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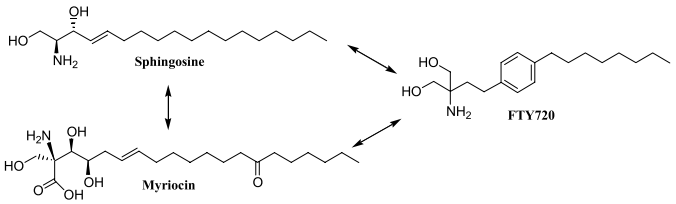
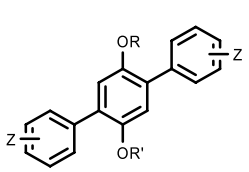
Contents

REPORT

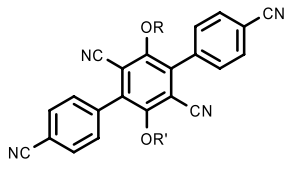


This review focuses on the bio- and chemical synthesis of sphingolipids, the cell surface receptor discoveries, and recent drug discovery effort targeting this family of receptors.

ARTICLES



R, R' = *n*-C_6H_{13}-, or *n*-$C_4H_9CH(CH_2CH_3)CH_2$-, Me-.
Z = H-, *o*-CN-, *m*-CN-, *p*-CN-, or 2 x *m*-CN-.



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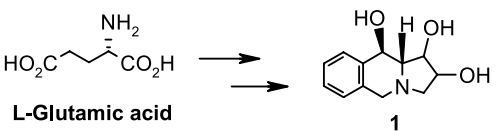
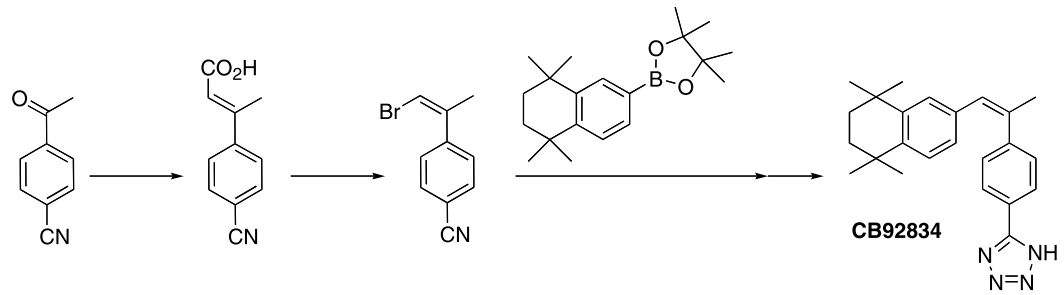
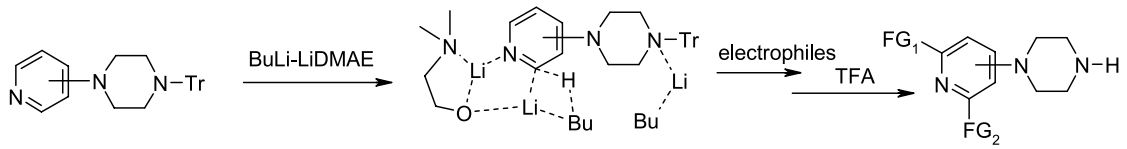
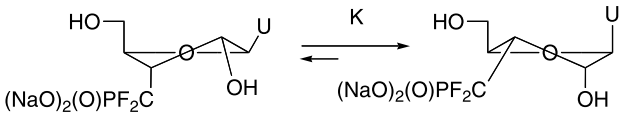
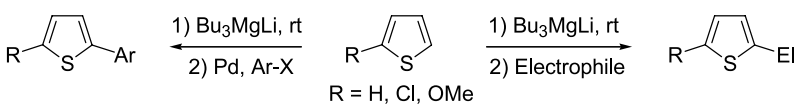
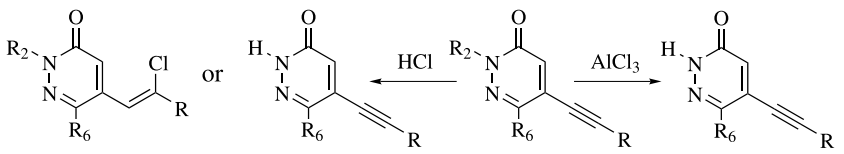


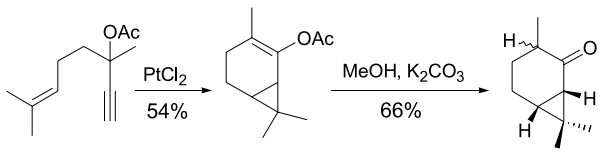


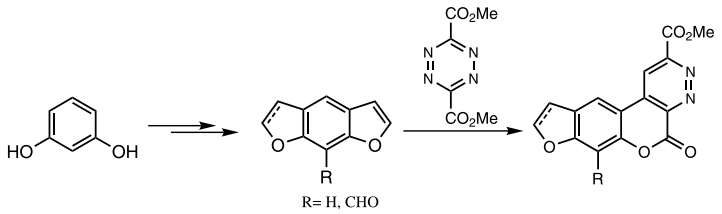




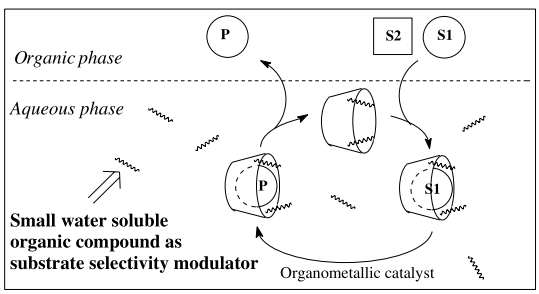


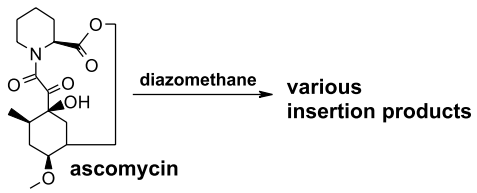


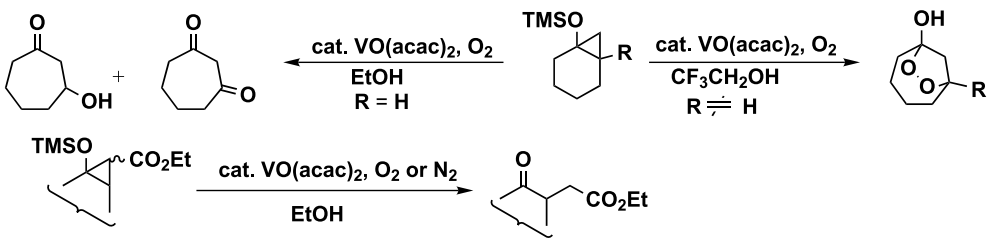


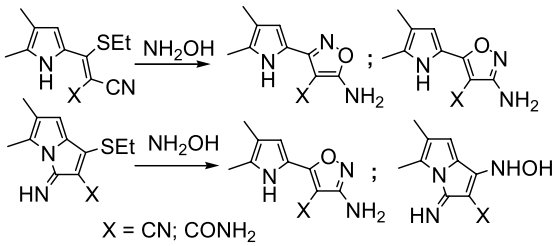


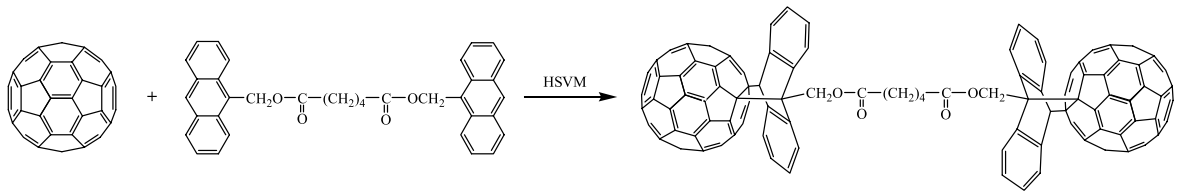
The addition of small organic hydrosoluble molecules such as amine or alcohol derivatives in the aqueous catalytic phase allowed to greatly increase the discriminating power of cyclodextrin derivatives.

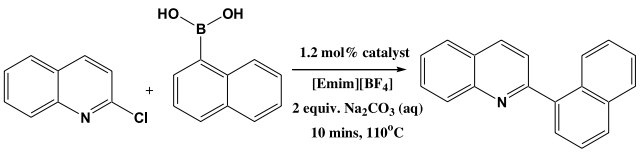




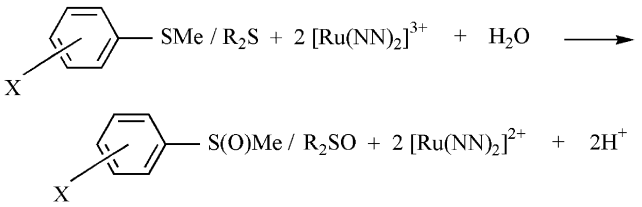








Readily available *N*-contained heterocyclic chlorides were coupled with naphthaleneboronic acids in ionic liquids. Desired products with good purity and high yield were obtained with short reaction time and easy isolation. Based on these advantages, we expect the efficient synthesis of these compounds can play an important role in OLEDs.



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Chemistry and biology of sphingolipids

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Contents

1. Introduction

Sphingosine-based (**1**, Fig. 1) and glycerol-based phospholipids are major structural components of cellular membranes. Upon cell activation by a variety of stimuli, including growth factors, inflammatory cytokines, antigens, and G-protein-coupled receptor (GPCR) agonists, membrane phospholipids are metabolized into potent mediators, such as sphingosine-1-phosphate (S1P) (**2**) and lysophosphatidic acid (LPA). Originally, S1P was thought to function as an intracellular secondary messenger, and act through cytoplasm protein(s), although these proteins have not been identified. Recently, it was shown that S1P could also activate members of the endothelial differentiation gene (EDG) family of G-protein-coupled receptors (namely Edg1, Edg3, Edg5, Edg6, and Edg8 at high affinity, and GPR3 (GPCR 3), GPR6, GPR12 and GPR63 at low affinity) as extracellular mediators,[1] whereas LPA can bind to other members of the family (namely Edg2, Edg4, and Edg7) at high affinity.[2] Thereafter, a family of related receptors was discovered to respond to other lysophospholipids such as sphingosylphosphorylcholine (SPC) (**3**), and lysophosphatidylcholine (LPC).[3] In this review, we will mainly focus on the recent development of biological functions and chemical

Keywords: Sphingosine; Lysophosphatidic acid; Sphingosine-1-phosphate.
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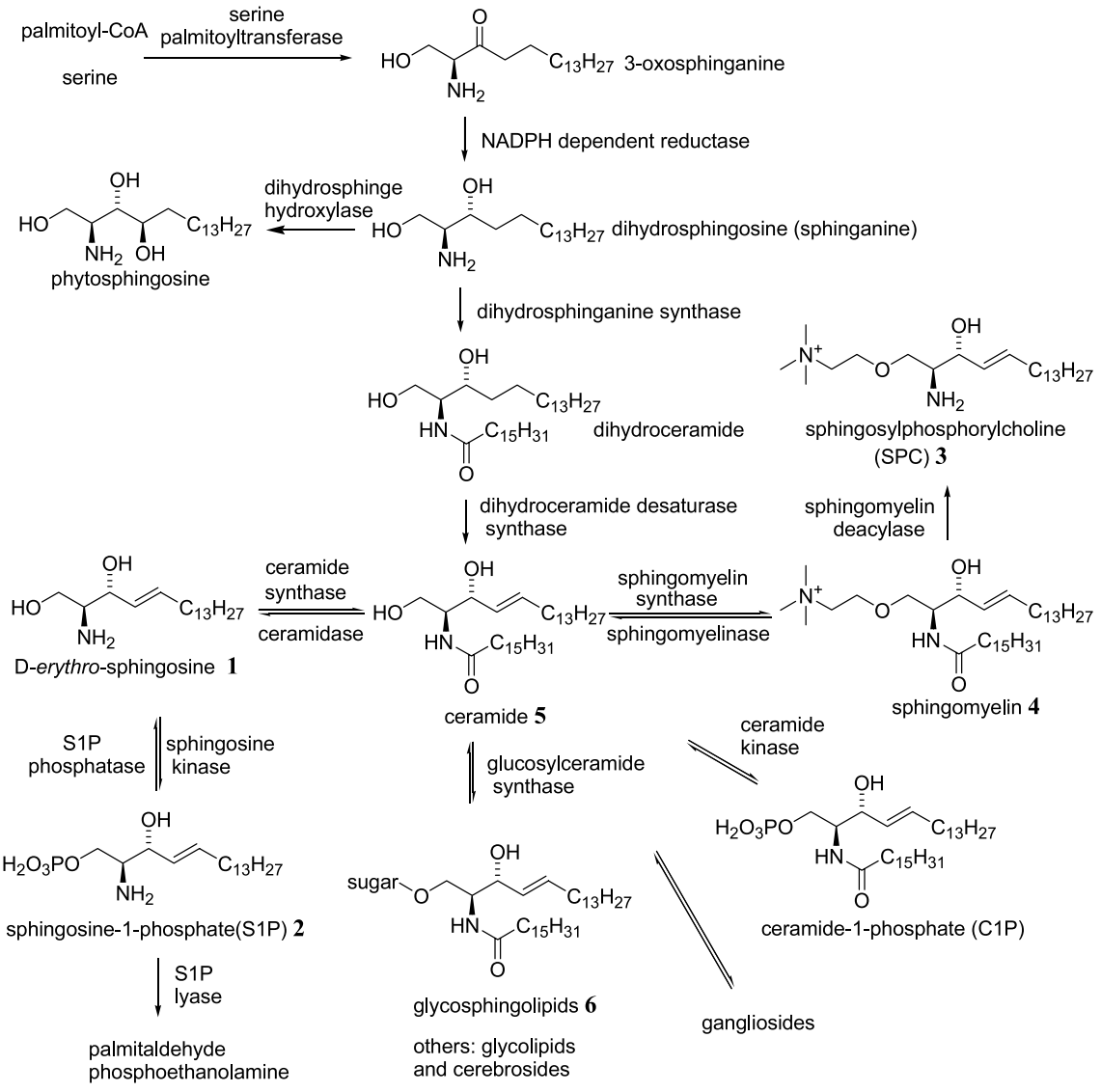


Figure 1. Biosynthesis of sphingolipids.

synthetic approaches of sphingolipids, especially sphingosine and its derivatives, and the recent target identification of a novel immunosuppressant FTY720.[4,5]

Although the intracellular target(s) of S1P is not clear, its extracellular action is well characterized. S1P binds cell surface receptors to stimulate small heterotrimeric G-proteins and kinase cascades, including ERK kinase activation, mobilization of calcium flux, Rac and Rho activation leading to stimulation of cell growth, prevention of apoptosis, cytoskeletal re-organization, cell invasion, and the modulation of cell migration in response to growth factors, such as PDGF.[6] Due to its fundamental activities and wide presence of its receptors, S1P has been shown to be involved in varieties of biological processes, including the development of normal immune responses, inflammatory reaction, development of vascular, cardiac myocyte hypertrophy, endothelial barrier integrity in blood vessels, angiogenesis and tumor cell dissemination. An increasing body of evidence suggests that other sphingolipids, such as SPC, are also involved in a variety of cellular regulations, such as cell growth, proliferation and migration.

While the interest in investigating their biological functions grew, the methodology of chemical synthesis of sphingolipids has been well studied. The challenge for the synthesis of sphingolipids has been to generate the stereogenic centers in the target compounds efficiently with high homogeneity. In the history of sphingolipid chemistry, natural chiral pools have been playing a significant role in their synthesis; however, for chirality economy, this protocol is not efficient because some chiral centers are always discarded in the process. Furthermore, it normally takes more synthetic steps from a natural chiral source. Asymmetric reactions have emerged as an alternative strategy with advantages over natural chiral sources in terms of chirality economy and efficiency. Therefore, tremendous efforts have been devoted to develop highly enantioselective asymmetric reactions in the last decades and significant progress has been made in this field, which has led to more asymmetric reactions being available to synthetic chemists with satisfactory enantioselectivity. As a result, these asymmetric approaches have been widely used in the synthesis of sphingolipids in recent years. In this review, emphasis will be put on the synthesis of some low organism sphingolipids because of

the additional challenges associated with the synthesis of these molecules.

While very important physiological roles of sphingolipids have been shown and chemical synthetic methods have been developed, the first therapeutic target of clinically investigated drugs from the sphingolipid family of receptors is just emerging. The recent identification of EDG1, an S1P receptor, as a molecular target for a novel immunosuppressive agent, FTY720—a previous orphan drug, has led to the first member of therapeutic targeting agents in this family of receptors.[4,5,7] The reverse pharmacological approach, using chemical reagents to dissect biological processes, together with biological approaches have been successfully applied in this investigation. These chemical probes have led to rapid advances in understanding S1P contributions to many physiological processes and the development of better therapeutic reagents based on clear understanding of molecular mechanisms. The combination of these approaches can be applied to other members of lipid receptors newly identified from the recently finished human genome project to quickly advance our understanding of lipid physiology in the future.

2. Sphingolipid signaling pathways and physiological roles (S1P, phytosphingosine, ceramide, and SPC)

Several lines of study from both signal transduction and physiological roles of sphingolipids through their cell surface G-protein-coupled receptors have indicated that sphingolipids play critical roles in modulating cell migration, proliferation, and apoptosis in response to various extracellular stimuli, such as stroma cell-lymphocyte cell communications, and in pathological conditions, such as inflammation, and stress.

Sphingolipids are highly enriched in the membrane of most mammalian cells. The compartment of sphingolipids in membranes serves as the starting pool for sphingolipid metabolism, which is a dynamic process from sphingomyelin (**4**) to ceramide (**5**), sphingosine and S1P (Fig. 1). All these metabolites of sphingolipids function either presumably as intracellular secondary messengers or recently as ligand molecules for cell surface receptors. Although it was hard to distinguish the individual functions of sphingosine or S1P in vivo because they are converted into each other by sphingosine kinase and S1P phosphatase, recent affinity assays suggest that S1P is much more potent to the cell surface receptors and therefore plays a more signaling role than sphingosine. Sphingosine is formed primarily from the breakdown of mammalian ceramide and, therefore, it appears to be strictly a catabolic product. Sphingosine is able to diffuse rapidly between cell membranes, unlike ceramide, which remains associated with the membrane. This property allows sphingosine to have effects in different cellular compartments. Initial studies have led to the identification of inhibitory effects of sphingosine on several enzymes, such as PKC (protein kinase C) in vitro and in cells,[8] and phosphatidic acid phosphohydrolase, while activating phospholipase D (PLD) and DAG kinase. In concert, these actions appear to result in the shutdown of the DAG/PKC pathway, while augmenting the levels of phosphatidic acid. Sphingosine has also been shown to affect other kinases, including activation of casein kinase 2 and p21-activated kinase.[9] At the level of the cell, the actions of sphingosine are cell type-specific, with sphingosine exerting antimitogenic effects in many cells, but promitogenic effects in others. In most cases, a unifying theme has been the anti-phorbol ester/DAG effects of sphingosine, consistent with its in vitro actions.

The recent identifications of EDG family members as sphingosine receptors, led to the signaling of sphingosine through GPCRs. Edg1 receptor are coupled exclusively via Gi/o to stimulate MARP kinase and inhibition of adenylate cyclase. Unlike Edg1, Edg3 and Edg5 are coupled to stimulation of phospholipase C (PLC) via Gq. Edg3 and Edg5, but not Edg1, are coupled to the activation of another small G-protein, Rho. More interesting is the bimodal regulation of Rac by Edg members. Edg1 and Edg3 mediate the cellular activation of Rac, whereas Edg5 inhibits Rac activation. These phenomena may explain the opposite roles of Edg1/3 and 5 in regulating cell migration. Edg1/3 mediate chemotaxis towards S1P, whereas Edg5 mediates marked inhibition of chemotaxis towards other attractants, such as insulin-like growth factor 1(IRF1). S1P as well as phorbol esters have also been shown to promote capillary-like network formation. Consistent with this activity of S1P, it acts on endothelial cells to stimulate cell migration and adherent junction assembly through the upregulation of VE-cadherin.

Yeast and plants contain predominantly phytosphingosine as their main sphingoid base. Phytosphingosine mainly comes from plant origin (Fig. 2). Phytosphingosines have been identified either as a free form or a component of glycosphingolipids in plants, marine organisms, mammalian tissues, and even in fungi. The most predominant stereoisomer is D-*ribo*-phytosphingosine (Fig. 2). Recent studies in *Saccharomyces cerevisiae* showed the key functions of phytosphingosine in heat stress response and in endocytosis.[10] Heat stress (change in temperature from 25–30 to 39–42 °C) results in a significant elevation in the levels of phytosphingosine (especially the C_{20} molecular species). A combination of pharmacological and genetic analysis shows that phytosphingosine (and dihydrosphingosine) is essential for the activation of an ubiquitin-dependent pathway of degradation of nutrient permeases that occurs upon heat stress. Similar studies show that yeast sphingoid bases are necessary for the transient cell cycle arrest by which yeast responds to heat stress.[11] In other studies, it was

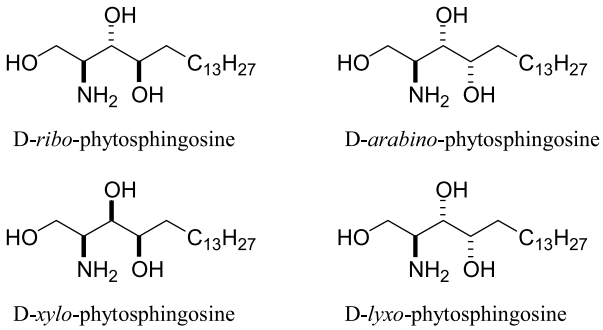


Figure 2. Phytosphingosine and its stereoisomers.

shown that defects in the formation of phytosphingosine result in defective endocytosis, and it was suggested that the sphingoid bases may act by either activating protein kinases or by inhibiting protein phosphatases. Thus, phytosphingosine is emerging as a bona fide signaling molecule in yeast.

Ceramide is important in determining apoptotic responses to stress,[12] and also serves as a precursor for the synthesis of S1P, which, in certain cell types, is implicated in cell survival. This suggests that the metabolic conversion of ceramide into S1P could switch cells from an apoptotic to a proliferative state. Therefore, inhibition of the conversion of ceramide into S1P might be usefully exploited to induce cell death in a disease, such as cancer. Recently, a study showed that ceramide-1-phosphate (C1P) (Fig. 1) is a potent and specific inducer of arachidonic acid and prostanoid synthesis in cells, which are major mediators in inflammation.[13] Glucosphingolipids and ceramide 1-phosphate can be transferred from ceramide by glucosylceramide synthase and ceramide kinase, respectively.

Sphingosylphosphorylcholine (SPC) was shown to induce a strong mitogenic action in a large number of cell types, such as 3T3 fibroblasts, endothelial cells, human keratinocytes and vascular smooth muscle cells.[14] This response seems to be dependent on ERK activation and Gi protein. SPC can inhibit the growth of other cell types, mostly tumor cells such as pancreatic, breast and ovarian cancer cells or Jurkat T cells, and induce a rise in $[Ca^{2+}]$ either through Ca^{2+} mobilization, Ca^{2+} flux or both, depending on the cell types. Since SPC induces an increase in $[Ca^{2+}]$ in vascular endothelial cells, as well as in vascular smooth muscle cells, it plays a regulatory role in the vasculature. Because of its strong growth-promoting effects in fibroblasts and other cells in the wound healing process, SPC effectively accelerates the closure of excision wounds, and enhances granulation for tissue remodeling.

3. Sphingolipid biosynthesis

Sphingolipid biosynthetic pathways have been extensively studied for more than three decades. The major pathways of biosynthesis from either de novo synthesis or degradation of membrane lipids, such as sphingomyelin, are conserved from lower to mammalian organisms. The regulation of signal molecule generations in the metabolic network, such as sphingosine 1-phosphate, is not, however, completely understood at present.

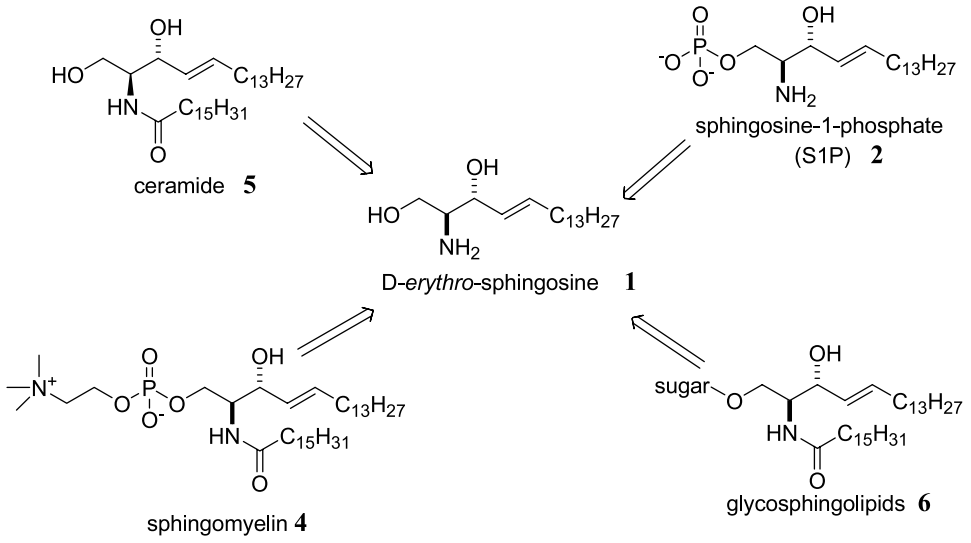
Sphingolipids are biosynthesized by cells either de novo through condensation of serine and palmitoyl-CoA by serine palmitoyltransferase (which occurs in the endoplasmic reticulum) to produce 3-oxosphinganine and CO_2 (Fig. 1) or through stimulus-coupled liberation of the sphingomyelin by several sphingomyelinases. 3-Oxosphinganine is rapidly reduced to dihydrosphingosine (sphinganine) by an NAD(P)H-dependent reductase that is stereospecific for the D-isomer. Subsequently, dihydrosphingosine is *N*-acylated to dihydroceramide, catalyzed by dihydroceramide synthase. Dihydroceramide desaturase catalyses the subsequent introduction of a *trans* double bond at C-4–C-5 to produce ceramide. De novo sphingolipid synthesis can be blocked at serine palmitoyltransferase by L-cycloserine[15] or by the fungal metabolite, myriocin,[16,17] whereas the mycotoxin, fumonisin, inhibits dihydroceramide synthase.[17] The degradation of membrane sphingolipids by stimuli is the major source of free and secreted S1P or ceramide. This degradation of membrane sphingolipids is mainly stimulated by inflammation or stress for platelets and leukocytes.

Ceramide can be produced either in response to the agonist-dependent activation of sphingomyelinases or de novo. Agonist-dependent activation of sphingomyelinases has been observed in response to growth factors, cytokines and arachidonic acid. Additionally, cellular stress and changes in the redox state of the cell can result in sphingomyelinase activation. To date, five distinct sphingomyelinases have been identified, based on their pH optima, cellular localization and cation dependence. Ceramidase catalyzes the deacylation of ceramide to produce non-esterified fatty acid and sphingosine. Both an acidic ceramidase (deficient in Farber's disease and inhibited by the ceramide analogue, *N*-oleoylethanolamine) and an alkaline ceramidase [inhibited by D-erythro-2-(*N*-myristoylamino)-1-phenylpropanol (D-MAPP)] exist. The resulting sphingosine may act as the substrate for sphingosine kinase (SPHK) to produce S1P. This is cleaved by S1P lyase (to produce palmitaldehyde and phosphoethanolamine) or dephosphorylated by S1P phosphatase. Alternatively, ceramide can be converted back into sphingomyelin by the addition of a phosphocholine head group (donated by phosphatidylcholine), catalyzed by sphingomyelin synthase.

Ceramide produced de novo can be metabolized to glycosphingolipids, the first step of which is catalyzed by a glucosylceramide synthase.[18] This enzyme is inhibited by the ceramide analogues, D-threo-1-phenyl-2-palmitoylamino-3-morpholino-1-propanol (PPMP) and D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), the latter compound being a potential anticancer agent.[19] Alternatively, ceramide can be phosphorylated by a calcium-activated ceramide kinase to produce ceramide-1-phosphate.[20]

4. Sphingolipid chemical synthesis

In mammalian cells, the diversity of sphingolipids is significantly reduced and, therefore, only general synthetic strategies will be discussed, which could be adapted to synthesize small-molecule analogs of sphingosine, S1P and ceramides. The emphasis of this section will be directed towards the synthesis of metabolites in the sphingolipid biosynthetic pathway in lower organisms. To our knowledge, despite the tremendous amount of synthetic efforts being invested in this class of molecules including myriocin, sphingofungins, penaresidins, penazetidine and many others (vide infra), no review has appeared on this topic. A review has been devoted to the specific synthesis of sphingosine prior to 1997.[21] The synthesis of phytosphingosines will only be discussed briefly, as a recent review has appeared with great details of this topic.[22] The synthetic methodologies towards glycosphingolipids will not be discussed



Scheme 1.

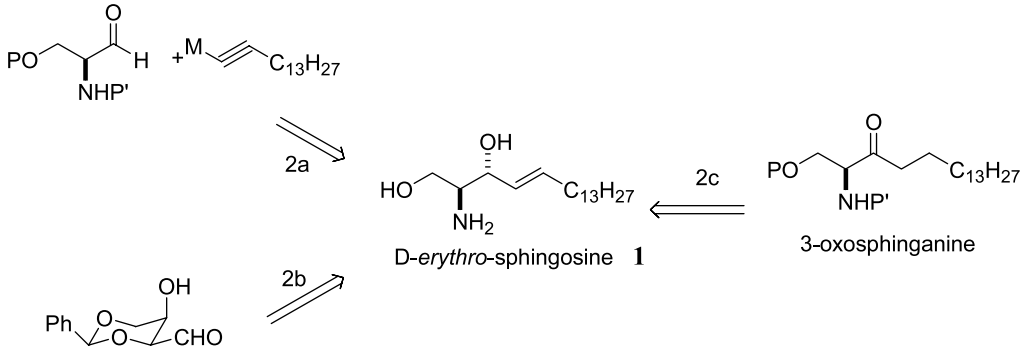
here, and interested readers can find details in a recent review paper.[23]

4.1. Synthesis of higher organism sphingolipids and analogs

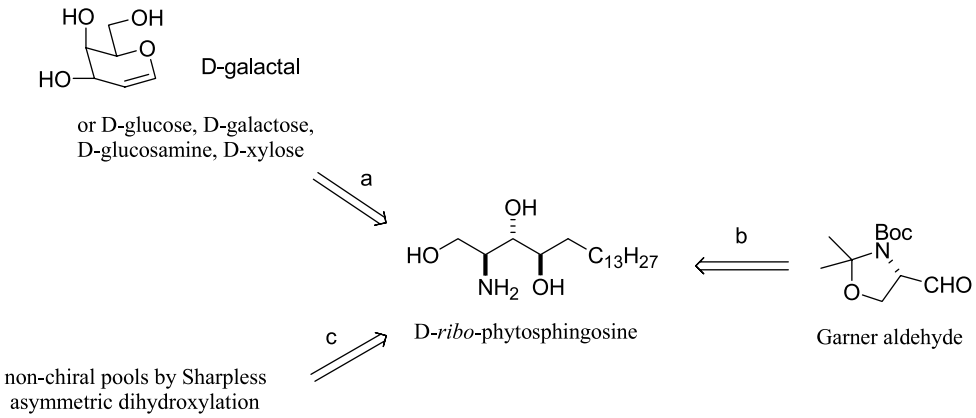
The variety of biological roles of sphingolipids has led to an explosion of their chemical synthesis. S1P, ceramides, SPC, sphingomyelin, glycosphingolipids and related sphingolipids in the mammalian biosynthetic pathway share the core motif of sphingosine (Scheme 1). Therefore, it is natural that most of these lipids were prepared from suitably protected sphingosines (Scheme 1). While the direction of this approach is different from metabolic flux, the resulting advantages are obvious. Once a suitably protected sphingosine is produced, *N*-acylation followed by deprotection will give ceramides, which can then be used to prepare sphingomyelin, SPC and glycosphingolipids. Direct terminal phosphorylation of the primary hydroxyl group affords S1P.

There are four sphingosine stereoisomers in vivo, although with biological activities of different degrees. The isomer with the D-erythro stereochemistry is the most common metabolite and has been studied in the most detail so far (Scheme 1).[24] In order to study the biological activities of sphingosine, homogeneous individual sphingosine is required, but this is difficult to isolate from a mixture of natural resources. Firstly, there are a large number of sphingolipids and their metabolites with variation in the head groups (modification of the primary hydroxyl group), *N*-acyl groups, and/or tail groups, thus making the isolation of the homogeneous material from natural sources problematic. Secondly, the allylic alcohol function in sphingosine is prone to epimerization during isolation or manipulation, producing partially epimerized mixtures.[25] An in vitro enzymatic reconstitution system has not yet been demonstrated. For these reasons, synthetic access to individual sphingosine stereoisomers is a viable approach. Two key issues must be addressed for all sphingosine syntheses. First, it is crucial to have high stereocontrol for the 2,3-aminohydroxy groups, since all of the four stereoisomers are bioactive. Second, the attachment of functionally diverse tail groups by a *trans* double bond is required to access many different sphingosine derivatives and analogs for biological studies. The *trans* geometry is essential for their biological activities.

A number of synthetic methodologies for sphingosine and its derivatives have been reported, and they can be classified into four categories.[21,26] The first relies on the stereoselective addition of a nucleophilic organometallic reagent (e.g., a lithium acetylide) to a protected serinal.[27] By this method, the 3,4-carbon–carbon bond is formed, with the stereochemistry of the C-3 hydroxyl group being set in one



Scheme 2.



Scheme 3.

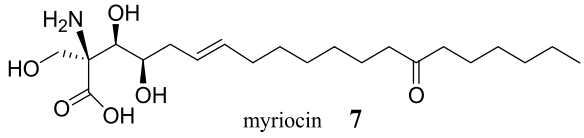
step (method 2a, Scheme 2). The second major strategy uses carbohydrate precursors as the starting material to relay the stereochemistry at C-2 and C-3.[26,28] The tail is then attached by an anionic addition (method 2b, Scheme 2). The third major class starts with a variety of other chiral precursors for chain elongation through nucleophilic addition (not shown).[29] In all these approaches, the common theme is to set the stereochemistry of the head groups early, followed by the manipulation of the tail, most commonly through a nucleophilic addition using an organometallic, Wittig reagent, etc. Finally, a fundamentally different strategy introduces the stereochemistry in the last stage of the synthesis in a more biomimetic fashion by reducing the metabolic precursor 3-oxosphinganine (method 2c, Scheme 2).[30]

Phytosphingosine has four stereoisomers in nature with the predominant isomer being D-*ribo*-phytosphingosine (Fig. 2). It is not surprising that most syntheses of this molecule start from carbohydrate precursors (method a, Scheme 3) and a few others from amino acids (method b, Scheme 3) or various achiral pools (method c, Scheme 3).[22] In method a, suitably protected D-galactal, D-glucose, D-galactose, D-glucosamine or D-xylose are mostly used as the starting materials, where the triol architecture was translated into the final *ribo*-phytosphingosine. In method b, the Garner aldehyde is the most common electrophile for subsequent asymmetric carbon–carbon bond formation, generating the amino diol groups. For method c, various alkenes were often incorporated at the beginning of the synthesis, followed by asymmetric Sharpless asymmetric dihydroxylation to establish the desired chiral diol moiety in high stereoselectivity.

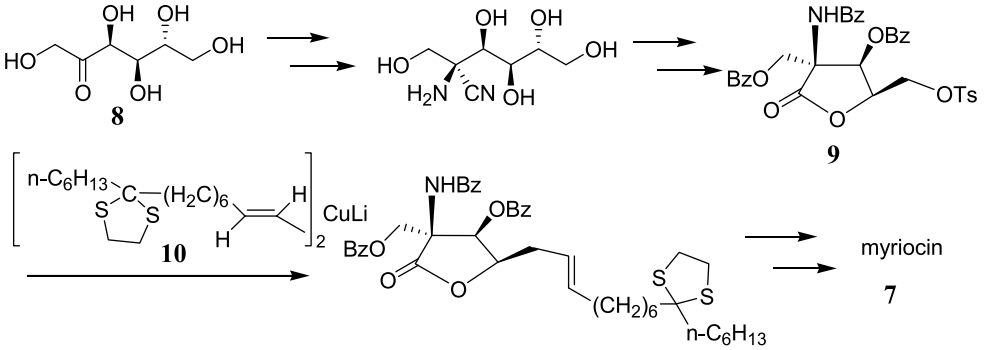
4.2. Synthesis of lower organism sphingolipids

In recent years, a variety of sphingosine-like compounds have been isolated from lower organisms including sponges, yeast and other fungi. While having a skeleton similar to sphingosine, these compounds feature more complicated structures in terms of the number of chiral centers and functional groups, which renders them more challenging for synthetic chemists. As with derivatives of sphingosine, these compounds have been shown to have a wide range of fascinating biological activities; therefore, it is not surprising that widespread interest has been provoked in the synthetic community.

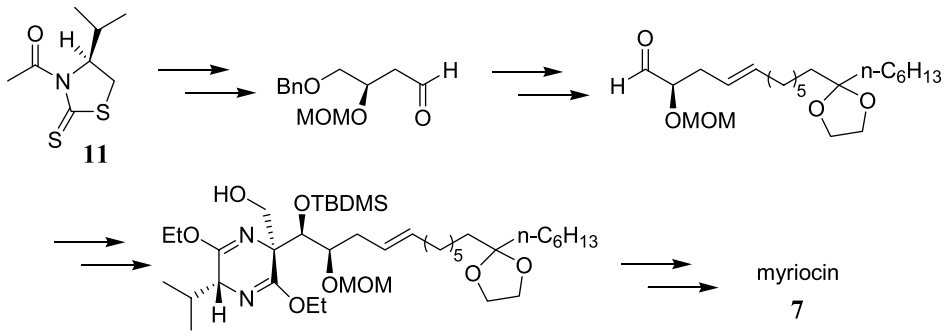
4.2.1. Myriocin.



The discovery of myriocin (7) dates back to 1972, when Klüpfel et al.[31] isolated it as an antibiotic from the culture broth of the thermophilic fungus, *Myriococcum albomyces*. It was later discovered that myriocin has a potent immunosuppressive activity and, thereafter, many synthetic chemists have been intrigued in developing a practically useful synthetic route for its synthesis.



Scheme 4.



Scheme 5.

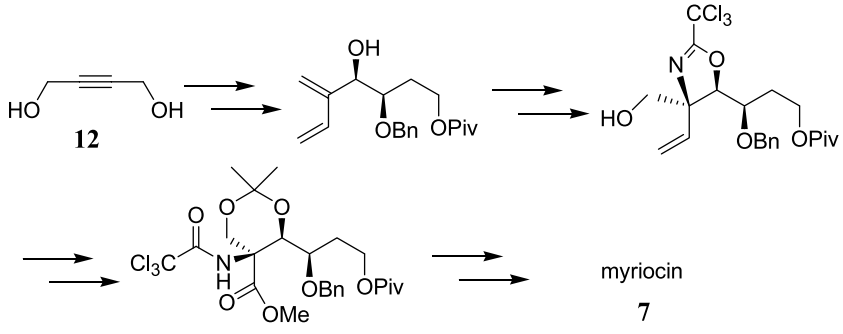
In 1982, the first total synthesis was accomplished by Scolastico et al. (Scheme 4).[32] In their work, D-fructose (8) was employed as the source of chirality. The key steps involved hydrocyanation of the fructosyl-*p*-tolyamine, which afforded the desired stereoisomer, and incorporation of the side chain, which was achieved by the coupling reaction of the alkenylcuprate (10) with the tosylate (9) with high stereocontrol of the *trans* double bond. The hydrocyanation step was, however, associated with poor stereoselectivity.

In 1995, Nagao et al.[33] reported an alternative asymmetric synthesis starting from 11 (Scheme 5). In their convergent route, all the stereogenic centers were generated by asymmetric aldol reactions employing chiral auxiliaries. Furthermore, the *E*-olefin was constructed in a highly selective manner by the Schlosser-modified Wittig reaction.

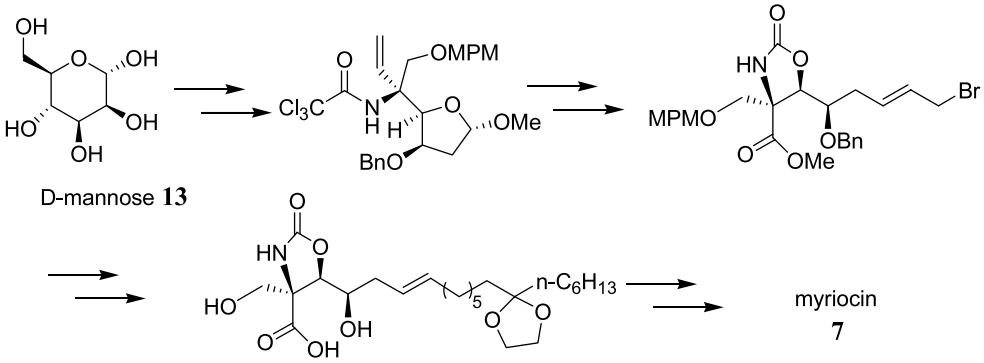
The first highly enantioselective synthesis of myriocin was reported by Susumi et al.[34] in 1997 (Scheme 6). Starting from 2-butyn-1,4-diol (12), they employed a Sharpless AE reaction and $TiCl_4$-catalyzed addition of 1-trimethylsilyl-buta-2,3-diene to an aldehyde to generate all the chiral centers in high enantioselectivity, and the chiral quaternary center of the α-substituted serine subunit was constructed by Lewis acid-catalyzed cyclization of an epoxytrichloroacetimidate intermediate.

Another stereoselective pathway to the synthesis of myriocin was described by Chida et al.[35] in 2001 (Scheme 7). Commencing with D-mannose (13) as the starting material, they utilized an Overman rearrangement reaction as the key step to construct the chiral quaternary center of the α-substituted serine subunit of myriocin.

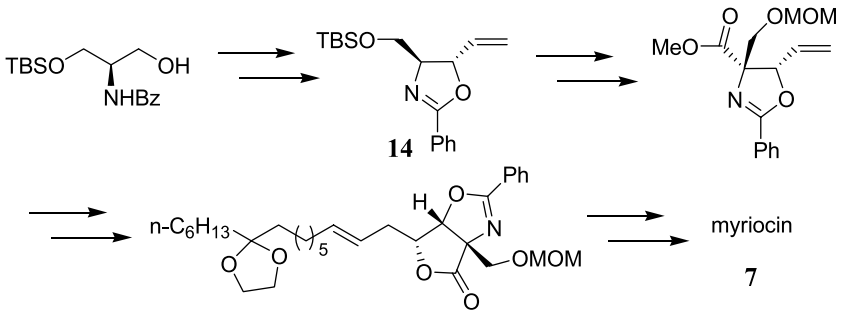
Very recently, Lee et al.[36] reported a novel and concise stereocontrolled synthesis of myriocin (Scheme 8). They employed an enantiopure oxazoline intermediate (14) as a



Scheme 6.



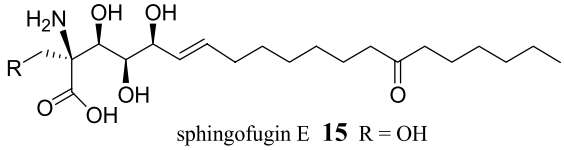
Scheme 7.



Scheme 8.

chiral building block, which was formed by intramolecular cyclization of homoallyl benzamide catalyzed by palladium(0), while the incorporation of the side chain was efficiently accomplished by palladium(0)-catalyzed coupling of a vinyl iodide with an organozinic reagent.

4.2.2. Sphingofungin E and F.

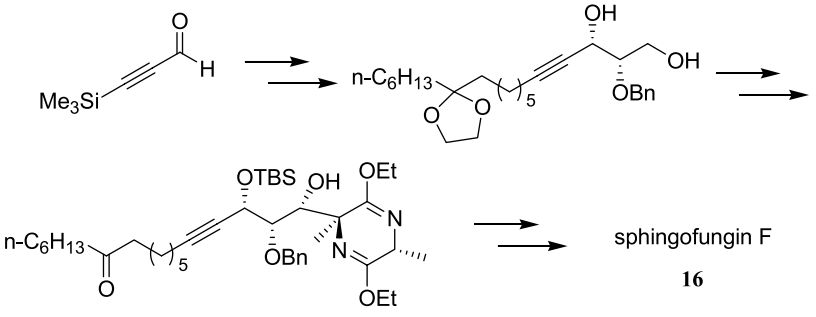


sphingofugin E **15** R = OH
F **16** R = H

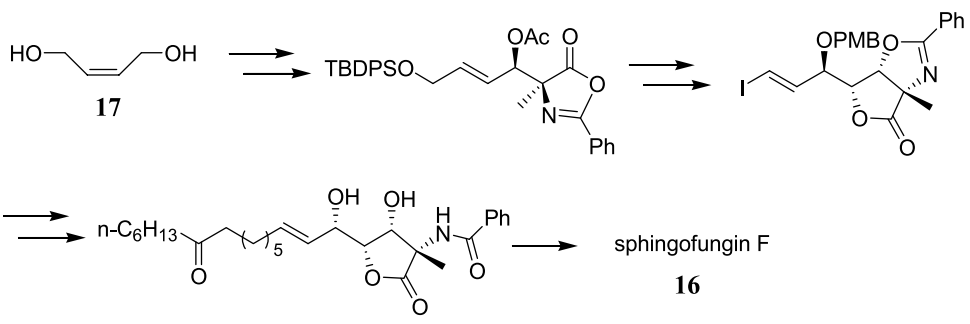
Sphingofungin E (15) and F (16) were first isolated from the fermentation broth of *Paecilomyces variotii* by a Merck group in 1992[37] These two compounds were found to block the biosynthesis of sphingolipids via inhibition of serine palmitoyl transferase, leading to apoptosis in both yeast and mammalian cells. With a structural resemblance to myriocin, both sphingofungin E and F have attracted widespread interest from the synthetic community. The first total synthesis of sphingofungin F was reported by Kobayashi et al.[38] In their work (Scheme 9), a tin(II)-catalyzed asymmetric aldol reaction was employed to generate the chiral centers on C-4 and C-5 in a highly stereocontrolled manner in the presence of a chiral Lewis acid and the quaternary center was constructed by asymmetric aldol reactions with the aid of chiral auxiliary groups.

An extremely efficient synthesis of sphingofungin F was reported by Trost et al.[39] in 1998 from the commercially available *cis*-2-buten-1,4-diol (17) (Scheme 10), which only take 15 linear steps and proceeds in 17% overall yield. In their synthesis, all the stereochemistry was established by asymmetric alkylation catalyzed by palladium(0) and Sharpless AD reaction with high stereocontrol, while Suzuki crosscoupling was employed to construct the *trans* double bond. Later, the same protocol was adopted in their synthesis of sphingofungin E (Scheme 11), but the stereocontrol was worse than that in sphingofugin F.

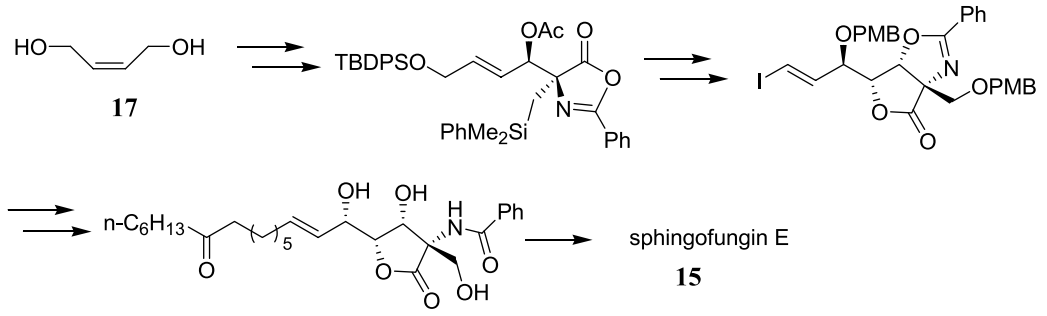
In 2000, Lin's group[40] published an alternative



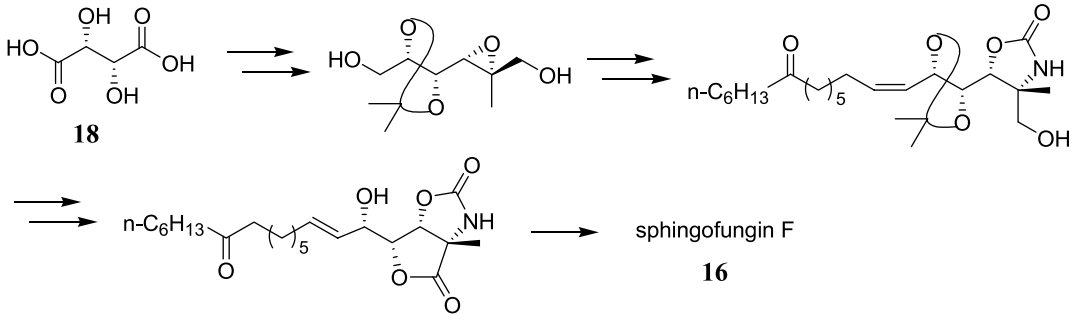
Scheme 9.



Scheme 10.



Scheme 11.

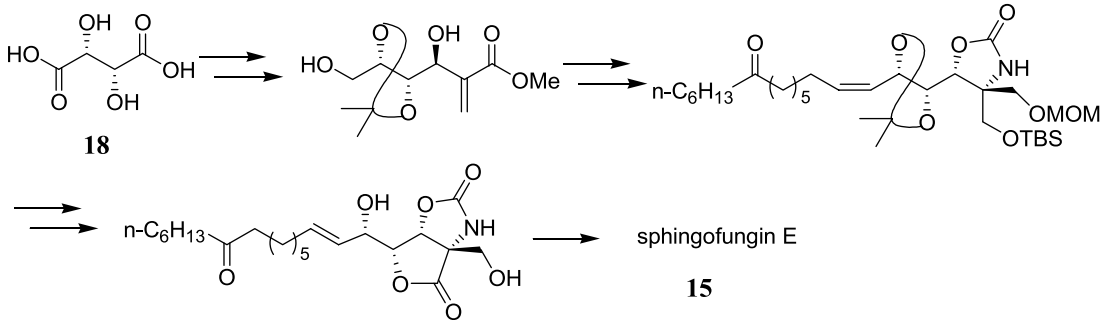


Scheme 12.

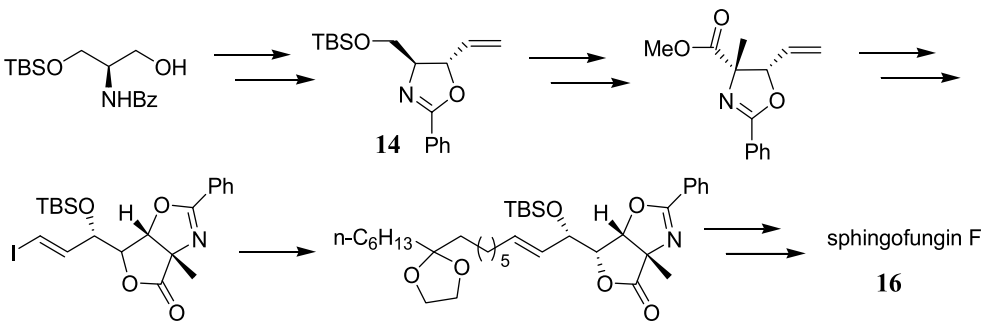
stereoselective approach to sphingofungin F, starting from a cheap material, L-tartaric acid (18) (Scheme 12). Their work features Sharpless asymmetric epoxidation and Lewis acid-catalyzed intramolecular epoxide opening as the key steps. Later, a similar strategy was applied to the synthesis of sphingofungin E, with a Baylis–Hillman reaction as an additional key step (Scheme 13).

Ham[41] has published an alternative method for the synthesis of sphingofungin F in 2002 (Scheme 14) in which they employed the same protocol in their work for myriocin.

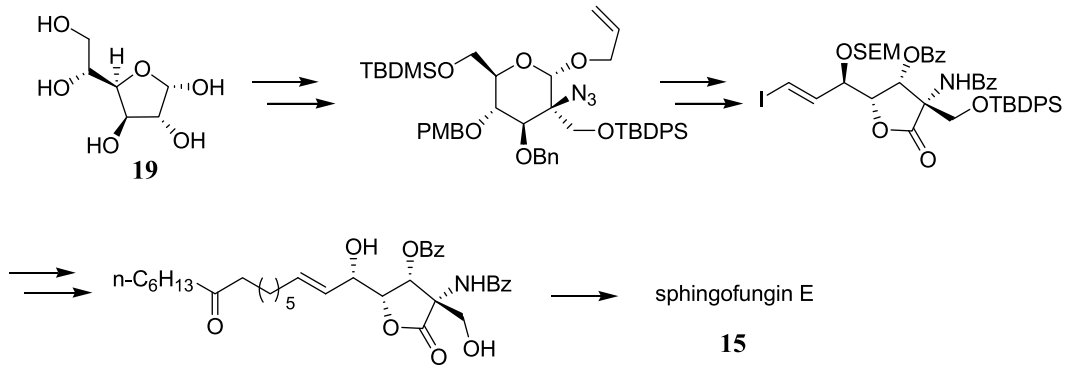
Recently, two additional approaches have been developed by Shiozaki[42] and Chida,[43] respectively, both of which are based on D-glucose (19) as the starting material.



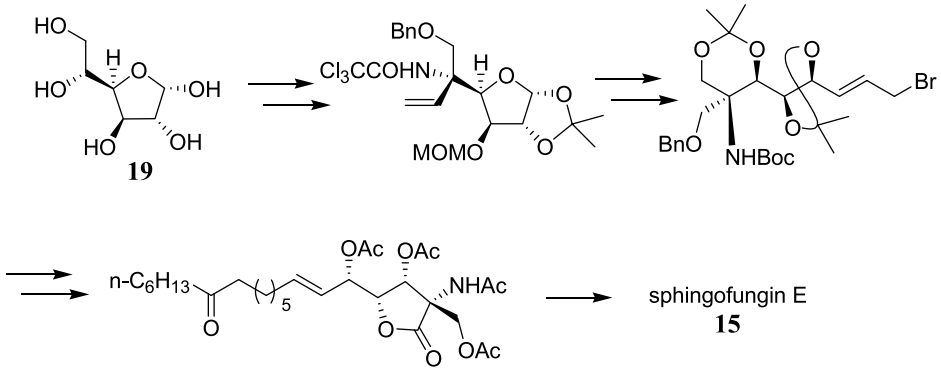
Scheme 13.



Scheme 14.



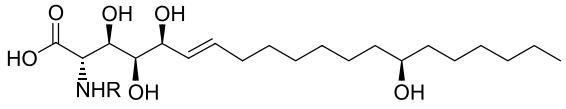
Scheme 15.



Scheme 16.

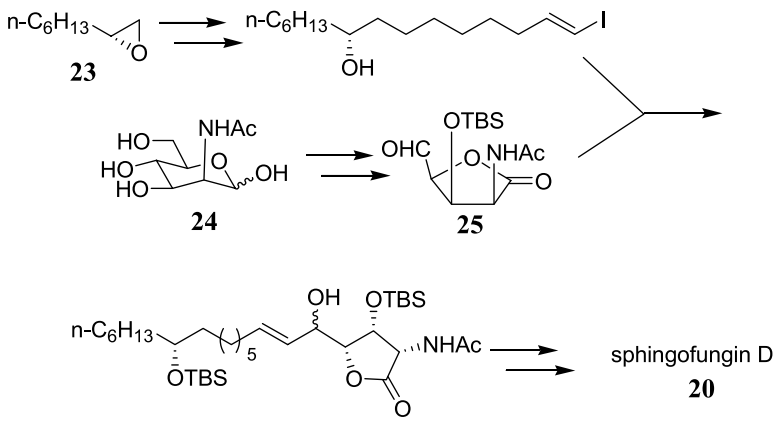
In Shiozaki's work (Scheme 15), the quaternary center was constructed *via* the ring opening of a spiro α-chloroepoxide and Trost's strategy was employed to assemble the two fragments. Chida's work was based on a similar strategy to their synthesis of myriocin (Scheme 16).

4.2.3. Sphingofungin D, B, and A.

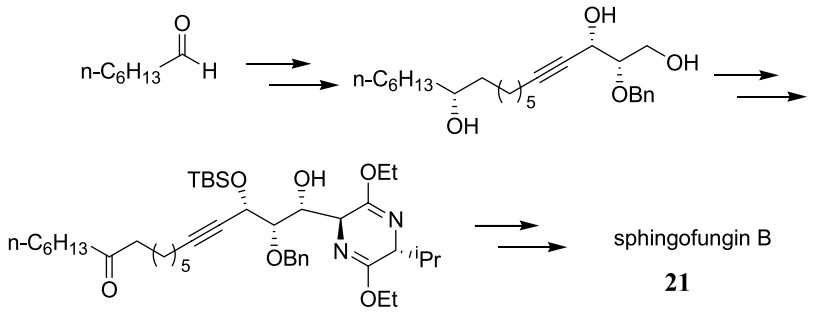


sphingofungin D **20** R = Ac
B **21** R = H
A **22** R = C(=NH)NH$_2$

Sphingofungin D (20), B (21) and A (22) were isolated by VanMiddlesworth et al. from metabolites of *Aspergillus fumigatus* ATCC 20857 in 1992.[44] All these compounds exhibit potent bioactivity as specific inhibitors of serine palmitoyl transferase. The total synthesis of sphingofungin D was first achieved by Mori et al.[45] In their synthesis (Scheme 17), the chiral center on the non-polar part was derived from a commercially available epoxide (23) and the polar part was synthesized from *N*-acetyl-D-manosamine (24), while the coupling of the two fragments was achieved by nickel(II) chloride-catalyzed addition of vinylchromium to the aldehyde (25). Unfortunately, the stereocontrol for the newly formed chiral center in the coupling step was poor. For the synthesis of sphingofungin B, the first method was



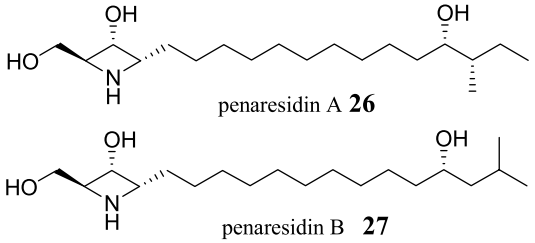
Scheme 17.



Scheme 18.

developed by Kobayashi et al. in 1996,[46] in which (Scheme 18) they adopted the same strategy as that in their synthesis of sphingofungin F and completed the synthesis of several stereoisomers to investigate their SPT inhibitory activity.

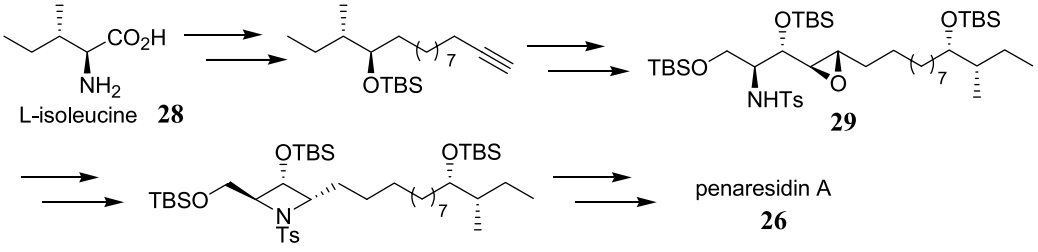
4.2.4. Penaresidin A and B.



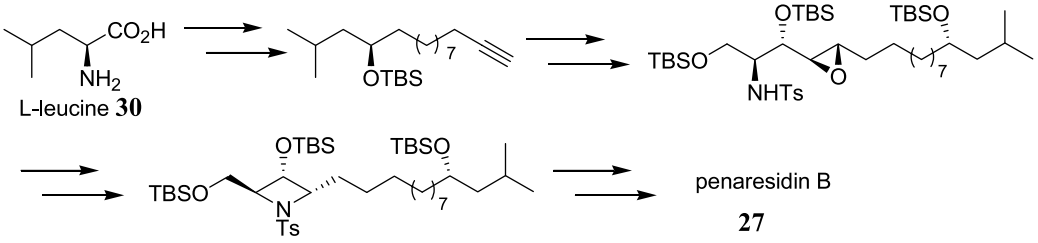
From an Okinawan marine sponge, *Penares* sp., two sphingosine-derived alkaloids, penaresidin A (26) and B (27), were isolated by Kobayashi et al. as an inseparable mixture in 1991.[47] The structural elucidation was eventually achieved by spectroscopic methods supplemented by synthetic studies in 1996.[48] Experiments indicated that the mixture of these two alkaloids was able to elevate the ATPase activity of myofibril from rabbit skeletal muscle to 181% of control at 3×10^{-5} mol dm^{-3}. The unique structure of these compounds and their fascinating bioactivities invoked much interest from organic chemists in pursuing their total syntheses. The first synthesis of penaresidin A was achieved by Mori et al. in 1995 (Scheme 19).[49] They started with L-isoleucine (28), which was used to furnish the side chain fragment, and Garner aldehyde, which was utilized to construct the azetidine part. The coupling of the two fragments was achieved by the addition reaction of lithium alkyne to Garner aldehyde, but the stereoselectivity in the epoxidation step was poor, with the desired isomer (29) as a minor product. Later, a similar strategy was also published for the synthesis of penaresidin B from L-leucine (30) and corrected the proposed structure (Scheme 20).[50]

In 1997, Knapp et al.[51] reported an alternative method for the synthesis of penaresidin A from Garner aldehyde (Scheme 21). High stereocontrol was achieved for the stereogenic centers in both the azetidine part and the side chain via Keck allylation and Roush reactions, respectively.

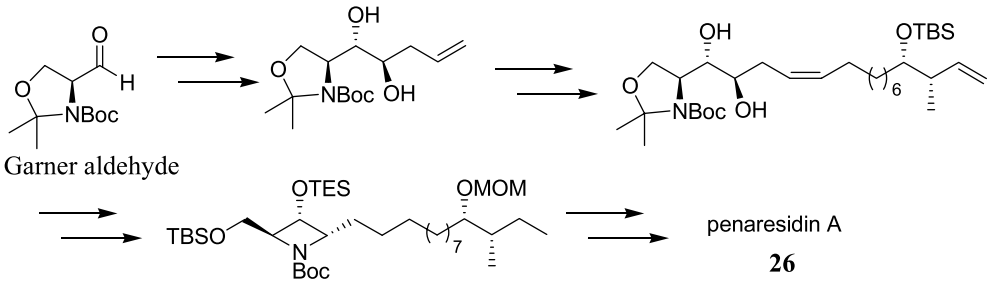
A novel highly enantioselective approach to penaresidin A was described by Lin's group[52] from the commercially available divinylcarbinol (31) in 1999 (Scheme 22). They utilized Sharpless AE and AD to establish the stereochemistry for the azetidine part and employed a Roush reaction to construct the stereogenic centers on the side



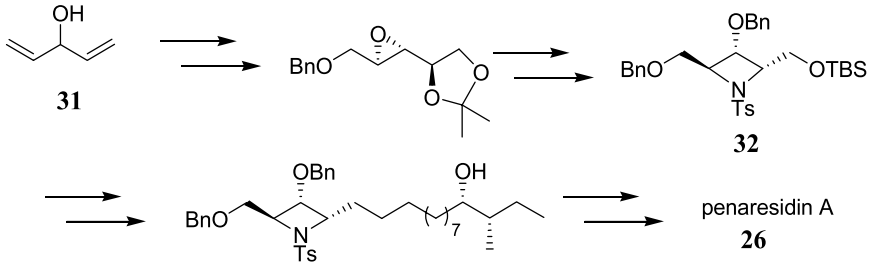
Scheme 19.



Scheme 20.



Scheme 21.

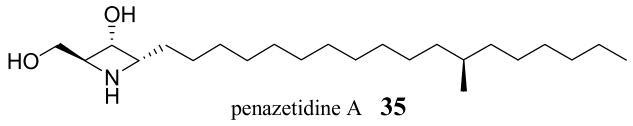


Scheme 22.

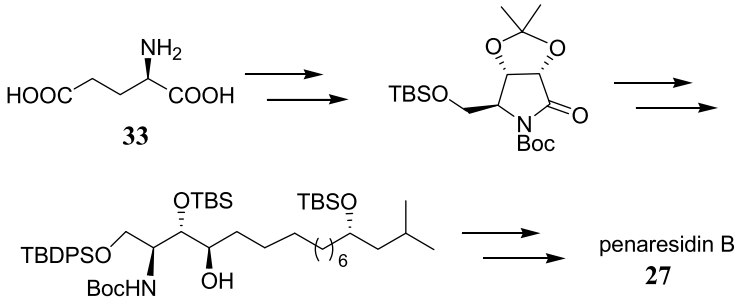
chain. It is noteworthy to mention that their method provided an access to a highly substituted azetidine intermediate (32), which can be regarded as a common advanced precursor for the synthesis of penaresidins and penazetidine A (vide infra).

In 1997, Yoda et al.[53] developed an alternative method for the synthesis of penaresidin B from D-glutamic acid (33) (Scheme 23). Recently, a revised strategy was reported by the same group based on a commercially available D-arabinose derivative (34) (Scheme 24).[54] The later work was accomplished concisely in 12% overall yield with very high stereoselectivity.

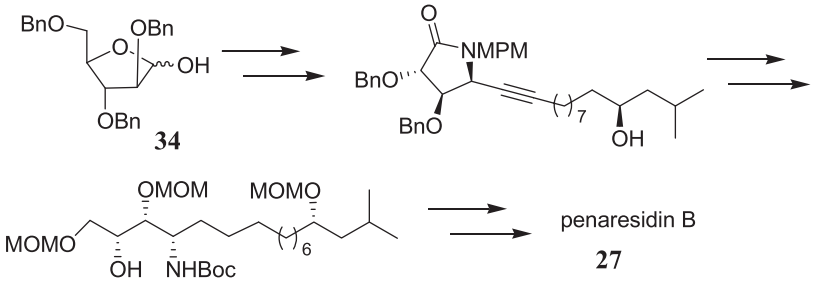
4.2.5. Penazetidine A.



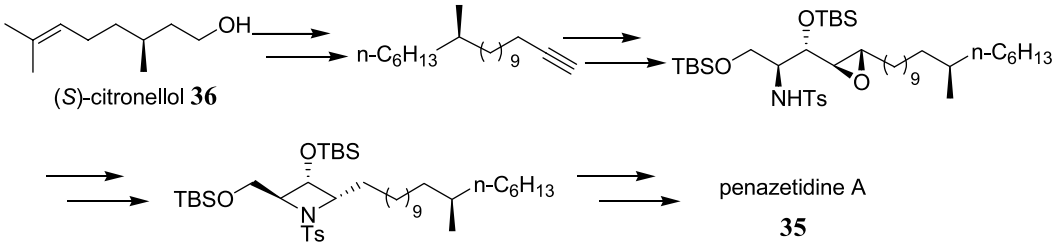
As a new compound structurally related to penaresidins, penazetidine A (35) was discovered by Crew et al. in 1994 from the Indo-Pacific marine sponge, *Penares sollasi*.[55] Experiments showed that penazetidine A exhibits potent specific inhibitory activity against rat brain PKCβ1 with an



Scheme 23.



Scheme 24.



Scheme 25.

IC_{50} value of 1 μM. The first synthesis of penazetidine A was reported by Mori et al. (Scheme 25),[56] in which the stereogenic center on the side chain was derived from citronellol (36) and the same strategy for their synthesis of penaresidins was adopted for the construction of the azetidine part. Since there was no difference in spectrum between the 16*S* and 16*R* isomers, the absolute stereochemistry on this stereogenic center has not yet been assigned.

5. Discovery of S1P, SPC, and LPA receptors

It was originally thought that lysophospholipids, such as S1P and lysophosphatidic acid, act as intracellular secondary messengers for cellular enzymes to regulate cellular activities until the first cell surface GPCR, Edg1, was identified as an S1P receptor about 6 years ago.[57] The binding of S1P to Edg1 at high affinity initiates a series of signaling events resulting in cell aggregation and adherent junction formation. The failure to discover S1P and LPA receptors earlier was partly due to the technical difficulties of handling the very lipophilic ligands. Since then, at least five closely related GPCRs of the EDG family (Edg1, Edg3, Edg5, Edg6, and Edg8) and three members of the EDG family (Edg2, Edg4, and Edg7) have been identified as high affinity S1P and LPA receptors, respectively.[2] Recent studies suggest that there may be several low affinity receptors (GPR3, GPR6, GPR12, and GPR63) for S1P.[1] Recently, OGR1 (ovarian cancer G-protein-coupled receptor 1) and GPR4 were shown to be activated by SPC at high affinity.[58,59] EDG1 was originally identified as an immediate-early gene product in phorbol ester-differentiated human umbilical vein endothelial cells. It has seven transmembrane helices, the signature of G-protein-coupled receptors. The biochemical characterization confirmed EDG1 to be a GPCR with high affinity for S1P (K_d value of 0.47 nM).[4] S1P induced ERK (extracellular-signal-regulated kinase) activation was blocked by pertussis toxin, suggesting that EDG1 is coupled to Gi/Go (heterotrimeric G-protein subtype i and o, respectively). However, the activity of EDG1-induced morphogenetic differentiation seems to be Gi-independent, but can be blocked by C3 exoenzyme, a specific inhibitor of the small GTPase, Rho, which regulates stress fibre formation and focal adhesions. In addition, S1P induces a Gi- and PI3K (phosphatidylinositol 3-kinase)-dependent activation of the protein kinase, Akt, which then binds to the third intracellular loop at the Thr^{236} residue.[60] This phosphorylation event is critical for the activation of the small GTPase, Rac, and, thereafter, the induction of cortical actin assembly, lamellopodia formation, and chemotaxis. Through these signal transduction pathways, S1P induces a series of cytoskeletal reorganizations of endothelial cells, which then play critical roles in angiogenesis and the maturation of the vascular system. In addition, EDG1 activation is also important for cell survival and the proliferation of vascular endothelial cells. Endothelial cell apoptosis is reverted by S1P through Gi- and ERK-dependent pathways.[61]

An expanding subfamily of GPCRs closely related to EDG allows the identification of other receptors for lysophospholipids. OGR1, originally isolated from ovarian cancer cells, was identified as a high affinity receptor for SPC.[58] Although the exact function of OGR1 is not completely understood, its ability to inhibit cell proliferation suggests potentially important functions. Recently, it was shown that SPC could activate another receptor, GPR4, at high affinity (K_d=36 nM).[59] The biological function of this receptor remains to be elucidated. In contrast, the LPA receptors were first identified in the superfamily of lysophospholipid receptors. LPA1 (also called EDG2) was first identified as a high affinity receptor for LPA in the ventricular zone of the developing cerebral cortex.[62] The expression of LPA1 is induced in the myelinating cells of an adult's nervous system, where LPA stimulates the survival of myelinated Schwann cells through LPA1-dependent activation of Akt. The deletion of LPA1 results in complex phenotype, suggesting multiple roles of LPA in other organs.[63] Indeed, it has been shown that LPA can protect T-cells from apoptosis and fibronectin matrix assembly in fibroblasts. Interestingly, LPA2 (EDG4) is strongly induced in ovarian cancer cell lines, where it regulates cellular proliferation. It is also constitutively expressed in CD4+ (cell surface expressed marker CD4 positive) T-cells and inhibits interleukin-2 (IL-2) secretion.

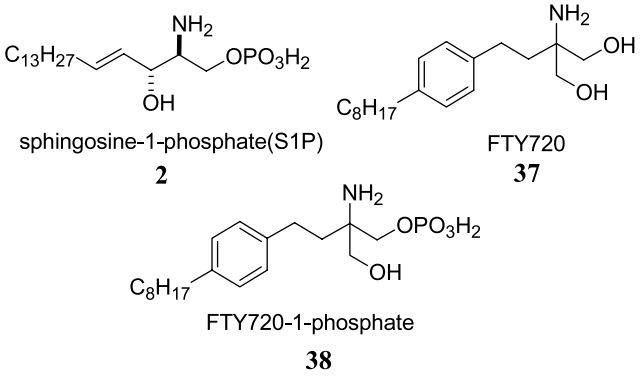


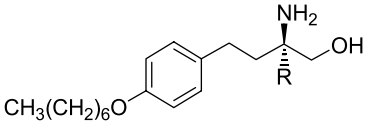
Figure 3. FTY720-1-phosphate as an analog of S1P.

6. SAR Studies of FTY720 and synthesis of other bioactive sphingolipid molecules

More recently, the novel immunosuppressant agent, FTY720 (**37**) (Fig. 3), which is in phase III clinical trials from Novartis, is remarkably effective in models of transplantation and autoimmunity.[64] FTY720 was derived from myriocin, a metabolite of the ascomycete, *Isaria sinclairii*, in traditional Chinese herbal medicine. Unlike myriocin, which often causes severe gastrointestinal side effects, probably due to its inhibition of serine palmitoyl transferase, the first enzyme in sphingolipid biosynthesis, FTY720 does not inhibit this enzyme. However, the molecular target and mechanism of FTY720 were not known until recently, when the EDG receptors were identified as the molecular targets of FTY720. Specifically, it was shown that FTY720, acting through the EDG1 receptor, causes lymphocyte depletion in the peripheral system, but the molecular mechanism in lymphocyte trafficking is not clear.[4,7] FTY720 acts on the EDG1 receptor in regulating multiple steps in lymphocyte trafficking, including emigration of mature single positive thymocytes from medulla into blood; the egress of bulk B- and T-cells from lymph nodes into lymph; and the blockade of effector CD4+ T-cells in lymph nodes. Through all these activities, S1P induces an ignorance of lymphocyte to peripheral antigen. Interestingly, FTY720 seems to have no effects on the generation of CD8 effectors and memory B-cells, which does not impair many antiviral activities mediated through these cells. The sequestration of lymphocytes in secondary lymphoid organs and therefore significantly reduced contact of T-cells and antigens formed the basis of the clinical application of this immunosuppressant in several autoimmune diseases. However, the detailed molecular mechanisms underline these processes are still under investigation.

Both myriocin and FTY720 are structurally similar to sphingosine. Several lines of evidence suggest that FTY720 is phosphorylated and acts as a high affinity EDG agonist after its phosphorylation. Molecular modeling has revealed the mechanisms of this action. The homology modeling and docking studies showed the interaction of basic amino acids Arg^{120} and Arg^{292} with the phosphate, whereas the acidic residue Glu^{121} interacts with the ammonium moiety of S1P, or FTY720-1-phosphate (**38**). Site-directed mutants in functional studies have also confirmed this predicted binding mode.[65]

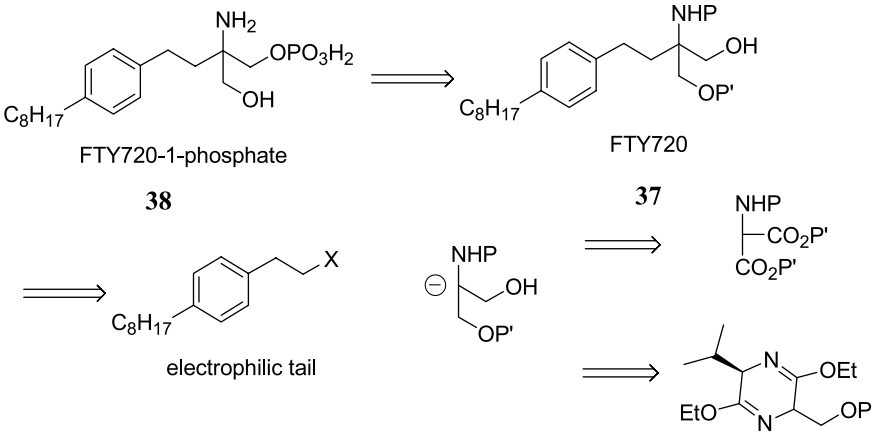
Clearly, the availability of FTY720-1-phosphate (**38**) and analogs will further help to clarify the molecular mechanism for small molecule-receptor interactions. The most common and straightforward approach to prepare FTY720 and its analogs is through alkylation of an anionic head by the electrophilic tail. The head can be a suitably protected amino diester[66] or chiral bislactam ether (Scheme 26).[67] For example, using this strategy, a series of compounds analogous to **39a** and **39b** were synthesized.[68] The two hydroxyl groups of FTY720 were found not to be necessary for the biological activity, since both (*R*)-**39a** and (*R*)-**39b** displayed remarkable activities and, when the R group increases in size, the activities decreases. Moreover, (*R*)-**39a** has a more than tenfold immunosuppresive activity, compared to (*S*)-**39a** (not shown), indicating that the pro-(*S*)-hydroxymethyl group is of critical importance for the potent activity, which may either be due to the efficiency differences of phosphorylation by sphingosine kinase and/or the differential preference of the receptor binding mode in vivo.



(*R*)-**39a** R = Me

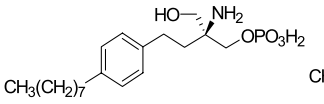
(*R*)-**39b** R = n-Pr

More recently, a similar strategy was used to synthesize stereoisomers for analogs and evaluate the effect of stereochemistry on S1P receptors. It was found that compound **40** is a full agonist of $S1P_1$ and an agonist of $S1P_3$, $S1P_4$ and $S1P_5$ with 70–90% maximal efficacy, compared to the endogenous ligand, S1P. On the other hand, compound **41** was found to be a weaker full agonist of $S1P_1$ and $S1P_2$, but a weak antagonist of $S1P_3$ and $S1P_5$. Therefore, each enantiomer could have different S1P receptor binding profiles. Similar synthetic methodologies have been used by a Novartis group to prepare a variety of chiral FTY720 analogs for mechanistic understanding and

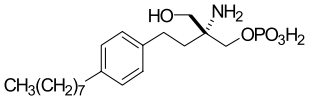


Scheme 26.

receptor subtype specific-agonist discovery.[69] Other approaches to the synthesis of FTY720 and its analogs include the modification of methodologies used to prepare sphingosines described in Section 4.1. For example, using the Garner aldehyde, all four stereoisomeric analogs of S1P were generated and their biological activities were investigated.[70] The D-erythro configuration of S1P was found to be important for high affinity binding to EDGs. Some simpler analogs have also been prepared, for example, to introduce rigidity in tails by incorporating phenyl rings[71] or benzoimidazole rings, which can potentially be used to provide novel scaffolds and constraints to enhance their binding affinities.[72]

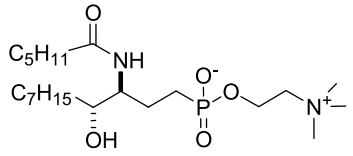


40



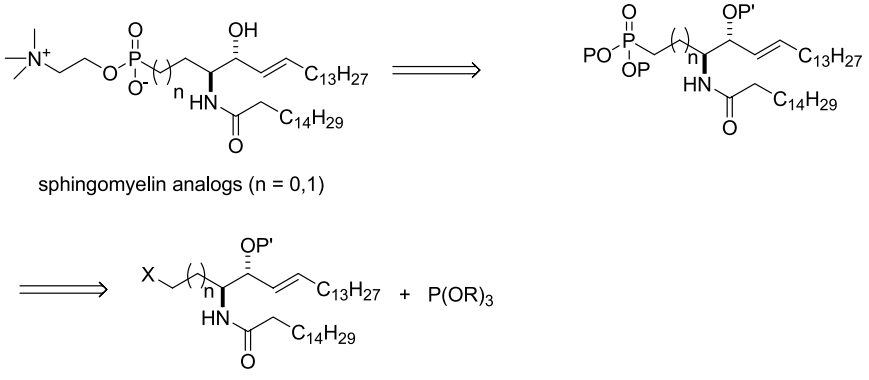
41

Compared with ceramidases and FTY720-related receptors, much less is known for sphingomyelinases, which hydrolyze sphingomyelins into ceramides, biosynthetic precursors to sphingosine. For a biological study, a number of non-hydrolytic sphingomyelin analogs have been designed, where a non-scissile P–C bond was used to replace the labile P–O bond. The most common access to these molecules utilizes a Michaelis–Arbuzov reaction between an alkyl bromide and phosphates (Scheme 27),[73,74] For example, this strategy has been adopted to prepare a sphingomyelin methylene analog **42**, which showed moderate inhibitory activity towards sphingomyelinase isolated from *B. cereus*.



42

The syntheses of ceramides and their analogs in general use the same approaches to prepare sphingosine analogs, and will not therefore be discussed in detail. For the recent literature on their synthesis and biological studies, the reader is directed to Ref. 75.



Scheme 27.

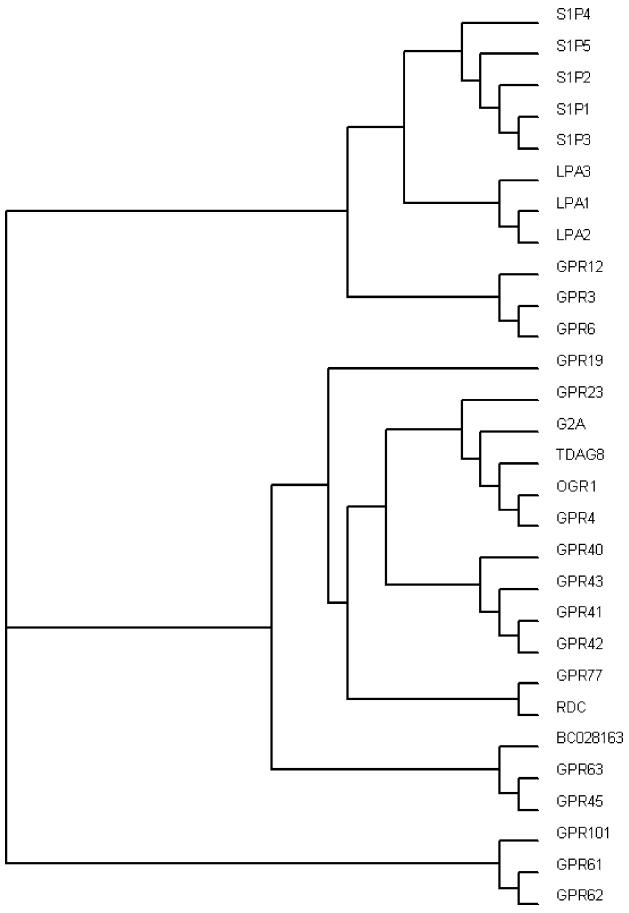


Figure 4. Dendrogram of the S1P-related G-protein-coupled receptor in human genome. This family of receptors represents potential receptors for lipid and lipid-like ligands. A combinatorial approach of biology and chemistry is being used to explore their functions in human lipid physiology.

7. Summary

Significant progress has been made in the last decade in both the chemical synthetic methodologies and the biological functional elucidation of sphingolipids. Various sphingolipids from lower organisms were identified and total synthesises have been successfully achieved for most of them using various asymmetric synthetic protocols. These methodologies can be applied to the synthesis of other small-molecule analogs of sphingolipids for the determination of individual receptor function. The rapid progress in

annotating the biological functions of sphingolipids and their receptors has significantly contributed to our understanding of sphingolipids in physiological and pathological conditions.

The recently finished human genome and developments in bioinformatics tools allow the discovery of a new family of receptors of putative lipid receptors (Fig. 4).[1] Among these receptors, only some ligands derived from nature have been discovered at high affinity. Many of the reported ligands for these receptors are of low affinity. These may be due to inefficiency of coupling of receptors to heterotrimeric G-proteins in heterologous cell systems or yet-to-be-discovered high affinity natural ligands. Given subnanomolar binding and activation of S1P receptors by S1P, the search for natural high affinity ligands remains a challenging task in the future, suggesting the structural diversity of lipid-signaling molecules and their importance in biology.

In addition to S1P receptors, many of these family receptors may play important roles in immunoregulation, obesity/diabetes, cardiovascular remodeling, and tumor invasion. Deletion of G2A in mice results in delayed onset of multisystem autoimmune disease after 1 year of age.[13] GPR40, a free fatty acid receptor, has been shown to mediate insulin secretion from pancreatic β-cells in the presence of high concentrations of glucose.[76] GPR41, another free fatty acid receptor, could mediate leptin secretion in response to fatty acids in mice.[77] All these data suggest that, in addition to nuclear hormone receptors, GPCR may represent another pathway for cells to sensitize lipids to regulate physiological processes in vivo. Therefore, the achievements in both chemical synthesis and biological discovery of lipid receptors in the human genome will lead to rapid progress in lipid research in the near future.

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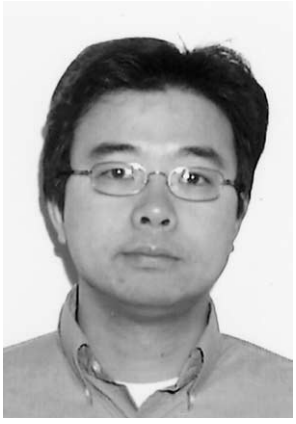
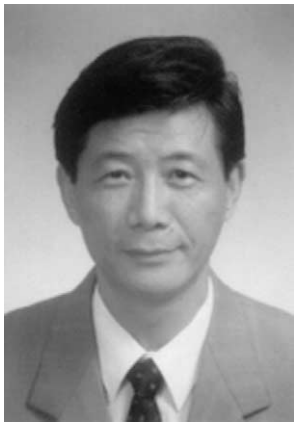
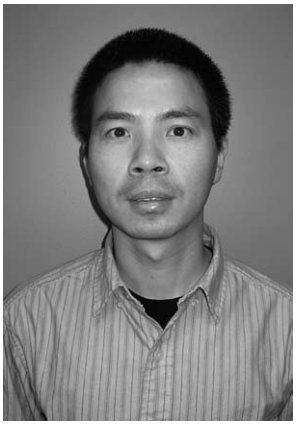
Biographical sketch



Jiayu Liao received his B.S. degree in biochemistry from Peking University, P.R. China in 1988. He served as assistant lecturer in National Protein Engineering Laboratory for two years in Peking University, P.R. China before he went to University of California, at Los Angeles for graduate school. His Ph.D. graduate work was focused on the signal transduction of cytokine signaling, which led to the isolation and discovery of PIAS (Protein Inhibitor of Activated Stat). He then joined Peter G. Schultz's group as postdoctoral research associate at The Scripps Research Institute and Genomic Institute of the Novartis Research Foundation, where he worked on the G-protein coupled receptor (GPCR) analysis in human genome and GPCR lead discovery.



Professor Guo-Qiang Lin was born in Shanghai, China. After he finished his graduate study in Shanghai Institute of Organic Chemistry in 1968, under the supervision of Professor Wei-Shan Zhou, he joined the same institute and worked on the natural products chemistry. He was promoted to a full professor in 1990, and was elected as the academician of CAS in 2001. His research interests include the synthesis of natural products and biologically active compounds, asymmetric catalysis and biotransformation. He is an Executive Board Member of Editors for *Tetrahedron* Publications, and he is also the Editors of *Acta Chemica Sinica*, *Chinese Journal of Organic Chemistry* and *Chinese Journal of Chemistry*.



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Preparation and photoluminescence of *p*-terphenyl derivatives containing cyano groups

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Abstract—Fifteen *p*-terphenyls containing alkoxylated backbones with and without cyano groups on the phenyl moieties have been designed and synthesized. The influences of the position and the number of cyano groups on the phenyl moieties as well as the skeleton to the absorption and emission spectra both, in solution and in solid state of these new *p*-terphenyls are discussed.

1. Introduction

Recently, we have reported a series of distyrylbenzene (DSB) derivatives, as the oligomeric analogue of poly-*para*-phenylene-vinylene (PPV), which was assessed as the emitter in organic light emitting diode (OLED) fabrication.[1] The presence of electron-withdrawing cyano group at various positions in the molecule may influence on the photophysical property and the electroluminescent behavior of these derivatives in OLED. Thus, bright blue emissions were achieved with these materials, as a dopant, in the device structure of ITO/NPB/CBP/TPBI:DSB/TPBI/Mg:Ag.[1] Although there were not much difference in the absorption and emission spectra of the analogues compounds containing *n*-hexyloxy and 2-ethylhexyloxy groups. However, 2-ethylhexyloxy groups could produce more saturated blue color in their EL. Our preliminary results from ZINDO calculations[2] on *p*-terphenyls with or without cyano groups on the phenylene moieties showed that *para*- or *meta*-substituted cyano groups on the peripheral rings could cause red shifts in the absorption spectra. The presence of the alkoxy unit should enhance the solubility of oligomers and the introduction of high electron affinity of cyano groups to oligo-*para*-phenylene-vinylene (OPV) derivatives has been reported to lower the energy of the LUMO and reduces the barrier to the electron injection in LED.[3] Thus, PPV derivatives containing cyano groups could present high electron affinity and therefore exhibit a relatively low threshold voltage and high quantum efficiency in LED devices even using stable aluminum electrodes.[4] However, despite its interesting properties in this field, as to our knowledge, there is no report in the literature about the synthesis of the *p*-terphenyls with or without cyano groups on the phenylene moieties. The aryl–aryl bond formation has been known for more than a century and was one of the first reaction using a transition metal.[5] Over the last ten years many articles have dealt with new results in the area of aryl–aryl bond formation. Nowadays, many more syntheses use palladium catalysts than their nickel and copper counterparts. As to our knowledge, the palladium-catalyzed Stille,[6] Suzuki,[7] Negishi,[8] and Kumada[9] reaction have been the most studied over the past few years. We have focused on the Suzuki coupling, a palladium(0)-catalyzed carbon–carbon bond-forming reaction between an organohalide and an organoboron reagent, in the α-arylation or α-vinylation of *N*,*N*-dimethylacetamide recently.[10,11] Since the boron reagents are compatible with a large number of functional groups and tolerate cyanides, thus fulfilling our goals for synthetic flexibility. Herein, we report the efficient synthesis of a series of *p*-terphenyl with and without cyano groups **1**–**10** and their photoluminescent behavior. As for comparison, we also synthesized *p*-terphenyl derivatives with cyano groups on the central benzene ring and *p*-terphenyl with hexahexyloxyl groups **11**–**15** (Scheme 1).

2. Results and discussion

The Suzuki cross-coupling reaction to form *p*-terphenyls with or without cyano groups were shown in Scheme 1. Thus, the palladium-catalyzed cross-coupling reaction of

Keywords: Suzuki–Miyaura reaction; *p*-Terphenyl containing cyano groups; Photoluminescence.
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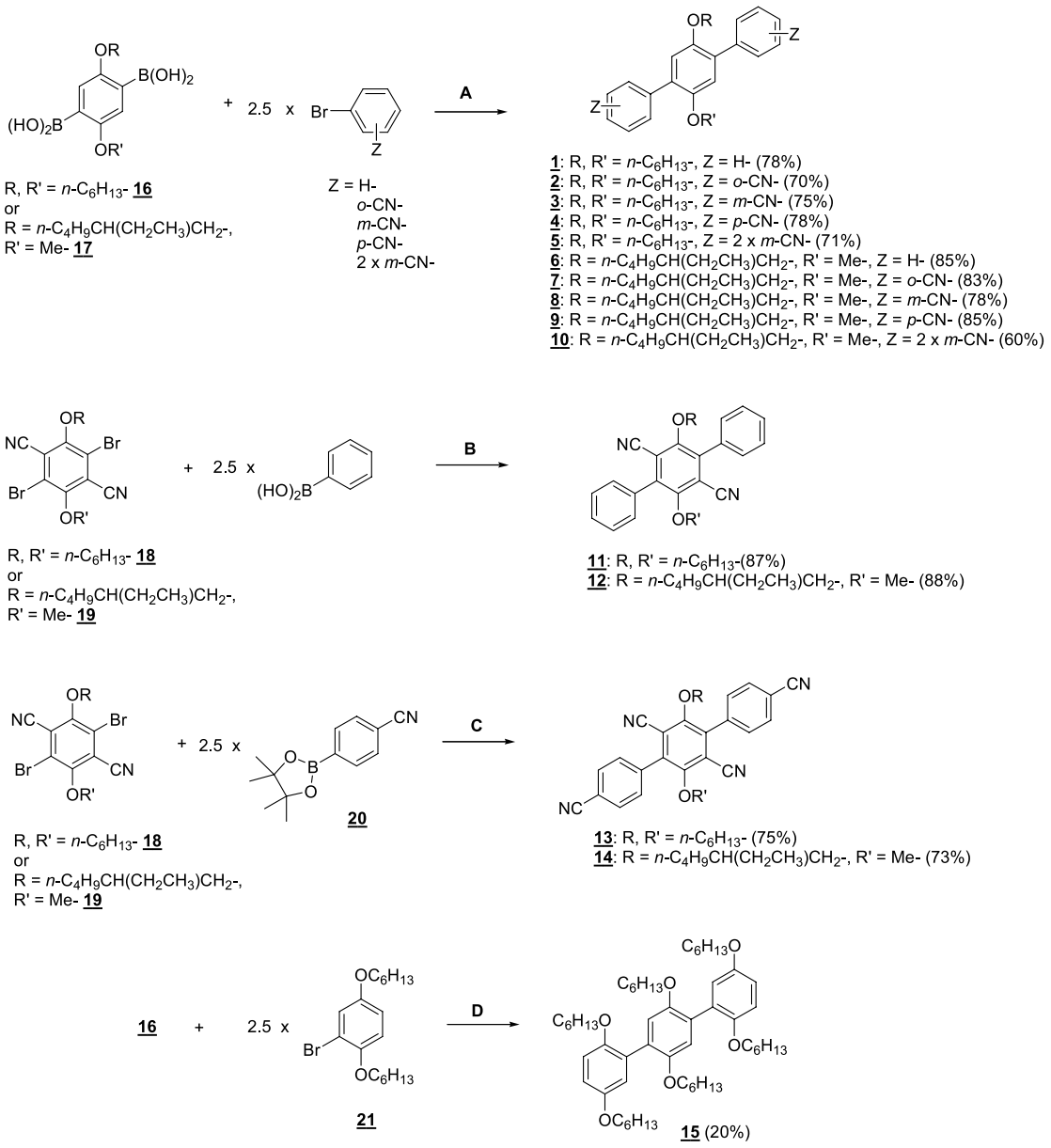

Scheme 1. Synthesis of a series of *p*-terphenyl with or without cyano groups.

2,5-dihexyloxy-1,4-benzenediboronic acid (**16**), prepared in 79% yield from the lithium–halogen exchange reaction of 2,5-dibromo-1,4-dihexyloxybenzene with *n*-butyllithium followed by the treatment of trimethylborate and dilute acid, with 2.5 equiv of bromoarene with or without cyano groups at *ortho*-, *meta*-, *para*-, or two *meta*-positions in the presence K_2CO_3 as the base in DMSO could give *p*-terphenyls **1**–**5** in fair to good yields (70 to 78%). Under the similar reaction conditions, the cross-coupling reaction of 2,5-dibromo-1,4-dihexyloxybenzene with arylboronic acid with or without cyano groups gave **1**–**5** in low yields (33 to 42%). Likewise, 2-(2-ethylhexyloxy)-5-methoxy-1,4-benzenediboronic acid (**17**) could give the corresponding *p*-terphenyls **6**–**10** in fair to good yields (60 to 85%). 2,5-Dibromo-3,6-dihexyloxybenzene-1,4-dicarbonitrile (**18**) and 2,5-dibromo-6-(2-ethylhexyloxy)-3-methoxybenzene-1,4-dicarbonitrile (**19**) could undergo Suzuki coupling reaction with 2.5 equiv of phenylboronic acid to give *p*-terphenyls **11** and **12** with cyano groups on the central benzene ring in 87 and 88% yields, respectively. The coupling of **18** and **19** with phenylboronic acid with cyano groups on the phenyl rings, prepared from lithium–halogen exchange of cyano-substituted bromobenzene and *n*-butyllithium at −78 °C in THF followed by the addition of trimethylborate, gave very low yields. However, the palladium-catalyzed cross-coupling reaction of 2.5 equiv of 4,4,5,5-tetramethyl-2-(4-cyanophenyl)-1,3,2-dioxaborolane (**20**) with **18** and **19** could give *p*-terphenyls **13**–**14** with two cyano groups on the central benzene ring and two cyano groups at the *para*-positions of the peripheral rings in 75 and 73% yields, respectively. The use of $PdCl_2$(dppf) as the catalyst and K_3PO_4 as the base could give better yields than

Table 1. UV spectral data of symmetric and asymmetric *p*-terphenyls

Compound	UV[a] λ_{max} (nm)	UV[b] λ_{max} (nm)	$\varepsilon^{a}\times10^{3}$ dm^{3} mol^{-1} cm^{-1}
1	320	357	7.96
2	331	372	2.20
3	332	337	7.55
4	346	383	8.81
5	344	361	7.98
6	318	320	10.22
7	327	335	9.38
8	329	346	12.32
9	342	368	9.62
10	345	356	8.96
11	341	355	9.61
12	336	349	6.61
13	337	347	11.95
14	336	347	8.88

[a] The UV spectra in ethyl acetate solution.
[b] The UV spectra in solid state.

the use of other kinds of catalysts ($Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$) and bases (K_2CO_3, CsF, Cs_2CO_3, *i*-Pr_2NEt) in the case of coupling 1,3,2-dioxaborolane with **18** and **19**. Attempts to prepare 3,6-dicyano-2,5-dihexyloxy-1,4-benzenediboronic acid from **18** by lithium–halogen exchange at low temperature and followed by the addition of trimethylborate gave only debrominated product, 2,5-dihexyloxybenzene-1,4-dicarbonitrile, in 70% yield. The palladium-catalyzed cross-coupling reaction of **16** with 2.5 equiv of 2-bromo-1,4-dihexyloxy-benzene (**21**), prepared in 86% yield by mono-lithium–halogen exchange of 2,5-dibromo-1,4-dihexyloxybenzene with *n*-butyllithium followed by acidic hydrolysis, gave *p*-terphenyl **15** with hexahexyloxyl groups. Attempts to couple **16** with 4-bromo-2,5-dihexyloxybenzenecarbonitrile in the presence of various palladium catalysts and bases failed.

Tables 1 and 2 showed the λ_{max} of their UV, PL, and EX spectral data along with the extinction coefficiency and the fluorescent quantum yield, Φ_F, of *p*-terphenyls **1**–**14** both in ethyl acetate solution and in their solid states. In general, the extinction coefficiencies of UV spectra in solution for *p*-terphenyls without cyano groups on the central benzene ring (**1**–**10**) are higher for asymmetric *p*-terphenyls (**6**–**10**) containing 2-ethylhexyloxy and methoxy groups than the corresponding symmetric *p*-terphenyls (**1**–**5**) containing two *n*-hexyloxy groups. The lower extinction coefficiency (a measure of transition probability or allowedness of an electronic transition at a given wavelength) for **1**–**5** may be due to their bigger steric hindrance than that for the corresponding **6**–**10**.[12] Since one of the *n*-hexyloxy group in **1**–**5** is a little bigger than the corresponding methoxy group in **6**–**10** so that the three phenyl groups tend to be non-coplanar in **1**–**5**, while the three phenyl groups are relatively not so non-coplanar in **6**–**10**.[13] That means that there is a bigger structure change in the excited states from the ground states for **1**–**5** than that for **6**–**10**. So, the transition probability for **6**–**10** is higher than that of **1**–**5**. In other words, the extinction coefficiencies for **6**–**10** is relatively higher than that for **1**–**5**. On the contrary, the extinction coefficiencies of UV spectra for *p*-terphenyls with cyano groups on the central benzene ring (**11**–**14**) is lower for asymmetric *p*-terphenyls (**12** and **14**) than the corresponding symmetric *p*-terphenyls (**11** and **13**). For *p*-terphenyls **1**–**14**, the λ_{max} in both UV absorption and PL emission spectra in solution shows a red shift (2 to 6 nm) for symmetric

Table 2. PL and EX spectral data of symmetric and asymmetric *p*-terphenyls

Compound	PL[a] λ_{max} (nm)	PL[b] λ_{max} (nm)	EX[a] λ_{max} (nm)	EX[b] λ_{max} (nm)	Φ_F [a,c]
1	385	384	319 277	329 283	0.530
2	413	403	330 274	344 244	0.513
3	402	411	331 278	332 268	0.573
4	424	420	344 290	358 294	0.834
5	419	452	347 280	351 281	0.867
6	381	397	321 277	323 281	0.571
7	408	401	328 276	344 259	0.560
8	399	415	333 279	344 270	0.616
9	420	418	344 288	360 291	0.921
10	422	448	341 280	353 284	0.823
11	419	402	338 278	348 265	0.159
12	413	394	337 279	344 284	0.183
13	431	409	339 279	342 268	0.210
14	430	408	335 277	339 259	0.231

[a] In ethyl acetate.
[b] In solid state.
[c] Use Coumarin I in ethyl acetate (Φ_F=0.99) as the standard.[15]

p-terphenyls than asymmetric *p*-terphenyls except the pair of **5** and **10**. Symmetric *p*-terphenyl **5** with four cyano groups at *meta*-positions on the peripheral rings has a blue shift (1 and 3 nm in UV and PL spectra, respectively), than the corresponding asymmetric *p*-terphenyl **10**. The fluorescence quantum yield for symmetric and asymmetric *p*-terphenyls with cyano groups at either *para*-positions or two *meta*-positions on the peripheral rings are much higher than that of other *p*-terphenyls. The results also showed that the fluorescence quantum yields decreased when cyano groups are substituted on the central benzene ring (**11**–**14**). All the excitation spectra of these *p*-terphenyls showed two electronic transitions. Such behavior points to a strong mesomeric interaction of the alkoxy groups with the terphenyl chromophore.[14]

The λ_{max} in both UV absorption and PL emission spectra for **15** with hexahexyloxyl groups (319 and 385 nm, respectively), are similar to that of symmetric *p*-terphenyl **1** and asymmetric *p*-terphenyl **6** with only two alkoxy groups on the central benzene ring. This indicated that alkoxy group influenced very little on the λ_{max} in both absorption and emission spectra.

It is interesting to know that the λ_{max} in UV of these symmetric and asymmetric *p*-terphenyls shows a red shift in solid state than that in ethyl acetate solution, especially for symmetric *p*-terphenyls **1**, **2**, and **4**, which could have 37–41 nm red shift in their solid states than that in ethyl acetate solution. Furthermore, symmetric *p*-terphenyls **1** and **2** both have a red shift (37 nm) in absorption than the corresponding asymmetric *p*-terphenyls **6** and **7** in their solid states. Contrast to the λ_{max} in UV of these symmetric and asymmetric *p*-terphenyls, only symmetric and asymmetric *p*-terphenyls with two or four cyano groups at the *meta*-positions of the peripheral rings (**3**, **5**, **8**, and **10**) showed a red shift (9–33 nm) of the emission spectra in their solid states than that in ethyl acetate solution, other symmetric and asymmetric *p*-terphenyls showed a blue shift (1–22 nm) in the emission of their solid states than that in ethyl acetate solution. Thus, the solid state of symmetric and asymmetric *p*-terphenyls with four cyano groups at the *meta*-positions of the peripheral rings could reach to the blue light range in PL spectra. The preparation of devices and their electro-optical properties are still under active investigation in our collaborator's lab, and their results will be reported elsewhere when they are available.

3. Conclusion

Fifteen alkoxylated *p*-terphenyls with or without cyano groups on either the central benzene ring or the peripheral rings have been synthesized efficiently. The extinction coefficiencies of UV spectra for *p*-terphenyls without cyano groups on the central benzene ring are higher for asymmetric *p*-terphenyls than the corresponding symmetric *p*-terphenyls. The fluorescence quantum yield for *p*-terphenyls with cyano groups at either *para*-positions or two *meta*-positions of the peripheral rings are much higher than that of other *p*-terphenyls. The fluorescence quantum yields decreased when cyano groups are substituted on the central benzene ring. Alkoxy group influenced very little on the λ_{max} in both UV absorption and PL emission spectra. The λ_{max} in UV of these *p*-terphenyls shows a red shift in solid state than that in solution. Furthermore, only *p*-terphenyls with two or four cyano groups at the *meta*-positions of the peripheral rings showed a red shift in emission spectra in their solid states than that in solution, other *p*-terphenyls showed a blue shift in the emission spectra in their solid states. The relationship between the position and number of cyano groups and their influence on the absorption and emission spectra of these *p*-terphenyls is very interesting as compared to the phenylene–vinylene analogues and need to have further studied.

4. Experimental

4.1. General

4.1.1. Representative procedure of Suzuki coupling reaction for the preparation of 2,5-dihexyloxy-1,4-diphenylbenzene (1). *o*-Xylene (25 mL) was added to a mixture of 2,5-dihexyloxy-1,4-benzenediboronic acid (2.20 g, 5 mmol), bromobenzene (1.95 g, 12.5 mmol), and potassium carbonate (4.15 g, 30 mmol) in a 100 mL round-bottom flask under nitrogen atmosphere. A solution of $Pd(PPh_3)_4$ (0.035 g, 0.03 mmol) in 5 mL of *o*-xylene was added into the above mixture at 130 °C. The mixture was cooled to room temperature after it was stirred and heated for 72 h. The mixture was worked up with water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtrated, and concentrated before recrystallization by ethyl acetate and methanol to give 1.81 g (83% yield) of the desired product. Mp 67–68 °C; R_f=0.9 (*n*-hexane/ethyl acetate=4:1) ; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J=7 Hz, 6H), 1.26–1.36 (m, 12H), 1.65–1.68 (m, 4H), 3.90 (t, J=6.4 Hz, 4H), 6.98 (s, 2H), 7.32 (t, J=7.5 Hz, 2H), 7.41 (t, J=7.5 Hz, 4H), 7.60 (d, J=7.5 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.96, 22.56, 25.72, 29.33, 31.45, 69.70, 116.44, 126.88, 127.89, 129.53, 130.91, 138.46, 150.31 ppm; IR ν 1484.8, 1400.4, 1211.4, 1054.1, 763.9, 698.1 cm^{-1}; MS *m*/*z* 430 (M^+), 347, 262; HRMS calcd for $C_{30}H_{38}O_2$: 430.2872; found: 430.2869. Anal. Calcd for $C_{30}H_{38}O_2$: C, 83.68; H, 8.89. Found: C, 83.82; H, 8.79.

4.1.2. 2-[4-(2-Cyanophenyl)-2,5-dihexyloxyphenyl]benzenecarbonitrile (2). Mp 129–130 °C; R_f=0.6 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, J=7 Hz, 6H), 1.21–1.28 (m, 12H), 1.64–1.67 (m, 4H), 3.94 (t, J=6.5 Hz, 4H), 6.94 (s, 2H), 7.44 (t, J=7.6 Hz, 2H), 7.56 (d, J=7.7 Hz, 2H), 7.64 (t, J=7.7 Hz, 2H), 7.74 (d, J=7.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.88, 22.47, 25.53, 29.05, 31.35, 69.19, 113.21, 115.51, 118.61, 127.42, 128.52, 131.11, 132.17, 132.74, 142.17, 149.80 ppm; IR ν 2228.1, 1513.9, 1390.7, 1215.4, 1035.9, 762.8 cm^{-1}; MS *m*/*z* 480.2 (M^+), 412.0, 395.2, 313.1; HRMS calcd for $C_{32}H_{36}O_2N_2$: 480.2777; found: 480.2786. Anal. Calcd for $C_{32}H_{36}O_2N_2$: C, 79.97; H, 7.55; N, 5.83. Found: C, 79.75; H, 7.67; N, 5.72.

4.1.3. 3-[4-(3-Cyanophenyl)-2,5-dihexyloxyphenyl]benzenecarbonitrile (3). Mp 102–103 °C; R_f=0.525 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J=7.5 Hz, 6H), 1.26–1.68 (m, 12H),

1.67–1.71 (m, 4H), 3.94 (t, J=6 Hz, 4H), 6.94 (s, 2H), 7.52 (t, J=7.7 Hz, 2H), 7.63 (d, J=7.7 Hz, 2H), 7.7 (d, J=7.7 Hz, 2H), 7.89 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.96, 22.53, 25.75, 29.17, 31.40, 69.58, 112.21, 115.48, 118.93, 128.77, 129.21, 130.57, 133.14, 133.89, 139.29, 150.16 ppm; IR ν 2232.1, 1478.3, 1397.7, 1216.6, 1037.7, 785.9 cm^{-1}; MS m/z 480.2 (M^+), 397.1, 325.1, 312.1; HRMS calcd for $C_{32}H_{36}O_2N_2$: 480.2777; found: 480.2772. Anal. Calcd for $C_{32}H_{36}O_2N_2$: C, 79.97; H, 7.55; N, 5.83. Found: C, 79.76; H, 7.73; N, 5.97.

4.1.4. 4-[4-(4-Cyanophenyl)-2,5-dihexyloxyphenyl]benzenecarbonitrile (4). Mp 153–154 °C; R_f=0.68 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J=7 Hz, 6H), 1.25–1.33 (m, 12H), 1.67–1.68 (m, 4H), 3.93 (t, J=6 Hz, 4H), 6.93 (s, 2H), 7.69 (s, 8H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 22.48, 25.65, 29.11, 31.31, 69.56, 110.70, 115.55, 118.96, 129.82, 130.13, 131.70, 142.80, 150.18 ppm; IR ν 2226.4, 1647.6, 1601.0, 1214.5, 776.0 cm^{-1}; MS m/z 480.2 (M^+), 397.1, 325.1, 312.1; HRMS calcd for $C_{32}H_{36}O_2N_2$: 480.2777; found: 480.2772. Anal. Calcd for $C_{32}H_{36}O_2N_2$: C, 79.97; H, 7.55; N, 5.83. Found: C, 79.82; H, 7.75; N, 5.94.

4.1.5. 1,4-Bis(3,5-dicyanophenyl)-2,5-dihexyloxybenzene (5). Mp 214–215 °C (dec); R_f=0.75 (ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J=7.0 Hz, 6H), 1.28–1.36 (m, 12H), 1.69–1.72 (m, 4H), 3.97 (t, J=6.4 Hz, 4H), 6.91 (s, 2H), 7.90 (s, 2H), 8.08 (s, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.93, 22.48, 25.79, 29.02, 31.35, 69.56, 113.88, 114.72, 116.67, 127.60, 133.47, 136.83, 140.50, 150.06 ppm; IR ν 2236.2, 1222.1, 1026.7, 871.8, 779.72, 676.5 cm^{-1}; MS m/z 530.1 (M^+) 443.1, 389.1, 362.0, 273.1; HRMS calcd for $C_{34}H_{34}O_2N_4$: 530.2682; found: 530.2688.

4.1.6. 2-(2-Ethylhexyloxy)-5-methoxy-1,4-diphenylbenzene (6). R_f=0.86 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82–0.88 (m, 6H), 1.23–1.38 (m, 8H), 1.60–1.64 (m, 1H), 3.79–3.83 (m, 5H), 6.99–7.01 (m, 2H), 7.34–7.36 (m, 2H), 7.41–7.47 (m, 4H), 7.60–7.62 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.07, 14.02, 23.00, 23.89, 30.54, 39.57, 56.42, 71.80, 114.64, 116.14, 126.89, 127.05, 127.81, 128.06, 129.46, 129.58, 130.39, 130.89, 138.39, 150.45, 150.55 ppm; IR ν 1600.1, 1519.9, 1393.4, 1208.3,1057.1, 760.2 cm^{-1}; MS m/z 388.2 (M^+), 289.1, 276.1, 262.1, 215; HRMS calcd for $C_{27}H_{32}O_2$: 388.2402; found: 388.2403.

4.1.7. 2-[4-(2-Cyanophenyl)-2-(2-ethylhexyloxy)-5-methoxyphenyl]benzenecarbonitrile (7). Mp 148–149 °C; R_f=0.38 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.76–0.89 (m, 6H), 1.14–1.24 (m, 8H), 1.60–1.62 (m, 1H), 3.79–3.81 (m, 5H), 6.91 (s, 1H), 6.94 (s, 1H), 7.42–7.43 (m, 2H), 7.53–7.55 (m, 2H), 7.61–7.65 (m, 2H), 7.73–7.75 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.04, 13.94, 22.91, 23.81, 28.89, 30.47, 39.38, 56.11, 71.58, 113.12, 113.26, 114.27, 115.49, 118.55, 118.58, 127.48, 127.54, 128.18, 128.65, 130.96, 131.14, 132.06, 132.42, 132.67, 132.88, 142.01, 142.13, 150.12 ppm; IR ν 2228.8, 1472.8, 1395.4, 1214.7, 1037.8, 757.6 cm^{-1}; MS m/z 438.1 (M^+), 327.1, 326.1, 311.1, 295.1; HRMS calcd for $C_{29}H_{30}O_2N_2$: 438.2307; found: 438.2309. Anal. Calcd for $C_{29}H_{30}O_2N_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.63; H, 7.05; N 6.54.

4.1.8. 3-[4-(3-Cyanophenyl)-2-(2-ethylhexyloxy)-5-methoxyphenyl]benzenecarbonitrile (8). Mp 89–90 °C; R_f=0.48 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81–0.85 (m, 6H), 1.21–1.35 (m, 8H), 1.60–1.62 (m, 1H), 3.78–3.83 (m, 5H), 6.92 (s, 1H), 6.93 (s, 1H), 7.50–7.54 (m, 2H), 7.61–7.63 (m, 2H), 7.79–7.81 (m, 2H), 7.87–7.88 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.06, 13.97, 22.92, 23.93, 28.97, 30.60, 39.49, 56.33, 71.74, 112.12, 11.29, 114.00, 115.33, 118.84, 118.94, 128.70, 128.90, 130.56, 130.63, 133.07, 133.18, 133.82, 133.88, 132.67, 132.88, 142.01, 139.19, 150.37, 150.43 ppm; IR ν 2228.0, 11518.3, 1396.4, 1216.1, 1039.0, 680.1 cm^{-1}; MS m/z 439.1 (M^++1), 326.1, 265.1, 190.1; HRMS calcd for $C_{29}H_{31}O_2N_2$: 439.2386; found: 439.2389. Anal. Calcd for $C_{29}H_{30}O_2N_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.66; H, 6.76; N, 6.31.

4.1.9. 4-[4-(4-Cyanophenyl)-2-(2-ethylhexyloxy)-5-methoxyphenyl]benzenecarbonitrile (9). Mp 192–193 °C; R_f=0.13 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.80–0.84 (m, 6H), 1.20–1.33 (m, 8H), 1.55–1.57 (m, 1H), 3.79–3.81 (m, 5H), 6.93 (s, 1H), 6.94 (s, 1H), 7.66–7.71 (m, 8H) ppm; ^{13}C NMR($CDCl_3$,125 MHz) δ 11.05, 13.96, 22.92, 23.90, 28.92, 30.54, 39.48, 56.35, 71.71, 110.74, 110.84, 114.14, 115.38, 118.97, 129.51, 129.84, 130.11, 130.19, 131.65, 131.86,142.70, 142.79, 150.44, 150.47 ppm; IR ν 2228.8, 1601.8, 1211.1, 1048.8, 846.1, 554.8 cm^{-1}; MS m/z 439.2 (M^++1), 339.1, 326.1, 267.1; HRMS calcd for $C_{29}H_{31}O_2N_2$: 439.2386; found: 439.2388. Anal. Calcd for $C_{29}H_{30}O_2N_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.56; H, 6.97; N, 6.66.

4.1.10. 1,4-Bis(3,5-dicyanophenyl)-2-(2-ethylhexyloxy)-5-methoxybenzene (10). Mp >300 °C; R_f=0.575 (ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83–0.87 (m, 6H), 1.20–1.38 (m, 8H), 1.60–1.68 (m, 1H), 3.84–3.87 (m, 5H), 6.91 (s, 1H), 6.92 (s, 1H), 7.90 (s, 2H), 8.06 (s, 2H), 8.08 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.11, 14.03, 22.94, 24.02, 29.05, 30.72, 39.47, 56.39, 71.86, 113.55, 113.91, 114.03, 114.77, 116.64, 116.78, 133.54, 133.60, 136.87, 136.91, 140.74, 150.38 ppm; IR ν 2237.7, 1593.0, 1388.2, 1218.4, 1028.8, 875.6 cm^{-1}; MS m/z 488.1 (M^+) 460.0, 443.1, 338.3, 195.1; HRMS calcd for $C_{31}H_{28}O_2N_4$: 488.2212; found: 488.2212.

4.1.11. 3,6-Dihexyloxy-2,5-diphenylbenzene-1,4-dicarbonitrile (11). Mp 134–135 °C; R_f=0.77 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (t, J=7 Hz, 6H), 1.08–1.20 (m, 12H), 1.47–1.49 (m, 4H), 3.62 (t, J=7 Hz, 4H), 7.52 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 22.38, 25.09, 29.65, 31.20, 75.54, 113.78, 114.32, 128.58, 129.36, 129.61, 132.44, 139.47, 155.67 ppm; IR ν 2226.8, 1660.0, 1217.3, 763.9, 667.9 cm^{-1}; MS m/z 481.2 (M^++1), 397.2, 325.5, 312.1; HRMS calcd for $C_{32}H_{37}O_2N_2$: 481.2855; found: 481.2852. Anal. Calcd for $C_{32}H_{36}O_2N_2$: C, 79.97; H, 7.55; N, 5.83. Found: C, 79.80; H, 7.65; N, 5.98.

4.1.12. 6-(2-Ethylhexyloxy)-3-methoxy-2,5-diphenylbenzene-1,4-dicarbonitrile (12). Mp 132–133 °C; R_f=0.7

(*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.67 (t, J=7.4 Hz, 3H), 0.82 (t, J=7.5 Hz, 3H), 1.01–1.23 (m, 8H), 1.34–1.39 (m, 1H), 3.54–3.55 (m, 5H), 7.48–7.55 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.84, 13.95, 22.80, 23.21, 28.80, 29.82, 40.17, 61.98, 78.01, 113.50, 114.19, 128.61, 129.73, 129.46, 129.64, 139.23, 139.65, 156.03, 156.11 ppm; IR ν 2231.7, 1444.2, 1378.5, 1240.2, 1010.5, 699.2 cm^{-1}; MS *m*/*z* 438.2 (M^+), 326.1, 311.1, 282.1, 256.1, 227.1; HRMS calcd for $C_{29}H_{30}O_2N_2$: 438.2307; found: 438.2299. Anal. Calcd for $C_{29}H_{30}O_2N_2$: C, 79.42; H, 6.89; N, 6.39. Found: C, 79.58; H, 6.97; N, 6.55.

4.1.13. 1,4-Bis(4-cyanophenyl)-3,6-dicyano-2,5-dihexyloxybenzene (13). Mp 112–113 °C; R_f=0.36 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.82 (t, J=7.3 Hz, 6H), 1.08–1.23 (m, 12H), 1.46–1.49 (m, 4H), 3.66 (t, J=6.4 Hz, 4H), 7.62 (d, J=8.3 Hz, 4H), 7.82 (d, J=8.3 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.92, 22.43, 25.13, 29.70, 31.20, 76.00, 113.56, 113.64, 113.78, 117.97, 130.60, 132.45, 136.71, 138.65, 155.67 ppm; IR ν 2236.2, 1435.9, 1373.3, 1306.9, 1218.4, 997.2, 757.6 cm^{-1}; MS *m*/*z* 530.1 (M^+), 443.1, 389.1, 362.0, 273.1; HRMS calcd for $C_{34}H_{34}O_2N_4$: 530.2682; found: 530.2686. Anal. Calcd for $C_{34}H_{34}O_2N_4$: C, 76.96; H, 6.46; N, 10.56. Found: C, 77.10; H, 6.65; N, 10.59.

4.1.14. 1,4-Bis(4-cyanophenyl)-3,6-dicyano-2-(2-ethylhexyloxy)-5-methoxybenzene (14). Mp 194–195 °C; R_f=0.3 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.68 (t, J=7.5 Hz, 3H), 0.84 (t, J=7.5 Hz, 3H), 1.00–1.25 (m, 8H), 1.35–1.38 (m, 1H), 3.56–3.62 (m, 5H), 7.63–7.66 (m, 4H), 7.84–7.89 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.87, 13.99, 22.83, 23.21, 24.85, 28.86, 29.83, 40.27, 62.55, 78.85, 113.37, 113.49, 113.56, 113.81, 113.88, 117.92, 130.43, 130.65, 132.44, 132.60, 135.09, 136.49, 136.66, 138.50, 138.77, 156.00, 156.09 ppm; IR ν 2231.1, 1376.5, 1101.4, 836.3, 558.5 cm^{-1}; MS *m*/*z* 489.1 (M^++1) 388.1, 376.0, 349.1, 263.1; HRMS calcd for $C_{31}H_{29}O_2N_4$: 489.2391; found: 489.2305. Anal. Calcd for $C_{31}H_{28}O_2N_4$: C, 76.21; H, 5.78; N, 11.47. Found: C, 76.42; H, 5.88; N, 11.62.

4.1.15. 2-[4-(2,5-Dihexyloxyphenyl)-2,5-dihexyloxyphenyl]-1,4-dihexyloxybenzene (15). Mp 64–65 °C (dec); R_f=0.9 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83–0.92 (m, 18H), 1.22–1.34 (m, 24H), 1.56–1.64 (m, 12H), 1.75–1.78 (m, 12H), 3.81–3.94 (m, 12H), 6.81–702 (m, 8H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.98, 22.55, 25.65, 25.68, 25.74, 29.39, 29.65, 31.56, 31.59, 68.55, 69.41, 69.47, 69.70, 114.07, 114.39, 116.72, 116.88, 117.06, 117.99, 127.44, 127.54, 129.35, 149.95, 150.00, 150.75, 152.74 ppm; MS *m*/*z* 830 (M^+), 630, 570, 554, 486, 470; IR ν 1465.4, 1207.4, 1037.8, 938.2, 798.2 cm^{-1}; HRMS calcd for $C_{54}H_{86}O_6$: 830.6424; found: 830.6425.

4.1.16. 2,5-Dihexyloxy-1,4-benzenediboronic acid (16). *n*-Butyllithium (2.5 M in hexanes, 5 mL, 12.5 mmol) was added dropwise to a solution of 2,5-dibromo-1,4-dihexyloxybenzene (2.2 g, 5 mmol) in dried diethyl ether (50 mL) for 1 h at 0 °C followed by the dropwise addition of trimethylborate (1.7 mL, 15 mmol). The mixture was gradually warmed up and stirred for another 12 h. Then, 2 N HCl (20 mL) was added and stirred for another 30 min before adding water (30 mL). The product was extracted by diethyl ether (50 mL×5), dried over magnesium sulfate, filtrated, and concentrated. Ethyl acetate (60 mL) was added to the concentrated mixture, filtrated and used ethyl acetate to washed the precipitate. After removing volatile solvents under vacuum, the product was obtained as a white powder (2.27 g, 79% yield). Mp 194–195 °C (dec); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.93 (t, J=7 Hz, 6H), 1.34–1.48 (m, 12H), 1.76–1.80 (m, 4H), 3.36 (s, 4H), 4.04 (t, J=6.5 Hz, 4H), 7.83 (s, 2H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 14.24, 22.42, 25.52, 29.14, 31.33, 68.82, 118.39, 124.87 (*C*–B(OH)$_2$), 157.31 ppm.

4.1.17. 2-(2-Ethylhexyloxy)-5-methoxy-1,4-benzenediboronic acid (17). Following the procedure as described above for the synthesis of **16**, compound **17** was prepared from 1,4-dibromo-2-(2-ethyl-hexyloxy)-5-methoxybenzene (1.97 g, 5 mmol), *n*-butyllithium (2.5 M in hexanes, 5 mL, 12.5 mmol), and trimethylborate (1.42 mL, 12.5 mmol). The crude product (1.26 g, 78% yield) was used without further purification. It can be further purified by recrystallization three times from ethyl acetate to give the desired product **17** as a white solid. Mp 114–115 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 0.77 (t, J=7 Hz, 6H), 1.17–1.33 (m, 8H), 1.58 (m, 1H), 3.67 (s, 3H), 3.78 (d, J=5.5 Hz, 2H), 7.07 (s, 1H), 7.08 (s, 1H), 7.68 (s, 4H) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz) δ 11.40, 14.34, 22.90, 23.89, 28.86, 30.45, 39.77, 56.17, 71.13, 117.18, 118.31, 124.68 (*C*–B(OH)$_2$), 125.18 (*C*–B(OH)$_2$), 157.48, 157.80 ppm.

4.1.18. 2,5-Dibromo-3,6-dihexyloxybenzene-1,4-dicarbonitrile (18). To a mixture of 2,5-dihexyloxybenzene-1,4-dicarbonitrile (1.65 g, 5 mmol) and *N*-bromosuccinimide (2.23 g, 12.5 mmol) in 100 mL round-bottom flask was added trifluoroacetic acid (2 mL) until all compounds are completely dissolved. Then, concentrated sulfuric acid (2.7 mL, 50 mmol) was added and stirred for another 4 h at room temperature. Saturated sodium bicarbonate (5 mL) was added to the mixture and extracted with ethyl acetate (30 mL×5), dried over magnesium sulfate, filtrated, and concentrated. The crude product was recrystallized by ethyl acetate (10 mL) and methanol (5 mL) to give 1.79 g (74% yield) of the desired product as a white powder. Mp 107–108 °C; R_f=0.775 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J=7 Hz, 6H), 1.32–1.54 (m, 12H), 1.83–1.93 (m, 4H), 4.16 (t, J=6.6 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.98, 22.50, 25.27, 29.94, 31.44, 76.75, 113.08, 117.00, 120.68, 156.43 ppm; IR ν 2234.0, 1427.9, 1371.9, 1204.4, 759.9 cm^{-1}; MS *m*/*z* 487.3 (M^++3), 484 (M^+), 219, 307, 370; HRMS calcd for $C_{20}H_{26}Br_2N_2O_2$: 484.0361; found: 484.0364. Anal. Calcd for $C_{20}H_{26}Br_2O_2N_2$: C, 49.40; H, 5.39; N, 5.76. Found: C, 49.62; H, 5.53; N, 5.89.

4.1.19. 2,5-Bibromo-6-(2-ethylhexyloxy)-3-methoxybenzene-1,4-dicarbonitrile (19). Following the procedure as described above for the synthesis of **18**, compound **19** was prepared from 2-(2-ethylhexyloxy)-5-methoxybenzene-1,4-dicarbonitrile (1.43 g, 5 mmol), *N*-bromosuccinimide (2.85 g, 15 mmol), trifluoroacetic acid (12 mL), and concentrated sulfuric acid (2.78 mL,

50 mmol). The crude product was recrystallized from ethyl acetate–methanol to give the desired product **19** as a white solid (1.95 g, 88% yield). Mp 125–126 °C; R_f=0.8 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90–0.99 (m, 6H), 1.34–1.62 (m, 8H), 1.82–1.85 (m, 1H), 4.05–4.09 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.08, 14.02, 22.91, 23.43, 28.98, 29.93, 40.24, 62.70, 79.12, 112.83, 112.98, 116.70, 116.78, 120.55, 167.76, 156.80 ppm; IR ν 2233.4, 1455.1, 1376.9, 1208.9, 1007.2, 730.64 cm^{-1}; MS *m/z* 445 (M^++3), 442 (M^+), 334, 332, 316, 288; HRMS calcd for $C_{17}H_{21}Br_2N_2O_2$: 442.9970; found: 442.9966. Anal. Calcd for $C_{17}H_{20}Br_2N_2O_2$: C, 45.97; H, 4.54; N, 6.31. Found: C, 46.12; H, 4.69; N, 6.46.

4.1.20. 4,4,5,5-Tetramethyl-2-(4-cyanophenyl)-1,3,2-dioxaborolane (20). The mixture of 4-bromobenzenecarbonitrile (0.91 g, 5 mmol), potassium acetate (1.17 g, 15 mmol), bis(pinaconato)diboron (1.40 g, 5.5 mmol), $PdCl_2$(dppf) (0.018 g, 0.015 mmol) in DMSO (5 mL) was heated under nitrogen at 80 °C for 6 h. The mixture was cooled to room temperature and water (50 mL) was added, and the product was extracted with ethyl acetate (50 mL×3), dried over magnesium sulfate, filtrated, and concentrated. The product was purified by column chromatography (silica gel, ethyl acetate /*n*-hexanes=1/20) to give 0.86 g (75% yield) of the desired product. Mp 94–95 °C; R_f=0.725 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35 (s, 12H), 7.65 (d, J=7.7 Hz, 2H), 7.87 (d, J=7.7 Hz, 2H) ppm; IR ν 2221.4, 1358.5, 1273.7, 1441.0, 838.7, 650.7 cm^{-1}.

4.1.21. 2-Bromo-1,4-dihexyloxybenzene (21). To a solution of 2,5-dibromo-1,4-dihexyloxybenzene (2.2 g, 5 mmol) in dried diethyl ether (50 mL) at 0 °C was added *n*-butyllithium (2.5 M in hexanes, 2.2 mL, 5.5 mmol) dropwise. After the temperature of the mixture was gradually warmed up to the room temperature for 12 h, 2 N HCl (20 mL) was added to it and stirred for another 30 min. The product was extracted with ethyl acetate (50 mL×3), dried over magnesium sulfate, filtrated, and concentrated. The product was purified by column chromatography (silica gel, ethyl acetate/*n*-hexanes=1/20) to give 1.45 g (80% yield) of the desired product as a liquid in orange color. R_f=0.85 (*n*-hexane/ethyl acetate=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J=7 Hz, 6H), 1.22–1.56 (m, 12H), 1.70–1.83 (m, 4H), 3.78–4.07 (m, 4H), 6.81 (d, J=9.3 Hz, 2H), 7.10 (d, J=3.5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 22.49, 25.59, 29.15, 31.46, 68.50, 69.87, 112.58, 113.99, 114.34, 119.33, 149.61, 153.43 ppm; MS *m/z* 358.1, 356.1 (M^+), 278.2, 190.0; HRMS calcd for $C_{18}H_{29}BrO_2$: 356.1351; found: 356.1352.

Acknowledgements

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Diastereoselective synthesis of new polyhydroxylated indolizidines from L-glutamic acid

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Abstract—A diastereoselective synthesis of two new swainsonine's analogues **1a** and **1b** with the piperidine ring fused to a phenyl nucleus at C6-C7, namely (1*R*, 2*S*, 10*R*, 10a*R*)-(+)-1,2,10-trihydroxy-1,2,3,5,10,10a-hexahydrobenzo[*f*] indolizine (**1a**) and (1*S*, 2*R*, 10*R*, 10a*R*)-(+)-1,2,10-trihydroxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*] indolizine (**1b**), is described. Throughout this work, the effectiveness of the tricyclic indolizidine dione **5**, readily available in three steps from the cheap L-glutamic acid, as an attractive platform for chemo- and stereodivergent transformations is illustrated. The key steps involved totally diastereoselective ketone reduction of compound **5** and catalytic *cis*-dihydroxylation of the unsaturated amide **10**. The synthetic strategy also allowed for the diastereoselective synthesis of benzoanalogues of the 1,8a-di-*epi*-lentiginosine **3a** ((1*R*, 2*S*, 10a*R*)-(+)-1,2-dihydroxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine) and 2,8a-di-*epi*-lentiginosine **3b** ((1*S*, 2*R*, 10a*R*)-(+)-1,2-dihydroxy-1,2,3,5,10,10a-hexahydrobenzo[*f*]indolizine).

1. Introduction

Indolizidine alkaloids, typified by lentiginosine, swainsonine and castanospermine (Fig. 1) and their derivatives display interesting biological activity as inhibitors of glycosidases.[1] Since glycosidases are key enzymes in biosynthesis and processing of glycoproteins, their inhibitors are widely investigated as potential antibacterial, antiviral, antitumoral, antidiabetic and antiinflammatory agents.[2]

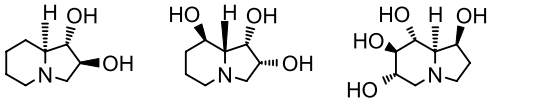

Figure 1. Major indolizidine alkaloids.

A plethora of synthetic methods has been continuously developed over the last two decades, that now provides an impressive library of such targets, which have been intensively studied for their biological properties.[3] These studies have revealed that even small structural modifications may induce very significant changes of the biological activities.[4] Since the structure–activity relationships in indolizidines are not straightforward, the need for new and stereodivergent methodologies to generate maximum structural diversity (stereomers and analogues) continues.

Due to their vicinal polyhydroxylated structure, these constrained bicyclic iminosugars have mostly been synthesized from natural sugars as starting materials. However, the preexisting chiral centers are incompatible with the criteria of flexibility, and thus limit the scope of carbohydrate-based methods. In addition, the need of orthogonal protection of the hydroxyl groups confines these methods to arduous and redundant sequences of protecting group manipulations, lengthens the procedure and reduces its overall efficiency. In light of these limitations, the demand for non-carbohydrate-based methods has become increasingly apparent.

We have previously described an effective, very convergent

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methodology that shortly provides ready access to enantiomerically pure *N*-benzyl, *N*-furyl- and *N*-thienyl- methyl pyroglutamic acids[5] and shown that these molecules can be translated into an efficient means for accessing a new family of tricyclic indolizidine diones.[6] We realized that such compounds, which are opened to ready modifications at the C1, C2 and C10 positions, should constitute an attractive platform to a range of new hydroxylated indolizidines.

In this paper, it is demonstrated that this chemistry can in fact be so extended as to provide potentially flexible access to the indolizidine alkaloids through the synthesis of benzoanalogues[7] of 1,8a-di-*epi*-lentiginosine,[8] 2,8a-di-*epi*-lentiginosine,[9] swainsosine[10] and 1,2-di-*epi*-swainsosine.[11] Syntheses of C3,[12] C6 and C7[13] substituted analogues of swainsonine have recently been described and the influence of the newly introduced substituents on the mannosidases inhibitory effect has been investigated.

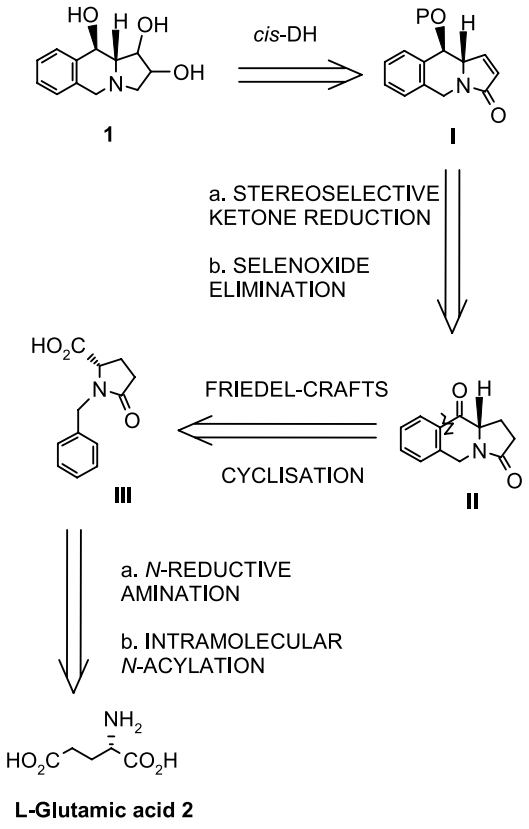
Swainsosine was first isolated from the fungus *Rhizoctonia leguminicola* in 1973[14] and has since attracted great attention from both biological and synthetic points of view. It was found to be an effective inhibitor of α-D-mannosidase, including the glycoprotein-processing key enzyme mannosidase II.[1,10] It also exhibits important antimetastatic, antitumor-proliferative, anticancer and immunoregulating activity.[2,3,10] Swainsonine was the first inhibitor to be selected for testing as an anticancer drug, reaching phase I clinical trials, among imisugars. Due to its promising biological profile, extensive effort has been devoted to the development of efficient syntheses of this azasugar.[10]

1,8a-Di-*epi*-lentiginosine,[8] 2,8a-di-*epi*-lentiginosine[9] and (+)-1,2-di-*epi*-swainsonine[11] are unnatural stereomers, which have been synthesized only very recently. To our knowledge, their biological profile has not yet been undertaken.

2. Synthetic strategy

Our retrosynthetic analysis of type **1** swainsonine benzoanalogues is shown in Scheme 1. The key steps involve *cis*-dihydroxylation of the conjugated lactam **I**, which itself can be prepared by selenoxide elimination of a protected hydroxy lactam derived from **II**. This oxy derivative can readily be obtained from Friedel-Crafts cyclisation of *N*-benzyl pyroglutamic acid **III**, followed by stereocontrolled reduction of the resulting indolizidine dione **II**.[6] Acid **III** is readily available from L-glutamic acid **2**.[5]

In principle, all the stereoisomers of type **1** swainsonine benzoanalogues can be accessed by divergent modifications of this amino acid-based approach[15] (Fig. 2). (1) Starting with D-versus L-glutamic acid inverts the enantiomeric series. (2) Either the α- or β-alcohol can be provided stereoselectively through reduction of **II** by a judicious choice of the metal-hydride reductant.[6] (3) Catalytic dihydroxylation versus sequential epoxidation-hydrolysis[16–18] of the conjugated lactam **I** could, in principle, alter the stereochemical relationship *cis* versus *trans* at C1-C2 on the pyrrolidine ring.



Scheme 1.

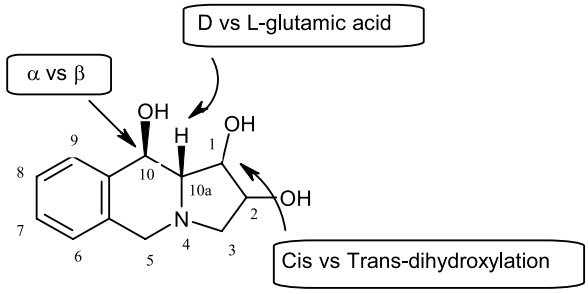


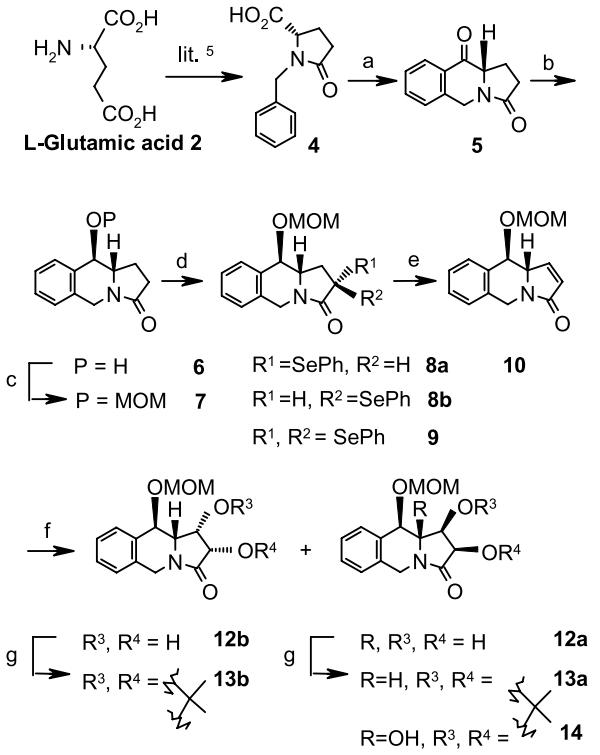
Figure 2. Enantiodivergent approach allows for the synthesis of various indolizidines from common intermediate and starting material.

In addition, selective deoxygenation at C10 or enolate hydroxylation of an intermediate derived from **II** could provide either 1,2-dihydroxy alkaloids (lentiginosine benzoanalogues) or 2,10-dihydroxy alkaloids.

3. Results and discussion

3.1. Synthesis of trihydroxy indolizidines (1a) and (1b)

Our synthesis started with commercially available L-glutamic acid **2**, which was converted into the known *N*-benzyl pyroglutamic acid **4**[5] in two high-yielding steps (Scheme 2). Friedel-Crafts cyclization of **4** using $AlCl_3$ introduced the indolizidine framework at the dione **5** in 78% yield. $NaBH_4$ reduction of the ketone function gave the (10*R*) alcohol **6** in 81% yield as a single product. There was



[a]: $SOCl_2$, CH_2Cl_2, 40°C, 5h, then $AlCl_3$, 0°C, 1h, then rt, 2h, 78%; [b] $NaBH_4$, MeOH, 0-5°C, 2h, 81%; [c] NaH, MOMCl, THF, rt, 1h, 75%; [d] LiHMDS, THF, -78°C, 30min, then PhSeBr, -80°C, 45min **8a** 50%, **8b** 16%, **9** 6%; [e] H_2O_2, EtOAc, 0°C, 30min, then $NaHCO_3$, 85%; [f] OsO_4 cat, NMO, acetone:H_2O 1:1, rt, 2h, 80%; [g] DMP, PTSA cat, CH_2Cl_2, rt, 2h30', **13a** 50%, **13b** 15%, **14** 14%

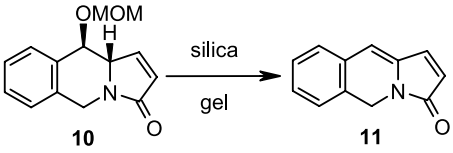
Scheme 2.

no evidence for the formation of the epimeric (10*S*) alcohol.[6]

The stage was now set for masking the alcohol function in compound **6**. It was anticipated that the diol moiety, resulting from the dihydroxylation step required at a later stage of the synthesis (Scheme 1), also should probably need protection. In an effort to reduce the number of synthetic manipulations required by combining two or more steps into one, we planned to use two protecting groups that could be removed under the same conditions at the final stage. Therefore, we assumed that this purpose could be addressed using a MOM and an acetonide to block the hydroxyl group in compound **6** and the diol moiety respectively. Exposure of the alcohol **6** to MOMCl in the presence of NaH readily gave the expected ether **7** in good yield.

The requisite double bond was installed using the selenoxide-elimination method. After initial screening of various conditions for selenylation, it was found that **7** could be efficiently functionalized with 2.3 equiv of LiHMDS and 1 equiv of PhSeBr (PhSeCl turned out to be poorly reactive in this case). The use of less than 2.3 equiv of the base resulted in incomplete enolization of the lactam **7**, while the utilization of an excess of PhSeBr markedly improved the yield of the biselenylated adduct **9**. Carrying out the overall procedure at −78 °C significantly reduced this competitive process, with the stereomers **8a** and **8b** being isolated in 66% combined yield and 3:1 dr along with only 6% of the biselenylated compound **9**.[19]

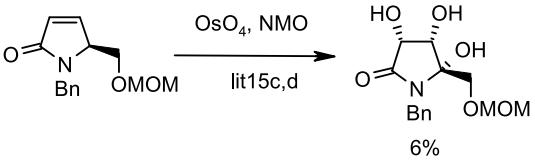
Oxidation of the mixture of diastereomers **8** with H_2O_2 rapidly led to the expected lactam **10**. This compound was found to be quite unstable under purification on column chromatography and decomposed into the known highly conjugated compound **11** (Eq. 1).[20]



(1)

Hence, the crude product was immediately dihydroxylated in usual conditions (catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide) to afford a mixture of inseparable diastereomers **12**. The crude oily product obtained was immediately treated with 2,2-dimethoxypropane and PTSA to provide the easily separable acetonides **13a** (less polar, major diastereoisomer, 50% yield) and **13b** (more polar, minor, 15% yield). **13b** exhibited spectroscopic properties consistent with a pure desired acetonide.

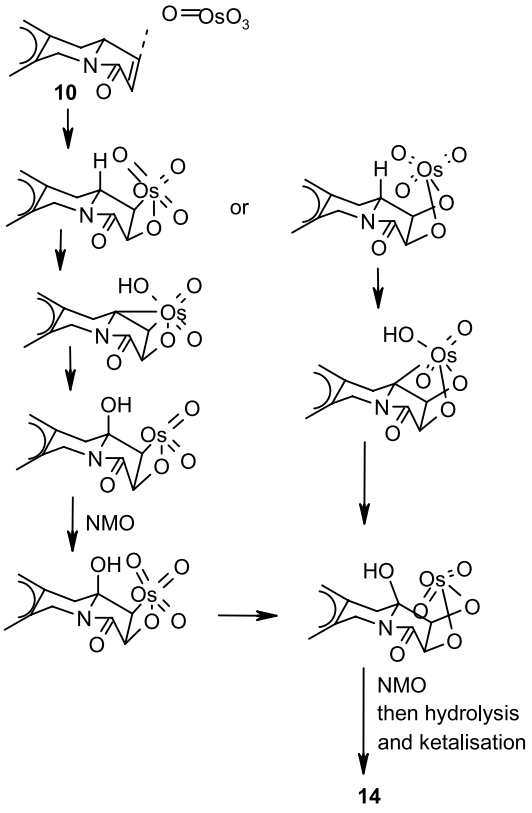
The ^1H NMR spectrum of the major fraction revealed a high degree of complexity that suggested the presence of one, or even several by-products. A pure compound could be isolated in 14% yield after trituration in ether; its structure was consistent with that of the hydroxy lactam **14** on the basis of NMR, IR and MS spectroscopic data. The most significant proofs were provided in the ^1H NMR spectrum by the disappearance of the doublet corresponding to H10a (generally observable at about 3.8 ppm) together with simplification of the signal corresponding to H1 at $\delta=$ 4.42 ppm (doublet) as well as by exhibition of a large singlet at $\delta=3.93$ ppm (exchangeable with D_2O). The IR spectrum confirmed the presence of a hydroxyl group with a large band at 3430 cm^{-1}. Additional support was provided by ^{13}C NMR spectroscopy which detected a carbon at $\delta=85.8$ ppm characteristic of a tertiary alcohol. This hydroxy lactam is likely to be the result of an allylic hydroxylation, which may has been achieved in concert with the osmylation of the double bond, a phenomenon that has already been observed, albeit to a smaller extent, during dihydroxylation on related pyroglutamic acid derivatives (Eq. 2).[15c,d]



(2)

The relative and absolute configurations for the oxidized carbons C1, C2 and C10a were proposed in agreement with NOE DIFF. experiments. Both H10 and H1 signals remained unaltered upon irradiation of the singlet corresponding to the hydroxyl group, suggesting that the contiguous OMOM, OH and acetonide substituents hold in an all *cis* relationship. The well accepted knowledge that oxidation of C–H bonds in chiral substrates generally occurs

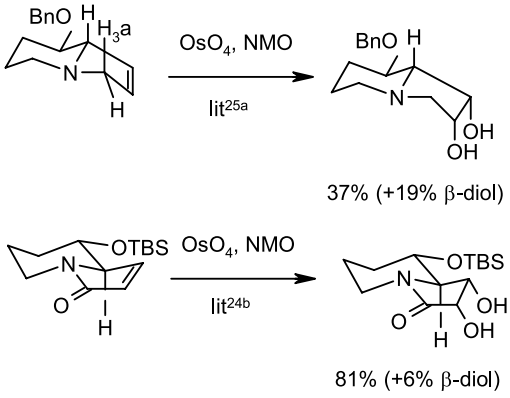
with retention of configuration[21] allowed us to propose all-*cis* stereochemistry for (1*R*,2*R*,10a*S*)-**14**. On the light of this stereochemical result, the formation of **14** may be explained by concomitent hydroxylation at C10a and olefin dihydroxylation from a common intermediate (Scheme 3). Support to this hypothesis was provided by an additional experiment establishing that acetonide **13a** remained untouched under standard osmylation conditions.



Scheme 3.

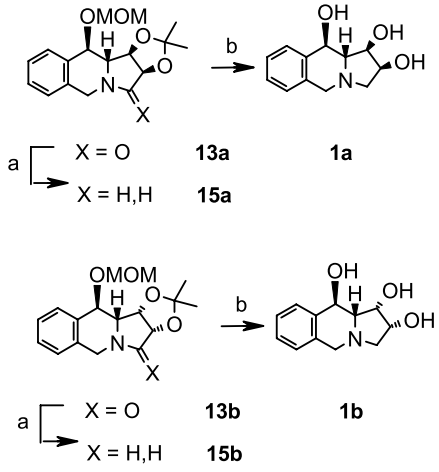
As we were unable to obtain a chromatographically pure sample of **13a**,[22] stereochemical investigations could not be undertaken in detail. In the ^{1}H NMR spectrum of the impure compound **13a**, the proton H10a resonates at 3.79 ppm as a doublet ($J_{H10a\text{-}H10}=9.9$ Hz). Consistently with literature precedents, the absence of coupling between H10a and H1 may be indicative of a *trans* relationship for these two vicinal protons that are confined in a constrained environment on a pyrrolidine ring.[23] It can then be postulated that compounds **13a** and **14** have the same (1*R*, 2*R*) configuration, an assumption that will be confirmed at the final stage of the synthesis (see below). It thus appears that dihydroxylation of lactam **10** has occurred in ~60% dr. The stereochemical outcome of this step was not of primary concern since both diastereomeric diols **12** were required in the present work. However, on the basis of literature precedents describing highly diastereoselective dihydroxylation of unsaturated indolizidine frameworks using AD-mix-α and β,[23] an improvement of the modest dr obtained herein could reasonably be envisaged.

The sense of stereoselectivity exhibited by dihydroxylation of lactam **10** parallels that obtained from analogous bicyclic amides,[24] but is opposite to that generally observed in the case of related indolizidines lacking the carbonyl functionality[25] (Eq. 3), although controversial results have been described in this series.[25a–c]



(3)

BH_3–Me_2S reduction of **13b** and **13a** gave the protected amino alcohols **15b** (72% yield) and **15a** (79% yield), respectively (Scheme 4). Acid-catalyzed complete deprotection of **15a** and **15b** with HCl completed the syntheses of the targeted **1a** and **1b**, which were isolated in 63% yield and 45% yield, respectively.



[a]: BH_3-Me_2S, THF, rt, 14h, then EtOH, 70°C, 5h, **15a** 79%, **15b** 72%; [b] HCl 6N, rt, 20-30h, then NH_4OH, **1a** 63%, **1b** 45%.

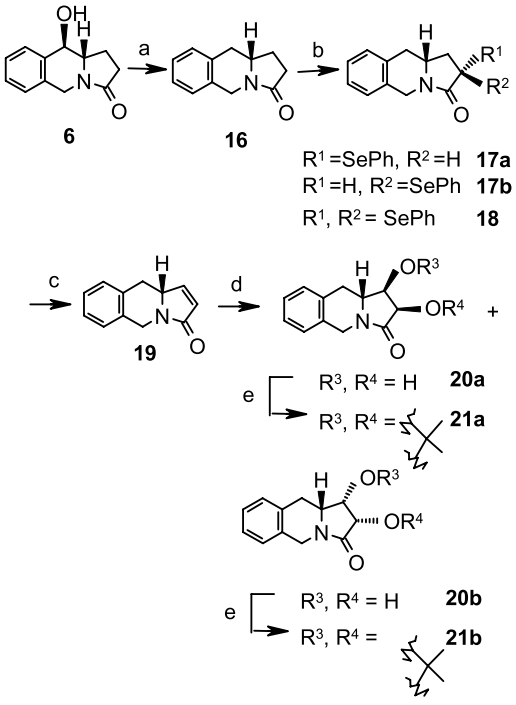
Scheme 4.

Our final efforts in this series were aimed at confirming the absolute configuration at C1 and C2. A series of NOE Diff. experiments were therefore conducted on **1a**. Irradiation of the proton H10 caused a significant interaction with H1 (11%), indicating an axial orientation for the latter and, therefore, allowed us to assume the (1*R*, 2*S*) configuration for C1-C2. This establishment is in accordance with the previously proposed (1*R*, 2*R*) stereochemistry for compound **13a**.

3.2. Synthesis of dihydroxy indolizidines (3a) and (3b)

For syntheses of 1,8a-di-*epi*-lentiginosine and 2,8a-di-*epi*-

lentiginosine analogues **3a** and **3b**, the key alcohol **6** was independently deoxygenated in the presence of triethylsilane and TFA to give the lactam **16** in good yield (Scheme 5). The completion of the synthesis was subsequently achieved applying analogous chemistry described for the synthesis of swainsonine analogues in Schemes 2 and 4. Conversion of **16** to the stereomeric mixture of selenyl lactams **17a–b** (1:2 ratio) was followed by selenoxide elimination, which proceeded cleanly in the absence of any oxy substituent at C10 to afford the unsaturated lactam **19** in 76% yield. Catalytic *cis*-dihydroxylation of **19** followed by ketalization gave a chromatographically separable mixture of diastereomers (**21a**:**21b** 3:1) in 68% yield. The stereochemistry of the major (less polar) stereomer **21a** was unequivocally established by single X-ray crystallography analysis (Fig. 3), from which it is apparent that the acetonide moiety



[a]: Et_3SiH TFA, reflux, 48h, 79%; [b] LiHMDS, THF, -78°C, 30min, then PhSeBr, -80°C, 45min **17a** 26%, **17b** 53%, **18** 3%; [c] H_2O_2, EtOAc, 0°C, 30min, then $NaHCO_3$, 76%; [d] OsO_4 cat, NMO, acetone:H_2O 1:1, rt, 6h, 68%; [e] DMP, PTSA cat, CH_2Cl_2, rt, 2h, **21a** 51%, **21b** 17%.

Scheme 5.

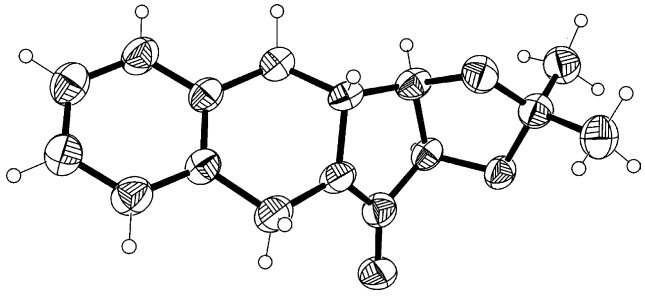
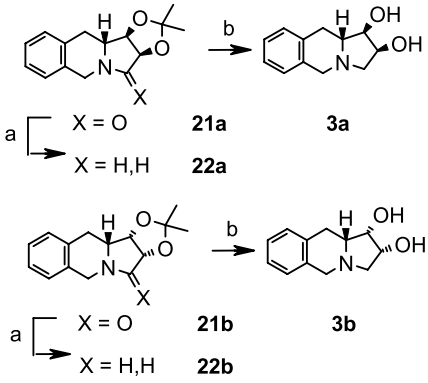


Figure 3. ORTEP view for compound **21a**.

and H10a lie in the same direction with dihedral angle between H1-C1-C10a-H10a: 105.5°.[26] This result is quite similar to that previously obtained in the synthesis of swainsonine's benzoanalogues (Scheme 2), and confirms that the stereochemical influence exerted by the oxy-substituent at C10 during dihydroxylation is negligible. We can then assume that dihydroxylation of conjugated lactams in the hexahydrobenzo[*f*]indolizidine series mainly provides diols with the (1*R*, 2*R*) configuration.

Finally, lactam reduction followed by acetonide removal afforded the desired targets **3a** and **3b** (Scheme 6).



[a]: BH_3-Me_2S, THF, rt, 12h, then EtOH, 70°C, 5h, **22a** 72%, **22b** 71%; [b] HCl 2N, MeOH-CH_2Cl_2, rt, 72h, then NH_4OH, **3a** 78%, **3b** 94%.

Scheme 6.

4. Conclusion

In conclusion, a synthetic strategy has been developed that allows the synthesis of new benzoanalogues of (−)-swainsonine, 1,2-di-*epi*-swainsonine, 1,8a-di-*epi*-lentiginosine and 2,8a-di-*epi*-lentiginosine. These syntheses start from the cheap L-glutamic acid and illustrate the potential of a key optically pure tricyclic indolizidine dione component as an attractive platform. All final compounds synthesized herein feature a *cis*-diol portion on the pyrrolidine ring at C1-C2, that has been introduced by catalytic *cis*-dihydroxylation. The present methodology could be readily adapted to the syntheses of other epimers using the D-glutamic acid or applying an epoxide-hydrolysis approach.

5. Experimental

5.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 and 50 MHz) and Varian VXR-300 (300 and 75 MHz) and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. The assignment of ^1H and ^{13}C signals was supported by one- and two-dimensional ^1H–^1H COSY, DEPT, ^1H–^{13}C HMBC and HSQC experiments. The infrared spectra were recorded on a Perkin–Elmer FT-IR paragon 1000 spectrometer. Thin-layer chromatographies (TLC) were performed with

aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230–400 mesh) was used for flash chromatography separations. Gas chromatography-mass spectrometry (GC-MS) was performed with a GC apparatus equipped with a 12 m capillary column, at 90 °C for 2 min, then 10 °C/min up to 290 °C. Optical rotations were determined with a Perkin–Elmer 241 MC instrument at 25 °C in the indicated solvent. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France.

5.2. Synthesis of trihydroxy indolizidines (1a) and (1b)

5.2.1. (*S*)-*N*-(phenylmethyl)-5-oxopyrrolidine-2-carboxylic acid (4). For preparation and analytical data, see Ref. 5a.

5.2.2. (*S*)-1, 2, 3, 5, 10, 10a-Hexahydrobenzo[*f*]indolizine-3, 10-dione (5). To a solution of carboxylic acid **4** (11.5 g, 52.5 mmol) in dichloromethane (220 ml) was added thionyl chloride (4.6 ml, 63 mmol) at 0–5 °C. The mixture was stirred under reflux for 5 h, and then cooled to 0 °C. Under vigourous stirring, $AlCl_3$ (11.5 g, 52.5 mmol) was added by small portions. The mixture was stirred for 1 h at 0 °C and then for additional 2 h at room temperature. After cooling to 0 °C, water (200 ml) was added carefully. The two phases were separated and the aqueous layer was extracted two times with dichloromethane. After washing with brine, the dichloromethane phase was dried with $MgSO_4$ and concentrated to afford a solid. Recrystallisation from EtOH gave **5** (8.25 g, 78%) as a colourless solid; mp 105–109 °C; $[\alpha]_D^{25} = -120.3°$ (*c* 1, ethanol); IR (ν, cm^{-1}, KBr) 2964, 1687 (C=O), 1670 (C=O); ^1H NMR (200 MHz, $CDCl_3$) δ 2.25–2.63 (m, 4H, H-1 and H-2), 4.25–4.45 (m, 1H, H-10a), 4.35 (d, 1H, $J=17.4$ Hz, H-5ax.), 5.25 (d, 1H, $J=17.4$ Hz, H-5eq), 7.32 (t, 1H, $J=7.7$ Hz, H-arom.), 7.33 (t, 1H, $J=7.7$ Hz, H-arom.), 7.54–7.64 (m, 1H, H–arom.), 8.07 (d, 1 H, $J=8.1$ Hz, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5 (C-1), 29.8 (C-2), 41.4 (C-5), 61.8 (C-10a), 126.5 (C-arom.), 127.6 (C-arom.), 127.8 (C-arom.), 130.1 (C-arom.), 134.5 (C-arom.), 139.6 (C-arom), 174.1 (C-3), 194.1 (C-10); LRMS *m*/*z* 201 (M^+, base), 159 (48), 128 (100), 127 (55), 90 (52); Anal. Calcd for $C_{12}H_{11}NO_2$ (201.22): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.41; H, 5.65; N, 7.28.

5.2.3. (10*R*,10a*S*)-10-Hydroxy-1,2,3,5,10,10a-hexahydrobenzo[*f*]indolizin-3-one (6). To a solution of ketone **5** (9.8 g, 48.7 mmol) in methanol (170 ml) was added sodium borohydride (2.02 g, 53.4 mmol) at 0–5 °C. The mixture was then stirred at 0 °C until total disappearance of starting material was observed, and the solvent was removed under vacuum. After addition of water (50 ml), the suspension was carefully acidified (HCl 10%) to pH 4. The aqueous layer was saturated with NaCl and extracted three times with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated to afford a solid. Recrystallisation from EtOAc:EtOH 85:15 gave the title compound (8.0 g, 81%) as a white solid; mp 150–151 °C; $[\alpha]_D^{25} = +109.6°$ (*c* 1, acetone); IR (ν, cm^{-1}, KBr) 3224 (OH), 2880, 1658 (C=O); ^1H NMR (200 MHz, DMSO-d_6) δ 2.15–2.35 (m, 1H, H-1), 2.40– 2.65 (m, 3H, H-1′ and H-2), 3.41–3.48 (m, 1H, H-10a), 3.96 (d, 1H, $J=8.6$ Hz, OH), 4.33 (d, 1H, $J=17.2$ Hz, H-5ax.), 4.55 (t, 1H, $J=8.6$ Hz, H-10), 5.01 (d, 1H, $J=17.2$ Hz, H-5eq), 7.15–7.32 (m, 1H, H-arom.), 7.34–7.48 (m, 2H, H-arom.), 7.70–7.96 (m, 1H, H-arom.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 22.9 (C-1), 30.0 (C-2), 42.6 (C-5), 58.9 (C-10a), 69.9 (C-10), 126.0 (C-arom.), 126.3 (C-arom.), 127.4 (C-arom.), 128.0 (C-arom.), 131.6 (C-arom.), 137.8 (C-arom), 175.0 (C-3); LRMS *m*/*z* 204 ($M^+ +1$, 5), 203 (M^+, 34), 120 (22), 119 (37), 91 (22), 84 (base), 41 (12), 28 (20); Anal. Calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N 6.89. Found: C, 70.85; H, 6.38; N, 7.03.

5.2.4. (10*R*,10a*S*)-10-Methoxymethyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (7). To a suspension of NaH (2.9 g, 72 mmol) in THF (20 ml) was added dropwise a solution of the alcohol **6** (5 g, 25 mmol) in THF (80 ml). The mixture was stirred for 30 min at room temperature and MOMCl (3.7 g, 49 mmol) was added dropwise. After total disappearance of starting material, the mixture was cooled to 0 °C and the excess of base was neutralized to pH 7 with an aqueous solution of 10% HCl. Water (200 ml) was added and the aqueous layer was extracted three times with dichloromethane. After washing with brine, the dichloromethane phase was dried with $MgSO_4$ and concentrated to afford a solid. Recrystallisation from diethyl ether gave **7** (4.64 g, 75%) as a colourless solid; mp 81–82 °C; $[\alpha]_D^{25} = -26.6°$ (*c* 1, dichloromethane); IR (ν, cm^{-1}, KBr) 3072, 2979, 2929, 2890, 2825, 1678; ^1H NMR (200 MHz, $CDCl_3$) δ 2.05–2.30 (m, 1H, H-1), 2.35–2.55 (m, 3H, H-1′ and H-2), 3.51 (s, 3H, CH_3O), 3.65–3.70 (m, 1H, H-10a), 4.24 (d, 1H, $J=17.2$ Hz, H-5ax.), 4.45 (d, 1H, $J=8.6$ Hz, H-10), 4.91 (d, 1H, $J=17.2$ Hz, H-5eq), 4.93 (s, 2H, OCH_2OCH_3), 7.10–7.23 (m, 1H, H-arom.), 7.25–32 (m, 2H. H-arom.), 7.39–7.52 (m, 1H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.5 (C-1), 30.2 (C-2), 42.6 (C-5), 56.5 (C-10a), 58.6 (CH_3O), 79.2 (C-10), 97.8 (CH_2OCH_3), 126.3 (C-arom.), 126.6 (C-arom.), 127.3 (C-arom.), 128.1 (C-arom.), 132.3 (C-arom.), 135.8 (C-arom.), 174.9 (C-3); LRMS *m*/*z* 247 (M^+, 2), 202 (38), 186 (41), 185 (100), 132 (43), 119 (50); Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.89; H, 6.97; N, 5.42.

5.3. Typical selenylation procedure

To a solution of the alcohol **7** (5 g, 20.2 mmol) in anhydrous THF (100 ml) was added dropwise under an argon atmosphere at −78 °C a commercially available solution of LiHMDS 1 M in THF (44.5 ml, 44.5 mmol). After stirring for 20 min at −78 °C, a solution of PhSeBr (4.77 g, 20.2 mmol) in THF (41 ml) was added dropwise, and the resulting yellow solution was stirred further at −78 °C. After total disappearance of starting material (TLC monitoring), the reaction was quenched with a 50% aqueous NH_4Cl solution (100 ml). After decantation, following by two extractions of the aqueous phase by CH_2Cl_2, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude mixture was purified by flash-column chromatography eluting with 2:3 hexanes/EtOAc to afford **8a** (4.06 g, 50%) and **8b** (1.3 g, 16%), along with the bi-selenylated compound **9** not described herein (562 mg, 5%).

5.3.1. (2*S*,10*R*,10a*S*)-10-Methoxymethyl-2-phenylselenyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine-3-one (8a). White solid; mp 102–104 °C; $[\alpha]_D^{25} = +7.4°$ (*c* 0.54 acetone); IR (ν, cm^{-1}, KBr) 3053, 2981, 2927, 2841, 1686; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20–2.38 (m, 1H, H-1), 2.80–3.0 (m, 1H, H-1′), 3.42 (s, 3H, CH_3O), 3.55–3.70 (m, 1H, H-10a), 3.90 (d, 1H, $J=9.0$ Hz, H-10), 4.02 (t, 1H, $J=9$ Hz, H-2.), 4.23 (d, 1H, $J=17.1$ Hz, H-5ax), 4.76 (d, 1H, $J=9.6$ Hz, OCH_2OCH_3), 4.81 (d, 1H, $J=9.6$ Hz, OCH_2OCH_3), 4.88 (d, 1H, $J=17.1$ Hz, H-5eq.), 7.05–7.40 (m, 7H, H-arom.), 7.66 (d, 2H, $J=9.6$ Hz, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.3 (C-1), 40.1 (C-2), 42.8 (C-5), 56.0 (CH_3O), 56.8 (C-10a), 78.9 (C-10), 97.6 (CH_2OCH_3), 126.1 (C-arom.), 126.1, (C-arom.), 127.0 (C-arom.), 127.5 (C-arom.), 127.8 (C-arom.), 128.5 (C-arom.), 129.1 (C-arom), 131.4 (C-arom.), 135.5 (C-arom.), 135.8 (C-arom.), 172.5 (C-3); LRMS *m*/*z* 402 (M^+, 7), 357 (56), 246 (38), 119 (64), 91 (67), 45 (100); Anal. Calcd for $C_{20}H_{21}NO_3Se$ (402.35): C, 59.70; H, 5.26; N, 3.48. Found: C, 59.73; H, 5.23; N, 3.39.

5.3.2. (2*R*,10*R*,10a*S*)-10-Methoxymethyl-2-phenylselenyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine-3-one (8b). Colourless oil; $[\alpha]_D^{25} = -33.4°$ (*c* 0.5 acetone); IR (ν, cm^{-1}, KBr) 3056, 2932, 2891, 2823, 1694; ^1H NMR (200 MHz, $CDCl_3$) δ 2.64–2.69 (m, 2H, H-1 and H-1′), 3.20–3.28 (m, 1H, H-10a), 3.45 (s, 3H, CH_3O), 3.95–4.0 (m, 1H, H-2), 4.02 (d, 1H, $J=17.4$ Hz, H-5ax.), 4.34 (d, 1H, $J=8.7$ Hz, H-10), 4.85 (d, 1H, $J=17.7$ Hz, H-5eq.), 4.85 (2d, 2H, $J=9.6$ Hz, OCH_2OCH_3), 7.15–7.45 (m, 7H, H-arom.), 7.55–7.70 (m, 2H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.9 (C-1), 40.2 (C-2), 42.7 (C-5), 56.2 (CH_3O), 56.9 (C-10a), 79.3 (C-10), 97.5 (CH_2OCH_3), 125.9 (C-arom.), 126.3 (C-arom.), 126.9 (C-arom.), 127.1 (C-arom.), 127.9 (C-arom.), 128.9 (C-arom.), 129.1 (C-arom.), 131.5 (C-arom.), 135.1 (C-arom.), 136.2 (C-arom.), 172.9 (C-3); LRMS *m*/*z* 402 (M^+, 4), 246 (14), 119 (27), 91 (27), 45 (100); Anal. Calcd for $C_{20}H_{21}NO_3Se$ (402.35): C, 59.70; H, 5.26; N, 3.48. Found: C, 59.81; H, 5.18; N, 3.35.

5.4. Typical procedure for selenoxide elimination of compounds 8a–b and 17a–b

To a mixture of the stereomers **8a** and **8b** (2.88 g, 7.14 mmol) in EtOAc (23 ml) was added dropwise a commercially available 30% aqueous solution of H_2O_2 (2.15 ml) at 0 °C. The mixture was stirred at room temperature until total disappearance of starting material was observed. The organic solution was then washed with a saturated aqueous solution of sodium hydrogen carbonate and then with brine, dried over $MgSO_4$ and concentrated. The pale yellow oil so obtained (1.5 g, 85%) was used without purification in the following dihydroxylation step.

5.4.1. (10*R*,10a*S*)-10-Methoxymethyl-3, 5, 10, 10a-tetrahydro-benzo[*f*]indolizin-3-one (10). Yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.56 (s, 3H, CH_3O), 4.15 (d, 1H, $J=9.3$ Hz, H-10a), 4.31 (d, 1H, $J=9.3$ Hz, H-10), 4.39 (d, 1H, $J=17.4$ Hz, H-5ax.), 4.93 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 4.97 (d, 1H, $J=6.9$ Hz, OCH_2OCH_3), 5.08 (d, 1H, $J=17.1$ Hz, H-5eq.), 6.35 (d, 1H, $J=6.0$ Hz, H-2), 7.53 (d, 1H, $J=5.7$ Hz, H-1), 7.20–7.35 (m, 2H, H-arom.), 7.50–7.70 (m, 2H, H-arom.). ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.6 (C-5), 56.5 (OCH_3), 63.0 (C-10a), 78.2 (C-10), 98.1 (CH_2OCH_3), 126.0 (C-arom.), 126.5 (C-arom.), 127.2 (C-arom.), 128.0 (C-arom.), 128.9 (C-2), 131.7 (C-arom.), 134.7 (C-arom.), 146.6 (C-1), 170.1 (C-3).

5.5. Typical procedure for sequential dihydroxylation–acetonidation of α,β-unsaturated lactams 10 and 19

To a solution of the crude enamide **10** (1.5 g, 6.12 mmol) in a 1:1 mixture of acetone and water (36 ml) was added dropwise a commercially available aqueous solution (4%) of osmium tetroxide (2 ml), immediately followed by addition of NMO (2.3 g, 19.6 mmol). The mixture was stirred at room temperature until total disappearance of starting material was observed. $Na_2S_2O_4$ (2.5 g, 14.4 mmol) was then added and the mixture was stirred for 15 min. Acetone was removed and the aqueous phase was extracted five times with EtOAc. The organic phase was dried with $MgSO_4$ and concentrated to afford a yellow oil which was rapidly purified by filtration on a pad of silica gel. The stereomeric mixture of diols **12a** and **12b** so obtained was dissolved in dichloromethane (50 ml), then 2-methoxy propene (3.2 ml, 26 mmol) and PTSA (0.28 g, 1.5 mmol) were added subsequently. After total disappearance of starting material was observed, the organic solution was washed twice with water, dried over $MgSO_4$ and concentrated. The crude product was purified by flash-column chromatography using hexanes:EtOAc (2:3). Trituration of the major fraction (less polar, 1.3 g) in Et_2O gave 0.3 g (14%) of **14** as a colourless solid. The mother liquors (1 g) consisted in a inseparable mixture of the desired acetonide **13a** and the triol **14** in a 9:1 ratio. The minor fraction (more polar, 0.31 g, 0.97 mmol, 15%) was assigned as the expected acetonide **13b.**

5.5.1. (1*R*,2*R*,10*R*,10a*R*)-1,2-(Isopropylidene)dioxy-10-metho-xymethyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (13a). Yellow oil (contaminated by 10% of product **14**); ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 3H, $(CH_3)_2C$), 1.5 (s, 3H, $(CH_3)_2C$), 3.55 (s, 3H, CH_3O), 3.79 (d, 1H, $J=9.9$ Hz, H-10a), 4.27 (d, 1H, $J=17.3$ Hz, H-5ax.), 4.41 (d, 1H, $J=9.9$ Hz, H-10), 4.74 (d, 1H, $J=6.7$ Hz, H-1), 4.95-5.05 (m, 4H, H-2, H-5eq., OCH_2OCH_3), 7.13–7.16 (m, 1H, H-arom.), 7.27–7.32 (m, 2H, H-arom.), 7.44–7.46 (m, 1H, H-arom.).

5.5.2. (1*S*,2*S*,10*R*,10a*R*)-1,2-(Isopropylidene)dioxy-10-methoxymethyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (13b). Colourless solid; mp 119–121 °C; $[\alpha]_D^{25} = +34.2°$ (*c* 0.43, acetone); IR (ν, cm^{-1}, KBr) 2995, 2935, 2900, 1701; ^1H NMR (200 MHz, acetone-d_6) δ 1.36 (s, 3H, $(CH_3)_2C$), 1.43 (s, 3H, $(CH_3)_2C$), 3.56 (s, 3H, CH_3O), 3.82 (dd, 1H, $J=4.7$, 8.6 Hz, H-10a), 4.21 (d, 1H, $J=17.2$ Hz, H-5ax.), 4.70 (*d*, 1H, $J=17.2$ Hz, H-5eq.), 4.76 (d, 1H, $J=5.5$ Hz, H-2), 4.89 (d, 1H, $J=7.0$ Hz, OCH_2-OCH_3), 5.05 (dd, 1H, $J=4.7$, 5.5 Hz, H-10), 5.08 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 7.21–7.38 (m, 3H, H-arom), 7.62–7.70 (m, 1H, H-arom.); ^{13}C NMR (50 MHz, acetone-d_6) δ 29.9 ($(CH_3)_2C$), 30.8 ($(CH_3)_2C$), 46.3 (C-5), 60.0 (OCH_3), 63.2 (C-10a), 76.5 (C-1), 78.4 (C-2), 82.3 (C-10), 101.6 (CH_2OCH_3), 116.2 ($(CH_3)_2C$), 130.4 (C-arom.), 133.9 (C-arom.), 131.4 (C-arom.), 131.5 (C-arom.), 136.4 (C-arom.), 140.6 (C-arom.), 174.8 (C-3); LRMS *m*/*z* 319

(M^+, 12), 274 (44), 257 (98), 188 (49), 119 (67), 45 (100); Anal. Calcd for $C_{17}H_{21}NO_5$ (319.14): C, 63.94; H, 6.63; N, 4.39. Found: C, 64.22; H, 6.58; N, 4.41.

5.5.3. (1*S*,2*R*,10*R*,10a*S*)-10a-Hydroxy-1,2-(isopropylidene)-dioxy-10-methoxymethoxy-1, 2, 3, 5, 10, 10a-hexahydro-benzo[*f*]indolizin-3-one (14). Colourless solid; mp 191–192 °C; $[\alpha]_D^{25}=-99.4°$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr) 3433, 3057, 2977, 2949, 2897, 1702; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 3H, $(CH_3)_2C$), 1.55 (s, 3H, $(CH_3)_2C$), 3.35 (s, 3H, CH_3O), 3.93 (s, 1H, OH), 4.32 (d, 1H, $J=17.5$ Hz, H-5ax.), 4.42 (d, 1H, $J=6.8$ Hz, H-1), 4.58 (d, 1H, $J=6.8$ Hz, H-2), 4.69 (s, 1H, H-10), 4.82 (d, 1H, $J=6.8$ Hz, CH_2OCH_3), 4.85 (d, 1H, $J=6.8$ Hz, CH_2OCH_3), 5.06 (d, 1H, $J=17.5$ Hz, H-5eq.), 7.23–7.40 (m, 4H, H-arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.3 ($(CH_3)_2C$), 27.1 ($(CH_3)_2C$), 40.2 (C-5), 55.9 (OCH_3), 73.1 (C-1), 76.4 (C-2), 78.5 (C-10), 85.8 (C-10a), 92.8 (CH_2OCH_3), 113.9 ($(CH_3)_2C$), 126.5 (C-arom.), 126.8 (C-arom.), 129.4 (2× C-arom.), 131.6 (C-arom.), 131.7 (C-arom.), 169.4 (C-3); LRMS *m*/*z* 335 (M^+, <1), 291 (19), 290 (94), 132 (29), 119 (48), 45 (100); Anal. Calcd for $C_{17}H_{21}NO_6$ (335.35): C, 60.89; H, 6.31; N, 4.18. Found: C, 60.67; H, 6.46; N, 4.17.

5.6. Typical procedure for reduction of lactams 13a, 13b, 21a and 21b

To a solution of the amide **13a** (580 mg, 1.816 mmol) in THF (19 ml) was added dropwise a commercially available solution of BH_3–Me_2S 1 M in THF (15.2 ml, 15.2 mmol). The mixture was stirred overnight, then EtOH (100 ml) was added slowly and the solution was refluxed for 5 h. After removal of the solvents, the crude mixture was treated three times with 10 ml of EtOH. After evaporation of the last volume, the oily crude mixture was purified by flash-column chromatography eluting with 2:3 hexanes/EtOAc to afford **15a** (438 mg, 79%).

5.6.1. (1*R*,2*S*,10*R*,10a*R*)-(+)-1,2-(Isopropylidene)dioxy-10-me-thoxymethyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo-[*f*]indolizine (15a). Colourless solid, mp 45–48 °C; $[\alpha]_D^{25}=+86.9°$ (*c* 0.52, acetone); IR (ν, cm^{-1}, KBr) 3037, 2978, 2926, 2822, 2795; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 3H, $(CH_3)_2C$), 1.52 (s, 3H, $(CH_3)_2C$), 2.56 (dd, 1H, $J=5.5$, 9.4 Hz, H-3), 2.67 (dd, 1H, $J=4.7$, 9.4 Hz, H-10a), 3.49 (dd, 1H, $J=5.5$, 9.4 Hz, H-3′), 3.57 (s, 3H, CH_3O), 3.67 (d, 1H, $J=14.9$ Hz, H-5ax.), 3.94 (d, 1H, $J=14.9$ Hz, H-5eq.), 4.66–4.86 (m, 3H, H-1, H-2 and H-10), 4.93 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 5.10 (d, 1H, $J=7.0$ Hz, OCH_2OCH_3), 7.0–7.07 (m, 1H, H-arom.), 7.15–7.20 (m, 2H, H-arom), 7.40–7.50 (m, 1H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 ($(CH_3)_2C$), 27.0 ($(CH_3)_2C$), 56.0 (OCH_3), 58.7 (C-3), 63.1 (C-5), 70.3 (C-10a), 73.1, 78.4 (C-1, C-2), 80.9 (C-10), 93.9 (CH_2OCH_3), 113.5 ($(CH_3)_2C$), 126.3 (C-arom.), 127.1 (C-arom.), 127.4 (C-arom.), 127.5 (C-arom.), 134.9 (C-arom.), 136.3 (C-arom.); LRMS *m*/*z* 305 (M^+, <1), 243 (42), 132 (94), 120 (65), 61 (100), 45 (58); Anal. Calcd for $C_{17}H_{23}NO_4$ (305.16): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.75; H, 7.63; N, 4.31.

5.6.2. (1*S*,2*R*,10*R*,10a*R*)-1, 2-(Isopropylidene)dioxy-10-methoxymethyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine (15b). The title compound (0.2 g, 72%) was obtained following the same procedure from **13b** (290 mg, 0.908 mmol). Colourless solid, mp 110–115 °C; $[\alpha]_D^{25}=+60.0°$ (*c* 0.47, acetone); IR (ν, cm^{-1}, KBr) 2994, 2942, 2910, 2789, 2795; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3H, $(CH_3)_2C$), 1.50 (s, 3H, $(CH_3)_2C$), 2.30 (dd, 1H, $J=4.7$, 8.6 Hz, H-10a), 2.31 (dd, 1H, $J=3.9$, 11.0 Hz, H-3), 3.35 (d, 1H, $J=11.0$ Hz, H-3′), 3.36 (d, 1H, $J=14.1$ Hz, H-5ax.), 3.56 (s, 3H, CH_3O), 4.06 (d, 1H, $J=14.1$ Hz, H-5eq.), 4.75 (dd, 1H, $J=4.7$, 6.3 Hz, H-1), 4.84 (dd, 1H, $J=3.9$, 6.3 Hz, H-2), 4.84 (d, 1H, $J=7.1$ Hz, OCH_2OCH_3), 5.10 (d, 2H, $J=7.1$ Hz, OCH_2OCH_3 and H-10); 7.04 (d, 1H, $J=7.0$ Hz, H-arom.), 7.15–7.31 (m, 2H, H-arom.), 7.58 (d, 1H, $J=7.8$ Hz, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.9 ($(CH_3)_2C$), 26.0 ($(CH_3)_2C$), 55.6 (C-3), 56.5 (OCH_3), 60.4 (C-5), 69.6 (C-10a), 74.1, 78.2 (C-1, C-2), 79.4 (C-10), 97.3 (CH_2OCH_3), 111.3 ($(CH_3)_2C$), 125.9 (C-arom.), 126.7 (C-arom.), 126.9 (C-arom.), 128.0 (C-arom.), 134.9 (C-arom.), 136.1 (C-arom.); LRMS *m*/*z* 305 (M^+, 2), 260 (29), 243 (43), 132 (100), 91 (31), 45 (97); Anal. Calcd for $C_{17}H_{23}NO_4$ (305.16): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.74; H, 7.52; N, 4.61.

5.6.3. (1*R*,2*S*,10*R*,10a*R*)-1, 2, 10-Trihydroxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine (1a). To an aqueous solution of HCl (8 ml, 6 N) was added the amine **15a** (220 mg, 0.72 mmol). After stirring for 72 h, the mixture was kept to 0 °C and a saturated aqueous solution of ammonia was added to pH 10. The aqueous phase was saturated with NaCl then extracted ten times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified on flash column chromatography, eluting with acetone to give **1a** (100 mg, 63%) as a colourless solid. mp 158–160 °C; $[\alpha]_D^{25}=+129.6°$ (*c* 0.46, acetone); IR (ν, cm^{-1}, KBr) 3330, 3020, 2953, 2878, 2806; ^1H NMR (200 MHz, D_2O) δ 2.49 (dd, 1H, $J=6.3$, 10.2 Hz, H-3), 2.53 (dd, 1H, $J=6.3$, 8.6 Hz, H-10a), 3.32 (dd, 1H, $J=6.3$, 10.2 Hz, H-3′), 3.63 (d, 1H, $J=14.9$ Hz, H-5ax.), 3.90 (d, 1H, $J=14.9$ Hz, H-5eq), 3.99 (d, 1H, $J=6.3$, Hz, H-1), 4.13 (q, 1H, $J=6.3$, Hz, H-2), 4.69 (d, 1H, $J=8.6$ Hz, H-10), 7.06–7.15 (m, 1H, H-arom.), 7.20–7.35 (m, 2H, H-arom.), 7.45–7.55 (m, 1H, H-arom.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 54.7 (C-5), 55.8 (C-3), 68.2 (C-2), 70.8 (C-10), 72.3 (C-10a), 73.9 (C-1), 125.4 (C-arom.), 126.0 (C-arom.), 126.3 (C-arom.), 126.6 (C-arom.), 134.8 (C-arom.), 140.1 (C-arom.); LRMS *m*/*z* 221 (M^+, 10), 203 (10), 119 (50), 102 (100), 91 (38); Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.91; N, 6.08.

5.6.4. (1*S*,2*R*,10*R*,10a*R*)-1, 2, 10-Trihydroxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine (1b). The title compound (50 mg, 45%) was obtained following the same procedure from **15b** (160 mg, 0.5 mmol) as a colourless solid. mp 165–170 °C (decomposition); $[\alpha]_D^{25}=+42.8°$ (*c* 0.16, D_2O); IR (ν, cm^{-1}, KBr) 3454, 3314, 2949, 2823, 2441; ^1H NMR (200 MHz, D_2O) δ 2.43 (dd, 1H, $J=3.9$, 9.4 Hz, H-10a), 2.73 (dd, 1H, $J=7.8$, 11.0 Hz, H-3), 2.98 (dd, 1H, $J=3.9$, 11.0 Hz, H-3′), 3.45 (d, 1H, $J=14.9$ Hz, H-5ax.), 3.89 (d, 1H, $J=14.9$ Hz, H-5eq), 4.28–4.45 (m, 2H, H-1 and H-2), 5.0 (d, 1H, $J=9.4$ Hz, H-10), 7.09 (d, 1H, $J=7.0$ Hz, H-arom.), 7.15–7.30 (m, 2H, H-arom.), 7.50 (d, 1H, $J=7.0$ Hz, H-arom.); ^{13}C NMR (50 MHz, DMSO-d_6) δ

54.6 (C-5), 59.0 (C-3), 65.0, 69.0, 69.1 (C-10a, C-1, C-2), 69.6 (C-10), 126.1 (C-arom.), 126.7 (C-arom.), 127.1 (C-arom.), 127.4 (C-arom.), 133.8 (C-arom.), 137.2 (C-arom.); LRMS *m/z* (*tri*-deuteriated product) 223 (M^+, 3), 120 (51), 119 (35), 103 (46), 91 (30), 71 (43), 28 (100); Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.91; N, 6.08.

5.7. Synthesis of dihydroxy indolizines (3a) and (3b)

5.7.1. (10a*S*)-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (16). To a solution of the alcohol **6** (15 g, 80.1 mmol) in trifluoroacetic acid (98 ml) was added dropwise triethylsilane (13.5 ml, 84.5 mmol) under argon. The mixture was refluxed for 48 h. TFA was then evaporated, followed by addition of water (20 ml) and a saturated aqueous solution of sodium carbonate to pH 7. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified on flash-column chromatography, eluting with cyclohexane:EtOAc (2:8). Subsequent recrystallization from Et_2O gave **16** (11.9 g, 79%) as a colourless solid. Mp 73–75 °C; $[\alpha]_D^{25} = +37.3°$ (*c* 1, acetone); IR (ν, cm^{-1}, KBr) 2890, 1674; ^1H NMR (200 MHz, $CDCl_3$) δ 1.75–1.92 (m, 1H, H-1), 2.30–2.44 (m, 3H, H-1′, H-2 and H-2′), 2.71 (dd, 1H, $J=11.0$, 15.7 Hz, H-10ax.), 2.98 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 3.71–3.90 (m, 1H, H-10a), 4.28 (d, 1H, $J=17.2$ Hz, H-5ax.), 4.95 (d, 1H, $J=17.2$ Hz, H-5eq.), 7.10–7.21 (m, 4H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 (C-1), 30.4 (C-2), 37.1 (C-5), 42.8 (C-10), 54.2 (C-10a), 126.9 (2 C-arom.), 127.0 (C-arom.), 129.3 (C-arom.), 132.0 (C-arom.), 133.5 (C-arom.), 174.6 (C-arom.); LRMS *m/z* 187 (M^+, 63), 104 (100); Anal. Calcd for $C_{12}H_{13}NO$ (187.24): C, 76.98; H, 7.0; N, 7.48. Found: C, 76.87; H, 7.29; N, 7.57.

5.7.2. (2*S*,10a*R*)-2-Phenylselenyl-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (17a). This compound (3.4 g, 53%) was obtained from the lactam **16** (3.5 g, 18.7 mmol) by applying the same procedure as described above (Section 5.3). Colorless solid, mp 95–98 °C; $[\alpha]_D^{25} = +26.8°$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr) 2193, 1686; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (ddd, 1H, $J=5.5$, 7.0, 14.1 Hz, H-1), 2.31 (dd, 1H, $J=11.0$, 15.7 Hz, H-10ax.), 2.79 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 2.87 (ddd, 1H, $J=7.8$, 9.4, 14.1 Hz, H-1′), 3.62–3.79 (dddd, 1H, $J=3.9$, 5.5, 7.8, 11.0 Hz, H-10a), 4.03 (dd, 1H, $J=7.0$, 9.4 Hz, H-2), 4.28 (d, 1H, $J=17.2$ Hz, H-5ax.), 4.89 (d, 1H, $J=17.2$ Hz, H-5eq.), 6.99–7.32 (m, 7 H, H-arom.), 7.56–7.69 (m, 2H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.0 (C-1), 37.1 (C-10), 40.8 (C-10a), 43.4 (C-5), 52.9 (C-2), 127.0 (C-arom.), 127.1 (C-arom.), 128.2 (C-arom.), 128.7 (C-arom.), 129.3 (C-arom), 129.5 (C-arom.), 131.6 (C-arom.), 133.3 (C-arom.), 135.8 (C-arom.), 172.6 (C-3); LRMS *m/z* 342 (M^+, 15), 186 (56), 185 (100), 104 (56); Anal. Calcd for $C_{18}H_{17}NOSe$ (342.29): C, 63.16; H, 5.01; N, 4.09. Found: C, 63.09; H, 4.92; N, 4.18.

5.7.3. (2*R*,10a*R*)-2-Phenylselenyl-1, 2, 3, 5, 10, 10a-hexahy-drobenzo[*f*]indolizin-3-one (17b). 1.66 g, 26% of the title compound was obtained from the lactam **16** (3.5 g, 18.7 mmol) by applying the same procedure as described in Section 5.3. Yellow solid, mp 85–87 °C; $[\alpha]_D^{25} = +2.8°$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr) 2178, 2034, 1676; ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (ddd, 1H, $J=7.0$, 9.4, 15.7 Hz, H-1), 2.48–2.66 (m, 2H, H-1′and H-10ax.), 2.90 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 3.19–3.36 (m, 1H, H-10a), 3.97 (dd, 1H, $J=3.9$, 9.4 Hz, H-2), 4.07 (d, 1H, $J=18.0$ Hz, H-5ax.), 4.88 (d, 1H, $J=18.0$ Hz, H-5eq.), 7.02–7.22 (m, 4H, H-arom.), 7.23–7.38 (m, 3H, H-arom.), 7.64–7.76 (m, 2H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.8 (C-1), 37.3 (C-10), 40.9 (C-10a), 43.1 (C-5), 52.8 (C-2), 126.9 (C-arom.), 127.0 (C-arom.), 127.2 (C-arom.), 127.3 (C-arom.), 129.2 (C-arom.), 129.2 (C-arom.), 129.4 (C-arom.), 131.5 (C-arom.), 132.9 (C-arom.), 136.4 (C-arom.), 172.8 (C-3); LRMS *m/z* 342 (M^+, 21), 262 (13), 186 (58), 185 (100), 104 (65); Anal. Calcd for $C_{18}H_{17}NOSe$ (342.29): C, 63.16; H, 5.01; N, 4.09. Found: C, 63.25; H, 4.99; N, 4.02.

5.7.4. (10a*R*)-3, 5, 10, 10a-tetrahydrobenzo[*f*]indolizin-3-one (19). The title compound (2.25 g, 76%) was obtained from a mixture of the selenylated amides **17a** and **17b** (5.49 g, 16 mmol) by applying the same procedure as described above (Section 5.4). The pure compound was isolated after recrystallization of the crude product from diethyl ether. Mp 77–78 °C; $[\alpha]_D^{25} = +41.8°$ (*c* 0.53, acetone); IR (ν, cm^{-1}, KBr) 3088, 3066, 2935, 2858, 1686; ^1H NMR (200 MHz, $CDCl_3$) δ 2.58 (dd, 1H, $J=12.5$, 15.7 Hz, H-10ax.), 3.17 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 4.24 (ddd, $J=1.6$, 3.9, 12.5 Hz, H-10a), 4.45 (d, 1H, $J=17.2$ Hz, H-5ax.), 5.15 (d, 1H, $J=17.2$ Hz, H-5eq.), 6.32 (dd, 1H, $J=1.6$, 5.5 Hz, H-2), 7.15 (m, 5H, H-arom. and H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.9 (C-10), 42.1 (C-5), 58.6 (C-10a), 127.2 (C-arom.), 127.3 (C-arom.), 127.4 (C-arom.), 128.6 (C-arom.), 129.4 (C-2), 131.98 (C-arom.), 132.03 (C-arom.), 147.5 (C-1), 170.2 (C-3); LRMS *m/z* 185 (M^+, 100), 104 (46), 28 (46); Anal. Calcd for $C_{12}H_{11}NO$ (185.22): C, 77.81; H, 5.99; N, 7.56. Found: C, 77.89; H, 5.92; N, 7.49.

5.7.5. (1*R*,2*R*,10a*R*)-1, 2-(Isopropylidene)dioxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (21a). The title compound (960 mg, 51%) was obtained from the conjugated lactam **19** (1.34 g, 7.23 mmol) by applying the same procedure as described above (Section 5.5). The pure compound was isolated after flash-column chromatography using hexanes:EtOAc (2:3). Colourless solid; mp 151–153 °C; $[\alpha]_D^{25} = +27.3$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr) 3066, 2986, 2924, 2854, 1708; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 3H, $(CH_3)_2C$), 1.49 (s, 3H, $(CH_3)_2C$), 2.63 (dd, 1H, $J=12.5$, 15.7 Hz, H-10ax.), 3.08 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 3.86 (dd, 1H, $J=3.9$, 12.5 Hz, H-10a), 4.28 (d, 1H, $J=17.2$ Hz, H-5ax.), 4.57 (d, 1H, $J=6.7$ Hz, H-1), 4.75 (d, 1H, $J=6.7$ Hz, H-2), 5.08 (d, 1H, $J=17.2$ Hz, H-5eq.), 7.09–7.25 (m, 4H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8 ((CH_3)$_2$C),), 27.2 ((CH_3)$_2$C), 34.0 (C-10), 42.6 (C-5), 58.6 (C-10a), 77.7 (C-1), 77.8 (C-2), 113.2 ((CH_3)$_2C$), 126.9 (C-arom.), 127.2 (C-arom.), 127.5 (C-arom.), 129.8 (C-arom), 131.7 (C-arom.), 132.2 (C-arom.), 169.6 (C-3); LRMS *m/z* 259 (M^+, 72), 184 (100), 104 (66), 28 (53); Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.54; H, 6.58; N, 5.32.

5.7.6. (1*S*,2*S*,10a*R*)-1,2-(Isopropylidene)dioxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizin-3-one (21b). The title compound (320 mg, 17%) was obtained from the conjugated lactam **19** (1.34 g, 7.23 mmol) by applying the same procedure as described above (Section 5.5). The pure compound was isolated after flash-column chromatography using hexanes:EtOAc (2:3). Colourless solid; mp 145–147 °C; $[\alpha]_D^{25} = +24.3°$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr) 3000, 2943, 1698, 1686; ^1H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 6H, $(CH_3)_2C$), 2.88 (dd, 1H, $J=3.9$, 15.7 Hz, H-10ax.), 3.20 (dd, 1H, $J=11.0$, 15.7 Hz, H-10eq.), 3.82 (ddd, 1H, $J=3.9$, 7.8, 11.0 Hz, H-10a), 4.36 (d, 1H, $J=18.00$ Hz, H-5ax.), 4.90 (d, 1H, $J=18.00$ Hz, H-5eq.), 4.76–4.96 (m, 2H, H-1 and H-2), 7.11–7.25 (m, 4H, H-arom); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.3 ($(CH_3)_2C$), 27.3 ($(CH_3)_2C$), 30.0 (C-10), 43.1 (C-5), 54.9 (C-10a), 75.0 (C-1), 78.6 (C-2), 113.2 ($(CH_3)_2C$), 127.1 (C-arom.), 127.1 (C-arom.), 127.3 (C-arom.), 129.5 (C-arom.), 130.8 (C-arom.), 133.6 (C-arom.), 170.9 (C-3); LRMS *m*/*z* 259 (M^+, 55), 184 (100), 131 (45), 104 (61), 28 (74); Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.35; H, 6.67; N, 5.32.

5.7.7. (1*R*,2*S*,10a*R*)-1, 2-(Isopropylidene)dioxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine (22a). The title compound (410 mg, 90%) was obtained from the parent lactam **21a** (480 mg, 1.85 mmol) by applying the same procedure as described above (Section 5.6). The pure compound was isolated after flash-column chromatography using hexanes:EtOAc (1:4). Colourless solid, mp 129–130 °C; $[\alpha]_D^{25} = +0.97°$ (*c* 1, acetone); IR (ν, cm^{-1}, KBr) 3061, 2987, 2976, 2911, 2803, 2759; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3H, $(CH_3)_2C$), 1.54 (s, 3H, $(CH_3)_2C$), 2.52 (dd, 1H, $J=5.5$, 9.5 Hz, H-3), 2.60–2.70 (m, 1H, H-10a), 2.63 (dd, 1H, $J=11.0$, 15.7 Hz, H-10ax.), 3.12 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 3.56 (dd, 1H, $J=6.3$, 9.5 Hz, H-3′), 3.64 (d, 1H, $J=14.8$ Hz, H-5ax.), 4.02 (d, 1H, $J=14.8$ Hz, H-5eq.), 4.39 (dd, 1H, $J=5.3$, 7.0 Hz, H-1), 4.81–4.88 (m, 1H, H-2), 6.99–7.19 (m, 4H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 ($(CH_3)_2C$), 27.5 ($(CH_3)_2C$), 33.5 (C-10), 55.2 (C-5), 60.4 (C-3), 65.4 (C-10a), 78.3 (C-2), 85.7 (C-1), 114.3 ($(CH_3)_2C$), 126.2 (C-arom.), 126.9 (C-arom.), 126.8 (C-arom.), 129.5 (C-arom.), 133.8 (C-arom.), 134.2 (C-arom.); LRMS *m*/*z* 245 (M^+, 52), 145 (100), 104 (55), 28 (52); Anal. Calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.49; H, 7.86; N, 5.72.

5.7.8. (1*S*,2*R*,10a*R*)-1, 2-(Isopropylidene)dioxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine (22b). The title compound (0.18 g, 71%) was obtained from the parent lactam **21b** (270 mg, 1.04 mmol) by applying the same procedure as described above (Section 5.6). The pure compound was isolated after flash-column chromatography using hexanes:EtOAc (1:4). Colourless solid, mp 61–62 °C; $[\alpha]_D^{25} = +12.7°$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr): 2979, 2936, 2804; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (s, 3H, $(CH_3)_2C$), 1.51 (s, 3H, $(CH_3)_2C$), 2.17–2.27 (m, 2H, H-3 and H-10a), 2.79 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq.), 3.22 (dd, 1H, $J=11.0$, 15.7 Hz, H-10ax.), 3.25–3.44 (m, 2H, H-3′ and H-5ax.), 4.15 (d, 1H, $J=14.1$ Hz, H-5eq.), 4.67 (dd, 1H, $J=4.7$, 6.3 Hz, H-1 or H-2), 4.76 (dd, 1H, $J=3.9$, 6.3 Hz, H-1 or H-2), 7.0–7.2 (m, 4H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.5 ($(CH_3)_2C$), 27.5 ($(CH_3)_2C$), 33.5 (C-10), 55.2 (C-5), 60.4 (C-3), 65.4 (C-10a), 78.3 (C-2), 85.7 (C-1), 114.3 ($(CH_3)_2C$), 126.2 (C-arom.), 126.9 (C-arom.), 126.8 (C-arom.), 129.5 (C-arom.), 133.8 (C-arom.), 134.2 (C-arom.); LRMS *m*/*z* 245 (M^+, 62), 145 (100), 104 (46), 28 (52); Anal. Calcd for $C_{15}H_{19}NO_2$ (245.32): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.43; H, 7.76; N, 5.65.

5.7.9. (1*R*,2*S*,10a*R*)-1, 2-dihydroxy-1, 2, 3, 5, 10, 10a-hexahydrobenzo[*f*]indolizine (3a). To a solution of the amine **22a** (200 mg, 0.82 mmol) in a mixture of MeOH (4 ml) and dichloromethane (1 ml) was added an aqueous solution of HCl 2 N (4.5 ml). The mixture was stirred for 48 h, cooled to 0 °C and basified to pH 10 with an aqueous solution of KOH 2 M. The aqueous phase was saturated with NaCl and extracted ten times with 3 ml of dichloromethane. The organic phase was dried over $MgSO_4$, the solvents were removed under vacuum and the product was purified by flash-column chromatography using 9:1 EtOAc:EtOH to afford the targeted amino diol **3a** (130 mg, 78%) as a colourless solid. mp 129–130 °C; $[\alpha]_D^{25} = +1.0°$ (*c* 0.5, acetone); IR (ν, cm^{-1}, KBr): 3388, 3154, 3062, 3017, 2922, 2827, 2727; ^1H NMR (200 MHz, $CDCl_3$) δ 2.33 (dd, 1H, $J=4.7$, 10.2 Hz, H-3), 2.50 (ddd, 1H, $J=3.9$, 7.0, 11 Hz, H-10a), 2.70 (dd, 1H, $J=11.0$, 15.7 Hz, H-10ax.), 3.07 (dd, 1H, $J=3.9$, 15.7 Hz, H-10eq), 3.10–3.30 (s, 2H, OH), 3.45 (d, 1H, $J=14.9$ Hz, H-5ax.), 3.54 (dd, 1H, $J=7.0$, 10.2 Hz, H-3′), 3.69 (t, 1H, $J=7.2$ Hz, H-1), 3.95 (d, 1H, $J=14.9$ Hz, H-5eq), 4.17 (ddd, 1H, $J=4.7$, 7.0, 7.0 Hz, H-2), 6.95–7.15 (m, 4H, H-arom.); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.7 (C-10), 55.5 (C-5), 61.9 (C-3), 64.8 (C-10a), 68.7 (C-2), 76.7 (C-1), 126.3 (C-arom.), 126.8 (C-arom.), 126.9 (C-arom.), 129.4 (C-arom.), 134.0 (C-arom.), 134.5 (C-arom.); LRMS *m*/*z* 206 ($M^+ + 1$, 9), 205 (M^+, 60), 204 (37), 146 (14), 145 (base), 144 (23), 132 (23), 130 (17), 118 (26), 117 (40), 116 (26), 115 (14), 104 (31), 28 (29); Anal. Calcd for $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.45; H, 7.41; N, 6.97.

5.7.10. (1*S*,2*R*,10a*R*)-1, 2-dihydroxy-1, 2, 3, 5, 10, 10a-hexa-hydrobenzo[*f*]indolizine (3b). The title compound (120 mg, 94%) was obtained from the parent amine **22b** (150 mg, 0.61 mmol) by applying the above procedure. The pure compound was isolated after flash-column chromatography eluting with EtOAc:EtOH (9:1). Colourless solid, mp 183–185 °C (decomposition); $[\alpha]_D^{25} = +19.0°$ (*c* 0.25, acetone); IR (ν,cm^{-1}, KBr) 3448, 3062, 3301, 2929, 2812, 2719; ^1H NMR (200 MHz, DMSO-d_6) δ 2.35–2.5 (m, 2H, H-3 and H-10a), 2.7–3.0 (m, 2H, OH), 2.76 (dd, 1H, $J=3.4$, 15.8 Hz, H-10eq), 3.1–3.25 (m, 2H, H-3′ and H-10ax), 3.37 (d, 1H, $J=14.9$ Hz, H-5ax.), 4.06 (d, 1H, $J=14.9$ Hz, H-5eq), 4.15 (t, 1H, $J=5.2$ Hz, H-1), 4.25–4.35 (m, 1H, H-2), 6.95–7.05 (m, 1H, H-arom.), 7.1–7.25 (m, 3H, H-arom.); ^{13}C NMR (50 MHz, DMSO-d_6) δ 28.5 (C-10), 55.6 (C-5), 61.8 (C-3), 64.0 (C-10a), 70.0 (C-2), 71.8 (C-1), 125.8 (C-arom.), 126.5 (C-arom.), 126.6 (C-arom.), 129.4 (C-arom), 133.5 (C-arom.), 134.0 (C-arom.); LRMS *m*/*z* 205 (M^+, 57), 204 (33), 145 (100), 117 (40), 105 (46); Anal. Calcd for $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82. Found: C, 70.18; H, 7.40; N, 6.79.

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26. X-ray Single-Crystal Structure of **21a** at 298(2) K. Crystal data: $C_{15}H_{17}NO_3$, Mr=259.30, monoclinic, space group $P2_1$ (No.4), a=12.421(2), b=7.522(2), c=14.578(3) Å, β=91.186(4)°, V=1361.7(5) Å^3, Z=4, ρ_{calc} 1.265 Mg m^{-3}, F000=552, λ(MoKα)=0.71073 Å, (=0.088 mm^{-1}. Data collection and reduction: crystal size, 0.20(0.08(0.05 mm^3, θ range, 1.40–23.26°, 6294 reflections collected, 3745 independent reflections (R_{int}=0.0496), final R indices (I>2σ(I)): R_1=0.0711, wR_2=0.1689 for 348 variable parameters, GOF=1.086. As expected, interatomic distances between carbon atoms forming aromatic benzene rings are in the range from 1.358(10) to 1.407(10) and are essentially shorter than the rest of C–C bonds (from 1.481(14) to 1.533(9)), which show a single bond character. Both symmetry independent molecules obey the same geometry within the experimental standard deviations. CCDC 261472 contains the supplementary data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_requist/cif, or by emailing data _request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Stereoselective synthesis of tetrazole CB92834, a potent retinoid compound

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Abstract—An improved, convergent synthesis of CB92834 is relying on a Suzuki cross-coupling reaction and easily allows multigram-scale preparation of the compound. The approach features three highly stereoselective steps.

1. Introduction

The increasing incidence of cancer in the world has induced massive efforts aiming at the development of the most efficient treatments of the disease.[1] Among the various approaches, chemoprevention is the use of non-cytotoxic therapeutic intervention at the early stages of carcinogenesis against the development and progression of mutant clones to invasive cancer. The chemopreventive potential of retinoids has been the focus of much attention over the last decade.[2] Retinoids are defined as molecules related to all-*trans*-retinoic acid, and for which biological activities are mediated by two types of receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs).[3] With respect to the various isotypes of these receptors, the retinoids-induced effects include modifications of (i) cell proliferation, (ii) apoptosis (cell death) and (iii) reversal of premalignancy by inducing differentiation processes. Retinoids have been shown to be active on breast, lung, cervical and head and neck cancers, as well as on neuroblastoma and acute promyelocytic leukemia. Although much important data has been obtained, the exact signaling pathways required for retinoids to exert their biological effects remain elusive.[4]

Recently, a class of 1,2-bisaryl alkenes featuring a *Z* configuration has been reported as displaying promising activities on RARs and RXRs.[5] The foremost representative of this class of compound is tetrazole **9**.[6] However, the published preparation of **9** suffers from several drawbacks which impede its use on multigram-scale synthesis. Not only is it linear, but it also relies on a Wittig reaction between the phosphorus ylid generated from phosphonium salt **5** (prepared from toluene (**2**) in three steps) and *p*-cyanoacetophenone (**6**) to create the carbon–carbon double bond featuring the requisite *Z* configuration (Scheme 1). The reaction is reported as being poorly stereoselective, delivering a 7:3 mixture of *Z* and *E* isomers (**7** and **8**, respectively). In addition, it suffers from a tedious separation procedure of the two isomers, requiring three sequential chromatography on silica to isolate the desired one **7** in only 35% yield. Attemps to either improve the stereoselectivity of this step or isomerize the *E* isomer into the *Z*, all failed in our hands.[7] We describe below a much improved preparation of **9** which allows easy, multi-gram scale synthesis of the compound.

The design of a more efficient synthesis of the target compound required the stereocontrolled production of the vinyl C–C double bond with the requisite *Z* stereochemistry. We chose to exploit the well-documented stereoselectivity of a Suzuki cross-coupling reaction between boronate **10** (subunit A) and *Z* vinyl bromide **11** (subunit B) (Scheme 2).[8]

Preparation of subunit A was accomplished through the three step sequence depicted in Scheme 3. Thus, bromide **12** was produced by a double Friedel–Crafts alkylation of bromobenzene and the resultant aryl bromide was transformed into boronate **10** by the method of Miyaura.[9,10] The use of $Pd(dppf)Cl_2$ proved to be particularly efficient, allowing a low loading of catalyst (1 mol%) and the isolation of **10** in good yield by simple distillation.

Quite obvious was the fact that the success of the new approach heavily depended on our ability to

Keywords: *Z*-alkene synthesis; Tetrazole; Retinoid; Suzuki cross-coupling reaction.
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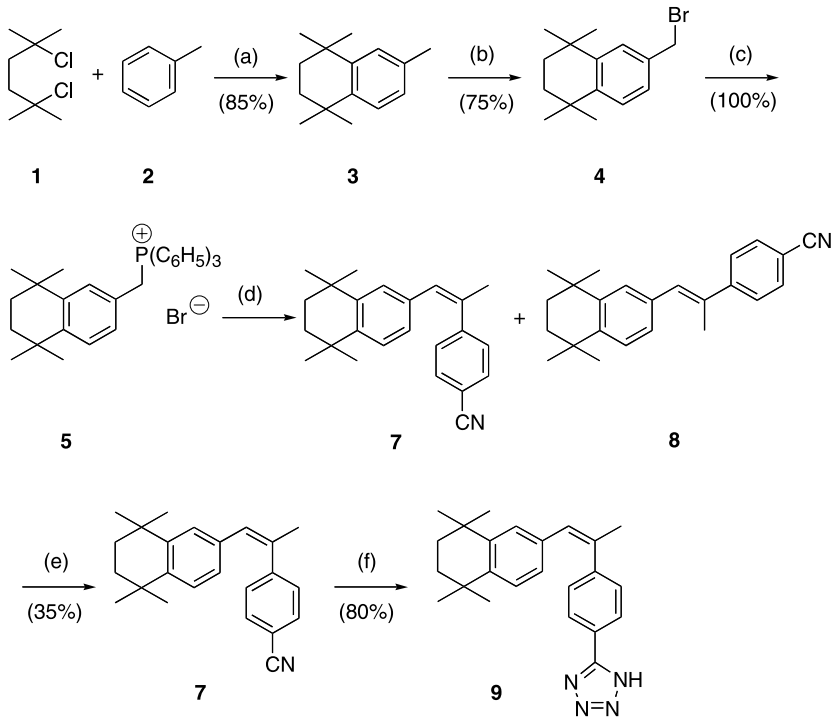
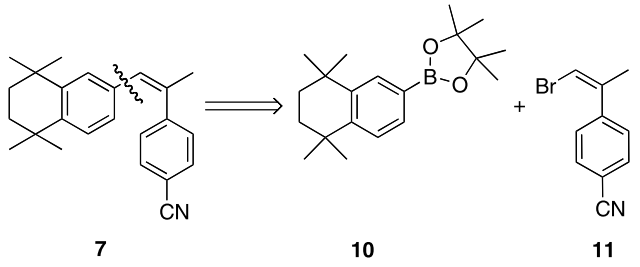


Scheme 1. Published synthesis of tetrazole **9**. Reagents and conditions: (a) $AlCl_3$, 110 °C; (b) *N*-bromosuccinimide, CH_2Cl_2; (c) $P(C_6H_5)_3$; (d) *n*-BuLi, 4-cyanoacetophenone (**6**); (e) three sequential chromatography separations; (f) Me_3SiN_3, $(n\text{-}Bu_3Sn)_2O$.

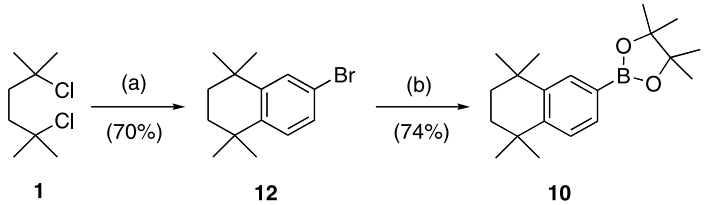


Scheme 2. Stereoselective approach to **7**

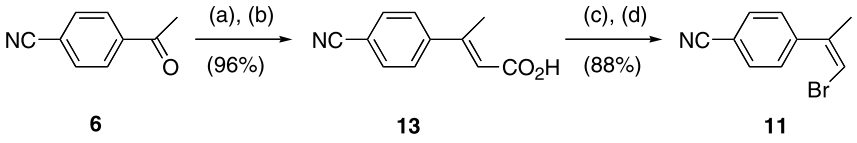
stereoselectively generate vinyl bromide **11**, with the requisite *Z* stereochemistry. Acid **13** was stereoselectively produced by a Wadsworth–Emmons reaction between ketone **6** and triethyl phosphonoacetate in dry ethanol followed by saponification and protonation of the resultant product (Scheme 4). The *Z/E* isomer ratio was found to strongly depend on the solvent. Thus, carrying out the Wadsworth–Emmons reaction in diethyl ether or tetrahydrofuran (THF) led to a 3:7 mixture in favor of the *E* isomer. Conducting the reaction in ethanol, however, led to an increase of the selectivity to 98:2. Hydrolysis of the ester group led to the desired acid, and a simple crystallisation from methanol allowed the isolation of the pure *E* isomer **13** in virtually quantitative yield.[11] A sequence of bromination/decarboxylative debromination proved to be particularly gratifying, delivering exclusively the *Z* vinyl bromide **11** in 88% yield, the result of an *anti* elimination of bromide.[12,13] The whole sequence of reactions (four steps) required a single purification by distillation and compound **11** could easily be produced on multi-gram scale without experiencing a drop in yields.

Coupling of subunits A and B (boronate **10** and vinyl bromide **11**) could again be achieved on multi-gram scale and was found to be completely stereoselective: product **7** was the sole isomer detected in the crude sample (Scheme 5).[14] Purification of this material reproducibly afforded the desired compound **7** in 71–74% isolated yield. Production of the tetrazole cycle present in the final product was then carried out on multi-gram scale according to literature procedure.[15] Treating (**7**) at 110 °C for 12 h with trimethylsilyl azide in the presence of a catalytic amount of bis-(tri-*n*-butyltin)oxide furnished target molecule **9** in 80% isolated yield.

Thus, this new, convergent approach allows the preparation of **9** with a global yield of 30%; three of the five steps of the

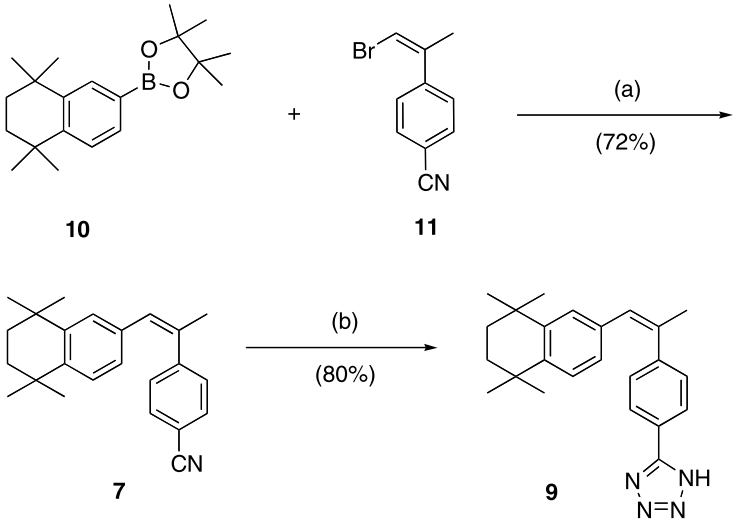


Scheme 3. Synthesis of subunit A. Reagents and conditions: (a) $AlCl_3$, bromobenzene; (b) bis-(pinacolato)diboron, KOAc, $Pd(dppf)Cl_2$ (1 mol%).



6 13 11

Scheme 4. Stereocontrolled synthesis of subunit B. Reagents and conditions: (a) dry ethanol, sodium, triethylphosphonoacetate; (b) KOH, methanol; (c) Br_2, $CHCl_3$; (d) dry acetone, K_2CO_3.



10 11 7 9

Scheme 5. Coupling of subunits A and B. Reagents and conditions: (a) $NaHCO_3$, $Pd(dppf)Cl_2$; (b) $TMSN_3$, $[n\text{-}Bu)_3Sn]_2O$ (10 mol%).

sequence (i. e., **6**→**13**, **13**→**11**, **10**+**11**→**7**) are highly stereoselective, providing the desired isomer in excess of 98% in each case. The synthesis is applicable to large-scale production of **9** and is potentially useful for the preparation of analogues structurally related to the parent compound.

2. Experimental

2.1. General

Unless otherwise stated, ^1H NMR, ^{13}C NMR spectra were recorded in deuterated chloroform on a Brucker AM200 spectrometer operating at 200 and 50 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) relative to $(CH_3)_4Si$ (^1H) and $CDCl_3$, (^{13}C). IR spectra were recorded on a FT-IR spectrometer. Combustion data were obtained from the analytical department of the University of Rouen. Commercially available chemicals were used without further purification.

2.1.1. (*E*) 3-(4-Cyanophenyl)-but-2-enoic acid (13). Sodium (3.5 g) is added in small portion to dry ethanol (250 mL). When reaction of the metal is complete, the solution is cooled down to 0 °C and neat triethylphosphonoacetate (30 g, 137 mmol) is added. After 15 min of stirring at the same temperature, the solution is warmed up to room temperature and a solution of 4-cyanoacetophenone (**6**) (20 g, 138 mmol) in dry ethanol (25 mL) is added dropwise. The resultant red solution is stirred for 30 min, after which period of time the solvent is evaporated. Extraction with 10% aqueous $NaHCO_3$/AcOEt, drying over $MgSO_4$ and evaporation yield 30 g of the desired ethyl ester as a 98:2 mixture of *E*/*Z* isomers. This crude material is then hydrolyzed by stirring overnight at room temperature in a solution of potassium hydroxide (16 g) in methanol (200 mL). Addition of concentrated HCl at 0 °C until pH=4 results in the precipitation of a white solid. Filtration, sequential washing of the solid with water and methanol, and drying in vacuum yield 25 g of pure (*E*) acid **13** (96% over two steps). Mp (methanol)=192 °C. ^1H NMR (DMSO-d_6) δ 7.64 (d, J=8.2 Hz, 2H), 7.53 (d, J=8.2 Hz, 2H), 6.02 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 167.8, 152.2, 145.9, 132.5, 127.2, 119.7, 118.8, 111.3, 17.1. IR (neat) ν 3448, 2258, 1654, 1026 cm^{-1}. Calcd for $C_{10}H_8BrN$: C, 71.03; H, 4.26. Found: C, 71.72; H, 5.02.

2.1.2. (*Z*) 1-Bromo-2-(4-cyanophenyl)propene (11). To a suspension of acid **13** (25 g, 134 mmol) in chloroform (300 mL) at 0 °C is added bromine (23.5 g, 146 mmol) and the resultant mixture is stirred for 12 h. The reaction can be monitored by ^1H NMR spectrometry (δ 7.7 (m, 4H), 5.0 (s, 1H), 2.52 (s, 3H)). The clear orange solution is then evaporated and the residue is dissolved in dry acetone (250 mL); $NaHCO_3$ (15 g) is added and the mixture is refluxed for 16 h. Filtration and evaporation under reduced pressure deliver a crude, oily residue which is partitioned between water and ethyl acetate. The water layer is extracted with additional AcOEt and the combined organic layers are dried over magnesium sulfate. Evaporation under reduced pressure and distillation (154 °C/0.5 mbar) give 16.5 g of product **11** as a colorless liquid (88% yield). ^1H NMR ($CDCl_3$) δ 7.60 (d, J=8.0 Hz, 2H), 7.38 (d, J=8.0 Hz, 2H), 6.27 (s, 2H), 2.1 (s, 3H). ^{13}C NMR ($CDCl_3$) δ

144.8, 140.0, 132.0, 128.6, 118.6, 111.2, 103.5, 24.4. IR (neat) ν 3072, 2914, 2850, 2228, 1604, 1500, 842 cm^{-1}. Calcd for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 54.12; H, 3.67; N, 6.57.

2.1.3. 1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-bromonaphthalene (12). To dry CH_2Cl_2 (20 mL) at 0 °C are sequentially added aluminium trichloride (5.6 g, 42 mmol), neat 2,5-dicloro-2,5-dimethylhexane[16] (20 g, 109 mmol) and a solution of bromobenzene (17.2 g, 109.3 mmol) in CH_2Cl_2 (20 mL). The mixture is warmed up to room temperature and stirred overnight. It is then slowly poured onto crushed ice (100 g). Extraction with AcOEt (200 mL), decantation, washing of the organic layer with 10% aqueous $NaHCO_3$ (100 mL), drying of the organic layer over magnesium sulfate and evaporation of the volatiles left an oily residue which was subjected to distillation (150 °C/0.5 mbar) to furnish 18.9 g of **12** (70% yield). ^1H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.22 (d, $J=8.8$ Hz, 2H), 7.16 (d, $J=8.8$ Hz, 2H), 1.65 (s, 4H), 1.25 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 147.4, 143.8, 141.7, 129.6, 129.0, 128.6, 35.1, 34.2, 32.0. IR (neat) ν 2960, 1458, 1364, 908, 816, 734 cm^{-1}. Calcd for $C_{14}H_{19}Br$: C, 63.20; H, 7.10. Found: C, 63.42; H, 6.81.

2.1.4. 1,2,3,4-Tetrahydro-1,1,4,4-tetramethyl-6-pinacolatoboronaphthalene (10). Compound **12** (6.3 g, 23.6 mmol), bis-(pinacolato)diboron (5.0 g, 19.7 mmol), Pd(dppf)Cl_2 (140 mg, 0.19 mmol (1 mol%)) and potassium acetate (5.2 g, 59.1 mmol) are sequentially added to degassed dimethyl sulfoxide (DMSO) (40 mL) under inert atmosphere. The reaction is carried out at 80 °C for 20 h. After cooling, the mixture is poured into water and extracted with AcOEt. The organic layer is evaporated and the residue is dissolved in a 1:1 mixture of heptane/AcOEt (15 mL) and filtered over a plug of silica gel. Washing with additional heptane/AcOEt (1:1) (10 mL) and evaporation of the volatiles delivers the crude product (10 g). Distillation (130 °C/0.5 mbar) yields 5.5 g (74%) of pure product **10**. ^1H NMR ($CDCl_3$) δ 7.75 (s, 1H), 7.55 (d, $J=8.0$ Hz, 1H), 7.28 (d, $J=8.0$ Hz, 2H), 1.66 (s, 4H), 1.3 (s, 12H), 1.26 (s, 12H). IR (neat) ν 2962, 2953, 1362, 1146, 1116, 852, 756 cm^{-1}. Calcd for $C_{20}H_{31}BO_2$: C, 76.43; H, 9.98. Found: C, 76.90; H, 10.49.

2.1.5. (*Z*) 4-[1-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2-propenyl]benzonitrile (7). Bromide **11** (3.7 g, 16.9 mmol), boronate **10** (5.3 g, 16.9 mmol), Pd(dppf)Cl_2 (124 mg, 0.17 mmol (1 mol%)) and $NaHCO_3$ (4.3 g, 50.3 mmol) are sequentially placed in a flask containing a degassed mixture of 1,4-dioxane (60 mL) and water (25 mL) under nitrogen. The reaction is stirred at 80 °C for 20 h. After cooling, the mixture is poured into water and extracted with AcOEt. Evaporation of the volatiles, filtration of the residue through silica and elution with heptane/AcOEt (2:1) give 4.0 g (72%) of product **7**. Mp=121–123 °C (lit.[5]: 95–97 °C).[17] ^1H NMR ($CDCl_3$) δ 7.58 (d, $J=8.4$ Hz, 2H), 7.32 (d, $J=8.4$ Hz, 2H), 7.12 (d, $J=8.0$ Hz, 1H), 6.79 (s, 1H), 6.75 (d, $J=87.0$ Hz, 1H), 6.54 (s, 1H), 2.20 (s, 3H), 1.61 (s, 4H), 1.23 (s, 6H), 1.00 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 148.3, 144.7, 144.0, 135.9, 134.0, 132.8, 129.7, 129.2, 127.9, 126.8, 126.7, 119.4, 110.8, 35.4, 35.4, 34.5, 34.3, 32.2, 32.0, 26.9. IR (neat) ν 2975, 2962, 2228, 1216, 756 cm^{-1}. Calcd for $C_{24}H_{27}N$: C, 87.49; H, 8.26; N, 4.25. Found: C, 87.51; H, 8.38; N, 4.23.

2.1.6. 5-{4-[1-Methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-vinyl]-phenyl}-1*H*-tetrazole 9. Nitrile **7** (3 g, 9.12 mmol), trimethylsilyl azide (3.15 g, 27.4 mmol) and bis-(tri-*n*-butyltin)oxide (540 mg, 0.91 mmol (10 mol%)) are added to toluene (10 mL). The reaction flask is flushed with nitrogen and the mixture is heated at 110 °C for 12 h. The mixture is then cooled down, the volatiles are removed under reduced pressure and the residue is filtered through silica which is washed with a 98:2 mixture of heptane/AcOEt. The solvents are evaporated and the resultant white solid is recrystallized from heptane to deliver 2.7 g (80%) of **9**. Mp=192–193 °C (lit.[5]: 191–193 °C). ^1H NMR ($CDCl_3$) δ 8.04 (d, $J=8.4$ Hz, 2H), 7.38 (d, $J=8.4$ Hz, 2H), 7.03 (d, $J=8.0$ Hz, 2H), 6.83 (s, 1H), 6.72 (d, $J=8.0$ Hz, 2H), 6.48 (s, 1H), 2.19 (s, 3H), 1.53 (s, 4H), 1.16 (s, 6H), 0.92 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 156.6, 147.2, 144.7, 143.7, 136.4, 134.2, 130.0, 128.6, 128.3, 127.9, 126.6, 126.5, 121.9, 35.4, 34.4, 34.2, 32.1, 31.9, 27.2. IR (neat) (ν 3420, 2962, 2856, 1614, 1490, 1456, 1362, 908, 732 cm^{-1}. Calcd for $C_{24}H_{28}N_4$: C, 77.32%; H, 7.53%. Fd: C, 77.61%; H, 7.63%.

Acknowledgements

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respectively. Attempts to isomerize the *E* double bond to its *Z* isomer (e.g., irradiation (mercury lamp) of solutions of pure **7** or **8** in dichloromethane in the presence of $(PhSe)_2$ (10 mol%)) were unsuccessful, invariably producing 1:1 mixtures of the two isomers.

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First selective lithiation of pyridylpiperazines: straightforward access to potent pharmacophores

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Abstract—The three isomers of pyridylpiperazines have been lithiated for the first time. The use of a superbase, an aminoalkoxide containing lithiating agent overcomes the chelating influence of the basic piperazine nitrogens, so that selective mono lithiation occurred alpha to pyridine nitrogen. This methodology offers a new access to diverse potent pharmacophores not easily prepared by other routes.

1. Introduction

The selective chemical modification of heterocyclic compounds to attain optimal bioactivity provides a challenge of modern synthetic chemistry for the discovery of new drug candidates. Pyridylpiperazines and analogs are key units found in a wide range of relevant pharmacophores with a broad spectrum of activity (Fig. 1). For example, ABT-724 (**A**)[1,2] and analogues have been reported as selective dopaminergic D_4 agonists (erectile dysfunction treatment). Compounds **B** and **C** containing a substituted pyridine were reported, respectively, as candidates with analgesic[3] and HIV-1 reverse transcriptase inhibitory activity.[4] A promising progress for treatment of diabetes was also found with pyrimidylpiperazine **D** which inhibits sorbitol dehydrogenase via chelation of the zinc atoms.[5] The ability to create variations of heteroarylpiperazines is an important task: a recent paper by Stewart and co-workers[6] showed that a variation in the nature and substitution of the (het)aryl ring on piperazine in **A** dramatically influenced the intrinsic activity. At this time, the number of available substituted pyridylpiperazines remains limited due to a lack of efficient methodologies for introduction of diversity on the pyridine ring. The SN_{Ar} reactions between piperazine and halogenopyridines require vigorous conditions (high temperatures, prolonged reaction times) sometimes conflicting with sensitive functionalities.[7] In addition, the Pd[8] or Ni-catalyzed[9] amination reactions which can be performed under milder conditions also sometimes hardly tolerate electrophilic substituents or protic moieties like alcohols.

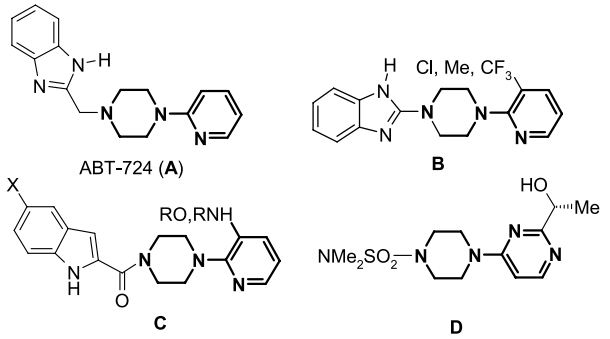

Figure 1. Pyridylpiperazines with important pharmacological activity.

A relatively unexplored route is the functionalization of the parent 2-, 3- and 4-pyridylpiperazines which are commercially available or easily prepared by literature procedures.[5] Our expertise in the field of selective lithiation of pyridine derivatives[10] and especially of aminosubstituted pyridines[11] drawn us to investigate the reaction of tritylated derivatives **1**–**3**[12] (Fig. 2) with the BuLi-LiDMAE (LiDMAE=$Me_2NCH_2CH_2OLi$) reagent developed in this laboratory.

The BuLi-LiDMAE reagent displays a strong affinity for pyridine nitrogen via chelation of lithium and promotes lithiation alpha to this atom. However, the piperazine nitrogens in **1**–**3** are also expected to chelate lithium cations and thus to compete with the target pyridine nitrogen for complexation of the lithiating agent. This was confirmed

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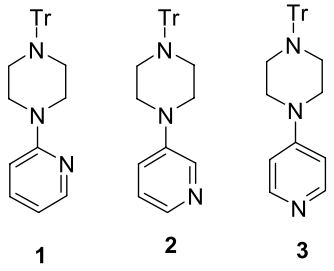


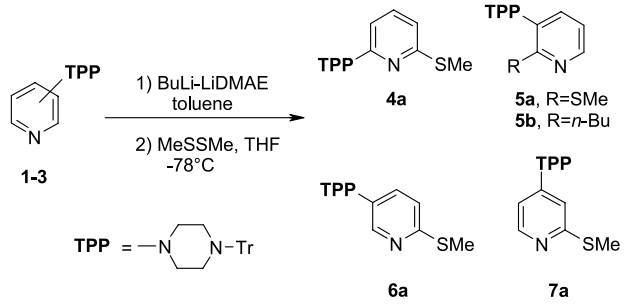
Figure 2. Tritylpiperazines used in metallation studies.

by our first attempts to metallate **1–3** with BuLi or LTMP. With these reagents, whatever the conditions, no reaction occurred and starting materials were fully recovered even when a large excess of base (up to 8 equiv) was used.[13] Thus it was hypothesized that a basic reagent containing a chelating agent like the BuLi-LiDMAE superbase might be able to favour complexation by pyridine nitrogen and promote selective metallation.

2. Results and discussion

Metallations with BuLi-LiDMAE are generally performed in hexane[14] but, as compounds **1–3** were sparingly soluble in this solvent, we turned to the more polar and also non complexing toluene. The substrates were reacted with BuLi-LiDMAE under various conditions and the reaction media were quenched with MeSSMe as electrophile (Table 1). In contrast with results obtained with BuLi, all substrates could be selectively lithiated alpha to pyridine nitrogen with BuLi-LiDMAE clearly demonstrating the role of lithium aminoalkoxide into the lithiation process. However, due to expected complexation by piperazine nitrogens, 8 equiv of reagent were necessary to achieve complete metallation. The ideal metallation temperature was found to be different for the three isomers. While **3** was efficiently lithiated at 0 °C, **1** was found inert at such temperature and warming to 20 °C was required to realize the reaction. Substrate **2** was found to be more sensitive since nucleophilic addition of BuLi was observed above −78 °C. In contrast, nucleophilic addition never occurred with **1** or **3**. Moreover, while compound **5a** was formed as a single product at −78 °C, formation of isomer **6a** was obtained in notable amount at 0 or −40 °C. From this, it appeared that the kinetic product was likely at C-2 and the thermodynamic product rather at C-6. Unfortunately we did not succeed in finding conditions able of forming exclusively compound **6a**.

Table 1. Lithiation of **1–3** with BuLi-LiDMAE[a]

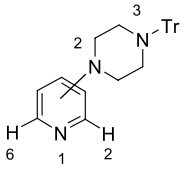


Substrate	Base (equiv)	T (°C)	Product, yield (%)[b]
1	4–8	0	n.r.
	4	20	**4a**, 40
	8	20	**4a**, 90
2	4	0	n.r.
	6	0	**5a**, 10
	8	0	**5a** (5)[c] + **5b** (60)[c] + **6a** (35)[c]
	8	−40	**5a** (40)[c] + **5b** (30)[c] + **6a** (30)[c]
	8	−78	**5a**, 90
3	4	0	**7a**, 45
	6	0	**7a**, 70
	8	0	**7a**, 91

[a] All reactions performed on 0.5 mmol of **1–3**.
[b] Isolated yields.
[c] Ratios determined by ^{1}H NMR.

We performed charge calculations in the three isomers to explore the possible reasons behind the different chelating ability of nitrogens and the relevant protons acidities (Table 2).

Table 2. Calculated Mulliken charges[a]



Substrate	N-1	N-2	N-3	H-2	H-6
1	−0.1489	0.0102	−0.0980	—	0.2057
2	−0.0652	0.0091	−0.0984	0.2154	0.2132
3	−0.1334	0.0036	−0.0981	0.2061	0.2061
Pyridine	−0.0987	—	—	0.2108	0.2108

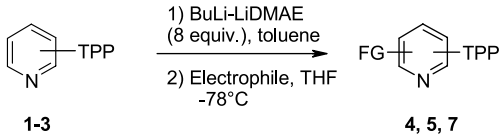
[a] Calculations performed using semi-emprical PM3 method.

The first observation was the expected increase of pyridine nitrogen electronegativity by incorporation of piperazine at C-2 or C-4 with a larger effect at C-2. On the contrary, piperazine at C-3 decreased notably the electronegativity of N-1. For all three compounds, the N-3 nitrogen had a notable electronegativity, supporting an ability to chelate lithium ions. The electronic influence of the piperazine moiety on the pyridine protons acidities was also assessed by comparison with pyridine itself, where it was revealed that with the substituted analogs (**1–3**), the piperazine at C-2 or C-4 decreased the charge on protons alpha to nitrogen while piperazine at C-3 induced a slight increase. Since these charge values reflected proton acidities, the following order of acidity can be established: **1–3** < **2**.

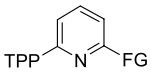
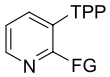
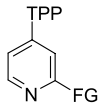
From our knowledge, this is the first reported direct lithiation of the pyridine ring of pyridylpiperazines. We further demonstrated this methodology for the preparation of addition derivatives by reaction with a set of electrophiles. Applying the best conditions found previously (Table 1), an array of pyridyl halides, alcohols and ketones was prepared in good to excellent yields (Table 3).

Derivatives **5a** and **7b** bearing base compatible

Table 3. Monofuntionalization of **1–3**[a]

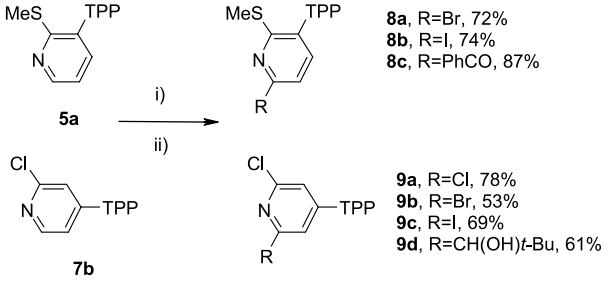


1-3 **4, 5, 7**

Electrophile	FG			
C_2Cl_6	Cl	**4b**, 95%	**5c**, 90%	**7b**, 89%
CBr_4	Br	**4c**, 95%	**5d**, 90%	**7c**, 95%
I_2	I	**4d**, 89%	**5e**, 80%	**7d**, 77%
$PhCONMe_2$	COPh	**4e**, 70%	—[b]	**7e**, 62%
t-BuCOCl	CO*t*-Bu	**4f**, 65%	**5f**, 50%	**7f**, 81%
t-BuCHO	CH(OH)*t*-Bu	**4g**, 60%	**5g**, 72%	**7g**, 65%

[a] All reactions performed on 0.5 mmol of **1–3**. All yields are given for isolated compounds.
[b] Reaction not performed.

substituents[15] were of particular interest since they could be lithiated at the other pyridine alpha carbon allowing further introduction of diversity. These substrates were then treated with the superbase at 0 °C to produce the 2,6-difunctional derivatives in excellent yields (Scheme 1). The high basicity and low nucleophilicity of the BuLi-LiDMAE superbase was therefore shown to be compatible with analogs containing synthetically useful C–Cl and C–SMe bonds.



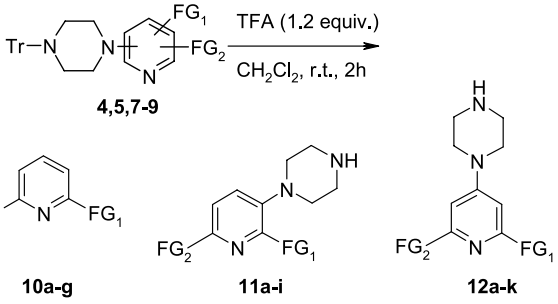
Scheme 1. Bis-functionalization. Conditions: (i) BuLi-LiDMAE (8 equiv), toluene, −20 °C, 1 h. (ii) CBr_4 or I_2 or $PhCONMe_2$ or C_2Cl_6 or *t*-BuCHO (9 equiv), THF, −78 to −20 °C, 1 h.

To liberate the free piperazines, detritylation was effected by treatment of products with a stoichiometric amount of TFA in dichloromethane at room temperature (Table 4). In all cases, the deprotection proceeded quantitatively affording a library of polyfunctional pyridylpiperazines which the free piperazine NH was available for introduction of, for example, benzimidazoles (see Fig. 1).

3. Conclusion

For the fist time, the three isomers of pyridylpiperazines have been selectively mono- and bis-functionalized on the carbon alpha to the pyridine nitrogen by use of a BuLi-LiDMAE superbase used in excess. The generality of the method was demonstrated by the synthesis of a wide variety of functionalized pyridylpiperazines. We believe this represents a new efficient methodology for chemical modification of pyridylpiperazines an important class of biologically active compounds.

Table 4. Regeneration of free pyridylpiperazines[a]



FG_1	FG_2	Product, yield (%)[b]		
SMe		**10a**, >99	**11a**, 95	**12a**, >99
Cl	—	**10b**, >99	**11b**, 96	**12b**, >99
Br	—	**10c**, >99	**11c**, >99	**12c**, >99
I	—	**10d**, >99	**11d**, >99	**12d**, >99
COPh	—	**10e**, 90	—	**12e**, 80
CO*t*-Bu	—	**10f**, 85	**11e**, 90	**12f**, 80
CH(OH)*t*-Bu	—	**10g**, 85	**11f**, 93	**12g**, 70[c]
Cl	Cl	—	—	**12h**, >99
Cl	Br	—	—	**12i**, >99
Cl	I	—	—	**12j**, >99
Cl	CH(OH)*t*-Bu	—	—	**12k**, 60
SMe	Br	—	**11g**, 97	—
SMe	I	—	**11h**, 91	—
SMe	COPh	—	**11i**, 75[c]	—

[a] All reactions performed on 0.25 mmol of tritylpiperazine.
[b] All reactions were found complete (TLC) and products obtained in pure form after basic aqueous work-up. The lack of material with oxygen-containing compounds was due to a partial solubility in water.

4. Experimental

4.1. General

All solvents were distilled and stored over sodium wire before use. 2-Dimethylaminoethanol was distilled under nitrogen and stored on molecular sieves. *n*-BuLi was used as

a 1.6 M solution in hexanes. All other reagents were commercially available and used as such. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker AC400 instrument at 200, 50 MHz, respectively. GC/MS (EI) were obtained on HP5971 spectrometer. Starting 2- and 4-pyridylpiperazines are commercially available. 3-Pyridylpiperazine was prepared by catalyzed amination of 3-bromopyridine according to a literature procedure.[5]

4.2. Preparation of tritylpyridylpiperazines 1–3

A mixture of the appropriate pyridylpiperazine (10 g, 61 mmol) triphenylmethyl chloride (20.5 g, 73 mmol) and triethylamine (7.5 g, 73 mmol) in DMF (50 mL) was stirred for 6 h at 20 °C for isomers **1** and **2** or at 100 °C for isomer **3**. The mixture was then filtered and the solid was washed with THF. The filtrate was evaporated under vacuum and the crude product purified by chromatography on silica gel using AcOEt/hexane as eluent.

4.2.1. (2-Pyridyl)-4-trityl-1-piperazine (1). Column chromatography (70/30 hexane/AcOEt) yielded 23.3 g (94%) of **1** as a light yellow solid. Mp: 200 °C. NMR ^{1}H ($CDCl_3$): δ=2.42 (s, 4H), 3.64 (s, 4H), 6.58 (m, 2H), 7.12–7.31 (m, 10H), 7.39–7.54 (m, 6H), 8.15 (d, J=6.5 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=45.8, 47.7, 76.9, 106.9, 113.1, 126.1, 127.5, 129.3, 137.3, 142.3, 147.7, 159.7.

4.2.2. (3-Pyridyl)-4-trityl-1-piperazine (2). Column chromatography (70/30 hexane/AcOEt) yielded 22 g (88%) of **2** as a light yellow solid. NMR ^{1}H ($CDCl_3$): δ=2.47 (m, 4H), 3.34 (t, J=4.8 Hz, 4H), 7.11–7.31 (m, 11H), 7.49–7.53 (m, 6H), 8.06 (d, J=3.1 Hz, 1H), 8.26 (s, 1H). NMR ^{13}C ($CDCl_3$): δ=47.7, 48.9, 77.0, 121.9, 123.5, 126.3, 127.7, 129.4, 138.1, 140.5, 142.8, 147.0.

4.2.3. (4-Pyridyl)-4-trityl-1-piperazine (3). Column chromatography (70/30 hexane/AcOEt) yielded 21 g (84%) of **3** as a light yellow solid. Mp: 204 °C. NMR ^{1}H ($CDCl_3$): δ=2.43 (m, 4H); 3.42 (t, J=4.8 Hz, 4H); 6.60 (d, J=5.8 Hz, 2H); 7.10–7.30 (m, 9H); 7.53 (d, J=7.2 Hz, 6H); 8.24 (d, J=5.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.6, 47.6, 77.0, 108.2, 126.4, 127.8, 129.4, 142.2, 150.1, 155.2.

4.3. Monofunctionalisation of tritylpyridylpiperazines

n-Butyllithium (4.92 mL, 7.87 mmol) was added dropwise to a solution of 2-dimethylaminoethanol (0.35 g, 3.93 mmol) in toluene (10 mL) at −5 °C. After 15 min of stirring, the mixture was allowed to warm to 20 °C for isomer **1**, cooled to −5 °C for isomer **3** or cooled to −78 °C for isomer **2**. A solution of **1**, **2** or **3** (0.2 g, 0.50 mmol) in toluene (2 mL) was then added dropwise. The solution was then stirred for 2.5 h at the same temperature then treated at −78 °C with a solution of the appropriate electrophile (9 mmol) in THF (10 mL). The temperature was maintained at −78 °C for 1 h and at 0 °C for 30 min. Hydrolysis was then performed at this temperature with water (3 mL). The reaction medium was then evaporated under vacuum and the crude product was purified by chromatography on silica gel using AcOEt/hexane as eluent.

4.3.1. ((6-Methylsulfanyl)-2-pyridyl)-4-trityl-1-piperazine (4a). Column chromatography (80/20 hexane/AcOEt) yielded 200 mg (90%) of **4a** as an oil. NMR ^{1}H ($CDCl_3$): δ=1.91 (s, 3H), 2.39 (m, 4H), 3.59 (m, 4H), 6.14 (d, J=8.2 Hz, 1H), 6.44 (d, J=7.5 Hz, 1H), 7.1–7.3 (m, 10H), 7.49–7.53 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=38.2, 45.4, 47.6, 76.9, 101.3, 110.1, 126.1, 127.5, 129.2, 137.2, 142.1, 157.2, 159.0.

4.3.2. ((2-Methylsulfanyl)-3-pyridyl)-4-trityl-1-piperazine (5a). Column chromatography (80/20 hexane/AcOEt) yielded 200 mg (90%) of **5a** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.25 (s, 3H), 2.32 (m, 4H), 3.00 (t, J=4.7 Hz, 4H), 6.72–6.78 (m, 1H), 6.93–7.13 (m, 10H), 7.37–7.41 (m, 6H), 8.01 (d, J=4.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=12.4, 47.9, 51.8, 76.7, 118.8, 125.2, 126.0, 127.5, 129.2, 142.4, 143.7, 145.9, 148.7.

4.3.3. ((2-Methylsulfanyl)-4-pyridyl)-4-trityl-1-piperazine (7a). Column chromatography (40/60 hexane/AcOEt) yielded 202 mg (91%) of as **7a** a light yellow solid. Mp: 193 °C. NMR ^{1}H ($CDCl_3$): δ=2.36 (m, 4H), 2.48 (s, 3H), 3.35 (t, J=4.8 Hz, 4H), 6.32 (dd, J=6.2 and 2.3 Hz, 1H), 6.45 (d, J=2.4 Hz, 1H), 7.12–7.27 (m, 9H), 7.45 (d, J=7.2 Hz, 6H), 8.04 (d, J=5.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=13.6, 46.6, 47.6, 77.1, 104.8, 105.5, 126.4, 127.8, 129.4, 141.9, 149.2, 155.2, 160.1.

4.3.4. ((6-Chloro)-2-pyridyl)-4-trityl-1-piperazine (4b). Column chromatography (80/20 hexane/AcOEt) yielded 206 mg (95%) of **4b** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.36 (m, 4H), 3.59 (m, 4H), 6.33 (d, J=8.2 Hz, 1H), 6.50 (d, J=7.5 Hz, 1H), 7.08–7.3 (m, 10H), 7.47–7.51 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=45.5, 47.6, 76.9, 105.1, 111.9, 126.2, 127.6, 129.3, 139.4, 142.3, 149.4, 159.2.

4.3.5. ((2-Chloro)-3-pyridyl)-4-trityl-1-piperazine (5b). Column chromatography (80/20 hexane/AcOEt) yielded 195 mg (90%) of **5b** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.24 (m, 4H), 3.07 (t, J=4.7 Hz, 4H), 6.93–7.49 (m, 18H), 8.06 (d, J=4.4 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.1, 56.0, 76.0, 123.1, 126.0, 127.5, 128.0, 129.2, 142.1, 142.8, 146.3, 156.2.

4.3.6. ((2-Chloro)-4-pyridyl)-4-trityl-1-piperazine (7b). Column chromatography (40/60 hexane/AcOEt) yielded 193 mg (89%) of **7b** as a light yellow solid. Mp: 191 °C. NMR ^{1}H ($CDCl_3$): δ=2.32 (m, 4H), 3.25 (t, J=4.8 Hz, 4H), 6.37 (d, J=6.2 Hz, 1H), 6.46 (s, 1H), 7.08–7.27 (m, 9H), 7.49 (d, J=7.2 Hz, 6H), 7.89 (d, J=6.0 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=45.9, 47.1, 76.6, 106.7, 106.8, 126.1, 127.5, 128.9, 141.8, 149.0, 152.2, 156.5.

4.3.7. ((6-Bromo)-2-pyridyl)-4-trityl-1-piperazine (4c). Column chromatography (80/20 hexane/AcOEt) yielded 226 mg (95%) of **4c** as a light yellow solid. Mp: 75 °C. NMR ^{1}H ($CDCl_3$): δ=2.37 (m, 4H), 3.62 (m, 4H), 6.41 (d, J=8.5 Hz, 1H), 6.67 (d, J=7.2 Hz, 1H), 7.21–7.51 (m, 16H). NMR ^{13}C ($CDCl_3$): δ=45.4, 47.5, 76.8, 104.5, 115.7, 126.1, 127.5, 129.2, 135.5, 139.2, 14, 159.2.

4.3.8. ((2-Bromo)-3-pyridyl)-4-trityl-1-piperazine (5c). Column chromatography (80/20 hexane/AcOEt) yielded

214 mg (90%) of **5c** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.12 (m, 4H), 3.22 (m, 4H), 7.13–7.25 (m, 11H), 7.48–7.52 (m, 6H), 7.97 (d, J=4.4 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=47.9, 52.0, 76.7, 123.2, 126.1, 127.7, 128.1, 129.2, 139.5, 142.8, 143.4, 147.7.

4.3.9. ((2-Bromo)-4-pyridyl)-4-trityl-1-piperazine (7c). Column chromatography (40/60 hexane/AcOEt) yielded 226 mg (95%) of **7c** as a light yellow solid. Mp: 168 °C. NMR ^{1}H ($CDCl_3$): δ=2.40 (m, 4H), 3.39 (t, J=4.8 Hz, 4H), 6.50 (d, J=5.8 Hz, 1H), 6.72 (d, J=1.2 Hz, 1H), 7.16–7.31 (m, 9H), 7.49 (d, J=7.6 Hz, 6H), 7.92 (d, J=6.2 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.4, 47.5, 77.0, 107.5, 110.9, 126.4, 127.8, 129.3, 142.1, 143.4, 149.7, 156.6.

4.3.10. ((6-Iodo)-2-pyridyl)-4-trityl-1-piperazine (4d). Column chromatography (80/20 hexane/AcOEt) yielded 233 mg (89%) of **4d** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.36 (m, 4H), 3.56 (m, 4H), 6.37–6.41 (m, 1H), 6.88–6.93 (m, 2H), 7.20–7.27 (m, 9H), 7.47–7.50 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=45.3, 47.5, 76.8, 104.9, 123.0, 126.1, 127.5, 129.2, 138.3, 141.6, 154.5, 159.1.

4.3.11. ((2-Iodo)-3-pyridyl)-4-trityl-1-piperazine (5d). Column chromatography (80/20 hexane/AcOEt) yielded 209 mg (80%) of **5d** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.03 (m, 4H), 3.18 (m, 4H), 7.13–7.31 (m, 11H), 7.43–7.53 (m, 6H), 8.04 (d, J=3.9 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=47.9, 52.8, 76.9, 123.2, 126.2, 127.6, 129.4, 131.0, 142.3, 145.1, 146.9, 150.8.

4.3.12. ((2-Iodo)-4-pyridyl)-4-trityl-1-piperazine (7d). Column chromatography (40/60 hexane/AcOEt) yielded 201 mg (77%) of **7d** as a light yellow solid. Mp: 183 °C. NMR ^{1}H ($CDCl_3$): δ=2.35 (m, 4H), 3.31 (t, J=4.8 Hz, 4H), 6.48 (d, J=6.2 Hz, 1H), 6.93 (d, J=2.4 Hz, 1H), 7.11–7.29 (m, 9H), 7.48 (d, J=7.6 Hz, 6H), 7.87 (d, J=6.2 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.2, 47.4, 77.2, 107.8, 117.9, 119.5, 126.4, 127.7, 129.2, 142.1, 150.0, 155.6.

4.3.13. ((6-Phenyl-methanone)-2-pyridyl)-4-trityl-1-piperazine (4e). Column chromatography (80/20 hexane/AcOEt) yielded 175 mg (70%) of **4e** as a light yellow solid. Mp: 75 °C. NMR ^{1}H ($CDCl_3$): δ=2.40 (m, 4H), 3.64 (m, 4H), 6.79 (d, J=8.6 Hz, 1H), 7.11–7.31 (m, 14H), 7.51–7.65 (m, 8H). NMR ^{13}C ($CDCl_3$): δ=45.7, 47.8, 76.6, 109.4, 113.7, 125.5, 128.0, 128.1, 128.5, 129.2, 132.3, 135.0, 141.2, 143.4, 159.2, 168.4, 187.5.

4.3.14. ((2-Phenyl-methanone)-4-pyridyl)-4-trityl-1-piperazine (7e). Column chromatography (40/60 hexane/AcOEt) yielded 155 mg (62%) of **7e** as a light yellow solid. Mp: 139 °C. NMR ^{1}H ($CDCl_3$): δ=2.43 (m, 4H), 3.44 (m, 4H), 6.72 (d, J=2.4 Hz, 1H), 7.07–7.54 (m, 13H), 7.93–8.02 (m, 8H). 8.32 (d, J=6.0 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.5, 47.6, 77.2, 108.8, 113.0, 125.6, 128.1, 128.3, 128.5, 129.2, 133.0, 135.0, 141.4, 154.5, 155.7, 160.8, 187.5.

4.3.15. ((6-(2,2-Dimethyl-propan-1-one))-2-pyridyl)-4-trityl-1-piperazine (4f). Column chromatography (80/20 hexane/AcOEt) yielded 156 mg (65%) of **4f** as an oil. NMR 1H (CDCl3): δ=1.18 (s, 9H), 2.43 (m, 4H), 3.63 (m, 4H), 6.66 (d, J=8.6 Hz, 1H), 7.09–7.31 (m, 11H), 7.45–7.58 (m, 6H). NMR 13C (CDCl3): δ=26.4, 44.9, 45.9, 47.7, 77.0, 109.4, 113.2, 126.2, 127.6, 129.3, 137.9, 141.6, 152.7, 157.8, 207.0.

4.3.16. ((2-(2,2-Dimethyl-propan-1-one))-3-pyridyl)-4-trityl-1-piperazine (5f). Column chromatography (80/20 hexane/AcOEt) yielded 120 mg (50%) of **5f** as an oil. NMR 1H (CDCl3): δ=1.02 (s, 9H), 2.18 (m, 4H), 3.00 (m, 4H), 6.99–7.30 (m, 11H), 7.52–7.64 (m, 6H), 8.57 (d, J=4.4 Hz, 1H). NMR 13C (CDCl3): δ=27.4, 41.5, 47.5, 55.3, 76.9, 122.4, 126.2, 127.6, 129.4, 131.0, 142.3, 145.1, 146.9, 150.8, 207.4.

4.3.17. ((2-(2,2-Dimethyl-propan-1-one))-4-pyridyl)-4-trityl-1-piperazine (7f). Column chromatography (40/60 hexane/AcOEt) yielded 195 mg (81%) of **7f** as a light yellow solid. Mp: 68 °C. NMR ^{1}H ($CDCl_3$): δ=1.41 (s, 9H), 2.39 (m, 4H), 3.39 (m, 4H), 6.59 (s, 2H), 7.24 (s, 9H), 7.48 (s, 6H), 8.20 (s, 1H). NMR ^{13}C ($CDCl_3$): δ=27.5, 44.1, 46.2, 47.4, 76.8, 107.8, 109.5, 126.3, 127.6, 129.1, 142.0, 147.0, 148.3, 155.5, 207.7.

4.3.18. ((6-(2,2-Dimethylpropyl-1-hydroxy))-2-pyridyl)-4-trityl-1-piperazine (4g). Column chromatography (80/20 hexane/AcOEt) yielded 145 mg (60%) of **4g** as an oil. NMR ^{1}H ($CDCl_3$): δ=0.88 (s, 9H), 2.44 (m, 4H), 3.61 (m, 4H), 4.16 (s, 1H), 6.44–6.48 (m, 2H), 7.15–7.27 (m, 9H), 7.50–7.55 (m, 7H). NMR ^{13}C ($CDCl_3$): δ=26.0, 36.2, 45.8, 47.8, 77.0, 79.9, 105.5, 112.3, 126.2, 127.6, 129.4, 137.1, 142.1, 157.5, 158.3.

4.3.19. ((2-(2,2-Dimethylpropyl-1-hydroxy))-3-pyridyl)-4-trityl-1-piperazine (5g). Column chromatography (80/20 hexane/AcOEt) yielded 174 mg (72%) of **5g** as an oil. NMR ^{1}H ($CDCl_3$): δ=0.75 (s, 9H), 2.13 (m, 4H), 3.22 (m, 4H), 4.09 (s, 1H), 7.06–7.29 (m, 11H), 7.50–7.56 (m, 6H), 8.27 (d, J=4.4 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=26.0, 37.1, 45.9, 47.8, 60.2, 76.5, 122.5, 126.0, 127.5, 128.7, 129.2, 142.1, 143.7, 147.0, 157.1.

4.3.20. ((2-(2,2-Dimethylpropyl-1-hydroxy))-4-pyridyl)-4-trityl-1-piperazine (7g). Column chromatography (40/60 hexane/AcOEt) yielded 157 mg (65%) of **7g** as a light yellow solid. Mp: 158 °C. NMR ^{1}H ($CDCl_3$): δ=0.90 (s, 9H), 2.29 (m, 4H), 3.36 (m, 4H), 4.18 (s, 1H), 4.71 (s, 1H), 6.44 (d, J=6.2 Hz, 1H), 6.49 (s, 1H), 7.09–7.28 (m, 9H), 7.50 (d, J=7.6 Hz, 6H), 8.10 (d, J=6.0 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=26.0, 36.0, 46.5, 47.4, 76.9, 80.5, 106.8, 107.1, 126.3, 127.6, 129.1, 142.2, 147.8, 154.0, 160.5.

4.4. Bis-functionalisation of tritylpyridylpiperazines

The second functionalisation was performed under conditions described in Section 4.3 except that the metallation step was performed at −20 °C for 2.5 h.

4.4.1. ((2-Bromo-6-methylsulfanyl)-3-pyridyl)-4-trityl-1 piperazine (8a). Column chromatography (90/10 hexane/AcOEt) yielded 169 mg (72%) of **8a** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.20 (s, 3H), 2.38 (m, 4H), 3.12 (m, 4H), 7.10–7.30 (m, 11H), 7.49–7.52 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=

13.1, 47.9, 51.7, 76.8, 122.6, 126.1, 127.6, 128.8, 129.4, 134.5, 142.6, 145.1, 157.0.

4.4.2. ((2-Iodo-6-methylsulfanyl)-3-pyridyl)-4-trityl-1-piperazine (8b). Column chromatography (90/10 hexane/AcOEt) yielded 189 mg (74%) of **8b** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.32 (s, 3H), 2.38 (m, 4H), 3.09 (m, 4H), 6.83 (d, J=8.2 Hz, 1H), 7.08–7.31 (m, 10H), 7.42–7.59 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=13.1, 47.8, 51.5, 76.7, 108.9, 122.6, 126.1, 127.6, 128.3, 129.3, 142.4, 145.6, 157.3.

4.4.3. ((2-Methylsulfanyl-6-phenyl-methanone)-3-pyridyl)-4-trityl-1-piperazine (8c). Column chromatography (90/10 hexane/AcOEt) yielded 214 mg (87%) of **8c** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.22 (s, 3H), 2.36 (m, 4H), 3.12 (m, 4H), 7.10–7.30 (m, 16H), 7.49–7.52 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=14.1, 47.8, 51.8, 76.5, 118.4, 122.6, 125.5, 127.6, 128.1, 128.4, 129.5, 132.2, 135.4, 141.4, 145.5, 150.3, 156.1, 187.6.

4.4.4. ((2,6-Dichloro)-4-pyridyl)-4-trityl-1-piperazine (9a). Column chromatography (20/80 hexane/AcOEt) yielded 168 mg (78%) of **9a** as a light yellow solid. Mp: 202 °C. NMR ^{1}H ($CDCl_3$): δ=2.40 (m, 4H), 3.42 (t, J=4.8 Hz, 4H), 6.51 (s, 2H), 7.17–7.32 (m, 9H), 7.49 (d, J=7.2 Hz, 6H). NMR ^{13}C ($CDCl_3$): δ=46.6, 47.4, 77.2, 106.1, 126.5, 127.8, 129.3, 141.9, 151.1, 158.0.

4.4.5. ((2-Bromo-6-chloro)-4-pyridyl)-4-trityl-1-piperazine (9b). Column chromatography (40/60 hexane/AcOEt) yielded 125 mg (53%) of **9b** as a light yellow solid. Mp: 112 °C. NMR ^{1}H ($CDCl_3$): δ=2.39 (m, 4H), 3.40 (t, J=4.8 Hz, 4H), 6.52 (d, J=1.8 Hz, 1H), 6.67 (d, J=1.8 Hz, 1H), 7.14–7.31 (m, 9H), 7.48 (d, J=7.2 Hz, 6H). NMR ^{13}C ($CDCl_3$): δ=46.8, 47.5, 77.0. 106.7, 110.2, 126.4, 127.6, 129.6, 142.0, 151.4, 158.0, 163.4.

4.4.6. ((2-Chloro-6-iodo)-4-pyridyl)-4-trityl-1-piperazine (9c). Column chromatography (40/60 hexane/AcOEt) yielded 177 mg (69%) of **9c** as a light yellow solid. Mp: 156 °C. NMR ^{1}H ($CDCl_3$): δ=2.40 m, 4H), 3.39 (t, J=5.2 Hz, 4H), 6.54 (d, J=2.0 Hz, 1H), 6.93 (s, 1H), 7.14–7.31 (m, 9H), 7.49 (d, J=7.2 Hz, 6H). NMR ^{13}C ($CDCl_3$): δ=46.5, 47.5, 77.2, 106.8, 116.2, 117.4, 126.5, 127.9, 129.3, 150.8, 156.9, 163.4.

4.4.7. ((2-Chloro-6-(2,2-dimethylpropyl-1-hydroxy))-4-pyridyl)-4-trityl-1-piperazines (7b). Column chromatography (40/60 hexane/AcOEt) yielded 145 mg (61%) of **7b** as a light yellow solid. Mp: 181 °C. NMR ^{1}H ($CDCl_3$): δ=0.88 (s, 9H), 2.41 (m, 4H), 3.40 (t, J=4.8 Hz, 4H), 4.12 (s, 1H), 6.41 (s, 1H), 6.49 (s, 1H), 7.17–7.31 (m, 9H), 7.50 (m, 6H). NMR ^{13}C ($CDCl_3$): δ=26.1, 36.1, 46.7, 47.5, 77.2, 80.8, 105.9, 106.1, 126.4, 127.8, 129.2, 142.1, 151.0, 156.8, 160.9.

4.5. Regeneration of free pyridylpiperazines

A solution of TFA (1 mL of a 25% solution in CH_2Cl_2, 1.2 equiv) was added to a solution of the tritylpyridylpiperazine (0.25 mmol) in dichloromethane (5 mL) at rt for 0.5 h. The solution was then extracted thrice with water and treated with a solution of satured Na_2CO_3 in order to obtain a pH >7. The solution was then extracted thrice with CH_2Cl_2. Evaporation of solvent under vacuum gave the free pyridylpiperazine in pure form.

4.5.1. ((6-Methylsulfanyl)-2-pyridyl)-1-piperazine (10a). Yielded 52 mg (>99%) of **10a** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.49 (s, 3H), 3.22 (t, J=4.9 Hz, 4H), 3.78 (t, J=4.9 Hz, 4H), 6.36 (d, J=8.2 Hz, 1H), 6.60 (d, J=7.5 Hz, 1H), 7.36 (t, J=8.0 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=22.2, 42.7, 45.2, 101.9, 111.1, 137.6, 157.7, 176.8. MS (EI) *m/z* (rel. int.): 209 (59, M+), 167 (92), 153 (100), 141 (72), 124 (14), 109 (14), 79 (12), 78 (12), 56 (25).

4.5.2. ((2-Methylsulfanyl)-3-pyridyl)-1-piperazine (11a). Yielded 49 mg (95%) of **11a** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.10 (s, 1H), 2.51 (s, 3H), 2.90–2.98 (m, 4H), 3.01–3.08 (m, 4H), 6.97 (t, J=4.8 Hz, 1H), 7.19 (d, J=7.8 Hz, 1H), 8.19 (d, J=4.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=12.5, 46.1, 52.3, 118.9, 125.2, 138.0, 143.8, 146.0. MS (EI) *m/z* (rel. int.): 209 (56, M+), 167 (78), 162 (100), 152 (55), 119 (18), 92 (11), 78 (21), 56 (22).

4.5.3. ((2-Methylsulfanyl)-4-pyridyl)-1-piperazine (12a). Yielded 52 mg (>99%) of **12a** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.53 (s, 3H), 3.06 (t, J=4.8 Hz, 4H), 3.37 (t, J=4.8 Hz, 4H), 6.45 (dd, J=6.2 Hz, 1H), 6.56 (d, J=2.4 Hz, 1H), 8.13 (d, J=5.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=13.6, 44.2, 45.8, 105.1, 105.8, 149.5, 154.9, 160.5. MS (EI) *m/z* (rel. int.): 209 (51, M+), 167 (100), 151 (17), 106 (18), 79 (21), 56 (37).

4.5.4. ((6-Chloro)-2-pyridyl)-1-piperazine (10b). Yielded 49 mg (>99%) of **10b** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.00 (s, 1H), 3.24 (t, J=5.6 Hz, 4H), 3.79 (t, J=5.1 Hz, 4H), 6.72 (m, 2H), 7.55 (t, J=6.5 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=42.5, 45.0, 107.3, 114.3, 142.5, 147.6, 158.1. MS (EI) *m/z* (rel. int.): 197 (30, M+), 155 (100), 141 (39), 129 (38), 113 (25), 78 (15), 56 (14).

4.5.5. ((2-Chloro)-3-pyridyl)-1-piperazine (11b). Yielded 47 mg (96%) of **11b** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.24 (s, 1H), 3.03–3.15 (m, 8H), 7.17–7.35 (m, 2H), 8.05 (d, J=4.3 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.1, 52.0, 123.1, 127.3, 128.1, 142.8, 146.3. MS (EI) *m/z* (rel. int.): 197 (15, M+), 162 (71), 155 (100), 140 (16), 78 (27), 76 (12), 56 (38).

4.5.6. ((2-Chloro)-4-pyridyl)-1-piperazine (12b). Yielded 49 mg (>99%) of **12b** as an oil. NMR ^{1}H ($CDCl_3$): δ=3.05 (t, J=4.9 Hz, 4H), 3.35 (t, J=4.8 Hz, 4H), 6.40 (d, J=6.2 Hz, 1H), 6.48 (s, 1H), 7.89 (d, J=5.9 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=45.9, 47.1, 106.7, 106.8, 149.0, 152.2, 156.5. MS (EI) *m/z* (rel. int.): 197 (27, M+), 155 (100), 139 (13), 112 (7), 56 (13).

4.5.7. ((6-Bromo)-2-pyridyl)-1-piperazine (10c). Yielded 60 mg (>99%) of **10c** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.48 (s, 1H), 2.95 (t, J=5.1 Hz, 4H), 3.51 (t, J=4.8 Hz, 4H), 6.50 (d, J=8.2 Hz, 1H), 6.73 (d, J=7.2 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=42.7, 45.3, 104.8, 116.0, 139.5, 142.8, 159.4. MS (EI) *m/z* (rel. int.): 243 (31, M+), 241 (33), 199 (100), 158 (26), 157 (25), 105 (17), 78 (26), 56 (25).

4.5.8. ((2-Bromo)-3-pyridyl)-1-piperazine (11c). Yielded 60 mg (>99%) of **11c** as an oil. NMR ^{1}H ($CDCl_3$): δ= 3.09–3.17 (m, 8H), 4.22 (s, 1H), 7.25–7.36 (m, 2H), 8.08 (d, J=4.4 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=45.5, 51.5, 123.1, 128.8, 139.9, 144.0, 147.8. MS (EI) *m/z* (rel. int.): 243 (7, M+), 241 (8), 201 (35), 199 (36), 162 (100), 105 (9), 78 (34), 56 (20).

4.5.9. ((2-Bromo)-4-pyridyl)-1-piperazine (12c). Yielded 60 mg (>99%) of **12c** as an oil. NMR ^{1}H ($CDCl_3$): δ=3.04 (t, J=4.8 Hz, 4H), 3.35 (t, J=4.8 Hz, 4H), 6.62 (dd, J= 6.0 Hz, 1H), 6.82 (d, J=6.2 Hz, 1H), 7.99 (d, J=6.2 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=44.7, 46.3, 107.8, 111.2, 143.4, 149.8, 156.5. MS (EI) *m/z* (rel. int.): 243 (22, M+), 241 (23), 201 (99), 199 (100), 105 (33), 56 (40).

4.5.10. ((6-Iodo)-2-pyridyl)-1-piperazine (10d). Yielded 72 mg (>99%) of **10d** as an oil. NMR ^{1}H ($CDCl_3$): δ=1.98 (s, 1H), 2.95 (t, J=4.1 Hz, 4H), 3.50 (t, J=4.1 Hz, 4H), 6.52 (d, J=7.5 Hz, 1H), 7.55 (m, 2H). NMR ^{13}C ($CDCl_3$): δ=42.8, 45.9, 105.2, 113.3, 123.3, 138.7, 168.0. MS (EI) *m/z* (rel. int.): 289 (23, M+), 247 (51), 233 (33), 221 (100), 120 (20), 105 (27), 78 (25), 56 (40).

4.5.11. ((2-Iodo)-3-pyridyl)-1-piperazine (11d). Yielded 72 mg (>99%) of **11d** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.00 (s, 1H), 2.99 (t, J=3.1 Hz, 4H), 3.10 (t, J=5.1 Hz, 4H), 7.20–7.30 (m, 2H), 8.08 (t, J=3.1 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=46.2, 53.4, 123.4, 127.9, 145.3, 146.3, 150.9. MS (EI) *m/z* (rel. int.): 289 (15, M+), 247 (33), 162 (100), 219 (14), 105 (15), 78 (35), 56 (25).

4.5.12. ((2-Iodo)-4-pyridyl)-1-piperazine (12d). Yielded 72 mg (>99%) of **12d** as an oil. NMR ^{1}H ($CDCl_3$): δ=3.00 (t, J=4.8 Hz, 4H), 3.31 (t, J=4.8 Hz, 4H), 4.23 (s, 1H), 6.62 (dd, J=6.2 Hz, 1H), 7.05 (d, J=2.4 Hz, 1H), 7.93 (d, J=6.2 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=44.8, 46.2, 108.0, 118.1, 119.3, 150.0, 155.5. MS (EI) *m/z* (rel. int.): 288 (13, M+), 258 (55), 105 (50), 78 (33), 69 (68), 56 (100).

4.5.13. ((6-Phenyl-methanone)-2-pyridyl)-1-piperazine (10e). Yielded 60 mg (90%) of **10e** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.28 (s, 1H), 2.93 (t, J=4.1 Hz, 4H), 3.49 (t, J=3.1 Hz, 4H), 6.62 (d, J=8.9 Hz, 1H), 6.79 (d, J=8.5 Hz, 1H), 7.27–7.71 (m, 4H), 8.09 (d, J=7.2 Hz, 2H). NMR ^{13}C ($CDCl_3$): δ=45.6, 46.3, 109.5, 113.7, 127.6, 130.9, 132.3, 138.0, 147.7, 152.8, 158.1, 194.0. MS (EI) *m/z* (rel. int.): 267 (21, M+), 225 (40), 221 (43), 199 (100), 105 (94), 77 (59).

4.5.14. ((2-Phenyl-methanone)-4-pyridyl)-1-piperazine (12e). Yielded 53 mg (80%) of **12e** as an oil. NMR ^{1}H ($CDCl_3$): δ=1.97 (s, 1H), 3.16 (t, J=5.5 Hz, 4H), 3.53 (t, J=5.1 Hz, 4H), 6.83 (dd, J=2.7 Hz, 1H), 7.37–7.57 (m, 4H), 7.98 (d, J=6.8 Hz, 2H). 8.36 (d, J=5.9 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=43.7, 45.0, 109.1, 110.4, 128.1, 130.9, 133.0, 136.3, 149.3, 155.4, 173.9, 194.9. MS (EI) *m/z* (rel. int.): 267 (48, M+), 225 (100), 197 (12), 182 (7), 154 (7), 119 (12), 105 (29), 77 (36), 56 (10).

4.5.15. ((6-(2,2-Dimethyl-propan-1-one))-2-pyridyl)-1-piperazine (10f). Yielded 52 mg (85%) of **10f** as an oil. NMR ^{1}H ($CDCl_3$): δ=1.43 (s, 9H), 1.75 (s, 1H), 2.99 (t, J= 4.2 Hz, 4H), 3.51 (t, J=4.1 Hz, 4H), 6.75 (d, J=8.2 Hz, 1H), 7.22 (d, J=8.2 Hz, 1H), 7.56 (t, J=8.2 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=27.5, 43.2, 45.8, 46.5, 105.1, 109.6, 113.1, 137.9, 157.9, 207.0. MS (EI) *m/z* (rel. int.): 247 (14, M+), 205 (36), 191 (35), 179 (100), 162 (16), 148 (12), 108 (16), 78 (11), 56 (28).

4.5.16. ((2-(2,2-Dimethyl-propan-1-one))-3-pyridyl)-1-piperazine (11e). Yielded 55 mg (90%) of **11e** as an oil. NMR ^{1}H ($CDCl_3$): δ=1.13 (s, 9H), 1.85 (s, 1H), 2.82 (t, J= 4.8 Hz, 4H), 2.98 (t, J=4.1 Hz, 4H), 7.14–7.21 (m, 1H), 7.56 (d, J=7.2 Hz, 1H), 8.61 (d, J=4.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=27.6, 41.9, 47.1, 55.9, 122.6, 128.9, 146.8, 157.2, 164.0, 208.8. MS (EI) *m/z* (rel. int.): 247 (14, M+), 205 (41), 163 (70), 157 (74), 135 (85), 121 (100), 115 (74), 73 (61), 59 (88).

4.5.17. ((2-(2,2-Dimethyl-propan-1-one))-4-pyridyl)-1-piperazine (12f). Yielded 49 mg (80%) of **12f** as oil. NMR ^{1}H ($CDCl_3$): δ=1.42 (s, 9H), 2.98 (t, J=4.1 Hz, 4H), 3.32 (t, J=4.8 Hz, 4H), 4.84 (s, 1H), 6.69–6.73 (m, 1H), 7.25 (d, J=2.7 Hz, 1H), 8.26 (d, J=5.9 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=27.5, 44.2, 45.6, 46.9, 108.1, 109.8, 113.3, 148.6, 155.7, 208.2. MS (EI) *m/z* (rel. int.): 247 (9, M+); 232 (5); 205 (5); 163 (100); 120 (5); 105 (5); 79 (4); 56 (6).

4.5.18. ((6-(2,2-Dimethylpropyl-1-hydroxy))-2-pyridyl)-1-piperazine (10g). Yielded 52 mg (85%) of **10g** as oil. NMR ^{1}H ($CDCl_3$): δ=0.91 (s, 9H), 2.96 (t, J=4.5 Hz, 4H), 3.47 (t, J=2.7 Hz, 4H), 4.20 (s, 1H), 6.49 (d, J=3.8 Hz, 1H), 6.53 (d, J=4.8 Hz, 1H), 7.42 (t, J=7.2 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=26.0, 36.1, 45.7, 46.2, 80.0, 105.4, 112.2, 127.9, 137.1, 157.2. MS (EI) *m/z* (rel. int.): 249 (22, M+); 192 (49); 181 (90); 163 (71); 149 (100); 135 (35); 121 (27); 107 (22); 78 (46); 56 (40).

4.5.19. ((2-(2,2-Dimethylpropyl-1-hydroxy))-3-pyridyl)-1-piperazine (11f). Yielded 57 mg (93%) of **11f** as an oil. NMR ^{1}H ($CDCl_3$): δ=0.92 (s, 9H), 2.92–3.12 (m, 8H), 4.85 (s, 1H), 7.14–7.22 (m, 1H), 7.46 (d, J=8.2 Hz, 1H), 8.33 (d, J=4.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=27.1, 31.6, 46.3, 47.1, 76.1, 122.7, 128.7, 143.8, 147.6, 157.1. MS (EI) *m/z* (rel. int.): 249 (26, M+), 192 (100), 174 (53), 145 (46), 107 (30), 79 (43), 56 (29).

4.5.20. ((2-(2,2-Dimethylpropyl-1-hydroxy))-4-pyridyl)-1-piperazine (12g). Yielded 43 mg (70%) of **12g** as an oil. NMR ^{1}H ($CDCl_3$): δ=0.92 (s, 9H), 3.00 (t, J=7.7 Hz, 4H), 3.29 (t, J=7.8 Hz, 4H), 4.21 (s, 1H), 6.54–6.60 (m, 2H), 8.20 (d, J=4.8 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=26.1, 36.2, 45.5, 47.1, 80.7, 107.5, 109.8, 148.6, 155.2, 160.4. MS (EI) *m/z* (rel. int.): 249 (2, M+); 234 (3); 192 (100); 163 (4); 149 (6); 135 (14); 121 (2); 107 (4); 79 (2); 57 (3).

4.5.21. ((2,6-Dichloro)-4-pyridyl)-1-piperazine (12h). Yielded 57 mg (>99%) of **12h** as an oil. NMR ^{1}H ($CDCl_3$): δ=2.41 (s, 1H), 2.99 (t, J=4.8 Hz, 4H), 3.33 (t, J=4.8 Hz, 4H), 6.58 (s, 2H). NMR ^{13}C ($CDCl_3$): δ=45.3, 47.0, 106.3, 151.2, 158.1. MS (EI) *m/z* (rel. int.): 231 (21, M+); 189 (100); 176 (7); 146 (3); 112 (3); 76 (4); 56 (13).

4.5.22. ((2-Bromo-6-chloro)-4-pyridyl)-1-piperazine (12i). Yielded 69 mg (>99%) of **12i** as an oil. NMR ^{1}H

($CDCl_3$): δ=1.54 (s, 1H), 2.97 (t, J=4.8 Hz, 4H), 3.31 (t, J=4.8 Hz, 4H), 6.60 (s, 1H), 6.75 (s, 1H). NMR ^{13}C ($CDCl_3$): δ=46.3, 50.7, 106.8, 110.3, 113.6, 141.5, 157.6. MS (EI) *m/z* (rel. int.): 277 (21, M+), 235 (100), 139 (12), 119 (8), 76 (12), 56 (19).

4.5.23. ((2-Chloro-6-iodo)-4-pyridyl)-1-piperazines (12j). Yielded 80 mg (>99%) of **12j** as an oil. NMR ^1H ($CDCl_3$): δ=1.65 (s, 1H), 2.61 (t, J=5.2 Hz, 4H), 3.32 (t, J=5.2 Hz, 4H), 6.61 (s, 1H), 6.99 (s, 1H). NMR ^{13}C ($CDCl_3$): δ=46.2, 51.0, 93.4, 104.5, 107.4, 117.8, 156.8. MS (EI) *m/z* (rel. int.): 323 (33, M+), 281 (100), 268 (10), 154 (9), 119 (9), 76 (9), 56 (14).

4.5.24. ((2-Chloro-6-(2,2-dimethylpropyl-1-hydroxy))-4-pyridyl)-1-piperazine (12k). Yielded 42 mg (60%) of **12k** as an oil. NMR ^1H ($CDCl_3$): δ=0.92 (s, 9H), 2.97 (t, J=4.8 Hz, 4H), 3.29 (t, J=4.8 Hz, 4H), 4.18 (s, 1H), 6.47 (s, 1H), 6.55 (s, 1H). NMR ^{13}C ($CDCl_3$): δ=25.9, 36.1, 45.6, 47.5, 81.0, 106.4, 113.7, 130.5, 143.2, 161.2. MS (EI) *m/z* (rel. int.): 283 (2, M+), 268 (3), 227 (76), 226 (100), 183 (8), 171 (11), 170 (13), 169 (20), 57 (8).

4.5.25. ((2-Bromo-6-methylsulfanyl-3-pyridyl)-1-piperazine (11g). Yielded 70 mg (97%) of **11g** as an oil. NMR ^1H ($CDCl_3$): δ=2.50 (s, 3H), 2.95–2.99 (m, 4H), 3.06–3.11 (m, 4H), 7.03–7.15 (m, 2H), 7.29 (d, J=3.1 Hz, 1H). NMR ^{13}C ($CDCl_3$): δ=13.1, 46.0, 51.9, 119.1, 122.7, 128.0, 134.9, 145.2. MS (EI) *m/z* (rel. int.): 289 (21, M+), 287 (21), 245 (26), 242 (49), 240 (45), 183 (42), 105 (100), 77 (69), 57 (58).

4.5.26. ((2-Iodo-6-methylsulfanyl)-3-pyridyl)-1-piperazine (11h). Yielded 76 mg (91%) of **11h** as an oil. NMR ^1H ($CDCl_3$): δ=2.20 (s, 1H), 2.47 (s, 3H), 2.92–2.94 (m, 4H), 2.99–3.04 (m, 4H), 6.83 (d, J=7.9 Hz, 1H), 7.29–7.36 (m, 1H). NMR ^{13}C ($CDCl_3$): δ=13.2, 46.1, 52.2, 119.1, 127.3, 129.6, 144.0, 146.0. MS (EI) *m/z* (rel. int.): 335 (45, M+), 288 (100), 277 (13), 96 (16), 84 (15), 78 (13), 56 (68).

4.5.27. ((2-Methylsulfanyl-6-(2-phenyl-methanone))-3-pyridyl)-1-piperazine (11i). Yielded 58 mg (75%) of **11i** as an oil. NMR ^1H ($CDCl_3$): δ=2.50 (s, 3H), 2.89–2.99 (m, 4H), 3.03–3.09 (m, 4H), 6.97 (d, J=3.3 Hz, 1H), 7.19 (d, J=5.1 Hz, 1H), 7.36–7.56 (m, 5H). NMR ^{13}C ($CDCl_3$): δ=12.5, 46.2, 52.5, 118.9, 125.2, 128.2, 129.6, 132.3, 135.3, 138.0, 143.8, 156.1, 186.3.

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12. All our first attempts at metallation of free amines resulted in sluggish reactions and degradation. To address this, the piperazine NH group was tritylated to avoid its deprotonation and consumption of basic reagents.
13. Metallation attempts were performed using 2–8 equiv of *n*-BuLi or LTMP in THF at −78 or 0 °C for 2–6 h.
14. Hexane is generally the best solvent for metallations with BuLi-LiDMAE since this non chelating solvent favours aggregates formation.
15. The C–Cl and C–SMe moieties were found stable under BuLi-LiDMAE lithiation conditions. See for example Refs. 7a–c and (a) Gros, Ph.; Viney, C.; Fort, Y. *Synlett* **2002**, *4*, 628–630. (b) Kaminski, T.; Gros, P. h.; Fort, Y. *Eur. J. Org. Chem.* **2003**, 3855–3860.

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A $C_{3'}$ modified nucleotide. The difluorophosphonate function, a phosphate mimic, governs the conformational behaviour of the ribofuranose

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Abstract—A conformational analysis using the Pseurot 6.3 software package of a modified nucleoside-3′-phosphate is reported and reveals that the phosphate mimic strongly influences the conformational behaviour of the ribose ring and shifts the North/ South equilibrium to a northern position. A rational classification by the group electronegativity of several phosphate analogues is presented. The λ factor of the difluorophosphonate group in water (Diez–Donders generalised Karplus equation) is also determined.

1. Introduction

The monoester, diester and anhydride derivatives of the phosphate function are among the most widespread functional groups in nature.[1] Of paramount importance is their ability to bend into enzyme pockets and to link two ribose units in oligonucleotides.[2] In bioorganic and medicinal chemistry the unwanted cleavability of the phosphate ester bond (P–O) has stimulated the development of several analogues such as phosphorothioate, phosphonate, boranophosphate.[3] Phosphonates have been explored with success since several decades but presently considered as the best mimic of the phosphates are the mono- (MFP) and difluorophosphonates (DFP) in which the hydrolysable P–O bond is replaced by a stable P–CXY bonds (X, Y=F or X=F, Y=H).[4] Since the breakthrough of Blackburn and Mc Kenna,[4j,k] particular attention has been devoted to α,α-difluorophosphonates: the physical parameters that favour this dihalogenophosphonate more than a phosphonate as an 'isosteric and isopolar' mimic of the phosphate function are a combination of (a) a reduced pK_a of the second acidity, (b) an increase of the P–CF_2–C valence angle connected with a decrease of the P–CF_2 length and (c) the high polarity of the CF_2 moiety. On the other hand, one could argue that the steric factors would disfavour the halogenophosphonates (the length of the C–F bond is about 1.4 Å). Also, it has been pointed out that the dihedral angles mismatch those of the phosphate and perturb the energetic torsion profile.[5] The apicophilicity of the halogenated carbons tends to mimic the pentacoordinate trigonal bipyramid geometry found in the transition state of the hydrolysis of the phosphates and would favour halogeno phosphonates as 'isodynamic' to the natural phosphate. In conclusion, all of these studies focus on a few factors: (a) pK_a, (b) valence angles, (c) bond lengths (d) apicophilicity, all of these have been centred on the phosphorus atom and the bonds surrounding it. To the best of our knowledge, no studies were reported on the influence of a CF_2P group on the conformational behaviour of a complex molecule.

In connection with a program directed to the synthesis of antisense oligonucleotides, we embarked on the determination of the impact that a CF_2 replacing an oxygen atom would display in the conformational North⇄South (N/S) equilibrium in a model nucleotide. This is particularly important as it is well recognised that the conformational state is of prime importance for the double strand association in RNA and DNA structures.[2] Reports from Isis Pharmaceuticals have demonstrated the ability of a simple phosphonate linkage to produce excellent target-binding affinity to the complementary RNA and a complete

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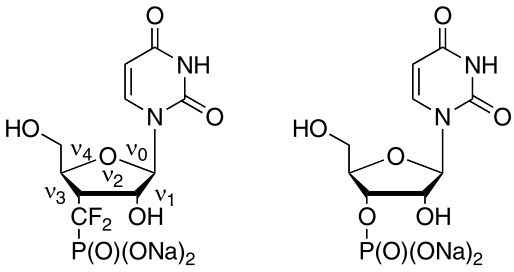


1 2

Figure 1.

resistance to hydrolysis in the presence of snake venom phosphodiesterase.[6] The present contribution describes the conformational analysis of 1-*N*-(3-Deoxy-3-(dihydroxyphosphono)difluoromethyl-β-D-*ribo*furanosyl) uracil **1**, a recent example of a $C_{3'}$ DFP modified nucleoside, and the difference in behaviour between **1** and its natural counterpart **2** (Fig. 1).[7]

2. The electronegativity factor, ι

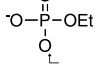
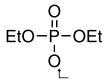
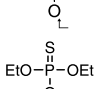
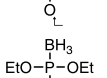
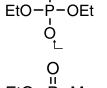
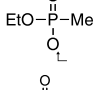
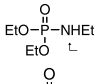
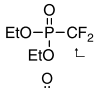
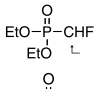
Chattopadhyaya et al. invested much effort in an attempt to quantify the various steric and stereoelectronic factors responsible for the conformational behaviour in nucleotides.[8] It appears that the N⇄S equilibrium is a function of the balance between the anomeric effect (AE) and several gauche effects (GE). For example, in a series of 2′,3′-dideoxythymidines the N⇄S equilibrium is described by the relative strength of the anomeric effect (displacement to an N form) and GE of $O_{3'}/O_{4'}$ (displacement to an S form). The replacement of the $O_{3'}$ atom by another group (from H to F) affects the strength of the GE and as a consequence the enthalpy of the equilibrium N⇄S (ΔH) is linearly linked to the group electronegativity of the 3′-substituent.[8b] Thus, one could expect that a $CF_2PO_3^{2-}$ group, aside from its steric differences compared with the OPO_3^{2-} group, would influence the conformational behaviour of **1** by its intrinsic electronegativity. Among the electronegativity scales available, the one proposed by Inamoto (ι: iota factor) shows one of the best correlations between ΔH and the group electronegativity.[9] Another advantage of the Inamoto's scale is a linear relation between the ι factor and the ^{13}C chemical shift of methylene carbon in ethane fragments CH_3–CH_2–X (X is the considered group). Thus, a simple experiment can quantify the group electronegativity according to Inamoto's relation:

$$\delta = 59.4(\iota - 2) + 7.77 \quad (1)$$

In Inamoto's scale, the atomic ι factor ranges from 2.0-hydrogen to 3.1-fluorine, the maximum reported value for a chemical group is 3.71 for N_2^+, for CF_3SO_2 ι=2.44. By measuring the chemical shift of the methylene carbon in a CH_3CH_2 moiety covalently linked to the group of interest depicted in Table 1, the corresponding electronegativities of the phosphate analogues are directly deduced.

The compounds displayed in Table 1 are classified into three groups: group I corresponds with high ι values (from ι=2.97 to 2.90 in entries 1–5); group II refers to the borderline value (at ι=2.50); and group III comprises the low values (from ι=2.33 to 2.14 in entries 7–9).

Table 1. Inamoto's electronegativity factor of the phosphate function and some analogues

Entry	Compound	Group[a]	δ (ppm)[b]	ι factor
1	$(Et_3NH,O)(EtO)_2P(O)$		65.9	2.97 2.8[8b]
2	$(EtO)_3P(O)$		64.1	2.95
3	$(EtO)_3P(S)$		64.0	2.95
4	$(EtO)_3P–BH_3$		62.4	2.92
5	$(EtO)_2P(O)Me$ Group I		61.0	2.86
6	$(EtO)_2P(O)N(Et)_3$ Group II		39.2	2.53
7	$(EtO)_2P(O)CF_2Et$		27.3	2.33
8	$(EtO)_3P(O)CFHEt$		23.1[10]	2.26
9	$(EtO)_2P(O)CH_2Et$ Group III		15.9	2.14

[a] The arrows represents the point of substitution.
[b] Chemical shifts were measured in $CDCl_3$.

Inspection of group I indicates that the anionic monoester and the neutral diester phosphates share close ι values (entries 1 and 2). The same trend is observed in Inamoto's report which shows that the neutral or ionic state of the considered group slightly influences the electronegativity when the charge is not localised on the central atom (CO_2^-: $\iota=2.33$; CO_2H: $\iota=2.36$; SO_3^-: $\iota=2.36$; SO_3Et: $\iota=2.30$; PO_3H^-: $\iota=2.03$; $PO(OR)_2$: $\iota=2.05$). Similarly, in group I, the substitution of the phosphorus atom only slightly affects the electronegativity of the group (entries 3–5). It should be noted that our determination of ι of the phosphate in $CDCl_3$ fits within the error range the value reported by Chattopadhyaya (2.8 ± 0.2 and 2.97 in entry 1) in D_2O, which was determined by a different technique.[8b]

Group II contains a phosphoramidate corresponding to the replacement of the oxygen by a nitrogen atom. The ι value is slightly superior to the reported value of the $N(Et)_2$ group ($\iota=2.48$).

Further replacement with a carbon atom results in another drop as indicated by the three phosphonates of group III. As expected in this carbon set, sequential introduction of fluorine atoms increases the group electronegativity from phosphonate (2.14, entry 9) to mono and difluorophosphonates (2.26, entry 8 and 2.33, entry 7).[10] The same trend is observed in the halogenated methyl series from the original Inamoto report (CH_3: $\iota=2.13$; with fluorine: CH_2F: $\iota=2.24$; CHF_2: $\iota=2.35$; CF_3: $\iota=2.47$; with chlorine: CH_2Cl: $\iota=2.18$; $CHCl_2$: $\iota=2.22$; CCl_3: $\iota=2.26$; with bromine: CH_2Br: $\iota=2.16$; $CHBr_2$: $\iota=2.18$; CBr_3: $\iota=2.20$). The fluorophosphonates display a considerable difference with respect to the phosphate group and should be considered as non-electronegative.

The influence of the low electronegativity of a DFP group on the conformational behaviour is the topic of the next part of the paper.

3. The γ rotamer population and the pseudorotation parameters

3.1. Assessment of the γ rotamer population

The assessment of the rotamer distribution along the $C_{4'}$-$C_{5'}$ side chain is usually performed with the aid of the Haasnoot method, which was developed on the basis of a crystallographic dataset.[11] According to this method, the two observed coupling constants ($J_{4'-5'}$ and $J_{4'-5''}$) are time-averages of the couplings found in each of the pure rotamers $\gamma+$, $\gamma-$, γt (γ refers to $C_{3'}$–$C_{4'}$–$C_{5'}$–$O_{5'}$ dihedral angle, Fig. 2).

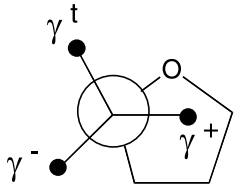


Figure 2. Definition of the rotamers orientation along the $C_{4'}$–$C_{5'}$ fragment relative to $C_{3'}$.

Therefore:

$$^3J = {}^3J(\gamma+)X^+ + {}^3J(\gamma-)X^- + {}^3J(\gamma t)X^t \quad (2)$$

$J(\gamma)$ are the limiting coupling constants at the respective γ angles and X are the respective molar fractions. The application of the Haasnoot method to compound **1** at 295 K reveals a partition between two major rotamers: $\gamma+$ is preferred (73%) and γt (31%) is the minor constituent. Moreover, an unrealistic percentage of -4% is found for the $\gamma-$ rotamer. This feature probably comes from the $C_{3'}$ modification that was not taken into account in the Haasnoot dataset. To consider this chemical modification, the limiting coupling constants were recalculated with the aid of the DD equation (Eq. 3, see Section 3.2.1) presuming $\gamma+=51$, $\gamma-=180$, $\gamma t=290$ and an estimated λ value of 0.60, corresponding to an isopropyl group, for the $C_{3'}$ carbon. Table 2 displays the angles and the calculated limiting coupling constants.

Table 2. Side chain torsion angles (degrees) and limiting coupling constants (Hz)

γ angle	$H_{4'}H_{5'}$ angle	$H_{4'}H_{5''}$ angle	^3J ($H_{4'}H_{5''}$)	^3J ($H_{4'}H_{5''}$)
51 ($\gamma+$)	−66	53	1.90	1.84
180 ($\gamma-$)	64	182	2.48	10.72
290 (γt)	174	−68	10.34	3.28

The population distribution of the three rotamers could now be determined by solving the second linear system:

Former Haasnoot linear system

$$\begin{vmatrix} 2.40 & 2.60 & 10.6 \\ 1.30 & 10.50 & 3.80 \\ 1 & 1 & 1 \end{vmatrix} \begin{pmatrix} X^+ \\ X^t \\ X^- \end{pmatrix} = \begin{pmatrix} J_{4'-5'} \\ J_{4'-5''} \\ 1 \end{pmatrix}$$

The new linear system used for **1**

$$\begin{vmatrix} 1.90 & 2.48 & 10.34 \\ 1.84 & 10.72 & 3.28 \\ 1 & 1 & 1 \end{vmatrix} \begin{pmatrix} X^+ \\ X^t \\ X^- \end{pmatrix} = \begin{pmatrix} J_{4'-5'} \\ J_{4'-5''} \\ 1 \end{pmatrix}$$

The temperature-dependent population distribution about the γ angle is displayed in Table 3. All values calculated are now in a physical range and clearly indicates a strong preference for the $\gamma+$ (70%) over the γt (30%) and the $\gamma-$ rotamers (1–3%). The Haasnoot method and our adaptation give very similar results; clearly, the classical procedure was also usable in the case of our DFP modification. The partition between $\gamma+$ (major) and $\gamma-$ (minor) rotamers is also encountered in the natural nucleotides where the $\gamma+$ rotamer is predominant over the two other possible positions.[11] It is clear that the replacement of the phosphate by a DFP group does not play a significant role in the $C_{4'}$–$C_{5'}$ rotamer distribution.

Table 3. $^{3}J_{H,H}$ coupling constants (Hz)[a] of **1** and population of the γ rotamers

T (K)	$^{3}J_{1'2'}$	$^{3}J_{2'3'}$	$^{3}J_{3'4'}$	$^{3}J_{4'5'}$	$^{3}J_{4'5''}$	%$\gamma+$	%γt	%$\gamma-$
295	1.42	5.32	10.30	2.13	4.04	74	25	1
306	1.45	5.45	10.19	2.04	4.16	74	26	0
315	1.42	5.54	10.15	2.06	4.19	73	27	0
325	1.70	5.61	10.08	2.20	4.30	71	27	2
335	1.85	5.72	10.04	2.13	4.36	71	28	1
345	1.99	5.79	9.90	2.27	4.41	69	29	2
355	2.02	5.85	9.85	2.30	4.51	68	30	2

[a] The accuracy of the measurement is $\pm$0.03 Hz.

3.2. The pseudorotation parameters

The pseudorotation model describes the conformational behaviour of a nucleotide in solution by a fast equilibrium between two discrete conformers (Fig. 3).[12] In Figure 3, T represents a twisted form, E an envelope form, the superscript and subscript numbers refer to the atom in *endo* and *exo* configuration relative to C_5, respectively. In practice, a substituted five-membered ring rarely adopts a pure T or E form because of the asymmetric surroundings induced by the substituents.

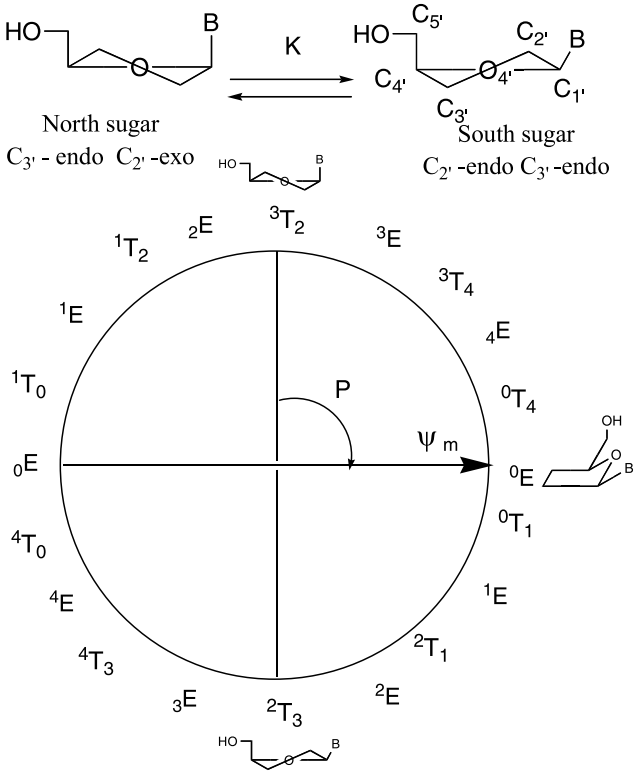


Figure 3. Discrete model and pseudo-rotation wheel of nucleotides.

This two state model is commonly accepted and has been delineated by a crystallographic survey of 178 X-ray structures in 1980 and recently revised on a dataset of 1161 structures from the Cambridge Structural and Nucleic Acid Databases by Marquez and Nicklaus.[13] These statistics show a fairly equal distribution of the nucleotides between N and S positions in the solid state.

Each of the two conformers are mathematically characterised by two pseudorotation parameters, one phase coordinate (P) and one puckering coordinate (ψ_{max}).[14,15] A couple of vectors in a three-dimensional space describes unambiguously the system: the coordinates are (P_1, ψ_1, $(1-X)$) and (P_2, ψ_2, X), X being the mole fraction of a given component. The coordinates are revealed by a regression calculation (Pseurot program) based on NMR measurements of the time-average vicinal coupling constants.[16] The aim of the Pseurot program is to find the best point describing the pseudorotational equilibrium by minimising the square of the difference (or the root mean square function, RMS) between simulated and measured coupling constants using a non-linear Newton–Raphson procedure. Figure 4 depicts the procedure used in the present work.

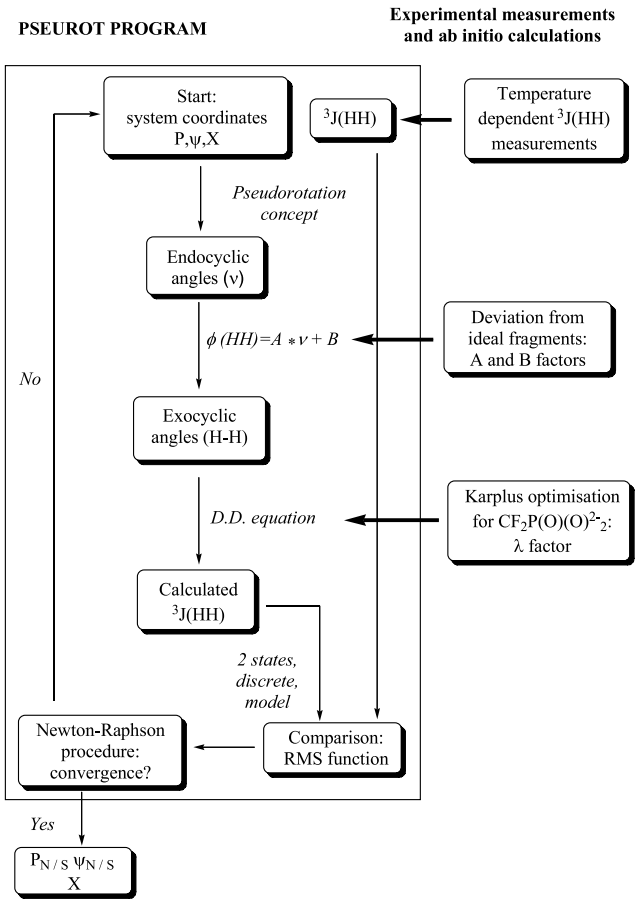


Figure 4. Pseurot procedure.

3.2.1. Parameterisation of the generalised Karplus equation for the difluoro phosphonate group. The Pseurot program uses the up to date generalised Karplus equation reported by Diez and Donders (DD).[17] This equation takes

advantage of the periodic property of a coupling constant over the torsion angle to describe it as a truncated Fourier series:

$$^3J(\alpha) = \sum_i C_i \cos(i\alpha) + S_2 \sin(2\alpha). \quad (3)$$

C_i and S_2 are calculated by the following set of equations[17b]:

$$C_0 = 7.01 - 0.58 \sum_i \lambda_i - 0.24(\lambda_1\lambda_2 + \lambda_3\lambda_4) \quad (4)$$

$$C_1 = -1.08 \quad (5)$$

$$C_2 = 6.54 - 0.82 \sum_i \lambda_i - 0.20(\lambda_1\lambda_4 + \lambda_2\lambda_3) \quad (6)$$

$$C_3 = -0.49 \quad (7)$$

$$S_2 = 0.68 \sum_i \zeta_i\lambda_i^2 \quad (8)$$

λ_i is an empirical parameter accounting for the influence of the ith substituent and ζ_i is an orientation parameter (± 1), its value depending on its spatial relation with respect to its geminal coupling proton (Fig. 5).[12]

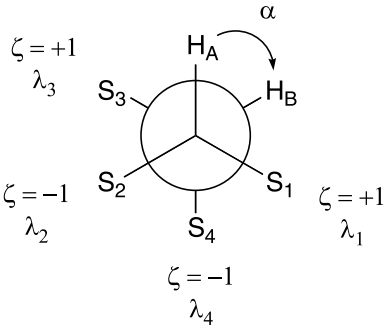


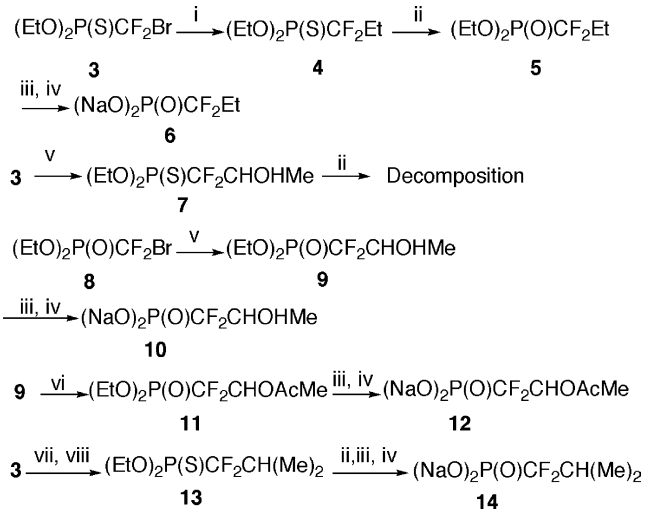
Figure 5. Numbering and sign convention used for an ethane fragment.

The λ parameter of a particular substituent R is easily determined with the aid of a CH_3–$CHRR'$ fragment as the fast rotation of the methyl group causes the orientation factor cos and sin to vanish. In this particular case, the vicinal ^{1}H–^{1}H coupling constant follows the empirical rule:[18]

$$^3J = 7.660 - 0.596(\lambda_1 + \lambda_2) - 0.419(\lambda_1\lambda_2) \quad (9)$$

For the DFPs λ determination, a set of four compounds containing substituents of known λ, covering a large range (from 0 to 1.25), was synthesised and the ^{1}H–^{1}H coupling constant determined in water. Scheme 1 depicts their synthesis.

The difluorothiophosphonate **3** was alkylated after a lithium–halogen exchange to afford **4** in good yield, which was treated with *m*-CPBA to replace the sulphur by an oxygen atom.[7a] The resulting difluorophosphonate **5** was saponified according to a classical protocol and afforded **6** in 58% overall yield. Synthesis of **10** is more troublesome: when the preceding synthetic route was followed the sulphur–oxygen exchange failed and only unidentified



Scheme 1. Reagents and conditions (i) *tert*-BuLi, EtBr, THF, −78 °C; (ii) *m*-CPBA, CH_2Cl_2, 0 °C; (iii) TMSBr, MeCN, 65 °C; (iv) Dowex 50X-2; (v) *tert*-BuLi, MeCHO, THF, −78 °C; (vi) *iso*-PrMgCl, AcCl, THF, 0 °C; (vii) *iso*-PrMgCl, acetone, THF, −78 °C to 0 °C, then $ClCOCO_2Me$; (viii) *tri-n*-BuSnH, AIBN, toluene, 110 °C.

compounds were observed (see reaction of **7**). To the best of our knowledge, this is the first reported limitation of this methodology.

We then retain the oxygen atom all along the pathway as depicted for the synthesis of **10** and **12** albeit lower yields (42 and 43%, respectively) are observed probably because of the weak thermal stability owing to the lithium cation.

Finally, the synthesis of **14** was conducted by enhancing the thermal stability by using both the sulphur atom and a magnesium cation.[7b] As previously observed, the deoxygenation of **13** takes place smoothly and efficiently and the final compound **14** is obtained after a classical saponification, cation-exchange sequence in 39% over six steps.

Table 4 displays the λ determination of a difluorophosphonate group in water.

It is noteworthy that the DFP and the phosphate λ value differ considerably (0.25 vs 1.27) and the numerical results of a DD equation will diverge between these two groups.

3.2.2. Translation of endocyclic torsion angles into exocyclic torsion angles. Each P and ψ_{max} value computed by the Pseurot program during the iterations of the Newton–Raphson procedure is used to calculate the corresponding endocyclic torsion angles (ν) using the Altona and Sundaralingam equation:[15a]

$$\nu_i = \psi_{max} \cos[P + (4\pi i/5)] \quad (10)$$

The endocyclic torsion angles (ν_i) are subsequently translated into exocyclic torsion angles (ϕ_i: H–C–C–H), the latter becoming the inputs used to calculate the ^{1}H–^{1}H coupling constants with the aid of the DD equation. The translation of endo- into exocyclic torsion angles is done by a linear transformation:

$$\phi(\mathrm{HH}) = A\nu_i + B \quad (11)$$

Table 4. Determination of the λ factor

Subst.	λ value (subst.)	^3J obs. (Hz)[a]	Calcd λ	Back calcd (Hz)	$^3J^{obs}-{}^3J^{calcd}$ (Hz)
H (**6**)	0	7.50	0.27	7.51	−0.01
OH (**10**)	1.25	6.66	0.23	6.64	0.02
OAc (**12**)	1.17	6.70	0.25	6.69	0.01
Me (**14**)	0.8	6.95	0.24	6.95	0.00

[a] The accuracy of the measurement is ±0.02 Hz.

A and *B* parameters represent the deviation from an ideal tetrahedral fragment (in such a case $A=1$ and $B=0$ or $\pm 120°$). We have obtained the *A* and *B* values corresponding to each of the three fragments $C_{1'}$–$C_{2'}$, $C_{2'}$–$C_{3'}$ and $C_{3'}$–$C_{4'}$ by optimising a set of 10 idealised envelopes of compound **1**, using ab initio calculations at the DFT/6-31G** level based on the Jaguar program (Table 5).[19] All envelopes were constrained at $\psi_m=36°$ and *P* sequentially at 18, 54, 90, 126, 162, 198, 234, 270, 306 and 342° by freezing two endocyclic angles. In addition, γ at 51° (major staggered rotamer, see Section 3.1) was selected as starting value (but freely optimised, in each case a small variation around the starting positions occurred).

Table 5. The *A* and *B* coefficients determined for compound **1**

Torsion angles	*A*	*B*	Correlation
$O_{4'}$ $C_{1'}$ $C_{2'}$ $C_{3'}$ (ν_1)	1.03	118.8	0.99
$C_{1'}$ $C_{2'}$ $C_{3'}$ $C_{4'}$ (ν_2)	1.22	4.9	0.99
$C_{2'}$ $C_{3'}$ $C_{4'}$ $O_{4'}$ (ν_3)	1.09	−132.5	0.98

3.2.3. Results of the pseudorotation analysis. The $^3J(^1H–^1H)$ of compound **1** were determined in water at seven temperatures (ranging from 295 to 355 K) with a 600 MHz spectrometer, using a $^1H\{^{19}F\}$ experiment (Table 3). The $^1H–^1H$ coupling constants were extracted after a gaussian treatment of the FID.

The problem is now the determination of 11 parameters: four pseudorotation coordinates (P_N, ψ_N, P_S, ψ_S) and seven thermodynamic parameters (the mol fraction of a component at every temperature). For this purpose, 21 $^1H–^1H$ coupling constants are accessible and give an over determined system (11 unknown parameters for 21 physical determinations). During the Pseurot procedure no parameters were constrained (e.g., starting from $P_N=18°$, $\psi_N=36°$, $P_S=160°$, $\psi_S=36°$, $X_s=0.2$; 50 iterations required for convergence) and the minimisation smoothly converges to the minimum: $P_N=27°$ ($^3E–^3T_4$), $\psi_N=25°$, $P_S=105°$ ($^OE–^OT_1$), $\psi_S=24°$, $X_N=0.98$ at 295 K with an overall RMS of 0.04 Hz. The major conformer is located at the border of the domain usually found in nucleotides and nucleosides: $0°<P<30°$ for the N conformer. The second puckering coordinate, $\psi_{max}=25°$, which represents the deviation from planarity, is also at an extreme limit, the usual range is $30<\psi_{max}<50°$ as noted by Marquez and Niklaus recently with the aid of a large survey of the crystallographic databases.[13b] Table 6 displays the temperature-dependent percentage of the major conformer.

4. Discussion

It is long recognised that natural nucleotide and nucleoside conformations are fairly evenly distributed between N and S positions on the pseurodoration wheel.[13] More precisely, the uridine 3-monophosphate **2** in water at 278 K occurs as 57% N form.[8a] By contrast, the modified nucleoside **1** occurs nearly exclusively in the N form (98%) at 295 K. The difference between modified (**1**) and natural nucleoside (**2**) is explained by the absence of the S-driving $O_{4'}$–$O_{3'}$ gauche effect in the former.[8a] The (near) lack of *gauche* effect along the $C_{3'}$–$C_{4'}$ bond arises from the much smaller group electronegativity of the DFP group compared to that of the parent phosphate (ι: 2.33 vs 2.97).[8a] The remaining predominant factors are: the GE present on the $C_{1'}$–$C_{2'}$ fragment ($O_{4'}$–$O_{2'}$ GE drives strongly to North, the base-O_2 GE weakly to S in the case of uridine) and the anomeric effect (strongly driving North in the case of uridine). The overall contribution will shift the equilibrium further to a N position of the pseudorotation wheel as shown by our pseudorotational analysis. Also, the DFP group flattens the ribose as revealed by the low ψ_{max} values of 25° whereas this puckering coordinate is usually about 38° in the natural ribonucleotides.[13,20]

The influence of the DFP group does not seem to reach further (the behaviour of the $C_{4'}$–$C_{5'}$ fragment is unchanged) and is limited as an intra-cyclic predominant factor.

The discrepancy between DFP modified **1** and the natural nucleoside **2** clearly shows that the introduction of a DFP group at the $C_{3'}$ position strongly affects the conformational distribution, although the DFP groups are considered as close mimics of the phosphate function. Therefore, as already noted by Thatcher,[5] not only bond lengths, valency angles and pK_a notions of mimics should be considered, but also more fine influences.

5. Experimental

5.1. General information

Unless specified otherwise, routine ^1H NMR (200 MHz),

Table 6. Population of the N conformer and errors of the analysis

T (K)	295	306	315	325	335	345	355
X^N (%)	98	95	95	90	87	83	82
ΔJ_{max} (Hz)	0.07	0.02	0.07	0.01	0.05	0.01	0.02
RMS (Hz)	0.06	0.02	0.06	0.01	0.03	0.01	0.02

^{13}C NMR (50 MHz), ^{19}F NMR (188 MHz) and ^{31}P (81 MHz) spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer. Chemical shifts are given in ppm and referenced to residual $CHCl_3$ at 7.27 ppm (^1H) and 77.16 ppm (^{13}C). ^{31}P and ^{19}F spectra are referenced to 85% H_3PO_4 and C_6F_6, respectively. Variable temperature NMR spectra were recorded on a Bruker DMX 600 spectrometer in D_2O using high digitalisation; accuracy of the measurement is ± 0.03 Hz. Splitting patterns are designated s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. THF and ether are distilled from sodium-benzophenone, acetone is distilled first over P_2O_5 and re-distilled over $KMnO_4$, ethyl bromide, ethanal, acetyl chloride, isopropyl chloride and methyloxalyl chloride are distilled under nitrogen atmosphere. *iso*-Propyl magnesium chloride is prepared from magnesium and isopropyl chloride in ether. *m*-CPBA (*meta*-chloroperbenzoic acid) used without purification. Computational details. All calculations have been performed with the aid of the standard 6-31G** basis set. Geometries have been optimised in vacuo, at 298 K within the Density Functional Theory framework using the B3P86 hybrid functional as implemented in the JAGUAR 4.1 software.[19] Pseudorotation non-linear fittings were performed using the Pseurot 6.3 software.[16]

5.1.1. *O*,*O*-Diethyl 1,1-difluoropropylphosphonothioate: 4. *tert*-BuLi (11 ml, 1.2 M in hexane, 13.2 mmol) is added to 15 ml of THF cooled at −78 °C. To this solution is added dropwise a solution of *O*,*O*-diethyl 1,1-difluoro-1-bromo methane phosphonothioate, **3** (1.5 g, 5.3 mmol) in 3 ml of THF. After 10 min, ethylbromide (1.09 g, 10 mmol) is added and the solution is slowly warmed-up to −10 °C. Aqueous saturated ammonium chloride is added (5 ml), the mixture is poured onto 20 ml of water and extracted with AcOEt (2×50 ml). The organic layer is dried over $MgSO_4$ and evaporated to give 860 mg (3.7 mmol; yield: 70%) of a colourless liquid. ^1H NMR δ 4.2 (br m, 4H); 2.1 (br m, 2H); 1.33 (t, J=7.3 Hz, 6H); 1.0 (t, J=7.3 Hz, 3H). ^{13}C NMR δ 64.2 (d, J=6 Hz, 26.4); (td, J=21, 15 Hz); 16.1 (d, J=6 Hz); 4.9 (d, J=6 Hz); CF_2 not found. ^{31}P NMR δ 77.1 (t, J=113 Hz). ^{19}F NMR δ 63.3 (dt, J=112, 20 Hz). IR (neat) 2987; 2940; 2904; 1020; 980; 815 cm^{-1}. Anal. Calcd for $C_7H_{15}F_2O_2PS$: C, 36.23; H, 6.46. Found: C, 36.51; H, 6.71.

5.1.2. *O*,*O*-Diethyl 1,1-difluoropropylphosphonate: 5. The crude product **4** is dissolved in 35 ml of dichloromethane, cooled to 0 °C and solid *m*-CPBA (80%, 3.6 g, 17 mmol) is added in four portions. The solution is stirred 2 h and extracted with aqueous NaOH (1 M, 3×25 ml), saturated aqueous NH_4Cl (15 ml) and brine (10 ml). The organic layer is dried over $MgSO_4$ and evaporated to yield 800 mg (3.7 mmol; quantitative yield) of a colourless oil. ^1H NMR δ 4.17 (q, J=7 Hz, 4H); 2.0 (m, 2H); 1.32 (t, J=7 Hz, 6H); 1.02 (t, 7.3 Hz, 3H). ^{13}C NMR δ 64.1 (d, J=6 Hz); 27.2 (m); 16.2 (d, J=6 Hz); 4.8 (t, J=6 Hz). ^{31}P NMR δ 7.8 (t, J=109 Hz). ^{19}F NMR δ 48.3 (t,d, J=108, 20 Hz). ^{31}P NMR δ 7.8 (t, J=108 Hz). IR (neat) 2987; 2940; 2904; 1020; 980; 815 cm^{-1}. Anal. Calcd for $C_7H_{15}F_2O_3P$: C, 38.91; H, 6.94. Found: C, 38.71; H, 7.12.

5.1.3. Sodium 1,1-difluoropropylphosphonate: 6, general procedure for deprotection. In a pressure tube, difluorophosphonate (1 mmol, 1 equiv) is dissolved in MeCN (10 ml), TMSBr (650 µl, 6 mmol, 6 equiv) is added and the solution is sealed and heated to 65 °C for 1 h 30 min, 10 drops of water are added and the solvent is removed under reduced pressure. The resulting viscous oil is dissolved in 10 ml of water and passed through a Dowex-Na column. Lyophilisation gives 170 mg of a white hygroscopic foam (0.83 mmol; yield: 83%). ^1H NMR (D_2O, 200 MHz) δ 1.8 (br m, 2H); 0.8 (t, J=7.7 Hz, 3H). ^{13}C NMR (D_2O, 50 MHz) δ 125.0 (dt, J=255, 198 Hz); 29.1 (m); 7.1 (m). ^{31}P NMR (D_2O, 81 MHz) δ 8.42 (t, J=99 Hz). ^{19}F NMR (D_2O, 188 MHz) δ 50.5 (td, J=20.3, 108 Hz); MS (FAB+, glycerol): $m+H^+/z$=205.

5.1.4. *O*,*O*-Diethyl 1,1-difluoro-2-hydroxypropylphosphonate: 9. *tert*-BuLi (4.2 ml, 1.7 M in hexane, 7.1 mmol) is added to 10 ml of THF cooled at −78 °C. To this solution is added dropwise a solution of diethylphosphono 1,1-difluoro-1-bromo methane, **8** (830 mg, 3.1 mmol) in 5 ml of THF. After 2 min, acetaldehyde (1 ml, large excess) is added and the solution is stirred for an additional 30 min before aqueous saturated NH_4Cl is added (5 ml). The solution is warmed to room temperature and poured into water (50 ml). The solution is extracted with AcOEt (2×50 ml), dried over $MgSO_4$ and evaporated. Bulk-to-bulk distillation gives 380 mg (1.6 mmol; 52%) of a colourless oil. ^1H NMR δ 4.20 (m, 5H); 2.8 (br s, 1H); 1.36 (t, J=6.9 Hz, 6H); 1.36 (m, 3H). ^{13}C NMR δ 118 (ddd, J=266, 262, 206 Hz); 67.1 (ddd, J=26, 23, 15 Hz); 64.5 (t, J=6 Hz); 16 (d, J=6 Hz); 14.7 (d, J=3 Hz). ^{31}P NMR δ 7.4 (dd, J=105, 100 Hz). ^{19}F NMR δ 44.5 (dd, d, J=301, 101, 7 Hz); 34.5 (ddd, J=304, 108, 20 Hz). IR (neat): 3382, 2988, 1259, 1024 cm^{-1}. Anal. Calcd for $C_7H_{15}F_2O_4P$: C, 36.23; H, 6.46. Found: C, 36.11; H, 6.74.

5.1.5. Sodium 1,1-difluoro-2-hydroxypropylphosphonate: 10. According to the general procedure for the deprotection (5-1-3). Yield: 82%. Spectroscopy data in agreement with literature.[21] MS (FAB+, glycerol): $m+H^+/z$=221.

5.1.6. *O*,*O*-Diethyl 1,1-difluoro-2-acetylpropyl phosphonate: 11. To a THF (10 ml) solution of **9** (348 mg, 1.50 mmol) cooled at 0 °C, is slowly added freshly prepared *iso*-propyl magnesium chloride (1.6 ml, 1.6 mmol, 1 M in ether). The solution is stirred 5 min and acetyl chloride (320 ml, 4.5 mmol) is added. After 90 min. the solution is warmed to room temperature and quenched with saturated aqueous ammonium chloride (10 ml). The solution is poured onto 50 ml of water, extracted with ether (2×50 ml) and dried over Na_2SO_4. Evaporation gives 380 mg (1.38 mmol; yield: 92%) of a colourless solid. ^1H NMR δ 5.40 (m, 1H); 4.2 (q, J=7 Hz, 4H); 2.1 (s, 3H); 1.34 (t, J=7 Hz, 6H). ^{13}C NMR δ 169; 117 (ddd, J=266, 262, 206 Hz); 67.1 (ddd, J=26, 23, 15 Hz); 64.4 (d, J=7.6 Hz); 20.5; 16.0; 12.7 (t, J=3 Hz). ^{31}P NMR δ 5.6 (dd, J=104, 98 Hz). ^{19}F NMR δ 43.5 (ddd, J=308, 102, 14 Hz, 1F); 39.0 (ddd, J=308, 105, 14 Hz, 1F). IR (neat): 2986, 1757, 1271, 1232, 1025 cm^{-1}. Anal. Calcd for $C_9H_{17}F_2O_5P$: C, 39.42; H, 6.20. Found: C: 39.51; H, 6.31.

5.1.7. Sodium 1,1-difluoro-2-acetylpropylphosphonate: 12. According to the general procedure for the deprotection (Section 5.1.3). Yield: 90% (white hygroscopic foam). ^1H

NMR (D_2O, 200 MHz) δ 5.1 (m, 1H); 1.92 (s, 1H); 1.17 (d, $J=6.9$ Hz, 3H). ^{13}C NMR (D_2O, 50 MHz) δ 175.1; 121.2 (td, $J=260$, 190 Hz); 71.7 (ddd, $J=27$, 24, 15 Hz); 22.8; 15.2. ^{31}P NMR (D_2O, 81 MHz) δ 5.4 (t, $J=92$ Hz). ^{19}F NMR (D_2O, 188 MHz) δ 43.3 (td, $J=91$, 14 Hz, 2F). MS (FAB+, glycerol): $m+H^+/z=263$.

5.1.8. Sodium 1,1-difluoro-2-methylpropylphosphonate: 14. To a cooled (−78 °C) THF solution (15 ml) is added isopropyl magnesium chloride (1 M in ether, 10.5 ml, 10 mmol) and **3** (2.5 g, 8.9 mmol) in THF (10 ml). After 5 min., acetone (1.5 ml, 20 mmol) is added and the solution is slowly warmed to 0 °C. Methyl oxallyl chloride (2 ml, excess) is slowly added and the solution is stirred an additional hour. The reaction is quenched with aqueous saturated ammonium chloride (5 ml), poured into 50 ml of water and extracted with ether (3×50 ml). The residue is heated at 120 °C under reduced pressure (bulk-to-bulk apparatus) to remove volatiles and leaves 2.0 g (5.78 mmol) of **13** (oil) that is immediately used for the next step.^{31}P NMR δ 73.8 (t, $J=109$ Hz). ^{19}F NMR δ 46 (d, $J=118$ Hz). In a pressure tube are introduced toluene (3 ml), crude **13** (500 mg, 1.44 mmol), tri-*n*-butyl tin hydride (580 ml, 2.16 mmol) and AIBN (100 mg, 0.61 mmol). The tube is sealed and heated at 110 °C for 2 h. The resulting colourless solution is poured into 75 ml AcOEt and washed with water (15 ml). After evaporation the residue is dissolved into CH_2Cl_2 (25 ml), cooled at 0 °C, *m*-CPBA (500 mg, 2.88 mmol) is added and the solution is stirred 1 h. The reaction is poured into CH_2Cl_2 (50 ml), extracted with saturated aqueous $NaHCO_3$ (3×50 ml), washed with brine, dried over Na_2SO_4 and evaporated. The residue is taken up with MeCN (25 ml), extracted with pentane (2×25 ml). To the acetonitrile layer is added TMSBr (0.300 ml,) and the solution is heated at 65 °C for 90 min. Water (5 drops) is added, the solution is stirred 15 min. and evaporated. The residue is dissolved in 10 ml of water and extracted with AcOEt (10 ml). The aqueous layer is passed through a Dowex-Na column and lyophilized to yield 123 mg of a white hygroscopic foam (0.57 mmol; yield over 6 steps: 39%). ^1H NMR (D_2O, 200 MHz) δ 2.0 (br m, 1H); 0.8 (d, $J=6.6$ Hz, 6H). ^{13}C NMR (D_2O, 50 MHz) δ 126.0 (td, $J=258$, 194 Hz); 34.9 (m); 17.1 (m). ^{31}P NMR (D_2O, 81 MHz) δ 8.28 (t, $J=101$ Hz). ^{19}F NMR (D_2O, 188 MHz) δ 48 (dd, $J=98$, 17 Hz); MS (FAB+, Glycerol): $m+H^+/z=219$.

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Deprotonation of thiophenes using lithium magnesates

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Abstract—Thiophene was regioselectively deprotonated at C2 on treatment with 1/3 equiv of Bu_3MgLi in THF at room temperature. The lithium arylmagnesate formed was either trapped with electrophiles or cross-coupled in a 'one-pot' procedure with aryl halides under palladium catalysis. 2-Chlorothiophene and 2-methoxythiophene were similarly deprotonated at C5 under the same reaction conditions. The enhancement of the reactivity of the base using TMEDA was evidenced using ^1H NMR spectroscopy.

1. Introduction

The preparation of functional heterocycles is an important synthetic goal because of the multiple applications of these molecules.[1] Deprotonation using alkyllithiums or lithium dialkylamides has been developed as one of the major tools since lithiated derivatives display a high reactivity towards many electrophilic functions.[2] Nevertheless, this methodology often requires low temperatures, which can be difficult to realize on an industrial scale. In addition, unlike organoboron, organotin, organozinc and organomagnesium compounds, organolithiums can hardly be involved in cross-coupling reactions.[3]

More recently, organomagnesium compounds have been prepared by deprotonation at higher temperatures, but the uses of such reactions have barely been explored. The pioneering work of Marxer and Siegrist in 1974 showed EtMgBr was capable of deprotonating 1-phenylpyrazole at the *ortho* position of the phenyl ring.[4] Eaton reported in 1989 the deprotonation of both methyl benzoate and *N*,*N*-diethylbenzamide with Hauser bases (iPr_2NMgBr or TMPMgBr, TMP = 2,2,6,6-tetramethylpiperidino) or magnesium diamides ($(iPr_2N)_2Mg$ or TMP_2Mg).[5] In 1995, Schlecker extended this methodology to the regioselective magnesiation of pyridine derivatives;[6] alkylmagnesium halides and dialkylmagnesiums rarely deprotonated such substrates because of easier 1,4-addition reactions.[7] Next, Kondo and Sakamoto described the regioselective magnesiation of *N*-substituted indoles,[8] thiophenes[9] and thiazole[9] using $(iPr_2N)_2Mg$, iPr_2NMgBr and iPr_2NMgCl. Nevertheless, because of the limited reactivity of these bases, an excess has in general to be used to ensure good yields. Pyrrole rings of numerous 1-phenyldipyrromethanes did not required protection step to be deprotonated at the position adjacent to the nitrogen atom using EtMgBr.[10]

Ten years after Eaton, Kondo achieved the deprotonation of methyl benzoate and other activated benzenes through the formation of an arylzincate using lithium di-*t*-butyl(2,2,6,6-tetramethylpiperidino) zincate as a base, a methodology extended to the pyridine, quinoline, isoquinoline and ethyl thiophenecarboxylates series,[11] but with limited applications due to their moderate reactivity with electrophiles. The arylmagnesates usually prepared by halogen–magnesium exchange reacting with a wider range of electrophiles than arylzincates, we have been interested in deprotonation reactions using lithium magnesates. This possibility has rarely been documented. Mulvey reported in 1999, the preparation of a mixed-metal sodium–magnesium macrocyclic amide which behaves like a template for the site selective dideprotonation of benzene and toluene.[12] This process cannot be used as it is for synthetic purposes because it involves a large excess of arene (5 mmol out of the 5 mL used are consumed in the reaction). Richey observed in 2004 that treating benzene halides with

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magnesates partially results in benzyne formation.[13] Even if the organometallic precursors have not been intercepted by electrophiles, the results show magnesates are capable of abstracting aromatic protons. Very recently, we studied the deprotonation of fluoro aromatics using lithium magnesates, the obtained arylmagnesates being either trapped with electrophiles or involved in a palladium-catalyzed cross-coupling.[14]

Herein, we describe the synthesis of lithium tri(2-thienyl) magnesates by deprotonation using lithium magnesates. To obtain more information on the efficiency on the process, the ^{1}H NMR spectra of the heterocyclic magnesium ate complexes were recorded. The reactivity of such magnesium intermediates towards electrophiles or in metal-catalyzed coupling reactions was studied.

2. Results and discussion

Lithiation of thiophene by BuLi is rapid in ethereal solvents, a result ascribed to the strong acidifying effect of the sulfur atom which compensates for an unlikely chelation of the base.[15] In addition, 2-substituted thiophenes generally give exclusive lithiation at the 5-position, whatever the nature of the substituent.

We attempted the deprotonation of thiophenes **1**–**3** using lithium magnesates.[16] The first experiments were conducted on thiophene (**1**) using 1/3 equiv of lithium tributylmagnesate (Bu_3MgLi) in THF at room temperature. Trapping the intermediate lithium magnesate with iodine or 4-anisaldehyde afforded the iodide **4a** and the alcohol **4b** in good yields (entries 1 and 2). Deprotonation of thiophene using BuLi being favored in the presence of TMEDA,[15] the reaction was also carried out using Bu_3MgLi in the presence of 1/3 equiv of this additive, and allowed the alcohol **4c** to be obtained after quenching with 3,4,5-trimethoxybenzaldehyde in 96% yield (entry 3). The reaction was next performed on 2-substituted thiophenes **2** and **3** to afford the 2,5-disubstituted compounds **5a–c** and **6a**,**b** (entries 4–8); excellent yields were again obtained adding TMEDA to the base (Table 1).

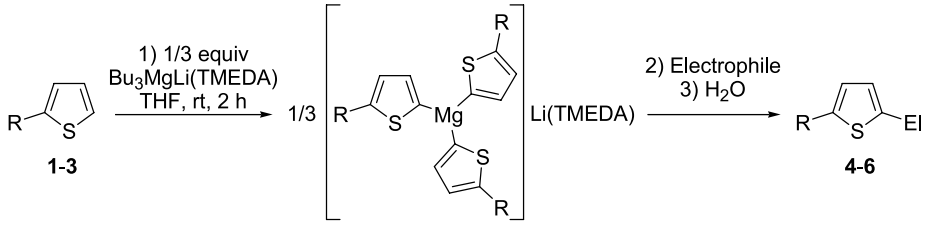
The role of TMEDA was ascertained by recording the ^{1}H NMR spectra of the reaction mixture obtained after the deprotonation step (Fig. 1): the hydrogen–magnesium exchange was quantitative using TMEDA whereas some substrate was detected without. The increasing reactivity may be accounted for by complexation of TMEDA to the lithium ion of the triorganomagnesate to separate the reactive magnesate ion from the intimate ion pair.

The lithium tri(2-thienyl)magnesates were next involved in cross-couplings with various aromatic halides under palladium catalysis using 1,1′-bis(diphenylphosphino)ferrocene (dppf) as ligand.[14,18] When lithium tri(2-thienyl)magnesate was subjected to the reaction with π-deficient substrates such as 2-bromopyridine and 3-bromoquinoline to give compounds **4d**,**e**, medium to good yields were obtained: the best results were observed with the 2-bromo substrate, for which the oxidative addition step is easier, while the other reacts moderately (entries 1 and 2). Using iodobenzene and 4-bromoanisole surprisingly allowed the syntheses of the phenyl derivatives **4f**,**g** in high yields (entries 3 and 4). Similar results were obtained starting from lithium (5-chloro-2-thienyl)magnesate, affording the biaryl compounds **5d**,**e** (entries 5 and 6), but a lower yield of 22% was noticed with methyl 4-iodobenzoate (entry 7), due to competitive reactions with the ester function. 2-Substituted 5-methoxythiophenes **6c–e** were obtained from lithium (5-methoxy-2-thienyl)magnesate under the same reaction conditions (entries 8–10, Table 2).

3. Conclusion

Thiophene was regioselectively deprotonated at C2 using

Table 1. Deprotonation of thiophenes **1**–**3** and trapping with electrophiles



Entry	Substrate	Product	Yield, (%)
1[a]	**1** (R=H)	**4a** (El=I)[b]	90
2[a]	**1** (R=H)	**4b** (El=CH(OH)-4-anisyl)[c]	60
3[d]	**1** (R=H)	**4c** (El=CH(OH)-3,4,5-trimethoxyphenyl)[e]	96
4[a]	**2** (R=Cl)	**5a** (El=I)[b]	68
5[a]	**2** (R=Cl)	**5b** (El=CH(OH)-4-anisyl)[c]	78
6[d]	**2** (R=Cl)	**5c** (El=CH(OH)-3,4,5-trimethoxyphenyl)[e]	93 (79)[f]
7[a]	**3** (R=OMe)	**6a** (El=I)[b]	75
8[d]	**3** (R=OMe)	**6b** (El=CH(OH)-3,4,5-trimethoxyphenyl)[e]	87

[a] The base is Bu_3MgLi (1/3 equiv).
[b] The electrophile is I_2.
[c] The electrophile is 4-anisaldehyde.
[d] The base is $Bu_3MgLi\cdot TMEDA$ (1/3 equiv).
[e] The electrophile is 3,4,5-trimethoxybenzaldehyde.
[f] Using BuLi (1 equiv), THF, −75 °C, 2 h.[17]

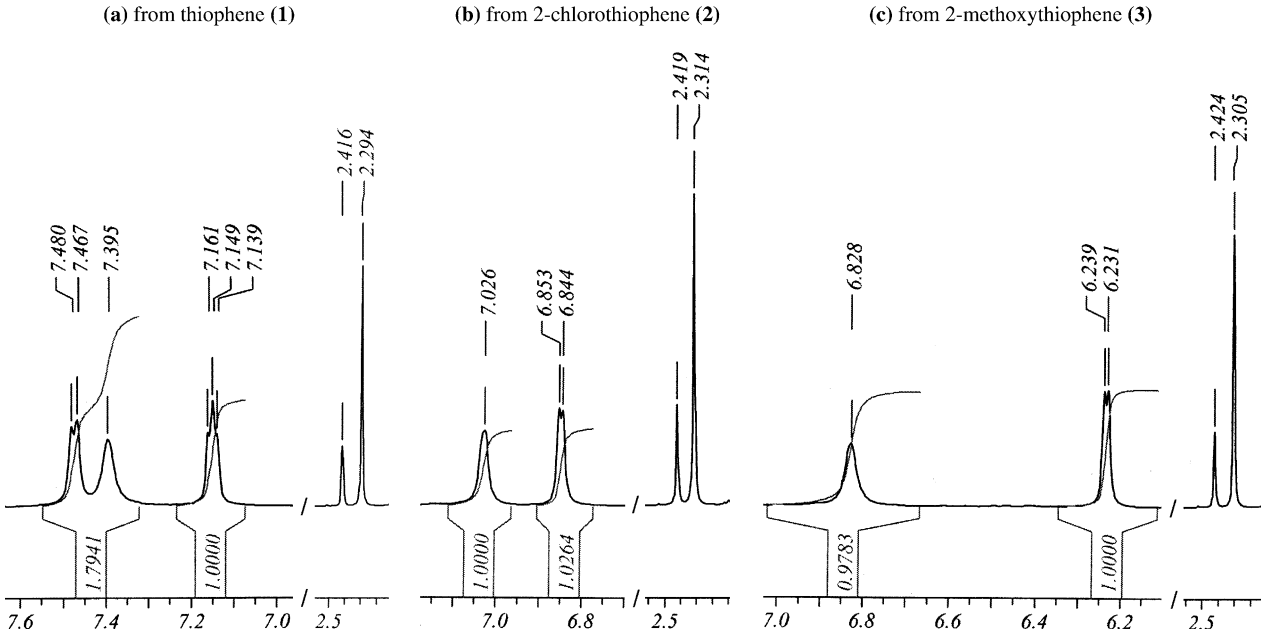
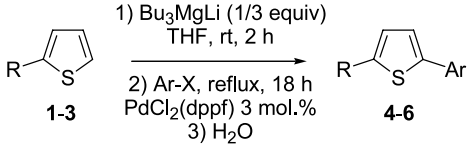


Figure 1. ^{1}H NMR spectra of lithium tri(2-thienyl) magnesates.TMEDA in THF (rt) (a) from thiophene (**1**); (b) from 2-chlorothiophene (**2**) and (c) from 2-methoxythiophene (**3**).

Table 2. Deprotonation of thiophenes **1**–**3** and cross-coupling with aromatic halides



Entry	Substrate	Product	Ar	Yield, (%)
1	**1** (R=H)	**4d**[a]	2-Pyridyl	77
2	**1** (R=H)	**4e**[b]	3-Quinolyl	56
3	**1** (R=H)	**4f**[c]	Phenyl	84
4	**1** (R=H)	**4g**[d]	4-Methoxyphenyl	92
5	**2** (R=Cl)	**5d**[a]	2-Pyridyl	68
6	**2** (R=Cl)	**5e**[d]	4-Methoxyphenyl	81
7	**2** (R=Cl)	**5f**[e]	4-(Methoxycarbonyl)phenyl	22
8	**3** (R=OMe)	**6c**[a]	2-Pyridyl	56
9	**3** (R=OMe)	**6d**[c]	Phenyl	67
10	**3** (R=OMe)	**6e**[e]	4-(Methoxycarbonyl)phenyl	40

[a] Using 2-bromopyridine.
[b] Using 3-bromoquinoline.
[c] Using iodobenzene.
[d] Using 4-bromoanisole.
[e] Using methyl 4-iodobenzoate.

1/3 equiv of Bu_3MgLi in THF at room temperature; the thienylmagnesate generated was either intercepted with electrophiles or cross-coupled in a 'one-pot' procedure. The enhancement of the reactivity of the base using TMEDA was evidenced by recording the ^{1}H NMR spectra of the reaction mixtures. Similar results were observed with 2-chloro and 2-methoxythiophenes.

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded with a Bruker AM 300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz). The solvent was $CDCl_3$, except for the lithium magnesates for which the spectra were recorded after addition of 20% THF-d^8 (to provide a lock signal) to the reaction mixtures. IR spectra were taken on a Perkin–Elmer FT IR 205 spectrometer, and main IR absorptions are given in cm^{-1}. Elemental analyses were performed on a Carlo Erba 1106 apparatus.

Starting materials. THF was distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[19] Metalation and cross-coupling reactions were carried out under dry N_2. Silica gel (Geduran Si 60, 0.063–0.200 mm)

was purchased from Merck. BuLi (1.6 or 2.5 M) in hexane and $PdCl_2$(dppf) were supplied by Aldrich. $MgBr_2$ was freshly prepared in THF using a described procedure.[20] Petrol refers to petroleum ether (bp 40–60 °C).

Unless otherwise noted, the reaction mixture was diluted with CH_2Cl_2 (50 mL) after the reaction. The organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and the crude product was chromatographed on a silica gel column (eluent is given in the product description).

4.2. General procedure 1: substituted thiophenes 4a,b, 5a,b and 6a by deprotonation of thiophenes 1–3 using Bu_3MgLi and subsequent trapping with electrophiles

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 mL) at −10 °C were added BuLi (6.0 mmol) and, 1 h later, the required thiophene (6.0 mmol). After 2 h at room temperature, the electrophile (6.0 mmol) was added and the mixture was stirred for 18 h at room temperature before addition of water saturated with NH_4Cl (1 mL).

4.2.1. 2-Iodothiophene (4a). The general procedure 1, starting from **1** (0.48 mL) and using a solution of I_2 (1.5 g) in THF (3 mL) (in this case, the reaction mixture was treated with $Na_2S_2O_3$ until bleaching), gave 90% (1.1 g) of **4a** (eluent: CH_2Cl_2) as a yellow oil. The physical and spectral data are analogous to those obtained for a commercial sample.

4.2.2. α-(4-Methoxyphenyl)-2-thiophenemethanol (4b).[21] The general procedure 1, starting from **1** (0.48 mL) and using 4-anisaldehyde (0.73 mL), gave 60% (0.79 g) of **4b** (eluent: CH_2Cl_2/AcOEt 90:10) as a yellow oil: ^{1}H NMR δ 7.36 (d, 2H, J=6.8 Hz), 7.25 (dd, 1H, J=3.8, 1.1 Hz), 6.91 (m, 4H), 5.97 (s, 1H), 3.80 (s, 3H), 2.61 (s, 1H); ^{13}C NMR δ 159.3 (q), 148.9 (q), 134.6 (q), 127.8 (t, 2C), 126.7 (t), 125.2 (t), 124.8 (t), 114.1 (t, 2C), 72.0 (t), 55.4 (p); IR (KBr) ν; 3429, 2836, 1610, 1511, 1248, 1174, 1033, 834, 704, 579. Anal. Calcd for $C_{12}H_{12}O_2S$ (220.29): C, 65.43; H, 5.49; S, 14.56. Found: C, 65.81; H, 5.87; S, 14.26.

4.2.3. 2-Chloro-5-iodothiophene (5a).[22] The general procedure 1, starting from **2** (0.55 mL) and using a solution of I_2 (1.5 g) in THF (3 mL) (in this case, the reaction mixture was treated with $Na_2S_2O_3$ until bleaching), gave 68% (1.0 g) of **5a** (eluent: petrol) as a yellow oil: ^{1}H NMR δ 7.06 (d, 1H, J=3.8 Hz), 6.61 (d, 1H, J=4.1 Hz); ^{13}C NMR δ 137.6 (t), 134.6 (q), 129.1 (t), 71.6 (q); IR (KBr) ν; 3094, 2923, 1515, 1408, 1204, 1062, 1003, 934, 785, 466. Anal. Calcd for C_4H_2ClIS (241.24): C, 19.65; H, 0.82; S, 13.12. Found: C, 20.02; H, 0.85; S, 13.21.

4.2.4. 5-Chloro-α-(4-methoxyphenyl)-2-thiophenemethanol (5b). The general procedure 1, starting from **2** (0.55 mL) and using 4-anisaldehyde (0.73 mL), gave 78% (1.2 g) of **5b** (eluent: cyclohexane/AcOEt 70:30) as a yellow oil: ^{1}H NMR δ 7.25 (d, 2H, J=8.3 Hz), 6.83 (d, 2H, J=8.3 Hz), 6.60 (d, 1H, J=3.8 Hz), 6.45 (d, 1H, J=3.8 Hz), 5.75 (d, 1H, J=3.8 Hz), 2.44 (d, 1H, J=3.8 Hz), 3.72 (s, 3H); ^{13}C NMR δ 159.3 (q), 147.1 (q), 134.6 (q), 129.6 (q), 127.5 (t, 2C), 125.5 (t), 123.7 (t), 113.8 (t, 2C), 71.9 (t), 55.2 (p); IR (KBr) ν; 3001, 2956, 2932, 2906, 2835, 1610, 1511, 1451, 1249, 1173, 1033, 996, 837, 801. Anal. Calcd for $C_{12}H_{11}ClO_2S$ (254.73): C, 56.58; H, 4.35; S, 12.59. Found: C, 56.69; H, 4.38; S, 12.29.

4.2.5. 2-Iodo-5-methoxythiophene (6a). The general procedure 1, starting from **3** (0.60 mL) and using a solution of I_2 (1.5 g) in THF (3 mL), gave 75% (1.1 g) of **6a** (eluent: petrol) as a yellow oil: ^{13}C NMR δ 169.9 (q), 134.4 (t), 105.7 (t), 60.3 (p), 57.2 (q); IR (KBr) ν; 3009, 2960, 2934, 2822, 1547, 1466, 1421, 1234, 1199, 1058, 995, 932, 762, 573. The other analyses are in accordance with those of the literature.[23]

4.3. General procedure 2: substituted thiophenes 4c, 5c and 6b by deprotonation of thiophenes 1–3 using Bu_3MgLi.TMEDA and subsequent trapping with electrophiles

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 mL) at −10 °C were added BuLi (6.0 mmol) and, 1 h later, TMEDA (0.30 mL, 2 mmol). After stirring for 1 h at −10 °C, the required thiophene (6.0 mmol) was introduced. After 2 h at room temperature, 3,4,5-trimethoxybenzaldehyde (1.2 g, 6.0 mmol) was added and the mixture was stirred for 18 h at room temperature before addition of water saturated with NH_4Cl (1 mL).

4.3.1. α-(3,4,5-Trimethoxyphenyl)-2-thiophenemethanol (4c). The general procedure 2, starting from **1** (0.48 mL), gave 96% (1.6 g) of **4c** (eluent: cyclohexane/AcOEt 70:30): mp 90–92 °C; ^{1}H NMR δ 7.25 (d, 1H, J=4.9 Hz), 6.94 (t, 1H, J=4.2 Hz), 6.89 (d, 1H, J=3.0 Hz), 6.66 (s, 2H), 5.96 (d, 1H, J=2.3 Hz), 3.82 (s, 9H), 2.74 (d, 1H, J=3.4 Hz); ^{13}C NMR δ 153.1 (q, 2C), 147.8 (q), 138.8 (q), 137.3 (q), 126.5 (t), 125.4 (t), 124.8 (t), 103.1 (t, 2C), 72.3 (t), 60.7 (p), 56.0 (p, 2C); IR (KBr) ν; 3495, 3377, 3005, 2940, 2833, 1597, 1508, 1464, 1421, 1332, 1234, 1126, 1065, 1007, 741, 719, 699. Anal. Calcd for $C_{14}H_{16}O_4S$ (280.35): C, 59.98; H, 5.75; S, 11.44. Found: C, 59.89; H, 5.82; S, 11.28.

4.3.2. 5-Chloro-α-(3,4,5-trimethoxyphenyl)-2-thiophenemethanol (5c). The general procedure 2, starting from **2** (0.55 mL), gave 93% (1.8 g) of **5c** (eluent: cyclohexane/AcOEt 70:30): mp 94–95 °C; ^{1}H NMR δ 6.70 (d, 1H, J=3.8 Hz), 6.59 (m, 3H), 3.80 (s, 9H), 5.77 (s, 1H), 3.38 (br s, 1H); ^{13}C NMR δ 153.1 (q, 2C), 146.7 (q), 138.3 (q), 137.2 (q), 129.7 (q), 125.5 (t), 123.9 (t), 103.0 (t, 2C), 72.3 (t), 60.7 (p), 55.9 (p, 2C); IR (KBr) ν; 3307, 3219, 2934, 2834, 1596, 1509, 1466, 1418, 1330, 1238, 1132, 1059, 993, 750. Anal. Calcd for $C_{14}H_{15}ClO_4S$ (314.79): C, 53.42; H, 4.80; S, 10.19. Found: C, 53.59; H, 4.94; S, 10.03.

4.3.3. 5-Methoxy-α-(3,4,5-trimethoxyphenyl)-2-thiophenemethanol (6b). The general procedure 2, starting from **3** (0.60 mL), gave 87% (1.6 g) of **6b** (eluent: cyclohexane/AcOEt 70:30): mp 80–82 °C; ^{1}H NMR δ 6.67 (s, 2H), 6.51 (d, 1H, J=3.8 Hz), 6.01 (d, 1H, J=3.8 Hz), 5.81 (d, 1H, J=3.0 Hz), 3.85 (s, 12H), 2.43 (d, 1H, J=3.8 Hz); ^{13}C NMR δ 166.8 (q), 153.2 (q, 2C), 138.4 (q), 137.3 (q), 133.5 (q), 122.8 (t), 103.1 (t, 2C), 102.8 (t), 72.8 (t), 60.8 (p), 60.2 (p), 56.1 (p, 2C); IR (KBr) ν; 3362, 2936, 2835, 1595, 1558, 1509, 1462, 1422, 1329, 1238, 1209,

1129, 1036, 1005, 757. Anal. Calcd for $C_{15}H_{18}O_5S$ (310.37): C, 58.05; H, 5.85; S, 10.33. Found: C, 58.26; H, 5.55; S, 10.19.

4.4. General procedure 3: substituted thiophenes 4d–g, 5d–f and 6c–e by deprotonation of thiophenes 1–3 using Bu_3MgLi and subsequent cross-coupling with aromatic halides

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 mL) at −10 °C were added BuLi (6.0 mmol) and, 1 h later, the required thiophene (6.0 mmol). After 2 h at room temperature, the mixture thus obtained was added dropwise to a solution of the aromatic halide (6.0 mmol) and $PdCl_2$(dppf) (49 mg, 60 μmol), and the mixture was heated at reflux for 18 h before addition of water saturated with NH_4Cl (1 mL).

4.4.1. 2-(2-Thienyl) pyridine (4d). The general procedure 3, starting from **1** (0.48 mL) and using 2-bromopyridine (0.58 mL), gave 77% (0.74 g) of **4d** (eluent: CH_2Cl_2) as a white solid. The physical and spectral data are analogous to those obtained for a commercial sample.

4.4.2. 3-(2-Thienyl) quinoline (4e). The general procedure 3, starting from **1** (0.48 mL) and using 3-bromoquinoline (0.83 mL), gave 56% (0.71 g) of **4e** (eluent: CH_2Cl_2/Et_2O 80:20) as a yellow solid. The physical and spectral data are in accordance with those of the literature.[18b,24]

4.4.3. 2-Phenylthiophene (4f). The general procedure 3, starting from **1** (0.48 mL) and using iodobenzene (0.67 mL), gave 84% (0.81 g) of **4f** (eluent: petrol/CH_2Cl_2 80:20) as a white solid: mp 94 °C. The physical and spectral data are analogous to those obtained for a commercial sample.

4.4.4. 2-(4-Methoxyphenyl) thiophene (4g). The general procedure 3, starting from **1** (0.48 mL) and using 4-bromoanisole (0.75 mL), gave 92% (1.1 g) of **4g** (eluent: petrol/CH_2Cl_2 60:40) as a white solid: mp 102 °C (lit.[25] 106–107 °C); IR (KBr) ν; 3099, 3072, 2961, 2930, 2835, 1604, 1500, 1293, 1274, 1261, 1104, 1031, 822, 810, 698. The other analyses were found identical to those previously described.[25]

4.4.5. 2-(5-Chloro-2-thienyl) pyridine (5d). The general procedure 3, starting from **2** (0.55 mL) and using 2-bromopyridine (0.58 mL), gave 68% (0.80 g) of **5d** (eluent: CH_2Cl_2): mp 69–70 °C (lit.[26] 69–70 °C); ^{1}H NMR δ 8.53 (d, 1H, J=4.9 Hz), 7.68 (td, 1H, J=7.9, 1.5 Hz), 7.58 (d, 1H, J=7.1 Hz), 7.33 (d, 1H, J=3.8 Hz), 7.15 (ddd, 1H, J=7.1, 4.9, 1.1 Hz), 6.92 (d, 1H, J=3.8 Hz); ^{13}C NMR δ 150.8 (q), 148.7 (t), 143.0 (q), 135.9 (t), 131.4 (q), 126.7 (t), 122.9 (t), 121.5 (t), 117.2 (t). Anal. Calcd for C_9H_9ClNS (195.67): C, 55.25; H, 3.09; N, 7.16; S, 16.39. Found: C, 55.16; H, 3.03; N, 7.07; S, 16.33. The other analyses were found identical to those previously described.[26]

4.4.6. 2-Chloro-5-(4-methoxyphenyl) thiophene (5e).[27] The general procedure 3, starting from **2** (0.55 mL) and using 4-bromoanisole (0.75 mL), gave 81% (1.1 g) of **5e** (eluent: petrol/CH_2Cl_2 60:40): mp 100 °C; ^{1}H NMR δ 7.40 (d, 2H, J=8.6 Hz), 6.91 (d, 1H, J=4.1 Hz), 6.87 (d, 2H, J=8.7 Hz), 6.82 (d, 1H, J=3.8 Hz), 3.74 (s, 3H); ^{13}C NMR δ 159.3 (q), 142.8 (q), 127.8 (q), 126.8 (t), 126.7 (t, 2C), 126.4 (q), 121.0 (t), 114.3 (t, 2C), 55.2 (p); IR (KBr) ν; 2956, 2836, 1603, 1505, 1438, 1288, 1257, 1180, 1031, 827, 793. Anal. Calcd for $C_{11}H_9ClOS$ (224.71): C, 58.80; H, 4.04; S, 14.27. Found: C, 58.53; H, 4.11; S, 14.48.

4.4.7. Methyl 4-(5-chloro-2-thienyl) benzoate (5f). The general procedure 3, starting from **2** (0.55 mL) and using methyl 4-iodobenzoate (1.6 g), gave 22% (0.33 g) of **5f** (eluent: petrol/CH_2Cl_2 70:30): mp 146–148 °C; ^{1}H NMR δ 8.03 (d, 2H, J=8.3 Hz), 7.56 (d, 2H, J=8.3 Hz), 7.19 (d, 1H, J=4.1 Hz), 6.93 (d, 1H, J=3.8 Hz), 3.93 (s, 3H); ^{13}C NMR δ 167.0 (q), 141.9 (q), 138.2 (q), 131.2 (q), 130.8 (t, 2C), 129.5 (q), 127.8 (t), 125.4 (t, 2C), 124.1 (t), 52.6 (p); IR (KBr) ν; 3014, 2958, 1725, 1603, 1436, 1291, 1277, 1187, 1112, 1007, 850, 801, 765, 695. Anal. Calcd for $C_{12}H_9ClO_2S$ (252.72): C, 57.03; H, 3.59; S, 12.69. Found: C, 56.95; H, 3.41; S, 12.63.

4.4.8. 2-(5-Methoxy-2-thienyl) pyridine (6c). The general procedure 3, starting from **3** (0.60 mL) and using 2-bromopyridine (0.58 mL), gave 56% (0.64 g) of **6c** (eluent: petrol/CH_2Cl_2 70:30): mp <50 °C (lit.[28] 42–43.5 °C); ^{13}C NMR δ 168.0 (q), 152.3 (q), 148.7 (t), 135.8 (t), 130.1 (q), 122.4 (t), 120.4 (t), 116.8 (t), 104.3 (t), 59.4 (p); IR (KBr) ν; 3072, 3007, 2965, 2936, 2873, 2827, 1589, 1556, 1494, 1461, 1427, 1299, 1278, 1237, 1209, 1151, 1091, 1067, 1043, 997, 961, 766, 744, 728, 620. The other analyses are in accordance with those of the literature.[28]

4.4.9. 2-Methoxy-5-phenylthiophene (6d). The general procedure 3, starting from **3** (0.60 mL) and using iodobenzene (0.67 mL), gave 67% (0.76 g) of **6d** (eluent: petrol/CH_2Cl_2 80:20) as a pale blue oil: ^{1}H NMR δ 7.48 (d, 2H, J=7.2 Hz), 7.33 (t, 2H, J=7.5 Hz), 7.21 (t, 1H, J=7.3 Hz), 6.18 (d, 1H, J=3.8 Hz), 6.18 (d, 1H, J=3.8 Hz), 3.92 (s, 3H); ^{13}C NMR δ 165.8 (q), 134.5 (q), 129.9 (q), 128.7 (t, 2C), 126.4 (t), 124.6 (t, 2C), 120.4 (t), 104.5 (t), 59.8 (p); IR (KBr) ν; 3023, 2939, 2827, 1555, 1508, 1480, 1446, 1428, 1269, 1231, 1204, 1059, 1000, 752, 690. Anal. Calcd for $C_{11}H_{10}OS$ (190.26): C, 69.44; H, 5.30; S, 16.85. Found: C, 69.23; H, 5.47; S, 16.81.

4.4.10. Methyl 4-(5-methoxy-2-thienyl) benzoate (6e). The general procedure 3, starting from **3** (0.60 mL) and using methyl 4-iodobenzoate (1.6 g), gave 40% (0.60 g) of **6e** (eluent: petrol/CH_2Cl_2 50:50): mp 126–127 °C; ^{1}H NMR δ 7.99 (d, 2H, J=8.3 Hz), 7.52 (d, 2H, J=7.9 Hz), 7.10 (d, 1H, J=3.8 Hz), 6.22 (d, 1H, J=4.1 Hz), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR δ 167.3 (q), 166.8 (q), 139.0 (q), 130.1 (t, 2C), 128.6 (q), 127.6 (q), 124.1 (t, 2C), 122.5 (t), 105.0 (t), 60.2 (p), 52.0 (p); IR (KBr) ν; 3084, 2942, 2831, 1709, 1604, 1511, 1482, 1430, 1411, 1291, 1212, 1180, 1111, 1065, 1014, 988, 848, 762, 696. Anal. Calcd for $C_{13}H_{12}O_3S$ (248.30): C, 62.88; H, 4.87; S, 12.91. Found: C, 62.59; H, 4.83; S, 12.81.

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Pyridazine derivatives. Part 40: Reactivity of 5-alkynylpyridazin-3(2*H*)-ones toward hydrochloric acid☆

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Abstract—5-Alkynylpyridazin-3(2*H*)-ones or 5-(2-chloroalkenyl)pyridazin-3(2*H*)-ones were isolated during the cleavage of the methoxymethyl group in a series of 5-alkynyl-2-methoxymethylpyridazin-3(2*H*)-ones by treatment with hydrochloric acid. The efficient and selective cleavage of the methoxymethyl group in these compounds can be performed under mild conditions by employing aluminium chloride.

1. Introduction

The recent advances in combinatorial chemistry and high-throughput screening have confirmed the tremendous importance of heterocycles as templates in the search for novel pharmacologically useful low molecular weight compounds.[2] Accordingly, the development of new, robust and efficient syntheses of functionalized heterocyclic compounds, both in solution or solid phase, is an expanding field. The numerous syntheses of pyridazin-3(2*H*)-ones published in recent years[3] represent significant progress in terms of the efficient protection and deprotection of position 2 of the heterocyclic ring. Although all structural studies on this nucleus have shown that pyridazin-3(2*H*)-ones exist in the keto form,[3] reactions involving ambident rings that possess a tautomeric or mesomeric structure are often inefficient and lack regiocontrol. For this reason, most of the studies reported for this scaffold use as starting materials pyridazinones in which position 2 is blocked. Numerous literature examples concern analogues in which position 2 is substituted by groups such as Me, or Ph, which are not strictly protecting groups in the true sense as they cannot be removed—their role being limited to blocking the enolizable carbonyl group. Elegant and selective transformations using the benzyloxymethyl (BOM) group have been described by Mátyus as part of a comprehensive program aimed at the synthesis of 4,5-disubstituted- and 4,5-heterofused pyridazinones.[4] Although the introduction of the benzyl group can be easily achieved, cleavage by classical methods (H_2/Pd) is sometimes problematic in polyfunctional derivatives.[5] In this respect, several authors have employed Lewis acids as an alternative and efficient deprotection procedure.[5a,b,6]

A survey of the literature on protecting groups[7] reveals that, although there are excellent methods available for the deprotection of *O*-alkyl and *O*-alkyloxyalkyl groups, methods for the deprotection of the amide or lactam functionality are limited and usually require acidic conditions.[7] As a consequence, new protecting groups and/or reagents that are able to perform deprotection under mild and selective conditions are lacking and new developments in this area are, therefore, of great interest.

In the course of our ongoing project aimed at the development of novel pyridazinone-based antiplatelet agents,[8] we recently described the synthesis of 5-aryl-, 5-alkenyl- and 5-alkynylpyridazin-3(2*H*)-ones through palladium-catalysed reactions.[1,9] The low reactivity of the starting 5-halopyridazin-3(2*H*)-ones in these transformations led us to block position 2 of the heterocycle by introducing a methoxymethyl group in the heterocyclic

☆ For the previous paper in this series, see Ref. 1.

Keywords: Pyridazinones; Electrophilic addition; Protecting groups; X-ray diffraction.
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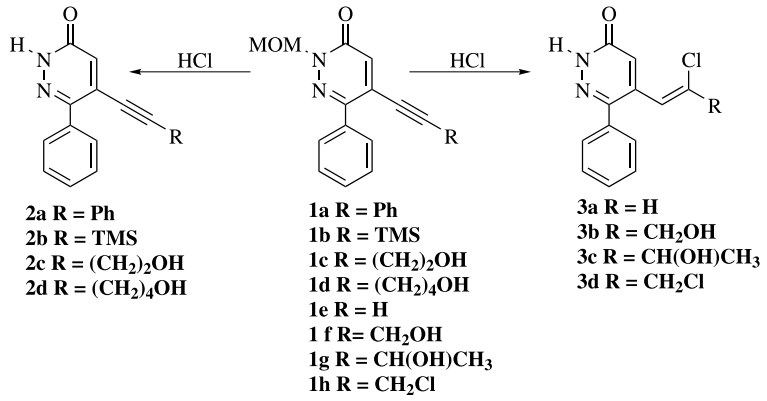


Scheme 1. Reaction of 5-alkynylpyridazin-3(2*H*)-ones **1** with hydrochloric acid.

lactam function. After the cross-coupling reaction had finished, the cleavage of the methoxymethyl group in most of these compounds was performed using the simplest method, that is, employing hydrochloric acid. Despite the fact that these conditions successfully afforded the expected pyridazin-3(2*H*)-ones bearing aryl or alkenyl groups in the 5-position,[9] we have recently documented[10] that this reagent failed in the deprotection of several pyridazin-3(2*H*)-ones that contained reactive alkynyl substituents.

The compounds obtained during the cleavage of the methoxymethyl group employing 6 N hydrochloric acid in a series of 5-alkynyl-6-phenyl-2-methoxymethylpyridazin-3(2*H*)-ones **1** are shown in Scheme 1. It can be seen that the behaviour of compounds **1** upon treatment with hydrochloric acid is highly dependent on the nature of the alkynyl group at position 5 (Table 1).

Table 1. Reaction of 5-alkynylpyridazin-3(2*H*)-ones **1** with hydrochloric acid

Compound	R	Yield (%)	Mp (°C)
2a	Ph	80	150–151
2b	TMS	85	157–158
2c	$(CH_2)_2OH$	78	201–202
2d	$(CH_2)_4OH$	70	189–190
3a	H	84	175–176
3b	CH_2OH	78	146–147
3c	$CH(OH)CH_3$	70	87–89
3d	CH_2Cl	83	197–199

Pyridazinones bearing a sterically hindered or less reactive acetylenic group (**1a**–**d**) afforded the desired 5-alkynyl-6-phenylpyridazin-3(2*H*)-ones **2**. In contrast, in compounds containing a reactive ethynyl or propargyl residue at position 5 (**1e**–**h**) hydrochloric acid promotes—in addition to cleavage of the protecting group (MOM)—electrophilic addition to the multiple bond to give 5-(chloroalkenyl)-6-phenylpyridazin-3(2*H*)-ones **3**. The screening of milder conditions to perform deprotection revealed that such addition even occurs when the experiments are performed at room temperature or using more dilute hydrochloric acid.

The identity of compounds **2**, and especially of the addition products **3**, was unambiguously established on the basis of their analytical and spectroscopic data (see Section 2). Additionally, the structure of 5-[(*Z*)-2-chloro-1-vinyl]-6-phenylpyridazin-3(2*H*)-one (**3a**) was confirmed by X-ray crystallography (Fig. 1).

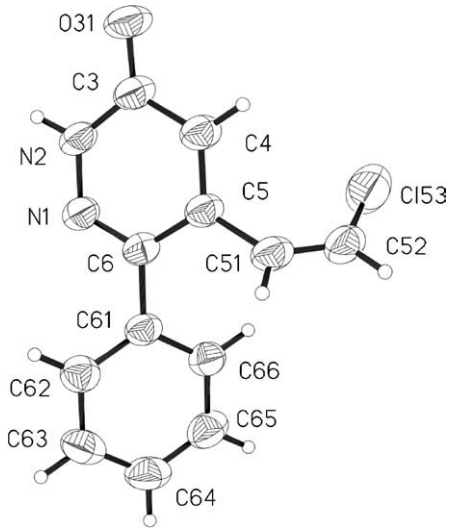


Figure 1. Plot showing the crystal structure and atomic numbering scheme for **3a**. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

In the crystal structure of **3a** the rings are essentially planar. The dihedral angle between the least-squares planes of the pyridazine moiety and the phenyl ring at C6 is 42.7(1)°. Average bond distances are as follows: in the phenyl ring, 1.383(2) Å; in the pyridazine ring, 1.372(1) Å. The crystal structure is stabilised by means of hydrogen bonds that lead to the formation of dimers [N2···O31 = 2.837(3) Å, $(2-x,-y,1-z)$, N2–H2···O31 = 159°]. A packing diagram for this system is shown in Figure 2.

The data obtained during the structural studies performed on compounds **3a**–**d** fully support the proposed structure, confirming in all cases the presence of the chlorine atom at C-2 of the alkenyl residue in the 5-position. Regiospecific formation of compounds **3** can be rationalised in terms of the conjugate electrophilic addition of the hydrochloric acid to the triple bond of the acetylenic-pyridazinone or, alternatively, as a consequence of the different stabilities of the possible carbocation intermediates (strongly affected by the π-deficient nature of the neighbouring azinone system).

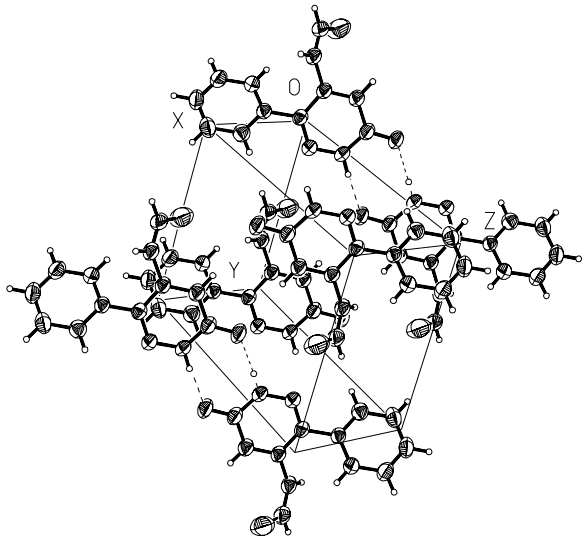


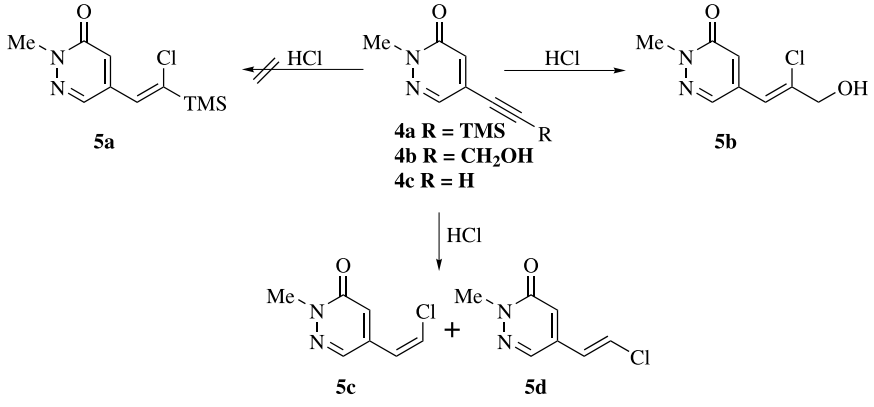
Figure 2. Packing of the molecules of **3a** in the unit cell, showing their dimeric association through H-bonds of the type N–H···O.

Encouraged by the observed reactivity of compounds **1e–h**, we became interested in studying similar transformations starting from derivatives without the phenyl group at position 6[1] (Scheme 2). More specifically, we selected several 5-alkynylpyridazin-3(2*H*)-ones that have a non-removable methyl group at position 2 of the heterocycle (**4**). The results of this study are represented in Scheme 2. The 5-alkynyl-2-methylpyridazin-3(2*H*)-ones **4** also proved to be highly reactive toward electrophilic addition of hydrochloric acid under the aforementioned experimental conditions. As shown in Scheme 2, the compounds isolated from transformations are similar to those previously described (i.e., having the 2-chloroalkenyl fragment at position 5 of the heterocyclic ring). Thus, 2-methyl-5-trimethylsilylethynylpyridazin-3(2*H*)-one (**4a**) is completely unreactive (even after more than 48 h of heating in 6 N hydrochloric acid). In contrast, pyridazinones **4b–c** proved to be highly reactive and afforded the addition products **5b–d** in satisfactory yields (Table 2).

Interestingly, the reaction of **4c** with hydrochloric acid yielded a 3:1 mixture of the isomeric (*E*)- or (*Z*)-5-(2-chloro-1-vinyl)pyridazin-3(2*H*)-ones **5c** and **5d** (see Section 2). Comparison of these results with similar experiments on the 5-ethynyl-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-one **1e** (Scheme 1) reveal the importance of steric effects, which are produced by the phenyl group at position 6, on the regiochemistry of these transformations.

While this work was in progress, a paper was published[11] describing the reactivity of a series of 5-alkynyl-4-chloro-2-methyl-and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones with oxygen and sulfur nucleophiles. Additionally this work studied the synthesis of different series of bicyclic pyridazinones but also mechanistic aspects of these transformations. These previous results, along with the findings presented here, confirm the high reactivity of alkynylpyridazin-3(2*H*)-ones and their usefulness as attractive starting materials for future functionalization of the heterocyclic scaffold.

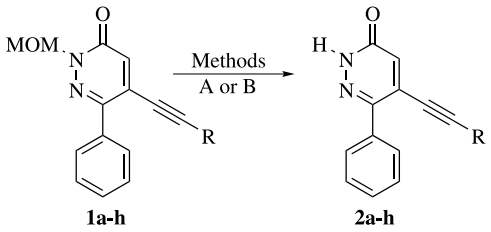
In an effort to find selective conditions to cleave the MOM group in pyridazinones bearing acid-sensitive functionalities in the 5-position (such as **1e–g**), other reagents capable of removing this group under mild conditions were studied. The best results were obtained on using Lewis acids such as aluminium chloride or boron tribromide (Scheme 3). These two compounds have come to be regarded as reagents of choice for the efficient cleavage of ethers[7] and have already been employed by several authors to remove the BOM[4] or benzyl groups[6] in pyridazinones. In order to test the scope of these reagents to perform the cleavage of the MOM group in these functionally sensitive pyridazinones, we also included in this study the 5-alkynylpyridazin-3(2*H*)-ones that were successfully deprotected using hydrochloric acid (Scheme 3).



Scheme 2. Reaction of 5-alkynylpyridazin-3(2*H*)-ones **4** with hydrochloric acid.

Table 2. Reaction of 5-alkynylpyridazin-3(2*H*)-ones **4** with hydrochloric acid

Compound	R_5	Yield (%)	Mp (°C)
5b	(*Z*) CH═C(Cl)CH_2OH	60	148–149
5c	(*Z*) CH═CH–Cl	68	240–241
5d	(*E*) CH═CH–Cl	23	181–182



1a-h **2a-h**

Scheme 3. Selective cleavage of the MOM group in **1** employing Lewis acids. Method A: $AlCl_3$/toluene or dichloromethane. Method B: (i) BBr_3/CH_2Cl_2, −78 °C; (ii) CH_3COONH_4.

A quick preliminary screening showed that both reagents cleaved the MOM group from the heterocyclic ring in satisfactory yields without affecting the acetylenic group in the 5-position. The best results were obtained working at −78 °C for boron tribromide (see Section 2) and in refluxing toluene or dichloromethane (Section 2) for aluminium chloride (Scheme 3).

Disappointingly, although not completely unexpectedly, the deprotection of compounds **1c**, **1d**, **1f**, **1g** (which contain an alcohol residue) with BBr_3 led to the formation of variable amounts of the corresponding bromo derivatives as a consequence of the brominating properties of this reagent.[12] These results, together with the easy manipulation and cheapness of $AlCl_3$, confirmed the superiority of this reagent in the deprotection of the MOM group at position 2 of the heterocycle (Table 3).

Table 3. Selective cleavage of the MOM group in 5-alkynyl-2-methoxymethyl-6-phenylpyridazin-3(2*H*)-ones employing $AlCl_3$

Compound	R	Yield (%)	Mp (°C)
2a	Ph	98	150–151
2b	TMS	97	156–157
2c	$(CH_2)_2OH$	80	201–202
2d	$(CH_2)_4OH$	88	189–190
2e	H	90	202–203
2f	CH_2OH	76	169–170
2g	$CH(OH)CH_3$	80	160–162

In summary, the electrophilic addition of hydrochloric acid to several 5-alkynylpyridazin-3(2*H*)-ones has been studied. The products obtained during these reactions have been identified, confirming the presence of a chlorine atom at position 2 of the double bond formed during the addition. The cleavage of the MOM group at position 2 of pyridazinones bearing acid-sensitive alkynyl substituents at position 5 can be successfully achieved using aluminium chloride.

2. Experimental

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured using a Perkin–Elmer 1640 FTIR spectrophotometer with samples as potassium bromide pellets. The NMR spectra were recorded on Bruker AM300 and XM500 spectrometers. Chemical shifts are given as δ values against tetramethylsilane as internal standard and *J* values are given in Hz. Mass spectra were obtained on a Varian MAT-711 instrument. High-resolution mass spectra were obtained on an Autospec Micromass spectrometer. Elemental analyses were performed on a Perkin–Elmer 240B apparatus at the Microanalysis Service of the University of Santiago de Compostela. The reactions were monitored by TLC with 2.5 mm Merck silica gel GF 254 strips, and the purified compounds each showed a single spot; unless stated otherwise, iodine vapour and/or UV light were used for detection of compounds. Commercially available starting materials and reagents were purchased and used without further purification. A series of NOE experiments provided unequivocal confirmation of proposed structures for compounds **3b–d** and **5b**.

The X-ray crystallographic determination of **3a** was performed using a Siemens P4 four-circle diffractometer with graphite monochromated Cu K_α radiation. The intensity data were collected using 2θ–ω scans, with ω scan width equal to the difference of the background and the high ω background plus the separation between the $K_{\alpha1}$ and $K_{\alpha2}$ positions; 2526 reflections measured ($3.71<\theta<68.94°$, $-1<h<6$, $-9<k<9$, $-14<l<14$), 1935 unique (merging $R=0.055$) and 1463 observed [$F^2\geq 2\sigma(F)^2$] reflections. Empirical absorption correction, via ψ scans was applied.[13] Three standard reflections were monitored every 100 reflections (intensity decay: 6%).

The crystal structure of **3a** was solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U_{eq} of their parent atoms. Data collection: XSCANS.[14] Cell refinement: XSCANS.[14] Data reduction: XSCANS.[14] Program used to solve structure: SIR92.[15] Program used to refine structure: SHELXL97.[16] Molecular graphics: DIAMOND.[17] Software used to prepare material for publication: PLATON.[18]

2.1. Reaction of 5-substituted pyridazin-3(2*H*)-ones with 6 N hydrochloric acid. Representative procedure for the synthesis of compounds 2a–d, 3a–b, and 5b–e

A mixture of the corresponding 5-alkynylpyridazin-3(2*H*)-one **1** or **4** (1.11 mmol), MeOH (5 mL) and 6 N HCl (15 mL) was heated under reflux until the starting material had been completely consumed (24–48 h). The mixture was extracted with dichloromethane, the organic layer dried with anhydrous Na_2SO_4 and the solvent evaporated in vacuo. The resulting residue was purified by column chromatography on silica gel and then crystallised from the appropriate solvent.

2.1.1. 6-Phenyl-5-(phenylethynyl)pyridazin-3(2*H*)-one (2a). Purification by column chromatography on silica gel (AcOEt/hexane 1:5) and then recrystallization gave a white solid; yield 80%. Mp: 158–160 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 2130 (C≡C), 1651 (CO), 1577 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 11.25 (br s, 1H, NH deuterium oxide exchangeable), 7.78 (m, 2H, Aromatics), 7.49 (m, 3H, Aromatics), 7.36 (m, 5H, Aromatics), 7.19 (s, 1H, H_4). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 160.7, 147.4, 134.9, 132.3, 132.2, 130.4, 130.1, 129.8, 129.2,

128.9, 128.4, 121.7, 101.2, 84.8. MS (70 eV) *m/z* (%): 272 (M^+, 100), 271 (40), 215 (32). Anal. Calcd for $C_{18}H_{12}N_2O$: C, 79.39; H, 4.44; N, 10.29. Found: C, 79.44; H, 4.49; N, 10.30.

2.1.2. 6-Phenyl-5-(trimethylsilylethynyl)pyridazin-3(2*H*)-one (2b). Purification by column chromatography on silica gel (AcOEt/hexane 1:3) and then recrystallization gave a white solid; yield 85%. Mp: 156–157 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 2855 (NH), 2136 (C≡C), 1654 (CO), 1555 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 12.46 (br s, 1H, NH deuterium oxide exchangeable), 7.73 (m, 2H, Aromatics), 7.42 (m, 3H, Aromatics), 7.13 (s, 1H, H_4), 0.16 (s, 9H, 3×CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 161.2, 147.4, 134.7, 133.1, 129.7, 129.5, 129.2, 128.2, 108.9, 99.3, −0.4. MS (70 eV) *m/z* (%): 268 (M^+, 100), 253 (94), 225 (24), 139 (26), 107 (28), 77 (60). Anal. Calcd for $C_{15}H_{16}N_2OSi$: C, 67.13; H, 6.01; N, 10.44. Found: C, 67.15; H, 6.04; N, 10.45.

2.1.3. 5-(4-Hydroxybut-1-yn-1-yl)-6-phenylpyridazin-3(2*H*)-one (2c). Purification by column chromatography on silica gel (AcOEt/hexane 1:5) and then recrystallization gave white crystals; yield 80%. Mp: 199–201 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3566–2920 (OH, NH), 2226 (C≡C), 1652 (CO), 1558 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 10.91 (br s, 1H, NH deuterium oxide exchangeable), 7.67 (m, 2H, Aromatics), 7.43 (m, 3H, Aromatics), 7.08 (s, 1H, H_4), 3.67 (t, J=6.2 Hz, 2H, –CH_2–), 2.62 (t, J=6.2 Hz, 2H, CH_2), 1.48 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 159.6, 145.6, 135.0, 132.3, 129.3, 128.9, 128.8, 128.2, 100.9, 77.0, 59.3, 23.8. MS (70 eV) *m/z* (%): 240 (M^+, 60), 209 (51), 181 (64), 152 (100), 77 (43). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.05; H, 5.06; N, 11.71.

2.1.4. 5-(6-Hydroxyhex-1-yn-1-yl)-6-phenylpyridazin-3(2*H*)-one (2d). Purification by column chromatography on silica gel (AcOEt/hexane 1:5) and then recrystallization gave white crystals; yield 80%. Mp: 189–190 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3450–2900 (OH, NH), 2500 (NH), 2250 (C≡C), 1625 (CO). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 12.12 (1H, br s, NH deuterium oxide exchangeable), 7.67 (m, 2H, Aromatics), 7.39 (m, 3H, Aromatics), 7.07 (s, 1H, H_4), 3.57 (t, J=6.4 Hz, 2H, –CH_2–), 2.61 (br s, 1H, OH), 2.35 (t, J=6.4 Hz, 2H, CH_2), 1.53 (m, 4H, 2×CH_2). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 161.1, 147.9, 135.1, 132.4, 130.7, 129.6, 129.1, 128.3, 103.7, 76.8, 62.2, 31.8, 24.5, 19.8. MS (70 eV) *m/z* (%): 267 (M^+, 48), 209 (51), 223 (30), 197 (100). Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.75; H, 6.11; N, 10.73.

2.1.5. 5-[(*Z*)-2-Chloro-1-vinyl]-6-phenylpyridazin-3(2*H*)-one (3a). Purification by column chromatography on silica gel (AcOEt/hexane 1:5) and then recrystallization gave crystals of **3a**; yield 90%. Mp: 175–176 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 2989 (NH), 1661 (CO), 1589 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 13.04 (br s, 1H, NH), 7.42 (m, 5H, Aromatics), 7.03 (s, 1H, H_4), 6.53 (d, J=8.2 Hz, 1H, CH), 6.32 (d, J=8.2 Hz, 1H, CH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 162.4, 147.6, 138.8, 135.0, 129.6, 129.5, 129.3, 128.8, 125.3, 125.2. MS (70 eV) *m/z* (%): 232 (M^+, 12), 197 (100). Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.99; H, 3.91; N, 11.89.

X-ray structure analysis. Crystals of **3a** were grown by slow evaporation from 1:1 isopropanol/ethanol solution. Crystal data. $C_{12}H_9N_2OCl$, M=232.66, Triclinic, a=5.7408(2) Å, b=7.8800(6) Å, c=12.3240(8) Å; α=85.145(6)°, β=77.999(4)°, γ=84.299(5)°, V=541.45(6) $Å^3$ (by least-squares refinement on diffractometer angles for 32 automatically centered reflections with $10.77<\theta<27.98°$, λ=1.54178 Å, T=293(2) K), space group $P\bar{1}$, Z=2, D_c=1.4271(2) g cm^{-3}, μ=2.946 mm^{-1}. A prism-like colourless crystal (0.40×0.18×0.04 mm^3) was used for the analysis. CCDC 230882 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

2.1.6. 5-[(*Z*)-2-Chloro-3-hydroxyprop-1-en-1-yl]-6-phenylpyridazin-3(2*H*)-one (3b). Purification by column chromatography on silica gel (AcOEt/hexane 1:3) and then recrystallization gave crystals of **3b**; yield 90%. Mp: 146–147 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3360–2900 (OH, NH), 1662 (CO), 1569 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 13.25 (br s, 1H, NH), 7.44 (m, 5H, Aromatics), 7.04 (s, 1H, H_4), 6.57 (s, 1H, CH), 5.71 (t, J=5.9 Hz, 1H, OH), 4.06 (d, J=5.9 Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.3, 146.0, 140.5, 139.2, 135.4, 129.1, 128.9, 128.7, 128.6, 118.5, 65.0. MS (70 eV) *m/z* (%): 262 (M^+, 10), 215 (54), 139 (26), 105 (100). Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.46; H, 4.21; N, 10.68.

2.1.7. 5-[(*Z*)-2-Chloro-3-hydroxybut-1-en-1-yl]-6-phenylpyridazin-3(2*H*)-one (3c). Purification by column chromatography on silica gel (AcOEt/hexane 1:3) and then recrystallization gave white crystals of **3c**; yield 68%. Mp: 87–89 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3566–2980 (OH, NH), 1654 (CO), 1586 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 13.26 (br s, 1H, NH), 7.42 (m, 5H, Aromatics), 6.96 (s, 1H, H_4), 6.59 (s, 1H, CH), 5.60 (dq, J=6.6 Hz, 2.1 Hz, 1H, OH), 4.25 (br s, 1H, OH), 1.18 (d, J=6.6 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.3, 144.5, 146.1, 139.5, 135.2, 129.1, 128.9, 128.8, 128.7, 118.8, 70.1, 21.7. MS (70 eV) *m/z* (%): 276 (M^+, 30), 258 (20), 139 (100). Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12. Found: C, 60.79; H, 4.73; N, 10.15.

2.1.8. 5-[(*Z*)-2-Chloro-3-chloroprop-1-en-1-yl]-6-phenylpyridazin-3(2*H*)-one (3d). Purification by column chromatography on silica gel (AcOEt/hexane 1:4) and then recrystallization gave white crystals of **3d**; yield 83%. Mp: 197–199 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 2852–3300 (NH), 1665 (CO). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 13.33 (br s, 1H, NH), 7.42 (m, 5H, Aromatics), 6.97 (s, 1H, H_4), 6.87 (s, 1H, CH), 4.55 (s, 2H, CH_2). ^{13}C NMR (DMSO-d_6 75 MHz), δ (ppm): 160.3, 145.7, 139.0, 135.8, 135.6, 129.3, 128.8, 128.6, 127.3, 125.5, 49.0. MS (70 eV) *m/z* (%): 280 (M^+, 38), 245 (50), 209 (40). Anal. Calcd for

$C_{13}H_{10}Cl_2N_2O$: C, 55.54; H, 3.59; N, 9.96. Found: C, 55.60; H, 3.78; N, 9.99.

2.1.9. 5-[(*Z*)-2-Chloro-3-hydroxyprop-1-en-1-yl]-2-methylpyridazin-3(2*H*)-one (5b). Purification by column chromatography on silica gel (AcOEt/hexane 1:4) and then recrystallization gave white crystals of **5b**; yield 60%. Mp: 148–149 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3347 (OH), 1650 (CO). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 8.06 (d, $J=2.0$ Hz, 1H, H_6), 7.12 (d, $J=2.0$ Hz, 1H, H_4), 6.81 (s, 1H, CH), 5.86 (t, $J=5.8$ Hz, 1H, OH), 4.15 (d, $J=5.8$ Hz, 2H, CH_2), 3.62 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 75 MHz), δ (ppm): 160.6, 142.1, 138.2, 136.9, 126.1, 117.2, 65.6, 39.7. MS (70 eV) *m/z* (%): 200 (M^+, 100). Anal. Calcd for $C_8H_9ClN_2O_2$, C 47.89, H 4.52, N 13.96; found, C 47.94, H 4.53, N 13.98.

2.1.10. 5-[(*Z*)-2-Chloro-1-vinyl]-2-methylpyridazin-3(2*H*)-one (5c). Purification by column chromatography on silica gel (AcOEt/hexane 1:6) and then recrystallization gave white crystals of **5d**; yield 68%. Mp: 240–241 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 1643. ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 7.95 (d, $J=1.93$ Hz, 1H, H_6), 7.17 (d, $J=1.93$ Hz, 1H, H_4), 6.56 (d, $J=8.2$ Hz, 1H, CH), 6.41 (d, $J=8.2$ Hz, 1H, CH), 3.75 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 75 MHz), δ (ppm): 160.4, 137.4, 136.2, 127.3, 125.7, 123.4, 39.9. MS (70 eV) *m/z* (%): 170 (M^+, 15), 142 (26). Anal. Calcd for $C_7H_7ClN_2O$: C, 49.28; H, 4.14; N, 16.42. Found: C, 49.28; H, 4.16; N, 16.40.

2.1.11. 5-[(*E*)-2-Chloro-1-vinyl]-2-methylpyridazin-3(2*H*)-one (5d). Purification by column chromatography on silica gel (AcOEt/hexane 1:5) and then recrystallization gave crystals of **5e**; yield 23%. Mp: 181–183 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 1645 (CO). ^1H NMR (DMSO-d_6 300 MHz), δ (ppm): 7.76 (d, $J=2.00$ Hz, 1H, H_6), 6.91 (d, $J=13.6$ Hz, 1H, CH), 6.72 (d, $J=2.00$ Hz, 1H, H_4), 6.63 (d, $J=13.6$ Hz, 1H, CH), 3.77 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6 75 MHz), δ (ppm): 162.1, 137.8, 133.7, 128.1, 127.0, 124.5, 40.3. MS (70 eV) *m/z* (%): 170 (M^+, 100). Anal. Calcd for $C_7H_7ClN_2O$: C, 49.28; H, 4.14; N, 16.42. Found: C, 49.31; H, 3.14; N, 16.41.

2.2. Cleavage of the MOM group employing $AlCl_3$ (Method A)—typical procedure

In a carefully purged flask, $AlCl_3$ (670 mg, 5.03 mmol) was suspended in dry toluene (8 mL) and the mixture was stirred at room temperature during 10 min. The corresponding 2-methoxymethylpyridazin-3(2*H*)-one **1** (1.00 mmol) in dry toluene (6 mL) was added dropwise and the mixture was heated under reflux for 1 h. Once the starting material had been consumed, 50 mL of ice was added and the mixture was stirred for 30 min. The mixture was extracted with chloroform and the organic layer dried with anhydrous Na_2SO_4. The solvent was removed in vacuo and the resulting solid was washed with ether, purified by column chromatography on silica gel and then recrystallized.

2.3. Cleavage of the MOM group employing BBr_3 (Method B)—typical procedure

A 2 M solution of boron tribromide (2.1 mmol) was slowly added under argon to a cold (−78 °C) solution of the 2-MOM-pyridazinone **1** (2 mmol) in dry dichloromethane. The mixture was stirred under these conditions until the starting material had been consumed (1–3 h) and a saturated solution of ammonium acetate was added. The mixture was stirred for a further 1 h and the resulting suspension was extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a solid residue, which was purified by column chromatography.

2.3.1. 5-Ethynyl-6-phenylpyridazin-3(2*H*)-one (2e). Further purification by column chromatography (AcOEt/hexane 1:1.5) and recrystallization from isopropanol furnished a white solid; yield 90%. Mp: 202–203 °C. IR (KBr): ν_{max}/cm^{-1} 2984 (NH), 2113 (C≡C), 1684 (CO), 1560 (Aromatics). ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm): 13.35 (br s, 1H, NH deuterium oxide exchangeable), 7.64 (m, 2H, Aromatics), 7.45 (m, 3H, Aromatics), 7.18 (s, 1H, H_4), 4.79 (s, 1H, CH). ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm): 159.4, 145.5, 134.9, 134.1, 129.4, 128.8, 128.3, 127.7, 91.8, 78.7. MS (70 eV) *m/z* (%): 196 (M^+, 66), 139 (38), 69 (41), 63 (51), 57 (100), 58 (93). Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.52; H, 4.14; N, 14.31.

2.3.2. 5-(3-Hydroxyprop-1-yn-1-yl)-6-phenylpyridazin-3(2*H*)-one (2f). Purification by column chromatography on silica gel (AcOEt/hexane 1:5) gave white crystals; yield 76%. Mp: 169–171 °C (Isopropanol). IR (KBr): ν_{max}/cm^{-1} 3566–2930 (OH, NH), 2237 (C≡C), 1654 (CO), 1558 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 11.33 (br s, 1H, NH deuterium oxide exchangeable), 7.73 (m, 2H, Aromatics), 7.48 (m, 3H, Aromatics), 7.16 (s, 1H, H_4), 4.35 (s, 2H, $-CH_2-$), 3.34 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 162.6, 148.9, 136.3, 133.7, 131.1, 130.8, 130.2, 129.5, 101.9, 80.6, 51.3. MS (70 eV) *m/z* (%): 226 (M^+, 60), 208 (100). Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.83; H, 4.69; N, 12.44.

2.3.3. 5-(3-Hydroxybut-1-yn-1-yl)-6-phenylpyridazin-3(2*H*)-one (2g). Purification by column chromatography on silica gel (AcOEt/hexane 2:1) gave a white solid; yield 80%. Mp 160–162 °C (Isopropanol). IR (KBr), ν (cm^{-1}): 3350–2920 (OH, NH), 2230 (C≡C), 1652 (CO), 1585 (Aromatics). ^1H NMR ($CDCl_3$ 300 MHz), δ (ppm): 12.25 (br s, 1H, NH deuterium oxide exchangeable), 7.67 (m, 2H, Aromatics), 7.41 (m, 3H, Aromatics), 7.12 (s, 1H, H_4), 4.61 (q, $J=6.6$ Hz, 1H, CH), 3.45 (br s, 1H, OH), 1.40 (d, $J=6.6$ Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$ 75 MHz), δ (ppm): 160.0, 146.7, 134.6, 132.8, 129.8, 129.3, 129.1, 128.4, 103.8, 79.0, 58.7, 23.6. MS (70 eV) *m/z* (%): 240 (M^+, 35), 197 (30), 165 (82), 139 (100), 115 (61), 77 (84), 51 (100). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.09; H, 5.12; N, 11.87.

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$PtCl_2$-mediated cycloisomerization of unsaturated propargylic carboxylates

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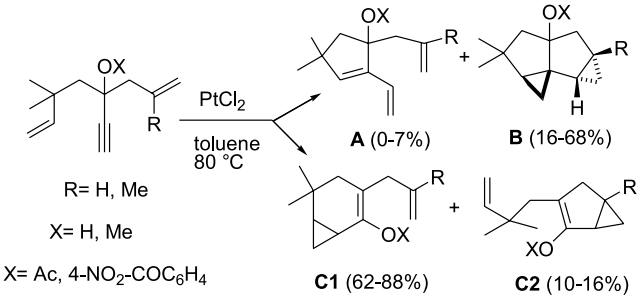
Abstract—The $PtCl_2$-mediated cycloisomerization of unsaturated propargylic carboxylates yields differently functionalized bicyclo[4.1.0]-heptane enol esters from moderate to good yield, in a very diastereoselective manner. We have prepared and submitted to $PtCl_2$-catalyzed cycloisomerization a series of differently substituted hept-1-en-6-ynes with different *O*-acyl (acetyl, trichloroacetyl, 3,4,5-trimethoxy-benzoyl, etc.) protecting groups at propargylic positions, investigating also the effect of the geometry at the double bond, as well as the effect of the number of substituents at the alkene moiety. As a result, we have found that the *O*-acetyl migrating group is the best one in terms of simplicity and chemical yields. In this reaction we have isolated mixtures of compounds formed by minor 1-acetoxy-allenes and major bicyclo[4.1.0]heptane derivatives. Major products are the result of a sequential process involving steps of cycloisomerization plus cyclopropanation, followed by acyl migration. The basic methanolysis (K_2CO_3, MeOH) of these intermediates gave mixtures of *cis* and *trans*-caran-2-ones. This two-step protocol (cycloisomerization plus basic methanolysis) for the syntheses of α,β-unsaturated cyclopropyl ketones constitutes a synthetic alternative to the usual unfriendly, intramolecular cyclopropanation of unsaturated α-diazocarbonyl derivatives. The formation of these bicyclo[4.1.0]heptane derivatives is a simple, but efficient entry into the skeleton of the 'carane' family of natural products.

1. Introduction

Transition-metal catalyzed cycloisomerization of 1,6-enynes[1] constitutes one of the best known examples of what has been called 'full atom economy' reactions.[2] Particularly attractive has been the use of the readily available and stable platinum salts and complexes as catalysts. Since the pioneer work by Trost,[3a–c] a number of reports from different laboratories have highlighted the mechanism of these isomerizations, as well as the scope and limitations of this synthetic procedure for the preparation of carbocycles and/or heterocycles.[3,4] In this context, Fensterbank, Malacria and Marco-Contelles[4a] have reported the critical effect that the type of the substituents at propargylic positions in differently functionalized 1,6-enynes have on the course of their $PtCl_2$-mediated cycloisomerization reactions. It was noticed that on going from the free alcohol (or ethers) to *O*-acyl derivatives the major final resulting products were completely different (Scheme 1).[4a] Compounds of type **A** and **B** were obtained after skeletal rearrangement, and sequential cycloisomerization plus cyclopropanation reactions, respectively, while products of type **C** were the formal result of a cycloisomerization and cyclopropanation followed by acyl migration, both transformations involving possibly Pt cyclopropyl carbenes. More recently Malacria and co-workers have reported the $PtCl_2$-catalyzed cycloisomerization of 5-en-1-yn-3-ol systems,[4b] as well as the tandem $PtCl_2$ catalyzed-thermal [3,3] rearrangements of enyne acetates.[4c]



Scheme 1.

A careful revision of the current literature has shown that this attractive $PtCl_2$-mediated cycloisomerization reaction[4a] has precedent on a work published by Ohloff et al. some

Keywords: Propargylic carboxylates; $PtCl_2$-mediated cycloisomerization; Hept-1-en-6-ynes; Cyclopropanes; Bicyclo[4.1.0]heptanes; Carane natural products.
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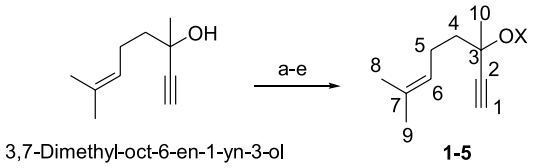
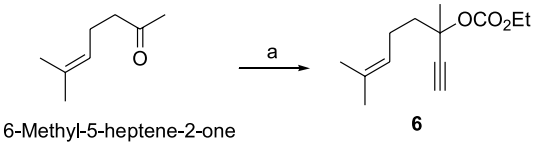


Scheme 2. Reagents: (a) Ac_2O, py, DMAP, rt, 12 h [(**1**): X=$COCH_3$, 81%]. (b) $(Cl_3CCO)_2O$, py, DMAP, rt, 45 min [(**2**): X=$COCCl_3$, 79%]. (c) C_6H_5COCl, py, DMAP, reflux, 46 h [(**3**): X=COC_6H_5, 64%]. (d) $C_6H_2(OCH_3)_3COCl$, py, DMAP, reflux, 24 h {(**4**): X=CO[3,4,5-$(OCH_3)_3C_6H_2$], 49%}. (e) 4-$(NO_2)C_6H_4COCl$, py, DMAP, 80 °C, 16 h [(**5**): X=CO[4-$(NO_2)C_6H_4$], 70%].



Scheme 3. Reagents: (a) Ethynylmagnesium bromide, 2 h, rt; then $ClCO_2Et$, py, DMAP, 5 h, rt (68%).

years ago.[5a] In 1984 Rautenstrauch described the same reaction,[5b] and found that from related precursors, but using $PdCl_2(CH_3CN)_2$ as catalyst, similar products were obtained in better yields (10–40%). After this preliminary communication, no further reports from this laboratory were available, and the potential interest of this new mode of cycloisomerization reaction, as well as the potential synthetic applications of the resulting building blocks, remained unexplored until was have rediscovered it by serendipity (Scheme 1).[4a] Ohe and Uemura have recently reported the intermolecular version[5c] of this reaction.

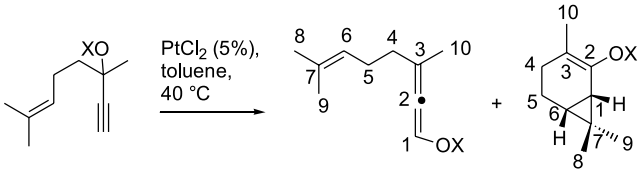
2. Results and discussion

The unexplored and high synthetic potential of these results led us to start a research program aimed at establishing the scope and generality of the $PtCl_2$-catalyzed cycloisomerization of unsaturated propargylic carboxylates. In order to do this, we have prepared new 1,6-enyne derivatives, simplifying the structure of our former precursors, with a methyl substituent at the quaternary propargylic center, fixing in two methylene carbons the tether connecting the unsaturated double bond with the quaternary center, and moving the gem-dimethyl groups at the allylic position to the terminal carbon of the alkene moiety. Then, compounds **1**–**6**, incorporating different acyloxy groups to operate in the presumed key isomerization process, were designed. These precursors were readily prepared in two steps, after Grignard reaction of commercial 6-methyl-5-heptene-2-one with ethynylmagnesium bromide, followed by O-acylation of the resulting 3,7-dimethyl-oct-6-en-1-yn-3-ol[6a] (Schemes 2 and 3).

Precursor **1**,[6a] under the standard conditions [$PtCl_2$ (5%), toluene, 40 °C], afforded the known 1-acetoxy allene **7**[6a,7] and the bicyclo[4.1.0]heptane enol acetate **8**[5a] (Table 1, entry a). Compound **8** has been already described in literature[5a] and the reported spectroscopic data are in good agreement with the ones that we have observed in our sample. The formation of the allenyl esters has not been detected in our previous experiments,[4a] but they are routinely found in the transition metal-catalyzed isomerization of propargylic acetates.[8] However, it has been reported that heating propargylic acetates in benzene or toluene with $PtCl_2$ or silver trifluoroacetate as catalyst gives a diene type of product, instead of the allenyl acetate, the product obtained with copper chloride as catalyst.[7b] Very interestingly, compound **1**, without catalyst, at 60 °C for 72 h, in toluene as solvent, was recovered unreacted, and when $PdCl_2$ (5% mol) was used as catalyst, no reaction was observed at 40 °C for 15 h, or after 44 h at 80 °C. Using gold trichloride ($AuCl_3$), in the same conditions, we were able to isolate compounds **7** and **8** in 33 and 29% yields, respectively. Regarding the solvent, with $PtCl_2$ as catalyst, in methylene chloride, only product **8** was isolated in 25%, after 70 h at 40 °C.

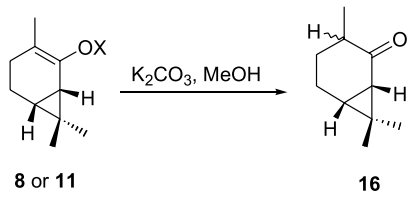
Trichloroacetate **2**, under the standard conditions for the cycloisomerization reaction, gave a complex reaction mixture, in a very slow reaction. After work-up and isolation, only product **9** was isolated in poor yield (20%) (Table 1, entry b). This result shows the importance of the anchimeric assistance of the acyloxy group at the propargylic position for the success of this process. Very clearly, the efficiency of the cycloisomerization reaction was hampered by the low anchimeric assistance ability of

Table 1. $PtCl_2$-mediated cycloisomerization reaction of compounds **1**–**6**



Entry	Precursor	Time (h)	Isolated yields (%)	
a	**1**[6a] X=$COCH_3$	72	**7**[6a,7] (8)	**8**[5a] (54)
b	**2** X=$COCCl_3$	46		**9** (20)
c	**3** X=COC_6H_5	26[a]	**10** (11)	**11** (40)
d	**4** X=CO[3,4,5-$(OCH_3)_3C_6H_2$]	62[a]		**12** (39)[a,b]
e	**5** X=CO[4-$(NO_2)C_6H_4$]	46[a]		**13** (34)
f	**6** X=$CO_2C_2H_5$	22[a]	**14**(3)	**15** (11)

[a] For **3**: Plus 4.5 h at 60 °C. For **4**: Plus 23 h at 60 °C. For **5**: At 60 °C. For **6**: Plus 19 h at 60 °C.
[b] 80% pure (glc).



Scheme 4. Conditions: From **8** (X=$COCH_3$): 15 min, rt (*cis/trans*: 1/3; 66%). From **11** (X=COC_6H_5): 24 h, rt (*only trans*; 50%).

the *O*-trichloroacetyl group due to the electron-withdrawing chlorine atoms.

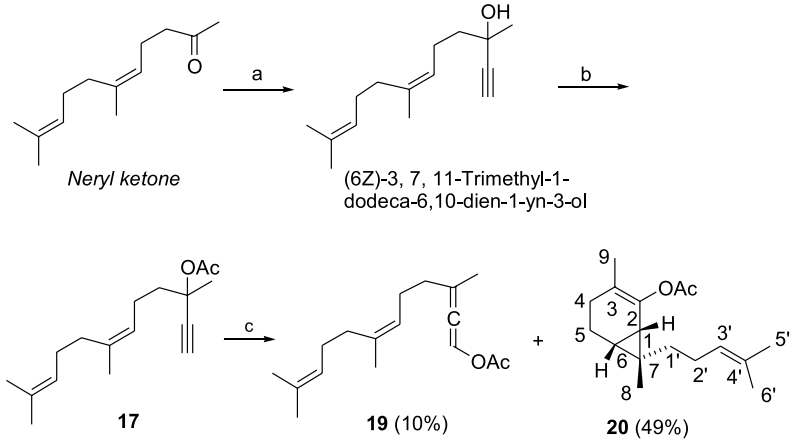
With this result in mind we tested new substrates containing differently substitued benzoyl groups (**3**–**5**). From compound **3**, after $PtCl_2$ catalyzed rearrangement, the allenyl ester **10** (11%) and product **11** (40%) (Table 1, entry c) were isolated, confirming the suitability of the unsubstituted benzoyl group to participate in this cycloisomerization reaction. In order to explore the influence of donor or electron-withdrawing substituents at the aromatic moiety we submitted to cyclization precursors **4** and **5**, with three methoxy and with one nitro groups, respectively, at the aromatic ring. As we can see, precursors **4** and **5** gave products **12** (39% yield) (Table 1, entry d) and **13** (34% yield) (Table 1, entry e) in moderate yield, and no traces of the allenyl derived molecules were detected. All these new compounds gave excellent analytical and spectroscopic data, similar to those described for the parent derivative **8**. In overall, and in good agreement with what has been reported,[8a] even an electron-withdrawing group, as the 4-nitrobenzoyl, promotes the cycloisomerization reaction, but less efficiently than the benzoyl or the substituted trimethoxybenzoyl group; in addition, the benzoyl behaves less efficiently than the acetyl group, probably due to a steric effect.

In this context, the analysis of the reactivity of a carbonate group seemed to us very promising. Thus, we prepared precursor **6** (Scheme 3). Unfortunately, this compound gave a complex reaction mixture, and we only could isolate products **14** and **15** in poor yield (Table 1, entry f).

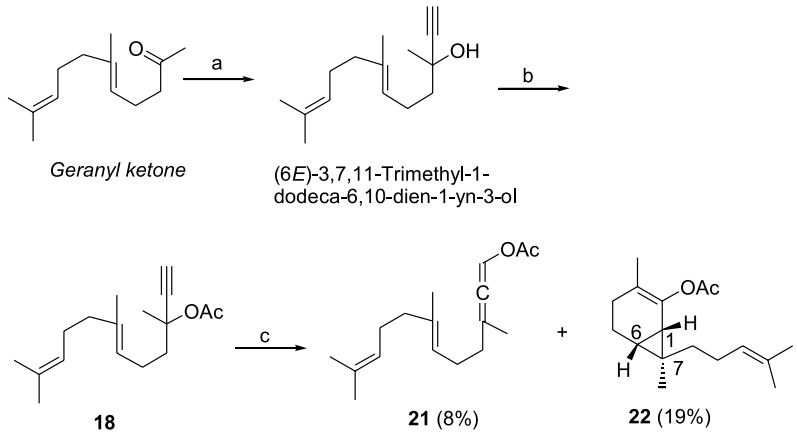
From these results we conclude that the acetyl group is the best migrating group in terms of simplicity and efficiency and, by comparison with the substrates having *gem*-dimethyl groups at the allylic position (Scheme 1),[4a] the presence of two methyl groups at the terminal double bond retards the speed of the reaction, giving moderate to low yields of the cycloisomerization reaction products. This is possibly a consequence of the higher steric hinderance at the transition state, due to the presence of the methyl groups at the terminal position, and points out to an accelerating factor due to the Thorpe-Ingold effect of the *gem*-dimethyl groups in the precursors shown in Scheme 1.[4a] Regarding the different tested acyl groups and their different anchimeric assistance properties, it seems that groups having functional moieties directly bonded to the carbonyl group, with a strong -I effect, as the trichloromethyl or the ethoxy in the carbonate, do not favour the Rautenstrauch isomerization, while electron-donating groups as the methyl or the phenyl accelerate it.

The formation of compounds **8**, **9**, **11**–**13** and **15** constitutes a simple, but efficient entry into the skeleton of the 'carane' family of natural products.[9] As expected, after treatment with K_2CO_3, MeOH, acetate **8** afforded a mixture of *cis* and *trans*-caran-2-one (**16**) in a 1/3 ratio (Scheme 4), that we were unable to separate by chromatography. The ^1H NMR analysis and the comparison of these data with those reported for these compounds[9a] clearly showed that our major compound was the *trans* isomer. The formation of major *trans*-isomer **16** is in good agreement with the reported base isomerization of mixtures of *cis* and *trans*-caran-2-one leading to the major, thermodynamically more stable *trans* isomer.[9b] Similarly, compound **11**, after a long base-mediated methanolysis, gave only *trans*-isomer **16** (Scheme 4).

Next we submitted to cycloisomerization the known precursors **17**[10] (Scheme 5) and **18**[10] (Scheme 6) in order to test the influence of a proximal triple substituted alkene, the stereochemistry at this double bond, as well as the presence of a second, terminal trisubstituted double bond. Compounds **17** (Scheme 5) and **18** (Scheme 6) have been synthesized using the same synthetic sequence, as previously shown for compounds **1**–**6** (Schemes 2 and 3), starting from commercial neryl and geranyl acetones, respectively.



Scheme 5. Reagents: (a) Ethynylmagnesium bromide, THF/Et_2O (1:1), rt, 4 h (80%); (b) Ac_2O, py, DMAP, rt, 40 h (63%); (c) $PtCl_2$ (5%), toluene, 40 °C, 32 h.



Scheme 6. Reagents: (a) Ethynylmagnesium bromide, THF/Et_2O (1:1), rt, 4 h (70%); (b) Ac_2O, py, DMAP, rt, 24 h (63%); (c) $PtCl_2$ (5%), toluene, 80 °C, 32 h.

Acetate **17**[10] gave the known allene **19**[11] and compound **20** (Scheme 5). After selective NOE experiments in the ^1H NMR spectrum we could determine that in acetate **20** the methyl at C-7 was *cis* to the cyclopropyl protons at C-1 and C-6.

Starting from precursor **18**,[10] after $PtCl_2$-mediated cycloisomerization, we isolated the known allene **21**[11] and compound **22** (Scheme 6), in lower yields compared with the results obtained form its isomer **17**. The relative configuration in compound **22**, around the fused rings, was proved to be as shown in Scheme 6, as no NOE effect was observed between the methyl group at C-7 and the cyclopropyl protons at C-1 and C-6 in the ^1H NMR spectrum.

From these results we conclude that the $PtCl_2$ -promoted cycloisomerization process of trisubstitued alkenes is possible, proceeds stereospecifically giving *cis*- or *trans*-products, depending on the stereochemistry at the double bond on the precursor, the *Z* isomer affording the *cis* isomer, while the *E* isomer leads to the corresponding *trans* derivative. Finally, note that the terminal double bond was not involved in the cyclization reaction. These results show also that the efficiency of the reaction is critically dependent on the stereochemistry at the central double bond: the *Z*-isomer provided a moderate yield of the bicyclic derivative, the *E* isomer giving a complex reaction mixture and the final products in poor overall chemical yields.

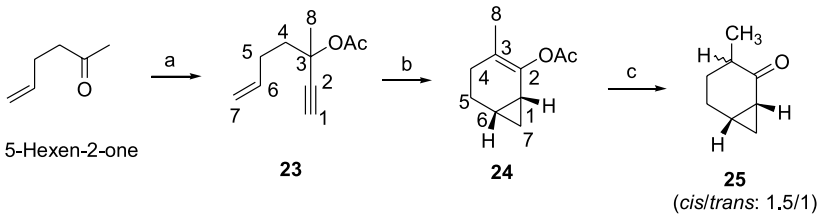
Our next precursor was acetate **23** (Scheme 7), where we have eliminated the methyl groups on the double bond or at allylic positions. Compound **23**[6b] has been synthesized from commercial 5-hexen-2-one following the standard sequence. The isomerization of precursor **23** afforded product **24** (Scheme 7) in a quick reaction and in quantitative chemical yield (99%). The clean and high yielding reaction of precursor **23**, compared with the results obtained in the previously reported results[4a] (Scheme 1) or the results obtained from precursors **1**–**6** (Table 1) clearly show the importance of steric interactions in the transition state in transition-metal catalyzed reactions.[12]

Next, product **24** was submitted to the basic methanolysis to give the known ketone **25**[13] (Scheme 7), isolated as a mixture of isomers *cis*/*trans* in 1.5:1 ratio, in 61% yield. The spectroscopic data of this mixture were in good agreement with the reported values for these compounds.[13a]

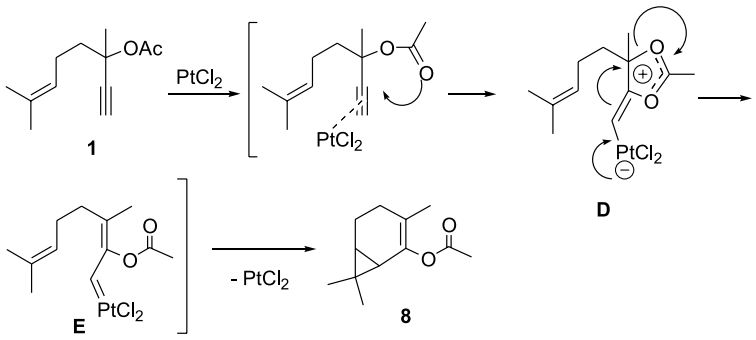
Finally, note that as an added bonus of the present cycloisomerization reaction of readily available propargylic carboxylates, the synthesis of α,β-unsaturated cyclopropyl ketones **16** and **25**, in a two-step protocol ($PtCl_2$-mediated cycloisomerization plus basic methanolysis), constitutes an alternative to the usual unfriendly, intramolecular cyclopropanation of unsaturated α-diazocarbonyl derivatives, prepared by reaction of carboxylic acid chlorides and diazomethane.[14]

Regarding the mechanism of this $PtCl_2$-madiated cycloisomerization reaction, in Scheme 8 we show a tentative proposal based on previous findings.[3g,4a,15] The intramolecular ester attack to the polarized metal-alkyne complex should give intermediate **D** that evolves to Pt carbene **E**, whose final reaction with the terminal double bond results in the formation of compound **8**.

In summary, in this paper we have presented additional synthetic details on the scope and generality of the $PtCl_2$-catalyzed cycloisomerization of unsaturated propargylic



Scheme 7. Reagents: (a) Ethynylmagnesium bromide, THF/Et_2O (1:1), rt, 3 h (50%); then, Ac_2O, py, DMAP, rt, 12 h (67%); (b) $PtCl_2$ (5%), toluene, rt, 18 h (99%); (c) K_2CO_3, MeOH, rt , 18 h (61%).



Scheme 8. Proposed mechanism for the $PtCl_2$-mediated cycloisomerization of compound **1**.

carboxylates.[4,5] This reaction yields differently functionalized bicyclo[4.1.0]heptane enol esters from moderate to good yield, in a very diastereoselective and stereospecific manner. Basic metanolysis (K_2CO_3, MeOH) of these intermediates gave mixtures of *cis*- and *trans*-caran-2-ones. The formation of these bicyclo[4.1.0]heptane derivatives is a simple but efficient entry into the skeleton of the 'carane' family of natural products.[16]

3. Experimental

3.1. General methods

Melting points were determined on a digital melting-point apparatus (Electrothermal) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, at 300.13 and at 75.47 MHz (Bruker Avance-300). TLC was performed on Silica F254 (Merck) and detection by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh). The assignment of chemical shifts are based on standard NMR experiments (^{1}H, ^{13}C, DEPT, ^{1}H–^{1}H COSY, HMQC, HMBC). In the NMR spectra values with (*) can be interchanged.

3.2. General procedure for the $PtCl_2$-catalyzed cycloisomerization reaction

To a degassed solution of the precursor in dry toluene (0.025 M) $PtCl_2$ (0.05 equiv) was added at room temperature (rt), under argon. The reaction mixture was stirred at 40–80 °C until complete reaction. Then, the reaction mixture was filtered and the solvent was evaporated under vacuum. Purification by flash chromatography, eluting with mixtures of EtOAc/hexane gave the corresponding products.

3.3. General procedure for the esterification reaction

To a solution of the respective alcohol in dry pyridine, DMAP (0.2 equiv) and the required acid chloride (or acid anhydride) (1.5 equiv) were added. The reaction mixture was refluxed until complete reaction. Then, the solvent was evaporated under vacuum, the crude was dissolved in dichloromethane and washed with an aqueous saturated solution of $NaHCO_3$, brine and water. Purification by flash chromatography eluting with mixtures of EtOAc/hexane gave the corresponding products.

3.4. General procedure for methanolysis of enol esters

Solid potassium carbonate (2.0 equiv) was added to a solution of the respective enol ester in methanol (0.05 M). The reaction mixture, stirred at rt until complete reaction, was quenched by adding brine. The reaction mixture was extracted by diethyl ether and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (EtOAc/hexane) afforded the corresponding ketones.

3.4.1. 3,7-Dimethyl-oct-6-en-1-yn-3-yl acetate ('dehydrodehydrolinalyl acetate') (1).[6a] A solution of 6-methyl-5-heptene-2-one (0.86 g, 6.8 mmol) in a mixture of dry THF/diethyl ether (1:1) (4 mL) was added dropwise, at rt, to a solution of ethynylmagnesium bromide (16 mL, 8.16 mmol, 0.5 M in THF) in anhydrous diethyl ether (16 mL), under argon. The reaction mixture was stirred at rt for 3 h. Then, water (25 mL) was added to quench the reaction and the mixture was extracted with diethyl ether (25×3 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum. Purification by flash chromatography (EtOAc/hexane, 5:95) gave 3,7-dimethyl-oct-6-en-1-yn-3-ol ('dehydrolinalool') (0.75 g, 72% yield) [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.18 (tm, J=7.4 Hz, 1H, H-6), 2.47 (s, 1H, H-1), 2.30–2.17 (m, 2H, H-5), 2.20 (br s, 1H, OH), 1.72 (s, 3H, H-8)*, 1.71 (s, 3H, H-9)*, 1.72–1.56 (m, 2H, H-4), 1.51 (s, 3H, H-10)]. Following the general procedure for the esterification reaction, to a solution of 'dehydrolinalool' (337 mg, 2.21 mmol) in dry pyridine (4 mL), DMAP (120 mg, 0.98 mmol) and acetic anhydride (339.2 mg, 5 mL, 3.32 mmol) were added. The reaction mixture was stirred 12 h at rt. The solvent was evaporated under vacuum and the crude was purified by flash chromatography (EtOAc/hexane, 2:98) to furnish (**1**) (350 mg, 81% yield) as a colorless oil, that showed spectroscopic data [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 (tm, J=7.0 Hz, 1H, H-6), 2.53 (s, 1H, H-1), 2.15–2.08 (m, 2H, H-5), 1.99 (s, 3H, $OCOCH_3$), 1.95–1.69 (m, 2H, H-4), 1.65 (s, 6H, H-8*, H-10), 1.31 (s, 3H, H-9*)] in agreement with the structure of this known product.[6a]

3.4.2. 3,7-Dimethyl-octa-1,2,6-trien-1-yl acetate (7)[6a,7] **and 3,7,7-trimethyl-bicyclo[4.1.0.]hept-2-en-2-yl acetate ('2-acetoxy-2-carene') (8).**[5a] Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of compound (**1**) (130.7 mg, 0.55 mmol) in dry toluene (27 mL) $PtCl_2$ (7.32 mg, 0.027 mmol) was added. The reaction mixture was stirred

for 72 h at 40 °C. Purification by flash chromatography (EtOAc/hexane, 0.5:99.5) afforded (**7**)[6a,7] (10.3 mg, 8% yield) and 2-acetoxy-2-caren (**8**)[5a] (70.7 mg, 54% yield). Both compounds (**7**[6a,7] and **8**[5a]) and are known and showed analytical and spectroscopic data, in good agreement with those described in literature. **7**: Oil; IR (film) ν 3065, 2919, 2857, 1976, 1750 ($OCOCH_3$), 1445, 1368, 1216, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1H, H-1), 5.12 (tm, $J=7.1$ Hz, 1H, H-6), 2.15 (m, 2H, H-5), 2.13 (s, 3H, $OCOCH_3$), 2.10–2.01 (m, 2H, H-4), 1.78 (d, $J=2.0$ Hz, 3H, H-10), 1.62 (s, 3H, H-8)*, 1.59 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7 (C-2), 169.2 ($OCOCH_3$), 132.5 (C-7), 123.6 (C-6), 116.2 (C-3), 110.1 (C-1), 35.6 (C-4), 26.3 (C-5), 26.0 (C-9), 21.3 ($OCOCH_3$), 20.9 (C-10), 18.1 (C-8); MS (70 eV) *m/z* 195 ($M^+ +1$, 4), 151 (30), 134 (21), 123 (30), 109 (42), 84 (71), 69 (43), 49 711), 43 (100). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.30; H, 9.18. **8**: Oil; IR (film) ν 2926, 2864, 1756 ($OCOCH_3$), 1698, 1450, 1368, 1213, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33–2.20 (m, 1H, H-4), 2.16 (s, 3H, $OCOCH_3$), 1.85–1.75 (m, 1H, H-5), 1.75–1.65 (m, 1H, H-4′), 1.65–1.59 (m, 1H, H-5′), 1.55 (s, 3H, H-10), 1.12–1.06 (m, 2H, H-1, H-6), 1.07 (s, 3H, H-9)*, 1.00 (s, 3H, H-8)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 ($OCOCH_3$), 141.7 (C-2), 119.4 (C-3), 29.9 (C-4), 28.3 (C-8)*, 25.2 (C-7), 24.9 (C-6)**, 24.1 (C-1)**, 21.3 ($OCOCH_3$), 17.9 (C-5), 16.4 (C-10), 16.1 (C-9)*; MS (70 eV) *m/z* 194 (M^+, 4), 193 (M^+-1, 4), 166 (6), 152 (49), 137 (38), 123 (22), 109 (100), 91 (27), 83 (13), 77 (16), 69 (29), 55 (17), 43 (83). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.96; H, 9.60.

3.4.3. 3,7-Dimethyloct-6-en-1-yn-3-yl trichloroacetate (2). Following the general procedure for the esterification reaction, to a solution of 'dehydrolinalool' (115.8 mg, 0.76 mmol) in dry pyridine (3 mL) DMAP (18.6 mg, 0.15 mmol) and trichloroacetic anhydride (0.35 mL, 1.14 mmol) were added. The reaction mixture was stirred at rt for 45 min. After usual workup, flash chromatography (EtOAc/hexane, 0.5:99.5) gave compound **2** (178.5 mg, 79% yield) as a colorless oil: IR (film) ν 3305, 2971, 2927, 2123, 1771 (OCO), 1673, 1449, 1377, 1343, 1238, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (tm, $J=7.0$ Hz, 1H, H-6), 2.71 (s, 1H, H-1), 2.38–2.13 (m, 2H, H-5), 2.08–1.82 (m, 2H, H-4), 1.82 (s, 3H, H-10), 1.71 (s, 3H, H-8)*, 1.65 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 ($OCOCCl_3$), 132.8 (C-7), 122.4 (C-6), 91.5 ($OCOCCl_3$), 81.2 (C-2), 80.3 (C-3), 75.4 (C-1), 41.2 (C-4), 25.7 (C-10), 25.6 (C-9), 22.7 (C-5), 17.5 (C-8); MS (70 eV) *m/z* 134, 135 (5, 5), 119 (88), 105 (21), 91 (40), 84 (36), 77 (15), 69 (100), 55 (19), 49 (44), 41 (63). Anal. Calcd for $C_{12}H_{15}Cl_3O_2$: C, 48.43; H, 5.08. Found: C, 48.36; H, 4.75.

3.4.4. 3,7,7-Trimethyl-bicyclo[4.1.0.]hept-2-en-2-yl trichloroacetate (9). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of 3,7-dimethyl-1-octyn-6-en-3-trichloroacetate (**2**) (105.7 mg, 0.37 mmol) in dry toluene (15 mL), $PtCl_2$ (4.98 mg, 0.18 mmol) was added. The reaction mixture was stirred for 46 h at 40 °C until complete the reaction. After flash chromatography (EtOAc/hexane, 1:99) (9) (14.7 mg, 20% yield) was isolated as a colorless oil: IR (film) ν 2923, 2865, 1774 (OCO), 1702, 1450, 1376, 1354, 1230, 1218, 1077 cm^{-1}; ^1H NMR (75 MHz, $CDCl_3$) δ 2.38–2.20 (m, 1H, H-4), 1.98–1.80 (m, 2H, H-4′, H-5), 1.78–1.68 (m, 1H, H-5′;), 1.66 (s, 3H, H-10), 1.28–1.10 (m, 2H, H-1, H-6), 1.10 (s, 3H, H-9)*, 1.05 (s, 3H, H-8)*; ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.4 ($OCOCCl_3$), 142.7 (C-2), 121.2 (C-3), 90.5 ($OCOCCl_3$), 30.3 (C-4), 28.2 (C-8)*, 25.9 (C-7), 25.4 (C-6)**, 23.2 (C-1)**, 18.0 (C-5), 16.1 (2C, C-10, C-9*); MS (70 eV) *m/z* 296, 298 (M^+, 6, 6), 281, 283 (M^+-15, 4, 4), 189, 191 (8, 8), 151 (9), 135 (18), 123 (21), 119 (100), 117 (34), 91 (38), 81 (31), 69 (24). Anal. Calcd for $C_{12}H_{15}Cl_3O_2$: C, 48.43; H, 5.08. Found: C, 48.66; H, 5.28.

3.4.5. 3,7-Dimethyloct-6-en-1-yn-3-yl benzoate (3). Following the general procedure for the esterification reaction, to a solution of 'dehydrolinalool' (250.1 mg, 1.65 mmol) in dry pyridine (5 mL), DMAP (40.2 mg, 0.33 mmol) and benzoyl chloride (0.46 mL, 3.29 mmol) were added. The reaction mixture was refluxed for 46 h. After standard work-up, flash chromatography (EtOAc/hexane, 2:98) gave (**3**) (272.0 mg, 64% yield) as a colorless thick oil: IR (film) ν 3301, 3062, 2971, 2926, 2117, 1725 (OCOPh), 1601, 1585, 1491, 1451, 1375, 1314, 1279, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (m, 2H), 7.55 (m, 1H), 7.49 (m, 2H) (5H, $OCOC_6H_5$), 5.16 (tm, $J=7.4$ Hz, 1H, H-6), 2.61 (s, 1H, H-1), 2.35–2.22 (m, 2H, H-5), 2.15–2.06 (ddd, $J=6.1$ Hz, $J=10.7$ Hz, $J=13.4$ Hz, 1H, H-4), 2.01–1.92 (ddd, $J=5.4$ Hz, $J=10.7$ Hz, $J=13.4$ Hz 1H, H-4′), 1.82 (s, 3H, H-10), 1.68 (s, 3H, H-8)*, 1.63 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 ($OCOC_6H_5$), 132.8 (C-7), 132.9, 132.3, 130.8, 128.3 (COC_6H_5), 123.1 (C-6), 83.6 (C-2), 75.2 (C-3), 73.5 (C-1), 41.6 (C-4), 26.5 (C-10), 25.6 (C-9), 22.9 (C-5), 17.6 (C-8); MS (70 eV) *m/z* 256 (M^+, 12), 134 (25), 119 (78), 105 (100), 91 (38), 77 (61), 69 (29), 51 (21), 41 (28). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.36; H, 8.14.

3.4.6. 3,7-Dimethyl-octa-1,2,6-trien-1-yl benzoate (10) and 3,7,7-trimethyl-bicyclo[4.1.0.]hept-2-en-2-yl benzoate (11). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of compound (**3**) (130.7 mg, 0.55 mmol) in dry toluene (20 mL), $PtCl_2$ (6.79 mg, 0.027 mmol) was added. The reaction mixture was stirred for 26 h at 40 °C and for 4.5 h at 60 °C. Purification by flash chromatography (EtOAc/hexane, 0.5:99.5) afforded compounds **10** (14.4 mg, 11% yield) and **11** (52.3 mg, 40% yield). **10**: Oil; IR (film) ν 3065, 2919, 2857, 1976, 1750 (OCOPh), 1445, 1368, 1216, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12–7.99 (m, 2H), 7.59–7.46 (m, 1H), 7.40–7.35 (m, 2H) (5H, $OCOC_6H_5$), 7.59–7.46 (m, 1H, H-1), 5.15 (tm, $J=7.2$ Hz, 1H, H-6), 2.18–1.98 (m, 4H, H-4, H-5), 1.80 (d, $J=1.8$ Hz, 3H, H-10), 1.64 (s, 3H, H-8)*, 1.58 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4 (C-2), 165.1 ($OCOC_6H_5$), 133.6, 132.5, 130.2, 128.8 ($OCOC_6H_5$), 130.0 (C-7), 123.9 (C-6), 116.3 (C-3), 110.4 (C-1), 35.7 (C-4), 26.3 (C-5), 26.0 (C-9), 21.0 (C-10), 18.2 (C-8); MS (70 eV) *m/z* 256 (M^+, 1), 187 (7), 151 (11), 119 (5), 105 (100), 77 (38), 51 (10), 41 (15). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.72; H, 8.01. **11**: Oil; IR (film) ν 3066, 2922, 1729 (OCOPh), 1601, 1584, 1492, 1451, 1375, 1314, 1272, 1176, 1106, 1069, 1026 cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 8.14 (m, 2H), 7.58 (m, 1H), 7.49 (m, 2H) (5H, $OCOC_6H_5$), 2.35–2.00 (m, 1H, H-4), 1.87–1.65 (m, 2H, H-5, H-4′), 1.60–1.55 (m, 1H, H-5′), 1.62 (s, 3H, H-10), 1.40–1.15 (m, 2H, H-1, H-6), 1.11 (s, 3H, H-9)*, 1.09 (s, 3H, H-8)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 ($OCOC_6H_5$), 142.0 (C-2), 135.1, 130.3, 129.9, 128.7 ($OCOC_6H_5$), 119.6 (C-3), 30.1 (C-4), 28.4 (C-8)*, 25.3 (C-7), 25.1 (C-6)**, 24.3 (C-1)**, 18.1 (C-5), 16.5 (C-10), 16.2 (C-9)*; MS (70 eV) *m/z* 256 (M^+, 38), 151 (3), 134 (7), 105 (100), 77 (56), 41 (12). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.54; H, 7.69.

3.4.7. 3,7-Dimethyloct-6-en-1-yn-3-yl(3′,4′,5′)-trimethoxy benzoate (4). Following the general procedure for the esterification reaction a solution of 'dehydrolinalool' (290.0 mg, 1.92 mmol) in dry pyridine (5 mL), DMAP (46.8 mg, 0.38 mmol) and 3,4,5-trimethoxybenzoyl chloride (886 mg, 3.84 mmol) were added. The reaction mixture was refluxed for 24 h. After usual workup, purification by flash chromatography (EtOAc/hexane, 4:96) furnished product **4** (272.0 mg, 49% yield) as white crystals: mp 45–47 °C; IR (film) ν 3234, 2973, 2936, 2111, 1721 (OCOAr), 1687, 1590, 1504, 1455, 1413, 1372, 1335, 1247, 1222, 1162 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 [s, 2H, $OCOC_6H_2(OCH_3)_3$], 5.18 (tm, J=7.0 Hz, 1H, H-6), 3.90 (s, 9H, 3×CH_3O), 2.62 (s, 1H, H-1), 2.40–2.21 (m, 2H, H-5), 2.20–1.95 (m, 2H, H-4), 1.82 (s, 3H, H-10), 1.65 (s, 3H, H-8)*, 1.61 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5 (*O*COAr), 152.9, 132.5, 125.9, 106.9 [$OCOC_6H_2(OCH_3)_3$], 132.1 (C-7), 123.2 (C-6), 83.7 (C-2), 75.5 (C-3), 73.7 (C-1), 61.0 (OCH_3), 56.2 (2×CH_3O), 41.9 (C-4), 26.6 (C-10), 25.7 (C-9), 23.1 (C-5), 17.6 (C-8); MS (70 eV) *m/z* 346 (M^+, 2), 212 (46), 195 (100), 134 (16), 119 (78), 91 (17), 41 (20). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.15; H, 7.48.

3.4.8. 3,7,7-Trimethyl-bicyclo[4.1.0.]hept-2-en-2-yl 3′,4′,5′-trimethoxybenzoate (12). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of compound **4** (101.6 mg, 0.29 mmol) in dry toluene (12 mL), $PtCl_2$ (3.9 mg, 0.14 mmol) was added. The reaction mixture was stirred for 62 h at 40 °C and for 23 h at 60 °C. Flash chromatography (EtOAc/hexane, 4:96) gave compound **12** [39.3 mg, 39% yield, (80% purity by glc)], as a light yellow oil: IR (film) ν 2925, 2853, 1727 (OCO), 1591, 1504, 1463, 1416, 1337, 1106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 [s, 2H, $OCOC_6H_2(OCH_3)_3$], 3.95 (s, 6H, 2×CH_3O), 3.94 (s, 3H, CH_3O), 2.40–2.18 (m, 1H, H-4), 2.00–180 (m, 2H, H-5, H-4′), 1.79–1.66 (m, 1H, H-5′), 1.61 (s, 3H, H-10), 1.25–1.18 (m, 2H, H-1, H-6), 1.10 (s, 3H, H-8)*, 1.09 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9 [*O*COC_6H_2-$(OCH_3)_3$], 153.3, 135.0, 125.6, 107.5 [$OCOC_6H_2(OCH_3)_3$], 142.0 (C-2), 119.3 (C-3), 61.3 (CH_3O), 56.6 (2×CH_3O), 30.0 (C-4), 28.4 (C-8)*, 26.0 (C-7), 25.4 (C-6)**, 24.5 (C-1)**, 17.9 (C-5), 16.5 (C-10), 16.2 (C-9)*; MS (70 eV) *m/z* 346 (M^+, 1), 229 (8), 212 (11), 209 (4), 195 (100), 167 (5), 152 (8), 137 (8), 123 (5), 111 (5), 95 (8), 85 (15), 77 (12), 69 (16), 51 (7), 43 (19). Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.30; H, 7.95.

3.4.9. 3,7-Dimethyloct-6-en-1-yn-3-yl 4-nitrobenzoate (5). Following the general procedure for the esterification reaction, to a solution of 'dehydrolinalool' (500.0 mg, 3.29 mmol) in dry pyridine (5 mL), DMAP (80.28 mg, 0.65 mmol) and 4-nitrobenzoyl chloride (915.3 mg, 4.93 mmol) were added. The reaction mixture was heated at 80 °C for 16 h until complete reaction. Purification by flash column chromatography (EtOAc/hexane, 4:96) afforded (**5**) (660.0 mg, 70% yield) as white crystals: mp 73–74 °C; IR (KBr) ν 3298, 3119, 2971, 2921, 1726 (OCOAr), 1607, 1590, 1526, 1446, 1377, 1351, 1323, 1290, 1166 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (dm, J=9.0 Hz, 2H, $OCOC_6H_4NO_2$), 8.19 (d, J=9.0 Hz, 2H, $OCOC_6H_4NO_2$), 5.19 (tm, J=7.1 Hz, 1H, H-6), 2.69 (s, 1H, H-1), 2.40–2.20 (m, 2H, H-5), 2.18–1.76 (m, 2H, H-4), 1.87 (s, 3H, H-10), 1.71 (s, 3H, H-8)*, 1.66 (s, 3H, H-9)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 ($OCOC_6H_4NO_2$), 153.0, 138.8, 135.1, 126.0 ($OCOC_6H_4NO_2$), 133.2 (C-7), 125.4 (C-6), 85.5 (C-2), 79.0 (C-3), 76.8 (C-1), 43.9 (C-4), 28.9 (C-10), 28.1 (C-9), 25.5 (C-5), 20.1 (C-8); MS (70 eV) *m/z* 301 (M^+, 1), 150 (70), 134 (8), 119 (100), 104 (29), 91 (42), 79 (9), 76 (21), 41 (37). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.42; H, 6.59; N, 4.77.

3.4.10. 3,7,7-Trimethyl-bicyclo[4.1.0.]hept-2-en-2-yl 4-nitrobenzoate (13). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of compound (**5**) (303.9 mg, 1.06 mmol) in dry toluene (43 mL), $PtCl_2$ (14.08 mg, 0.053 mmol) was added. The reaction mixture was stirred for 46 h at 60 °C. Purification by flash chromatography (EtOAc/hexane, 4:96) gave compound **13** (103.3 mg, 34% yield) as yellow crystals: mp 78–80 °C; IR (KBr) ν 2918, 1724 (OCOAr), 1605, 1529, 1449, 1349, 1320, 1276, 1166 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 4H, $OCOC_6H_4NO_2$), 2.41–2.24 (m, 1H, H-4), 2.00–1.80 (m, 2H, H-5, H-4′), 1.78–1.69 (m, 1H, H-5′), 1.61 (s, 3H, H-10), 1.24–1.18 (m, 2H, H-1, H-6), 1.09 (s, 2×3H, 6H, H-8, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 ($OCOC_6H_4NO_2$), 153.7, 144.7, 134.2, 126.7 ($OCOC_6H_4NO_2$), 142.4 (C-2), 117.2 (C-3), 32.9 (C-4), 28.3 (C-8)*, 28.3 (C-7), 27.9 (C-6)**, 26.9 (C-1)**, 20.7 (C-5), 19.3 (C-10), 18.9 (C-9)*; MS (70 eV) *m/z* 301 (M^+, 55), 286 (6), 258 (5), 231 (4), 150 (100), 134 (12), 119 (17), 104 (34), 92 (15), 81 (7), 76 (16). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.52; H, 6.60; N, 4.98.

3.4.11. Carbonic acid (3,7-dimethyl-1-octyn-6-en-3-yl) ethyl ester (6). A solution of of 6-methyl-5-heptene-2-one (1.0 g, 7.94 mmol) in a mixture of THF/diethyl ether (1:1) (20 mL) was added dropwise, at rt, to a solution of ethynylmagnesium bromide (20 mL, 9.53 mmol, 0.5 M in THF), under argon. The reaction mixture was stirred at rt for 2 h. After completion of reaction, ethyl chloroformiate (1.12 g, 10.32 mmol) was added at 0 °C and the reaction was stirred at rt for 5 h. Then reaction was quenched by adding cold water (100 mL), and the organic layer was extracted with diethyl ether (100×3 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, purification by flash chromatography (EtOAc/hexane, 0.5:99.5) gave (**6**) (1.22 g, 68% yield) as a yellow oil: IR (film) ν 3290, 2981, 2930, 2120, 1754 [OC(O)OEt], 1447, 1371, 1261, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (m, 1H, H-6), 4.15 (q, J=7.0 Hz, 2H, $OCO_2CH_2CH_3$), 2.58 (s, 1H,

H-1), 2.25–2.08 (m, 2H, H-5), 2.05–1.90 (m, 1H, H-4), 1.90–1.75 (m, 1H, H-5′), 1.69 (s, 3H, H-10), 1.66 (s, 3H, H-8)*, 1.60 (s, 3H, H-9)*, 1.27 (t, $J=7.0$ Hz, 3H, $OCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3 ($OCO_2CH_2CH_3$), 132.8 (C-7), 123.3 (C-6), 83.6 (C-2), 77.5 (C-3), 74.2 (C-1), 63.9 ($OCO_2CH_2CH_3$), 41.5 (C-4), 26.6 (C-10), 26.0 (C-9), 23.2 (C-5), 18.0 (C-8), 14.6 ($OCO_2CH_2CH_3$); MS (70 eV) *m/z* 165 (4), 152 (10), 137 (23), 119 (100), 109 (19), 105 (16), 91 (49), 81 (8), 79 (12), 69 (58), 55 (13), 49 (55), 41 (35). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.50; H, 9.02.

3.4.12. Carbonic acid-(3,7-dimethyl-octa-1,2,6-trien-1-yl) ethyl ester (14) and carbonic acid-(3,7,7-trimethyl-bicyclo[4.1.0.]hept-2-en-2-yl) ethyl ester (15). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerization reaction, to a degassed solution of compound **6** (224 mg, 1.0 mmol) in dry toluene (25 mL), $PtCl_2$ (13.3 mg, 0.05 mmol) was added. The reaction mixture was stirred for 7 h at rt, heated at 40 °C for 22 h and at 60 °C for 19 h. After usual workup, purification by flash chromatography (EtOAc/hexane, 0.2:99.8) afforded compounds **14** (9.9 mg, 3%) and **15** (25.2 mg, 11% yield, 80% purity) as colorless oils. **14**: IR (film) ν 3068, 2927, 2855, 1981, 1754, 1452, 1370, 1254, 1094 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (br s, 1H, H-1), 5.32 (m, 1H, H-6), 4.26 (q, $J=7.1$ Hz, 2H, $OCO_2CH_2CH_3$), 2.20–2.06 (m, 4H, H-4, H-5), 1.85 (d, $J=1.8$ Hz, 3H, H-10), 1.70 (s, 3H, H-9)*, 1.62 (s, 3H, H-8)*, 1.28 (t, $J=7.1$ Hz, 3H, $OCO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.6 (C-2), 153.4 ($OCO_2CH_2CH_3$), 132.6 (C-7), 123.9 (C-6), 117.4 (C-3), 112.3 (C-1), 64.9 ($OCO_2CH_2CH_3$), 35.7 (C-4), 26.3 (C-5), 26.1 (C-9), 21.1 (C-10), 18.1 (C-8), 14.6 ($OCO_2CH_2CH_3$); MS (70 eV) *m/z* 224 (M^+, 2), 151 (25), 137 (18), 134 (38), 123 (37), 119 (50), 109 (62), 105 (78), 95 (31), 91 (47), 77 (37), 69 (84), 41 (100). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.50; H, 9.02. **15**: IR (film) ν 2983, 2929, 2865, 1755 ($OCO_2CH_2CH_3$), 1701, 1450, 1369, 1245, 1169, 1135, 1094, 1045, 1003 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (q, $J=7.2$ Hz, 2H, $OCO_2CH_2CH_3$), 2.35–2.20 (m, 1H, H-4), 1.95–1.70 (m, 3H, H-5, H-4′), 1.61 (s, 3H, H-10), 1.37 (t, $J=7.2$ Hz, 3H, $OCO_2CH_2CH_3$), 1.30–1.12 (m, 2H, H-1, H-6), 1.09 (s, 3H, H-9)*, 1.01 (s, 3H, H-8)*; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8 ($OCO_2CH_2CH_3$), 142.1 (C-2), 119.8 (C-3), 65.1 ($OCO_2CH_2CH_3$), 30.2 (C-4), 28.2 (C-8)*, 25.4 (C-7), 25.0 (C-6)**, 23.8 (C-1)**, 17.9 (C-5), 16.1 (C-10), 16.0 (C-9)*, 14.6 ($OCO_2CH_2CH_3$); MS (70 eV) *m/z* 224 (M^+, 20), 165 (12), 152 (37), 137 (98), 123 (23), 119 (38), 109 (100), 105 (25), 91 (50), 81 (40), 69 (30), 51 (8), 41 (53). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.70; H, 8.74.

3.4.13. Caran-2-one (16).[9] Following the general procedure for hydrolysis of enol esters, to a solution of '2-acetoxy-2-carene' (**8**) (70 mg, 0.36 mmol) in methanol (2 mL, 0.05 M), solid potassium carbonate (70.5 mg, 0.72 mmol) was added. The reaction mixture was stirred at rt. After complete reaction (15 min) the reaction was quenched by adding brine (5 mL), extracted with diethyl ether and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (EtOAc/hexane, 2:98) afforded caran-2-one (**16**)[9] (35.6 mg, 66% yield), isolated as an inseparable mixture of *cis/trans* isomers in a 1:3 ratio, which showed identical spectroscopic data to those described for these isomers in literature[9a]: Oil; IR (film) ν 2931, 2869, 1682, 1454, 1376, 1225, 1179 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (major *trans* isomer) 1.99 (m, 1H, H-3), 1.82 (m, 2H, H-4), 1.57 (m, 2H, H-5), 1.44 (m, 1H, H-1), 1.22 (s, 3H, H-8), 1.17 (m, 1H, H-6), 1.16 (s, 3H, H-9), 1.06 (d, $J=6.6$ Hz, 3H, H-10); (minor *cis* isomer)[9d] 1.13 (s, 3H, H-8), 1.12 (s, 3H, H-9), 1.04 (d, $J=6.6$ Hz, 3H, H-10); ^{13}C NMR (300 MHz, $CDCl_3$) δ (major *trans* isomer) 212.2 (C-2), 43.7 (C-3), 35.9 (C-4), 35.7 (C-1), 32.4 (C-9), 29.8 (C-6), 28.2 (C-7), 19.3 (C-5), 17.0 (C-8), 15.9 (C-10); (minor isomer *cis*)[9d] 211.8 (C-2), 43.1 (C-3), 34.6 (C-1), 30.3 (C-9), 28.8 (C-4), 26.1 (C-6), 24.1 (C-7), 19.7 (C-5), 18.2 (C-8), 14.6 (C-10); MS (70 eV) *m/z* 152 (M^+, 2) 149 (77), 135 (40), 111 (37), 97 (55), 84 (95), 69 (92), 57 (100), 49 (75), 43 (75). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.65; H, 10.32.

3.5. Methanolysis of enol ester 11

Following the general procedure for the methanolysis of enol esters compound **11** (200 mg, 0.78 mmol), dissolved in methanol (15 mL, 0.05 M), was treated with solid potassium carbonate (153.1 mg, 1.56 mmol). The reaction mixture was stirred at rt for 24 h. Purification by flash column chromatography (EtOAc/hexane, 2:98) afforded *trans*-2-caranone (**16**)[9a] (59.3 mg, 50% yield), which showed identical spectroscopic to those observed for the major isomer obtained in the methanolysis of compound **8**.

3.5.1. (6*Z*)-3,7,11-Trimethyl-6,10-dodecadien-1-yn-3-yl acetate (17).[10] To a solution of neryl acetone (0.5 g, 2.6 mmol) in dry THF/diethyl ether (1:1) (2 mL) was added dropwise ethynylmagnesium bromide (6.5 mL, 3.1 mmol, 0.5 M in THF), at rt, in anhydrous diethyl ether (5 mL), under argon. The reaction mixture was stirred at rt for 4 h. Then water (20 mL) was added to quench the reaction and the mixture was extracted with diethyl ether (2×3 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum. Purification by flash chromatography (EtOAc/hexane, 2:98) gave (6*Z*)-3,7,11-trimethyl-1-dodeca-6,10-dien-1-yn-3-ol (0.451 g, 80%) [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.06–5.01 (m, 2H), 2.35 (s, 1H), 2.35–1.90 (m, 8H), 2.01 (br s, 1H), 1.59 (s, 6H), 1.51 (s, 3H), 1.39 (s, 3H)]. Following the General Protocol for the Esterification to a solution of compound (6*Z*)-3,7,11-trimethyl-1-dodeca-6,10-dien-1-yn-3-ol (0.2 g, 0.91 mmol) in dry pyridine (3 mL), DMAP (21.96 mg, 0.18 mmol) and acetic anhydride (139.2 mg, 0.19 mL, 1.37 mmol) were added. The reaction mixture was stirred 40 h at rt. The solvent was evaporated under vacuum and the crude was purified by flash chromatography (EtOAc/hexane, 0.4:99.6) to give compound **17** (150 mg, 63% yield) as a colorless oil, that showed analytical and spectroscopic data [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.02 (tm, $J=7.1$ Hz, 2H), 2.46 (s, 1H), 2.20–2.00 (m, 2H), 1.98–1.94 (m, 4H), 1.93 (s, 3H), 1.90–1.65 (m, 4H), 1.58 (s, 9H), 1.51 (s, 3H)] in agreement with the structure of this known product.[10]

3.5.2. (6*Z*)-3,7,11-Trimethyl-1,2,6,10-dodecatetraen-1-yl acetate (19) and (1*S,6*R**,7*R**)-3,7-dimethyl-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-2-en-2-yl acetate (20).** Following the general procedure for the

$PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of compound **17** (100 mg, 0.382 mmol) in dry toluene (15 mL) $PtCl_2$ (5.1 mg, 0.19 mmol) was added. The reaction mixture was stirred for 32 h at 40 °C. Purification by flash chromatography (EtOAc/hexane, 0.4:99.6) afforded compounds (**19**) {(13 mg, 10% yield, 80% pure)][^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 1H, H-1), 5.02 (m, 2H), 2.15–1.90 (m, 8H), 2.03 (s, 3H), 1.73 [d, J=2.0 Hz, 3H], 1.58 (s, 2×3H, 6H), 1.50 (s, 3H)] that showed spectroscopic data in good agreement with those described in literature[11]} and (**20**) (49 mg, 49% yield). **20**: Oil; IR (film) ν 2959, 2925, 2856, 1756 ($OCOCH_3$), 1451, 1368, 1260, 1213, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (tm, J=7.1 Hz, 1H, H-3′), 2.20–2.00 (m, 2H), 2.05 (s, 3H, $OCOCH_3$), 2.00–1.64 (m, 2H), 1.58 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H), 1.30–1.13 (m, 4H), 1.06–0.98 (m, 2H, H-1, H-6), 0.93 (s, 3H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 ($OCOCH_3$), 141.4 (C-2), 131.7 (C-4′), 125.4 (C-3′), 122.9 (C-3), 30.4 (C-4), 30.2 (C-2′), 29.0 (C-7), 26.1 (C-9), 25.7 (C-1′), 25.6 (C-6), 25.5 (C-8), 24.4 (C-1), 21.3 ($OCOCH_3$), 18.3 (C-5), 17.8 (C-6′), 16.4 (C-5′); MS (70 eV) m/z 262 (M^+, 12), 220 (63), 177 (17), 164 (13), 151 (42), 135 (100), 133 (5), 123 (18), 109 (44), 95 (20), 83 (11), 43 (38). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.76; H, 10.03.

3.5.3. (6*E*)-3,7,11-Trimethyl-6,10-dodecadien-1-yn-3-yl acetate (18).[10] To a solution of geranyl acetone (0.5 g, 2.6 mmol) in dry THF/diethyl ether (1:1) (2 mL) was added dropwise ethynylmagnesium bromide (6.5 mL, 3.1 mmol, 0.5 M in THF), at rt, in anhydrous diethyl ether (5 mL), under argon. The reaction mixture was stirred at rt for 4 h. Then water (20 mL) was added to quench the reaction and the mixture was extracted with diethyl ether (2×3 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum. Purification by flash chromatography (EtOAc/hexane, 2:98) gave unreacted starting material (91 mg) and the known derivative (6*E*)-3,7,11-trimethyl-1-dodeca-6,10-dien-1-yn-3-ol (0.325 g, 70% yield) [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.08 (m, 2H), 2.36 (d, J=2.0 Hz, 1H), 2.30–1.82 (m, 8H), 1.60 (s, 3H), 1.59 (s, 3H), 1.55 (s, 1H, OH), 1.50 (s, 3H), 1.39 (s, 3H)]. Following the general protocol for the esterification reaction, to a solution of (6*E*)-3,7,11-trimethyl-1-dodeca-6,10-dien-1-yn-3-ol (0.3 g, 1.36 mmol) in dry pyridine (5 mL), DMAP (32.2 mg, 0.27 mmol) and acetic anhydride (208.1 mg, 0.28 mL, 2.04 mmol) were added. The reaction mixture was stirred 24 h at rt. The solvent was evaporated under vacuum and the crude was purified by flash chromatography (EtOAc/hexane, 0.4:99.6) to give compound **18** (150 mg, 63% yield) as a colorless oil, that showed spectroscopic data [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.03 (m, 2H, H-6, H-10), 2.46 (d, J=1.7 Hz, 1H, H-1), 2.18–1.60 (m, 8H), 1.93 (s, 3H, $OCOCH_3$), 1.58 (s, 6H), 1.52 (s, 6H)] in agreement with the structure of this known product.[10]

3.5.4. (6*E*)-3,7,11-Trimethyl-1,2,6,10-dodecatetraen-1-yl acetate (21).[11] and (1*S**,6*R**,7*S**)-3,7-dimethyl-7-(4-methyl-3-pentenyl)bicyclo[41.0]hept-2-en-2-yl acetate (22). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of compound (**18**) (120 mg, 0.458 mmol) in dry toluene (18 mL) $PtCl_2$ (6.1 mg, 0.023 mmol) was added. The reaction mixture was stirred for 32 h at 80 °C. Purification by flash chromatography (CH_2Cl_2/hexane, 1:9) afforded products **21**[11] (9.4 mg, 8% yield) and **22** (23.1 mg, 19% yield). **21**[11]: Oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, 1H, H-1), 5.12 (m, 2H, H-6, H-10), 2.13 (s, 3H, $OCOCH_3$), 2.11–1.98 (m, 8H), 2.03 (s, 3H), 1.83 (d, J=1.8 Hz, 3H, H-15), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 169.2, 136.1, 131.7, 124.7, 124.5, 116.3, 110.2, 40.0, 35.9, 26.9, 26.2, 26.0, 23.7, 21.0, 18.0, 16.4; MS (70 eV) m/z 262 (32), 151 (73), 133 (91), 109 (90), 69 (100), 43 (80). **22**: Oil; IR (film) ν 2961, 2918, 2855, 1756 ($OCOCH_3$), 1448, 1368, 1214, 1099 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.98 (tm, J=7.1 Hz, 1H, H-3′), 2.20–1.65 (m, 2H, H-2′), 2.25–2.08 (m, 1H), 2.06 (s, 3H, $OCOCH_3$), 2.00–1.85 (m, 2H),1.78–1.62 (m, 1H), 1.57 (s, 3H, H-5′), 1.50 (s, 3H, H-6′), 1.44 (s, 3H, H-9), 1.22–1.05 (m, 2H), 1.03–0.98 (m, 2H, H-1, H-6), 0.86 (s, 3H, H-8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 ($OCOCH_3$), 140.7 (C-2), 130.7 (C-4′), 124.1 (C-3′), 118.8 (C-3), 41.6 (C-4), 29.2 (C-2′), 28.5 (C-7), 25.2 (C-1′), 25.0 (C-9), 23.5 (C-6), 22.7 (C-1), 20.4 ($OCOCH_3$), 17.1 (C-5), 17.0 (C-5′), 15.6 (C-6′), 12.4 (C-8); MS (70 eV) m/z 262 (M^+, 4), 220 (47), 177 (13), 164 (10), 149 (27), 135 (100), 121 (30), 109 (56), 41 (82). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.58; H, 9.67.

3.5.5. 3-Methyl-hept-6-en-1-yn-3-yl acetate (23).[6b] A solution of of 6-hexene-2-one (0.50 g, 5.1 mmol) in a mixture of dry THF/diethyl ether (1:1) (4 mL) was added dropwise, at rt, to a solution of ethynylmagnesium bromide (13 mL, 6.1 mmol, 0.5 M in THF) in anhydrous diethyl ether (15 mL), under argon. The reaction mixture was stirred at rt for 3 h. Then water (20 mL) was added to quench the reaction and the mixture was extracted with diethyl ether (2×3 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum. Purification by flash chromatography (EtOAc/hexane, 5: 95) gave 3-methyl-hept-6-en-1-yn-3-ol (0.32 g, 50% yield) [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.76 (ddt, J=6.6 Hz, J=10.0 Hz, J=17.2 Hz, 1H), 5.01 (dm, J=17.2 Hz, 1H), 4.86 (dm, J=10 Hz, 1H), 2.35 (s, 1H), 2.34–2.09 (m, 2H), 2.07 (br s, 1H), 1.69–1.61 (m, 2H), 1.39 (s, 3H)]. Following the general method for the esterification reaction, to a solution of 3-methyl-hept-6-en-1-yn-3-ol (200 mg, 1.60 mmol) in dry pyridine (4 mL), DMAP (39 mg, 0.32 mmol) and acetic anhydride (0.32 mg, 0.36 mL, 2.42 mmol) were added. The reaction mixture was stirred 12 h at rt. The solvent was evaporated under vacuum and the crude was purified by flash chromatography (EtOAc/hexane, 0.8:99.2) to furnish acetate **23** (180 mg, 67% yield) as a colorless oil, that spectroscopic data [^{1}H NMR (200 MHz, $CDCl_3$) δ 5.72 (ddt, J=6.6 Hz, J=10.0 Hz, J=17.2 Hz, 1H, H-6), 4.96 (dm, J=17.2 Hz, 1H, H-7), 4.87 (dm, J=10 Hz, 1H, H-7′), 2.45 (s, 1H, H-1), 2.25–2.06 (m, 2H, H-5), 1.92 (s, 3H, $OCOCH_3$), 2.00–1.86 (m, 1H, H-4), 1.84–1.69 (m, 1H, H-4′), 1.57 (s, 3H, H-8)] in good agreement with the structure of this known product.[6b]

3.5.6. 3-Methylbicyclo[4.1.0] hept-2-en-2-yl acetate (24). Following the general procedure for the $PtCl_2$-catalyzed cycloisomerisation reaction, to a degassed solution of 1-ethynyl-1-methyl-4-pentenyl acetate (**23**) (140.8 mg,

0.81 mmol) in dry toluene (32 mL), $PtCl_2$ (10.8 mg, 0.04 mmol) was added. The reaction mixture was stirred for 18 h at rt. Purification by flash chromatography (EtOAc/hexane, 0.8:99.2) afforded the expected product **24** (140.0 mg, 99% yield): Oil; IR (film) ν 3074, 3005, 2919, 2859, 1755 ($OCOCH_3$), 1698, 1445, 1368, 1320, 1228, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H, $OCOCH_3$), 1.84–1.54 (m, 4H, H-4, H-5), 1.38 (br s, 3H, H-8), 1.38–1.18 (m, 1H, H-6), 1.07 (td, $J=4.6$ Hz, $J=8.5$ Hz, 1H, H-1), 0.67 (dt, $J=4.6$ Hz, $J=8.0$ Hz, 1H, H-7), 0.59 (m, 1H, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 ($OCOCH_3$), 143.4 (C-2), 115.3 (C-3), 26.2 (C-4), 21.1 ($OCOCH_3$), 19.6 (C-5), 16.5 (C-8), 14.6 (C-6), 12.3 (C-1), 10.4 (C-7). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.33; H, 8.25.

3.5.7. 2-Methyl bicyclo[4.1.0]heptan-2-one (25).[13] Following the general method for the methanolysis of the enol esters, to a solution of 3-methylbicyclo[4.1.0]hept-2-en-2-yl acetate (**24**) (200 mg, 1.15 mmol) in methanol (22 mL, 0.05 M) solid potassium carbonate (225.3 mg, 2.29 mmol) was added. The reaction mixture was stirred at rt for 18 h, quenched by adding brine (25 mL), extracted with diethyl ether and dried over anhydrous Na_2SO_4. Purification by flash column chromatography (EtOAc/hexane, 2:98) afforded 2-methyl bicycle[4.1.0]heptan-2-one (**25**) (87 mg, 61% yield), isolated as an inseparable mixture of *cis/trans* diastereomers in a 1.5:1 ratio, which showed identical spectroscopic to those described for these isomers in literature:[13] Oil; IR (film) ν 3081, 3015, 2960, 2931, 2872, 1688, 1456, 1376, 1351, 1214, 1192 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.20–1.72 (m, 2H), 1.70–15.2 (m, 3H), 1.32–1.12 (m, 2H), 0.98 (d, $J=7.0$ Hz, H-8, major *trans* isomer), 0.91 (d, $J=7.0$ Hz, H-8, minor *trans* isomer), 0.94–0.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major *cis* isomer) 211.3 (C-2), 42.5 (C-3), 25.5 (C-6), 25.0 (C-4), 21.8 (C-5), 16.6 (C-1), 16.6 (C-8), 8.5 (C-7); (minor *trans* isomer) 212.8 (C-2), 39.2 (C-3), 30.0 (C-4), 20.9 (C-5), 19.6 (C-6), 14.2 (C-1), 16.4 (C-8), 15.6 (C-7); GLC/MS *m/z* (major *cis* isomer) (retention time: 10.99 min) 124 (M^+, 36) 109 (15), 95 (12), 81 (62), 67 (25), 54 (100), 51 (7) 39 (50); (minor *trans* isomer) (retention time: 11.22 min) *m/z* 124 (M^+, 34) 109 (13), 97 (8), 95 (11), 81 (60), 67 (21), 54 (100), 39 (50).

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16. During the preparation of this manuscript we were aware of a communication (Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546–2547) on the same subject, describing the $AuCl_3$-catalyzed cycloisomerization reaction of similar propargylic carboxylates.

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A furan ring expansion approach to the synthesis of novel pyridazino-psoralen derivatives

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Abstract—A convenient preparation of the parent tetrahydrobenzodifuran **2** was developed from resorcinol. The oxidation of one or both furan rings of this key intermediate was accomplished with DDQ and the resulting benzodifuran was subsequently reacted with 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine to afford the expected pyridazino-psoralen derivative in good yield. This simple method allowed the efficient preparation of a pyridazino-psoralen derivative with a formyl group at C-7, which was introduced by directed *ortho*-lithiation in the intermediate **2**. An aminoalkyl side-chain was also introduced to the tetracyclic skeleton through the aldehyde functionality in a reductive amination process, which was accompanied by an unprecedented reduction of the pyridazine ring.

1. Introduction

Psoralens form a group of natural or synthetic compounds that are of great pharmacological interest.[1] One of the most important applications of these compounds is in the field of photochemotherapy, where psoralens are capable of undergoing photoaddition with thymine units present in DNA.[2] However, the utility of the most effective compounds in this class is limited by side-effects that are mainly related to their ability to cross-link the two strands of the DNA helix.[3] One of the most promising strategies to obtain monofunctional psoralens involves incorporating one of the reactive double bonds in a benzene nucleus by forming benzopsoralens (Fig. 1). This approach results in molecules that have a high propensity for intercalation and photoreaction with DNA and also helps to overcome some of the negative phototoxic effects.[4]

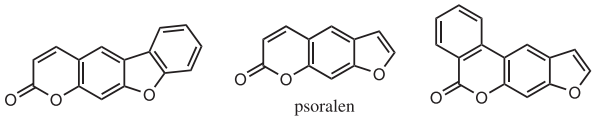

Figure 1.

With this information in mind, we embarked on the preparation of nitrogenated analogues of benzopsoralens reasoning that the inclusion of nitrogen atoms in the polycyclic skeleton may lead to improved interaction with DNA.[5] In particular, we were encouraged by the remarkable antiproliferative activity recently reported for pyrone side tetracyclic psoralen derivatives.[6] Prompted by this result and the widely used Diels–Alder of 1,2,4,5-tetrazines;[7] we focused on the development of a general synthetic route to novel pyridazino psoralens in which the pyridazine ring is attached to the pyrone nucleus of the psoralen skeleton.[8]

In a preliminary attempt to fuse a pyridazine ring to psoralens using 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine, we observed that the cycloaddition was accompanied by opening of the furan ring and concomitant expansion to a pyrone ring upon intramolecular transesterification.[9] We decided to exploit this interesting domino reaction pathway[10] to explore the use of benzodifuran derivatives to prepare these novel pyridazino-psoralens (Scheme 1).

2. Results and discussion

An important intermediate in our synthetic proposal is the tetrahydrobenzodifuran **2** and the synthesis of this compound has been reported from 6-hydroxy-dihydrobenzofuran in three steps.[11] Our initial goal was to develop a more convenient preparation of this intermediate and, in this respect, we envisaged a route based on a magnesium mediated cyclization process, which was reported by Nichols et al. for similar symmetrical benzodifuran derivatives.[12] The synthesis of this compound commenced with dialkylation of resorcinol using excess 1-bromo-2-

Keywords: Psoralens; Benzofurans; Tetrazines; Diels–Alder; DNA intercalants.
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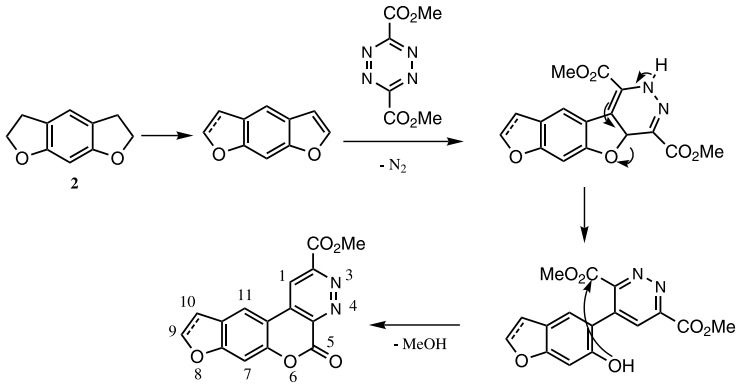
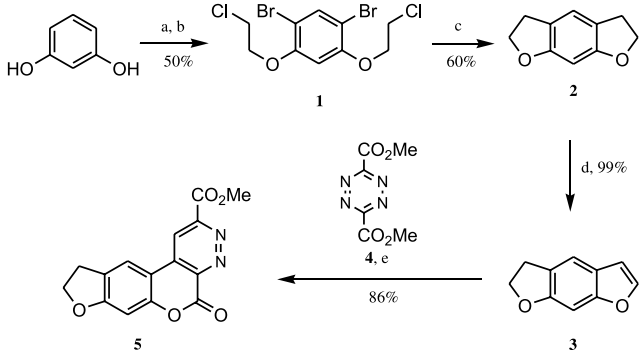


Scheme 1.

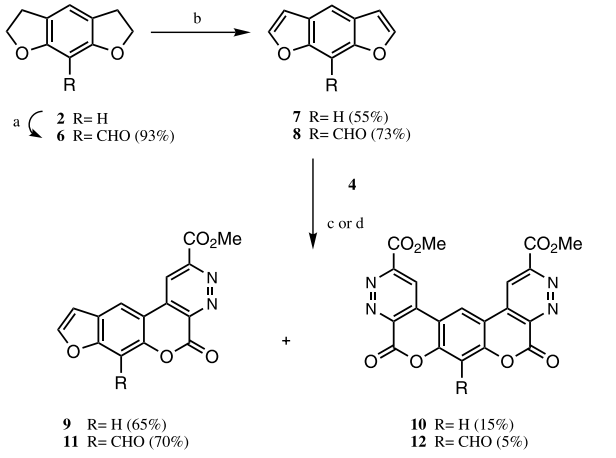
chloroethane and potassium carbonate in acetone reflux. Aromatic dibromination was accomplished using bromine in acetic acid and the product was subjected to Grignard conditions to effect ring closure[13] and afford the desired compound **2** (Scheme 2). This three step procedure only require one chromatographic purification and allowed the preparation of pure compound **2** in useful scale quantities (4.5 g). Starting from other commercially available or easily prepared resorcinol derivatives, this procedure could also be extended to other tetrahydrobenzodifuran derivatives.



Scheme 2. (a) $BrCH_2CH_2Cl$, K_2CO_3, $(CH_3)_2CO$, reflux, 48 h; (b) Br_2, AcOH, rt, 3 h; (c) Mg, EtMgBr (cat) , THF, reflux, 4 h; (d) 1 equiv DDQ, dioxane, rt, 2 h; (e) dioxane, reflux, 6 h.

With an efficient synthesis of **2** established, we attempted the dehydrogenation of only one dihydrofuran ring in order to achieve ring expansion in the Diels–Alder reaction with the tetrazine **4**. It was believed that this approach would avoid competition through reaction of the other ring. Selective oxidation of a dihydrofuran ring of **2** was accomplished using 1 equiv of DDQ in dioxane at room temperature to afford **3** in almost quantitative yield. This result was very satisfactory because this simple conventional oxidation method furnished the unsymmetrical compound **3** in excellent yield; compound **3** could also prove very useful for a variety of different synthetic purposes.[14] The Diels–Alder reaction between tetrazine **4** and compound **3** was performed in refluxing dioxane and gave the expected compound **5**. Under these conditions, analytically pure **5** was obtained in 86% yield by simple filtration of the cold reaction mixture (Scheme 2).

Although the oxidation of the residual dihydrofuran ring in compound **5** seems reasonable, the very low solubility of this compound in common organic solvents is a serious limitation in terms of reactivity. At this point, we examined the selectivity of the Diels–Alder reaction of benzodifurans. Oxidation of both dihydrofuran rings of compound **2** was performed using an excess of DDQ in refluxing dioxane and afforded compound **7** in 55% yield.[15] The Diels–Alder reaction of benzodifuran **7** with tetrazine **4** furnished the expected compound **9** in 65% yield; this compound was isolated pure after filtration of the cold reaction mixture. The filtrate of this reaction was then treated with boiling acetic acid and the symmetrical compound **10** crystallized in 15% yield (Scheme 3).



Scheme 3. (a) (i) *n*-BuLi, Et_2O, −78 °C, then 0 °C, 4 h; (ii) DMF, 0 °C, then rt, 16 h; (b) 3.3 equiv DDQ, dioxane, reflux, 18 h; (c) dioxane, reflux, 2 h; (d) 6:1 dioxane/AcOH, reflux, 8 h.

It was anticipated that analogues of compound **9** bearing an aldehyde group at C-7 would allow the facile preparation of side chain analogues at a later stage in the synthesis of these tetracyclic compounds. With this aim in mind, we planned to examine the reactivity of benzodifuran **8**.

Regioselective *ortho* lithiation of compound **2** followed by quenching the resulting anion with DMF furnished compound **6** in 93% yield. The oxidation of this intermediate with excess of DDQ to give **8** was performed under identical conditions to the oxidation of **2**, but a higher yield (73%) was obtained. Nichols et al. have also noted that the yield of this oxidation is strongly dependent on the nature of the substituents attached to the benzodifuran nucleus.[16] The

first attempt at a Diels–Alder reaction between compound **8** and tetrazine **4** in refluxing dioxane was unsuccessful. We reasoned that the final lactonization would prove difficult due to an intramolecular hydrogen bond with the formyl group that stabilizes the open intermediate (Fig. 2). The stabilizing effect was overcome by performing the reaction in the presence of acetic acid as a protic additive. This modification allowed compounds **11** and **12** to be obtained in 70 and 5% yield, respectively. Once again, the major compound **11** crystallized pure from the reaction mixture and the minor compound was recrystallised from AcOH. As one would anticipate,[13] the introduction of the electron-withdrawing formyl group in the benzodifuran nucleus decreased the reactivity of the dienophile in the inverse-electron demand Diels–Alder reaction; more importantly, such a change increased the monoadduct **11**/diadduct **12** ratio.

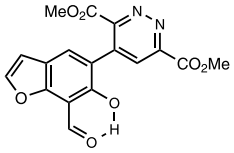


Figure 2.

Finally, we examined the attachment of an aminoalkyl chain to the skeleton of compound **11** through its formyl group on the basis that this kind of side chain usually plays an important role in the biological activity of DNA intercalant agents and other drugs.[17] The reductive amination of compound **11** was performed with *N*,*N*-dimethylethylenediamine in the presence of excess of $NaCNBH_3$.[18] To our surprise, the reduction of the pyridazine ring also occurred under the reaction conditions and compounds **13** and **14** were obtained in 65 and 30% yield, respectively. Unfortunately, assays with 0.5, 1.0 and 1.5 equiv of $NaCNBH_3$ afforded complex mixtures of products. The reaction was also performed with 1.1 equiv of $NaBH(OAc)_3$,[19] but no single major product was detected and further experiments are required to obtain the expected fully aromatised compound. Nevertheless, it was considered appropriate to report this preliminary result because this reduction of the pyridazine ring is unprecedented and could be a valuable synthetic tool in future studies (Scheme 4).[20]

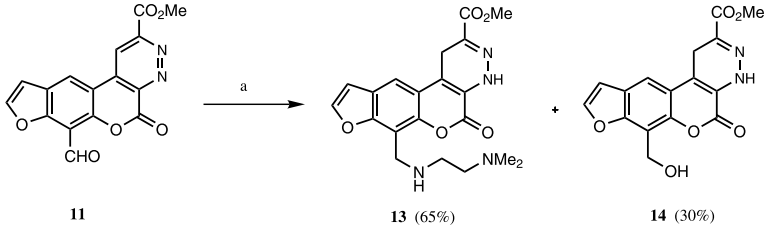
In conclusion, we have described a general procedure for the preparation of novel pyridazino-psoralens, that is both convenient and operationally simple. The synthesis is based on the Diels–Alder reaction between 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine and benzodifuran derivatives. This reaction is followed by a domino furan ring expansion to give a pyrone nucleus. Given the fact that benzofurocoumarins have been shown to possess significant photochemotherapeutic activity, ready access to these new pyridazine analogues provides avenues for investigations.

3. Experimental

3.1. General

All reactions were performed using oven-dried glassware under an atmosphere of dry argon. Solvents were distilled and dried before use-except DMF, which was purchased anhydrous from Aldrich. Reagents were purchased from Aldrich and used without further purification. Chromatographic purification of products was accomplished using forced flow chromatography on silica gel 60 (230–400 mesh). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm). Melting points were determined in capillary tubes using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1640FT spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX spectrometer at 300 and 75.5 MHz, respectively, using TMS as internal standard (chemical shifts are given as δ values, J in Hz). Mass spectra were obtained using a Hewlet Packard 5988A spectrometer.

3.1.1. 1,5-Dibromo-2,4-bis(2-chloroethoxy)benzene (1). A mixture of resorcinol (10.00 g, 91 mmol), 1-bromo-2-chloroethane (60 mL, 728 mmol), finely powdered K_2CO_3 (38.00 g, 137 mmol) and acetone (60 mL) was stirred and heated at reflux under argon for 72 h. The reaction was cooled to room temperature and filtered through a short pad of Celite 535. The Celite was washed with CH_2Cl_2, and the filtrate and washes were combined and evaporated to dryness by rotatory evaporation. The residue was partitioned between Et_2O and H_2O. The organic phase was extracted with 2 M NaOH (2×100 mL), then H_2O (2×100 mL) and brine (100 mL), dried over Na_2SO_4 and evaporated under vacuum. The resulting yellow solid (11.10 g) was suspended in glacial acetic acid (30 mL) and a solution of Br_2 (6 mL) in AcOH (15 mL) was added dropwise at 0–5 °C. The reaction mixture was allowed to reach room temperature and stirred for 3 h. The mixture was poured into ice/water (50 mL) and stirred for 15 min. The precipitate was filtered off and the solid was washed with cold 1:1 AcOH/H_2O (2×50 mL), then with cold H_2O until neutral pH (5×50 mL) and dried under vacuum with P_2O_5 until constant weight (17.73 g, 50%); mp 102–105 °C. ^1H NMR ($CDCl_3$) δ 7.60 (s, 1H, H_6), 6.45 (s, 1H, H_3), 3.80 (t, 4H, J=8.95 Hz, $2CH_2$), 3.07 (t, 4H, J=8.95 Hz, $2CH_2$).



Scheme 4. (a) $NH_2CH_2CH_2NMe_2$, $NaCNBH_3$, DMF–AcOH, rt, 7 h.

EI-MS *m/z* (%) 396 (34), 394 (92), 392 (97), 390 (37), 332 (38), 330 (52), 269 (51), 268 (100), 266 (51).

3.1.2. 2,3,5,6-Tetrahydrobenzo[1,2-*b*;5,4-*b*′]difuran (2). To a suspension of magnesium turnings (3.40 g, 141 mmol) in anhydrous THF (40 mL) was slowly added EtMgBr (3.4 mL, 10 mmol, 3 M solution in Et_2O). An anhydrous THF solution (115 mL) of the dibrominated compound **1** (18.20 g, 46.2 mmol) was then added dropwise under argon atmosphere such that the internal reaction temperature did not exceed 40 °C. Upon completion of the addition, the reaction was heated under reflux for 3 h, after which time TLC (95:5 hexane/EtOAc) indicated completion of the reaction. The reaction was then cooled to room temperature and 1 M HCl (200 mL) was carefully added while cooling with an external ice/water bath. Upon cessation of gas evolution, the solution was extracted with Et_2O (3× 300 mL). The organic layers were combined and washed with aqueous 1 M NaOH (5×75 mL), brine (50 mL), dried (Na_2SO_4), filtered, and evaporated to afford a tan solid (6.16 g). This solid was purified by column chromatography (95:5 hexane/EtOAc) to yield a white solid (4.45 g, 60%); mp 60–63 °C (lit.[11] 75 °C). ^{1}H NMR ($CDCl_3$) δ 6.93 (m, 1H, H_4), 6.26 (s, 1H, H_8), 4.53 (t, 4H, J=8.95 Hz, H_2+H_6), 3.07 (t, 4H, J=8.95 Hz, H_3+H_5). ^{13}C NMR ($CDCl_3$) δ 160.25, 120.31 (CH), 118.16, 92.57 (CH), 72.13 (CH_2), 29.27 (CH_2). EI-MS *m/z* (%) 162 (M^+, 100), 133 (12), 58 (24). HRMS-EI Calcd for $C_{10}H_{10}O_2$: 162.0681. Found: 162.0685.

3.1.3. 2,3-Dihydrobenzo[1,2-*b*;5,4-*b*′]difuran (3). A solution of DDQ (113 mg, 0.5 mmol) in dioxane (8 mL) was added slowly (over 1 h) to a solution of compound **2** (81 mg, 0.5 mmol) in dioxane (2 mL). The reaction mixture was stirred at room temperature for a further 1 h and the precipitate was filtered off and washed thoroughly with CH_2Cl_2. The filtrate and the washes were combined and evaporated to dryness under vacuum. The residue was purified by column chromatography (hexane) to afford a white solid (78 mg, 99%); mp 58–60 °C. ^{1}H NMR ($CDCl_3$) δ 7.47 (d, 1H, J=2.20 Hz, H_2), 7.30 (s, 1H, H_4), 6.90 (s, 1H, H_8), 6.62 (d, 1H, J=2.20 Hz, H_3), 4.60 (t, 2H, J=8.45 Hz, H_6), 3.24 (t, 2H, J=8.45 Hz, H_5). ^{13}C NMR ($CDCl_3$) δ 158.46, 155.27, 143.80 (CH), 123.24, 120.82, 116.05 (CH), 106.35 (CH), 93.14 (CH), 72.15 (CH_2), 29.42 (CH_2). EI-MS *m/z* (%) 160 (M^+, 100), 131 (60). HRMS-EI Calcd for $C_{10}H_8O_2$: 160.0524. Found: 160.0520.

3.1.4. 9,10-Dihydro-pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (5). A mixture of compound **3** (82 mg, 0.51 mmol) and 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine[21] (83 mg, 0.42 mmol) in dioxane (3 mL) was heated under reflux for 6 h until the red colour of the tetrazine had disappeared. The mixture was allowed to reach room temperature and the precipitate was filtered off and washed with fresh dioxane (1 mL) and diethyl ether (2× 1 mL). A pure yellow solid (TLC 4:1 CH_2Cl_2/EtOAc) was obtained (96 mg, 77%). The filtrate was concentrated under vacuum and purified by column chromatography (9:1 CH_2Cl_2/EtOAc) to afford another crop of pure **5** (12 mg, 9%); mp 279–281 °C (dec). IR (KBr) 1758, 1713, 1580, 1451, 1412, 1265, 1164, 1134 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 8.94 (s, 1H, H_1), 8.51 (s, 1H, H_{11}), 6.95 (s, 1H, H_7), 4.75 (t, 2H, J=8.50 Hz, H_9), 4.05 (s, 3H, OMe), 3.55 (t, 2H, J=8.50 Hz, H_{10}). EI-MS *m/z* (%) 298 (M^+, 100), 240 (72), 185 (38). HRMS-EI Calcd for $C_{15}H_{10}N_2O_5$: 298.0589. Found: 298.0587.

3.1.5. 2,3,5,6-Tetrahydrobenzo[1,2-*b*;5,4-*b*′]difuran-8-carboxaldehyde (6). To a solution of compound **2** (1.62 g, 10 mmol) in anhydrous Et_2O (100 mL) was added *n*-BuLi (10 mL, 1.6 M in hexane) by syringe at −78 °C under argon. The mixture was stirred for 30 min. The external cool bath was replaced by an ice/water bath and the reaction mixture was stirred at 0–5 °C. Upon completion of the reaction (4 h), DMF (2.5 mL, 30 mmol) was added and the mixture was stirred for a further 16 h while the temperature was allowed to increase slowly to room temperature. Then 0.5 M HCl (50 mL) was added at 0 °C to quench the reaction and the mixture was stirred 15 min. The resulting mixture was extracted with Et_2O (4× 100 mL), the organic phases were combined and washed with H_2O (3×50 mL) until neutral pH and finally with brine (50 mL). The organic phase was dried over Na_2SO_4 and the solvent evaporated under vacuum to afford a tan solid (TLC 7:3 hexane/EtOAc, R_f 0.15), which was used in the next step without further purification (1.76 g, 93%). A sample was purified by column chromatography (7:3 hexane/EtOAc) to yield a yellow crystalline solid; mp 133–134 °C. IR (KBr) 1674, 1610, 1453, 1408, 1234, 1073 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H, CHO), 7.12 (s, 1H, H_4), 4.69 (t, 4H, J=8.60 Hz, H_3+H_5), 3.07 (t, 4H, J=8.60 Hz, H_2+H_6). ^{13}C NMR ($CDCl_3$) δ 186.98 (CH), 160.96, 126.75 (CH), 119.34, 106.76, 73.62 (CH_2), 28.29 (CH_2). EI-MS *m/z* (%) 190 (M^+, 100), 189 (51), 161 (25), 133 (29), 91 (14), 77 (19). HRMS-EI Calcd for $C_{11}H_{10}O_3$: 190.0630. Found: 190.0627.

3.1.6. Benzo[1,2-*b*;5,4-*b*′]difuran (7). A solution of DDQ (3.00 g, 13.2 mmol) in dioxane (70 mL) was added slowly (over 1 h) to a solution of compound **2** (648 mg, 4 mmol) in dioxane (70 mL). Once the addition was complete, the reaction mixture was heated under reflux for 18 h, after which time TLC indicated completion of the reaction. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica gel. The silica gel was washed well with CH_2Cl_2, and the filtrate and washes were evaporated to dryness under vacuum. The residue was purified by column chromatography (hexane) to give an off-white solid product (347 mg, 55%); mp 57–59 °C (lit.[15] 55–58.5 °C). ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H, H_4), 7.62 (s, 1H, H_8), 7.60 (d, 2H, J=2.20 Hz, H_2), 6.80 (d, 2H, J=2.20 Hz, H_3). ^{13}C NMR ($CDCl_3$) δ 153.36, 145.26 (CH), 124.25, 111.33 (CH), 106.39 (CH), 94.44 (CH). EI-MS *m/z* (%) 158 (M^+, 36), 58 (100). HRMS-EI Calcd for $C_{10}H_6O_2$: 158.0368. Found: 158.0372.

3.1.7. Benzo[1,2-*b*;5,4-*b*′]difuran-8-carboxaldehyde (8). This compound was prepared from **6** (1.76 g, 9.2 mmol) in an analogous manner to **7** from **2**. The crude product was purified by flash chromatography using 9:1 CH_2Cl_2/EtOAc to give a white solid product (1.25 g, 73%); mp 103–104 °C. IR (KBr) 1677, 1592, 1548, 1115, 1016, 743 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 10.84 (s, 1H, CHO), 8.00 (s, 1H, H_4), 7.78 (d, 2H, J=2.20 Hz, H_2), 6.89 (d, 2H, J=2.20 Hz, H_3). ^{13}C NMR ($CDCl_3$) δ 185.77 (CHO), 152.61, 146.51 (CH),

125.33, 119.24 (CH), 106.36 (CH). EI-MS *m/z* (%) 186 (M^+, 100), 185 (87), 157 (26), 129 (22). HRMS-EI Calcd for $C_{11}H_6O_3$: 186.0317. Found: 186.0314.

3.1.8. Pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (9) and 5,9-dioxo-benzo[1,2-*b*;5,6-*b'*]dipyran-bis[3,4-*c*]pyridazine-2,12-di(carboxylic acid, methyl esther) (10). A mixture of compound **7** (128 mg, 0.81 mmol) and 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine (134 mg, 0.68 mmol) in dioxane (3 mL) was heated under reflux for 2 h until the red colour of the tetrazine had disappeared. The mixture was allowed to reach room temperature. The precipitate was filtered off and washed with fresh dioxane (2×1 mL) and diethyl ether (2×1 mL) to give **9** as a pure yellow solid (131 mg, 65%); mp >350 °C (dec 220 °C). IR (KBr) 1760, 1715, 1580, 1455, 1262, 1131 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.12 (s, 1H), 9.00 (s, 1H), 8.16 (d, 1H, J=2.30 Hz, H_9), 7.84 (s, 1H, H_7), 7.10 (d, 1H, J=2.30 Hz, H_{10}), 4.06 (s, 3H, OMe). EI-MS *m/z* (%) 296 (M^+, 76), 238 (100), 210 (44), 183 (32). HRMS-EI Calcd for $C_{15}H_8N_2O_5$: 296.0433. Found: 296.0433.

The filtrate was concentrated under vacuum and glacial AcOH (5 mL) was added to the residue. The mixture was heated under reflux for 30 min and then cooled to room temperature. The off-white precipitate was filtered off and washed with AcOH (1 mL) and diethyl ether (2×1 mL) to give pure **10** (22 mg, 15%); mp >350 °C (dec 250 °C). IR (KBr) 1774 (broad), 1628, 1583, 1282, 1162, 1121, 1050 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.75 (s, 1H, H_{14}), 9.50 (s, 2H, H_1+H_{13}), 7.73 (s, 1H, H_7), 4.11 (s, 6H, 2OMe). ^{13}C NMR (DMSO-d_6) δ 163.92, 156.06, 155.22, 152.40, 143.56, 133.35, 125.01 (CH), 120.96 (CH), 113.04, 106.02 (CH), 53.52 (OCH_3). HRMS-EI Calcd for $C_{20}H_{10}N_4O_8$: 434.0499. Found: 434.0494.

3.2. 7-Formyl-pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (11) and 7-formyl-5,9-dioxo-benzo[1,2-*b*;5,6-*b'*]dipyran-bis[3,4-*c*]pyridazine-2,12-di(carboxylic acid, methyl esther) (12)

These compounds were prepared from **8** (270 mg, 1.45 mmol) in an analogous manner to **9** and **10** from **7**, but using 6:1 Dioxane/AcOH (10 mL) as solvent and heating under reflux for 8 h.

3.2.1. Compound 11. Yield 273 mg (70%); mp >350 °C (dec 225 °C). IR (KBr) 1739 (broad), 1693, 1587, 1341, 1267, 1170, 1141 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.74 (s, 1H, CHO), 9.37 (s, 1H, H_{11}), 9.21 (s, 1H, H_1), 8.33 (d, 1H, J=2.20 Hz, H_9), 7.20 (d, 1H, J=2.20 Hz, H_{10}), 4.08 (s, 3H, OMe). ^{13}C NMR (DMSO-d_6) δ 185.55 (CHO), 163.63, 155.64, 153.95, 152.26, 151.58, 149.60 (CH), 142.72, 133.99, 125.82, 125.12 (CH), 120.64 (CH), 111.56, 109.20, 106.57 (CH), 53.37 (CH_3). EI-MS *m/z* (%) 324 (M^+, 38), 266 (84), 237 (16), 210 (100), 183 (27). HRMS-EI Calcd for $C_{16}H_8N_2O_6$: 324.0390. Found: 324.0385.

3.2.2. Compound 12. Yield 15 mg (5%); mp >350 °C (dec 285 °C). IR (KBr) 1778, 1742, 1719, 1695, 1599, 1279, 1129 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.69 (s, 1H, CHO), 9.95 (s, 1H, H_{14}), 9.57 (s, 2H, H_1+H_{13}), 4.11 (s, 6H, 2OMe). ^{13}C NMR (DMSO-d_6) δ 185.71 (CHO), 163.81, 155.18, 154.69, 152.45, 143.26, 132.96, 130.06, 128.99 (CH), 121.13 (CH), 113.09, 53.49 (CH_3). HRMS-EI Calcd for $C_{21}H_{10}N_4O_9$: 462.0448. Found: 462.0444.

3.3. 7-{[2-(Dimethylamino)ethyl]aminomethyl}-1,4-dihydropyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (13) and 7-hydroxymethyl-1,4-dihydro-pyridazino[3,4-*c*]psoralen-2-carboxylic acid, methyl esther (14)

To a suspension of compound **11** (65 mg, 0.2 mmol) in DMF (3 mL)/AcOH (0.2 mL) was added *N*,*N*-dimethyl-ethylenediamine (0.055 mL, 0.5 mmol) followed by $NaCNBH_3$ (38 mg, 0.6 mmol). The mixture was stirred at room temperature for 7 h. The reaction was quenched by adding 1 M HCl (1.5 mL) at 0 °C and the reaction mixture was concentrated until dryness under vacuum. Saturated solution of $NaHCO_3$ (5 mL) was added to the residue and diluted with H_2O (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (6×10 mL). The organic phases were combined, washed with brine (10 mL) and dried over Na_2SO_4. After filtration and evaporation of organic solvent, the crude mixture was purified by flash chromatography (9:1 CH_2Cl_2/EtOH, then 9:1:0.1 CH_2Cl_2/EtOH/NH_4OH) to give **13** (52 mg, 65%) and **14** (20 mg, 30%).

3.3.1. Compound 13. Mp >350 °C (dec 180 °C). IR (KBr) 3363, 1726, 1601, 1435, 1387, 1349, 1169, 1101, 1046 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.45 (s, 1H exch., NH), 7.75 (d, 1H, J=2.20 Hz, H_9), 7.55 (s, 1H, H_{11}), 6.85 (d, 1H, J=2.20 Hz, H_{10}), 4.35 (s, 2H, $ArCH_2N$), 3.95 (s, 3H, OCH_3), 3.80 (s, 2H, H_1), 2.75 (t, 2H, J=6.20 Hz), 2.45 (t, 2H, J=6.20 Hz), 2.15 (s, 6H, NMe_2), 2.00 (s, 1H exch., NH). ^{13}C NMR ($CDCl_3$) δ 164.71, 155.08, 154.30, 146.93 (CH), 146.55, 131.23, 124.85, 119.95, 119.53, 114.92, 113.15 (CH), 112.66, 106.68 (CH), 58.91 (CH_2), 52.80 (CH_3), 46.77 (CH_2), 45.38 (CH_3), 41.94 (CH_2), 21.45 (CH_2). EI-MS *m/z* (%) 398 (M^+, 6), 339 (17), 311 (77), 310 (27), 196 (21), 171 (25), 170 (19), 140 (18), 58 (100). HRMS-EI Calcd for $C_{20}H_{22}N_4O_5$: 398.1590. Found: 398.1586.

3.3.2. Compound 14. Mp >350 °C (dec 205 °C). IR (KBr) 3482, 3337, 1705 (broad), 1595, 1444, 1349, 1184, 1109 cm^{-1}. ^1H NMR (DMSO-d_6) δ 10.90 (s, 1H exch., NH), 8.12 (d, 1H, J=2.20 Hz, H_9), 7.77 (s, 1H, H_{11}), 7.07 (d, 1H, J=2.20 Hz, H_{10}), 5.31 (t, 1H exch., J=5.40 Hz, OH), 4.90 (d, 2H, J=5.40 Hz, CH_2O), 3.78 (s, 3H, OCH_3), 3.74 (s, 2H, H_1). ^{13}C NMR (DMSO-d_6) δ 164.55, 154.37, 1543.12, 147.56 (CH), 145.63, 129.87, 124.46, 119.88, 119.14, 114.85, 114.18 (CH), 112.61, 106.97 (CH), 51.92 (CH_2), 51.77 (CH_3), 21.07 (CH_2). EI-MS *m/z* (%) 328 (M^+, 29), 310 (26), 268 (53), 240 (49), 222 (100), 196 (74), 140 (44). HRMS-EI Calcd for $C_{16}H_{12}N_2O_6$: 328.0695. Found: 328.0699.

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Substrate-selective aqueous organometallic catalysis. How small water-soluble organic molecules enhance the supramolecular discrimination

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Abstract—Selective decarboxylation of two alkylallylurethane isomers into alkylallylamines has been performed in a biphasic system by using randomly hydroxypropylated and methylated cyclodextrins as discriminating agents. Surprisingly, the presence of small organic hydrosoluble molecules such as amine or alcohol derivatives appeared to be crucial in the discriminating process. Indeed, it was clearly proved that the presence of such additives enhances greatly the substrate selectivity. For instance, the addition of triethylamine to the reaction medium allows to improve the discriminating power of methylated-β-cyclodextrin by a factor 7. These unexpected results were explained by considering the formation of ternary cyclodextrin/substrate/additive complexes.

1. Introduction

The outstanding efficiency of biological processes led numerous research groups to understand the functioning of biological systems to equal or at least approach their performances. Thus, many elaborated technical devices were born from a careful observation of living organisms.[1] One of the remarkable properties of biological systems is the ability to select only relevant structures and reject the irrelevant ones. On the way to a deeper understanding of this selectivity process, a huge amount of studies have already been made in varied fields such as biology, biochemistry and chemistry.[2] Actually, on a molecular scale, organic chemistry has for long constituted an efficient tool to mimic the behaviour of biological entities such as biomembranes, cells or enzymes.[3] Though the path to a complete understanding of the selectivity phenomena occurring in those entities will still be long and arduous, many chemical systems have already proved to be very efficient in mimicking the substrate-, regio-, stereo- or enantioselectivity of these biological systems. As an example, the use of cyclodextrin (α-(1-4)-linked cyclic oligosaccharides usually consisting of 6 (α), 7(β) or 8(γ) glucopyranose units) was an original way to synthesize molecular scaffolds that help assemble the machinery of recognition process known to be necessary for selective chemical reactions.[4] Indeed, the selective binding of the substrate by a properly modified CD cavity lead to substrate selective reaction when the cyclodextrin itself catalyzes the reaction.[5]

The combination of an aqueous organometallic catalyst and water soluble CD derivatives is also an original way to obtain substrate selective reactions.[6] In fact, when the organic phase contains an isomers mixture, the CD preferentially transfers into the aqueous phase the isomer that interacts stronger with the CD cavity. The substrate/CD complex can then react with the aqueous organometallic catalyst to give the product that is released into the organic phase, according to Figure 1.

The feasibility of this approach was recently demonstrated in deprotection reactions of alkylallylcarbonates and alkylallylurethanes (removal of the allyloxycarbonyl group of protected alcohols or amines) by using differents pairs of structural isomers.[7] In particular, it has been shown that high substrate selectivities could be obtained with highly water-insoluble isomers having pronounced structural differences.[8] We have also demonstrated that the performances of a CD carrier in these deprotection reactions strongly depended on the size of the cavity in which the

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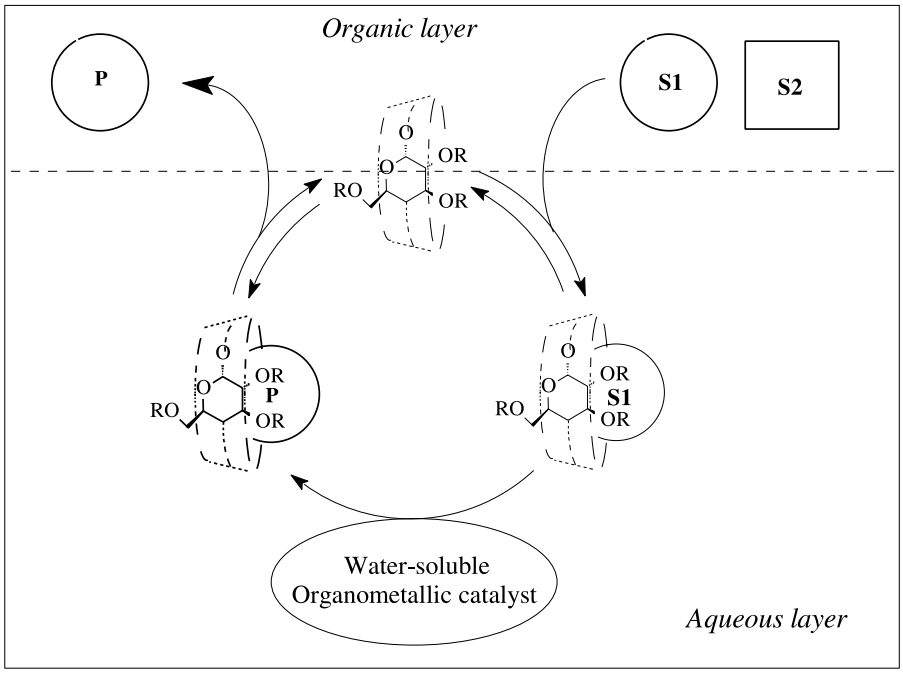


Figure 1. Concept of the substrate-selective aqueous organometallic catalysis mediated by cyclodextrin derivatives. Only the substrate **S1** fits properly in the host cavity of the cyclodextrin and, consequently reacts with the water soluble catalyst to give the product **P**.

substrate had to fill in as close as possible the available space.[9] In this paper, we investigated the selective decarboxylation of two alkylallylurethane isomers into alkylallylamines in the presence of hydroxypropylated cyclodextrins (HP-α-CD, HP-β-CD and HP-γ-CD) and methylated cyclodextrins (Me-α-CD, Me-β-CD and Me-γ-CD) (Fig. 2).

The results obtained were compared with those previously obtained when diethylamine was added in the biphasic medium as allyl scavenger. The role of diethylamine and other small water-soluble organic additives towards the discriminant power of the CD carriers was also discussed.

2. Results and discussion

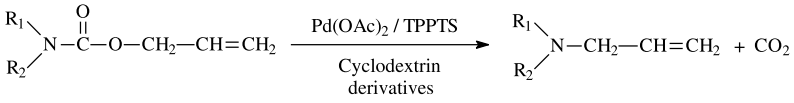
The linear *N*-dodecyl-*O*-allylurethane and the symmetric disubstituted *N*,*N*-dihexyl-*O*-allylurethane have been chosen as allylalkylurethane isomers. These two molecules strongly differed from their shape and, consequently, from the space they occupied in the CD cavity. Reactions were carried out using $Pd(OAc)_2$ as catalyst precursor and tris(3-sodium sulfonatophenyl)phosphine (TPPTS) as a ligand.[10] The results are gathered in Figure 3.

First, it must be noticed that both substrates have the same reactivity when no cyclodextrin was added in the reaction medium (initial catalytic activity: $0.03\ h^{-1}$ for the two allylic urethanes), leading to no substrate selectivity. In contrast, a visible difference of relative reaction rates (defined as the ratio between the initial catalytic activity in the presence of CD and the initial catalytic activity without cyclodextrin) were measured in the presence of CD derivatives.

Comparing the three HP-CDs, the best relative reaction rates were obtained with HP-β-CD which relative reaction rate was 46 for the linear *N*-dodecyl-*O*-allylurethane and only 9.3 for the disubstituted *N*,*N*-dihexyl-*O*-allylurethane. Dividing the former by the latter led to a substrate selectivity of 5.0. Its discriminating power was slightly lower than HP-α-CD which appeared to be less efficient in terms of relative reaction rates (38 for the linear isomer and 6.7 for the disubstituted isomer) but more selective towards the linear and branched structures of the urethanes (substrate selectivity of 5.7) certainly due to its smaller cavity. Consequently, there is no connection between the relative reaction rates and the substrate selectivity. A modified cyclodextrin could be a worse phase transfer catalyst in terms of initial activity but a good discriminating agent towards two structural isomers. The relative reaction rates measured with HP-γ-CD were lower than those of the other HP-CDs (17 and 3.7 for the linear and disubstituted substrates respectively) and the ratio between them led to a low substrate selectivity of 4.5.

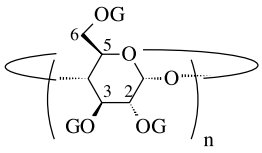
What struck when looking at the values obtained with Me-α-CD, Me-β-CD and Me-γ-CD was their greater ability to improve the performances of the system in terms of reaction rate. The effect of methylation on the reaction rate was particularly visible with Me-α-CD and Me-β-CD for which a relative reaction rate of 156 and 155 was measured with the *N*-dodecyl-*O*-allylurethane (it was only 38 and 46 with HP-α-CD and HP-β-CD, respectively). Similarly, the relative reaction rate observed with the *N*,*N*-dihexyl-*O*-allylurethane was more than threefold higher in the presence of methylated CDs. In fact, the better initial activities obtained with Me-CDs when compared to HP-CDs have already been discussed earlier and have been attributed to the higher surface activity of Me-CDs and to the presence of an enlarged hydrophobic cavity able to receive the

Decarboxylation of allylic urethanes



(R_1,R_2): $C_{12}H_{25}$, H or C_6H_{13}, C_6H_{13}

Structure of the chemically modified cyclodextrin



G: **H** or **R**

Abbreviations	n	**R**: group attached to the cyclodextrin	Carbon bearing the OR group	Average number of OH group substituted per glucopyranose unit
HP-α-CD	6	$-CH_2-CH(OH)-CH_3$	2	0.6
HP-β-CD	7	$-CH_2-CH(OH)-CH_3$	2	0.6
HP-γ-CD	8	$-CH_2-CH(OH)-CH_3$	2	0.6
Me-α-CD	6	$-CH_3$	2, 3, 6	1.8
Me-β-CD	7	$-CH_3$	2, 3, 6	1.8
Me-γ-CD	8	$-CH_3$	2, 3, 6	1.8

Figure 2. Decarboxylation of *N*-dodecyl-*O*-allylurethane and *N*,*N*-dihexyl-*O*-allylurethane in the presence of chemically modified cyclodextrins.

lipophilic substrates in a more effective way.[9] From substrate selectivity point of view, a similar behaviour could be noticed with the Me-CDs. The higher substrate selectivity was obtained with Me-α-CD, probably because of its smaller cavity (7.1 versus 3.5 for Me-β-CD and 4.2 for Me-γ-CD).

When comparing the above results with those of previous studies,[9] we were struck by the difference of relative reaction rates obtained when the reaction was carried out with or without diethylamine. Accordingly, when diethylamine was used as an allyl scavenger, the results were quite different (Fig. 4).

First, without cyclodextrin, the initial activities were the same than those obtained without diethylamine (initial catalytic activities: 0.03 h^{-1} for the two allylic urethanes) and no substrate selectivity was detected. Thus, diethylamine alone did not have neither cosolvent effects nor discriminating ability in our system. When a CD derivative was added to the aqueous phase, it clearly appeared that the presence of diethylamine led to lower relative reaction rates whatever the CD and whatever the isomer (compare values of Figure 3 and those of Figure 4). Manifestly, diethylamine reduced the rate of the reaction. Interestingly, the inhibiting effect of diethylamine on the reaction rate was more marked for the disubstituted isomer than for the linear one which resulted in an enhanced substrate selectivity. For a given CD, the ratio obtained when dividing the substrate selectivity measured with diethylamine and that measured without diethylamine allowed us to quantify the importance of the phenomenon: when diethylamine was added to the catalytic system, the substrate selectivity was multiplied by 1.2 for HP-α-CD, 1.4 for HP-β-CD and 1.2 for HP-γ-CD. The effect was even more appreciable with Me-CDs. As a matter of fact, with diethylamine as a scavenger, the ratios were multiplied by 2.7 for Me-α-CD, 5.7 for Me-β-CD and 3.3 for Me-γ-CD.

Our first intuition to explain the differences observed when diethylamine was added or not in the catalytic solution was to incriminate the catalytic processes. Actually, when diethylamine was used as a scavenger, π-allylic palladium intermediate reacts with diethylamine to lead to diethylallylamine (pathway 1 in Scheme 1). By contrast, without diethylamine, the π-allylic palladium intermediate reacts

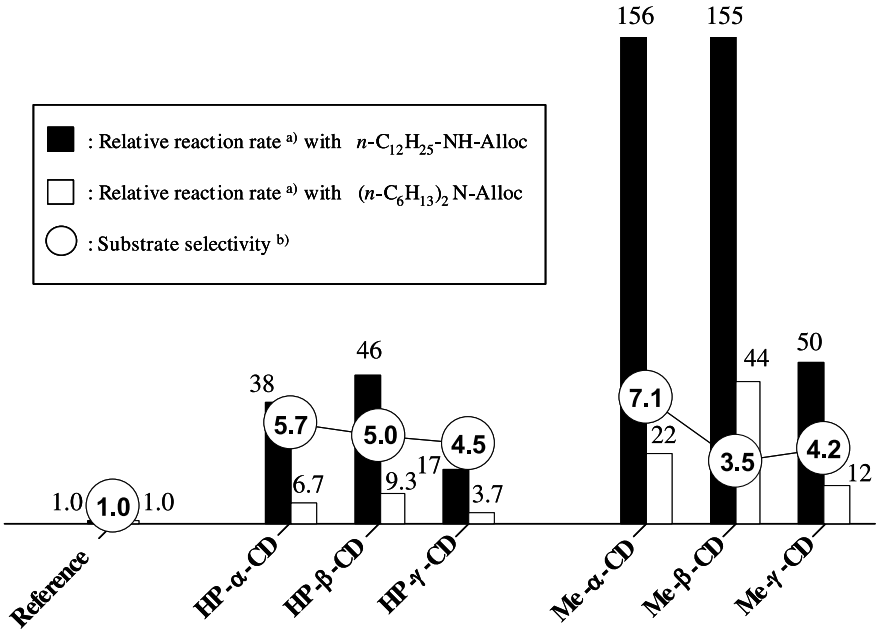


Figure 3. Reaction rate and substrate selectivity observed during the decarboxylation of *N*-dodecyl-*O*-allylurethane and *N*,*N*-dihexyl-*O*-allyluethane. (a) The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of cyclodextrin and the initial catalytic activity without cyclodextrin. The initial catalytic activity without cyclodextrin is 0.03 h^{-1} for each isomer (reference). (b) The substrate selectivity was defined as the ratio between the relative reaction rates observed between the two isomers.

with the in situ generated alkylamine to give rise to the alkylallylamine (pathway 2 in Scheme 1)

Because of this difference, one could think that the initial catalytic activities would not be comparable. In fact, experiments have shown that an increase in the introduced amount of cyclodextrin led to a linear increase in the rate of both reactions, whatever the presence of diethylamine. Therefore, the organometallic catalytic cycle do not constitute the rate determining step of the system which is rather connected with the mass transfer. Thus, the initial catalytic activities measured in this study do account for the capability of the modified cyclodextrins to transfer the substrates from the organic to the aqueous phase.

As a consequence, the above results may be interpreted as follows: by interfering with the CD, diethylamine hindered the molecular recognition of the branched isomer more than

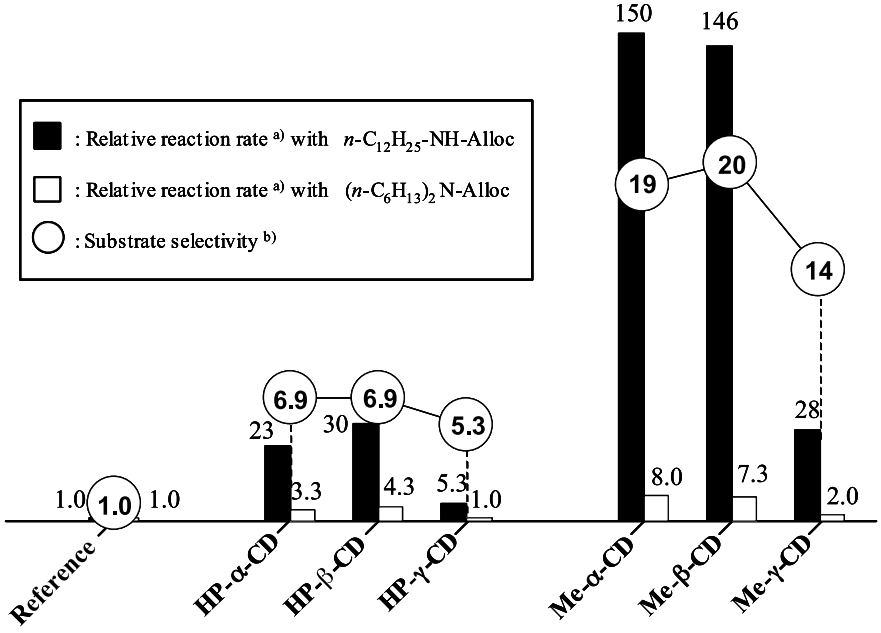
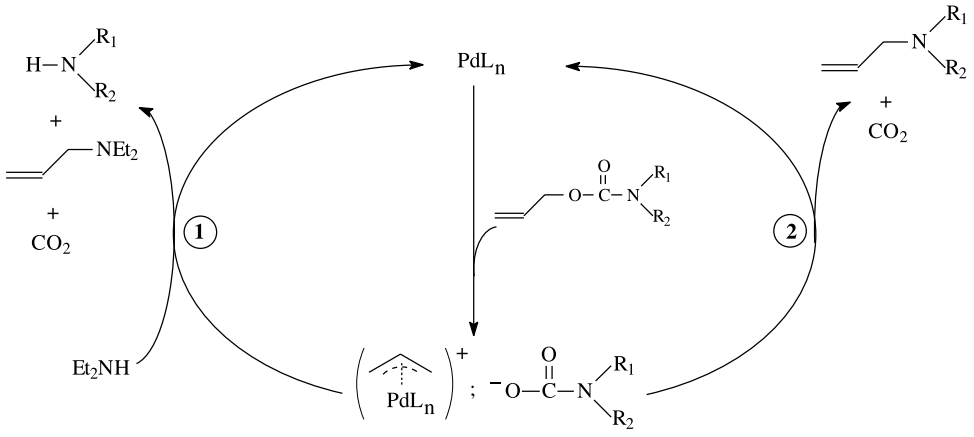


Figure 4. Reaction rate and substrate selectivity observed in the presence of diethylamine (7 equiv/cyclodextrin). (a) The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of cyclodextrin and the initial catalytic activity without cyclodextrin. The initial catalytic activity without cyclodextrin is 0.03 h^{-1} for each isomer (reference). (b) The substrate selectivity was defined as the ratio between the relative reaction rates observed between the two isomers.



Scheme 1.

that of the linear one. To confirm this hypothesis, experiments have been carried out with triethylamine which is well known to not be an allyl scavenger. The mechanism of the reaction in that case is comparable to that described without diethylamine (that is to say, formation of fat allylamines). The results are summarized in Figure 5.

In the same way than diethylamine, addition of triethylamine in the solution enhanced, in the most cases, the substrate selectivity in the detriment of the reaction rate. For HP-CDs, triethylamine appeared to be more appropriate to differentiate the urethane isomers in the presence of HP-α-CD (substrate selectivity of 11 vs 6.6 for HP-β-CD and 3.4 for HP-γ-CD). Here again, the best results were obtained with Me-β-CD with which the linear isomer was more easily recognised by a factor of 25 than the branched urethane. Me-α-CD and Me-γ-CD gave substrate selectivities of 13 and 6.8, respectively.

The results obtained with the triethylamine reinforce the assumption that diethylamine or triethylamine may act as a space-filling molecule in the CD cavity, impeding the molecular recognition between the CD and the allylurethane. The detrimental effect of these water soluble amines is more marked with the branched urethane than with the linear urethane, leading to higher substrate selectivity. In order to get a better insight into this phenomenon, we have tested in the last part of this study other small water soluble organic compounds capable of interfering in the formation of inclusion complexes and thus, modulating the substrate selectivity. In Figure 6 are summarized the results relative to reaction rates of *N*-dodecyl-*O*-allylurethane and *N*,*N*-dihexyl-*O*-allylurethane with various organic hydrosoluble compounds which were added to the catalytic solution in the same amount than that used for diethylamine and triethylamine (7 equiv/cyclodextrin). Me-β-CD has been chosen as a

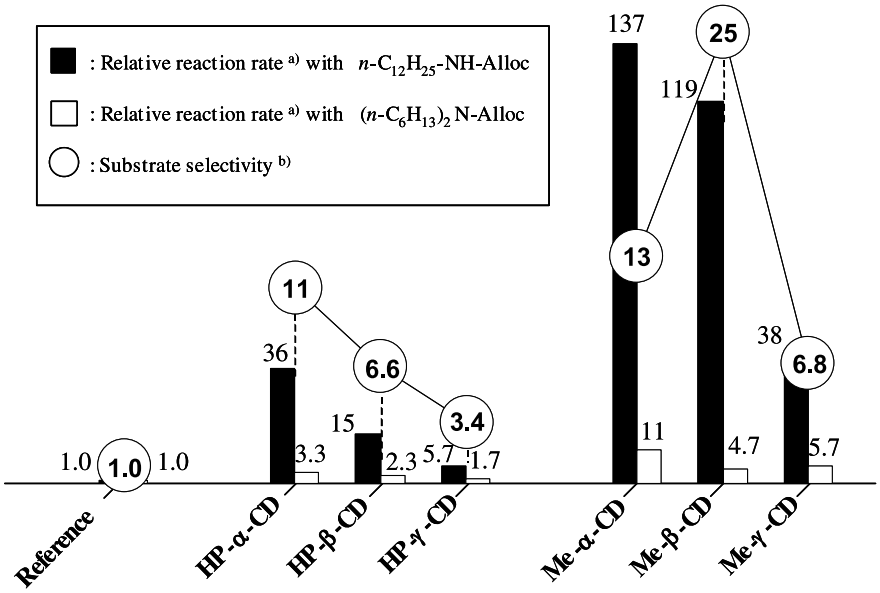


Figure 5. Reaction rate and substrate selectivity observed in the presence of triethylamine (7 equiv/cyclodextrin). (a) The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of cyclodextrin and the initial catalytic activity without cyclodextrin. The initial catalytic activity without cyclodextrin is 0.03 h^{-1} for each isomer (reference). (b) The substrate selectivity was defined as the ratio between the relative reaction rates observed between the two isomers.

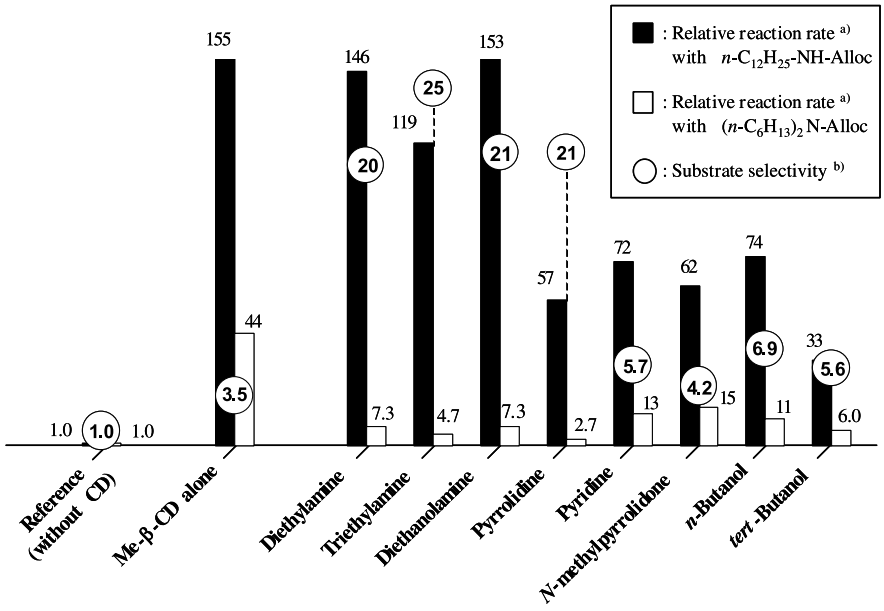


Figure 6. Reaction rate and substrate selectivity observed with RAME-β-CD, in the presence of different water-soluble organic compounds (7 equiv/cyclodextrin). (a) The relative reaction rate was defined as the ratio between the initial catalytic activity in the presence of RAME-β-CD and the initial catalytic activity without RAME-β-CD. The initial catalytic activity without RAME-β-CD is 0.03 h^{-1} for each isomer, whatever the introduced water soluble organic compound (reference). (b) The substrate selectivity was defined as the ratio between the relative reaction rates observed between the two isomers.

carrier because of the better performances obtained in these experimental conditions when compared to the other CDs.

All the added compounds gave better substrate selectivities than those obtained without any additive. However, not only the substrate selectivity but also the reaction rate strongly depended on the nature of the water-soluble additive. The best results in terms of reaction rate and substrate selectivity were obtained with diethylamine, triethylamine and diethanolamine. The pyrrolidine was a particular case as this compound gave a substrate selectivity similar to those obtained with the previous additives (21) but a significant decrease in the reaction rate was observed for each isomer. With pyridine and *N*-methylpyrrolidone, both the substrate selectivity and the reaction rate decreased. Alcohols with short alkyl chains have also been tried as substrate selectivity modulator. Significant substrates selectivities were measured for *n*-butanol (6.9) and *tert*-butanol (5.6) but the substrate selectivity and the reaction rate remained weak compared to that obtained with other compounds.

The above results confirm that the small water-soluble organic compounds strongly affect the behavior of the CD derivatives. The existence of ternary CD/substrate/additive complexes appears us to be the most probable explanation of the observed rate decrease and substrate selectivity enhancement. In fact, the presence of small polar organic compounds near or inside the CD cavity reduce the size of the cavity, which is less defavorable for the linear urethane than for the branched urethane, inducing a higher substrate selectivity. Concomitantly, the presence of these polar organic compounds near or inside the cavity induces a less hydrophobic microenvironment inside the CD cavity.[11] This change in the polarity of the CD microenvironment contributes also to reduce the affinity of the CD for the highly hydrophobic urethanes, resulting in a lower reaction rate. Finally, although we have not been able to spectroscopically characterized such ternary complexes due to the too low solubility of allylic urethanes, it must be noticed that existence of such ternary complexes has already been reported in the literature.[12]

3. Conclusion

A the end of this study, we are confronted with a very delicate matter for which a subtle adjustment is required. Actually, the discriminating power of modified CDs appeared to be a notion much more complex than it first, appeared to be. It does not only depend on the interaction between the substrate and the carrier but also on the presence of small organic hydrosoluble molecules which may influence the stability of the inclusion complexes. According to their structure, these small compounds can modulate the substrate selectivity. Ternary substrate/CD/additive supramolecular complexes are thought to be responsible for the enhancement of the substrate selectivity. Experiments are currently under way with small chiral water-soluble organic additives to perform enantioselective reactions.

4. Experimental

4.1. Materials

HP-α-CD and HP-β-CD were obtained from Aldrich Chemical Co. and was used as received without further purification. HP-γ-CD was a generous gift of Wacker Chemie Co. These HP-CDs were native CDs partially

O−2-hydroxypropylated with statistically 0.6 OH groups modified per glucopyranose unit. Me-β-CD was purchased from Aldrich Chemical Co. The Me-α-CD and Me-γ-CD were prepared by adapting a procedure reported by Y. Kenichi et al.[13] These CDs were partially methylated; statistically 1.8 OH groups per glucopyranose unit were modified. Palladium acetate and organic compounds were purchased from Strem Chemicals, Aldrich Chemical Co. and Acros Organics in their highest purity and used without further purification. Trisodium tris(*m*-sulfonatophenyl)-phosphine ($(P(C_6H_4SO_3Na)_3$; TPPTS)) was synthesized as reported by Gärtner et al.[14] The purity of the TPPTS was carefully controlled. In particular, $^{31}P\{^1H\}$ solution NMR indicated that the product was a mixture of TPPTS (ca 98%) and its oxide (ca 2%). Distilled deionized water was used in all experiments. All catalytic reactions were performed under nitrogen using standard Schlenk techniques. All solvents and liquid reagents were degassed by bubbling nitrogen for 15 min before each use or by two freeze-pump-thaw cycles before use.

4.2. Catalytic experiments

In a typical experiment, $Pd(OAc)_2$ (0.045 mmol, 10 mg), TPPTS (0.40 mmol, 227 mg), cyclodextrin (0.31 mmol) and water (2 g) were introduced under nitrogen atmosphere into a Schlenk tube. After stirring with a magnetic bar for 1 h, the yellow solution was transferred into a mixture of the substrate (1.12 mmol), toluene (2 g) and dodecane as internal standard (0.10 g, 0.588 mmol). The medium was stirred at 1000 rpm at room temperature and the reaction was monitored by quantitative gas chromatographic analysis of the organic layer. When the presence of water-soluble organic compounds was required, 2.24 mmol of this additive was added to the mixture of substrate, toluene and dodecane.

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On the reactivity of ascomycin at the binding domain. Part 3: Reactivity of the binding domain towards diazomethane

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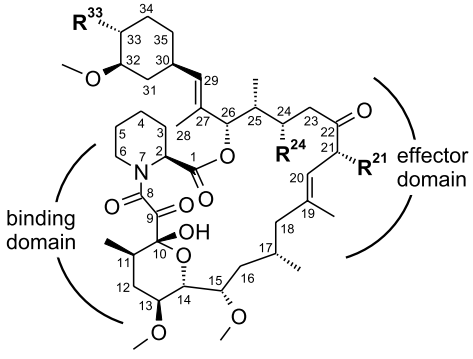
Abstract—A thorough product analysis of the reaction of ascomycin with diazomethane has been performed. Apart from the expected oxiranes (epimeric at C9), a whole range of novel derivatives bearing various modifications in the binding domain were obtained. Proposed mechanisms for their formation and stereochemical aspects are discussed.

1. Introduction

Ascomycin (**1**) and FK 506 (**2**), the 21-allyl congener (Fig. 1), are 23-membered macrolactams isolated from the fermentation broth of a streptomyces strain.[1–3] The left hand part of the macrocycles ('binding domain') mediates the binding to their common immunophilin (FKBP, macrophilin, a peptidyl-prolyl *cis–trans* isomerase), whereas the right hand part ('effector domain'), together with residues of macrophilin, interacts with the target molecule, the calmodulin- and Ca^{2+}-dependent serine-threonine phosphatase calcineurin.[4–6] SDZ ASM 981 (**3**), the 33-epi-chloro-derivative of ascomycin, is a safe and effective new drug for the treatment of atopic dermatitis (pimecrolimus cream 1%, Elidel®) and proved to have therapeutic potential also in other skin diseases.[7–9] FK 506 is an immunosuppressant, used in the clinic to prevent transplant organ rejection (tacrolimus, Prograf®), and was recently introduced in the market also for the topical treatment of atopic dermatitis (Protopic®).[10–12] The molecular structure of both, ascomycin and FK 506 features the unusual and highly reactive region of three adjacent carbonyl groups (C8–C10, tricarbonyl unit), one of which is masked by intramolecular hemiketal formation with the 14-hydroxy group. In solution, *cis–trans* isomerisation at the amide bond and ketone–ketal isomerisation at the tricarbonyl region occurs.[13–16] In a previous communication, we reported on a simple conversion of the C9 carbonyl of FK 506 (**1**, the 21-allyl congener of ascomycin) into two diastereoisomeric epoxides via addition of diazomethane (**A** in Figure 2).[17] Obviously, such epoxides may serve as versatile key intermediates for manifold further manipulations within the binding domain. However, taking into consideration the reactivity of diazomethane, the structural flexibility at the binding domain and the inherent reactivity of three adjacent carbonyl groups,[18,19] in addition to oxirane formation at C9, several alternative methylene insertions can be anticipated. Especially, as depicted in Figure 2, insertion reactions between or adjacent to carbonyl groups



1 ascomycin (R^{21} = ethyl, R^{24} = R^{33} = OH)
2 FK 506 (R^{21} = allyl, R^{24} = R^{33} = OH)
3 SDZ ASM 981 (R^{21} = ethyl, R^{24} = OH, R^{33} = *epi*-Cl)
4 24,33-bis-OTBDMS-ascomycin (R^{21} = ethyl, R^{24} = R^{33} = OTBDMS)

Figure 1.

Keywords: Ascomycin; Diazomethane; Binding domain; Methylene insertion; X-ray analysis.
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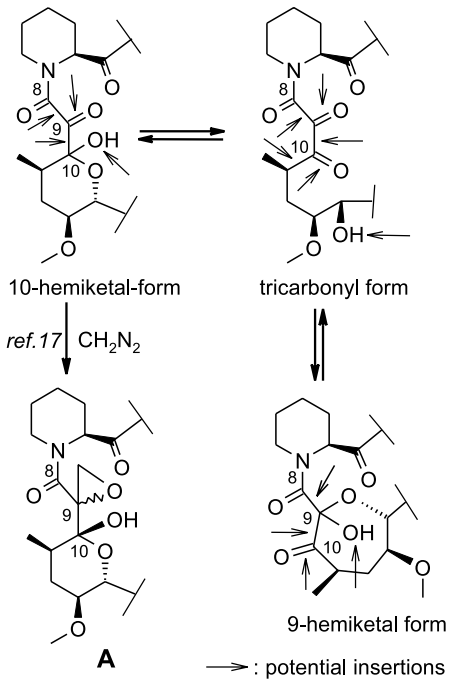
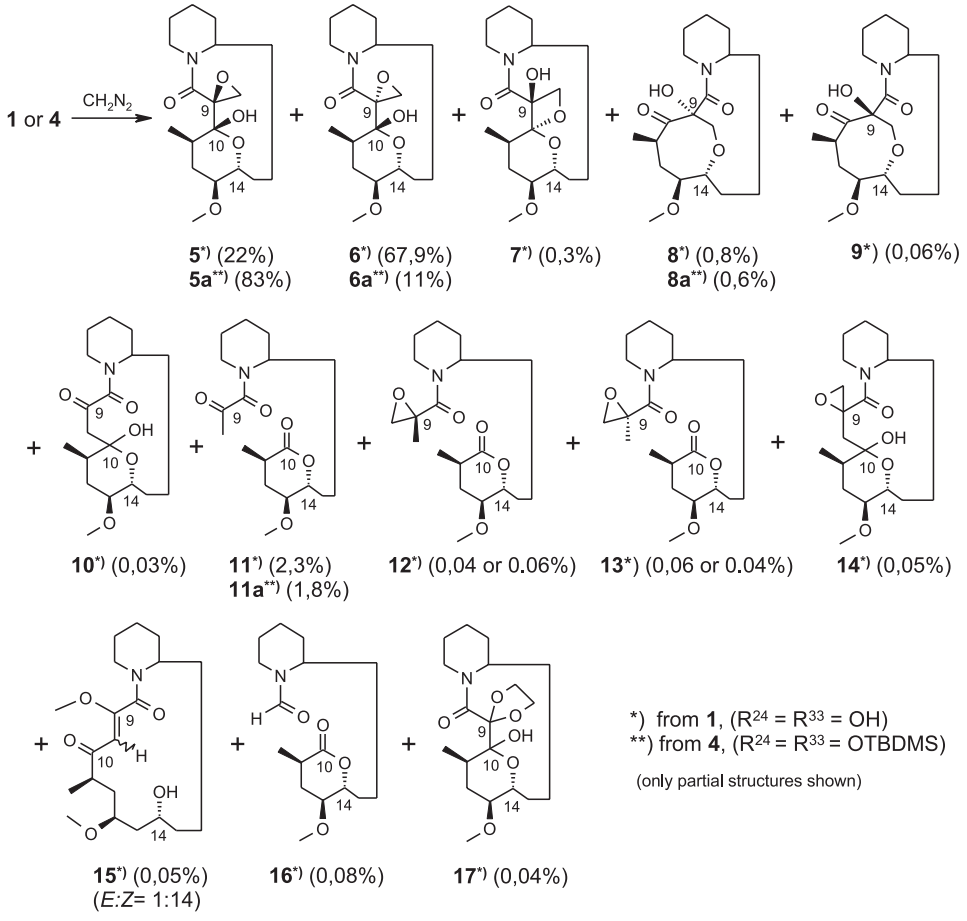


Figure 2.

(either between C8–C9, C9–C10 or C10–C11, which would yield novel ring-enlarged ascomycin derivatives), alternative oxirane formation at the 10-carbonyl group or various O-methylation reactions can be considered. In order to explore the synthetic potential of this specific reaction in more detail, we performed a detailed product analysis. Herein we report on the identification of novel methylene insertion products, mechanistic aspects of their formation and stereochemical aspects.

2. Reaction of ascomycin 1 and 24,33-bis-OTBDMS-ascomycin 4 with diazomethane

In order to allow a thorough product analysis, the reaction of ascomycin **1** with diazomethane was performed on a large scale. Thus, 30 g ascomycin **1**, dissolved in 600 ml methylene chloride, were reacted with excess (2.6 equiv) etheral diazomethane solution (prepared from Diazald® following a standard procedure).[20] After consumption of all starting material (10 h) excess diazomethane and solvents were removed at reduced pressure. As expected, the two epimeric oxirane derivatives **5** (22%) and **6** (67.9%) were formed as the major products in the ratio **5**:**6**=1:3. However, multiple chromatographic separations allowed the isolation of an additional set of 11 novel ascomycin derivatives (i.e., **6**–**17**). Remarkably, products being formed in amounts below $<0.1\%$ could be isolated and an overall recovery yield of $>93\%$ could be achieved. In order to explore the influence of the substitution pattern of ascomycin on the outcome of the reaction, we also reacted 24,33-bis-OTBDMS-ascomycin **4**[21] with excess diazomethane. Again, the diastereoisomeric 9-epoxides



Scheme 1.

(i.e., **5a** and **6a**) were formed as the major products together with minor amounts of the 24,33-bis-OTBDMS-protected oxecanone-derivative **8a** and the *seco*-compound **11a** (Scheme 1). Notably, in contrast to the reaction of unprotected ascomycin, now the 9(*S*)-oxirane **5a** (**5a**: **6a** = 7.5:1) was obtained preferentially.

2.1. Stereochemistry, structural evidence

All structures depicted in Scheme 1 are fully supported by their MS, ^{1}H NMR, ^{13}C NMR and two-dimensional NMR-spectra. With the exception of the enol ether **15**, which could only be isolated as an *E*/*Z*-mixture (*E*:*Z* = 1:14), all compounds described herein were isolated as single diastereoisomers. In deuterochloroform solution, the compounds **10**–**16** exist as mixtures of rotamers with respect to the geometry (*cis* vs *trans*) at the amide bond. All other compounds adopt to >90% a single amide conformation. The rapid interconversoin of the amide configuration of **10**–**16** could easily be visualised, by detecting the relevant negative cross peaks in their T-ROESY spectra.[22] The stereochemical relationship of the sylilated derivatives **5a**, **6a**, **8a** and **11a** to their corresponding unprotected congeners (i.e., **5**, **6**, **8** and **11**) could be substantiated by removal of the silyl groups, applying aqueous hydrogen fluoride in acetonitrile (see Section 5). The unprotected 9-epoxides **5**, **6** and the protected epoxide **6a** adopt exclusively the 10(*R*)-hemiketal form. The 10(*R*)-stereochemistry in these compounds could be deduced from ROE's between H14 and the 10-hydroxy group (1,3-diaxial pattern at the pyran ring). The 24,33-bis-OTBDMS-protected 9-epoxide **5a** exists in deuterochloroform solution partially in the 10-ketone-form with a liberated 14-hydroxy group (10-hemiketal/10-ketone = 3:1). As only two signal sets can be seen in the NMR-spectra of **5a**, it can be assumed, that both forms adopt a single amide configuration. A significant ROE-effect from 10-OH to H14 of the 10-hemiketal form of **5a** allows the absolute configuration at C10 to be defined as 10(*R*). The interconversion between these two forms is rather slow and thus enrichment of both forms by chromatography on silica gel is possible. However, evaporation or storage on the shelf of the enriched fractions leads back to the 3:1 mixture. Assuming, that methylene insertion causes no epimerization at any other stereocenter, the absolute configurations of all 9-epoxides could be obtained from only one single crystal structure analysis, the X-ray analysis of the 9(*R*)-epoxide **6** (Fig. 3).[23]

The stereochemistry at C9 and C10 of the unusual spiro-oxetane derivative **7** could be deduced from characteristic ROE signals, i.e. strong ROE interactions $H12_{ax} \leftrightarrow H14$, $H11 \leftrightarrow H13$ and $H12_{eq} \leftrightarrow H11$/11-methyl give evidence that the pyran ring adopts a chair conformation with equatorial orientations of the space filling substituents at C11, C13 and C14, respectively. An additional strong ROE-effect, observed between 9-OH and $H12_{ax}$ can only be explained assuming a 10(*S*),9(*R*) geometry at the oxetane unit. The oxecanone-derivative **9**, where methylene insertion has taken place between C9 and 14-OH, exhibits strong ROE's from H14 to 11-methyl and 13-methoxy, thus corroborating the assigned 9(*S*)-configuration. Consequently, the opposite 9(*R*) stereochemistry for its stereoisomeric congener **8** can be assumed. Due to the absence of diagnostically relevant ROE's, the absolute configuration at newly formed or potentially labile (C10-hemiketal portion) chiral positions of the single isomers **10**, **12**, **13**, **14** and **17** could not be determined. The NMR-spectra of the *E*/*Z*-mixture of the enol ether **15** consists of three signal sets in the ratio 1:3:11 (*E*/*Z*-enol, *cis*/*trans*-amide). The *E*-orientation at the enol ether unit of the minor isomer (one part), which exist as a single rotamer, is justified by a significant nuclear Overhauser interaction between the olefinic proton and the adjacent methoxy-group. Consequently, the major component, which adopts two amide conformations in the ratio 3:11, represents the *Z*-enol ether. Due to signal overlapping, only the major amide conformer of the *Z*-enol ether could be fully assigned. However, hydrolysis of the enol ether **15**, applying aqueous hydrogen fluoride in acetonitrile solution, yielded the ring enlarged α-keto amide **10** quantitatively, thus giving additional evidence for the assigned structures of both compounds.

2.2. Mechanistic aspects

Inspection of the structures (compare Scheme 1) reveals, that the compounds **5**–**11**, **5a**, **6a**, **8a** and **11a** are the result of single methylene insertion reactions. Their formation can be explained, assuming the betaines **A** (keto-form) and **B** (hemiketal form) as key intermediates (Fig. 4).

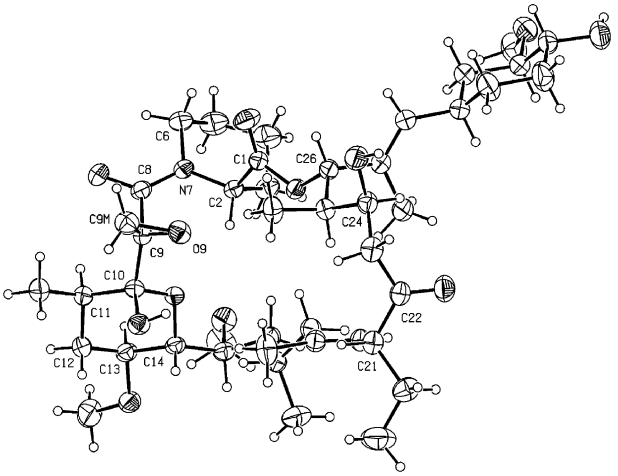


Figure 3.

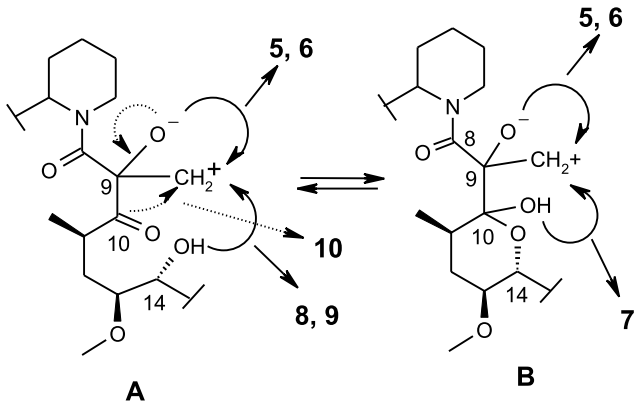


Figure 4.

Thus, dependent on whether ring closure occurs with 9-OH, 10-OH or 14-OH, either the formation of the oxiranes **5** and **6**, the appearance of the unusual oxetane derivative **7** or formation of the isomeric oxecanone derivatives **8** and **9** can be explained. Production of the ring enlarged derivative **10** can be rationalized by the migration of the C10-carbonyl to the positively charged carbon atom of the betaine **A**. Ring cleavage to the *seco*-compounds **11** and **11a** might occur starting again from the betaine **B** via a fragmentation reaction as outlined in Figure 5, to provide the enol forms **C** of the observed seco-compounds **11** and **11a**.

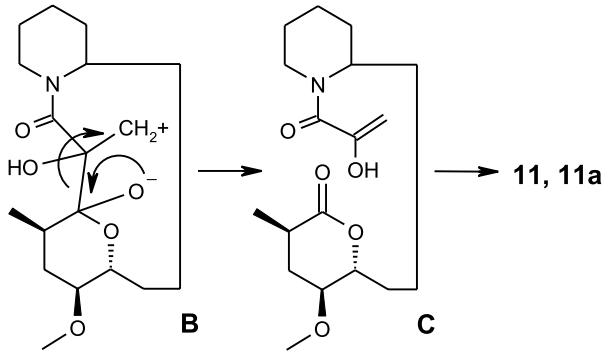


Figure 5.

Apparently, compounds **12**–**15** are the result of twofold methylene insertions. Obviously, the epimeric *seco*-epoxides **12** and **13** as well as the ring enlarged oxirane derivative **14** are generated via a second methylene-addition to the still activated alpha-keto amide moiety of their corresponding mono-insertion products **11** and **10**, respectively. Formation of the enol ether **15** can easily be explained as the result of a simple O-methylation of the enolized mono-insertion product **10**. The ring cleavage product **16** turned out to be identical with a known photo-degradation product of ascomycin[24] and thus was most probably already present in the starting material. The same might hold true for the novel cyclic 9-ketal **17**, since no reasonable pathway for its formation with the participation of diazomethane can be formulated.

3. Preferential formation of the oxocanone-derivatives 8 and 8a

Having in mind that Lewis acids accelerate the equilibrium between the six- and seven-membered hemiketal forms of ascomycin via the free tricarbonyl form,[16] we suspected that methylene insertion in presence of a Lewis acid might cause significant changes in the product distribution. To prove this concept, a solution of ascomycin **1** and 10 equiv titanium tetraisopropylate in dichloromethane, was reacted with excess diazomethane.

As a result, in a very fast reaction (<7 min), the 9(*R*)-oxecanone derivative **8** (47%) was formed as the major constituent together with an increased amount of the *seco*-derivative **11** (15.5%) and the 9(*S*)-epoxide **5** (19%, see Scheme 1). Applying the same reaction conditions to 24,33-bis-OTBDMS-ascomycin **4** led to an increase in formation of the oxecanone derivative **8a** as well, but to a lesser extent. Thus, chromatographic separation provided the 9(*S*)-epoxide **5a** (52%), the 24,33-bis-OTBDMS-oxocanone **8a** (12%) and the *seco*-derivative **11a** (15%), respectively. Interestingly, in both cases, the 9(*R*)-epoxides **6** and **6a** could not be detected in the crude reaction mixtures, thus suggesting, that the oxecanone derivatives **8** and **8a** are formed at their expense. As the compounds **6**, **6a**, **8** and **8a** exhibit the same (*R*)-configuration at C9, these findings correspond to the stereochemical determinations mentioned above. Control experiments revealed that the formation of **8** or **8a** proceeds not via the intermediate formation of **6** or **6a**: i.e. reaction of **6** and **6a** with excess titanium tetraisopropylate in dichloromethane resulted, even at reflux temperature, in no reaction.

4. Conclusions

In summary, a thorough product analysis of the reaction of ascomycin with diazomethane has been performed. As a result, a set of novel ascomycin derivatives, being modified in the binding domain, could be isolated. By changing the protection pattern of ascomycin, either the 9(*S*)-oxirane-derivatives or their 9(*R*)-congeners could be obtained with reasonable selectivity in useful preparative yields. In addition, a methodology allowing the preferential formation of the oxocanone derivative **8** has been elaborated. Gratifyingly, ring enlargement within the binding domain of ascomycin (i.e., **10**, **14**, and **15**) was observed for the first time, albeit in very low yield. The absolute configuration of the major compounds at newly formed chiral positions could be defined unambiguously by X-ray analysis and NMR-methods. Obviously, the simple availability of the diastereoisomeric 9-oxirane derivatives and the oxocanone derivative offer numerous possibilities for further manipulations within the binding domain of ascomycin. In addition, having now made available a representative set of insertion products as reference compounds, a focused chemistry program, aiming at their preferential formation can be performed more easily.

5. Experimental

5.1. General

All NMR spectra were performed on a BRUKER AVANCE 500 MHz spectrometer (resonance frequencies 500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C), equipped with a broadband inverse probe head with z-gradients, in 0.6 ml $CDCl_3$ (Merck Uvasol®, 99.8% D) at 301 K. Chemical shifts are given in values of ppm, referenced to residual $CHCl_3$ signals (7.26 for ^{1}H, 77.0 for ^{13}C). Proton and carbon-13 signal assignments were deduced from ^{1}H, ^{13}C, gradient-selected ^{1}H, ^{1}H-COSY (correlated spectroscopy), gradient-selected inverse ^{1}H, ^{13}C-HSQC (heteronuclear single-quantum correlation), and gradient-selected inverse ^{1}H, ^{13}C HMBC (heteronuclear multiple-bond correlation) experiments.[25] Stereochemical informations were extracted from two-dimensional T-ROESY (transverse rotating-frame Overhauser effect spectroscopy)[22] or selective one-dimensional ROESY[26] experiments. Routine mass spectroscopy (ESI, electrospray ionization) was performed on a Finnigan

Navigator AQA mass spectrometer with HP 1100 LC system, using methanol (Merck LiChrosolv®, gradient grade) as solvent. Solutions of approx. 50–100 μg/ml of the test compound in acetonitrile (Merck LiChrosolv®) were used for injection. Two scans in each experiment were applied, with 25 and 50 V cone voltages, respectively. The probe temperature was 523 K. High-resolution mass spectra (HRMS) were measured on a Finnigan MAT900 S mass spectrometer or on a 9.4T Bruker APEX III Fourier Transform mass spectrometer in positive-ESI mode. All reactions were monitored by HPTLC (Merck HPTLC-plates, silica gel 60, F_{254}). Visualisation of the reaction components was obtained by spraying with a solution of molybdatophosphoric acid (20% in EtOH/H_2O, 3:1). Flash column chromatography was performed on silica gel (Merck, silica gel 60, 0.04–0.063 mm, 230–400 mesh ASTM) at approx. 3–5 bar. Preparative HPLC were performed on a TOSOH TSK Prep 200 using columns (250×40 mm or 250×25 mm) packed with Nucleosil®100 (5μ particle size). The solvents used for chromatography (reagent grade) were used as purchased. Isolated minor by-products were subjected to molecular size exclusion chromatography (Sephadex® LH20, ethyl acetate) in order to remove low molecular weight impurities (originating from the solvent used for chromatography) which might have been enriched during chromatographic isolation.

5.2. Preparation and isolation of the compounds 5–17

A stirred solution of 30 g (37.8 mmol) ascomycin **1** dissolved in 600 ml dichloromethane was treated, at room temperature, with 50 ml (1.3 equiv) of an approx. 1 M etheral solution of diazomethane in one portion. After disappearance of the characteristic yellow colour of diazomethane (2 h) an additional portion of 50 ml (1.3 equiv) diazomethane solution was added. After consumption of all starting material (12 h, rt) excess diazomethane and the solvent were evaporated at reduced pressure. Multiple flash chromatography (Fig. 6) of the residual foam (30.3 g) provided, after filtration of each fraction <1 g through Sephadex® LH-20 (eluent ethylacetate) and lyophilization from benzene the title compounds as colourless powders.

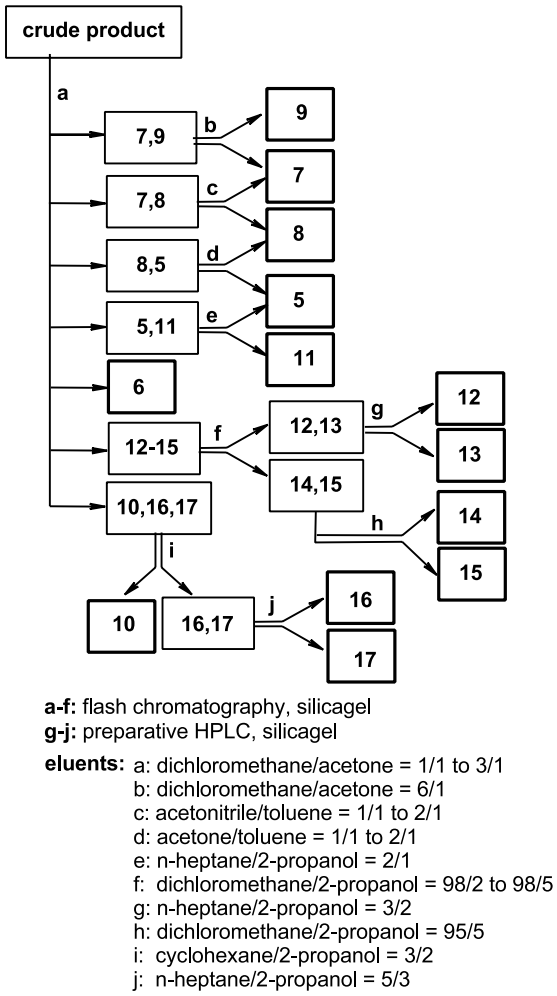


Figure 6.

5.2.1. Compound 5. (6.72 g, 22%): CHN ($C_{44}H_{71}NO_{12}$) calcd.: 65.57/8.88/1.74%, found: 65.62/9.05/1.71. HRMS (M+Na; calcd./found): 828.48736/828.48729. ^{13}C NMR ($CDCl_3$), major conformer, δ (ppm): 170.21 (C-1); 56.45 (C-2); 28.16 (C-3); 21.84 (C-4); 24.91 (C-5); 39.75 (C-6); 166.10 (C-8); 62.00 (C-9); 95.84 (C-10); 36.46 (C-11); 33.35 (C-12); 73.75 (C-13); 72.36 (C-14); 75.19 (C-15); 32.62 (C-16); 26.38 (C-17); 49.73 (C-18); 140.04 (C-19); 123.40 (C-20); 55.55 (C-21); 209.96 (C-22); 42.95 (C-23); 70.58 (C-24); 39.22 (C-25); 77.62 (C-26); 131.97 (C-27); 14.36 (C-28); 128.94 (C-29); 34.84 (C-30); 35.02 (C-31); 84.21 (C-32); 73.58 (C-33); 31.24 (C-34); 30.67 (C-35); 24.97 (C-36); 11.64 (C-37); 57.85 (13-OMe); 56.13 (15-OMe); 56.69 (32-OMe); 15.30 (11-methyl); 20.03 (17-methyl); 16.14 (19-methyl); 6.40 (25-methyl); 48.40 (oxirane-CH_2). ^1H NMR ($CDCl_3$, selected data), major conformer, δ (ppm): 5.62 (d, J=4.4 Hz, H-2); 4.52 (d, J=12.2 Hz, H-6eq); 2.71 (ψtd, J=12.2+2.8 Hz, H-6ax); 2.95 (d, J=4.8 Hz, H-9′a); 2.89 (d, J=4.8 Hz, H-9′b); 1.89 (m, H-11); 3.22 (m, H-13); 3.56 (d, J=10.0 Hz, H-14); 3.62 (dd, J=11.5+3.8 Hz, H-15); 5.00 (d, J=8.7 Hz, H-20); 3.09 (dd, J=15.8+7.4 Hz, H-21); 2.47 (dd, J=15.8+10.6 Hz, H-23a); 2.27 (dd, J=15.8+2.1 Hz, H-23b); 4.19 (dψt, J=10.5+2.0 Hz, H-24); 5.54 (s, H-26); 5.10 (d, J=6.0 Hz, H-29); 2.29 (m, H-30); 3.01 (m, H-32); 3.39 (m, H-33); 0.86 (t, J=7.5 Hz, CH_3-37); 3.42 (s, 10-O*H*); 1.05 (d, 3H, J=6.5 Hz, 11-Me); 3.37 (s, 3H, 13-OMe); 3.33 (s, 3H, 15-OMe); 1.54 (s, 3H, 19-Me); 1.63 (s, 3H, 27-Me); 3.41 (s, 3H, 32-OMe).

5.2.2. Compound 6. (20.73 g, 67.9%): CHN ($C_{44}H_{71}NO_{12}$) calcd.: 65.57/8.88/1.74%, found: 65.35/8.99/1.61. HRMS (M+Na; calcd./found): 828.48736/828.48742. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm): 170.45 (C-1); 56.50 (C-2); 26.77 (C-3); 21.38 (C-4); 24.52 (C-5); 39.84 (C-6); 165.82 (C-8); 61.55 (C-9); 96.66 (C-10); 33.94 (C-11); 32.72 (C-12); 74.15 (C-13); 73.58 (C-14); 75.70 (C-15); 33.68 (C-16); 26.93 (C-17); 48.37 (C-18); 138.93 (C-19); 122.66 (C-20); 55.60 (C-21); 213.68 (C-22); 42.40 (C-23); 70.31 (C-24); 39.48 (C-25); 76.78 (C-26); 132.36 (C-27); 14.19 (C-28); 129.32 (C-29); 34.91 (C-30); 34.89 (C-31); 84.21 (C-32); 73.51 (C-33); 31.24 (C-34); 30.66 (C-35); 24.68 (C-36); 11.78 (C-37); 56.28 (13-OMe); 56.56 (15-OMe); 56.68 (32-OMe); 16.50 (11-methyl); 20.77 (17-methyl); 16.15 (19-methyl); 10.01 (25-methyl); 50.59

(oxirane-CH_2). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 4.97 (d, J=5.0 Hz, H-2); 4.44 (d, J=13.1 Hz, H-6eq); 2.80 (ψtd, J=13.1+2.4 Hz, H-6ax); 2.94 (d, J=5.1 Hz, H-9′a); 2.79 (d, J=5.1 Hz, H-9′b); 2.40 (m, H-11); 3.34 (m, H-13); 3.50 (d, J=9.8 Hz, H-14); 3.47 (d, J=10.3 Hz, H-15); 5.09 (d, J=9.5 Hz, H-20); 3.08 (m, H-21); 2.96 (dd, J=15.1+2.8 Hz, H-23a); 2.32 (dd, J=15.1+9.9 Hz, H-23b); 3.96 (m, H-24); 5.29 (d, J=2.6 Hz, H-26); 5.05 (d, J=8.9 Hz, H-29); 2.27 (m, H-30); 3.00 (m, H-32); 3.39 (m, H-33); 0.86 (t, J=7.4 Hz, CH_3-37); 2.48 (d, J=1.7 Hz, 10-O*H*); 1.01 (d, 3H, J=6.7 Hz, 11-Me); 3.35 (s, 3H, 13-OMe); 3.28 (s, 3H, 15-OMe); 0.98 (d, 3H, J=6.3 Hz, 17-Me); 1.55 (s, 3H, 19-Me); 2.67 (s, broad, 24-O*H*); 0.91 (d, 3H, J=7.2 Hz, 25-Me); 1.63 (s, 3H, 27-Me); 3.40 (s, 3H, 32-OMe); 3.06 (s, 33-O*H*).

5.2.3. Compound 7. (92 mg, 0.3%): CHN ($C_{44}H_{71}NO_{12}$) calcd.: 65.57/8.88/1.74%, found: 65.35/8.99/1.61. HRMS (M+Na; calcd./found): 828.48736/828.48732. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm): 169.91 (C-1); 55.76 (C-2); 28.56 (C-3); 20.50 (C-4); 24.94 (C-5); 39.53 (C-6); 167.16 (C-8); 79.17 (C-9); 106.46 (C-10); 35.14 (C-11); 32.78 (C-12); 73.20 (C-13); 72.85 (C-14); 75.13 (C-15); 32.78 (C-16); 26.08 (C-17); 49.52 (C-18); 139.58 (C-19); 124.12 (C-20); 54.02 (C-21); 212.36 (C-22); 42.93 (C-23); 70.93 (C-24); 40.16 (C-25); 75.64 (C-26); 133.45 (C-27); 14.35 (C-28); 128.13 (C-29); 34.79 (C-30); 35.00 (C-31); 84.21 (C-32); 73.61 (C-33); 31.24 (C-34); 30.66 (C-35); 23.81 (C-36); 11.72 (C-37); 56.34 (13-OMe); 57.70 (15-OMe); 56.62 (32-OMe); 15.75 (11-methyl); 20.19 (17-methyl); 15.69 (19-methyl); 7.73 (25-methyl); 76.25 (oxetane-CH_2). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 4.47 (d, J=3.8 Hz, H-2); 4.49 (m, H-6eq); 3.25 (m, H-6ax); 5.08 (d, J=7.2 Hz, H-9′a); 4.12 (d, J=7.2 Hz, H-9′b); 1.71 (m, H-11); 3.37 (m, H-13); 3.61 (dd, J=9.5+0.7 Hz, H-14); 3.66 (m, H-15); 4.95 (d, J=8.8 Hz, H-20); 3.25 (m, H-21); 2.47 (dd, J=16.8+1.9 Hz, H-23a); 2.38 (dd, J=16.8+9.7 Hz, H-23b); 4.08 (m, H-24); 5.52 (s, H-26); 5.08 (d, J=9.0 Hz, H-29); 2.28 (m, H-30); 3.01 (m, H-32); 3.40 (m, H-33); 0.85 (t, J=7.4 Hz, CH_3-37); 4.62 (s, 9-O*H*); 1.09 (d, 3H, J=6.6 Hz, 11-Me); 3.37 (s, 3H, 13-OMe); 3.32 (s, 3H, 15-OMe); 1.70 (s, 3H, 19-Me); 3.39 (s, 24-O*H*); 1.66 (s, 3H, 27-Me); 3.41 (s, 3H, 32-OMe); 2.66 (s, 33-O*H*).

5.2.4. Compound 8. (245 mg, 0.8%): CHN ($C_{44}H_{71}NO_{12}$) calcd.: 65.57/8.88/1.74%, found: 65.65/8.65/1.59. HRMS (M+Na; calcd./found): 828.48736/828.48728. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm): 169.17 (C-1); 52.93 (C-2); 26.28 (C-3); 20.46 (C-4); 24.70 (C-5); 44.46 (C-6); 166.12 (C-8); 86.08 (C-9); 212.14 (C-10); 38.36 (C-11); 39.28 (C-12); 77.65 (C-13); 80.01 (C-14); 78.32 (C-15); 33.10 (C-16); 25.45 (C-17); 49.58 (C-18); 136.87 (C-19); 124.15 (C-20); 52.93 (C-21); 212.75 (C-22); 46.83 (C-23); 64.83 (C-24); 41.30 (C-25); 82.36 (C-26); 131.02 (C-27); 13.07 (C-28); 131.83 (C-29); 34.93 (C-30); 34.32 (C-31); 84.28 (C-32); 73.55 (C-33); 31.23 (C-34); 30.44 (C-35); 25.38 (C-36); 11.52 (C-37); 57.47 (13-OMe); 57.19 (15-OMe); 56.39 (32-OMe); 19.84 (11-methyl); 20.82 (17-methyl); 15.72 (19-methyl); 9.90 (25-methyl); 69.96 (oxetane-CH_2-O). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 5.31 (s, broad, H-2); 3.85 (m, H-6eq); 2.84 (ψt, J=11.7 Hz, H-6ax); 4.64 (d, J=12.6 Hz, H-9′a); 3.58 (d, J=12.6 Hz, H-9′b); 3.11 (m, H-11); 3.86 (m, H-13); 3.16 (dd, J=9.4+2.5 Hz, H-14); 3.45 (m, H-15); 5.14 (d, J=9.6 Hz, H-20); 3.22 (m, H-21); 2.76 (dd, J=18.0+9.3 Hz, H-23a); 2.58 (dd, J=18.0+3.2 Hz, H-23b); 4.26 (d, J=7.6 Hz, H-24); 4.86 (d, J=4.6 Hz, H-26); 5.17 (d, J=9.5 Hz, H-29); 2.28 (m, H-30); 2.98 (m, H-32); 3.40 (m, H-33); 0.87 (t, J=7.4 Hz, CH_3-37); 4.01 (s, 9-O*H*); 1.19 (d, 3H, J=6.8 Hz, 11-Me); 3.33 (s, 3H, 13-OMe); 3.32 (s, 3H, 15-OMe); 1.52 (s, 3H, 19-Me); not identified; 1.65 (s, 3H, 27-Me); 3.38 (s, 3H, 32-OMe).

5.2.5. Compound 9. (19 mg, 0.06%): HRMS (M+Na; calcd./found): 828.48736/828.48742. ^{13}C NMR ($CDCl_3$), mixture of conformers 1:1, δ (ppm): 172.14/170.44 (C1); 57.51/51.07 (C2); 25.47$^{\#}$/24.04 (C3); 21.09/19.75 (C4); 25.44$^{\#}$/24.86 (C5); 43.49/42.13 (C6); 171.17/170.44 (C8); 82.81/81.70 (C9); 214.94/209.82 (C10); 38.36/36.23 (C11); 35.85/35.63 (C12); 79.87/79.23 (C13); 74.69/74.05 (C14); 80.72/78.49 (C15); 37.66/37.04 (C16); 30.58/30.17 (C17); 49.66/48.39 (C18); 139.99/139.94 (C19); 124.55/123.26 (C20); 55.38/54.74 (C21); 210.78/209.52 (C22); 42.75/39.05 (C23); 81.86/79.23 (C24); 40.25/38.42 (C25); 82.76/79.60 (C26); 130.39/130.23 (C27); 14.40/14.05 (C28); 129.01/128.45 (C29); 34.94/34.92 (C30); 34.79/34.54 (C31); 84.27/84.18 (C32); 73.51/73.49 (C33); 31.20/31.20 (C34); 30.44/30.39 (C35); 24.30/23.94 (C36); 11.65/11.49 (C37); 57.14/56.46* (13-OMe); 59.67/57.35 (15-OMe); 56.44*/56.37 (32-OMe); 19.95/15.26 (11-Me); 22.41/21.43 (17-Me); 17.71/16.61 (19-Me); 7.04/4.88 (25-Me); 71.14/69.00 (–C9–*CH_2*O–); * and $^{\#}$: opposite assignments possible. ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 1:1, δ (ppm/ppm*): 5.42 (d, J=4.8 Hz, H-2)/4.25 (d, J=5.6 Hz, H-2); 4.85 (m, H-6eq)/4.57 (d, J=12.7 Hz, H-6eq); 3.15 (m, H-6ax)/2.73 (m, H-6ax); 4.16 (d, J=10.4 Hz, H-9′a)/3.80 (d, J=10.0 Hz, H-9′a); 3.53 (d, J=10.4 Hz, H-9′b)/3.26 (d, J=10.0 Hz, H-9′b); 3.46 (m, H-11)/3.25 (m, H-11); 3.25 (m, H-13)/3.06 (m, H-13); 3.46 (m, H-14)/3.16 (m, H-14); 3.43 (m, H-15)/3.43 (m, H-15); 5.08 (d, J=9.0 Hz, H-20)/5.02 (d, J=8.9 Hz, H-20); 3.16 (m, H-21)/3.00 (m, H-21); 2.97 (m, H-23a)/2.74 (m, H-23a); 2.51 (m, H-23b)/2.51 (m, H-23b); 3.86 (m, H-24)/3.75 (m, H-24); 5.58 (s, H-26)/4.87 (s, H-26); 5.10 (d, J=9.5 Hz, H-29)/4.98 (d, J=9.1 Hz, H-29); 2.27 (m, H-30)/2.27 (m, H-30); 3.00 (m, H-32)/3.00 (m, H-32); 3.40 (m, H-33)/3.40 (m, H-33); 0.86 (t, J=7.4 Hz, CH_3-37)/0.84 (t, J=7.4 Hz, CH_3-37); 5.88 (s, 9-O*H*)/4.73 (s, 9-O*H*); 1.41 (d, 3H, J=6.7 Hz, 11-Me)/1.11 (d, 3H, J=6.7 Hz, 11-Me); 3.34 (s, 3H, 13-OMe)/3.09 (s, 3H, 13-OMe); 3.43 (s, 3H, 15-OMe)/3.38 (s, 3H, 15-OMe); 1.08 (d, 3H, J=6.4 Hz, 17-Me)/1.03 (d, 3H, J=6.4 Hz, 17-Me); 1.70 (s, 3H, 19-Me)/1.64 (s, 3H, 19-Me); 0.80 (d, 3H, J=6.4 Hz, 25-Me)/0.76 (d, 3H, J=6.4 Hz, 25-Me); 1.59 (s, 3H, 27-Me)/1.58 (s, 3H, 27-Me); 3.40 (s, 3H, 32-OMe)/3.38 (s, 3H, 32-OMe); * opposite assignments possible.

5.2.6. Compound 10. (10 mg, 0.03%): HRMS (M+Na; calcd./found): 828.48736/828.48734. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm): 169.87 (C-1); 55.87 (C-2); 27.90 (C-3); 19.77 (C-4); 24.11 (C-5); 39.04 (C-6); 164.50 (C-8); 195.10 (C-9); 97.12 (C-10); 39.59 (C-11); 33.34 (C-12); 74.16 (C-13); 71.15 (C-14); 76.06 (C-15); 33.10 (C-16); 26.06 (C-17); 50.08 (C-18); 139.24 (C-19); 123.52 (C-20); 55.26 (C-21); 213.80 (C-22); 45.27 (C-23); 71.40 (C-24);

39.71 (C-25); 78.63 (C-26); 136.23 (C-27); 13.68 (C-28); 131.58 (C-29); 34.72 (C-30); 34.85 (C-31); 84.09 (C-32); 73.52 (C-33); 31.15 (C-34); 30.64 (C-35); 23.31 (C-36); 11.62 (C-37); 56.20 (13-OMe); 57.62 (15-OMe); 56.55 (32-OMe); 16.83 (11-methyl); 19.64 (17-methyl); 15.68 (19-methyl); 10.09 (25-methyl); 49.64 (–(CO)*C*H$_2$(CO)–). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 4.61 (d, J=5.0 Hz, H-2); 4.43 (d, J=11.6 Hz, H-6eq); 3.33 (m, H-6ax); 3.13 (d, J=13.4 Hz, H-9′a); 3.00 (d, J=13.4 Hz, H-9′b); 1.67 (m, H-11); 3.36 (m, H-13); 3.71 (dd, J=9.6+1.6 Hz, H-14); 3.57 (ddd, J=11.3+4.0+1.5 Hz, H-15); 4.77 (d, J=9.5 Hz, H-20); 3.45 (m, H-21); 2.91 (dd, J=16.4+5.0 Hz, H-23a); 2.65 (dd, J=16.4+5.1 Hz, H-23b); 3.83 (m, H-24); 5.19 (d, J=3.5 Hz, H-26); 5.07 (d, J=8.3 Hz, H-29); 2.27 (m, H-30); 3.01 (m, H-32); 3.38 (m, H-33); 0.86 (t, J=7.3 Hz, CH_3-37); 5.95 (s, 10-O*H*); 0.99 (d, 3H, J=6.7 Hz, 11-Me); 3.36 (s, 3H, 13-OMe); 3.34 (s, 3H, 15-OMe); 0.83 (d, 3H, J=6.4 Hz, 17-Me); 1.58 (s, 3H, 19-Me); 0.97 (d, 3H, J=6.9 Hz, 25-Me); 1.57 (s, 3H, 27-Me); 3.40 (s, 3H, 32-OMe).

5.2.7. Compound 11. (705 mg, 2.3%): CHN ($C_{44}H_{71}NO_{12}$) calcd.: 65.57/8.88/1.74%, found: 65.25/9.05/1.81. HRMS (M+Na; calcd./found): 828.48736/828.48740. ^{13}C NMR ($CDCl_3$), mixture of conformers 2:1, δ (ppm) for the major conformer: 169.33 (C-1); 51.83 (C-2); 26.38 (C-3); 20.94 (C-4); 25.12 (C-5); 43.78 (C-6); 166.87 (C-8); 198.51 (C-9); 173.63 (C-10); 33.35 (C-11); 32.28 (C-12); 73.66 (C-13); 82.43 (C-14); 77.30 (C-15); 35.02 (C-16); 24.28 (C-17); 48.48 (C-18); 138.41 (C-19); 124.24 (C-20); 54.52 (C-21); 212.15 (C-22); 45.80 (C-23); 67.25 (C-24); 38.91 (C-25); 82.60 (C-26); 130.88 (C-27); 12.38 (C-28); 133.73 (C-29); 34.94 (C-30); 34.45 (C-31); 84.18 (C-32); 73.74 (C-33); 31.25 (C-34); 30.28 (C-35); 24.29 (C-36); 11.63 (C-37); 56.77 (13-OMe); 57.56 (15-OMe); 56.37 (32-OMe); 17.03 (11-methyl); 19.59 (17-methyl); 16.41 (19-methyl); 8.89 (25-methyl); 29.66 (–(CO)*C*H$_3$). ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 2:1, δ (ppm) for the major conformer: 5.19 (d, J=5.4 Hz, H-2); 3.64 (m, H-6eq); 3.30 (ψtd, J=13.2+3.1 Hz, H-6ax); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (dd, J=7.8+1.5 Hz, H-14); 3.46 (m, H-15); 4.94 (d, J=9.9 Hz, H-20); 3.22 (m, H-21); 2.64 (m, H-23a); 2.64 (m, H-23b); 3.97 (m, H-24); 5.22 (d, J=8.0 Hz, H-26); 5.34 (d, J=9.0 Hz, H-29); 2.24 (m, H-30); 2.95 (m, H-32); 3.40 (m, H-33); 0.84 (t, J=7.6 Hz, CH_3-37); 2.41 (s, 3H, 9-Me); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.35 (s, 3H, 15-OMe); 0.88 (d, 3H, J=6.5 Hz, 17-Me); 1.68 (s, 3H, 19-Me); 0.90 (d, 3H, J=6.5 Hz, 25-Me); 1.62 (s, 3H, 27-Me); 3.38 (s, 3H, 32-OMe). δ (ppm) for the minor conformer: 4.67 (d, J=5.4 Hz, H-2); 4.39 (d, J=12.2 Hz, H-6eq); 2.86 (ψtd, J=13.3+3.2 Hz, H-6ax); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (dd, J=7.8+1.5 Hz, H-14); 3.46 (m, H-15); 4.94 (d, J=9.9 Hz, H-20); 3.22 (m, H-21); 2.64 (m, H-23a); 2.64 (m, H-23b); 3.97 (m, H-24); 5.22 (d, J=8.0 Hz, H-26); 5.34 (d, J=9.0 Hz, H-29); 2.24 (m, H-30); 2.95 (m, H-32); 3.40 (m, H-33); 0.84 (t, J=7.6 Hz, CH_3-37); 2.40 (s, 3H, 9-Me); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.35 (s, 3H, 15-OMe); 0.88 (d, 3H, J=6.5 Hz, 17-Me); 1.68 (s, 3H, 19-Me); 0.90 (d, 3H, J=6.5 Hz, 25-Me); 1.62 (s, 3H, 27-Me); 3.38 (s, 3H, 32-OMe).

5.2.8. Compound 12. (13 mg, 0.04%): HRMS (M+Na; calcd./found): 842.50302/842.50295. ^{13}C NMR ($CDCl_3$), mixture of conformers 5:2, δ (ppm) for the major conformer: 169.94 (C-1); 52.20 (C-2); 26.49 (C-3); 21.07 (C-4); 25.13 (C-5); 43.21 (C-6); 169.31 (C-8); 57.20 (C-9); 173.63 (C-10); 33.35 (C-11); 32.28 (C-12); 73.67 (C-13); 82.61 (C-14); 77.30 (C-15); 35.03 (C-16); 27.00 (C-17); 48.47 (C-18); 138.38 (C-19); 124.25 (C-20); 54.52 (C-21); 212.14 (C-22); 45.79 (C-23); 67.25 (C-24); 38.90 (C-25); 82.09 (C-26); 130.94 (C-27); 12.40 (C-28); 133.62 (C-29); 35.03 (C-30); 34.45 (C-31); 84.21 (C-32); 73.49 (C-33); 31.24 (C-34); 30.29 (C-35); 24.36 (C-36); 11.65 (C-37); 56.78 (13-OMe); 57.57 (15-OMe); 56.38 (32-OMe); 17.04 (11-methyl); 19.49 (17-methyl); 16.43 (19-methyl); 8.98 (25-methyl); 57.20 (oxirane-CH_2); 19.56 (9-methyl). ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 5:2, δ (ppm) for the major conformer: 5.17 (d, J=5.1 Hz, H-2); 4.08 (d, J=13.7 Hz, H-6eq); 3.26 (m, H-6ax); 2.91 (d, J=5.0 Hz, H-9′a); 2.79 (d, J=5.0 Hz, H-9′b); 2.47 (m, H-11); 3.69 (m, H-13); 4.07 (dd, J=7.8+1.4 Hz, H-14); 3.46 (m, H-15); 4.94 (d, J=10.0 Hz, H-20); 3.22 (m, H-21); 2.64 (m, H-23a); 2.64 (m, H-23b); 3.97 (m, H-24); 5.22 (d, J=8.2 Hz, H-26); 5.34 (d, J=9.0 Hz, H-29); 2.28 (m, H-30); 3.00 (m, H-32); 3.43 (m, H-33); 0.83 (t, J=7.5 Hz, CH_3-37); 1.58 (s, 3H, 9-Me); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.36 (s, 3H, 15-OMe); 0.87 (d, 3H, J=6.5 Hz, 17-Me); 1.68 (s, 3H, 19-Me); 0.90 (d, 3H, J=6.5 Hz, 25-Me); 1.62 (d, 3H, J=1.2 Hz, 27-Me); 3.39 (s, 3H, 32-OMe). δ (ppm) for the minor conformer: 4.96 (m, H-2); 4.45 (d, J=13.6 Hz, H-6eq); 2.90 (ψtd, J=13.6+3.3 Hz, H-6ax); 2.85 (d, J=5.1 Hz, H-9′a); 2.71 (d, J=5.1 Hz, H-9′b); 2.47 (m, H-11); 3.69 (m, H-13); 4.07 (m, H-14); 3.46 (m, H-15); 4.94 (d, J=10.0 Hz, H-20); 3.22 (m, H-21); 2.64 (m, H-23a); 2.64 (m, H-23b); 3.98 (m, H-24); 5.23 (d, J=8.2 Hz, H-26); 5.31 (d, J=9.4 Hz, H-29); 2.28 (m, H-30); 3.00 (m, H-32); 3.43 (m, H-33); 0.83 (t, J=7.5 Hz, CH_3-37); 1.55 (s, 3H, 9-Me); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.36 (s, 3H, 15-OMe); 0.86 (d, 3H, J=6.5 Hz, 17-Me); 1.68 (s, 3H, 19-Me); 0.91 (d, 3H, J=6.5 Hz, 25-Me); 1.63 (s, 3H, 27-Me); 3.38 (s, 3H, 32-OMe).

5.2.9. Compound 13. (19 mg, 0.06%): HRMS (M+Na; calcd./found): 842.50302/842.50296. ^{13}C NMR ($CDCl_3$), mixture of conformers 2:1, δ (ppm) for the major conformer: 169.80 (C-1); 51.94 (C-2); 26.43 (C-3); 21.02 (C-4); 25.47 (C-5); 43.59 (C-6); 169.06 (C-8); 56.78 (C-9); 173.61 (C-10); 33.35 (C-11); 32.28 (C-12); 73.66 (C-13); 82.63 (C-14); 77.30 (C-15); 35.03 (C-16); 27.00 (C-17); 48.45 (C-18); 138.38 (C-19); 124.23 (C-20); 54.52 (C-21); 212.14 (C-22); 45.79 (C-23); 67.22 (C-24); 38.91 (C-25); 82.11 (C-26); 130.89 (C-27); 12.32 (C-28); 133.62 (C-29); 35.01 (C-30); 34.44 (C-31); 84.20 (C-32); 73.47 (C-33); 31.25 (C-34); 30.28 (C-35); 24.37 (C-36); 11.64 (C-37); 56.36 (13-OMe); 57.58 (15-OMe); 55.94 (32-OMe); 17.04 (11-methyl); 19.54 (17-methyl); 16.43 (19-methyl); 8.93 (25-methyl); 52.96 (oxiran-CH_2); 19.76 (9-methyl). ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 2:1, δ (ppm) for the major conformer: 5.28 (d, J=5.6 Hz, H-2); 4.05 (m, H-6eq); 3.31 (m, H-6ax); 2.95 (d, J=5.1 Hz, H-9′a); 2.79 (d, J=5.1 Hz, H-9′b); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (dd, J=7.8+1.3 Hz, H-14); 3.45 (m, H-15); 4.94 (dq, J=9.8+1.0 Hz, H-20); 3.21 (m, H-21); 2.63 (m, H-23a); 2.63 (m, H-23b); 3.95 (m, H-24); 5.19 (d,

J=8.2 Hz, H-26); 5.32 (d, J=8.7 Hz, H-29); 2.28 (m, H-30); 2.99 (m, H-32); 3.38 (m, H-33); 0.83 (t, J=7.5 Hz, CH_3-37); 1.58 (s, 3H, 9-Me); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.36 (s, 3H, 15-OMe); 0.87 (d, 3H, J=6.5 Hz, 17-Me); 1.68 (s, 3H, 19-Me); 0.88 (d, 3H, J=6.5 Hz, 25-Me); 1.59 (d, 3H, J=1.3 Hz, 27-Me); 3.39 (s, 3H, 32-OMe). δ (ppm) for the minor conformer: 5.14 (d, J=4.8 Hz, H-2); 4.37 (d, J=13.6 Hz, H-6eq); 2.78 (m, H-6ax); 2.96 (d, J=5.0 Hz, H-9′a); 2.76 (d, J=5.0 Hz, H-9′b); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (dd, J=7.8+1.3 Hz, H-14); 3.45 (m, H-15); 4.93 (m, H-20); 3.21 (m, H-21); 2.63 (m, H-23a); 2.63 (m, H-23b); 3.96 (m, H-24); 5.27 (d, J=8.6 Hz, H-26); 5.40 (d, J=8.8 Hz, H-29); 2.28 (m, H-30); 2.99 (m, H-32); 3.38 (m, H-33); 0.83 (t, J=7.5 Hz, CH_3-37); 1.50 (s, 3H, 9-Me); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.35 (s, 3H, 15-OMe); 0.87 (d, 3H, J=6.5 Hz, 17-Me); 1.68 (s, 3H, 19-Me); 0.88 (d, 3H, J=6.5 Hz, 25-Me); 1.64 (d, 3H, J=0.9 Hz, 27-Me); 3.38 (s, 3H, 32-OMe).

5.2.10. Compound 14. (16 mg, 0.05%): HRMS (M+Na; calcd./found): 842.50302/842.50305. ^{13}C NMR ($CDCl_3$), mixture of conformers 3:2, δ (ppm) for the major conformer: 170.16 (C-1); 51.91 (C-2); 26.38 (C-3); 20.64 (C-4); 25.27 (C-5); 44.11 (C-6); 168.74 (C-8); 49.37 (C-9); 212.11 (C-10); 35.49 (C-11); 36.28 (C-12); 74.02 (C-13); 72.37 (C-14); 77.33 (C-15); 35.16 (C-16); 27.13 (C-17); 47.95 (C-18); 138.73 (C-19); 123.31 (C-20); 54.97 (C-21); 211.38 (C-22); 45.31 (C-23); 68.22 (C-24); 38.97 (C-25); 80.83 (C-26); 130.54 (C-27); 12.22 (C-28); 131.83 (C-29); 34.54 (C-30); 34.93 (C-31); 84.17 (C-32); 73.50 (C-33); 31.19 (C-34); 30.51 (C-35); 23.59 (C-36); 11.66 (C-37); 19.27 (11-methyl); 20.53 (17-methyl); 16.95 (19-methyl); 8.92 (25-methyl); 49.37 (oxiran-CH_2); 34.90 (–(C-9)–*CH_2*–(C-10)–]); 57.64/57.34/56.87/56.56/56.45/56.26 (13-,15- and 32-OMe for both conformers). ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 3:2, δ (ppm) for the major conformer: 5.25 (d, overlapped, H-2); 3.68 (d, J=14.2 Hz, H-6eq); 3.27 (m, H-6ax); 3.03 (d, J=4.7 Hz, H-9′a); 2.95 (d, J=4.7 Hz, H-9′b); 3.37 (d, J=15.5 Hz, H-10′a); 2.76 (d, J=15.5 Hz, H-10′b); 3.00 (m, H-11); 3.55 (m, H-13); 3.40 (m, H-14); 3.34 (m, H-15); 4.94 (d, J=9.5 Hz, H-20); 3.16 (m, H-21); 2.81 (dd, J=17.7+5.4 Hz, H-23a); 2.53 (dd, J=17.7+7.3 Hz, H-23b); 4.00 (m, H-24); 5.14 (d, J=5.9 Hz, H-26); 5.23 (d, J=10.2 Hz, H-29); 2.28 (m, H-30); 3.01 (m, H-32); 3.41 (m, H-33); 0.84 (t, J=7.6 Hz, CH_3-37); 1.04 (d, 3H, J=6.9 Hz, 11-Me); 3.36 (s, 3H, 13-OMe);* 3.32 (s, 3H, 15-OMe);* 1.72 (d, 3H, J=1.1 Hz, 19-Me); 1.64 (d, 3H, J=1.1 Hz, 27-Me); 3.40 (s, 3H, 32-OMe). δ (ppm) for the minor conformer: 5.02 (d, overlapped, H-2); 4.52 (d, J=13.1 Hz, H-6eq); 2.56 (m, H-6ax); 2.86 (m, H-11); 3.81 (dd, J=9.6+1.6 Hz, H-14); 5.07 (d, J=8.8 Hz, H-20); 3.17 (m, H-21); 4.04 (m, H-24); 5.16 (m, H-26); 5.00 (d, J=8.3 Hz, H-29); 2.30 (m, H-30); 3.01 (m, H-32); 3.41 (m, H-33); 0.84 (t, J=7.6 Hz, CH_3-37); 1.13 (d, 3H, J=6.9 Hz, 11-Me); 3.39 (s, 3H, 13-OMe);** 3.37 (s, 3H, 15-OMe);** 1.73 (d, 3H, J=1.1 Hz, 19-Me); 1.66 (d, 3H, J=1.1 Hz, 27-Me); 3.40 (s, 3H, 32-OMe). *, **: opposite assignment possible.

5.2.11. Compound 15. (16 mg, 0.05%): HRMS (M+Na; calcd./found): 842.50302/842.50293. ^{13}C NMR ($CDCl_3$), 9(E):9(Z)=14:1, 9(E): mixture of conformers 11:3, δ (ppm) for the 9(E)-major conformer: 169.24 (C-1); 51.92 (C-2); 26.07 (C-3); 20.92 (C-4); 25.49 (C-5); 45.42 (C-6); 163.43 (C-8); 159.07 (C-9); 201.94 (C-10); 43.91 (C-11); 35.50* (C-12); 74.02 (C-13); 79.65 (C-14); 77.30 (C-15); 35,39* (C-16); 27.30 (C-17); 47.85 (C-18); 138.38 (C-19); 124.34 (C-20); 54.94 (C-21); 212.47 (C-22); 45.41 (C-23); 67.03 (C-24); 38.33 (C-25); 82.56 (C-26); 130.62 (C-27); 12.33 (C-28); 133.95 (C-29); 34.98 (C-30); 34.45 (C-31); 84.17 (C-32); 73.47 (C-33); 31.22 (C-34); 30.38 (C-35); 24.16 (C-36); 11.65 (C-37); 56.46 (13-OMe); 57.19 (15-OMe); 58.26 (32-OMe); 17.87 (11-methyl); 20.79 (17-methyl); 16.94 (19-methyl); 9.63 (25-methyl); 102.80 (MeO–C=*C*–H); 58.71 (9-OMe). ^{1}H NMR ($CDCl_3$, selected data), δ (ppm) for the 9-(E)-major conformer: 5.32 (s, broad, H-2); 3.92 (d, J=14.2 Hz, H-6eq); 3.10 (m, H-6ax); 5.37 (s, H-9′); 2.91 (m, H-11); 3.11 (m, H-13); 3.00 (m, H-14); 3.28 (m, H-15); 4.90 (d, J=10.5 Hz, H-20); 3.21 (m, H-21); 2.76 (dd, J=18.0+2.9 Hz, H-23a); 2.51 (dd, J=18.0+9.4 Hz, H-23b); 3.98 (m, H-24); 5.22 (d, J=8.1 Hz, H-26); 5.32 (d, J=7.6 Hz, H-29); 2.30 (m, H-30); 2.99 (m, H-32); 3.40 (m, H-33); 0.82 (t, J=7.4 Hz, CH_3-37); 3.86 (s, 3H, 9-OMe); 1.15 (d, 3H, J=7.0 Hz, 11-Me); 3.31 (s, 3H, 13-OMe); 3.37 (s, 3H, 15-OMe); 0.92 (d, 3H, J=6.5 Hz, 17-Me); 1.70 (d, 3H, J=1.2 Hz, 19-Me); 0.95 (d, 3H, J=7.0 Hz, 25-Me); 1.58 (d, 3H, J=1.2 Hz, 27-Me); 3.39 (s, 3H, 32-OMe).

5.2.12. Compound 16. (23 mg, 0.08%): CHN ($C_{42}H_{69}NO_{11}$) calcd.: 66.03/9.10/1.83%, found: 65.78/9.26/1.71%. ^{13}C NMR ($CDCl_3$), mixture of conformers 5:2, δ (ppm) for the major conformer: 169.57 (C-1); 50.75 (C-2); 26.43 (C-3); 21.50 (C-4); 25.56 (C-5); 44.07 (C-6); 161.86 (C-8. –N–CHO); 173.63 (C-10); 33.35 (C-11); 32.28 (C-12); 73.67(C-13); 82.60 (C-14); 77.31 (C-15); 35.02 (C-16); 26.98 (C-17); 48.49 (C-18); 138.41 (C-19); 124.26 (C-20); 54.51 (C-21); 212.13 (C-22); 45.81 (C-23); 67.12 (C-24); 38.89 (C-25); 82.34 (C-26); 130.94 (C-27); 12.31 (C-28); 133.83 (C-29); 34.93 (C-30); 34.47 (C-31); 84.19 (C-32); 73.48 (C-33); 31.25 (C-34); 30.29 (C-35); 24.29 (C-36); 11.63 (C-37); 56.78 (13-OMe); 57.56 (15-OMe); 56.36 (32-OMe); 17.04 (11-methyl); 19.59 (17-methyl); 16.41 (19-methyl); 8.98 (25-methyl). ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 5:2, δ (ppm) for the major conformer: 5.13 (d, J=5.1 Hz, H-2); 3.52 (d, J=13.1 Hz, H-6eq); 3.36 (m, H-6ax); 8.08 (s, H-9); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (dd, J=7.8+1.5 Hz, H-14); 3.45 (m, H-15); 4.94 (dq, J=9.7+1.1 Hz, H-20); 3.22 (m, H-21); 2.64 (m, H-23a); 2.64 (m, H-23b); 3.96 (m, H-24); 5.20 (d, J=8.2 Hz, H-26); 5.35 (d, J=9.4 Hz, H-29); 2.27 (m, H-30); 2.99 (m, H-32); 3.38 (m, H-33); 0.84 (t, J=7.6 Hz, CH_3-37); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.35 (s, 3H, 15-OMe); 0.89 (d, 3H, J=6.5 Hz, 17-Me); 1.69 (d, 3H, J=1.4 Hz, 19-Me); 0.88 (d, 3H, J=6.5 Hz, 25-Me); 1.62 (d, 3H, J=1.2 Hz, 27-Me); 3.38 (s, 3H, 32-OMe). δ (ppm) for the minor conformer: 4.24 (d, J=5.6 Hz, H-2); 4.32 (d, J=13.9 Hz, H-6eq); 2.80 (ψtd, J=13.3+3.9 Hz, H-6ax); 8.03 (s, H-9); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (dd, J=7.8+1.5 Hz, H-14); 3.45 (m, H-15); 4.94 (dq, J=9.7+1.1 Hz, H-20); 3.22 (m, H-21); 2.64 (m, H-23a); 2.64 (m, H-23b); 3.96 (m, H-24); 5.23 (d, J=8.5 Hz, H-26); 5.35 (d, J=9.4 Hz, H-29); 2.27 (m, H-30); 2.99 (m, H-32); 3.38 (m, H-33); 0.84 (t, J=7.6 Hz, CH_3-37); 1.28 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.35 (s, 3H, 15-OMe); 0.89 (d, 3H, J=

6.5 Hz, 17-Me); 1.69 (d, 3H, J=1.4 Hz, 19-Me); 0.88 (d, 3H, J=6.5 Hz, 25-Me); 1.61 (d, 3H, J=1.4 Hz, 27-Me); 3.38 (s, 3H, 32-OMe).

5.2.13. Compound 17. (13 mg, 0.04%): HRMS (M+Na; calcd./found): 858.49794/858.49789. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm): 171.11 (C-1); 56.84 (C-2); 26.45 (C-3); 21.41 (C-4); 24.93 (C-5); 39.88 (C-6); 165.48 (C-8); 65.64 (C-9); 96.70 (C-10); 33.80 (C-11); 32.72 (C-12); 74.12 (C-13); 73.66 (C-14); 75.73 (C-15); 33.38 (C-16); 27.10 (C-17); 48.29 (C-18); 139.02 (C-19); 122.58 (C-20); 55.63 (C-21); 213.94 (C-22); 41.65 (C-23); 70.38 (C-24); 38.97 (C-25); 76.90 (C-26); 132.26 (C-27); 14.32 (C-28); 129.08 (C-29); 34.91 (C-30); 34.91 (C-31); 84.20 (C-32); 73.60 (C-33); 31.22 (C-34); 30.70 (C-35); 24.43 (C-36); 11.75 (C-37); 56.84 (13-OMe); 56.30 (15-OMe); 56.63 (32-OMe); 16.55 (11-methyl); 20.98 (17-methyl); 16.11 (19-methyl); 10.13 (25-methyl); 60.29/59.58 (–OCH_2CH_2-O–). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 5.05 (d, J=9.0 Hz, H-2); 4.47 (d, J=13.4 Hz, H-6eq); 2.79 (ψtd, J=13.4+3.0 Hz, H-6ax); 3.76 (dd, J=13.4+5.1 Hz, H-9′a); 3.61 (dd, J=13.4+5.8 Hz, H-9′b); 3.29 (ψt, 2H, J=5.5 Hz, CH_2-9″); 2.38 (m, H-11); 3.33 (m, H-13); 3.45 (m, H-14); 3.46 (m, H-15); 5.12 (d, J=9.5 Hz, H-20); 3.08 (m, H-21); 2.96 (dd, J=15.5+2.3 Hz, H-23a); 2.32 (dd, J=15.5+10.0 Hz, H-23b); 3.99 (m, H-24); 5.34 (d, J=2.3 Hz, H-26); 4.99 (d, J=5.0 Hz, H-29); 2.26 (m, H-30); 3.01 (m, H-32); 3.40 (m, H-33); 0.87 (t, J=7.3 Hz, CH_3-37); 2.45 (d, J=1.8 Hz, 10-O*H*); 1.04 (d, 3H, J=6.8 Hz, 11-Me); 3.29 (s, 3H, 13-OMe); 3.36 (s, 3H, 15-OMe); 1.00 (d, 3H, J=6.5 Hz, 17-Me); 1.55 (s, 3H, 19-Me); 0.90 (d, 3H, J=7.3 Hz, 25-Me); 1.65 (d, 3H, J=1.0 Hz, 27-Me); 3.41 (s, 3H, 32-OMe).

5.3. Preparation of the compounds 5a, 6a, 8a and 11a

At room temperature, a stirred solution of 3.0 g (2.94 mmol) 24,33-bis-OTBDMS-ascomycin **4** dissolved in 50 ml dichloromethane was treated with 10 ml (3.4 equiv) of an approx. 1 M etheral solution of diazomethane in one portion. After disappearance of the characteristic yellow colour of diazomethane (3 h) excess diazomethane and the solvent were evaporated at reduced pressure. Flash chromatography on silicagel (eluent: dichloromethane/acetone=50/1 to 30/1) of the residual foam yielded, after filtration of each fraction through Sephadex® LH-20 (eluent ethylacetate) and lyophilization from benzene the title compounds as colourless powders.

5.3.1. Compound 5a. (2.52 g, 83%): CHN ($C_{56}H_{99}NO_{12}Si_2$) calcd.: 65.01/9.65/1.35%, found: 64.74/9.85/1.23%. HRMS (M+Na; calcd./found): 1056.66032/1056.66035. ^{13}C NMR ($CDCl_3$), mixture of 10-ketone- and 10-hemiketal-form (1:3), δ (ppm) for the 10-ketone-form (single conformer): 169.36 (C-1); 52.53 (C-2); 25.87 (C-3); 21.13 (C-4); 27.31 (C-5); 43.76 (C-6); 168.23 (C-8); 61.50 (C-9); 207.24 (C-10); 37.22 (C-11); 39.50 (C-12); 79.87 (C-13); 70.57 (C-14); 76.97 (C-15); 32.52 (C-16); 25.58 (C-17); 47.20 (C-18); 138.83 (C-19); 122.20 (C-20); 55.11 (C-21); 209.37 (C-22); 67.99 (C-24); 38.9 (C-25); 82.0 (C-26); 132.35 (C-27); 13.4 (C-28); 133.78 (C-29); 35.03 (C-30); 36.19 (C-31); 84.13 (C-32); 74.99 (C-33); 33.94 (C-34); 30.82 (C-35); 23.89 (C-36); 11.72 (C-37); 19.37 (11-methyl); 25.58 (17-methyl); 19.08 (19-methyl); 10.04 (25-methyl); 57.65/56.73 (13-OMe, 15-OMe); 57.75 (32-OMe); 46–47 (broad, C-23 and oxirane-CH_2). δ (ppm) for the 10-hemiketal form (single conformer): 170.73 (C-1); 55.86 (C-2); 25.85 (C-3); 21.18 (C-4); 28.19 (C-5); 39.72 (C-6); 165.69 (C-8); 61.20 (C-9); 96.28 (C-10); 36.57 (C-11); 33.03 (C-12); 73.51 (C-13); 73.16 (C-14); 75.16 (C-15); 32.06 (C-16); 26.17 (C-17); 49.21 (C-18); 137.69 (C-19); 123.83 (C-20); 54.88 (C-21); 210.68 (C-22); 46.22 (C-23); 71.20 (C-24); 40.54 (C-25); 78.90 (C-26); 132.35 (C-27); 12.68 (C-28); 133.78 (C-29); 34.99 (C-30); 36.30 (C-31); 84.08 (C-32); 75.06 (C-33); 33.84 (C-34); 30.67 (C-35); 24.87 (C-36); 11.61 (C-37); 15.71 (11-methyl); 20.09 (17-methyl); 16.05 (19-methyl); 10.42 (25-methyl); 57.04 (13-OMe); 56.18 (15-OMe); 57.82 (32-OMe); 46.85 (oxirane-CH_2);TBDMS for both isomers: 18.31/18.13/17.90/17.97 (4× -Si*C*$(CH_3)_3$); 25.85/25.87 (4× –SiC(*C*$H_3)_3$); −4.19/−4.25/−4.27/−4.52 (4× –Si(*C*$H_3)_2$). ^{1}H NMR ($CDCl_3$, selected data), δ (ppm) for the 10-hemiketal form (single conformer): 5.49 (d, J=5.0 Hz, H-2); 4.49 (d, J=13.3 Hz, H-6eq); 2.79 (ψtd, J=13.3+2.6 Hz, H-6ax); 2.98 (d, J=5.8 Hz, H-9′a); 2.96 (d, J=5.8 Hz, H-9′b); 1.89 (m, H-11); 3.29 (m, H-13); 3.66 (dd, J=9.6+1.0 Hz, H-14); 3.58 (dd, J=11.1+4.1 Hz, H-15); 4.94 (d, J=9.8 Hz, H-20); 3.25 (m, H-21); 2.66 (dd, J=15.1+5.6 Hz, H-23a); 2.26 (dd, J=15.1+7.4 Hz, H-23b); 4.11 (m, H-24); 5.33 (d, J=4.8 Hz, H-26); 5.24 (d, J=11.9 Hz, H-29); 2.21 (m, H-30); 2.94 (m, H-32); 3.38 (m, H-33); 0.82 (t, J=7.5 Hz, CH_3-37); 3.05 (s, 10-O*H*); 1.08 (d, 3H, J=6.7 Hz, 11-Me); 3.36 (s, 3H, 13-OMe); 3.27 (s, 3H, 15-OMe); 1.64 (s, 3H, 19-Me); 1.59 (d, 3H, J=1.2 Hz, 27-Me); 3.37 (s, 3H, 32-OMe). δ (ppm) for the 10-keto form (single conformer): 5.27 (m, H-2); 3.85 (d, J=13.5 Hz, H-6eq); 3.06 (ψtd, J=13.5+2.7 Hz, H-6ax); 3.26 (d, $J\approx$5 Hz, H-9′a); 3.15 (d, $J\approx$5 Hz, H-9′b); 2.93 (m, H-11); 3.17 (m, H-13); 3.72 (m, H-14); 3.43 (ddd, J=9.3+4.5+1.4 Hz, H-15); 4.98 (d, J=9.9 Hz, H-20); 3.18 (m, H-21); 2.81 (m, H-23a); 2.32 (dd, J=17.2+5.1 Hz, H-23b); 4.18 (m, H-24); 5.09 (d, J=8.0 Hz, H-26); 5.27 (d, $J\approx$8 Hz, H-29); 2.22 (m, H-30); 2.94 (m, H-32); 3.38 (m, H-33); 0.82 (t, J=7.5 Hz, CH_3-37); 1.08 (d, 3H, J=6.7 Hz, 11-Me); 3.16 (s, 3H, 13-OMe); 3.37 (s, 3H, 15-OMe); 1.71 (d, 3H, J=1.1 Hz, 19-Me); 1.53 (d, 3H, J=1.1 Hz, 27-Me); 3.37 (s, 3H, 32-OMe).

5.3.2. Compound 6a. (335 mg, 11%): CHN ($C_{56}H_{99}NO_{12}Si_2$) calcd.: 65.01/9.65/1.35%, found: 64.81/9.90/1.19%. HRMS (M+Na; calcd./found): 1056.66032/1056.66036. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm): 170.35 (C-1); 55.90 (C-2); 27.52 (C-3); 20.94 (C-4); 24.47 (C-5); 39.62 (C-6); 156.84 (C-8); 61.10 (C-9); 96.82 (C-10); 34.01 (C-11); 32.73 (C-12); 73.81 (C-13); 72.80 (C-14); 75.60 (C-15); 35.05 (C-16); 25.86 (C-17); 49.02 (C-18); 138.45 (C-19); 123.42 (C-20); 56.19 (C-21); 210.38 (C-22); 48.40 (C-23); 69.88 (C-24); 40.53 (C-25); 80.20 (C-26); 131.77 (C-27); 12.71 (C-28); 133.60 (C-29); 35.05 (C-30); 36.41 (C-31); 84.16 (C-32); 75.17 (C-33); 33.89 (C-34); 30.76 (C-35); 24.25 (C-36); 11.47 (C-37); 56.26 (13-OMe); 56.87 (15-OMe); 57.91 (32-OMe); 16.57 (11-methyl); 19.54 (17-methyl); 15.72 (19-methyl); 10.21 (25-methyl); 50.86 (oxirane-CH_2); 25.85/25.76/18.14/17.99/−4.32/−4.41/−4.52/−4.75 (2× TBDMS). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 5.00 (d, J=4.8 Hz, H-2);

4.43 (d, J=13.9 Hz, H-6eq); 2.91 (m, H-6ax); 2.94 (d, J=5.2 Hz, H-9′a); 2.81 (d, J=5.2 Hz, H-9′b); 2.42 (m, H-11); 3.44 (m, H-13); 3.70 (d, J=9.1 Hz, H-14); 3.54 (ddd, J=11.7+3.4+2.0 Hz, H-15); 4.86 (d, J=9.8 Hz, H-20); 3.24 (m, H-21); 2.84 (dd, J=14.7+6.8 Hz, H-23a); 2.35 (dd, J=14.7+8.7 Hz, H-23b); 4.11 (d, J=7.6 Hz, H-24); 5.19 (m, H-26); 5.18 (m, H-29); 2.24 (m, H-30); 2.93 (m, H-32); 3.38 (m, H-33); 0.82 (t, J=7.4 Hz, CH_3-37); 0.07+0.06+0.03+0.01 (4s, 12H, 24/33-SiC$(CH_3)_3$*Me*$_2$); 0.88+0.85 (2s, 18H, 24/33-SiC(*C*H_3)$_3$Me$_2$); 2.53 (d, J=1.5 Hz, 10-O*H*); 1.03 (d, 3H, J=6.7 Hz, 11-Me); 3.36 (s, 3H, 13-OMe); 3.29 (s, 3H, 15-OMe); 1.63 (s, 3H, 19-Me); 1.50 (s, 3H, 27-Me); 3.39 (s, 3H, 32-OMe).

5.3.3. Compound 8a. (19 mg. 0.6%): HRMS (M+Na; calcd./found): 1056.66032/1056.66025. ^{13}C NMR ($CDCl_3$), single conformer, δ (ppm):169.09 (C-1); 53.78 (C-2); 24.97 (C-3); 20.78 (C-4); 25.70 (C-5); 45.29 (C-6); 167.40 (C-8); 86.53 (C-9); 212.12 (C-10); 38.43 (C-11); 39.15 (C-12); 77.81 (C-13); 79.88 (C-14); 78.27 (C-15); 33.63 (C-16); 26.05 (C-17); 49.67 (C-18); 136.97 (C-19); 123.46 (C-20); 53.73 (C-21); 209.82 (C-22); 47.00 (C-23); 67.64 (C-24); 38.30 (C-25); 83.55 (C-26); 131.24 (C-27); 11.42 (C-28); 135.75 (C-29); 35.07 (C-30); 36.36 (C-31); 84.23 (C-32); 75.23 (C-33); 34.00 (C-34); 30.81 (C-35); 25.66 (C-36); 11.37 (C-37); 57.24 (13-OMe); 57.34 (15-OMe); 57.85 (32-OMe); 19.56 (11-methyl); 20.55 (17-methyl); 15.30 (19-methyl); 9.48 (25-methyl); 70.37 (oxocanone-CH_2); 25.87/25.83/18.17/ 18.10/−3.73/−4.17/−4.50/−4.77 (2x TBDMS). ^{1}H NMR ($CDCl_3$, selected data), single conformer, δ (ppm): 5.22 (d, J=4.8 Hz, H-2); 3.85 (d, J=13.3 Hz, H-6eq); 3.01 (ψtd, J=13.3+2.4 Hz, H-6ax); 4.73 (d, J=12.4 Hz, H-9′a); 3.57 (d, J=12.4 Hz, H-9′b); 3.20 (m, H-11); 3.93 (ψt, J=9.2 Hz, H-13); 3.21 (m, H-14); 3.48 (m, H-15); 5.13 (d, J=8.9 Hz, H-20); 3.17 (m, H-21); 2.87 (dd, J=16.9+9.1 Hz, H-23a); 2.47 (dd, J=16.9+4.7 Hz, H-23b); 4.16 (m, H-24); 4.96 (d, J=9.2 Hz, H-26); 5.30 (d, J=8.7 Hz, H-29); 2.26 (m, H-30); 2.93 (m, H-32); 3.39 (m, H-33); 0.88 (t, J=7.4 Hz, CH_3-37); 0.07+0.06+0.04+0.02 (4s, 12H, 24/33-SiC$(CH_3)_3$*Me*$_2$); 0.88+0.87 (2s, 18H, 24/33-SiC(*C*H_3)$_3$Me$_2$); 4.05 (s, 9-O*H*); 1.18 (d, 3H, J=6.7 Hz, 11-Me); 3.34 (s, 3H, 13-OMe); 3.30 (s, 3H, 15-OMe); 0.84 (d, 3H, J=6.4 Hz, 17-Me); 1.52 (s, 3H, 19-Me); 0.92 (d, 3H, J=6.4 Hz, 25-Me); 1.56 (s, 3H, 27-Me); 3.39 (s, 3H, 32-OMe).

5.3.4. Compound 11a. (55 mg. 1.8%): CHN ($C_{56}H_{99}NO_{12}Si_2$) calcd.: 65.01/9.65/1.35%, found: 65.24/10.05/1.34%. HRMS (M+Na; calcd./found): 1056.66032/1056.66028. ^{13}C NMR ($CDCl_3$), mixture of conformers 2:1, δ (ppm) for the major conformer: 169.12 (C-1); 51.81 (C-2); 26.59 (C-3); 20.91 (C-4); 25.14 (C-5); 43.65 (C-6); 166.82 (C-8); 198.42 (C-9); 173.23 (C-10); 33.37 (C-11); 32.39 (C-12); 73.68 (C-13); 82.93 (C-14); 77.36 (C-15); 36.19 (C-16); 27.70 (C-17); 47.97 (C-18); 138.1 (C-19); 124.24 (C-20); 54.61 (C-21); 2o9.67 (C-22); 46.67 (C-23); 67.60 (C-24); 39.25 (C-25); 81.75 (C-26); 131.23 (C-27); 12.06 (C-28); 135.23 (C-29); 35.12 (C-30); 36.29 (C-31); 84.16 (C-32); 75.10 (C-33); 33.90 (C-34); 30.71 (C-35); 24.41 (C-36); 11.64 (C-37); 56.66 (13-OMe); 57.73/57.80 (15-OMe. 32-OMe); 17.05 (11-methyl); 18.94 (17-methyl); 16.60 (19-methyl); 9.17 (25-methyl); 26.59 (9-CO*C*H$_3$); 18.13/18.06 (–Si*C*(CH$_3$)$_3$); 25.90/25.85 (–Si*C*(*C*H$_3$)$_3$); −4.53/−4.76 (–Si(*C*H$_3$)$_2$). ^{1}H NMR ($CDCl_3$, selected data), mixture of conformers 2:1, δ (ppm) for the major conformer: 5.16 (d, J=4.8 Hz, H-2); 3.64 (d, J=13.2 Hz, H-6eq); 3.30 (ψtd, J=13.2+3.2 Hz, H-6ax); 2.47 (m, H-11); 3.69 (m, H-13); 4.07 (d, J=7.9 Hz, H-14); 3.49 (m, H-15); 4.94 (d, J=9.8 Hz, H-20); 3.19 (m, H-21); 2.72 (dd, J=17.8+7.5 Hz, H-23a); 2.49 (m, H-23b); 4.12 (m, H-24); 5.20 (d, J=8.3 Hz, H-26); 5.31 (d, J=9.0 Hz, H-29); 2.25 (m, H-30); 2.93 (m, H-32); 3.38 (m, H-33); 0.82 (t, J=7.6 Hz, CH_3-37); 0.07+0.05+0.04+ −0.02 (4s, 12H, 24/33-SiC$(CH_3)_3$*Me*$_2$); 0.88+0.86 (2s, 18H, 24/33-SiC(*C*H_3)$_3$-Me$_2$); 2.41 (s, 3H, 9-Me); 1.29 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.39 (s, 3H, 15-OMe); 1.68 (d, 3H, J=1.1 Hz, 19-Me); 1.63 (d, 3H, J=1.1 Hz, 27-Me); 3.38 (s, 3H, 32-OMe). δ (ppm) for the minor conformer: 4.66 (d, J=4.4 Hz, H-2); 4.38 (d, J=13.5 Hz, H-6eq); 2.87 (ψtd, J=13.5+3.1 Hz, H-6ax); 2.47 (m, H-11); 3.69 (m, H-13); 4.06 (d, J=7.9 Hz, H-14); 3.49 (m, H-15); 4.93 (d, J=9.8 Hz, H-20); 3.19 (m, H-21); 2.73 (dd, J=17.8+7.9 Hz, H-23a); 2.49 (m, H-23b); 4.11 (m, H-24); 5.16 (d, J=4.8 Hz, H-26); 5.31 (d, J=9.0 Hz, H-29); 2.25 (m, H-30); 2.93 (m, H-32); 3.38 (m, H-33); 0.82 (t, J=7.6 Hz, CH_3-37); 0.07+0.05+0.04+ −0.02 (4s, 12H, 24/33-SiC$(CH_3)_3$*Me*$_2$); 0.88+0.86 (2s, 18H, 24/33-SiC(*C*H_3)$_3$Me$_2$); 2.39 (s, 3H, 9-Me); 1.29 (d, 3H, J=7.0 Hz, 11-Me); 3.41 (s, 3H, 13-OMe); 3.39 (s, 3H, 15-OMe); 1.68 (d, 3H, J=1.1 Hz, 19-Me); 1.62 (d, 3H, J=1.1 Hz, 27-Me); 3.38 (s, 3H, 32-OMe).

5.4. Preparation of 5, 6, 8 and 11 from 5a, 6a, 8a and 11a

Representative procedure. To a solution of 0.5 g (0.48 mmol) **5a** in 50 ml acetonitrile were added 1.5 ml aq. hydrogen fluoride (40 w/w%) in one portion. After completion of the reaction (TLC, 6 h), the mixture was partitioned between ethylacetate and saturated aq. sodium hydrogen carbonate. The separated organic layer was washed twice with brine, dried over anhydrous sodium sulfate and evaporated at reduced pressure to dryness. A short flash column chromatography (silicagel, eluent: ethylacetate), followed by a filtration through Sephadex® LH-20 (eluent ethylacetate) and lyophilization from benzene yielded the title compound **5** (382 mg, 98%) as a colourless powder.

Analogously **6** (96%), **8** (95%) and **11** (95%) were prepared from **6a**, **8a** and **11a**, respectively (analytical data in accordance with the data given above).

5.5. Preparation of 10 from 15

10 mg **15** (0.012 mmol), dissolved in a mixture of 2 ml acetonitrile and 0.3 ml water were treated with 0.1 ml aq. hydrogen fluoride (40 w/w%) and stirred at rt for 10 min. After partitioning the mixture between ethylacetate and a saturated aq. sodium hydrogen carbonate solution, the organic layer was washed twice with brine, dried over sodium sulfate and evaporated at reduced pressure. The residual foam was filtered through Sephadex® LH-20 (eluent ethylacetate) and lyophilized from benzene to give **10** (5 mg, 50.8%) as a colourless powder (analytical data in accordance with the data given above).

5.6. Crystallisation of the 9(*S*)-epoxide 5 for X-ray crystallography

0.5 g amorphous **6** were dissolved in 6 ml acetone and distilled water (10 ml) was added until a slight turbidity remained. The cloudy solution was filtered through a glass micro fibre filter (GF/A Whatman®) and a still remaining slight turbidity of the filtrate was removed by de addition of a few drops acetone. The clear solution was stored at room temperature for two weeks for crystallisation. The crystals obtained thereof were used for X-ray analysis.

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Fragmentation of tertiary cyclopropanol compounds catalyzed by vanadyl acetylacetonate

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Abstract—Tertiary cyclopropanol compounds react with a catalytic amount of vanadyl acetylacetonate in the presence of oxygen affording β-hydroxyketones and β-diketones. For 3-substituted-bicyclo[4.1.0]alkanols, peroxides are obtained, as are the β-hydroxyketones. Conversely, 2-ethoxycarbonylcyclopropyl silyl ethers produce ethyl γ-oxocarboxylate derivatives given the same reaction conditions.

1. Introduction

Tertiary cyclopropanol compounds (**1**) are important synthetic intermediates owing to their great reactivity. Many different reactions have been developed using derivatives of **1** as reagents,[1] including those whose purpose is to specifically cleave at bonds 'a' and/or 'b'[2–4] (Scheme 1).

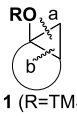
We found that when tertiary cyclopropyl silyl ethers or tertiary cyclopropanols (**1**) are treated with a catalytic amount of vanadyl acetylacetonate under oxygen and in ethanol, the cyclopropyl ring fragments and β-hydroxyketones (**2**) and β-diketones (**3**) are produced (Scheme 2). We described these findings in a preliminary communication.[5] We have further investigated the properties of the reactions and report full experimental details herein.

2. Results and discussion

To begin, we aerobically reacted ethanolic **1a** with 1.0 equiv of vanadyl acetylacetonate [$VO(acac)_2$][6] at room temperature and obtained as products, β-hydroxyketone (**2a**) and β-diketone (**3a**). The reaction also occurred in the presence of a catalytic amount of $VO(acac)_2$ (0.1 equiv; Scheme 3). β-Diketone (**3a**) was the major product when a stoichiometric amount of $VO(acac)_2$ was present. However, β-hydroxyketone (**2a**) predominated when a catalytic amount of $VO(acac)_2$ was used.

Generally, reactions involving derivatives of **1** and 0.1 equiv of $VO(acac)_2$ under oxygen and in ethanol caused the cyclopropane ring to fragment and produced β-hydroxy ketones and β-diketones (Table 1). For 1-(trimethylsiloxy)bicyclo[*n*.1.0]alkanes or bicyclo[n.1.0]alkanols (entries 1–6), the 'b' bond was specifically cleaved yielding ring-enlarged β-hydroxyketones and β-diketones. With $VO(acac)_2$ present, silyl ethers hydrolyzed immediately upon dissolution into ethanol and the corresponding alcohols were formed. Here, the reactive species are the tertiary cyclopropanols rather than the starting materials. When the cyclopropane ring lacked an oxygen functionality, the reaction did not occur (entry 6, Table 1).

Although vanadyl acetylacetonate did not react with **1a** or **1b** in an aprotic solvent (e.g., dichloromethane), it did



1 (R=TMS, H)

a: $Hg(OAc)_2$,[2e] ZnI_2,[2a] base,[2b] Br_2,[2d] $AgBF_4$,[2f,g] $Cu(BF_4)_2$,[2f,g] $SnCl_4$,[2h,l] PhPdOTf,[2i] $[Pt(C_2H_4)Cl_2]_2$,[2j] $TeCl_4$[2k]
b: $FeCl_3$,[3a-e] $Mn(pic)_3$,[3g-i] electrolysis[3f]
a & b: $Pb(OAc)_4$,[4a,b] $PhI(OAc)_2$[4c-h]

Scheme 1.

Keywords: Fragmentation reactions; Cyclopropanes; Peroxides; Vanadium compounds.
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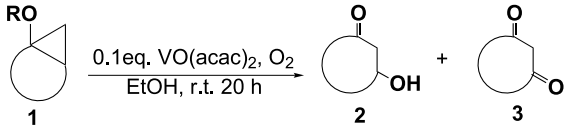
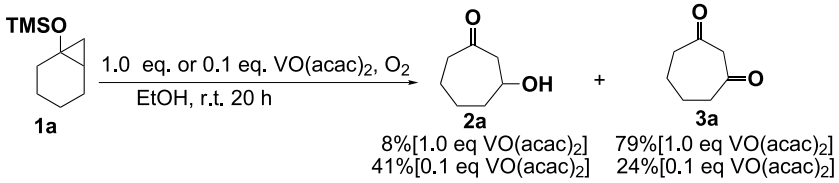


Scheme 2.

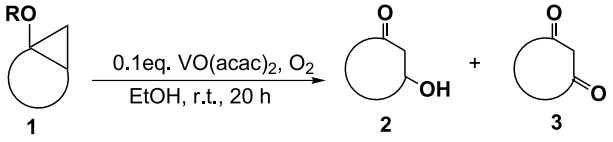
react with those compounds in trifluoroethanol with the β-diketones (**3a** and **3b**) as the main products (Scheme 4).

Interestingly, reaction of 5-but-3-enylbicyclo[4.1.0]heptane-1-ol (**1i**) did not result in a tandem ring expansion and cyclization, but instead a simple ring expansion

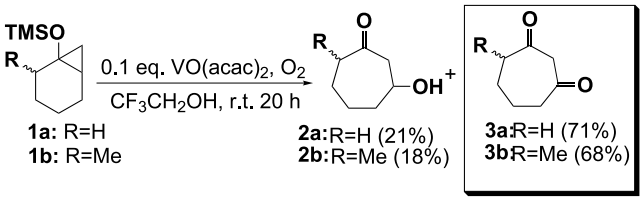


Scheme 3.

Table 1.



Entry	Starting material	Products	
1	TMSO **1a**	**2a** 41%	**3a** 24%
2	RO, Me **1b** (R=TMS) **1b′** (R=H)	**2b** R=TMS (40%) R=H (36%)	**3b** R=TMS (25%) R=H (39%)
3	RO, *t*-Bu **1c** (R=TMS) **1c′** (R=H)	**2c** R=TMS (25%) R=H (21%)	**3c** R=TMS (30%) R=H (35%)
4	TMSO **1d**	**2d** 31%	**3d** 33%
5	TMSO **1e**	**2e** 75%	**3e** 10%
6	TMSO **1f**	**2f** 29%	**3f** 31%
7	TMSO **1g**	**2g** 47%	
8	TMSO, C_9H_{19} **1h**	C_9H_{19} **2h** 80%	

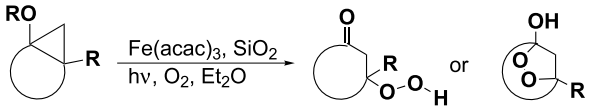


Scheme 4.

occurred giving **2i** and **3i**. This result contrasts sharply with the reaction of **1i** with an equimolar or excess amount of iron(III) chloride[3c,d] or manganese(III) picolinate[3g] under an inert atmosphere. For the latter, a radical tandem reaction occurs (Scheme 5).

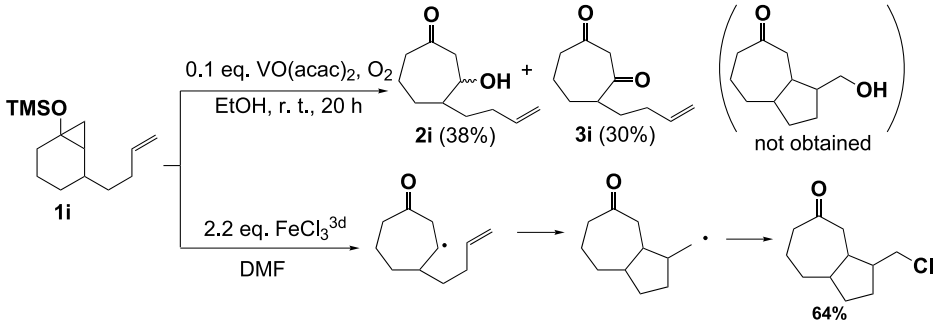
We assumed that the reaction of $VO(acac)_2$ is a radical reaction and molecular oxygen reacted with the radical faster than the radical reacted with the alkene. Actually, in the presence of oxygen, the cyclopropanol (**1i'**)[†] reacted with Fe(III) or Mn(II) producing **2i** and **3i** (Scheme 6).

Recently, Blanco and co-workers reported that ether solutions of 3-alkylbicyclo[*n*.1.0]alkanols when treated with ferric acetylacetonate and light in the presence of oxygen and silica gel produced peroxidated compounds (Scheme 8).[7]

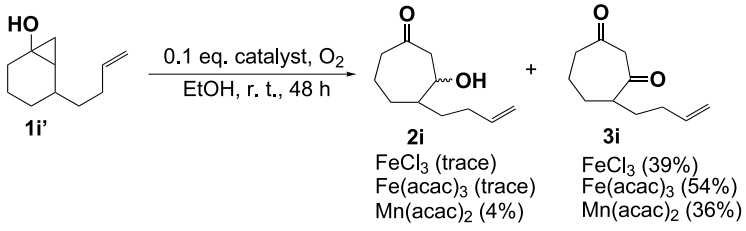


Scheme 8.

We also found that both peroxidated compounds (**4**) and β-hydroxyketones (**2**) were produced when 3-substituted bicyclo[4.1.0]alkanols (**1j**, **1k**, and **1l**) were treated with a catalytic amount of $VO(acac)_2$ under oxygen. Peroxides **4** were the principal products when trifluoroethanol was the solvent (Table 2).

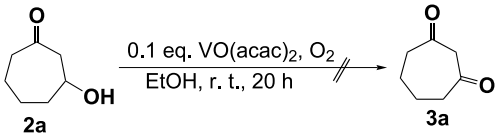


Scheme 5.



Scheme 6.

The β-diketone (**3a**) was not obtained by reaction of the β-hydroxyketone (**2a**) with $VO(acac)_2$ (Scheme 7). Therefore, most likely, β-diketones are directly produced from cyclopropanol derivatives.



Scheme 7.

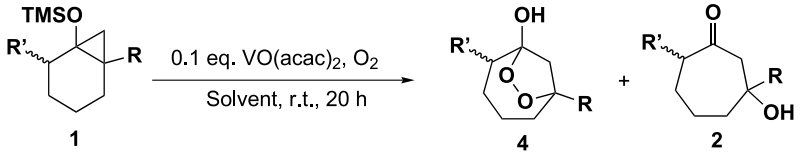
[†] The tertiary cyclopropyl silyl ether (**1i**) did not react under the same reaction condition.

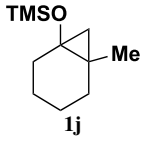
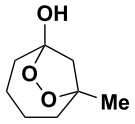
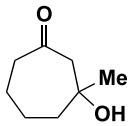
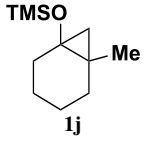
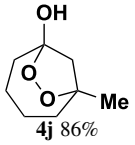
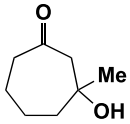
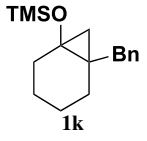
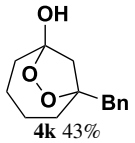
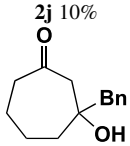
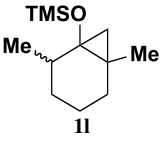
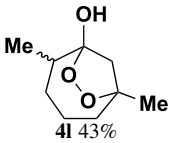
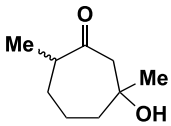
The structure of **4j** was determined by X-ray crystallography. The ORTEP plot shows the X-ray structure of **4j** (Scheme 9).

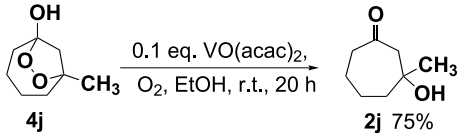
Treatment of **4j** with a catalytic amount of $VO(acac)_2$ in ethanol and oxygen afforded β-hydroxyketone **2j** at 75% yield (Scheme 10). Therefore, peroxide derivatives are probably reaction intermediates formed during production of β-hydroxyketones and β-diketones from cyclopropyl compounds. For 3-unsubstituted bicyclo[4.1.0]alkanols (**1**), peroxidated species might be unstable reaction intermediates and immediately form β-hydroxyketones and β-diketones.

A plausible reaction mechanism is depicted in Scheme 11. Tertiary cyclopropyl silyl ethers are immediately

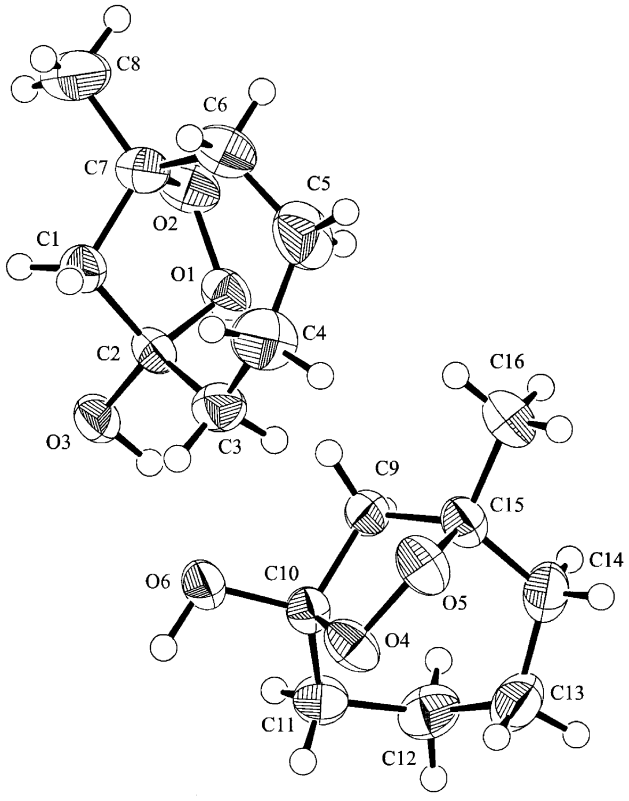
Table 2.



Entry	Starting material	Solvent	Products	
1	 **1j**	EtOH	 **4j** 45%	 **2j** 53%
2	 **1j**	CF_3CH_2OH	 **4j** 86%	 **2j** 10%
3	 **1k**	CF_3CH_2OH	 **4k** 43%	 **2k** trace
4	 **1l**	CF_3CH_2OH	 **4l** 43%	 **2l** 26%



Scheme 10.

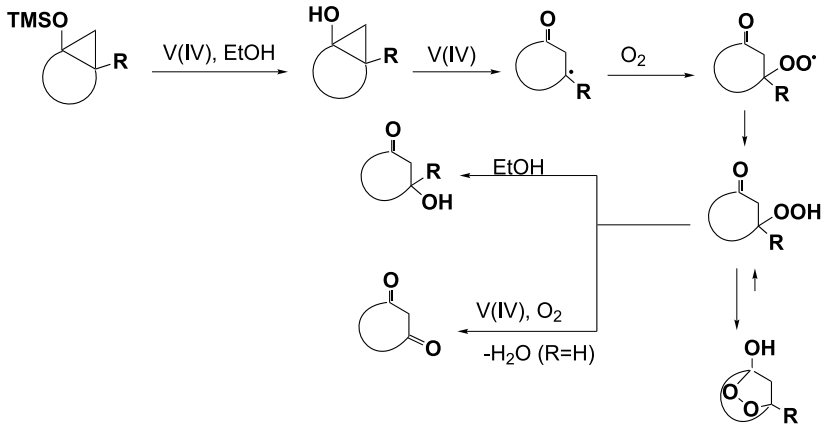


Scheme 9.

hydrolyzed into the corresponding alcohols by V(IV) in ethanol. The resulting cyclopropanols react with V(IV) resulting in the ring expansion and free radical formation. The radical then reacts with molecular oxygen to provide β-perhydroxyketones which are, in turn, transformed into endoperoxide compounds.[‡] The peroxy compounds then react with ethanol to provide β-hydroxyketones. β-Diketones might be obtained by reaction of the peroxy compounds with V(IV) and molecular oxygen, because a β-diketone was the main product a stoichiometric amount of $VO(acac)_2$.

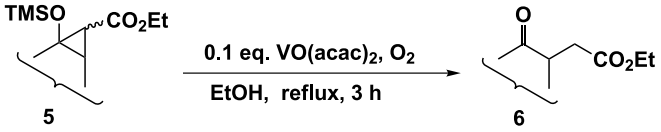
We also examined the reaction of 1-(trimethylsiloxy)bicyclo[*n*.1.0]alkanes bearing an ethoxycarbonyl group (**5**) at the 2-position and found that the 'a' bond was specifically cleaved to provide non-oxygenated compounds (**6**; Table 3). The same result was obtained when **5b** reacted in the absence of oxygen (Scheme 12). In these cases, $VO(acac)_2$ might act as a simple Lewis Acid.

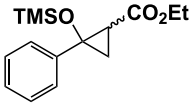
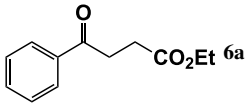
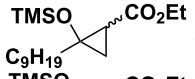
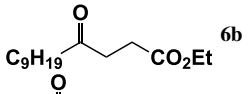
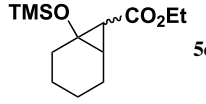
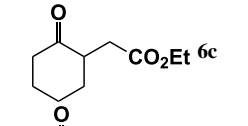
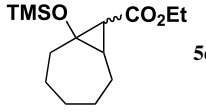
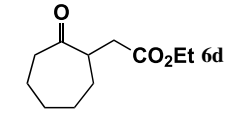
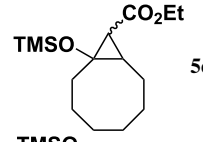
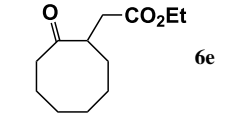
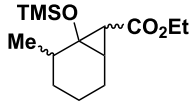
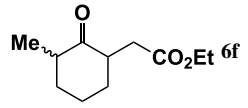
[‡] Although we reported previously that a stoichiometric amount of $VO(acac)_2$ reacted with 1-(trimethylsiloxy)bicyclo[4.1.0]heptane in the absence of oxygen,[5] it is possible that a trace amount of oxygen that was dissolved in the solvent might have reacted with 1-(trimethylsiloxy)bicyclo[4.1.0]heptane.

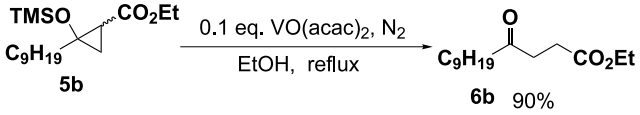


Scheme 11.

Table 3.



Entry	Starting material	Products	Yield (%)
1			84
2			82
3			86
4			90
5			90
6			88



Scheme 12.

3. Conclusions

Tertiary cyclopropyl silyl ethers react with a catalytic amount of $VO(acac)_2$ to provide β-hydroxyketones and β-diketones. For 3-substituted-bicyclo[*n*.1.0]alkanol derivatives, peroxides and with β-hydroxyketones are produced. The β-hydroxyketones and β-diketones obtained from the tertiary cyclopropyl silyl ethers must be derived from peroxide intermediates. Conversely, 2-ethoxycarbonyl-cyclopropyl silyl ethers afford ethyl γ-oxocarboxylate given the same conditions. In these cases, $VO(acac)_2$ probably acts as a Lewis acid.

4. Experimental

4.1. General

IR spectra were recorded using a Perkin–Elmer 1600 FT-IR or a Jasco IR-8300 FT-IR spectrophotometer. NMR spectra acquired using a Varian Gemini 300, a JEOL JNM-400, or a Varian UNITY plus 500 spectrometer. All NMR samples

were dissolved in $CDCl_3$ containing tetramethylsilane as an internal standard. Coupling constants (J) are given in hertz (Hz). Low-resolution and high-resolution mass spectra (electron impact) were recorded on using a JEOL D-200, a JEOL JMS D-200 or a JEOL AX505 spectrometer. Melting points were determined using a Yanagimoto micro-melting point apparatus and are reported as uncorrected values. For column chromatography, silica gel (Merck Kieselger 60) was the support.

Tertiary cyclopropyl silyl ethers and tertiary cyclopropanols were prepared according to reported methods.[1b,8]

4.2. General procedure for the syntheses of β-hydroxy ketones and β-diketones from tertiary cyclopropyl silyl ethers using vanadyl acetylacetonate

A mixture of a tertiary cyclopropyl silyl ether (or a tertiary cyclopropanol) (**1**) (0.50 mmol), vanadyl acetylacetonate (0.50 mmol or 0.05 mmol) and ethanol (5 ml) was stirred at room temperature under an oxygen atmosphere for 20 h. Saturated aqueous sodium bicarbonate (3 ml) was added to the mixture, and that was then extracted with ethyl acetate (20 ml $\times 3$). The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated to give a crude mixture of a β-hydroxy ketone (**2**) and a β-diketone (**3**). Separation and purification by column chromatography (hexane-ethyl acetate) gave pure samples.

4.2.1. 3-Hydroxycycloheptanone (2a). IR (neat) cm^{-1}: 3420, 1696; ^1H NMR ($CDCl_3$) δ: 1.67–1.93 (4H, m), 1.94–2.03 (2H, m), 2.46–2.56 (2H, m), 2.75–2.83 (2H, m) 4.08–4.14 (1H, m); MS (m/z) 128 (M^+); HRMS calcd for $C_7H_{12}O_2$ (M^+): 128.0837, found 128.0840.

4.2.2. Cyclohepta-1,3-dione (3a). IR (neat) cm^{-1}: 1670; ^1H NMR ($CDCl_3$) δ: 1.97–2.04 (4H, m), 2.57–2.60 (4H, m), 3.60 (2H, s); MS (m/z) 126 (M^+); HRMS calcd for $C_7H_{10}O_2$ (M^+): 126.0681, found 126.0685.

4.2.3. 6-Hydroxy-2-methylcycloheptanone (3:1 mixture of stereoisomers) (2b). IR (neat) cm^{-1}: 3427, 1694; ^1H NMR ($CDCl_3$) δ: 1.03 (3H, d, $J=6.8$ Hz), 1.36–1.47 (2H, m), 1.56–1.70 (2H, m), 1.89–2.02 (1H, m), 2.39–2.44 (1H, m), 2.60–2.80 (3H, m), 3.96–4.06 (3/4H, m), 4.08–4.16 (1/3H, m); MS (m/z) 142 (M^+); HRMS calcd for $C_8H_{14}O_2$ (M^+): 142.0995, found 142.0994.

4.2.4. 4-Methylcyclohepta-1,3-dione (3b). IR (neat) cm^{-1}: 1698; ^1H NMR ($CDCl_3$) δ: 1.08 (3H, d, $J=6.6$ Hz), 1.57–1.63 (1H, m), 1.89–1.97 (1H, m), 1.98–2.03 (2H, m), 2.44–2.50 (1H, m), 2.52–2.58 (1H, m), 2.69–2.73 (1H, m), 3.53 (1H, d, $J=15.0$ Hz), 3.60 (1H, d, $J=15.0$ Hz); MS (m/z) 140 (M^+); HRMS calcd for $C_8H_{12}O_2$ (M^+): 140.0995, found 140.0994.

4.2.5. 5-*t*-Butyl-3-hydroxycycloheptanone (2.7:1 mixture of stereoisomers) (2c). IR (neat) cm^{-1}: 3420, 1698; ^1H NMR ($CDCl_3$) δ: 0.98 (9H, s), 1.08–1.11 (1H, m), 1.38–1.48 (2H, m), 1.95–2.01 (1H, m), 2.28–2.32 (2H, m), 2.51–2.60 (1H, m), 2.65–2.74 (1H, m), 2.80–2.92 (1H, m), 3.90–3.95 (2.7/3.7H, m), 4.30–4.35 (1/3.7H; MS (m/z) 184 (M^+); HRMS calcd for $C_{11}H_{20}O_2$ (M^+): 184.1444, found 184.1468.

4.2.6. 5-*t*-Butylcyclohepta-1,3-dione (3c). IR (neat) cm^{-1}: 1699; ^1H NMR ($CDCl_3$) δ: 0.91 (9H, s), 1.59–1.71 (2H, m), 2.08–2.16 (1H, m), 2.38–2.51 (2H, m), 2.60–2.67 (2H, m), 3.56 (2H, s); MS (m/z) 182 (M^+); HRMS calcd for $C_{11}H_{18}O_2$ (M^+): 182.1326, found 182.1303.

4.2.7. 3-Hydroxycyclooctanone (2d). IR (neat) cm^{-1}: 3420, 1696; ^1H NMR ($CDCl_3$) δ: 1.23–1.29 (1H, m), 1.46–1.67 (4H, m), 1.80–1.82 (1H, m), 1.84–2.03 (2H, m), 2.33–2.42 (2H, m), 2.66–2.70 (1H, m), 2.78–2.81 (1H, m), 4.05–4.10 (1H, m); MS (m/z) 142 (M^+); HRMS calcd for $C_8H_{14}O_2$ (M^+): 142.0994, found 142.1001.

4.2.8. Cycloocta-1,3-dione (3d). IR (neat) cm^{-1}: 1700; ^1H NMR ($CDCl_3$) δ: 1.62–1.70 (2H, m), 1.80–1.84 (4H, m), 2.50 (4H, t, $J=6.5$ Hz), 3.52 (2H, s); MS (m/z) 140 (M^+); HRMS calcd for $C_8H_{12}O_2$ (M^+): 140.0837, found 140.0812.

4.2.9. 3-Hydroxycyclohexanone (2e). IR (neat) cm^{-1}: 3420, 1696; ^1H NMR ($CDCl_3$) δ: 1.66–1.82 (2H, m), 1.99–2.16 (2H, m), 2.31 (2H, t, $J=6.7$ Hz), 2.40 (1H, dd, $J=14.1$, 7.5 Hz), 2.65 (1H, dd, $J=14.1$, 3.2 Hz), 4.19 (1H, heptet, $J=3.7$ Hz); MS (m/z) 114 (M^+); HRMS calcd for $C_6H_{10}O_2$ (M^+): 114.0681, found 114.0622.

4.2.10. 4-Hydroxybicyclo[5.1.0]octan-2-one (2:1 mixture of stereoisomers) (2f). IR (neat) cm^{-1}: 3405, 1665; ^1H NMR ($CDCl_3$) δ: 1.04–1.19 (1H, m), 1.24–1.38 (1H, m), 1.41–1.54 (1H, m), 1.66–2.37 (5H, m), 2.52–2.71 (2H, m), 3.70–3.78 (2/3H, m), 3.94–3.98 (1/3H, m); MS (m/z) 140 (M^+); HRMS calcd for $C_8H_{12}O_2$ (M^+): 140.0837, found 140.0852.

4.2.11. Bicyclo[5.1.0]octane-2,4-dione (3f). IR (neat) cm^{-1}: 1698, 1676; ^1H NMR ($CDCl_3$) δ: 1.19–1.28 (5H, m), 2.40–2.52 (3H, m), 3.79 (2H, s); MS (m/z) 138 (M^+); HRMS calcd for $C_8H_{10}O_2$ (M^+): 138.0681, found 138.0686.

4.2.12. 3-Hydroxy-1-phenylpropan-1-one (2g). IR (neat) cm^{-1}: 3422, 1680; ^1H NMR ($CDCl_3$) δ: 2.78 (1H, s), 3.15 (2H, t, $J=5.4$ Hz), 3.95 (2H, t, $J=5.4$ Hz), 7.36–7.53 (3H, m), 7.86–7.90 (2H, m); MS (m/z) 150 (M^+); HRMS calcd for $C_9H_{10}O_2$ (M^+): 150.0681, found 150.0622.

4.2.13. 1-Hydroxydodecan-3-one (2h). IR (neat) cm^{-1}: 3381, 1703; ^1H NMR ($CDCl_3$) δ: 0.81 (3H, t, $J=6.4$ Hz), 1.19–1.28 (14H, m), 2.37 (2H, t, $J=5.3$ Hz), 2.60 (2H, t, $J=5.5$ Hz), 3.81 (2H, t, $J=5.5$ Hz); MS (m/z) 200 (M^+); HRMS calcd for $C_{12}H_{24}O_2$ (M^+): 200.1776, found 200.1781.

4.2.14. 4-(3-Butenyl)-3-hydroxycycloheptanone (2i). IR (neat) cm^{-1}: 3417, 1694; ^1H NMR ($CDCl_3$) δ: 1.17–2.36 (7H, m), 2.83–2.88 (1H, m), 3.36–3.39 (2H, m), 3.43–3.49 (2H, m), 4.23–4.26 (2H, m), 4.92–5.03 (2H, m), 5.72–5.79 (1H, m); MS (m/z) 182 (M^+); HRMS calcd for $C_{11}H_{18}O_2$ (M^+): 182.1307, found 182.1320.

4.2.15. 4-(3-Butenyl)-3-hydroxycycloheptane-1,3-dione (3i). IR (neat) cm^{-1}: 1697; ^1H NMR ($CDCl_3$) δ: 1.20–1.35 (2H, m), 1.58–1.70 (2H, m), 1.75–1.99 (2H, m), 2.00–2.04 (2H, m), 2.49–2.59 (2H, m), 2.60–2.70 (1H, m), 3.53 (2H, s), 4.94–5.06 (2H, m), 5.65–5.80 (1H, m); MS (*m/z*) 180 (M^+); HRMS calcd for $C_{11}H_{16}O_2$ (M^+): 180.1158, found 180.1150.

4.3. General procedure for the syntheses of 2i and 3i from 1i using Fe(III) or Mn(II)

A mixture of the tertiary cyclopropanol (**1i**) (83.1 mg, 0.50 mmol), iron(III) chloride, iron(III) acetylacetonate or manganese(II) acetylacetonate (0.05 mmol) and ethanol (5 ml) was stirred at room temperature under an oxygen atmosphere for 48 h. Next, saturated aqueous sodium bicarbonate (3 ml) was added to the mixture, that was then extracted with ethyl acetate (20 ml ×3). The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated to provide a crude mixture of **2i** and **3i**. Separation and purification by column chromatography (hexane–ethyl acetate) gave pure samples.

4.4. General procedure for the syntheses of β-hydroxyketones and peroxidated compounds from a tertiary cyclopropyl silyl ethers

A mixture of a tertiary cyclopropyl silyl ether (**1j**, **1k** or **1l**) (0.50 mmol), vanadyl acetylacetonate (0.05 mmol), and either ethanol or 2,2,2-trifluoroethanol (5 ml) was stirred at room temperature under an oxygen atmosphere for 20 h. Saturated aqueous sodium bicarbonate (3 ml) was added to the mixture, that was then extracted with ethyl acetate (20 ml×3). The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated to afford a crude mixture of a β-hydroxy ketone and a peroxidated compound. Separation and purification by column chromatography (hexane-ethyl acetate) gave pure samples.

4.4.1. 6-Methyl-7,8-dioxabicyclo[4.2.1]nonan-1-ol (4j). Colorless crystals, Mp 85–86 °C (*n*-hexane–$CHCl_3$); IR (KBr) cm^{-1}: 3354, 2915; ^1H NMR ($CDCl_3$) δ: 1.30 (3H, s), 1.41–1.49 (1H, m), 1.51–1.74 (2H, m), 1.83–1.93 (4H, m), 1.99–2.03 (1H, m), 2.41 (1H, d, J=12.0 Hz), 2.79 (1H, d, J=12.0 Hz), 3.00–3.34 (1H, br); MS (*m/z*) 158 (M^+); HRMS calcd for $C_8H_{14}O_3$ (M^+): 158.0943, found 158.0923. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.70; H, 8.88.

X-ray crystallographic data for **4j**. Colorless prisms, $C_8H_{14}O_3$, M=158.20, monoclinic, a=5.665(1) Å, b=23.297(7) Å, c=14.969(5) Å, β=121.71(2)°, V=1680.8(8) $Å^3$, space group $P2_1/c$ (#14), Z=8, D_c=1.25 g cm^{-3}, $F(000)$=688.00, μ(Mo Kα)=0.94 cm^{-1}, R=0.046, Rw=0.064.

There are two independent molecules in the asymmetric unit of **4j**.

4.4.2. 3-Hydroxy-3-methylcycloheptanone (2j)

A colorless oil; IR (neat) cm^{-1}: 3854, 2932, 1696; ^1H NMR ($CDCl_3$) δ: 1.26 (3H, s), 1.56–1.74 (6H, m), 2.32–2.52 (3H, br), 2.60 (1H, dd, J=14.0, 1.7 Hz), 2.83 (1H, d, J=13.0 Hz); MS (*m/z*) 142 (M^+); HRMS calcd for $C_8H_{14}O_2$ (M^+): 142.0994, found 142.1003.

4.4.3. 6-Benzyl-7,8-dioxabicyclo[4.2.1]nonan-1-ol (4k)

Colorless crystals, Mp 89–91 °C (*n*-hexane–$CHCl_3$); IR (KBr) cm^{-1}: 3346, 2924; ^1H NMR ($CDCl_3$) δ: 1.35–1.64 (3H, m), 1.77–2.04 (5H, m), 2.45 (1H, d, J=13.0 Hz), 2.64–2.72 (2H, m), 2.88 (2H, d, J=4.0 Hz), 7.16–7.30 (5H, m); MS (*m/z*) 234 (M^+); HRMS calcd for $C_{14}H_{18}O_3$ (M^+): 234.1256, found 234.1212.

4.4.4. 2,6-Dimethyl-7,8-dioxabicyclo[4.2.1]nonan-1-ol (2:1 mixture of stereoisomers) (4l)

A colorless oil, IR (neat) cm^{-1}: 3447, 2919; ^1H NMR ($CDCl_3$) δ: 0.97 (3H×1/3, d, J=6.6 Hz), 1.04 (3H×2/3, d, J=7.1 Hz), 1.30 (3H×2/3, s), 1.32–2.13 (8H, m), 2.22 (1H×1/3, brd, J=13.0 Hz), 2.43 (1H×2/3, brd, J=13.0 Hz), 2.71 (1H×1/3, d, J=13.0 Hz), 2.86 (1H×2/3, d, J=13.0 Hz); MS (*m/z*) 172 (M^+); HRMS calcd for $C_9H_{16}O_3$ (M^+): 172.1099, found 172.1052.

4.4.5. 6-Hydroxy-2,6-dimethylcycloheptanone (4:1 mixture of stereoisomers) (2l)

A colorless oil, IR (neat) cm^{-1}: 3853, 2929, 1699; ^1H NMR ($CDCl_3$) δ: 1.08 (3H×1/5, d, J=6.3 Hz), 1.09 (3H×4/5, d, J=7.1 Hz), 1.30 (3H×4/5, s), 1.31 (3H×1/5, s), 1.36–2.57 (8H, m), 2.48 (1H×1/5, d, J=12.0 Hz), 2.62 (1H×4/5, d, J=12.0 Hz), 2.85 (1H×4/5, d, J=12.0 Hz), 2.93 (1H×1/5, d, J=13.0 Hz); MS (*m/z*) 156 (M^+); HRMS calcd for $C_9H_{16}O_2$ (M^+): 156.1150, found 156.1175.

4.5. General procedure for the syntheses of an ethyl γ-oxocarboxylates from a tertiary cyclopropyl silyl ethers

A mixture containing a tertiary cyclopropyl silyl ether (**5**) (0.50 mmol), vanadyl acetylacetonate (0.05 mmol) and ethanol (5 ml) was refluxed under an oxygen or a nitrogen atmosphere for 3 h. Next, saturated aqueous sodium bicarbonate (3 ml) was added to the mixture, that was then extracted with ethyl acetate (20 ml×3). The combined organic extracts were washed with brine, dried over magnesium sulfate, and evaporated to afford the crude product. Separation and purification by column chromatography (hexane-ethyl acetate) gave pure samples.

4.5.1. Ethyl 4-oxophenylbutanoate (6a)

A colorless oil, IR (neat) cm^{-1}: 1732, 1687; ^1H NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.1 Hz), 2.69 (2H, t, J=7.2 Hz), 3.25 (2H, t, J=7.2 Hz), 4.11 (2H, q, J=7.2 Hz), 7.37–7.42 (1H, m), 7.47–7.53 (2H, m), 7.90–7.94 (2H, m); MS (*m/z*) 206 (M^+); HRMS calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943, found 206.0988.

4.5.2. Ethyl 4-oxotridecanoate (6b)

A colorless oil, IR (neat) cm^{-1}: 1736, 1717; ^1H NMR

($CDCl_3$) δ: 0.86 (3H, t, $J=6.6$ Hz), 1.19–1.26 (17H, m), 2.42 (2H, t, $J=7.3$ Hz), 2.55 (2H, t, $J=6.3$ Hz), 2.70 (2H, t, $J=6.3$ Hz), 4.10 (2H, q, $J=6.6$ Hz); MS (*m/z*) 256 (M^+); HRMS calcd for $C_{15}H_{28}O_3$ (M^+): 256.2038, found 256.2035.

4.5.3. Ethyl 2-(2-oxocyclohexyl)acetate (6c)

A colorless oil, IR (neat) cm^{-1}: 1734, 1713; ^1H NMR ($CDCl_3$) δ: 1.23 (3H, t, $J=7.3$ Hz), 1.36–1.83 (4H, m), 2.07–2.15 (2H, m), 2.33–2.40 (2H, m), 2.70–2.88 (3H, m), 4.11 (2H, q, $J=7.3$ Hz); MS (*m/z*) 184 (M^+); HRMS calcd for $C_{10}H_{16}O_3$ (M^+): 184.1099, found 184.2033.

4.5.4. Ethyl 2-(2-oxocycloheptyl)acetate (6d)

A colorless oil, IR (neat) cm^{-1}: 1732, 1704; ^1H NMR ($CDCl_3$) δ: 1.23 (3H, t, $J=7.0$ Hz), 1.28–1.85 (8H, m), 2.23–2.31 (1H, m), 2.37–2.48 (1H, m), 2.57–2.67 (1H, m), 2.74–2.84 (1H, m), 3.03–3.13 (1H, m), 4.80 (2H, q, $J=7.0$ Hz); MS (*m/z*) 198 (M^+); HRMS calcd for $C_{11}H_{18}O_3$ (M^+): 198.1256, found 198.1277.

4.5.5. Ethyl 2-(2-oxocyclooctyl)acetate (6e)

A colorless oil, IR (neat) cm^{-1}: 1732, 1704; ^1H NMR ($CDCl_3$) δ: 1.21 (3H, t, $J=7.2$ Hz), 1.36–1.87 (10H, m), 2.21–2.33 (2H, m), 2.64–2.73 (1H, m), 2.79–2.89 (1H, m), 3.17–3.28 (1H, m), 4.05 (2H, q, $J=7.2$ Hz); MS (*m/z*) 212 (M^+); HRMS calcd for $C_{12}H_{20}O_3$ (M^+): 212.1412, found 212.1444.

4.5.6. Ethyl 2-(3-methyl-2-oxocyclohexyl)acetate (6f)

A colorless oil, IR (neat) cm^{-1}: 1737, 1711; ^1H NMR ($CDCl_3$) δ: 1.00 (3H, d, $J=6.7$ Hz), 1.38–1.91 (6H, m), 1.17–1.26 (3H, m), 2.06–2.23 (2H, m), 2.66–2.79 (1H, m), 2.98–3.04 (1H, m), 4.11 (2H, q, $J=6.7$ Hz); MS (*m/z*) 198 (M^+); HRMS calcd for $C_{11}H_{18}O_3$ (M^+): 198.1256, found 198.1257.

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Synthesis of 3- and 5-amino-5-(3)-(pyrrol-2-yl)isoxazoles

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Abstract—5-Amino-3-(pyrrol-2-yl)isoxazoles were selectively prepared by the reaction of 2-(2,2-dicyano-1-ethylthioethenyl)pyrroles with hydroxylamine in methanol. Under analogous conditions, 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl) pyrroles with hydroxylamine gave 5-aminoisoxazoles and their structural isomers, 3-aminoisoxazoles (3–5% yield). The latter were selectively prepared by reacting 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles with hydroxylamine in the presence of aqueous NaOH and from the products of intramolecular cyclization of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles, 1-ethylthio-3-iminopyrrolizines and hydroxylamine.

1. Introduction

Isoxazoles and their derivatives are key intermediates for the preparation of natural compounds and related structures.[1] Derivatives of aminoisoxazoles are used as antimicrobial, antifungal and herbicide agents.[2,3] However, the isoxazole series attract large interest mainly thanks to their high pharmacological activity. Thus, isoxazole rings are present in sulfonamide drugs (sulfisoxazoles),[4] antibiotics (oxacillin, cloxacillin and dicloxacillin),[4] an antileprous agent,[4] a monoaminoxidase inhibitor used in psychotherapy—isocarboxazide[4] and agarin, which acts on the central nervous system.[5] Condensed isoxazole rings occur in the structure of anabolic steroids[4] and compounds, possessing metastatic activity.[6]

The high potential of isoxazoles as protecting functions and ease of their transformation into other functionalized derivatives through the ring opening reaction at the labile nitrogen–oxygen bond ensure broad application of these compounds in organic synthesis.[1]

The discovery of important application areas where isoxazole compounds could be successfully utilized has not only stimulated intense investigations of their chemical and practically useful properties, but also intensified the search for simpler and cheaper routes to isoxazoles, including new amino derivatives. The latter compounds are of special interest among isoxazoles as the presence of the amino group makes them capable of facile modification, allowing transformation of relatively simple structures into complex functionalized compounds.

The most common methods for the synthesis of aminoisoxazoles are reactions of hydroxylamine with ketonitrile derivatives,[7] as well as with acetylenic,[8] propargylic,[9] allenic[8,10] and polarized ethylenic nitriles.[11] However, 2-ethenylpyrroles with a push–pull combination of substituents at the vinyl group, which can now be readily prepared from pyrrolecarbodithioates and methylene active nitriles,[12] have not yet been investigated in this reaction, although earlier studies[13] have revealed their significant potential for solving various synthetic problems.

The aim of this work was to investigate the reaction of 2-(2,2-dicyano-1-ethylthioethenyl)- (**1a–d**) and 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles **1e–h** with hydroxylamine and to synthesize previously unknown compounds, combining pyrrole and aminoisoxazole rings in a single molecule, while retaining other (apart from the amino group) functional substituents, such as nitrile and carbamide groups available for further modifications.

Taking into account the possibility of cyclization of 2-(1-alkylthio-2-cyanoethenyl)pyrroles to 3-iminopyrrolizines through interaction of the pyrrole NH group with the nitrile function,[13a,b] as well as bifunctionality of hydroxylamine[14] and the NO bond lability in isoxazoles, the outcome of the

Keywords: 5-Aminopyrrolylisoxazoles; 3-Aminopyrrolylisoxazoles; 2-(2-Cyano-1-ethylthioethenyl)pyrroles; 1-Ethylthio-3-iminopyrrolizines; Hydroxylamine.
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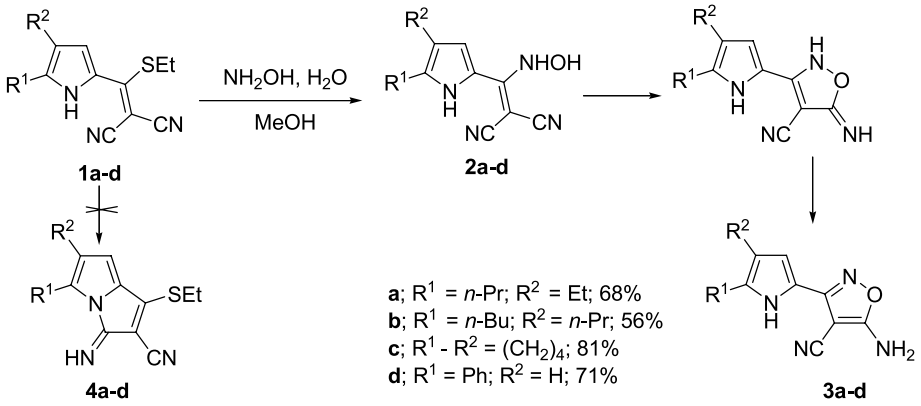


Scheme 1.

reaction was quite ambiguous and could not have been predicted in advance.

2. Results and discussion

We have shown that on heating (40–45 °C, 30 min) in methanol with aqueous hydroxylamine, 2-(2,2-dicyano-1-ethylthioethenyl)pyrroles **1a–d** readily exchange their ethylthio group for a hydroxylamino moiety to form, after subsequent cyclization of intermediates **2a–d**, 5-amino-3-(pyrrol-2-yl)isoxazoles **3a–d** in 56–81% yield (Scheme 1).

The reaction was found to be chemoselective: other products, including 3-iminopyrrolizines **4a–d** were not detected in the reaction mixture (the reaction was monitored by TLC). In the ^{1}H NMR spectra of the reaction mixture there are no signals for the SCH_2-group in the 3.14–3.45 ppm region; NH_2-protons appears as broad singlets in the 6.92–8.48 ppm region. The character and integral intensities of the signals are in full agreement with the structure of 5-aminoisoxazoles **3a–d**.

Under analogous conditions, with 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles **1e–h**, which exist exclusively as isomers with the *syn* disposition of carbamoyl and NH-pyrrole groups, the reaction chemoselectivity breaks: along with 5-amino-3-(pyrrol-2-yl)isoxazoles **3e–h** [the content in the reaction mixture of 5-aminoisoxazoles **3e–h** is 95–97% (^{1}H NMR data)], their structural isomers, 3-amino-5-(pyrrol-2-yl)isoxazoles **5e–h** are also formed (the content in the reaction mixture of 3-aminoisoxazoles **5e–h** is 3–5%), (Scheme 2).

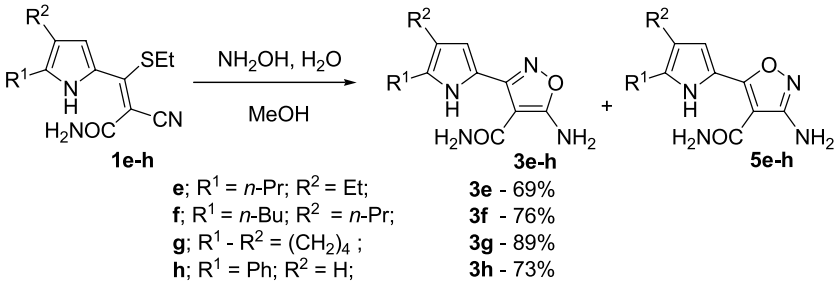
After removal of methanol and recrystallization from aqueous acetone, 5-aminoisoxazoles **3e–h** were isolated in pure state in 69–89% yield.

The selective formation of 5-aminoisoxazoles **3e–h** is observed upon refluxing 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles **1e–h** with hydroxylamine in tetrahydrofuran. However, in this case, in spite of longer reaction time (1 h) (TLC monitoring), the yields of 5-aminoisoxazoles are lower (45–67%) than those in methanol.

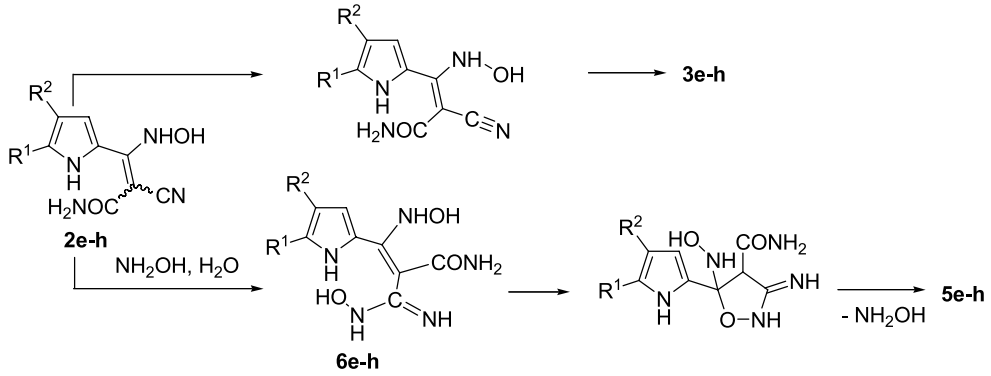
Formation of two isomeric aminoisoxazoles in these reaction may be explained (by analogy to the literary data[8]) by the existence of intermediates **2e–h** as *E*- and *Z*-isomers. While the *Z*-isomers readily cyclize to 5-amino-isoxazoles **3e–h**, the *E*-isomers either partially transform to the *Z*-form or add a second hydroxylamine molecule to the nitrile carbon to form the bis-adducts **6**, which further cyclize with elimination of a hydroxylamine molecule giving the minor reaction products, 3-aminoisoxazoles **5e–h** (Scheme 3).

Since 2-(2-cyano-1-ethylthioethenyl)pyrroles are known to be inert towards the hydroxyl group (confirmed earlier by their selective cyclization to 1-ethylthio-3-iminopyrrolizines upon refluxing in methanol in the presence of triethylamine[13b,15]), in this case we can rule out the probability that hydroxylamine acts as an *O*-nucleophile.

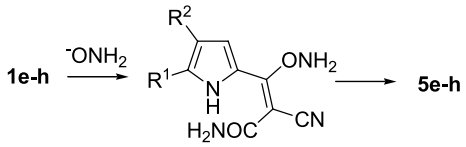
pK_a Values for the first and the second dissociation steps of hydroxylamine (5.97 and 13.7, respectively)[14] indicate that in highly basic media the latter exists mostly as the aminohydroxy anion, whereas under neutral or weakly



Scheme 2.



Scheme 3.



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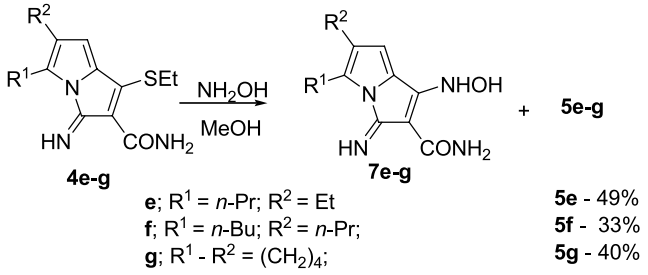


Scheme 5.

basic conditions it exists as free hydroxylamine. Therefore, we anticipated that in the presence of NaOH, hydroxylamine would react with 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles **1e**–**h** as an *O*-nucleophile giving exclusively 3-aminoisoxazoles **5e**–**h** (Scheme 4).

These expectations eventually came true: under the above conditions, 3-aminoisoxazoles were obtained selectively in 12–48% yield, whereas their regioisomers, 5-aminoisoxazoles **3e**–**h**, were not detected in the reaction mixture. However, the formation of 3-iminopyrrolizines **4e**–**g** (products of intramolecular cyclization of pyrroles **1e**–**g**) at the initial reaction stage (TLC), which completely disappear by the end of the reaction, indicates the existence of an alternative route to 3-aminoisoxazoles.

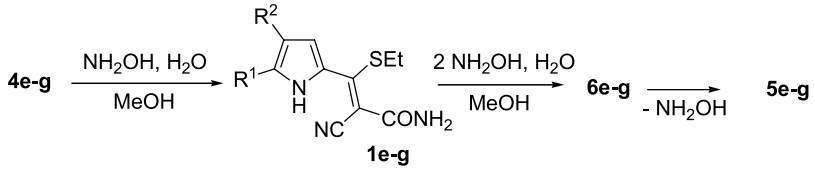
A proof of this route is the reaction of 3-iminopyrrolizines **4e**–**g** with hydroxylamine affording under analogous conditions mainly 3-aminoisoxazoles **5e**–**g** (Scheme 5). A side pathway of the reaction is the exchange of ethylthio group in the initial pyrrolizines for hydroxylamine to give 1-hydroxyamino-3-iminopyrrolizines **7e**–**g**. The ratio of products **5e**–**g**:**7e**–**g** is ~2.5:1. 3-Aminoisoxazoles **5e**–**g** were isolated by column chromatography (Al_2O_3, eluent: methanol), while 1-hydroxyamino-3-iminopyrrolizines **7e**–**g** were only characterized by ^1H NMR spectroscopy of the reaction mixtures.

Reacting the pyrrole **1g** with hydroxylamine in propanol (85 °C, 10 min) allows one to isolate 3-aminoisoxazole **5g** from the reaction mixture in pure form (as a precipitate).

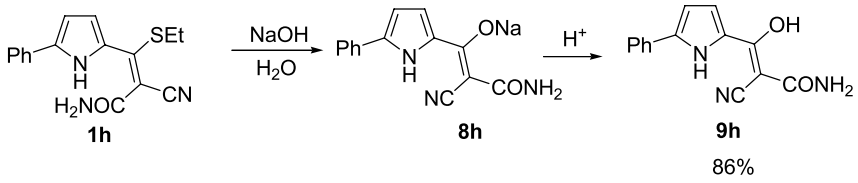
The formation of isoxazoles **5e**–**g** is likely to be a result of ring opening of the starting pyrrolizines **4e**–**g** and formation of the pyrroles **1e**–**g** with the *Z*-configuration of nitrile and NH groups, formation of the adducts **6e**–**g** and their subsequent cyclization (Schemes 3 and 6) (ring opening of pyrrolizines **4** in methanol on an example of the compound **4g** was described previously[13b]).

The product of intramolecular cyclization of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)-5-phenylpyrrole (**1h**), 3-iminopyrrolizine **4h** was not detected in the reaction mixture. It should be noted that unlike the pyrroles **1e**–**g**, the pyrrole **1h** does not cyclize to 3-iminopyrrolizine **4h** upon refluxing in methanol in the presence of triethylamine. On heating in methanol (1 h) in the presence of aqueous NaOH the pyrrole **1h** transforms, after acidification of the enolate **8h**, into 2-(2-carbamoyl-2-cyano-1-hydroxyethenyl)-5-phenylpyrrole (**9h**) (Scheme 7), which remains intact upon treatment with aqueous hydroxylamine (refluxing, 30 min). The same product was solely obtained in the reaction of the pyrrole **1h** with hydroxylamine in the presence of aqueous KOH (methanol, 50 °C, 10 min).

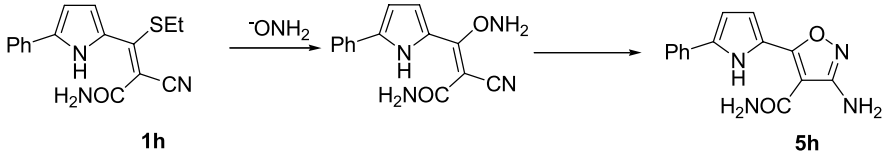
Therefore, the most probable pathway of the formation of



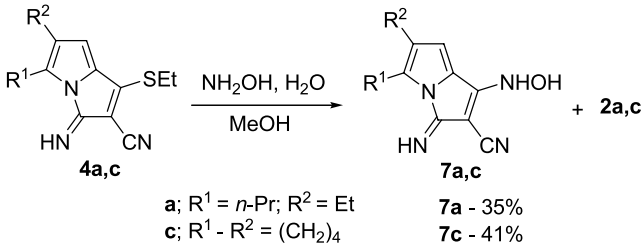
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

3-aminoisoxazole **5h** seems to be the attack of the pyrrole **1h** by the aminohydroxy anion (Scheme 8).

The only pathway of the reaction of 3-iminopyrrolizines **4a**,**c**, bearing a nitrile group, with hydroxyamine in methanol is the exchange of an ethylthio group for hydroxylamine to form 1-hydroxylamino-3-iminopyrrolizines **7a**,**c** (Scheme 9). The latter are unstable in DMSO solutions and transform to 2-(2,2-dicyano-1-hydroxyaminoethenyl)pyrroles **2a**,**c**, the concentration of which reaches 12% after 1 h (^{1}H NMR).

Unexpectedly, on treatment with hydroxylamine in THF (50–55 °C, 1 h), the pyrrolizine **4a** transforms to diamidotrioxime **10a** in 61% yield. Formation of the latter is likely a result of pyrrolizine ring opening, exchange of ethylthio group for hydroxylamine and addition of the latter to both nitrile groups.

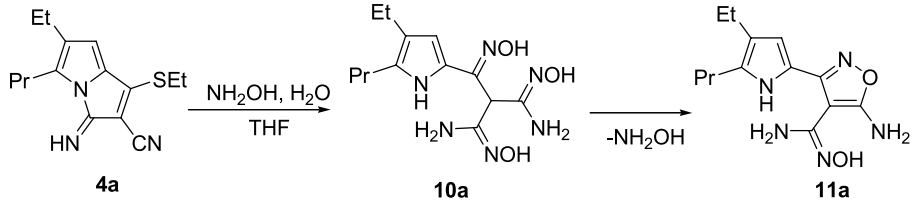
On longer heating (50–55 °C, 4 h and 20–25 °C, 12 h), the treatment of the pyrrolizine **4a** with hydroxylamine results in 5-aminoisoxazole with an amidoxime moiety, **11a**, a product of intramolecular cyclization of diamidtrioxime **10a** with elimination of a hydroxylamine molecule (Scheme 10).

The only result of replacing methanol by THF in the reaction of the pyrrolizine **4c** with hydroxylamine is lower yield of the pyrrolizine **7c** (20%).

Structures of 5- (**3a–h**, **11a**) and 3-aminoisoxazoles **5e–h** were reliably confirmed by a series of ^{1}H and ^{13}C NMR experiments including homo- (NOESY, COSY) and heteronuclear (HMBC and HSQC) 2D correlations. Additionally, using the 2D HSQC technique optimized for the value of the direct ^1J(H,N) coupling constant, which equals 90 Hz, ^{15}N chemical shifts for nitrogen atoms in 3- and 5-amino groups were obtained. They are in agreement with the known values.[16]

The ^{1}H NMR spectra of compounds synthesized show peaks of the pyrrole ring protons as a doublet (H-3 in compounds **3a–c**, **3e–g**, **5e–g**) or as a multiplet, corresponding to a spin system of ABX type (H-3,4 in compounds **3d**,**h**, **5h**), as well as broadened peaks of NH protons of pyrrole, amino and carbamoyl moieties. The major difference of ^{1}H NMR spectra of 3- and 5-aminoisoxazoles is that amino group protons in 3-aminoisoxazoles **5e–h** resonate in the 5.61–5.74 ppm region, whereas in 5-aminoisoxazoles **3e–h**, this resonance is observed at 6.92–7.53 ppm (at 8.33–8.48 ppm in 5-aminoisoxazoles **3a–d**).

In the 2D HMBC spectrum of 3-aminoisoxazole **5g**, the protons of 3-amino group, representing a rather narrow singlet in ^{1}H NMR spectrum (in DMSO), show cross-peaks with the ^{13}C signals at 162.1 ppm (isoxazole C-3) and 98.5 ppm (isoxazole C-4). The peak of H-3 in the pyrrole ring has cross-peaks with the ^{13}C resonances of quaternary carbon atoms in the pyrrole ring and the signal at 162.9 ppm, assigned to C-5 in isoxazole.



Scheme 10.

Analysis of 2D NOESY spectra[17] allows to determine exactly the position of $CONH_2$ group as C-4. This group has NOE with H-3 proton and 3- or 5-amino group.

The formation of aminoisoxazoles can be revealed by IR spectroscopy: infrared absorption of the nitrile group in the spectra of aminoisoxazoles **3e–h**, **5e–h** (ν CN in isoxazoles **3a–d** is in the 2218–2231 cm^{-1} region) disappears and intense bands at 1499–1509 (δ NH) and 1649–1652 cm^{-1} (C=N) appear. Exact assignment of NH groups' absorption bands in the 3180–3445 cm^{-1} region, which represent sharp peaks on the background of a broad band at 3150–3625 cm^{-1} resulting from simultaneous presence of pyrrole, carbamoyl and NH_2 groups in the molecules, seems not possible in the solid state.

In conclusion, mild reaction conditions, availability of the starting reactants and possibility of varying their structure, good preparative yields and high selectivity make our methods prospective for the synthesis of so far unknown polyfunctional pyrrole–isoxazole assemblies, containing, apart from the amino group, also nitrile, amide or other functions originated from CH-acids employed in the synthesis of starting 2-ethenylpyrroles.

3. Experimental

3.1. General methods

IR spectra of compounds synthesized (400–4000 cm^{-1}) were taken in KBr pellets on a Bruker IFS-25 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 250 [250.13 (^1H) and 62.5 (^{13}C) MHz, respectively] and Bruker DPX 400 [400.13 (^1H) MHz] instruments in DMSO-d_6 and referenced to internal HMDS. Structure of compounds was established by ^1H and ^{13}C NMR data obtained using 2D NMR techniques. Assignment of ^{13}C resonances was made by employing the 2D HSQC[18] and HMBC[19] heteronuclear correlation techniques.

For recording of 2D HMBC spectra, pulse sequence delays optimized for values of the direct $^1J(H,C)=145$ Hz and far $^nJ(H,C)=5$ Hz coupling constants were used.

Analysis of reaction mixtures and purity control of compounds obtained were performed by TLC on Silufol UV-254 plates, eluent: diethyl ether–ethanol, 10:1. 3-Amino- and 5-aminoisoxazoles were recrystallized from a 1:1 acetone–water mixture.

The starting 2-(2-cyano-1-ethylthioethenyl)pyrroles were synthesized according to a procedure published in Ref. 12a. Commercial hydroxylamine (Aldrich) was used as a 50% aqueous solution.

3-Amino- (**5e–h**) and 5-aminoisoxazoles **3a–h**, **11a** represent cream-colored lustrous crystalline solids. For some of them, determination of the melting point was not possible (5-aminopyrazoles **3e**,**d**,**g** melt above 350 °C or do not melt at all). 1-Hydroxyamino-3-iminopyrrolizines **7a**,**c** represent orange crystals.

According to elemental analyses, in some cases the compounds incorporate a molecule of water (5-aminopyrazole **3d**) or acetone (1-hydroxyamino-3-iminopyrrolizine **7c**). The presence of acetone in the molecule of the latter was also revealed by ^1H NMR.

3.2. Reaction of 2-(2,2-dicyano-1-ethylthioethenyl)-pyrroles 1a–d with hydroxylamine

General procedure for the synthesis of 5-amino-3-(pyrrol-2-yl)isoxazole-4-carbonitriles **3a–d**. A mixture of 2-(2,2-diacyano-1-ethylthioethenyl)pyrrole (0.40 mmol) and hydroxylamine (132 mg, 2.00 mmol) in 5 mL of methanol was heated at 40–45 °C for 30 min, cooled to room temperature and diluted with water (1:5). Crystalline solid formed was filtered off and recrystallized to give 5-amino-isoxazoles **3a–d**.

3.2.1. 5-Amino-3-(4-ethyl-5-propyl-1*H*-pyrrol-2-yl)-isoxazole-4-carbonitrile (3a). Cream solid (66 mg, 68%), mp 128–129 °C. [Found: C, 63.60; H, 6.87; N, 22.56. $C_{13}H_{16}N_4O$ requires C, 63.93; H, 6.56; N, 22.95%]; ν_{max} (KBr) 3351–3159, 2214, 1662, 1603, 1593, 1530, 1502, 1150, 817, 732 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.08 (1H, br s, N*H*), 8.33 (2H, br s, NH_2), 6.55 (1H, d, $J=1.8$ Hz, *H*-3), 2.47 (2H, m, CH_2-1 of propyl), 2.35 (2H, q, $J=7.4$ Hz, CH_2 of ethyl), 1.51 (2H, m, CH_2-2 of propyl), 1.08 (3H, t, $J=7.4$ Hz, CH_3 of ethyl), 0.84 (3H, t, $J=7.3$ Hz, CH_3 of propyl); δ_C (62.5 MHz, DMSO-d_6) 172.9 (C-5 of isoxazole), 154.5 (C-3 of isoxazole), 132.6 (C-5 of pyrrole), 122.2 (C-4 of pyrrole), 115.1 (C-2 of pyrrole), 114.1 (CN), 110.7 (C-3 of pyrrole), 61.4 (C-4 of isoxazole), 26.9 (C-1 of propyl), 23.1 (C-2 of propyl), 18.3 (C-1 of ethyl), 15.9 (C-2 of ethyl), 13.6 (C-3 of propyl); δ_N (25.36 MHz, DMSO-d_6): −230 (NH), −312 (NH_2).

3.2.2. 5-Amino-3-(5-butyl-4-propyl-1*H*-pyrrol-2-yl)-isoxazole-4-carbonitrile (3b). Cream solid (61 mg, 56%), mp 121–122 °C. [Found: C, 65.95; H, 7.38; N, 20.16. $C_{15}H_{20}N_4O$ requires C, 66.18; H, 7.35; N, 20.59%]; ν_{max} (KBr) 3339–3195, 3162, 2216, 1673, 1650, 1600, 1528, 1500, 1409, 1148, 857, 817, 737 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.07 (1H, br s, N*H*), 8.34 (2H, br s, NH_2), 6.53 (1H, d, $J=1.5$ Hz, *H*-3), 2.29 (2H, m, CH_2-1 of butyl), 1.49 (4H, m, CH_2 of propyl and butyl), 1.26 (2H, m, CH_2-2 of butyl), 1.10 (4H, m, CH_2-3 of butyl, CH_2-2 of propyl), 0.88 (6H, m, CH_3 of butyl and propyl).

3.2.3. 5-Amino-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-isoxazole-4-carbonitrile (3c). Cream solid (74 mg, 81%). [Found: C, 63.17; H, 5.34; N, 25.04. $C_{12}H_{12}N_4O$ requires C, 63.16; H, 5.26; N, 24.56%]; ν_{max} (KBr) 3361–3157, 2231, 1652, 1603, 1531, 1505, 1355, 1240, 807, 737 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.11 (1H, br s, N*H*), 8.36 (2H, br s, NH_2), 6.48 (1H, d, $J=2.4$ Hz, *H*-3), 2.52 (2H, m, CH_2-7), 2.48 (2H, m, CH_2-4), 1.74 (4H, m, CH_2-5,6).

3.2.4. 5-Amino-3-(5-phenyl-1*H*-pyrrol-2-yl)isoxazole-4-carbonitrile (3d). Cream solid (71 mg, 71%). [Found: C, 62.41; H, 4.55; N, 20.63. $C_{14}H_{10}N_4O\cdot H_2O$ requires C, 62.66; H, 4.51; N, 20.88%]; ν_{max} (KBr) 3541–3158, 2212, 1683, 1651, 1598, 1534, 1506, 1485, 1308, 854, 747 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.93 (1H, br s, N*H*), 8.48 (2H,

br s, NH_2), 7.81 (2H, m, H_o–Ph), 7.37 (1H, m, H_p–Ph), 7.23 (2H, m, H_m-Ph), 6.81 (1H, m, *H*-3), 6.70 (1H, m, *H*-4); δ_C (62.5 MHz, DMSO-d_6) 173.0 (C-5 of isoxazole), 154.4 (C-3 of isoxazole), 135.4 (C-5 of pyrrole), 131.6 (C_i–Ph), 128.7 (C_m–Ph), 126.9 (C_p–Ph), 124.8 (C_o–Ph), 119.3 (C-2 of pyrrole), 113.9 (CN), 112.6 (C-3 of pyrrole), 107.7 (C-4 of pyrrole), 62.1 (C-4 of isoxazole); δ_N (25.36 MHz, DMSO-d_6) −235 (NH), −311 (NH_2).

3.3. Reaction of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrroles 1e–h with hydroxylamine

General procedures for the synthesis of 5-amino-3- (**3e–h**) *and 3-amino-5-(pyrrol-2-yl)isoxazole-4-carboxamides* **5e–h**. (A) A solution of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrrole (0.40 mmol) and hydroxylamine (132 mg, 2.00 mmol) in 5 mL of methanol was heated at 40–45 °C for 30 min, then methanol was removed under reduced pressure. The residue was washed with water and recrystallized to give 5-aminoisoxazoles **3e–h**.

(B) A solution of 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrrole (0.40 mmol) and hydroxylamine (132 mg, 2.00 mmol) in 5 mL of THF was heated at 40–45 °C for 1 h, then THF was removed under reduced pressure. The residue was washed with water and recrystallized to give 5-aminoisoxazoles **3e–h**.

(C) A solution of hydroxylamine (297 mg, 4.5 mmol) and NaOH (100 mg, 2.5 mmol) in aqueous methanol (7 mL of methanol and 4 mL of water) was stirred for 10 min, heated to 40–45 °C, then 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)pyrrole **1e–h** (1.5 mmol) was added. 3 min after addition of pyrrole, TLC analysis revealed the formation of 3-iminopyrrolizines **4e–g**. After the end of the reaction (20 min), the mixture was cooled and the solvent was evaporated under vacuum to a 5 mL volume. Precipitate thus formed was filtered off, washed with water and recrystallized to give 3-amino-5-(2-pyrrolyl)isoxazoles **5e–h**.

3.3.1. 5-Amino-3-(4-ethyl-5-propyl-1*H*-pyrrol-2-yl)-isoxazole-4-carboxamide (3e) (by the method A). Cream solid (72 mg, 69%); mp 147–148 °C. [Found: C, 59.38; H, 6.87; N, 21.22. $C_{13}H_{18}N_4O_2$ requires C, 59.54; H, 6.87; N, 21.37%]; ν_{max} (KBr) 3450 – 3192, 1643, 1596, 1541, 1149, 790 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.28 (1H, br s, N*H*), 7.53 (2H, br s, NH_2), 6.71 (2H, br s, CONH_2), 6.30 (1H, d, J=2.0 Hz, *H*-3), 2.47 (2H, m, CH_2-1 of propyl), 2.35 (2H, q, J=7.5 Hz, CH_2 of ethyl), 1.53 (2H, m, CH_2-2 of propyl), 1.09 (3H, t, J=7.5 Hz, CH_3 of ethyl), 0.86 (3H, t, J=7.4 Hz, CH_3 of propyl).

3.3.2. 5-Amino-3-(5-butyl-4-propyl-1*H*-pyrrol-2-yl)-isoxazole-4-carboxamide (3f) (by the method A). Cream solid (88 mg, 76%), mp 103 °C. [Found: C, 61.82; H, 7.54; N, 18.98. $C_{15}H_{22}N_4O_2$ requires C, 62.07; H, 7.59; N, 19.31%]; ν_{max} (KBr) 3451–3194, 1645, 1595, 1540, 1518 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.30 (1H, br s, N*H*), 7.53 (2H, br s, NH_2), 6.69 (2H, br s, CONH_2), 6.27 (1H, d, J=1.8 Hz, *H*-3), 2.48 (2H, m, CH_2-1 of butyl), 2.32 (2H, m, CH_2-1 of propyl), 1.49 (4H, m, CH_2-2 of butyl and propyl), 1.28 (2H, m, CH_2-3 of butyl), 0.88 (6H, m, CH_3 of propyl and butyl); δ_C (62.5 MHz, DMSO-d_6) 171.1 ($CONH_2$), 164.8 (C-5 of isoxazole), 154.1 (C-3 of isoxazole), 131.3 (C-5 of pyrrole), 120.0 (C-4 of pyrrole), 116.3 (C-2 of pyrrole), 110.3 (C-3 of pyrrole), 86.1 (C-4 of isoxazole), 31.9 (C-2 of butyl), 27.4 (C-1 of propyl), 24.8 (C-1 of butyl), 24.1 (C-2 of propyl), 21.8 (C-3 of butyl), 13.8 (C-3 and C-4 of butyl and propyl); δ_N ^{15}N NMR (25.36 MHz, DMSO-d_6) −224 (NH), −279 ($CONH_2$), −316 (NH_2).

3.3.3. 5-Amino-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-isoxazole-4-carboxamide (3g) (by the method A). Cream solid (88 mg, 89%). [Found: C, 58.28; H, 5.86; N, 22.35. $C_{12}H_{14}N_4O_2$ requires C, 58.54; H, 5.69; N, 22.76%]; ν_{max} (KBr) 3440–3191, 1637, 1615, 1594, 1541, 1526, 1509, 1440, 1401, 1355 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.17 (1H, br s, N*H*), 7.53 (2H, br s, NH_2), 6.72 (2H, br s, CONH_2), 6.23 (1H, d, J=1.8 Hz, *H*-3), 2.53 (2H, m, CH_2-7), 2.43 (2H, m, CH_2-4), 1.70 (4H, m, CH_2-5,6); δ_C (62.5 MHz, DMSO-d_6) 171.3 ($CONH_2$), 164.7 (C-5 of isoxazole), 154.2 (C-3 of isoxazole), 129.7 (C-5 of pyrrole), 117.4 (C-4 of pyrrole), 116.8 (C-2 of pyrrole), 109.1 (C-3 of pyrrole), 85.9 (C-4 of isoxazole), 23.4 (CH_2-7), 23.2 (CH_2-5), 22.9 (CH_2-6), 22.5 (CH_2-4); δ_N (25.36 MHz, DMSO-d_6) −221 (NH), −273 ($CONH_2$), −307 (NH_2).

3.3.4. 5-Amino-3-(5-phenyl-1*H*-pyrrol-2-yl)isoxazole-4-carboxamide (3h) (by the method A). Cream solid (78 mg, 73%), mp 182–183 °C. [Found: C, 62.40; H, 4.47; N, 20.57. $C_{14}H_{14}N_4O_2$ requires C, 62.69; H, 4.48; N, 20.90%]; ν_{max} (KBr) 3456–3184, 1646, 1580, 1484, 1449, 1291, 1269 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 12.64 (1H, br s, N*H*), 7.65 (2H, m, H_o–Ph), 7.38 (2H, m, H_m–Ph), 7.21 (1H, m, H_p–Ph), 6.92 (2H, br s, NH_2), 6.67 (1H, m, *H*-3), 6.60 (1H, m, *H*-4).

3.3.5. 3-Amino-5-(4-ethyl-5-propyl-1*H*-pyrrol-2-yl)-isoxazole-4-carboxamide (5e) (by the method C). Cream solid (47 mg, 12%), mp 207–208 °C. [Found: C, 59.29; H, 6.87; N, 21.56. $C_{13}H_{18}N_4O_2$ requires C, 59.54; H, 6.87; N, 21.37%]; ν_{max} (KBr) 3406–3197, 1676, 1652, 1569, 1521, 1455, 1273, 1132, 825, 787 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.93 (1H, br s, N*H*), 7.35 (2H, br s, CONH_2), 6.63 (1H, d, J=2.3 Hz, *H*-3), 5.62 (2H, br s, NH_2), 2.52 (2H, m, CH_2-1 of propyl), 2.37 (2H, q, J=7.4 Hz, CH_2 of ethyl), 1.56 (2H, m, CH_2-2 of propyl), 1.10 (3H, t, J=7.4 Hz, CH_3 of ethyl), 0.90 (3H, t, J=7.4 Hz, CH_3 of propyl). δ_C (62.5 MHz, DMSO-d_6) 164.7 (C-5 of isoxazole), 163.1 ($CONH_2$), 161.9 (C-3 of isoxazole), 132.9 (C-5 of pyrrole), 123.4 (C-4 of pyrrole), 116.6 (C-2 of pyrrole), 111.6 (C-3 of pyrrole), 98.4 (C-4 of isoxazole), 27.2 (C-1 of propyl), 22.4 (C-2 of propyl), 18.3 (C-1 of ethyl), 15.6 (C-2 of ethyl), 13.7 (C-3 of propyl); δ_N (25.36 MHz, DMSO-d_6) −227 (NH), −276 ($CONH_2$), −340 (NH_2).

3.3.6. 3-Amino-5-(5-butyl-4-propyl-1*H*-pyrrol-2-yl)-isoxazole-4-carboxamide (5f) (by the method C). Cream solid (87 mg, 20%), mp 212–214 °C. [Found: C, 61.79; H, 7.37; N, 19.56. $C_{15}H_{22}N_4O_2$ requires C, 62.07; H, 7.59; N, 19.31%]; ν_{max} (KBr) 3450–3191, 1639, 1615, 1585, 1521, 1464, 1262 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.96 (1H, br s, N*H*), 7.41 (2H, br s, CONH_2), 6.60 (1H, d, J=1.8 Hz, *H*-3), 5.61 (2H, br s, NH_2), 2.54 (2H, m, CH_2-1 of butyl),

2.33 (2H, m, CH_2-1 of propyl), 1.50 (4H, m, CH_2-2 of butyl and propyl), 1.31 (2H, m, CH_2-3 of butyl), 0.89 (6H, m, CH_3 of butyl and propyl); δ_C (62.5 MHz, DMSO-d_6) 164.7 ($CONH_2$), 163.1 (C-5 of isoxazole), 161.9 (C-3 of isoxazole), 133.5 (C-5 of pyrrole), 121.5 (C-4 of pyrrole), 116.7 (C-2 of pyrrole), 112.1 (C-3 of pyrrole), 98.5 (C-4 of isoxazole), 31.3 (C-2 of butyl), 27.2 (C-1 of propyl), 24.8 (C-1 of butyl), 23.9 (C-2 of propyl), 21.8 (C-3 of butyl), 13.8 (C-3 and C-4 of butyl and propyl); δ_H (25.36 MHz, DMSO-d_6) −226 (NH), −273 ($CONH_2$), −339 (NH_2).

3.3.7. 3-Amino-5-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-isoxazole-4-carboxamide (5g) (by the method C). Cream solid (133 mg, 36%), mp 231–232 °C. [Found: C, 58.17; H, 5.82; N, 22.63. $C_{12}H_{14}N_4O_2$ requires C, 58.54; H, 5.69; N, 22.76%]; ν_{max} (KBr) 3395–3198, 1655, 1546, 1515, 1428, 1358, 1317, 1268, 1228, 1124, 1108, 1018, 834, 818, 786, 673 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.70 (1H, br s, N*H*), 7.35 (2H, br s, CONH_2), 6.55 (1H, s, *H*-3), 5.61 (2H, br s, NH_2), 2.58 (2H, m, CH_2-7), 2.45 (2H, m, CH_2-4), 1.71 (4H, m, CH_2-5,6); δ_C (62.5 MHz, DMSO-d_6) 164.5 ($CONH_2$), 162.9 (C-5 of isoxazole), 162.1 (C-3 of isoxazole), 131.9 (C-5 of pyrrole), 118.2 (C-4 of pyrrole), 117.2 (C-2 of pyrrole), 110.8 (C-3 of pyrrole), 98.5 (C-4 of isoxazole), 23.2 (CH_2-7), 22.7 (CH_2-5), 22.5 (CH_2-6), 21.9 (CH_2-4); δ_N (25.36 MHz, DMSO-d_6) −223 (NH), −332 (NH_2).

3.3.8. 3-Amino-5-(5-phenyl-1*H*-pyrrol-2-yl)-isoxazole-4-carboxamide (5h) (by the method C). Cream solid (193 mg, 48%), mp 252 °C. [Found: C, 62.40; H, 4.47; N, 20.37. $C_{14}H_{14}N_4O_2$ requires C, 62.69; H, 4.48; N, 20.90%]; ν_{max} (KBr) 3456–3184, 1646, 1603, 1579, 1531, 1484, 1469, 1449, 1290, 1269, 794, 763 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 13.08 (1H, br s, N*H*), 7.67 (2H, m, H_o–Ph), 7.43 (2H, m, H_m–Ph), 7.28 (1H, m, H_p–Ph), 6.88 (1H, m, *H*-3), 6.78 (1H, m, *H*-4), 5.74 (2H, br s, NH_2).

3.4. Reaction of 1-ethylthio-3-iminopyrrolizines 4a,c,4e–g with hydroxylamine

(A) A solution of 3-iminopyrrolizine **4a**,**c** (1 mmol) in 9 mL of methanol was heated with aqueous hydroxylamine (5 mmol) at 45–50 °C for 30 min. The solvent was partially removed under vacuum, water was added, and the precipitate formed was filtered off and washed with aqueous methanol. Recrystallization from aqueous acetone gave 1-hydroxyamino-3-iminopyrrolizines **7a**,**c** in 92 and 99% purity, respectively.

(B) A solution of 3-iminopyrrolizine **4a** (1 mmol) in 5 mL of THF was heated with aqueous hydroxylamine (5 mmol) at 45–50 °C for 1 h. The solvent was then removed under vacuum, 5 mL of a 1:1 methanol–water mixture was added, and the crystalline solid was filtered off to afford the pyrrole **10a** in 61% yield and 90% purity. On standing for several days in DMSO, the purity of the pyrrole **10a** reaches 100%.

(C) A solution of 3-iminopyrrolizine **4a** (1 mmol) in 5 mL of THF was heated with aqueous hydroxylamine (5 mmol) at 45–50 °C for 4 h and then allowed to stand at room temperature for 12 h. The solvent was removed under vacuum, 5 mL of a 1:1 methanol–water mixture was added, and the crystalline solid was filtered off to afford the 5-aminoisoxazole **11a** in 78% yield.

Under conditions described in method C, 3-iminopyrrolizine **4c** with hydroxylamine form 1-hydroxyamino-3-iminopyrrolizine **7c** (45 mg, 20%).

(D) A solution of 3-iminopyrrolizine **4e**–**g** (1 mmol) in 9 mL of methanol was heated with aqueous solution of hydroxylamine (5 mmol) at 45–50 °C for 30 min. The solvent was then removed under vacuum, the residue was analyzed (according to ^{1}H NMR, in all cases, mixtures of 3-aminoisoxazoles **5e**–**g** and 1-hydroxylamino-3-iminopyrrolizines **7e**–**g**, ~2.5:1, are formed) and then recrystallized from aqueous methanol to give either pure 3-aminoisoxazole (in the case of the pyrrolizine **4f**) or a mixture of isoxazoles **5e**,**g** and 1-hydroxyamino-3-iminopyrrolizines **7e**,**g** (in the case of the pyrrolizines **4e**,**g**). After isolation of the isoxazole **5f**, the mixtures obtained and the mother liquor were separated by column chromatography (Al_2O_3, methanol).

3-Aminoisoxazoles **5e**–**g** were isolated in the following yields.

Compound **5e**. 128 mg, 49%.

Compound **5f**. 96 mg, 33%

Compound **5g**. 98 mg, 40%, while 1-hydroxyamino-3-iminopyrrolizines were lost during the workup.

(E) A suspension of 3-iminopyrrolizine **4g** (275 mg, 1 mmol) in 9 mL of propanol was heated with hydroxylamine (330 mg, 5 mmol) at 85 °C for 15 min. After cooling of the reaction mixture to room temperature and partial removal of the solvent under vacuum, crystalline solid was formed. When washed with methanol, these crystals represent pure isoxazole **5g** (98 mg, 40%).

3.4.1. 6-Ethyl-1-(hydroxyamino)-3-imino-5-propyl-3*H*-pyrrolizine-2-carbonitrile (7a). Orange solid (85 mg, 35%), purity 92% (NMR data), mp 222–224 °C. [Found: C, 63.99; H, 6.59; N, 22.69. $C_{13}H_{16}N_4O$ requires C, 63.93; H, 6.56; N, 22.95%]; ν_{max} (KBr) 3392–3071, 2191, 1681, 1656, 1571, 1523, 1292 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.00 (1H, br s, O*H*), 7.77 (2H, br s, N*H*), 6.45 (1H, s, *H*-3), 2.75 (2H, m, CH_2-1 of propyl), 2.34 (2H, q, J=7.6 Hz, CH_2 of ethyl), 1.47 (2H, m, CH_2-2 of propyl), 1.08 (3H, t, J=7.6 Hz, CH_3 of ethyl), 0.86 (3H, t, J=7.1 Hz, CH_3 of propyl).

3.4.2. 1-(Hydroxyamino)-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indole-2-carbonitrile (7c). Orange solid (93 mg, 41%), mp 242–244 °C. [Found: C, 62.78; H, 6.65; N, 19.76. $C_{12}H_{12}N_4O\cdot(CH_3)_2CO$ requires C, 62.94; H, 6.29; N, 19.58%]; ν_{max} (KBr) 3388–3192, 2197, 1711, 1662, 1640, 1570, 1522, 1468, 1281, 1135, 1007, 935, 913, 751 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 10.97 (1H, br s, O*H*), 7.77 (2H, br s, N*H*), 6.34 (1H, s, *H*-3), 2.75 (2H, m, CH_2-5), 2.43 (2H, m, CH_2-8), 1.69 (4H, m, CH_2-6,7); δ_C (62.5 MHz, DMSO-d_6) 154.7 (C-1), 144.1 (C-3), 126.2 (C-10), 125.2 (C-11), 123.7 (C-12), 115.9 (CN), 111.8

(C-9), 60.8 (C-2), 22.9 (CH_2-5), 22.3 (CH_2-7), 22.2 (CH_2-6), 21.9 (CH_2-8); δ_N (25.36 MHz, DMSO-d_6) −299 (NH).

3.4.3. 6-Ethyl-1-(hydroxyamino)-3-imino-5-propyl-3*H*-pyrrolizine-2-carboxamide (7e). δ_H (400.13 MHz, DMSO-d_6) 10.90 (1H, br s, O*H*), 7.84 (2H, br s, *NH*OH, =N*H*), 6.80 (2H, br s, CONH_2), 6.43 (1H, s, *H*-3), 2.75 (2H, m, CH_2-1 of propyl), 2.37 (2H, m, CH_2 of ethyl), 1.55 (2H, m, CH_2-2 of propyl), 1.09 (3H, m, CH_3 of ethyl), 0.86 (3H, m, CH_3 of propyl).

3.4.4. 6-Butyl-1-(hydroxyamino)-3-imino-5-propyl-3*H*-pyrrolizine-2-carboxamide (7f). δ_H (400.13 MHz, DMSO-d_6) 10.90 (1H, br s, O*H*), 7.84 (2H, br s, *NH*OH=N*H*), 6.80 (2H, br s, CONH_2), 6.40 (1H, s, *H*-3), 2.75 (2H, m, CH_2-1 of butyl), 2.30 (2H, m, CH_2-1 of propyl), 1.50 (4H, m, CH_2-2, of butyl and propyl), 1.31 (2H, m, CH_2-3 of butyl), 0.89 (6H, m, CH_3 of butyl and propyl).

3.4.5. 1-(Hydroxyamino)-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indole-2-carboxamide (7g). δ_H (400.13 MHz, DMSO-d_6) 10.88 (1H, br s, O*H*), 7.71 (2H, br s, *NH*OH,=NH), 6.77 (2H, br s, CONH_2), 6.33 (1H, s, *H*-3), 2.75 (2H, m, CH_2-5), 2.45 (2H, m, CH_2-8), 1.70 (4H, m, CH_2-6,7).

3.4.6. 2-[(4-Ethyl-5-propyl-1*H*-pyrrol-2-yl)(hydroxyimino)methyl]-*N*′^{1},*N*′^{3}-dihydroxypropanediimidamide (10a). Cream solid (189 mg, 61%, acetone–water); δ_H (400.13 MHz, DMSO-d_6) 11.25 (1H, br s,=NO*H*), 10.53 (1H, br s, N*H* of pyrrole), 9.07 (2H, br s, NH_2C=NO*H*), 6.39 (1H, d, J=1.5 Hz, *H*-3), 5.26 (4H, d, J=5.2 Hz, NH_2), 4.19 (1H, s, C*H*), 2.45 (2H, m, CH_2-1 of propyl), 2.33 (2H, q, J=7.3 Hz, CH_2 of ethyl), 1.48 (2H, m, CH_2-1 of propyl), 1.07 (3H, t, J=7.3 Hz, CH_3 of ethyl), 0.86 (3H, t, J=7.3 Hz, CH_3 of propyl); δ_C (62.5 MHz, DMSO-d_6) 150.9 (C(NH_2)=NOH), 143.3 (C=NOH), 131.3 (C-5 of pyrrole), 122.1 (C-4 of pyrrole), 120.7 (C-2 of pyrrole), 112.0 (C-3 of pyrrole), 46.7 (CH), 27.1 (C-1 of propyl), 23.2 (C-2 of propyl), 18.3 (C-1 of ethyl), 15.8 (C-2 of ethyl), 13.8 (C-3 of propyl); δ_N (25.36 MHz, DMSO-d_6) −227 (NH), −317 (NH_2).

3.4.7. 5-Amino-3-(4-ethyl-5-propyl-1*H*-pyrrol-2-yl)-*N*′-hydroxyisoxazole-4-carboximidamide (11a). Cream solid (216 mg, 78%), mp 163–164 °C. [Found: C, 56.69; H, 6.92; N, 25.60. $C_{13}H_{19}N_5O_2$ requires C, 56.32; H, 6.86; N, 25.27%]; ν_{max} (KBr) 3452–3125, 2961, 1645, 1614, 1590, 1527, 1489, 1145, 1112, 916, 871, 818, 791 cm^{-1}; δ_H (400.13 MHz, DMSO-d_6) 11.00 (1H, br s, N*H*), 9.34 (1H, br s, O*H*), 6.79 (2H, br s, NH_2C=NOH), 6.33 (1H, d, J=2.4 Hz, *H*-3), 5.45 (2H, br s, NH_2), 2.47 (2H, m, CH_2-1 of propyl), 2.33 (2H, q, J=7.6 Hz, CH_2 of ethyl), 1.52 (2H, m, CH_2-2 of propyl), 1.07 (3H, t, J=7.6 Hz, CH_3 of ethyl), 0.90 (3H, t, J=7.4 Hz, CH_3 of propyl); δ_C (62.5 MHz, DMSO-d_6) 168.2 (C-3 of isoxazole), 154.1 (C-5 of isoxazole), 146.6 (NH_2C=NOH), 130.1 (C-5 of pyrrole), 121.4 (C-4 of pyrrole), 117.2 (C-2 of pyrrole), 109.8 (C-3 of pyrrole), 83.6 (C-4 of isoxazole), 27.1 (C-1 of propyl), 23.2 (C-2 of propyl), 18.5 (C-1 of ethyl), 16.0 (C-2 of ethyl), 13.7 (C-1 of propyl); δ_N (25.36 MHz, DMSO-d_6) −227 (NH), −316 (NH_2 of oxazole), −323 (C(*N*H_2)=NOH).

3.4.8. 2-(2-Carbamoyl-2-cyano-1-hydroxyethenyl)-5-phenylpyrrole (9h). To a heated (45 °C) solution of NaOH (40 mg, 1 mmol) in 1 mL of water and 2 mL of methanol, 2-(2-carbamoyl-2-cyano-1-ethylthioethenyl)-5-phenylpyrrole (**1h**) (150 mg, 0.5 mmol) was added, and the solution was stirred at the same temperature for 1 h. After the end of the reaction, methanol was removed under vacuum, the residue was dissolved in 10 mL of H_2O, acidified with diluted HCl (pH 5). Crystalline solid formed was filtered off, washed with water and recrystallized from benzene to give pyrrole **9h** (109 mg, 86%) as cream crystals, mp 193–194 °C (benzene). [Found: C, 66.64; H, 4.59; N, 16.05. $C_{14}H_{11}N_3O_2$ requires C, 66.40; H, 4.38; N, 16.59%]; ν_{max} (KBr) 3427, 3335, 3245, 2206, 1653, 1593, 1559, 1469, 1455, 1295, 1071, 790, 756, 687 cm^{-1}; δ_H (400.13 MHz, $CDCl_3$) 16.68 (1H, s, O*H*), 9.47 (1H, br s, N*H*), 7.59 (3H, m, H_o–Ph, *H*-4), 7.43 (2H, m, H_m–Ph), 7.25 (1H, m, H_p–Ph), 6.68 (1H, m, *H*-4), 6.01 (1H, br s, CONH_2), 5.48 (1H, br s, CONH_2); δ_H (DMSO-d_6) 11.03 (1H, br s, N*H*), 9.25 (1H, br s, CONH_2), 7.77 (2H, m, H_o–Ph), 7.32 (2H, m, H_m–Ph), 7.16 (1H, m, H_p–Ph), 7.00 (1H, m, *H*-3), 6.49 (1H, m, *H*-4), 6.00 (1H, br s, CONH_2); δ_C (62.5 MHz, DMSO-d_6) 174.8 (=C=OH or =CONH_2), 173.8 (CONH_2 or =C=OH), 137.8 (C-5 of pyrrole), 131.0 (C_i–Ph), 128.8 (C_m–Ph), 127.7 (C_p–Ph), 127.0 (CN), 125.5 (C_o–Ph), 119.3 (C-2 of pyrrole), 117.0 (C-3 of pyrrole), 109.1 (C-4 of pyrrole), 69.1 (=*C*(CN)CONH_2).

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[60]Fullerene adducts with 9-substituted anthracenes: mechanochemical preparation and retro Diels–Alder reaction

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Abstract—Three 9-substituted anthracene derivatives, that is, 9-hydroxymethylanthracene (**2**), 9-methoxymethylanthracene (**3**) and bis(9-anthrylmethyl) adipate (**6**), were chosen as the model compounds to evaluate the reactivity in their Diels–Alder reactions with [60]fullerene and in retro Diels–Alder reactions of the formed cycloadducts. Corresponding adducts **4**, **5** and **7** were prepared in high yields under solvent-free conditions using high-speed vibration milling technique. In order to determine thermal stabilities of adducts **4**, **5** and **7**, their dissociations in the temperature range of 40–65 °C were investigated. Fitting the dissociation rates and temperatures to the Arrhenius equation gives the activation energies of 25.8, 21.8 and 24.9 kcal/mol for compounds **4**, **5** and **7**, respectively.

1. Introduction

[60]Fullerene (C_{60}) behaves as an electron-deficient alkene and exhibits a remarkable array of thermal and photochemical reactions. Over the past ten years, a number of chemical reactions have been devised for fullerene functionalization.[1] The scope for the preparation of fullerene derivatives in solutions is limited due to the low solubilities of fullerenes in common organic solvents. Therefore, alternative synthetic methods such as solvent-free mechanochemical reactions have been explored for fullerene functionalization.[2] Since the first solid-state Reformatsky-type reaction of C_{60} with ethyl bromoacetate and zinc under the high-speed vibration milling (HSVM) conditions was studied in 1996,[3] there have been reports on various reactions of C_{60} under HSVM conditions such as the Prato reaction,[4] reaction of C_{60} with active methylene compounds,[5] Diels–Alder reaction of C_{60},[6] reactions of C_{60} to prepare fullerene dimers and trimers catalyzed by various potassium salts, alkali metals or solid amines,[7] reaction of C_{60} with organic bromides and alkali metals,[8] and reaction of C_{60} with dichlorodiphenylsilane[9] or with dichlorodiphenylgermane[10] in the presence of lithium powder to provide novel fullerene dimers connected by a silicon or a germanium bridge.

The methodologies of fullerene isolation rely upon column chromatography using neutral alumina,[11] silica gel,[12] Norit-A/silica gel,[13] graphite,[14] etc. and modern high-pressure liquid chromatographic techniques.[15] As an alternative to these methods, a convenient purification method by selective complexation of fullerenes with calixarenes[16] was reported. Another method suggested by Rotello's group employed non-chromatographic purification of fullerenes via reversible addition to resin-supported cyclopentadiene/furan[17] or silica-supported cyclopentadiene.[18] Both of the latter two methods for fullerene release requires relatively high temperature (i.e., 180 or 100 °C), thus makes the recovery of the fullerene purification difficult at ambient temperature. Nevertheless, Hirsch and his co-workers have demonstrated that at room temperature the Diels–Alder reaction of 9,10-dimethylanthracene with C_{60} is reversible,[19] and the equilibrium of this reaction has been studied extensively using ^{3}He NMR spectroscopy.[20] It is conjectured that resin- or silica-supported 9,10-bissubstituted anthracene is ideal for the isolation of fullerenes via reversible addition at ambient temperature. As the initial stage for this project, three 9-substituted anthracene derivatives have been chosen as the model compounds. Therefore, the mechanochemical synthesis of the Diels–Alder adducts of C_{60} with 9-substituted anthracene

Keywords: [60]Fullerene, anthracene derivatives; Diels–Alder reaction; Solvent-free; Mechanochemical reaction.
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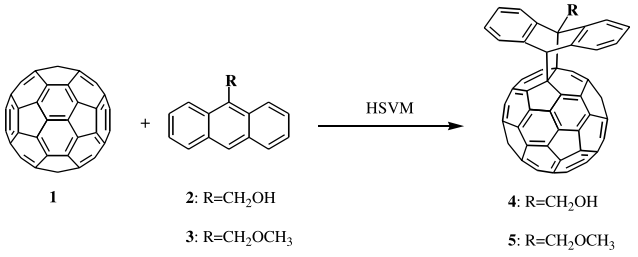
derivatives and the dissociation properties of the Diels–Alder adducts upon heating were investigated. The result of our preliminary experiment indicated that the content of C_{60} in a C_{60}/C_{70} mixture could be increased from 79 to 97% after four cycles of Diels–Alder reaction and thermal dissociation.

2. Results and discussion

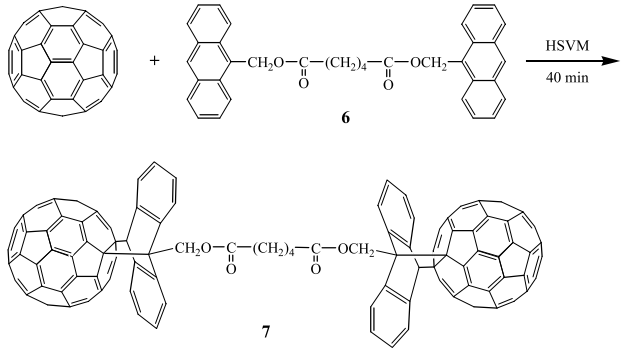
The high symmetry and noted dienophilic reactivity of C_{60} have rendered it an attractive molecule for a variety of [4+2] cycloaddition reactions,[21] which were found to occur at one of the 30 equiv (6:6)-bonds exclusively.[1] Among a large variety of conjugated dienes, anthracene and its derivatives were proved to be versatile reagents for fullerene functionalization.[22] The Diels–Alder mono-adduct of C_{60} and anthracene in solution under conventional thermal conditions was obtained in 39% yield using naphthalene as a solvent at 200 °C for 48 h,[22a] in 13% yield using toluene at 115 °C for 72 h,[22b] and in 25% yield using benzene at 80 °C for 12 h.[22c] Instead of conventional heating, microwave irradiation of a toluene solution of C_{60} and anthracene afforded the mono-adduct in 35% yield.[22e] A better yield (55%) for the mono-adduct was achieved by the solid-state reaction of C_{60} and anthracene for a much shorter reaction time (1 h) using the high-speed vibration milling (HSVM) technique,[6a] exhibiting the advantages of mechanochemical solid-state reactions. Therefore, the HSVM technique was applied to the solid-state Diels–Alder reaction of C_{60} with 9-hydroxymethylanthracene (**2**) or 9-methoxymethylanthracene (**3**), which was conducted at room temperature (Scheme 1).



Scheme 1.

After the treatment of a mixture of 28.8 mg of C_{60} and 10.0 mg (1.2 equiv) of **2** under HSVM conditions for 30 min, fullerene derivative **4** was isolated by column chromatography over silica gel in 70% yield along with 17% of recovered C_{60}. The UV–vis spectrum of **4** showed peaks at 258, 313, 433 and 700 nm. The absorption at around 430 nm is characteristic of [60]fullerene mono-adducts with 1,2-addition pattern. The ^{1}H NMR spectrum of **4** displayed a singlet at 5.81 ppm for the bridgehead CH group, a doublet at 5.71 ppm and a triplet at 2.14 ppm for the CH_2OH group, and multiplets at 7.49–8.01 ppm for the aromatic ring protons. The ^{13}C NMR spectrum of **4** revealed 33 signals with two half-intensity peaks at 146.62 and 146.47 ppm in the range of 124–156 ppm, which were ascribed to the fifty-eight sp^2 carbons of the fullerene core and ten sp^2 carbons of the phenyl ring protons along with two peaks located at 74.00 and 73.92 ppm, which were assigned to the two fullerenyl sp^3 carbons and three peaks in the range of 55–62 ppm due to the rest three sp^3 carbons, consistent with the C_s symmetry. The MALDI-TOF mass spectrum of **4** displayed a peak at *m/z* 911, due to the loss of the OH group, under the MALDI-TOF MS conditions. The IR spectrum of **4** showed four characteristic vibrational frequencies of the fullerene moiety at 1429, 1184, 575 and 527 cm^{-1} as well as a band at 3442 cm^{-1} due to the OH group. Likewise, the HSVM reaction of C_{60} with 1.0 equiv of **3** for 45 min afforded **5** in 74% yield along with 24% of unreacted C_{60}. Compound **5** was also fully characterized by ^{1}H NMR, ^{13}C NMR, IR and UV–vis spectral data, which exhibited similar spectral patterns as adduct **4**.

In order to investigate the feasibility of grafting compounds containing two or more anthracene units to a support for efficient isolation of fullerenes, we selected bis(9-anthrylmethyl) adipate **6** as the model compound to study its cycloaddition with C_{60}. After the treatment of a mixture of 28.8 mg of C_{60} and 12.6 mg (0.6 equiv) of **6** under HSVM conditions for 40 min followed by usual work-up, bis-fullerene compound **7** (mono-adduct for each C_{60}) was obtained in 34% yield together with 24% of unreacted C_{60} (Scheme 2). Although some oligomers/polymers, the main products obtained from the reaction of C_{60} with bis-anthracene compound in solution,[23] were formed simultaneously, symmetrical bis-fullerene compound **7** was obtained preferentially by using our HSVM technique.



Scheme 2.

The UV–vis spectrum of **7** is very similar to those of **4** and **5**. The characteristic absorption at 433 nm in its UV–vis spectrum indicates that compound **7** is a mono-adduct rather than a bis-adduct or multi-adduct of C_{60}. The IR spectrum of **7** showed absorptions at 1741 cm^{-1} for the carbonyl group besides peaks at 1429, 1183, 575, 527 cm^{-1} for the C_{60} skeleton. The ^{1}H NMR spectrum of **7** revealed a singlet at 5.76 ppm for the bridgehead CH group, another singlet at 6.00 ppm for the CH_2O group, two multiplets at 2.36–2.43 and 1.72–1.77 ppm for the CH_2CH_2 fragment along with three peaks at 7.37–7.71 ppm for the aromatic ring protons. The ^{13}C NMR spectrum of **7** was not recorded successfully due to its low solubility. The molecular ion peak of **7** could not be obtained possibly due to the facile retro Diels–Alder dissociation of **7** under the MS conditions.

Liquid-phase reaction of C_{60} with anthracenes **2**, **3** and **6** was also examined to compare with the reactions in the solid

state under HSVM conditions. The reaction of C_{60} with 1.2 equiv of **2** or **3** in toluene at room temperature for 24 h afforded products **4** or **5** in 27 and 28% yield, respectively. These yields are comparable to or higher than those[24] reported for the reaction of C_{60} with other 9-substituted anthracences, for example, 27% based on reacted C_{60} for the reaction of C_{60} with 8-(9-anthryl)-7-oxaoctanoic acid for one week at 60 °C,[24a] 30% for the solid-state photochemical reaction of C_{60} with 9-methylanthracene,[24b] 21% for the photochemical reaction (1 h) or 12% for the thermal reaction (45 °C, 4d) of C_{60} with an anthracene bearing a dendritic poly(amidoamine),[24c] 18% or 19% for the reaction of C_{60} with malonic acid anthracen-9-yl methyl ester ethyl ester or with malonic acid dianthracen-9-yl methyl ester for 48 h at room temperature.[24d] It should be noted that a much higher yield (66%) for the reaction of C_{60} with 9-methylanthracene was achieved by running the reaction in CS_2 at −20 °C for 24 h and repeating the same reaction for the chromatographically isolated reactants for three times.[22h] However, when the reaction of C_{60} with 0.5 equiv of **6** was conducted for 3 days only 4% yield of **7** was obtained along with oligomers/polymers as the main products. This was confirmed by a comparison of the UV–vis spectrum of the main product with that of the reported polymer obtained from the reaction of a bis-anthracene ether[23a] or bis-anthracene ester[23b] with C_{60}. Thus, under HSVM conditions the yields are much higher than those in the liquid phase demonstrating the advantage of solid-state mechanochemical reaction.

As was previously observed with Diels–Alder adducts of C_{60}, adducts **4**, **5** and **7** readily underwent cycloreversion to give C_{60} and component molecules upon heating. The thermal dissociation of the Diels–Alder adducts of C_{60} with amphiphilic anthracenes bearing a carboxylic group have been utilized to prepare Langmiur–Blodgett films of C_{60},[22g] and C_{60} layer and/or mixed layers.[24a] Studies on the kinetic stability of C_{60}-cyclopentadiene adduct[25] and of C_{60}-bisanthracene copolymer have been reported.[23b] In the present work, we chose a temperature range of 40–65 °C to determine kinetic parameters for the dissociation of **4**. The concentration of **4** was determined by HPLC measurements based on calibration curves. As shown in Figure 1, the concentration decay of **4** can be well expressed by first-order kinetics.

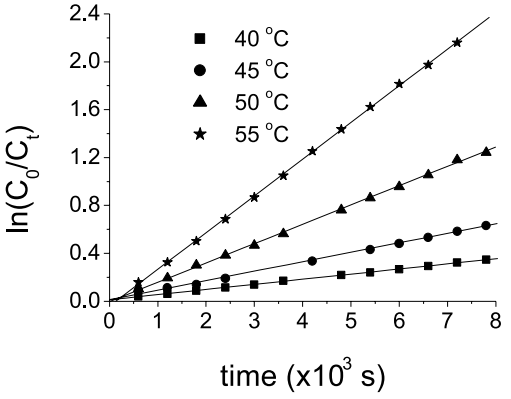


Figure 1. Plot of $\ln(C_0/C_t)$ versus time for the dissociation of **4** in toluene at temperatures of 40, 45, 50 and 55 °C with initial concentration of 1.7655×10^{-4} M.

From Figure 1, the dissociation rates k of **4** at different temperatures were determined and were treated by the Arrhenius equation to give an activation energy of 25.8 kcal/mol for this reaction (Fig. 2).

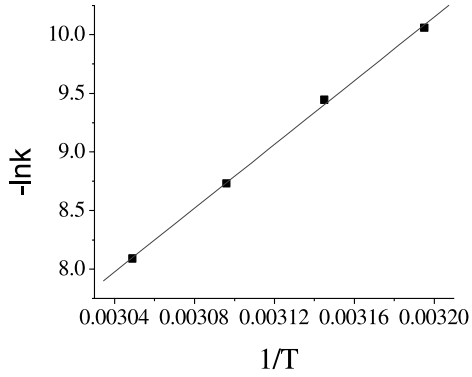


Figure 2. Plot of $-\ln k$ versus $1/T$ (K) for the dissociation of **4**.

The kinetic parameters for the dissociation of **5** and **7** were obtained in the same way. The derived dissociation rate constants of adducts **5** and **7** along with those of adduct **4** are listed in Table 1.

Arrhenius fitting of the $\ln k$ and T for compounds **5** and **7** gives activation energy of 21.8 and 24.9 kcal/mol respectively. The activation energies of compounds **4**, **5** and **7** are comparable to those of other Diels–Alder adducts of C_{60}.[23b,25]

The mono-adducts[25a,25c,25d] and oligomers/copolymers[23] of C_{60} and 9-substituted anthracenes were reported to dissociate at 45–90 °C. Heating at 60 °C for 1.5 h, **4** and **5** resulted in almost complete dissociation to the component species. The dissociation of **7** was different from that of **4** or **5**. Some oligomers/polymers was observed together with the component molecules C_{60} and bis-anthracene **6** at the beginning of the retro-cycloaddition reaction revealing that oligomerization/polymerization took place concurrently with the dissociation. Interestingly, the concentration decay of **7** was still correlated well with first order kinetics, which might indicate that the formation of oligomers/polymers was not the rate-determining step and the dissociation rate of the oligomers/polymers was either not slower than or comparable with that of **7**.

The possibility of separating fullerene mixture via the reversible reaction with silica- or resin-supported anthracene derivatives was examined by running the reaction of a fullerene mixture with anthracene **2**. It was found that the content of C_{60} in a C_{60}/C_{70} mixture could be increased from 79 to 85% after one cycle of Diels–Alder reaction of the fullerene mixture with **2** and then thermal dissociation of the obtained fullerene adducts. The content of C_{60} increased to 89, 93 and 97% after the second, third and fourth cycle, respectively. It is anticipated that a simple non-chromatographic purification of fullerenes could be realized by repeatedly treating the fullerene mixture with mono-substituted anthracenes-grafted silica or resin and then the bound fullerenes are released by thermal heating.

Table 1. Dissociation rates for the cycloreversions of **4**, **5**, and **7**

4		**5**		**7**	
T (°C)	K (s^{-1})×10^4	T (°C)	k (s^{-1})×10^4	T (°C)	k (s^{-1})×10^4
40	0.42817	50	1.50284	40	0.75205
45	0.79099	55	2.65967	45	1.35471
50	1.61481	60	4.37386	50	2.65416
55	3.06760	65	6.73651	55	4.83024

In conclusion, solvent-free mechanochemical reaction using HSVM technique provides an expeditious method for the preparation of mono-adducts of C_{60} and anthracene derivatives. The kinetic parameters for the dissociation of the Diels–Alder products were obtained. The work on the fullerene separation based on the reversible Diels–Alder reactions of fullerenes with 9,10-disubstituted anthracenes is under way.

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in CS_2–$CDCl_3$ or CS_2–DMSO–d_6. MALDI-TOF mass spectra in negative mode were taken on a Bruker BiFlexIII mass spectrometer with 4-hydroxy-α-cyano-cinnamic acid as the matrix. IR spectra were recorded on a Shimadzu 8600 FT IR spectrometer. UV–vis spectra were obtained on a Shimadzu UV-2100 PC spectrometer.

All solvent-free reactions were performed using a vibration mill that consists of a capsule and a milling ball made of stainless steel. The capsule containing the milling ball was fixed in a home-built vibration arm, which was vibrated vigorously at a rate of 3500 cycles per minute and conducted at room temperature.[7b]

C_{60} (>99.9%) were purchased from 3D Carbon Cluster Material Co. of Wuhan University in China. **2**[26] and **3**[27] was synthesized according to the procedures described in literature. All other commercial available reagents are of analytical grade.

3.1.1. HSVM reaction of C_{60} with anthracene 2. A mixture of C_{60} (28.8 mg, 0.04 mmol), **2** (10.0 mg, 0.048 mmol) was vigorously shaken by HSVM for 30 min. The combined reaction mixture from two runs was separated on a silica gel column with toluene as the eluent to afford recovered C_{60} (10.0 mg, 17%) and adduct **4** (51.7 mg, 70%). Spectral data of adduct **4**: ^{1}H NMR (300 MHz, CS_2–$CDCl_3$) δ 8.01 (2H, d, J=7.3 Hz), 7.80 (2H, d, J=7.5 Hz), 7.58–7.49 (4H, m), 5.81 (1H, s), 5.71 (2H, d, J=5.1 Hz,), 2.14 (1H, t, J=5.1 Hz, –OH); ^{13}C NMR (75 MHz, CS_2–DMSO-d_6 with $Cr(acac)_3$ as relaxation agent, all 2C unless indicated) δ 155.81, 153.42, 146.62 (1C), 146.47 (1C), 145.71, 145.56, 145.48, 145.26, 145.23, 144.65, 144.51, 144.44 (4C), 144.37 (4C), 143.75, 143.70, 142.00, 141.74, 141.69, 141.37, 141.25, 141.20, 141.13, 140.81, 140.52 (4C), 140.36, 139.24, 137.56, 136.05, 135.95, 126.15, 126.08, 125.42, 124.64, 74.00 (1C, sp^3-C of C_{60}), 73.92 (1C, sp^3-C of C_{60}), 61.48 (1C), 58.00 (1C), 55.41 (1C); IR (KBr) ν_{max} 3442, 2921, 2859, 1511, 1458, 1429, 1184, 1066, 741, 712, 575, 527 cm^{-1}; UV–vis (CCl_3) λ_{max} 258, 313, 433, 700 nm; MALDI-TOF MS m/z 911 (M^- −OH).

3.2. Reaction of C_{60} with anthracene 2 in toluene solution

A mixture of C_{60} (28.8 mg, 0.04 mmol) and anthracene **2** (10 mg, 0.048 mmol) in toluene (25 mL) was stirred at room temperature for 24 h. After condensation in vacuo, the residue of the reaction mixture was separated on a silica gel column with toluene as the eluent to afford unreacted C_{60} (19.9 mg, 69%) and **4** (10.0 mg, 27%).

3.2.1. HSVM reaction of C_{60} with anthracene 3. A mixture of C_{60} (28.8 mg, 0.04 mmol), **3** (8.88 mg, 0.04 mmol) was vigorously shaken by HSVM for 45 min. The combined reaction mixture from two runs was separated on a silica gel column with CS_2 as the eluent to afford recovered C_{60} (14.1 mg, 24%) and adduct **5** (56.0 mg, 74%). Spectral data of adduct **5**: ^{1}H NMR (300 MHz, CS_2-$CDCl_3$) δ 7.79 (2H, d, J=7.4 Hz), 7.70 (2H, d, J=7.4 Hz), 7.49–7.40 (4H, m), 5.75 (1H, s), 5.32 (2H, s), 3.74 (3H, s); ^{13}C NMR (75 MHz, CS_2-$CDCl_3$ with $Cr(acac)_3$ as relaxation agent, all 2C unless indicated) δ 156.12, 153.36, 147.49 (1C), 147.29 (1C), 146.38, 146.26, 146.07, 146.05, 146.00, 145.28, 145.26, 145.22, 145.18, 145.14 (4C), 144.54, 144.41, 142.80, 142.56, 142.53, 142.11, 142.05, 141.95, 141.93, 141.61, 141.29, 141.14, 140.50, 140.12, 138.40, 136.96, 136.62, 127.11, 127.09, 125.54, 125.18, 74.61 (1C, sp^3-C of C_{60}), 74.25 (1C, sp^3-C of C_{60}), 73.37 (1C), 59.41 (1C), 58.95 (1C), 55.23 (1C); IR (KBr) ν_{max} 2921, 2859, 1456, 1422, 1172, 1096, 738, 708, 595, 575, 525 cm^{-1}; UV–vis (CCl_3) λ_{max} 258, 312, 433, 700 nm; MALDI-TOF MS m/z 942 (M^-).

3.3. Reaction of C_{60} with anthracene 3 in toluene solution

A mixture of C_{60} (28.8 mg, 0.04 mmol) and anthracene **3** (10.7 mg, 0.048 mmol) in toluene (25 mL) was stirred at room temperature for 24 h. After condensation in vacuo, the residue of the reaction mixture was separated on a silica gel column with CS_2 as the eluent to afford unreacted C_{60} (17.0 mg, 59%) and **5** (10.6 mg, 28%).

3.3.1. Preparation of bis-anthracene 6. A mixture of 9-hydroxymethylanthracene (2.08 g, 10 mmol), adipic acid (0.73 g, 5 mmol) and 4-dimethylaminopyridine (0.12 g, 1 mmol) was dissolved in dry acetonitrile (60 mL) and stirred for 10 min, 1,3-dicyclohexylcarbodiimide (2.27 g, 11 mmol) was then added. After refluxed for 4 h, the reaction mixture was filtered when hot. The filtrate was allowed to stand overnight at room temperature to give a light yellow solid. Recrystallization from 5% ethyl acetate in petroleum ether (60–90 °C) gave **6** (1.40 g, 53%) as

yellow needle-shaped crystals. Selected spectral data of bis-anthracene **6**: mp 180–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (2H, s), 8.29 (4H, d, J=8.8 Hz), 8.00 (4H, d, J=8.8 Hz), 7.56–7.46 (8H, m), 6.13 (4H, s), 2.30–2.27 (4H, m), 1.64–1.61 (4H, m); IR (KBr) ν_{max} 2931, 1728, 1622, 1464, 1447, 1417, 1388, 1254, 1177, 1155, 1058, 959, 903, 883, 866, 787, 732 cm^{-1}.

3.3.2. HSVM reaction of C_{60} with bis-anthracene 6. A mixture of C_{60} (28.8 mg, 0.04 mmol), **6** (12.6 mg, 0.024 mmol) was vigorously shaken by HSVM for 40 min. The combined reaction mixture from two runs was separated on a silica gel column with toluene/CS_2 (1:3 v/v) as the eluent to afford recovered C_{60} (13.6 mg, 24%) and **7** (26.8 mg, 34%). Spectral data of **7**: ^{1}H NMR (300 MHz, CS_2-$CDCl_3$) δ 7.71–7.69 (4H, m), 7.60–7.57 (4H, m), 7.44–7.37 (8H, m), 6.00 (4H, s), 5.76 (2H, s), 2.43–2.36 (4H, m), 1.77–1.72 (4H, m); IR (KBr) ν_{max} 2921, 2859, 1741, 1459, 1429, 1183, 1157, 738, 713, 575, 527 cm^{-1}; UV–vis (CCl_3) λ_{max} 257, 314, 433, 703 nm.

3.4. Reaction of C_{60} with bis-anthracene 6 in toluene solution

A mixture of C_{60} (28.8 mg, 0.04 mmol) and 0.5 equiv of anthracene **6** (10.5 mg, 0.02 mmol) in toluene (25 mL) was stirred at room temperature for 3 days. After condensation in vacuo, the residue of the reaction mixture, was separated on a silica gel column with toluene/CS_2 (1:3 v/v) as an eluent to afford unreacted C_{60} (22.5 mg, 78%) and **7** (1.6 mg, 4%).

3.5. Retro Diels–Alder reaction kinetics of adducts 4, 5 and 7

High-pressure liquid chromatography (HPLC) analysis was conducted on an Agilent 1100 liquid chromatograph with a diode-array detector (DAD) using a Cosmosil Buckyprep column (4.6×250 mm) with toluene as the eluent at 1 mL/min. The detector was set at 326 nm and a series of **4**, **5** and **7** of known concentrations was run through the HPLC to establish a quantitative correlation curve between the peak area and the substrate concentration. In the range of concentrations used, a linear relationship between these two variables was found for the mono-adducts of fullerene and anthracene derivatives. In the kinetic study, the concentration was determined from the calibration curve for each substrate.

3.6. HSVM reaction of a fullerene mixture with anthracene 2 and dissociations of fullerene adducts

After the reaction of a fullerene mixture (30.0 mg, C_{60}/C_{70}=79:21) and anthracene **2** (10.0 mg, 1.2 equiv) was milled for 30 min, the reaction mixture was dissolved in toluene and monitored by HPLC on the Cosmosil Buckyprep column. The HPLC analysis showed that the ratio of unreacted C_{60} and C_{70} in the reaction mixture changed to 74:26. Anthracene adducts of C_{60} and C_{70} (26.6 mg) were obtained by separation of the reaction mixture on a silica gel column with toluene as the eluent. The isolated fullerene adducts was dissolved in 25 mL of toluene and heated to 85 °C for 1 h in the presence of 68.3 mg of dimethyl acetylenedicarboxylate, and then was analyzed by HPLC, which indicated that the ratio of liberated C_{60} and C_{70} was 85:15. The same procedure was repeated for the C_{60}-enriched sample and the content of C_{60} was 89, 93, 97% after the second, third and fourth cycle, respectively.

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Ionic liquid promoted palladium-catalyzed Suzuki cross-couplings of *N*-contained heterocyclic chlorides with naphthaleneboronic acids

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Abstract—Suzuki cross-couplings of *N*-contained heterocyclic chlorides with naphthaleneboronic acids in the ionic liquids can be performed with excellent yield. The use of ILs appears to be advantageous in comparison with the conventional organic solvent; products with good purity and higher yield were obtained with shorter reaction time, the product isolation was simple and the ILs could be reused.

1. Introduction

Ionic liquids (ILs), especially those derived from 1,3-diakylimidazolium cation, are attractive clean media for various applications.[1] The ILs exhibit obvious advantageous properties including wide liquid range, good thermal and chemical stability, high ionic conductivity, negligible vapor pressure, and the potential for recycling. Because of these properties, ILs are regarded as 'Green' solvents which provide an excellent medium for performing transition metal catalyzed reactions such as Heck reaction,[1b,2] Diels–Alder reaction,[3] and Suzuki cross-coupling reaction.[1a,c,4]

Suzuki cross-coupling reaction is a versatile method for the carbon–carbon bond formation, especially in the synthesis of biaryls.[5a,b] However, the reaction carried out in conventional organic solvents suffers from several drawbacks including high catalyst consumption, high reaction temperature, decomposition of catalyst, and poor reagent solubility. Recently, these problems were resolved successfully by the use of ILs in place of conventional organic solvents in Suzuki cross-coupling reactions for the synthesis of biaryls.[1a,c,4] The highly polar nature of ILs exhibits immiscibility with many organic solvents, offering unique properties for recycling and phase-switching techniques.

Most of the previous researches on Suzuki cross-coupling reaction in ILs focused on the biaryl synthesis. We set out to examine whether the beneficial effects of ILs were extendable to the synthesis of quinoline and isoquinoline heterocyclic compounds, which have recently attracted great attention in emitting materials for organic light-emitting diodes (OLEDs).[6] The efficient synthesis of these compounds is desired for reducing the manufacturing cost and accelerating the production of OLEDs.

2. Results and discussion

The yields of quinoline and isoquinoline heterocyclic compounds are from conventional organic solvents frequently low. For example, the reaction of 1-chloroquinoline with 1-naphthalene boronic acid using toluene as solvent (Fig. 1) was not a clean process affording 2-naphthalin-1-yl-quinoline in a 57.8% yield and two by-products: [2,2′] biquinolinyl (12.2%) and [1,1′]-binaphthalenyl (1%) after 24 h reaction. To improve this reaction, we tried the same reaction in two ILs-[bmim][BF_4] and [emie][BF_4] (Table 1, entries 1 and 2). Apparently, the results obtained in the ILs are far superior to that in toluene. There are no impurities such as [2,2′]biquinolinyl and [1,1′]binaphthalenyl after reaction except desired product and reactants. This result suggests that the Suzuki cross-coupling in ILs is a clean reaction. While Welton reported that increasing the size of the *N*-substituent on the imidazole ring from [emim]$^+$ to [bmim]$^+$ lead to an improved yield for biaryls,[4d] our data revealed that [emim][BF_4] gave a better yield for 2-naphthalin-1-yl-quinoline. Therefore, [emim][BF_4] IL was chosen for the subsequent experiments in this work.

Keywords: Suzuki coupling; Heterocyclic compound; Ionic liquids.
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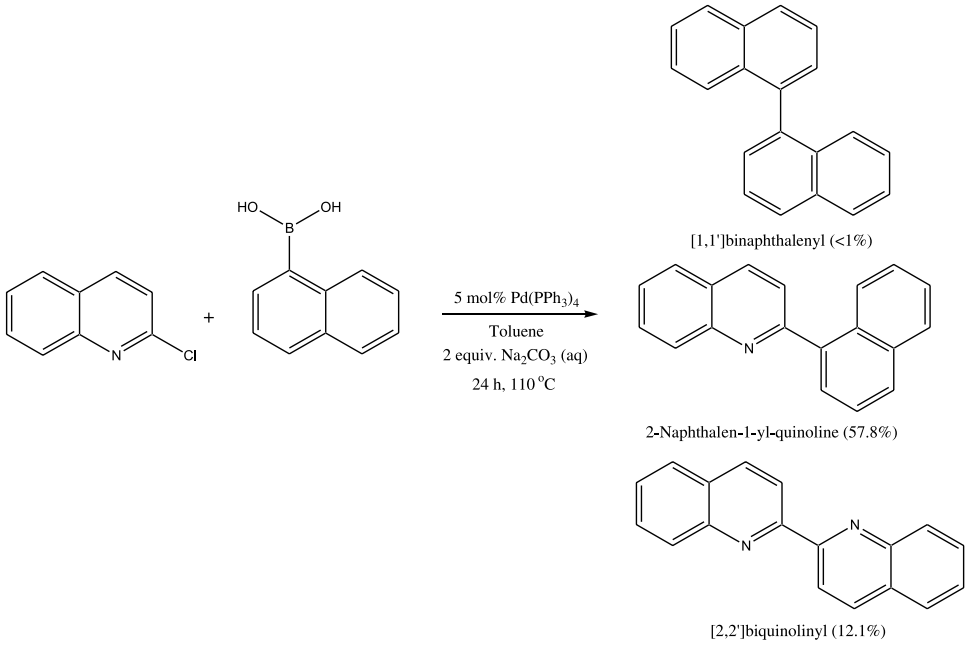


Figure 1. The original Suzuki cross-coupling.

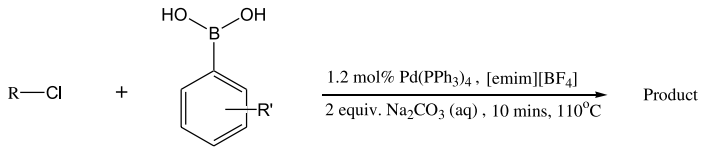
Previous literature showed that, in Suzuki cross-coupling reaction, chlorobenzene was a practically non-reactive substrate affording only traces of biaryl.[1a,7] Similar behavior is observed for the 2-chloronaphthalene (Table 1, entry 8) in this work. We speculate that introducing nitrogen atom to the ring would improve the reactivity. Indeed, the results shown in Table 1 (entries 1–7 and 9) indicate that the yield is greatly improved with the presence of nitrogen atom on the same ring with chlorine. When nitrogen atom is not on the same ring with chlorine, however, no desired product is obtained (Table 1, entries 10 and 11). It is possible that when nitrogen atom is near the chlorine, the electron-rich effect of the lone pair electrons on nitrogen atom favors the oxidative-addition step (Step 1 in Fig. 2)[1c,5] of the reaction course. These results identifies that the lone pair of nitrogen atom has materialized a new life for electron-poor substrates by helping them work efficiently in oxidative-addition of Suzuki reaction. It is noticed that the yield for 2-naphthaleneboronic acid (Table 1, entries 3, 5, and 7) is lower than for 1-naphthaleneboronic acid (Table 1, entries 2, 4 and 6). Probably this is due to the slower rate-determining reductive-elimination step (Step 3 in Fig. 2) in the reaction course resulting from the conformation of the palladium-2-naphthaleneboronic complexes.

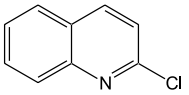
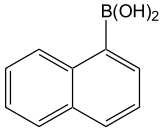
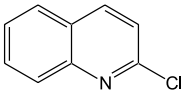
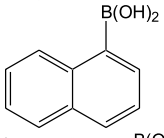
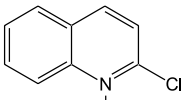
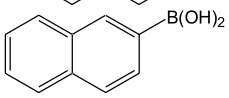
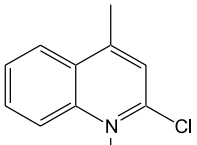
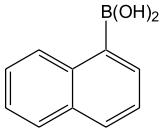
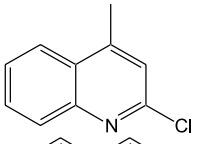
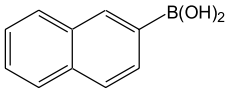
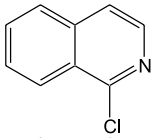
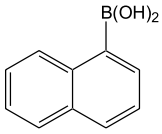
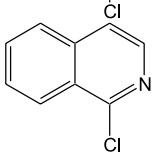
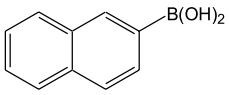
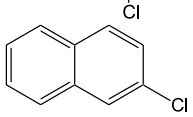
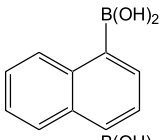
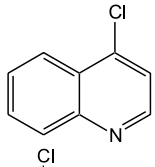
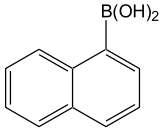
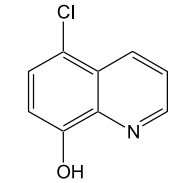
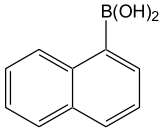
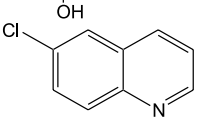
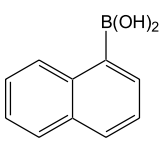
The effect of different palladium catalysts on the reaction was examined. The standard catalyst-$Pd(PPh_3)_4$ was found to be efficient (Table 2, entry 4). However, this Pd(0)-catalyst is very air-sensitive, unstable and thus difficult to handle. In addition, it is fairly expensive. These problems could be overcome by using the Pd(II)-catalyst in place of $Pd(PPh_3)_4$. As shown in Table 2 (entry 1), $Pd(PPh_3)_2Cl_2$ provides a yield (82%) slightly higher than $Pd(PPh_3)_4$ does. The similar efficiency of these two catalysts suggests that both catalysts may form the same catalytically active intermediate complex-$[(PPh_3)_2Pd(emim)Cl]^+$ in the reaction.[4d] On the other hand, when $Pd(OAc)_2$ was used as the catalyst without any (PPh_3) ligand in the reaction solution, the product yield was only 23% (Table 2, entry 2) with catalyst decomposition-black solid formed in solution. However, when $Pd(OAc)_2$ was used together with 2 equiv of ligand-PPh_3, the yield was greatly raised to 63% (Table 2, entry 3), indicating that $Pd(OAc)_2$ has reacted with ligand-PPh_3 to form the catalytically more effective $[(PPh_3)_2$-$Pd(emim)Cl]^+$ complex without catalyst decomposition, which apparently is critical for the reaction to be effective. After the product was separated by extraction, the ionic liquid reaction bath was reused in subsequent reactions. It was found that the product yield dropped to 46% in the second run, indicating that part of the palladium catalyst might have lost to the ethyl ether extractant during the separation step of the previous run. However, the yield was recovered when another portion of the palladium catalyst was added to the recycled ionic liquid, indicating that the ionic liquid itself is indeed recyclable.[8]

3. Conclusions

In summary, this paper reports for the first time the use of ILs as reaction medium for the Suzuki cross-coupling synthesis of heterocyclic compounds from quinoline and isoquinoline with naphthaleneboronic acids. The use of ILs appears to be advantageous in comparison with the conventional organic solvent; products with good purity and higher yield were obtained with shorter reaction time, the product isolation was simple and the ILs could be reused. Further investigations concerning the utility of different ILs for the synthesis of other types of heterocyclic compounds and the relationship between substrates, catalysts are currently in progress.

Table 1. Scope of the Suzuki cross-coupling reaction in [emim][BF_4]



Entry	Substrate	Boronic acid	Product	Yield (%)[a,b]	R_f[c]
1			**1**	75[d]	0.35
2			**1**	79	0.35
3			**2**	43	0.47
4			**3**	81	0.31
5			**4**	61	0.44
6			**5**	80	0.45
7			**6**	52	0.18
8			**7**	0	—
9			**8**	53	0.13
10			**9**	0	—
11			**10**	0	—

[a] Isolated yields.
[b] All reactions were monitored by TLC.
[c] Ethyl acetate:*n*-hexane (1:10).
[d] [bmim][BF_4].

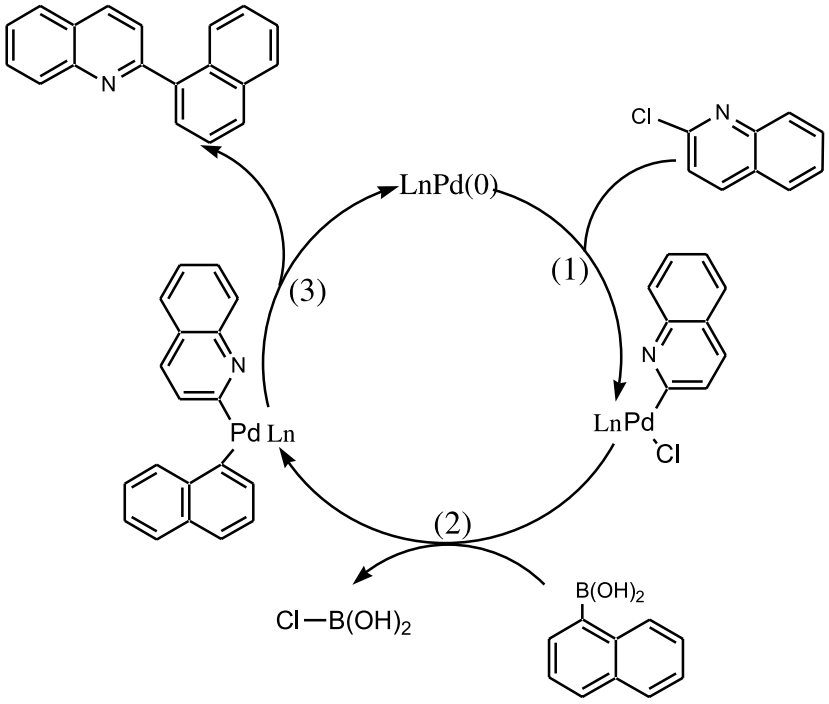
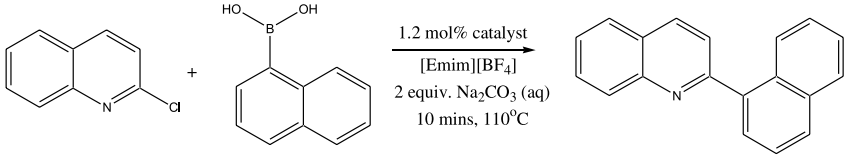


Figure 2. Cycle for the palladium-catalyzed Suzuki cross-coupling reaction.

Table 2. Alternative palladium catalytic systems in [emim][BF_4]



Entry	Palladium source	PPh_3 (equiv with respect to Pd)	Yield (%)[a,b]
1	$Pd(PPh_3)_2Cl_2$	None	82
2	$Pd(OAc)_2$	None	23
3	$Pd(OAc)_2$	2	63
4	$Pd(PPh_3)_4$	None	79
5	2nd run	None	46

[a] Isolated yields.
[b] All reactions were monitored by TLC.

4. Experimental

4.1. Instrumentation

^1H NMR spectra were taken in $CDCl_3$ on a Bruker AMX-400 (400 MHz) system using TMS as internal standard. EI Mass spectra were collected with a Bruker APEX II, and HREI Mass spectra were acquired using a MAT-95XL high resolution mass spectrometer.

4.2. General information

1. All materials were obtained from Aldrich or TCI and used without further purification.
2. All reactions were carried out under an atmosphere of nitrogen in oven-dried-glassware with magnetic stirring.
3. [emim][BF_4] and [bmim][BF_4] were prepared according to reported procedures.[1b]

4.3. General procedure for Suzuki cross-coupling in [emim][BF_4]

In a two-necked round-bottomed flask (25 mL) equipped with a reflux condenser, 2-chloroquinoline (3.06 mmol, 1 equiv) was added to a suspension of $Pd(PPh_3)_4$ (1.2 mol%) in [emim] [BF_4] (6 mL) at ambient temperature under nitrogen. The reaction mixture was heated to 110 °C (oil bath temperature) with rapid stirring affording a yellow catalytic solution. After cooling to ambient temperature, to the yellow solution was added with 1-naphthaleneboronic acid (3.06 mmol, 1 equiv) and a solution of Na_2CO_3 (6.43 mmol, 2.1 equiv) in water (3 mL). The reaction mixture was again heated to 110 °C with rapid stirring for 10 min. After cooling, the mixture was extracted with

diethyl ether (3×15 mL), the combined extracts were washed successively by brine, water and dried ($MgSO_4$). Diethyl ether was removed under reduced pressure and then purified by flash chromatography.

4.3.1. 2-Naphthalen-1-yl-quinoline (1). Table 1, entry 2, yield 79%. White powder. Mp 96.5–96.8 °C. EIMS: *m/z* 255, $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29–8.33 (m, 2H), 8.11 (d, $J=8.4$ Hz, 1H), 7.98–7.92 (m, 3H), 7.80 (t, $J=8.4$ Hz, 1H), 7.76–7.73 (m, 2H), 7.64–7.59 (m, 2H), 7.54–7.46 (m, 2H). HREIMS Calcd for $C_{19}H_{13}N$: 255.1048. Found 255.1046. Anal. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.09; H, 5.17; N, 5.42.

4.3.2. 2-Naphthalen-2-yl-quinoline (2). Table 1, entry 3, yield 43%. White powder. Mp 146.9–153.9 °C. EIMS: *m/z* 255, $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (s, 1H), 8.42–8.36 (m, 3H), 8.12–8.02 (m, 3H), 7.90–7.81 (m, 3H), 7.61–7.55 (m, 3H). HREIMS Calcd for $C_{19}H_{13}N$: 255.1048. Found 255.1049. Anal. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.36; H, 5.13; N, 5.44.

4.3.3. 4-Methyl-2-naphthalen-1-yl-quinoline (3). Table 1, entry 4, yield 81%. White powder. Mp 125.6–128.2 °C. EIMS: *m/z* 269, $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.23 (d, $J=8.4$ Hz, 1H), 8.10 (t, $J=9.5$ Hz, 2H), 7.94 (t, $J=6.8$ Hz, 2H), 7.77 (t, $J=8.4$ Hz, 1H), 7.71 (d, $J=6.8$ Hz, 1H), 7.65–7.45 (m, 6H). HREIMS Calcd for $C_{20}H_{15}N$: 269.1204. Found 269.1200. Anal. Calcd for $C_{20}H_{15}N$: C, 89.19; H, 5.61; N, 5.20. Found: C, 88.52; H, 5.68; N, 5.01.

4.3.4. 4-Methyl-2-naphthalen-2-yl-quinoline (4). Table 1, entry 5, yield 61%. White powder. Mp 122.2–126.9 °C. EIMS: *m/z* 269, $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1H), 8.35 (dd, $J=8.6$, 1.6 Hz, 1H), 8.22 (d, $J=8.6$ Hz, 1H), 8.03–7.98 (m, 3H), 7.90–7.88 (m, 2H), 7.74 (td, $J=7.0$, 1.6 Hz, 1H), 7.58–7.52 (m, 3H). HREIMS Calcd for $C_{20}H_{15}N$: 269.1204. Found 269.1205. Anal. Calcd for $C_{20}H_{15}N$: C, 89.19; H, 5.61; N, 5.20. Found: C, 88.71; H, 5.61; N, 5.15.

4.3.5. 1-Naphthalen-1-yl-isoquinoline (5). Table 1, entry 6, yield 80%. Pale-yellow powder. Mp 126–129.7 °C. EIMS: *m/z* 255, $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (d, $J=5.6$ Hz, 1H), 8.00 (d, $J=7.8$ Hz, 1H), 7.96–7.93 (m, 2H), 7.77 (d, $J=5.6$ Hz, 1H), 7.70 (td, $J=7.8$, 1.1 Hz, 1H), 7.64–7.58 (m, 3H), 7.50–7.32 (m, 4H). HREIMS Calcd for $C_{19}H_{13}N$: 255.1048. Found 255.1046. Anal. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.19; H, 5.17; N, 5.43.

4.3.6. 1-Naphthalen-2-yl-isoquinoline (6). Table 1, entry 7, yield 52%. Pale-yellow powder. Mp 156.1–160.5 °C. EIMS: *m/z* 255, $[M]^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, $J=5.8$ Hz, 1H), 8.19 (s, 1H), 8.17 (d, $J=8.5$ Hz, 1H), 8.01 (d, $J=8.5$ Hz, 1H), 7.96–7.91 (m, 3H), 7.84 (dd, $J=8.5$, 1.7 Hz, 1H), 7.74–7.69 (m, 2H), 7.59–7.53 (m, 3H). HREIMS Calcd for $C_{19}H_{13}N$: 255.1048. Found 255.1049. Anal. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.16; H, 5.15; N, 5.40.

4.3.7. 4-Naphthalen-1-yl-quinoline (8). Table 1, entry 9, yield 53%. Pale-yellow powder. Mp 145.0–146.0 °C. EIMS: *m/z* 255, $[M]^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 9.04 (d, $J=4.4$ Hz, 1H), 8.31 (d, $J=8.5$ Hz, 1H), 8.03–7.96 (m, 2H), 7.76 (t, $J=7.9$ Hz, 1H), 7.62 (t, $J=7.9$ Hz, 1H), 7.54–7.34 (m, 7H). HREIMS Calcd for $C_{19}H_{13}N$: 255.1048. Found 255.1049. Anal. Calcd for $C_{19}H_{13}N$: C, 89.38; H, 5.13; N, 5.49. Found: C, 89.06; H, 5.16; N, 5.45.

Acknowledgements

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8. After completing the reaction, we added diethyl ether for extraction and a tri-phase system with ILs, water and diethyl ether phases could be formed. The aqueous phase which was saturated with $KHCO_3$ and $K[XB(OH)_3]$ was filtered through sieve and the clean ILs were used for the second runs.

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Electron transfer reactions of tris(polypyridine)ruthenium(III) complexes with organic sulfides: importance of hydrophobic interaction

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Abstract—Ruthenium(III)–polypyridyl complexes, generated from the photochemical oxidation of Ru(II) complexes with molecular oxygen, undergo facile electron transfer reaction with dialkyl and aryl methyl sulfides. The rate controlling electron transfer process is confirmed from the absorption spectrum of the transient sulfide radical cation. The spectrophotometric kinetic study shows that the reaction is of total second order, first order in Ru(III) complex and in the organic sulfide. The reaction rate is susceptible to the change of ligand in $[Ru(NN)_3]^{3+}$ and the structure of organic sulfide.

1. Introduction

Organic sulfides serve an important function in many materials such as coal, organic polymers, biological macromolecules and xenobiotics.[1] They are highly susceptible to oxidation and different pathways have been established depending on the oxidizing species.[2–4] Among these pathways the sulfoxidation of organic sulfide proceeding via sulfide radical cation is a subject of current interest.[5–10] In these oxidation reactions suitable oxidants can remove an electron from a lone pair on the sulfur atom to produce radical cations, important intermediates in a great number of chemical processes, extending from those of industrial importance to biological systems.[11–18] The formation of sulfide radical cation as intermediate has been proposed in electrochemical oxidation,[19] in chemical oxidation with Fe(III),[8] Ce(IV),[20] Cr(VI),[21] Cr(V),[6] Mn(III),[22] Ru(IV),[9] cytochrome P-450,[23,24] peroxidase,[7a,25] in photosensitised oxidation[2,3,18,26–28] and in the irradiation of the charge-transfer complex of sulfides with electron acceptors.[29–31]

Though electron transfer (ET) from the aromatic sulfide to the oxidant as the rate-determining step has been proposed in many oxidation reactions, the formation of sulfide radical cation as the intermediate has only been confirmed in a few studies[5,7,32–34] since the lifetime of sulfide radical cation, $-S-^{+\cdot}$, is short. Recently, Baciocchi, Steenken and others recorded the absorption spectrum of the sulfide radical cation.[5,7,32–34] The sulfide radical cation can undergo deprotonation at a C_α–H bond, C–S fragmentation, oxidation, aromatic substitution and dimerisation.[5,7,11–14,18] After the formation of sulfide radical cation, one of the major products is the sulfoxide, $S^{+\cdot} \rightarrow >SO$. Though the formation of $>S^{+\cdot}$ as the transient has been proposed for the oxidation of organic sulfides, the mechanism for the conversion of $>S^{+\cdot} \rightarrow >SO$ is not yet clearly established, though the process is very important from a biotechnological point of view.[3] Thus, a mechanistic understanding of the processes which lead to the conversion of $>S^{\cdot+}$ into $>S \rightarrow O$ is important.

In our recent study we have proposed an ET mechanism for the iron(III)–polypyridine complexes, $[Fe(NN)_3]^{3+}$, oxidation of organic sulfides based on the successful application of Marcus theory of ET to the reaction.[8] Ruthenium(III)–polypyridine complexes, $[Ru(NN)_3]^{3+}$, are better oxidants than $[Fe(NN)_3]^{3+}$ (vide infra) and they undergo efficient ET reactions with a number of organic and inorganic electron donors.[35–39] Apart from the similarity between Fe(III) and Ru(III) complexes, the study of redox reaction of $[Ru(NN)_3]^{3+}$ complexes with organic sulfides is

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important as Ru(III) complexes carrying organic sulfoxides as ligands are now used as drugs.[40–45]

To confirm the formation of sulfide radical cation as intermediate of the reaction, we have followed the reaction by flash photolysis technique from which we are able to get the transient absorption spectrum supporting the formation of $-S^{+\cdot}-$ and $[>S:\cdot S<]^{+}$ species during the course of reaction.[32] The results of the kinetic and spectral studies on the reaction of five $[Ru(NN)_3]^{3+}$ complexes with 15 aliphatic and aromatic sulfides are presented in this report. Though several chemical and electrochemical methods are available for the generation of Ru(III) from Ru(II) complexes, in the present study Ru(III) complexes have been generated using visible light irradiation of $[Ru(NN)_3]^{2+}$ in the presence of molecular oxygen.[46–49]

2. Results and discussion

The structures of ligands of $[Ru(NN)_3]^{3+}$ and organic sulfides used in the present study are shown in Chart 1. It is important to mention here that the major oxidized organic product of the reaction is the corresponding sulfoxide and the percentage of sulfoxide formed is in the range 60–90% depending on the nature of sulfide and the Ru(III) complex. The details of percentage of sulfoxide formed and product analysis are given in Section 4. The percentage of sulfone formed from this reaction is negligible and the oxidation of sulfoxide to sulfone is slow. The kinetic and mechanistic details of the redox reaction between these Ru(III) complexes and organic sulfoxides under the present experimental conditions have been already published by us.[50]

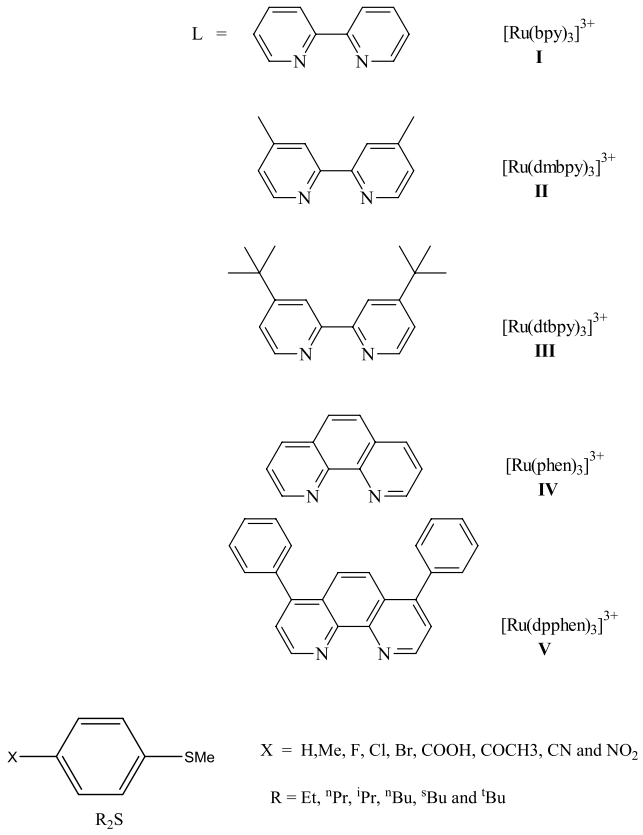


Chart 1. Structures of NN in $[Ru(NN)_3]^{3+}$ and organic sulfides.

The kinetics of oxidation of 15 organic sulfides with five $[Ru(NN)_3]^{3+}$ complexes have been studied by spectrophotometric techniques under pseudo first-order conditions. The progress of the reaction has been followed by measuring the increase in absorbance (OD) of Ru(II) ion formed as the product of the reaction and a sample kinetic run is shown in Figure 1. The linear log OD vs time plot (Figure not shown) and constant k_1 value at different concentration of $[Ru(NN)_3]^{3+}$ indicate that the reaction is first-order in Ru(III). The kinetic data observed at different [sulfide] but at constant [Ru(III)] show that the reaction is first-order in sulfide also (Fig. 2). In order to understand the influence of other parameters on the rate of the reaction, the kinetics of the reaction has been followed at different solvent composition and the results are collected in Table 1. Generally the increase in water content favours the reaction when charge development takes place in the transition state of reaction. As the titled reaction involves electron transfer from sulfide to Ru(III), positive charge is developed on the sulfur centre of the substrate in the transition state. Thus the solvent effect supports the formulation of electron transfer in the rate-controlling step. The behaviour of $[Ru(dpphen)_3]^{3+}$ towards solvent effect seems to be reverse to other Ru(III) complexes which may be attributed to greater hydrophobicity of the ligand (vide infra). The reaction is sensitive to the change of substituent in the phenyl ring of $X–C_6H_4SMe$ and nature of alkyl group in R_2S as well as to the nature of the ligand of $[Ru(NN)_3]^{3+}$ and the

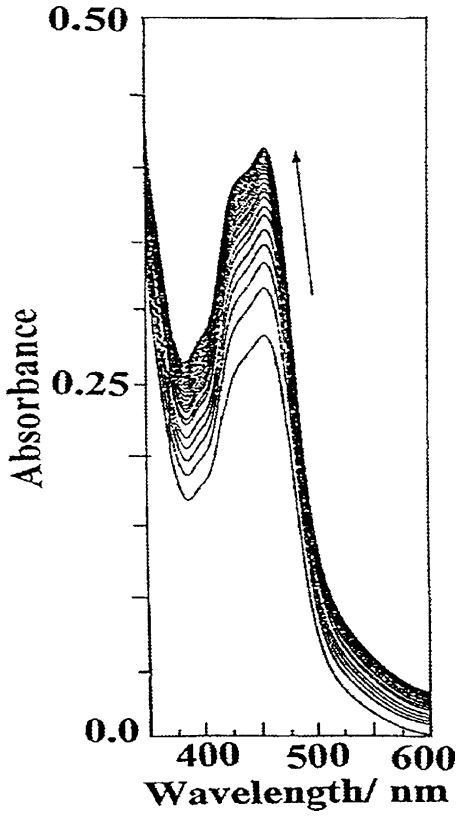


Figure 1. The absorption spectral changes for the reaction between $[Ru(dmbpy)_3]^{3+}$ (5×10^{-5} M) and methyl phenyl sulfide (5×10^{-4} M) at different time intervals (20 s).

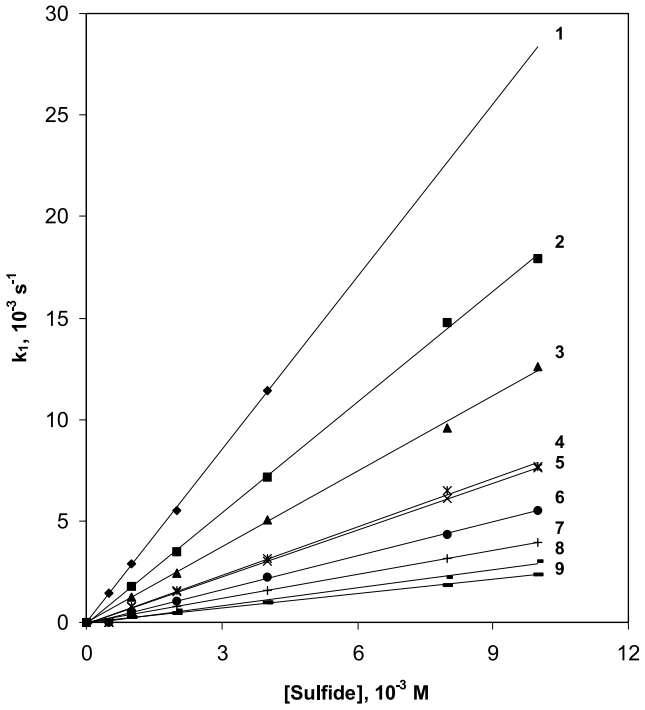


Figure 2. Plot of k_1 vs [sulfide] for the oxidation of aryl methyl sulfides by $[Ru(dmbpy)_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K. The numbers refer to the sulfides given in Table 2a.

observed data are collected in Table 2a and b. The data given in Table 2a show that introduction of electron-donating groups in the phenyl ring of C_6H_5SMe facilitates the reaction and electron-withdrawing groups inhibit the reaction. Application of Hammett equation[51] for the analysis of kinetic data points out that a good correlation is obtained between log k_2 and Hammett σ values (Fig. 3) and the reaction constant values (ρ) are also collected in Table 2a. The ρ value is slightly sensitive to the structure of the ligand of $[Ru(NN)_3]^{3+}$ and varies from -1.0 to -1.2. It is interesting to compare these kinetic results with those observed for the oxidation of organic sulfides with $[Fe(NN)_3]^{3+}$.[8] The k_2 values observed for $[Ru(NN)_3]^{3+}$ are more than two orders higher than the values obtained for $[Fe(NN)_3]^{3+}$ (Table 2a). These results are expected since the reduction potentials of $[Ru(NN)_3]^{3+}$ (1.0 V vs SCE) are higher than those of $[Fe(NN)_3]^{3+}$ (0.8 V vs SCE). When we compare the reaction constant (ρ) values, the ρ value for $[Fe(bpy)_3]^{3+}$ is -3.0 which is high compared to the ρ value of -1.0 obtained for $[Ru(bpy)_3]^{3+}$. Thus the trends in reactivity and ρ values are as expected on the basis of the reactivity–selectivity principle (RSP).

2.1. Steric effect

The k_2 values obtained for dialkyl sulfides (Table 2b) show that the reaction is influenced predominantly by steric rather than polar effects. When we change the nature of the alkyl group from ethyl to *tert*-butyl the rate constant decreases with an increase in the bulkiness of the substrate. If the reaction was controlled by the polar effect, the reverse would have been the trend. It is relevant to recall that the Taft's σ^* values become more negative when we move from ethyl to *tert*-butyl. Thus if the polar effect is predominant, substitution of ethyl by *tert*-butyl would facilitate the reaction which is not observed. It is to be remembered that a negative ρ value was obtained when the kinetic data for aryl methyl sulfides were analyzed in terms of the Hammett equation. Thus, realising the importance of steric effect in this reaction, the k_2 values obtained for six dialkyl sulfides are treated with Taft's steric energy relationship, $\log k = \log k_o + \delta E_s$ where E_s is the steric substituent constant and δ, the susceptibility of reaction to the steric effect.[52] The values of δ obtained for all five Ru(III) complexes are given in Table 2b and the δ value is sensitive to the bulkiness of the ligands. For $[Ru(bpy)_3]^{3+}$ and $[Ru(phen)_3]^{3+}$ complexes the δ value is $\sim$0.25 and for complexes containing bulky ligands it is in the range of 0.50–0.58. But the behaviour of $[Ru(dpphen)_3]^{3+}$ seems to be exceptional and the δ value for the reaction of this complex is 0.29. The exceptional behaviour of $[Ru(dpphen)_3]^{3+}$ deserves explanation. It seems to be reasonable to consider the importance of hydrophobic interactions here since $[Ru(dpphen)_3]^{3+}$ contains a larger number of phenyl groups. Though the presence of such bulky groups may entail a greater steric effect, the greater hydrophobicity of these ligands may offset to some extent the steric effect. The hydrophobic interaction may bring the reactants closer and facilitate the reaction. It has been recently established by us that hydrophobic interactions may overcome electrostatic interactions when excited state $[Ru(dpphen)_3]^{2+}$ is used as the reagent for electron transfer reaction with organic substrates.[53] The results observed here point out that hydrophobic interaction may lead to less steric effect. Thus the present system seems to be one of the rare examples where hydrophobic interaction offsets the steric effect thereby facilitating ET from the electron donor to acceptor. Thus the low δ value ($\sim$0.29) observed with $[Ru(dpphen)_3]^{3+}$ may be attributed to the importance of hydrophobic interaction here. A similar explanation may be extended to the exceptional solvent effect observed with this complex (vide supra). Since the correlation is good with the E_s values, we tried multiple correlation with σ^* and E_s but

Table 1. Effect of varying the solvent composition on the reaction of $[Ru(NN)_3]^{3+}$ with sulfides at 298 K

Solvent composition CH_3CN/H_2O (v/v)	$[Ru(bpy)_3]^{3+}$, k_2, $(M^{-1}\,s^{-1})$		$[Ru(phen)_3]^{3+}$, k_2, $(M^{-1}\,s^{-1})$	$[Ru(dpphen)_3]^{3+}$, k_2 $(M^{-1}\,s^{-1})$
	MPS	DES	MPS	MPS
80:20	475	320	533	1115
70:30	533	515	656	978
60:40	590	532	705	686
50:50	653	543	759	576
40:60	746	611	860	559
20:80	918	705	989	233

(Reaction conditions: $[Ru(NN)_3]^{3+} = 5\times10^{-5}$ M, [MPS]/[DES] $= 4\times10^{-6}$ M and $[H^+] = 4.5$ M).

Table 2a. Second order rate constant (k_2, $M^{-1}\,s^{-1}$) values for the oxidation of *p*-XC_6H_4SMe by $[Ru(NN)_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K

Sl. no.	*p*-XC_6H_4SMe; X=	Oxidation potential, E^o vs SCE(V)	k_2, $M^{-1}\,s^{-1}$		
			$[Ru(bpy)_3]^{3+}$ (1.02 V) (**I**)[a]	$[Ru(dmbpy)_3]^{3+}$ (0.86 V) (**II**)[b]	$[Ru(dtbpy)_3]^{3+}$ (0.87 V) (**III**)[b]
1	Me	1.24	938±25 (16.9)[c]	10.9±0.44 (0.38)[c]	2.85±0.11
2	H	1.34	655±12 (1.40)[c]	2.1±0.08 (0.17)[c]	1.79±0.05
3	F	1.35	481±13	1.44±0.07	1.23±0.04
4	Br	1.41	320±15	0.95±0.03	0.76±0.04
5	Cl	1.37	401±13 (1.01)[c]	0.93±0.05 (0.14)[c]	0.79±0.04
6	COOH	1.51	179±11 (1.18)[c]	0.50±0.02	0.54±0.02
7	$COCH_3$	1.54	138±10	0.45±0.03	0.39±0.02
8	CN	1.61	127±7.5	0.36±0.01	0.28±0.01
9	NO_2	1.70	116±5	0.25±0.01	0.24±0.01
			r=0.993	r=0.990	r=0.985
			ρ=−1.04±0.08	ρ=−1.16±0.05	ρ=−1.14±0.06

Sl. no.	*p*-XC_6H_4SMe; X=	Oxidation potential, E^o vs SCE(V)	k_2, $M^{-1}\,s^{-1}$	
			$[Ru(phen)_3]^{3+}$ (1.02 V) (**IV**)[a]	$[Ru(dpphen)_3]^{3+}$ (0.96 V) (**V**)[a]
1	Me	1.24	1017±36 (51.5)[c]	746±22
2	H	1.34	759±30 (7.3)[c]	583±23
3	F	1.35	642±23	438±17
4	Br	1.41	446±13	324±11
5	Cl	1.37	428±21 (3.9)[c]	299±13
6	COOH	1.51	280±11 (2.86)[c]	171±8.2
7	$COCH_3$	1.54	206±9.3	149±7.5
8	CN	1.61	176±4.9	118±6.5
9	NO_2	1.70	127±4.6	101±4.7
			r=0.997	r=0.991
			ρ=−0.97±0.03	ρ=−0.98±0.05

Reaction conditions: $[Ru(NN)_3]^{3+}=5\times10^{-5}$ M. [a] [Sulfide]=10^{-6} M. [b] [Sulfide]=10^{-3} M and $[H^+]$=4.5 M).
[c] k_2, $M^{-1}\,s^{-1}$ values for the $[Fe(NN)_3]^{3+}$ oxidation of *p*-XC_6H_4SMe collected from Ref. 8.

the correlation was only slightly improved. This analysis indicates the importance of the steric effect in this reaction.

2.2. Formation of sulfide radical cation

In this work we propose that the reaction of $[Ru(NN)_3]^{3+}$ with organic sulfide produces sulfide radical cation. This proposal gets support from the absorption spectrum of the transient, sulfide radical cation, recorded using conventional flash photolysis technique (Fig. 4). The experiment was designed as follows. The reaction mixture consisting of $[Ru(bpy)_3]^{2+}$ and methyl phenyl sulfide (MPS), taken in aqueous CH_3CN (50% v/v), was purged with molecular oxygen for 20 min. Then the reaction mixture was irradiated with flash of light and the absorption spectrum of the reaction solution was monitored at different time intervals. The irradiation of $[Ru(NN)_3]^{2+}$ in the presence of O_2 leads to the formation of Ru(III) which is formed due to the oxidative quenching of $*[Ru(NN)_3]^{2+}$ with molecular oxygen particularly at high $[H^+]$ as per reactions shown in Eqs. 1–5.

$$[Ru(NN)_3]^{2+} \xrightarrow{h\nu} *[Ru(NN)_3]^{2+} \quad (1)$$

$$*[Ru(NN)_3]^{2+} + {}^3O_2 \rightarrow [Ru(NN)_3^{2+}\cdots O_2]* \quad (2)$$

$$[Ru(NN)_3^{2+}\cdots O_2]* \xrightarrow{\text{Electron transfer}} [Ru(NN)_3^{3+}\cdots O_2^{-\cdot}] \quad (3)$$

$$[Ru(NN)_3^{3+}\cdots O_2^{-\cdot}] + H^+ \rightarrow [Ru(NN)_3]^{3+} + HO_2^{\cdot} \quad (4)$$

$$2HO_2^{\cdot} \rightarrow H_2O_2 + O_2 \quad (5)$$

It is pertinent to mention that the reaction of H_2O_2 with organic sulfides is slow.[14] The spectra given in Figure 4 shows two strong absorptions at 300–350 nm and around 510–520 nm. Steenken and others[5,7,32] have assigned the bands at 300–350 and 500–520 nm to the radical cation of sulfide in the monomeric form which are produced by electron-transfer reaction of organic sulfides with $SO_4^{-\cdot}/Tl^{2+}$. From the spectrum of the transient shown in Figure 4 we understand that in addition to the two bands indicated above, other bands appeared at 480 nm (shoulder) and 600–700 nm. In the present study our aim is to confirm the formation of sulfide radical cation as one of the important intermediates of the titled reaction. To establish this, we have recorded the spectrum of the transient of the reaction. The peak at 470 nm was observed recently by Sawaki and co-workers[32] and they assigned the peak at around 460–500 nm to σ-type complex of the sulfur–sulfur two-centre three electron bonded dimers (i.e., σ* type). The peak at 600–700 nm disappears with time. It is known that Ru(III) ion has the absorption maximum at 600–700 nm. Thus these spectral changes show that during the course of the reaction Ru(III) disappears and other products are formed. It is interesting to note that with the increase of time the peak at 310 nm disappears and a new peak at 340 nm appears. In a recent paper Bobrowski et al,[54] have indicated that the absorption band with λ_{max}=340 nm represents a hydroxy–sulfuranyl radical $-\dot{S}-OH$. In the present study, $ArS\bullet(OH)CH_3$ is formed at the expense of $Ar\overset{+\cdot}{S}CH_3$ (Eq. 8, Scheme 1). Thus the appearance of peak at 340 nm may be

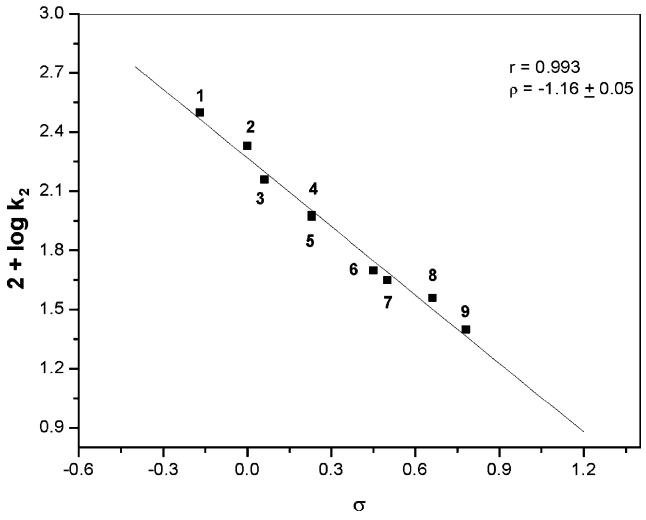
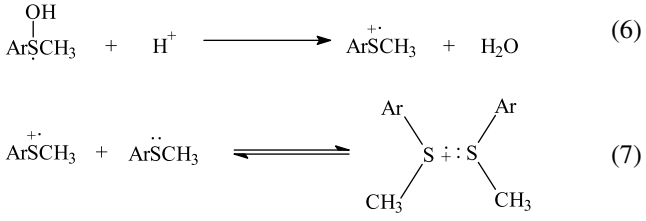


Figure 3. Hammett plot for the oxidation of aryl methyl sulfides by $[Ru(phen)_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K. The numbers refer to the sulfides given in Table 2a.

attributed to $ArS\bullet(OH)CH_3$. As the present reaction has been studied at high $[H^+]$, the presence of high $[H^+]$ facilitates the following processes (Eqs. 6 and 7).



The formation of intermolecularly $>S^+\therefore S<$ bonded dimeric radical cation is confirmed from the peak at 480 nm. In the present study we are able to detect the short lived species $Ar\overset{+\cdot}{S}CH_3$ and dimeric radical cation $>S^+\therefore S<$ by conventional flash photolysis technique with ms time resolution because these species appear to be more stable at high $[H^+]$.[55] This appears to be the first report for the detection of these species using conventional flash photolysis technique. Similar transient absorption spectrum was obtained when $[Ru(phen)_3]^{3+}$ was used instead of $[Ru(bpy)_3]^{3+}$. It has been well established that sulfide radical cation derived from dialkyl sulfide forms sulfide cation dimer more efficiently compared to aromatic sulfides.[18,32] In order to check this, we have recorded the transient absorption spectra using diethyl and di-propyl sulfides also and the transient spectra obtained at different time intervals for the reaction between $[Ru(bpy)_3]^{3+}$ and diethyl sulfide are shown in Figure 5. Here the peak for the dimer at 480 nm is obtained confirming the earlier postulations.[18,56]

2.3. Cyclic voltammetry

Though the E^0 values of all five Ru(III) complexes used in the present study are available in the literature,[57] because of the different reaction conditions used here, the redox potentials were measured using cyclic voltammetry technique (details are given in Section 4). The redox potentials of Ru(III) complexes and organic sulfides are given in Table 2a. The redox potential values measured in the present study are in close agreement with the reported values.[10,39,57]

2.4. Mechanism of the $[Ru(NN)_3]^{3+}$ oxidation of organic sulfides

Ruthenium(III) complexes used in the present study are well-known one-electron oxidants.[35–39] The progress of the

Table 2b. Second order rate constant (k_2, $M^{-1}s^{-1}$) values for the oxidation of R_2S by $[RuL_3]^{3+}$ in aqueous CH_3CN (50% v/v) at 298 K

Sl. no.	Dialkyl sulfides R_2S	Oxidation potential, E^o vs SCE(V)	k_2, M^{-1} s^{-1}		
			$[Ru(bpy)_3]^{3+}$ (1.02 V) (**I**)[a]	$[Ru(dmbpy)_3]^{3+}$ (0.86 V) (**II**)[b]	$[Ru(dtbpy)_3]^{3+}$ (0.87 V) (**III**)[b]
1	DES	1.46	569±15	2.18±0.09	1.60±0.06
2	DPS	1.44	501±18	1.50±0.05	1.13±0.05
3	DIPS	1.44	443±10	1.14±0.06	0.85±0.07
4	DBS	1.46	456±15	1.53±0.07	1.18±0.06
5	DSBS	—	381±13	0.87±0.03	0.65±0.03
6	DTBS	1.46	231±10	0.28±0.02	0.28±0.02
		δ	0.26±0.02	0.58±0.05	0.50±0.04

Sl. no.	Dialkyl sulfides R_2S	Oxidation potential, E^o vs SCE(V)	k_2, M^{-1} s^{-1}	
			$[Ru(phen)_3]^{3+}$ (1.02 V) (**IV**)[a]	$[Ru(dpphen)_3]^{3+}$ (0.96 V) (**V**)[a]
1	DES	1.46	646±26	484±16
2	DPS	1.44	573±20	434±17
3	DIPS	1.44	504±19	371±12
4	DBS	1.46	532±16	397±13
5	DSBS	—	417±15	248±11
6	DTBS	1.46	294±15	189±6.7
		δ	0.23±0.01	0.29±0.03

Reaction conditions: $[Ru(NN)_3]^{3+}=5\times10^{-5}$ M. DES=diethyl sulfide, DPS=dipropyl sulfide, DIPS=diisopropyl sulfide, DBS=dibutyl sulfide, DSBS=di-secondary butyl sulfide, DTBS=di-*tertiary* butyl sulfide.
[a] [Sulfide]=10^{-6} M.
[b] [Sulfide]=10^{-3} M and $[H^+]$=4.5 M.

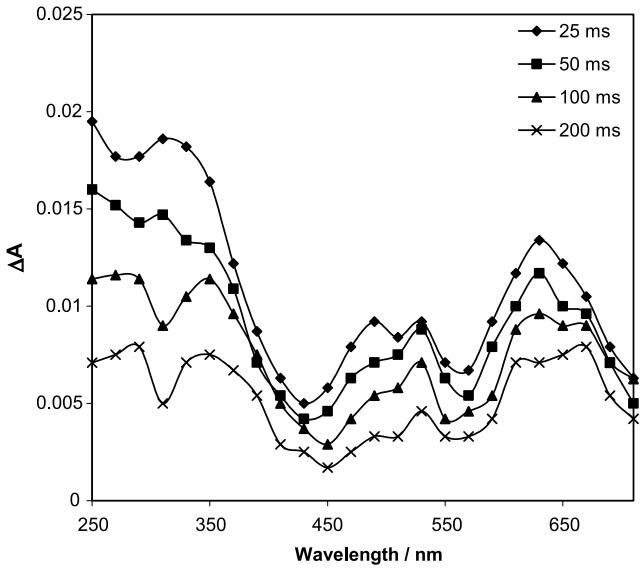


Figure 4. The absorption spectra of transients at different time intervals formed from the reaction of $[Ru(bpy)_3]^{3+}$ with MPS in oxygen-saturated aqueous CH_3CN (50% v/v) solution at 298 K by flash photolysis experiment.

$$ArSMe + [Ru(NN)_3]^{3+} \xrightarrow{k} ArS^{\cdot+}Me + [Ru(NN)_3]^{2+} \quad (8)$$

$$ArS^{\cdot+}Me + H_2O \xrightarrow{fast} ArS(OH)^{\cdot}Me + H^+ \quad (9)$$

$$ArS(OH)^{\cdot}Me + [Ru(NN)_3]^{3+} \xrightarrow{fast} ArS^{+}(OH)Me + [Ru(NN)_3]^{2+} \quad (10)$$

$$ArS(OH)^{\cdot}Me \xrightarrow{fast} ArS(O)Me + H^+ \quad (11)$$

Scheme 1.

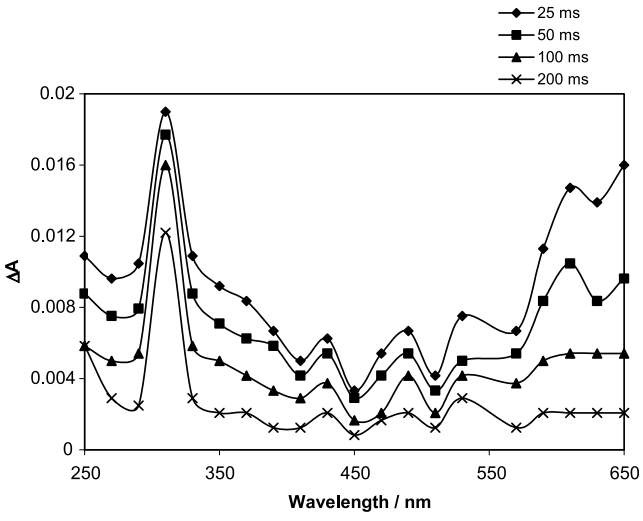


Figure 5. The absorption spectra of transients at different time intervals formed in the electron-transfer oxidation of R_2S with $[Ru(bpy)_3]^{3+}$ in oxygen-saturated aqueous CH_3CN (50% v/v) solution at 298 K by flash photolysis experiment.

reaction has been followed with an increase in OD at 450 nm which is the characteristic absorption of Ru(II) complex (Fig. 1). Thus, Ru(III) is reduced to Ru(II) in the rate controlling step. Further, the formation of sulfide radical cation as a transient is confirmed from its absorption spectrum (Figs. 4 and 5). These experimental observations are strongly in favour of electron transfer (ET) from sulfide to Ru(III) in the rate determining step. The additional support for the ET mechanism comes from the substituents effect study. The reaction constant (ρ) value is around -1.0. This ρ value is close to the value reported for the $Ru^{IV}=O$ oxidation of organic sulfides wherein ET mechanism has been proposed.[9]

The formation of sulfoxide as the major product of the reaction helps us to conclude that the major portion of sulfide radical cation is consumed by the solvent, water or superoxide ion formed due to the oxidative quenching of the excited state Ru(II) ion with molecular oxygen, though fragmentation and back ET may be competing processes. The formation of sulfoxide from sulfide radical cation may be shown as a three step process (Eqs. 9–11). Similar formulation for the conversion of $ArS^{\cdot+}Me$ to ArS(O)Me has been proposed in the polyoxometalate catalysed *tert*-butylhydroperoxide oxidation of organic sulfides.[58]

3. Conclusion

The oxidation of 15 organic sulfides with five $[Ru(NN)_3]^{3+}$ ions proceeds through rate determining electron transfer(ET) from the substrate to the oxidant. The ET nature of the reaction is confirmed by the identification of the sulfide cation radical using flash photolysis technique and formation of Ru(II) ion as the product of the reaction. The metal complex containing dpphen ligand behaves differently from other complexes indicating the importance of hydrophobic interaction in this ET reaction. This study highlights the importance of Ru(III) ions as suitable reagents to have ET reactions with biologically important organic sulfides.

4. Experimental

4.1. Materials

The $[Ru(NN)_3]^{2+}$ complexes (where NN = 2,2′-bipyridine (bpy), 4,4′-dimethyl-2,2′-bipyridine (dmbpy), 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), 1,10-phenanthroline (phen) and 4,7-diphenyl-1,10-phenanthroline (dpphen) were synthesised by known procedures[52,57,59–63] and the purity was confirmed by absorption and emission spectra of the Ru(II) complexes. Our group has already used these complexes for photochemical studies.[53,64,65] The steady-state photolysis of $[Ru(NN)_3]^{2+}$ in 4.5 M H_2SO_4 using a 500 W tungsten–halogen lamp led to the formation of corresponding Ru(III) complex.[46–49] The light beam was made parallel by using a planoconvex lens. The infrared (IR) and ultraviolet (UV) radiations were cut off by passing the light beam through the 5 cm quartz cell filled with water and pyrex glass filter. It was observed that the colour of the solution readily changed from orange-yellow to green during irradiation. The

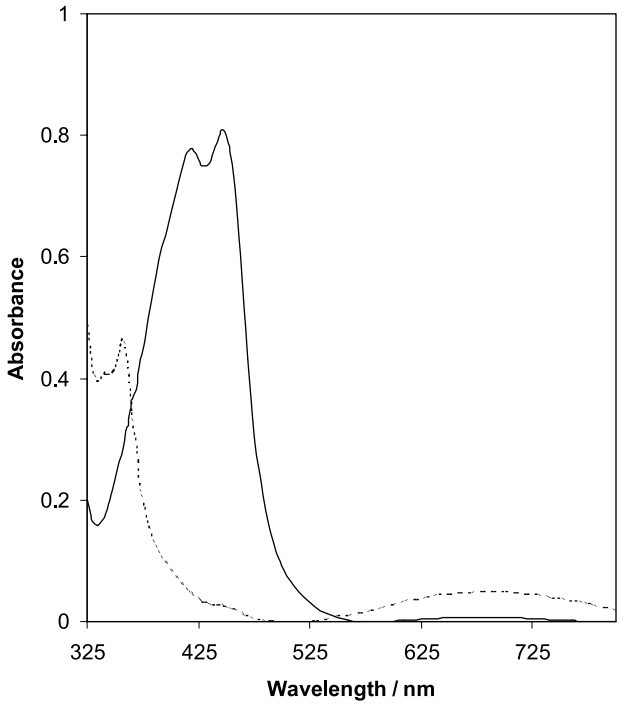


Figure 6. The absorption spectra of (—) $[Ru(phen)_3]^{2+}$ and (– – –) $[Ru(phen)_3]^{3+}$ complexes in 50% CH_3CN.

formation of $[Ru(NN)_3]^{3+}$ complexes was confirmed by recording the absorption spectrum of the irradiated solution. $[Ru(NN)_3]^{3+}$ complexes showed peaks around 420–430 and 650–670 nm.[47,66,67] and the absorption spectrum of $[Ru(phen)_3]^{3+}$ is shown in Figure 6.

para-Methyl phenyl thiol was obtained from Aldrich and converted to sulfide by the known procedure.[68] *p*-Bromo, *p*-cyano, *p*-fluoro and *p*-nitrophenyl methyl sulfides and dialkyl sulfides purchased from Aldrich were used as received. The other sulfides used in the present investigation were prepared and purified by reported procedures.[6,21,26,69–71] All other reagents were of AnalaR grade or used after purification. The kinetic study of the reaction was performed after confirming the purity of the reagents and solvents used in the system.

4.2. Electrochemical measurements

The oxidation potentials of sulfides and the reduction potentials of $[Ru(NN)_3]^{3+}$ complexes were determined using EG and G 273A Princeton Applied Research Potentiostat/Galvanosat equipped with a X–Y-t-recorder. The stock solutions of the metal complexes and sulfides for the electrochemical studies were prepared in aqueous CH_3CN (50% v/v). The supporting electrolyte was 0.1 M $NaClO_4$. A two compartment three electrode cell was used to record the cyclic voltammograms. A glassy carbon working electrode (area = 0.07 cm^2), 1 cm^2 platinum plate counter electrode and a standard calomel reference electrode (SCE) were used in the electrochemical experiments. Cyclic voltammograms were recorded after purging the solution with nitrogen gas for 30 min.

4.3. Conventional flash kinetic spectrometer

Flash photolysis experiments were carried out using an Applied Photophysics Ltd, KN-020 model flash kinetic spectrometer. The cell solution containing an oxygenated aqueous CH_3CN (50% v/v) solution of $[Ru(NN)_3]^{2+}$ and sulfide was subjected to flash photolysis. The reaction between the photogenerated $[Ru(NN)_3]^{3+}$ and sulfide was followed at different wavelengths. The output signal from the PMT was fed into an International Electronics India digital storage oscilloscope and hard copies of the traces were obtained using a printer.

4.4. Kinetic measurements

A JASCO UV–Vis Spectrophotometer (Model 7800) was employed to record the absorption spectra of $[Ru(NN)_3]^{2+}$ and $[Ru(NN)_3]^{3+}$ complexes used in the present study and to follow the electron transfer reactions of $[Ru(NN)_3]^{3+}$ complexes with organic sulfides. The kinetic study was carried out in aqueous CH_3CN (50%, v/v) under pseudo first-order condition. The progress of the reaction was monitored by following the increase in absorbance of $[Ru(NN)_3]^{2+}$ (λ_{max} = 450 nm) at definite time intervals at 298 K.[39]

The pseudo first-order rate constant (k_1) for each kinetic run was evaluated from the slope of linear plot of log OD vs time by the method of least squares. The linearity of each fit is confirmed from the values of correlation co-efficient (r) and standard deviation(s). The second-order rate constant (k_2) is evaluated from the relation $k_2 = k_1/[\text{sulfide}]$.

4.5. Product analysis

In a typical experiment, 0.5 mM of substrate (ArSMe) was added to a 0.5 mM solution of $[Ru(NN)_3]^{3+}$ complex in 5 ml of aqueous CH_3CN (50% v/v). The solution was stirred at 298 K for ~1 h depending upon the nature of sulfide and Ru(III) complex. The products of the reaction were extracted with chloroform and dried and the solvent was removed. Then the resulting residue was analysed by IR spectroscopy and GC. The IR spectrum of the product (sulfoxide) was found to have stretching frequency in the characteristic region 1070–1030 cm^{-1}. The GC analysis (Model GC17A Shimadzu) of the product also indicated the formation of sulfoxide as the only product under the present experimental conditions. Sulfides and sulfoxides were identified by their characteristic retention times and also by co-injuction with authentic samples. The details of the

Table 3. Percentage of sulfoxide formed by the $[Ru(NN)_3]^{3+}$ oxidation of aryl methyl sulfides

p-XC_6H_4SMe; X=	Percentage of sulfoxide formed	
	$[Ru(bpy)_3]^{3+}$	$[Ru(phen)_3]^{3+}$
H	82	69
Me	88	77
OMe	94	82
Cl	65	63
COOH	61	60

Conditions: refer Section 4.

percentage of sulfoxide formed using $[Ru(bpy)_3]^{3+}$ and $[Ru(phen)_3]^{3+}$ as oxidants are given in the Table 3.

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