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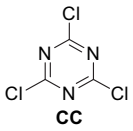
Contents

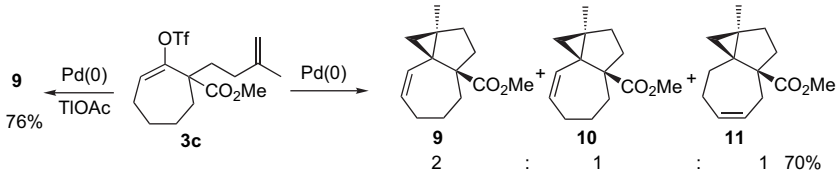
REPORT

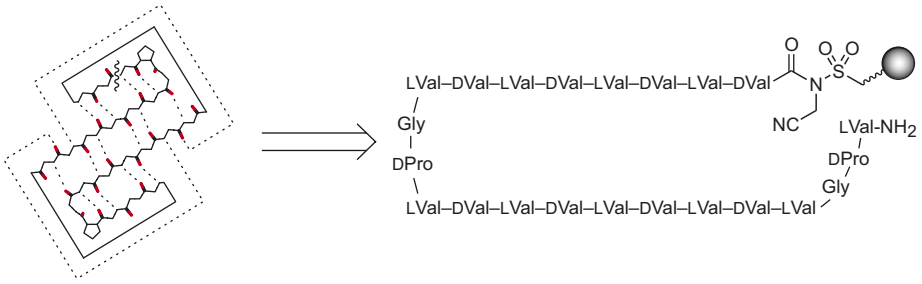


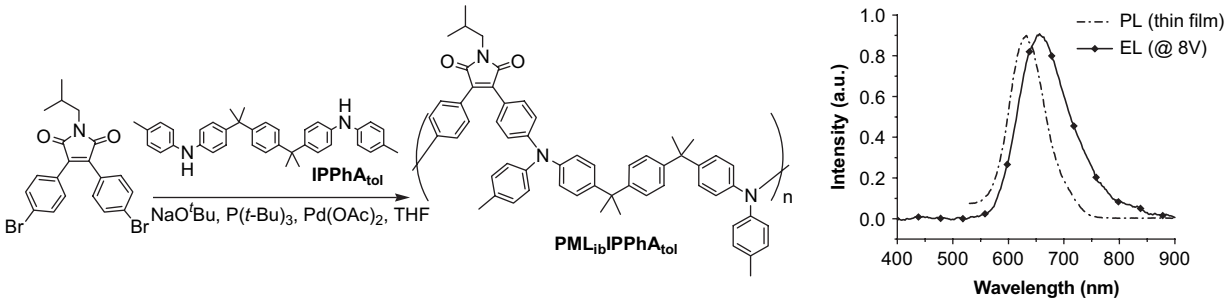
CC

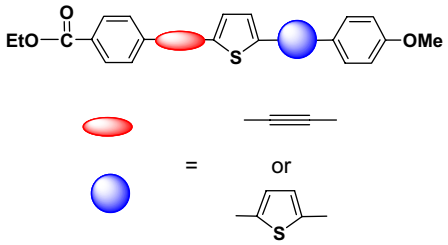
A new recently published application of 2,4,6-trichloro-1,3,5-triazine (CC) and its derivatives in organic synthesis are reviewed.

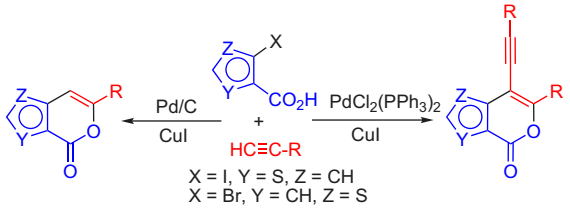
ARTICLES

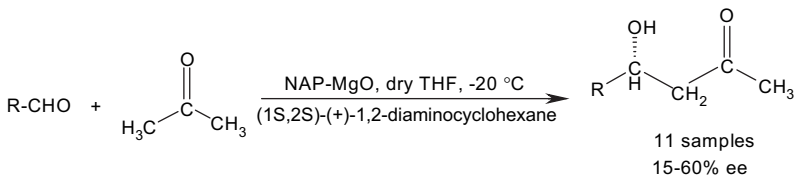


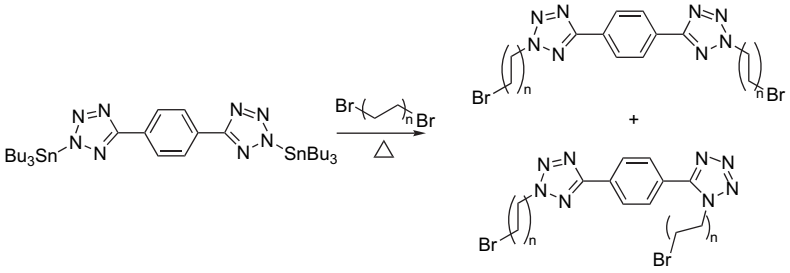




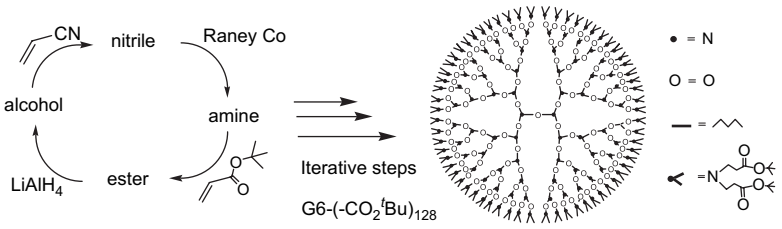


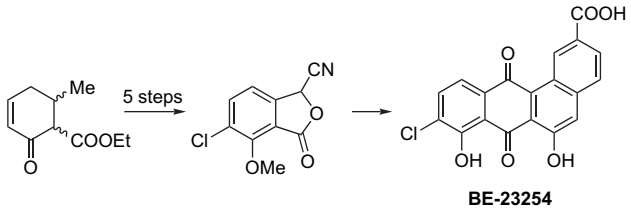


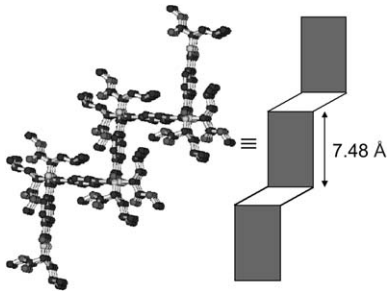


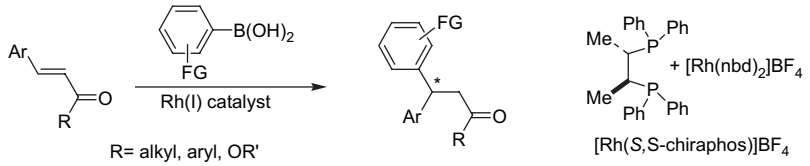


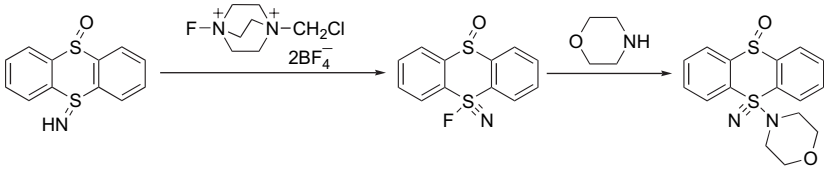
Reactions of 1,4-bis[2-(tributylstannyl)tetrazol-5-yl]benzene with α,ω-dibromoalkanes led to the formation of several alkyl halide derivatives, substituted variously at N1 or N2 on the tetrazole ring. The X-ray crystal structures of a number of derivatives are discussed.

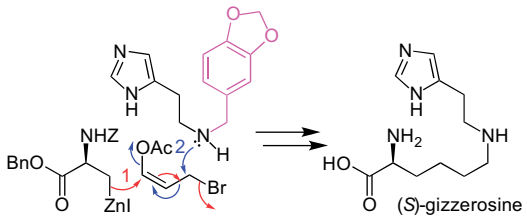






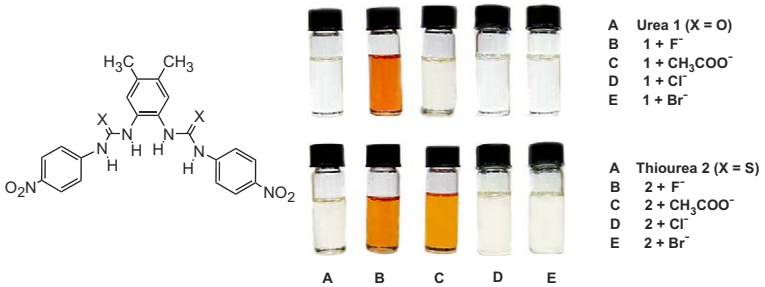


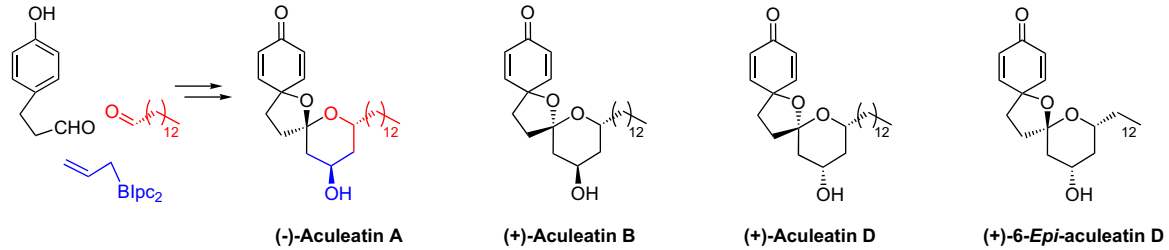




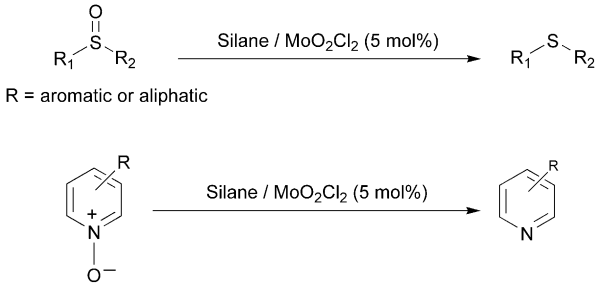
(*S*)-Gizzerosine, a potent inducer of gizzard erosion in chicks, was synthesized using successive zinc-mediated and palladium-catalyzed coupling reactions as the key steps.

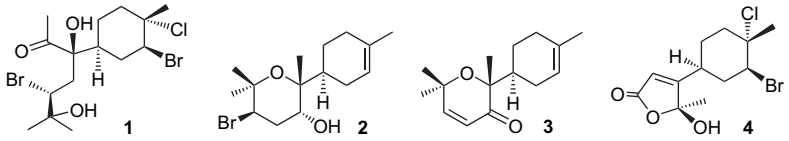
Urea **1** and thiourea **2**, effectively and selectively, recognized the biologically important F^- and carboxylate anions from other anions such as Cl^- and Br^- in DMSO.



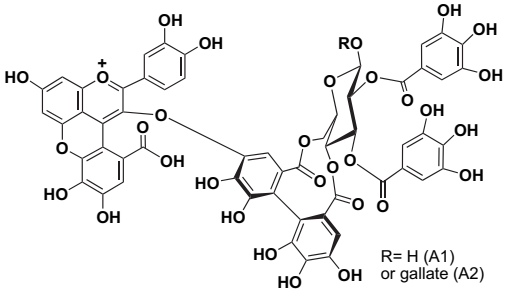


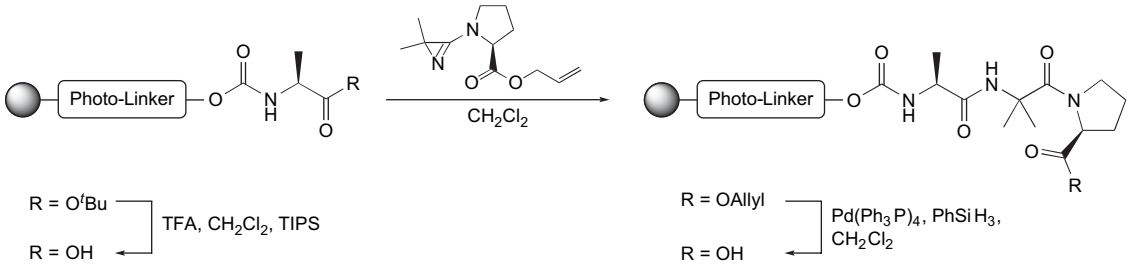
The system silane/MoO_2Cl_2 (5 mol %) proved to be very efficient for the reduction of aliphatic and aromatic sulfoxides and pyridine *N*-oxides to the corresponding sulfides and pyridines in good yields.

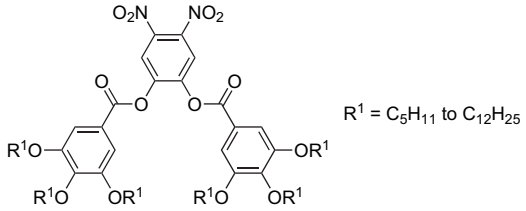


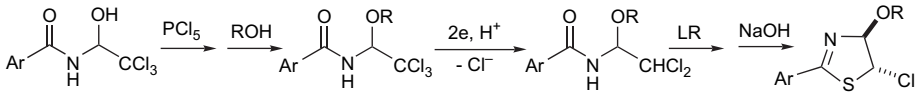


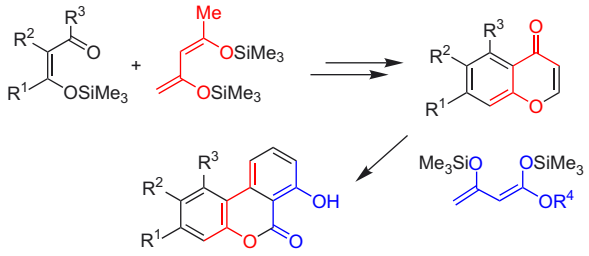
The structure of rosacynanin A1 and A2 consisted of a common chromophore containing cyanidin with a galloyl group link between positions 4 and 5 of the flavylium nucleus and tellimagrandins (1 or 2).

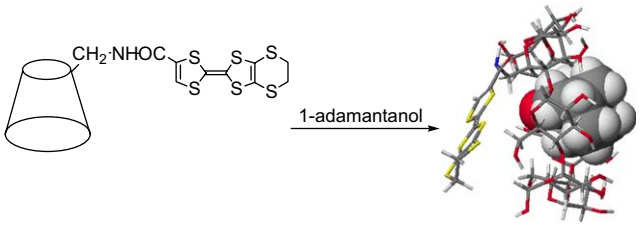


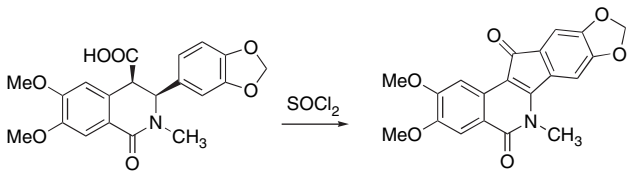


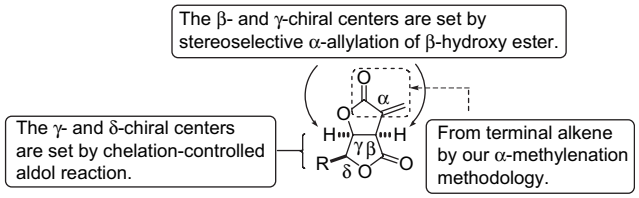




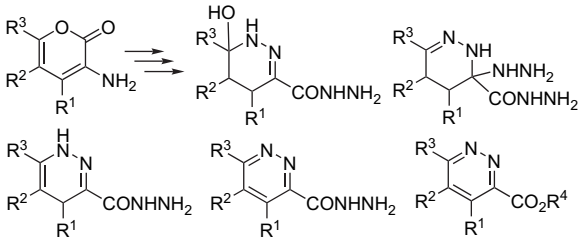


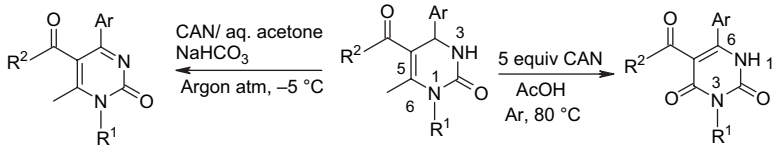


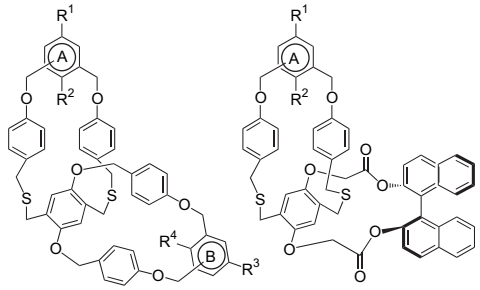


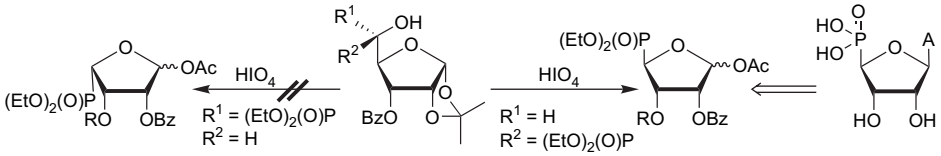


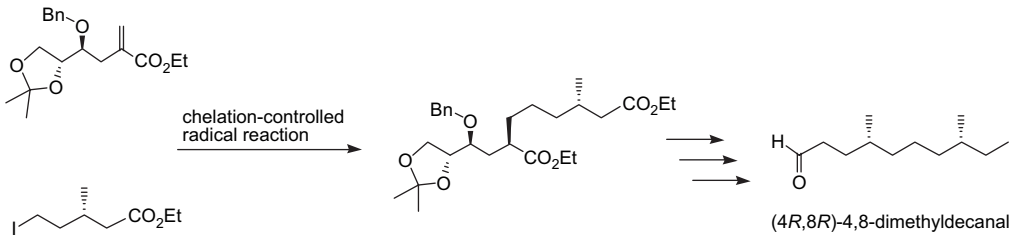
A diastereoselective total synthesis of (±)-canadensolide is described. The key step is to introduce the α-methylene group by the ozonolysis of mono-substituted alkenes followed by reaction with a preheated mixture of CH_2Br_2–Et_2NH.

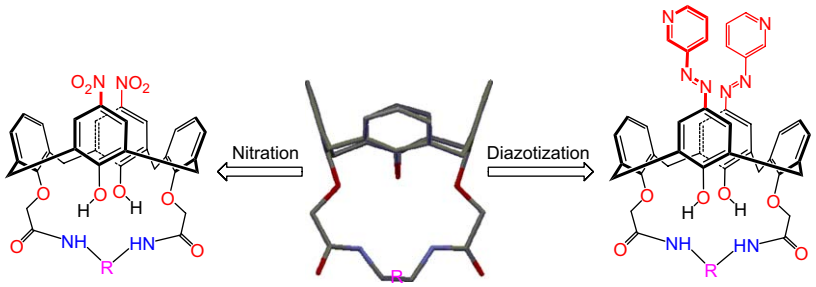




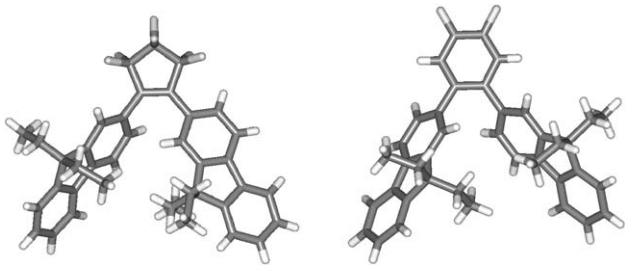








A series of fluorene- and anthracene-based compounds linked by perfluorocyclopentene core unit have been synthesized and characterized, and compounds **1** and **5** have been confirmed by X-ray single-crystal analysis. These compounds show a bright blue emission with high photoluminescence quantum efficiency.



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Supplementary data available via ScienceDirect

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Recent applications of 2,4,6-trichloro-1,3,5-triazine and its derivatives in organic synthesis

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Contents

1. Introduction

1,3,5-Triazine derivatives have been known for a long period of time. They have found widespread applications in the pharmaceutical, textile, plastic, and rubber industries, and are used as pesticides, dyestuffs, optical bleaches, explosives, and surface active agents. The chemistry of this group of compounds has been studied intensively and has been the subject of many reviews.[1–6]

Development of valuable methods for the preparation of many substances is still a challenge. The main issues in modern synthetic organic chemistry are selectivity, mildness, improvement of efficiency, and the avoidance of toxic reagents and by-products. From this point of view, considerable attention has been devoted to the development of new 1,3,5-triazine derivatives as reagents in organic synthesis.

Because common, nonsystematic nomenclature is prevalent in the chemical literature of triazine, it is important to briefly review the systematic and common names of some important derivatives, which are shown in Figure 1.

All of the *s*-triazine derivatives that have wide practical applications are 2,4,6-mono, di- or tri-substituted, symmetrical and nonsymmetrical compounds bearing different substituents. The most important reagent for obtaining these compounds is cyanuric chloride (CC), because of the

Keywords: 2,4,6-Trichloro-1,3,5-triazine; 2-Chloro-4,6-dimethoxy-s-triazine; Functional group transformations.
Abbreviations: CA, cyanuric acid; ICA, isocyanuric acid; CC, cyanuric chloride; TCICA, trichloroisocyanuric acid; M, melamine; BNCT, boron neutron capture therapy; TEMPO, 2,2,6,6-tetramethyl piperidine-1-oxyl; Z, benzyloxycarbonyl; Boc, *tert*-butoxycarbonyl; Fmoc, 9-fluorenylmethoxycarbonyl; NMM, 4-methylmorpholine; DMF, dimethylformamid; MW, microwave irradiation; DMSO, dimethylsulfoxide; PEG, polyethylene glycol; CDMT, 2-chloro-4,6-dimethoxy-1,3,5-triazine; DMTMM, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride; ^{F}CDMT, 2-chloro-4,6-bis[(heptadecafluorononyl)oxy]-1,3,5-triazine; CF, 2,4,6-trifluoro-1,3,5-triazine; Trt, trityl; THF, tetrahydrofuran; TEA, triethylamine; Py, pyridine; *m*-CPBA, *meta*-chloroperbenzoic acid; DME, 1,2-dimethoxyethane; DIPEA, diisopropylethylamine.
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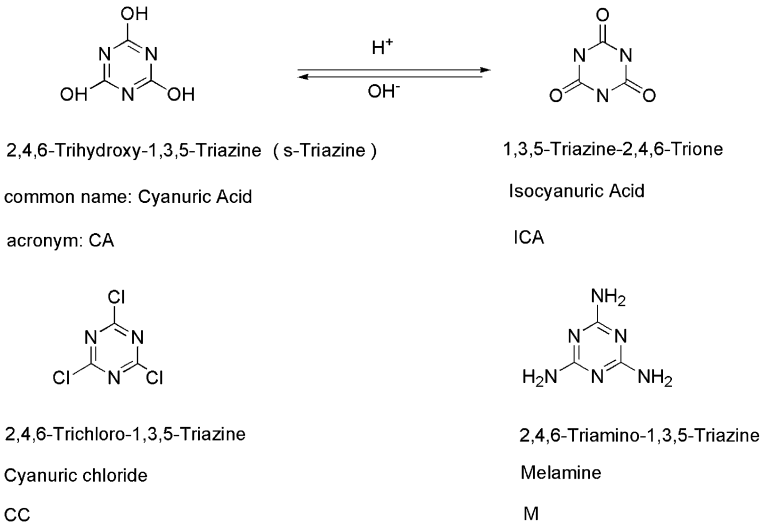


Figure 1.

reactivity of its chlorine atoms toward nucleophiles. It is also important to stress that CC is commercially available and a very inexpensive reagent, which makes its applications even more attractive. In this review, the synthesis of new 2,4,6-derivatives of 1,3,5-triazine together with novel applications of cyanuric chloride and its derivatives, in a variety of synthetic transformations, will be presented. Because of the large volume of work in this area, only the most relevant recently published applications will be presented.

2. 2,4,6-Trichloro-1,3,5-triazine (CC)

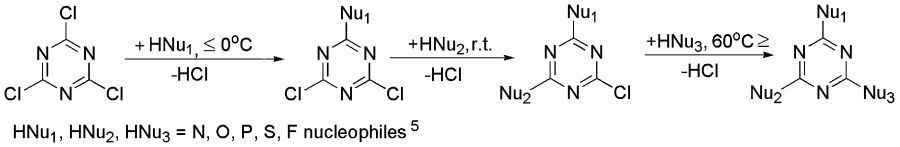
The ease of displacement of chlorine atoms in cyanuric chloride by various nucleophiles, in the presence of a hydrochloride acceptor (usually sodium carbonate, bicarbonate, hydroxide or tertiary amines), makes this reagent useful for the preparation of mono-, di- and tri-substituted 1,3,5-triazines.[2] The substitution of chlorine can be controlled by temperature to run in a stepwise manner. An empirical rule, based upon observation, is that mono-substitution of chlorine occurs below or at 0 °C, di-substitution at room temperature and tri-substitution above 60 °C (Scheme 1).

The substitution pattern also depends on the structure of the nucleophile, its basic strength and steric factors, the substituent already present in the *s*-triazine ring and the nature of solvent used. Therefore the empirical rule given above is just a rough guideline, and there are many variations from these conditions. By controlling the temperature, time, and optimization of variables, such as solvent and base, the substitution of chlorine in CC with different substituents can be accomplished in one pot, if the correct order of addition of nucleophiles is followed (e.g., O-nucleophiles followed by N-nucleophiles). For example, Menicagli [7,8] achieved nearly quantitave yields of both symmetric and nonsymmetric mono-, di- and tri-substituted alkoxy and amino 1,3,5-triazines by nucleophilic substitution of CC in one pot in the presence of a catalytic amount of 18-crown-6.

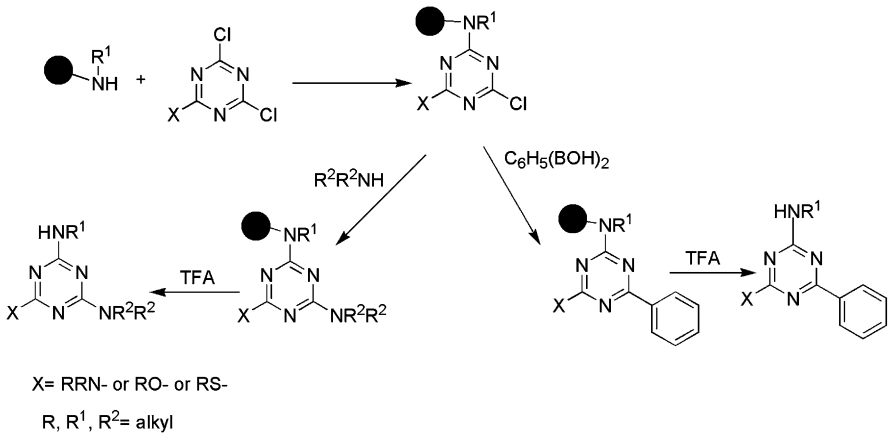
A new orthogonal method for solid-phase synthesis of 2,4,6-trisubstituted 1,3,5-triazine was developed by Chang et al.[9,10] They attached a primary amine to an aldehyde resin by reductive amination. This was then reacted with separately prepared mono-substituted dichloro-*s*-triazine. The trisubstituted derivatives were obtained by nucleophilic reaction with an amine,[9] or by a Suzuki coupling reaction with phenylboronic acid.[9] Cleavage of the resin gave the trisubstituted product (Scheme 2) with high purity. Unfortunately, the authors did not report the yields of this reaction.[9,10]

An interesting strategy based on sulfones was presented by the same authors.[11] Separately synthesized 2-benzylsulfanyl-2,6-dichloro-1,3,5-triazine was reacted with amine bonded to the resin. After substitution of the third chlorine atom with a primary or secondary amine, the thioether was oxidized to benzyl sulfone generating a good leaving group. Reaction with another amine and cleavage of the resin gave the trisubstituted *s*-triazine (Scheme 3).

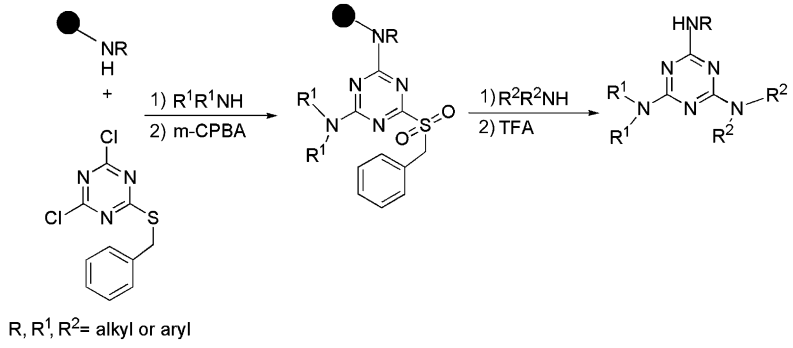
To avoid harsh conditions in the substitution of the last chlorine atom by an amino group Simanek et al.[12] treated chlorotriazine with either triphenylmethylamine and diphenylmethylamine or 2,4-dimethoxybenzylamine. The substitution was accomplished in 5–15 min using microwave technique. The acid labile benzylic groups were removed by trifluoroacetic acid giving the product with high yield.



Scheme 1.



Scheme 2.



Scheme 3.

3. Applications of CC in synthesis of substituted *s*-triazines

Falorni et al.[13] synthesized tri-functionalized orthogonally protected templates **1** (Fig. 2) in a one-pot procedure, which was used in a liquid-phase parallel synthesis.

By reacting CC with 3 equiv of *p*-hydroxybenzaldehyde, Tahmassebi and Sasaki[14] obtained, a triangular- 'tripod' in a single step **2** (Fig. 2). It was used for the imprinting of a silica surface[14] or for linking to N-terminus peptides by reductive amination to assemble three-helix bundle proteins.[15] A linear template- 'dipod' **3** was also synthesized using a 2,4-dichloro-6-methoxy-1,3,5-triazine with 2 equiv of aldehyde, instead of CC.[16]

Gustafson,[17] for the first time, incorporated a triazine ring in carbohydrates, peptides, aminimides, and α-ketoamides by the selective derivatization of CC in a one-pot procedure using automated parrallel solution synthesis, e.g., **4** (Fig. 2).

Recently, the synthesis of a novel disubstituted exocyclic triazylamino nucleoside **5** (Fig. 3) library was reported using a stepwise amination of CC on a semiautomated synthesizer.[18,19] The natural mimic nucleosides were obtained as potential antitumor and antiviral agents.

The temperature dependent reactivity of CC was exploited for the synthesis of different kinds of calix[*n*]arens,[20,21] e.g., **6** and **7** (Fig. 3), as well as macrocycles containing triazine moeties linked by diamines,[22] e.g., **8** (Fig. 3). Because of the presence of many hydrogen bond donors and acceptors these compounds exhibit very promising binding properties. CC was also used to link a calix[4]arene to a carbohydrate natural polymer.[23]

By stepwise amination of CC with 5-(4-aminophenyl)-10,15,20-triphenylporphyrin, Carofiglio et al.[24] synthesized

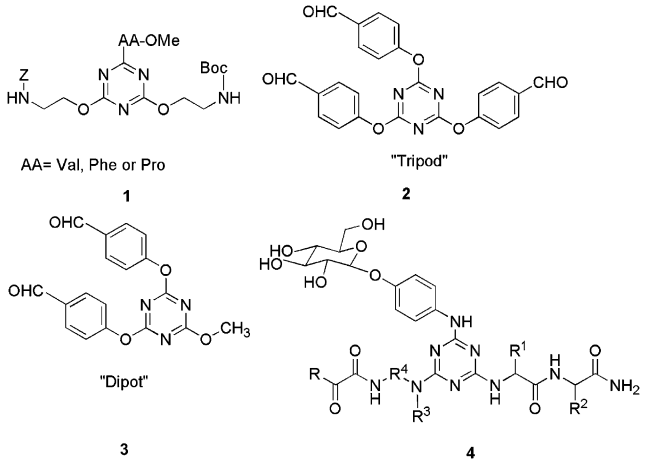


Figure 2.

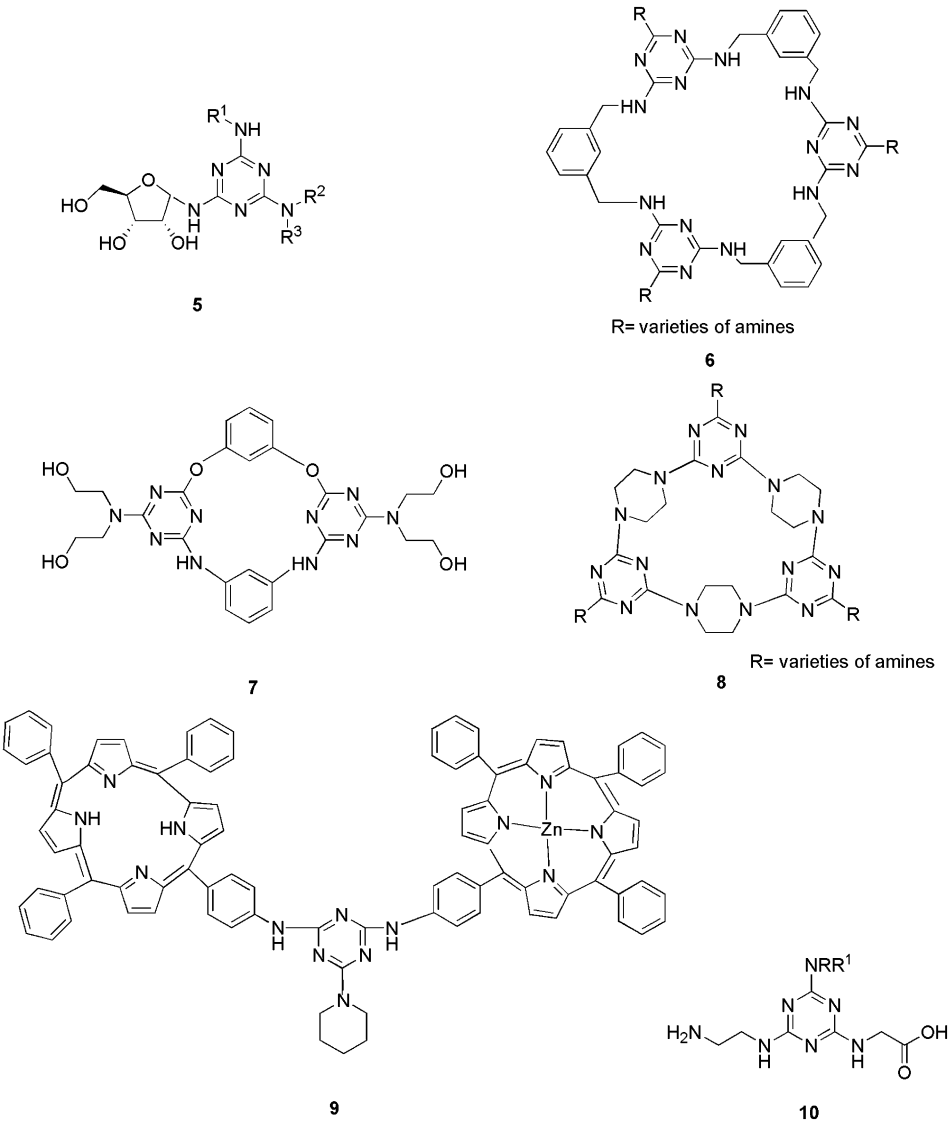


Figure 3.

porphyrin-dyads. Similarly amination with aminoporphyrin produced Zn(II) complex metaloporphyrin dyads like **9** (Fig. 3). CC was also used for obtaining porphyrin oligomers.[25] These compounds have found various applications like mimicking the selectivity and reactivity of enzymes, and as material for optoelectronics.

Zerkowski[26] utilized triazinyl amino acid **10** (Fig. 3) as building block for unnatural peptide analogs, which were obtained from CC by nucleophilic substitution with diamines and amino acid esters. The third chlorine in the triazine ring can be used for incorporation of other functionalities, or for attachment to a solid-phase resin. Several macrocyclic pseudopeptides were synthesized using these derivatives.

Recently, different *o*-carboranyl derivatives of 1,3,5-triazine were synthesized from CC as tumor targeting agents for boron neutron capture therapy (BNCT). One, two or three *o*-carboranyl residues were incorporated into *s*-triazine.[27–29] The remaining chlorine atoms were substituted by various amines[27,28] or acids,[29] e.g., **11** and **12** (Fig. 4).

A new Sharpless asymmetric ligand was synthesized using CC, quinine, and 4-bromoaniline[30] **13** (Fig. 4). This new catalyst is inexpensive, and gives a good yield and enantioselectivity in the dihydroxylation of alkenes.

The carbon nitride was synthesized by heating CC and sodium azide in benzene at 220 °C, which forms high quality nanotubes **14** (Fig. 4), by self-assembly.[31]

A fluorous derivative of a radical 2,2,6,6-tetramethyl piperidine-1-oxyl (TEMPO) was synthesized using CC **15** (Fig. 4), which is efficient, selective, and an easily recoverable catalyst for oxidation of alcohols.[32]

N^{α}-dichlorotriazinyl-arginylalkyl-amide monohydrochlorides, e.g., **16** (Fig. 4) were synthesized as new surfactants for application as antimicrobial and antihelminthic agents

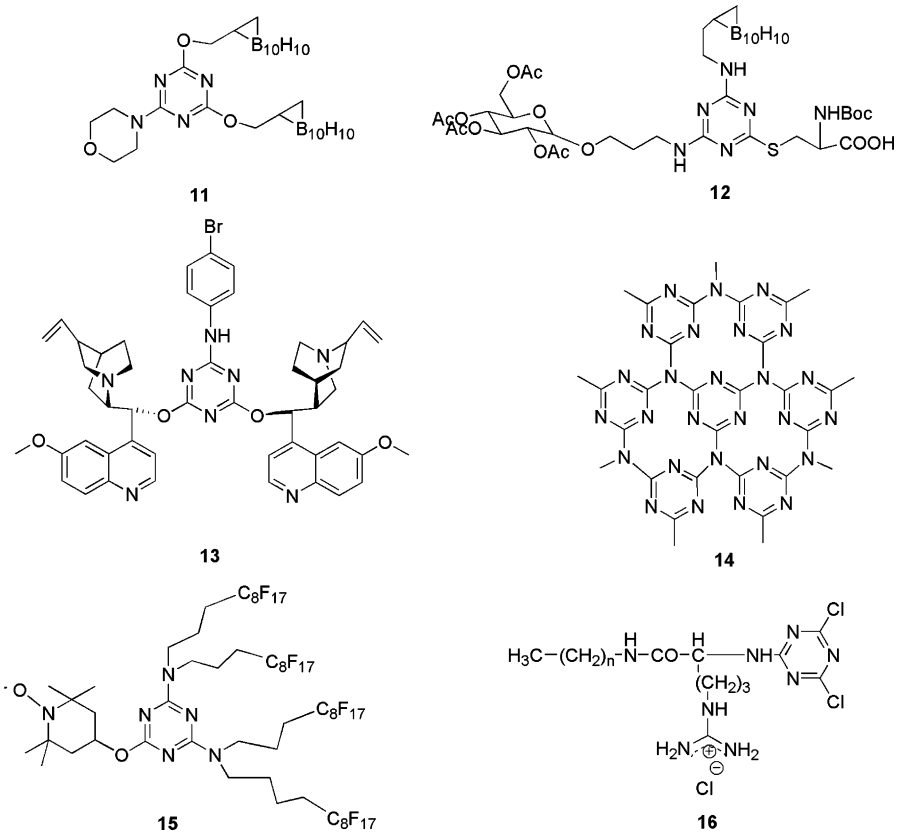


Figure 4.

for wool and cotton, to protect these material from degradation.[33]

4. CC in dendrimers synthesis and supramolecular complexes

Controlling the reaction temperature of CC with different diamines allowed Simanek's group[34–40] and Lai et al.[41] to synthesize dendrimers, e.g., **17** (Fig. 5), even without employing protection and deprotection processes. They have potential applications in medicine as vehicles for drug delivery, and in the area of electro- and optomaterials.

Triazine derivatives, such as cyanuric or isocyanuric acids and melamines (obtained from CC), can act as both hydrogen bond donors and acceptors. The hydrogen-bonding networks that form between them are responsible for forming supramolecular, well defined and stable aggregates. These aggregates were first described by Lehn[42] and by Whitesides.[43] The noncovalently bonded assemblies can exist in different forms, e.g., as a cyclic rosette **18** (Fig. 5), and have been the subject of many structural studies[44–53] and reviews.[54–56] The Reinhoudt group[46,52,56,57] combined synthesized calix[4] arene dimelamine with cyanuric or barbituric acid, and studied the aggregates formed between them.

5. Cyanuric chloride in functional group transformation

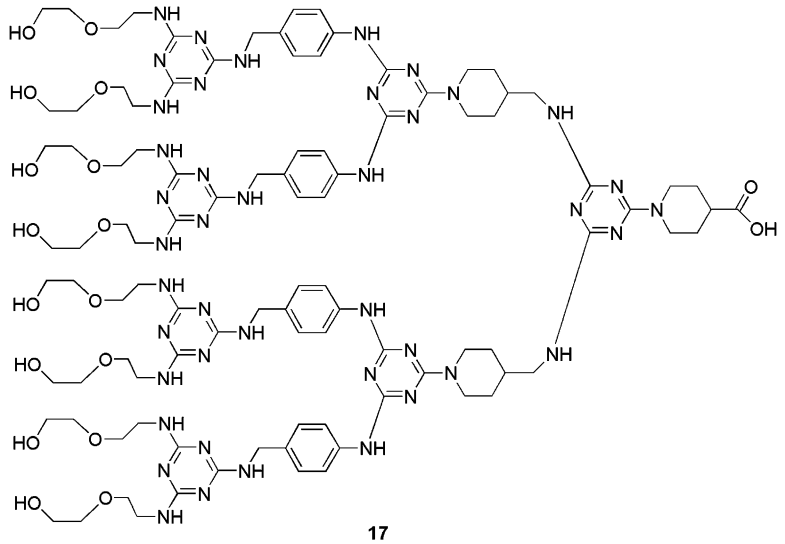
In spite of the enormous number of publications devoted to functional group transformation,[58] there is still a need for mild methods that exhibit selectivity among functional groups, especially in the case of polyfunctional derivatives. In the older literature, one can find examples of applications of 2,4,6-trichloro-1,3,5-triazine in synthesis.[59–66] Recently there has been a considerable growth of interest in the use of cyanuric chloride and its derivatives in organic synthesis.

Cyanuric chloride is often used for activation of carboxylic acids in various transformations. There is disagreement about the initial product of the reaction of carboxylic acids with CC. Some claim that the product is acid chloride,[59,61–63,67] which was isolated and characterized in some cases. Others[68–72] argue that the acylated *s*-triazine is an intermediate, but there is a lack of direct proof of its formation.[73]

Falorni[68] reported that carboxylic acids, including *N*-protected amino acids, can be activated with CC and subsequently reduced to their corresponding alcohols with sodium borohydride in water (Scheme 4). This method is particularly suitable for the reduction of *N*-*Z*, *N*-Boc, and *N*-Fmoc amino acids, and results in high yields without racemization. The authors suggest that 2-acyloxy-4,6-dichloro-1,3,5-triazine is formed as an intermediate.

Rayle and Fellmeth[70] successfully used CC for the preparation of amides, and claim that 2,4,6-triacyloxy-1,3,5-triazine is an intermediate (Scheme 5).

A new route in the synthesis of diazo ketones was reported by the Forbes group.[71] Aryl carboxylic acids were activated by CC, and reacted with diazomethane (Scheme 6) to diazocarbonyl compounds with moderate yields. Unfortunately,



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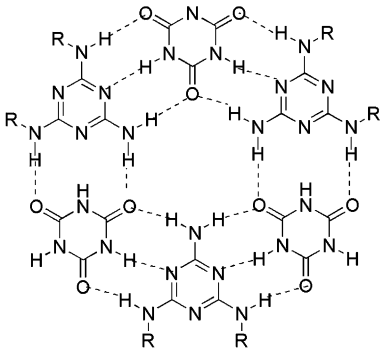
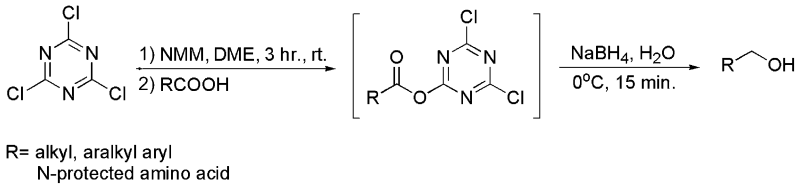
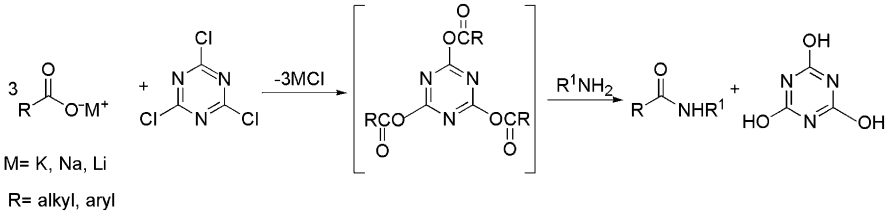


18

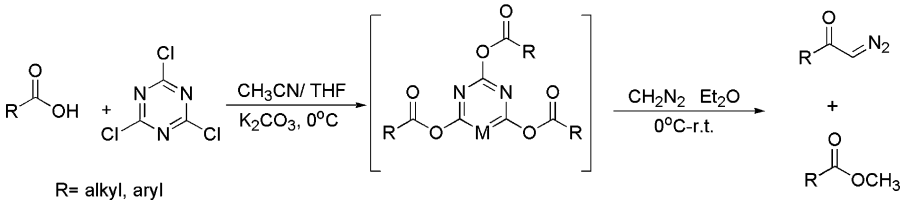
Figure 5.



Scheme 4.



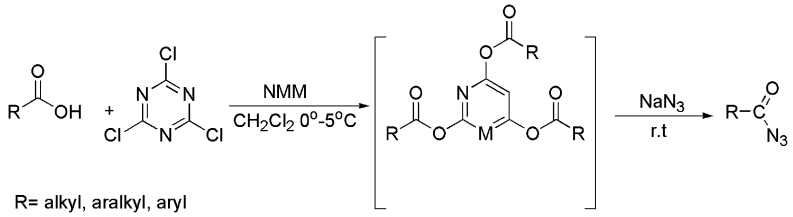
Scheme 5.



Scheme 6.

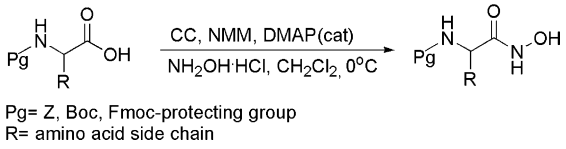
during this reaction a significant amount of methyl esters were formed as a by-product. This reaction was carried out in water, in a one-pot procedure, which is an advantage over other methods.

Bandgar and Pandit[72] applied CC for synthesis of acyl azides directly from carboxylic acids (Scheme 7). Various aryl, heteroaryl, alkylaryl, and alkyl carboxylic acyl azides were obtained under mild conditions with high yields.



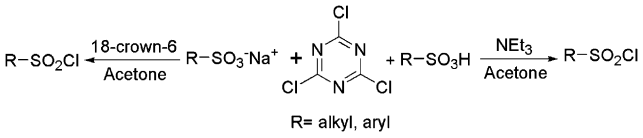
Scheme 7.

Recently, Giacomelli[74] reported a mild and simple one-step method for the preparation of hydroxamic acids. The carboxylic acid or *N*-protected α-amino acid was treated with CC in the presence of NMM followed by hydroxylamine hydrochloride (Scheme 8). Even though the reaction took 6–12 h, the purity and yields were high and no significant racemization was observed. No *O*-acyl or di and triacylated products were formed. Also, hydroxamic acids of *N*-protected dipeptides were obtained by this method.



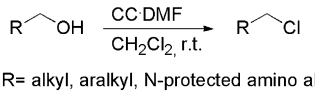
Scheme 8.

2,4,6-Trichloro-1,3,5-triazine was applied as a chlorinating agent for the preparation of sulfonyl chlorides from sulfonic acids under neutral conditions.[75] CC, sulfonic acids, and triethylamine or CC, sodium sulfonates, and catalytic amounts of 18-crown-6 acetone, after heating under reflux gave, good to excellent yields of alkyl and aryl sulfonyl chlorides (Scheme 9).



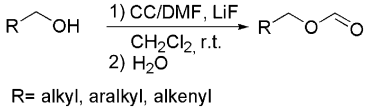
Scheme 9.

Although Sandler[60] used CC for the preparation of alkyl chlorides from their corresponding alcohols, Giacomelli[76] elegantly improved the reaction by using CC and a dimethylformamid adduct[77] for chlorination (Scheme 10). Also, alkyl bromides were obtained by addition of sodium bromide to the CC/DMF adduct. The method was very mild, efficient, and chemoselective. *N*-protected-β-aminochlorides were obtained from their corresponding amino alcohols as well as chloroalcohols from diols.



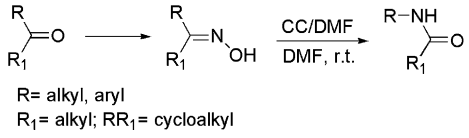
Scheme 10.

The CC/DMF complex was also used for selective protection of primary alcohols by a formyl residue[78] (Scheme 11). Phenols, along with 2°, 3° benzylic, allylic, and propargylic alcohols did not react in the given conditions. *N*-protected β-amino alcohols were also converted to *O*-formates with some exceptions.



Scheme 11.

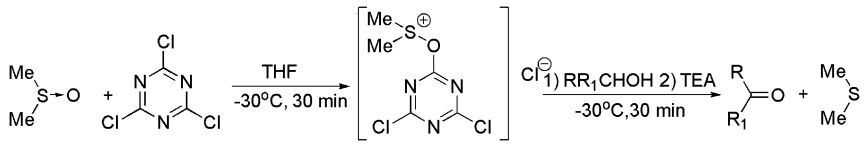
Ketoxime, upon treatment with the CC/DMF complex in dimethylformamide at room temperature, underwent the Beckmann rearrangement[79] with high yields and purity (Scheme 12). In the case of cyclic ketones, lactams were obtained in high yields. Aldoximes gave nitriles under the same conditions. Recently, other authors[80] performed a Beckmann rearrangement in acetonitrile using an acidic cocatalyst besides CC.



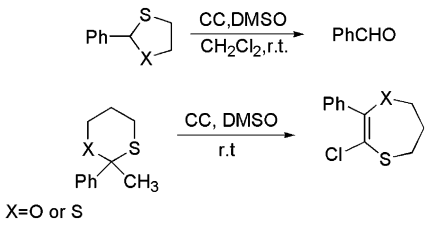
Scheme 12.

Cyanuric chloride catalyzes the oxidation of different types of thiols to disulfides using dimethylsulfoxide, resulting in high yields and purity.[81] De Luca et al.[82] used CC for activation of DMSO in the Swern oxidation (Scheme 13). A variety of aldehydes, ketones, and *N*-protected amino aldehydes were prepared with high yields.

Karimi[83] reported efficient deprotection of a variety of 1,3-dithioacetals and 1,3-oxathiolanes to their corresponding carbonyl compounds using CC. The reaction conditions were mild and time short, and the isolated products were pure and of high yields. 1,3-Oxathioacetals and 1,3 dithioacetals of enolizable ketones gave ring enlargement product derivatives, for example, see Scheme 14.

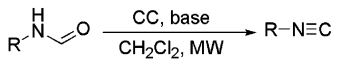


Scheme 13.



Scheme 14.

A very mild method for the conversion of formamides to isonitriles using CC in the presence of a base was recently published by Porcheddu et al.[84] They postulate that the reaction proceeds through the formation of an *O*-acylated intermediate (Scheme 15).



Scheme 15.

Using microwave irradiation (MW), alkyl, cyclic, acyclic benzylic and aromatic, and optically active isonitriles were obtained in a matter of minutes with high yields.

6. Cyanuric chloride in solid-phase synthesis

Solid-phase synthesis, since it's discovery by Merifield,[85] is now routinely used in automated synthesizers.[86] Cyanuric chloride also found applications in solid-supported strategy.

Masala and Tadei[69] loaded CC on different types of amino functionalized resins. These new reagents were used for activation of carboxylic acids to give amides and dipeptides (Scheme 16). A series of aliphatic and aromatic carboxylic acids, and primary and secondary amines, gave amides with good yields.

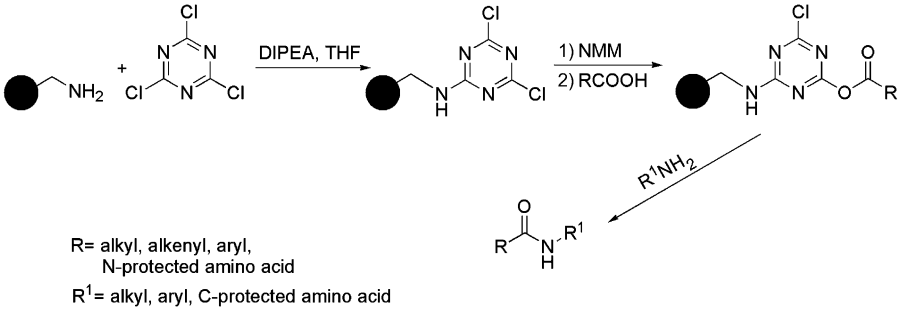
A new resin supported chlorinating reagent, based on CC, has been developed by Luo and co-workers.[67] Cyanuric chloride, loaded on a modified Wang resin, was used for the preparation of acyl chlorides (Scheme 17). The acyl chlorides were not isolated, but were converted to their benzylamides or esters. The yields were good, but chiral amino acids were racemized.

Polyethylene glycol (MeO–PEG–OH) was reacted with CC to give PEG-dichlorotriazine,[87] which was used as a soluble electrophilic scavenger that removes alcohols, thiols, triphenylphosphine, and phosphine oxide from the reaction mixture by selective precipitation and filtration (Scheme 18).

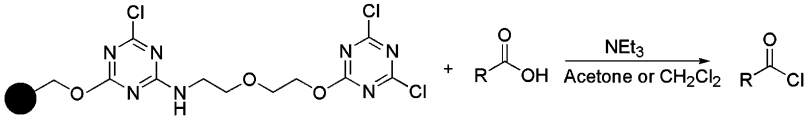
Marsh[88] loaded resins with *s*-triazine dendrimers, which have been used as proton and nucleophile scavengers **18** and **19**, respectively (Fig. 6) in the purification of combinatorially derived products.

7. 2-Chloro-4,6-dimethoxy-1,3,5-triazine in functional group transformation

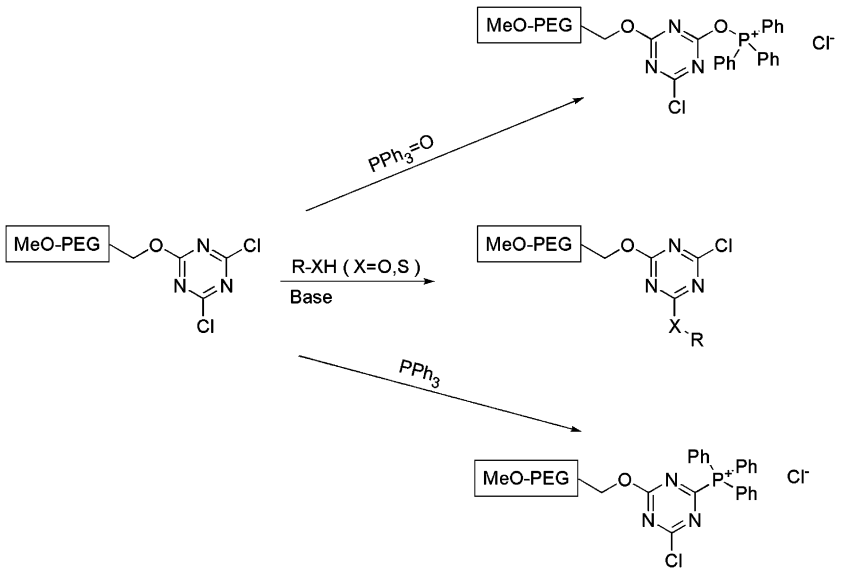
2-Chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) was recently found to have wide applications as a condensing reagent in peptide chemistry.[73] It is commercially available, but can also be easily synthesized.[7,89] Activation of carboxylic acids by means of CDMT is a multi-step process, and was elegantly and thoroughly examined by Kaminski.[73,90,91] It depends upon the specific reaction conditions, such as the order of addition of reagents.[92] The reaction



Scheme 16.



Scheme 17.



Scheme 18.

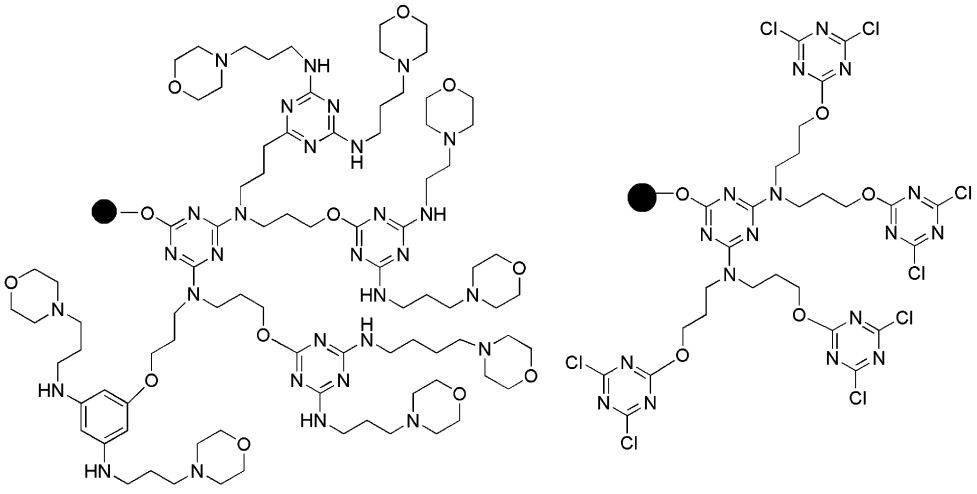


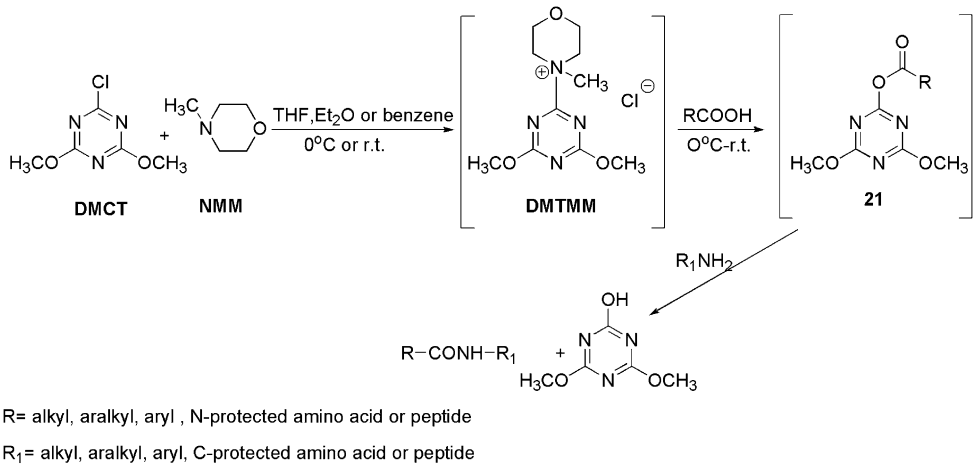
Figure 6.

requires the presence of a tertiary amine, usually *N*-methylmorpholine (NMM). In standard procedure, the first step was reacting CDMT with NMM to form 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), and then the carboxylic acid was added in the next step generating an active ester **21** (Scheme 19), which subsequently gave with an amine the desired product.

No significant racemization was observed during the synthesis of peptides. Optical purity was found to be more that 99.5%.[73] Another sequence of addition of reagents, e.g., mixing CDMT with carboxylic acid and NMM, stirring for 1 h, then adding amino acid ester, lead to significant racemization via formation of azlactone.[92] Another protocol was suggested by Garrett et al.[92] The reaction was provided in a one-pot, one-step procedure, i.e., they mixed CDMT with acid and amine reagents and then NMM to the reaction medium. No significant loss of configuration was observed, and the reaction was finish faster. When chiral tertiary amines such as strychnine, brucine or sparteine were used instead of NMM, using CDMT in coupling of racemic *N*-protected amino acid with amino components, the reaction proceeds enantioselectively.[91]

4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride was isolated and fully characterized.[90,93] It is a stable compound that can be stored in the solid state at room temperature for up to a month or for several months in the refrigerator, without detectable decomposition. This reagent combined with carboxylic acid gave an active ester **21** (Scheme 19), and was used as condensing reagent for synthesis of esters and amides.[94–96]

Taddei[97] reported the application of DMTMM to the solid-phase synthesis of peptides. The yields and purity of the products were high.



Scheme 19.

Recently, Kaminski et al.[98] introduced 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium tetrafluoroborate as a more stable reagent than the corresponding DMTMM chloride. The new coupling reagent was used in ester and peptide synthesis, in solution, and in solid-phase synthesis.

DMTMM **21** (Scheme 20) can be generated by different protocols mentioned above. This active ester, without isolation was used for many transformation of carboxylic group.

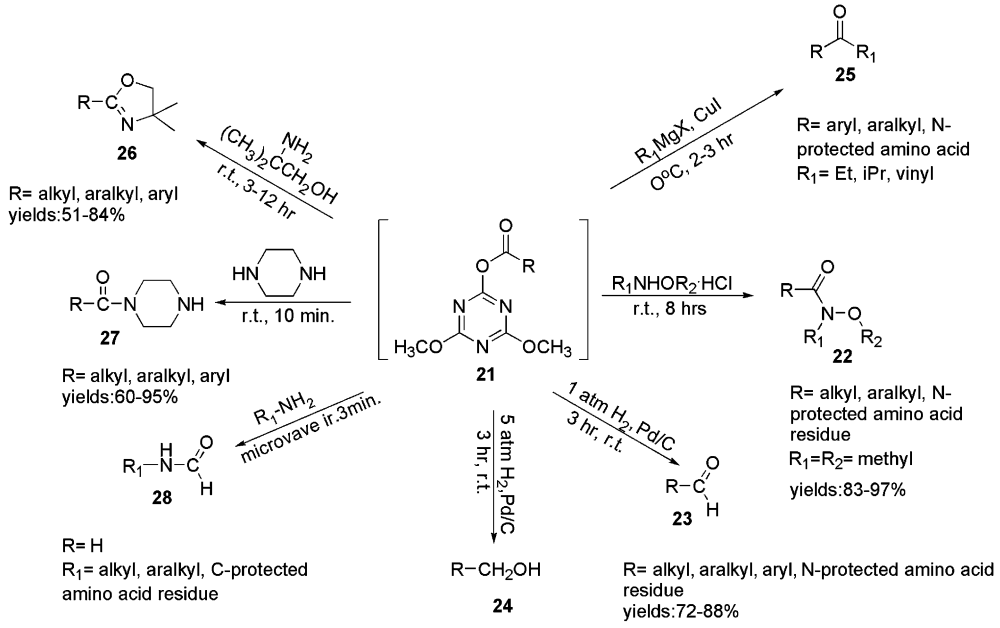
Giacomelli et al.[99] prepared it using CDMT and applied it to the synthesis of *N*-methoxy-*N*-methylamides, commonly named Weinreb amides **22** (Scheme 20), a useful precursor to ketones.[100] A variety of these compounds were obtained quantitatively from carboxylic acids, and *N*-protected amino acids with high yields and purity. DMTMM was also used for this purpose, but the yields of Weinreb amides were lower.

It was reported that active ester **21** (Scheme 20), prepared from DMTMM was reduced by hydrogen and Pt/C as the catalyst to the corresponding aldehyde **23** (Scheme 20) in good yields.[101] Required optimization of the solvent, hydrogen pressure, temperature, and time of reduction are disadvantages to this method. Higher hydrogen pressure (5 atm) gave alcohols.

Activated esters of aromatic carboxylic acid, and *N*-Boc or *N*-*Z* protected α-amino acids were converted to ketones **25** (Scheme 20) or α-amino ketones by Grignard reagent in the presence of stoichiometric amounts of CuI.[102]

Bandar and Pandit[103] reported the synthesis of 2-oxazolines **26** (Scheme 20) from acyloxy triazine. The active ester was reacted at room temperature with 2-amino-2-methyl-1-propanol giving the desired product with good yields.

The same conditions, were used for the selective preparation of monoacylated piperazine derivatives **27** (Scheme 20) with good yields.[104] Monoacylation of symmetrical diamines often becomes problematic due to competitive bisacylation.



Scheme 20.

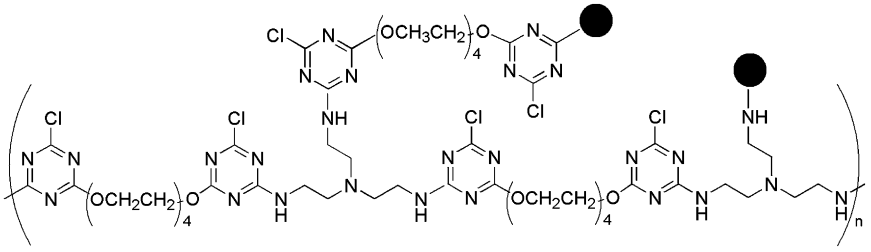
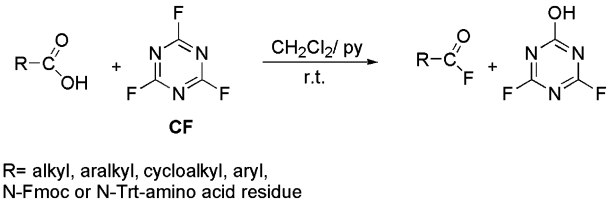


Figure 7.

Recently, active ester **21** of formic acid was used for the formylation of amines and α-amino acid esters **28** (Scheme 20).[105] The reaction was conducted under reflux in methylene chloride, or under microwave irradiation to reduce the reaction time from hours to a few minutes. The yields were high, the products pure and no significant racemization of the chiral centers was observed.

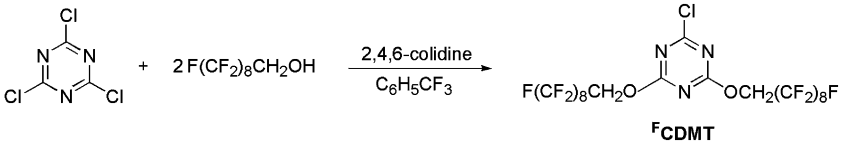
Based on the reactivity of CC, Kunishima et al.[106] published preliminary data about a new immobilized dehydrocondensing reagent in a polymerized form (Fig. 7). This polymer reacts with carboxylic acids, in the presence of a NMM like CDMT or DMTMM, giving active esters, which with amines, gave amides in good yields.



Scheme 22.

8. Applications of other derivatives of *s*-triazine in organic synthesis

Markowicz and Dembinski developed a fluorous 2-chloro-4,6-bis-[(heptadecafluorononyl)oxy]-1,3,5-triazine (^{F}CDMT), an analog of CDMT, as a new coupling reagent in peptide synthesis.[107] It was prepared from CC and heptadecafluorononan-1-ol (Scheme 21), and fully characterized. It is believed that the mechanism of activation of a carboxylic acid by ^{F}CDMT is similar to that of CDMT (Scheme 19). The advantage of this method lies in nonaqueous and non-acidic isolation protocol. The fluorous by-product is insoluble in organic solvents. Extraction by chloroform or ethyl acetate gave, after filtration, di and tripeptides in excellent yields.



Scheme 21.

2,4,6-Trifluoro-1,3,5-triazine CF (Scheme 22), with the common name of cyanuric fluoride, was prepared from CC.[108] It easily converts carboxylic acids as well as *N*-Fmoc and *N*-Trt amino acids, to the corresponding fluorides, which in turn gave excellent yields in both solution and solid-phase peptide synthesis.[109,110] The fluorides were especially useful in the incorporation of sterically hindered amino acids without loss of configuration.

1,3,5-Trichloro-2,4,6-trioxo-*s*-triazine, with the commonly used name-trichloroisocyanuric acid (TCICA), is produced on a large scale for household and industry use, but has found less applications in organic synthesis. As a *N*-chloramine it was used mostly as a chlorination and oxidation agent, and was the subject of a review where references to it's different applications can be found.[111]

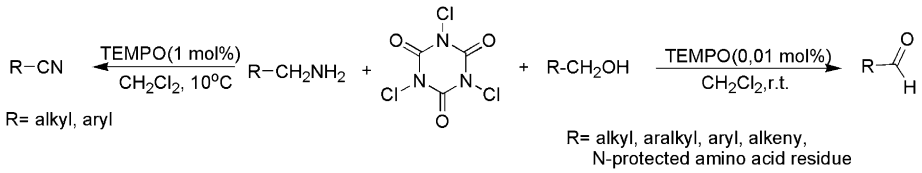
Giacomelli applied TCICA for oxidation of primary alcohols, and *N*-protected-β-amino alcohols to aldehydes (Scheme 23).[112] The reaction was fast (15–20 min), yields high, and no overoxidation to carboxylic acids was detected. The secondary alcohols can be oxidized to ketones, but the reaction requires more than 6 h for completion. Because of this, primary alcohols can be selectively oxidized in the presence of secondary alcohols.

Very recently other authors[113] found that TCICA in the presence of catalytic amount of potassium bromide and wet silica gel selectively oxidized benzylic and secondary alcohols.

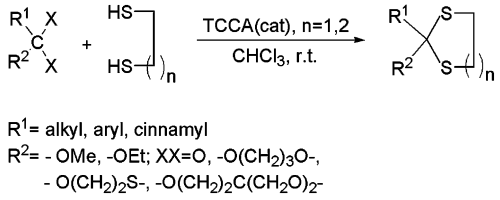
It was reported that TCICA, in the presence of free radical TEMPO, converts primary amines to their corresponding nitriles in mild conditions and with high yields (Scheme 23).[114]

Frouzabadi et al.[115] published that TCICA is an efficient catalyst for the thioacetalization of aldehydes, and the transthioacetalization of *O*,*O*- and *S*,*O*-acetals (Scheme 24). The reaction was run at room temperature and was very selective in the presence of ketones.

Zolfigol et al. recently used TCICA to oxidize 1,3,5-trisubstituted pyrazolines to their corresponding pyrazoles (Scheme 25).[116] The reaction was run at room temperature

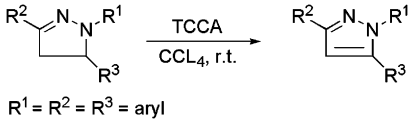


Scheme 23.



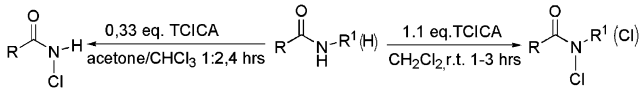
Scheme 24.

in carbon tetrachloride, or under solvent free conditions. In both cases the yields were good.



Scheme 25.

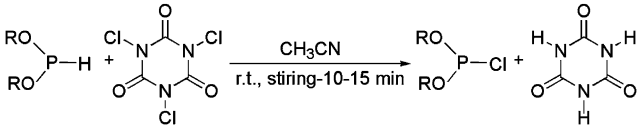
Trichloroisocyanuric acid was also applied for *N*-chlorination of amides, lactams, and carbamates as intermediates in organic synthesis.[117] Primary amides gave *N*-mono or *N*,*N*-dichloroamides, depending on the ratio of reagents and the reaction conditions (Scheme 26). Chlorination of amino acid carbamates does not need the protection of the carboxylic function.



Scheme 26.

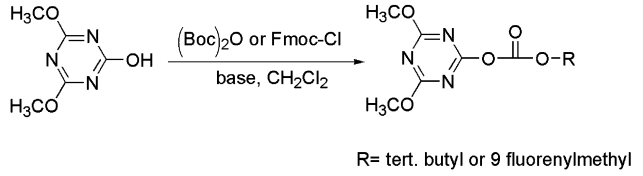
Carboxylic acids can be converted to acid chlorides by a reaction with TCICA in the presence of triphenylphosphine under mild conditions.[118] The acid chlorides were not isolated, but reaction with amines or alcohols afforded corresponding amides or esters (Scheme 27).

A very mild method for obtaining dialkyl chlorophosphates, by stirring TCICA with dialkyl phosphites in acetonitrile at room temperature was published (Scheme 28).[119] The reaction was finished in 10–15 min, giving products in excellent yields.



Scheme 28.

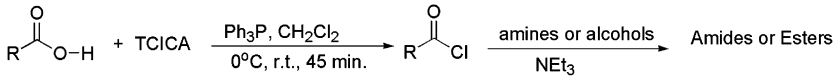
Kunishima et al.[120] very recently reported synthesis of new reagents for introduction of Boc and Fmoc protective groups into amines. By reaction of 4,6-dimethoxy-1,3,5-triazin-2-ol (obtained from CC) with di-*tert*-butyl dicarbonate or with 9-fluorenylmethyl chloroformate, they obtained *tert*-butyl 2,4-dimethoxy-1,3,5-triazinyl carbonate or 9-fluorenylmethyl 4,6-dimethoxy-1,3,5-triazinyl carbonate, respectively (Scheme 29). Both are stable nonirritating compounds, which allowed the introduction of Boc or Fmoc group into amines and amino acids in the range of minutes, without detectable side reactions.



Scheme 29.

9. Conclusion

This paper has reviewed recently published applications of 2,4,6-trichloro-1,3,5-triazine, and its related derivatives in organic synthesis. Increased interest in CC lies in the different reactivities of chlorine atoms, which are easily controlled by temperature. It allows sequential introduction of various substituents into a *s*-triazine ring using a one-pot procedure. These reagents also found applications in solid-phase synthesis by a combinatorial approach, as a template for peptides, for synthesis of dendrimers and noncovalently bonded supramolecular aggregates. Carboxylic acid's activation by CC or DMCT was used in many chemical transformations, and can be a valid alternative to other methods so as to avoid the use of toxic or expensive reagents. Sometimes the reactions needed hours to be completed, but these procedures have advantages over older methods in terms of yields, mildness, and green chemistry.



Scheme 27.

Further applications of cyanuric chloride and its derivatives can be expected.

Acknowledgements

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Biographical sketch

Grzegorz Blotny was born in Bydgoszcz (Poland). He studied chemistry at Gdansk Technical University (Gdansk, Poland) and completed his PhD in the field of peptide chemistry in 1966 with Emil Taschner and Zygmunt Ledochowski. As faculty at Gdansk Technical University, he completed his habilitation in 1983. During the period of 1983–1984, he was a visiting scientist at N.I.H. (USA). In 1985 he moved to the University of Maryland Baltimore County (Baltimore, USA), where he is a Research Associate Professor. His research interests focus on peptide chemistry and the development of new methodologies in organic synthesis.

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Palladium catalysed bis- and tris-cyclisations furnishing fused cyclopropyl carbo/heterocycles

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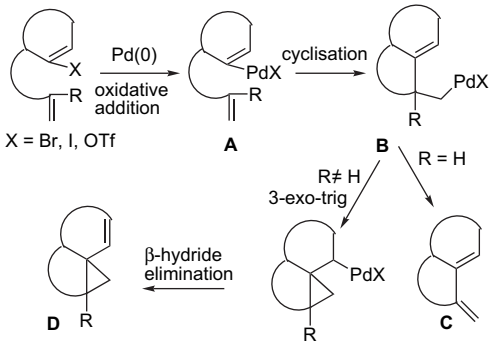
Abstract—Catalytic bis- and tris-cyclisation of a series of acyclic carbo- and heterocyclic precursors results in formation of two or three rings, two or three C–C bonds and two asymmetric tetrasubstituted C-centres regio- and stereoselectively in excellent yield.

1. Introduction

Palladium catalysed cascade reactions provide valuable strategies for the constructions of fused, bridged and spiro carbo/heterocyclic systems.[1,2] Furthermore such cascades have demonstrated their utility for the construction of small strained rings. We and others have reported palladium catalysed cyclisations leading to di-, tri- and tetracyclic compounds containing fused cyclopropane rings.[3–10] Additionally palladium catalysed tandem cyclisation–cyclopropanation is a novel way of assembling a variety of carbo/heterocyclic skeletons with concomitant engineering of considerable additional molecular complexity not available via classical methods for the formation of cyclopropanes such as the reaction of diazo compounds with alkenes catalysed by Rh,[11a–e] Ru,[11f] Cu,[12] Pd[13] and Pt[14] complexes, and Pt[15a] and Au[15b] catalysed cycloisomerisation.

In this paper we report full details of palladium catalysed bis- and tris-cyclisation cascades affording fused/spiro cyclopropyl carbo/heterocycles.[3a–c] A general palladium catalysed bis-cyclisation cascade is shown in Scheme 1.

Oxidative addition of Pd(0) to the carbon–halide/triflate bond gives a vinyl palladium(II) species **A**. Cyclisation of **A** onto a proximal alkene gives the alkyl palladium(II) intermediate **B**. When R=H then **B** may undergo a β-hydride elimination to give **C**. If R≠H a second cyclisation occurs to form the tricyclic cyclopropane **D**.



Scheme 1.

2. Bis-cyclisation cascades

2.1. 5-*exo-trig*/3-*exo-trig* Cascades

2.1.1. Carbocyclic systems. Enol triflates **3a–c** were prepared (Scheme 2) to explore palladium catalysed 5-*exo-trig*/3-*exo-trig* cascades forming tricyclic cyclopropanes. Thus **1a–c** were treated with 1.1 mol equiv ^{t}BuOK in ^{t}BuOH and 4-iodo-2-methylbut-3-ene to give **2a–c** in good yields. Subsequent treatment of **2a–c** with Comins triflating agent[16] in the presence of LDA at −78 °C afforded enol triflates **3a–c** in 77–81% yields.

When enol triflate **3a** was reacted in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, Na_2CO_3 (2 mol equiv), Et_4NCl (1 mol equiv) in boiling acetonitrile it afforded **4** as a single diastereoisomer in 88% yield. The bond forming sequence is detailed in Scheme 3. The relative stereochemistry of **4** was established by NOE studies on **5**, which was prepared

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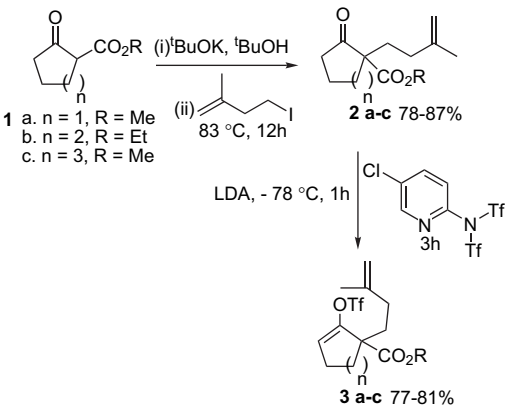
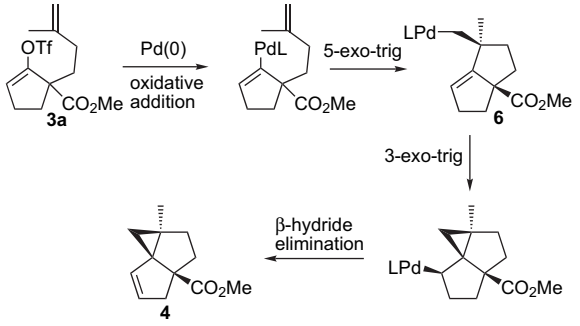
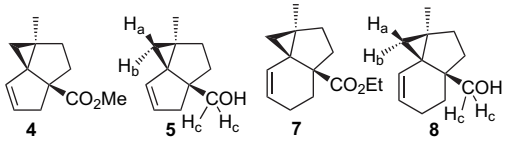


Scheme 2.



Scheme 3.

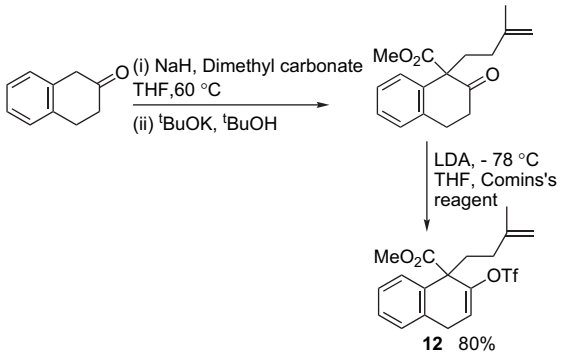
by $LiAlH_4$ reduction of **4**. Thus irradiation of both of the diastereotopic protons H_c (δ 3.45) resulted in 3% enhancement of the signal for the proton H_a (δ 0.90) showing that the cyclopropane ring and the $-CH_2OH$ group are cis-related.



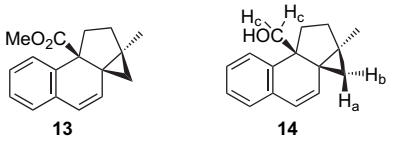
In a similar manner the analogous six-membered enol triflate **3b** underwent consecutive stereo- and regiospecific 5-*exo-trig* and 3-*exo-trig* cyclisations to give the 3/5/6-ring system **7** in 73% yield. The relative stereochemistry was established by NOE studies on **8**, which was obtained by $LiAlH_4$ reduction of **7**. Irradiation of both of the diastereotopic protons H_c (δ 3.45) resulted in 2.5% enhancement of the signal for H_a (δ 1.05).

The seven-membered ring enol triflate **3c** cyclised under similar conditions to afford a 2:1:1 mixture of **9**, **10** and **11** in 75% yield (Scheme 4). In this case double bond isomerisation proved more facile than in the case of the 3/5/5- and 3/5/6-ring systems. It would be expected that addition of Ag^+ or Tl^+ salts[17,18] would suppress double bond isomerisation (vide infra **21**, **22**). Indeed addition of TlOAc (1.2 mol equiv) and reducing the reaction time to 5 h afforded **9** (76%) as the sole product.

The vinyl triflate **12** was prepared in 70% yield from β-tetralone in three steps by carboxymethylation, alkylation and triflation (Scheme 5) in order to study the formation of a tetracyclic cyclopropyl system. Cyclisation of **12** under the same conditions as described above afforded **13** in 90% yield. The relative stereochemistry of **13** was also established by $LiAlH_4$ reduction to give **14** followed by NOE studies. Irradiation of both of the diastereotopic H_c protons (δ 3.45) resulted in enhancement (2.5%) of the signal for H_a (δ 0.90) thus establishing their cis-relationship.



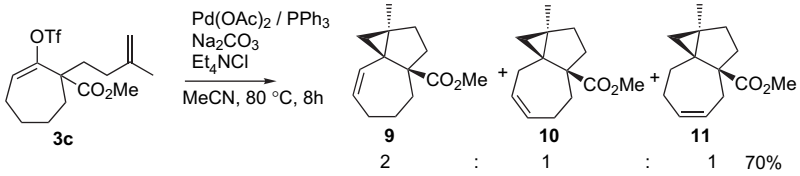
Scheme 5.



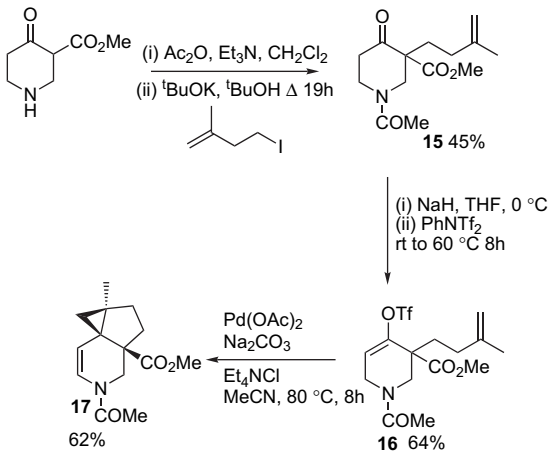
2.1.2. Heterocyclic systems. Enol triflate **16** was synthesised in three steps in good yield (Scheme 6). Methyl 4-oxopiperidine-3-carboxylate was *N*-acetylated in the presence of Et_3N in CH_2Cl_2. The alkyl side chain was then introduced in the presence of ^{t}BuOK as base. Triflation of **15** was carried out using McMurry's method[19] to afford **16** in 64% yield.

Enol triflate **16** successfully underwent a palladium catalysed 5-*exo-trig*/3-*exo-trig* cyclisation cascade to give **17** as a single stereoisomer in 62% yield.

A further heterocyclic precursor, vinyl bromide **18**, was prepared from 2,3-dibromocyclohexene and 2-methyl-2-propen-1-ol in 68% yield. It cyclised in the presence of 5 mol % $PdCl_2(PPh_3)_2$, Et_4NCl (1 mol equiv) and Zn dust

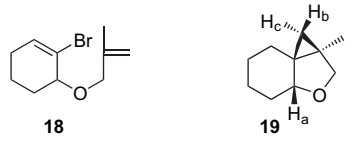


Scheme 4.



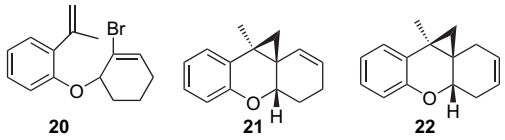
Scheme 6.

(2 mol equiv) in MeCN at 80 °C to afford **19** in 50% yield. There are two potential roles for the Zn dust: (a) as a reductant of Pd(II) to Pd(0) and (b) as a halogen sink[20] promoting formation of a more reactive, coordinatively unsaturated palladium intermediate. The relative stereochemistry of **19** was established by NOE studies. Thus irradiation of proton H_a (δ 3.92) effected enhancement (2%) of the signal of H_b (δ 1.10) establishing that the cyclopropane ring and H_a are cis-related.

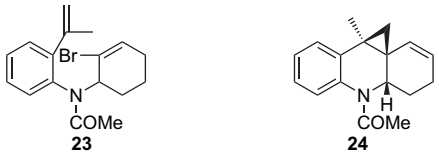


2.2. 6-*exo-trig*/3-*exo-trig* Cascades

Vinyl halide **20** was synthesised in 55% yield from 2-hydroxyacetophenone and 2,3-dibromocyclohex-1-ene in boiling THF, followed by a Wittig reaction. Under standard palladium catalysed cyclisation conditions **20** gave a 10:1 mixture of **21** and **22** in 71% yield via successive 6-*exo-trig* and 3-*exo-trig* cyclisations. The isomeric product **22** was suppressed by using modified reaction conditions previously developed by us.[18] Thus when the reaction was repeated with 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3 and 1.2 mol equiv TlOAc in boiling MeCN, **21** was obtained as the sole product in 76% yield.

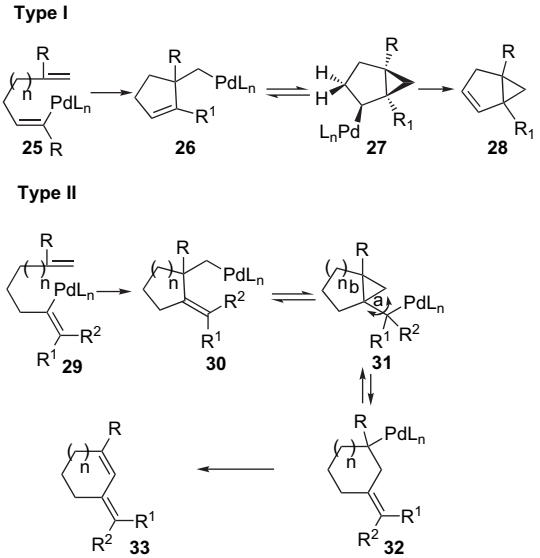


We briefly looked at the *N*-analogue of **20**. Compound **23** was prepared in 70% yield from *N*-acetyl-2-isopropenylaniline in two steps by acetylation followed by alkylation. Cyclisation of **23** under our standard conditions over 8 h afforded **24** in a disappointing 37% yield. However, addition of Zn dust (2 mol equiv) improved the yield from 37 to 72% and reduced the reaction time to 3 h.



All the foregoing cyclopropyl forming cyclisations proceed regio- and stereoselectively and involve the formation of two rings, two C–C bonds and two chiral tetrasubstituted C-centres.

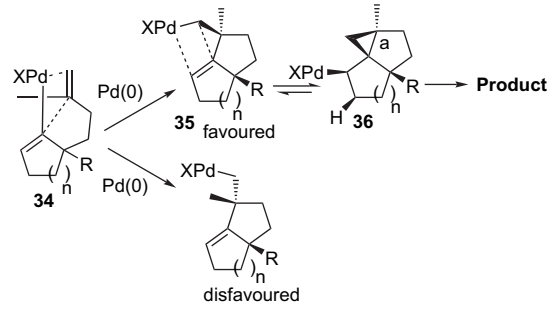
2.2.1. Mechanism. Cyclopropanation as an integral part of palladium catalysed cascades is often concealed by rearrangement of a cyclopropylcarbinylpalladium intermediate with accompanying ring expansion in appropriate cases. This process was first identified and explained, essentially simultaneously, by Torii[21] and Negishi.[22] Negishi formalised the rearrangement in terms of type I **25** and type II **29** substrates (Scheme 7).[22] The key difference is that a type I substrate is processed via intermediate **27** in which the required *syn* alignment of bonds β to the palladium only allows either equilibration with **26** or β-H elimination to form **28**. In contrast type II substrates **29** proceed via **31**, which can equilibrate with **30** but additionally now possess a rotatable bond **31** (↷) allowing the palladium to attain a *syn* alignment with either cyclopropyl bond a or b. *syn* Alignment with bond b triggers a cyclopropylcarbinylpalladium ring expansion affording **32** and subsequently **33** (or double bond isomer) in which the diagnostic olefinic geometry (R^1/R^2) has been inverted.[23] For very elegant examples of stereochemical control of such processes see Torii et al.[21] Solvent effects on type II processes have been interpreted in terms of equilibration of **31** and **32**.[24]



Scheme 7.

A stereochemical feature not heretofore discussed is the influence of an allylic stereocentre in the type I substrates, which is present in **3a–c**, **16**, **20** and **23** in this work. The fusion of a new five- or six-membered ring onto an existing 5–7-membered ring in these examples always results in a cis-arrangement of the allylic substituent and the

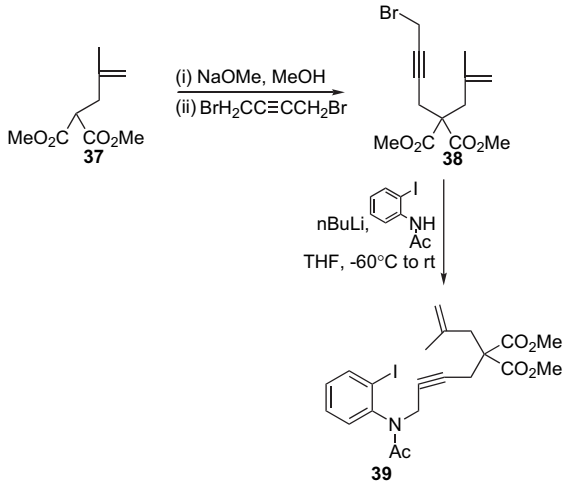
cyclopropyl ring (vide infra). Mechanistically the initial cyclisation pre-ordains all the subsequent cascade stereochemistry (Scheme 8) and is controlled by the four-centre C–Pd/alkene transition state **34**, ease of coordination of the alkene and (presumably) tether length. The reaction then proceeds via a second four-centre transition state **35** to product. The initial cyclisation **34**→**35** places the CH_2PdX group on the *exo* face of a bowl shaped transition state minimising steric interactions. The second cyclisation affords **36**, which lacks the rotatable C–C bond necessary to effect a *syn* relationship between the Pd–C bond and the cyclopropyl 'a' bond in **36**.



Scheme 8.

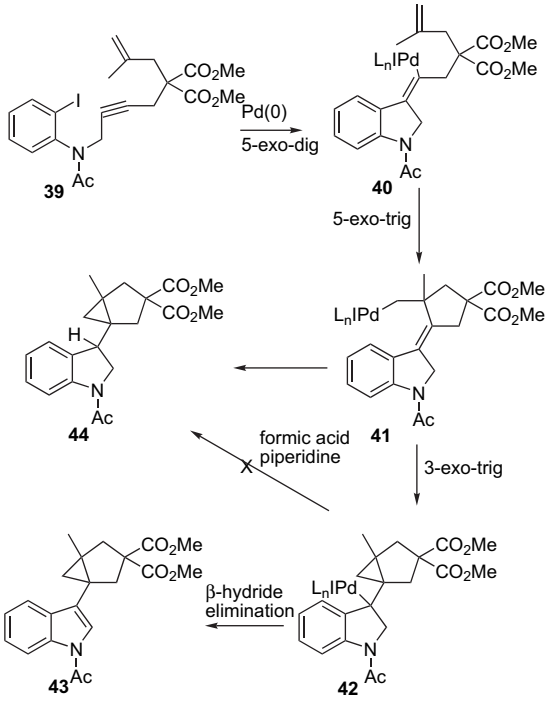
2.3. Tris-cyclisation cascades

Tris-cyclisation substrate **39** was prepared in two steps via sequential alkylation procedures in good yield (Scheme 9).



Scheme 9.

Under our standard palladium catalysed conditions **39** undergoes an initial 5-*exo-dig* cyclisation to give a vinyl palladium intermediate **40**, followed by a 5-*exo-trig* cyclisation process forming an alkyl palladium intermediate **41**, which then undergoes a 3-*exo-trig* cyclisation followed by β-hydride elimination to give **44** in 62% yield (Scheme 10).[3a] Addition of formic acid and piperidine as hydride ion source in place of Na_2CO_3 also afforded **44**. This indicates that all three cyclisation processes: 5-*exo-dig*, 5-*exo-trig* and 3-*exo-trig* are faster than hydride ion capture processes and also that β-hydride elimination **42**→**43** is faster than hydride ion capture e.g. **42**→**44**. This process results in formation of three rings, three C–C bonds, and two chiral tetrasubstituted C-centres.



Scheme 10.

3. Summary

We have demonstrated novel regio- and stereoselective palladium catalysed bis- and tris-cyclisation cascades allowing access to polyclic cyclopropyl carbo- and heterocycles, regio- and stereoselectively in good yields. The stability of the cyclopropyl products arises by suppression of the cyclopropylcarbinyl palladium(II) rearrangement due to lack of a rotatable C–C bond, which prevents a *syn* alignment between the Pd–C bond and the relevant cyclopropyl C–C bond. Related cyclisations[7–10] were reported subsequent to our preliminary communications.[3]

4. Experimental

4.1. General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec instrument operating at 70 eV (EI and FAB) or ZD 2000 electrospray instrument (ES). Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. IR spectra were determined on a Nicolet Magna FT-IR 560 spectrometer. The IR samples were prepared as thin films by evaporation of a solution of the compound in DCM onto a germanium plate. Nuclear magnetic resonance spectra were recorded on QE 300 and Bruker 400 instruments operating at, 300 and 400 MHz, respectively. Solvents

were dried according to established methods, unless purchased dry from Aldrich in sure-seal bottles. Palladium acetate was supplied by Johnson Matthey and used as received. The term ether refers to diethyl ether and the term petrol refers to the 40–60 °C boiling point fraction of petroleum ether.

4.2. General procedure for alkylation of 2-oxocycloalkane carboxylates

2-Methyl-4-iodo-1-butene (1 mmol) was added to a stirred solution of methyl 2-oxocycloalkane carboxylate (1 mmol) and KO^{t}Bu (1 mmol) in Bu^{t}OH (10 ml). The solution was slowly heated to boiling and maintained under reflux for 19 h. After cooling, the mixture was treated with water to dissolve precipitated salts and extracted with ether (3×25 ml). The combined ether extracts were washed with saturated brine, dried ($MgSO_4$) and evaporated in vacuo to leave an oil, which was purified by column chromatography or kugelrohr distillation.

4.2.1. Methyl 1-(3-methyl-3-butenyl)-2-oxocyclopentane carboxylate (2a). 2-Methyl-4-iodo-1-butene (6.89 g, 35 mmol), methyl 2-oxocyclopentane carboxylate (5.0 g, 35 mmol) and 1 M potassium *tert*-butoxide in *tert*-butanol (42 ml) were reacted by the general method. Workup in the usual way followed by distillation afforded the product (6.0 g, 81%) as a colourless oil, bp 77–79 °C/0.03 mmHg. Found: C, 68.35; H, 8.40; $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.50%; δ_H: 1.75 (s, 3H, Me), 1.91–2.30 (m, 10H, 5×CH_2), 3.75 (s, 3H, OMe), 4.70 (s, 2H, =CH_2); *m*/*z* (%): 210 (M^+, 1), 151 (4), 142 (100), 110 (89), 55 (36) and 41 (28); ν_{max}: 1770, 1680, 1485, 1280, 1190 and 930 cm^{-1}.

4.2.2. 1-(3-Methyl-3-butenyl)-1-methoxycarbonyl-2-cyclopentenol triflate (3a). *n*-Butyllithium (19.64 ml, 1.6 M solution in hexane, 0.03 mol) was added slowly via a syringe to a stirred solution of diisopropylamine (4.4 ml, 0.031 mol) in freshly distilled THF (10 ml) while maintaining the temperature between −30 and −20 °C. The resulting solution was stirred at that temperature for 0.5 h. Compound **2a** (6 g, 0.028 mol) in THF (10 ml) was added dropwise at −78 °C and the resulting solution stirred at −78 °C for 1 h. *N*-(5-Chloro-2-pyridyl)triflimide (12.3 g, 0.031 mol) in THF (15 ml) was then added dropwise at −78 °C and the resulting solution maintained at that temperature for 3 h. After allowing the reaction mixture to come to room temperature, water was added, the mixture extracted with ether, washed with 10% NaOH and the organic extracts dried ($MgSO_4$) and evaporated. The residual oil was distilled under vacuum to afford the product (7.5 g, 77%) as a colourless oil, bp 82–85 °C/0.03 mmHg. Found: C, 45.80; H, 5.00; S, 9.50; F, 16.60; $C_{13}H_{17}F_3O_5S$ requires: C, 45.60; H, 4.95; S, 9.35; F, 16.65%; δ_H: 1.72 (s, 3H, Me), 1.92–2.54 (m, 8H, 4×CH_2), 3.72 (s, 3H, OMe), 4.75 (d, 2H, *J* 10 Hz, =CH_2), 5.78 (s, 1H, CH=C); *m*/*z* (%): 342 (M^+, 1), 273 (100), 149 (7), 133 (50), 108 (94), 69 (80), 55 (47) and 41 (56); ν_{max} (film): 2880, 1700, 1610, 1380, 1200, 1190 and 820 cm^{-1}.

4.2.3. 1-(3-Methyl-3-butenyl)-1-ethoxycarbonyl-2-cyclohexenol triflate (3b). *n*-Butyllithium (14.44 ml, 1.6 M solution in hexane, 0.023 mol) was added slowly via a syringe to a stirred solution of diisopropylamine (3.23 ml, 0.023 mol) in THF (10 ml) while maintaining the temperature between −30 and −20 °C. The resulting solution was stirred at that temperature for 0.5 h. Compound **2b** (5 g, 0.02 mol) in THF (10 ml) was added dropwise at −78 °C and the solution was stirred at −78 °C for 1 h. *N*-(5-Chloro-2-pyridyl)triflimide (8.24 g, 0.02 mol) in THF (15 ml) was then added dropwise at −78 °C and the resulting mixture maintained at −78 °C for 3 h. The solvent was then removed under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (150 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:1 v/v ether–petroleum ether to afford the product (6.5 g, 83%) as a pale yellow oil, bp 96–102 °C/0.02 mmHg. Found: C, 48.75; H, 5.70; S, 8.60; F, 15.25; $C_{15}H_{21}F_3O_5S$ requires: C, 48.65; H, 5.65; S, 8.65; F, 15.4%; δ_H: 1.27 (t, 3H, *J* 6 Hz, Me), 1.73 (s, 3H, =CMe), 1.31–2.47 (m, 10H, 5×CH_2), 4.23 (m, 2H, OCH_2), 4.71 (m, 2H, =CH_2) and 5.91 (m, 1H, =CH); *m*/*z* (%): 370 (M^+, 1), 325 (5), 302 (100), 221 (11), 69 (93), 55 (63) and 41 (47); ν_{max} (film): 1735, 1425, 1220, 1150, 1100, 1040, 920, 840 and 775 cm^{-1}.

4.2.4. Methyl 1-(3-methyl-3-butenyl)-2-oxocycloheptane carboxylate (2c). Prepared from 2-methyl-4-iodo-1-butene (12.6 g, 0.06 mol) and methyl 2-oxocycloheptane carboxylate (10 g, 0.058 mol) in 1 M potassium *tert*-butoxide in *tert*-butanol (70 ml) by the general procedure. The yellow solution was heated slowly to reflux and maintained there for 19 h. The solvent was then removed under reduced pressure and the residue partitioned between water (150 ml) and dichloromethane (200 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford the product (12.2 g, 87%) as a colourless oil, bp 90–93 °C/0.03 mmHg. Found: C, 70.35; H, 9.20; $C_{14}H_{22}O_3$ requires: C, 70.60; H, 9.25%; δ_H: 1.72 (s, 3H, Me), 1.43–2.61 (m, 14H, 7×CH_2), 3.71 (s, 3H, OMe), 4.70 (m, 2H, =CH_2); *m*/*z* (%): 238 (M^+, 1), 207 (5), 170 (100), 138 (95), 110 (37) and 55 (18); ν_{max} (film): 2900, 1730, 1450, 1220 and 910 cm^{-1}.

4.2.5. 1-(3-Methyl-3-butenyl)-1-methoxycarbonyl-2-cycloheptenol triflate (3c). *n*-Butyllithium (28.9 ml, 1.6 M solution in hexane, 0.046 mol) was added slowly via a syringe to a stirred solution of diisopropylamine (6.46 ml, 0.046 mol) in THF (15 ml) while maintaining the temperature between −30 and −20 °C and stirring continued at this temperature for a further 0.5 h. Compound **2c** (10 g, 0.04 mol) in THF (10 ml) was then added dropwise at −78 °C, and the solution was stirred at −78 °C for 1 h. *N*-(5-Chloro-2-pyridyl)triflimide (16.48 g, 0.04 mol) in THF (15 ml) was added dropwise at −78 °C and the resulting mixture maintained at −78 °C for 3 h. The solvent was then removed under reduced pressure and the residue partitioned between water (200 ml) and dichloromethane (240 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:16 v/v ether–petroleum ether to afford the product (12.8 g, 81%)

as a pale yellow oil, bp 102–104 °C/0.02 mmHg. Found: C, 48.50; H, 5.65; S, 8.70; F, 15.10; $C_{15}H_{21}F_3O_5S$ requires: C, 48.65; H, 5.65; S, 8.65; F, 15.40%; δ_H: 1.70 (s, 3H, Me), 1.88–2.18 (m, 12H, 6×CH_2), 3.75 (s, 3H, OMe), 4.7 (m, 2H, C=CH_2), 6.01 (m, 1H, =CH); *m/z* (%): 370 (M^+, 1), 302 (51), 152 (77), 69 (100) and 55 (43); ν_{max} (film): 3300, 2900, 1740, 1410, 1210, 1170, 1000 and 890 cm^{-1}.

4.2.6. Methyl 1a-methyl-1,1a,2,3-tetrahydrocyclopropa[*c*]pentalene-3a(4*H*)-carboxylate (4). Enol triflate **2a** (0.3 g, 0.87 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.019 g, 0.087 mmol), PPh_3 (0.046 g, 0.175 mmol), Na_2CO_3 (0.185 g, 1.75 mmol) and Et_4NCl (0.145 g, 0.87 mmol) in acetonitrile (8 ml). The resulting mixture was boiled under reflux under a nitrogen atmosphere for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:16 v/v ether–petroleum ether to afford the product (0.15 g, 89%) as a colourless oil; δ_H: 0.95 and 1.00 (2×d, 2×1H, *J* 6 Hz, cyclopropyl H), 1.08 (s, 3H, Me), 1.80–2.14 (m, 4H, 2×CH_2), 2.36 and 2.92 (2×d, 2×1H, *J* 16 Hz, CH_2), 3.54 (s, 3H, OMe), 5.43 and 5.75 (2×m, 2×1H, 2×=CH); *m/z* (%): 192 (M^+, 15), 133 (100), 115 (16), 91 (49) and 39 (19); ν_{max} (film): 1720, 1600, 1445, 1380, 1300, 1260, 1200, 1080, 800 and 735 cm^{-1}.

4.2.7. (1a-Methyl-1,1a,2,3-tetrahydro-cyclopropa[*c*]pentalen-3a(4*H*)-yl) methanol (5). Compound **4** (0.15 g, 0.781 mmol), in dry ether (9 ml) was added dropwise to the stirred suspension of $LiAlH_4$ (0.03 g, 0.781 mmol) in ether (6 ml). The resulting suspension was boiled under reflux for 2 h, cooled and the excess $LiAlH_4$ decomposed by successive addition of H_2O (1 ml), 15% NaOH (1 ml) and H_2O (2 ml). After the addition was complete, the solution was stirred for 1 h, filtered and the precipitate washed with ether (2×20 ml). The combined ether layers were dried ($MgSO_4$), concentrated in vacuo and the residue purified by column chromatography eluting with 1:2 v/v ether–petroleum ether to afford the product (0.102 g, 80%) as a colourless oil. Found: C, 80.50; H, 10.00; $C_{11}H_{16}O$ requires: C, 80.50; H, 9.75%; δ_H: 0.821 and 0.952 (2×d, 2×1H, *J* 6 Hz, cyclopropyl H), 1.06 (s, 3H, Me), 1.30–1.84 (m, 5H, 2×CH_2 and OH), 2.28 and 2.43 (2×d, 2H, *J* 16 Hz, CH_2), 3.41 and 3.49 (2×d, 2H, *J* 10 Hz, OCH_2) and 5.49 and 5.75 (2×br s, 2×1H, =CH_2); *m/z* (%): 164 (M^+, 8), 133 (100), 105 (50), 91 (61), 79 (16), 55 (14) and 41 (17); ν_{max} (film): 3475, 1730, 1485, 1290, 1180 and 760 cm^{-1}.

4.2.8. Ethyl 1a-methyl-1,1a,2,3,4,5-hexahydro-3a*H*-cyclopropa[*c*]indene-3a-carboxylate (7). Enol triflate **3b** (0.3 g, 0.81 mmol) was added to a suspension of $Pd(OAc)_2$ (0.018 g, 0.081 mmol), PPh_3 (0.042 g, 0.l62 mmol), Na_2CO_3 (0.171 g, 1.62 mmol) and Et_4NCl (0.134 g, 0.81 mmol) in acetonitrile (8 ml). The resulting mixture was boiled under reflux under a nitrogen atmosphere for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (60 ml) and dichloromethane (60 ml). The water layer was extracted with dichloromethane (60 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:16 v/v ether–petroleum ether to afford the product (0.12 g, 71%) as a colourless oil. Found: C, 76.20; H, 9.15; $C_{14}H_{20}O_2$ requires: C, 76.35; H, 9.10%; δ_H: 0.52 (d, 1H, *J* 6 Hz, cyclopropyl H), 1.03 (s, 3H, Me), 1.21 (t, 3H, *J* 6 Hz, Me), 1.23–2.07 (m, 9H, 4×CH_2 and cyclopropyl H), 4.05 (m, 2H, OCH_2), 5.23 and 5.72 (2×m, 2×1H, 2×=CH); *m/z* (%): 220 (M^+, 3), 147 (100), 131 (31), 105 (61) and 91 (62); ν_{max} (film): 2900, 1740, 1650, 1460, 1400, 1380, 1280, 1200, 1090, 1050, 975 and 700 cm^{-1}.

4.2.9. (1a-Methyl-1,1a,2,3,4,5-hexahydro-3a-cyclopropa[*c*]inden-3a-yl) methanol (8). Compound **7** (0.1 g, 0.454 mmol) in dry ether (8 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.018 g, 0.454 mmol) in ether (8 ml). The resulting suspension was boiled under reflux for 2 h, cooled and the excess $LiAlH_4$ destroyed by successive addition of H_2O (1 ml), 15% NaOH (1 ml) and H_2O (2 ml). After the addition was complete, the solution was stirred for 1 h, filtered and the precipitate washed with ether (2×15 ml). The combined ether layers were dried ($MgSO_4$), concentrated in vacuo and the residue purified by column chromatography eluting with 1:4 v/v ether–petroleum ether to afford the product (0.063 g, 78%) as a colourless oil. Found: C, 81.00; H, 10.20; $C_{12}H_{18}O$ requires: C, 80.90; H, 10.10%; δ_H: 0.35 and 1.02 (2×d, 2×1H, *J* 5 Hz, cyclopropyl H), 1.16 (s, 3H, Me), 1.30–2.12 (m, 9H, 4×CH_2 and OH), 3.46 and 3.75 (2×d, 2H, *J* 10 Hz, OCH_2), 5.19 and 5.23 (2×br s, 2×1H, CH=CH); *m/z* (%): 178 (M^+, 9), 147 (100), 117 (27), 105 (43), 91 (64), 77 (18) and 41 (16); ν_{max} (film): 3330, 1480, 1390, 1045 and 940 cm^{-1}.

4.2.10. Methyl 1a-methyl-1,1a,2,3,5,6-hexahydrocyclopropa[*c*]azulene-3a(4a*H*)-carboxylate (9). (a) Enol triflate **3c** (0.2 g, 0.54 mmol) was added to a suspension of $Pd(OAc)_2$ (0.012 g, 0.054 mmol), PPh_3 (0.028 g, 0.l08 mmol), Na_2CO_3 (0.114 g, 1.08 mmol) and Et_4NCl (0.089 g, 0.54 mmol) in acetonitrile (6 ml). The resulting mixture was boiled under reflux under a nitrogen atmosphere for 9 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (60 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2), eluting with 1:16 v/v ether–petroleum ether, to afford **9** (0.035 g, 30%), and a 1:1 mixture of **10** and **11** (0.053 g, 45%) as colourless oils. Found (mixed isomers): C, 76.20; H, 9.15; $C_{14}H_{20}O_2$ requires: C, 76.35; H, 9.05%; **9** δ_H: (500 MHz): 0.42 and 1.00 (2×d, 2×1H, *J* 5.0 Hz, cyclopropyl H), 1.14 (s, 3H, Me), 1.5–2.2 (m, 10H, 5×CH_2), 3.68 (s, 3H, OMe), 5.10 (dd, 1H, *J* 12.0, 2.6 Hz, =CH) and 5.7 (ddd, 1H, *J* 12.0, 6.8, 3.0 Hz, =CH); **10** and **11** (1:1 mixture) δ_H: 0.02 and 0.73 (2×d, 2H, *J* 5 Hz, cyclopropyl H), 0.08 and 0.54 (2×d, 2H, *J* 5 Hz, cyclopropyl H), 1.12 and 1.23 (2×s, 6H, 2×Me), 1.43–2.42 (m, 20H, 10×CH_2), 3.16 (d, 1H, *J* 3 Hz, =CH), 3.64 and 3.65 (2×s, 6H, 2×OMe), 5.63 (m, 2H, HC=CH), 5.98 (m, 1H, =CH); *m/z* (%): 220 (M^+, 22), 161 (100), 160 (50), 145 (42), 105 (95) and 77 (17); ν_{max} (film): 1730, 1650, 1450, 1250, 1200, 1110, 1080, 1020 and 840 cm^{-1}.

(b) Repeating the reaction but with a reaction time of 5 h and the addition of TlOAc (0.315 g, 1.2 mmol) afforded **9** (76%) as the sole product.

4.2.11. Methyl 1-(3-methyl-3-butenyl)-2-tetralone-1-carboxylate (12). 2-Methyl-4 iodo-1-butene (2.05 g, 10.7 mmol) was added to a stirred solution of 1-carbomethoxy-2-tetralone (2 g, 9.8 mmol) and KO^{t}Bu (1.21 g, 10.7 mmol in 1 M solution of ^{t}BuOH). The pale yellow solution was boiled under reflux for 10 h, cooled, water added to dissolve the precipitate and extracted with ether (3×20 ml). The combined ether extracts were washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated in vacuum to leave an oil, which was distilled under reduced pressure to afford the product (1.5 g, 57%) as a colourless oil, bp 120–122 °C/0.01 mmHg. Found: C, 74.75; H, 7.60; $C_{17}H_{20}O_3$ requires: C, 75.00; H, 7.35%; δ_H: 1.61 (s, 3H, Me), 2.29–3.19 (m, 8H, 4×CH_2), 3.6 (s, 3H, OMe), 4.60 and 4.46 (2×s, 2×1H, =CH_2), 7.21–7.24 (m, 4H, ArH); *m*/*z* (%): 272 (M^+, 1), 204 (46), 172 (100), 129 (22), 115 (34), 77 (6) and 65 (3); ν_{max} (film): 1780, 1700, 1550, 1505, 1440, 1410, 1370, 1280, 1140 and 960 cm^{-1}.

4.2.12. Methyl 1-(3-methylbut-3-enyl)-2-trifluoromethylsulfonyloxy-1,4-dihydronaphthalene-1-carboxylate (12). 1-Carbomethoxy-1-(3-methylbut-3-enyl)-2-tetralone (1.15 g, 4.2 mmol) in THF (8 ml) was added dropwise at −78 °C to a stirred solution of lithium diisopropylamide [from *n*-BuLi (3.17 ml, 1.6 M solution in hexane, 5.0 mmol) and diisopropylamine (0.71 ml, 5.0 mmol)] in THF (10 ml). The resulting solution was stirred at −78 °C for 1 h and *N*-(5-chloro-2-pyridyl)triflimide (1.74 g, 4.86 mmol) in THF (10 ml) was then added dropwise with stirring and the resulting mixture stirred at −78 °C for 3 h. The solvent was then removed under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (150 ml). The water layer was extracted with dichloromethane (100 ml), the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford the product (1.1 g, 65%) as a colourless oil. Found: C, 53.04; H, 4.70; S, 8.00; F, 14.30; $C_{18}H_{19}F_3O_5S$ requires: C, 53.45; H, 4.70; S, 7.90; F, 14.1%; δ_H: 1.44–2.27 (m, 6H, 3×CH_2), 1.63 and 3.70 (2×s, 2×3H, 2×Me), 4.62 and 4.65 (2×s, 2×1H, =CH_2), 6.23–6.26 (m, 1H, =CH), 7.19–7.33 (m, 4H, ArH); *m*/*z* (%): 404 (M^+, 1), 345 (4), 289 (100), 255 (12), 69 (69) and 41 (45); ν_{max} (film): 1780, 1450, 1270, 1175, 1060, 1000, 930, 840 and 740 cm^{-1}.

4.2.13. Methyl 7a-methyl-6b,7,7a,8-tetrahydrocyclopropa[3,4] cyclopenta[1,2-*a*] naphthalene (13). Enol triflate **12** (0.3 g, 0.742 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.016 g, 0.074 mmol), PPh_3 (0.038 g, 0.148 mmol), Na_2CO_3 (0.157 g, 1.48 mmol) and Et_4NCl (0.122 g, 0.742 mmol) in CH_3CN (10 ml). The resulting mixture was boiled under reflux for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml), the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was subjected to flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford a solid, which was crystallised from ether–petroleum ether to give the product (0.17 g, 90%) as colourless prisms, mp 59–61 °C. Found: C, 80.35; H, 7.15; $C_{17}H_{18}O_2$ requires: C, 80.30; H, 7.10%; δ_H: 0.77 and 1.25 (2×d, 2×1H, *J* 5 Hz, cyclopropyl H), 1.11 (s, 3H, Me), 1.58–2.56 (m, 4H, 2×CH_2), 3.58 (s, 3H, OMe), 5.59 and 6.53 (2×d, 2×1H, *J* 9 Hz, =CH), 7.08–7.35 (m, 4H, ArH); *m*/*z* (%): 254 (M^+, 12), 195 (100), 179 (32), 165 (37) and 77 (3); ν_{max} (film): 750, 1500, 1410, 1260 and 750 cm^{-1}.

4.2.14. (6a-Methyl-5,6,6a,7-tetrahydro-4b*H*-cyclopropa[2,3] cyclopenta[1,2-*a*] naphthalen-4b-yl) methanol (14). Compound **13** (0.045 g, 0.177 mmol) in dry ether (8 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.0068 g, 0.177 mmol) in ether (6 ml). The resulting suspension was boiled under reflux for 2 h, cooled, and the excess $LiAlH_4$ destroyed by careful successive addition of H_2O (0.5 ml), 15% NaOH (0.5 ml) and H_2O (1 ml). After the addition was complete, the solution was stirred for 1 h, filtered and the precipitate washed with ether (2×20 ml). The combined ether layers were dried ($MgSO_4$), concentrated in vacuo and the residue subjected to column chromatography eluting with 1:8 v/v ether–petroleum ether to afford the product (0.033 g, 82%) as a colourless oil. Found: 226.1355; $C_{16}H_{18}O$ requires: 226.1357; δ_H: 0.78 and 1.42 (2×d, 2H, *J* 5 and 4 Hz, cyclopropyl H), 1.26 (s, 3H, Me), 1.5–2.48 (m, 5H, 2×CH_2+OH), 3.64 and 3.75 (2×d, 2H, *J* 11 Hz, OCH_2), 5.70 and 6.67 (2×d, 2H, *J* 9 Hz, 2×=CH), 7.25–7.45 (m, 4H, ArH); *m*/*z* (%): 226 (M^+, 25), 195 (100), 77 (8), 65 (4) and 43 (4).

4.2.15. Methyl 1-acetyl-3-(3-methyl-3-butenyl)-4-oxopiperidine-3-carboxylate (15). Methyl 1-acetyl-4-oxopiperidine-3-carboxylate (2.00 g, 10.05 mmol) was added to a stirred solution of KO^{t}Bu (1.17 g, 10.42 mmol) in DMSO (20 ml). The resulting solution was stirred at room temperature for 1 h, when 2-methyl-4-iodo-1-butene (2.00 g, 10.2 mmol) was added and stirring continued at room temperature for a further 14 h. The solution was then diluted with water (30 ml) and extracted with EtOAc (3×30 ml). The combined ethyl acetate extracts were washed with saturated brine (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residual oil was purified by column chromatography (SiO_2) eluting with 10:1 v/v ether–petroleum ether to afford the product (1.25 g, 46%) as a pale yellow oil. Found: C, 62.70; H, 8.05; N, 5.25; $C_{14}H_{21}NO_4$ requires: C, 62.90; H, 7.90; N, 5.25%; δ_H: 1.61–2.37 (m, 10H, 5×CH_2), 1.65 (s, 3H, =CMe), 2.18 (s, 3H, COMe), 3.49 (s, 3H, OMe), 4.8 (s, 2H, =CH_2); *m*/*z* (%): 267 (M^+, 4), 239 (27), 199 (78), 69 (36), 55 (51) and 43 (100); ν_{max} (film): 2800, 1720, 1690, 1500, 1410 and 1290 cm^{-1}.

4.2.16. Methyl 1-acetyl-3-(3-methyl-3-butenyl)-4-trifluoromethylsulfonyloxy piperidine-3-carboxylate (16). Compound **15** (0.2 g, 0.75 mmol) in THF (5 ml) was added dropwise to a suspension of NaH (0.043 g, 1.8 mmol) in freshly distilled THF (10 ml) at 0 °C. The resulting mixture was allowed to warm to room temperature and then $PhNTf_2$ (0.28 g, 0.786 mmol) in THF (6 ml) was added dropwise and the mixture heated at 60 °C for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml)

and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:8 v/v ether–petroleum ether to afford the product (0.19 g, 64%) as a colourless oil. Accurate mass: 399.0961; $C_{15}H_{20}F_3N0_6S$ requires: 399.0963; δ_H: 1.11–4.3 (m, 8H, 4×CH_2), 1.66 (s, 3H, =CMe), 2.16 (s, 3H, COMe), 3.69 (s, 3H, CO_2Me), 4.63 and 4.7 (2×s, 2H, =CH_2), 5.8 (br s, 1H, =CH); *m/z* (%): 399 (M^+, 7), 368 (12), 331 (40), 266 (76), 198 (47), 166 (100), 69 (72) and 43 (83); ν_{max} (film): 3400, 1800, 1700, 1480, 1260, 1200, 1140 and 930 cm^{-1}.

4.2.17. Methyl 2-acetyl-5a-methyl-1,2,5,5a,6,7-hexahydro-7a*H*-cyclopropa[2,3] cyclopenta[1,2-*c*] pyridine-7a carboxylate (17). The enol triflate **16** (0.13 g, 0.325 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.007 g, 0.0325 mmol), PPh_3 (0.017 g, 0.065 mmol), Na_2CO_3 (0.069 g, 0.651 mmol) and Et_4NCl (0.053 g, 0.325 mmol) in CH_3CN (8 ml). The resulting mixture was stirred and boiled under reflux for 8 h. Standard workup followed by column chromatography eluting with 4:1 v/v ether–petroleum ether afforded the product (0.05 g, 62%) as a colourless oil. Found: C, 67.50; H, 7.80; N, 5.50; $C_{14}H_{19}NO_3$ requires: C, 67.50; H, 7.65; N, 5.60%; δ_H: 0.6 and 1.2 (d, 2H, *J* 5 Hz, cyclopropyl H), 1.12 (s, 3H, Me), 1.1–1.8 (m, 6H, 3×CH_2), 2.02 (s, 3H, COMe), 3.63 (s, 3H, OMe) and 6.62 and 7.27 (2×m, 2×H, 2×=CH); *m/z* (%): 249 (M^+, 33), 206 (93), 189 (77), 146 (100) and 43 (57); ν_{max} (film): 1720, 1450, 1375, 1250, 1110, 1080 and 1040 cm^{-1}.

4.2.18. 2-Bromocyclohex-2-en-1-yl 2-methylprop-2-en-1-yl ether (18). 2-Methyl-2-propen-1-ol (0.546 g, 7.57 mmol) in THF (5 ml) was added to a stirred suspension of NaH (0.45 g, 60% dispersion in oil, 9 mmol) in freshly distilled THF (10 ml) at 0 °C and stirring continued for 1 h at room temperature. 2,3-Dibromocyclohexene (2 g, 8.7 mmol) was then added and stirring continued for a further 8 h at room temperature at which time the solvent was removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure to afford the product (1.2 g, 68%) as a colourless oil, bp 62–65 °C/0.25 mmHg. Accurate mass: 230.0305; $C_{10}H_{15}BrO$ requires: 230.0306; δ_H: 1.50–2.05 (m, 6H, 3×CH_2), 1.74 (s, 3H, Me), 3.79 (br s, 1H, OCH), 3.98 (m, 2H, OCH_2), 4.82 and 4.94 (2×s, 2×lH, =CH_2), 6.14–6.16 (m, 1H, =CH); *m/z* (%): 232 (M^+, 1), 230 (M^+, 1), 175 (31), 151 (35), 79 (100), 55 (34) and 41 (15); ν_{max} (film): 3200, 1670, 1470, 1350, 1100 and 910 cm^{-1}.

4.2.19. 1a-Methyl-1a,2,4,5-tetrahydro-1*H*,3a*H*-cyclopropa[*c*] [1] benzofuran (19). Vinyl bromide **18** (0.05 g, 0.216 mmol) was added to a stirred suspension of $PdC1_2(PPh_3)_2$ (0.015 g, 0.0216 mmol), Zn dust (0.028 g, 0.432 mmol) and Et_4NCl (0.035 g, 0.216 mmol) in CH_3CN (5 ml) and the resulting mixture was stirred and boiled under reflux for 2 h. Standard workup followed by column chromatography eluting with 1:4 v/v ether–petroleum ether afforded the product (0.016 g, 50%) as a colourless oil. Accurate mass: 150.1045; $C_{10}H_{14}O$ requires: 150.1044; δ_H: 0.529 and 0.964 (2×d, 2×1H, *J* 4.4 and 4.5 Hz, cyclopropyl H), 1.1 (s, 3H, Me), 1.43–2.13 (m, 4H, 2×CH_2), 3.61 and 3.72 (2×d, 2H, *J* 8.1 Hz, OCH_2), 3.87–3.93 (m, 1H, OCH), 5.15–5.19 (m, 1H, =CH), 5.69–5.72 (m, 1H, =CH); *m/z* (%): 150 (M^+, 34), 135 (27), 91 (100), 55 (23) and 41 (31); ν_{max} (film): 1750, 1500, 1090 and 740 cm^{-1}.

4.2.20. 6-(2-Acetylphenoxy)-l-bromocyclohexene. 2-Hydroxyacetophenone (1.8 g, 0.013 mol) in freshly distilled THF (15 ml) was added to a stirred suspension of NaH (0.634 g, 60% dispersion in oil, 0.013 mol) in freshly distilled THF (10 ml) at 0 °C. The resulting mixture was stirred for 1 h at room temperature when 2,3-dibromohexene (3.2 g, 0.013 mol) was added and the resulting mixture was boiled under reflux for 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (70 ml) and dichloromethane (100 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane layers dried ($MgSO_4$) and evaporated. The residue was distilled under reduced pressure to give the product (1.9 g, 49%) as a colourless oil, bp 140–148 °C/0.03 mmHg. Found: C, 56.90; H, 5.20; Br, 27.30; $C_{14}H_{15}BrO_2$ requires: C, 56.95; H, 5.05; Br, 27.10%; δ_H: 1.05–2.21 (m, 6H, 3×CH_2), 2.66 (s, 3H, COMe), 4.8 (br s, 1H, OCH), 6.39–6.41 (m, 1H, =CH), 6.95–7.75 (m, 4H, ArH); *m/z* (%): 296 (M^+, 2), 294 (M^+, 2), 215 (13), 160 (23), 121 (21), 79 (100) and 43 (22); ν_{max} (film): 2900, 1700, 1630, 1510, 1480, 1330, 1270, 1000 and 780 cm^{-1}.

4.2.21. 2-Bromocyclohex-2-en-1-yl 2-isopropenylphenyl ether (20). *n*-Butyllithium (5.16 ml, 1.6 M solution in hexane, 8.27 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (2.95 g, 8.27 mmol) in ether (40 ml) under nitrogen and stirring continued at room temperature for an hour. 6-(2-Acetylphenoxy)-l-bromocyclohexene (1.22 g, 4.13 mmol) in ether (20 ml) was added dropwise over 30 min. The resulting mixture was stirred for 15 h, then diluted with water (20 ml) and extracted with ether (3×20 ml). The combined ether extracts were dried ($MgSO_4$), evaporated in vacuo and the residue distilled to afford the product (0.64 g, 53%) as colourless oil, bp 100–110 °C/0.02 mmHg. Found: C, 61.45; H, 5.85; Br, 27.30; $C_{15}H_{17}BrO$ requires: C, 61.45; H, 5.80; Br, 27.30%; δ_H: 1.65–2.03 (m, 6H, 3×CH_2), 2.06 (s, 3H, Me), 4.69 (br s, 1H, CH), 4.96, 5.02 (2×s, 2×1H, =CH_2), 6.26 (m, 1H, =CH) and 6.84–7.14 (m, 4H, ArH); *m/z* (%): 294 (M^+, 3), 292 (M^+, 3), 213 (21), 134 (100), 91 (30) and 79 (93).

4.2.22. 10b-Methyl-1,5,5a,10b-tetrahydro-4*H*-cyclopropaxanthene (21). Vinyl bromide **20** (0.15 g, 0.508 mmol) was added to a stirred suspension of $Pd(OAc)_2$ (0.011 g, 0.0508 mmol), PPh_3 (0.026 g, 0.101 mmol) and TlOAc (0.162 g, 0.616 mmol) in CH_3CN (8 ml). The resulting mixture was stirred and boiled under reflux for 5 h. The solvent was then removed under reduced pressure and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The water layer was extracted with dichloromethane (50 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:2 v/v ether–petroleum ether to afford the product **21** (0.074 g, 76%) as a pale yellow oil. Accurate mass: 212.1209; $C_{15}H_{16}O$ requires: 212.1209; δ_H: 0.872 and 1.36 (2×d, 2H, *J* 5 Hz, cyclopropyl H), 1.40 (s, 3H, Me), 1.18–2.23 (m, 4H, 2×CH_2),

4.27 (m, 1H, OCH), 5.35 and 5.70 (2×m, 2×1H, 2×=CH), 6.70–7.24 (m, 4H, ArH); *m/z* (%): 212 (M^+, 21), 197 (42), 91 (18), 77 (13) and 32 (100); ν_{max} (film): 1620, 1505, 1470, 1240 and 770 cm^{-1}.

4.2.23. *N*-Acetyl-*N*-(2-bromocyclohex-2-enyl)-2-isopropenylaniline (23). *N*-Acetyl-2-isopropenylaniline (1.74 g, 0.01 mol) in freshly distilled THF (15 ml) was added to a stirred suspension of NaH (0.58 g, 0.0l2 mol, 60% dispersion in oil) in THF (10 ml) at 0 °C. The resulting mixture was stirred for 1 h at room temperature when 2,3-dibromocyclohexene (2.77 g, 0.011 mol) was added and stirring continued for further 8 h. The solvent was then removed under reduced pressure and the residue partitioned between water (100 ml) and dichloromethane (150 ml). The water layer was extracted with dichloromethane (100 ml) and the combined dichloromethane extracts dried ($MgSO_4$) and evaporated. The residual pale yellow solid was crystallised from ether–petroleum ether to give the product (2.32 g, 70%) as pale yellow prisms, mp 86–88 °C. Found: C, 61.00; H, 6.00; N, 4.05; Br, 24.10; $C_{17}H_{20}BrNO$ requires: C, 61.05; H, 5.95; N, 4.20; Br, 23.95%; δ_H: 1.15–2.08 (m, 6H, 3×CH_2), 1.80 (s, 3H, =CMe), 2.02 (s, 3H, COMe), 4.94 and 5.14 (2×s, 2×1H, =CH_2), 5.61–5.73 (m, 1H, NCH), 6.15–6.23 (m, 1H, =CH), 7.20–7.34 (m, 4H, ArH); *m/z* (%): 335 (M^+, 1), 333 (M^+, 1), 254 (100), 212 (12), 174 (17), 91 (51) and 43 (39); ν_{max} (Nujol): 3400, 3050, 1790, 1480, 1320, 1080 and 820 cm^{-1}.

4.2.24. 6-Acetyl-10b-methyl-1,4,5,5a,6,10b-hexahydrocyclopropa[1]acridine (24). Vinyl bromide **23** (0.05 g, 0.0149 mmol) was added to a stirred suspension of $PdCl_2(PPh_3)_2$ (0.01 g, 0.0149 mmol), Zn dust (0.019 g, 0.299 mmol) and Et_4NCl (0.024 g, 0.149 mmol) in CH_3CN (5 ml). The resulting mixture was stirred and boiled under reflux for 4 h. The solvent was then removed under reduced pressure and the residue partitioned between water (30 ml) and dichloromethane (30 ml). The water layer was extracted with dichloromethane (30 ml) and the combined dichloromethane layers dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (SiO_2) eluting with 1:4 v/v ether–petroleum ether to afford the product (0.0275 g, 73%) as a pale yellow oil. Found: C, 80.65; H, 7.60; N, 5.25; $C_{17}H_{19}NO$ requires: C, 80.65; H, 7.50; N, 5.55%; δ_H: 0.96 and 1.36 (2×d, 2×1H, *J* 6 Hz, cyclopropyl H), 1.46 (s, 3H, Me), 2.14 (s, 3H, COMe), 1.1–2.4 (m, 4H, 2×CH_2), 5.10 and 5.49 (2×d, 2H, *J* 11 Hz, =CH), 5.75–5.8 (m, 1H, NCH), 6.95–7.43 (m, 4H, ArH); *m/z* (%): 253 (M^+, 35), 238 (7), 210 (61), 160 (100), 77 (19) and 43 (25); ν_{max} (Nujol): 3000, 1690, 1490, 1410 and 750 cm^{-1}.

4.2.25. Dimethyl 4-bromobut-2-ynyl-2-methylprop-2-enylmalonate (38). Dimethyl 2-methylprop-2-enylmalonate (9.31 g, 0.05 mol) was slowly added to a methanolic solution of sodium methoxide [prepared from Na (1.15 g) and absolute MeOH (25 ml)] and stirred the mixture at room temperature for 15 min. 1,4-Dibromobut-2-yne (12.71 g, 0.06 mol) was then added and stirring continued at room temperature for a further 16 h when water (25 ml) was added and the mixture extracted with ether (3×40 ml). The combined ether layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residual oil was distilled to give the product as a pale yellow liquid (5.0 g, 32%), bp 105–110 °C/0.1 mmHg. Found: C, 49.30; H, 5.45; $C_{13}H_{17}BrO_4$ requires: C, 49.23; H, 5.40%; δ_H: 2.90, 2.83 and 1.66 (3×s, 2H, 2H and 3H, C=CCH_2, CH_2 and C=CCH_3), 3.75 and 3.88 (2×s, 2H and 3H, CH_2Br and OCH_3), 4.85 and 4.92 (2×d, 2×1H, *J* 1.3 Hz, C=CH_2); *m/z* (%): 319 and 317 (1.6), 177 (100), 145 (16), 117 (40), 59 (28); ν_{max} (film): 2237, 1735, 1434, 1276, 1206, 1183 cm^{-1}.

4.2.26. Dimethyl {4-[acetyl (2-iodophenyl) amino] but-2-yn-1-yl}(2-methylprop-2-en-1-yl) malonate (39). *n*-BuLi (4.2 ml of 1.6 M solution in hexane, 0.0066 mol) was added from a syringe to a cooled solution (0–4 °C) of *N*,*N*-diisopropylamine (0.84 ml, 0.006 mol) in dry THF (25 ml) under an atmosphere of N_2 and stirring and cooling continued for 15 min. The reaction mixture was then cooled to −60 °C, a solution of 2-iodoacetanilide (1.56 g, 0.006 mol) in dry THF (10 ml) was added and the mixture stirred at −60 °C for 15 min. A solution of **38** (1.903 g, 0.006 mol) in THF (5ml) was added next and the mixture allowed to warm to room temperature with stirring over 15 h. The mixture was then quenched with a saturated solution of NH_4Cl (20 ml) and extracted with ether (3×25 ml). The combined ether layers were dried over anhydrous $MgSO_4$, evaporated and the residue purified by flash column chromatography, eluting with 7:3 v/v ether–petroleum ether to give the product (1.44 g, 49%), which crystallised as colourless plates from ether–petroleum ether, mp 63–65 °C. Found: C, 50.60; H, 4.85; N, 2.70; I, 25.70; $C_{21}H_{24}INO_5$ requires: C, 50.70; H, 4.86; N, 2.82; I, 25.52%; δ_H: 1.52 and 1.71 (2×s, 2×3H, $COCH_3$ and C=CCH_3), 2.6 5 and 2.71 (2×s, 2×2H, 2×CH_2), 3.62 and 3.63 (2×s, 2×3H, 2×$COOCH_3$), 4.63 and 4.78 (2×s, 2×1H, C=CH_2), 3.70 and 4.96 (2×dd, 2×1H, *J* 17.2 and 2 Hz, NCH_2), 7.06 and 7.39 (2×m, 2H and 1H, ArH), 7.87 (dd, 1H, *J* 7.8 and 1.7 Hz, ArH); *m/z* (%): 497 (M^+, 42), 482 (50), 370 (22), 366 (92), 312 (25), 244 (100), 177 (28); 43; ν_{max} (KBr): 1736, 1666, 1469, 1280, 1206, 1194 cm^{-1}.

4.2.27. Dimethyl 1-(1-acetyl-1*H*-indol-3-yl)-5-methylbicyclo [3.1.0] hexane-3,3-dicarboxylate (43). A mixture of **39** (0.248 g, 0.0005 mol), $Pd(OAc)_2$ (0.011 g, 10 mol %), PPh_3 (0.026 g, 20 mol %), Na_2CO_3 (0.046 g, 0.0005 mol) and Et_4NCl (0.082 g, 0.0005 mol) in dry acetonitrile (7 ml) was heated at 70 °C for 0.5 h. The palladium residue was filtered off, the solvent evaporated, the residue dissolved in EtOAc (15 ml) and washed with water (15 ml). The organic layer was separated, dried over anhydrous $MgSO_4$ and evaporated to leave a brown solid, which was purified by preparative TLC, eluting with 3:2 v/v ether–petroleum ether to give the product (0.12 g, 65%) as a colourless solid, which became an amorphous pale yellow solid when exposed to air. Found: C, 66.85; H, 6.30; N, 3.45; $C_{21}H_{23}NO_5 \cdot 0.5H_2O$ requires: C, 66.65; H, 6.39; N, 3.70%; δ_H: 0.66 (br s, 2H, CH_2), 0.93 and 2.52 (2×s, 2×3H, $COCH_3$ and CH_3), 2.57 (d, 1H, *J* 13.7 Hz), 2.85 (m, 3H), 3.66 and 3.67 (2×s, 2×3H, 2×CH_3), 7.13 –7.29 (m, 2H, ArH), 7.50 and 8.34 (2×d, 2×lH, *J* 7.2 Hz, ArH); *m/z* (%): 369 (M^+, 100), 327 (25), 250 (29), 208 (70), 49 (57), 47 (43), 43 (37).

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Solid-phase synthesis of backbone-cyclized β-helical peptides

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Abstract—This paper describes the synthesis and purification of two 22-residue cyclic peptides, *cyclo*{[(L-Val-D-Val)$_4$-(L-Val-D-Pro-Gly)]$_2$-} **3** and *cyclo*{[(D-Leu-L-Leu)$_4$-(D-Leu-L-Pro-Gly)]$_2$-} **4**, that were designed to fold into double-stranded antiparallel β-helical structures. Due to intramolecular hydrogen bonding and the conformational constraints imposed by the two reverse-turn segments (D-Pro-Gly and L-Pro-Gly, respectively), the linear precursors to **3** and **4** (lin-**3** and lin-**4**) were expected to adopt preorganized conformations that would bring the N and C termini close together and thereby favor ring closure. Precursors lin-**3** and lin-**4** were constructed by stepwise Boc solid-phase peptide synthesis using the commercially available alkanesulfonamide 'safety-catch' linker and cyclized head-to-tail via the method of cleavage-by-cyclization. The crude cyclic peptides were highly hydrophobic and contained minor impurities that could not be removed solely by reversed-phase HPLC (RP-HPLC); however, two-step purification—first by RP-HPLC with *i*-PrOH/water gradients, followed by gel-permeation chromatography (GPC) on Sephadex LH-20 with $CHCl_3$/MeOH—afforded both peptides in pure form (≥95% by ^{1}H NMR) and in acceptable yield (23%). Subsequent ^{1}H NMR experiments supported the expected structures of **3** and **4**. The successful formation of the 66-membered rings of **3** and **4** is consistent with the notion of conformational preorganization in the linear precursors; furthermore, the protocols for synthesis and purification described should prove useful for preparing additional cyclic β-helical peptides, including longer peptides and peptides having polar residues.

1. Introduction

In this article, we present the solid-phase synthesis and backbone-to-backbone cyclization of peptides that are designed to fold into β-helices—i.e., helices formed by peptides composed of alternating D- and L-amino acids (D,L-peptides) and stabilized by β-sheet hydrogen bonding.[1] β-Helical peptides are of interest not only for their ability to form transmembrane ion channels, the most notable example of which is the naturally occurring peptide antibiotic gramicidin A,[2] but also as prospective structural components for new biomolecular architectures. The conformational promiscuity of linear D,L-peptides, however, has limited the usefulness of β-helices; for example, a given D,L-peptide often folds in solution to give a mixture of single-stranded (ss), double-stranded (ds) parallel (↑↑), and ds antiparallel (↑↓) forms.[1–4] In order to overcome these limitations, we sought a means of constraining a D,L-peptide into a single β-helical species. Cyclization is known to provide an important conformational constraint in many natural and designed peptides;[5] here, we use cyclization to prevent interconversion between ss and ds β-helices and to generate a well-defined ds antiparallel species having ca. 5.6 residues per turn (a ↑↓ $\beta^{5.6}$-helix).

2. Experimental design

Conceptually, we designed *cyclo*{[(L-Val-D-Val)$_4$-(L-Val-D-Pro-Gly)]$_2$-} **3** and *cyclo*{[(D-Leu-L-Leu)$_4$-(D-Leu-L-Pro-Gly)]$_2$-} **4** (Fig. 1) by joining two copies of the corresponding linear D,L-peptide with two copies of the reverse-turn[6] sequences D-Pro-Gly and L-Pro-Gly, respectively. In practice, we chose to synthesize the linear precursors to **3** and **4** (lin-**3** and lin-**4**) via stepwise solid-phase peptide synthesis (SPPS) using an alkanesulfonamide safety-catch linker (AS-SCL),[7] originally developed by Kenner[8] and subsequently modified by Ellman,[9,10] and then cyclize the linear peptides with concomitant cleavage

Keywords: Alkanesulfonamide; Safety-catch linker; Cyclic peptide; Solid-phase peptide synthesis; β-Hairpin; β-Turn; β-Helix; HPLC; Gel-permeation chromatography.
Abbreviations: AS-SLC, alkanesulfonamide safety-catch linker; CBC, cleavage-by-cyclization; Boc, *t*-butoxycarbonyl; Fmoc, 9-fluorenylmethoxycarbonyl; PyBop, (benzotriazol-1-yloxy)tris-pyrroli-dinophosphonium hexafluorophosphate; SPPS, solid-phase peptide synthesis; HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazo-[4,5-*b*]pyridinium hexafluorophosphate 3-oxide; HBTU, 1-[bis(dimethylamino)methylene]-1*H*-benzotriazolium hexafluorophosphate 3-oxide; DMF, *N*,*N*-dimethylformamide; NMP, *N*-methylpyrrolidinone; FSW, flow/shake wash; TFA, trifluoroacetic acid; DIEA, *N*,*N*-diisoprolylethylamine; RP-HPLC, reversed-phase high-performance liquid chromatography; HFIP, hexafluoroisopropanol; HFA·3H_2O, hexafluoroacetone trihydrate; MALDI-MS, matrix-assisted laser desorption ionization mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; IR, infrared spectroscopy; GPC, gel-permeation chromatography.
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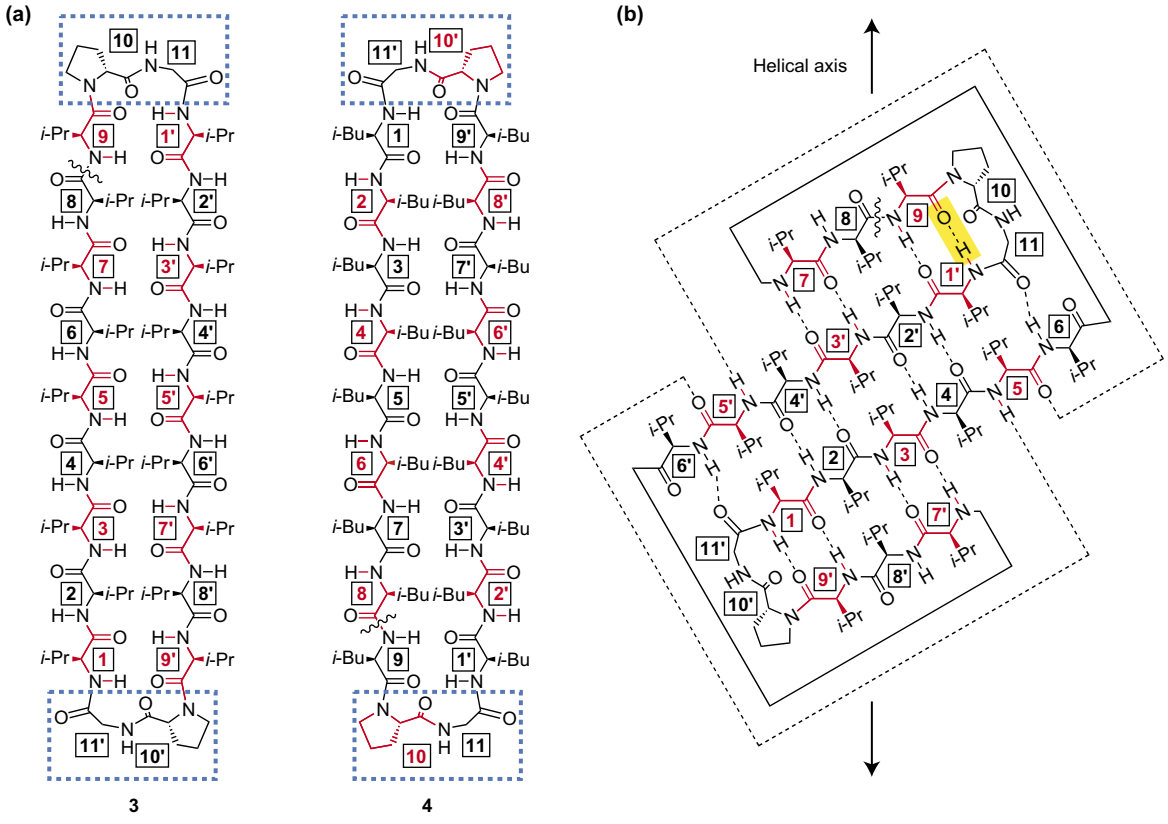


Figure 1. (a) Chemical structures of the peptides prepared in this study: *cyclo*{[(L-Val-D-Val)$_4$-(L-Val-D-Pro-Gly)]$_2$-} **3** and *cyclo*{[(D-Leu-L-Leu)$_4$-(D-Leu-L-Pro-Gly)]$_2$-} **4**. D Residues and Gly are shown in black, while L residues are shown in red and black; residues that comprise the two symmetry-related halves of the molecules are labeled 1 through 11 and 1′ through 11′. The reverse-turn sequences of **3** and **4** (D-Pro-Gly and L-Pro-Gly, respectively) are boxed in blue. In both **3** and **4**, the amide bond that is formed during CBC (between the carboxyl of residue 8 and the amine of residue 9) is marked with a wavy line. (b) Schematic side view of the anticipated $\uparrow\downarrow\beta^{5,6}$-helical structure of **3**, showing hydrogen-bonding interactions; **4** was expected to have an analogous $\uparrow\downarrow\beta^{5,6}$-helical structure (not shown). We anticipated that, in the linear precursor to **3**, a hydrogen bond between the carboxyl of residue 9 and the NH of residue 1′ (highlighted in yellow) would position the amino group of residue 9 favorably for amide bond formation with the carboxyl of residue 8.

from the resin—a process known as cleavage-by-cyclization (CBC). The AS-SCL has been used previously for the synthesis of cyclic peptides via CBC,[11–17] and resins functionalized with this linker are commercially available, making it a convenient choice for our purposes. We decided to pursue the CBC route rather than the alternative—cleavage of the linear precursor followed by cyclization in solution—in order to save one synthetic step and to avoid the strong acid cleavage that is typically required in Boc SPPS.[18]

At the outset of this work, we noted that the target cyclic peptides **3** and **4** differ in two important ways from those prepared previously via CBC using the AS-SCL. First, prior reports by others had demonstrated CBC of peptides up to 10 residues long,[11–17] while **3** and **4** are both 22 residues long. The ease of macrocyclization reactions tends to correlate inversely with the number of atoms in the ring, and thus the prospect of forming the 66-membered rings of **3** and **4** at first appeared daunting. We reasoned, however, that the two reverse-turn regions of each peptide, together with alternating chirality of the residues and intramolecular hydrogen bonding,[1] would cause the lin-**3** and lin-**4** to fold into preorganized $\uparrow\downarrow\beta^{5,6}$-helical structures that would place the N and C termini close in space and thus encourage ring closure. In a retrosynthetic sense, we made a disconnection between the carboxyl function of residue 8 and the amino group of residue 9 (Fig. 1), so that the forward reaction (ring closure) would take place between residues at the ends of the putative helices and avoid any steric congestion in the middle. Furthermore, we envisaged that hydrogen bonding between the carbonyl of residue 9 and the NH of residue 1′ (Fig. 1b), together with the presence of the nearby reverse-turn residues, would place the amino group of residue 9 in a favorable position for ring closure.

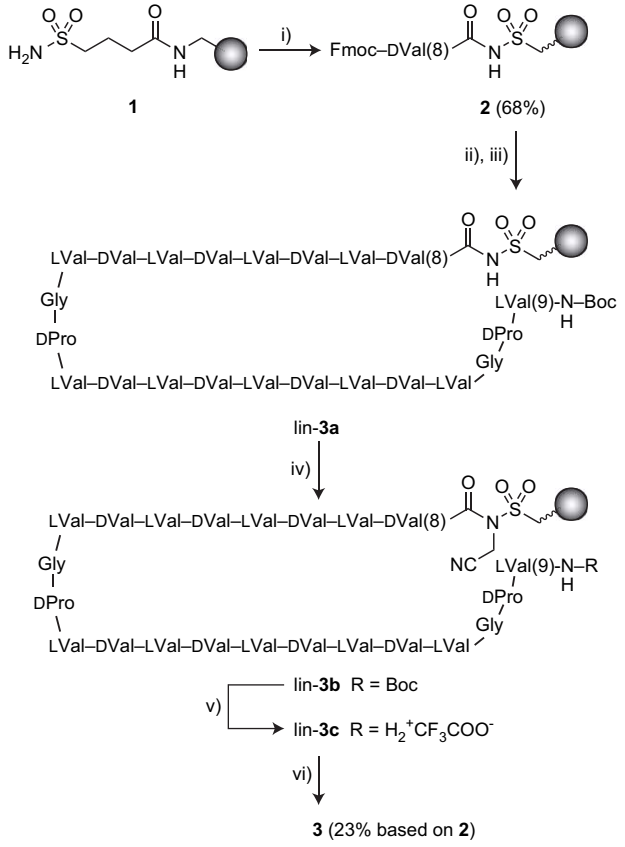
Peptides **3** and **4** also differ in polarity from those prepared earlier via CBC using AS-SCL. The previously reported cyclic peptides all contained at least one polar residue,[11–17] while **3** and **4** are comprised of only nonpolar residues. We, therefore, expected **3** and **4** to be highly hydrophobic. Although the purification of highly hydrophobic peptides is known to be difficult,[19–22] we hoped that, by using high-resolution techniques of separation such as RP-HPLC,[23] we would obtain products pure enough for characterization by high-field NMR.

3. Results

3.1. Solid-phase synthesis of 3 and 4

Here, we describe the synthesis and purification of **3**, but the synthesis and purification of **4** were carried out in an analogous manner. Beginning with 4-sulfamylbutyryl AM resin

1,[9,10] we anchored the C-terminal residue, D-Val(8), as the preformed Fmoc-amino acid fluoride (Scheme 1). We chose to use the acid fluoride rather than in situ activation with PyBop for the sake of convenience: the former allowed us to carry out the coupling at room temperature in a SPPS vessel,[24] while the latter requires the coupling to be carried out at −20 °C in a round-bottom flask.[9,10] Furthermore, the presence of the Fmoc protecting group let us determine the yield of the anchoring reaction using the quantitative variant of the Fmoc UV absorbance assay.[25] In our hands, double coupling with Fmoc-D-Val-F[26] furnished the Fmoc-amino-acylated resin **2** in 68% yield; we attribute this modest yield to the steric hindrance posed by the β-branched side chain of D-Val. Consistent with this interpretation, de Visser et al. reported a yield of 64% for the anchoring of β-branched Fmoc-L-Thr(^{t}Bu)-F to **1**,[12] while during the synthesis of peptide **4**, we found that double coupling of the non-β-branched Fmoc-L-Leu-F proceeded in 91% overall yield.



Scheme 1. (i) 2×Fmoc-D-Val-F, DIEA, CH_2Cl_2, room temperature; (ii) 4×20% piperidine in DMF; (iii) Boc SPPS; (iv) ICH_2CN, DIEA, NMP; (v) 2×TFA (neat); (vi) DIEA, THF. (In **2** and lin-**3a–c**, the residues that react during ring closure, D-Val(8) and L-Val(9), are numbered as in Figure 1, while, for clarity, the numbering of all other residues is omitted.)

Following the removal of the Fmoc group with 20% piperidine in DMF,[27] we continued the synthesis at the appropriate scale using manual Boc SPPS and following the in situ neutralization protocol of Kent,[28] with the exception that the more efficient coupling reagent HATU was used in place of HBTU,[29] NMP was used in place of DMF, and a combination of flow and shake washes (FSW) was used in place of a single flow wash (see Section 6 for details).

After we had coupled the final residue, L-Val(9), we activated the C terminus of the resin-bound linear peptide lin-**3a** via cyanomethylation with ICH_2CN and DIEA in NMP[9,10] to give activated species lin-**3b**. We then removed the *N*-terminal Boc group with neat trifluoroacetic acid (TFA)[28] and effected CBC by suspending the TFA-peptidyl resin lin-**3c** in THF and adding 3 equiv DIEA.[11] The CBC reaction was accompanied by the formation of a white precipitate, which we collected by filtering the resin and washing copiously with $CHCl_3$. Evaporation of the $CHCl_3$ yielded crude **3**.

3.2. Purification and characterization of 3 and 4

Crude peptide **3** proved insoluble in solvents such as MeOH, EtOH, *i*-PrOH, and CH_3CN that are typically used for RP-HPLC; we attribute this insolubility to the highly hydrophobic nature of the peptide. However, dissolution of the crude peptide in HFIP at a concentration of ca. 80 mg mL^{-1}, followed by twofold dilution with HFA·3H_2O, furnished a solution that was suitable for use in RP-HPLC. Initial attempts at RP-HPLC using a C4 column with CH_3CN/water failed to elute any peaks, but switching to *i*-PrOH/water and also using a C4 column gave predominantly a single, broad peak (Fig. 2), which we collected as two fractions (fractions *a* and *b*) and analyzed using MS and ^{1}H NMR spectroscopy.

Both RP-HPLC fractions showed the anticipated molecular ions by MALDI-MS. 1D ^{1}H NMR spectroscopy revealed that fraction *a* consisted of a ca. 10:1 ratio of major and minor species (Fig. 3a), which we tentatively assigned as the desired peptide **3** and an epimerized product, respectively; this assignment is supported by the absence of additional peaks in the mass spectrum, which suggests that the minor species has the same molecular weight as the desired peptide **3**. In addition, NMR spectroscopy indicated that fraction *b* contained the desired peptide **3**, the putative epimerized material, and at least one additional contaminant (Fig. 3b). We note that the chemical shifts of the corresponding amide protons in Figure 3a and b differ somewhat due to differing amounts of water and impurities in the two samples. When

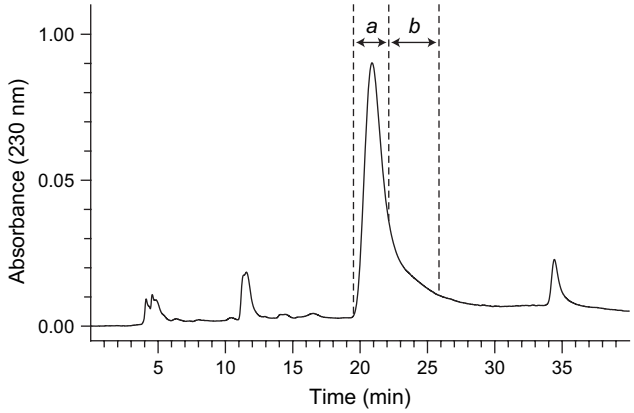


Figure 2. RP-HPLC profile of as-synthesized crude peptide **3**. The major peak was collected as two fractions, *a* and *b*. Conditions: 22×250 mm C4 column; 20 mL min^{-1}; gradient=50% B→50% B (1 min), 50→100% B (30 min), 100→100% B (5 min); solvent A=0.1% TFA and 1% *i*-PrOH in H_2O, solvent B=0.07% TFA and 90% *i*-PrOH in H_2O. The data were baseline-corrected by subtracting a blank chromatogram run with the same gradient.

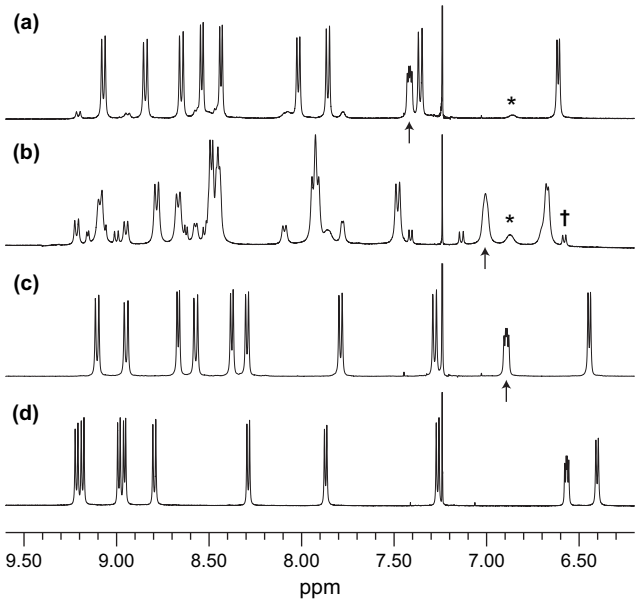


Figure 3. NH region of the 1D ^{1}H NMR spectra of peptides **3** and **4** (500 or 600 MHz, ca. 10 mM, 295 K, $CDCl_3$; residual $CHCl_3$ appears as a singlet at 7.24 ppm). (a) RP-HPLC fraction *a* (Fig. 2a), prior to repurification by GPC, which contains signals corresponding to a ca. 10:1 ratio of desired peptide **3** and putative epimerized material (one peak due to this material is marked with an asterisk). (b) RP-HPLC fraction *b* (Fig. 2b), prior to repurification by GPC, which shows signals from peptide **3**, the putative epimerized material (one peak due to this material is marked with an asterisk), and at least one additional contaminant (one peak due to this contaminant is marked with a dagger sign). (c) RP-HPLC fraction *a* (Fig. 2a) after repurification by GPC, which contains only signals arising from the desired peptide **3** (the spectrum of RP-HPLC/GPC-purified fraction *b* was identical). (d) RP-HPLC/GPC-purified peptide **4**, which contains only signals arising from the desired peptide. In (a–c), the chemical shifts of the amide protons of **3** vary due to different amounts of water and impurities in each sample. For example, the NH peak of Gly (easily identified by its multiplicity and marked in each spectrum with an arrow) appears at 7.42, 7.01, and 6.89 ppm in (a), (b), and (c), respectively.

we sought to purify both fractions further using RP-HPLC, we found that repeated chromatography on a C4, C8, or C18 column failed to completely remove the putative epimerized material.

We next attempted to repurify fraction *a* of the RP-HPLC-purified material using gravity-driven GPC on Sephadex LH-20.[30] These efforts were complicated by the lack of a suitable pure solvent that would satisfy the following criteria: (1) the solvent must be able to dissolve the partially purified peptide, and (2) the solvent must be sufficiently polar to prevent irreversible adsorption of the peptide to the LH-20 stationary phase.[30] One obvious choice was $CHCl_3$, in which the peptide is soluble to ca. 20 mM; $CHCl_3$, however, is a nonpolar solvent. Moreover, $CHCl_3$ is denser than LH-20 and therefore inconvenient for GPC using gravity-driven flow. After some experimentation, we determined that the solvent mixture $CHCl_3$/MeOH (65:35) satisfies both of the criteria stated above; in addition, this mixture is less dense than LH-20. We found that a single pass of fraction *a* through a 2.5×55 cm column of LH-20 in $CHCl_3$/MeOH gave material that was ≥95% pure as estimated by 1D ^{1}H NMR (Fig. 3c). Furthermore, even fraction *b* of the RP-HPLC-purified material, which contained ca. 30% contaminant (Fig. 3b), could be purified in this manner. Using this two-step method of purification, we obtained both **3** and **4** in 23% yield based on Fmoc-aminoacyl resin (e.g., **2**).

Figure 3c and d, respectively, shows the 1D ^{1}H NMR spectra of peptides **3** and **4** after RP-HPLC/GPC purification and thorough drying. Both spectra consist of a single set of sharp, well-dispersed resonances, with no minor peaks that would indicate multiple conformers or oligomers interconverting on the NMR time scale. Three additional observations concerning the NMR spectra support the expected ↑↓ $\beta^{5.6}$-helical structures of **3** and **4**. First, both the ^{1}H and proton-decoupled ^{13}C spectra are consistent with the anticipated twofold symmetrical structures of the 22-mers: the NH region of each ^{1}H spectrum (Fig. 3c and d, δ 6.44–9.23) contains the expected 10 NH peaks, while the ^{13}C spectra (see Section 6) each contain 11 peaks in the carbonyl region (C′, δ 169–175) and 11 peaks in the C$^\alpha$ region (δ 47–62). Second, both ^{1}H spectra (Fig. 3c and d) show 8 NH resonances downfield from 7.2 ppm, chemical shifts consistent with the 16 hydrogen bonds[3,31,32] anticipated for the ↑↓ $\beta^{5.6}$-helical structures of **3** and **4**. Finally, the majority of the $^3J_{NH-H\alpha}$ values in the ^{1}H spectra are greater than 8 Hz, which is typical for residues having β-sheet-like ϕ dihedral angles.[33] The detailed structural analysis of **3** and **4** using 2D ^{1}H NMR spectroscopy and structure calculations is reported elsewhere.[34]

4. Discussion

Over the past two decades, a number of studies have established CBC as an effective strategy for the solid-phase synthesis of cyclic peptides. Several linkers have been used for this purpose, including those having amine-labile anchors such as the Kaiser oxime[35] and thioester[36] linkers, as well as 'safety-catch' linkers that employ aryl hydrazide,[37,38] catechol,[39,40] or alkanesulfonamide[11–17] functions. Safety-catch linkers are particularly useful for the synthesis of cyclic peptides because they exploit amine-stable anchors that prevent premature cyclization during elongation of the peptide chain; at the conclusion of the synthesis, however, these same anchors can be activated for nucleophilic attack in order to effect CBC. Resins functionalized with the AS-SCL are commercially available, and Yang and Morriello have reported the use of such resin for the synthesis of cyclic peptides by CBC.[11] Subsequent reports by Noort,[12] Guo,[13–16] and Ganesan[17] have begun to define the scope of this approach.

The 22-residue peptides **3** and **4**, both of which contain 66-membered rings, are noteworthy in that they are among the longest cyclic peptides yet prepared via CBC using the AS-SCL. In both cases, the CBC reaction proceeded smoothly without resorting to low-loading resins ('pseudo-high-dilution'[12] conditions). These results support our expectation that the linear precursors to **3** and **4** would adopt preorganized ↑↓ $\beta^{5.6}$-helical conformations in which the N and C termini are close together. We note that Guo et al. have advanced similar arguments to rationalize the success of CBC for backbone-to-backbone cyclization of linear precursors having unprotected ornithine side chains.[13–16]

As mentioned above, the as-synthesized crude peptides **3** and **4** were contaminated with minor products that could

not be removed by repeated RP-HPLC. The purification of highly hydrophobic peptides is notoriously difficult;[19–22] nevertheless, we were able to purify **3** and **4** to near homogeneity using a facile two-step procedure of RP-HPLC followed by GPC on Sephadex LH-20. In our case, the GPC step could be carried out with gravity-driven flow and without the use of an in-line UV detector (see Section 6 for details), thus minimizing capital outlay. We note that Rijkers et al. have reported a similar two-step RP-HPLC/GPC strategy for the purification of hydrophobic *S*-palmitoyl peptides.[41] The success of this twofold approach is likely due to the orthogonal nature of the separation techniques: RP-HPLC operates by adsorption of molecules onto a stationary phase on the basis of molecular hydrophobicity,[23] while GPC works by partitioning of molecules into a porous stationary phase on the basis of molecular shape and size.[42] In the case of **3** and **4**, one of the hard-to-remove contaminants is probably an epimer resulting from loss of configuration at residue 8 during the CBC step, and we note that GPC on Sephadex media is known to be capable of resolving peptides that differ only in the chirality of a single residue.[43] An alternative strategy would be to avoid epimerization altogether by using the aryl hydrazide linker, which is reported to suppress epimerization during CBC.[37,38] For our future work, however, we wish to synthesize cyclic β-helical peptides having a range of side-chain functionalities, and CBC using the aryl hydrazide linker requires an oxidation step, a process that may not be compatible with sensitive side-chain groups.

5. Conclusion

The foregoing results show that CBC using the commercially available AS-SCL is an effective route for the solid-phase synthesis of backbone-cyclized ↑↓ $\beta^{5,6}$-helical peptides. The successful preparation of the 66-membered-ring-containing peptides **3** and **4** suggests that the linear precursors also possess significant ↑↓ $\beta^{5,6}$-helical structure, which presumably facilitates ring closure by placing the N and C termini close in space. In the case of **3** and **4**, two-step purification via RP-HPLC followed by GPC yielded these highly hydrophobic peptides in pure form. We are currently working to establish the generality of these procedures by preparing longer cyclic β-helical peptides and peptides having polar side chains.[11–17] We anticipate that the latter peptides will find application as ligands for macromolecular targets and as building blocks for new protein architectures.

6. Experimental

6.1. Materials

Before use, DIEA was distilled first from ninhydrin and then from CaH_2,[44] and ICH_2CN was filtered through a plug of basic alumina;[9,10] otherwise, all materials were used as received from the source indicated: 4-sulfamylbutyryl AM resin, EMD Biosciences, San Diego, CA, USA; anhydrous CH_2Cl_2 and THF, Sigma–Aldrich, Milwaukee, WI, USA; anhydrous NMP (Biotech Grade, over 4 Å molecular sieves), Pharmco, Brookfield, CT, USA; HATU, Applied Biosystems, Foster City, CA, USA; HFIP, TCI America, Portland, OR, USA; $HFA \cdot 3H_2O$, Sigma–Aldrich; and Sephadex LH-20, Amersham Biosciences, Piscataway, NJ, USA. $CHCl_3$ used in GPC was of HPLC-grade and stabilized with ca. 50 ppm pentene.

6.2. General procedures for manual solid-phase peptide synthesis. Procedure for flow/shake washes (FSW)

A single round of FSW consisted of a brief (ca. 10–15 s) vacuum-assisted flow wash (ca. 5 mL s^{-1}), taking care not to let the resin go dry, followed by a 5 s shake with ca. 10 mL solvent.

6.3. Representative procedures for manual solid-phase peptide synthesis. Synthesis of *cyclo*{[(L-Val-D-Val)$_4$-(L-Val-D-Pro-Gly)]$_2$-} (3)

6.3.1. Anchoring the first amino acid. 4-Sulfamylbutyryl AM resin[9,10] (1.0 mmol, 0.91 g of 1.1 mequiv g^{-1}, 1 equiv) was placed in a SPPS vessel[18,28] having a coarse porosity sintered glass frit and Teflon stopcock. Anhydrous CH_2Cl_2 (10 mL) was added and the resin was allowed to swell by shaking for 1 h. The CH_2Cl_2 was drained to the top of the resin, taking care not to let the resin go dry, and the resin was rinsed using two rounds of FSW. A solution of Fmoc-D-Val-F[26] (1.02 g, 3 mmol, 3 equiv) in anhydrous CH_2Cl_2 (6 mL) was added, followed by DIEA (0.35 mL, 2 mmol, 2 equiv),[24] and the reaction mixture was shaken for 1 h and then drained. After 2×FSW with CH_2Cl_2, the coupling was repeated as before. The resin was again rinsed via 2×FSW with CH_2Cl_2, followed by Et_2O, and then dried overnight under vacuum. Two ca. 5 mg samples of the aminoacyl resin were removed and subjected to the quantitative Fmoc UV absorbance assay,[25] by which the loading of the resin was determined to be 0.60 mmol g^{-1} (coupling yield=68%). A portion of the resin (600 mg) was removed and transferred to another SPPS vessel, and the synthesis was carried forward at the appropriate scale (0.36 mmol).

6.3.2. Elongation of the peptide chain. The Fmoc group of the aminoacyl resin obtained by using the procedure given in Section 6.3.1 was removed by shaking with 20% piperidine in DMF for 4×3 min,[27] and the resin was rinsed via 2×FSW with NMP. The synthesis was then carried forward using Boc manual SPPS according to the following modified version of the in situ neutralization protocol:[28,29]

Boc-amino acid (1.44 mmol, 4 equiv) and HATU (0.521 g, 1.37 mmol, 3.8 equiv) were dissolved in anhydrous NMP (3 mL) and DIEA was added (0.38 mL, 2.16 mmol, 6 equiv). The mixture was shaken until a homogeneous solution was obtained and then allowed to sit for an additional 1 min in order to preactivate the amino acid. The resulting solution of activated amino acid was added to the peptidyl resin; the resin was shaken for 30 min and then rinsed via 2×FSW with NMP. The resin was tested for the presence of unreacted amines using the qualitative ninhydrin test[18] (for primary amines) or the qualitative chloranil test[18,45] (for secondary amines), and couplings that yielded a positive test were repeated. If the resin continued to give a positive test after recoupling, it was capped by treatment with Ac_2O (0.34 mL, 3.6 mmol, 10 equiv) and DIEA (0.31 mL,

1.8 mmol, 5 equiv) in NMP (5 mL) for 2 h. When all the amino groups had reacted, the *N*-terminal Boc group was deprotected by shaking for 2×1 min with neat TFA and the resin was rinsed via 3×FSW with NMP. The next Boc-amino acid was then coupled as before.

6.3.3. Activation and cyclization. When the last Boc-amino acid had been coupled, the *N*-terminal Boc group was left on, and the C terminus was activated by shaking the resin for 24 h with ICH_2CN (0.66 mL, 9.08 mmol, 25 equiv) and DIEA (0.63 mL, 3.63 mmol, 10 equiv) in NMP (5 mL).[9,10] The resin was rinsed via 3×FSW with NMP, the *N*-terminal Boc group was removed as before, and the resin was washed via 3×FSW with NMP and 3×FSW with anhydrous THF. The resin was then transferred to a round-bottom flask; anhydrous THF (7 mL) was added, followed by DIEA (127 μL, 1.09 mmol, 3 equiv), and the resulting reaction mixture was stirred magnetically under Ar. Although a white precipitate began to form within 1 h, the mixture was stirred for 3 days in order to ensure complete reaction.

The crude peptide was collected by filtering the resin through a medium porosity sintered glass funnel and rinsing copiously with $CHCl_3$ (ca. 100 mL). Removal of the $CHCl_3$ under reduced pressured afforded crude **3** (431 mg).

6.4. Representative procedure for RP-HPLC. Chromatography of crude peptide 3

Crude peptide **3** (431 mg) was dissolved in HFIP (ca. 5 mL) and diluted with $HFA\cdot 3H_2O$ (ca. 10 mL). The resulting solution was clarified by filtration using a 0.45-μm in-line syringe filter, and then subjected to RP-HPLC in 3 mL injections on a 22×250 mm C4 column run at 20 mL min^{-1} using a gradient of 60% B to 77% B over 17 min (solvent A=0.1% TFA and 1% *i*-PrOH in H_2O; solvent B=0.07% TFA and 90% *i*-PrOH in H_2O). The absorbance of the eluant was monitored at 230 nm, and the major peak was collected as two fractions as indicated in Figure 2. Yield: fraction *a*, 145 mg; fraction *b*, 73 mg.

6.5. Representative procedure for GPC. Chromatography of HPLC-purified peptide 3

Fraction *a* of RP-HPLC-purified peptide **3** (140 mg) was dissolved in 10 mL $CHCl_3$/MeOH (65:35 v/v), and 5 mL of this solution was loaded onto a 2.5×55 cm column of LH-20 in $CHCl_3$/MeOH (65:35 v/v; degassed separately before mixing) using a Pasteur pipette, taking care not to let the top of the resin go dry.[42] The column was then run overnight using gravity-driven flow at ca. 1 mL min^{-1}. Fractions of 5 mL were collected, and peptide-containing fractions were identified by transferring an aliquot to a quartz cuvette and reading the absorbance at 245 nm. Pure **6** eluted first, followed by the putative epimerized material, and the two species were typically separated by 2–3 fractions that contained no peptide. The remaining 5 mL of fraction *a* was chromatographed in an identical manner. Fraction *b* of the HPLC-purified material was dissolved in 5 mL $CHCl_3$/MeOH 65:35 v/v and chromatographed in a single aliquot as described above. In this manner, a total of 170 mg of pure **3** was obtained (0.083 mmol, 23% based on **2**).

6.6. Synthesis of peptide 4

For the synthesis of **4**, resin **1** (0.45 g, 0.5 mmol, 1 equiv) was loaded with Fmoc-L-Leu-F[26] (0.53 g, 1.5 mmol, 3 equiv) in 91% yield as described above for **3**. The remainder of the synthesis and purification of **4** was then carried out analogously to the procedures used for **3**, to give 245 mg pure **4** (0.104 mmol, 23% yield).

6.7. Spectral characterization of peptides 3 and 4

Mass spectral analysis was performed by the Laboratory for Biological Mass Spectrometry of Texas A&M University (College Station, TX, USA). Samples of RP-HPLC/GPC purified **3** and **4** were dried under vacuum for at least 12 h prior to NMR analysis. ^1H NMR and proton-decoupled ^{13}C NMR spectra were referenced to $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77.0 ppm), respectively. The ^1H NMR resonances were assigned using 2D NMR spectroscopy as described elsewhere.[34] We were able to partially assign the ^{13}C NMR resonances by comparison of the 1D proton-decoupled ^{13}C spectra with residue-dependent chemical shift values from the literature,[46] and by cross-correlating the shifts observed for **3** and **4**; we did not attempt more to fully assign the ^{13}C resonances. Due to the twofold symmetry of **3** and **4**, we observed NMR signals corresponding to only half the total number of residues. IR spectra were recorded on a Nicolet 750 FTIR spectrometer at a resolution of 8 cm^{-1}, and samples were held in a liquid cell having BaF_2 windows and a path length of 50 μm. IR spectra were corrected for background by taking the ratio of the sample spectra to a blank spectrum.

6.7.1. *cyclo*{[(L-Val-D-Val)$_4$-(L-Val-D-Pro-Gly)]$_2$-} (3). ^1H NMR (500 MHz, 289 K, 10 mM in $CDCl_3$): *L-Val(1)*, NH (7.28, d, J=9.6 Hz), $C^{\alpha}H$ (4.74), $C^{\beta}H$ (2.12), $C^{\gamma}H_3$ (0.95, 0.91); *D-Val(2)*, NH (8.68, d, J=6.3 Hz), $C^{\alpha}H$ (4.64), $C^{\beta}H$ (2.32), $C^{\gamma}H_3$ (1.03, 0.99); *L-Val(3)*, NH (8.58, d, J=9.8 Hz), $C^{\alpha}H$ (4.89), $C^{\beta}H$ (2.00), $C^{\gamma}H_3$ (0.92, 0.84); *D-Val(4)*, NH (8.38, d, J=6.8 Hz), $C^{\alpha}H$ (4.76), $C^{\beta}H$ (2.10), $C^{\gamma}H_3$ (0.95); *L-Val(5)*, NH (8.96, d, J=10.1 Hz), $C^{\alpha}H$ (5.11), $C^{\beta}H$ (2.06), $C^{\gamma}H_3$ (0.90, 0.81); *D-Val(6)*, NH (8.30, d, J=7.5 Hz), $C^{\alpha}H$ (4.62), $C^{\beta}H$ (2.10), $C^{\gamma}H_3$ (0.94, 0.90); *L-Val(7)*, NH (9.14, d, J=9.1 Hz), $C^{\alpha}H$ (4.03), $C^{\beta}H$ (1.91), $C^{\gamma}H_3$ (0.89); *D-Val(8)*, NH (6.45, d, J=6.4 Hz), $C^{\alpha}H$ (4.92), $C^{\beta}H$ (2.20), $C^{\gamma}H_3$ (1.06, 0.93); *L-Val(9)*, NH (7.78, d, J=8.4 Hz), $C^{\alpha}H$ (4.39), $C^{\beta}H$ (2.13), $C^{\gamma}H_3$ (1.05, 0.95); *D-Pro(10)*, $C^{\alpha}H$ (4.40), $C^{\beta}H$ (2.27, 2.05), $C^{\gamma}H$ (2.02), $C^{\delta}H$ (4.27, 3.63); *Gly(11)*, NH (6.91), $C^{\alpha}H$ (4.31, 3.60). ^{13}C NMR (75 MHz, 295 K, 10 mM in $CDCl_3$): δ 173.2 (C′), 172.5 (C′), 172.1 (C′), 171.8 (C′), 171.7 (C′), 171.4 (C′), 171.3 (C′), 171.2 (C′), 170.8 (C′), 170.7 (C′), 169.5 (C′), 61.7 (D-Pro10 C^{α}), 59.0 (Val C^{α}), 59.0 (Val C^{α}), 58.9 (Val C^{α}), 58.8 (Val C^{α}), 58.6 (Val C^{α}), 58.0 (Val C^{α}), 57.2 (Val C^{α}), 56.6 (Val C^{α}), 56.2 (Val C^{α}), 48.0, 42.5, 32.4, 32.4, 32.2, 31.7, 31.7, 31.6, 31.3, 30.6, 30.5, 29.6, 25.9 (D-Pro10 C^{γ}), 20.1 (Val C^{γ}), 19.9 (Val C^{γ}), 19.8 (Val C^{γ}), 19.7 (Val C^{γ}), 19.6 (Val C^{γ}), 19.5 (Val C^{γ}), 19.4 (Val C^{γ}), 19.3 (Val C^{γ}), 19.3 (Val C^{γ}), 19.3 (Val C^{γ}), 19.2 (Val C^{γ}), 19.0 (Val C^{γ}), 18.9 (Val C^{γ}), 18.7 (Val C^{γ}), 18.4 (Val C^{γ}), 17.8 (Val C^{γ}), 17.7 (Val C^{γ}), 17.2 (Val C^{γ}) ppm. IR (liquid, BaF_2, 295 K, 2 mM in $CDCl_3$): ν 3413 (amide A, nonhydrogen-bonded), 3278 (amide A, hydrogen-bonded),

3066 (amide B), 1682 (amide I parallel component), 1635 (amide I perpendicular component), 1543 (amide II) cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{104}H_{183}N_{22}O_{22}$ $[M+H]^+$: 2092.3877, found: 2092.3845; calcd for $C_{104}H_{182}N_{22}NaO_{22}$ $[M+Na]^+$: 2114.3697, found: 2114.3662; calcd for $C_{104}H_{182}N_{22}KO_{22}$ $[M+K]^+$: 2130.3436, found: 2130.3501.

6.7.2. *cyclo*{[(D-Leu-L-Leu)$_4$-(D-Leu-L-Pro-Gly)]$_2$-} 4. ^1H NMR (600 MHz, 283 K, 12 mM in $CDCl_3$): *D-Leu(1)*, NH (7.28, d, J=8.9 Hz), $C^{\alpha}H$ (4.75), $C^{\beta}H$ (1.64, 1.54), $C^{\delta}H_3$ (0.86, 0.80); *L-Leu(2)*, NH (8.92, d, J=7.1 Hz), $C^{\alpha}H$ (4.62), $C^{\beta}H$ (1.77, 1.37), $C^{\gamma}H$ (1.48), $C^{\delta}H_3$ (0.93, 0.87); *D-Leu(3)*, NH (8.80, d, J=9.3 Hz), $C^{\alpha}H$ (4.81), $C^{\beta}H$ (1.54, 1.42); *L-Leu(4)*, NH (8.35, d, J=8.4 Hz), $C^{\alpha}H$ (4.79), $C^{\beta}H$ (1.59, 1.14), $C^{\gamma}H$ (1.37), $C^{\delta}H_3$ (0.81, 0.82); *D-Leu(5)*, NH (9.22, d, J=9.4 Hz), $C^{\alpha}H$ (4.85), $C^{\beta}H$ (1.62, 1.35), $C^{\delta}H_3$ (0.86, 0.79); *L-Leu(6)*, NH (8.95, d, J=8.3 Hz), $C^{\alpha}H$ (4.67), $C^{\beta}H$ (1.71, 1.32), $C^{\gamma}H$ (1.43), $C^{\delta}H_3$ (0.87); *D-Leu(7)*, NH (9.23, d, J=9.0 Hz), $C^{\alpha}H$ (4.32), $C^{\beta}H$ (1.61, 1.37), $C^{\gamma}H$ (1.58), $C^{\delta}H_3$ (0.87); *L-Leu(8)*, NH (6.44, d, J=6.9 Hz), $C^{\alpha}H$ (4.99), $C^{\beta}H$ (1.59, 1.48), $C^{\delta}H_3$ (0.94); *D-Leu(9)*, NH (7.85, d, J=7.7 Hz), $C^{\alpha}H$ (4.60), $C^{\beta}H$ (1.71), $C^{\gamma}H$ (1.63), $C^{\delta}H_3$ (0.98, 0.94); *L-Pro(10)*, $C^{\alpha}H$ (4.40), $C^{\beta}H$ (2.28, 2.03), $C^{\gamma}H$ (2.06), $C^{\delta}H$ (4.74, 3.60); *Gly(11)*, NH (6.70, dd, J=4.8, 7.9 Hz), $C^{\alpha}H$ (4.22, 3.44). ^{13}C NMR (75 MHz, 295 K, 12 mM in $CDCl_3$): δ 174.7 (C′), 173.2 (C′), 172.5 (C′), 172.2 (C′), 171.5 (C′), 171.4 (C′), 171.4 (C′), 171.2 (C′), 170.7 (C′), 170.6 (C′), 169.8 (C′), 61.8 (l-Pro10 C^{α}), 51.9 (Leu C^{α}), 51.9 (Leu C^{α}), 51.3 (Leu C^{α}), 51.1 (Leu C^{α}), 51.0 (Leu C^{α}), 51.0 (Leu C^{α}), 50.9 (Leu C^{α}), 50.8 (Leu C^{α}), 50.1 (Leu C^{α}), 47.7, 43.8, 43.3, 43.1, 42.6, 42.4, 42.3, 42.0, 41.6, 41.0, 40.2, 29.4, 25.2, 25.1, 25.0, 25.0, 24.9, 24.8, 24.8, 24.7, 24.6, 24.5, 23.7 (Leu C^{δ}), 23.6 (Leu C^{δ}), 23.3 (Leu C^{δ}), 23.2 (Leu C^{δ}), 23.2 (Leu C^{δ}), 23.0 (Leu C^{δ}), 22.9 (Leu C^{δ}), 22.8 (Leu C^{δ}), 22.7 (Leu C^{δ}), 22.7 (Leu C^{δ}), 22.7 (Leu C^{δ}), 22.4 (Leu C^{δ}), 22.4 (Leu C^{δ}), 22.3 (Leu C^{δ}), 22.2 (Leu C^{δ}), 21.8 (Leu C^{δ}), 21.7 (Leu C^{δ}), 21.7 (Leu C^{δ}) ppm. IR (liquid, BaF_2, 295 K, 2 mM in $CDCl_3$): ν 3417 (amide A, nonhydrogen-bonded), 3267 (amide A, hydrogen-bonded), 3070 (amide B), 1682 (amide I parallel component), 1639 (amide I perpendicular component), 1551 (amide II) cm^{-1}. HRMS (MALDI) *m/z* calcd for $C_{122}H_{219}N_{22}O_{22}$ $[M+H]^+$: 2344.6694, found: 2344.6670; calcd for $C_{122}H_{218}N_{22}NaO_{22}$ $[M+Na]^+$: 2366.6514, found: 2366.6489; calcd for $C_{122}H_{218}N_{22}KO_{22}$ $[M+K]^+$: 2382.6253, found: 2382.6099.

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Achieving saturated red photoluminescence and electroluminescence with readily synthesized maleimide-arylamine copolymers

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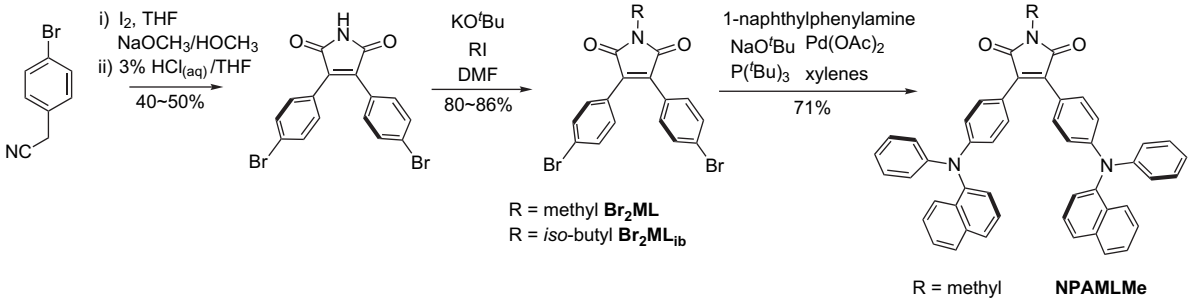
Abstract—Maleimide-based red fluorescent copolymers were easily synthesized from palladium catalyzed polycondensation of *N*-alkyl-3,4-bis(4-bromophenyl)maleimide with commercially available or readily prepared secondary aryldiamines. The copolymers were characterized by gel permeation chromatography, differential scanning calorimetry, cyclic voltammetry, UV–vis absorption, and fluorescence spectroscopy. They showed brilliant red fluorescence in solution (toluene) with emission maximum in the range of 617–638 nm, although severely red-shifted in thin films. With judicious selection of aryldiamine monomers, the red-shifting of the thin film fluorescence can be largely diminished. The structure and property (molecular weight, glass transition temperature, and fluorescence) relationships were analyzed and deciphered as well. A light-emitting device has been fabricated with maleimide-arylamine copolymer in demonstrating the potentials for saturated red polymer light-emitting diodes (PLEDs).

1. Introduction

We have recently reported *N*-methyl-3,4-bis(4-(*N*-(1-naphthyl)phenylamino)phenyl)maleimide (**NPAMLMe**) as the novel host light-emitter in the fabrication of rare non-dopant red organic light-emitting diodes (OLEDs).[1] The triarylamine-substituted maleimide showed unusual amorphous property (glass transition temperature, T_g, at 126 °C) and strong red fluorescence in solid state. This is pretty extraordinary for red fluorophores, which usually possess extended π-conjugation or dipolar donor–acceptor substituents and tend to be crystallinic and fluorescence-quenching in solid state. Specifically, the precursor in preparing **NPAMLMe** is a dibromo-substituted species, *N*-methyl-3,4-bis(4-bromophenyl)maleimide (**Br_2ML**), which is easily synthesized from 4-bromophenylacetonitrile (Scheme 1).[1,2] This is an appropriate monomer in synthesizing high molecular weight polyarylenes through Yamamoto-type Ni-catalyzed or Suzuki or Heck-type Pd-catalyzed polycondensation. **Br_2ML** also can be a suitable monomer in Sonogashira-type Pd/Cu-catalyzed co-polycondensation of arylalkynes. About half a dozen of reports taking a good utilization of **Br_2ML** or different



Scheme 1. Synthesis of **Br_2ML**, **Br_2Ml_{ib}**, and **NPAMLMe**.

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alkyl derivatives in the preparation of 3,4-diphenylmaleimide-based polyaryl macromolecules have illustrated this point.[3] Only yellow to orange fluorescent polymers derived from maleimides have been known thus far.

In addition to non-doped red OLEDs, we have been interested in developing the readily prepared red fluorescent polymers for applications in polymer light-emitting diodes (PLEDs). Red light-emitting polymer is one of the three indispensable components (red, green, and blue) in the fabrication of full color display based on OLEDs. However, when compared with either green or blue light-emitting polymers, red light-emitting polymer is relatively scarce. Moreover, most of the known red light-emitting polymers are not easily accessible and require lengthy synthesis procedure in the preparation of suitable monomers.[4] For generating long wavelength red emission, it is necessary to attach arylamino unit to the maleimide moiety shown by a series of fluorescent 3,4-diaryl-substituted maleimides.[2] Pd-catalyzed aromatic amination reactions, which are commonly employed in the high-yield synthesis of triarylamines, will be promising for synthesizing red fluorescent polymer based on *N*-alkyl-3,4-bis(4-bromophenyl)maleimide bearing secondary arylamines.[5] Accordingly, herein we report the easy syntheses and physical characterizations, including gel permeation chromatography, differential scanning calorimetry, cyclic voltammetry, UV–vis absorption, and fluorescence spectroscopy, of a series of red fluorescent maleimides-arylamine copolymers. A preliminary test of the red electroluminescence of the copolymers is reported here as well.

2. Experimental

2.1. Materials and measurement

All chemicals were purchased from Aldrich and Acros chemical companies and were used without any further purification. All the solvents such as toluene, DMSO, and THF were distilled after drying with appropriate drying agents. The dried solvents were stored over 4 Å molecular sieves before usage. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 MHz or AMX-400 MHz Fourier transform spectrometer at room temperature. The number- and weight-average molecular weight of polymers were determined by gel permeation chromatography (GPC) on a Waters GPC-1515 with a 2414 refractive index detector, using THF as the eluent and polystyrene as the standard. UV–vis absorption and fluorescence spectra were recorded by Hewlett–Packard 8453 and Hitachi F-450 spectrophotometers, respectively. Glass transition temperatures (T_gs) of the copolymers were determined by differential scanning calorimetry (DSC) using a Perkin–Elmer DSC-6 analyzer system. Thermal analyses were performed with a scanning (both heating and cooling) rate of 10°/min in an atmosphere of nitrogen. The temperatures at the intercept of the curves on the thermogram (endothermic or exothermic) and the leading baseline were taken as the estimates for the onset T_g. The oxidation potentials of the copolymers were determined by cyclic voltammetry (CV) using an Electrochemical Analyzer BAS 100B. The electrochemical measurement of the copolymers was performed in a 0.1 M tetrabutylammonium perchlorate (Bu_4NClO_4) solution in toluene with scanning rate of 100 mV/s at room temperature. A platinum wire was used as counter electrode, and $Ag/AgNO_3$ was employed as reference electrode. Ferrocene was used for potential calibration (all reported potentials are referenced against ferrocene/ferrocenium, FOC) and for reversibility criteria. Both solution and solid-state fluorescence quantum yields of the model compounds and maleimide-based copolymer were determined by integrating sphere method described by de Mello et al.[6] The thin films of the copolymers were spin-casted from the toluene solution on the glass substrate and subjected to vacuumed drying at room temperature for at least 16 h before the experimental measurement.

2.2. Syntheses of the monomers

Monomer **Br$_2$ML** was prepared following the already published procedure,[2,7] and the synthesis of **Br$_2$ML$_{ib}$** was also conducted according to the known literature (Scheme 1),[2,7] but *iso*-butyl iodide was used as the alkylating reagent. **OPhA$_{tol}$** and **IPPhA$_{tol}$** were synthesized (with isolated yields of 67 and 51%, respectively) by the amination of 4-tolyl iodide with 4,4′-oxydianiline or 4,4′-(1,4-phenylenediisopropylide)bisaniline, respectively, by using (DPPF)$PdCl_2$/DPPF as the catalyst.[8a] **OPhA$_{nhx}$** was prepared by a two-step reaction. First, 4,4′-oxydianiline was converted to a diamide derivative in near quantitative yield with *tert*-butylacetyl chloride, and then the amide groups were conveniently reduced to secondary amine (with isolated yield of 63%) using $NaBH_4/I_2$ in THF followed by the acidic treatment with 3 N hydrochloric acid solution.[8b]

2.2.1. *N*-Isobutyl-3,4-bis(4-bromophenyl)maleimide, Br$_2$ML$_{ib}$. Yellow-greenish powder with a yield of 80%. ^{1}H NMR (DMSO, 400 MHz, δ/ppm): 7.49 (d, 4H, J=8.7 Hz), 7.34 (d, 4H, J=8.7 Hz), 3.44 (d, 2H, J=7.3 Hz), 2.11–2.04 (m, 1H), 0.93 (d, 6H, J=6.7 Hz). ^{13}C NMR (DMSO, 100 MHz, δ/ppm): 170.4, 135.0, 132.0, 131.3, 127.2, 124.7, 45.8, 27.9, 20.1. Anal. Calcd for $C_{20}H_{17}Br_2NO_2$: C, 51.86; H, 3.70; N, 3.02. Found: C, 51.66; H, 3.57; N, 3.02.

2.2.2. *N*,*N*′-Di-neo-hexyl-4,4′-oxydianiline, OPhA$_{nhx}$. White powder with a yield of 63%. ^{1}H NMR (DMSO, 400 MHz, δ/ppm): 6.69 (d, 4H, J=8.8 Hz), 6.49 (d, 4H, J=8.8 Hz), 5.16 (s, 2H), 2.93 (t, 4H, J=8.1 Hz), 1.47–1.43 (m, 4H), 0.92 (s, 18H). ^{13}C NMR (DMSO, 100 MHz, δ/ppm): 148.7, 144.0, 119.1, 113.6, 42.3, 40.3, 29.6, 29.4. Anal. Calcd for $C_{24}H_{36}N_2O$: C, 78.21; H, 9.85; N, 7.60. Found: C, 78.29; H, 9.60; N, 7.57.

2.2.3. *N*,*N*′-Di(4-tolyl)-4,4′-oxydianiline, OPhA$_{tol}$. Off-white powder with a yield of 67%. ^{1}H NMR (DMSO, 400 MHz, δ/ppm): 7.84 (s, 2H), 7.01–6.99 (m, 8H), 6.92–6.85 (m, 8H), 2.20 (s, 6H). ^{13}C NMR (DMSO, 100 MHz, δ/ppm): 150.4, 141.5, 139.4, 129.6, 128.0, 119.2, 118.2, 116.5, 20.3. Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.10; H, 6.31; N, 7.39.

2.2.4. *N*,*N*′-Di(4-tolyl)-4,4′-(1,4-phenylenediisopropylide)bisaniline, IPPhA$_{tol}$. White powder with a yield of 51%. ^{1}H NMR (DMSO, 400 MHz, δ/ppm): 7.85 (br, 2H), 7.11 (s, 4H), 7.06–6.99 (m, 8H), 6.94–6.90 (m, 8H), 2.20 (s, 6H). ^{13}C NMR (DMSO, 100 MHz, δ/ppm): 147.6, 141.5, 141.1, 141.0, 129.5, 128.2, 127.1, 125.9, 117.0,

115.9, 41.3, 30.5, 20.3. Anal. Calcd for $C_{38}H_{40}N_2$: C, 86.98; H, 7.68; N, 5.34. Found: C, 86.87; H, 7.62; N, 5.22.

2.3. General procedure of the copolymer synthesis

Following a pertinent procedure[5] in the high-yield synthesis of triarylamines, a mixture of **Br_2ML** (0.42 g, 1.0 mmol), appropriate aryldiamine (1.0 equiv amount), NaO^{t}Bu (0.21 g, 2.2 mmol), P(^{t}Bu)$_3$ (0.049 g, 0.2 mmol), and $Pd(OAc)_2$ (0.01 g, 0.04 mmol) in dry THF (8 mL) was stirred at refluxing temperature under a nitrogen atmosphere for about 2 days. After cooling to room temperature, the solution mixture was then poured into a solution of methanol and deionized water (10:1). The precipitates were collected by filtration. The solid was redissolved in either chloroform or dichloromethane and then reprecipitated by the addition of either methanol or hexane. The reprecipitation procedure was repeated at least three or four times, followed by Soxhlet extraction using methanol first then hexane for 24 h. Yields of all polymerization reactions were in a range of 63 and 84% depending on the aryldiamine used. All products have been structurally characterized by NMR spectroscopy and elemental analysis.

2.3.1. PMLPhA$_{Ph}$. The copolymer was obtained as a deep red semifibrous material with a yield of 62% after drying under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.41–6.96 (m, 22H), 3.08 (s, 3H). Anal. Calcd for $(C_{35}H_{25}N_3O_2)_n$: C, 80.89; H, 4.82; N, 8.09. Found: C, 80.53; H, 4.84; N, 7.99.

2.3.2. PMLBPhA$_{Ph}$. The copolymer was obtained as a deep red fibrous powder with a yield of 84% after drying under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.45–6.99 (m, 26H), 3.10 (s, 3H). Anal. Calcd for $(C_{41}H_{29}N_3O_2)_n$: C, 82.66; H, 4.87; N, 7.06. Found: C, 82.28; H, 4.82; N, 7.01.

2.3.3. PMLOPhA$_{tol}$. The copolymer was obtained as a red powder with a yield of 65% after drying under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.38 (d, 4H, J=8.2 Hz), 7.07–6.86 (m, 20H), 3.08 (s, 3H), 2.29 (s, 6H). Anal. Calcd for $(C_{43}H_{33}N_3O_3)_n$: C, 80.72; H, 5.16; N, 6.57. Found: C, 80.48; H, 5.15; N, 6.44.

2.3.4. PMLOPhA$_{nhx}$. The copolymer was obtained as a deep red powder with a yield of 80% after drying under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.42 (d, 4H, J=8.4 Hz), 7.14 (d, 4H, J=8.4 Hz), 7.02 (d, 4H, J=8.5 Hz), 6.64 (d, 4H, J=8.5 Hz), 3.66 (br, 4H), 3.06 (s, 3H), 1.57 (br, 4H), 0.92 (s, 18H). Anal. Calcd for $(C_{41}H_{45}N_3O_3)_n$: C, 78.42; H, 7.17; N, 6.69. Found: C, 78.22; H, 7.21; N, 6.56.

2.3.5. PMLIPPhA$_{tol}$. The copolymer was obtained as a red powder with a yield of 69% after drying under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.37 (d, 4H, J=8.3 Hz), 7.11–6.96 (m, 20H), 6.86 (d, 4H, J=7.8 Hz), 3.06 (s, 3H), 2.28 (s, 6H), 1.62 (s, 12H). Anal. Calcd for $(C_{55}H_{49}N_3O_2)_n$: C, 84.25; H, 6.25; N, 5.36. Found: C, 83.99; H, 6.22; N, 5.37.

2.3.6. PML$_{ib}$IPPhA$_{tol}$. The copolymer was obtained as a bright red powder with a yield of 63% after drying under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ/ppm): 7.38 (br, 4H), 7.09–6.81 (m, 24H), 3.38 (br, 2H), 2.28 (s, 6H), 2.05 (br, 2H), 1.61 (s, 12H), 0.90 (s, 6H). Anal. Calcd for $(C_{58}H_{55}N_3O_2)_n$: C, 84.32; H, 6.66; N, 5.09. Found: C, 83.96; H, 6.59; N, 5.08.

3. Results and discussion

3.1. Synthesis and characterization

The syntheses of red polymers shown in Scheme 2 proceeded via a Pd-catalyzed polycondensation of *N*-methyl-3,4-bis-(4-bromophenyl)maleimide with secondary aryldiamines, such as *N*,*N*′-diphenyl-1,4-phenylenediamine (**PhA$_{Ph}$**), and *N*,*N*′-diphenylbenzidine (**BPhA$_{Ph}$**) are commercially available and can be adopted in the polycondensation as well. Other secondary aryldiamines, such as *N*,*N*′-di(4-tolyl)-4,4′-oxydianiline (**OPhA$_{tol}$**), *N*,*N*′-di-neo-hexyl-4,4′-oxydianiline (**OPhA$_{nhx}$**), and *N*,*N*′-di(4-tolyl)-4,4′-(1,4-phenylenediisopropylide)bisaniline (**IPPhA$_{tol}$**), (Scheme 2) are readily prepared.

The resulting copolymers, except **PMLPhA$_{Ph}$**, are readily soluble in common organic solvents, such as toluene, chloroform, dichloromethane, and THF. Their molecular weights were determined by gel permeation chromatography (GPC) using THF as the eluent and polystyrene standard for calibration. The results are listed in Table 1. These copolymers in general show average molecular weight (M_w) from 5400 to 15,200 with polydispersity indices (M_w/M_n) of 1.4–3.9. It is somewhat to our surprise that **PMLPhA$_{Ph}$** and **PMLBPhA$_{Ph}$** have the highest molecular weights among these copolymers prepared in this study. At this stage, we can only surmise that difference in the reactivity of aryldiamine may be accounted for the varied molecular weight of these copolymers, in addition to the solubility concern of these copolymers.

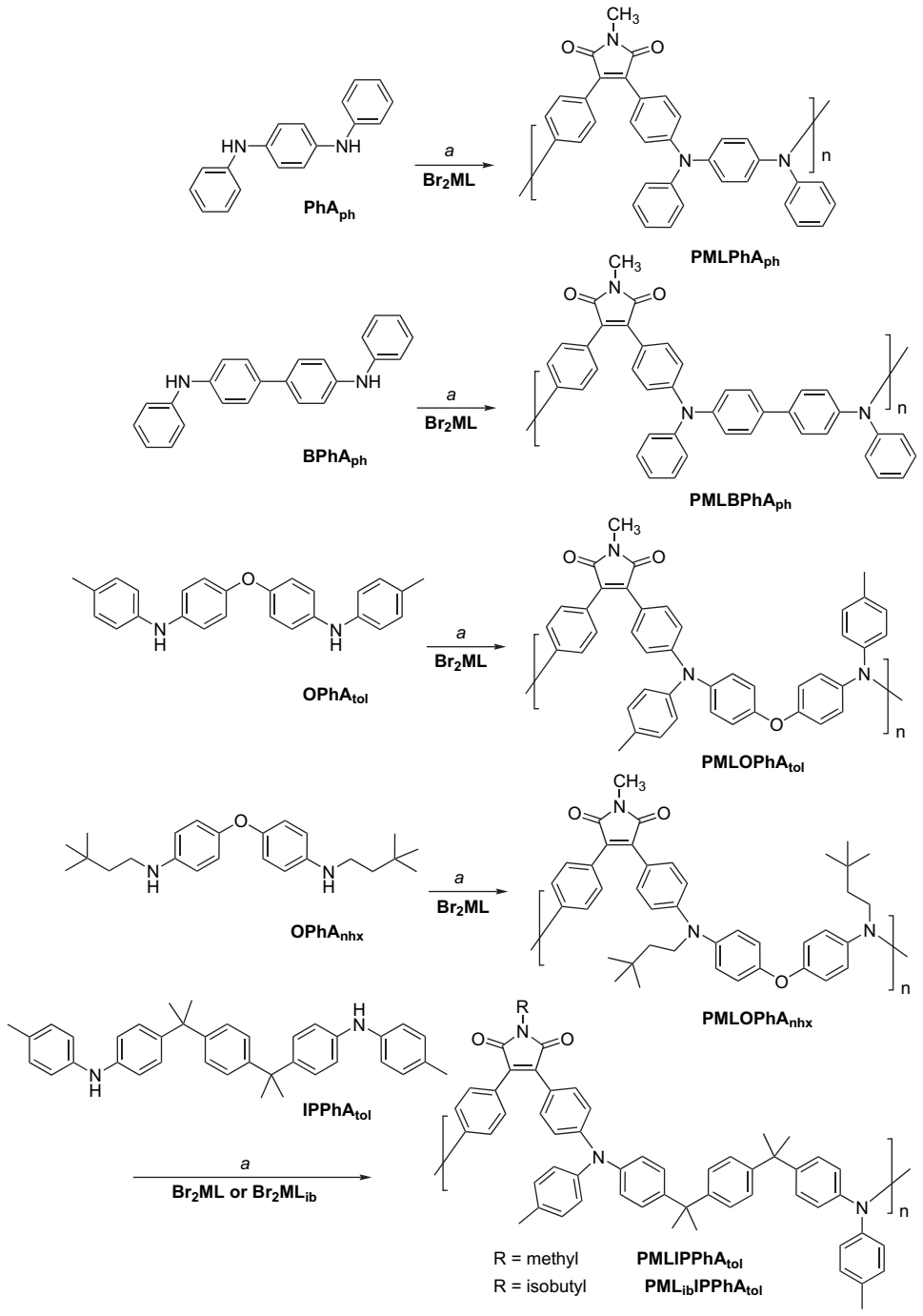
3.2. Thermal properties and optical absorption characterization

The thermal properties of the copolymers were determined by differential scanning calorimetry (DSC) as shown in Table 1. The T_gs of these copolymers in general follow the variation of M_w values, i.e., the higher the M_w values, the higher the T_g values, although the structural flexibility is the factor affecting T_g values as well.

The absorption spectra were measured from the copolymers dissolved in toluene. All copolymers show very similar absorption spectra with peaks locating at 283–342 nm, which are attributable to the π–π* electronic transitions of the copolymer backbones. The additional absorption peaks at 485–490 nm are due to the n–π* transition of the diarylmaleimide units in the copolymer main chain.[3f,3g] From the on-set absorption wavelengths of the absorption spectra, the optical band gaps (E_{opt}) are estimated to be 2.05–2.12 eV. The physical characterization and absorption spectra are summarized in Table 1, Table 2, and Figure 1.

3.3. Fluorescent characterization

The most intriguing property of these copolymers is the long wavelength fluorescence. All copolymers showed strong red



Scheme 2. Syntheses of red polymers derived from **Br$_2$ML** (or **Br$_2$ML$_{ib}$**) and secondary aryldiamines. (a) Reagents and conditions: THF, NaO^{t}Bu, P(^{t}Bu)$_3$, Pd(OAc)$_2$, reflux, 48 h.

Table 1. Physical data of the copolymers

	Yield (%)	λ_{max}^{ab}, nm[a] (ε, M^{-1} cm^{-1})	T_g (°C)	M_w	M_n	PDI[b]
PMLPhA$_{Ph}$	62	311, 485 (10,200)	201	15,200	3900	3.9
PMLBPhA$_{Ph}$	84	342, 485 (11,500)	222	14,500	6800	2.1
PMLOPhA$_{tol}$	65	303, 485 (8500)	189	5400	3300	1.6
PMLOPhA$_{nhx}$	80	283, 485 (8900)	168	8200	5700	1.4
PMLIPPhA$_{tol}$	69	303, 490 (7700)	200	12,400	6400	1.9
PML$_{ib}$IPPhA$_{tol}$	63	300, 485 (7100)	163	9000	5600	1.6

[a] In toluene.
[b] Poydispersity index (M_w/M_n).

Table 2. Optical and Electrochemical Properties of the copolymers

	λ_{max}^{em} (nm)[b]		ϕ[d] (%)	Δ[e] (nm)	E^{OX} versus E^{FOC}	E_{opt}[f] (eV)	HOMO[g] (eV)	LUMO[h] (eV)
	Solution[a]	Film[c]						
PMLPhA$_{Ph}$	638 (95)	694 (115)	4	56	0.46	2.05	−5.26	−3.21
PMLBPhA$_{Ph}$	631 (75)	677 (111)	13	46	0.65	2.06	−5.45	−3.39
PMLOPhA$_{tol}$	626 (73)	667 (122)	16	41	0.68	2.11	−5.48	−3.37
PMLOPhA$_{nhx}$	617 (73)	672 (122)	24	55	0.53	2.12	−5.33	−3.21
PMLIPPhA$_{tol}$	624 (72)	661 (111)	31	37	0.67	2.10	−5.47	−3.37
PML$_{ib}$IPPhA$_{tol}$	620 (73)	633 (81)	30	13	0.67	2.10	−5.47	−3.37

[a] In toluene.
[b] Numbers in parenthesis denote the full-width-at-half-maximum of the emission spectra.
[c] Spin-casted solid film from toluene solution and vacuum-dried.
[d] Fluorescence quantum yield in toluene using ϕ=98% of rubrene in benzene as the reference.[10]
[e] $\Delta = \lambda_{max}^{em}(\text{film}) - \lambda_{max}^{em}(\text{solution})$.
[f] Band gaps were calculated from the on-set absorption edge of the UV–Vis spectrum.
[g] HOMO levels were calculated from $E_{1/2}$ of the oxidation voltammograms by comparing with the ferrocene value of 4.8 eV below the vacuum level.[9]
[h] LUMO levels were estimated from the HOMO energy levels and the optical band gap of the copolymers.

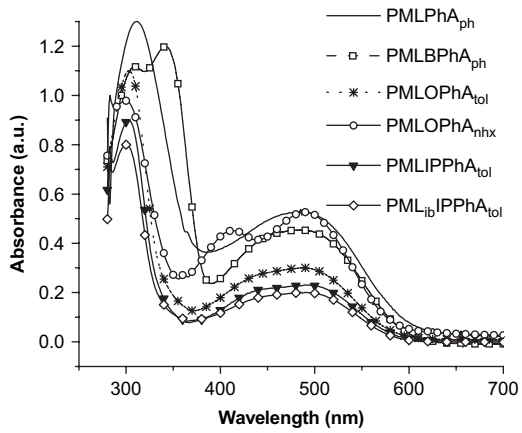


Figure 1. UV–Vis absorption spectra of copolymers in toluene solution.

fluorescence in toluene solution with λ_{max}^{em} in the range of 617–638 nm (Fig. 2). Polymer **PMLPhA$_{Ph}$** is the exception regarding the intensity of fluorescence, because it is the only weak fluorescent in solution. Although fluorescence is highly visible, the solution quantum yields of these polymers were low to moderate (4–31%). **PMLPhA$_{Ph}$** possesses the widest full-width-at-half-maximum (95 nm) and the longest wavelength (638 nm) of the emission band. The unique spectroscopic property of **PMLPhA$_{Ph}$** may be attributed to its high molecular weight (the highest among all copolymers) accompanying with wide distribution of the molecular weight as indicated by its high PDI value. The relatively rigid and short π-conjugation of the aryldiamine segment causes the copolymer chain more folding, which is believed to be the reason for the low solubility of **PMLPhA$_{Ph}$**. The puckered copolymer chain also increases the chance of intra-copolymer interaction even in diluted solution condition. Such interaction severely quenches the fluorescence and the lowest solution fluorescence quantum yield (only 4%) observed for **PMLPhA$_{Ph}$** is as a consequence of the copolymer chain structure.

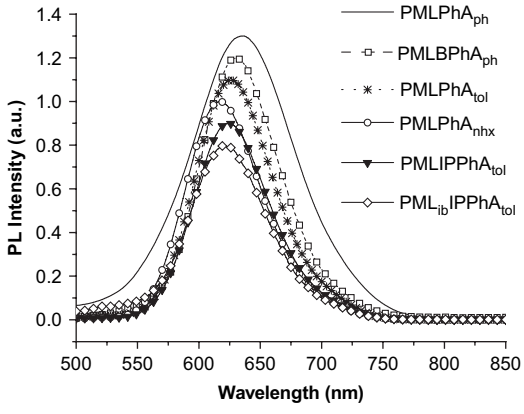


Figure 2. Photoluminescence spectra of the copolymers in toluene solution.

As shown for **PMLPhA$_{Ph}$**, fluorescence spectroscopic properties are closely related to the chemical structure of the copolymers. Copolymers with more extended π-conjugation structure will show longer fluorescence wavelength. Furthermore, aryl substituent of the diamine moiety has a stronger effect than the alkyl substituent in pushing the fluorescence toward longer wavelengths, such as 617 and 626 nm of λ_{max}^{em} for **PMLOPhA$_{nhx}$** and **PMLOPhA$_{tol}$** in solution, respectively.

In thin films, when compared with solution fluorescence spectra (Fig. 3), the red-shifting of the thin film fluorescence is considerably large, in the range of 13–56 nm (Table 2). With the exception of **PML$_{ib}$IPPhA$_{tol}$**, almost all copolymers exhibit fluorescence beyond 660 nm (Table 2). Emission at wavelength longer than 650 nm is not practical for the display

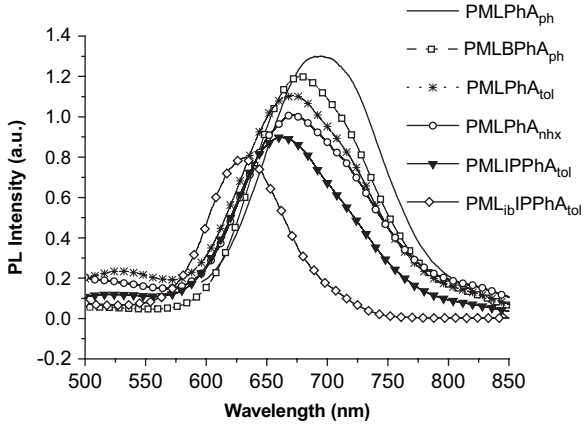


Figure 3. Photoluminescence spectra of the polymers in thin films spin-coated from toluene solution.

application, because of the poor spectral response of the human eye at such long wavelength. Therefore, it is necessary to prevent fluorescence in thin film from red-shifting for practical concern.

The red-shifting fluorescence in thin film is frequently attributed to molecular aggregation, particularly involving π–π interaction of aromatic moiety. Therefore, preventing π–π interaction between copolymer chains should inhibit the red-shifting of the fluorescence in thin film. Followings are a few observations from the study that help in designing copolymers with reduced aggregation in thin film. First, **PMLPhA$_{Ph}$** has the worst red-shifting in its class of the copolymer. The structural rigidity is the cause, but electronic donor substituent, in this case, the *para*-substituted amino group, may be another reason. Second, we notice that **PMLOPhA$_{nhx}$** has a larger red-shifting (Δ=55 nm) fluorescence spectrum than its tolyl analog **PMLOPhA$_{tol}$** (Δ=41 nm) (Table 2). This result suggests that the rigid aryl substituent is better than flexible alkyl substituent in preventing the copolymer aggregation in thin film. On the other hand, by breaking up the π-conjugation as well as by replacing of electronic donating oxygen-bridge with weaker donor of isopropyl group, the extent of the red-shifting fluorescence can be further reduced to Δ=37 nm for **PMLIPPhA$_{tol}$**.

Based on the above observations and inductions, **PML$_{ib}$IPPhA$_{tol}$** was designed and synthesized to reduce the red-shifting of fluorescence in thin film. **PML$_{ib}$IPPhA$_{tol}$** can be considered as the improved version of **PMLIPPhA$_{tol}$**. Having a longer and bulkier alkyl substituent on the nitrogen of maleimide, **PML$_{ib}$IPPhA$_{tol}$** really exhibits the desired improvement on fluorescence (Fig. 4), i.e., shorter fluorescence wavelength both in solution (620 nm, the second shortest of all) and thin film (633 nm, the shortest of all) (Table 2), smaller red-shifting in thin film (only 13 nm, the smallest among all), and narrower full-width-at-half-maximum (81 nm, the narrowest among all copolymers).

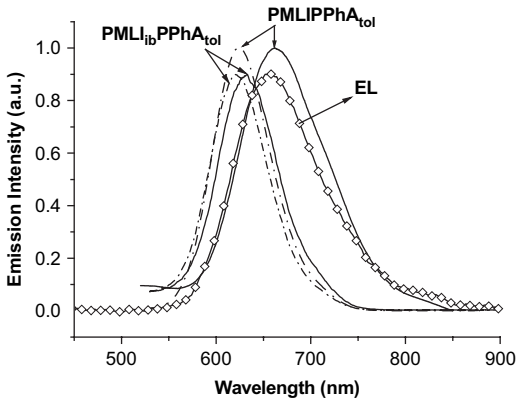


Figure 4. Fluorescence spectra of **PMLIPPhA$_{tol}$** and **PML$_{ib}$IPPhA$_{tol}$** both in toluene solution (dotted lines) and solid film (solid lines). EL spectrum of the device ITO/**PML$_{ib}$IPPhA$_{tol}$**/LiF/Al is also illustrated (diamond symbols).

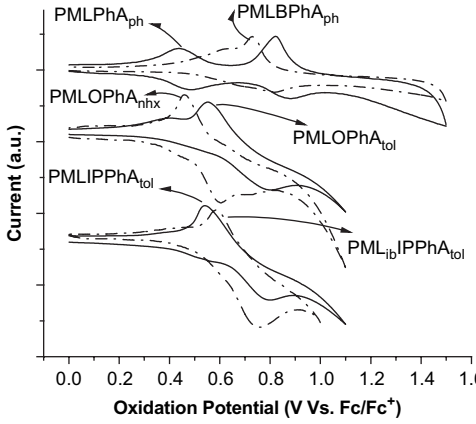


Figure 5. Cyclic voltammograms (oxidation) of copolymers in toluene, containing 0.1 M Bu_4NClO_4 versus Ag/Ag^+ reference electrode, scan rate: 100 mV/s.

3.4. Electrochemical characterization and HOMO–LUMO energy levels

Cyclic voltammetry (CV) was employed to investigate the electrochemical behaviors of the synthesized copolymers and to estimate their HOMO energy levels. Figure 5 depicts cyclic voltammograms of the polymers in the oxidation process. The copolymers showed reversible peak under oxidation process, which indicates their electrochemical stability in the hole-carrying process. Similar observations have been found for the non-dopant red emitter **NPANLMe** as before.[1] The HOMO energy level of the polymers was calculated using the ferrocene (FOC) value of −4.8 eV as the standard.[9] The electrochemical characteristics of the polymers are summarized in Table 2. The HOMO energy levels of the copolymers were estimated from −5.26 to −5.48 eV. The slight difference may be rationalized by the electron-donating ability of arenes to the nitrogen. By calculating from HOMO levels and optical band gaps (from on-set absorption energy), the LUMO energy levels of the copolymers were found to be −3.21 to −3.39 eV. With the appropriately aligned HOMO and LUMO energy levels to the work function of the anode and cathode, respectively, these red fluorescent copolymers have a chance to be used as the single layer light-emitting device (see below).

3.5. Application to PLED

PLED was fabricated for preliminary test of the red electroluminescence (EL). The device was constructed by spin-casting (1500 rpm) of a toluene solution of a mixture of **PMLI$_{ib}$PPhA$_{tol}$** (10 mg/mL) followed by vacuum (~10^{-5} Torr) deposition of LiF and Al, sequentially, on PEDOT–PSS/ITO (indium tin oxide) glass substrate, where PEDOT–PSS is the conducting polyethylene dioxythiophene/polystyrene sulfonate. The device had the simple configuration of ITO/PEDT–PSS/**PMLI$_{ib}$PPhA$_{tol}$**/LiF/Al. It showed EL with λ_{max}^{el} at 656 nm (Fig. 4) corresponding to $CIE_{x,y}$ of (0.66, 0.33), which is comparable with or better than $CIE_{x,y}$ of (0.64, 0.33), the standard red color of National Television System Committee (NTSC). For the single layer device of **PMLI$_{ib}$PPhA$_{tol}$**, the maximum electroluminance was around 9 cd/m^2, and the maximum luminous efficiency was 0.01 cd/A (Fig. 6). As compared with PL emission, the EL spectrum is red-shifted slightly (23 nm) and the band width becomes broadened.

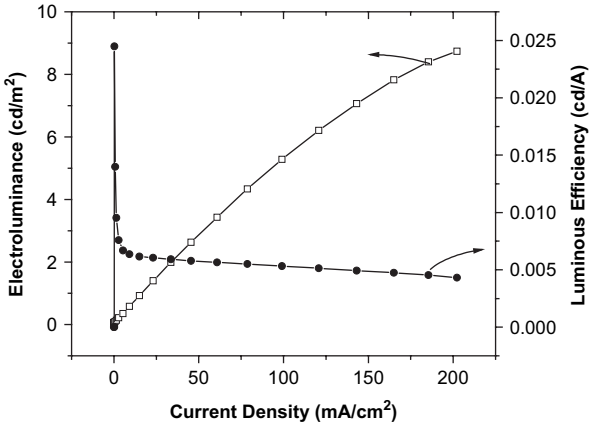


Figure 6. L-I-Luminous efficiency characteristics of $\mathbf{PML_{ib}IPPhA_{tol}}$ device.

4. Conclusion

We have shown that a new type of red fluorescent copolymers based on arylamine-derived 3,4-diphenylmaleimide can be easily synthesized. We have successfully achieved the copolymers showing saturated red fluorescence in thin films. Applications of the copolymer for saturated red PLEDs have been demonstrated primarily. This study is valuable for the further optimization of the readily prepared maleimide-arylamine copolymers, in enhancing solubility, and fluorescence quantum yield in both solution and thin film.

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Introduction of ethynylene and thienylene spacers into 2,5-diarylthiazole and 2,5-diarylthiophene

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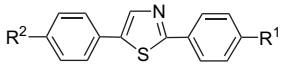
Abstract—Syntheses of 2,5-diarylthiazole and 2,5-diarylthiophene derivatives bearing ethynylene and thienylene spacers are performed. With the methods for coupling reactions of terminal alkynes and at the CH bond of heteroaromatic compounds, which we have developed, five kinds of thiazole and thiophene derivatives **3**–**7** are prepared. Spectroscopic characteristics of **3**–**7** are also measured.

1. Introduction

We have recently shown syntheses and properties of 2,5-diarylthiazoles **1** and 2,5-diarylthiophenes **2**. These molecules bearing donor–acceptor-type substituents showed intense photoluminescent properties and liquid crystalline characteristics based on the difference of the heteroaromatic ring structure.[1] Preparations of **1** and **2** were carried out by utilizing palladium-catalyzed C–H substitution reactions of 5-membered heteroaromatic compounds with various aryl halides, which we developed recently.[1–3] Introduction of conjugative spacer molecules into thiazole and thiophene derivatives is of considerable interest in the studies on the relationship of the structure and physical properties.[4] We envisaged that synthetic strategies utilizing transition metal-catalyzed coupling reactions show great advantage in the facile preparation of such compounds.[5] In particular, Sonogashira coupling is a powerful tool for the introduction of carbon–carbon triple bond.[6,7] Hence, the reaction using aqueous ammonia or 2-ethanolamine as an additive, which we have recently shown, play a significant role for the efficient synthesis of such derivatives.[8] Herein, we report synthesis of the derivatives of **1** and **2** bearing ethynylene spacers. Synthesis of 2,5-diarylthiophene bearing thienylene spacer is also described. Effect of the introduction of such spacers to spectroscopic characteristics is studied.[9]



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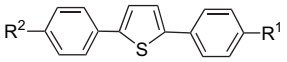

2

2. Results and discussion

2.1. Syntheses of 2,5-diarylthiazole 3 and 2,5-diarylthiophenes 4–7 bearing ethynylene and thienylene spacers

We have designed several 2,5-diarylated thiazole and thiophene derivatives bearing ethynylene and thienylene spacers **3**–**7** as summarized in Chart 1. Preparation of these compounds were carried out as shown in Schemes 1–5.

Introduction of the arylethynyl group into the 2-position of a thiazole ring was performed by utilizing the coupling reaction of terminal alkynes, which we developed recently.[7] The reaction of the terminal alkyne **8** with 2-bromothiazole in the presence of a palladium catalyst/CuI (3 mol %/2 mol %) using 2-ethanolamine as an activator afforded 2-arylethynylthiazole **9** in 77% yield after stirring at 60 °C for 5 h. Arylation of **9** at the 5-position was carried out with the palladium-catalyzed C–H substitution reaction using silver(I) fluoride as an activator.[1] Treatment of **9** with ethyl 4-iodobenzoate (**10**) in the presence of $PdCl_2(PPh_3)_2$ (3 mol %) and AgF (2 equiv) furnished the 2,5-diarylthiazole derivative bearing ethynylene spacer at the 2-position of thiazole **3** in 46% yield as shown in Scheme 1.

Scheme 2 shows synthesis of the thiophene derivative bearing the spacer. The arylethynyl group was introduced in a similar manner as in the case of the thiazole **9** with

Keywords: Sonogashira coupling; 2-Ethanolamine; Palladium catalyst; CH arylation.
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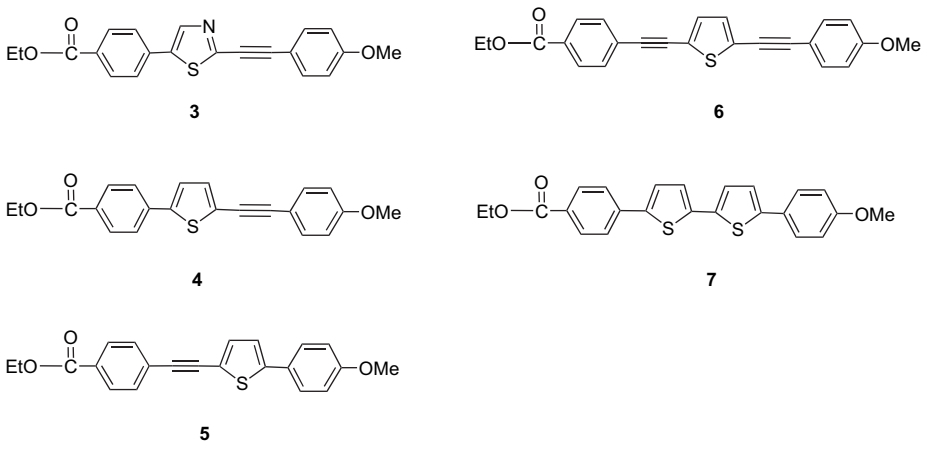
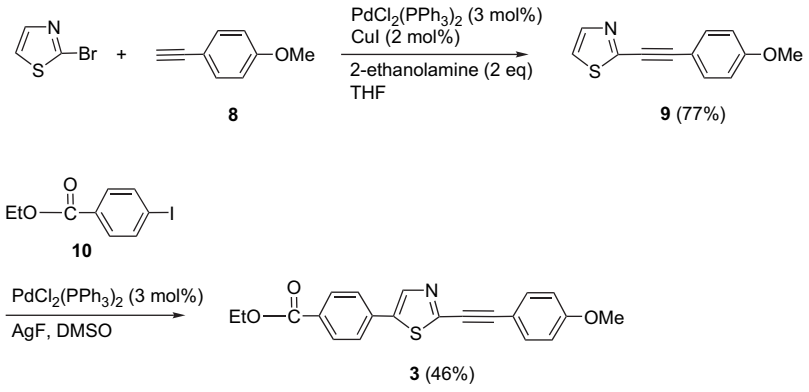
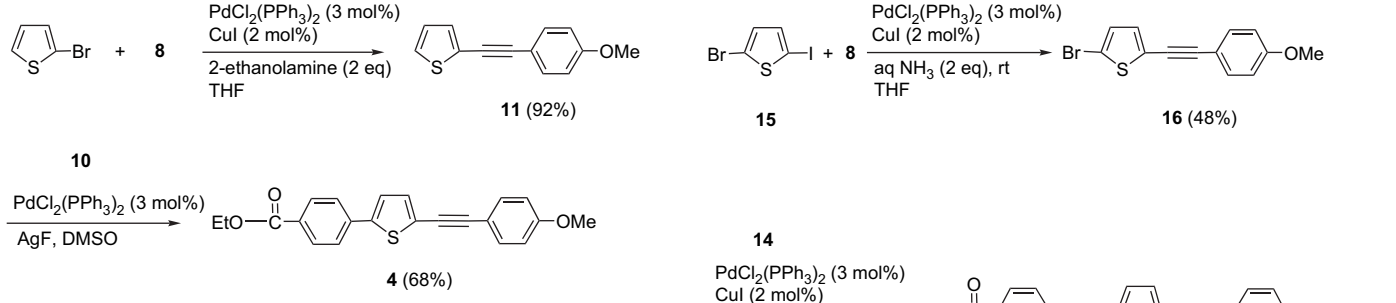


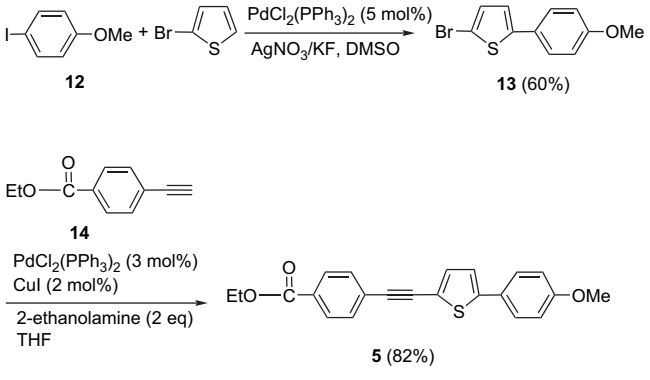
Chart 1.



Scheme 1.



Scheme 2.

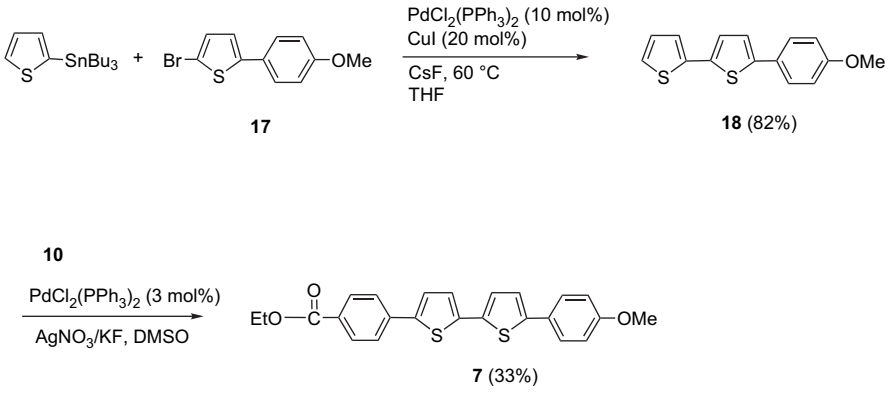


Scheme 3.

Scheme 4.

2-bromothiophene to afford 2-(arylethynyl)thiophene **11** in 92% yield.[8c] Following introduction of the aryl group bearing an electron-withdrawing substituent with **8** was also performed similarly to the manner of the thiazole case[1] to afford **4** in 68% yield.

Synthesis of the thiophene derivative bearing ethynylene spacer between the electron-deficient aryl group and thiophene was performed as shown in Scheme 3. As we reported that CH coupling occurred in the reaction of bromothiophenes



Scheme 5.

with the bromo group intact even in the presence of a palladium catalyst,[2c] synthesis of the 5-aryl-2-bromothiophene was performed by utilizing the CH coupling reaction with aryl iodide. Treatment of 2-bromothiophene with 1-iodo-4-methoxybenzene **12** in the presence of $PdCl_2(PPh_3)_2$ (5 mol %) and KF/$AgNO_3$ as an activator furnished 2-aryl-5-bromothiophene **13** in 60% yield. The reaction of the ethyl 4-ethynylbenzoate **14** with **13** in the presence of a palladium catalyst/CuI using 2-ethanolamine as an activator[8c] afforded **5** in 82% yield.

Preparation of the 2,5-diarylthiophene derivative bearing ethynyl groups at the both positions was carried out as shown in Scheme 4. The reaction of 2-iodo-5-bromothiophene **15** with a terminal alkyne using Sonogashira coupling with aqueous ammonia at room temperature[8a] selectively took place at the carbon–iodine bond to afford **16** in 48% yield. Introduction of the second arylethynyl group was performed with the Sonogashira coupling reaction of **16** with **14** in the presence of aqueous 2-ethanolamine at 60 °C to afford **6** in 88% yield.[8c]

Bithiophene **7** was also synthesized as shown in Scheme 5. Palladium-catalyzed cross-coupling of bromothiophene **17** with thienyl(tributyl)tin was effected to afford **18**.[10] CH substitution reaction of **18** with aryl iodide **10** in the presence of $AgNO_3$/KF afforded **7**.[2c]

For the coupling reactions of a (hetero)aryl bromide with terminal alkynes, for which higher reaction temperature was necessary to proceed, the method using 2-ethanolamine as an additive[8c] was found to be highly effective, while the reaction with aryl iodide at room temperature was carried out with aqueous ammonia.[8a] The reaction with ammonia at room temperature was found to proceed selectively at the carbon–iodine bond of 2-bromo-5-iodo-thiophene **15**.

CH arylation reactions of thiazole and thiophene derivatives were shown to proceed with AgF[1] or $AgNO_3$/KF.[2c] Both protocols were similarly effective for the reaction with aryl halides. Introduction of aryl group by the reaction at the CH bonds of heteroaromatic groups proceeds with a palladium or palladium/copper catalyst system in the presence of an activator. As shown in Scheme 2, the method was found to be effective for the substrate bearing a carbon–carbon triple bond.

2.2. Properties of thiazole and thiophene derivatives bearing ethynylene spacers

Measurements of UV–vis absorption and photoluminescent spectra were carried out and the results were summarized in Table 1. The λ_{max} value of thiazole **3** was slightly red-shifted compared with **1** by the introduction of ethynylene group at the 2-position compared with the corresponding 2,5-diarylthiazole, while the λ_{max} value of **4** was observed at the slightly smaller wavelength than that of **2**.[1] Properties of **5**, which possessed ethynylene spacer into the opposite position, were also found to show similar values. The λ_{max} value of thiophene **6**, which possessed two ethynylene groups at the 2- and 5-positions was observed at 364 nm, which red-shifted ca. 5–10 nm. On the other hand, the λ_{max} value of the corresponding bithiophene derivative was observed at 395 nm suggesting that the introduction of the thiophene ring showed more remarkable than ethynylene. Concerning photoluminescent spectra of thiophene and thiazole derivatives, quantum yields were found to decrease by the introduction of spacers compared with the corresponding 2,5-diarylthiazole **1** (Φ=0.24) and 2,5-diarylthiophene **2** (Φ=0.79).[1]

Table 1. Spectroscopic characteristics of 2,5-diarylthiazole and 2,5-thiophenes bearing ethynylene and thienylene spacers[a]

Compound	UV–vis absorption spectrum		Photoluminescent spectrum	
	λ_{max}, nm	ε	E_m	Φ
3	354	26 500	429	0.20
4	350	24 013	438	0.40
5	358	29 875	445	0.11
6	364	69 565	437	0.03
7	395	31 655	485	0.10
1[b]	347	26 800	424	0.24
2[b]	357	32 200	441	0.79

[a] See Section 4. E_m: wavelength maximum of the photoluminescent spectrum. Φ: quantum yield of the photoluminescence.
[b] Data from Ref. 1 (R^1=OMe, R^2=COOEt).

3. Conclusion

In summary, several thiazole and thiophene derivatives, which possessed ethynylene and thiophene spacers were synthesized and UV–vis absorption and photoluminescent properties were examined. These thiazole and thiophene

derivatives, which had not been synthesized previously, were prepared in a facile manner by employing coupling methodologies at the CH bond of heteroaromatic compounds and coupling of terminal alkynes using 2-ethanolamine as an activator that underwent the reaction smoothly and efficiently. Although remarkable spectroscopic characteristics were not observed in these thiazole and thiophene derivatives bearing a spacer molecule, the synthesis demonstrated that coupling methodologies with a transition metal catalyst were highly effective for the synthesis of compounds bearing heteroaromatic and/or alkyne moieties.

4. Experimental

4.1. General

DMSO was distilled from CaH_2 and stored over MS 4A under an argon atmosphere. THF (anhydrous grade) was purchased from Kanto Chemicals Co. Ltd and used without further purification. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured on Varian Mercury 300 NMR spectrometer. Infrared spectra were measured with Shimadzu FTIR-8000A. High-resolution mass spectra (EI) were obtained by JEOL MStation. Elemental analyses were carried out at Elemental Analysis Center of Chemical Resources Laboratory, Tokyo Institute of Technology using Yanako MT2 CHN CORDER. UV–vis spectra were measured as a 1×10^{-5} M chloroform solution with JASCO Ubest V-550. Photoluminescent spectra were measured as a 1×10^{-6} M chloroform solution with JASCO FP-6300. Quantum yields (Φ) were estimated with an aqueous solution of quinine sulfate (Φ=0.59) as a reference.

4.1.1. 2-(4-Methoxyphenylethynyl)thiazole (9). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (10.5 mg, 0.015 mmol), CuI (1.7 mg, 0.010 mmol), 2-bromothiazole (82.0 mg, 0.5 mmol), 4-(methoxyphenyl)acetylene (**8**, 79.2 mg, 0.6 mmol), and 3 mL of THF under an argon atmosphere. Then, 2 mL of aqueous 2-ethanolamine solution (0.5 M, 1.0 mmol) was added to the mixture and the Schlenk tube was heated at 60 °C for 5 h. After cooling to room temperature, the solution was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 82.9 mg of **9** as a colorless oil (77%): ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.90 (d, J=9.0 Hz, 2H), 7.35 (d, J=3.3 Hz, 1H), 7.54 (d, J=9.0 Hz, 2H), 7.84 (d, J=3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.28, 81.24, 94.26, 113.33, 114.14, 120.27, 133.51, 143.38, 149.17, 160.53; IR (KBr) 2837, 2206, 1605, 1514, 1294, 1252, 1175, 1091, 1055, 831 cm^{-1}. HRMS (EIMS) m/z calcd for $C_{12}H_9NOS$; 215.0405, found; 215.0404.

4.1.2. 5-(4-Ethoxycarbonylphenyl)-2-(4-methoxyphenylethynyl)thiazole (3). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (10.5 mg, 0.015 mmol), ethyl 4-iodobenzoate (**10**, 0.101 mL, 0.6 mmol), **9** (107.6 mg, 0.5 mmol), and 3 mL of DMSO under an argon atmosphere. AgF (64 mg, 0.5 mmol) was added to the mixture and the Schlenk tube was heated at 80 °C for 24 h. After cooling to room temperature, the resulting suspension was filtered and the residue was washed with dichloromethane repeatedly. The filtrate was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 83.4 mg of **3** as a yellow solid (46%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, J=7.2 Hz, 3H), 3.84 (s, 3H), 4.39 (q, J=7.2 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 7.55 (d, J=8.7 Hz, 2H), 7.62 (d, J=8.4 Hz, 2H), 8.07 (d, J=8.4 Hz, 2H), 8.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.28, 55.32, 61.14, 81.50, 95.67, 113.18, 114.21, 126.41, 130.25, 130.41, 133.62, 133.66, 134.97, 140.11, 141.04, 160.70, 165.86; IR (KBr) 2978, 2924, 2581, 2548, 2207, 1703, 1605, 1516, 1275, 1254, 1190, 1106, 1026, 841, 772, 695 cm^{-1}. HRMS (EIMS) m/z calcd for $C_{19}H_{22}OS$; 363.0929, found; 363.0903.

4.1.3. 2-(4-Methoxyphenylethynyl)thiophene (11). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (10.5 mg, 0.015 mmol), CuI (1.7 mg, 0.010 mmol), 2-bromothiophene (0.048 mL, 0.5 mmol), 4-(methoxyphenyl)acetylene (**8**, 79.2 mg, 0.6 mmol), and 3 mL of THF under an argon atmosphere. Then, 2 mL of 2-ethanolamine aqueous solution (0.5 M, 1.0 mmol) was added to the mixture and the Schlenk tube was heated at 60 °C for 5 h. After cooling to room temperature, the solution was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 98.6 mg of **11** as a colorless oil (92%): ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 6.87 (d, J=9.0 Hz, 2H), 7.00 (dd, J=2.7 Hz, 1H), 7.25 (m, 2H), 7.45 (d, J=9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.09, 81.22, 93.01, 113.93, 114.81, 123.57, 126.73, 126.96, 131.34, 132.80, 159.63; IR (KBr) 3102, 3073, 2963, 2842, 1603, 1524, 1501, 1460, 1289, 1246, 1186, 1175, 1109, 1021, 853, 700 cm^{-1}. HRMS (EIMS) m/z calcd for $C_{13}H_{10}OS$; 214.0452, found; 214.0427.

4.1.4. 5-(4-Ethoxycarbonylphenyl)-2-(4-methoxyphenylethynyl)thiophene (4). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (17.5 mg, 0.025 mmol), ethyl 4-iodobenzoate (**10**, 0.100 mL, 0.6 mmol), **11** (107.0 mg, 0.5 mmol), and 3 mL of DMSO under an argon atmosphere. AgF (64 mg, 0.5 mmol) was added to the mixture and the Schlenk tube was heated at 100 °C for 5 h. After cooling to room temperature, the resulting suspension was filtered and the residue was washed with dichloromethane repeatedly. The filtrate was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 123.1 mg of **4** as a yellow solid (68%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, J=8.4 Hz, 3H), 3.84 (s, 3H), 4.39 (q, J=8.4 Hz, 2H), 6.89 (d, J=8.7 Hz, 2H), 7.23 (d, J=3.6 Hz, 1H), 7.31 (d, J=3.6 Hz, 1H), 7.47 (d, J=8.7 Hz, 2H), 7.64 (d, J=8.4 Hz, 2H), 8.05 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 14.33, 55.31, 61.02, 81.27, 94.65, 114.10, 114.77, 124.39, 125.36, 129.46, 130.28, 132.63, 132.97, 137.87, 143.78, 159.92, 166.14; IR (KBr) 2988, 2940, 2842, 1713, 1603, 1514, 1291, 1275, 1248, 1186, 1109, 1028, 851, 837, 808, 768 cm^{-1}. HRMS (EIMS) *m/z* calcd for $C_{22}H_{18}O_3S$; 363.0929, found; 363.0903.

Synthesis of *2-bromo-5-(4-methoxyphenyl)thiophene (**13**)* was carried out in a similar manner to that we described previously. Spectroscopic characteristics and physical properties of **13**[2c] were identical with those of the authentic sample.

4.1.5. 2-(4-Ethoxycarbonylphenylethynyl)-5-(4-methoxyphenyl)thiophene (5). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (10.5 mg, 0.015 mmol), CuI (1.7 mg, 0.010 mmol), **13** (134.6 mg, 0.5 mmol), 4-(ethoxycarbonylphenyl)acetylene (**14**, 104.5 mg, 0.6 mmol), and 3 mL of THF under an argon atmosphere. Then, 2 mL of 2-ethanolamine aqueous solution (0.5 M, 1.0 mmol) was added to the mixture and the Schlenk tube was heated at 60 °C for 5 h. After cooling to room temperature, the solution was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 147.2 mg of **5** (82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J*=7.2 Hz, 3H), 3.84 (s, 3H), 4.39 (q, *J*=7.2 Hz, 2H), 6.93 (d, *J*=9.0 Hz, 2H), 7.11 (d, *J*=3.9 Hz, 1H), 7.26 (d, *J*=3.9 Hz, 1H), 7.53 (d, *J*=9.0 Hz, 2H), 7.55 (d, *J*=9.0 Hz, 2H), 8.03 (d, *J*=9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.26, 55.29, 61.07, 86.05, 92.90, 114.36, 120.59, 122.08, 126.37, 127.15, 127.55, 129.44, 131.01, 132.35, 133.70, 146.70, 159.68, 165.96; IR (KBr) 2965, 2936, 2840, 1723, 1605, 1514, 1497, 1306, 1291, 1252, 1181, 1105, 1028, 801, 764 cm^{-1}. Anal. Calcd for $C_{22}H_{18}O_3S$: C, 72.90; H, 5.01; S, 8.85. Found: C, 72.72; H, 4.85; S, 8.70.

4.1.6. 2-Bromo-5-(4-methoxyphenylethynyl)thiophene (16). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (10.5 mg, 0.015 mmol), CuI (1.7 mg, 0.010 mmol), 2-bromo-5-iodothiophene (**15**, 173.4 mg, 0.6 mmol), **8** (66.1 mg, 0.5 mmol), and 3 mL of THF under an argon atmosphere. Then, 2 mL of aqueous ammonia (0.5 M, 1.0 mmol) was added to the mixture and stirred at room temperature for 5 h. The solution was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 70.4 mg of **16**. The product **16**, whose yield was estimated to be 48% by ^{1}H NMR analysis, contained a trace amount of impurity, which was hardly eliminated by column chromatography on silica gel. Thus, the mixture was conducted to the following reaction without further purification.

4.1.7. 5-(4-Ethoxycarbonylphenylethynyl)-2-(4-methoxyphenylethynyl)thiophene (6). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (10.5 mg, 0.015 mmol), CuI (1.7 mg, 0.010 mmol), **16** (146.6 mg, 0.5 mmol), **12** (104.5 mg, 0.6 mmol), and 3 mL of THF under an argon atmosphere. Then, 2 mL of 2-ethanolamine aqueous solution (0.5 M, 1.0 mmol) was added to the mixture and the Schlenk tube was heated at 60 °C for 5 h. After cooling to room temperature, the solution was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 70.4 mg of **6** as a yellow solid (88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, *J*=7.2 Hz, 3H), 3.84 (s, 3H), 4.39 (q, *J*=7.2 Hz, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=3.9 Hz, 1H), 7.19 (d, *J*=3.9 Hz, 1H), 7.46 (d, *J*=8.7 Hz, 2H), 7.57 (d, *J*=8.4 Hz, 2H), 8.03 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.25, 55.22, 61.11, 80.85, 85.22, 93.13, 94.58, 114.03, 114.40, 123.28, 125.86, 127.10, 129.43, 131.15, 131.34, 132.25, 132.34, 132.44, 132.99, 159.93, 165.88; IR (KBr) 2979, 2842, 2197, 1715, 1605, 1528, 1512, 1308, 1287, 1281, 1173, 1107, 1028, 831, 768 cm^{-1}. HRMS (EIMS) *m/z* calcd for $C_{24}H_{18}O_3S$; 386.0977, found; 386.0988.

4.1.8. 2-(4-Methoxyphenyl)-5,5′-bithiophene (18).[2c] To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added **17** (0.135 g, 0.5 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), CuI (0.019 g, 0.10 mmol), and DMF (3 mL) under an argon atmosphere. To the mixture was added tributyl(2-thienyl)stannane (0.190 mL, 0.6 mmol) dropwise. CsF (0.151 g, 1.0 mmol) was then added in one portion. The resulting mixture was heated at 60 °C and stirring was continued for 8 h. After cooling to room temperature, the mixture was poured into 20 mL of water. The aqueous was extracted with chloroform twice (20 mL×2) and the combined organic layers were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel using hexanes–ethyl acetate (5:1) as an eluent to afford 0.111 g of 5-(4-methoxyphenyl)-2,2′-bithiophene (**18**) in 82% yield: ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 6.91 (d, *J*=9.0 Hz, 2H), 7.02 (dd, *J*=4.8, 3.6 Hz, 1H), 7.12 (AB, 2H), 7.17–7.22 (m, 2H), 7.53 (d, *J*=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 57.70, 114.35, 122.64, 123.37, 124.11, 124.56, 126.92, 127.80, 135.69, 137.58, 143.14, 147.96, 159.31; IR (KBr) 3070, 2960, 2910, 2845, 1605, 1497, 1289, 1246, 1183, 1032, 797.

4.1.9. 2-(4-Ethoxycarbonylphenyl)-2′-(4-methoxyphenyl)-5,5′-bithiophene (7). To a 25-mL of Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_3$ (17.5 mg, 0.025 mmol), **10** (0.100 mL, 0.6 mmol), **18** (136.2 mg, 0.5 mmol), potassium fluoride (72.6 mg, 1.25 mmol), and 5 mL of DMSO under an argon atmosphere. The mixture was heated in an oil bath at 100 °C for 8 h, during which period $AgNO_3$ (168.9 mg, 1.0 mmol) was added in 4 portions with a 2 h interval. After cooling to room temperature, the resulting suspension was filtered and the residue was washed with dichloromethane repeatedly. The filtrate was washed with water and the aqueous layer was extracted with chloroform. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 40.9 mg of **7** as a yellow solid (33%): ^{1}H NMR ($CDCl_3$) δ 1.41 (t, *J*=7.2 Hz, 3H), 3.85 (s, 3H), 4.39 (q, *J*=7.2 Hz, 2H), 6.93 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=3.9 Hz, 1H), 7.18

(d, J=3.3 Hz, 2H), 7.35 (d, J=3.6 Hz, 1H), 7.54 (d, J=8.7 Hz, 2H), 7.65 (d, J=8.7 Hz, 2H), 8.05 (d, J=8.7 Hz, 2H); IR (KBr) 2910, 2890, 1709, 1605, 1283, 1184, 1111, 1030, 830, 795, 770. HRMS (EIMS) *m/z* calcd for $C_{24}H_{20}O_3S_2$; 420.0854, found; 420.0833.

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Tandem versus single C–C bond forming reaction under palladium–copper catalysis: regioselective synthesis of α-pyrones fused with thiophene☆

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Abstract—We herein report a highly convenient protocol for rapid construction of α-pyrone fused with thiophene. This includes one-pot and regioselective synthesis of 4,5-disubstituted and 5-substituted thieno[2,3-*c*]pyran-7-ones, 6,7-disubstituted and 6-substituted thieno[3,2-*c*]pyran-4-ones. The synthesis of thieno[2,3-*c*]pyran-7-ones involves palladium mediated cross coupling of 3-iodothiophene-2-carboxylic acid with terminal alkynes in a simple synthetic operation. The coupling–cyclization reaction was initially studied in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in a variety of solvents. 5-Substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones were isolated in good yields when the reaction was performed in DMF. Similarly, 6-substituted 7-alkynylthieno[3,2-*c*]pyran-4-ones were synthesized via palladium-catalyzed cross coupling of 2-bromothiophene-3-carboxylic acid with terminal alkynes. A tandem C–C bond forming reaction in the presence of palladium catalyst rationalizes the formation of coupled product in this apparently three-component reaction. The cyclization step of this coupling–cyclization–coupling process occurs in a regioselective fashion to furnish products containing six-membered ring only. This sequential C–C bond forming reaction however, can be restricted to the formation of single C–C bond by using 10% Pd/C–Et_3N–CuI–PPh_3 as catalyst system in the cross coupling reaction. 5-Substituted thieno[2,3-*c*]pyran-7-ones were obtained in good yields when the coupling reaction was performed under this condition. Some of the compounds synthesized were tested in vitro for their anticancer activities.

1. Introduction

α-Pyrones[1a] and their benzo derivatives, e.g., isocoumarins[2a] are of considerable synthetic and pharmacological interest because of their wide range of activities[2b–d] such as antifungal, antimicrobial, phytotoxic and other effects. 3-Substituted isocoumarins in particular have shown promising pharmacological activities.[2e] The angiogenesis inhibitor NM-3,[2f] which belongs to this class is presently undergoing Phase-I clinical trials. More recently, promising cytotoxic activities of substituted pyrones especially 4-alkynyl substituted 2-pyrones (A, Fig. 1) have been reported.[2g] In continuation of our research under the new drug discovery program, we were in need of a combinatorial library based on the scaffold of α-pyrone fused with five-membered heterocycles (B, Fig. 1). The library model, as shown in Figure 1, has three centers for the introduction of diversity into α-pyrone molecule. While much effort has been devoted toward the introduction/modification of C-3 and C-4 substituents on the benzo derivative, i.e., isocoumarin ring,[2h–j] replacing the benzene ring by a suitable heterocyclic moiety is not common in the literature. We envisioned that α-pyrone fused with a five- or six-membered heterocycle might lead to a novel class of compounds useful for the Structure–Activity Relationship (SAR) studies. The thiophene moiety is common in many bioactive agents and drugs[3a] and is considered as a bioisostere of the benzene ring.[3a] (The distance between two neighboring carbon atoms in benzene is roughly equivalent to the diameter of the sulfur atom in thiophene and the latter often displays pharmacological properties similar to those of benzene.[3b]) On the other hand pyrazole fused with pyran and benzopyran rings has shown affinity and selectivity toward A_1 adenosine receptor.[3c,d] Thus, one can anticipate that

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Keywords: α-Pyrone; 4,5-Disubstituted thieno[2,3-*c*]pyran-7-one; 6,7-Disubstituted thieno[3,2-*c*]pyran-4-ones; Palladium catalyst; Terminal alkynes; 3-Iodothiophene-2-carboxylic acid; 2-Bromothiophene-3-carboxylic acid.

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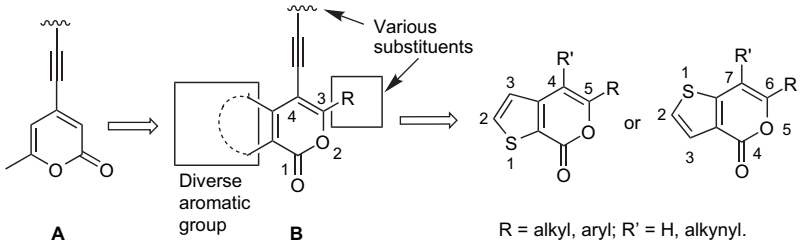


Figure 1. Design of α-pyrones fused with 5-membered heterocycles derived from diversity based isocoumarin scaffold.

replacing the benzene ring of isocoumarin by a five-membered ring such as thiophene would afford compounds (i.e., thienopyranones, Fig. 1) of potential pharmacological interest.[3e,f] Additionally, thiophene derivatives are excellent synthetic intermediates because of the unique electronic properties of sulfur as well as the steric constraints of a five-membered ring.[3g] However, as a class of compounds the thienopyranones are rather unusual. Only a few number of thieno[2,3-*c*]pyran-4-ones were synthesized and evaluated for their antileishmanial and antifungal activities.[3h]

Based on above considerations and our continuing interest in the synthesis of oxygen containing heterocycles we decided to synthesize pyranones fused with thiophene. A thorough literature search revealed that methodologies devised for the elaboration of this framework are generally limited and not investigated extensively.[4a–e] Moreover, synthesis of thieno[2,3-*c*]pyran-7-ones/thieno[3,2-*c*]pyran-4-ones (and their 4-/7-alkynyl analogues) has not been reported thus far. Therefore, to synthesize a library of isocoumarins[5a] for biological screening we became interested in the synthesis of pyranones fused with five-membered heterocycles.[5b]

The construction of functionalized α-pyrone ring incorporated into the isocoumarin system is the most commonly used strategy for a rapid assemblage of isocoumarin derivatives. On the other hand palladium-catalyzed reactions have become most attractive and powerful tool for C–C bond forming reaction due to their generality and superiority over many tedious classical methods. Thus, among the many methods reported for the synthesis of isocoumarins one widely used process is Sonogashira-type coupling followed by electrophilic or transition metal mediated cyclization of the resulting alkynes possessing a carboxylate or an equivalent group in proximity to the triple bond.[6] Attractive features of this process include its versatility and ability to tolerate a wide range of important organic functional groups. Thus, isocoumarins have been prepared in a efficient manner by reacting *o*-iodobenzoic acid with terminal alkynes in the presence of $Pd(PPh_3)_4$, Et_3N, and a stoichiometric amount of $ZnCl_2$.[7a] The use of $ZnCl_2$ in place of CuI[7b,c] was found to be responsible for the predominant formation of isocoumarins over phthalides. However, very recently we have shown that isocoumarins can be obtained as major products even in the presence of CuI when the coupling reaction was performed in the presence of 10% Pd/C–Et_3N–CuI–PPh_3 as catalyst system in ethanol (Fig. 2).[5a] More recently, we have noted that 3-iodothiophene-2-carboxylic acid (**1a**) reacts smoothly with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$–Et_3N–CuI as a catalyst system affording 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones (**2a–j**) in good yields (Scheme 1). This palladium-catalyzed

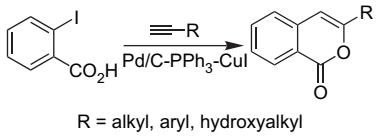
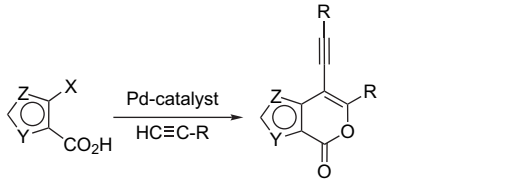


Figure 2. Pd/C-mediated synthesis of 3-substituted isocoumarins.

transformation is particularly interesting, because apart from providing an easy access to thieno[2,3-*c*]pyran-7-one ring it affords novel conjugated enynes that could be utilized further as precursors to construct even more complex molecules. Only four examples of analogue 3-substituted 4-alkynyl isocoumarins have been reported during Pd–Zn mediated synthesis of 3-substituted isocoumarins where these derivatives were isolated as minor products in 3–5% yield.[7a] Alternatively, 4-alkynyl isocoumarins/coumarins have been prepared via multistep synthesis that usually involves ring construction followed by Sonogashira coupling.[8] Being arguably the most versatile transition metal for catalysis palladium features prominently in a number of tandem transformations[9] and we have recently shown that terminal alkynes participate in tandem coupling reactions depending on the reaction condition employed.[9g] Herein, we report further study on our previously communicated one-step synthesis of 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones[5b] along with the synthesis of isomeric 6-substituted-7-alkynylthieno[3,2-*c*]pyran-4-ones under palladium catalysis. Additionally, we report detailed study on Pd/C-mediated synthesis of 6-substituted thieno[3,2-*c*]pyran-4-ones and 5-substituted thieno[2,3-*c*]pyran-7-ones where no significant formation of corresponding alkynyl analogues was observed.



Scheme 1. Synthesis of thienopyranones having disubstitutions on the pyranone ring.

2. Results and discussion

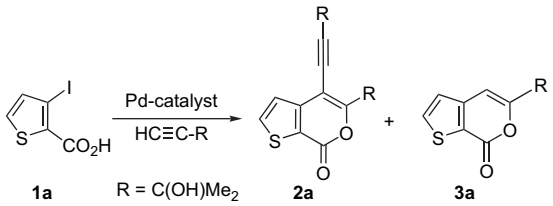
2.1. Optimization of reaction conditions and product characterization

To evaluate the potential of the use of palladium mediated coupling cyclization methodology[10] for the synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones (**3**), we first selected

1a as a model substrate with 2-methyl-3-butyn-2-ol as the terminal alkyne. We observed that Pd-catalyzed coupling of **1a**[11] with 2-methyl-3-butyn-2-ol in ethanol afforded 5-alkylthieno[2,3-*c*]pyran-7-ones (**3a**, R=–C(CH$_3$)$_2$OH, Table 1) in 24% yield and the unexpected 4-(3-hydroxy-3-methylbut-1-ynyl)-5-(1-hydroxy-1-methylethyl)thieno[2,3-*c*]pyran-7-one (**2a**) in 50% purified yield, with a 2/1 ratio of **2a** and **3a** (Entry 1, Table 1). Compound **2a** was characterized by ^{1}H and ^{13}C NMR and other spectroscopic methods and identified as an alkyne possessing the thieno[2,3-*c*]-pyran-7-one ring at one end. This was supported by the molecular structure of **2b** (R=–CH$_2$CH$_2$OH), which was confirmed by X-ray analysis.[5b] The ORTEP diagram of **2b** (Fig. 3) shows a planar thieno[2,3-*c*]pyran-7-one core with a disordered hydroxyl group due to the alkynyl side chain along with the other hydroxy group oriented in the opposite direction. The molecular structure of **3a** was also confirmed by X-ray analysis (Fig. 3).[12] The noteworthy features of this structure include (a) two independent molecules of **3a** in the unit cell are differentiated by the presence of one molecule of water, (b) the water molecule present in the lattice bridges the C=O of one molecule and O–H of other one, by inter molecular hydrogen bonding. Nevertheless, the unexpected formation of **2a** prompted us to investigate this tandem C–C bond forming reaction in a more systematic manner.

The initial reaction was carried out in ethanol in the presence of PdCl$_2$(PPh$_3$)$_2$ (0.048 equiv), CuI (0.06 equiv), Et$_3$N (5.0 equiv), and 2.0 equiv of the terminal alkyne at 75 °C. A series of optimization experiments on the reaction of **1a** with 2-methyl-3-butyn-2-ol were carried out by keeping the molar ratio of Pd/Cu at 1/1.3 and changing a number of parameters, e.g., effect of catalysts, solvent, base, and temperature (Table 1). Change of solvent from ethanol to a non-protic solvent such as 1,4-dioxane or dimethylacetamide (DMA) suppressed the formation of **3a** dramatically (Entries 2 and 3, Table 1) and **2a** was isolated in 30 and 55% yield, respectively. While the reason for these observations was not clear the non-protic solvents perhaps allowed the participation of second equivalent of alkyne used in the crucial cyclization process. The yield of **2a** was increased significantly when DMF was used (Entry 4, Table 1). To assess the role of solvent we carried out this reaction using a lesser amount of terminal alkyne (1.0 equiv) in DMF where **2a** was isolated in 28% yield and the reaction did not reach completion. This observation clearly suggests that formation of **2a** was not dependent on the concentration of alkyne used but was favored by the non-polar solvent employed. Both Pd and Cu catalysts played crucial roles as no reaction was observed when either was omitted. The use of other Pd catalysts, e.g., Pd(PPh$_3$)$_4$, Pd(OAc)$_2$ or PdCl$_2$(dppf)$_2$ was investigated (Entries 5–7, Table 1) where **2a** was isolated as major product albeit in low yield (35–40%). Significant amount of **3a** was isolated when PdCl$_2$(dppf)$_2$ was used as catalyst (Entry 7, Table 1). Thus, PdCl$_2$(PPh$_3$)$_2$ was identified as the best catalyst for the synthesis of **2a** and was used for further studies. The use of commercially available 3-bromothiophene-2-carboxylic acid however, did not afford **2a** in good yield even after 48 h when reacted with 2-methyl-3-butyn-2-ol in the presence of PdCl$_2$(PPh$_3$)$_2$ and CuI (Entry 8, Table 1). Remarkably, the use of 0.035 equiv of 10% Pd/C

Table 1. Effect of reaction conditions on the palladium-catalyzed coupling reaction of 3-iodothiophene-2-carboxylic acid with 2-methyl-3-butyn-2-ol[a]



Entry	Pd catalyst	Solvent; time	Yield (%)[b]	
			2a	**3a**
1	PdCl$_2$(PPh$_3$)$_2$	EtOH; 12 h	50	24
2	PdCl$_2$(PPh$_3$)$_2$	1,4-Dioxane; 12 h	30	0
3	PdCl$_2$(PPh$_3$)$_2$	DMA; 12 h	55	5
4	PdCl$_2$(PPh$_3$)$_2$	DMF; 8 h	80	0
5	Pd(PPh$_3$)$_4$	DMF; 12 h	40	0
6[c]	Pd(OAc)$_2$–PPh$_3$	DMF; 12 h	35	0
7	PdCl$_2$(dppf)$_2$	DMF; 12 h	35	28
8[d]	PdCl$_2$(PPh$_3$)$_2$	DMF; 48 h	12	0
9[c]	10% Pd/C–PPh$_3$	EtOH; 12 h	8	68
10[c,e]	10% Pd/C–PPh$_3$	1,4-Dioxane; 12 h	6	80

[a] Reaction conditions: **Ia** (1.0 equiv), terminal alkyne (2.0 equiv), Pd(II)-catalyst (0.048 equiv) or Pd/C (0.035 equiv), CuI (0.06 equiv), Et$_3$N (5 equiv) in a solvent at 70–80 °C under N$_2$.
[b] Isolated yield of **2a** and **3a**.
[c] PPh$_3$ used: 0.3 equiv.
[d] 3-Bromothiophene-2-carboxylic acid was used in place of **1a**.
[e] Terminal alkyne used: 1.5 equiv.

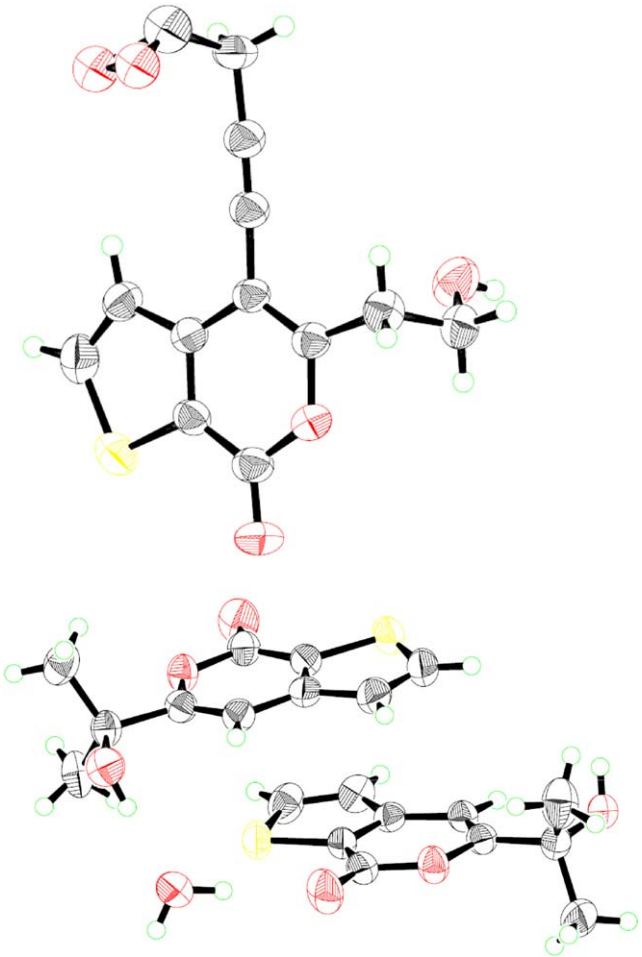


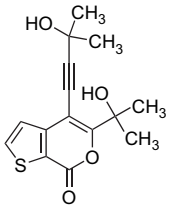
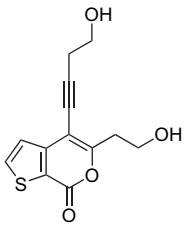
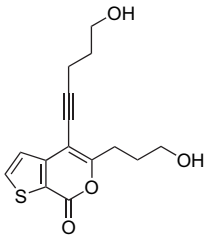
Figure 3. X-ray crystal structure of **2b** and **3a** (ORTEP diagram).

in place of $PdCl_2(PPh_3)_2$ in ethanol during coupling reaction of **1a** with 2-methyl-3-butyn-2-ol afforded **3a** as major product in good yield with trace amount of **2a** (Entry 9, Table 1). Indeed, a better yield of **3a** was achieved in 1,4-dioxane using lesser quantity, i.e., 1.5 equiv of terminal alkyne (Entry 10, Table 1). Less than 0.035 equiv of 10% Pd/C can be used to afford **3a**, but the yield of product was found to be often irreproducible. The use of 5% Pd/C also afforded lower yield of **3a**. All the reactions were usually carried out at 70–80 °C under nitrogen. The use of higher or lower reaction temperature led to the inferior results. Originally, we speculated that the formation of **2a** might first involve the formation of **3a**, which subsequently reacted with another mole of the terminal alkyne under Pd–Cu catalysis. However, formation of **2a** was not observed when **3a** was subjected to the same Pd-catalyzed reaction conditions.

2.2. Scope of the reaction

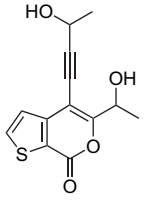
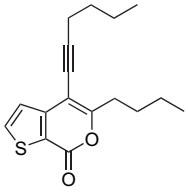
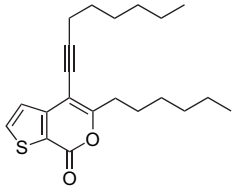
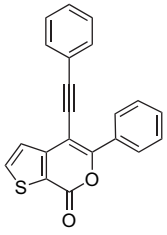
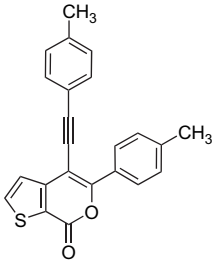
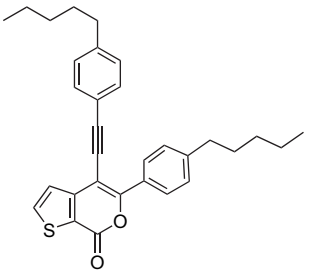
2.2.1. Synthesis of 5-substituted 4-alkynyl thieno[2,3-*c*]pyran-7-ones and 6-substituted 7-alkynyl thieno[3,2-*c*]pyran-4-ones. To examine the effect on the yield of the substituents on the terminal alkynes we next tested the optimized reaction conditions from Entry 4 of Table 1 (Method A: $PdCl_2(PPh_3)_2$, CuI, Et_3N in DMF) with other terminal alkynes (Entries 1–10, Table 2). Like *o*-iodobenzoic acid, 3-iodothiophene-2-carboxylic acid showed good reactivity toward the present coupling reaction and various functional groups including aryl, alkyl, hydroxyl, ether etc. present in terminal alkynes were well tolerated. This allowed the preparation of a variety of 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones (**2**) under mild condition. However, yields of compound **2** varied depending on the nature of alkynes used. While alkynes bearing a tertiary and secondary hydroxyl group on the carbon next to the triple bond provided best yields of **2** (Entries 1 and 4, Table 2), the presence of long alkyl chains on the triple bond did not affect the yields drastically (Entries 5 and 6, Table 2). A hydroxyl group at the end of the long alkyl chain of the alkyne however, lowered the yields of **2** slightly (Entries 2 and 3, Table 2). Among the aryl acetylenes used, phenyl acetylene afforded only a modest 57% yield of **2** under the reaction condition studied. A mild electron-donating group at the *para* position of the benzene ring however, improved the yield of **2** compared to phenyl acetylene (Entries 8 and 9 vs Entry 7, Table 2). The use of alkyne where $–CH_2O–$ moiety linked the triple bond with the phenyl group provided better yield of **2** than phenyl acetylene (Entry 10 vs Entry 7, Table 2). All these facts clearly indicated that yields of **2** were partially dependent on the nature of the substituent present on the terminal alkynes. Generally, **2** was isolated as the sole product in all cases except when 1-hexyne and 1-octyne were used. Compound **3** was also isolated as minor product in these cases (Entries 5 and 6, Table 2). In contrary to the 3-bromothiophene-2-carboxylic acid, isomeric and commercially available 2-bromothiophene-3-carboxylic acid **1b** provided

Table 2. Pd-mediated synthesis[a] of 5-substituted 4-alkynylthieno[2,3-*c*]pyran-7-ones and 6-substituted 7-alkynylthieno[3,2-*c*]pyran-4-ones

Entry	Alkyne (R)	Time (h)	Products (**2**)	Yield (%)	
				2	**3**
1	**a**; $–C(CH_3)_2OH$	8	 **2a**	80	0
2	**b**; $–(CH_2)_2OH$	12	 **2b**	53	0
3	**c**; $–(CH_2)_3OH$	12	 **2c**	61	0

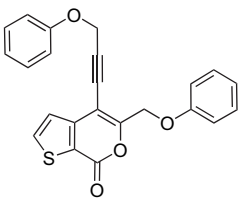
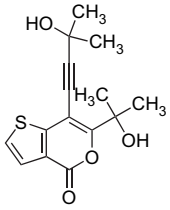
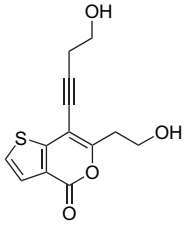
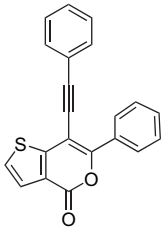
(*continued*)

Table 2. (*continued*)

Entry	Alkyne (R)	Time (h)	Products (**2**)	Yield (%)	
				2	**3**
4	**d**; –CH(OH)CH_3	10	 **2d**	82	0
5	**e**; –$(CH_2)_3CH_3$	12	 **2e**	65	15
6	**f**; –$(CH_2)_5CH_3$	12	 **2f**	62	35
7	**g**; –C_6H_5	12	 **2g**	57	0
8	**h**; –$C_6H_4CH_3$-*p*	12	 **2h**	62	0
9	**i**; –$C_6H_4C_5H_{11}$-*p*	8	 **2i**	73	0

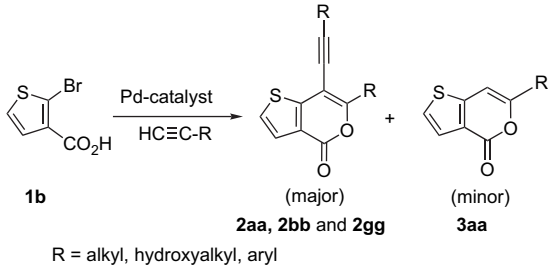
(*continued*)

Table 2. (*continued*)

Entry	Alkyne (R)	Time (h)	Products (**2**)	Yield (%)	
				2	**3**
10	**j**; $-CH_2OC_6H_5$	8	 **2j**	75	0
11[b]	**a**	10	 **2aa**	55	40
12[b]	**b**	10	 **2bb**	88	0
13[b]	**g**	10	 **2gg**	60[c]	0

[a] All reactions were carried out using **1** (1.0 equiv), terminal alkyne (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.048 equiv), CuI (0.06 equiv) and Et_3N (5 equiv) in DMF at 70–80 °C under nitrogen.
[b] 2-Bromothiophene-3-carboxylic acid was used in place of **1**.
[c] 1,4-Diphenyl-1,3-butadiyne was isolated in 35% yield in addition to **2gg**.

better yield of corresponding 6,7-disubstituted thieno[3,2-*c*]pyran-4-ones (Scheme 2), e.g., **2aa**, **2bb**, and **2gg** (Entry 8 of Table 1 vs Entries 11–13 of Table 2) under the condition studied. Higher reactivity shown by 2-bromo derivative over 3-bromo toward the present palladium-catalyzed reaction was perhaps aided by the electron withdrawing inductive effect of sulfur at the nearby position. Nevertheless, the success of this tandem reaction is presumably due to the in situ generation of the Pd(II)-complex after normal Sonogashira coupling, which facilitates the insertion of another alkyne moiety on the intermediate generated upon cyclization (see later for mechanistic discussion).

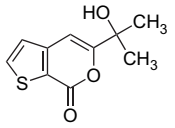
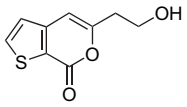
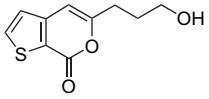
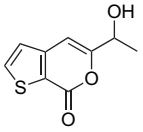
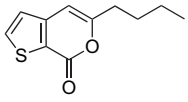
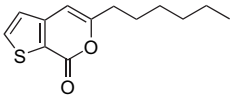
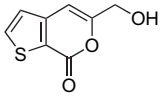
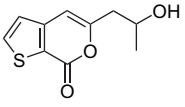
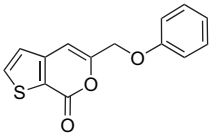
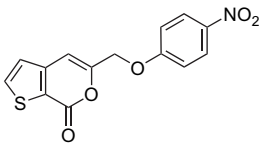


Scheme 2. Synthesis of 6-substituted 7-alkynylthieno[3,2-*c*]pyran-4-ones.

2.2.2. Synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones. We have found that 5-substituted thieno[2,3-*c*]pyran-7-one (**3**) can also be prepared as a major product by coupling **1a** with terminal alkynes using 10% Pd/C–Et_3N–CuI–PPh_3 (Method B) as a catalyst system (Entries 9 and 10, Table 1). Pd/C catalyzed reactions are particularly attractive because the catalyst can be removed easily by filtration at the end of the reaction allowing product isolation without transition metal impurities, the removal of which could be tedious and cumbersome. Thus, to assess the generality of this approach, the scope of the Pd/C-mediated coupling of **1a**

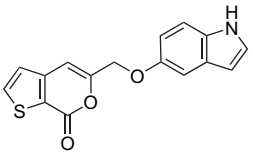
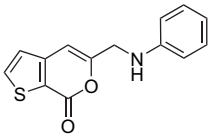
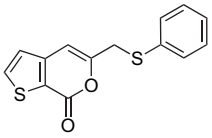
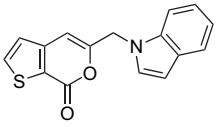
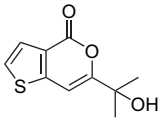
has been studied. Treatment of **1a** with a variety of terminal alkynes under the condition described in Table 1 [1.0 equiv of 3-iodothiophene-2-carboxylic acid, 1.5 equiv of terminal alkyne, 10% Pd/C (0.035 equiv), PPh_3 (0.3 equiv), CuI (0.06 equiv), and Et_3N (5 equiv) in 1,4-dioxane at 70–80 °C under nitrogen] afforded moderate to good yields of 5-substituted thieno[2,3-*c*]pyran-7-ones (Table 3). In addition to alkynes used earlier a number of other alkynes

Table 3. Pd/C-mediated synthesis of 5-substituted thieno[2,3-*c*]pyran-7-ones[a]

Entry	Alkyne (R)	Time (h)	Products (**3**)	Yield (%)	
				2	**3**
1	**a**; $-C(CH_3)_2OH$	12	 **3a**	6	80
2	**b**; $-(CH_2)_2OH$	12	 **3b**	30	60
3	**c**; $-(CH_2)_3OH$	12	 **3c**	10	60
4	**d**; $-CH(OH)CH_3$	12	 **3d**	0	55
5	**e**; $-(CH_2)_3CH_3$	12	 **3e**	17	50
6	**f**; $-(CH_2)_5CH_3$	12	 **3f**	0	55
7	**k**; $-CH_2OH$	12	 **3g**	0	35
8	**l**; $-CH_2CH(OH)CH_3$	12	 **3h**	0	55
9	**j**; $-CH_2OC_6H_5$	10	 **3i**	0	72
10	**m**; $-CH_2OC_6H_4NO_2$-*p*	10	 **3j**	0	60

(*continued*)

Table 3. (*continued*)

Entry	Alkyne (R)	Time (h)	Products (**3**)	Yield (%)	
				2	**3**
11	**n**; 5-Indolyloxy	10	 **3k**	0	70
12	**o**; $-CH_2NC_6H_5$	10	 **3l**	0	65
13	**p**; $-CH_2SC_6H_5$	10	 **3m**	0	65
14	**q**; 1-Indolyl	10	 **3n**	0	68
15	**a**; $-C(CH_3)_2OH$	12	 **3aa**	0	72

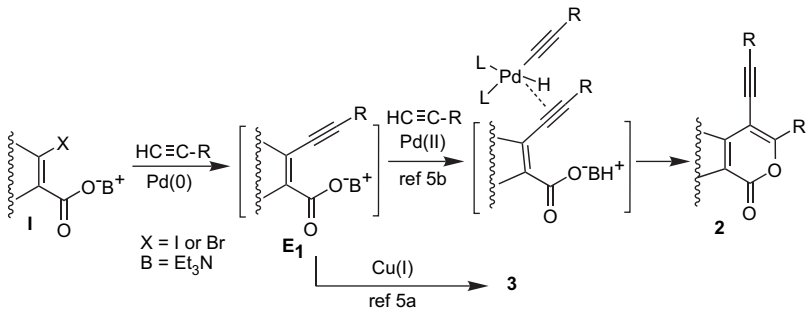
[a] All reactions were carried out by using **I** (1.0 equiv), terminal alkyne (1.5 equiv), 10% Pd/C (0.035 equiv), PPh_3 (0.3 equiv), CuI (0.06 equiv), Et_3N (5 equiv) in 1,4-dioxane at 70–80 °C under nitrogen.

containing ether, amine, thioether, and indole functionality were tested and the reaction proceeded well affording good yields of product **3** (Entries 10–14, Table 3). The use of 2-bromothiophene-3-carboxylic acid afforded 6-substituted thieno[3,2-*c*]pyran-4-one in good yield (Entry 15, Table 3). Except in four cases (Entries 1–3 and 5, Table 3), no significant amount of **2** was isolated from the reaction mixture indicating the high product selectivity of this coupling–cyclization process under Pd/C–Cu catalysis. Presumably, participation of the copper salt in the cyclization step was responsible for the predominant formation of **3** over **2** (see later for mechanistic discussion). Notably, the use of Pd/C as a source of 'ligandless palladium' in arylation of thiophene was found to be unsuccessful, which was thought to be due to the poisoning of the heterogenous catalyst.[13]

We have shown that 5-substituted thieno[2,3-*c*]pyran-7-ones (**3**) and their 4-alkynyl analogues (**2**) can be prepared via coupling reaction of 3-iodothiophene-2-carboxylic acid with terminal alkynes depending on the reaction condition employed (Method A or B). The nature of the palladium catalysts played an important role in these coupling–cyclization reactions. The use of Pd(II) or Pd(0) complexes generally led to the formation of 4-alkynyl analogues (**2**) via tandem coupling–cyclization–coupling reaction whereas the use of Pd/C facilitated only coupling–cyclization to afford **3** in good yields. Nevertheless, the reaction showed very high regioselectivity in both cases as no isomeric thieno[2,3-*c*]-furan-6-ones resulting from '5-*exo-dig*' cyclization were detected under the reaction conditions studied. This is in sharp contrast to the earlier observations[7] where the coupling–cyclization followed 5-*exo-dig* ring closure predominantly under Pd–Cu catalysis in DMF.

2.3. Proposed reaction mechanism

A reasonable pathway for $PdCl_2(PPh_3)_2$ mediated tandem reaction leading to compound **2** and Pd/C-mediated coupling–cyclization to compound **3** is shown in Scheme 3. The possibility of generating **2** via **3** can be ruled out, because it requires palladium mediated C–H activation at C-4 of thieno[2,3-*c*]pyran-7-one ring (**3**) followed by interaction of the resulting Pd(II) intermediate with the copper acetylide. This is not only an energetically unfavorable process, but also would afford copper hydride as a side product, which is unlikely. Moreover, formation of **2a** was not observed when **3a** was reacted with another mole of terminal alkyne under Pd–Cu catalysis. Thus, the reaction seems to



Scheme 3. A plausible mechanism for Pd-catalyzed formation of **2** and **3**.

proceed via in situ generation of intermediate $\mathbf{E_1}$ according to a typical Sonogashira pathway.[7b,14] Once formed this acid then undergoes intramolecular cyclization aided by the Pd(II)-complex[6a] or copper salt[5a] to give **2** or **3**. However, formation of **2** clearly suggests that the corresponding pathway is a Pd(II)-mediated process. Presumably, this proceeds via insertion of the Pd(0) complex into the acetylenic C–H bond of the terminal alkyne leading to a Pd(II) intermediate[15] ($\mathbf{E_2}$) that catalyzes the '6-*endo-dig*' ring closure. Although we have no actual proof for the generation of $\mathbf{E_2}$, insertion of Pd(0) complex into the acetylenic C–H bond however, has been suggested by Trost and co-workers earlier.[16] Additionally, a closely related intramolecular oxypalladation of the complex formed by the coordination of organo Pd(II)-complex [generated by oxidative addition of the aryl halide to Pd(0) in situ] with the C–C triple bond of the 2-(1-alkynyl)benzoate anion has also been proposed by Rossi and co-workers.[2i] Thus, reductive elimination of Pd(0) followed the '6-*endo-dig*' ring closure to afford thieno[2,3-*c*]pyran-7-one derivative. A '5-*exo-dig*' ring closure, although allowed by Baldwin's rule, was not observed in the present case because of the favorable geometry associated with the 5-6 ring formation rather than the 5-5 ring. This also accounts for observation of no solvent effect on using 1,4-dioxane and ethanol in the present synthesis of **3**, which is in contrast with the earlier synthesis of isocoumarin.[5a] It is noteworthy that due to the electron-donating resonance effect of thiophene moiety the carbon–carbon triple bond of $\mathbf{E_1}$ is more nucleophilic than that of analogue 2-(1-alkynyl)benzoic acid and therefore interacts better with the Pd(II)-complex ($\mathbf{E_2}$) generated in situ under the condition studied. This perhaps accounts for the isolation of 4-alkynyl isocoumarins as side products in poor yield during the preparation of isocoumarins under palladium–zinc catalysis. Although the reason for preferential interaction of $\mathbf{E_1}$ with Pd(II)-complex ($\mathbf{E_2}$) over CuI is not clear at this stage a possible explanation for the change of product selectivity on going from Method A to Method B is a change in the reaction mechanism in the cyclization step (Scheme 3). While generation of **3** is arguably feasible via Pd(II)-mediated cyclization of corresponding 1-alkynyl substituted thiophene carboxylic acid, isolation of **3** as only product under Pd/C–Cu catalysis in most of the cases suggests that perhaps copper salt plays a major role in Pd/C-mediated coupling–cyclization process.[5a] This was further supported by the isolation of **3e** as a sole product when 3-hex-1-ynyl thiophene-2-carboxylic acid[17] was treated with CuI in DMF at 70–80 °C for 2 h.

2.4. In vitro anticancer activity

Based on the promising cytotoxic activities reported for substituted pyrones especially 4-alkynyl substituted 2-pyrones earlier[2g] we evaluated some of the thienopyranones synthesized for in vitro anticancer activity. Selected compounds were tested on a panel of cancer cell lines, e.g., HT-29 (colon), NCI-H460 (lung), and LoVo (colon) using the NCI standard protocol for screening anticancer molecules.[18] After treating the cells with compounds at 100 μM concentration initially the percentage growth of cells was measured, which is shown in Table 4. Based on the result obtained for compound **2g** against LoVo cell line we tested this compound further at lower concentrations such as 10, 1.0, 0.1, and 0.01 μM against the same cancer cell line and the percentage growth was noted as 77, 86, 97, and 102, respectively. The GI_{50} value (the concentration that causes 50% inhibition of cancer cell growth against a cell line is expressed as GI_{50}) for compound **2g** was found to be 83.4 μM compared to 23 μM of Glevec™, an well known anticancer drug developed by Novartis. Additionally, the LC50 (Lethal Concentration 50 is the concentration of a compound that kills 50% of cells treated) of **2g** was noted as 100 μM. The present study thus indicates that alkynyl substituted thienopyranone moiety could be a new and potential scaffold that needs further exploration for design and SAR studies for the development of novel anticancer agents.

Table 4. In vitro anticancer activities of thienopyranone derivatives

Compound no	Cell line	Percentage growth @ 100 μM
2g	LoVo	48
	H460	71
	HT-29	71
2h	LoVo	61
	H460	87
	HT-29	61
3a	LoVo	68
	H460	84
	HT-29	77
3i	LoVo	72
	H460	73
	HT-29	72

3. Conclusions

In summary, a catalytic approach to thienopyranones of potential pharmacological interest has been developed through the coupling of bromo or iodo substituted thiophenecarboxylic acid with terminal alkynes under palladium–copper catalysis. A detailed study related to the effect of reaction conditions on product distribution was carried out. Conditions were developed that allow for the selective synthesis of either 4,5-disubstituted or only 5-substituted thieno-[2,3-*c*]pyran-7-ones. The best process for the preparation of 4,5-disubstituted derivatives involved the use of $PdCl_2(PPh_3)_2$ as a catalyst source and was found to be quite general and highly regioselective, placing the alkynyl moiety at the C-4 position of the thieno[2,3-*c*]pyran-7-one ring. This process was extended to the regioselective synthesis of 7-alkynylthieno[3,2-*c*]pyran-4-ones successfully. 5-Substituted thieno[2,3-*c*]pyran-7-ones on the other hand was obtained easily by using Pd/C-mediated coupling–cyclization of 3-iodothiophene-2-carboxylic acid with terminal alkynes. All these processes worked well with a broad range of terminal alkynes to afford the corresponding products in good isolated yields. The scope and limitations of both the process along with the mechanism of the reaction have been discussed. The sequencing of two or more reactions in a one-pot process, as illustrated in this report, not only makes better use of precious reagents as well as solvents but also has the benefit of eliminating cumbersome separation and purification after each step. Since the use of single catalyst source for tandem reaction is a powerful strategy for generating complex structures, we believe that the novel palladium-catalyzed transformation described here would find wide usage for the synthesis of similar class of compounds.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on 200 and 400, and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as br (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using melting point apparatus and are uncorrected. Thermal analysis data [Differential Scanning Calorimetry (DSC)] were generated with the help of DSC-50 detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, retention times. All terminal alkynes, 3-bromothiophene-2-carboxylic acid and 2-bromothiophene-3-carboxylic acid used are commercially available.

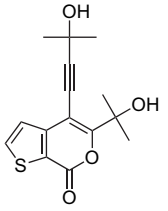
4.2. Preparation of 3-iodo thiophene-2-carboxylic acid[19] (1a)

To a solution of thiophene-2-carboxylic acid (5.0 g, 39 mmol) in dry THF (50 mL) *n*-butyl lithium (6.25 g, 41.6 mL, 97 mmol) was added slowly and dropwise at −78 °C under nitrogen atmosphere over a period of 1 h. The mixture was stirred for 1 h at the same temperature (−78 °C) and a solution of iodine (11.8 g, 46 mmol) in THF (25 mL) was added slowly by maintaining the temperature at −78 °C. The mixture was stirred initially for 8 h at −78 °C and then at 25–35 °C for 30 h. After completion of the reaction the mixture was diluted with 5% aqueous HCl (10 mL) followed by water (100 mL) and extracted with ethyl acetate (3×100 mL). The organic layers were collected, combined, washed with 10% aq sodium thiosulfate (3×50 mL) followed by water (3×50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude compound was triturated with light petroleum ether (distillation range 60–80 °C) to get the title compound as light brown solid (6 g, 60% yield); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26 (d, J=5.6 Hz, 1H), 7.52 (d, J=5.1 Hz, 1H); IR (cm^{-1}, $CHCl_3$) 3092, 2852, 1670; *m*/*z* (ES Mass) 255 (M^+, 100%).

4.3. Preparation of 5-substituted 4-alkynyl thieno[2,3-*c*]pyran-7-ones (2)

4.3.1. General procedure. A mixture of 3-iodo thiophene-2-carboxylic acid (0.787 mmol), $PdCl_2(PPh_3)_2$ (0.038 mmol), CuI (0.047 mmol), and Et_3N (4 mmol) in DMF (10 mL) was stirred for 1 h under nitrogen. The acetylenic compound (1.57 mmol) was added and the mixture was stirred at room temperature for 1 h and then at 70–80 °C for 8–12 h. After completion of the reaction, DMF was removed under reduced pressure and the residue was extracted with ethyl acetate (3×50 mL). The organic layers were collected, combined, washed with saturated aq $NaHCO_3$ (2×25 mL) followed by water (2×25 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude compound was purified by column chromatography on silica gel using light petroleum ether (60–80 °C)–ethyl acetate.

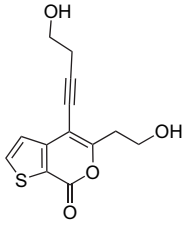
4.3.2. 4-(3-Hydroxy-3-methyl-but-1-ynyl)-5-(1-hydroxy-1-methyl-ethyl)thieno[2,3-*c*]pyran-7-one (2a).



Low melting light brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.85 (d, J=5.0 Hz, 1H), 7.34 (d, J=5.0 Hz, 1H), 2.24 (br s, –OH), 1.61 (s, 12H, CH_3); IR (cm^{-1}, $CHCl_3$) 3391, 2981, 1715 (C=O), 1626; *m*/*z* (ES Mass) 293 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.4 (C=O), 148.3, 144.0,

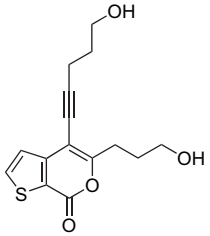
138.8 (2C), 124.7, 105.6, 104.0, 74.1, 73.6, 65.6, 31.1 (2C, CH_3), 28.5 (2C, CH_3); UV (nm, MeOH) 312.0, 252.8, 238.4, 214.2; HPLC 96.3%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 11.3 min; Elemental analysis found C, 61.77; H, 5.45; $C_{15}H_{16}O_4S$ requires C, 61.62; H, 5.52.

4.3.3. 4-(4-Hydroxy-but-1-ynyl)-5-(2-hydroxy-ethyl)-thieno[2,3-*c*]pyran-7-one (2b).



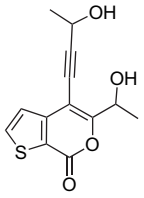
White solid; mp 116–116.5 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.83 (d, J=5.0 Hz, 1H), 7.32 (d, J=5.0 Hz, 1H), 4.03 (t, J=5.7 Hz, 2H, CH_2), 3.86 (t, J=5.7 Hz, 2H, CH_2), 3.08 (t, J=5.7 Hz, 2H, CH_2), 2.74 (t, J=6.0 Hz, 2H, CH_2), 1.66 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3390, 3015, 2927, 1715 (C═O), 1602; *m*/*z* (ES Mass) 265 (M^+, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.4 (C═O), 157.4, 157.2, 136.8, 124.6, 123.9, 104.2, 94.0, 72.3, 61.1 (CH_2OH), 60.4 (CH_2OH), 29.7 (CH_2), 23.9 (CH_2); UV (nm, MeOH) 315.2, 313.4, 252.8, 238.4, 201.6; HPLC 98.8%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 8.4 min; Elemental analysis found C, 59.15; H, 4.51; $C_{13}H_{12}O_4S$ requires C, 59.08; H, 4.58.

4.3.4. 4-(5-Hydroxy-pent-1-ynyl)-5-(3-hydroxy-propyl)-thieno[2,3-*c*]pyran-7-one (2c).



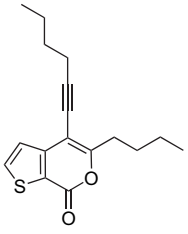
Low melting light brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.83 (d, J=4.7 Hz, 1H), 7.23 (d, J=4.7 Hz, 1H), 3.85 (t, J=4.7 Hz, 2H, CH_2), 3.75 (t, J=4.6 Hz, 2H, CH_2), 2.9 (t, J=4.6 Hz, 2H, CH_2), 2.6 (t, J=4.68 Hz, 2H, CH_2), 2.10–1.90 (m, 2H, CH_2), 1.85–1.80 (m, 2H, CH_2), 1.69 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3429, 3019, 2400, 1719 (C═O), 1601; *m*/*z* (ES Mass) 293 (M^+, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.7 (C═O), 157.2, 153.8, 136.7, 132.1, 124.5, 106.6, 94.6, 72.4, 61.4 (CH_2OH), 58.3 (CH_2OH), 30.2 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 16.1 (CH_2); UV (nm, MeOH) 317.2, 253.0, 235.4, 210.8; HPLC 98.2%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 11.0 min; Elemental analysis found C, 61.32; H, 5.57; $C_{15}H_{16}O_4S$ requires C, 61.62; H, 5.52.

4.3.5. 4-(3-Hydroxy-but-1-ynyl)-5-(1-hydroxy ethyl)-thieno[2,3-*c*]pyran-7-one (2d).



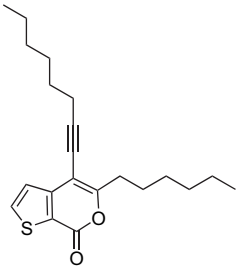
Low melting light brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.87 (d, J=5.0 Hz, 1H), 7.33 (d, J=5.0 Hz, 1H), 5.14 (q, J=6.3 Hz, 1H, CH), 4.82 (q, J=6.7 Hz, 1H, CH), 1.61 (d, J=3.4 Hz, 3H, CH_3), 1.57 (d, J=3.7 Hz, 3H, CH_3), 1.75 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3307, 2919, 1713 (C═O), 1600; *m*/*z* (CI Mass) 265 (M^+, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.7 (C═O), 153.7, 144.2, 137.1, 127.4, 124.6, 104.2, 99.4, 75.4, 66.0 (CH), 58.8 (CH), 24.3 (CH_3), 21.2 (CH_3); UV (nm, MeOH) 313.4, 253.2, 235.8, 201.8; HPLC 96.4%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 9.7 min; HRMS Calcd for $C_{13}H_{12}O_4S$ ($M+H^+$): 265.0534. Found: 265.0540.

4.3.6. 5-Butyl-4-hex-1-ynyl-thieno[2,3-*c*]pyran-7-one (2e).



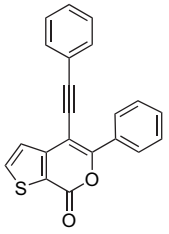
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, J=5.1 Hz, 1H), 7.28 (d, J=5.1 Hz, 1H), 2.79 (t, J=7.5 Hz, 2H, CH_2), 2.48 (t, J=7.2 Hz, 2H, CH_2), 1.74–1.66 (m, 2H, CH_2), 1.61–1.59 (m, 2H, CH_2), 1.45–1.50 (m, 2H, CH_2), 1.41–1.36 (m, 2H, CH_2), 0.93–0.99 (m, 6H, CH_3); IR (cm^{-1}, $CHCl_3$) 2958, 1729 (C═O); *m*/*z* (ES Mass) 289 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.2 (C═O), 154.6, 152.3, 136.4, 124.6, 123.4, 105.6, 96.6, 71.5, 31.8, 30.8, 29.7, 29.5, 22.2, 22.0, 19.2 (CH_3), 13.7 (CH_3); UV (nm, MeOH) 325.2, 252.6, 238.4, 209.6; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 18.3 min; Elemental analysis found C, 70.87; H, 6.95; $C_{17}H_{20}O_2S$ requires C, 70.80; H, 6.99.

4.3.7. 5-Hexyl-4-oct-1-ynyl-thieno[2,3-*c*]pyran-7-one (2f).



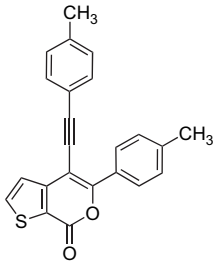
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, J=5.1 Hz, 1H), 7.29 (d, J=5.1 Hz, 1H), 2.78 (t, J=7.8 Hz, 2H, CH_2), 2.47 (t, J=6.9 Hz, 2H, CH_2), 1.79–1.65 (m, 2H, CH_2), 1.68–1.58 (m, 2H, CH_2), 1.61–1.4 (m, 6H, CH_2), 1.39–1.26 (m, 6H, CH_2), 0.91–0.87 (m, 6H, CH_3); IR (cm^{-1}, $CHCl_3$) 2929, 1727 (C═O), 1600; *m/z* (ES Mass) 345 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 136.3 (C═O), 124.6, 32.1 (2C), 31.5 (2C), 31.3 (2C), 29.7 (2C), 28.7 (2C), 28.6 (2C), 27.4 (2C), 22.50 (2C), 19.5 (2C), 14.0; UV (nm, MeOH) 322.0, 252.8, 239.4, 214.8; HPLC 98.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 19.9 min; Elemental analysis found C, 73.37; H, 8.10; $C_{21}H_{28}O_2S$ requires C, 73.21; H, 8.19.

4.3.8. 5-Phenyl-4-phenyl ethynyl-thieno-[2,3-*c*]pyran-7-one (2g).



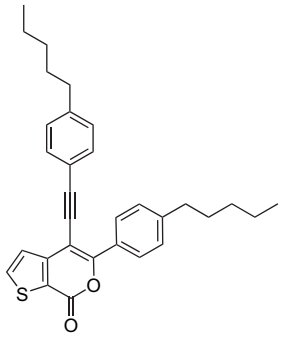
Pale yellow solid; mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25–8.22 (m, 2H), 7.90 (d, J=5.1 Hz, 1H), 7.90 (d, J=5.1 Hz, 1H), 7.50–7.30 (m, 8H); IR (cm^{-1}, KBr) 3107, 1723 (C═O); *m/z* (ES Mass) 329 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.6 (C═O), 148.4, 136.7, 131.9, 313.6 (2C), 131.4, 131.2, 130.5, 130.2, 129.5, 128.8, 128.5, 128.4, 128.3 (2C), 125.3, 122.6, 105.1, 96.6, 88.3; UV (nm, MeOH) 313.4, 217.4, 247.8; HPLC 99.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 18.0 min; Elemental analysis found C, 76.87; H, 3.66; $C_{21}H_{12}O_2S$ requires C, 76.81; H, 3.68.

4.3.9. 5-*p*-Tolyl-4-*p*-tolylethynyl-thieno[2,3-*c*]pyran-7-one (2h).



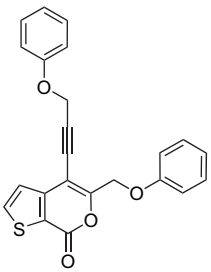
Pale yellow solid; mp 171.5–171.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J=8.3 Hz, 2H), 7.87 (d, J=5.1 Hz, 1H), 7.53 (d, J=5.1 Hz, 1H), 7.40 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 2.35–2.43 (m, 6H, CH_3); IR (cm^{-1}, KBr) 3072, 1727 (C═O), 1584; *m/z* (CI Mass) 358 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.9 (C═O), 148.6, 140.9, 139.1, 136.5, 133.3 (2C), 131.2, 129.3 (2C), 128.9, 128.7 (2C), 126.2, 125.2 (2C), 123.3, 119.6, 103.6, 96.8, 82.3, 22.6 (CH_3), 21.5 (CH_3); UV (nm, MeOH) 317.4, 252.8; HPLC 96.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 18.7 min; Elemental analysis found C, 77.37; H, 4.54; $C_{23}H_{16}O_2S$ requires C, 77.50; H, 4.52.

4.3.10. 5-(4-Pentyl-phenyl)-4-(4-pentyl-phenylethynyl)-thieno[2,3-*c*]pyran-7-one (2i).



Low melting brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, J=8.3 Hz, 2H), 7.87 (d, J=5.1 Hz, 1H), 7.53 (d, J=5.1 Hz, 1H), 7.43 (d, J=8.3 Hz, 2H), 7.30 (d, J=8.3 Hz, 2H), 7.19 (d, J=8.1 Hz, 2H), 2.69–2.61 (m, 4H, CH_2), 1.67–1.61 (m, 4H, CH_2), 1.37–1.25 (m, 8H, CH_2), 0.92–0.87 (m, 6H, CH_3); IR (cm^{-1}, $CHCl_3$) 2928, 1736 (C═O), 1598; *m/z* (CI Mass) 469 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 158.6 (C═O), 148.7, 147.5, 145.9, 144.1, 136.5, 132.4, 131.3 (2C), 129.3 (2C), 128.6 (2C), 128.3 (2C), 127.3, 123.2, 120.8, 103.8, 96.9, 82.4, 35.9 (2C), 31.4 (2C), 30.8 (2C), 22.5 (2C), 14.0 (2C); UV (nm, MeOH) 317.8, 254.0, 202.0; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 23.4 min; HRMS Calcd for $C_{31}H_{32}O_2S$ (M+H^+): 469.2201. Found: 469.2216.

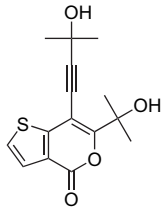
4.3.11. 5-Phenoxymethyl-4-(3-phenoxy-prop-1-ynyl)-thieno[2,3-*c*]pyran-7-one (2j).



White solid; mp 115.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J=7.5 Hz, 1H), 7.34–7.23 (m, 6H), 7.22–7.0 (m,

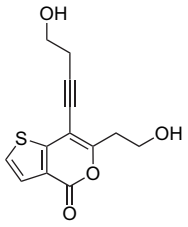
5H), 4.93 (s, 2H, CH_2), 5.03 (s, 2H, CH_2); IR (cm^{-1}, KBr) 2925, 1733 (C=O), 1598, 1240; *m/z* (CI Mass) 389 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) 157.9 (C=O), 156.9, 154.5, 153.8, 152.7, 137.0, 129.6 (2C), 129.5 (2C), 126.6, 124.7, 121.8, 121.7, 115.0 (2C), 114.9 (2C), 101.2, 92.7, 78.1, 65.0, 56.2; UV (nm, MeOH) 313.0, 255.8, 202.8; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.0 mL/min, UV 254 nm, retention time 17.4 min; Elemental analysis found C, 71.22; H, 4.10; $C_{23}H_{16}O_4S$ requires C, 71.12; H, 4.15.

4.3.12. 6-(1-Hydroxy-1-methyl-ethyl)-7-(3-hydroxy-3-methyl-but-1-ynyl)-thieno[3,2-*c*]pyran-4-one (2aa).



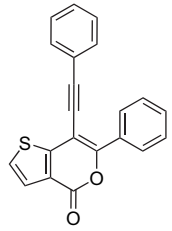
Low melting light brown solid; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.54 (d, *J*=5.2 Hz, 1H), 7.37 (d, *J*=5.3 Hz, 1H), 2.24 (br s, –OH), 1.68 (s, 12H); IR (cm^{-1}, $CHCl_3$) 3272, 1722 (C=O); *m/z* (CI Mass) 293 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.9 (C=O), 156.7, 153.9, 132.1, 128.3, 126.3, 125.7, 104.4, 95.8, 73.6, 65.4, 30.8 (2C, CH_3), 28.5 (2C, CH_3); UV (nm, MeOH) 314.8, 264.4, 231.8, 203.4; HPLC 96.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 12.5 min; Elemental analysis found C, 61.32; H, 5.58; $C_{15}H_{16}O_4S$ requires C, 61.62; H, 5.52.

4.3.13. 6-(2-Hydroxy-ethyl)-7-(4-hydroxy-but-1-ynyl)-thieno [3,2-*c*]pyran-4-one (2bb).



Brown color solid; mp 101–102 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.54 (d, *J*=5.6 Hz, 1H), 7.34 (d, *J*=5.6 Hz, 1H), 4.02 (t, *J*=5.9 Hz, 2H), 3.88 (t, *J*=5.9 Hz, 2H), 3.08 (t, *J*=5.9 Hz, 2H), 2.75 (t, *J*=5.9 Hz, 2H), 1.66 (br s, –OH); IR (cm^{-1}, KBr) 3381, 2919, 1712 (C=O); *m/z* (CI Mass) 265 (M^+, 100%); ^{13}C ($CDCl_3$, 50 MHz) δ 160.3 (C=O), 158.1, 152.4, 132.1, 128.4, 125.8, 102.1, 95.3, 73.6, 60.8 (CH_2OH), 59.9 (CH_2OH), 35.6 (CH_2), 23.9 (CH_2); UV (nm, MeOH) 316.4, 276.0, 264.8, 232.8; HPLC 98.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 8.9 min; Elemental analysis found C, 59.17; H, 4.47; $C_{13}H_{12}O_4S$ requires C, 59.08; H, 4.58.

4.3.14. 6-Phenyl-7-phenyl ethyl-thieno-[3,2-*c*]pyran-4-one (2gg).

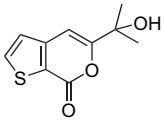


Pale yellow solid; mp 183–184 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.25 (m, 2H), 7.63 (d, *J*=5.4 Hz, 1H), 7.43 (d, *J*=5.4 Hz, 1H), 7.55–7.50 (m, 5H), 7.40–7.38 (m, 3H); IR (cm^{-1}, KBr) 3421, 2962, 1738 (C=O); *m/z* (CI Mass) 329 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.0 (C=O), 131.4 (2C), 130.6 (2C), 129.0 (2C), 128.5 (2C), 128.3, 128.2, 126.6 (2C), 126.0 (2C), 125.4, 122.6, 122.2, 101.6, 97.6 (2C); UV (nm, MeOH) 340.6, 300.0, 239.0, 203.2; HPLC 98.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 18.0 min; Elemental analysis found C, 76.63; H, 6.77; $C_{21}H_{12}O_2S$ requires C, 76.81; H, 3.68.

4.4. Preparation of 5-substituted thieno[2,3-*c*]pyran-7-ones (3)

4.4.1. General procedure. A mixture of 3-iodo thiophene-2-carboxylic acid (1.18 mmol), 10% Pd/C (0.035 mmol), PPh_3 (0.14 mmol), CuI (0.07 mmol), and triethylamine (6.0 mmol) in 1,4-dioxane (10 mL) was stirred at 25–30 °C for 30 min under nitrogen and acetylinic compound (1.8 mmol) was added. The mixture was then stirred at room temperature for 1 h and then at 75–80 °C for 10–12 h. After completion of the reaction the mixture was cooled to room temperature, diluted with EtOAc (50 mL), and filterd through Celite. The filtrate was washed with saturated aq sodium hydrogen carbonate (2×25 mL) followed by water (2×25 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silicagel, using light petroleum (distillation range 60–80 °C)–ethylacetate as eluent.

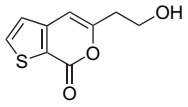
4.4.2. 5-(1-Hydroxy-1-methyl-ethyl)-thieno-[2,3-*c*]-pyran-7-one (3a).



White solid, mp 87–88 °C; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (d, *J*=5.3 Hz, 1H), 7.17 (d, *J*=5.0 Hz, 1H), 6.8 (s, 1H, CH=C), 2.24 (br s, –OH), 1.61 (s, 6H, CH_3); IR (cm^{-1}, KBr) 3499, 1736 (C=O); *m/z* (ES Mass) 211 (M^+, 100%); ^{13}C ($CDCl_3$, 50 MHz) δ 164.7 (C=O), 155.7, 147.3, 136.8, 124.7 (2C), 97.3, 71.2, 28.4 (2C, CH_3); UV (nm, MeOH) 360.0, 353.8, 310.4, 282.0, 230.8; HPLC 99.2%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70,

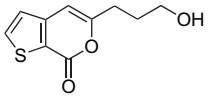
15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 7.2 min; Elemental analysis found C, 57.24; H, 4.75; $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79.

4.4.3. 5-(2-Hydroxy-ethyl)-thieno[2,3-*c*]pyran-7-one (3b).



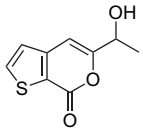
Low melting brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J=5.0 Hz, 1H), 7.14 (d, J=5.3 Hz, 1H), 6.58 (s, 1H), 4.02 (t, J=6.0 Hz, 2H), 2.84 (t, J=6.0 Hz, 2H), 1.65 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3430, 1717 (C=O); m/z (ES Mass) 197 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.6 (C=O), 152.2, 147.4, 136.7, 124.2 (2C), 102.2, 59.6 (CH_2), 29.6 (CH_2); UV (nm, MeOH) 312.4, 231.4, 210.0; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 5.2 min; Elemental analysis found C, 55.15; H, 4.10; $C_9H_8O_3S$ requires C, 55.09; H, 4.11.

4.4.4. 5-(3-Hydroxy-propyl)-thieno[2,3-*c*]pyran-7-one (3c).



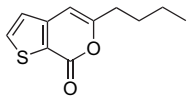
Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80 (d, J=5.1 Hz, 1H), 7.12 (d, J=5.1 Hz, 1H), 6.49 (s, 1H), 2.70 (t, J=7.5 Hz, 2H), 2.39 (t, J=6.9 Hz, 2H), 2.05–1.94 (m, 2H), 1.56 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3361, 1713 (C=O); m/z (CI Mass) 211 (M^+, 100%); UV (nm, MeOH) 308.8, 231.2, 209.8; HPLC 96.5%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 8.1 min; Elemental analysis found C, 57.24; H, 4.77; $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79.

4.4.5. 5-(1-Hydroxy-ethyl)-thieno[2,3-*c*]pyran-7-one (3d).



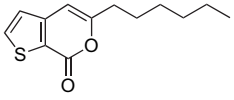
Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.83 (d, J=5.0 Hz, 1H), 7.16 (d, J=5.0 Hz, 1H), 6.75 (s, 1H), 4.75–4.66 (m, 1H), 2.58 (br s, –OH), 1.56 (d, J=6.7 Hz, 3H); IR (cm^{-1}, $CHCl_3$) 3331, 1712 (C=O); m/z (CI Mass) 197 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.0 (C=O), 151.0, 147.0, 136.8, 124.6 (2C), 98.6, 66.8 (CHOH), 21.5 (CH_3); UV (nm, MeOH) 309.4, 231.4, 209.8; HPLC 98.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 6.4 min; HRMS Calcd for $C_9H_8O_3S$ ($M+H^+$): 197.0272. Found: 197.0271.

4.4.6. 5-Butyl-thieno[2,3-*c*]pyran-7-one (3e).



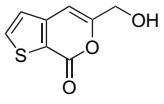
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, J=5.1 Hz, 1H), 7.10 (d, J=5.1 Hz, 1H), 6.43 (s, 1H), 2.56 (t, J=7.3 Hz, 2H), 1.74–1.66 (m, 2H), 1.46–1.36 (m, 2H), 0.94 (t, J=7.3 Hz, 3H); IR (cm^{-1} $CHCl_3$) 2957, 1720 (C=O); m/z (ES Mass) 209 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.0 (C=O), 156.7, 147.5, 136.4, 124.0 (2C), 100.3, 33.1, 29.6, 22.0, 13.7 (CH_3); UV (nm, MeOH) 315.0, 281.6, 231.2, 210.4; HPLC 98.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 16.9 min; Elemental analysis found C, 63.39; H, 5.83; $C_{11}H_{12}O_2S$ requires C, 63.43; H, 5.81.

4.4.7. 5-Hexyl-thieno [2,3-*c*] pyran-7-one (3f).



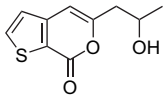
^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.79 (d, J=5.0 Hz, 1H), 7.11 (d, J=5.0 Hz, 1H), 6.43 (s, 1H), 2.59–2.52 (m, 2H), 1.78–1.70 (m, 2H), 1.40–1.25 (m, 6H), 0.92–0.85 (m, 3H); IR (cm^{-1}, $CHCl_3$) 3390, 1718 (C=O); m/z (CI Mass) 237 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.0 (C=O), 156.3, 147.5, 136.4, 124.0 (2C), 100.3, 33.4, 31.4, 28.5, 27.0, 22.4, 13.9; UV (nm, MeOH) 314.8, 231.4, 210.0; HPLC 96.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 17.1 min; HRMS Calcd for $C_{13}H_{16}O_2S$ ($M+H^+$): 237.0949. Found: 237.0943.

4.4.8. 5-Hydroxymethyl-thieno[2,3-*c*]pyran-7-one (3g).



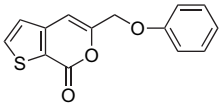
Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.84 (d, J=5.1 Hz, 1H), 7.18 (d, J=5.1 Hz, 1H), 6.74 (s, 1H), 4.54 (s, 2H), 1.65 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3388, 2926, 1696 (C=O); m/z (CI Mass) 183 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.3 (C=O), 144.7, 142.5, 136.9, 124.5 (2C), 100.3, 61.4 (CH_2OH); UV (nm, MeOH) 306.6, 231.0, 209.2; HPLC 95.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 4.9 min; Elemental analysis found C, 52.69; H, 3.34; $C_8H_6O_3S$ requires C, 52.74; H, 3.32.

4.4.9. 5-(2-Hydroxy-propyl)-thieno[2,3-*c*]pyran-7-one (3h).



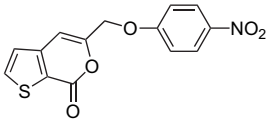
Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80 (d, J=5.1 Hz, 1H), 7.12 (d, J=5.1 Hz, 1H), 6.54 (s, 1H), 4.31–4.25 (m, 1H), 2.77–2.66 (m, 5H), 1.83 (br s, –OH); IR (cm^{-1}, $CHCl_3$) 3366, 1713 (C=O); *m/z* (CI Mass) 211 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1 (C=O), 157.7, 147.3, 136.7, 124.2 (2C), 102.4, 66.2, 43.0 (CHOH), 23.1 (CH_3); UV (nm, MeOH) 237.6, 231.4, 210.6; HPLC 96.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention of time 7.3 min; Elemental analysis found C, 57.24; H, 4.78; $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79.

4.4.10. 5-Phenoxymethyl-thieno[2,3-*c*]pyran-7-one (3i).



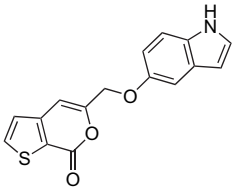
Pale yellow solid; mp 105.2–105.5 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.83 (d, J=2.4 Hz, 1H), 7.34–7.30 (m, 2H), 7.19 (d, J=2.9 Hz, 1H), 7.17–6.99 (m, 3H), 6.86 (s, 1H), 4.93 (s, 2H); IR (cm^{-1}, $CHCl_3$) 3411, 1722 (C=O); *m/z* (CI Mass) 259 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.7 (C=O), 155.1, 146.7, 136.9, 130.7, 129.9 (2C), 129.5, 124.6, 121.8, 114.6 (2C), 101.2, 65.7; UV (nm, MeOH) 304.2, 231.6, 209.8; HPLC 95.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention of time 15.3 min; Elemental analysis found C, 65.21; H, 3.88; $C_{14}H_{10}O_3S$ requires C, 65.10; H, 3.90.

4.4.11. 5-(4-Nitro-phenoxymethyl)-thieno-[2,3-*c*]pyran-7-one (3j).



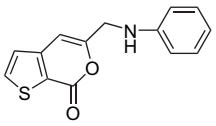
Pale yellow solid; mp 212–213 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.24 (d, J=9.4 Hz, 2H), 7.87 (d, J=5.1 Hz, 1H), 7.23 (d, J=5.1 Hz, 1H), 7.06 (d, J=9.4 Hz, 2H), 6.81 (s, 1H), 5.01 (s, 2H); IR (cm^{-1}, KBr) 3106, 1713 (C=O), 1591, 1338, 1265; *m/z* (CI Mass) 304 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.5 (C=O), 154.8, 144.9, 142.5 (2C), 130.6 (2C), 124.9, 121.3 (2C), 114.2 (2C), 104.6, 64.3 (CH_2); UV (nm, MeOH) 308.4, 228.8, 219.4; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention of time 14.5 min; Elemental analysis found C, 55.49; H, 3.05; N, 4.59; $C_{14}H_9NO_5S$ requires C, 55.44; H, 2.99; N, 4.62.

4.4.12. 5-(1*H*-Indol-5-yloxymethyl)-thieno-[2,3-*c*]pyran-7-one (3k).



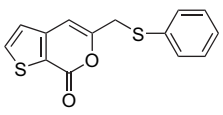
White crystalline solid; mp 130–131 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (d, J=5.1 Hz, 1H), 7.34–6.91 (m, 5H), 6.46 (d, J=11.8 Hz, 1H), 6.85 (s, 1H), 4.98 (s, 2H); IR (cm^{-1}, KBr) 2924, 2854, 1710 (C=O); *m/z* (CI Mass) 298 (M^+, 100%); UV (nm, MeOH) 360.4, 298.6, 211.6; Elemental analysis found C, 64.69; H, 3.72; N, 4.68; $C_{16}H_{11}NO_3S$ requires C, 64.63; H, 3.73; N, 4.71.

4.4.13. 5-Phenyl aminomethyl-thieno-[2,3-*c*]pyran-7-one (3l).



Pale yellow solid; mp 156–157 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.79 (d, J=5.1 Hz, 1H), 7.08–7.23 (m, 4H), 6.80–6.63 (m, 3H), 4.27 (s, 2H); IR (cm^{-1}, KBr) 3389, 1709 (C=O), 1603; *m/z* (CI Mass) 258 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.5 (C=O), 146.7 (2C), 136.7 (2C), 129.3 (2C), 124.4 (2C), 118.4, 112.9 (2C), 100.3, 45.2 (CH_2); UV (nm, MeOH) 310.6, 283.8, 240.0, 204.2; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention of time 12.4 min; Elemental analysis found C, 65.53; H, 4.26; N, 5.33; $C_{14}H_{11}NO_2S$ requires C, 65.35; H, 4.31; N, 5.44.

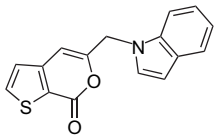
4.4.14. 5-Phenylsulfanylmethyl-thieno[2,3-*c*]pyran-7-one (3m).



Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.78 (d, J=5.1 Hz, 1H), 7.39–7.29 (m, 5H), 7.07 (d, J=5.1 Hz, 1H), 6.53 (s, 1H), 3.94 (s, 2H); IR (cm^{-1}, $CHCl_3$) 3347, 2924, 1719 (C=O); *m/z* (CI Mass) 275 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.9 (C=O), 146.7, 136.7, 134.5, 131.1, 130.8, 129.4, 129.1, 128.2, 127.3, 124.3 (2C), 101.8, 36.6; UV (nm, MeOH) 315.4, 238.2, 206.4; HPLC 96.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 15.6 min; Elemental analysis

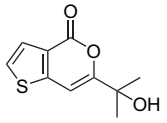
found C, 61.37; H, 3.65; $C_{14}H_{10}O_2S_2$ requires C, 61.29; H, 3.67.

4.4.15. 5-Indol-1-ylmethyl-thieno[2,3-*c*]pyran-7-one (3n).



Pale yellow solid; mp 179–180 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.75 (d, J=5.1 Hz, 1H), 7.67 (d, J=6.9 Hz, 1H), 7.32 (d, J=7.5 Hz, 1H), 7.25–7.14 (m, 3H), 6.98 (d, J=5.3 Hz, 1H), 6.62 (s, 1H), 6.05 (d, J=1.3 Hz, 1H), 5.20 (s, 2H); IR (cm^{-1}, KBr) 3364, 2931, 1709 (C=O); *m/z* (CI Mass) 282 (M^+, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.8 (C=O), 155.3, 146.5 (2C), 136.9 (2C), 128.2, 124.5, 122.3, 121.2 (2C), 120.1, 109.2, 102.9, 100.3, 47.1 (CH_2); UV (nm, MeOH) 360.0, 291.0, 281.0, 219.6; HPLC 98.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention of time 15.7 min; Elemental analysis found C, 68.52; H, 3.90; N, 4.85; $C_{16}H_{11}NO_2S$ requires C, 68.31; H, 3.94; N, 4.98.

4.4.16. 6-(1-Hydroxy-1-methyl-ethyl)-thieno[3,2-*c*]-pyran-4-one (3aa).



Off-white solid; mp 115–116 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56 (d, J=5.3 Hz, 1H), 7.30 (d, J=5.3 Hz, 1H), 6.9 (s, 1H), 2.24 (br s, –OH), 1.60 (s, 6H); IR (cm^{-1}, KBr) 3231, 2981, 1723 (C=O); *m/z* (CI Mass) 211 (M^+, 100%); ^{13}C ($CDCl_3$, 50 MHz) δ 163.6 (C=O), 158.2, 147.3, 125.5, 125.2, 96.4, 83.9, 65.5, 31.0 (2C, CH_3); UV (nm, MeOH) 310.6, 283.4, 230.6, 210.5; HPLC 97.0%, column: Zorbax Eclipse XDB C-18 (150×4.6 mm), mobile phase A: 0.05% TFA in water, mobile phase B: 0.05% TFA in methanol, gradient (T/%B): 0/30, 13/70, 15/100, 25/100, flow rate: 1.5 mL/min, UV 254 nm, retention time 8.1 min; Elemental analysis found C, 57.40; H, 4.75; $C_{10}H_{10}O_3S$ requires C, 57.13; H, 4.79.

4.5. Protocol for in vitro cell growth assay

Anticancer activity of selected compounds has been tested in HT-29 (ATCC NO# HTB-38 Colon adenocarcinoma), NCI-H460 (ATCC NO# HTB-177 Large cell lung cancer), and LoVo (ATCC NO# CCL-229 Colon adenocarcinoma) cell lines by using Sulforhodamine B (SRB) assay.[18] Cells were maintained in RPMI 1640 with 10% FBS (Fatal Bovine Serum), Penicillin (50 μg/mL), and Streptomycin (100 μg/mL). Cells were seeded in a 96-well cell culture plates at a concentration of 10,000 cells per well and incubated at 37 °C in CO_2 incubator. Twenty-four hours later cells were treated with different concentrations (100, 10, 1, 0.1, and 0.01 μM) of compound dissolved in DMSO and incubated for 48 h. Cells were fixed by adding ice-cold 50% trichloroacetic acid (TCA) and incubating for 1 h at 4 °C. The plates were washed with distilled water, air-dried, and stained with SRB solution (0.4% wt/vol in 1% acetic acid) for 30 min at room temperature. Unbound SRB was removed by washing thoroughly with 1% acetic acid and the plates were air-dried. The bound SRB stain was solubilized with 10 mM Tris buffer, and the optical densities were read on a spectrophotometric plate reader at 515 nm. At the time of drug addition separate reference plate for cell growth at time 0 h (the time at which drugs were added) was also terminated as described above. From the optical densities the percentage growths were calculated using the following formulae: if T is greater than or equal to T_0, percentage growth= $100\times[(T-T_0)/(C-T_0)]$ and if T is less than T_0, percentage growth=$100\times[(T-T_0)/T_0)]$, where T is optical density of test, C is the optical density of control, and T_0 is the optical density at time zero. From the percentage growths a dose response curve was generated and GI_{50} values were interpolated from the growth curves.

Acknowledgements

The authors thank Dr. A. Venkateswarlu, Dr. R. Rajagopalan, Professor J. Iqbal and Dr. Vilas Dahanukar for their encouragement and the analytical group for spectral data. S. Raju thanks DRL for allowing him to pursue this work as a part of his Ph.D. dissertation. M.P. thanks DRL for allowing him to attend the Symposium on Chemistry, Biology and Medicine organized on the occasion of the 60th Birthday of Professor K. C. Nicolaou, from May 28 till June 1, 2006, in Paphos, Cyprus.

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Direct asymmetric aldol reaction catalyzed by nanocrystalline magnesium oxide

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Abstract—Nanomaterials with their three-dimensional structure and defined size and shape are considered to be suitable candidates for proper alignment with prochiral substrates for unidirectional introduction of reacting species to induce an asymmetric centre. The reusable and suitably aligned nanocrystalline magnesium oxide catalyzed direct asymmetric aldol reaction afforded the chiral β-hydroxy carbonyl compounds in good yields and moderate ee's.

1. Introduction

The aldol reaction is considered to be one of the most important carbon–carbon bond forming reactions in both the biochemical and chemical domains. The aldol reaction is ubiquitous in synthetic organic chemistry to generate the elegant intermediates of anti-hypertensive drugs and calcium antagonists.[1] Chiral β-hydroxy carbonyl compounds can be readily converted to 1,3-*syn*- and *anti*-diols and amino alcohols, which are the building blocks in many natural products such as antibiotics, pheromones and in many biologically active compounds.[1b] The aldol products have been successfully converted to key synthetic intermediates of epithilone A and bryostatin 7.[1c]

The direct aldol reaction, starting from an aldehyde and an unmodified ketone, is highly atom efficient[2] compared with the process in which the preconversion of a ketone moiety to a more reactive species such as an enol silyl ether, enol methyl ether or ketone silyl acetal as the aldol donor (Mukaiyama aldol reaction) takes place.[3]

Shibasaki et al. achieved the first catalytic asymmetric aldol reaction between aldehydes and unmodified ketones by using heterobimetallic multifunctional catalysts.[1c,4] Later, the direct asymmetric aldol reactions with good to excellent enantioselectivities (ee's) were accomplished by using dinuclear transition metal catalysts by Trost et al.,[5] Barbas III et al.[6] reported the direct asymmetric aldol reactions catalyzed by aldolase enzymes and antibodies. List, Barbas and their co-workers have explored the asymmetric aldol reactions with excellent enantioselectivity by using L-proline[7] and its structural analogues[8] for α-branched aliphatic aldehydes. Only fair ee's were observed for the reaction of aromatic aldehydes with acetone either by L-proline[6,9] or its derivatives and its structural analogues[10] with the exception of *N*-substituted L-prolinamide derivatives.[11] L-Prolinamide derivatives from β-amino alcohols[11] gave high ee's for *p*-substituted benzaldehydes. In the area of heterogenized catalysts, solid supported proline-terminated peptides and benzylpencillin derivatives in conjunction with proline grafted into mesoporous MCM-41 provide moderate ee's for the direct asymmetric aldol reaction.[12] L-Proline in ionic liquids and silica supported ionic liquids also provided moderate enantioselectivity.[13]

A breakthrough in the asymmetric aldol reaction is achieved with the introduction of in situ prepared heterobimetallic catalysts, composed of both Lewis acidic sites and Lewis/Bronsted basic sites.[2,14] Evans et al. and other groups have explored the asymmetric direct enolate–electrophile reactions catalyzed by Mg and its derived complexes.[15] Transition metal chiral complexes, single-site catalysts with a defined shape and stereochemistry, induce, in general, higher enantioselectivity in asymmetric synthesis since they permit unidirectional introduction of the reacting species onto a prochiral substrate in the three-dimensional space to generate the asymmetric centre. Conversely, heterogeneous catalysts

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are not as effective as transition metal chiral complexes due to their multisite active sites resulting from assorted crystal structures with different shapes and sizes and also their steric restrictions. Hence, creation of desired stereochemistry with defined shape and size in heterogeneous catalysts to build the asymmetric centre is a challenging problem.

Nanocrystalline metal oxides[16] with their three-dimensional structure and defined size and shape are considered to be suitable candidates for proper alignment with prochiral substrates for unidirectional introduction of reacting species to induce an asymmetric centre. Recently, our group evolved the single-site nanocrystalline magnesium oxide (MgO) for the synthesis of chiral epoxy ketones, chiral nitro alcohols and Michael adducts.[17]

We herein report the direct asymmetric aldol reaction of aldehydes and ketones catalyzed by nanocrystalline magnesium oxide (MgO) to afford the optically active β-hydroxy carbonyl compounds in good yields and moderate ee's.

2. Results and discussions

Various magnesium oxide crystals[16] [commercial MgO, CM-MgO (SSA: 30 m^2/g), conventionally prepared MgO, NA-MgO (SSA: 250 m^2/g) and aerogel-prepared MgO, NAP-MgO (SSA: 590 m^2/g)] were initially screened in the achiral aldol reaction between *p*-nitrobenzaldehyde and acetone at room temperature. Based on the results of the achiral aldol reaction, we carried out direct asymmetric aldol reaction.

In the process of optimization of the reaction conditions, we explored different samples of MgO and NAP-MgO was found to be superior to others (Table 1). We have screened different chiral auxiliaries for the asymmetric aldol reaction between *p*-nitrobenzaldehyde and acetone catalyzed by NAP-MgO as specified in Table 2 and optimum ee was obtained with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane.

(1*S*,2*S*)-(+)-1,2-Diaminocyclohexane (20 mol %) was used as the chiral auxiliary with respect to the aldehyde.

Later, we explored the activity of NAP-MgO with different solvents at different temperatures (Table 3). As the temperature decreases, enantioselectivity increases with decrease in rate of reaction. The solvent THF and a temperature −20 °C showed optimum enantioselectivity.

To evaluate the importance of our catalytic system, we have carried out the aldol reaction with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (20 mol %), 1 mmol of aldehyde and 1 mL of acetone in the absence of NAP-MgO at room temperature. No aldol adduct was formed.

Table 1. Achiral aldol reaction between *p*-nitrobenzaldehyde and acetone at room temperature catalyzed by different crystallites of MgO[a]

Entry	Catalyst	Solvent	Time (h)	Conversion (%)
1	NAP-MgO	THF	24	75
2	CP-MgO	THF	36	10
3	CM-MgO	THF	36	0

[a] Conditions: catalyst (100 mg), aldehyde (1 mmol), acetone (13.7 mmol).

Table 2. Effect of ligand on asymmetric aldol reaction between *p*-nitrobenzaldehyde and acetone catalyzed by NAP-MgO at room temperature[a]

Entry	Ligand	Time (h)	Yield (%)[b]	ee (%)[c]
1	(1*R*,2*R*)-(+)-1,2-Diphenylethylenediamine	24	75	15
2	(1*R*,2*R*)-(−)-1,2-Diaminocyclohexane	24	75	12
3	(1*S*,2*S*)-(+)-1,2-Diphenylethylenediamine	24	75	16
4	(1*S*,2*S*)-(+)-1,2-Diaminocyclohexane	24	75	25
5	(*S*)-(−)-1,1′-Binaphthyl-2,2′-diamine	24	75	0
6	(*R*)-(−)-1,1′-Binaphthyl-2,2′-diamine	24	75	0
7	(+)-Diethyl-L-tartrate	24	75	0
8	(*S*)-(−)-Binol	24	60	0
9	(*R*)-(−)-Binol	24	60	0
10	(−)-Diethyl-L-tartrate	24	75	0

[a] Conditions: aldehyde (1.0 mmol), acetone (13.7 mmol), NAP-MgO (0.100 g), dry THF (2 mL). In all cases 20 mol % of ligand was used.
[b] Isolated yields.
[c] The ee% was determined by HPLC analysis using a chiral column (chiralpak AS-H, AD-RH).

Table 3. Asymmetric aldol reaction between *p*-nitrobenzaldehyde and acetone with different solvents by using (1*S*,2*S*)-(+)-1,2-diaminocyclohexane as chiral ligand at room temperature[a]

Entry	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	THF	24	75	17
2	DMF	24	62	0
3	DMSO	24	60	0
4	$CHCl_3$	24	5	0
5	DCM	24	5	0

[a] Conditions: aldehyde (1.0 mmol), acetone (13.7 mmol), (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (20 mol %), NAP-MgO (0.100 g), dry THF (2 mL).
[b] Isolated yields.
[c] The ee% was determined by HPLC analysis using a chiral column (chiralpak AS-H, AD-RH).

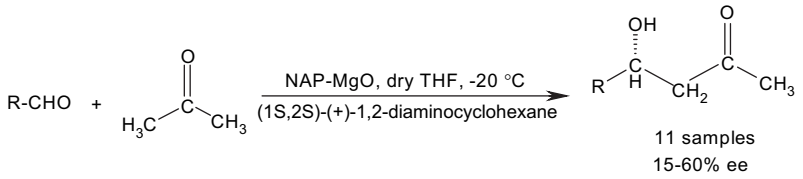
NAP-MgO was tested in the direct asymmetric aldol reaction of various substituted aromatic aldehydes (Table 4). When benzaldehydes were substituted at the 4-position with electron-withdrawing (EW) groups or electron-donating (ED) groups, higher ee's were observed when compared with the corresponding 2-substituted benzaldehydes with either EW or ED groups, which may be ascribed to the steric hindrance for the unidirectional entry of reacting species.

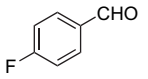
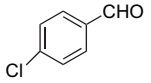
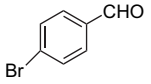
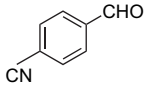
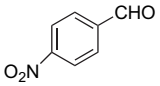
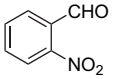
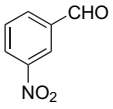
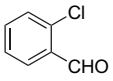
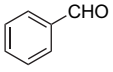
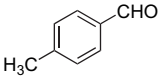
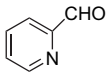
To understand the relation between the structure and reactivity in the direct asymmetric aldol reaction, it is better to know the structure and nature of the reactive species of the catalyst. NAP-MgO has a three-dimensional structure, which, having high surface concentrations of edge/corner and various exposed crystal planes (such as 002, 001 and 111), leads to inherently high surface reactivity per unit area. Thus, NAP-MgO indeed displayed the highest activity compared to that of NA-MgO and CM-MgO. Besides this, the NAP-MgO has a Lewis acid site Mg^{2+}, Lewis basic sites O^{2-} and O^-, lattice bound and isolated Bronsted hydroxyls and anionic and cationic vacancies.[16]

The aldol reaction was known to be driven by base catalysts and accordingly, the surface –OH and O^{2-} of these magnesium oxide crystals are expected to trigger this reaction.

The NAP-MgO was reused after heating the catalyst at 250 °C for 1 h under nitrogen atmosphere. Thus the catalyst was reused for four times, which showed consistent yields and ee's.

Table 4. Direct asymmetric aldol reaction of aldehydes and acetone with NAP-MgO[a]



Entry	Aldehyde	Time (h)	Yield (%)[b]	ee (%)[c]
1		24	70	60
2		24	65	48
3		24	67	40
4		24	60	40
5		24	75, 72,[d] 0[e]	53, 53[e]
6		24	70	15
7		24	70	27
8		24	55	33
9		36	60	23
10		36	50	17
11		24	75	43

[a] All reactions were performed on 1 mmol substrate in 1 mL (13.7 mmol) acetone using 100 mg of NAP-MgO.
[b] Yield of the product after isolation by column chromatography.
[c] The ee% was determined by HPLC analysis using a chiral column (chiralpak AS-H, AD-RH).
[d] Fifth cycle.
[e] Without catalyst.

3. Conclusion

In conclusion, the NAP-MgO is an active, reusable catalyst for the production of chiral β-hydroxy carbonyl compounds through direct asymmetric aldol reaction. Thus nanocrystalline MgO with its definite shape, size and accessible –OH groups and higher density of Mg^{2+} at the edges/corner shows higher activity in the direct asymmetric aldol reaction.

4. Experimental

4.1. General

All chemicals were purchased from Aldrich and were used as received. All solvents were of analytical grade from Merck India Pvt. Ltd and used as such. All reactions were conducted under nitrogen atmosphere at −20 °C in THF. The ^{1}H NMR

spectra of samples were recorded on a Varian-Unity 400 MHz and Bruker-Avance-300 MHz spectrometer using TMS as an internal standard in $CDCl_3$. High Performance Liquid Chromatography (HPLC) was performed using AGILENT-1100 series liquid chromatograph equipped with a single pump and UV detector (fixed at 216 nm) using chiralcel AS-H column with isopropanol/hexane as eluting agent. Optical rotations were obtained on an automated JASCO P-1020 polarimeter, and the values were reported in absolute rotations: $[\alpha]_D^{temperature}$ [concentration c g/100 mL of solvent]. The absolute stereochemistry was assigned as (*R*) by comparison of the optical rotation with the literature values. For energy calibration, we have used the carbon 1s photoelectron line. The carbon 1s binding energy was taken to be 285.0 eV. Spectra were deconvoluted using the Sun Solaris based vision 2 curve resolver. The location and the full width at half maximum (FWHM) for a species were first determined by using the spectrum of a pure sample.

4.2. General procedure for the aldol reaction

A mixture of acetone (1 mL, 13.7 mmol), (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (20 mol %, 22.8 mg) and catalyst (100 mg) was introduced into a 25 mL round bottomed flask containing dry THF (2 mL) at −20 °C and stirred for 30 min under nitrogen atmosphere. To the reaction mixture, aldehyde (1 mmol) was added at that temperature and stirring was continued. After completion of the reaction (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed several times with THF. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After purification by column chromatography on silica gel using 10% ethyl acetate in petroleum ether, the aldol adduct was obtained.

The chiral auxiliary (1*S*,2*S*)-(+)-1,2-diaminocyclohexane can be recovered quantitatively with no observable change in enantiomeric purity from the same chromatographic column by increasing the proportion of ethyl acetate in the eluent.

4.2.1. (4*R*)-Hydroxy-4-(4′-fluorophenyl)-butan-2-one (2a). Yield, 70% (127 mg); colourless oil, ^{1}H NMR ($CDCl_3$): δ 7.38 (d, J=8.0 Hz, 2H, Ar-H), 7.09 (d, J=8.0 Hz, 2H, Ar-H), 5.16 (dd, J=4.6, 6.6 Hz, 1H, –CHOH), 3.35 (br s, 1H, –OH), 2.87 (m, 2H, $-CH_2CO$), 2.23 (s, 3H, $-COCH_3$); IR (neat): 3445, 2925, 1713, 1509, 1377; Mass (EI): m/z 182 (M^+), 43; HRMS (ESI-MS) (−ve): exact mass calcd for (M−H−H_2O): 163.0559. Found: 163.0559; enantiomeric excess: 60%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 20:80), UV 257 nm, flow rate 1.0 mL/min; major isomer, t_R 8.9 min and minor isomer, t_R 11.2 min.

4.2.2. (4*R*)-Hydroxy-4-(4′-chlorophenyl)-butan-2-one (2b). Yield, 65% (128 mg); colourless oil, ^{1}H NMR ($CDCl_3$): δ 7.36 (d, J=8.2 Hz, 2H, Ar-H), 7.20 (d, J=8.2 Hz, 2H, Ar-H), 5.10 (dd, J=5.0, 7.0 Hz, 1H, –CHOH), 3.55 (br s, 1H, –OH), 2.67 (m, 2H, $-CH_2CO$), 2.10 (s, 3H, $-COCH_3$); IR (neat): 3433, 2924, 1709, 1463, 1370, 1079, 567 cm^{-1}; Mass (EI): m/z 179 (M^+), 43; HRMS (ESI-MS) (−ve): exact mass calcd for (M−H−H_2O): 179.0264. Found: 179.0265; enantiomeric excess: 48%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 10:90), UV 254 nm, flow rate 1.0 mL/min; major isomer, t_R 14.8 min and minor isomer, t_R 20.1 min.

4.2.3. (4*R*)-Hydroxy-4-(4′-bromophenyl)-butan-2-one (2c). Yield, 67% (156 mg); colourless oil, ^{1}H NMR ($CDCl_3$): δ 7.47 (d, J=8.4 Hz, 2H, Ar-H), 7.22 (d, J=8.4 Hz, 2H, Ar-H), 5.08 (dd, J=5.6, 7.8 Hz, 1H, –CHOH), 3.38 (br s, 1H, –OH), 2.80–2.70 (m, 2H, $-CH_2CO$), 2.20 (s, 3H, $-COCH_3$); IR (neat): 3427, 2913, 1703, 1438, 1369, 1071, 546 cm^{-1}; Mass (EI): m/z 243 (M^+), 43; HRMS (ESI-MS) (−ve): exact mass calcd for (M−H−H_2O): 222.9759. Found: 222.9768; enantiomeric excess: 40%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 15:85), UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 14.5 min and minor isomer, t_R 19.8 min.

4.2.4. (4*R*)-Hydroxy-4-(4′-cyanophenyl)-butan-2-one (2d). Yield, 60% (113 mg); pale yellow viscous oil, ^{1}H NMR ($CDCl_3$): δ 7.64 (d, J=8.1 Hz, 2H, Ar-H), 7.47 (d, J=8.1 Hz, 2H, Ar-H), 5.20 (m, 1H, –CHOH), 3.32 (br s, 1H, –OH), 2.82 (m, 2H, $-CH_2CO$), 2.21 (s, 3H, $-COCH_3$); IR (neat): 3418, 2934, 1713, 1489, 1369, 1077, 538 cm^{-1}; Mass (EI): m/z 189 (M^+), 43; HRMS (ESI-MS) (−ve): exact mass calcd for (M−H−H_2O): 170.0606. Found: 170.0600; enantiomeric excess: 30%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 30:70), UV 254 nm, flow rate 1.0 mL/min; major isomer, t_R 10.6 min and minor isomer, t_R 19.8 min.

4.2.5. (4*R*)-Hydroxy-4-(4′-nitrophenyl)-butan-2-one (2e). Yield, 75% (156 mg); pale brown viscous oil, ^{1}H NMR ($CDCl_3$): δ 8.20 (d, J=7.0 Hz, 2H, Ar-H), 7.52 (d, J=7.0 Hz, 2H, Ar-H), 5.30–5.20 (m, 1H, –CHOH), 3.56 (br s, 1H, OH), 2.85–2.80 (m, 2H, $-CH_2CO$), 2.21 (s, 3H, $-COCH_3$); Mass (EI): m/z 209 (M^+), 43; HRMS (ESI):[6] exact mass calcd for $C_{10}H_{11}NO_4$: 209.06809. Found: 232.1411 (M+Na)$^+$; IR (neat): 3419, 2930, 1716, 1514, 1480, 1370 cm^{-1}; enantiomeric excess: 53%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 15:85), UV 254 nm, flow rate 1.0 mL/min; major isomer, t_R 14.2 min and minor isomer, t_R 20.3 min.

4.2.6. (4*R*)-Hydroxy-4-(2′-nitrophenyl)-butan-2-one (2f). Yield, 70% (146 mg); pale brown viscous oil, ^{1}H NMR ($CDCl_3$): δ 7.96 (dd, J=1.2, 8.1 Hz, 1H, Ar-H), 7.91 (dd, J=1.2, 8.1 Hz, 1H, Ar-H), 7.71 (dt, J=1.2, 8.1 Hz, 1H, Ar-H), 7.44 (dt, J=1.2, 8.1 Hz, 1H, Ar-H), 5.70 (dd, J=9.3 Hz, 1H, –CHOH), 3.76–3.70 (br s, 1H, OH), 2.70–2.85 (m, 2H, $-CH_2CO$), 2.24 (s, 3H, $-COCH_3$); Mass (EI): m/z 209 (M^+), 43; IR (neat): 3416, 2934, 1719, 1512, 1376 cm^{-1}; enantiomeric excess: 15%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 30:70), UV 254 nm, flow rate 1.0 mL/min; major isomer, t_R 10.4 min and minor isomer, t_R 13.1 min.

4.2.7. (4*R*)-Hydroxy-4-(3′-nitrophenyl)-butan-2-one (2g). Yield, 70% (146 mg); yellow viscous oil, ^{1}H NMR ($CDCl_3$): δ 8.24 (s, 1H, Ar-H), 8.13 (d, J=8.6 Hz, 1H, Ar-H), 7.71 (d, J=7.5 Hz, 1H, Ar-H), 7.53 (t, J=7.5 Hz, 1H, Ar-H), 5.27–5.15 (m, 1H, –CHOH), 3.50 (br s, 1H, OH), 2.82 (m, 2H,

–CH_2CO), 2.23 (s, 3H, –$COCH_3$); IR (neat): 3414, 2931, 1715, 1519, 1370 cm^{-1}; Mass (EI): *m/z* 209 (M^+), 43; enantiomeric excess: 27%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 20:80), UV 254 nm, flow rate 1.0 mL/min; major isomer, t_R 11.1 min and minor isomer, t_R 15.0 min.

4.2.8. (4*R*)-Hydroxy-4-(2′-chlorophenyl)-butan-2-one (2h). Colourless oil, ^1H NMR ($CDCl_3$): δ 7.60 (d, J=8.6 Hz, 1H, Ar-H), 7.34–7.14 (m, 3H, Ar-H), 5.46 (m, J=10.4 Hz, 1H, –CHOH), 3.58 (br s, 1H, –OH), 2.90–3.05 (m, 2H, –CH_2CO), 2.22 (s, 3H, –$COCH_3$); IR (neat): 3410, 2930, 1712, 1440, 840 cm^{-1}; Mass (EI): *m/z* 179 (M^+), 43; enantiomeric excess: 33%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 8:92), UV 262 nm, flow rate 1.0 mL/min; major isomer, t_R 18.2 min and minor isomer, t_R 20.1 min.

4.2.9. (4*R*)-Hydroxy-4-phenyl-butan-2-one (2i). Yield, 60% (98 mg); colourless oil, ^1H NMR ($CDCl_3$): δ 7.33–7.17 (m, 5H, Ar-H), 5.15–5.04 (m, 1H, –CHOH), 3.17 (br s, 1H, –OH), 2.80–2.75 (m, 2H, –CH_2CO), 2.17 (s, 3H, –$COCH_3$); IR (neat): 3413, 2932, 1718, 1450, 890 cm^{-1}; Mass (EI): *m/z* 164 (M^+), 43; HRMS (EI):[13a] exact mass calcd for $C_{10}H_{12}O_2$: 164.0833. Found: 164.0837 (M^+); enantiomeric excess: 23%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 20:80), UV 254 nm, flow rate 1.0 mL/min; major isomer, t_R 16.0 min and minor isomer, t_R 19.2 min.

4.2.10. (4*R*)-Hydroxy-4-(4′-methylphenyl)-butan-2-one (2j). Yield, 50% (89 mg); colourless oil, ^1H NMR ($CDCl_3$): δ 7.26 (d, J=7.8 Hz, 2H, Ar-H), 7.17 (d, J=7.8 Hz, 2H, Ar-H), 5.25 (m, 1H, –CHOH), 3.32 (br s, 1H, –OH), 2.77–2.88 (m, 2H, –CH_2CO), 2.35 (s, 3H, –CH_3), 2.20 (s, 3H, –$COCH_3$); IR (neat): 3423, 2925, 1710, 1464, 808 cm^{-1}; Mass (EI): *m/z* 178 (M^+), 43; HRMS (EI): exact mass calcd for $C_{11}H_{14}O_2$: 178.09938. Found: 160.08882 ($M-H-H_2O$); enantiomeric excess: 17%, which was determined by HPLC analysis using chiralcel AS-H column (isopropyl alcohol/hexane 15:85), UV 257 nm, flow rate 1.0 mL/min; major isomer, t_R 9.4 min and minor isomer, t_R 11.2 min.

4.2.11. 4-Hydroxy-4-(2′-pyridyl)-butan-2-one (2k). Yield, 75% (124 mg); white solid, ^1H NMR ($CDCl_3$): 8.50–8.53 (m, 1H, PyH), 7.71 (dt, 1H, J=7.9, 1.7 Hz, PyH), 7.45 (d, 1H, J=7.9, 1.7 Hz, PyH), 7.16–7.23 (m, 1H, PyH), 5.19 (dd, 1H, J=8.2, 3.9 Hz, –CHOH), 2.90–3.06 (m, 2H, –CH_2CO), 2.21 (s, 3H, –$COCH_3$); IR (neat): 3133, 1718, 1595 cm^{-1}; Mass (EI): *m/z* 166 $(M+1)^+$, 43; HRMS (ESI-MS) (+ve): exact mass calcd for (M+H): 166.0868. Found: 166.0856; enantiomeric excess: 43%, which was determined by HPLC analysis using chiralcel OJ-H column (isopropyl alcohol/hexane 1:3), UV 206 nm, flow rate 1.0 mL/min; major isomer, t_R 19.5 min and minor isomer, t_R 21.5 min.

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Reactions of 1,4-bis(tetrazole)benzenes: formation of long chain alkyl halides

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Abstract—The reactions of 1,4-bis[2-(tributylstannyl)tetrazol-5-yl]benzene with α,ω-dibromoalkanes were carried out in order to synthesise pendant alkyl halide derivatives of the parent bis-tetrazole. This led to the formation of several alkyl halide derivatives, substituted variously at N1 or N2 on the tetrazole ring. The crystal structures of 1,4-bis[(2-(4-bromobutyl)tetrazol-5-yl)]benzene (2-*N*,2-*N*′), 1,4-bis[(2-(4-bromobutyl)tetrazol-5-yl)]benzene (1-*N*,2-*N*′) and 1,4-bis[(2-(8-bromooctyl)tetrazol-5-yl)]benzene (2-*N*,2-*N*′) are reported. Further discussion involves the structure of 1,4-bis[2-(6-bromohexyl)-2*H*-tetrazol-5-yl]benzene (2-*N*,2-*N*′) previously reported.

1. Introduction

The synthesis of tetrazoles from a cycloaddition reaction between a nitrile and an azide is well documented[1–6] since tetrazoles have roles in coordination chemistry as ligands, in medicinal chemistry as metabolically stable surrogates for carboxylic acids and in materials science applications, including photography and explosives. The interest in the ability of tetrazoles to mimic the carboxylic acid group has motivated the incorporation of tetrazoles into biologically active molecules.[2] This potential use has led to the incorporation in therapeutic applications, including their incorporation in pharmacologically active compounds with anti-hypertensive, anti-allergic and antibiotic activities.[3]

In recent years, particular attention has been directed towards the use of polydentate aromatic nitrogen heterocycles, specifically ligands with five-membered rings (azoles). Among these, imidazoles and triazoles have been extensively used for their ability to construct open framework networks with a wide variety of topologies. Tetrazoles exhibit a strong networking ability usually acting as mono- or bidentate ligands in most of the reported complexes.[7–9] A possible application for these materials as molecular hosts is in generating supramolecular arrays, which embody additional functional groups capable of metal complexation. This would result in a metallotetrazole framework with potential as new catalysts, anti-bacterial or therapeutic agents. Our interest in macrocycles containing tetrazoles surrounds their use as precursors for the formation of new functionalised poly-tetrazoles as, for example, sensors or in molecular recognition.

Molloy et al.,[5] Butler and Fleming[10] have synthesised bis-(bromoalkyltetrazolyl)benzenes from either tributylstannyl-substituted bis-tetrazoles or *N*-unsubstituted tetrazoles with dihaloalkanes with the 2-*N*,2-*N*′-isomer again being the predominant product; Molloy et al. studied both the 1,2- and 1,3-substituted bis-tetrazole while Butler and Fleming looked only at the 1,3-unsubstituted bis-tetrazoles. In fact, Butler has succeeded in using these bis-(bromoalkyltetrazolyl)-benzenes to generate the tetra-tetrazolemacrocycle (Fig. 1), which include a cavity of variable dimensions tailored by both the length and flexibility of the alkyl chain and also the substitution position on the benzene ring.[10–12] Furthermore, the X-ray crystal structure of one such macrocycle has been reported.[13]

We have previously reported our initial findings regarding the addition of pendant short-chain alkyl halide arms of some bis-tetrazoles, which yielded not only bis-tetrazole

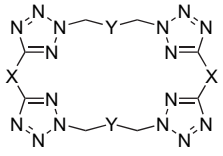

Figure 1. Schematic of tetratetrazole macrocycle with X=substituted benzene and Y=alkyl chain.

Keywords: Tetrazole; Organotin; X-ray; Alkyl halide; NMR spectroscopy.
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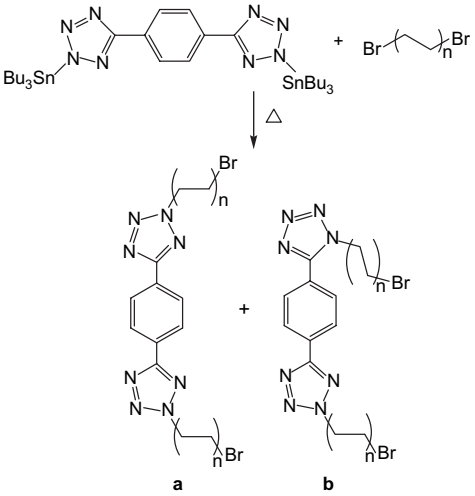
derivatives with pendant alkyl halide arms but also, and rather surprisingly, bis-tetrazole derivatives with pendant vinyl arms.[14] The X-ray crystal structure of 1,4-bis(tetrazole)-benzene with bromohexyl pendant arms has been reported, but with limited structural and spectroscopic discussion.[15] In this paper, we report the reactions of 1,4-bis(tetrazole)-benzenes with various long chain α,ω-dibromoalkanes and discuss their spectroscopic results. The crystal structures of three derivatives are also presented herein.

2. Results and discussion

While alkylation of 5-substituted mono-tetrazole derivatives is known to lead to mixtures of 1-*N*- and 2-*N*-substituted products,[1] the regioselectivity being dependent on the reaction conditions and the nature of the *C*- and *N*-substituents, the alkylation of bis-tetrazole derivatives can lead to several diverse products. For example, the reaction of 1,2-bis[2-(tributylstannyl)tetrazol-5-yl]benzene (1,2-$(Bu_3SnN_4C)_2C_6H_4$) with 1,2-dibromoethane, reported by Molloy et al.,[5] has been shown to form either a cyclophane or bis(bromoethyltetrazolyl)benzenes, depending on the ratio of the dibromoethane employed in the reaction. When using a 10-fold excess, the cyclophane was obtained; a larger excess (25:1) resulted in the formation of the bis(bromoethyltetrazolyl)-benzenes, either the 2-*N*,2-*N*′- or the 1-*N*,2-*N*′-isomer, with the 2-*N*,2-*N*′-isomer predominating in a ratio of ca. 3:1. We have recently reported the reactions of either 1,*n*-bis(tetrazol-5-yl)benzene (1,*n*-$(HN_4C)_2C_6H_4$) or 1,*n*-bis[2-(tributylstannyl)tetrazol-5-yl]benzene (1,*n*-$(Bu_3SnN_4C)_2C_6H_4$) (*n*=2, 3, 4) with 1,2-dibromoethane, which yielded compounds containing pendant bromoethyl or vinyl groups with substitution occurring at either 1-*N*,2-*N*′ or 2-*N*,2-*N*′, respectively.[14]

Our strategy was to use both of these approaches, that is, the use of both 1,*n*-bis(tetrazol-5-yl)benzene and 1,*n*-bis[2-(tributylstannyl)tetrazol-5-yl]benzene, to obtain sufficient quantities of the 2-*N*,2-*N*′-isomer of various bis(bromoalkyltetrazolyl)benzenes with a view towards generating derivatised tetra-tetrazole macrocycles. One approach involved the reactions of the 1,4-bis(tetrazole)benzene with long chain α,ω-dibromoalkanes. When the reactions of 1,4-bis(tetrazol-5-yl)benzene (1,4-$(HN_4C)_2C_6H_4$) with either 1,4-dibromobutane, 1,6-dibromohexane or 1,8-dibromooctane were heated as neat suspensions, no products were obtained and starting materials were recovered in all cases. Furthermore, when the reactions were carried out in the presence of triethylamine in either methanol or toluene with heating to reflux for 24 h, we found that the recovered material, after work-up, contained mainly starting bis-tetrazoles, with approx. 30% of products. We were able to grow crystals of 1,4-bis[(2-bromohexyl)tetrazol-5-yl]benzene, prepared by this method, which we have already reported.[8] However, when the reactions of 1,4-bis[2-(tributylstannyl)tetrazol-5-yl]benzene (1,4-$(Bu_3SnN_4C)_2C_6H_4$) with either 1,4-dibromobutane, 1,6-dibromohexane or 1,8-dibromooctane were heated as neat suspensions, two products were obtained in relatively high yields, in all the reactions, as well as some recovered starting material (Scheme 1), suggesting that the organotin route was the better method for the synthesis of this particular type of material. It should be pointed out that neither the cyclophane product nor any products containing additions on one ring only were obtained.



	a	b
2 (n = 2)	2a (64 %)*	2b (21 %)
3 (n = 3)	3a (65 %)	3b (12 %)
4 (n = 4)	4a (68 %)	4b (10 %)

* % Yield in parentheses

Scheme 1.

Column chromatography, using hexane/ethyl acetate mixtures as eluent, separated the products from the reactants. ^{1}H and ^{13}C NMR spectra were obtained for all samples and revealed that both the 2-*N*,2-*N*′- and the 1-*N*,2-*N*′-isomers of the bis(bromoalkyltetrazolyl)benzene had formed in the reaction, but the expected cyclophane was not present. The isomeric 2-*N*,2-*N*′- and 1-*N*,2-*N*′-derivatives are readily distinguishable by their ^{1}H and ^{13}C NMR spectra,[5,10,14] with the ^{13}C NMR chemical shift of the tetrazole carbon atom appearing at ca. 154.0 and 164.0 ppm in 1,5- and 2,5-disubstituted tetrazoles, respectively. The symmetrical 2-*N*,2-*N*′-substituted compounds thus gave rise to a single resonance at 164.0 ppm while both signals were apparent in the 1-*N*,2-*N*′-substituted compounds. For example, 1,4-bis[(2-bromobutyl)tetrazol-5-yl]benzene (2-*N*,2-*N*′) (**2a**) has a single peak at 164.6 ppm while 1,4-bis[(2-bromobutyl)tetrazol-5-yl]benzene (1-*N*,2-*N*′) (**2b**) has two peaks at 153.8 and 164.0 ppm. The main difference in the ^{1}H NMR spectra of the isomers was the doubling of signals in the case of the 1-*N*,2-*N*′-derivatives.

Crystals of compounds **2a**, **2b** and **4a**, suitable for an X-ray diffraction study, were obtained from chloroform and the structures confirmed the presence of the pendant bromoalkyl groups at the 2-*N*,2-*N*′-positions for **2a** and **4a** and at the 1-*N*,2-*N*′-positions for **2b** (Figs. 2, 3 and 4). Table 1 shows important bond lengths and angles for the three structures. We have previously published the structure of **3a**,[15] allowing us to include this also in our comparison of the 2-*N*,2-*N*′ compounds.

The structures of **2a**, **3a** and **4a** exhibit regularity. In each case, the molecular unit is centrosymmetric in the solid state and is sited on a crystallographic inversion centre. The tetrazole rings are essentially coplanar with the benzene ring to

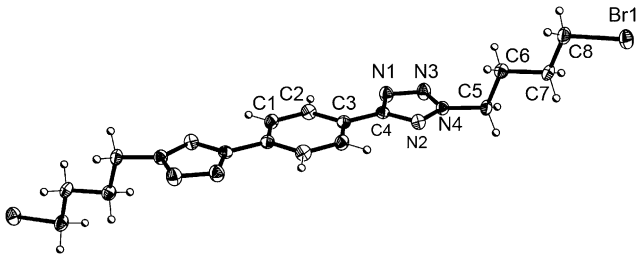


Figure 2. Molecular structure of **2a**, showing the labelling scheme for the crystallographically independent atoms. The non-labelled half of the molecule is related to the labelled half by a centre of inversion. Ellipsoids are represented at 50% probability for non-H atoms.

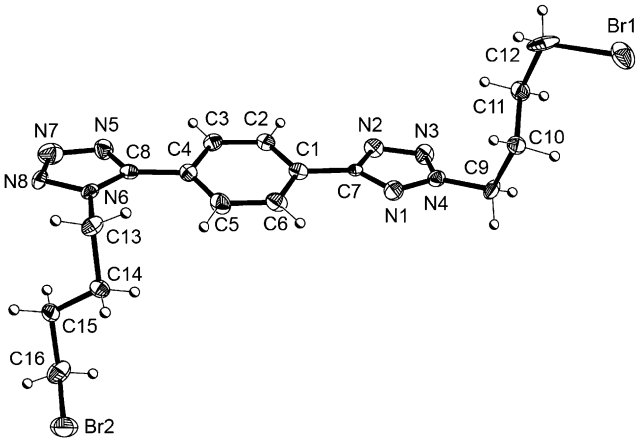


Figure 3. Molecular structure of **2b**, showing the labelling scheme used. Ellipsoids are represented at 50% probability for non-H atoms.

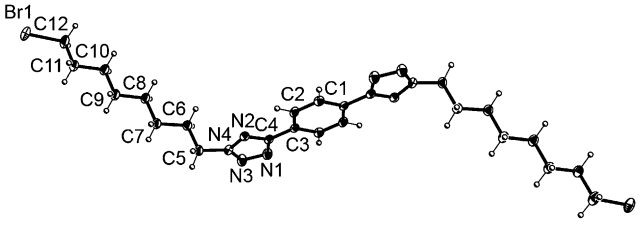


Figure 4. Molecular structure of **4a**, showing the labelling scheme for the crystallographically independent atoms. The non-labelled half of the molecule is related to the labelled half by a centre of inversion. Ellipsoids are represented at 50% probability for non-H atoms.

which they are attached, and the bromoalkyl groups adopt fully extended conformations, projecting to either side of this plane. The long axes of the alkyl chains form angles of ca. 145° to the molecular plane (measured by the N4–C5–C7 angle in **2a**, and equivalent angles in **3a** and **4a**). Adjacent molecules adopt slipped π-stacking arrangements, with distances of ca. 3.4 Å between the least squares planes of the molecules, and centroid–centroid separations of ca. 4.6 Å (the lattice parameter *a*). The stacks are arranged into 2-D layers so that molecules in adjacent stacks are close to co-planar, introducing relatively short contacts in the range 2.7–2.8 Å between one H atom of the first methylene group in the bromoalkyl chain and the 1-N atom of the neighbouring tetrazole rings. The alignment of neighbouring stacks into a 2-D arrangement is consistent with effective lateral packing of the alkyl chains: in each case, the H atoms of the methylene groups in one chain project into the gaps between methylene groups in the neighbouring chains. The 2-D layer arrangements are effectively identical in each of **2a**, **3a** and **4a**. Adjacent 2-D layers meet so as to bring the terminal CH_2–Br bonds into an offset co-linear alignment, forming 'Type I' Br···Br interactions, as classified previously by Pedireddi et al.[16] The intermolecular Br···Br distances lie in the range 3.4802(4)–3.5351(8) Å, considerably shorter than twice the bromine van der Waals radius (3.90 Å) and within the range of those values previously reported, 3.415–3.691 Å.[17–20]

Table 1. Selected bond lengths (Å) and angles (°) for **2a**, **3a** and **4a**

	2a	**3a**	**4a**
Bond lengths			
C(1)–C(2)	1.389(4)	1.389(4)	1.378(3)
C(2)–C(3)	1.399(4)	1.402(3)	1.395(3)
C(3)–C(4)	1.477(4)	1.463(3)	1.469(3)
C(4)–N(1)	1.352(4)	1.356(3)	1.360(3)
C(4)–N(2)	1.334(4)	1.340(3)	1.323(3)
N(1)–N(3)	1.324(4)	1.321(3)	1.324(3)
N(3)–N(4)	1.325(4)	1.333(3)	1.319(3)
N(4)–N(2)	1.330(3)	1.328(3)	1.329(3)
N(4)–C(5)	1.472(4)	1.463(3)	1.458(3)
Bond angles			
C(4)–N(1)–N(3)	106.1(3)	106.2(2)	105.7(2)
N(1)–N(3)–N(4)	105.9(2)	106.2(2)	106.35(19)
N(3)–N(4)–N(2)	114.2(2)	113.8(2)	113.7(2)
N(4)–N(2)–C(4)	101.4(3)	102.2(2)	102.1(2)
N(2)–C(4)–N(1)	112.4(3)	112.2(2)	112.2(2)

In the crystal structure of **2b**, the two tetrazole rings in each molecule are essentially co-planar (rms deviation of 10 fitted atoms=0.007 Å), but the plane of the central benzene ring forms a dihedral angle of 9.7(3)° with this plane. The bromobutyl chains form greater angles to the molecular plane (N4–C9–C11 and N6–C13–C15 both ca. 95.5°), and the terminal CH_2–Br bond vectors lie perpendicularly close to each other (Fig. 3). The arrangement of the central portions of the molecules in the crystal structure is closely comparable to that in **2a**, **3a** and **4a**. The least-squares planes of the π-stacked molecules are separated by ca. 3.5 Å, with centroid–centroid separations of ca. 4.4 Å. Adjacent molecules in the stacks are related by centres of inversion. The molecules in adjacent stacks are again close to co-planar, but with a slightly greater lateral offset along the long axes of the molecules in **2b** compared to **2a**. The introduction of a short H···H contact (ca. 2.29 Å) between adjacent benzene rings, and the twisting of these rings from the planes of the tetrazole rings may be attributed at least in part to alleviation of the steric constraints associated with this close contact. The terminal CH_2–Br bonds again form 'Type I' Br···Br interactions, with intermolecular Br···Br distances of 3.591(2) and 3.677(2) Å. It is noteworthy that while one of these Br···Br distances is closely comparable to those in **2a**, **3a** and **4a**, the second is significantly longer. This less-than-optimal intermolecular contact presumably contributes to the significantly lower melting point of **2b** (ca. 110 °C) compared to the isomeric **2a** (ca. 140 °C).

3. Conclusions

The reactions of 1,4-$(Bu_3SnN_4C)_2C_6H_4$ with 1,4-dibromobutane, 1,6-dibromohexane and 1,8-dibromooctane yield compounds containing pendant bromoalkyl groups with

substitution occurring at either 1-*N*,2-*N*′ or 2-*N*,2-*N*′. The crystal structures of three derivatives were obtained, including both the 1-*N*,2-*N*′ and 2-*N*,2-*N*′-isomers of one derivative. No cyclophane products were observed from any of the reactions. Similar reactions involving 1,3-dibromopropane, 1,5-dibromopentane and 1,7-dibromoheptane are currently being investigated, as are macrocyclic ring closure reactions with 1,4-$(Bu_3SnN_4C)_2C_6H_4$ and metal complexation reactions with the resulting macrocyclic ring.

4. Experimental

4.1. General

^1H and ^{13}C NMR (δ ppm; J Hz) spectra were recorded on a JOEL JNM-LA300 FT-NMR spectrometer using saturated $CDCl_3$ solutions with Me_4Si reference, unless indicated otherwise, with resolutions of 0.18 Hz and 0.01 ppm. Infrared spectra (cm^{-1}) were recorded as KBr discs or liquid films between KBr plates using a Nicolet Impact 410 FT-IR. Melting points were measured with a Stuart Scientific melting point apparatus (SMP1) without correction. Microanalysis was carried out at the Microanalytical Laboratory of University College, Dublin. Standard Schlenk techniques were used throughout.

4.2. Syntheses

1,4-$(Bu_3SnN_4C)_2C_6H_4$ (**1**) was prepared as described previously.[14] All other reagents were commercially obtained and used without further purification. *Caution*: owing to their potentially explosive nature, all preparations of and subsequent reactions with organotin azides and tetrazoles were conducted under an inert atmosphere behind a rigid safety screen.

The numbering scheme for the 1,4-bis-tetrazoles is shown in Figure 5 and all NMR assignments are based on these diagrams.

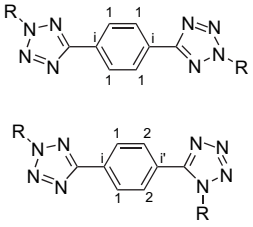


Figure 5. Labelling scheme used for central core in the 1,4-bis(tetrazole) derivatives.

4.3. General synthesis of compounds

1,4-$(Bu_3SnN_4C)_2C_6H_4$ (**1**) (10 g, 126.2 mmol) and the appropriate α,ω-dibromoalkane (300 mmol) were heated to 120 °C for 24 h, under nitrogen. After cooling, the excess α,ω-dibromoalkane was removed under reduced pressure to afford the mixture of isomers **a** and **b**, as well as some starting bis-tetrazole. These were seperated by column chromatography on silica gel (initially at the ratio of hexane/ethyl acetate 80:20, followed by the ratio 60:40). All compounds were recrystallised from chloroform.

4.3.1. 1,4-Bis[2-(4-bromobutyl)tetrazol-5-yl]benzene (2-*N*,2-*N*′) (2a). White solid. Anal. Calcd for $C_{16}H_{20}Br_2N_8$: C, 39.69; H, 4.16; N, 23.14. Found: C, 39.61; H, 4.15; N, 22.85; Yield: 64%, 3.91 g, 8.1 mmol; ν_{max} (KBr) 2958, 1609, 1584, 1538, 1503, 1443, 1384, 1357, 1254, 1222, 1190, 1035, 1006, 875, 782, 753 cm^{-1}; mp 138–142 °C; δ_H: 1.95 [m, 4H, CH_2], 2.75 [m, 4H, CH_2], 3.47 [t, 4H, J=6.6 Hz, CH_2Br], 4.74 [t, 4H, J=6.6 Hz, NCH_2], 8.28 [s, 4H, H^1–C_6H_4]; δ_C: 27.8 [CH_2], 29.2 [CH_2], 32.2 [CH_2], 52.3 [CH_2N], 127.3 [C^1–C_6H_4], 129.1 [i–C_6H_4], 164.6 [CN_4].

4.3.2. 1,4-Bis[2-(4-bromobutyl)tetrazol-5-yl]benzene (1-*N*,2-*N*′) (2b). White solid. Anal. Calcd for $C_{16}H_{20}Br_2N_8$: C, 39.69; H, 4.16; N, 23.14. Found: C, 39.92; H, 4.13; N, 23.04; Yield: 21%, 1.28 g, 2.6 mmol; mp 108–112 °C; ν_{max} (KBr) 2929, 2853, 1628, 1558, 1538, 1469, 1438, 1370, 1307, 1260, 1225, 1195, 1112, 1037, 1005, 847, 734, 645 cm^{-1}; δ_H: 1.95 [m, 4H, CH_2], 2.15 [m, 2H, CH_2], 2.28 [m, 2H, CH_2], 3.40 [t, 2H, J=6.6 Hz, CH_2Br], 3.47 [t, 2H, J=6.6 Hz, CH_2Br], 4.52 [t, 2H, J=6.6 Hz, N^1CH_2], 4.75 [t, 2H, J=6.6 Hz, N^2CH_2], 7.85 [d, 2H, J=6.6 Hz, H^2–C_6H_4], 8.38 [d, 2H, J=6.6 Hz, H^1–C_6H_4]; δ_C: 27.8 [CH_2], 28.2 [CH_2], 29.1 [CH_2], 29.2 [CH_2], 32.0 [CH_2], 32.1 [CH_2], 47.3 [CH_2N], 52.4 [CH_2N], 125.5 [i–C_6H_4], 127.7 [C^1–C_6H_4], 129.3 [C^2–C_6H_4], 130.3 [i′–C_6H_4], 153.8 [CN_4], 164.0 [CN_4].

4.3.3. 1,6-Bis[2-(6-bromohexyl)tetrazol-5-yl]benzene (2-*N*,2-*N*′) (3a). White solid. Anal. Calcd for $C_{20}H_{28}Br_2N_8$: C, 44.46; H, 5.22; N, 20.74. Found: C, 44.45; H, 5.20; N, 20.35; Yield: 65%, 4.43 g, 8.2 mmol; mp 104–106 °C; ν_{max} (KBr) 2931, 2862, 1610, 1580, 1543, 1515, 1449, 1396, 1352, 1293, 1250, 1182, 1150, 1082, 1041, 897, 783, 756 cm^{-1}; δ_H: 1.40 [m, 4H, CH_2], 1.55 [m, 4H, CH_2], 1.88 [m, 4H, CH_2], 2.11 [m, 4H, CH_2], 3.41 [t, 4H, J=6.6 Hz, CH_2Br], 4.69 [t, 4H, J=6.6 Hz, NCH_2], 8.28 [s, 4H, H^1–C_6H_4]; δ_C: 25.6 [CH_2], 27.5 [CH_2], 29.2 [CH_2], 32.4 [CH_2], 33.5 [CH_2], 53.1 [CH_2N], 127.3 [C^1–C_6H_4], 129.1 [i–C_6H_4], 164.5 [CN_4].

4.3.4. 1,6-Bis[2-(6-bromohexyl)tetrazol-5-yl]benzene (1-*N*,2-*N*′) (3b). White solid. Anal. Calcd for $C_{20}H_{28}Br_2N_8$: C, 44.46; H, 5.22; N, 20.74. Found: C, 44.40; H, 5.20; N, 20.45; Yield: 12%, 0.82 g, 1.5 mmol; mp 84–86 °C; ν_{max} (KBr) 2930, 2865, 1625, 1550, 1538, 1470, 1436, 1379, 1316, 1262, 1224, 1195, 1110, 1036, 1015, 846, 734, 649 cm^{-1}; δ_H: 1.46 [m, 4H, CH_2], 1.84 [m, 4H, CH_2], 2.05 [m, 8H, CH_2], 3.36 [t, 2H, J=6.6 Hz, CH_2Br], 3.41 [t, 2H, J=6.6 Hz, CH_2Br], 4.51 [t, 2H, J=6.6 Hz, N^1CH_2], 4.70 [t, 2H, J=6.6 Hz, N^2CH_2], 7.84 [d, 2H, J=6.6 Hz, H^2–C_6H_4], 8.32 [d, 2H, J=6.6 Hz, H^1–C_6H_4]; δ_C: 25.3 [CH_2], 25.4 [CH_2], 27.1 [CH_2], 27.2 [CH_2], 28.9 [CH_2], 29.3 [CH_2], 32.1 [CH_2], 32.2 [CH_2], 33.3 [CH_2], 33.4 [CH_2], 47.9 [CH_2N], 53.0 [CH_2N], 125.5 [i–C_6H_4], 127.7 [C^1–C_6H_4], 129.3 [C^2–C_6H_4], 130.3 [i′–C_6H_4], 153.8 [CN_4], 164.1 [CN_4].

4.3.5. 1,8-Bis[2-(8-bromooctyl)tetrazol-5-yl]benzene (2-*N*,2-*N*′) (4a). White solid. Anal. Calcd for $C_{24}H_{36}Br_2N_8$: C, 48.33; H, 6.08; N, 18.79. Found: C, 47.95; H, 6.08; N, 18.48; Yield: 68%, 5.12 g, 8.6 mmol; mp 88–94 °C; ν_{max} (KBr) 2929, 2852, 1629, 1557, 1468, 1430, 1354, 1357, 1266, 1226, 1198, 1048, 1006, 854, 744, 723, 647 cm^{-1}; δ_H: 1.39 [m, 16H, CH_2], 1.85 [m, 4H, CH_2], 2.08 [m, 4H, CH_2],

3.39 [t, 4H, J=6.6 Hz, CH_2Br], 4.67 [t, 4H, J=6.6 Hz, NCH_2], 8.28 [s, 4H, H^1–C_6H_4]; δ_C: 26.3 [CH_2], 27.9 [CH_2], 28.5 [CH_2], 28.7 [CH_2], 29.3 [CH_2], 32.7 [CH_2], 33.9 [CH_2], 53.3 [CH_2N], 127.3 [C^1–C_6H_4], 129.1 [i–C_6H_4], 164.5 [CN_4].

4.3.6. 1,8-Bis[2-(8-bromooctyl)tetrazol-5-yl]benzene (1-*N*,2-*N*′) (4b). White solid. Anal. Calcd for $C_{24}H_{36}Br_2N_8$: C, 48.33; H, 6.08; N, 18.79. Found: C, 48.16; H, 6.07; N, 18.58; Yield: 10%, 0.75 g, 1.3 mmol; mp 64–68 °C; ν_{max} (KBr) 2929, 2853, 1626, 1550, 1538, 1469, 1434, 1378, 1303, 1271, 1226, 1197, 1112, 1044, 1003, 848, 736, 645 cm^{-1}; δ_H: 1.29 [m, 8H, CH_2], 1.37 [m, 8H, CH_2], 1.82 [m, 4H, CH_2], 1.95 [m, 2H, CH_2], 2.09 [m, 2H, CH_2], 3.38 [t, 2H, J=6.6 Hz, CH_2Br], 3.40 [t, 2H, J=6.6 Hz, CH_2Br], 4.46 [t, 2H, J=6.6 Hz, N^1CH_2], 4.69 [t, 2H, J=6.6 Hz, N^2CH_2], 7.82 [d, 2H, J=6.6 Hz, H^2–C_6H_4], 8.36 [d, 2H, J=6.6 Hz, H^1–C_6H_4]; δ_C: 26.2 [CH_2], 26.3 [CH_2], 27.9 [CH_2], 28.0 [CH_2], 28.4 [CH_2], 28.5 [CH_2], 28.7 [CH_2], 29.3 [CH_2], 29.7 [CH_2], 32.6 [CH_2], 32.7 [CH_2], 33.8 [CH_2], 48.2 [CH_2N], 53.4 [CH_2N], 125.7 [i–C_6H_4], 127.6 [C^1–C_6H_4], 129.3 [C^2–C_6H_4], 130.3 [i′–C_6H_4], 153.8 [CN_4], 163.8 [CN_4].

4.4. X-ray crystallography

Suitable crystals of **2a**, **2b** and **4a** for X-ray study were obtained by recrystallisation from chloroform solutions. Data were collected at 180(2) K on a Bruker Nonius X8 APEX II diffractometer,[21] and a multi-scan correction was applied.[22] The structures were refined against F^2 using all data.[23] Hydrogen atoms were placed at calculated positions and refined using a riding model.

4.4.1. Compound 2a. *Crystal data*: $C_{16}H_{20}Br_2N_8$, M=484.22, triclinic, a=4.5722(7), b=5.8805(9), c=18.119(3) Å, α=96.943(6), β=96.426(6), γ=101.287(6)°, U=469.61(13) Å^3, space group $P1$, Z=1, μ(Mo−Kα)=4.334 mm^{-1}. 7346 data (1717 unique, R_{int}=0.0386) were measured in the range 3.59<θ<25.74°. $R_1(I>2\sigma(I))$=0.0321 and wR_2(all data)=0.0815. Goodness of fit on F^2=1.06. CCDC No. 604247.

4.4.2. Compound 2b. *Crystal data*: $C_{16}H_{20}Br_2N_8$, M=484.22, triclinic, a=6.7256(14), b=8.1427(19), c=17.186(4) Å, α=96.972(8), β=92.193(8), γ=90.034(8)°, U=933.5(4) Å^3, space group $P1$, Z=2, μ(Mo−Kα)=4.361 mm^{-1}. 11127 data (3428 unique, R_{int}=0.0607) were measured in the range 3.59<θ<25.84°. $R_1(I>2\sigma(I))$=0.0906 and wR_2(all data)=0.2519. Goodness of fit on F^2=1.04. CCDC No. 604248.

4.4.3. Compound 4a. *Crystal data*: $C_{24}H_{36}Br_2N_8$, M=596.43, triclinic, a=4.6665(5), b=5.6593(5), c=25.284(2) Å, α=92.812(3), β=90.773(4), γ=102.138(3)°, U=651.82(10) Å^3, space group $P1$, Z=1, μ(Mo−Kα)=3.138 mm^{-1}. 11318 data (2448 unique, R_{int}=0.0477) were measured in the range 3.69<θ<25.84°. $R_1(I>2\sigma(I))$=0.0338 and wR_2(all data)=0.0863. Goodness of fit on F^2=1.04. CCDC No. 604249.

4.5. Crystallographic data

Crystallographic data for **2a**, **2b** and **4a** have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk.

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Synthesis of large generation poly(propyl ether imine) (PETIM) dendrimers

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Abstract—Large generation poly(propyl ether imine) (PETIM) dendrimers are synthesized in iterative synthetic cycles of two reductions and two Michael addition reactions. Dendrimers up to sixth generation, containing up to 128 peripheral functionalities, are synthesized. Growth of the PETIM dendrimers, possessing a tertiary amine as the branch juncture and an ether as the linker component, is assessed systematically by routine spectroscopic methods. The peripheries of these dendrimers possess either alcohols, amines, carboxylic acids, esters, or nitriles, thereby opening up possibilities for varied studies involving PETIM dendrimers.

1. Introduction

The number of studies involving dendrimers has increased remarkably, ever since the dendrimers came to prominence in the chemical literature. The unique architectures, nanometric dimensions, ability to exercise *endo*- and *exo*-receptor properties, and monomolecular features have, in part, contributed to the general acceptance of dendrimers in many varied types of studies.[1] More often, monomers of the type AB_2, AB_3, and occasionally AB_4 and higher order are subjected to grow uniformly, leading, thereby, to a dendritic architecture.[2] Prominent among the dendrimers are the poly(amido amine),[3] poly(propylene imine),[4] poly(benzyl aryl ether),[5] polysilane,[6] polyphosphane,[7] polylysine,[8] and triallyl phenol based dendrimers.[9] Few of these dendrimers, namely, poly(amido amine), poly(propylene imine), polyphosphane, and triallyl phenol also represent the highest generation systems known in the literature. Synthesis of high generation dendrimers, useful for exploring the nature of the dendritic architecture, depends critically on the nature of the constituent monomers, their reactivities, and the method of their preparation. Larger generation dendrimers tend to provide a 'dendritic state', in which the peripheries become more dense than the corresponding lower generation dendrimers. A few common features of currently known large generation dendrimer synthesis are: (i) a divergent synthetic route for their preparation, (ii) the use of linear linkers, and (iii) avoiding protection/deprotection synthetic sequences. In a program aimed to develop dendrimers initiated with 3-amino-propan-1-ol as the monomer, a series of lower generation poly(propyl ether imine) (PETIM) dendrimers were reported previously.[10] A tertiary amine and an ether functionality form the branch juncture and the linker of the PETIM dendrimers, respectively. Iterative synthetic sequences of two alternate Michael additions and two reduction reactions were established to synthesize the PETIM dendrimers. Continuing efforts to produce larger generation dendrimers led to the isolation of PETIM dendrimers up to sixth generation, with 128 peripheral functionalities. Details of the synthesis of the larger generation PETIM dendrimers are presented herein.

2. Results and discussion

2.1. Synthesis

A tertiary amine branch juncture and an ether linker represent an AB_2 type monomer and, in PETIM dendrimers, 3-amino-propan-1-ol constitutes the required monomer. Synthesis of the PETIM dendrimers was initiated from a Michael addition reaction between acrylonitrile and water, to afford 2-cyanoethyl ether. Subsequent reduction of the nitrile groups, Michael addition with *tert*-butyl acrylate, reduction of the ester to an alcohol, and Michael addition of the resulting alcohol with acrylonitrile form an iterative cycle for the divergent synthesis of PETIM dendrimers. Three generations of PETIM dendrimers with up to 16 peripheral functionalities were synthesized previously,[10] thereby evolving the synthetic route to this new class of dendrimers. An advantage of the synthetic protocol is that it allows installation of varied functional groups, namely an acid, an alcohol, an amine, an ester, and a nitrile at the peripheries of the dendrimers. Synthesis of larger generation

Keywords: Dendrimers; Iterative synthesis; Michael addition; Raney cobalt.
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dendrimers was initiated from the third generation ester dendrimer (Fig. 1). Thus, reduction of dendrimer containing 16 *tert*-butyl esters with $LiAlH_4$, provided the third generation dendrimer **1** containing 16 alcohol group (Scheme 1). Complete removal of the inorganic salts was possible through solubilization of the crude product in MeOH, filtration, and evaporation of MeOH. Repetition of the process with MeOH, followed by $CHCl_3$, a few times led to the isolation of alcohol containing dendrimers with excellent purities and yields. Michael addition of the resulting alcohol **1** with excess acrylonitrile, in the presence of aq NaOH (cat.), provided the 16-nitrile containing dendrimer **2**, quantitatively. Excess acrylonitrile was transformed to an intractable polymer and 2-cyanoethyl ether, both of which could be separated through column chromatography (Al_2O_3 (neutral)). Reduction of nitrile **2** to amine **3** was conducted in the presence of Raney Co catalyst, under a moderately high pressure of H_2 (46 atm). The reduction reaction required control of temperature, pressure, and the solution concentrations. Thus, dilute solutions of the nitrile in MeOH (0.26 mM) at a temperature of 70 °C and at a pressure of 46 atm were found to be optimal for the reduction reaction. The progress of the reaction was followed upon analyzing the IR spectrum of an aliquot of the reaction mixture. The complete disappearance of nitrile stretching frequency at 2251 cm^{-1} was used to confirm the reduction reaction. Michael addition of 16 amine-terminated dendrimer **3** with *tert*-butyl acrylate in MeOH led to the isolation of fourth generation 32 ester-functionalized dendrimer **4**, in excellent yields. Solubility differences between the amine and the ester in hexane allowed facile separation of the ester from the amine component. The ester dendrimer, devoid of polar impurities was purified further by column chromatography (Al_2O_3 (neutral)). Iteration of the synthetic sequence of (i) reduction of ester **4** to alcohol **5**, (ii) reaction of alcohol **5** with acrylonitrile to afford nitrile **6**, (iii) reduction of nitrile **6** to amine **7**, and (iv) reaction of amine **7** with *tert*-butyl acrylate led to the preparation of fifth generation 64 ester-functionalized PETIM dendrimer **8**. Continuation of the iterative cycle, starting from ester **8** afforded alcohol **9**, nitrile **10**, amine **11**, and 128 ester-functionalized sixth generation dendrimer **12**. Molecular structures of the four, five, and six generation dendrimers are shown in Figures 1 and 2.

2.2. Characterization

Characterization of the newly formed dendrimers was possible through routine physical methods of analysis. As the synthetic sequence involved functional group changes at the peripheries of the dendrimers, following the IR spectral changes was useful to assess the presence or disappearance of the functional groups. Thus, spectral frequencies at 2251 cm^{-1} (–CN), 3460 cm^{-1} ($–NH_2$), 1729 cm^{-1} ($–CO_2{}^tBu$), and 3390 cm^{-1} (–OH) were diagnostic to estimate the presence or absence of the respective functional groups. The IR spectral changes for the conversion of the fifth generation ester **8** to the sixth generation ester **12** are compiled in Figure 3. Such a pattern of IR spectral changes could be observed for all other dendrimers, thereby IR spectroscopy became a diagnostic tool to assess the growth of dendrimers. Characterization of the newly formed dendrimers by ^1H and ^{13}C NMR spectroscopies further confirmed the constitution and the growth of dendrimers. The relative change in the chemical shifts of the $–CH_2–$ group adjacent to the peripheral functionality was observed to be a characteristic feature of each dendrimer growth reaction.

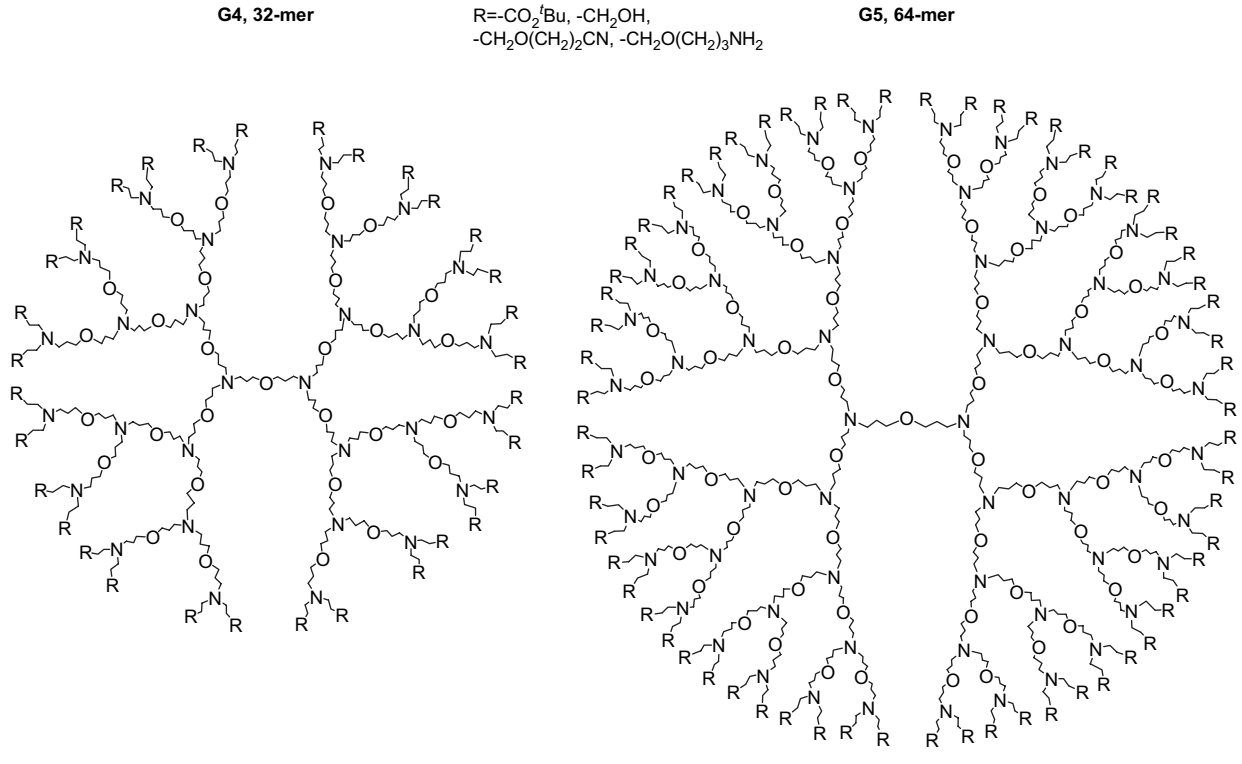
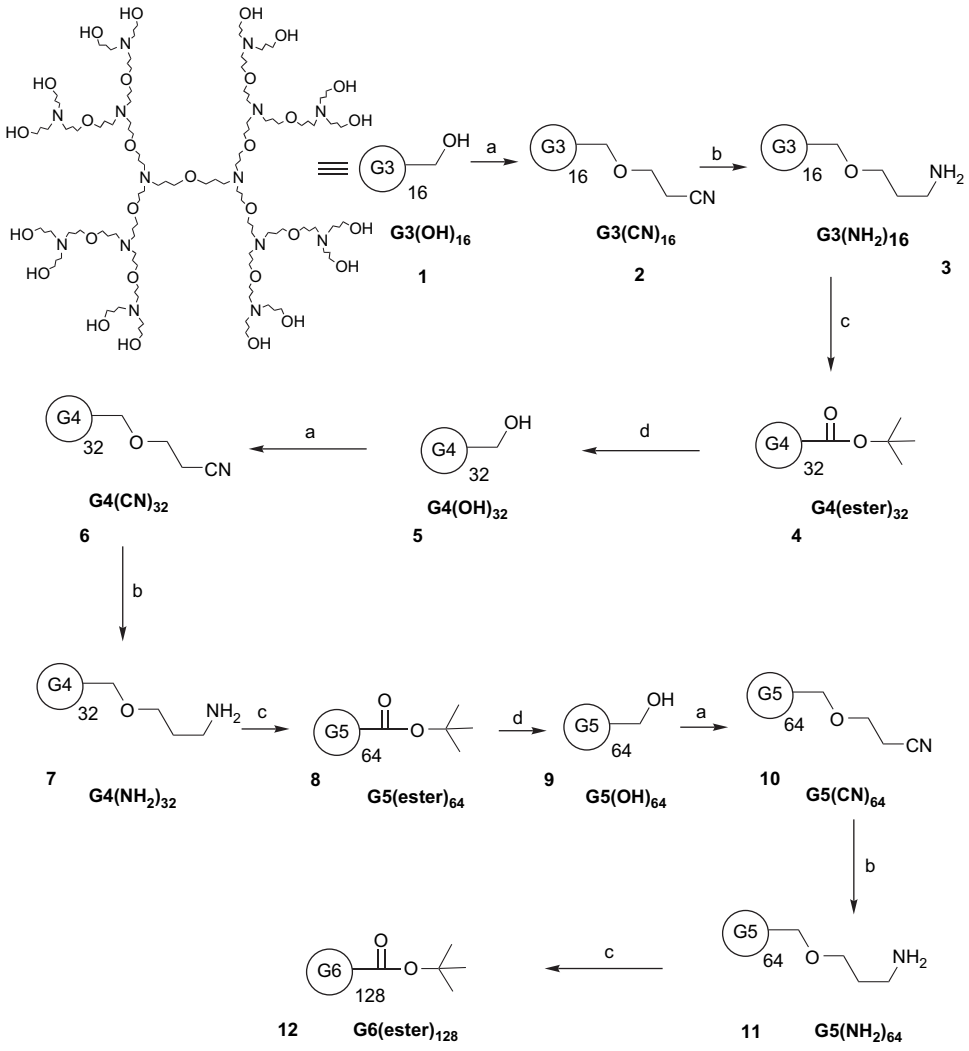


Figure 1. Molecular structures of the fourth and the fifth generation PETIM dendrimers.



Scheme 1. Reagents and conditions: (a) 40% aq NaOH (cat.), acrylonitrile, rt, 15 h; (b) Raney Co, H_2O, H_2 (46 bar), 3 h, 70 °C; (c) *tert*-butyl acrylate, MeOH, rt, 72 h; (d) $LiAlH_4$, THF, 0 °C to rt, 4 h.

Thus, disappearance of resonances at ~2.60 ppm and appearance of resonances at ~1.70 and ~2.50 ppm signified the reduction of peripheral nitrile functionality and formation of aminopropyl functionality, respectively. Ester-terminated dendrimers showed the $–CH_2–CH_2–CO_2{}^tBu$ protons at 3.40 and 2.34 ppm and, upon reduction of the esters with $LiAlH_4$, disappearance of the peak at 2.34 ppm and appearance of a resonance at ~3.70 ppm, corresponding to the formation of $–CH_2–CH_2OH$ peripheral functionalities, were observed. Finally, Michael addition of the alcohol-functionalized dendrimers with acrylonitrile provided a spectrum showing disappearance of the peak at ~3.70 ppm and appearance of a set of triplet peaks at ~3.55 and 3.65 ppm. The relative intensity changes of the respective resonances confirmed the constitution of the dendrimers. The series of ^1H NMR spectra, corresponding to the growth of G5-(ester)$_{64}$ (**8**) to the G6-(ester)$_{128}$ (**12**), are presented in Figure 4.

Changes at the peripheries of the dendrimers as a result of advancing the generations could be confirmed by ^{13}C NMR spectroscopy. Complete disappearance of –CN resonance in the ^{13}C NMR spectrum at ~117.9 ppm and the appearance of carbonyl group resonance of the ester functionality at ~172 ppm provided the completion of nitrile reduction to amine followed by Michael addition with *tert*-butyl acrylate. Similarly reduction of the ester to the alcohol (CH_2OH ~62 ppm) and the Michael addition of alcohol to the nitrile could be ascertained by appropriate changes in the ^{13}C NMR resonances.

Characterization of the dendrimers by gel permeation chromatography (GPC), MALDI-TOF mass spectrometry, and elemental analysis was also performed. GPC was performed on a Phenogel (1000 Å) semipreparative column (300× 7.80 mm), and eluted with THF (flow rate: 1 mL/min), using a refractive index detector. The GPC chromatograms of each *tert*-butyl ester terminated poly(propyl ether imine) dendrimers exhibited decreasing retention time from first generation dendrimer to the sixth generation poly(propyl ether imine) dendrimers (Fig. 5).

MALDI-TOF mass spectra up to four generations could be secured (Table 1). The observed mass spectrometric peaks corresponded to the $[M]^+$ or $[M+1]^+$ molecular ion largely. The mass spectrum of fifth and sixth generation dendrimers could not be secured, however. Elemental composition

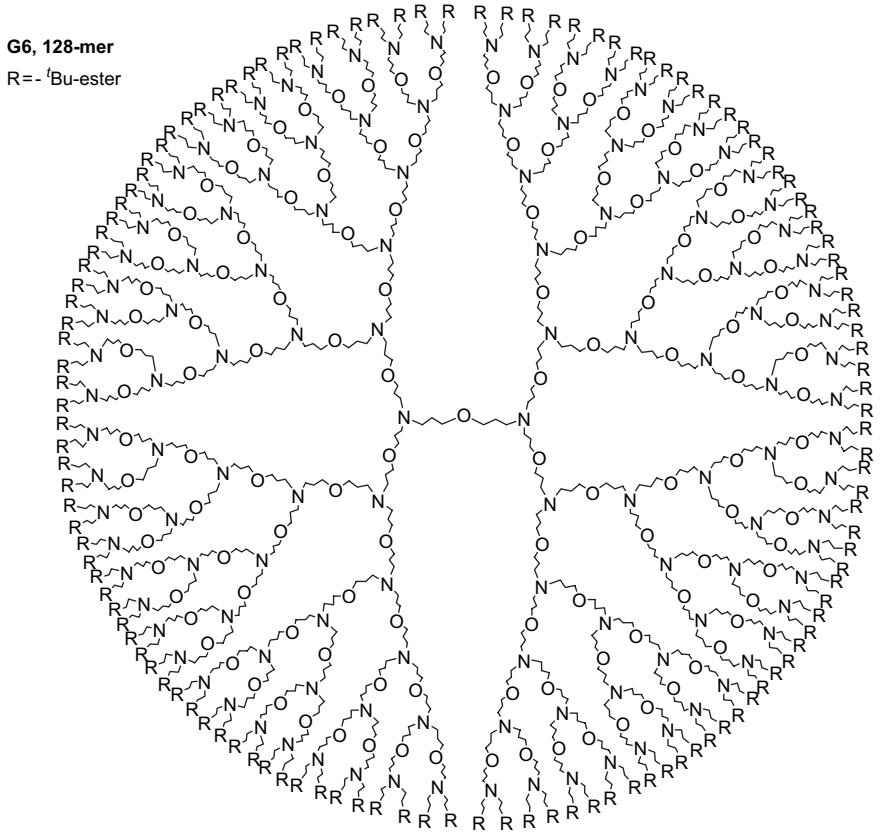


Figure 2. Molecular structure of the sixth generation of ester-functionalized PETIM dendrimer.

analyses were performed mostly with the ester-functionalized dendrimers. The alcohol and the amine-terminated dendrimers were hygroscopic and their elemental analysis could not be routinely secured.

3. Conclusion

Following the earlier synthesis of PETIM dendrimers up to three generations, the present report establishes the synthesis of PETIM dendrimers up to the sixth generation, presenting 128 peripheral functionalities at their peripheries. Facile synthesis, with high yields in each synthetic step, and easy characterization made these PETIM dendrimers attractive for further studies. Accordingly, studies of the *endo*- and *exo*-receptor properties of the PETIM dendrimers are currently being undertaken.

4. Experimental

4.1. General methods

Chemicals were purchased from commercial sources and were used without further purification. Solvents were dried and distilled according to literature procedures. Analytical TLC was performed on commercial Merck plates coated with alumina GF_{254} (0.25 mm). Neutral alumina was used for column chromatography. Microanalyses were performed on an automated C, H, and N analyzer. ^{1}H and ^{13}C NMR spectral analyses were performed on a 300 and 75.5 MHz spectrometer, respectively, with residual solvent signal acting as the internal standard. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet.

4.2. General procedure for Michael addition of acrylonitrile

Acrylonitrile and aq NaOH (40%) were added to the alcohol-functionalized dendrimer at room temperature and the mixture was allowed to stir for 15 h. Excess acrylonitrile was added further and the reaction mixture left to stir for another 6 h, then diluted with $CHCl_3$, filtered through Celite, and the filtrate concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (neutral Al_2O_3), to afford the desired compound.

4.3. General procedure for the reduction of nitrile-functionalized PETIM dendrimer using Raney Co and subsequent Michael addition of the resulting amines

The nitrile-functionalized PETIM dendrimer was transferred to a hydrogenation reactor vessel and was mixed with Raney Co in H_2O. The mixture was hydrogenated (H_2, 46 atm) at 70 °C for 3 h. The reaction mixture was cooled and filtered through a Celite pad. The filtrate was concentrated to afford the corresponding amine-functionalized dendrimer. A solution of the crude amine in MeOH was treated with excess *tert*-butyl acrylate and stirred for 72 h at room temperature. Excess *tert*-butyl acrylate and MeOH were removed under reduced pressure and the crude

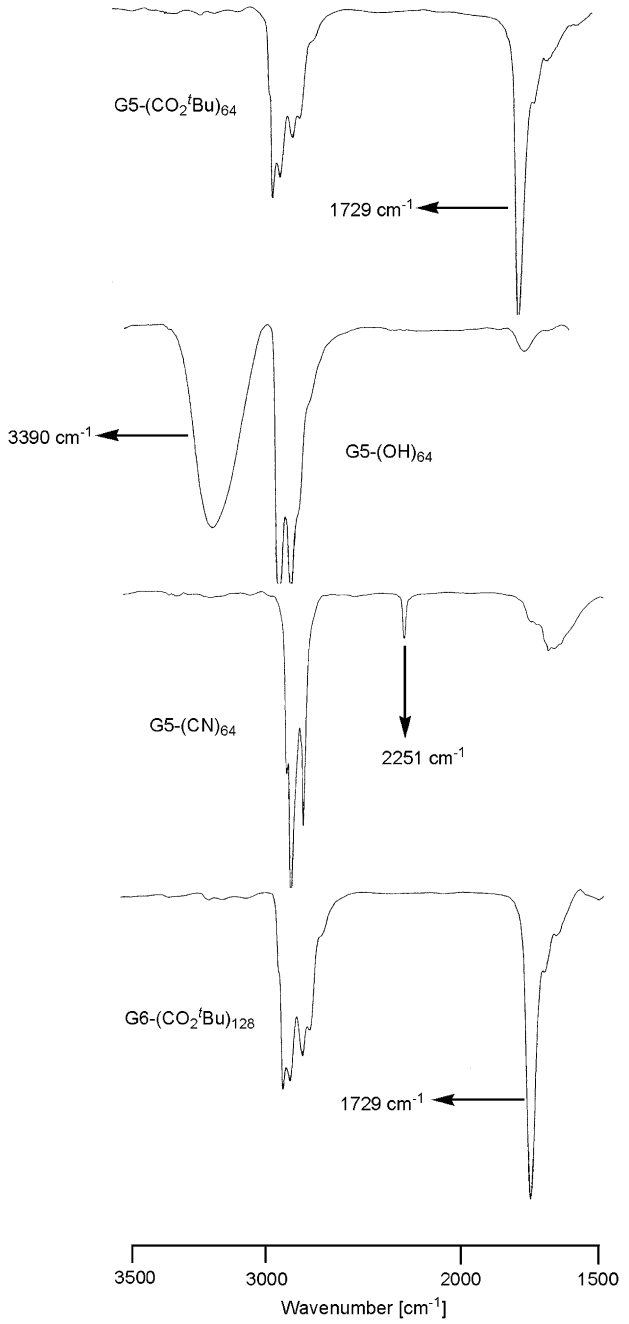


Figure 3. IR spectral comparison of the conversion of fifth generation ester **8** to sixth generation ester **12**.

product was purified by column chromatography (neutral Al_2O_3).

4.4. General procedure for reduction of *tert*-butyl esters

A solution of the ester-functionalized dendrimer in THF was added drop-wise to a suspension of $LiAlH_4$ (2.0 equiv per one ester group) in THF over a period of 15 min, at 0 °C, and the stirring was continued for 4 h at room temperature. The reaction mixture was cooled to 0 °C, quenched with excess ice, passed through Celite, and the filtrate concentrated under reduced pressure. The inorganic material was precipitated using MeOH, filtered, and the filtrate concentrated. The alcohol-functionalized PETIM dendrimer was obtained upon extraction of the crude material with $CHCl_3$ and removal of the solvents.

4.4.1. G3-$(CN)_{16}$ (2). A mixture of **1** (0.73 g), acrylonitrile (0.63 mL), and aq NaOH (40%, 53 μL) was stirred for 15 h. Acrylonitrile (1 mL) was added, the reaction mixture stirred for 6 h and worked up as described in Section 4.2 to obtain **2**, as a colorless liquid (0.93 g, 94%). TLC (Al_2O_3): R_f 0.45 ($CHCl_3$/MeOH=94:6). FTIR (neat) ν: 2250, 1466, 1367, 1116. MALDI-TOF *m/z*: 3292.36 $[M]^+$ (100%), 3066.23 (30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.68 (m, 84H), 2.46 (m, 84H), 2.59 (t, 32H, J=6.3 Hz), 3.40 (t, 52H, J=6.0 Hz), 3.51 (t, 32H, J=6.0 Hz), 3.63 (t, 32H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 18.8, 27.3, 27.4, 50.5, 50.8, 65.3, 69.1, 69.2, 69.3, 69.4, 117.9. Anal. Calcd for $C_{174}H_{316}N_{30}O_{29}$: C, 63.47; H, 9.68; N, 12.76. Found: C, 63.33; H, 9.69; N, 12.59.

4.4.2. G4-$(CO_2{}^tBu)_{32}$ (4). The nitrile derivative **2** (0.20 g) was added with Raney Co (0.80 g) in water (150 mL) and the reaction was continued further as given in Section 4.3 to afford amine **3** derivative. A solution of amine in MeOH (5 mL) was treated with *tert*-butyl acrylate (3 mL) and the reaction was followed as given in Section 4.2 to afford ester **4**, as a colorless liquid (0.42 g, 93% combined yield for nitrile reduction and Michael addition reaction). TLC (Al_2O_3): R_f 0.52 ($CHCl_3$/MeOH=97:3). FTIR (neat) ν: 1730, 1462, 1367, 1157. MALDI-TOF *m/z*: 7465.46 $[M+Li]^+$ (99%), 7408.09 (100%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 288H), 1.68 (q, 116H, J=6.9 Hz), 2.34 (t, 64H, J=7.2 Hz), 2.47 (t, 116H, J=6.9 Hz), 2.72 (t, 64H, J=7.5 Hz), 3.39 (t, 116H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 27.4, 27.7, 28.1, 33.8, 47.4, 50.5, 50.8, 68.9, 69.2, 69.3, 80.1, 172.0. Anal. Calcd for $C_{398}H_{764}N_{30}O_{93}$: C, 64.02; H, 10.25; N, 5.63. Found: C, 64.12; H, 9.92; N, 5.69.

4.4.3. G4-$(OH)_{32}$ (5). To a suspension of $LiAlH_4$ (0.20 g) in THF (5 mL), **4** (0.60 g) in THF (20 mL) was added drop-wise, at 0 °C, the reaction continued further as described in Section 4.4 to obtain **5**, as a colorless liquid (0.41 g, 98%). FTIR (neat) ν: 3388, 1658, 1469, 1370, 1114, 1059. MALDI-TOF *m/z*: 5217.12 $[M+H]^+$ (100%), 5158.88 (78%), 5100.23 (30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (m, 180H), 2.50 (m, 116H), 2.60 (t, 64H, J=6.6 Hz), 3.41 (m, 116H), 3.70 (t, 64H, J=5.7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 26.9, 27.2, 28.7, 28.77, 50.7, 50.8, 50.9, 52.7, 62.3, 68.8, 69.1, 69.2.

4.4.4. G4-$(CN)_{32}$ (6). A mixture of **5** (0.40 g), acrylonitrile (0.32 mL), and aq NaOH (40%, 27 μL) was stirred for 15 h. Acrylonitrile (0.80 mL) was added further, left to stir for 6 h, and worked up as described in Section 4.2 to obtain **6**, as a colorless liquid (0.49 g, 93%). TLC (Al_2O_3): R_f 0.60 ($CHCl_3$/MeOH=92:8). FTIR (neat) ν: 2251, 1467, 1367, 1117. MALDI-TOF *m/z*: 6913.23 $[M]^+$ (18%), 6460.28 (100%), 6686.85 (45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.69 (m, 180H), 2.48 (m, 180H), 2.60 (t, 64H, J=6.0 Hz), 3.41 (t, 116H, J=6 Hz), 3.52 (t, 64H, J=6.3 Hz), 3.63 (t, 64H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 18.9, 27.3, 27.4, 50.5, 50.8, 65.3, 69.1, 69.20, 69.24, 69.4, 118.0.

4.4.5. G5-$(CO_2{}^tBu)_{64}$ (8). The nitrile derivative **6** (0.21 g) was added with Raney Co (0.6 g) in water (150 mL) and

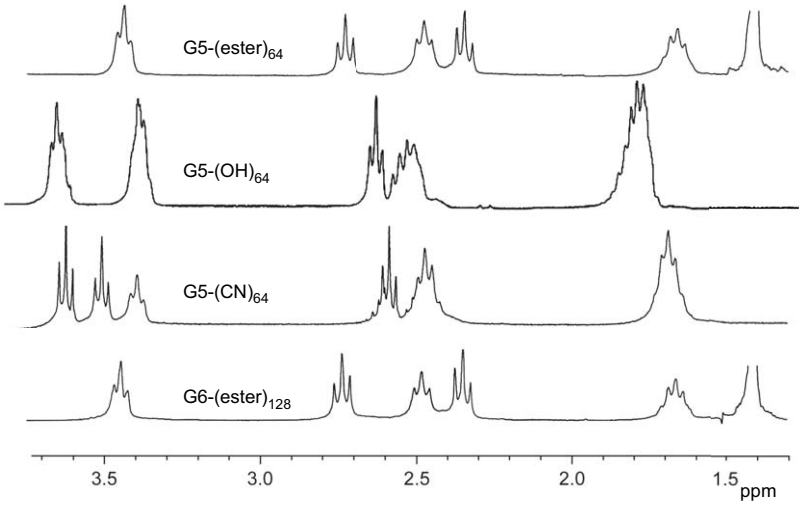


Figure 4. ^{1}H NMR spectral changes during the conversion of the fifth generation ester **8** to the sixth generation ester **12**.

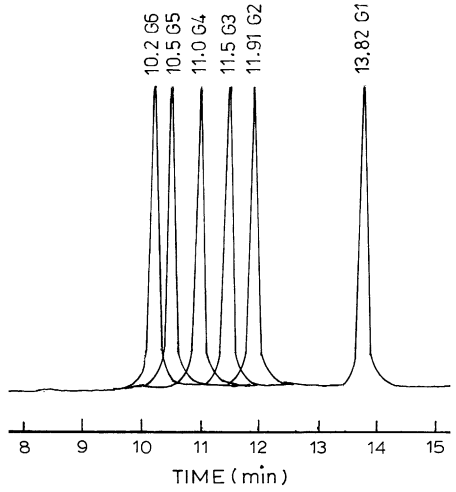


Figure 5. Gel permeation chromatography traces of *tert*-butyl ester group functionalized PETIM dendrimers.

Table 1. Physical characteristics of PETIM dendrimers

Compound[a]	Molecular formula	Molecular mass[b]	R_g (Å)[11]
G1-($CO_2{}^tBu$)$_4$	$C_{34}H_{64}O_9N_2$	644.88 (645.47)	5.65
G1-(OH)$_4$	$C_{18}H_{40}O_5N_2$	364.52 (365.30)	
G1-(CN)$_4$	$C_{30}H_{52}O_5N_6$	576.77 (577.41)	
G1-(NH_2)$_4$	$C_{30}H_{68}O_5N_6$	592.90 (594.40)	
G2-($CO_2{}^tBu$)$_8$	$C_{86}H_{164}O_{21}N_6$	1618.25 (1618.40)	8.90
G2-(OH)$_8$	$C_{54}H_{116}O_{13}N_6$	1057.53 (1087)	
G2-(CN)$_8$	$C_{78}H_{140}O_{13}N_{14}$	1482.032 (1482)	
G2-(NH_2)$_8$	$C_{78}H_{172}O_{13}N_{14}$	1514.29	
G3-($CO_2{}^tBu$)$_{16}$	$C_{190}H_{364}O_{45}N_{14}$	3564.99 (3563.80)	14.14
G3-(OH)$_{16}$	$C_{126}H_{268}O_{29}N_{14}$	2443.55 (2442.73)	
G3-(CN)$_{16}$	$C_{174}H_{316}O_{29}N_{30}$	3292.55 (3292.37)	
G3-(NH_2)$_{16}$	$C_{174}H_{380}O_{29}N_{30}$	3357.06	
G4-($CO_2{}^tBu$)$_{32}$	$C_{398}H_{764}O_{93}N_{30}$	7458.47 (7465.46)	17.73
G4-(OH)$_{32}$	$C_{270}H_{572}O_{61}N_{30}$	5215.60 (5217.14)	
G4-(CN)$_{32}$	$C_{366}H_{668}O_{61}N_{62}$	6913.60 (6913.23)	
G4-(NH_2)$_{32}$	$C_{366}H_{796}O_{61}N_{62}$	7042.62	
G5-($CO_2{}^tBu$)$_{64}$	$C_{814}H_{1564}O_{189}N_{62}$	15245.43	21.13
G5-(OH)$_{64}$	$C_{558}H_{1180}O_{125}N_{62}$	10759.68	
G5-(CN)$_{64}$	$C_{750}H_{1372}O_{125}N_{126}$	14155.70	
G5-(NH_2)$_{64}$	$C_{750}H_{1628}O_{125}N_{126}$	14413.72	
G6-($CO_2{}^tBu$)$_{128}$	$C_{1646}H_{3164}O_{381}N_{126}$	30819.35	26.63

[a] Codes for various dendrimers.
[b] Molecular mass obtained from mass spectrometric analysis is given in parenthesis.

the reaction was continued further as given in Section 4.2 to afford amine **7** derivative. A solution of amine **7** in MeOH (3 mL) was treated with *tert*-butyl acrylate (2.84 mL) and the reaction was followed as given in Section 4.3 to afford **8**, as a colorless liquid (0.36 g, 78% combined yield for nitrile reduction and Michael addition reaction). TLC (Al_2O_3): R_f 0.66 ($CHCl_3$/MeOH=95:5). FTIR (neat) ν: 1729, 1462, 1367, 1157. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 576H), 1.69 (q, 244H, J=6.3 Hz), 2.34 (t, 128H, J=6.9 Hz), 2.47 (t, 244H, J=6.9 Hz), 2.71 (t, 128H, J=6.9 Hz), 3.39 (t, 244H, J=6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 27.5, 27.7, 28.1, 33.8, 49.4, 50.6, 50.9, 69.0, 69.3, 80.2, 172.1. Anal. Calcd for $C_{398}H_{764}N_{30}O_{93}$: C, 64.09; H, 10.33; N, 5.71. Found: C, 63.89; H, 9.92; N, 5.45.

4.4.6. G5-(OH)$_{64}$ (9). To a suspension of $LiAlH_4$ (0.13 g) in THF (5 mL), **8** (0.4 g) in THF (15 mL) was added drop-wise, at 0 °C, the reaction continued further as described in the Section 4.4 to obtain **9** quantitatively, as a colorless liquid. FTIR (neat) ν: 3384, 1656, 1464, 1371, 1113, 1058. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.72 (m, 372H), 2.51 (m, 244H), 2.60 (t, 128H, J=6.6 Hz), 3.41 (m, 244H), 3.70 (t, 128H, J=5.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 26.9, 27.2, 28.7, 29.8, 50.7, 50.8, 50.9, 52.8, 62.3, 62.6, 68.8, 69.1, 69.2.

4.4.7. G5-(CN)$_{64}$ (10). A mixture of **9** (0.55 g), acrylonitrile (0.43 mL), and aq NaOH (40%, 72 μL) was stirred for 15 h. Acrylonitrile (0.43 mL) was added further, left to stir for 6 h, and worked up as described in Section 4.2 to obtain **10**, as a colorless liquid (0.66 g, 91%). TLC (Al_2O_3): R_f 0.46 ($CHCl_3$/MeOH=92:8). FTIR (neat) ν: 2251, 1464, 1377, 1115. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (m, 372H), 2.48 (m, 372H), 2.60 (t, 128H, J=6.0 Hz), 3.41 (t, 244H, J=6 Hz), 3.52 (t, 128H, J=6.3 Hz), 3.64 (t, 128H, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 18.9, 27.3, 27.4, 50.5, 50.8, 65.3, 69.1, 69.2, 69.3, 69.4, 118.0.

4.4.8. G6-($CO_2{}^tBu$)$_{128}$ (12). The nitrile derivative **10** (0.10 g) was added with Raney Co (0.5 g) in water (120 mL) and the reaction was continued further as given in Section 4.3 to afford amine **11** derivative. A solution of amine **11** in MeOH (2 mL) was treated with excess *tert*-butyl

acrylate (1.32 mL) and the reaction was followed as given in Section 4.3 to afford **12**, as a colorless liquid (0.16 g, 73% combined yield for nitrile reduction and Michael addition reaction). TLC (Al_2O_3): R_f 0.6 ($CHCl_3$/MeOH=93:7). FTIR (neat) ν: 1729, 1458, 1367, 1157. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 1152H), 1.69 (q, 500H, J=6.9 Hz), 2.34 (t, 256H, J=7.2 Hz), 2.47 (t, 500H, J=7.2 Hz), 2.71 (t, 256H, J=7.2 Hz), 3.39 (t, 500H, J=6.9 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 27.3, 27.6, 28.1, 33.7, 49.4, 50.5, 50.8, 68.9, 69.2, 69.3, 80.1, 172.1.

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Synthesis of chlorine-containing angucycline BE-23254 and its analogs

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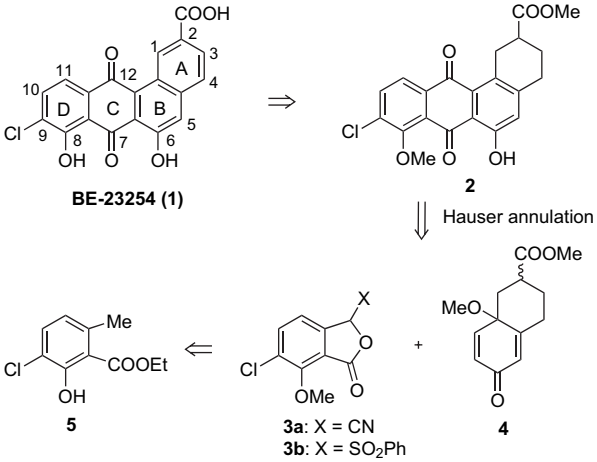
Abstract—The total synthesis of BE-23254, an unusual angucycline antibiotic is reported. This is achieved by adopting a Hauser annulation and a DDQ-promoted aromatization as the key steps. The strategy has been generalized for the synthesis of several analogs of the target molecule. A regioselective preparation of chlorine-containing phenols is also described.

1. Introduction

Angucyclines and angucyclinones are a large group of quinonoid natural products characterized by a benz[*a*]anthraquinone or a variant thereof as the core structure originating from a decaketide chain precursor.[1,2] This class of compounds often displays a broad spectrum of biological activities, which include antiviral and antitumor activities, cytotoxic activity against various cancer cell lines, inhibition of angiogenesis and platelet aggregation, and inhibitory activity against the pentagastrin-stimulated acid secretion. BE-23254 (**1**), an unusual angucycline antibiotic with aromatic A ring was isolated by Okabe et al.[3] in 1992 from *Streptomyces* sp. A 23254. It was reported to possess activity against the human colon cancer DLD-1 (IC_{50} 0.75 μg mL^{-1}). It is structurally unique in that it is the only member of angucyclines to contain a chlorine atom at the C-9 position of the ring skeleton. The methyl group at C-3, which is present in almost all other angucyclines numbering about 150, is absent in BE-23254 (**1**). In addition, the presence of a carboxylic acid at the C-2 position of BE-23254 is a rare structural feature of angucycline antibiotics. These unusual structural features coupled with its bioactivity prompted us to execute a short and efficient total synthesis of the molecule that has been the subject of a recent communication[4] from our laboratory. We now report a full account of the investigation and the synthesis of analogs of the target molecule.

2. Synthetic strategy

During the past two decades, a good number of methodologies have been developed and employed for the total synthesis of angucycline targets.[5] While the Diels–Alder strategy has been very successful for the total syntheses of complex angucyclines, we introduced the notion of employing Hauser annulation[6a] as a complementary means.[6] We were particularly attracted by the unambiguous regiochemical integrity of the methodology in addition to the mildness of the reaction conditions. The retrosynthetic disconnections for BE-23254 (**1**) featuring a Hauser annulation are shown in Scheme 1. It was planned to condense naphthalenone **4** (AB ring synthon) with the isobenzofuranones **3a** and **3b** (D ring synthons) for the regiospecific fabrication of the tetracyclic framework **2**. DDQ-promoted aromatization of



Scheme 1. Retrosynthetic plan for BE-23254 (**1**).

Keywords: Angucyclines; Hauser annulation; Naphthalenone; Chlorinative aromatization.
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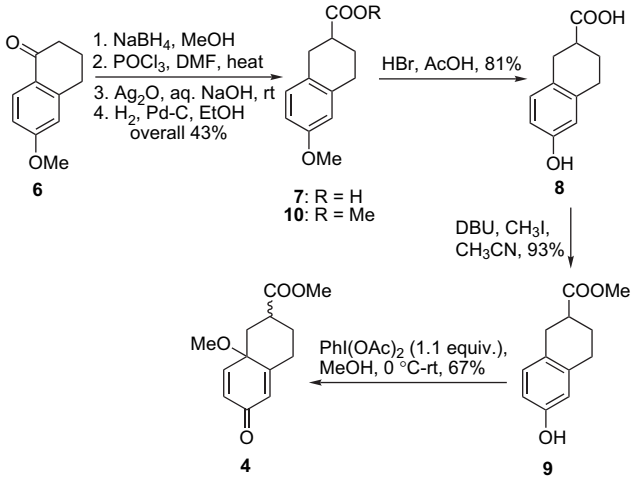
the nonaromatic A ring of the product **2** was expected to furnish the complete chromophoric structure of the target molecule.

3. Results and discussion

3.1. Synthesis of naphthalenone 4 (AB ring synthon)

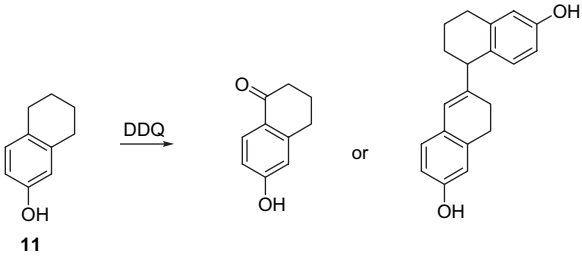
We began the synthesis of hitherto unreported naphthalenone **4** (Scheme 2) starting from commercially available 6-methoxytetralone (**6**) through compound **7**. Compound **7** was prepared from compound **6** in four steps in 43% overall yield by the reported sequence[7] of reactions. The IR and NMR spectroscopic data of all the intermediate compounds were in agreement with the reported[7] values. It was then demethylated by treatment with HBr–AcOH under reflux conditions to give the hydroxyacid **8**[8] in 81% yield. In order to protect the acid functionality, the acid **8** was selectively esterified with DBU–MeI[9] in acetonitrile to afford compound **9**. Doubly methylated compound **10** was also isolated as a co-product when a slight excess of MeI was used. Compound **9** on treatment with 1.1 equiv of phenyliodonium diacetate (PIDA) in MeOH at 0 °C to rt furnished the naphthalenone **4** in 67% yield together with a small amount of unknown byproducts. The structure of this compound was established by analysis of its IR, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **4** showed two doublets at δ 6.64 and 6.21 and one doublet of doublets at δ 6.63 corresponding to olefinic protons at C-8, C-5, and C-7, respectively, along with other characteristic signals.



Scheme 2. Synthesis of naphthalenone **4**.

3.2. Model synthetic study of benz[*a*]anthraquinones

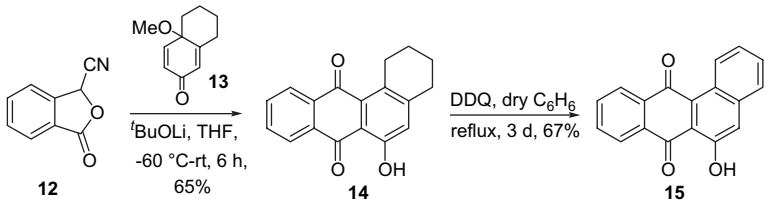
At the outset, the synthesis of compound **15** representing the chromophoric part of BE-23254 (**1**) was chosen for the model study. We were apprehensive that compound **14** might undergo benzylic oxidation or oxidative dimerization under the influence of DDQ, which is known to cause such reactions[10] with structurally similar hydroxytetralin **11** (Eq. 1). Yet, the easy accessibility of compound **14** led us to examine Scheme 3. Isobenzofuranone **12**[11] was annulated with naphthalenone **13** in the presence of ^{t}BuOLi in dry THF at −60 °C and benz[*a*]anthraquinone **14** with a nonaromatic A ring was obtained in 65% yield. This was then subjected to aromatization by DDQ in dry benzene under reflux for 3 days to furnish benz[*a*]anthraquinone **15** in 67% yield (Scheme 3). Comparison of its ^{1}H NMR and ^{13}C NMR spectroscopic data with the literature[12] data confirmed the structure.



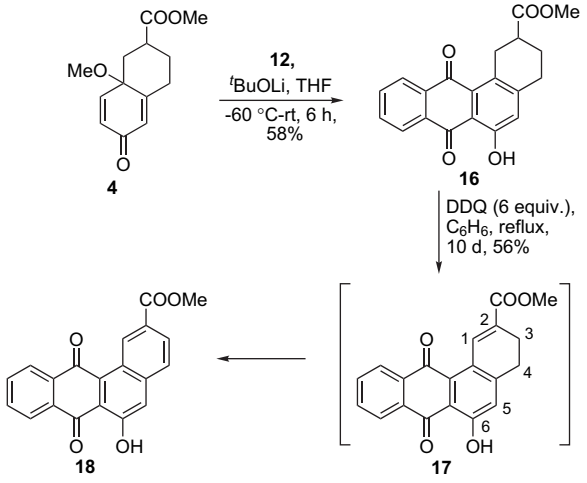
(1)

We then proceeded to execute the crucial annulation reaction of cyanophthalide **12** with naphthalenone **4** to install the carboxylic acid group at C-2 (AB ring synthon). Annulation of naphthalenone **4** with cyanophthalide **12** was carried out in the presence of ^{t}BuOLi, which has proved to be the best base for such purposes, in THF at −60 °C ($CHCl_3$/liq. N_2 bath) under an inert atmosphere. After usual work-up of the reaction mixture and chromatographic purification of the crude product, compound **16** was obtained in an unoptimized yield of 58%. It is noteworthy that the ester functionality in **4** did not interfere with the annulation process. For aromatization, compound **16** was treated with DDQ (6.0 equiv) in dry benzene at reflux for 10 days. Monitoring the course of the reaction required recording ^{1}H NMR spectra of the reaction mixture at regular intervals because TLC experiments were not useful. Formation of an inseparable mixture of didehydro intermediate **17** and the desired product **18** was revealed by analysis of the ^{1}H NMR spectra. The formation of didehydro intermediate **17** was ascertained by appearance of two triplets at δ 2.63 and 2.92 for two CH_2 groups at C-4 and C-3, respectively, two singlets: one at δ 8.87 for =CH at C-1 and other at δ 13.48 for hydrogen bonded –OH group at C-6. Although it was possible to record the ^{1}H NMR spectrum of **18** in $CDCl_3$, its ^{13}C NMR spectrum could not be recorded due to its poor solubility in common deuterated solvents (e.g., $CDCl_3$, CD_3OD, acetone-d_6, DMSO-d_6). This compound was further characterized by analysis using IR spectroscopy and HRMS.

With the two successes (Schemes 3 and 4), we next examined annulation of the naphthalenone **4** with isobenzofuranones **19** and **20**. This model study entails the differences in the isobenzofuranone parts. Isobenzofuranones **19** and **20** were prepared from ethyl 2-hydroxy-5-methylbenzoate (**26**), which, in turn, was obtained in two steps starting from ethyl acetoacetate and crotonaldehyde according to the published procedure.[13] Transformation of compound **26** to **19** and **20** were achieved in four steps by literature methods.[11,14] Annulation reaction between **20** and **4** in the presence of ^{t}BuOLi under the typical conditions used previously, afforded the angucycline analog **21** in 69% yield (Scheme 5) after chromatographic purification. This was aromatized by DDQ oxidation to give compound **22**, which was demethylated by treatment with anhydrous $AlCl_3$ in CH_2Cl_2 to furnish compound **23**. Compounds **22** and **23** were primarily characterized by IR, ^{1}H NMR, and mass



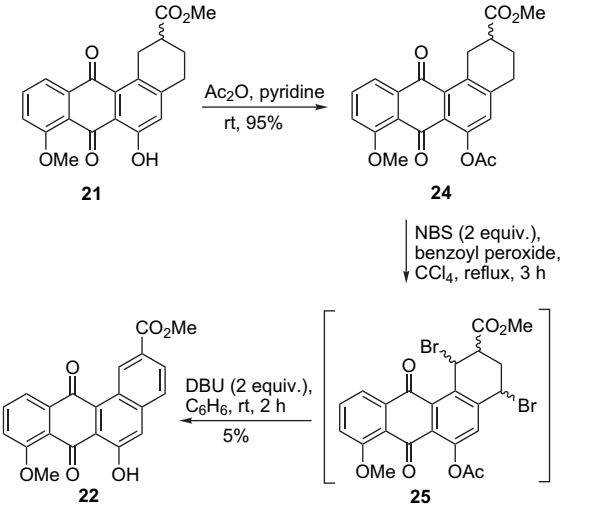
Scheme 3. Synthesis of model compound **15**.



Scheme 4. Synthesis of model compound **18**.

spectral data. The poor solubility of the compounds in common deuterated solvents precluded recording of ^{13}C NMR spectra. The ^1H NMR spectrum of compound **23** showed two sharp singlets at δ 12.10 and 11.80 characteristics of two H-bonded OH groups present at C-6 and C-8 positions. In the aromatic region it showed two sharp singlets, one at δ 10.15, characteristic of the proton at C-1 and the other at δ 7.67 for the aromatic proton at C-5. It may be noted that the use of sulfone phthalide **19** in the above reaction with naphthalenone **4** provided no annulation product, i.e., **21**. Naphthalenone **4** could be recovered in a substantial amount from the reaction, whereas sulfone phthalide **19** was destroyed during the reaction. The failure of the reaction is presumably due to a steric interaction between the sulfone group of phthalide and the OMe group at C-4a position of the naphthalenone.

In order to find a suitable substitute for the DDQ-promoted aromatization, which typically gave nearly 50% yields of the aromatized products for compounds **14**, **16**, and **21**, we examined a sequence of NBS bromination and HBr elimination. This sequence was applied to compound **21** (Scheme 6).

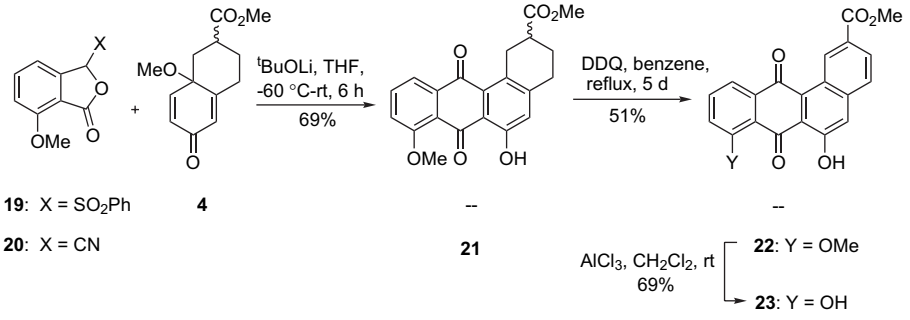


Scheme 6. Bromination and HBr elimination approach for aromatization study.

Compound **24**, prepared by acetylation of **21**, was brominated with NBS (2 equiv) in the presence of benzoyl peroxide and the resulting crude brominated product **25** was treated with DBU (2 equiv). However, the yield of the expected aromatized product **22** was very low (5%).

3.3. Synthesis of isobenzofuranones 3a and 3b (D ring synthons)

For the synthesis of key isobenzofuranones **3a** and **3b** (D ring synthons), the phenolic ester **26** was chosen as the starting material, since it had all the necessary substituents except the chlorine, and it was easily accessible.[13] We studied its direct chlorination with different chlorinating agents, while we were aware that methods for selective *ortho*



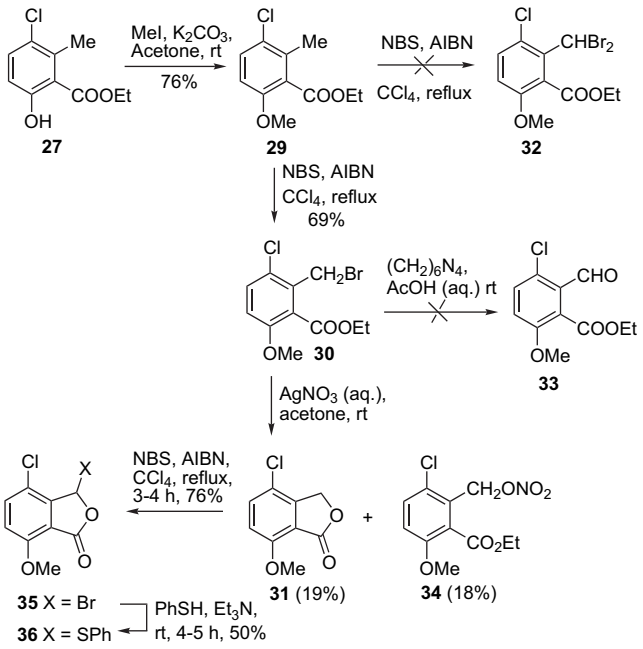
Scheme 5. Synthesis of dechloro analog of BE-23254 (**1**).

Table 1. Product distribution of chlorination of phenol **26**

Entry	Reagents and conditions	Yield of **5** (%)	Yield of **27** (%)	Yield of **28** (%)
1	Cl_2 (excess), AcOH, rt	—	—	79
2	SO_2Cl_2, 100 °C, 3 h	—	—	65
3	NCS (1.1 equiv), CCl_4, reflux, 4–5 h	11	53	—
4	NCS (1.1 equiv), AcOH, reflux, 4–5 h	Trace	35	—
5	NaOCl (1.1 equiv), AcOH, reflux, 4–5 h	Trace	15	49
6	Cl_2 (1.2 equiv), AcOH, rt	—	47	21
7	Cl_2 (1.2 equiv), AcOH, rt (inverse addition)	—	74	—

chlorination of substituted phenols are rare in the literature.[15] Initially, the phenolic ester was subjected to chlorination by passing chlorine gas through a stirred solution of the phenol **26** dissolved in AcOH (entry 1, Table 1; Scheme 7). It was difficult to control the absorption of the required amount of chlorine gas. As a result, an excess of chlorine gas was absorbed and only the dichlorophenol **28** was obtained in 79% yield as a white solid after column chromatographic purification. The same dichloro compound **28** was also obtained in 65% yield by heating the phenolic ester **26** with sulfuryl chloride (1.5 equiv). Alternatively, the chlorination at C-3 position of compound **26** was tried with NCS (1.1 equiv) in CCl_4, NCS (1.1 equiv) in AcOH, and aq NaOCl in AcOH. However, in each of these cases, an inseparable mixture of monochloro compounds **5**, **27**, and dichloro compound **28** was obtained in different ratios. In another mode, the phenol **26** was added to a solution of chlorine gas (1.2 equiv) dissolved in acetic acid (entry 6) and a 2:1 mixture of monochlorophenol **27** and dichlorophenol **28** was obtained in 68% yield. The monochloro compound **27** was obtained as the sole chlorinated product in 74% yield on addition of chlorine (1.2 equiv) in acetic acid to a stirred solution of the phenolic ester **26** taken in acetic acid (entry 7). The structure of product **27** was confirmed by analysis of ^{1}H NMR, ^{13}C NMR, and NOE spectra and also by a number of chemical transformations (Scheme 8). In the NOE spectrum of **27**, irradiation of the Me-signal at δ 2.62 produced no NOE enhancement of the Ar-H signal at δ 6.79.

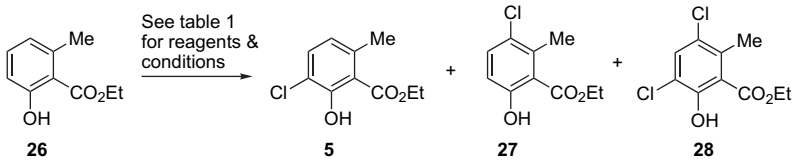
The chlorophenol **27** was methylated with methyl iodide in the presence of K_2CO_3 and the methoxy compound **29**, when reacted with NBS (2.2 equiv) and AIBN in CCl_4, gave monobromo derivative **30**, instead of dibromo compound **32** (Scheme 8). The monobromo compound **30** was then subjected to Sommelet reaction with urotropine in acetic acid, but aldehyde **33** was not formed. Alternatively, compound **30** was treated with aqueous silver nitrate solution. After stirring at room temperature for 2 h, a mixture of chlorophthalide **31**[16] and nitrite **34** was obtained. The two products



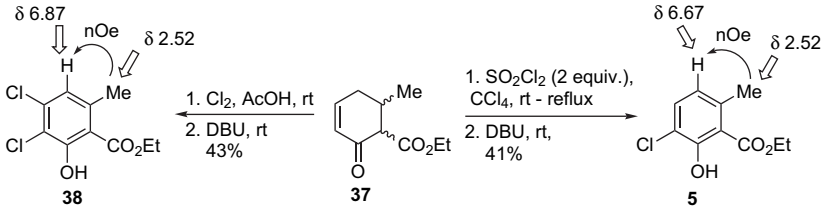
Scheme 8. Chemical transformations of monochlorophenol **27**.

were separated by column chromatography. The chlorophthalide **31** was then transformed into phenylthiophthalide **36** by reaction with NBS (1.1 equiv) followed by the treatment of the resulting bromophthalide **35** with a 1:1 mixture of thiophenol and triethylamine in chloroform at room temperature.

The above unwanted results on chlorination of phenolic ester **26** led us to select cyclohexenone **37** as the alternative starting material, the immediate precursor of the phenolic ester **26**. In the first attempt on the way to compound **5**, excess of chlorine gas was passed through a solution of cyclohexenone ester **37** taken in AcOH during 2 h at room temperature and the resulting crude product was treated with DBU (2 equiv) to afford the dichloro compound **38** in 43% yield (Scheme 9). The structure of this product was confirmed by analysis of its NMR and NOE spectra. In the NOE spectrum, irradiation of the Me-signal at δ 2.52 produced NOE enhancement of the Ar-H signal at δ 6.87. This indicated that the Ar-H and the Me group are present on vicinal carbon atoms of compound **38**. Finally, the problem of preparing monochloro compound **5** was solved by sulfuryl chloride promoted chlorination of cyclohexenone **37**. Its reaction with sulfuryl chloride (2 equiv) followed by treatment with DBU (3 equiv) at room temperature afforded, after usual work-up, the desired chloro compound **5** in 41% yield (Scheme 9). The structure of this product was confirmed by analysis of its NMR and NOE spectra. In the NOE spectrum, irradiation of the Me-signal at δ 2.52 produced NOE



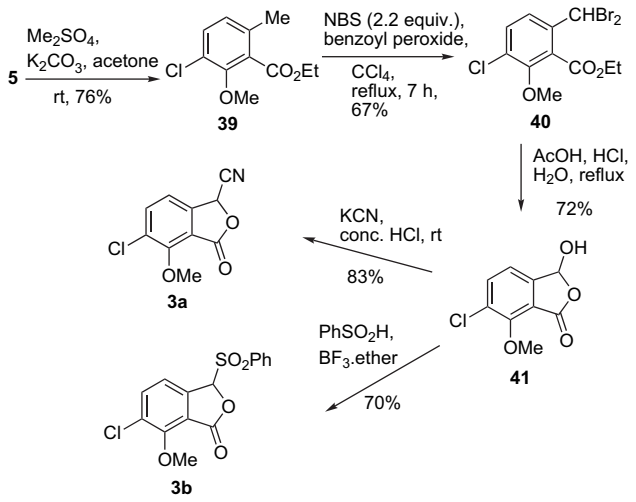
Scheme 7. Product distribution of chlorination of phenol **26**.



Scheme 9. Chlorination study on cyclohexenone **37**.

enhancement of the Ar-H signal at δ 6.67. This observation indicated that the Ar-H and the benzylic CH_3 group are present on vicinal carbon atoms of compound **5**.

Chlorophenol **5** was then transformed into isobenzofuranones **3a** and **3b** in four steps (Scheme 10). The phenolic OH group of compound **5** was methylated (Me_2SO_4, K_2CO_3) to give ester **39**, which was subjected to benzylic bromination with NBS (2.2 equiv) to furnish compound **40**. Dibromo compound **40** was hydrolyzed with a refluxing mixture of AcOH, HCl, and H_2O to produce corresponding phthalaldehydic acid **41**. This five-step synthesis of **41** appears to be competitive to its earlier synthesis.[17] Two key



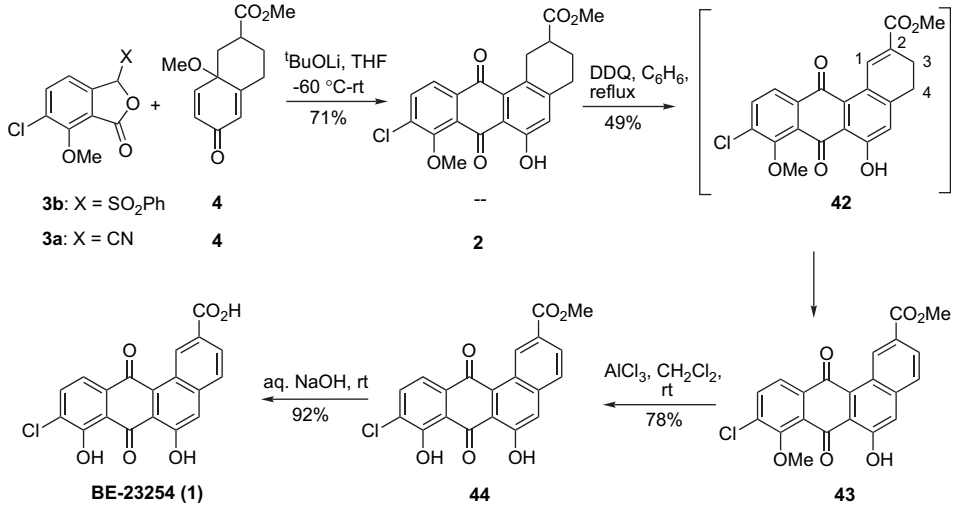
Scheme 10. Synthesis of isobenzofuranones **3a** and **3b**.

synthons **3a** and **3b** were then prepared according to the general procedures reported for the preparation of cyanophthalides[11] and phenylsulfone phthalides.[18] Reaction of phthalaldehydic acid **41** with KCN in the presence of concd HCl afforded cyanophthalide **3a** in 83% yield. Its structure was established by analysis of IR, NMR (^1H and ^{13}C), and mass spectral data. Similarly, the corresponding sulfone phthalide **3b** was prepared in 70% yield from phthalaldehydic acid **41** by its reaction with phenylsulfinic acid in the presence of $BF_3\cdot$etherate.

3.4. Total synthesis of BE-23254 (1)

3-Phenylsulfonylphthalides are generally preferred to the 3-cyanophthalides as the Hauser-donors due to difficulties in the preparation of the latter. Consequently, we first attempted to condense sulfone phthalide **3b** with naphthalenone **4** (Scheme 11). Their reaction in the presence of lithium *tert*-butoxide from −60 to 0 °C, followed by stirring overnight at room temperature and routine work-up did not yield the expected annulation product **2**. Naphthalenone **4** could be recovered from the reaction in a substantial amount, whereas sulfone phthalide **3b** was destroyed during the reaction. This failure with the sulfone phthalide was apprehended on the basis of the experiment described for **19** (Scheme 5). However, this experiment was performed to reinforce our explanation that this failure was due to the steric effect. The polar effect of the chlorine atom has little influence on the failure.

Alternatively, reaction of cyanophthalide **3a** with naphthalenone **4** in the presence of ^{t}BuOLi at −60 °C followed by stirring at room temperature for 6 h provided the



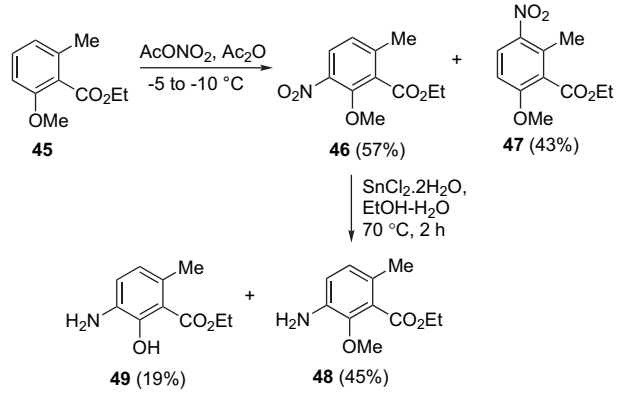
Scheme 11. Total synthesis of BE-23254 (**1**).

tetrahydrobenz[*a*]anthraquinone **2** in 71% yield, which was characterized by analysis of IR, NMR (^{1}H and ^{13}C), and mass spectral data. The ^{1}H NMR spectrum of the compound **2** showed three sharp singlets: at δ 13.00 (H-bonded OH group at C-6), 4.01 (OCH_3), and 3.74 ($COOCH_3$). In the aromatic region, it revealed two one-hydrogen doublets at δ 7.99 and 7.82, and one singlet at δ 7.06 for hydrogen at C-5. The nonequivalent protons of the CH_2 group at C-1 appeared as doublet of doublets at δ 3.61 and 3.30. Each proton was equally splitted by the other (J_{gem}=18.6 Hz) and unequally by the neighboring proton (i.e., α to ester functionality) at C-2 (J_{vic}=10.0 and 5.6 Hz). IR, ^{13}C NMR, and mass spectral data of this compound were also in accordance with the structure. Aromatization of the A-ring in **2** was effected by DDQ in refluxing benzene to provide **43** in 49% yield. This reaction required careful monitoring by ^{1}H NMR spectra of the interrupted reaction mixtures because the reaction progressed through the formation of inseparable mixtures of didehydro intermediate **42** and the desired product **43**. Prolonged refluxing seemed to destroy the aromatized product **43** into an unidentified product. Formation of the didehydro intermediate **42** was ascertained by the appearance of two triplets at δ 2.89 and 2.60 for two CH_2 groups at C-4 and C-3, respectively, and two singlets: one at δ 8.70 for C-1 hydrogen and other at δ 13.43 for hydrogen bonded –OH group. Demethylation of compound **43** was done by treatment with anhydrous $AlCl_3$ in CH_2Cl_2 at room temperature to afford **44** in 78% yield. Base (NaOH) catalyzed hydrolysis of **44** yielded the natural product BE-23254 (**1**) in 92% yield. All the A-ring aromatic compounds of this series (**1**, **43**, and **44**) were characterized by analysis of IR, ^{1}H NMR, and HRMS spectra. ^{13}C NMR spectra of compounds **1**, **43**, and **44** could not be recorded due to their poor solubility in common deuterated solvents including pyridine-d_5.

3.5. Synthesis of fluoro analog of BE-23254

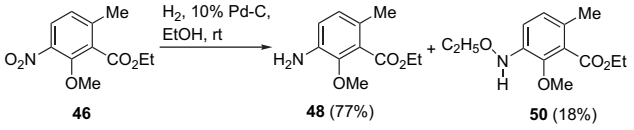
As a matter of course, our next effort was directed at synthesizing a fluorine-containing analog of BE-23254 (**1**). It is well established that the selective introduction of a fluorine atom or a fluorinated residue into a biologically active molecule is an effective means for modifying its physicochemical properties and consequently its physiological behavior.[19]

For the synthesis of the required fluoro cyanophthalide **55**, we commenced with anisic ester **45**, obtained from phenolic ester **25**. Considering the fact that acetyl nitrate is orthoselective,[20] anisic ester **45** was treated with acetyl nitrate[21] at −5 to −10 °C in acetic anhydride (Scheme 12). It yielded a mixture of *ortho*- and *para*-nitro anisic esters **46** and **47** in 57 and 43% yield, respectively. These were separated by column chromatography and characterized by analysis of their IR and NMR (^{1}H and ^{13}C) spectra. Both the compounds **46** and **47** showed the same coupling pattern in their ^{1}H NMR spectrum but they were distinguished by comparing the chemical shift of the methyl groups at C-6. In compound **46**, the methyl group appeared at δ 2.36, while that in compound **47** appeared at δ 2.48 as it is closer to the electron withdrawing nitro group. These data are comparable to that of the corresponding methyl esters.[22] Ester **46** was then transformed to the corresponding amine **48** by treatment with stannous chloride dihydrate in ethanol at 70 °C in accordance with the literature procedure.[23] The amine **48** was obtained in 45% yield along with hydroxy amine compound **49** in 19% yield.



Scheme 12. Synthesis of amine **48**.

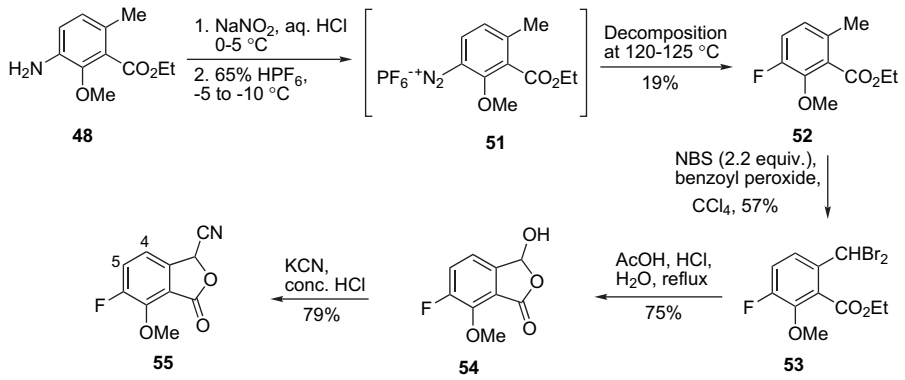
In order to avoid the formation of **49** and thereby increase the yield of **48**, we submitted compound **46** to hydrogenation over 10% Pd–C[24] in absolute ethanol at room temperature. In this case (Scheme 13), the amine **48** was obtained in 77% yield with the side product **50** in 18% yield.



Scheme 13. Reduction of nitro compound **46** to amine **48**.

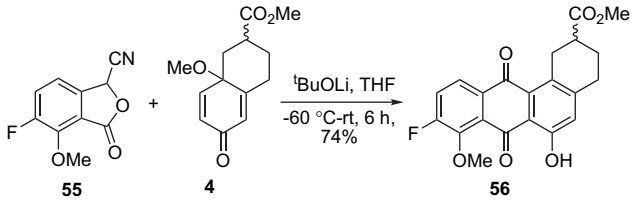
The required fluorophthalide **55** was synthesized from amine **48** in five steps (Scheme 14). Amine **48** was treated with $NaNO_2$ and HCl followed by cold HPF_6 solution to obtain the corresponding phosphorus hexafluoride salt **51**, which was filtered, dried, and without purification decomposed at 120–125 °C.[25] After the decomposition was complete, the residue was processed in usual manner to yield fluoro compound **52**, after purification, in overall 19% yield. Compound **52** was then subjected to benzylic bromination with NBS (2.2 equiv) to furnish dibromo compound **53**, which was then hydrolyzed with a refluxing mixture of AcOH, HCl, and H_2O to yield corresponding phthalaldehydic acid **54** in 75% yield. Finally, the cyanophthalide **55** was prepared according to the general procedure.[11] Reaction of phthalaldehydic acid **54** with KCN in the presence of concd HCl afforded, after column chromatographic purification, the cyanophthalide **55** in 79% yield. Structures of the compounds **52**–**55** were established by the analysis of IR, NMR (^{1}H and ^{13}C), and mass spectral data. The ^{1}H NMR spectra of compounds **54** and **55** had a pair of double doublets corresponding to C-4 and C-5 hydrogens due to coupling with each other and with fluorine at C-6. In addition, these also showed a doublet for the methoxy group at C-7 due to its coupling with the fluorine.

Treatment of naphthalenone **4** with the anion of fluorophthalide **55** (Scheme 15) generated with lithium *tert*-butoxide in THF at −60 °C ($CHCl_3$/liq. N_2 bath) under N_2 atmosphere provided tetracyclic compound **56**. The structure of the annulated product **56** was characterized by examination of



Scheme 14. Synthesis of fluoro cyanophthalide **55**.

IR, NMR, and mass spectral data. Its ^{1}H NMR spectrum showed a sharp singlet at δ 13.02 for the H-bonded hydroxyl group at C-6. In the aromatic region, it revealed two double doublets at δ 8.02 ($J_{H-F(o)}$=10.1 Hz and $J_{H-H(o)}$=8.7 Hz) and 7.45 ($J_{H-F(m)}$=5.0 Hz and $J_{H-H(o)}$=8.7 Hz) corresponding to C-10 and C-11 hydrogens. The singlet at δ 7.06 corresponds to hydrogen at C-5. In addition, it also exhibited a doublet at δ 4.08 (J_{OMe-F}=3.3 Hz) for the methoxy group at C-8 due to its coupling with fluorine and another singlet at δ 3.74 for carbomethoxy group. Due to the inefficiency in the conversion of **48**→**52**, further investigations with **56** on the way to obtain fluoro analog of BE-23254 (**1**) were stalled.



Scheme 15. Annulation of cyanophthalide **55** with naphthalenone **4**.

4. Conclusions

In conclusion, we have presented a regiospecific total synthesis of BE-23254 (**1**) starting from commercially available 6-methoxytetralone, and showcased the applicability and brevity of Hauser annulation–DDQ-promoted aromatization strategy in the synthesis of angucyclines. Use of the strategy has culminated in the synthesis of several angucycline analogs, namely **15**, **18**, **22**, and fluoro analog **56**. We have also executed a new regiospecific preparation of *ortho*-chlorinated phenols based on chlorinative aromatization of a cyclohexenone derivative (Scheme 9). It would be interesting to examine the biological activities of the newly prepared A-ring nonaromatic benz[*a*]anthraquinone derivatives like **2**, **14**, **16**, **21**, and **56**.

5. Experimental

5.1. General

^{1}H NMR spectra were recorded on a 200, 300, or a 500 MHz spectrometer (Brücker) as solution in ^2H-chloroform or mixture of ^2H-chloroform and CCl_4, or in mixture of ^2H-chloroform and DMSO-d_6 with TMS as an internal standard. Chemical shifts are expressed in δ unit and ^{1}H–^{1}H coupling constants in hertz. ^{13}C NMR spectra were recorded on a 50, 75, or a 125 MHz spectrometer (Brücker) instrument with solution of compounds in ^2H-chloroform, mixture of ^2H-chloroform and CCl_4, and mixture of ^2H-chloroform and DMSO-d_6. IR spectra were recorded on a Thermo Nicolet Nexus 870 FTIR spectrometer using KBr pellets. EIMS (70 eV) spectra were taken using a VG Autospec M mass spectrometer. Elemental analyses were carried out by using an elemental analyzer VARIO EL instrument. All solvents for chromatography (column and preparative layer chromatography) were distilled prior to use. In most of the column chromatographic separations, ethyl acetate, chloroform, and petroleum ether (60–80 °C) were used as eluants. Columns were prepared with silica gel (60–120 mesh). For preparative thin layer chromatographic (PLC) separations, the layer was prepared over a glass plate using water gel. The mixture of silica gel-GF_{254} and silica gel-G was used for the PLC plate preparation. The phrase 'usual work-up' or 'worked up in usual manner' refers to washing of the organic phase with water and brine, drying (Na_2SO_4), filtration, and concentration under reduced pressure. Solid compounds were recrystallized from ethyl acetate–petroleum ether or otherwise mentioned.

5.2. General procedure for annulation reaction

To a stirred solution of lithium *tert*-butoxide (9.84 mmol) in THF (40 mL) at −60 °C (chloroform/liq. N_2 bath) under an inert atmosphere was added a solution of a phthalide (3.28 mmol) in THF (5 mL). The resulting yellowish solution was stirred at −60 °C for 30 min, after which a solution of a Michael acceptor (1.0–1.5 equiv unless otherwise stated) in THF (5 mL) was added to it. Cooling bath was removed after about 1 h at −60 °C and the reaction mixture was brought to room temperature over a period of 1 h and further stirred for 2–6 h. The reaction was then quenched with 10% NH_4Cl (15 mL) and the resulting solution was concentrated in vacuo. Generally, a bright yellow solid appeared, which was filtered and washed with 1:1 mixture (20 mL) of diethyl ether and petroleum ether. Otherwise, the residue was diluted with ethyl acetate (50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3×25 mL). The combined extracts were washed with brine, H_2O, dried (Na_2SO_4), and

concentrated. The crude product was purified by column chromatography or by recrystallization to get a pure product.

5.3. General procedure for DDQ oxidation

To a stirred solution of 1,2,3,4-tetrahydrobenz[*a*]anthraquinone compound (280 mmol) in dry benzene (10 mL) under an inert atmosphere was added DDQ (6 equiv). The resulting mixture was refluxed with stirring for 3–12 days under inert atmosphere. The progress of the reaction was monitored by ^{1}H NMR spectroscopy and disappearance of the signals in the aliphatic region was followed. TLC was not useful for the purpose because of the formation of the inseparable mixtures of didehydro compound and final aromatized product at the intermediate stage of the reaction. After completion of the reaction, benzene was removed under reduced pressure. The aromatized product was purified by column chromatography using mixtures of $CHCl_3$ and petroleum ether (5:1) as eluant.

5.4. General procedure for O-demethylation of phenolic ether

To a stirred solution of a methoxy compound (0.105 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under Ar-atmosphere was added anhydrous $AlCl_3$ (5 equiv). After 1 h of stirring at 0 °C, the reaction mixture was allowed to come to room temperature and stirring was continued for additional 6 h. The reaction mixture was quenched with 2 M HCl (4 mL). Usual work-up of the organic extract afforded a solid that was further purified by column chromatography (3:1 mixture of $CHCl_3$/petroleum ether).

5.5. General procedure of O-methylation of phenolic compounds

A phenolic compound (3.0 mmol) was dissolved in dry acetone (15 mL) under N_2-atmosphere. To this solution were added dry K_2CO_3 (15 mmol) and Me_2SO_4 (6 mmol) (freshly washed with cold water, saturated $NaHCO_3$ solution, brine, and then dried over anhydrous K_2CO_3). After 2 h of reflux, on completion of the reaction, inorganic salts were filtered and the filtrate was concentrated. The residue was diluted with ether, treated with Et_3N (6 mmol) at room temperature, and stirred for 30 min. The reaction mixture was then diluted with ethyl acetate (50 mL), washed with water and 5% HCl, and subjected to usual work-up to get a crude residue, which was further purified by recrystallization or by column chromatography to give a pure methoxy compound.

5.5.1. BE-23254 (1). To a stirred solution of ester compound **44** (20 mg, 0.05 mmol) in methanol (5 mL), 20% aq solution of NaOH (2 mL) was added. The resulting pink colored solution was allowed to stir overnight. Then the reaction mixture was acidified with dilute HCl and extracted with ethyl acetate (3×30 mL). Usual work-up of the organic extract afforded a red solid that was further purified by column chromatography (3:1 $CHCl_3$/petroleum ether). Yield: 92%; mp: 324–326 °C; ν_{max} (KBr, cm^{-1}): 3409, 1705, 1618, 1425, 1233, 1050, 759; ^{1}H NMR (200 MHz, pyridine-d_5): δ 10.9 (s, 1H), 8.55 (d, 1H, J=8.3 Hz), 7.90–7.81 (m, 4H); MS *m*/*z* (EI): 368 (M$^+$), 354, 323, 256, 236, 194, 152, 137, 129, 111, 97, 83, 69; HRMS *m*/*z* (ESI) calcd for $C_{19}H_9{}^{35}ClO_6$ (M$^+$−H): 367.0009; found: 367.0026.

5.5.2. Methyl 9-chloro-6-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (2). This compound was prepared as a yellow solid by annulation of 6-chloro-7-methoxy cyanophthalide (**3a**) with Michael acceptor **4** following the general procedure in Section 5.2. Yield: 71%; mp: 135–136 °C; ν_{max} (KBr, cm^{-1}): 3408, 1733, 1634, 1273, 1025, 763, 697; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 13.00 (s, 1H), 7.99 (d, 1H, J=8.0 Hz), 7.82 (d, 1H, J=8.0 Hz), 7.06 (s, 1H), 4.01 (s, 3H), 3.74 (s, 3H), 3.61 (dd, 1H, J=5.6 and 18.6 Hz), 3.30 (dd, 1H, J=10.0 and 18.6 Hz), 2.94–2.89 (m, 2H), 2.80–2.68 (m, 1H), 2.21–2.12 (m, 1H), 2.03–1.90 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 187.8, 183.7, 175.4, 160.7, 156.1, 147.8, 136.5, 135.8, 135.2, 131.8, 129.9, 126.2, 124.5, 124.2, 116.4, 61.6, 51.9, 39.8, 30.9, 29.9, 24.1; MS *m*/*z* (EI): 400 (M$^+$), 369, 340, 326, 322, 297, 284, 256, 236, 197; HRMS *m*/*z* (ESI) calcd for $C_{21}H_{13}{}^{35}ClO_6$ (M$^+$+H): 401.0792; found: 401.0755.

5.5.3. 6-Chloro-3-cyano-7-methoxyphthalide (3a). To a solution of KCN (1.25 g, 19.2 mmol) in water (5 mL) was added phthalaldehydic acid **41** (0.5 g, 2.78 mmol). The clear reddish solution was stirred for 10 min at room temperature and cooled to 0 °C. After addition of ice (~5 g), concentrated HCl (4 mL) was added and the resulting clear colorless solution was removed from the ice bath and stored at room temperature for 5 h. A white precipitate deposited. This was filtered, dried, and recrystallized from ethyl acetate to give a white crystalline solid (430 mg, 1.92 mmol). Yield: 83%; mp: 90–91 °C; ν_{max} (KBr, cm^{-1}): 1788, 1601, 1390, 1024, 768; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.84–7.80 (d, 1H, J=8.0 Hz), 7.33–7.28 (d, 1H, J=8.0 Hz), 6.97 (s, 1H), 4.21 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 163.8, 155.5, 141.6, 137.5, 130.3, 117.4, 116.6, 113.2, 64.6, 62.9; MS *m*/*z* (EI): 223 (M$^+$), 205, 194, 177, 167, 149, 137, 100, 75; HRMS *m*/*z* (ESI) calcd for $C_{10}H_6N{}^{35}ClO_3$ (M$^+$+H): 224.0114; found: 224.0106.

5.5.4. 3-Benzenesulfonyl-6-chloro-7-methoxy-3*H*-isobenzofuran-1-one (3b). This compound was prepared from compound **41** following the procedure of Mal et al.[18] To a stirred mixture of phthalaldehydic acid **41** (200 mg, 0.93 mmol) and a freshly prepared benzenesulfinic acid (400 mg, 2.82 mmol) in dry dichloromethane (5 mL) at room temperature under Ar-atmosphere was added 4–5 drops of boron trifluoride diethyl etherate. The mixture was stirred for about 12 h. A pale yellow solid separated on addition of ice-cold water (15 mL) into the reaction mixture. It was filtered and recrystallized from ethyl acetate–hexane to give sulfone phthalide **3b** as white crystalline solid (220 mg, 0.65 mmol). Yield: 70%, mp: 138–139 °C; ν_{max} (KBr, cm^{-1}): 1781, 1596, 1469, 1348, 1155, 1004, 835, 719, 682, 593; ^{1}H NMR (200 MHz, $CDCl_3$): 7.84–7.48 (m, 7H), 6.07 (s, 1H), 4.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 164.2, 155.2, 139.5, 137.1, 135.0, 140, 130.5, 129.7, 129.3, 120.1, 118.3, 89.5, 62.0; HRMS *m*/*z* (ESI) calcd for $C_{15}H_{11}{}^{35}ClO_5S$ (M$^+$+H): 339.0094; found: 339.0107.

5.5.5. Methyl 1,2,3,4-tetrahydro-4a-methoxy-6-oxonaphthalene-2-carboxylate (4). To a stirred solution of

compound **9** (300 mg, 1.46 mmol) in methanol (10 mL) at 0 °C under N_2 atmosphere was portionwise added PIDA (560 mg, 1.74 mmol). The temperature was held at 0 °C for about 30 min. Then the mixture was allowed to come to ambient temperature during a period of 1 h. Bulk of methanol was removed under reduced pressure and the residue upon quick silica gel filtration afforded compound **4** as waxy solid. Yield: 65%; ν_{max} (KBr, cm^{-1}): 1735, 1667, 1636, 1441, 1305, 1207, 1085, 987, 891; ^1H NMR (200 MHz, $CDCl_3$): 6.64 (d, 1H, J=10.0 Hz), 6.63 (dd, 1H, J=1.9 and 10.0 Hz), 6.21 (d, 1H, J=1.4 Hz), 3.65 (s, 3H), 3.02 (s, 3H), 2.53–2.20 (m, 5H), 1.60–1.41 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 185.8, 174.6, 160.5, 149.8, 131.3, 127.1, 72.7, 51.82, 51.7, 40.5, 37.5, 31.0, 29.9. No attempt was made for preparing an analytical sample due to its propensity to decomposition on silica gel chromatography or standing.

5.5.6. Ethyl 3-chloro-2-hydroxy-6-methylbenzoate (5). To the stirred solution of cyclohexenone **37** (4.22 g, 23.2 mmol) in CCl_4 at 0 °C was added SO_2Cl_2 (3.8 mL, 46.9 mmol) dropwise. The reaction mixture was allowed to stir for additional half an hour at room temperature. Thereafter, it was heated at reflux for 4 h. After completion of the reaction, the product was extracted with dichloromethane, dried over sodium sulfate, and solvent was then removed. The crude residue was then dissolved in benzene (10 mL) and treated with 3 equiv of DBU with occasional stirring at room temperature for about 4–5 h. Benzene was removed under reduced pressure. Finally, the mixture was extracted with ethyl acetate (3×25 mL) and washed with cold 10% aq HCl (15 mL). The extract was worked up in usual manner to give the desired product, which was further purified by column chromatography using petroleum ether and ethyl acetate (15:1) to afford a pure product **5** as white solid (2.04 g). Yield: 41%; mp: 55–56 °C; ν_{max} (KBr, cm^{-1}): 3442, 1663, 1424, 1256, 1205, 802; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): 11.97 (s, 1H), 7.37 (d, 1H, J=8.0 Hz), 6.67 (d, 1H, J=8.0 Hz), 4.50 (q, 2H, J=7.0 Hz), 2.52 (s, 3H), 1.44 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 172.4, 158.1, 140, 134, 122.8, 120, 113.6, 62.1, 23.8, 14.1; HRMS m/z (ESI) calcd for $C_{10}H_{11}{}^{35}ClO_3$ (M^++H): 215.0475; found: 215.0461.

5.5.7. 1,2,3,4-Tetrahydro-6-methoxynaphthalene-2-carboxylic acid (7). This compound was prepared following the procedure reported by Reddy and Rao[7] in four steps starting from 6-methoxytetralone (**6**) . White solid. Yield: 91%, mp: 146–147 °C (lit.[7] mp: 152 °C). ν_{max} (KBr, cm^{-1}): 2947, 1694, 1431, 1302, 1264, 959; ^1H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 6.86 (1H, d, J=8.0 Hz), 6.57–6.46 (m, 2H), 5.15 (br s, 1H), 2.80–2.66 (m, 4H), 2.60–2.43 (m, 1H), 2.12–1.99 (m, 1H), 1.74–1.60 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6): δ 176.6, 156.7, 136.1, 129.0, 126.4, 112.5, 111.3, 54.3, 39.1, 30.0, 27.9, 24.9; HRMS m/z (ESI) calcd for $C_{12}H_{14}O_3$ (M^++H): 207.1021; found: 207.1014.

5.5.8. 6-Hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (8). A mixture of naphthalene-2-carboxylic acid **7** (2.5 g, 12.13 mmol), 20 mL of hydrobromic acid (48% aq solution), and 20 mL of acetic acid was heated at reflux for 3–4 h. After completion of the reaction, acetic acid was removed. Usual work-up of the residue furnished the desired product **8** as a white solid. This was recrystallized from ethyl acetate and petroleum ether. Yield: 81%; mp: 137–138 °C; ν_{max} (KBr, cm^{-1}): 3257, 1691, 1608, 1456, 1239, 942; ^1H NMR (200 MHz, DMSO-d_6+$CDCl_3$): δ 7.72 (d, 1H, J=8.0 Hz), 6.46–6.38 (m, 2H), 3.91 (br s, 1H), 2.75–2.39 (m, 5H), 2.04–1.94 (m, 1H), 1.72–1.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.9, 154.2, 136, 129.0, 124.9, 114.3, 112.7, 39.3, 30.1, 27.8, 25.0.

5.5.9. Methyl 6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (9). This was prepared in accordance with the procedure[9] of Mal. To a solution of 1,2,3,4-tetrahydro-6-hydroxynaphthalene-2-carboxylic acid (1.00 g, 7.81 mmol) and DBU (1.20 g, 7.88 mmol) in acetonitrile (15 mL) cooled to 0 °C was slowly added methyl iodide (0.5 mL, 8.1 mmol) over 5 min. The resulting solution was stirred for 30 min at 0 °C and then for 2 h at room temperature. Solvent was removed under reduced pressure and the residue was diluted with water (30 mL). The aqueous solution was extracted with ether (3×25 mL). The combined organic layer was washed with $NaHCO_3$ solution (20 mL), brine, and concentrated. Purification of the crude residue by column chromatography (3:7 mixture of ethyl acetate–petroleum ether) gave compound **9** as a white solid. Yield: 96%; mp: 90–91 °C; ν_{max} (KBr, cm^{-1}): 3439, 1701, 1619, 1587, 1499, 1266, 1221, 1145, 1009, 808, 584; ^1H NMR (200 MHz, $CDCl_3$): δ 6.93 (d, 1H, J=8.2 Hz), 6.65 (dd, 1H, J=2.0 and 8.2 Hz), 6.59 (d, 1H, J=2.0 Hz), 3.74 (s, 3H), 2.95–2.89 (m, 2H), 2.82–2.63 (m, 3H), 2.22–2.10 (m, 1H), 1.89–1.75 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.6, 153.9, 136.9, 129.0, 126.6, 115.1, 113.4, 51.9, 40.2, 30.9, 28.5, 25.7; HRMS m/z (ESI) calcd for $C_{12}H_{14}O_3$ (M^+−H): 205.0779; found: 205.0788.

5.5.10. Methyl 1,2,3,4-tetrahydro-6-methoxynaphthalene-2-carboxylate (10). This product was obtained as a side product during the esterification of compound **8** with DBU–MeI in acetonitrile. Colorless liquid. Yield: 5%; ν_{max} (KBr, cm^{-1}): 1734, 1613, 1502, 1443, 1265, 1227, 1166, 1035, 821; ^1H NMR (200 MHz, $CDCl_3$+CCl_4): δ 6.98 (d, 1H, J=8.3 Hz), 6.64 (dd, 1H, J=2.1 and 8.3 Hz), 6.57 (d, 1H, J=2.1 Hz), 3.76 (s, 3H), 3.72 (s, 3H), 2.84 (m, 4H), 2.68 (m, 1H), 2.18 (m, 1H), 1.85 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): δ 175.3, 157.6, 136.3, 129.6, 126.6, 113.1, 112.0, 54.8, 51.3, 39.9, 30.7, 28.6, 25.6.

5.5.11. 6-Hydroxybenz[*a*]anthracene-7,12-dione (15). This compound was prepared from **14** according to the general procedure in Section 5.3. Red solid. Yield: 67%; mp: 203 °C (lit.[12] mp: 201–204 °C); ν_{max} (KBr, cm^{-1}): 3429, 1641, 1589, 1442, 1379, 1307; ^1H NMR (300 MHz, $CDCl_3$): δ 12.46 (s, 1H), 9.49–9.46 (m, 1H), 8.30–8.28 (m, 2H), 7.82 (m, 2H), 7.88–7.77 (m, 1H), 7.74–7.69 (s, 1H), 7.58–7.52 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.1, 185.4, 156.8, 139.2, 135.0, 133.6, 132.0, 129.9, 129.5, 128.9, 128.5, 127.9, 127.3, 127.2, 126.4, 126.2, 121.1, 119.5.

5.5.12. Methyl 6-hydroxy-1,2,3,4-tetrahydrobenz[*a*]-anthracene-7,12-dione-2-carboxylate (16). This compound was prepared as a yellow solid by annulation of cyanophthalide **12** with Michael acceptor **4** following the general procedure of annulation in Section 5.2. Yield: 58%;

mp: 196–197 °C; ν_{max} (KBr, cm^{-1}): 3435, 1739, 1660, 1634, 1587, 1456, 1360, 1283, 1250, 1176, 1017, 795, 722; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 13.03 (s, 1H), 8.40–8.09 (m, 2H), 7.92–7.60 (m, 2H), 7.04 (s, 1H), 3.75 (s, 3H), 3.64–3.61 (m, 1H), 3.40–3.25 (m, 1H), 2.96–2.89 (m, 2H), 2.79–2.65 (m, 1H), 2.15–2.10 (m, 1H), 2.05–1.92 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 188.7, 175.4, 160.9, 148.1, 135.5, 134.5, 133.4, 132.3, 130.5, 130.1, 127.3, 126.2, 124.1, 121.3, 115.7, 51.9, 39.9, 31.0, 30.0, 24.1; HRMS *m/z* (ESI) calcd for $C_{20}H_{16}O_5$ (M^++H): 337.1017; found: 337.1021.

5.5.13. Methyl 6-hydroxybenz[*a*]anthracene-7,12-dione-2-carboxylate (18). This compound was prepared from **16** according to the general procedure in Section 5.3. Red solid. Yield: 56%; mp: 262–263 °C; ν_{max} (KBr, cm^{-1}): 3444, 1720, 1639, 1587, 1533, 1662, 1319, 1275, 1216, 748; ^{1}H NMR (200 MHz, $CDCl_3$): 12.56 (s, 1H), 10.19 (s, 1H), 8.36–8.25 (m, 2H), 8.14 (dd, 1H, *J*=2.0 and 8.0 Hz), 7.91–7.69 (m, 4H), 4.02 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{20}H_{12}O_5$ (M^++H): 333.0763; found: 333.0761.

5.5.14. Methyl 6-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (21). This compound was prepared by annulation of cyanophthalide **20** with Michael acceptor **4** following the general procedure in Section 5.2. Orange solid. Yield: 69%; mp: 174–175 °C; ν_{max} (KBr, cm^{-1}): 3432, 1730, 1632, 1582, 1466, 1361, 1290, 1229, 1174, 1031, 1065, 948, 919, 838, 785; ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.23 (s, 1H), 7.86 (d, 1H, *J*=7.8 Hz), 7.72 (dd, 1H, *J*=7.8 and 8.2 Hz), 7.30 (d, 1H, *J*=8.2 Hz), 7.03 (s, 1H), 4.01 (s, 3H), 3.70 (s, 3H), 3.68–3.56 (m, 1H), 3.38–3.24 (m, 1H), 2.97–2.85 (m, 2H), 2.80–2.65 (m, 1H), 2.20–1.80 (m, 2H).

5.5.15. Methyl 6-hydroxy-8-methoxybenz[*a*]anthracene-7,12-dione-2-carboxylate (22). This compound was prepared from **21** according to the general procedure in Section 5.3. Red solid. Yield: 51%; mp: 266–267 °C; ν_{max} (KBr, cm^{-1}): 3414, 1710, 1643, 1452, 1286, 1255, 1221, 1033, 939, 763. ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.67 (s, 1H), 9.98 (s, 1H), 8.06 (d, 1H, *J*=9.0 Hz), 7.90 (d, 1H, *J*=7.7 Hz), 7.72 (m, 2H), 7.60 (s, 1H), 7.31 (d, 1H, *J*=8.1 Hz), 4.04 (s, 3H), 3.95 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{21}H_{14}O_6$ (M^++H): 363.0869; found: 363.0872.

5.5.16. Methyl 6,8-dihydroxybenz[*a*]anthracene-7,12-dione-2-carboxylate (23). This compound was prepared as a brick red solid by $AlCl_3$ catalyzed demethylation of compound **22** following the procedure adopted for compound **43**. Yield: 69%; mp: 278–279 °C; ν_{max} (KBr, cm^{-1}): 3410, 1716, 1633, 1590, 1457, 1409, 1309, 1223, 1106, 1081, 758; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.10 (1H, s), 11.80 (s, 1H), 10.15 (s, 1H), 8.13 (d, 1H, *J*=8.6 Hz), 7.85 (d, 1H, *J*=7.6 Hz), 7.79–7.68 (m, 2H), 7.67 (s, 1H), 7.31 (d, 1H, *J*=8.3 Hz), 4.02 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{20}H_{12}O_6$ (M^++H): 349.0712; found: 349.0721.

5.5.17. Methyl 6-acetoxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (24). Phenolic compound **20** (100 mg, 0.27 mmol) was dissolved in a mixture of distilled acetic anhydride (0.5 mL) and pyridine (1.5 mL). The resulting solution was allowed to stir for about 6 h at ambient temperature and then poured into crushed ice (25 g) and extracted with ether (3×15 mL). The extract was washed several times with $CuSO_4$ solution followed by usual work-up gave a crude product. This was purified by column chromatography (ethyl acetate–petroleum ether) to furnish **24** as a yellow solid. Mp: 168–169 °C; ν_{max} (KBr, cm^{-1}): 1768, 1727, 1668, 1587, 1469, 1369, 1257, 1031, 944, 790, 759, 678, 584; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74–7.58 (m, 3H), 7.09 (s, 1H), 4.07 (s, 3H), 3.73 (s, 3H), 3.68–3.58 (m, 1H), 3.43–3.29 (m, 1H), 2.97–2.89 (m, 2H), 2.78–2.68 (m, 1H), 2.47 (s, 3H), 2.17–2.03 (m, 1H), 1.98–1.86 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 185.7, 181.9, 175.3, 170.1, 159, 147.3, 144.1, 136.8, 136.1, 134.5, 132.6, 129.8, 126.5, 122.1, 119.1, 117.1, 56.6, 51.9, 39.7, 31, 29.4, 24.1, 21.2; HRMS *m/z* (ESI) calcd for $C_{23}H_{20}O_7$ (M^++H): 409.1229; found: 409.1239.

5.5.18. Ethyl 3-chloro-6-hydroxy-2-methylbenzoate (27). To a stirred solution of ethyl 2-hydroxy-6-methylbenzoate (**26**) (1 g, 5.55 mmol) in acetic acid (5 mL) was added dropwise a solution of chlorine (0.470 g, 6.62 mmol) in acetic acid (3 mL) and stirring was continued for additional 2 h. The solution was evaporated to dryness and the residue was extracted with ethyl acetate (2×25 mL) and usual work-up of the extract furnished the product **27**, which was further purified by column chromatographic separation using petroleum ether–ethyl acetate (10:1). White solid. Yield: 75%; mp: 54–55 °C; ν_{max} (KBr, cm^{-1}): 3439, 1664, 1597, 1452, 1382, 1320, 1293, 1213, 1023, 914; ^{1}H NMR (200 MHz, $CDCl_3$): 10.95 (s, 1H), 7.38 (d, 1H, *J*=10.0 Hz), 6.79 (d, 1H, *J*=10.0 Hz), 4.44 (q, 2H, *J*=7.0 Hz), 2.62 (s, 3H), 1.43 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 170.7, 160.6, 137.6, 134.7, 125.8, 122.6, 116.4, 62.0, 19.4, 14.0; HRMS *m/z* (ESI) calcd for $C_{10}H_{11}{}^{35}ClO_3$ (M^++H): 215.0475; found: 215.0466.

5.5.19. Ethyl 3,5-dichloro-2-hydroxy-6-methylbenzoate (28). To a stirred solution of phenolic ester **26** (1.5 g, 8.3 mmol) in acetic acid, excess of chlorine gas (generated by dropwise addition of concd HCl to solid $KMnO_4$) was absorbed at room temperature for 2 h. After completion of the reaction, acetic acid was removed under reduced pressure and the residue was extracted with ethyl acetate (3×20 mL) and usual work-up of the combined extract furnished crude product **28**, which was purified by column chromatography. Yield: 79%; ν_{max} (KBr, cm^{-1}): 3408, 1577, 1453, 1387, 1319, 1287, 1278, 1031, 957, 808, 670; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 11.31 (s, 1H), 7.53 (s, 1H), 4.53–4.40 (q, 2H, *J*=7.2 Hz), 2.56 (s, 3H), 1.48–1.40 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 170.4, 156.1, 136.6, 134.3, 125.7, 120.4, 115.6, 62.7, 19.3, 14.1; HRMS *m/z* (ESI) calcd for $C_{10}H_{10}{}^{35}Cl_2O_3$ (M^++H): 249.0035; found: 249.0039.

5.5.20. Ethyl 3-chloro-6-methoxy-2-methylbenzoate (29). This compound was prepared from ethyl 3-chloro-6-hydroxy-2-methylbenzoate (**27**) following the general procedure in Section 5.5. Colorless liquid. Yield: 76%; ν_{max} (KBr, cm^{-1}): 2988, 1733, 1566, 1468, 1261, 1024, 808; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.30 (d, 1H, *J*=8 Hz), 6.70 (d, 1H, *J*=8 Hz), 4.40 (q, 2H, *J*=7 Hz), 3.79 (s, 3H), 2.81 (s, 3H), 1.37 (t, 3H, *J*=7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 167.4, 154.7, 133.8, 130.3, 126.3, 125.7, 109.8, 61.4, 56.0, 17.0, 14.1.

5.5.21. Ethyl 2-bromomethyl-3-chloro-6-methoxybenzoate (30). Benzylic bromination was performed using 1.1 equiv of NBS following the procedure adopted for the preparation of compound **40** from **39**. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.37 (d, 1H, J=8.8 Hz), 6.83 (d, 1H, J=8.8 Hz), 4.53 (s, 2H), 4.48 (q, 2H, J=7.2 Hz), 3.83 (s, 3H), 1.42 (t, 3H, J=7.2 Hz).

5.5.22. 4-Chloro-7-methoxyphthalide (31). An aqueous solution of silver nitrate (0.270 g, 1.6 mmol) was added to 50% ethanolic solution of ethyl 2-bromomethyl-3-chloro-6-methoxybenzoate (**30**) (0.410 g, 1.33 mmol). The resulting mixture was then stirred at room temperature for about 4–5 h. Solid materials were filtered off and the filtrate was evaporated. The residue on usual work-up furnished a crude mixture of products **31** and **34**. Phthalide **31** was separated by column chromatographic separation using petroleum ether and ethyl acetate (3:1). White solid. Yield: 19%; mp: 163–164 °C (lit.[16] mp: 167–168 °C); ν_{max} (KBr, cm^{-1}): 1759, 1485, 1288, 1028, 819; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.54 (d, 1H, J=8.6 Hz), 6.92 (d, 1H, J=8.6 Hz), 5.20 (s, 2H), 3.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 167.3, 157.4, 146.6, 135.2, 118.9, 115.2, 112.4, 67.4. 56.1; HRMS m/z (ESI) calcd for $C_9H_7{}^{35}ClO_3$ (M^+−H): 197.0005; found: 197.0004.

5.5.23. Ethyl 3-chloro-6-methoxy-2-nitrooxymethylbenzoate (34). This was obtained as a co-product in the reaction of ethyl 2-bromomethyl-3-chloro-6-methoxybenzoate (**30**) with aq silver nitrate as described above. Colorless liquid. Yield: 18%; ν_{max} (KBr, cm^{-1}): 1730, 1639, 1275, 851; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.40 (d, 1H, J=8.8 Hz), 6.91 (d, 1H, J=8.8 Hz), 5.59 (s, 2H), 4.39 (q, 2H, J=7.2 Hz), 3.84 (s, 3H), 1.37 (t, 3H, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 165.6, 155.4, 131.4, 128.0, 126.6, 113.7, 68.8, 61.7, 56.1, 29.6, 14.0.

5.5.24. 3-Bromo-4-chloro-7-methoxyphthalide (35). Benzylic bromination of compound **31** was performed using 1.2 equiv of *N*-bromosuccinimide according to the procedure adopted for compound **39**. Light brown colored liquid. Crude yield: 75% (as judged by NMR); ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.63 (d, 1H, J=8.8 Hz), 7.23 (s, 1H), 7.02 (d, 1H, J=8.8 Hz), 4.02, (s, 3H).

5.5.25. 4-Chloro-3-phenylthio-7-methoxyphthalide (36). To a stirred solution of 3-bromo-4-chloro-7-methoxyphthalide (**35**) (20 mg, 0.072 mmol) in dry chloroform, triethylamine (0.072 mmol) and thiophenol (0.072 mmol) were added and the resulting mixture was stirred for 4–5 h. After completion of the reaction, it was diluted with diethyl ether (15 mL), washed with 5% NaOH (15 mL) solution, and worked up in usual manner. Crude product **36** was purified by column chromatography. Yield: 50%; mp: 117–118 °C; ν_{max} (KBr, cm^{-1}): 1754, 1590, 1473, 1442, 1281, 1199, 1160, 1046, 946; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.52–7.43 (m, 3H), 7.26–7.19 (m, 3H), 6.82 (d, 1H, J=8.6 Hz), 6.50 (s, 1H), 3.90 (s, 3H).

5.5.26. Ethyl 3,4-dichloro-2-hydroxy-6-methylbenzoate (38). Excess chlorine gas was passed through a stirred solution of ethyl 6-methyl-2-oxo-3-cyclohexenecarboxylate (**37**) (1.00 g, 5.46 mmol) in acetic acid during half an hour and stirring was continued for additional 2 h. Acetic acid was removed in vacuo. The product was extracted with ethyl acetate (3×15 mL). The extract was dried over Na_2SO_4 and solvent was removed. The residue was then dissolved in CCl_4 (10 mL) and treated with 2 equiv of DBU with stirring at room temperature. Stirring was continued for 5–6 h. The reaction mixture was extracted with ethyl acetate (3×10 mL) and washed with cold 10% aq HCl. The extract was worked up in usual manner to give a crude product, which was purified by column chromatography to get pure **38**. White solid. Yield: 43%; mp: 98–99 °C; ν_{max} (KBr, cm^{-1}): 3445, 1657, 1387, 1259, 1193, 860, 800. ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 12.33 (s, 1H), 6.87 (s, 1H), 4.46 (q, 2H, J=7.2 Hz), 2.52 (s, 3H), 1.44 (t, 3H, J=7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 171.2, 159.7, 140.0, 138.2, 134.0, 123.6, 111.7, 62.4, 23.8, 14.1; HRMS m/z (ESI) calcd for $C_{10}H_{10}{}^{35}Cl_2O_3$ (M^++H): 249.0035; found: 249.0037.

5.5.27. Ethyl 3-chloro-2-methoxy-6-methylbenzoate (39). This compound was prepared as a colorless liquid from phenolic ester **5** (2.11 g, 9.84 mmol) following the general procedure in Section 5.5. Yield: 68%; ν_{max} (KBr, cm^{-1}): 1731, 1461, 1272, 1107, 807; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.27 (d, 1H, J=8.0 Hz), 6.88 (d, 1H, J=8.0 Hz), 4.41 (q, 2H, J=7.0 Hz), 3.90 (s, 3H), 2.28 (s, 3H), 1.39 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$+CCl_4): 166.8, 152.9, 134.9, 130.9, 130.6, 126.3, 125.1, 61.7, 61.1, 18.8, 14.2.

5.5.28. Ethyl 3-chloro-2-methoxy-6-dibromomethylbenzoate (40). A mixture of compound **39** (1.17 g, 5.12 mmol) and NBS (2.00 g, 11.2 mmol) in CCl_4 (15 mL) containing a catalytic amount of benzoyl peroxide was heated at reflux for 1 h while irradiated by a 100 W electric bulb. At the end of the reaction, the mixture was chilled (ice bath) and filtered. Removal of solvent from the filtrate furnished the crude dibromo compound **40**. This was further purified by column chromatography separation. Light yellow colored liquid. Yield: 67%; ν_{max} (KBr, cm^{-1}): 1720, 1461, 1268, 938, 692; ^{1}H NMR (200 MHz, $CDCl_3$+CCl_4): 7.72 (d, 1H, J=8.0 Hz), 7.51 (d, 1H, J=8.0 Hz), 6.75 (s, 1H), 4.46 (q, 2H, J=7.0 Hz), 3.91 (s, 3H), 1.44 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.0, 152.2, 138.5, 132.4, 131.7, 129.2, 126.2, 62.2, 62.0, 35.4, 14.1.

5.5.29. 6-Chloro-3-hydroxy-7-methoxyphthalide (41). A mixture of dibromo compound **40** (2.20 g, 5.7 mmol), concd hydrochloric acid (3 mL), acetic acid (3 mL), and water (10 mL) was heated at reflux for 4 h. The solution was concentrated to dryness under reduced pressure and the concentrate was extracted with saturated sodium bicarbonate solutions, which on acidification (10% aq HCl), extraction into ethyl acetate layer, and usual work-up of the organic phase furnished compound **41** as a crystalline solid. The undissolved part of the residue was further hydrolyzed by repeating the procedure described above to furnish **41** as a crystalline solid. Yield: 72%; mp: 147–148 °C (lit.[17] mp: 159–163 °C); ν_{max} (KBr, cm^{-1}): 1741, 1633, 1383; ^{1}H NMR (200 MHz, DMSO-d_6+$CDCl_3$): 7.60 (d, 1H, J=8.0 Hz), 7.16 (d, 1H, J=8.0 Hz), 6.42 (s, 1H), 5.16 (br s, 1H), 4.05 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$): 165.2, 153.9, 147.8, 136.1, 128.7, 119.2, 118.5, 96.5, 62.2; MS m/z (EI): 214 (80) M^+, 203, 196, 184, 178, 169, 156, 139, 126, 110, 99, 77.

5.5.30. Methyl 9-chloro-6-hydroxy-8-methoxybenz[*a*]-anthracene-7,12-dione-2-carboxylate (43). This compound was prepared from compound **2** according to the general procedure in Section 5.3. Red solid. Yield: 49%; mp: 234–235 °C; ν_{max} (KBr, cm^{-1}): 3426, 1725, 1644, 1570, 1459, 1314, 1265, 1222, 1019, 760; ^1H NMR (200 MHz, $CDCl_3$): δ 12.42 (s, 1H), 10.04 (s, 1H), 8.12 (d, 1H, J=8.4 Hz), 8.08 (d, 1H, J=8.6 Hz), 7.86 (d, 1H, J=8.4 Hz), 7.75 (d, 1H, J=8.6 Hz). 7.68 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H); HRMS *m/z* (ESI) calcd for $C_{21}H_{13}{}^{35}ClO_6$ (M^++H): 397.0479; found: 397.0468.

5.5.31. Methyl 9-chloro-6,8-dihydroxy-benz[*a*]anthracene-7,12-dione-2-carboxylate (44). To a stirred solution of compound **43** (40 mg, 0.105 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C under Ar-atmosphere was added anhydrous $AlCl_3$ (5 equiv). After 1 h of stirring at 0 °C, the reaction mixture was allowed to come to room temperature and stirring was continued for additional 6 h. The reaction mixture was quenched with 2 M HCl (4 mL). Usual work-up of the organic extract afforded a solid, which was purified by column chromatography ($CHCl_3$–petroleum ether, 3:1) to give **44** as a red solid. Yield: 78%; mp: 273–274 °C; ν_{max} (KBr, cm^{-1}): 3407 (br s), 1713, 1627, 1419, 1282, 1224, 1128, 1080, 994, 761; ^1H NMR (200 MHz, $CDCl_3$): δ 12.34 (s, 1H), 11.90 (s, 1H), 10.15 (s, 1H), 8.14 (dd, 1H, J=1.5 and 8.7 Hz), 7.83 (s, 2H), 7.76 (d, 1H, J=8.7 Hz), 7.71 (s, 1H), 4.02 (s, 3H); MS *m/z* (EI): 382 (100) M^+, 351 (64), 323 (39), 256, 236, 175, 137, 123, 103, 91, 80, 69, 54; HRMS *m/z* (ESI) calcd for $C_{20}H_{11}{}^{35}ClO_6$ (M^+−H): 381.0166; found: 381.0150.

5.5.32. Ethyl 2-methoxy-6-methyl-3-nitrobenzoate (46). Acetyl nitrate was prepared by dropwise addition of fuming HNO_3 (0.270 mg, 3 mmol) with rapid stirring to 1.5 mL of acetic anhydride taken in a flask at 0–10 °C. After 15 min, the resulting solution was added to a stirred solution of ethyl 2-methoxy-6-methylbenzoate (460 mg, 2.8 mmol) in acetic anhydride (4 mL) at temperature between 0 and −10 °C. Stirring was continued at this temperature for about 1 h and then allowed to come to room temperature. The mixture was then poured into 10 mL of cold water and triturated with saturated solution of $NaHCO_3$ solution and then extracted with ether (3×20 mL). Usual work-up of the combined extracts furnished a light yellow liquid. The crude product was purified by column chromatography to give compound **46** as a yellow liquid. Yield: 57%; ν_{max} (KBr, cm^{-1}): 1730, 1592, 1526, 1351, 1273, 1120, 1066; ^1H NMR (200 MHz, $CDCl_3$): 7.85 (d, 1H, J=8.4 Hz), 7.06 (d, 1H, J=8.4 Hz), 4.42 (q, 2H, J=7.1 Hz), 3.87 (s, 3H), 2.36 (s, 3H), 1.39 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.7, 150.7, 142.6, 140.8, 131.4, 125.8, 125.5, 63.3, 61.5, 19.0, 13.8.

5.5.33. Ethyl 6-methoxy-2-methyl-3-nitrobenzoate (47). This was obtained as a co-product during the nitration (described above) of ethyl 2-methoxy-6-methylbenzoate by acetyl nitrate. Light yellow solid. Yield: 43%; mp: 70 °C; ν_{max} (KBr, cm^{-1}): 1730, 1603, 1583, 1513, 1471, 1347, 1261, 1110, 1070, 1027, 824, 650; ^1H NMR (200 MHz, $CDCl_3$): δ 8.07 (d, 1H, J=9.2 Hz), 6.83 (d, 1H, J=9.2 Hz), 4.41 (q, 2H, J=6.9 Hz), 3.90 (s, 3H), 2.48 (s, 3H), 1.37 (t, 3H, J=6.9 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): 166.2, 159.3, 142.6, 132.5, 127.7, 126.3, 108.5, 61.7, 56.2, 16.9, 13.9.

5.5.34. Ethyl 3-amino-6-methoxy-2-methylbenzoate (48). To a solution of nitro compound **46** (1.5 g, 6.24 mmol) in ethanol (25 mL), 20 mg of 10% Pd–C was added. The solution was then deoxygenated under vacuum and was allowed to absorb hydrogen gas from a balloon. The mixture was stirred at rt for 5–6 h under hydrogen atmosphere. After completion of the reaction, the catalyst was removed by filtration and solvent was removed under vacuum. The crude product was purified by column chromatographic separation using a 1:5 mixture of ethyl acetate and petroleum ether as eluant. Colorless liquid. Yield: 77%; ν_{max} (KBr, cm^{-1}): 3447, 3369, 1718, 1652, 1550, 1506, 1495, 1264, 1058, 817; ^1H NMR (200 MHz, $CDCl_3$): δ 6.80–6.76 (d, 1H, J=8.4 Hz), 6.74–6.70 (d, 1H, J=8.4 Hz), 4.46–4.35 (q, 2H, J=7.0 Hz), 3.80 (s, 3H), 2.20 (s, 3H), 1.42–1.35 (t, 3H, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 167.9, 143.4, 137.4, 128.1, 125.6, 124.2, 116.7, 60.6, 60.0, 17.8, 13.7.

5.5.35. Ethyl 3-amino-2-hydroxy-6-methylbenzoate (49). A mixture of nitro compound **46** (250 mg, 1.04 mmol), $SnCl_2\cdot 2H_2O$ (1.17 g, 5.18 mmol), and ethanol (8 mL) was heated at 70 °C for 1 h. After the reaction was cooled to room temperature, 10% aq NaOH was added until the mixture became strongly alkaline. Extraction of the mixture with ethyl acetate (15 mL) followed by usual work-up yielded, after column chromatographic separation, amino phenol **49** as a colorless liquid in 19% yield along with amine **48** in 45% yield. ν_{max} (KBr, cm^{-1}): 3457, 3376, 1723, 1655, 1598, 1451, 1291, 1261, 1189, 1026, 799, 758; ^1H NMR (200 MHz, $CDCl_3$): δ 11.61 (br s, 1H), 6.78 (d, 1H, J= 8.1 Hz), 6.56 (d, 1H, J=8.1 Hz), 4.43 (q, 2H, J=7.2 Hz), 3.80 (s, 3H), 2.83 (br s, 2H), 1.42 (t, 3H, J=7.2 Hz).

5.5.36. Ethyl 3-ethoxyamino-2-methoxy-6-methylbenzoate (50). This was obtained as a co-product during the reduction of nitro compound **46** by hydrogenation over 10% Pd–C in ethanol. Reddish liquid. Yield: 18%; ν_{max} (KBr, cm^{-1}): 3401 (br s), 1728, 1608, 1504, 1456, 1329, 1265, 1118, 1062, 802; ^1H NMR (200 MHz, $CDCl_3$): δ 6.83 (d, 1H, J=8.2 Hz), 6.31 (d, 1H, J=8.2 Hz), 4.40 (q, 2H, J=7.1 Hz), 3.80 (s, 3H), 3.14 (q, 2H, J=7.1 Hz), 2.20 (s, 3H), 1.38 (t, 3H, J=7.1 Hz), 1.25 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$,): 168.3, 149.4, 143.6, 139.5, 127.9, 126.1, 122.7, 112.2, 60.9, 60.7, 38.2, 18.2, 14.7, 14.1.

5.5.37. Ethyl 3-fluoro-2-methoxy-6-methylbenzoate (52). Amine **48** (210 mg, 1.0 mmol) was dissolved in a mixture of concd HCl (2 mL) and water (5 mL). The solution was cooled and held at the range of 0 to −10 °C. Diazotization was done by dropwise addition of an aq solution of $NaNO_2$ (80 mg, 1.16 mmol) dissolved in water. While this solution was still cold, 65% aq HPF_6 (0.2 mL) was added rapidly in one portion with the help of plastic disposal syringe. The mixture was cooled again to 0–5 °C before filtration. The phosphorous hexafluoride salt **51** was collected by filtration, washed with cold water followed by a 4:1 mixture of diethyl ether, and MeOH to facilitate drying. The solid was powdered and dried in vacuum overnight. Decomposition of phosphorous hexafluoride salt **51** was carried out by portionwise addition through the condenser fitted with a flask held at decomposition temperature at 120–125 °C. After the decomposition was complete, the residue was extracted with ethyl acetate (20 mL) and worked up in the

usual manner to furnish the crude product. The crude product was purified by column chromatography (ethyl acetate–petroleum ether, 1:15) to give **52** as a colorless liquid. Yield: 19%; ν_{max} (KBr, cm^{-1}): 1731, 1608, 1490, 1417, 1276, 1133, 1066, 1020, 958, 813; ^1H NMR (200 MHz, $CDCl_3$): δ 7.00 (dd, 1H, J=8.5 and 11.2 Hz), 6.83 (dd, 1H, J=5.1 and 8.5 Hz), 4.39 (q, 2H, J=7.1 Hz), 3.93 (d, 3H, J=1.8 Hz), 2.25 (s, 3H), 1.38 (t, 3H, J=7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 167.0 (d, J=3.5 Hz), 153.3 (d, J=244 Hz), 144.5 (d, J=12.3 Hz), 131.4 (d, J=3.6 Hz), 129.6, 125.2 (d, J=6.7 Hz), 117.5 (d, J=18.9 Hz), 61.8 (d, J=5.6 Hz), 61.3, 18.6, 14.2.

5.5.38. Ethyl 6-dibromomethyl-3-fluoro-2-methoxybenzoate (53). This compound was prepared from **52** using 2 equiv of NBS following the procedure described for the preparation of compound **40** from **39**. Colorless liquid. Yield: 57%; ν_{max} (KBr, cm^{-1}): 1723, 1458, 1266, 935, 703; ^1H NMR (200 MHz, $CDCl_3$): δ 7.71 (dd, 1H, J=4.5 and 9.0 Hz), 7.31 (dd, 1H, J=9.0 and 15.3 Hz), 6.79 (s, 1H), 4.45 (q, 2H, J=6.9 Hz), 3.96 (d, 3H, J=1.9 Hz), 1.42 (t, 3H, J=6.9 Hz).

5.5.39. 6-Fluoro-3-hydroxy-7-methoxy-3*H*-isobenzofuran-1-one (54). This compound was prepared from the dibromo compound **53** following the procedure described for the synthesis of compound **41** from **40**. White crystalline solid. Yield: 75%; mp: 131 °C; ν_{max} (KBr, cm^{-1}): 3352, 1731, 1503, 1426, 1294, 1261, 1139, 1108, 1057, 1031, 908, 839, 772, 732; ^1H NMR (200 MHz, $CDCl_3$): δ 7.42 (dd, 1H, J=8.2 and 11.6 Hz), 7.20 (dd, 1H, J=3.5 and 8.2 Hz), 6.50 (s, 1H), 4.20 (d, 3H, J=2.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 165.4, 154.7 (d, J=247 Hz), 145.8 (d, J=11.5 Hz), 142.4, 123.3 (d, J=21.6 Hz), 119.2, 117.3 (d, J=8.1 Hz), 96.4, 62.0 (d, J=4.9 Hz); HRMS m/z (ESI) calcd for $C_9H_7FO_4$ (M^++H): 199.0407; found: 199.0406.

5.5.40. 3-Cyano-6-fluoro-7-methoxy-3*H*-isobenzofuran-1-one (55). This compound was prepared from the phthalaldehydic acid **54** according to the procedure adopted for the preparation of chlorocyanophthalide **3a** from **41**. White crystalline solid. Yield: 83%; mp: 104–105 °C; ν_{max} (KBr, cm^{-1}): 1789, 1603, 1501, 1291, 1255, 1087, 1022, 971, 925; ^1H NMR (200 MHz, $CDCl_3$): δ 7.53 (dd, 1H, J=8.3 and 11.7 Hz), 7.24 (dd, 1H, J=8.3 and 8.5 Hz), 5.98 (d, 1H, J=0.7 Hz), 4.24 (d, 3H, J=3.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): 159.1, 151.5 (d, J=250 Hz), 146.3 (d, J=11.8 Hz), 137.3, 124.1 (d, J=22.6 Hz), 111.5, 111.3 (d, J=8.1 Hz), 108.6, 59.5, 57.4 (d, J=6.0 Hz); HRMS m/z (ESI) calcd for $C_{10}H_6FNO_3$ (M^++H): 208.0410; found: 208.0405.

5.5.41. Methyl 9-fluoro-6-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione-2-carboxylate (56). This compound was prepared by annulation of 6-fluoro-7-methoxycyanophthalide (**55**) with Michael acceptor **4** following the general procedure in Section 5.2. Orange solid. Yield: 74%; mp: 153–54 °C; ν_{max} (KBr, cm^{-1}): 3432, 1731, 1631, 1572, 1449, 1411, 1327, 1262, 1102, 1017, 796; ^1H NMR (200 MHz, $CDCl_3$): δ 13.02 (s, 1H), 8.02 (dd, 1H, J=5.0 and 8.7 Hz), 7.45 (dd, 1H, J=8.8 and 10.1 Hz), 7.06 (s, 1H), 4.08 (d, 3H, J=1.3 Hz), 3.74 (s, 3H), 3.60 (dd, 1H, J=5.3 and 18.2 Hz), 3.30 (dd, 1H, J=9.5 and 18.2 Hz), 2.97–2.89 (m, 2H), 2.76–2.68 (m, 1H), 2.21–2.12 (m, 1H), 1.98–1.90 (m, 1H); HRMS m/z (ESI) calcd for $C_{21}H_{17}FO_6$ (M^++H): 385.1087; found: 385.1057.

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Nanostaircase formation in the solid state from self-assembling synthetic terephthalamides with a common molecular scaffold

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Abstract—The design and construction of nanostructured materials using proper self-assembling molecular building blocks is a real challenge to scientists. Here, we present the formation of a new nano-architecture, i.e., nanostaircase in the solid state by using molecular building blocks, which are amenable to self-assembly in a directed manner to form the specific nanostructure. The molecular building blocks are terephthalamides **1**–**4**, which are bis-terephthalamides of methyl esters of various α-amino acids including L-leucine **1**, D-leucine **2**, L-isoleucine **3**, and α-aminoisobutyric acid (Aib) **4**. All terephthalamides presented here, irrespective of their different side chain residues or stereochemistry, self-assemble to form supramolecular nanostaircase structures in crystals. Each terephthalamide contains two good hydrogen-bond donors and two hydrogen-bond acceptors. Two N–H···O hydrogen bonds and C–H···π interactions are responsible for the formation and stabilization of the nanostaircase structures in crystals. The molecular building blocks are packed orthogonally to each other in crystals and this arrangement can help the formation of nanostaircase structure upon self-assembly.

1. Introduction

Fabrication of various nanomaterials can be achieved by mainly two approaches: one approach is photolithography and the other is the 'bottom-up' approach. Using photolithography only two-dimensional nano-scaled materials can be prepared. However, using 'bottom-up' approach, where molecular self-assembly plays a key role, three-dimensional nanostructured materials can be constructed.[1] Another advantage of using a bottom-up approach is that well-defined nanostructured materials can be prepared by using suitable molecular building blocks and the property of the nanomaterials can be tuned by designing appropriate, self-assembling, molecular building blocks. The design and construction of various nanostructured materials using molecular self-assembly is a very active area of current research.[2] Nanotubes obtained from various, suitable, self-assembling, organic compounds based molecular building blocks have been well studied.[3] Similarly peptide based nanorods have been constructed using oligopeptide scaffolds.[4] Peptide nanotubes have been used in many applications such as structure directed synthesis of silver nanowires,[5] electrochemical applications.[6] There are also numerous examples of self-assembling peptide based nanofibers.[7]

There are several examples of metal ion directed supramolecular staircase formation.[8] Several structures of terephthalamides have also been reported using either single crystal X-ray diffraction studies or neutron fiber diffraction studies. However, in all previously mentioned bis-terephthalamide structures only intermolecularly hydrogen-bonded supramolecular β-sheets,[9] ribbon[10] or helix[11] are reported, but not a supramolecular nanostaircase. We decided it would be interesting to use a conformationally rigid molecular scaffold, which can pack at about right angles to each other using intermolecular hydrogen bonding and other noncovalent interactions like C–H···π, π···π interactions to form a specific, well-defined, supramolecular nano-architecture.

In the course of our continuing interest in constructing various supramolecular nano-architectures including nanorod[4] and nanotube,[12] we have synthesized and characterized four compounds **1**–**4**, which are bis-terephthalamides of methyl esters of α-amino acids L-leucine, D-leucine, L-isoleucine, and α-aminoisobutyric acid (Aib), respectively. A schematic representation of all four terephthalamides is shown in Figure 1. In this paper, we present the formation of nanostaircase structures in crystals from a series of self-assembling terephthalamides with a common molecular scaffold.

Keywords: C–H···π interactions; Nanostaircase; Terephthalamide; Self-assembly; Hydrogen bonds.
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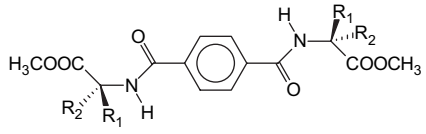

1: R_1 = -$CH_2CH(CH_3)_2$, R_2 = H
2: R_1 = H, R_2 = -$CH_2CH(CH_3)_2$
3: R_1 = -$CH(CH_3)(CH_2CH_3)$, R_2 = H
4: R_1 = R_2 = -CH_3

Figure 1. Schematic representation of terephthalamides **1**, **2**, **3**, and **4**.

These supramolecular nanostaircase structures are formed and stabilized by various noncovalent interactions including intermolecular hydrogen bonding and C–H$\cdots\pi$ interactions.

2. Results and discussion

Colorless single crystals of terephthalamides **1**–**4** were grown from methanol–water solution by slow evaporation. The crystal structure data for four terephthalamides are given in Table 1. Terephthalamides **1**–**3** crystallize in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit. The monoclinic crystals of terephthalamide **4** crystallize in the centrosymmetric space group $P2_1/c$ with 1/2 molecule in the asymmetric unit. Selected backbone torsion angles of all terephthalamides are listed in Table 2. In terephthalamides **1** and **2** the isobutyl groups have large atomic displacement parameters (ADPs). In residues with long side chains, the side chains are more flexible, hence large ADPs are observed for these groups. From the crystal structure of terephthalamide **1**, it is evident that there is no intramolecular

Table 1. Crystallographic data for terephthalamides **1**, **2**, **3**, and **4**

	1	**2**	**3**	**4**
Formula	$C_{22}H_{32}N_2O_6$	$C_{22}H_{32}N_2O_6$	$C_{22}H_{32}N_2O_6$	$C_{18}H_{24}N_2O_6$
Formula weight	420.5	420.5	420.5	364.39
Crystallizing solvent	Methanol–water	Methanol–water	Methanol–water	Methanol–water
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Temperature [K]	293	293	293	293
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_1/c$
a [Å]	10.022 (6)	9.9970 (12)	10.148 (7)	11.288 (5)
b [Å]	10.094 (6)	10.1066 (13)	10.645 (7)	9.657 (4)
c [Å]	12.626 (7)	12.6432 (16)	11.592 (8)	9.601 (4)
β [°]	108.719 (9)	108.679 (2)	109.795 (10)	110.008 (7)
V [Å^3]	1209.7 (12)	1210.1 (3)	1178.2 (14)	983.3 (7)
Z	2	2	2	2
ρ_{calcd} [g cm^{-3}]	1.154	1.154	1.185	1.231
λ [Å]	0.71073	0.71073	0.71073	0.71073
μ [mm^{-1}]	0.084	0.084	0.086	0.093
$2\theta_{max}$	46.6	46.6	53	53.2
F(000)	452	452	452	388
Total reflns	7458	7471	8599	7173
Unique reflns	1831	1834	2344	1925
Reflns used	1610	1630	2065	1654
Parameters	271	271	303	166
$R1$ [$I>2\sigma(I)$]	0.0884	0.0925	0.0480	0.0665
$wR2$	0.2586	0.2742	0.1376	0.1984
Max. and min. electron density [e/Å^3]	0.31, −0.20	0.35, −0.25	0.19, −0.14	0.50, −0.25

Table 2. Selected backbone torsional angles (°) of terephthalamides **1**, **2**, **3**, and **4**

Terephthalamide **1**			
C2M–O2M–C2′–C2A	174.6 (14)	C1M–O1M–C1′–C1A	−170.3 (16)
O2M–C2′–C2A–N2	167.8 (8)	O1M–C1′–C1A–N1	−45.5 (13)
C2′–C2A–N2–C8	−110.6 (8)	C1′–C1A–N1–C1	−82.0 (9)
C2A–N2–C8–C5	−179.8 (6)	C1A–N1–C1–C2	179.5 (7)
Terephthalamide **2**			
C2M–O2M–C2′–C2A	167.8 (16)	C1M–O1M–C1′–C1A	−176.1 (14)
O2M–C2′–C2A–N2	45.9 (12)	O1M–C1′–C1A–N1	−167.9 (8)
C2′–C2A–N2–C8	83.4 (8)	C1′–C1A–N1–C1	110.3 (8)
C2A–N2–C8–C5	179.0 (6)	C1A–N1–C1–C2	179.4 (6)
Terephthalamide **3**			
C2M–O2M–C2′–C2A	177.2 (4)	C1M–O1M–C1′–C1A	−179.2 (4)
O2M–C2′–C2A–N2	168.4 (3)	O1M–C1′–C1A–N1	169.6 (3)
C2′–C2A–N2–C8	−133.6 (3)	C1′–C1A–N1–C1	−103.7 (3)
C2A–N2–C8–C5	178.0 (2)	C1A–N1–C1–C2	175.6 (3)
Terephthalamide **4** (the atom names with a terminating 'a' belong to the second half of the molecule related by a inversion center)			
C1M–O1M–C1′–C1A	−174.8 (3)	C1Ma–O1Ma–C1′a–C1Aa	174.8 (3)
O1M–C1′–C1A–N1	−49.6 (3)	O1Ma–C1′a–C1Aa–N1a	49.6 (3)
C1′–C1A–N1–C4	−47.6 (3)	C1′a–C1Aa–N1a–C4a	47.6 (3)
C1A–N1–C4–C2	−175.36 (16)	C1Aa–N1a–C4a–C2a	175.36 (16)

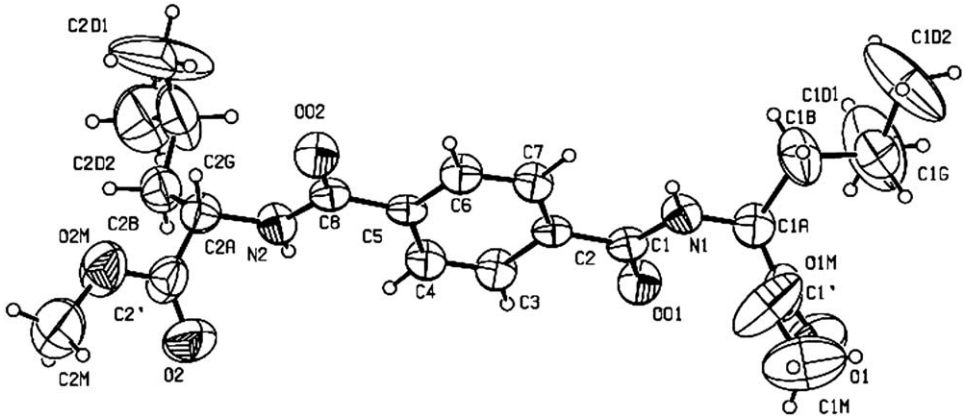

Figure 2. ORTEP diagram of terephthalamide **1** with atomic numbering scheme. Ellipsoids at 30% probability.

hydrogen bond and the molecule possesses an overall extended backbone conformation (Fig. 2). Terephthalamide **1** self-assembles to form a supramolecular nanostaircase structure in crystals with various noncovalent interactions being present including intermolecular hydrogen bonding and CH···π interactions (Fig. 3). There are two intermolecular hydrogen bonds (N1–H1···O02, 2.058 (5) Å, 2.882 (7) Å, 160.03 (35)°, symmetry equivalent $-x+1$, $y+0.5$, $-z+2$ and N2–H2···O01, 2.141 (5) Å, 2.945 (7) Å, 155.35 (36)°, symmetry equivalent $-x$, $y-0.5$, $-z+2$) that connect the individual molecules of terephthalamide **1** to form supramolecular nanostaircase structure in which the length of the steps is 7.5 Å (0.75 nm) and the height of the steps of the staircases is also 7.5 Å (0.75 nm). In crystals, individual molecules are stacked orthogonally to each other using N–H···O hydrogen bonding and C–H···π interactions and this particular arrangement helps to form the supramolecular nanostaircase structure. There is a C–H···π interaction[13] between C2D2–H2D6 with the centroid of the phenyl ring of terephthalamide moiety (C2D2–H2D6···π, 3.26 Å, 4.047 Å, 140.97°) (Fig. 6a) in supramolecular nanostaircase of the terephthalamide **1**.

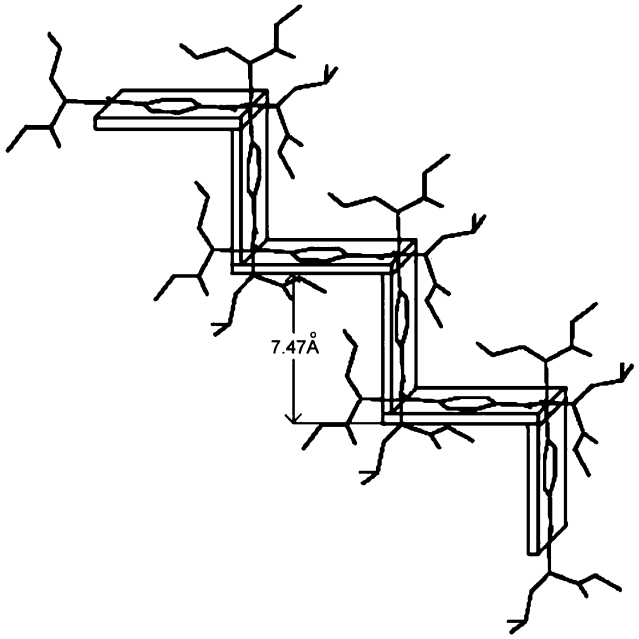

Figure 3. Crystal packing diagram of the terephthalamide **1** illustrating the supramolecular nanostaircase structure.

Terephthalamide **2** contains two D-leucine residues and adopts a molecular structure, which is a mirror image of terephthalamide **1** (Fig. 4). The only difference between them is the reversal of sign of the comparable backbone torsion angles (O2M–C2′–C2A–N2 and O1M–C1′–C1A–N1; C2′–C2A–N2–C8 and C1′–C1A–N1–C1) of terephthalamide **2** with respect to terephthalamide **1** (Table 2). Terephthalamide **2** also self-assembles to form a supramolecular nanostaircase (Fig. 5) in crystals through various noncovalent interactions including intermolecular hydrogen bonding (N1–H1···O02, 2.144 (5) Å, 2.946 (8) Å, 154.90 (39)°, symmetry equivalent $-x+2$, $y+0.5$, $-z+2$ and N2–H2···O01,

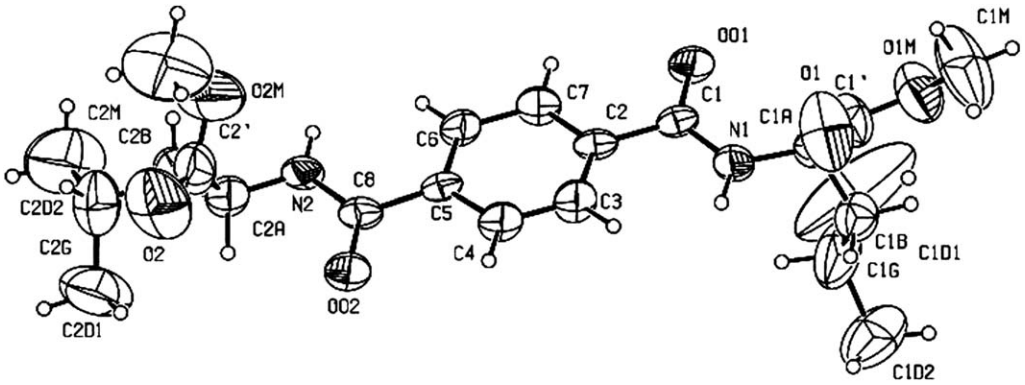

Figure 4. ORTEP representation of terephthalamide **2** with atomic numbering scheme. Ellipsoids at 30% probability.

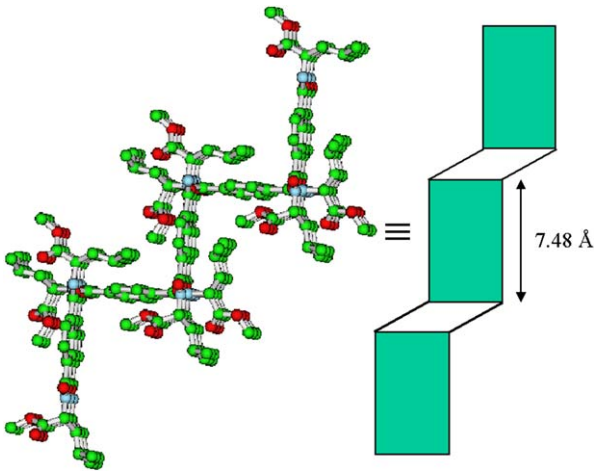

Figure 5. Nanostaircase arrangement of terephthalamide **2** in crystals and its schematic representation.

2.050 (5) Å, 2.877 (7) Å, 160.84 (35)°, symmetry equivalent $-x+1$, $y-0.5$, $-z+2$). There is a C–H···π interaction between C1D2–H1D5 with centroid of the phenyl ring of terephthalamide moiety (C1D2–H1D5···π, 3.18 Å, 3.982 Å, 142.66°) (Fig. 6b) in supramolecular nanostaircase of the terephthalamide **2**.

Both L-leucine residues of terephthalamide **1** have been substituted by L-isoleucine residues in terephthalamide **3** (Fig. 7). However, the inherent characteristic feature of terephthalamide **3** is similar to that of terephthalamide **1**. The only difference between them is the difference among numerical values of the comparable backbone torsion angles (O2M–C2′–C2A–N2 and O1M–C1′–C1A–N1; C2′–C2A–N2–C8 and C1′–C1A–N1–C1) of terephthalamide **3** (Table 2). Terephthalamide **3** also self-associates to form a supramolecular nanostaircase architecture utilizing two intermolecular hydrogen bonds (N1–H1···O02, 2.211 (36) Å, 2.999 (4) Å, 166.88 (341)°, symmetry equivalent $-x+1$, $y+0.5$, $-z+1$ and N2–H2···O01, 2.337 (42) Å, 3.089 (5) Å, 163.16 (387)°, symmetry equivalent $-x$, $y-0.5$, $-z+1$) (Fig. 8). There is a C–H···π interaction between C2D1–H2D2 with centroid of the phenyl ring of terephthalamide moiety (C2D1–H2D2···π, 3.378 Å, 4.009 Å, 125.2°) in the supramolecular nanostaircase of terephthalamide **3**.

The achiral terephthalamide **4** also adopts an extended backbone molecular conformation (Fig. 9). The comparable backbone torsion angles of the symmetric terephthalamide **4** (O1M–C1′–C1A–N2 and O1Ma–C1′a–C1Aa–N1a; C1′–C1A–N1–C4 and C1′a–C1Aa–N1a–C4a) have the same numerical values but are opposite in sign (Table 2). Utilizing two intermolecular hydrogen bonds (N1–H3···O01, 2.022 (25) Å, 2.856 (3) Å, 174.10 (221)°, symmetry equivalent x, $-y+0.5$, $z-0.5$ and N1a–H3a···O01, 2.022 (25) Å, 2.856 (3) Å, 174.10 (221)°, symmetry equivalent $-x+1$, $y+0.5$, $-z+0.5$, the 'a' after atom name indicates that the second half of the molecule is related by an inversion center), terephthalamide **4** forms a supramolecular nanostaircase architecture (Fig. 10). The nanostaircase structure is also stabilized by C–H···π interaction between C1B2–H1B5 with centroid of the phenyl ring of terephthalamide

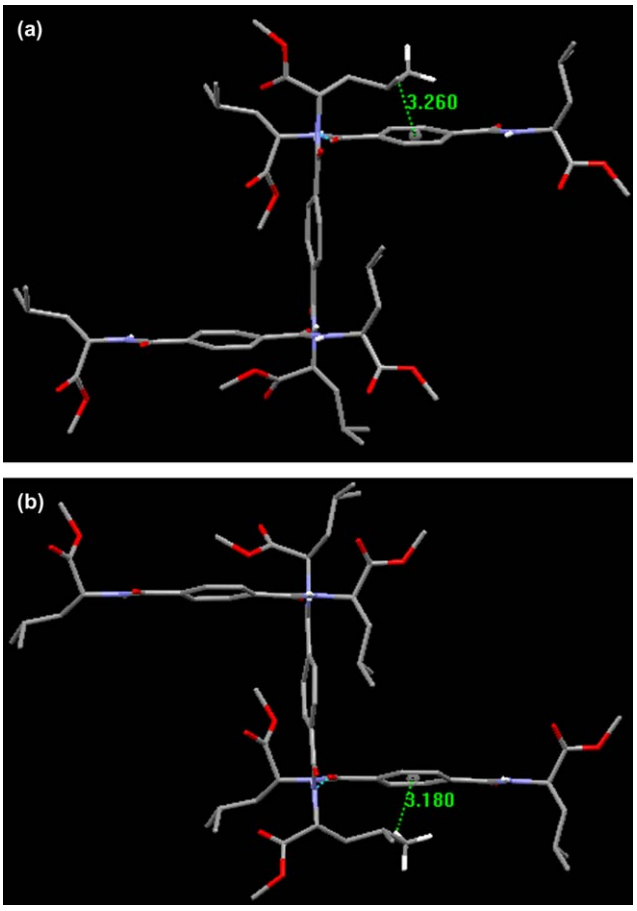

Figure 6. Packing modes of nanostaircase structures by C–H···π interactions in (a) terephthalamide **1** and (b) terephthalamide **2** in crystals.

moiety (C1B2–H1B5···π, 3.427 Å, 4.355 Å, 162.54°) (Fig. 11) of the terephthalamide **4**.

All four terephthalamides with different amino acid side chains or stereochemistry self-assemble in a similar manner in which the molecular building blocks are packed against each other orthogonally to form a nanostaircase structure utilizing N–H···O hydrogen bonding and C–H···π interactions. It is interesting to note that the previously reported crystal structure of *N*,*N*′-bis(methoxycarbonylmethyl)-terephthalamide[10] (molecule **A**), reveals that the molecule **A** self-assembles through two intermolecular hydrogen bonds along the crystallographic *b* axis to form a supramolecular ribbon or sheet-like structure (Fig. 12). In this molecular packing, the aromatic rings of these adjacent molecules are close to perpendicular direction with a distance of 5.13 Å between the centers of the two aromatic rings. In the formation of the above mentioned ribbon or sheet-like structure, the self-assembling molecules are stacked atop one another and they are interconnected by only N–H···O hydrogen bonding. However, in our case molecular building blocks are stacked almost orthogonally to each other in all four terephthalamides and they are associated with intermolecular –C═O···H–N– hydrogen bonding as well as C–H···π interactions. This helps to form supramolecular nanostaircase structures. The step-length of the nanostaircase is ~7.5 Å and the height of the steps is ~7.5 Å. Here, the reported terephthalamides **1**–**4** fail to stack atop one another to

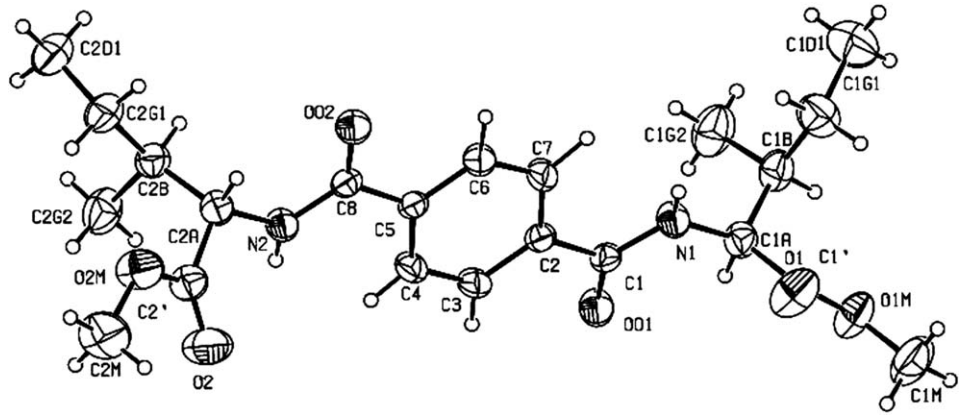

Figure 7. Molecular conformation of terephthalamide **3** with atomic numbering scheme. Thermal ellipsoids are shown at 30% probability level.

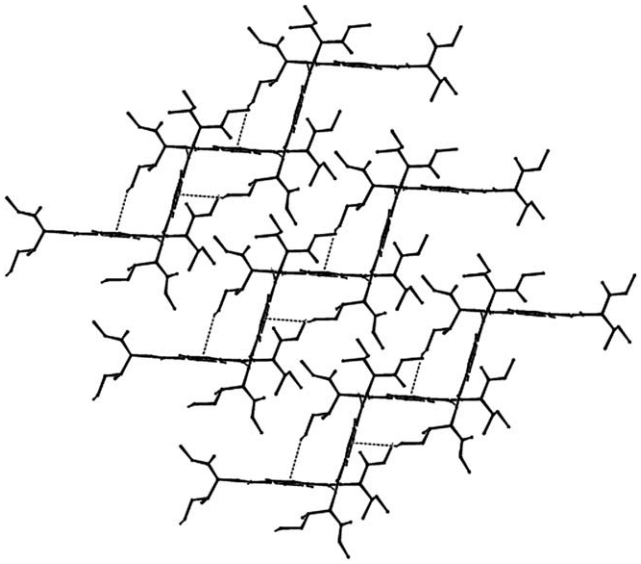

Figure 8. Supramolecular staircase structure obtained from the higher order self-assembly of the terephthalamide **3** in crystals. The C–H$\cdots\pi$ interactions are shown as dotted line.

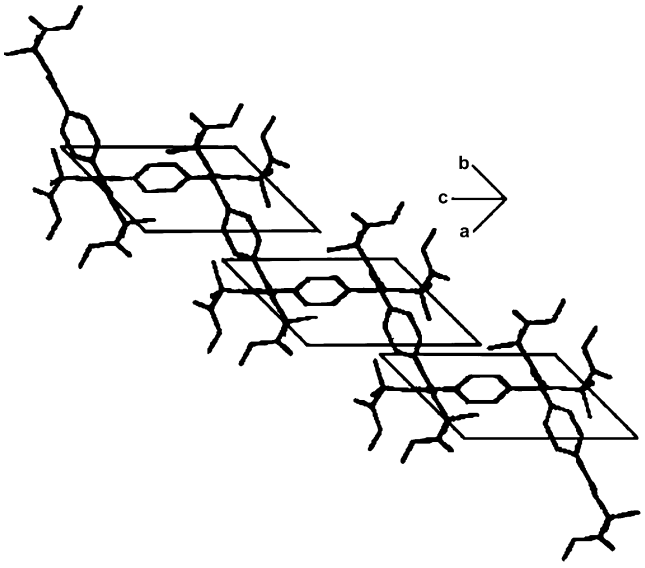

Figure 10. Packing diagram of the terephthalamide **4** showing the supramolecular staircase architecture in crystals stabilized by multiple intermolecular hydrogen bonds.

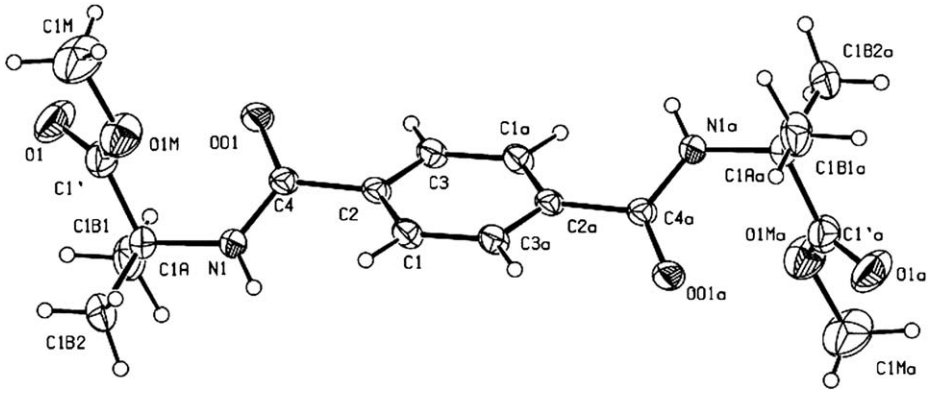

Figure 9. The molecular structure of terephthalamide **4** with atomic numbering scheme. Ellipsoids at 30% probability.

form supramolecular sheet- or ribbon-like structure, which might be due to the steric hindrances associated with the bulky amino acid side chains. Orthogonal packing between the self-associating molecular building blocks (terephthalamides **1**–**4**) may be favored by the presence of C–H$\cdots\pi$ interactions between the amino acid side chain H-atoms and the centrally located aromatic moiety, which was absent in the molecular packing of the molecule **A**.

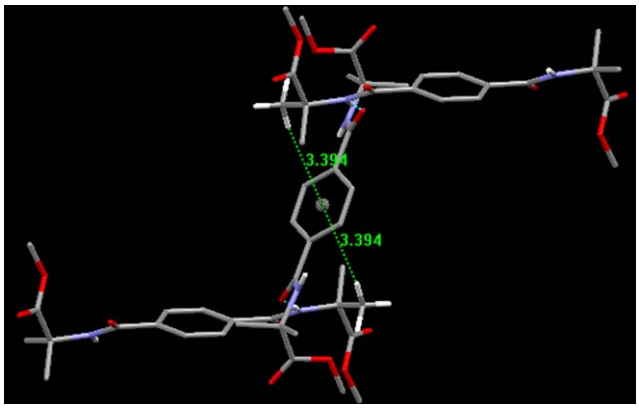

Figure 11. A view of interconnected C–H···π interactions in terephthalamide **4**.

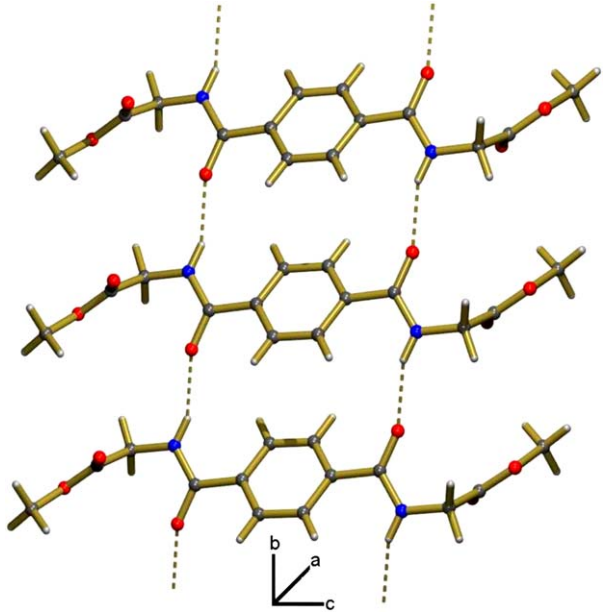

Figure 12. Crystal packing of terephthalamide **A** showing the formation of intermolecularly hydrogen-bonded ribbon-like structure. Intermolecular hydrogen bonds are shown as dotted lines.

3. Conclusion

This paper clearly demonstrates the formation and stabilization of supramolecular nanostaircase structures in crystals using suitable self-assembling synthetic terephthalamides with a common molecular scaffold. Here, the self-assembly of molecular building blocks is guided in such a way that individual molecules can pack at about right angles to each other using various noncovalent interactions including C═O···H–N hydrogen bonding and CH···π interactions to form nanostaircase structures. We have identified here a common structural unit (i.e., bis-terephthalamide based methyl esters of various α-amino acids containing different side chains or stereochemistry), which self-assembles in similar fashion to form a well-defined nanostructure, namely, a nanostaircase. This result may open up a new field of constructing new supramolecular nano-structures (using appropriate molecular building blocks), which has some useful implications in supramolecular chemistry and as well as in crystal engineering.[14]

4. Experimental

4.1. General

Reagent or analytical grade material was obtained from commercial suppliers and used without further purification. Terephthalamides **1**, **2**, **3**, and **4** were synthesized by the conventional solution phase methodology.[15] A solution of terephthalic acid (0.83 g, 5 mmol) in 10 mL of DMF was cooled in an ice-water bath. The H–Xxx–OMe (Xxx=Leu, D-Leu, Ile, and Aib) was isolated from the corresponding methyl ester hydrochloride (20 mmol) by neutralization, subsequent extraction with ethyl acetate and the ethyl acetate extract was concentrated to 10 mL. This was then added to the reaction mixture, followed immediately by DCC (2.06 g, 10 mmol) and HOBt (1.35 g, 10 mmol). The reaction mixture was stirred for three days. The residue was taken in ethyl acetate (60 mL) and the DCU was filtered off. The organic layer was washed with 2 M HCl (3×50 mL), brine (2×50 mL), 1 M sodium carbonate (3×50 mL), and brine (2×50 mL), then dried over anhydrous sodium sulfate and evaporated in vacuo to yield terephthalamides **1**–**4** as white solid. Purification was done by silica gel column (100–200 mesh) using ethyl acetate as eluent. The final compounds were fully characterized by IR spectroscopy, 300 MHz ^{1}H NMR spectroscopy, and mass spectrometry. Optical rotations were measured on a Perkin–Elmer 341LC polarimeter. IR spectra were recorded on a Shimadzu (Japan) model FTIR spectrophotometer with KBr pellets. ^{1}H NMR spectra were recorded with a Brüker DPX 300 MHz spectrometer. Mass spectra were recorded on a Hewlett Packard Series 1100MSD spectrometer.

4.1.1. Terephthalamide 1. Yield=1.68 g (4 mmol, 80%); R_f=0.72 (EtOAc); $[\alpha]_D^{20}$ +42.3 (c=0.7 in chloroform); mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 7.85 (s, 4H; Aromatic ring Hs), 6.65 (d, J=8.1 Hz, 2H; Leu NH), 4.9–4.83 (m, 2H; Leu C$^{\alpha}$H), 3.78 (s, 6H; –OCH_3), 1.79–1.65 (m, 6H; Leu C$^{\beta}$H & C$^{\gamma}$H), 1.01–0.97 ppm (m, 12H; Leu C$^{\delta}$H); IR (KBr): $\bar{\nu}$=3325, 1747, 1635, 1550 cm^{-1}; MS (ESI): m/z (%): 421.3 (48) $[M+H]^+$, 841.5 (100) $[2M+H]^+$; elemental analysis calcd (%) for $C_{22}H_{32}N_2O_6$ (420): C 62.85, H 7.6, N 6.66; found: C 63.1, H 7.8, N 7.03.

4.1.2. Terephthalamide 2. Yield=1.50 g (3.5 mmol, 71%); R_f=0.75 (EtOAc); $[\alpha]_D^{20}$ −42.9 (c=0.7 in chloroform); mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 7.85 (s, 4H, Aromatic ring Hs), 6.69 (d, J=8.4 Hz, 2H; D-Leu NH), 4.87–4.83 (m, 2H; D-Leu C$^{\alpha}$H), 3.79 (s, 6H; –OCH_3), 1.78–1.65 (m, 6H; D-Leu C$^{\beta}$H & C$^{\gamma}$H), 1.01–0.93 ppm (m, 12H; D-Leu C$^{\delta}$H); IR (KBr): $\bar{\nu}$=3325, 1746, 1636, 1548, 1500 cm^{-1}; MS (ESI): m/z (%): 421.3 (33) $[M+H]^+$; 863.3 (100) $[2M+Na]^+$; elemental analysis calcd (%) for $C_{22}H_{32}N_2O_6$ (420): C 62.85, H 7.6, N 6.66; found: C 62.51, H 7.92, N 7.15.

4.1.3. Terephthalamide 3. Yield=1.6 g (3.8 mmol, 76%); R_f=0.6 (EtOAc); $[\alpha]_D^{20}$ +46.4 (c=0.7 in chloroform); mp 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ 7.87 (s, 4H, Aromatic ring H), 6.70 (d, J=8.4 Hz, 2H; Ile NH), 4.84–4.8 (m, 2H; Ile C$^{\alpha}$H), 3.79 (s, 6H; –OCH_3), 2.17–2.0 (m, 2H; Ile C$^{\beta}$H), 1.16–1.5 (m, 10H; Ile C$^{\gamma}$H),

0.99–0.97 ppm (m, 6H; Ile $C^{\delta}H$); IR (KBr): $\bar{\nu}$=3411, 3345, 1744, 1636, 1548, 1503 cm^{-1}; MS (ESI): *m/z* (%): 421.3 (55) $[M+H]^+$; 841.5 (100) $[2M+H]^+$; elemental analysis calcd (%) for $C_{22}H_{32}N_2O_6$ (420): C 62.85, H 7.6, N 6.66; found: C 63.21, H 7.52, N 6.95.

4.1.4. Terephthalamide 4. Yield=1.3 g (3.5 mmol, 72%); R_f=0.7 (EtOAc); $[\alpha]_D^{20}$ 0.01 (*c*=0.7 in chloroform); mp 220–222 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ 7.84 (s, 4H; Aromatic ring H), 6.84 (s, 2H; Aib NH), 3.80 (s, 6H; $-OCH_3$), 1.7 ppm (s, 12H; Aib $C^{\beta}H$); IR (KBr): $\bar{\nu}$=3322, 3226, 1741, 1631, 1560 cm^{-1}; MS (ESI): *m/z* (%): 388.0 (100) $[M+Na+H]^+$; 366.0 (52) $[M+2H]^+$; elemental analysis calcd (%) for $C_{18}H_{24}N_2O_6$ (364): C 59.34, H 6.59, N 7.69; found: C 60.01, H 6.98, N 7.75.

4.2. X-ray crystallography

All crystal data were measured on a Bruker AXS Smart Apex CCD diffractometer with Mo K_α (λ=0.71073 Å) radiation at 20 °C. The structure was obtained by direct methods using SHELXS-97.[16] Refinement was carried out with a full matrix least squares method against F^2 using SHELXL97.[17] CCDC-229937 (**1**), CCDC-600050 (**2**), CCDC-229938 (**3**), and CCDC-229939 (**4**) contain the supplementary crystallographic data for the paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

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1,4-Addition of arylboronic acids to β-aryl-α,β-unsaturated ketones and esters catalyzed by a rhodium(I)–chiraphos complex for catalytic and enantioselective synthesis of selective endothelin A receptor antagonists

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Abstract—An enantioselective synthesis of acyclic β-diaryl ketones and esters via 1,4-addition of arylboronic acids to β-aryl-α,β-unsaturated ketones or esters is described. The complex in situ prepared from $[Rh(nbd)_2]BF_4$ and chiraphos was found to be an excellent catalyst to achieve high enantioselectivities in a range of 83–89% ee for the ketone derivatives and 78–94% ee for *tert*-butyl β-arylacrylate derivatives. The protocol provided a catalytic method for the enantioselective synthesis of selective endothelin A receptor antagonists (**7**, **8**) reported by SmithKline Beecham and Merck–Banyu. The enantioselection mechanism and efficiency of the chiraphos ligand for β-aryl-α,β-unsaturated ketones and esters are discussed on the basis of results of DFT computational studies on the modes of coordination of the enone substrates to the phenylrhodium(I)–(*S*,*S*)-chiraphos complex.

1. Introduction

1,4-Additions of electrophiles to α,β-unsaturated carbonyl compounds are a versatile methodology for forming carbon–carbon bonds.[1] Among these extensive studies in conjugate additions, we have disclosed the rhodium-catalyzed reaction of aryl- and 1-alkenylboronic acids.[2] Since the reaction yields a stereogenic center at the β-carbon, considerable efforts have been devoted to the development of asymmetric syntheses via metal-catalyzed 1,4-addition of organoboron,[3] silicon,[4] magnesium,[5] zinc,[6] tin,[7] bismuth,[8] titanium,[9] and indium[10] compounds to cyclic and acyclic α,β-unsaturated ketones,[3] esters,[3] amides,[11] phosphonates,[12] and nitro[13] compounds. A rhodium(I)–binap catalyst was the first catalyst to be successfully used in enantioselective 1,4-addition of aryl- and 1-alkenylboronic acids to cyclic and acyclic enones.[3a] Other ligands effective for rhodium(I) catalysts are bisphosphine ligands of chiraphos[14] and diphosphonites,[3e] P–N ligands of amidomonophosphines,[15] bis(alkene) ligands based on a norbornadiene skeleton,[16] and monophosphine ligands of phosphoramidites.[17] For the corresponding palladium-catalyzed reactions of organoboron,[18–20] silicon,[20–22] and bismuth[20,22] compounds, bisphosphines bridged by two carbons, such as chiraphos and dipamp, resulted in high yields and high enantioselectivities. Among these extensive studies on 1,4-addition of organoboronic acids, the synthesis of β-diaryl carbonyl ketones or esters (**4**) has attracted much attention in recent years (Scheme 1). Since compounds incorporating a diarylmethine stereogenic centers are an important class of compounds due to the frequent occurrence of these fragments in natural products,[23] there are excellent precedents achieved by Friedel–Crafts alkylation of arenes[24] and 1,4-addition of electron-rich arenes to enals.[25] Another reliable and flexible approach for introducing two different aryl fragments is 1,4-addition of aryl metal reagents to α,β-unsaturated carbonyl compounds, which was recently accomplished by using rhodium complexes of chiral dienes (**5**)[16] or a dicationic palladium(II)–chiraphos complex.[19,20,22] In this paper, we show the efficiency of a rhodium(I)–chiraphos complex (**3**) for enantioselective preparation of β-diaryl carbonyl compounds (**4**) via the 1,4-addition of arylboronic acids (**2**) to β-aryl-α,β-unsaturated ketones or esters (**1**). The protocol

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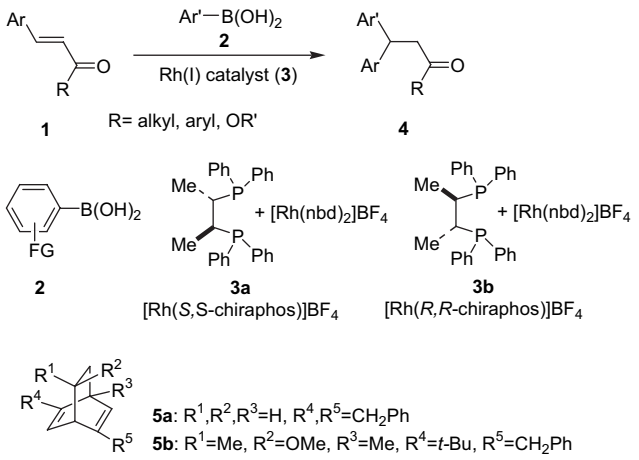
provides the first catalytic method for enantioselective synthesis of endothelin receptor antagonists.



Scheme 1. Rhodium(I)-catalyzed 1,4-addition of arylboronic acids to β-aryl-α,β-unsaturated ketones and esters.

2. Results and discussion

2.1. Enantioselective addition to β-aryl-α,β-unsaturated ketones and esters

The performance of a rhodium–chiraphos catalyst (**3a**, 3 mol %) in the 1,4-addition of 3-methoxyphenylboronic acid (1.5 equiv) to (*E*)-4-phenyl-3-buten-2-one (entries 1–5) or (*E*)-cinnamates (entries 6–13) was investigated (Table 1). The catalyst was prepared in situ by mixing (*S*,*S*)-chiraphos (3.3 mol %) and $[Rh(nbd)_2]BF_4$ (3 mol %) at room temperature. The addition to (*E*)-4-phenyl-3-buten-2-one was very slow at room temperature (entry 1), but inorganic bases exerted a remarkable accelerating effect (entries 2–4), as has been demonstrated in related 1,4-addition reactions using other phosphine–rhodium complexes.[3k] This effect of bases on yields was in the order of their basic strength: KOH> K_2CO_3>$KHCO_3$. The reaction temperature effects on the enantioselectivity is being increased at lower temperature.

Table 1. Effects of reaction temperatures, catalysts, and bases on yields and enantioselectivities[a]

Entry	**1** (Ar=Ph) R=	Base (equiv)	Temp/time (°C/h)	Yield/%[b]	% ee[c]
1	Me	None	20/5	0	—
2	Me	$KHCO_3$ (1)	20/5	0	—
3	Me	K_2CO_3 (1)	20/5	94	84
4	Me	KOH (1)	20/5	99	84
5	Me	KOH (1)	0/18	31	89
6	OMe	KOH (1)	20/21	94	84
7	O*i*-Pr	KOH (1)	20/19	58	92
8	O*t*-Bu	KOH (1)	50/6	92	93
9	O*t*-Bu	K_2CO_3 (1)	65/21	76	91
10	O*t*-Bu	Cs_2CO_3 (1)	65/21	83	92
11	O*t*-Bu	KF (3)	65/21	75	80
12	O*t*-Bu	CsF (3)	65/21	77	83
13	O*t*-Bu	NEt_3 (1)	65/21	40	91

[a] A mixture of an unsaturated ketone or ester (**1**, Ar=Ph) (0.5 mmol), 4-$MeOC_6H_4B(OH)_2$ (0.75 mmol), and base (0.5 mmol) in dioxane–H_2O (3 mL/0.5 mL) was stirred in the presence of $[Rh(nbd)_2]BF_4$ (3 mol %) and (*S*,*S*)-chiraphos (3.3 mol %).
[b] Isolated yields by chromatography.
[c] Enantiomer excess determined by a chiral stationary column.

Reaction at room temperature resulted in 84% ee (entry 4) and selectivity was increased to 89% ee by lowering the reaction temperature to 0 °C (entry 5). The bulkiness of ester groups of cinnamates greatly affected on both the reaction rates and enantioselectivities (entries 6–9). The reaction was slow at room temperature, but the best enantioselectivity (92%, 93% ee) was obtained by using the most hindered *tert*-butyl cinnamate at 50 °C in the presence of KOH (1 equiv) (entry 8) rather than methyl and isopropyl esters (entries 6 and 7). Carbonates, fluorides, and triethylamine were less effective (entries 9–13). These results are in contrast to the low efficiency of previous rhodium(I)–binap catalysts for β-aryl-α,β-unsaturated carbonyl compounds. A $Rh(acac)(C_2H_4)_2$–binap catalyst resulted in 28% yield and 78% ee for isopropyl cinnamate[3d] and 4-tolylboronic acid at 100 °C, and [Rh-(binap)(nbd)]BF_4 resulted in 84% yield and 76% ee in addition of 3-methoxyphenylboronic acid to 4-phenyl-3-buten-2-one at 50 °C in the presence of Et_3N.[20]

1,4-Additions of representative arylboronic acids to β-aryl-α,β-unsaturated ketones and *tert*-butyl esters with a rhodium(I)/(*S*,*S*)-chiraphos catalyst are shown in Table 2. All additions to ketones were completed within 5 h at room temperature with enantioselectivities in a range of 83–89% ee (entries 1–5). Additions to *tert*-butyl esters were carried out at 50 or 80 °C, but these reactions resulted in 5–10% higher enantioselectivities than those of ketone series (entries 6–16). Substituents on arylboronic acids (FG in **2**) and β-substituents of carbonyl compounds (Ar in **1**) affected the enantioselectivities, suggesting their participation in enantioselection as is discussed in the mechanistic section. Substituents of arylboronic acids increased the selectivities in the order of 3,4-methylenedioxy (entries 2 and 9)>4-methoxy (entries 1 and 6)>3-methoxy (entry 7)>3,4-dimethoxy (entry 8)≫4-dimethylamino (entry 10). In additions of 3-methoxyphenylboronic acid to a series of β-arylacrylates, the selectivities of 4-methoxyphenyl, 4-methylphenyl, and 2-methoxyphenyl derivatives were comparable to that of the phenyl group (entries 7 and 11–13), but 4-trifluoromethylphenyl and 2-naphthyl derivatives resulted in significantly lower enantioselectivities presumably due to steric reason (entries 14 and 15). Although the pyridine nitrogen often retards metal-catalyzed reactions due to its strong ability to coordinate to most metal catalysts, it was interesting that arylboronic acids underwent very smooth addition to *tert*-butyl 3-pyridylacrylate under standard conditions (entry 16). The absolute configurations of most products were not known, but the formation of *S*-product from (*S*,*S*)-chiraphos complex was established by the specific rotation reported for (*S*)-3-(3-methoxyphenyl)-1,3-diphenylpropan-1-one ($[\alpha]_D$ +7.1 (*c* 0.71, $CHCl_3$))[20] (entry 4).

2.2. Synthesis of endothelin receptor antagonists

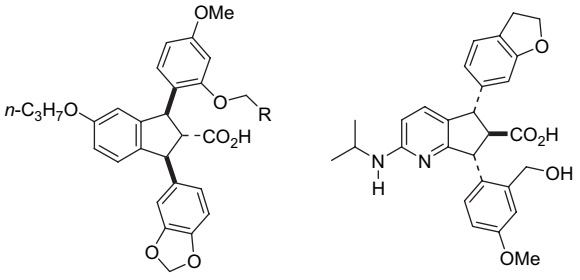
Much effort has been made by many research groups to prepare selective antagonists of endothelin receptors, which are currently being evaluated as potential therapeutic agents for the treatment of hypertension, congestive heart failure, and renal diseases. 1,3-Diarylindan-2-caraboxylic acid derivatives are highly potent antagonists selective for endothelin receptors among non-peptide antagonists reported by Shionogi,[26] Hoffmann-La Roche,[27] Bristol-Myers Squibb,[28] SmithKline Beecham (**6**, **7**),[29] and Merck–Banyu (**8**).[30]

Table 2. Asymmetric addition of arylboronic acids to β-aryl-α,β-unsaturated ketones and esters (**1**)[a]

Entry	**1**		**2** FG=	Base	Temp/time (°C/h)	Product	Yield/%[b]	% ee[c]
	Ar=	R=						
1	Ph	Me	4-MeO	K_2CO_3	20/5	**4a**	96	84
2	Ph	Me	3,4-O_2CH_2[d]	K_2CO_3	20/5	**4b**	99	89
3	2-Naphthyl	Me	3-MeO	K_2CO_3	20/5	**4c**	95	83
4	Ph	Ph	3-MeO	K_2CO_3	20/5	**4d**	99	86 (*S*)
5	Ph	4-$MeOC_6H_4$	3-MeO	K_2CO_3	20/5	**4e**	99	83
6	Ph	O*t*-Bu	4-MeO	KOH	50/6	**4f**	92	93
7	Ph	O*t*-Bu	3-MeO	KOH	50/6	**4g**	95	90
8	Ph	O*t*-Bu	3,4-$(MeO)_2$	KOH	50/6	**4h**	88	88
9	Ph	O*t*-Bu	3,4-O_2CH_2[d]	KOH	50/6	**4i**	94	94
10	Ph	O*t*-Bu	4-Me_2N	KOH	50/6	**4j**	59	82
11	4-$MeOC_6H_4$	O*t*-Bu	3-MeO	KOH	80/6	**4k**	97	90
12	2-$MeOC_6H_4$	O*t*-Bu	3-MeO	KOH	80/6	**4l**	96	91
13	4-MeC_6H_4	O*t*-Bu	3-MeO	KOH	80/6	**4m**	92	91
14	4-$CF_3C_6H_4$	O*t*-Bu	3-MeO	KOH	80/6	**4n**	94	85
15	2-Naphthyl	O*t*-Bu	3-MeO	KOH	80/6	**4o**	81	78
16	3-Pyridyl	O*t*-Bu	3-MeO	KOH	80/6	**4p**	90	89

[a] A mixture of **1** (1 mmol), $ArB(OH)_2$ (1.5 mmol), and base (1 mmol) in dioxane–H_2O (6/1) was stirred in the presence of $[Rh(nbd)_2]BF_4$ (3 mol %) and (*S*,*S*)-chiraphos (3.3 mol %).
[b] Isolated yields by chromatography.
[c] Enantiomer excess determined by a chiral stationary column.
[d] O_2CH_2 is a methylenedioxy group.

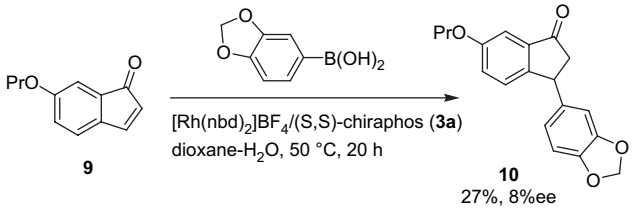
Two general and flexible methods for the synthesis of such a fused five-membered ring with three contiguous chiral centers have recently been accomplished by SmithKline Beecham[31] and Merck–Banyu.[30] In this approach, the major challenge of Merck–Banyu's group was enantioselective 1,4-addition of aryl metal reagents to β-aryl-α,β-unsaturated esters to build a five-membered ring and three chiral centers based on the first stereogenic center. Although they achieved excellent enantioselectivities by using a stoichiometric chiral auxiliary for 1,4-addition of aryllithium reagents, the catalytic protocol is preferred in large-scale preparations of these antagonists (Fig. 1).



6: R=CO_2H (SB-209670)
7: R=CH_2OH (SB-217242)
8

Figure 1. Endothelin receptor antagonists reported by SmithKline Beecham and Merck–Banyu.

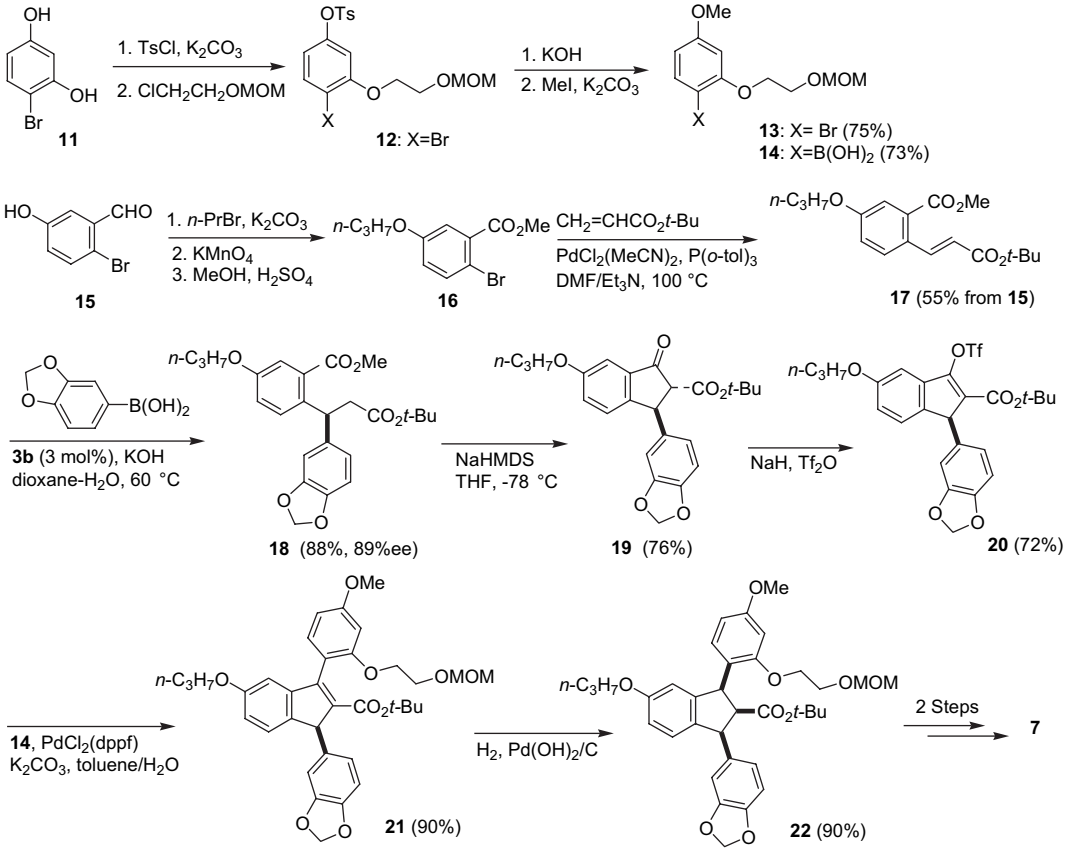
2.2.1. SmithKline Beecham's antagonist (7). Most rhodium(I) catalysts previously reported for 1,4-addition of arylboronic acids achieved significantly higher enantioselectivity for cyclic enones and esters than those for acyclic derivatives. Thus, addition to benzo-fused 2-cyclopentenone **9** was the first choice for the synthesis of endothelin receptor antagonists (**6** and **7**) reported by SmithKline Beecham (Scheme 2). However, the substrate **9** was unfortunately very labile as neat or even in solutions. Thus, all attempts to use **9** as the starting compound failed. $[Rh(nbd)_2]BF_4$–chiraphos (**3a**) resulted in 27% yield and 8% ee.



Scheme 2. 1,4-Addition to indenone (**9**).

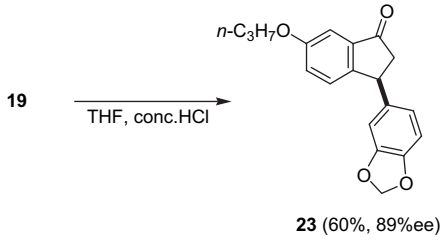
An alternative approach for the synthesis of **7** from arylboronic acids and acyclic unsaturated esters is shown in Scheme 3. An aryl moiety **14** desired for introduction of the top functionality of **7** via palladium-catalyzed cross-coupling was obtained from readily available 4-bromoresorcinol (**11**). Chemoselective protection of the 4-hydroxy group of **11** with tosyl chloride was directly followed by treatment with $ClCH_2CH_2OMOM$. Deprotection and methylation of **12** furnished **13** in 75% total yield. A sequential treatment of **13** with magnesium turning and $B(OMe)_3$ gave the desired boronic acid **14** in 73% yield.

The α,β-unsaturated ester (**17**) desired as a substrate for enantioselective 1,4-addition was synthesized by Heck coupling of 2-bromo-5-propoxybenzaldehyde (**16**), which was obtained from 2-bromo-5-hydroxybenzaldehyde (**15**) via an etherification, oxidation, and esterification sequence. (*E*)-Selective Heck coupling with *tert*-butyl acrylate then furnished the Michael acceptor (**17**) in 55% yield from **15**. Addition of 3,4-methylenedioxyphenylboronic acid (1.5 equiv) to **17** smoothly occurred at 60 °C under optimal conditions shown in Table 1. The desired enantiomer (**18**) was obtained with 89% ee when (*R*,*R*)-chiraphos (3.3 mol %) was used for $[Rh(nbd)_2]BF_4$ (3 mol %). Claisen cyclization of **18** with NaHMDS gave **19** in 76% yield. The absolute configuration of **18** ($[\alpha]_D^{22}$ −46.5 (*c* 0.70, $CHCl_3$)) was established to be *S* by conversion of **19** to the known compound **23** ($[\alpha]_D^{22}$ +49.7 (*c* 0.25, $CHCl_3$)) via decarboxylation of the resulting keto ester **19** (Scheme 4). The specific rotation of **23** reported in



Scheme 3. SmithKline Beecham's antagonist (**7**).

the literature is $[\alpha]_D^{25}$ +43.6 (*S*, 94% ee).[31] The enantiomer thus obtained was produced by the same mode of face selection as that discussed in the later section.



Scheme 4. Absolute configuration of **23**.

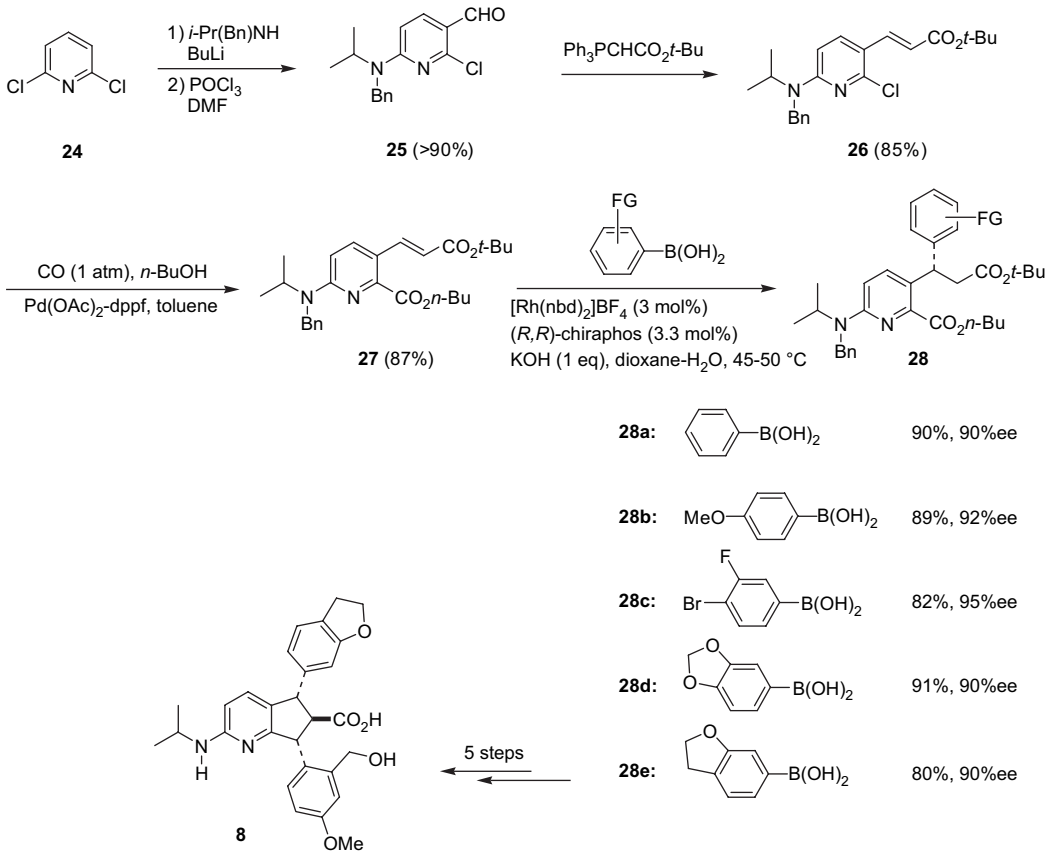
The chiral diester **19** thus obtained was led to the target antagonist **7** by a method similar to that previously reported by SmithKline Beecham. Thus, the enolate resulting from **19** with NaH was sulfonylated with trifluoromethanesulfonic anhydride to yield the triflate **20** in 72% yield (89% ee). Cross-coupling of **20** with **14** in the presence of $PdCl_2$(dppf) and K_2CO_3 to give **21** in 90% yield was followed by olefin reduction with H_2 and a palladium catalyst to give **22** in 90% yield. Finally, epimerization of the *tert*-butyl ester group in **22** was followed by deprotection of *tert*-butyl ester and MOM group to furnish **7**.[31]

The strategy thus achieved by asymmetric 1,4-addition and cross-coupling reaction of arylboronic acids has a structural flexibility for both top and bottom aryl groups for parallel synthesis of candidates.

2.2.2. Merck–Banyu's antagonists. For the synthesis of Merck–Banyu's antagonist **8**, an unsaturated ester (**27**) was chosen as a substrate for the enantioselective addition of arylboronic acids to introduce the chiral stereogenic center, which was previously achieved by 1,4-addition of aryllithiums to unsaturated esters possessing a chiral auxiliary (Scheme 5). Ester **27** was obtained in a high yield by the reported procedures starting from 2,6-dichloropyridine (**24**).[32] With the substrate **27** in hand, the key asymmetric step was then investigated. The optimal conditions shown in Table 1 worked well for variously functionalized arylboronic acids with selectivities in a range of 90–95% ee, thus allowing the parallel synthesis of chiral β-aryl ester derivatives (**28a–e**). It was interesting that neither the substituents on the pyridyl ring nor the two nitrogens of **27** significantly affected the yields or enantioselectivities. They were comparable or even higher than those of unsaturated esters shown in Table 2. The absolute configurations of **28e** thus obtained by the (*R*,*R*)-chiraphos complex was established to be *S* by the specific rotation reported for (*S*)-**28e** (Fig. 2).[33] Thus, the product was produced by the same mode of face selection same as that discussed in the later section (Fig. 3). In five steps, **28e** completes a formal synthesis of one of Merck–Banyu's antagonists (**8**).[32]

2.3. DFT computational study on enantioselection

The catalytic cycle of rhodium(I)-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds in aqueous media involves (i) transmetalation of an arylboronic acid to a HO–[Rh] complex (**29**) giving an Ar′–[Rh]



Scheme 5. Merck–Banyu's endothelin A receptor antagonists (**8**).

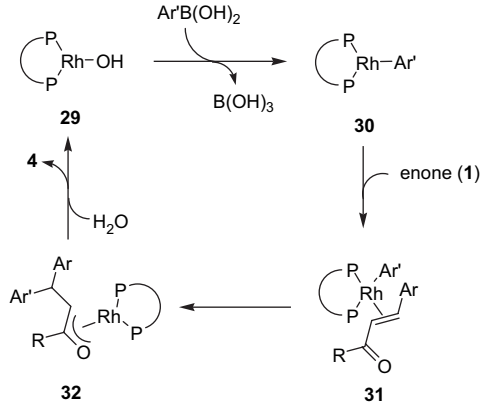


Figure 2. A catalytic cycle.

species (**30**), (ii) insertion of alkene into the Ar′–Rh bond (**31**) to yield a rhodium enolate (**32**) and finally (iii) formation of an addition product (**4**) and regeneration of **29** via hydrolysis of the rhodium enolate intermediate with water.[3j]

Thus, absolute configuration and enantioselectivity can be determined at the insertion step of alkenes into an arylrhodium(I)–phosphine intermediate (**31**). There is a precedent for the X-ray structure of a rhodium(I)–chiraphos complex; however, the solid-state structure of such a conformationally flexible complex, in general, is not reliable for the mechanism of enantioselection since the intermediate conformation differs from the structure of the catalyst precursor. Thus, the mode of a coordination of (*E*)-4-phenyl-3-buten-2-one to the [Rh(Ph)(*S*,*S*-chiraphos)] intermediate was calculated, i.e., the reaction stage directly preceding the stereodetermining insertion step by DFT computations at the B3LYP/LANL2DZ level of theory. The four modes of coordination of the enone substrate to the current phenylrhodium(I) intermediate are shown in Scheme 5. Two stable adducts between [Pd(Ph)(*S*,*S*-chiraphos)] and (*E*)-4-phenyl-3-buten-2-one located computationally are shown in **33** and **35**, which are skewed 28.9° and 127°, respectively, from the orientation required for insertion of an enone (**34** and **36**). Although both *si*- and *re*-coordination of the substrate is preferred thermodynamically without significant steric interaction, only the precursor of the experimentally observed enantiomer giving an *S* product has a low energy barrier (**34**, 20.8 kcal/mol) for parallel coordination of the C–C double bond to the Pd–P bond. In mode **34**, the two phenyl groups on rhodium and phosphine atoms constitute a planar free space for coordination of an enone to the metal center and the upper-right area is being blocked by one of the equatorial phenyl groups of the (*S*,*S*)-chiraphos ligand. The efficiency of chiraphos for planer α,β-unsaturated carbonyl compounds, the participation of Rh-bound aryls in enantioselectivity, and the substituent effect of arylboronic acids can be interpreted by this model (**34**). On the other hand, the coordination of an enone from its opposite *re* face is also probable with an analogous low energy level (**35**, 1.6 kcal/mol), but the subsequent insertion process can be strongly retarded, because of a high energy barrier for parallel orientation of the C–C double bond and the Ph–Rh bond (**36**, 231.8 kcal/mol).

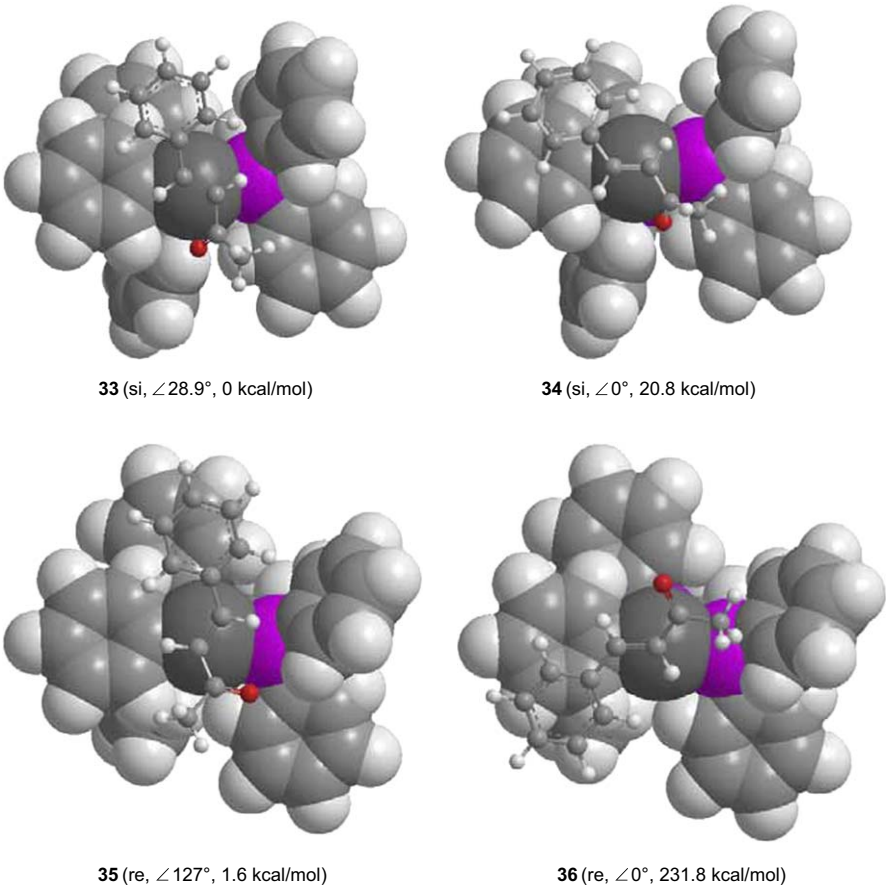


Figure 3. Transition states for coordination of (*E*)-PhCH=CHCOCH$_3$ to a [Rh(Ph)(*S*,*S*-chiraphos)] intermediate.

3. Conclusion

We have documented the successful use of a traditional chiraphos ligand for rhodium(I)-catalyzed 1,4-additions of arylboronic acids to β-aryl unsaturated ketones and esters for enantioselective synthesis of β-diaryl carbonyl compounds. The high flexibility of this ligand widely applicable even for sterically hindered carbonyl compounds or substrates possessing a donating pyridine nitrogen was demonstrated in two syntheses of selective endothelin antagonists. The DFT calculation revealed that the catalyst has a planar free space for coordination of an enone to the metal center and that one of quadrants is being blocked by an equatorial phenyl group of the chiraphos ligand, thus suggesting high performance in recognition of planar alkene substrates such as β-aryl ketones and esters. This model would present an alkene recognition mechanism with square planar metal–chiraphos complexes.

4. Experimental

4.1. General

All experiments were carried out under an argon or nitrogen atmosphere. HPLC analysis was directly performed with chiral stationary phase column, Chiralcel OD-H, AD, AD-H, OJ-H, and OB-H purchased from Dicel Co., Ltd. Phenylboronic acid and (4-methylphenyl)boronic acid were commercially available from Lancaster. Other boronic acids were synthesized from the corresponding Grignard or lithium reagents and trimethyl borate or isopropyl borate.[34] [Rh(nbd)$_2$]BF$_4$,[35] PdCl$_2$(MeCN)$_2$,[36] and PdCl$_2$(dppf)[37] were synthesized by reported procedures. (*S*,*S*)-Chiraphos and (*R*,*R*)-chiraphos were purchased.

4.2. Asymmetric addition to α,β-unsaturated ketones and esters (Table 2)—A general procedure

A solution of [Rh(nbd)$_2$]BF$_4$ (3.0 mol %) and (*S*,*S*)-chiraphos (3.3 mol %) in 1,4-dioxane (3.0 mL) and water (0.1 mL) was stirred for 15 min at room temperature under N_2 atmosphere. Alkene (0.5 mmol), aqueous KOH (0.4 mL, 1.25 M), and arylboronic acid (1.5 mmol) were then added. The mixture was stirred at the temperature shown in Table 1. The product was purified by column chromatography on silica gel.

Following products were synthesized by the above general method. The spectral data of compounds **4a**,[38] **4c**,[20] **4d**,[20] and **4f**[39] were previously reported.

4.2.1. Compound (4b). Colorless oil; $[\alpha]_D^{23}$ +1.8 (*c* 0.41, $CHCl_3$); IR (neat): 1486, 1230, 1036, 699, 533 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.14 (d, J=7.3 Hz, 2H), 4.52 (t, J=7.6 Hz, 1H), 5.91 (s, 2H), 6.70–6.74 (m, 3H), 7.17–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.6, 45.7, 49.7, 100.9, 108.2, 108.2, 120.5, 126.5, 127.5, 128.6, 137.8, 143.9, 146.0, 147.7, 206.7; MS

(*m*/*z*) 77 (4.8), 152 (22), 211 (100), 225 (3.2), 268 (44, M^+); exact mass calcd for $C_{17}H_{16}O_3$: 268.1099; found: 268.1101.

4.2.2. Compound (4e). Colorless oil; $[\alpha]_D^{21}$ +11 (*c* 0.63, $CHCl_3$); IR (neat): 1252, 1597, 1167, 832, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (d, *J*=7.3 Hz, 2H), 3.85 (s, 3H), 4.77 (s, 3H), 4.79 (t, *J*=7.3 Hz, 1H), 6.69–6.72 (m, 1H), 6.80–6.92 (m, 4H), 7.15–7.27 (m, 6H), 7.90–7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.3, 46.0, 55.1, 55.4, 111.2, 113.7, 114.0, 120.2, 126.3, 127.8, 128.5, 129.5, 130.3, 144.1, 145.9, 159.6, 163.4, 196.4; MS (*m*/*z*) 77 (12), 107 (5.8), 197 (22), 211 (36), 346 (51, M^+); exact mass calcd for $C_{23}H_{22}O_3$: 346.1569; found: 346.1565.

4.2.3. Compound (4g). Colorless oil; $[\alpha]_D^{23}$ +2.2 (*c* 0.52, $CHCl_3$); IR (neat): 1725, 1255, 1141, 769, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (s, 9H), 2.85 (d, *J*=8.3 Hz, 2H), 3.61 (s, 3H), 4.35 (t, *J*=8.3 Hz, 1H), 6.59–6.62 (m, 1H), 6.69–6.75 (m, 2H), 7.03–7.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9, 41.9, 47.3, 54.9, 80.3, 111.4, 113.7, 120.0, 126.3, 127.6, 128.3, 129.3, 143.3, 145.1, 159.5, 170.9; MS (*m*/*z*) 197 (100), 210 (30.2), 211 (7.8), 239 (12.7), 312 (6.0, M^+); exact mass calcd for $C_{20}H_{24}O_3$: 312.1725; found: 312.1719.

4.2.4. Compound (4h). Colorless oil; $[\alpha]_D^{23}$ +0.71 (*c* 0.21, $CHCl_3$); IR (neat): 1253, 1138, 1028, 700, 511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 9H), 2.93 (d, *J*=8.3 Hz, 2H), 3.80 (s, 6H), 4.43 (t, *J*=8.1 Hz, 1H), 6.75–6.80 (m, 3H), 7.13–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 42.1, 46.8, 55.5, 80.2, 110.9, 111.1, 119.3, 126.2, 127.4, 128.2, 136.0, 143.6, 147.4, 148.6, 170.8; MS (*m*/*z*) 57 (10.1), 227 (100), 269 (5.9), 285 (78.1), 342 (34.6, M^+); exact mass calcd for $C_{21}H_{26}O_4$: 342.1831; found: 342.1827.

4.2.5. Compound (4i). Colorless oil; $[\alpha]_D^{22}$ +0.35 (*c* 0.43, $CHCl_3$); IR (neat): 1243, 1141, 1037, 699, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 2.91–2.93 (m, 2H), 4.41 (t, *J*=8.1 Hz, 1H), 5.87 (s, 2H), 6.70–6.75 (m, 3H), 7.17–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 42.1, 47.0, 80.4, 100.8, 108.0, 108.2, 120.5, 126.4, 127.5, 128.4, 137.5, 143.6, 146.0, 147.6, 170.9; MS (*m*/*z*) 57 (6.8), 211 (100), 253 (9.7), 269 (43.9), 326 (15.4, M^+); exact mass calcd for $C_{20}H_{22}O_4$: 326.1518; found: 326.1519.

4.2.6. Compound (4j). White solids; mp 76–77 °C; $[\alpha]_D^{23}$ +3.8 (*c* 0.18, $CHCl_3$); IR (neat): 1716, 1149, 812, 696, 533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 2.88 (s, 6H), 2.92 (d, *J*=8.8 Hz, 2H), 4.38 (t, *J*=8.3 Hz, 1H), 6.63–6.67 (m, 2H), 7.05–7.27 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 40.6, 42.3, 46.5, 80.2, 112.7, 126.1, 127.7, 128.2, 128.3, 131.7, 144.3, 149.2, 171.3; MS (*m*/*z*) 57 (6.6), 210 (100), 224 (3.9), 268 (56.0), 325 (29.0, M^+); exact mass calcd for $C_{21}H_{27}NO_2$: 325.2042; found: 325.2044; Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50%; H, 8.36%. Found: C, 77.55%; H, 8.35%.

4.2.7. Compound (4k). White solids; mp 54–55 °C; $[\alpha]_D^{22}$ +1.3 (*c* 0.41, $CHCl_3$); IR (neat): 1247, 1511, 1176, 1142, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H), 2.82 (d, *J*=8.3 Hz, 2H), 3.62–3.63 (m, 6H), 4.31 (t, *J*=8.3 Hz, 1H), 6.59–6.62 (m, 1H), 6.67–6.73 (m, 4H), 7.04–7.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 42.1, 46.5, 54.9, 55.0, 80.3, 111.3, 113.6, 113.7, 119.9, 128.5, 129.3, 135.5, 145.5, 158.0, 159.5, 171.0; MS (*m*/*z*): 57 (6.0), 227 (100), 269 (6.4), 285 (54), 342 (8.0, M^+); exact mass calcd for $C_{21}H_{26}O_4$: 342.1831; found: 342.1826; Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66%; H, 7.65%. Found: C, 73.81%; H, 7.69%.

4.2.8. Compound (4l). Colorless oil; $[\alpha]_D^{23}$ +21 (*c* 0.47, $CHCl_3$); IR (neat): 1490, 1242, 1142, 752, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H), 2.89 (dd, *J*=8.7, 15 Hz, 1H), 2.96 (dd, *J*=7.8, 15 Hz, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 4.87 (t, *J*=8.3 Hz, 1H), 6.66–6.69 (m, 1H), 6.78–6.88 (m, 4H), 7.11–7.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 40.4, 40.8, 54.9, 55.2, 80.0, 110.5, 111.1, 113.9, 120.2, 120.3, 127.4, 127.7, 128.9, 131.7, 144.9, 156.7, 159.3, 171.2; MS (*m*/*z*) 57 (21), 227 (29), 241 (9.8), 269 (22), 342 (5.0, M^+); exact mass calcd for $C_{21}H_{26}O_4$: 342.1831; found: 342.1843.

4.2.9. Compound (4m). Colorless oil; $[\alpha]_D^{21}$ −1.0 (*c* 0.53, $CHCl_3$); IR (neat): 1726, 1255, 1142, 779, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 9H), 2.18 (s, 3H), 2.83 (d, *J*=7.8 Hz, 2H), 3.63 (s, 3H), 4.36 (t, *J*=8.1 Hz, 1H), 6.59–6.62 (m, 1H), 6.69–6.74 (m, 2H), 6.96–7.11 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 27.8, 42.0, 46.9, 55.0, 80.3, 111.4, 113.7, 120.0, 127.5, 129.0, 129.3, 135.8, 140.4, 145.4, 159.5, 171.0; MS (*m*/*z*) 57 (21), 211 (100), 225 (3.9), 253 (7.9), 269 (16), 326 (4.9, M^+); exact mass calcd for $C_{21}H_{26}O_3$: 326.1882; found: 326.1887.

4.2.10. Compound (4n). Colorless oil; $[\alpha]_D^{22}$ +2.5 (*c* 0.55, $CHCl_3$); IR (neat): 1323, 1257, 1113, 1068, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 9H), 2.96 (t, *J*=8.3 Hz, 2H), 3.74 (s, 3H), 4.52 (t, *J*=8.1 Hz, 1H), 6.73–6.82 (m, 3H), 7.18–7.23 (m, 1H), 7.36 (d, *J*=8.3 Hz, 2H), 7.52 (d, *J*=8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 41.5, 47.1, 55.0, 80.7, 111.7, 113.8, 119.9, 122.8, 125.3, 125.3, 128.0, 129.6, 144.2, 147.5, 159.7, 170.5; MS (*m*/*z*) 57 (24), 265 (64), 279 (9.9), 307 (18), 323 (7.2), 380 (6.0, M^+); exact mass calcd for $C_{21}H_{23}F_3O_3$: 380.1599; found: 380.1608.

4.2.11. Compound (4o). White solids; mp 72 °C; $[\alpha]_D^{23}$ −18 (*c* 0.51, $CHCl_3$); IR (neat): 1719, 1244, 1140, 758, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 9H), 2.89–2.99 (m, 2H), 3.60 (s, 3H), 4.53 (t, *J*=8.1 Hz, 1H), 6.59–6.61 (m, 1H), 6.73–6.77 (m, 2H), 7.07 (t, *J*=7.8 Hz, 1H), 7.21–7.33 (m, 3H), 7.59–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 41.8, 47.3, 55.0, 80.4, 111.5, 113.9, 120.2, 125.4, 125.6, 125.9, 126.5, 127.5, 127.7, 128.1, 129.4, 132.2, 133.3, 140.8, 145.0, 159.6, 171.0; MS (*m*/*z*) 57 (9.0), 247 (100), 261 (3.2), 289 (8.3), 305 (32), 362 (12, M^+); exact mass calcd for $C_{24}H_{26}O_3$: 362.1882; found: 362.1879; Anal. Calcd for $C_{24}H_{26}O_3$: C, 79.53%; H, 7.23%. Found: C, 79.62%; H, 7.37%.

4.2.12. Compound (4p). Colorless oil; $[\alpha]_D^{22}$ +9.7 (*c* 0.52, $CHCl_3$); IR (neat): 1723, 1257, 1143, 715, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 2.84–2.94 (m, 2H), 3.68 (s, 3H), 4.39 (t, *J*=8.3 Hz, 1H), 6.66–6.75 (m, 3H), 7.10–7.21 (m, 2H), 7.45–7.47 (m, 1H), 8.36–8.37 (m, 1H), 8.48–8.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 27.8, 41.5, 44.9, 55.1, 80.9, 111.8, 113.7, 119.9, 123.3, 129.6, 135.0, 138.8, 143.9, 147.9, 149.3, 159.7, 170.4; MS (*m*/*z*) 57 (35), 198 (44), 212 (100), 240 (12), 313 (7.0, M^+); exact mass calcd for $C_{19}H_{23}NO_3$: 313.1678; found: 313.1674.

4.3. SmithKline Beecham's antagonist (Scheme 3)

4.3.1. Toluene-4-sulfonic acid 4-bromo-3-(2-methoxymethoxyethoxy)phenyl ester (12).[40a] A mixture of 4-bromoresorcinol (**11**) (5.5 g, 29.1 mmol), K_2CO_3 (14 g, 101 mmol), and *p*-TsCl (6 g, 35.7 mmol) in acetone (100 mL) was refluxed for 21 h. The solvent was removed in vacuo and 1-chloro-2-methoxymethoxyethane (5.5 g, 44.4 mmol), K_2CO_3 (5.5 g, 39.9 mmol), NaI (2.9 g, 19.3 mmol), and DMF (100 mL) were then added. The resulting mixture was stirred for 24 h at 90 °C. The product (**12**) was isolated by chromatography on silica gel (hexane/EtOAc=10/1 to 5/1) (11.3 g, 90%). Colorless viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J*=8.3 Hz, 2H), 7.39 (d, *J*=8.7 Hz, 1H), 7.32 (d, *J*=8.3 Hz, 2H), 6.63 (d, *J*=2.4 Hz, 1H), 6.40 (dd, *J*=8.3, 2.4 Hz, 1H), 4.72 (s, 2H), 4.06–4.08 (m, 2H), 3.89–3.91 (m, 2H), 3.40 (s, 3H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.7, 149.4, 145.6, 133.3, 131.9, 129.8, 128.5, 115.4, 110.4, 108.1, 96.5, 68.8, 65.3, 55.3, 21.7; IR (neat): 2938, 2885, 1594, 1477, 1372, 1273, 1191, 1179, 1143, 1117, 1036, 983, 810, 784, 724, 661, 549 cm^{-1}; MS (*m*/*z*): 45 (87), 91 (100), 155 (67), 430 (M^+, 18), 432 (M^++2, 19); exact mass calcd for $C_{17}H_{19}BrO_6S$: 430.0085; found: 430.0087.

4.3.2. 1-Bromo-4-methoxy-2-(2-methoxymethoxyethoxy)-benzene (13). A solution of **12** (8.3 g, 19.2 mmol) and KOH (5.9 g, 105 mmol) in EtOH (250 mL) and water (30 mL) was heated under reflux for 2 h. The solvent was evaporated to reduce the volume. HCl (4 M) was added at room temperature until pH 4. The product (**13**) extracted with Et_2O was isolated by chromatography on silica gel (hexane/EtOAc=25/1 to 5/1) (4.1 g, 74%). Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (d, *J*=8.7 Hz, 1H), 6.49 (d, *J*=2.4 Hz, 1H), 6.41 (dd, *J*=8.7, 2.4 Hz, 1H), 4.74 (s, 2H), 4.15–4.17 (m, 2H), 3.92–3.95 (m, 2H), 3.78 (s, 3H), 3.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 155.8, 133.1, 106.3, 103.0, 101.1, 96.6, 68.5, 65.5, 55.5, 55.3; IR (neat, cm^{-1}): 2937, 2885, 1582, 1485, 1442, 1304, 1281, 1203, 1168, 1116, 1060, 1022, 917, 823, 608; MS (*m*/*z*): 45 (100), 89 (47), 202 (7), 290 (M^+, 16), 292 (M^++2, 16); exact mass calcd for $C_{11}H_{15}BrO_4$: 290.0153; found: 290.0155.

4.3.3. 4-Methoxy-2-(2-methoxymethoxyethoxy)phenylboronic acid (14). A solution of **13** (4.4 g, 15 mmol) in THF (5 mL) was dropwise added to Mg turnings (368 mg, 16 mmol) to prepare Grignard solution. To this solution was then added $(MeO)_3B$ (2 mL, 18 mmol in 10 mL of THF) at −78 °C. The resulting mixture was allowed to stir overnight, treated with dil HCl, extracted with Et_2O, and finally washed with brine. A pure boronic acid (**14**) was isolated by recrystallization (2.8 g, 11 mmol, 73% yield). White solids; mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, *J*=8.3 Hz, 1H), 6.57 (dd, *J*=2.4, 8.3 Hz, 1H), 6.45 (d, *J*=2.4 Hz, 1H), 5.87 (s, 2H), 4.73 (s, 2H), 4.20–4.22 (m, 2H), 3.91–3.93 (m, 2H), 3.86 (s, 3H), 3.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.0, 163.4, 138.0, 105.8, 99.1, 96.5, 67.5, 65.7, 55.4, 55.3; Anal. Calcd for $C_{11}H_{17}BO_6$: C, 51.60%; H, 6.69%. Found: C, 51.45%; H, 6.62%.

4.3.4. 2-(2-*tert*-Butoxycarbonylvinyl)-5-propoxybenzoic acid methyl ester (17). A solution of 2-bromo-5-hydroxybenzaldehyde (**15**)[40b] (6 g, 30.0 mmol), 1-bromopropane (4.5 mL, 50.0 mmol), and K_2CO_3 (6.6 g, 48.0 mmol) in EtOH (60 mL) and water (20 mL) was heated under reflux for 17 h. The solvent was then evaporated and the residue was filtrated through silica gel pad with hexane/EtOAc (1/1). The combined filtrate was concentrated to dryness.

The crude product was dissolved in acetone (56 mL) and water (18 mL), and slowly treated with $KMnO_4$ (9.5 g, 60.0 mmol) with stirring on a water bath. After being stirred for 30 min, it was heated for 1 h at 70 °C. The reaction mixture was passed through Celite 545, rinsed with acetone, and then concentrated to a small volume. The reaction mixture was extracted with AcOEt and the organic layer was washed with dil HCl. The organic layer was dried over $MgSO_4$ and, finally, concentrated to dryness.

The crude product was dissolved in MeOH (100 mL) and H_2SO_4 (2 mL), and heated under reflux for 6 h using Dean–Stark apparatus. The solution was concentrated to a small volume and extracted with Et_2O. The organic layer was washed successively with brine and water. The organic layer was dried over $MgSO_4$ and concentrated to dryness to give crude **16** (6.3 g).

A solution of the crude **16**, $PdCl_2(MeCN)_2$ (204 mg, 0.79 mmol), P(*o*-tol)$_3$ (458 mg, 1.50 mmol), and *tert*-butyl acrylate (3.6 mL, 24.9 mmol) in DMF (23 mL) and Et_3N (7.6 mL) was stirred at 100 °C for 10 h. The product (**17**) was isolated by recrystallization from pentane (four steps from **15**, 5.3 g, 55%). White solids; mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (d, *J*=15.8 Hz, 1H), 7.56 (d, *J*=8.3 Hz, 1H), 7.40 (d, *J*=2.4 Hz, 1H), 7.03 (dd, *J*=2.4, 8.3 Hz, 1H), 6.18 (d, *J*=8.3 Hz, 1H), 3.97 (t, *J*=6.8, 7.3 Hz, 2H), 3.93 (s, 3H), 1.83 (sext, *J*=6.8, 7.3 Hz, 2H), 1.53 (s, 9H), 1.04 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 166.2, 159.8, 141.8, 131.4, 129.0, 128.2, 120.8, 118.8, 115.7, 80.3, 69.8, 52.4, 28.2, 22.4, 10.4; IR (neat): 2975, 1719, 1707, 1601, 1499, 1296, 1238, 1142, 1065, 982, 866, 831, 784, 593, 566 cm^{-1}; MS (*m*/*z*): 177 (39), 219 (100), 320 (M^+, 13); exact mass calcd for $C_{18}H_{24}O_5$: 320.1624; found: 320.1626; Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48%; H, 7.55%. Found: C, 66.43%; H, 7.38%.

4.3.5. (−)-(*S*)-2-(1-Benzo[1,3]dioxol-5-yl-2-*tert*-butoxycarbonylethyl)-5-propoxy-benzoic acid methyl ester (18). To the round-bottom flask charged with $[Rh(nbd)_2]BF_4$ (39.2 mg, 3.0 mol %), (*R*,*R*)-chiraphos (49.2 mg, 3.3 mol %), and **17** (1.2 g, 3.5 mmol) were added 1,4-dioxane (10.5 mL) and water (0.7 mL). After being stirred for 15 min at ambient temperature, a KOH solution (1.25 M in H_2O, 4.2 mL) and 3,4-(methylenedioxy)phenylboronic acid (970 mg, 5.3 mmol) were added. The mixture was stirred at 60 °C for 20 h. The mixture was filtered through a silica and $MgSO_4$ pad, and the pad was then rinsed with hexane/EtOAc (1/1). The product (**18**, 1.36 g, 88%) was isolated by chromatography on silica gel with hexane/EtOAc

(20/1). Ee (89%) (Chiralcel AD-H, *n*-hexane/2-propanol=9/1). Colorless oil; $[\alpha]_D^{22}$ −46.5 (*c* 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, *J*=2.9 Hz, 1H), 7.22 (d, *J*=8.8 Hz, 1H), 6.97 (dd, *J*=8.8, 2.9 Hz, 1H), 6.74–6.86 (m, 3H), 5.87 (s, 2H), 5.31 (t, *J*=8.3 Hz, 1H), 3.90 (t, *J*=6.3, 6.8 Hz, 2H), 3.87 (s, 3H), 2.87 (dd, *J*=3.4, 8.3 Hz, 2H), 1.76 (sext, *J*=6.8, 7.3 Hz, 2H), 1.01 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 168.0, 157.0, 147.5, 145.7, 137.8, 136.2, 131.0, 129.4, 120.6, 118.3, 115.7, 108.6, 107.8, 100.7, 80.3, 69.6, 52.0, 42.6, 41.3, 27.8, 22.4, 10.4; IR (neat): 2971, 1720, 1487, 1436, 1285, 1216, 1143, 1073, 1038, 933, 803 cm^{-1}; MS (*m*/*z*): 57 (12), 253 (20), 267 (18), 295 (65), 309 (41), 327 (40), 340 (54), 354 (100), 367 (27), 386 (68), 442 (M^+, 11); exact mass calcd for $C_{25}H_{30}O_7$: 442.1992; found: 442.1995.

4.3.6. 1-Benzo[1,3]dioxol-5-yl-3-oxo-5-propoxyindan-2-carboxylic acid *tert*-butyl ester (19). A solution of NaHMDS (1 M, 3.6 mL) in THF was slowly added to a solution of **18** (797 mg, 1.8 mmol) in THF (18 mL) at −78 °C. The mixture was stirred for 30 min at −78 °C and for 3 h at −15 °C. The reaction was quenched with satd aqueous NH_4Cl. Isolation by chromatography on neutral silica gel with hexane/EtOAc (30/1 to 20/1) gave **19** (560 mg, 76% yield). Pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.15–7.21 (m, 3H), 6.75 (d, *J*=7.8 Hz, 1H), 6.65 (dd, *J*=1.4, 7.8 Hz, 1H), 6.53 (s, 1H), 5.93 (s, 1H), 4.77 (d, *J*=4.4 Hz, 1H), 3.96 (t, *J*=6.3, 6.8 Hz, 1H), 3.50 (d, *J*=4.4 Hz, 2H), 1.82 (sext, 6.8, 7.3 Hz, 2H), 1.49 (s, 9H), 1.04 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 159.4, 148.8, 148.1, 146.7, 136.4, 136.2, 127.3, 125.3, 121.1, 108.4, 107.8, 105.6, 101.1, 82.1, 69.9, 65.3, 47.7, 28.2, 22.3, 10.4; IR (neat): 2971, 1708, 1486, 1440, 1273, 1228, 1145, 1037, 931, 842, 823, 801, 766 cm^{-1}; MS (*m*/*z*): 59 (81), 149 (24), 266 (39), 308 (98), 336 (100), 354 (81), 410 (M^+, 33); exact mass calcd for $C_{24}H_{26}O_6$: 410.1729; found: 410.1733.

4.3.7. 1-Benzo[1,3]dioxol-5-yl-5-propoxy-3-trifluoromethanesulfonyloxy-1*H*-indene-2-carboxylic acid *tert*-butyl ester (20). A solution of **19** (324 mg, 0.79 mmol) and NaH (38 mg, 1.58 mmol) in ether (7.9 mL) was stirred for 45 min at −5 °C. Tf_2O (0.22 mL, 1.18 mmol) was added and the mixture was then stirred for 1 h at −5 °C. The product was extracted with Et_2O and the organic layer was washed successively with brine and water. Isolation by chromatography on silica gel (hexane/EtOAc=30/1 to 15/1) gave **20** (390 mg, 72% yield). White solids; mp 105–106 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.10 (d, *J*=7.8 Hz, 1H), 6.94 (s, 1H), 6.91 (dd, *J*=2.4, 8.3 Hz, 1H), 6.72 (d, *J*=7.8 Hz, 1H), 6.67 (dd, *J*=1.4, 7.8 Hz, 1H), 6.44 (d, *J*=1.4 Hz, 1H), 5.90 (dd, *J*=1.4, 7.3 Hz, 1H), 4.77 (s, 1H), 3.93 (t, *J*=6.8 Hz, 2H), 1.82 (sext, *J*=6.8, 7.3 Hz, 2H), 1.40 (s, 9H), 1.04 (t, *J*=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.0, 159.2, 150.3, 147.7, 146.7, 138.3, 135.5, 130.7, 130.5, 125.3, 121.3, 119 (q, *J*=320 Hz), 117.1, 108.3, 107.5, 105.2, 100.9, 82.5, 69.8, 52.5, 27.8, 22.4, 10.4; IR (neat): 2966, 1702, 1490, 1423, 1337, 1249, 1202, 1124, 1040, 860, 808, 601 cm^{-1}; MS (*m*/*z*): 57 (69), 309 (100), 325 (55), 353 (45), 542 (M^+, 60); exact mass calcd for $C_{25}H_{25}O_8F_3S$: 542.1222; found: 542.1211; Anal. Calcd for $C_{25}H_{25}O_8F_3S$: C, 55.35%; H, 4.64%. Found: C, 54.29%; H, 4.58%.

4.3.8. 1-Benzo[1,3]dioxol-5-yl-3-[4-methoxy-2-(2-methoxymethoxyethoxy)phenyl]-5-propoxy-1*H*-indene-2-carboxylic acid *tert*-butyl ester (21). A solution of **20** (155 mg, 0.29 mmol), boronic acid **14** (80.5 mg, 0.31 mmol), and K_2CO_3 (59 mg, 0.43 mmol) in toluene (1.1 mL) and water (0.19 mL) was stirred for 4 h at 70 °C. The mixture was filtered through a silica gel and $MgSO_4$ pad, and the pad was then rinsed with hexane/EtOAc (1/1). The coupling product (**21**) was isolated by chromatography on silica gel (hexane/EtOAc=5/1 to 3/1) (155 mg, 90% yield). Pale yellow oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, *J*=8.3 Hz, 0.44H), 7.13 (d, *J*=8.3 Hz, 0.56H), 7.07 (d, *J*=8.3 Hz, 1H), 5.88–6.82 (m, 7H), 5.87 (m, 2H), 4.79 (s, 0.44H), 4.78 (s, 0.56H), 4.46–4.48 (m, 2H), 4.05–4.15 (m, 2H), 3.86 (s, 3H), 3.70–3.83 (m, 4H), 3.19 (s, 1.3H), 3.13 (s, 1.7H), 1.73–1.75 (m, 2H), 1.17–1.19 (m, 9H), 0.96–1.00 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.6, 160.74, 160.70, 158.7, 156.9, 149.2, 147.5, 147.4, 146.1, 146.0, 145.0, 141.0, 140.8, 139.6, 139.2, 133.8, 133.5, 130.9, 130.8, 124.3, 124.2, 121.28, 121.25, 117.0, 116.4, 114.6, 114.4, 108.4, 108.2, 108.1, 108.0, 107.7, 107.4, 104.6, 100.7, 100.6, 99.8, 99.7, 96.49, 96.46, 79.8, 79.7, 69.6, 67.8, 67.6, 65.9, 65.7, 55.37, 55.33, 55.2, 54.9, 27.9, 27.8, 22.5, 10.5; IR (neat): 2932, 1694, 1595, 1578, 1502, 1484, 1440, 1352, 1242, 1220, 1151, 1111, 1035, 919, 799, 782 cm^{-1}; MS (*m*/*z*): 441 (35), 472 (86), 503 (96), 530 (100), 604 (M^+, 42); exact mass calcd for $C_{35}H_{40}O_9$: 604.2672; found: 604.2674.

4.3.9. 1-Benzo[1,3]dioxol-5-yl-3-[4-methoxy-2-(2-methoxymethoxyethoxy)phenyl]-5-propoxyindan-2-carboxylic acid *tert*-butyl ester (22). The coupling product (**21**, 155 mg, 0.26 mmol) was dissolved in EtOH (1.3 mL) and treated with 20 wt % $Pd(OH)_2/C$ (8.9 mg) for 5 h at 60 °C under hydrogen atmosphere (0.3 MPa). The mixture was filtered through Celite 545 and the pad was rinsed with EtOH. The product (**22**) was isolated by chromatography on silica gel (hexane/EtOAc=5/1 to 2/1) (140 mg, 90% yield). Colorless oil; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37 (d, *J*=8.3 Hz, 1H), 7.09 (d, *J*=8.3 Hz, 1H), 6.90 (s, 1H), 6.88–6.90 (m, 2H), 6.79–6.80 (m, 2H), 6.74 (d, *J*=7.8 Hz, 1H), 6.48 (m, 1H), 6.44 (dd, *J*=2.4, 8.7 Hz, 1H), 5.90 (dd, *J*=1.4, 11.7 Hz, 1H), 5.05 (d, *J*=7.8 Hz, 1H), 4.75 (s, 2H), 4.66 (d, *J*=7.8 Hz, 1H), 4.11–4.23 (m, 2H), 3.83–3.99 (m, 5H), 3.78 (s, 3H), 3.43 (s, 3H), 1.78 (sext, *J*=6.8, 7.3 Hz, 2H), 1.03 (t, *J*=7.3 Hz, 3H), 0.78 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 159.5, 158.4, 158.1, 147.0, 146.1, 145.7, 136.1, 133.3, 130.9, 125.2, 123.0, 119.8, 112.9, 111.2, 110.4, 107.6, 104.0, 100.7, 98.9, 96.5, 79.2, 69.7, 67.7, 66.0, 58.8, 55.3, 55.2, 52.3, 46.0, 27.4, 22.6, 10.5; IR (neat): 2933, 1727, 1609, 1488, 1441, 1366, 1283, 1248, 1229, 1198, 1145, 1113, 1036, 917, 815, 796, 731 cm^{-1}; MS (*m*/*z*): 251 (24), 321 (80), 337 (53), 473 (40), 487 (100), 505 (49), 606 (M^+, 22); exact mass calcd for $C_{35}H_{42}O_9$: 606.2828; found: 606.2824.

4.4. Merck–Banyu's antagonists (Scheme 4)

4.4.1. 3-[6-Benzyl-isopropyl-amino]-2-chloro-pyridine-3-yl]acrylic acid *tert*-butyl ester (26).[32] To the vessel were added **25** (5.0 g, 17.3 mmol),[32] THF (75 mL), and *tert*-butyl diethylphosphonoacetate (4.6 g, 18.2 mmol), and the mixture was then stirred for 5 h at 40 °C. The completion

of the reaction was confirmed by HPLC. *i*-PrOAc (50 mL) and aqueous NaOH (0.5 M, 20 mL) were added at ambient temperature. The resulting aqueous layer was extracted again with *i*-PrOAc (20 mL). The combined organic layers were washed with brine and concentrated to ca. 20 mL. To this slurry was added *n*-heptane (50 mL) to precipitate the product. Compound **26** was collected by filtration and washed with *n*-heptane/*i*-PrOAc (5/1, 20 mL). The wet solid was dried under reduced pressure at 40 °C to afford 5.7 g of slightly yellow solids (85% yield). Mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (d, J=15.9 Hz, 1H), 7.54 (d, J=8.8 Hz, 1H), 7.18–7.35 (m, 5H), 6.20 (d, J=8.8 Hz, 1H), 6.07 (d, J=15.9 Hz, 1H), 5.10 (sept, J=6.7 Hz, 1H), 4.56 (s, 2H), 1.52 (s, 9H), 1.20 (t, J=6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4, 158.3, 150.3, 138.9, 138.4, 136.6, 128.7, 127.0, 126.2, 117.6, 116.2, 106.1, 80.3, 46.9, 46.5, 28.2, 20.2; IR (KBr): 2975, 1702, 1601, 1532, 1485, 1363, 1140, 981, 935, 862, 832, 803, 719, 696, 681, 635, 609, 463 cm^{-1}; exact mass calcd for $C_{22}H_{28}ClN_2O_2$ (M^++H): 387.1839; found: 387.1867.

4.4.2. 6-(*N*-Benzyl-*N*-isopropylamino)-3-(2-*tert*-butoxycarbonylvinyl)pyridine-2-carboxylic acid butyl ester (27). To the vessel were added **26** (5 g, 12.9 mmol), $AcONa\cdot 3H_2O$ (2.6 g, 19.1 mmol), toluene (19 mL), and *n*-BuOH (38 mL). The mixture was degassed three times by vacuum/N_2 cycle. $Pd(OAc)_2$ (145 mg, 5 mol %) and DPPF (536 mg, 7.5 mol %) were then added, and the vessel was again degassed twice. The mixture was stirred at 120 °C for 16 h. After the completion of the reaction was confirmed by HPLC, the vessel was cooled to ambient temperature. The insoluble material was filtered through Celite and rinsed with EtOAc. The product was isolated by column chromatography (*n*-heptane/EtOAc=20/1 to 10/1) to give **27** as oil. The oil was dissolved in EtOAc (30 mL) and was treated with activated carbon (Darco KB-B, 250 mg) for 2 h. Filtration through Celite and concentration to dryness under reduced pressure gave 5.1 g (87% yield) of **27** as yellow viscous oil. R_f=0.65 (*n*-heptane/ethyl acetate=2/1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (d, J=15.8 Hz, 1H), 7.61 (d, J=9.1 Hz, 1H), 7.21–7.31 (m, 5H), 6.40 (d, J=9.1 Hz, 1H), 6.07 (d, J=15.8 Hz, 1H), 5.13 (br t, J=6.2 Hz, 1H), 4.59 (s, 2H), 4.37 (t, J=6.6 Hz, 2H), 1.73–1.79 (m, 2H), 1.51 (s, 9H), 1.43–1.52 (m, 2H), 1.21 (d, J=6.7 Hz, 6H), 0.96 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 166.3, 158.0, 148.3, 139.1, 138.8, 135.7, 128.6, 126.9, 126.3, 118.3, 117.8, 109.3, 80.1, 65.5, 46.7, 46.6, 30.7, 28.3, 28.2, 20.2, 19.2, 13.7; IR (neat): 2972, 1712, 1597, 1547, 1484, 1143, 1075, 982, 870, 814, 732, 609 cm^{-1}; exact mass calcd for $C_{27}H_{37}N_2O_4$ (M^++H): 453.2753; found: 453.2714.

4.4.3. Rh-catalyzed asymmetric addition to 27. To a round-bottom flask were added 1,4-dioxane (2.0 mL) and water (0.5 mL), and the flask was then degassed three times by vacuum/N_2 cycle. To this solution were added $[Rh(nbd)_2]BF_4$ (3.0 mol %) and (*R*,*R*)-chiraphos (3.3 mol %) and the flask was again degassed twice. After the mixture was aged for 15 min at ambient temperature, unsaturated ester (**27**, 0.4 mmol) in 1,4-dioxane (1.0 mL), KOH (0.8 mmol), and arylboronic acid (1.2 mmol) were added. The flask was degassed twice. The mixture was heated to 50 °C for 14 h with vigorous stirring. The product was purified by column chromatography on silica gel.

The following compounds were synthesized by the above general procedure.

4.4.4. *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-phenylpropanoate (28a). Yield, 90%; R_f=0.61 (*n*-heptane/ethyl acetate=2/1); 89.8% ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28a**: 8.3 min, t_R for enantiomer: 9.7 min); $[\alpha]_D^{20}$ −40.2 (*c* 3.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.12–7.28 (m, 11H), 6.31 (d, J=9.0 Hz, 1H), 5.04 (sept, J=6.7 Hz, 1H), 4.96 (t, J=8.2 Hz, 1H), 4.48 (s, 2H), 2.87 (d, J=8.2 Hz, 2H), 1.68–1.76 (m, 2H), 1.40–1.48 (m, 2H), 1.25 (s, 9H), 1.16 (d, J=6.7 Hz, 6H), 0.94 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 167.6, 156.2, 146.4, 143.1, 139.8, 137.5, 128.4, 128.3, 127.8, 127.6, 126.6, 126.3, 125.7, 109.3, 80.4, 65.1, 46.6, 46.2, 42.0, 41.0, 30.6, 27.9, 27.8, 20.2, 20.1, 19.2, 13.7; exact mass calcd for $C_{33}H_{43}N_2O_4$ (M^++H): 531.3223; found: 531.3319.

4.4.5. *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-(4-methoxyphenyl)-propanoate (28b). Yield, 89%; R_f=0.48 (*n*-heptane/ethyl acetate=2/1); 92.1% ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28b**: 9.7 min, t_R for enantiomer: 13.7 min); $[\alpha]_D^{20}$ −28.4 (*c* 2.125, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15–7.28 (m, 8H), 6.78 (d, J=8.7 Hz, 2H), 6.31 (d, J=8.9 Hz, 1H), 5.04 (sept, J=6.7 Hz, 1H), 4.89 (t, J=8.3 Hz, 1H), 4.48 (s, 2H), 4.30–4.34 (m, 2H), 3.74 (s, 3H), 2.83 (d, J=8.3 Hz, 2H), 1.72 (m, 2H), 1.38–1.50 (m, 2H), 1.26 (s, 9H), 1.16 (d, J=6.7 Hz, 6H), 0.94 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 167.6, 158.0, 156.2, 146.4, 139.8, 137.4, 135.3, 128.7, 128.4, 126.6, 126.3, 126.0, 113.7, 109.3, 80.4, 65.0, 55.2, 46.6, 46.2, 42.1, 40.3, 30.6, 27.9, 27.8, 20.2, 20.1, 19.2, 13.7; IR (KBr): 2972, 1730, 1600, 1553, 1481, 1146, 1077, 1037, 961, 843, 731, 697 cm^{-1}; exact mass calcd for $C_{34}H_{45}N_2O_5$ (M^++H): 561.3328; found: 561.3418.

4.4.6. *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-(4-bromo-3-fluorophenyl)propanoate (28c). Yield, 82%; R_f=0.68 (*n*-heptane/ethyl acetate=2/1); 95.4% ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28c**: 8.4 min, t_R for enantiomer: 11.8 min); $[\alpha]_D^{20}$ −32.8 (*c* 1.145, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (dd, J=7.5, 8.0 Hz, 1H), 7.18–7.28 (m, 6H), 7.03 (dd, J=1.8, 9.9 Hz, 1H), 6.94 (dd, J=1.5, 8.3 Hz, 1H), 6.34 (d, J=9.0 Hz, 1H), 5.03 (sept, J=6.7 Hz, 1H), 4.98 (t, J=8.1 Hz, 1H), 4.50 (s, 2H), 4.29–4.35 (m, 2H), 2.83 (d, J=8.1 Hz, 2H), 1.68–1.73 (m, 2H), 1.40–1.47 (m, 2H), 1.28 (s, 9H), 1.18 (dd, J=1.5, 6.7 Hz, 6H), 0.94 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 167.3, 156.4, 146.3, 139.5, 137.2, 133.2, 128.5, 126.7, 126.3, 124.7, 116.1, 115.9, 109.5, 80.8, 65.2, 46.7, 46.3, 41.5, 40.3, 30.6, 27.8, 20.1, 19.2, 13.7; exact mass calcd for $C_{33}H_{41}BrFN_2O_4$ (M^++H): 627.2234; found: 627.2415.

4.4.7. *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-(3,4-methylenedioxyphenyl)propanoate (28d). Yield, 91%; R_f=0.52 (*n*-heptane/ethyl acetate=2/1); 89.8% ee (Chiralcel OD-H, *n*-hexane/

2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28d**: 10.0 min, t_R for enantiomer: 13.0 min); $[\alpha]_D^{20}$ −36.5 (*c* 1.76, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.18–7.28 (m, 6H), 6.73 (s, 1H), 6.67–6.72 (m, 2H), 6.32 (d, *J*=9.0 Hz, 1H), 5.87 (s, 2H), 5.04 (sept, *J*=6.7 Hz, 1H), 4.88 (t, *J*=8.2 Hz, 1H), 4.49 (s, 2H), 4.31–4.34 (m, 2H), 2.80 (d, *J*=8.2 Hz, 2H), 1.69–1.75 (m, 2H), 1.41–1.48 (m, 2H), 1.28 (s, 9H), 1.16 (d, *J*=6.7 Hz, 6H), 0.94 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.7, 167.6, 156.2, 147.6, 146.4, 145.9, 139.7, 137.3, 137.2, 128.4, 126.6, 126.3, 125.7, 120.5, 109.3, 108.6, 107.9, 100.8, 80.5, 65.1, 46.6, 46.2, 42.1, 40.7, 30.7, 27.9, 20.2, 20.1, 19.2, 13.7; IR (KBr): 2974, 1731, 1600, 1553, 1484, 1146, 1039, 937, 813, 731, 697 cm^{-1}; exact mass calcd for $C_{34}H_{43}N_2O_6$ (M^++H): 575.3121; found: 575.3218.

4.4.8. *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (28e). Yield, 80%; R_f=0.55 (*n*-heptane/ethyl acetate=2/1); 90.3% ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28e**: 11.2 min, t_R for enantiomer: 16.9 min); $[\alpha]_D^{20}$ −39.7 (*c* 1.06, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.18–7.28 (m, 6H), 7.04 (d, *J*=7.6 Hz, 1H), 6.74 (d, *J*=7.6 Hz, 1H), 6.67 (s, 1H), 6.31 (d, *J*=9.0 Hz, 1H), 5.04 (sept, *J*=6.6 Hz, 1H), 4.91 (t, *J*=8.2 Hz, 1H), 4.50 (t, *J*=8.6 Hz, 2H), 4.49 (s, 2H), 4.30–4.35 (m, 2H), 3.11 (t, *J*=8.6 Hz, 2H), 2.82 (d, *J*=8.1 Hz, 2H), 1.69–1.74 (m, 2H), 1.40–1.47 (m, 2H), 1.27 (s, 9H), 1.16 (d, *J*=6.6 Hz, 6H), 0.94 (t, *J*=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 167.5, 160.3, 156.2, 146.4, 143.7, 139.8, 137.4, 128.4, 126.6, 126.3, 125.8, 124.8, 124.5, 120.0, 109.3, 108.7, 80.4, 71.2, 65.0, 46.6, 46.2, 42.0, 40.8, 30.7, 29.5, 27.9, 20.2, 20.1, 19.2, 13.7; IR (KBr): 2975, 1730, 1599, 1481, 1147, 1078, 989, 947, 813, 759, 697 cm^{-1}; exact mass calcd for $C_{35}H_{45}N_2O_5$ (M^++H): 573.3328; found: 573.3412.

4.5. Computational details

Geometries of all stationary points were optimized using analytical energy gradients of self-consistent field[41] and density functional theory (DFT).[42] The latter utilized Becke's three-parameter exchange-correlation functional[43] including the nonlocal gradient corrections described by Lee–Yang–Parr (LYP),[44] as implemented in the Gaussian 03 program package.[45] All geometry optimizations were performed using the LANL2DZ basis set.[46]

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10-Oxo-10*H*-5λ⁴,10λ⁴-thianthren-5-ylideneamine as a probe for stereochemistry in the formation and amination of fluoro-λ⁶-sulfanenitriles

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Abstract—The fluorination of 10-oxo-10*H*-5λ⁴,10λ⁴-thianthren-5-ylideneamine (**2**) with Selectfluor™ affords 5-fluoro-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (**4**). The amination of **4** with morpholine gives 5-morpholino-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (**5**). The stereochemical course of both reactions has been studied, while the configurations of their products, *cis*-isomer **4** and *trans*-5-morpholino-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (*trans*-**5**) are elucidated by the use of X-ray crystallographic analyses.

1. Introduction

Thianthrene derivatives are one of the most important chemical probes in organic reactions.[1–3] In particular, the oxidation of thianthrene-5-oxide has been used as a mechanistic probe for the assessment of the electronic character of various oxidants.[1,2] Recently, Morita and co-workers have been able to prepare 10-oxo-10*H*-5λ⁴,10λ⁴-thianthren-5-ylideneamine (**2**) by hydrolysis of its *N*-*p*-toluenesulfonyl precursor **1** with concentrated H_2SO_4.[3] Furthermore, the *cis*- and *trans*-isomers of **1** and **2** were separated and their stereochemical interconversions were studied under hydrolytic conditions in acidic media and thermal conditions. Thus, *trans*-**1** or *cis*-**1** was hydrolyzed with concentrated H_2SO_4 to give a mixture of the corresponding *trans*-**2** and *cis*-**2**, in the respective ratio ca. 5:1. In 20% aqueous H_2SO_4 the hydrolysis of *trans*-**2** or *cis*-**2** led to a mixture of the corresponding disulfoxides, indicating that substitution of the NH group with H_2O proceeds through inversion (ca. 86–89%). For the thermal interconversion of **1** and **2**, *cis* derivatives were preferentially formed. The structures of these sulfimides were also determined by X-ray crystallographic analyses.[3]

We have been investigating the syntheses, structures, and reactivities of organic λ⁶-sulfanenitriles bearing an SN triple bond.[4] Particularly, we have succeeded in transforming fluoro-λ⁶-sulfanenitrile to the various substituted λ⁶-sulfanenitriles such as alkoxy-, amino-, imino-, methyl-, and arylsulfanenitriles.[4,5] Quite recently, we have found that several diaryl(fluoro)-λ⁶-sulfanenitriles are prepared by the reaction of *S*,*S*-diarylsulfimides with Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) and this reaction allows the first preparation of 5-fluoro-10,10-dioxo-5,10-dihydro-5λ⁶,10λ⁶-thianthren-5-nitrile.[6] We have also shown a new synthetic route for heterocyclic fluoro-λ⁶-sulfanenitrile, due to the fact that conversion of cyclic-*N*-bromosulfimide with the fluoride anion to the corresponding λ⁶-sulfanenitriles is difficult.

However, the stereochemistry of the formation of fluoro-λ⁶-sulfanenitriles by the reaction of sulfimides with Selectfluor™ and substitution of fluoro-λ⁶-sulfanenitriles with some nucleophiles is completely unknown, due to the lack of a facile preparation of optically active fluoro-λ⁶-sulfanenitriles.[7] It is quite interesting to prepare 5-fluoro-10-oxo-5,10-dihydro-5-λ⁶,10-λ⁴-thianthren-5-nitrile (**4**). We have now investigated (1) reaction of *cis*- and *trans*-10-oxo-10*H*-5λ⁴,10λ⁴-thianthren-5-ylideneamines (**2**) with Selectfluor™ and their stereochemical courses and (2) reaction of 5-fluoro-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (**4**) with morpholine and its stereochemical course.

Keywords: λ⁶-Sulfanenitrile; Sulfimides; Selectfluor™; Thianthrene; Fluorination; Amination; X-ray crystallographic analysis.
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2. Results and discussion

2.1. Reaction of 10-oxo-10*H*-5λ⁴,10λ⁴-thianthren-5-ylideneamine (2) with Selectfluor™

The reaction of *trans*-10-oxo-10*H*-5λ⁴,10λ⁴-thianthren-5-ylideneamine (*trans*-**2**) with Selectfluor™ was carried out at ambient temperature in CH_3CN to give the *cis*-isomer of 5-fluoro-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (**4**) (the SN group and the SO group are in *cis*-relation) and acid salt of starting material *trans*-**2**, in 48 and 43% yields, respectively, together with thianthren-5-oxide in 7% yield (Scheme 1). Neither the corresponding *N*-fluorosulfimide **3** nor the *trans*-isomer of **4** was obtained. The composition of *cis*-**4** was identified by NMR and IR spectroscopies as well as elemental analysis, and its stereochemistry was determined by X-ray crystallographic analysis (Fig. 1 and Table 1). Because of the low relative solubility of *cis*-**2** in CH_3CN, the reaction with Selectfluor™ was carried out at 50 °C. Interestingly, this reaction gave the corresponding *cis*-isomer of **4** and acid salt of *cis*-**2** in 35 and 39% yields, respectively, together with thianthrene-5-oxide, *cis*-, and *trans*-thianthrene-5,10-dioxides in 12, 11, and 2% yields (Scheme 1).

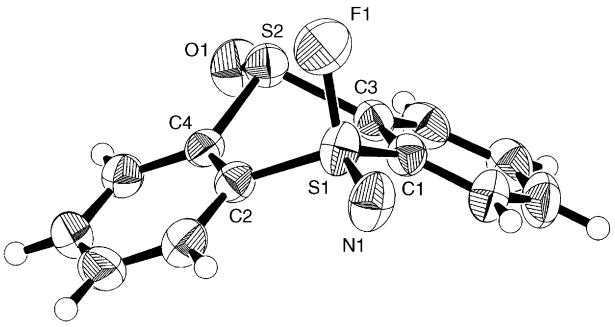


Figure 1. The molecular structure of *cis*-**4**.

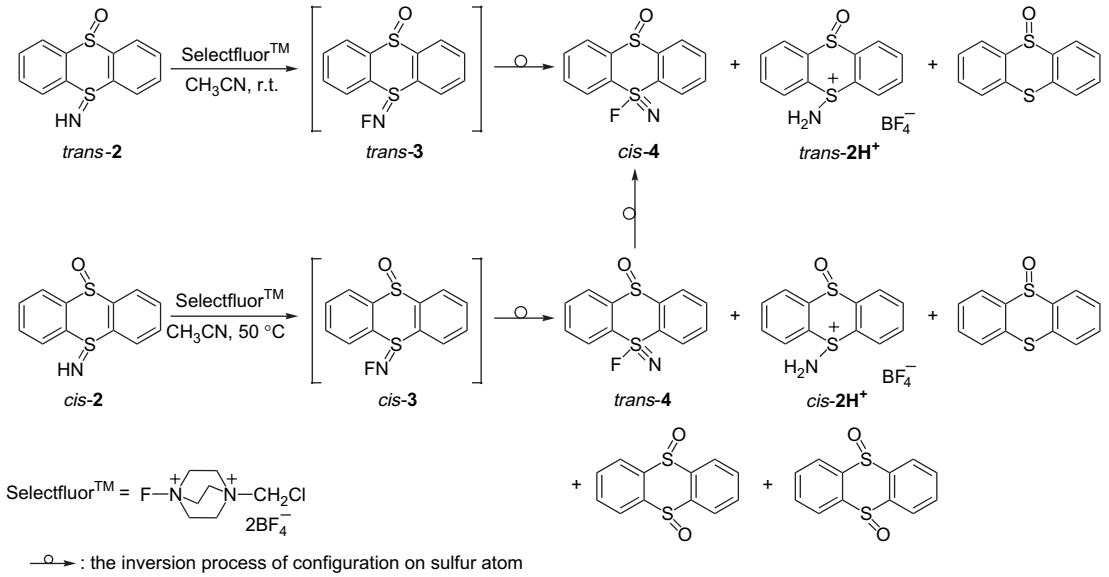
Table 1. Selected bond lengths (Å) and angles (°) for *cis*-**4**[a]

S1–F1	1.573(3)	S1–N1	1.436(3)
S1–C1	1.785(3)	S1–C2	1.775(3)
S2–O1	1.484(3)	S2–C3	1.811(3)
S2–C4	1.800(3)		
F1–S1–N1	122.0(2)	F1–S1–C1	102.2(2)
F1–S1–C2	99.4(2)	N1–S1–C1	115.2(2)
N1–S1–C2	114.4(2)	C1–S1–C2	100.3(2)
O1–S2–C3	107.8(2)	O1–S2–C4	108.0(2)
C3–S2–C4	96.6(1)		

[a] The atom-labeling scheme is shown in Figure 1.

To understand this reaction pathway, the conversion into products during the reaction of *cis*- and *trans*-isomers of sulfimides **2** with Selectfluor™ in CH_3CN was followed by time interval ^{19}F NMR spectroscopy (Fig. 2). In the reaction of *trans*-**2** at 23 °C, the ^{19}F NMR peak of Selectfluor™ at δ 46.1 (N–F) gradually diminished and the peak of *cis*-**4** appeared at δ 114.4 (Fig. 2 (left)). At a low temperature (−20 °C), *trans*-**2** slowly reacted with Selectfluor™ to give the same results under the above conditions. Although we were unable to detect *N*-fluorosulfimide **3** by ^{19}F NMR spectroscopy, its analogue, *S*-(4-nitrophenyl)-*S*-phenyl-*N*-fluorosulfimide and its conversion into the corresponding fluoro-λ⁶-sulfanenitrile were observed by ^{19}F NMR spectroscopy as we reported in a preliminary communication.[6] We have also studied on density functional theory (DFT) calculations (B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d) level) of *syn*- (12.1 kcal/mol (relative to Me_2FSN): F *syn* with respect to SMe_2) and *anti*-*S*,*S*-dimethyl-*N*-fluorosulfimides (18.0 kcal/mol (relative to Me_2FSN): F *anti* with respect to SMe_2) and fluoro(dimethyl)-λ⁶-sulfanenitrile (0.0 kcal/mol), suggesting that *N*-fluorosulfimides should be converted to thermodynamically stable fluoro-λ⁶-sulfanenitrile.[6] This present reaction would also be relative to the above manner (Scheme 1).

The reaction of *cis*-**2** with Selectfluor™ in CH_3CN was monitored at 50 °C by ^{19}F NMR spectroscopy. The ^{19}F NMR peak of Selectfluor™ at δ 46.1 (NF) gradually reduced, while two resonance signals at δ 114.4 and 117.2 increased (Fig. 2 (right)). The former signal was assigned to that of *cis*-**4**. The



Scheme 1.

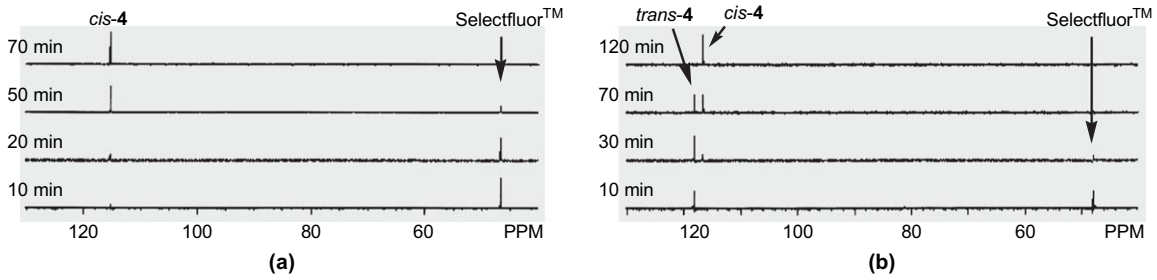


Figure 2. Time course of the change in ^{19}F NMR spectra of the reaction of *trans*- (left) and *cis*-**2** (right) with Selectfluor™ in CD_3CN: (a) rt, (b) 50 °C.

latter peak reached an approximate maximum of 55% of the reaction mixture as determined by the relative integrals of the reaction mixture in ^{19}F NMR spectrum, and then completely disappeared and the spectra changed to that of *cis*-**4**. This intermediate is amenable to detection by ^{19}F NMR spectroscopy, but we could not isolate it from the reaction mixture. The ^{19}F NMR resonance of the latter (δ 118.2) is observed in a similar that of *cis*-fluoro-λ^6-sulfanenitrile *cis*-**4** (δ 115.4) and is shifted to the lower field relative to those of *S*-(4-nitrophenyl)-*S*-phenyl- (δ −125.2)[6] and *S*,*S*-bis(trifluoromethyl)-*N*-fluorosulfimides (δ −50, NF)[8], and hence, the formation of *cis*-isomer of fluoro-λ^6-sulfanenitrile *cis*-**4** can be accounted for the formation of *trans*-**4**, followed by isomerization (Scheme 1).

These results imply that the formation of fluoro-λ^6-sulfanenitrile is as follows. (i) The initial process was that the reaction of sulfimide **2** with Selectfluor™ afforded the corresponding *N*-fluorosulfimide **3** and acid salt of **2**. The fluorination of nitrogen atom in **2** evidently does not involve the inversion process.[3] (ii) The *N*-fluorosulfimide **3** underwent 1,2-migration of fluorine atom yielding the corresponding fluoro-λ^6-sulfanenitrile **4**. This migration (*cis*- and *trans*-**3** to *trans*- and *cis*-**4**, respectively) proceeds via inversion mechanism (Scheme 1). As mentioned above, the DFT calculations predicted that *syn* conformation of *S*,*S*-dimethyl-*N*-fluorosulfimide is more stable than its *anti* conformation by 5.9 kcal/mol.[6] Therefore, *cis-syn* and *trans-syn* isomers of *N*-fluorosulfimide **3** should be converted to the respective *trans*- and *cis*-isomers of fluoro-λ^6-sulfanenitrile **4**, which seem to be formed by a stepwise or a concerted rearrangement.

DFT calculations were performed on the various conformers of *cis*- and *trans*-5-fluoro-10-oxo-5,10-dihydro-5λ^6,10λ^6-thianthren-5-nitriles (*cis*-**4A**, *cis*-**4B**, *trans*-**4A**, and *trans*-**4B**) (Fig. 3). The structures of the four possible conformations were optimized at the B3LYP/6-31G(d) level. All conformers correspond to stable structure. Selected structural parameters of optimized structures are shown in Table 2. The optimized structure of *cis*-**4A** is in good agreement with the experimental structure, except that the calculated S–N and S–F bond lengths are significantly longer than the experimental ones. Such overestimation of S–N and S–F bond lengths by DFT methods has been reported earlier.[9] Calculated relative energies were obtained at the B3LYP/6-311++G(3df,2pd) level using the data from the optimized structures of **4**. Stabilities of **4** are in the order: *cis*-**4A**>*trans*-**4B**>*trans*-**4A**>*cis*-**4B** (Fig. 3). *cis*-**4A** is more stable than *trans*-**4A** and *trans*-**4B** by 7.27 and 5.51 kcal/mol, respectively. These results imply that *trans*-isomer of **4** should be converted to thermodynamically stable *cis*-**4A**.

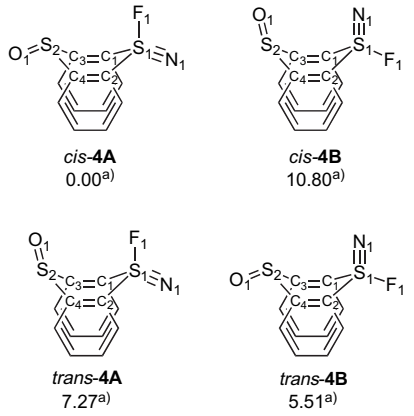


Figure 3. Calculated relative energies of **4**. a) B3LYP/6-311++G(3df,2pd)//B3LYP/6-31G(d), ZPE corrected values (kcal/mol).

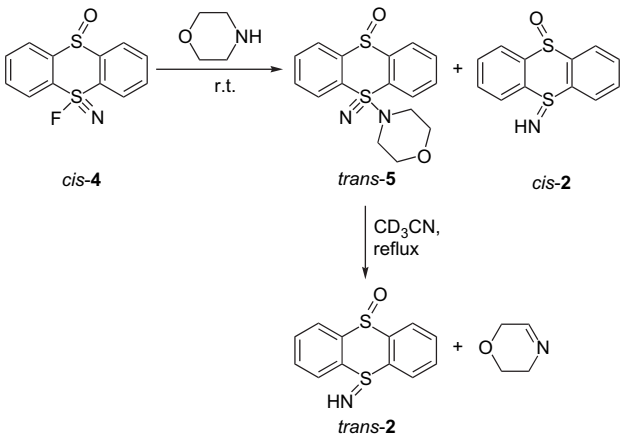
Table 2. Optimized geometries for *cis*- and *trans*-**4A** and -**4B**[a]

	cis-**4A**	*cis*-**4B**	*trans*-**4A**	*trans*-**4B**
Bond lengths (Å)				
S1–F1	1.708	1.715	1.679	1.706
S1–N1	1.462	1.462	1.462	1.464
S1–C1	1.811	1.819	1.813	1.815
S1–C2	1.811	1.819	1.813	1.815
S2–O1	1.509	1.508	1.506	1.509
S2–C3	1.833	1.829	1.832	1.832
S2–C4	1.833	1.829	1.832	1.832
Bond angles (°)				
F1–S1–N1	120.6	117.3	119.7	118.6
F1–S1–C1	93.7	93.0	95.3	94.8
F1–S1–C2	93.7	93.0	95.3	94.8
N1–S1–C1	120.7	122.4	119.6	121.4
N1–S1–C2	120.7	122.4	119.6	121.4
C1–S1–C2	101.3	101.2	102.2	99.6
O1–S2–C3	107.6	108.5	109.9	107.9
O1–S2–C4	107.6	108.5	109.9	107.9
C3–S2–C4	95.7	97.5	97.0	96.0

[a] Calculated at the B3LYP/6-31(d) level. The atom-labeling scheme is shown in Figure 3.

2.2. Reaction of *cis*-5-fluoro-10-oxo-5,10-dihydro-5λ^6,10λ^4-thianthren-5-nitrile (*cis*-**4**) with morpholine

The reaction of *cis*-**4** with a large excess of morpholine at room temperature gave the *trans*-isomer of 5-morpholino-10-oxo-5,10-dihydro-5λ^6,10λ^4-thianthren-5-nitrile (*trans*-**5**) in 56% yield (Scheme 2). The structure of *trans*-**5** was determined by X-ray crystallography (Fig. 4 and Table 3). In this reaction, an unexpected *cis*-10-oxo-10*H*-5λ^4,10λ^4-thianthren-5-ylideneamine (*cis*-**2**) was also obtained in 40% yield.



Scheme 2.

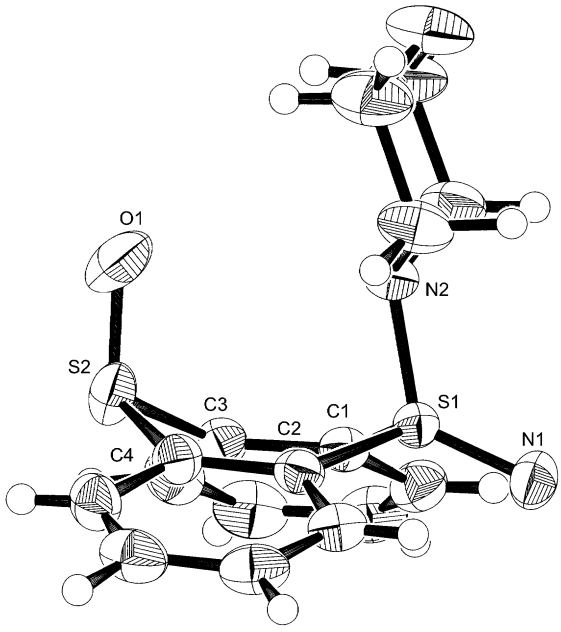


Figure 4. The molecular structure of *trans*-**5**.

We have already reported that diphenyl(piperidino)-λ^6-sulfanenitrile decomposes to the corresponding diphenylsulfimide and 3,4,5,6-tetrahydropyridine.[5a] Therefore, thermal stabilities of *trans*-**5** were examined. When *trans*-**5** was refluxed in CD_3CN, the retention product *trans*-**2** was obtained together with 3,6-dihydro-2*H*-[1,4]oxazine (Scheme 2). However, *trans*-**5** was stable under the above reaction conditions. These results suggest that the formation of *cis*-sulfimide *cis*-**2** is probably due to the concurrent electron-transfer reduction of the starting material *cis*-**4** and the substitution of S–F to S–N$(CH_2)_2$O involves the inversion process through an S_N2 or an addition–elimination mechanism.

2.3. X-ray crystallographic analysis of *cis*-5-fluoro-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (*cis*-4) and *trans*-5-morpholino-10-oxo-5,10-dihydro-5λ⁶,10λ⁴-thianthren-5-nitrile (*trans*-5)

The detailed structural analyses of *cis*-**4** and *trans*-**5** were performed by X-ray crystallographic analyses. Selected bond lengths and angles of *cis*-**4** and *trans*-**5** are collected in Tables 1 and 3, respectively. The ORTEP drawings of *cis*-**4** and *trans*-**5** are depicted in Figures 1 and 4, respectively.

Table 3. Selected bond lengths (Å) and angles (°) for *trans*-**5**[a]

S1–N1	1.464(2)	S1–N1	1.690(2)
S1–C1	1.807(2)	S1–C2	1.809(2)
S2–O1	1.490(2)	S2–C3	1.790(2)
S2–C4	1.802(2)		
N1–S1–N2	123.5(1)	N1–S1–C1	116.9(1)
N1–S1–C2	116.4(1)	N2–S1–C1	97.90(9)
N2–S1–C2	97.23(9)	C1–S1–C2	105.0(10)
O1–S2–C3	108.4(1)	O1–S2–C4	109.9(1)
C3–S2–C4	98.1(1)		

[a] The atom-labeling scheme is shown in Figure 4.

The X-ray structure of *cis*-**4** shows two independent molecules with nearly identical bond lengths and angles (an ORTEP drawing and the selected bond lengths and angles of one of the two independent molecules). The thianthrene ring system is found in the boat configuration. The nitrogen or oxygen bonded to sulfur assumes a pseudoequatorial position in the six-membered ring, whereas the fluorine bonded to sulfur assumes a pseudoaxial position. The S1–N1 and S1–F1 bond lengths (1.436(3) and 1.573(3) Å) in *cis*-**4** are much closer to those of 5-fluoro-10,10-dioxo-5,10-dihydro-5λ^6,10λ^6-thianthren-5-nitrile (S–N; 1.435(2) Å, S–F; 1.584(2) Å).[6]

The crystal lattice of *trans*-**5** consists of morpholino-λ^6-sulfanenitrile and $CHCl_3$ molecule. The distance between the nitrogen and carbon atoms is 3.067(4) Å. This value is significantly shorter than the sum of the van der Waals radii (3.39 Å) of the two elements[10] and is indicative of the N⋯H–C hydrogen bond. In the conformation of *trans*-**5**, the morpholino group and oxygen atom at S1 and S2 atoms lie in a pseudoaxial position, while the nitrogen atom at S1 atom is in a pseudoequatorial position. The S1–N1 bond length of 1.464(2) Å in *trans*-**5** is very close to that of 2,2-biphenylylene(phenyl)-λ^6-sulfanenitrile (1.470(2) Å),[5e] but significantly longer than that of fluorosulfanenitrile *cis*-**4**, which would be due to the influence of the electronegativity of substituents at S atom. The S1–N2 bond length (1.690(2) Å) is significantly shorter than the sum of the covalent radii of S and N (1.74 Å),[10] suggesting the polarization of the S1–N2 bond.

3. Conclusion

In the study of stereochemistry of formation of fluoro-λ^6-sulfanenitriles by the reaction of sulfimides with Selectfluor™, we investigated the fluorination of 10-oxo-10*H*-5λ^4,10λ^4-thianthren-5-ylideneamine (**2**). The *cis*- and *trans*-**2** reacted with Selectfluor™ to give a *cis*-isomer of 5-fluoro-10-oxo-5,10-dihydro-5λ^6,10λ^4-thianthren-5-nitrile (**4**), which is determined by X-ray crystallographic analysis. Inspection of the present results shows that the reaction proceeds through the mechanism outlined in Scheme 1. The initial product, *N*-fluorosulfimide **3** undergoes 1,2-migration of fluorine atom yielding the corresponding fluoro-λ^6-sulfanenitrile **4** via inversion process. In addition, *trans*-isomer of **4** should be converted to thermodynamically stable *cis*-**4**.

Further, the reaction of *cis*-**4** with morpholine gave the *trans*-isomer of 5-morpholino-10-oxo-5,10-dihydro-5λ^6,10λ^4-thianthren-5-nitrile (*trans*-**5**), indicating that substitution of fluorine with morpholine proceeds through inversion. The structure of *trans*-**5** was determined by X-ray crystallography, which reveals that **5** is a new type of heterocyclic amino-λ^6-sulfanenitrile.

4. Experimental

4.1. General

NMR spectra were obtained on a JEOL-JNM 400 NMR spectrometer and calibrated by the use of tetramethylsilane (TMS) as an internal reference. Chemical shifts (δ) were measured in parts per million, and coupling constants (J values) were in hertz (Hz). Mass spectra were recorded on a JEOL-JMS 700 mass spectrometer. Infrared spectra (IR) were recorded on a Horiba FT-710 spectrometer. Melting point was measured on a Yanaco Mp-J3 melting point apparatus. Elemental analyses were performed on a Yanaco MT-5 CHN CORDER. The X-ray crystallographic analyses were performed on a Rigaku AFC7R four-circle diffractometer using graphite monochromated Mo Kα radiation at 296 K.

All reagents and solvents were obtained commercially and were further purified by general methods when necessary. *cis*- and *trans*-10-Oxo-10*H*-5λ^4,10λ^4-thianthren-5-ylideneamines (**2**) were prepared according to the method reported in our previous articles.[3]

4.1.1. Reaction of 2 with Selectfluor™. Selectfluor™ (85 mg, 0.24 mmol) was added to a solution of *trans*-**2** or *cis*-**2** (100 mg, 0.40 mmol) in CH_3CN (100 ml) at ambient temperature or 50 °C. When the reaction was completed (monitored by TLC), the solution was poured into ice-water and then extracted with $CHCl_3$, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford *cis*-5-fluoro-10-oxo-5,10-dihydro-5λ^6,10λ^4-thianthren-5-nitrile (*cis*-**4**) and acid salt of *trans*-**2** or *cis*-**2** together with thianthren-5-oxide and/or *cis*- and *trans*-thianthrene-5,10-dioxides, which were identified by comparison with authentic samples[2a].

cis-**4**: mp 198–200 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.87 (m, 4H), 8.16 (dd, 2H, J_1=7.6 Hz, J_2=1.2 Hz, 2H), 8.43 (dd, 2H, J_1=7.6 Hz, J_2=1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.3, 127.3, 131.1, 133.6, 134.1 (d, J_{CF}=25 Hz), 145.4 (d, J_{CF}=2.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 114.4; IR (KBr) 1379 cm^{-1} (SN), 1087 (SO); FAB (*m*/*z*) 266 (M^++1). Calcd for $C_{12}H_8FNOS_2$: C, 54.32; H, 3.04; N, 5.28. Found: C, 54.56; H, 3.12; N, 5.33.

4.1.2. Reaction of *cis*-4 with morpholine. Fluorosulfanenitrile *cis*-**4** (265 mg, 1 mmol) was dissolved in moropholine (3 ml) for 2 h at ambient temperature. The solution was poured into ice-water and then extracted with $CHCl_3$, and dried over anhydrous Na_2SO_4. After the solvent was removed under reduced pressure, the residue was chromatographed ($CHCl_3$–CH_3OH=16:1) through a column packed with silica gel to afford *trans*-5-morpholino-10-oxo-5,10-dihydro-5λ^6,10λ^4-thianthren-5-nitrile (*trans*-**5**, 196 mg, 59%) and *cis*-**2** (98 mg, 40%).

trans-**5**: mp 153–154 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.07 (t, J=4.6 Hz, 4H), 3.71 (t, J=4.6 Hz, 4H), 7.73–7.82 (m, 4H), 8.01 (dd, 2H, J_1=7.4 Hz, J_2=1.2 Hz, 2H), 8.42 (dd, 2H, J_1=7.4 Hz, J_2=1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.7, 66.1, 129.1, 131.2, 132.4, 132.7, 139.2, 140.9; IR (KBr) 1321 cm^{-1} (SN), 1098 (SO); FAB (*m*/*z*) 333 (M^++1). Calcd for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; H, 4.85; N, 8.43. Found: C, 57.59; H, 4.82; N, 8.12.

4.1.3. X-ray crystal structure analysis of *cis*-4. The single crystals were obtained by recrystallization from $CHCl_3$–*n*-hexane. Diffraction data were measured with ω–2θ scan technique at 296 K on a Rigaku AFC7R diffractometer using graphite monochromated Mo Kα radiation (λ=0.7107 Å). A total of 6966 reflections were collected. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR 92)[11] and expanded using Fourier techniques (DIRDIF)[12]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 4365 observed reflections ($I>3.00\sigma(I)$) and 307 variable parameters converged with the unweighted and weighted agreement factors equal to $R=(\Sigma||Fo|-|Fc||)/(\Sigma|Fo|)=0.054$; $R_w=[(\Sigma\omega(|Fo|-|Fc|)^2/\Sigma\omega Fo^2)]^{1/2}=0.088$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.90 and −0.39 e$^-$/Å^3, respectively. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation (1985) and (1999). Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 600495 for compound *cis*-**4**.

4.1.4. X-ray crystal structure analysis of *trans*-5. The single crystals were obtained by recrystallization from $CHCl_3$–*n*-hexane. Diffraction data were measured with ω–2θ scan technique at 296 K on a Rigaku AFC7R diffractometer using graphite monochromated Mo Kα radiation (λ=0.7107 Å). A total of 5724 reflections were collected. The data were corrected for Lorentz and polarization effects. The structure was solved by direct methods (SIR 92)[11] and expanded using Fourier techniques (DIRDIF)[12]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 4065 observed reflections ($I>3.00\sigma(I)$) and 303 variable parameters converged with the unweighted and weighted agreement factors equal to $R=(\Sigma||Fo|-|Fc||)/(\Sigma|Fo|)=0.043$; $R_w=[(\Sigma\omega(|Fo|-|Fc|)^2/\Sigma\omega Fo^2)]^{1/2}=0.063$. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.54 and −0.63 e$^-$/Å^3, respectively. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation (1985) and (1999). Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 600496 for compound *cis*-**5**.

4.1.5. Ab initio calculation of 4. The geometries of *cis*-**4A** and -**4B** and *trans*-**4A** and -**4B** were optimized by the use of the Gaussian 98 program at B3LYP/6-31(d) levels of density

functional theory.[13] The relative energies of the optimized structures of **4** were carried out with B3LYP/6-311++G(3df,2pd).

Acknowledgements

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Synthesis of (*S*)-gizzerosine, a potent inducer of gizzard erosion in chicks

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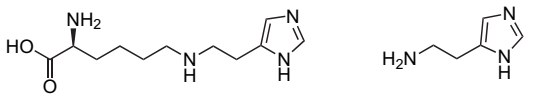
Abstract—(*S*)-Gizzerosine, a potent inducer of gizzard erosion in chicks, was synthesized using successive zinc-mediated and palladium-catalyzed coupling reactions as the key steps.

1. Introduction

Gizzerosine [(*S*)-2-amino-9-(4-imidazolyl)-7-azanonanoic acid (**1**) (Fig. 1)], generated during the heat treatment of brown fish meal, brings about gizzard erosion and ulceration in chicks, which cause a serious disease 'Black vomit'.[1,2] The structure and absolute stereochemistry of **1** were confirmed by the chemical synthesis of racemic[3–5] and optically active samples.[3,6] Biological studies of **1** showed it to be a potent agonist for the H_2-receptor of histamine (**2**),[7,8] causing 10 times more gastric secretions than **2**, and thereby, promoting acid indigestion and gizzard erosion. In addition, cAMP synthesis was enhanced by **1** 1000 times more than **2**.[9] On the other hand, **1** did not show any visible effects on rat stomach, though the gastric secretions being promoted.[2,10,11] This biological profile suggests **1** could be a possible drug candidate for gastric achlorhydria and osteoporosis. Since **1** can only be isolated in small amounts from fish meal (0.2 mg kg^{-1}),[2] synthetic supply is necessary for the standard of the quality control of fish meal and further biological studies. In a previous communication, we reported a facile and practical synthesis of (*S*)-**1**.[12,13] Herein, we describe in detail this synthesis and report the development of another.



(*S*)-gizzerosine (**1**) histamine (**2**)

Figure 1.

2. Results and discussion

2.1. Synthesis of Mori's intermediate (formal synthesis)

Mori et al. used enzymatic optical resolution of α-acylaminoadipic acid **3** as the key reaction and determined the absolute configuration to be *S* (Scheme 1).[6] We targeted the Mori's intermediates **4**[6,14] and **5** for the formal synthesis of **1** using (*S*)-serine as the starting material. (*S*)-Serine was first converted to the known iodide **6** in four steps.[15] Conversion of **6** to the aldehyde **5** via **9** using a zinc-mediated coupling reaction[16,17] with acrolein was attempted; however, 1,4-addition[18] did not occur and only the corresponding alanine derivative **10** (formed by quenching of the intermediate zinc iodide **7**) could be isolated. Next we aimed to prepare the alcohol **4** in a two-step procedure. The coupling reaction with allyl bromide[19] afforded the desired olefin **8**, but the use of propargyl bromide gave not alkyne **11** but allenyl compound **12**.[18] Hydroboration–oxidation of **8** under mildly basic conditions using sodium acetate[20] gave **4** without concomitant hydrolysis of the benzyl group, which was converted to (*S*)-gizzerosine **1** according to Mori's procedure.[6] The overall yield of **4** from (*S*)-serine was 58% over six steps (Scheme 1).

2.2. New synthesis using successive metal-mediated coupling reactions

2.2.1. Initial zinc-mediated coupling reaction with enol acetate. Whilst preparing Mori's intermediate **5**, we found that the coupling of the organozinc iodide **7** with 3-bromo-1-propenyl acetate (**13**)[21] afforded allylic acetate **14** as a 2:1 diastereomeric mixture at the 4-position in 98% yield, instead of enol acetate **15** (Scheme 2). Allylic acetate **14** was

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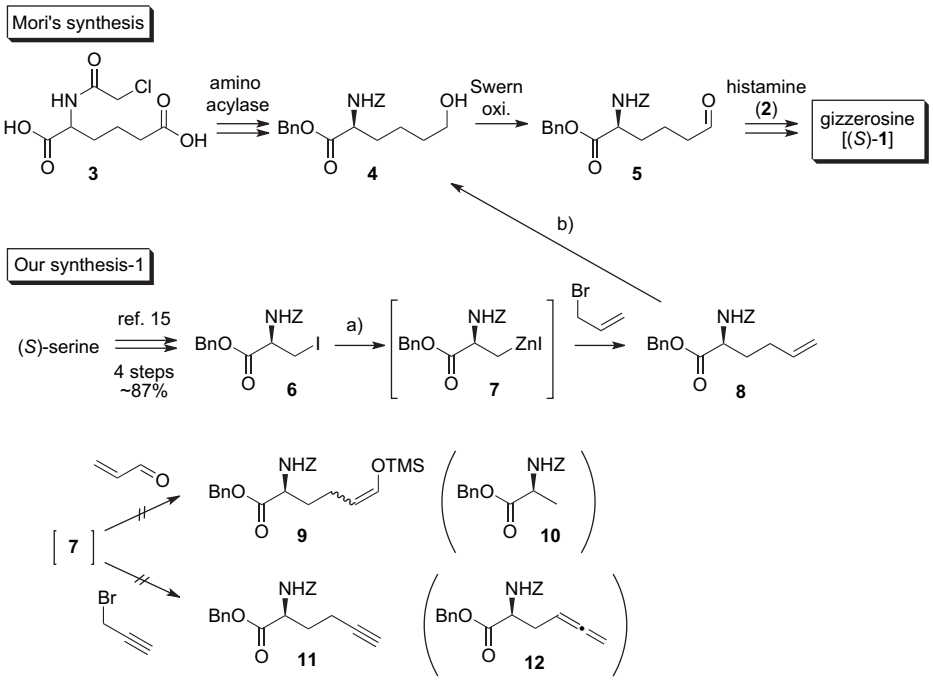
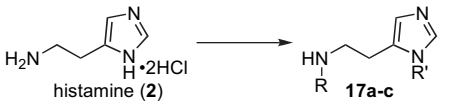


Scheme 1. Mori's synthesis and our formal synthesis of **1** using zinc-mediated coupling reaction: (a) i. Zn, $(CH_2Br)_2$, TMSCl, DMF, then **6**, ii. CuCN, LiCl, allyl bromide (quant.); (b) i. $BH_3 \cdot SMe_2$, THF, ii. 30% H_2O_2, NaOAc (68%).

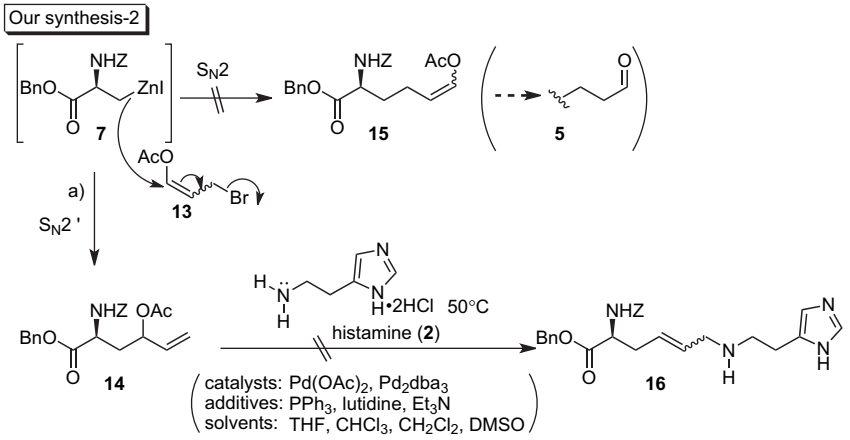
expected to be a good substrate for palladium-catalyzed coupling reactions with nitrogen nucleophiles,[22] but the coupling reaction with histamine (**2**) did not afford the desired product **16** under various conditions.

2.2.2. Protection of histamine. It was thought that this unreactivity was due to the insolubility of histamine itself and/or the poor nucleophilicity of the terminal amino group. Therefore, we prepared several histamine derivatives bearing electron-donating or electron-withdrawing protecting groups. Table 1 shows the protection of histamine (**2**) by nucleophilic substitution reactions. Bis-Boc product **17a** was the main product in entry 1. The primary amino group was selectively masked for benzyl carbamate **17b**[23] and trityl (Tr) ether **17c** but in low yields. Formation of benzyloxymethyl (BOM) ether and *m*-nitrobenzenesulfonamide (Ns) was observed only slightly by TLC. Since none of the product was formed in entry 6, benzyl derivatives were synthesized by reductive amination.

Table 1. Protection of histamine by nucleophilic substitution reactions

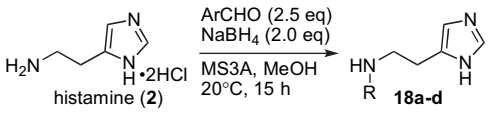


Entry	Conditions	Products	R	R′	Yields (%)
1	$(Boc)_2O$, Et_3N, MeOH	**17a**	Boc	Boc	83
2	ZCl, NaOMe, MeOH	**17b**	Z	H	36
3	TrCl, Et_3N, $CHCl_3$	**17c**	Tr	H	36
4	BOMCl, Et_3N, $CHCl_3$	—	BOM	H	Trace
5	NsCl, K_2CO_3, DMF	—	Ns	H	Trace
6	PMBCl, NaOMe, MeOH	—	PMB	H	—



Scheme 2. Preparation of **14** and trials of palladium-catalyzed coupling reaction with histamine: (a) CuCN, LiCl, **13**, DMF (98%).

Table 2. Protection of histamine by reductive amination reactions



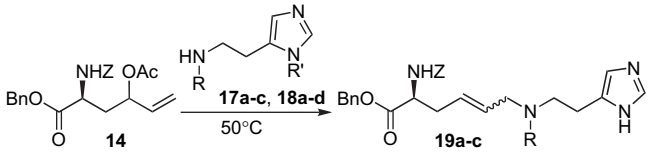
Entry	ArCHO	Products	R	Yields (%)
1	Benzaldehyde	**18a**	Benzyl	93
2	Anisaldehyde	**18b**	*p*-Methoxybenzyl	94
3	Piperonal	**18c**	Piperonyl	89
4	3,4-Dimethoxy-benzaldehyde	**18d**	3,4-Dimethoxybenzyl	10

As shown in Table 2, reductive amination of benzaldehyde, anisaldehyde, and piperonal with **2** afforded the desired compounds **18a**,[24] **18b**,[25] and **18c**,[25] respectively, in excellent yields.

2.2.3. Second palladium-catalyzed coupling reaction. The palladium-catalyzed coupling reactions of **14** with the histamine derivatives were examined under a variety of conditions (Table 3). The histamines with electron-withdrawing groups **17a** and **17b** did not react even in the presence of strong bases. Trityl derivative **17c** was also unreactive, probably due to its steric bulk. However, **18a** bearing an electron-donating benzyl group afforded the desired product **19a** in a yield of 50% when a mixture of PPh_3 (0.5 mol %) and Pd(II) (1 mol %) was used. Since increasing the amount of PPh_3 (1 mol %) gave multiple products, this mixture was subjected to further investigation. As expected, the more electron-donating derivatives **18b** and **18c** gave better yields of the coupling products **19b** and **19c**, respectively. The *E*/*Z* ratio of the products could not be ascertained due to overlappings in NMR spectra.

2.2.4. Total synthesis. We aimed to simultaneously carry out the deprotection of all three protecting groups and reduction of the chain double bond. Although the benzyl ester group and *N*-benzyloxycarbonyl group were easily deprotected and the double bond was reduced by hydrogenation, removal of the *N*-benzyl group of **19a** was unsuccessful (Table 4) and prolonged reaction times caused decomposition of gizzerosine framework. Additional experiments showed that gizzerosine itself was not stable under these reaction conditions. The *N*-PMB group (**19b**) was also largely inert to

Table 3. Palladium-catalyzed coupling reactions



Entry	Histamines	Catalysts	Additive	Solvents	Products	R	Yields (%)
1	**17a**	Pd_2dba_3	PPh_3, (base)[a]	THF	—	—	—
2	**17b**	Pd_2dba_3	PPh_3, (base)[b]	THF/DMF	—	—	—
3	**17c**	Pd_2dba_3	PPh_3	THF	—	—	—
4	**18a**	$Pd(OAc)_2$	PPh_3	THF[c]	—	—	—
5	**18a**	Pd_2dba_3	PPh_3	THF	**19a**	Bn	50
6	**18b**	Pd_2dba_3	PPh_3	THF	**19b**	PMB	92
7	**18c**	Pd_2dba_3	PPh_3	THF	**19c**	Piperonyl	71
8	**18d**	Pd_2dba_3	PPh_3	THF	—	—	—

[a] The following bases were used respectively: none, K_2CO_3, Et_3N, NaH, and KHMDS.
[b] The following bases were used respectively: none, NaH, and KHMDS.
[c] DMSO and MeCN were used respectively, besides THF.

Table 4. Hydrogenation and hydrolysis of **19a–c** toward the total synthesis

Entry	Substrate	R	Conditions	Yields (%)
1	**19a**	Bn	H_2, Pd/C, MeOH	—
2			H_2, $Pd(OH)_2$/C, THF/EtOH/H_2O	Trace
3			Raney Ni, MeOH/H_2O	—
4	**19b**	PMB	H_2, 5% Pd/C, THF/EtOH/H_2O	Trace
5			H_2, 5% Pd/C, 2 M HCl aq/EtOH	Trace
6			H_2, $Pd(OH)_2$/C, EtOH/H_2O	Trace
7			H_2, $Pd(OH)_2$, 2 M HCl aq/THF/EtOH	Trace
8	**19c**	Piperonyl	H_2, 10% Pd/C, THF/EtOH/H_2O	22
9			H_2, 10% Pd/C, $Pd(OH)_2$/C, THF/EtOH/H_2O	Decomp.
10			H_2, $Pd(OH)_2$/C, THF/EtOH/H_2O	Trace
11			H_2, $Pd(OH)_2$/C (excess), THF/EtOH/H_2O	47
12			Raney Ni, THF/EtOH/H_2O	Decomp.

hydrogenolysis. Selective removal under oxidative (CAN or DDQ), reductive (Li/NH_3), and acidic (2 M HCl aq) conditions also resulted in either decomposition or no reaction. On the other hand, the *N*-piperonyl group was readily removed, and finally, gizzerosine (*S*)-**1** was obtained from **19c** in 47% yield using excess amount of $Pd(OH)_2$/C. The overall yield was 29% in seven steps from (*S*)-serine.

3. Conclusion

We have developed new and facile synthesis of (*S*)-gizzerosine (**1**), a potent inducer of gizzard erosion, using successive zinc-mediated and palladium-catalyzed coupling reactions as the key steps. *N*-Piperonyl group was successfully applied as a new *N*-protecting group.

4. Experimental

4.1. General

The melting points measured by Yanaco MP-J3 micromelting point apparatus were uncorrected. Optical rotation values were measured by a Horiba Sepa-300 polarimeter. IR spectra were recorded by a Jasco FT-IR 4100 spectrometer (ATR, Zn–Se). ^{1}H and ^{13}C NMR spectra were recorded with Varian Inova 600 (150 MHz for ^{13}C), Inova 500 (500 MHz for ^{1}H and125 MHz for ^{13}C), and Gemini 2000 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometers in $CDCl_3$ with tetramethylsilane (δ_H 0 ppm) and $CHCl_3$ (δ_C 77.00 ppm) or in D_2O with acetone (δ_H 2.22 ppm and δ_C 215.48 ppm) as internal standards. Mass spectra were recorded with a Jeol JMS-700 spectrometer using glycerol matrix. Merck silica gel 60 (63–212 μm) and Kanto silica gel 60N (spherical, neutral, 100–210 μm) were used for column chromatography.

4.1.1. Benzyl (*S*)-2-(benzyloxycarbonylamino)-5-hexenoate (8). A 500 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, an N_2 inlet adapter, and a septum was placed under a nitrogen atmosphere. In the flask was placed zinc powder (15.2 g, 232 mmol) and 1,2-dibromoethane (1.00 ml, 11.6 mmol) in dry DMF (170 ml) was stirred at room temperature for 20 min. To the reaction mixture was added TMSCl (0.30 ml, 2.32 mol) and stirred at 60 °C for 30 min. Then to this mixture was added dropwise iodide **6** (MW: 439.24, 17.0 g, 38.7 mmol) in dry DMF (50 ml) and stirred at 60 °C for 20 min. A solution of CuCN (3.80 g, 42.5 mmol) and LiCl (3.60 g, 85.1 mmol) in dry DMF (40 ml) was added to the mixture at −55 °C. This was warmed to 0 °C and stirred for 10 min. Then the mixture was cooled to −55 °C again, allyl bromide (6.44 ml, 50.3 mmol) was added to this mixture. After the mixture was stirred at 0 °C for 2 h, unreacted zinc was filtrated through a Celite® pad and the filtrate was quenched with satd aq NH_4Cl soln. This mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc gave **8** (MW: 353.41, 13.7 g, 38.7 mmol, quantitative yield from **6**) as a colorless oil, which very slowly crystallized to form colorless needles; mp 37–38 °C, R_f 0.50 (hexane/EtOAc=3:1), $[\alpha]_D^{25}$ +1.80 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35 (s, 10H), 5.82–5.64 (m, 1H, H-5), 5.33 (pseudo d, 1H, *J*=8.1 Hz, NH), 5.17 (pseudo d, 2H, *J*=5.4 Hz), 5.12 (s, 2H), 5.02–4.92 (m, 2H), 4.50–4.40 (m, 1H, H-2), 2.20–1.70 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.38, 155.94, 136.85, 136.29, 135.33, 128.69, 128.60, 128.56, 128.37, 128.26, 128.18, 115.87, 67.12, 66.97, 53.45, 31.76, 29.18. IR: ν=3341 (m, N–H), 3064 (w), 3034 (w), 2953 (w), 1718 (s, C=O), 1641 (w), 1521 (m), 1454 (m), 1387 (w), 1343 (m), 1254 (m), 1211 (m), 1115 (w), 1047 (m), 1028 (m), 913 (m), 736 (m), 695 (s), 584 (w) cm^{-1}. FABMS: *m*/*z*=354 $(M+H)^+$, 310, 91 $(Bn)^+$. FABHRMS: calcd for $C_{21}H_{24}O_4N$ $(M+H)^+$ *m*/*z*=354.1705; found, 354.1709.

4.1.2. Benzyl (*S*)-2-(benzyloxycarbonylamino)-5-hydroxy-5-hexenoate (4). A 100 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, an N_2 inlet adapter, and a septum was placed under a nitrogen atmosphere. To a solution of **8** (MW: 353.41, 1.70 g, 4.81 mmol) in dry THF (20 ml) was added dropwise $BH_3 \cdot SMe_2$ (2.0 M in THF, 1.20 ml, 2.41 mmol) at 0 °C and the mixture was stirred while the reaction temperature gradually raised to 20 °C. To this was again added dropwise $BH_3 \cdot SMe_2$ (1.20 ml, 2.41 mmol) and the mixture was further stirred at 20 °C for 12 h. The reaction mixture was cooled to 0 °C before being quenched with H_2O. To the resulting solution were added successively aq H_2O_2 (30%, 8.82 M, 1.8 ml, 16 mmol) and NaOAc (0.99 g, 12 mmol) in H_2O (3 ml), and the mixture was stirred at 20 °C for 12 h. The reaction mixture was extracted with EtOAc. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc gave **4** (MW: 371.43, 1.22 g, 3.28 mmol, 68.3%) as a colorless oil; R_f 0.27 (hexane/EtOAc=1:1), $[\alpha]_D^{26}$ −5.09 (*c* 1.06, $CHCl_3$) {lit.[6] $[\alpha]_D^{23}$ −3.9 (*c* 1.06, $CHCl_3$)}. ^{1}H NMR spectral data were in agreement with the published data.[14]

4.1.3. Benzyl (2*S*,4*RS*)-4-acetoxy-2-(benzyloxycarbonylamino)-5-hexenoate (14). A 100 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, an N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with zinc powder (5.36 g, 82.0 mmol) and 1,2-dibromoethane (0.353 ml, 4.10 mmol) in dry DMF (20 ml) and stirred at room temperature for 20 min. To the reaction mixture was added TMSCl (104 μml, 822 μmol) and stirred at 60 °C for 30 min. Then to this mixture was added dropwise iodide **6** (MW: 439.24, 6.00 g, 13.7 mmol) in dry DMF (10 ml) and stirred at 60 °C for 20 min. A solution of CuCN (1.23 g, 13.7 mmol) and LiCl (1.16 g, 27.4 mmol) in dry DMF (10 ml) was added to the mixture at −55 °C. After being warmed to 0 °C and stirred for 10 min, the mixture was cooled to −55 °C again, and then bromide **13** (MW: 179.01, 2.94 g, 16.4 mmol) in dry THF (7 ml) was added. After the mixture was stirred for 2 h, unreacted zinc was filtrated through Celite® pad and the filtrate was quenched with satd aq NH_4Cl soln. This mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc gave **14** (a 2:1 diastereomeric mixture, MW: 411.45, 5.52 g, 13.4 mmol, 98% from **6**) as a colorless oil; R_f 0.28 (hexane/EtOAc=4:1),

$[\alpha]_D^{24}$ +16.9 (*c* 1.27, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=7.35 (s, 10H), 5.81–5.64 (m, 1H, H-5), 5.50 (d, 1H, *J*=8.0 Hz, NH), 5.38–5.06 (m, 7H), 4.59–4.48 (m, 1H, H-2), 2.20 (t, 2H, *J*=6.0 Hz, H-3), 1.93 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.71, 170.12, 155.72 (NCO), 136.09, 135.35, 135.15, 128.66, 128.64, 128.57, 128.53, 128.51, 128.40, 128.23, 128.20, 128.13, 128.10, 117.71, 117.55, 70.80, 70.78, 67.43, 67.29, 67.13, 67.09, 51.05, 50.95, 36.67, 36.12, 21.08, 20.89. IR: ν=3450–3200 (br, m), 3033 (w), 2947 (w), 1719 (s), 1523 (m), 1455 (m), 1372 (m), 1341 (m), 1229 (s), 1047 (m), 738 (m), 696 (m) cm^{-1}. FABMS: *m*/*z*=412 $(M+H)^+$, 352 $(M+H-AcOH)^+$, 308, 91 $(Bn)^+$. FABHRMS: calcd for $C_{23}H_{26}O_6N$ $(M+H)^+$ *m*/*z*=412.7601; found, 412.1767.

4.1.4. N^{α},N^{τ}-Bis(*tert*-butoxycarbonyl)histamine (17a). A 100 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, an N_2 inlet adapter, and a septum was placed under a nitrogen atmosphere. The flask was charged with histamine·2HCl (**2**·2HCl, MW: 184.07, 1.00 g, 5.43 mmol) and Et_3N (1.65 g, 16.3 mmol) in dry MeOH (20 ml) at room temperature and stirred for 30 min. After to this being added di-*tert*-butyl dicarbonate (Boc_2O, 2.37 g, 10.9 mmol), the mixture was stirred for 30 min. The reaction mixture was quenched with water and concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with $CHCl_3$/EtOH (30:1) gave **17a** (MW: 311.38, 1.41 g, 4.53 mmol, 83%) as a white powder; mp 129.5–130.5 °C, R_f 0.36 ($CHCl_3$/EtOH=30:1). ^1H NMR (300 MHz, $CDCl_3$): δ=8.00 (s, 1H), 6.82 (s, 1H), 4.99 (br s, 1H), 3.42 (t, 2H, *J*=6.3 Hz), 2.74 (t, 2H, *J*=6.6 Hz), 1.61 (s, 9H), 1.44 (s, 9H). IR: ν=3258 (m), 3130 (w), 2980 (m), 2933 (m), 1736 (s), 1700 (s), 1536 (m), 1391 (s), 1365 (s), 1274 (s), 1255 (s), 1155 (s), 1009 (s), 846 (m), 777 (m), 750 (m) cm^{-1}. FABMS: *m*/*z*=312 $(M+H)^+$, 256 $(M+H-t\text{-}Bu)^+$, 200 $(M+H-t\text{-}Bu_2)^+$, 156 $(M+H-Boc)^+$, 112 $(M+H-Boc_2)^+$, 57. FABHRMS: calcd for $C_{15}H_{26}O_4N_3$ $(M+H)^+$ *m*/*z*=312.1923; found, 312.1927.

4.1.5. N^{α}-(Benzyloxycarbonyl)histamine (17b). A 10 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a Dimroth condenser, and a septum was charged with **2**·2HCl (30.0 mg, 0.163 mmol) and NaOMe (17.6 mg, 0.326 mmol) in MeOH (800 µl) and stirred at 50 °C for 2 h. Then the mixture was cooled to room temperature and then were added Na_2CO_3 (25.9 mg, 0.245 mmol), benzyl chloroformate (27.9 µl, 0.196 mmol), and H_2O (100 µl). This was stirred for 3 h. To the reaction mixture was added H_2O and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with $CHCl_3$/MeOH (1:1) gave **17b** (MW: 245.28, 14.2 mg, 59.1 µmol, 36%); R_f 0.63 ($CHCl_3$/MeOH=1:1). ^1H NMR (300 MHz, $CDCl_3$): δ=7.54 (s, 1H, NCH=N), 7.40–7.25 (m, 6H), 6.80 (s, 1H), 5.38 (s, 2H, $ArCH_2$), 3.37–3.45 (m, 2H), 2.72–2.82 (m, 2H). FABMS: *m*/*z*=246 $(M+H)^+$, 136, 91 $(Bn)^+$.

4.1.6. N^{α}-(Triphenylmethyl)histamine (17c). A 10 ml, round bottomed flask equipped with a magnetic stirrer bar, was charged with **2**·2HCl (15.0 mg, 81.5 µmol), Et_3N (24.9 µl, 179 µmol), and triphenylmethyl chloride (TrCl, 37.0 mg, 133 µmol) in $CHCl_3$ (600 µl). The mixture was stirred for 20 h at room temperature. Then this mixture was quenched with cold H_2O and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with $CHCl_3$/EtOH (10:1) gave **17c** (MW: 353.49, 10.0 mg, 28.3 µmol, 35%); R_f 0.61 ($CHCl_3$/EtOH=10:1). ^1H NMR (300 MHz, $CDCl_3$): δ=7.40–7.10 (m, 16H), 6.50 (d, 1H, *J*=1.5 Hz), 2.72 (t, 2H, *J*=6.9 Hz), 2.39 (t, 2H, *J*=6.0 Hz).

4.1.7. N^{α}-Benzylhistamine (18a). A 100 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a Dimroth condenser, and a septum was charged with **2**·2HCl (500 mg, 2.72 mmol) and NaOMe (293 mg, 5.43 mmol) in dry MeOH (20 ml) at room temperature. Then the mixture was stirred at 50 °C for 1 h. To the solution were added benzaldehyde (0.69 ml, 6.8 mmol) and MS3A (25 mg) at 0 °C and the mixture was stirred at 50 °C for 30 min. Then to the solution was added $NaBH_4$ (308 mg, 8.15 mmol) at −78 °C and the mixture was gradually warmed to room temperature. The reaction mixture was filtrated through a Celite® pad and concentrated in vacuo. The residue was diluted with water and extracted with $CHCl_3$. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on neutral silica gel. Elution with $CHCl_3$/EtOH (1:1) gave **18a** (MW: 202.13, 513 mg, 2.54 mmol, 93%) as a pale yellow oil; R_f 0.23 ($CHCl_3$/MeOH=30:1, 1% Et_3N). ^1H NMR (300 MHz, $CDCl_3$): δ=7.51 (d, 1H, *J*=0.9 Hz, NCH=N), 7.38–7.20 (m, 5H), 6.79 (d, 1H, *J*=0.6 Hz), 3.82 (s, 2H), 2.95 (pseudo t, 2H, *J*=6.0 Hz), 2.80 (pseudo t, 2H, *J*=6.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ=139.88, 134.32, 128.49, 128.13, 127.10, 53.81, 48.63, 26.11. IR: ν=3650–2200 (br s), 1567 (w), 1494 (m), 1453 (s), 1261 (w), 1104 (m), 938 (w), 820 (m), 733 (s), 697 (s), 662 (m), 624 (m) cm^{-1}. FABMS: *m*/*z*=202 $(M+H)^+$, 91 $(Bn)^+$. FABHRMS: calcd for $C_{12}H_{16}N_3$ $(M+H)^+$ *m*/*z*=202.1344; found, 202.1342.

4.1.8. N^{α}-(*p*-Methoxybenzyl)histamine (18b). In the same manner as described for **18a**, **18b** (MW: 231.29, 2.95 g, 12.8 mmol) was obtained from **2**·2HCl (2.50 g, 13.6 mmol) and *p*-methoxybenzylaldehyde (4.14 ml, 34.0 mmol) in a yield of 94% based on **2**·2HCl, as a pale yellow oil; R_f 0.29 ($CHCl_3$/MeOH=5:1). ^1H NMR (300 MHz, $CDCl_3$): δ=7.49 (s, 1H, NCH=N), 7.20 (pseudo d, 2H, *J*=8.7 Hz), 6.85 (pseudo d, 2H, *J*=8.7 Hz), 6.77 (s, 1H), 3.79 (s, 3H, OMe), 3.74 (s, 2H), 2.92 (pseudo t, 2H, *J*=7.2 Hz), 2.76 (pseudo t, 2H, *J*=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.80, 134.51, 132.15, 129.38, 113.89, 55.18, 53.10, 48.50, 26.26. IR: ν=3500–2200 (br s), 1611 (m), 1584 (w), 1509 (s), 1460 (m), 1441 (m), 1301 (w), 1244 (s), 1175 (m), 1104 (m), 1032 (m), 938 (w), 813 (s), 773 (w), 662 (w), 626 (w) cm^{-1}. FABMS: *m*/*z*=232 $(M+H)^+$, 121 $(PMB)^+$. FABHRMS: calcd for $C_{13}H_{18}O_3N_3$ $(M+H)^+$ *m*/*z*=232.1450; found, 232.1453.

4.1.9. N^{α}-Piperonylhistamine (18c). In the same manner as described for **18a**, **18c** (MW: 2456.28, 238 mg, 0.970 mmol) was obtained from **2**·2HCl (200 mg, 1.09 mmol) and

piperonal (408 mg, 2.72 mmol) in a yield of 89% based on **2**·2HCl, as a pale yellow oil; R_f 0.79 ($CHCl_3$/EtOH/28% NH_3 aq=3:3:1). ^1H NMR (300 MHz, $CDCl_3$): δ=7.54 (d, 1H, J=1.2 Hz, NCH=N), 6.82–6.79 (m, 2H), 6.78–6.72 (m, 2H), 5.95 (s, 2H, OCH_2O), 3.73 (s, 2H, $ArCH_2$), 2.92 (pseudo t, 2H, J=5.7 Hz), 2.79 (pseudo t, 2H, J=5.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ=147.69, 146.58, 133.62, 121.30, 108.63, 108.11, 100.89, 53.46, 48.41, 26.29. IR: ν=3500–2400 (br s), 1503 (m), 1489 (s), 1442 (m), 1246 (s), 1215 (m), 1103 (w), 1039 (m), 931 (w), 810 (w), 744 (s), 665 (w), 626 (w) cm^{-1}. FABMS: m/z=246 $(M+H)^+$, 135 $(piperonyl)^+$. FABHRMS: calcd for $C_{13}H_{16}O_2N_3$ $(M+H)^+$ m/z=246.1242; found, 246.1248.

4.1.10. N^{α}-(3,4-Methoxybenzyl)histamine (18d). In the same manner as described for **18a**, **18d** (MW: 245.28, 71.0 mg, 0.289 mmol, 11%) was obtained from **2**·2HCl (500 mg, 2.72 mmol) and 3,4-dimethoxybenzaldehyde (1.13 g, 6.79 mmol) in a yield of 11% based on **2**·2HCl, as a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ=7.44 (s, 1H, NCH=N), 6.78 (s, 1H), 6.75 (s, 2H), 6.71 (s, 1H), 3.79 [s, 6H, $(OMe)_2$], 3.69 (s, 2H, $ArCH_2$), 2.86 (t, 2H, J=6.5 Hz), 2.73 (t, 2H, J=6.5 Hz).

4.1.11. Benzyl (2*S*,4*EZ*)-2-(benzyloxycarbonylamino)-6-(benzyl)[2-(4-imidazolyl)ethyl]amino-4-hexenoate (19a). In the similar manner as described for **19c**, **19a** (MW: 552.66, 671 mg, 1.22 mmol) was obtained from **14** (MW: 411.45, 1.00 g, 2.43 mmol) and N^{α}-benzylhistamine **18a** (587 mg, 2.91 mmol) in a yield of 50% based on **14**, as a yellow oil; R_f 0.29 ($CHCl_3$/MeOH=10:1). ^1H NMR (300 MHz, $CDCl_3$): δ=7.45 (s, 1H, NCH=N), 7.40–7.15 (m, 15H), 6.73 (s, 1H, NCH=C), 5.56–5.35 (m, 2H), 5.20–5.00 (m, 4H), 4.55–4.45 (m, 1H, H-2), 3.58 (s, 2H, NCH_2Ph), 3.00 (d, 2H, J=5.7 Hz, H-6), 2.80–2.40 (m, 6H). FABMS: m/z=553 $(M+H)^+$, 471, 279, 91 $(Bn)^+$. FABHRMS: calcd for $C_{33}H_{37}O_4N_4$ $(M+H)^+$ m/z=553.2815; found, 553.2819.

4.1.12. Benzyl (2*S*,4*EZ*)-2-(benzyloxycarbonylamino)-6-[2-(4-imidazolyl)ethyl](*p*-methoxybenzyl)amino-4-hexenoate (19b). In the similar manner as described for **19c**, **19b** (MW: 582.69, 262 mg, 449 μmol) was obtained from **14** (MW: 411.45, 200 mg, 0.486 mmol) and N^{α}-(*p*-methoxybenzyl)histamine **18b** (135 mg, 533 μmol) in a yield of 92% based on **14**, as a yellow oil; R_f 0.50 ($CHCl_3$/EtOH=10:1). ^1H NMR (300 MHz, $CDCl_3$): δ=7.46 (s, 1H, NCH=N), 7.36–7.28 (m, 10H), 7.16 (d, 2H, J=8.4 Hz), 6.83 (d, 2H, J=8.7 Hz), 6.74 (s, 1H, NCH=C), 5.58–5.36 (m, 3H), 5.20–5.00 (m, 4H), 4.54–4.45 (m, 1H), 3.78 (s, 3H, OMe), 3.52 (s, 2H), 2.99 (d, 2H, J=5.4 Hz), 2.68 (dd, 2H, J=16.5, 5.4 Hz), 2.56 (t, 2H, J=5.7 Hz), 2.49 (t, 2H, J=6.6 Hz). FABMS: m/z=583 $(M+H)^+$, 501, 230, 121 $(PMB)^+$, 91 $(Bn)^+$. FABHRMS: calcd for $C_{34}H_{39}O_5N_4$ $(M+H)^+$ m/z=583.2921; found, 583.2922.

4.1.13. Benzyl (2*S*,4*EZ*)-2-(benzyloxycarbonylamino)-6-[2-(4-imidazolyl)ethyl](piperonyl)amino-4-hexenoate (19c). A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, an N_2 inlet adapter, and a septum was placed under a nitrogen atmosphere. The flask was charged with **14** (MW: 411.45, 540 mg, 1.31 mmol), $Pd_2(dba)_3$ (60.0 mg, 65.6 μmol), and PPh_3 (18.2 mg, 69.4 μmol) in dry THF, and stirred for 15 min at room temperature. To the suspension was added N^{α}-piperonylhistamine **19c** (555 mg, 1.58 mmol), warmed up to 50 °C, and the mixture was stirred for 1 h. The reaction mixture was filtrated through a Celite® pad, added water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with $CHCl_3$/EtOH (20:1) gave **19c** (MW: 507.27, 550 mg, 0.922 mmol, 71% based on **14**) as a yellow oil; R_f 0.57 ($CHCl_3$/EtOH=30:1), $[\alpha]_D^{24}$ −0.703 (c 1.28, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=7.47 (s, 1H, NCH=N), 7.40–7.25 (m, 10H), 6.75–6.65 (m, 4H), 5.91 (s, 2H, OCH_2O), 5.64–5.36 (m, 3H), 5.22–5.00 (m, 4H), 4.54–4.45 (m, 1H, H-2), 3.47 (d, 2H, NCH_2Ar), 2.98 (d, 2H, J=5.4 Hz, NCH_2C=), 2.78–2.40 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.79, 155.91, 147.76, 146.66, 136.19, 135.19, 134.30, 132.84, 131.73, 128.67, 128.56, 128.36, 128.23, 128.05, 127.07, 121.97, 109.19, 107.93, 100.86, 67.20, 66.93, 57.85, 54.78, 53.66, 52.56, 35.35, 23.18. IR: ν=3493–2100 (br s), 1717 (s), 1500 (s), 1487 (s), 1454 (m), 1440 (s), 1342 (w), 1244 (s), 1214 (s), 1187 (m), 1093 (w), 1038 (s), 975 (w), 930 (w), 810 (w), 749 (s), 696 (s), 665 (w) cm^{-1}. FABMS: m/z=597 $(M+H)^+$, 154, 136, 91 $(Bn)^+$, 73. FABHRMS: calcd for $C_{34}H_{37}O_6N_4$ $(M+H)^+$ m/z=597.2713; found, 597.2718.

4.1.14. (*S*)-2-Amino-9-(4-imidazolyl)-7-azanonanoic acid (gizzerosine, 1). A 30 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, an N_2 inlet adapter, and a septum was placed under a hydrogen atmosphere. The flask was charged with **19c** (MW: 596.67, 54.4 mg, 91.1 μmol) and $Pd(OH)_2$/C (110 mg) in 5 ml of EtOH/THF/H_2O (3:1:1). The mixture was stirred for 5 h at room temperature. Then this was filtrated through a Celite® pad and the filtrate was concentrated in vacuo. The resulting solid was purified through Sephadex® LH-20 column. Elution with MeOH/H_2O (1:1) gave gizzerosine **1** (MW: 240.30, 10.4 mg, 0.433 mmol, 47%) as a white solid. This solid was dissolved in 1 M HCl aq and stirred for 5 min. Then this solution was concentrated in vacuo. This resulting white amorphous solid was used for analysis; R_f 0.09 ($CHCl_3$/MeOH/28% NH_3 aq=3:3:1), mp 250–251 °C (dec) [lit.[6] 251–252 °C (dec)]; $[\alpha]_D^{22}$ +9.45 (c 0.555, H_2O) {lit.[6] $[\alpha]_D^{22}$ +10.3 (c 1.28, H_2O)}. ^1H NMR (300 MHz, D_2O): δ=8.30 (br s, 1H), 7.26 (br s, 1H), 3.75 (t, 1H, J=6.0 Hz), 3.37 (pseudo t, 2H, J=7.2 Hz), 3.11 (pseudo t, 4H, J=6.6 Hz), 1.89 (m, pseudo q, 2H, J=7.4 Hz), 1.74 (quint, 2H, J=7.5 Hz), 1.60–1.35 (m, 2H). ^{13}C NMR (75 Hz, D_2O): δ=175.08, 135.69, 131.45, 116.93, 54.99, 47.72, 46.86, 30.38, 25.65, 22.91, 22.04. IR: ν=3300–2300 (br s), 3116 (s), 2786 (s), 2450 (m), 1634 (s), 1601 (s), 1522 (s), 1462 (s), 1395 (s), 1348 (m), 1329 (m), 1235 (w), 1052 (w), 957 (w), 839 (w), 794 (w), 719 (w), 623 (m) cm^{-1}. FABMS: m/z=241 $(M+H)^+$, 207, 185, 93, 75, 57, 45. FABHRMS: calcd for $C_{11}H_{21}N_4O_2$ $(M+H)^+$ m/z=241.1665; found, 241.167. These spectral data are in good agreement with those reported.[6]

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Urea/thiourea-based colorimetric chemosensors for the biologically important ions: efficient and simple sensors

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Abstract—Some colorimetric anion sensors have been synthesized where 4-nitrophenyl was treated as a signaling unit and urea/thiourea moieties as binding sites. The receptors, effectively and selectively, recognized the biologically important F^- and carboxylate anions from other anions such as Cl^- and Br^- in DMSO.

1. Introduction

The development of simple receptors capable of recognizing biologically relevant anions such as fluoride, chloride, phosphate, and carboxylate has attracted considerable interest in the recent past.[1] The design of these receptors has been focused on having the ability to selectively recognize and sense the biologically important anions through the naked eye, electrochemical, and optical responses.[2] While the incorporation of fluorescent chromophores into the receptor has gained considerable attention owing to their high sensitivity and easy detection for a long time,[3] the investigation of anion-selective receptors based on color chromophores has just recently begun.[4] In particular, the development of colorimetric anion sensing is even more important and useful since the colorimetric anion sensing system would allow the so-called 'naked-eye' detection of anions without use of any spectroscopic instrumentation, being simple and convenient for detection. Such receptors would be more valuable if they can be obtained by a simple synthetic method.[5]

Many chemical sensors follow the approach of the covalent attachment of signaling subunits and binding sites.[6] Hydrogen-bonding sites typically used in chromogenic or fluorogenic chemosensors are ureas, thioureas, calyx[4]pyrroles, sapphyrins, and amides.[7] Among them, the urea or thiourea groups have been often focused as anion binding sites, because the hydrogen-bonding ability of these functional groups can result in quite stable complexes strongly hydrogen-bonded with biologically important anions such as acetate, phosphate or chloride, and because they can be often easily synthesized from commercially available reagents by a single-step procedure.[7a–c] Therefore, a variety of receptors containing one or more urea subunits have been designed and tested for anion recognition and sensing over the past years. Especially, several urea or thiourea derivatives connected with a series of spacer units including cyclic structures (naphthalene, anthracene etc.) have been synthesized and proved to be very efficient for the anion sensors.[8] Very recently, Jose et al. have reported the new colorimetric receptors by introducing two phenylurea/phenylthiourea into an anthraquinone spacer acting as a signaling subunit.[9] The thiourea receptor has shown the efficient colorimetric sensing, while the urea one needs a certain temperature (above 60 °C) to display the colorimetric action. This result led us to suggest that if the acidity of the urea/thiourea increases, the colorimetric receptors will be more efficient even at room temperature. Therefore, we have planned to design new urea/thiourea with a nitrophenyl group as a signaling group to enhance both hydrogen-bond donor tendency and acidity and to be well known as a chromophore for color change. We have attached two *p*-nitrophenylurea groups or two *p*-nitrophenylthiourea groups to a simple 4,5-dimethyl-1,2-diaminobenzene ring, in which the methyl groups help easy observation of ^1H NMR spectral shift. Anion binding properties of the new urea/thiourea anion sensors were investigated by UV–vis spectroscopy and color changes. As expected, they have shown a unique color change and UV–vis absorption peak in the presence of

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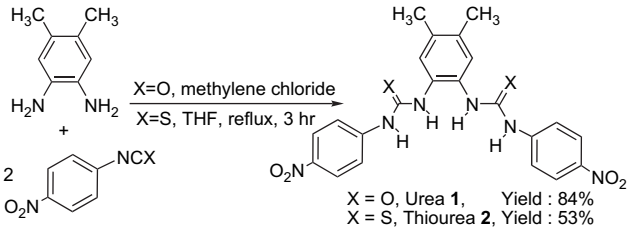
fluoride or acetate ions. During the preparation of the manuscript, we found a related publication where bis-urea compounds based on *ortho*-phenylenediamine function have been used as carboxylate anion receptors. The recognition was monitored by NMR method, however, there were no results and discussion for the color changes or UV–vis observation.[10]

We report herein on novel colorimetric receptors for selective fluoride or acetate ion sensing containing nitrophenyl group as chromogenic signaling subunit and urea/thiourea as binding sites. The anion recognition via hydrogen-bonding interactions can be easily monitored by anion-complexation induced changes in UV–vis absorption spectra and with the naked eye. Moreover, the hydrogen bonds between N-H of the urea/thiourea and fluoride or carboxylate ions are described on the basis of the ^{1}H NMR experiments, and a feature of the binding mode is predicted on the basis of ab initio calculations.

2. Results and discussion

Urea **1** and thiourea **2** were synthesized using the one-step reaction of 4,5-dimethyl-1,2-phenylenediamine and 4-nitrophenyl isocyanate or 4-nitrophenyl isothiocyanate in a reasonably good yield (Scheme 1). Urea **1** was immediately precipitated when 4,5-dimethyl-1,2-phenylenediamine and 4-nitrophenyl isocyanate were mixed together in methylene chloride at room temperature. Thiourea **2** was obtained from the reflux condition in THF, meaning that 4-nitrophenyl isothiocyanate is less reactive with 4,5-dimethyl-1,2-phenylenediamine than 4-nitrophenyl isocyanate.



Scheme 1. Synthesis of the receptors **1** and **2**.

The selective recognition of urea **1** and thiourea **2** with F^- over other halides such as Cl^- and Br^- was evident in ^{1}H NMR titration experiment. ^{1}H NMR spectrum of urea **1** in DMSO-d_6 showed N-H protons at 9.79 and 8.16 ppm.

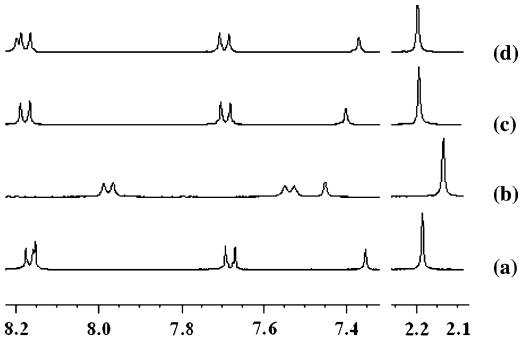


Figure 1. Partial ^{1}H NMR spectra of urea **1** (2.5×10^{-3} M) in DMSO-d_6. (a) **1** only; (b) **1**+2 equiv F^-; (c) **1**+2 equiv Cl^-; (d) **1**+2 equiv Br^-.

Aromatic protons and methyl group were shown at 8.18, 7.68, and 7.36 ppm and at 2.19 ppm, respectively. ^{1}H NMR peaks of urea **1** were changed dramatically in the presence of 2 equiv of F^- whereas there were no significant spectral changes in the phenyl and methyl proton regions for the addition of Cl^- and Br^- (Fig. 1). Two N-H proton peaks disappeared in the presence of F^- and shifted to the downfield in the presence of Cl^- or Br^-. The ^{1}H NMR peaks at 8.18 and 7.68 ppm from nitrophenyl group and a single peak at 2.19 ppm from methyl moved to the upfield, and another singlet (7.36 ppm) from the phenylene moved to the downfield with the addition of 2 equiv of F^- ion as shown in Figure 2a.

The ^{1}H NMR spectra of thiourea **2** were also changed selectively in the presence of F^-. By the titration of F^-, all proton signals from phenylene group (8.14, 7.83, and 7.23 ppm) as well as methyl group (2.22 ppm) shifted to the upfield (Fig. S1). Line broadening of the peaks was observed in the addition of F^- ion. It is clear that F^- binds to four urea N-H protons in both urea **1** and thiourea **2** since the N-H signals were all broadened in the presence of small amounts of F^-. When more than 1 equiv of F^- was added, all N-H peaks disappeared. Addition of acetate ion also developed some changes in the ^{1}H NMR spectra of urea **1** as well as thiourea **2**. The changes by acetate ion in ^{1}H NMR spectra of thiourea **2** were similar to those caused by F^-. On the other hand, in urea **1** case, the chemical shift changes by acetate anion were smaller when compared to those caused by F^- and were not observed after the addition of 1 equiv of acetate anion in the titration (Fig. 2b).

Based on the NMR experiment result for qualitatively selective recognition of some anions by the host molecules, urea **1** and thiourea **2**, further study of the anion recognition has

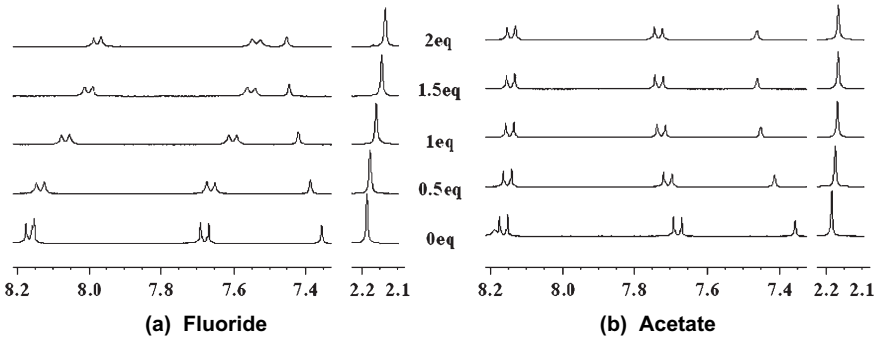


Figure 2. Titration of a 2.5×10^{-3} M solution of urea **1** in DMSO-d_6 with (a) F^- and (b) CH_3COO^- ions.

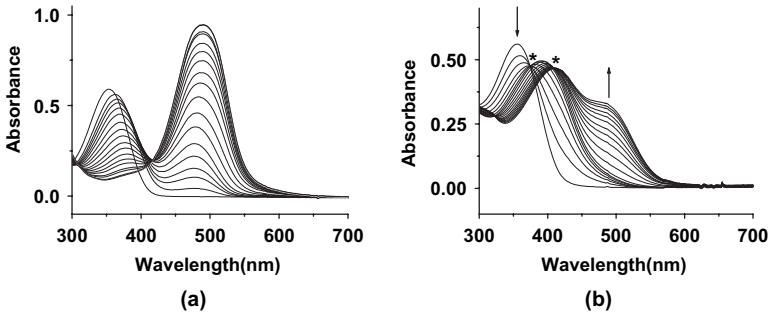


Figure 3. UV–vis spectral changes observed for **1** and **2**, upon addition of fluoride anion in DMSO at room temperature. (a) Urea **1** (2.5×10^{-5} M) with F^- (0–105 equiv) and (b) thiourea **2** (3.4×10^{-5} M) with F^- (0–3.4 equiv).

been carried out. The remarkable preference in binding ability of urea **1** and thiourea **2** for F^- was observed with clear color change *even at room temperature*, unlike the phenylurea receptor with an anthraquinone spacer designed by Jose et al.,[9] and monitored with UV–vis spectroscopy. The UV–vis spectra of urea **1** and thiourea **2** changed dramatically when small amounts of F^- ions were added whereas there were no UV–vis spectral changes upon the addition of up to 250 equiv of Cl^- or Br^- ions. In the course of addition of F^- ion to urea **1**, a new peak at λ_{max}=488 nm was developed and the isosbestic point was observed at 416 nm as shown in Figure 3a.

The more drastic UV–vis spectral change was observed for thiourea **2** as shown in Figure 3b. Again, a new peak was shown at λ_{max}=488 nm. There are two isosbestic points: one at 374 nm and the other at 409 nm. A maximum intensity of ~90% at 488 nm was obtained for thiourea **2** when less than 10 equiv of F^- were added, whereas ~70 equiv of F^- were needed for urea **1** to obtain the same intensity. This result shows that F^- binds with thiourea **2** more tightly than with urea **1**, indicating stronger hydrogen bonds of acidic N-H groups in thiourea **2**.

Figure S2a shows that UV–vis absorption of urea **1** also changes in the presence of acetate ion. The λ_{max} slowly moved from 354 to 366 nm when 10 equiv of acetate ion were added. Addition of more than 10 equiv of acetate ion did not give any further spectral changes. The presence of one isosbestic point at 359 nm implies that two species, **1** and **1**-acetate, are present in equilibrium, and the analysis of the set of UV–vis spectra indicates the 1:1 complex with a complexation constant $K=1.1(\pm0.1)\times10^5$.[11]

The UV–vis spectrum of thiourea **2** showed dramatic changes in the course of titration with acetate ion as shown in Figure S2b. The UV–vis spectral change of urea **1** with acetate ion was significantly different from that with fluoride ion. However, the change of thiourea **2** with acetate was similar to that with fluoride ion. Even though the binding constant for complexation of thiourea **2** with acetate was not obtained, it is expected to be the same order of magnitude (~10^5) since the binding constant for the urea with F^- was reported to be about half of that for the thiourea analogue due to the less acidic protons.[9]

Pfeffer group reported complexation constants of some thioureas with acetate ion where the log *K* values were 3.6 for the aliphatic thiourea and 3.9–4.0 for aromatic thioureas, and explained the difference in terms of the acidity of thiourea protons.[2e,2f,4a] Other studies also reported that thiourea-based anion sensors have the binding constant values of the order of magnitude (~10^5)[4f,12] with acetate anion, which is comparable to our result.

The anion recognition is also detectable at room temperature with naked eyes as shown in Figure 4. Again, Cl^- and Br^- did not give any noticeable color changes in the DMSO solution of urea **1** and thiourea **2**. For urea **1**, only F^- gave significant color changes to reddish orange. Acetate ion made the solution turn pale yellow, but the color change was not noticeable at low concentration with naked eyes. Color change of thiourea **2** was much more sensitive to F^- than urea **1**. One equivalent of F^- was enough to recognize color change from colorless to yellow with naked eyes. More addition of F^- changed the color to reddish orange. In contrast to urea **1**, the solution of thiourea **2** with acetate ion turned yellow at low concentration of acetate ion and reddish orange at high concentration.

Two isosbestic points in UV–vis spectra and two different colors, yellow and reddish orange, in naked-eye detection

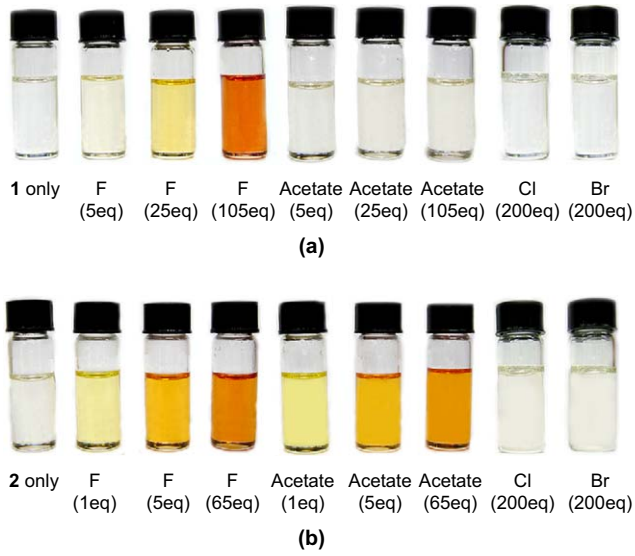


Figure 4. Color changes observed for **1** and **2** in DMSO upon the addition of anions as tetraethylammonium salts at room temperature. (a) Urea **1** (2.5×10^{-5} M) and (b) thiourea **2** (2.5×10^{-5} M) (number of equivalents in parenthesis).

during the host–guest complexation suggest the following equilibria for the interaction between urea/thiourea and F^- as Fabbrizzi et al. proposed.[2g,2h,4c,4d]

Equilibrium I: $RH + L^- \leftrightarrows RH\cdots L^-$

Equilibrium II: $RH\cdots L^- + L^- \leftrightarrows R^- + LHL^-$

The first equilibrium is accomplished for the complexation between the host (RH=urea **1**/thiourea **2**) and the guest (L^-=anion). If there are more free anions, the host molecules can be deprotonated and exist in the form of an anion R^- as shown in equilibrium II. The equilibrium constants of these two processes would be mainly dependent on the binding constant value of the host–guest complex and the acidity of host or the basicity of anions.

For both urea **1** and thiourea **2**, the host–guest complex is responsible for ~370 nm peak in the UV–vis spectra or pale yellow color in the naked-eye detection. On the other hand, the new anion species R^-, in the equilibrium II, are responsible for the 488 nm peak in the UV–vis spectra and reddish orange color in the naked-eye detection. Both urea **1** and thiourea **2** are believed to reach the equilibria I and II with F^- probably due to strong hydrogen-bonding interaction between urea/thioura N-H and F^-, which eventually generates a highly stable anion species FHF^- in the equilibrium II.

To support the suggested equilibrium profile, the geometries of all species involved in equilibria I and II were optimized in gas phase at the HF/6-31+G(d) level using ab initio calculation (Fig. 5). All four protons of urea/thiourea are directed toward anion ligands but each hydrogen-bond distance is different as shown in Table 1. Two protons (H(3) and H(4)) connected to nitrophenyl group have much shorter distances to the anions than the other N-H protons. The hydrogen-bond distances increase as the sizes of the anion ligands from fluoride to bromide increase. The two oxygen

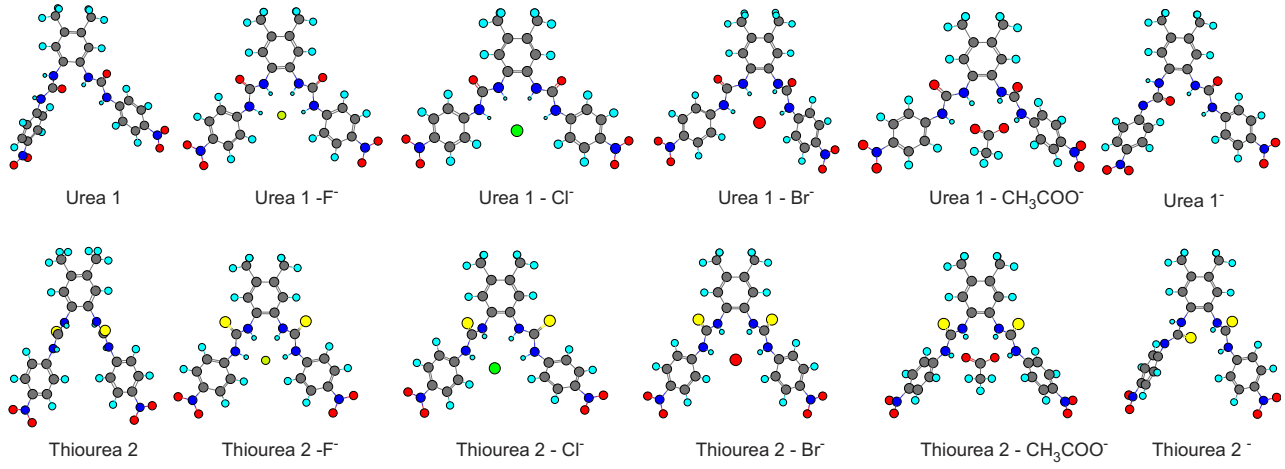
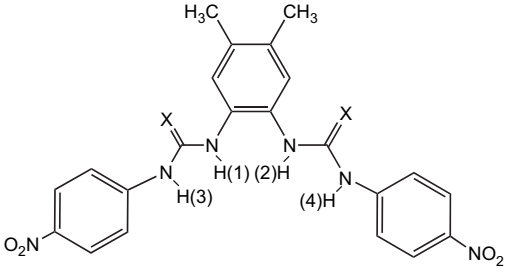


Figure 5. Optimized geometries from ab initio HF/6-31+G(D) calculations.

Table 1. Computed distances[a] of $NH\cdots L^-$ hydrogen bonds from ab initio HF/6-31+G(D) calculations



Ligand	H(1)···L^-	H(2)···L^-	H(3)···L^-	H(4)···L^-
Receptor: urea **1** (X=O)				
F^-	1.924	1.919	1.753	1.755
Cl^-	2.614	2.637	2.333	2.336
Br^-	2.655	2.479	2.448	2.509
CH_3COO^-[b]	2.025(O1)	2.155(O2)	1.836(O1)	1.870(O2)
Receptor: thiourea **2** (X=S)				
F^-	2.056	2.056	1.649	1.649
Cl^-	2.570	2.992	2.289	2.321
Br^-	2.575	2.577	2.536	2.535
CH_3COO^-[b]	1.957(O1)	1.957(O2)	1.910(O1)	1.910(O2)

[a] The unit of the computed distances is Å.
[b] Two oxygen atoms (O1 and O2) of CH_3COO^- form hydrogen bonds with the receptors where O1 is hydrogen-bonded to H1 and H3 and O2 to H2 and H4.

atoms of CH_3COO^- effectively form four hydrogen bonds (two per oxygen atom) with each receptor and their hydrogen-bond distances are within the typical hydrogen-bond distance ranges between 1.86 and 2.16 Å. In general, the anions are well-positioned into the hydrogen-bond cage in the complexes through favorable hydrogen-bonding interactions. The reaction energies between the reactants and the products were also calculated based on the optimized geometries using the density functional theory at the B3LYP/6-31G+(d)//HF/6-31+G(d) level (Table S1). The preference of both urea/thiourea receptors for the anions can be ordered as follows: $F^->CH_3COO^->Br^->Cl^-$. In the equilibrium II, thiourea **2** is more favorable than urea **1** for all anions mainly due to the higher acidity of thiourea protons.

Deprotonation of nitrophenyl connected urea protons are well known and the resulting R^- is a push–pull chromophore, which is responsible for the 488 nm peak in the UV–vis and the development of the reddish orange color.[4] Acetate ion is basic enough to deprotonate the protons of thiourea **2**, but is not basic enough to deprotonate those of urea **1**. Therefore, only the equilibrium I exists between urea **1** and acetate ion, and the resulting complexation constant was found to be $K=1.1(\pm0.1)\times10^5$ with high accuracy. From the computational results, the value of the complexation constant for thiourea **2**-F^- is expected to be more or less the same as that for urea **1**-F^-.

3. Conclusion

We have developed new colorimetric anion sensors having both 4-nitrophenyl as a signaling unit and urea/thiourea moieties as binding sites, and investigated their affinity and selectivity to the halide and acetate anion experimentally and theoretically. The receptors effectively and selectively recognize the biologically important F^- and carboxylate anions over other anions such as Cl^- and Br^- in DMSO. More importantly, the new colorimetric chemosensors for anions have displayed naked-eye detection *at room temperature*, unlike the phenylurea receptor with an anthraquinone spacer designed by Jose et al.[9] In addition, the NMR and ab initio calculations are in good agreement with the color changes. Therefore, it is believed that 4-nitrophenylurea and -thiourea binding sites attached to a simple benzene ring are suitable colorimetric reagents for fluoride and carboxylate sensing. We have also shown that even simple chromophores such as cheap and easy-to-make anion receptors containing hydrogen-bonding donor groups can operate as efficient colorimetric sensors for the naked-eye detection of anions.

4. Experimental

4.1. General

All reagents were purchased from Aldrich and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 spectrometer, operating at 9.39 T. UV–vis spectra were obtained using a Cary 3 spectrophotometer with a quartz cuvette (path length=1 cm). IR spectra were measured on a BIO RAD FTS 135 spectrometer as KBr pellets. Elemental analysis for carbon, nitrogen, and hydrogen was carried out by using an EA1108 (Carlo Erba Instrument, Italy) in the Organic Chemistry Research Center of Sogang University, Korea.

4.2. Synthesis of *N*,*N*′′-1,2-(4,5-dimethylphenylenebis-[*N*′-*p*-nitrophenylurea]) (1) and *N*,*N*′′-1,2-(4,5-dimethylphenylenebis[*N*′-*p*-nitrophenyl(thiourea)]) (2)

To a methylene chloride (5 ml)/THF (3 ml) solution of 4-nitrophenyl isocyanate (0.37 g, 2.2 mmol), 4,5-dimethyl-1,2-phenylenediamine (0.14 g, 1.0 mmol) in methylene chloride (3 ml) was added slowly while being stirred vigorously. The orange solid (**1**) was immediately formed, filtered, and dried (yield 84%). Anal. Calcd for $C_{20}H_{20}N_6O_6$, **1**: C, 56.89; H, 4.34; N, 18.10. Found: C, 56.82; H, 4.46; N, 18.33%. ^1H NMR (DMSO-d_6) δ 9.79 (s, 2H), 8.18 (d, 4H, J_3=9.3 Hz), 8.16 (s, 2H), 7.68 (d, 4H, J_3=9.3 Hz), 7.36 (s, 2H), 2.19 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 152.6, 146.4, 140.8, 132.6, 128.4, 125.4, 125.0, 117.3, 19.1. IR (KBr): 3340, 1678, 1504, 1327 cm^{-1}.

4,5-Dimethyl-1,2-phenylenediamine (0.14 g, 1.0 mmol) in THF (3 ml) was added to a THF (5 ml) solution of 4-nitrophenyl isothiocyanate (0.38 g, 2.1 mmol). The mixture was stirred at reflux for 3 h. After the solution was concentrated to 1 ml, methylene chloride and hexane were gradually added until precipitate was formed. The light yellow solid (**2**) was filtered and dried (yield 53%). Anal. Calcd for $C_{22}H_{20}N_6O_4S_2$, **2**: C, 53.21; H, 4.06; N, 16.92; S, 12.91. Found: C, 53.15; H, 4.15; N, 17.01; S, 12.75%. ^1H NMR (DMSO-d_6) δ 10.44 (s, 2H), 9.52 (s, 2H), 8.14 (d, 4H, J_3=8.8 Hz), 7.83 (d, 4H, J_3=8.8 Hz), 7.23 (s, 2H), 2.22 (s, 6H). ^{13}C NMR (DMSO-d_6) δ 179.7, 145.8, 142.3, 135.1, 131.4, 128.8, 124.1, 121.5, 19.0. IR (KBr): 3320, 3272, 1507, 1347, 1113 cm^{-1}.

4.3. UV–vis and NMR titrations

UV–vis titrations were performed on $1–5\times10^{-5}$ M solutions of urea **1** or thiourea **2** in DMSO. Typically, aliquots of freshly prepared Et_4NX (X=F^-, Cl^-, Br^-, and CH_3COO^-) standard solutions ($10^{-1}–10^{-3}$ M in DMSO) were added and the UV–vis spectra of the samples were recorded. ^1H NMR titrations were carried out in DMSO-d_6.

4.4. Ab initio calculation

The geometries of all species such as the reactants and products involved in the equilibria I and II were optimized in gas phase at the HF/6-31+G(d) level using the GAMESS quantum mechanical calculation program.[13] The computed geometrical quantities are shown in Table 1. The reaction energies for both equilibria were also calculated based on the above optimized geometries using the density functional theory at the B3LYP/6-31G+(d)//HF/6-31+G(d) level. The reaction energies were simply obtained by taking the energy difference between the reactant and the product molecules. The energetic results are shown in Table S1.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.081.

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11. One of the reviewers has been interested in the *K* value for **1** with phosphate ion and comparison of its *K* value and those values obtained with the similar receptor (1-(4-nitrophenyl)-3-{2-[3-(4-nitrophenyl)ureido]cyclohexyl}urea=**3**) reported in Ref. 7i. Our preliminary *K* value ($\sim 2\times10^5$) for **1** with phosphate ion was found to be two orders of magnitude bigger than that (log K=2.96) for **3** with phosphate ion as shown in Ref. 7i. This difference could come from the structure difference between **1** and **3**. More details will be explained in the next paper.
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Enantioselective synthesis and absolute configurations of aculeatins A, B, D, and 6-*epi*-aculeatin D

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Abstract—The three naturally occurring, bioactive spiroacetals aculeatins A, B, and D, as well as the non-natural 6-*epi*-aculeatin D have been synthesized for the first time in enantiopure form using an asymmetric allylation as the only chirality source. A further key step was a stereoselective aldol reaction with remote induction. The absolute configurations of the natural products have been established and an erroneous structural assignment has been corrected.

1. Introduction

The aculeatins A and B are two epimeric spiroacetals isolated six years ago from the terrestrial plant species *Amomum aculeatum* Roxb. (fam. Zingiberaceae). They were assigned structures (*relative* configurations) **1** and **2**, respectively. A more complex variant, aculeatin C-**3**, was also isolated from the same plant (Fig. 1). Later, the same authors reported the isolation of a fourth member of this compound family, named aculeatin D and assigned structure and relative configuration **4**.[1,2] These compounds were found to display antiprotozoal activity against some *Plasmodium* and *Trypanosoma* species. In addition, they showed antibacterial activity and were cytotoxic against the KB cell line.

The aculeatins A–D represent a novel type of natural compounds displaying the unusual, previously unreported 1,7-dioxadispiro[5.1.5.2]pentadecane system. The observed biological activity of the aculeatins may be related to the presence of a Michael acceptor moiety.[3] Spiroacetals themselves are also interesting molecular fragments, which are present in many pharmacologically relevant substances such as macrolide or polyether antibiotics.[4] In view of this and of the aforementioned biological activities, it is not surprising that the aculeatins have already aroused interest in the synthetic community. As a matter of fact, two papers have recently appeared, which deal with the synthesis of aculeatins A, B, and D in racemic form.[5] Both syntheses relied upon the same type of phenolic oxidation to form the 1,7-dioxadispiro[5.1.5.2]pentadecane system (see below). In this paper, we present with full detail the first synthesis of **1**, **2**, and **4** in enantiopure form.[6] Another product generated in our synthesis was optically pure 6-*epi*-aculeatin D, previously synthesized in racemic form[5b] but not reported as a natural product so far.

The retrosynthetic concept for aculeatins A and B is depicted in Scheme 1. The dispirocyclic system is generated via

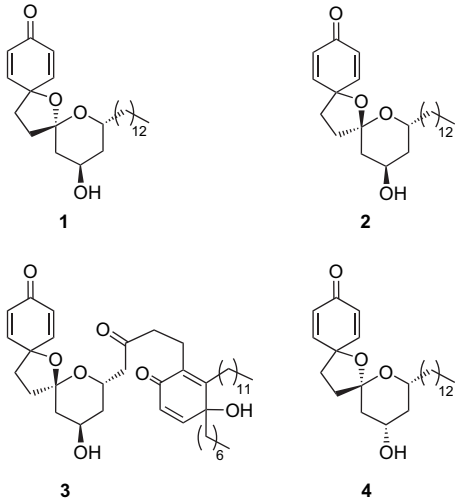

Figure 1. Published structures and relative configurations of the aculeatins A–D (**1**–**4**).

Keywords: Aculeatins; Absolute configuration; Asymmetric allylation; Aldol reaction; Remote induction; Spiroacetals; Hypervalent iodine; Oxidative spiroacetalization.
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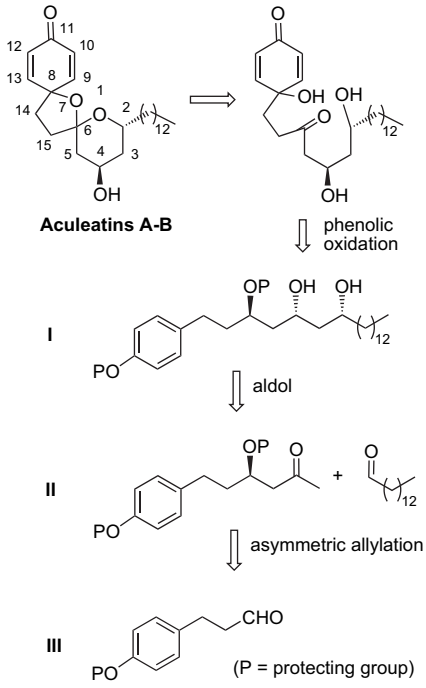
phenolic oxidation of an appropriately substituted intermediate ketone, related in turn to the protected triol **I**. The latter is derived from the aldol reaction of ketone **II** with *n*-tetradecanal. Intermediate **II** should be obtained from a suitably protected dihydro-*p*-coumaraldehyde **III** by means of asymmetric allylation and further functional manipulation.

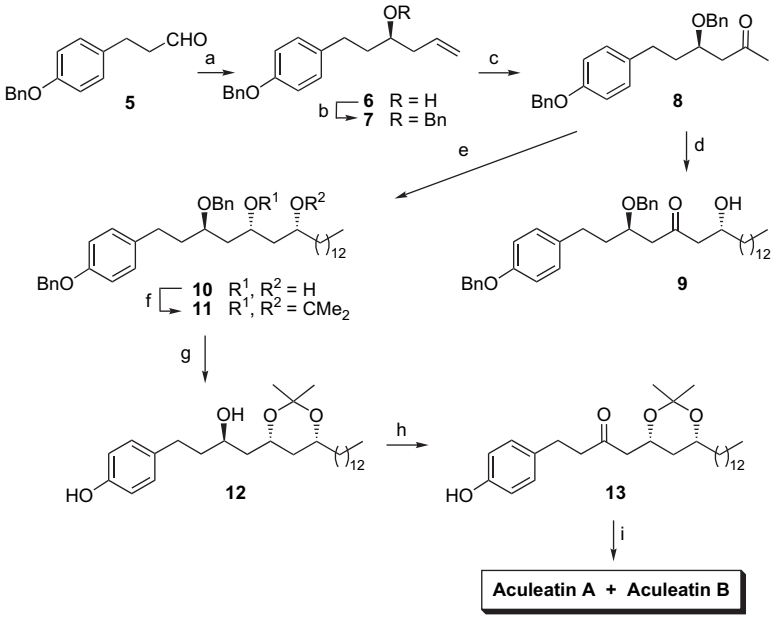


Scheme 1. Retrosynthetic analysis of aculeatins A and B.

2. Results and discussion

Scheme 2 shows the details of the synthesis of spiroacetals **1** and **2**. Thus, the known 3-(*p*-benzyloxyphenyl)propanal **5**[7] was subjected to asymmetric allylation using the chiral allylborane prepared from allylmagnesium bromide and (−)-DIP–Cl [(−)-diisopinocampheylchloroborane].[8] In this way, homoallyl alcohol **6** was obtained in over 96% ee as judged by NMR examination of the Mosher ester.[9] Benzylation of the hydroxyl group followed by Wacker oxidation[10] provided methyl ketone **8**. Boron aldol reaction[11] of this ketone with *n*-tetradecanal afforded the desired aldol **9** in 70% yield as a single diastereomer. The aldol can be then reduced to the monobenzylated *anti*,*syn*-1,3,5-triol **10** but it was much more expedient to perform the aldol reduction in situ with $LiBH_4$ to stereoselectively yield **10**.[12] Protection of the two free hydroxyl groups as an acetonide followed by hydrogenolytic debenzylation afforded **12**. Swern oxidation of the latter compound furnished ketone **13**, which was then submitted to hydrolytic cleavage of the acetonide moiety. However, while the expected β,δ-dihydroxy ketone was formed, the yield was low (<35%). Fortunately, treatment of acetonide **12** with phenyliodonium bis(trifluoroacetate) not only caused the desired phenolic oxidation[5,13,14] but also acetonide hydrolysis and subsequent spiroacetalization. This cleanly yielded a 5.5:1 mixture of two optically active products with spectral properties identical to those reported for aculeatins A and B.[1] Intermediates or by-products of 4-hydroxycyclohexa-2,5-dienone type[5b] (see Scheme 1) were not detected.

A closer examination of the respective NMR spectral properties revealed, however, an important issue. The major product exhibited in fact the optical rotation and spectral



Scheme 2. Synthesis of aculeatins A and B. Reaction conditions: (a) allylBIpc$_2$ from (−)-Ipc$_2$BCl and allylmagnesium bromide, Et_2O, 3 h, −90 °C; (b) NaH; THF, then BnBr, rt, overnight, 85% overall from **5**; (c) $PdCl_2$, $CuCl_2$, aq DMF, O_2, 2 d, 75%; (d) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, 1 h, followed by addition of *n*-tetradecanal, 3 h, −78 °C, 70%; (e) Bu_2BOTf, $EtNiPr_2$, CH_2Cl_2, −78 °C, 1 h, followed by addition of *n*-tetradecanal, 3 h, −78 °C, then $LiBH_4$, 2 h, −78 °C, 65% overall; (f) 2,2-dimethoxypropane, CSA (cat.), Me_2CO, rt, 1 d, 72%; (g) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 6 h, 70%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→0 °C, 87% and (i) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 24 h, 65% overall, 5.5:1 mixture of aculeatins A and B. Acronyms: Ipc, isopinocampheyl; CSA, camphorsulfonic acid.

properties associated with aculeatin A.[1] It was stable and showed no noticeable tendency to isomerize to the minor stereoisomer. NOE measurements pointed out the absence of dipolar correlations between the methine proton H-2 and one methylene proton at C-15 (for numbering, see Scheme 1). This strongly suggests that its configuration corresponds to **2** (Fig. 2), not to **1** as proposed.[1] In addition,

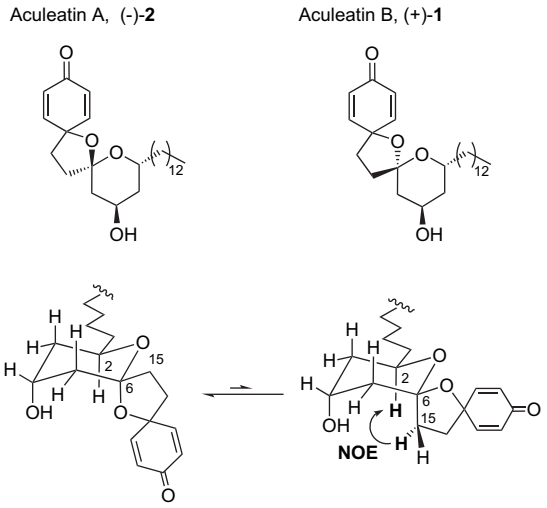
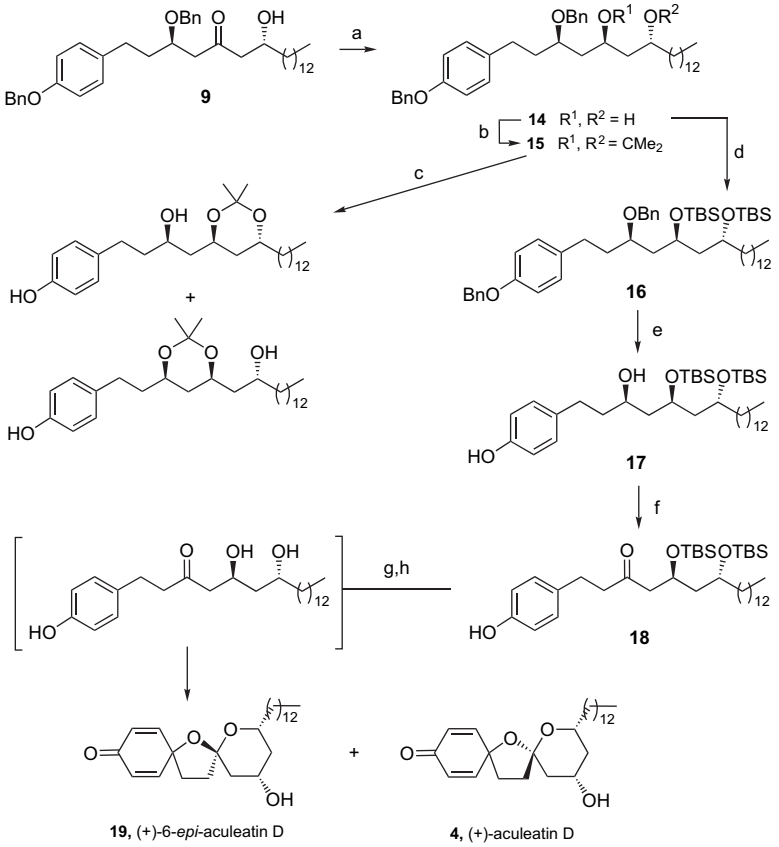


Figure 2. Corrected structures and absolute configurations of aculeatins A and B.

structure **2** benefits from a favorable anomeric effect,[15] in agreement with the higher stability of aculeatin A. In support of this reasoning, the minor isomer, which was unstable and isomerized slowly to the major one, showed a marked NOE between the methine proton H-2 and one methylene proton at C-15. These properties, which are associated to aculeatin B,[1a] are only compatible with stereostructure **1** (Fig. 2), which does not exhibit a favorable anomeric effect. A further support is given by the markedly higher δ value of H-2 in aculeatin A (δ 4.10 vs δ 3.86 ppm in aculeatin B), which points to its 1,3-diaxial relation with the anomeric oxygen atom. In summary, the Swiss workers[1] erroneously interchanged the relative stereostructures of the aculeatins A and B, *which are therefore **2** and **1**, respectively.*[16] The optical rotation values of the synthetic compounds were very similar to those of the natural compounds and the signs are the same. Our synthesis therefore has led to the natural enantiomers of both aculeatins and permitted the establishment of their absolute configurations (Fig. 2).

The same retrosynthetic concept depicted in Scheme 1 was applied to aculeatin D with only a change, related to the inverted configuration at C-4. Thus, aldol **9** was reduced with TABH[17] to stereoselectively afford the expected *anti*-1,3-diol **14** (minor isomer not detected by means of NMR), subsequently transformed into its acetonide **15** (Scheme 3). Problems arose, however, during hydrogenolytic cleavage of the two benzyl groups. Under all conditions we tried,



Scheme 3. Synthesis of aculeatin D and 6-*epi*-aculeatin D. Reaction conditions: (a) TABH, AcOH–MeCN, −30 °C, 12 h, 86%; (b) 2,2-dimethoxypropane, CSA (cat.), Me_2CO, rt, 12 h, 89%; (c) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 6 h, 40%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, Δ, 91%; (e) H_2 (1 atm), 10% Pd–C, EtOAc, rt, 15 min, 74%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, −78 °C→0 °C, 81%; (g) TASF, DMF, 0 °C, 90 min, then rt, 4 h and (h) $PhI(OOCCF_3)_2$, Me_2CO–H_2O (9:1), rt, 30 min, 77% overall for the two steps, 2.7:1 mixture of aculeatin D (minor) and 6-*epi*-aculeatin D (major). Acronyms: TABH, tetramethylammonium triacetoxyborohydride; TASF, tris(dimethylamino)sulfonium difluoro-trimethylsilicate; TBSOTf, *tert*-butyldimethylsilyl triflate.

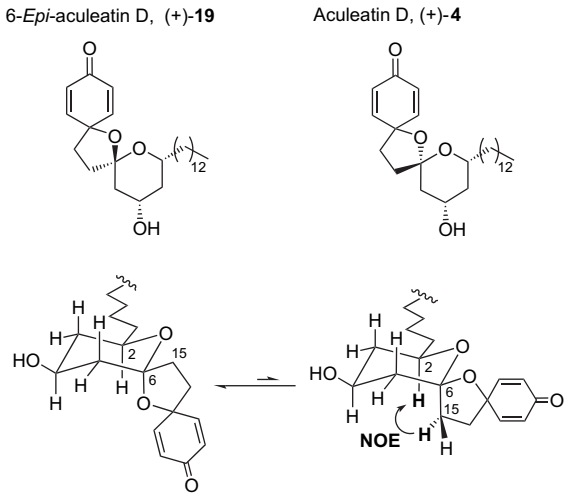


Figure 3. Structures and absolute configurations of aculeatin D **4** and 6-*epi*-aculeatin D **19**.

partial migration (transacetalization) of the acetonide group took place with formation in low yield of two isomeric acetonides, the undesired one being the major compound. We then replaced the acetonide moiety by other protecting groups such as MOM, MEM or TES (triethylsilyl), all cleavable under mild conditions.[18] However, no success was achieved with these groups, either. The acetal-like MOM or MEM groups were introduced with unsatisfactory yields and showed a marked tendency to form six-membered formaldehyde acetals with the proximal hydroxy group.[19] The TES group behaved better in this aspect but was partially cleaved under hydrogenolytic conditions. Eventually, the TBS group proved appropriate. Double silylation of diol **14** worked well, as did the subsequent hydrogenolysis and oxidation steps, which finally yielded ketone **18**. The latter was desilylated under mild conditions with TASF.[20] Without purification, the intermediate diol was subjected as above to oxidative spiroacetalization with $PhI(OCOCF_3)_2$ to yield a 2.7:1 mixture of compounds **4** (minor) and **19** (major), again with no 4-hydroxycyclohexa-2,5-dienone being isolated. Compounds **4** and **19** displayed physical and spectral features identical to those reported for natural aculeatin D[1b] and synthetic 6-*epi*-aculeatin D,[5b] respectively. NOE measurements were consistent with the published structures (Fig. 3). The absolute configuration of natural aculeatin D turns out to be as depicted in the figure.

3. Conclusions

The naturally occurring, bioactive spiroacetals aculeatins A, B, and D, as well as the hitherto non-natural 6-*epi*-aculeatin D, have been synthesized for the first time in enantiopure form. Their absolute configurations have been established, and a previous structural misassignment has been corrected.

4. Experimental

4.1. General

$^1H/^{13}C$ NMR spectra were measured at 500/125 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). Carbon atom types (C, CH, CH_2, and CH_3) were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV), the CIMS (CH_4 as the gas carrier) or the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR data are given only for compounds with relevant functions (OH, C=O, and C≡C–H) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions, which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium–benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Toluene was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into brine, followed by extraction with the solvent indicated in parenthesis. If the reaction medium was acidic (basic), an additional washing with 5% aq $NaHCO_3$ (aq NH_4Cl) was performed. Drying over anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure were followed by chromatography of the residue on a silica gel column (60–200 μm) with the indicated eluent. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. Reagent acronyms are explained in the captions of Schemes 2 and 3.

4.1.1. (*R*)-1-(4-Benzyloxyphenyl)hex-5-en-3-ol (6). Allylmagnesium bromide (commercial 1 M solution in Et_2O, 2.5 mL, 2.5 mmol) was added dropwise under N_2 via syringe to a solution of (−)-DIP–Cl (0.97 g, 3 mmol) in dry Et_2O (12 mL) cooled in a dry ice-acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was allowed to stand, whereby precipitation of magnesium chloride took place. The supernatant solution was carefully transferred to another flask via cannula. After cooling this flask at −90 °C, a solution of freshly prepared[7] 3-(4-benzyloxyphenyl)-propanal (480 mg, ca. 2 mmol) in dry Et_2O (5 mL) was added dropwise via syringe. The resulting solution was further stirred at −90 °C for 3 h. The reaction mixture was quenched through addition of phosphate pH 7 buffer solution (12 mL), MeOH (12 mL), and 30% H_2O_2 (6 mL). After stirring for 30 min, the mixture was poured onto satd aq $NaHCO_3$ and worked-up (extraction with Et_2O). For synthetic purposes, the oily residue was used directly in the next step. For analytical characterization, an aliquot of the residue was subjected to a careful column chromatography on silica gel (hexane, then hexane–EtOAc, 19:1 and 9:1) yielding pure **6** (>98:2 mixture of enantiomers as estimated via the Mosher ester): colorless solid, mp 61–63 °C; $[\alpha]_D$ +12.7 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (5H, m), 7.14 (2H, d, *J*=8.5 Hz), 6.93 (2H, d, *J*=8.5 Hz), 5.85 (1H, m), 5.20–5.15 (2H, m), 5.06 (2H, s), 3.70 (1H, m), 2.78 (1H, m), 2.67 (1H, m), 2.33 (1H, m), 2.22 (1H, m), 1.80–1.75 (2H, m) (hydroxyl proton not detected); ^{13}C NMR (125 MHz) δ 157.1, 137.2, 134.4 (C), 134.6, 129.3 (×2), 128.5 (×2), 127.8, 127.4 (×2), 114.8 (×2), 69.9 (CH), 118.2, 70.1, 42.0, 38.6, 31.1 (CH_2); IR ν_{max} 3370 (br, OH), 3076, 1513, 1453, 1254,

913 cm^{-1}; HR EIMS *m/z* (rel int.) 282.1619 (M^+, 20), 197 (10), 91 (100). Calcd for $C_{19}H_{22}O_2$, 282.1620. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.89; H, 7.83.

4.1.2. (*R*)-4-Benzyloxy-6-(4-benzyloxyphenyl)hex-1-ene (7). Solid sodium hydride 95% (125 mg, ca. 5 mmol) was suspended under N_2 in dry THF (5 mL). A solution of the crude residue of the previous reaction in dry THF (5 mL) was added. The mixture was stirred at room temperature for 45 min and treated with tetra-*n*-butyl ammonium iodide (18 mg, 0.05 mmol) and benzyl bromide (0.6 mL, ca. 5 mmol). The mixture was stirred overnight at room temperature. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexane–EtOAc, 99:1) furnished **7** (630 mg, 85% overall from **5**): oil; $[\alpha]_D$ +21.7 (*c* 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.13 (2H, d, *J*=8.5 Hz), 6.94 (2H, d, *J*=8.5 Hz), 5.90 (1H, m), 5.15–5.10 (2H, m), 5.08 (2H, s), 4.65 (1H, d, *J*=11.5 Hz), 4.53 (1H, d, *J*=11.5 Hz), 3.53 (1H, m), 2.78 (1H, m), 2.66 (1H, m), 2.50–2.40 (2H, m), 1.95–1.85 (2H, m); ^{13}C NMR (125 MHz) δ 157.0, 138.8, 137.3, 134.7 (C), 134.8, 129.3 (×2), 128.5 (×2), 128.3 (×2), 127.8, 127.7 (×2), 127.5, 127.4 (×2), 114.8 (×2), 77.7 (CH), 117.1, 70.9, 70.1, 38.2, 35.9, 30.8 (CH_2); IR ν_{max} 3065, 3031, 1511, 1454, 1239, 736 cm^{-1}; HR EIMS *m/z* (rel int.) 372.2101 (M^+, 10), 287 (13), 119 (37), 91 (100). Calcd for $C_{26}H_{28}O_2$, 372.2089. Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.89; H, 7.50.

4.1.3. (*R*)-4-Benzyloxy-6-(4-benzyloxyphenyl)hexan-2-one (8). Olefin **7** (615 mg, 1.65 mmol) was dissolved in DMF containing 10% water (40 mL) and treated with $PdCl_2$ (90 mg, ca. 0.5 mmol) and CuCl (500 mg, ca. 5 mmol). The mixture was stirred at room temperature under O_2 for 48 h, then poured onto satd aq NH_4Cl and worked-up (extraction with Et_2O). Column chromatography on silica gel (hexane–EtOAc, 9:1) provided **8** (480 mg, 75%): oil; $[\alpha]_D$ +3.5 (*c* 1.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.12 (2H, d, *J*=8.5 Hz), 6.94 (2H, d, *J*=8.5 Hz), 5.07 (2H, s), 4.57 (2H, s), 4.00 (1H, br quintuplet, $J\approx6$ Hz), 2.82 (1H, dd, *J*=15.5, 7 Hz), 2.75–2.65 (2H, m), 2.59 (1H, dd, *J*=15.5, 5 Hz), 2.18 (3H, s), 1.95–1.85 (2H, m); ^{13}C NMR (125 MHz) δ 207.3, 157.0, 138.4, 137.2, 134.1 (C), 129.2 (×2), 128.5 (×2), 128.3 (×2), 127.8, 127.7 (×2), 127.5, 127.4 (×2), 114.8 (×2), 74.9 (CH), 71.5, 70.0, 48.4, 36.3, 30.5 (CH_2), 31.0 (CH_3); IR ν_{max} 3063, 3031, 1714 (C=O), 1610, 1511, 1454, 1239, 1074, 1027, 738 cm^{-1}; HR FABMS *m/z* 388.2037 (M^+). Calcd for $C_{26}H_{28}O_3$, 388.2038. Anal. Calcd for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26. Found: C, 80.49; H, 7.33.

4.1.4. (*R*)-4-Benzyloxy-6-(4-benzyloxyphenyl)hexan-2-one (8). Olefin **7** (615 mg, 1.65 mmol) was dissolved in DMF containing 10% water (40 mL) and treated with $PdCl_2$ (90 mg, ca. 0.5 mmol) and CuCl (500 mg, ca. 5 mmol). The mixture was stirred at room temperature under O_2 for 48 h, poured onto satd aq NH_4Cl and worked-up (extraction with Et_2O). Column chromatography on silica gel (hexane–EtOAc, 9:1) provided **8** (480 mg, 75%): oil; $[\alpha]_D$ +3.5 (*c* 1.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.12 (2H, d, *J*=8.5 Hz), 6.94 (2H, d, *J*=8.5 Hz), 5.07 (2H, s), 4.57 (2H, s), 4.00 (1H, br quintuplet, $J\approx6$ Hz), 2.82 (1H, dd, *J*=15.5, 7 Hz), 2.75–2.65 (2H, m), 2.59 (1H, dd, *J*=15.5, 5 Hz), 2.18 (3H, s), 1.95–1.85 (2H, m); ^{13}C NMR (125 MHz) δ 207.3, 157.0, 138.4, 137.2, 134.1 (C), 129.2 (×2), 128.5 (×2), 128.3 (×2), 127.8, 127.7 (×2), 127.5, 127.4 (×2), 114.8 (×2), 74.9 (CH), 71.5, 70.0, 48.4, 36.3, 30.5 (CH_2), 31.0 (CH_3); IR ν_{max} 3063, 3031, 1714 (C=O), 1610, 1511, 1454, 1239, 1074, 1027, 738 cm^{-1}; HR FABMS *m/z* 388.2037 (M^+). Calcd for $C_{26}H_{28}O_3$, 388.2038. Anal. Calcd for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26. Found: C, 80.49; H, 7.33.

4.1.5. (3*R*,5*R*,7*R*)-3-Benzyloxy-1-(4-benzyloxyphenyl)-eicosane-5,7-diol (10). A solution of ketone **8** (466 mg, 1.2 mmol) in dry CH_2Cl_2 (8 mL) was cooled under N_2 to −78 °C and treated sequentially with diisopropyl ethyl amine (260 μL, 1.5 mmol) and a 1 M solution of Bu_2BOTf in CH_2Cl_2 (1.35 mL, 1.35 mmol). The mixture was stirred for 1 h at the same temp, followed by addition of a solution of *n*-tetradecanal (287 mg, 1.35 mmol)[21] in dry CH_2Cl_2 (5 mL). The mixture was stirred at −78 °C for further 3 h, treated with a 2 M solution of $LiBH_4$ in THF (1.2 mL, 2.4 mmol), and further stirred at −78 °C for 2 h. The reaction was quenched by addition of phosphate pH 7 buffer solution (7 mL) and MeOH (7 mL), followed by 30% aq H_2O_2 solution (3.5 mL). After stirring for 30 min at room temperature, the mixture was worked-up (extraction with CH_2Cl_2). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexane–EtOAc, 9:1) yielded diol **10** (470 mg, 65%): amorphous solid; $[\alpha]_D$ −10.2 (*c* 0.75, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.08 (2H, d, *J*=8.5 Hz), 6.91 (2H, d, *J*=8.5 Hz), 5.05 (2H, s), 4.56 (1H, d, *J*=11.5 Hz), 4.54 (1H, d, *J*=11.5 Hz), 4.18 (1H, m), 3.85 (1H, m), 3.75 (1H, m), 2.70–2.60 (2H, m), 2.00 (1H, m), 1.85–1.75 (2H, m), 1.65 (1H, ddd, *J*=14.5, 7, 2.5 Hz), 1.55–1.45 (2H, m), 1.40–1.25 (24H, br m), 0.90 (3H, t, *J*=7 Hz) (hydroxyl protons not detected); ^{13}C NMR (125 MHz) δ 157.2, 138.1, 137.2, 134.2 (C), 129.3 (×2), 128.6 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.4 (×2), 114.9 (×2), 76.3, 72.7 (CH), 70.7 (CH+CH_2), 71.3, 43.4, 40.5, 38.0, 35.5, 31.9, 30.8, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.4, 25.4, 22.7 (CH_2), 14.1 (CH_3); IR ν_{max} 3420 (br, OH), 3032, 1511, 1455, 1240, 736 cm^{-1}; HR FABMS *m/z* 603.4363 (M+H^+). Calcd for $C_{40}H_{59}O_4$, 603.4413. Anal. Calcd for $C_{40}H_{58}O_4$: C, 79.69; H, 9.70. Found: C, 79.79; H, 9.53.

4.1.6. (4*S*,6*R*)-4-[(*R*)-2-Benzyloxy-4-(4-benzyloxyphenyl) butyl]-2,2-dimethyl-6-*n*-tridecyl-[1,3]dioxane (11). Diol **10** (452 mg, 0.75 mmol) was dissolved in dry acetone (15 mL) and treated with camphorsulfonic acid (10 mg, ca. 0.05 mmol) and 2,2-dimethoxypropane (3 mL). After adding activated 3 Å molecular sieves (0.5 g), the mixture was stirred overnight at room temperature. The mixture was then poured onto satd aq $NaHCO_3$ and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 99:1) furnished **11** (347 mg, 72%): amorphous solid; $[\alpha]_D$ −12.7 (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.10 (2H, d, *J*=8.5 Hz), 6.91 (2H, d, *J*=8.5 Hz), 5.06 (2H, s), 4.58 (1H, d, *J*=11.5 Hz), 4.50 (1H, d, *J*=11.5 Hz), 4.10 (1H, m), 3.81 (1H, m), 3.75 (1H, m), 2.66 (2H, m), 1.90–1.85 (2H, m),

1.70–1.65 (2H, m), 1.50 (1H, m), 1.41 (6H, s), 1.40–1.25 (24H, br m), 1.16 (1H, q, J=11.5 Hz), 0.91 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 157.0, 138.9, 137.3, 134.8, 98.4 (C), 129.3 (×2), 128.6 (×2), 128.4 (×2), 127.9 (×2), 127.8, 127.5, 127.4 (×2), 114.8 (×2), 74.7, 69.1, 65.8 (CH), 71.6, 70.1, 42.1, 37.7, 36.6, 36.5, 31.9, 30.3, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 30.4, 20.0, 14.1 (CH_3); IR ν_{max} 3031, 1511, 1455, 1379, 1241, 736 cm^{-1}; HR EIMS *m/z* (rel int.) 642.4664 (M^+, 1), 627 (14), 584 (5), 476 (59), 197 (33), 91 (100). Calcd for $C_{43}H_{62}O_4$, 642.4648. Anal. Calcd for $C_{43}H_{62}O_4$: C, 80.33; H, 9.72. Found: C, 80.22; H, 9.84.

4.1.7. (4*S*,6*R*)-4-[(*R*)-2-Hydroxy-4-(4-hydroxyphenyl) butyl]-2,2-dimethyl-6-*n*-tridecyl-[1,3]dioxane (12). Pd–C 10% (50 mg) was suspended in EtOAc (5 mL) and stirred under an H_2 atmosphere for 15 min. Compound **11** (321 mg, 0.5 mmol) dissolved in EtOAc (10 mL) was added via syringe. The mixture was stirred at room temperature and ambient pressure for 6 h, and filtered through Celite. Solvent removal in vacuo and column chromatography on silica gel (hexane–EtOAc, 4:1) gave **12** (162 mg, 70%): colorless solid, mp 80–82 °C; $[\alpha]_D$ −1.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 5.40 (1H, br s, OH), 4.20 (1H, m), 3.94 (1H, m), 3.82 (1H, m), 3.10 (1H, br s, OH), 2.73 (1H, m), 2.59 (1H, m), 1.80–1.50 (6H, br m), 1.45 (3H, s), 1.40 (3H, s), 1.40–1.25 (24H, br m), 0.88 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 153.9, 134.2, 98.7 (C), 129.5 (×2), 115.3 (×2), 69.2, 68.3, 67.5 (CH), 41.9, 39.3, 36.4, 36.3, 31.9, 31.2, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 30.3, 19.7, 14.1 (CH_3); IR ν_{max} 3370 (br, OH), 1514, 1459, 1262, 828 cm^{-1}; HR EIMS *m/z* (rel int.) 462.3732 (M^+, 1), 447 (14), 386 (16), 107 (100). Calcd for $C_{29}H_{50}O_4$, 462.3709. Anal. Calcd for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.22; H, 10.84.

4.1.8. 1-[(4*R*,6*R*)-(2,2-Dimethyl-6-tridecyl-[1,3]dioxan-4-yl)]-4-(4-hydroxyphenyl)-butan-2-one (13). Oxalyl chloride (62 μL, ca. 0.7 mmol) was dissolved under N_2 in dry CH_2Cl_2 (3 mL). After cooling the solution to −78 °C, dry DMSO (56 μL, 0.8 mmol) was added dropwise with stirring for 5 min. A solution of alcohol **12** (162 mg, 0.35 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise, with additional stirring for 15 min. Addition of Et_3N (210 μL, 1.5 mmol) was followed by stirring for 15 min at −78 °C and for further 1 h at 0 °C. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 7:3) gave ketone **13** (140 mg, 87%): colorless solid, mp 53–55 °C; $[\alpha]_D$ −4.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 5.90 (1H, br s, OH), 4.32 (1H, m), 3.81 (1H, m), 2.85–2.70 (4H, br m), 2.67 (1H, dd, J=15.7, 7.2 Hz), 2.40 (1H, dd, J=15.7, 5.3 Hz), 1.50 (1H, m), 1.42 (3H, s), 1.37 (3H, s), 1.40–1.25 (24H, br m), 1.11 (1H, q, J=11.5 Hz), 0.88 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 209.0, 154.2, 132.7, 98.8 (C), 129.3 (×2), 115.4 (×2), 69.0, 65.9 (CH), 36.8, 36.3, 31.9, 29.6 (several overlapped signals), 29.5 (several overlapped signals), 29.3, 24.9, 22.7 (CH_2), 30.1, 19.7, 14.1 (CH_3); IR ν_{max} 3390 (br, OH), 1712 (C=O), 1614, 1515, 1379, 828 cm^{-1}; HR EIMS *m/z* (rel int.) 460.3568 (M^+, 1), 445 (8), 402 (18), 107 (100). Calcd for $C_{29}H_{48}O_4$, 460.3552. Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.61; H, 10.50. Found: C, 75.69; H, 10.63.

4.1.9. (2*R*,4*R*,6*S*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin B) (1) and (2*R*,4*R*,6*R*)-4-hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin A) (2). Ketone **13** (140 mg, 0.3 mmol) was dissolved in a 9:1 acetone–water mixture (10 mL) and treated in four portions with $PhI(OCOCF_3)_2$ (430 mg, 1 mmol), each portion being added every hour. The reaction mixture was stirred overnight at room temperature in the dark. Work-up (extraction with EtOAc) and careful column chromatography on silica gel (hexane–EtOAc, 4:1, then 3:2) yielded **1** (12.5 mg) and **2** (69 mg).

*Aculeatin A (**2**):* oil; $[\alpha]_D$ −5.2 (*c* 0.9; $CHCl_3$), lit.[1a] $[\alpha]_D$ −5.3 (*c* 0.2, $CHCl_3$); IR ν_{max} 3550 (br, OH), 1673 (ketone C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (1H, dd, J=10, 3 Hz), 6.76 (1H, dd, J=10, 3 Hz), 6.14 (1H, dd, J=10, 1.7 Hz), 6.10 (1H, dd, J=10, 1.7 Hz), 4.15–4.10 (2H, m), 3.35 (1H, br d, J=10 Hz, OH), 2.38 (1H, m), 2.24 (1H, m), 2.05–2.00 (3H, m), 1.93 (1H, br d, J=14 Hz), 1.79 (1H, br dd, J=13.7, 2 Hz), 1.60–1.40 (5H, br m), 1.40–1.20 (20H, br m), 0.88 (3H, t, J=6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.3, 109.2, 79.8 (C), 150.9, 148.7, 127.4, 127.2, 65.4, 64.9 (CH), 39.2, 38.0, 36.0, 34.2, 32.0, 29.7 (several overlapped signals), 29.4, 25.7, 22.7 (CH_2), 14.1 (CH_3); HR EIMS *m/z* (rel int.) 418.3117 (M^+, 2), 400 (M^+-H_2O, 6), 310 (6), 236 (25), 165 (100), 107 (73). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

*Aculeatin B (**1**)*: oil; $[\alpha]_D$ +53.2 (*c* 0.4, $CHCl_3$), lit.[1a] $[\alpha]_D$ +50 (*c* 0.8, $CHCl_3$); IR ν_{max} 3460 (br, OH), 1670 (ketone C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, dd, J=10, 2.9 Hz), 6.77 (1H, dd, J=10, 2.9 Hz), 6.13 (1H, dd, J=10, 1.8 Hz), 6.10 (1H, dd, J=10, 1.8 Hz), 4.36 (1H, apparent quintuplet, J=3.2 Hz), 3.86 (1H, m), 2.68 (1H, br dd, J=12.8, 7.2 Hz), 2.30 (1H, td, J=12.3, 7.2), 2.10–2.00 (2H, m), 1.95–1.85 (2H, m), 1.60–1.40 (8H, br m), 1.40–1.20 (19H, br m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 108.6, 77.6 (C), 152.2, 149.2, 127.2, 127.1, 69.5, 65.2 (CH), 40.7, 38.0, 35.8, 35.4, 35.3, 31.9, 29.7 (several overlapped signals), 29.4, 29.3, 25.9, 22.7 (CH_2), 14.1 (CH_3); HR EIMS *m/z* (rel int.) 418.3108 (M^+, 9), 400 (M^+-H_2O, 24), 310 (16), 235 (85), 165 (100), 107 (23). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

4.1.10. (3*R*,5*S*,7*R*)-3-Benzyloxy-1-(4-benzyloxyphenyl) eicosane-5,7-diol (14). Tetramethylammonium triacetoxyborohydride (1.05 g, ca. 4 mmol) was dissolved under N_2 in an acetonitrile–acetic acid 1:1 mixture (5 mL). After stirring for 1 h at room temperature, the mixture was cooled to −30 °C and treated dropwise with a solution of aldol **9** (300 mg, 0.5 mmol) in dry acetonitrile (3 mL). The solution was stirred at −30 °C for 12 h and at 0 °C for further 2 h. After quenching with aq 1 M sodium potassium tartrate (2 mL), the mixture was stirred for 1 h at room temperature. Work-up (extraction with CH_2Cl_2) and column chromatography of the residue on silica gel (hexane–EtOAc, 4:1) afforded diol **14** (260 mg, 86%): colorless solid, mp 57–59 °C; $[\alpha]_D$ −19.6 (*c* 1.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.45–7.30 (10H, m), 7.10 (2H, d, J=8.5 Hz), 6.92 (2H, d, J=8.5 Hz), 5.06 (2H, s), 4.63 (1H, d, J=11 Hz), 4.44 (1H, d, J=11 Hz), 4.18 (1H, m), 3.92 (1H, m), 3.78 (1H, m), 2.70–2.60 (2H, m), 2.00 (2H, br s, OH), 2.00–1.90 (2H, m), 1.70–1.40 (4H, m), 1.40–1.25 (24H, br m), 0.91 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 157.1, 137.8, 137.2, 134.2 (C), 129.3 (×2), 128.6 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.4 (×2), 114.9 (×2), 79.2, 69.4, 68.8 (CH), 70.6, 70.1, 43.0, 40.7, 37.6, 35.3, 31.9, 30.0, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.3, 25.7, 22.7 (CH_2), 14.1 (CH_3); IR ν_{max} 3420 (br, OH), 3063, 3031, 1511, 1455, 1240, 736 cm^{-1}; HR FABMS m/z 603.4401 (M+H$^+$). Calcd for $C_{40}H_{59}O_4$, 603.4413. Anal. Calcd for $C_{40}H_{58}O_4$: C, 79.69; H, 9.70. Found: C, 79.82; H, 9.82.

4.1.11. (4*R*,6*R*)-4-[(*R*)-2-Benzyloxy-4-(4-benzyloxyphenyl) butyl]-2,2-dimethyl-6-*n*-tridecyl-[1,3]dioxane (15). Diol **14** (45 mg, 0.075 mmol) was dissolved in dry acetone (1 mL) and treated with camphorsulfonic acid (1 mg, ca. 0.005 mmol) and 2,2-dimethoxypropane (0.5 mL). After adding activated 3 Å molecular sieves (50 mg), the mixture was stirred overnight at room temperature. The mixture was then poured onto satd aq $NaHCO_3$ and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 99:1) furnished **15** (43 mg, 89%): oil; $[\alpha]_D$ −4 (*c* 2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.08 (2H, d, J=8.5 Hz), 6.91 (2H, d, J=8.5 Hz), 5.06 (2H, s), 4.53 (1H, d, J=11.5 Hz), 4.51 (1H, d, J=11.5 Hz), 3.94 (1H, m), 3.78 (1H, m), 3.55 (1H, br quintuplet, $J\approx$6 Hz), 2.75–2.65 (2H, m), 2.00 (1H, m), 1.95–1.85 (2H, m), 1.65–1.50 (3H, m), 1.40 (2H, m), 1.37 (3H, s), 1.40–1.25 (25H, br m), 0.92 (3H, t, J=7 Hz); ^{13}C NMR (125 MHz) δ 157.0, 138.9, 137.3, 134.7, 100.1 (C), 129.3 (×2), 128.5 (×2), 128.3 (×2), 127.9, 127.8, 127.5, 127.4 (×2), 114.8 (×2), 74.7, 66.6, 63.7 (CH), 70.6, 70.1, 40.1, 39.0, 36.0, 35.9, 31.9, 30.5, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.5, 29.3, 25.4, 22.7 (CH_2), 24.8, 24.7, 14.1 (CH_3); IR ν_{max} 3031, 1511, 1455, 1378, 1224, 734 cm^{-1}; HR EIMS m/z (rel int.) 642.4645 (M$^+$, 1), 627 (1), 584 (25), 566 (5), 476 (9), 197 (13), 91 (100). Calcd for $C_{43}H_{62}O_4$, 642.4648. Anal. Calcd for $C_{43}H_{62}O_4$: C, 80.33; H, 9.72. Found: C, 80.41; H, 9.62.

4.1.12. 1-Benzyloxy-4-[(3*R*,5*R*,7*R*)-3-benzyloxy-5,7-bis-(*tert*-butyldimethylsilyloxy)eicosyl]benzene (16). Diol **14** (193 mg, 0.32 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and treated sequentially with 2,6-lutidine (350 μL, 3 mmol) and TBSOTf (550 μL, ca. 2.5 mmol). The reaction mixture was stirred at reflux for 6 h and worked-up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 19:1) gave **16** (242 mg, 91%): oil; $[\alpha]_D$ +13.6 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (10H, m), 7.06 (2H, d, J=8.5 Hz), 6.88 (2H, d, J=8.5 Hz), 5.02 (2H, s), 4.54 (1H, d, J=11.5 Hz), 4.44 (1H, d, J=11.5 Hz), 3.84 (1H, br quintuplet, $J\approx$6 Hz), 3.72 (1H, br quintuplet, $J\approx$5.5 Hz), 3.57 (1H, br quintuplet, $J\approx$5.5 Hz), 2.70 (1H, m), 2.58 (1H, m), 1.90–1.75 (3H, br m), 1.60 (2H, m), 1.40 (1H, m), 1.40–1.25 (24H, br m), 0.86 (21H, br s), 0.05 (3H, s), 0.02 (6H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz) δ 157.1, 139.0, 137.3, 134.8, 18.1, 18.0 (C), 129.3 (×2), 128.6 (×2), 128.5 (×2), 128.1 (×2), 127.9 (×2), 127.4 (×2), 114.8 (×2), 75.7, 70.0, 67.7 (CH), 70.8, 70.1, 46.2, 42.7, 37.8, 36.3, 31.9, 30.7, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 25.0, 22.7 (CH_2), 26.0 (×6), 14.1, −3.9 (×2), −4.0 (×2) (CH_3); IR ν_{max} 3032, 1511, 1250, 1078, 835 cm^{-1}; HR EIMS m/z (rel int.) 773.5371 (M$^+$−*t*Bu, 1), 641 (4), 549 (6), 327 (58), 91 (100). Calcd for $C_{52}H_{86}O_4Si_2$–*t*Bu, 773.5360. Anal. Calcd for $C_{52}H_{86}O_4Si_2$: C, 75.12; H, 10.43. Found: C, 75.24; H, 10.54.

4.1.13. 4-[(3*R*,5*R*,7*R*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-3-hydroxyeicosyl]phenol (17). Pd–C 10%(250 mg) was suspended in EtOAc (8 mL) and stirred under H_2 atmosphere for 15 min. Compound **16** (233 mg, 0.28 mmol) dissolved in EtOAc (5 mL) was added via syringe. The mixture was stirred at room temperature and ambient pressure for 15 min and filtered through Celite *(caution: longer reaction times lead to partial desilylation!)*. Solvent removal in vacuo and column chromatography on silica gel (hexane–EtOAc, 4:1) furnished **17** (135 mg, 74%): oil; $[\alpha]_D$ +14 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 4.90 (1H, br s, OH), 3.89 (1H, br quintuplet, $J\approx$5 Hz), 3.78 (1H, m), 3.65 (1H, br quintuplet, $J\approx$5.5 Hz), 3.30 (1H, br s, OH), 2.70 (1H, m), 2.61 (1H, m), 1.80–1.55 (6H, m), 1.40–1.25 (24H, br m), 0.90 (21H, br s), 0.11 (6H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz) δ 153.7, 134.4, 18.1, 17.9 (C), 129.5 (×2), 115.2 (×2), 71.7, 70.2, 70.1 (CH), 46.5, 44.3, 39.7, 37.4, 31.9, 30.8, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 26.0 (×3), 25.9 (×3), 14.1, −3.9, −4.2 (×2), −4.3 (CH_3); IR ν_{max} 3380 (br, OH), 1515, 1471, 1463, 1255, 1078, 835 cm^{-1}; HR FABMS m/z 651.5209 (M+H$^+$). Calcd for $C_{38}H_{75}O_4Si_2$, 651.5204. Anal. Calcd for $C_{38}H_{74}O_4Si_2$: C, 70.09; H, 11.45. Found: C, 69.94; H, 11.54.

4.1.14. (5*S*,7*R*)-5,7-Bis(*tert*-butyldimethylsilyloxy)-1-(4-hydroxyphenyl)eicosan-3-one (18). Oxalyl chloride (34 μL, ca. 0.4 mmol) was dissolved under N_2 in dry CH_2Cl_2 (2 mL). After cooling the solution to −78 °C, dry DMSO (35 μL, ca. 0.5 mmol) was added dropwise with stirring for 5 min. A solution of alcohol **17** (130 mg, 0.2 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise, with additional stirring for 15 min. Addition of Et_3N (120 μL, 0.85 mmol) was followed by stirring for 10 min at −78 °C. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane–EtOAc, 7:3) gave **18** (105 mg, 81%): oil; $[\alpha]_D$ +10.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.5 Hz), 5.50 (1H, br s, OH), 4.21 (1H, br quintuplet, $J\approx$6 Hz), 3.69 (1H, br quintuplet, $J\approx$6 Hz), 2.80 (2H, m), 2.72 (2H, m), 2.60 (1H, dd, J=15, 7.5 Hz), 2.60 (1H, dd, J=15, 4.7 Hz), 1.62 (1H, m), 1.58 (1H, m), 1.42 (2H, m), 1.40–1.25 (22H, br m), 0.89 (12H, br s, overlapping a methyl triplet), 0.86 (9H, s), 0.08 (3H, s), 0.05 (6H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 209.3, 154.0, 133.0, 18.1, 18.0 (C), 129.4 (×2), 115.4 (×2), 70.1, 67.5 (CH), 51.3, 46.4, 45.8, 37.7, 31.9, 30.8, 29.7 (several overlapped signals), 29.6 (several overlapped signals), 29.4, 25.0, 22.7 (CH_2), 26.0 (×3), 25.9 (×3), 14.1, −4.1, −4.2 (×2), −4.4 (CH_3); IR ν_{max} 3400 (br, OH), 1704 (C=O), 1515, 1466, 1362, 1255, 1077, 835 cm^{-1}; HR FABMS m/z 649.5052 (M+H$^+$). Calcd for $C_{38}H_{73}O_4Si_2$, 649.5047. Anal. Calcd for $C_{38}H_{72}O_4Si_2$: C, 70.31; H, 11.18. Found, C, 70.44; H, 11.24.

4.1.15. (2*R*,4*S*,6*S*)-4-Hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (aculeatin D) (4) and (2*R*,4*S*,6*R*)-4-hydroxy-2-tridecyl-1,7-dioxadispiro [5.1.5.2]pentadeca-9,12-dien-11-one (6-*epi*-aculeatin D) (19). Ketone **18** (65 mg, 0.1 mmol) was dissolved under N_2 in dry DMF (2 mL), cooled to 0 °C and treated with TASF (138 mg, 0.5 mmol). The mixture was stirred for 90 min at 0 °C, then for further 4 h at room temperature. Work-up (extraction with Et_2O) and solvent removal in vacuo gave an oily residue, which was directly used in the next step.

The crude material from above was dissolved in a 9:1 acetone–water mixture (10 mL) and treated with PhI-$(OCOCF_3)_2$ (86 mg, 0.2 mmol). The reaction mixture was stirred at room temperature in the dark until disappearance of the starting material (ca. 25 min, *monitoring with TLC!*). Work-up (extraction with EtOAc) and careful column chromatography on silica gel (hexane–EtOAc, 4:1, then 3:2) yielded **4** (9 mg) and **19** (24 mg).

*Aculeatin D (**4**)*: oil; $[\alpha]_D$ +43.5 (*c* 0.2, $CHCl_3$), lit.[1b] $[\alpha]_D$ +46.5 (*c* 1, $CHCl_3$); IR ν_{max} 3430 (br, OH), 1670 (ketone C=O) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.89 (1H, dd, *J*=10, 3 Hz), 6.21 (1H, dd, *J*=10, 2.8 Hz), 6.07 (1H, dd, *J*=10, 1.8 Hz), 6.04 (1H, dd, *J*=10, 1.8 Hz), 3.37 (1H, m), 2.95 (1H, m), 1.88 (1H, m), 1.79 (1H, m), 1.73 (1H, m), 1.55 (2H, m), 1.50–1.20 (26H, br m), 1.14 (1H, m), 1.01 (1H, m), 0.91 (3H, t, *J*=7 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 185.0, 109.6, 78.5 (C), 152.0, 149.0, 127.5, 127.3, 71.8, 66.9 (CH), 44.2, 41.5, 36.5, 35.4, 33.2, 32.5, 30.5 (br, several overlapped signals), 26.5, 23.5 (CH_2), 14.8 (CH_3); HR EIMS *m*/*z* (rel int.) 418.3059 (M^+, 2), 400 (M^+-H_2O, 16), 310 (5), 235 (35), 165 (80), 120 (94), 107 (100). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

*6-Epi-aculeatin D (**19**)*: oil; $[\alpha]_D$ +5.7 (*c* 0.3, $CHCl_3$); IR ν_{max} 3430 (br, OH), 1671 (ketone C=O) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.68 (1H, dd, *J*=10, 3.2 Hz), 6.15–6.10 (2H, m), 6.01 (1H, dd, *J*=10, 2 Hz), 3.90 (1H, m), 3.70 (1H, m), 2.00 (1H, m), 1.87 (2H, m), 1.65 (1H, m), 1.55 (1H, m), 1.50–1.20 (27H, br m), 1.07 (1H, q, *J*=12 Hz), 0.90 (3H, t, *J*=6.9 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 185.2, 109.6, 79.7 (C), 151.4, 149.3, 127.5, 127.2, 69.7, 65.7 (CH), 44.3, 41.8, 39.4, 37.0, 35.5, 32.9, 30.5 (br, several overlapped signals), 26.6, 23.5 (CH_2), 14.8 (CH_3); HR EIMS *m*/*z* (rel int.) 418.3068 (M^+, 6), 400 (M^+-H_2O, 23), 310 (27), 235 (35), 165 (100), 107 (70). Calcd for $C_{26}H_{42}O_4$, *M*=418.3083.

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A novel method for the reduction of sulfoxides and pyridine *N*-oxides with the system silane/MoO_2Cl_2

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Abstract—A novel method for the reduction of sulfoxides and pyridine *N*-oxides using a silane and a catalytic amount of MoO_2Cl_2 in excellent yields and with a wide functional group tolerance is reported. A green protocol for this reaction was developed in water with the air-stable catalytic system PMHS/$MoO_2Cl_2(H_2O)_2$.

1. Introduction

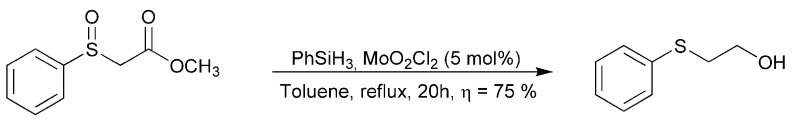
The reduction (or deoxygenation) of sulfoxides and amine *N*-oxides to the corresponding sulfides and amines is an important organic and biological reaction. Over the years, several methods have been developed to reduce sulfoxides[1–8] and amine *N*-oxides,[9–15] however, many of these transformations are limited by side reactions, low yields, lack of chemoselectivity or harsh conditions. For example, the use of hydrogen halides is somewhat restricted with acid-sensitive substrates, the reductions with the strong hydride systems $LiAlH_4$–$TiCl_4$ and $NaBH_4$–$CoCl_2$ are incompatible with several functional groups, and the reactions with phosphorus reagents, in most cases, require elevated temperature and/or prolonged reaction times.

Among the variety of metal complexes that have been used as catalysts for the deoxygenation of sulfoxides and amine *N*-oxides, molybdenum complexes have attracted considerable interest. This metal is found in a class of enzymes that are commonly referred to as mononuclear molybdoenzymes or oxotransferases, such as dimethyl sulfoxide reductases, that catalyze oxygen atom transfer to or from a physiological donor/acceptor.[16,17]

Several studies have shown that Mo(VI)O_2 complexes catalyze the oxygen atom transfer reaction from the sulfoxides or aromatic *N*-oxides to a phosphine, yielding the corresponding sulfides or amines and the oxidized phosphine.[5,9,18–20]

Recently, we have demonstrated that the high valent molybdenum-dioxo complex, MoO_2Cl_2, is an effective catalyst for organic reductions, such as hydrosilylation of aldehydes and ketones,[21] and reduction of imines[22] and esters.[23] These results confirm the new role of oxo complexes in catalytic reductions, which unexpectedly adds to their well-established abilities to catalyze oxygen-transfer reactions to olefins, phosphines, and sulfites.

During the course of our studies on the reaction of esters with the system $PhSiH_3$/MoO_2Cl_2, we observed the reduction of both sulfinyl and carboxyl groups of methyl(phenylsulfinyl)acetate, giving the 2-(phenylthio)ethanol in 75% yield (Scheme 1). This result suggested the extension of the system silane/MoO_2Cl_2 for the reduction of other sulfoxides. In this work, we investigated the deoxygenation of sulfoxides and pyridine *N*-oxides using the catalysts MoO_2Cl_2 and $MoO_2Cl_2(H_2O)_2$ in the presence of a silane in organic and aqueous solvents.



Scheme 1.

Keywords: Reduction; Sulfoxides; Pyridine *N*-oxides; Dioxomolybdenum dichloride.
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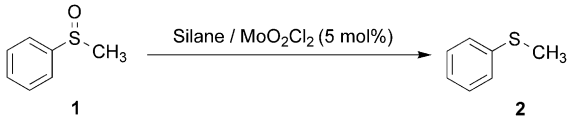
2. Results and discussion

To optimize the reaction conditions, we first studied the reduction of methyl phenyl sulfoxide **1** with several silanes and solvents as summarized in Table 1. This sulfoxide was completely reduced with phenylsilane ($PhSiH_3$) in the presence of 5 mol % of MoO_2Cl_2 in refluxing tetrahydrofuran after 2 h (entry 1). At room temperature, the reaction required significantly longer reaction times (20 h) and sulfide **2** was obtained in only 66% conversion (entry 2).

Table 1. Reduction of methyl phenyl sulfoxide **1** catalyzed by MoO_2Cl_2



1 **2**

Entry	Silane[a]	Solvent	Temperature (°C)	Time (h)	Conversion[b] (%)
1	$PhSiH_3$	THF	67	2	100
2	$PhSiH_3$	THF	rt	20	66
3	$PhSiH_3$	Toluene	110	2	100
4	$PhSiH_3$	CH_2Cl_2	40	2	95
5	$PhSiH_3$	CH_3CN	80	2	21
6	PMHS	THF	67	20	100
7	DMPHS	THF	67	24	65
8	Et_3SiH	THF	67	24	35
9	Ph_3SiH	THF	67	48	No reaction

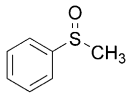
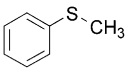
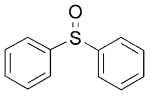
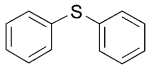
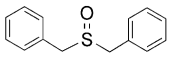
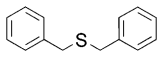
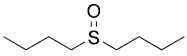
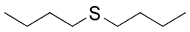
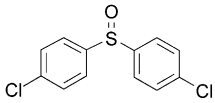
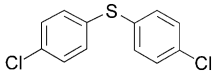
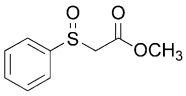
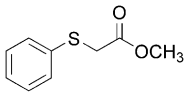
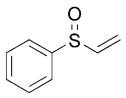
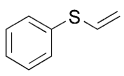
[a] The reactions were carried out with 100 mol % of $PhSiH_3$, DMPHS, Et_3SiH or Ph_3SiH and with 0.3 mol % of PMHS.
[b] Conversion was determined by ^1H NMR.

To evaluate the effect of solvents, the reduction of sulfoxide **1** was carried out in tetrahydrofuran, toluene, dichloromethane, and acetonitrile. Sulfide **2** was obtained in 100% conversion in THF and toluene (entries 1 and 3), in 95% conversion in dichloromethane (entry 4), but in acetonitrile it was obtained in only 21% conversion (entry 5).

This reaction was also investigated with several silanes. With the polymethylhydrosiloxane (PMHS), sulfoxide **1** was completely reduced (entry 6) and with dimethylphenylsilane (DMPHS) and triethylsilane (Et_3SiH), sulfide **2** was obtained in 65% and 35% conversion, respectively (entries 7 and 8). No catalysis was observed with the triphenylsilane (entry 9).

To explore the scope of this catalytic reaction, the reduction of a variety of sulfoxides with the system $PhSiH_3/MoO_2Cl_2$ (5 mol %), in refluxing tetrahydrofuran, was investigated (Table 2). As shown in Table 2, the sulfoxides were reduced in excellent yields. This catalytic reaction is suitable for the deoxygenation of aromatic and aliphatic sulfoxides, in particular, for the reduction of benzyl sulfoxide (entry 3), since several methods fail completely with this substrate or only provide poor yields of benzyl sulfide. This reaction is also compatible with other functional groups such as halo, carboxyl, and vinyl (entries 5–7). The chemoselective reduction of methyl(phenylsulfinyl)acetate, in 97% yield (Table 2, entry 6), was possible in THF, contrary to the reduction of both sulfinyl and carboxyl groups observed in refluxing toluene (Scheme 1) and reported in our previous work.[23]

Table 2. Reduction of sulfoxide with the system $PhSiH_3/MoO_2Cl_2$[a]

Entry	Sulfoxide	Sulfide	Time (h)	Yield[b] (%)
1			2	97
2			2	97
3			20	96
4			7	92
5			2	96
6			2.5	96
7			2	92

[a] All reactions were carried out in refluxing THF with 1.0 mmol of sulfoxide, 1.0 mmol of $PhSiH_3$, using 5 mol % of MoO_2Cl_2.
[b] Isolated yield.

Attempted reduction of phenyl sulfone and 4-fluorophenyl methyl sulfone resulted in only the recovery of starting material.

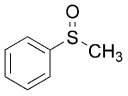
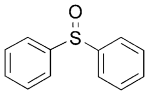
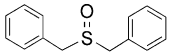
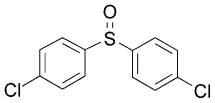
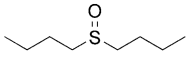
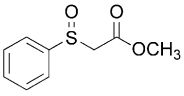
The reduction of sulfoxides was also carried out with the complex $MoO_2Cl_2(H_2O)_2$, which was easily prepared by extraction from a hydrochloric acid solution of Na_2MoO_4 with diethyl ether.[19]

The catalytic activity of $MoO_2Cl_2(H_2O)_2$ was studied with the silanes $PhSiH_3$ and PMHS. The reduction of the substrates, methyl phenyl sulfoxide, phenyl sulfoxide, and benzyl sulfoxide with the system $PhSiH_3/MoO_2Cl_2(H_2O)_2$ (5 mol %) in refluxing THF, afforded the corresponding sulfides in 95%, 96%, and 95%, respectively (Table 3, entries 1, 4, and 7). These yields and the reaction times are comparable to those obtained with the system $PhSiH_3/MoO_2Cl_2$ (Table 2, entries 1–3).

The reaction of sulfoxides with PMHS in the presence of 5 mol % of $MoO_2Cl_2(H_2O)_2$, in refluxing methanol, was carried out in air and produced the sulfides in excellent yields (Table 3). The chemoselective reduction of methyl(phenylsulfinyl)acetate was also possible in this reaction conditions in good yield (entry 12).

Finally, we tried the reduction of sulfoxides with the system $PMHS/MoO_2Cl_2(H_2O)_2$ in water at 80 °C (Table 3). This green system reduced the methyl phenyl sulfoxide in 52%

Table 3. Reduction of sulfoxides catalyzed by $MoO_2Cl_2(H_2O)_2$[a]

Entry	Sulfoxide	Silane	Solvent[b]	Time (h)	Yield (%)[c]
1		$PhSiH_3$	THF	1.5	95
2		PMHS	Methanol	2	95
3		PMHS	H_2O[d]	20	52
4		$PhSiH_3$	THF	2	96
5		PMHS	Methanol	20	96
6		PMHS	H_2O[d]	20	92
7		$PhSiH_3$	THF	20	95
8		PMHS	Methanol	20	95
9		PMHS	Methanol	20	95
10		PMHS	H_2O[d]	20	50
11		PMHS	Methanol	20	94
12		PMHS	Methanol	20	90

[a] All reactions were carried out with 1.0 mmol of sulfoxide, 100 mol % of $PhSiH_3$ or 0.3 mol % of PMHS, using 5 mol % of $MoO_2Cl_2(H_2O)_2$.
[b] Reflux temperature.
[c] Isolated yield.
[d] The reaction was carried out at 80 °C.

yield, the phenyl sulfoxide in 92% yield, and the 4-chlorophenyl sulfoxide in 50% yield (Table 3, entries 3, 6, and 10). The benzyl sulfoxide and butyl sulfoxide did not react in water.

The analysis of the ^1H NMR spectrum of the reaction mixture obtained in the reduction of the phenyl vinyl sulfoxide with the system PMHS/$MoO_2Cl_2(H_2O)_2$ in methanol or in water showed that the double bond was affected.

The system PMHS/$MoO_2Cl_2(H_2O)_2$ proved to be very efficient for the reduction of sulfoxides in organic solvents. The use of PMHS is more attractive than $PhSiH_3$ because it is easily handled, stable to air and water, inexpensive, and non-toxic. However, the reductions with PMHS required longer reaction times.

The easy and inexpensive preparation of ether solution of $MoO_2Cl_2(H_2O)_2$ and its air stability make this catalyst an excellent alternative to MoO_2Cl_2, which has a difficult preparation and a great air instability.

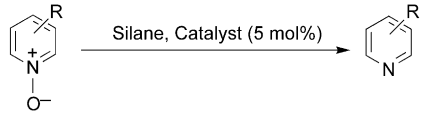
Other important advantage of the system PMHS/$MoO_2Cl_2(H_2O)_2$ is related to the environmental concerns and increased restrictions on the use of hazardous organic solvents. With this system, the reduction, in water, was possible for some sulfoxides in moderate to good yields.

In this work, we also performed a brief investigation of the deoxygenation of pyridine *N*-oxides with the silanes $PhSiH_3$ and PMHS catalyzed by MoO_2Cl_2 and $MoO_2Cl_2(H_2O)_2$ (Table 4). As shown in Table 4, the catalytic systems $PhSiH_3/MoO_2Cl_2$, $PhSiH_3/MoO_2Cl_2(H_2O)_2$, and PMHS/$MoO_2Cl_2(H_2O)_2$ reduced the 3- and 4-methylpyridine *N*-oxides in good yields in organic solvents. As observed in the reduction of sulfoxides, the reaction with PMHS required longer reaction times than with $PhSiH_3$. Due to the wide functional group tolerance verified in the reduction of sulfoxides, we believe that this novel method can be suitable for the deoxygenation of other pyridine *N*-oxides. Unfortunately, the pyridine *N*-oxides were not reduced in water with the system PMHS/$MoO_2Cl_2(H_2O)_2$.

In order to verify that MoO_2Cl_2 plays an active role in the deoxygenation process, we carried out the reaction of sulfoxide **1** with an excess of phenylsilane without catalyst and the reaction of sulfoxide **1** with 5 mol % of MoO_2Cl_2 without phenylsilane in refluxing THF during 2 h. In both cases, sulfoxide **1** was not reduced. These results suggest that MoO_2Cl_2 catalyzes the reaction by activation of the silane, producing a hydride species (Mo-H).

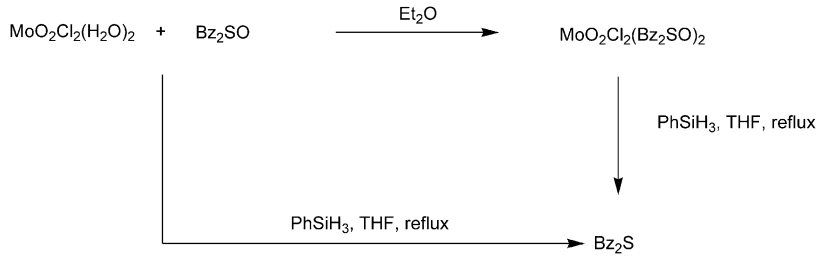
In the reaction of the complex $MoO_2Cl_2(Bz_2SO)_2$, prepared by the addition of benzyl sulfoxide to the ether solution of $MoO_2Cl_2(H_2O)_2$,[19] with 1 equiv of the phenylsilane in refluxing THF was observed the reduction of the sulfoxide,

Table 4. Deoxygenation of pyridine *N*-oxides catalyzed by MoO_2Cl_2 or $MoO_2Cl_2(H_2O)_2$[a]



Entry	R	Silane	Catalyst	Solvent[b]	Time (h)	Yield (%)[c]
1	4-CH_3	$PhSiH_3$	MoO_2Cl_2	THF	3	85
2		$PhSiH_3$	$MoO_2Cl_2(H_2O)_2$	THF	3	84
3		PMHS	$MoO_2Cl_2(H_2O)_2$	Methanol	20	86
4		PMHS	$MoO_2Cl_2(H_2O)_2$	H_2O[d]	20	No reaction
5	3-CH_3	$PhSiH_3$	MoO_2Cl_2	THF	3	85
6		$PhSiH_3$	$MoO_2Cl_2(H_2O)_2$	THF	3	83
7		PMHS	$MoO_2Cl_2(H_2O)_2$	Methanol	20	85
8		PMHS	$MoO_2Cl_2(H_2O)_2$	H_2O[d]	20	No reaction

[a] All reactions were carried out with 1.0 mmol of pyridine *N*-oxide, 100 mol % of $PhSiH_3$ or 0.3 mol % of PMHS using 5 mol % of catalyst.
[b] Reflux temperature.
[c] Isolated yield.
[d] The reaction was carried out at 80 °C.



Scheme 2.

giving the benzyl sulfide (Scheme 2). A similar result was obtained when the benzyl sulfoxide was reduced with the system $PhSiH_3/MoO_2Cl_2(H_2O)_2$ (Table 3, entry 7). This result suggests the initial activation of the sulfoxide by the oxygen coordination to the molybdenum, yielding the complex $MoO_2Cl_2(sulfoxide)_2$. This complex weakens the S–O bond and renders the sulfur atom more susceptible to the reduction. After the addition of the silane, the complex $MoO_2Cl_2(sulfoxide)_2$ is reduced with elimination of the sulfide and a siloxane.

3. Conclusion

In summary, we have developed a novel method for the reduction of sulfoxide and pyridine *N*-oxides to the corresponding sulfides and pyridines using the silane $PhSiH_3$ in the presence of a catalytic amount of MoO_2Cl_2 in excellent yields and with a wide functional group tolerance. This catalytic system can be a useful alternative to the traditional methods for the reduction of sulfoxides, especially, in natural products and pharmaceutical synthesis, which require mild conditions, selectivity, and functional group tolerance.

A green protocol for the reduction of sulfoxides was also developed with the system $PMHS/MoO_2Cl_2(H_2O)_2$ in water or methanol. This novel, air-stable catalyst system reduced sulfoxides in moderate to excellent yields. The simplicity and environmental-friendly conditions of this protocol make this novel method suitable for large-scale reductions.

Other organic reductions with this system are now under investigation in our group.

4. Experimental

4.1. General methods

Toluene and THF were distilled under nitrogen from sodium, and CH_2Cl_2 and acetonitrile from CaH_2 before use. Silanes were obtained from Aldrich, PMHS (M_n=1700–3200). Flash chromatography was performed on MN Kieselgel 60 M 230–400 mesh. All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AMX 300 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from an internal Me_4Si standard. IR spectra were measured on a Unicam Mattson model 7000 FTIR spectrometer.

4.2. General procedures

4.2.1. General procedure for the reduction of sulfoxides and pyridine *N*-oxides with the system $PhSiH_3/MoO_2Cl_2$. To a solution of MoO_2Cl_2 (5 mol %) in dry THF (5 ml) was added the sulfoxide or the pyridine *N*-oxide (1.0 mmol) and $PhSiH_3$ (1.0 mmol) under nitrogen atmosphere. The reaction mixture was stirred at reflux temperature (the reaction times are indicated in Tables 2 and 4) and monitored periodically by TLC. Upon completion, the reaction mixture was evaporated and purified by silica gel column chromatography with the appropriate mixture of *n*-hexane and ethyl acetate to afford the sulfides and pyridines, which are all known compounds.

4.2.2. Green protocol for the reduction of sulfoxides with the system $PMHS/MoO_2Cl_2(H_2O)_2$. To a solution of the sulfoxide (1.0 mmol) in water (5 ml) or in methanol (3 ml) were added the ether solution of $MoO_2Cl_2(H_2O)_2$ (5 mol %) and PMHS (0.3 mol %). The reaction mixture was stirred at reflux temperature in methanol or at 80 °C in water (the reaction times are indicated in Table 3). Upon completion, the reaction mixture was extracted with diethyl ether (3×20 ml), dried over sodium sulfate, evaporated, and purified by silica gel column chromatography with the appropriate mixture of *n*-hexane and ethyl acetate.

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Aplysiadiol from *Aplysia dactylomela* suggested a key intermediate for a unified biogenesis of regular and irregular marine algal bisabolene-type metabolites

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Abstract—The rearranged compound **1**, the regular **2** and **3** and the degraded **4** are novel bisabolene-type metabolites that along with the known compounds caespitol, 8-acetylcaespitol, caespitane, caespitenone, laucapyranoid A, and furocaespitane have been isolated from the sea hare *Aplysia dactylomela*. The structures of these compounds were determined on the basis of spectroscopic evidence. The irregular network of **1** suggested that the halogenated epoxide **6** is a key intermediate for a unified biogenetic pathway of naturally occurring marine algal bisabolene-type metabolites.

1. Introduction

Molluscs of the genus *Aplysia* are one among the best studied of all marine invertebrates, serving as a model system for neurological studies.[1] *Aplysia dactylomela* (Opisthobranchia: Anaspidea) like other sea hares thrive on algae, acquiring and storing many algal metabolites in their digestive gland.[2] This species alone sequesters some 80 different secondary metabolites from its algal diet,[3] but their function is a subject of debate because the dynamics of metabolites of sea hares is poorly understood.[4] *Laurencia caespitosa*, a red alga common in the diet of *A. dactylomela* from the Canary Islands, was the first source[5] of a marine algal bisabolene-type sesquiterpenoid, and since then a number of metabolites belonging to this skeletal class has been found in other taxa including sponges, nudibranchs, octocorals, and, more recently, microorganisms.

From a survey on marine bisabolene metabolites interesting analogies can be observed regarding structural and/or functional features. For example, all bisabolene derivatives from sponges can be grouped into two structural classes. One class of metabolites bear an aromatic ring[6–14] related to (+)-curcuphenol and the other features a diverse nitrogenous substitution pattern in a non-aromatic network[15–21] (Fig. 1). Moreover, all bisabolene compounds from octocoral

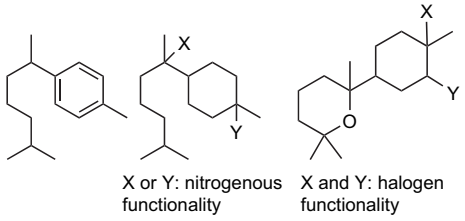

Figure 1. Representative structural classes of bisabolene-type metabolites from diverse marine taxa.

are aromatic, sharing with sponges some identical but, interestingly, antipodal metabolites related to (−)-curcuphenol.[22–25] Recently discovered microbial bisabolene compounds[26] were also related to the curcumene skeleton whereas bisabolene products from red algae are mostly characterized, unlike the other taxa, by high halogen content.[5,27–29]

A. dactylomela has proved to be a rich source of structural variety of bisabolenic metabolites, depending on where they are located.[5,30–33] We now report on the discovery of new bisabolene derivatives **1–4** from this species, along with the previously characterized caespitol,[5] furocaespitane,[27] laucapyranoid A,[28] 8-acetylcaespitol,[32] caespitane,[28,32] and caespitenone[28,32] (Fig. 2). Most of the compounds reported here are halogenated, following the general pattern of algal bisabolene sesquiterpenoids, **1** and **4** being a rearranged and a degraded bisabolene skeleton derivative, respectively.

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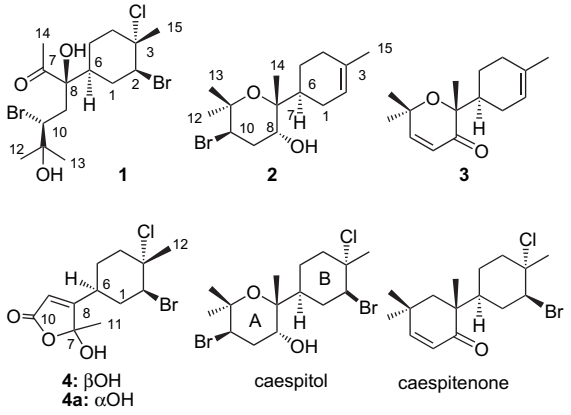


Figure 2. Metabolites from *A. dactylomela*.

2. Results and discussion

A. dactylomela was collected off the SW coast of La Palma (Canary Islands). From the crude extracts the new compounds **1**–**4** were isolated after gel filtration on Sephadex LH-20 chromatography followed by successive HPLC.

Aplysiadiol **1** was a colorless oil and its NMR spectroscopic data are summarized in Table 1. Its EIMS spectrum showed peaks at *m/z* 413/415/417/419 with relative intensities suggestive of one chlorine and two bromine atoms, which correspond to the empirical formula $C_{14}H_{20}O_2ClBr_2$ $[M-Me-H_2O]^+$ (HREIMS). Absorption for a carbonyl and a hydroxyl group at 1722 and 3448 cm^{-1}, respectively, were observed in its IR spectrum. The ^{13}C NMR and DEPT spectra of **1** showed the presence of 15 carbon signals assigned to $4\times CH_3$, $4\times CH_2$, $3\times CH$ (two bearing bromine), and four quaternary carbons (one ketone). The ^1H NMR spectrum displayed signals for two protons geminal to bromine at δ 3.67 (dd, J=2.1, 9.5 Hz) and δ 4.27 (dd, J=4.3, 12.8 Hz); eight methylene protons between δ 2.55 and 1.60; a methine proton at 1.84 (br s); and four methyl groups [δ 2.30 (s), δ 1.68 (s), δ 1.35 (s), δ 1.32 (s)]. According to the degree of unsaturation, the molecular formula of **1** expressed a monocyclic network.

Connectivity information obtained from COSY, HSQC, and HMBC experiments unambiguously determined a cyclohexyl moiety with a halogen substitution pattern identical with that in the corresponding ring B of caespitol (Fig. 2). The complementary half of the molecule attached to the ring is a highly functionalized open chain where the regiochemistry of a carbinolic bromohydrin, involving a gem-dimethyl group, becomes readily apparent by the mutual HMBC correlations C-13/H_3-12, C-12/H_3-13 and those with H-10 and C-11, respectively. The COSY correlation of H-10 with a remaining methylene placed a carbinolic methyl ketone at C-8, establishing the planar structure of **1** as an irregular sesquiterpene.

The coupling constant of H-2 (J=4.3, 12.8 Hz) as well as the ^{13}C-chemical shifts of C-2, C-3, and C-15 are in agreement with the regiochemistry and configuration of a vicinal chlorobromo system on a cyclohexane ring with a chair conformation such as that of caespitol (Table 1). An equatorial disposition of the side chain residue on the ring was

Table 1. NMR data of compounds **1**–**4** and caespitol [500 MHz, δ ppm, (J) Hz, $CDCl_3$]

#	1		2		3		4		Caespitol	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	1.80 (m), 1.98 (m)	35.7	1.73 (m), 1.99 (m)	25.9	1.87 (m), 2.09 (m)	25.1	2.00 (m), 2.00 (m)	39.8	α: 2.21 (m), β: 1.57 (ddd, 12.6, 12.6, 12.6)	36.3
2	4.27 (dd, 4.3, 12.8)	62.0	5.32 (br s)	119.8	5.37 (br s)	120.6	4.38 (dd, 4.1, 12.4)	60.8	4.34 (dd, 4.5, 12.4)	63.7
3	—	71.0	—	134.5	—	133.9	—	70.2	—	72.0
4	α: 2.06 (m), β: 2.45 (ddd, 3.4, 3.4, 13.7)	42.2	1.90 (m), 2.03 (m)	30.9	1.89 (m), 2.00 (m)	30.6	α: 2.16 (ddd, 3.9, 13.7, 13.7), β: 2.48 (ddd, 3.4, 3.4, 13.9)	42.2	α: 2.00 (ddd, 3.8, 13.5, 13.5), β: 2.35 (ddd, 3.3, 3.3, 13.5)	42.9
5	1.76 (m), 1.60 (m)	23.8	1.19 (m), 1.99 (m)	22.5	1.47 (m), 1.56 (m)	24.0	1.50 (m), 1.50 (m)	28.8	1.18 (m), 1.82 (m)	22.7
6	1.84 (br s)	46.3	1.70 (br s)	41.4	2.07 (m)	41.6	2.53 (dddd, 3.2, 3.2, 12.0, 12.0)	36.9	1.85 (m)	45.8
7	—	212.7	—	77.8	—	81.9	—	106.8		77.2
8	—	82.7	—	71.4	—	199.9	5.80 (s)	170.4	3.52 (dd, 2.3, 3.3)	70.8
9	a: 2.55 (dd, 2.1, 15.6), b: 2.27 (dd, 9.5, 15.6)	39.4	3.52 (ddd, 3.6, 3.6, 6.2) α: 2.47 (ddd, 2.3, 13.6, 13.6), β: 2.26 (ddd, 4.1, 4.1, 13.9)	35.8	5.92 (d, 10.4)	122.8	—	116.4	α: 2.17 (m), β: 2.46 (ddd, 2.3, 13.4, 13.4)	36.2
10	3.67 (dd, 2.1, 9.5)	60.4	4.33 (dd, 4.1, 13.2)	53.9	6.80 (d, 10.4)	154.7	—	172.6	4.28 (dd, 4.2, 13.2)	53.2
11	—	72.9	—	75.3	—	71.2	1.71 (s)	24.1	—	75.4
12	1.35 (s)	27.6	1.32 (s)	31.2	1.36 (s)	30.0	1.75 (s)	24.1	1.26 (s)	31.0
13	1.32 (s)	25.5	1.40 (s)	24.3	1.41 (s)	29.7	—	—	1.32 (s)	24.0
14	2.30 (s)	26.6	1.13 (s)	19.2	1.30 (s)	23.4	—	—	1.08 (s)	19.9
15	1.68 (s)	22.8	1.62 (s)	23.4	1.62 (s)	23.4	—	—	1.63 (s)	24.3
7-OH							1.56 (br s)			
8-OH	3.85 (s)		1.84 (d, 6.4)						2.43 (br s)	

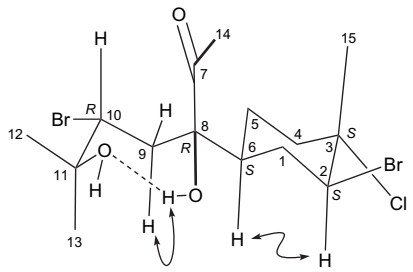
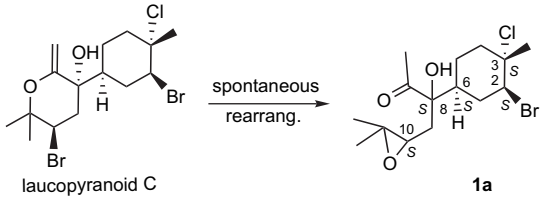


Figure 3. Selected NOEs of compound **1**.

established by the strong NOE observed between H-2 and H-6 (Fig. 3).

The energy-minimized conformation of **1** deduced by molecular mechanics[34] is shown in Figure 3. This conformer showed a hydrogen bond between the hydroxyl groups so that the proton of the hydroxyl at C-8 and the trans-diaxial proton at C-9 are at a suitable interatomic distance to allow the observed NOE between them. For the acyl group at C-8 an *R* configuration is given to allow an atomic cluster compatible with the H_2-9/H-10 *J*-coupling and the observed NOE. This point has been further reinforced by comparison of the NMR data of **1** with those of a related compound **1a** generated by spontaneous rearrangement of laucopyranoid C and whose absolute configuration was established by X-ray crystallography.[28] Whereas the ^{13}C chemical shifts of the carbons of the cyclohexane ring are almost identical in both compounds, the inversion of the configuration at C-8 of **1** produced a variation in the chemical shift of this carbon and the comparable vicinal carbons. For ^{13}C chemical shifts of **1a** see the experimental part. This spectroscopic correlation allowed us to propose for **1** the 2*S*, 3*S*, 6*S*, 8*R*, 10*R* configuration depicted in Figure 3.



Deschlorobromo caespitol **2** was obtained as a white powder. The EIMS spectrum showed peaks at *m/z* 316/318, with relative intensities for one bromine atom. NMR data coupled with the $[M]^+$ peak in the HREIMS of **2** suggested a molecular formula $C_{15}H_{25}O_2Br$ with three degrees of unsaturation indicating that the molecule is bicyclic. The ^{13}C NMR and DEPT spectra of **2** (Table 1) showed the presence of 15 carbon signals assigned to $4\times CH_3$, $4\times CH_2$, $4\times CH$ (one olefinic and two bearing heteroatoms), and three quaternary carbons (one olefinic and two bearing heteroatoms). The following ^1H NMR signals were observed: one olefinic proton at δ 5.32 (br s); two protons geminal to heteroatom [δ 4.33 (dd, J=4.1, 13.2 Hz), δ 3.52 (ddd, J=3.6, 3.6, 6.2 Hz)]; one methine proton at δ 1.70 (br s); eight methylene protons between δ 2.03 and 1.19; four methyl groups [δ 1.62 (br s), δ 1.40 (s), δ 1.32 (s), δ 1.13 (s)], and one D_2O interchangeable proton at δ 1.84 (d, J=6.4 Hz).

Connectivity information obtained from COSY, HSQC, and HMBC as well as NOESY experiments secured an oxane ring moiety bearing the same heteroatoms, regiochemistry and relative configuration as those of comparable atoms of ring A of caespitol (Table 1). The remaining two degrees of unsaturation correspond to a trisubstituted double bond in a residual cyclohexene ring, which suggests that the typical chlorobromo system of ring B of caespitol was lost in compound **2**. On the other hand, it has been reported that the $LiAlH_4$ reduction of caespitol yielded a compound[5] with same planar structure as **2**. The ^{13}C NMR chemical shifts reported later[35] for this synthetic compound were very similar to those of **2** except for the corresponding C-3 and C-15 carbon atoms ($\Delta_{\delta C\text{-}3}$=5.6, $\Delta_{\delta C\text{-}15}$=10 ppm). Since ring A of both natural and synthetic compounds are identical in all respects, and because such differences are improbable for a putative diastereomer at C-6, we suspect these values were mistaken or incorrectly assigned. In order to corroborate this point, caespitol was efficiently dehalogenated by reaction with Zn–NaI in DMF at 115 °C to give a compound identical with that depicted in **2**. Thus, the correct NMR data of **2** are assigned in Table 1.

Deschlorobromo caespitenone **3** was isolated as an oil. NMR spectroscopic data coupled with a molecular ion peak at *m/z* 234 $[M]^+$ (HREIMS) suggested a molecular formula of $C_{15}H_{22}O_2$ indicating five degrees of unsaturation. The ^1H and ^{13}C NMR data of **3** are similar to those of the known compound caespitenone,[28,32] also isolated in this work. The main difference is that the chlorobromo system characteristic of ring B of caespitenone has been lost in **3**, leading to the corresponding cyclohexene ring, which is in accord with the degrees of unsaturation. Thus, **3** is the dehalogenated derivative of caespitenone. This was corroborated by oxidation–dehydration of compound **2** with Jones reagent to give a compound identical with that depicted in **3**.

Since the optical rotation of caespitol isolated in this study is coincident with that previously reported,[28] the chemical transformation of caespitol into compounds **2** and **3** allowed us to establish their absolute streochemistries as 6*S*,7*R*,8*R*,10*R* and 6*S*,7*R*, respectively.

Furocaespitanelactol **4** was isolated as a white powder. Its EIMS spectrum showed peaks at *m/z* 322/324/326 with relative intensities suggestive of one chlorine and one bromine atom, which correspond to the empirical formula $C_{12}H_{16}O_3ClBr$ $[M]^+$ (HREIMS). The molecular formula of **4** resembled that of furocaespitane, a degraded bisabolene-type derivative previously isolated by us from *L. caespitosa*[27] and also now isolated in this work from *A. dactylomela*.

Oxidation of furocaespitane with *m*-chloroperbenzoic acid has been reported to give an epimeric mixture[27] at C-7 of butenolides **4** and **4a** (Fig. 2). The spectroscopic data of our single naturally occurring compound indicates that its structure is a lactol identical to one of the epimers present in the synthetic mixture. The energy-minimized conformation of both epimers **4** and **4a** deduced by molecular mechanics is shown in Figure 4.

The orthogonal joining of the lactone and cyclohexane rings placed the methyl group of the respective carbinols of each epimer at such a similar distance from H-6 that it does not allow us to discern to which one of the epimers the NOE

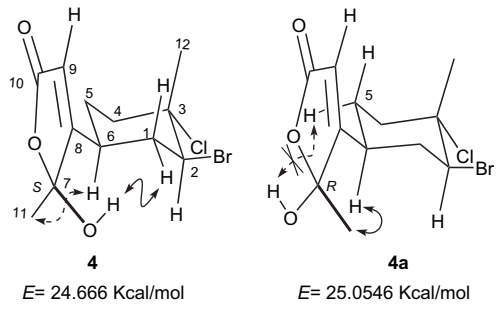


Figure 4. Selected NOEs of **4** and **4a**.

observed between CH_3-11 and H-6 corresponds. However, the interatomic distance between the hydrogen of the hydroxyl group and the equatorial proton H_2-1 of **4** measured by the program is 2.446 Å, whereas in the epimer **4a** the distance to H-5_{eq} is 3.111 Å, which appears to be too large for a clear NOE to be expected. Thus, the observed NOE in the natural compound was assigned to the epimer with an *S* stereochemistry at C-7. Because the remaining chiral centers of the compound are identical with the corresponding centers of furocaespitane, the stereochemistry of the degraded bisabolene metabolite was assigned as depicted in **4** (Fig. 4).

On standing, **4** isomerizes to **4a** until a 1:1 equilibrium mixture is reached (Fig. 5). This is the first time that **4** has been isolated as a natural product. Due to the lack of ^{13}C NMR data and assigned ^{1}H NMR chemical shifts, we provide complete NMR data of the natural compound **4** in Table 1 and those of **4a** in the experimental part.

A bisabolyl cation is expected to be converted into the possible precursor of the naturally occurring algal bisabolene derivatives, the true producer of this type of metabolite found in *A. dactylomela*. It appears that in this process the trienic system of the bisabolene is sequentially oxidized, starting with chlorobromo addition to the endocyclic double bond. This seems to be supported by finding the natural halogenated addition products puertitols A and B[36] by stabilization of the intermediate **5** (Fig. 6).

Although **6**, a putative derivative from a second oxidation step of the central double bond of the halogenated bisabolol **5**, is unknown at present, it can be postulated as a precursor in the biogenesis of these compounds. The nascent intermediate **6** rearranges, by 1,2-migration of the bond connecting both the linear and cyclic halves induced by epoxide ring opening, to **7**. The transformation of **6**→**7** is a key step to account for naturally occurring marine algal irregular and degraded bisabolene-type network metabolites.

From **7**, and in virtue of the biogenetically interconvertible **8**↔**9**, alternative path a and/or path b may provide a non-regular network **8** (Box **A**) from which laucopyranoid A could be generated by stabilization of carbocation **8**.

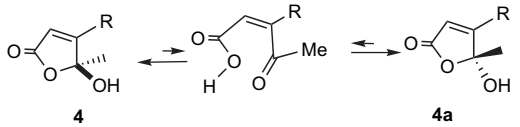


Figure 5. Equilibrium leading to a mixture of epimers at C-7.

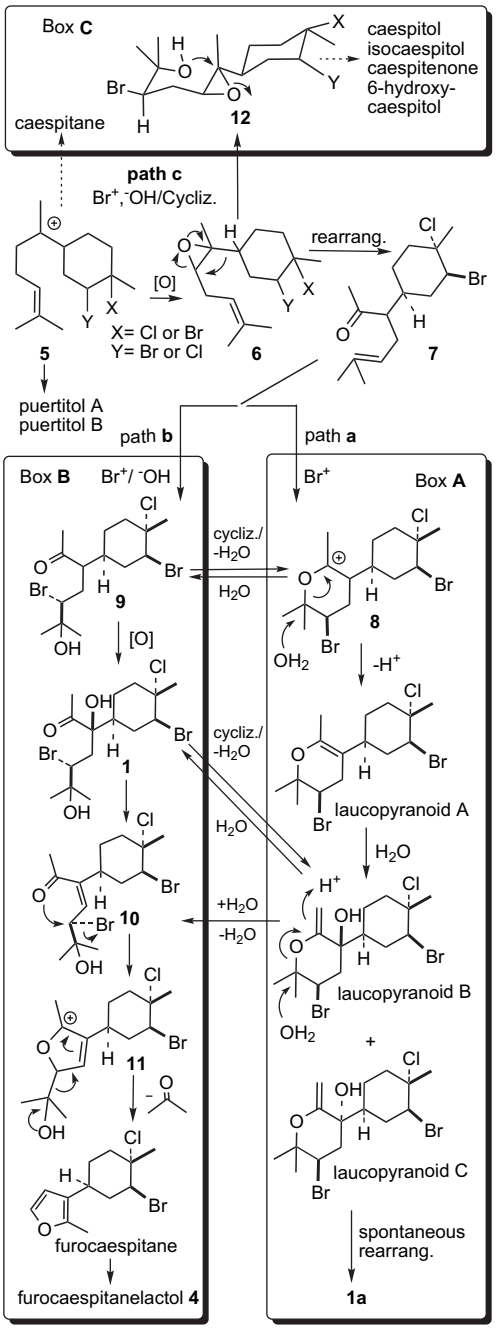


Figure 6. Unified biogenesis for marine algal bisabolene-type metabolites.

Hydration of laucopyranoid A may afford the epimeric laucopyranoid B and laucopyranoid C. Whereas laucopyranoid C spontaneously rearranges to **1a**, laucopyranoid B as well as aplysiadiol **1**, derived from extensive oxidation of **7**, Box **B**, may evolve to degraded furocaespitane and related lactol **4** following path **b** indicated in Figure 6. This route involves dehydration of **1** and/or hydration/dehydration of laucopyranoid B to a conjugated ketone **10**, formation of a furane ring by intramolecular displacement of the bromine atom and, finally, trapping of the resulting carbocation **11** by loss of the terminal isopropyl carbinol as acetone.

On the other hand, the key precursor **6** may evolve by oxidizing the remaining olefin, the terminal isopropylidene, to a fully oxidized bromohydrin derivative **12** (Box **C**) from

which the regular sesquiterpenoid caespitol, and related compounds such as isocaespitol,[37] caespitenone,[32] and 6-hydroxycaespitol[28] may originate through path **c**. Cyclization of the $Br^+/^-OH$ addition product of **5** will produce caespitane. Thus, we propose a unified pathway for the biogenesis of regular, irregular rearranged, and degraded bisabolene-type metabolites isolated from red algae of genus *Laurencia* and the sea hares that thrive on them.

Until now all reported marine algal bisabolene-type metabolites bear a vicinal chlorobromo system on their carbocyclic ring. However, the corresponding dehalogenated derivatives of caespitol and caespitenone, compounds **2** and **3**, respectively, have been found for the first time as naturally occurring metabolites in *A. dactylomela*, suggesting that these compounds have been chemically transformed by the mollusc to store them as less toxic compounds. This statement is supported by the recent finding that the naturally occurring deschloroelatol found in *A. dactylomela* is less toxic than the co-occurring chlorinated elatol.[33] This resembles the known[38,39] strategy used by *A. dactylomela* by which some acquired algal metabolites are occasionally acetylated to decrease the toxicity[33] of the corresponding alcohols.

Furthermore, the butenolide unit is widespread in natural products from terrestrial to marine organisms and irrespective of an isoprenic or polyketide origin, has been purported to possess enzyme-inhibiting functions.[40] Plants appear to use lactones to prevent being eaten and to avoid biofouling by bacteria while some animals use lactones to regulate their biochemical processes.[40] Since the butenolide **4** does not occur as an algal metabolite a question arises as to whether this unit has been biosynthesized by *A. dactylomela* as an additional ability (one more to add to acetylation and dehalogenation) to enhance the fitness of the sea hare.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a Perkin–Elmer model 343 Plus polarimeter using a Na lamp at 20 °C. IR spectra were obtained with a Perkin–Elmer 1600/FTIR spectrometer. EIMS and HRMS spectra were taken on a Vg-Micromass Zab 2F spectrometer. ^{1}H NMR and ^{13}C NMR, HSQC, HMBC, COSY, and NOESY spectra were measured employing a Bruker AMX 500 instrument operating at 500 MHz for ^{1}H NMR and at 125.7 MHz for ^{13}C NMR, using $CHCl_3$ as an internal standard. Two-dimensional spectra were obtained with the standard Bruker software. HPLC separations were performed with a Hewlett–Packard HP 1050 (Jaigel-Sil semipreparative column, 10 μ, 20×250 mm) with hexane–EtOAc mixture. The gel filtration column (Sephadex LH-20) used hexane–MeOH–$CHCl_3$ (3:1:1) as solvent. Merck Si gels 7734 and 7741 were used in column chromatography. The spray reagent for TLC was H_2SO_4–H_2O–AcOH (1:4:20).

3.2. Animal material

Eight specimens of *A. dactylomela* were collected off the SW coast of La Palma Island at −1.5 m depth. Specimens were dissected and their digestive system along with the mantle were separated and analyzed independently.

3.3. Extraction and isolation

A. dactylomela digestive glands were extracted with acetone at room temperature. The extract was concentrated to give a dark green residue (31.0 g) and partitioned with H_2O–CH_2Cl_2. The resulting fraction of CH_2Cl_2 (7.5 g) was then submitted to a gel filtration column to give fraction A (822.9 mg), which was subjected to flash chromatography on Si gel. The fraction eluted with hexane–EtOAc (8:2) gave a mixture that was further separated by HPLC (Jaigel-sil column 20×250 mm, flow 4.5 ml/min, hexane–EtOAc (8:2)) to yield the new sesquiterpene **1** (0.7 mg) and the known compound 8-acetylcaespitol (35.0 mg), caespitane (14.0 mg), and laucapyranoid A (4.0 mg). Fraction D was processed using flash chromatography on Si gel eluting with hexane–EtOAc (1:1) to give a mixture that was further separated by HPLC (Jaigel-sil column, flow 4.5 ml/min, hexane–EtOAc (1:1)) to yield the new compounds **2** (5.5 mg) and **4** (9.0 mg), and the known compound caespitenone (4.9 mg). Caespitol (73.6 mg) was isolated from fraction F by crystallization.

A. dactylomela mantles were extracted and processed following the same scheme. Thus, the acetonic extract was partitioned with H_2O–CH_2Cl_2 and the resulting fraction of CH_2Cl_2 (3.8 g) was submitted to a gel filtration column to give a fraction (308.3 mg), which after flash chromatography on Si gel eluted with hexane–EtOAc (1:1) gave a mixture that was further separated by HPLC (Jaigel-sil column, flow 4.5 ml/min, hexane–EtOAc (1:1)) to yield the new compounds **2** (30.0 mg), **3** (1.5 mg), and **4** (1.3 mg) together with the known metabolites caespitol (3.1 mg), 8-acetylcaespitol (3.3 mg), and furocaespitane (1.4 mg).

3.3.1. Compound 1. Colorless oil; $[\alpha]_D^{25}$ +492 (*c* 0.047, $CHCl_3$); IR ν_{max} (film) 3448, 1722 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 413/415/417/419 $[M-Me-H_2O]^+$ (<1, <1, <1, <1), 403/405/407/409 $[M-MeCO]^+$ (<1, <1, <1, <1), 385/387/389/391 $[M-MeCO-H_2O]^+$ (36, 87, 62, 11), 237/239/241 $[C_8H_{11}OBrCl]^+$ (30, 39, 3), 209/211/213 $[C_7H_{11}BrCl]^+$ (9, 12, 3), 173/175 $[C_7H_{10}Br]^+$ (13, 13); HREIMS 412.9480 (calcd for $C_{14}H_{20}O_2{}^{35}Cl^{79}Br_2$, 412.9518), 402.9596 (calcd for $C_{13}H_{22}O_2{}^{35}Cl^{79}Br_2$, 402.9675), 384.9512 (calcd for $C_{13}H_{20}O^{35}Cl^{79}Br_2$, 384.9569).

3.3.2. Compound 1a. ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.9 (C-7), 81.5 (C-8), 71.1 (C-3), 62.1 (C-2), 59.3 (C-10), 58.2 (C-11), 44.8 (C-6), 42.3 (C-4), 35.7 (C-1), 35.5 (C-9), 31.1 (C-14), 24.8 (C-13), 23.9 (C-15), 23.0 (C-5), 19.1 (C-12).

3.3.3. Compound 2. White powder; $[\alpha]_D^{25}$ −1.72 (*c* 1.74, $CHCl_3$); IR ν_{max} (film) 3384 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* 316/318 $[M]^+$ (<1, <1), 298/300 $[M-H_2O]^+$ (2, 2), 236 $[M-HBr]^+$ (8), 23 (28), 139 (100); HREIMS 316.1050 (calcd for $C_{15}H_{25}O_2{}^{79}Br$, 316.1037), 298.0900 (calcd for $C_{15}H_{23}O^{79}Br$, 298.0932), 236.1751 (calcd for $C_{15}H_{24}O_2$, 236.1776).

3.3.4. Compound 3. Colorless oil; $[\alpha]_D^{25}$ −90.9 (*c* 0.03, $CHCl_3$); IR ν_{max} (film) 1738 cm^{-1}; ^{1}H and ^{13}C NMR, see

Table 1; EIMS *m/z* 234 $[M]^+$ (<1), 219 $[M-Me]^+$ (1), 140 (94), 125 (61), 96 (100); HREIMS 234.1665 (calcd for $C_{15}H_{22}O_2$, 234.1619), 219.1412 (calcd for $C_{14}H_{19}O_2$, 219.1385).

3.3.5. Compound 4. White powder; $[\alpha]_D^{25}$ +55 (*c* 0.25, $CHCl_3$); IR ν_{max} (film) 3352, 1751 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; EIMS *m/z* 322/324/326 $[M]^+$ (<1, <1, <1), 307/309/311 $[M-Me]^+$ (25, 33, 9), 243/245 $[M-Br]^+$ (20, 6), 225/227 $[M-Br-H_2O]^+$ (77, 26), 207 $[M-HBr-Cl]^+$ (100); HREIMS 321.9934 (calcd for $C_{12}H_{16}O_3{}^{35}Cl^{79}Br$, 321.9971), 306.9639 (calcd for $C_{11}H_{13}O_3{}^{35}Cl^{79}Br$, 306.9736), 243.0723 (calcd for $C_{12}H_{16}O_3{}^{35}Cl$, 243.1643), 225.0595 (calcd for $C_{12}H_{14}O_2{}^{35}Cl$, 225.0682), 207.0933 (calcd for $C_{12}H_{15}O_3$, 207.1021).

3.3.6. Compound 4a. ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 172.6 (C-10), 170.4 (C-8), 116.3 (C-9), 106.8 (C-7), 70.2 (C-3), 60.7 (C-2), 41.9 (C-4), 39.7 (C-1), 36.8 (C-6), 28.6 (C-5), 23.9 (2C, C-11, C-12).

3.4. Dehalogenation of caespitol

A solution of caespitol (20.0 mg) in DMF (1.5 ml) was treated with NaI–Zn and stirred at 115 °C for 2 h. The reaction was quenched with H_2O and extracted with EtOAc to give a mixture that after silica gel chromatography (hexane–EtOAc, 95:5) gave 7.9 mg of compound **2**.

3.5. Oxidation of compound 2

A solution of compound **2** (12.4 mg) in acetone was treated with Jones reagent and stirred at room temperature for 1.5 h. The reaction was quenched with H_2O and extracted with EtOAc to give 8.3 mg of compound **3**.

Acknowledgements

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Two novel blue pigments with ellagitannin moiety, rosacyanins A1 and A2, isolated from the petals of *Rosa hybrida*

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Abstract—Two novel blue pigments, rosacyanins A1 and A2, were isolated from the petals of *Rosa hybrida* cv. 'M'me. Violet'. Their structures were elucidated on the basis of high-resolution Fourier transform ion cyclotron resonance mass spectroscopy (HR-FT-ICR-MS), FABMS/MS/MS, ^{1}H, ^{13}C and two-dimensional NMR. The molecular formulas of rosacyanin A1 (**1**) and A2 (**2**) are $C_{56}H_{37}O_{31}$ and $C_{63}H_{41}O_{35}$, respectively. The structures of rosacyanins A1 and A2 consisted of a common chromophore containing cyanidin with a galloyl group link between positions 4 and 5 of the hydroxyl group of the flavylium nucleus and tellimagrandins (1 or 2). These pigments in which anthocyanidin nuclei linked to ellagitannin through an ether bond are the first compounds isolated from natural sources.

1. Introduction

Flower colour is mainly determined by the structures of anthocyanins. In particular, the structures of the chromophores, i.e., anthocyanidins, are important. Most blue flowers contain delphinidin-type anthocyanins, while orange to red flowers contain pelargonidin- and cyanidin-type anthocyanins.[1] Several factors in addition to anthocyanidin structure influence flower colour. It is well known that the bathochromic shift of anthocyanins is caused by their structure and interaction with co-existing compounds and the vacuolar pH.[1] The factors that contribute to the blue colour in flowers are (1) inter-molecular co-pigmentation with flavone or flavonol,[2] as reported for *Iris ensata* Thunb;[3] (2) intramolecular co-pigmentation, as observed in polyacylated anthocyanin, e.g., in *Gentiana makinoi*,[4] *Ipomoea tricolour*,[5] *Platycoden grandiflorum*,[6] *Clitoria ternatea*,[7] and *Senecio cruenthus*;[8] (3) high vacuolar pH, as in *Ipomoea tricolour* cv. 'Heavenly Blue';[9] (4) formation of a metal complex[10] (often called metallo-anthocyanin), such as commelinin isolated from *Commelina communis*[11] and *Hydrangea macrophylla*;[12] (5) the intra-molecular bonding of anthocyanidin and flavone in one molecule;[13,14] and (6) the intra-molecular co-pigment and high vacuolar pH occurring in one *Petunia hybrida* mutant[15] and a combination of these. Anthocyanins are usually stable under acidic conditions, when anthocyanins form a flavylium cation and exhibit red colour; on the other hand, under neutral and weakly acidic conditions, anthocyanins form a violet quinonoidal base[1] that is stabilised via intra-molecular co-pigmentation by polyacylation, as is the case for triacylated heavenly blue anthocyanin in *Ipomoea tricolour*[5] and diacylated gentiodelphin in *Gentiana makinoi*.[16]

Hybridisation breeding of floricultural plants has contributed to increase the number of flower colour varieties. However, rose breeders have failed to obtain blue roses. Roses cannot synthesise delphinidin in their petals due to a deficiency of the flavonoid 3′,5′-hydroxylase gene,[17] which is critical to synthesise delphinidin. In addition, roses usually have low vacuolar pH and the anthocyanins in the petals

Keywords: Rose; *Rosa hybrida*; Rosacyanin; Anthocyanidin; Ellagitannin; Blue pigment; FABMS/MS/MS; ^{13}C isotope shift.
Abbreviations: TFA, trifluoroacetic acid (CF_3COOH); TFA-*d*, CF_3COOD; DMSO-d_6, $(CD_3)_2SO$; MeOH, methanol; EtOH, ethanol; BuOH, *n*-butanol; HPLC, high-pressure liquid chromatography; t_R, retention time; FABMS, fast atom bombardment mass spectrometry; ESIMS, electro spray ionisation mass spectrometry; HR-FT-ICR-MS, high-resolution Fourier transform ion cyclotron resonance mass spectrometry; NMR, nuclear magnetic resonance; DQF-COSY, double quantum filtered correlation spectroscopy; NOESY, nuclear Overhauser and exchange spectroscopy; ROESY, rotating frame Overhauser enhancement spectroscopy; TOCSY, total correlation spectroscopy; $^{1}H\{^{13}C\}$-HSQC, $^{1}H\{^{13}C\}$-heteronuclear single quantum coherence; $^{1}H\{^{13}C\}$-HMBC, $^{1}H\{^{13}C\}$-heteronuclear multiple bond correlation; CD, circular dichroism; FTIR, Fourier transform infrared spectroscopy.
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are rarely acylated, if at all; rose anthocyanins are pelargonidin/cyanidin 3-glucoside or 3,5-diglucoside, in which the cyanidin or pelargonidin was modified by one or two sugar molecules.[18] Rose petals do not contain flavones, which have stronger co-pigment effects than the flavonols that roses accumulate. Therefore, roses lack the genetic background to become blue. Genetic engineering of roses makes it possible to generate varieties with a novel blue hue; these varieties express a heterologous F3′5′H gene and accumulate delphinidin almost exclusively.[19] During our research for blue pigments from a large variety of roses, we found a small number of blue pigments (rosacyanin As) that mauve-type roses, such as 'M'me. Violet,' contain and have been studying their structure. In a previous study, we reported the structure of rosacyanin B,[20] which is a chromophore skeleton of rosacyanin As. The accumulation of rosacyanin As may be a better way to engineer blue roses than that of delphinidin, as rosacyanin As are consistently blue even when co-pigments and metal ions are absent and the vacuolar pH is low. In this paper, we reveal the unique structure of rosacyanin As, in which rosacyanin B and tannin bind together.

2. Results and discussion

2.1. Structural determination of rosacyanins A1 and A2

2.1.1. Structure of rosacyanin A1. Rosacyanin A1 (**1**) showed four absorption maxima in the UV–vis region [585 nm (log ε, 4.33), 424 nm (3.75), 354 nm (3.96) and 263 nm (4.65) in HCl/MeOH]. The addition of $AlCl_3$ to the MeOH solution caused a bathochromic shift of the λ_{max} from 590 to 622 nm. This phenomenon of rosacyanin A1 is usually diagnostic of the presence of the *ortho* hydroxyl group in the B-ring. In the visible spectrum of **1**, the λ_{max} and optical density of **1** at pH 1–8 are shown in Table 1. The λ_{max} values were very different from those of typical anthocyanins, such as malvidin 3,5-diglucoside.[21]

In the positive mode, the FABMS of **1** showed a molecular ion at *m*/*z* 1205 $[M]^+$ and in the negative mode, FABMS gave a molecular ion peak at *m*/*z* 1203 $[M-2H]^-$. The molecular formula of **1** was established on the basis of high-resolution Fourier transform ion cyclotron resonance mass spectra (HR-FT-ICR-MS), as $C_{56}H_{37}O_{31}$ was supported by a molecular ion peak at *m*/*z* 1205.13255 $[M]^+$ (err. −1.009 ppm).

The ^1H NMR spectrum of **1** showed the duplication of each proton signal (totally 1H), which is characteristic of anomeric mixture formation.[22] However, all proton signals in the sugar region of the two anomers were unambiguously distinguished from each other by ^1H–^1H COSY and the axial orientation of H-2, 3, 4 and 5, except for the anomeric proton H-1 (α-form: δ 5.30, J=2.0 Hz; β-form: δ 4.64, J=8.0 Hz) in the glucopyranose moiety, was evident from the coupling constant of the signals (Table 2).

Table 1. Change of the absorption maxima and optical densities of rosacyanin A1 in pH 1–8

pH	λ_{max} (nm)	Optical density
1	567.0	0.1157
2	565.5	0.1274
3	557.5	0.1368
4	554.5	0.1455
5	555.0	0.1467
6	557.0	0.1390
7	564.0	0.1312
8	573.0	0.1392

The solution used for pH 1 and 2 was a Tris–HCl buffer and that for pH 3–8 was a McIlvaine buffer.

Additionally, the H-6 methylene proton signals of the glucose moiety were observed at δ 3.60 and 5.03 in the α-anomer (δ 3.77 and 5.00 in the β-anomer) and the H-4 proton signal of the glucose moiety was observed at δ 4.87 in the α-anomer (δ 4.97 in the β-anomer). The H-6 proton had $^1H\{^{13}C\}$-HMBC cross peaks at δ 166.91 (Ha-7), while the H-4 proton had them at δ 167.64 (Hb-7′). The large difference in the chemical shift between geminal protons at the C-6 position is characteristic of an ellagitannin having an esterified hexahydroxydiphenoyl (HHDP) group at C-4/C-6 of the hydroxyl groups on the glucose moiety in many hydrolysable tannins.[22] The Ha-3 (δ 6.29) and Hb-3′ (δ 6.22) signals showed a cross peak with the carboxylic carbonyl carbon signals Ha-7 and Hb-7′, respectively (Fig. 1).

Among the glucose proton signals, the H-2 and H-3 [δ 4.96 and 5.66 in the α-anomer (δ 4.83 and 5.51 in the β-anomer)] signals were shifted to a lower magnetic field from the corresponding glucose. In the ^1H NMR spectrum of **1**, the presence of two galloyl groups was revealed by the galloyl proton signals (δ 6.85, 6.78 each s, 2H in total and δ 6.78, 6.79 each s, 2H in total) with $^1H\{^{13}C\}$-HMBC correlation through carbonyl carbons (δ 165.11 and 165.40).

The enzymatic hydrolysis of **1** with tannase yielded degalloyl rosacyanin A1 (**4**). Its HR-FT-ICR-MS exhibited a molecular ion at *m*/*z* 901.10994 $[M]^+$ and the molecular formula was $C_{42}H_{29}O_{23}$, losing two molecules of the galloyl moieties from the molecular ion of **1**.

In order to clarify all the proton signals of **1** and **4**, their $NaBH_4$ reduction gave the dihydro derivatives **5** and **6**, respectively (Scheme 1). HR-FT-ICR-MS of **5** and **6** exhibited a molecular ion at *m*/*z* 1207.14794 $[M]^+$ ($C_{56}H_{39}O_{31}$) and 903.12406 $[M]^+$ ($C_{42}H_{31}O_{23}$), respectively. These products, **5** and **6**, allowed a straightforward structural elucidation in the NMR spectrum. The assignments of the ^1H and ^{13}C signals of **5** and **6** are shown in Tables 2 and 3.

For further details of the structural determination, $^1H\{^{13}C\}$-HMBC of compound **6** was measured, and its network and numbering of atoms are shown in Figure 2. Thus, the 1H singlet proton signal (δ 6.28) due to Hb-3′ showed a cross peak with the ester carbonyl carbon Hb-7′ signals (δ 170.56) on the same ring and the Ha-1 aromatic carbon signal (δ 115.67) of the neighbouring Ha benzene. On the other hand, the 1H singlet proton signal (δ 6.69) due to Ha-3 also observed a cross peak with the Ha-7 carbon signal (δ 169.36) and the Hb-1′ carbon (δ 115.91), indicating that two gallate moieties formed an HHDP group by connecting with a C–C bond. In addition, two carboxylic carbonyl carbons (δ 169.36 and 170.56) of the HHDP group correlated through three-bond coupling with the H-4 proton (δ 4.74) and H-6 methylene protons (δ 4.39 and 3.66) on the glucitol moiety, suggested

Table 2. ^{1}H NMR assignment of compounds **1**, **2**, **5**, **6** and **7**

	1: α-form	**1**: β-form	**2**	**5**	**6**	**7**
Chromophore						
A-6	6.82d (2)	6.81	6.84d (2)	6.82br s	6.28 (1)	6.89d (1)
A-8	6.98d (2)	6.98	7.04d (2)	7.01br s	6.36d (1)	7.06d (1)
B-2′	8.33d (2)	8.34	8.32d (2)	8.32br s	7.63d (2)	8.14br s
B-5′	6.96d (8)	6.96	6.97d (8)	6.96d (8)	6.60d (8)	6.92d (9)
B-6′	8.10dd (2, 8)	8.10	8.08dd (2, 8)	8.07d (8)	7.65dd (2, 8)	8.11dd (1, 9)
D-3″	6.80s	6.80	6.78s	6.77s	6.49s	6.85s
HHDP						
Ha-3	6.29s	6.26s	6.26s	6.72s	6.69s	7.17s
Hb-3′	6.22s	6.22s	6.23s	6.13s	6.28s	7.56s
Glucose				Glucitol	Glucitol	
1 (a)	5.30d (2)	4.87d (8)	6.14d (8)	3.73br d (8)	3.54dd (4, 13)	
1b				3.62br d (8)	3.45m	
2	4.96dd (2, 9)	4.83t (9)	5.34dd (8, 10)	5.12br d (8)	3.52dd (4, 5)	
3	5.66t (10)	5.51t (10)	5.76t (10)	5.79d (8)	3.71dd (1.5, 5)	
4	4.87t (10)	4.97t (10)	4.92t (10)	5.05d (8)	4.74dd (1.5, 8.5)	
5	4.49dd (7, 10)	4.28dd (7, 10)	4.59ddd (2, 6, 10)	3.80d (8)	4.11dd (2, 8.5)	
6a	5.03dd (7, 12)	5.00dd (7, 12)	5.04dd (6, 12)	4.24br d (12)	4.39dd (2, 13)	
6b	3.67d (12)	3.77br d (12)	3.76dd (2, 12)	3.68br d (12)	3.66d (13)	
GA						
GA1-2,6			6.87s			
GA2-2,6	6.85s	6.79s	6.796s	6.85s		
GA3-2,6	6.78s	6.78s	6.805s	6.78s		

Chemical shift in δ (*J* in hertz). Compounds **1**, **2**, **5** and **7** were measured in DMSO-d_6 containing 1% DCl and compound **6** was measured with coaxial tube in CD_3CN:D_2O:TFA-*d*=50:50:0.5 (inner tube)/CD_3CN:H_2O:TFA=50:50:0.5 (outer tube).

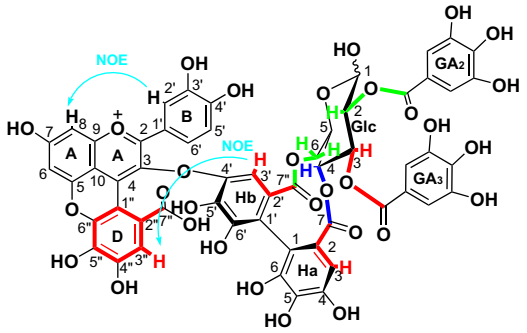


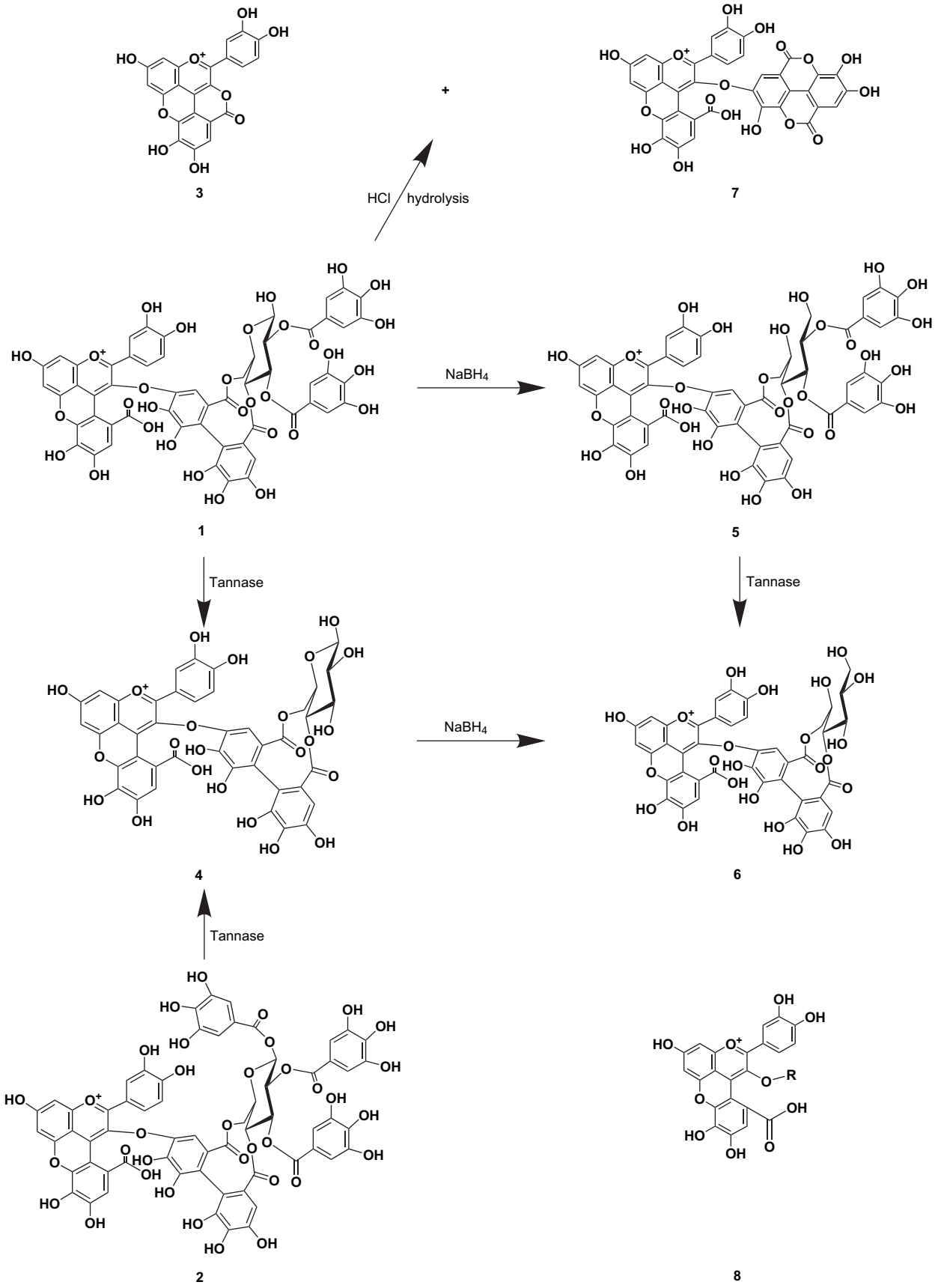
Figure 1. Structure of compound **1** with HMBC and NOE. The significant HMBCs are shown in coloured bonds. NOE is shown with arrows. Atom numbers are shown on each atom.

that **1** has a kind of ellagitannin, the tellimagrandin 1[23,24] moiety.

The findings described above were also supported by FABMS/MS fragment ions at *m/z* 721 generated by cleavage, as shown in Figure 3. In addition to the above-mentioned proton signals, five of the six 1H proton signals in the aromatic region were attributed to H-6 (δ 6.82, d, 2) and H-8 (δ 6.98, d, 2) in the A ring and H-2′ (δ 8.33, d, 2), H-5′ (δ 6.96, d, 8) and H-6′ (δ 8.10, dd, 2, 8) in the B-ring of the flavylium form of the cyanidin nucleus. The low-field singlet (δ 8.60–9.10) characteristic of the H-4 of anthocyanidin was missing in the spectrum of **1**. In the ^{1}H{^{13}C}-HMBC spectrum of **1**, the remaining proton signal (D-3″: δ 6.80, s) showed cross peaks with five carbon signals of a benzene ring and the carbonyl carbon signal at δ 166.17 (Fig. 1) as well as with rosacyanin B.

FABMS/MS for the molecular ion *m/z* 1205 $[M]^+$ showed fragment ion peaks at *m/z* 153, 420, 721 and 1053, and the prominent ion at *m/z* 420 generated the ether bond cleavage between the C-3 of cyanidin in the chromophore and tellimagrandin 1 moiety, as shown in Figure 3 (Supplementary Fig. 1). FABMS/MS/MS of **1** for the ion at *m/z* 420 gave fragment ion peaks at *m/z* 137 and 109; these were the same as those observed in the FABMS/MS spectrum of rosacyanin B[20] or flavone.[25] These facts suggested that the C-4 position of the cyanidin nucleus in **1** was substituted with the gallic acid moiety as in rosacyanin B. Therefore, these results indicated that **1** consisted of a cyanidin nucleus with C-4 gallate (the chromophore part) and tellimagrandin 1 (the tannin part).

In order to determine the linkage position of the chromophore and tannin parts, we assigned all of the ^{1}H and ^{13}C NMR signals of **6** using ^{1}H{^{13}C}-HSQC, ^{1}H{^{13}C}-HMBC, TOCSY and DQF-COSY, as shown in Tables 2 and 3. Next, a deuterium-induced ^{13}C isotope shift experiment of **6** in 50% CD_3CN/D_2O with TFA-*d* and 50% CD_3CN/H_2O with TFA was carried out. All carbon signals bearing the hydroxyl or phenolic hydroxyl group were observed as a doublet with an isotope shift, except for two singlet carbon signals at δ 145.06 due to A-3 of the cyanidin nucleus and at δ 146.97 attributed to Hb-4 of the HHDP group (Supplementary Fig. 2). In addition, the D-7 carboxy-carbonyl carbon signal at δ 167.57 appeared as a doublet peak and shifted to a lower magnetic field than that in rosacyanin B (δ 156.67). In the FTIR spectrum of **1**, rather than the disappearance of a peak due to the α-pyrone ring at 1725 cm^{-1} that was noted in rosacyanin B, a peak attributed to the carboxylic group was observed at 1707 cm^{-1}. In the NOESY spectrum of **6**, the NOE correlation of the signal of D-3″ with the signal of Hb-3′ of the HHDP moiety suggested a spatial proximity of the D gallory ring to Hb of HHDP (Fig. 4). In addition, the 6 N-HCl hydrolysis of **1** gave gallic acid, cyanidin, rosacyanin B and an unknown blue pigment



Scheme 1. Structure of rosacyanins and their derivatives: **1**, rosacyanin A1; **2**, rosacyanin A2; **3**, rosacyanin B; **4**, degalloyl rosacyanins A1 and A2; **5**, $NaBH_4$ reduced rosacyanin A1; **6**, degalloyl $NaBH_4$ reduced rosacyanin A1; **7**, HCl hydrolysed rosacyanin A1; **8**, chromophore moiety of rosacyanins A1 and A2.

Table 3. ^{13}C NMR assignment of compounds **1**, **2**, **5**, **6** and **7**

	1 (α-form)		**2**		**5**	**6**	**7**	
Chromophore								
A-2	156.76		156.53		156.56	157.79s	156.7	
A-3	145.30		145.16		145.17	145.06s	145.3	
A-4	132.13		131.88		132.03	131.06s	131.9	
A-5	149.94		149.76		149.84	150.19s	150.2	
A-6	99.41		99.20		99.29	100.33s	99.1	
A-7	162.66		162.49		162.63	163.12s	163.0	
A-8	96.77		96.58		96.65	97.68s	96.4	
A-9	150.87		150.71		150.79	151.20s	150.9	
A-10	106.50		106.35		106.38	106.86s	106.5	
B-1′	122.31		122.13		122.15	123.20s	122.2	
B-2′	117.61		117.08		117.17	117.63s	116.9	
B-3′	144.59		145.00		144.36	145.15d	145.4	
B-4′	151.22		150.91		151.07	151.46d	151.2	
B-5′	116.18		115.58		116.79	116.43s	115.1	
B-6′	123.87		123.28		123.70	126.12s	124.2	
D-1″	113.37		111.21		111.19	113.58s	111.6	
D-2″	111.37		111.21		111.19	112.53s	111.6	
D-3″	101.80		101.50		101.60	104.79s	101.7	
D-4″	150.30		150.13		150.10	151.11d	151.4	
D-5″	139.74		139.27		140.03	140.66d	139.0	
D-6″	139.14		136.69		139.17	138.47s	138.7	
D-7″	166.17		166.01		166.13	167.57d	165.8	
HHDP								
Ha-1	115.00		114.78		115.36	115.67s	114.2	
Ha-2	123.72		123.65	a	123.03	125.16s	123.1	c
Ha-3	105.39		105.19		106.38	108.83s	109.5	
Ha-4	144.59		144.25		144.36	145.41d	148.5	
Ha-5	135.37		135.12		135.58	136.71d	140.6	
Ha-6	144.72		144.53	b	145.10	144.56d	145.9	d
Ha-7	166.91		166.71		167.07	169.36s	159.1	
Hb-1′	117.30		117.55		116.07	115.91s	111.8	
Hb-2′	123.60		123.43	a*	124.70	126.82s	123.8	c*
Hb-3′	104.48		104.64		103.79	104.7s	110.5	
Hb-4′	145.64		145.33		144.73	146.97s	148.6	
Hb-5′	136.70		139.68		136.01	136.28d	139.4	
Hb-6′	144.59		144.38	b*	145.10	144.8d	146.9	d*
Hb-7′	167.64		167.27		168.75	170.56s	158.9	
Glucose	≅–form							
1	89.73		91.87		59.14	63.29d		
2	72.17		70.39		72.88	72.91d		
3	69.90		71.58		69.61	69.96d		
4	70.22		69.52		72.07	75.83s		
5	65.68		71.03		66.97	68.35d		
6	62.65		61.85		67.47	68.87s		
GA (Glc-2,3)								
GA2-1	118.76		118.0		118.90			
GA2-2,6	108.89		108.74		108.80			
GA2-3,5	145.51		145.07		145.17			
GA2-4	138.76		138.79		138.21			
GA2-C═O	165.11		164.22		165.10			
GA3-1	118.77		117.83		119.38			
GA3-2,3	108.82		108.61		108.90			
GA3-3,5	145.30		145.25		145.26			
GA3-4	138.93		138.60		138.46			
GA3-C═O	165.40		165.01		165.40			
Glucose	≅–form		GA1 (Glc-1)					
1	95.1	GA1-1	117.20	a and a*, b and b*, c and c*, d and d*, these				
2	70.2	GA1-2,6	108.86	signals may be interchangeable with each other.				
3	72.2	GA1-3,5	145.39					
4	73.1	GA1-4	139.08					
5	70.2	GA1-C═O	163.80					
6	62.6							

Chemical shift in δ. Compounds **1, 2, 5** and **7** were measured in DMSO-d_6 containing 1% DCl and compound **6** was measured in CD_3CN/D_2O containing TFA-*d*. In the chemical shift of compound **1** in the β-form, only the glucose moiety is distinguishable. In compound **6,** s means singlet and d means doublet in the isotope shift.

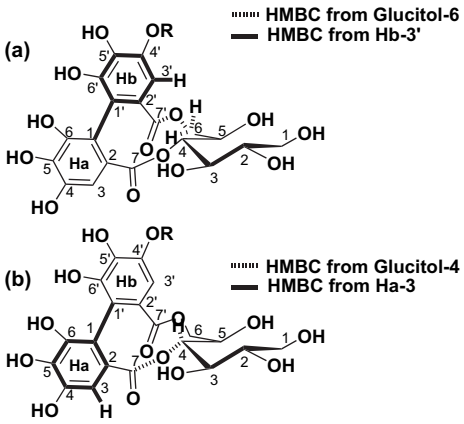


Figure 2. Long-range HMBC of **6** in the tannin part. (a): The HMBCs from the Hb-3′ proton are shown in thick lines, (b): the HMBCs from the Ha-3 proton are shown in thick lines. Both protons have cross peaks to the C-1 carbon on the opposite benzene.

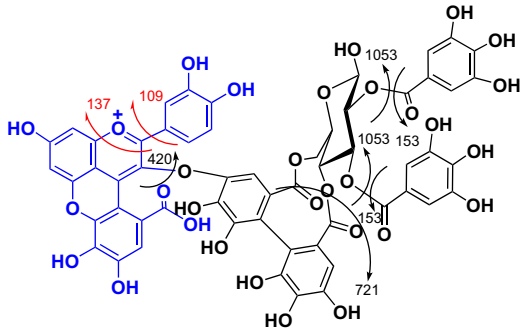


Figure 3. FABMS/MS and MS/MS/MS assignments of **1**. Black arrows show the MS/MS assignment from *m/z* 1205 and red arrows show the MS/MS/MS assignment from *m/z* 420.

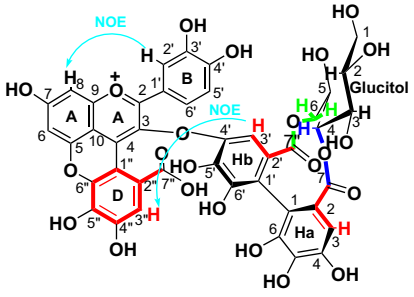


Figure 4. HMBC and NOE of compound **6**.The significant HMBCs are shown in coloured lines. NOE is shown with arrows. Atom numbers are shown on each atom.

(**7**), which had λ_{max} of 590 nm in 90% CH_3CN with 0.5% TFA. ESIMS of **7** exhibited molecular ions at *m/z* 721 $[M]^+$, losing two molecules of the galloyl groups, two H_2O molecules and one glucose molecule from the molecule of **1**. In the ^1H NMR spectrum of **7**, all proton signals were only observed in the aromatic region, namely, two proton signals due to the ellagic acid group (δ 7.17, s and 7.56, s), five *ortho*- and *meta*-coupled signals attributed to the flavylium nucleus (δ 6.89, d, J=1; 7.06, d, J=1; 8.14, br s; 6.92, d, J=9; 8.11, dd, J=9.1) and one additional proton signal assigned to D-3 on the galloyl moiety (δ 6.85, s). Furthermore, the chemical shifts of two carbonyl carbons (δ 159.14 and 158.92) coincided with those of α-pyrone ring systems,

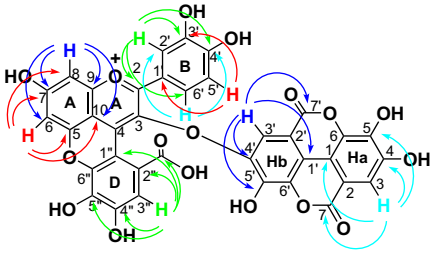


Figure 5. HMBC of compound **7**. The HMBC network of compound **7** is shown with curved arrows.

such as rosacyanin B[20] and ellagic acid.[26] The $^1H\{^{13}C\}$-HMBC spectrum supported the structure of **7**. Thus, the structure of **7** was illustrated by the formula with the HMBC network shown in Figure 5.

In the CD spectrum, **1** has a positive cotton effect at around 260 nm, similarly to tellimagrandin 1; therefore, the HHDP moiety has an *S* configuration, which is the same as tellimagrandin 1. Considering the results reported above, the structure of rosacyanin A1 was proposed to be **1**, as shown in Figure 1.

2.1.2. Structure of rosacyanin A2. The UV–vis spectrum of rosacyanin A2 (**2**) is very similar to that of **1** and had λ_{max} 585 nm. The molecular formula of **2** was determined to be $C_{63}H_{41}O_{35}$ on the basis of a molecular ion at *m/z* 1357.144794 $[M]^+$ (err. −1.633 ppm) in its HR-FT-ICR-MS. The molecular ion at *m/z* 1357 $[M]^+$ increased 152 mass units, corresponding to one molecule of the galloyl group, compared to the peak of the molecular ion of **1** at *m/z* 1205 $[M]^+$. In the positive mode, FABMS/MS of **2** from *m/z* 1357 gave a fragment ion at *m/z* 420, which was the same chromophore (**8**) as rosacyanin A1. The ^1H and ^{13}C NMR spectra of **2** indicated the presence of chromophore (**8**), three galloyl groups, an HHDP and a glucose moiety. In ^1H NMR, the anomeric proton of **2** was observed as a doublet with a coupling constant of 8 Hz at δ 6.14 demonstrating that an additional β-oriented galloyl group in **2** was substituted at the C-1 position on the glucose moiety. Moreover, the tannase hydrolysis of **2** yielded degalloyl rosacyanin A1 (**4**). This finding and the NMR result (Tables 2 and 3) suggested that the structure of **2** was gallate-esterified at C-1 of the glucose moiety. The tannin part of **2** was identified as tellimagrandin 2.[23] In the CD spectrum, **2** has a positive cotton effect around 260 nm and the HHDP moiety has an *S* configuration that is identical to that of tellimagrandin 2. Finally, the structure of rosacyanin A2 was established as **2**, as shown in Figure 6.

2.2. Properties of rosacyanins

Since both rosacyanins (**1** and **2**) have their 4-position substituted, it is predicted that this substitution affects the properties of these rosacyanins in a neutral or weakly acidic aqueous solution. This is because the substitution at position 4 of the flavylium cation affects the distribution of the charge throughout the molecule and, as a result, positions 2 and 4 become less reactive to the nucleophilic attack.[27] Thus, the presence of a 4-substituent on the cyanidin nuclei provides great resistance to hydration at the 2-position; in other words, it increases the stability of the anthocyanidin nuclei.

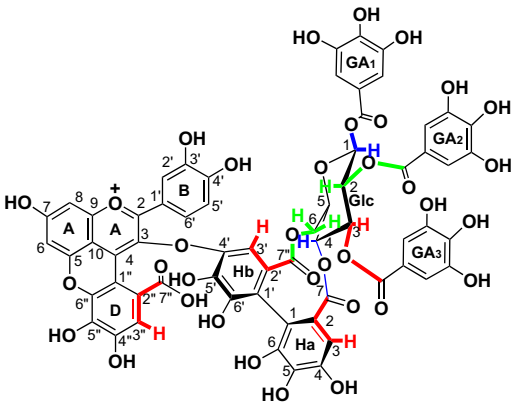


Figure 6. Structure and HMBC of rosacyanin A2 (**2**). The significant HMBCs are shown in coloured lines. Atom numbers are shown on each atom.

Under acidic condition (pH<2), the flavylium cation form (Fig. 7a1) and the pyrylium cation form (Fig. 7a2) are predominant, whereas under weakly acidic conditions (pH 3–6), the opposite is true, i.e., it displays a violet quinonoidal form (Fig. 7b1–3). Above pH 7, a quinonoidal base anion structure (Fig. 7c1–3) that is blue in colour is formed. In the pH range of 3–6, the λ_{max} of rosacyanin shifted from 567 to 555 nm. An explanation for this hypochromic effect may be that the positive charge on the flavylium ring may be delocalised by resonance and reside largely on the oxygen atom on the newly formed pyrylium ring (Fig. 7a1). Thus, the chromophore of rosacyanin has many resonance forms to inhibit hydration at the 2-position, which is the hydrobase.

In general, simple anthocyanins, mono- or diglucoside, are red or orange at low pH; however, under weakly acidic conditions, their 2-positions are easily hydrated and become colourless pseudobases. Rosacyanins are blue or violet in a wide pH range (pH 1–7). A possible explanation for the bluing mechanism of rosacyanin molecules may be that they form a horizontally or vertically stacked molecule. No NOE, however, was observed at the signals of the tellimagrandin 1 moiety between the cyanidin nuclei, but NOE was observed between A-8 and B-2″/B-6″, suggesting that the protons on the cyanidin nucleus and tellimagrandin 1

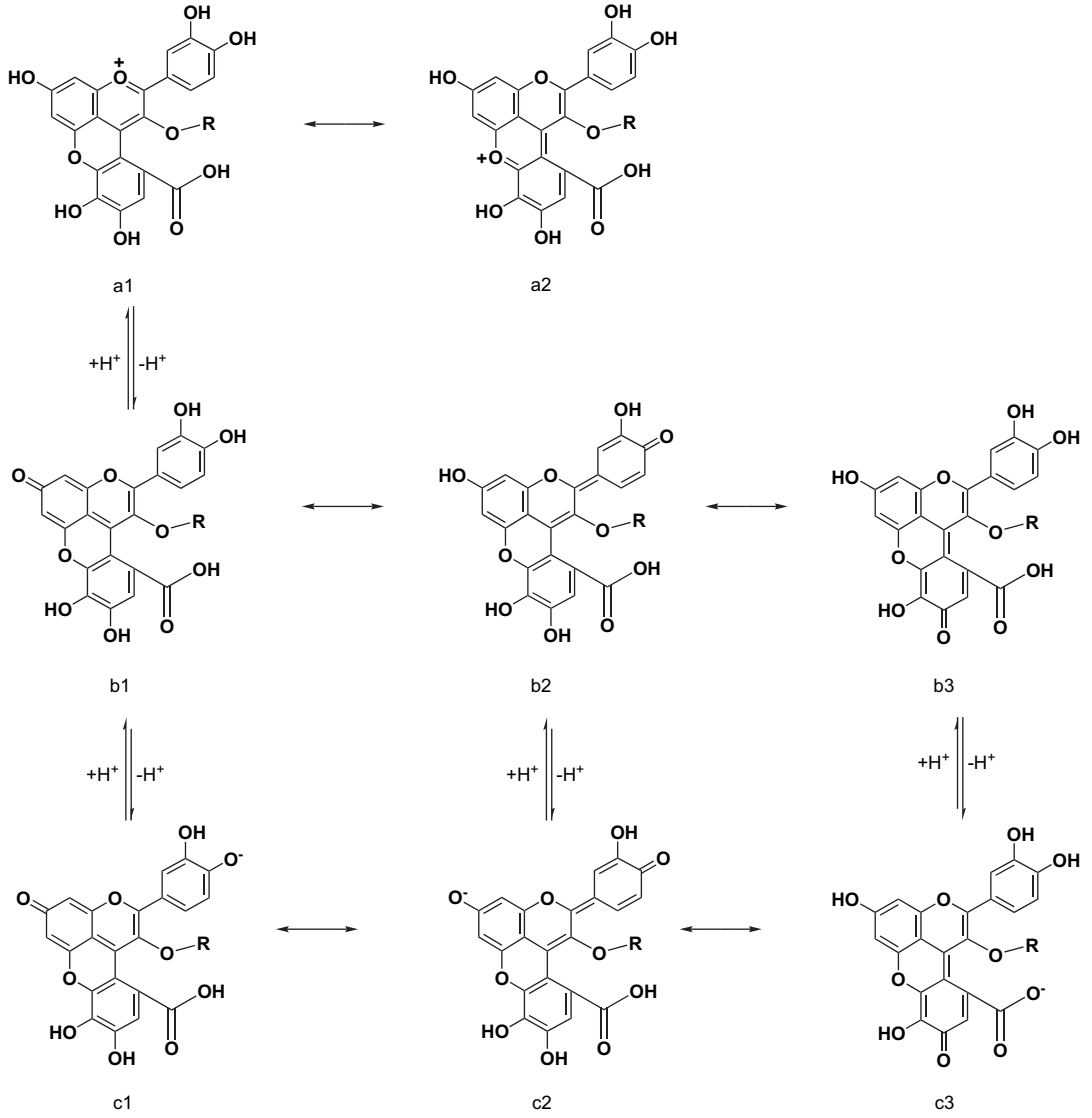


Figure 7. Possible mesomeric forms of the chromophore of rosacyanin: a1, flavylium cation; a2, pyrylium cation; b, quinonoidal base; b1, A7 oxo-type; b2, B4′ oxo-type; b3, D4″ oxo-type; c, quinonoidal base anion; c1, A7 oxo-type; c2, B4′ oxo-type; c3, D4 ″ oxo-type.

are located at a greater distance than A-8 and B-2″/B-6″ (Fig. 1). Therefore, the chromophore of rosacyanins is considered to have no intra-molecular stacking with any aromatic ring in the HHDP and galloyl groups of the tellimagrandin 1 moiety.

2.3. Conclusion

We have found mauve roses containing a small amount of blue pigments co-existing with a red anthocyanin and cyanidin 3,5-diglucoside, and determined that the coexistence of a small quantity of the present blue pigments (rosacyanins) is the reason that the roses look bluish. These pigments are called 'rosacyanin' because of their true blue colour and they were isolated from the petals of *Rosa hybrid* cv. 'M'me. Violet'.

Rosacyanins A1 (**1**) and A2 (**2**) had a common chromophore, which contained cyanidin with a galloyl group link between positions 4 and 5 of the hydroxy group of the flavylium nucleus, and tellimagrandin 1 and 2, respectively, at C-3 of cyanidin nucleus.

To our knowledge, this is the first natural pigment in which the flavylium nucleus binds to ellagitannin but not through sugar. Similar compounds, including tannins, are known and have been isolated from *Camellia japonica* L.,[28] *Quercus* and *Castanopsis asicies*,[29,30] in which the sugar moieties of ellagitannins bind to catechin by the C–C bond.

The HCl hydrolysis product (**7**) of **1** has λ_{max} 590 nm and is still blue. When the bluish polyacylated anthocyanins isolated hitherto, such as gentiodelphin,[16] were compared with rosacyanins (**1** and **2**) or **7**, the bathochromic shift of the latter pigments was not explained as former pigments result from the stacking of the chromophore and tannin moieties. This is because no NOE was observed between the signals of the cyanidin nucleus proton between the tellimagrandin moieties. From now on, detailed studies will be conducted to elucidate the bluish mechanism on rosacyanins and their derivative molecules.

Rosacyanins, which not only are 4-substituted but also have their 5 position substituted, showed a greater resistance to hydration, a greater colour expression at higher pH values and increased stability of the molecules. Rosacyanins are thought to be biosynthesised by an enzymatic cycloaddition or by a nucleophilic and electrophilic addition of cyanidin with a large amount of tellimagrandin 1 and 2 distributed in the rose petals.[31,32] It is very interesting that cyanidin changed to blue by binding to tellimagrandin, although the change cannot be attributed to coexistence with tellimagrandin 1, but with pentagalloyl-glucose.[32,33] The accumulation of a large amount of rosacyanins in the petals will result in a blue rose.

3. Experimental

3.1. General

Compounds **1**, **2**, **5** and **7** were dissolved in DMSO-d_6 containing 1% DCl and compound **6** was dissolved in 50% CD_3CN/D_2O containing 0.5% TFA-*d*; ^1H NMR, ^{13}C NMR, $^1H\{^{13}C\}$-HSQC, $^1H\{^{13}C\}$-HMBC, TOCSY, DQF-COSY and NOESY spectra were obtained on an AVANCE-750 spectrometer (BRUKER BIOSPIN, Germany). The method used for the $^1H\{^{13}C\}$-HMBC measurement to observe a long-range spin–spin coupling between a proton and a carbon is shown below. To observe a long-range spin–spin coupling between a proton and a carbon, the delay for the evolution of small couplings in the gradient-enhanced HMBC pulse sequence was set to 300 ms. This value optimises the observation at around 1.7 Hz of the spin–spin coupling constant, whereas the usual HMBC delay parameter was set to 65 ms, which is focused on the coupling constant 8 Hz.

The deuterium induced a differential ^{13}C isotope shift[34] that was obtained with a dual sample tube consisting of an inner tube (2.9 mmϕ) with 0.11 mM of **6** in 50% CD_3CN/D_2O with 0.5% TFA-*d* and an outer tube (5 mmϕ) with 0.11 mM of **6** in 50% CD_3CN/H_2O with 0.5% TFA. ^{13}C NMR was measured on a DMX-500 spectrometer (BRUKER BIOSPIN, Germany). The residual proton peaks and ^{13}C peaks of CD_3CN (δ 1.94 for ^1H and δ 1.36: *C*D_3 and 118.32: *C*N for ^{13}C) or DMSO-d_6 (δ 2.50 for ^1H and δ 39.43 for ^{13}C) were used as the internal standard (the assignment of data are shown in Tables 2 and 3).

Fast atom bombardment mass spectra (FABMS) and FABMS/MS or FABMS/MS/MS of **1** and **2** were recorded on a JMS-HX110/HX110A tandem mass spectrometer (JEOL, Japan) in the positive mode with a nitrobenzylalcohol matrix. The ESIMS of **7** was obtained by Q-TOF with a z-spray ion source (Micromass, Manchester, UK) in the positive mode. High-resolution mass spectra (HRMS) of **1**, **2**, **4**, **5** and **6** were recorded on a 9.4T FT-ICR MS APEX-Q spectrometer (BRUKER Daltonics, Germany) with an Apollo ESI ion source in the positive mode.

Compounds **1**, **2**, **4** and **6** were dissolved in MeOH containing 0.1% HCl (0.02 mM) and the UV–vis spectrum was measured at 700–200 nm. Compound **1** was diluted with pH 1–8 in 0.01 mM buffers and the visible spectra at 780–400 nm were measured with a 5-cm light-pass crystal cell. The solution used for pH 1 and 2 was a 0.1 M Tris–HCl buffer, and that for pH 3–8 consisted of a McIlvaine buffer prepared with 0.1 M citric acid and 0.2 M Na_2HPO_4 (Table 1). Compound **1** (86 μg) was dissolved in 5 mL of MeOH (0.0143 mM) and the UV–vis spectrum was measured; then, a 1% $AlCl_3$ solution was added and the UV–vis spectrum was measured at 780–250 nm. These analyses were conducted using a Shimadzu UV-2500PC spectrophotometer (Shimadzu Corporation, Japan).

The FTIR spectra of **1** and **2** were measured on a Nicolet 710 FT-IR with single-reflection ATR using a diamond crystal.

The CD spectra of **1**, **2** and **5** were measured on a J-725 spectropolarimeter (Jasco Corporation, Japan) in MeOH (0.1 mM) with a 1 mm crystal cell.

3.2. Materials

Rosa hybrida cv. M'me. Violet, purchased from the Tsukimoto Rose Garden (Kyoto, Japan), was grown in a typical greenhouse.

3.3. Purification of rosacyanins

Petals of *Rosa hybrida* cv. 'M'me. Violet'(7.9 kg) upon storage at −80 °C were pulverised in liquid N_2 and extracted with 15 L of 80% aqueous acetonitrile containing 0.1% TFA. After filtration, the extract was concentrated under vacuum and applied on a Sephadex LH-20 (9 L, Pharmacia Biotech, Sweden) column and eluted step-wise with 30% CH_3CN containing 0.1% TFA and 60% CH_3CN.

The 60% CH_3CN fraction was separated into two fractions; the former fraction was concentrated under vacuum and applied on HP-20 (1.5 L, Mitsubishi Chemical Co., Ltd, Japan). The column was washed with 2 L of H_2O and then eluted with 3 L of 10% CH_3CN containing 0.1% TFA and 3 L of 50% CH_3CN containing 0.1% TFA step-wise. The fraction including rosacyanin A1 (**1**) was eluted with 50% CH_3CN fraction.

This fraction was purified by preparative HPLC as below. The HPLC was accomplished with the use of a Develosil-ODS-UG-15/30 (50 cm×5 cm, Nomura Chemical, Ltd, Japan) column with a flow rate of 32 mL/min and the absorbance was monitored at 260 nm. The solvent system used included gradient elution for 80 min using 30–100% of solvent B (50% CH_3CN/H_2O, 0.5% TFA) in solvent A (0.5% TFA/H_2O).

The fraction including **1** was further purified using a Sephadex LH-20 (600 mL, Pharmacia Biotech, Sweden) column with 50% CH_3CN/H_2O. After 1.5 L elution, rosacyanin A1 was eluted. This fraction was finally applied on the HPLC using a YMC-pack Polymer C18 (30 cm×2 cm, YMC Co., Ltd, Japan) with a flow rate of 6 mL/min and monitoring by UV Abs. at 260 nm. The solvent system used was as follows: after 30 min of isocratic elution with 70% solvent B, gradient elution for 20 min using 70–90% of solvent B (50% CH_3CN/H_2O, 0.5% TFA) in solvent A (0.5% TFA/H_2O) was carried out. After these chromatograms, 80 mg of **1** was obtained.

The latter 60% CH_3CN fraction of the first LH-20 column chromatogram was purified by preparative HPLC as below. The HPLC was accomplished by using a Develosil-ODS-UG-15/30 (50 cm×5 cm, Nomura Chemical, Ltd, Japan) column with a flow rate of 32 mL/min and monitoring at A260 nm. The solvent system used included gradient elution for 80 min using 40–100% of solvent B (50% CH_3CN/H_2O, 0.5% TFA) in solvent A (0.5% TFA/H_2O).

The fraction including rosacyanin A2 (**2**) was applied on the HPLC using a YMC-pack Polymer C18 (30 cm×2 cm, YMC Co., Ltd, Japan) column with a flow rate of 6 mL/min and monitoring at A260 nm. The solvent system used was as follows: after 30 min of isocratic elution with 75% solvent B, gradient elution for 20 min using 75–100% of solvent B (50% CH_3CN/H_2O, 0.5% TFA) in solvent A (0.5% TFA/H_2O) was carried out. The fraction including **2** was finally applied on the HPLC using a Develosil C30-UG-5 (30 cm×2 cm, Nomura Chemical, Ltd, Japan) column with a flow rate of 6 mL/min and monitoring at A260 nm. The solvent system used was as follows: after 30 min of isocratic elution with 70% solvent B, gradient elution for 20 min using 70–90% of solvent B (50% CH_3CN/H_2O, 0.5% TFA) in solvent A (0.5% TFA/H_2O) was carried out. After these chromatograms, 8 mg of **2** was obtained.

3.3.1. Rosacyanin A1 (1). Blue amorphous powder. IR ν_{max}: 1707, 1606, 1327, 1191, 1028 cm^{-1}; UV–vis (0.1% HCl/MeOH) λ_{max}: 585 (log ε, 4.26), 424 (3.753), 354 (3.950), 263 (4.581) and 216 nm (4.87); CD (MeOH): $[\theta]_{284}$ $+1.23\times10^4$, $[\theta]_{261}$ -1.00×10^4, $[\theta]_{232}$ $+1.88\times10^4$; FABMS/MS *m/z*: 1205, 1053, 721, 420, 153; HR-FT-ICR-MS: 1205.13255 calculated for $C_{56}H_{37}O_{31}$ (1205.13133, err. −1.009 ppm); ^1H and ^{13}C NMR (1% DCl/DMSO-d_6): Tables 2 and 3.

3.3.2. Rosacyanin A2 (2). Blue amorphous powder. IR ν_{max}: 1719, 1603, 1321, 1185, 1020 cm^{-1}; UV–vis (0.1% HCl/MeOH) λ_{max}: 585 (log ε, 3.74), 267 (4.51) and 216 nm (4.87); CD (MeOH): $[\theta]_{281}$ $+6.84\times10^3$, $[\theta]_{256}$ -4.28×10^3, $[\theta]_{225}$ $+1.29\times10^4$; FABMS/MS *m/z*: 1053, 721, 420, 153; HR-FT-ICR-MS: 1357.14451 calculated for $C_{63}H_{41}O_{35}$ (1357.14229, err. −1.633 ppm); ^1H and ^{13}C NMR (1% DCl/DMSO-d_6): Tables 2 and 3.

3.4. HCl hydrolysis of 1

Rosacyanin A1 **1** (8 mg) was hydrolysed in 25 mL of 6 N HCl at 100 °C for 18 min. The hydrolysate was extracted with 4 mL of BuOH and the organic layer was purified by reverse-phase HPLC using a Polymer C18 (2 cmϕ×30 cm, YMC Co., Ltd, Japan) column to obtain four fractions. Fraction A was gallic acid, fraction B was cyanidin and fraction C was Rosacyanin B, as determined by HPLC and TOFMS analysis and their molecular ions at *m/z* 169 $[M-H]^-$, *m/z* 287 $[M]^+$ and *m/z* 419 $[M]^+$, respectively. Fraction D (**7**) contained 1.8 mg of blue pigment, which has λ_{max} of 590 nm in 90% CH_3CN with 0.5% TFA, and its structure was determined by TOFMS and NMR analyses.

3.5. Enzymatic hydrolysis of 1

The enzymatic hydrolysis of 30 mg of **1** was performed with 20 mg of tannase (Kikkoman Co., Ltd) in 100 mL of 0.1 M potassium phosphate buffer, pH 5.5, at room temperature for 24 h. The reactant was purified using Superdex Peptide HR10/30 (1 cmϕ×30 cm, Pharmacia Biotech, Sweden) with 50% CH_3CN/H_2O containing 0.01% TFA to yield 15 mg of hydrolysate (**4**). In the same procedure, **4** was obtained from **2**.

3.5.1. Degalloyl rosacyanin A1 (4). Blue amorphous powder. UV–vis (0.1% HCl/MeOH) λ_{max}: 585 (log ε, 4.40), 360 (4.02), 260 (sh, 4.56) and 211 nm (4.83); CD (MeOH): $[\theta]_{282}$ $+5.93\times10^3$, $[\theta]_{259}$ -1.16×10^4, $[\theta]_{216}$ $+1.41\times10^4$, HR-FT-ICR-MS: 901.10994 calculated for $C_{42}H_{29}O_{23}$ (901.10941, err. −0.585 ppm).

3.6. $NaBH_4$ reduction of 1 and 4

$NaBH_4$ (120 mg) was added to a solution of 60 mg of **1** in 100 mL MeOH; the reaction mixture was left for 30 min and then 15 mL of 1 N HCl was added to it. The reactant was purified by reverse-phase HPLC using a Polymer C18 (2 cmϕ×30 cm, YMC Co., Ltd, Japan) column to obtain 24 mg of **5**. Compound **4** (15 mg) was reduced in the same

manner as for **1** to obtain 6 mg of **6**. The structures of the derivatives of **1** are shown in Scheme 1.

3.6.1. Reduced rosacyanin A1 (5). Blue amorphous powder. UV–vis (0.1% HCl/MeOH) λ_{max}: 587 (log ε, 4.03), 260 (4.45) and 214 nm (4.83); HR-FT-ICR-MS: 1207.14794 calculated for $C_{56}H_{34}O_{31}$ (1207.14698, err. −0.794 ppm); ^{1}H and ^{13}C NMR (1% DCl/DMSO-d_6): Tables 2 and 3.

3.6.2. Degalloyl-reduced rosacyanin A1 (6). Blue amorphous powder. UV–vis (0.1% HCl/MeOH) λ_{max}: 582 (log ε, 4.28), 360 (3.89), 260 (sh, 4.43) and 211 nm (4.70); HR-FT-ICR-MS: 903.12406 calculated for $C_{42}H_{31}O_{23}$ (903.12506, err. 1.116 ppm); ^{1}H and ^{13}C NMR [CD_3CN (CD_3CN):D_2O (H_2O):TFA-*d* (TFA)=50:50:0.5]: Tables 2 and 3.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.068.

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Introduction of the Aib-Pro unit into peptides by means of the 'azirine/oxazolone method' on solid phase

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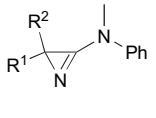
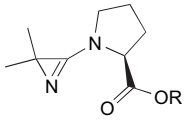
Abstract—A method for the direct introduction of Aib-Pro into peptides on solid phase was developed. The Aib-Pro unit was introduced by means of the 'azirine/oxazolone method' using allyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate as the synthon. After the reaction of the resin-bound amino or peptide acid with allyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate, the allyl protecting group of the resulting extended peptide could be removed by a mild Pd^0-promoted procedure. Cleavage of the peptide from the resin was performed with UV light at 352 nm and yielded C-terminal protected peptides. The method found a successful application in the syntheses of different Aib-Pro containing peptaibol segments. Furthermore, a protected derivative of the peptide antibiotic *Trichovirin I 1B* was prepared by segment condensation.

1. Introduction

2*H*-Azirin-3-amines are highly strained systems with versatile reactivity.[1] One very interesting and useful reaction is their application in peptide synthesis. In the 'azirine/oxazolone method', 2*H*-azirin-3-amines such as **1** or **2** are used as synthons for the introduction of sterically demanding α,α-disubstituted α-amino acids into peptides.[1–3] Thus, the reaction of 2*H*-azirin-3-amines, e.g., the α-aminoisobutyric acid (Aib) synthon **1a**, with amino or peptide acids leads to peptide amides, the terminal amide bonds of which can be hydrolyzed selectively to give extended peptide acids. In solution-phase chemistry, the 'azirine/oxazolone method' has proven to be successful for the introduction of a variety of sterically demanding α,α-disubstituted α-amino acids into oligopeptides,[4–13] endothiopeptides,[14–16] cyclic peptides,[17–18] and cyclic depsipeptides.[19–23]



1a $R^1 = R^2 = Me$
1b $R^1 - R^2 = -(CH_2)_4-$
1c $R^1 - R^2 = -(CH_2)_2O(CH_2)_2-$
1d $R^1 = Me$, $R^2 = PhCH_2$



2a R = Me
2b $R = CH_2CHCH_2$
2c $R = PhCOCH_2$

Recently, we adapted the 'azirine/oxazolone method' to solid-phase conditions, in order to additionally benefit from their advantages,[24] e.g., the rapid access to peptides without the need for the isolation of the sometimes cumbersome peptide acid intermediates. In this method, the growing peptide was attached through a carbamate linker to a [4-(hydroxymethyl)phenyl]acetamidomethyl (PAM) polystyrene resin (**3**) (Scheme 1). After deprotection of ^{t}Bu ester **4a**, resin-bound amino acid **4b** was treated with a solution of **1a**. It is worth mentioning that unconsumed **1a** could easily be recovered and re-used. The terminal amide **5a** was selectively hydrolyzed with 3 M HCl in THF/H_2O to provide the resin-bound peptide acid **5b**. Further extension of the peptide chain could be achieved either with a ^{t}Bu-protected amino acid and a coupling reagent or with **1a**. Cleavage of the peptide from the resin was achieved with HBr (33%) in acetic acid, and yielded the tripeptide **6**. In a recent paper, we showed that the method is not restricted to the Aib synthon **1a**, and that it was successfully extended to the 1-aminocyclopentane-1-carboxylic acid synthon **1b**, the 4-amino-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid synthon **1c**, and the α-methylphenylalanine synthon **1d**.[25]

Peptaibols are linear, amphiphilic oligopeptides from fungal sources with a high proportion of α,α-disubstituted α-amino acids, primarily, Aib.[26–27] Peptaibols show antibiotic properties due to self-association in lipid membranes forming ion channels.[28] Several peptaibols, or segments thereof, were synthesized by means of the 'azirine/oxazolone method'.[4,8–13] The 2*H*-azirin-3-amine **2a** played an important role in these syntheses, since **2a** allowed the direct

Keywords: α-Aminoisobutyric acid; Azirine/oxazolone method; Peptaibols; Peptide synthesis; Photocleavable linker.
Abbreviations: Aib, α-aminoisobutyric acid; DIPEA, *N*,*N*-diisopropylethylamine; HOBt, 1-hydroxybenzotriazole; PyBOP, (1*H*-benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate; TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; TFA, trifluoroacetic acid; TIPS, triisopropylsilane; Z, benzyloxycarbonyl; Z-ONSu, *N*-[(benzyloxycarbonyl)oxy]succinimide.
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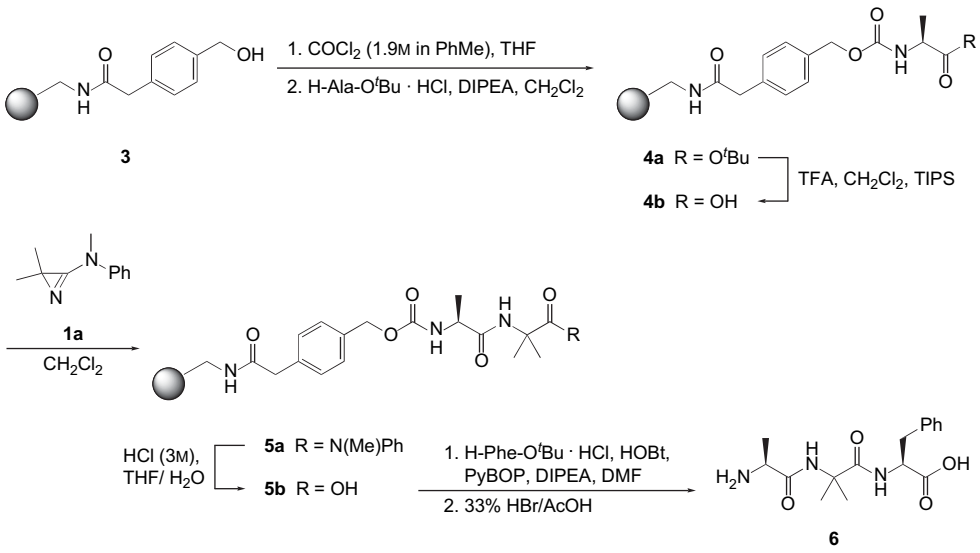


Scheme 1.

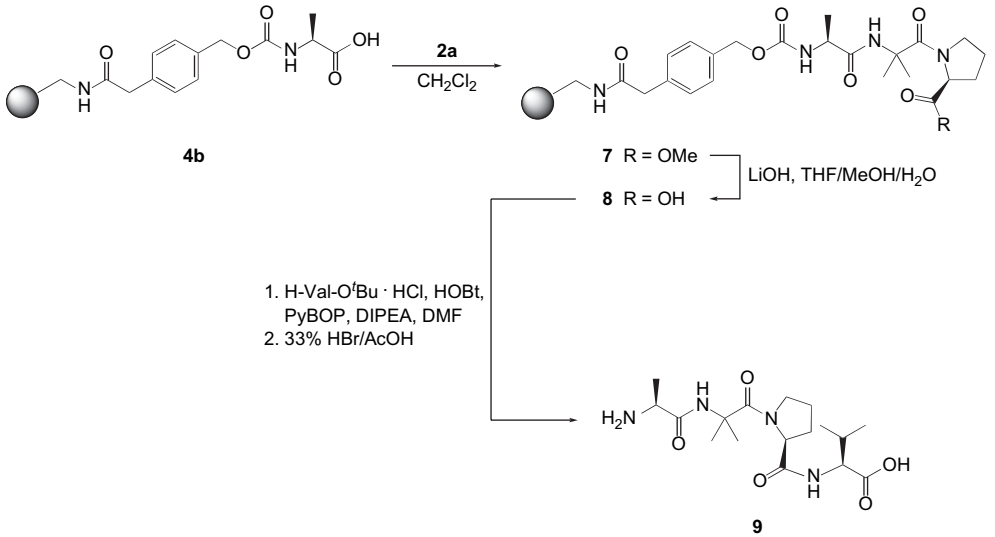
introduction of the frequently present, but relatively acid labile, Aib-Pro unit.[9] Unexpectedly, the use of **2a** on solid phase was not successful (vide infra).

Herein we report a method for the introduction of the Aib-Pro unit into peptides on solid phase, using a photolabile linker and a new Aib-Pro synthon (**2b**), which was especially developed for this purpose.[29]

2. Results and discussion

The most obvious approach to the introduction of the Aib-Pro unit was the use of synthon **2a** in analogy to the method outlined in Scheme 1. In doing so, the resin-bound amino acid **4b** was treated with a solution of **2a**, and the resulting resin-bound tripeptide methyl ester **7** was saponified with LiOH in a mixture of THF, MeOH, and H_2O (Scheme 2). After coupling with H-Val-O^{t}Bu by using PyBOP as the coupling reagent, the peptide was cleaved from the resin with HBr (33%) in acetic acid to give H-Ala-Aib-Pro-Val-OH (**9**) in 20% yield. In order to guarantee proper swelling of the resin during the saponification, the experiment was repeated with a Tentagel resin. However, the yield of 21% was still conspicuously lower in comparison with the introduction of the synthons **1a–d** (37–50%). The problem was recognized, when the synthesis of the model peptide H-Ala-Aib-Pro-Leu-Aib-Val-OH (on Tentagel resin) and the peptaibol segment (A8–A14 of *Trichovirin Ia*) H-Val-Aib-Gly-Aib-Aib-Pro-Leu-OH (on polystyrene resin) failed. Only peptide fragments, which are caused by Aib-Pro fissions, were detected. The analysis of the fragments revealed that the cleavage of the Aib-Pro amide bond occurred during the HBr-promoted cleavage of the peptide from the resin, and not during the hydrolysis of the terminal amide, which was necessary after the incorporation of **1a**.

Thus, a linker was required, which can be cleaved under milder conditions, but is still stable in TFA (50%) and HCl (3 M). Some years ago, Kunz introduced a Pd^0-labile allyl

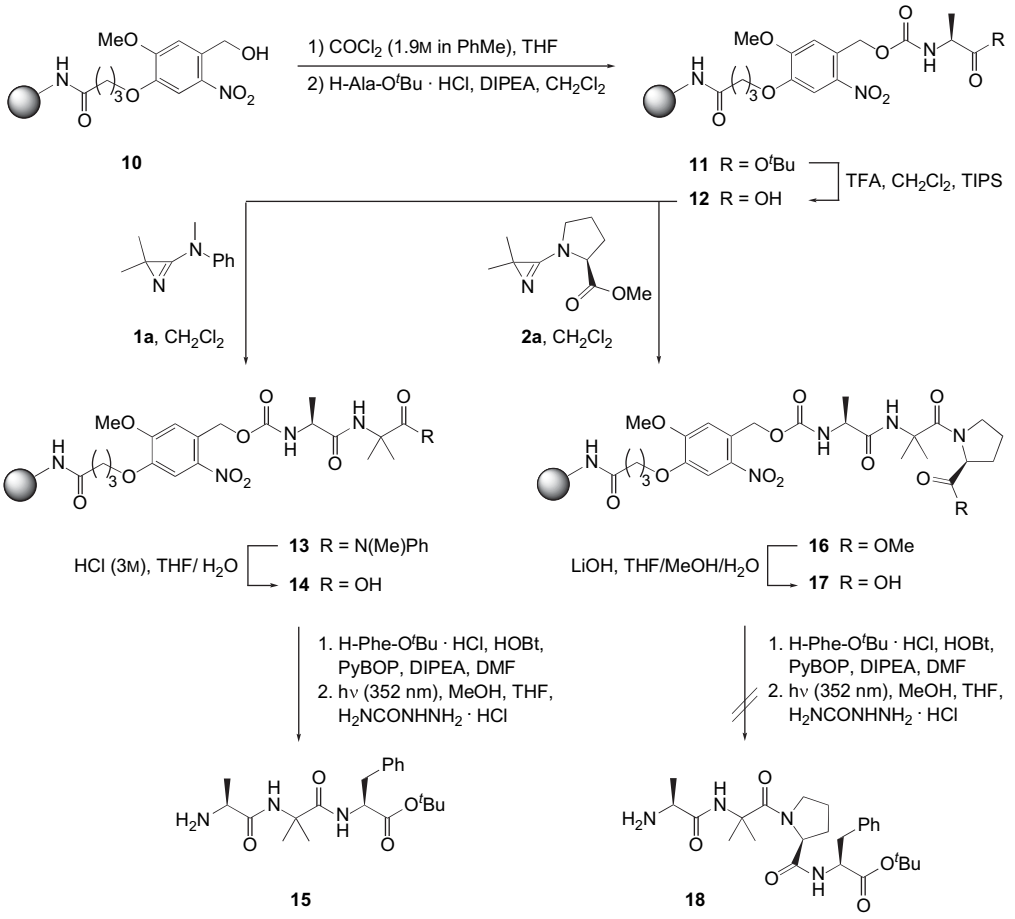


Scheme 2.

linker for the synthesis of peptide acids.[30] Therefore, we synthesized 2-{[(*Z*)-4-(triisopropylsilyloxy)but-2-enyl]oxy}-ethanoic acid[31] and attached its carboxy group via an alanine spacer to an aminomethyl polystyrene resin.[32] Additionally, (*E*)-7-hydroxyhept-5-enoic acid was prepared,[33] and its carboxy group was attached to an aminomethyl polystyrene resin. In both cases, the N-terminus of the first amino acid was immobilized through a carbamate group to the resin (in the first case after removing the TIPS-protecting group with TFA), and the resin-bound peptides **6** and **9** were synthesized analogously to the 'PAM/HBr-strategy'. Cleavage from the resin was performed with $Pd(Ph_3P)_4$ and $PhSiH_3$ in $DMSO/CH_2Cl_2$, but the desired peptides could only be obtained in low yield and after a painstaking purification of the Pd-containing crude product.

In 1995, Holmes introduced a photolabile nitroveratryl linker and immobilized peptides by coupling their C-terminus to the resin.[34–36] This photolinker is among the most effective ever described—it is stable to various chemical reactions, but can easily be cleaved with UV light with λ=365 nm, a wavelength that does not affect aromatic amino acids such as Trp or Tyr. The corresponding photocleavable resin **10** (Scheme 3) is commercially available from Novabiochem.

With the aim of testing the stability under acidic conditions, *N*-(4,5-dimethoxy-2-nitrobenzyloxy)carbonyl-L-alanine *tert*-butyl ester (NVOC-Ala-O^{t}Bu) was prepared by reaction of 4,5-dimethoxy-2-nitrobenzyl alcohol and $COCl_2$ in THF, and subsequently with H-Ala-O^{t}Bu·HCl under Schotten–Baumann conditions to give NVOC-Ala-O^{t}Bu, which was then subjected to acidic conditions. Apart from ^{t}Bu hydrolysis, neither in TFA (50%) nor in HCl (3 M) cleavage or decomposition of the linker was observed. Hence, the chloroformate of the photocleavable resin **10** was reacted with H-Ala-O^{t}Bu (Scheme 3). Deprotection of the ^{t}Bu ester **11** with TFA afforded the resin-bound amino acid **12**, which was treated with a solution of **1a**. Selective hydrolysis of the terminal amide of the resin-bound dipeptide **13** with 3 M HCl afforded the resin-bound peptide acid **14**, which was coupled with H-Phe-O^{t}Bu. Cleavage of the peptide from the resin was performed with UV light (16×8 W, λ_{max}=352 nm) in MeCN/H_2O, but the initial yields were disappointing. Most probably, the remaining nitrosoaldehyde functionalized resin captured the peptide **15** via imine formation with its amino group.[37] This assumption was supported by ^{1}H NMR experiments: the formyl signal of methyl 4-[(4-formyl-2-methoxy-5-nitrophenyl)oxy]butanoate disappeared within 20 min on reaction with isopropylamine, and a new signal at 8.65 ppm, typical for imines, appeared. To overcome the interception of the peptide, the cleavage from the resin was performed in a solution of semicarbazide hydrochloride in THF/MeOH.[37] Although **15** was now obtained in much better yield (ca. 30–40%), its purity was unsatisfactory. Therefore, the general procedures had to be slightly modified again. The reaction time for the ^{t}Bu ester hydrolysis was extended to 60 min to avoid the previously detected H-Ala-Phe-O^{t}Bu side product. Moreover, the synthesis was carried out on



Scheme 3.

a polystyrene instead of a Tentagel resin. The use of Tentagel resin suffered from (poly)ethylene glycol loss. Finally, model peptide **15** was prepared in high purity and in 33% yield (after prep. HPLC, based on resin loading).

After having established the protocol for the use of Aib synthon **1a**, the preparation of Aib-Pro containing peptides was attempted. But when dipeptide synthon **2a** was used to incorporate the Aib-Pro unit, the experiment failed again (Scheme 3). During the saponification of resin-bound methyl ester **16** to give **17**, we observed a considerable darkening of the resin, which prevented the subsequent photoinduced cleavage of the peptide from the resin.

This issue was addressed by the synthesis of the new Aib-Pro synthons allyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2b**) and phenacyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2c**), which contain easily removable carboxy-protecting groups.[29] The resin-bound amino acid **12** was reacted with a solution of **2c**, and the resulting resin-bound phenacyl ester was treated with tetrabutylammonium fluoride. Again, considerable darkening of the resin was observed. On the other hand, the allyl protecting group of resin-bound peptide **19**, obtained from the reaction of **12** and **2b**, was smoothly removed with $Pd(Ph_3P)_4$ and $PhSiH_3$[38] in CH_2Cl_2 to give the resin-bound peptide acid **17** (Scheme 4). The latter was then coupled with H-Phe-O^{t}Bu and PyBOP as the coupling reagent affording the corresponding resin-bound tetrapeptide. Cleavage from the resin was achieved with UV light (16×8 W, λ_{max}=352 nm) in a solution of semicarbazide hydrochloride in THF/MeOH and gave H-Ala-Aib-Pro-Phe-O^{t}Bu (**18**) in high purity and in 35% yield (after prep. HPLC, based on resin loading).

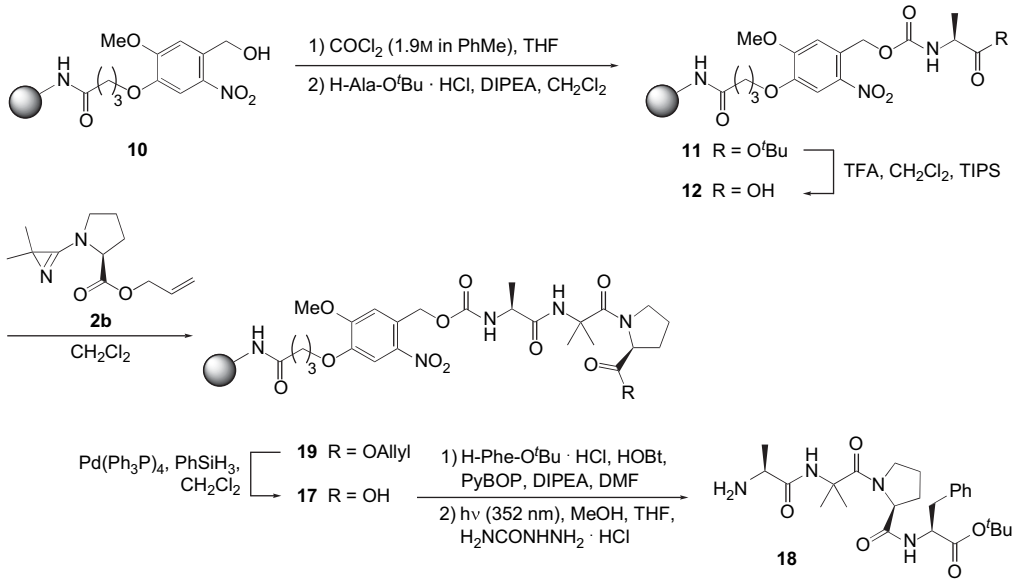
To evaluate the described protocol for the introduction of the Aib-Pro motif into peptides, the preparation of some peptaibol segments was attempted. The heptapeptide H-Val-Aib-Gly-Aib-Aib-Pro-Leu-O^{t}Bu (**20**, A8–A14 of *Trichovirin Ia*; Table 1), whose synthesis failed with the 'PAM/HBr-strategy' (see above), was prepared in 42% yield using the photocleavable resin **10**, the Aib synthon **1a**, and the allyl-protected Aib-Pro synthon **2b**. Gly and Leu were introduced with PyBOP as the coupling reagent. Analogously, the syntheses of the hexa- and octapeptides H-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-O^{t}Bu (**21**, A1–A6 of *Trichovirin I 1B*) and H-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leu-O^{t}Bu (**22**, A7–A14 of *Trichovirin I 1B*) were carried out. Sequence **21** was chosen to evaluate the introduction of non-aliphatic amino acids, while in the synthesis of **22**, an Aib-Pro unit had to be installed prior to an Aib residue and another Aib-Pro unit. Both peptides were prepared on the photocleavable resin **10** using the Aib synthon **1a** and the allyl-protected Aib-Pro synthon **2b**. All other amino acids were introduced with PyBOP as the coupling reagent. The side chain of Asn was not protected, while the hydroxy group of the serine side chain was masked as benzyl ether, a protecting group which is orthogonal to the ^{t}Bu protecting group. The peptides were obtained in 34% yield each (after prep. HPLC, based on resin loading), which is comparable to that of tetrapeptide **18** and therefore indicating a good linker stability.

In contrast to the 'PAM/HBr-strategy' (Scheme 1), the use of the photolinker allows the preparation of ^{t}Bu-protected peptides, which, in turn, offers the possibility of segment condensations. For that purpose, the C-terminal ^{t}Bu-protected peptides had to be transformed into N-terminal protected

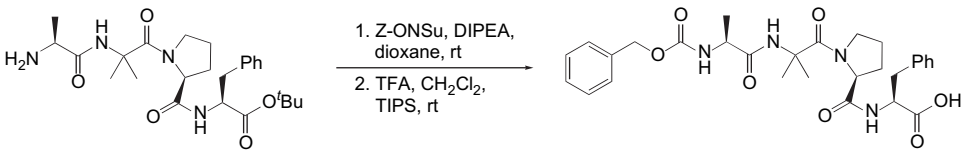
Table 1. Peptides synthesized by means of the 'azirine/oxazolone method' on solid phase

Sequence	Description	Yield [%][a]
H-Ala-Aib-Phe-O^{t}Bu (**15**)	Model peptide	33
H-Ala-Aib-Pro-Phe-O^{t}Bu (**18**)	Model peptide	35
H-Val-Aib-Gly-Aib-Aib-Pro-Leu-O^{t}Bu (**20**)	A8–A14 of *Trichovirin Ia*	42
H-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-O^{t}Bu (**21**)	A1–A6 of *Trichovirin I 1B*	34
H-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leu-O^{t}Bu (**22**)	A7–A14 of *Trichovirin I 1B*	34

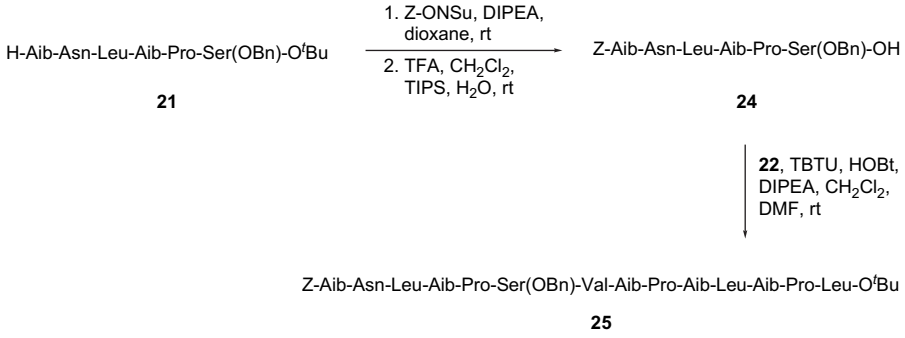
[a] Based on resin loading, after prep. HPLC.



Scheme 4.



Scheme 5.



Scheme 6.

peptides. Therefore, the ^{t}Bu-protected peptide **18** was reacted with *N*-[(benzyloxycarbonyl)oxy]succinimide (Z-ONSu), and the corresponding ^{t}Bu protecting group was hydrolyzed to give the *N*-protected peptide **23** (Scheme 5).

Analogously, the heptapeptide **21** (A1–A6 of *Trichovirin I 1B*) was transformed into the *N*-protected peptide **24** (Scheme 6). Due to steric hindrance of Aib, the reaction time for the introduction of the *Z*-protecting group was extended to 8 h. However, the transformation was not complete, and **21** (20%) was partially recovered. The hydrolysis of the corresponding ^{t}Bu ester with TFA was accompanied by partial cleavage of the Aib-Pro amide bond. Most probably, the extent of this side reaction could be reduced by shortening the reaction time (HPLC/MS indicates complete deprotection already after 20 min). Finally, **24** was coupled with **22** (A7–A14 of *Trichovirin I 1B*) and TBTU as the coupling reagent, and the protected *Trichovirin I 1B* derivative (Z-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leu-O^{t}Bu; **25**) was obtained in 73% yield (Scheme 5).[39]

3. Conclusions

A method for the direct introduction of Aib-Pro into peptides via 'azirine coupling' on solid phase was developed. The protocol is based on a photocleavable resin (**10**) and the Aib-Pro synthon **2b**. After the coupling of the resin-bound peptide acid with **2b**, the allyl protecting group of the extended peptide was removed by a mild Pd^0-promoted procedure. In contrast to the previously described 'PAM/HBr-strategy', this protocol allows the isolation of peptides with a protected C-terminus. The method found a successful application in the syntheses of different Aib-Pro containing peptaibol segments. A subsequent segment condensation led to the *Trichovirin I 1B* derivative **25**, an oligopeptide containing three Aib-Pro units and two additional Aib residues.

4. Experimental

4.1. General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Aminomethyl polystyrene resin (1% divinylbenzene, 100–200 mesh, loading 1.14 mmol/g) and aminomethyl Tentagel resin (90 μm, loading 0.28 mmol/g) from *Rapp Polymere* (*Rapp Polymere*, Tübingen, Germany). Hydroxymethyl-photolinker AM resin (**10**) (polystyrene, 1% divinylbenzene, 100–200 mesh, loading 0.75 mmol/g) from *Novabiochem* (*Calbiochem-Novabiochem*, Läufelfingen, Switzerland). *N*,2,2-Trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a**) was synthesized according to the method of Villalgordo and Heimgartner.[40,41] Methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2a**), allyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2b**), and phenacyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**2c**) were synthesized according to Ref. 9 (**2a**) and Ref. 29 (**2b**, **2c**), respectively. H-Ser(OBn)-O^{t}Bu was prepared by treatment of Fmoc-Ser(OBn)-OH with *tert*-butyl trichloroacetamidate and removal of Fmoc with Et_2NH. The ^{1}H NMR spectra of H-Ser(OBn)-O^{t}Bu were in accordance with the data given in Ref. 42. Reaction vessels for solid-phase synthesis: Single fritted (20 μm) PE reservoir (15 ml) (*Separtis*, Grenzach-Wyhlen, Germany) was wrapped with aluminum foil and used on an *Advanced ChemTech PLS 4×6* Shaker (*Advanced ChemTech, Inc.*, Louisville, KY, USA) with a self-made adapter. The original *Advanced ChemTech* reaction vessels were used for reactions with $COCl_2$. Photolysis was performed in a quartz tube (13.5 cm, 13 mm i.d.) and irradiation with circularly arranged *sterilAir BLB8* lamps (16×8 W, λ_{max}=352 nm) (*sterilAir AG*, Weinfelden, Switzerland). High-performance liquid chromatography (HPLC) instrument: *Waters 600E* multisolvent delivery system equipped with a *Waters 996 PDA* (*Waters*, Milford, CA, USA); column: *Interchim Uptisphere WOD C18*, 300 Å, 10 μm, 250×21.2 mm (*Interchim*, Montluçon,

France); eluents: A=H_2O/TFA (0.1%), B=MeCN/TFA (0.1%); flow rate: 10 ml/min; various gradients. Column chromatography (CC): Silica gel *C-560* from *Chemie Uetikon* (*CU Chemie Uetikon GmbH*, Uetikon, Switzerland). IR spectra: *Perkin–Elmer*, *Spectrum one FT-IR* spectrophotometer (*Perkin–Elmer*, Wellesley, MA, USA), absorptions in cm^{-1}. NMR spectra: *Bruker AV-600* (*Bruker Biospin*, Karlsruhe, Germany). Chemical shifts in parts per million relative to tetramethylsilane as internal standard. 2D-NMR experiments were performed for assignment of the signals. The integer *n* in Xaa^n corresponds to the position of the amino acid within the peptide, but is only given if the amino acid was present more than once in the peptide and if the NMR signal could be assigned unambiguously. HPLC/MS: The system consists of a *Rheos 2000* pump, a *Rheos CPS-LC* degasser (*Flux Instruments*, Basel, Switzerland) and a *Thermo Finnigan Surveyor* photodiode array detector (*Thermo Finnigan*, San Jose, CA, USA). The HPLC system is equipped with a *HTS PAL* autosampler (*CTC Analytics*, Zwingen, Switzerland) and connected to a *Thermo Finnigan MSQ* linear quadrupole instrument. *Interchim Uptisphere C18-ODB*, 120 Å, 3 μm, 50×2.0 mm column; eluents: A=H_2O, B=MeCN, C=HCOOH (1%) in H_2O; flow rate: 0.2 ml/min, gradient (A/B/C): 0.0–15.0 min: 87:3:10 to 40:50:10. MS: *Bruker ESQUIRE-LC* quadrupole instrument (*Bruker Daltonik GmbH*, Bremen, Germany) or *Finnigan TSQ-700* triple quadrupole instrument (*Finnigan* MAT, San Jose, CA, USA). Direct infusion ESI-MS were performed with a syringe infusion pump at a flow rate of 5 μl/min.

4.2. General procedures 1–7 (GP 1–GP 7)

4.2.1. GP 1: attachment of the first amino acid. All manipulations were carried out under N_2. Hydroxymethyl-photolinker AM resin was swollen in THF. After filtration, a solution of $COCl_2$ (*CAUTION*) in toluene (ca. 20%, 10 equiv) and THF (ca. 0.7 ml/100 mg resin) were added to the resin, which was agitated at rt for 2 h, then washed with THF (2×) and CH_2Cl_2 (2×). In a separate vial, H-Xaa-O^{t}Bu·HCl (4 equiv) was dissolved in DIPEA (8 equiv) and CH_2Cl_2 (concn of H-Xaa-O^{t}Bu·HCl=ca. 0.2 M). This mixture was added to the resin and any ammonium salt that occurred was removed by filtration. The resin was agitated at rt overnight, then washed with DMF (3×) and CH_2Cl_2 (3×).

4.2.2. GP 2: removing the ^{t}Bu protecting group. The resin was swollen in CH_2Cl_2. TFA in CH_2Cl_2 (2 ml, 1×15 s, 25%; 2 ml, 1×60 min, 50%) and TIPS (5%, in each case) were added, and the resin was agitated at rt. Then, the resin was washed with CH_2Cl_2 (3×), DMF (2×), and CH_2Cl_2 (3×).

4.2.3. GP 3: coupling with 2*H*-azirin-3-amines 1a, 2a, and 2b. The corresponding resin was swollen in CH_2Cl_2. A solution of 2*H*-azirin-3-amine (4 equiv) in CH_2Cl_2 (concn of 2*H*-azirin-3-amine=ca. 0.2 M) was added, the resin was agitated at rt overnight, and then washed with CH_2Cl_2 (3×). Unconsumed 2*H*-azirin-3-amine could easily be recovered.

4.2.4. GP 4: hydrolysis of the terminal amide. The resin was swollen in THF. Aq HCl (ca. 2 ml/100 mg resin, 3 M in THF/H_2O, prepared from concd HCl and THF) was added, and the resin was agitated at rt overnight, then washed with THF (3×), DMF (3×), and CH_2Cl_2 (3×).

4.2.5. GP 5: coupling with H-Xaa-O^{t}Bu·HCl. The resin was swollen in DMF. HOBt (6 equiv) in DMF, PyBOP (4 equiv) in DMF, H-Xaa-O^{t}Bu·HCl (4 equiv) in DMF, and DIPEA (12 equiv) were added (concn of H-Xaa-O^{t}Bu·HCl=ca. 0.2 M), the resin was agitated at rt, and then washed with DMF (3×) and CH_2Cl_2 (3×).

4.2.6. GP 6: removal of the allyl protecting group. The resin was dried i.v. All manipulations were carried out under Ar. The resin was swollen in CH_2Cl_2. A mixture of $Pd(Ph_3P)_4$ (0.3 equiv) and $PhSiH_3$ (20 equiv) in CH_2Cl_2 (ca. 2 ml/100 mg resin) was added, the resin was agitated at rt for 1.5 h, and then washed with CH_2Cl_2 (3×), DMF, CH_2Cl_2 (2×), THF (1% H_2O) (2×), THF (1×), MeOH, and CH_2Cl_2 (2×).

4.2.7. GP 7: cleavage. The resin (ca. 0.075 mmol) was swollen in a solution of semicarbazide hydrochloride (24 mg) in MeOH/THF (2:1, 6 ml), and the mixture was degassed by bubbling Ar into the mixture. Under vigorous stirring, the resin was irradiated with 16×8 W (λ_{max}=352 nm) for 2 h, then the supernatant solution was removed, and the irradiation process was repeated two times. Afterwards, the resin was washed with MeOH/THF (2:1, 3×). All solutions were combined, concentrated under reduced pressure, and the crude product was purified by means of HPLC. The purified product was lyophilized.

4.3. Synthesis of peptides

4.3.1. H-Ala-Aib-Pro-Val-OH (9). Aminomethyl Tentagel resin (350 mg, 0.098 mmol) was swollen in DMF. 4-(Hydroxymethyl)phenylacetic acid (33 mg, 0.199 mmol), DIPEA (103 μl, 0.602 mmol), and PyBOP (104 mg, 0.200 mmol) in DMF (1.5 ml) were added, and the resin was agitated at rt for 30 min (negative Kaiser test), then washed with DMF (3×), CH_2Cl_2 (3×), and THF (3×). The resin was treated as described in GP 1–3. Then, the resin was swollen in a mixture of THF (1 ml) and MeOH (0.7 ml), and LiOH·H_2O (33 mg, 0.787 mmol) in H_2O (0.3 ml) was added. The resin was agitated at rt overnight, washed with THF/MeOH/H_2O (4:3:1, 3×), and DMF (3×). The resin was treated as described in GP 5 (2 h), then swollen in CH_2Cl_2. HBr in AcOH (33%, 3 ml) and two drops of H_2O were added, and the resin was agitated at rt for 4 h. The resin was separated by filtration and washed with AcOH/CH_2Cl_2 (1:1, 3×) and MeCN/CH_2Cl_2 (1:1, 3×). The solvents were evaporated under reduced pressure and the crude product was purified by means of HPLC. The purified product was lyophilized and yielded **9** (10 mg, 21%) as a colorless powder. IR (KBr): 3435s, 3271s, 3068s, 2969s, 2882s, 1674vs, 1630vs, 1548s, 1472m, 1422s, 1369m, 1338w, 1310w, 1269m, 1202vs, 1183vs, 1138vs, 1005w, 979w, 929w, 837w, 800w, 722m. ^{1}H NMR (DMSO-d_6, 600 MHz): ca. 10.0–7.0 (br s, NH_3(Ala)); 8.61 (s, NH(Aib)); 7.73 (d, *J*=8.2 Hz, NH(Val)); 4.42–4.41 (m, CH(α)(Pro)); 4.06–4.04 (m, CH(α)(Val)); 3.88–3.87 (m, CH(α)(Ala)); 3.57–3.54, 3.38–3.34 (2m, CH_2(δ)(Pro)); 2.04 (dsept., *J*=6.6, 6.6 Hz, CH(β)(Val)); 1.88–1.83, 1.81–1.76 (2m, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.37, 1.34 (2s, 2 Me(Aib)); 1.36 (d, *J*=7.6 Hz, Me(Ala)); 0.90, 0.89 (2d, *J*=6.8 Hz, 2 Me(Val)). ^{13}C NMR (DMSO-d_6, 150 MHz): 173.0 (s, CO(Val)); 171.9 (s, CO(Pro)); 170.4 (s, CO(Aib)); 168.4

(s, CO(Ala)); 60.6 (d, CH(α)(Pro)); 57.2 (d, CH(α)(Val)); 56.0 (s, C(α)(Aib)); 47.9 (d, CH(α)(Ala)); 47.6 (t, CH_2(δ)(Pro)); 29.9 (d, CH(β)(Val)); 27.9, 25.2 (2t, CH_2(β)(Pro), CH_2(γ)(Pro)); 24.9, 24.5 (2q, 2 Me(Aib)); 19.1, 18.1 (2q, 2 Me(Val)); 17.3 (q, Me(Ala)). ESI-MS: 371 (100, $[M+H]^+$), 215 (34, $[Pro\text{-}Val]^+$).

4.3.2. H-Ala-Aib-Phe-O^{t}Bu (15). Aminomethyl polystyrene resin (62 mg, 0.071 mmol) was swollen in DMF. 4-[(4-Hydroxymethyl-2-methoxy-5-nitrophenyl)oxy]butanoic acid (40 mg, 0.140 mmol), PyBOP (72 mg, 0.138 mmol), and DIPEA (72 μl, 0.421 mmol) in DMF (1.5 ml) were added, and the resin was agitated at rt for 30 min, then washed with DMF (3×), CH_2Cl_2 (2×), and THF (2×). The resin was treated as described in GP 1–5 (overnight), and 7 to yield **15** (11.4 mg, 33%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3426s, 3399s, 3288s, 3065m, 3032m, 2983s, 2939s, 1724s, 1674vs, 1549s, 1516s, 1457m, 1440m, 1393m, 1368s, 1324w, 1259s, 1204vs, 1180vs, 1156vs, 1139vs, 1079w, 1030w, 1015w, 1003w, 948w, 929w, 881w, 839m, 800w, 754w, 739w, 722m, 700m. ^{1}H NMR (DMSO-d_6, 600 MHz): 8.31 (s, NH(Aib)); 8.01 (br s, NH_3(Ala)); 7.67 (d, J=7.8 Hz, NH(Phe)); 7.29–7.19 (m, 5 arom. H); 4.34 (ddd, J=8.2, 7.8, 6.4 Hz, CH(α)(Phe)); 3.84 (q, J=6.9 Hz, CH(α)(Ala)); 3.02 (dd, J=13.8, 6.4 Hz, 1 H of CH_2(Phe)); 2.95 (dd, J=13.8, 8.2 Hz, 1 H of CH_2(Phe)); 1.38, 1.37 (2s, 2 Me(Aib)); 1.33 (s, Me_3C); 1.32 (d, J=7.3 Hz, Me(Ala)). ^{13}C NMR (DMSO-d_6, 150 MHz): 172.9 (s, CO(Aib)); 170.4 (s, CO(Phe)); 168.8 (s, CO(Ala)); 137.4 (s, arom. C); 129.2, 128.1, 126.4 (3d, 5 arom. CH); 80.7 (s, Me_3C); 56.3 (s, C(α)(Aib)); 54.2 (d, CH(α)(Phe)); 48.3 (d, CH(α)(Ala)); 36.8 (t, CH_2(Phe)); 27.5 (q, Me_3C); 24.7, 24.6 (2q, 2 Me(Aib)); 17.1 (q, Me(Ala)). ESI-MS: 378 (53, $[M+H]^+$), 322 (100, $[M-{}^t\text{Bu}]^+$). HPLC/MS: t_R 10.3 min, m/z 378 (16, $[M+H]^+$), 322 (100, $[M-{}^t\text{Bu}]^+$), 157 (27, $[M-(\text{Phe-O}^t\text{Bu})]^+$).

4.3.3. H-Ala-Aib-Pro-Phe-O^{t}Bu (18). Hydroxymethyl-photolinker AM resin (101 mg, 0.075 mmol) was treated as described in GP 1–3, 6, 5 (2 h), and 7 to yield **18** (15.6 mg, 35%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3428s, 3293s, 3065s, 3032s, 2983s, 2940s, 1728s, 1674vs, 1548s, 1536s, 1499m, 1472m, 1456m, 1422m, 1415m, 1395m, 1369m, 1258m, 1203vs, 1177vs, 1156vs, 1135vs, 1052w, 1029w, 1004w, 928w, 879w, 836w, 800w, 740w, 721m, 701m. ^{1}H NMR (DMSO-d_6, 600 MHz): 8.65 (s, NH(Aib)); 8.08 (br s, NH_3(Ala)); 7.91 (d, J=7.4 Hz, NH(Phe)); 7.29–7.20 (m, 5 arom. H); 4.33–4.31 (m, CH(α)(Pro)); 4.26 (ddd, J=7.3, 7.3, 7.3 Hz, CH(α)(Phe)); 3.88–3.87 (m, CH(α)(Ala)); 3.52–3.50, 3.38–3.35 (2m, CH_2(δ)(Pro)); 2.97–2.95 (m, CH_2(Phe)); 1.86–1.76, 1.69–1.67 (2m, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.36 (d, J=7.1 Hz, Me(Ala)); 1.35, 1.34 (2s, 2 Me(Aib)); 1.30 (s, Me_3C). ^{13}C NMR (DMSO-d_6, 150 MHz): 171.7 (s, CO(Pro)); 170.4 (s, CO(Phe)); 170.3 (s, CO(Aib)); 168.3 (s, CO(Ala)); 137.3 (s, arom. C); 129.2, 128.0, 126.3 (3d, 5 arom. CH); 80.3 (s, Me_3C); 60.7 (d, CH(α)(Pro)); 55.9 (s, C(α)(Aib)); 54.2 (d, CH(α)(Phe)); 47.8 (d, CH(α)(Ala)); 47.5 (t, CH_2(δ)(Pro)); 36.6 (t, CH_2(Phe)); 27.9 (t, CH_2(β)(Pro)); 27.4 (s, Me_3C); 25.0 (t, CH_2(γ)(Pro)); 24.7, 24.6 (2q, 2 Me(Aib)); 17.1 (q, Me(Ala)). ESI-MS: 497 (10, $[M+Na]^+$), 475 (100, $[M+H]^+$), 419 (17, $[M-{}^t\text{Bu}]^+$), 319 (7, $[M-(\text{Ala-Aib})]^+$). HPLC/MS: t_R 9.9 min, m/z 497 (10, $[M+Na]^+$), 475 (30, $[M+H]^+$), 419 (24, $[M-{}^t\text{Bu}]^+$), 319 (32, $[M-(\text{Ala-Aib})]^+$), 263 (100, $[M-(\text{Ala-Aib})-{}^t\text{Bu}]^+$).

4.3.4. H-Val-Aib-Gly-Aib-Aib-Pro-Leu-O^{t}Bu (20). Hydroxymethyl-photolinker AM resin (100 mg, 0.075 mmol) was treated as described in GP 1–5 (overnight), 2–4, 3, 6, 5 (2 h), and 7 to yield **20** (25.7 mg, 42%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3433vs, 3317vs, 3063m, 2978s, 2939s, 2877m, 1725m, 1671vs, 1543vs, 1537vs, 1469m, 1440m, 1416m, 1397m, 1384m, 1368m, 1333w, 1282m, 1248m, 1203vs, 1178vs, 1146s, 1018w, 947w, 878w, 837w, 801w, 722w. ^{1}H NMR (DMSO-d_6, 600 MHz): 8.82 (s, NH(Aib^2)); 8.20 (s, NH(Gly)); 8.08 (br s, NH_3(Val)); 7.81 (d, J=8.1 Hz, NH(Leu)); 7.72 (s, NH(Aib^4)); 7.43 (s, NH(Aib^5)); 4.37–4.35 (m, CH(α)(Pro)); 4.11–4.07 (m, CH(α)(Leu)); 3.61–3.59 (m, CH(α)(Val), 1 H of CH_2(Gly), 1 H of CH_2(δ)(Pro)); 3.55–3.51 (m, 1 H of CH_2(Gly)); 3.43–3.39 (m, 1 H of CH_2(δ)(Pro)); 2.12 (dsept., J=6.7, 6.7 Hz, CH(β)(Val)); 2.02–1.98 (m, 1 H of CH_2(β)(Pro)); 1.74–1.69 (m, 1 H of CH_2(β)(Pro), CH_2(γ)(Pro)); 1.63–1.57 (m, CH(γ)(Leu), 1 H of CH_2(β)(Leu)); 1.51–1.45 (m, 1 H of CH_2(β)(Leu)); 1.403, 1.398 (2s, 2 Me(Aib^2), 2 Me(Aib^4)); 1.38 (s, Me_3C); 1.35, 1.33 (2s, 2 Me(Aib^5)); 0.96, 0.94 (2d, J=7.0 Hz, 2 Me(Val)); 0.89, 0.82 (2d, J=6.3 Hz, 2 Me(Leu)). ^{13}C NMR (DMSO-d_6, 150 MHz): 174.6 (s, CO(Aib^2)); 174.3 (s, CO(Aib^4)); 171.7 (s, CO(Pro)); 171.1 (s, CO(Leu)); 171.0 (s, CO(Aib^5)); 168.4 (s, CO(Gly)); 168.0 (s, CO(Val)); 79.9 (s, Me_3C); 60.8 (d, CH(α)(Pro)); 57.5 (d, CH(α)(Val)); 56.13 (s, C(α)(Aib^4)); 56.09 (s, C(α)(Aib^2)); 56.0 (s, C(α)(Aib^5)); 50.9 (d, CH(α)(Leu)); 47.2 (t, CH_2(δ)(Pro)); 43.8 (t, CH_2(Gly)); 39.3 (t, CH_2(β)(Leu)); 29.5 (d, CH(β)(Val)); 28.4 (t, CH_2(β)(Pro)); 27.5 (q, Me_3C); 25.8 (q, 1 Me of 2 Me(Aib^4)); 25.6 (q, 1 Me of 2 Me(Aib^2)); 25.2 (q, 1 Me of 2 Me(Aib^5)); 25.0 (t, CH_2(γ)(Pro)); 24.5 (q, 1 Me of 2 Me(Aib^4)); 24.2 (d, CH(γ)(Leu)); 24.0 (q, 1 Me of 2 Me(Aib^5)); 23.7 (q, 1 Me of 2 Me(Aib^2)); 22.7, 21.2 (2q, 2 Me(Leu)); 18.4, 17.5 (2q, 2 Me(Val)). ESI-MS: 718 (17, $[M+Na]^+$), 696 (100, $[M+H]^+$). HPLC/MS: t_R 11.5 min, m/z 696 (100, $[M+H]^+$), 640 (27, $[M-{}^t\text{Bu}]^+$), 412 (24, $[M-(\text{Pro-Leu-O}^t\text{Bu})]^+$), 339 (16).

4.3.5. H-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-O^{t}Bu (21). Hydroxymethyl-photolinker AM resin (100 mg, 0.075 mmol) was treated as described in GP 1, 2, 5 (overnight), 2, 5 (90 min), 2, 3, 6, 5 (90 min), and 7 to yield **21** (21.7 mg, 34%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3427s, 3301s, 3066m, 2979m, 2961m, 2938m, 2875m, 1673vs, 1535s, 1470m, 1453m, 1424m, 1412m, 1369m, 1247m, 1203vs, 1182vs, 1138vs, 837w, 800w, 742w, 722m, 700w. ^{1}H NMR (DMSO-d_6, 600 MHz): 8.39–8.37 (m, NH(Asn)); 8.17–8.13 (m, NH(Leu), NH_3(Aib^1), NH(Aib^4)); 7.99 (d, J=8.0 Hz, NH(Ser)); 7.42–7.41 (m, 1 H of $CONH_2$(Asn)); 7.36–7.32, 7.29–7.27 (2m, 5 arom. H); 6.98 (s, 1 H of $CONH_2$(Asn)); 4.70 (ddd, J=7.5, 7.5, 7.5 Hz, CH(α)(Asn)); 4.49, 4.53 (AB, J=12.1 Hz, OCH_2Ph(Ser)); 4.42–4.40 (m, CH(α)(Pro)); 4.36–4.33 (m, CH(α)(Ser)); 4.29–4.25 (m, CH(α)(Leu)); 3.72 (dd, J=9.7, 5.8 Hz, 1 H of CH_2(β)(Ser)); 3.65 (dd, J=9.7, 4.4 Hz, 1 H of CH_2(β)(Ser)); 3.46–3.44, 3.42–3.38 (2m, CH_2(δ)(Pro)); 2.64–2.60, 2.43–2.39 (2m,

CH_2(β)(Asn)); 1.90–1.87, 1.77–1.72 (2m, CH_2(β)(Pro), CH_2(γ)(Pro)); 1.60–1.55 (m, CH(γ)(Leu)); 1.49–1.43 (m, CH_2(β)(Leu)); 1.45, 1.43 (2s, 2 Me(Aib[1])); 1.37 (s, Me_3C); 1.34, 1.30 (2s, 2 Me(Aib[4])); 0.86, 0.80 (2d, J=6.6 Hz, 2 Me(Leu)). ^{13}C NMR (DMSO-d_6, 150 MHz): 171.9 (s, CO(Pro)); 171.2 (s, CO(Leu), $CONH_2$(Asn)); 171.1 (s, CO(Aib[1])); 170.8 (s, CO(Aib[4])); 170.3 (s, CO(Asn)); 169.0 (s, CO(Ser)); 137.9 (s, arom. C); 128.1, 127.5, 127.4 (3d, 5 arom. CH); 80.5 (s, Me_3C); 72.1 (t, OCH_2Ph(Ser)); 69.3 (t, CH_2(β)(Ser)); 60.5 (d, CH(α)(Pro)); 56.2 (s, C(α)(Aib[1])); 55.6 (s, C(α)(Aib[4])); 52.8 (d, CH(α)(Ser)); 50.8 (d, CH(α)(Leu)); 49.8 (d, CH(α)(Asn)); 47.3 (t, CH_2(δ)(Pro)); 40.3 (t, CH_2(β)(Leu)); 36.8 (t, CH_2(β)(Asn)); 28.0 (t, CH_2(β)(Pro)); 27.5 (q, Me_3C); 25.0 (t, CH_2(γ)(Pro)); 24.9, 24.7 (2q, 2 Me(Aib[4])); 24.1 (d, CH(γ)(Leu)); 23.3, 23.1 (2q, 2 Me(Aib[1])); 22.9, 21.3 (2q, 2 Me(Leu)). ESI-MS: 768 (100, $[M+Na]^+$), 746 (48, $[M+H]^+$), 712 (28, $[M-{}^t\text{Bu}+Na]^+$), 622 (17). HPLC/MS: t_R 12.4 min, m/z 746 (100, $[M+H]^+$), 398 (34, [M−(Pro-Ser(OBn)-^{t}Bu)]$^+$).

4.3.6. H-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leu-O^{t}Bu (22). Hydroxymethyl-photolinker AM resin (100 mg, 0.075 mmol) was treated as described in GP 1–3, 6, 3–5 (overnight), 2, 3, 6, 5 (2 h), and 7 to yield **22** (24.8 mg, 34%) as a colorless powder after prep. HPLC purification and lyophilization. IR (KBr): 3440vs, 3330sh, 3058m, 2961s, 2874m, 1724sh, 1653vs, 1627vs, 1536vs, 1471s, 1451m, 1440m, 1416s, 1385m, 1368m, 1344w, 1249m, 1241m, 1203vs, 1178vs, 1146s, 839w, 833w, 800w, 722w. ^{1}H NMR (DMSO-d_6, 600 MHz): 9.00 (s, NH(Aib[2])); 8.13 (br s, NH_3(Val)); 7.77 (d, J=7.8 Hz, NH(Leu[8])); 7.72 (s, NH(Aib[4])); 7.69 (s, NH(Aib[6])); 7.38 (d, J=8.5 Hz, NH(Leu[5])); 4.37–4.35 (m, CH(α)(Pro[7])); 4.17–4.12 (m, CH(α)(Leu[5]), CH(α)(Pro[3])); 4.04–4.00 (m, CH(α)(Leu[8])); 3.76–3.73 (m, CH(α)(Val)); 3.60–3.55 (m, 3 H of 2 CH_2(δ)(Pro)); 3.40–3.36 (m, 1 H of 2 CH_2(δ)(Pro)); 2.21–2.18 (m, CH(β)(Val)); 2.12–2.08 (m, 1 H of 2 CH_2(β)(Pro)); 2.00–1.95 (m, 1 H of 2 CH_2(β)(Pro), 1 H of 2 CH_2(γ)(Pro)); 1.89–1.85 (m, 1 H of 2 CH_2(γ)(Pro)); 1.74–1.68 (m, 2 H of 2 CH_2(β)(Pro), 2 H of 2 CH_2(γ)(Pro)); 1.66–1.57 (m, 3 H of 2 CH_2(β)(Leu), 2 CH(γ)(Leu)); 1.48–1.44 (m, 1 H of 2 CH_2(β)(Leu)); 1.42, 1.40 (2s, 2 Me of 6 Me(Aib)); 1.38 (s, Me_3C, 1 Me of 6 Me(Aib)); 1.36, 1.35 (2s, 3 Me of 6 Me(Aib)); 1.00, 0.94 (2d, J=7.0 Hz, 2 Me(Val)); 0.91, 0.87, 0.82, 0.78 (4d, J=6.2 Hz, 4 Me(Leu)). ^{13}C NMR (DMSO-d_6, 150 MHz): 173.9 (s, CO(Aib[4])); 172.6 (s, CO(Pro[3])); 172.2 (s, CO(Aib[2])); 171.7 (s, CO(Leu[5]), CO(Pro[7])); 171.3 (s, CO(Leu[8])); 170.8 (s, CO(Aib[6])); 167.5 (s, CO(Val)); 79.9 (s, Me_3C); 63.2 (d, CH(α)(Pro[3])); 60.8 (d, CH(α)(Pro[7])); 56.9 (d, CH(α)(Val)); 56.2 (s, C(α)(Aib[4])); 56.1 (s, C(α)(Aib[2])); 55.6 (s, C(α)(Aib[6])); 51.1 (s, 2 CH(α)(Leu)); 48.0, 47.5 (2t, 2 CH_2(δ)(Pro)); 39.6, 39.2 (2t, 2 CH_2(β)(Leu)); 29.6 (d, CH(β)(Val)); 28.3, 27.6 (2t, 2 CH_2(β)Pro); 27.5 (q, Me_3C); 26.4 (q, 1 Me of 6 Me(Aib)); 25.5 (t, 1 CH_2 of 2 CH_2(γ)(Pro)); 25.4 (q, 1 Me of 6 Me(Aib)); 25.1 (t, 1 CH_2 of 2 CH_2(γ)(Pro)); 24.6, 24.32, 24.29 (3q, 3 Me of 6 Me(Aib)); 24.27, 24.2 (2d, 2 CH(γ)(Leu)); 23.9 (q, 1 Me of 6 Me(Aib)); 23.0, 22.9, 21.2, 20.6 (4q, 4 Me(Leu)); 18.6, 16.7 (2q, 2 Me(Val)). ESI-MS: 871 (19, $[M+Na]^+$), 849 (100, $[M+H]^+$). HPLC/MS: t_R 13.9 min, m/z 849 (100, $[M+H]^+$), 565 (93, [M−(Pro-Leu-O^{t}Bu)]$^+$).

4.3.7. Z-Ala-Aib-Pro-Phe-OH (23). Z-ONSu (4.3 mg, 17.3 μmol) and DIPEA (8.1 μl, 47.3 μmol) were added to a solution of **18** (9.3 mg, 15.8 μmol) in dioxane (2.5 ml) at rt, and the solution was stirred at rt for 3 h. The mixture was concentrated, and the crude product was purified by prep. HPLC. After lyophilization, Z-Ala-Aib-Pro-Phe-O^{t}Bu (HPLC/MS: t_R 16.5 min, m/z 631 (100, $[M+Na]^+$)) (8.5 mg, 89%) was obtained as a colorless powder, which was dissolved in CH_2Cl_2/TFA (1:1, 2 ml) and TIPS (100 μl). The solution was stirred at rt for 1 h, then it was concentrated under reduced pressure, and the crude product was purified by prep. HPLC. The purified product was lyophilized and yielded **23** (7.5 mg, 97%) as a colorless powder. IR (KBr): 3412vs, 3292vs, 3063m, 3032m, 2984s, 2940m, 2876m, 1722vs, 1650vs, 1535vs, 1499s, 1469m, 1454s, 1411s, 1380m, 1366m, 1340m, 1328m, 1317m, 1282m, 1243vs, 1215s, 1203s, 1177s, 1116m, 1072m, 1040m, 1028m, 1002w, 977w, 911w, 824w, 743m, 700s. ^{1}H NMR (DMSO-d_6, 600 MHz): ca. 13.2–11.2 (br s, COOH); 8.20 (s, NH(Aib)); 7.77 (d, J=8.0 Hz, NH(Phe)); 7.44 (d, J=7.6 Hz, NH(Ala)); 7.38–7.18 (m, 10 arom. H); 5.01, 5.06 (AB, J=12.6 Hz, CH_2(carbamate)); 4.37 (ddd, J=8.4, 8.4, 5.3 Hz, CH(α)(Phe)); 4.29–4.27 (m, CH(α)(Pro)); 4.10 (dq, J=7.2, 7.2 Hz, CH(α)(Ala)); 3.54–3.50, 3.35–3.31 (2m, CH_2(δ)(Pro)); 3.05 (dd, J=13.9, 5.1 Hz, 1 H of CH_2(Phe)); 2.93 (dd, J=13.9, 9.2 Hz, 1 H of CH_2(Phe)); 1.79–1.73 (m, 1 H of CH_2(β)(Pro)); 1.61–1.58 (m, CH_2(γ)(Pro)); 1.51–1.48 (m, 1 H of CH_2(β)(Pro)); 1.30, 1.29 (2s, 2 Me(Aib)); 1.21 (d, J=7.1 Hz, Me(Ala)). ^{13}C NMR (DMSO-d_6, 150 MHz): 172.6 (s, CO(Phe)); 171.9 (s, CO(Ala)); 171.7 (s, CO(Pro)); 170.9 (s, CO(Aib)); 155.6 (s, CO(carbamate)); 137.6, 137.0 (2s, 2 arom. C); 129.1, 128.2, 128.0, 127.7, 127.6, 126.2 (6d, 10 arom. CH); 65.2 (t, CH_2(carbamate)); 60.9 (d, CH(α)(Pro)); 55.5 (s, C(α)(Aib)); 53.2 (d, CH(α)(Phe)); 49.9 (d, CH(α)(Ala)); 47.2 (t, CH_2(δ)(Pro)); 36.6 (t, CH_2(Phe)); 27.8 (t, CH_2(β)(Pro)); 25.0 (q, 1 Me of 2 Me(Aib)); 24.9 (t, CH_2(γ)(Pro)); 24.6 (q, 1 Me of 2 Me(Aib)); 17.9 (q, Me(Ala)). ESI-MS: 591 (67, $[M+K]^+$), 575 (100, $[M+Na]^+$), 553 (44, $[M+H]^+$), 263 (96, [M−(Pro-Phe)−CO]$^+$, [Pro-Phe]$^+$). HPLC/MS: t_R 14.0 min, m/z 591 (51, $[M+K]^+$), 263 (100, [M−(Pro-Phe)−CO]$^+$, [Pro-Phe]$^+$).

4.3.8. Z-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-OH (24). Z-ONSu (6.0 mg, 24.1 μmol) and DIPEA (11.6 μl, 67.8 μmol) were added to a solution of **21** (19.4 mg, 22.6 μmol) in MeCN (5 ml) at rt, and the solution was stirred at rt for 6 h. Additional Z-ONSu (0.6 mg, 2.3 μmol) and DIPEA (3.9 μl, 22.6 μmol) were added, and the solution was stirred at rt for further 2 h. Then, the mixture was concentrated, and the crude product was purified by prep. HPLC. After lyophilization, Z-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-O^{t}Bu (HPLC/MS: t_R 16.6 min, m/z 880 (62, $[M+H]^+$)) (13.8 mg, 70%; additionally, **21** (3.8 mg, 20%) was isolated) was obtained as a colorless powder, which was dissolved in CH_2Cl_2/TFA (1:1, 2 ml), H_2O (1 drop), and TIPS (100 μl). The solution was stirred at rt for 45 min, then it was concentrated under reduced pressure, and the crude product was purified by prep. HPLC. The purified product was lyophilized and yielded **24** (8.9 mg, 67%) as a colorless powder. IR (KBr): 3418sh, 3308vs, 3063m, 3033m, 2957m, 2872m, 1660vs, 1532vs, 1469s, 1454s, 1412s, 1387m, 1366m, 1267s, 1203s, 1176s, 1094s, 1078m, 1028w, 740m, 698m.

^{1}H NMR (DMSO-d_6, 600 MHz): ca. 13.2–11.3 (br s, COOH); 8.49 (d, J=6.0 Hz, NH(Asn)); 8.06 (s, NH(Aib^1)); 7.96 (d, J=7.9 Hz, NH(Ser)); 7.74 (d, J=8.5 Hz, NH(Leu)); 7.49 (s, 1 H of $CONH_2$(Asn)); 7.48 (s, NH(Aib^4)); 7.40–7.26 (m, 10 arom. H); 7.04 (s, 1 H of $CONH_2$(Asn)); 5.08, 5.00 (AB, J=12.4 Hz, CH_2(carbamate)); 4.51 (s, OCH_2Ph(Ser)); 4.43–4.38 (m, CH(α)(Ser), CH(α)(Pro)); 4.32–4.29 (m, CH(α)(Asn)); 4.25–4.21 (m, CH(α)(Leu)); 3.75 (dd, J=9.8, 5.9 Hz, 1 H of CH_2(β)(Ser)); 3.68 (dd, J=9.8, 4.2 Hz, 1 H of CH_2(β)(Ser)); 3.45–3.42 (m, CH_2(δ)(Pro)); 2.67–2.63, 2.57–2.54 (2m, CH_2(β)(Asn)); 1.90–1.86, 1.75–1.56 (2m, CH_2(β)(Pro), CH_2(γ)(Pro), CH_2(β)(Leu), CH(γ)(Leu)); 1.36 (s, 1 Me of 2 Me(Aib^1)); 1.35, 1.332 (2s, 2 Me(Aib^4)); 1.325 (s, 1 Me of 2 Me(Aib^1)); 0.81, 0.74 (2d, J=6.3 Hz, 2 Me(Leu)). ^{13}C NMR (DMSO-d_6, 150 MHz): 175.3 (s, CO(Aib^1)); 172.1 (s, $CONH_2$(Asn)); 172.0 (s, CO(Pro)); 171.4 (s, CO(Ser)); 171.2 (s, CO(Leu)); 170.9 (s, CO(Asn)); 170.8 (s, CO(Aib^4)); 156.2 (s, CO(carbamate)); 138.1 (s, arom. C(Bn)); 136.4 (s, arom. C(Z)); 128.4, 128.2, 128.0, 127.7, 127.5, 127.4 (6d, 10 arom. CH); 72.2 (t, OCH_2Ph(Ser)); 69.4 (t, CH_2(β)(Ser)); 65.7 (t, CH_2(carbamate)); 60.7 (d, CH(α)(Pro)); 56.1 (s, C(α)(Aib^1)); 55.8 (s, C(α)(Aib^4)); 52.4 (d, CH(α)(Ser)); 51.6 (d, CH(α)(Asn)); 50.9 (d, CH(α)(Leu)); 47.5 (t, CH_2(δ)(Pro)); 39.4 (t, CH_2(β)(Leu)); 35.1 (t, CH_2(β)(Asn)); 27.9 (t, CH_2(β)(Pro)); 26.1 (q, 1 Me of 2 Me(Aib^1)); 25.1 (q, 1 Me of 2 Me(Aib^4)); 25.0 (t, CH_2(γ)(Pro)); 24.8 (q, 1 Me of 2 Me(Aib^4)); 24.0 (d, CH(γ)(Leu)); 23.9 (q, 1 Me of 2 Me(Aib^1)); 23.1, 20.7 (2q, 2 Me(Leu)). ESI-MS: 868 (45, [M−H+2Na]$^+$), 846 (100, [M+Na]$^+$). HPLC/MS: t_R 15.6 min, m/z 824 (11, [M+H]$^+$), 532 (100, [M−(Pro-Ser(OBn)-O^{t}Bu)]$^+$), 447 (40, [M−(Aib-Pro-Ser(OBn)-O^{t}Bu)]$^+$).

4.3.9. Z-Aib-Asn-Leu-Aib-Pro-Ser(OBn)-Val-Aib-Pro-Aib-Leu-Aib-Pro-Leu-O^{t}Bu (25). HOBt, TBTU, and DIPEA were taken from stock solutions. HOBt (1.7 mg, 11.1 μmol), TBTU (3.5 mg, 11.0 μmol), DIPEA (5.4 μl, 31.3 μmol), and **22** (10.6 mg, 11.0 μmol) were added to a solution of **24** (8.6 mg, 10.4 μmol) in CH_2Cl_2/DMF (1:1, 3 ml). The mixture was stirred at rt for 4 h, the solvent was evaporated under reduced pressure, and the crude product was purified by prep. HPLC. After lyophilization, **25** (12.5 mg, 73%) was obtained as a colorless powder. IR (KBr): 3435sh, 3306s, 2958m, 2872w, 1648vs, 1623vs, 1536vs, 1470s, 1454m, 1412s, 1385m, 1366m, 1269m, 1203m, 1172s, 1152m, 1094w, 1028w, 740w, 698w. ^{1}H NMR (DMSO-d_6, 600 MHz): 8.57 (d, J=5.5 Hz, NH(Asn)); 8.11 (s, 1 NH of 5 NH(Aib)); 7.90 (d, J=6.7 Hz, NH(Ser)); 7.82 (d, J=7.7 Hz, 1 NH of 3 NH(Leu)); 7.82, 7.79 (2s, 2 NH of 5 NH(Aib)); 7.74 (d, J=7.7 Hz, 1 NH of 3 NH(Leu)); 7.55, 7.54 (2s, 2 NH of 5 NH(Aib)); 7.53 (s, 1 H of CONH_2(Asn)); 7.39–7.30, 7.27–7.24 (2m, 10 arom. H, 1 NH of 3 NH(Leu), NH(Val)); 7.07 (s, 1 H of $CONH_2$(Asn)); 5.07, 5.00 (AB, J=12.3 Hz, CH_2(carbamate)); 4.55, 4.51 (AB, J=11.9 Hz, OCH_2Ph(Ser)); 4.38–4.36 (m, 1 H of 3 CH(α)(Pro)); 4.33–4.26 (m, CH(α)(Ser), CH(α)(Asn), 1 H of 3 CH(α)(Leu), 1 H of 3 CH(α)(Pro)); 4.19–4.14 (m, 1 H of 3 CH(α)(Leu), CH(α)(Val)); 4.08 (dd, J=8.4, 8.4 Hz, 1 H of 3 CH(α)(Pro)); 4.04–4.00 (m, 1 H of 3 CH(α)(Leu)); 3.86–3.83 (m, 1 H of CH_2(β)(Ser)); 3.77–3.68 (m, 1 H of CH_2(β)(Ser), 2 H of 3 CH_2(δ)(Pro)); 3.65–3.61, 3.52–3.48, 3.38–3.34, 3.30–3.25 (4m, 4 H of 3 CH_2(δ)(Pro)); 2.68–2.64, 2.60–2.56 (2m, CH_2(β)(Asn)); 2.24–2.19 (m, 2 H of 3 CH_2(β)(Pro)); 2.09 (dsept., J=6.8, 6.8 Hz, CH(β)(Val)); 2.01–1.98 (m, 1 H of 3 CH_2(β)(Pro)); 1.93–1.83 (m, 4 H of 3 CH_2(γ)(Pro)); 1.74–1.57 (m, 3 CH(γ)(Leu), 4 H of 3 CH_2(β)(Leu), 3 H of 3 CH_2(β)(Pro), 2 H of 3 CH_2(γ)(Pro)); 1.54–1.51 (m, 1 H of 3 CH_2(β)(Leu)); 1.48 (s, 1 Me of 10 Me(Aib)); ca. 1.44 (m, 1 H of 3 CH_2(β)(Leu)); 1.43, 1.42, 1.38, 1.37, 1.364, 1.358, 1.34 (7s, 9 Me of 10 Me(Aib), Me_3C); 0.91 (d, J=6.4 Hz, 1 Me of 6 Me(Leu)); 0.87, 0.83 (2d, J=6.8 Hz, 2 Me(Val)); 0.82 (d, J=6.4 Hz, 2 Me of 6 Me(Leu)); 0.749, 0.745 (2d, J=6.0 Hz, 2 Me of 6 Me(Leu)); 0.63 (d, J=6.2 Hz, 1 Me of 6 Me(Leu)). ^{13}C NMR (DMSO-d_6, 150 MHz): 175.7, 174.2, 173.0, 172.8, 172.74, 172.70, 172.6, 171.90, 171.86, 171.6, 171.3, 171.2, 171.1, 170.9, 169.6 (15s, 15 CO); 156.2 (s, CO(carbamate)); 137.9 (s, arom. C of CH_2Ph(Ser)); 136.2 (s, arom. C(Z)); 128.3, 128.1, 127.9, 127.6, 127.4, 127.2 (6d, 10 arom. CH); 79.8 (s, Me_3C); 72.0 (t, OCH_2Ph(Ser)); 68.6 (t, CH_2(β)(Ser)); 65.8 (t, CH_2(carbamate)); 63.9, 62.9, 60.8 (3d, 3 CH(α)(Pro)); 58.3 (d, CH(α)(Val)); 56.1, 56.0, 55.9, 55.8, 55.6 (5s, 5 C(α)(Aib)); 55.4, 51.9 (2d, CH(α)(Asn), CH(α)(Ser)); 51.1, 51.0 (2d, 3 CH(α)(Leu)); 48.3, 48.2, 47.6 (3t, 3 CH_2(δ)(Pro)); 39.5, 39.1, 39.1 (3t, 3 CH_2(β)(Leu)); 34.9 (t, CH_2(β)(Asn)); 29.6 (d, CH(β)(Val)); 28.4, 28.3, 28.1 (3t, 3 CH_2(β)(Pro)); 27.5 (q, Me_3C); 26.5, 26.0, 25.7 (3q, 3 Me of 10 Me(Aib)); 25.6 (t, 1 CH_2 of 3 CH_2(γ)(Pro)); 25.5 (q, 1 Me of 10 Me(Aib)); 25.4 (t, 1 CH_2 of 3 CH_2(γ)(Pro)); 25.3 (q, 1 Me of 10 Me(Aib)); 25.1 (t, 1 CH_2 of 3 CH_2(γ)(Pro)); 24.2 (q, d, 1 Me of 10 Me(Aib), 2 CH of 3 CH(γ)(Leu)); 23.81 (q, 1 Me of 10 Me(Aib)); 23.76 (d, 1 CH of 3 CH(γ)(Leu)); 23.3 (q, 2 Me of 10 Me(Aib)); 23.1 (q, 1 Me of 10 Me(Aib)); 23.0, 22.93, 22.89, 21.1, 20.3, 20.2 (6q, 6 Me(Leu)); 18.8, 17.9 (2q, 2 Me(Val)). ESI-MS: 1693 (17, [M+K]$^+$), 1677 (85, [M+Na]$^+$). HPLC/MS: t_R 18.1 min, m/z 1676 (2, [M+H]$^+$), 846 (100), 819 (35).

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Gallic esters of 4,5-dinitrocatechol as potential building blocks for thermotropic liquid crystals

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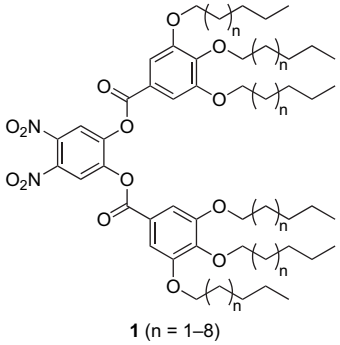
Abstract—A series of unsubstituted and 1,4-disubstituted gallic catecholates **1**, **6** and **7** as possible candidates for wedge-shaped mesogens were prepared starting from the respective benzene derivatives **2a–c** and gallic esters **5a–h**. The mesomorphic properties were investigated by DSC. However, only the 4,5-dinitro derivatives **1d**,**f–h** with C_8H_{17} and $C_{10}H_{21}$ to $C_{12}H_{25}$ alkyl side chains displayed mesophases, as evaluated by fluidity and optical anisotropy.

1. Introduction

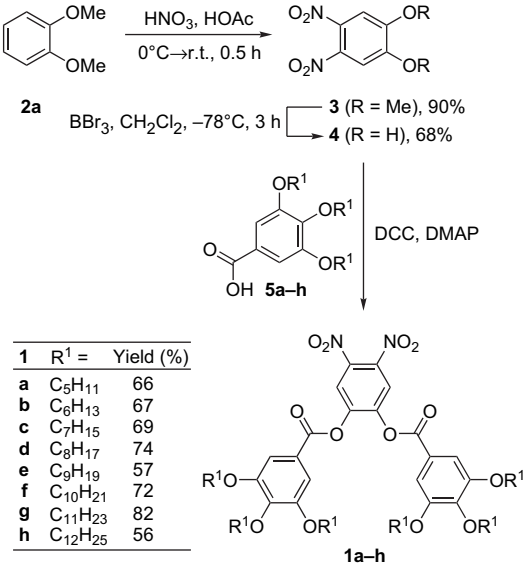
The effect of nitro groups on the mesomorphic and optical properties of low molecular weight thermotropic liquid crystals has been studied by several groups during the last couple of years.[1] In most cases molecules exhibiting smectic, nematic and banana phases have been investigated, whereas wedge-shaped systems were not considered. Bushby[2,3] and Kumar[4] observed that nitration of hexaalkyloxy-substituted triphenylenes leads to enhanced mesophase behaviour. This prompted us to prepare gallic ester **1** of 4,5-dinitrocatechol as potential candidates for wedge-shaped mesogens (Scheme 1). Herein we report their synthesis and the study of mesomorphic properties.



Scheme 1. Gallic ester **1** derived from 4,5-dinitrocatechol.

2. Results and discussion

As shown in Scheme 2, target compound **1** was accessible via three-step reaction. 1,2-Dimethoxybenzene **2a** was treated with nitric acid to give 1,2-dimethoxy-4,5-dinitrobenzene **3** in 90% yield following a procedure by Marquet.[5] Compound **3** was subsequently demethylated with BBr_3 at −78 °C in CH_2Cl_2 to afford 4,5-dinitrocatechol **4** in 68% yield.[6] The latter was esterified with tris(alkyloxy)gallic acids **5a–h** in the presence of DCC and DMAP[7] to yield the target gallic esters **1a–h** in 56–82% (Scheme 2). Compound **5**



1	R^1 =	Yield (%)
a	C_5H_{11}	66
b	C_6H_{13}	67
c	C_7H_{15}	69
d	C_8H_{17}	74
e	C_9H_{19}	57
f	$C_{10}H_{21}$	72
g	$C_{11}H_{23}$	82
h	$C_{12}H_{25}$	56

Scheme 2. Synthesis of target gallic ester **1** starting from 1,2-dimethoxybenzene **2a**.

Keywords: Catechol; Esterification; Gallic esters; Mesogens.
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was prepared from ethyl 3,4,5-trihydroxybenzoate via O-alkylation and subsequent saponification.[7] Slight modification of this protocol by replacing DMF with acetonitrile as the solvent and slow addition of the alkyl bromide[8] markedly improved the yields up to 99%.

The mesomorphic properties of ester **1** were investigated by differential scanning calorimetry (DSC) and polarizing optical microscopy (POM). The results are summarized in Table 1. Whereas the derivatives **1a–c** with R^1=C_5H_{11} to C_7H_{15} side chain displayed only isotropic melting during the DSC heating scans, a melting transition at 37 °C and a clearing transition at 55 °C were observed for octyloxy ester **1d**. Surprisingly, only isotropic melting was found for the homologous nonyloxy ester **1e**. In contrast, derivatives **1f–h** with longer alkyl chains (R^1=$C_{10}H_{21}$ to $C_{12}H_{25}$) again displayed a mesophase. The high clearing enthalpies of compounds **1d**,**f–h** deserve some additional comment. Although they may be taken as evidence for plastic crystals,[9] we have previously reported high clearing enthalpies for both columnar[10,11] and smectic mesophases.[11]

Under the polarizing optical microscope small, poorly defined textures were observed for compounds **1d**,**f–h** upon cooling from the isotropic liquid. Typical examples are shown in Figure 1. Unfortunately, we were not able to obtain suitable X-ray diffraction data. Thus, a crystal to crystal transition instead of a crystal to mesophase (i.e., smectic) transition cannot be completely excluded. However, the fluidity of the birefringent phase, which was obtained upon cooling from the isotropic liquid, was proven by mechanically shearing the sample between the cover slip and the slide. The combination of fluidity and optical anisotropy gives clear evidence of a liquid crystalline state.

In order to study the effect of the nitro groups on the mesomorphic properties, the unsubstituted gallic esters **6a–h** (R=H) were prepared as described above by esterification of 1,2-dihydroxybenzene **2b** with gallic acids **5a–h** in the presence of DCC and DMAP in CH_2Cl_2 at room temperature.[7] In an analogous manner, the corresponding 4,5-dibromo gallic esters **7f–h** were obtained in 77–87% yield starting from 4,5-dibromo-1,2-dihydroxybenzene **2c**[12] and gallic ester derivatives **5f–h** (Scheme 3).

In contrast to the dinitro ester **1** the corresponding unsubstituted derivative **6** did not display any mesophases. Only crystal to crystal transitions and isotropic melting were observed (Table 2). All melting points were much lower than those of the dinitro compound **1**, resulting from the decreased polarity.

Table 1. Phase transition temperatures [°C] and enthalpies [kJ mol^{-1}] of gallic esters **1a–h**

Compd	R^1	Cr_1	T (ΔH)	I	T (ΔH)	
1a	C_5H_{11}	Cr	69 (65.8)	I		
1b	C_6H_{13}	Cr	75 (51.7)	I		
1c	C_7H_{15}	Cr	63 (85.9)	I		
1d	C_8H_{17}	Cr	37 (10.6)	M_x	55 (28.1)	I
1e	C_9H_{19}	Cr	62 (71.5)	I		
1f	$C_{10}H_{21}$	Cr	44 (42.0)	M_x	61 (66.4)	I
1g	$C_{11}H_{23}$	Cr	46 (49.1)	M_x	63 (77.0)	I
1h	$C_{12}H_{25}$	Cr	61 (63.5)	M_x	65 (13.0)	I

Cr=crystalline, M_x=mesophase, I=isotropic.

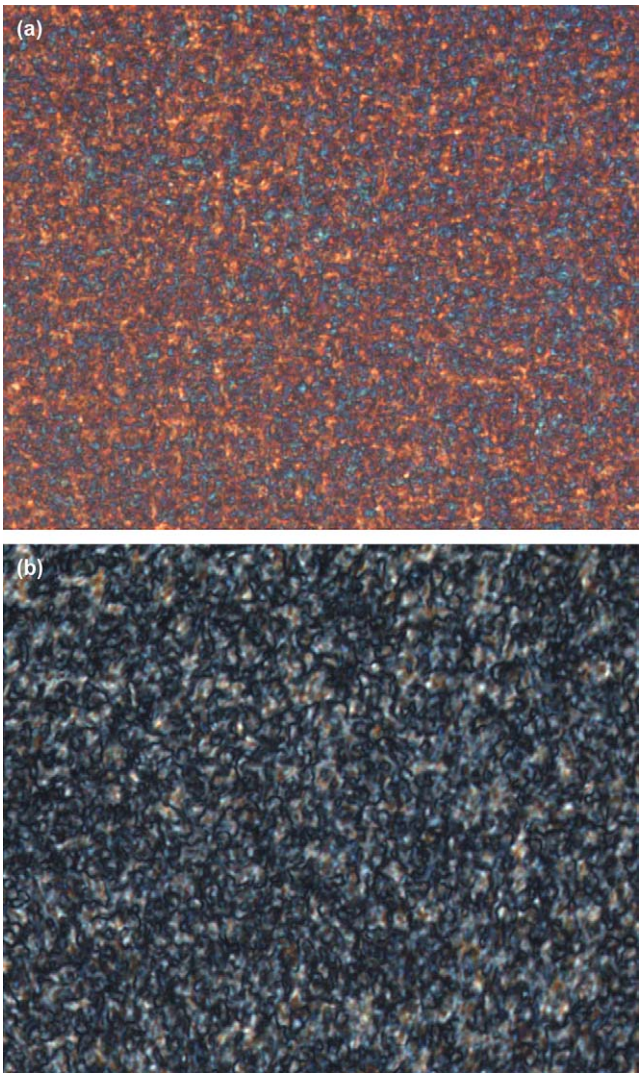
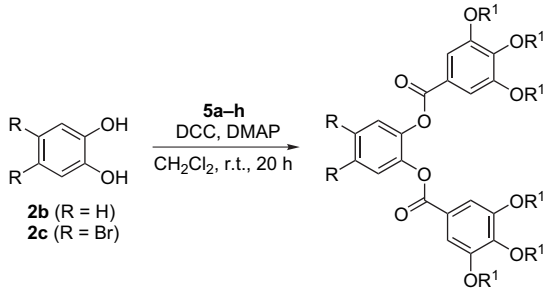


Figure 1. Optical textures of compounds **1d** at 50 °C (a) and **1f** at 64 °C (b) upon cooling from the isotropic liquid (cooling rate 1 K min^{-1}, magnification ×200).



6, 7	a	b	c	d	e	f	g	h
	R^1 = C_5H_{11}	C_6H_{13}	C_7H_{15}	C_8H_{17}	C_9H_{19}	$C_{10}H_{21}$	$C_{11}H_{23}$	$C_{12}H_{25}$
6 Yield (%)	90	84	90	92	77	94	94	89
7 Yield (%)						77	84	87

Scheme 3. Preparation of gallic esters **6a–h** and 4,5-dibromo derivatives **7f–h**.

As can be seen from Table 2, even the dibromo derivatives **7f–h** with long alkyl chains (R^1=$C_{10}H_{21}$ to $C_{12}H_{25}$) did not show any mesophases but crystal to crystal transitions.

Table 2. Phase transition temperatures [°C] and enthalpies [kJ mol^{-1}] of gallic ester derivatives **6a–h** and **7f–h**

Compd	R^1	Cr_1	T (ΔH)	I	T (ΔH)	
6a	C_5H_{11}	Cr	4 (12.4)	I		
6b	C_6H_{13}	Cr	−5 (9.7)	I		
6c	C_7H_{15}	Cr_1	3 (0.8)	Cr_2	9 (1.5)	I
6d	C_8H_{17}	Cr_1	8 (1.3)	Cr_2	11 (2.3)	I
6e	C_9H_{19}	Cr	18 (3.6)	I		
6f	$C_{10}H_{21}$	Cr_1	−56 (8.2)	Cr_2	22 (12.0)	I
6g	$C_{11}H_{23}$	Cr_1	−22 (26.3)	Cr_2	25 (12.7)	I
6h	$C_{12}H_{25}$	Cr_1	5 (28.9)	Cr_2	28 (8.7)	I
7f	$C_{10}H_{21}$	Cr	33 (71.2)	I		
7g	$C_{11}H_{23}$	Cr_1	−2 (49.0)	Cr_2	42 (47.1)	I
7h	$C_{12}H_{25}$	Cr_1	5 (28.9)	Cr_2	42 (64.2)	I

Cr=crystalline, I=isotropic.

In conclusion, substituent effects on the phase behaviour of gallic catecholates **1**, **6** and **7** were evaluated. While some of the dinitro derivative **1** displayed mesophases, both the corresponding unsubstituted gallic ester **6** and the dibromo-substituted derivative **7** are certainly not mesomorphic. However, in the case of **1** it cannot be differentiated undoubtedly between true mesophases or just soft crystal phases. In general, phase transition temperatures decrease in the order **1**>**7**>**6** with an approximate temperature difference of 20 °C between the different series. Although compounds **6** and **7** did not show any mesomorphic properties, they are useful building blocks for the convergent preparation of larger mesogenic subunits via oxidative coupling (Schöll reaction)[13] or Pd-catalyzed cross coupling.[14]

3. Experimental

3.1. General

Column chromatography was accomplished using SiO_2 60, grain size 0.063–0.200 mm (Merck) with hexanes (PE, bp 30–60 °C), EtOAc, and dichloromethane (CH_2Cl_2) as eluents. Starting materials **2a**,**b** are commercially available. ^{13}C NMR multiplicities were determined with DEPT experiments. DSC was performed on a Mettler Toledo DSC822. Compounds **2c**, **3** and **4** were prepared according to literature procedures.[5,6,12]

3.1.1. General procedure for the preparation of gallic esters 5a–h. A mixture of K_2CO_3 (9 equiv) and ethyl 3,4,5-trihydroxybenzoate (1 equiv) in MeCN (30–60 mL) was refluxed for 30 min under N_2 atmosphere. A solution of the respective alkyl bromide (4 equiv) in MeCN (6–12 mL) was added dropwise to the slurry, maintaining reflux and stirring for 20 h. The reaction was cooled to room temperature and filtered. The inorganic residue was washed with CH_2Cl_2 (2×50 mL). The filtrate was concentrated under vacuum, the residue dissolved in CH_2Cl_2 (75 mL) and washed with a 0.5 M NaOH solution (50 mL) and water (2×50 mL), dried ($MgSO_4$) and concentrated, yielding an oil. A solution of KOH (14 equiv) in EtOH (75 mL) was added to the gained oil and the mixture was refluxed for 6 h. After evaporation of the solvent, the oily solid was cooled at 0 °C, then treated with H_2O (50 mL) followed by 36.5% HCl (20 mL) after 10 min. The white precipitate was isolated by filtration, washed with water and dried under vacuum. In the case of **5g** and **5h**, the mixture was treated with cold MeOH (20 mL), stirred for 30 min at 0 °C, filtrated and dried. The spectroscopic data of products **5** are in accordance with those in the literature.[7]

3.1.2. General procedure for the preparation of 4,5-dinitro-2-{[3,4,5-tris(alkyloxy)benzoyl]oxy}phenyl 3,4,5-tris(alkyloxy)benzoates 1a–h. DCC (3.1 equiv) was added to a cooled solution of the appropriate acid **5** (2.2 equiv) in CH_2Cl_2 (14 mL) at 0 °C, and the reaction mixture was stirred for 10 min. Then DMAP (1.0 equiv) and **3** (1.0 equiv) were added and after stirring for five days, the reaction mixture was treated with CH_2Cl_2 (20 mL), washed with 1 M HCl (3×30 mL) and H_2O (30 mL), dried ($MgSO_4$) and concentrated. The oily residue was treated with PE (30 mL) and the white solid was filtered off. The filtrate was evaporated and the residue purified by repeated flash chromatography on SiO_2 with PE/CH_2Cl_2 [1:3, then 10:27 (**1a**), 2:2.3 (**1b**), 2:2.1 (**1c**), 2:2.2 (**1d**), 11:1 (**1e**), 20:23 (**1f**), 13:10 (**1g**,**h**)] to give product **1** as bright yellow solid.

3.1.2.1. 4,5-Dinitro-2-{[3,4,5-tris(pentyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(pentyloxy)benzoate (1a). Mp 69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, J=6.8 Hz, 18H; 6CH_3), 1.30–1.51 (m, 24H; 6(CH_2)$_2$$CH_3$), 1.70–1.80 (m, 12H; 6$OCH_2CH_2$), 3.82 (t, J=6.4 Hz, 8H; 4OCH_2), 4.02 (t, J=6.4 Hz, 4H; 2OCH_2), 7.23 (s, 4H; Ar-H), 8.07 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (4CH_3), 14.0 (2CH_3), 22.41 (2CH_3CH_2), 22.47 (CH_3CH_2), 28.1 (2$CH_3CH_2CH_2$), 28.2 ($CH_3CH_2CH_2$), 28.8 (2CH_3(CH_2)$_3$), 29.9 (CH_3(CH_2)$_3$), 69.1 (2OCH_2), 73.5 (OCH_2), 108.5 (4CH), 120.7 (2CH), 121.0, 140.0, 144.0, 145.8, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2954 (m), 2932 (vs), 2870 (vs), 1746 (vs), 1732 (vs), 1588 (m), 1540 (vs), 1430 (m), 1333 (vs), 1270 (vs), 1180 (vs), 1157 (vs), 1084 (s), 934 (m), 743 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=309 (3.29), 276 (3.42), 229 (0.74), 213 (0.61). EIMS, *m/z* (%): 924.5 (40) [M$^+$], 880.8 (100) [M$^+$−CO_2], 809.8 (20), 742.6 (15), 696.4 (100), 626.5 (15), 562.3 (25), 517.3 (40), 380.2 (45), 310.2 (28), 170.0 (100), 43 (75). MS (ESI), *m/z* (%): 947.5 (100) [M$^+$+Na], 942.6 (25) [M$^+$+NH_4], 925.6 (10) [M$^+$+H]. Anal. calcd for $C_{50}H_{72}N_2O_{14}$ (924.5): C, 64.91; H, 7.84; N, 3.03. Found: C, 64.70; H, 7.81; N, 2.98.

3.1.2.2. 4,5-Dinitro-2-{[3,4,5-tris(hexyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(hexyloxy)benzoate (1b). Mp 75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, J=6.6 Hz, 18H; 6CH_3), 1.30–1.57 (m, 36H; 6(CH_2)$_3$$CH_3$), 1.69–1.80 (m, 12H; 6$OCH_2CH_2$), 3.82 (t, J=6.3 Hz, 8H; 6CH_3), 4.02 (t, J=6.5 Hz, 4H; 2OCH_2), 7.23 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (4CH_3), 14.0 (2CH_3), 22.5, 22.6, 25.6, 25.7, 29.1, 30.2, 31.5, 31.6 (6CH_3(CH_2)$_4$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.5 (4CH), 120.7 (2CH), 121.0, 140.0, 144.0, 145.8, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2926 (vs), 2855 (vs), 1747 (vs), 1735 (vs), 1552 (s), 1540 (vs), 1430 (s), 1332 (vs), 1276 (vs), 1187 (vs), 1159 (vs), 1113 (vs), 930 (m), 744 (m), 631 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=282 (3.37), 229 (0.67), 208 (0.51). MS (ESI), *m/z* (%): 1031.6 (100) [M$^+$+Na], 1026.7 (15) [M$^+$+NH_4], 1009.6 (8) [M$^+$+H], 1008.6 (5) [M$^+$]. Anal. calcd for $C_{56}H_{84}N_2O_{14}$

(1008.6): C, 66.64; H, 8.39; N, 2.78. Found: C 66.73; H, 8.38; N, 2.75.

3.1.2.3. 4,5-Dinitro-2-{[3,4,5-tris(heptyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(heptyloxy)benzoate (1c). Mp 63 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, J=6.6 Hz, 18H; 6CH_3), 1.30–1.57 (m, 48H; 6(CH_2)$_4$$CH_3$), 1.70–1.80 (m, 12H; 6$OCH_2CH_2$), 3.82 (t, J=6.3 Hz, 8H; 4OCH_2), 4.01 (t, J=6.5 Hz, 4H; 2OCH_2), 7.22 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (6CH_3), 22.6, 22.7, 25.9, 26.0, 29.0, 29.1, 29.2, 30.3, 31.8, 31.9 (6CH_3(CH_2)$_5$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.5 (4CH), 120.7 (2CH), 121.0, 140.0, 144.0, 145.8, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2924 (vs), 2854 (vs), 1746 (vs), 1735 (vs), 1589 (m), 1552 (vs), 1539 (vs), 1466 (m), 1429 (vs), 1332 (vs), 1276 (vs), 1186 (vs), 1159 (vs), 1113 (vs), 930 (m), 744 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=277 (3.42), 229 (0.74). MS (ESI), m/z (%): 1115.7 (100) [M$^+$+Na], 1110.7 (35) [M$^+$+NH_4], 1093.7 (12) [M$^+$+H], 1092.7 (10) [M$^+$]. Anal. calcd for $C_{62}H_{96}N_2O_{14}$ (1092.7): C, 68.10; H, 8.85; N, 2.56. Found: C, 68.01; H, 8.70; N, 2.48.

3.1.2.4. 4,5-Dinitro-2-{[3,4,5-tris(octyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(octyloxy)benzoate (1d). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.3 Hz, 18H; 6CH_3), 1.28–1.56 (m, 60H; 6(CH_2)$_5$$CH_3$), 1.68–1.79 (m, 12H; 6$OCH_2CH_2$), 3.82 (t, J=6.3 Hz, 8H; 4OCH_2), 4.01 (t, J=6.5 Hz, 4H; 2OCH_2), 7.22 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (6CH_3), 22.6, 26.1, 29.2, 29.3, 29.5, 30.3, 31.8, 31.9 (6CH_3(CH_2)$_6$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.5 (4CH), 120.7 (2CH), 121.0, 140.0, 144.0, 145.8, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2918 (vs), 2851 (s), 1740 (vs), 1735 (vs), 1591 (m), 1534 (vs), 1430 (m), 1333 (vs), 1276 (vs), 1193 (vs), 1166 (vs), 1115 (vs), 743 (m), 633 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=282 (3.37), 229 (0.67), 208 (0.51). MS (ESI), m/z (%): 1199.8 (100) [M$^+$+Na], 1194.8 (35) [M$^+$+NH_4], 1177.8 (37) [M$^+$+H]. HRMS (EI) calcd 1176.7801 (for $C_{68}H_{108}N_2O_{14}$), found 1176.7838 [M$^+$]. Anal. calcd for $C_{68}H_{108}N_2O_{14}$ (1176.8): C, 69.36; H, 9.24; N, 2.38. Found: C, 69.19; H, 9.11; N, 2.40.

3.1.2.5. 4,5-Dinitro-2-{[3,4,5-tris(nonyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(nonyloxy)benzoate (1e). Mp 62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.3 Hz, 18H; 6CH_3), 1.27–1.56 (m, 72H; 6(CH_2)$_6$$CH_3$), 1.68–1.79 (m, 12H; 6$OCH_2CH_2$), 3.82 (t, J=6.3 Hz, 8H; 4OCH_2), 4.01 (t, J=6.5 Hz, 4H; 2OCH_2), 7.22 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (6CH_3), 22.6, 29.2, 29.32, 29.37, 29.4, 29.61, 29.68, 30.3, 31.91, 31.94 (6CH_3(CH_2)$_7$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.6 (4CH), 120.7 (2CH), 121.1, 140.0, 144.0, 145.9, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2918 (vs), 2849 (vs), 1743 (vs), 1735 (vs), 1590 (m), 1535 (vs), 1430 (vs), 1332 (vs), 1277 (vs), 1193 (vs), 1166 (vs), 1115 (vs), 742 (m), 722 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=286 (1.16), 230 (0.45), 221 (0.42), 208 (0.35). MS (ESI), m/z (%): 1284.0 (100) [M$^+$+Na], 1278.9 (18) [M$^+$+NH_4], 1262.0 (35) [M$^+$+2H], 1260.8 (8) [M$^+$]. Anal. calcd for $C_{74}H_{120}N_2O_{14}$ (1260.9): C, 70.44; H, 9.59; N, 2.22. Found: C, 70.22; H, 9.48; N, 2.10.

3.1.2.6. 4,5-Dinitro-2-{[3,4,5-tris(decyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(decyloxy)benzoate (1f). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.4 Hz, 18H; 6CH_3), 1.27–1.56 (m, 84H; 6(CH_2)$_7$$CH_3$), 1.68–1.79 (m, 12H; 6$OCH_2CH_2$), 3.82 (t, J=6.3 Hz, 8H; 4OCH_2), 4.01 (t, J=6.5 Hz, 4H; 2OCH_2), 7.22 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (6CH_3), 22.6, 26.0, 26.1, 29.3, 29.4, 29.5, 29.6, 29.66, 29.74, 30.3, 31.9 (6CH_3(CH_2)$_8$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.6 (4CH), 120.7 (2CH), 121.0, 140.0, 144.0, 145.9, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2917 (vs), 2849 (vs), 1743 (vs), 1590 (m), 1535 (vs), 1430 (vs), 1334 (vs), 1277 (vs), 1192 (s), 1167 (vs), 1117 (vs), 784 (s), 743 (m), 633 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=276 (3.42), 229 (0.70), 205 (0.53). MS (ESI), m/z (%): 1367.9 (100) [M$^+$+Na], 1362.9 (20) [M$^+$+NH_4], 1345.9 (10) [M$^+$+H]. Anal. calcd for $C_{80}H_{132}N_2O_{14}$ (1345.0): C, 71.39; H, 9.89; N, 2.08. Found: C, 71.47; H, 9.95; N, 2.05.

3.1.2.7. 4,5-Dinitro-2-{[3,4,5-tris(undecyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(undecyloxy)benzoate (1g). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.2 Hz, 18H; 6CH_3), 1.26–1.58 (m, 96H; 6(CH_2)$_8$$CH_3$), 1.68–1.79 (m, 12H; 6$OCH_2CH_2$), 3.81 (t, J=6.3 Hz, 8H; 4OCH_2), 4.01 (t, J=6.5 Hz, 4H; 2OCH_2), 7.22 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (6CH_3), 22.6, 26.0, 26.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 30.3, 31.9 (6CH_3(CH_2)$_9$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.6 (4CH), 120.7 (2CH), 121.1, 140.0, 144.0, 145.9, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2917 (vs), 2849 (vs), 1743 (vs), 1590 (m), 1535 (vs), 1430 (vs), 1334 (vs), 1277 (vs), 1192 (vs), 1167 (vs), 1118 (vs), 930 (m), 742 (m), 721 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=285 (3.17), 229 (0.66), 207 (0.51). MS (MALDI-TOF), m/z (%): 1431.0 (92) [M$^+$+H], 1430.0 (100) [M$^+$]. Anal. calcd for $C_{86}H_{144}N_2O_{14}$ (1429.1): C, 72.23; H, 10.15; N, 1.96. Found: C, 71.59; H, 9.96; N, 1.89.

3.1.2.8. 4,5-Dinitro-2-{[3,4,5-tris(dodecyloxy)benzoyl]-oxy}phenyl 3,4,5-tris(dodecyloxy)benzoate (1h). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.2 Hz, 18H; 6CH_3), 1.26–1.56 (m, 108H; 6(CH_2)$_9$$CH_3$), 1.68–1.76 (m, 12H; 6$OCH_2CH_2$), 3.81 (t, J=6.3 Hz, 8H; 4OCH_2), 4.01 (t, J=6.4 Hz, 4H; 2OCH_2), 7.22 (s, 4H; Ar-H), 8.08 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (6CH_3), 22.6, 26.0, 26.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 30.3, 31.9 (6CH_3(CH_2)$_{10}$), 69.1 (4OCH_2), 73.6 (2OCH_2), 108.5 (4CH), 120.7 (2CH), 121.0, 140.0, 144.0, 145.9, 153.0, 162.5 (2CO) ppm. FTIR (ATR): 2917 (vs), 2849 (vs), 1742 (vs), 1591 (m), 1534 (vs), 1430 (vs), 1334 (s), 1277 (vs), 1192 (vs), 1167 (s), 1116 (vs), 933 (m), 825 (m), 742 (m), 721 (m), 606 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=229 (0.74), 216 (0.64), 208 (0.59), 202 (0.54). MS (MALDI-TOF), m/z (%): 1515.1 (100) [M$^+$+2H], 1514.1 (100) [M$^+$+H], 1513.0 (10) [M$^+$]. Anal. calcd for $C_{92}H_{156}N_2O_{14}$ (1513.2): C, 72.97; H, 10.38; N, 1.85. Found: C, 72.95; H, 10.14; N, 1.87.

3.1.3. General procedure for the preparation of 2-{[3,4,5-tris(alkyloxy)benzoyl]oxy}phenyl 3,4,5-tris(alkyloxy)-benzoates 6a–h. DCC (3.1 equiv) was added to a cooled solution of the appropriate **5** (2.2 equiv) in CH_2Cl_2 (7–10 mL) at 0 °C. After stirring for 10 min, DMAP and **2b**

(1.0 equiv each) were added and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was treated with CH_2Cl_2 (10 mL), washed with 1 M HCl (2×20 mL) and H_2O (20 mL), dried ($MgSO_4$) and concentrated. The oily solid was treated with PE (30 mL) and the white solid was filtered off. The filtrate was evaporated and the residue purified by flash chromatography on SiO_2 with PE/CH_2Cl_2 [20:29 (**6a**), 20:27 (**6b**), 20:24 (**6c**), 20:22 (**6d**), 1:1 (**6e**,**f**), 22:20 (**6g**), 26:20 (**6h**)] to give the products **6a–h** as yellowish to white oils, which were dried for 1 h under freezing conditions (liquid N_2) and vacuum (10^{-3} mbar).

3.1.3.1. 2-{[3,4,5-Tris(pentyloxy)benzoyl]oxy}phenyl 3,4,5-tris(pentyloxy)benzoate (6a). Mp 4 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.92 (t, J=7.0 Hz, 18H; 6CH_3), 1.32–1.50 (m, 24H; 6(CH_2)$_2$CH$_3$), 1.71–1.78 (m, 12H; 6OCH$_2$CH_2), 3.83 (t, J=6.4 Hz, 8H; 4OCH_2), 3.99 (t, J=6.4 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.32–7.40 (2m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.9 (4CH$_3$), 14.0 (2CH$_3$), 22.4 (2CH$_3$$CH_2$), 22.5 (CH$_3$$CH_2$), 28.1 (2CH$_3$$CH_2$$CH_2$), 28.2 (CH$_3$$CH_2$$CH_2$), 28.94 (2CH$_3$$CH_2$$CH_2$$CH_2$), 29.98 (CH$_3$$CH_2$$CH_2$$CH_2$), 69.0 (2O$CH_2$), 73.4 (O$CH_2$), 108.3 (4$C$H), 123.1 (2$C$H), 123.5 (2$C$H), 126.5, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2954 (s), 2930 (vs), 2870 (vs), 1738 (vs), 1585 (vs), 1495 (s), 1428 (s), 1334 (vs), 1241 (m), 1192 (vs), 1102 (vs), 948 (m), 748 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=257 (3.39), 210 (0.63). MS (ESI), m/z (%): 853.5 (50) [M$^+$+NH$_4$+H], 852.5 (100) [M$^+$+NH$_4$], 836.5 (20), 835.5 (32) [M$^+$+H]. Anal. calcd for $C_{50}H_{74}O_{10}$ (834.6): C, 71.91; H, 8.93. Found: C, 72.07; H, 8.94.

3.1.3.2. 2-{[3,4,5-Tris(hexyloxy)benzoyl]oxy}phenyl 3,4,5-tris(hexyloxy)benzoate (6b). Mp −5 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.90 (t, J=6.3 Hz, 18H; 6CH$_3$), 1.28–1.50 (m, 36H; 6(CH_2)$_3$CH$_3$), 1.70–1.77 (m, 12H; 6OCH$_2$CH_2), 3.83 (t, J=6.4 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.32–7.40 (2m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0 (4CH$_3$), 14.1 (2CH$_3$), 22.6, 22.7, 25.6, 25.7, 29.2, 30.2, 31.5, 31.7 (6CH$_3$(CH$_2$)$_4$), 69.0 (4OCH$_2$), 73.4 (2OCH$_2$), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.5, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2927 (vs), 2858 (vs), 1738 (vs), 1585 (vs), 1495 (s), 1428 (s), 1334 (vs), 1241 (m), 1192 (vs), 1102 (vs), 957 (m), 748 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=260 (3.33), 236 (2.54), 209 (0.63). MS (ESI), m/z (%): 937.6 (50) [M$^+$+NH$_4$+H], 936.6 (90) [M$^+$+NH$_4$], 919.6 (100) [M$^+$+H], 918.6 (5) [M$^+$]. Anal. calcd for $C_{56}H_{86}O_{10}$ (918.6): C, 73.17; H, 9.43. Found: C, 73.40; H, 9.44.

3.1.3.3. 2-{[3,4,5-Tris(heptyloxy)benzoyl]oxy}phenyl 3,4,5-tris(heptyloxy)benzoate (6c). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.89 (t, J=6.5 Hz, 18H; 6CH$_3$), 1.27–1.50 (m, 48H; 6(CH_2)$_4$CH$_3$), 1.70–1.77 (m, 12H; 6OCH$_2$CH_2), 3.82 (t, J=6.4 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.31–7.40 (2m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.08 (4CH$_3$), 14.09 (2CH$_3$), 22.6, 22.7, 25.9, 26.0, 29.1, 29.2, 29.3, 30.3, 31.8, 31.9 (6CH$_3$(CH$_2$)$_5$), 69.0 (4OCH$_2$), 73.4 (2OCH$_2$), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.5, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2924 (vs), 2855 (vs), 1738 (vs), 1585 (vs), 1495 (s), 1428 (s), 1334 (vs), 1241 (m), 1196 (vs), 1103 (vs), 937 (m), 861 (m), 748 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=255 (3.39), 210 (0.60). MS (ESI), m/z (%): 1022.7 (10), 1021.7 (25), 1020.7 (30) [M$^+$+NH$_4$], 1005.7 (22), 1004.7 (65), 1003.7 (100) [M$^+$+H], 1002.6 (5) [M$^+$]. Anal. calcd for $C_{62}H_{98}O_{10}$ (1002.7): C, 74.21; H, 9.84. Found: C, 74.20; H, 9.81.

3.1.3.4. 2-{[3,4,5-Tris(octyloxy)benzoyl]oxy}phenyl 3,4,5-tris(octyloxy)benzoate (6d). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, J=6.7 Hz, 18H; 6CH$_3$), 1.25–1.50 (m, 60H; 6(CH_2)$_5$CH$_3$), 1.70–1.77 (m, 12H; 6OCH$_2$CH_2), 3.82 (t, J=6.4 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.32–7.40 (2m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0 (6CH$_3$), 22.67, 22.69, 26.0, 26.1, 29.3, 29.38, 29.41, 29.5, 30.3, 31.8, 31.9 (6CH$_3$(CH$_2$)$_6$), 69.0 (4OCH$_2$), 73.4 (2OCH$_2$), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.4, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2922 (vs), 2853 (vs), 1738 (vs), 1585 (vs), 1495 (s), 1429 (s), 1335 (vs), 1241 (m), 1196 (vs), 1104 (vs), 947 (w), 861 (m), 748 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=256 (3.37), 212 (0.57). MS (ESI), m/z (%): 1104.8 (20) [M$^+$+NH$_4$], 1089.8 (25), 1088.8 (60), 1087.7 (100) [M$^+$+H], 1086.7 (10) [M$^+$]. Anal. calcd for $C_{68}H_{110}O_{10}$ (1086.8): C, 75.09; H, 10.19. Found: C, 75.48; H, 10.27.

3.1.3.5. 2-{[3,4,5-Tris(nonyloxy)benzoyl]oxy}phenyl 3,4,5-tris(nonyloxy)benzoate (6e). Mp 18 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, J=6.8 Hz, 18H; 6CH$_3$), 1.28–1.50 (m, 72H; 6(CH_2)$_6$CH$_3$), 1.70–1.77 (m, 12H; 6OCH$_2$CH_2), 3.82 (t, J=6.4 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.32–7.40 (2m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.1 (6CH$_3$), 22.6, 26.0, 26.1, 29.3, 29.4, 29.5, 29.6, 29.7, 30.3, 31.9, 32.0 (6CH$_3$(CH$_2$)$_7$), 69.0 (4OCH$_2$), 73.4 (2OCH$_2$), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.5, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2921 (vs), 2852 (vs), 1738 (vs), 1585 (vs), 1495 (s), 1429 (s), 1335 (vs), 1241 (m), 1196 (vs), 1104 (vs), 748 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=256 (3.37), 212 (0.57). MS (ESI), m/z (%): 1188.8 (18) [M$^+$+NH$_4$], 1173.8 (30), 1172.8 (75), 1171.8 (100) [M$^+$+H], 1170.8 (20) [M$^+$]. Anal. calcd for $C_{74}H_{122}O_{10}$ (1170.9): C, 75.85; H, 10.49. Found: C, 76.19; H, 10.59.

3.1.3.6. 2-{[3,4,5-Tris(decyloxy)benzoyl]oxy}phenyl 3,4,5-tris(decyloxy)benzoate (6f). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, J=6.5 Hz, 18H; 6CH$_3$), 1.27–1.50 (m, 84H; 6(CH_2)$_7$CH$_3$), 1.68–1.78 (m, 12H; 6OCH$_2$CH_2), 3.82 (t, J=6.4 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.31–7.40 (m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0 (6CH$_3$), 22.6, 26.0, 26.1, 29.3, 29.38, 29.40, 29.5, 29.6, 29.7, 29.8, 30.3, 31.92, 31.93 (6CH$_3$(CH$_2$)$_8$), 69.0 (4OCH$_2$), 73.4 (2OCH$_2$), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.5, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2920 (vs), 2852 (vs), 1738 (vs), 1585 (vs), 1495 (s), 1429 (s), 1335 (vs), 1241 (m), 1196 (vs), 1105 (vs), 749 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=277 (2.74), 232 (1.58). MS (ESI), m/z (%): 1272.9 (15) [M$^+$+NH$_4$], 1257.9 (35), 1256.9 (80), 1255.9 (100) [M$^+$+H]. Anal. calcd for

$C_{80}H_{134}O_{10}$ (1255.0): C, 76.51; H, 10.75. Found: C, 76.79; H, 10.86.

3.1.3.7. 2-{[3,4,5-Tris(undecyloxy)benzoyl]oxy}phenyl 3,4,5-tris(undecyloxy)benzoate (6g). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, J=6.8 Hz, 18H; 6CH_3), 1.27–1.50 (m, 96H; 6(CH_2)$_8$$CH_3$), 1.70–1.77 (m, 12H; 6OCH$_2$CH_2), 3.82 (t, J=6.3 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.33–7.40 (m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.1 (6CH_3), 22.6, 26.0, 26.1, 29.3, 29.39, 29.40, 29.5, 29.6, 29.69, 29.72, 29.8, 30.3, 31.93, 31.95 (6CH_3(CH_2)$_9$), 69.0 (4OCH_2), 73.4 (2OCH_2), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.4, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2920 (vs), 2852 (vs), 1738 (vs), 1585 (vs), 1496 (s), 1466 (m), 1429 (s), 1336 (vs), 1241 (m), 1198 (vs), 1115 (vs), 1104 (vs), 750 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)= 277 (2.74), 232 (1.58). MS (ESI), *m/z* (%): 1341.0 (80), 1340.0 (100) [M$^+$+H], 1338.9 (20) [M$^+$], 1338.0 (10). Anal. calcd for $C_{86}H_{146}O_{10}$ (1339.1): C, 77.08; H, 10.98. Found: C, 77.35; H, 11.03.

3.1.3.8. 2-{[3,4,5-Tris(dodecyloxy)benzoyl]oxy}phenyl 3,4,5-tris(dodecyloxy)benzoate (6h). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, J=6.8 Hz, 18H; 6CH_3), 1.26–1.50 (m, 108H; 6(CH_2)$_9$$CH_3$), 1.70–1.77 (m, 12H; 6OCH$_2$CH_2), 3.82 (t, J=6.4 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.26 (s, 4H; Ar-H), 7.32–7.40 (m, 4H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.1 (6CH_3), 22.7, 26.0, 26.1, 29.3, 29.39, 29.41, 29.5, 29.6, 29.69, 29.71, 29.75, 29.76, 29.78, 30.3, 31.9 (6CH_3(CH_2)$_{10}$), 69.0 (4OCH_2), 73.4 (2OCH_2), 108.3 (4CH), 123.1 (2CH), 123.5 (2CH), 126.4, 142.5, 142.9, 152.8, 164.0 (2CO) ppm. FTIR (ATR): 2953 (s), 2920 (vs), 2852 (vs), 1739 (vs), 1586 (vs), 1496 (s), 1430 (s), 1337 (vs), 1242 (m), 1199 (vs), 1105 (vs), 751 (m) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=276 (2.90), 232 (1.66). MS (ESI), *m/z* (%): 1426.1 (50), 1425.1 (90), 1424.1 (100) [M$^+$+H], 1423.1 (15) [M$^+$]. Anal. calcd for $C_{92}H_{158}O_{10}$ (1423.2): C, 77.58; H, 11.18. Found: C, 77.96; H, 11.14.

3.1.4. General procedure for the preparation of 4,5-dibromo-2-{[3,4,5-tris(alkyloxy)benzoyl]oxy}phenyl 3,4,5-tris(alkyloxy)benzoates 7f–h. DCC (3.1 equiv) was added to a cooled solution of the appropriate **5** (2.2 equiv) in CH_2Cl_2 (10 mL) at 0 °C and after stirring for 10 min, DMAP and **2c** (1 equiv each) were added and the reaction mixture was stirred at room temperature for a further 20 h. The reaction mixture was treated with CH_2Cl_2 (30 mL), washed with 1 M HCl (2×30 mL) and H_2O (30 mL), dried ($MgSO_4$) and concentrated. The oily solid was treated with PE (30 mL) and the white solid was filtered off. The filtrate was evaporated and the residue purified by flash chromatography on SiO_2 with PE/CH_2Cl_2 (15:10) to give product **7** as white solid, which was dried for 1 h under freezing conditions (liquid N_2) and high vacuum (10^{-3} mbar).

3.1.4.1. 4,5-Dibromo-2-{[3,4,5-tris(decyloxy)benzoyl]oxy}phenyl 3,4,5-tris(decyloxy)benzoate (7f). Mp 33 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, J=6.4 Hz, 18H; 6CH_3), 1.27–1.50 (m, 84H; 6(CH_2)$_7$$CH_3$), 1.69–1.76 (m, 12H; 6OCH$_2$CH_2), 3.81 (t, J=6.3 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.21 (s, 4H; Ar-H), 7.69 (s, 2H; Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.0 (6CH_3), 22.6, 26.0, 26.1, 29.2, 29.3, 29.4, 29.6, 29.7, 30.3, 31.9 (6CH_3(CH_2)$_8$), 69.0 (4OCH_2), 73.5 (2OCH_2), 108.3 (4CH), 121.3 (2CBr), 122.3, 128.1 (2CH), 142.1, 143.1, 152.9, 163.6 (2CO) ppm. FTIR (ATR): 2953 (s), 2917 (vs), 2849 (vs), 1743 (vs), 1589 (s), 1468 (s), 1430 (s), 1335 (vs), 1256 (m), 1196 (vs), 1112 (vs), 944 (m), 740 (w), 720 (w), 637 (w), 609 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)= 283 (2.94), 229 (0.52). MS (ESI), *m/z* (%): 1436.1 (45) [M$^+$+Na+H], 573.7 (100), 433.6 (35). Anal. calcd for $C_{80}H_{132}Br_2O_{10}$ (1410.8): C, 67.97; H, 9.41. Found: C, 67.97; H, 9.37.

3.1.4.2. 4,5-Dibromo-2-{[3,4,5-tris(undecyloxy)benzoyl]oxy}phenyl 3,4,5-tris(undecyloxy)benzoate (7g). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, J=6.4 Hz, 18H; 6CH_3), 1.21–1.50 (m, 96H; 6(CH_2)$_8$$CH_3$), 1.67–1.78 (m, 12H; 6OCH$_2$CH_2), 3.81 (t, J=6.3 Hz, 8H; 4OCH_2), 3.98 (t, J=6.5 Hz, 4H; 2OCH_2), 7.21 (s, 4H; Ar-H), 7.69 (s, 2H; Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (6CH_3), 22.6, 26.0, 26.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 30.3, 31.9 (6CH_3(CH_2)$_9$), 69.0 (2OCH_2), 73.5 (2OCH_2), 108.3 (4CH), 121.3 (2CBr), 122.3, 128.1 (2CH), 142.1, 143.1, 152.9, 163.6 (2CO) ppm. FTIR (ATR): 2953 (s), 2916 (vs), 2849 (vs), 1744 (vs), 1589 (s), 1471 (s), 1463 (s), 1429 (s), 1336 (vs), 1259 (m), 1196 (vs), 1113 (vs), 944 (m), 739 (w), 720 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=276 (3.36), 229 (0.54), 211 (0.47), 208 (0.47). MS (ESI), *m/z* (%): 1520.1 (100) [M$^+$+Na], 615.5 (90), 461.4 (35). Anal. calcd for $C_{86}H_{144}Br_2O_{10}$ (1497.9): C, 68.96; H, 9.69. Found: C, 68.95; H, 9.69.

3.1.4.3. 4,5-Dibromo-2-{[3,4,5-tris(dodecyloxy)benzoyl]oxy}phenyl 3,4,5-tris(dodecyloxy)benzoate (7h). ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.88 (t, J=6.1 Hz, 18H; 6CH_3), 1.20–1.52 (m, 108H; 6(CH_2)$_9$$CH_3$), 1.61–1.80 (m, 12H; 6OCH$_2$CH_2), 3.81 (t, J=6.2 Hz, 8H; 4OCH_2), 3.98 (t, J=6.4 Hz, 4H; 2OCH_2), 7.21 (s, 4H; Ar-H), 7.69 (s, 2H; Ar-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=14.1 (6CH_3), 22.7, 26.0, 26.1, 29.2, 29.3, 29.4, 29.6, 29.7, 29.8, 30.3, 31.9 (6CH_3(CH_2)$_{10}$), 69.0 (4OCH_2), 73.5 (2OCH_2), 108.3 (4CH), 121.3 (2CBr), 122.3, 128.1 (2CH), 142.1, 143.1, 152.9, 163.6 (2CO) ppm. FTIR (ATR): 2953 (s), 2916 (vs), 2849 (vs), 1744 (vs), 1589 (s), 1464 (s), 1430 (s), 1336 (vs), 1258 (m), 1197 (vs), 1113 (vs), 945 (m), 739 (w), 720 (w), 607 (w) cm^{-1}. UV–vis (CH_2Cl_2): λ_{max} (log ε)=277 (3.37), 229 (0.60), 219 (0.56). MS (Micro Tof), *m/z* (%): 1604.0 (75) [M$^+$+Na−H], 711.5 (12). Anal. calcd for $C_{92}H_{156}Br_2O_{10}$ (1579.0): C, 69.85; H, 9.94. Found: C, 70.21; H, 10.02.

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Stereoselective synthesis of (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines

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Abstract—The first synthesis of the title compounds has been achieved starting from chloralamides by a route involving chemical and electrochemical steps. *N*-(1-Alkoxy-2,2,2-trichloroethyl)benzamides were efficiently prepared from chloralbenzamides and were electrochemically converted into *N*-(1-alkoxy-2,2-dichloroethyl)benzamides in high yields by cathodic reduction in a protic medium. Thionation of these compounds with Lawesson's reagent followed by basic treatment gave novel (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines in fair to quantitative yields.

1. Introduction

Thiazoline chemistry is receiving considerable attention because of its occurrence in biologically active natural products of interest such as curacin A,[1] thiangazole,[2] mirabazoles,[3] apratoxins,[4] etc. Furthermore, thiazolines are being used as building blocks in pharmaceutical drug discovery.[5,6] Some thiazoline derivates present interesting activity such as anti-HIV,[2a] anti-cancer,[7] antimitotic,[1b,1c] and antibiotic[5c] agents. Therefore, new procedures for preparing these compounds attract substantial research interest.

Over the years, a number of approaches to make these heterocycles have been developed.[8] The most commonly used synthetic approaches to these compounds are based on cyclodehydration of β-hydroxythioamides under the Mitsunobu conditions,[5a,9] the Burgess reagent [methyl *N*-(triethylammonium sulfonyl)carbamate],[5a,9b] [bis(2-methoxyethyl)amino]-sulfur trifluoride,[10] or diethylamidosulfur trifluoride.[11] Condensations of 2-aminothiols with nitriles,[12] carboxylic acids,[13] esters,[14] iminoethers,[15] or iminotriflates[16] is also exploitable reactions. Thiazolines have also been prepared from acylamino and thioacylamino alcohols[11,17,18] or by multistep conversions from oxazolines.[19] More recent methods have been described, like ruthenium-catalyzed oxidation of thiazolidine to thiazoline,[20] reaction of aminothiols with *N*-acylbenzotriazoles under microwave irradiation,[21] or annulation of thioamides with 2-alkynoates.[22]

Chloral is an inexpensive multipurpose starting material for organic synthesis.[23] We have recently developed a new preparative methodology based on using chloral derivates having a molecular arrangement suitable to undergo a direct heterocyclization process that is promoted electrochemically. This method was successfully applied to prepare new types of 2-oxazolines,[23,24] which provided access to novel 2-imidazolidinones,[25] 1,3-oxazolidines, and 1,3-thiazolidines.[26] One of the most advantageous features of this synthetic tactic lies in the synthesis of chlorinated oxazolines, since severe problems of chemical incompatibility with the usual chlorinating reagents can be avoided by using certain prechlorinated synthons derived from chloral. Given the previous success of our methodology on the synthesis of 2-oxazolines, and in order to expand the number of 2-thiazoline derivatives available, we recognized the opportunity to attempt an approach to synthesis 5-chloro-2-thiazolines, since these products pertain to a hitherto unknown family of compounds, of interest by themselves, as well as for their synthetic potential.

With the aim of exploring the possibility of adaptation of our earlier preparative strategy to this new objective, chloralamide **2a** was transformed to trichloromethyl thioamide **8a** (Scheme 1, route A) by treatment with Lawesson's reagent[27,28] (LR). In contrast to what was expected on the basis of our previous experiments on 2-oxazoline electrosynthesis, a direct generation of the targeted (*E*)-5-chloro-4-methoxy-2-thiazoline **7a** by cathodic reduction of **8a** was not feasible. This process was found to be totally unselective, probably due to equality in electroactivity at thiocarbonyl and trichloromethyl centers. Fortunately, this adversity could be overcome by carrying out an electroreduction–thionation

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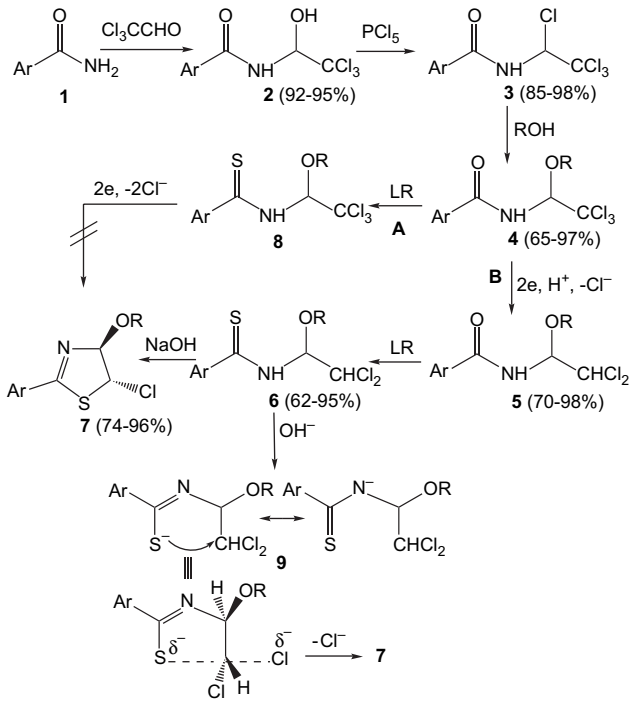
steps run (Scheme 1, route B), instead of the failed thionation–electroreduction reaction sequence.



Entry	Ar	R
a	C_6H_5	CH_3
b	C_6H_5	CH_3CH_2
c	C_6H_5	$C_6H_5CH_2CH_2$
d	4-ClC_6H_4	$C_6H_5CH_2CH_2$
e	4-MeC_6H_4	$C_6H_5CH_2$
f	4-MeC_6H_4	4-$MeOC_6H_5CH_2$
g	2-ClC_6H_4	3,4,5-$(MeO)_3C_6H_2CH_2$
h	2-MeC_6H_4	3,4,5-$(MeO)_3C_6H_2CH_2$

Scheme 1.

2. Results and discussion

Chloralamides **2** were prepared[29] in almost quantitative yields by reaction of chloral hydrate with benzamides **1** (Scheme 1). In order to prepare *N*-(1-alkoxy-2,2,2-trichloroethyl)benzamides **4**, compounds **2** were firstly converted into *N*-(1,2,2,2-tetrachloroethyl)benzamides **3** in high yields by treatment with phosphorus pentachloride, as described previously.[29b,30] Products **3** were selectively monoalkoxylated by simple treatment with a mixture of the corresponding alcohol and triethylamine (ratio 1:1) to give the targeted intermediates **4** in good to quantitative yields.[24]

The viability of a direct transformation of intermediates **4** to products **7** based on previous results concerning the electrosynthesis of 2-oxazolines[23,24] was investigated (route A). Thionation of compound **4a** with LR gave **8a** (72 %), which was electrolyzed in an aprotic medium (−1.6 V vs SCE) leading to a complex mixture of unidentified products instead of the expected thiazoline **7a**, due to an indiscriminate electrode process. In view of this difficulty it was intended that an alternative reaction sequence like route B would be able to provide the required compounds **7**, since the non-sulfurated intermediates **4** would be able to undergo a more selective electrochemical reduction than the sulfurated intermediates **8**. Thus, cathodic reductions of compounds **4** in a protic medium were carried out under constant potential of −1.7 V vs SCE. The electricity consumption was 2 F/mol of **4** in all cases. After electrolyses the reaction products were easily isolated in high yields by simple mixing of the catholyte solution with water and filtration. After crystallization highly pure white compounds were isolated and identified by elemental analysis and IR, MS, and NMR spectroscopy as intermediates **5**.

Complete conversions of amides **5** into thioamides **6** were achieved by treatment with Lawesson's reagent on refluxing toluene for 1 h and isolated by column chromatography, resulting in yellow products in fair to high yields that were identified and characterized by elemental analysis and IR, MS, and NMR spectroscopy.

Alkaline treatment of compounds **6** under mild temperature conditions provided products in good to quantitative yields, which were identified by the usual techniques as (*E*)-4-alkoxy-5-chloro-2-thiazolines **7**. As far as we know, this is the first time that compounds of this type have been synthesized. They seem to have special interest due to a potential capacity to be used as synthetic intermediates to prepare many other heterocyclic derivatives.

^{1}H NMR spectroscopic analyses confirmed that transformation of compounds **6** to products **7** occurs with total stereoselectivity toward the formation of (*E*)-isomers. A transition state between anionic species **9** and final products **7** involving minimal steric interactions between the stationary chlorine atom and a vicinal alkoxyl group explains the stereochemical fate of this internal displacement process. This configurational assignment is firmly supported by categorical studies[31] on stereochemistry of substituted five-membered cyclic compounds, from which it has been established as a general rule that the arrangement of vicinal protons corresponds to a (*E*)-configuration when they show spin coupling constants of $J<5$ Hz, whereas a (*Z*)-configuration always shows coupling constants with $J>5$ Hz, being ~8 Hz the value most frequently found. This method clearly leads to the conclusion that the stereochemistry of compounds **7** corresponds to a (*E*)-configuration, since the coupling constant between H-4 and H-5 protons is remarkably small, with *J* values ranging from 1.0 to 1.2 Hz in all cases.

To conclude, an effective method for the synthesis of previously unattainable (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines is reported. Versatility, good yields, easy availability of starting materials, mildness, and simple experimental procedure are noteworthy advantages of this approach.

3. Experimental

3.1. General

NMR spectra were determined on Bruker AV-200, Bruker AV-300, or Bruker AV-400 with tetramethylsilane as internal reference. Electron-impact mass spectra were obtained on Thermoquest trace MS spectrometer under an ionizing voltage of 70 eV. FAB^+ were obtained on Autospec 5000 VG spectrometer. IR spectra (Nujol emulsions) were recorded on a Nicolet Impact 400 spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Büchi Melting point B-540, and are uncorrected. Electrochemical experiments were performed with an Amel 552 potentiostat coupled to an Amel 721 integrator.

3.2. Electrochemical preparation of *N*-(1-alkoxy-2,2-dichloroethyl)benzamides (5)

Electrolysis of compounds **4** was carried out under constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The temperature was kept at approximately 18 °C by external cooling. The reduction was performed in DMF (50 mL)–AcOH (1 mL)–$LiClO_4$ 0.5 M. Anhydrous sodium carbonate (1 g) was placed in the anode compartment to prevent accumulation of electrogenerated acid. Solutions of compounds **4** (5 mmol) were electrolyzed under a cathodic potential of −1.7 V vs SCE. The duration of the electrolyses ranged from 1.8 to 2.0 h. The average current intensity was 10.7 mA/cm^2 at the beginning, and 1.02 mA/cm^2 at the end. The cell voltage values remained below 5 V in all cases. The electricity consumption was 2 F/mol in all cases. Electrolyses carried out using $NaBF_4$, which is a less potentially hazardous electrolyte[32] than $LiClO_4$, gave similar results. These syntheses were found to be reproducible but with moderate current efficiency (around 40%) by working in DMF (50 mL)–AcOH (0.6 mL)–$NaBF_4$ 0.5 M and using graphite (−1.8 V vs SCE) instead of mercury as cathodic material.

All the electrolysis products were isolated by pouring the catholyte solution into ice–water, and the resulting solids were collected by filtration and dried under vacuo. Products **5** were isolated as white solids and were crystallized from the appropriated solvents giving satisfactory IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses.

3.2.1. *N*-(2,2-Dichloro-1-methoxyethyl)benzamide (5a). Crystallization from petroleum ether gave white needles (70%); mp 98–99 °C (Found: C 48.21; H 4.37; N 5.70, $C_{10}H_{11}Cl_2NO_2$ requires: C 48.41; H 4.47; N 5.65); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.53 (s, 3H), 5.70 (dd, 1H, *J*=9.0, 2.2 Hz), 5.90 (d, 1H, *J*=2.2 Hz), 6.82 (d, 1H, *J*=9.0 Hz), 7.46–7.59 (m, 3H), 7.84 (d, 2H, *J*=7.3 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 56.88, 72.26, 82.91, 127.16, 128.78, 132.42, 132.94, 167.69; MS *m*/*z* (%) 215 (3), 182 (12), 176 (23), 164 (52), 105 (100), 77 (82); IR (Nujol) 3222, 1646, 1526, 1460, 1343, 1276, 1191, 1117, 1074, 1026, 784, 694 cm^{-1}.

3.2.2. *N*-(2,2-Dichloro-1-ethoxyethyl)benzamide (5b). Crystallization from petroleum ether gave white needles (80%); mp 98–99 °C (Found: C 50.47; H 4.95; N 5.37, $C_{11}H_{13}Cl_2NO_2$ requires: C 50.40; H 5.00; N 5.34); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 1.26 (t, 3H, *J*=7.0 Hz), 3.71–3.82 (m, 2H), 5.78 (dd, 1H, *J*=9.5, 2.4 Hz), 5.89 (d, 1H, *J*=2.4 Hz), 6.85 (d, 1H, *J*=9.5 Hz), 7.44–7.57 (m, 3H), 7.84 (d, 2H, *J*=6.8 Hz); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz) 14.95, 65.23, 72.67, 81.54, 127.24, 128.83, 132.42, 133.16, 167.59; MS *m*/*z* (%) 224 (4), 218 (14), 216 (22), 178 (11), 105 (100), 77 (58), 51 (18); IR (Nujol) 3211, 1635, 1524, 1466, 1379, 1085, 791, 696 cm^{-1}.

3.2.3. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]benzamide (5c). Crystallization from petroleum ether gave white needles (75%); mp 88 °C (Found: C 60.45; H 4.99; N 4.16, $C_{17}H_{17}Cl_2NO_2$ requires: C 60.37; H 5.07; N 4.14); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.93 (t, 2H, *J*=6.8 Hz), 3.89–3.94 (m, 2H), 5.76 (dd, 1H, *J*=9.5, 2.3 Hz), 5.84 (d, 1H, *J*=2.3 Hz), 6.59 (d, 1H, *J*=9.5 Hz), 7.20–7.26 (m, 5H), 7.45 (t, 2H, *J*=7.7 Hz), 7.58 (t, 1H, *J*=7.7 Hz), 7.71 (d, 2H, *J*=7.2 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 36.00, 70.17, 72.49, 81.59, 126.41, 127.17, 128.39, 128.75, 129.08, 132.39, 132.97, 138.29, 167.53; MS *m*/*z* (%) 216 (3), 182 (4), 105 (77), 104 (100), 91 (22), 77 (68); IR (Nujol) 3250, 1638, 1525, 1467, 1347, 1278, 1122, 1081, 1027 cm^{-1}.

3.2.4. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]-4-chlorobenzamide (5d). Crystallization from petroleum ether gave white needles (78%); mp 91–93 °C (Found: C 54.77; H 4.28; N 3.80, $C_{17}H_{16}Cl_3NO_2$ requires: C 54.79; H 4.33; N 3.76); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.91 (t, 2H, *J*=6.7 Hz), 3.86–3.96 (m, 2H), 5.72 (dd, 1H, *J*=9.4, 2.3 Hz), 5.82 (d, 1H, *J*=2.3 Hz), 6.50 (d, 1H, *J*=9.4 Hz), 7.19–7.26 (m, 5H), 7.41 (d, 2H, *J*=8.5 Hz), 7.62 (d, 2H, *J*=8.5 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 36.03, 70.29, 72.40, 81.73, 126. 44, 128.40, 128.61, 129.01, 129.09, 131.35, 138.33, 138.74, 166.48; MS *m*/*z* (%) 250 (2), 216 (3), 141 (44), 139 (85), 111 (49), 104 (100), 91 (37), 7 (19); IR (Nujol) 3287, 1653, 1526, 1464, 1379, 1344, 1102, 1018, 850, 793, 702 cm^{-1}.

3.2.5. *N*-(2,2-Dichloro-1-benzyloxyethyl)-4-methylbenzamide (5e). Crystallization from petroleum ether gave white needles (98%); mp 120–121 °C (Found: C 60.33; H 5.10; N 4.11, $C_{17}H_{17}Cl_2NO_2$ requires: C 60.37; H 5.07; N 4.14); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.42 (s, 3H), 4.71 (d, 1H, *J*=11.9 Hz), 4.77 (d, 1H, *J*=11.9 Hz), 5.86–5.88 (m, 2H), 6.77 (d, 1H, *J*=9.7 Hz), 7.26–7.42 (m, 7H), 7.69 (d, 2H, *J*=8.1 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 21.52, 71.07, 72.62, 80.96, 127.19, 128.01, 128.11, 128.51, 129.43, 130.13, 136.80, 143.08, 167.48; MS *m*/*z* (%) 230 (11), 196 (75), 160 (16), 119 (94), 91 (100), 77 (23), 65 (41); IR (Nujol) 3275, 1645, 1522, 1505, 1462, 1344, 1098, 794, 738, 695 cm^{-1}.

3.2.6. *N*-[2,2-Dichloro-1-(4-methoxybenzyloxy)ethyl)]-4-methylbenzamide (5f). Crystallization from a mixture of petroleum ether and chloroform gave white needles (72%); mp 97–99 °C (Found: C 58.69; H 5.18; N 3.83, $C_{18}H_{19}Cl_2NO_3$ requires: C 58.71; H 5.20; N 3.80); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.42 (s, 3H), 3.79 (s, 3H), 4.63 (d, 1H, *J*=11.7 Hz), 4.72 (d, 1H, *J*=11.7 Hz), 5.82–5.85

(m, 2H), 6.77 (d, 1H, J=9.6 Hz), 6.87 (d, 2H, J=8.6 Hz), 7.28 (d, 2H, J=8.1 Hz), 7.32 (d, 2H, J=8.6 Hz), 7.70 (d, 2H, J=8.1 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.51, 55.22, 70.76, 72.70, 80.57, 113.90, 127.19, 128.73, 129.41, 129.87, 130.16, 143.04, 159.56, 167.43; FAB$^+$ 368 (M^++1, 30); IR (Nujol) 3289, 1639, 1614, 1535, 1504, 1342, 1299, 1249, 1176, 1089, 1033, 788, 764 cm^{-1}.

3.2.7. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy)-ethyl]-2-chlorobenzamide (5g). Crystallization from a mixture of petroleum ether and chloroform gave white needles (80%); mp 93–96 °C (Found: C 50.91; H 4.54; N 3.08, $C_{19}H_{20}Cl_3NO_5$ requires: C 50.86; H 4.49; N 3.12); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.83 (s, 3H), 3.86 (s, 6H), 4.67 (d, 1H, J=11.9 Hz), 4.78 (d, 1H, J=11.9 Hz), 5.84–5.87 (m, 2H), 6.66 (s, 2H), 6.97 (d, 1H, J=9.9 Hz), 7.35–7.47 (m, 3H), 7.68 (dd, 1H, J=7.5 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 56.17, 60.87, 71.23, 72.33, 80.63, 105.46, 127.35, 130.33, 130.57, 130.79, 132.06, 132.18, 133.75, 137.90, 153.34, 166.90; MS *m*/*z* (%) 449 (M^++2, 1), 447 (M^++1, 1), 216 (21), 196 (47), 181 (37), 169 (18), 139 (100), 111 (30), 75 (22); IR (Nujol) 3219, 3181, 1659, 1591, 1525, 1506, 1328, 1231, 1128, 1078, 822, 760 cm^{-1}.

3.2.8. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy-ethyl)]-2-methylbenzamide (5h). Crystallization from a mixture of petroleum ether and chloroform gave white needles (81%); mp 107–109 °C (Found: C 55.92; H 5.46; N 3.30, $C_{20}H_{23}Cl_2NO_5$ requires: C 56.08; H 5.41; N 3.27); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.51 (s, 3H), 3.85 (s, 3H), 3.87 (s, 6H), 4.67 (d, 1H, J=12.0 Hz), 4.76 (d, 1H, J=12 Hz), 5.83–5.87 (m, 2H), 6.49 (d, 1H, J=9.5 Hz), 6.66 (s, 2H), 7.23–7.39 (m, 4H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 20.02, 56.11, 60.81, 71.17, 72.51, 80.42, 105.28, 125.97, 126.66, 130.75, 131.36, 132.18, 134.85, 136.46, 137.86, 153.33, 170.16; MS *m*/*z* (%) 429 (M^++2, 1), 427 (M^+, 1), 198 (41), 196 (72), 181 (36), 169 (16), 160 (8), 148 (8), 138 (7), 119 (100), 91 (48), 65 (16); IR (Nujol) 3292, 3243, 1679, 1592, 1511, 1332, 1236, 1130, 1091, 993, 784, 732 cm^{-1}.

3.3. Preparation of *N*-(1-alkoxy-2,2-dichloroethyl)thiobenzamides (6)

A toluene solution (50 mL) of **5** (3 mmol) and LR (3 mmol) was refluxed for 1 h. After cooling, the suspended solid was filtered off and the solvent was evaporated under reduced pressure. The products were isolated by silica gel column chromatography. Products **6a–e** (ethyl acetate–hexane 1:6); product **6f** (ethyl acetate–hexane 1:3); product **6g** (diethyl ether–hexane 1:1), and product **6h** (dichloromethane–hexane 2:3). Afterward the yellow solids were crystallized from the appropriated solvents. All compounds gave satisfactory IR, ^{1}H NMR, ^{13}C NMR, mass spectra, and elemental analyses.

3.3.1. *N*-(2,2-Dichloro-1-methoxyethyl)thiobenzamide (6a). Crystallization from hexane gave yellow prisms (79%); mp 100–101 °C (Found: C 45.62; H 4.13; N 5.22; S 12.08, $C_{10}H_{11}Cl_2NOS$ requires: C 45.47; H 4.20; N 5.30; S 12.14); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 3.66 (s, 3H), 6.06 (d, 1H, J=2.1 Hz), 6.29 (dd, 1H, J=8.7, 2.1 Hz), 7.43–7.53 (m, 3H), 7.79–7.82 (m, 2H), 7.90 (br s, 1H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 58.25, 71.19, 87.45, 126.72, 128.73, 132.01, 140.97, 201.84; MS *m*/*z* (%) 263 (M^+, 2), 227 (8), 192 (33), 164 (13), 121 (100), 104 (26), 77 (34); IR (Nujol) 3273, 1510, 1459, 1365, 1235, 1098, 1011, 959, 794, 697 cm^{-1}.

3.3.2. *N*-(2,2-Dichloro-1-ethoxyethyl)thiobenzamide (6b). Crystallization from hexane gave yellow needles (70%); mp 90–91 °C (Found: C 47.55; H 4.66; N 5.01; S 11.70, $C_{11}H_{13}Cl_2NOS$ requires: C 47.49; H 4.71; N 5.03; S 11.53); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 1.31 (t, 3H, J=7.0 Hz), 3.84–3.96 (m, 2H), 6.06 (d, 1H, J=2.2 Hz), 6.34 (dd, 1H, J=8.4, 2.2 Hz), 7.41–7.45 (m, 2H), 7.52 (tt, 1H, J=7.4, 1.2 Hz), 7.78–7.81 (m, 2H), 7.89 (d, 1H, J=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 14.99, 66.49, 71.39, 86.01, 126.70, 128.69, 131.96, 140.92, 201.26; FAB$^+$ 278 (M^++1); IR (Nujol) 3287, 1500, 1464, 1378, 1333, 1231, 1087, 947, 798, 694 cm^{-1}.

3.3.3. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]thiobenzamide (6c). Crystallization from petroleum ether gave yellow needles (76%); mp 86–87 °C (Found: C 57.58; H 4.83; N 4.02; S 9.00, $C_{17}H_{17}Cl_2NOS$ requires: C 57.63; H 4.84; N 3.95; S 9.05); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.97 (t, 2H, J=6.2 Hz), 3.94–4.12 (m, 2H), 6.01 (d, 1H, J=2.2 Hz), 6.32 (dd, 1H, J=8.40, 2.2 Hz), 7.22–7.63 (m, 11H); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz): 36.06, 71.28, 71.35, 86.11, 126.53, 126.71, 128.46, 128.61, 129.12, 131.94, 138.18, 140.68, 201.27; FAB$^+$ 354 (M^++1); IR (Nujol) 3288, 1499, 1459, 1367, 1226, 1144, 1088, 1011, 945, 794, 751, 695, 672 cm^{-1}.

3.3.4. *N*-[2,2-Dichloro-1-(2-phenylethoxy)ethyl]-4-chlorothiobenzamide (6d). Crystallization from hexane gave yellow needles (62%); mp 62–65 °C (Found: C 52.62; H 4.22; N 3.55; S 8.23, $C_{17}H_{16}Cl_3NOS$ requires: C 52.52; H 4.15; N 3.60; S 8.25); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.92–2.99 (m, 2H), 3.87–3.99 (m, 1H), 4.05–4.16 (m, 1H), 5.98 (d, 1H, J=2.2 Hz), 6.25 (dd, 1H, J=8.2, 2.2 Hz), 7.20–7.27 (m, 5H), 7.32 (d, 2H, J=8.4 Hz), 7.50 (d, 2H, J=8.4 Hz), 7.54 (d, 1H, J=8.2 Hz); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz) 36.04, 71.20, 71.38, 86.17, 126.54, 128.01, 128.46, 128.73, 129.13, 138.27, 138.82, 199.57; MS *m*/*z* (%) 352 (1), 316 (6), 232 (6), 212 (7), 157 (15), 155 (36), 138 (26), 105 (100), 77 (30); IR (Nujol) 3297, 1594, 1507, 1468, 1406, 1371, 1239, 1094, 1013, 948, 841, 793, 762, 701 cm^{-1}.

3.3.5. *N*-(2,2-Dichloro-1-benzyloxyethyl)-4-methylthiobenzamide (6e). Crystallization from petroleum ether gave yellow needles (64%); mp 88 °C (Found: C 57.72; H 4.78; N 3.99; S 9.00, $C_{17}H_{17}Cl_2NOS$ requires: C 57.63; H 4.84; N 3.95; S 9.05); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.38 (s, 3H), 4.87 (s, 2H), 6.02 (d, 1H, J=2.2 Hz), 6.43 (dd, 1H, J=8.0, 2.2 Hz), 7.19 (d, 2H, J=7.9 Hz), 7.30–7.43 (m, 5H), 7.58 (d, 2H, J=8.2 Hz), 7.83 (d, 1H, J=8.0 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.40, 71.45, 72.50, 85.77, 126.75, 128.10, 128.35, 128.63, 129.26, 136.60, 137.98, 142.81, 200.89; MS *m*/*z* (%) 318 (1), 262 (6), 247 (9), 212 (51), 176 (29), 135 (97), 118 (49), 91 (100), 65 (33); IR (Nujol) 3297, 1492, 1458, 1366, 1325, 1230, 1181, 1139, 1076, 1035, 925, 786, 756, 706, 662 cm^{-1}.

3.3.6. *N*-[2,2-Dichloro-1-(4-methoxybenzyloxy)ethyl]-4-methylthiobenzamide (6f). Crystallization from a mixture

of hexane and dichloromethane gave yellow prisms (95%); mp 92–94 °C (Found: C 56.38; H 5.07; N 3.55; S 8.31, $C_{18}H_{19}Cl_2NO_2S$ requires: C 56.25; H 4.98; N 3.64; S 8.34); ^{1}H NMR. δ ($CDCl_3$, 400 MHz) 2.39 (s, 3H), 3.79 (s, 3H), 4.80 (s, 2H), 6.00 (d, 1H, J=2.2 Hz), 6.38 (dd, 1H, J=8.3, 2.2 Hz), 6.88 (d, 2H, J=8.7 Hz), 7.20 (d, 2H, J=8.1 Hz), 7.35 (d, 2H, J=8.7 Hz), 7.61 (d, 2H, J=8.3 Hz), 7.81 (d, 1H, J=8.1 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.42, 55.25, 71.50, 72.25, 85.50, 114.01, 126.76, 128.53, 129.25, 129.97, 137.98, 142.80, 159.76, 200.70; FAB$^+$ 384 (M^++1, 13); IR (Nujol) 3379, 3277, 1610, 1513, 1489, 1342, 1248, 1176, 1076, 935, 821, 789 cm^{-1}.

3.3.7. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy)ethyl]-2-chlorothiobenzamide (6g). Crystallization from hexane gave pale yellow needles (94%); mp 146–147 °C (Found: C 48.89; H 4.34; N 3.10; S 7.01, $C_{19}H_{20}Cl_3NO_4S$ requires: C 49.10; H 4.34; N 3.01; S 6.90); ^{1}H NMR. δ ($CDCl_3$, 400 MHz) 3.85 (s, 3H), 3.87 (s, 6H), 4.77 (d, 1H, J=11.9 Hz), 4.88 (d, 1H, J=11.9 Hz), 5.99 (d, 1H, J=2.3 Hz), 6.38 (dd, 1H, J=8.4, 2.3 Hz), 6.67 (s, 2H), 7.30–7.42 (m, 3H), 7.51 (dd, 1H, J=7.1, 2.1 Hz), 7.84 (d, 1H, J=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 56.12, 60.82, 71.08, 72.29, 84.49, 105.64, 127.18, 128.12, 130.09, 130.97, 131.48, 137.99, 141.21, 153.25, 200.05; FAB$^+$ 464 (M^++1, 2); IR (Nujol) 3180, 1597, 1542, 1508, 1332, 1235, 1153, 1128, 1099, 974, 943 cm^{-1}.

3.3.8. *N*-[2,2-Dichloro-1-(3,4,5-trimethoxybenzyloxy)ethyl]-2-methylthiobenzamide (6h). Crystallization from a mixture of petroleum ether and chloroform gave pale yellow prisms (68%); mp 128–130 °C (Found: C 54.14; H 5.28; N 3.20; S 7.20, $C_{20}H_{23}Cl_2NO_4S$ requires: C 54.06; H 5.22; N 3.15; S 7.22); ^{1}H NMR. δ ($CDCl_3$, 400 MHz) 2.43 (s, 3H), 3.86 (s, 3H), 3.87 (s, 6H), 4.77 (d, 1H, J=11.9 Hz), 4.84 (d, 1H, J=11.9 Hz), 5.99 (d, 1H, J=2.2 Hz), 6.44 (dd, 1H, J=8.5 Hz, J=2.2 Hz), 6.67 (s, 2H), 7.21–7.32 (m, 4H), 7.67 (d, 1H, J=8.5 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 19.68, 56.14, 60.84, 71.38, 72.52, 84.34, 105.45, 126.11, 126.38, 129.58, 131.01, 131.69, 132.90, 137.99, 143.21, 153.31, 204.61; FAB$^+$ 444 (M^++1, 5); IR (Nujol) 3189, 1598, 1508, 1332, 1236, 1151, 1130, 1091, 939, 786, 761 cm^{-1}.

3.4. Preparation of (*E*)-4-alkoxy-2-aryl-5-chloro-2-thiazolines (7)

Sodium hydroxide (10 mmol) was added to acetonitrile solutions of compounds **6** (1 mmol), and the reaction mixture was stirred at room temperature for 6 h. After filtration and evaporation of the solvent under reduced pressure, compounds **7** were collected as yellow oils, and were purified by column chromatography. All novel compounds gave satisfactory elemental analyses and IR, ^{1}H NMR, ^{13}C NMR, and mass spectra (FAB$^+$).

3.4.1. 5-Chloro-2-phenyl-4-methoxy-2-thiazoline (7a). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (74%); (Found: C 52.83; H 4.49; N 6.07; S 14.14, $C_{10}H_{10}ClNOS$ requires: C 52.75; H 4.43; N 6.15; S 14.08); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.61 (s, 3H), 5.71 (d, 1H, J=1.2 Hz), 6.00 (d, 1H, J=1.2 Hz), 7.40–7.47 (m, 2H), 7.51–7.60 (m, 1H), 7.87–7.91 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 56.98, 69.79, 115.33, 128.71, 128.94, 132.10, 132.49, 170.08; FAB$^+$ 228 (M^++1); IR 2931, 2834, 1606, 1527, 1448, 1335, 1308, 1229, 1092, 1035, 944, 909, 814, 767, 733, 690 cm^{-1}.

3.4.2. 5-Chloro-4-ethoxy-2-phenyl-2-thiazoline (7b). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (79%); (Found: C 54.73; H 4.89; N 5.86; S 13.32, $C_{11}H_{12}ClNOS$ requires: C 54.65; H 5.00; N 5.79; S 13.26); ^{1}H NMR δ (CD_3COCD_3, 300 MHz) 1.20 (t, 3H, J=6.0 Hz), 3.79–3.91 (m, 2H), 6.00 (d, 1H, J=0.9 Hz) 6.08 (d, 1H, J=0.9 Hz), 7.53–7.61 (m, 3H), 7.89–7.92 (m, 2H); ^{13}C NMR δ (CD_3COCD_3, 75.4 MHz) 15.59, 65.54, 71.58, 115.04, 129.53, 129.78, 130.81, 133.39, 169.33; MS m/z (%) 241 (M^+, 7), 206 (14), 196 (8), 161 (15), 138 (20), 104 (100), 93 (12), 77 (21), 58 (15); IR 2979, 2900, 1611, 1452, 1326, 1231, 1176, 1090, 1037, 942, 813, 769, 691 cm^{-1}.

3.4.3. 5-Chloro-2-phenyl-4-(2-phenylethoxy)-2-thiazoline (7c). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (80%); (Found: C 64.40; H 5.11; N 4.43; S 10.17, $C_{17}H_{16}ClNOS$ requires: C 64.24; H 5.07; N 4.41; S 10.09); ^{1}H NMR δ ($CDCl_3$, 200 MHz) 2.94 (t, 2H, J=7.2 Hz), 3.87–4.15 (m, 2H), 5.59 (d, 1H, J=1.2 Hz), 6.08 (d, 1H, J=1.2 Hz), 7.23–7.30 (m, 5H), 7.39–7.48 (m, 3H), 7.86 (dd, 2H, J=8.0, 1.4 Hz); ^{13}C NMR δ ($CDCl_3$, 50.4 MHz) 36.28, 70.14, 70.34, 114.31, 126.33, 128.37, 128.67, 128.88, 128.92, 132.11, 132.42, 138.25, 169.80; FAB$^+$ 318 (M^++1); IR 3063, 3023, 2928, 1607, 1525, 1497, 1451, 1327, 1234, 1173, 1090, 908, 816, 733, 695 cm^{-1}.

3.4.4. 5-Chloro-2-(4-chlorophenyl)-4-(2-phenylethoxy)-2-thiazoline (7d). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (94%); (Found: C 58.10; H 4.30; N 4.00; S 9.03, $C_{17}H_{15}Cl_2NOS$ requires: C 57.96; H 4.29; N 3.98; S 9.10); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.95 (t, 2H, J=7.2 Hz), 3.94 (dt, 1H, J=9.5, 7.2 Hz), 4.09 (dt, 1H, J=9.5, 7.2 Hz), 5.63 (d, 1H, J=1.2 Hz), 6.05 (d, 1H, J=1.2 Hz), 7.20–7.28 (m, 5H), 7.41 (dd, 2H, J=6.7, 2.0 Hz), 7.80 (dd, 2H, J=6.7, 2.0 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 36.33, 70.28, 70.54, 114.35, 126.41, 128.44, 128.91, 129.02, 130.19, 130.66, 138.27, 138.75, 168.62; FAB$^+$ 352 (M^++1); IR 2919, 1603, 1491, 1401, 1311, 1242, 1176, 1092, 944, 837, 739, 703 cm^{-1}.

3.4.5. 4-Benzyloxy-5-chloro-2-(4-methylphenyl)-2-thiazoline (7e). Chromatography (silica gel, hexane–ethyl acetate 6:1) gave yellow oil (96%); (Found: C 64.12; H 5.11; N 4.31; S 10.16, $C_{17}H_{16}ClNOS$ requires: C 64.24; H 5.07; N 4.41; S 10.09); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.41 (s, 3H), 4.80 (d, 1H, J=11.7 Hz), 4.91 (d, 1H, J=11.7 Hz), 5.73 (d, 1H, J=1.2 Hz), 6.15 (d, 1H, J=1.2 Hz), 7.24–7.38 (m, 7H), 7.77 (d, 2H, J=8.2 Hz); ^{13}C NMR δ ($CDCl_3$, 100.4 MHz) 21.62, 70.28, 71.23, 113.47, 128.00, 128.02, 128.50, 128.97, 129.40, 129.52, 137.24, 143.19, 170.07; FAB$^+$ 318 (M^++1); IR 3031, 2925, 1605, 1507, 1455, 1311, 1178, 1073, 940, 818, 734, 699 cm^{-1}.

3.4.6. 5-Chloro-4-(4-methoxybenzyloxy)-2-(4-methylphenyl)-2-thiazoline (7f). Chromatography (silica gel, hexane–ethyl acetate 4:1) gave yellow oil (95%); (Found: C 62.27; H 5.17; N 4.10; S 9.31, $C_{18}H_{18}ClNO_2S$ requires: C 62.15; H 5.22; N 4.03; S 9.22); ^{1}H NMR δ ($CDCl_3$,

400 MHz) 2.41 (s, 3H), 3.81 (s, 3H), 4.74 (d, 1H, J=11.3 Hz), 4.84 (d, 1H, J=11.3 Hz), 5.70 (d, 1H, J= 1.1 Hz), 6.13 (d, 1H, J=1.1 Hz), 6.90 (d, 2H, J=8.4 Hz), 7.25 (d, 2H, J=8.3 Hz), 7.33 (d, 2H, J=8.3 Hz), 7.78 (d, 2H, J=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.62, 55.27, 70.34, 70.98, 113.17, 113.91, 128.97, 129.24, 129.40, 129.53, 129.83, 143.17, 159.49, 169.94; MS m/z (%) 348 (M^++1, 1), 350 (M^++3, 1), 311 (1), 176 (33), 121 (100), 118 (14), 91 (10), 77 (12), 58 (7); IR 2999, 2954, 2931, 2834, 1608, 1514, 1465, 1303, 1248, 1178, 1038 cm^{-1}.

3.4.7. 5-Chloro-2-(2-chlorophenyl)-4-(3,4,5-trimethoxybenzyloxy)-2-thiazoline (7g). Chromatography (silica gel, hexane–ethyl acetate 3:1) gave yellow oil (93%); (Found: C 53.39; H 4.52; N 3.23; S 7.58, $C_{19}H_{19}Cl_2NO_4S$ requires: C 53.28; H 4.47; N 3.27; S 7.49); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.84 (s, 3H), 3.87 (s, 6H), 4.76 (d, 1H, J=11.5 Hz), 4.88 (d, 1H, J=11.5 Hz), 5.75 (d, 1H, J=1.3 Hz), 6.15 (d, 1H, J=1.3 Hz), 6.63 (s 2H), 7.33–7.50 (m, 3H), 7.76 (dd, 1H, J=1.8, 7.6 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 56.12, 60.83, 70.60, 71.61, 105.20, 112.51, 126.92, 130.82, 131.28, 131.43, 132.14, 132.61, 132.86, 137.81, 153.35, 168.07; FAB$^+$ 428 (M^++1, 12); IR 3293, 3056, 2996, 2935, 2838, 1668, 1592, 1506, 1461, 1126, 833, 755 cm^{-1}.

3.4.8. 5-Chloro-2-(2-methylphenyl)-4-(3,4,5-trimethoxybenzyloxy)-2-thiazoline (7h). Chromatography (silica gel, hexane–ethyl acetate 3:1) gave yellow oil (95%); (Found: C 58.94; H 5.33; N 3.38; S 7.82, $C_{20}H_{22}ClNO_4S$ requires: C 58.89, H 5.44; N 3.43; S 7.86); ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.61 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 4.76 (d, 1H, J=12.0 Hz), 4.87 (d, 1H, J=12.0 Hz), 5.72 (d, 1H, J=1.2 Hz), 6.19 (d, 1H, J=1.2 Hz), 6.63 (s, 2H), 7.24–7.41 (m, 3H), 7.59 (dd, 1H, J=1.3, 7.6 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.29, 56.06, 60.82, 70.19, 71.59, 105.01, 113.88, 125.95, 130.23, 131.06, 131.47, 131.52, 132.64, 137.66, 137.82, 153.31, 170.42; MS m/z (%) 407 (M^+, 1), 225 (2), 196 (4), 182 (12), 181 (100), 176 (53), 151 (3), 148 (10), 117 (8), 90 (6), 77 (4); IR 3063, 2997, 2961, 2935, 2876, 1731, 1593, 1507, 1461, 1339, 1235, 1127 cm^{-1}.

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32. Caution must be exercised when handling perchlorates in order to exclude explosion risk. Evaporation of organic solutions containing perchlorates requires to be carried out in vacuo and at moderate temperature. Contact with strong acids must be avoided.

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Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on a '[3+3] cyclization/domino retro-Michael–aldol–lactonization' strategy

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Abstract—The $TiCl_4$-mediated [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-silyloxyalk-2-en-1-ones afforded 2-acetylphenols, which were transformed into functionalized chromones. The Me_3SiOTf-mediated condensation of the latter with 1,3-bis(silyl enol ethers) and subsequent domino 'retro-Michael–aldol–lactonization' reaction afforded 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones.

1. Introduction

Functionalized 6*H*-benzo[*c*]chromen-6-ones (dibenzo[*b*,*d*]-pyran-6-ones) are present in a number of pharmacologically relevant natural products. For example, autumnariol has been isolated from *Eucomis autumnalis* Greab. (Liliaceae).[1] The isolation of related 6*H*-benzo[*c*]chromen-6-ones, such as autumnariniol,[2] alternariol,[3] or altenuisol,[4] has been reported (Chart 1).[5] It has been demonstrated that 6*H*-benzo[*c*]-chromen-6-ones are specific inhibitors of the growth of endothelic cells[6] and represent estrogen receptors.[7] Ellagic and coruleoellagic acid, which have been isolated mainly from plant sources,[8] occur both as glycosides and aglycons. Dibenzo[*c*,*d*]chromen-6-ones occur in a number of natural antibiotics and antitumor agents, such as the gilvocarcins, chrysomycins, and ravidomycins.[9]

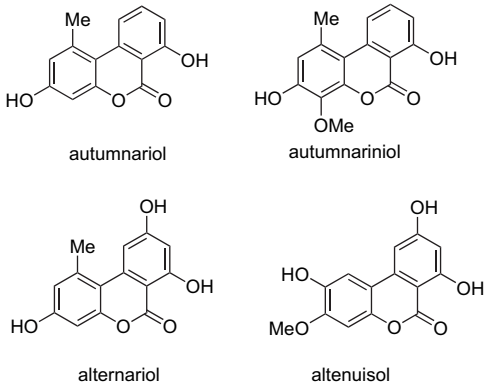

Chart 1. 7-Hydroxy-6*H*-benzo[*c*]chromen-6-ones in nature.

6*H*-Benzo[*c*]chromen-6-ones have been prepared by cyclizations of *o*-bromobenzoic acids with phenols,[10] intramolecular palladium(II) catalyzed coupling reactions of aryl benzoates,[11] and Suzuki reactions.[12–14] Harris et al. reported the synthesis of 9-*O*-methylalternariol by condensation of the dianion of acetylacetone with a protected salicylate.[15,16] We have recently reported[17] the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones by condensation of 1,3-bis(silyl enol ethers)[18] with 4-silyloxybenzopyrylium triflates, in situ generated from chromones,[19] and subsequent base-mediated domino 'retro-Michael–aldol–lactonization' reaction. The preparative scope of this method severely depends on the availability of the chromones as starting materials. Chan and co-workers developed an elegant approach to arenes by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-siloxyalk-2-en-1-ones.[20] Based on this work we herein report a new approach to functionalized chromones by [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-silyloxyalk-2-en-1-ones. The combination of these reactions with the domino reaction of chromones with 1,3-bis(silyl enol ethers) provides a versatile strategy for the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones. Notably, this strategy relies on the sequential use of 1,3-bis(silyl enol ethers)[18] at two stages of the synthesis.

Keywords: Chromones; Cyclizations; Domino reactions; Oxygen heterocycles; Silyl enol ethers.
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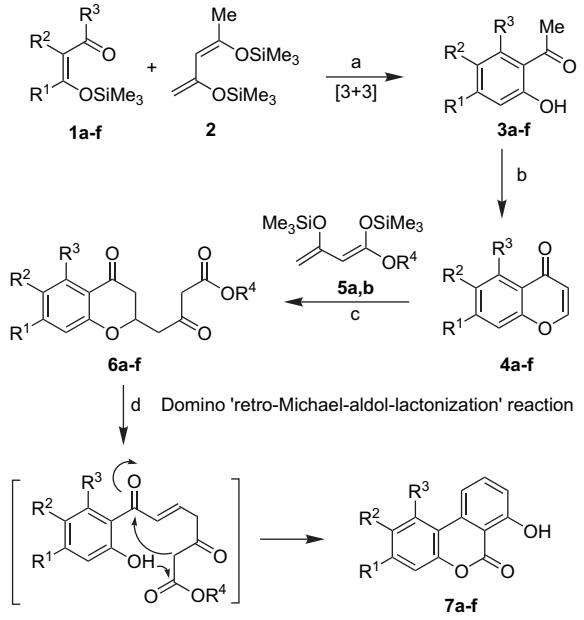
2. Results and discussion

The $TiCl_4$-mediated [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene (**2**) with 3-silyloxyalk-2-en-1-ones, following the conditions reported by Chan[20] and us,[21] afforded the 2-acetylphenols **3a–f** (Scheme 1, Table 1). The synthesis of chloro-[21e] and acetoxy-substituted[21f] salicylates by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with appropriate 3-silyloxyalk-2-en-1-ones has been previously reported. The cyclization of 1,3-bis(silyl enol ether) **2** with **1d** and **1e** proceeded with very good regioselectivity, which can be explained as previously reported.[20,21i] Treatment of the acetylphenols with $HC(OEt)_3$ and $HClO_4$ afforded the chromones **4a–f**. During the formation of **4f**, the acetoxy group was cleaved to give a hydroxyl group. The Me_3SiOTf-mediated condensation of **4a–f** with 1-ethoxy or 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**,**b**) gave the 2,3-dihydrobenzopyrans **6a–f**. Treatment of the latter with NEt_3 in EtOH afforded the novel 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **7a–f**. The formation of the latter can be explained by a domino 'retro-Michael–aldol–lactonization' reaction.[17] The synthesis of compounds **3b**,[22] **3c**,[23] and **4c**[24] has been previously reported.



Scheme 1. Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **7a–f**: (a) $TiCl_4$, CH_2Cl_2, −78 °C; (b) $HC(OEt)_3$, $HClO_4$ (70%), reflux, 12 h; (c) (1) Me_3SiOTf (1.3 equiv), 20 °C, 1 h; (2) **5a**,**b** (1.3 equiv), CH_2Cl_2, 0→20 °C, 12 h; (3) HCl (10%); (d) NEt_3 (2.0 equiv), EtOH, 20 °C, 12 h.

The combination of two different cyclization reactions of 1,3-bis(silyl enol ethers) allows a facile approach to a number of novel 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones. The core structure of the products contains 13 carbon atoms out of which 9 carbons are derived from the two 1,3-bis(silyl enol ethers), 3 carbons from the 3-silyloxyalk-2-en-1-one and 1 carbon from the orthoformate.

In conclusion, we have reported the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on sequential reactions of 1,3-bis(silyl enol ethers) with 3-silyloxyalk-2-en-1-ones and chromones.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (^1H, 7.26 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. ^{13}C NMR spectral assignments are supported by DEPT analyses. Mass spectral data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography silica gel (60–200 mesh) was used. Melting points are uncorrected.

3.2. General procedure for the synthesis of 2-acetylphenols 3a–f

To a stirred CH_2Cl_2 solution (2 mL/mmol) of 1,3-bis(silyl enol ether) **2** (1.0 mmol) and 3-siloxyalk-2-en-1-one **1** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at −78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 20 h and a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The organic layer was separated and extracted with diethyl ether (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/heptane=1:4).

3.2.1. 1-(3-Chloro-2,4-diethyl-6-hydroxyphenyl)ethanone (3a). Starting with 4-chloro-5-(trimethylsilyloxy)hept-4-en-3-one (**1a**) (1.021 g, 4.3 mmol), 2,4-bis(trimethylsilyloxy)penta-1,3-diene (**2**) (1.041 g, 4.3 mmol), and $TiCl_4$ (0.812 g, 4.3 mmol), **3a** was obtained (0.490 g, 50%) as

Table 1. Products and yields

	R^1	R^2	R^3	R^4	**3** (%)[a]	**4** (%)[a]	**6** (%)[a]	**7** (%)[a]
a	Et	Cl	Et	Me	50	80	77	28 (48)
b	Me	Me	Me	Et	51	70	65	22 (42)
c	Me	H	Me	Et	40	84	68	24 (46)
d	Me	$-(CH_2)_4-$		Et	36	78	61	50
e	Me	$-(CH_2)_3-$		Me	20	69	73	35 (60)
f	Me	OAc	Me	Me	42	—	—	—
f	Me	OH	Me	Me	—	70	68	33 (40)

[a] Yields of isolated products; the synthesis of compounds **3b**,[22] **3c**,[23] and **4c**[24] has been previously reported; values in brackets: yields based on recovered starting material.

a yellow solid; mp 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.40 (s, 1H, OH), 6.74 (s, 1H, Ar-H), 3.00 (q, 2H, J=7.6 Hz, CH_2), 2.75 (q, 2H, J=7.3 Hz, CH_2), 2.67 (s, 3H, CH_3), 1.32–1.19 (m, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.8 (CO), 157.9 (C–OH), 148.7, 141.6 (C), 125.8 (C–Cl), 122.8 (C), 116.8 (CH), 32.8 (CH_3), 28.3, 26.0 (CH_2), 14.7, 13.7 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3229 (w), 1678 (m), 1225 (s), 1081 (s), 856 (w). MS (EI, 70 eV): *m*/*z* (%) 226 (M^+, 34), 211 (100), 193 (17), 173 (10). Anal. Calcd for $C_{12}H_{15}O_2Cl$ (226.0): C 63.57, H 6.62; found: C 63.97, H 6.57.

3.2.2. 1-(6-Hydroxy-2,3,4-trimethylphenyl)ethanone (3b). The synthesis of **3b** has been previously reported.[22] Starting with 3-methyl-4-(trimethylsilyloxy)pent-3-en-2-one (**1b**) (0.500 g, 2.68 mmol), **2** (0.653 g, 2.68 mmol), and $TiCl_4$ (0.506 g, 2.68 mmol), **3b** (0.241 g, 51%) was obtained as a slight yellow solid; mp 62 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.87 (s, 1H, OH), 6.66 (s, 1H, Ar-H), 2.58 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.12 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 206.3 (CO), 157.7, 144.2, 136.4, 128.1, 122.3 (C), 116.6 (CH), 32.7, 21.5, 20.2, 15.0 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3191 (m), 2975 (s), 1661 (m), 1450 (s), 1304 (m), 845 (s). MS (EI, 70 eV): *m*/*z* (%) 178 (M^+, 30), 163 (100), 135 (8), 91 (12), 44 (14). Anal. Calcd for $C_{11}H_{14}O_2$ (178.1): C 74.15, H 7.86; found: C 74.00, H 7.96.

3.2.3. 1-(6-Hydroxy-2,4-dimethylphenyl)ethanone (3c). The synthesis of **3c** has been previously reported.[23] Starting with 4-trimethylsilyloxy-pent-3-en-2-one (**1b**) (1.000 g, 5.81 mmol), **2** (1.417 g, 5.81 mmol), and $TiCl_4$ (1.098 g, 5.81 mmol), **3b** (0.380 g, 40%) was obtained as a slight yellow solid; mp 42 °C.

3.2.4. 1-(2-Hydroxy-4-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethanone (3d). Starting with 1-(2-trimethylsilyloxycyclohex-1-enyl)ethanone (**1d**) (0.500 g, 2.35 mmol), **2** (0.573 g, 2.35 mmol), and $TiCl_4$ (0.444 g, 2.35 mmol), **3d** (0.172 g, 36%) was obtained as a brownish solid; mp 55 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.49 (s, 1H, OH), 6.67 (s, 1H, Ar-H), 2.93 (t, 2H, J=6.4 Hz, CH_2), 2.64 (s, 3H, CH_3), 2.57 (t, 2H, J=6.7 Hz, CH_2), 2.19 (s, 3H, CH_3), 1.87–1.68 (m, 4H, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 206.1 (CO), 158.9, 145.1, 137.6, 127.3, 121.0 (C), 117.2 (CH), 33.4 (CH_3), 31.3, 26.6, 22.9, 22.6 (CH_2), 20.4 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3410 (w), 2950 (s), 1629 (m), 1460 (s), 1340 (s), 1298 (m). MS (EI, 70 eV): *m*/*z* (%) 204 (M^+, 64), 189 (100), 161 (43), 146 (15), 44 (39). HRMS (EI) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1145; found: 204.1141.

3.2.5. 1-(5-Hydroxy-7-methylindan-4-yl)ethanone (3e). Starting with 2-(1-trimethylsilyloxy-ethylidene)cyclopentanone (**1a**) (1.000 g, 5.04 mmol), **2** (1.230 g, 5.04 mmol), and $TiCl_4$ (0.952 g, 5.04 mmol), **3e** (0.200 g, 20%) was obtained as a yellow solid; mp 58 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 12.18 (s, 1H, OH), 6.74 (s, 1H, Ar-H), 2.92 (t, 2H, J=7.3 Hz, CH_2), 2.83 (t, 2H, J=7.6 Hz, CH_2), 2.66 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2.07 (quint, 2H, J=7.6 Hz, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 205.8 (CO), 161.8. 152.0, 135.4, 134.1, 120.3 (C), 111.6 (CH), 33.8 (CH_2), 33.0 (CH_3), 31.5, 24.3 (CH_2), 20.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 2952 (s), 1622 (w), 1470 (s), 1353 (s), 1234 (w), 841 (w). MS (EI, 70 eV): *m*/*z* (%) 190 (M^+, 40), 175 (100), 115 (12), 91 (16), 43.0 (24). HRMS (EI) calcd for $C_{12}H_{14}O_2$ $[M]^+$: 190.0988; found: 190.0985.

3.2.6. 1-[3-(Acetoxy)-6-hydroxy-2,4-dimethylphenyl]-ethanone (3f). Starting with **1f** (1.005 g, 4.37 mmol), **2** (1.066 g, 4.37 mmol), and $TiCl_4$ (0.825 g, 4.37 mmol), **3f** (0.410 g, 42%) was obtained as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.80 (s, 1H, OH), 6.71 (s, 1H, Ar-H), 2.61 (s, 3H, CH_3COO), 2.34 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 169.1(CO), 159.5, 141.0, 138.6, 130.4, 121.2 (C), 118.3 (CH), 33.3, 20.7, 17.5, 16.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3407 (br), 2929 (w), 1760 (s), 1198 (s), 908 (w). MS (EI, 70 eV): *m*/*z* (%) 222 (M^+, 9), 180 (84), 165 (100), 43 (23). HRMS (EI) calcd for $C_{12}H_{14}O_4$ $[M]^+$: 222.0887; found: 222.0881.

3.3. General procedure for the synthesis of chromones 4a–f

To ethanone **3** (1.0 equiv) were slowly added triethyl orthoformate (20 equiv) and perchloric acid (70%, 1.3 equiv) and the reaction mixture was refluxed for 20 h at 80 °C. After cooling to 20 °C, the reaction mixture was filtered and washed with cold water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel).

3.3.1. 6-Chloro-5,7-diethylchromen-4-one (4a). Starting with **3a** (0.302 g, 1.33 mmol), triethyl orthoformate (3.936 g, 26.60 mmol, 20 equiv), and perchloric acid (70%) (0.172 g, 1.72 mmol), **4a** (0.251 g, 80%) was obtained as a colorless solid; mp 80 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.68 (d, 1H, J=6.1 Hz, CH), 7.18 (s, 1H, Ar-H), 6.23 (d, 1H, J=5.8 Hz, CH), 3.55 (q, 2H, J=7.3 Hz, CH_2), 2.85 (q, 2H, J=7.6 Hz, CH_2), 1.32–1.19 (m, 6H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 178.4 (CO), 156.5 (C), 153.1 (CH), 148.0, 144.2, 131.7, 121.0 (C), 116.3, 114.4 (CH), 28.0, 24.3 (CH_2), 13.7, 13.3 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3436 (br), 2970 (w), 1648 (s), 1436 (s), 1254 (s), 843 (s). MS (EI, 70 eV): *m*/*z* (%) 236 (M^+, 89), 219 (100), 193 (20), 115 (11). Anal. Calcd for $C_{13}H_{13}O_2Cl$ (236.0): C 66.10, H 5.55; found: C 65.97, H 5.63.

3.3.2. 5,6,7-Trimethylchromen-4-one (4b). Starting with **3b** (0.202 g, 1.15 mmol), triethyl orthoformate (3.400 g, 23.00 mmol), and perchloric acid (70%) (0.152 g, 1.50 mmol), **4b** (0.151 g, 70%) was obtained as a white solid; mp 124 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.64 (d, 1H, J=5.8 Hz, CH), 7.07 (s, 1H, Ar-H), 6.20 (d, 1H, J=5.7 Hz, CH), 2.83 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 180.0 (CO), 156.0 (C), 153.0 (CH), 143.0, 138.5, 133.2, 121.3 (C), 116.2, 114.1 (CH), 21.6, 17.3, 15.2 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3438 (br), 2925 (w), 1647 (s), 1428 (s), 1236 (s), 1001 (s), 848 (s). MS (EI, 70 eV): *m*/*z* (%) 188 (M^+, 100), 173 (57), 145 (9), 91 (7). Anal. Calcd for $C_{12}H_{12}O_2$ (188.0): C 76.60, H 6.38; found: C 76.20, H 6.31.

3.3.3. 5,7-Dimethylchromen-4-one (4c). The synthesis of **4c** has been previously reported.[24] Starting with **3c**

(0.175 g, 1.07 mmol), triethyl orthoformate (3.502 g, 21.34 mmol), and perchloric acid (70%) (0.140 g, 1.40 mmol), **4c** (0.156 g, 84%) was obtained as a brownish solid; mp 58 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.66 (d, 2H, J=5.8 Hz, CH), 7.04 (s, 1H, Ar-H), 6.92 (s, 1H, Ar-H), 6.20 (d, 2H, J=6.1 Hz, CH), 2.80 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6 (CO), 158.1 (C), 153.5 (CH), 143.7, 140.7 (C), 129.2 (CH), 121.0 (C), 116.3, 114.5 (CH), 22.7, 21.5 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3432 (br), 2925 (m), 1648 (s), 1350 (s), 1239 (s), 827 (s). MS (EI, 70 eV): *m*/*z* (%) 174 (M^+, 100), 159 (12), 145 (30), 91 (36), 39 (21). Anal. Calcd for $C_{11}H_{10}O_2$ (174.1): C 75.58, H 5.74; found: C 75.23, H 5.80.

3.3.4. 6-Methyl-7,8,9,10-benzo[*f*]chromen-1-one (4d). Starting with **3d** (0.150 g, 0.73 mmol), triethyl orthoformate (2.161 g, 14.60 mmol), and perchloric acid (0.095 g, 0.95 mmol), **4d** (0.122 g, 78%) was obtained as a white solid; mp 70 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.66 (d, 1H, J=5.7 Hz, CH), 7.07 (s, 1H, Ar-H), 6.23 (d, 1H, J=6.1 Hz, CH), 3.45 (t, 2H, J=6.4 Hz, CH_2), 2.64 (t, 2H, J=5.4 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.80–1.77 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.9 (CO), 156.2 (C), 153.3 (CH), 143.6, 139.7, 133.3, 120.9 (C), 116.5, 114.7 (CH), 30.1, 27.8, 23.1, 22.5 (CH_2), 20.8 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3437 (br), 2925 (s), 1620 (s), 1605 (s), 1455 (s), 1232 (s), 850 (m). MS (EI, 70 eV): *m*/*z* (%) 214 (M^+, 100), 199 (80), 181 (29), 131 (33), 69 (51). Anal. Calcd for $C_{14}H_{14}O_2$ (214.1): C 78.85, H 6.94; found: C 78.70, H 6.30.

3.3.5. 4-Methyl-2,3-dihydro-1*H*-6-oxacyclopenta[*a*]-naphthalen-9-one (4e). Starting with **3e** (0.240 g, 1.30 mmol), triethyl orthoformate (3.863 g, 26.10 mmol), and perchloric acid (0.170 g, 1.70 mmol), **4e** (0.180 g, 69%) was obtained as a colorless solid; mp 130 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70 (d, 1H, J=6.1 Hz, CH), 7.03 (s, 1H, Ar-H), 6.21 (d, 1H, J=5.8 Hz, CH), 3.50 (t, 2H, J=7.6 Hz, CH_2), 2.81 (t, 2H, J=7.6 Hz, CH_2), 2.33 (s, 3H, CH_3), 2.15 (p, 2H, J=7.6 Hz, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 179.4 (CO), 157.0 (C), 154.6 (CH), 144.6, 141.3, 140.7, 133.9 (C), 116.4, 113.9 (CH), 34.0, 29.3, 24.0 (CH_2), 20.3 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3438 (br), 2914 (w), 1662 (s), 1603 (s), 1230 (m), 849 (m). MS (EI, 70 eV) *m*/*z* (%) 199 (M^+, 100), 184 (5), 128 (12), 115 (7). HRMS (EI, 70 eV) calcd for $C_{13}H_{11}O_2$ $[M]^+$: 199.0754; found: 199.0747.

3.3.6. 6-Hydroxy-5,6-dimethylchromen-4-one (4f). Starting with **3f** (0.205 g, 0.90 mmol), triethyl orthoformate (2.666 g, 18.01 mmol), and perchloric acid (70%) (0.117 g, 1.17 mmol), **4f** (0.120 g, 70%) was obtained as a colorless solid; mp 140 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.67 (d, 1H, J=5.8 Hz, CH), 7.10 (s, 1H, Ar-H), 6.20 (d, 1H, J=7.1 Hz, CH), 2.81 (s, 3H, CH_3), 2.36 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 177.0 (CO), 154.8 (CH), 149.5, 148.5, 131.6, 121.7, 119.4 (C), 117.0, 113.0 (CH), 17.7, 13.9 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3410 (br), 2950 (s), 1642 (w), 1634 (w), 1294 (w), 1280 (w). MS (EI, 70 eV): *m*/*z* (%) 190 (M^+, 94), 161 (56), 147 (54), 43 (100). HRMS (EI, 70 eV) calcd for $C_{11}H_{10}O_3$ $[M]^+$: 190.0624; found: 190.0621.

3.4. General procedure for the synthesis of 4-(chroman-2-yl)-3-oxobutyrates 6a–f

To chromone **4** (1.0 equiv) was added Me_3SiOTf (1.3 equiv) at 20 °C. After stirring for 1 h, CH_2Cl_2 (8 mL) and the 1,3-bis(silyl enol ether) **5** (1.3 equiv) were added at 0 °C. The mixture was stirred for 12 h at 20 °C and was subsequently poured into an aqueous solution of hydrochloric acid (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified from polar side-products by column flash chromatography (silica gel, *n*-hexane/EtOAc=1:1) to give **6a–f**. Products **6a–f** were isolated and characterized and subsequently transformed into **7a–f**.

3.4.1. 4-(6-Chloro-5,7-diethyl-4-oxochroman-2-yl)-3-oxobutyric acid methyl ester (6a). Starting with **4a** (0.212 g, 0.89 mmol), TMSOTf (0.256 g, 1.15 mmol), and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**) (0.300 g, 1.15 mmol), **6a** (0.240 g, 77%) was obtained as a brownish solid; mp 72 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.73 (s, 1H, Ar-H), 4.95–4.84 (m, 1H, CH chain), 3.76 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2), 3.32–3.27 (m, 2H, CH_2), 3.14 (dd, 1H, ^2J=17.0 Hz, ^3J=7.3 Hz, CH_2), 2.90 (dd, 1H, ^2J=17.0 Hz, ^3J=7.1 Hz, CH_2), 2.79–2.70 (m, 4H, CH_2), 1.22 (t, 3H, J=7.6 Hz, CH_3), 1.16 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.0, 191.4, 160.9 (CO), 150.3, 148.1, 148.5, 145.5, 145.4 (C), 115.9, 73.0 (CH), 53.0 (OCH_3), 50.0, 47.7, 44.4, 28.5, 24.7 (CH_2), 14.0 (2C, CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3437 (br), 2977 (m), 1746 (s), 1677 (s), 1417 (s), 1194 (s), 867 (m). MS (EI, 70 eV): *m*/*z* (%) 352 (M^+, 78), 320 (14), 237 (100), 167 (40), 115 (9). Anal. Calcd for $C_{18}H_{21}O_5Cl$ (352.0): C 61.27, H 5.95; found: C 61.19, H 6.10.

3.4.2. 3-Oxo-4-(5,6,7-trimethyl-4-oxochroman-2-yl)-butyric acid ethyl ester (6b). Starting with **4b** (0.13 g, 0.70 mmol), TMSOTf (0.20 g, 0.91 mmol), and 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5b**) (0.25 g, 0.91 mmol), **6b** (0.145 g, 65%) was obtained as a yellow solid; mp 56 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.63 (s, 1H, Ar-H), 4.90–4.79 (m, 1H, CH), 4.20 (q, 2H, J=7.0 Hz, CH_2), 3.53 (s, 2H, CH_2), 3.15 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.85 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.72–2.70 (m, 2H, CH_2), 2.67 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.28 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.4, 193.2, 166.8 (CO), 159.9, 145.0, 139.7, 129.6, 118.0 (C), 116.2, 72.4 (CH), 61.6, 50.0, 47.5, 44.4 (CH_2), 21.7, 17.5, 14.9, 14.0 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3435 (br), 2982 (w), 1741 (s), 1677 (s), 1271 (s), 1100 (m), 857 (w). MS (EI, 70 eV): *m*/*z* (%) 318 (M^+, 60), 272 (20), 203 (9), 189 (42), 162 (100), 91 (16). HRMS (EI, 70 eV) calcd for $C_{18}H_{22}O_5$ $[M]^+$: 318.1462; found: 318.1458. Anal. Calcd for $C_{18}H_{22}O_5$ (318.0): C 67.92, H 6.91; found: C 68.44, H 6.75.

3.4.3. 4-(5,7-Dimethyl-4-oxochroman-2-yl)-3-oxobutyric acid ethyl ester (6c). Starting with **4c** (0.228 g, 1.30 mmol), TMSOTf (0.375 g, 1.70 mmol), and 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5b**) (0.465 g, 1.70 mmol), **6c** (0.265 g, 68%) was obtained as a yellow

oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.61 (s, 2H, Ar-H), 4.93–4.82 (m, 1H, CH), 4.21 (q, 2H, J=7.3 Hz, CH_2), 3.53 (s, 2H, CH_2), 3.14 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.85 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.71–2.67 (m, 2H, CH_2), 2.58 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 1.28 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 192.2, 166.5 (CO), 162.07, 146.0, 141.9 (C), 126.2 (CH), 117.2 (C), 116.3, 73.1 (CH), 61.9, 50.3, 47.8, 44.2 (CH_2), 23.0, 22.0, 14.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3436 (br), 2979 (m), 1744 (s), 1614 (s), 1326 (s), 1029 (s), 846 (w). MS (EI, 70 eV): m/z (%) 304 (M^+, 71), 189 (34), 175 (100), 148 (96), 91 (40). Anal. Calcd for $C_{17}H_{20}O_5$ (304.1): C 67.67, H 6.57; found: C 67.84, H 6.61.

3.4.4. 4-(6-Methyl-1-oxo-2,3,7,8,9,10-hexahydro-1*H*-benzo[*f*]chromen-3-yl)-3-oxobutyric acid ethyl ester (6d). Starting with **4d** (0.092 g, 0.43 mmol), TMSOTf (0.124 g, 0.56 mmol), and 1-ethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5b**) (0.153 g, 0.56 mmol), **6d** (0.091 g, 61%) was obtained as a yellow oil. ^{1}H NMR (keto/enol=10:1, 250 MHz, $CDCl_3$, only keto tautomer was listed): δ 6.63 (s, 1H, Ar-H), 4.91–4.80 (m, 1H, CH), 4.21 (q, 2H, J=7.3 Hz, CH_2), 3.53 (s, 2H, CH_2), 3.17–3.0 (m, 1H, CH_2), 2.85 (dd, 1H, ^2J=16.3 Hz, ^3J=7.1 Hz, CH_2), 2.70–2.67 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.19–1.17 (m, 2H, CH_2), 1.73–1.66 (m, 6H, CH_2), 1.28 (t, 3H, J=7.0 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 192.7, 166.7 (CO), 159.9, 145.6, 140.7, 130.0, 117.1 (C), 116.3, 72.4 (CH), 61.3, 49.9, 47.3, 44.3, 30.9, 26.8, 23.3, 22.6 (CH_2), 20.41, 14.03 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3437 (br), 2925 (s), 1620 (s), 1605 (s), 1455 (s), 1232 (s), 850 (m). MS (EI, 70 eV): m/z (%) 344 (M^+, 73), 298 (15), 272 (17), 214 (100), 188 (85), 91 (11). Anal. Calcd for $C_{20}H_{24}O_5$ (344.2): C 69.73, H 6.97; found: C 69.72, H 7.16.

3.4.5. 4-(9-Methyl-8-oxo-1,2,3,6,7,8-hexahydro-5-oxacyclopenta[*b*]naphthalen-6-yl)-3-oxabutyric acid methyl ester (6e). Starting with **4e** (0.100 g, 0.54 mmol), TMSOTf (0.155 g, 0.70 mmol), and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**) (0.182 g, 0.70 mmol), **6e** (0.125 g, 73%) was obtained as a yellow solid; mp 68 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.59 (s, 1H, Ar-H), 4.93–4.82 (m, 1H, CH), 3.76 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2), 3.28 (t, 2H, J=7.9 Hz, CH_2), 3.18 (dd, 1H, ^2J=16.7 Hz, ^3J=7.3 Hz, CH_2), 2.88 (dd, 1H, ^2J=16.5 Hz, ^3J=7.3 Hz, CH_2), 2.72–2.66 (m, 4H, CH_2), 2.24 (s, 3H, CH_3), 2.15–2.06 (m, 2H, CH_2). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.4, 192.4, 167.2 (CO), 160.8, 148.6, 146.4, 142.8, 138.0 (C), 116.6, 73.5 (CH), 53.0 (OCH_3), 50.0, 47.8, 43.8, 34.7, 30.5, 25.2 (CH_2), 21.0 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3435 (br), 2982 (w), 1741 (s), 1677 (s), 1271 (s), 1100 (m), 857 (w). MS (EI, 70 eV): m/z (%) 316 (M^+, 59), 284 (15), 200 (100), 174 (50), 115 (12). HRMS (EI, 70 eV) calcd for $C_{18}H_{20}O_5$ $[M]^+$: 316.1305; found: 316.1303.

3.4.6. Methyl 4-(3,4-dihydroxy-5,7-dimethyl-4-oxo-2*H*-chromen-2-yl)-3-oxobutanoate (6f). Starting with **4f** (0.082 g, 0.45 mmol), TMSOTf (0.129 g, 0.58 mmol), and 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**) (0.150 g, 0.58 mmol), **6f** (0.093 g, 68%) was obtained as a yellow oil. ^{1}H NMR (keto/enol=10:3, 250 MHz, $CDCl_3$, only keto tautomer was listed): δ 6.69 (s, 1H, Ar-H), 4.95–4.77 (m, 1H, ring CH), 3.75 (s, 3H, OCH_3), 3.56 (s, 2H, chain CH_2), 3.19–3.07 (m, 1H, ring CH_2), 2.91–2.80 (m, 1H, ring CH_2), 2.72–2.66 (m, 2H, chain CH_2), 2.55 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 199.2, 192.7, 169.0 (CO), 159.5 (C–OH), 147.1, 138.9, 133.4, 133.1 (C), 117.7, 73.1 (CH), 53.0 (OCH_3), 50.0, 47.8, 44.6 (CH_2), 17.6, 14.6 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3476 (br), 2955 (w), 1748 (s), 1614 (s), 1196 (s), 1073 (m), 862 (w). MS (EI, 70 eV): m/z (%) 306 (M^+, 97), 274 (18), 191 (51), 164 (100), 135 (10). HRMS (EI, 70 eV) calcd for $C_{16}H_{18}O_6$ $[M]^+$: 306.1098; found: 306.1097.

3.5. General procedure for the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones 7a–f

To an EtOH solution (10 mL) of **6** was added NEt_3 (2.0 equiv) and the mixture was refluxed for 12 h at 80 °C. After cooling down to 20 °C, an aqueous solution of hydrochloric acid (1 M) and Et_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc=20:1→3:1) to give product **7**.

3.5.1. 3-Chloro-2,4-diethyl-8-hydroxy-10*H*-phenanthren-9-one (7a). Starting with **6a** (0.170 g, 0.48 mmol) and NEt_3 (0.097 g, 0.96 mmol), **7a** (0.041 g, 28%; 48% based on recovered starting material) was obtained as a colorless solid; mp 140 °C. Starting material **6a** (0.070 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.70 (s, 1H, OH), 8.14–8.06 (m, 2H, Ar-H), 7.55 (s, 1H, Ar-H), 7.47 (dd, 1H, J=6.4 Hz, J=2.7 Hz, Ar-H), 3.30 (q, 2H, J=7.3 Hz, CH_2), 2.82 (q, 2H, J=7.6 Hz, CH_2), 1.50 (t, 3H, J=7.3 Hz, CH_3), 1.28 (t, 3H, J=7.3 Hz, CH_3). ^{13}C NMR (62 MHz, $CDCl_3$): δ 165.7, 163.2, 150.0, 145.0, 140.2 (C), 137.0 (CH), 135.8, 133.0, 117.3 (C), 116.7, 116.5, 116.0 (CH), 107.0 (C), 27.6, 26.2 (CH_2), 13.3, 12.7 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3430 (br), 2910 (s), 1678 (s), 1224 (m), 1081 (w), 856 (w). MS (EI, 70 eV): m/z (%) 302 (M^+, 100), 287 (44), 267 (20), 152 (15), 57 (20). HRMS (EI, 70 eV) calcd for $C_{17}H_{15}O_3Cl$ $[M]^+$: 302.0704; found: 302.0704.

3.5.2. 7-Hydroxy-1,2,3-trimethylbenzo[*c*]chromen-6-one (7b). Starting with **6b** (0.120 g, 0.37 mmol) and NEt_3 (0.076 g, 0.75 mmol), **7b** (0.021 g, 22%; 42% based on recovered starting material) was obtained as a white solid; mp 182 °C. Starting material (**6b**) (0.040 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.68 (s, 1H, OH), 7.68 (d, 1H, J=7.9 Hz, Ar-H), 7.66 (s, 1H, Ar-H), 7.06–7.03 (m, 2H, Ar-H), 2.71 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 162.8, 152.2, 149.9, 139.9 (C), 136.9 (CH), 135.0, 134.0, 117.9 (C), 116.6, 116.4, 115.9 (CH), 107.3 (C), 21.6, 21.5, 16.7 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ 2952 (s), 1671 (w), 1477 (s), 1371 (s), 1238 (w), 817 (w). MS (EI, 70 eV): m/z (%) 254 (M^+, 100), 239 (32), 211 (47), 149 (19), 91 (5). HRMS (EI, 70 eV) calcd for $C_{16}H_{14}O_3$ $[M]^+$: 254.0937; found: 254.0940.

3.5.3. 7-Hydroxy-1,3-dimethylbenzo[*c*]-6-one (7c). Starting with **6c** (0.091 g, 0.30 mmol) and NEt_3 (0.060 g,

0.60 mmol), **7c** (0.017 g, 24%; 46% based on recovered starting material) was obtained as a white solid; mp 180 °C. Starting material (**6c**) (0.042 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.79 (s, 1H, OH), 7.80 (d, 1H, J=7.6 Hz, Ar-H), 7.70 (t, 1H, J=8.2 Hz, Ar-H), 7.08 (s, 1H, Ar-H), 7.31 (d, 1H, J=7.0 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.25 (s, 1H, Ar-H), 2.82 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 162.8, 152.2, 149.4, 140.1, 136.8, 136.7 (C), 136.6, 130.6, 116.6, 116.2, 115.7 (CH), 115.2, 106.3 (C), 25.4, 20.9, 16.7 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3410 (br), 2930 (s), 1675 (m), 1460 (s), 1225 (w), 814 (w). MS (EI, 70 eV): *m/z* (%) 240 (M^+, 100), 197 (15), 165 (10), 111 (21), 97 (30). HRMS (EI, 70 eV) calcd for $C_{15}H_{12}O_3$ $[M]^+$: 240.0781; found: 240.0781.

3.5.4. 4-Hydroxy-8-methyl-9,10,11,12-tetrahydro-6-oxabenzo[*c*]phenanthren-5-one (7d). Starting with **6d** (0.072 g, 0.20 mmol) and NEt_3 (0.041 g, 0.40 mmol), **7d** (0.028 g, 50%) was obtained as a slight yellow solid; mp 115 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.82 (s, 1H, OH), 7.78–7.66 (m, 2H, Ar-H), 7.08–7.03 (m, 2H, Ar-H), 3.45 (t, 2H, J=6.1 Hz, CH_2), 2.84 (t, 2H, J=5.4 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.89–1.77 (m, 4H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 163.0, 149.4, 139.0, 137.4 (C), 136.6 (CH), 123.9, 118.5, 118.2 (C), 116.8, 115.9 (CH), 107.2 (C), 33.3, 30.9, 23.8, 22.7 (CH_2), 20.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3130 (br), 1719 (w), 1663 (w), 1098 (w), 700 (w). MS (EI, 70 eV): *m/z* (%) 280 (M^+, 100), 265 (25), 214 (15), 149 (13), 57 (18). HRMS (EI, 70 eV) calcd for $C_{18}H_{16}O_3$ $[M]^+$: 280.1094; found: 280.1090.

3.5.5. 8-Hydroxy-4-methyl-2,3-dihydro-1*H*-6-oxacyclopenta[*c*]phenanthren-7-one (7e). Starting with **6e** (0.100 g, 0.31 mmol) and NEt_3 (0.063 g, 0.63 mmol), **7e** was obtained (0.030 g, 35%; 60% based on recovered starting material) as a colorless solid; mp 202 °C. Starting material (**6e**) (0.041 g) was recovered. ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.74 (s, 1H, OH), 7.68 (t, 1H, J=7.0 Hz, Ar-H), 7.63 (s, 1H, Ar-H), 7.06–7.03 (m, 2H, Ar-H), 3.42 (t, 2H, J=7.3 Hz, CH_2), 2.90 (t, 2H, J=7.9 Hz, CH_2), 2.34 (s, 3H, CH_3), 2.30–2.18 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.6, 165.9, 162.6, 150.0, 141.4, 140.6, 136.8 (C), 135.8, 115.3, 114.6, 114.6 (CH), 106.2 (C), 35.1, 29.5, 23.8 (CH_2), 18.5 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3420 (br), 2910 (s), 1653 (w), 1320 (w), 1229 (w), 846 (w). MS (EI, 70 eV): *m/z* (%) 266 (M^+, 100), 251 (24), 207 (10), 165 (8), 57 (10). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}O_3$ $[M]^+$: 266.0937; found: 266.0930.

3.5.6. 2,7-Dihydroxy-1,3-dimethyl-6*H*-benzo[*c*]chromen-6-one (7f). Starting with **6f** (0.120 g, 0.41 mmol) and NEt_3 (0.083 g, 0.82 mmol), **7f** (0.035 g, 33%; 40% based on recovered starting material) was obtained as a slight brownish solid mp 190 °C. Starting material (**6f**) (0.020 g) was recovered. ^{1}H NMR (250 MHz, DMSO-d_6): δ 11.69 (s, 1H, OH), 8.65 (s, 1H, OH), 7.87–7.77 (m, 2H, Ar-H), 7.12 (s, 1H, Ar-H), 7.09 (dd, 1H, J=8.2, 7.3 Hz, Ar-H), 2.64 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (62 MHz, DMSO-d_6): δ 165.3, 161.8, 151.0, 144.5 (C), 137.2 (CH), 136.6, 129.2, 122.8 (C), 117.6, 117.5, 116.3, 115.6 (CH), 106.3 (C), 17.3, 17.0 (CH_3). IR (Nujol, cm^{-1}): $\tilde{\nu}$ 3415 (br), 2940 (s), 1635 (m), 1240 (s), 1120 (m), 810 (w). MS (EI, 70 eV): *m/z* (%) 256 (M^+, 100), 213 (5), 207 (10), 165 (8), 57 (10). HRMS (ESI) calcd for $C_{15}H_{13}O_4$ $[M+H]^+$: 257.08084; found: 257.08069.

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Synthesis and inclusion capability of a β-cyclodextrin-tetrathiafulvalene derivative

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Abstract—The synthesis of 4,5-ethylenedithio-4′-[6-deoxy-β-cyclodextrin-6-yl-aminocarbonyl]-tetrathiafulvalene **3** is reported. Dominantly, the structure of **3** has been established on the basis of mass spectrometry, ROESY and ^{1}H NMR spectra, combined with a theoretical MM3 study, indicating an 'open-cavity structure'. The sensing ability of **3** and the formation constant of the complex [(**3**)-(1-adamantanol)] have been evaluated experimentally by UV–vis spectroscopy and theoretically by the MM3 docking procedure method.

1. Introduction

During the past decade much effort has been devoted to developing analysis systems for the detection of chemical and biological compounds, without any modification of the analytes.[1–5] Some chemically modified cyclodextrins (CDs) form relatively stable host-guest complexes, due to their inclusion capability, with a large variety of organic compounds.[6,7] Such derivatives might be useful for constructing molecule-sensing systems.[8–13] In previous papers we reported the synthesis[14–17] and sensing abilities[18,19] towards volatile organic compounds (VOC) of a new class of fluorescent sensors based on β-cyclodextrin fragment (β-CD) and indolizine unit. On the other hand, electrochemical sensors based on tetrathiafulvalene (TTF), a redox active unit extensively studied in the field of conducting molecular materials,[20] and various receptors such as crown ethers,[21] calix-arenes[22] or calix-pyrroles[23] have proved their efficiency in the sensing of anions or metallic cations. Therefore, the covalent association of the cyclodextrin platform with a TTF derivative appears to be particularly attractive in the prospective of controlling the host TTF–cyclodextrin—guest interaction through an electrochemical switch. At our knowledge, only two reports in the literature deal with covalent TTF–cyclodextrin derivatives,[24] prepared as precursors for Langmuir–Blodgett films, whereas inclusion TTF–cyclodextrin complexes have been used as mediators in the glucose–glucose oxidation reaction.[25] We report herein the synthesis and characterization of a new type of sensor consisting of β-CD and TTF units covalently linked, together with its sensing ability towards the 1-adamantanol.

2. Results and discussion

2.1. Synthesis

The covalent link between the β-CD and TTF units has been performed upon reaction of 6-deoxy-6-aminocyclodextrin **1**[26] and 4,5-ethylenedithio-4′-chlorocarbonyl-tetrathiafulvalene (EDT–TTF–COCl) **2** in homogenous phase in dry DMF, under argon, thus providing the mixed β-CD–TTF derivative **3** (Scheme 1). Indeed, the reaction of **2** with various primary amines has been described as a straightforward method for the preparation of EDT–TTF–amides.[27] The chemical structure of **3** has been established by NMR and mass spectra. In the latter, the presence of $[M^+ + 23]$ at 1477 and $[\beta\text{-CD} + CO + 23]^+$ at 1185 fragments prove undoubtedly the proposed molecular structure. In order to assign all the chemical shifts of the protons, the ^{1}H NMR spectra have been performed in two different solvents, e.g., DMSO-d_6 and D_2O. The ROESY 2D spectrum, measured in D_2O, shows clearly the lack of interaction between the TTF fragment and the CD cavity, very likely because of

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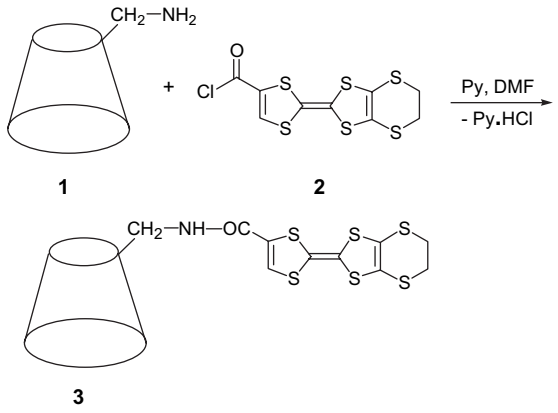
the short covalent link between the TTF and the CD, thus preventing the inclusion of the former in the latter.



Scheme 1. Synthesis of 4,5-ethylenedithio-4′-[6-deoxy-β-cyclodextrin-6-yl-aminocarbonyl]-tetrathiafulvalene **3**.

2.2. Inclusion of 1-adamantanol

The evaluation of the host inclusion ability towards 1-adamantanol has been carried out by UV–vis spectroscopy combined with the well-known direct titration method. For a 1:1 molar ratio, the calculation of the formation constant K_f was developed as follows:

$$\mathrm{HOST} + \mathrm{GUEST} \rightleftharpoons \mathrm{HOST/GUEST}$$

$$K_f = \frac{[\mathrm{HOST/GUEST}]}{[\mathrm{HOST}]^{*}[\mathrm{GUEST}]} \tag{1}$$

$$K_f = \frac{[\mathrm{HOST/GUEST}]}{([\mathrm{GUEST}]_T - [\mathrm{HOST/GUEST}]) - ([\mathrm{HOST}]_T - [\mathrm{HOST/GUEST}])} \tag{2}$$

$$[\mathrm{HOST/GUEST}] = -\frac{1}{2}\sqrt{\left[\left(\frac{1}{K_f} + [\mathrm{HOST}]_T + [\mathrm{GUEST}]_T\right)^2 - 4[\mathrm{HOST}]_T[\mathrm{GUEST}]_T\right]} + \frac{1}{2}\left(\frac{1}{K_f} + [\mathrm{HOST}]_T + [\mathrm{GUEST}]_T\right) \tag{3}$$

where K_f and T stand for formation constant and total, respectively. For a given value of K_f the [HOST/GUEST] concentration is known, thus allowing the calculation of the molecular absorptivity of the inclusion compound. An algorithm treatment was then applied to minimize the difference of the spectral characteristics over the various solutions.

The absorbance of the host was recorded in function of different concentrations of the added guest. The spectral variations, although weak, lead to well defined isobestic points. The data fit well with a 1:1 binding isotherm, especially for the 265–280 nm range concerned by the strongest spectral modifications. The resulting value of the formation constant, amounting at 1538 M^{-1}, shows that the newly synthesized β-CD–TTF derivative still possesses inclusion properties, which could eventually vary upon changing the TTF oxidation state (Figs. 1 and 2).

2.3. Molecular modelling

The docking of the guest (1-adamantanol) with respect to the locked β-CD unit has been performed using three dummy

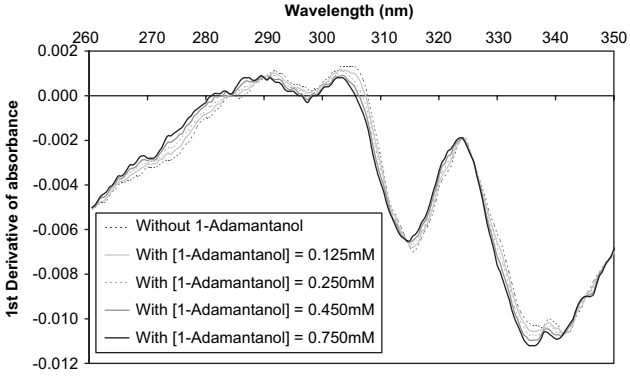


Figure 1. First derivative of the UV spectra of the TTF modified β-cyclodextrin in the absence and presence of increasing concentrations of 1-adamantanol.

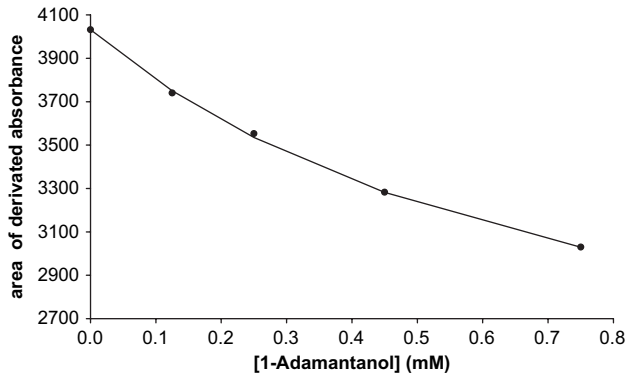


Figure 2. Adjustment, in function of the guest concentration, between the experimental area of the first derivative of absorbance (discrete points) and the theoretical values (continuous line) according to a 1:1 equilibrium.

atoms, in such a way that the molecule of 1-adamantanol crosses the cyclodextrin ring while making a continuous rotation (Fig. 3).

Two regiochemical ways E1 and E2 have been considered. By A and B are notified the two atoms from 1-adamantanol taken into account in defining distances A-D2 and B-D2, also the dihedral angles A-D1-D2-D3-D4 and B-D1-D2-D3.

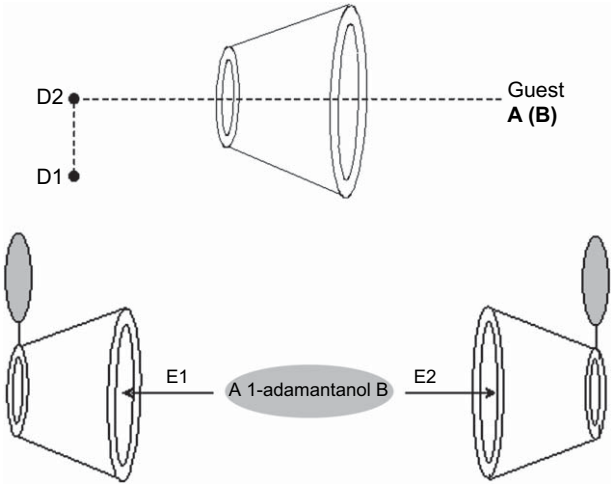


Figure 3. Docking and regiochemical ways.

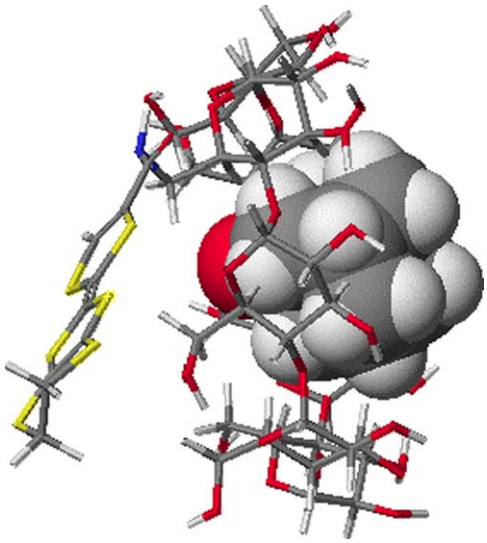


Figure 4. Complex CD–TTF(**3**)-1-adamantanol.

The most stable configuration of the inclusion complex CD–TTF **3** with the 1-adamantanol, obtained by the MM3 method, is shown in Figure 4.

The computed complexation energy ΔE, corresponding to the difference between the potential energy of the inclusion complex and the sum of their individual components in their optimized ground states, amounts at −10.92 Kcal/mol. Such a value is in good agreement with those for other host-guest complexes.[19,28]

3. Conclusions

A water soluble β-cyclodextrin–TTF derivative has been synthesized and characterized. Its inclusion properties towards the guest 1-adamantanol have been experimentally and theoretically determined. The compound described herein represents the first step in the elaboration of a new class of water soluble electroactive sensing systems. The inclusion of other molecules, as well as the TTF electrochemical response, is currently under investigation in our groups.

4. Experimental

4.1. General comments

^{1}H NMR spectra were recorded with a Bruker AM 400 spectrometer with tetramethylsilane (TMS) as an internal standard. Chemical shift values δ are reported in parts per million and coupling constants J are in hertz. The following abbreviations have been used: s (singlet), d (doublet), m (multiplet), C (cyclodextrin). Mass spectra were measured using a Platform II Micromass Apparatus. IR spectra were recorded on a Perkin–Elmer instrument. Melting point was obtained with a Reichert Thermopan apparatus and is uncorrected. Chromatographic separation was carried out on Sephadex G15.

4.2. Synthesis of 4,5-ethylenedithio-4′-[6-deoxy-β-cyclodextrin-6-yl-aminocarbonyl]-tetrathiafulvalene 3

In a 100-mL round-bottomed flask 0.567 g (0.5 mmol) 6-deoxy-6-aminocyclodextrin (**1**) was dissolved in dry DMF (35 mL). Then, 0.178 g (0.5 mmol) solid 4,5-ethylenedithio-4′-chlorocarbonyl-tetrathiafulvalene was gradually added under stirring. To the stirred reaction mixture pyridine (0.08 mL) in DMF (5 mL) was added over a period of 15 min using a dropping funnel. Stirring under argon and warming (65 °C) of the reaction mixture were continued for 14 h. After cooling the mixture was poured drop wise into acetone (100 mL). The resulting precipitate was collected and washed with acetone. The crude solid was dissolved in distilled water (50 mL), filtered and then concentrated to provide 10 mL of solution, which was purified on a Sephadex G-15 column to give the compound **3** as a yellow-orange powder. Yield 47%. Mp=220 °C, dec. IR (KBr, cm^{-1}): 3390, 1634 ($\nu_{C=O}$), 1385, 1156, 1029. ^{1}H NMR (DMSO-d_6): δ 7.99 (m, 1H, NH), 6.69 (s, 1H, =CH), 5.92–5.75 (m, 14H, –OH-2$_C$, –OH-3$_C$), 4.98–4.80 (m, 7H, H-1$_C$), 4.60–4.42 (m, 8H, –O–CH$_{2C}$–, –OH-6$_C$), 3.85–3.10 (m, 44H, H-2$_C$, H-4$_C$, H-3$_C$, H-5$_C$, H-6$_C^{A,B}$, S–*CH*$_2$–*CH*$_2$–S). ^{1}H NMR (D$_2$O): δ 8.01–7.85 (m, 1H, NH), 7.03 (s, 1H, =CH), 5.05–4.90 (m, 7H, CH-1$_C$), 4.74–4.63 (H$_2$O+–OH 2$_C$,3$_C$,6$_C$), 3.97–3.73 (m, 28H, CH–3$_C$,5$_C$,6$_C^{AB}$), 3.57–3.51 (m, 14H, CH-2$_C$,4$_C$), 3.53–3.44 (m, 4H, S–*CH*$_2$–*CH*$_2$–S). MS (ES$^+$, cone 40) *m*/*z* (%): 1447 (M+23) (15%), 1157 (CD-6-yl-NH+23) (80%), 1185 (CD-6-yl-NH–CO+23) (100%). Anal. calcd for $C_{51}H_{75}NO_{35}S_6$: C, 42.11; H, 5.20; S, 13.23. Found: C, 40.56; H, 4.85; S, 12.64.

4.3. UV–vis spectroscopy

Spectra were recorded at 298 K using a Perkin–Elmer Lambda 2S double beam spectrometer and a quartz cell with optical path length of 1 cm. The compounds were dissolved in phosphate buffer at pH 5.8. All spectra were used in the derivative form in order to avoid the influence of diffraction on the titration experiment.

4.4. Molecular modelling

Compound **3** and 1-adamantanol were built starting from data provided by the Cambridge Structural Data Base Center. The structural manipulations on β-CD were made using the CAChe library[29] on PC-Computer. The study of compound **3** was performed by applying a general procedure of multiconformational search with the MM3 force field.[30] The potential energy variation (ΔE) depending on the variation of the dihedral angles (defined between the TTF and cyclodextrin moieties) is recorded with rotational increments of 15°. The minimum value of ΔE is chosen according to the curve scribing. The analysis was developed taking into account all the exocyclic single bonds in the compound **3**. Then, the docking of the guest (1-adamantanol) with respect to the locked β-CD unit has been performed using three dummy atoms, one centrally placed in the inner cavity of the cyclodextrin ring and the two others in opposite sites towards the guest (Fig. 3). Two parameters, i.e., the host/guest distance and the orientation of 1-adamantanol inside the cyclodextrin cavity, are submitted to systematic

variations (0.1 Å for the distance, 10° for the dihedral), the energy being evaluated by MM3. The resulting conformations are minimized at each step of the docking simulation, thus allowing the remaining intermolecular variables to be taken into account.

Acknowledgements

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On the mechanism of conversion of 4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)-isoquinolones to indeno[1,2-*c*]isoquinolines by thionyl chloride

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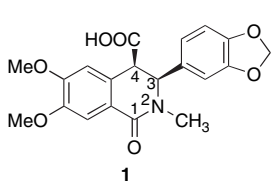
Abstract—It has been known for a long time that thionyl chloride can effectively mediate the transformation of 4-carboxy-3,4-dihydro-3-phenyl-1(2*H*)-isoquinolones to indeno[1,2-*c*]isoquinolines. The mechanism of this unique transformation, however, remains to be established. Evidence is presented to demonstrate that (1) the two-electron dehydrogenation precedes Friedel–Crafts cyclization and (2) the two-electron dehydrogenation occurs via H-4 deprotonation and subsequent O-sulfinylation of the lactam moiety instead of C-sulfinylation of the carbon α to the carboxyl group.

1. Introduction

In 1978, the direct transformation of *cis* acid **1** to indeno-[1,2-*c*]isoquinoline **2** by thionyl chloride was reported.[1] Since the establishment of compound **2** as a novel non-camptothecin topoisomerase I inhibitor,[2] a number of analogs of **2** have been synthesized using this thionyl chloride-mediated oxidation/Friedel–Crafts cyclization methodology.[3–9] Despite its effectiveness in providing access to different substituted indenoisoquinolines, the exact mechanism of the thionyl chloride-mediated oxidation/Friedel–Crafts cyclization of **1** is still not established. Herein, detailed studies are described on the mechanism of this conversion employing differentially substituted substrate analogs to support a mechanism in which dehydrogenation precedes Friedel–Crafts cyclization and the lactam functionality plays an essential role in the dehydrogenation process.



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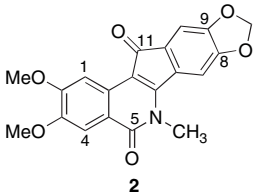

2

Keywords: Thionyl chloride; Oxidation; Indenoisoquinoline; Intramolecular Friedel–Crafts reaction.
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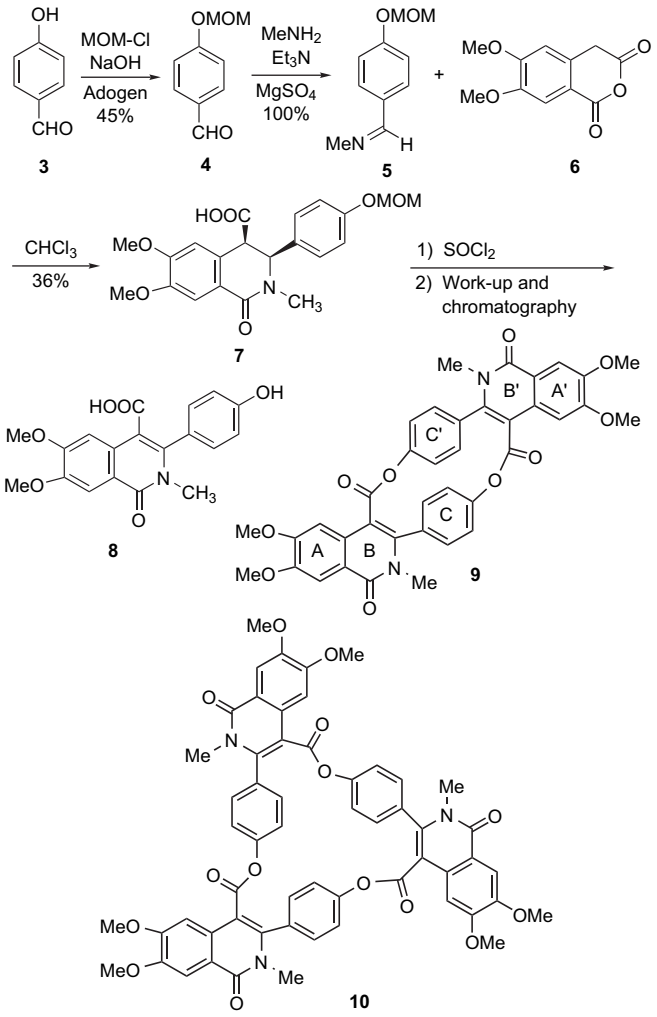
2. Results and discussion

To determine if $SOCl_2$-mediated oxidation can proceed without prior Friedel–Crafts acylation, *cis* acid **7** with a less-activated 3-phenyl ring than **1** was designed and synthesized (Scheme 1). Condensation of 3,4-dimethoxyhomophthalic anhydride (**6**)[1] with Schiff base **5**, prepared from MOM-protected aldehyde **4** and $MeNH_2$, yielded the *cis* acid **7**, whose relative stereochemistry was determined by the observed 6.2 Hz coupling constant for the two methine protons.[10] Treatment of the *cis* acid **7** with $SOCl_2$ gave three isolated compounds **8**, **9**, and **10** in 11, 31, and 28% yields, respectively. Therefore, it is clear that the $SOCl_2$-mediated dehydrogenation step can proceed without prior Friedel–Crafts cyclization. Previous studies indicated that the dehydrogenated intermediate derived from **1** could undergo Friedel–Crafts cyclization in the presence of thionyl chloride to afford **2**, but the Friedel–Crafts product derived from **1** did not undergo dehydrogenation to yield **2** with thionyl chloride.[1] These results, in combination with the present study, make it clear that dehydrogenation precedes the Friedel–Crafts acylation during the conversion of **1** to **2** by thionyl chloride. What remains to be determined is the mechanism of the dehydrogenation step.

Compounds **9** and **10** are novel macrocyclic systems containing 16-membered and 24-membered rings with either two or three benzene rings, respectively. Interestingly, the chemical shifts of the four protons in the substituted benzene



Scheme 1.

ring C of macrodilide **9** are different from each other[11] and one of the protons is significantly shifted upfield to 5.60 ppm. The C and C′ rings are equivalent so that the eight protons on the two rings appear as four doublets of doublets. In order to understand the unusual ^{1}H NMR spectrum of this compound, the geometry was optimized at the AM1 theory level in Gaussian03.[12] It is reasonable to assume that the optimized AM1 structure (Fig. 1) would provide a valid model on which to base the interpretation of the ^{1}H NMR data. Due to the differential shielding effect from the C′ ring, the two pairs of protons on the C ring are no longer identical, and vice versa. Furthermore, since the proton labeled 'a' in Figure 1 is located directly over the ring current from ring C′, it experiences an unusually strong shielding effect and thus appears more upfield in the ^{1}H NMR spectrum. The

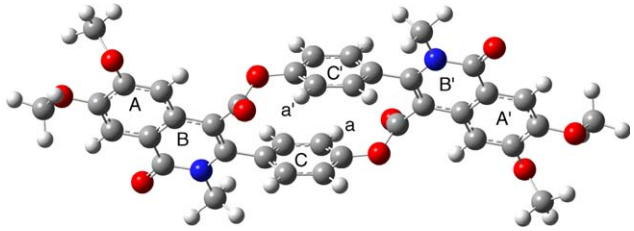
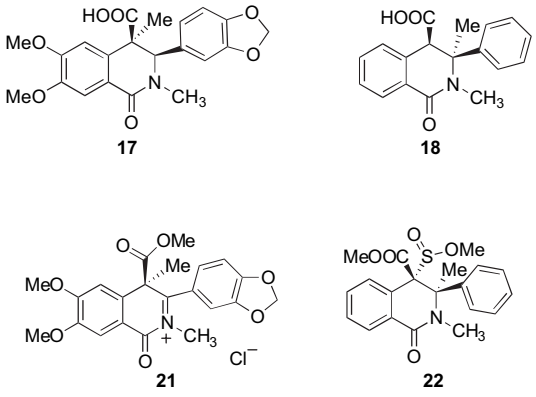


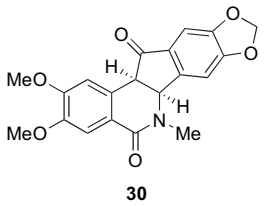
Figure 1. AM1 optimized geometry of compound **9**.

NMR results indicate that the conformational mobility of the macrodilide ring of **9** is limited by the π–π stacking interaction of the two aromatic rings, and this conclusion is also consistent with the AM1 calculation (Fig. 1). The predominant formation of this macrodilide in the reaction mixture is likely due to the effect of a combination of predisposed orientation of 3-phenyl and 4-carboxyl groups in **8**[13] and product stability rendered by the π–π stacking interaction of the C and C′ rings, which have an appropriate distance of 3.45 Å for stacking.[14]

Originally, we proposed the oxidation step involving Mechanism 1 as shown in Scheme 2 on the basis of the reported $SOCl_2$ dehydrogenation reactions of substrates lacking lactam functionality.[1] However, two alternative Mechanisms 2 and 3 involving participation of the lactam functionality are also intriguing,[15] especially because Mechanism 1 entails the formation of a quaternary carbon in a very sterically congested environment. In order to distinguish these mechanisms, two interrupting analogs **17**[16] and **18** were designed and synthesized. When **17** was treated with $SOCl_2$ at room temperature for 5 h, the typical time frame to convert *cis*-**1** to **2**,[1] followed by methanol work up, only ester **19**[16] was obtained quantitatively. However, prolonged reaction of **17** with $SOCl_2$ for 36 h resulted in the formation of 18% chlorinated compound **20** and 77% of ester **19** (Scheme 3). The failure to observe the formation of **21**, or a derivative of it, argues against Mechanism 2 (Scheme 2). Based on the relatively high pK_a of H-3 compared to H-4, which is doubly activated by both carboxyl group and lactam, Mechanism 2 requiring deprotonation at H-3 in the presence of H-4 is also not favored.



To avoid the complications resulting from the nucleophilic aromatic rings present in **17**, a simplified analog **18** was designed and synthesized (Scheme 4). Ketimine formation between acetophenone and methylamine in the presence of $TiCl_4$[17] afforded **24**, which was condensed with homophthalic anhydride (**25**) to give a pair of diastereomers **26** and **18** in 16 and 3% yields, respectively. The corresponding methyl esters were furnished by treating the individual acids with $TMSCHN_2$ in MeOH–benzene. The relative configurations of **18**, **26**, **27**, and **28** were determined primarily by the chemical shift differences of H-4, 3-Me, and 4-COOMe due to the shielding effect of the 3-phenyl ring and the electron-withdrawing effect of the 4-carbonyl (Table 1).[18,19] The structure of compound **28** was further confirmed by single crystal X-ray analysis (see Supplementary data).



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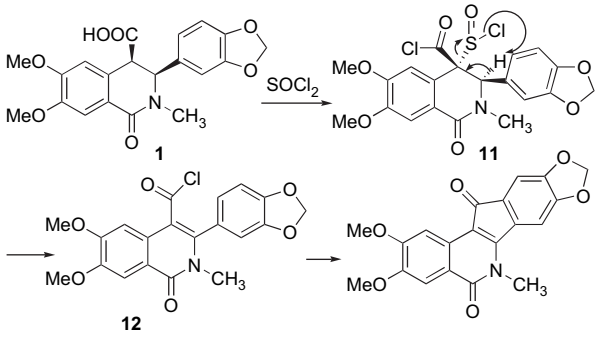
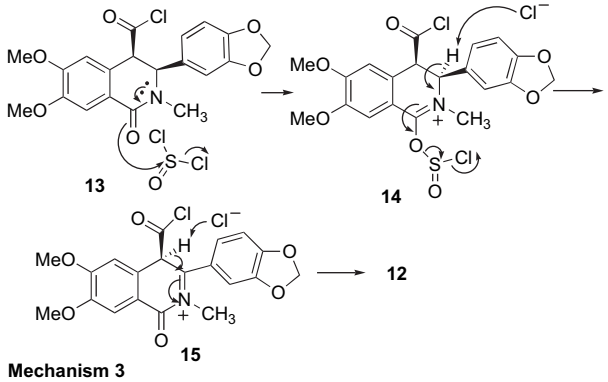
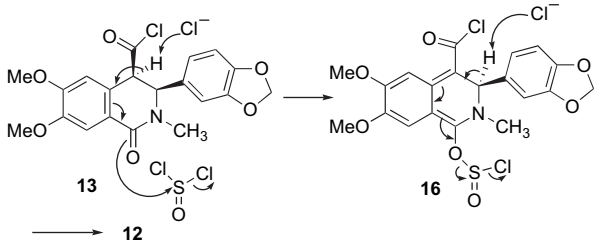
Mechanism 1



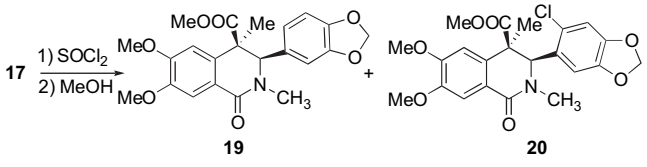
Mechanism 2



Mechanism 3

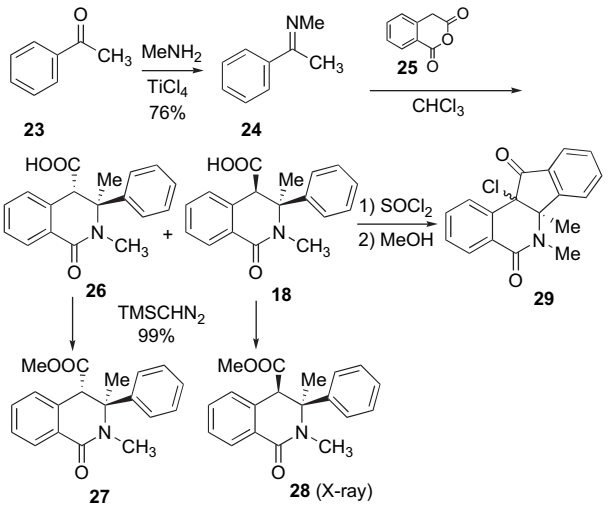


Scheme 2.



Scheme 3.

When acid **18** was treated with $SOCl_2$ at room temperature for 5 h, followed by methanol treatment, the only product formed was the ester **28**. On the other hand, when the reaction time of $SOCl_2$ treatment was prolonged to 36 h, a minor product **29** (5%) was also formed besides the ester **28** (92%). The formation of cyclized product **29** is very informative as it suggests that C-4 must become sp^2-hybridized before



Scheme 4.

Table 1. Chemical shift differences (ppm) between **18**, **26**, **27**, and **28**

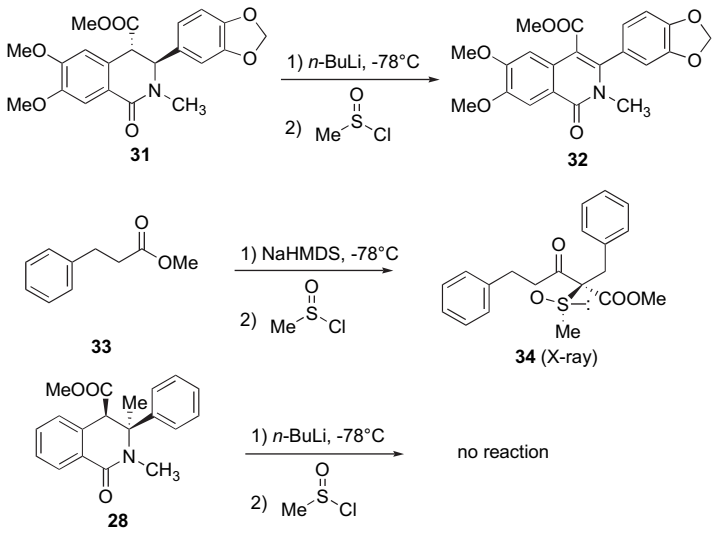
Compound	H-4	3-Me	4-COOMe
18	3.82	1.66	N/A
26	4.12	1.86	N/A
27	4.18	1.81	3.62
28	3.75	1.58	3.14

cyclization instead of cyclizing from the original sp^3-hybridization state, which does not cyclize as evidenced by the failure to form any cyclized product derived from **17**, and failure to form **30** from **1** under similar treatment.[1] The failure to form even a trace of the sulfinate ester **22** and formation of **29** suggests that Mechanism 3 is the most likely one accounting for the oxidation step mediated by $SOCl_2$.

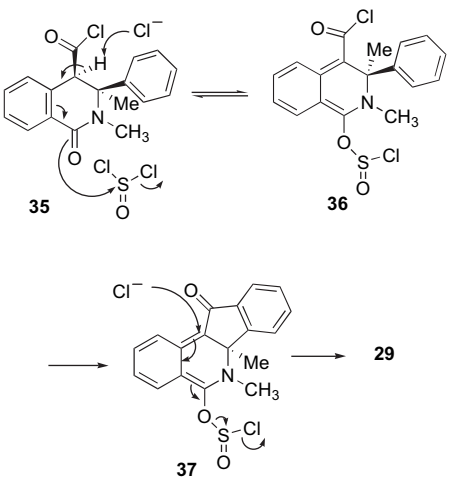
Further evidence to support Mechanism 3 comes from the reactions of methanesulfinyl chloride[20] with various esters (Scheme 5). Reaction of the enolate derived from ester **31** with methanesulfinyl chloride resulted in the formation of dehydrogenated product **32** in 75% yield. On the other hand, treatment of methyl 3-phenylpropionate (**33**) with NaHMDS followed by methanesulfinyl chloride gave methyl sulfoxide **34** diastereoselectively, whose structure was confirmed by single crystal X-ray analysis (see Supplementary data).

The formation of **34** is expected since elimination of sulfinic acid usually is slow[21,22] and requires high temperature compared to elimination of selenic acid.[23,24] If the oxidation reaction were to involve Mechanism 1, then similar treatment of ester **28** with methanesulfinyl chloride would generate the corresponding methyl sulfoxide. However, this treatment only resulted in the recovery of starting material. These observations indicate the mechanism shown in Scheme 6 for the formation of **29**. The acyl chloride **35** undergoes a reversible reaction with $SOCl_2$ to give *O*-sulfinilated species **36**, whose C-4 is in an sp^2 hybridization state, followed by cyclization to afford **37**. Chloride addition and elimination of sulfur monoxide from **37** provide the observed chloride **29**.

More direct evidence to support the participation of the amide functionality in the oxidation process is the

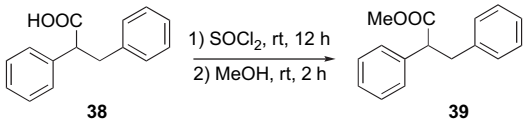


Scheme 5.



Scheme 6.

observation that treatment of 2,3-diphenyl-propionic acid (**38**) with $SOCl_2$, followed by MeOH, only resulted in the formation of the corresponding methyl ester **39** (Scheme 7). No oxidation product was observed in this case. The acid **38** is a simplified analog of **1** lacking the lactam functionality, and the inability of **38** to undergo the oxidation reaction indicates lactam participation in the oxidation of **1** by $SOCl_2$.



Scheme 7.

3. Conclusions

The transformation from *cis* acid **1** to indenoisoquinoline **2** by thionyl chloride involves a two-electron dehydrogenation followed by Friedel–Crafts cyclization. Although Mechanism 1 (Scheme 2) has been proposed for most of the oxidations mediated by thionyl chloride,[25–31] Mechanism 3 involving deprotonation at H-4 and subsequent O-sulfinylation of the amide is the most likely one accounting for the dehydrogenation of *cis* acid **1** based on the present experimental data presumably due to the sterics and the presence of an additional amide functionality.

4. Experimental

4.1. 4-Methoxymethoxybenzaldehyde (4)[32]

Method A: a solution of NaOH (1.3 g in 16 mL H_2O) was added to a stirred solution of 4-hydroxybenzaldehyde (2.0 g, 16.4 mmol) and Adogen® (1.3 g) in CH_2Cl_2 (50 mL). Then MOM-Cl (1.98 g, 24.5 mmol) was added. The resulting biphasic mixture was stirred at room temperature for 20 h. CH_2Cl_2 (100 mL) was added and the organic phase was separated and then washed successively with 1 N HCl (2×25 mL), H_2O (2×25 mL), and brine (2×25 mL) and dried over Na_2SO_4. The solution was filtered and evaporated in vacuo and the resulting residue was subjected to flash column chromatography, eluting with *n*-hexane–ethyl acetate (10:1), furnishing **4** as a colorless oil (1.2 g, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.80 (d, J=8.7 Hz, 2H), 7.11 (d, J=8.7 Hz, 2H), 5.22 (s, 2H), 3.46 (s, 3H); ESIMS m/z (rel intensity) 167 (MH^+, 100). *Method B*: 4-hydroxybenzaldehyde (2.000 g, 16.37 mmol) was dissolved in dry DMF (50 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil) (0.786 g, 19.65 mmol) was carefully added and the reaction mixture was allowed to stir at 0 °C for 30 min. MOM-Cl (1.582 g, 19.65 mmol) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 1 h, then at room temperature for 1 h. The reaction was quenched with the addition of saturated aq NH_4Cl (50 mL) and the solution was extracted with EtOAc (3×25 mL). The combined organic layers were washed with saturated aq K_2CO_3 (3×25 mL), saturated aq NH_4Cl (3×25 mL), and brine (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography (SiO_2), eluting with a gradient of hexanes to 30% EtOAc/hexanes,

to provide a colorless oil (2.374 g, 87%) identical to the material furnished by Method A.

4.2. (4-Methoxymethoxy-benzylidene)methylamine (5)

Anhydrous $MgSO_4$ (1.8 g) and aldehyde **4** (817.5 mg, 4.92 mmol) were added sequentially to a stirred solution of $MeNH_2$ (2 M in methanol, 3.0 mL, 6.0 mmol) and Et_3N (1 mL, 7.39 mmol) in $CHCl_3$ (10 mL). The resulting mixture was stirred at room temperature for 18 h. CH_2Cl_2 (50 mL) was added and the solution was washed with H_2O (2×10 mL) and brine (2×10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo giving **5** as a colorless oil (882.8 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.62 (d, J=8.7 Hz, 2H), 7.03 (d, J=8.7 Hz, 2H), 5.18 (s, 2H), 3.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 159.1, 130.2, 129.3 (2C), 116.1 (2C), 94.2, 56.1, 48.1; IR (KBr) 2938, 1652, 1607, 1510, 1237, 1153, 1081, 1003 cm^{-1}; ESIMS m/z (rel intensity) 180 (MH^+, 100). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.37; H, 7.18; N, 7.59.

4.3. *cis*-4-Carboxy-6,7-dimethoxy-3-(4-methoxymethoxy-phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydroisoquinoline (7)

Anhydride **6** (269 mg, 1.2 mmol) was added in one portion to a stirred solution of imine **5** (217.2 mg, 1.2 mmol) in $CHCl_3$ (1.2 mL). The solution became clear and 3 h later a light yellow precipitate formed in the reaction mixture. The precipitate was collected and washed with $CHCl_3$ (1 mL) giving **7** as an off-white powder (173 mg, 36%): mp 218–220 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (s, 1H), 7.11 (s, 1H), 6.96 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 5.12 (s, 2H), 5.01 (d, J=6.2 Hz, 1H), 4.59 (d, J=6.2 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.32 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.8, 163.0, 156.5, 151.2, 147.7, 130.1, 128.9 (2C), 127.2, 121.5, 115.8 (2C), 110.8, 109.8, 93.6, 62.6, 55.6, 55.5 (2C), 47.5, 33.4; ESIMS m/z (rel intensity) 402 (MH^+, 100); IR (film) 2939, 1739, 1596, 1511, 1489, 1287, 1230, 1147, 1079, 754, 624 cm^{-1}. Anal. Calcd for $C_{21}H_{23}NO_7 \cdot H_2O$: C, 60.14; H, 6.01; N, 3.34. Found: C, 60.45; H, 5.64; N, 3.36.

4.4. 4-Carboxy-1,2-dihydro-3-(4-hydroxyphenyl)-6,7-dimethoxy-2-methyl-1-oxo-isoquinoline (8), dilide (9) and trilide (10)

Acid **7** (39.5 mg, 0.098 mmol) was treated with thionyl chloride (0.4 mL) at room temperature for 4 h. Then excess thionyl chloride was evaporated in vacuo and benzene (3×3 mL) was added and evaporated in vacuo. The residue was subjected to flash column chromatography, eluting with $CHCl_3$–MeOH (100:0–4:1), to provide a white powder **8** (4 mg) and a mixture of **9** and **10**. The mixture of **9** and **10** was further purified by preparative TLC on silica gel [$CHCl_3$–MeOH (50:1)] giving **9** (10 mg) and **10** (9 mg) as white powders. Product **8**: mp>254 °C (dec). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.90 (br s, 1H), 7.87 (s, 1H), 7.40 (d, J=8.4 Hz, 2H), 7.05 (s, 1H), 6.86 (d, J=8.4 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 160.6, 158.0, 153.2, 148.9, 141.1, 130.6 (2C), 128.3, 124.8, 117.8, 115.2 (2C), 112.9, 107.3, 104.3, 55.6 (2C), 33.5; IR (KBr) 3489, 3441, 3137, 2956, 1685, 1609, 1512, 1274, 1225, 1176 cm^{-1}; ESIMS m/z (rel intensity) 356 (MH^+, 100). Anal. Calcd for $C_{19}H_{17}NO_6 \cdot 1.5H_2O$: C, 59.68; H, 5.27; N, 3.66. Found: C, 59.93; H, 5.05; N, 3.51. Product **9**: mp 383–385 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.60 (dd, J=8.4, 2.4 Hz, 2H), 7.45 (dd, J=8.4, 2.4 Hz, 2 H), 7.29 (dd, J=8.1, 2.1 Hz, 2H), 7.23 (s, 2H), 5.60 (dd, J=8.1, 2.1 Hz, 2H), 4.02 (s, 6H), 4.00 (s, 6H), 3.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (2C), 161.7 (2C), 154.1 (2C), 150.8 (2C), 149.9 (2C), 142.6 (2C), 133.2 (2C), 131.0 (2C), 130.4 (2C), 128.3 (2C), 123.8 (2C), 122.7 (2C), 118.8 (2C), 110.7 (2C), 108.2 (2C), 103.7 (2C), 56.3 (2C), 34.2 (2C), 29.7 (2C); ESIMS m/z (rel intensity) 1349 (2M+H^+, 53), 675 (MH^+, 100); IR (film) 2963, 2905, 1732, 1651, 1609, 1502, 1415, 1260, 1094, 1019, 799, 703 cm^{-1}. Anal. Calcd for $C_{38}H_{30}N_2O_{10}$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.34; H, 4.46; N, 3.98. Product **10**: mp 402–404 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 3H), 7.58 (s, 3H), 7.36 (d, J=9.0 Hz, 6H), 7.04 (d, J=9.0 Hz, 6H), 4.03 (s, 9H), 3.95 (s, 9H), 3.31 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5 (3C), 162.2 (3C), 157.4 (3C), 154.0 (3C), 149.7 (3C), 142.5 (3C), 130.7 (6C), 129.0 (3C), 126.3 (3C), 118.5 (3C), 116.0 (6C), 112.5 (3C), 107.9 (3C), 104.2 (3C), 56.3 (6C), 34.5 (3C); ESIMS m/z (rel intensity) 1012 (MH^+, 100); IR (film) 2921, 2851, 1722, 1647, 1610, 1501, 1422, 1312, 1267, 1200, 1147, 1053, 1023 cm^{-1}. Anal. Calcd for $C_{57}H_{45}N_3O_{15}$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.46; H, 4.32; N, 3.96.

4.5. *cis*-3-(2-Chloro-4,5-methylenedioxyphenyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-4-methoxycarbonyl-2,4-dimethyl-1-oxo-isoquinoline (20)

$SOCl_2$ (1 mL) was added to a stirred solution of acid **17** (10 mg, 0.025 mmol) at room temperature. The resulting mixture was stirred at room temperature for 36 h and then the excess $SOCl_2$ was evaporated under reduced pressure. The resulting residue was treated with MeOH (5 mL) and the reaction mixture was heated under reflux for 2 h. Methanol was evaporated and the residue was separated by preparative TLC, developing with $CHCl_3$–MeOH (100:1), yielding compound **20** (2 mg, 18%) and ester **19** (8 mg, 77%). Compound **20** was isolated as a viscous oil that became a white solid upon standing: mp 145–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.78 (s, 1H), 6.75 (s, 1H), 6.41 (s, 1H), 5.88 (d, J=1.2 Hz, 1H), 5.86 (d, J=1.2 Hz, 1H), 5.18 (s, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.51 (s, 3H), 3.00 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 162.7, 152.2, 148.3, 148.2, 147.1, 132.9, 128.4, 125.6, 120.2, 110.4, 109.9, 109.2, 107.7, 102.0, 65.5, 56.1, 52.2, 34.1, 29.7; IR (film) 3451, 2925, 2854, 1736, 1651, 1602, 1508, 1479, 1283, 1237, 1120, 1038, 928, 782 cm^{-1}; ESIMS m/z (rel intensity) 450 (^{37}Cl−MH^+, 34), 448 (^{35}Cl−MH^+, 100); HRESIMS m/z calcd for 448.1163, found 448.1161.

4.6. Phenylethylidene-*N*-methylamine (24)[33]

$MeNH_2$ (2.0 M in THF, 15 mL, 30 mmol) was added to a stirred solution of acetophenone (**23**) (1.2 g, 10 mmol) in toluene (10 mL) at −10 °C. A solution of $TiCl_4$ (0.55 mL,

5 mmol) in toluene (2 mL) was then added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature and then heated at 90 °C for 2 h. After cooling to room temperature, the reaction mixture was allowed to stand overnight, filtered, and washed with toluene (100 mL). Evaporation of toluene yielded **24** as a blood-red oil (1.0 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.76 (m, 2H), 7.33–7.40 (m, 3H), 3.34 (s, 3H), 2.23 (s, 3H); IR (film) 3057, 2961, 1635, 1445, 1285, 1026, 761, 694; EIMS *m*/*z* (rel intensity) 133 (MH^+, 8), 118 (100), 91 (33), 77 (88), 51 (62).

4.7. *cis*-4-Carboxy-1,2,3,4-tetrahydro-2,3-dimethyl-3-phenyl-1-oxo-isoquinoline (18) and *trans*-4-carboxy-1,2,3,4-tetrahydro-2,3-dimethyl-3-phenyl-1-oxo-isoquinoline (26)

Homophthalic anhydride (**25**) (520 mg, 3.2 mmol) was added to a stirred solution of ketimine **24** (427 mg, 3.2 mmol) in $CHCl_3$ (4 mL) at room temperature. The mixture was heated at reflux for 5 h. $CHCl_3$ was evaporated and the residue was subjected to flash column chromatography, eluting with $CHCl_3$ and $CHCl_3$–MeOH (10:1), yielding acid **18** (150 mg, 16%) and acid **26** (30 mg, 3%). Product **18**: a white solid, mp>200 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J=6.6 Hz, 1H), 7.35–7.45 (m, 4H), 7.07–7.22 (m, 4H), 3.82 (s, 1H), 2.83 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 165.9, 140.0, 133.0, 132.1, 128.9, 128.6, 128.5, 128.4 (2C), 128.0, 127.2, 127.0 (2C), 64.9, 58.3, 32.4, 24.0; IR (film) 2983, 1727, 1622, 1575, 1385, 1165, 1028, 760, 703; ESIMS *m*/*z* (rel intensity) 296 (MH^+, 100); HRESIMS *m*/*z* calcd for 296.1287, found 296.1281. Product **26**: a white solid, mp>186 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J=6.6 Hz, 1H), 7.08–7.30 (m, 7H), 6.98–7.00 (m, 1H), 4.12 (s, 1H), 3.10 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 165.8, 142.7, 132.6, 132.0, 129.2, 128.8 (2C), 128.5 (2C), 127.5, 127.0, 125.3 (2C), 63.0, 57.1, 29.3, 25.4; IR (film) 3406, 2983, 1723, 1626, 1575, 1381, 1218, 1029, 762, 700; ESIMS *m*/*z* (rel intensity) 296 (MH^+, 100); HRESIMS *m*/*z* calcd for 296.1287, found 296.1287.

4.8. *trans*-1,2,3,4-Tetrahydro-4-methoxycarbonyl-2,3-dimethyl-1-oxo-3-phenylisoquinoline (27) and *cis*-1,2,3,4-tetrahydro-4-methoxycarbonyl-2,3-dimethyl-1-oxo-3-phenylisoquinoline (28)

$TMSCHN_2$ (2.0 M in hexane, 25 μL, 0.044 mmol) was added to a stirred suspension of acid **18** or **26** (10 mg, 0.033 mmol) in MeOH–benzene (1:3.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min and the solution became clear. The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography, eluting with $CHCl_3$–MeOH (20:1), yielding a white solid (10 mg, 99%). Product **28**: a chunk crystal (from *n*-hexane–EtOAc), mp 174–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, J=6.0, 3.3 Hz, 1H), 7.17–7.34 (m, 7H), 7.00 (dd, J=6.0, 3.3 Hz, 1H), 3.75 (s, 1H), 3.14 (s, 3H), 2.77 (s, 3H), 1.58 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 165.6, 140.7, 133.1, 132.0, 128.8, 128.7, 128.5 (3C), 128.0, 127.1, 126.8 (2C), 65.1, 58.5, 52.0, 32.3, 23.9; ESIMS *m*/*z* (rel intensity) 310 (MH^+, 100). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 74.02; H, 6.36; N, 4.39. Summary of X-ray crystal data: $C_{19}H_{11}NO_3$; FW=309.37; a=11.4459(3) Å; b=7.8559(2) Å; c=18.1780(5) Å; β=104.6058(17)°; vol=1581.70(7) Å^3; monoclinic; space group $P21/n$; Z=4; crystal size=0.41×0.39×0.35 mm; GOF=1.071; $R(F_o)$=0.039, $Rw(F_o^2)$=0.107. Product **27**: a white solid, mp 153–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (td, J=6.3, 1.2 Hz, 1H), 7.12–7.33 (m, 7H), 6.95 (dd, J=6.9, 1.8 Hz, 1H), 4.18 (s, 1H), 3.62 (s, 3H), 3.12 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 165.5, 142.9, 132.8, 131.8, 129.2, 128.7 (2C), 128.5, 128.3, 127.5, 126.7, 125.4 (2C), 63.3, 57.4, 52.4, 30.4, 24.8; ESIMS *m*/*z* (rel intensity) 310 (MH^+, 100); HRESIMS *m*/*z* calcd for 310.1443, found 310.1444.

4.9. 12-Chloro-5,6,12,13-tetrahydro-6,13-dimethyl-5,11-dioxo-11*H*-indeno[1,2-*c*]isoquinoline (29)

The acid **18** (90 mg, 0.3 mmol) was treated with $SOCl_2$ (2 mL) at room temperature for 36 h. Then the excess $SOCl_2$ was evaporated to afford a residue, which was immediately dissolved in anhydrous MeOH (2 mL). The mixture was stirred at room temperature for 2 h. MeOH was removed in vacuo and the residue was subjected to flash column chromatography, eluting with *n*-hexane–EtOAc (3:1), yielding ester **28** (87 mg, 92%) and **29** (5 mg, 5%). Product **29**: a white solid, mp 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J=7.8 Hz, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.67 (t, J=7.5 Hz, 2H), 7.59 (t, J=7.5 Hz, 1H), 7.52 (td, J=7.5, 1.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 1H), 7.41 (td, J=7.5, 1.5 Hz, 1H), 3.39 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 159.1, 142.9, 135.9 (2C), 133.7, 132.8, 131.8, 129.8, 129.6, 128.9, 128.1, 125.1, 123.8, 76.8, 67.1, 30.4, 26.8; ESIMS *m*/*z* (rel intensity) 312 ($^{35}ClMH^+$, 100), 314 ($^{37}ClMH^+$, 31); HRESIMS *m*/*z* calcd for $C_{18}H_{14}{}^{35}ClNO_2$ 311.0713, found 311.0720.

4.10. 6,7-Dimethoxy-4-methoxycarboxy-*N*-methyl-3-(3′,4′-methylenedioxyphenyl)-1(2*H*)-isoquinolone (32)

n-BuLi (0.16 mL, 2.5 M in hexane, 0.39 mmol) was slowly added to a stirred solution of ester **31** (129 mg, 0.32 mmol) in THF (2 mL) at −78 °C. The resulting solution was then stirred at −78 °C for 15 min and then a solution of methanesulfinyl chloride (32 mg, 0.32 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at −78 °C for 1 h. The reaction was quenched by slow addition of a saturated solution of NH_4Cl (5 mL) and the product was extracted with $CHCl_3$ (3×20 mL). The combined organic layers were washed with H_2O (2×5 mL) and brine (2×5 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was subjected to flash column chromatography, eluting with $CHCl_3$, yielding **32** as a light yellow solid (92 mg, 72%), which displayed identical physical data with an authentic sample of **32** obtained differently.[15]

4.11. (±)-Methyl 2(*R*)-benzyl-2-(*S*)-methanesulfinyl-3-oxo-5-phenylpentanoate (34)

NaHMDS (3.04 mL, 1.0 M in THF, 3.04 mmol) was slowly added to a stirred solution of ester **33** (415 mg, 2.53 mmol) in THF (5 mL) at −78 °C. The resulting solution was then stirred at −78 °C for 30 min when methanesulfinyl chloride

(299 mg, 3.04 mmol) was added. The reaction mixture was then stirred at −78 °C for 1 h. The reaction was quenched by slow addition of H_2O (5 mL) and the product was extracted with EtOAc (3×30 mL). The combined organic layers were washed with H_2O (2×10 mL) and brine (2×10 mL). The organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was subjected to flash column chromatography, eluting with *n*-hexane–EtOAc (4:1), yielding a white solid **34** as colorless needles (320 mg, 71%): mp 119–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.36 (m, 10H), 3.83 (d, J=13.8 Hz, 1H), 3.71 (s, 1H), 3.46 (d, J=13.8 Hz, 1H), 3.08–3.21 (m, 2H), 2.95–3.03 (m, 2H), 2.41 (s, 3H). Summary of X-ray crystal data: $C_{20}H_{22}O_4S$; FW=358.46; a=24.0662(7) Å; b=6.2232(2) Å; c=26.5189(9) Å; β=111.6340(15)°; vol=3691.9(2) Å^3; monoclinic; space group $P121/n1$; Z=8; crystal size=0.50×0.31×0.13 mm; GOF=1.018; $R(F_o)$=0.039, $Rw(F_o^2)$=0.088. Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.01; H, 6.19; S, 8.95. Found: C, 66.74; H, 6.02; O, 8.66.

4.12. Methyl 2,3-diphenyl-propanoate (39)[33]

Thionyl chloride (1 mL) was added to acid **38** (116 mg, 0.5 mmol) at room temperature. The mixture was stirred at room temperature for 12 h. Excess thionyl chloride was removed under reduced pressure. The residue was treated with methanol (2 mL) and stirred at room temperature for 2 h. Methanol was removed under reduced pressure giving a colorless oil (120 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99–7.20 (m, 10H), 3.75 (dd, J=9.0, 6.9 Hz, 1H), 3.45 (s, 3H), 3.31 (dd, J=13.8, 8.7 Hz, 1H), 2.91 (dd, J=13.8, 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 138.9, 138.5, 128.8 (2C), 128.5 (2C), 128.2 (2C), 127.8 (2C), 127.3, 126.2, 53.5, 51.8, 39.7.

4.13. X-ray crystallographic data for 28 and 34

Crystallographic data (excluding structure factors) for the compounds **28** and **34** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 601047 and 601048, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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Supplementary data

ORTEP drawings and crystallographic information files of compounds **28** and **34**. ^{1}H NMR spectra of compounds **9**, **10**, **20**, **27**–**29**, and **39**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.072.

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Dibromomethane as one-carbon source in organic synthesis: total synthesis of (±)-canadensolide

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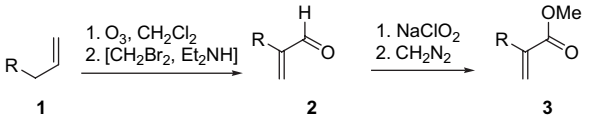
Abstract—A diastereoselective total synthesis of (±)-canadensolide is described. The key step is to introduce the α-methylene group by the ozonolysis of mono-substituted alkenes followed by reaction with a preheated mixture of CH_2Br_2–Et_2NH.

1. Introduction

We have reported that the ozonolysis of mono-substituted alkenes **1** followed by reaction with a preheated mixture of CH_2Br_2–Et_2NH affords α-substituted acroleins **2** in good yields.[1] The α-substituted acroleins **2** were easily oxidized by $NaClO_2$ and then treated with CH_2N_2 to give α-substituted acrylate **3** in excellent yields (Scheme 1).[2] This methodology was also applied to prepare the α-methylene lactones with different ring sizes from the corresponding alkenol.[3]



Scheme 1.

Various bioactive α-methylene-γ-butyrolactones and bislactones have been isolated from microorganisms and some specific examples are shown in Figure 1.[4] The structures **4**–**6** contain α-methylene, β-carboxylic acid, and γ-alkyl groups in different chain lengths. Both the β- and γ-substituents are *trans* to each other. We have successfully applied the methodology described in Scheme 1 in the total synthesis of the (±)- and (−)-methylenolactocin (**4**).[4]

Naturally occurring bislactones such as canadensolide (**7**),[5] xylobovide (**8**),[6] and sporothriolide (**9**)[7] are metabolites of *Penicillium canadense*, *Xylaria obovata*, and *Sporothrix* sp., respectively. They are closely related natural products that differ simply in the length of their side chain (Fig. 1). The interest in these compounds lies not only in their significant biological activities but also their unique stereochemical features. The fungicidal activity of canadensolide (**7**), the phytotoxic activity of xylobovide (**8**), and the antibacterial, fungicidal, algicidal, and herbicidal activities of sporothriolide (**9**) are noteworthy. These compounds contain all *cis* stereochemistry of the three adjacent methine protons and the alkyl substituent is interestingly situated in the sterically less accessible concave face. These structures have received considerable attention as synthetic targets, with several reported total syntheses of canadensolide,[8,9] xylobovide,[10] and sporothriolide[11] appearing in the literature.

In continuation of our interest in the synthetic applications of the α-methylenation methodology in natural product synthesis,[4] we want to develop a general synthetic pathway, which is applicable to prepare natural products **7**–**9**. In this article, our effort in the stereoselective total synthesis of canadensolide (**7**) will be described.

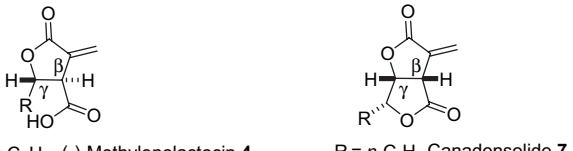


Figure 1. Natural products with β,γ-disubstituted-α-methylene-γ-butyrolactone moiety and α-methylene-furofurandione moiety.

Keywords: Canadensolide; α-Methylene-γ-butyrolactones; Bislactones; α-Methylenation.
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2. Results and discussions

2.1. The retrosynthetic analysis of bislactone-type natural product

The retrosynthetic analysis of bislactone-type natural product **A** is shown in Figure 2. The bislactone **A** should be easily prepared by the bislactonization of the diester **B**. The methyl

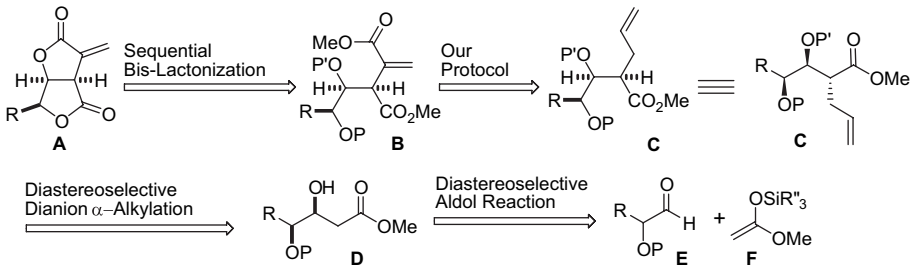


Figure 2. Retrosynthetic analysis of the total synthesis of bislactone natural products.

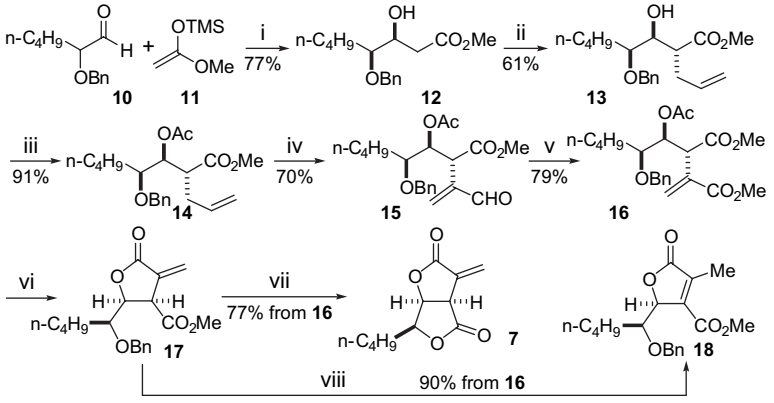
acrylate **B** should be easily prepared from allylacetate **C** by our methodology as shown in Scheme 1. The stereoselective introduction of the α-stereogenic center of compound **C** from the allylation of the dianion of β-hydroxy ester **D** is a well known procedure in the literature.[12] The *syn*-β-hydroxy-γ-alkoxy ester **D** formed from the Lewis acid-catalyzed addition of the silyl enol ether **F** to α-alkoxy aldehyde **E** via chelation-controlled intermediate should be a diastereoselective process (Fig. 2).[13]

2.2. The total synthesis of canadensolide

The readily available α-benzyloxyhexanal (**10**)[14] undergoes aldol additions with trimethylsilyl ketene acetal **11** catalyzed by $TiCl_4$ at −78 °C to give the chelation-controlled 1,2-asymmetric induction[13] *syn* product **12** in 77% yield (Scheme 2). Essentially only one of two possible diastereomers is formed. The allylation of β-hydroxy ester **12** following the procedure of Frater[12] gave the 2,3-*anti*-β-hydroxy ester **13** in 61% yield. The acetylation of the secondary alcohol **13** gave the corresponding acetate **14** in 91% yield. The ozonolysis of terminal olefin **14** followed by addition of of the crude product. However, we found that compound **17** undergoes isomerization to the endocyclic olefin **18** during the silica gel column chromatography. Fortunately, the debenzylation of the crude product **17** with a stoichiometric amount of $SnCl_4$[15] was tried and canadensolide (**7**) was isolated in 77% yield for two steps as a white solid. Presumably, the isomerization to the extended conjugated product is a facile process only for the monocyclic compound **17** but not the bicyclic compound **7**.

3. Conclusions

The special features of our synthetic design are described as follows. The relative stereochemistry of γ- and δ-substituents was established by the $TiCl_4$-catalyzed aldol reaction via chelation-controlled intermediate. The relative stereochemistry of β- and γ-substituents was established by the stereoselective allylation of the dianion of β-hydroxy ester **12**. Furthermore, the α-methylene-γ-butyrolactone moiety was derived from the corresponding terminal alkene by the methodology developed in our laboratory (Fig. 3). We



Scheme 2. Reagents and conditions: (i) $TiCl_4$, −78 °C, CH_2Cl_2, 8 h; (ii) (a) 2.2 equiv LDA, −78 °C, 6 h; (b) $H_2C{=}CHCH_2Br$; (iii) Ac_2O, Et_3N, cat. DMAP; (iv) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2, 2 h; (v) (a) $NaClO_2$, *t*-BuOH, $NaH_2PO_4{\cdot}2H_2O$, $MeCH{=}CMe_2$, 8 h; (b) CH_2N_2; (vi) cat. MeCOCl, MeOH, 24 h; (vii) $SnCl_4$, CH_2Cl_2, reflux, 2.5 h; (viii) silica gel column chromatography.

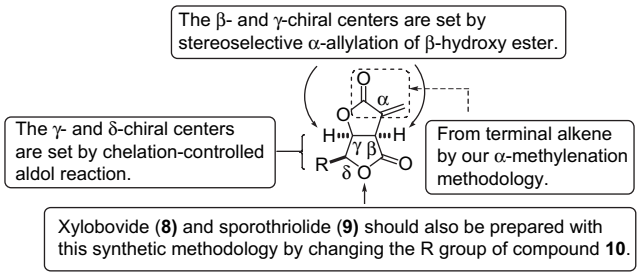


Figure 3. Summary of the special features of our natural product synthesis.

complete the total synthesis of canadensolide (**7**) in nine operation steps in 18% overall yield starting from α-benzyloxy aldehyde **10**.

Our synthetic design should be extendable to the total synthesis of xylobovide (**8**) and sporothriolide (**9**) by replacing the α-substituent of compound **10** from *n*-butyl to ethyl and *n*-hexyl, respectively.

4. Experimental

4.1. General

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX400 spectrometer, and chemical shifts were given in parts per million downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorptions were listed. Mass spectra were measured on a Micromass Trio-2000 GC–MS spectrometer (National Chiao-Tung University) by electronic impact at 70 eV (unless otherwise indicated). High Resolution Mass Spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT (National Chung Hsing University) mass spectrometer. 3-Nitrobenzyl alcohol (NBA) was used as FAB Mass matrix. Compound **10** was prepared by the reported procedure.[14]

4.2. (3*S**,4*S**)-4-(Benzyloxy)-3-hydroxyoctanoic acid methyl ester (12)

To a mixture of aldehyde **10** (1.2 g, 5.82 mmol) and enol silyl ether **11** (1.02 g, 6.98 mmol) in 23 mL of CH_2Cl_2 was added $TiCl_4$ (6.4 mmol, 6.4 mL, 1.0 M in CH_2Cl_2) by syringe pump at −78 °C over 1 h. The reaction mixture was warmed to rt and continued to stir for another 8 h. The reaction mixture was neutralized slowly by saturated aqueous $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the crude product. The crude product was purified by silica gel column chromatography to give β-hydroxy ester **12** (1.26 g, 4.49 mmol) as a pale yellow oil in 77% yield. R_f=0.39 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.38 (m, 5H, Ph-H), 4.64 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 4.51 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 4.08–4.14 (m, 1H, –C*H*OH), 3.68 (s, 3H, OMe), 3.37 (td, J=6.1 and 4.1 Hz, 1H, –C*H*OBn), 2.70 (d, J=5.8 Hz, 1H, OH), 2.53–2.55 (m, 2H, –CH_2CO$_2$Me), 1.32–1.67 (m, 6H), 0.91 (t, J=7.0 Hz, 3H, –CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 138.2, 128.3, 127.8, 127.7, 80.8, 72.2, 69.0, 51.6, 38.0, 29.4, 27.6, 22.8, 13.9; IR (thin film, NaCl plates): 3471, 2953, 2930, 2859, 1736, 1455, 1437, 1275, 1170, 1072, 736, 699 cm^{-1}; FAB Mass (*m*/*z*): 281 (M$^+$+l, 30), 280 (M$^+$, 0.2), 263 (4), 249 (2), 173 (12), 91 (100); HRMS calcd for $C_{16}H_{24}O_4$: 280.1675, found: 280.1673.

4.3. (2*R**,3*S**,4*S**)-2-Allyl-4-(benzyloxy)-3-hydroxyoctanoic acid methyl ester (13)

n-Butyllithium (4.9 mL, 7.85 mmol, 1.6 M in hexane) was added to a stirring solution of diisopropylamine (1.10 mL, 7.85 mmol) in THF (12 mL) at −78 °C. To the LDA solution, β-hydroxy ester **11** (1.0 g, 3.57 mmol) in 5 mL of THF was added at −78 °C and stirred at this temperature for 1 h. At −78 °C, a mixture of allyl bromide (0.37 mL, 4.27 mmol) and HMPA (1.2 mL) in THF (4.8 mL) was added to the reaction mixture. After stirring at −78 °C for 1 h, the reaction mixture was partitioned between 40% ethyl acetate/petroleum ether and saturated aqueous NH_4Cl. The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed on silica gel column to afford product **13** (698 mg, 2.44 mmol) in 61% yield as a colorless oil. TLC R_f=0.58 (hexane/EtOAc=5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.37 (m, 5H, Ph-H), 5.62–5.73 (m, 1H, –C*H*=CH$_2$), 5.01–5.07 (m, 2H, –CH=CH_2), 4.66 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 4.42 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 3.70 (ddd, J=9.4, 5.8, and 2.7 Hz, 1H, –C*H*OH), 3.54 (s, 3H, OMe), 3.38 (ddd, J=7.7, 5.2, and 2.6 Hz, 1H, –C*H*OBn), 2.85 (d, J=9.5 Hz, 1H, OH), 2.64 (dt, J=9.0 and 5.8 Hz, 1H, –C*H*CO$_2$Me), 2.22–2.41 (m, 2H, –CH_2CH=CH$_2$), 1.29–1.64 (m, 6H), 0.91 (t, J=7.0 Hz, 3H, –CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 138.1, 134.7, 128.4, 127.9, 127.7, 117.2, 79.3, 72.8, 71.5, 51.6, 48.5, 33.8, 29.3, 27.6, 22.9, 14.0; IR (thin film, NaCl plates): 3481, 2953, 2932, 2861, 1736, 1455, 1437, 1267, 1195, 1167, 1069, 916, 734, 699 cm^{-1}; FAB Mass (*m*/*z*): 321 (M$^+$+l, 31), 320 (M$^+$, 0.2), 281 (28), 213 (32), 207 (21), 147 (28), 91 (100), 73 (42); HRMS calcd for $C_{19}H_{28}O_4$: 320.1988, found: 320.1990.

4.4. (2*R**,3*S**,4*S**)-3-Acetoxy-2-allyl-4-(benzyloxy)octanoic acid methyl ester (14)

To a solution of the alcohol **13** (500 mg, 1.56 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 19.0 mg, 0.156 mmol) and Et_3N (0.26 mL, 1.87 mmol) in 3.1 mL of CH_2Cl_2 was added acetic anhydride (0.17 mL, 1.87 mmol) at rt and stirred for 2 h. The reaction mixture was concentrated and chromatographed on silica gel column to afford the acetate **14** (515 mg, 1.42 mmol) in 91% yield as a pale yellow oil. TLC R_f=0.67 (hexane/EtOAc=3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.37 (m, 5H, Ph-H), 5.67–5.69 (m, 1H, –C*H*=CH$_2$), 5.24 (dd, J=8.3 and 3.7 Hz, 1H, –C*H*OAc), 4.99–5.03 (m, 2H, –CH=CH_2), 4.64 (ABq, J=11.7 Hz, 1H, –CH_2Ph), 4.54 (ABq, J=11.7 Hz, 1H, –CH_2Ph), 3.64 (s, 3H, OMe), 3.52 (td, J=6.4 and 3.7 Hz, 1H, –C*H*OBn), 2.96 (td, J=8.3 and 6.3 Hz, 1H, –C*H*CO$_2$Me), 2.24–2.28 (m, 2H, –CH_2CH=CH$_2$), 2.03 (s, 3H, –COCH_3), 1.28–1.51

(m, 6H), 0.88 (t, J=7.2 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 169.9, 138.0, 134.2, 128.3, 127.9, 127.7, 117.3, 77.3, 73.4, 71.7, 51.4, 46.5, 32.8, 29.2, 27.4, 22.6, 20.8, 13.8; IR (thin film, NaCl plates): 2954, 2935, 2871, 1746, 1455, 1436, 1372, 1233, 1169, 1026, 918, 736, 699 cm^{-1}; EI Mass (m/z): 362 (M^+, 1), 255 (74), 177 (24), 155 (20), 143 (65), 135 (40), 123 (45), 105 (93), 91 (100), 77 (49), 55 (19); HRMS calcd for $C_{21}H_{30}O_5$: 362.2093, found: 362.2101.

4.5. (2*S**,3*R**,4*R**)-3-Acetoxy-4-(benzyloxy)-2-(1-formylvinyl)octanoic acid methyl ester (15)

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube, and a magnetic stirring bar were charged with terminal alkene **14** (400 mg, 1.10 mmol) in CH_2Cl_2 (20 mL). The flask was cooled to −78 °C and ozone was bubbled through the solution. When the solution turned blue, ozone addition was stopped. Nitrogen was passed through the solution until the blue color was discharged. A mixture of Et_2NH (0.62 mL, 16.7 mmol) and CH_2Br_2 (1.2 mL, 5.6 mmol) was heated to 55 °C for 1.5 h to give a yellow solution and then cooled to rt. To a solution of ozonide in CH_2Cl_2 generated above was added a preheated mixture of Et_2NH and CH_2Br_2 at −78 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at rt. The reaction was complete in 2.5 h and the reaction mixture was concentrated. To the crude mixture, ether was added and most of the ammonium salts were precipitated out. After filtration, the filtrate was concentrated, chromatographed on the silica gel column to give the desired acrolein **15** (290 mg, 0.77 mmol) in 70% yield as a pale yellow oil; TLC R_f=0.32 (hexane/EtOAc=5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.40 (s, 1H, CHO), 7.26–7.35 (m, 5H, Ph-H), 6.59 (s, 1H, –C=CH_2), 6.14 (s, 1H, –C=CH_2), 5.52 (dd, J=8.8 and 3.8 Hz, 1H, –CHOAc), 4.49 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.42 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.20 (d, J=8.8 Hz, 1H, –CHCO$_2$Me), 3.64 (s, 3H, OMe), 3.44 (ddd, J=7.2, 5.5, and 3.8 Hz, 1H, –CHOBn), 2.05 (s, 3H, –COCH_3), 1.28–1.49 (m, 6H), 0.87 (t, J=7.0 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 170.7, 169.9, 144.2, 137.9, 136.5, 128.2, 127.7, 127.5, 77.8, 72.7, 71.6, 52.1, 43.2, 29.1, 27.5, 22.5, 20.8, 13.8; IR (thin film, NaCl plates): 2955, 2934, 2870, 1747, 1696, 1455, 1435, 1372, 1232, 1168, 1027, 914, 734, 699 cm^{-1}; FAB Mass (m/z): 376 (M^+, 1), 316 (17), 284 (88), 270 (16), 230 (51), 210 (65), 199 (81), 177 (90), 157 (98), 139 (91), 125 (95), 109 (22), 91 (100), 65 (84), 55 (27); HRMS calcd for $C_{21}H_{29}O_6$ (M^++1): 377.1964, found: 377.1956.

4.6. (2*R**)-[(1*S**,2*S**)-1-Acetoxy-2-(benzyloxy)hexyl]-3-methylenesuccinic acid dimethyl ester (16)

To a solution of acrolein **15** (200 mg, 0.53 mmol), *tert*-butyl alcohol (2.7 mL), and 2-methyl-2-butene (0.18 mL, 111.7 mg, 1.59 mmol) was added dropwise a solution of sodium chlorite (110.7 mg, 1.21 mmol) and sodium dihydrogenphosphate dihydrate (163.7 mg, 1.06 mmol) in 0.8 mL of water. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 1.6 mL of water, and this extracted with 6 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 5 mL portions of ether. The combined ether layers were washed with 6 mL of water, dried with Na_2SO_4, concentrated to give the crude carboxylic acid. To a solution of α-substituted acrylic acid in 2 mL of CH_2Cl_2 was added a solution of CH_2N_2 in ethyl ether at rt. The progress of the reaction should be monitored carefully by TLC. Excess of the CH_2N_2 will cause further 1,3-dipolar cycloaddition on the double bond. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **16** (171 mg, 0.42 mmol) as a pale yellow oil in 79% yield. TLC R_f=0.6 (hexane/EtOAc=3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.35 (m, 5H, Ph-H), 6.38 (s, 1H, –C=CH_2), 5.90 (s, 1H, –C=CH_2), 5.59 (dd, J=9.0 and 3.4 Hz, 1H, –CHOAc), 4.51 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.41 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.17 (d, J=9.0 Hz, 1H, –CHCO$_2$Me), 3.68 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.49 (td, J=6.4 and 3.4 Hz, 1H, –CHOBn), 2.05 (s, 3H, –COCH_3), 1.28–1.35 (m, 6H), 0.86 (t, J=7.1 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.0, 166.0, 138.1, 135.2, 128.8, 128.1, 127.5, 127.4, 77.9, 72.9, 71.6, 52.1, 47.2, 29.0, 27.4, 22.5, 20.8, 13.8; IR (thin film, NaCl plates): 2953, 2932, 2860, 1748, 1455, 1436, 1372, 1229, 1172, 1027, 917, 736, 699 cm^{-1}; EI Mass (m/z): 406 (M^+, 5), 375 (18); HRMS calcd for $C_{22}H_{30}O_7$: 406.1992, found: 406.1990.

4.7. (2*R**)-[(1*R**)-1-(Benzyloxy)pentyl]-2,5-dihydro-4-methyl-5-oxofuran-3-carboxylic acid methyl ester (18)

To a mixture of acetoxy-acrylate **16** (40 mg, 0.098 mmol) in 1 mL of MeOH was added a catalytic amount of acetyl chloride (2 μL, 29 μmol) and stirred at rt for 24 h. The reaction mixture was concentrated to give the crude α-methylene-γ-butyrolactone **17**. The crude product **17** was chromatographed on silica gel column to give the isomerized product **18** (29.3 mg, 0.088 mmol) in 90% yield as a pale yellow oil. TLC R_f=0.33 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14–7.35 (m, 5H, Ph-H), 5.10–5.11 (m, 1H, CHOCO), 4.50 (ABq, J=11.9 Hz, 1H, –CH_2Ph), 4.27 (ABq, J=11.9 Hz, 1H, –CH_2Ph), 3.89 (td, J=7.0 and 1.7 Hz, 1H, –CHOBn), 3.75 (s, 3H, OMe), 2.16 (d, J=2.0 Hz, 3H, =CCH_3), 1.28–1.49 (m, 6H), 0.92 (t, J=7.0 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 162.6, 144.7, 138.3, 137.8, 128.3, 127.6, 81.9, 76.4, 72.3, 52.2, 31.2, 27.9, 22.6, 13.9, 10.8; IR (thin film, NaCl plates): 2955, 2931, 2862, 1768, 1728, 1455, 1438, 1339, 1225, 1098, 1026, 737, 699 cm^{-1}; EI Mass (m/z): 332 (M^+, 1), 258 (58), 215 (88), 199 (66), 187 (69), 156 (95), 145 (52), 127 (56), 124 (88), 105 (100), 91 (97), 65 (73), 55 (63); HRMS calcd for $C_{19}H_{24}O_5$: 332.1624, found: 332.1626.

4.8. (3a*S**,6*R**,6a*R**)-6-Butyl-tetrahydro-3-methylene-furo[3,4-*b*]furan-2,4-dione [i.e., (±)-canadensolide] (7)

To a solution of acetoxy-acrylate **16** (40 mg, 0.098 mmol) in 1 mL of MeOH was added a catalytic amount of acetyl chloride (2 μL, 29 μmol) and stirred at rt for 24 h. The reaction mixture was neutralized by $NaHCO_3$, filtered, and the filtrate was concentrated to give the crude α-methylene-γ-butyrolactone **17**. To a solution of the crude product **17** in 2 mL of anhydrous CH_2Cl_2 was added $SnCl_4$ (0.1 mmol, 0.1 mL,

1 M in CH_2Cl_2) at rt. The solution was refluxed for 2.5 h, and then saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried over Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by silica gel column chromatography to afford 15.9 mg of canadensolide (**7**) as a white solid in 77% yield. TLC R_f=0.68 (hexane/EtOAc=l:2), mp 95.3–96.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, J=2.0 Hz, 1H, –C=CH_2), 5.16 (d, J=1.9 Hz, 1H, –C=CH_2), 5.15 (dd, J=6.8 and 4.7 Hz, 1H, –C*H*OCO), 4.65 (ddd, J=7.6, 6.6, and 4.8 Hz, 1H, –C*H*OCO), 4.01 (dt, J=6.7 and 2.0 Hz, 1H, –C*H*CO_2), 1.40–1.90 (m, 6H), 0.94 (t, J=7.2 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 167.4, 129.9, 127.2, 82.8, 77.2, 46.2, 28.5, 27.5, 22.4, 13.8; IR (thin film, NaCl plates): 2954, 2928, 2858, 1762, 1664, 1464, 1363, 1306, 1269, 1118, 1069, 934, 727 cm^{-1}; EI Mass (*m*/*z*): 211 (M^++1, 1), 156 (12), 124 (30), 110 (45), 96 (100), 85 (16), 68 (53), 55 (18); HRMS calcd for $C_{11}H_{15}O_4$ (M^++1): 211.0970, found: 211.0975.

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The synthesis of heterocyclic derivatives from pyran-2-ones and hydrazine hydrate. Ammonium cerium(IV) nitrate as an efficient oxidant in pyridazine chemistry

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Dedicated to Professor Miha Tišler on the occasion of his 80th birthday

Abstract—A novel reaction of 3-amino-2*H*-pyran-2-ones and their fused derivatives with hydrazine hydrate leading to the corresponding pyridazine derivatives is reported. Further oxidation with ammonium cerium(IV) nitrate (CAN, from Cerium(IV) Ammonium Nitrate) yields a collection of pyridazine-3-carboxylates.

1. Introduction

Pyridazines and fused pyridazines are of considerable interest because of their synthetic utility[1] and important pharmacological activities,[2] many of them related to the cardiovascular system. 1,4-Dihydropyridazine derivatives including their carboxylic esters can be obtained in the cycloaddition reactions of 1,2,4,5-tetrazines with different dienophiles,[3] by the reaction of aminocarbonylazoalkenes with β-tricarbonyl compounds,[4] via the cycloaddition of diazomethane to cyclopropenes,[5] etc. Since the 1,4-dihydropyridazine system represents an intermediate for aromatized pyridazines, a plethora of inorganic and organic oxidants have been found to readily dehydrogenate dihydropyridazines.[3c,d,4,5,6] Among them, CAN,[7] a powerful one-electron oxidant, which has already shown great utility in carbon–carbon[7a] or carbon–heteroatom[7b] bond-forming reactions, was previously used as a reagent for the cleavage of the hydrazine moiety of carbohydrazides.[8] Recently, we have also reported on its applicability as an oxidant for 1,4,6,7,8,9-hexahydro-5*H*-pyridazino[4,3-*c*]azepine-3-carboxylic acid hydrazides in the presence of an alcohol, where both the pyridazine moiety and the carbohydrazido group were successfully oxidized, resulting in the corresponding aromatic pyridazine esters.[9] The main advantages of CAN are its experimental simplicity, easy handling, non-toxicity, and solubility in many common organic solvents.

Many transformations of pyran-2-ones with nucleophilic reagents yielding different types of products have been investigated.[10] As part of our continuing interest in the transformations of pyran-2-one derivatives with hydrazine and its derivatives[11] we preliminarily reported on a new conversion of pyrano[3,2-*c*]azepines with hydrazine hydrate into representatives of pyridazino[4,3-*c*]azepines.[11e] The presence of a free amino group at position 3 in the starting pyran-2-ones was found to be crucial for the synthesis of pyridazine derivatives, because all other fused pyran-2-ones, possessing a benzoyl-protected amino group, led in the reaction with hydrazine hydrate (or its derivatives) to different products: to fused pyridine derivatives,[11a,b] in some cases the reaction took place at the side group,[11b,d,g,h] in other cases β-heteroaryl-α,β-didehydro-α-amino acid derivatives were obtained.[11c,h,i] In this paper we report on the exploration of the scope and limitations of the reaction starting from a variety of 2*H*-pyran-2-ones and fused pyran-2-ones, bearing a free amino group at position 3, with hydrazine hydrate into representatives of the pyridazine system, which were further oxidized by CAN toward different types of pyridazines.

2. Results and discussion

In the first stage we examined the preparation of 1,4-dihydropyridazines **2**, containing a fused polymethylene chain, by the reaction of fused pyran-2-ones **1** with hydrazine hydrate (Scheme 1). The reaction of cyclooctene-fused pyran-2-one **1b** with hydrazine hydrate, when using similar conditions to those that we preliminarily applied for the

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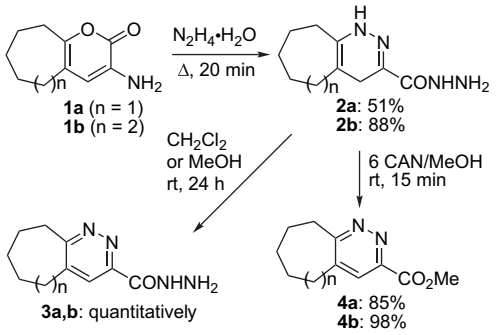
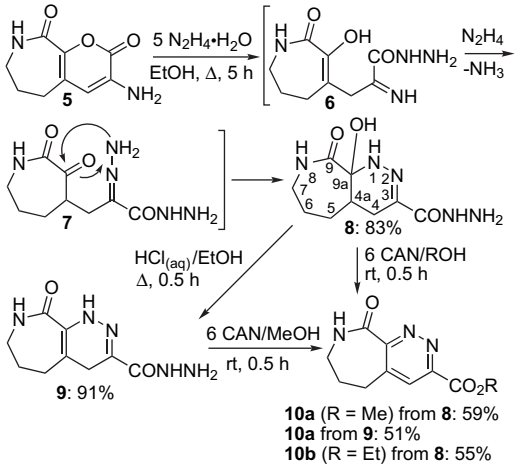
transformation of pyrano[3,2-*c*]azepines,[11e] was not complete after 9 h, as indicated by TLC. On the other hand, when the reactions of **1a**,**b** were carried out in boiling hydrazine hydrate, which served as the reagent and as a solvent, pure dihydropyridazine derivatives **2a**,**b** were isolated after a short reaction time (20 min) with good-to-excellent yields (up to 88%).



Scheme 1. Synthesis of cycloalkene-fused pyridazines.

^{1}H NMR spectra of **2a** and **2b** in DMSO-d_6 solutions revealed that these compounds have the 1,4-dihydropyridazine structure and no trace of any other tautomer was observed. In fact, a characteristic two-proton signal appeared at ~2.85 ppm (A_2 system) for methylene protons at position 4, whereas 1-H protons showed a resonance around 9 ppm. Compounds **2** are sensitive to oxidation from the air in solution, as well as in the crystalline form, and readily transformed into their aromatic analogues **3**. Thus, stirring of the compounds **2a**,**b** for 24 h in methylene chloride (or methanol) at room temperature in the presence of air afforded **3a**,**b** in a quantitative yield, whereas in the crystalline form after 24 h an ~90% aromatization of the compound **2b** took place. This transformation can be considerably reduced by storing compounds **2** in an argon atmosphere at low temperature. For example, with the compound **2b**, after three months at approximately −30 °C in a closed bottle under argon atmosphere only an approximately 5% conversion into **3b** was observed. It has been reported that dihydropyridazines are reactive toward molecular oxygen, normally forming the corresponding aromatic pyridazines;[12] however, in certain cases they gave hydroperoxides and endoperoxides.[12a] With our compounds, though, we were not able to detect or isolate any other intermediate: only pyridazine derivatives **3** were obtained as the final products. Additionally, we could accelerate the above dehydrogenation by bubbling oxygen into the refluxed mixture of **2b** in methanol; in this particular case the reaction was completed within 4 h to give **3b**. When bubbling oxygen in the presence of 50 mass % of activated carbon (DARCO® KB)[13] the reaction was finished in 3 h to give quantitatively **3b**. Compounds **2** can also be smoothly oxidized with CAN in a methanolic solution to give the pyridazine esters **4** in 85% (**4a**) and 98% (**4b**) yields. In the course of this reaction the formation of the ester from the hydrazide is accompanied by a concomitant aromatization of the 1,4-dihydropyridazine ring.

In contrast to our previous observation of the behavior of pyrano[3,2-*c*]azepines in a reaction with hydrazine hydrate,[11e] the reaction of the isomeric pyrano[2,3-*c*]azepine derivative **5** with 5 equiv of hydrazine hydrate in boiling ethanol led to the 9a-hydroxypyridazino[3,4-*c*]azepine derivative **8** with a high yield (Scheme 2).



Scheme 2. Pyrano[2,3-*c*]azepine **5** as a synthon for pyridazino[3,4-*c*]azepines.

The structure of the compound **8** was established on the basis of its NMR spectroscopic data. The two- and three-bond H, C connectivities, obtained from the HMBC measurement, strongly support the 9a-hydroxy-4,4a,5,6,7,8,9,9a-octahydro-1*H*-pyridazino[3,4-*c*]azepine structure; namely, 1-H, 8-H, the methylene protons at position 4 (4-CH_aH_b protons not being chemically and magnetically equivalent), and the hydroxy group correlate with 9a-C (78.7 ppm) in the HMBC spectrum, whereas the 1-H and 4-CH_aH_b protons correlate with 3-C (135.5 ppm), thus revealing an azepine-fused pyridazine skeleton and not an open-ring intermediate **7** (or its tautomer) (Fig. 1).

Compound **8** has been found to readily eliminate a water molecule when treated with aqueous HCl in absolute ethanol, thus giving the 4,5,6,7,8,9-hexahydro-1*H*-pyridazino[3,4-*c*]azepine derivative **9**. Treatment of the compound **8** with 6 equiv of CAN in an alcoholic solution led to the isolation of the fused pyridazine esters **10** in moderate yields (55–59%). Alternatively, the esters **10** can also be prepared by the oxidation of the compound **9** with CAN, as shown in

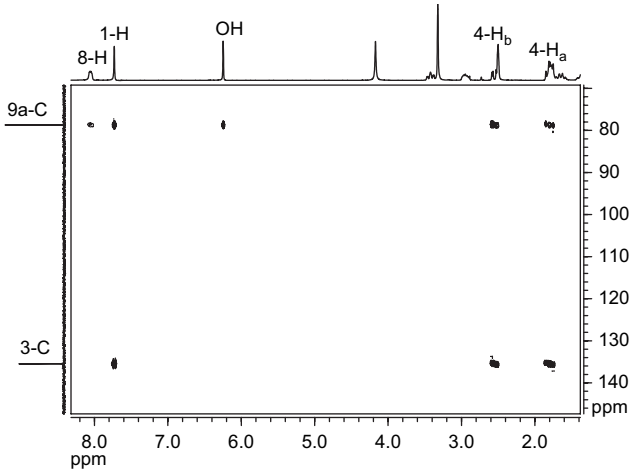
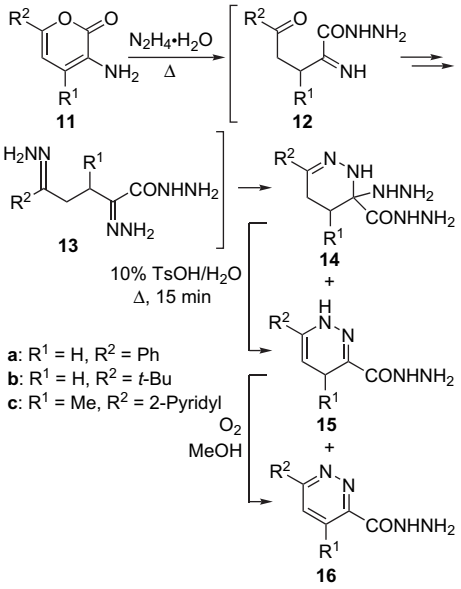


Figure 1. A part of the ^{1}H–^{13}C HMBC spectrum of the compound **8**.

the case of the methyl ester **10a**. On the basis of the above results we can assume that an acidic medium catalyzes the elimination of a water molecule from the compound **8** during the oxidation with CAN, thus initially giving the 1,4-dihydropyridazine intermediate, which is further dehydrogenated and transformed to the aromatic pyridazine esters **10** as the final products. The described method is very convenient for the preparation of pyridazino[3,4-*c*]azepines for which, to our knowledge, only two representatives have been previously described.[14]

Bearing in mind the above results of the fused pyran-2-ones, we decided to focus our attention on studies of the susceptibility of non-fused 2*H*-pyran-2-ones **11** to nucleophilic attack by a hydrazine molecule (Scheme 3, Table 1).



Scheme 3. Reaction of 2*H*-pyran-2-ones **11** with hydrazine.

Due to the absence of a fused ring in the compounds **11**, after the opening of the lactone ring with hydrazine the formation of a more flexible intermediate might be expected; this might then open up possibilities for different reactions. For example, one might expect that such an open-ring system would not be prone to cyclization, thus allowing an attack of additional hydrazine molecule(s). Indeed, when 6-substituted 2*H*-pyran-2-ones **11a** and **11b** were allowed to react with boiling hydrazine hydrate for 20 min the products **14a** and **14b** were isolated in 76 and 67% yields, respectively. The product **14b** was also accompanied by a small quantity (17%) of the 1,4-dihydropyridazine derivative **15b**. On the other hand, after refluxing the 2*H*-pyran-2-one **11c** in the presence of 5 equiv of hydrazine hydrate using ethanol or butanol as a solvent, we isolated the 1,4-dihydropyridazine derivative **15c**, which in ethanol was accompanied by the aromatic pyridazine **16c** (entries 3 and 4, Table 1). Compounds **14a**,**b** can easily eliminate a hydrazine molecule, when applying acidic conditions (10 mol % of TsOH in aqueous solution), to give **15a**,**b** in 90 and 71% yields, respectively. Compounds **15** have been found to be sensitive to the oxygen in air. For example, if **15b** was stirred in methylene chloride for 24 h at room temperature, a conversion into the aromatic pyridazine **16b** was observed in more than 95% (according to the ^{1}H NMR spectrum). On the other hand, 1,4-dihydropyridazine **15c** was found to be more resistant toward such oxidation in air; 72-h-stirring of its methanolic solution at room temperature resulted only in negligible formation of the aromatic analogue **16c** (as indicated by TLC). Aromatization was successfully accomplished by 7-h-bubbling of oxygen into the refluxed mixture of **15c** and 50 mass % of activated carbon (DARCO® KB) in methanol. For comparison, in the absence of activated carbon, but just bubbling oxygen into the refluxed mixture for 10 h, a conversion of about 40% of **15c** took place.

Table 1. Reaction of 2*H*-pyran-2-ones **11** with hydrazine

Entry	Starting **11**	*t*	Products (yield, %)[a]
1	**11a**	20 min[b]	**14a** (76)
2	**11b**	20 min[b]	**14b** (67)+**15b** (17)
3	**11c**	22 h[c]	**15c** (41)[d]+**16c** (7)[d]
4	**11c**	4.5 h[e]	**15c** (71)[d]

[a] Yields of isolated products are given.
[b] Hydrazine hydrate used as a solvent.
[c] Five equivalents of $N_2H_4 \cdot H_2O$ in ethanol.
[d] Yield after isolation by column chromatography.
[e] Five equivalents of $N_2H_4 \cdot H_2O$ in butanol.

The structures of the compounds **14** were determined on the basis of microanalyses, mass spectra, and NMR data. The mass spectra of the compounds **14a** and **14b** only showed peaks after the elimination of a hydrazine molecule ($MH^+ - N_2H_4$ or $M^+ - N_2H_4$), thus indicating that they contain in their structure a labile hydrazine moiety. In the HMBC spectrum of the compound **14a**, the *ortho* protons of the phenyl group and the 2-H correlate with the 6-C of the pyridazine ring, thus supporting the 2,3,4,5-tetrahydropyridazine structure (Fig. 2).

Additionally, it has been reported previously that the imine fragments of 2,3,4,5-tetrahydro-3-pyridazine carboxylic acid derivatives show characteristic signals at $\delta_C \approx$ 140 ppm.[15] This is in agreement with our observation for the compound **14a**, where the resonance signal for 6-C appears at 140.9 ppm. Furthermore, the 2-H as well as the methylene protons at positions 4 and 5 of the pyridazine

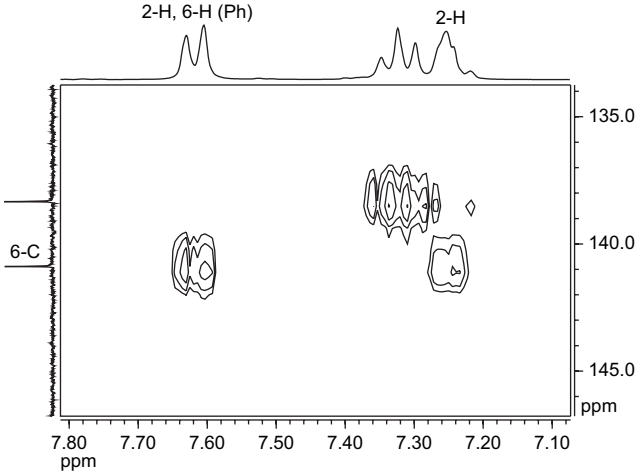


Figure 2. A part of the ^{1}H–^{13}C HMBC spectrum of the compound **14a**.

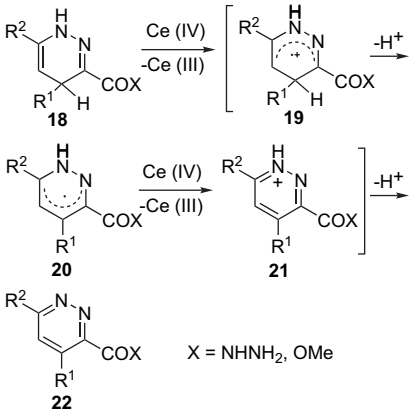
ring in compound **14a** correlate with the 3-C. This carbon atom shows a resonance at 71.9 ppm, which is consistent with the chemical shift of a quaternary sp^3 carbon atom deshielded by the neighboring heteroatoms.[16]

The formation of the products **14** and **15** from **11** might be explained as follows. We assume that after the opening of the lactone ring of the 2*H*-pyran-2-ones **11** with hydrazine, yielding the intermediate **12**, the attack of two additional hydrazine molecules at the electrophilic C=O and C=N groups of **12** takes place, thus leading to the α,δ-dihydrazonohydrazide derivative **13** as an intermediate. Furthermore, compounds **14** could be formed from **13** by the cyclization of the amino group of the δ-hydrazone moiety with the C=N group of α-hydrazone. After the elimination of a hydrazine molecule from **14** the dihydropyridazine **15** is finally formed in a 1,4-dihydro tautomeric form.

To demonstrate the utility of the compounds **14** and **15**, we treated them with 6–8 equiv of CAN in the presence of methanol and, after isolation by extraction, pyridazine-3-carboxylic esters **17a–c** were obtained as the sole products in a 79–93% yield (Table 2). It is obvious that an oxidation of the hydrazide function was accompanied by an acid-catalyzed elimination of hydrazine from compounds **14** (as mentioned above), and the dehydrogenation of a 1,4-dihydropyridazine ring.

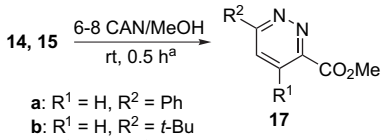
In all the above transformations with CAN a 1,4-dihydropyridazine ring was dehydrogenated in addition to the oxidation of the carbohydrazide moiety. The latter reaction toward the corresponding esters proceeds probably via acyl diimides as intermediates and eventually also via the formation of the acyl cation as discussed previously.[8]

On the other hand, to our knowledge, the oxidation of the 1,4-dihydropyridazine ring has not yet been rationalized. It seems reasonable to propose a tentative pathway related to those depicted for oxidations of 1,4-dihydropyridines.[17] Oxidation of a 1,4-dihydropyridazine **18** with CAN is presumably initiated by a single electron transfer to Ce(IV) generating a resonance stabilized radical cation **19** (Scheme 4), which then loses a proton to give a stabilized radical **20**. In the subsequent oxidation the protonated pyridazine **21** is produced and further transformed to the aromatized derivative **22**.



Scheme 4. Dehydrogenation of the 1,4-dihydropyridazine ring with Ce(IV).

Table 2. Oxidation of compounds **14** and **15** with CAN in the presence of methanol



a: R^1 = H, R^2 = Ph
b: R^1 = H, R^2 = *t*-Bu
c: R^1 = Me, R^2 = 2-Pyridyl

Entry	Starting **14** or **15**	Product (yield, %)[b]
1	**14a**	**17a** (93)[c]
2	**14b**	**17b** (89)[c]
3	**15b**	**17b** (84)[d]
4	**15c**	**17c** (79)[d]

[a] Reaction time after the addition of the entire amount of compound **14** or **15** to the mixture of CAN in methanol.
[b] Yields of isolated products are given.
[c] Eight equivalents of CAN used.
[d] Six equivalents of CAN used.

3. Conclusion

We have presented a new transformation of a variety of 2*H*-pyran-2-ones and fused pyran-2-ones with hydrazine hydrate into the corresponding 1,4-dihydropyridazine derivatives. We found that different pyran-2-ones required different reaction conditions for successful transformation to the pyridazine system. We have also shown that CAN is able to serve as a very useful oxidant for the carbohydrazide moiety as well as for the dehydrogenation of the 1,4-dihydropyridazine ring. Since it was previously shown that representatives of 2,3,4,5-tetrahydropyridazine-3-carboxylic acids and their derivatives possess a variety of biological activities,[2,15] the reported method and transformation might be of interest for the further design of similar novel compounds.

4. Experimental

4.1. General

Compounds **1** and **11** were prepared from 3-benzoylamino-substituted pyran-2-one derivatives by a known method.[18,19] Compound **5** was prepared as described in the literature.[11d] All other reagents and solvents were used as obtained from commercial suppliers. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 29 °C using TMS as an internal standard. ^{13}C NMR spectra are referenced against the central line of DMSO-d_6 at δ=39.5 ppm and $CDCl_3$ at δ=77.0 ppm. TLC was carried out on silica-gel TLC cards. Column chromatography was carried out with silica-gel 60 (220–440 mesh).

4.2. General procedure for the preparation of pyridazines 2a,b, 14a,b, and 15b

A mixture of **1a**,**b**[18] or **11a**,**b**[18] (2 mmol) and hydrazine hydrate (1.5 g, 98%, 29.36 mmol) was refluxed for 20 min and then evaporated under reduced pressure. A mixture of water/methanol (5:1) (3 mL) in the case of **2a** or water (3 mL) in the case of **2b** was added to the residue. Upon cooling, the precipitated yellow solid was filtered off and washed with

a small amount of water to give **2a** (or **2b**). For **14a**,**b**, methanol (3 mL) was added to the residue, and upon cooling the white solid product **14a**,**b** was filtered off. After the separation of **14a** the filtrate was concentrated to 50% of its volume under reduced pressure to give an additional quantity of **14a**. The filtrate after the filtration of **14b** was evaporated to dryness, and diethyl ether (1.5 mL) was added to the residue. Upon cooling, a yellow solid **15b** was filtered off.

4.3. General procedure for the preparation of pyridazines 8, 15c, and 16c

A mixture of **5**[11d] or **11c**[18] (2 mmol), hydrazine hydrate (511 mg, 98%, 10 mmol), and absolute ethanol (8 mL) was refluxed for 5 h (for **8**) or for 22 h (for **15c**/**16c**). For the preparation of pure **15c** the solution of **11c** and hydrazine hydrate in butanol (8 mL) was refluxed for 4.5 h. The solvent was evaporated under reduced pressure. For **8**, methanol (4 mL) was added to the solid residue and, upon cooling, a white solid was filtered off and washed with a small amount of methanol. For the separation of the mixture **15c**/**16c** column chromatography (ethyl acetate/MeOH 25:1) of the solid residue was applied. For the isolation of pure **15c** (in the case where butanol was used as a solvent) column chromatography (ethyl acetate/MeOH 25:1) was applied.

4.4. Transformation of 8 to 9

A mixture of **8** (241 mg, 1 mmol), aqueous hydrochloric acid (200 mg, 9%), and absolute ethanol (5 mL) was refluxed for 0.5 h. The reaction mixture was evaporated, water (5 mL) was added to the residue and the mixture was neutralized with solid $NaHCO_3$. Upon cooling, the precipitate was filtered off and washed with water to give **9** (203 mg, 91%) as a yellow solid.

4.5. Transformation of 14 to 15

A mixture of **14a**,**b** (1 mmol), *p*-toluenesulfonic acid (19 mg, 0.1 mmol), and water (3 mL) was refluxed for 15 min. Upon cooling, the precipitate was collected by filtration and washed with a small amount of water, affording **15a**,**b** as yellow solids. Yields: **15a** (194 mg, 90%), **15b** (139 mg, 71%).

4.6. Aromatization of 1,4-dihydropyridazine derivatives 2 and 15

A solution of **2** or **15b** (1 mmol) in MeOH or CH_2Cl_2 (4 mL) was stirred at room temperature in the presence of air for 24 h. The solvent was evaporated in vacuo to afford **3** in a quantitative yield. In the case of **15b**, over 95% conversion to **16b** occurred as indicated on the basis of ^{1}H NMR spectrum of the crude product. By bubbling oxygen into the refluxed mixture of **15c** (50 mg, 0.216 mmol) and activated charcoal DARCO® KB (Aldrich) (25 mg) in methanol (4 mL) for 7 h a complete conversion to **16c** was observed.

4.7. General procedure for the oxidation of the pyridazine derivatives 2, 8, 9, 14, and 15 with CAN

To a stirred mixture of CAN (6–8 mmol; see Schemes 1 and 2, and Table 2) in methanol (10–15 mL) at room temperature **2**, **8**, **9**, **14** or **15** (1 mmol) was added over a period of 10–20 min. The stirring was continued for 0.25–0.5 h, then the solvent was evaporated under reduced pressure, the solid residue was treated with water (10 mL), and the aqueous mixture was extracted with methylene chloride (6×10 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and evaporated to give **4**, **10** or **17**. In the case of **4a**, further purification by column chromatography ($CHCl_3$/MeOH 25:1) was applied.

4.8. Analytical and spectroscopic data of products

4.8.1. 4,5,6,7,8,9-Hexahydro-1*H*-cyclohepta[*c*]pyridazine-3-carbohydrazide (2a). Mp 80–84 °C (MeOH/H_2O). IR (KBr): 3376, 2918, 1648, 1608, 1504 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.47 (m, 4H), 1.63 (m, 2H), 1.99 (m, 2H), 2.12 (m, 2H), 2.86 (s, 2H), 4.20 (s, 2H), 8.74 (s, 1H), 8.96 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.5, 26.3, 26.9, 28.9, 30.8, 32.3, 103.0, 131.6, 135.5, 164.5. EI-MS: *m*/*z* (%) 208 (M$^+$, 15), 192 (100). Anal. Calcd for $C_{10}H_{16}N_4O$: C, 57.67; H, 7.74; N, 26.90. Found: C, 57.69; H, 8.01; N, 27.25.

4.8.2. 1,4,5,6,7,8,9,10-Octahydrocycloocta[*c*]pyridazine-3-carbohydrazide (2b). Mp 93–94 °C (MeOH/H_2O). IR (KBr): 3356, 2920, 2849, 1626, 1497 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (m, 8H), 2.03 (m, 2H), 2.15 (m, 2H), 2.83 (s, 2H), 4.20 (s, 2H), 8.74 (s, 1H), 9.04 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 24.3, 25.8, 25.9, 26.0, 27.2, 28.9, 29.1, 100.6, 131.4, 133.0, 164.6. EI-MS: *m*/*z* (%) 222 (M$^+$, 15), 206 (100). Anal. Calcd for $C_{11}H_{18}N_4O$: C, 59.44; H, 8.16; N, 25.20. Found: C, 59.64; H, 8.34; N, 25.50.

4.8.3. 6,7,8,9-Tetrahydro-5*H*-cyclohepta[*c*]pyridazine-3-carbohydrazide (3a). Mp 172.8–173.4 °C (EtOAc). IR (KBr): 3307, 3256, 3206, 2935, 2923, 2854, 1682, 1668, 1632, 1585, 1501 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (m, 4H), 1.84 (m, 2H), 2.90 (m, 2H), 3.24 (m, 2H), 4.64 (s, 2H), 7.88 (s, 1H), 10.23 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.9, 26.7, 31.3, 33.4, 35.8, 124.4, 143.8, 151.7, 161.7, 166.7. EI-MS: *m*/*z* (%) 206 (M$^+$, 99.5), 148 (100). Anal. Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.16. Found: C, 58.54; H, 7.00; N, 26.89.

4.8.4. 5,6,7,8,9,10-Hexahydrocycloocta[*c*]pyridazine-3-carbohydrazide (3b). Mp 168–171 °C (EtOAc). IR (KBr): 3310, 3248, 3202, 2931, 2858, 1679, 1631, 1505 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.31 (m, 4H), 1.73 (m, 4H), 2.87 (m, 2H), 3.16 (m, 2H), 4.69 (br s, 2H), 7.91 (s, 1H), 10.22 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.1, 25.2, 30.0, 30.5, 30.9, 31.6, 124.7, 142.1, 151.6, 161.7, 165.3. EI-MS: *m*/*z* (%) 220 (M$^+$, 100). Anal. Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.94; H, 7.56; N, 25.60.

4.8.5. Methyl 6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridazine-3-carboxylate (4a). Mp 58.5–59.2 °C (Et_2O). IR (KBr): 3045, 2920, 2848, 1729 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65 (m, 4H), 1.86 (m, 2H), 2.90 (m, 2H), 3.26 (m, 2H), 3.94 (s, 3H), 7.97 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.8, 26.5, 31.3, 33.2, 35.9, 52.6, 126.7, 143.4, 150.0, 164.5, 167.5. EI-MS: *m*/*z* (%)

206 (M^+, 18), 148 (100). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.31; H, 7.01; N, 13.41.

4.8.6. Methyl 5,6,7,8,9,10-hexahydrocycloocta[*c*]pyridazine-3-carboxylate (4b). Mp 60–62 °C (Et_2O). IR (KBr): 2940, 2911, 2859, 1715 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.31 (m, 4H), 1.73 (m, 4H), 2.87 (m, 2H), 3.19 (m, 2H), 3.94 (s, 3H), 8.00 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 25.0, 25.2, 29.8, 30.4, 30.8, 31.7, 52.6, 127.1, 141.7, 149.8, 164.5, 166.1. EI-MS: *m*/*z* (%) 220 (M^+, 30), 162 (100). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.18; H, 7.53; N, 13.01.

4.8.7. 9a-Hydroxy-9-oxo-4,4a,5,6,7,8,9,9a-octahydro-1*H*-pyridazino[3,4-*c*]azepine-3-carbohydrazide (8). Mp 166–169 °C (MeOH/DMF). IR (KBr): 3318 br, 1678, 1656, 1616, 1507 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.24 (m, 1H), 1.38 (m, 1H), 1.64 (m, 1H), 1.79 (m, 3H), 2.56 (dd, J=17.3, 4.7 Hz, 1H), 2.95 (m, 1H), 3.42 (m, 1H), 4.16 (br s, 2H), 6.24 (s, 1H), 7.72 (s, 1H), 8.05 (dd, J=ca. 3.7 and 7.6 Hz, 1H), 8.77 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 24.3, 28.9, 31.4, 31.9, 41.0, 78.7, 135.5, 163.9, 172.7. EI-MS: *m*/*z* (%) 241 (M^+, 30), 163 (100). Anal. Calcd for $C_9H_{15}N_5O$: C, 44.81; H, 6.37; N, 29.03. Found: C, 45.06; H, 6.43; N, 29.32.

4.8.8. 9-Oxo-4,5,6,7,8,9-hexahydro-1*H*-pyridazino[3,4-*c*]azepine-3-carbohydrazide (9). Mp 196–198 °C (MeOH/DMF). IR (KBr): 3392, 3333, 3317, 3291, 3212, 1659, 1640 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.82 (m, 2H), 2.34 (m, 2H), 2.90 (s, 2H), 3.09 (m, 2H), 4.27 (s, 2H), 8.15 (dd, $J_1 \approx J_2 \approx 5.0$ Hz, 1H), 8.92 (s, 1H), 9.02 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 27.1, 27.7, 33.1, 40.2, 113.6, 127.5, 132.5, 163.2, 164.2. EI-MS: *m*/*z* (%) 223 (M^+, 29), 163 (100). Anal. Calcd for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.37. Found: C, 48.42; H, 6.16; N, 31.66.

4.8.9. Methyl 9-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[3,4-*c*]azepine-3-carboxylate (10a). Mp 206–208 °C (EtOH). IR (KBr): 3196, 3075, 1742, 1665, 1584 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.93 (m, 2H), 2.92 (m, 4H), 3.98 (s, 3H), 8.24 (s, 1H), 8.63 (dd, $J_1 \approx J_2 \approx 5.7$ Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 27.0, 28.3, 37.4, 53.0, 127.9, 138.9, 151.4, 158.3, 164.0, 166.5. EI-MS: *m*/*z* (%): 221 (M^+, 27), 163 (100). Anal. Calcd for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.36; H, 5.18; N, 19.16.

4.8.10. Ethyl 9-oxo-6,7,8,9-tetrahydro-5*H*-pyridazino[3,4-*c*]azepine-3-carboxylate (10b). Mp 210–212 °C (EtOH). IR (KBr): 3200, 3090, 2931, 1720, 1668 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.39 (t, J=7.1 Hz, 3H), 1.95 (m, 2H), 2.93 (m, 4H), 4.46 (q, J=7.1 Hz, 2H), 8.23 (s, 1H), 8.64 (dd, $J_1 \approx J_2 \approx 5.9$ Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 14.0, 27.0, 28.3, 37.5, 61.9, 127.8, 138.9, 151.5, 158.3, 163.5, 166.5. EI-MS: *m*/*z* (%) 235 (M^+, 4), 163 (100). Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.03; H, 5.74; N, 17.94.

4.8.11. 3-Hydrazino-6-phenyl-2,3,4,5-tetrahydropyridazine-3-carbohydrazide (14a). Mp 108–111 °C (pyridine). IR (KBr): 3306, 3264, 3164, 1667, 1603, 1498 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.90 (m, 2H), 2.50 (m, 2H), 3.31 (br s, 2H), 4.10 (br s, 1H), 4.26 (br s, 2H), 7.29 (m, 4H), 7.62 (m, 2H), 9.03 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 19.5, 24.9, 71.9, 123.9, 127.2, 128.0, 138.3, 140.9, 171.2. FABMS: *m*/*z* (%) 217 ($MH^+-N_2H_4$, 52), 185 (100). HRMS (EI) calcd for $C_{11}H_{12}N_4O$ ($M^+-N_2H_4$) 216.1011, found 216.1017. Anal. Calcd for $C_{11}H_{16}N_6O$: C, 53.21; H, 6.50; N, 33.85. Found: C, 53.49; H, 6.68; N, 33.54.

4.8.12. 6-*tert*-Butyl-3-hydrazino-2,3,4,5-tetrahydropyridazine-3-carbohydrazide (14b). Mp 108–109 °C (pyridine). IR (KBr): 3305, 3267, 3170, 2962, 1666, 1608, 1507 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.02 (s, 9H), 1.67 (m, 2H), 2.07 (m, 2H), 3.20 (br s, 2H), 3.93 (br s, 1H), 4.21 (br s, 2H), 6.44 (s, 1H), 8.91 (br s, 1H). FABMS: *m*/*z* (%) 197 ($MH^+-N_2H_4$). HRMS (EI) calcd for $C_9H_{16}N_4O$ ($M^+-N_2H_4$) 196.1324, found 196.1330. Anal. Calcd for $C_9H_{20}N_6O$: C, 47.35; H, 8.83; N, 36.81. Found: C, 47.09; H, 8.83; N, 37.10.

4.8.13. 6-Phenyl-1,4-dihydropyridazine-3-carbohydrazide (15a). Mp 162–164 °C (EtOAc/MeOH). IR (KBr): 3368, 3318, 3203, 1670, 1653, 1628, 1506 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.06 (d, J=3.9 Hz, 2H), 4.31 (s, 2H), 4.89 (dt, J=2.3, 3.9 Hz, 1H), 7.38 (m, 3H), 7.50 (m, 2H), 8.93 (s, 1H), 9.75 (d, J=2.3 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 21.1, 92.0, 125.3, 128.3, 128.4, 132.8, 133.8, 138.5, 164.0. EI-MS: *m*/*z* (%) 216 (M^+, 26), 200 (100). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.09; H, 5.79; N, 25.62.

4.8.14. 6-*tert*-Butyl-1,4-dihydropyridazine-3-carbohydrazide (15b). Mp 144–146.5 °C (EtOAc/light petroleum). IR (KBr): 3391, 3372, 3304, 3274, 3205, 2961, 1672, 1621, 1499 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.07 (s, 9H), 2.85 (d, J=3.6 Hz, 2H), 4.24 (br s, 2H), 4.30 (dt, J=2.6, 3.6 Hz, 1H), 8.72 (s, 1H), 9.17 (d, J=2.6 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 20.6, 27.9, 32.6, 87.0, 132.0, 147.0, 164.2. EI-MS: *m*/*z* (%) 196 (M^+, 33), 180 (100). Anal. Calcd for $C_9H_{16}N_4O$: C, 55.08; H, 8.22; N, 28.55. Found: C, 54.95; H, 8.45; N, 28.80.

4.8.15. 4-Methyl-6-(pyridin-2-yl)-1,4-dihydropyridazine-3-carbohydrazide (15c). Mp 130–132.5 °C (EtOAc/light petroleum). IR (KBr): 3385, 3314, 3202, 1660, 1634, 1594 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.96 (d, J=6.5 Hz, 3H), 3.60 (dq, J=6.5, 6.5 Hz, 1H), 4.32 (s, 2H), 5.71 (dd, J=2.2, 6.5 Hz, 1H), 7.37 (ddd, J=1.4, 4.9, 7.0 Hz, 1H), 7.80 (ddd, J=1.4, 1.4, 7.6 Hz, 1H), 7.85 (ddd, J=1.8, 7.0, 7.6 Hz, 1H), 8.57 (ddd, J=1.4, 1.8, 4.9 Hz, 1H), 9.00 (s, 1H), 9.71 (d, J=2.2 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 19.5, 24.8, 100.4, 119.1, 123.3, 135.8, 137.1, 137.2, 148.4, 149.8, 163.5. EI-MS: *m*/*z* (%) 231 (M^+, 36), 216 (100). Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.20; H, 5.69; N, 29.91.

4.8.16. 6-*tert*-Butylpyridazine-3-carbohydrazide (16b). Mp 109–111 °C (Et_2O). IR (KBr): 3387, 3325, 2962, 1671, 1601, 1515 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.42 (s, 9H), 4.68 (br s, 2H), 7.96 (d, J=8.9 Hz, 1H),

8.08 (d, J=8.9 Hz, 1H), 10.30 (br s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 29.6, 36.9, 124.7, 125.3, 151.1, 161.6, 171.2. EI-MS: m/z (%) 194 (M^+, 100). Anal. Calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.85. Found: C, 55.83; H, 7.42; N, 28.85.

4.8.17. 4-Methyl-6-(pyridin-2-yl)pyridazine-3-carbohydrazide (16c). Mp 177.5–180 °C (MeOH). IR (KBr): 3314 br, 1661, 1626, 1580, 1503 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.56 (d, J=1 Hz, 3H), 4.69 (s, 2H), 7.59 (ddd, J=1.1, 4.8, 7.7 Hz, 1H), 8.05 (ddd, J=1.8, 7.7, 7.9 Hz, 1H), 8.47 (q, J=1 Hz, 1H), 8.57 (ddd, J=1.1, 1.1, 7.9 Hz, 1H), 8.78 (ddd, J=1.1, 1.8, 4.8 Hz, 1H), 10.06 (s, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.1, 121.3, 125.3, 126.2, 137.7, 138.1, 149.7, 152.4, 154.9, 157.7, 163.8. EI-MS: m/z (%) 229 (M^+, 100). Anal. Calcd for $C_{11}H_{11}N_5O$: C, 57.63; H, 4.84; N, 30.55. Found: C, 57.91; H, 5.04; N, 30.24.

4.8.18. Methyl 6-phenylpyridazine-3-carboxylate (17a). Mp 194–197 °C (MeOH/H_2O). IR (KBr): 3062, 2952, 1717, 1575, 1442, 1409 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (s, 3H), 7.56 (m, 3H), 8.00 (d, J=8.9 Hz, 1H), 8.17 (m, 2H), 8.24 (d, J=8.9 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 53.2, 123.9, 127.6, 128.0, 129.2, 130.9, 135.4, 150.0, 160.7, 164.7. EI-MS: m/z (%) 214 (M^+, 45), 156 (100). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.15; H, 4.84; N, 12.88.

4.8.19. Methyl 6-*tert*-butylpyridazine-3-carboxylate (17b). Mp 115–116.5 °C (MeOH/H_2O). IR (KBr): 2963, 1721, 1576, 1448, 1359, 1298 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.42 (s, 9H), 3.97 (s, 3H), 7.98 (d, J=8.9 Hz, 1H), 8.14 (d, J=8.9 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 29.5, 37.0, 52.7, 124.3, 127.7, 149.4, 164.3, 171.9. EI-MS: m/z (%) 194 (M^+, 15), 152 (100). HRMS calcd for $C_{10}H_{14}N_2O_2$ 194.1055, found 194.1060. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.56; H, 7.39; N, 14.85.

4.8.20. Methyl 4-methyl-6-(pyridin-2-yl)pyridazine-3-carboxylate (17c). Mp 106.5–108 °C (EtOAc/light petroleum). IR (KBr): 1719, 1579, 1441, 1379 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.58 (d, J=0.8 Hz, 3H), 3.99 (s, 3H), 7.60 (ddd, J=1.1, 4.8, 7.7 Hz, 1H), 8.07 (ddd, J=1.8, 7.7, 7.9 Hz, 1H), 8.53 (q, J=ca. 0.8 Hz, 1H), 8.60 (ddd, J=1.1, 1.1, 7.9 Hz, 1H), 8.79 (ddd, J=1.1, 1.8, 4.8 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 18.5, 52.7, 121.6, 125.5, 126.3, 137.7, 139.2, 149.8, 152.0, 152.5, 158.1, 165.2. EI-MS: m/z (%) 229 (M^+, 35), 171 (100). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.66; H, 5.02; N, 18.25.

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18. Starting compounds **1a** and **1b** were prepared from the corresponding ketones (cycloheptanone and cyclooctanone), *N*,*N*-dimethylformamide dimethyl acetal, and hippuric acid by a modification of the method described in Ref. 19a, followed by the removal of the benzoylamino group using the method described in Ref. 19b. 3-Amino-2*H*-pyran-2-ones **11** were prepared from previously known 3-benzoylamino-2*H*-pyran-2-ones by the known method.[19b]
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Regioselective dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones mediated by ceric ammonium nitrate

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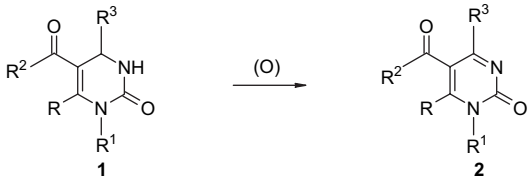
Abstract—Ceric ammonium nitrate (CAN) has been explored for the regioselective oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs). Interestingly, we obtained ethyl 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylates as the major products during the oxidation of DHPMs by CAN/AcOH at 80 °C. The reaction afforded a mixture of products while employing CAN in organic solvents without additives. However, the regioselective dehydrogenated product, ethyl 6-methyl-4-aryl(alkyl)-pyrimidin-2(1*H*)-one-5-carboxylate was obtained by performing the reaction with $NaHCO_3$. The single crystal X-ray crystallography of ethyl 6-methyl-4-(2-phenyl)-pyrimidin-2(1*H*)-one-5-carboxylate revealed that the oxidized product existed in amidic form rather than aromatized enol form of pyrimidines. The efficiency of the present protocol enabled the synthesis of structurally diverse pyrimidines in moderate to good yields under milder reaction conditions.

1. Introduction

The pyrimidine core possesses potential biological applications.[1a,b] The pyrimidine derivative MKC-442 is already in clinical trials and similar compounds are expected to inhibit the HIV virus.[1c] A series of pyrazolo[1,5-*a*]pyrimidines derivatives were shown to be potent and orally active corticotropin-releasing factor receptor antagonists.[1d] Nucleosides containing the 5-substituted pyrimidine moiety have been demonstrated to inhibit growth of murine mammary carcinoma and HIV virus.[2] Pyrimidine based molecules with extended π-systems exhibited interesting fluorescent properties.[3a] Kang et al. employed readily accessible multifunctionalized pyrimidine templates for diversity-oriented synthesis.[3b]

Recently, various protocols have been utilized for the synthesis of pyrimidines.[4] The synthesis of pyrimidin-2(1*H*)-ones by oxidation of DHPMs (Scheme 1) has rarely been explored.[5a] Unlike a large number of oxidizing agents available for achieving nearly quantitative transformation of Hantzsch dihydropyridine (DHPs) to pyridine,[5b,c] the regioselective oxidation of DHPMs is not easy.[5a] A few available literature procedures required large volumes of highly acidic and corrosive reagents or multistep strategies.[6a,7a–c] $CuCl_2$/TBHP/K_2CO_3[7d] and Jone's reagent[7e] were employed for the above conversion, but they failed to yield the desired regioselective products for oxidatively sensitive functionalities. Consequently, it is of interest to synthesize structurally diverse pyrimidines by oxidizing DHPMs under mild conditions.



Scheme 1. Oxidation of DHPMs into pyrimidin-2(1*H*)-ones.

2. Results and discussion

2.1. Screening oxidants for the regioselective oxidation of DHPMs

It is well known that DHPMs are structurally similar to DHPs.[5a] Oxidants[8a–j] that efficiently convert the DHPs into pyridine were screened for the conversion of 3,4-dihydropyrimidin-2(1*H*)-ones to pyrimidin-2(1*H*)-ones. But DHPMs are highly stable toward powerful oxidants such as PCC, MnO_2, $KMnO_4$ adsorbed on clay, chloranil, DDQ, Pd/C, and sodium nitrate in acetic acid.[6a] In addition we found that MTO,[8c] $RuCl_3$ (5 mol %)/O_2 in AcOH (room temperature),[8d] Br_2,[8e] sulfur,[8g] $FeCl_3$ (in CH_3OH and CH_2Cl_2 under room temperature and reflux),[8i] $FeCl_3$/AcOH (room temperature), and $FeCl_3$/AcOH/H_2O (1:1, room temperature) were inefficient to dehydrogenate **1a**. Concd HNO_3,[8a] MnO_2,[8b]

Keywords: Oxidation; Pyrimidines; 3,4-Dihydropyrimidin-2(1*H*)-ones; Ceric ammonium nitrate.
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$Bi(NO_3)_3$, $FeCl_3$, IBX,[8j] and CAN[8h] afforded **2a** with moderate selectivity. Among them CAN was found to be selective and its application in organic synthesis is promising (Fig. 1).[9] $FeCl_3$ and CAN furnished reasonable amount of 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylates as well (Fig. 1).

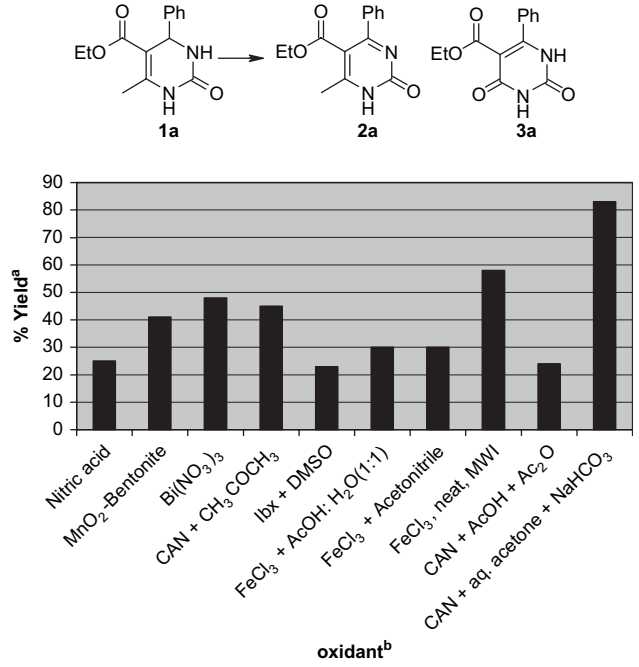
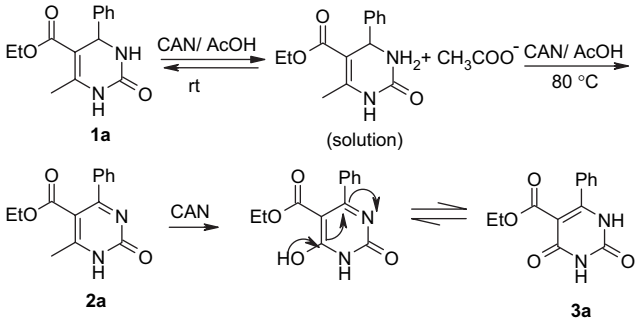


Figure 1. Screening of oxidants for the conversion of **1a** to **2a**. [a]Isolated yield. [b]The stoichiometry of oxidants was employed as used in literature for 1,4-dihydropyridine.[8a–j] And **3a** was formed in 21, 30, 10, and 33% yields, respectively, for the corresponding oxidants CAN+CH_3COCH_3, $FeCl_3$+acetonitrile, $FeCl_3$+heat+MWI, and CAN+AcOH+Ac_2O.

2.2. Synthesis of 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylates

Initially, AcOH was chosen as solvent because it dissolved DHPMs completely and is widely employed during the oxidation of DHPs.[8d,f,i,10] The addition of CAN to a stirred solution of **1a** in acetic acid did not afford the expected dehydrogenated product at ambient temperature (Scheme 2). However, the reaction furnished an unstable salt of acetic acid and **1a** in solution and was decomposed to **1a** during the workup. The trifluoroacetate salt of 4-anisyl-DHPM was trapped and characterized by NMR in solution. Ce(IV)'s inability to dehydrogenate **1a** in AcOH at room temperature might be due to coordination of **1a** with acetic acid.



Scheme 2. CAN mediated oxidation of DHPMs in AcOH.

Serendipitously, an unusual oxidation–dealkylation product, **3a**, ethyl 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylate, formed at 80 °C (Scheme 2). The ^{1}H NMR spectrum of product (**3a**) showed two new peaks with an integration of one proton each between 10 and 12 ppm. The characteristic peaks corresponding to NH(3), CH(4), and 6-methyl protons of the starting material (**1a**) (δ 8.9, 5.2, and 2.3 ppm, respectively) were absent. The *m*/*z* value of products **3a–i** is the same as DHPMs.

Therefore, an X-ray structure of **3g** was further needed to confirm the structure of the product (Fig. 2).[11] Since **3a** exhibited structural resemblance with anti-HIV agents,[1c,2] **1b–i** have been subjected to typical oxidation and the reactions afforded **3b–i** in reasonable yields (Table 1).

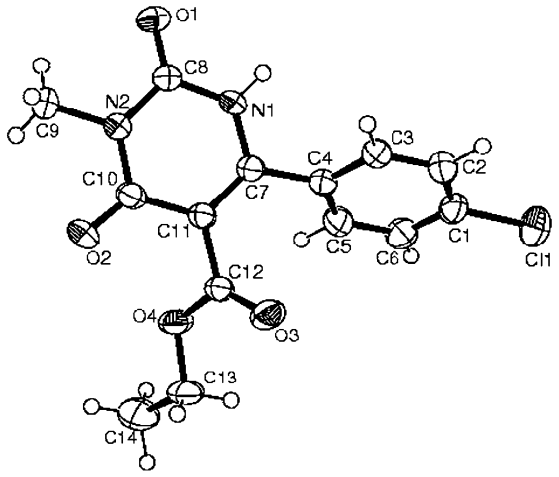
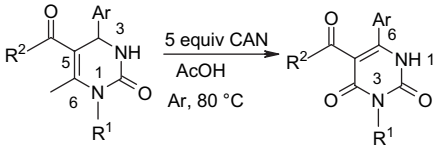


Figure 2. XRD structure of **3g**, ORTEP diagram.

Table 1. Oxidation of DHPM mediated by CAN in AcOH



Product	Ar	R^1	R^2	Time (h)	Yield (%)[a]
3a	C_6H_5	H	OEt	1.5	61
3b	3-NO_2-C_6H_4	Me	OEt	1.5	65
3c	2-NO_2-C_6H_4	H	OEt	1.0	55
3d	3-NO_2-C_6H_4	H	OEt	1.0	57
3e	4-Cl-C_6H_4	H	OEt	2.0	68
3f	1-Naphthyl	H	OEt	2.0	65
3g	4-Cl-C_6H_4	Me	OEt	1.0	62
3h	2,4-Cl_2-C_6H_3	H	Ph	2.5	63
3i	4-MeO-C_6H_4	H	OEt	1.5	68

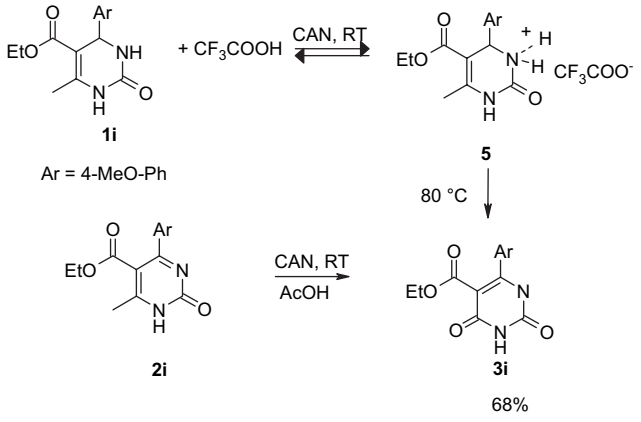
[a] The reaction was conducted using 1 mmol of DHPM and 5 mmol of CAN in 7 mL of acetic acid at 80 °C.

2.3. Trapping of 1i as trifluoroacetate salt

To confirm the formation of a salt in acetic acid, we have dissolved **1i** in trifluoroacetic acid and a small amount of TMS was added to the solution. The ^{1}H NMR spectrum of **5** in solution showed that the CH(4) of the product has been shifted 0.5 ppm to downfield. The quaternary N(3) of **5** has

no redox reaction with Ce^{4+} due to the unavailability of the N(3) lone pair electrons. This might be the reason that stirring with CAN in acetic acid at room temperature did not yield the expected product. The complex was labile at higher temperature and yielded **3i** at 80 °C.

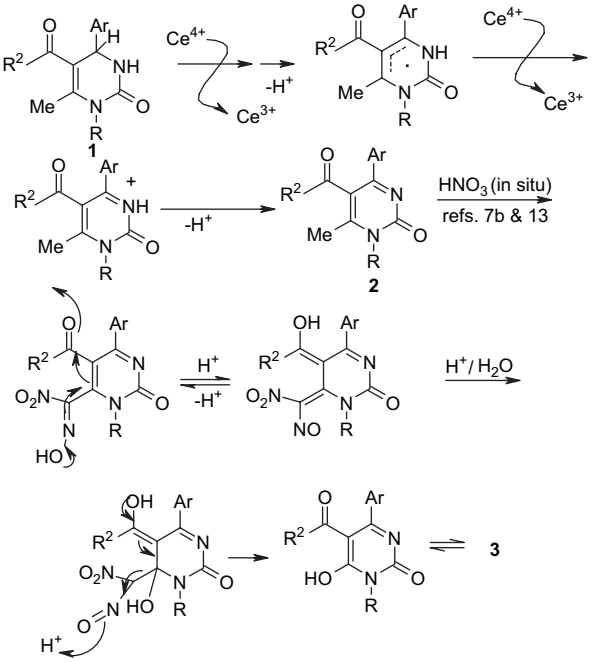
Independently prepared **2i** has been converted into the corresponding tetrahydropyrimidin-2,4(1*H*,3*H*)-dione **3i** at room temperature mediated by CAN/AcOH confirming the protonation of **1i** (Scheme 3).



Scheme 3. Trapping of **1i** as trifluoroacetate salt in solution.

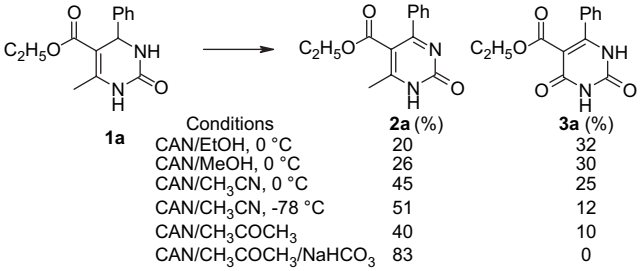
2.4. Mechanistic considerations

The mechanism of dehydrogenation mediated by Ce^{4+} expected to be the same as that of dihydropyridine.[12] But the dealkylation of 6-methyl pyrimidin-2(1*H*)-ones, **2** to **3** was uncertain; however, it was believed to proceed through nitrolic acid intermediate and hydrolysis of the same produced **3a–i**.[7b] We have proposed a tentative mechanism for the formation of products (Scheme 4).



Scheme 4. Mechanistic outlines for the formation of **3a–i**.

Despite the oxidation of **1a** to **3a** by CAN/AcOH, the regioselective oxidation to **2a** was not achieved. The following conditions (Scheme 5) were additionally screened to obtain **2a** exclusively but the formation of **3a** was inevitable. To our interest, the reaction mixture was acidic (pH=2) after addition of CAN in aqueous acetone. The decomposition of CAN during oxidation might generate nitric acid and a similar kind of observation has recently been reported in literature for high acidity of solution.[13] Presumably, as with CAN/AcOH, the acidic medium has facilitated the conversion of **2a** into **3a**.



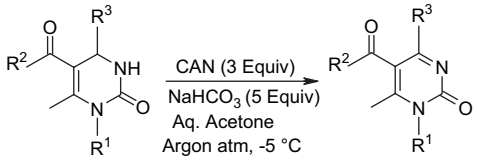
Scheme 5. CAN mediated oxidation of DHPMs.

2.5. Regioselective oxidation of DHPMs

To oxidize DHPMs regioselectively, we have demonstrated a new procedure herein using $NaHCO_3$ as buffering agent at −5 to 0 °C under Ar atmosphere. In a typical example, addition of CAN (3 equiv) to a mixture of **1a** and $NaHCO_3$ (5 equiv) suspended in acetone under inert atmosphere at ice-cold conditions followed by stirring the reaction mixture at ambient temperature for 1 h afforded **2a**.[6]

This methodology has been successfully employed to electron rich and deficient substrates (**2c**, **2k**, **2m**, **2o**, and **2i**) with satisfactory yields (Table 2). In addition, this methodology was found to be successful for higher homologues of aryl groups of DHPM to form **2j** and **2l**. The ^1H NMR spectrum of the product showed the absence of CH(4) and NH(3) peaks. The identity of C-4, C-6, and substituted aromatic

Table 2. Regioselective oxidation of DHPM mediated by CAN



Product	R^3	R^2	R^1	Time (h)	Yield (%)[a,b]
2a	C_6H_5	OEt	H	1	83[6]
2j	4-Biphenyl	OEt	H	1.5	79
2k	2-Cl-C_6H_4	OEt	H	1	85
2c	2-NO_2-C_6H_4	OEt	H	1	80
2l	3-HO-C_6H_4	OEt	H	1	81
2m	4-MeO-C_6H_4	OMe	H	1.5	83
2n	C_6H_5	OEt	Me	0.5	85[7b]
2o	4-MeO-C_6H_4	OEt	Me	3	69
2i	4-MeO-C_6H_4	OEt	H	1	81

[a] The reaction was conducted using 1 mmol of DHPM, 3 mmol of CAN, and 5 mmol of $NaHCO_3$ in 10 mL of acetone at −5 to 0 °C.
[b] Isolated yield.

carbons (asterisks) of **2a**, **2c**, **2i** and **2j**–**2m** was difficult to locate in the ^{13}C NMR spectrum due to tautomerization of NH(1) to N(3) in solution (Fig. 3a and b).[7b] *N*(1)-Alkyl substituted pyrimidin-2(1*H*)-ones, **2n** and **2o**, have no tautomerization in solution (Fig. 3c) and the ^{13}C NMR spectrum contained all peaks. The X-ray structure of **2k**[14] has confirmed that CONH group existed as amide form in solid state unlike reported as enol form (Fig. 4).[7d]

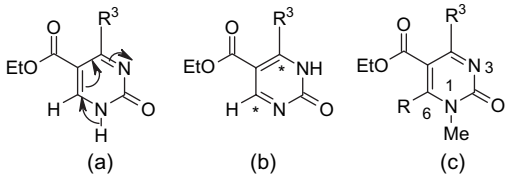


Figure 3. Tautomerism of pyrimidines in solution.

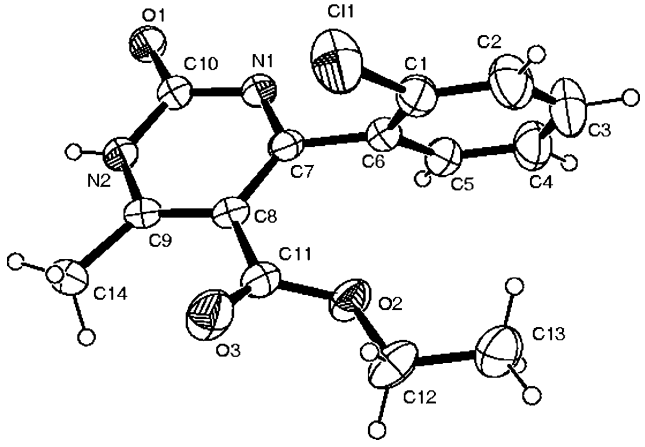


Figure 4. XRD structure of **2k**, ORTEP diagram.

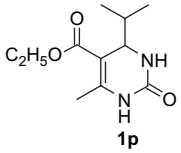
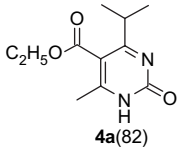
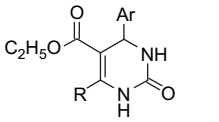
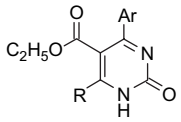
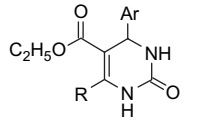
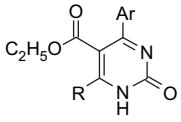
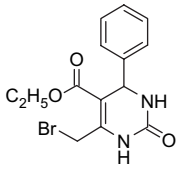
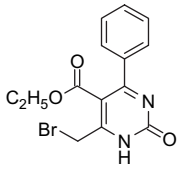
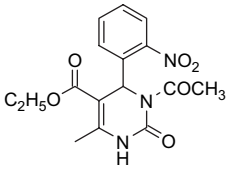
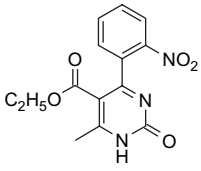
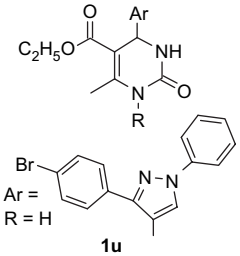
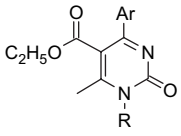
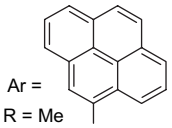
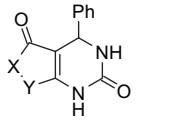
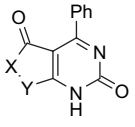
2.6. Synthesis of structurally diverse pyrimidines

To prove the mildness and efficacy of the procedure, we have subjected 4-alkyl DHPM (Table 3, entry 1) to the typical reaction conditions and the corresponding pyrimidin-2(1*H*)-one **4a** was obtained in good yield. It is noteworthy to mention here that other method furnished a lower yield or the dealkylated product.[5c,7d,e] The current procedure did not affect the Ph- and CF_3-groups at C-6 of DHPM (entries 2 and 3).[7d] Furthermore, highly regioselective dehydrogenation was achieved by subjecting 6-bromomethylene DHPM to the typical oxidation procedure (entry 4).

Notably, N(3)-acylated DHPM afforded the typical 3,4-dehydrogenated product **2c** (entry 5). DHPMs bearing bulky aryl groups furnished the corresponding oxidized products in reasonable yields (entries 6 and 7). Cyclohexane-fused and indenone-fused DHPMs yielded **4g** and **4h** (entries 8 and 9) in a short span of time. Oxidation of bisaryl DHPM (**1y**) under CAN in AcOH medium resulted in **4i**.

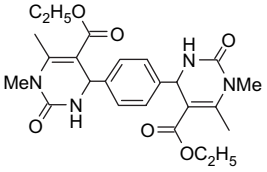
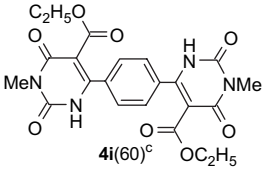
In conclusion, the highly regioselective oxidation did not affect sensitive or bulky aryl or alkyl pendant groups of pyrimidin-2(1*H*)-ones. Pyrimidines with extensive π-conjugation, **2j**, **4b**, **4e**, **4f**, **4h**, and **4i**, may be used for the preparation of photonic materials.[3a] The unexpected formation of **3a**–**i** deserves further investigation.

Table 3. Synthesis of structurally diverse pyrimidines, **4a**–**i** and **2c** via CAN mediated oxidation of DHPMs at different conditions

Entry	Reactant	Time (h)	Product (yield)[a,b]
1	 **1p**	2	 **4a**(82)
2	 Ar = $MeOC_6H_4$, R = Ph **1q**	4	 **4b**(80)
3	 Ar = $MeOC_6H_4$, R = CF_3 **1r**	4	 **4c**(76)
4	 **1s**	2	 **4d**(80)
5	 **1t**	3	 **2c**(85)
6	 **1u**	6	 **4e**(71)
7	 **1v**	6	**4f**(65)
8	 -X-Y-CH_2-(CMe_2)-CH_2 **1w**	1	 **4g**(61)

(*continued*)

Table 3. (*continued*)

Entry	Reactant	Time (h)	Product (yield)[a,b]
9	-X-Y- =  **1x**	1	**4h**(71)
10	 **1y**	4	 **4i**(60)[c]

[a] Isolated yield.
[b] The reaction was conducted using 1 mmol of DHPM, 3 mmol of CAN, and 5 mmol of $NaHCO_3$ in 10 mL of acetone at −5 to 0 °C.
[c] The reaction was conducted using 1 mmol of DHPM and 10 mmol of CAN in 15 mL of acetic acid at 80 °C.

3. Experimental

3.1. General introduction

Melting points were determined in open capillary tubes and were uncorrected. IR measurements were carried out using KBr pellets in FTIR. The ^{1}H NMR and ^{13}C NMR spectra were recorded in 500, 400, and 300 MHz high-resolution NMR spectrometers with TMS as an internal standard. All NMR spectra of pyrimidin-2(1*H*)-ones were recorded in $CDCl_3$. ^{1}H NMR of 4-anisylpyrimidinonium acetate (**5**) was recorded by dissolving ethyl 4-anisylpyrimidin-2(1*H*)-one-5-carboxylate in trifluoroacetic acid using TMS as an internal standard. Mass spectra were obtained in EI ionization mode at 70 eV. TLC was performed on precoated Polygram sheets. Column chromatography was carried out using 100–200 mesh silica gel or flash-column with 200–400 mesh silica gel.

3.2. Experimental procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

All the DHPMs needed for oxidation were prepared by using reported procedure and purified through column chromatography before subjecting to dehydrogenation. The column purified samples furnished better yields over re-crystallized DHPMs. Ethyl 6-bromomethylene-4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (**1s**) was prepared by the addition of Br_2 in $CHCl_3$ to the stirred solution of ethyl 6-methyl-4-phenylpyrimidin-2(1*H*)-one-5-carboxylate at 0 °C. The DHPMs (**1q**, **1r**, **1w**, and **1x**) were prepared by reported procedures.[15] 4-Pyrazolyl 3,4-dihydropyrimidin-2(1*H*)-ones (**1u**)[15c] were prepared by pyrazole aldehyde (1 mmol), ethyl acetoacetate (1.2 mmol), urea (1.2 mmol), and phosphotungstic acid (0.1 mmol) in methanol at reflux conditions. *N*(3)-Acetyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate ester (**1t**) was prepared by stirring the reaction of corresponding DHPM in acetic anhydride in an oil bath for 2 h at 120 °C and re-crystallized in ethanol. Bis-DHPM (**1y**) was prepared using classical Biginelli conditions involving 1 mmol of terephthalaldehyde, 3 mmol of urea, and 5 mmol of ethyl acetoacetate at reflux in acidified ethanol.[15a–d]

3.3. Experimental procedure for oxidation of 3,4-dihydropyrimidin-2(1*H*)-ones

3.3.1. Optimization of oxidation of DHPMs by various oxidants. The regioselective oxidation of ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate, **1a** was optimized by employing various oxidants and experimental procedure was strictly followed as described for the oxidation of dihydropyridine.[8a–j]

3.3.2. Oxidation of DHPM by CAN in acetic acid (3a–i). Ethyl 2,4-dioxo-6-phenyl-tetrahydropyrimidin-5-carboxylate (**3a**): a 50 mL round bottom flask containing magnetic bar was charged with **1a** (1 mmol, 0.260 g) and acetic acid (7 mL). To this solution, ceric ammonium nitrate (5 mmol, 2.740 g) was added in one portion. The solution was stirred at 80 °C for appropriate time (Table 2) until TLC showed the complete disappearance of **1a**. Then the reaction mixture was poured into crushed ice, neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (3×20 mL). The organic extracts were pooled up, washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford 0.230 g of **3a** as crude product. The column purification of crude product using 1:1 petroleum ether and ethyl acetate yielded 0.160 g of **3a** as colorless crystalline solid. The same procedure was followed for preparation of **4i** except 10 mmol of CAN was employed.

3.3.2.1. Ethyl 2,4-dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3a). Mp: 224–226 °C. IR (KBr): 1236, 1420, 1600, 1630, 1675, 1705, 3257, 3340 cm^{-1}. ^{1}H NMR: δ 0.83 (t, J=6.9 Hz, 3H), 3.87 (q, J=6.9 Hz, 2H), 7.40 (d, J=6.9 Hz, 2H), 7.45 (doublet of triplet, J=1.6 and 6.9 Hz, 2H), 7.50 (doublet of triplet, J=7.6 and 2.2 Hz, 1H), 11.42 (s, 1H, D_2O-exchangeable), 11.46 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 13.4, 60.5, 106.5, 127.6, 128.4, 130.6, 131.5, 150.2, 153.5, 161.1, 163.9. EIMS (*m*/*z*): 260 (M^+). Anal. calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.93; H, 4.61; N, 10.82.

3.3.2.2. Ethyl 2,4-dioxo-3-methyl-6-(3-nitrophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3b). Mp: 234–237 °C. IR (KBr): 1232, 1415, 1607, 1635, 1670, 1702, 3255 cm^{-1}. ^{1}H NMR: δ 0.86 (t, J=6.9 Hz, 3H), 3.16 (s, 3H), 3.89 (q, J=6.9 Hz, 2H, CH_3CH_2), 7.40 (d, J=8.6 Hz, 1H), 7.51 (doublet of triplet, J=1.7 and 6.9 Hz, 2H), 7.9 (d, J=8.6 Hz, 1H), 11.77 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 14.0, 27.4, 61.4, 106.6, 129.1, 129.3, 130.3, 131.7, 136.1, 138.3, 151.2, 160.8, 164.4, 167.0. EIMS (*m*/*z*): 319 (M^+). Anal. calcd for $C_{14}H_{13}N_3O_6$: C, 52.67; H, 4.10; N, 13.16. Found: C, 52.58; H, 4.03; N, 13.21.

3.3.2.3. Ethyl 2,4-dioxo-6-(2-nitrophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3c). Mp: 230–233 °C. IR (KBr): 1234, 1425, 1605, 1634, 1670, 1705, 3257, 3340 cm^{-1}. ^{1}H NMR: δ 0.71 (t, J=7.5 Hz, 3H, CH_3CH_2), 3.71 (q, J=7.5 Hz, 2H, CH_3CH_2), 7.59 (doublet of doublet, J=1.2 and 7.5 Hz, 1H), 7.75 (doublet of triplet, J=8.6 and 1.2 Hz, 1H), 7.83 (doublet of triplet, J=1.2 and 7.8 Hz, 1H), 7.85 (doublet of doublet, J=1.1 and 8.0 Hz, 1H), 11.55 (s, 1H, D_2O-exchangeable), 11.71 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 13.9, 60.7, 105.4, 125.0, 128.2, 130.9, 132.1, 135.2, 146.9, 150.5, 155.0, 161.2, 163.2.

EIMS (*m/z*): 305 (M^+). Anal. calcd for $C_{13}H_{11}N_3O_6$: C, 51.15; H, 3.63; N, 13.77. Found: C, 51.19; H, 3.61; N, 13.69.

3.3.2.4. Ethyl 2,4-dioxo-6-(3-nitrophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3d). Mp: 243–245 °C. IR (KBr): 1237, 1421, 1603, 1633, 1674, 1705, 3259, 3340 cm^{-1}. ^1H NMR: δ 0.85 (t, J=6.8 Hz, 3H), 3.90 (q, J=6.8 Hz, 2H), 7.44 (t, J=7.4 and 8.0 Hz, 1H), 7.89 (d, J=7.4 Hz, 1H), 8.3 (m, 1H), 8.38 (doublet of doublet, J=2.3 and 8.0 Hz, 1H), 11.58 (s, 1H, D_2O-exchangeable), 11.66 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 14.0, 61.3, 107.5, 123.5, 125.8, 130.8, 133.7, 135.1, 147.9, 150.7, 152.6, 161.6, 164.1. EIMS (*m/z*): 305 (M^+). Anal. calcd for $C_{13}H_{11}N_3O_6$: C, 51.15; H, 3.63; N, 13.77. Found: C, 51.09; H, 3.64; N, 13.81.

3.3.2.5. Ethyl 2,4-dioxo-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3e). Mp: 240–242 °C. IR (KBr): 1231, 1418, 1603, 1621, 1673, 3251, 3342 cm^{-1}. ^1H NMR: δ 0.86 (t, J=6.8 Hz, 3H), 3.89 (q, J=6.8 Hz, 2H), 7.43 (d, J=8.3 Hz, 2H), 7.58 (d, J=8.3 Hz, 2H), 11.51 (s, 2H). EIMS (*m/z*): 294 (M^+). Anal. calcd for $C_{13}H_{11}ClN_2O_4$: C, 52.98; H, 3.76; N, 9.51. Found: C, 52.85; H, 3.69; N, 9.55.

3.3.2.6. Ethyl 2,4-dioxo-6-(1-naphthyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3f). Mp: 224–226 °C. IR (KBr): 1235, 1421, 1604, 1631, 1673, 1706, 3258, 3342 cm^{-1}. ^1H NMR: δ 0.32 (t, J=6.9 Hz, 3H, CH_3CH_2), 3.48–3.60 (quartet of quartet, J=6.9 Hz, 2H, CH_3CH_2), 7.5 (d, J=6.9 Hz, 1H), 7.52 (s, J=8.0 Hz, 1H), 7.54 (quintet, J=2.9, 3.5, and 1.7 Hz, 2H), 7.81 (sextet, J=2.9, 3.5, and 6.9 Hz, 1H), 7.95 (sextet, J=3.5, 2.9, and 6.9 Hz, 1H), 8.02 (d, J=7.9 Hz, 1H), 11.50 (s, 1H, D_2O-exchangeable), 11.54 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 13.5, 60.4, 108.5, 125.4, 125.6, 126.1, 126.8, 127.1, 127.6, 128.7, 129.2, 140.2, 148.3, 150.7, 154.3, 161.7, 163.8. EIMS (*m/z*): 310 (M^+). Anal. calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.81; H, 4.56; N, 9.02.

3.3.2.7. Ethyl 2,4-dioxo-3-methyl-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3g). Mp: 230–232 °C. IR (KBr): 1236, 1419, 1600, 1630, 1673, 1704, 3257 cm^{-1}. ^1H NMR: δ 1.06 (t, J=7.5 Hz, 3H), 3.65 (s, 3H), 4.08 (q, J=7.5 Hz, 2H), 7.43 (s, 4H), 10.42 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 13.8, 27.5, 62.0, 107.7, 129.0, 129.1, 129.3, 138.0, 149.9, 151.9, 160.5, 164.0. EIMS (*m/z*): 308 (M^+). Anal. calcd for $C_{14}H_{13}ClN_2O_4$: C, 54.47; H, 4.24; N, 9.07. Found: C, 54.43; H, 4.23; N, 9.06.

3.3.2.8. 5-Benzoyl-2,4-dioxo-6-(2,4-dichlorophenyl)-pyrimidin-2(1*H*)-one (3h). Mp: >300 °C. IR (KBr): 1235, 1419, 1605, 1628, 1676, 3255, 3341 cm^{-1}. ^1H NMR: δ 7.38 (t, J=7.4 and 8.0 Hz, 2H), 7.42 (m, 2H), 7.57 (d, J=7.4 Hz, 1H), 7.82 (d, J=7.7 Hz, 1H), 8.2 (d, J=10.2 Hz, 1H), 8.27 (s, 1H). ^{13}C NMR: δ 117.6, 128.5, 130.04, 133.5, 134.0, 134.8, 137.7, 138.5, 139.5, 142.3, 152.4, 154.8, 160.0, 167.5, 174.3. EIMS (*m/z*): 361 (M^+). Anal. calcd for $C_{17}H_{10}Cl_2N_2O_3$: C, 56.53; H, 2.79; N, 7.76. Found: C, 56.57; H, 2.79; N, 7.76.

3.3.2.9. Ethyl 2,4-dioxo-6-(4-anisyl)-1,2,3,4-tetrahydropyrimidin-5-carboxylate (3i). Mp: 228–230 °C. IR (KBr): 1241, 1421, 1603, 1629, 1675, 1701, 3261 cm^{-1}. ^1H NMR: δ 1.05 (t, J=7.5 Hz, 3H), 3.84 (s, 3H), 4.13 (q, J=7.5 Hz, 2H), 6.95 (d, J=9.2 Hz, 2H), 7.41 (d, J=7.2 Hz, 2H). ^{13}C NMR: δ 13.8, 56.1, 62.1, 101.0, 108.1, 114.5, 124.5, 130.3, 147.1, 147.9, 156.2, 162.2, 164.4. EIMS (*m/z*): 290 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.86; H, 4.78; N, 9.69.

3.3.3. Trapping of 1i as trifluoroacetate salt in solution. Compound **1i** (30 mg) was dissolved in trifluoroacetic acid (1.5 mL) and a drop of TMS was added to the solution as internal reference. ^1H NMR of the solution was recorded in JEOL 500 MHz instrument with 16 scans. TLC of the solution showed disappearance of **1i** and a new spot above the starting material. The dissolution of **1i** in DMSO-d_6 or $CDCl_3$ and (trifluoro)acetic acid did not form salt in solution.

Compound **5**: ^1H NMR (CF_3COOH, TMS): 1.17 (t, J=6.9 Hz, 3H), 2.42 (s, 3H), 3.87 (s, 3H), 4.07 (q, J=6.9 Hz, 2H), 5.49 (s, 1H), 6.97 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.6 Hz, 2H), 8.32 (s, 1H).

Compound **1j**: ^1H NMR (DMSO-d_6): 1.08 (t, J=6.9 Hz, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.98 (q, J=6.9 Hz, 2H), 5.10 (s, 1H), 6.86 (d, J=8.6 Hz, 2H), 7.13 (d, J=8.6 Hz, 2H), 7.65 (s, 1H), 9.15 (d, 1H).

3.3.4. Highly regioselective oxidation of DHPMs mediated by CAN. Ethyl 6-methyl-4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate: a 50 mL round bottom flask containing magnetic bar was charged with **1a** (1 mmol, 0.260 g), $NaHCO_3$ (5 mmol, 0.420 g), and 10 mL of acetone. To this suspension was added CAN (3 mmol, 1.65 g) in water for 1 h stirred at −5 °C under argon atmosphere. The stirring continued overnight at room temperature and the reaction mixture was diluted with $CHCl_3$ (20 mL) and decanted. The residue was washed with $CHCl_3$ (2×30 mL). The combined $CHCl_3$ layer was neutralized, washed with NaCl solution, dried over anhydrous Na_2SO_4, and column chromatographed using 1:1 mixture of ethyl acetate/petroleum ether to afford 0.214 g of **2a**. The same reaction when conducted without using $NaHCO_3$ yielded a mixture of **2a** and **3a**.

3.3.4.1. Ethyl 6-methyl-4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2a). Mp: 216–218 °C. IR (KBr): 1410, 1625, 1655, 1705, 3420 cm^{-1}. ^1H NMR: δ 0.68 (t, J=7.5 Hz, 3H), 2.45 (s, 3H, 6-Me), 3.80 (q, J=7.5 Hz, 2H), 7.31 (d, J=7.5 Hz, 1H), 7.36 (t, J=6.9 Hz, 1H), 7.45 (d, J=6.9 Hz, 2H), 7.47 (t, J=6.3 Hz, 1H), 11.71 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 13.6, 19.1, 60.9, 109.2, 127.5, 129.4, 129.7, 130.7, 139.7, 156.6, 162.5, 164.7. EIMS (*m/z*): 258 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.09; H, 5.54; N, 10.24.

3.3.4.2. Ethyl 6-methyl-4-biphenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2j). Mp: 178–179 °C. IR (KBr): 1412, 1624, 1655, 1703, 3423 cm^{-1}. ^1H NMR: δ 0.98 (t, J=6.9 Hz, 3H), 2.45 (s, 3H), 3.12 (q, J=6.9 Hz, 2H), 7.32 (t, J=7.6 Hz, 2H), 7.41 (t, J=7.6 Hz, 2H), 7.53 (d, J=8.5 Hz, 2H), 7.66 (d, J=7.6 Hz, 2H), 7.68 (d, J=8.4 Hz, 1H), 11.35 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 14.3, 61.5, 108.3, 126.2, 127.8, 128.3, 129.6, 129.7, 130.1, 139.6, 142.7, 146.7, 156.7, 158.0, 164.3, 174.6. EIMS (*m/z*): 334 (M^+).

Anal. calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.76; H, 5.21; N, 8.73.

3.3.4.3. Ethyl 6-methyl-4-(2-chlorophenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2k). Mp: 164–166 °C. IR (KBr): 1106, 1422, 1505, 1658, 1713, 1732, 2827, 3147, 3345 cm^{-1}. ^1H NMR: δ 0.69 (t, J=6.8 Hz, 3H), 2.49 (s, 3H), 3.80 (q, J=6.8 Hz, 2H), 7.37–7.45 (m, 4H), 11.53 (s, 1H, NH). ^{13}C NMR: δ 13.6, 19.1, 60.9, 109.5, 127.5, 129.4, 129.7, 130.0, 130.7, 140.1, 155.3, 162.5, 164.7, 172.1. EIMS (*m*/*z*): 292 (M^+). Anal. calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.44; H, 4.48; N, 9.57. Found: C, 57.32; H, 4.42; N, 9.55.

3.3.4.4. Ethyl 6-methyl-4-(2-nitrophenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2c). Mp: 180–182 °C. IR (KBr): 1208, 1421, 1543, 1641, 1693, 1715, 2827, 3345 cm^{-1}. ^1H NMR: δ 0.67 (t, J=7.5 Hz, 3H), 2.49 (s, 3H), 3.78 (q, J=7.5 Hz, 2H), 7.40 (d, J=7.5 Hz, 1H), 7.67 (t, J=7.5 Hz, 1H), 7.77 (t, J=7.5 Hz, 1H), 8.17 (d, J= 8.1 Hz, 1H), 11.50 (s, 1H, NH). ^{13}C NMR: δ 13.7, 20.5, 61.0, 107.5, 124.6, 129.7, 130.5, 134.05, 134.7, 146.6, 152.3, 162.2, 164.3, 173.3. EIMS (*m*/*z*): 303 (M^+). Anal. calcd for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.32; H, 4.27; N, 13.74.

3.3.4.5. Ethyl 6-methyl-4-(3-hydroxyphenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2l). Mp: 180–182 °C. IR (KBr): 1132, 1463, 1643, 1693, 3204, 3421 cm^{-1}. ^1H NMR: δ 0.82 (t, J=6.5 Hz, 3H), 2.4 (s, 3H), 3.9 (q, J=6.5 Hz, 2H), 6.8 (m, 3H), 7.2 (t, 7.5 Hz, 1H), 9.7 (s, 1H), 11.32 (s, 1H). ^{13}C NMR: δ 13.8, 21.1, 61.4, 102.6, 114.8, 117.7, 118.7, 128.5, 129.9, 146.5, 157.7, 160.1, 163.2, 172.4. EIMS (*m*/*z*): 274 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.28; H, 5.16; N, 10.20.

3.3.4.6. Methyl 6-methyl-4-(4-methoxyphenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2m). Mp: 180–181 °C. IR (KBr): 1228, 1456, 1547, 1660, 1681, 1715, 2827, 3348 cm^{-1}. ^1H NMR: δ 2.32 (s, 3H), 3.57 (s, 3H), 3.77 (s, 3H), 6.97 (d, J=8.4 Hz, 2H), 7.40 (d, J=8.4 Hz, 2H), 12.23 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 19.2, 52.6, 55.9, 102.3, 114.3, 116.4, 130.0, 136.1, 156.3, 161.7, 167.4, 174.2. EIMS (*m*/*z*): 274 (M^+). Anal. calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.28; H, 5.08; N, 10.13.

3.3.4.7. Ethyl 1,6-dimethyl-4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (2n). Mp: 212–213 °C. IR (KBr): 1103, 1197, 1286, 1439, 1494, 1616, 1679, 1722, 2990 cm^{-1}. ^1H NMR: δ 1.14 (t, J=7.6 Hz, 3H, CH_3CH_2), 2.41 (s, 3H), 3.35 (s, 3H, N-Me), 3.97 (q, J=7.6 Hz, 2H, CH_3CH_2), 7.38 (t, J=6.8 Hz, 2H), 7.41 (t, J=7.6 and 2.3 Hz, 1H), 7.54 (t, J=6.9 Hz, 2H). ^{13}C NMR: δ 13.8, 20.2, 39.3, 61.0, 108.8, 127.9, 128.6, 130.5, 137.1, 153.1, 155.3, 163.5, 173.5. EIMS (*m*/*z*): 272 (M^+). Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.08; H, 5.83; N, 10.17.

3.3.4.8. Ethyl 1,6-dimethyl-4-(4-methoxyphenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2o). Mp: 140–142 °C. IR (KBr): 1231, 1453, 1549, 1662, 1683, 1720, 3351 cm^{-1}. ^1H NMR: δ 0.85 (t, J=6.7 Hz, 3H), 2.38 (s, 3H), 3.46 (s, 3H), 3.73 (s, 3H), 3.92 (q, J=6.8 Hz, 2H), 6.77 (d, J=9.2 Hz, 2H), 7.4 (d, J=9.2 Hz, 2H). ^{13}C NMR: δ 13.6, 18.1, 33.1, 55.4, 61.8, 111.5, 113.7, 129.8, 130.3, 155.9, 158.4, 161.7, 167.3, 169.8. EIMS (*m*/*z*): 302 (M^+). Anal. calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.44; H, 5.92; N, 9.31.

3.3.4.9. Ethyl 6-methyl-4-(4-methoxyphenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (2i). Mp: 172–173 °C. IR (KBr): 1132, 1463, 1643, 1693, 3220 cm^{-1}. ^1H NMR: δ 0.9 (t, J=6.5 Hz, 3H), 2.3 (s, 3H), 3.81 (s, 3H), 3.93 (q, J=6.8 Hz, 2H), 6.8 (m, 2H), 7.2 (t, J=8.4 Hz, 2H), 9.7 (s, 1H). ^{13}C NMR: δ 13.8, 21.1, 55.2, 61.4, 102.6, 114.8, 118.7, 128.5, 129.9, 146.5, 157.7, 160.1, 172.1. EIMS (*m*/*z*): 288 (M^+). Anal. calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.35; H, 5.52; N, 9.70.

3.3.4.10. Ethyl 6-methyl-4-(2-propyl)-pyrimidin-2(1*H*)-one-5-carboxylate (4a). Mp: 232–234 °C. IR (KBr): 1131, 1455, 1642, 1688, 3205, 3433 cm^{-1}. ^1H NMR: δ 1.34 (t, J=7.5 Hz, 3H), 1.39 (d, J=6.8 Hz, 6H), 2.45 (s, 3H), 3.15 (m, J=6.8 Hz, 1H), 4.32 (q, J=7.5 Hz, 2H), 13.65 (s, 1H). ^{13}C NMR: δ 14.2, 21.1, 29.7, 61.9, 112.5, 145.6, 159.6, 163.1, 173.6. EIMS (*m*/*z*): 224 (M^+). Anal. calcd for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.68; H, 7.12; N, 12.42.

3.3.4.11. Ethyl 4-(4-methoxyphenyl)-6-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (4b). Mp: 153–154 °C. IR (KBr): 1163, 1238, 1328, 1446, 1517, 1599, 1668, 1709, 2280, 2808, 2984, 3213 cm^{-1}. ^1H NMR: δ 0.85 (t, J=6.8 Hz, 3H), 3.82 (s, 3H), 3.90 (q, J=6.8 Hz, 2H), 6.94 (d, J=9.2 Hz, 1H), 7.00 (d, J=8.5 Hz, 1H), 7.40 (m, J=6.9 and 7.6 Hz, 2H), 7.49 (d, J=3.8 Hz, 1H), 7.58 (t, J=8.5 Hz, 2H), 8.01 (q, J=8.5 and 9.2 Hz, 2H), 13.32 (s, 1H, D_2O-exchangeable). ^{13}C NMR: δ 13.5, 55.4, 61.9, 106.5, 114.2, 128.6, 129.2, 129.6, 130.2, 138.5, 139.7, 150.2, 158.2, 162.2, 162.9, 174.1. EIMS (*m*/*z*): 350 (M^+). Anal. calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.49; H, 5.12; N, 8.02.

3.3.4.12. Ethyl 4-(4-methoxyphenyl)-6-trifluoromethyl-pyrimidin-2(1*H*)-one-5-carboxylate (4c). Mp: 136–138 °C. IR (KBr): 1017, 1127, 1162, 1210, 1299, 1509, 1605, 1699, 1739, 3188 cm^{-1}. ^1H NMR: δ 1.15 (t, J=6.8 Hz, 3H), 3.85 (s, 3H), 4.17 (q, J=6.8 Hz, 2H), 7.05 (d, J=8.4 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 11.50 (s, 1H). ^{13}C NMR: δ 13.7, 55.6, 62.8, 109.5, 114.9, 122.0 (q, J=275 Hz), 130.2, 138.6, 155.6 (q, J=34 Hz), 161.2, 163.2, 164.1, 174.2. EIMS (*m*/*z*): 342 (M^+). Anal. calcd for $C_{15}H_{13}F_3N_2O_4$: C, 52.64; H, 3.83; N, 8.18. Found: C, 52.59; H, 3.77; N, 8.19.

3.3.4.13. Ethyl 6-bromomethyl-4-phenyl-pyrimidin-2(1*H*)-one-5-carboxylate (4d). Mp: 181–182 °C. IR (KBr): 1125, 1468, 1651, 1689, 3253, 3455 cm^{-1}. ^1H NMR: δ 0.86 (t, J=7.5 Hz, 3H), 3.84 (s, 2H, CH_2Br), 3.93 (q, J=7.5 Hz, 2H), 7.42 (m, 2H), 7.59 (t, J=6.8 Hz, 3H), 13.52 (s, 1H, D_2O-exchangeable, NH). ^{13}C NMR: δ 13.5, 25.9, 55.5, 105.3, 128.1, 128.7, 130.2, 140.5, 158.1, 162.3, 166.8, 173.1. EIMS (*m*/*z*): 337 (M^+). Anal. calcd for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; N, 8.31. Found: C, 49.78; H, 3.92; N, 8.27.

3.3.4.14. Ethyl 6-methyl-4-(4-(4-bromophenyl)-1-phenyl-1*H*-pyrazolyl)-pyrimidin-2(1*H*)-one-5-carboxylate (4e). Mp: 221–223 °C. IR (KBr): 1058, 1464, 1645, 1693, 3258 cm^{-1}. ^1H NMR: δ 0.78 (t, J=6.8 Hz, 3H), 2.34 (s, 3H), 3.67 (q, J=6.8 Hz, 2H), 7.32 (t, J=7.6 Hz, 1H), 7.43 (d, J=8.4 Hz, 2H), 7.49 (t, J=7.6 Hz, 2H), 7.56 (d, J=7.6 Hz, 2H), 7.89 (d, J=7.6 Hz, 2H), 8.77 (s, 1H), 12.39 (s, 1H, NH(3)). ^{13}C NMR: δ 13.7, 20.2, 61.2, 105.7, 119.0, 124.2, 126.5, 128.5, 130.1, 130.3, 131.2, 132.1, 132.6, 148.3, 149.8, 156.5, 162.3, 163.9, 174.9. EIMS (*m*/*z*): 479 (M^+). Anal. calcd for $C_{23}H_{19}BrN_4O_3$: C, 57.63; H, 4.00; N, 11.69. Found: C, 57.58; H, 3.92; N, 11.67.

3.3.4.15. Ethyl 1,6-dimethyl-4-(1-pyrenyl)-pyrimidin-2(1*H*)-one-5-carboxylate (4f). Mp: 231–232 °C. IR (KBr): 1109, 1463, 1649, 1703 cm^{-1}. ^1H NMR: δ 1.24 (t, J=6.7 Hz, 3H), 2.61 (s, 3H), 3.71 (s, 3H), 4.11 (q, J=7.5 Hz, 2H), 7.93 (t, J=7.5 and 6.8 Hz, 1H), 7.99 (t, J=7.5 Hz, 1H), 8.03 (t, J=8.6 and 8 Hz, 2H), 8.09 (s, 1H), 8.15 (m, 4H). ^{13}C NMR: δ 12.8, 18.5, 33.4, 61.4, 114.0, 124.3, 124.4, 124.5, 125.6, 125.7, 125.8, 126.3, 127.3, 128.1, 128.5, 130.8, 131.3, 132.1, 133.3, 155.8, 159.4, 166.2, 172.7. EIMS (*m*/*z*): 398 (M^+). Anal. calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.31; H, 5.31; N, 7.12.

3.3.4.16. 7,7-Dimethyl-4-phenyl-7,8-dihydroquinazoline-2,5(1*H*,6*H*)-dione (4g). Mp: 196–198 °C. IR (KBr): 1092, 1323, 1640, 1722, 2956, 3208 cm^{-1}. ^1H NMR: δ 1.35 (s, 6H), 2.58 (s, 2H), 2.88 (s, 2H), 7.01 (q, J=1.7, 5.2, and 7.5 Hz, 2H), 7.40 (q, J=1.7 and 5.2 Hz, 3H), 11.83 (s, 1H). ^{13}C NMR: δ 25.4, 28.3, 32.1, 48.1, 54.1, 108.5, 126.6, 127.8, 128.0, 138.8, 152.3, 167.7, 172.2, 194.8. EIMS (*m*/*z*): 268 (M^+). Anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.58; H, 5.96; N, 10.46.

3.3.4.17. 4-Phenyl-1*H*-indeno[1,2-*d*]pyrimidin-2,5-dione (4h). Mp: 210–212 °C. IR (KBr): 1276, 1378, 1459, 1576, 1617, 1659, 1723, 2854, 2923, 3484 cm^{-1}. ^1H NMR: δ 7.60 (t, J=6.8 Hz, 2H), 7.65 (q, J=7.5 and 6.3 Hz, 2H), 7.71 (t, J=7.5 and 6.3 Hz, 1H), 7.82 (d, J=7.5 Hz, 1H), 7.89 (d, J=7.5 Hz, 2H), 8.11 (d, J=6.8 Hz, 1H). ^{13}C NMR: δ 106.2, 120.8, 121.5, 126.7, 128.3, 128.9, 130.1, 132.1, 133.7, 135.2, 143.5, 151.2, 157.4, 173.9, 187.5. EIMS (*m*/*z*): 274 (M^+). Anal. calcd for $C_{17}H_{10}N_2O_2$: C, 74.44; H, 3.67; N, 10.21. Found: C, 74.38; H, 3.61; N, 10.20.

3.3.4.18. Ethyl 3-methyl-6-{4-[1-methyl-5-(ethoxycarbonyl)-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-yl]-phenyl}-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i). Mp: >260 °C. IR (KBr): 1050, 1510, 1620, 1690, 3248 cm^{-1}. ^1H NMR: δ 0.97 (t, J=7.5 Hz, 6H), 3.17 (s, 6H), 3.93 (q, J=7.5 Hz, 4H), 7.54 (s, 4H), 11.90 (s, 2H). ^{13}C NMR: δ 14.2, 27.4, 61.5, 112.5, 122.3, 128.5, 131.7, 152.9, 153.0, 161.5, 164.1. EIMS (*m*/*z*): 470 (M^+). Anal. calcd for $C_{22}H_{22}N_4O_8$: C, 56.17; H, 4.71; N, 11.91. Found: C, 56.03; H, 4.59; N, 11.95.

Acknowledgements

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11. Crystal analysis for **3g**: MF: $C_{14}H_{13}ClN_2O_4$, formula weight: 308.71, crystal system: monoclinic, space group: *P*21/*n*, cell length: *a* 9.5074, *b* 15.158, *c* 9.882, cell angle: α 90°, β 94.149°, γ 90°. Volume (cubic angstroms): 1420.4(5), *Z*: 4, temperature: 293(2) K, absorption coefficient: 0.28. Calculated

density: 1.444, reflections collected/unique 2653/2497 [R(int)=0.0169] R indices (all data) $R1$=0.0672, $wR2$=0.0979. Final R indices [$I>2\sigma(I)$] $R1$=0.0377, $wR2$=0.0861. Crystallographic data was submitted in Cambridge Crystallographic Centre and CCDC no. is 26952.

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14. Compound **2c**: MF: $C_{14}H_{13}ClN_2O_3$, formula weight: 292.71, crystal system: monoclinic, space group: *C* 2/*c*, cell length: *a* 11.391, *b* 9.324, *c* 27.37, cell angle: α 90°, β 93.267°, γ 90°. Cell volume (cubic angstroms): 2902.23, *Z*: 4, temperature: 293(2) K. Crystallographic data was submitted in Cambridge Crystallographic Centre and CCDC no. is 26950.
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Synthesis and complexation studies of intra annularly linked bicyclic cyclophanes

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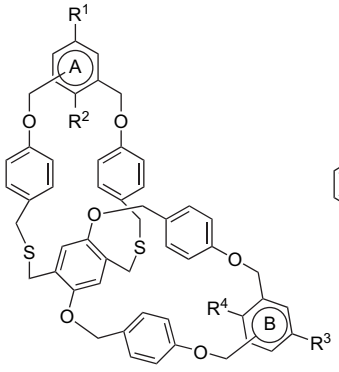
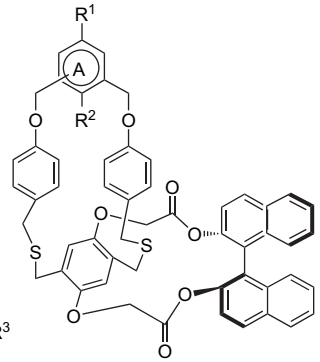
Abstract—The cyclophanes derived from 2,6-bis(chloromethyl)benzoquinone and suitable dithiols were reduced with sodium dithionate and then further coupled with various dibromides to give intra annularly linked bicyclic cyclophanes, which forms charge transfer complexes with TCNQ and TCNE.

1. Introduction

Pre-organization[1] of macrocycles plays a vital role in many biological mechanisms such as enzyme–substrate activity,[2] protein folding,[3] antisense application[4] and molecular recognition.[5] Hart and Vinod[6] have reported various novel cyclophanes with a *m*-terphenyl unit embedded within a cavity lined by three aryl rings. Stoddart and Spencer[7] have reported the synthesis of chiral macrobicyclic cyclophanes. Chiral Binol based cyclophanes[8,9] and bicompartmental bicyclic cyclophanes[10] have also been recently reported. However, to the best of our knowledge, the synthesis of self-complementary bicompartmental bicyclic cyclophanes remains to be explored. Hence, we report herein the synthesis and characterization of bicompartmental self-complementary cyclophanes **10**–**13** and **19**–**22** with electron rich and electron deficient counterparts.



10, 11, 12, 19, 20, 21



13, 22

Keywords: Cyclophanes; Bicompartmental; Self-complimentary; Electron rich; Electron deficient.
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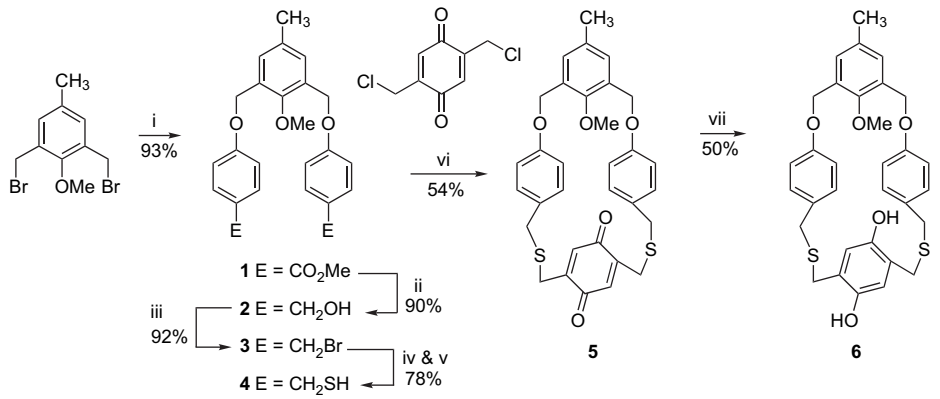
Compd	A	B	R^1	R^2	R^3	R^4
10	*m*-	*m*-	Me	OMe	Me	OMe
11	*m*-	*m*-	Me	OMe	NO_2	OAc
12	*m*-	*o*-	Me	OMe	H-	H-
13	*m*-	Binol	Me	OMe	—	—
19	*o*-	*o*-	H-	H-	H-	H-
20	*o*-	*m*-	H-	H-	Me	OMe
21	*o*-	*m*-	H-	H-	NO_2	OAc
22	*o*-	Binol	H-	H-	—	—

2. Results and discussion

In order to synthesize bicompartmental self-complementary cyclophane **10**, 2 equiv of methyl *p*-hydroxybenzoate was treated with 1 equiv of 4-methyl 2,6-bis-(bromomethyl)anisole[11] in the presence of K_2CO_3 in DMF to give diester **1** in 93% yield. Reduction of diester with $LiAlH_4$ gave diol **2**, which on further reaction with PBr_3 gave dibromide **3** in 92% yield. The thiouronium salt derived from dibromide **3** and thiourea, on hydrolysis with KOH in THF/H_2O gave dithiol **4** in 78% yield. The structure of the dithiol **4** has been confirmed from the spectral and analytical data.

Treatment of equimolar amounts of dithiol **4** and 2,6-bis-(chloromethyl)benzoquinone in EtOH/benzene under high dilution conditions[12] gave thiacyclophane **5** in 54% yield. Thiacyclophane **5** was found to be unstable and hence complete characterization could not be carried out.

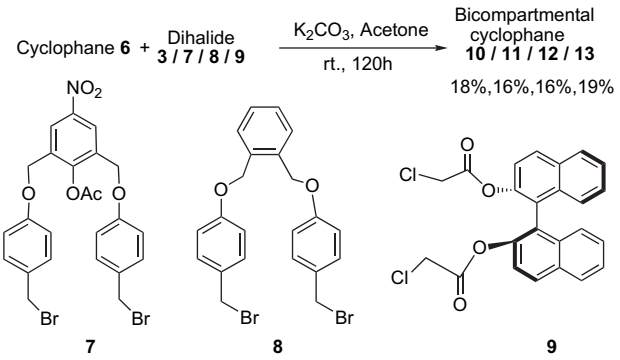
Reduction of thiacyclophane **5** with sodium dithionate in EtOAc at 0 °C afforded cyclophane **6** in 50% yield. The sulfide bonds in cyclophane **6** are not affected during the course of reaction. In the ^{1}H NMR spectrum of cyclophane **6**, the methyl and methoxy protons appeared as singlets at δ 2.06 and 3.16. Further the *S*-methylene and *O*-methylene protons



Scheme 1. Reagents and conditions: (i) methyl *p*-hydroxybenzoate, K_2CO_3, DMF, 60 °C, 48 h; (ii) $LiAlH_4$, THF, 60 °C, 12 h; (iii) PBr_3, CH_2Cl_2, 0 °C, 12 h; (iv) thiourea, THF, 60 °C, 12 h; (v) KOH, 60 °C, 12 h, THF/H_2O (1:1); (vi) EtOH/benzene, rt, 24 h; (vii) $Na_2S_2O_4$, EtOAc, 0 °C, 3 h.

appeared as two singlets at δ 3.77 and 5.22 for eight and four protons, respectively, in addition to the aromatic protons (Scheme 1).

Treatment of cyclophane **6** with dibromide **3**, in the presence of K_2CO_3 in dry acetone at room temperature for 120 h afforded the annularly linked bicyclic cyclophane **10** in 18% yield (Scheme 2). The ^{1}H NMR spectrum of electron rich bicompartmental cyclophane **10** showed two singlets for methyl and methoxy protons at δ 2.32 and 3.80 and *S*-methylene and *O*-methylene protons as singlets at δ 4.60 and δ 5.08, respectively, in addition to the aromatic protons.

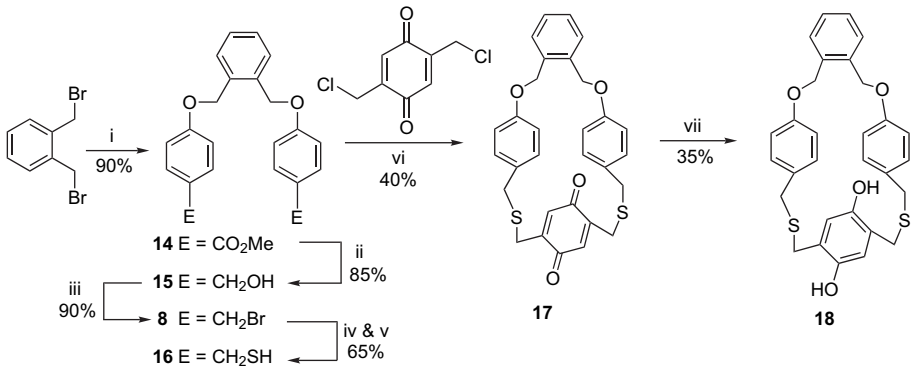


Scheme 2.

By similar methodology, electron rich cyclophane **6** was treated with various dihalides such as dibromides **7**[13] and **8**,[14] and chiral dichloride **9**[15] to give the bicompartmental cyclophanes **11** and **12** and chiral cyclophane **13** in 16, 16 and 19% yield, respectively. Bicompartmental cyclophanes **11–13** were characterized by spectroscopic and analytical data (Scheme 2).

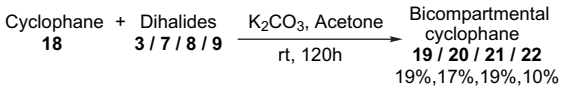
Attention was then focused on the synthesis of bicompartmental cyclophanes **19–22** by similar methodology. Dibromide **8** was obtained from *o*-xylenyl dibromide by the known procedure.[14] Treatment of dibromide **8** with thiourea in THF afforded the thiouronium salt, which on hydrolysis with KOH in THF/H_2O gave dithiol **16** in 65% yield. Treatment of equimolar amounts of dithiol **16** with 2,6-bis-(chloromethyl)benzoquinone in EtOH/benzene under high dilution conditions gave neutral thiacyclophane **17** in 40% yield. Thiacyclophane **17** could not be completely characterized due to its instability. Reduction of cyclophane **17** with sodium dithionate in EtOAc at 0 °C afforded cyclophane **18** in 35% yield (Scheme 3).

Treatment of cyclophane **18** with dibromide **8** in dry acetone and in the presence of K_2CO_3 at room temperature for 120 h afforded the bicompartmental cyclophane **19** in 19% yield. In the ^{1}H NMR spectrum, bicompartmental cyclophane **19** showed two *S*-methylene protons as two singlets at δ 4.09 and 4.55 and *O*-methylene protons as another singlet at



Scheme 3. Reagents and conditions: (i) methyl *p*-hydroxybenzoate, K_2CO_3, DMF, 60 °C, 48 h; (ii) $LiAlH_4$, THF 60 °C, 12 h; (iii) PBr_3, CH_2Cl_2, 0 °C, 12 h; (iv) thiourea, THF, 60 °C, 12 h; (v) KOH, 60 °C, 12 h, THF/H_2O (1:1); (vi) EtOH/benzene, rt, 24 h; (vii) $Na_2S_2O_4$, EtOAc, 0 °C, 3 h.

δ 5.15 in addition to aromatic protons. Using similar methodology, cyclophane **18** was treated with various dihalides such as dibromides **3** and **7**[13] and chiral dichloride **9**[15] to give bicompartmental cyclophanes **20** and **21** and bicompartmental chiral cyclophane **22** in 17, 19 and 10% yield, respectively (Scheme 4).



Scheme 4.

Bicompartmental cyclophanes **20**–**22** were characterized by spectroscopic and analytical data.

Semi empirical calculations based on MOPAC (AM_1) have been carried out for the bicompartmental cyclophane **10**–**13** and **19**–**22** and show that the two cyclophane rings are perpendicular to each other. It also reveal that the central benzene ring through which both the macrocyclic rings are connected lies in a perpendicular plane (Figs. 1 and 2).

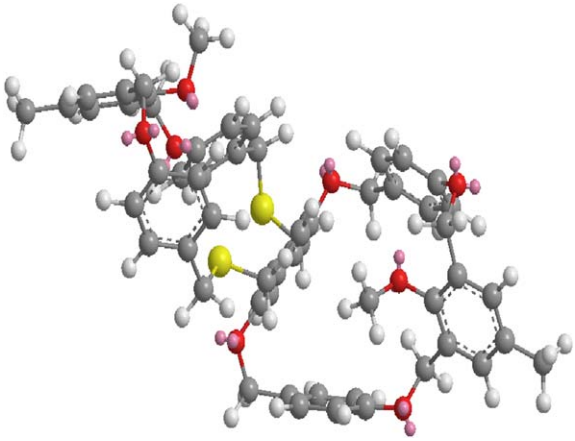


Figure 1. Energy minimization of cyclophane **10**: heat of formation of cyclophane **10** 15.0752 kcal/mol.

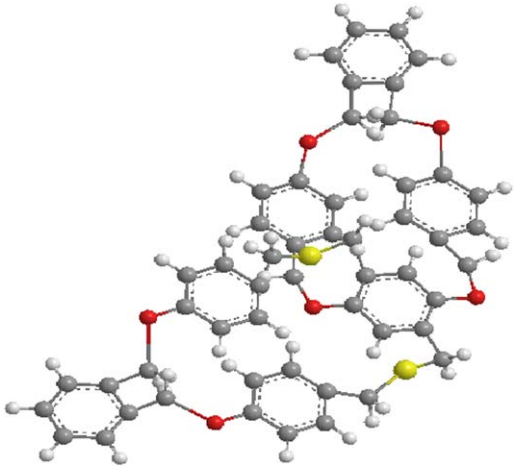


Figure 2. Energy minimization of cyclophane **19**: heat of formation of cyclophane **19** 16.7920 kcal/mol.

Cyclophanes **10**, **19**, **20** and **21** show UV–vis absorption maxima at 318, 276 and 288 nm in DMF solvent medium. However the acceptors TCNQ and TCNE show absorption maxima at 410 and 322 nm, respectively, in the same solvent. Cyclophanes **10**, **19**, **20** and **21** form charge transfer complexes with TCNQ as evident by the appearance of absorption maxima at 751, 775 and 850 nm, respectively. The equilibrium constant for the charge transfer complexation of **21** with TCNQ was observed at 850 nm (Fig. 3). Cyclophane **21** also formed a charge transfer complex with TCNE, as indicated by absorption at 825 and 849 nm, respectively. The charge transfer complexation of **21** with TCNE was observed at 848 nm (Fig. 4).

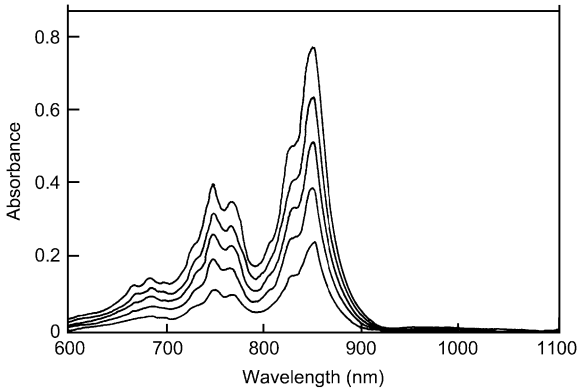


Figure 3. Charge transfer complexation behaviour of cyclophane **21** with variable concentration of TCNQ.

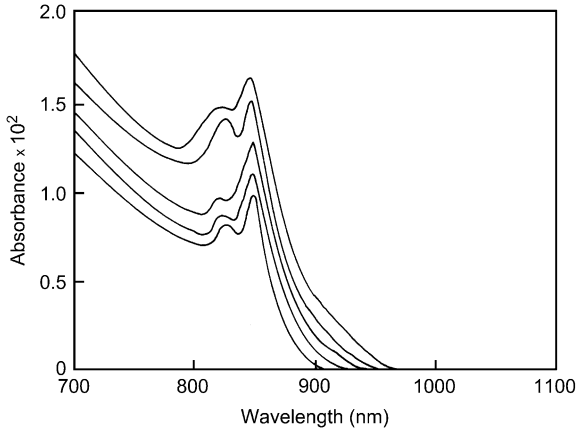


Figure 4. Charge transfer complexation behaviour of cyclophane **21** with variable concentration of TCNE.

The stability constants of the charge transfer complexes for cyclophanes **10**, **19**, **20** and **21** with acceptors TCNQ and TCNE were also determined (Table 1).

It is noteworthy to mention that cyclophane **21** forms a strong charge transfer complex with TCNQ (K_c^{AD} 1343 M^{-1} and ε^{AD} 2.19×10^5). By comparing the stability constants of the CT complexes derived from cyclophanes **10**, **19**, **20** and **21** and TCNQ and TCNE it is clear that the cavity size has no significant influence on the stability of the charge transfer complexes.

Table 1. Stability constants for the charge transfer complexes of **10**, **19**, **20** and **21** with accepters TCNQ and TCNE

Cyclophane	TCNQ		TCNE	
	K_c^{AD}	ε^{AD}	K_c^{AD}	ε^{AD}
10	183	5.9×10^5	222	5.2×10^3
19	147	2.17×10^5	189	2.0×10^6
20	128	2.0×10^5	287	2.27×10^3
21	1343	2.19×10^5	170	1.0×10^4

In conclusion, we have synthesized a new class of bicompartmental cyclophanes with electron rich, electron deficient and neutral macrocyclic units and made a preliminary study on their CT complexation ability with electron poor guest molecules TCNQ and TCNE.

3. Experimental

3.1. General

All melting points are uncorrected. The IR spectra were recorded using Shimadzu FT-IR 8000 Infrared Spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on JEOL GSX 500 NMR Spectrometer at 500 and 125 MHz, respectively, and coupling constants (*J*) are expressed in hertz, using TMS as an internal standard. The Mass spectra were recorded using a JEOL mass Spectrometer (EI, 70 eV). THF was freshly distilled from Na/benzene kettle before use. The column chromatography was performed using silica gel (Acme, 100–200 mesh). The organic layer extracts were dried using anhydrous sodium sulfate. The dibromide **7** and the dichloride **15** were prepared according to literature procedures.[13–15]

3.2. General procedure for the synthesis of diesters

Dibromide (2.0 equiv) and methyl *p*-hydroxybenzoate (2.2 equiv) were stirred with K_2CO_3 (5.0 equiv) in dry DMF (25 mL) at 60 °C for 48 h. The reaction mixture was poured into water (2 L) and stirred. The resulting precipitate was filtered, washed with water (3×150 mL) and dissolved in CH_2Cl_2 (350 mL). The organic layer was washed with NaOH solution (5% w/v, 2×100 mL), dried over Na_2SO_4 and evaporated to give a residue that was purified by column chromatography using hexane/$CHCl_3$ (4:1) as eluent.

3.2.1. Diester 1. Colourless solid; yield 93%; R_f 0.6 (hexane/$CHCl_3$ 4:1); mp 197–201 °C; IR (cm^{-1}) 1679 (C=O); ^{1}H NMR ($CDCl_3$) δ 8.01 (4H, d, *J* 8.8 Hz, Ph), 7.29 (2H, s, Ph), 7.02 (4H, d, *J* 8.8 Hz, Ph), 5.14 (4H, s, C*H*$_2$OPh), 3.89 (6H, s, COO*Me*), 2.74 (3H, s, O*Me*), 2.34 (3H, s, Me); ^{13}C NMR ($CDCl_3$) δ 180.2, 170.1, 166.7, 134.3, 133.9, 129.2, 128.9, 128.8, 114.3, 65.5, 65.1, 63.1, 20.9; *m*/*z* 450 (M^+); Anal. Calcd for $C_{26}H_{26}O_7$: C, 69.33; H, 5.78. Found: C, 69.34; H, 5.79.

3.2.2. Diester 14. Colourless solid; yield 90%; R_f 0.5 (hexane/$CHCl_3$1:1); mp 82–85 °C; IR (cm^{-1}) 1715 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.19–7.65 (4H, m, Ph), 7.10 (4H, d, *J* 8.4 Hz, Ph), 6.71 (4H, d, *J* 8.4 Hz, Ph), 5.12 (4H, s, C*H*$_2$OPh), 3.82 (6H, s, COO*Me*); ^{13}C NMR ($CDCl_3$) δ 180.3, 165.0, 144.2, 140.2, 130.9, 127.9, 127.7, 122.5, 64.7, 51.5; *m*/*z* 406 (M^+); Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.94; H, 5.42. Found: C, 70.95; H, 5.43.

3.3. General procedure for the synthesis of diols

To a solution of the appropriate diester (1.0 equiv) in dry THF (300 mL) was added $LiAlH_4$ (2.2 equiv) at 0 °C in portions. The reaction mixture was stirred at room temperature for 1 h and then run into $Na_2SO_4\cdot10H_2O$ (40 g) and stirred. The reaction mixture was then digested on a water bath for 20 min and then filtered. The inorganic residue was further extracted with THF (200 mL) using a Soxhlet apparatus. The combined THF fractions were evaporated to give the diol. The crude product was purified by column chromatography using hexane/$CHCl_3$ (1:1) as eluent.

3.3.1. Diol 2. Colourless solid; yield 90%; R_f 0.3 (hexane/$CHCl_3$ 1:1); mp 183–185 °C; IR (cm^{-1}) 3340 (br, OH); ^{1}H NMR ($CDCl_3$) δ 7.29 (4H, d, *J* 8.7 Hz, Ph), 7.25 (2H, s, Ph), 6.98 (4H, d, *J* 8.7 Hz, Ph), 6.32 (2H, s, O*H*), 5.07 (4H, s, C*H*$_2$OH), 4.61 (4H, s, C*H*$_2$OPh), 3.81 (3H, s, O*Me*), 2.32 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ 158.3, 154.4, 134.2, 133.3, 130.7, 129.8, 128.6, 114.8, 65.1, 65.0, 63.0, 20.8; *m*/*z* 394 (M^+); Anal. Calcd for $C_{24}H_{26}O_5$: C, 73.10; H, 6.60. Found: C, 73.11; H; 6.61.

3.3.2. Diol 15. Colourless solid; yield 90%; R_f 0.4 (hexane/$CHCl_3$ 1:1); mp 194–198 °C (lit. 196 °C).[14]

3.4. General procedure for the synthesis of dibromides

To a stirred solution of diol (1.0 equiv) in dry CH_2Cl_2 (120 mL), PBr_3 (3.0 equiv) was added and the reaction mixture was stirred at 0 °C for 12 h. The reaction mixture was poured into water (500 mL) and the organic layer was extracted with water (3×150 mL) followed by brine (200 mL) and then dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give dibromide, which was purified by recrystallization from hexane/CH_2Cl_2 (3:1).

3.4.1. Dibromide 3. Colourless solid; yield 92%; R_f 0.7 (hexane/$CHCl_3$ 3:1); mp 160–164 °C; IR (cm^{-1}) 2924, 1610, 1218, 1009, 770; ^{1}H NMR ($CDCl_3$) δ 7.33 (4H, d, *J* 8.6 Hz, Ph), 7.25 (2H, s, Ph), 7.21 (4H, d, *J* 8.6 Hz, Ph), 4.51 (4H, s, C*H*$_2$OPh), 4.44 (4H, s, C*H*$_2$Br), 3.97 (3H, s, O*Me*), 2.28 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ 154.4, 132.9, 131.6, 130.7, 130.6, 121.0, 120.8, 116.2, 62.3, 39.8, 27.8, 20.7; *m*/*z* 520 (M^+); Anal. Calcd for $C_{24}H_{24}O_3Br_2$: C, 55.38; H, 4.62. Found: C, 55.39; H, 4.63.

3.4.2. Dibromide 8. Colourless solid; yield 92%; R_f 0.65 (hexane/$CHCl_3$ 3:1); mp 136–139 °C (lit. 134 °C).[14]

3.5. General procedure for the synthesis of dithiols

A stirred solution of the dibromide (1.0 equiv) and thiourea (2.2 equiv) in THF (150 mL) was refluxed for 12 h. The mixture was cooled and the thiouronium salt was filtered and dried. The salt was dissolved in H_2O/THF (1:1) under nitrogen and KOH (2.2 equiv) was added. The reaction mixture was refluxed under nitrogen for 12 h, cooled and carefully quenched with 4 M HCl (40 mL). The solvent was removed

in vacuo and the crude product was purified by column chromatography using hexane/$CHCl_3$ (4:1) to give the corresponding dithiol.

3.5.1. Dithiol 4. Colourless solid; yield 78%; R_f 0.5 (hexane/$CHCl_3$ 1:3); mp 105–110 °C; IR (cm^{-1}) 2958, 1628, 1230, 1000, 664; ^1H NMR ($CDCl_3$) δ 7.26 (4H, d, *J* 8.4 Hz, Ph), 7.19 (2H, s, Ph), 6.95 (4H, d, *J* 8.4 Hz, Ph), 5.04 (4H, s, C*H*$_2$OPh), 3.85 (3H, s, O*Me*), 3.77 (4H, d, *J* 7.6 Hz, C*H*$_2$SH), 2.23 (3H, s, *Me*), 1.92 (2H, t, *J* 7.6 Hz, S*H*); ^{13}C NMR ($CDCl_3$) δ 158.0, 154.0, 133.6, 131.0, 130.1, 130.0, 129.3, 115.0, 65.4, 63.1, 62.9, 21.0; *m*/*z* 426 (M^+); Anal. Calcd for $C_{24}H_{26}O_3S_2$: C, 67.60; H, 6.10. Found: C, 67.61; H, 6.11.

3.5.2. Dithiol 16. Colourless solid; yield 65%; R_f 0.6 (hexane/$CHCl_3$ 1:3); mp 155–158 °C; IR (cm^{-1}) 2962, 1609, 1616, 1201, 1112, 701; ^1H NMR ($CDCl_3$) δ 7.09 (4H, d, *J* 8.8 Hz, Ph), 7.21–7.35 (4H, m, Ph), 6.76 (4H, d, *J* 8.8 Hz, Ph), 4.99 (4H, s, C*H*$_2$OPh), 3.53 (4H, d, *J* 7.3 Hz, C*H*$_2$SH), 1.12 (2H, t, *J* 7.1 Hz, CH$_2$S*H*); ^{13}C NMR ($CDCl_3$) δ 130.5, 130.2, 129.6, 128.6, 151.1, 115.0, 114.8, 68.1, 59.7; *m*/*z* 382 (M^+); Anal. Calcd for $C_{22}H_{22}O_2S_2$: C, 69.11; H, 5.76. Found: C, 69.12; H, 5.77.

3.6. General procedure for the synthesis of cyclophanes

A solution containing an equimolar amount of dithiol (1.0 equiv) and dichloride (1.0 equiv) in nitrogen degassed benzene (200 mL) was added dropwise over the period of 8 h to a well stirred solution of KOH (1.2 equiv) in dry ethanol (800 mL). After the addition was complete, the reaction mixture was stirred for 12 h and then evaporated to dryness. The residue was purified by column chromatography using hexane/$CHCl_3$ (1:1) as eluent.

3.6.1. Cyclophane 5. Pale yellow solid; yield 54%; R_f 0.45 (hexane/$CHCl_3$ 1:1); mp 143–147 °C; IR (cm^{-1}) 1716 (C=O).

3.6.2. Cyclophane 17. Pale yellow solid; yield 40%; R_f 0.5 (hexane/$CHCl_3$ 1:1); mp 154–159 °C; IR (cm^{-1}) 1715 (C=O).

3.7. General procedure for dithionate reduction

To a solution of cyclophane (1.0 equiv) in ethyl acetate (25 mL) was added $Na_2S_2O_4$ (2.2 equiv) in H_2O (15 mL) at 0 °C. The reaction mixture was stirred for 3 h and then evaporated to dryness. The residue was extracted with ethyl acetate (2×100 mL), washed with water (3×150 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography using $CHCl_3$/MeOH (49:1).

3.7.1. Cyclophane 6. Colourless solid; yield 50%; R_f 0.55 ($CHCl_3$/MeOH 3:1); mp 189–192 °C; IR (cm^{-1}) 3280 (br, OH); ^1H NMR ($CDCl_3$) δ 7.15 (2H, s, Ph), 7.04 (2H, s, Ph), 6.81 (2H, s, O*H*), 6.76 (4H, d, *J* 8.4 Hz, Ph), 6.68 (4H, d, *J* 8.4 Hz, Ph), 5.22 (4H, s, C*H*$_2$OPh), 3.77 (8H, s, C*H*$_2$SPh), 3.16 (3H, s, O*Me*), 2.06 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ 166.9, 162.4, 154.6, 134.5, 131.9, 131.7, 131.1, 129.4, 128.9, 122.9, 114.4, 65.2, 63.2, 62.2, 52.0, 20.9; *m*/*z* 560 (M^+); Anal. Calcd for $C_{32}H_{32}S_2O_5$: C, 68.57; H, 5.71. Found: C, 68.58; H, 5.72.

3.7.2. Cyclophane 18. Colourless solid; yield 35%; R_f 0.6 ($CHCl_3$/MeOH 3:1); mp 167–170 °C; IR (cm^{-1}) 3442 (br, OH); ^1H NMR ($CDCl_3$) δ 7.33 (4H, d, *J* 8.4 Hz, Ph), 7.25 (4H, m, Ph), 7.16 (2H, s, Ph), 6.94 (4H, d, *J* 8.4 Hz, Ph), 6.37 (2H, s, O*H*), 5.04 (4H, s, CH$_2$OPh), 3.98 (4H, s, CH$_2$SPh), 2.29 (4H, s, CH$_2$SPh); ^{13}C NMR ($CDCl_3$) δ 167.6, 152.1, 145.6, 133.1, 132.2, 129.2, 126.3, 125.8, 82.7, 40.8, 29.7, 27.4, 27.2; *m*/*z* 516 (M^+); Anal. Calcd for $C_{30}H_{28}S_2O_4$: C, 69.77; H, 5.43. Found: C, 69.78; H, 5.44.

3.8. General procedure for the synthesis of bicompartmental cyclophanes

A solution of cyclophane (1.0 equiv) and dihalide (1.0 equiv) was stirred with K_2CO_3 (4.0 equiv) in dry acetone for 120 h. The reaction mixture was then acidified with 4 M HCl (10 mL) and evaporated to dryness. The residue was extracted with CH_2Cl_2 (3×100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the organic layer gave a residue, which was purified by column chromatography using hexane/$CHCl_3$ (1:4) to give the corresponding bicompartmental cyclophane.

3.8.1. Bicompartmental cyclophane 10. Colourless solid; yield 18%; R_f 0.55 (hexane/$CHCl_3$ 3:1); mp 190–192 °C; IR (cm^{-1}) 2915, 1650, 1550, 1300, 1235, 1019, 665; ^1H NMR ($CDCl_3$) δ 7.30 (8H, d, *J* 8.4 Hz, Ph), 7.28 (4H, s, Ph), 7.25 (2H, s, Ph), 6.99 (8H, d, *J* 8.4 Hz, Ph), 5.80 (12H, s, CH$_2$OPh), 4.60 (8H, s, C*H*$_2$SPh), 3.80 (6H, s, O*Me*), 2.32 (6H, s, *Me*); ^{13}C NMR ($CDCl_3$) 158.4, 154.2, 134.3, 133.3, 130.8, 129.9, 128.1, 114.9, 114.7, 71.6, 65.4, 65.2, 65.1, 63.1, 59.8, 21.0; *m*/*z* 918 (M^+); Anal. Calcd for $C_{56}H_{54}O_8S_2$: C, 73.20; H, 5.88: Found: C, 73.21; H, 5.89.

3.8.2. Bicompartmental cyclophane 11. Colourless solid; yield 16%; R_f 0.5 (hexane/$CHCl_3$ 3:1); mp 182–185 °C; IR (cm^{-1}) 2980, 1728, 1609, 1520, 1308, 1212, 666; ^1H NMR ($CDCl_3$) δ 7.30 (4H, d, *J* 8.6 Hz, Ph), 7.25 (4H, m, Ph), 7.21 (4H, d, *J* 8.6 Hz, Ph), 7.15 (2H, s, Ph), 6.82 (4H, d, *J* 8.6 Hz, Ph), 6.80 (4H, d, *J* 8.6 Hz, Ph), 5.15 (4H, s, C*H*$_2$OPh), 5.13 (4H, s, C*H*$_2$OPh), 4.66 (4H, s, C*H*$_2$OPh), 4.10 (4H, s, C*H*$_2$SPh), 4.09 (4H, s, C*H*$_2$SPh), 3.97 (3H, s, COO*Me*), 3.80 (3H, s, O*Me*), 2.27 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) 168.0, 152.8, 133.6, 133.1, 132.8, 132.4, 131.3, 131.0, 130.1, 129.8, 129.4, 128.9, 128.8, 127.5, 124.3, 124.0, 117.9, 115.3, 114.1, 111.2, 68.3, 38.8, 32.0, 29.5, 23.8, 23.1, 22.8; *m*/*z* 979 (M^+); Anal. Calcd for $C_{56}H_{51}O_{11}S_2N$: C, 68.78; H, 5.22; N, 1.43. Found: C, 68.79; H, 5.21; N, 1.44.

3.8.3. Bicompartmental cyclophane 12. Colourless solid; yield 16%; R_f 0.6 (hexane/$CHCl_3$ 3:1); mp123–126 °C; IR (cm^{-1}) 2958, 1653, 1206, 658; ^1H NMR ($CDCl_3$) δ 8.80 (4H, m, Ph), 7.50 (4H, d, *J* 8.4 Hz, Ph), 7.45–7.47 (4H, m, Ph), 7.41 (4H, d, *J* 8.4 Hz, Ph), 7.32 (4H, d, *J* 8.4 Hz, Ph), 7.12 (4H, d, *J* 8.4 Hz, Ph), 5.92 (4H, s, C*H*$_2$OPh), 4.33 (4H, s, C*H*$_2$OPh), 4.00 (4H, s, C*H*$_2$OPh), 3.98 (8H, s, C*H*$_2$SPh), 3.34 (3H, s, O*Me*), 2.04 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ 152.7, 151.7, 130.8, 129.5, 128.3, 127.8, 127.3, 126.9, 126.3, 125.9, 124.5, 124.4, 124.1, 123.8, 121.2,

118.2, 117.9, 115.5, 46.2, 44.1, 42.8, 40.7, 40.5, 40.3, 38.2; *m/z* 874 (M^+); Anal. Calcd for $C_{54}H_{50}O_7S_2$: C, 74.14; H, 5.72. Found: C, 74.15; H, 5.73.

3.8.4. Bicompartmental cyclophane 13. Colourless solid; yield 19%; R_f 0.55 (hexane/$CHCl_3$ 3:1); $[\alpha]_D^{25}$ −108 (*c* 0.2, $CHCl_3$); mp 175–178 °C; IR (cm^{-1}) 2915, 1729, 1646, 1201, 693; ^1H NMR ($CDCl_3$) δ 8.06 (2H, s, Ph), 8.02 (2H, s, Ph), 7.90–7.95 (4H, m, Binol *H*), 7.8 (4H, d, *J* 8.4 Hz, Ph), 7.41–7.44 (4H, m, Binol *H*), 7.34–7.35 (2H, m, Binol *H*), 7.25–7.30 (2H, m, Binol *H*), 7.12 (4H, d, *J* 8.4 Hz, Ph), 5.95 (4H, s, C*H*$_2$OPh), 4.45 (4H, s, C*H*$_2$OPh), 3.79 (4H, s, C*H*$_2$SPh), 3.78 (4H, s, C*H*$_2$SPh), 3.71 (3H, s, O*Me*), 2.09 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ 172.1, 152.6, 133.6, 133.4, 131.8, 131.3, 130.9, 130.7, 130.2, 129.4, 128.4, 128.2, 128.1, 127.7, 127.4, 127.2, 127.1, 126.9, 126.7, 126.3, 126.1, 125.9, 46.3, 42.9, 40.7, 40.6, 40.3, 28.2; *m/z* 926 (M^+); Anal. Calcd for $C_{56}H_{46}O_9S_2$: C, 72.57; H, 4.97. Found: C, 72.58; H, 4.98.

3.8.5. Bicompartmental cyclophane 19. Colourless solid; yield 19%; R_f 0.65 (hexane/$CHCl_3$ 3:1); mp 106–108 °C; IR (cm^{-1}) 2914, 1620, 1190, 997, 670; ^1H NMR ($CDCl_3$) δ 7.51 (4H, d, *J* 5.4 Hz, Ph), 7.37 (4H, d, *J* 5.4 Hz, Ph), 7.05 (4H, d, *J* 8.4 Hz, Ph), 6.91 (4H, d, *J* 8.4 Hz, Ph), 5.15 (12H, s, C*H*$_2$OPh), 4.55 (4H, s, C*H*$_2$SPh), 4.09 (4H, s, C*H*$_2$SPh); ^{13}C NMR ($CDCl_3$) δ 166.9, 162.4, 154.6, 134.5, 131.9, 131.7, 131.1, 129.4, 128.9, 114.4, 65.6, 65.2, 52.0, 30.1; *m/z* 830 (M^+); Anal. Calcd for $C_{52}H_{46}O_6S_2$: C, 75.18; H, 5.54. Found: C, 75.19; H, 5.55.

3.8.6. Bicompartmental cyclophane 20. Colourless solid; yield 17%; R_f 0.55 (hexane/$CHCl_3$ 3:1); mp 134–136 °C; IR (cm^{-1}) 2952, 1610, 1200, 1005, 665; ^1H NMR ($CDCl_3$) δ 7.39–7.40 (2H, s, Ph), 7.33 (4H, d, *J* 8.6 Hz, Ph), 7.25 (2H, s, Ph), 7.21 (4H, d, *J* 8.6 Hz, Ph), 7.15 (4H, m, Ph), 6.82 (4H, d, *J* 8.6 Hz, Ph), 6.77 (4H, d, *J* 8.6 Hz, Ph), 4.55 (4H, s, C*H*$_2$OPh), 4.50 (8H, s, C*H*$_2$OPh), 4.43 (4H, s, C*H*$_2$SPh), 4.37 (4H, s, C*H*$_2$SPh), 3.97 (3H, s, O*Me*), 3.80 (3H, s, *Me*); ^{13}C NMR ($CDCl_3$) δ 170.4, 162.9, 162.8, 158.2, 154.6, 154.4, 142.7, 142.5, 134.7, 132.8, 132.5, 131.3, 131.2, 130.7, 130.5, 121.1, 121.0, 120.8, 62.7, 62.3, 60.5, 39.8, 32.5, 27.8, 20.7; *m/z* 874 (M^+); Anal. Calcd for $C_{54}H_{50}O_7S_2$: C, 74.14; H, 5.72. Found: C, 74.15; H, 5.73.

3.8.7. Bicompartmental cyclophane 21. Colourless solid; yield 19%; R_f 0.6 (hexane/$CHCl_3$ 3:1); mp 157–160 °C; IR (cm^{-1}) 2928, 1720, 1650, 1525, 1358, 1218, 628; ^1H NMR ($CDCl_3$) δ 7.83 (4H, m, Ph), 7.59 (4H, m, Ph), 7.57 (4H, d, *J* 6.9 Hz, Ph), 7.52 (4H, d, *J* 6.9 Hz, Ph), 6.99 (4H, d, *J* 8.4 Hz, Ph), 6.66 (4H, d, *J* 8.4 Hz, Ph), 4.29 (4H, s, C*H*$_2$OPh), 4.10 (4H, s, C*H*$_2$OPh), 3.98 (4H, s, C*H*$_2$OPh), 3.86 (8H, s, C*H*$_2$SPh), 2.47 (3H, s, COOMe); ^{13}C NMR ($CDCl_3$) 163.4, 156.2, 140.1, 134.1, 132.9, 132.6, 132.0, 131.9, 130.5, 130.3, 129.9, 129.3, 129.2, 124.0, 115.8, 114.2, 113.9, 103.7, 77.6, 68.1, 67.9, 59.7, 53.4, 49.3, 35.0; *m/z* 933 (M^+); Anal. Calcd for $C_{54}H_{47}O_{10}S_2N$: C, 69.45; H, 5.04. Found: C, 69.46; H, 5.05.

3.8.8. Bicompartmental cyclophane 22. Colourless solid; yield 10%; R_f 0.5 (hexane/$CHCl_3$ 3:1); $[\alpha]_D^{25}$ −120 (*c* 0.2, $CHCl_3$); mp 118–120 °C; IR (cm^{-1}) 2958, 1710, 1201, 998, 706; ^1H NMR ($CDCl_3$) δ 7.95 (4H, d, *J* 9.2 Hz, Ph), 7.87–7.89 (4H, m, Binol *H*), 7.38 (2H, s, Ph), 7.36 (4H, d, *J* 9.2 Hz, Ph), 7.32–7.33 (4H, m, Ph), 7.30–7.31 (2H, m, Binol *H*), 7.28–7.29 (2H, m, Binol *H*), 7.25 (4H, s, Binol *H*), 5.11 (4H, s, C*H*$_2$OPh), 3.95 (4H, s, C*H*$_2$SPh), 3.38 (4H, s, C*H*$_2$SPh); ^{13}C NMR ($CDCl_3$) δ 188.2, 155.2, 153.2, 152.8, 152.0, 149.7, 146.3, 137.6, 136.0, 136.4, 135.8, 133.5, 132.8, 129.1, 128.9, 127.6, 127.5, 127.4, 127.2, 123.1, 83.3, 80.7, 80.2, 80.1, 27.8; *m/z* 882 (M^+); Anal. Calcd for $C_{54}H_{42}O_8S_2$: C, 73.47; H, 4.76. Found: C, 73.48; H, 4.77.

3.9. Complexation studies

Charge transfer complexation studies were carried out by preparing a 1×10^{-6} M solution of cyclophanes **10**, **19**, **20** and **21** with gradual addition of acceptor (2 mg) in DMF solvent (10 mL). Gradual addition of TCNQ to cyclophanes **10**, **19**, **20** and **21** rapidly increased the intensity of charge transfer bands at 751, 775 and 850 nm. The equilibrium constant was measured at 850 nm only. The equilibrium constant for the CT complex derived from **10**, **19**, **20** and **21** with TCNE was measured at 849 nm though absorption bands were also observed at 825 and 849 nm. Absorbance was measured at a suitable wavelength while the concentration of TCNQ and TCNE was varied and the concentration of the cyclophane receptor was kept constant. Plot of D_0/A (D_0 is the concentration of cyclophane and A is the concentration of acceptor) versus $1/A_0$ (A_0 is the absorbance of the complex at charge transfer transition) gave a straight line that indicated that the stoichiometry of the complex was 1:1. Applying Benesi–Hildebrabd equation, the reciprocal of the intercept on the *Y*-axis was used to provide ε^{AD} (ε of the donor–acceptor complex) and from the slope of the line K_c^{AD} (equilibrium constant of the donor–acceptor complex) was calculated. From this data the stability constants of the charge transfer complexes of cyclophanes **10**, **19**, **20** and **21** with the acceptors TCNQ and TCNE were determined.

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Oxidative cleavage of ribofuranose 5-(α-hydroxyphosphonates): a route to erythrofuranose-based nucleoside phosphonic acids

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Abstract—We report here an oxidative cleavage of (5*R*)- and (5*S*)-ribofuranosyl-5-*C*-phosphonate derivatives with periodate anion under both strong acidic and neutral conditions. In both cases, only (5*R*)-configured compound underwent the expected oxidation reaction and afforded the desired (4*R*)-erythrofuranosylphosphonate, whereas the second epimer, (5*S*)-ribofuranosyl-5-*C*-phosphonate did not provide the corresponding (4*S*)-erythrofuranosylphosphonate derivative. This different behavior of epimers toward oxidative cleavage is an important phenomenon. The obtained (4*R*)-erythrofuranosylphosphonate was used for the preparation of phosphonate mimic of adenosine 5′-phosphate via classical nucleosidation reaction. Condensation of the protected shortened AMP analogue with adenosine derivatives, however, provided only the 2′,5′-linked ApA analogue. Study on hybridization of the modified 2′-5′ ApA with polyU revealed its ability to form stable triplex-like complex, similar to natural 2′-5′ r(ApA) and 3′-5′ r(ApA). NMR spectroscopy study showed that the erythrofuranose part of the phosphonate nucleotide unit of modified 2′-5′ ApA was predominantly in the C2′-*endo* conformation, which is characteristic for B-DNA.

1. Introduction

Structurally diverse isopolar phosphonate nucleotide analogues containing a bridging *P–C* bond have attracted our attention for many years.[1–7] This class of compounds, known as nucleoside phosphonic acids, represents a pool of potential antimetabolites exhibiting absolute stability against phosphomonoesterase and nucleotidase cleavage.[8] Some of these compounds have already found clinical use as potent antivirals.[9–11] The search for novel nucleotide analogues can reveal new biologically active compounds capable of discriminating between cellular and viral or tumor enzymes of nucleic acid metabolism, which could be used as antiviral and/or anticancer agents. In addition, novel phosphonate nucleotide analogues can be used for the construction of isopolar chimeric oligonucleotides containing nuclease-stable internucleotide linkages,[7] for instance, similar to already prepared phosphonate 2′,5′-oligoadenylates, which are potent, enzyme stable RNase L activators[12] intended for RNase L-mediated cleavage of pathogenic RNA.[13]

Here we present the synthesis of the isopolar, nonisosteric AMP analogue **13**, a representative of a new class of modified nucleoside 5′-phosphates, the structure of which resembles the features of the earlier reported nucleoside phosphonic acids **1**[14,15] and **2**[16,17] (Fig. 1), and the *ribo* ApA dimer **18a** with the isopolar, shortened phosphonate internucleotide linkage.

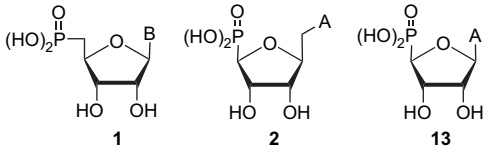

Figure 1.

2. Results and discussion

The strategy for the synthesis of **13** originated from the suitably protected ribofuranosyl-5-*C*-phosphonate derivative **7a**, the key compound obtained by a four-step synthesis from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**).[18] Benzoylation of **3** afforded compound **4**, which was selectively deprotected in 60% aqueous acetic acid at 50 °C to give **5**. Oxidation of the vicinal diol of **5** with sodium periodate in aqueous acetone resulted in the aldehyde **6**. Subsequent addition of diethyl phosphite to aldehyde **6** in the presence of triethylamine provided a 1:1 epimeric mixture of (*R*)- and (*S*)-5-*C*-phosphonates **7a** and **7b**, respectively, in an overall 54% yield (Scheme 1). The epimers were

Keywords: AMP analogue; Nucleoside phosphonic acid; Sugar phosphonate; Periodate oxidation; NMR conformational analysis.
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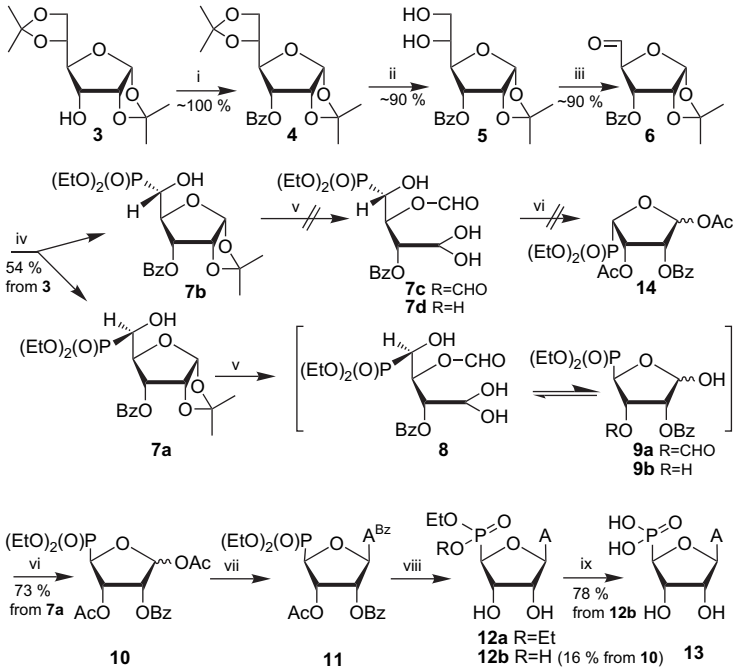


Scheme 1. (i) Benzoylcyanide, CH_3CN, TEA; (ii) 60% aq acetic acid, 50 °C, 3 h; (iii) $NaIO_4$, 70% aq acetone, 0 °C, 8 h; (iv) $HP(O)(OEt)_2$, TEA, DCM, 80 °C, 24 h; (v) (a) HIO_4, 50% aq dioxane, 60 °C, 3 days; (b) 0.1 M TEAB; (vi) Ac_2O, DMAP, pyridine, 16 h, rt; (vii) silylated 6-*N*-benzoyladenine, $SnCl_4$, CH_3CN, 24 h , rt; (viii) 1 M NaOH, 48 h, rt; (ix) Me_3SiBr, CH_3CN, 24 h, rt. Yields of compounds **4**, **5**, and **6** were estimated from TLC (compounds were used for further reaction step without purification).

separated by silica gel chromatography and subjected to subsequent oxidative cleavage separately.

2.1. Oxidative cleavage of 7a (Scheme 1)

Hydrolysis of the 1,2-*O*-isopropylidene group of **7a** and subsequent oxidative cleavage of the C1–C2 bond, performed in one step by aqueous periodic acid, led to an equilibrium mixture of **8** and **9a** in which the 3-*O*-formyl group protects the acyclic form **8** (if present) from further oxidative cleavage of the C4–C5 bond. We attempted to verify the presence of the 3-*O*-formyl group in the product (**8** or **9a**) but neither treatment with 0.1 M TEAB in aqueous dioxane[19] nor heating in 80% aqueous pyridine[20] changed the mobility on TLC or RP HPLC. It did not seem that the 3-*O*-formyl group in **8** could survive in strongly acidic conditions during several days' treatment with aqueous periodic acid. Thus, we concluded that the nascent acyclic form **8** has to undergo a very fast cyclization reaction to furanose **9a**. Then both the formyl derivative **9a** and the deformylated compound **9b** are resistant against oxidative cleavage by periodic acid. Since the subsequent acetylation resulted in the expected acetyl derivative **10** in good yield, the final product of oxidative cleavage of **7a** with periodic acid must have been predominantly the furanose **9b**.

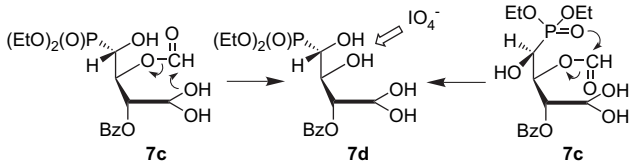
Note: the transformation of compound **9b** to **10**, which we performed several times has resulted in several cases in pure β-anomer of **10** (3-*O*-acetyl-2-*O*-benzoyl) but in several cases also in an anomeric mixture of both 3-*O*-acetyl-2-*O*-benzoyl and 2-*O*-acetyl-3-*O*-benzoyl regioisomers. We believe that each of these isomers afforded, after nucleosidation and deprotection, the identical product. The formation of the regioisomers (migration of the benzoyl group) seems to depend on the time of oxidation of **7a**, workup of **9a**, and conditions for acetylation of **9a** to **10**.

2.2. Oxidative cleavage of 7b (Scheme 1)

On the other hand, treatment of **7b** with periodic acid to obtain **14** caused a total decomposition of compound **7b** with the formation of a very complex mixture of derivatives. Application of a two-step procedure[20] using 90% aqueous TFA for hydrolysis of 1,2-*O*-isopropylidene group in **7b** in the first step, and then, after removal of TFA, sodium periodate oxidative cleavage in the second step also led to a total decomposition of **7b**. Under the same conditions, the epimer **7a** reacted as smoothly as with periodic acid alone and following acetylation provided a comparable yield of product **10**.

The nature of the very different reactivities of **7a** and **7b** toward periodic acid (or TFA–sodium periodate[20]) is not quite clear. The explanation for this phenomenon could perhaps be seen in the equilibrium between acyclic structure **7c** and its furanose form, which can be shifted in favor of the acyclic compound **7c**. Under such conditions, hydrolysis of the 3-*O*-formyl group in the acyclic structure **7c** leads to **7d** and this compound, bearing a C3–C4 vicinal diol, is immediately cleaved by periodic acid (or sodium periodate) (Scheme 2). It can be speculated that the cleavage of the *O*-formyl group could proceed in an oxidative manner via the extremely labile carbonic acid monoester (R-OCOOH) but, more likely, groupings like P═O or hydrated C1 aldehyde $CH(OH)_2$ in **7c** could facilitate the formyl group hydrolysis via intramolecular participation due to a favorable conformation (Scheme 2). Similarly, the different reactivity of epimers **7a** and **7b** toward acetolysis was described recently; whereas the epimer **7a** provided the expected

product, the second epimer **7b** afforded a mixture of compounds.[21]



Scheme 2. Proposed mechanisms of periodate degradation of (*S*)-configured 5-hydroxyphosphonate **7c**.

Concerning the different reactivity of **7a** and **7b** toward periodate oxidation, the separation of epimers **7a** and **7b** does not seem to be, from a practical point of view, too advantageous since the yield of **10**, when the reaction was carried out with an epimeric mixture, varied in the range of 38–51% whereas with pure epimer **7a**, it was 65–73%.

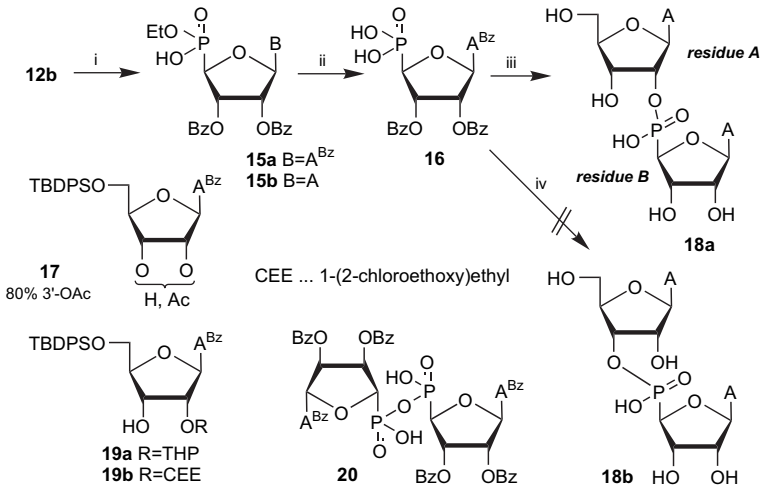
The nucleosidation reaction of the sugar phosphonate **10** with silylated 6-*N*-benzoyladenine in the presence of $SnCl_4$ provided a mixture of products in which the expected derivative **11** was not recognized. Therefore, the mixture was treated with concentrated aqueous ammonia to remove acyl-protecting groups, and the adenine-containing compounds were desalted on Dowex 50. A mixture of diethyl- and monoethyl ester **12a** and **12b** was obtained as the only products in a low yield of 13–20%. Diester **12a** was converted to the monoester **12b** by treatment with dilute sodium hydroxide and compound **12b** was isolated on Dowex 1 by a gradient elution with acetic acid in water. With respect to the low yield, the nucleosidation reaction, a weak point of the synthesis, still remains open for improvement. Replacement of tin tetrachloride by trimethylsilyl triflate in the nucleosidation reaction did not provide any of the expected products **12a** and **12b**. Compound **12b** was transformed into the free phosphonic acid **13** by treatment with bromotrimethylsilane in the presence of 2,6-lutidine to prevent potential furanose ring cleavage. Ion exchange chromatography on Dowex 1 afforded the pure free phosphonic acid **13**.

Since compound **13** is a 'shortened' nucleotide analogue, its incorporation into an oligonucleotide chain was considered to be very interesting with respect to hybridization properties of the modified chain. Shortening of the internucleotide linkage renders the chain with reduced number of degrees of freedom, which could positively influence hybridization ability as it was found recently for another type of shortened linkage.[22] For the study of changes induced by the presence of a modified internucleotide linkage, the dimers, as the shortest oligonucleotides capable of base-stacking and base-pairing, have been employed as model compounds.[23,24] For the synthesis of modified ApA dimers **18a** and **18b**, the monoester **12b** was benzoylated by *N*-benzoyltetrazole[25] to yield a mixture of fully and partially benzoylated phosphonates **15a** and **15b**, which was resolved by silica gel chromatography. Derivative **15a** was converted into the protected phosphonic acid **16** by bromotrimethylsilane treatment, and this compound was condensed with a mixture of 2′(3′)-*O*-acetyl derivatives **17** in pyridine using DCC. Deprotection in concentrated ammonia and chromatography on Dowex 1 in acetate form afforded only the 2′-5′ regioisomer **18a** in a low yield (15%). No 3′-5′ regioisomer **18b** was isolated. Concerning the ratio of the 2′-*O*- and 3′-*O*-acetyl derivatives of **17**, we found by NMR for regioisomers at the beginning of the condensation and after 48 h of standing in pyridine solution practically identical ratios (31:69 and 29:71, respectively). Since we still reasoned that 3′-5′ dimer **18b** was not obtained due to both low yield of condensation and relatively low content of 2′-*O*-acetyl regioisomer in the mixture of acetyl derivatives **17**, we prepared compounds **19a** and **19b** in which the 2′-hydroxyl was protected with nonmigrating, alkali-stable tetrahydropyranyl and 1-(2-chloroethoxy)ethyl groups, respectively, and condensed them with **16**. Surprisingly, also in this case we did not obtain the expected 3′-5′ isomer **18b**. Neither higher concentration of the reactants nor the presence of DMAP gave rise to the product **18b**. Concerning the formation of the phosphonate anhydride **20** as the primary product in the DCC-induced condensation, and its further activation by DCC, it can be concluded that the DCC-activated anhydride **20** cannot be attacked, due to a steric hindrance, by the 3′-hydroxyl of compounds **19a** and **19b**. We did not find any other reasonable explanation for this phenomenon.

2.3. Conformational features of dimer 18a

Strong NOE contacts between H-8 of the adenine, and H-2′ and H-3′ of the furanose ring in both nucleoside residues indicate the preferred *anti* conformation of both adenine moieties. The only interresidual NOE contact was observed between H-2′and H-8 that is commonly used for sequential assignment in oligonucleotides. From the vicinal proton couplings in the furanose rings (Table 2), a generalized Karplus–Haasnoot equation,[26] and the two-state pseudorotation model we could establish for dimer **18a** (Scheme 3) in aqueous solution a similar population of C3′-*endo* and C2′-*endo* form (ratio ≈58:42) for 'upper' furanose ring (residue A), whilst for the 'lower' furanose ring (residue B) the C2′-*endo* form significantly prevails (ratio C3′-*endo*:C2′-*endo* ≈ 14:86). For comparison, in natural *ribo* ApA dimers (for NMR data see Tables 1–3) we estimated the ratios of C3′-*endo*:C2′-*endo* form to be approximately 45:55 for 'upper' ring and 55:45 for 'lower' ring in the case of 2′-5′ r(ApA), and ≈58:42 for both rings in 3′-5′ r(ApA). The dimer **18a** differs from natural *ribo* ApA dimers mainly in the preference for the C2′-*endo* conformation in the 'lower' ring with a phosphonate group in position C4′.

Concerning the conformational features of the prepared dimer **18a**, we have subjected it to a study of hybridization properties with polyU to compare them with those of natural 2′-5′ r(ApA) and 3′-5′ r(ApA) isomers. The hypochromic effect of the complexes [**18a***polyU] at various ratios of **18a** and polyU was measured at 260 nm in the presence of Mg^{2+} ions at 3 °C, and at total base concentration of 0.15 mM. The obtained mixing curve exhibited a local minimum at 1A:2U ratio, indicating triplex-like complex formation (curve not shown). The same stoichiometry was found for both natural ApA dimers. The thermal characteristics of the complex [polyU***18a***polyU] exhibited only single transition profile suggesting direct dissociation of pseudo triplex structure into individual strands. Shortening of the internucleotide linkage in ApA analogue **18a** does not influence the complex stability in comparison with natural phosphodiester linkage. Under experimental conditions, the T_m value of the complex is 15 °C and lies very close



Scheme 3. (i) *N*-Benzoyltetrazole, DMAP, DMF, 55 °C; (ii) Me_3SiBr, CH_3CN, 24 h, rt; (iii) (a) **16**, DCC, pyridine, 5 days, rt; (b) 1 M TBAF in THF, 16 h, rt; (c) concd aq ammonia, 48 h, rt; (iv) (a) **16** and **17a** or **17b**, DCC, pyridine, 5 days, rt; (b) 1 M TBAF in THF, 16 h, rt; (c) concd aq ammonia, 48 h, rt; (d) aq 0.1 M HCl, 16 h, rt.

Table 1. Proton NMR chemical shifts

Compd	Solv.	H-1′	H-2′	H-3′	H-4′	H-5′	H-5″	H-2	H-8	Other protons
13	D_2O+NaOD	5.81	4.75	4.33	4.08	—	—	8.67	8.22	—
7a	DMSO	5.91	4.88	5.20	4.63	4.16	—	—	—	5′-OH: 6.10; 2×OEt: 3.95 (4H), 1.15 (3H), 1.09 (3H); *i*-Pr: 1.41 (3H), 1.26 (3H); Bz: 8.01 (2H), 7.65 (1H), 7.54 (1H)
7b	DMSO	5.90	4.90	4.96	4.43	3.99	—	—	—	5′-OH: 5.85; 2×OEt: 4.05 (4H), 1.22 (3H), 1.21 (3H); *i*-Pr: 1.42 (3H), 1.26 (3H); Bz: 8.02 (2H), 7.70 (1H), 7.56 (1H)
10	DMSO	6.27	5.53	5.69	4.57	—	—	—	—	2×OAc: 2.10 (3H), 1.96 (3H); Bz: 8.03 (2H), 7.71 (1H), 7.57 (2H); 2×OEt: 4.09 (4H), 1.25 (3H), 1.245 (3H)
	$CDCl_3$	6.34	5.64	5.90	4.44	—	—	—	—	2×OAc: 2.15 (3H), 2.01 (3H); Bz: 8.04 (2H), 7.62 (1H), 7.48 (2H); 2×OEt: 4.20 (4H), 1.35 (6H)
12b	DMSO	5.99	4.62	4.34	4.15	—	—	8.50	8.24	NH_2: 7.83; 2×OH: 5.69 and 5.61; OEt: 3.93 (2H), 1.16 (3H)
	D_2O	6.11	4.79	4.60	4.30	—	—	8.53	8.18	OEt: 3.98 (2H), 1.24 (3H)
18a residue A	D_2O	6.17	5.16	4.61	4.24	3.90	3.77	7.72	8.06	—
18a residue B		5.60	4.41	4.49	4.26	—	—	8.11	8.21	—
2′-5′ ApA residue A	D_2O	5.79	4.62	4.60	4.31	3.85	3.7	7.86	8.19	—
2′-5′ ApA residue B		5.92	4.53	4.46	4.32	4.32	4.14	8.01	8.13	—

Table 2. Coupling constants of protons

Compd	Solv.	Proton–proton						Proton–phosphorus				
		1′,2′	2′,3′	3′,4′	4′,5′	4′,5″	5′,5″	1′,P	2′,P	3′,P	4′,P	5′,P
13	D_2O	7.4	5.3	2.2	—	—	—			7.2	6.2	
7a	DMSO	3.9	5.6	7.6	2.4	—	—				3.9	13.0
7b	DMSO	3.8	5.1	8.5	2.7	—	—				2.7	13.0
10	DMSO	1.2	4.6	7.6	—	—	—			13.8	1.0	
	$CDCl_3$	1.4	4.7	8.0	—	—	—			14.2	0.9	
12b	DMSO	7.6	4.6	1.6	—	—	—	2.0		6.1	3.5	
	D_2O	6.7	5.1	3.1	—	—	—	1.2		7.8	4.3	
18a residue A	D_2O	4.1	5.3	5.5	2.2	3.2	13.1		9.3			
18a residue B	D_2O	6.9	4.8	2.4	—	—	—			7.4	5.4	
2′-5′ ApA residue A	D_2O	3.5	5.0	5.0	2.5	3.6	13.1			9.0		
2′-5′ ApA residue B	D_2O	4.1	5.1	5.4	2.5	3.8	12.2					3.8

Table 3. Carbon-13 NMR data

Compd	Solv.	Chemical shift (coupling constants J(C,P))										
		C-1′	C-2′	C-3′	C-4′	C-5′	P-OEt	C-2	C-4	C-5	C-6	C-8
7a[a]	DMSO	104.79	78.00	79.52 (12.7)	71.30	66.32 (165.0)	62.48 (6.8)	—	—	—	—	—
							62.21 (6.8)					
7b[b]	DMSO	104.79	77.15	78.20 (2.4)	72.24 (9.8)	65.70 (165.0)	62.68 (6.8)	—	—	—	—	—
							62.10 (6.8)					
10[c]	$CDCl_3$	98.31	74.11	70.51	75.41	—	63.41 (5.9)	—	—	—	—	—
							64.57 (5.9)					
12b	DMSO	87.32	74.53	71.15 (6.8)	81.38 (155.3)	—	61.22 (6.3)	156.48	151.32	119.25	156.48	140.26
12b	D_2O	89.27 (4.4)	77.88 (3.4)	73.93 (5.4)	83.97 (158.2)	—	64.57 (5.9)	155.57	152.01	121.28	158.30	142.85
18a residue A	D_2O	91.32 (6.4)	81.16 (6.3)	79.07 (2.9)	87.61	63.77	—	155.60	151.06	120.86	158.12	143.64
18a residue B	D_2O	88.76 (3.9)	73.27	73.56 (7.3)	84.88 (157.2)	—	—	154.66	150.33	120.77	157.47	141.91
2′-5′ ApA residue A	D_2O	87.23	72.55	73.09	83.24	60.23	—	151.55	147.76	118.26	154.58	138.51
2′-5′ ApA residue B	D_2O	88.77	73.88	68.98	82.37	64.04	—	152.12	147.13	117.78	154.45	139.47

[a] Additional signals, OBz: 165.22, 133.82, 129.70 (2), 129.57, 128.97 (2); >$C(CH_3)_2$: 112.57, 27.19, 26.94.
[b] Additional signals, OBz: 165.48, 134.16, 129.82 (2), 129.35, 129.25 (2); >$C(CH_3)_2$: 112.68, 27.06, 26.91.
[c] Additional signals, 2×OAc: 169.21, 169.06, 20.91, 20.33; OBz: 164.89, 133.72, 129.79 (2), 128.71, 128.58 (2).

to the T_m values of both 2′-5′ and 3′-5′ natural *ribo* (ApA) dimers, which are 13 and 16 °C, respectively.[23]

3. Conclusion

Only (*R*)-epimer of the erythrofuranosyl-4-*C*-phosphonate has been prepared via periodic acid-mediated oxidative cleavage of an epimeric mixture of the pentofuranosyl-5-*C*-phosphonate derivatives. We proposed a mechanism for explaining different reactivities of starting (5*R*)- and (5*S*)-pentofuranosylphosphonates toward oxidation. The usefulness of the prepared sugar phosphonate derivative for the synthesis of novel nucleoside phosphonic acids was proved at the nucleosidation reaction with protected adenine giving an isopolar, nonisosteric AMP analogue. Besides, the corresponding 2′-5′-linked diadenosine monophosphate analogue was prepared and its hybridization properties were evaluated. NMR spectroscopy study of the dimer showed that the sugar part of the *ribo*-configured phosphonate nucleotide unit was predominantly in the C2′-*endo* conformation, which is characteristic for B-DNA and not for RNA. The obtained results suggest that a thorough study on the synthesis of nucleoside phosphonic acids with various nucleobases, their 2′- and 3′-deoxy derivatives, and also their incorporation into longer oligonucleotides seems to be fully justified and highly desirable.

4. Experimental

4.1. General

Unless stated otherwise, the solvents were concentrated at 40 °C using a rotary evaporator. The products were dried over phosphorus pentoxide at 40–50 °C and 13 Pa. The course of the reactions was followed by TLC on silica gel Merck and Fluka UV 254 foils and the products were visualized by UV monitoring. Preparative column chromatography (PLC) was performed on silica gel (40–60 μm, Fluka) whereby the amount of sorbent used was 20–40 times the weight of the mixture separated. Elution was performed at the linear flow rate of 2–4 cm min^{-1}. For TLC and PLC runs, the following solvent systems were used (v/v): toluene–ethyl acetate 1:1 (T), chloroform–ethanol 9:1 (C), ethyl acetate–acetone–ethanol–water 4:1:1:1 (H1) and 12:2:2:1 (H3), 2-propanol–concentrated aqueous ammonia–water 7:1:2 (IPAW). The HPLC analyses were performed on a LC 5000 liquid chromatograph (INGOS, Czech Republic) using Luna C18 5 μm reverse phase column (4.6×150 mm; Phenomenex), by gradient of methanol in 0.1 M triethylammonium acetate buffer. Mass spectra (*m*/*z*) were recorded on ZAB-EQ (VG Analytical) instrument, using FAB in both positive and negative modes (ionization by Xe, accelerating voltage 8 kV) with glycerol–thioglycerol (3:1) and 2-hydroxyethyldisulfide as matrices. ^1H and ^{13}C NMR spectra were measured on Varian Unity 500 instrument (^1H at 500 MHz, ^{13}C at 125.7 MHz) in DMSO (referenced to the solvent signals δ_H=2.50 and δ_C=39.7), $CDCl_3$ (referenced to TMS), and D_2O (referenced to DSS). Signals in the ^1H NMR spectra were assigned to protons on the basis of chemical shifts, observed multiplicities, and homonuclear 2D-COSY experiments. Chemical shifts and interaction constants were obtained from a first-order spectra analysis as

read from expanded records. The exchange of hydroxyl protons for deuterium was carried out using several drops of tetradeuterioacetic acid. Assignments of signals in ^{13}C NMR spectra were accomplished on the basis of J-modulated spectra (APT) enabling to discriminate between C, CH, CH_2, and CH_3 signals, and in some cases confirmed by ^{1}H, ^{13}C-correlated HMQC spectra. The ^{1}H and ^{13}C NMR data are summarized in Tables 1–3.

4.2. (5*RS*)-3-*O*-Benzoyl-1,2-*O*-isopropylidene-D-ribofuranos-5-*C*-ylphosphonate (7a, 7b)

The 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[18] **3** (13.01 g, 50 mmol) was treated with benzoylcyanide (7.21 g, 55 mmol) and triethylamine (0.695 mL, 5 mmol) in acetonitrile (60 mL) at 0 °C under exclusion of moisture (TLC in T-1) overnight. The reaction mixture was quenched by addition of methanol (5 mL) and the solvent was evaporated in vacuo. The residue was dissolved in chloroform and the organic layer was washed several times with water. After evaporation of solvent, the benzoyl derivative **4** was treated with 60% aqueous acetic acid (600 mL) at 50 °C for 3 h (TLC in T-1 and C-1). The acid was evaporated in vacuo, the residue was taken into chloroform (300 mL), and the organic layer was washed with saturated aqueous solution of NaCl (250 mL). The layers were separated by centrifugation, the organic layer was washed with water (4×250 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in 70% aqueous acetone (650 mL) and to this solution, saturated aqueous solution of sodium periodate (12.84 g, 60 mmol) was added at 0 °C. Resulting solution was stirred for 8 h at rt (TLC in C-1) and, after cooling the mixture in an ice bath, the suspension was filtered through Celite. Filtration cake was washed with acetone, and the combined filtrates were evaporated. The residue was re-dissolved in acetone (200 mL) and the rest of sodium iodate was filtered off. Crude aldehyde **6** was co-distilled with dry toluene, dissolved in dichloromethane (50 mL), and treated with diethyl phosphite (7.74 mL, 60 mmol) and triethylamine (2.78 mL, 20 mmol) at 80 °C for 24 h (TLC in T-1 and C-1). The solvent was evaporated in vacuo and the crude epimeric phosphonates **7a** and **7b** were purified on silica gel using elution with a linear gradient of ethyl acetate in toluene. Yield: 1.27 g (5%) of **7a**, 1.82 g (7%) of **7b**, and 10.72 g (42%) of the mixture of **7a** and **7b**. HR-FAB calcd for $C_{19}H_{28}O_9P$ $(M+H)^+$: 431.1471; found: 431.1470. Compound **7a**: ν_{max} (KBr) 3430 (w, br, OH), 3243 (m, OH), 3072 (w, C–H), 2986 (m, CH_3), 2876 (w, CH_3), 1251 (s, P═O), 1219 (m), 1206 (m), 1131 (s, COCOC), 1032 (vs, POC), 1480 (w, OCH_2CH_3), 1602 (w), 1584 (w), 1492 (w), 1452 (w), 1731 (m, C═O), 1724 (s, C═O), 1275 (s, C═O), 1217 (s, $C(CH_3)_2$), 1098 (m, COCOC), 1002 (m), 688 (w) cm^{-1}. Compound **7b**: ν_{max} (KBr) 3506 (w, br, OH), 3272 (m, OH), 3066 (w, C–H), 2992 (m, CH_3), 2871 (w, CH_3), 1256 (s, P═O), 1236 (s, P═O), 1219 (m), 1206 (m), 1152 (s, COCOC), 1033 (vs, POC), 1601 (w), 1583 (w), 1492 (w), 1452 (w), 1731 (m, C═O), 1720 (s, C═O), 1711 (s, C═O), 1282 (s, C═O), 1100 (s, COCOC), 999 (m), 692 (w) cm^{-1}. Compound **7a**: δ_H (500 MHz, DMSO) 8.01 (2H, m, *ortho*-Ar-H), 7.65 (1H, m, *para*-Ar-H), 7.54 (2H, *meta*-Ar-H), 6.10 (1H, br s, OH), 5.91 (1H, d, *J*=3.9 Hz, H-1′), 5.20 (1H, dd, *J*=7.6, 5.6 Hz, H-3′), 4.88 (1H, dd, *J*=5.6, 3.9 Hz, H-2′), 4.63 (1H, ddd, *J*=7.6, 3.9, 2.4 Hz, H-4′), 4.16 (1H, *J*=13.0, 2.4 Hz, H-5′), 3.95 (4H, q, *J*=7.0 Hz, 2×OCH_2), 1.41 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.15 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.09 (3H, t, *J*=7.0 Hz, OCH_2CH_3); δ_C (125.7 MHz, DMSO) 165.22, 133.82, 129.70 (2), 129.57, 128.97 (2), 112.57, 104.79, 79.52 (d, *J*=12.7 Hz), 78.00, 71.30, 66.32 (d, *J*=165.0 Hz), 62.48 (d, *J*=6.8 Hz), 62.21 (d, *J*=6.8 Hz), 27.19, 26.94, 16.44 (d, *J*=5.9 Hz), 16.38 (d, *J*=4.4 Hz). Compound **7b**: δ_H (500 MHz, DMSO) 8.02 (2H, m, *ortho*-Ar-H), 7.70 (1H, m, *para*-Ar-H), 7.56 (2H, *meta*-Ar-H), 5.85 (1H, br s, OH), 5.90 (1H, d, *J*=3.8 Hz, H-1′), 4.96 (1H, dd, *J*=8.5, 5.1 Hz, H-3′), 4.90 (1H, dd, *J*=5.1, 3.8 Hz, H-2′), 4.43 (1H, dt, *J*=8.5, 2.7, 2.7 Hz, H-4′), 3.99 (1H, *J*=13.0, 2.7 Hz, H-5′), 4.05 (4H, q, *J*=7.0 Hz, 2×OCH_2), 1.42 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.22 (3H, t, *J*=7.0 Hz, OCH_2CH_3), 1.21 (3H, t, *J*=7.0 Hz, OCH_2CH_3); δ_C (125.7 MHz, DMSO) 165.48, 134.16, 129.82 (2), 129.35, 129.25 (2), 112.68, 104.79, 78.20 (d, *J*=2.4 Hz), 77.15, 72.24 (d, *J*=9.8 Hz), 68.68 (d, *J*=6.8 Hz), 62.10 (d, *J*=6.8 Hz), 27.06, 26.91, 16.69 (d, *J*=5.9 Hz), 16.62 (d, *J*=5.9 Hz). For ^{1}H and ^{13}C NMR data see Tables 1–3.

4.3. (4*R*)-Diethyl-[1,3-di-*O*-acetyl-2-*O*-benzoyl-D-erythrofuranos-4-yl]phosphonate (10)

Periodic acid dihydrate (0.99 g, 4.35 mmol) was added to a solution of phosphonate **7a** (1.25 g, 2.9 mmol) in 50% aqueous dioxane (20 mL), and the reaction mixture was heated at 60 °C in the dark for 1–3 days (TLC in C-1). The solution was treated with Dowex 1×2 in acetate form (10 mL) under stirring for 10 min to remove periodate and iodate anions, the resin was filtered off, washed with 50% dioxane (30 mL), and the combined filtrates were evaporated. The residue was co-distilled several times with water to remove acetic acid, and finally treated with 0.1 M TEAB (30 mL) for 20 min. The aqueous solution was evaporated to dryness, the crude **9b** was co-distilled with methanol (3×50 mL), dried with pyridine (3×10 mL), and treated with acetic anhydride (1.21 mL, 12.8 mmol) and DMAP (20 mg) in pyridine (12 mL) overnight (TLC in C-1). The reaction mixture was quenched by addition of water (1 mL) at 0 °C, the solvent was evaporated in vacuo, and the crude product **10** was purified on silica gel by elution with a linear gradient of acetone in toluene. Yield: 940 mg (73%, yellow oil) of **10** (β-anomer). HR-FAB calcd for $C_{19}H_{26}O_{10}P$ $(M+H)^+$: 445.1264; found: 445.1273. δ_H (500 MHz, $CDCl_3$) 8.04 (2H, m, *ortho*-Ar-H), 7.62 (1H, m, *para*-Ar-H), 7.48 (2H, *meta*-Ar-H), 6.34 (1H, d, *J*=1.4 Hz, H-1′), 5.90 (1H, ddd, *J*=14.2, 8.0, 4.7 Hz, H-3′), 5.64 (1H, dd, *J*=4.7, 1.4 Hz, H-2′), 4.44 (1H, dt, *J*=8.0, 0.9 Hz, H-4′), 4.20 (4H, q, *J*=7.0 Hz, 2×OCH_2), 2.15 (3H, s, OAc), 2.01 (3H, s, OAc), 1.35 (6H, t, *J*=7.0 Hz, 2×OCH_2CH_3); δ_C (125.7 MHz, $CDCl_3$) 169.21, 169.06, 164.89, 133.72, 129.79 (2), 128.71, 128.58 (2), 98.31, 75.41, 74.11, 70.51, 64.57 (d, *J*=5.9 Hz), 63.41 (d, *J*=5.9 Hz), 16.40 (2C, d, *J*=5.9 Hz), 20.91, 20.33. For ^{1}H and ^{13}C NMR data see Tables 1–3.

4.4. (4*R*)-Ethyl-[1-(adenin-9-yl)-1-deoxy-β-D-erythrofuranos-4-yl]phosphonate (12b)

6-*N*-Benzoyladenine (598 mg, 2.5 mmol) in hexamethyldisilazane (HMDS) (25 mL, 118 mmol) was refluxed in the presence of chlorotrimethylsilane (2.5 mL, 20 mmol) under

stirring and exclusion of moisture for 10 h. Volatiles were removed under reduced pressure and the resulting oil was co-distilled with xylene (2×15 mL) and acetonitrile (2×15 mL) to remove traces of HMDS and xylene, respectively. A solution of diethyl phosphonate **10** (940 mg, 2.1 mmol) (dried by co-distillation with toluene and acetonitrile) in acetonitrile (6 mL) was added via septum under argon to the silylated adenine derivative followed by the addition of tin tetrachloride (0.24 mL, 2 mmol). The mixture was kept at rt for 24 h (TLC in C-1, H-1). The reaction mixture was then diluted with pyridine (1 mL) and toluene (20 mL) and stirred overnight. The thick suspension (precipitated complex of tin tetrachloride with pyridine) was filtered through Celite, washed with chloroform, and the solvents were removed under diminished pressure. The residue was treated with aqueous 1 M NaOH (50 mL) at rt for 48 h to remove the acyl-protecting groups and one ethyl ester group from **12a** (TLC in C-1, H-1). The solution was neutralized by addition of Dowex 50 (H^+), the monoethyl ester **12b** was eluted with 2.5% aqueous ammonia, and the crude product **12b** was purified on Dowex 1×2 (CH_3COO^-) column (elution with a linear gradient of 0–0.5 M aqueous acetic acid). Yield: 160 mg (16%, related to **7a**) of ethyl phosphonate **12b**. HR-FAB calcd for $C_{11}H_{17}N_5O_6P$ $(M+H)^+$: 346.0917; found: 346.0913. δ_H (500 MHz, DMSO) 8.50 (1H, s, H-2), 8.24 (1H, s, H-8), 5.69 (1H, br s, OH), 5.61 (1H, s, OH), 5.99 (1H, dd, J=7.6, 2.0 Hz, H-1′), 4.62 (1H, dd, J=7.6, 4.6 Hz, H-2′), 4.34 (1H, ddd, J=6.1, 4.6, 1.6 Hz, H-3′), 4.15 (1H, dd, J=3.5, 1.6 Hz, H-4′), 3.93 (2H, q, J=7.0, 2×OCH_2), 1.16 (3H, t, J=7.0 Hz, OCH_2CH_3); δ_C (125.7 MHz, DMSO) 156.48 (2), 151.32, 140.26, 119.25, 87.32, 81.38 (d, J=155.3 Hz), 74.53, 71.15 (d, J=6.8 Hz), 61.22 (d, J=6.3 Hz), 16.71 (d, J=4.9 Hz). For ^{1}H and ^{13}C NMR data see Tables 1–3.

4.5. (4*R*)-[1-(Adenin-9-yl)-1-deoxy-β-D-erythrofuranos-4-yl]phosphonic acid (13)

Carefully dried phosphonate **12b** (142 mg, 0.41 mmol) was treated with bromotrimethylsilane (0.32 mL, 2.46 mmol) and 2,6-lutidine (0.29 mL, 2.46 mmol) in acetonitrile (5 mL) at rt for 20 h (TLC in C-1, H-1). The reaction mixture was concentrated in vacuo, 2 M TEAB (2 mL) was added, and the resulting solution was evaporated to dryness. The crude phosphonic acid **13** was purified on Dowex 1×2 (CH_3COO^- form) column (elution with a linear gradient of 0–0.5 M aqueous acetic acid). Conversion into the sodium salt on Dowex 50×2 (Na^+) and freeze-drying from water afforded 101 mg (78%) of phosphonic acid **13**. HR-FAB calcd for $C_9H_{11}N_5O_6P$ $(M-H)^-$: 316.0447; found: 316.0443; ν_{max} (KBr) 3407 (s, vbr, OH), 3184 (s, vbr, OH), 2800–2200 (m–w, P-OH), 1691 (vs, NH_3^+), 1647 (m, NH_2), 1506 (w), 1419 (m), 1330 (w), 1222 (m, br), 1161 (m, br), 1128 (s, br), 785 (w), 721 (w), 643 (w) cm^{-1}. Compound **13**: δ_H (500 MHz, D_2O+NaOD) 8.67 (1H, s, H-2), 8.22 (1H, s, H-8), 5.81 (1H, d, J=7.4 Hz, H-1′), 4.75 (1H, dd, J=7.4, 5.3 Hz, H-2′), 4.33 (1H, ddd, J=7.2, 5.3, 2.2 Hz, H-3′), 4.08 (1H, dd, J=6.2, 2.2 Hz, H-4′). For ^{1}H NMR data see Tables 1 and 2.

4.6. 2′(3′)-*O*-Acetyl-6-*N*-benzoyl-5′-*O*-*tert*-butyldiphenylsilyladenosine (17)

6-*N*-Benzoyl-5′-*O*-*tert*-butyldiphenylsilyladenosine[1] (3 g, 4.92 mmol) was treated at rt with trimethyl orthoacetate (1 mL, 7.86 mmol) in DCM (50 mL) in the presence of toluenesulfonic acid hydrate (0.19 g, 1 mmol) at rt for 2 h. The resulting clear solution was washed with saturated aqueous solution of sodium hydrogen carbonate, the organic layer was dried over sodium sulfate, and evaporated. The residue was treated with 80% aqueous acetic acid (50 mL) for 30 min, the solution was concentrated in vacuo, and crude **17** was purified on a silica gel column in chloroform–10% ethanol. Yield: 2 g (62%; white foam) of **17** (a mixture of 2′-*O*-Ac and 3′-*O*-Ac regioisomers in a ratio 3:7 assigned from NMR). HR-FAB calcd for $C_{35}H_{38}N_5O_6Si$ $(M+H)^+$: 652.2591; found: 652.2581.

4.6.1. ^{1}H NMR (pyridine-d_5). Compound **17**, minor regioisomer (2′-*O*-Ac): 8.87 (1H, s, H-8), 8.77 (1H, s, H-2); 8.23 (2H, m), 7.75 (1H, m), 7.35 (2H, m, CO-C_6H_5), 7.75 (4H, m), 7.30–7.40 (6H, m, Si(C_6H_5)$_2$), 6.725 (1H, d, J(1′,2′)=4.1 Hz, H-1′), 6.32 (1H, dd, J(2′,1′)=4.1 Hz, J(2′,3′)=5.5 Hz, H-2′), 5.35 (1H, dd, J(3′,2′)=5.5 Hz, J(3′,4′)=5.0 Hz, H-3′), 4.56 (1H, ddd, J(4′,3′)=5.0 Hz, J(4′,5′)=3.2 Hz, J(4′,5″)=4.4 Hz, H-4′), 4.25 (1H, dd, J(5′,5″)=11.6 Hz, J(5′,4′)=3.2 Hz, H-5′), 4.11 (1H, dd, J(5″,5′)=11.6 Hz, J(5″,4′)=4.4 Hz, H-5″), 1.98 (3H, s, 2′-OAc), 0.99 (9H, s, C(CH_3)$_3$).

Compound **17**, major regioisomer (3′-*O*-Ac): 8.83 (1H, s, H-8), 8.78 (1H, s, H-2), 8.24 (2H, m), 7.75 (1H, m), 7.35 (2H, m, CO-C_6H_5), 7.75 (4H, m), 7.30–7.40 (6H, m, Si(C_6H_5)$_2$), 6.625 (1H, d, J(1′,2′)=6.0 Hz, H-1′), 5.58 (1H, dd, J(2′,1′)=6.0 Hz, J(2′,3′)=5.5 Hz, H-2′), 5.94 (1H, dd, J(3′,2′)=5.5 Hz, J(3′,4′)=3.9 Hz, H-3′), 4.59 (1H, q, J(4′,3′)=3.9 Hz, J(4′,5′)=4.0 Hz, J(4′,5″)=4.5 Hz, H-4′), 4.18 (1H, dd, J(5′,5″)=11.5 Hz, J(5′,4′)=4.0 Hz, H-5′), 4.06 (1H, dd, J(5″,5′)=11.5 Hz, J(5″,4′)=4.5 Hz, H-5″), 2.06 (3H, s, 2′-OAc), 1.02 (9H, s, C(CH_3)$_3$).

4.6.2. ^{13}C NMR (pyridine-d_5). Compound **17**, minor regioisomer (2′-*O*-Ac): 169.72 (CO(Ac)), 167.40 (N-CO), 151.95 (C-2), 151.67 (C-4), 151.17 (C-6), 142.35 (C-8), 125.52 (C-5), 137.40–127.40 (3×C_6H_5), 86.78 (C-1′), 85.11 (C-4′); 76.05 (C-2′), 68.74 (C-3′), 63.53 (C-5′), 20.10 (CH_3(Ac)), 18.76 and 26.32 (Si-C(CH_3)$_3$).

Compound **17**, major regioisomer (3′-*O*-Ac): 169.86 (CO(Ac)), 167.40 (N-CO), 152.47 (C-4), 151.95 (C-2), 151.17 (C-6), 142.02 (C-8), 125.52 (C-5), 137.40–127.40 (3×C_6H_5), 88.66 (C-1′), 82.78 (C-4′), 72.51 (C-2′), 72.88 (C-3′), 63.85 (C-5′), 20.27 (CH_3(Ac)), 18.76 and 26.36 (Si-C(CH_3)$_3$).

4.7. Adenosin-2′-yl-(4*R*)-[1-(adenin-9-yl)-1-deoxy-β-D-erythrofuranos-4-yl]phosphonate (18a)

A mixture of phosphonate **12b** (391 mg, 1.13 mmol), aqueous 1.89 M tetraethylammonium hydroxide (0.598 mL, 1.13 mmol), and ethanol (10 mL) was evaporated to dryness, and the residue was dried by co-distillation with ethanol (2×15 mL) and DMF (2×10 mL). Resulting tetraethylammonium salt of the phosphonate **12b** was treated with benzoyltetrazole (1.18 g, 6.8 mmol) in DMF (10 mL) in the presence of DMAP (0.83 g, 6.8 mmol) at 55 °C under exclusion of moisture until the starting compound disappeared (ca. 24 h, TLC in H-1). The reaction mixture was quenched

by addition of methanol (0.5 mL) and the solvent was evaporated in vacuo. The residue was treated with 60% aqueous pyridine overnight to destroy the mixed anhydride. The solvent was evaporated in vacuo, and the residue was partitioned between chloroform (150 mL) and 1 M TEAB (3×100 mL). The organic layer was dried over anhydrous Na_2SO_4 and the crude product **15a** was purified on silica gel (elution with a linear gradient of H-3 in ethyl acetate followed by H-1 in H-3). Yield: 299 mg (40%) of **15a** and 141 mg (24%) of **15b**. HR-FAB calcd for $C_{32}H_{29}N_5O_9P$ $(M+H)^+$: 658.1703; found: 658.1704.

4.7.1. Preparation of protected phosphonic acid 16. The carefully dried phosphonate **15b** (265 mg, 0.4 mmol) was treated with bromotrimethylsilane (0.26 mL, 2.0 mmol) and 2,6-lutidine (0.23 mL, 2.0 mmol) in acetonitrile (4 mL) at rt for 48 h (TLC in H-1). The reaction mixture was concentrated in vacuo, 2 M TEAB (2 mL) was added, the solution was evaporated, and the product **16** was purified by reversed-phase chromatography (elution with a linear gradient of methanol in water). Yield: 190 mg (75%) of triethylammonium salt of **16**. HR-FAB calcd for $C_{30}H_{25}N_5O_9P$ $(M+H)^+$: 630.1390; found: 630.1383.

4.7.2. Preparation of dimer 18a. A mixture of triethylammonium salt of the phosphonic acid **16** (190 mg, 0.3 mmol) and 2′(3′)-*O*-acetyl-6-*N*-benzoyl-5′-*O*-*tert*-butyldiphenylsilyladenosine (**17**) (254 mg, 0.4 mmol) was treated with DCC (619 mg, 3 mmol) in pyridine (4 mL) at rt overnight and then concentrated to a thick oil that was set aside at rt for 5 days (disappearance of the starting phosphonic acid **16**, TLC in H-1). Reaction mixture was diluted with 60% aqueous pyridine (10 mL) and, after 2 h of standing, concentrated in vacuo. The residue was co-distilled with ethanol (2×20 mL) and toluene (2×10 mL), and finally treated, under stirring and exclusion of moisture, with 0.5 M TBAF in tetrahydrofuran (5 mL, 2.5 mmol) at rt for 16 h (TLC in H-1). The reaction mixture was diluted with concentrated aqueous ammonia (50 mL), the suspension was stirred at rt for 3 days, and then evaporated to dryness. The residue in 50% aqueous ethanol (20 mL) was deionized (removal of *tetra*-*n*-butylammonium cations) on Dowex 50×2 (Et_3NH^+), the resin was filtered off, washed with aqueous ethanol, and the combined filtrates were concentrated. The residue was suspended in 3% aqueous ammonia (50 mL) under sonication, dicyclohexylurea was filtered off, the filtrate was evaporated, and the crude dimer **18a** was purified on Dowex 1×2 (CH_3COO^-) column (elution with a linear gradient of aqueous 0–0.5 M acetic acid). Conversion into the sodium salt on Dowex 50×2 (Na^+) and freeze-drying from water afforded 26 mg (15%) of 2′,5′-isomer **18a**. HR-FAB calcd for $C_{19}H_{24}N_{10}O_9P$ $(M+H)^+$: 567.1466; found: 567.1469. ν_{max} (KBr) 3401 (s, br, OH), 3192 (br, OH), 1646 (vs, NH_2), 1602 (m), 1578 (m), 1507 (w), 1420 (w), 1333 (m), 1216 (m, br, P═O), 1068 (s, br, C-OH), 797 (w), 725 (w), 648 (w), 550 (w, br, POC) cm^{-1}. Compound **18a**: δ_H (500 MHz, D_2O) 8.21 (1H, s, H-8 (res. B)), 8.11 (1H, s, H-2 (res. B)), 8.06 (1H, s, H-8 (res.A)), 7.72 (1H, s, H-2 (res.A)), 6.17 (1H, d, *J*=4.1 Hz, H-1′ (res. A)), 5.60 (1H, d, *J*=6.9 Hz, H-1′ (res. B)), 5.16 (1H, ddd, *J*=9.3, 5.3, 4.1 Hz, H-2′ (res. A)), 4.61 (1H, dd, *J*=5.5, 5.3 Hz, H-3′ (res. A)), 4.49 (1H, ddd, *J*=7.4, 4.8, 2.4 Hz, H-3′ (res. B)), 4.41 (1H, dd, *J*=6.9, 4.8 Hz, H-2′ (res. B)), 4.26 (1H, dd, *J*=5.4, 2.4 Hz, H-4′ (res. B)), 4.24 (1H, ddd, *J*=5.5, 3.2, 2.2 Hz, H-4′ (res. A)), 3.90 (1H, dd, *J*=13.1, 2.2 Hz, H-5′ (res. A)), 3.77 (1H, dd, *J*=13.1, 3.2 Hz, H-5″ (res. A)); δ_C (125.7 MHz, D_2O) 158.12, 157.47, 155.60, 154.66, 151.06, 150.33, 143.64, 141.91, 120.86, 120.77, 91.32 (d, *J*=6.4 Hz), 88.76 (d, *J*=3.9 Hz), 87.61, 84.88 (d, *J*=157.2 Hz), 81.16 (d, *J*=6.3 Hz), 79.07 (d, *J*=2.9 Hz), 73.56 (d, *J*=7.3 Hz), 73.27, 63.77. For ^1H and ^{13}C NMR data see Tables 1–3.

4.8. 6-*N*-Benzoyl-5′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-(tetrahydropyran-2-yl)adenosine (19a)

6-*N*-Benzoyl-2′-*O*-(tetrahydropyran-2-yl)adenosine[27] (0.456 g, 1 mmol) was treated with *tert*-butylchlorodiphenylsilane (0.3 mL, 1.15 mmol) in pyridine (3 mL) at rt for 48 h (TLC in C-1). The reaction mixture was quenched by addition of methanol (0.2 mL) followed by triethylamine (0.2 mL, 1.4 mmol), the resulting suspension was diluted with ethyl acetate (20 mL), filtered, the precipitate was washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was applied on a silica gel column in chloroform and the compound was eluted with a linear gradient of ethanol in chloroform (0→10%). Yield: 0.645 g (93%, white foam) of **19a** (a mixture of diastereoisomers). HR-FAB calcd for $C_{38}H_{44}N_5O_6Si$ $(M+H)^+$: 694.3061; found: 694.3052. Compound **19a**: δ_H (500 MHz, DMSO) mixture of two diastereoisomers in the ratio∼1:1; most of the signals are doubled: 11.20 (2H, br s, NH), 8.655 (1H, s), 8.65 (1H), 8.60 (1H, s), 8.59 (1H, s, H-2 and H-8), 8.05 (4H, m), 7.70–7.50 (13H, m), 7.50–7.30 (13H, m, 2×C_6H_5 (TBDPS) and C_6H_5 (N-Bz)), 6.235 (1H, d, *J*=5.6 Hz), 6.23 (1H, d, *J*=6.0 Hz, H-1′), 5.41 (1H, d, *J*=5.5 Hz), 5.26 (1H, d, *J*=5.8 Hz, 3′-OH), 4.96 (1H, t, *J*=5.5 Hz), 4.95 (1H, t, *J*=5.1 Hz, H-2′), 4.76 (1H, dd, *J*=3.7, 2.7 Hz), 4.66 (1H, t, *J*=3.5 Hz), 3.40 (2H, m), 3.28 (1H, m), 3.13 (1H, m), 1.90–1.20 (12H, m, OTHP), 4.52 (1H, m), 4.51 (1H, m, H-3′), 4.12 (1H, m), 4.115 (1H, m, H-4′), 3.96 (1H, dd), 3.955 (1H, dd, *J*=11.2, 3.5 Hz, H-5′a), 3.82 (1H, dd), 3.815 (1H, dd, *J*=11.2, 4.5 Hz, H-5′b), 0.98 (18H, s, *t*-Bu).

4.9. 6-*N*-Benzoyl-5′-*O*-*tert*-butyldiphenylsilyl-2′-*O*-[1-(2-chloroethoxy)ethyl]adenosine (19b)

6-*N*-Benzoyl-2′-*O*-[1-(2-chloroethoxy)ethyl]adenosine[28] (0.487 g, 1 mmol) was treated with *tert*-butylchlorodiphenylsilane (0.3 mL, 1.15 mmol) in pyridine (3 mL) at rt for 48 h (TLC in C-1). The workup of the reaction mixture was performed as described for **19a**. Yield: 0.609 g (85%, white foam) of **19b** (a mixture of diastereoisomers). HR-FAB calcd for $C_{37}H_{43}ClN_5O_6Si$ $(M+H)^+$: 716.2671; found: 716.2679. Compound **19b**: δ_H (500 MHz, DMSO) mixture of two diastereoisomers in the ratio ∼1.7:1. Major diastereoisomer: 11.25 (1H, br s, NH), 8.68 (1H, s), 8.62 (1H, H-2 and H-8), 8.05 (2H, m), 7.70–7.30 (13H, m, 2×C_6H_5 (TBDPS) and C_6H_5 (N-Bz)), 6.193 (1H, d, *J*=5.6 Hz, H-1′), 5.38 (1H, d, *J*=5.6 Hz, 3′-OH), 4.935 (1H, br t, *J*=5.2 Hz, H-2′), 4.88 (1H, q, *J*=5.4 Hz), 3.70–3.40 (4H, m), 1.24 (3H, d, *J*=5.4 Hz, 2′-O-CH(CH_3)-CH_2CH_2Cl), 4.47 (1H, br q, H-3′), 4.12 (1H, br q, H-4′), 3.987 (dd, 1H, *J*=11.5, 4.1 Hz, H-5′a), 3.847 (1H, dd, *J*=11.5, 4.9 Hz, H-5′b), 0.97 (9H, s, *t*-Bu). Minor diastereoisomer: 11.25 (1H, br s,

NH), 8.64 (1H, s), 8.62 (1H, H-2 and H-8), 8.05 (2H, m), 7.70–7.30 (13H, m, $2\times C_6H_5$ (TBDPS) and C_6H_5 (N-Bz)), 6.186 (1H, d, J=5.1 Hz, H-1′), 5.44 (1H, d, J=6.0 Hz, 3′-OH), 4.949 (1H, br t, J=5.1 Hz, H-2′), 4.55 (1H, br q, H-3′), 4.24 (1H, q, J=5.4 Hz), 3.70–3.40 (4H, m), and 1.19 (3H, d, J=5.4 Hz, (2′-O-CH(CH_3)-CH_2CH_2Cl)), 4.10 (1H, br q, H-4′), 3.989 (1H, dd, J=11.5, 3.9 Hz, H-5′a), 3.837 (1H, dd, J=11.5, 5.1 Hz, H-5′b), 0.99 (18H, s, *t*-Bu).

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Radical mediated stereoselective synthesis of (4*R*,8*R*)-4,8-dimethyldecanal, an aggregation pheromone of *Tribolium* flour beetles

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Abstract—(4*R*,8*R*)-4,8-Dimethyldecanal, a common aggregation pheromone of *Tribolium* flour beetles, has been synthesized from (*R*)-2,3-*O*-isopropylideneglyceraldehyde in 11 steps and 7% overall yield. The key step in the synthesis is the highly diastereoselective chelation-controlled radical reaction of ethyl (4*S*,5*R*)-4-benzyloxy-5,6-(isopropylidenedioxy)-2-methylenehexanoate with ethyl (*R*)-5-iodo-3-methylpentanoate performed in the presence of 7 equiv of $MgBr_2 \cdot OEt_2$.

1. Introduction

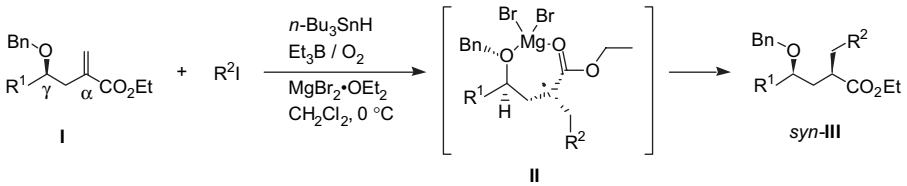
The 1,5-*syn*-dimethylalkyl motif is ubiquitous in many natural products such as tocopherols, several insect pheromones, and membrane lipids of archaebacteria. The stereoselective construction of the structural motif is therefore of particular interest[1–3] and we intend to apply the chelation-controlled radical reaction of γ-benzyloxy-α-methylenecarboxylic acid ester **I** yielding *syn*-adduct **III**, recently developed in our laboratory,[4] to the synthesis of these natural products (Scheme 1). The highly *syn*-selective addition of alkyl iodide R^2I to **I** is referred to the H-atom transfer to the outside face of radical center in the sharply folded seven-membered chelate intermediate **II**.[4c–e]

We now report the radical mediated stereoselective synthesis of (4*R*,8*R*)-4,8-dimethyldecanal (**1**), a common aggregation pheromone produced by the male flour beetles of *Tribolium castaneum*, *Tribolium confusum*, *Tribolium freemani*, and *Tribolium madens* (Coleoptera: Tenebrionidae).[5,6] The pheromone possessing a 1,5-dimethylalkyl motif would be synthesized by using the radical addition of alkyl iodide **IV** to optically active γ-benzyloxy-α-methylenecarboxylic acid ester **I** followed by the reduction of the ethoxycarbonyl group to a methyl group (Scheme 2).

The first synthesis of (4*R*,8*R*)-4,8-dimethyldecanal (**1**) and three other stereoisomers from (*R*)-citronellol and (*R*)-citronellic acid has established that the absolute configuration of the pheromone is (4*R*,8*R*).[7,8] Since the identification of the structure, several stereoselective syntheses of the pheromone **1** have been reported.[9]

2. Results and discussion

Scheme 3 shows the synthetic route of (4*R*,8*R*)-4,8-dimethyldecanal (**1**) starting from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**), which is prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol.[10] The Reformatsky reaction of aldehyde **2** with ethyl 2-(bromomethyl)propeonate (**3**) gave an inseparable diastereomeric mixture of γ-hydroxy



Scheme 1. Chelation-controlled diastereoselective radical reactions of α-methylene-γ-oxycarboxylic acid esters **I** with alkyl iodides R^2I yielding *syn*-adducts **III**.

Keywords: *Tribolium* flour beetle; Pheromone; (4*R*,8*R*)-4,8-Dimethyldecanal; Radical reaction; 1,3-Asymmetric induction.
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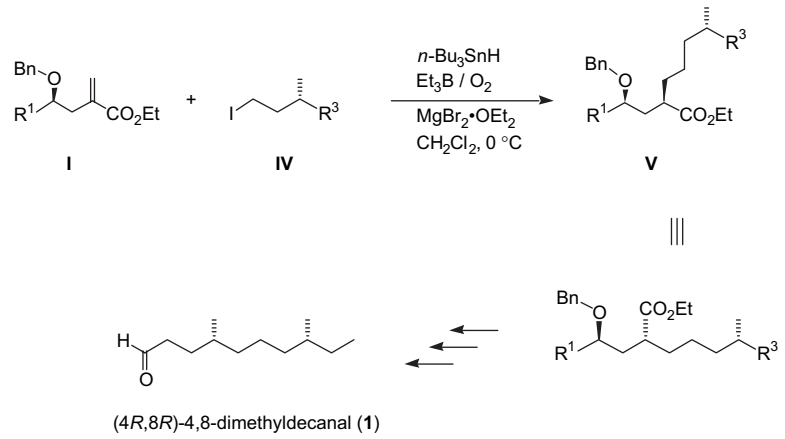
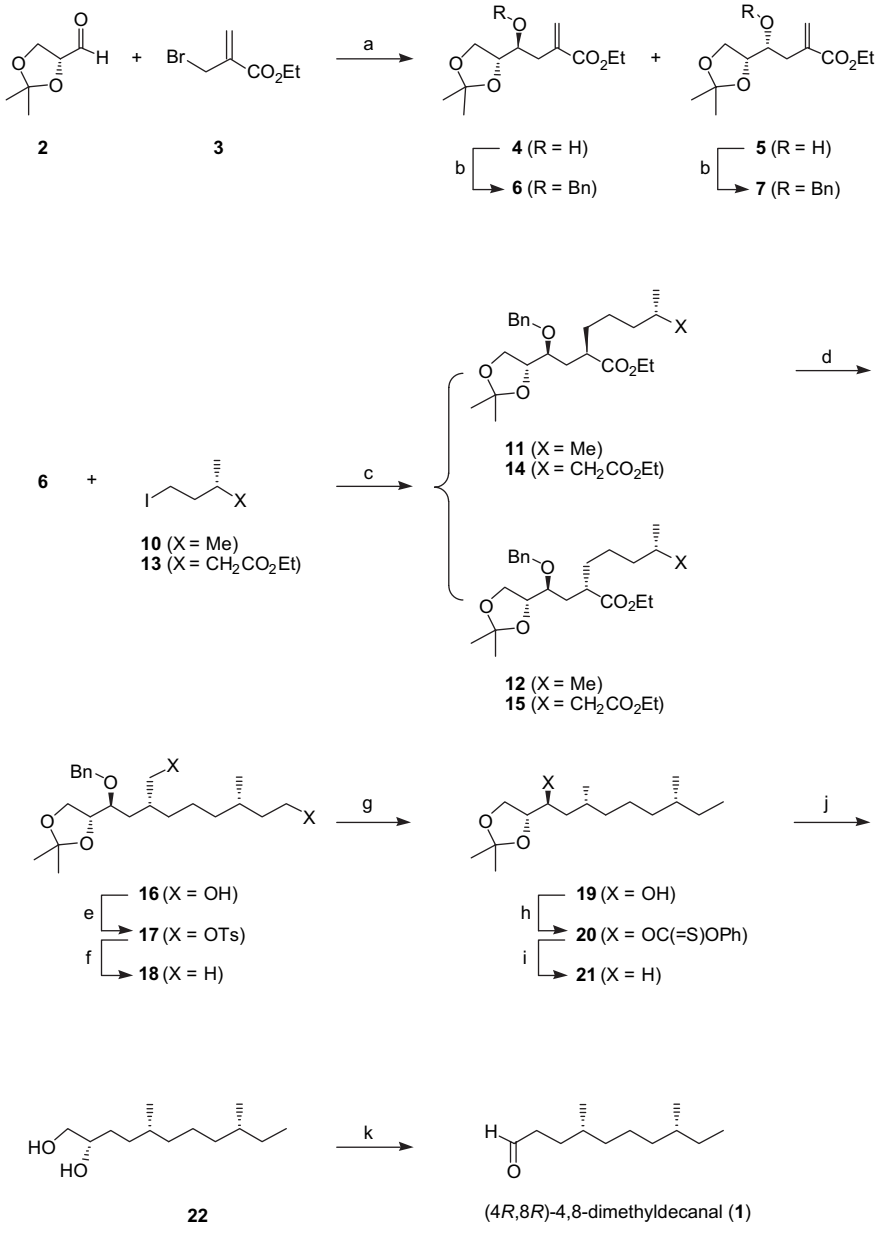
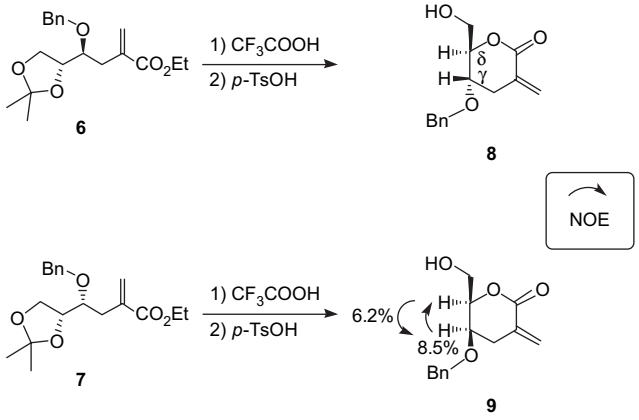


Scheme 2. Synthetic plan of (4*R*,8*R*)-4,8-dimethyldecanal (**1**).



Scheme 3. Synthetic route of (4*R*,8*R*)-4,8-dimethyldecanal (**1**). Reagents: (a) Zn, THF, aq NH_4Cl; (b) $PhCH_2Br$, Ag_2O, toluene; (c) *n*-Bu_3SnH, Et_3B, $MgBr_2 \cdot OEt_2$, CH_2Cl_2; (d) $LiAlH_4$, diethyl ether; (e) *p*-TsCl, pyridine, CH_2Cl_2; (f) $LiAlH_4$, diethyl ether; (g) H_2, Pd–C, ethanol; (h) $PhOC(=S)Cl$, pyridine, CH_2Cl_2; (i) *n*-Bu_3SnH, AIBN, toluene, 85 °C; (j) 1 mol dm^{-3} HCl, THF–H_2O (1:1); (k) $NaIO_4$, aq CH_3CN.

esters **4** and **5** in a ratio of 2.8:1.[11] Treatment of the mixture with benzyl bromide and silver oxide gave a mixture of benzyl ethers **6** and **7**, which was easily separated by silica gel column chromatography to give **6** in 26% yield from 1,2:5,6-di-*O*-isopropylidene-D-mannitol. To assign unambiguously the stereochemistry of the newly formed chiral center in the Reformatsky reaction,[11] the benzyl ethers **6** and **7** were transformed into δ-lactones **8** and **9**, respectively, and their NOE experiments were performed (Scheme 4). For the lactone **9**, NOE enhancements of γ-H (6.2%) and δ-H (8.5%) were observed by irradiating δ-H and γ-H, respectively, while for the lactone **8**, irradiation of γ-H and δ-H did not enhance the signals of their vicinal methine protons. The NOE difference spectra of the δ-lactones **8** and **9** thus established the stereochemistry of **6** and **7** as 4,5-*anti* and 4,5-*syn*, respectively.



Scheme 4. Determination of the configurations of **6** and **7**.

The radical reaction of the major diastereomer **6** with 1-iodo-3-methylbutane (**10**) was at first performed under the reaction conditions used in our previous work[4] [iodide **10** (3 equiv), *n*-Bu_3SnH (2 equiv), Et_3B (1 equiv), $MgBr_2\cdot OEt_2$ (3 equiv) in CH_2Cl_2 at 0 °C] to give the 2,4-*syn*-adduct **11** and 2,4-*anti*-adduct **12** in 63% yield and 14:1 diastereomer ratio. In order to ameliorate the stereoselectivity, the radical reaction was then performed using 7 equiv of $MgBr_2\cdot OEt_2$. The diastereoselectivity and yield were improved to **11**/**12**>50:1 and 73%, respectively.

In our previous work,[4c] we confirmed the seven-membered chelate ring formation of the starting material **I** (R^1=Ph) by the complexation experiment with 3 equiv of $MgBr_2\cdot OEt_2$ in $CDCl_3$. The large difference in chemical shift increments $\Delta\delta=[\delta_H$ (substrate+$MgBr_2\cdot OEt_2)-\delta_H$ (substrate)] by adding the Lewis acid between the diastereotopic β-methylene protons suggests the formation of bidentate complexation. However, in the complexation experiment of **6** with 3 equiv of $MgBr_2\cdot OEt_2$, only slight chemical shift increments were observed. The results of the complexation experiment of **6** with 7 equiv of $MgBr_2\cdot OEt_2$ are shown in Figure 1. The large $\Delta\delta$ values suggest that the addition of 7 equiv of the Lewis acid is required to achieve the chelate ring formation and the highly diastereoselective radical addition reaction.[12]

The radical addition of ethyl (*R*)-5-iodo-3-methylpentanoate (**13**)[13] to **6**, i.e., the key step in the synthesis of (4*R*,8*R*)-4,8-

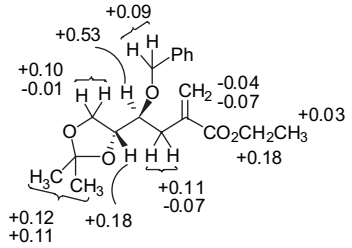
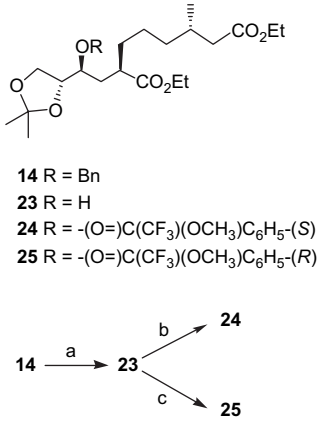


Figure 1. $\Delta\delta$ values (ppm) for the substrate **6**. $\Delta\delta_H=\delta_H$ (substrate **6**+$MgBr_2\cdot OEt_2)-\delta_H$ (substrate **6**). The δ_H (substrate **6**+$MgBr_2\cdot OEt_2$) value was obtained after sonication of **6** with 7 equiv of $MgBr_2\cdot OEt_2$ in $CDCl_3$.

dimethyldecanal (**1**), was carried out using 7 equiv of $MgBr_2\cdot OEt_2$. The desired 2,4-*syn*-adduct **14** was obtained in 71% yield and >96% de. The ^1H NMR and ^{13}C NMR spectra of α-methoxy-α-(trifluoromethyl)phenylacetates **24** and **25**, which were transformed from **14** via the corresponding alcohol **23**, did not show the epimerization of aldehyde **2** during the Reformatsky reaction of **2** with **3** (Scheme 5).



Scheme 5. Reagents: (a) H_2, Pd–C, ethanol; (b) (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 4-dimethylaminopyridine, pyridine; (c) (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 4-dimethylaminopyridine, pyridine.

The diester **14** was then reduced with lithium aluminium hydride to give the corresponding diol **16** in 89% yield. The tosylation of the diol with *p*-toluenesulfonyl chloride followed by the reduction with lithium aluminium hydride gave compound **18** in 76% yield. The hydrogenolysis of **18** over Pd–C gave alcohol **19** quantitatively. The alcohol was then treated with phenyl chlorothionoformate to give phenoxythiocarbonyl ester **20**, which was then reduced under radical conditions using AIBN and *n*-Bu_3SnH to give compound **21** in 71% two-step yield. The acid catalyzed hydrolysis of **21** followed by the oxidative cleavage of the resulting diol **22** with sodium periodate gave (4*R*,8*R*)-4,8-dimethyldecanal (**1**), as an oil, $[\alpha]_D^{23}$ −5.7 (*c* 1.0, $CHCl_3$) (lit.[7b] $[\alpha]_D^{22.5}$ −7.3 (*c* 2.04, $CHCl_3$)), in 85% two-step yield. The IR, ^1H NMR, ^{13}C NMR, and MS spectral data of the synthetic aldehyde **1** were identical with those of (4*R*,8*R*)- and (4*S*,8*S*)-4,8-dimethyldecanals reported in the literatures.[7,9,14]

We have thus synthesized (4*R*,8*R*)-4,8-dimethyldecanal (**1**) from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**) in 11 steps and 7% overall yield.

3. Conclusion

We have synthesized (4*R*,8*R*)-4,8-dimethyldecanal (**1**) from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**2**), easily prepared from D-mannitol, in 11 steps and 7% overall yield. The key step in the synthesis is the highly diastereoselective chelation-controlled radical reaction of γ-benzyloxy-α-methylenecarboxylic acid ester **6** and ethyl (*R*)-5-iodo-3-methylpentanoate (**13**) performed in the presence of 7 equiv of $MgBr_2 \cdot OEt_2$.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a JEOL GSX-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the instrument operating at 100.5 MHz with $CDCl_3$ as the solvent and internal standard (*δ* 77.0). IR spectra were taken on a SIMADZU FTIR-8700 spectrometer. Mass spectra (EI^+) were obtained on a JEOL JMS-700 mass spectrometer. Precoated Merck Kieselgel 60 F_{254} and Kanto silica gel 60 (spherical neutral) were used for thin layer chromatography and column chromatography, respectively.

4.1.1. Ethyl (4*S*,5*R*)- and (4*R*,5*R*)-4-hydroxy-5,6-(isopropylidenedioxy)-2-methylenehexanoates (4) and (5). (*R*)-2,3-*O*-Isopropylideneglyceraldehyde (**2**) was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.87 g, 10.9 mmol) following the reported procedures.[10] To a solution of the aldehyde **2** in THF (36 cm^3) were added ethyl 2-(bromomethyl)propeonate (**3**) (5.95 g, 30.8 mmol), saturated aqueous NH_4Cl (57 cm^3), and activated zinc powder (3.34 g, 51.3 mmol) and the mixture was stirred at 0 °C for 3 h. The product was extracted with ethyl acetate and the extract was washed with saturated brine and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (8:1)] to give an inseparable mixture of **4** and **5** (3.38 g, 63% yield from 1,2:5,6-di-*O*-isopropylidene-D-mannitol; **4**/**5**=2.8:1) as an oil. MS *m*/*z* 229 (M^+−Me, 68%), 143 (94), 123 (71), 101 (100); HRMS calcd for $C_{11}H_{17}O_5$ [M^+−Me] 229.1076, found 229.1082. *Major diastereomer* **4**. ^{1}H NMR *δ* 1.32 (3H, t, *J*=7.2 Hz, CH_3), 1.36 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.37 (1H, ddd, *J*=14.2, 8.4, 0.8 Hz, C*H*HC=CH_2), 2.70 (1H, ddd, *J*=14.2, 3.6, 0.8 Hz, CH*H*C=CH2), 2.86 (1H, d, *J*=3.6 Hz, OH), 3.75–4.10 (4H, m, C*H*(–O)C*H*OH, $CO_2CH_2CH_3$), 4.21 (1H, dd, *J*=14.2, 7.0 Hz, C*H*HO), 4.25 (1H, dd, *J*=14.2, 7.0 Hz, CH*H*O), 5.74 (1H, d, *J*=1.6 Hz, C=C*H*H), 6.29 (1H, d, *J*=1.2 Hz, C=CH*H*); ^{13}C NMR *δ* 14.20, 25.30, 26.67, 36.15, 61.19, 65.94, 71.28, 78.10, 109.12, 128.00, 136.92, 167.89. *Minor diastereomer* **5**. ^{1}H NMR *δ* 1.31 (3H, t, *J*=7.2 Hz, CH_3), 1.37 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.41–2.49 (2H, m, CH_2C=CH_2), 2.86 (1H, d, *J*=3.6 Hz, OH), 3.75–4.10 (4H, m, C*H*(–O)C*H*OH, $CO_2CH_2CH_3$), 4.20 (1H, dd, *J*=14.2, 6.8 Hz, C*H*HO), 4.23 (1H, dd, *J*=14.2, 6.8 Hz, CH*H*O), 5.72 (1H, d, *J*=1.6 Hz, C=C*H*H), 6.28 (1H, d, *J*=1.2 Hz, C=CH*H*); ^{13}C NMR *δ* 14.22, 25.30, 26.58, 36.77, 60.93, 66.00, 70.62, 78.40, 109.36, 127.69, 136.64, 167.08.

4.1.2. Ethyl (4*S*,5*R*)- and (4*R*,5*R*)-4-benzyloxy-5,6-(isopropylidenedioxy)-2-methylenehexanoates (6) and (7). To a solution of alcohols **4** and **5** (29.2 mg, 0.12 mmol) in toluene (2 cm^3) were added benzyl bromide (0.05 cm^3, 0.36 mmol) and freshly prepared silver oxide (84.5 mg, 0.36 mmol). The mixture was stirred at room temperature for 48 h and then filtered through a pad of Celite. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (20:1)] to give **6** (14 mg) and **7** (8.3 mg), and **6** (12.3 mg). *Major diastereomer* **6**. $[\alpha]_D^{23}$ +22.0 (*c* 1.95, $CHCl_3$); ^{1}H NMR *δ* 1.28 (3H, t, *J*=7.0 Hz, CH_3), 1.35 (3H, s, CH_3), 1.43 (3H, s, CH_3), 2.46 (1H, dd, *J*=14.2, 7.8 Hz, C*H*HC=CH_2), 2.72 (1H, ddd, *J*=14.2, 4.4, 0.8 Hz, CH*H*C=CH_2), 3.73 (1H, m, CH–O), 3.90 (1H, dd, *J*=7.8, 6.0 Hz, C*H*H–O), 4.03 (1H, d, *J*=7.8, 6.4 Hz, CH*H*–O), 4.12 (1H, dd, *J*=10.5, 6.0 Hz, CH–O), 4.16 (2H, q, *J*=7.0 Hz, CH_2–O), 4.59 (2H, s, PhCH_2O), 5.68 (1H, d, *J*=1.2 Hz, C=C*H*H), 6.23 (1H, d, *J*=1.2 Hz, C=CH*H*), 7.28–7.32 (5H, m, Ph); ^{13}C NMR *δ* 14.24, 25.36, 26.56, 34.25, 60.72, 66.00, 72.98, 77.42, 77.82, 109.12, 127.50, 127.63, 127.78, 128.17, 136.91, 138.16, 166.91; MS *m*/*z* 319 (M^+−Me, 26%), 233 (95), 101 (58), 91 (100); HRMS calcd for $C_{18}H_{23}O_5$ [M^+−Me] 319.1545, found 319.1552. *Minor diastereomer* **7**. ^{1}H NMR *δ* 1.28 (3H, t, *J*=7.2 Hz, CH_3), 1.37 (3H, s, CH_3), 1.45 (3H, s, CH_3), 2.42–2.52 (2H, m, CH_2C=CH_2), 3.63 (1H, m, CH–O), 3.79 (1H, dd, *J*=8.0, 7.3 Hz, C*H*H–O), 3.99 (1H, d, *J*=8.0, 6.5 Hz, CH*H*–O), 4.13–4.23 (3H, m, CH–O, CH_2–O), 4.59 (1H, d, *J*=11.7 Hz, PhC*H*H–O), 4.70 (1H, d, *J*=11.7 Hz, PhCH*H*–O), 5.69 (1H, d, *J*=1.2 Hz, C=C*H*H), 6.23 (1H, d, *J*=1.6 Hz, C=CH*H*), 7.26–7.36 (5H, m, Ph); ^{13}C NMR *δ* 14.24, 25.47, 26.53, 34.09, 60.72, 65.88, 72.93, 77.95, 78.05, 109.30, 127.41, 127.83, 127.88, 128.11, 136.64, 138.38, 166.80. MS *m*/*z* 319 (M^+−Me, 25%), 233 (94), 101 (54), 91 (100); HRMS calcd for $C_{18}H_{23}O_5$ [M^+−Me] 319.1545, found 319.1597.

4.1.3. (5*S*,6*R*)-5-Benzyloxy-6-hydroxymethyl-3-methylenetetrahydropyran-2-one (8). To a solution of **6** (18.2 mg, 0.054 mmol) in THF–H_2O (4:1, 1 cm^3) was added trifluoroacetic acid at 0 °C. The solution was stirred at room temperature overnight and then the product was extracted with ethyl acetate and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. Concentration of the solution gave a crude product, which was used without further purification. To a solution of the crude product in benzene (1 cm^3) was added catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (2:1)] to give **8** (6.9 mg, 51%) as an oil. ^{1}H NMR *δ* 2.66 (1H, m, C*H*HCHOBn), 3.03 (1H, m, CH*H*CHOBn), 3.85 (1H, m, C*H*OBn), 3.86 (1H, dd, *J*=12.3, 3.4 Hz, C*H*HOH), 3.93 (1H, dd, *J*=12.3, 3.4 Hz, CH*H*OH), 4.34 (1H, dt, *J*=7.8, 3.4 Hz, C*H*CH_2OH), 4.60 (1H, d, *J*=11.5 Hz, PhC*H*H), 4.68 (1H, d, *J*=11.5 Hz, PhCH*H*), 5.65 (1H, m, C=C*H*H), 6.46 (1H, m, C=CH*H*), 7.30–7.39 (5H, m, Ph); ^{13}C NMR *δ* 33.16, 61.74, 70.14, 71.50, 82.14, 127.72, 128.06,

128.52, 130.18, 131.19, 137.20, 164.53; MS *m/z* 248 (M^+, 14%), 124 (15), 97 (41), 91 (100); HRMS calcd for $C_{14}H_{16}O_4$ [M^+] 248.1049, found 248.1055.

4.1.4. (5*R*,6*R*)-5-Benzyloxy-6-hydroxymethyl-3-methylenetetrahydropyran-2-one (9). To a solution of **7** (12.9 mg, 0.039 mmol) in THF–H_2O (4:1, 1 cm^3) was added trifluoroacetic acid at 0 °C. The solution was stirred at room temperature overnight and then the product was extracted with ethyl acetate and the extract was washed with saturated brine and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo gave the product, which was used without further purification. To a solution of the product in benzene (1 cm^3) was added catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (2:1)] to give **9** (3.5 mg, 37%) as an oil. ^{1}H NMR δ 2.65 (1H, m, C*H*HCHOBn), 3.07 (1H, dd, *J*=16.4, 3.9 Hz, CH*H*CHOBn), 3.78 (1H, dd, *J*=11.9, 5.1 Hz, C*H*HOH), 3.93 (1H, m, C*H*OBn), 3.99 (1H, dd, *J*=11.9, 6.6 Hz, CH*H*OH), 4.42 (1H, d, *J*=12.1 Hz, PhC*H*H), 4.45 (1H, m, C*H*CH_2OH), 4.66 (1H, d, *J*=12.1 Hz, PhCH*H*), 5.63 (1H, m, C=C*H*H), 6.52 (1H, m, C=CH*H*), 7.28–7.38 (5H, m, Ph); ^{13}C NMR δ 31.88, 62.42, 69.33, 70.22, 82.00, 127.69, 128.09, 128.53, 130.31, 130.57, 137.03, 164.16; MS *m/z* 248 (M^+, 7%), 124 (18), 97 (27), 91 (100); HRMS calcd for $C_{14}H_{16}O_4$ [M^+] 248.1049, found 248.1058.

4.1.5. Ethyl (2*R*)-2-[(2*S*,3*R*)-2-benzyloxy-3,4-(isopropylidenedioxy)butyl]-6-methyl-heptanoate (11). To a solution of α-methylene ester **6** (21.5 mg, 0.064 mmol) in dry CH_2Cl_2 (1.3 cm^3) was added $MgBr_2\cdot OEt_2$ (117 mg, 0.45 mmol) under N_2 and the mixture was stirred at room temperature for 15 min. To the suspension cooled to 0 °C were added 1-iodo-3-methylbutane (**10**) (0.026 cm^3, 0.19 mmol), *n*-Bu_3SnH (0.036 cm^3, 0.13 mmol), and Et_3B (0.064 cm^3, 1.0 mol dm^{-3} in hexane). The mixture was stirred at 0 °C for 6 h. KF and water were added and the mixture was stirred at room temperature overnight. After filtration through a pad of Florisil, the filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel [2 g; eluent: hexane then hexane–ethyl acetate (30:1)] to give a mixture of **11** and **12** (19 mg, 73% yield; **11/12**>50:1) as an oil. ^{1}H NMR δ 0.85 (6H, d, *J*=6.3 Hz, 2×CH_3), 1.22 (3H, t, *J*=7.0 Hz, CH_3), 1.13–1.65 (8H, m, C*H*HCH(CH_2)$_3$C*H*(CH_3)$_2$), 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.95 (1H, ddd, *J*=14.2, 11.3, 3.0 Hz, C*H*H), 2.68 (1H, m, CHC=O), 3.52 (1H, m, CH–O), 3.88 (1H, dd, *J*=8.0, 7.6 Hz, C*H*H–O), 4.00–4.14 (4H, m, CH*H*–O, CH–O, CH_2–O), 4.55 (1H, d, *J*=11.0 Hz, PhC*H*H), 4.65 (1H, d, *J*=11.0 Hz, PhCH*H*), 7.26–7.34 (5H, m, Ph); ^{13}C NMR δ 14.39, 22.57, 22.66, 25.02, 25.33, 26.59, 27.84, 33.72, 33.98, 38.77, 41.54, 60.13, 66.06, 73.36, 77.62, 77.73, 109.04, 127.54, 127.85, 128.23, 138.34, 176.09; MS *m/z* 391 (M^+−Me, 13%), 305 (76), 101 (32), 91 (100); HRMS calcd for $C_{23}H_{35}O_5$ [M^+−Me] 391.2485, found 391.2504.

4.1.6. Diethyl (2*R*,6*S*)-2-[(2*S*,3*R*)-2-benzyloxy-3,4-(isopropylidenedioxy)butyl]-6-methyl-1,8-octanedioate (14). The radical reaction of **6** (83 mg, 0.25 mmol) with iodide **13** (210 mg, 0.78 mmol) in the presence of $MgBr_2\cdot OEt_2$ (453 mg, 1.75 mmol) as described above gave **14** (85 mg, 71% yield; 96% de) as an oil. $[\alpha]_D^{23}$ −3.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 0.91 (3H, d, *J*=6.3 Hz, CH_3), 1.22 (3H, t, *J*=7.3 Hz, CH_3), 1.25 (3H, t, *J*=7.3 Hz, CH_3), 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.13–1.62 (7H, m), 1.92–1.99 (2H, m, CH_2C=O), 2.07 (1H, dd, *J*=14.7, 7.8 Hz, C*H*H), 2.26 (1H, dd, *J*=14.7, 5.8 Hz, CH*H*), 2.65 (1H, m, CHC=O), 3.52 (1H, m, C*H*OBn), 3.86 (1H, dd, *J*=8.0, 6.5 Hz, C*H*H–O), 4.00–4.16 (6H, m, CH–O, CH*H*–O, 2×CH_2–O), 4.55 (1H, d, *J*=11.0 Hz, PhC*H*H), 4.64 (1H, d, *J*=11.0 Hz, PhCH*H*), 7.27–7.34 (5H, m, Ph); ^{13}C NMR δ 14.41, 19.75, 24.64, 25.36, 26.65, 30.30, 33.59, 33.95, 36.57, 41.49, 41.87, 60.13, 60.20, 66.08, 73.34, 77.59, 77.68, 109.02, 127.51, 127.80, 128.19, 138.25, 172.94, 175.85; MS *m/z* 463 (M^+−Me, 22%), 377 (95), 285 (46), 101 (45), 91 (100); HRMS calcd for $C_{26}H_{39}O_7$ [M^+−Me] 463.2695, found 463.2740.

4.1.7. (2*R*,6*S*)-2-[(2*S*,3*R*)-2-Benzyloxy-3,4-(isopropylidenedioxy)butyl]-6-methyloctane-1,8-diol (16). To a solution of diester **14** (248 mg, 0.52 mmol) in dry diethyl ether (13 cm^3) was added lithium aluminium hydride (3.3 equiv) at 0 °C and the mixture was stirred at room temperature for 12 h. To the mixture cooled to 0 °C were added dropwise water, then 15% aqueous sodium hydroxide. After filtration through a pad of Celite, the filtrate was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (2:1)] to give diol **16** (181 mg, 89%) as an oil. $[\alpha]_D^{23}$ −0.52 (*c* 2.2, $CHCl_3$); ^{1}H NMR δ 0.88 (3H, d, *J*=6.3 Hz, CH_3), 1.36 (3H, s, CH_3), 1.11–1.40 (7H, m, (CH_2)$_3$CH), 1.43 (3H, s, CH_3), 1.44–1.64 (4H, m, 2×CH_2), 1.73 (1H, m, CH), 3.42 (1H, dd, *J*=11.2, 6.4 Hz, CH–O), 3.51 (1H, dd, *J*=11.2, 4.4 Hz, CH–O), 3.63–3.72 (3H, m, CH–O, CH_2–O), 3.86–4.18 (3H, m, CH–O, CH_2–O), 4.61 (1H, d, *J*=11.3 Hz, PhC*H*H), 4.71 (1H, d, *J*=11.3 Hz, PhCH*H*), 7.26–7.37 (5H, m, Ph); ^{13}C NMR δ 19.71, 24.26, 25.28, 26.55, 29.36, 32.26, 33.54, 37.18, 39.91, 61.10, 65.63, 66.31, 72.80, 78.05, 109.02, 127.79, 127.96, 128.38, 137.87; MS *m/z* 379 (M^+−Me, 4%), 185 (91), 101 (24), 91 (100); HRMS calcd for $C_{22}H_{35}O_5$ [M^+−Me] 379.2485, found 379.2516.

4.1.8. (2*R*,3*S*,5*R*,9*S*)-3-Benzyloxy-1,2-(isopropylidenedioxy)-9-methyl-11-(*p*-toluenesulfonyloxy)-5-(*p*-toluenesulfonyloxymethyl)undecane (17). To a solution of diol **16** (181 mg, 0.46 mmol) in dry CH_2Cl_2 (7 cm^3) were added pyridine (0.3 cm^3) and *p*-toluenesulfonyl chloride (879 mg, 4.6 mmol) at 0 °C. The solution was stirred at room temperature overnight. After dilution with water, the product was extracted with chloroform. The extract was washed with water, saturated sodium hydrogencarbonate solution, and saturated brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (6:1)] to give tosylate **17** (294 mg, 91%) as an oil. $[\alpha]_D^{23}$ −7.5 (*c* 2.1, $CHCl_3$); ^{1}H NMR δ 0.74 (3H, d, *J*=6.1 Hz, CH_3), 0.97–1.48 (10H, m), 1.34 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.60 (1H, m, CH), 1.80 (1H, m, CH), 2.44 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.49 (1H, m, CH–O), 3.77 (1H, dd, *J*=9.8, 4.9 Hz, CH–O), 3.83 (2H, m, CH–O), 3.97–4.11 (4H, m, CH–O), 4.45 (1H,

d, J=11.7 Hz, PhC*H*H), 4.67 (1H, d, J=11.7 Hz, PhCH*H*), 7.25–7.38 (9H, m, Ar), 7.73 (2H, d, J=8.3 Hz, Ar), 7.78 (2H, d, J=8.3 Hz, Ar); ^{13}C NMR δ 19.01, 21.69, 23.74, 25.23, 26.45, 29.10, 31.78, 32.44, 33.91, 35.67, 36.61, 65.70, 68.88, 71.92, 72.88, 76.06, 78.11, 108.98, 127.66, 127.77, 127.78, 127.84, 128.29, 129.75, 132.75, 133.01, 138.13, 144.58, 144.66.

4.1.9. (2*R*,3*S*,5*R*,9*R*)-3-Benzyloxy-1,2-(isopropylidenedioxy)-5,9-dimethylundecane (18). To a solution of tosylate **17** (134.3 mg, 0.19 mmol) in dry diethyl ether (10 cm^3) was added lithium aluminium hydride (3.3 equiv) at 0 °C. The mixture was stirred at room temperature for 12 h. To the mixture cooled to 0 °C were added dropwise water and then 15% aqueous sodium hydroxide. After filtration through a pad of Celite, the filtrate was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (40:1)] to give **18** (57.3 mg, 83%) as an oil. $[\alpha]_D^{23}$ −6.6 (c 1.8, $CHCl_3$); ^{1}H NMR δ 0.83 (6H, d, J=6.4 Hz, 2×CH_3), 0.85 (3H, t, J=7.3 Hz, CH_3), 1.03–1.66 (12H, m, 5×CH_2, 2×CH), 1.37 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.70 (1H, dt, J=10.0, 3.4 Hz, C*H*OBn), 3.94 (1H, dd, J=7.8, 7.3 Hz, C*H*H–O), 4.02 (1H, dd, J=7.8, 6.3 Hz, CH*H*–O), 4.10 (1H, m, CH–O), 4.59 (1H, d, J=11.2 Hz, PhC*H*H), 4.77 (1H, d, J=11.2 Hz, PhCH*H*), 7.27–7.34 (5H, m, Ph); ^{13}C NMR δ 11.47, 19.31, 19.41, 24.42, 25.43, 26.53, 29.12, 29.49, 34.42, 36.87, 38.25, 39.43, 65.59, 73.41, 76.62, 79.08, 108.84, 127.47, 127.74, 128.23, 138.66; MS m/z 347 (M^+−Me, 16%), 261 (23), 101 (73), 91 (100); HRMS calcd for $C_{22}H_{35}O_3$ [M^+−Me] 347.2587, found 347.2578.

4.1.10. (2*R*,3*S*,5*R*,9*R*)-1,2-(Isopropylidenedioxy)-5,9-dimethylundecan-3-ol (19). A solution of **18** (47.2 mg, 0.13 mmol) in dry ethanol (5 cm^3) was stirred with Pd–C (35.5 mg, 0.032 mmol) under hydrogen atmosphere at room temperature for 12 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to give **19** in quantitative yield. $[\alpha]_D^{23}$ −0.73 (c 1.86, $CHCl_3$); ^{1}H NMR δ 0.84 (3H, d, J=6.4 Hz, CH_3), 0.85 (3H, t, J=7.3 Hz, CH_3), 0.90 (3H, d, J=6.8 Hz, CH_3), 1.05–1.69 (12H, m, 5×CH_2, 2×CH), 1.37 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.92 (1H, br s, OH), 3.87–4.02 (4H, m, CH_2–O, CH–O, C*H*OH); ^{13}C NMR δ 11.47, 19.09, 19.30, 24.43, 25.37, 26.52, 29.18, 29.48, 34.42, 36.88, 38.24, 39.70, 64.44, 68.29, 79.15, 108.83; MS m/z 257 (M^+−Me, 100%), 229 (18), 101 (13); HRMS calcd for $C_{15}H_{29}O_3$ [M^+−Me] 257.2117, found 257.2121.

4.1.11. (2*R*,3*S*,5*R*,9*R*)-3-Phenoxythiocarbonyloxy-1,2-(isopropylidenedioxy)-5,9-dimethylundecane (20). To a solution of alcohol **19** (55.5 mg, 0.20 mmol) in dry CH_2Cl_2 (3 cm^3) were added dry pyridine (0.050 cm^3, 0.60 mmol) and *O*-phenyl chlorothionoformate (0.032 cm^3, 0.23 mmol) at 0 °C. The solution was stirred at room temperature for 3 h. The reaction mixture was then washed with water, saturated sodium hydrogencarbonate solution, and saturated brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (60:1)] to give phenoxythiocarbonyl ester **20** (62.1 mg, 75%) as an oil. $[\alpha]_D^{23}$ −18.7 (c 1.74, $CHCl_3$); ^{1}H NMR δ 0.85 (3H, d, J=6.4 Hz, CH_3), 0.86 (3H, d, J=6.4 Hz, CH_3), 0.98 (3H, d, J=6.8 Hz, CH_3), 1.22–1.43 (10H, m, 4×CH_2, 2×CH), 1.39 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.62 (1H, m, CH), 1.84 (1H, ddd, J=14.1, 10.0, 3.9 Hz, CH), 3.94 (1H, dd, J=8.3, 6.4 Hz, CH–O), 4.12 (1H, m, CH–O), 4.33 (1H, m, CH–O), 5.69 (1H, m, PhOC(=S)OC*H*), 7.09–7.44 (5H, m, Ph); ^{13}C NMR δ 11.49, 19.32, 19.78, 24.37, 25.32, 26.32, 29.03, 29.51, 34.42, 36.83, 37.36, 37.86, 65.55, 76.91, 82.48, 109.86, 121.87, 126.47, 129.41, 153.28, 195.09; MS m/z 393 (M^+−Me, 10%), 254 (54), 239 (56), 197 (32), 179 (47), 149 (48), 127 (100), 123 (45), 101 (55), 97 (47), 69 (95); HRMS calcd for $C_{22}H_{33}O_4S$ [M^+−Me] 393.2099, found 393.2053.

4.1.12. (2*S*,5*R*,9*R*)-1,2-(Isopropylidenedioxy)-5,9-dimethylundecane (21). To a solution of **20** (23.8 mg, 0.059 mmol) in dry toluene (2 cm^3) were added n-Bu_3SnH (0.027 cm^3, 0.12 mmol) and AIBN (12.8 mg, 0.064 mmol). The mixture was stirred at 85 °C for 3 h. KF and water were then added and the reaction mixture was stirred at room temperature overnight. After filtration though a pad of Florisil, the filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel to give **21** (14.1 mg, 95%) as an oil. $[\alpha]_D^{23}$ +10.8 (c 1.95, $CHCl_3$); ^{1}H NMR δ 0.84 (3H, d, J=6.9 Hz, CH_3), 0.85 (3H, t, J=7.6 Hz, CH_3), 0.87 (3H, d, J=6.3 Hz, CH_3), 1.08–1.45 (13H, m, 5×CH_2, 3×CH), 1.36 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.68 (1H, m, CH), 3.52 (1H, m, CH–O), 4.02–4.07 (2H, m, CH_2–O); ^{13}C NMR δ 11.48, 19.32, 19.67, 24.47, 25.81, 27.02, 29.50, 31.17, 32.82, 32.90, 34.44, 36.95, 37.19, 69.58, 76.49, 108.52; MS m/z 241 (M^+−Me, 100%), 101 (9); HRMS calcd for $C_{15}H_{29}O_2$ [M^+−Me] 241.2246, found 241.2218.

4.1.13. (2*S*,5*R*,9*R*)-5,9-Dimethyl-1,2-undecanediol (22). To a solution of **21** (32.1 mg, 0.12 mmol) in THF–H_2O (1:1, 2 cm^3) was added 1 mol dm^{-3} HCl at 0 °C. The solution was stirred at room temperature overnight. The reaction mixture was then extracted with ethyl acetate. The extract was washed with saturated brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (3:1)] to give **22** (24.0 mg, 89%) as an oil. $[\alpha]_D^{23}$ −3.4 (c 1.0, $CHCl_3$); ^{1}H NMR δ 0.84 (3H, d, J=5.9 Hz, CH_3), 0.85 (3H, t, J=7 Hz, CH_3), 0.87 (3H, d, J=6.8 Hz, CH_3), 1.06–1.45 (14H, m, 6×CH_2, 2×CH), 2.02 (1H, br s, OH), 2.13 (1H, br s, OH), 3.45 (1H, m, C*H*OH), 3.66–3.68 (2H, m, CH_2OH); ^{13}C NMR δ 11.48, 19.32, 19.63, 24.51, 29.50, 30.75, 32.73, 32.87, 34.44, 36.96, 37.34, 66.89, 72.66; MS m/z 185 (M^+−CH_2OH, 100%), 111 (43), 97 (64), 83 (56), 69 (50); HRMS calcd for $C_{12}H_{25}O$ [M^+−CH_2OH] 185.1905, found 185.1854.

4.1.14. (4*R*,8*R*)-4,8-Dimethyldecanal (1). To a solution of **22** (24.0 mg, 0.11 mmol) in aqueous acetonitrile (60%, 2 cm^3) was added $NaIO_4$ (18.4 mg, 0.079 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was then filtered through a pad of Celite and extracted with chloroform. The extract was washed with water and saturated brine, and then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel

[eluent: hexane–ethyl acetate (60:1)] to give (4*R*,8*R*)-4,8-dimethyldecanal (**1**) (18.5 mg, 91%) as an oil. $[\alpha]_D^{23}$ −5.6 (*c* 1.1, $CHCl_3$); IR (neat) 2961, 2929, 2714, 1712, 1463, 1379 cm^{-1}; ^1H NMR δ 0.84 (3H, d, *J*=6.3 Hz, CH_3), 0.85 (3H, d, *J*=7.2 Hz, CH_3), 0.88 (3H, d, *J*=5.6 Hz, CH_3), 1.04–1.14 (12H, m, 5×CH_2, 2×CH), 2.40–2.46 (2H, m, C*H*$_2$CH═O), 9.78 (1H, t, *J*=1.2 Hz, CH═O); ^{13}C NMR δ 11.47, 19.30, 19.45, 24.43, 28.92, 29.48, 32.46, 34.43, 36.88, 37.07, 41.77, 202.95; MS *m*/*z* 184 (M^+, 1%), 140 (67), 111 (42), 85 (54), 81 (57), 70 (90), 57 (100); HRMS calcd for $C_{12}H_{24}O$ [M^+] 184.1827, found 184.1802.

4.1.15. α-Methoxy-α-(trifluoromethyl)phenylacetate 24. ^1H NMR δ 0.88 (3H, d, *J*=6.3 Hz, CH_3), 1.00–1.40 (4H, m), 1.25 (3H, t, *J*=7.3 Hz, CH_3), 1.29 (3H, t, *J*=7.0 Hz, CH_3), 1.33 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.46–1.60 (1H, m), 1.65 (1H, ddd, *J*=14.1, 10.7, 3.4 Hz), 1.89 (1H, m), 1.99 (1H, ddd, *J*=14.1, 11.9, 2.4 Hz), 2.05 (1H, dd, *J*=15.1, 7.8 Hz), 2.15–2.25 (1H, m), 2.23 (1H, dd, *J*=14.6, 5.9 Hz), 3.59 (3H, s, OCH_3), 3.76 (1H, dd, *J*=8.3, 6.4 Hz, C*H*H–O), 3.99 (1H, dd, *J*=8.3, 6.4 Hz, CH*H*–O), 4.12 (2H, q, *J*=7.3 Hz, CH_2–O), 4.17 (2H, q, *J*=7.0 Hz, CH_2–O), 4.22 (1H, m, CH–O), 5.13 (1H, m, CH–O), 7.39–7.43 (3H, m, Ph), 7.57–7.60 (2H, m, Ph); ^{13}C NMR δ 14.30, 14.34, 19.61, 24.34, 24.94, 26.21, 30.14, 32.28, 33.18, 36.26, 41.02, 41.78, 55.54, 60.15, 60.59, 65.58, 74.30, 76.23, 77.20, 109.75, 127.36, 128.31, 129.58, 132.03, 165.90, 173.01, 175.06.

4.1.16. α-Methoxy-α-(trifluoromethyl)phenylacetate 25. ^1H NMR δ 0.91 (3H, d, *J*=6.4 Hz, CH_3), 1.13 (1H, m), 1.25 (3H, t, *J*=7.0 Hz, CH_3), 1.20–1.35 (3H, m), 1.27 (3H, t, *J*=67.0 Hz, CH_3), 1.30 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.43 (1H, m), 1.56–1.64 (1H, m), 1.69 (1H, ddd, *J*=14.1, 10.2, 39 Hz), 1.92 (1H, m), 2.03–2.13 (2H, m), 2.25 (1H, dd, *J*=15.0, 6.0 Hz), 2.39 (1H, m), 3.69 (1H, dd, *J*=8.5, 6.9 Hz, C*H*H–O), 3.52 (3H, s, OCH_3), 3.91 (1H, dd, *J*=8.5, 6.4 Hz, CH*H*–O), 4.10 (1H, m, CH–O), 4.12 (2H, q, *J*=6.4 Hz, CH_2–O), 4.16 (2H, q, *J*=7.0 Hz, CH_2–O), 5.14 (1H, m, CH–O), 7.39–7.43 (3H, m, Ph), 7.57–7.60 (2H, m, Ph); ^{13}C NMR δ 14.29, 14.35, 19.67, 24.43, 25.17, 26.26, 30.18, 33.08, 33.27, 36.37, 41.26, 41.81, 55.36, 60.16, 60.63, 65.93, 74.34, 76.35, 109.69, 127.55, 128.26, 128.38, 129.66, 131.62, 165.90, 173.01, 174.96.

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Synthesis of calix[4]arene(amido)monocrowns and their photoresponsive derivatives

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Abstract—A series of new calix[4]arene(amido)mono-crown compounds have been synthesized through aminolysis of calix[4]arene esters and intramolecular cyclization of the intermediates. The title compounds were converted into their nitro and azo substituted derivatives to provide novel photoresponsive molecular receptors for transition metal ions. Single crystal X-ray analysis of calix[4]arene(ethyleneamido)-mono-crown (**2a**) revealed that the compound is present in a cone conformation with an amido loop that caps the lower rim of calix[4]arene cavity to result in stacking along axis *a* and axis *c* to provide supramolecular aggregates in the solid state. Evaluation of synthesized macrocycles in the solution phase for recognition of transition metal cations (Cr^{3+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ag^{+}, Cd^{2+}, Pb^{2+}, Hg^{+}, Hg^{2+}, Pd^{2+}, and Pt^{2+}) by UV–visible spectroscopy revealed that *p-tert*-butyl-calix[4]arene mono-(amidocrown) **1c** selectively shows a blue shift at 38 nm on interaction with Hg^{+} ions.

1. Introduction

Calix[*n*]arenes (*n*=4–20) are phenolic [1$_n$]-*meta*cyclophanes that are known to provide useful building blocks for hollow molecular architectures with functionalizable hydrophilic and hydrophobic sites.[1] Calixarenes containing –CONH– groups at their hydrophilic end possess inherent hydrogen bond possibilities akin to those present in neutral peptides and proteins[2] and possibly can resolve some complex issues in molecular recognition. Literature search on calixarene based molecular receptors revealed that *p-tert*-butyl-calix[4]arene tetraethyl acetate, on treatment with mono-amines, provides amido calix[4]arenes in good yield. However, when the mono-amines are replaced by diamines and triamines, the same reaction provides double amido bridged calix[4]arenes[3] (Fig. 1). Recently, it has been suggested that the latter series of compounds results from a regioselective but sequential reaction of one of the amino functions of the diamine with the ester function followed by an intramolecular nucleophilic reaction of the remaining amino group with ester functions as depicted in Figure 1.[3] The reaction of calix[4]arene tetraethyl acetate should, therefore, lead to possible proximal or distal calix[4]arene mono-(amido)crowns, bis(amido)crowns, and alkyl amino amido methoxy calix[4]arenes. Since no other product could be isolated in the published experiments, the proposed pathway based upon precedents in esterification reactions of calix[4]arenes remains a conjecture. In this paper, we report

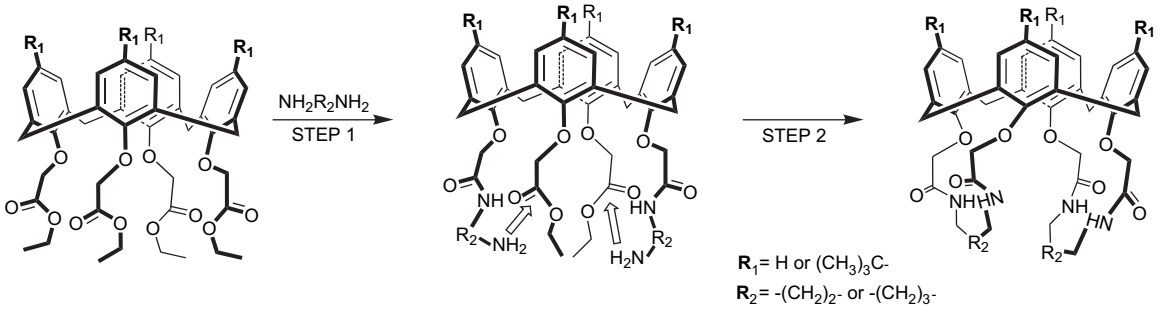

Figure 1. Proposed mechanism for the synthesis of 1,2,3,4-bis-amide-bridge calix[4]arenes.

Keywords: Calix[*n*]arenes; Diazotization; Nitration; Aminolysis.
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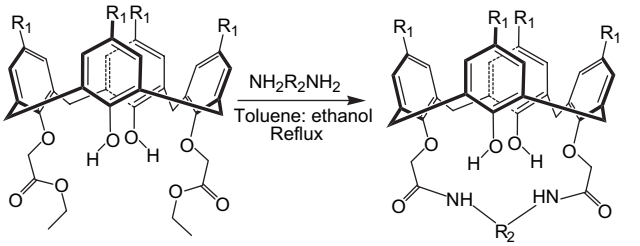
the synthesis of *p-tert*-butyl-calix[4]arene mono-(amido-crown) derivatives and their debutylated analogs to suggest a plausible mechanism for the reaction and to obtain photoresponsive derivatives of calix[4]amidocrowns for recognition of transition metal ions. The structures of the calix[4]arene(amido) crowns were established by spectroscopic and single crystal X-ray diffraction analyses.

2. Results and discussion

2.1. Characterization of the products

5,11,17,23-Tetra(*p-tert*-butyl)-25,27-di(ethoxycarbonylmethoxy)-26,28-dihydroxy-calix[4]arene (**1**) and 25,27-di-(ethoxycarbonylmethoxy)-26,28-dihydroxy-calix[4]arene (**2**) were synthesized by refluxing the corresponding calix[4]arene with ethyl bromoacetate in the presence of K_2CO_3 in acetone for 15 h.[4] When **1** and **2** were refluxed with different diamines in a mixture of toluene and methanol (Scheme 1) for a period of 24 h, they were converted into **1a**–**2e**, which could be isolated by recrystallization from the solvents mentioned in Section 4.



S.N.	R_1
1	*p-tert* butyl-
2	H

S.N.	R_1	R_2	Yield (%)
1a	*p-tert* butyl-	$-(CH_2)_2-$	92
1b	*p-tert* butyl-	$-(CH_2)_4-$	88
1c	*p-tert* butyl-	$-CH_2CH_2NHCH_2CH_2-$	72
1d	*p-tert* butyl-	$-CH_2(CH_2NHCH_2)_2CH_2-$	56
1e	*p-tert* butyl-	$-(CH_2)_6-$	48
2a	H	$-(CH_2)_2-$	83
2b	H	$-(CH_2)_4-$	82
2c	H	$-CH_2CH_2NHCH_2CH_2-$	76
2d	H	$-CH_2(CH_2NHCH_2)_2CH_2-$	51
2e	H	$-(CH_2)_6-$	26

Scheme 1. Synthesis of calix[4]arene(amido)mono-crown derivatives. Reagents: 20 equiv, diamine (H_2N-R_2-NH_2), toluene/MeOH (1:1), refluxing, 24 h.

The structures of **1a**–**1e** and **2a**–**2e** were established by the analysis of their ^1H and ^{13}C NMR spectra as well as other NMR experiments. For instance, the molecular structure of **2b** could be confirmed by the analysis of its two dimensional HSQC spectrum (Fig. 2). It was determined that the pair of doublets at δ 4.18 and 3.51 for ArCH_2Ar protons in the ^1H NMR spectrum could be correlated with the signal at δ 31.17 in its ^{13}C NMR spectrum. A multiplet at δ 6.74–6.81 region in the ^1H NMR spectrum for ArH_{para} protons correlated well with two signals at δ 120.4 and 126.3 in the ^{13}C NMR spectrum of **2b**. Similarly, two doublets at δ 6.88 and 7.14 for ArH_{meta} protons observed in the ^1H NMR spectrum correlated well with the two signals at 129.0 and 129.5 ppm in the ^{13}C NMR spectrum of **2b**. This specific correlation pattern indicated that **2b** is a symmetrical compound

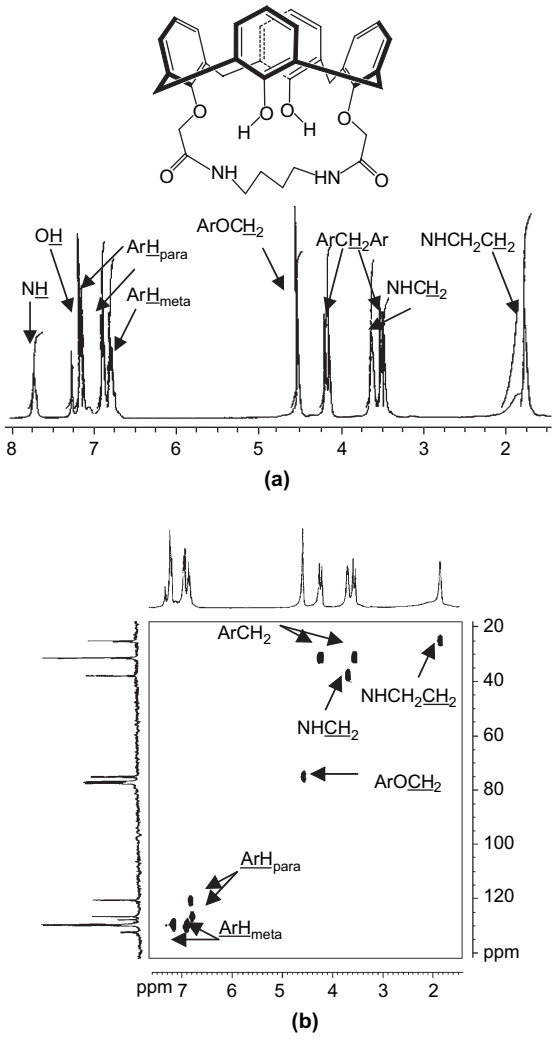
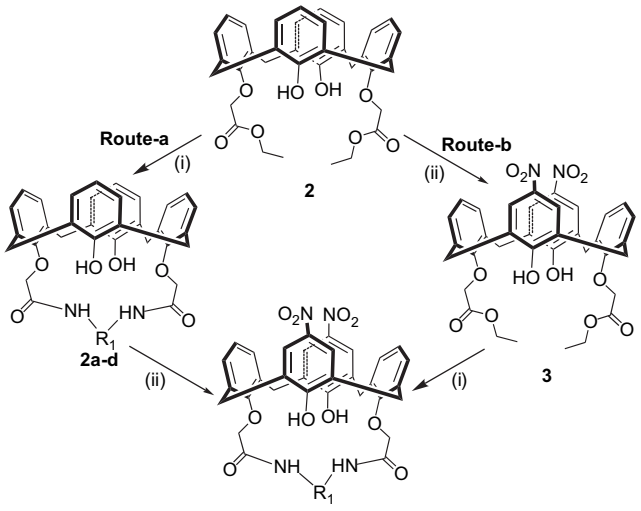


Figure 2. (a) Molecular structure and ^1H NMR spectrum of **2b**; (b) HSQC spectrum of **2b** in $CDCl_3$ at 25 °C and 300 MHz.

in its cone conformation. Similarly, the presence of a pair of doublets for ArCH_2Ar protons in the ^1H NMR spectra of synthesized derivatives and only one signal for methylene carbon in the range of 29–32 ppm in their ^{13}C NMR spectra suggested that the synthesized calix[4]arene(amido)-mono-crowns were in a symmetrical cone conformation in solution.[5]

When **2a**–**2d** were reacted with HNO_3/CH_3COOH, they gave products, which were identified as their nitro derivatives **3a**–**3d** (Scheme 2, route a).[6]

Compound **3a** exhibited prominent signals at δ 9.41 and 8.14 for hydroxyl and amide protons, while signals for aromatic protons appeared at δ 8.27, 7.28, and 6.95. The ArOCH_2–protons appeared at δ 4.57 while ArCH_2Ar and –NHCH_2 protons appeared at δ 4.26 and 3.82, and δ 3.51, respectively (Fig. 3). These data suggested that **3a** possessed a symmetric cone structure. A prominent downfield shift in the position of hydroxyl signal suggested that nitro groups were present at positions *para* to the hydroxyl groups. Similarly, other compounds of the series (**3b**–**3d**) could be characterized by their ^1H NMR spectra.



	R_1	Yield (%)
3a	$-(CH_2)_2-$	78
3b	$-(CH_2)_4-$	80
3c	$-CH_2CH_2NHCH_2CH_2-$	77
3d	$-CH_2CH_2NHCH_2CH_2NHCH_2CH_2-$	58

Scheme 2. Synthesis of *p*-nitro calix[4]arene(amido)mono-crown derivatives Reagents: (i) 20 equiv, diamine, toluene/MeOH (1:1), refluxing, 24 h; (ii) 100% nitric acid, glacial acetic acid/dichloromethane (1:1), 0 °C, 10 min.

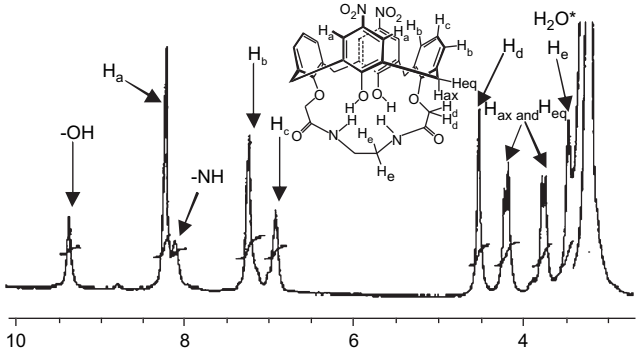
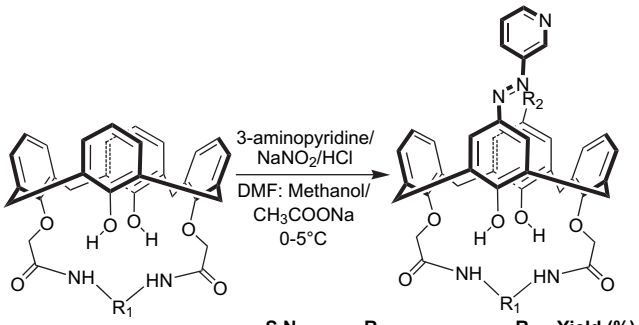


Figure 3. Molecular structure and ^{1}H NMR spectrum of **3a**.

The same nitro substituted derivatives could also be obtained by nitration of 25,27-di(ethoxycarbonylmethoxy)-26,28-dihydroxy-calix[4]arene (**2**) followed by aminolysis with diamines as depicted in Scheme 2, but it was determined that nitration of amidocrowns (route a) resulted in better yields of **3a** and **3b**. When the compounds were less soluble in dichloromethane (e.g., **2c** and **2d**), the reaction gave lower yields of the products (**3c** and **3d**). In such cases, route b was determined to be a better pathway for obtaining products in good yields.

To confer chromogenicity of calix[4]arene(amido)mono-crown derivatives for ionic and molecular recognitions, compounds **2a**–**2d** were also reacted with diazotized 3-aminopyridine under basic conditions to provide mixtures of compounds, which could be separated by column chromatography to give **4a**, **4b**, **5a**, **5b**, **6a**, and **6b** in moderate yields[7] as described in Section 4 (Scheme 3).

The ^{1}H NMR spectra of **4a**–**6b** suggested them to be (pyridylazo)calix[4]arene(amido)mono-crown derivatives. For instance, **4b** exhibited broad signals at δ 8.94 and 8.38 for



S.N	R_1	R_2	Yield (%)
4a	$-(CH_2)_2-$	H	28
4b	$-(CH_2)_2-$	3-AP	58
5a	$-(CH_2)_4-$	H	7
5b	$-(CH_2)_4-$	3-AP	28
6a	$-CH_2CH_2NHCH_2CH_2-$	H	27
6b	$-CH_2CH_2NHCH_2CH_2-$	3-AP	51

Scheme 3. Synthesis of (pyridylazo)calix[4]arene(amido)mono-crown derivatives. Reagents: (i) diazonium salt obtained from 3-aminopyridine, DMF/MeOH (8:5), CH_3COONa, 0–5 °C, 3 h.

hydroxyl and amide group protons in its ^{1}H NMR spectrum, while 3-azopyridyl protons appeared at δ 9.15, 8.65, 8.10, and 7.44, calix[4]arene core aromatic protons appeared at δ 7.81, 7.19, and 6.99. The ArOCH_2–, ArCH_2Ar, and –NHCH_2 protons could be observed at δ 4.65, 4.25, and 3.73, respectively, in its ^{1}H NMR spectrum (Fig. 4). The pattern of a pair of doublets for methylene protons suggested that **4b** was present in its cone conformation. Assignment of different NMR signals has been indicated in Figure 4. Similarly, other (pyridylazo)calix[4]arene(amido)mono-crown derivatives could be characterized.

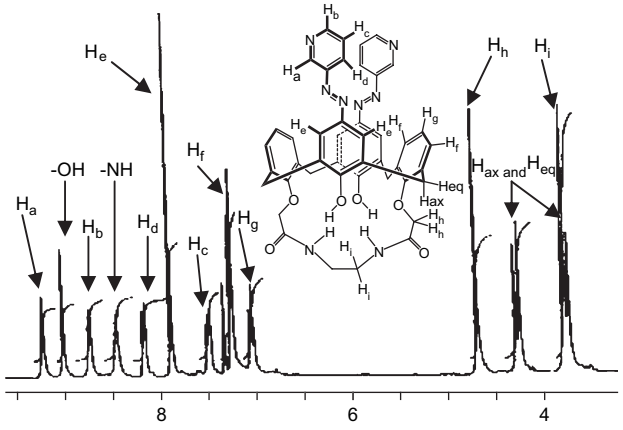


Figure 4. Molecular structure and ^{1}H NMR spectrum of **4b**.

2.2. X-ray crystal structural analysis of the calix[4]arene (ethyleneamido)crown (2a)

The ORTEP diagram of **2a** is shown in Figure 5a. The torsion angles φ and χ around ArCH_2Ar bonds about C7, C14, C21, and C28 are 77.5°(12), −100.6°(°(12), 98.3°(12), −78.0°(13), 74.4°(12), −103.9°(12), 100.7°(11), and −78.5°(13), respectively. This alternate ± sequence is characteristic for the cone conformation.[8] All the four aromatic rings are planar with a maximum deviation of 0.022 Å from a least square plane. The connecting methylene carbon

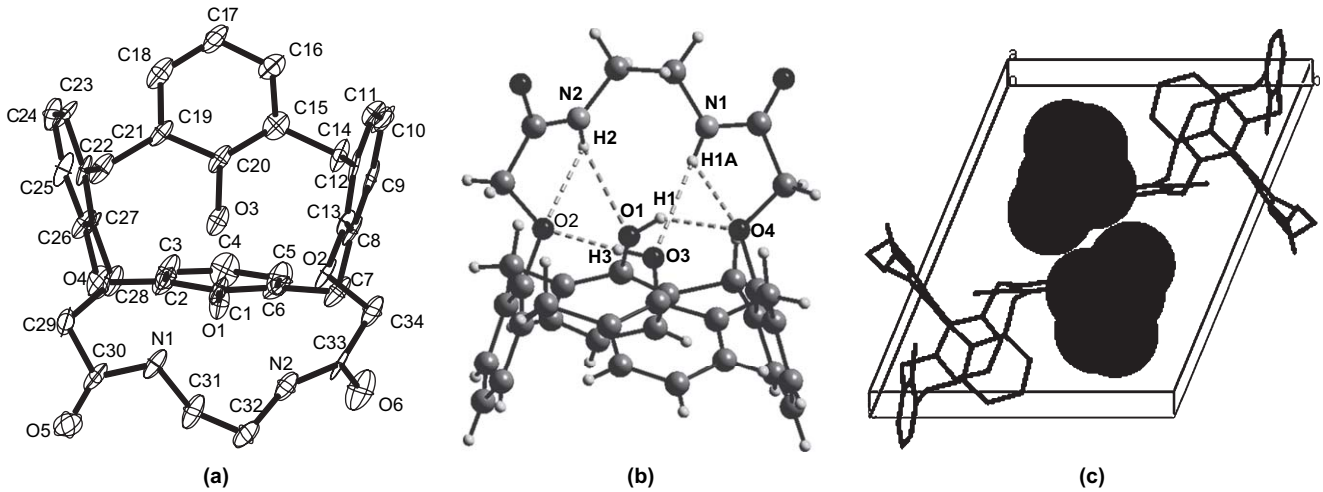


Figure 5. (a) ORTEP diagram showing labeling of atoms in **2a** (hydrogens and solvent molecule have been omitted for clarity); (b) intramolecular hydrogen bonding in **2a**; (c) the content of a single unit cell.

atoms C7, C14, C21, and C28 form an approximate plane where alternate carbon atoms lie ±0.136 and ±0.137 Å above and below the plane. The interplanar angles found between this plane (hypothetical plane along methylene carbons C7, C14, C21, and C28) and the rings A(C1–C6), B(C8–C13), C(C15–C20), D(C22–C27) are 40.39°(1), 73.62°(1), 35.19°(2), 71.95°(1), respectively. The interplanar angle between the pairs A and C is determined to be 75.57(2)° while it is 34.45(2)° between ring B and D. Thus, two opposite rings B and D are almost parallel while rings A and C are almost perpendicular to each other. The O···O separation between O(1) and O(3), and O(2) and O(4) is 3.151 and 4.542 Å, respectively. Likewise, the O···O distance between adjacent phenolic oxygens O(1)–O(2), O(2)–O(3), O(3)–O(4), O(4)–O(1) is 2.879, 2.735, 2.851, and 2.705 Å, respectively. Both the O2–C34–C33–O6 and O4–C29–C30–O5 are *trans* thereby making both the carbonyl groups *exo* with respect to the calixarene cavity.

The main deciding factor for determining the conformation of this molecule is the presence of four intramolecular H-bond (H···O) interactions (Fig. 5b) given in Table 1. The protons of the nitrogen atoms N1 and N2 point inward to the calixarene cavity and are bound to the phenolic oxygens of the calixarene through hydrogen bonds. The contents of the unit cell are shown in Figure 5c.

Table 1. Intramolecular H-bonding interactions of **2a**

S.no.	D–H···A	D–H(Å)	H···A(Å)	D···A(Å)	∠D–H···A(°)
1	O1–H1···O4	0.820	2.121	2.706	128.12
2	O3–H3···O2	0.820	1.937	2.734	163.77
3	N1–H1A···O3	0.860	2.500	3.356	173.23
4	N2–H2···O1	0.860	2.519	3.338	159.56

D = Donor, A = Acceptor.

Dimer formation via tail to tail (Fig. 6a) and head to head (Fig. 6b) has been observed in the X-ray diffraction pattern of **2b**. Two sets of intermolecular hydrogen bonds among C31–H31A···O3′ [C–H···O=2.705 Å] and a prominent C–H–π interaction between C31–H31B and ring C′ (3.147 Å) bring the ethyleneamido crown ring much closer to the plane of ring C, which results in a tail to tail dimer (Fig. 6a). A set of a strong intermolecular C–H–π interaction between *para*-hydrogen of ring D′ (C24′–H24′) with ring B (3.080 Å) and *ortho*-hydrogens of ring D′, i.e., C23′–H23′ with ring A (3.432 Å) and C25′–H25′ with ring C (3.008 Å), seems to be responsible for the formation of head to head dimer (Fig. 6b). A weak intermolecular hydrogen bond between C34–H34B···O5′ (2.669 Å) was associated with the formation of a long supramolecular chain in the solid state (Fig. 6c, Fig. 7).

2.3. Discussion

It has earlier been proposed that aminolysis of the cone conformation of 25,26,27,28-tetra(ethoxycarbonylmethoxy)-calix[4]arene with diamine to yield bisamido-calix[4]arenes (Fig. 1)[3] proceeds through a distally substituted intermediate to yield 25,27-bis(amino alkyl amido methoxy)-26,28-bis(ethoxycarbonylmethoxy)-calix[4]arene (Fig. 8a). Consequently, the reaction of diamine with diester derivatives of calix[4]arenes should result in a 25,27-bis(amino alkyl amido methoxy)-26,28-bishydroxycalix[4]arenes (Fig. 8b). However, it has been observed that the reaction gives only the mono-(amido)crown derivatives. This suggests that the reaction of diamines with 25,26,27,28-tetra-(ethoxycarbonylmethoxy)calix[4]arene would have also proceeded in a manner different from the previously proposed reaction of amine with calix[4]arene ethyl acetates.

The formation of proximally substituted calix[4]arene(bisamido)crowns can be considered to proceed stepwise via aminolysis to yield the alkyl amino amido methoxy calix[4]-arenes followed by intramolecular cyclization as depicted in Figure 9. The possibility of intermolecular reaction of intermediate aminoamides could be discounted as biscalix[4]arenes could not be isolated or detected in the reaction mixture (FABMS analysis). This conclusion was confirmed by repeating the reaction with excess of diamine (40 equiv) when the reaction resulted in the synthesis of calix[4]arene mono-(amidocrown) derivatives in very good yield. The aminolysis reaction of calix[4]arene ester with diamines

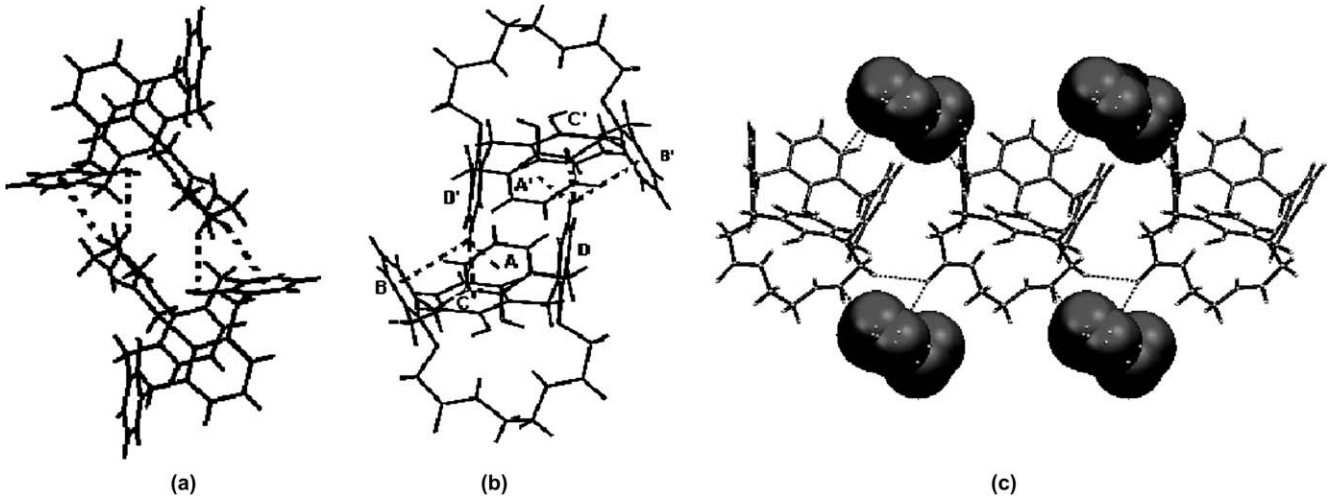


Figure 6. (a) A tail to tail dimer; (b) a head to head dimer; (c) supramolecular aggregates along *c* axis (intermolecular interactions are shown as dotted lines).

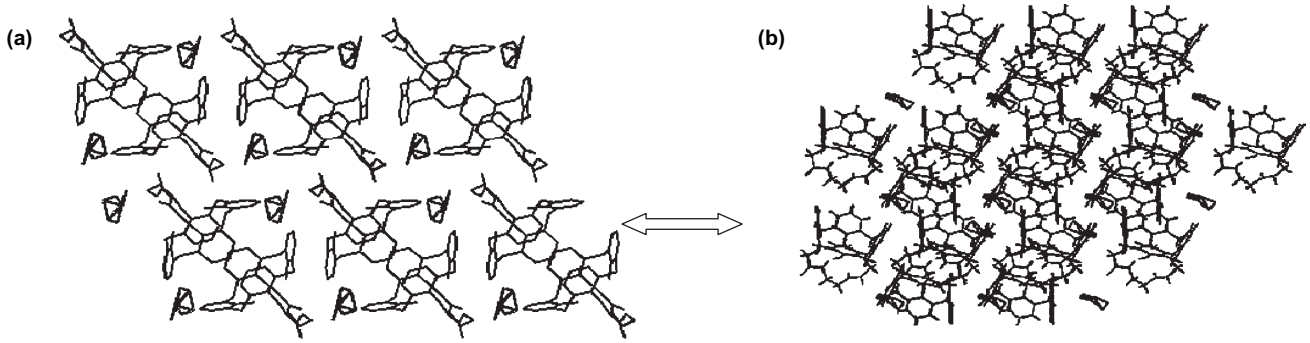


Figure 7. (a) Stacking of molecules along *a* axis; (b) stacking of molecules along *c* axis to yield supramolecular aggregates with disordered chloroform.

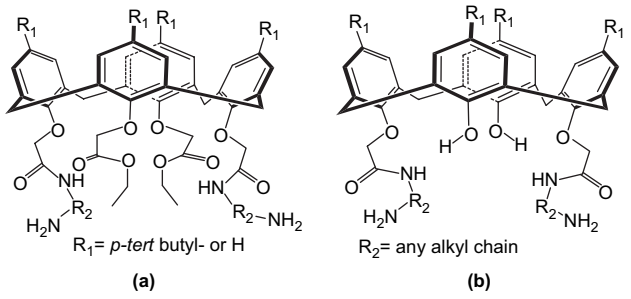


Figure 8. Ester derivatives with pendant amine groups.

can, therefore, lead to monoamido crown compounds or proximally substituted bisamido crown compounds as depicted in Figure 9. Thus, one of the ester groups in the tetraester (**A**) can be envisaged to get aminolyzed to yield mono-amide (**B**) when reacted with diamines in first step. This intermediate can be considered to react with the neighboring ester group to form a calix[4]arene (monoamido)crown (**C**) in second step, which can further react in a similar fashion to provide proximally bridged calix[4]arene(bisamido)crowns (**E**). Alternatively, the mono-amide (**B**) formed in the first step can further react with the diamine to provide a di-amide (**F**), which in turn can give calix[4]arene monoamido crown (**D**) or proximally bridged calix[4]arene-(bisamido)crowns (**E**).

It was interesting to note that the nitration of calix[4]arene mono-(amido)crown derivatives (**2a**–**2d**) with 5 equiv of HNO_3 (100%) in CH_3COOH/dichloromethane was determined to be complete within 5 min at room temperature to yield **3a**–**3d** (monitored by TLC). When the reaction was continued for more than 10 min, it gave a complex mixture while prolonged reaction almost always resulted in the degradation of calixarene framework. Again when the reaction was not conducted under dry conditions, it resulted in the hydrolysis of the ester function in **2a**–**2d**.

3. Preliminary investigation of synthesized calix[4]-amidocrowns for ionic recognition

In order to obtain insight into the affinity of the synthesized calix[4]amidocrowns for metal ions, the changes in their λ_{max} upon interaction with a variety of hard and soft metal cations were investigated. The affinity of calix[4]amidocrowns (**1c**, **2b**) and chromogenic calix[4]amidocrowns (**4a**, **4b** and **6a**, **6b**) for group I (Li^+, Na^+, K^+, Cs^+, and Rb^+), group II (Ca^{2+}, Mg^{2+}, and Ba^{2+}), and transition metal cations (Cr^{3+}, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ag^+, Cd^{++}, Pb^{++}, Hg^+, Hg^{2+}, Pd^{2+}, and Pt^{2+}) was examined in solution using methanol as the solvent. The changes in λ_{max} of these chromoionophores upon addition of various cations are listed in Table 2. Fig. 10 depicts the change in wavelength of absorption

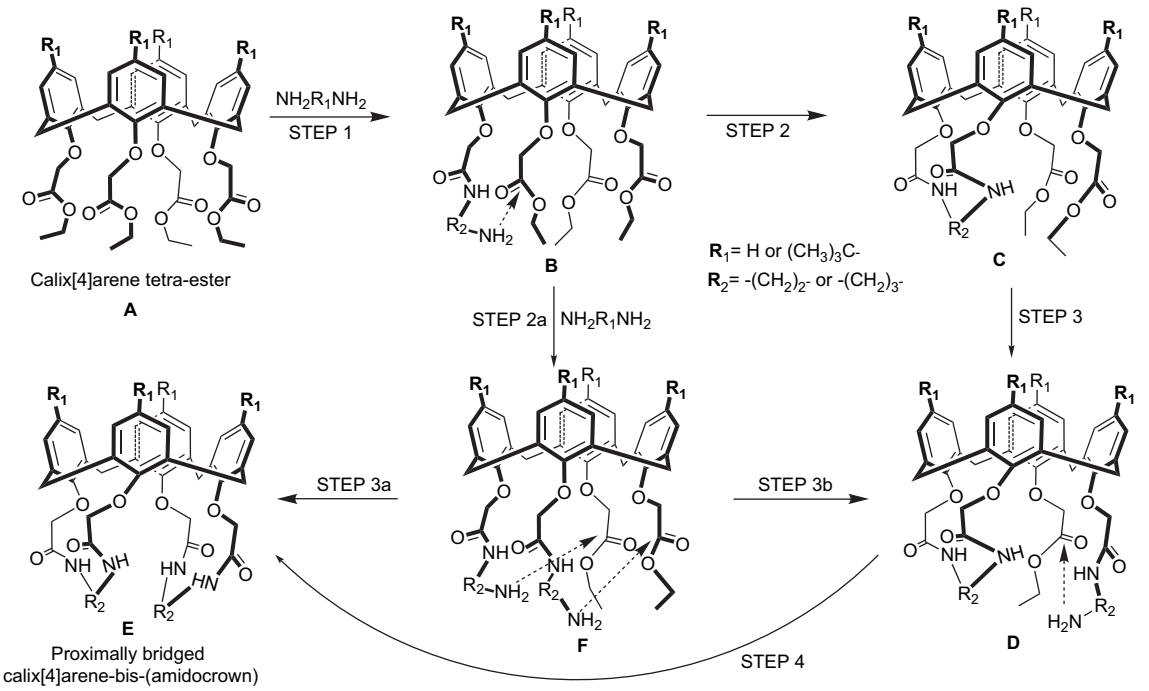


Figure 9. Mechanistic possibilities for the synthesis of proximally bridged calix[4]arene-bis-(amidocrown) derivatives from calix[4]arene tetraester.

of the synthesized compounds on addition of different alkali metal salts. Calix[4]arene (amido)crowns (**4a**, **4b** and **6a**, **6b**) were found to exhibit a red shift at about 130 nm accompanied by a profound color change on addition of excess of alkali metal ions with the appearance of a new absorption band near 500 nm. These changes could be ascribed to the basicity of the alkali metal carbonates, which tends to ionize the phenolic hydroxyls.

Table 2. Observed $\Delta\lambda_{max}$ (nm) of synthesized compounds on addition of 100 equiv. of metal ions

No.	**1c**	**2b**	**4a**	**4b**	**6a**	**6b**
λ_{max} (nm)	214, 281[a]	215, 276[a]	257, 360[a]	273, 361[a]	273, 361[a]	269, 365[a]
Salts	Metal-induced wavelength changes ($\Delta\lambda_{max}$, nm)					
Li^+	nc[b]	nc	+137	+138	+138	nc
Na^+	nc	nc	+133	+137	+138	+114
K^+	nc	nc	+134	+137	+138	+113
Rb^+	nc	nc	+134	+137	+138	+117
Cs^+	nc	nc	+130	+133	+133	+131
Mg^{2+}	nc	nc	nc	nc	nc	nc
Ca^{2+}	nc	nc	nc	nc	nc	nc
Ba^{2+}	nc	nc	nc	nc	nc	nc
Cr^{3+}	nc	nc	nc	nc	nc	nc
Fe^{3+}	nc	nc	nc	nc	nc	nc
Co^{2+}	nc	nc	nc	nc	nc	nc
Ni^{2+}	nc	nc	nc	nc	nc	nc
Cu^{2+}	nc	nc	nc	nc	nc	nc
Hg^+	−38	−4	+16	+16	+17	+15
Cd^{2+}	nc	nc	nc	nc	nc	nc
Ag^+	nc	nc	nc	+14	nc	nc
Pb^{2+}	nc	nc	nc	nc	nc	nc
Pd^{2+}	nc	nc	+10	+6	nc	nc
Pt^{2+}	nc	−12	nc	nc	nc	nc

[a] Metal-induced wavelength changes have been shown with regard to this absorption peak.
[b] nc = no change.

A selective but significant interaction was observed when Hg^+ metal ion interacted with a dilute solution of calix[4]-arene(amido)crown **1c**. A blue shift at 38 nm could be observed when excess of Hg^+ (Fig. 11a) was added to a solution of **1c** in methanol. The observed change ($\Delta\lambda_{max}$, nm) in the absorption maxima of synthesized derivatives (**1c**, **2b**, **4a**, **4b**, **6a**, and **6b**) on addition of 100 equiv of various transition metal ions has been tabulated in Table 2. It is clear from Table 2 that **1c** and **2b** have the capability to interact with Hg^+. These ionophores did not give any shift in the λ_{max} when interacted with other transition metal ions examined (Fig. 11b) (a marginal shift with platinum was observed in the case of **2b**). No interference from other ions could be observed in the present study. The inference that the interaction is due to the mercurous ions and not due to nitrate ions was confirmed by examining the effect of addition of tetrabutyl ammonium nitrate to a methanolic solution of **1c** when no shift in its λ_{max} or its intensity was observed.

We conclude that the reaction of di(ethoxycarbonylmethoxy)calix[4]arenes with diamines results in the formation of calix[4]arene(amido)mono-crown compounds through aminolysis followed by an intramolecular cyclization reaction. The calix[4]arene(amido)mono-crown compounds could be nitrated with HNO_3 (100%, obtained from the distillation of a mixture of HNO_3 and H_2SO_4)/glacial acetic acid to provide nitro substituted calix[4]arene(amido)-mono-crown compounds. They can also be converted to their azo calix[4]arene(amido)mono-crown compounds to provide additional hydrophilic and hydrophobic cavities at the lower rim and upper rim of calix[4]arenes, which can be tailored for sensing toxic and precious metal ions. Further work to modify calix[4]arene(amido) crown compounds for end use applications is in progress.

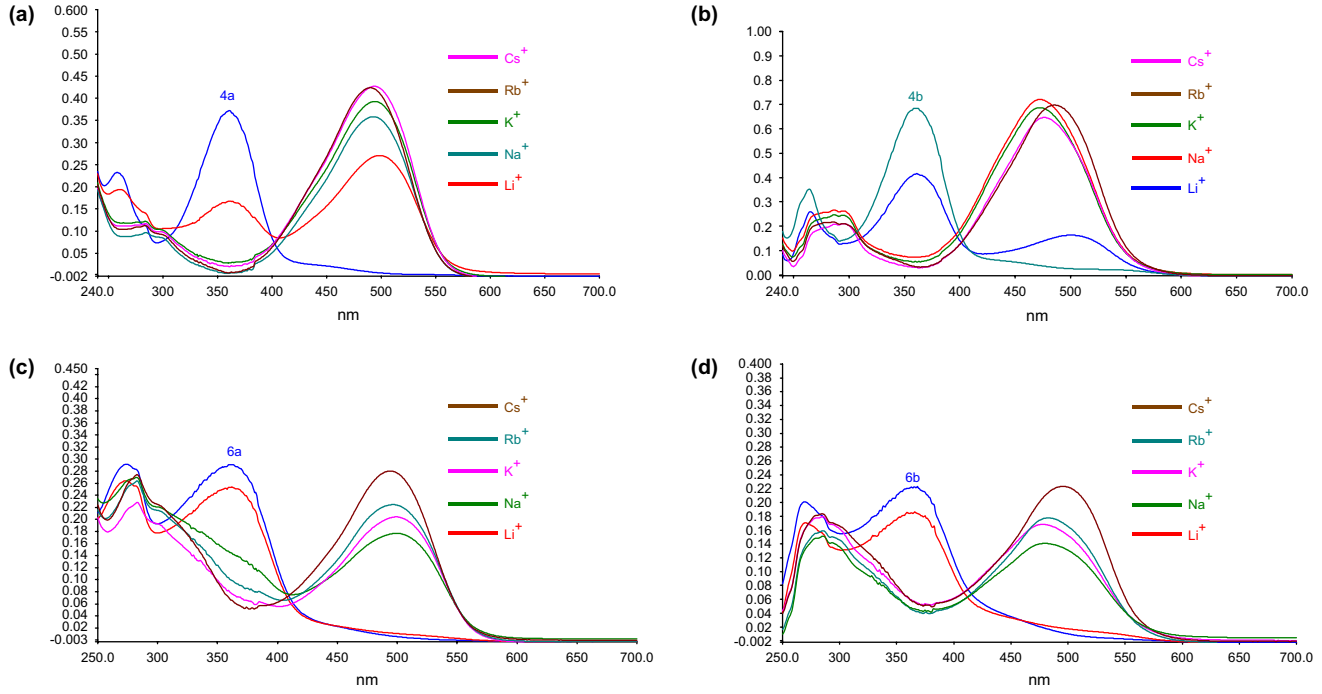


Figure 10. (a) UV–visible spectra of **4a** and shifts in its λ_{max} upon the addition of 100 equiv of alkali metal salts; (b) UV–visible spectra of **4b** and shifts in its λ_{max} upon the addition of 100 equiv of alkali metal salts; (c) UV–visible spectra of **6a** and shifts in its λ_{max} upon the addition of 100 equiv of alkali metal salts; (d) UV–visible spectra of **6b** and shifts in its λ_{max} upon the addition of 100 equiv of alkali metal salts.

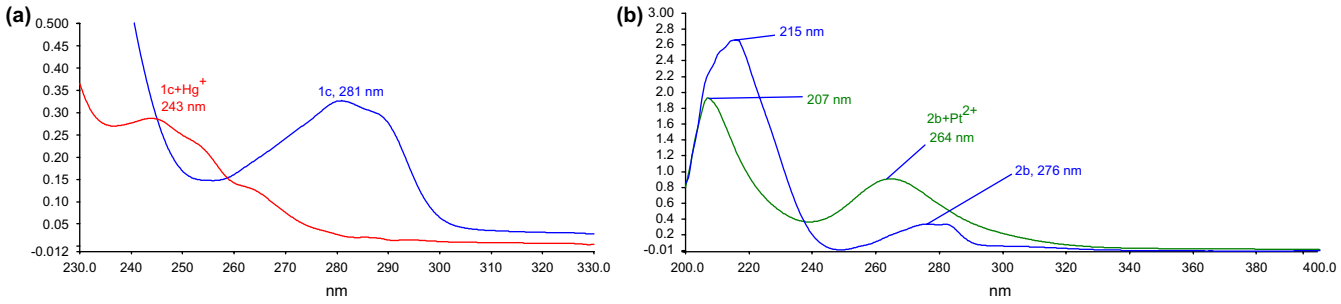


Figure 11. (a) UV–visible spectra of **1c** and shifts in its λ_{max} upon the addition of 100 equiv of Hg^{+} metal salts; (b) UV–visible spectra of **2b** and shifts in its λ_{max} upon the addition of 100 equiv of Pt^{2+} metal salts.

4. Experimental

4.1. General

All the reagents used in the study were purchased from Sigma–Aldrich or Merck and were chemically pure. The solvents used were distilled. Column chromatography was performed on silica gel (60–120 mesh) obtained from Merck. ^{1}H NMR, ^{13}C NMR, DEPT-135, and HSQC spectra were recorded on a 300 MHz Bruker DPX 300 instrument at room temperature using tetramethylsilane (TMS) at 0.00 as an internal standard. IR spectra were recorded on a Nicolet Protégé 460 spectrometer in KBr disks while X-ray data were recorded using a Bruker SMART CCD single crystal diffractometer. UV–visible spectra were obtained on a Perkin–Elmer (Lambda-3B) recording spectrophotometer. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer/Data System using Argon/Xenon (6 kV, 10 mA) as the FAB gas. Melting points were determined on an electrothermal melting point apparatus obtained from M/S Toshniwal and were uncorrected.

4.2. Preparation of starting materials

p-tert-Butylcalix[4]arene, calix[4]arene, 5,11,17,23-tetra (*p-tert*-butyl)-25,27-di(ethoxycarbonylmethoxy)-26,28-dihydroxy-calix[4]arene (**1**), 25,27-di(ethoxycarbonylmethoxy)-26,28-dihydroxy-calix[4]arene (**2**), and 5,17-dinitro-25,27-di(ethoxycarbonylmethoxy)-26,28-dihydroxy-calix[4]arene (**3**) were synthesized as described previously.[4] The analytical data for compounds **1a**, **1c**, and **2c** were found to be same as reported earlier.[9]

4.3. General procedure for the synthesis of calix[4]-arene(amido)mono-crown derivatives

Diesters (**1**, **2**) and diamines (20-30 equiv) were taken in toluene:methanol (1:1 ratio) and refluxed for 24 h. The solvent was removed under reduced pressure to yield yellowish semisolid (or solid), which was dissolved in chloroform or ethyl acetate and washed with 1 N H_2SO_4 followed by washing with water. The organic layer was collected and evaporated to dryness under reduced pressure to yield

calix[4]arene(amido)mono-crown derivatives as white solids, which were further purified by recrystallization from $CHCl_3/CH_3OH$ or CH_3OH/H_2O. Pure compounds could be isolated by leaving the recrystallizing mixture overnight at 0 °C.

4.3.1. Compound 1a. White solid, yield: 92%, mp>232 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3366, 2958, 1689. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.58 (br t, 2H, CONH), 8.29 (s, 2H, OH), 7.06 (s, 4H, ArH), 7.04 (s, 4H, ArH), 4.53 (s, 4H, OCH_2), 4.16 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 3.67 (br d, 4H, $NHCH_2$), 3.49 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 1.24 (s, 18H, $C(CH_3)_3$), 1.15 (s, 18H, $C(CH_3)_3$). FABMS m/z: 789 (M^+). Anal. Calcd for $C_{50}H_{64}N_2O_6$: C, 76.11; H, 8.18; N, 3.55. Found: C, 76.25; H, 8.20; N, 3.61. UV (λ_{max}, MeOH): 223, 280, 288 nm.

4.3.2. Compound 1b. White solid, yield: 88% mp>285 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3369, 2958, 1684. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.02 (br t, 2H, NH), 7.13 (s, 4H, ArH), 6.77 (s, 4H, ArH), 6.75 (s, 2H, OH), 4.50 (s, 4H, OCH_2), 4.14 (d, 4H, J=13.5 Hz, $ArCH_2Ar$), 3.57 (br s, 4H, NCH_2), 3.44 (d, 4H, J=13.5 Hz, $ArCH_2Ar$), 1.75 (br s, 4H, NCH_2CH_2), 1.31 (s, 18H, $C(CH_3)_3$), 0.90 (s, 18H, $C(CH_3)_3$). FABMS m/z: 817 (M^+). Anal. Calcd for $C_{52}H_{68}N_2O_6$: C, 76.44; H, 8.39; N, 3.43. Found: C, 76.61; H, 8.37; N, 3.49. UV (λ_{max}, MeOH): 208, 282, 287 nm.

4.3.3. Compound 1c. White solid, yield: 72%, mp 185 °C. IR (KBr, ν_{max}/cm^{-1}): 3430, 2958, 1673. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.89 (br s, 1H, NH), 8.35 (br t, 2H, NH), 8.03 (br s, 2H, NH), 7.13 (s, 4H, ArH), 7.11 (s, 4H, ArH), 4.54 (s, 4H, OCH_2), 4.19 (d, 4H, J=12.3 Hz, $ArCH_2Ar$), 3.57 (br s, 4H, $CONHCH_2CH_2$), 3.46 (d, 4H, J=12.3 Hz, $ArCH_2Ar$), 3.30 (br s, 4H, $CONHCH_2CH_2$), 1.15 (s, 18H, $C(CH_3)_3$), 1.09 (s, 18H, $C(CH_3)_3$). FABMS m/z: 832 (M^+). Anal. Calcd for $C_{52}H_{69}N_3O_6$: C, 75.06; H, 8.36; N, 5.05. Found: C, 75.29; H, 8.38; N, 5.15. UV (λ_{max}, MeOH): 221, 281, 287 nm.

4.3.4. Compound 1d. White solid, yield: 56%. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.88 (br s, 2H, OH), 8.33 (br t, 2H, NH), 8.03 (br s, 2H, NH), 7.13 (d, 4H, ArH), 7.11 (s, 4H, ArH), 4.54 (s, 4H, OCH_2), 4.22 (d, 4H, J=12.9 Hz, $ArCH_2Ar$), 3.67 (br s, 4H, $CONHCH_2$), 3.50 (d, 4H, J=12.9 Hz, $ArCH_2Ar$), 3.24 (br m, 8H, $CONHCH_2CH_2NHCH_2$), 1.17 (s, 18H, $C(CH_3)_3$), 1.02 (s, 18H, $C(CH_3)_3$). FABMS m/z: 875 (M^+). Anal. Calcd for $C_{54}H_{74}N_4O_6$: C, 74.11; H, 8.52; N, 6.40. Found: C, 74.34; H, 8.54; N, 6.47. UV (λ_{max}, MeOH): 220, 282, 288 nm.

4.3.5. Compound 1e. White solid, yield: 48%, mp 180 °C. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.03 (br t, 2H, NH), 7.79 (s, 2H, OH), 7.13 (s, 4H, ArH), 6.67 (s, 4H, ArH), 4.48 (s, 4H, OCH_2), 4.16 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 3.45 (br s, 4H, NCH_2), 3.39 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 1.78 (br s, 4H, $NHCH_2CH_2CH_2$), 1.25 (s, 18H, $C(CH_3)_3$), 1.03 (br s, 4H, $NHCH_2CH_2CH_2$), 0.87 (s, 18H, $C(CH_3)_3$). FABMS m/z: 845 (M^+). Anal. Calcd for $C_{54}H_{72}N_2O_6$: C, 76.74; H, 8.59; N, 3.31. Found: C, 76.95; H, 8.57; N, 3.23. UV (λ_{max}, MeOH): 220, 281, 288 nm.

4.3.6. Compound 2a. White solid, yield: 83%, mp 352 °C. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.43 (br s, 2H, NH), 8.26 (s, 2H, OH), 7.03 (d, 4H, J=7.5 Hz, ArH), 6.96 (d, 4H, J=7.5 Hz, ArH), 6.82 (t, 2H, J=7.5 Hz, ArH), 6.68 (t, 2H, J=7.5 Hz, ArH), 4.49 (s, 4H, OCH_2), 4.10 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 3.63 (br s, 4H, NCH_2), 3.46 (d, 4H, J=13.2 Hz, $ArCH_2Ar$). FABMS m/z: 565 (M^+). Anal. Calcd for $C_{34}H_{32}N_2O_6$: C, 72.32; H, 5.71; N, 4.96. Found: C, 72.48; H, 5.71; N, 4.86. UV (λ_{max}, MeOH): 218, 276, 283 nm.

4.3.7. Compound 2b. White solid, yield: 82%, mp 260 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3410, 3355, 1683. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 7.71 (br t, 2H, NH), 7.15 (s, 2H, OH), 7.14 (d, 4H, J=7.2 Hz, ArH), 6.88 (d, 4H, J=7.2 Hz, ArH), 6.81–6.74 (m, 4H, ArH), 4.51 (s, 4H, OCH_2), 4.18 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 3.63 (br s, 4H, NCH_2), 3.51 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 1.77 (br s, 4H, NCH_2CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, δ in ppm): 168.0, 152.2, 150.3, 132.1, 129.5, 129.0, 127.6, 126.3, 120.4 (ArCH, ArC, CONH), 74.9 (OCH_2), 37.6 ($CONHCH_2$), 31.1 ($ArCH_2Ar$), 25.0 ($CONHCH_2CH_2$). FABMS m/z: 593 (M^+). Anal. Calcd for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.73. Found: C, 72.69; H, 6.13; N, 4.78. UV (λ_{max}, MeOH): 218, 276, 282 nm.

4.3.8. Compound 2c. White solid, yield: 76%, mp 265 °C. IR (KBr, ν_{max}/cm^{-1}): 3405, 3350, 1680. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 9.02 (br s, 1H, NH), 8.73 (br t, 2H, CONH), 8.03 (s, 2H, OH), 7.19 (d, 4H, J=7.5 Hz, ArH), 7.06 (d, 4H, J=7.5 Hz, ArH), 6.85 (t, 2H, J=7.5 Hz, ArH), 6.66 (t, 2H, J=7.5 Hz, ArH), 4.53 (s, 4H, OCH_2), 4.22 (d, 4H, J=12.9 Hz, $ArCH_2Ar$), 3.67 (br s, 4H, $CONHCH_2$), 3.50 (d, 4H, J=12.9 Hz, $ArCH_2Ar$), 3.30 (br s, 4H, $CONHCH_2CH_2$). ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm): 170.6, 152.3, 134.0, 129.7, 129.3, 127.9, 126.4, 120.3 (ArCH, ArC, CONH), 74.4 (OCH_2), 47.3, 36.2, 30.9 ($CONHCH_2CH_2$, $ArCH_2Ar$). FABMS m/z: 608 (M^+). Anal. Calcd for $C_{36}H_{37}N_3O_6$: C, 75.15; H, 6.14; N, 6.91. Found: C, 75.32; H, 6.12; N, 6.97. UV (λ_{max}, MeOH): 210, 276, 282 nm.

4.3.9. Compound 2d. White solid, yield: 51%, mp 210 °C. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.05 (br s, 2H, NH), 8.54 (br t, 2H, CONH), 8.10 (s, 2H, OH), 7.15 (d, 4H, J=7.5 Hz, ArH), 6.86 (t, 2H, J=7.5 Hz, ArH), 6.76 (d, 4H, J=7.5 Hz, ArH), 6.62 (t, 2H, J=7.5 Hz, ArH), 4.58 (s, 4H, OCH_2), 4.32 (d, 4H, J=12.9 Hz, $ArCH_2Ar$), 3.69 (br s, 4H, $CONHCH_2$), 3.51 (d, 4H, J=12.9 Hz, $ArCH_2Ar$), 3.24 (br s, 8H, $CONHCH_2CH_2NHCH_2$). FABMS m/z: 651(M^+). Anal. Calcd for $C_{38}H_{42}N_4O_6$: C, 70.13; H, 6.51; N, 8.61. Found: C, 70.30; H, 6.53; N, 8.65. UV (λ_{max}, MeOH): 216, 276, 283 nm.

4.3.10. Compound 2e. White solid, yield: 26%, mp 290 °C. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.73 (br s, 2H, NH), 8.01 (s, 2H, OH), 7.01 (d, 4H, J=7.2 Hz, ArH), 6.88 (d, 4H, J=7.2 Hz, ArH), 6.76 (t, 2H, J=7.2 Hz, ArH), 6.66 (t, 2H, J=7.2 Hz, ArH), 4.51 (s, 4H, OCH_2), 4.07 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 3.44 (br s, 4H, NCH_2), 3.40 (d, 4H, J=13.2 Hz, $ArCH_2Ar$), 1.70 (br s, 8H, $NHCH_2CH_2CH_2$). FABMS m/z: 621 (M^+). Anal. Calcd for $C_{38}H_{40}N_2O_6$: C, 73.53; H, 6.50; N, 4.51. Found: C, 73.79; H, 6.51; N, 4.57. UV (λ_{max}, MeOH): 218, 277, 284 nm.

4.4. General procedure for the synthesis of nitro substituted calix[4]arene(amide)mono-crown analogs

4.4.1. Route-A. To a solution of corresponding calix[4]-arene(amide)mono-crown (**2a**, **2b**, **2d**, and **2e**) in a mixture of dichloromethane and glacial acetic acid was added 100% HNO_3 at 0 °C. The reaction mixture was stirred at room temperature for 5–10 min after which it was poured into water. The water layer was extracted with dichloromethane, the organic layer was washed with water, and then evaporated. Recrystallization of the residue from chloroform/methanol produced sufficiently pure compounds for characterization through spectroscopy.

4.4.2. Route-B. Dinitro diester derivative (**3**) and diamine (20–30 equiv) in toluene:ethanol (1:1 ratio) were refluxed for 24 h. The solvent was removed under reduced pressure to yield a yellowish solid, which was dissolved in chloroform or ethyl acetate and washed with 1 N H_2SO_4 followed by washing with water. The organic layer was collected and evaporated to dryness under reduced pressure to yield nitro substituted calix[4]arene(amido)mono-crown derivatives as yellowish solids.

4.4.2.1. Compound 3a. Yellow solid, yield: 78%, mp>220 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3376, 1687, 1520, 1442, 1338. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.41 (s, 2H, O*H*), 8.27 (s, 4H, Ar*H*), 8.14 (br s, 2H, N*H*), 7.28 (d, 4H, *J*=5.7 Hz, Ar*H*), 6.97 (t, 2H, *J*=5.7 Hz, Ar*H*), 4.57 (s, 4H, OCH_2), 4.26 (d, 4H, *J*=12.9 Hz, ArCH_2Ar), 3.82 (d, 4H, *J*=12.9 Hz, ArCH_2Ar), 3.51 (br s, 4H, NCH_2). FABMS *m/z*: 655 (M^+). Anal. Calcd for $C_{34}H_{30}N_4O_{10}$: C, 62.38; H, 4.62; N, 8.56. Found: C, 62.54; H, 4.60; N, 8.59.

4.4.2.2. Compound 3b. Yellow solid, yield: 80%, mp>220 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3410, 3355, 1683. ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 8.17 (s, 2H, O*H*), 8.11 (s, 4H, Ar*H*), 7.31 (br s, 2H, N*H*), 6.99 (d, 2H, *J*=7.2 Hz, Ar*H*), 6.92 (t, 2H, *J*=7.2 Hz, Ar*H*), 4.65 (s, 4H, OCH_2), 4.22 (d, 4H, *J*=13.2 Hz, ArCH_2Ar), 3.66 (br s, 4H, NCH_2), 3.62 (d, 4H, *J*=13.2 Hz, ArCH_2Ar), 1.77 (br s, 4H, NCH$_2$CH_2). FABMS *m/z*: 683 (M^+). Anal. Calcd for $C_{36}H_{34}N_4O_{10}$: C, 63.34; H, 5.02; N, 8.21. Found: C, 63.61; H, 5.00; N, 8.25.

4.4.2.3. Compound 3c. Yellow solid, yield: 77%, mp>220 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3394, 1655, 1592, 1464, 1263. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 8.31 (D_2O exchangeable, br s, 2H, O*H*), 8.24 (br s, 4H, ArH_{nitro}), 7.80 (D_2O exchangeable, br t, 2H, N*H*), 7.17 (br d, 4H, Ar*H*), 6.90 (br t, 2H, Ar*H*), 4.47–2.91 (br m, 21H, CH_2, N*H*). FABMS *m/z*: 698 (M^+). Anal. Calcd for $C_{36}H_{35}N_5O_{10}$: C, 61.97; H, 5.06; N, 10.04. Found: C, 62.02; H, 5.05; N, 10.08.

4.4.2.4. Compound 3d. Yellow solid, yield: 58%, mp>220 °C (decomp.). IR (KBr, ν_{max}/cm^{-1}): 3390, 1659, 1547, 1464, 1259. ^1H NMR (300 MHz, DMSO-d_6, δ in ppm): 8.38 (D_2O exchangeable, br s, 2H, O*H*), 8.26 (br s, 4H, ArH_{nitro}), 7.82 (D_2O exchangeable, br t, 2H, N*H*), 7.17 (br d, 4H, Ar*H*), 6.95 (br t, 2H, Ar*H*), 4.50–2.82 (br m, 26H, CH_2, N*H*). DEPT-135 NMR (75 MHz, DMSO-d_6, δ in ppm): 129.5, 125.4, 124.4 (Ar*C*H), 73.1 (O*C*H_2), 46.4, 42.3, 35.3, 30.9 (NH*C*H_2, Ar*C*H_2Ar). FABMS *m/z*: 741 (M^+). Anal. Calcd for $C_{38}H_{40}N_6O_{10}$: C, 61.61; H, 5.44; N, 11.35. Found: C, 61.81; H, 5.46; N, 11.40.

4.5. General procedure for the synthesis of (pyridylazo)calix[4]arene(amido)mono-crown derivatives

The pyridyl diazonium chloride solutions were prepared by the addition of an aqueous solution of sodium nitrite (1.5 equiv of amine) into a solution of 3-aminopyridine (3 equiv of calix[4]arene(amido)mono-crown) in concd HCl (10–20 equiv) and distilled water (5–10 ml) at 0–5 °C. The diazotized 3-aminopyridine solution was slowly added into an ice-cold (0–5 °C) solution of calix[4]arene(amido)-mono-crown in dimethylformamide/methanol (8:5) and sodium acetate (pH 7–9) with constant stirring to give a dark red suspension. The reaction mixture was stirred for 3 h at 0–5 °C and then for 30 min at room temperature. The suspension was poured into water, acidified with concd HCl to give a yellow to dark red precipitate, which was filtered to give a mixture of products. The mixture was then separated by column chromatography (silica gel) to give substituted (pyridylazo)calix[4]arene(amido)mono-crown derivatives.

4.5.1. Compound 4a. This was separated by column chromatography of the crude mixture by using chloroform/methanol (9.9:0.1) as the eluant as a yellowish solid, yield: 28%, mp>240 °C (decomp.). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.08 (s, 1H, Py*H*), 8.88 (s, 1H, O*H*), 8.58 (d, 1H, *J*=7.5 Hz, Py*H*), 8.37 (br s, 2H, N*H*), 8.25 (s, 1H, O*H*), 8.02 (d, 1H, *J*=8.1 Hz, Py*H*), 7.72 (s, 2H, Ar*H*), 7.35 (dd, 1H, *J*=4.8 Hz, Py*H*), 7.10–6.63 (m, 9H, Ar*H*), 4.57 (t, 4H, OCH_2), 4.17 (d, 4H, *J*=13.5 Hz, ArCH_2Ar), 4.11 (d, 2H, *J*=13.5 Hz, ArCH_2Ar), 3.63 (br s, 4H, NCH_2), 3.62 (d, 2H, *J*=13.2 Hz, ArCH_2Ar), 3.50 (d, 2H, *J*=13.2 Hz, ArCH_2Ar). FABMS *m/z*: 670 (M^+). Anal. Calcd for $C_{39}H_{35}N_5O_6$: C, 69.94; H, 5.27; N, 10.46. Found: C, 69.78; H, 5.29; N, 10.49. UV (λ_{max}, MeOH): 257, 360 nm.

4.5.2. Compound 4b. This was separated by column chromatography using chloroform/methanol (9.9:0.1) as the eluant as a yellowish solid, yield: 58%, mp>240 °C (decomp.). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.15 (s, 2H, Py*H*), 8.94 (s, 2H, O*H*), 8.65 (br s, 2H, Py*H*), 8.43 (broad s, 2H, N*H*), 8.10 (d, 2H, *J*=8.1 Hz, Py*H*), 7.81 (s, 2H, Ar*H*), 7.44 (dd, 2H, *J*=4.8 Hz, Py*H*), 7.19 (d, 4H, *J*=7.8 Hz, Ar*H*), 6.99 (t, 2H, *J*=7.5 Hz, Ar*H*), 4.65 (s, 4H, OCH_2), 4.25 (d, 4H, *J*=13.5 Hz, ArCH_2Ar), 3.74 (s, 4H, NCH_2), 3.73 (d, 4H, *J*=13.5 Hz, ArCH_2Ar). FABMS *m/z*: 775 (M^+). Anal. Calcd for $C_{44}H_{38}N_8O_6$: C, 68.21; H, 4.94; N, 14.46. Found: C, 68.01; H, 4.96; N, 14.51. UV (λ_{max}, MeOH): 263, 360 nm.

4.5.3. Compound 5a. This was obtained by column chromatography using chloroform/methanol (9.9:0.1) as the eluant in the form of a yellowish solid, yield: 7%, mp>240 °C (decomp.). ^1H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.14 (s, 1H, Py*H*), 8.88 (s, 1H, OH), 8.58 (d, 1H, *J*=7.5 Hz, Py*H*), 8.37 (br s, 2H, N*H*), 8.25 (s, 1H, O*H*), 8.02 (d, 1H, *J*=8.1 Hz, Py*H*), 7.72 (s, 2H, Ar*H*), 7.35 (dd, 1H, *J*=4.8 Hz, Py*H*), 7.10–6.63 (m, 9H, Ar*H*), 4.51 (s, 4H, OCH_2), 4.18 (d, 4H, *J*=13.2 Hz, ArCH_2Ar), 3.63 (br s, 4H, NCH_2), 3.51 (d,

4H, J=13.2 Hz, ArCH_2Ar), 1.77 (br s, 4H, NCH$_2$CH_2). FABMS m/z: 698 (M^+). Anal. Calcd for $C_{41}H_{39}N_5O_6$: C, 69.94; H, 5.27; N, 10.04. Found: C, 69.78; H, 5.28; N, 9.98.

4.5.4. Compound 5b. This was obtained by column chromatography using chloroform/methanol (9.9:0.1) as the eluant as a yellowish solid, yield: 28%, mp>240 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$, δ in ppm): 9.15 (s, 2H, PyH), 8.94 (s, 2H, OH), 8.65 (br s, 2H, PyH), 8.43 (br s, 2H, NH), 8.10 (d, 2H, J=8.1 Hz, PyH), 7.81 (s, 2H, ArH), 7.44 (dd, 2H, J=4.8 Hz, PyH), 7.19 (d, 4H, J=7.8 Hz, ArH), 6.99 (t, 2H, J=7.5 Hz, ArH), 4.51 (s, 4H, OCH_2), 4.18 (d, 4H, J=13.2 Hz, ArCH_2Ar), 3.63 (br s, 4H, NCH_2), 3.51 (d, 4H, J=13.2 Hz, ArCH_2Ar), 1.77 (br s, 4H, NCH$_2$CH_2). FABMS m/z: 803 (M^+). Anal. Calcd for $C_{46}H_{42}N_8O_6$: C, 68.81; H, 5.27; N, 13.96. Found: 68.72; H, 5.29; N, 13.76.

4.5.5. Compound 6a. This was purified by column chromatography using chloroform/methanol (9.9:0.1) as the eluant as a red solid, yield: 27%, mp>240 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6, δ in ppm): 9.10 (s, 1H, PyH), 8.64 (s, 1H, OH), 8.61 (d, 1H, J=2.7 Hz, PyH), 8.24–8.16 (br m, 4H, OH and NH), 8.05 (d, 1H, J=8.1 Hz, PyH), 7.70 (s, 2H, ArH), 7.38 (dd, 1H, J=4.5 Hz, PyH), 7.07–6.71 (m, 9H, ArH), 4.48 (dd, 4H, J=5.1 Hz, OCH_2), 4.11 (d, 4H, J=13.2 Hz, ArCH_2Ar), 3.91–3.31 (br m, 8H, CONHCH_2CH_2), 3.54 (d, 2H, J=13.5 Hz, ArCH_2Ar), 3.43 (d, 2H, J=13.5 Hz, ArCH_2Ar). FABMS m/z: 713 (M^+). Anal. Calcd for $C_{41}H_{40}N_6O_6$: C, 69.09; H, 5.66; N, 11.79. Found C, 68.90; H, 5.64; N, 11.76. UV (λ_{max}, MeOH): 273, 361 nm.

4.5.6. Compound 6b. This was separated by column chromatography using chloroform/methanol (9.8:0.2) as the eluant as a red solid, yield: 51%, mp>240 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6, δ in ppm): 9.17 (s, 2H, PyH), 8.73 (s, 2H, OH), 8.68 (d, 2H, J=3.3 Hz, PyH), 8.28–8.16 (br m, 3H, NH), 8.13 (d, 2H, J=8.4 Hz, PyH), 7.77 (s, 4H, ArH), 7.46 (dd, 2H, J=5.1 Hz, PyH), 6.97 (d, 4H, J=8.4 Hz, PyH), 6.83 (t, 2H, J=8.4 Hz, PyH), 4.57 (s, 4H, OCH_2), 4.18–3.82 (br m, 12H, ArCH_2Ar and CONHCH_2CH_2), 3.56 (d, 4H, J=13.8 Hz, ArCH_2Ar). FABMS m/z: 818 (M^+). Anal. Calcd for $C_{46}H_{43}N_9O_6$: C, 67.55; H, 5.30; N, 15.41. Found C, 67.42; H, 5.28; N, 15.37. UV (λ_{max}, MeOH): 269, 365 nm.

4.6. X-ray structure determination of 2a

The crystals of **2a** were obtained when the compound was crystallized from $CHCl_3$/CH_3OH (9:1). X-ray crystal data for **2a**—$C_{34}H_{32}N_2O_6\cdot CCl_3$, M=682.98, triclinic, a=10.170(11) Å, b=12.208(13) Å, c=14.442(16) Å, α=112.667(19)°, β=95.41(2)°, γ=90.08(2)°, V=1646(3) Å^3, Z=2, Dc=1.378 gcm^{-3}, μ (Mo Kα)=0.327 mm^{-1}, GOF = 1.065, space group = P-1. Intensity data were collected up to θ=40° by using 2θ scanning mode with graphite filtered Mo Kα radiation (λ=0.71073) on a 0.219×0.168×0.098 mm^3 crystal at 298 K. A total of 8897 reflections were measured, 3075 were independent and of which 1463 [I>2(I)] were observed. The structure was solved by direct methods and refined by full matrix least-square techniques on F^2 using SHELXTL. All the nonhydrogen atoms were refined anisotropically. The solvent molecule present in exocyclic fashion was highly disordered. C–H hydrogen atoms were placed in geometrically calculated positions by using a riding model. SADABS was applied for absorption correction. Final R indices [I>2σ(I)]R1=0.0987, wR2=0.2044, and R indices (all data) R1=0.1600, wR2=0.2435 was found for 3075 observed reflections, 0 restraints, and 444 parameters. The apparently high value for R factor probably originates from the disorder due to the solvent. Torsion angles and H-bonding were calculated by using PARST. Crystal data have been deposited at the Cambridge Crystallographic Data Center, under reference CCDC 281639.

4.7. General procedures for UV–visible experiments

All the UV–visible experiments were carried out in methanol unless otherwise specified. Any shifts in the UV–visible spectra of the synthesized compound were recorded on addition of metal salt (100 equiv) solutions. Carbonates-(Li^+, Na^+, K^+, Rb^+, Cs^+, Ag^+), Chlorides-(Mg^{2+}, Ca^{2+}, Ba^{2+}, Cr^{3+}, Fe^{2+}, Cd^{2+}, Pb^{2+}, Hg^{2+}, Pd^{2+}, and Pt^{2+}), acetate (Co^{2+}, Ni^{2+}, Cu^{2+}), and nitrate (Hg^+) salts were used for the UV–visible experiments.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.047.

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Effect of a perfluorocyclopentene core unit on the structures and photoluminescence of fluorene- and anthracene-based compounds

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Abstract—A novel series of blue luminescent compounds, in which three identical functional groups, such as fluorene, anthracene, and spirobifluorene, are linked distortedly around a perfluorocyclopentene core, have been synthesized and characterized. The introduction of a perfluorocyclopentene linkage into the molecular framework leads to an enhancement of the photoluminescence (PL) efficiency and thermal stability. All compounds exhibit intense blue photoluminescence, which has been attributed to fluorene- or anthracene-based $\pi \rightarrow \pi^*$ transitions. The maximum emission wavelengths of all compounds at room temperature are in the region of 420–480 nm, with higher PL quantum efficiencies than in 9,10-diphenylanthracene. The electroluminescent (EL) properties of compound **4**, 1,2-bis(9,9′-spirobifluoren-2-yl)-3,3,-4,4,5,5-hexafluorocyclopentene, were investigated. A multilayer EL device with the configuration of ITO/2TNATA(60 nm)/NPB(20 nm)/ADN:2%-compound-**4**(35 nm)/Alq_3(20 nm)/LiF(2 nm)/Al has been successfully fabricated.

1. Introduction

Luminescent organic/organometallic materials are currently of great interest due to their various applications in photochemistry,[1] organic light-emitting diodes (OLEDs),[2] and chemical sensors for small molecules.[3] Among these organic materials, fluorene and/or anthracene-based compounds have been regarded as excellent fluorescent materials because of their ability to achieve high thermal stability as well as high photoluminescent (PL) efficiency.[4] Fluorene and/or anthracene-based compounds, in particular, are often used as emitting materials in electroluminescent (EL) devices.[5] Based on previous reports, promising low molecular weight emitter for use in OLEDs should have an appropriate HOMO/LUMO band gap as compared to those of the electron- and hole-transporting materials, high photoluminescent quantum yield (Φ_{PL}), good film-forming properties, and durability to heat during the vacuum deposition.[6] The Φ_{PL} is a major interest associated with the improvement of EL device efficiency, since the two properties are generally related.[7] With the aim of increasing PL efficiency, several approaches have been introduced. These include the attachment of strongly fluorescent units,[5j] such as anthracene, fluorene, and pyrene to the molecular framework, the extension of π-conjugation[8] and the combination of host–guest functions by energy transfer.[5i,9] Especially, the introduction of electron-withdrawing groups, such as fluoro- or cyano groups, renders a molecule with high PL efficiency by inter- or intramolecular interactions despite of the diminution of the HOMO and LUMO levels.[10] Moreover, it is well known that the fluorine groups bound to molecular frameworks enhance a molecule's thermal stability and enable it to sublime easily without decomposition.[11]

During our ongoing effort on the development of a variety of luminescent materials, we have observed that the presence of a linker between two chromophores has a remarkable influence on the thermal and photophysical properties.[12] The perfluorocyclopentene moiety as a linker was chosen for following reasons: (i) in EL devices performance using low-weight molecules, the molecules should be easily sublimed thermally stable, and have high PL efficiency, as the fabrication of these devices is generally performed by vacuum deposition at high temperature. Based on previous reports, compounds bearing fluorinated functional groups are satisfactory to these considerations. (ii) Photochromic materials, such as diarylethene, have recently attracted

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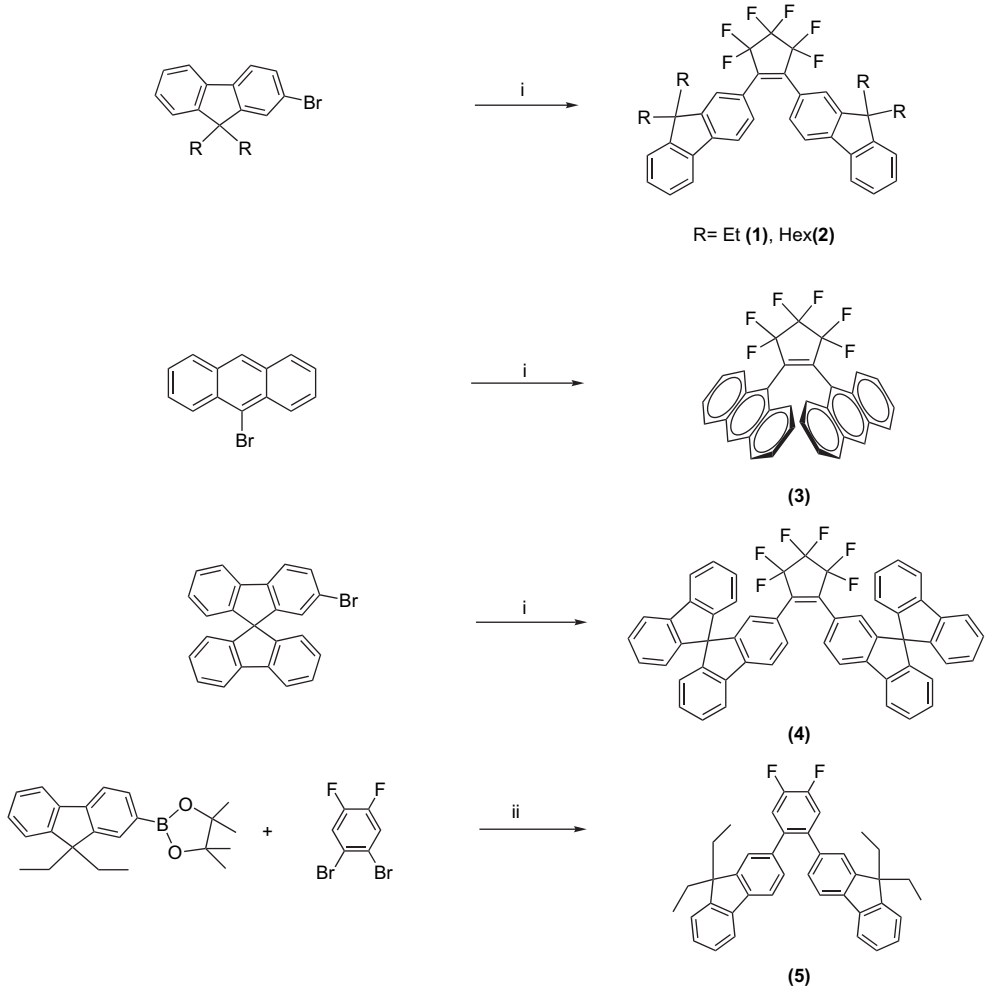
interest in view of their potential applications for visible image formation, optical data storage, and optical switching.[13] Dithienylethene derivatives were not only regarded as promising photochromic compounds, but they also showed high thermal stability and excellent fatigue-resistant properties. In diarylethene systems, the perfluorocyclopentene unit could play a key role in the alteration of confomers and photophysical properties.[13] Therefore, we expected that the combination of highly fluorescent fluorene or anthracene groups and fluorinated functional groups would be the best way to develop efficient emitting materials and satisfy above considerations. (iii) The introduction of two bulky triphenylamine moieties into the dithienylethene framework increases the population of the antiparallel conformer of the molecule, leading to higher conversion of a photocyclization reactions.[13a] Very high quantum efficiency is shown for these molecules in photocyclization reactions ($\Phi_{o\text{-}c}$), however, the study on OLED performance using their derivatives still remains scarce. Herein, we describe the results of our investigation on the preparation, structural characterization, electrochemical behavior, optical properties, and the fabrication of multilayer light-emitting devices of a series of fluorene and anthracene derivatives based on perfluorocyclopentene.

2. Result and discussion

2.1. Syntheses and structures

To develop new molecules with high fluorescence quantum efficiency, we have designed and synthesized a novel class of compounds based on diarylethene. The synthetic routes to **1**–**4** are given in Scheme 1. These compounds were prepared by the addition of octafluorocyclopentene to the corresponding lithiated compound, prepared from the reaction of a small excess of *n*-BuLi and the bromoarene at −78 °C. The standard workup and crystallization from CH_2Cl_2/hexane gives the titled compounds as pure pale yellow or colorless solids in moderate yields (69–82%). In addition, to evaluate the effect of a perfluorocyclopentene ring on structural features and photoluminescence, we have synthesized an aromatic analogue of compound **1**, compound **5**, through Pd-mediated Suzuki coupling. All compounds are stable in air and soluble in common organic solvents but only slightly soluble in hexane and pentane. The structures of **1**–**5** have been characterized by ^{1}H NMR, ^{13}C NMR, and elemental analyses, including X-ray diffraction analysis of **1** and **5**. In order for molecular organic materials to be useful in EL devices, they should be thermally and morphologically



Scheme 1. Synthetic routes of **1**–**5**. Reagents and conditions: (i) *n*-BuLi/THF at −78 °C, octafluorocyclopentene (0.5 equiv); (ii) K_2CO_3, benzyltrimethylammoniumchloride, $Pd(PPh_3)_4$ (5 mol %), toluene.

Table 1. Thermal properties of **1**–**5**

Compound	T_g/°C	T_m/°C
1	—	116
2	—	93
3	—	365
4	115	273
5	—	173

stable.[17] Therefore, we performed DSC experiments to investigate the glass-transition temperatures and phase transitions for compounds **1**–**5**. Well-resolved melting transitions were observed in all cases (Table 1).

Compounds **1**–**3** did not show glass transition during either the first or second heating cycle. The melting transitions of **1**, **2**, and **3** are at 116, 93, and 365 °C, respectively. This suggests that the combination of the perfluorocyclopentene linkage and anthracene unit leads to a dramatic increase in melting transition. In contrast, the first heating cycle of **4** revealed high glass-transition temperature at 115 °C without any crystallization transition, followed by melting at 273 °C. The glass transition observed is likely attributable to a nonplanar structure and the spiro-linked bifluorene moieties of **4**. All compounds showed consistent and fully reproducible DSC diagrams during two cycles of heating and cooling, indicating that these compounds are thermally stable up to their melting points at least. The high glass-transition temperature of **4** makes it potentially useful for applications in EL devices.

To better understand the solid-state nature, single crystal X-ray diffraction analysis was conducted for **1** and **5**. Colorless crystals of **1** and **5** suitable for X-ray analysis were obtained by the slow evaporation in CH_2Cl_2 and hexane. The crystal structures and selected bond lengths and angles of **1** and **5** are presented in Figures 1 and 2, respectively.

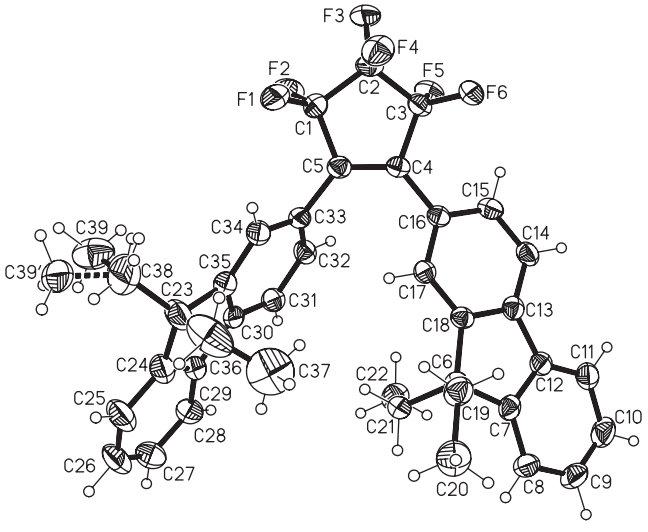


Figure 1. Molecular structure of **1** with atom labeling schemes and 50% thermal ellipsoids. Selected bond distances and angles: F(1)–C(1) 1.359(4), F(2)–C(1) 1.355(4), F(3)–C(2) 1.344(3), F(4)–C(2) 1.341(3), F(5)–C(3) 1.367(3), F(6)–C(3) 1.354(3), C(4)–C(16) 1.475(4), C(5)–C(33) 1.484(4), F(1)–C(1)–F(2) 105.8(2), F(3)–C(2)–F(4) 107.9(2), F(5)–C(3)–F(6) 105.9(2), C(16)–C(4)–C(5)–C(33) 7.5(5).

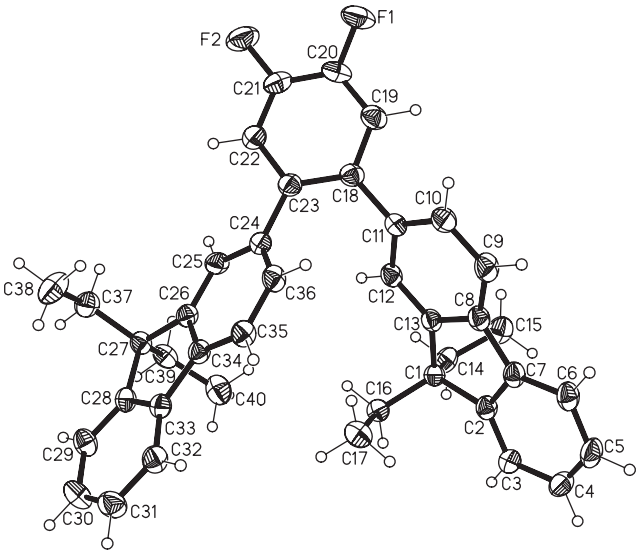


Figure 2. Molecular structure of **5** with atom labeling schemes and 50% thermal ellipsoids. Selected bond distances and angles: F(1)–C(20) 1.352(2), F(2)–C(21) 1.356(2), C(11)–C(18) 1.494(3), C(18)–C(23), 1.411(3), C(23)–C(24) 1.492(3), C(11)–C(18)–C(23)–C(24) 9.4(4).

As shown in Figure 1, two fluorene groups connected by the hexafluorocyclopentene linker in compound **1** are twisted with respect to each other, and the hexafluorocyclopentene ring is not coplanar with either of the two fluorene rings. Interestingly, the dihedral angles between hexafluorocyclopentene ring and two fluorene rings are not the same (54.3(1)° and 29.3(1)° for the C1–C5 ring and the C33 or C16 fluorene rings, respectively) and the dihedral angle between the two fluorene rings is 50.38(5)°. The nonplanarity of **1** is clearly caused by the steric hindrance between C32–H and C17–H atoms. The bond lengths C5–C33 and C4–C16 are 1.484(4) and 1.475(4) Å, respectively, and the torsion angle of C33–C5–C4–C16 is 7.5(5)°, similar to those of previously reported diarylethene compounds.[18] Compound **1** has several intermolecular interactions that appear to direct the expanded packing of the solid-state structure. The packing diagram (see Supplementary data) displays puckered 2-D sheets of molecules with slipped C–H···F intermolecular interactions (C9···F1, 3.602(4) Å; C9–H9–F1, 171.8°; C28···F2, 3.298(4) Å; C28–H28–F2, 128.4°; C15···F5, 3.305(3)Å; C15–H15–F5, 148.6°). Moreover, a F···Cπ interaction (F4···C5) also exists between two adjacent sheets, with a distance of ca. 3.160(3) Å. Additional intermolecular interactions, such as π–π stacking, were not found in the packing structure of **1**.

For compound **5**, the bond lengths of C11–C18 and C23–C24 are 1.494(3) and 1.492(3) Å, respectively, the torsion angle of C11–C18–C23–C24 is 9.4(4)°, and the dihedral angle between two fluorene rings is 54.95(3)°, which are slightly longer and larger than those of compound **1**. The differences of these values between **1** and **5** may be caused by the fact that the geometry of the linker between the two fluorene moieties changes from a pentagon to hexagon. This geometrical change leads to a reduction in the linkage angle from 72° to 60°. In contrast to **1**, the dihedral angles in **5** between the phenyl ring and the two fluorene rings are almost identical (48.82(6)° and 44.80(7)° between the phenyl ring and C11 or C24 fluorene ring, respectively). Several

intermolecular interactions are also observed in crystal packing. The distances between the carbon (C9, C12, C15C, and C32) and the fluorine (F1, F2) atoms on two adjacent molecules are in the range of approximately 2.59–2.64 Å. The packing diagram (see Supplementary data) of **5** displays a 1-D column-like structure along the *b*-axis, using the C–H···F intermolecular interactions.

Although compounds **1** and **5** have similar arrangements and intermolecular interactions in the crystal lattice, it is noteworthy that the perfluorocyclopentene ring of compound **1** has considerable conjugation with two fluorene groups, as indicated by their much smaller dihedral angles (29.3(1)°–35.7(1)°) with the perfluorocyclopentene ring relative to those of compound **5**. Both compounds **1** and **5** have interesting spatial arrangements in the crystal lattice. The fluorene groups linked by cyclopentene are oriented in the same direction, despite the presence of bulky alkyl groups at the fluorene 9-position.

2.2. Optical and electrochemical properties

The absorption and photoluminescence spectra in dilute solution and in the solid state (thin film) are depicted in Figures 3 and 4, respectively. Table 2 summarizes the optical data of **1**–**5**.

The optical band gaps of all compounds were determined by their corresponding absorption threshold in thin films. UV–vis spectra of **1**, **2**, and **4** exhibit intense absorption band between 250 and 400 nm (ε>23,800 $mol^{-1}\,dm^3\,cm^{-1}$), indicating that the electronic transitions are mostly fluorene-centered π–π*. For compound **3**, the absorption spectrum exhibits the characteristic vibrational pattern of the isolated anthracene group at 353, 370, and 409 nm. The absorption patterns of **1**, **2**, and **4** are similar in the 280–450 nm region. To examine the effect of the perfluorocyclopentene linkage on the electronic transition, we measured the absorption spectrum of **5**, in which perfluorocyclopentene is replaced by 1,2-difluorobenzene, under the same conditions. Interestingly, the maximum peak observed for **5** exhibits a significant blue shift (λ_{max}=392 nm) relative to those of **1**, **2**, and **4**. In addition, the UV edge in **5** appears at much higher energy than in **1**, **2**, and **4**. This result can be explained by strong π(fluorene) conjugation associated with π(perfluorocyclopentene) in **1**, **2**, and **4**. Considering these observations,

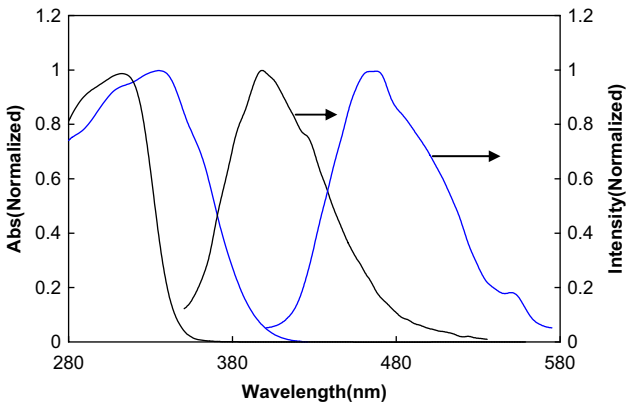


Figure 3. Absorption and emission spectra of **1** and **5** in CH_2Cl_2 at room temperature; compound **1** (blue), compound **5** (black), respectively.

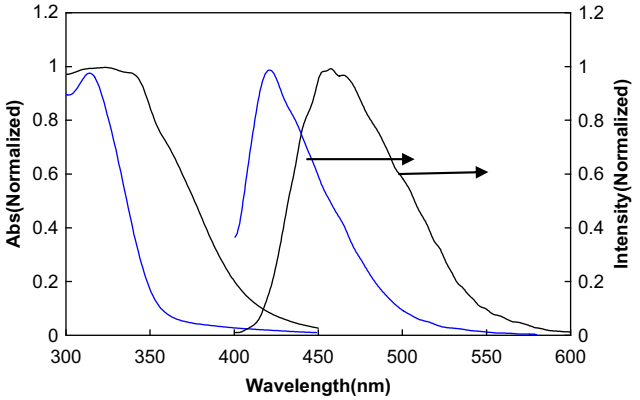


Figure 4. Absorption and emission spectra of **1** and **5** in thin film at room temperature; compound **1** (blue), compound **5** (black), respectively.

Table 2. Optical and electrochemical data for **1**–**5**

Compound	λ_{abs} (nm)		λ_{PL} (nm)		Φ_{PL}	E_g^{opt} (eV)
	Solution	Film	Solution	Film		
1	332, 353	323	455	458	>0.95	3.06
2	335	321	451	456	>0.95	3.19
3	353, 370, 392	362, 383, 409	421	501	0.41	2.76
4	328	309	459	461	0.90	3.09
5	312	314	392	421	>0.95	3.50

perfluorocyclopentene unit has a significant effect on the electronic transition energies. The emission spectra of compounds **1**–**5** in solution and as thin films at room temperature are dominated by fluorescence in the region of 400–550 nm, as supported by less than 1 ns lifetime in excited state. The emissions of all compounds in thin films, prepared by spin coating from a CH_2Cl_2/toluene solution onto a quartz plate, exhibit red-shifts of 5–20 nm to those in dilute solution. These red-shifts observed in the solid state are likely attributable to the difference in dielectric constant of the environment.[19] For compounds **1**, **2**, and **4**, the λ_{max} values of emission spectra in both solution and thin films are similar (~460 nm in thin films), and still red-shifted relative to **5**. This result can be also explained by correlating the electronic and structural effects due to the perfluorocyclopentene unit. To further investigate the electronic effects caused by the addition of perfluorocyclopentene unit, cyclic votammetry experiments were carried out using ferrocene (Fc/Fc^+) as the internal standard. Due to the limited range available in CH_2Cl_2, and inability of our instrument to measure reliable reduction potentials in the range of −2.4 to −3.5 V, we have obtained only the reliable oxidation potentials for **1** and **5**. The electrochemical behavior in aryl-substituted fluorene analogues has been described such that the irreversible oxidative and reductive processes involve the fluorene and various aryl-substituents, respectively.[4] Molecular orbital calculations for **1** and **5** provide evidence that the HOMO levels are mostly due to fluorene-based π-orbitals involving some π-orbital contributions from the linker. Upon the anodic sweep in a solvent mixture of CH_2Cl_2 and CH_3CN, irreversible oxidations are observed at 0.86 and 0.89 V for **1** and **5**, respectively. However, similar onset potentials of **1** and **5** appear at 0.75 and 0.74 V, respectively (see Supplementary data). These electrochemical behaviors indicate that the electron-withdrawing effect from the

perfluorocyclopentene unit does not have a significant influence on the HOMO energy levels, as compared to 1,2-difluorobenzene. The reductive process of the fluorene derivatives was also shown to be due to the fluorine, and is affected by the various substituents bound to the fluorene moiety. More effective conjugation stabilizes the LUMO, leading to a decreased reduction potential. Although we could not observe the reductive process, the reduction potential of **1** should be lower relative to compound **5**, as supported by the structural data and the optical absorption threshold. Another fact affecting the nature of the luminescence in molecular materials is intermolecular interactions in the solid state. There were F···Cπ interactions in crystal packing for **1**, while the intermolecular interactions, such as those of C–F, C–H, and π–π stacking, were not observed in **5**. In general, effective intermolecular interactions contribute to red-shifted absorption and emission energies, leading to lower band gaps. Therefore, the red-shifted absorption and emission maxima for **2** could be attributed to the increase of π-orbital conjugation between the perfluorocyclopentene and fluorene rings as well as the presence of intermolecular interactions in the solid state. Based on our observations and above elucidations, we believe that the observed red-shifted absorption and emission spectra of compound **1** are likely due to the strong electron-withdrawing effect of the perfluorocyclopentene unit and the more extended conjugation. The PL efficiencies of **1**, **2**, and **4** were noteworthy. It has been well known that DPA (9,10-diphenylanthracene) is regarded as a standard for blue fluorescence with a Φ_{PL} of 0.95.[20] As compared to that of DPA, compounds **1**, **2**, and **4** show high PL quantum efficiency and increase in the order **2**>**1**>**4**>**3**. The extended conjugation and the lack of thermal vibrations caused by strong C–F bonds may be responsible for the enhanced PL efficiencies. To gain a deeper insight into the electronic and luminescent properties, we performed ab initio calculations (level of calculation B3LYP/3-21G*) on **1** and **5** employing the Gaussian 98 package.[21] The geometrical parameters employed in the calculations were taken from their structural data. A contour plot showing the electron density of highest occupied molecular orbitals (HOMO's), second HOMO's, lowest unoccupied molecular orbitals (LUMO's), and second LUMO's for compounds **1** and **5** along with the orbital energy for each levels is depicted in Figure 5. As one may see, the HOMOs and LUMOs of both compounds are similar. The HOMOs of both compounds are dominated by π-orbitals of fluorene but involve some contribution of the π-orbital on the perfluorocyclopentene or benzene moiety. The second HOMO of **1** shows that the π-orbitals of fluorene overlap with the π-orbitals of the ethene unit in the perfluorocyclopentene ring. In contrast, an effective π-orbital overlap between the benzene and fluorene units in the second HOMO level for **5** was not observed. The effective overlap of the HOMO level for **1** certainly should lead to the decrease of the HOMO energy level relative to that of **5**. Although the surfaces of the LUMOs of both compounds are similar (fluorene-based π* orbitals), the π* orbitals contribution of the perfluorocyclopentene ring for **1** is greater than that of the difluorobenzene ring of **5**. It is noteworthy that the perfluorocyclopentene ring greatly influences the LUMO levels, as compared to the benzene moiety. The energy differences between **1** and **5** in the LUMO level is 0.026 Hartree (16.315 kcal/mol), while in the HOMO level

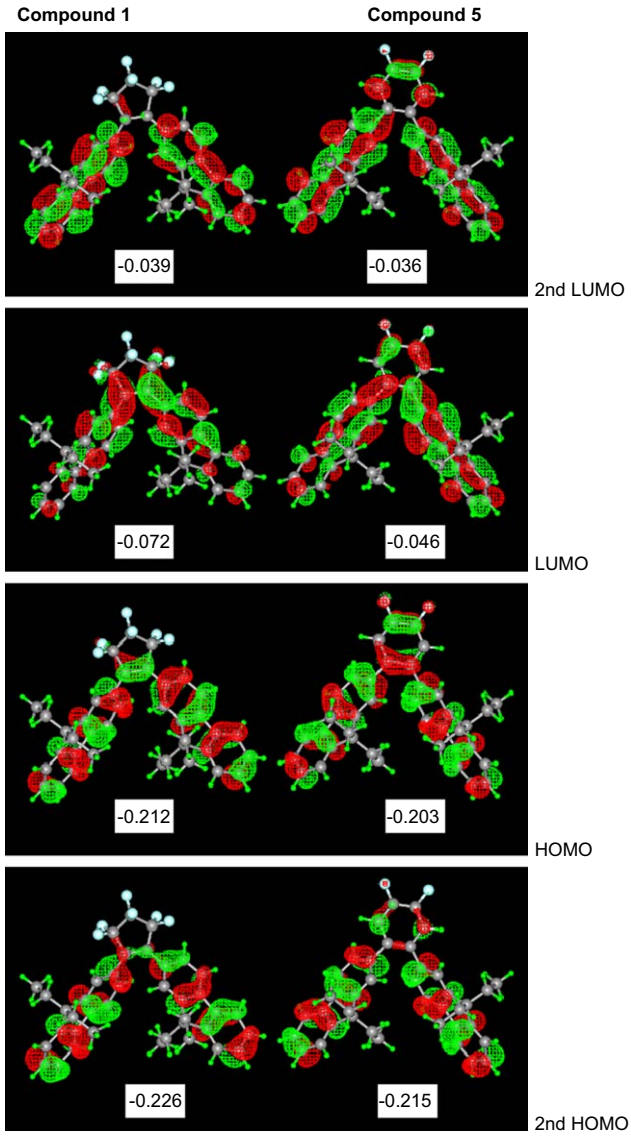


Figure 5. Diagram showing the surfaces and energies of second HOMOs, HOMOs, LUMOs, and second LUMOs for **1** and **5**.

is 0.009 Hartree (5.648 kcal/mol). This result provides support to the evidence that the perfluorocyclopentene unit in **1** plays a key role in the diminution of LUMO energy, bringing about a smaller band gap energy relative to **5**.

The band gaps between the HOMO and LUMO are 3.81 eV (325 nm) for **1** and 4.12 eV (301 nm) for **5**, which are in agreement with their corresponding UV–vis spectra. Judging from these calculations, the luminescence observed in **1**–**4** is indeed believed to originate from fluorene-based π–π* transitions from the perfluorocyclopentene linkage.

2.3. Electroluminescence properties

The electroluminescence (EL) properties of compound **4**, as a representative, were investigated because compound **4** showed high glass-transition temperature. We fabricated a multilayer device with the configuration of ITO/2TNATA (60 nm)/NPB(20 nm)/ADN:2%-compound-**4**(35 nm)/Alq_3 (20 nm)/LiF(2 nm)/Al. The layers of the device consist of

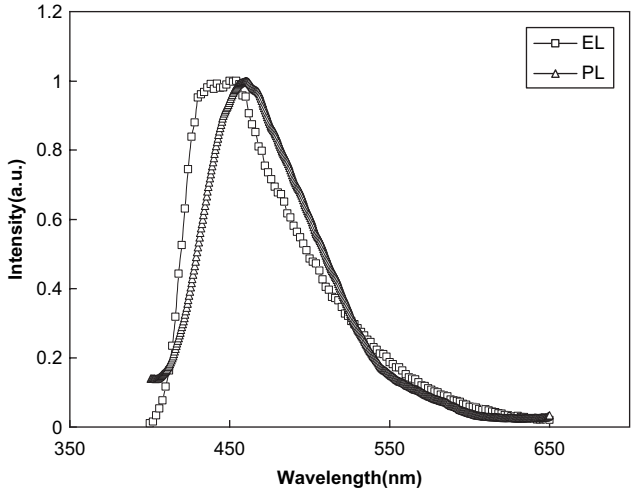


Figure 6. PL (thin film) and EL spectra of **4**. (device structure: ITO/2TNATA(60 nm)/NPB(20 nm)/ADN:2%-compound-**4**(35 nm)/Alq_3(20 nm)/LiF(2 nm)/Al).

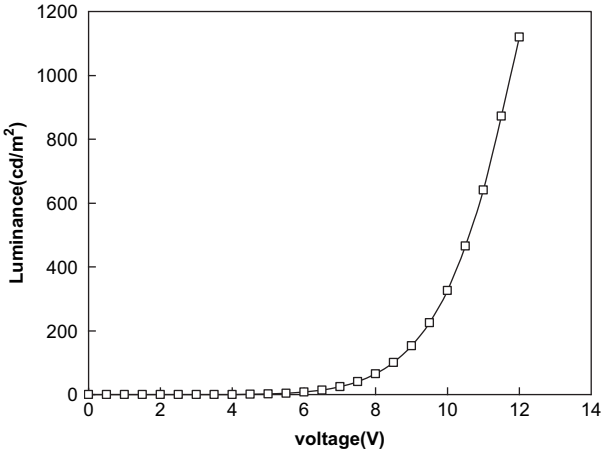


Figure 7. Luminance versus voltage characteristics of **4**-doped devices.

ITO as the anode, 2TNATA as the hole injection layer, NPN as the hole-transporting layer, AND:2%-compound-**4** as the emitter, Alq_3 as the electron transporting layer, LiF as the electron injection layer, and Al as the cathode, respectively. In this study, we chose ADN as the host material, which is a prototypical host with a wide band gap for blue OLEDs. In the EL device, compound **4** displays a blue emission at λ_{max}=458 nm with a shoulder at 438 nm, as shown in Figure 6.

The dominant peak originates from compound **4**, while the shoulder originates from the ADN. The emission observed in the EL device support the suggestion that an incomplete energy transfer from the host to the dopant occurs at the 2 wt %-doped level. The operating voltage (defined as 20 mA/cm^2) of the device is observed at 9 V, which is relatively high. The ability to trap charges in the emissive layer is considered as one of the most important factors in determining the operating voltage.[22] Effective charge trapping by the dopants gives rise to increasing driving voltages in OLEDs. If the dopant material functions as a hole trap, the HOMO level of the dopant could be above that of the host material. In other words, materials having a lower oxidation potential can function as effective hole trapping materials in OLEDs.[27] Therefore, the high operating voltage observed is very likely to stem from the effective hole trapping caused by perfluorocyclopentene unit. The luminescence efficiency of 0.82 cd/A (1120 cd/m^2),with CIE coordinates of x=0.169 and y=0.146, at a current density of 95 mA/cm^2 and a voltage of 12 V was achieved, as shown in Figure 7.

More detailed *I–V–L* characteristics are deposited in electronic supplementary material. The low efficiency in the EL device could be due to the poor of energy transfer between the host and dopant. Although the efficiency is low, we believe that high efficiency should be achieved by changing the concentration of compound **4**. Energy transfers, in general, are quite sensitive upon doping concentration, complete energy transfers tend to emerge at higher doping levels. Further improvement and optimization of EL devices using compound **4** are being investigated in our laboratory.

3. Conclusions

In summary, a series of perfluorocyclopentene-based luminescent compounds have been synthesized and characterized, including their photo- and electroluminescent spectra and electrochemical properties, and the nature of their solid-state structures. The perfluorocyclopentene linkage incorporated with fluorene, anthracene, or spiro-bifluorene moieties can give rise to several distinct characteristics, impacting their solid-state structures, the electrochemical behavior, and photoluminescence. As expected, fluorine atoms on the perfluorocyclopentene ring induce strong intermolecular interaction between two adjacent molecules, leading to high PL efficiency. Moreover, this functional group considerably perturbed the absorption, redox potentials, and photo- and electroluminescent efficiency. In particular, lower HOMO and LUMO energies than those of related compounds were observed, indicating that the perfluorocyclopentene linkage induced a relative ease of hole trapping and the diminution of the band gap. Compound **4**, containing spiro-bifluorene unit, exhibits a bright blue emission in a multilayered EL device.

4. Experimental

4.1. General

All experiments were performed under dry N_2 atmospheres using standard Schlenk techniques. All solvents were freshly distilled over appropriate drying reagents prior to use. The starting materials 2-bromo-9,9′-diethylfluorene, 2-bromo-9,9′-dihexylfluorene, and 2-bromo-9,9′-spirobifluorene were prepared according to the literature procedures.[4] For general experimental details, see the electronic supplementary material.

4.2. Fluorescence quantum yield measurements

The relative quantum yields of PL (Φ_{PL}) for all compounds were determined relative to 9,10-diphenylanthracene (Φ_{PL}=0.95) as the standard in THF or CH_2Cl_2 at 298 K. A range of concentrations of solution of all compounds and standard were measured such that absorbances were less than 0.10 at the excitation wavelength (λ_{ex}=360 nm). The fluorescence

quantum yield was then measured by the previously known process.[14]

4.3. X-ray crystallographic analysis

Suitable crystals of **1** and **5** were obtained from slow vapor diffusion of benzene/hexane (1:1) into solutions of **1** or **5** in CH_2Cl_2. The crystals of **1** and **5** were attached to glass fibers and mounted on a Bruker SMART diffractometer equipped with graphite monochromated Mo Kα (λ= 0.71073 Å) radiation, operating at 50 kV and 30 mA, and a CCD detector; 45 frames of two-dimensional diffraction images were collected and processed to obtain the cell parameters and orientation matrix. All data collections were performed at 173 K. The data collection 2θ ranges for **1** and **5** are 3.32–52.74 and 3.54–56.64, respectively. The first 50 frames were retaken after complete data collection and compared. Both crystals showed no significant decay and no corrections were applied for the decay. The raw data were processed to give structure factors using the SAINT program.[15] Each structure was solved by direction methods and refined by full matrix least squares against F^2 for all data using SHELXTL software (version 5.10).[16] All non-hydrogen atoms in compounds **1** and **5** were anisotropically refined. All hydrogen atoms were placed in idealized positions and refined using a riding model. The crystal system in compound **1** belongs to the monoclinic and $P2_1/c$ space group. One methyl carbon atom of the ethyl groups at the 9-position of the fluorene unit in compound **1** is disordered. The disordered carbon atom was modeled successfully and its contribution to structure factor was included. The crystal system in compound **5** belongs to the triclinic *P*-1 space group. Crystal data for **1** and **5** are summarized in Table 3. The refined atomic coordinates and anisotropic thermal parameters are included electronic supplementary data. Crystallographic data for the structure reported here have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC-609630 for **1**, CCDC-609631 for **5**). The data can be obtained free of charge via http://www.ccdc.cam.ac.uk./perl/catreq/catreq.cgi (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. Crystallographic data for **1** and **5**

	1	**5**
Formula	$C_{39}H_{34}F_6$	$C_{40}H_{36}F_2$
M_W	616.66	554.69
T/K	173(2)	173(2)
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	*P*-1
a/Å	9.5813(4)	8.5214(10)
b/Å	22.8232(10)	11.8260(14)
c/Å	14.6165(6)	15.5735(18)
α/deg		78.631(2)
β/deg	97.4790(10)	83.042(2)
γ/deg		81.673(2)
V/Å^3	3169.1(2)	1515.4(3)
Z	4	2
μ(Mo Kα)/mm^{-1}	0.098	0.077
Crystal size/mm	0.35×0.30×0.30	0.30×0.30×0.20
Reflections collected	18442	9779
Independent reflections	6437	6809
Goodness-of-fit on F^2	1.153	0.992
Final *R*1, *wR*2 [$I>2\sigma(I)$]	0.0770, 0.1638	0.0573, 0.1252
(All data)	0.1007, 0.1752	0.1225, 0.1522

4.4. Fabrication of electroluminescent devices

The glass substrate, pre-coated with indium-tin-oxide (ITO), was cleaned by an ultrasonic bath of acetone, followed by 2-propanol. Surface treatment was carried out by exposing ITO to a UV-ozone plasma. An OLED using AND (9,10-bis(2-naphthyl)anthracene) as host material was fabricated as follows. The hole-injecting layer, a 60 nm thick film of 2TNATA (4,4′,4″-tris[*N*-(2-naphthyl)-*N*-phenylamino)triphenylamine) was deposited on the ITO surface by high vacuum thermal evaporation, and a 20 nm thickness of NPB (*N*,*N*′-di(naphthalen-1-yl)-*N*,*N*′-diphenylbenzidine) as hole-transporting layer was deposited onto the 2TNATA. Compound **4** was 2 wt % doped into a host AND layer by thermal co-evaporation on the NPB layer. A 20 nm thick Alq_3 (tris(8-hydroxyquinolinato)aluminum(III)) layer was then deposited as an electron transporting layer. Finally, LiF (2 nm) and Al (100 nm) were deposited on top of the organic layers by thermal evaporation. The fabricated multilayer organic light-emitting device had the structure of ITO/2TNATA(60 nm)/α-NPB(20 nm)/ADN-compound **4**(35 nm)/Alq_3(20 nm)/LiF(2 nm)/Al(100 nm).

4.5. General syntheses of 1–4

A solution of *n*-BuLi (1.44 mmol, 1.6 M in hexane) was added slowly to the corresponding bromoarenes (1.2 mmol) in THF (25 mL) at −78 °C and stirred for 30 min. To this solution was added octafluorocyclopentene (0.25 mL, 0.6 mmol). Upon addition of octafluorocyclopentene to the lithiated solutions, the color changed rapidly from pale yellow to brown. The reaction mixture was warmed slowly to ambient temperature and stirred overnight. The reaction mixture was poured into water and repeatedly extracted with CH_2Cl_2 (3–50 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The pure corresponding compounds were isolated by chromatographic workup.

4.5.1. 1,2-Bis(9,9′-diethylfluoren-2-yl)-3,3,4,4,5,5-hexafluorocyclopentene (1). Yield: 67% (eluent: hexane, R_f=0.15); mp 113–115 °C MS(EI): *m*/*z*=618 [M]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.67–7.65 (2H, m), 7.60 (2H, d, *J*=7.81 Hz), 7.35–7.28 (10H, m), 1.94–1.80 (8H, m), 0.24 (12H, t, *J*=7.34 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.3, 150.2, 143.5, 140.3, 139.6, 128.4, 128.0, 127.0, 126.5, 123.9, 122.9, 120.1, 119.9, 116.6, 56.2, 32.4, 8.4 (C–F resonances not located). Anal. Calcd for $C_{39}H_{34}F_6$: C, 75.96; H, 5.56. Found: C, 75.81; H, 5.44.

4.5.2. 1,2-Bis(9,9′-dihexylfluoren-2-yl)-3,3,4,4,5,5-hexafluorocyclopentene (2). Yield: 67% (eluent: hexane, R_f=0.35); mp 100–103 °C. MS(EI): *m*/*z*=841 [M]$^+$. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64–7.62 (2H, m), 7.58 (2H, d, *J*=7.86 Hz), 7.34–7.29 (10H, m), 1.90–1.74 (8H, m), 1.09–1.03 (8H, m), 1.01–0.94 (16H, m), 0.75 (12H, t, *J*=7.07 Hz), 0.52–0.51 (8H, m), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 151.1, 151.0, 143.1, 139.8, 128.3, 128.0, 126.9, 126.4, 123.8, 122.8, 120.2, 119.9, 55.2, 40.2, 31.5, 29.6, 23.6, 22.5, 13.9 (C–F resonances not located). Anal. Calcd for $C_{55}H_{66}F_6$: C, 78.54; H, 7.91. Found: C, 78.48; H, 7.85.

4.5.3. 1,2-Bis(anthracen-9-yl)-3,3,4,4,5,5-hexafluorocyclopentene (3). The pure compound **3** was obtained by the recrystallization from CH_2Cl_2 and hexane. Yield: 59%; mp 362–364 °C. MS(EI): m/z=528 $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.23 (4H, d, J=8.82 Hz), 8.11 (s, 2H), 7.66 (4H, t, J=8.45 Hz), 7.42 (4H, t, J=7.71 Hz), 7.28 (4H, t, J=8.03 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 130.7, 130.0, 129.6, 128.9, 128.4, 126.1, 125.2 (C–F resonances not located). Anal. Calcd for $C_{33}H_{18}F_6$: C, 75.00; H, 3.43. Found: C, 74.87; H, 3.39.

4.5.4. 1,2-Bis(9,9′-spirobifluoren-2-yl)-3,3,4,4,5,5-hexafluorocyclopentene (4). Yield: 70% (eluent: ethylacetate/hexane (1/20:v/v), R_f=0.25); mp 275–277 °C. MS(EI): m/z=804 $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.82 (2H, d, J=7.66 Hz), 7.73 (4H, d, J=7.63 Hz), 7.60 (2H, d, J=8.02 Hz), 7.40 (2H, t, J=7.49 Hz), 7.25 (6H, t, J=7.11 Hz), 7.15 (2H, t, J=7.51 Hz), 7.08 (4H, t, J=7.50 Hz), 6.66 (2H, d, J=7.59 Hz), 6.55 (4H, d, J=7.53 Hz), 6.50 (2H, s), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.6, 148.8, 147.6, 143.8, 141.5, 140.2, 128.9, 128.7, 127.9, 127.8, 127.7, 126.8, 124.9, 123.9, 123.8, 120.6, 120.2, 119.9, 65.7, 53.4, 31.6, 22.6, 14.1 (C–F resonances not located). Anal. Calcd for $C_{55}H_{30}F_6$: C, 82.08; H, 3.76. Found: C, 82.05; H, 3.59.

4.5.5. Synthesis of 1,2-difluoro-4,5-bis(9,9′-diethylfluoren-2-yl)benzene (5). Aqueous K_2CO_3 (2.0 M, 3.0 mL) and benzyltrimethylammoniumchloride (30.6 mg, 0.165 mmol) were added to a solution of 1,2-dibromo-4,5-difluorobenzene (444.7 mg, 1.648 mmol) and 2-(9,9-diethyl-9H-fluoren-2-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1435 mg, 4.12 mmol) in toluene (17 mL). The mixture was degassed and tetrakis(triphenylphosphine)palladium (76 mg, 4 mol %) was added in one portion under an atmosphere of N_2. The reaction mixture was refluxed for 24 h. After the solution cooled, the solvent was evaporated under vacuum and then extracted with CH_2Cl_2. The solution was washed with brine and H_2O, and then dried over $MgSO_4$. Evaporation of the solvent, followed by column chromatography from hexane, afforded titled product. Yield: 61% (eluent: hexane, R_f=0.15); mp 175–177 °C. MS(EI): m/z=554 $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.61–7.59 (2H, m), 7.50 (2H, d, J=8.03 Hz), 7.34 (2H, t, J=9.64 Hz), 7.28–7.26 (6H, m), 1.89–1.75 (8H, m), 0.22 (12H, t, J=7.23 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 150.1, 149.8, 141.0, 140.5, 138.5, 137.8, 128.7, 127.1, 126.8, 124.4, 122.8, 119.6, 119.3, 119.3, 119.2, 119.2, 119.1, 56.0, 32.5, 8.5 (C–F resonances not located). Anal. Calcd for $C_{40}H_{30}F_2$: C, 86.61; H, 6.54. Found: C, 86.55; H, 6.59.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.065.

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