorylpropoxy)calix[4]arene. 5,11,17,23-tetra-*tert*-Butyl-25,26,27,28-tetrakis(3-diethoxyphosphorylpropoxy)calix[4]arene (**3**) (68 mg, 0.05 mmol) was added in one portion to a stirred slurry of potassium trimethylsilanolate $K^+{}^-OSi(CH_3)_3$ (38 mg, 0.3 mmol) in dry methylene chloride (3 mL) at ambient temperature under argon. The reaction mixture was stirred for 72 h and evaporated in vacuo. The residue was taken up in methylene chloride (6 ml) and washed with 1 M hydrogen chloride (4 mL) and water (4 mL). The organic layer was dried with $MgSO_4$ and filtered. After evaporation of the solvent, the solid residue was purified using preparative TLC in solvent system *i*-PrOH:NH_4OH:H_2O 6:1:1. R_f=0.2. Ammonium salt of the product was acidified with Dowex 50×8 H^+ ion exchange resin. The acid was eluted with 10 mL of methanol and evaporated. Yield 37 mg (60%).

$C_{64}H_{100}O_{16}P_4$: 1249.33 MS (MALDI TOF) *m/z*=1249.7, 1271.7 [M+Na]$^+$, 1287.6 [M+K^+]; ^{1}H NMR (CD_3OD) δ (ppm): 1.07 (s, 36H, *t*-But), 1.32 (t, $J_{H,H}$=6.8 Hz, 12H, 4CH_2CH_3), 1.85–2.05 (m, 8H, 4CH_2), 2.20–2.40 (m, 8H, 4CH_2), 3.14 (d, AB $^{2}J_{H,H}$=12.7 Hz, 4H, ArCH_2Ar eq), 3.98 (t, $^{3}J_{H,H}$=7 Hz, 8H, ArOCH_2), 4.05–4.20 (m, 8H, POCH_2), 4.40 (d, AB $^{2}J_{H,H}$=12.7 Hz, 4H, ArCH_2Ar), 6.76 (s, 8H, ArH); ^{31}P NMR (CD_3OD) δ (ppm): 32.7.

Synthesis of 5,11,17,23-tetra-tert-butyl-25,26,27,28-tetrakis(3-ethoxymethoxyphosphorylpropoxy)calix[4]arene (**2**). To an ice-cooled solution of (63 mg, 0.05 mmol) of 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis(3-ethoxyhydroxyphophorylpropoxy)calix[4]arene in methanol an etherial solution of diazomethane was added portion wise until the solution became light yellow. Volatile components of the reaction mixture were distilled off under reduced pressure. Yield of oil, 65 mg, 100%. R_f=0.33 in $CHCl_3$: CH_3OH 10:1.

$C_{68}H_{108}O_{16}P_4$: 1305.4 MS (MALDI TOF) *m/z*=1305.5, 1327.6 [M+Na^+], 1343.6 [M+K^+]; ^{1}H NMR (CD_3OD) δ (ppm): 1.10 (s, 36H, *t*-But), 1.35 (t, J_{H-}=6.8 Hz, 12H, 4CH_2CH_3), 1.88–2.10 (m, 8H, 4PH_2CH_2), 2.12–2.36 (m, 8H, 4PCH_2CH_2), 3.18 (d, AB $^{2}J_{H,H}$=12.6 Hz, 4H, ArCH_2-Ar eq), 3.77 (t, $^{3}J_{P,H}$=10.9 Hz, 12H, POCH_3), 4.01 (t, $^{3}J_{H,H}$=7 Hz, 8H, ArOCH_2), 4.08–4.22 (m, 8H, POCH_2), 4.40 (d, AB $^{2}J_{H,H}$=12.6 Hz, 4H, ArCH_2Ar), 6.85 (s, 8H, ArH); ^{31}P NMR (CD_3OD) δ (ppm): 35.5; IR (film) (ν cm^{-1}): 3452, 1472, 1241, 1205, 1115, 1026, 959, 877, 813; EA Calcd for $C_{68}H_{108}O_{16}P_4$: C, 62.50; H, 8.27; Found: C, 62.26; H, 8.28.

3.2. Membrane preparation and EMF measurements

Poly(vinyl chloride) high molecular (PVC), bis(2-ethylhexyl)sebacate (BEHS), bis(butylpentyl)adipate (BBPA), *o*-nitrophenyloctylether (*o*-NPOE) and potassium tetrakis(*p*-chlorophenyl)borate (KTClPB) were from Fluka. Tetrahydrofuran (THF) p.a., from POCh, was dried and freshly distilled before use. All aqueous salt solutions were prepared with ultra-pure water (conductivity below 0.1 μS/cm). The salts LiCl, NaCl, KCl, NH_4Cl, $MgCl_2$, $SrCl_2$, $NiCl_2$, $CuCl_2$, $ZnCl_2$, $CdCl_2$, $Pb(NO_3)_2$ (POCh) and $CaCl_2$, tetramethylammonium chloride (TMA$^+$Cl$^-$) (Fluka), RbCl and CsCl (Ubichem Ltd) were of p.a. grade.

The preparation of the membrane for ion-selective electrodes (ISE) was described in Ref. 8. The membrane

composition: ionophore (2.2%), PVC (32.5%), plasticizer (65%) (optionally three plasticizers: BEHS, *o*-NPOE and BBPA were used) and KTpClPB (0.27%) were dissolved in 1.5 mL of dried and distilled THF. The solution was poured into a glass ring fixed on the glass plate. Membranes of 7 mm diameter were incorporated into Ag/AgCl electrode bodies of IS 561 type (Moeller AG-Zurich). A double-junction reference Radelkis 0P0820P electrode was used with 1 M NH_4NO_3 solution in a bridge cell. Measurements were carried out at 20 ± 1 °C using 16-channel Lawson Labs station 16 EMF (USA); the cells were of the type: Ag|AgCl|1 M KCl|1 M NH_4NO_3 |sample||membrane||0.01 M NaCl|AgCl|Ag.

For the characteristics of the electrodes the measurements were carried out by titration with the appropriate salt solutions of 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} and 10^{-1} mol/L concentration. For $NiCl_2$, $CuCl_2$, $ZnCl_2$, $CdCl_2$ and $Pb(NO_3)_2$ salts the solutions were made in 10^{-4} M HCl solution and pH=4 was controlled during the titration. The characteristics of the studied electrodes 1–6 are shown in Table 1. The typical calibration curves obtained for the NPOE/PVC and BEHS/PVC membrane electrodes in $CaCl_2$ solutions are shown in Figures 1 and 2.

3.2.1. Selectivity coefficients and electrode characteristics. Potentiometric selectivity coefficients ($\log K^{pot}_{Ca,J}$) were determined by the separate solution method (SSM)[23] and were calculated using the EMF values for the measured ion activities at concentration 10^{-2} M. The results for six membrane electrodes containing ionophores **1** and **2** are presented in Diagram 1a, b.

3.3. Preparation of the complexes—general procedure

All complexes were prepared under similar conditions. To a solution of metal nitrate (0.003 mmol) in methanol (1 mL) the ligand **1** (0.003 mmol) in methanol (1 mL) was added dropwise with stirring. The reaction was carried out for 3–5 days. The solution volume was then reduced to 0.3 mL by roto-evaporation and yellow precipitate formed on addition of a small amount of diethyl ether. This precipitate was filtered off, washed with ether, and dried in vacuo.

3.3.1. $La(NO_3)_3(1)]\cdot CH_3OH\cdot 6H_2O$ ($1=C_{80}H_{132}O_{16}P_4$). IR (KBr, cm^{-1}): 3446m, br, (OH), 1192s, (P═O), 543m, (M–), 1481–1293, 817m, (NO_3^-); ^1H NMR ($CDCl_3$, ppm): $\delta=1.07$ (s, 36H, *t*-But), 1.34 (m, 48H, $CH(CH_3)_2$), 1.80, (m, 8H, PCH_2CH_2) 2.25 (m, 8H, P–H_2–CH_2), 3.16 (d, $J=$ 12.8 Hz, 4H, Ar–CH_2–Ar eq); 3.90 (m, 8H, Ar–O–CH_2), 4.33 (d, 4H, $J=12.8$ Hz, Ar–CH_2–Ar ax), 4.80 (8H, m, P—*CH*–$(CH_3)_2$), 6.70 (s, 8H, Ar*H*); ^{31}P NMR ($CDCl_3$, ppm): $\delta=27.93$; ESI^+ $m/z=837.0$ $[La(NO_3)(\mathbf{1})]^{2+}$. Anal. Calcd C, 50.18; H, 7.69; N, 2.17. Found: C, 50.67; H, 7.35; N, 1.97.

3.3.2. $Eu(NO_3)_3(1)]\cdot CH_3OH$. IR (KBr, cm^{-1}): $\nu=1181$s, (P═O), 551m, (M–), 1482–1299s, 817m, (NO_3^-); ESI^+ $m/z=571.0$ $[Eu(\mathbf{1})\cdot 3H_2O\cdot CH_3OH]^{3+}$. Anal. Calcd C, 52.70, H, 7.37, N, 2.27. Found: C, 54.09, H, 7.35, N, 2.24.

3.3.3. $Gd(NO_3)_3(1)]\cdot 6CH_3OH\cdot 10H_2O$. IR (Kbr, cm^{-1}): $\nu=3446$m, (OH), 1195s, (P═O), 553m, (M–), 1481–1301s, 815m, (NO_3^-); ESI^+ $m/z=888.0$ $[Gd(NO_3)(\mathbf{1})\cdot H_2O\cdot 2CH_3OH]^{2+}$. Anal. Calcd C, 47.89, H, 8.16, N, 1.94. Found: C, 47.51, H, 7.92, N, 2.22.

3.3.4. $Ca(NO_3)(1)][Ca(NO_3)_3]\cdot 4CH_3OH\cdot 7H_2O$. IR (KBr, cm^{-1}): $\nu=3422$m, (OH), 1196s, (P═O), 546m, (M–), 1481–1318s, 819m, (NO_3^-); ^1H NMR ($CDCl_3$, ppm): $\delta=$ 1.06 (s, 36H, *t*-But), 1.33 (m, 48H, $CH(CH_3)_2$), 1.78, (m, 8H, PCH_2CH_2) 2.22 (m, 8H, PCH_2CH_2), 3.16 (d, $J=$ 12.8 Hz, 4H, Ar–CH_2–Ar eq); 3.93 (m, 8H, Ar–O–CH_2), 4.33 (d, 4H, $J=12.8$ Hz, Ar–CH_2–Ar ax), 4.78 (8H, m, P*CH*–$(CH_3)_2$), 6.70 (s, 8H, Ar*H*); ^{31}P NMR ($CDCl_3$, ppm): 28.72; ESI^+ $m/z=799.0$ $[Ca(\mathbf{1})\cdot 3H_2O\cdot CH_3OH]^{2+}$, 757.0 $[Ca(\mathbf{1})]^{2+}$; ESI^- $m/z=226.0$ $[Ca(NO_3)_3]^-$. Anal. Calcd C, 49.01, H, 7.88, N, 2.72. Found: C, 48.97, H, 8.03, N, 2.72.

Acknowledgements

Financial support from Gdańsk University of Technology (DS 014668/003) are gratefully acknowledged.

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Tetrahedron 61 (2005) 12314–12322
Tetrahedron

Synthesis of dendritic oligo(aryl sulfone)s as supports for synthesis

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Received 27 May 2005; revised 25 August 2005; accepted 22 September 2005

Available online 25 October 2005

Abstract—A short, divergent route to G_1 oligo(aryl sulfone)s and a G_2 oligo(aryl sulfone) dendrimer using nucleophilic aromatic substitution reactions is described. A range of tetrasubstituted pentasulfones are proposed for applications as homogeneous supports for synthesis. Key to achieving selectivity in the syntheses is the activation of leaving groups by sulfide to sulfone oxidation. Preparation of the G_2 oligo(aryl sulfone) is low-yielding due to competition from SET processes that are interesting from a mechanistic point of view. The utility of the supports is exemplified with a four step synthesis of a dipeptide and by 'react and release' synthesis of amides.

1. Introduction

The use of solid-supports is now widespread in organic synthesis. In 1963, Merrifield introduced cross-linked polystyrene for the synthesis of oligopeptides.[1] Since then, this approach has been extended to numerous other classes of compounds, in particular following the advent of parallel synthesis in 1985.[2] The development of solid supported analogues of homogeneous catalysts has also been an area of significant activity for a number of years.[3] More recently, solid supported reagents and scavenger resins have become popular synthetic tools.[4] In all these cases, the salient advantage of the solid supported technology is that separation of the supported species from products or by-products in the solution phase is extremely facile.

In the first two of the areas mentioned above, namely solid-supported synthesis and catalysis there are significant disadvantages with the technology.[5] In particular, it is difficult to characterise the supported species using conventional spectroscopic techniques. The principal drawbacks of solid supports can, to some extent, be avoided by using soluble polymer supports, for example poly(ethylene glycol) (PEG) supports.[6] While these supports do not permit separation from the solution phase by conventional filtration, separation can be achieved readily by centrifugation, precipitation or membrane filtration. Unfortunately, supports such as PEG permit only low loadings.

Dendrimers are soluble polymers that are highly symmetrical and have a large number of surface functional groups. These two features make dendrimers highly attractive as supports for synthesis and for catalysis, since they are readily characterised, for example by conventional NMR spectroscopy, all the surface functional groups are identical, which should lead to high selectivities, and high loadings can be achieved.[7] It should be noted that dendrimers are, in general, much more expensive than their conventional polymer analogues.

There has been a good number of reports of dendrimers as supports for, in particular, catalysis.[8] Separation of the supported catalysts can be achieved by membrane filtration.[9–11] We felt that there was a need for the de novo design of dendrimers to be used as supports and that the new dendrimer supports should meet the following criteria: be stable to a wide range of reaction conditions; have very simple NMR spectra to allow integration relative to the supported species; have good solubility in common organic solvents; be easy to prepare without needing protecting group strategies.

2. Results and discussion

Our chosen class of dendrimer supports was poly(aryl sulfone)s, since these compounds appeared to meet all the criteria listed above. Taking into account the literature precedent on synthesis of oligo(aryl sulfide) dendritic species[12] and initial experiments in our laboratory, we decided on a divergent synthesis of our target sulfone **6** (Scheme 1), which has eight functional groups for

Keywords: Dendrimer; Sulfone; Nucleophilic aromatic substitution; Single electron transfer; Supported synthesis.
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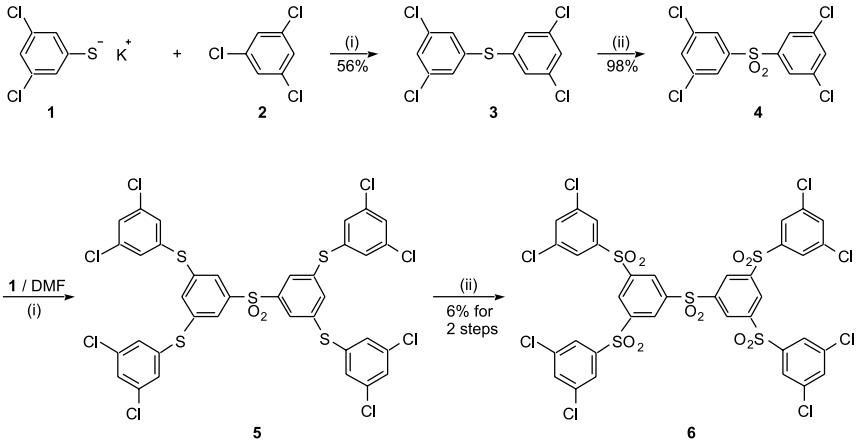
doi:10.1016/j.tet.2005.09.103



Scheme 1. (i) 80 °C, 60–80 h; (ii) H_2O_2/AcOH/H_2O.

derivatisation. The key reaction in the series is the repeated nucleophilic aromatic substitution of chloride by thiolate **1**. At all stages, there are a number of chloride groups that can be substituted. We reasoned that a good yield of **3** would be achieved by using an excess of trichlorobenzene **2**. In the other nucleophilic aromatic substitution reaction, the desired selectivity (i.e., substitution of chloride groups of the substrate **4** rather than that of the product **5** or of **1**) was to be achieved by prior activation of the sulfide group through oxidation to the corresponding sulfone, since electron-demanding groups, even in the *meta* orientation, are known to favour nucleophilic aromatic substitution.[13]

Reaction of the thiolate **1**, derived from commercially available 3,5-dichlorobenzenethiol, with excess trichlorobenzene, using a modification of the conditions developed by Testaferri et al., led to sulfide **3** in 56% yield.[14] Quantitative oxidation to the sulfone **4** was achieved by modification of a literature procedure.[15] Repetition of these two steps was all that was required to complete the synthesis of **6**, but unfortunately the next substitution step did not proceed smoothly and led to a mixture of mono- **7**, di- **8**, tri- **9** and tetra-substituted products **5**. Nevertheless, a mixture of tri-substituted **9** and tetra-substituted **5** products was isolated and oxidised to the corresponding mixture of sulfones, from which our target compound **6** was isolated pure by chromatography. The yield of **6** from the two steps was a very disappointing 6%.

The troublesome substitution reaction was monitored by HPLC. Authentic samples of di- and tri-substituted products **8** and **9** were obtained by preparative HPLC and characterised by mass spectrometry. It should be noted that two isomeric disubstituted products **8** are possible. We believe from chromatographic evidence that only one of the two is formed, but insufficient material was isolated to permit structural characterisation. A simple plot of % conversion versus time (Fig. 1) suggested that the reaction could be reaching equilibrium and that only a 10% yield of the desired product was possible. To prove this hypothesis it would be necessary to resubmit **6** to the reaction conditions, but the very low yield precluded this.

In an attempt to push the reaction to completion, excess thiolate **1** was used under numerous different reaction conditions. In all these cases a very complex mixture of products resulted, which on one occasion was characterised by mass spectrometry (Fig. 2). The mass spectrum showed an apparent series of envelopes of peaks separated on average by ca. 35 amu, fortuitously leading us to the idea that carbon–chlorine bonds were being reduced.

The formation of the reduced products is consistent with a single electron transfer (SET) mechanism competing with, or supplanting, the nucleophilic aromatic substitution (S_NAr) mechanism we assume to be predominant in the reactions described above. That aryl halides can react via an

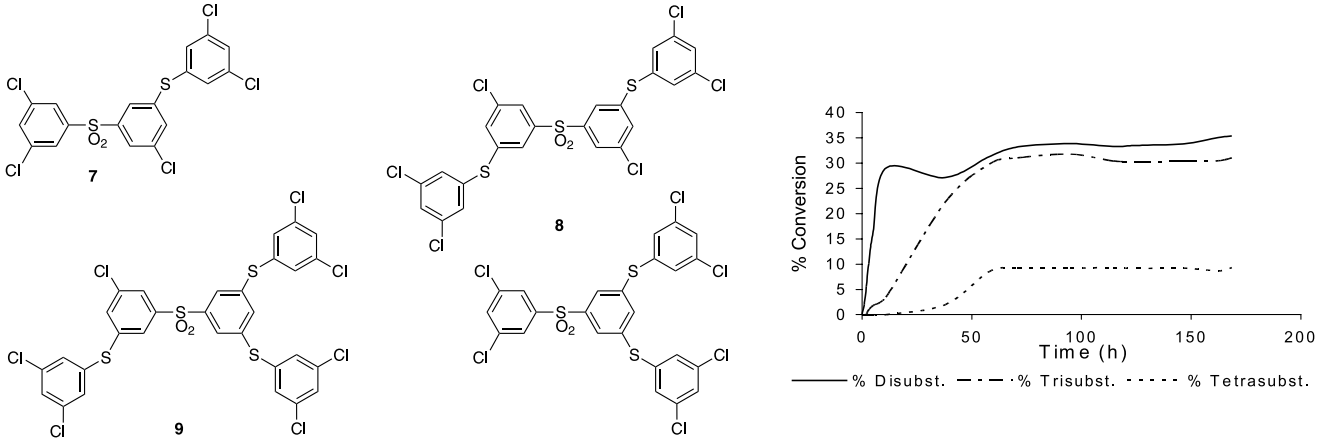


Figure 1. % Di-, tri- and tetra-substituted products in the reaction of sulfone **4** with thiolate **1**.

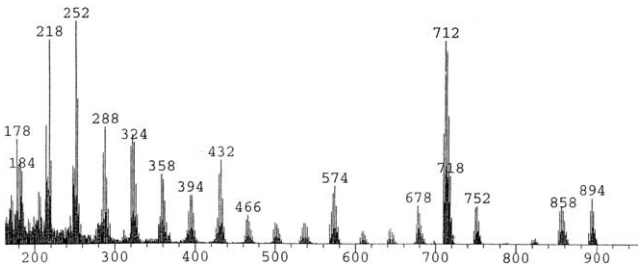


Figure 2. Detail from EI mass spectrum of product mixture from reaction of **4** with excess thiolate **1**.

SET mechanism is well known.[16–18] However, reactivity decreases through the series ArI > ArBr > ArCl > ArF and indeed there are relatively few examples of $S_{RN}1$ substitution of chlorobenzenes.[16] $S_{RN}1$ substitutions are normally 'stimulated' photochemically, electrochemically, by solvated electrons or by transition metal salts, yet the reactions described here take place on warming with no external source of electrons other than laboratory lights. A number of factors may explain the surprising SET reactivity of these chlorobenzene substrates. In particular, sulfone **4** and substitution products **5**, **7**, **8** and **9** should be excellent electron acceptors and the radical that is formed by SET from thiolate **1** is significantly stabilised.

Our suggested mechanism for reaction of **4** with excess **1** is shown in Scheme 2. The closest precedent for the proposed intermediates is found in the work of Bunnett and Creary[19] and of Amatore et al.[20] on the photostimulated substitution of *meta*-chloroiodobenzene by phenylthiolate. In contrast to their work, the substitution processes here appear to be reversible. This will ensure a high enough concentration of radical species to permit H-abstraction to become a significant pathway, thus explaining the preponderance of reduced products in our case.

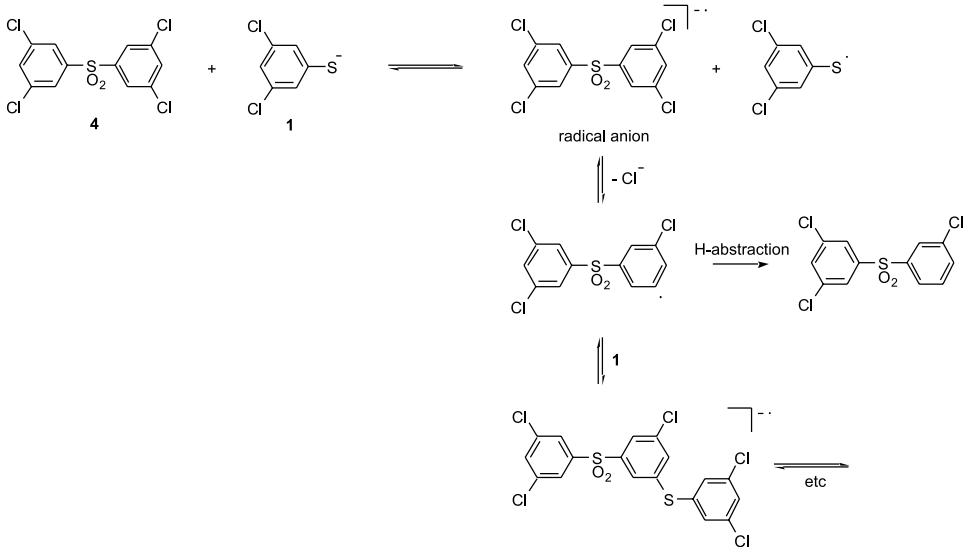
Whether the sulfides observed result from $S_{RN}1$ or S_NAr processes, or both, is not known. Reaction of thiolates and aryl radicals has been shown to be slow,[21] but there is evidence of simultaneous operation of the two mechanisms in a similar system.[22] Whichever mechanism is operating, it seems that a substitution reaction requires a sulfone substituent on the ring being substituted, since higher oligomers were never observed. The two possible processes are thus reduction of any carbon chlorine bonds in any of **4**, **5**, **7**, **8** and **9** alongside substitution of any or all of the four chlorides in **4** to give sulfides **5**, **7**, **8** or **9**. The two processes correspond to a loss of 34.45 amu or an increase of 142.61 amu, respectively. Therefore, the isotopically averaged masses for all the possible products are predicted by $M = 356.06 + 142.61m - 34.45n$ where: m = number of substitutions and $0 \le m \le 4$; n = number of reductions and $0 \le n \le (m+4)$. The series generated is given below, with predicted masses that lie in the same region being linked in parentheses and masses for which there are two isomers in italics.

(926.5), (892.0), (857.6), (823.2), (788.7, 783.9), (754.2, 749.4), (719.8, 715.0), (685.4, 680.5), (650.9, 646.1, *641.3*), (611.6, *606.8*), (577.2, *572.4*), (542.7, *537.4*), (*503.5*, 498.7), (*469.0*, 464.2), (*434.6*, 429.8), (395.3), (360.9, 356.1), (326.4, 321.6), (287.2), (252.7), (218.3).

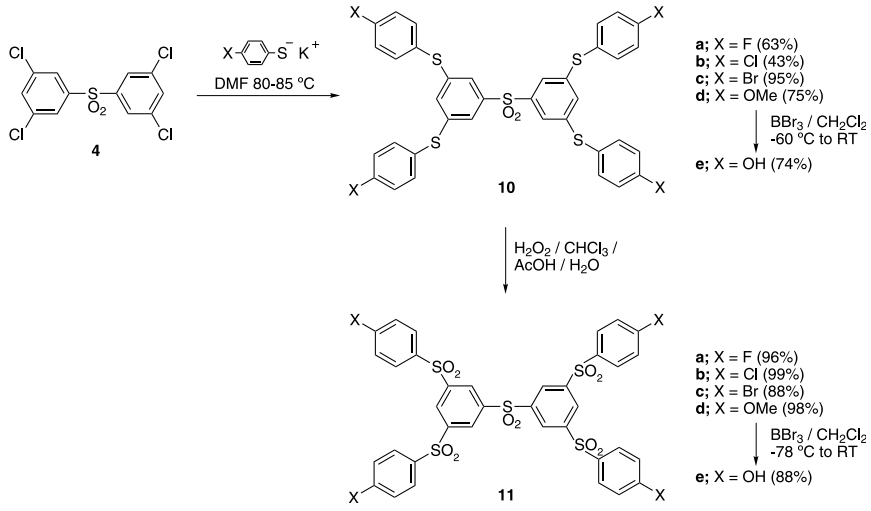
This series corresponds very closely to the 20 observed envelopes of peaks in the mass spectrum (Fig. 2), although we have not analysed the isotope patterns. The only predicted mass to be totally absent is the highest (926.5). Thus, we have a remarkable situation in which the mass spectrum is consistent with the presence of the starting material and all 40 predicted by-products yet none of the desired product!

In fact, dendrimers as complex as **6** are not required for most applications. Hence, we proceeded to investigate reactions of **4** with monosubstituted phenylthiolates, since these were predicted to be poorer both as leaving groups and as electron donors, thus avoiding the problems we had encountered with the dichlorophenylthiolate.

To provide supports that could be derivatised by reaction with either nucleophiles or electrophiles, we prepared the



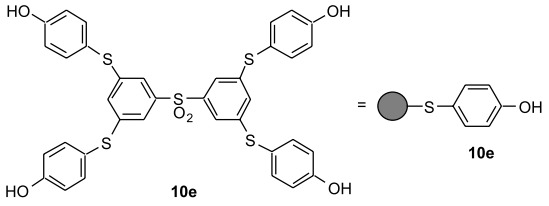
Scheme 2.



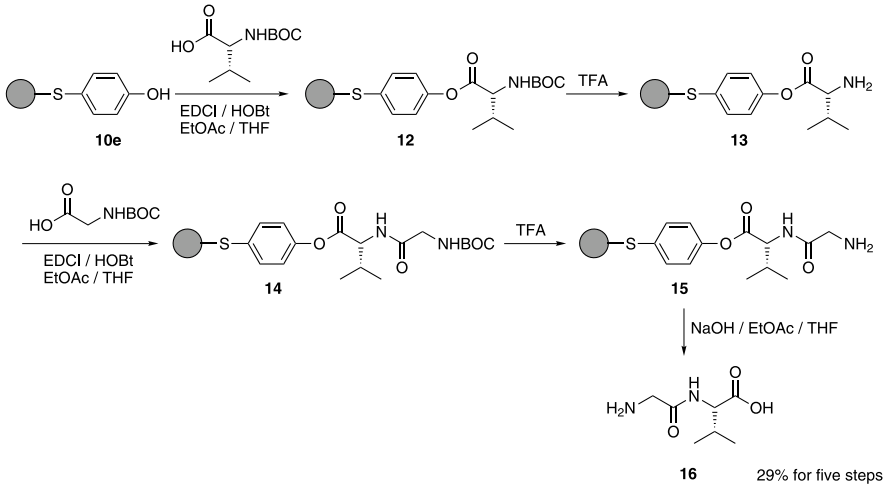
Scheme 3.

p-halo and *p*-hydroxy derivatives **10a–c** and **10e** and **11a–c** and **11e** (Scheme 3). In all these cases the aromatic substitution reaction proceeded smoothly to yield tetrasulfides **10**, as did the subsequent oxidation to **11**. Deprotection of the methoxy compounds **10d** and **11d** was also high yielding. However, despite repeated purification attempts, we were unable to remove all traces of complexed boron species from products **10e** and **11e**. The range of compounds **11** prepared will allow derivatisation by nucleophilic aromatic substitution with both hard (when X=F) and soft (when X=Cl) nucleophiles, by palladium catalysed coupling reactions (when X=Br) and by simple reactions with electrophiles (when X=OH). While compounds **10** do not meet all of our design criteria, they are also potentially useful supports if oxidising agents are not being used (vide infra).

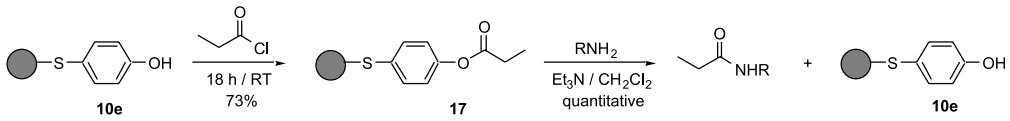
To demonstrate that the new supports have potential in synthesis, we focussed on the phenolic tetrasulfide support **10e**. It should be noted that we did not have facilities for membrane separation in our laboratories, hence conventional purification methods were used.



Firstly, a five step supported synthesis of a dipeptide was realised. The choice of a peptide synthesis was somewhat arbitrary and many more classes of synthesis need to be explored to fully assay the potential of the new supports. Purities of 90% or greater as judged by NMR spectra were considered sufficient to proceed to the next step. Boc protected valine was coupled to the support using an adaptation of the EDCI–OBt method for peptide coupling.[23] After deprotection, Boc protected glycine was coupled using the same method, again with TFA mediated deprotection. Finally, sodium hydroxide was used to hydrolyse the ester, yielding the desired dipeptide **16** pure in 29% overall yield and recovered support **10e** (Scheme 4).



Scheme 4.



Scheme 5.

For applications in combinatorial synthesis, it is advantageous for the final cleavage step to permit the further introduction of diversity, the so-called 'react and release' method.[24] This was demonstrated by the formation of a model tetrapropionyl ester of **10e**. Reaction of ester **17** with both benzylamine and cyclohexylamine yielded the desired amides in good yield, with the support being recovered in both cases (Scheme 5). Aniline, which is less nucleophilic, did not function well in the react and release protocol.

3. Conclusion

In summary, a short, divergent synthesis of G_1 and G_2 oligo(aryl sulfones) has been achieved using nucleophilic aromatic substitution reactions. Activation of the G_n leaving groups prior to formation of G_{n+1} by a sulfide to sulfone oxidation allows good selectivity. However, preparation of the G_2 oligo(aryl sulfone) was largely thwarted by competition from SET processes, this being unusual for chlorobenzene substrates. A range of tetrasubstituted pentasulfones have been prepared for applications as homogeneous supports for synthesis and the utility of one of them has been demonstrated through supported preparation of a dipeptide and through 'react and release' synthesis of amides.

4. Experimental

4.1. Bis-(3,5-dichlorophenyl) sulfide 3

To a round bottomed flask containing 3,5-dichlorothiophenol (5.0 g, 27.9 mmol) was added potassium carbonate (9.71 g, 69.8 mmol) and 1,3,5-trichlorobenzene (10.6 g, 58.7 mmol). The mixture was heated to 80 °C under a dry nitrogen atmosphere for 2.5 days. The solution was poured onto ice and the resulting solid precipitate was collected by filtration to yield an off-white solid (15.4 g), which was passed through a silica column using cyclohexane–ethyl acetate (10/1) yielding 2.72 g of a two component mixture, containing the desired product and 1,3,5-trichlorobenzene. This mixture was heated to 75 °C under vacuum to remove the trichlorobenzene. The liquid product was cooled to crystallize as a white solid (450 mg, 56%), R_f (eluent: hexane): 0.75 (Found: C, 44.47; H, 1.86. $C_{12}H_6SCl_4$ requires C, 44.36; H, 1.86); ν_{max} (cm^{-1}) 1575; δ_H (300 MHz; $CDCl_3$) 7.18 (4H, d, $J=1.8$ Hz, ArH), 7.25 (2H, t, $J=1.8$ Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 128.58 (ArH), 129.55 (ArH), 136.19 (quat), 137.78 (quat); *m/z* (EI) 324, ($[M\cdot]^+$ 50%), 252 (26), 182 (86), 145 (33), 83 (100).

4.2. Bis-(3,5-dichlorophenyl) sulfone 4

Hydrogen peroxide (30%, 20 ml) and acetic acid (17 M, 15 ml), in water (10 ml) were added to a round bottomed flask and heated to reflux. A solution of sulfide **3** (3.0 g, 9.26 mmol), in chloroform (10 ml) was added with care and the biphasic mixture was heated at reflux for 18 h. The mixture was cooled and the product extracted with chloroform (2×25 ml). The combined organic layers were washed several times with water, $NaHCO_3$ (5%, 2×50 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The white crystalline solid was passed through a silica column to reveal pure sulfone **4** in 98% yield, R_f (eluent: hexane): 0.63; mp 167–169 °C (Found: C, 40.98; H, 1.84. $C_{12}H_6SO_2Cl_4$ requires C, 40.48; H, 1.70); ν_{max} (cm^{-1}) 1144 (S=O); δ_H (300 MHz; $CDCl_3$) 7.60 (2H, t, $J=1.8$ Hz, ArH), 7.80 (4H, d, $J=1.8$ Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 126.34 (ArH), 134.43 (ArH), 137.08 (quat), 143.45 (quat); *m/z* (EI) 356, ($[M\cdot]^+$65%), 292 (7), 193 (100), 164 (12); *m/z* 353.8843 ($C_{12}H_6SO_2Cl_4$ requires 353.8838).

4.3. Bis-(3,5-bis-(3,5-dichlorophenylsulfanyl)phenyl) sulfone 5

To a solution of 3,5-dichlorothiophenol (2.1 mmol, 329 mg) in DMF (10 ml), was added potassium carbonate (1 equiv, 2.1 mmol, 255 mg) and **4** (0.13 equiv, 0.281 mmol, 100 mg). The solution was stirred under a nitrogen atmosphere at 80 °C for 80 h. The cooled solution was added to ice and the resulting solid precipitate was filtered, washed with water, redissolved in chloroform (20 ml) and washed with water, $NaHCO_3$, water and brine. The organic fraction was dried over $MgSO_4$ and concentrated under vacuum to furnish 290 mg of a four-component mixture. The mixture was subjected to flash chromatography on silica (eluent: hexanes/ethyl acetate 15:1), to furnish an inseparable mixture of **5** and tri-substituted impurity **9** (ratio by ^1H NMR, 5:1), R_f (eluent: petrol/ethyl acetate 10:1): 0.31; ν_{max} (cm^{-1}) 1159, 1128 (S=O); δ_H (300 MHz; $CDCl_3$) 7.06 (major, 2H, t, $J=1.5$ Hz, ArH), 7.20 (major, 8H, d, $J_m=1.9$ Hz, ArH), 7.35 (major, 4H, t, $J_m=1.9$ Hz, ArH), 7.60 (major, 4H, d, $J_m=1.5$ Hz, ArH), 7.10 (minor, t, $J_o=1.5$ Hz, ArH), 7.24 (minor, d, $J=1.9$ Hz, ArH), 7.30, (minor, t, $J=1.7$ Hz, ArH), 7.37, (minor, t, $J=1.7$ Hz, ArH), 7.40 (minor, t, $J=1.7$ Hz, ArH), 7.66, (minor, t, $J=1.7$ Hz, ArH), 7.70 (minor, t, $J=1.7$ Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 126.79 (major, ArH), 129.54 (major, ArH), 130.84 (major, ArH), 134.45 (major, ArH), 135.72 (major, quat), 136.44 (major, quatH), 140.16 (major, quat), 143.24 (major, quat), 126.71 (minor, ArH), 127.20 (minor, ArH), 129.74 (minor, ArH), 130.47 (minor, ArH), 130.90 (minor, ArH), 134.37 (minor, ArH), 134.78 (minor, ArH), 140.28 (minor, quat); *m/z* (EI) 926, ($[M\cdot]^+$100%), 784 ($[M\cdot]^+$, 35%), 748 (14), (CI, NH_4^+) 944 ($[M\cdot]^+ + NH_4^+$86), 802 ($[M\cdot]^+ + NH_4^+$).

4.4. Bis-(3,5-bis-(3,5-dichlorophenylsulfonyl)phenyl) sulfone 6

To a solution of crude **5** (720 mg, 0.778 mmol), in chloroform (20 ml), was added H_2O_2 (30%, 10 ml) and glacial acetic acid (9 ml) in water (5 ml). The biphasic mixture was heated to reflux with vigorous stirring for 4 h. The mixture was cooled and the organic layer separated, washed with water, NaOH (10%), water and brine. The solution was dried over $MgSO_4$ and concentrated under vacuum to give a crude white solid (710 mg), which was subjected twice to flash chromatography on silica (eluents: hexanes/ethyl acetate 15:1; cyclohexane/ethyl acetate 20:1), to give the target molecule as a white solid (50 mg, 6%) that was still contaminated by traces of the trisubstituted compound. R_f (eluent: petrol/ethyl acetate, 10:1): 0.25; ν_{max} (cm^{-1}) 1150, 1080 (S=O); δ_H (250 MHz; $CDCl_3$) 7.55 (4H, t, J_m=1.8 Hz, ArH), 7.75 (8H, d, J_m=1.8 Hz, ArH), 8.55 (6H, s, ArH); δ_C (75.5 MHz; $CDCl_3$) 126.86 (ArH), 132.18 (ArH), 132.64 (ArH), 135.32 (ArH), 137.60 (quat), 141.99 (quat), 143.69 (quat), 145.54 (quat); *m/z* (EI) 1054, ($[M\cdot]^+$36%), 880 (39), 844 (14), 670 (20), 496 (53), 333 (42), 193 (100); (CI, NH_4^+) 1072 ($[M\cdot]^+ + NH_4^+$23), 862 (29), 654 (68), 514 (100).

4.5. Bis-(3,5-bis-(4-fluorophenylsulfanyl) sulfone 10a

To a solution of 4-fluorothiophenol (395.5 mg, 3.1 mmol) in DMF (25 ml) was added potassium carbonate (390.3 mg, 2.8 mmol). The mixture was stirred at 20 °C for 20 min and heated to 85 °C. Sulfone **6** (250.0 mg, 0.7 mmol) was added the mixture and stirred under nitrogen at 85 °C for 7 days. The mixture was cooled and the solvent removed under vacuum. The resulting solid was washed several times with water, dried and subjected to flash chromatography on silica (eluent: cyclohexane/ethyl acetate 20:1) to reveal pure **11a** in 63% yield, R_f (eluent: hexane): 0.63; mp 154–156 °C (Found: C, 59.57; H, 3.01. $C_{36}H_{22}F_4O_2S_5$ requires C, 59.83; H, 3.05); ν_{max} (cm^{-1}) 1159 (S=O); δ_H (300 MHz; $CDCl_3$) 6.65 (2H, t, J_m=1.8 Hz, ArH), 7.06 (8H, AA′ of AA′BB′, C_6H_4), 7.31 (14H, m, ArH); δ_C (75.5 MHz; $CDCl_3$) 117.54 (d, $^2J_{CF}$=21.7 Hz, ArH), 123.06 (ArH), 126.04 (quat), 129.40 (ArH), 137.04 (d, $^3J_{CF}$=15 Hz, ArH), 142.70 (quat), 162.14 (quat), 163.64 (d, $^1J_{CF}$=251 Hz, Ar); *m/z* (EI) 722, ($[M\cdot]^+$100%), 724 (65), 726 (10), 630 (30).

4.6. Bis-(3,5-bis-(4-fluorophenylsulfonyl) sulfone 11a

To a solution of sulfide **10a** (84.0 mg, 0.1 mmol) in chloroform (0.5 ml) was added hydrogen peroxide (30%, 1.2 ml) glacial acetic acid (1 ml, 17 mmol) and water. The resulting mixture was stirred vigorously under reflux conditions for 12 h. The mixture was cooled and diluted with chloroform (20 ml) separated and washed with sodium hydroxide (10%, 10 ml), water and brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give **11a** as a white solid (98 mg, 96%). Satisfactory microanalysis was not obtained, R_f (eluent: cyclohexane/ethyl acetate 1:1): 0.21; mp>200 °C, (decomp.); ν_{max} (cm^{-1}) 1152 (S=O); δ_H (300 MHz; $CDCl_3$) 7.28 (8H, AA′ of AA′BB′, J_o=8.8 Hz, C_6H_4), 7.99 (8H, BB′ of AA′BB′, J_o=8.8 Hz, C_6H_4) 8.57 (2H, t, J_m=1.5 Hz, ArH), 8.59 (4H, d, J_m=1.5 Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 118.05 (d, J=22.9 Hz, ArH), 131.21 (ArH), 131.65 (d, J=9.9 Hz, ArH), 131.81 (ArH), 135.18 (quat), 143.58 (quat), 146.52 (quat), 164.18 (quat); *m/z* (EI) 850 ($[M\cdot]^+$45%), 818 (20), 692 (43), 143 (100).

4.7. Bis-(3,5-bis-(4-chlorophenylsulfanyl) sulfone 10b

To a solution of 4-chlorothiophenol (1.95 g, 13.48 mmol) and potassium-*t*-butoxide (1.51 g, 13.48 mmol) in DMF (90 ml) was added sulfone **6**. The mixture was heated to 85 °C for 12 days. After cooling the mixture was added to water and basified with sodium hydroxide (10%). The mixture was extracted with dichloromethane, washed with water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was subjected to flash chromatography on silica (eluent: cyclohexane/dichloromethane 10:1) to yield **10b** (500 mg, 23%) and trisubstituted product (755.0 mg, 1.1 mmol) that was further reacted with 4-chlorothiophenol (406 mg, 2.83 mmol) and potassium-*t*-butoxide (315.0 mg, 2.6 mmol) in DMF (50 ml) for 72 h. Usual workup and flash chromatography on silica afforded a further 420 mg **10b** (total yield=43%), R_f (eluent: cyclohexane/dichloromethane 3:1): 0.25; mp 133–136 °C (Found: C, 54.37; H, 2.74. $C_{36}H_{22}Cl_4O_2S_5$ requires C, 54.84; H, 2.79); ν_{max} (cm^{-1}) 1159, 1087 (S=O); δ_H (300 MHz; $CDCl_3$) 6.82 (2H, t, J_m=1.6 Hz, ArH), 7.25 (16H, m, ArH) 7.41 (4H, d, J_m=1.6 Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 124.27 (ArH), 130.18 (quat), 130.46 (ArH), 131.21 (ArH), 135.40 (ArH), 136.1 (quat), 141.84 (quat), 142.85 (quat); *m/z* (EI) 788, ($[M\cdot]^+$100%), 646 (35), 504 (72); (CI NH_4^+) 805 ($[M\cdot]^+ + NH_4^+$100).

4.8. Bis-(3,5-bis-(4-chlorophenylsulfonyl) sulfone 11b

To a solution of tetrachlorosulfide **10b** (410 mg, 0.5 mmol) in dichloromethane (30 ml) was added *m*-chloroperbenzoic acid 30–50% (2.52 g, 8.32 mmol). The mixture was stirred at room temperature for 18 h after which calcium hydroxide (1.0 g, 17.5 mmol) was added and the mixture stirred for a further 1 h. The solid precipitate was filtered and the organic layer washed with sodium hydroxide (10%, 50 ml) water and brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give **11b** as a white solid (472 mg, 99%). R_f (eluent: cyclohexane/ethyl acetate 1:1): 0.85; mp>200 °C (decomp.) (Found: C, 47.06; H, 2.36. $C_{36}H_{22}Cl_4O_{10}S_5$ requires C, 47.18; H, 2.40); ν_{max} (cm^{-1}) 1149, 1082 (S=O); δ_H (300 MHz; CD_6SO) 7.65 (8H, AA′ of AA′BB′, J_o=8.7 Hz, C_6H_4), 8.64 (8H, BB′ of AA′BB′, J_o=8.7 Hz, C_6H_4), 8.73 (2H, t, J_m=1.5 Hz, ArH), 9.07 (4H, d, J_m=1.5 Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 130.37 (ArH), 130.75 (ArH), 131.93 (ArH), 132.87 (ArH), 138.17 (quat), 140.26 (quat), 143.35 (quat), 144.50 (quat); *m/z* (FAB$^+$) 917, ($[M\cdot]^+$30%), MALDI (DHB-K^+) 955.1 ($[M\cdot]^+ + K^+$).

4.9. Bis-(3,5-bis-(4-bromophenylsulfanyl) sulfone 10c

To a solution of 4-bromothiophenol (581 mg, 3.1 mmol) and potassium-*t*-butoxide (378 mg, 3.4 mmol) in DMAC (10 ml) was added sulfone **6** (250 mg, 0.7 mmol). The reaction was heated to 80 °C for 72 h. The mixture was cooled and poured onto ice with stirring then basified with sodium hydroxide (10%). The resulting off white solid material was collected by filtration and washed with water (5×50 ml) and sodium hydroxide (10%, 2×50 ml). The solid was dried to furnish

tetrabromosulfide **10c** (648 mg, 95%), mp>200 °C (Found: C, 44.62; H, 2.34. $C_{36}H_{22}Br_4O_2S_5$ requires C, 44.73; H, 2.27); ν_{max} (cm^{-1}) 1159, 1097 (S=O); δ_H (300 MHz; $CDCl_3$) 6.88 (2H, t, J=1.8 Hz, ArH), 7.19 (8H, AA′ of AA′BB′, J=10.3 Hz, C_6H_4) 7.42 (4H, d, J=1.8 Hz, ArH), 7.48 (8H, BB′ of AA′BB′, J=10.3 Hz, C_6H_4); δ_C (75.5 MHz; $CDCl_3$) 124.1 (quat), 124.6 (ArH), 130.98 (quat), 131.68 (ArH), 133.41 (ArH), 135.42 (ArH), 141.59 (quat), 142.87 (quat); *m/z* (EI) 966, $[M\cdot]^+$(100%), 888 (80) 814 (98), 640 (96).

4.10. Bis-(3,5-bis-(4-bromophenylsulfonyl) sulfone 11c

To a solution of tetrabromosulfide **10c** (20 mg, 21 μmol) in dichloromethane (20 ml) was added *m*-chloroperbenzoic acid 35% (163 mg, 0.3 mmol). The resulting solution was allowed to stir for 16 h at room temperature after which it was diluted with dichloromethane (30 ml) and washed with sodium hydroxide 10% (2×50 ml) water (100 ml) and brine. The organic layer was separated, dried over $MgSO_4$ and concentrated under vacuum to furnish tetrabromosulfone **11c** (20 mg, 88%). Satisfactory microanalysis was not obtained, R_f (eluent: cyclohexane/ethyl acetate1:1): 0.68; mp>200 °C; ν_{max} (cm^{-1}) 1154 (S=O); δ_H (300 MHz; CD_6SO) 7.83 (8H, AA′ of AA′BB′, J=8.8 Hz, C_6H_4), 8.11 (8H, BB′ of AA′BB′, J=8.8 Hz, C_6H_4) 8.69 (2H, t, J=1.6 Hz, ArH), 9.05 (4H, d, J_m=1.6 Hz, ArH); δ_C (75.5 MHz; $CDCl_3$) 128.23 (quat), 129.41 (ArH), 130.7 (ArH), 131.9 (ArH), 133.29 (ArH), 138.54 (quat), 143.35 (quat), 144.54 (quat); *m/z* (FAB) 1094, $[M\cdot]^+$(61%), 1062 (100), 1032 (43), 690 (100).

4.11. Bis-(3,5-bis-(4-methoxyphenylsulfanyl) sulfone 10d

To a solution of 4-methoxythiophenol (983 mg, 7.0 mmol) in DMF (25 ml) was added potassium-*t*-butoxide (803 mg, 7.2 mmol) and sulfone **6** (500 mg, 1.4 mmol). The solution was heated to 80 °C for 16 h. The crude mixture was cooled and quenched on ice. The aqueous layer was extracted into dichloromethane, the solvent dried and removed under vacuum to reveal an off-white solid. This solid was triturated in cold acetone to give an off-white solid (810 mg, 75%) of tetramethoxy **10d**. R_f (eluent: petrol/ethyl acetate 10:1): 0.59; mp. 174–176.5 °C (Found: C, 61.07; H, 4.27. $C_{40}H_{34}O_6S_5$ requires C, 62.33; H, 4.41); ν_{max} (cm^{-1}) 1164, 1025 (S=O); δ_H (300 MHz; $CDCl_3$), 3.85 (12H, s, OMe), 6.63 (2H, t, J_m=1.8 Hz, ArH), 6.86 (8H, AA′ of AA′BB′, J=9.0 Hz, C_6H_4), 7.21 (4H, d, J_m=1.8 Hz, ArH), 7.29 (8H, BB′ of AA′BB′, J=9.0 Hz, C_6H_4); δ_C (75.5 MHz; $CDCl_3$) 55.70 (OMe), 115.75 (ArH), 121.04 (quat), 121.75 (ArH), 127.85 (ArH), 136.99 (ArH), 142.49 (quat), 143.55 (quat), 161.04 (quat); *m/z* (EI) 770, ($[M\cdot]^+$15%), 632 (63), 492 (100), (CI NH_4^+) 788 ($[M\cdot]^+ + NH_4^+$100).

4.12. Bis-(3,5-bis-(4-hydroxyphenylsulfanyl) sulfone 10e

To a solution of tetramethoxy sulfide **10d** (50 mg, 65 μmol) in dichloromethane (10 ml), which was cooled to −60 °C under nitrogen, was added boron tribromide 1.0 M in dichloromethane (1.3 ml, 1.3 mmol) with care. The resulting solution was stirred for a further 15 min at −60 °C then at room temperature for 18 h. Deionised water (5 ml) was added with care and the mixture stirred for a further 30 min, then diluted with ethyl acetate/acetone (1:1, 50 ml). The organic layer was separated, washed with water and brine, dried over $MgSO_4$ and the solvent removed under vacuum to furnish, after trituration with cold chloroform, tetraphenol **10e** (34 mg, 74%) estimated to be >90% pure by NMR, as an off-white waxy solid, R_f (eluent: petrol/ethyl acetate 1:1): 0.1; ν_{max} (cm^{-1}) 3320 (OH); δ_H (300 MHz; CD_6CO), 6.78 (2H, t, J_m=1.6 Hz, ArH), 6.95 (8H, AA′ of AA′BB′, J=8.8 Hz, C_6H_4), 7.17 (4H, d, J_m=1.6 Hz, ArH), 7.30 (8H, BB′ of AA′BB′, J=8.8 Hz, C_6H_4), 9.06 (4H, br s, OH); δ_C (75.5 MHz; CD_6CO), 118.44 (ArH), 119.90 (quat), 121.89 (ArH), 128.04 (ArH), 138.28 (ArH), 143.95 (quat), 145.09 (quat), 160.47 (quat); *m/z* (FAB) 714, ($[M\cdot]^+$56%), 624 (52), 500 (74), 358 (100).

4.13. Bis-(3,5-bis-(4-methoxyphenylsulfonyl) sulfone 11d

To a solution of tetramethoxysulfide **10d** (600 mg, 0.8 mmol) in dichloromethane (50 ml) was added *m*-chloroperbenzoic acid 57%, (3.6 g, 12.5 mmol). The solution was stirred at room temperature for 12 h. The solvent was removed to furnish a white solid which was triturated with sodium hydroxide 10% (50 ml) for 2 h. The organic solid was separated by filtration, dissolved in chloroform, dried over $MgSO_4$ and the solvent removed under vacuum to furnish tetramethoxy sulfone **11d** (689 mg, 98%) as a white solid, R_f (eluent: petrol/ethyl acetate 10:1): 0.1; mp 150 °C (decomp.) (Found C, 53.58; H, 3.65. $C_{40}H_{34}O_6S_5$ requires C, 53.45; H, 3.78); ν_{max} (cm^{-1}) 1138, 1102 (S=O); δ_H (300 MHz; $CDCl_3$) 3.87 (12H, s, OMe), 7.04 (8H, AA′ of AA′BB′, J=9.2 Hz, C_6H_4), 7.87 (8H, BB′ of AA′BB′, J=9.2 Hz, C_6H_4), 8.50 (4H, d, J_m=1.8 Hz, ArH), 8.54 (2H, t, J_m=1.8 Hz, ArH); δ_C (75.5 MHz; CD_6SO) 56.20 (OMe), 115.61 (ArH), 130.52 (quat), 130.71 (ArH), 131.03 (ArH), 131.46 (ArH), 143.16 (quat), 145.79 (quat), 164.30 (quat); *m/z* (EI) 898, ($[M\cdot]^+$5%), 728 (31), 588 (100), 556 (35), (CI NH_4^+) 915 ($[M\cdot]^+ + NH_4^+$10).

4.14. Bis-(3,5-bis-(4-hydroxyphenylsulfonyl) sulfone 11e

To a solution of tetramethoxy sulfone **11d** (50 mg, 60 μmol) in dichloromethane (10 ml), which was cooled to −78 °C under nitrogen, was added boron tribromide 1.0 M in dichloromethane (0.8 ml, 0.8 mmol) with care. The resulting solution was stirred for a further 15 min at −78 °C then at room temperature for 70 h. Deionised water (5 ml) was added with care and the mixture stirred for a further 30 min, then diluted with ethyl acetate/acetone (1:1, 50 ml). The organic layer was separated, washed with water and brine, dried over $MgSO_4$ and the solvent removed under vacuum to furnish tetraphenol **11e** (41 mg, 88%) estimated to be >90% pure by NMR, as an off-white waxy solid, R_f (eluent: petrol/ethyl acetate 1:1): 0.1; ν_{max} (cm^{-1}) 3310 (OH); δ_H (300 MHz; CD_6CO), 6.89 (8H, AA′ of AA′BB′, J=8.8 Hz, C_6H_4), 7.78 (8H, BB′ of AA′BB′, J=8.8 Hz, C_6H_4), 8.41 (2H, t, J_m=1.5 Hz, ArH), 8.61 (4H, d, J_m=1.5 Hz, ArH), 9.6 (4H, br s, OH); δ_C (75.5 MHz; CD_6CO), 117.76 (2× ArH), 131.12 (quat), 131.80 (ArH), 131.18 (ArH), 144.55 (quat), 147.80 (quat), 164.1 (quat); *m/z* (FAB) 843, ($[M\cdot]^+$20%), 667 (94), 638 (100).

4.15. Supported synthesis of dipeptide 12

To a cooled solution of *N*-Boc-L-valine (243 mg, 1.12 mmol), and EDCI (1.12 mmol, 215 mg), which had been stirred in ethyl acetate–THF (1/1), at 0 °C for 1 h was added HOBT (1.12 mmol, 151 mg). The solution was allowed to stand for a further 1 h at 0 °C after which was added **10e** (0.14 mmol, 100 mg), and triethylamine (1.9 equiv, 2.1 mmol, 212.1 mg) in one portion. The reaction mixture was stirred at room temperature for 48 h, diluted with ethyl acetate (50 ml) and washed with water and NaOH (10%). The organic layer was dried over $MgSO_4$ and concentrated to give **12** as a crude oil; δ_H (300 MHz; CD_3CO) 1.08 (12H, d, $J=6.6$ Hz, $CHCH_3$), 1.10 (12H, d, $J=6.6$ Hz, $CHCH_3$), 1.41 (36H, s, $C(CH_3)_3$), 2.33–2.41 (4H, m, $CH(CH_3)_2$), 4.39 (4H, m, $J=5.8$ Hz, CH), 6.50 (4H, d, $J=8.3$ Hz, NH), 6.9–7.6 (22H, m, Ar); δ_C (75.5 MHz; CD_6CO) 18.95 (Me), 20.02 (Me), 28.97 (*t*-Bu), 31.67 ($CHMe_2$), 60.88 (CH), 79.94 (quat), 118.56, 124.78, 129.65, 131.75, 136.49, 143.09, 144.20, 153.07, 157.29 (C=O), 171.94 (C=O).

To a solution of **12** in dichloromethane (10 ml) was added TFA (10 ml). The solution was stirred for 2 h after which the solvent and excess TFA were removed in vacuo below 40 °C to yield **13** as a crude brown oil; δ_H (300 MHz; CD_3CO) 1.25 (12H, d, $J=6.6$ Hz, $CHCH_3$), 1.28 (12H, d, $J=6.6$ Hz, $CHCH_3$), 2.64–2.77 (4H, m, $CH(CH_3)_2$), 4.57 (4H, br s, CH), 5.33 (8H, d, $J=6.1$ Hz, NH_2), 7.1–7.6 (22H, m, Ar); δ_C (75.5 MHz; CD_6CO) 18.45 (Me), 19.07 (Me), 31.15 ($CHMe_2$), 59.93 (CH), 118.56, 124.45, 131.50, 136.00, 136.14, 151.91, 168.95 (C=O), two Ar signals not observed.

The two steps above were repeated using crude **13** as substrate and *N*-Boc-N-glycine in place of *N*-Boc-L-valine. Crude supported dipeptide **15** was then dissolved in ethyl acetate–acetone (1/1) (50 ml) and sodium hydroxide (10%, 10 ml) was added. The biphasic solution was stirred vigorously for 30 min. The aqueous layer was neutralised to pH 7 with HCl (1 M). The water was removed in vacuo and the solid residue was extracted thoroughly with methanol. The methanol was removed in vacuo to reveal the pure target dipeptide in 29% yield for the five steps; δ_H (400 MHz; CD_3OD) 1.00 (6H, 2×d, *J* $CHCH_3$), 2.24 (1H, d, $J=5.8$ Hz, $CHCH_3$), 3.80 (2H, s, CH_2), 4.41 (1H, d, $J=5.8$ Hz, CH); *m/z* (EI) 174 (M^+ 100%). The organic layer was dried over $MgSO_4$ to return the support **10e** as a crude sodium salt; δ_H (400 MHz; CD_3OD) 6.62 (2H, t, $J=1.5$ Hz), 6.92 (8H, AA′ of AA′BB′, $J=8.6$ Hz), 7.22–7.25 (12H, m).

4.16. React and release synthesis of amides

To a cooled solution of tetrasulfide **10e** (100 mg, 140 μmol) in DMF (10 ml) was added triethylamine (0.71 ml, 0.70 mmol) and propionyl chloride (0.57 ml, 0.63 mmol). The resulting solution was stirred at room temperature for 18 h. The solution was reduced in volume and diluted with dichloromethane (30 ml), washed with water (50 ml), HCl (1 M, 50 ml), water and finally brine. The solution was dried over $MgSO_4$ and the solvent removed under vacuum to yield bis-(3,5-bis-(4-hydroxyphenylsulfanyl) sulfone tetrapropionate ester **17** (96 mg, 73%) as a crude oil, R_f (eluent: petrol/ethyl acetate 1:1): 0.77; ν_{max} (cm^{-1}) 1710 (C=O); δ_H (300 MHz; CD_6CO), 1.21 (12H, t, $J=7.5$ Hz, Me), 2.64 (8H, q, $J=7.5$ Hz, CH_2), 6.94 (2H, t, $J_m=1.5$ Hz, ArH), 7.21 (8H, AA′ of AA′BB′, $J=8.7$ Hz, C_6H_4), 7.45–7.47 (12H, m, ArH); δ_C (75.5 MHz; CD_6CO), 9.41, 28.16, 123.52, 124.20, 135.41, 137.37, 138.70, 142.01, 151.85, 172.85.

To a solution of tetraester **17** (0.1 mmol) in dichloromethane (10 ml) was added either cyclohexylamine or benzylamine (0.5 mmol) and triethylamine (0.1 mmol). The solution was stirred for 26 h and the solvent was removed in vacuo. The crude residue was dissolved in ethyl acetate/acetone (1:1, 50 ml) and washed with HCl (1 M) and water. The organic layer was dried over $MgSO_4$ and concentrated to provide a mixture of the product amide and the recovered support **10e**, as determined by NMR spectroscopy.

Acknowledgements

We thank GlaxoSmithKline and the EPSRC for financial support, Dr. Alison Rodger and Mr. Muftah Darwish for assistance with HPLC and Prof. Andrew Livingston for bibliography on membrane separation.

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Tetrahedron 61 (2005) 12323–12329

Convenient synthesis of selectively substituted tribenzo[*a*,*d*,*g*]cyclononatrienes

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Received 11 May 2005; revised 30 August 2005; accepted 22 September 2005

Available online 14 November 2005

Dedicated to Professor S. Chandrasekharan on his birthday

Abstract—Convenient laboratory procedures for obtaining selectively substituted dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononatrienes have been achieved. X-ray structure determination indicates that **2d** is present in the solid state in the crown conformation to yield H-bonded columns and pillars with a hydrophilic interior and hydrophobic exterior that can be used for the design of specific sensor materials.

1. Introduction

Tribenzocyclononatriene (TBCN) represented by the general structure **1** is an important core structure around which a large number of molecular receptors have been constructed for studying molecular recognition, conformational isomerism, structural chirality, mesomorphism and for obtaining novel materials.[1–5] The parent hydrocarbon cyclotribenzylene (R_1, R_2, R_3=H) or cyclotriveratrylene **1a** (CTV, R_1=H, R_2 and R_3=OMe) and all other peripherally substituted derivatives are occasionally referred to as substituted cyclotriveratrylenes. They usually occur in the 'crown' conformation though their 'saddle' conformation has also been recently isolated and characterized through thermal isomerization[6] (Fig. 1). Different TBCN derivatives have been previously obtained through elaborate synthetic methodologies.

Despite their importance in forming interesting molecular scaffolds, very little work seems to have been reported on optimization of their synthesis through partial dealkylation of readily obtainable cyclotriveratrylene.[3]

We report herein an easy and direct route to phenolic cyclononatrienes through selective demethylation of cyclotriveratrylene to yield one, three or six free –OH groups in a CTV molecular bowl for further utilization (Scheme 1).

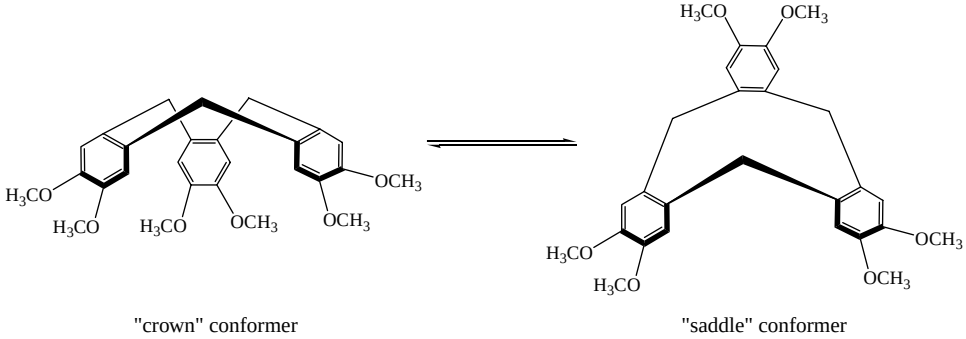

Figure 1. 'Crown' and 'saddle' forms of cyclotriveratrylene.

Keywords: Cyclotriveratrylenes; Cyclononatrienes; Demethylation; Lewis acids.
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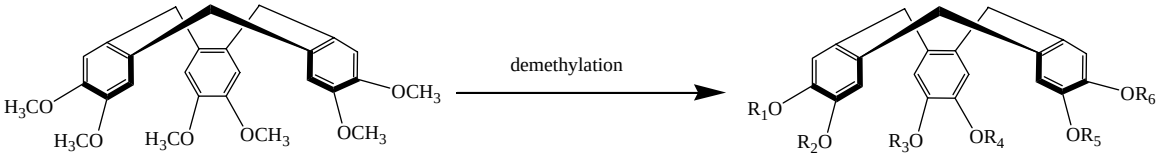
doi:10.1016/j.tet.2005.09.101



1a **2**

2a R_1= H; R_2, R_3, R_4, R_5, R_6 =CH_3
2b R_1, R_3, R_5 =H; R_2, R_4, R_6 =CH_3
2c R_1, R_2, R_3 =H; R_4, R_5, R_6 =CH_3
2d R_1, R_2, R_3, R_4, R_5, R_6 =H

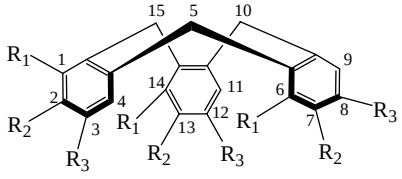
Scheme 1.

Table 1. Summary of results obtained under different reaction parameters

Entry	Reagent	Solvent	Reaction condition	Time	Results obtained
1	HI	Acetonitrile	Reflux	17 h	Complicated mixture
2	$TiCl_4$ (6 equiv)	DCM	rt	48 h	**2a** as well as starting **1a**
3	$TiCl_4$ (36 equiv)	DCM	rt	24 h	**2a**
4	$AlCl_3$ (5 equiv)	DCM	rt	48 h	**2a** as the major product
5	$AlCl_3$ (36 equiv)	DCM	rt	48 h	**2b**
6	$AlCl_3$ (36 equiv)	Toluene	rt	2 h 30 min	**2a** as the major product
7	BBr_3 (7 equiv)	DCM	rt	30 min	Mixture of **2a** and **2b**
8	BBr_3 (16 equiv)	DCM	rt	45 min	**2b** as well as starting **1a**
9	BBr_3 (7 equiv)	DCM	Reflux	18 h	Mixture of **2b** and **2c**
10	BBr_3 (16 equiv)	DCM	Reflux	24 h	**2d**
11	BBr_3 (10.5 equiv)	Benzene	Reflux	2 h	Mixture of **2a**, **2b** and **2c**
12	BF_3 (6 equiv)	DCM	rt	48 h	No reaction
13	$SnCl_4$ (6 equiv)	DCM	rt	36 h	No reaction
14	Lithium diphenylphosphide	DCM	rt	24 h	**2b**

DCM = dichloromethane, rt = room temperature.

Cyclotriveratrylene **la** was synthesized in moderate yields by the acid catalyzed condensation of 3,4-dimethoxybenzyl-alcohol[7] by a modified recrystallization procedure. Demethylation of cyclotriveratrylene was carried out by using different reagents and reaction conditions as given in Table 1.



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2. Results and discussion

It has now been observed that dealkylation with hydriodic acid results in a complicated mixture of CTVs, which could not be resolved. Use of $TiCl_4$ for the reaction afforded a product which exhibited a pair of two proton doublets at δ 3.45 and 4.68 for $ArCH_2Ar$ and a D_2O exchangeable singlet at δ 5.33 due to OH. It was identified as 2-hydroxy-3,7,8,12,13-pentamethoxy-10,15-dihydro-5H-tribenzo-[*a*,*d*,*g*]cyclononene **2a**.

It was observed that two trihydroxy trimethoxydihydro-5H-tribenzo[*a*,*d*,*g*]cyclononenes could be obtained on reaction of **1a** with $AlCl_3$ (36 equiv) and BBr_3 in dichloromethane. Structural identification of **2b** and **2c** was done on the basis of direct comparison of authentic sample of **2b** and detailed ^{1}H NMR and ^{13}C NMR analysis of **2b** and **2c**. Out of five possible structures for the trihydroxy derivatives (**A**-**E**), with varying disposition of methoxy and hydroxyl substituents (Fig. 2), the appearance of four signals in the aromatic position of the NMR of **2c**, allowed us to exclude possibility of **D** and **E**. Though structure **C** is expected to exhibit the same number of signals in its ^{1}H NMR, it should exhibit one ^{13}C NMR signal for the methylene bridge carbons as against three methylene carbon signals observed in **2c**. This leaves structures **A** and **B** for **2c**. While **A** is a known compound and has been identified as cyclotriguaiacyclene, **2b**, it leaves **B** as the structure for **2c**.

When $AlCl_3$ (36 equiv) was used as the dealkylation reagent, the reaction led to demethylation of three of the six methoxyl groups of CTV to yield 2,7,12-trihydroxy-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene **2b** under optimized conditions given in Table 1. The ^{1}H NMR spectrum of **2b** exhibited a deuterium exchangeable singlet for the OH protons at δ 8.65, two doublets at δ 3.39 and 4.62 for the $ArCH_2Ar$ protons, a singlet for the methoxy protons at δ 3.78 and two singlets for the aromatic protons at δ 6.88 and 6.90. This procedure allowed us to obtain cyclotriguaiacyclene in one step in good yield as against the earlier reported procedure starting from vanillyl alcohol[8] and involving cumbersome separations. Interestingly, when the solvent in the above reaction was changed from dichloromethane to toluene, the major product obtained was found to be **2a**. The same product

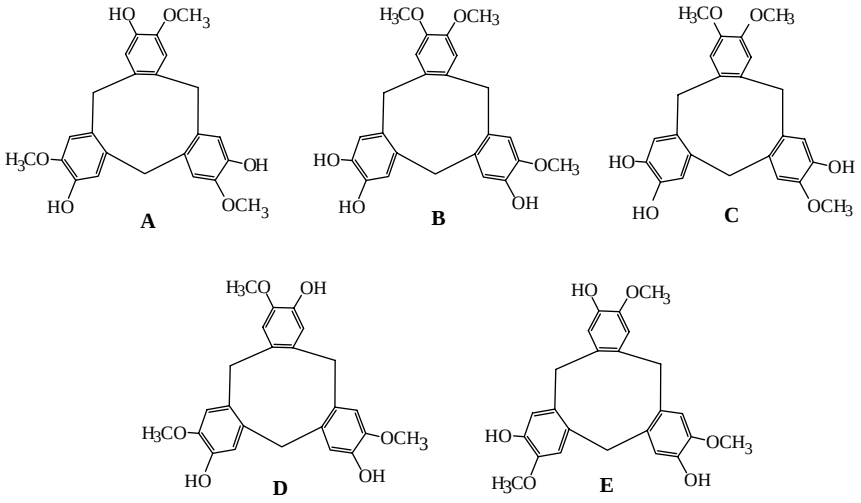

Figure 2. The five possible structures of CTV with three methoxy and three hydroxyl groups.

was also obtained when lower equivalents of $AlCl_3$ (5 equiv) was used with dichloromethane as the solvent. On the other hand, it was found that the reaction of CTV with boron tribromide leads to different products under different reaction conditions of solvent, amount of BBr_3, temperature and reaction time (Table 1) as against earlier reports on the reaction, which leads to the formation of 2,3,7,8,12,13-hexahydroxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene in low yields.[5] For example, excess of boron tribromide leads to demethylation of the maximum number of methoxy groups in CTV. Likewise, pure crystals of 2,3,7,8,12,13-hexahydroxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene (cyclotricatechylene) **2d** were obtained on refluxing the parent CTV in dichloromethane using 16 equiv of BBr_3 for 24 h in high yield (78%) to allow its isolation without elaborate chromatographic separations. The ^{1}H NMR spectrum of **2d** exhibited a deuterium exchangeable singlet for the OH proton at δ 8.55 and a broad singlet for the aromatic protons at δ 6.64. However, **2b** was obtained as the major product when the reaction was performed at room temperature for 45 min. Use of lower equivalents of BBr_3, shorter reaction times and low reaction temperatures also led to an indicated mixture of products (Table 1), which had to be separated by column chromatography. **2c**, for instance, was obtained when **1a** was refluxed with BBr_3 in dichloromethane for 18 h. The ^{1}H NMR spectrum of **2c** exhibited four peaks in the aromatic region in

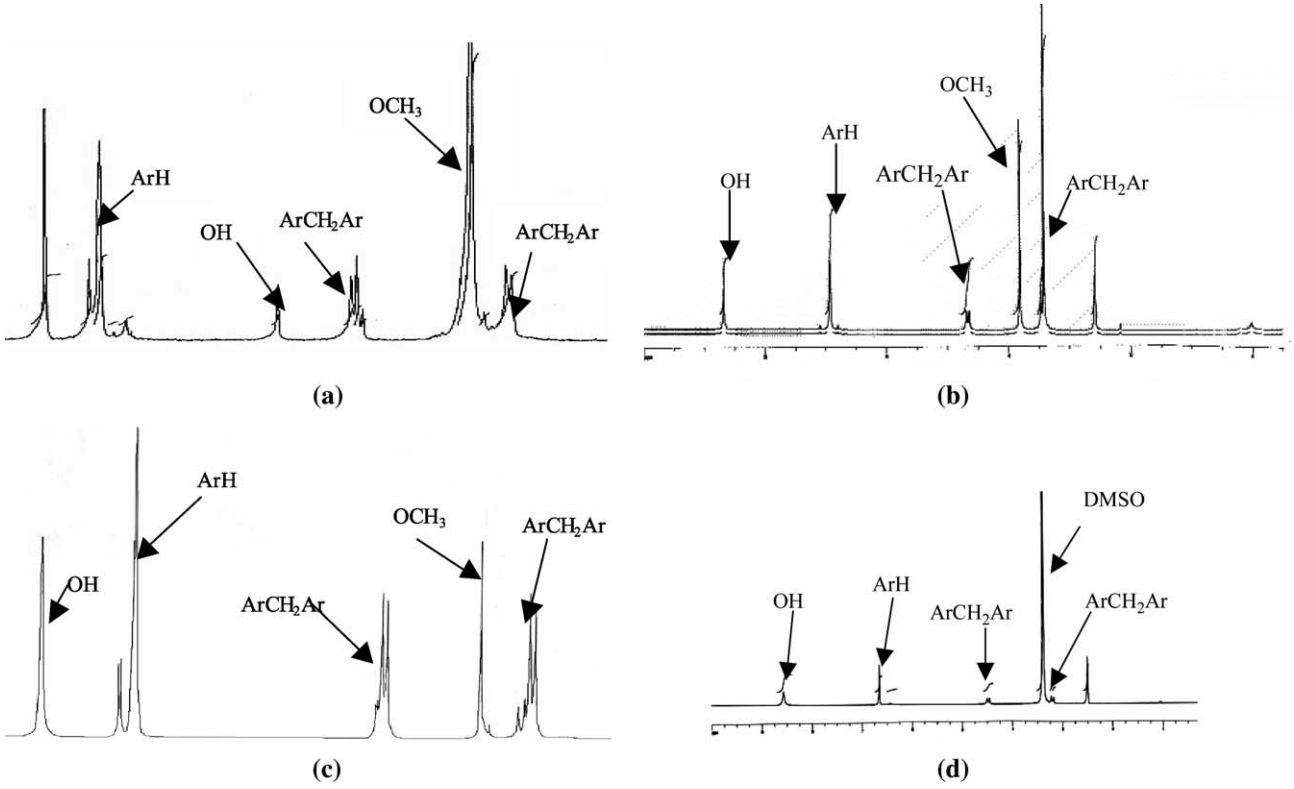

Figure 3. ^{1}H NMR spectra of (a) **2a**, (b) **2b**, (c) **2c** and (d) **2d**.

Table 2. ^{1}H NMR spectral data of CTVs (chemical shifts from tetramethylsilane (ppm))

Entry	Compound	Solvent	ArH	$ArCH_2Ar$	$ArCH_2Ar$	OMe	OH
1	**2a**	$CDCl_3$	6.83, 6.76, 6.74	4.68	3.45	3.76	5.33
2	**2b**	DMSO	6.90, 6.88	4.62	3.39	3.78	8.65
3	**2c**	CD_3COCD_3	6.94, 6.92, 6.83, 6.80	4.65	3.41	3.79	7.61
4	**2d**	DMSO	6.64	4.50	3.22	—	8.55

the range of δ 6.80–6.94. The pair of doublets appearing at δ 3.41 and 4.65 for the methylene bridge protons appears to be somewhat distorted indicating deviation from the symmetric CTV framework.

The Lewis acids like BF_3 and $SnCl_4$ did not result in a tangible reaction even after 48 h. Optimized reaction conditions for obtaining different dihydrotribenzo cyclononatriene analogs are given in Table 1. It appears that the use of lithium diphenylphosphide[9] as the demethylating agent allows one to obtain 2,7,12-trihydroxy-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene (with three hydroxy and three methoxy groups) (cyclotriguaiacyclene). Solvent plays an important role in the reactions initiated by $AlCl_3$ and BBr_3 in consonance with earlier observations on π-complexation of aromatic compounds with Lewis acids.[10] For example, when a solvent like toluene was used, even an excess of $AlCl_3$ could only demethylate one of the six methoxy groups of the parent cyclotriveratrylene. Similar observations were made in the reaction with BBr_3 whereby the use of benzene as the solvent at refluxing temperature did not yield the completely demethylated analog.

The NMR spectra (Fig. 3) of different dihydrotribenzo-cyclononatriene analogs were characteristic and could also be used for diagnostic purposes for deciding its crown conformation. The appearance of a pair of doublets due to the presence of axial and equatorial protons in their ^{1}H NMR spectrum (Table 2) is indicative of the locked crown conformation of the demethylated analogues of cyclotriveratrylene, which could be further confirmed by the signal at around δ 35 ppm in the ^{13}C NMR of the above synthesized compounds except in the case of **2c** where three signals are observed in the same region. Predictably the chemical shift for methylene group in **2d** is comparatively more upfield than methylene groups in other derivatives of CTV ($\Delta\delta$= 0.17–0.23 ppm).

3. Results obtained for X-ray crystallography of 2,3,7,8,12,13-hexahydroxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene

Single crystals of **2d** could be grown from a mixture of ethanol and dimethylsulfoxide. It has been observed that the compound crystallizes in parallel piped form with strong hydrogen bonding; having space group $P2_{1/n}$. An ORTEP diagram of a single molecule of an exclusion complex of 2,3,7,8,12,13-hexahydroxy-10,15-dihydro-5H-tribenzo-[*a*,*d*,*g*]cyclononene and dimethylsulfoxide (DMSO) is shown in Figure 4a. All the bond lengths and bond angles are normal and lie within the expected ranges; i.e. C (sp^3)–C (aromatic) 1.516(5)–1.532(5) and C–C (phenyl) 1.375(4)–1.410(5) Å. The torsion angles about the three methylene groups are 96.2(2), −95.6(2), 94.3(2), −92.2(2), 99.8(2) and −89.1(2)° varying alternately around ±90 to confer a crown conformation on the molecule. All the rings point towards the bottom of the crown to provide a conical architecture lacking an exact C_3 symmetry as expected. The position of hydroxyl groups is the major factor that destroys the threefold molecular symmetry axis. The phenyl rings A (C1–C6), B (C8–C13) and C (C15–C20) have been observed to have their hydroxyl groups point in one direction. Thus each catechol moiety can give only one intramolecular H-bond with itself. O1–H1, O2–H2, O3–H3, O4–H4 and O5–H5, O6–H6 are rotated by 28, 5, 39, 10, 31 and 25°, respectively, vis-a-vis their rings A, B and C. Out of these hydroxyl groups O2, O4 and O6 are involved in intramolecular H-bonding with O1, O3 and O5, respectively. Thus one hydroxyl group per ring is rotated more with respect to its phenyl ring than the other one and does not seem to act as an intramolecular H-bond donor but as a bifurcated intermolecular H-bond donor (Table 3). The less rotated O2, O4, O6 behave as bifurcated intra- as well as intermolecular H-bond donors.

An extensive intermolecular H-bonding among various hydroxyl groups results in the formation of two centro-symmetric channels in each unit cell running in the *ac* plane.

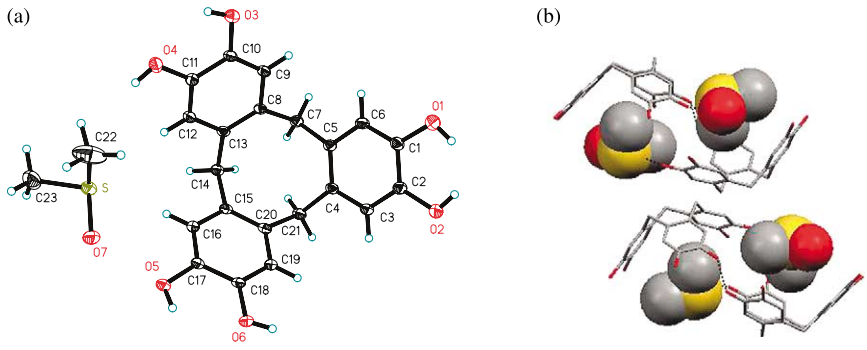

Figure 4. (a) ORTEP diagram of the exclusion complex showing labeling scheme used, and (b) the contents of a single unit cell having two centrosymmetric dimers of the exclusion complex.

Table 3. H-bond interactions (Å and °)

O2···O1	2.712(2)	H2···1	2.3	O2–H2···O1	114
O4···O3	2.712(2)	H4···O3	2.3	O4–H4···O3	113
O6···O5	2.730(2)	H6···O5	2.3	O6–H6···O5	110
O5···S	3.692(2)	H5···S	2.9	O5–H5···S	161
O5···O7	2.650(3)	H5···O7	1.8	O5–H5···O7	164
C16···S	3.741(2)	H16A···S	2.9	C16–H16A···S	140
O6···O7^{i}	2.801(2)	H6···O7^{i}	2.0	O6–H6···O7^{i}	161
O3···O6^{i}	2.819(2)	H3···O6^{i}	2.0	O3–H3···O6^{i}	166
O1···O5^{i}	2.886(2)	H1···O5^{i}	2.0	O1–H1···O5^{i}	171
O1···O5^{ii}	3.218(3)	H1···O5^{ii}	2.8	O1–H1···O5^{ii}	112
O2···O4^{iii}	2.766(2)	H2···O4^{iii}	2.0	O2–H2···O4^{iii}	145
O3···O3^{iv}	3.064(2)	H3···O3^{iv}	2.7	O3–H3···O3^{iv}	103
O5···O5^{iv}	2.743(2)	H5···O5^{iv}	2.6	O5–H5···O5^{iv}	88
O4···O6^{v}	2.969(2)	H4···O6^{v}	2.2	O4–H4···O6^{v}	148

i, $x-0.5$, $-y+0.5+1$, $z-0.5$; ii, $-x+0.5+1$, $y+0.5$, $-z+0.5+2$; iii, x, $y+1$, z; iv, $-x+1$, $-y+1$, $-z+2$; v, $-x+0.5+1$, $y-0.5$, $-z+0.5+2$.

Each channel forms a layered structure that constitutes columns running along the *b* axis. The formation of these channels and columns may be understood by starting from a single unit cell containing four dihydrocyclononatriene molecules and four DMSO solvent molecules when visualized down the *b* axis to appear as two centrosymmetric dimers (Fig. 4b).

Two dihydrotribenzocyclononatriene molecules, say X and Y in each dimer, are related to each other by a 2_1 screw axis. There are two H-bonding interactions O4–H4···O6^{v} and O1···O5^{ii} between X and Y molecules of this dimer. Each dimer creates a cavity, which holds two DMSO solvent molecules related again by a twofold screw axis. The solvent molecule does not seem to reside deep into the cavity but lies above the concave cavity near the phenyl ring C and is held in place by bifurcated H-bonds from O5 to S and O7 (Table 3). A weak H-bond occurs between methylene C16 and S. Each X and Y molecule of a dimer is H-bonded to the centrosymmetric counterparts of Y and X, respectively, via O3···O6^{i} and O1···O5^{i} H-bonds and to their own centrosymmetric counterparts by O3···O3^{iv} and O5···O5^{iv} in the *ac* plane (Fig. 5). Thus, there is a pair of intertwining zigzag chains of dihydrotribenzo cyclononatriene molecules running in the *ac* plane in the unit cell. Each such pair constructs a channel along the *ac* plane. O3···O6^{i} and O1···O5^{i} H-bonds maintain the walls of this channel. The channel is cross linked by the above mentioned O4···O6^{v}, O1···O5^{ii}, O3···O3^{iv} and O5···O5^{iv} H-bonds as shown in Figure 6a.

The crystal structure of the **2d**·DMSO complex therefore consists of infinite numbers of such channels running perpendicular to the *b* axis. Such, centrosymmetrically related channels are held to each other by face to face π–π interactions between rings A with a distance of 3.8 Å between them. There are no other H-bond interactions between them. The solvent molecule in one dimeric unit (XY) of these channels is also H-bonded to the neighboring dimeric unit by O6···O7^{i} bond. Finally the H-bond O2···O4^{iii} forms layers of molecules above these channels along the *b* axis to yield columns or pillars down the *b* axis

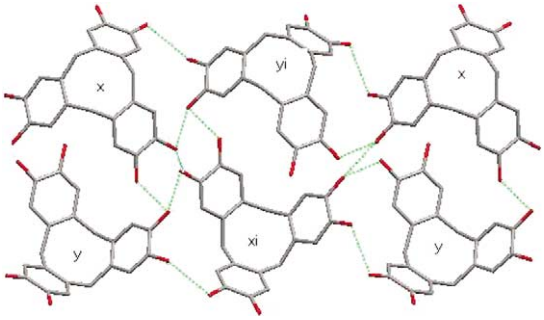

Figure 5. H-bonding interactions between successive dimeric pairs. X and y represent two molecules of a dimer related by the screw axis whereas x^{i} and y^{i} are their centrosymmetric counterparts. The solvent molecules and hydrogens have been omitted for clarity.

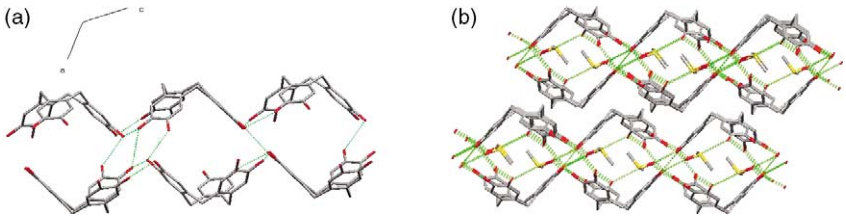

Figure 6. (a) Two intertwined zigzag chains of dihydrotribenzocyclononatriene molecules to form a channel in the *ac* plane. The solvent molecules and hydrogens have been omitted for clarity and (b) stacking along the *b* axis to yield H-bonded columns or pillars. Each pillar contains a hydrophilic interior and a hydrophobic exterior.

(Fig. 6b). The interiors of these columns contain solvent molecules piled one above the other and constitute a hydrophilic center while the outskirts of these columns offer a hydrophobic region formed of the hydrocarbon skeleton. Efforts are on to devise ways and means to utilize these channels for obtaining solid state sensor materials.

4. Experimental

NMR spectra were recorded on a 300 MHz Bruker DPX 300 instrument. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while X-ray data was recorded using a Bruker SMART CCD single crystal diffractometer. All the solvents used were distilled or dried according to the requirement. Column chromatography was performed on silica gel (60–120 mesh) obtained from Merck.

4.1. Synthesis of 2,3,7,8,12,13-hexamethoxy-10, 15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene 1

Compound **1** was synthesized according to the literature procedure.[1] The dried crude product, constituting a mixture of **1** with its higher oligomers, was dissolved in chloroform whereby pure shining crystals of **1** were obtained on selective recrystallisation with hexane.

4.1.1. Synthesis of 2-hydroxy-3,7,8,12,13-pentamethoxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene 2a. To a solution of **1** (1.00 g, 2.22 mmol) in 30 ml of dry dichloromethane, freshly distilled $TiCl_4$ (1.5 ml, 13.5 mmol) was added and the reaction mixture stirred at room temperature for 48 h after which it was poured into ice-cold water and extracted twice with 20 ml portions of dichloromethane. The organic layer was then dried over anhydrous sodium sulfate and evaporated in vacuo. The crude mixture thus obtained was further purified by column chromatography using chloroform–ethyl acetate (9/1) as the eluent to yield a white solid **2a**. (0.29 g, 30%). Mp > 250 °C. [Found: C 71.28; H 6.54. $C_{26}H_{28}O_6$ requires C 71.54; H 6.47]. ^{1}H NMR ($CDCl_3$, δ): 3.45 (d, 3H, ArCH_2Ar), 3.76 (s, 27H, OCH_3), 4.68 (d, 3H, ArCH_2Ar), 5.33 (s, 1H, O*H*), 6.74 (s, 1H, Ar*H*), 6.76 (s, 1H, Ar*H*), 6.83 (s, 4H, Ar*H*). MS-FAB (*m*/*z*): Found 436.

4.1.2. Synthesis of 2,7,12-trihydroxy-3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene (cyclotriguaiacyclene) 2b. To a solution of **1** (0.50 g, 1.11 mmol) in 25 ml of dry dichloromethane, anhydrous $AlCl_3$ (5.33 g, 39.96 mmol) was added and the reaction mixture stirred at room temperature for 12 h. The reaction mixture was then poured into water and the organic layer extracted twice with 20 ml dichloromethane. The organic layer was then dried over anhydrous sodium sulfate and evaporated in vacuo. The crude product thus obtained was washed with methanol to obtain TLC pure **2b** as a beige coloured solid (0.385 g, 85%). Mp > 250 °C. [Found: C 70.28; H 6.08. $C_{24}H_{24}O_6$ requires C 70.57; H 5.92]. ^{1}H NMR (DMSO-d_6, δ): 3.39 (d, 3H, ArCH_2Ar), 3.78 (s, 9H, OCH_3), 4.62 (d, 3H, ArCH_2Ar), 6.88 (s, 3H, Ar*H*), 6.90 (s, 3H, Ar*H*), 8.65 (s, 3H, O*H*). ^{13}C NMR (DMSO-d_6, δ): 145.9, 144.8, 132.5, 130.4, 116.7, 113.9 (Ar); 55.9 (OCH_3); 35.0 (ArCH_2Ar). MS-FAB (*m*/*z*): Found 408.

4.1.3. Synthesis of 2,3,7-trihydroxy-8,12,13-trimethoxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene 2c. To a solution of **1** (0.50 g, 1.11 mmol) in 30 ml of dry dichloromethane, BBr_3 (4.6 ml, 16.67 mmol) was added and the reaction mixture stirred at room temperature for 45 min. The reaction mixture was then poured into ice-cold water and the solid obtained was filtered. The crude product was purified by subjecting it to column chromatography using chloroform–ethyl acetate (9/1) as the eluent to give TLC pure **2c** as a brown solid (0.10 g, 23%). Mp > 250 °C. [Found: C 70.96; H 6.09. $C_{24}H_{24}O_6$ requires C 70.57; H 5.92]. ^{1}H NMR (CD_3COCD_3, δ): 3.41 (d, 3H, ArCH_2Ar), 3.79 (s, 9H, OCH_3), 4.65 (d, 3H, ArCH_2Ar), 6.80 (s, Ar*H*), 6.83 (s, Ar*H*), 6.92 (s, Ar*H*), 6.94 (s, Ar*H*), 7.61 (s, 3H, O*H*). ^{13}C NMR ($CDCl_3$, δ): 148.4, 146.8, 143.5, 135.7, 132.6, 131.8, 122.9, 115.8, 113.6, 110.1 (Ar); 56.2, 54.8 (OCH_3); 36.4, 35.2, 34.4 (ArCH_2Ar). MS-FAB (*m*/*z*): Found 408.

4.1.4. Synthesis of 2,3,7,8,12,13-hexahydroxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene (cyclotricatechylene) 2d. To a solution of **1** (0.50 g, 1.11 mmol) in dry dichloromethane (30 ml), BBr_3 (4.6 ml, 16.67 mmol) was added and the reaction mixture stirred at room temperature for 45 min followed by reflux for 24 h. The contents were cooled and poured into ice-cold water to yield a white solid, which was filtered and recrystallized from ethanol and dimethylsulfoxide to obtain TLC pure **2d** as colourless prisms. Yield 78%, Mp > 250 °C. [Found: C 68.18; H 5.01. $C_{21}H_{18}O_6$ requires C 68.85; H 4.95]. ^{1}H NMR (DMSO-d_6, δ): 3.22 (d, 3H, ArCH_2Ar), 4.50 (d, 3H, ArCH_2Ar), 6.64 (s, 6H, Ar*H*), 8.55 (s, 6H, O*H*). ^{13}C NMR (DMSO-d_6, δ): 143.5, 130.8, 116.7 (Ar); 35.1 (ArCH_2Ar). MS-FAB (*m*/*z*): Found 366.

4.2. Crystallography

The crystals were obtained by warming a solution of **2d** in ethanol and dimethylsulfoxide and then cooling to room temperature. Pale yellow rod shaped crystals of **2d**. DMSO complex were obtained, which was found to be a 1:1 exclusion complex having molecular formula $C_{23}H_{24}O_7S$, $M=444.48$, monoclinic, $a=10.586(2)$ Å, $b=11.536(2)$ Å, $c=17.202(3)$ Å, $\alpha=90°$, $\beta=98.14(2)°$, $\gamma=90°$, $V=2079.6(6)$ Å^3, $Z=4$, $D_c=1.420$ g/cm^{-3} and space group $P2_{1/n}$. Intensity diffraction data were calculated up to $\theta=28.15°$ by using a Bruker SMART CCD single crystal diffractometer with Mo Kα radiation ($\lambda=0.71073$ Å) on a $0.15\times0.12\times0.10$ mm crystal at 293 K. A total of 11,868 reflections were calculated, 4624 were independent and of which 4174 [$I\geq2\sigma(I)$] were considered observed and used in the structure analysis and refinement. The structure was solved by direct methods and refined by full matrix least square techniques in $P21/n$ space group. All nonhydrogen atoms were refined anisotropically. All hydrogen atoms were placed in their geometrical positions as riding atoms on their bearer C and O atoms with thermal parameters as 1.5 for methyl carbons and 1.2 for the rest and were not refined. The final R index using observed data, refining 287 parameters is $R_1=0.0771$, $wR_2=0.2014$ and $R_1=0.0805$ and $wR_2=0.2072$ for all reflections. All the calculations involving structure solution, refinement and graphics were

performed using SHELXTL-PC.[11] Least squares planes and H-bonding was calculated using PARST.[12] Crystallographic data for the structure have been deposited with Cambridge Crystallographic Database as supplementary publication number CCDC 268606.

Acknowledgements

Authors acknowledge the financial assistance received from the Department of Science and Technology (Govt. of India), CSIR and UGC for a junior research fellowship to one of the authors (AC).

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Tetrahedron 61 (2005) 12330–12338
Tetrahedron

The optimization for cyclization reaction of 2-(2-carbomethoxyethynyl)aniline derivatives and formal synthesis of pyrroloquinoline quinone and its analogue utilizing a sequential coupling-cyclization reaction

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Received 26 August 2005; revised 20 September 2005; accepted 21 September 2005

Available online 10 October 2005

Abstract—The reaction conditions for the Pd-catalyzed cyclization reaction of 2-(2-carbomethoxyethynyl)aniline derivatives were investigated. The amounts of $Pd(PPh_3)_4$, methyl propiolate, and $ZnBr_2$ could be significantly reduced compared with those reported in our preliminary publication by careful tuning of the solvent and the reaction temperature. In addition to the above results, formal syntheses of pyrroloquinoline quinone (PQQ) and its analogue from 2-amino-5-nitrophenol using a Pd-complex-catalyzed sequential coupling-cyclization reaction between methyl propiolate and 2-iodoaniline derivatives are described.

1. Introduction

1.1. Cyclization reaction of 2-(2-carbomethoxylethynyl)-aniline derivatives

In our continuing efforts to develop new methods of synthesis for heterocyclic compounds, we have previously discovered both Cu(II)-catalyzed synthesis of indoles from 2-ethynylaniline derivatives[1] and Pd-complex-catalyzed sequential coupling-cyclization reactions between methyl propiolate and 2-iodoaniline derivatives, and the latter's application to duocarmycin SA synthesis.[2,3] Although the true catalytic species in the Pd-complex-catalyzed reactions has not yet been identified, these reactions are an effective method for the synthesis of indole-2-carboxylate derivatives, which are commonly found in biologically active compounds.

Unfortunately, the substrates for the Pd-complex-catalyzed sequential reaction are limited to compounds having at least one electron-withdrawing group on the aromatic ring (Scheme 1, **1a**→**3a**; 69% vs **1b**→**3b**; 10%).[2] However, the cyclization reactions for the compound **2b** can be realized in almost perfect yield when both $Pd(PPh_3)_4$ and methyl propiolate are present in the reaction medium (Scheme 1, **2b**→**3b**; 94%).[2] These results suggest that the coupling reaction rate for the electron-rich substrate is slower than that for the electron-poor compound in the sequential processes, and it seems likely that the catalyst was deactivated during the long reaction time.

In our previous communication, we reported that methyl propiolate is essential for the Pd-catalyzed cyclization reactions of **2b**.[2] However, we did not optimize the reaction conditions, including the amount of each reagent and the solvent, reaction temperature, and ligand for Pd. In the first half of this article, we describe the results of the optimization for the Pd-catalyzed cyclization reaction conditions (**2b**→**3b**).

1.2. Pyrroloquinoline quinone (PQQ) and its analogues

The characterization of pyrroloquinoline quinone (PQQ) (**4**) from *Pseudomonas* TP1[4] was first reported in 1979 by Salisbury. Initially, the role of PQQ in bacteria seemed to be limited to that of a redox cofactor, but later it was found that

Keywords: Palladium; 2-Ethynylaniline; Methyl propiolate; Indole; Cyclization reaction; Pyrroloquinoline quinone.
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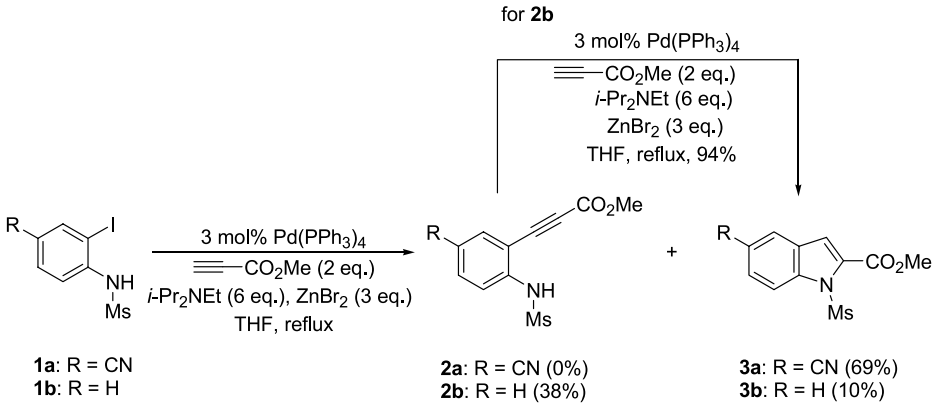
doi:10.1016/j.tet.2005.09.084



Scheme 1. Sequential coupling-cyclization reactions for **1a** and **1b** and cyclization reaction for **2b**.

PQQ also acts as a growth factor and tissue-protective agent.[5] Quite recently, another important role for PQQ as the 14th vitamin in mammals was established by Kasahara and Kato.[6,7]

The first total synthesis of PQQ was reported by Corey in 1981, in 11 steps starting from commercially available 2-methoxy-5-nitroaniline.[8a] After this communication, seven articles on the total synthesis of PQQ were published in the 1980s,[8b–h] and three papers reported the preparation of PQQ and/or its trimethyl ester in the 1990s.[8i–k] Interest in PQQ has recently shifted toward understanding the mechanisms of its biological activity[9] and biosynthetic pathway.[10] Thus, the synthetic targets have been not only PQQ itself, but also PQQ analogues, in order to understand the structure–activity relationships of PQQ. Hence, many kinds of PQQ analogues have been synthesized, including mono- and dicarboxylic acid derivatives,[11] 6-deaza derivatives,[12] benzo-,[13a] furo- (FQQ),[13b] thieno- (TQQ),[13b] and imidazole[13c] analogues in place of the pyrrole ring, and azaisomers involving both the pyrrole and pyridine rings.[14,15]

Our synthetic strategies for PQQ (**4**) and its analogue **5** are shown in Figure 1. Briefly, the conversions from **9** via **7** and **6** to PQQ (**4**) and from **8** to PQQ analogue **5** had been reported by Rees's[8g] and Hudson's[14b] research groups, respectively. Thus, compound **8** can be synthesized from **10** by same pyridine ring formation reactions as for **9**. Since both **11** and **12** have the nitro group on the aromatic ring, we planned to use our sequential coupling-cyclization reaction[2], followed by reduction of nitro group to form the indoles **9** and **10**, respectively. Iodides **11** and **12** may be

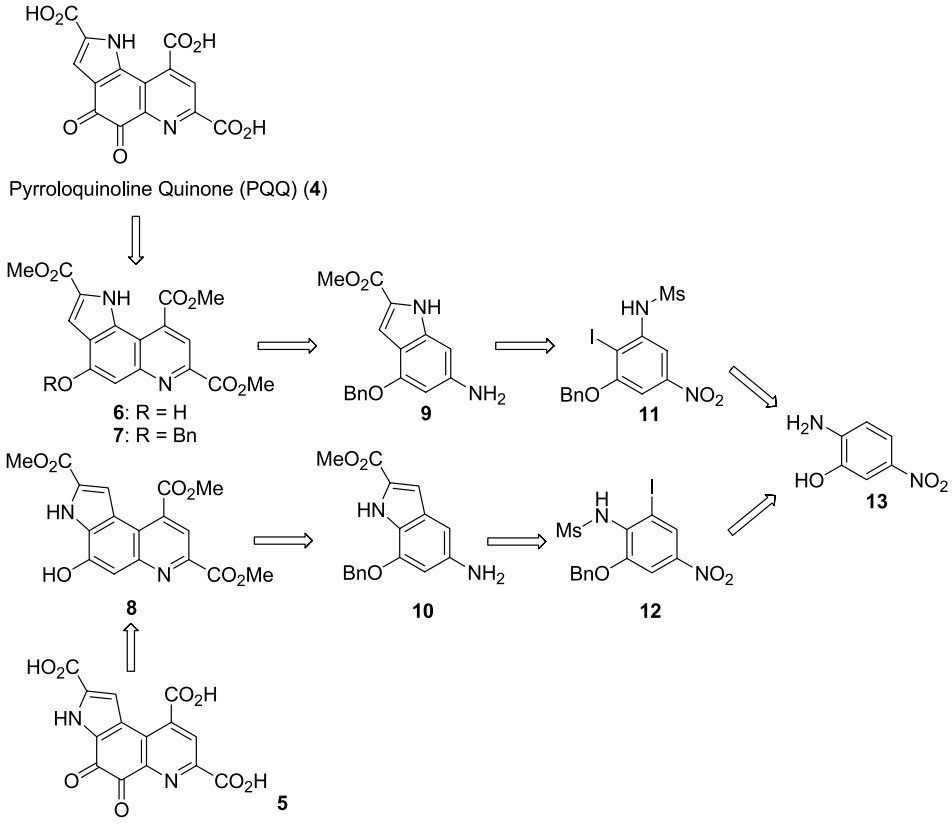


Figure 1. Retrosynthetic analysis for PQQ (**4**) and its analogue **5**.

synthesized from 2-amino-5-nitrophenol (**13**) as the common starting material by regioselective functional group installations.

In the second half of this article, we describe a relatively short synthesis of **7**[8g] and **8**,[14] which are intermediates for the synthesis of PQQ (**4**) and its analogue **5** by Pd-complex-catalyzed sequential coupling-cyclization reactions as the key steps.

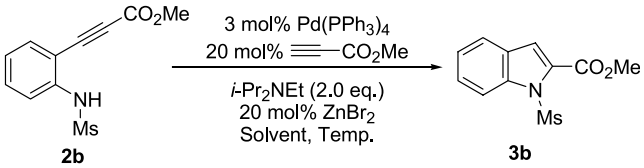
2. Results and discussion

2.1. Optimization of the reaction conditions

Since we have already established that both $Pd(PPh_3)_4$ and methyl propiolate are essential for the cyclization reactions,[2] we first experimented with reducing the amounts of the reagents. The results are summarized in Table 1. When the amount of *i*-Pr_2NEt was reduced from 2.0 to 1.0 equiv, the yield of **3b** was markedly reduced compared to that from the original conditions (Table 1, entry 1 [94%] vs entry 2 [28%]). In contrast, the amount of methyl propiolate could be reduced from 600 to 20 mol%, but not to 10 mol% (Table 1, entries 2–6). Since higher reaction temperature was required for the reactions with less than 100 mol% of methyl propiolate, the reactions were carried out in a sealed tube (Table 1, entry 4 vs entries 5–8). In the presence of 20 mol% of methyl propiolate, the amount of $ZnBr_2$ could also be reduced from 300 to 20 mol% without any loss of yield (Table 1, entry 5 [87%] vs entry 7 [88%]). However, in the absence of $ZnBr_2$, the yield of **3b** decreased from 88 to 35% (Table 1, entries 7 and 8). Presumably, the role of $ZnBr_2$ might be acceleration of the formation of the catalyst, or its activation, or both.

Next, we examined the influence of the solvent and the reaction temperature using optimized amounts of $ZnBr_2$, methyl propiolate, and *i*-Pr_2NEt (Table 2). The reaction barely proceeded in the tested solvents at ambient temperature (ca. 20 °C, Table 2, entries 1–3). At 50 °C, the yield of **3b** was quite low under the original conditions[2] (in THF, Table 2, entry 4) and reasonable yields were observed in both DMF and trifluorotoluene at 50 °C (Table 2, entries 5 and 6). The fastest reaction was observed in CH_2Cl_2 at 50 °C (Table 2, entry 7) and these reaction conditions were included in the further optimizations (Tables 3 and 4).

Table 2. Optimization of the solvent and the reaction temperature



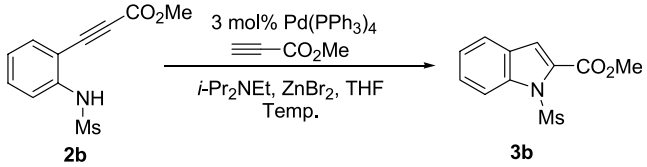
Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	THF	17	Ambient	0
2	DMF	65	Ambient	0
3	CH_2Cl_2	76	Ambient	5
4[a]	THF	12	50	4
5[a]	DMF	12	50	74
6[a]	Trifluorotoluene	12	50	88
7[a]	CH_2Cl_2	6	50	85

[a] Reactions were carried out in a sealed tube.

Because of the volatile nature of methyl propiolate, we were worried that it might evaporate from the reaction mixture. However, contrary to our speculation, the propiolates possessing bulkier ester moieties tended to reduce the reaction rate. When benzyl propiolate was used, there is advantage that the reaction can be carried out without using a sealed tube. However, since no difference in yield between the methyl and benzyl esters was observed and the reaction rate with methyl propiolate is much faster than that with benzyl propiolate (Table 3, entry 1 vs 2), we chose commercially available methyl propiolate in subsequent experiments. The other acetylenes, which do not have an electron withdrawing group, did not show any catalytic activities, even when reacted for 30 h (Table 3, entries 3 and 4).

Finally, the effects of the ligand, using $Pd_2(dba)_3$ as the palladium source, were investigated (Table 4). $Pd_2(dba)_3$ without any ligand did not have effective catalytic activity (Table 4, entry 1). Surprisingly, the yield of **3b** in the reaction with PPh_3 was much lower than that with $Pd(PPh_3)_4$ (Table 4, entry 2 [35%] vs Table 2, entry 7 [85%]). The

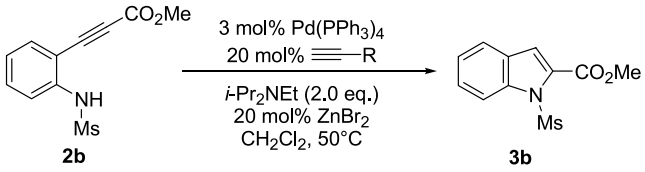
Table 1. The optimized amounts of the reagents for the cyclization reaction



Entry	$ZnBr_2$ (mol%)	Methyl propiolate (mol%)	*i*-Pr_2NEt (equiv)	Temperature (°C)	Time (h)	Yield (%)
1	300	600	2.0	65–67 (Reflux)	17	94
2	300	600	1.0	65–67 (Reflux)	17	28
3	300	100	2.0	65–67 (Reflux)	17	100
4	300	50	2.0	65–67 (Reflux)	22	56 (27)[a]
5[b]	300	20	2.0	100	17	87
6[b]	300	10	2.0	100	17	54
7[b]	20	20	2.0	100	4	88
8[b]	—	20	2.0	100	17	35

[a] The numbers in the parenthesis are the yields of the recovered **2b**.
[b] Reactions were carried out in a sealed tube.

Table 3. The effect of the substituent of the acetylenes



Entry	R	Time (h)	Yield (%)
1[a]	CO_2Me	6	85
2	CO_2Bn	17.5	86
3[a]	Ph	30	15 (85)[b]
4[a]	Bu	30	16 (83)[b]

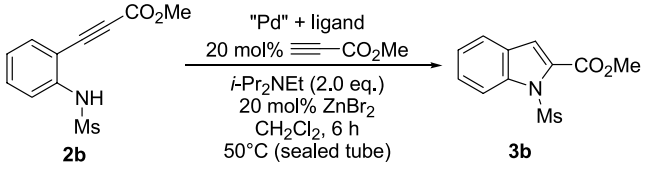
[a] Reactions were carried out in a sealed tube.
[b] The numbers in the parenthesis are the yields of the recovered **2b**.

ligands that have larger cone angles [P(*o*-tol)$_3$ or PBn$_3$] or smaller one (PBu$_3$) or more π-acid character [P(OPh)$_3$] than PPh$_3$ also gave disappointing results (Table 4, entries 3–6). The catalyst with bidentate ligands (BINAP or dppf) also did not show any catalytic activity (Table 4, entries 6 and 7). At this stage, we gave up investigating the reactions with the other ligands and focused on reducing the catalyst [Pd(PPh$_3$)$_4$] loading. The yield was essentially the same between 3 and 1 mol% Pd(PPh$_3$)$_4$ (Table 4, entries 9 and 10). Consequently, the amount of the catalyst could be reduced to 0.5 mol%, although the yield was decreased slightly (Table 4, entry 11). From the above results, we could establish the optimized conditions.

2.2. Synthesis of PQQ and its analogues

Following the retro synthetic scheme (Fig. 1), we began with the synthesis of PQQ. Both the amino and phenol groups of commercially available 2-amino-5-nitrophenol (**13**) were protected as cyclic carbamates by treatment with 1,1′-carbonyldiimidazole in THF in 96% yield. Regioselective nitration was performed by standard reaction conditions to yield dinitro compound **15** as the major product (78%). The cyclic carbamate was essential as the protecting group in achieving the regioselective nitration.

Table 4. Palladium species and ligand effect



Entry	Pd source (mol%)	Ligand (mol%)	Yield (%)
1	Pd$_2$(dba)$_3$ (3)	—	8 (50)[a]
2	Pd$_2$(dba)$_3$ (3)	PPh$_3$ (24)	34 (50)[a]
3	Pd$_2$(dba)$_3$ (3)	P(*o*-tol)$_3$ (24)	Trace
4	Pd$_2$(dba)$_3$ (3)	PBn$_3$ (24)	12 (68)[a]
5	Pd$_2$(dba)$_3$ (3)	PBu$_3$ (24)	14 (51)[a]
6	Pd$_2$(dba)$_3$ (3)	P(OPh)$_3$ (24)	Trace
7	Pd$_2$(dba)$_3$ (3)	BINAP (6)	0
8	Pd$_2$(dba)$_3$ (3)	dppf (12)	Trace
9	Pd(PPh$_3$)$_4$ (3)	—	85
10	Pd(PPh$_3$)$_4$ (1)	—	87
11	Pd(PPh$_3$)$_4$ (0.5)	—	76

[a] The numbers in the parentheses are the yields of recovered **2b**.

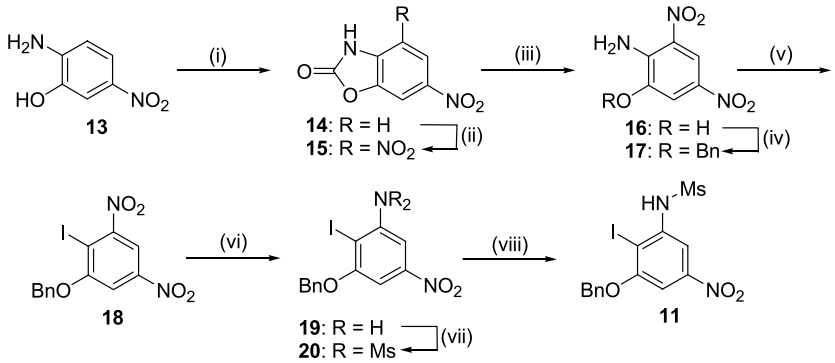
Alkaline hydrolysis of the carbamate moiety of **15** followed by benzylation of the resulting phenol group afforded the amine **17** in good overall yield (91% for two steps). The amino group of **17** was converted to an iodine atom under Sandmeyer conditions to provide 2-benzyloxy-1-iodo-4,6-dinitrobenzene (**18**). It was difficult to reduce only the C6-nitro group of **18**; we tested several reaction conditions (e.g., H_2, Pd/C; H_2, PtO_2; $H_2NNH_2 \cdot H_2O$, etc.). However, the reaction of **18** in the presence of metallic iron in a mixture of AcOH–EtOH (1/1) at 100 °C[16] gave **19** as the major product. Next, the amino group of **19** was converted to the corresponding mesylamide **11** via bis-mesylate **20**, followed by methanolysis, with 89% yield from **19** (Scheme 2).

Having established the synthesis of the desired 2-iodoaniline derivative **11** in large quantities, we applied the sequential coupling-cyclization reaction to **11** (Scheme 3). The coupling reaction of **11** in the presence of methyl propiolate, Pd(PPh$_3$)$_4$, ZnBr$_2$, and *i*-Pr$_2$NEt in THF as previously reported,[2] followed by cyclization, proceeded smoothly to afford the indole **21** in 65% yield.[17] Only the cyclized compound **21** was isolated, and the 2-ethynylaniline derivative produced in the first reaction was not detected. Methanolysis of the mesylamide group on **21** followed by reduction of the nitro group was carried out to produce the aniline **9**[8g] in reasonable yield (73%). The pyridine ring was constructed using the procedure reported by MacKenzie et al.[8g] [dimethyl (*E*)-2-oxoglutaconate, CH_2Cl_2, room temperature 12 h, then cat. HCl in Et_2O, room temperature 12 h] to permit synthesis of the three-ring system of PQQ in 71% yield. The spectral data (IR, ^{1}H NMR, and MS) of **7** were identified with the reported data.[8g] This compound was converted to PQQ (**4**) via ortho-quinone **23**[8a–c,g,i] by four steps. Thus, we furnished formal synthesis of PQQ (**4**) (Scheme 3).

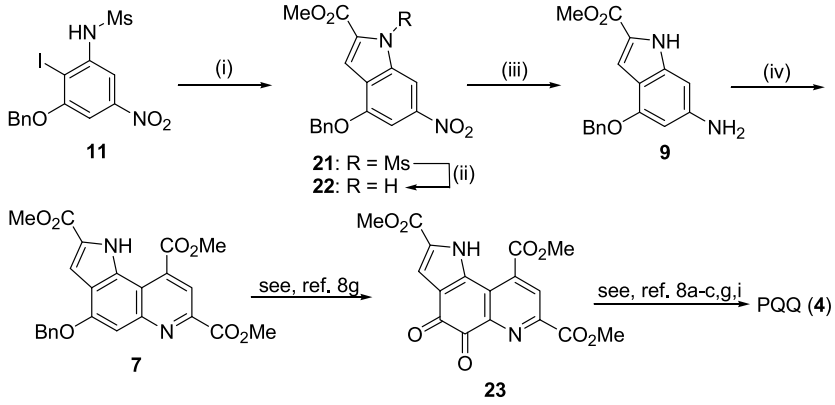
Synthesis of the PQQ analogue was started from the indole derivative **24**, which was synthesized from **13** via **12** in our synthesis of duocarmycin SA.[2] The selective removal of the methanesulfonyl group under methanolysis conditions was followed by reduction of the nitro group on **25** by hydrogenation to provide **10**. The third ring was constructed using the same procedure as in the synthesis of PQQ, to afford **26** (45% yield for two steps). Finally, the benzyl ether of **26** was cleaved under hydrogenolysis conditions to give **8**, which yielded spectral data that matched those previously reported[14b] (Scheme 4).

3. Conclusion

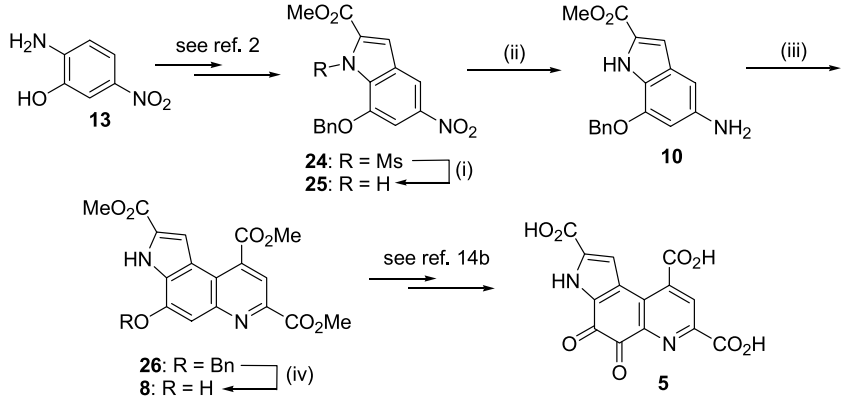
In summary, we optimized the Pd-catalyzed cyclization reaction of 2-(2-carbomethoxyethynyl)aniline derivatives. Namely, the amounts of Pd(PPh$_3$)$_4$, methyl propiolate, and ZnBr$_2$ could be significantly reduced compared with those reported in our previous communication. We also successfully applied a Pd-complex-catalyzed sequential coupling-cyclization reaction between methyl propiolate and 2-iodoaniline derivatives to the synthesis of PQQ and its analogues. The further application is currently underway in our laboratory.



Scheme 2. Reagents and conditions: (i) $(Imid)_2CO$, THF, rt, 2 h (96%); (ii) f. HNO_3, concd H_2SO_4, 0 °C, 5 min (78%); (iii) NaOH, 50 °C, 22 h; (iv) BnBr, K_2CO_3, acetone, reflux, 2 h (91% from **15**); (v) $NaNO_2$, H_2SO_4, AcOH, 5 °C, 5 min, then KI, rt, 2 h (54%); (vi) Fe, AcOH–EtOH (1/1), 100 °C, 1 h (55%); (vii) MsCl, Et_3N, CH_2Cl_2, rt, 5 min; (viii) K_2CO_3, MeOH, rt, 15 min (89% from **19**).



Scheme 3. Reagents and conditions: (i) methyl propiolate, $Pd(PPh_3)_4$, $ZnBr_2$, *i*-Pr_2NEt, THF, 100 °C in a sealed tube, 11 h (65%); (ii) K_2CO_3, MeOH–THF (1/1), rt, 15 min (78%); (iii) H_2, PtO_2, AcOEt–THF (1/1), rt, 2 h (73%); (iv) dimethyl (*E*)-2-oxoglutaconate, CH_2Cl_2, rt, 12 h, then cat. HCl in Et_2O, rt, 12 h (71%).



Scheme 4. Reagents and conditions: (i) K_2CO_3, MeOH–THF (1/1), rt, 20 min (89%); (ii) H_2, PtO_2, AcOEt, rt, 2 h; (iii) dimethyl (*E*)-2-oxoglutaconate, CH_2Cl_2, rt, 12 h, then cat. HCl in MeOH, rt, 10 h (45% from **25**); (iv) H_2, Pd/C, $CHCl_3$–MeOH (1/3), rt, 1.5 h, (97%).

4. Experimental

4.1. General

All melting points were determined with a Yazawa Micro Melting Point BY-2 and are uncorrected. ^1H NMR spectra (400 and 600 MHz) were recorded on JEOL JMN AL-400 and JEOL ECA-600 spectrometers, respectively. ^{13}C NMR spectra (100, 125, 150 MHz) were recorded on JEOL JMN AL-400, JEOL ECP-500, and JEOL ECA-600 spectrometers, respectively. For ^1H NMR spectra, chemical shifts (δ) are given from TMS (0 ppm) in $CDCl_3$ and from residual non-deuterated solvent peak in the other solvents (acetone-d_6:2.04 ppm, DMSO-d_6:2.49 ppm, methanol-d_4:3.30 ppm, and THF-d_8:3.58 ppm) as internal standards. For ^{13}C NMR spectra, chemical shifts (δ) are given from $^{13}CDCl_3$ (77.0 ppm), $(^{13}CD_3)_2CO$ (29.8 ppm), $(^{13}CD_3)_2SO$ (39.7 ppm), and $(^{13}CD_2\text{-}CD_2)_2O$ (25.2 ppm) as internal standards. Standard and high-resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. IR spectra were recorded on a Shimadzu FTIR-8400.

4.1.1. Methyl 1-methylsulfonyl-2-indolecarboxylate (3b) (Table 4, entry 11). *i*-Pr_2NEt (69 μl, 0.4 mmol), **2b** (50.0 mg, 0.2 mmol), methyl propiolate (4 μl, 0.04 mmol), and $Pd(PPh_3)_4$ (1.4 mg, 0.001 mmol) were successively added to a solution $ZnBr_2$ (8.8 mg, 0.04 mmol) in CH_2Cl_2 (2.0 ml) and the mixture was stirred at 50 °C for 6 h in a sealed tube. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous phase was extracted with $CHCl_3$. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/3)] to afford **3b** (38.2 mg, 76%) as a colorless solid. The spectral data of **3b** were identified with those of the authentic sample.[1a]

4.1.2. 6-Nitro-3*H*-benzooxazol-2-one (14). 1,1′-Carbonyldiimidazole (5.77 g, 35.6 mmol) was added to a solution of **13** (5.0 g, 32.4 mmol) in anhydrous THF (100 ml) at room temperature and stirred for 2 h at the same temperature. Diluted aqueous HCl solution (50 ml) was added to the mixture and the aqueous phase was extracted with Et_2O. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The resulting solid **14** (5.58 g, 96%) was essentially pure and could be used to the following reaction. Analytical sample was recrystallized from AcOEt–hexane to provide colorless needles. Mp 254–255 °C; IR (film, cm^{-1}) 1794, 1508, 1342; ^1H NMR (400 MHz, methanol-d_4) δ 7.22 (1H, d, $J=8.7$ Hz), 8.11 (1H, d, $J=2.1$ Hz), 8.17 (1H, dd, $J=8.7$, 2.1 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 105.3, 109.2, 120.5, 136.4, 142.8, 143.3, 153.6; MS *m/z* 180 (M^+, 100), 134 (19.0), 106 (21.1); HRMS Calcd $C_7H_4N_2O_4$: 180.0171. Found: 180.0154.

4.1.3. 4,6-Dinitro-3*H*-benzooxazol-2-one (15). Concd H_2SO_4 (0.83 ml) was slowly added to 1.52 M f. HNO_3 solution (5.6 ml, 8.51 mmol) at 0 °C. After being stirred for 5 min at the same temperature, **14** (1.4 g, 7.77 mmol) was added to the mixture. After the addition was completed, the solution was poured into a mixture of ice and water. The aqueous phase was extracted with AcOEt and the combined organic solution was successively washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution. The organic solution was dried over anhydrous $MgSO_4$ and concentrated at the reduced pressure. The residue was purified by silica gel column chromatography [AcOEt–hexane (2/3)] to afford **15** (1.09 g, 78%) as a colorless powder. Colorless powder from AcOEt–hexane; mp 200–202 °C; IR (film, cm^{-1}) 3099, 1790, 1634, 1541, 1344; ^1H NMR (400 MHz, acetone-d_6) δ 8.47 (1H, d, $J=2.0$ Hz), 8.80 (1H, d, $J=2.0$ Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 109.7, 115.1, 130.1, 132.9, 141.5, 145.2, 152.9; MS *m/z* 225 (M^+, 100), 209 (3.0), 179 (3.3); HRMS Calcd $C_7H_3N_3O_6$: 225.0022. Found: 225.0000. Anal. Calcd for $C_7H_3N_3O_6$: C, 37.35; H, 1.34; N, 18.67. Found: C, 37.15; H, 1.63; N, 18.66.

4.1.4. 2-Benzyloxy-4,6-dinitroaniline (17). A suspension of **15** (570 mg, 2.53 mmol) in 0.2 N NaOH (50 ml) was stirred for 22 h at 50 °C. The solution was neutralized with 3 N HCl (3.1 ml) at 0 °C and the aqueous phase was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford the crude **16**, which was used to the next reaction without further purification.

K_2CO_3 (455 mg, 3.29 mmol) and benzyl bromide (454 mg, 2.65 mmol) were added successively to a solution of the crude **16** in acetone (25 ml) and the mixture was refluxed for 2 h. After being cooled to room temperature, the inorganic precipitate was filtered through a Celite™ pad and the filtrate was concentrated at the reduced pressure. The resulting solid was recrystallized from AcOEt to afford **17** (557 mg) as yellow needles and the mother liquid was chromatographed on silica gel [AcOEt–hexane (1/2)] to afford **17** (110 mg) as a yellow solid (total yield of **17**: 667 mg, 91%). Yellow needles from AcOEt; mp 187–189 °C; IR (film, cm^{-1}) 3489, 3369, 1624, 1541, 1328; ^1H NMR (400 MHz, $CDCl_3$) δ 5.23 (2H, s), 7.41–7.44 (5H, m), 7.81 (1H, d, $J=2.4$ Hz), 8.81 (1H, d, $J=2.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1, 108.1, 108.3, 115.6, 115.8, 128.1, 129.0, 129.1, 134.2, 141.2, 146.4; MS *m/z* 289 (M^+, 4.1), 91 (100); HRMS Calcd $C_{13}H_{11}N_3O_5$: 289.0699. Found: 289.0683. Anal. Calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53. Found: C, 53.90; H, 3.87; N, 14.47.

4.1.5. 2-Benzyloxy-1-iodo-4,6-dinitrobenzene (18). $NaNO_2$ (65.4 mg, 0.948 mmol) was slowly added to concd H_2SO_4 (1 ml) at 0 °C and the mixture was dropped to a solution of **17** (203 mg, 0.702 mmol) in AcOH (10 ml) at 5 °C. After being stirred for 5 min, a solution of KI (157 mg, 0.946 mmol) in ice and H_2O (10 ml) was added to the reaction mixture and the mixture was stirred for another 2 h at room temperature. The mixture was extracted with AcOEt and the combined organic solution was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution. The organic solution was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/9)] to afford **18** (157 mg, 54%) as a light yellow solid. Light yellow plates from AcOEt–hexane; mp 152–154 °C; IR (film, cm^{-1}) 1527; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (2H, s), 7.40–7.51 (5H, m), 7.83 (1H, d, $J=2.2$ Hz), 8.14 (1H, d, $J=2.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.7, 89.6, 108.3, 111.7, 127.3, 128.9, 129.0, 134.1, 148.8, 155.4, 159.7; MS *m/z* 400 (M^+, 2.1), 91 (100); HRMS Calcd $C_{13}H_9IN_2O_5$: 399.9556. Found: 399.9556. Anal. Calcd for $C_{13}H_9IN_2O_5$: C, 39.02; H, 2.27; N, 7.00. Found: C, 39.22; H, 2.45; N, 6.88.

4.1.6. 3-Benzyloxy-2-iodo-5-nitroaniline (19). Fe (75 mg, 1.34 mmol) was added to a solution of **18** (135 mg, 0.337 mmol) in AcOH (3.4 ml) and EtOH (3.4 ml) and the mixture was stirred for 1 h at 100 °C. H_2O was added and the mixture was filtered through a Celite™ pad and the filtrate was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/9)] to afford **19** (68.4 mg, 55%) as a yellow solid. Yellow needles from AcOEt–hexane; mp 147–148 °C; IR (film, cm^{-1}) 3464, 3369, 1622, 1501, 1435, 1346; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58 (2H, s), 5.19 (2H, s), 7.07 (1H, d, $J=1.6$ Hz), 7.25–7.51 (6H, m); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 71.3, 83.5, 96.0, 101.8, 127.0, 128.1, 128.6, 135.5, 148.5, 149.5, 158.1; MS *m/z* 370 (M^+, 29.8), 264 (7.7), 243 (14.3), 91 (100); HRMS Calcd $C_{13}H_{11}IN_2O_5$: 369.9814. Found: 369.9799. Anal. Calcd for $C_{13}H_{11}IN_2O_5$: C, 42.18; H, 3.00; N, 7.57. Found: C, 42.27; H, 3.18; N, 7.32.

4.1.7. *N*-methanesulfonyl-3-benzyloxy-2-iodo-5-nitroaniline (11). MsCl (0.23 ml, 2.97 mmol) was added to a solution of **19** (432 mg, 1.17 mmol) and Et_3N (0.49 ml, 3.52 mmol) in anhydrous CH_2Cl_2 (1.0 ml) at 0 °C and stirred for 5 min at the same temperature. H_2O was added to the mixture and the aqueous phase was extracted with $CHCl_3$. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford **20**, which was used to the next reaction without further purification.

K_2CO_3 was added to a solution of the crude **20** in a mixture of MeOH–THF (1/1, 10 ml) and stirred for 15 min at room temperature. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous phase was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The resulting solid was recrystallized from AcOEt–hexane to afford **11** (400 mg) as colorless needles and mother liquor was chromatographed on silica gel [AcOEt–hexane (1/2)] to afford **11** (68.9 mg) as colorless solid (total yield of **11**:468.9 mg, 89% from **19**). Colorless needles from AcOEt–hexane; mp 182–184 °C; IR (film, cm^{-1}) 3273, 1609, 1518, 1327, 1151; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (3H, s), 5.27 (2H, s), 7.11 (1H, s), 7.37–7.50 (5H, m), 7.53 (1H, d, J=3.2 Hz), 8.14 (1H, d, J=3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.9, 72.0, 91.5, 102.4, 107.1, 127.2, 128.6, 128.8, 134.6, 140.0, 149.8, 158.3; MS *m/z* 448 (M^+, 5.5), 321 (2.6), 91 (100); HRMS Calcd $C_{14}H_{13}IN_2O_5S$: 447.9590. Found: 447.9592.

4.1.8. Methyl 4-benzyloxy-1-methanesulfonyl-6-nitroindole-2-carboxylate (21). *i*-Pr_2NEt (11 µl, 0.0631 mmol), **11** (14.5 mg, 0.0324 mmol), methyl propiolate (17 µl, 0.19 mmol), and $Pd(PPh_3)_4$ (5.6 mg, 4.8 µmol) were successively added to a solution of $ZnBr_2$ (22 mg, 0.098 mmol) in THF (1 ml) at room temperature and the mixture was heated at 100 °C in a sealed tube for 11 h. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous solution was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated at reduced pressure. The residue was chromatographed on silica gel [AcOEt–hexane (1/4)] to provide **21** (8.5 mg, 65%) as a colorless solid. Colorless needles from AcOEt–MeOH; mp 173–175 °C; IR (film, cm^{-1}) 1732, 1522, 1371, 1335; ^1H NMR (600 MHz, $CDCl_3$) δ 3.80 (3H, s), 3.97 (3H, s), 5.28 (2H, s), 7.39–7.49 (6H, m), 7.66 (1H, s), 8.63 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 43.9, 53.0, 71.0, 99.9, 105.1, 113.5, 123.0, 127.7, 128.6, 128.8, 133.0, 135.3, 137.8, 147.9, 153.0, 160.7; MS *m/z* 404 (M^+, 11.2), 326 (3.9), 91 (100); HRMS Calcd $C_{18}H_{16}N_2O_7S$: 404.0678. Found: 404.0692.

4.1.9. Methyl 4-benzyloxy-6-nitroindole-2-carboxylate (22). K_2CO_3 was added to a solution of **21** (73.5 mg, 0.182 mmol) in a mixture of MeOH–THF (1/1, 2.0 ml) and stirred for 15 min at room temperature. Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous solution was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated at reduced pressure. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/4)] to afford **22** (46.4 mg, 78%) as a yellow powder. Yellow powder from AcOEt–hexane; mp 262–263 °C; IR (film, cm^{-1}) 3296, 1693, 1524; ^1H NMR (400 MHz, THF-d_8) δ 3.89 (3H, s), 5.32 (2H, s), 7.29 (1H, s), 7.31 (1H, t, J=7.2 Hz), 7.38 (2H, t, J=7.2 Hz), 7.49 (1H, s), 7.54 (2H, d, J=7.2 Hz), 7.98 (1H, s), 11.8 (1H, s); ^{13}C NMR (100 MHz, THF-d_8) δ 51.8, 70.8, 96.0, 102.9, 105.9, 123.5, 127.9, 128.3, 128.8, 131.6, 136.9, 137.1, 146.9, 153.8, 161.3; MS *m/z* 326 (M^+, 23.0), 91 100); HRMS Calcd $C_{17}H_{14}N_2O_5$: 326.0903. Found: 326.0894.

4.1.10. Methyl 6-amino-4-benzyloxyindole-2-carboxylate (9). PtO_2 (3 mg, 0.0132 mmol) was added to a solution of **22** (45 mg, 0.138 mmol) in a mixture of AcOEt–THF (1/1, 2.0 ml) and the mixture was vigorously stirred under hydrogen atmosphere for 2 h. PtO_2 was filtered off and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography [AcOEt–hexane (1/1)] to provide **9** (30 mg, 73%) as a tan solid. IR (film, cm^{-1}) 3352, 2924, 1682, 1634, 1520, 1279; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (2H, br s), 3.91 (3H, s), 5.18 (2H, s), 6.06 (1H, d, J=1.8 Hz), 6.28 (1H, s), 7.30 (1H, d, J=1.8 Hz), 7.36–7.51 (5H, m), 8.54 (1H, s); ^{13}C NMR (100 MHz, THF-d_8) δ 50.7, 69.7, 88.0, 93.6, 107.0, 112.5, 123.8, 127.5, 127.8, 128.6, 138.3, 141.4, 148.6, 154.4, 162.2; MS *m/z* 296 (M^+, 100), 264 (26.3), 205 (54.8), 173 (34.8); HRMS Calcd $C_{17}H_{16}N_2O_3$: 296.1161. Found: 296.1154.

4.1.11. Trimethyl 4-benzyloxy-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylate (7). Dimethyl (*E*)-2-oxoglutaconate (22.8 mg, 0.132 mmol) was added to a solution of **9** (26.2 mg, 0.0884 mmol) in anhydrous CH_2Cl_2 (0.5 ml) at room temperature. After being stirred for 12 h at the same temperature, one drop of hydrogen chloride in diethyl ether was added to the mixture and stirred for another 12 h. Saturated aqueous $NaHCO_3$ solution was added to the mixture and the aqueous phase was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residual solid was triturated with methanol and dried to give **7** (28.3 mg, 71%) as a bright yellow solid. Mp 211–213 °C (lit.[8g] 215–217 °C); IR (film, cm^{-1}) 3299, 2954, 1717, 1436, 1259; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (3H, s), 4.10 (3H, s), 4.16 (3H, s), 5.35 (2H, s), 7.37–7.55 (7H, m), 8.75 (1H, s), 12.56 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 53.3, 53.9, 70.2, 102.0, 106.8, 113.1, 121.2, 122.0, 126.9, 127.3, 128.1, 128.5, 129.4, 131.4, 136.0, 144.7, 151.7, 155.6, 161.3, 165.3, 168.5; MS *m/z* 448 (M^+, 100), 416 (14.4), 388 (23.3); HRMS Calcd $C_{24}H_{20}N_2O_7$: 448.1271. Found: 448.1254.

4.1.12. Methyl 7-benzyloxy-5-nitroindole-2-carboxylate (25). K_2CO_3 (247 mg, 1.79 mmol) was added to a solution of **24**[2] (725 mg, 1.79 mmol) in a mixture of MeOH–THF (1/1, 20 ml) and stirred for 20 min at room temperature.

Saturated aqueous NH_4Cl solution was added to the mixture and the aqueous solution was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was triturated with diethyl ether to afford **25** (520 mg, 89%) as a light yellow solid. Light yellow needles from AcOEt–hexane; mp 165–167 °C; IR (film, cm^{-1}) 3294, 1705, 1524; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (3H, s), 5.26 (2H, s), 7.31 (1H, s), 7.42 (5H, m), 7.68 (1H, s), 8.31 (1H, s), 9.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 71.0, 100.3, 110.8, 113.1, 126.6, 128.1, 128.68, 128.73, 129.5, 130.7, 135.1, 143.0, 145.0, 161.2; MS *m/z* 326 (M^+, 14.6), 91 (100); HRMS Calcd $C_{17}H_{14}N_2O_5$: 326.0903. Found: 326.0891. Anal. Calcd $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.71; H, 4.52; N, 8.46.

4.1.13. Trimethyl 4-benzyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2,7,9-tricarboxylate (26). PtO_2 (3.2 mg, 0.014 mmol) was added to a solution of **25** (22.8 mg, 0.0699 mmol) in AcOEt (2.3 ml) and the mixture was stirred under hydrogen atmosphere for 2 h. PtO_2 was filtered off and the filtrate was concentrated in vacuo to afford the crude **10**, which was used to the next reaction without further purification.

Dimethyl (*E*)-2-oxoglutaconate (14.4 mg, 0.0837 mmol) was added to a solution of **10** in anhydrous CH_2Cl_2 (1 ml) at room temperature. After being for 12 h at the same temperature, anhydrous MeOH (6.2 μl) and AcCl (10 μl) was added to the mixture and stirred for another 10 h. Saturated aqueous $NaHCO_3$ solution was added to the mixture and the aqueous solution was extracted with $CHCl_3$. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by preparative TLC [CH_2Cl_2–MeOH (95/5)] to afford **26** (14 mg, 45% from **25**) as a light yellow solid. Semi-opaque powder from Et_2O–hexane; mp 164 °C; IR (film, cm^{-1}) 3287, 2951, 1717, 1252; ^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (3H, s), 4.08 (3H, s), 4.15 (3H, s), 5.35 (2H, s), 7.41–7.63 (7H, m), 8.30 (1H, s), 9.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.1, 53.1, 53.2, 70.9, 105.9, 111.7, 118.1, 119.1, 119.8, 126.3, 128.0, 128.6, 128.7, 129.4, 135.2, 136.1, 144.4, 148.8, 149.2, 161.4, 165.4, 168.5; MS *m/z* 448 (M^+, 58.9), 420 (14.3), 389 (18.4), 343 (12.9), 91 (100); HRMS Calcd $C_{24}H_{20}N_2O_7$: 448.1271. Found: 448.1277.

4.1.14. Trimethyl 4-hydroxy-3*H*-pyrrolo[3,2-*f*]quinoline-2,7,9-tricarboxylate (8). Ten percentage Pd/C (3 mg) was added to a solution of **26** (99.7 mg, 0.222 mmol) in a mixture of $CHCl_3$–MeOH (1/3, 4.0 ml) and the mixture was stirred under hydrogen atmosphere for 1.5 h. Pd/C was filtered off eluting with $CHCl_3$ and the filtrate was concentrated in vacuo to afford **8** (77.5 mg, 97%) as a light yellow solid. Light yellow needles from MeOH–$CHCl_3$; mp 294 °C (decomposition) [lit.[14b] 276–278 °C (decomposition)]; IR (film, cm^{-1}) 3292, 2955, 1717, 1254; ^1H NMR (400 MHz, DMSO-d_6) δ 3.88 (3H, s), 3.93 (3H, s), 4.05 (3H, s), 7.24 (1H, s), 7.39 (1H, s), 8.07 (1H, s), 11.17 (1H, s), 12.77 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 51.9, 52.5, 53.3, 106.6, 110.5, 115.5, 116.8, 119.1, 126.8, 129.8, 135.7, 143.8, 148.1, 149.0, 160.7, 164.8, 168.1; MS *m/z* 358 (M^+, 100), 326 (24.9), 300 (61.9), 268 (89.0); HRMS Calcd $C_{17}H_{14}N_2O_7$: 358.0801. Found: 358.0785.

References and notes

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17. Since the sequential coupling-cyclization reaction was employed for the preparation of indole **21** from 2-iodoaniline derivative **11**, excess methyl propiolate (5.9 equiv) was used and heating is essential for this reaction.

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Tetrahedron 61 (2005) 12339–12342

Aliphatic thioacetate deprotection using catalytic tetrabutylammonium cyanide

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Received 23 August 2005; revised 21 September 2005; accepted 21 September 2005

Available online 11 October 2005

Abstract—A series of thiol-functionalized organic compounds were selected to analyze the scope and efficiency of a new thioacetate deprotection method using catalytic tetrabutylammonium cyanide (TBACN) to effect the transformation of a thioacetate group to a free thiol in the presence of a protic solvent. Particularly attractive are the mild reaction and workup conditions, reduced byproduct formation typically seen using literature methods and yields of greater than 80% for the free aliphatic thiols. This method is effective on aliphatic thiols with trityl, benzyl, *p*-halo-benzyl, phenethyl, phenoxyethyl, and cyclohexylethyl structural moieties, but it is not effective with thiophenols. Published by Elsevier Ltd.

1. Introduction

The synthesis of thiol protected molecules and their deprotection are increasingly important prerequisites in the development of chemical self-assembly methods. Many applications are dependent on this chemistry. These include the fabrication of nano and molecular electronic structures,[1–4] soft lithography,[5] contact printing,[6] fabrication of nanoparticulate composites,[7,8] vapor and condensed phase sensors,[9] surface immobilization of biomolecular[10] and synthetic dye[11] functionalities, corrosion resistance treatments,[12] adhesion promotion,[13] biomolecular surface passivation[14] and electrode modification.[15]

A particularly important issue in employing the thiol group for these purposes is its shelf life prior to use. The thiol group is sensitive to slow oxidation to a disulfide or sulfoxide under ambient conditions. As such, derivatization with a protecting group provides for long term stability.[16] Acylation to a thioacetate is the most frequently employed protective chemistry. Deprotection of this thioacetate group back to the thiol is a necessary step for practical use thiol agents. Although numerous deprotection methods for this transformation of the thioacetate to the free thiol have been developed, many involve harsh conditions and are accompanied by significant formation of unwanted side-products including disulfides. Reported conditions include strong acids or bases, which can be particularly adverse to multifunctional thioacetate moieties and often result in poor yields and mixtures. Deprotecting reagents such as ammonium hydroxide, potassium hydroxide, sulfuric acid, hydrogen cyanide, hydrochloric acid, sodium thiomethoxide, potassium carbonate, and lithium aluminum hydride are employed with variable results.[17–23] These methods typically produce better results when the *S*-acetyl is attached to a lengthy methylene chain segment ($(CH_2)_n$; $n \geq 6$).[24] Herein, we describe the development of a general, effective and mild method practicable in organic solvents for the deprotection of thioacetate protected molecules.

2. Results and discussion

This new method centers on the use of tetrabutylammonium cyanide salt (TBACN) to catalyze the transformation of a thioacetate functional group to a free thiol at room temperature. Initial work was based on the O-deacylation of polyacylated sugars using catalytic potassium cyanide in methanol.[25] Compared to more standard methods, initial studies of catalyst and solvent mixtures were promising on several model thioacetate compounds. Using potassium cyanide, the mild conditions and workup reduced side product formation and the thioacetates were all converted to thiols to some degree, but it was deduced that an organo-cyanide salt was ideal for solubility issues that probably hampered potassium cyanide catalysis and resulted in only partial conversion to the free thiol. We have adapted this cyanide-catalyzed methanolysis of acylated sugars to an organic medium cyanide-catalyzed deprotection of thioacetates by using a tetrabutylammonium counter ion in

Keywords: Thioacetate; Deprotection; Tetrabutylammonium cyanide; Thiol.

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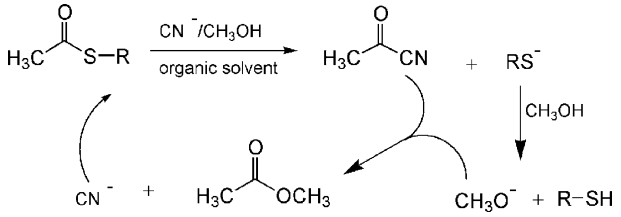
0040–4020/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.09.092

place of the potassium ion. It is reasonable to believe that the catalytic thioacetate deprotection pathway, shown below, is similar in mechanism to the solvolytic O-deacylation initially reported.



Deacylation is readily accomplished upon stirring for 3 h a solution of an aliphatic thioacetate in methanol and a cosolvent in the presence of a catalytic amount (0.5 mol equiv per thioacetate) of TBACN. The reaction typically proceeds in high yields (>80%) at room temperature and under an oxygen-free atmosphere (see Fig. 1). Catalytic residue can be removed during workup, by column chromatography or distillation. Experiments reveal that the free thiols can be obtained without significant isolation/purification difficulties commonly caused by side product formation. Reactions incorporating chloroform as the cosolvent are ideal, although dichloromethane has been adequate. This deprotect reaction is sensitive to selection of solvent as well as the presence of oxygen. It has been observed that the use of tetrahydrofuran as a cosolvent can result in the formation of disulfides. Additionally, disulfide formation has been observed if the reaction is not performed in an inert, oxygen-free atmosphere.

A protic solvent is required for this method. Reactions incorporating methanol are ideal, denoted by higher yields and absence of side product formation in comparison to ethanol and halogen-substituted alcohols. Acidic solvents ($pK_a<15$) or certain functional groups such as amines, haloaliphatics, and fluoroaromatics hinder the catalytic process. In difunctional aliphatic systems that include thioacetate and acetate functional groups, it has been observed that the cyanide can chemoselectively deprotect the thioacetate, maintaining the unhindered acetate (Fig. 2). A similar effect was originally explored with the use of HCN buffered by H_2O for ethyl benzoate and ethyl-*p*-nitrobenzoate, which were unaffected, whereas ethyl thiolacetate was deprotected.[26]

The efficiency of the method is denoted by the amount of tetrabutylammonium cyanide required for conversion of the thioacetate to the free thiol. Standard literature procedures employ an excess (>1 mol equiv) of the deprotecting agent per thioacetate group, whereas catalytic amounts of tetrabutylammonium cyanide sufficiently convert the thioacetate to the free thiol product, ultimately lowering the quantity of material needed for each reaction. Several experiments implemented a variety of reaction times and TBACN quantities (0.1–0.7 mol equiv) to determine the effective limits of the catalytic process. Longer reaction times (≥5 h) were generally required for catalytic amounts lower than 0.5 equiv and for greater than 60% conversion to the free thiol. Higher amounts of catalyst usually fully converted the thioacetates to the free thiol in a shorter

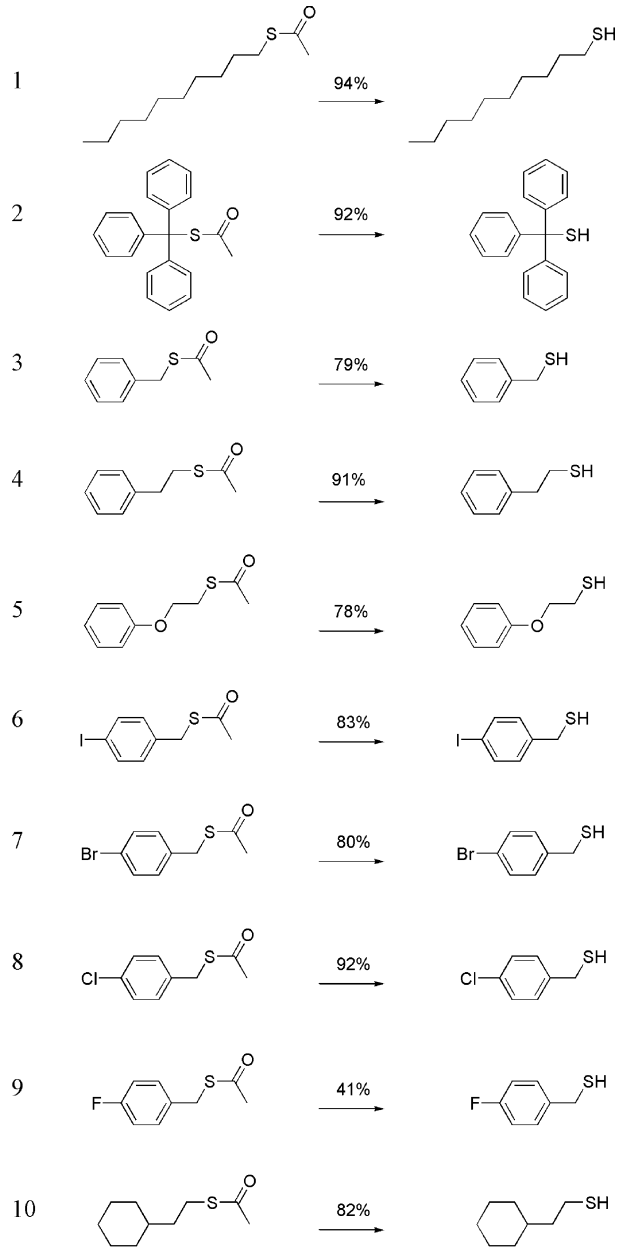


Figure 1. Catalytic deprotection yields of a series of available or readily synthesized aliphatic thioacetates **1**–**10**. Reactions were performed in a 1:1 chloroform/MeOH solvent mixture under nitrogen using 0.5 equiv of TBACN for 3 h. Note: conditions were not optimized.

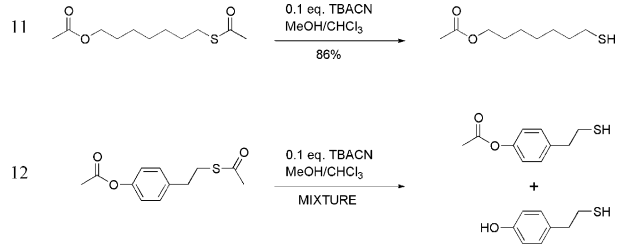


Figure 2. Selective deprotection of difunctional thioacetates **11** and **12**. Although a mixture of products was observed for **12**, a higher ratio of thioacetate was deprotected than acetate (~65/35).

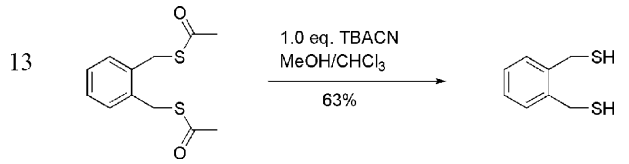


Figure 3. Deprotection of dithioacetate **13** revealed some side product formation and generally lower yields than for the monothioacetates.

amount of time (<3 h), but revealed a higher tendency for side products to form.

Initially a series of both aliphatic (compounds **1**–**13**) and aromatic thiol and thioacetate functionalized compounds were chosen for deprotection studies. The thiols were converted to their respective thioacetates by reaction with acetic anhydride in a pyridine–dichloromethane mixture in high yield.[27] Proton and carbon NMR spectra of reacted thioacetates were compared to the commercial materials and analyzed for side products, conversion and yields.

The aliphatic thiol series includes normal alkane, trityl, ethyl-cyclohexyl, phenethyl, phenoxyethyl, benzyl, and *p*-halobenzyl moieties. With the exception of the *p*-fluorobenzyl thioacetate, all yields were $\geq 80\%$. The effect of the fluorine substitution or even a fluorocarbon presence in the reaction medium is not understood at this time. In the case for compound **9** there was no evidence of ring substitution by the cyanide at the fluorine position.[28] As a control experiment a small amount of α,α,α-trifluorotoluene was added to the deprotect reaction of compound **4**. This resulted in a large amount of complex byproduct formation and only traces of thiol observed.

Difunctional α-thiol-ω-alcohol and α-thiol-ω-phenol were acylated to the corresponding acetates (compounds **11** and **12**, respectively) and competitive deprotection reaction undertaken. Compound **11** displayed a sequential cleavage wherein the thioacetate was converted to the thiol prior to any conversion of the acetate. Similar deprotection conditions for compound **12**[32] resulted in concurrent cleavage of both the thioacetate and phenylacetate functionalities.

The bifunctional *o*-xylylene dithiol (compound **13**) was acylated and then deprotected using TBACN (Fig. 3). The yield was 63% with some byproduct formation, probably disulfide.

The effectiveness of TBACN does not apparently include aromatic thiol deprotections. Experiments with thiophenyl acetate were unsuccessful. Only starting reagent and disulfide were isolated. We speculate that the thiophenolate anion is insufficiently basic to abstract a proton from methanol. More acidic alcohols were added to counter this effect, but this approach was not successful. Apparently, the cyanide ion is protonated by the more acidic alcohols and the initial reaction does not occur. WARNING: it should be noted that the reactivity of cyanide salts with acids to generate HCN gas can be potentially dangerous and fatal if improperly supervised or inhaled.

3. Summary

A series of aliphatic thioacetates were efficiently deprotected in high yield and with minimal side product formation using catalytic tetrabutylammonium cyanide in the presence of a protic solvent. The combination of methanol and chloroform is ideal at room temperature under an inert atmosphere. Experiments revealed that aliphatic thioacetates are selectively deprotected in the presence of acetates whereas phenylacetates react competitively. This deprotection method appears to be ineffective with aromatic thiols and is adversely affected by fluorinated moieties.

4. Experimental

4.1. General

All synthetic procedures were performed under an inert nitrogen atmosphere with oven dried glassware. Solvents were dried by passage through activated alumina columns and degassed with nitrogen prior to use. All reagents and catalysts were purchased from Aldrich and used as received except for compounds **10** and **11**, which were synthesized previously in our lab (**Note: without proper storage in a dry box or dessicator, it has been observed that tetrabutylammonium cyanide can lose effectiveness over time). ^{1}H and ^{13}C NMR were recorded on a Bruker Avance-300 instrument. Chemical shifts are reported in parts per million (ppm) and referenced to the residual chloroform peak at 7.28 and 77.0 ppm, respectively.

4.2. General deprotection procedure for monothioacetates 1–10

Under an atmosphere of nitrogen, tetrabutylammonium cyanide (0.5 mol equiv) was added to chloroform (2 mL), methanol (2 mL), and monothioacetate reagent (0.1 g). After stirring for 3 h at room temperature under nitrogen, distilled water (10 mL) and chloroform (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with chloroform (10 mL). The organic layers were combined, washed with ammonium chloride (aq) (10 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. After purification by column chromatography on silica gel (hexane), the product was obtained and dried in vacuo. The spectral data for **1**–**9** are analogous to those obtained for a commercial sample. The synthesis, boiling point, and elemental data for compound **10** has previously been reported and are analogous to our product.[29]

4.2.1. Cyclohexylethanethiol (10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.56 (q, 2H, $J=6.3$ Hz), 1.64–1.73 (m, 5H), 1.53 (q, 2H, $J=7.8$ Hz), 1.17–1.41 (m, 5H), 0.83–1.0 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.8, 36.5, 32.9, 26.6, 26.2, 22.2.

4.3. General selective deprotection procedure for diacetate 11

Analogous procedure for reactions **1**–**10** except 0.1 mol equiv of tetrabutylammonium cyanide was used and the reaction was stirred for 16 h. The synthesis and

elemental data for compound **11** has previously been reported and are analogous to our product.[30,31]

4.3.1. 7-Mercaptoheptylacetate (11). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (t, 2H, $J=6.6$ Hz), 2.53 (q, 2H, $J=7.2$ Hz), 2.06 (s, 3H), 1.56–1.65 (m, 5H), 1.26–1.45 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 64.5, 33.9, 28.7, 28.5, 28.2, 25.8, 24.5, 21.0.

4.4. General deprotection procedure for dithioacetate 13

Analogous procedure for reactions **1–10** except 1.0 mol equiv of tetrabutylammonium cyanide was used and the reaction was stirred for 16 h. The spectral data are analogous to those obtained for a commercial sample.

Acknowledgements

We thank Dr. James H. Wynne for supplying cyclohexylethanethiol, ASEE Postdoctoral fellowship and the Office of Naval Research for financial support of this work.

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A study of NMR chemical shielding in 5-coordinate phosphorus compounds (phosphoranes)

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Received 3 August 2005; revised 19 September 2005; accepted 21 September 2005

Available online 24 October 2005

Abstract—Calculations of the phosphorus NMR chemical shielding in 5-coordinate phosphorus compounds have been carried out using the gauge-including-atomic-orbital (GIAO) 6-311+G(nd,p) basis set at both scaled density functional theory (sDFT) and estimated infinite order Møller–Plesset (EMPI) approaches. Results are generally in accord with previous studies on 3-coordinate phosphorus compounds but fail badly for compounds containing multiple chlorine atoms and indicate a need for a relativistic treatment of these species. We observe that some compounds with reported experimental ^{31}P NMR chemical shifts far downfield of the calculated values are in fact in the range known from experiment and calculation to be in that expected for phosphonium ions; the reported structures need to be reconsidered.

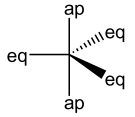
1. Introduction

Surveys of theoretical phosphorus-31 chemical shieldings[1–6] have involved for the most part 3-coordinate phosphorus, mainly because ab initio theoretical methods have generally been limited to smaller species. Our own earlier work[4] focused on what we termed the estimated infinite order Møller–Plesset or EMPI method.[7] This method is based on the observation that contributions to the theoretical shielding from higher orders of Møller–Plesset perturbation theory tend to be in a particular ratio, thus allowing the estimation of the summed infinite series. When applied to C, N, O, and Se, it produced results in agreement with much more sophisticated theoretical approaches at a fraction of the computational cost.

More recently we have developed a scaled density functional theory or sDFT method.[8] It is based on the observation that plots of calculated versus observed shielding show greater differences as the shielding is lower, suggesting that the calculation of the paramagnetic term is at fault. By scaling the paramagnetic term against the difference of the total observed shielding and the calculated diamagnetic contribution, very good agreement was found for C, N, O, F, S, and P nuclei. The great advantage of density functional theory is that it can handle large systems with reasonable basis sets at very reasonable CPU times.

The compounds included in our studies[1–4] and those from other laboratories[5,6] have had phosphorus in coordination states 2-, 3-, and 4-, and the important 5-coordinate phosphorane family has received little consideration despite the fact that thousands of such compounds and chemical shifts are known. In the present paper, we focus on 5-coordinate phosphorus compounds and show that, with the exception of those compounds containing multiple chlorine substituents, results of goodness similar to those found before are obtained. A number of 5-coordinate phosphorus species are also studied where phosphorus-containing rings are present. We do note that our methods fail badly when multiple chlorine atoms are present; as discussed later, we believe this problem is due to the presence of relativistic effects which we are currently not able to handle.

In the 5-coordinate state, trigonal bipyramidal (TBP) geometry is generally adopted, although in special cases square pyramidal structures (or partially so) can be found. Our calculations are based only on TBP structures, where substituents may be bonded to P in either the equatorial (eq) plane or perpendicular to this plane, these latter positions referred to as apical (ap) or axial. From experimental observations, the preferred structure can be predicted from the empirical rule that the



Keywords: ^{31}P NMR; Phosphoranes; Density functional theory; Møller–Plesset theory.
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doi:10.1016/j.tet.2005.09.130

most electronegative groups will occupy the apical positions in the most stable isomeric structure. In performing the calculations of the present study, energy differences, as well as the ^{31}P NMR shifts, were obtained for isomeric forms of a given phosphorane. As will be seen, the empirical prediction of structures based on the electronegativity relations were confirmed in the several structures studied.

It has been known for many years that phosphoranes, with a trivial number of special exceptions, have shifts well upfield of the common reference 85% phosphoric acid, mostly in the range δ −50 to −100,[9] and this generalization has been employed in many cases to decide if a structure truly is a phosphorane, or is the 4-coordinate phosphonium ion (with positive shifts of δ+15–20) from separation of one covalent bond. In studying the recent literature for this research we indeed encountered some instances where phosphorus is probably incorrectly assigned phosphorane structures when the experimental shifts are clearly in the phosphonium ion region.

2. Theoretical procedures

Non-relativistic calculations of absolute chemical shieldings (ppm) were carried out both in a scaled B3LYP[10,11] DFT approach[8] and, in a number of cases, our estimated infinite-order Møller–Plesset[7] (EMPI) method employing Gaussian 03.[12] Gauge-including atomic orbitals[13,14] (GIAO) in a 6-311+G(nd,p) basis were used with six Cartesian d-functions per set and $n=2$ for phosphorus, 1 for all other elements. Geometries were optimized at the B3LYP/6-311+G(d,p) and MP2/6-311+G(d,p) levels for the sDFT and EMPI shielding calculations, respectively, with frequency calculations confirming the theoretical geometries as energy minima.

Our sDFT method[8] results from the discovery that a simple constant rescaling of the paramagnetic contribution can be made such that quantitative predictions are possible. We performed a least squares fit of the DFT paramagnetic contribution, σ_{para}, against the difference of the observed isotropic shielding and the diamagnetic contribution, σ_{dia}, thus deriving a scaling factor, k, for the DFT paramagnetic term. A scaled DFT shielding is then calculated as

$$\sigma_{sDFT} = \sigma_{dia} + k\sigma_{para} \quad (1)$$

where σ_{sDFT} is the new estimate of the shielding. The redetermined shieldings are in good agreement with experiment and rival some of the more sophisticated ab initio theoretical approaches. For phosphorus we find $k=0.912$ ($\pm$0.010), the value we use in this study. This differs slightly from that value reported earlier[8] and is based on a larger (16 molecules) and more representative set of molecules.

Our EMPI method[7] uses a particular mixture of RHF and MP2 GIAO approaches. We found that in many cases the Møller–Plesset series of corrections appears to converge in a manner that allows the infinite series to be summed (approximately), so that the EMPI shielding is given by

$$\sigma_{EMPI} = \sigma_{RHF} + \frac{2}{3}(\sigma_{MP2} - \sigma_{RHF}) \quad (2)$$

To simulate species in (aqueous) solution we employed the conductor-like solvation model (COSMO) based on the work of Barone and co-workers.[15,16] This procedure was first proposed by Klamt and Schüürmann[17] for classical calculations and then implemented by Andzelm et al.[18] and Truong and Stefanovich[19] for quantum mechanical calculations. COSMO describes the solvent reaction field by means of apparent polarization charges distributed on a cavity surface of molecular shape formed by interlocking spheres centered on the solute atoms or atomic groups. The polarization charges are determined by requiring the total electrostatic potential on the cavity surface to cancel out. Only our density functional theory calculations used this method.

3. Results and discussion

3.1. General considerations

Calculated and observed shieldings (in ppm) are given in Table 1 with a few examples of cyclic phosphorus species given in Table 2. One may convert to chemical shifts (also in ppm) relative to 85% phosphoric acid using the latter's absolute shielding of 328.4.[20] Figure 1 is a plot

$$\delta_i = 328.4 - \sigma_i \quad (3)$$

of the sDFT calculated results against experimental results. There are a few examples of 3-coordinate phosphorus species in Table 1 (and the 1-coordinate PN molecule) that allow the data in Figure 1 to cover a broader range.

Several things are clear from Figure 1 and the data in Table 1. First, phosphorus bound to more than three non-chlorine neighbors yields calculated results of basically the same degree of agreement with experiment as has been seen in the past; for example, see Refs. 4 and 8. The root-mean-square-error (rmse) is of the order of 15 ppm for the sDFT method and 21 for the EMPI approach, essentially equal to the figure we have often quoted of 20 ppm. Results cluster nicely about the 45-degree line in the figure. Secondly, the calculated results for the multi-chloro compounds are poor, the errors seeming to be larger at the diamagnetic end of the scale. We discuss the chlorine-containing species in a separate section.

In studying the recent literature, we noted that some compounds were assigned a structure of general formula Ph_3RP-OH, purported to be the first examples of stable hydroxyphosphoranes.[21] The ^{31}P NMR shifts of δ+18.74 to +18.76 were reported for four derivatives. These shifts are far from the range we calculate for related structures. Thus, Me_3PhP-OH and Me_4P-OH are calculated to have δ −112.4 and −120.3, respectively. The related structure Me_4P-OMe is reported to have an experimental value of δ −87.6,[22] while our calculation gives δ −113.4. The compounds reported to be hydroxyphosphoranes are probably of structure Ph_3RP^+; supporting this, a model compound Ph_3MeP^+ has experimental shifts of δ +18.8 to +22.7.[23a]

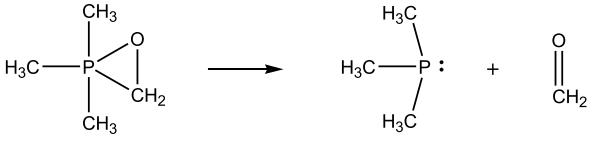
Table 2 exhibits sDFT results for several ring systems

Table 1. Calculated and observed shieldings (ppm)

	Calculated (absolute)		Observed		
	SDFT	EMPI	δ ppm	Ref.	Absolute
A. Non-chlorine-containing compounds					
PH_5	598.2	609.4			
PH_3	593.6	602.8	−266.0	20	594.4
$Si(PH_2)_4$	553.8	585.1	−205	34	533
$P(CH_3)_5$	494.2	510.0			
PF_6^-	454.9	475.1	−143.7	35	472.1
$(HO)P(CH_3)_4$[a]	448.7				
$(CF_3)_2P(CH_3)(CF_3)H$[b]	442.7		−103.7	23b	432.1
$(CH_3O)P(CH_3)_4$[c]	441.8		−88	23c	416
$(HO)P(CH_3)_3$phenyl[a]	440.8				
$(HS)P(CH_3)_4$[d]	427.6	458.6			
2[e]	413.8				
$P(CH_3)_3$	398.7	421.7	−62.0	23d	390.4
PF_5	393.2	404.0	−80.3	23e	408.7
$(CH_3O)PF_4$	396.2	403.9	−79.0	23e	407.4
PF_4^+	359.5	356.3			
$F_3P(NH_2)_2$[f]	394.6	399.4	−58.6	23e	387.0
$(CH_3S)PF_4$[g]	343.1		−34.2	23e	362.6
$(CH_3)PF_4$[h]	349.6		−29.9	23f	358.3
PF_3	214.0	214.2	+105.7	20	222.7
PN	38.3	40.6	+275	36	53
B. Chlorine-containing compounds					
PCl_6^-	415.1	500.2	−298.5	23g	626.9
$CH_3PCl_5^-$	415.0	499.4			
PCl_5	283.4	332.6	−80.9	37	409.3
$(CH_3)PCl_4$[i]	297.6	348.5			
$FPCl_4$	278.8	314.2	−46	23h	374
PhenylPCl$_4$[j]	301.4		−45.4	23i	373.8
PCl_4^+	193.0	194.5	+86.0	23j	242.4
PCl_3	53.8	108.3	+217.1	20	111.3

[a] Axial OH group.
[b] Axial CF_3 groups.
[c] Axial CH_3O group.
[d] Equatorial HS group.
[e] See text.
[f] Equatorial NH_2 groups.
[g] Equatorial CH_3S group.
[h] Equatorial CH_3 group.
[i] Axial CH_3 group.
[j] Equatorial phenyl group.

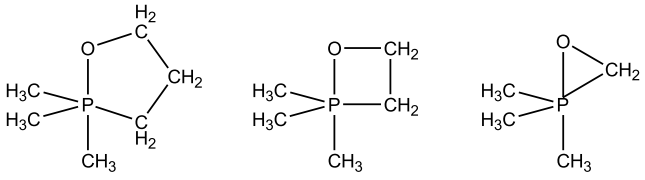
containing phosphorus and the effect on the shielding of ring size and whether or not other positions are occupied by hydrogen or a methyl group. Methyl groups cause a noticeable deshielding effect (shifts of 75–100 ppm to lower fields) as is true for many other typical phosphorus compounds,[9a] while the shieldings themselves move upfield as the size of the ring decreases. The R=CH_3 three-membered ring molecule in Table 2 is an interesting case in that as the optimization proceeds the OCH_2 group drifts away from the rest of the molecule; that is, $(CH_3)_3POCH_2$ is unstable with respect to $(CH_3)_3P$ and OCH_2:



(4)

Our values of δ −89.8 calculated for the five-membered cyclic compound **1** and δ −85.4 for **2** receive validation

Table 2. sDFT shieldings (ppm) for some cyclic $R_3PO(CH_2)_n$ compounds not shown in Table 1



R=CH_3	418.2 (δ −89.8)	426.1 (δ −97.7)	—[a]
R=H	493.8 (δ −165.4)	516.7 (δ −188.3)	551.5 (δ −223.1)

δ-values for the calculated shieldings with respect to the experimental shielding for phosphorus in 85% phosphoric acid are given in parentheses.
[a] Molecule unstable; breaks into H_2CO and $P(CH_3)_3$.

from the experimental value of δ −58.9 reported for the related structure **3**,[24] noting that P-phenyl compounds are generally downfield of P-methyl compounds. Substituent effects in ^{31}P NMR are usually additive;[9] we know from the calculated shifts in Table 1 for Me_3PhP-OH and Me_4P-OH that replacing one methyl by phenyl causes a downfield shift of 7.9 ppm. Thus, ignoring other structural differences we might expect, as is observed, a difference of about 25 ppm between **2** and **3**. However, our values for **1** and **2** differ greatly from those reported for several compounds with the same basic ring system, although differing in P substituents (**4**, δ +18.88;[25] **5**, δ +17.48 to +19.50;[26] **6**, δ +17.26 to +18.92[27]). We must note that the ^{31}P shifts reported for **4–6** do not support these structures, but indeed indicate none are phosphoranes and all have shifts in the phosphonium ion range. The assigned structures need re-consideration. The ^{31}P NMR shift criterion was used in a related case[28] to discriminate in favor of open phosphonium ion **7** rather than cyclic phosphorane **8**. The experimental values were in the range δ +16.7 to +43.6. A similar conclusion was reached in a recent prediction of the shift for **5** (δ −47.4) using an algorithm based purely on experimental data from related structures.[9b]

Yet another illustration of the relative insensitivity of phosphorus to its environment is seen in Table 4. There sDFT results are given for several related neutral and ionic compounds where the shieldings are obtained from gas phase calculations on gas-phase optimized species (gas), from aqueous-phase calculations on aqueous-phase optimized species (water), and from gas-phase calculations using aqueous-phase optimized species (gas/water). We note quickly that even though the calculated absolute shieldings of the chlorine-containing molecules are poor, the results in Table 4 still yield a valid comparison of the effects of solvent. Changes in a nucleus's shielding can come from several sources when solvent, in our case water, is present: the shielding can change due to the presence of the solvent, and it can also change from solvent-induced geometry changes. The results of Table 4 show without a doubt that none of these changes appear for phosphorus, the calculated shieldings being virtually changeless from state to state. This is a bit surprising and likely comes about from the fact that phosphorus is located at the center of the molecular species and is protected from effects external to the molecule. Although not shown, such changes are observed for the chlorine nuclear shieldings, mainly associated with a solvent effect.

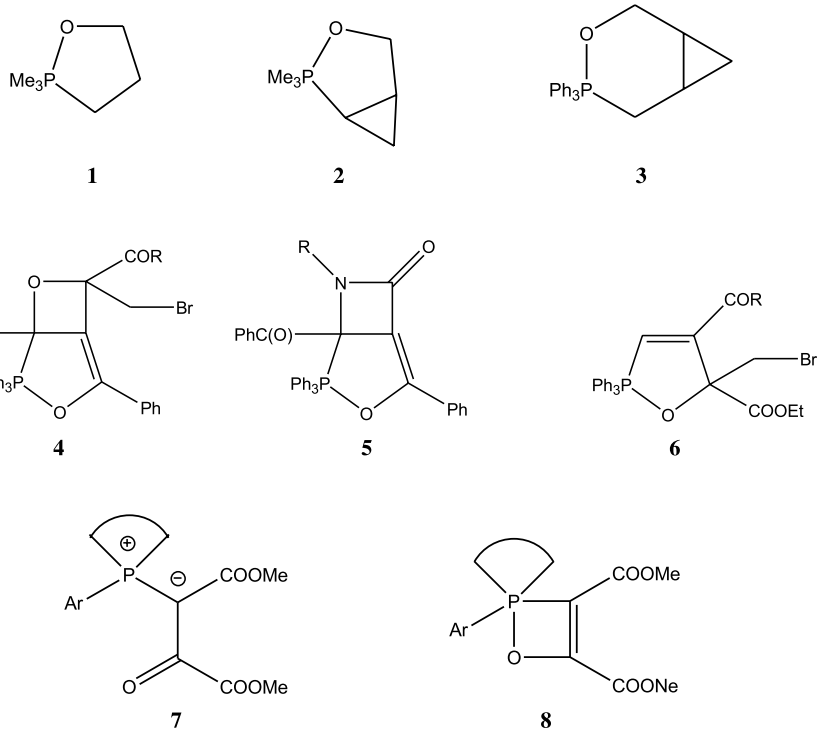


Table 1 indicates the low-energy disposition of the phosphorus ligands, and we find as is known experimentally that generally the relatively more electronegative groups tend to be found in axial positions. Several species were studied that have both stable axial and equatorial conformations of the unique ligand. The shieldings of the two species and their relative energies (at the B3LYP/6-311+G(d,p) level) are shown in Table 3 and one can readily see that while the different configurations have different energies, the phosphorus shieldings in the two cases are nearly identical. Although experiment could likely discern these two types of molecules, they are indistinguishable at current levels of theory.

3.2. The phosphorus chloride problem

The agreement between experiment and theory in Table 1 for the simple phosphorus chlorides is not good, with the exception of PCl_3 which is very good for EMPI and could perhaps be deemed acceptable for sDFT. Because our other results are quite good, and because we take a non-relativistic approach, we must conclude that relativistic effects are important for the multi-chloro compounds.

Schreckenbach and Ziegler[29] have given a clear description of when and how relativistic effects come about and present

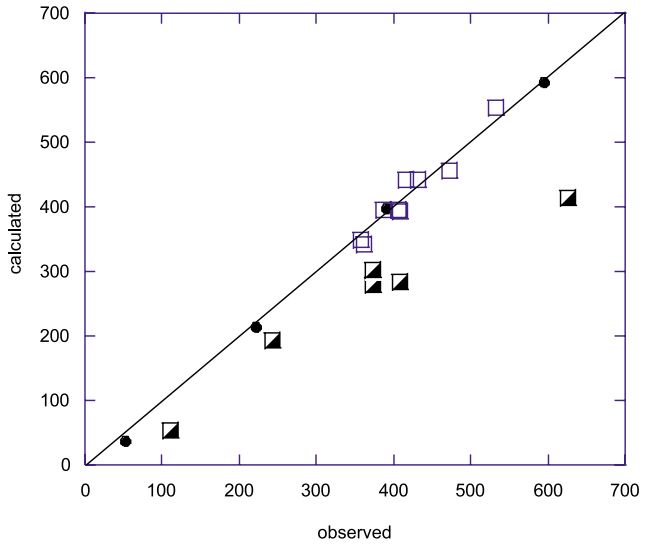


Figure 1. Observed and sDFT calculated phosphorus shieldings from Table 1. Open squares are for 5-coordinate species, closed circles for 3- and 1-coordinate compounds, and half-filled squares are for the phosphorus chlorides. The 45-degree line represents exact agreement between experiment and theory.

a model of their effects on chemical shieldings, as do Bühl et al.[30]

More extensive treatments may be found in the reviews by Pyykkő[31] and by Almlőf and Groppen.[32] For inner shells in particular, increase in the relativistic mass of the electron shrinks the size of the orbit giving rise to an enhanced diamagnetic shielding. Similar effects occur for the valence electrons although the increased screening of the nuclear charge from the valence orbitals has an opposite effect. The net result is that s and p orbitals contract leading to bond shortening while d and f orbitals tend to expand and are destabilized. This latter effect is important in the para-magnetic part of the NMR shielding, which is sensitive to orbital excitation energies. Finally, since spin in a relativistic quantity, spin-orbit coupling provides a mechanism for a magnetic interaction between orbital and spin angular momenta and the magnetic moment of the nucleus.

While often the presence of chlorine is not considered requiring a relativistic approach, the case for phosphorus compounds containing more than 3 ligands has not been treated. Because the Fermi contact interaction is key in the shielding effect and because valence s-character is critical in the Fermi interaction, Bühl et al.[30] have suggested that the relatively very small presence of relativistic effects in the 3-coordinate species like PCl_3 may be due to the dominant involvement of the phosphorus 3s orbital(s) in that species

Table 3. sDFT shieldings (ppm) and relative energies (kcal/mol) for unique ligands in axial and equatorial positions

		sDFT	E_{rel}
$(CH_3)PF_4$			
CH3 group:	Axial	347.5	8.0 kcal
	Equatorial	349.6	0.0
$(CH_3O)PF_4$			
CH_3O group:	Equatorial	396.2	0.0 kcal
	Axial	386.8	8.4

Table 4. Geometry and solvent (water) effects (via COSMO)

	Gas	Water	Gas/water
A. Several phosphorus chlorides			
Scaled DFT:			
PCl_5	283.4	285.5	283.4
PCl_4^+	193.0	190.1	191.2
PCl_6^-	415.1	423.4	416.9
EMPI:			
PCl_5	332.6	335.4	334.7
PCl_4^+	194.5	194.1	195.0
PCl_6^-	500.2	506.9	502.1
B. Several non-chlorine containing species			
Scaled DFT:			
$(HO)P(CH_3)_4$[a]	448.7	441.0	443.3
$P(CH_3)_4^+$	326.2	325.3	326.7
EMPI:			
$(HO)P(CH_3)_4$[a]	462.4	455.5	457.3
$P(CH_3)_4^+$	329.8	328.0	329.4

Species are optimized in the environment indicated (gas, water), while the notation gas/water is for species optimized in aqueous solution but with shieldings calculated in the gas phase. All the shieldings are in ppm.
[a] HO group is axial.

with the phosphorus lone pair and not with the PCl bonds, which conduct the effect from chlorine to phosphorus. Of course there are no lone pairs in 4-, 5-, or 6-coordinate phosphorus species.

Spin-orbit contributions to shielding can be huge when atoms like Br or I are involved in a molecule, and noticeable but much smaller when chlorine is present. For example, Malkin et al.[33] show in the series CCl_nH_{4-n} that the spin-orbit contributions to the carbon (absolute) shielding are $+2.9, +6.0, +10.7$, and $+17.5$ as n varies from one to four. These are not big numbers, although for phosphorus one might well expect larger values because of its larger shielding range.

We can present additional data, which illustrate the inadequacy of a non-relativistic treatment. If one examines the data for the sequence PCl_nF_{5-n}, it appears that the experimental (and theoretical) data can be fit with a

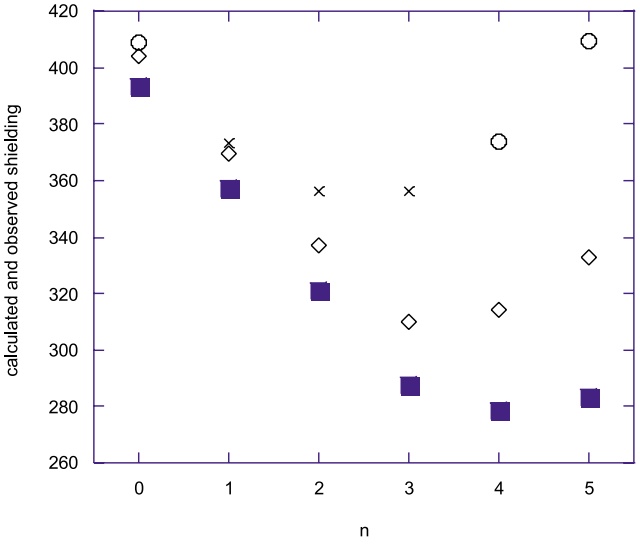


Figure 2. Observed (open circles), interpolated observed (x), and calculated EMPI (open triangles) and sDFT (closed squares) shieldings for PCl_nF_{5-n} as a function of the chlorine number, n.

Table 5. Shieldings (ppm) for the PCl_nF_{5-n} series

Molecule	Calculated		Observed	Calcd minus obs.	
	SDFT	EMPI		SDFT	EMPI
PF_5	393.2	404.0	408.7	−15.5	−4.7
PF_4Cl	357.2	369.3	(373.5)[a]	−16.3	−4.2
PF_3Cl_2	321.4	336.9	(356.0)[a]	−34.6	−19.1
PF_2Cl_3	287.4	310.0	(356.2)[a]	−68.0	−46.2
$PFCl_4$	278.8	314.2	374	−95.2	−59.8
PCl_5	283.4	332.6	409.3	−129.5	−76.7

[a] Values in parentheses are interpolated estimates of the experimental shielding.

quadratic equation in n. Forcing the experimental data into such a fit allows for the estimation of the cases $n=1,2$, and 3; the data are shown in Figure 2 and Table 5. Again, the problem with chlorine is exhibited, although it is clear that EMPI does a better job than sDFT.

Another complication has to do with the predicted geometries, illustrated in Table 6 for PCl_3 and PCl_5. All the calculations for a particular approach were done on systems energy optimized by the same method. While both approaches do well on angles (generally so for almost any theoretical procedure), sDFT does not do as good a job on the PCl_3 and PCl_5 bond distances as does MP2 (the first step in the EMPI procedure). Shieldings calculated at the experimental geometries are improved, but the errors are still large for PCl_5. Again, the semi-empirical sDFT procedure should partly take into account geometrical defects. Both van Wullen[5] and Patchkovskii and Ziegler[6] refuse optimized geometries for the halides they studied, using experimental geometries instead.

Finally, as noted earlier, the deviations from experiment for the multi-chloro compounds are greater as the number of chlorine atoms increases and as the non-relativistic calculated shieldings show a positive, upfield increase. The corrections to NMR shieldings from relativistic effects are generally positive and should be larger as the number of chlorine atoms increases. The disposition of our data is consistent with the notion that relativistic effects are responsible for the errors shown.

It seems clear that, in the absence of a relativistic treatment, the chemical shieldings of phosphorus in molecules containing chlorine and certainly the higher-Z halides cannot be calculated well theoretically.

Table 6. Effects of geometry on the phosphorus shielding in PCl_3 and PCl_5

A. Calculated and observed PCl distances (Å).

	R(PCl-axial)			R(PCl-equatorial)		
	Calculated		Observed	Calculated		
	sDFT	EMPI		sDFT	EMPI	
PCl_3	2.0934	2.0568	2.043(5)			
PCl_5	2.1871	2.1480	2.124(9)	2.0709	2.0391	2.020(7)

B. Shieldings calculated for optimized (opt) and experimental (exp) geometries.

		SDFT	EMPI	Observed
PCl_3	opt	53.8	108.3	111.3
	exp	104.3	121.9	
PCl_5	opt	283.4	332.6	409.3
	exp	326.7	346.8	

Distances, R, are in Å units, and shieldings in ppm.

Acknowledgements

We are indebted to the North Carolina Microelectronics Center and the Center for Applied Computational Studies at East Carolina University for providing CPU time that allowed these calculations to be carried out, and to Mr. W. Day for technical assistance.

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Tetrahedron
Tetrahedron 61 (2005) 12350–12357

Wurster's crownophanes: an alternate topology for *para*-phenylenediamine-based macrocycles

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Received 15 July 2005; revised 20 September 2005; accepted 21 September 2005

Available online 14 October 2005

Abstract—Six redox-active cyclophane/crown hybrid molecules (crownophanes) were prepared via cyclization reactions involving *N*,*N*′-dimethyl-*p*-phenylenediamine and tosylated oligoethylene glycols of varying length. These new host molecules differ from other phenylenediamine-containing crown ethers in that the electron-rich π face is designed to be part of the ligating group. Their electrochemical properties were determined by cyclic voltammetry with a correlation found between macrocyclic architecture and ease of oxidation. The affinity of the smaller crownophanes for cations was studied by cyclic voltammetry with the result that these hosts show no electrochemical response to alkali metal cations, but, dependent on macrocycle size, modest selectivity for alkaline earth metal cations. This stands in contrast to previously reported phenylenediamine-containing crown ethers in which the redox centers are linked to guest ions through a macrocyclic amino group.

1. Introduction

Macrocycles containing electrochemically active subunits are of interest because of their ability both to sense bound guest species and control the coordination environment of the host.[1] We[2] and others[3] have previously prepared a series of redox-active ligands centered around the electrochemically active phenylenediamine structure. The ligands reported to date have been referred to as 'Wurster's crowns' (see Fig. 1) because they are formally derived from the famed Wurster's reagent (*N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine or TMPD).[4] In all reported examples, the phenylenediamine moiety has been attached to a crown ether by a single phenylenediamine nitrogen atom within the macrocycle framework. Such structures preserve the rich electrochemical properties of the phenylenediamine subunit, thereby allowing for the sensing of bound metal ions via the accompanying change in ligand oxidation potential upon coordination.

Motivated by the efficient metal binding properties of the Wurster's crowns, we became interested in an alternate structural motif for incorporating the electrochemically active phenylenediamine unit into the body of a crown. In these macrocycles, both N atoms of the phenylenediamine moiety are now contained within the macrocyclic framework to produce hybrid crown/cyclophane[5] structures called 'Wurster's crownophanes' (see Fig. 1). Similar to previously

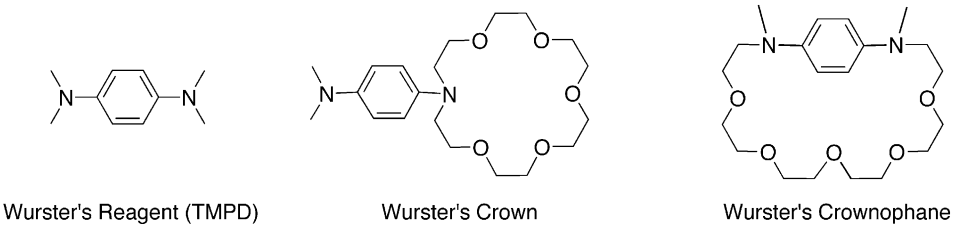

Figure 1. Representative macrocycles derived from Wurster's reagent (*N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine or TMPD).

Keywords: Cyclophane; Crown; Crownophane; Wurster; Redox.
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doi:10.1016/j.tet.2005.09.091

reported redox-active crown ethers, these hosts are designed to be electrochemically responsive to cations. However, the mode of communication between the redox center and guest ions in presumed endocyclic complexes should prove quite distinct, occurring through the electron-rich π face of the phenylenediamine moiety and not the amino group. In addition to potential utility in electrochemical sensing and/or switching applications, these compounds may prove useful in probing hard cation-π interactions, a topic of considerable recent interest due to an established significance in controlling protein folding and enzyme-substrate recognition.[6]

Related crownophanes containing the electron-rich π systems 1,4-dialkoxybenzene[7] and tetrathiafulvalene (TTF)[8] have been previously reported. In the latter case, the reversible electrochemistry of TTF has led to their study as electrochemical sensors for metal cations. It is worth noting that these ligands are typically synthesized as mixtures of *Z* and *E* isomers. Further investigation by mass spectrometry has indicated that the *Z* isomer alone participates in binding allowing for the TTF moiety to potentially interact either through the π system, heterocyclic S atoms or through distortions of the π system caused by complex formation.

Both Staab, et al.[9] and, more recently, Takemura, et al.[10] have reported on the redox properties and charge transfer complexes of Wurster-type cyclophanes containing phenylenediamine subunits. In both studies, the cyclophanes contain alkyl linkages between two *p*-phenylenediamine subunits and were, therefore, not designed nor studied for metal chelation. Interestingly, however, the length of the alkyl spacers and their respective points of attachment on the phenylenediamine subunits gave clear differences in the resulting electrochemical properties of the cyclophanes with shorter linkages giving rise to cooperative effects between the two redox centers.

In this report, we describe the synthesis and properties of Wurster's crownophanes along with unanticipated larger macrocyclic byproducts and explore their ability to complex hard cations.

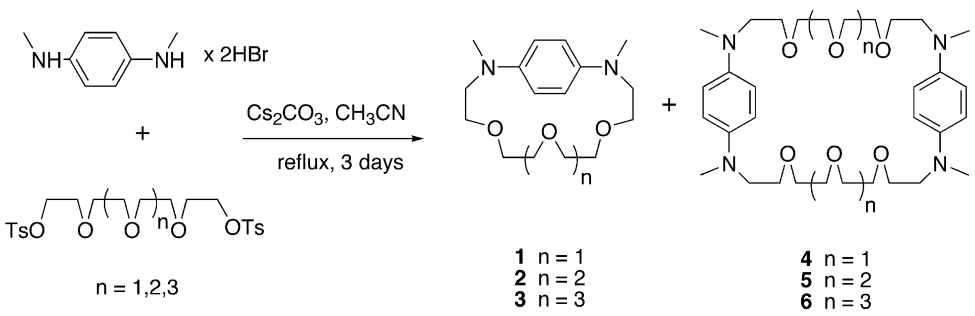
2. Results and discussion

2.1. Ligand synthesis

As shown in Scheme 1, the synthesis of macrocycles **1**, **2** and **3** was accomplished using a general method that can be extended by choice of electrophile to produce a range of redox-active crownophanes. Specifically, *N*,*N*′-dimethyl-*p*-phenylenediamine dihydrobromide, an oligoethylene glycol ditosylate of appropriate length (tetraethylene glycol for **1**, pentaethylene glycol for **2**, hexaethylene glycol for **3**), and carbonate base were refluxed for 3 days in acetonitrile to yield the desired ligands. Following radial chromatography on alumina, the crownophanes were isolated in approximately 20–25% yield as light brown oils. Shorter reaction times revealed the presence of significant amounts of starting materials as monitored by thin layer chromatography (TLC) while longer reaction times gave no improvement in cyclization yields. Further, the reaction yields were largely insensitive to the choice of alkali metal carbonate used as base. While the yields are modest, the products can be quickly and definitively identified by TLC analysis. *N*-peralkylated *p*-phenylenediamines, like TMPD, oxidize upon exposure to UV light resulting in the characteristic blue color of the radical cation. As such, TLC analysis of successful crude reaction mixtures show the presence of a 'Wurster's blue' spot that can be attributed to the formation of the target Wurster's crownophane. However, during the preparation of the anticipated products **1**, **2** and **3**, additional products were formed as evidenced by the presence of a second 'Wurster's blue' spot on the TLC of each crude reaction mixture. These minor products proved to be the larger '2+2' cyclization crownophanes **4**, **5**, and **6**, isolated from the reaction mixtures in approximately 3–5% yield. These larger macrocycles are currently being studied for their utility in the assembly of more intricate supramolecular structures (e.g., rotaxanes and catenanes).

2.2. Crystallographic study of 4

Unlike the smaller crowns **1**, **2** and **3**, which were isolated as thick oils, macrocycle **4** is a crystalline solid. In fact, the crude reaction mixtures containing **1** and **4** can be separated by recrystallization from methanol with **4** forming crystals and **1** remaining in solution. As shown in Figure 2, **4** contains a large cavity with dimensions of 6.4 Å (from the centroid of one aromatic ring to the other) by 14.4 Å. The two methyl groups are positioned 'trans' with respect to the phenyl moiety. Individual molecules of **4** are stacked in the crystal lattice to give long channels throughout the structure (Fig. 3). The closest π–π distance between neighboring molecules (6.6 Å) rules out the possibility of intermolecular π–π stacking.



Scheme 1.

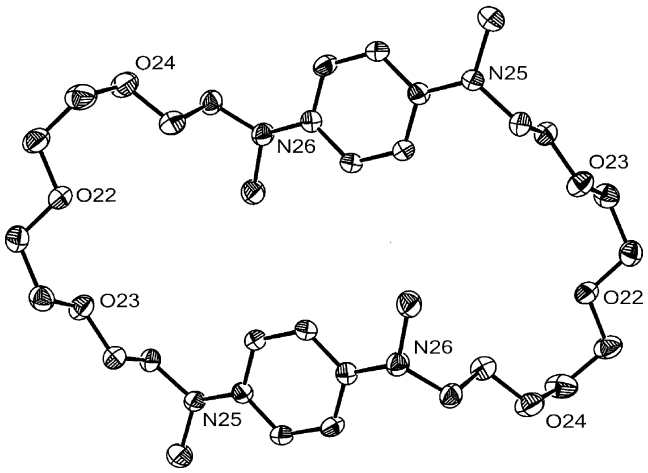


Figure 2. X-ray crystal structure of **4** showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level with H atoms omitted for clarity.

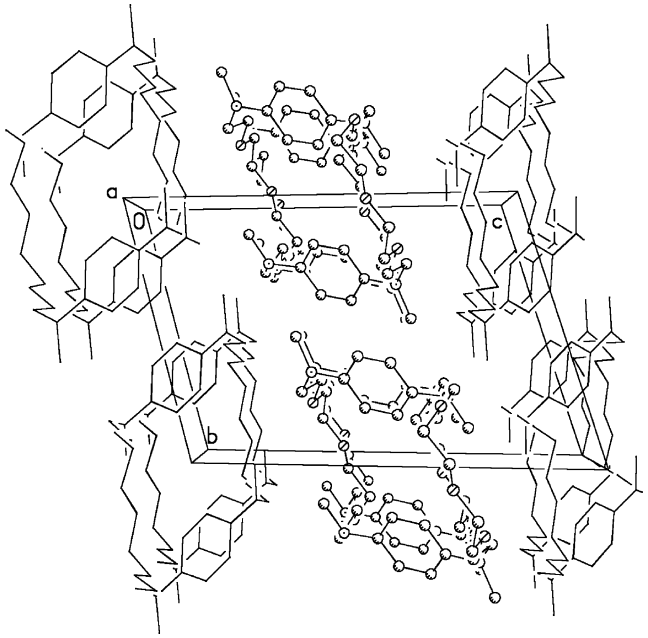


Figure 3. Unit cell packing diagram for **4**. The view is approximately down the *a*-axis. Crystallographic structures 1 are shown in ball-and-stick fashion while crystallographic structures 2 are in wireframe display form.

2.3. Electrochemistry

Cyclic voltammetry was used to explore the relationship between the electrochemical properties of **1**–**6** and ligand architecture. All six compounds show two reversible one-electron oxidations, like TMPD. For the larger cyclophanes **4**–**6**, the two phenylenediamine subunits behave as independent redox centers as might be expected considering the long aliphatic linkages between them. In fact, Takemura, et al. demonstrated that a five carbon chain between two *p*-phenylenediamine units is sufficient for the redox centers to behave as discrete electrochemical entities.[10] As shown in Table 1, the smaller Wurster's crownophanes oxidize more easily than TMPD with the effect strongest for the smallest crownophane **1**. Considering the three larger cyclophanes **4**, **5** and **6** oxidize at

Table 1. Half-wave potentials (vs Ag/AgCl, 0.1 M $TEABF_4$, CH_3CN, 100 mV/s) of TMPD and Wurster's crownophanes **1**–**6**

Compound	$E_{1/2}$ (mV)	$E_{1/2}$ (mV)
TMPD	124	708
1	64	677
2	70	697
3	93	709
4	132	743
5	131	753
6	128	734

potentials similar to that of TMPD, the facile oxidation of **1**, **2** and **3** must be associated with their common intramolecular arrangement of a polyether fragment directly across from the redox center. That **1** exhibits the most facile oxidation (60 mV easier to oxidize than TMPD) indicates that its smaller ring size positions the polyether subunit closest to the phenyl ring and, thus, best able to stabilize the radical cation formed upon oxidation. An alternate explanation is that compound **1** has the most electronic strain between the dipoles created by the ether groups and the electron rich π system. This strain is relieved by oxidation which allows for a favorable electrostatic interaction between the polyether and radical cationic phenylenediamine subunits (vide infra).

Cyclic voltammetry was also used to probe the electrochemical responses of **1**, **2**, and **3** to various hard cations. Indeed, both aniline-[11] and phenylenediamine-containing crown ethers[2a,2b,3c] respond to the coordination of cations through anodic shifts in their oxidation potentials. For the alkali metal cations, the magnitude of the response correlates well to complex stabilities. The electrochemical responses of the Wurster's crownophanes (as measured by a shift in the first oxidation potential of the phenylenediamine unit) after addition of 1.2 equiv of metal or ammonium salts were analyzed. Interestingly, and in contrast to redox-active crown ethers, the Wurster's crownophanes show no evidence for the binding of alkali metal ions. However the first oxidation potential of the largest crownophane, **3**, shifts anodically in the presence of alkaline earth metal ions and the ammonium cation (ΔE_{pa}: 21 mV for Ca^{2+}, 27 mV for Sr^{2+}, 54 mV for Ba^{2+}, 21 mV for NH_4^+). This is likely due to a generally enhanced affinity of this host for cations because of its greater number of donor atoms and, in the former case, the larger charge density of alkaline earth metal cations in comparison to the alkali metal cations. The response of **3** to alkaline earth metal cations but not alkali metal cations is notable and suggests potential application in the selective sensing of the former. Crownophane **3** shows the greatest electrochemical response to Ba^{2+} with its first oxidation potential anodically shifted 54 mV from that of the free ligand (Fig. 4). Similar to **3**, a TTF-containing crownophane of comparable size displays a preference for alkaline earth versus alkali metal cations.[8a] In this case, the TTF host showed a 100 mV anodic shift in its first oxidation potential in the presence of a stoichiometric amount of Ba^{2+}. Interestingly, however, an X-ray structure of the TTF-crownophane complex with Ba^{2+} shows only the participation of the polyether subunit in coordination of the metal cation.[8a] Perhaps, then, it is not surprising that compound **3** is the only Wurster's crownophane to

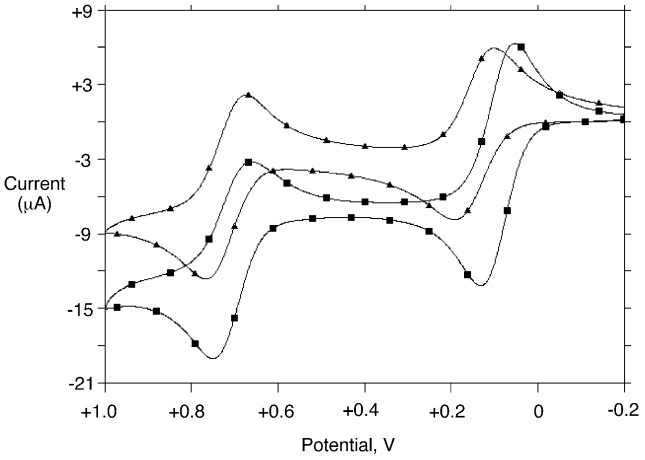


Figure 4. Cyclic voltammograms (0.1 M $TEABF_4$, CH_3CN, 100 mV/s) of Wurster's crownophane **3** (■), and **3** in the presence of 1.2 equiv of $Ba(OTf)_2$ (▲).

demonstrate an ability to form complexes with hard cations among the three ligands studied. In complexes of **3**, the second oxidation potential is unshifted relative to that of the free crownophane (see Fig. 4, for example) indicating that the second oxidation in the cyclic voltammogram of each complex is, in actuality, that of the free ligand. Therefore, the dicationic form of **3** does not support complexation with ejection of the ion from the macrocyclic cavity presumed upon its formation.

2.4. Computational analysis

Proton NMR spectra of **1**, **2** and **3** show a single aromatic peak indicative of the equilibration of cis and trans conformers in solution. Consistent with these results, gas-phase B3LYP/6-31+G* calculations reveal that the cis and trans conformers of **1** are very close in energy, with the latter only 0.59 kcal/mol more stable than the former. An analysis of each of these conformers supports the electrochemical results that Wurster's crownophanes should indeed oxidize more easily than TMPD (Fig. 5) through the intramolecular stabilization of the radical cationic form of the phenylenediamine moiety by the polyether subunit. In the neutral state, the dipole moment of each conformer is oriented with the negative end directed toward the electron-rich phenylenediamine moiety. Upon oxidation, the positive charge of the radical cation is localized on the phenylenediamine portion of the Wurster's crownophane. The calculated natural atomic charges, listed in Figure 5, become considerably less negative, or more positive, on the phenylenediamine heavy atoms (excluding the terminal methyl groups) thereby corroborating this view. Not only does the magnitude of the dipole moment significantly decrease (2.532–1.131 D for the *trans*, 4.209 to 2.996 D for the *cis*), but the direction of the dipole moment changes as well, with the positive end residing near the phenylenediamine group. Motivated by the ensuing stabilization of the radical cation charge, the molecular geometry responds to this shift in the charge distribution by decreasing the distance between the

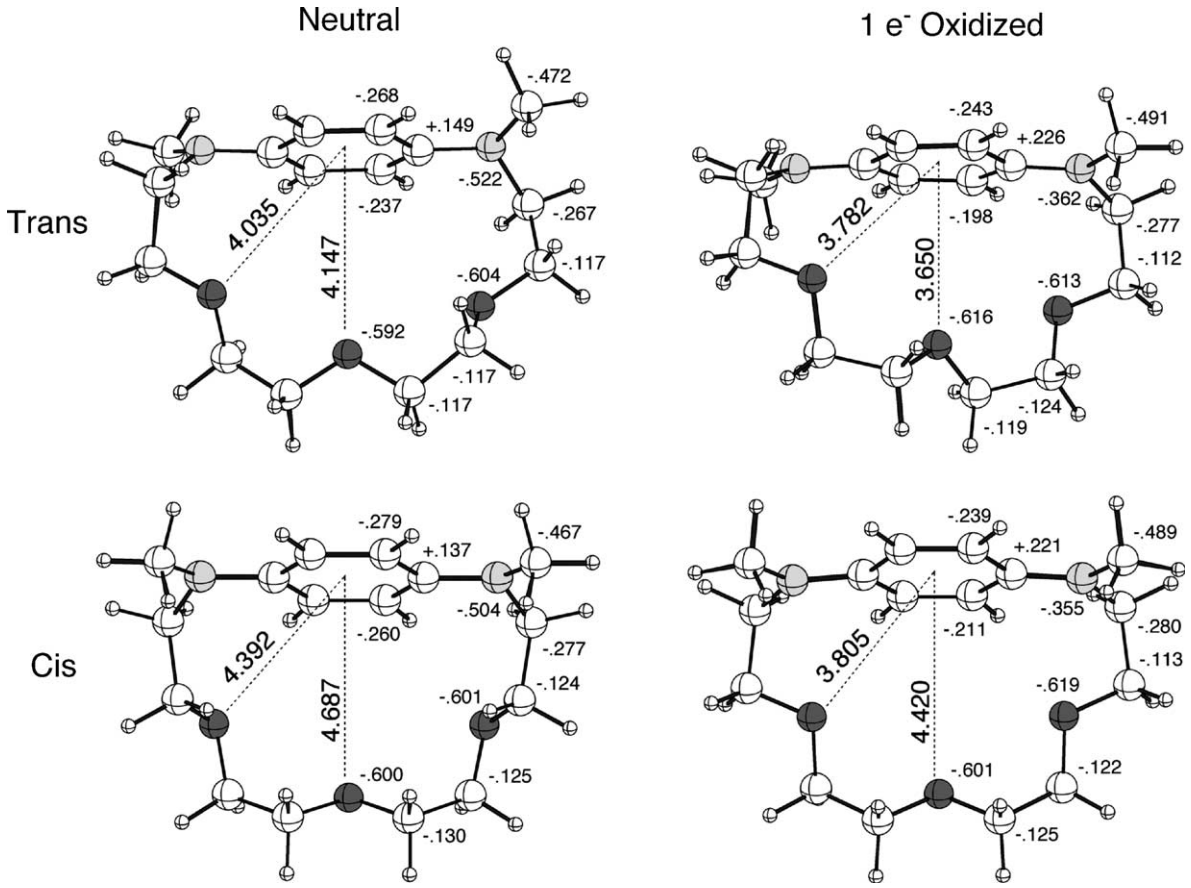


Figure 5. B3LYP/6-31+G* and UB3LYP/6-31-G* optimized geometries of the neutral and radical cation states, respectively, of the cis and trans forms of compound **1**. Natural atomic charges are listed beside the symmetry unique heavy atoms.

oxygen donor groups of the crown ether and the phenylenediamine moiety. Figure 5 illustrates how, upon oxidation, the average X–O_{ave} distance (where X is the centroid of the phenyl ring) in the trans isomer decreases by 0.334 Å, while X–O_{ave} in the cis conformer decreases by 0.480 Å. It is interesting to note that in the C_2-symmetric trans conformer, the distal X–O distance decreases more than the proximal X–O distance (0.497 Å vs 0.253 Å), while for the C_s-symmetric cis conformer, the proximal X–O distance decreases more than the distal X–O distance (0.587 Å vs 0.267 Å). That the cis conformer exhibits both the largest ΔX–O_{ave} as well as the largest discrete ΔX–O helps explain the lower calculated ionization potential for it relative to that for trans (124.7 vs 128.3 kcal/mol, respectively).

3. Conclusion

We have established a simple synthetic procedure to the Wurster's crownophanes and demonstrated, both electrochemically and computationally, a relationship between their structure and ease of oxidation. The general lack of response to alkali metal cations and the modest magnitude of the electrochemical shifts of **3** in the presence of cations indicates that the electron-rich π face is a poor ligating group for hard cations in polar media. As such, in contrast to the Wurster's crown ethers, complexes of the Wurster's crownophanes presumably involve little contribution from the redox center. However, the anodic shift in the first oxidation potential of **3** in response to alkaline earth but not alkali metal cations is notable and demonstrates a selectivity among the hard cations that is not observed in the alternate Wurster's crown ether topology.

4. Experimental

4.1. General information

All solvents and reagents were of reagent grade quality, purchased commercially, and unless noted, used without further purification. All reactions were carried out under dry argon unless stated otherwise. The precursor *N*,*N*′-dimethyl-*p*-phenylenediamine dihydrobromide was synthesized in three steps from 1,4-phenylenediamine using a modification of the procedure of Michaelis, et al.[12] As full experimental details and characterization were not included in that report, we provide procedures and characterization in this work. All ^{1}H and ^{13}C NMR spectra were recorded on a JEOL Eclipse 270 MHz NMR spectrometer in chloroform-*d*, acetone-d_6 or deuterium oxide (Aldrich Chemical Co.) referencing peaks to solvent. Mass spectra were acquired by the analytical services laboratories at Northwestern University and the University of Texas at Austin. Preparative chromatography columns were packed with activated neutral aluminum oxide (~150 mesh, 58 Å surface area). Alumina (60 GF_{254} Neutral Type E) was used for radial chromatography (Chromatotron, Harrison Research, Model 7924 T).

4.1.1. Synthesis of *N*,*N*′-di-*p*-toluenesulfonyl-1,4-phenylenediamine. A solution of NaOH (2 M, 200 mL) and 1,4-phenylenediamine (10.0 g, 92.5 mmol) was cooled to 0 °C. A solution of *p*-toluenesulfonyl chloride (38.6 g, 202 mmol) in diethyl ether (200 mL) was added dropwise. The dark reddish brown solution was allowed to warm to room temperature overnight. The reaction mixture, containing a large amount of product as precipitate, was then neutralized with the careful addition of 1 M hydrochloric acid to complete the precipitation process. The precipitate was collected and washed with water. The crude product was washed with boiling methanol, filtered and then washed with ethyl ether to afford the desired product (38.6 g, 90%) as a tan powder. ^{1}H NMR (CD_3COCD_3): δ 2.38 (s, 6H, ArCH_3), 7.05 (s, 4H, Ar), 7.32 (d, J=8.0 Hz, 4H, Ar), 7.63 (d, J=8.0 Hz, 4H, Ar), 8.79 (s, 2H, N*H*). ^{13}C NMR (CD_3COCD_3): δ 21.8, 123.3, 128.3, 130.7, 135.9, 144.7. MS (EI): *m*/*z* (%) 416 (100) [M^+]. HR CI MS *m*/*z* 417.0937 [$M+H^+$] (calcd for $C_{20}H_{21}N_2O_4S_2$, *m*/*z* 417.0943).

4.1.2. Synthesis of *N*,*N*′-dimethyl-*N*,*N*′-di-*p*-toluenesulfonyl-1,4-phenylenediamine. To a 60% dispersion of NaH in mineral oil (2.2 g) and *N*,*N*′-di-*p*-toluenesulfonyl-1,4-phenylenediamine (10.0 g, 24.0 mmol) was added anhydrous DMF (100 mL). The reaction mixture was then heated at 90 °C for 60 min. Upon cooling to room temperature, a solution of methyl iodide (3.15 mL, 51.0 mmol) in DMF (100 mL) was added dropwise and the reaction stirred for 12 h. The solvent was removed in vacuo and the resulting solids washed thoroughly with water. The crude reaction product was washed with hot methanol and then ether to afford the desired product as an off-white powder (9.66 g, 90%). ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 6H, ArCH_3), 3.13 (s, 6H, NCH_3), 7.00 (s, 4H, Ar), 7.22 (d, J=8.2 Hz, 4H, Ar), 7.40 (d, J=8.2 Hz, 4H, Ar). ^{13}C NMR ($CDCl_3$): δ 22.1, 38.4, 127.2, 128.3, 129.9, 133.7, 140.8, 144.3. MS (FAB): *m*/*z* 445.1 [$M+H^+$], 467.1 [$M^+ + Na^+$]. HR CI MS *m*/*z* 445.1253 [$M+H^+$] (calcd for $C_{22}H_{25}N_2O_4S_2$, *m*/*z* 445.1256).

4.1.3. Synthesis of *N*,*N*′-dimethyl-*p*-phenylenediamine dihydrobromide. Treatment of *N*,*N*′-dimethyl-*N*,*N*′-di-*p*-toluenesulfonyl-1,4-phenylenediamine (15 g, 33.8 mmol) with HBr in acetic acid (30 wt%, 225 mL) in the presence of phenol (26 g, 276 mmol) at 90 °C for 40 h afforded a tan precipitate. The precipitate was isolated by filtration and washed with ether to yield a white solid (7.91 g, 79%). ^{1}H NMR (D_2O): δ 2.76 (s, 6H, NCH_3), 6.57 (s, 4H, Ar). ^{13}C NMR (D_2O): δ 39.6, 126.9, 140.2. HR EI MS *m*/*z* 136.0998 [M^+] (calcd for $C_8H_{12}N_2$, *m*/*z* 136.1000).

4.1.4. Syntheses of crownophanes 1–6. The three congeners **1**, **2** and **3** were synthesized according to the same procedure with **4**, **5** and **6** being isolated, respectively, from the same reaction mixtures. Tetraethylene, pentaethylene and hexaethylene glycol ditosylate were used to synthesize **1**, **2** and **3**, respectively. The following representative procedure is for the synthesis of **1**. *N*,*N*′-dimethyl-*p*-phenylenediamine dihydrobromide (1.00 g, 3.36 mmol) and cesium carbonate (4.88 g, 15.0 mmol) were added to dry acetonitrile (350 mL). Following the addition of tetraethylene glycol ditosylate (2.10 g, 4.20 mmol), the reaction was stirred at reflux for 72 h. The solvent was then removed in vacuo. The resulting solid was partitioned between water and $CHCl_3$. The organic layer was dried with magnesium sulfate and filtered. The crude product mixture

was purified via column chromatography (alumina, $CHCl_3$ as eluent) followed by radial chromatography (alumina, $CHCl_3$ as eluent). The corresponding larger ring, '2+2' cycloaddition product **4**, was isolated in 5% yield as a slower moving fraction (in comparison to **1**). Mixtures containing **1** and **4** could be separated by crystallization from methanol with **4** forming colorless crystals and **1** remaining in solution. In the cases of the other pairs of crownophanes (**2** and **5**, **3** and **6**), chromatography was the only purification method used. With the exception of **4**, all crownophanes were isolated as light brown oils. Yield of **1**: 0.216 g (23%). Compound **1**: ^{1}H NMR ($CDCl_3$): δ 2.84 (s, 6H, NCH_3), 3.17 (t, J=5.2 Hz, 4H, CH_2N), 3.30 (t, J=4.9 Hz, 4H, CH_2O), 3.50 (t, J=4.6 Hz, 4H, CH_2O), 3.60 (t, J=4.7 Hz, 4H, CH_2O), 6.81 (s, 4H, Ar). ^{13}C NMR ($CDCl_3$): δ 38.4, 53.6, 68.0, 69.8, 70.6, 116.6, 143.1. MS (EI): *m/z* (%) 294 (100) [M^+], 295 (17.5) [$M+1^+$]. HR MS (ESI, 70 eV) *m/z* 294.19390 [M^+] (calcd for $C_{16}H_{26}N_2O_3$, *m/z* 294.19434). Compound **2** Yield 25%. ^{1}H NMR ($CDCl_3$): δ 2.86 (s, 6H, NCH_3), 3.42 (m, 8H, CH_2N, CH_2O), 3.53 (br m, 8H, CH_2O), 3.63 (t, J=5.0 Hz, 4H, CH_2O), 6.80 (s, 4H, Ar). ^{13}C NMR ($CDCl_3$): δ 39.2, 53.7, 68.6, 70.6, 70.8, 115.1, 141.8. MS (EI): *m/z* (%) 337.1 (100) [$M-1^+$], 338.1 (17.5) [M^+]. HR MS (ESI, 70 eV) *m/z* 338.22111 [M^+] (calcd for $C_{18}H_{30}N_2O_4$, *m/z* 338.22056). Compound **3**: Yield 21%. ^{1}H NMR ($CDCl_3$): δ 2.87 (s, 6H, NCH_3), 3.41 (t, J=5.6 Hz, 4H, CH_2N), 3.60 (m, 20H, CH_2O), 6.80 (s, 4H, Ar). ^{13}C NMR ($CDCl_3$): δ 39.5, 54.7, 68.8, 70.7, 70.9, 115.3, 142.5. MS (EI): *m/z* (%) 382 (100) [M^+], 383 (29.5) [$M+1^+$]. HR MS (ESI, 70 eV) *m/z* 382.24693 [M^+] (calcd for $C_{20}H_{34}N_2O_5$, *m/z* 382.24677). Compound **4**: mp (uncorrected): 66–67 °C. ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 12H, CH_3N), 3.36 (m, 8H, CH_2N), 3.59 (m, 24H, CH_2O), 6.71 (s, 8H, Ar). ^{13}C NMR ($CDCl_3$): δ 39.4, 53.6, 68.5, 70.5, 114.8, 142.0. MS (ESI): *m/z* (%) 588.38 (100) [M^+], 589.39 (37.5) [$M+1^+$], 590.39 (8.1) [$M+2^+$]. HR MS (ESI, 70 eV) *m/z* 588.39053 [M^+] (calcd for $C_{32}H_{52}N_4O_6$, *m/z* 588.38867). Compound **5**: Yield 3%. ^{1}H NMR ($CDCl_3$): δ 2.85 (s, 12H, CH_3N), 3.39 (m, 8H, CH_2N), 3.61 (m, 32H, CH_2O), 6.68 (s, 8H, Ar). ^{13}C NMR ($CDCl_3$): δ 39.6, 53.8, 68.7, 70.6, 115.1, 142.2. MS (EI): *m/z* (%) 676 (100) [M^+], 677 (41) [$M+1^+$]. HR MS (ESI, 70 eV) *m/z* 676.44241 [M+] (calcd for $C_{36}H_{60}N_4O_8$, *m/z* 676.44110). Compound **6**: Yield 3%. ^{1}H NMR ($CDCl_3$): δ 2.87 (s, 12H, CH_3N), 3.40 (br, 8H, CH_2N), 3.61 (m, 40H, CH_2O), 6.73 (s, 8H, Ar). ^{13}C NMR ($CDCl_3$): δ 39.8, 53.8, 68.6, 70.6, 115.1, 142.2. MS (EI): *m/z* (%) 764.3 (100) [M^+], 765.3 (59) [$M+1^+$]. HR MS (ESI, 70 eV) *m/z* 764.4931 (calcd for $C_{40}H_{68}O_{10}N_4$, *m/z* 764.4930).

4.2. Computational methods

Full-gradient geometry optimizations[13] were performed in redundant internal coordinates[14] with ab initio DFT methods. Becke's three-parameter hybrid exchange functional (B3)[15] was used in conjunction with the Lee–Yang–Parr correlation functional (LYP)[16] and a 6-31+G* basis.[17] Previous studies have demonstrated that a careful application of theory is required to accurately model the hybridization of the amine groups and their orientation with respect to the plane of the phenyl ring in the electron rich phenylenediamine moiety.[18,19] In this context, the B3LYP/6-31+G* and UB3LYP/6-31+G* methods should be reliable for the evaluation of the neutral and radical cation forms of the Wurster's crownophanes, respectively. Atomic charges were calculated by the natural population analysis (NPA)/natural bond orbital (NBO) method.[20] All calculations were performed with either the G94[21] or G98[22] program suite.

4.3. Cyclic voltammetry

Tetraethylammonium tetrafluoroborate ($TEABF_4$) was purchased as electrochemical grade from Acros and was not purified further. Acetonitrile (low water 99.9+% grade, Burdick and Jackson) was distilled from CaH_2. Electrochemical experiments were performed using a BAS CV-50W Voltammetric Analyzer (Bioanalytical Systems, Inc.). The electrochemical system was comprised of a platinum working electrode, a Ag/AgCl reference electrode and a platinum wire auxiliary electrode. Acetonitrile solutions (containing 0.1 M $TEABF_4$ electrolyte and 1.0–1.5 mM ligand) were placed in an electrochemical cell and purged with dry N_2. For cation binding experiments, 1.2 equiv of salt were used. The salts used were $LiBF_4$, $NaClO_4\cdot H_2O$, KPF_6, $RbClO_4$, $CsClO_4$, $Mg(ClO_4)_2$, $Ca(ClO_4)_2$, $Sr(ClO_4)_2$, $Ba(OTf)_2$, and NH_4PF_6. Rubidium, cesium, and all alkaline earth salts were stirred for 1 h prior to obtaining a voltammogram; all others were stirred 5 min or until no further change in oxidation potential was observed.

4.4. X-ray experimental for 4

Crystals were grown from a methanolic solution of **4**. The data crystal was cut from a larger crystal and had approximate dimensions of 0.31×0.31×0.25 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with Mo Kα radiation (λ=0.71073 Å). A total of 538 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 27 s per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 2. Data reduction were performed using DENZO-SMN.[23] The structure was solved by direct methods using SIR97[24] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[25] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2×Ueq of the attached atom (1.5×Ueq for methyl hydrogen atoms).

There are two crystallographically independent molecules per asymmetric unit. Each molecule lies around a different crystallographic inversion center. Molecule 1, composed of non-H atoms labeled O1 to C21, resides around an inversion center at 0, 1, 1/2. Molecule 2, composed of non-H atoms labeled O22–C42, resides around an inversion center at 1, 1, 0. The function, $\Sigma w(|F_o|^2-|Fc|^2)^2$, was minimized, where $w=1/[(\sigma(Fo))^2+(0.0787\times P)^2+(0.9425\times P)]$ and $P=(|F_o|^2+2|F_c|^2)/3$. $R_w(F^2)$ was refined to 0.177, with $R(F)$ equal to 0.0587 and a goodness of fit, S=1.01. Definitions used for calculating $R(F)$, $R_w(F^2)$ and S are given below.[26] The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr}=kF_c/[1+(7(2)\times 10^{-6})\times F_c^2\,\lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral

Table 2. Crystallographic data for compound **4**

Empirical formula	$C_{32}H_{52}N_4O_6$
Formula weight	588.78
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P-1$
Unit cell dimensions	$a=9.7927(1)$ Å, $\alpha=69.800(1)°$ $b=11.5821(2)$ Å, $\beta=74.668(1)°$ $c=16.1542(2)$ Å, $\gamma=69.689(1)°$
Volume	1590.70(4) Å^3
Z	2
Density (calculated)	1.229 mg/m^3
Absorption coefficient	0.085 mm^{-1}
$F(000)$	640
Crystal size	$0.35\times0.31\times0.25$ mm^3
Theta range for data collection	2.97–27.49°
Index ranges	$-9\le h\le12$, $-12\le k\le15$, $-19\le l\le20$
Reflections collected	11,329
Independent reflections	7279 [R(int)=0.0246]
Completeness to theta=27.49°	99.7%
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	7279/0/380
Goodness-of-fit on F^2	1.012
Final R indices [$I>2\sigma(I)$]	$R1=0.0587$, $wR2=0.1503$
R indices (all data)	$R1=0.1135$, $wR2=0.1773$
Extinction coefficient	$7.2(17)\times10^{-6}$
Largest diff. peak and hole	0.538 and −0.460 e Å^{-3}

atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[27] All figures were generated using SHELXTL/PC.[28] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 274269. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1233 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work was supported by the Robert A. Welch Foundation (AT-1527).

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Tetrahedron 61 (2005) 12358–12365
Tetrahedron

Oxidations of erogorgiaene in pseudopterosin biosynthesis

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Received 15 September 2005; accepted 20 September 2005

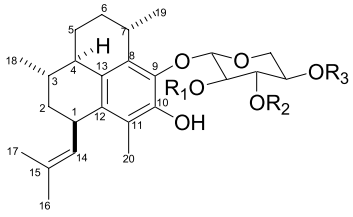
Available online 19 October 2005

Abstract—Pseudopterosins are potent anti-inflammatory diterpene glycosides initially isolated from the gorgonian coral *Pseudopterogorgia elisabethae*. In continuation of pathway elucidation studies focused on this family of terpenes, we report the isolation of 7-hydroxyerogorgiaene and 7,8-dihydroxyerogorgiaene from *P. elisabethae* and confirm the intermediacy of these compounds in pseudopterosin biosynthesis by in vitro incubation experiments with these metabolites in radiolabeled form.

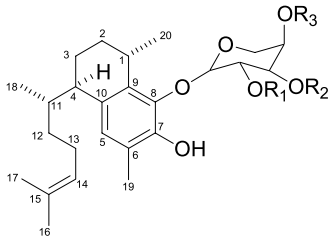
1. Introduction

The pseudopterosins (e.g., **1**–**4** in Fig. 1) represent a class of structurally diverse diterpene glycosides isolated from the marine octocoral *Pseudopterogorgia elisabethae*.[1] Collections of this coral from various geographic locations have yielded different members of the pseudopterosin family. All 26 pseudopterosin congeners contain an amphilectane skeleton and a glycoside linkage at either C-9 or C-10. Structural variations for this class of diterpenes are limited to the identity of the glycoside, the degree of its acetylation, and the stereochemistry observed for the isobutenyl group at C-1. The major constituents of *P. elisabethae* from Grand Bahama Island are pseudopterosins A–D, of which pseudopterosin C represents 7.5% of the lipid extract.[1]

The structurally related seco-pseudopterosins (**5**–**8**) belong to the serrulatane class of diterpenes and were initially isolated from *Pseudopterogorgia kallos* collected in the Florida Keys.[2] More recently, novel seco-pseudopterosins and pseudopterosins were reported to co-occur in *P. elisabethae* collected from the Florida Keys, where seco-pseudopterosin J (**9**), and pseudopterosins F (**10**) and Y (**11**) were the major constituents (Scheme 1).[3]



Ps A (**1**) R_1=R_2=R_3=H
Ps B (**2**) R_1=Ac, R_2=R_3=H
Ps C (**3**) R_2=Ac, R_1=R_3=H
Ps D (**4**) R_3=Ac, R_1=R_2=H



Seco-Ps A (**5**) R_1=R_2=R_3=H
Seco-Ps B (**6**) R_1=Ac, R_2=R_3=H
Seco-Ps C (**7**) R_2=Ac, R_1=R_3=H
Seco-Ps D (**8**) R_3=Ac, R_1=R_2=H

Figure 1. Representative pseudopterosins and seco-pseudopterosins.

The pseudopterosins and seco-pseudopterosins are anti-inflammatory agents that exhibit a novel spectrum of activity when compared to existing topical anti-inflammatory agents. In animal models the pseudopterosins block

Keywords: Biosynthesis; Diterpene; Erogorgiaene; 7-Hydroxyerogorgiaene; 7,8-Dihydroxyerogorgiaene; *Pseudopterogorgia elisabethae*; Pseudopterosin; seco-Pseudopterosin; Natural product.
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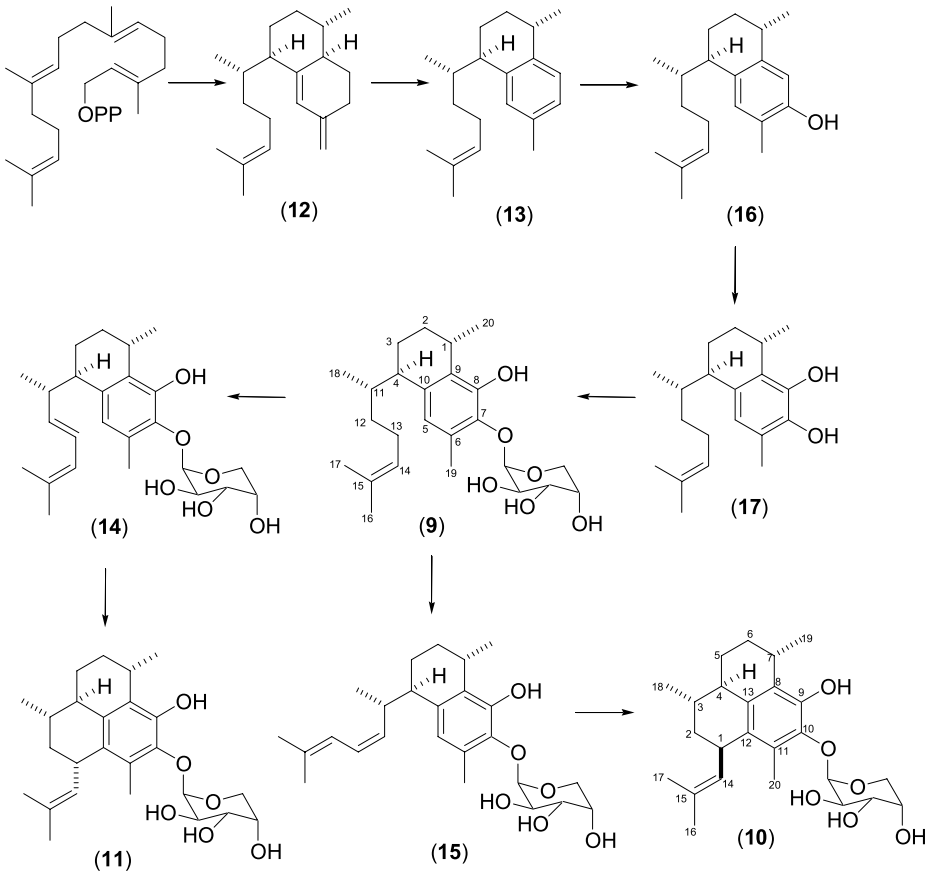
doi:10.1016/j.tet.2005.09.088



Scheme 1. Biosynthesis of pseudopterosins.

edema produced by acute application of phorbol 12-myristate 13-acetate (PMA).[4] In harvested human polymorphonuclear granulocytes (PMNs), the pseudopterosins block calcium ionophore induced degranulation and release of leukotriene B (LTB),[4] neutrophil myeloperoxidase and lactoferrin.[5] Recent studies have indicated that the release of eicosanoids is blocked without interrupting biosynthesis.[6] Pseudopterosin A has been found, in cultured cells, to stabilize nuclear lamina in dividing sea urchin embryos[7] and decrease phagosome formation in *Tetrahymena* cultures activated with calcium or zymosan.[6,8] There is also recent evidence suggesting that pseudopterosins may serve as antioxidants.[9] Lastly, from a commercial point of view, pseudopterosins are currently used as additives in a number of cosmetic products.[10]

We have recently described in vitro and in vivo systems, which were developed as tools to elucidate the biosynthesis of the pseudopterosins. Previously we used our in vitro technique to confirm the intermediacy of elisabethatriene (**12**), erogorgiaene (**13**), seco-pseudopterosin J (**9**), amphilectosin A (**14**), and amphilectosin B (**15**) in pseudopterosin biosynthesis (Scheme 1).[3,11–13] In a continuation of these metabolic studies, we undertook a study to search for and evaluate the intermediacy of oxidation products of erogorgiaene in pseudopterosin biosynthesis. Here, we report the isolation and metabolism of 7-hydroxyerogorgiaene (**16**), and 7,8-dihydroxyerogorgiaene (**17**).

2. Results and discussion

In an effort to identify plausible intermediates involved in pseudopterosin biosynthesis we have examined the terpene chemistry of *P. elisabethae* from various geographic locations. *P. elisabethae* from the Florida Keys contain a low concentration of pseudopterosins but have a great variety of serrulatane diterpenes. Conversely, extracts of *P. elisabethae* from the Bahamas have higher concentrations of pseudopterosins, but a much lower diversity of diterpenes. For this reason, we used coral material from Florida for this search for new presumed intermediates. Specifically, we were interested in determining if 7- or 8-hydroxyerogorgiaene and 7,8-dihydroxyerogorgiaene (**17**) were present in this extract as these were obvious candidates for the oxidation of hydrocarbon **13**. To aid in the search for catechol **17**, an authentic sample was prepared by the treatment of seco-pseudopterosin J (**9**) with methanolic HCl.[3,14] To confirm the structure of this somewhat unstable catechol, a portion was methylated with methyl iodide and potassium carbonate to the more stable, and known derivative 7,8-dimethoxyerogorgiaene (**18**, Fig. 2). The ^{1}H NMR spectrum was found to be identical to that previously reported.[2]

Samples of *P. elisabethae* were collected at a depth of 80 ft off Long Key, Florida and dried by lyophilization. Dried coral material was extracted and the hexanes fraction further separated using a gradient silica gel flash column to afford

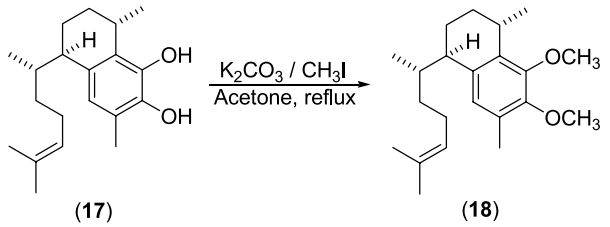


Figure 2. Derivatization of 7,8-dihydroxyerogorgiaene (**17**).

11 fractions (F1–11). Analysis of the fractions by thin-layer chromatography, using aglycone **17** as a standard, revealed that fractions F1–4 contained metabolites of the appropriate polarity for the desired compounds. Erogorgiaene (**13**) was isolated from F1 as previously described.[13] Further fractionation of F3 by RP C18 HPLC followed by RP HPLC with a phenyl hexyl column afforded a peak whose ^{1}H and ^{13}C NMR spectra were identical to that reported for 7-hydroxyerogorgiaene (**16**) by Rodriguez et al.[15] Despite the similarity of our spectral data with the reported values, we were unable to unambiguously determine whether the hydroxyl moiety was on C-7 or C-8. In order to confirm the location of the hydroxyl moiety we transformed this isolated product to its methyl ether derivative (**19**) for further NMR analysis. The methylation was carried out using sodium hydride and methyl iodide (Fig. 3). The observed spectra of the reaction product were similar to that of 7-hydroxyerogorgiaene with the addition of a signal in the ^{1}H NMR at δ 3.90 (s, 3H), and a ^{13}C NMR signal at δ 56.9 (Table 1). These resonances are consistent with an aromatic methoxy group. Furthermore, HRMS of this derivative gave a sodium adduct at 323.2353 confirming a molecular formula of $C_{21}H_{32}O$. The position of the methoxy group in the derivative and hence the location of the hydroxyl group in the natural product could now be readily established by examining NOE interactions. Irradiation of the methoxy group resulted in strong NOEs with the C-8 aromatic proton (δ 6.66, s, 1H) and the aromatic methyl (δ 2.19, s, 3H), confirming that the methoxy group in **19** is on C-7, and that the structure of the natural product is 7-hydroxyerogorgiaene (**16**).

Diol **17** could not be detected despite a detailed analysis of HPLC fractions, however, a preliminary cleanup by preparative TLC proved to be effective. F1–11 and the 7,8-dihydroxyerogorgiaene standard were analyzed by TLC using hexanes as the eluent. F4 had a spot with the same R_f as the standard sample and was subjected to prep TLC. The spot with the same R_f as the standard was isolated and further purified by RP C18 HPLC. A peak with the same retention time as the standard was shown to have an ^{1}H NMR identical to that of the synthetic sample of 7,8-dihydroxyerogorgiaene (**17**).

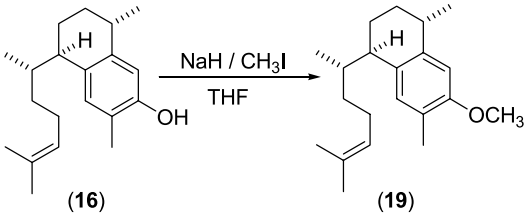


Figure 3. Derivatization of 7-hydroxyerogorgiaene (**16**).

Table 1. ^{1}H and ^{13}C NMR data for 7-methoxyerogorgiaene (**19**)

Atom	δ_H, intgr, mult (*J*)	δ_C (mult)
1	2.66, 1H, m	33.1 (d)
2α	1.30, 1H, m	31.9 (t)
2β	1.91, 1H, m	
3α	1.79, 1H, m	21.6 (t)
3β	1.42, 1H, m	
4	2.80, 1H, m	40.8 (d)
5	6.94, 1H, s	129.9 (d)
6	—	123.7 (s)
7	—	154.3 (s)
8	6.67, 1H, s	111.3 (d)
9	—	142.2 (s)
10	—	132.2 (s)
11	2.09, 1H, m	36.5 (d)
12α	1.42, 1H, m	35.4 (t)
12β	1.34, 1H, m	
13α	2.08, 1H, m	26.2 (t)
13β	2.02, 1H, m	
14	5.14, 1H, J=7.0 Hz	124.9 (d)
15	—	131.2 (s)
16	1.70, 3H, s	26.0 (q)
17	1.61, 3H, s	17.7 (q)
18	0.61, 3H, d, J=6.7 Hz	14.4 (q)
19	2.19, 3H, s	15.7 (q)
20	1.22, 3H, d, J=6.7 Hz	21.8 (q)
7-OCH_3	3.70, 3H, s	56.9 (q)

2.1. Biosynthetic experiments

The isolation of 7-hydroxyerogorgaiene (**16**) and 7,8-dihydroxyerogorgiaene (**17**) from an extract of *P. elisabethae* suggested that these were intermediates in pseudopterosin biosynthesis. To experimentally test this hypothesis, radiolabeled **16** and **17** were prepared, incubated with a cell-free extract of *P. elisabethae,* and the production of labeled pseudopterosins monitored by scintillation counting. Previously we have shown that we can obtain radiolabeled putative precursors by the incubation of ^{3}H-GGPP with a cell-free extract prepared from *P. elisabethae*.[3,11–13] To obtain radiolabeled erogorgiaene (**13**) as well as the two oxidized derivatives, ^{3}H-GGPP (20 μCi) was incubated with a cell-free extract that was prepared from *P. elisabethae* collected in the Florida Keys. Erogorgiaene (**13**, 67,510 dpm, 6.4×10^5 dpm/mmol) and 7-hydroxyerogorgiaene (**16**, 100,760 dpm, 8.3×10^5 dpm/mmol) were both isolated in radiolabeled form. Due to the low abundance of 7,8-dihydroxyerogorgiaene (**17**) and relatively high abundance of seco-pseudopterosin J (**9**) in the cell-free extract, catechol **17** (167,000 dpm, 3.0×10^7 dpm/mmol) was produced from the hydrolysis of **9**.

To ensure that these metabolites were radiochemically pure, a portion of each was derivatized and these derivatives

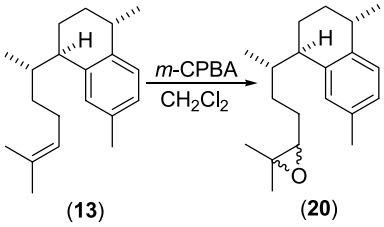


Figure 4. Derivatization of erogorgiaene (**13**).

Table 2. Recovered radioactivities and specific activities for incubation with ^{3}H-labeled **16** (99,755 dpm used in trial 1, 110,000 dpm used in trial 2)

	Trial 1		Trial 2	
Metabolite	Activity (dpm)	Specific activity (dpm/mmol)	Activity (dpm)	Specific activity (dpm/mmol)
Background	10		10	
Ps A	560	6.0×10^{5}	1150	6.7×10^{5}
Ps B	675	1.0×10^{4}	1200	1.7×10^{4}
Ps C	1610	1.2×10^{4}	3185	2.6×10^{4}
Ps D	675	9.0×10^{4}	1075	8.5×10^{4}

rigorously purified by HPLC to constant specific activity. In a previous report,[13] we demonstrated radiochemical purity for erogorgiaene (**13**) by derivatization to its epoxide **20**. We used the same approach in this study and thus erogorgiaene (950 dpm, 6.4×10^{5} dpm/mmol) was oxidized to its epoxy derivative using *m*-CPBA under standard conditions and then purified by HPLC (Fig. 4). The resulting derivative was found to have the same specific activity as the reaction substrate (920 dpm, 6.1×10^{5} dpm/mmol). 7-Hydroxyerogorgiaene (1010 dpm, 8.3×10^{5} dpm/mmol) was methylated to 7-methoxyerogorgiaene (**19**) using sodium hydride and methyl iodide, which upon purification by HPLC was shown to have the same specific activity as the starting material (850 dpm, 7.9×10^{5} dpm/mmol). Finally, 7,8-dihydroxyerogorgiaene (1670 dpm, 3.0×10^{7} dpm/mmol) was transformed to 7,8-dimethoxyerogorgiaene (1170 dpm, 2.7×10^{7} dpm/mmol) using potassium carbonate and an excess of methyl iodide. ^{3}H-Labeled **13**, **16**, and **17** were therefore confirmed to be radiochemically pure as their derivatives were shown to have the same specific activities as the isolated natural products.

In order to assess the intermediacy of alcohol **16** in pseudopterosin biosynthesis, 7-hydroxyerogorgiaene (99,755 dpm) was incubated with a cell-free extract prepared from Bahamian *P. elisabethae* and the production of labeled pseudopterosins monitored by scintillation counting. Rigorous purification of pseudopterosins A–D by HPLC and subsequent scintillation counting revealed that pseudopterosins A– were all radioactive (Table 2, trial 1). Radiochemical purity for the pseudopterosins was demonstrated by two separate methods. Firstly, pseudopterosin A was hydrogenated to its dihydro derivative (**21**, Fig. 5, Table 3) and subsequently purified by HPLC.[1] This reduced product had approximately the same specific activity (5.4×10^{5} dpm/mmol) as the isolated pseudopterosin A (6.0×10^{5} dpm/mmol). Secondly, pseudopterosin C was hydrolyzed to pseudopterosin A under basic conditions. The subsequently HPLC purified pseudopterosin A (1.2×10^{4} dpm/mmol) had a specific activity that was comparable to that of the isolated pseudopterosin C (1.2×10^{4} dpm/mmol). A duplicate trial with radiochemically pure 7-hydroxyerogorgiaene (110,000 dpm) was conducted and in this case, 100% of pseudopterosins A–D were each subjected to scintillation counting. As is evident from Table 2 (trial 2), all pseudopterosins were found to be radioactive.

The experiments described above indicate that 7-hydroxyerogorgiaene (**16**) is an intermediate in pseudopterosin biosynthesis suggesting that the first oxidation of erogorgiaene is at C-7. To confirm the existence of this transformation, erogorgiaene (**13**, 66,560 dpm) was incubated with a cell-free extract prepared from Bahamian *P. elisabethae* and monitored for the production of labeled **16**. Purification of 7-hydroxyerogorgiaene from the cell-free extract by repeated HPLC injections, and scintillation counting indicated that erogorgiaene was transformed to 7-hydroxyerogorgiaene (7080 dpm, 5.0×10^{4} dpm/mmol). A portion of recovered 7-hydroxyerogorgiaene was methylated to 7-methoxyerogorgiaene (**19**), as previously described, in order to establish radiochemical purity. After purification by HPLC and scintillation counting, 7-methoxyerogorgiaene (3.9×10^{4} dpm/mmol) was shown to have a similar specific activity to the isolated 7-hydroxyerogorgiene.

Previously, we demonstrated that the seco-pseudopterosins are precursors to the pseudopterosins,[3] which suggested that 7,8-dihydroxyerogorgiaene (**17**), the seco-pseudopterosin aglycone, is an intermediate in pseudopterosin biosynthesis. To test this hypothesis, a cell-free extract of *P. elisabethae* was incubated with ^{3}H-labeled 7,8-dihydroxyerogorgiaene (165,330 dpm) and monitored for the production of radioactive pseudopterosins. Rigorous purification and

Table 3. ^{1}H and ^{13}C NMR data for 14,15-dihydropseudopterosin A (**21**)

Atom	δ_H, intgr, mult (J)	δ_C (mult)
1	2.95, 1H, m	26.8 (d)
2α	1.30, 1H, m	40.0 (t)
2β	1.90, 1H, m	
3	1.59, 1H, m	31.1 (d)
4	3.58, 1H, m	35.4 (d)
5α	0.92, 1H, m	26.3 (t)
5β	2.00, 1H, m	
6α	2.13, 1H, m	29.6 (t)
6β	1.39, 1H, m	
7	3.53, 1H, m	28.0 (d)
8	—	133.9 (s)
9	—	140.6 (s)
10	—	144.2 (s)
11	—	121.3 (s)
12	—	135.2 (s)
13	—	128.6 (s)
14	1.72, 2H, m	41.7 (t)
15	1.83, 1H, m	25.4 (d)
16	0.98, 3H, d, J=6.5 Hz	23.6 (q)
17	0.88, 3H, d, J=6.7 Hz	23.5 (q)
18	1.04, 3H, d, J=6.3 Hz	23.0 (q)
19	1.15, 3H, d, J=7.1 Hz	17.4 (q)
20	2.03, 3H, s	21.2 (q)
1′	4.55, 1H, d, J=7.4 Hz	106.0 (d)
2′	3.73, 1H, m	76.1 (d)
3′	3.79, 1H, m	74.0 (d)
4′	3.75, 1H, m	69.3 (d)
5′	3.21, 1H, dd, J=10.4, 11.4 Hz 4.02, 1H, dd, J=5.5, 12.3 Hz	65.1 (t)

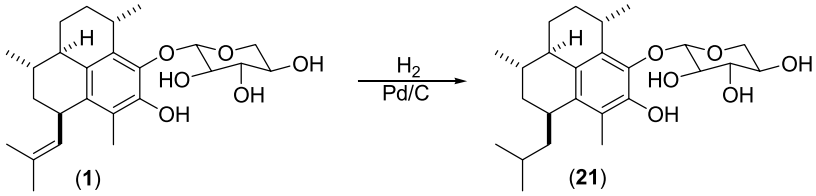


Figure 5. Derivatization of pseudopterosin A (**1**).

Table 4. Recovered radioactivities and specific activities for incubation with ^{3}H-labeled **17** (165,330 dpm used in trial 1, 170,000 used in trial 2)

	Trial 1		Trial 2	
Metabolite	Activity (dpm)	Specific Activity (dpm/mmol)	Activity (dpm)	Specific Activity (dpm/mmol)
Background	10		15	
Ps A	845	1.9×10^{5}	1820	2.5×10^{5}
Ps B	860	6.7×10^{4}	1675	7.4×10^{4}
Ps C	2145	8.3×10^{4}	4210	8.7×10^{4}
Ps D	800	6.4×10^{4}	1540	7.3×10^{4}

subsequent scintillation counting of pseudopterosins A–D indicated that all four compounds were radioactive (Table 4, trial 1). Radiochemical purity of the recovered pseudopterosins was demonstrated by a simple hydrolysis reaction. A portion of pseudopterosins B (430 dpm, 6.7×10^{4} dpm/mmol) and C (1070 dpm, 8.3×10^{4} dpm/mmol) were separately hydrolyzed to pseudopterosin A, which in both cases was found to have similar specific activity to the starting materials (350 dpm, 5.5×10^{4} dpm/mmol, and 970 dpm, 7.2×10^{4} dpm/mmol, respectively). A duplicate trial with 7,8-dihydroxyerogorgiaene (170,000 dpm) was conducted. In this case, pseudopterosins A–D were purified and 100% of each was subjected to scintillation counting. Table 4 (trial 2) summarizes these data, which indicate that all pseudopterosins were radioactive.

The conversion of 7-hydroxyerogorgiaene (**16**) to 7,8-dihydroxyerogorgiaene (**17**) was confirmed by conducting one additional incubation. Radiolabeled 7-hydroxyerogorgiaene (300,000 dpm, 5.7×10^{6} dpm/mmol) was isolated from a cell-free extract that was incubated with ^{3}H-GGPP (20 μCi). This was shown to be radiochemically pure as previously described. Incubation of 7-hydroxyerogorgiaene (297,400 dpm, 5.7×10^{6} dpm/mmol) with a cell-free extract resulted in the production of radioactive 7,8-dihydroxyerogorgiaene (**17**, 3460 dpm, 4.0×10^{4} dpm/mmol). Radiochemical purity for **17** was addressed by derivatization to its dimethyl ether **18**. Rigorous purification of **18** by HPLC indicated that this derivative had a similar specific activity (1510 dpm, 3.5×10^{4} dpm/mmol) as that of the isolated 7,8-dihydroxyerogorgiaene.

The intermediacy of 7-hydroxyerogorgiaene (**16**) and 7,8-dihydroxyerogorgiaene (**17**), together with our previous data, suggests that pseudopterosin biosynthesis occurs as described in Scheme 1. Specifically, pseudopterosin biosynthesis involves cyclization of the universal diterpene precursor GGPP to elisabethatriene, aromatization to erogorgiaene, two successive hydroxylations, glycosylation to afford a seco-pseudopterosin, dehydrogenation to the cis and trans amphilectosins, and finally a cyclization to afford the amphilectane framework. To our knowledge this study is the first complete pathway elucidation for a marine derived terpene.

3. Experimental

3.1. General

Scintillation counting was performed on a Perkin Elmer Tri-Carb 2900TR scintillation counter with Fisherbrand Econo F economical safety liquid scintillation cocktail. All aliquots subjected to scintillation counting were counted for 5 min and in triplicate. [1-^{3}H] Geranylgeranyl diphosphate (60 Ci/mmol) was purchased from MP Biomedicals. All other chemicals and reagents were purchased from Fisher Scientific, Sigma Chemical Co., or Aldrich Chemical Co. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian 400 NMR spectrometer at 400 MHz. IR spectra were recorded on a Thermoelectron Nicolet FT-IR spectrometer. Polarimetry was performed on a JASCO Dip 310 polarimeter. High performance liquid chromatography (HPLC) was performed using a Perkin Elmer Series 410 pump with a Perkin Elmer 235 diode array detector. Normal phase high performance liquid chromatography separations were performed using a Vydac Unbonded silica column (300 Å, 250 mm×10 mm). Reversed phase HPLC separations were carried out using a Phenomenex Gemini ODS column (5 μ, 250 mm×10 mm) or a Phenomenex Luna phenyl-hexyl column (5 μ, 250 mm×10 mm). Analytical thin-layer chromatography was performed using Whatman aluminum backed (UV 254 nm) 250 μm silica gel plates. Preparative TLC was performed using Whatman (silica gel, 60 Å, 1000 μm) TLC plates. All solvents used were of HPLC grade.

3.2. Coral material

Pseudopterogorgia elisabethae was collected by SCUBA in the Florida Keys or at Sweetings Cay, Bahamas and allowed to dry in the sun or flash frozen using liquid nitrogen. The

sun-dried material was further dried by lyophilization while the flash frozen material was stored in an ultra freezer at −80 °C.

3.3. Extraction and isolation

Dried *P. elisabethae* (415 g) was extracted with ethyl acetate (2×500 mL) and methylene chloride (2×500 mL). The extracts were filtered, combined, and evaporated to dryness under reduced pressure, yielding a black gummy residue (170 g). The crude material was dissolved in methanol–water (9/1) (600 mL) and partitioned with hexanes (3×600 mL). The ratio of the methanol/water layer was adjusted to 1:1 and the layer partitioned with methylene chloride (3×600 mL). The hexanes and methylene chloride partitions were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The hexanes partition (95 g) was subjected to silica gel flash chromatography and the column eluted with a step gradient of hexanes and ethyl acetate as the mobile phase (100–0% hexanes) to afford eleven fractions (F1–11). The methylene chloride partition (70 g) was also subjected to silica gel flash chromatography using the same mobile phase to afford an additional 11 fractions (C1–11).

3.3.1. Isolation of erogorgiaene (13). Fraction F1 was purified by reversed phase C-18 HPLC (λ=215 nm) using 100% methanol over 30 min to yield erogorgiaene (2.0 mg, 7.4 μmol) as a colorless oil; ^{1}H NMR was identical with that previously reported.[15]

3.3.2. Epoxidation of erogorgiaene (13) to 14,15-epoxyerogorgiaene (20). To a stirred solution of erogorgiaene (1.1 mg, 4.1 μmol) in dry methylene chloride (1 mL) at 0° was added a solution of *meta*-chloroperoxybenzoic acid (1.5 equiv). After 3 h, the reaction was quenched by the addition of water (3 mL) and the reaction extracted with methylene chloride (3×4 mL). The combined methylene chloride partitions were dried over anhydrous sodium sulfate, filtered, and the solvent allowed to evaporate under a stream of nitrogen. The crude organic material was subjected to RP-C18 HPLC (λ=215 nm) using methanol over 30 min as the mobile phase to afford derivative **20** (1.0 mg, 3.7 μmol) as a colorless oil. All spectral data were as previously reported.[13]

3.3.3. Isolation of 7-hydroxyerogorgiaene (16). Fraction F3 was subjected to RP-C18 HPLC (λ=283 nm) using acetonitrile–water (50/50–100% acetonitrile over 30 min, hold for 10 min) as mobile phase to afford five UV active fractions (A1–5). A4 was further purified by RP-phenyl hexyl HPLC using the same HPLC conditions to afford **16** (4.3 mg, 15.0 μmol). The ^{1}H NMR of 7-hydroxyerogorgiaene was consistent with the lit.[15]

3.3.4. Conversion of 7-hydroxyerogorgiaene (16) to 7-methoxyerogorgiaene (19). To a stirred solution of 7-hydroxyerogorgiaene (1.4 mg, 4.9 μmol) at 0 °C in dry THF (1 mL) was added a cold solution of 1 N sodium hydride in dry THF (1 mL). The reaction was allowed to warm to room temperature, followed by the addition of methyl iodide (3 equiv). After 12 h the solvent was removed under a stream of nitrogen and the crude material partitioned between methylene chloride and water (3×3 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent evaporated under a stream of nitrogen. Subjection of the crude organic material to RP-C18 HPLC, using methanol as eluent, afforded **19** (1.4 mg, 4.6 μmol) as a colorless solid. *Compound* **19**. $[\alpha]_D^{20}$ 37 (*c* 0.0009 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (3H, d, J=6.7 Hz), 1.22 (3H, d, J=6.7 Hz), 1.34 (1H, m), 1.42 (1H, m), 1.61 (3H, s), 1.70 (3H, s), 1.79 (1H, m), 1.91 (1H, m), 2.02 (1H, m), 2.08 (1H, m), 2.09 (1H, m), 2.19 (3H, s), 2.66 (1H, m), 2.80 (1H, m), 3.70 (3H, s), 5.14 (1H, t), 6.67 (1H, s), 6.94 (1H, s); ^{13}C NMR (100 mHz, $CDCl_3$) δ 14.4 (q), 15.7 (q), 17.7 (q), 21.6 (t), 21.8 (q), 26.0 (q), 26.2 (t), 31.9 (t), 33.1 (d), 35.4 (t), 36.5 (d), 40.8 (d), 56.9 (q), 111.3 (d), 123.7 (s), 124.9 (d), 129.9 (d), 131.2 (s), 132.2 (s), 142.2 (s), 154.3 (s). IR ($CHCl_3$) ν 2929, 2846, 1645, 1510, 1465, 1120 cm^{-1}. HRMS calculated for $C_{21}H_{32}ONa$: 323.2351; found 323.2353.

3.3.5. Isolation of seco-pseudopterosin J (9). Fraction C11 was subjected to semi-preparative RP-C18 HPLC using a gradient of acetonitrile–water (50/50 to 100% acetonitrile over 30 min, hold for 10 min) as mobile phase to afford **9** (7.2 mg, 16.6 μmol). All spectral data for **9** were identical to that previously reported.[3]

3.3.6. Acid hydrolysis of seco-pseudopterosin J (9) to 7,8-dihydroxyerogorgiaene (17). To seco-pseudopterosin J (3.2 mg, 6.9 μmol) was added a 1 N HCl methanolic solution (2 mL). After stirring at 35 °C for 3 h, the solution was cooled to room temperature, and water added (10 mL). The solution was extracted with methylene chloride (3×2 mL), the combined organic extracts dried over anhydrous sodium sulfate, filtered, and the solvent allowed to evaporate under a stream of nitrogen. The residue was purified by semi-preparative RP-C18 HPLC using a gradient of acetonitrile–water (50/50 to 100% acetonitrile over 30 min, hold for 10 min) as mobile phase to afford **17** (1.6 mg, 73%). The ^{1}H NMR for 7,8-dihydroxyerogorgiaene was consistent with the lit.[14]

3.3.7. Methylation of 7,8-dihydroxyerogorgiaene (17) to 7,8-dimethoxyerogorgiaene (18). To a stirred solution of 7,8-dihydroxyerogorgiaene (1.0 mg, 3.3 μmol) in dry acetone was added an excess of anhydrous potassium carbonate and methyl iodide. After refluxing for 8 h, the reaction mixture was allowed to cool to room temperature. The acetone was evaporated under a stream of nitrogen, 5 mL H_2O added, and the aqueous layer extracted with methylene chloride (3×5 mL). The combined methylene chloride layers were dried over anhydrous sodium sulfate, filtered, and allowed to evaporate under a stream of nitrogen. The crude organic layer was separated by semi-preparative normal phase HPLC using a gradient of hexanes–ethyl acetate as mobile phase (60/40 to 100% ethyl acetate over 35 min, 100% for 5 min) to afford **18** (1.0 mg, 91%). The ^{1}H NMR for **18** was consistent with that previously reported.[2]

3.3.8. Catalytic hydrogenation of pseudopterosin A (1) to 14,15-dihydropseudopterosin A (21). Pseudopterosin A (1.2 mg, 2.8 μmol) was dissolved in ethyl acetate (10 mL) and transferred to an Erlenmeyer vacuum flask containing

3% Pd–C and a magnetic stir bar. The reaction vessel was maintained under positive pressure of hydrogen and vigorously stirred at 25 °C for 8 h. The resulting mixture was filtered through a column of Celite and solvent removed under nitrogen gas. The residue was purified by semi-preparative RP-C18 reversed phase HPLC using a gradient of acetonitrile–water (50/50 to 100% acetonitrile over 30 min, hold for 10 min) as a mobile phase to afford dihydro derivative **21** (1.1 mg, 90%). *Compound* **21**. $[\alpha]_D^{20}$ −35 (*c* 0.0007 in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, $J=6.7$ Hz), 0.92 (1H, m), 0.98 (3H, d, $J=6.5$ Hz), 1.04 (3H, d, $J=6.3$ Hz), 1.15 (3H, d, $J=7.1$ Hz), 1.30 (1H, m), 1.39 (1H, m), 1.59 (1H, m), 1.72 (2H, m), 1.83 (1H, m), 1.90 (1H, m), 2.00 (1H, m), 2.03 (3H, s), 2.13 (1H, m), 2.95 (1H, m), 3.21 (1H, dd, $J=10.4$, 11.4 Hz), 3.53 (1H, m), 3.58 (1H, m), 3.73 (1H, m), 3.75 (1H, m), 3.79 (1H, m), 4.02 (1H, dd, $J=5.5$, 12.3 Hz), 4.55 (1H, d, $J=7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4 (q), 21.2 (q), 23.0 (q), 23.5 (q), 23.6 (q), 25.4 (d), 26.3 (t), 26.8 (d), 28.0 (d), 29.6 (t), 31.1 (d), 35.4 (d), 40.0 (t), 41.7 (t), 65.1 (t), 69.3 (d), 74.0 (d), 76.1 (d), 106.0 (d), 121.3 (s), 128.6 (s), 133.9 (s), 135.2 (s), 140.6 (s), 144.2 (s). IR ($CHCl_3$) ν 2240, 2920, 2960, 3030, 3500 cm^{-1}. HRMS calculated for $C_{25}H_{38}O_6Na$: 457.2566; found 457.2569.

3.3.9. Base hydrolysis of pseudopterosin B (2) to pseudopterosin A (1). To pseudopterosin B (1.6 mg, 3.4 μmol) was added 3 mL of 5% KOH/methanol, and the reaction mixture allowed to stir overnight. Ice was then added followed by 10 mL H_2O. The solution was acidified and the aqueous phase extracted with methylene chloride (3×15 mL). The combined methylene chloride layers were dried over anhydrous sodium sulfate, filtered, and allowed to evaporate to yield **1** (1.3 mg, 89%). The crude organic layer was purified by normal phase HPLC using hexanes–ethyl acetate (60/40 to 100% ethyl acetate over 35 min, 100% for 5 min) as mobile phase to afford **1**. The ^1H NMR for the product was identical in all respects to the reported spectral data.[1]

3.3.10. Base hydrolysis of pseudopterosin C (3) to pseudopterosin A (1). Conversion of pseudopterosin C (2.3 mg, 4.8 μmol) to pseudopterosin A (1.9 mg, 91%) was performed as described for the conversion of pseudopterosin B to pseudopterosin A. The ^1H NMR for the product was identical in all respects to the reported spectral data.[1]

3.4. Isolation of pseudopterosins A–D

Pseudopterosins A–D were purified from the methylene chloride partition by normal phase HPLC ($\lambda=283$ nm) with a hexanes–ethyl acetate gradient (60/40 to 100% ethyl acetate over 35 min, 100% for 5 min).

3.5. Preparation of cell-free extracts for biosynthetic studies

Flash frozen *P. elisabethae* (150 g) was homogenized in a blender with liquid nitrogen and 300 mL of a 0.1 mM Tris–HCl buffer (pH=7.7) containing 3 mM EDTA and 0.035% β-mercaptoethanol and the resulting homogenate centrifuged at 9600 g for 15 min. The pellet was discarded and the supernatant centrifuged at 39,000 g for 60 min. The supernatant (cell-free extract) was stored in 40 mL aliquots at −80 °C.

3.6. Incubation of cell-free extract with ^3H-GGPP and purification of triturated 13, 16, and 17

An aliquot of cell-free extract (40 mL) was incubated with 20 μCi [1-^3H] GGPP (60 Ci/mmol) for 24 h at 29 °C. The reaction was quenched and extracted with ethyl acetate (3× 40 mL). Centrifugation (9600 g, 2 min) was used to separate the layers in cases where an emulsion was formed. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. The organic residue was partitioned and subjected to silica gel chromatography, and the putative precursors purified as described above.

3.7. Incubation of cell-free extract with triturated 13, 16, and 17

Triturated metabolites (**13**, **16**, and **17**) were prepared as described above. The ^3H-labeled metabolite (**13**, **16** or **17**) was transferred to a 50 mL Falcon tube using ethyl acetate and the solvent removed under nitrogen gas. To the Falcon tube was added, glycerol (4 mL), Tween 20 (0.05%), and 0.1 mM Tris–HCl buffer (1 mL). The mixture was vortexed for 10 min followed by the addition of an aliquot of cell-free extract (35 mL). The CFE was incubated at 29 °C for 24 h, quenched and extracted with ethyl acetate (3×40 mL). Target molecules were purified from the organic residue as described above.

Acknowledgements

Financial support of this research has been provided by the National Science Foundation (0119011, 6130486, and 0311369) and is gratefully acknowledged. We also wish to thank the Florida Institute of Oceanography for providing ship time aboard the R/V Suncoaster and the Keys Marine Lab for assistance with fieldwork. High-resolution mass spectrometry was performed at the University of Florida. In addition, we acknowledge Harbor Branch Oceanographic Institute for the use of their polarimeter. This is contribution no. P200512 from the Center of Excellence in Biomedical and Marine Biotechnology.

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Tetrahedron 61 (2005) 12366–12370
Tetrahedron

A hyodeoxycholic acid-based molecular tweezer: a highly selective fluoride anion receptor

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Received 10 August 2005; revised 20 September 2005; accepted 20 September 2005

Available online 26 October 2005

Abstract—A new molecular tweezer receptor **Hc1** based on hyodeoxycholic acid has been synthesized and its binding properties were accessed by ^{1}H NMR and isothermal titration calorimetry experiments. Molecular tweezer **Hc1** shows a high selectivity toward F^- over Cl^-, Br^-, I^-, and $H_2PO_4^-$.

1. Introduction

Considerable attention has been focused upon the design of synthetic receptors for the detection of biologically relevant anions.[1] Fluoride ions are important anions because of their important role in dental care and the clinical treatment of osteoporosis.[2,3] Direct detection of fluoride ions in aqueous systems is essential for the development of ion sensors for applications in clinical and environmental analyses. The steroid nucleus is one of the largest rigid and chiral ubiquitous natural materials. Based on these preorganized structural characteristics, cholesterol and bile acid derivatives have been used as a building block for extended, well defined molecular architectures and a scaffold of synthetic receptors, and they have shown selectivity toward cations, anions, and organic molecules.[4] Davis et al. have synthesized cryptand[5] and tripodal anionophore[6,7] derived from cholic acid and used for halide anion binding and recognition. Among them 7,12-biscarbamoyl-3-sulfonamide derivative shows high affinity for fluoride ion in $CDCl_3$. ($K_a = 1.54 \times 10^4\ M^{-1}$).[6]

Maitra et al. have synthesized cholaphane from cholic acid, which has shown moderate binding affinity toward fluoride ions ($K_1 = 10^3\ M^{-1}$, $K_2 = 10^2\ M^{-1}$).[8]

Recently we designed and synthesized bile acid-based receptors, and found that the introduction of ion-recognizing moieties on the rigid chenodeoxycholic and cholic acid derivative frames resulted in tweezer-type receptors.[9] It is known that receptors bearing two urea groups at suitable positions bind anions through hydrogen bondings.[10] Continuing our efforts to develop a highly selective anion receptor, we synthesized neutral anion receptors using cholic acid derivative as the building block and urea as anion recognizing pendant at the different positions as shown in Figure 1. In this paper, we report that the synthesis of a new hyodeoxycholic acid-based molecular tweezer receptor (**Hc1**) and its high fluoride ion recognition selectivity in comparison with that of lithocholic acid (**Lc2**) and deoxycholic acid-based receptor (**Dc3**).

2. Results and discussion

Hyodeoxycholic acid-based molecular tweezer **Hc1**, which contains ureidopropoxyl groups at C_3 and C_6, was synthesized according to Scheme 1. Allylation of **2** was prepared by reduction of methyl hyodeoxycholate with lithium aluminum hydride followed by protection with *tert*-butyldimethylsilyl chloride in 68% overall yield, with allyl bromide in the presence of sodium hydride in THF afforded

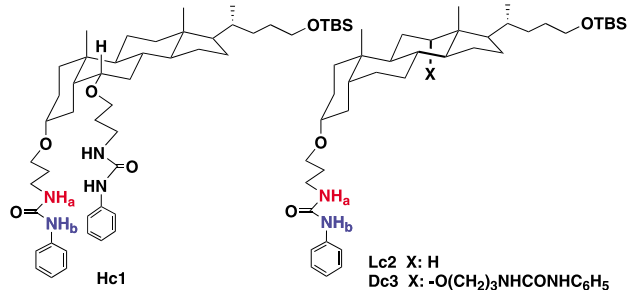

Figure 1.

Keywords: Hyodeoxycholic acid; Urea; Hydrogen bond; Fluoride ion.
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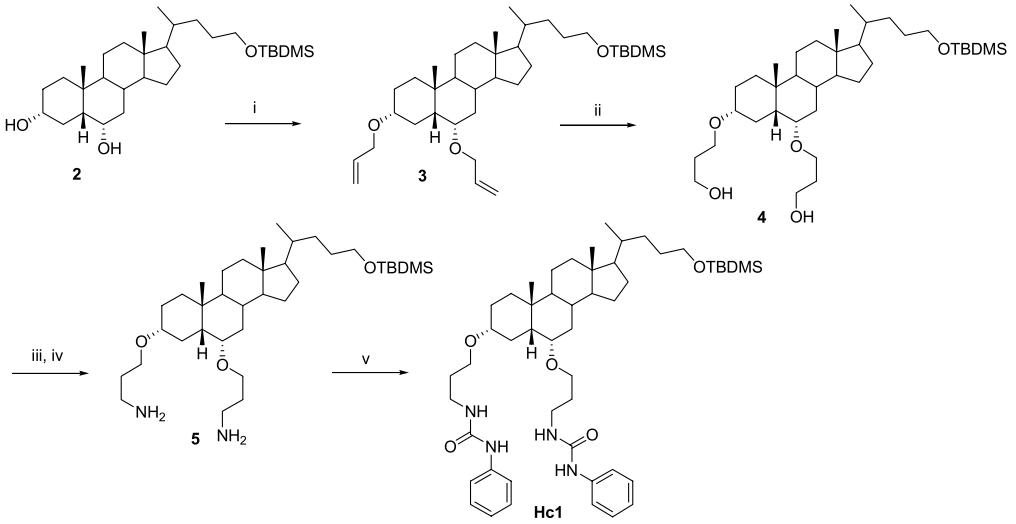
doi:10.1016/j.tet.2005.09.082



Scheme 1. Reagents and conditions: (i) NaH, allyl bromide, THF; (ii) 9-BBN, THF then OH^-, H_2O_2; (iii) DEAD, PPh_3, phthalimide, THF; (iv) $H_2NNH_2\times H_2O$, EtOH; (v) C_6H_5NCO, TEA, $CHCl_3$.

allyl ether **3** in 85% yield. Hydroboration of the latter with 9-BBN provided the diol **4** in the 75% yield. Transformation of **4** to diamine **5** was carried out with phthalimide, triphenylphosphine, and DEAD, followed by subsequent hydrazinolysis with hydrazine hydrate. These two step reactions gave 3α,6α-di(3′-aminopropoxy)-5β-cholane **5** in 91%. Coupling of **5** with phenyl isocyanate in dry $CHCl_3$ at room temperature resulted in the bis(phenylurea) receptor **Hc1** in 90%. The structure of **Hc1** was confirmed by ^1H and ^{13}C NMR, mass spectroscopy, and elemental analysis.

Initial anion binding properties of receptor **Hc1** have been studied by ^1H NMR experiments in DMSO-d_6 solution in the presence of various anions (F^-, Cl^-, Br^-, I^-, and $H_2PO_4^-$) present as *n*-tetrabutylammonium salts (TBA). The ^1H NMR spectrum of **Hc1** showed dramatic changes upon the addition of 1 equiv of F^- and $H_2PO_4^-$ while no significant spectral changes were observed upon the addition of Cl^-, Br^-, and I^- (Fig. 2).

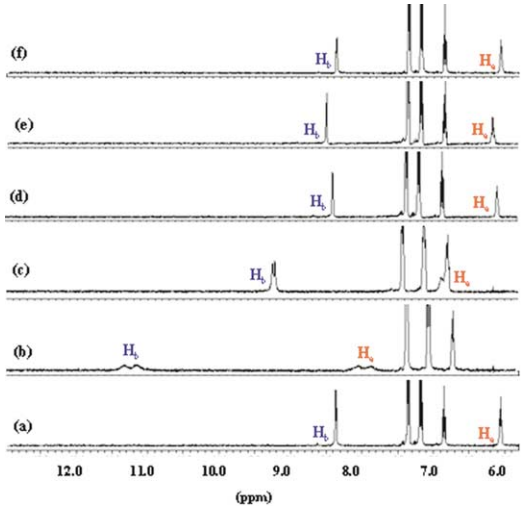


Figure 2. Partial ^1H NMR spectra of **Hc1** in DMSO-d_6 (a) **Hc1**; (b) **Hc1**+ F^- (1.0 equiv); (c) **Hc1**+$H_2PO_4^-$ (1.0 equiv); (d) **Hc1**+Cl^- (1.0 equiv); (e) **Hc1**+ Br^- (1.0 equiv); (f) **Hc1**+I^- (1.0 equiv). Anions used were in the form of their TBA salts.

Upon treatment of **Hc1** with 1 equiv of F^-, the signals of the urea protons shifted downfield pronouncedly; the signals at 6.06 (H_a) and 8.37 ppm (H_b) were broadened and shifted downfield ($H_a=1.99$, $H_b=2.97$), as a result of strong hydrogen bonding between the fluoride ion and two urea N–protons. Whereas 1 equiv of $H_2PO_4^-$ was added to **Hc1**, the signal at 8.37 ppm (H_b) shifted downfield a little ($H_b=0.88$) owing to the formation of weak hydrogen bonds with the tetrahedral oxoanion. A job plot indicated that **Hc1** formed a complex with F^- in a 1:1 ratio (Fig. 3).[11]

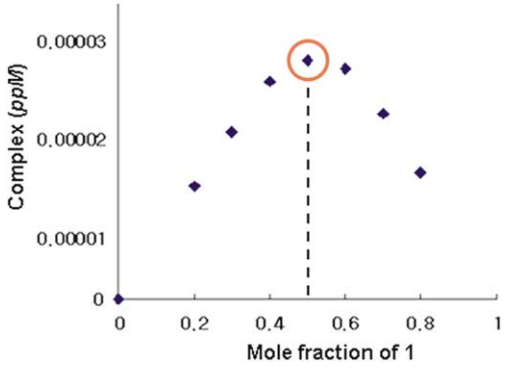


Figure 3. Job plot of **Hc1** with TBAF.

From the nonlinear curve fitting EQ NMR program,[12] association constants (K_a) of **Hc1**, **Lc2**, and **Dc3** were determined and results are summarized in Table 1.

Table 1. Association constants (M^{-1}) of **Hc1**, **Lc2**, and **Dc3** obtained from ^1H NMR titrations with various anions[a]

Host	Guest, K_a			
	F^-	Cl^-	Br^-	$H_2PO_4^-$
Hc1	15,300	89	50	389
Lc2	NDT[b]	65	NM[c]	266
Dc3	1360	92	66	630

[a] Determined in DMSO-d_6, at 25 °C, [host] $=4.5\times10^{-3}$ M. Errors estimated to be ≤15%. Anions used were in the form of their TBA salts.
[b] NDT= not determined.
[c] NM= not measured.

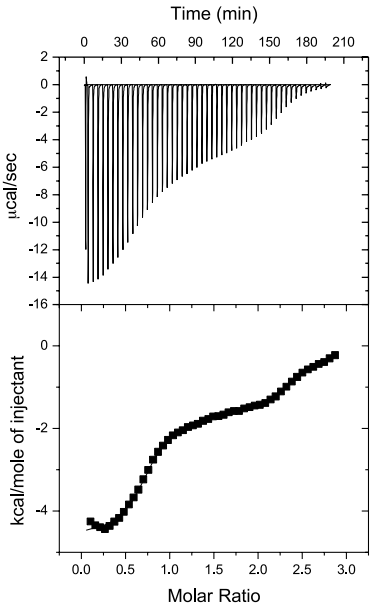


Figure 4. Isothermal titration calorimetry of **Hc1** (1 mM) with TBAF (15 mM) in DMSO at 25 °C.

Association constant of **Hc1** shows 15,300, 89, 50, and 389 M^{-1} (errors $\leq$15%) for the binding of F^-, Cl^-, Br^-, and $H_2PO_4^-$, respectively. Association constants of **Lc2** for Cl^- and $H_2PO_4^-$ were smaller than those of **Hc1**, indicating that two urea groups of **Hc1** act as cooperative binding sites. Unfortunately, attempt to calculate complex association constant of **Lc2** for F^- from ^1H NMR titration curves was unsuccessful. This may be due to the formation of very weak complex. Association constant of **Dc3** for F^- (K_a= 1360) was smaller than that of **Hc1**, whereas association constants for Cl^-, Br^-, and $H_2PO_4^-$ were larger than those of **Hc1**. Receptor **Hc1** showed a highly selective binding with F^- over Cl^-, Br^-, and $H_2PO_4^-$. The selectivity of **Hc1** for F^- (K_a=15,300) was about 170 times that for Cl^-, and over 40 times that for $H_2PO_4^-$.

Further binding studies were carried out by isothermal titration calorimetry (ITC) of **Hc1** and **Dc3** with TBAF in DMSO solution. Significantly **Hc1** reveals two kinds of binding mode as shown in Figure 4. ^1H NMR titration results in $K_1=1.53\times10^4\ M^{-1}$ only due to its detection limit ($<10^5\ M^{-1}$), but ITC shows two sequential association constants $K_1=2.99\times10^4\ M^{-1}$ and $K_2=1.37\times10^6\ M^{-1}$. These results suggest that addition of F^- **Hc1** forms a 1:1 complex and becomes 1:2 with an increasing concentration of F^-. **Dc3** shows similarly two kinds of binding mode for F^-, but the association constants ($K_1=2.91\times10^2\ M^{-1}$ and $K_2=1.14\times10^4\ M^{-1}$, errors $\leq$40%) are smaller than those of **Hc1**, because the distance between two urea pendants in **Dc3** is longer than that of **Hc1** to disfavor the complexation with F^- ions. The thermodynamic values ($\Delta H°$, $\Delta S°$) for the two sequential binding are presented in Table 2.

To better understand this behavior of the **Hc1** with F^-, we optimized structures of the possible complex between F^- with **Hc1** (Fig. 5).[13]

In a 1:1 **Hc1**–F^- complex the estimated distance between urea N–H and F^- (H—CO—H–$^-$) is 1.93–1.99 Å, whereas that of the 1:2 **Hc1**–F^- complex is 1.81–1.88 Å, indicating that urea N–H protons strongly bind with F^- ions through the hydrogen bonds. Similar structural analysis of **Dc3**–F^- shows that the distance between urea N–H and F^- is 1.86–3.15 Å as a result of moderate hydrogen bonds between them. The size of the anion and distance between two pendants of receptor seem to determine binding selectivity; Cl^- ions are too large to fit in a **Hc1** tweezer's pocket, whereas the smaller F^- ions fit well.

3. Conclusion

We have shown a neutral hyodeoxycholic acid based on molecular tweezer receptor **Hc1** containing urea pendants selectively recognizes the biologically important fluoride ion over other halides and $H_2PO_4^-$. The selectivity of **Hc1** for F^- is better than that of **Dc3**. The selectivity of **Hc1** for F^- is about 170 times that for Cl^-, and over 40 times that

Table 2. Association constants (M^{-1}) and thermodynamic data from ITC of **Hc1** and **Dc3** with TBAF at 25 °C

Host	K_1	ΔH_1	ΔS_1	K_2	ΔH_2	ΔS_2
Hc1	2.99×10^4	−1752	14.7	1.37×10^6	−4615	12.9
Dc3[a]	2.91×10^2	−970	14.5	1.14×10^4	−1857	24.7

[a] Errors estimated to be $\leq$40%.

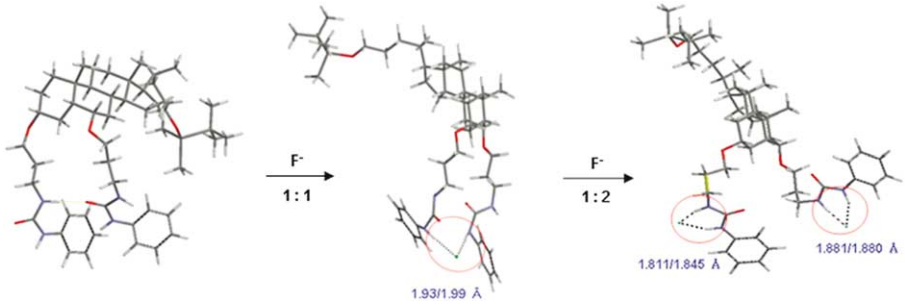


Figure 5. Energy-minimized geometries of **Hc1**–F^-. The dotted lines represent the H-bond distances.

for $H_2PO_4^-$. **Hc1** binds sequentially with F^- from 1:1 to 1:2 in DMSO.

4. Experimental

4.1. General information

General experimental procedures for melting points, FT-IR spectra, mass spectra, high resolution MS, elemental analysis, and TLC analysis have been described previously.[14] ^1H and ^{13}C NMR spectra were recorded either on Bruker AM-400 (400 MHz) or Varian unity-plus 300 (300 MHz) spectrometers. ^1H and ^{13}C NMR assignments were made by comparison with spectra of similar steroids.[9,15] Isothermal titration calorimetry (ITC) measurements were performed as described in the literature.[16] TLC analyses were carried out on a precoated 0.2 mm HPTLC silica gel 60 plate (Merck, Darmstadt); substances were visualized by spraying with 5% ammonium molybdate in 10% H_2SO_4 followed by heating. Flash column chromatography was performed with silica gel Merck silica gel 60 (70–230 mesh). Reactions were carried out under argon atmosphere, and the solution was dried over anhydrous sodium sulfate. Syntheses of **Lc2** and **Dc3** will be described in elsewhere. ^1H NMR titrations were run at 45 mM concentrations, with aliquots of a 0.25 M $(nBu)_4N^+X^-$ salts solution added. The non-linear curve fittings program (EQ NMR) was used for curve fitting. Chemicals were purchased from either Aldrich Chemicals or Fluka Co. Dichloromethane and chloroform were dried over CaH_2 and THF was dried over sodium and benzophenone and distilled prior to use.

4.1.1. 24-*tert*-Butyldimethylsilyloxy-3α,6α-dihydroxy-5β-cholane (2). $LiAlH_4$ (2 equiv, 370 mg) was added to a solution of hyodeoxycholic methyl ester (2.00 g, 4.92 mmol) in dry THF at 0 °C, and stirred for 16 h. The mixture was treated with 10% HCl and ethyl acetate. After the precipitant was removed, the filtrate was dried, and evaporated to dryness. To a solution of the resulting residue, imidazole (500 mg, 7.40 mmol, 1.5 equiv) and a catalytic amount of 4-DMAP (10 mg) in dry dichloromethane (100 mL) and DMF (10 mL) was added *tert*-butyldimethylsilyl chloride (890 mg, 5.90 mmol) in dry dichloromethane (5 mL) at room temperature. After the reaction was completed, the solution was treated with 10% HCl and extracted with dichloromethane, dried, and evaporated to dryness. The residue was purified by silica gel chromatography (elution with EtOAc–hexane 1:3) to give 1.65 g of **2** (68%). Mp 120–122 °C (CH_2Cl_2–hexane); IR (KBr) 3343, 2935, 2859, 1470, 1254, 1096, 872, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (m, 1H, 3β-H), 3.52 (m, 3H, 6β-H and 24-CH_2), 0.86 (s, 3H, 19-CH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.59 (s, 3H, 18-CH_3), 0.03 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 71.6 (C-3), 68.1 (C-6), 63.8 (C-24), 56.2, 48.4, 42.8, 40.0, 39.9, 36.0, 35.5, 35.0, 34.8, 31.9, 30.2, 29.5, 29.2, 28.2, 26.0, 24.2, 23.5, 20.7, 18.6, 18.3, 12.0, −5.3; TLC R_f 0.22 (EtOAc–hexane 1:1).

4.1.2. 24-*tert*-Butyldimethylsilyloxy-3α,6α-diallyloxy-5β-cholane (3). NaH (390 mg, 16.23 mmol) was added to a solution of **2** (2.00 g, 4.06 mmol) in dry THF (100 mL) and heated at 60 °C for 30 min. Allyl bromide (1.34 mL, 16.23 mmol) was added to the resulting mixture, which was heated for 24 h. After that NaH (4 equiv) and allyl bromide (4 equiv) was added again and heated for another 24 h. Then the solvent was removed, and the residue was extracted with diethyl ether, washed with brine, dried, and evaporated. The residue was purified by column chromatography (elution with EtOAc–hexane 1:10) to give 1.98 g of **3** (85%). Oil; IR (neat) 2938, 1723, 1463, 1254, 1053, 835, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (m, 2H), 5.22 (dd, J=17.6, 1.0 Hz, 2H), 5.09 (dd, J=10.0, 1.0 Hz, 2H), 4.03–3.85 (m, 4H), 3.63 (m, 1H), 3.52 (t, J=6.5 Hz, 2H, 24-CH_2), 3.24 (m, 1H), 0.86 (d, J=7.0 Hz, 21-CH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.84 (s, 3H, 19-CH_3), 0.58 (s, 3H, 18-CH_3), 0.05 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 135.9, 116.8, 116.7, 78.7, 75.4, 69.3, 69.1, 64.2, 56.6, 45.8, 43.2, 40.4, 40.4, 36.4, 36.1, 35.9, 35.2, 32.5, 32.3, 29.9, 28.6, 27.7, 26.6, 26.4, 26.0, 24.6, 23.9, 21.2, 19.0, 18.7, 12.4, −3.2, −4.9; FAB-MS calcd for $C_{36}H_{64}O_3Si$: 572.46, found: m/z 571 $(M-H)^+$; TLC R_f 0.54 (5% EtOAc–hexane).

4.1.3. 24-*tert*-Butyldimethylsilyloxy-3α,6α-di(3′-hydroxypropanoxy)-5β-cholane (4). 9-BBN in THF (0.5 M, 14 mL) was added to a solution of allyl ether **3** (1.00 g, 1.75 mmol) in dry THF (100 mL) and stirred at room temperature for 12 h. After the reaction was completed, it was quenched with 20% NaOH (5 mL) and 30% H_2O_2 (5 mL) sequentially and refluxed for 1 h. After the solvent was removed, it was extracted with ethyl acetate, washed with brine, dried, and concentrated to dryness. The residue was purified by column chromatography (elution with EtOAc–hexane 2:1) to give 938 mg of **4** (88%). Oil; IR (neat) 3356, 2933, 1463, 1369, 1256, 1094, 836, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (t, J=5.5 Hz, 4H), 3.66–3.55 (m, 5H), 3.54–3.47 (m, 4H), 3.22–3.15 (m, 1H), 2.8 (br s, 2H, NH_2), 0.86 (d, J=7.0 Hz, 21-CH_3), 0.85 (s, 3H, 19-CH_3), 0.85 (s, 9H, SiC(CH_3)$_3$), 0.58 (s, 3H, 18-CH_3), 0.04 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 79.6, 76.5, 67.6, 67.3, 62.3, 62.2, 56.5, 45.6, 43.1, 40.4, 40.2, 36.4, 36.0, 35.9, 35.1, 32.7, 32.5, 32.4, 32.2, 29.8, 28.5, 27.6, 26.6, 26.4, 26.1, 24.6, 24.0, 21.2, 19.0, 18.7, −4.9; FAB-MS calcd for $C_{36}H_{68}O_5Si$: 608.48, found: m/z 609 $(M+H)^+$; TLC R_f 0.40 (EtOAc–hexane 2:1).

4.1.4. 24-*tert*-Butyldimethylsilyloxy-3α,6α-di(3′-aminopropanoxy)-5β-cholane (5). After a mixture of **4** (500 mg, 0.82 mmol), phthalimide (710 mg, 4.1 mmol) and triphenyl phosphine (1.00 g, 4.1 mmol) was stirred in dry THF (50 mL) at room temperature, diethyl azodicarboxylate (DEAD, 0.63 mL, 4.1 mmol) was added and stirring continued. Then the solvent was removed, and the residue was extracted with ethyl acetate, washed with brine, dried, and concentrated. Without further purification, the residue and hydrazine monohydrate (410 mg, 8.2 mmol, 10 equiv) were refluxed in ethanol (200 mL) for 24 h. Then the solvent was removed, it was extracted with diethyl ether, washed with brine, dried, and concentrated. The residue was purified by column chromatography (elution with CH_2Cl_2–MeOH–H_4OH 16:3:0.5) to give 458 mg of **5** (91%). Oil; IR (neat) 2936, 1469, 1378, 1254, 1100, 836, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.56–3.35 (m, 4H, OCH_2CH$_2$), 3.43 (m, 1H, OC*H*–), 3.23 (m, 1H, OC*H*–), 2.84 (br t, 4H, CH_2NH), 0.90 (d, J=6.0 Hz, 3H, 21-CH_3), 0.89 (s, 9H, SiC(CH_3)$_3$),

0.89 (s, 3H, 19-CH_3), 0.62 (s, 3H, 18-CH_3), 0.05 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 79.0 (C-3), 75.8 (C-6), 66.1, 65.9, 63.8 (C-24), 56.1, 45.3, 42.7, 40.0, 39.9, 39.7, 39.5, 36.0, 35.6, 35.5, 34.7, 33.0, 32.1, 31.8, 29.5, 28.1, 27.1, 26.4, 25.9, 24.2, 23.6, 20.8, 18.6, 18.3, 12.0, −5.3; HRMS (EI) calcd for $C_{36}H_{70}N_2O_3Si$ (M^+) 606.5156, found: 606.5165; TLC R_f 0.28 (CH_2Cl_2–MeOH–H_4OH 16:3:1).

4.1.5. Receptor Hc1. A solution of **5** (1.00 g, 0.165 mmol) in dry chloroform (10 mL) was reacted with phenyl isocyanate (0.09 mL, 0.825 mmol) at room temperature for 2 h. Then the solvent was removed, extracted with ethyl acetate, washed in brine, dried, and concentrated to dryness. The residue was purified by column chromatography (elution with EtOAc–hexane 1:1) to give 125 mg of **Hc1** (90%) as a white solid. Mp 80–82 °C; IR (KBr) 3315, 3205, 2937, 2864, 1530, 1497, 1310, 1252, 1095, 774 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.37 (s, 1H, Ar-N*H*), 8.35 (s, 1H, Ar-N*H*), 7.35 (d, J= 8.5 Hz, 4H, *ortho*-ArH), 7.18 (dd, J=8.0, 7.5 Hz, 4H, *meta*-ArH), 6.85 (dd, J=7.5, 7.5 Hz, 2H, *para*-ArH), 6.06 (t, J= 5.5 Hz, 2H, CH_2–N*H*), 3.52 (t, J=6.0 Hz, 3H, OCH_2CH$_2$, OC*H*–), 3.41 (t, J=6.0 Hz, 3H, OCH_2CH$_2$, OC*H*–), 3.10 (dd, J=12.5, 5.5 Hz, 4H, CH_2NH), 0.86 (d, J=7.4 Hz, 3H, 21-CH_3), 0.84 (s, 9H, SiC(CH_3)$_3$), 0.84 (s, 3H, 19-CH_3), 0.58 (s, 3H, 18-CH_3), −0.02 (s, 6H, Si(CH_3)$_2$); ^{13}C NMR (DMSO-d_6) δ 155.5, 140.9, 128.9, 121.2, 117. 9, 78.5, 75.2, 65.2, 65.1, 63.2, 56.0, 44.9, 42.6, 37.0, 36.9, 35.9, 35.2, 34.5, 32.2, 31.9, 30.7, 30.7, 29.2, 27.1, 26.4, 26.1, 23.7, 20.8, 18.9, 18.3, 14.3, 12.2, −4.9; Anal. Calcd for $C_{50}H_{80}N_4O_3S_2Si$: C, 68.44; H, 9.19; N, 6.39; S, 7.31. Found C, 68.70; H, 9.49; N, 6.28; S, 6.92; TLC R_f 0.60 (EtOAc–hexane 1:1).

Acknowledgements

This work was supported by grant from the KOSEF (R05-2001-000-00227-0) and the BK21 program.

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Proton affinities and relative basicities of two 1,4,7-triazacyclononanes, Me_3TACN and TP-TACN. Quantum-chemical ab initio calculations, solution measurements, and the structure of $[TP\text{-}TACN \cdot 2H]^{2+}$ in the solid state☆

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Received 23 June 2005; revised 20 September 2005; accepted 20 September 2005

Available online 10 October 2005

Abstract—Quantum-chemical ab initio calculations have been carried out to determine the proton affinities of tripyrollidinyl- and 1,4,7-trimethyl-1,4,7-triazacyclononane. Due to an effective stabilization of the ammonium cations the proton affinities of both compounds have been found to be up to 20 kcal/mol higher than the values of non-cyclic tertiary aliphatic amines. The computational results have been compared to those from solution measurements and X-ray structure determination.

1. Introduction

In a preceding communication we reported on the synthesis of novel C_3-symmetric enantiopure 1,4,7-triazacyclononane TP-TACN (**1**) and its metal complexes $[(TP\text{-}TACN)M(\mu_2\text{-}OAc)_2(\mu_2\text{-}O)M(TP\text{-}TACN)]^{2+}$ **2** (**2a**: M=Mn; **2b**: M=Fe).[1] A comparison of the properties of **2** with those of the metal complexes $[(Me_3TACN)M(\mu_2\text{-}OAc)_2(\mu_2\text{-}O)M(Me_3\text{-}TACN)]^{n+}$ **3** (**3a**: M=Mn; **3b**: M=Fe) of the extensively studied analogous trimethyl derivative Me_3TACN (**4**)[2] pointed towards a stronger complexing ability of **1** in comparison with **4**. Thus, cyclovoltammetric reduction of **2a** showed enhanced reversibility for the Mn(III)–Mn(II) and in particular for the Mn(II)–Mn(II) complex as compared with the analogous electron transitions for **3a**. Furthermore, **2b** directly revealed an Fe(III)–Fe(IV) transition in the cyclic voltammogram, whereas the analogous wave for **3b** was more difficult to extract. These observations led to the hypothesis of a sterically more favorable disposition of the three nitrogen lone pairs towards an electrophilic center in **1** as compared to **4**. This concept was supported by the ^{1}H NMR spectrum of **1** showing a single set of protons for the chemically non-equivalent sites of each third of the molecule, thus, indicating an effective C_3-symmetry in solution (Fig. 1).

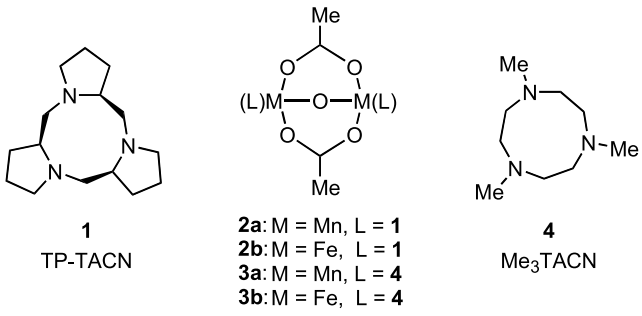

Figure 1. TACNs involved in this study and their metal complexes.

The most simple reaction of **1** and **4** with an electrophile that could mirror the proposed lone pair disposition is their protonation. We, therefore, studied the comparative Brønstedt basicities of **1** and **4** by proton transfer reactions between $[\mathbf{4}\cdot H]^+$ and **1** in solution (Fig. 2).

A theoretical study calculating proton affinities was performed in order to reveal the reason for the extraordinary properties of **1** and **4** and to account for the differences in reactivity of these two compounds.

☆ Presented in part at the 11th annual meeting of the Deutsche Gesellschaft für Kristallographie, March 11–13, 2003, Berlin, Germany.

Keywords: Ab initio calculations; Basicity; Cation; Proton affinity; Triazacyclononane.
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doi:10.1016/j.tet.2005.09.083

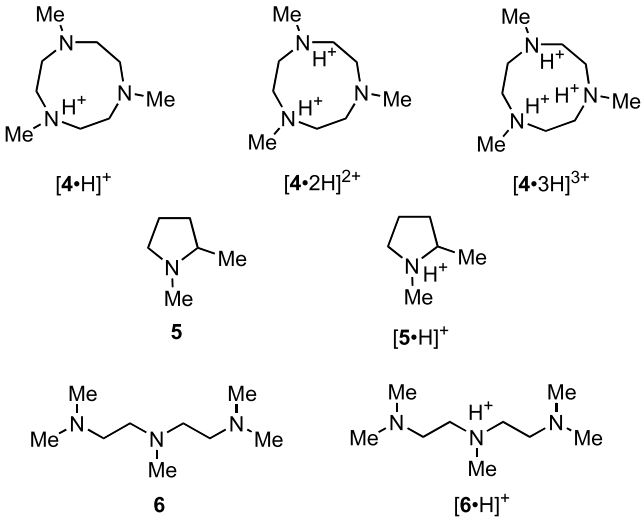

Figure 2. Protonated TACN **4** and amines **5** and **6** as well as their monoprotonated forms.

2. Results and discussion

2.1. Calculations on the proton affinities of 1 and 4

The proton affinity (PA) of a base (**B**) is defined as the negative change of enthalpy (ΔH_{prot}) associated with the protonation reaction (Eq. 1).

$$\mathbf{B} + H^+ \rightarrow \mathbf{B}H^+; \quad PA \equiv -\Delta H_{prot} \tag{1}$$

Approximate values of the PA can be calculated using the semiclassical expression[3] (Eq. 2; R is the gas constant and T the temperature in K),

$$\Delta H_{prot} = \Delta E_{prot} - \frac{5}{2}RT \tag{2}$$

where ΔE_{prot} is the difference between the total energies of the cation ($E_{tot}(\mathbf{B}H^+)$) and the base ($E_{tot}(\mathbf{B})$) including correlation as well as zero point energy (ZPE) (Eq. 3).

$$\Delta E_{prot} = E_{tot}(\mathbf{B}H^+) - E_{tot}(\mathbf{B}) \tag{3}$$

The geometries of all molecules under consideration have been fully optimized at the MP2/6-31+G* level of ab initio theory (see Section 4). If not mentioned otherwise zero point energies have been calculated at the Hartree Fock level using a slightly smaller basis set (HF/6-31G*//HF/6-31G*).

The structures of **1**, $[\mathbf{1}\cdot H]^+$, and $[\mathbf{1}\cdot 2H]^{2+}$, as well as those of **4**, $[\mathbf{4}\cdot H]^+$, and $[\mathbf{4}\cdot 2H]^{2+}$ optimized at the MP2/6-31+G* level are shown in Figure 3. At 298 K the first and second proton affinities of **1** calculated at the ZPE+MP2/6-31+G*//MP2/6-31+G* level are 257.7 and 153.2 kcal/mol, respectively. To extrapolate to 'experimental' values we used the correlation equation obtained from the comparison of the experimentally determined proton affinities of 12 aliphatic amines (NH_3, $MeNH_2$, $EtNH_2$, nPrNH$_2$, nBuNH$_2$, Me_2NH, EtMeNH, Et_2NH, Me_3N, Me_2EtN, $MeEt_2N$, Et_3N)[4] with the values calculated at the same level of theory[5] ($PA_{exp} = 1.03435 \cdot PA_{calcd} - 2.80984$, $|r| = 0.9991$). The 'experimental' first PA of **1** obtained in this way is 263.7 kcal/mol. This value is almost 30 kcal/mol above those usually found for simple tertiary aliphatic amines (~228–235 kcal/mol),[4] and similar to the value predicted for 1,6-diazabicyclo[4.4.4]tetrahedrane at a different level of theory (~260 kcal/mol).[6] At 155.7 kcal/mol the second 'experimental' PA of **1** lies between the proton affinities of water (173 kcal/mol)[7] and carbon monoxide (139 kcal/mol).[7] No attempts have been made to correct for the basis set superposition error (BSSE). The calculations on the 12 aliphatic amines mentioned above[5] showed that the theoretical PAs are systematically lower than their experimental counterparts (average value ~4.8 kcal/mol), and a similar result has been obtained at a somewhat different level of theory.[8] It is, therefore, reasonable to assume that the first PAs calculated for **1** and **4** are also too low. Since a counterpoise correction[9] (1.86 kcal/mol for **1**, and 1.96 kcal/mol for **4**) would further increase this discrepancy it was omitted.

Two reasons might account for the extraordinarily high proton affinities of **1** and **4**. Firstly, the neutral bases might be destabilized with respect to an ordinary tertiary amine, and this destabilization could be lowered upon protonation. Thus, incorporation of the nitrogen atoms of **1** and **4** in a cyclic system leads to a high electron density in the nine-membered ring. It is intuitively felt that such an accumulation of negative charge is energetically unfavourable and that this repulsion will be released upon protonation of one of the nitrogen atoms. The second possibility is that stabilizing effects (vide infra), which are not available to ordinary open-chained cations of tertiary amines are active in $[\mathbf{1}\cdot H]^+$ and $[\mathbf{4}\cdot H]^+$.

In search for the reason for the high PA of **1** we first investigated the influence of the $-(CH_2)_3-$ bridge linking the nitrogen atoms to one of the α carbon atoms. We, therefore, calculated the PA of the 'fragment molecule' amine **5** (Fig. 4) at the ZPE+MP2/6-31+G*//MP2/6-31+G* level.

At 228.8 kcal/mol the calculated proton affinity of **5** is almost identical to the corresponding value of methyldiethylamine (228.2 kcal/mol).[5] The fact that participation of the three methylene groups in a five-membered ring obviously contributes little to the proton affinity of **1** is further reflected by the calculated PA of **4**, which is 251.8 kcal/mol at the ZPE+MP2/6-31+G*//MP2/6-31+G* level, corresponding to a difference between the PAs of **1** and **4** of about 6 kcal/mol, which is similar to the difference between the experimental proton affinities of methyl- and n-propylamine (4.4 kcal/mol).[4] We, therefore, conclude that the enhanced PA of **1** compared to **4** is largely an effect of the extension of the third alkyl substituent at nitrogen and only to a smaller amount of the involvement of the tertiary amino groups in a five-membered ring.

We next investigated the influence of the inclusion of the three tertiary amino groups in a nine-membered ring on the proton affinities of **1** and **4**. The calculated PA of **6** (Fig. 5), which can be considered as an open chain derivative of **4**, amounts to 229.1 kcal/mol and, therefore, lies within the range usually given for ordinary tertiary amines (vide supra). Thus, the high PA of **1** and also that of **4** is obviously due to the participation of the three tertiary amino groups in a cyclic system. We, therefore, used the somewhat smaller molecule **4** to further determine whether the height PAs of **1** and **4** are due to an effect active in the base or in the cation.

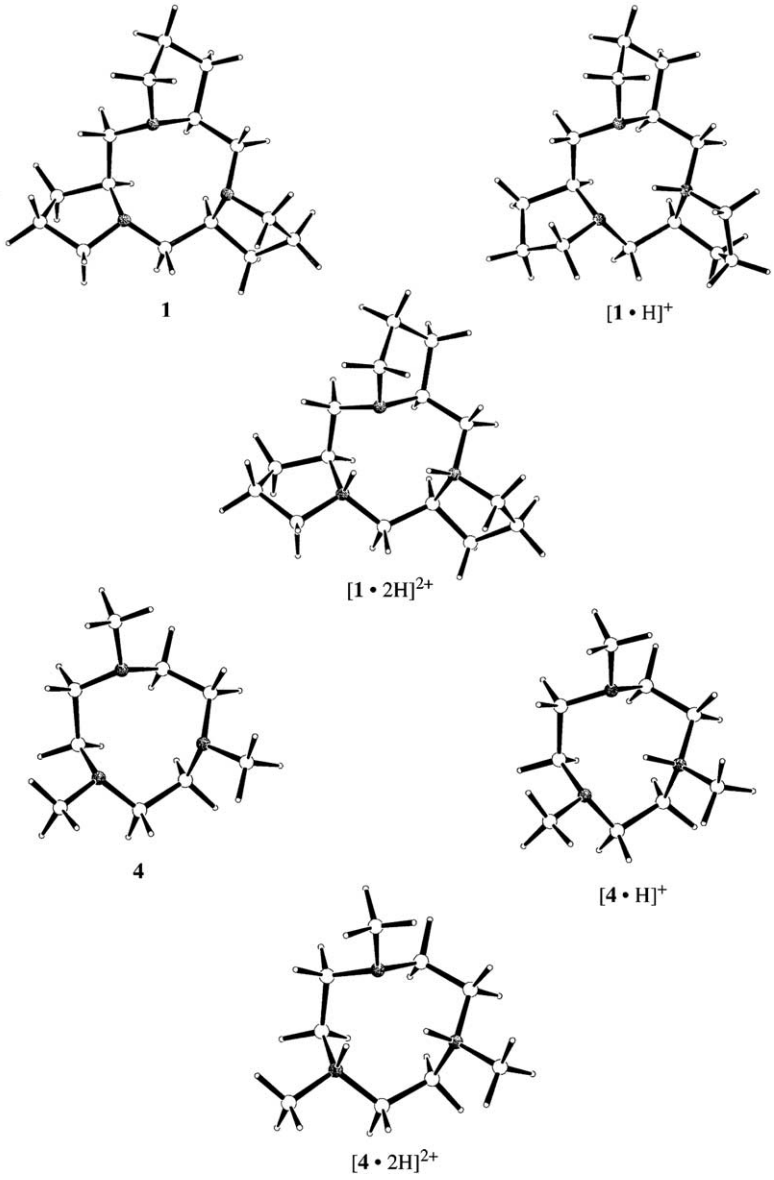

Figure 3. The structures of **1**, $[\mathbf{1}\cdot H]^+$, $[\mathbf{1}\cdot 2H]^{2+}$, **4**, $[\mathbf{4}\cdot H]^+$, and $[\mathbf{4}\cdot 2H]^{2+}$, obtained at the MP2/6-31+G* level.

Reductive cleavage of **4** resulting in **6** (Eq. 4) is formally similar to the reaction of ethane with dihydrogen, yielding two molecules of methane, since in both cases one C– bond is broken while two C–H bonds are formed. At the ZPE+MP2/6-31+G*//MP2/6-31+G* level, we calculated an energy of reaction of $\Delta E_r = -13.4$ kcal/mol for the reductive cleavage of ethane ($C_2H_6 + H_2 \rightarrow 2CH_4$). This value falls within the range of -10 to -16 kcal/mol obtained using bond energy increments from different empirical schemes.[10,11]

$$4 + H_2 \rightarrow 6 \quad (4)$$

If some effects destabilize **4** with respect to its open chain derivative **6** the change of energy associated with the reaction should be more negative than the value calculated for the corresponding cleavage of ethane. However, the energy of reaction calculated from the total energies of the molecules in Eq. 4 at the same level is $\Delta E_r = -15.7$ kcal/mol. While this value, which is only slightly more negative than that for the cleavage of ethane, indicates some relief of strain upon opening of the ring,[12] it is certainly not the only reason for the high PA of **4**. If, on the other hand, stabilizing effects are active in the cyclic cation but are not available to the open

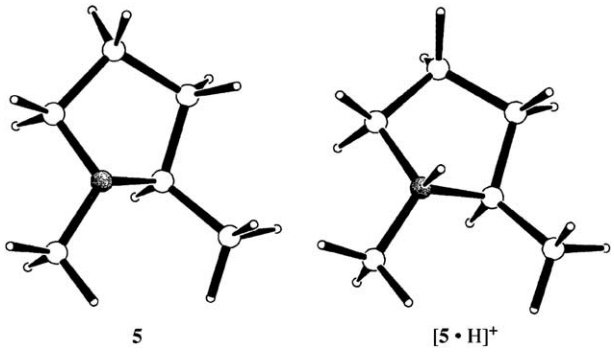

Figure 4. The structures of **5**, and $[\mathbf{5}\cdot H]^+$ obtained at the MP2/6-31+G* level.

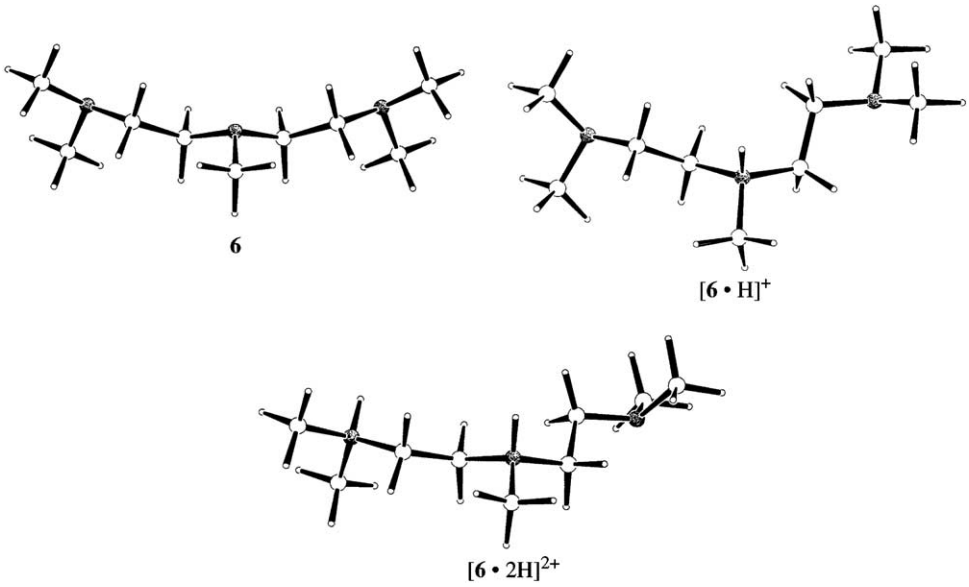

Figure 5. The structures of **6**, $[\mathbf{6}\cdot H]^+$, and $[\mathbf{6}\cdot 2H]^{2+}$, obtained at the MP2/6-31+G* level.

chain derivative isomer, the reaction depicted in Eq. 5 should result in a change of energy, which is more positive than the one resulting from the corresponding reaction of ethane.

$$[4\cdot H]^+ + H_2 \rightarrow [6\cdot H]^+ \quad (5)$$

Indeed, the change of energy associated with this reaction (Eq. 5) is +7.0 kcal/mol and, therefore, more than 20 kcal/mol more positive compared with the value for the reaction of ethane. Thus, the cyclic cation $[\mathbf{4}\cdot H]^+$ is obviously stabilized efficiently with respect to its open chain derivative $[\mathbf{6}\cdot H]^+$. Since there is no reason to assume that this feature is significantly different in the case of **1** and $[\mathbf{1}\cdot H]^+$ we conclude that an effective stabilization of the positive charge in the cations is the source of the high proton affinity of both **4** and **1**. This stabilizing effect might be an energy-lowering interaction between the lone pairs of the unprotonated nitrogen atoms with the positive charge of the ammonium group. Very high proton affinities caused by stabilization of the corresponding cations probably due to the proximity of amino groups have also been reported for 1,8-bis(dimethylamino)naphthalene,[13] 1,6-diazabicyclo-[4.4.4]tetrahedrane,[6] an other compounds.[12] Geometry changes that occur upon protonation of **1** and **4** support this notion.

The average distance between the nitrogen atoms in the MP2/6-31+G* structure of **4** is 2.93 Å, and a slightly larger value of 2.96 Å is obtained for **1**. Upon protonation this value is reduced to 2.75 Å in $[\mathbf{4}\cdot H]^+$ and 2.76 Å in $[\mathbf{1}\cdot H]^+$. At 2.89 and 2.88 Å in $[\mathbf{4}\cdot H]^+$ and $[\mathbf{1}\cdot H]^+$ the distance between the unprotonated nitrogen atoms of the nine-membered rings is similar to the value for the neutral bases. However, the average transanular distances between the protonated and the non-protonated nitrogen atom is about 0.2 Å smaller, that is, 2.68 Å in $[\mathbf{4}\cdot H]^+$ and 2.70 Å in $[\mathbf{1}\cdot H]^+$, respectively. This shortening of the intermolecular distances is due to an energetically favourable interaction between the ammonium moieties and the opposing tertiary amino groups. Moreover, the length of the N^+–H bond, which is 1.06 Å in $[\mathbf{1}\cdot H]^+$ and 1.07 Å in $[\mathbf{4}\cdot H]^+$, indicates the presence of intramolecular hydrogen bonds since the corresponding bond length in Et_3NH^+ calculated at the same level of precision is 1.03 Å. The structure of $[\mathbf{4}\cdot H]^+$ in the solid state has been determined by Wieghardt and Simon.[14] These experimental data support our computational results showing that the hydrogen atom of the ammonium group interacts with both non-protonated nitrogen atoms via hydrogen bridges. Especially the experimentally determined distances between the amino nitrogen atoms (2.905 Å) on the one and the protonated and the non-protonated N atoms (2.707, 2.712 Å) on the other hand compare nicely with our computational results.

Protonation of $[\mathbf{1}\cdot H]^+$ yielding $[\mathbf{1}\cdot 2H]^{2+}$ results in further significant changes of the geometry. Compared with the average distance between the nitrogen atoms in **1**, and probably as a result of the electrostatic repulsion between

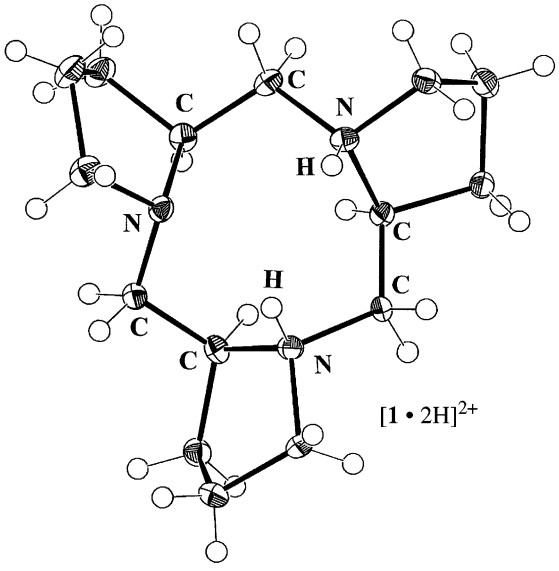

Figure 6. The structure of $[\mathbf{1}\cdot 2H]^{2+}$ in the solid state. The PF_6^- units and the water molecule have been omitted for clarity.

the two ammonium groups, the distance between the two protonated nitrogens is increased significantly (3.16 Å at the MP2/6-31+G* level) as compared with the average N···N distance in **1**, while at 2.69 and 2.79 Å the distance between the amino- and the ammonium nitrogens are quite similar to the corresponding interatomic distances in $[\mathbf{1}\cdot\mathrm{H}]^+$ and $[\mathbf{4}\cdot\mathrm{H}]^+$. However, the N^+–H bond lengths of 1.03 and 1.04 Å are very similar to the values for the Et_3NH^+ cation and, therefore, do not indicate presence of intramolecular hydrogen bonds.

The structure of $[\mathbf{1}\cdot 2\mathrm{H}]^{2+}$ in the solid state has also been determined by X-ray diffraction methods. The dication crystallizes together with two PF_6^- anions and a single water molecule. The arrangement of the components in the solid state might be described as a layer structure with strata containing the dication, the PF_6^- anions, and the water molecule in layers running parallel to the *ac* plane. The solid state structure of $[\mathbf{1}\cdot 2\mathrm{H}]^{2+}$ is shown in Figure 6 and except for the folding of one of the five-membered rings the calculated and the experimentally determined structures are visually indistinguishable.

At distances of 3.138(3) Å between the two ammonium nitrogens and of 2.763(3) and 2.849(3) Å between the protonated and the non-protonated nitrogen atoms these interatomic distances in the solid state are quite similar to our computational results.

2.2. Proton transfer between $[\mathbf{4}\cdot\mathrm{H}]^+$ and 1 in solution

The Brønsted basicity of **4** had been determined in aqueous solution by potentiometric titration by Geraldes and co-workers,[2] who found pK_a values for $[\mathbf{4}\cdot 3\mathrm{H}]^{3+}$, $[\mathbf{4}\cdot 2\mathrm{H}]^{2+}$, and $[\mathbf{4}\cdot\mathrm{H}]^+$ as ~0.4(2), 5.1, and 11.7, respectively. Since the available amount of **1** was insufficient for such a titration experiment and the expected difference in basicity of **1** and **4** is expected to be small, a more direct comparison was achieved by determining the extent of proton transfer (Eq. 6) by NMR spectroscopy.

$$[4\cdot\mathrm{H}]^+ + 1 \rightarrow [1\cdot\mathrm{H}]^+ + 4 \qquad (6)$$

The proton transfer experiment was performed in CD_2Cl_2. The ^1H NMR spectrum of **4**, protonated with CF_3COOH to an extent of more than 80% (to make sure that no diprotonation had occurred) shows methyl and methylene signals shifted to lower field with respect to the unprotonated base (see Section 4). Addition of one equivalent of **1** caused both signals to move upfield nearly to the original positions. From the observed shift differences and the known stoichiometry **4**:CF_3COOH as well as the ratio **4**:**1** we calculated the ratio of base constants as $K_b(\mathbf{4}):K_b(\mathbf{1}) = 15$. Thus, in an unpolar solvent **1** is a 15 times stronger Brønstedt base compared to **4**. If the ratio of K_b values is transferred to an aqueous solution a pK_b of 12.8 (11.7+1.1) would result for TP-TACN (**1**). The result clearly indicates a significantly higher Brønstedt basicity of the TP-TACN in comparison to the Me_3TACN (**4**), which is in accord with both the observed enhanced complexation ability of the polycyclic triamine towards hard transition metal centers as well as with the higher proton affinity of **4**.

3. Conclusion

1,4,7-Triazacyclononanes **1** and **4**, which both are strong ligands towards divalent and trivalent transition metal ions, also have extraordinarily high proton affinities. A theoretical study revealed that this is due to an effective stabilization of the protonated molecule, which is not available to non-cyclic ammonium cation analogues. A proton transfer experiment in deuterated dichloromethane revealed that **1** is a 15 times stronger Brønsted base than **4**.

4. Experimental

4.1. Full geometry optimizations

Total energies at the MP2/6-31+G* level and HF/6-31G* zero point energies in parentheses (in Hartrees). Zero point energies printed in italics have been calculated at the MP2/6-31+G* level.

1: −749.529331 (0.446626), $[\mathbf{1}\cdot\mathrm{H}]^+$: −749.955203 (0.464222), $[\mathbf{1}\cdot 2\mathrm{H}]^{2+}$: −750.212920 (0.480235), **4**: −518.016340 (0.328848), $[\mathbf{4}\cdot\mathrm{H}]^+$: −518.433047 (0.346702), $[\mathbf{4}\cdot 2\mathrm{H}]^{2+}$: −518.669374 (0.362861), **5**: −290.180029 (0.199063, *0.189139*), $[\mathbf{5}\cdot\mathrm{H}]^+$: −290.558781 (0.215540, *0.204834*), **6**: −519.195814 (0.349734), $[\mathbf{6}\cdot\mathrm{H}]^+$: −519.574856 (0.366065), $[\mathbf{6}\cdot 2\mathrm{H}]^{2+}$: −519.822543, CH_4: −40.334082 (*0.046047*), C_2H_6: −79.497603 (*0.076684*), H_2: −1.144141 (*0.010326*).

All calculations have been performed with the Gaussian03 package of quantum-chemical routines.[15]

4.2. Proton transfer from $[\mathbf{4}\cdot\mathrm{H}]^+$ to 1

Spectra were taken at ambient temperature on a Varian Unity 500 NMR spectrometer operating at 500 MHz proton NMR frequency. Shift values are versus the residual absorption of CD_2Cl_2 set as 5.300 ppm. Compounds were assayed by weighing the µl syringe charged with liquid before and after transfer of the liquid to the NMR tube. A solution of **4** (0.158 mmol) in CD_2Cl_2 (0.5 mL) showed signals at 2.304 (CH_2) and 2.625 ppm (CH_3), respectively. After addition of CF_3COOH (0.131 mmol; 0.83 equiv) the signals shifted to 2.491 and 2.896 ppm, respectively, yielding extrapolated shifts for $[\mathbf{4}\cdot\mathrm{H}]^+$ of 2.514 and 2.922 ppm. Addition of **1** caused signals to move back to 2.327 and 2.67 ppm leading to mole fractions of $[\mathbf{4}\cdot\mathrm{H}]^+$ from both signals of 0.109 and 0.151, respectively, mean 0.13, leading to a ratio of concentrations $c(\mathbf{4})/c\{[\mathbf{4}\cdot\mathrm{H}]^+\} = 6.69$. The amount of protons transferred is thus, 0.11 mmol, which gives $c\{[\mathbf{1}\cdot\mathrm{H}]^+\}/c(\mathbf{4}) = 2.306$ leading finally to

$$K_b(1) = K_b(4)\frac{c(4)\cdot c\{[1\cdot\mathrm{H}]^+\}}{c\{[4\cdot\mathrm{H}]^+\cdot c(1)\}} = 15\cdot K_b(4).$$

4.3. Determination of the structure of $[\mathbf{1}\cdot 2\mathrm{H}]^{2+}$ in the solid state

Suitable crystals of $\{[\mathbf{1}\cdot 2\mathrm{H}]^{2+}\}[PF_6^-]_2[H_2O]$ have been obtained from methanol. Diffraction data have been collected at 100 K on a BRUKER SMART CCD

diffractometer employing Mo K_α radiation. A total number of 16,839 reflections have been collected in the range $-16 \le h \le 15$, $-10 \le k \le 20$, and $-14 \le l \le 24$, merged to give 4668 independent reflections ($R_{int} = 0.05(7)$). The compound ($C_{15}H_{31}F_{12}N_3OP_2$) crystallizes in orthorhombic space group $P2_12_12_1(19)$ with the cell constants $a = 10.6331(21)$ Å, $b = 13.1431(26)$ Å, and $c = 15.8606(32)$ Å. At a molecular weight of 559.36, $Z = 4$, and a cell volume of 2216.5(8) Å^3 the density and the linear absorption coefficients are 1.676 g cm^{-3} and 0.311 mm^{-1}. No absorption correction. The structure has been solved by direct methods as implemented in the XTAL3.7 package of crystallographic routines,[16] employing GENSIN[17] to generate structure-invariant relationships and GENTAN[18] for the general tangent phasing procedure. Observed reflections (3722) ($I > 4\sigma(I)$) have been included in a full-matrix least squares refinement of 306 variables converging at $R(R_w) = 0.044(0.036$; $w = \sigma^{-2})$, a residual electron density of $-0.60/+0.88$ e Å^{-3}, and a goodness of fit of $S = 1.904$. Part of the hydrogen positions including the two ammonium protons could be located in a difference Fourier map. Both ammonium protons could be refined isotropically. The isotropic displacement factors of all other hydrogens have been fixed at 1.5 times the equivalent displacement factor of the relevant heavy atom and have been kept constant in the final refinement. The absolute configuration of $[\mathbf{1}\cdot 2H]^{2+}$ as shown in Figure 5 has been determined in a separate calculation by refinement of Flack's absolute structure parameter[19] ($X_{abs} = -0.025(100)$).[20]

Acknowledgements

We are grateful to the Deutsche Forschungsgemeinschaft (SPP 1118) and the Fonds der Chemischen Industrie for financial support. Thanks are due to Prof. Dr. Jörg Fleischhauer for helpful discussions and Dr. C. Lehmann (Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr) for data collection.

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Tetrahedron
Tetrahedron 61 (2005) 12377–12385

Regioselective formation of *N*-alkyl-3,5-pyrazole derived ligands. A synthetic and computational study

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Received 23 June 2005; revised 16 September 2005; accepted 19 September 2005

Available online 10 October 2005

Abstract—New *N*-alkyl-3,5-pyrazole derived ligands were synthesized by reaction between 3,5-pyrazole derived ligands and the appropriate haloalkane in toluene or THF using NaOEt or NaH as base. When the precursor ligand bears a pyridyl substituent the alkylation reaction presents a large regioselectivity. Theoretical calculations have been carried out to rationalize the experimental observations. It has been shown that regioselectivity is governed by the formation of Na^+-pyrazolide chelate complexes.

1. Introduction

Bidentate and tridentate nitrogen heterocyclic compounds containing six-membered rings such as 2,2′-bipyridine, 1,10-phenantroline and 2,2′:6′,2″-terpyridine have been extensively used in transition metal chemistry.[1,2] The key feature of these heterocycles is their π-electron deficiency. Hence they behave as good π-acceptors and in turn they provide soft sites for metal coordination. On the other hand, the π-excessive five-membered nitrogen heterocycle, pyrazole, is a poorer π-acceptor and behaves as a π-donor site.[3,4]

Convenient routes to aromatic heterocycles are of ongoing interest. Especially desirable are methods for synthesis of pyrazole derivatives for pharmaceutical evaluation,[5,6] as anti-inflammatory[7,8] and anti-tumour agents.[9–13] Pyrazoles also are of particular interest to the chemical community because they exhibit pesticide properties.[14,15] In particular, there is an increasing interest in pursuing the study of pyrazole-containing chelating ligands. During the last years three interesting review articles on biological model systems containing pyrazole chelates have been published.[16–18]

The synthesis and characterization of a family of 3,5-pyrazole derived ligands has been recently reported in the literature (Scheme 1).[19–22] The reactivity of some of these ligands with divalent metal ions has been studied in our laboratory.[20–28]

A common problem in the coordination chemistry of pyridyl-pyrazole ligands to metal ions is the low solubility of ligands and complexes in organic solvents, mainly caused by π–π stacking interactions. This solubility can be increased by incorporating an alkyl group at the N1-position of the pyrazole ring. In this work we report the synthesis and characterization of the several *N*-alkyl-3,5-pyrazole derived ligands (see Scheme 2), and a theoretical study of the alkylation mechanism. The synthetic path involves an intermolecular nucleophilic reaction (S_N2) at a carbon center of an alkyl halide. These kinds of reaction have been the subject of numerous theoretical studies.[29] The prototype reaction $Y^- + CH_3X \rightarrow CH_3Y + X^-$ has been extensively used to check the performance of different computational methods. In particular, it has been shown that density functional methods have a tendency to underestimate potential energy barriers.[30] Grisenko et al. have related this error to deficiencies of the GGA exchange functionals.[31] The use of hybrid exchange functionals leads to better results, but the transition states are still too low in energy.[32,33] In the last years Truhlar et al. have developed new hybrid density functionals designed to provide accurate potential energy barriers.[34–36] One of these methods, mPW1K, has been used by Martin et al. in the study of several S_N2 reactions, obtaining results in very good agreement with experimental data and highly correlated ab initio calculations.[37] In this work, the reactions between chloromethane and three different pyrazolide anions have

Keywords: *N*-alkyl-3,5-pyrazole derived ligands; *N*-alkylation; Regioisomers.
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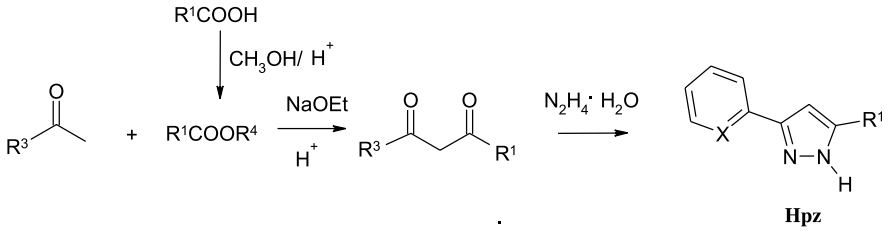
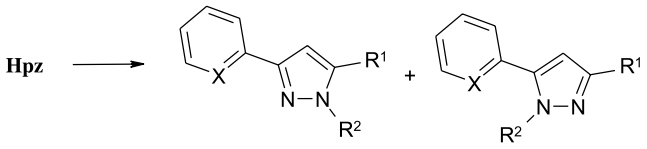
doi:10.1016/j.tet.2005.09.085



Hpz1: R^1 = Me, R^3 = Ph, R^4 = Et, X= CH
Hpz2: R^1 = o-Py, R^3 = Ph, R^4 = Me, X= CH
Hpz3: R^1 = Me, R^3 = o-Py, R^4 = Et, X= N
Hpz4: R^1 = CF_3, R^3 = o-Py, R^4 = Et, X= N

Scheme 1.



L1a/L1a': X=C, R^1=Me, R^2=octyl
L2a/L2a': X=N, R^1=Ph, R^2=octyl
L3a: X=N, R^1=Ph, R^2=octyl
L4a: X=N, R^1= CF_3, R^2=octyl
L1b/L1b': X=C, R^1=Me, R^2=Et
L2b/L2b': X=N, R^1= Ph, R^2=Et
L3b: X=N, R^1=Me, R^2=Et
L4b: X=N, R^1= CF_3, R^2=Et

L1c/L1c': X=C, R^1=Ph R^2=Me
L2c/L2c': X=N, R^1=Ph R^2=Me

Scheme 2.

been theoretically studied to rationalize the experimental results.

2. Results and discussion

2.1. Synthesis and characterisation

The ligands considered in this work are shown in Scheme 2. **L1a**, **L2a**, **L1b**, **L2b**, **L3b**, and **L4b** have been synthesized in this work for the first time, whereas the synthesis of **L2a**, **L3a** and **L4a** had already been reported in the literature.[22] **L1c** and **L2c** have been used as models of **L1b** and **L2b**, respectively, in the theoretical calculations.

The ligands have been obtained from their respective precursors (β-diketones and 3,5-pyrazole derived ligands). The β-diketones have been synthesized following a Claisen condensation of the appropriate ketones and esters, using NaOEt as base and dry toluene as solvent. This route has lead to 1-phenyl-3-pyridin-2-yl-propane-1,3-dione,[20,38] 1-phenyl-butane-1,3-dione,[39] 4,4,4-trifluoro-1-phenyl-butane-1,3-dione[22] and 1-pyridin-2-yl-butane-1,3-dione.[21] Further treatment of these compounds with hydrazine in dry toluene yielded the 3,5-pyrazole-derived ligands: **Hpz1**,[19] **Hpz2**,[20] **Hpz3**,[21] and **Hpz4**.[22]

For the procurement of ligands substituted at position 1, we have used two different *N*-alkylation methods (methods A and B).

In method A, the alkylating agents are iodoethane or 1-iodooctane, NaH is used as base and dry THF as solvent. The results obtained are summarized in Table 1. In method B, the alkylating agent is 1-bromoethane, the base NaOEt and the solvent dry toluene. This method has been used in the synthesis of the ligands **L1a/1a′**, **L2a/2a′** and **L4a/4a′** (Table 2). In general, method A leads to higher yields and shorter reaction times than method B. On the other hand, the observed regioselectivities are the same with both methods. The use of KO^{t}Bu as base was tested in method B, but the observed regioselectivities decreased.

All synthesized ligands have been characterised by elemental analysis, infrared spectra, ^{1}H and ^{13}C{^{1}H} NMR, and electrospray mass spectra. For the correct assignation of the carbons we have employed HMQC techniques.

The ratio of the regioisomers has been calculated through ^{1}H NMR experiments, especially from the integration of the pyrazolic proton.

The results obtained show that the regioselectivity is much larger when the precursor ligand bears a pyridyl group (**Hpz2**, **Hpz3** and **Hpz4**) than for **Hpz1**. The presence of the pyridyl group allows the formation of Na^+-chelate complexes which can play a determining role in the observed regioselectivity.

2.2. Computational study

We have studied the reactions of pyrazolides **pz1** and **pz2** with chloromethane. The structures of the pyrazolides are shown in Figure 1. For **pz2** we have considered two different conformers, *cis* and *trans*, associated to rotation around the

Table 1. Method A: synthetic data

	L1a/1a′	**L2a/2a′**	**L3a/3a′**	**L4a/4a′**	**L1b/1b′**	**L2b/2b′**	**L3b/3b′**	**L4b/4b′**
Pyrazole	**Hpz1** 0.66 g (4.2 mmol)	**Hpz2** 0.93 g (4.2 mmol)	**Hpz3** 0.67 g (4.2 mmol)	**Hpz4** 0.89 g (4.2 mmol)	**Hpz1** 0.66 g (4.2 mmol)	**Hpz2** 0.93 g (4.2 mmol)	**Hpz3** 0.67 g (4.2 mmol)	**Hpz4** 0.89 g (4.2 mmol)
$I(CH_2)_nCH_3$	($n=7$) 1.01 g (4.2 mmol)	($n=7$) 1.01 g (4.2 mmol)	($n=7$) 1.01 g (4.2 mmol)	($n=7$) 1.01 g (4.2 mmol)	($n=1$) 0.65 g (4.2 mmol)	($n=1$) 0.65 g (4.2 mmol)	($n=1$) 0.65 g (4.2 mmol)	($n=1$) 0.65 g (4.2 mmol)
Solvent	Dry THF (50 ml)	Dry THF (50 ml)	Dry THF (50 ml)	Dry THF (50 ml)	Dry THF (50 ml)	Dry THF (50 ml)	Dry THF (50 ml)	Dry THF (50 ml)
Base	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)	NaH 0.17 g (4.2 mmol)
Reaction time	48 h	48 h	48 h	48 h	48 h	48 h	48 h	48 h
Purification	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$	Extraction H_2O/ $CHCl_3$
Yield	0.91 g (80%)	1.33 g (95%)	0.80 (70%)	1.22 (90%)	0.74 g (95%)	0.84 g (80%)	0.59 (75%)	0.81 g (80%)
Regioselectivity	60:40	98:2	95:5	100:0	60:40	98:2	100:0	100:0

Hpz1, 5-methyl-3-phenyl-1*H*-pyrazole;[19] **Hpz2**, 2-(5-phenyl-1*H*-pyrazol-3-yl)-pyridine;[20] **Hpz3**, 2-(5-methyl-1*H*-pyrazol-3-yl)pyridine;[21] **Hpz4**, 2-(5-trifluoromethyl-1*H*-pyrazol-3-yl)pyridine.[22]

C–C bond between the pyridyl and pyrazole rings. The *trans* conformer is the most stable one and Table 3 presents the computed Gibbs energies associated to the *trans*/*cis* rearrangement.

We can observe that both the Gibbs reaction energy and the Gibbs activation energy decrease as the polarity of the solvent increases.

Figure 2 presents a schematic energy profile for the S_N2 reaction between chloromethane and a pyrazolide anion.

For the reactions of the pyzazolide anion **pz1** leading to the formation of regioisomers **L1c** and **L1c′** we have located the corresponding intermediates and transition states. The relative Gibbs energies of all the stationary points are presented in Table 4 and the structures of the transitions states are shown in Figure 3.

In the gas phase, the reactant-like ion-dipole complexes (INT1) are slightly more stable than the isolated reactants, but when the solvent effect is taken into account the intermediates become unstable. The product-like ion-dipole complexes (INT2) also become less stable than the reaction products in solution. For this reason we will focus our attention only in the transition states.

The Gibbs activation energies increase when we go from the gas phase reaction to the reaction in toluene and in THF. At the same time the reaction becomes more exergonic. This result is not surprising, since the solvent tends to stabilize the isolated reactants and products, where the negative charge is more localized.

Both in the gas phase and in solution the formation of the **L1c** regioisomer involves a lower Gibbs activation energy than the formation of **L1c′**. The differences between Gibbs activation energies are 2.5 kcal mol^{-1} for the reaction in toluene and 2.0 kcal mol^{-1} for the reaction in THF. These values are in qualitative agreement with the experimentally observed regioselectivity. The most favorable regioisomer involves the attack of chloromethane to the N atom closest to the methyl group of **pz1**. This process does not alter the electron delocalization to the phenyl group. On the other hand, in the transition state corresponding to the formation of **L1c′** a twisting of 22° around the C(pyrazole)–C(phenyl) bond is observed leading to a partial loss of conjugation. In the reaction product the twisting is 48°.

Given that the ion-dipole intermediates become unstable when the solvent effect is taken into account, for the reaction between **pz2** and chloromethane we have only studied the transition states corresponding to the formation of the two regioisomers **L2c**/**L2c′**. The structures of these transition states have been included in Figure 3 and the corresponding Gibbs activation energies are presented in Table 5.

There is a slight preference for the attack to the N closest to the phenyl group (**L2c**). In this case, the formation of both isomers involves loss of conjugation with an aromatic ring. Delocalization seems larger to the pyridyl ring than to phenyl. In fact, rotation around the C–C(pyridyl) ring involves a Gibbs activation energy of 11 kcal mol^{-1} (see

Table 2. Method B: synthetic data

	L1a/1a′	**L2a/2a′**	**L4a/4a′**
Pyrazole	**Hpz1** 0.66 g (4.2 mmol)	**Hpz2** 0.92 g (4.2 mmol)	**Hpz4** 0.89 g (4.2 mmol)
$Br(CH_2)_nCH_3$	(n=7) 0.81 g (4.2 mmol)	(n=7) 0.81 g (4.2 mmol)	(n=7) 0.81 g (4.2 mmol)
Solvent	Dry toluene (50 ml)	Dry toluene (50 ml)	Dry toluene (50 ml)
Base	NaOEt 0.28 g (4.2 mmol)	NaOEt 0.28 g (4.2 mmol)	NaOEt 0.28 g (4.2 mmol)
Reaction time	72 h	72 h	72 h
Purification	Extraction $H_2O/CHCl_3$	Extraction $H_2O/CHCl_3$	Extraction $H_2O/CHCl_3$
Yield	0.79 g (70%)	1.26 g (90%)	1.02 g (75%)
Regioselectivity	60:40	90:10	100:0

Hpz1, 5-methyl-3-phenyl-1*H*-pyrazole;[19] **Hpz2**: 2-(5-phenyl-1*H*-pyrazol-3-yl)pyridine;[20] **Hpz4**, 2-(5-trifluoromethyl-1*H*-pyrazol-3-yl)pyridine.[22]

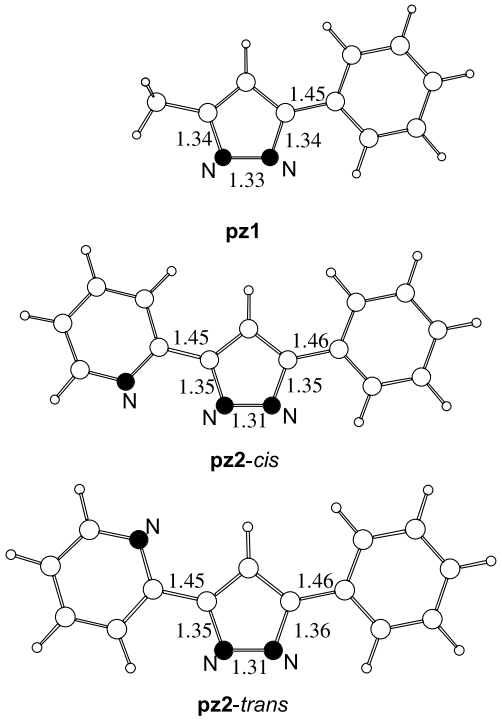


Figure 1. Structures of pyrazolides **pz1** and **pz2**. Selected interatomic distances in Å.

Table 3. Gibbs activation energy and Gibbs reaction energy[a] computed for the *trans*/*cis* rearrangement in pyrazolide **pz2** in the gas phase and in solution

	Gas phase	Toluene	THF
$\Delta G^{\ddagger}$	11.0	8.9	7.3
ΔG°	5.0	3.1	1.7

[a] At 1 atm and 298.15 K relative to the *trans* conformer. All values in kcal mol^{-1}.

Table 3), whereas for the rotation around C–C(phenyl) the Gibbs activation energy is only 7.3 kcal mol^{-1}.

The difference between Gibbs activation energies corresponding to the formation of **L2c** and **L2c′** isomers in solution are in the 0.5–0.6 kcal mol^{-1} range. These values are notably lower than those obtained for the reactions of **pz1** (Table 4). This result is not in agreement with experiments that show a large regioselectivity for the reaction of **pz2**.

We have considered the effect of complexation by Na^+.

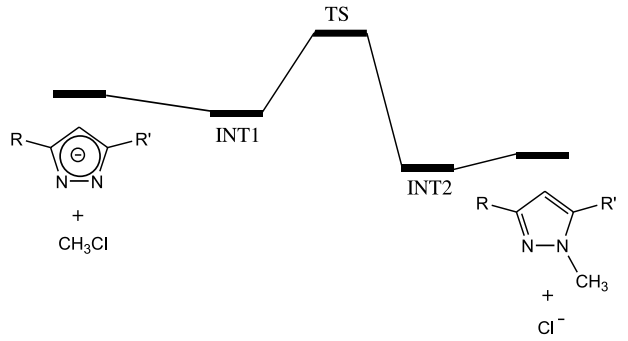


Figure 2. Schematic energy profile for the S_N2 reaction between chloromethane and a pyrazolide anion.

Table 4. Gibbs energies[a] relative to reactants computed for the stationary points corresponding to the reactions between chloromethane and pyrazolide **pz1**

Regioisomer	Stationary point	Gas phase	Toluene	THF
L1c	INT1	−1.0	6.0	9.9
	TS	12.9	19.9	24.1
	INT2	−28.2	−28.0	−29.9
	L1c+Cl^-	−19.8	−31.9	−36.8
L1c′	INT1	−1.0	6.2	10.2
	TS	15.9	22.4	26.1
	INT2	−24.4	−21.0	−19.3
	L1c′+Cl^-	−17.2	−28.7	−33.5

[a] At 1 atm and 298.15 K. All values in kcal mol^{-1}.

There are three different structures for the complex between **pz2** and Na^+, which are shown in Figure 4. The chelate complex is the most stable one and its Gibbs formation energy is −123.2 (gas phase), −61.7 (toluene), and −30.4 (THF) kcal mol^{-1}. Table 6 presents the computed relative Gibbs energies for these structures and for transition states that interconnect them.

We have located the transition states for the reaction between Na**pz2** and chloromethane and the results are shown in Figure 5 and Table 7.

The Gibbs activation energies are larger than the ones correspond the reaction of free **pz2** (see Table 5). However, in the gas phase and in toluene the transition states are below the **pz2**+Na^++CH_3Cl asymptote, while in THF they are 6.2 (**L2c**) and 12.8 (**L2c′**) kcal mol^{-1} above. So, complexation by Na^+ favors the reaction. Regarding the regioselectivity, Table 7 shows a clear preference for the formation of **L2c**. The difference between Gibbs activation

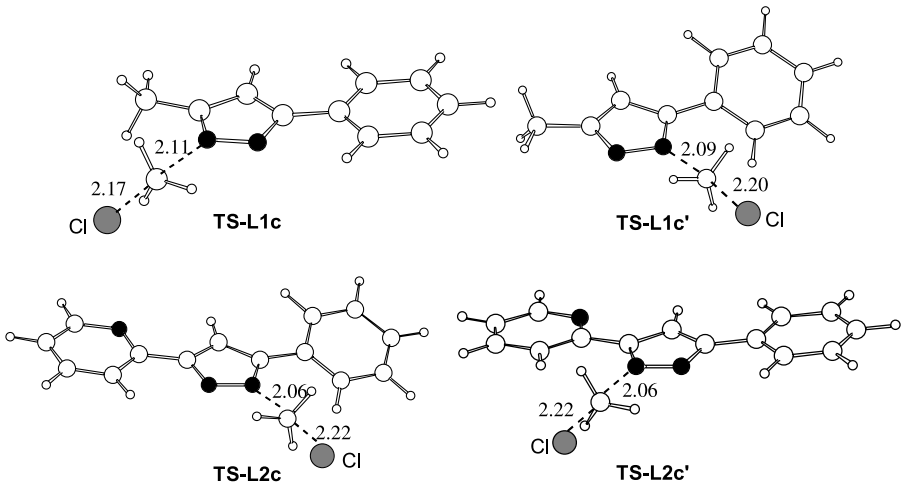


Figure 3. Structures of the transition states corresponding to the reactions of chloromethane with **pz1** (**TS-L1c** and **TS-L1c**′) and **pz2** (**TS-L2c** and **TS-L2c**′). Selected interatomic distances in Å.

Table 5. Gibbs activation energies[a] computed for the reactions between **pz2** and chloromethane

Regioisomer	Gas phase	Toluene	THF
L2c	18.6	24.2	27.0
L2c′	19.0	24.7	27.6

[a] At 1 atm and 298.15 K. All values in kcal mol^{-1}.

Table 6. Relative Gibbs energies[a] computed for the different structures Na**pz2** complex and the transition states connecting them

	Gas phase	Toluene	THF
TS(*chelate*/*cis*)	7.6	7.8	7.9
cis	5.5	5.3	5.4
TS(*cis*/*trans*)	11.7	11.6	11.5
Trans	5.9	5.5	5.3

[a] Relative to the chelate complex. At 1 atm and 298.15 K. All values in kcal mol^{-1}.

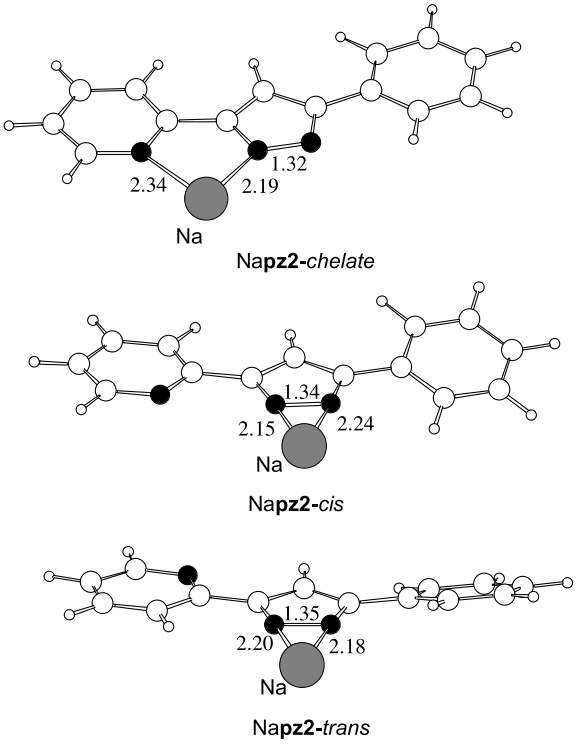


Figure 4. Structure of complexes between **pz2** and Na^+. Selected interatomic distances in Å.

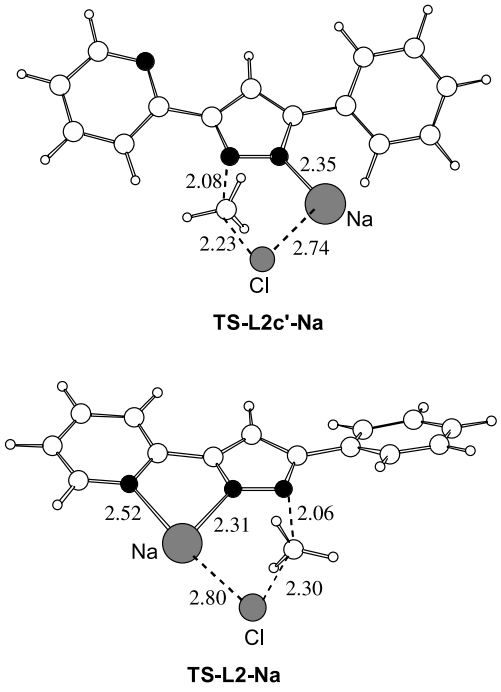


Figure 5. Structures of transition states corresponding to the reaction between methyl chloride and the Na**pz2** complex. Selected interatomic distances in Å.

energies is 7.5 kcal mol^{-1} in toluene and 6.6 kcal mol^{-1} in THF. These values agree well with the high regioselectivity experimentally observed. The formation of the chelate complex is the main factor governing the regioselectivity.

3. Conclusion

New *N*-alkyl-3,5-pyrazole derived ligands were synthesized by reaction between 3,5-pyrazole derived ligands and the

Table 7. Gibbs activation energies[a] computed for the reactions between Na**pz2** and chloromethane

Regoisomer	Gas phase	Toluene	THF
L2c	28.0	33.8	36.6
L2c′	36.6	41.3	43.2

[a] At 1 atm and 298.15 K referred to the Na**pz2**+CH_3Cl asymptote. All values in kcal mol^{-1}.

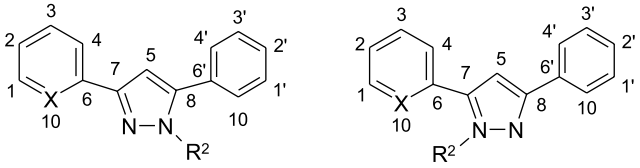


Figure 6. Numbering scheme for NMR data.

appropriate haloalkane. The most efficient procedure involves the use of NaH as base and THF as solvent. The alkylation reactions may lead to the formation of two different regioisomers. For the reactions of 5-methyl-3-phenyl-1*H*-pyrazole (**Hpz1**) the two regioisomers are formed in a 60:40 ratio. However, the presence of a pyridyl group as substituent leads to much larger regioselectivities. Theoretical calculations carried out to rationalize the experimental observations show that the formation of Na^+-pyrazolide chelate complexes plays a determinant role in the observed regioselectivity.

4. Experimental

4.1. General

Ligands were prepared under nitrogen atmosphere using the usual vacuum line and Schlenk techniques; solvents were dried and distilled by standard methods and deoxygenated in the vacuum line before used. All reagents were commercial grade and were used without further purification.

Analyses (C, N, H) were performed in our analytical laboratory on a Carlo Erba CHNS EA-1108 instrument. Electrospray Mass Spectra was obtained on an Esquire 3000 apparatus. Infrared spectra were recorded as NaCl pellets in the range 4000–500 cm^{-1} under a nitrogen atmosphere employing a Perkin-Elmer 2000. The ^1H and $^{13}C\{^1H\}$ NMR and HMQC spectra were obtained either on a Bruker AC-250 MHz. $CDCl_3$ is used as solvent in ^1H and $^{13}C\{^1H\}$ NMR and chemical shifts (δ) were determined relative to internal TMS and are given in ppm.

4.2. General procedure for the syntheses of the ligands: method A

NaH (0.17 g, 4.2 mmol) was suspended in THF (50 ml). To this suspension 4.2 mmol of the corresponding pyrazolic ligands (**Hpz1**, **Hpz2**, **Hpz3**, **Hpz4**) were added and the mixture was stirred until the evolution of hydrogen stopped. Then the iodoalcane (iodoethane, 1-iodooctane) (4.2 mmol) was added and the resulting solution was refluxed for 48 h. After removing the solvent in vacuo, the product was extracted from the oily residue with $H_2O/CHCl_3$. Ligands were obtained in 70–95% yields as oils with sufficient purity (^1H NMR). The separation of regioisomers was done by silica column chromatography using ethyl acetate except for ligand **L1a/1a′** where CH_2Cl_2 was used.

4.3. General procedure for the syntheses of the ligands: method B

NaOEt (0.28 g, 4.2 mmol) was dissolved in toluene (50 ml). To this solution 4.2 mmol of the corresponding pyrazolic ligands (**Hpz1**, **Hpz2**, **Hpz4**) were added and the mixture was stirred and heated under reflux for 1 h. Then the bromoalcane (1-bromooctane) (4.2 mmol) was added and the resulting solution was refluxed for 72 h. After removing the solvent in vacuo, the product was extracted from the oily residue with $H_2O/CHCl_3$. Ligands were obtained in 70–90% yields as oils with sufficient purity (^1H NMR) (Fig. 6). The separation of regioisomers was done by silica column chromatography using ethyl acetate.

4.3.1. 5-Methyl-1-octyl-3-phenyl-1*H*-pyrazole (L1a)/ 5-methyl-2-octyl-3-phenyl-1*H*-pyrazole (L1a′). $C_{18}H_{26}N_2$ (270.2): calcd: C, 80.00; H, 9.63; N, 10.37, found C, 80.02; H, 9.56; N, 9.98%. IR (NaCl, cm^{-1}) ν $(C–H)_{ar}$ 3060, ν $(C–H)_{al}$ 2926, ν $((C{=}N), (C{=}C))_{ar}$ 1549, δ $((C{=}N), (C{=}C))_{ar}$ 1457, δ $(C–H)_{ar,oop}$ 788, 760. MS (ESI): *m/z* (%)=293.2 $[MNa^+]$ (58%), 271.2 $[MH^+]$ (100%), 159.0 $[MH^+-(CH_2)_7CH_3]$ (7%). (**L1a**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$): δ=0.95 (t, ^3J=7.0 Hz, 3H, pz-$(CH_2)_7$–CH_3), 1.24–1.38 (m, 10H, pz-CH_2–CH_2–$(CH_2)_5$), 1.87–1.92 (m, 2H, pz-CH_2–CH_2), 2.31 (s, 3H, pz-CH_3), 4.07 (t, 2H, ^3J=7.0 Hz, pz-CH_2), 6.34 (s, 1H, H-5), 7.31 (t, $^3J_{2-1,3}$= 7.0 Hz, 1H, H-2), 7.85 (d, 2H, $^3J_{10,4-1,3}$=7.0 Hz, H-4, H-10), 7.42 (t, 2H, $^3J_{1,3-10,4}$=7.0 Hz, H-1, H-3). $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): δ=11.2 (pz-CH_3), 14.2 (pz-$(CH_2)_7$–CH_3), 22.8, 26.8, 29.4, 29.4, 30.6 (pz-CH_2–CH_2–$(CH_2)_5$), 31.9 (pz-CH_2–CH_2), 49.2 (pz-CH_2), 102.5 (C-5), 127.3 (C-2), 125.6 (C-1, C-3), 128.6 (C-4, C-10), 134.1, 139.1, 150.1 (C-6, C-7, C-8) ppm. (**L1a′**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$): δ=0.86 (t, ^3J=7.0 Hz, 3H, pz-$(CH_2)_7$–CH_3), 1.20–1.27 (m, 10H, pz-CH_2–CH_2–$(CH_2)_5$), 1.75–1.81 (m, 2H, pz-CH_2–CH_2), 2.32 (s, 3H, pz-CH_3), 4.03 (t, 2H, ^3J=7.0 Hz, pz-CH_2), 6.05 (s, 1H, H-5), 7.35–7.47 (m, 5H, H_{Py}).$^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): δ= 13.8 (pz-CH_3), 14.3 (pz-$(CH_2)_7$–CH_3), 22.9, 26.8, 29.3, 29.4, 30.9 (pz-CH_2–CH_2–$(CH_2)_5$), 32.0 (pz-CH_2–CH_2), 49.5 (pz-CH_2), 105.8 (C-5), 128.5 (C-2), 128.8–129.0 (C-1, C-3, C-4, C-10), 131.5, 144.5, 147.8 (C-6, C-7, C-8) ppm.

4.3.2. 2-(1-Octyl-5-phenyl)-1*H*-pyrazol-3-yl)-pyridine (L2a)/2-(2-octyl-5-phenyl-1*H*-pyrazol-3-yl)-pyridine (L2a′). $C_{22}H_{27}N_3$ (333.2): calcd C, 79.28; H, 8.11; N, 12.61, found C, 79.07; H, 8.39; N, 12.44%. IR (NaCl, cm^{-1}) ν $(C–H)_{ar}$ 3050, ν $(C–H)_{al}$ 2925, ν $((C{=}N), (C{=}C))_{ar}$ 1595, 1567, δ $((C{=}N), (C{=}C))_{ar}$ 1476, 1464, δ $(C–H)_{ar,oop}$ 787, 764. MS (ESI): *m/z* (%)=356.2 $[MNa^+]$ (100%), 334.2 $[MH^+]$ (69%), 222.9 $[MH^+-(CH_2)_7CH_3]$ (2%). (**L2a**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$): δ=0.86 (t, ^3J=7.0 Hz, 3H, pz-$(CH_2)_7$–CH_3), 1.21–1.27 (m, 10H, (pz-CH_2–CH_2–$(CH_2)_5$), 1.87 (m, 2H, pz-CH_2–CH_2), 4.18 (t, ^3J=7.0 Hz, 2H, pz-CH_2), 6.91 (s, 1H, H-5), 7.19 (dd, $^3J_{2-3}$=7.0 Hz, $^3J_{2-1}$=5.0 Hz, 1H, H-2), 7.46 (m, 5H, H_{Ph}), 7.72 (t,

$^3J_{3-2,4}=8.0$ Hz, 1H, H-3), 7.99 (d, $^3J_{4-3}=8.0$ Hz, 1H, H-4), 8.65 (d, $^3J_{1-2}=5.0$ Hz, 1H, H-1). $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=14.3$ (pz-$(CH_2)_7$–CH_3), 22.9–30.8 (pz-CH_2–CH_2–$(CH_2)_5$), 32.0 (pz-CH_2–CH_2), 50.2 (pz-CH_2), 105.0 (C-5), 122.5 (C-2), 128.8–129.2 (C_{Ph}, C-3), 120.3 (C-4), 150.0 (C-1), 131.2 (C-6′), 145.3, 150.9, 152.8 (C-6, C-7, C-8) ppm.

4.3.3. 2-(5-Methyl-1-octyl-1*H*-pyrazol-3-yl)-pyridine (L3a). $C_{17}H_{25}N_3$ (271.2) calcd: C, 75.23; H, 9.28; N, 15.48, found C, 75.20; H, 9.52; N, 16.08%. IR (NaCl, cm^{-1}) ν $(C–H)_{ar}$ 3061, ν $(C–H)_{al}$ 2925, ν ((C=N), $(C=C))_{ar}$ 1606, 1551, δ ((C=N), $(C=C))_{ar}$ 1456, 1441, δ $(C–H)_{ar,oop}$ 786, 762. MS (ESI): *m/z* (%)=294.2 [MNa^+] (54%), 272.2 [MH^+] (100%). ^1H NMR (250 MHz, 25 °C, $CDCl_3$ solution): $\delta=0.87$ (t, $^3J=7.0$ Hz, 3H, pz-$(CH_2)_7$–CH_3), 1.26–1.31 (m, 10H, pz-CH_2–CH_2–$(CH_2)_5$), 1.83–1.90 (m, 2H, pz-CH_2–CH_2), 2.33 (s, 3H, pz-CH_3), 4.07 (t, 2H, $^3J=7.3$ Hz, pz-CH_2), 6.62 (s, 1H, H-5), 7.15 (dd, $^3J_{2-3}=7.3$ Hz, $^3J_{2-1}=4.8$ Hz, 1H, H-2), 7.63 (dd $^3J_{2-3}=7.3$ Hz, $^3J_{3-4}=8.1$ Hz, 1H, H-3), 7.89 (dt, 1H, $^3J_{4-3}=8.1$ Hz, $J_{4-2,1}=1.1$ Hz, H-4), 8.60 (d, 1H, $^3J_{1-2}=4.8$ Hz, H-1). $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=11.3$ (pz-CH_3), 14.1 (pz-$(CH_2)_7$–CH_3), 22.7, 26.8, 29.2, 29.3, 30.5 (pz-CH_2–CH_2–$(CH_2)_5$), 31.8 (pz-CH_2–CH_2), 49.5 (pz-CH_2), 104.0 (C-5), 122.1 (C-2), 136.5 (C-3), 139.4 (C-8), 149.4 (C-1), 150.1 (C-7), 152.8 (C-6) ppm.

4.3.4. 2-(1-Octyl-5-trifluoromethyl-1*H*-pyrazol-3-yl)-pyridine (L4a). $C_{17}H_{22}N_3F_3$ (325.2) calcd: C, 62.75; H, 6.81; N, 12.91, found C, 62.72; H, 7.28; N, 13.39%. IR (NaCl, cm^{-1}) ν $(C–)_{ar}$ 3063, ν $(C–)_{al}$ 2960, ν ((C=N), $(C=C))_{ar}$ 1596, 1569, δ ((C=N), $(C=C))_{ar}$ 1456, 1416, ν (C–H) 1274, δ $(C–H)_{ar,oop}$ 789, δ (C–H) 743. MS (ESI): *m/z* (%)=348.2 [MNa^+] (20%), 326.2 [MH^+] (100%). ^1H NMR (250 MHz, 25 °C, $CDCl_3$ solution): $\delta=0.89$ (t, $^3J=7.0$ Hz, 3H, pz-$(CH_2)_7$–CH_3), 1.28–1.39 (m, 10H, pz-CH_2–CH_2–$(CH_2)_5$), 1.93–1.98 (m, 2H, pz-CH_2–CH_2), 4.26 (t, 2H, $^3J=7.0$ Hz, pz-CH_2–CH_2–$(CH_2)_5$), 7.20–7.28 (m, 1H, H-2), 7.24 (s, 1H, H-5), 7.73 (t, $^3J_{3-2,4}=7.0$ Hz, 1H, H-3), 7.95 (d, $^3J_{4-3}=8.0$ Hz, 1H, H-4), 8.64 (d, $^3J_{1-2}=5.0$ Hz,1H, H-1), $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=14.4$ (pz-$(CH_2)_7$–CH_3), 23.0, 26.9, 29.4, 29.5, 30.7 (pz-CH_2–CH_2–$(CH_2)_5$), 32.1 (pz-CH_2–CH_2), 52.0 (pz-CH_2), 106.2 (q, $^3J_{C,F}=2.4$ Hz, C-5), 120.4 (C-4), 120.5 (q, $^1J_{C,F}=268.7$ Hz, CF_3), 123.3 (C-2), 133.4 (q, $^2J_{C,F}=39.3$ Hz, C-8), 137.1 (C-3), 149.9 (C-1), 151.0, 151.5 (C-6, C-7) ppm.

4.3.5. 1-Ethyl-5-methyl-3-phenyl-1*H*-pyrazole (L1b)/2-ethyl-5-methyl-3-phenyl-1*H*-pyrazole (L1b′). $C_{12}H_{14}N_2$ (186.0): calcd C, 77.42; H, 7.53; N, 15.05, found C, 77.43; H, 7.96; N, 14.64%. IR (NaCl, cm^{-1}) ν $(C–)_{ar}$ 3061, ν $(C–)_{al}$ 2935, ν ((C=N), $(C=C))_{ar}$ 1605, 1552, δ ((C=N), $(C=C))_{ar}$ 1455, 1440 δ $(C–)_{ar,oop}$ 796, 765. MS (ESI): *m/z* (%)=209.0 [MNa^+] (50%), 187.0 [MH^+] (100%). (**L1b**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$): $\delta=1.47$ (t, $^3J=7$ Hz, 3H, pz-CH_2–CH_3), 2.33 (s, 1H, pz-CH_3), 4.15 (q, $^3J=7.0$ Hz, 2H, pz-CH_2–CH_3), 6.33 (s, 1H, H-5), 7.29 (t, $^3J_{3-2,4}=7.0$ Hz, 1H, H-2), 7.40 (t, $^3J_{10,4-1,3}=7.0$ Hz, 2H, H-10, H-4), 7.80 (d, $^3J_{1,3-2}=7.0$ Hz, 2H, H-1, H-3), $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=11.4$ (pz-CH_3), 15.8 (pz-CH_2–CH_3), 44.3 (pz-CH_2–CH_3), 102.9 (C-5) 127.6 (C-2), 125.8 (C-1, C-3), 128.8 (C-10, C-4), 134.3, 139.0, 150.3 (C-6, C-7, C-8) ppm. (**L1b′**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$ solution): $\delta=1.41$ (t, $^3J=7.0$ Hz, 3H, pz-CH_2–CH_3), 2.33 (s, 1H, pz-CH_3), 4.11 (q, $^3J=7.0$ Hz, 2H, pz-CH_2–CH_3), 6.07 (s, 1H, H-5), 7.39–7.49 (m, 5H, H-1, H-2, H-3, H-4, H-10) ppm. $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=13.8$ (pz-CH_3), 16.2 (pz-CH_2–CH_3), 44.4 (pz-CH_2–CH_3), 105.9 (C-5) 128.6 (C-2), 128.9–129.0 (C-1, C-3, C-4, C-10), 131.6, 144.6, 147.9 (C_6, C_7, C_8) ppm.

4.3.6. 2-(1-Ethyl-5-phenyl-1*H*-pyrazol-3-yl)-pyridine (L2b)/2-(2-ethyl-5-phenyl-1*H*-pyrazol-3-yl)-pyridine (L2b′). $C_{16}H_{15}N_3$ (249.1): calcd C, 77.11; H, 6.02; N, 16.87, found C, 77.18; H, 5.84; N, 16.15%. IR (NaCl, cm^{-1}) ν $(C–H)_{ar}$ 3052, ν $(C–H)_{al}$ 2975, ν ((C=N), $(C=C))_{ar}$ 1595, 1567, δ ((C=N), $(C=C))_{ar}$ 1475, δ $(C–H)_{ar,oop}$ 788, 766. MS (ESI): *m/z* (%)=272.1 [MNa^+] (46%), 250.1 [MH^+] (100%), 222.0 [$MH^+-CH_2CH_3$] (3%). (**L2b**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$): $\delta=1.41$ (t, $^3J=7.0$ Hz, 3H, pz-CH_2–CH_3), 4.19 (q, $^3J=7.0$ Hz, 2H, pz-CH_2–CH_3), 6.87 (s, 1H, H-5), 7.13 (t, $^3J_{2-1,3}=5.0$ Hz, 1H, H-2), 7.40 (m, 5H, H_{Ph}), 7.66 (t, $^3J_{3-2,4}=8.0$ Hz, 1H, H-3), 7.93 (d, $^3J_{4-3}=8.0$ Hz, 1H, H-4), 8.60 (d, $^3J_{1-2}=5.0$ Hz, 1H, H-1) ppm. $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=15.7$ (pz-CH_2–CH_3), 44.7 (pz-CH_2–CH_3), 104.6 (C-5), 119.8 (C-4), 122.1 (C-2), 128.6 (C_{Ph}), 136.3 (C-3), 149.2 (C-1), 130.5, 144.5, 150.5, 152.2 (C-6, C-7, C-8, C-6′) ppm. (**L2b′**) ^1H NMR (250 MHz, 25 °C, $CDCl_3$): $\delta=1.51$ (t, $^3J=7.0$ Hz, 3H, pz-CH_2–CH_3), 4.19 (q, $^3J=7.0$ Hz, 2H, pz-CH_2–CH_3), 6.88 (s, 1H, H-5), 7.26 (m, 1H, H-2), 7.33 (t, $^3J_{2'-1',3'}=7.0$ Hz, 1H, H-2′), 7.44 (m, 2H, H-1′, H-3′), 7.89 (d, $^3J_{10',4'-3',1'}=7.0$ Hz, 2H, H-10′, H-4′), 7.77 (t, $^3J_{3-2,4}=8.0$ Hz, 1H, H-3), 7.64 (d, $^3J_{4-3}=8.0$ Hz, 1H, H-4), 8.70 (d, $^3J_{1-2}=5.0$ Hz, 1H, H-1) ppm. $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=16.4$ (pz-CH_2–CH_3), 46.9 (pz-CH_2–CH_3), 104.0 (C-5), 122.8 (C-2), 123.2 (C-4) 126.0 (C-4′, C-10′), 127.9 (C-2′), 129.0 (C-1′, C-3′), 137.0 (C-3), 149.7 (C-1), 133.9, 142.3, 150.4, 150.5 (C-6, C-7, C-8, C-6′) ppm.

4.3.7. 2-(1-Ethyl-5-methyl-1*H*-pyrazol-3-yl)-pyridine (L3b). $C_{11}H_{13}N_3$ (187.0) calcd: C, 70.56; H, 7.00; N, 22.44, found C, 70.17; H, 7.34; N, 23.18%. IR (NaCl, cm^{-1}) ν $(C–H)_{ar}$ 3061, ν $(C–H)_{al}$ 2979, ν ((C=N), $(C=C))_{ar}$ 1592, 1566, δ ((C=N), $(C=C))_{ar}$ 1499, δ $(C–H)_{ar,oop}$ 785. MS (ESI): *m/z* (%)=210.0 [MNa^+] (100%), 188.0 [MH^+] (31%). ^1H NMR (250 MHz, 25 °C, $CDCl_3$ solution): $\delta=1.46$ (t, $^3J=7.0$ Hz, 3H, pz-CH_2–CH_3), 2.33 (s, 3H, pz-CH_3), 4.16 (q, 2H, $^3J=7.0$ Hz, pz-CH_2–CH_3), 6.62 (s, 1H, H-5), 7.15 (ddd, $^3J_{2-3}=8.0$ Hz, $^3J_{2-1}=4.0$ Hz, $^4J_{2-4}=1.0$ Hz, 1H, H-2), 7.68 (td, $^3J_{3-2,4}=7.0$ Hz, $^4J_{3-1}=2$Hz, 1H, H-3), 7.88 (d, $^3J_{4-3}=8.0$ Hz, 1H, H-4), 8.61 (d, $^3J_{1-2}=5.0$ Hz, 1H, H-1), $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=11.5$ (pz-CH_3), 15.9 (pz-CH_2–CH_3), 44.6 (pz-CH_2–CH_3), 104.4 (C-5), 120.2 (C-4), 122.4 (C-2), 136.8 (C-3), 139.4 (C-8), 149.8 (C-1), 150.5 (C-7), 153.0 (C-6).

4.3.8. 2-(1-Ethyl-5-trifluoromethyl-1*H*-pyrazol-3-yl)-pyridine (L4b). $C_{11}H_{10}N_3F_3$ (241.0): calcd: C, 54.77; H, 4.15; N, 17.43, found C, 54.32; H, 4.36; N, 17.85%. IR (NaCl, cm^{-1}) ν $(C–H)_{ar}$ 3061, ν $(C–H)_{al}$ 2962, ν ((C=N), $(C=C))_{ar}$ 1597, 1558, δ ((C=N), $(C=C))_{ar}$ 1448, 1417, δ $(C–H)_{ar,oop}$ 788. MS (ESI): *m/z* (%)=264.0 [MNa^+] (3%), 242.0 [MH^+] (100%), 214.0 [$MH^+-CH_2CH_3$] (3%). ^1H

NMR (250 MHz, 25 °C, $CDCl_3$ solution): $\delta=1.51$ (t, $^3J=$ 7.0 Hz, 3H, pz-CH_2–CH_3), 4.31 (q, $^3J=7.0$ Hz, 2H, pz-CH_2–CH_3), 7.18 (m, 1H, H-2), 7.22 (s, 1H, H-5), 7.69 (td, $^3J_{3-2,4}=7.0$ Hz, $^3J_{3-1}=2.0$ Hz, 1H, H-2), 7.92 (t, $^3J_{4-3}=$ 8.0 Hz, 1H, H-4), 8.60 (d, $^3J_{1-2}=3.0$ Hz, 1H, H-1), $^{13}C\{^1H\}$ NMR (63 MHz, 25 °C, $CDCl_3$): $\delta=15.8$ (pz-CH_2–CH_3), 46.8 (pz-CH_2–CH_3), 106.2 (q, $^3J_{C,F}=2$ Hz, C-5), 120.2 (C-4), 120.4 (q, $^1J_{C,F}=269$ Hz, CF_3), 123.1 (C-2), 134.5 (q, $^2J_{C,F}=40$ Hz, C-8), 136.9 (C-3), 149.7 (C-1), 151.4, 151.1, (C-6, C-7) ppm.

4.4. Computational details

All calculations have been done using the Gaussian-98 program.[40] Geometries have been fully optimized using the mPW1K[34–36] density functional method with the 6-31+G(d) basis set. This functional is a modification of the MPW1PW91 hybrid functional derived by Adamo and Barone[41] from the exchange and correlation functional of Perdew and Wang.[42] The amount of Hartree–Fock exchange has been obtained by minimizing the average deviation between computed and experimental potential energy barriers for a set of 40 reactions.[34–36] Harmonic vibrational frequencies have been computed for all structures to characterize them as energy minima (all frequencies are real) or transition states (one and only one imaginary frequency). Energies have been recalculated using the 6-311+G(2d,p) basis set. The effect of solvation by toluene ($\varepsilon=2.379$) and THF ($\varepsilon=7.58$) has been included using the CPCM method[43,44] for the gas phase optimized geometries.

Acknowledgements

Support by the Spanish Ministerio de Educación y Ciencia (Projects BQU-2003-03582 and CTQ2004-01067) is gratefully acknowledged.

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Ionic liquid phase technology supported the three component synthesis of Hantzsch 1,4-dihydropyridines and Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones under microwave dielectric heating

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Received 22 July 2005; revised 15 September 2005; accepted 15 September 2005

Available online 26 October 2005

Abstract—A microwave dielectric heating assisted liquid phase synthesis of 1,4-dihydropyridines, 3,4-dihydropyrimidin-2(1*H*)-ones, pyridines and polyhydroquinolines using task-specific ionic liquid as a soluble support was described. The efficiency of the ionic liquid phase organic synthesis (IoLiPOS) methodology was demonstrated by using a one-pot three component condensation. The structure of the intermediates in each step was verified routinely by spectroscopic analysis and, after cleavage the target compounds were obtained in good yields and high purities.

1. Introduction

Faced with the increasing demand of novel drug targets, there is considerable current interest to accelerate the technologies associated with combinatorial chemistry and high-throughput synthesis.[1] The initial efforts were focused on the use of automated solid phase organic synthesis (SPOS) based on the original Merrifield method for the preparation of peptides[2] and oligonucleotides, by taking advantage of simple filtration techniques to wash off the excess reagents and by-products from the desired polymer bound product. However, one disadvantage of this methodology compared to standard solution-phase synthesis is the comparatively long reaction times that are usually required owing to the heterogeneous reaction conditions involving insoluble polymer supports and the difficulties to monitor reaction progress. The use of these cross-linked polystyrene based resins[3] is important due to their good stability, high compatibility and good swelling characteristic with non-polar solvents.[4] Nevertheless, these resins fail when polar solvents are needed due to hindered accessibility to the reactive sites.[5] Polystyrene can be modified by grafting poly(ethyleneglycol) to the hydrophobic core to produce a polymer that swells in both non-polar and polar solvents.[6] Among these PEG-grafted polystyrene supports (PS-*g*-PEG), TentaGel has been used extensively in solid phase synthesis because of the mechanical stability of the beads and swelling properties in organic and aqueous media.[7] ArgoGel displays a similar characteristic to TentaGel yet swells more extensively because of a higher PEG content.[8] Liquid phase combinatorial synthesis offers several advantages: the large excess of reagents typically used in solid-supported synthesis is normally not required in liquid-phase organic synthesis (LPOS), reactions may be carried out in homogeneous solution and purification is possible after each step.[9] The chemistry of PS-*g*-PEG and PEG-resins is not limited by the hydroxyl group (sometimes its weak nucleophilicity restricts the resin from wide application), and conversion of the hydroxyl group is possible by using standard methods.[10]

The utility of microwave irradiation (mw) to carry out organic reactions has now become a regular feature. This is evident from the increasing number of reviews and books[11]

Keywords: Ionic liquid phase; Hantzsch reaction; Biginelli reaction; Oxidation; Pyridine; Polyhydroquinoline; Three component synthesis; Microwave.
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doi:10.1016/j.tet.2005.09.118

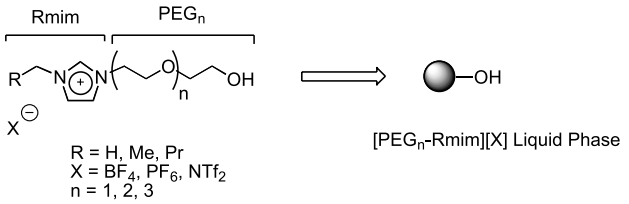


Figure 1. PEG-ionic liquid matrices used for ionic liquid phase organic synthesis (IoLiPOS).

published on the use of microwave technology for carrying out organic reactions. The main benefits of performing reactions under microwave irradiation conditions are the significant rate-enhancements and the higher product yields that can be observed. It is clear that the application of microwave technology to rapid synthesis of potential biological molecules on liquid phases or hybrid polymers and solid phases is a useful tool for the combinatorial and/or medicinal community, for whom reaction speed is of great importance.[12]

Recently, we have shown that the use of task-specific ionic liquids[13] (TSILs) on which poly(ethyleneglycol) units are grafted (Fig. 1), can be used as alternatives to classical soluble polymeric matrices in combinatorial chemistry.[14] This new class of soluble support used in ionic liquid phase organic synthesis (IoLiPOS) methodology was valided by examples in various chemistries.[15] An attracting feature of ionic liquid phases is that their solubilities can be turned readily, so they can phase separate from organic as well as aqueous media, depending on the choice of cation and anions. An illustration of ionic liquid phase supported synthesis is given in Figure 2. After the first reactant is anchored to an ionic liquid phase (ILP), the excess reagents and byproducts in subsequent reactions can be removed easily by simple solvent washing. The advantages offered by the use of PEG-ionic liquid phases (PEG-ILPs) are: (i) the possibility of homogeneous reaction, (ii) the compatibility to standard analytical methods, (iii) the high loading capacity, (iv) the routine product isolation by simple extraction and washings, (v) the high absorption of microwave energy by which the reaction rate is accelerated remarkably. In connection with our research program on exploitation of the PEG-ILPs as tools in liquid phase organic synthesis (LPOS), we choose to explore now the 1,4-dihydropyridines and 1,4-dihydropyrimidines as new heterocyclic scaffolds on PEG-ILPs. Hantzsch 3,4-dihydropyridines[16] and Biginelli 1,4-dihydropyrimidines[17] are a biological, medicinally and synthetically important class of compounds in the field of drugs and pharmaceuticals.

2. Results and discussion

For this study (Scheme 1), we have chosen to examine the

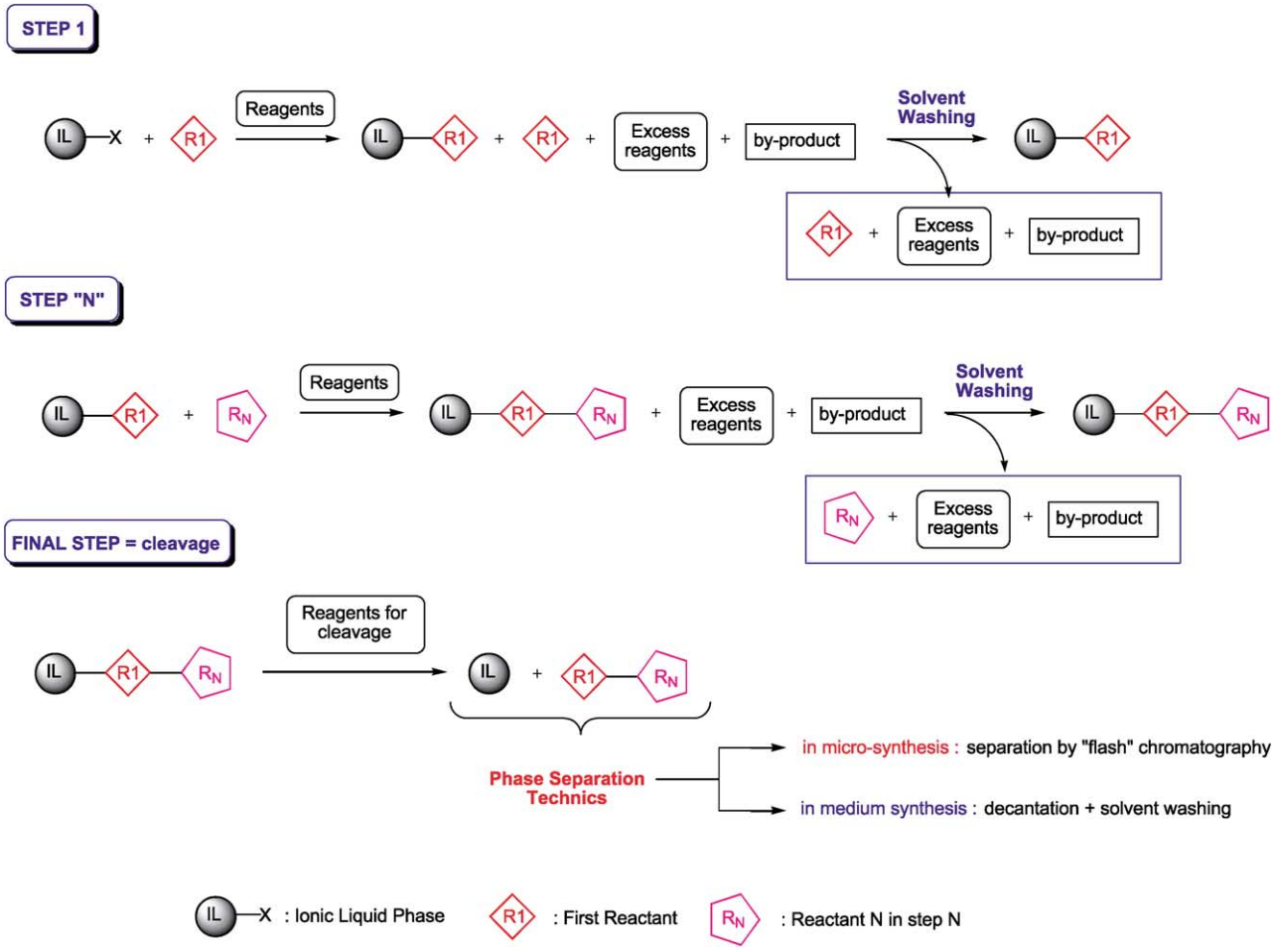
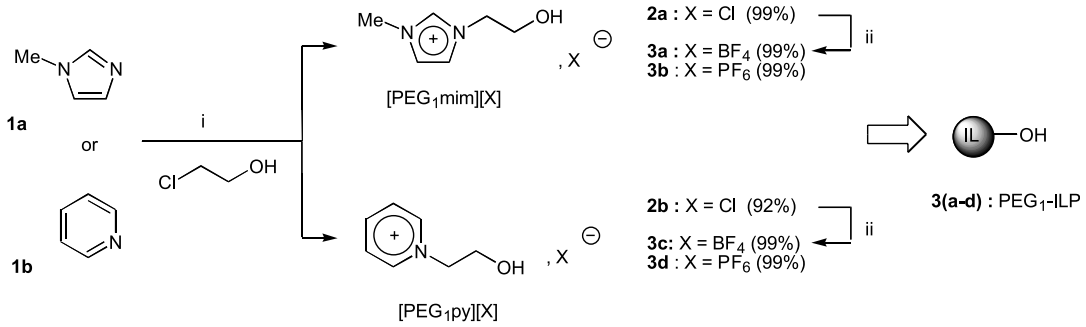


Figure 2. General concept of ionic liquid phase organic synthesis (IoLiPOS).



Scheme 1. Reagents and reactions conditions: (i) chloroethanol (1 equiv), mw: 180 °C (power level: 20%, 60 W), 10 min, N_2; (ii) NH_4BF_4 or KPF_6 (1 equiv), MeCN, 80 °C, 24 h.

Table 1. Starting ILPs used and prepared

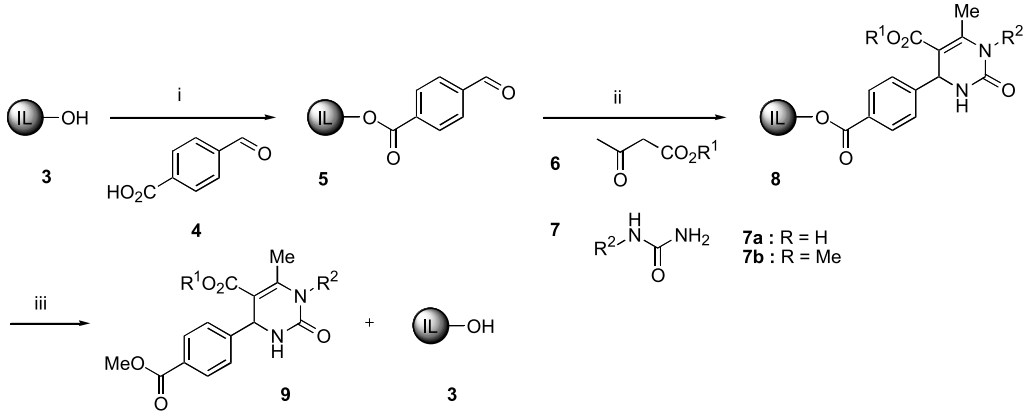
Product	Cation	Anion	Yield (%)[a]
2a	[PEG_1mim]	Cl	99
3a	[PEG_1mim]	BF_4	99
3b	[PEG_1mim]	PF_6	99
2b	[PEG_1py]	Cl	92
3c	[PEG_1py]	BF_4	99
3d	[PEG_1py]	PF_6	99

[a] Yield of isolated product.

chemical properties of the respective 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate **3a** or hexafluoroborate **3b** (**3a**: [PEG_1mim][BF_4], **3b**: [PEG_1mim][PF_6]) and *N*-(2-hydroxyethyl)pyridinium tetrafluoroborate **3c** or hexafluoroborate **3d** (**3c**: [PEG_1py][BF_4], **3d**: [PEG_1py][PF_6]) in IoLiPOS methodology. The starting PEG-ILPs **3**(**a**,**b**) were synthesized according to our previous method[18] (Table 1).

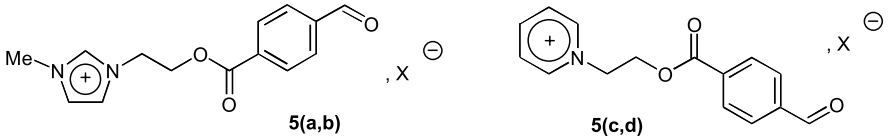
Esterification of PEG-ILPs **3**(**a**–**d**) with 4-formylbenzoic acid **4** were realised in dry MeCN with dicyclohexylcarbodiimide[19] (DCC) and 5% of dimethylamino pyridine[20] (DMAP) as catalyst and afforded the functionalized ILP bound aldehydes **5** in high yields (Scheme 2). During the work-up, insoluble dicyclohexyl urea (DCHU) was easily removed by filtration to ensure the final purity of aldehydes **5** and the resulting ILPs **5** were washed with AcOEt (1:5 w/v). The structure of ILPs **5** was ascertained by mass spectrometry and proton NMR, confirming that the major compound is the expected aldehydes **5** (Table 2).

With the desired ILP bound aldehydes **5** in hand, we have



Scheme 2. Reagents and reactions conditions: (i) DCC (1 equiv), DMAP (5%), dry MeCN, rt, 24 h; (ii) **6** (1 equiv), **7** (3 equiv), concd HCl (0.5%), mw: 120 °C (power level: 50%, 150 W), 10 min; (iii) MeONa (1 equiv), MeOH, reflux, 18 h.

Table 2. Results for the preparation of aldehydes **5**(**a**–**d**) from ILPs **3**(**a**–**d**) and 4-formylbenzoic acid **4**



Product	Anion	Yield (%)[a]
5a	BF_4	96
5b	PF_6	95
5c	BF_4	98
5d	PF_6	98

[a] Yield of isolated product.

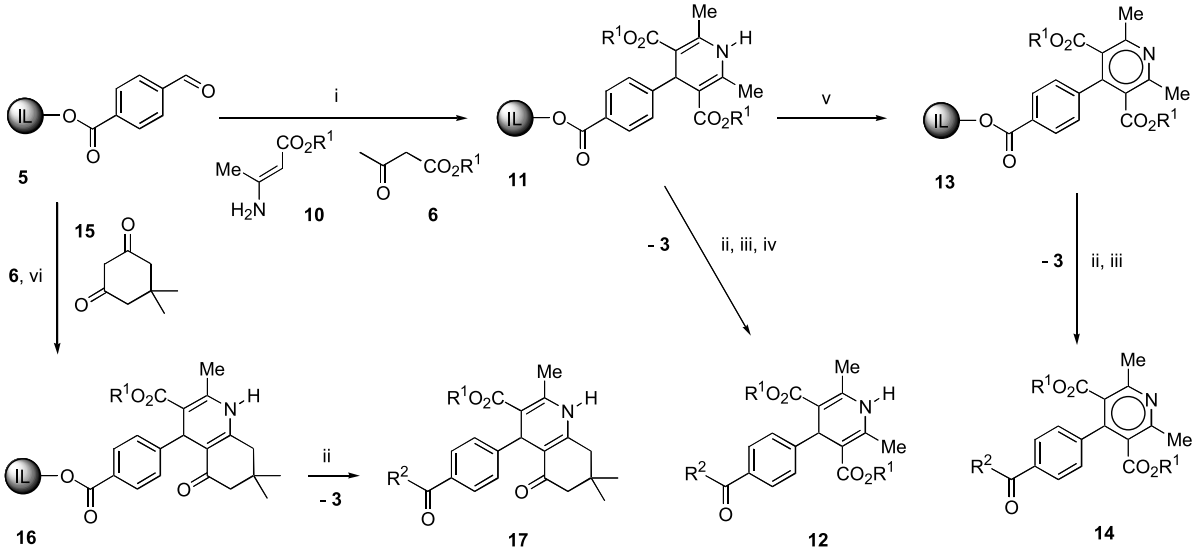
Table 3. Results for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones **8**(**a**–**d**) and **9a** from aldehydes **5**, β-ketoesters **6**(**a**,**b**) and ureas **7**(**a**,**b**)

Compound	Starting products	R^1	R^2	Reaction conditions	Yield (%)[a]
8a	**5d**+**6a**+**7a**	Me	H	120 °C, 10 min, mw[b]	86
8b	**5d**+**6b**+**7a**	Et	H	120 °C, 10 min, mw[b]	80
8c	**5d**+**6a**+**7b**	Me	Me	120 °C, 10 min, mw[b]	83
8c′	**5b**+**6a**+**7b**	Me	Me	110 °C, 1 h.[c]	88
8d	**5b**+**6b**+**7b**	Et	Me	110 °C, 1 h.[c]	87
9a	**8a**	Me	H	MeOH, Δ, 18 h[d]	80

[a] Yield of isolated product after purification.
[b] mw=under microwave irradiation (Power level: 50%, 150W).
[c] Neat conditions.
[d] Catalyst: MeONa (1 equiv).

examined the Biginelli 3,4-dihydropyrimidine (3,4-DHPM) synthesis (Scheme 2). For the 3,4-DHPM preparation, we have used a one-pot three component formation[21] under microwave[22] for a rapid synthesis of ILP bound 3,4-DHPMs **8**. A stoichiometry of 1/1.06/3 of IL-phase **5d**/β-ketoester **6**/ urea **7**, respectively, was found to react completely without solvent in the three component Hantzsch condensation at 120 °C under microwave exposure (120 W, 50% power level) during 10 min with two drops of concentrated HCl as catalyst. In the same manner, the reaction of IL-phase **5b** with β-ketoester **6**(**a**,**b**) and urea **7** produced, respectively, the desired 3,4-DHPMs **8c′** and **8d** using neat conditions (110 °C, 1 h). The excess of urea (**7a**: R=H or **7b**: R=Me) could be removed by simple washings with cold deionized water (1:10 w/v), due to the low miscibility of the ILPs **8** in cold water. Finally, the ILP **8a** was treated with sodium methoxide (1 equiv) in refluxed MeOH for 24 h. On completion of the cleavage step (monitored by TLC or ^{1}H NMR), the solvent was removed in vacuo, and the expected ester **9a** was obtained in good yields (Table 3) by precipitation in cold water. The 3,4-DHPM methyl ester **9a** was characterized by conventional techniques (^{1}H, ^{13}C NMR and HRMS) and the purity was controlled by HPLC.

In order to determine the ability of the ILP **5** in ionic liquid-phase combinatorial synthesis, we have also checked the reactivity of the aldehyde covalently grafted on the IL-phase in Hantzsch condensation (Scheme 3). For the synthesis of ILP bound aryl-1,4-dihydropyridine **11** (1,4-DHP) under microwave irradiation, we have studied two experimental procedures: (a) in the first method, the ILP **5** was treated with 1 equiv of β-ketoester **6** (**6a**: R=Me, **6b**: R=Et) and 1 equiv of aminocrotonate **10** (**10a**: R=Me, **10b**: R=Et) to form the Il-phases **11** using solvent-free conditions associated with microwave irradiation (120 °C, 150 W, 50% power level, time exposure: 10 min), (b) in the second method the Il-phase bound 1,4-DHP **11** was prepared by an one-pot three component condensation from β-ketoester **6** (2 equiv) and NH_4AcO (2 equiv) using the same microwave reaction conditions (120 °C, 10 min). Following AcOEt or Et_2O washings (1:10 w/v) of the IL-phase, the bound products **11** were subjected to cleavage by: (a) transesterification with 30% of MeONa in refluxed MeOH during 18 h, (b) saponification with 60% of LiOH in THF at room temperature, followed by controlled acidification with a solution of 3 M HCl or (c) ester aminolysis with propylamine or butylamine (10 equiv) under microwave (80 °C, 15 min). Owing to the small quantities of the starting IL-phase bound 1,4-DHP **11** (~500 mg) used in the cleavage step, the desired compounds **12**(**a**–**c**) were purified by filtration on alumina gel using AcOEt–DCM (1/1) as washing eluent (Table 4). Next, the IL-phase bound 1,4-



Scheme 3. Reagents and reactions conditions: (i) method A: **6** (1 equiv), **10** (1 equiv), mw: 120 °C (power level: 50%, 150 W), 10 min or method B: **6** (2 equiv), NH_4AcO (2 equiv), mw: 120 °C (power level: 50%, 150 W); (ii) MeONa 30%, MeOH, reflux, 18 h; (iii) LiOH 60%, THF, rt, 20 h then 3 M HCl; (iv) $PrNH_2$ or $BuNH_2$ (10 equiv), mw: 80 °C (power level: 50%, 150 W), 15 min; (v) DDQ (1.1 equiv), DCM, reflux, 2 h; (vi) **15** (1 equiv), **6** (1 equiv), NH_4AcO (1 equiv), mw: 120 °C (power level: 50%, 150 W), 10 min.

Table 4. Results for the preparation of various Hantzsch 1,4-dihydropyridines, pyridines and polyhydroquinolines

Compound	Starting products	R^1	R^2	Yield (%)[a]
11a	**5d**+**10a**[b]	Me	—	94
11a	**5d**+**6a**[c]	Me	—	96
11b	**5d**+**10b**[b]	Et	—	95
11b	**5d**+**6b**[c]	Et	—	97
12a	**11a**+MeONa[d]	Me	OMe	86
12b	**11b**+MeONa[d]	Et	OMe	85
12c	**11a**+LiOH, HCl	Me	OH	85
12d	**11a**+$PrNH_2$	Me	$NH(CH_2)_2Me$	45
12e	**11a**+$BuNH_2$	Me	$NH(CH_2)_3Me$	35
13a	**11a**+DDQ	Me	—	90
13b	**11a**+DDQ	Et	—	88
14a	**13a**+MeONa[d]	Me	OMe	94
14b	**13b**+MeONa[d]	Et	OMe	90
14c	**13b**+LiOH, HCl	Et	OH	87
16a	**5d**+**10a**+**15**	Me	—	97
16b	**5d**+**10b**+**15**	Et	—	90
17a	**16a**+MeONa[d]	Me	OMe	85
17b	**16b**+MeONa[d]	Et	OMe	80

[a] Yield of isolated product after purification.
[b] Method A.
[c] Method B.
[d] MeONa as catalyst (1 equiv).

DHP **11** was also submitted to oxidation[23] with DDQ (1.1 equiv) in refluxed DCM for 2 h to afford the corresponding bound pyridines **13**(**a**,**b**) (quantitative conversion by ^1H NMR). After removal solvent in vacuo, the expected pyridines **13**(**a**,**b**) were separated from $DDQH_2$ by filtration on a small pad of alumina gel with DCM-MeOH (95/5) as eluent. Subsequent cleavage (transesterification or saponification–acidification methods) of the pyridines **13** led, respectively, to the esters **14**(**a**,**b**) and the acid **14c** in good yields (87–94%) (Table 4).

Having established the effectiveness of IL-phase **5** in the synthesis of 1,4-DHPs[24] and pyridines,[25] we set out to explore its potential in the preparation of polyhydroquinoline[26] derivatives under microwave conditions. Solvent-free addition of dimedone **15** (1 equiv), β-ketoester **6** (1 equiv) and NH_4AcO (1 equiv) to the IL-phase bound aldehyde **5** at 120 °C (150 W, 50% power level, time exposure: 10 min) provided the desired compounds **16** (Table 4). After washing with Et_2O (1:10 w/v), the ILP intermediates **16** were cleaved under basic conditions (MeONa 30%) in refluxing MeOH (18 h) and the structure of **17**(**a**,**b**) was confirmed by ^1H, ^{13}C NMR and HRMS.

3. Conclusion

In conclusion, we have demonstrated that the combination of IL-phase bound aldehyde and microwave dielectric heating allows a rapid and practical preparation of Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones, Hantzch 1,4-dihydropyridines, pyridines by oxidation and polyhydroquinolines[27] using a one-pot three component methodology. The specific advantages of the IoLiPOS methodology are the following: (i) the reactions under microwave irradiation are performed in homogeneous solution without solvent, (ii) the loading capacity of the ILPs is higher because only a molar equivalent of the low molecular weigh ionic liquid phase is used, (iii) the stable intermediates in the sequence can be purified by simple washings with the appropriate solvent and the structure could be verified easily by routine spectroscopic methods at each step, (iv) the final cleavage is possible by transesterification, saponification/acidification or ester aminolysis. We are currently exploring the scope of IoLiPOS methodology to the synthesis of small library of 3,4-DHPMs and 1,4-DHPs that will be much more reliable for biological screening.[28]

4. Experimental

4.1. General

Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck) or neutral alumina oxide gel 60F 254 (Merck). Visualisation was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. For preparative column chromatography, silica gel 60F 254 Merck (230–240 Mesh ASTM) and neutral alumina oxide gel 90 (Merck) were used. IR spectra were recorded on a BIORAD FTS 175C spectrophotometer. ^1H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) and BRUKER ARX 200 (200 MHz) spectrometers, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants J are given in Hertz. The mass spectra (HRMS) were taken, respectively, on a MS/MS ZABSpec TOF Micromass (EBE TOF geometry) at an ionizing potential of 8 eV for the ILPs and on a VARIAN MAT 311 at an ionizing potential of 70 eV for the other compounds in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Synthewave® 402 apparatus[22] (Merck Eurolab, Div. Prolabo, France) in quartz open reactor vessel prolonged by a condenser. The microwave instrument consists of a continuous focused microwave power output from 0 to 300 W. All the experiments were performed using stirring option. The target temperature was reached with a ramp of 3 min and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time include the ramp period. Acetonitrile was distilled over calcium chloride after standing overnight and stored over molecular sieves (3 Å). Solvents were evaporated with a BUCHI rotary evaporator. All reagents were purchased from Acros, Aldrich Chimie, Fluka France and used without further purification. The starting $[PEG_1\text{-mim}][X]$ ionic liquid phases **2a** and **3**(**a**,**b**) were synthesized according to our previous method[14b] for 1-(2-hydroxy-ethyl)-3-methyl-imidazolium chloride $[PEG_1mim][Cl]$ **2a**, 1-(2-hydroxy-ethyl)-3-methyl-imidazolium tetrafluoroborate $[PEG_1mim][BF_4]$ **3a**, 1-(2-hydroxy-ethyl)-3-methyl-imidazolium hexafluorophosphate $[PEG_1mim][PF_6]$ **3b**.

4.1.1. 1-(2-Hydroxy-ethyl)pyridinium chloride (2b). A mixture of freshly distilled pyridine **1b** (9.81 g, 124 mmol) and commercial 2-chloroethanol (10 g, 124 mmol) was

heated at 120 °C for 24 h under nitrogen with vigorous magnetic stirring. Then the mixture was allowed to cool down and a white solid formed rapidly (~15 min) at 25 °C. The crude solid that had formed was filtered off (under nitrogen), washed with anhydrous ether (3×30 ml), and vacuum dried in a dessicator over $CaCl_2$ for 4 h. The solid salt [PEG_1py][Cl] **2b** was further dried under high vacuum (10^{-2} Torr) at 60 °C for 8 h and was stored (17.62 g, 92% yield) in the dark at 4 °C under nitrogen. Mp=128–130 °C. ^{1}H NMR (D_2O, 300 MHz) δ=4.00 (t, 2H, J=5.1 Hz, OCH_2), 4.86 (t, 2H, J=4.9 Hz, NCH_2), 7.98 (t, 2H, J=6.9 Hz, H-3, H-5), 8.74 (t, 1H, J=8.0 Hz, H-4), 8.77 (d, 2H, J=6.5 Hz, H-2, H-6).

4.1.2. 1-(2-Hydroxy-ethyl)pyridinium tetrafluoroborate (3c). A mixture of 1-(2-hydroxy-ethyl)pyridinium chloride **2b** (2.50 g, 15.7 mmol) and NH_4BF_4 (1.65 g, 15.7 mmol) in dry acetonitrile (100 ml) was stirred vigorously at 25 °C under nitrogen for 24 h. After elimination of the precipitated salt (NH_4Cl) on a filter paper, the resulting filtrate was quickly refiltered through a short column of Celite® to remove some residual salt and finally concentrated by rotary evaporation that gave the expected mobile liquid phase **3c** in 99% yield. The ionic liquid phase **3c** was further dried under high vacuum (10^{-2} Torr) at 60 °C for 6 h. It is recommandle to handle the [PEG_1py][BF_4] ionic liquid phase **3c** in the dark under an inert atmosphere at 4 °C. ^{1}H NMR (D_2O, 200 MHz) δ=4.06 (t, 2H, J=4.8 Hz, CH_2O), 4.71 (t, 2H, J=5.0 Hz, CH_2N), 8.07 (t, 2H, J=7.2 Hz, H-3, H-5), 8.57 (t, 1H, J=7.9 Hz, H-4), 8.84 (d, 2H, J=5.7 Hz, H-2, H-6); ^{13}C NMR (75 MHz, D_2O) δ=60.49 (CH_2O), 63.64 (CH_2N), 128.23 (C-3, C-5), 144.72 (C-2, C-6), 146.07 (C-4). HRMS, *m/z*: 335.1558 found (calculated for $C_{14}H_{20}N_2O_2F_4B$, [$2C^+$, BF_4^-]$^+$ requires 335.1554).

4.1.3. 1-(2-Hydroxy-ethyl)pyridinium hexafluorophosphate (3d). The [PEG_1py][PF_6] ionic liquid phase **3d** was prepared according to the method used for the synthesis of **3c** from 1-(2-hydroxy-ethyl)pyridinium chloride **2b** (2.50 g, 15.7 mmol) and KPF_6 (2.89 g, 15.7 mmol) that gave the desired ionic liquid phase **3d** in 99% yield as colourless needles. Mp=28–30 °C. ^{1}H NMR (D_2O, 200 MHz) δ=4.10 (t, 2H, J=4.9 Hz, OCH_2), 4.72 (t, 2H, J=5.0 Hz, NCH_2), 8.10 (t, 2H, J=7.2 Hz, H-3, H-5), 8.56 (t, 1H, J=7.9 Hz, H-4), 8.84 (d, 2H, J=5.9 Hz, H-2, H-6); ^{13}C NMR (75 MHz, D_2O) δ=60.39 (CH_2O), 63.52 (CH_2N), 128.17 (C-3, C-5), 144.63 (C-2, C-6), 146.00 (C-4). HRMS, *m/z*: 393.1158 found (calculated for $C_{14}H_{20}N_2O_2F_6P$, [$2C^+$, PF_6^-]$^+$ requires 393.1167).

4.2. Standard procedure for the synthesis of the aldehydes 5(a–d) from imidazolium or pyridinium ionic liquid phases 3(a–d) and 4-formylbenzoic acid 4

To a mixture of dicyclohexylcarbodiimide (2.97 g, 14.42 mmol) and dimethylaminopyridine 5% (88 mg, 0.7 mmol) in dry acetonitrile (75 ml) were added successively the ionic liquid phase **3** ([PEG_1mim][BF_4] **3a** (3.08 g, 14.42 mmol), or [PEG_1mim][PF_6] **3b** (3.08 g, 14.42 mmol), or [PEG_1py][BF_4] **3c** (3.08 g, 14.42 mmol), or [PEG_1py][PF_6] **3d** (3.08 g, 14.42 mmol)) in one portion, then 4-formylbenzoic acid **4** (3 g, 14.42 mmol). After vigorous stirring at room temperature for 24 h, the insoluble *N*,*N*′-dicyclohexylurea (DCHU) was removed by filtration. The filtrate was concentrated under reduced pressure and the resulting crude reaction mixture was washed three times with AcOEt (20 ml). Removal of the solvent in vacuo lead to a pale yellow viscous oil in yield ranging from 95 to 98%. The desired ionic liquid phase **3** was stored under inert atmosphere at 4 °C. The aldehydes **5(a–d)** were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

4.2.1. 1-[2-(4-Formylbenzoyloxy)ethyl]-3-methylimidazolium tetrafluoroborate (5a). Yield=96%. Mp=85–87 °C. IR (KBr): 1275, 1561, 1574, 1649, 1721, 2852, 3153 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=4.04 (s, 3H), 4.79 (t, 2H, J=5.0 Hz, CH_2N), 4.87 (t, 2H, J=4.9 Hz, CH_2O), 7.72 (s, 1H, Ar, H-4, H-5), 7.91 (s, 1H, H-4, H-5), 8.01 (d, 2H, J=8.2 Hz, H-3′, H-5′), 8.20 (d, 2H, J=8.2 Hz, H-2′, H-6′), 9.19 (s, 1H, H-2), 10.13 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=36.62 (NCH_3), 49.35 (CH_2O), 64.53 (NCH_2), 123.92 (C-4, C-5), 124.85 (C-4, C-5), 130.26 (C-1′), 131.05 (C-3′, C-5′), 134.94 (C-4′), 138.16 (C-2), 140.54 (C-1′), 165.61 (CO), 192.91 (CHO). HRMS, *m/z*: 259.1082 found (calculated for $C_{14}H_{15}N_2O_3$, C^+ requires 259.1082).

4.2.2. 1-[2-(4-Formylbenzoyloxy)ethyl]-3-methylimidazolium hexafluorophosphate (5b). Yield=95%. Mp=95–97 °C. IR (KBr): 1281, 1568, 1574, 1695, 1733, 2852, 3178 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=4.00 (s, 3H), 4.74 (t, 2H, J=3.1 Hz,CH_2N), 4.82 (t, 2H, J=3.9 Hz, CH_2O), 7.65 (d, 1H, J=1.6 Hz, H-4, H-5), 7.84 (d, 1H, J=1.6 Hz, H-4, H-5), 7.95 (d, 2H, J=8.4 Hz, H-3′, H-5′), 8.13 (d, 2H, J=8.4 Hz, H-2′, H-6′), 9.12 (s, 1H, H-2), 10.10 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=36.70 (NCH_3), 49.47 (CH_2O), 64.39 (NCH_2), 123.97 (C-4, C-5), 124.93 (C-4, C-5), 130.26 (C-1′), 131.02 (C-3′, C-5′), 134.96 (C-1′), 137.93 (C-2), 140.61 (C-4′), 165.60 (CO), 192.85 (CHO). HRMS, *m/z*: 259.1082 found (calculated for $C_{14}H_{15}N_2O_3$, C^+ requires 259.1082).

4.2.3. 1-[2-(4-Formylbenzoyloxy)ethyl]pyridinium tetrafluoroborate (5c). Yield=98%. Mp=127–129 °C. IR (KBr): 1272, 1487, 1699, 1722, 2852, 2944, 3088, 3132 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=4.99 (t, 2H, J=5.0 Hz, NCH_2), 5.35 (t, 2H, J=5.0 Hz, OCH_2), 8.01 (d, 2H, J=8.4 Hz, H-3′, H-5′), 8.18 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.32 (t, 2H, J=7.4 Hz, H-3, H-5), 8.77 (t, 1H, J=7.8 Hz, H-4), 9.34 (d, 2H, J=5.6 Hz, H-2, H-6), 10.13 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=61.27 (CH_2O), 64.73 (CH_2N), 129.40 (C-3′, C-5′), 130.25 (C-3, C-5), 130.99 (C-2′,C-6′), 134.68 (C-1′), 140.50 (C-4′), 146.36 (C-2, C-6), 147.37 (C-4), 165.45 (CO), 192.93 (CHO). HRMS, *m/z*: 256.0965 found (calculated for $C_{14}H_{14}NO_3$, C^+ requires 256.0974).

4.2.4. 1-[2-(4-Formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate (5d). Yield=98%. Mp=139–141 °C. IR (KBr): 1272, 1491, 1499, 1690, 1718, 1737, 2879, 3073, 3097, 3141 cm^{-1}. ^{1}H NMR (($CD_3)_2CO$, 200 MHz) δ=5.02 (t, 2H, J=4.9 Hz, NCH_2), 5.35 (t, 2H, J=5.0 Hz, OCH_2), 8.00 (d, 2H, J=8.2 Hz, H-3′, H-5′), 8.16 (d, 2H, J=8.2 Hz, H-2′, H-6′), 8.32 (t, 2H, J=7.2 Hz, H-3, H-5), 8.78 (t, 1H, J=7.8 Hz, H-4), 9.29 (d, 2H, J=5.6 Hz, H-2, H-6), 10.12 (s, 1H, CHO); ^{13}C NMR (($CD_3)_2CO$, 75 MHz) δ=61.40

(CH_2O), 64.58 (CH_2N), 129.43 (C-3′, C-5′), 130.23 (C-3, C-5), 130.93 (C-2′, C-6′), 134.67 (C-1′), 140.54 (C-4′), 146.21 (C-2, C-6), 147.42 (C-4), 165.44 (CO); 192.15 (CHO). HRMS, *m/z*: 256.0965 found (calculated for $C_{14}H_{14}NO_3$, C^+ requires 256.0974).

4.3. Standard procedure for the one-pot three component synthesis of 3,4-DHPMs 8(a–c) from aldehydes 5d, β-ketoesters 6(a,b) and ureas 7(a,b) under solventless microwave dielectric heating

In a cylindrical quartz reactor (Ø=1.8 cm) was placed a mixture of 1-[2-(4-formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate **5d** (539.2 mg, 1.34 mmol), methyl acetoacetate **6a** (164.8 mg, 1.42 mmol, 1.06 equiv) or ethyl acetoacetate **6b** (184.6 mg, 1.42 mmol, 1.06 equiv) and commercial urea **7a** (241.2 mg, 4.02 mmol, 3 equiv) or methylurea **7b** (297.5 mg, 4.02 mmol, 3 equiv) followed by addition of three drops of concentrated HCl as catalyst. The reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was irradiated at 120 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and deionized water (10 ml) was added in the reactor. The desired insoluble 3,4-DHPM **8** was collected by filtration and was purified by washing with diethylether (2× 10 ml). The expected 3,4-DHPM **8** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **8(a–c)** were characterized by ^{1}H, ^{13}C NMR and HRMS.

4.3.1. 1-[2-[4-[5-(Methoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (8a). Yield=86%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ=2.38 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 4.95 (t, 2H, J=4.6 Hz, NCH_2), 5.32 (t, 2H, J=4.6 Hz, OCH_2), 5.43 (d, 1H, J=3.2 Hz, CH), 7.15 (br s, 1H, NH), 7.46 (d, 2H, J=8.3 Hz, Ar), 7.93 (d, 2H, J=8.3 Hz, Ar), 8.33 (t, 2H, J=7.4 Hz, H-3′,H-5′), 8.64 (br s, 1H, NH), 8.77 (t, 1H, J=7.8 Hz, H-4′), 9.32 (d, 2H, J=6.5 Hz, H-2,H-6′); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=17.95 (CH_3), 50.99 (OCH_3), 53.76 (C-4″), 59.76 (CH_2O), 63.44 (CH_2N), 98.43 (Ar), 126.10 (Ar), 127.95 (Ar), 128.14 (Ar), 129.78 (Ar), 145.50 (C-2, C-6), 146.22 (C-4), 149.32–150.24–152.05 (C-1′, C-4′, C-2″, C-6″), 164.91 (ArCO), 165.75 (CO). HRMS, *m/z*: 396.1561 found (calculated for $C_{21}H_{22}N_3O_5$, C^+ requires 396.1560).

4.3.2. 1-[2-[4-[5-(Ethoxycarbonyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (8b). Yield=80%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ=1.14 (t, 3H, J=7.1 Hz, CH_3), 2.38 (s, 3H, CH_3), 4.04 (q, 2H, J=7.1 Hz, OCH_2), 4.93 (t, 2H, J=4.8 Hz, NCH_2), 5.34 (t, 2H, J=4.8 Hz, OCH_2), 5.44 (d, 1H, J=2.7 Hz, CH), 7.26 (br s, 1H, NH), 7.46 (d, 2H, J=8.3 Hz, Ar), 7.92 (d, 2H, J=8.3 Hz, Ar), 8.31 (t, 2H, J=7.3 Hz, H-3, H-5), 8.76 (t, 1H, J=7.8 Hz, H-4), 8.82 (br s, 1H, NH), 9.31 (d, 2H, J=5.5 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=14.09 (CH_3), 17.90 (CH_3), 53.91 (CH), 59.39 (CH_2O), 59.78 (OCH_2), 63.39 (CH_2N), 98.63 (C-4″), 126.80 (Ar), 127.91 (C-1′, C-4′), 128.15 (C-5, C-3), 129.74 (Ar), 145.45 (C-2, C-6), 146.26 (C-4′), 149.05–150.46–152.00 (C-1′, C-4′, C-2″, C-6″), 164.92 (ArCO), 165.23 (CO). HRMS, *m/z*: 410.1712 found (calculated for $C_{22}H_{24}N_3O_5$, C^+ requires 410.1716).

4.3.3. 1-[2-[4-[5-(Methoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (8c). Yield=83%. Viscous oil. ^{1}H NMR ($(CD_3)_2SO$, 200 MHz) δ=2.10 (s, 3H, CH_3), 3.11 (s, 3H, NCH_3), 3.59 (s, 3H, OCH_3), 4.79 (t, 2H, J=4.6 Hz, NCH_2), 5.06 (t, 2H, J=4.5 Hz, OCH_2), 5.24 (d, 1H, J=3.8 Hz, CH), 7.37 (d, 2H, J=8.3 Hz, Ar), 7.87 (d, 2H, J=8.4 Hz, Ar), 8.12 (d, 1H, J=3.9 Hz, NH), 8.23 (t, 2H, J=7.4 Hz, H-3, H-5), 8.66 (t, 1H, J=7.7 Hz, H-4), 9.21 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ=16.18 (CH_3), 29.86 (NCH_3), 51.25 (OCH_3), 52.20 (C-4″), 59.82 (CH_2O), 63.45 (CH_2N), 101.51 (C-5″), 126.57 (Ar), 128.03 (C-1′, C-4′), 128.18 (C-5, C-3), 129.84 (Ar), 145.47 (C-2, C-6), 146.27 (C-4), 149.53–151.66–153.00 (C-1′, C-4′, C-2″, C-6″), 164.93 (ArCO), 166.00 (CO). HRMS, *m/z*: 410.1722 found (calculated for $C_{22}H_{24}N_3O_5$, C^+ requires 410.1716).

4.4. Procedure for the one-pot three component synthesis of 3,4-DHPMs 8c′ and 8d from aldehydes 5d, β-ketoesters 6(a,b) and methylurea 7b in oil bath using solvent-free reaction conditions

A mixture of 1-[2-(4-formylbenzoyloxy)ethyl]imidazolium hexafluorophosphate **5b** (845.0 mg, 2.09 mmol), methyl acetoacetate **6a** (248.0 mg, 2.14 mmol, 1.02 equiv) or ethyl acetoacetate **6b** (280.0 mg, 2.13 mmol, 1.02 equiv), commercial methylurea **7b** (485.0 mg, 6.48 mmol, 3.1 equiv) and three drops of concentrated HCl as catalyst was stirred vigorously at 110 °C without solvent for 1 h. After cooling down to room temperature, deionized water (10 ml) was added in the crude reaction mixture. The desired insoluble 3,4-DHPM **8c′** or **8d** was collected by filtration and was purified by washing with diethylether (2×10 ml). The expected 3,4-DHPM **8** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **8c′** or **8d** was characterized by ^{1}H, ^{13}C NMR and HRMS.

4.4.1. 1-[2-[4-[5-(Methoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]3-methylimidazolium hexafluorophosphate (8c′). Yield=88%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ=2.58 (s, 3H, CH_3), 3.20 (s, 3H, $CONCH_3$), 3.62 (s, 3H, OCH_3), 4.07 (s, 3H, NCH_3), 4.76 (t, 2H, J=4.1 Hz, NCH_2), 4.86 (t, 2H, J=4.2 Hz, OCH_2), 5.43 (d, 1H, J=3.5 Hz, H-4″), 7.17 (d, 1H, J=3.2 Hz, NH), 7.44 (d, 2H, J=8.2 Hz, Ar), 7.74 (s, 1H, H-4, H-5), 7.91 (s, 1H, H-4, H-5), 7.95 (d, 2H, J=8.3 Hz, Ar), 9.20 (s, 1H, H-2); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=16.53 (CH_3), 30.30 (NCH_3), 36.65 (NCH_3), 49.55 (CH_2O), 51.43 (OCH_3), 53.78 (C-4″), 63.86 (CH_2N), 103.16 (C-5″), 123.94 (C-4, C-5), 124.84 (C-4, C-5), 127.38 (Ar), 129.34 (C-1′, C-4′), 130.73 (Ar), 137.90 (C-2), 150.46–152.14–154.13 (C-1′, C-4′, C-2″, C-6″), 166.02 (ArCO), 166.86 (CO). HRMS, *m/z*: 413.1823 found (calculated for $C_{21}H_{25}N_4O_5$, C^+ requires 413.1825).

4.4.2. 1-[2-[4-[5-(Ethoxycarbonyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl] 3-methylimidazolium (8d). Yield=87%. Viscous oil. ^{1}H

NMR ($(CD_3)_2CO$, 200 MHz) $\delta=1.17$ (t, 3H, $J=7.1$ Hz, CH_3), 2.58 (s, 3H, CH_3), 3.20 (s, 3H, NCH_3), 4.07 (s, 3H, NCH_3), 4.08 (q, 2H, $J=7.0$ Hz, OCH_2), 4.76 (t, 2H, $J=4.2$ Hz, NCH_2), 4.86 (t, 2H, $J=4.3$ Hz, OCH_2), 5.44 (d, 1H, $J=3.6$ Hz, H-4″), 7.01 (d, 1H, $J=3.5$ Hz, NH), 7.45 (d, 2H, $J=8.3$ Hz, Ar), 7.74 (s, 1H, H-4 or H-5), 7.91 (s, 1H, H-4 or H-5), 7.96 (d, 2H, $J=8.3$ Hz, Ar), 9.19 (s, 1H, H-2); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) $\delta=14.46$ (CH_3), 16.50 (CH_3), 30.27 (NCH_3), 36.64 (NCH_3), 49.56 (CH_2O), 53.98 (C-4″), 60.51 (CH_2O), 63.86 (CH_2N), 103.40 (C-5″), 123.95 (C-4, C-5), 124.86 (C-4, C-5), 127.47 (Ar), 129.34 (C-1′, C-4′), 130.70 (Ar), 137.89 (Ar, C-2), 150.66–151.86–154.06 (C-1′, C-4′, C-2″, C-6″), 166.02 (CO), 166.36 (CO). HRMS, *m/z*: 427.1982 found (calculated for $C_{22}H_{27}N_4O_5$, C^+ requires 427.1982).

4.4.3. Methyl 4-[4-(methoxycarbonyl)phenyl]-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (9a). To a solution of 1-[2-[4-[5-(methoxycarbonyl)-6-methyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-4-yl]benzoyloxy]ethyl]-pyridinium hexafluorophosphate **8a** (539 mg, 1 mmol) in anhydrous methanol (10 ml) was added commercial sodium methoxide (54 mg, 1 mmol) in one portion under nitrogen. After vigorous stirring at 78 °C for 18 h, the solvent was eliminated in vacuo. Then 10 ml of deionized water was added to the crude reaction mixture and a crude solid (**9a**) was obtained after 30 min of stirring. The precipitated ester **9a** was filtered, washed with dionized water (2×10 ml) and dried under reduced pressure (10–2 Torr) during 3 h. The expected ester **9a** was obtained in 80% yield (243 mg) as colourless needles (mp=212–214 °C). ^1H NMR ($(CD_3)_2SO$, 200 MHz) $\delta=2.38$ (s, 3H); 3.59 (s, 3H); 3.86 (s, 3H); 5.44 (d, 1H, $J=2.7$ Hz); 7.20 (br s, 1H, NH); 7.47 (d, 2H, $J=8.2$ Hz, Ar); 7.97 (d, 2H, $J=8.2$ Hz, Ar); 8.71 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) $\delta=17.93$; 50.85; 52.10; 53.81; 98.44; 126.66; 128.70; 129.55; 149.21; 149.83; 152.02; 165.72; 166.01. HRMS, *m/z*=304.1054 found (calculated for $C_{15}H_{16}N_2O_5$, M^+ requires 304.1059).

4.5. Procedures for the one-pot three component synthesis of 3,4-DHPs 11(a,b) under solventless microwave dielectric heating

Method A. A mixture of 1-[2-(4-formylbenzoyloxy)ethyl]-pyridinium hexafluorophosphate **5d** (1.29 g, 3.2 mmol), methyl 3-aminocrotonate **10a** (0.38 g, 3.2 mmol, 1 equiv) or ethyl 3-aminocrotonate **10b** (0.414 g, 3.2 mmol, 1 equiv) and methyl acetoacetate **6a** (0.376 g, 3.2 mmol, 1 equiv) or ethyl acetoacetate **6b** (0.417 g, 3.2 mmol, 1 equiv) was placed in a cylindrical quartz reactor (Ø=1.8 cm). Then, the reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was stirred mechanically and was irradiated at 120 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and chloroform (10 ml) was added in the cylindrical quartz reactor. The resulting solution was concentrated by rotary evaporation under reduced pressure. The desired 3,4-DHP **11** was purified by washing with diethylether or AcOEt (2×10 ml). The expected 3,4-DHP **11** was further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **8**(**a–c**) were characterized by ^1H, ^{13}C NMR, IR and HRMS.

Method B. The 3,4-DHPs **11**(**a**,**b**) were prepared according to the general solvent-free reaction conditions of method A under microwave dielectric heating (120 °C, power=150 W, 10 min) with a mixture of 1-[2-(4-formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate **5d** (1.29 g, 3.2 mmol), commercial ammonium acetate (0.247 g, 3.2 mmol, 1 equiv) and methyl acetoacetate **6a** (0.834 g, 6.4 mmol, 2 equiv) or ethyl acetoacetate **6b** (0.834 g, 6.4 mmol, 2 equiv).

4.5.1. 1-[2-[4-[3,5-(Dimethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (11a). Yield=94% (method A), 96% (method B). Viscous oil. IR (KBr): 1117, 1273, 1489, 1694, 1719, 2952, 3093, 3141, 3314 cm^{-1}. ^1H NMR ($(CD_3)_2CO$, 300 MHz) $\delta=2.34$ (s, 6H, CH_3), 3.60 (s, 6H, CO_2CH_3), 4.94 (t, 2H, $J=4.4$ Hz, NCH_2), 5.08 (s, 1H, Ar, H-5″), 5.32 (t, 2H, $J=4.7$ Hz, CH_2O), 7.38 (d, 2H, $J=8.4$ Hz, H-3′, H-5′), 7.83 (d, 2H, $J=8.4$ Hz, H-2′, H-6′), 8.01 (br s, 1H, NH), 8.34 (t, 2H, $J=7.0$ Hz, H-3, H-5), 8.79 (t, 1H, $J=7.7$ Hz, H-4), 9.32 (d, 2H, $J=5.4$ Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) $\delta=18.67$ (CH_3), 18.75 (CH_3), 40.50 (C-5″), 51.00 (OCH_3), 61.67 (OCH_2), 63.87 (NCH_2), 102.70 (C-3″, C-5″), 102.74 (C-3″, C-5″), 127.73 (C-1′), 128.64 (C-3′, C-5′), 129.41 (C-3, C-5), 130.20 (C-2′, C-6′), 146.24 (C-2, C-6), 146.62 (C-2″, C-6″), 146.71 (C-4′), 147.38 (C-4), 154.78 (C-2″, C-6″), 166.11 (ArCO), 168.15 (CO). HRMS, *m/z*: 451.1868 found (calculated for $C_{25}H_{27}N_2O_6$, C^+ requires 451.1869).

4.5.2. 1-[2-[4-[3,5-(Diethoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (11b). Yield=95% (method A), 97% (method B). Viscous oil. IR (KBr): 1489, 1684, 1719, 2898, 2984, 3070, 3313 cm^{-1}. ^1H NMR ($(CD_3)_2CO$, 300 MHz) $\delta=1.17$ (t, 6H, $J=7.1$ Hz, CH_3), 2.33 (s, 6H, CH_3), 4.04 (qd, 4H, $J=7.1$, 1.7 Hz, OCH_2), 4.93 (t, 2H, $J=4.7$ Hz, NCH_2), 5.07 (s, 1H, H-5″), 5.30 (t, 2H, $J=4.6$ Hz, CH_2O), 7.40 (d, 2H, $J=8.4$ Hz, H-3′, H-5′), 7.82 (d, 2H, $J=8.3$ Hz, H-2′, H-6′), 7.93 (br s, 1H, NH), 8.32 (t, 2H, $J=6.8$ Hz, H-3, H-5), 8.77 (t, 1H, $J=7.8$ Hz, H-4), 9.29 (d, 2H, $J=5.4$ Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) $\delta=14.60$ (CH_3), 18.81 (OMe), 18.73 (OMe), 40.81 (C-5″), 60.01 (OCH_2), 61.74 (OCH_2), 63.88 (NCH^2), 103.08 (C-3″, C-5″), 127.71 (C-1′), 129.02 (C-3′, C-5′), 129.45 (C-3, C-5), 130.08 (C-2′, C-6′), 146.34 (C-2, C-6), 146.41 (C-4′), 147.44 (C-4), 155.16 (C-2″, C-6″), 166.15 (ArCO), 167.69 (CO). HRMS, *m/z*: 479.2167 found (calculated for $C_{27}H_{31}N_2O_6$, C^+ requires 479.2182).

4.5.3. Dimethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12a). To a solution of 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **11a** (517 mg, 0.87 mmol) in anhydrous methanol (20 ml) was added commercial sodium methoxide (15 mg, 0.28 mmol, 0.32 equiv) in one portion under nitrogen. After vigorous stirring at 78 °C for 18 h, the solvent was eliminated in vacuo. The crude reaction mixture was submitted directly to purification by flash chromatography (column: Ø=1 cm, H=7 cm) on neutral alumina oxide 90 gel (Merck) using CH_2Cl_2–AcOEt (1/1) as eluent. The desired fraction was concentrated in

vacuo and gave the desired compound **12a** in 86% yield as a yellowish nearly pure oil, which crystalized on standing. The pure product **12a** was characterized by ^{1}H, ^{13}C NMR, IR and HRMS. Mp = 238–240 °C. IR (KBr): 1290, 1430, 1492, 1687, 1700, 2946, 3014, 3097, 3301 cm^{-1}. ^{1}H NMR (CD_3Cl_3, 300 MHz) δ = 2.31 (s, 6H, CH_3), 3.63 (s, 6H, CO_2CH_3), 3.87 (s, 3H, $ArCO_2CH_3$), 5.05 (s, 1H, H-4), 5.78 (br s, 1H, NH), 7.33 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.88 (d, 2H, J = 8.4 Hz, H-3′, H-6′); ^{13}C NMR (CD_3Cl_3, 75 MHz) δ = 19.42 (CH_3), 39.76 (C-4), 51.09 (CO_2CH_3), 52.08 ($ArCO_2CH_3$), 103.15 (C-3, C-5), 127.85 (C-2′, C-6′), 127.97 (C-4′), 129.56 (C-3′, C-5′), 145.13 (C-1′), 152.99 (C-2, C-6), 167.46 (ArCO), 167.97 (CO). HRMS, *m*/*z*: 359.1369 found (calculated for $C_{19}H_{21}NO_6$, M^+ requires 359.1369).

4.5.4. Diethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12b). The desired compound **12b** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate **11b** according to the experimental procedure used for the preparation of **12a**. Yield = 85%. Mp = 180–182 °C. IR (KBr): 1289, 1442, 1491, 1650, 1695, 2989, 3336 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 1.17 (t, 6H, J = 7.1 Hz, CH_3), 2.34 (s, 6H, CH_3), 3.83 (s, 3H, $ArCO_2CH_3$), 4.04 (m, 4H, J = 7.1, 3.2 Hz, CH_2O), 5.09 (s, 1H, H-4), 7.42 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.86 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 7.92 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ = 14.62 ($CO_2CH_2CH_3$), 18.82 (CH_3), 40.72 (C-4), 52.08 ($ArCO_2CH_3$), 59.97 (OCH_2), 103.24 (C-3, C-5), 128.80 (C-4′), 128.94 (C-2′, C-6′), 129.82 (C-3′, C-5′), 146.20 (C-3, C-5), 146.29 (C-3, C-5), 154.59 (C-2, C-6), 167.21 (ArCO), 167.68 (CO). HRMS, *m*/*z*: 387.1685 found (calculated for $C_{21}H_{25}NO_6$, M^+ requires 387.1682).

4.5.5. Dimethyl 4-(4-carboxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (12c). To a solution of 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate **11a** (571 mg, 0.96 mmol) in 10 ml of THF–$_2$O (2/1) was added dropwise over 10 min a solution of LiOH (47 mg, 0.63 mmol, 65%) under vigorous magnetic stirring. The reaction mixture was stirred for 20 h at room temperature. After elimination of solvent in a rotary evaporator under reduced pressure and addition of deionized water (10 ml), the precipitated crude acid **12c** was obtained at pH 2 by addition of a solution of 3 M HCl in the crude residue. The precipitated crude acid **12c** was filtered off and washed with deionized water (2×10 ml). The crude acid **12c** was directly purified by flash chromatography (column: Ø = 1 cm, H = 4 cm) on silica gel 60F 254 (Merck) using CH_2Cl_2–MeOH (9/1) as eluent. The desired fraction was concentrated in vacuo and gave the desired compound **12c** in 85% yield as white needles. Mp = 240–242 °C. IR (KBr): 1212, 1484, 1654, 1697, 2524, 2950, 3339 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 2.34 (s, 6H, CH_3), 3.59 (s, 6H, CO_2CH_3), 5.09 (s, 1H, H-4), 7.39 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.89 (d, 2H, J = 8.3 Hz, H-3′, H-5′), 8.01 (br s, 2H, NH, CO_2H); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ = 18.71 (CH_3), 40.42 (C-4), 50.98 (CO_2CH_3), 102.88 (C-3, C-5), 128.50 (C-2′, C-6′), 129.00 (C-4′), 130.28 (C-3′, C-5′), 146.57 (C-3, C-5), 146.66 (C-1′), 154.22 (C-2, C-6), 167.83 (ArCO), 168.20 (CO). HRMS, *m*/*z*: 345.1225 found (calculated for $C_{18}H_{19}NO_6$, M^+ requires 345.1212).

4.6. Standard procedure for the synthesis of 3,4-DHPs 12(d,e) by ester aminolysis of ILPs-bound 3,4-DHP 11a using solvent-free reaction conditions under microwave dielectric heating.

A mixture of 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **11a** (310 mg, 0.52 mmol) and commercial butylamine (385 mg, 5.26 mmol, 10 equiv) or propylamine (645 mg, 10.91 mmol, 21 equiv) was placed in a cylindrical quartz reactor (Ø = 1.8 cm). Then, the reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was stirred mechanically and was irradiated at 80 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and acetone (20 ml) was added in the cylindrical quartz reactor. The resulting solution was concentrated by rotary evaporation under reduced pressure. The crude mixture was purified by distillation with a Büchi B-585 microdistillator (to remove excess of volatile amine), followed by flash chromatography (column: Ø = 1 cm, H = 4 cm) on neutral alumina oxide 90 gel (Merck) using CH_2Cl_2 as first eluent then CH_2Cl_2–MeOH (4/1) as second eluent. The desired fraction was controlled by TLC analysis with 0.2 mm precoated plates of neutral alumina oxide gel 60F 254 (Merck) and visualization was made with UV light at 254 or 365 nm. The second fraction was concentrated in vacuo and further dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h, which gave the desired amide **12** as a nearly yellowish pure oil. The pure products **12**(**d**,**e**) were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

4.6.1. Dimethyl 2,6-dimethyl-4-(4-propylcarbamoylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (12d). Yield = 45%. R_f = 0.5 from CH_2Cl_2–MeOH (4/1) as eluent. Viscous oil. IR (KBr): 1214, 1433, 1499, 1548, 1686, 1707, 2946, 3085, 3278 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 0.91 (t, 3H, J = 7.4 Hz, CH_3), 1.58 (m, 2H, J = 7.4, 7.2 Hz, CH_2), 2.32 (s, 6H, CH_3), 3.31 (q, 2H, J = 7.1 Hz, CH_2), 3.58 (s, 6H, CO_2CH_3), 5.05 (br s, 1H, H-4), 7.31 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.58 (br s, 1H, NH), 7.70 (d, 2H, J = 8.3 Hz, H-3, H-5), 8.06 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ = 11.76 (CH_3), 18.69 (CH_3), 18.77 (CH_3), 23.61 (CH_2), 40.24 (C-4), 42.10 (NCH_2), 50.93 (OCH_3), 103.16 (C-3, C-5), 103.20 (C-3, C-5), 127.68 (C-3′, C-5′), 128.25 (C-2′, C-6′), 134.05 (C-4′), 146.32, 146.41 (C-1′), 152.05 (C-2, C-6), 167.50 (ArCO), 168.24 (CO). HRMS, *m*/*z*: 386.1831 found (calculated for $C_{21}H_{26}N_2O_5$, M^+ requires 386.1841).

4.6.2. Dimethyl 2,6-dimethyl-4-(4-butylcarbamoylphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (12e). Yield = 35%. R_f = 0.62 from CH_2Cl_2–MeOH (4/1) as eluent. Viscous oil. IR (KBr): 1216, 1433, 1498, 1541, 1650, 1697, 2930, 3346, 3628 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ = 0.91 (t, 3H, J = 7.3 Hz, CH_3), 1.36–1.56 (m, 2H, CH_2), 2.33 (s, 6H, CH_3), 2.84 (m, 2H, CH_2), 3.36 (s, 6H, CO_2CH_3), 5.06 (br s, 1H, H-4), 7.31 (d, 2H, J = 8.3 Hz, H-2′, H-6′), 7.59 (br s, 1H, NH), 7.70 (d, 2H, J = 8.3 Hz, H-3′, H-5′),

8.10 (br s, 1H, NH); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=13.12 (CH_3), 17.77 (CH_3), 19.88 (CH_2), 31.60 (CH_2), 39.00 (NCH_2), 39.23 (C-4), 49.92 (OMe), 102.30 (C-3, C-5), 126.70 (C-3′, C-5′), 127.25 (C-2′, C-6′), 133.06 (C-4′), 145.43 (C-1′), 151.05 (C-2, C-6), 166.44 (ArCO), 167.25 (CO). HRMS, *m/z*: 400.1989 found (calculated for $C_{22}H_{28}N_2O_5$, M^+ requires 400.111998).

4.6.3. 1-[2-[4-[3,5-(Dimethoxycarbonyl)-2,6-dimethylpyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (13a). The compound **13a** was prepared in 90% yield from 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **11a** (715 mg, 1.2 mmol) and commercial 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (306 mg, 1.32 mmol, 1.1 equiv) in refluxed CH_2Cl_2 (40 ml) for 2 h with vigorous magnetic stirring. After cooling down to room temperature, the solvent was eliminated in a rotary evaporator under reduced pressure. Then, the crude reaction mixture was submitted to purification by flash chromatography (column: Ø=1 cm H=4 cm) on neutral alumina oxide 90 gel (Merck) with CH_2Cl_2–MeOH (95/5) as eluent. Removal of solvent in vacuo gave the desired compound **13e** as a viscous oil. IR (KBr): 1246, 1273, 1492, 1557, 1723, 2855, 3098, 3372, 3628 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=2.54 (s, 6H, CH_3), 3.55 (s, 6H, CO_2CH_3), 4.99 (t, 2H, J=4.7 Hz, NCH_2), 5.36 (t, 2H, J=4.6 Hz, OCH_2), 7.35 (d, 2H, J=8.3 Hz, H-3′, H-5′), 8.07 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.32 (t, 2H, J=6.8 Hz, H-3, H-5), 8.77 (t, 1H, J=7.8 Hz, H-4), 9.35 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=23.09 (CH_3), 52.63 (OCH_3), 61.50 (OCH_2), 64.39 (NCH_2), 127.18 (C-1′), 129.13 (C-3′, C-5′), 129.44 (C-3, C-5), 130.18 (C-3″, C-5″), 130.26 (C-2′, C-6′), 142.46 (C-4″), 145.58 (C-4′), 146.36 (C-2, C-6), 147.44 (C-4), 156.46 (C-2″, C-6″), 165.70 (ArCO), 168.32 (CO). HRMS, *m/z*: 449.1712 found (calculated for $C_{25}H_{25}N_2O_6$, C^+ requires 449.1713).

4.6.4. 1-[2-[4-[3,5-(Diethoxycarbonyl)-2,6-dimethylpyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (13b). The desired compound **13b** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate **11b** according to the experimental procedure used for the preparation of **13a**. Yield=88%. Viscous oil. IR (KBr): 1239, 1271, 1490, 1557, 1716, 2981, 3097, 3648 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=0.93 (t, 6H, J=6.8 Hz, CH_3), 2.56 (s, 6H, CH_3), 4.04 (q, 4H, J=6.8 Hz, OCH_2), 5.00 (br s, 2H, NCH_2), 5.33 (br s, 2H, OCH_2), 7.39 (d, 2H, J=8.2 Hz, H-3′, H-5′), 8.09 (d, 2H, J=8.1 Hz, H-2′, H-6′), 8.30 (t, 2H, J=6.8 Hz, H-3, H-5), 8.76 (t, 1H, J=7.7 Hz, H-4), 9.29 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=13.81 (CH_3), 23.02 (CH_3), 61.33 (OCH_2), 62.03 (OCH_2), 64.26 (NCH_2), 127.16 (C-1′), 129.29 (C-3, C-5), 129.33 (C-3′, C-5′), 130.00 (C-3″, C-5″), 130.08 (C-2′, C-6′), 142.39 (C-4″), 145.42 (C-4′), 146.12 (C-2, C-6), 147.31 (C-4), 156.20 (C-2″, C-6″), 165.67 (ArCO), 167.69 (CO). HRMS, *m/z*: 477.2029 found (calculated for $C_{27}H_{29}N_2O_6$, C^+ requires 477.2026).

4.6.5. Dimethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethylpyridine-3,5-dicarboxylate (14a). The product **14a** was prepared from 1-[2-[4-[3,5-(dimethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate **13a** according to the experimental procedure used for the preparation of **12a**. Yield=94%. White needles. Mp=110–112 °C. IR (KBr): 1234, 1289, 1436, 1557, 1725, 2950 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=2.56 (s, 6H, CH_3), 3.55 (s, 6H, CO_2CH_3), 3.80 (s, 3H, $ArCO_2CH_3$), 7.39 (d, 2H, J=8.4 Hz, H-2′, H-6′), 8.08 (d, 2H, J=8.4 Hz, H-3′, H-5′); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=23.11 (CH_3), 52.49 (OCH_3), 52.55 ($ArCO_2CH_3$), 52.55 (CO_2CH_3), 127.10 (C-4′), 128.97 (C-2′, C-6′), 129.99 (C-3′, C-5′), 131.05 (C-3, C-5), 142.06 (C-4), 145.72 (C-1′), 156.46 (C-2, C-6), 166.63 (ArCO), 168.30 (CO). HRMS, *m/z*: 357.1231 found (calculated for $C_{19}H_{19}NO_6$, M^+ requires 357.1212).

4.6.6. Diethyl 4-[4-(methoxycarbonyl)phenyl]-2,6-dimethylpyridine-3,5-dicarboxylate (14b). The product **14b** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate **13b** according to the experimental procedure used for the preparation of **12a**. Yield=90%. White needles. Mp=120–122 °C. IR (KBr): 1228, 1289, 1437, 1556, 1715, 1726, 2973 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=0.92 (t, 6H, J=7.1 Hz, CH_3), 2.56 (s, 6H, CH_3), 3.91 (s, 3H, $ArCO_2CH_3$), 4.02 (q, 4H, J=7.1 Hz, OCH_2), 7.38 (d, 2H, J=8.4 Hz, H-2′, H-6′), 8.07 (d, 2H, J=8.4 Hz, H-3′, H-5′); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=13.90 (CH_3), 23.06 (CH_3), 52.53 ($ArCO_2CH_3$), 62.00 (OCH_2), 127.37 (C-4′), 129.36 (C-2′, C-6′), 129.94 (C-3′, C-5′), 131.13 (C-3, C-5), 142.13 (C-4), 145.65 (C-1′), 156.29 (C-2, C-6), 166.73 (ArCO), 167.80 (CO). HRMS, *m/z*: 385.1536 found (calculated for $C_{21}H_{23}NO_6$, M^+ requires 385.1525).

4.6.7. Diethyl 4-[4-(carboxyphenyl)]-2,6-dimethylpyridine-3,5-dicarboxylate (14c). The product **14c** was prepared from 1-[2-[4-[3,5-(diethoxycarbonyl)-2,6-dimethyl-2-oxo-1,4-dihydropyridin-4-yl]benzoyloxy]ethyl] pyridinium hexafluorophosphate **13b** according to the experimental procedure used for the preparation of **12c**. Yield=87%. Brown needles. Mp=220–222 °C. IR (KBr): 1238, 1557, 1574, 1654, 1731, 2600, 2979 cm^{-1}. ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ=0.84 (t, 6H, J=6.9 Hz, CH_3), 2.54 (s, 6H, CH_3), 3.99 (q, 4H, J=6.9 Hz, OCH_2), 7.32 (d, 2H, J=7.8 Hz, H-2′, H-6′), 8.02 (d, 2H, J=7.8 Hz, H-3′, H-5′); ^{13}C NMR ($(CD_3)_2SO$, 75 MHz) δ=13.31 (CH_3), 22.57 (CH_3), 61.30 (OCH_2), 126.10 (C-4′), 128.17 (C-2′, C-6′), 129.23 (C-3′, C-5′), 131.02 (C-3, C-5), 140.29 (C-4), 144.74 (C-1′), 155.61 (C-2, C-6), 166.74 (CO), 166.91 (ArCO). HRMS, *m/z*: 371.1383 found (calculated for $C_{20}H_{21}NO_6$, M^+ requires 371.1369).

4.7. Standard procedure for the one pot three component synthesis of ILP bound polyhydroquinolines 16(a,b) using solvent-free reaction conditions under microwave dielectric heating

A mixture of 1-[2-(4-formylbenzoyloxy)ethyl]pyridinium hexafluorophosphate **5d** (580 mg, 1.45 mmol), methyl 3-aminocrotonate **10a** (173 mg, 1.45 mmol, 1 equiv) or

ethyl 3-aminocrotonate **10b** (188 mg, 1.45 mmol, 1 equiv) and 5,5-dimethyl-1,3-cyclohexanedione **15** (204 mg, 1.45 mmol, 1 equiv) was placed in a cylindrical quartz reactor (Ø=1.8 cm). Then, the reactor was then introduced into a Synthewave® 402 Prolabo microwave reactor. The stirred mixture was stirred mechanically and was irradiated at 120 °C (Power level: 50%, 150 W) for 10 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and acetone (10 ml) was added in the cylindrical quartz reactor. The resulting solution was concentrated by rotary evaporation under reduced pressure. The desired 3,4-DHP **11** was purified by washing with diethylether (2×10 ml) or flash chromatography (column: Ø=1 cm, H=4 cm) on neutral alumina oxide 90 gel (Merck) with CH_2Cl_2–MeOH (9/1) as eluent. The expected compounds **16**(**a**,**b**) were further dried under high vacuum (10^{-2} Torr) at 25 °C for 3 h. The pure products **16**(**a**,**b**) were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.

4.7.1. 1-[2-[4-[(3-(Methoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate (16a). Yield= 97%. Viscous oil. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ= 0.86 (s, 3H, *gem*-CH_3), 1.05 (s, 3H, *gem*-CH_3), 2.09–2.53 (m, 4H, H-8″, H-6″), 2.38 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 4.92 (m, 2H, NCH_2), 5.07 (s, 1H, H-4″), 5.31 (t, 2H, J= 4.9 Hz, OCH_2), 7.38 (d, 2H, J=8.3 Hz, H-3′, H-5′), 7.79 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.21 (br s, 1H, NH), 8.32 (t, 2H, J=7.0 Hz, H-3, H-5), 8.78 (t, 1H, J=7.8 Hz, H-4), 9.32 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=19.89 (CH_3), 26.95 (*gem*-CH_3), 29.60 (*gem*-CH_3), 32.99 (C-7″), 37.73 (C-4″), 40.69 (C-8″), 51.02 (OCH_3), 51.24 (C-6″), 61.72 (OCH_2), 63.88 (NCH_2), 104.35 (C-3″), 111.15 (C-4a″), 127.57 (C-1′), 128.98 (C-3′, C-6′), 129.47 (C-3, C-5), 130.05 (C-2′, C-6′), 146.34 (C-4), 146.50 (C-4′), 147.43 (C-2, C-6), 150.26 (C-2″), 154.45 (C-8a″), 166.13 (ArCO), 168.07 (CO), 195.03 (CO, C-5″). HRMS, *m*/*z*: 475.2227 found (calculated for $C_{28}H_{31}N_2O_5$, C^+ requires 475.2223).

4.7.2. 1-[2-[4-[3-(Ethoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy] ethyl]pyridinium hexafluorophosphate (16b). Yield= 90%. Viscous oil. IR (KBr): 1220, 1273, 1488, 1717, 2872, 2958, 3069, 3285 cm^{-1}. ^{1}H NMR ($(CD_3)_2CO$, 300 MHz) δ=0.87 (s, 3H, *gem*-CH_3), 1.05 (s, 3H, *gem*-CH_3), 1.15 (t, 3H, J=7.0 Hz, CH_3), 2.09–2.53 (m, 4H, H-8″, H-6″), 2.38 (s, 3H, CH_3), 4.01 (q, 2H, J=7.0 Hz, OCH_2), 4.91 (m, 2H, NCH_2), 5.07 (s, 1H, H-4″), 5.31 (t, 2H, J=4.9 Hz, OCH_2), 7.40 (d, 2H, J=8.3 Hz, H-3′, H-5′), 7.80 (d, 2H, J=8.3 Hz, H-2′, H-6′), 8.22 (br s, 1H, NH), 8.32 (t, 2H, J=7.2 Hz, H-3, H-5), 8.78 (t, 1H, J=7.8 Hz, H-4), 9.32 (d, 2H, J=5.6 Hz, H-2, H-6); ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ=14.45 (CH_3), 18.88 (CH_3), 26.85–29.48 (*gem*-CH_3), 32.83 (C-7″), 37.76 (C-4″), 40.64 (C-8″), 51.04 (C-6″), 60.06 (OCH_2), 61.34 (OCH_2), 63.76 (NCH_2), 104.55 (C-3″), 110.75 (C-4a″), 127.32 (C-1′), 128.99 (C-3′, C-5′), 129.18 (C-3, C-5), 129.87 (C-2′, C-6′), 145.95 (C-4), 146.46 (C-4′), 147.17 (C-2, C-6), 150.85 (C-2″), 154.38 (C-8a″), 166.00 (ArCO), 167.70 (CO), 195.54 (CO, C-5″). HRMS, *m*/*z*: 489.2386 found (calculated for $C_{29}H_{33}N_2O_5$, C^+ requires 489.2390).

4.7.3. Methyl 4-[4-(methoxycarbonyl)phenyl]-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-3-carboxylate (17a). The product **17a** was prepared from 1-[2-[4-[3-(methoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (**16a**) according to the experimental procedure used for the preparation of **12a**. Yield=85%. Yellow needles. Mp=228–230 °C. IR (KBr): 1227, 1282, 1489, 1600, 1647, 1687, 1719, 2952, 3078, 3204 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.83 (s, 3H, *gem*-CH3), 1.00 (s, 3H, *gem*-CH3), 2.06–2.27 (m, 4H, H-8, H-6), 2.32 (s, 3H, CH_3), 3.58 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3), 5.10 (s, 1H, H-4), 7.37 (d, 2H, J=8.2 Hz, H-2′, H-6′), 7.54 (br s, 1H, NH), 7.87 (d, 2H, J=8.2 Hz, H-3′, H-6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=19.18 (CH_3), 26.91–29.57 (*gem*-CH3), 32.65 (C-7), 36.91 (C-4), 40.66 (C-8), 50.78 (C-6), 51.09 (OCH_3), 52.08 (OCH_3), 104.84 (C-3), 111.08 (C-4a), 127.82 (C-4′), 128.02 (C-2′, C-6′), 129.49 (C-3′, C-6′), 145.03 (C-1′), 149.82 (C-2), 152.51 (C-8a), 167.46 (ArCO), 167.77 (CO), 195.83 (CO, C-5). HRMS, *m*/*z*: 383.1744 found (calculated for $C_{22}H_{25}NO_5$, M^+ requires 383.1733).

4.7.4. Ethyl 4-[4-(methoxycarbonyl)phenyl]-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-3-carboxylate (17b). The product **17a** was prepared from 1-[2-[4-[3-(ethoxycarbonyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolin-4-yl]benzoyloxy]ethyl]pyridinium hexafluorophosphate (**16b**) according to the experimental procedure used for the preparation of **12a**. Yield=80%. Yellow viscous oil. IR (KBr): 1220, 1280, 1487, 1605, 1648, 1700, 1721, 2954, 3074, 3194, 3294 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.83 (s, 3H, *gem*-CH3), 1.00 (s, 3H, *gem*-CH3), 1.15 (t, 3H, J=7.1 Hz, CH_3), 2.04–2.26 (m, 4H, H-8, H-6), 2.31 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.02 (q, 2H, J=7.1 Hz, OCH_2), 5.08 (s, 1H, H-4), 7.37 (d, 2H, J= 8.2 Hz, H-2′, H-6′), 7.50 (br s, 1H, NH), 7.86 (d, 2H, J= 8.2 Hz, H-3′, H-5′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.26 (CH_3), 19.12 (CH_3), 26.91–29.55 (*gem*-CH3), 32.62 (C-7), 37.10 (C-4), 40.65 (C-8), 50.75 (C-6), 51.04 (OCH_3), 59.90 (OCH_2), 105.10 (C-3), 111.12 (C-4a), 127.74 (C-4′), 128.20 (C-2′, C-6′), 129.37 (C-3′, C-5′), 144.73 (C-1′), 149.74 (C-2), 152.68 (C-8a), 167.31 (CO), 167.46 (ArCO), 195.77 (CO, C-5). HRMS, *m*/*z*: 397.1880 found (calculated for $C_{23}H_{27}NO_5$, M^+ requires 397.1889).

Acknowledgements

One of us (J.C.L.) wishes to thank the 'Ministère de la Recherche et de l'Enseignement Supérieur' for a research fellowship. We also thank Professor Jack Hamelin for fruitful discussions, Dr. Pierre Guénot (CRMPO) for the mass spectrometry measurements and Merck Eurolab Prolabo (Fr.) for providing the Synthewave 402® apparatus.

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28. The new 3,4-DHPMs and 1,4-DHPs will be evaluated in a drug discovery program (protein kinase C inhibition activities) at the 'Station Biologique de Roscoff, BP 74, 29682 - Roscoff Cedex, France.'

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Tetrahedron 61 (2005) 12398–12404

Unexpected sulfonylamino migration in the reactions of carbazole derivatives with fluoroalkanesulfonyl azides

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Received 11 July 2005; revised 29 August 2005; accepted 30 August 2005

Available online 7 November 2005

Abstract—The reactions of fluoroalkanesulfonyl azides **1** with carbazole derivatives have been studied in detail. At room temperature **1** reacted with 1,2,3,4-tetrahydrocarbazole **2** readily to afford ring-contraction spiroindole derivatives **3** together with an unexpected 4a-fluoroalkanesulfonylamino-1,2,3,4-tetra-hydrocarbazoles **4**. However, in the case of 9-methyl-1,2,3,4-tetrahydrocarbazole **5**, unexpected sulfonylamino migration occurred and a similar product 9-methyl-1-fluoroalkanesulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazoles **6** were obtained as major products in moderate yields. These new products were fully characterized by spectral methods and single X-ray diffraction analyses. Possible mechanisms for these reactions were proposed.

1. Introduction

Carbazole compounds have demonstrated a range of biological activities, which make them attractive compounds to synthetic and medicinal chemists.[1–3] As a result, numerous carbazole alkaloids and synthetic analogues, many of them possessing useful pharmacological properties, have been studied in the past two decades. Some of the most important compounds with proven chemotherapeutic value belong to the ellipticine class.[4,5] The introduction of different substitutents onto carbazole is essential to optimize its absorption, luminescence and electronic properties. Some reactions of sulfonyl azides with carbazole derivatives have been studied extensively.[6] It is well documented that the replacement of a hydrogen atom with a fluorine atom or a fluoroalkyl group in an organic molecule may profoundly influence its physical and biological properties.[7] Recently, we have investigated the reactions of fluoroalkanesulfonyl azides **1** with various enamine such as in situ generated enamines from carbonyl compounds and secondary amine, indoles and TDAE, etc. In these reactions, *N*-fluoroalkanesulfonyl amidines were formed through a cycloaddition process and the nitrene intermediate was not involved (Scheme 1).[8]

Keywords: Fluoroalkanesulfonyl azides; Carbazole derivatives; 1,3-Dipolar cycloaddition; X-ray crystal structure.

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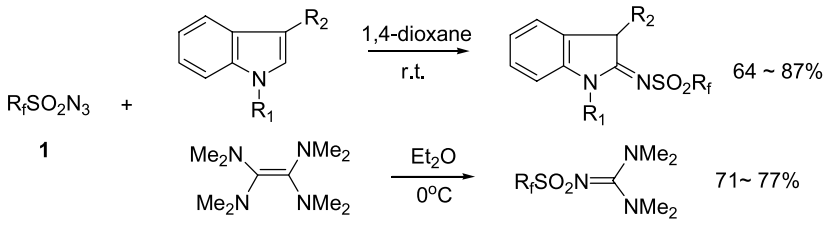
0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.08.100

However, we observed that under the similar reaction conditions, the reaction of azides **1** with carbazole derivatives **2** and **5** give an unexpected 4a-fluoroalkanesulfonylamino-1,2,3,4-tetrahydro-carbazoles **4** and 9-methyl-1-fluoroalkanesulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazoles **6**, respectively. Herein we wish to report these results.

2. Results and discussion

Considering the special enamine structure of 1,2,3,4-tetrahydrocarbazole **2**, the reaction of perfluoroalkanesulfonyl azide **1a** with equimolar of **2** was firstly investigated in anhydrous ether at room temperature. An immediate nitrogen gas release was observed. After stirring for 0.5 h, the starting reagents had disappeared (monitored by TLC). General work-up and purification gave two products. The major product **3a**, obtained in 50% yield, was readily identified as an amidine. A typical strong absorption at 1588 cm^{-1} in IR spectrum also confirmed the existence of C=N functional group. Another product **4a** with a yellow fluorescence property was also isolated successfully in 36% yield. During the identification process, we noticed that the same molecular ion peaks (*m/z* 468) were observed evidently in the corresponding mass spectra, which indicated that **3a** and **4a** are isomeric compounds, even though the intensities of the other fragmental ion peaks were different. This point was further substantiated by the elemental analysis of **3a** and **4a**. Comparing the ^{1}H NMR spectra of **2** and **3a**, the product **3a** showed a single strong peak at δ



Scheme 1.

10.1, corresponding to the active NH, which is similar to the chemical shift of NH in substrate **2**. The assignment of this active proton was further confirmed by deuterium exchange. A clear disappearance of the amino proton (NH) peak was observed. Thus, according to the above spectral data and the previous results of fluoroalkanesulfonyl azides **1** with enamines, the product **3a** was finally determined as a ring-contraction product 2-fluoroalkanesulfonimino-3′-oxoindoline-3-spiro-cyclopentane. Comparing with the previous literatures, we found that the regiospecific result (spiro in 3-position of indole system) in our case was opposite to those Bailey et al. reported[6a] in the case of arylsulfonyl azides with 9-methyl-1,2,3,4-tetrahydrocarbazole, but similar to the results in the cases of 9-methyl-2-oxo-1,2,3,4-tetrahydrocarbazole.[9] By comparison with **3a**, we notice that the ^{1}H NMR spectrum of **4a** did not show the active carbazole NH at δ 10 but rather at δ 5.56 ppm, which indicated that the migration of NH group was involved during the formation of **4a**. However, we found that according to the above spectral data it was still difficult to determine the concrete structure of **4a**. Finally, **4a** was further elucidated by a single crystal X-ray diffraction analysis.

The molecular structure of **4a** is shown in Figure 1. It is an unexpected fluoroalkanesulfonylamino migration product 4a-fluoroalkanesulfonylamino-1,2,3,4-tetrahydrocarbazole. The bond lengths of N_1–C_1, N_2–C_7, N_1–C_{12} are 1.439, 1.473 and 1.292 Å, respectively. The N_1–C_{12} bond length is close to the normal C=N (1.29 Å) double bond and the other two C–N bonds, N_1–C_1, N_2–C_7, belong to single bond (1.47 Å). The cyclohexyl group adopts the stable chair conformation in the molecule structure. In addition, an intermolecular hydrogen bond between N_1 and H_{14} (attached to N_2) was observed and the three atoms are almost in a line (see Fig. 1). Under the same reaction conditions, other fluoroalkanesulfonyl azides **1**(**b**–**f**) also reacted smoothly with the 1,2,3,4-tetrahydrocarbazole, giving the corresponding spiroindole derivatives **3** and fluoroalkanesulfonylamino migration product **4** in comparative yields (Scheme 2, Table 1).

As seen in Table 1, all reactions were completed within 0.5–4 h affording the two isomeric compounds **3** and **4** in excellent yields. In all reactions the ring-contraction amidines **3** were obtained as major products. We found that the fluoroalkyl chain length of the fluoroalkanesulfonyl

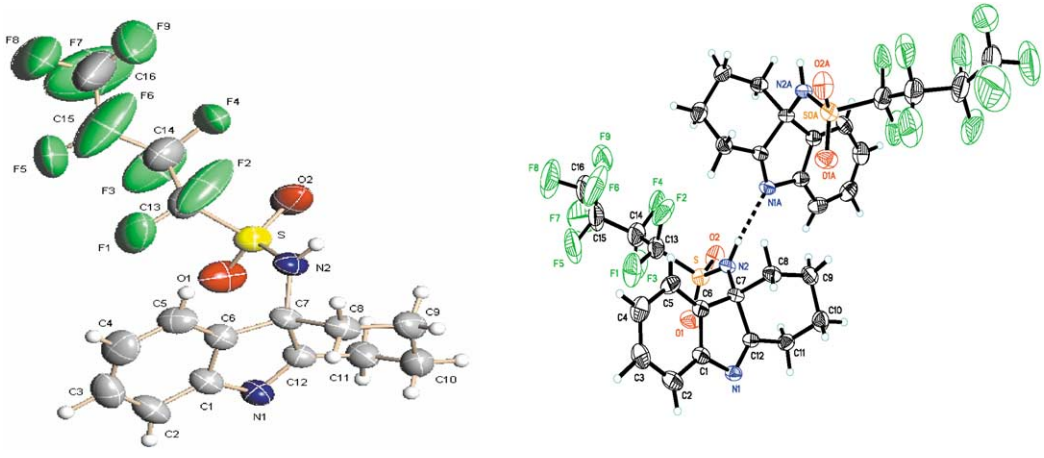
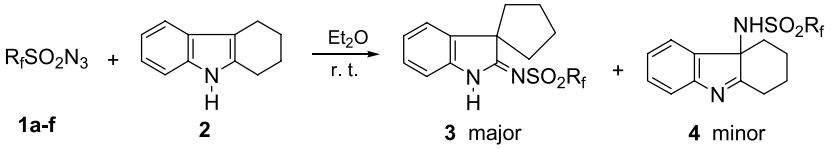


Figure 1. The molecular structure of compound **4a**.



R_f = C_4F_9 (**1a**); $ClC_2F_4OC_2F_4$ (**1b**); $HC_2F_4OC_2F_4$ (**1c**); $IC_2F_4OC_2F_4$ (**1d**); $(CH_3)_2CHOCOCF_2$ (**1e**); $ClC_8F_{16}OC_2F_4$ (**1f**)

Scheme 2.

Table 1. Reaction results of fluoroalkanesulfonyl azides with 1,2,3,4-tetrahydrocarbazole

Entry	Azides	Time (h)	Products (%)[a]	
1	**1a**	0.5	**3a** (50)	**4a** (36)
2	**1b**	2	**3b** (48)	**4b** (34)
3	**1c**	2	**3c** (44)	**4c** (33)
4	**1d**	1.5	**3d** (55)	**4d** (35)
5	**1e**	4	**3e** (24)	**4e** (20)
6	**1f**	4	**3f** (44)	**4f** (22)

[a] Isolated yields.

azides has a dramatic impact on the reaction time and yields of the products dramatically. The longer chain length, the longer time was needed to finish the reaction giving both products in low yields (Table 1, entries 2, 6). While in the case of azide **1e**, which has relative lower reactivity among all the azides, the yields of **3e** and **4e** were decreased significantly (Table 1, entry 5).

According to the results obtained from the reaction of **1** and indole derivatives,[8b,c] when we added 2.0 equiv azides to 1,2,3,4-tetrahydrocarbazole in anhydrous Et_2O or EtOH, no corresponding diazo compounds but the same product **3** and **4** were isolated. This might be attributed to the absence of active methylene in the structure of intermediate product **3**, whose C-3 position has been saturated with cyclopentyl group, thus the transfer of the diazo group from fluoroalkanessulfonyl azides was not observed. When tosyl azide was used instead of **1** to react with the 1,2,3,4-tetrahydrocarbazole in Et_2O at room temperature, no reaction occurred according to ^1H NMR and TLC analysis even after 3 days. These results revealed that fluoroalkanesulfonyl azides are more reactive than its hydrocarbon analogues.

To further determine the feasibility of this method and introduce more useful functional groups to the carbazole ring, the reactions of 9-methyl-1,2,3,4-tetrahydrocarbazole **5** with fluoroalkanesulfonyl azides **1** were also investigated. Under the same reaction conditions, by adding equimolar amount of fluoroalkanesulfonyl azides **1b** slowly to an ether solution of **5**, the color of the reaction system turned to nacarat immediately. According to TLC analysis, the reaction was complete within 10 min. The fast reaction might be attributed to the presence of *N*-methyl group enriching the electron density of the carbazole ring. After general work-up, a white solid **6b** was isolated in 54% yield accompanied with a mixture of unseparated products (almost in the same position shown in TLC analysis and at least 3 products were observed in the ^{19}F NMR spectrum). To our surprise, according to the NMR spectral data, the product **6** was not close to any kinds of the structure of **3** or **4** obtained in the case of 1,2,3,4-tetrahydrocarbazole. A single X-ray diffraction analysis of the product **6b** was carried out to determine the concrete molecular structure of **6**. The molecular structure of **6b** was shown in Figure 2. We found that a similar R_fSO_2NH migration product 9-methyl-1-fluoroalkanesulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazole was formed. Similar results were also obtained when other azides **1a**, **1c–d** reacted with 9-methyl-1,2,3,4-tetrahydrocarbazole **5** (Scheme 3, Table 2).

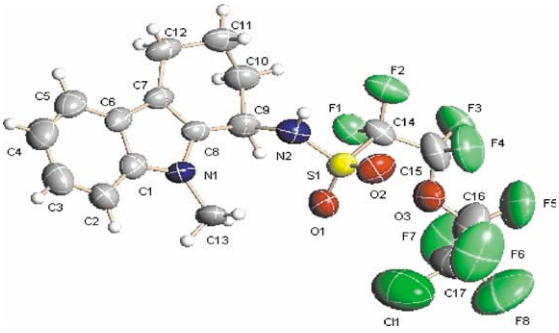


Figure 2. The molecular structure of compound **6b**.

Based on the above results, the possible mechanisms for the formation of **3**, **4**, and **6** were proposed (Scheme 4). Like other electron-riched enamines, the regiospecific [3+2] cycloaddition process happened initially to form the intermediate **I**. Accompanying the release of nitrogen gas from the intermediate **I**, a 1,2-carbon migration occurred to afford the ring-contraction amidines **3** (path a). Another aziridine intermediate **II** also could be formed from **I** and followed either by the intramolecular hydrogen-elimination or by 1,3-C shift aromatization to give more stable carbazole derivatives **4** and **6** (path b).[10]

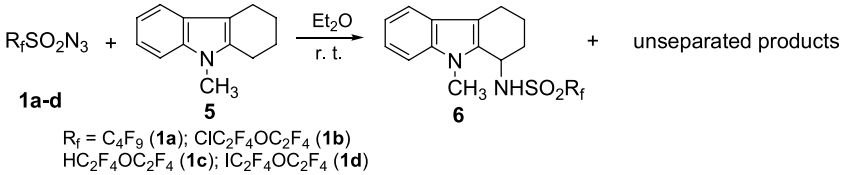
3. Conclusion

In conclusion, the reactions of fluoroalkanesulfonyl azides **1** with 1,2,3,4-tetrahydrocarbazole derivatives were studied. 1,2,3,4-Tetrahydrocarbazole **2** reacted with **1** to afford ring-contraction spiroindole derivatives **3** together with an unexpected 4a-fluoroalkanesulfonylamino-1,2,3,4-tetrahydrocarbazoles **4**. However, more electron-rich 9-methyl-1,2,3,4-tetrahydrocarbazole **5** reacted with **1** giving

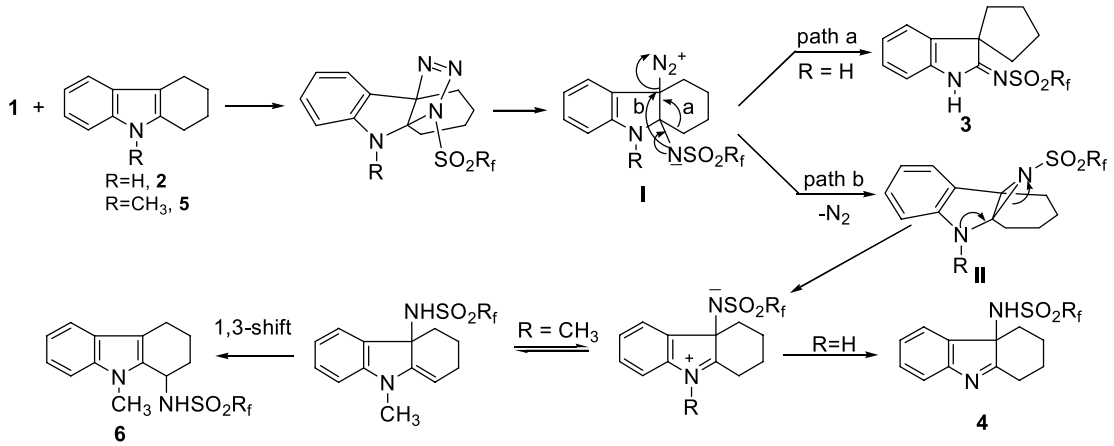
Table 2. Reaction results of fluoroalkanesulfonyl azides with 9-methyl-1,2,3,4-tetrahydrocarbazole

Entry	Azides	Time (min)	Products	Yields (%)[a]
1	**1a**	10	**6a**	44
2	**1b**	10	**6b**	54
3	**1c**	10	**6c**	50
4	**1d**	10	**6d**	49

[a] Isolated yields.



Scheme 3.



Scheme 4.

9-methyl-1-fluoroalkanesulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazoles **6** via an unexpected 1,3-C migration aromatization process. The chemical properties of the fluorinated carbazole derivatives are under investigation in our laboratory.

4. Experimental

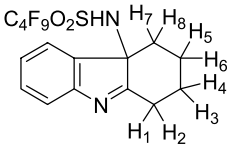
Melting points were measured in Temp-Melt apparatus and were uncorrected. ^{1}H and ^{19}F NMR spectra were recorded in $CDCl_3$ (unless mentioned in text), Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum or high resolution mass spectra (HRMS) were obtained on a Finnigan GC–MS 4021 or a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 eV), respectively. Elemental analyses were performed by this institute. All solvents were purified before use. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument. Fluoroalkanesulfonyl azides **1** and 9-methyl-1,2,3,4-tetrahydrocarbazole **5** were prepared according to literature.[11,12]

4.1. General procedure for the reaction of fluoroalkanesulfonyl azides with 1,2,3,4-tetrahydrocarbazole

To a 10 mL round-bottom flask containing 1,2,3,4-tetrahydrocarbazole **2** (257 mg, 1.5 mmol) in 2 mL anhydrous ether was added slowly fluoroalkanesulfonyl azides **1d** (0.674 g, 1.5 mmol) at room temperature within 2 min. Then the mixture was continuously stirred at room temperature for 1.5 h until TLC analysis showed the reaction finished. The solvent was evaporated and the residue was chromatographed on a silica column using petroleum ether–ethyl acetate (10/1 v:v) as eluant to give pure product **3d** as a white solid (487 mg, 55%). Changing the eluant to petroleum ether–ethyl acetate (3/1 v:v) afforded the yellow solid product **4d** (309 mg, 35%).

4.1.1. 2-Perfluorobutylsulfonimino-3′-oxoindoline-3-spirocyclopentane (3a). White solid. Mp 119–121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.07 (1H, s), 7.37–7.12 (4H, m), 2.31–2.25 (2H, m), 2.18–2.14 (2H, m), 2.10–1.97 (4H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −80.7 (3F, t, J=10 Hz, CF_3), −113.3 (2F, t, J=14 Hz, CF_2S), −121.0 (2F, d, J=7 Hz, CF_3CF_2), −125.9 (2F, t, J=14 Hz, CF_2CF_2S). IR (KBr) cm^{-1}: 3336, 2966, 2881, 1588, 1483, 1352, 1335, 1202, 1138, 1105, 1039. MS (70 eV, EI) *m/z* (%): 469 (M^++1, 35), 468 (M^+, 62), 427 ($M^+-C_3H_5$, 93), 249 ($M^+-C_4F_9$, 16), 185 ($M^+-C_4F_9SO_2$, 100), 168 ($MH^+-C_4F_9SO_2NH_2$, 58), 157 ($M^+-C_4F_9SO_2-C_2H_4$, 31), 144 ($M^+-C_4F_9SO_2-C_3H_5$, 38). Anal. Calcd for $C_{16}H_{13}F_9N_2O_2S$: C, 41.03; H, 2.78; N, 5.98. Found: C, 41.09; H, 2.89; N, 5.98.

4.1.2. 4a-Perfluorobutylsulfonylamino-1,2,3,4-tetrahydrocarbazole (4a).



Yellow solid. Mp 148–150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.26 (4H, m, ArH), 5.65 (1H, s, NH), 3.05–2.97 ($1H_1$, m), 2.92–2.86 ($1H_2$, m), 2.65–2.58 ($1H_5$, m), 2.34–2.23 ($1H_6$, m), 1.94–1.76 (2H, m, H_3, H_4), 1.52–1.30 (2H, m, H_7, H_8). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.0 (3F, m, CF_3), −111.7 (2F, m, CF_2S), −121.3 (2F, t, J=7 Hz, CF_3CF_2), −126.3 (2F, t, J=14 Hz, CF_2CF_2S). IR (KBr) cm^{-1}: 3025, 2965, 2871, 1620, 1604, 1501, 1460, 1382, 1232, 1139, 1049. MS (70 eV, EI) *m/z* (%): 468 (M^+, 12), 427 ($M^+-C_3H_5$, 1), 185 ($M^+-C_4F_9SO_2$, 47), 168 ($MH^+-C_4F_9SO_2NH_2$, 100). Anal. Calcd for $C_{16}H_{13}F_9N_2O_2S$: C, 41.03; H, 2.78; N, 5.98. Found: C, 40.98; H, 2.88; N, 5.89.

Crystal data for 4a $C_{16}H_{13}F_9N_2O_2S$ (CCDC 281323): M_W=468.34, monoclinic, space group $P2(1)/c$, a=12.6526(16) Å, b=11.4234(14) Å, c=13.7251 (17) Å, β=105.278(3)°, V=1913.7(4) Å^3, Z=4, D_c=1.626 mg/m^3, F (000)=944, crystal dimension 0.58×0.35×0.12 mm, radiation, Mo Kα (λ=0.711 Å), $3.34\leq 2\theta\leq 51.00$, intensity data were collected at 293 K with a Bruker axs D8 diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-9\leq h\leq 15$, $-13\leq k\leq 13$, $-16\leq l\leq 14$; the structure was solved by a direct method, all non-hydrogen

atoms were positioned and anisotropic thermal parameters refined from 3572 observed reflections with R (int) = 0.1071 by a full-matrix least-squares technique converged to $R=0.1193$ and $R_w=0.2559$.

4.1.3. 2-(5′-Chloro-3′-oxa-octafluoropentyl)-sulfonimino-3′-oxoindoline-3-spiro-cyclopentane (3b). White solid. Mp 81–83 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.05 (1H, s), 7.35–7.10 (4H, m), 2.32–2.26 (2H, m), 2.19–2.12 (2H, m), 2.10–1.96 (4H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.0 (2F, s, $ClCF_2$), −81.5 (2F, t, $J=12$ Hz, CF_2O), −87.0 (2F, t, $J=12$ Hz, OCF_2), −117.0 (2F, s, CF_2S). IR (KBr) cm^{-1}: 3335, 2969, 2881, 1584, 1482, 1338, 1307, 1190, 1167, 1119, 968. MS (70 eV, EI) *m/z* (%): 502/500 (M^+, 24/55), 459/461 ($M^+-C_3H_5$, 100/37), 465 (M^+-Cl, 9), 249 (M^+-R_fCl, 21), 185 ($M^+-ClR_fSO_2$, 99), 168 ($MH^+-ClR_fSO_2NH_2$, 56), 157 ($M^+-ClR_fSO_2-C_2H_4$, 37), 144 ($M^+-ClR_fSO_2-C_3H_5$, 46). Anal. Calcd for $C_{16}H_{13}ClF_8N_2O_3S$: C, 38.37; H, 2.62; N, 5.59. Found: C, 38.43; H, 2.55; N, 5.60.

4.1.4. 4a-(5′-Chloro-3′-oxa-octafluoropentyl)-sulfonylamino-1,2,3,4-tetrahydro-carbazole (4b). Yellow solid. Mp 138–140 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.24 (4H, m, ArH), 5.92 (1H, s, NH), 3.03–2.99 ($1H_1$, m), 2.92–2.84 ($1H_2$, m), 2.65–2.59 ($1H_5$, m), 2.30–2.25 ($1H_6$, m), 1.92–1.74 (2H, m, H_3, H_4), 1.59–1.38 (2H, m, H_7, H_8). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.1 (2F, s, $ClCF_2$), −81.7 (2F, m, CF_2O), −87.1 (2F, t, $J=12$ Hz, OCF_2), −115.1 (2F, s, CF_2S). IR (KBr) cm^{-1}: 3432, 2960, 2868, 1602, 1381, 1309, 1201, 1144, 1044, 967. MS (70 eV, EI) *m/z* (%): 502/500 (M^+, 4/12), 459/461 ($M^+-C_3H_5$, 3/1), 249 (M^+-R_fCl, 2), 185 ($M^+-ClR_fSO_2$, 58), 168 ($MH^+-ClR_fSO_2NH_2$, 100). Anal. Calcd for $C_{16}H_{13}ClF_8N_2O_3S$: C, 38.37; H, 2.62; N, 5.59. Found: C, 38.15; H, 2.88; N, 5.42.

4.1.5. 2-(1′,1′,2′,2′,4′,4′,5′,5′-Octafluoro-3′-oxa-pentyl)-sulfonimino-3′-oxo-indoline-3-spirocyclopentane (3c). White solid. Mp 56–58 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.10 (1H, s), 7.35–7.12 (4H, m), 5.87 (1H, t-t, $J=53.1$, 3.0 Hz), 2.33–2.25 (2H, m), 2.20–2.12 (2H, m), 2.09–1.95 (4H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.2 (2F, t, $J=12$ Hz, CF_2), −88.8 (2F, s, CF_2O), −117.1 (2F, s, CF_2S), −137.6 (2F, d, $J=53$ Hz, HCF_2). IR (KBr) cm^{-1}: 3322, 2973, 2878, 1587, 1482, 1400, 1340, 1135, 1107, 915. MS (70 eV, EI) *m/z* (%): 466 (M^+, 34), 425 ($M^+-C_3H_5$, 100), 249 (M^+-R_fH, 18), 185 ($M^+-HR_fSO_2$, 66), 168 ($MH^+-HR_fSO_2NH_2$, 48), 157 ($M^+-HR_fSO_2-C_2H_4$, 28), 144 ($M^+-HR_fSO_2-C_3H_5$, 40). Anal. Calcd for $C_{16}H_{14}F_8N_2O_3S$: C, 41.20; H, 3.00; N, 6.01. Found: C, 41.15; H, 3.23; N, 6.00.

4.1.6. 4a-(1′,1′,2′,2′,4′,4′,5′,5′-Octafluoro-3′-oxa-pentyl)-sulfonylamino-1,2,3,4-tetrahydrocarbazole (4c). Yellow solid. Mp 146–148 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.24 (4H, m, ArH), 5.80 (1H, t-t, $J=53.1$, 3.0 Hz), 5.53 (1H, s), 3.04–2.98 ($1H_1$, m), 2.92–2.86 ($1H_2$, m), 2.63–2.57 ($1H_5$, m), 2.31–2.26 ($1H_6$, m), 1.86–1.78 (2H, m, H_3, H_4), 1.50–1.26 (2H, m, H_7, H_8). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.4 (2F, m, CF_2), −88.8 (2F, s, CF_2O), −115.3 (2F, d, $J=19$ Hz, CF_2S), −137.6 (2F, d, $J=58$ Hz, HCF_2). IR (KBr) cm^{-1}: 2958, 2871, 1601, 1459, 1376, 1135, 1281, 1146, 1129, 1039. MS (70 eV, EI) *m/z* (%): 466 (M^+, 18), 425 ($M^+-C_3H_5$, 2), 249 (M^+-R_fH, 1), 185 ($M^+-HR_fSO_2$, 49), 168 ($MH^+-HR_fSO_2NH_2$, 100). Anal. Calcd for $C_{16}H_{14}F_8N_2O_3S$: C, 41.20; H, 3.00; N, 6.01. Found: C, 41.41; H, 3.16; N, 5.87.

4.1.7. 2-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonimino-3′-oxoindoline-3-spiro-cyclopentane (3d). White solid. Mp 118–120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.04 (1H, s), 7.36–7.10 (4H, m), 2.31–2.25 (2H, m), 2.19–2.13 (2H, m), 2.09–1.96 (4H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.0 (2F, s, ICF_2), −81.5 (2F, t, $J=12$ Hz, CF_2O), −85.7 (2F, t, $J=12$ Hz, OCF_2), −116.9 (2F, s, CF_2S). IR (KBr) cm^{-1}: 3314, 2964, 1586, 1482, 1333, 1191, 1134, 1096. MS (70 eV, EI) *m/z* (%): 592 (M^+, 29), 551 ($M^+-C_3H_5$, 100), 465 (M^+-I, 5), 249 (M^+-R_fI, 12), 227 ($IC_2F_4^+$, 7), 185 ($M^+-IR_fSO_2$, 57), 168 ($MH^+-IR_fSO_2NH_2$, 34), 157 ($M^+-IR_fSO_2-C_2H_4$, 19), 144 ($M^+-IR_fSO_2-C_3H_5$, 24). Anal. Calcd for $C_{16}H_{13}F_8IN_2O_3S$: C, 32.45; H, 2.21; N, 4.73. Found: C, 32.70; H, 2.23; N, 4.63.

4.1.8. 4a-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonylamino-1,2,3,4-tetrahydro-carbazole (4d). Yellow solid. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.24 (4H, m), 5.56 (1H, s, NH), 3.00–2.98 ($1H_1$, m), 2.90–2.86 ($1H_2$, m), 2.64–2.58 ($1H_5$, m), 2.29–2.20 ($1H_6$, m), 1.86–1.80 (2H, m, H_3, H_4), 1.38–1.25 (2H, m, H_7, H_8). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.3 (2F, s, ICF_2), −81.8 (2F, m, CF_2O), −85.8 (2F, t, $J=12$ Hz, OCF_2), −115.0 (2F, s, CF_2S). IR (KBr) cm^{-1}: 3423, 1603, 1381, 1295, 1199, 1141, 1098, 1043. MS (70 eV, EI) *m/z* (%): 592 (M^+, 9), 551 ($M^+-C_3H_5$, 1), 249 (M^+-R_fI, 1), 227 ($IC_2F_4^+$, 4), 185 ($M^+-IR_fSO_2$, 66), 168 ($MH^+-IR_fSO_2NH_2$, 100), 144 ($M^+-IR_fSO_2-C_3H_5$, 4). Anal. Calcd for $C_{16}H_{13}F_8IN_2O_3S$: C, 32.45; H, 2.21; N, 4.73. Found: C, 32.60; H, 2.16; N, 4.77.

4.1.9. 2-(2′-Isopropoxylcarbonyl-1′-difluoromethyl)-sulfonimino-3′-oxoindoline-3-spiro-cyclopentane (3e). White solid. Mp 104–106 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.00 (1H, s), 7.33–7.06 (4H, m), 5.29–5.19 (1H, m), 2.34–2.28 (2H, m), 2.19–2.11 (2H, m), 2.08–1.94 (4H, m), 1.39 (6H, d, $J=6$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −109.8 (2F, s, CF_2). IR (KBr) cm^{-1}: 3329, 2972, 2877, 1768, 1613, 1467, 1360, 1325, 1306, 1168, 1157, 1099. MS (70 eV, EI) *m/z* (%): 386 (M^+, 29), 345 ($M^+-C_3H_5$, 34), 303 ($M^+-C_3H_5-iC_3H_7$, 54), 249 (M^+-R_f, 27), 185 ($M^+-R_fSO_2$, 100), 168 ($MH^+-R_fSO_2NH_2$, 57), 157 ($M^+-R_fSO_2-C_2H_4$, 29), 144 ($M^+-R_fSO_2-C_3H_5$, 23). Anal. Calcd for $C_{17}H_{20}F_2N_2O_4S$: C, 52.85; H, 5.18; N, 7.25. Found: C, 52.88; H, 5.02; N, 7.21.

4.1.10. 4a-(2′-Isopropoxylcarbonyl-1′-difluoromethyl)-sulfonylamino-1,2,3,4-tetrahydrocarbazole (4e). Yellow solid. Mp 134–136 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.22 (4H, m, ArH), 5.68 (1H, s, NH), 5.21–5.12 (1H, m), 3.00–2.90 (2H, m), 2.64–2.58 ($1H_5$, m), 2.29–2.24 ($1H_6$, m), 1.95–1.69 (2H, m, H_3, H_4), 1.55–1.34 (2H, m, H_7, H_8), 1.31 (6H, d, $J=5$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −107.3 (2F, s, CF_2). IR (KBr) cm^{-1}: 2984, 2865, 1769, 1601, 1459, 1366, 1296, 1153, 1098, 1042. MS (70 eV, EI) *m/z* (%): 386 (M^+, 43), 345 ($M^+-C_3H_5$, 26), 303 ($M^+-C_3H_5-iC_3H_7$, 43), 249 (M^+-R_f, 15), 185 (M^+

$-R_fSO_2$, 65), 168 ($MH^+-R_fSO_2NH_2$, 100). HRMS for $C_{17}H_{20}F_2N_2O_4S$ Calcd: 386.1112. Found: 386.1067.

4.1.11. 2-(11′-Chloro-3′-oxa-eicosafluoro-undecayl)-sulfonimino-3′-oxoindoline-3-spiro-cyclopentane (3f). White solid. Mp 108–110 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 10.02 (1H, s), 7.36–7.09 (4H, m), 2.31–2.25 (2H, m), 2.17–2.13 (2H, m), 2.09–1.98 (4H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −68.4 (2F, t, J=15 Hz, $ClCF_2$), −81.2 (2F, t, J=15 Hz, CF_2O), −83.1 (2F, d, J=12 Hz, OCF_2), −117.1 (2F, s, CF_2S), −120.4 (CF_2, s), −121.5 (CF_2, s), 122.2 (6F, m), −125.6 (CF_2, s). IR (KBr) cm^{-1}: 3306, 2967, 2885, 1616, 1600, 1482, 1364, 1335, 1219, 1151, 1108. MS (70 eV, EI) *m/z* (%): 802/800 (M^+, 4/12), 761/759 ($M^+-C_3H_5$, 52/100), 249 (M^+-R_fCl, 15), 185 ($M^+-ClR_fSO_2$, 49), 168 ($MH^+-ClR_fSO_2NH_2$, 93), 157 ($M^+-ClR_fSO_2-C_2H_4$, 40), 144 ($M^+-ClR_fSO_2-C_3H_5$, 33). Anal. Calcd for $C_{22}H_{13}ClF_{20}N_2O_3S$: C, 33.00; H, 1.64; N, 3.50. Found: C, 32.96; H, 1.78; N, 3.41.

4.1.12. 4a-(11′-Chloro-3′-oxa-eicosafluoro-undecayl)-sulfonylamino-1,2,3,4-tetrahydrocarbazole (4f). Yellow solid. Mp 148–150 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.18 (4H, m, ArH), 5.49 (1H, s, NH), 3.03–3.01 ($1H_1$, m), 3.00–2.90 ($1H_2$, m), 2.63–2.58 ($1H_5$, m), 2.31–2.27 ($1H_6$, m), 1.86–1.76 (2H, m, H_3, H_4), 1.55–1.31 (2H, m, H_7, H_8). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −68.3 (2F, t, J=14 Hz, $ClCF_2$), −81.4 (2F, d, J=25 Hz, CF_2O), −83.1 (2F, t, J=11 Hz, OCF_2), −115.1 (2F, d, J=12 Hz, CF_2S), −120.4 (CF_2, d, J=14 Hz), −121.5 (CF_2, s), 122.17 (6F, m), −125.52 (CF_2, s). IR (KBr) cm^{-1}: 3466, 2982, 1620, 1604, 1460, 1381, 1215, 1147, 1046. MS (70 eV, EI) *m/z* (%): 802/800 (M^+, 2/7), 761/759 ($M^+-C_3H_5$, 16/45), 249 (M^+-R_fCl, 23), 185 ($M^+-ClR_fSO_2$, 100), 168 ($MH^+-ClR_fSO_2NH_2$, 93), 157 ($M^+-ClR_fSO_2-C_2H_4$, 26), 144 ($M^+-ClR_fSO_2-C_3H_5$, 39). Anal. Calcd for $C_{22}H_{13}ClF_{20}N_2O_3S$: C, 32.98; H, 1.62; N, 3.50. Found: C, 32.93; H, 1.78; N, 3.40.

4.2. General procedure for the reaction of fluoroalkanesulfonyl azides with 9-methyl-1,2,3,4-tetrahydrocarbazole

To a 10 mL round-bottom flask containing 9-methyl-1,2,3,4-tetrahydrocarbazole **5** (139 mg, 0.75 mmol) in 2 mL anhydrous ether was added slowly fluoroalkanesulfonyl azides **1b** (0.268 g, 0.75 mmol) at room temperature within 2 min. TLC analysis indicated the reaction finished within 10 min. The solvent was evaporated and the residue was chromatographed on a silica column using petroleum ether–ethyl acetate (10/1 v:v) as eluant to give pure product **6b** as a white solid (210 mg, 54%).

4.2.1. 9-Methyl-1-perfluorobutylsulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazole (6a). White solid. Mp 122–124 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.11 (4H, m), 5.21 (1H, br), 5.08–5.06 (1H, m), 3.77 (3H, s), 2.95–1.80 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.3 (3F, t, J=10 Hz, CF_3), −113.2 (2F, m, CF_2S), −121.6 (2F, m, CF_2), −126.6 (2F, m, CF_3CF_2). IR (KBr) cm^{-1}: 3277, 2941, 1472, 1381, 1236, 1198, 1141, 1039, 748. MS (70 eV, EI) *m/z* (%): 482 (M^+, 41), 184 ($M^+-R_fSO_2NH$, 100). Anal. Calcd for $C_{17}H_{15}F_9N_2O_2S$: C, 42.32; H, 3.11; N, 5.81. Found: C, 42.40; H, 3.13; N, 5.75.

4.2.2. 9-Methyl-1-(5′-Chloro-3′-oxa-octafluoropentyl) sulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazole (6b). White solid. Mp 82–84 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.11 (4H, m), 5.13–5.08 (2H, m), 3.78 (3H, s), 2.95–1.80 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.0 (2F, s, $ClCF_2$), −81.7 (2F, t, J=13 Hz, CF_2O), −87.0 (2F, t, J=13 Hz, OCF_2), −116.4 (2F, s, CF_2S). IR (KBr) cm^{-1}: 3290, 2940, 2841, 1615, 1471, 1424, 1373, 1310, 1210, 1144, 1052, 972. MS (70 eV, EI) *m/z* (%): 516/514 (M^+, 20/52), 184 ($M^+-ClR_fSO_2NH$, 100). Anal. Calcd for $C_{17}H_{15}ClF_8N_2O_3S$: C, 39.65; H, 2.92; N, 5.44. Found: C, 39.62; H, 3.27; N, 5.32.

Crystal data for **6b** $C_{17}H_{15}ClF_8N_2O_3S$ (CCDC 281324): M_W=514.82, monoclinic, space group $P2(1)/n$, a=18.829(3) Å, b=8.4499(13) Å, c=26.582(4) Å, β=90.36(3)°, V=4229.2(11) Å^3, Z=8, D_c=1.617 mg/m^3, F (000)=2080, crystal dimension 0.52×0.43×0.38 mm, radiation, Mo Kα (λ=0.711 Å), $3.06\leq 2\theta\leq 50.98$, intensity data were collected at 293 K with a Bruker axs D8 diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-21\leq h\leq 22$, $-10\leq k\leq 9$, $-32\leq l\leq 30$; The structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 7840 observed reflections with R (int) =0.0676 by a full-matrix least-squares technique converged to R=0.1753 and R_w=0.2986.

4.2.3. 9-Methyl-1-(1′,1′,2′,2′,4′,4′,5′,5′-octafluoro-3′-oxa-pentyl)sulfonylamino-2,3,4,9-tetrahydro-1*H*-carbazole (6c). Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.11 (4H, m), 5.89 (1H, t-t, J=52.5, 3.0 Hz), 5.15–5.04 (2H, m), 3.77 (3H, s), 2.94–1.79 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.3 (2F, t, J=13 Hz, CF_2), −88.6 (2F, s, CF_2O), −116.4 (2F, s, OCF_2), −137.6 (2F, d, J=48 Hz, HCF_2). IR (KBr) cm^{-1}: 3297, 2937, 1615, 1471, 1423, 1329, 1285, 1145, 1066, 953. MS (70 eV, EI) *m/z* (%): 480 (M^+, 29), 184 ($M^+-R_fSO_2NH$, 100). HRMS for $C_{17}H_{16}F_8N_2O_3S$ Calcd: 480.0764. Found: 480.0754.

4.2.4. 9-Methyl-1-(5′-iodo-3′-oxa-octafluoropentyl)sulfonylamino-2,3,4,9-tetra-hydro-1*H*-carbazole (6d). White solid. Mp 88–90 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.11 (4H, m), 5.11–5.04 (2H, m), 3.77 (3H, s), 2.94–1.79 (6H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.2 (2F, t, J=5.08 Hz, ICF_2), −81.6 (2F, m, CF_2O), −85.7 (2F, m, OCF_2), −116.3 (2F, s, CF_2S). IR (KBr) cm^{-1}: 3331, 2957, 2865, 1615, 1473, 1426, 1336, 1291, 1197, 1137, 1086, 1013, 904. MS (70 eV, EI) *m/z* (%): 606 (M^+, 62), 227 ($IC_2F_4^+$, 3), 184 ($M^+-IR_fSO_2NH$, 100). Anal. Calcd for $C_{17}H_{15}F_8IN_2O_3S$: C, 33.68; H, 2.49; N, 4.62. Found: C, 33.78; H, 2.79; N, 4.51.

Acknowledgements

This work is supported by the National Science Foundation of China (Nos. 20372077 and 20472106).

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