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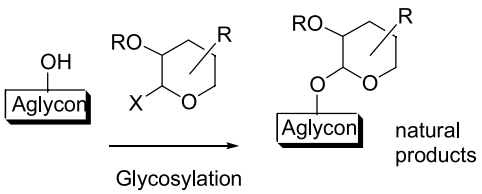
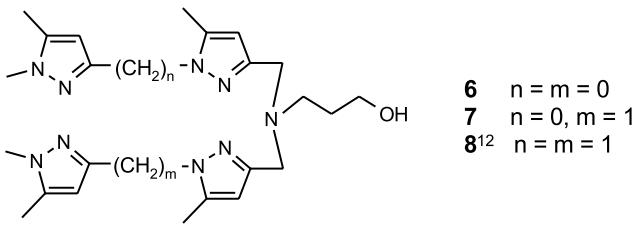
Contents

REPORT

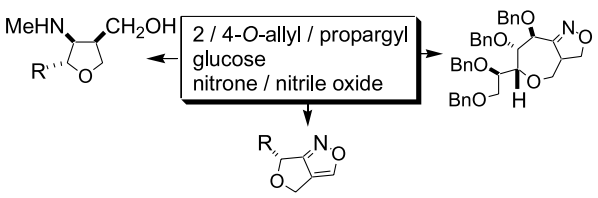


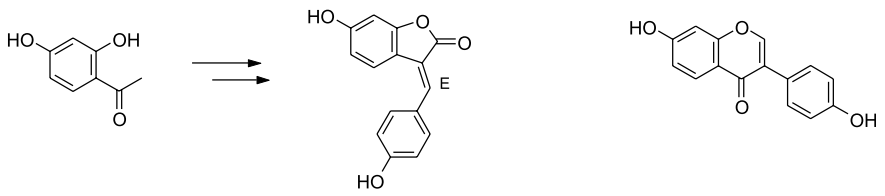
The applications of the *O*-glycosylation reaction for the synthesis of natural products and analogues are reviewed.

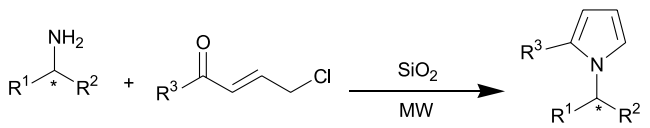
ARTICLES

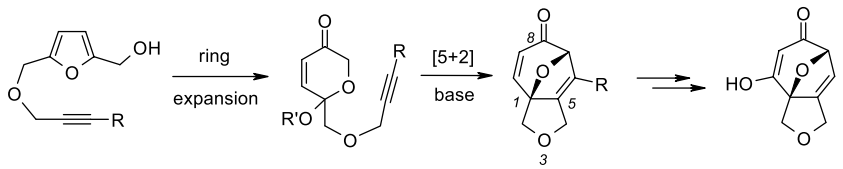


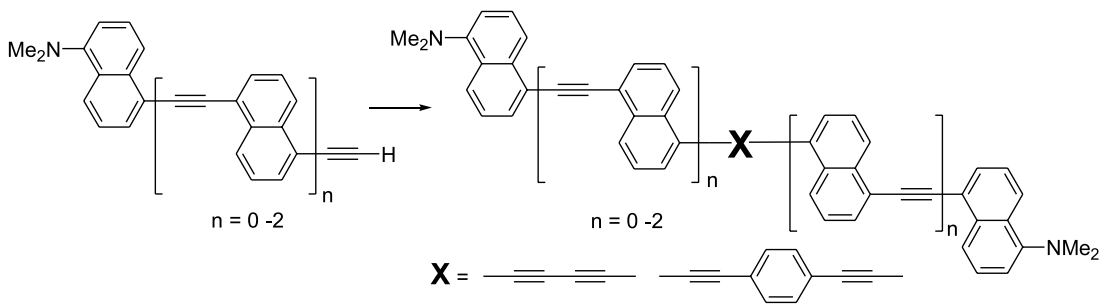
Hg^{2+}, Cd^{2+}, Pb^{2+}, K^{+}, Na^{+} and Li^{+}

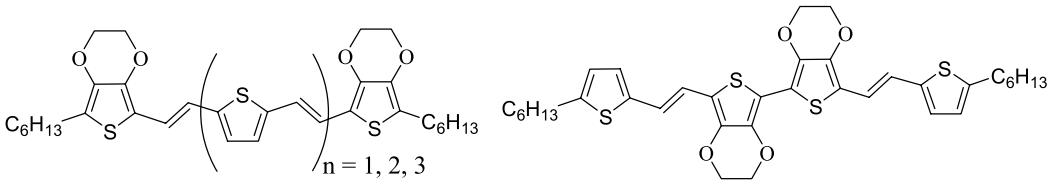




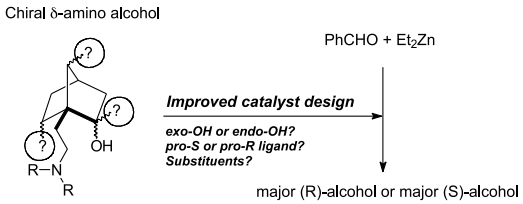


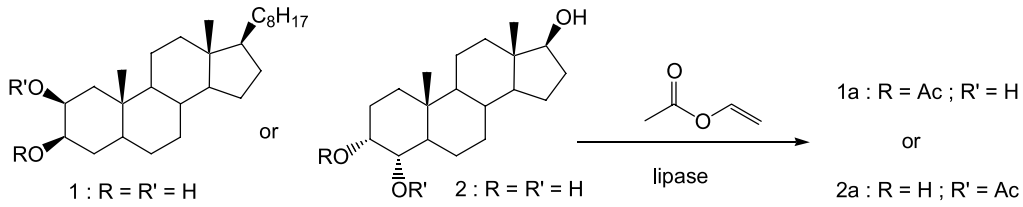




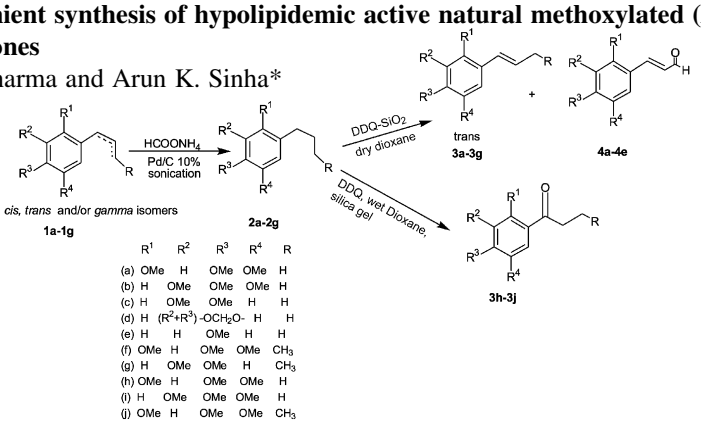


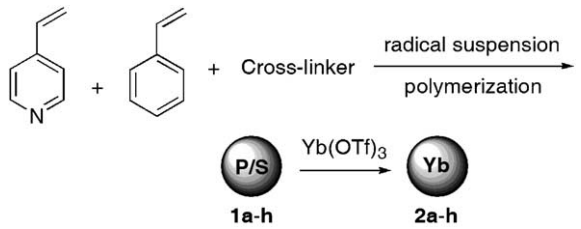
New π-conjugated oligomers based on various combinations of thiophene and EDOT units and double bonds have been synthesized. Optical and electrochemical results evidence the crucial role of the EDOT moiety for modulating the electronic properties of the oligomers.

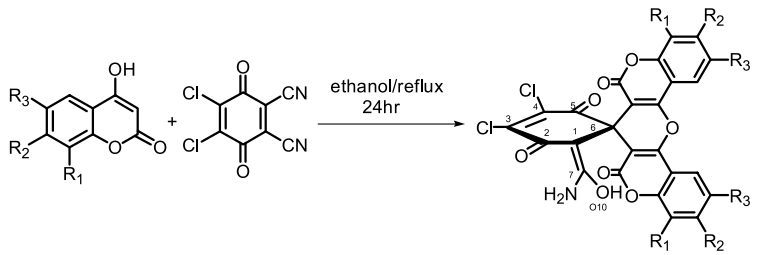


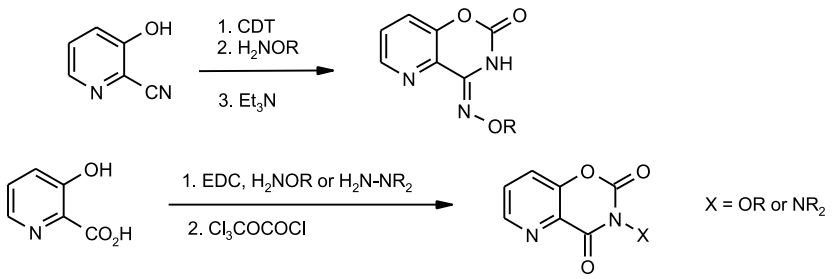


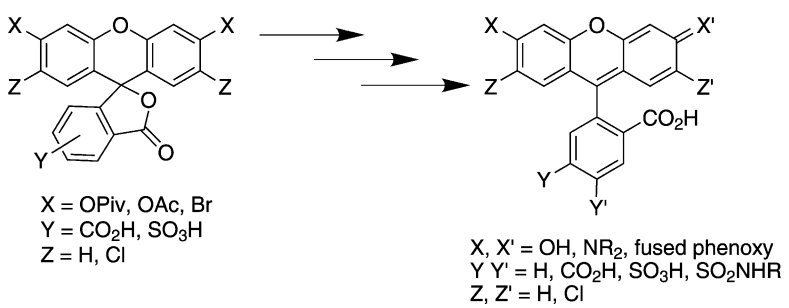
Regioselective lipase-catalysed esterification of a complete set of 2,3- and 3,4-vicinal diols of steroids (i.e., **1** or **2**) gave the corresponding monoacylated derivatives (i.e., **1a** or **2a**).

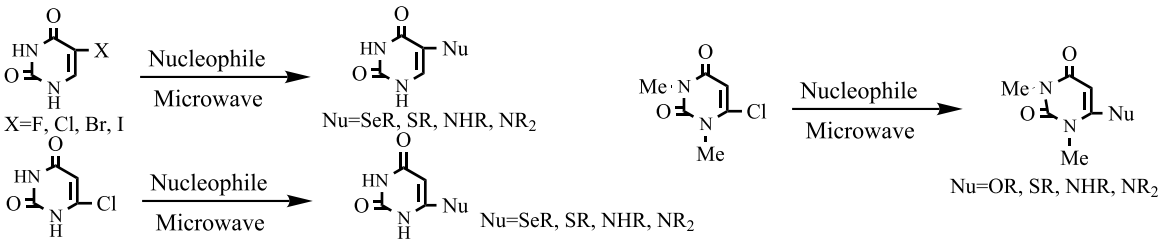


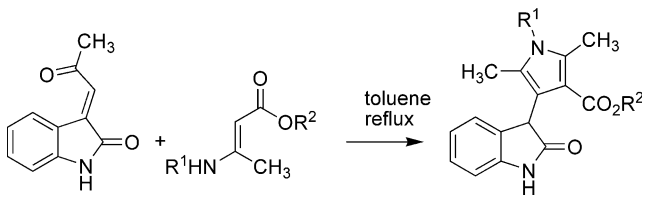












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Use of *O*-glycosylation in total synthesis

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Contents

Keywords: *O*-Glycosylation; Total synthesis.

Abbreviations: Ac, acetyl; ACF, activated carbon fiber; AIBN, 2,2′-azobiisobutyronitrile; Alloc, allyloxycarbonyl; Ar, aryl; AtOH, 7-aza-1-hydroxy-1*H*-benzotriazole; $BF_3(Et_2O)$, boron trifluoride etherate; DMB, 3,4-dimethoxybenzyl; DMTSB, dimethyl(methylthio)sulfonium tetrafluoroborate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BOP, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluoride; BOM, benzyloxymethyl; BTOH, 1-hydroxybenzotriazole; Bu, butyl; Bz, benzoyl; CA, chloroacetyl; CAN, ceric ammonium nitrate; Cbz, benzyloxycarbonyl; Cp, cyclopentadienyl; CSA, 10-camphorsulfonic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DAST, (diethylamino)sulphur trifluoride; Dba, *trans*,*trans*-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; DECP, diethylcyanophosphate; DHP, 3,4-dihydro-2*H*-pyran; DIAD, diisopropylazodicarboxylate; DIBAL, diisobutylaluminiumhydride; DIPEA, diisopropylethylamine; DISAL, methyl 3,5-dinitrosalicylate; DMAP, 4-dimethylaminopyridine; DMB, 3,4-dimethoxybenzyl; DMDO, 2,2-dimethyldioxirane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DMTr, 4,4′-dimethoxytrityl; DMTSB, dimethyl(methylthio)sulfonium tetrafluoroborate; DMTST, (dimethylthio)methylsulfonium trifluoromethane sulfonate; DNA, desoxyribonucleic acid; DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; EDCI, (1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride; EEDQ, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline; Et, ethyl; FMOC, 9-fluorenylmethoxycarbonyl; fuc, fucose; Gal, galactose; GDP, guanosine diphosphate; Glc, glucose; GlcNAc, 2-*N*-acetyl-2-deoxyglucose; GPI, glycosylphosphatidylinositol; HMDS, bis(trimethylsilyl)amide; IDCP, iodonium dicollidine perchlorate; im, imidazolyl; imid, imidazole; LDA, lithium diisopropylamide; Lev, levulinoyl; MCPBA, 3-chloroperoxybenzoic acid; Me, methyl; MMTr, 4-methoxytrityl; MOM, methoxymethyl; MOP, 3-methoxypyridyloxy; Ms, mesyl; MP, 4-methoxyphenyl; NB, nitrobenzyl; NBD, nitrobenzoxadiazole; NBS, *N*-bromosuccinimide; NIS, *N*-iodosuccinimide; NMO, 4-methylmorphine-*N*-oxide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; PEGA, (polyethylene glycol) polyacrylamide; Pent, 4-pentenyl; Pfp, pentafluorophenyl; Ph, phenyl; Phth, phthalimido; Piv, pivaloyl; PMB, *p*-methoxybenzoyl; PNB, *p*-nitrobenzoyl; PPTS, pyridinium 4-toluenesulfonate; Pr, propyl; py, pyridine; RNA, ribonucleic acid; SEM, [2-(trimethylsilyl)ethoxy]methyl; Ser, serine; SLe^x, sialyl Lewis x; TBAB, tetra-*n*-butylammonium bromide; TBAF, tetra-*n*-butylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; TEOC, *N*-trimethylsilylethyloxycarbonyl; TES, triethylsilyl; THF, tetrahydrofuran; THP, tetrahydropyranyl; Thr, threonine; TIPS, triisopropylsilyl; Tf, trifluoromethanesulphonyl; TFA, trifluoroacetic acid; TfOH, triflic acid; Tf_2O, triflic anhydride; Tips, triisopropylsilyl; TMAD, *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; TMU, *N*,*N*,*N*′,*N*′-tetramethylurea; Tol, toluene; TPS, triphenylsilyl; Tr, triphenylmethyl (trityl); Troc, 2,2,2-trichloroethoxycarbonyl; $TrtClO_4$, triphenylmethyl perchlorate; Ts, 4-toluenesulfonyl (tosyl); TsOH, *p*-toluenesulfonic acid; UDP, uridine-5′-diphosphate.

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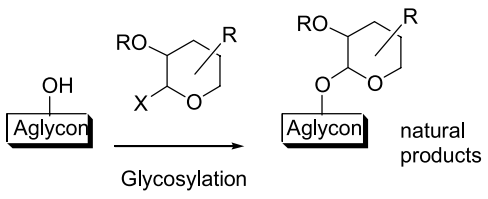
1. Introduction

Carbohydrates are the most abundant group of natural products and the role of sugars as energy and biosynthetic resources (glycolysis, pentose phosphate cycle, etc.), 'energy storage devices' (photosynthesis) and key structural elements in the formation of biological backbones (2-deoxyribose for DNA or *N*-acetylglucosamine for murein) is general knowledge.[1] Carbohydrates and carbohydrate-containing structural moieties are also involved in more active biochemical and bioorganic processes. An enormous amount of precise biological studies of naturally occurring products and the mechanisms of action of these substances have shed light on the biological significance of the glycons of glycoconjugates (glycoproteins, glycolipids) in various domains such as the molecular recognition for the transmission of biological information.[2] Indeed, the presence of the sugars greatly modifies the biological activity of all the drugs. For instance, the glycan chains control the pharmacokinetics of the drugs, such as absorption, distribution, metabolism and excretion. Clearly, the aglycon itself is not active in most instances, as was demonstrated for many antibiotics and antitumour compounds, with erythromycin, daunomycin or amphotericin B being prominent examples. It is now well established that protein- and lipid-bound saccharides play essential roles in many molecular processes impacting eukaryotic biology and disease.[3] Examples of such processes include fertilisation, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organisation into specific tissues. Carbohydrates are found in nature as monomers, oligomers, or polymers, or as components of biopolymers and other naturally occurring substances. As domains of natural products, they play important roles in conferring certain physical, chemical, and biological properties to their carrier molecules. In addition, they have been implicated in many cellular processes, including cell–cell recognition, cellular transport, and adhesion; they appear in all cells in some form or another, for example, as peptido- and proteoglycans, glycoproteins, nucleic acids, lipopolysaccharides or glycolipids.[4] Indeed, carbohydrates are important elements of recognition and specificity in cell–cell interactions,[5,6] for example, as cell surface oligosaccharides,[7,8] for example, tumour-associated antigens,[9] lectins,[10,11] glycoproteins, glycolipids, and immunodeterminants. They also play a part in the mode of action of many drugs as they contribute to a variety of processes, including active transmembrane transport,[12,13] stabilization of protein folding,[14] and enzyme inhibition.[15,16] With this stimulating biological background, the *O*-glycosylation method, which is a crucial synthetic organic methodology to attach sugars to other sugar moieties or other molecules (aglycon), is again becoming more and more important. Since the major historical advance of the Koenigs–Knorr method was shown in 1901, considerable attention has been directed towards the efficiency of the *O*-glycosylation method.[17] From a synthetic standpoint, the efficiency of the *O*-glycosylation reaction generally involves a high chemical yield, regioselectivity, and stereoselectivity. Among these, the high regioselectivity was easily realised by the selective protection of the hydroxyl group of the glycosyl acceptor. Therefore, many organic chemists have focused on the high chemical yield and high stereoselectivity of this reaction. This review concentrates on the applications of the *O*-glycosylation reaction for the synthesis of biologically attractive natural products and analogues except steroidal glycosides, which have been the subject of a recent review (Scheme 1).[18]



Scheme 1. Glycosylations of aglycons in the formation of natural products and analogues.

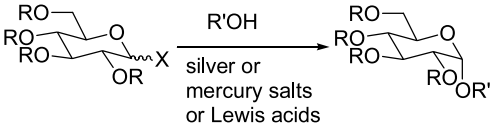
This review is an update of the use of *O*-glycosylation in total synthesis covering the literature from 1993 to date, since early work has already been reviewed.[19] For a survey on the applications of the *O*-glycosylation reaction for the total synthesis of natural products and related compounds, glycosyl donors are roughly classified into five groups,

based on the type of anomeric functional group and their activating methods, which are discussed in an early part of this review: (1) glycosyl halides, (2) 1-*O*-derivatives, (3) 1-*S*-derivatives, (4) glycals, and (5) others. Further recent special methods, providing efficient routes towards glycoconjugates of biological consequence, such as solid-phase synthesis, one-pot sequential glycosylation, and chemoenzymatic or enzymatic methods, are also reviewed in the later sections.

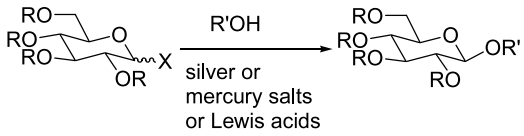
Natural glycoconjugates consist of oligosaccharides, which are glycosidically linked to lipids (diacylglycerol, ceramide, steroids, long-chain fatty alcohols, etc.), to phospholipids (phosphatidylinositol-GPI anchors), to peptides (*O*- and *N*-linkage), and to a combination of all these compounds (as an example, in the GPI-anchored proteins/glycoproteins). Therefore, the synthesis of glycoconjugates consists of the oligosaccharide synthesis, the aglycon synthesis, and their linkage to yield the target molecule. Commonly, glycoconjugate synthesis follows this convergent strategy, hence the glycosidic linkage between the two moieties is generally performed at a very late stage. In some cases—starting from the oligosaccharide—the aglycon is, however, constructed in a linear strategy, because the formation of the final glycosidic linkage is not compatible with the completed aglycon moiety.

2. Halides as glycosyl donors

The earliest known glycosylation method is that of Koenigs and Knorr, which was first reported a century ago.[20] This reaction involves the coupling of a glycosyl bromide or chloride with a hydroxyl component upon activation of the former with a heavy metal ion, typically silver or mercury.[21,17] In most glycosidation reactions, the resulting anomeric stereochemistry is controlled by the nature of the C2 substituent. Thus, when the C2 oxygen is protected with an alkyl or benzyl group, the anomeric effect dominates and the α-anomer is preferentially formed (Scheme 2). The same configuration is obtained with 2-deoxyglycosyl donors. On the other hand, when the C2 position is occupied by a participating group, such as an ester group, the stereochemical outcome is opposite to that of the C2 substituent and a 1,2-*trans* product is formed (Scheme 3).[22] Extensions of the Koenigs–Knorr conditions include the use of Lewis acids and phase-transfer catalysis[23] to activate the anomeric halides. Glycosyl fluorides were first introduced as glycosyl donors in 1981 by Mukaiyama.[24] One of the notable advantages of these latter compounds is their higher thermal and chemical stability, as compared to the low stability of the other glycosyl halides and, moreover, they can often be purified by chromatography.



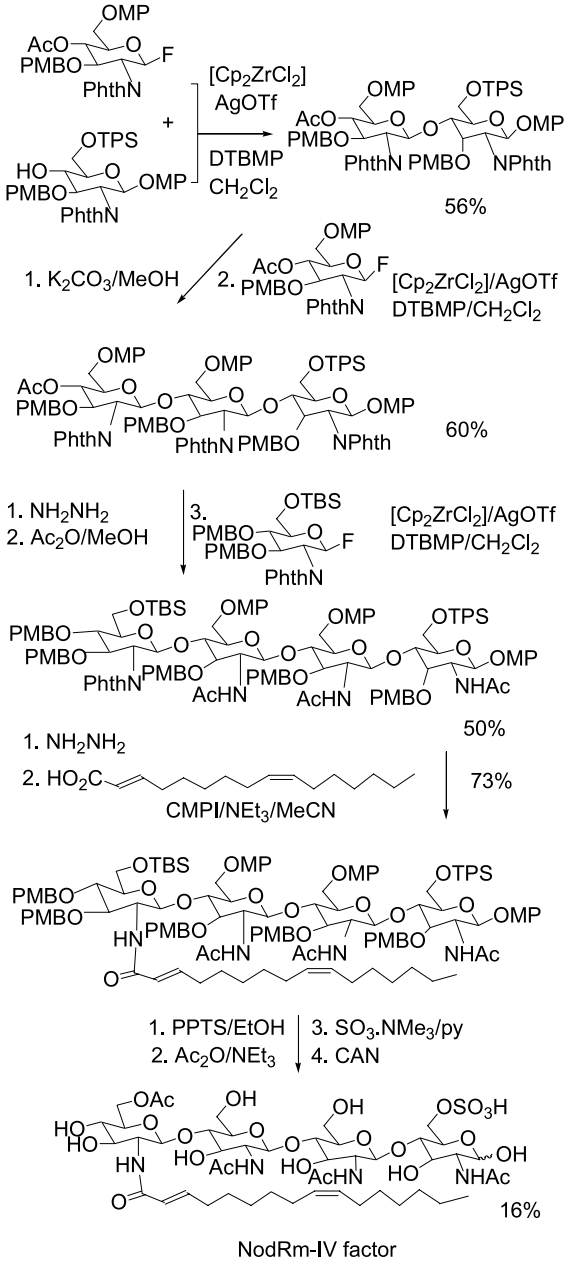
Scheme 2. Formation of α-glycosides.



Scheme 3. Formation of β-glycosides.

2.1. Synthesis of glycolipids

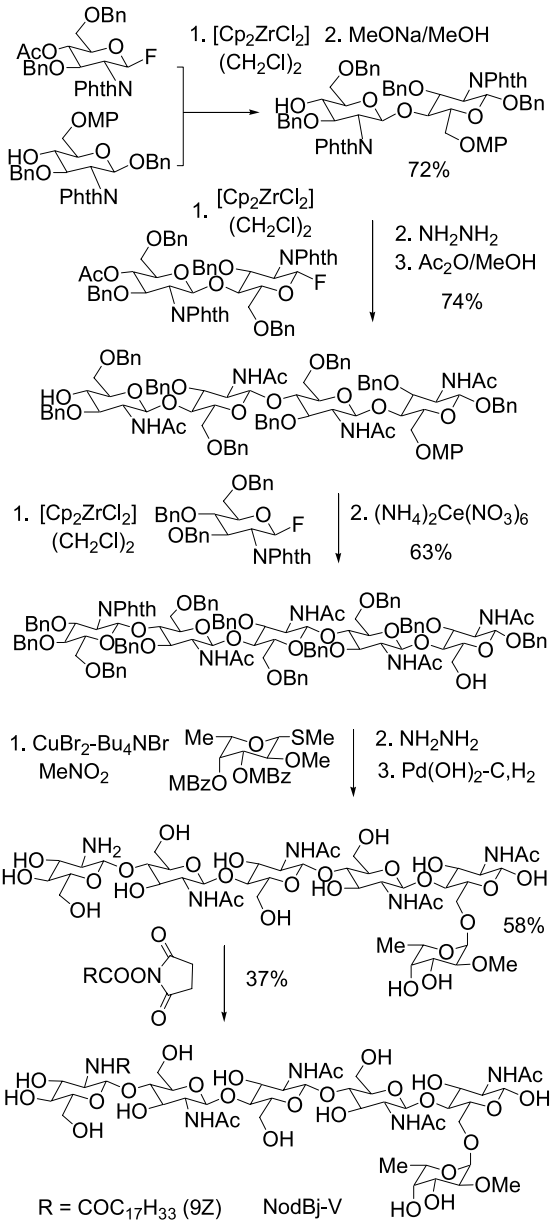
More than 300 naturally occurring glycolipids have been isolated. These are structurally diverse in their core carbohydrates, and are generally typically limited to oligosaccharides containing less than five residues.[25] Unlike glycoproteins, the smaller size of the glycolipids has allowed a number of total syntheses to be completed.[26] Nodulation factors are important signalling molecules involved in the symbiosis between bacteria of the family



Scheme 4. Synthesis of NodRm-IV factor.

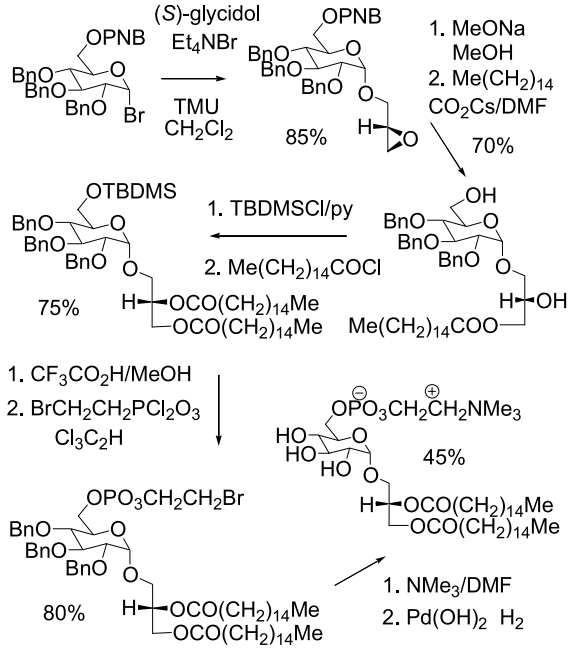
Rhizobium and legumes. They are typically sulfated lipooligosaccharides of *N*-acetyl-D-glucosamine. Secreted by the microorganism *Rhizobium meliloti*, these molecules elicit the formation of nitrogen-fixing root nodules. The synthesis of the most challenging member of this group of naturally occurring substances, NodRm-IV, was based on the use of glycosyl fluorides activated by the combination Cp_2ZrCl_2–AgOTf (Scheme 4).[27]

In the same way, the first synthesis of a lipohexasaccharide nodulation signal, NodBj-V, isolated from *Bradyrhizobium japonicum*, was reported by Ogawa et al. (Scheme 5).[28] This natural compound is responsible for an early event of the nodulation process on the host legume soybean. Three successive glycosylations involving glycosyl fluorides were successfully performed in this way.



Scheme 5. Synthesis of lipohexasaccharide NodBj-V.

In order to investigate alterations of the glycolipid composition due to HTLV-I virus (human T-lymphotropic virus type I) infections, a new glucosyl glycerolipid with a 6-*O*-phosphocholine group was isolated from the culture of HTLV-I-infected human helper T-cells, and synthesised by coupling a glucopyranosyl bromide with (*S*)-glycidol (Scheme 6).[29] The mild glycosylation was carried out in the presence of Bu_4NBr combined with TMU as acid scavenger and in the absence of any metal.

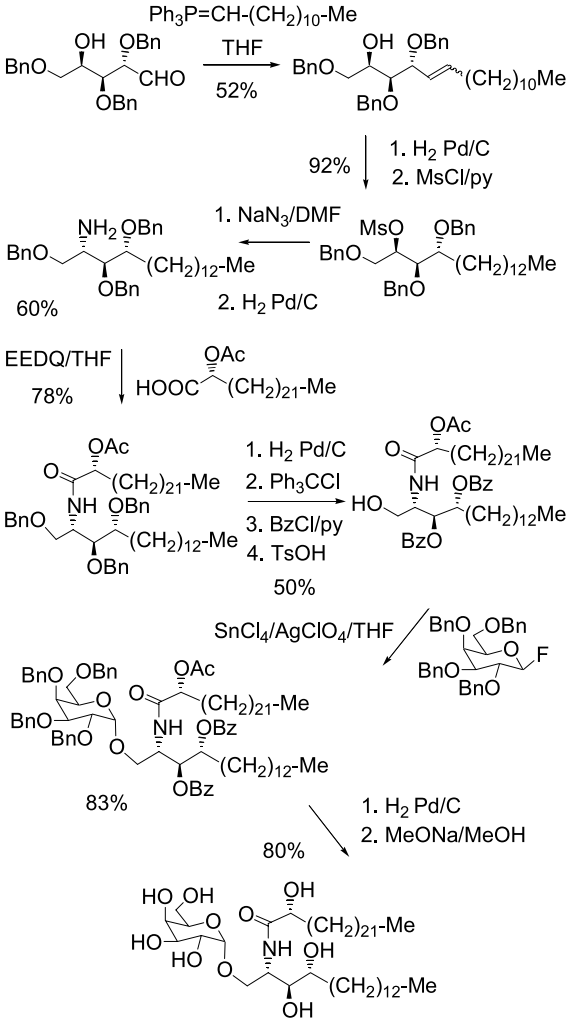


Scheme 6. Synthesis of a glycoglycerolipid isolated from HTLV-I infected T-cell lines.

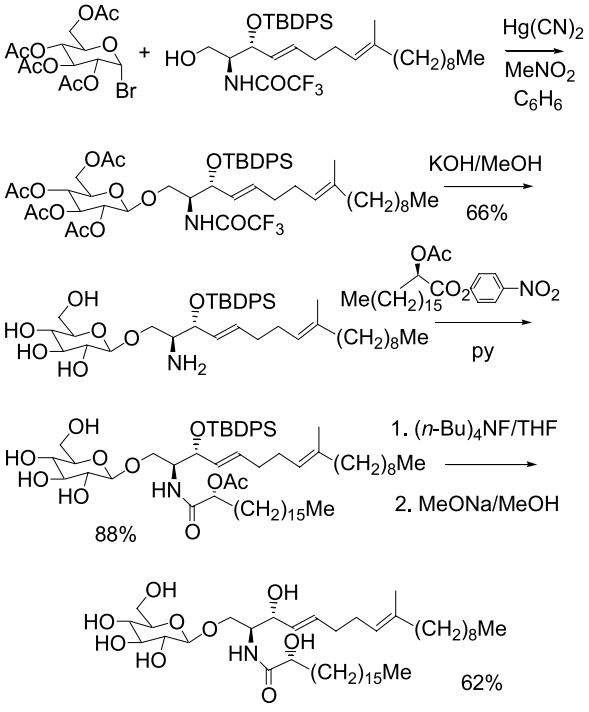
Glycosphingolipids, commonly found in eukaryotic cells, are key constituents of the membranes of most cell types, and are recognized as fundamental mediators of cell–cell recognition and communication, cell-growth regulation, and antibody interactions. The biological significance of these cell markers has made them important targets for chemical synthesis. Among them, cerebrosides, named agelasphins, isolated from the marine sponge *Agelas mauritianus*, have shown high in vivo antitumour activity against murine B16 melanoma and enhanced the mixed lymphocyte reaction in vitro. In 1994, Natori et al. performed the first total synthesis of this type of novel antitumour and immunostimulatory cerebroside involving a glycosylation with a glycosyl fluoride in the presence of $SnCl_4$ and $AgClO_4$ (Scheme 7).[30]

The total synthesis of another cerebroside, isolated from *Penicillium funiculosum* as the fruiting inducer against Basidiomycete *Schizophyllum commune*, was reported by Mori et al., starting from D-glucose, L-serine, homoprenyl acetate and stearic acid (Scheme 8).[31] The Koenigs–Knorr reaction was suitable for the first step of the synthesis.

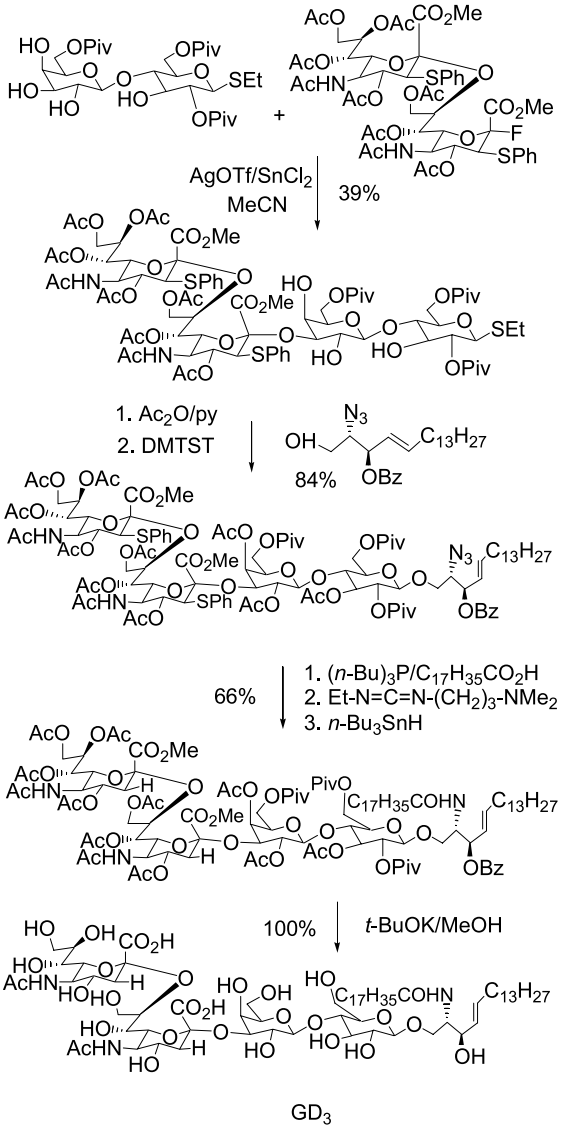
The disialyl ganglioside, GD3, is a very attractive target molecule for organic synthesis due to its various biological activities, especially as a human melanoma-associated antigen. An efficient total synthesis of this ganglioside,



Scheme 7. Synthesis of an antitumour and immunostimulatory cerebroside.



Scheme 8. Synthesis of a cerebroside isolated from *P. funiculosum*.

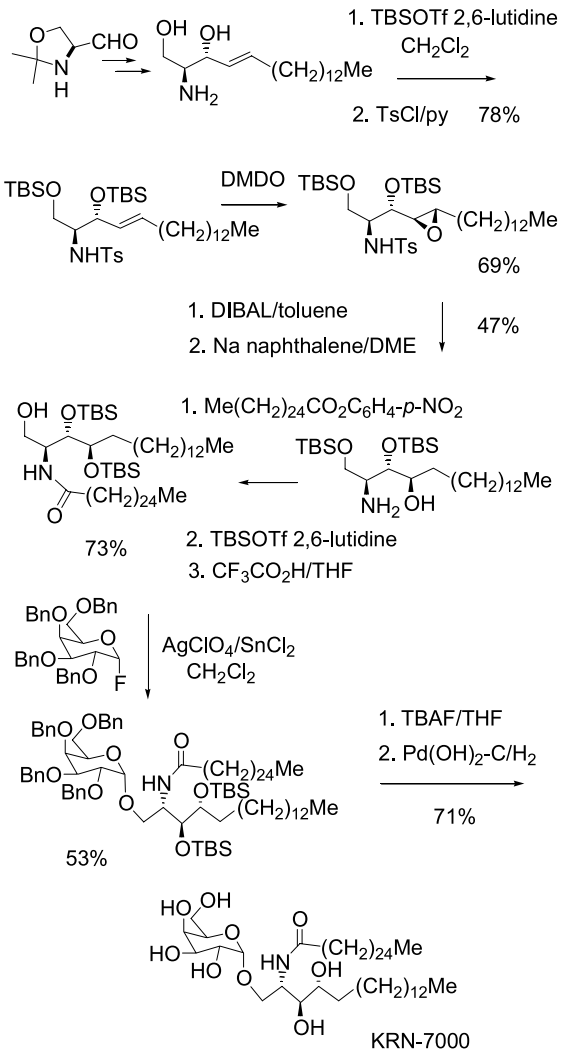


Scheme 9. Synthesis of ganglioside GD_3.

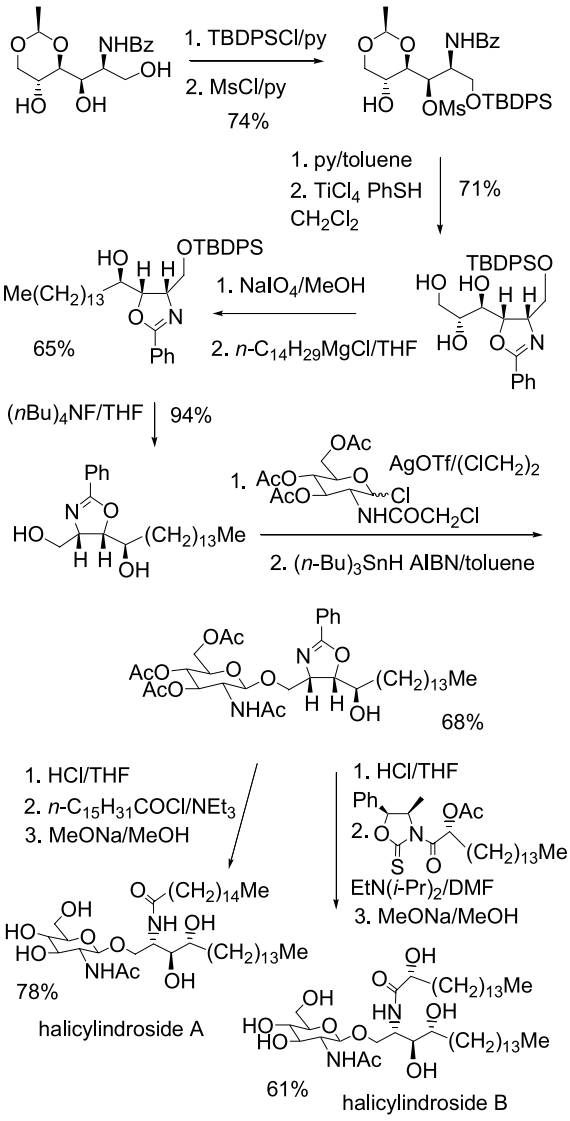
based on an α-stereocontrolled sialylation, was developed by Kondo et al. (Scheme 9).[32]

In 1998, Mori et al. reported a new synthesis of the α-galactosylceramide KRN-7000, having an enhancing effect on the activity of natural killer cells, which are antitumour effector cells, both in vitro and in vivo.[33] The key steps of the synthesis were a diastereoselective epoxidation of a protected C18-sphingosine derived from (*S*)-serine and 1-pentadecyne, combined with a glycosylation with tetra-*O*-benzyl α-D-galactopyranosyl fluoride in the presence of the mixed catalyst, $AgClO_4$ and $SnCl_2$ (Scheme 10).

β-Glucosaminylceramides such as halicylindrosides, isolated from the sponge *Halichondria cylindrata*, have shown antifungal and cytotoxic activities. Unnatural homologues of antifungal cerebrosides, halicylindrosides were efficiently prepared by Murakami et al. by involving the coupling of a glycosyl chloride (Scheme 11).[34]



Scheme 10. Synthesis of KRN-7000.



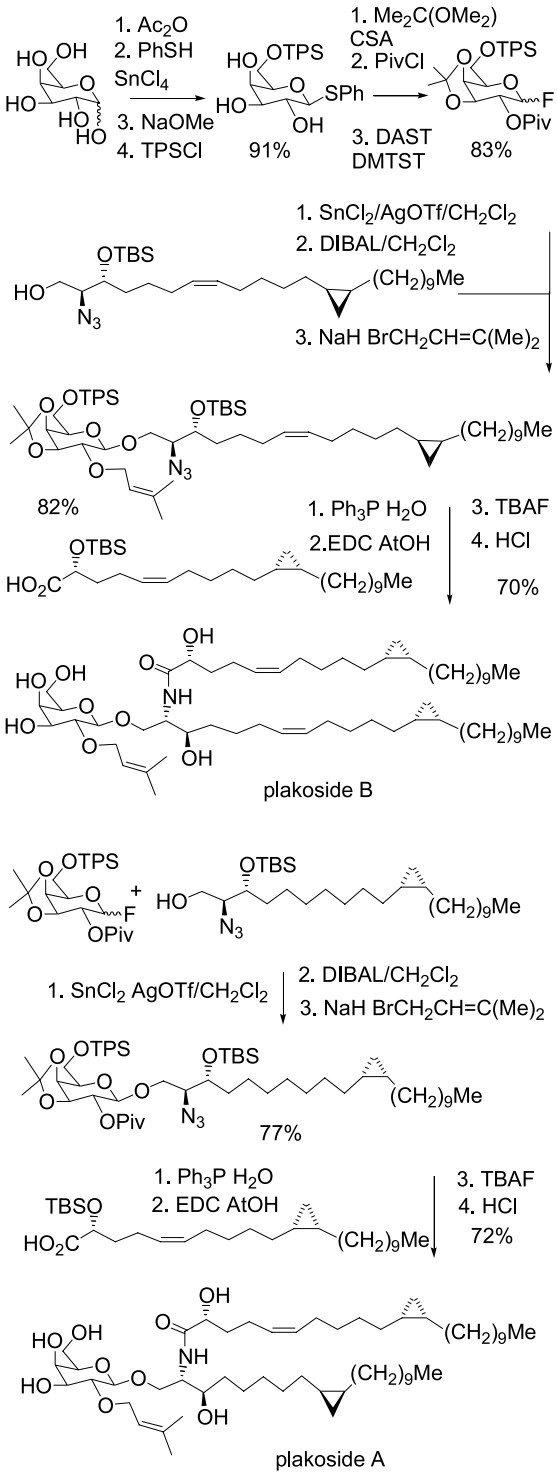
Scheme 11. Synthesis of novel cerebrosides, halicylindrosides.

Plakosides A and B, recently isolated from the marine sponge, *Plakortis simplex*, are potent immunosuppressive agents and contain interesting functionalities not common to other glycosphingolipids. Among these features are a cyclopropane ring on their sphingosine chain and a prenyloxy group on the C2 position of the carbohydrate moiety, which makes them interesting candidates for total synthesis. The synthesis of these target molecules, based on the coupling of a galactosyl fluoride with an azido-sphingosine, was achieved by Nicolaou et al. in 2000 (Scheme 12).[35]

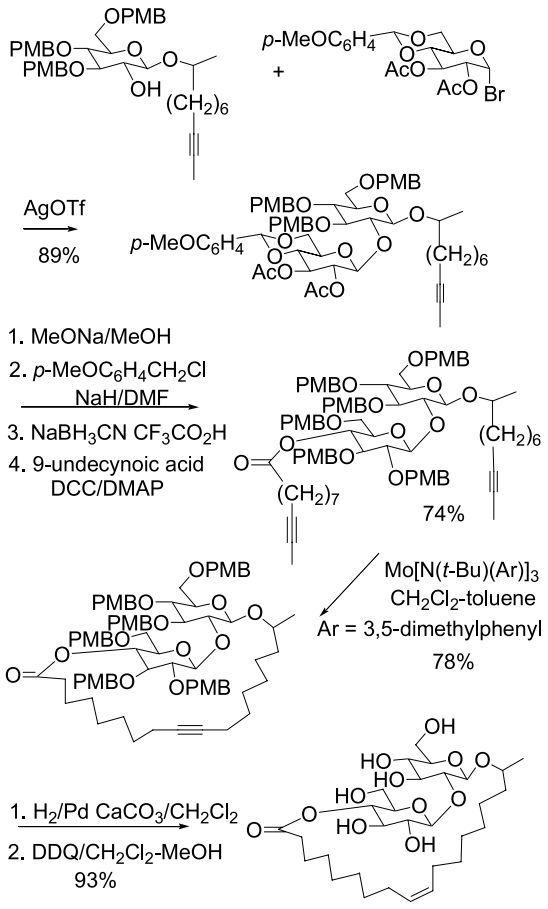
The yeast *Candida bombicola* is able to grow even on pure hydrocarbons as the only carbon source. It emulsifies hydrophobic culture media by the production of extracellular biosurfactants called sophorolipids. The first total synthesis of a major component of the microbial biosurfactant sophorolipid was reported by Fürstner et al.[36] This synthesis was based on a ring-closing metathesis reaction catalysed by Mo[N(*t*-Bu)(Ar)]$_3$ (Ar=3,5-dimethylphenyl) and a modified Koenigs–Knorr reaction (Scheme 13).

Recent studies indicate that glycosphingolipids (GSL) are clustered at the cell surface in close association with various signal-transducer molecules, and are involved in initiation of signal transduction coupled with GSL-dependent cell adhesion. These compounds may have potential interest in relation to lactosyl ceramide, which initiates signal transduction as a component of GSD (glycosignaling domain), to activate neutrophils, including phagocytosis. A one-pot synthesis of mono- and dilactosyl sphingosines was described by Zhang et al. in 2001 (Scheme 14).[37]

Lipopolysaccharides (LPS) are ubiquitous glycoconjugates located on the surface of Gram-negative bacteria such as *Escherichia coli*, and exhibit multiple and potent biological activity, both toxic and beneficial, towards higher animals. LPS consist of a phosphorylated acyl glucosamine disaccharide covalently bonded to a polysaccharide. The former glycolipid, lipid A, is the entity responsible for most of the biological activity of LPS. The simplest lipopolysaccharide molecule that is known to be present on bacterial cells and that comes into contact with animal cells is the so-called Re-type lipopolysaccharide produced by the



Scheme 12. Synthesis of plakosides A and B.



Scheme 13. Synthesis of a sophorolipid lactone.

E. coli Re mutant (Re LPS). In 2001, Oikawa et al. developed the first total synthesis of Re lipopolysaccharide in order to elucidate the biological and physicochemical role of the sugar moieties linked to lipid A (Scheme 15).[38]

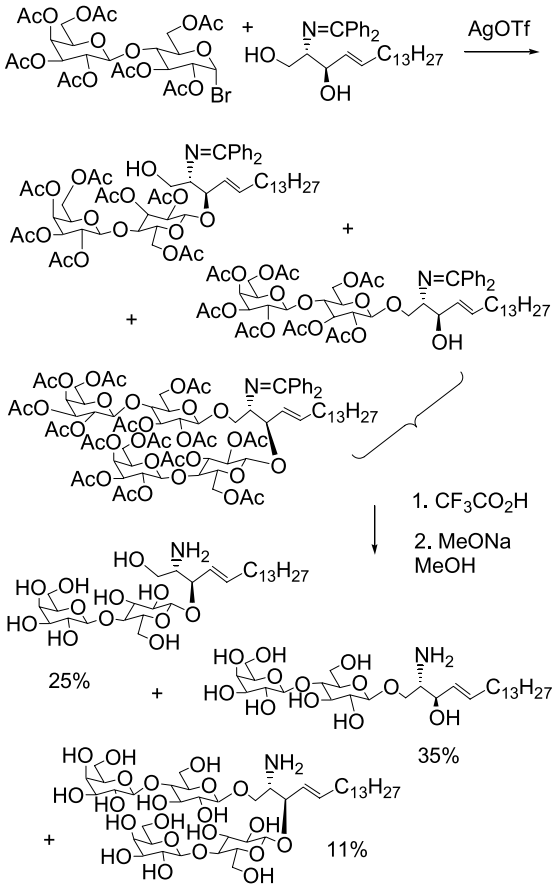
2.2. Synthesis of oligosaccharides

The recognition of the important role of selectins in the recruitment of leukocytes to inflammation sites through vascular adhesion has evoked extensive studies in this field over the last few years. Such studies have led to the isolation and identification of the two sulfated tetrasaccharides Le^x and Le^a, as naturally occurring ligands for E-selectin with binding affinities. The potential of these Lewis determinants in biology and medicine made them prime targets for chemical synthesis. In 1993, Nicolaou et al. reported the first total syntheses of sulfated Le^x (Scheme 16) and sulfated Le^a (Scheme 17) that utilise glycosyl fluoride chemistry in the key coupling processes.[39]

Another glucopyranosyl fluoride was used as key intermediate for a very original cyclo-glycosylation reported by Ogawa et al. in 1993.[40] An excellent yield of cyclodextrin was observed in the case of preparation of cyclolactohexaose (Scheme 18).

The α- and β-2-deoxyglycosides frequently appear in naturally occurring bioactive substances such as enediyne antibiotics like esperamicin A_1. The carbohydrate units of esperamicin A_1 were prepared by Nicolaou et al. in 1994 (Scheme 19).[41]

Glycosylphosphatidylinositol (GPI) anchors occur throughout the eukaryotic kingdom, but are much more common in lower organisms, such as protozoa, than in higher organisms, where they make up only a small percentage of the cell surface. In 1997, Konradsson et al. reported the synthesis of



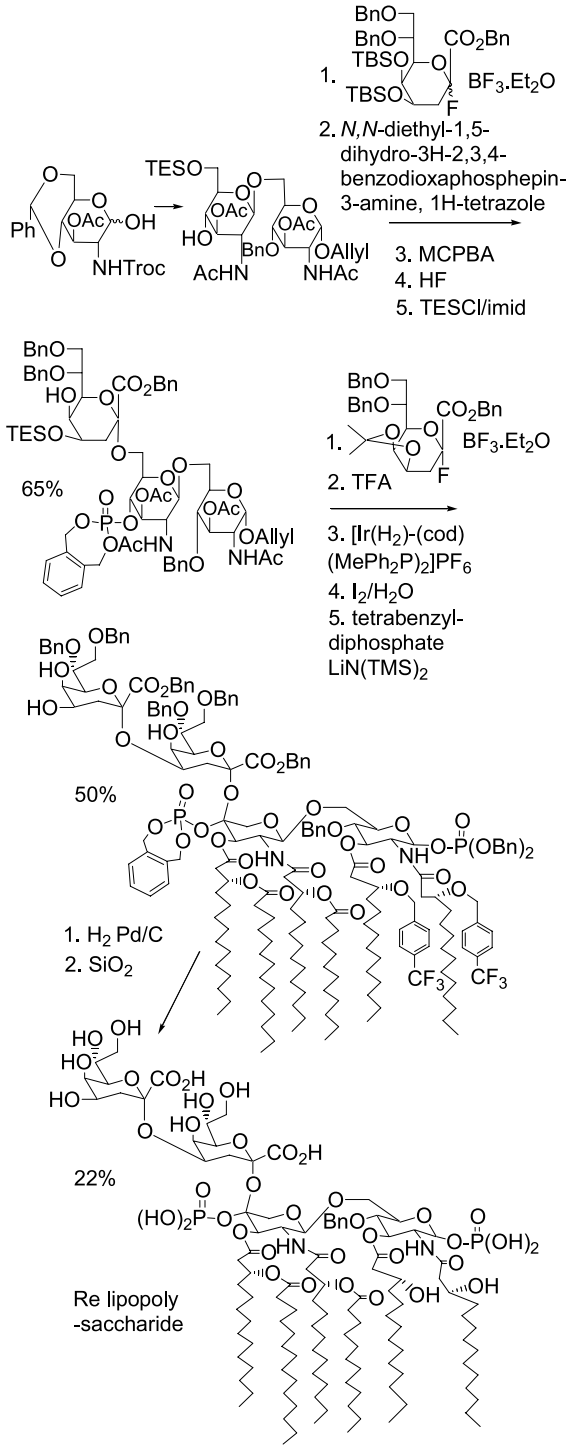
Scheme 14. One-pot synthesis of mono- and di-lactosyl sphingosines.

6-*O*-(2-amino-2-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol 1-phosphate, an inner core structure found in various glycosylphosphatidylinositols, and the corresponding 1,2-cyclic phosphate, proposed as part of an insulin second messenger glycosylinositol phosphate, with the use of a glycosyl fluoride in the crucial glycosylation step (Scheme 20).[42]

In 1999, Nicolaou et al. developed the synthesis of the A–C disaccharide of namenamicin, the only enediyne antitumour antibiotic of marine origin, performed in part by $SnCl_2$-mediated glycosylation with a glycosyl fluoride (Scheme 21).[43]

A highly convergent approach for the synthesis of a spacer-modified hexasaccharide derived from the tumour-associated antigen, Globo-H, was reported by Boons et al.[44] Among five glycosylation steps, the final and key step was a $[Cp_2ZrCl_2]$/AgOTf-mediated glycosylation with a disaccharide fluoride (Scheme 22).

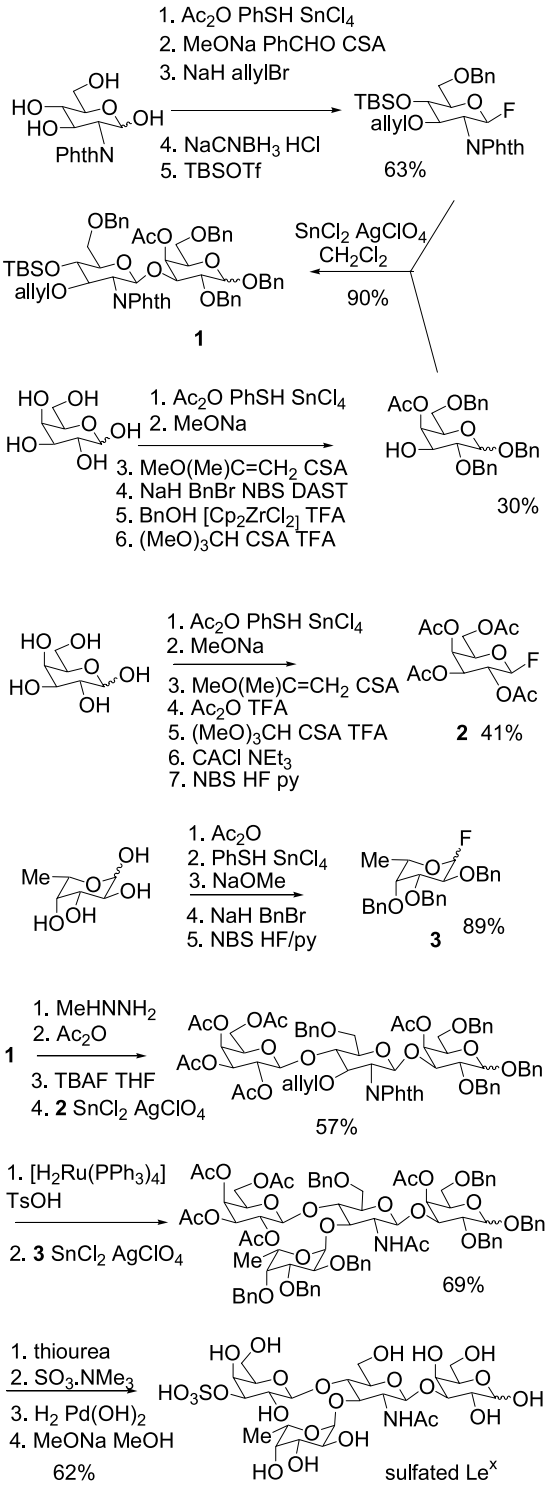
Primary cell walls of all higher plants contain rhamnogalacturonan-II (RG-II), a unique mega-oligosaccharide that belongs to the pectic polysaccharide family. The first synthesis of a disaccharide fragment of RG-II, incorporating β-linked rhamnopyranose and apiofuranose, was accomplished in 2004 by Nepogodiev et al., by coupling a rhamnopyranosyl bromide with a ribofuranoside in the presence of Ag_2O (Scheme 23).[45]



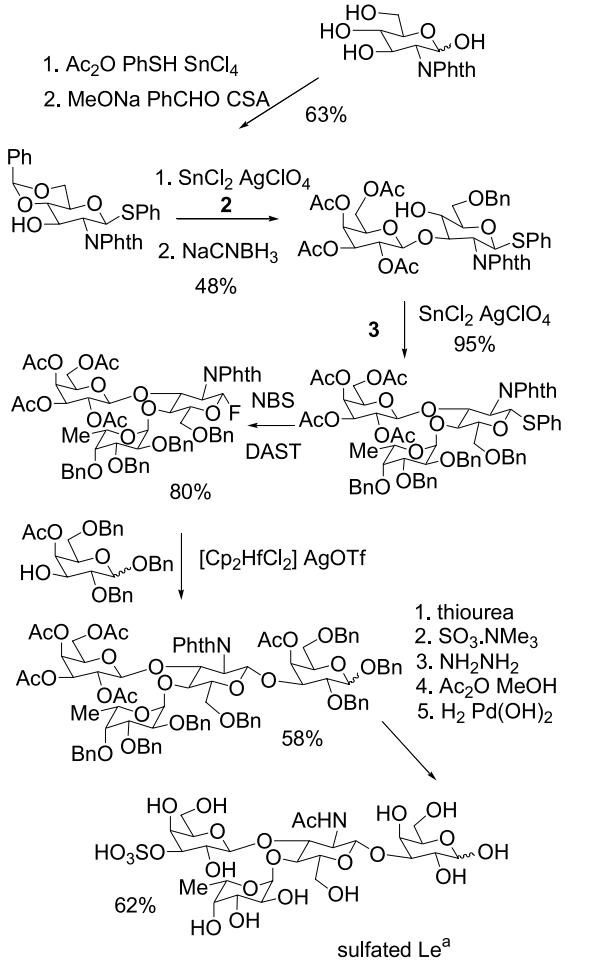
Scheme 15. Synthesis of Re lipopolysaccharide.

2.3. Synthesis of glycopeptides and glycoproteins

Glycopeptides are a rapidly growing family of molecules which contain a carbohydrate domain and a peptide domain. Glycoproteins are larger variants which contain more than about 50 amino acids per peptide (or protein) component. The carbohydrate can be a single monosaccharide or a complex, possibly branched, oligosaccharide containing up to about 20 monosaccharide units. The biological functions of glycopeptides are many and varied, and scientists have



Scheme 16. Synthesis of sulfated Le^x.



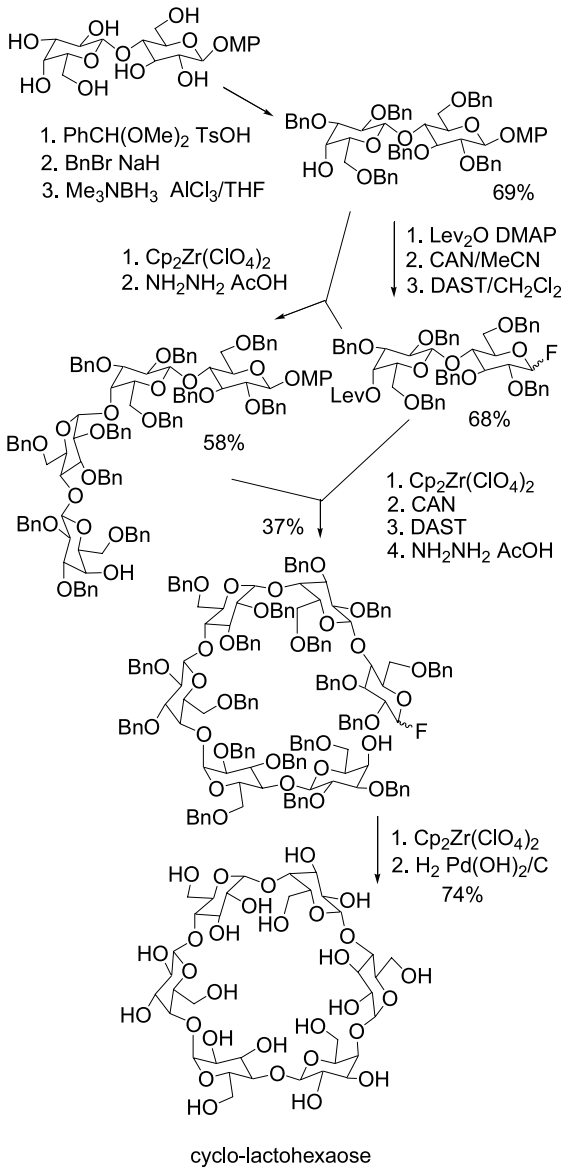
Scheme 17. Synthesis of sulfated Le^a.

probably only uncovered a fraction of these novel biomolecules todate. The carbohydrate often alters the structure and function of the peptide/protein. Carbohydrates exposed on the surface of a protein can serve as recognition elements—either on the molecular level, between molecules and cells, or on an intercellular level. The nature, and indeed existence, of the carbohydrate can vary during the life cycle of a cell, as a sophisticated battery of glycosyl transfer enzymes operate on it. The level of interest in this field has grown exponentially and, as a consequence, several reviews have appeared on the chemical synthesis of glycopeptides and glycoproteins.[46] The glycosylation of a primary or secondary alcohol in the side chain of an amino acid is not so conceptually different to forming a glycosidic linkage between two monosaccharide units. Indeed, most standard glycosylation methods have been applied in this domain. In 1997, Paulsen et al. reported a Koenigs–Knorr reaction in order to prepare a building block used in the synthesis of partial structures of the octapeptides of human glycophorin A^N (Scheme 24).[47]

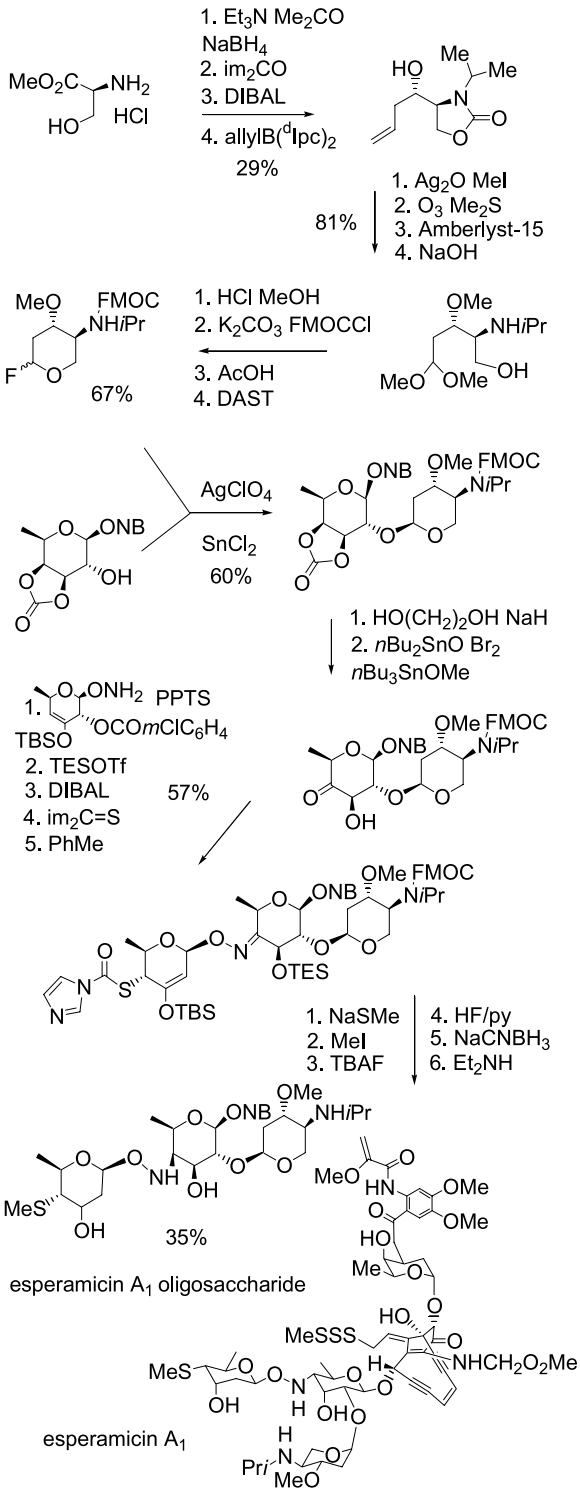
In their recent synthesis of a tumour-associated sialyl-T_N antigen, Liebe and Kunz prepared almost the same building block to that depicted in Scheme 24, by applying the same methodology (Scheme 25).[48]

A glycosyl fluoride was used as a precursor by Nishimura and Tsuda in their construction of a synthetic antifreeze glycoprotein (Scheme 26).[49] After deprotection, the corresponding glycopeptide was polymerized using diphenylphosphoryl azide.

In addition to the range of known *O*-glycosylation sites in naturally occurring glycoproteins, *O*-glycosylated tyrosine



Scheme 18. Synthesis of cyclo-lactohexaose.



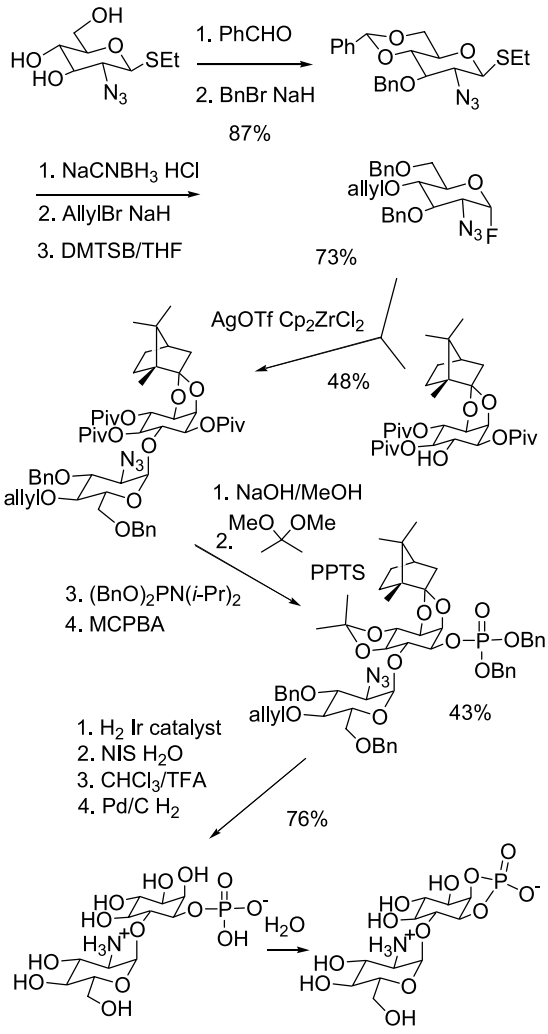
Scheme 19. Synthesis of esperamicin A_1 oligosaccharides.

has been identified in glycogenin, the 38 kDa primer protein for the biosynthesis of glycogen. The preparation of glycosylated tyrosine building blocks for solid-phase peptide synthesis was investigated by Meldal et al.[50] Scheme 27 illustrates the first example of glycosylation of a *tert*-butyl-protected aromatic hydroxyl group in an amino acid derivative.

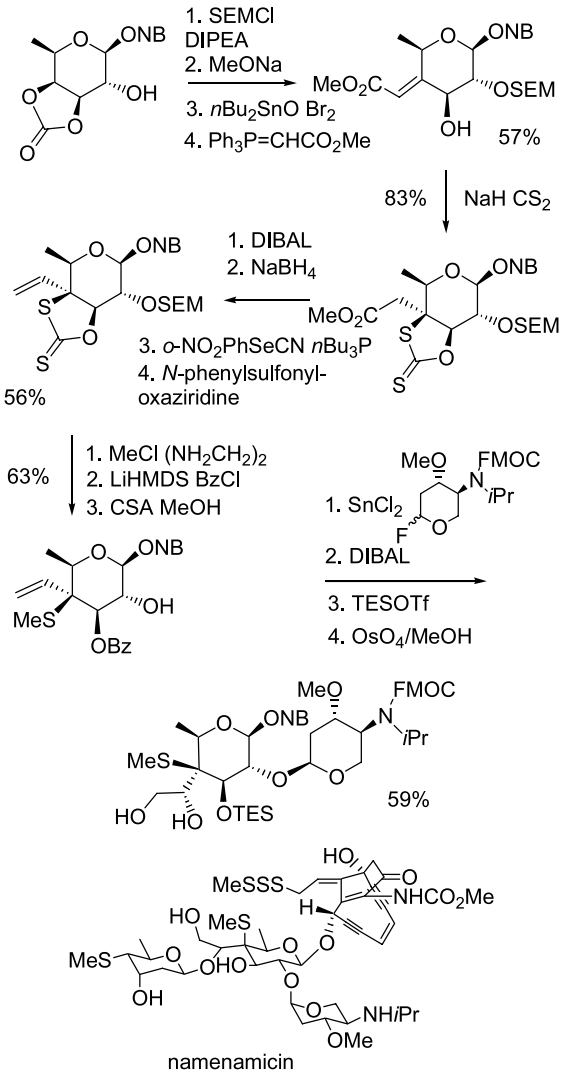
2-Acetamido-2-deoxy-β-D-glucopyranose (GlcNAc), in an *O*-glycosidic linkage to the side-chain hydroxyls of serine (Ser) and threonine (Thr) residues, is often found in nuclear and cytoplasmic proteins. In 1996, Barany et al. developed an efficient procedure for the synthesis of glycosides of serine and threonine, depicted in Scheme 28.[51]

Sialyl-Tn (sTn) is found on the HIV envelope glycoprotein gp120 and in tumour-associated antigens present in the glycoproteins on the surface of cancer cells. In order to develop a new vaccine candidate against HIV, Linhardt et al. have reported the synthesis of a C-glycoside analogue of this tumour antigen sTn, on the basis of a Koenigs–Knorr reaction as first step (Scheme 29).[52]

Very recently, Le Merrer et al. developed an efficient glycosylation between 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, via its corresponding unstable 1-brominated derivative, and *N*-benzyloxycarbonyl-L-serine *tert*-butyl



Scheme 20. Synthesis of inositol phosphoglycans proposed as a second messenger of insulin.



Scheme 21. Synthesis of namenamicin A–C disaccharide.

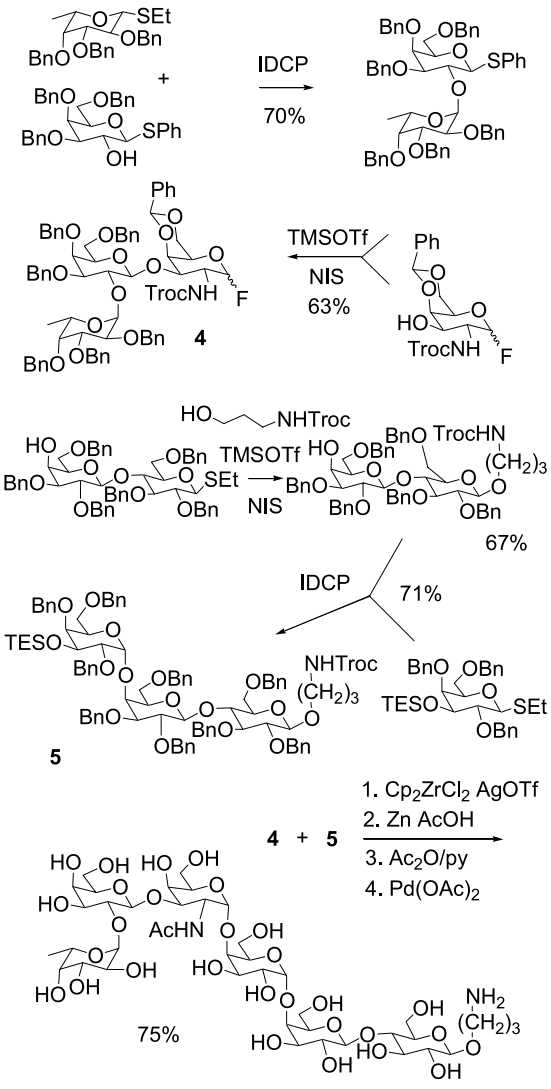
ester (Scheme 30).[53] This reaction represents a key step towards the synthesis of the scaffold, which should allow the acquisition of a library of liposidomycin analogues. These latter compounds are natural inhibitors of the translocase MraY, an essential enzyme involved in the biosynthesis of bacterial cell wall peptidoglycans.

2.4. Synthesis of natural products

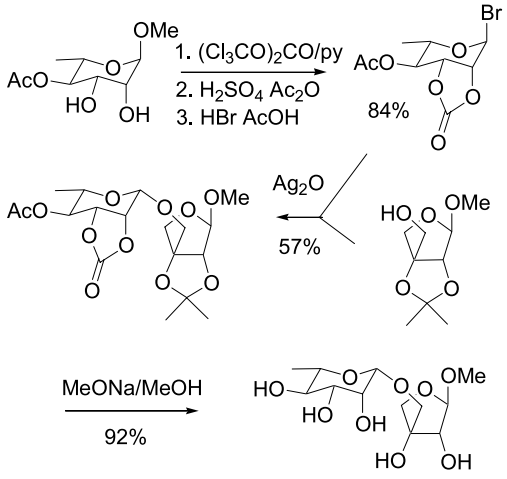
A number of natural products have been prepared by the use of the *O*-glycosylation reaction with glycosyl halides, amongst which are pheromones[54] and naturally occurring antitumour cyanoglucosides such as bauhinin[55] and (−)-lithospermoside[56] (Scheme 31), synthesised for the first time by Le Drian et al.

Some morphine metabolites,[57,58] such as morphine-6-glucuronide, are more effective and longer-lasting analgesic drugs than morphine, with fewer side effects. There is much interest in using this latter compound, rather than morphine, as a pain-killing drug. Thus, a practical synthesis of morphine-6-glucuronide was developed by coupling 2α-bromoglucuronate with 3-acetylmorphine in the presence of silver carbonate, followed by deprotection with aqueous NaOH (yield: 45%).[59] More generally, adding carbohydrates to natural products substantially changes the hydrophilic–lipophilic balance and, therefore, transport in biological systems is affected. In order to determine the influence of the carbohydrate component on the biological activity of various natural compounds, the glycosylation reactions of these latter compounds were reported. Thus, Zemlyakov et al. described the synthesis of *N*-acetyl-glucosamidines with coumarin and chromone aglycones.[60] In the same way, several authors have reported the glycosylation of flavonoid derivatives, since flavonoid glycosides play a variety of essential roles in the growth and development of plants.[61] On the other hand, Dangles has developed the synthesis of 3-glycosylated callistephin, a natural anthocyanin, which is a natural pigment.[62] The major metabolite of quercetin, a very efficient antioxidant, was prepared by Rolando via glycosylation, followed by clean oxidation, providing the final corresponding glucuronide (Scheme 32).[63]

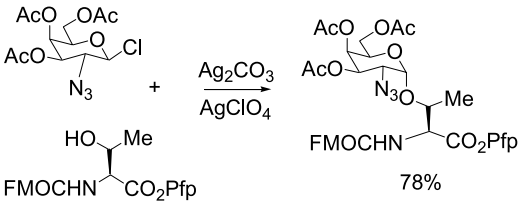
Linhardt et al. recently reported the first total synthesis of



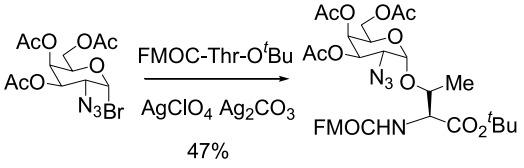
Scheme 22. Synthesis of the Globo-H hexasaccharide.



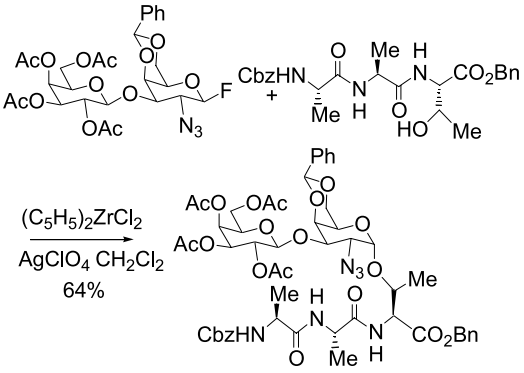
Scheme 23. Synthesis of β-rhamnosyl-apiofuranose disaccharide of RG-II.



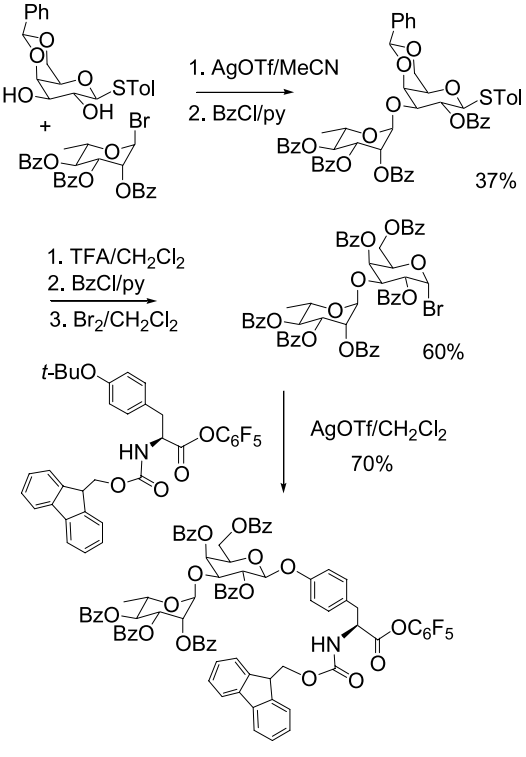
Scheme 24. Synthesis of a precursor of octapeptides of human glycophorin A^N.



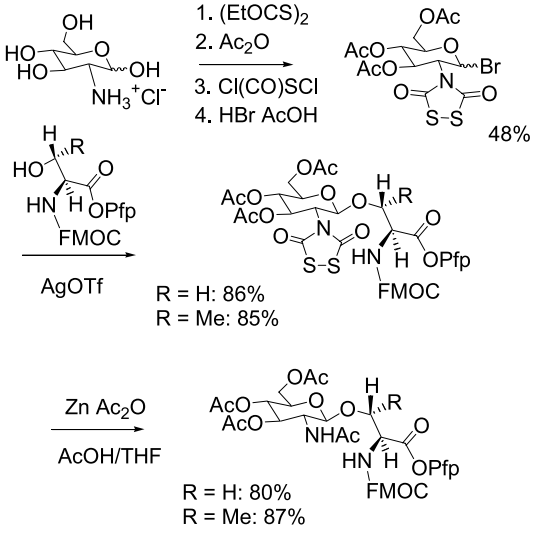
Scheme 25. Partial synthesis of a tumour-associated sialyl-T_N antigen.



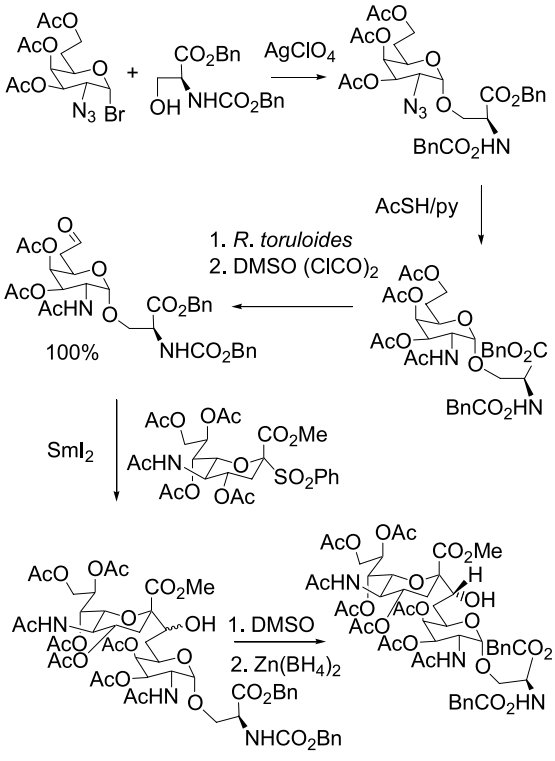
Scheme 26. Partial synthesis of a synthetic antifreeze glycoprotein.



Scheme 27. Synthesis of glycosyltyrosine building blocks for solid-phase peptide synthesis.



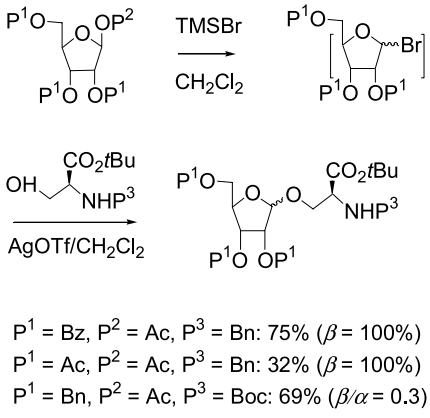
Scheme 28. Synthesis of 2-acetamido-2-deoxy-β-D-glucopyranose *O*-glycopeptides.



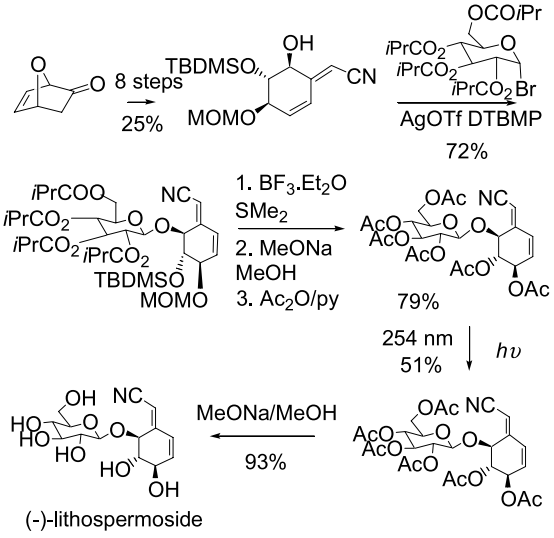
Scheme 29. Synthesis of a C-glycoside analogue of sTn.

another quercetin derivative, quercetin 3-sophorotrioside, which has shown protective effects on liver injury induced by chemicals. The key steps of the strategy were successive couplings using both sugar bromides and a trichloroacetimidate donor.[64] In the same way, this group has described the first synthesis of calabricoside A, a new flavonol triglycoside, from quercetin (Scheme 33).[65]

Moreover, Kondo et al. have succeeded in the first total synthesis of apigenin 7,4′-di-*O*-β-D-glucopyranoside, a



Scheme 30. Synthesis of liposidomycin analogues via serine *O*-glycosylation.

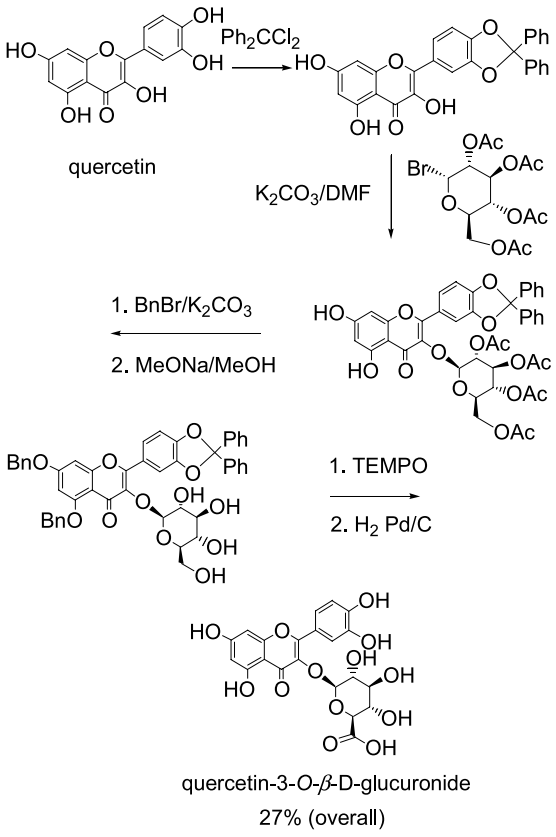


Scheme 31. Synthesis of (−)-lithospermoside.

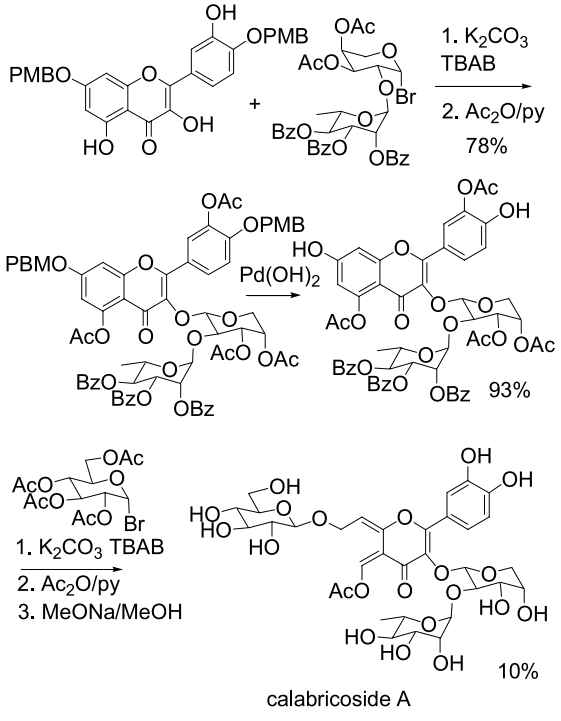
component of the blue pigment, protodelphin, from naringenin (Scheme 34).[66] The synthesis was based on two successive couplings with a glycosyl bromide and a glycosyl fluoride, respectively, activated by Ag_2CO_3 and $BF_3 \cdot Et_2O$.

The naturally occurring doubly glucosylated gibberellin A_5 was synthesised by base-catalysed (triethylamine) reaction of gibberellin A_5 13-*O*-β-D-glucopyranoside with acetobromoglucose, followed by mild deacetylation.[67] In 2003, Harding et al. developed the synthesis of carbohydrate derivatives of the antitumour alkaloid 9-hydroxyellipticine using Koenigs–Knorr conditions.[68] Adenophostin A, a potent IP_3 receptoragonist, was constructed by $AgClO_4$-γ-collidine-promoted glycosylation employing a glucopyranosyl bromide as a glycosyl donor (Scheme 35).[69]

A lithium hydroxide-promoted simple glycosylation of 4-hydroxyindole-3-acetonitrile with a glucopyranosyl bromide was applied for the first synthesis of cappariloside A,



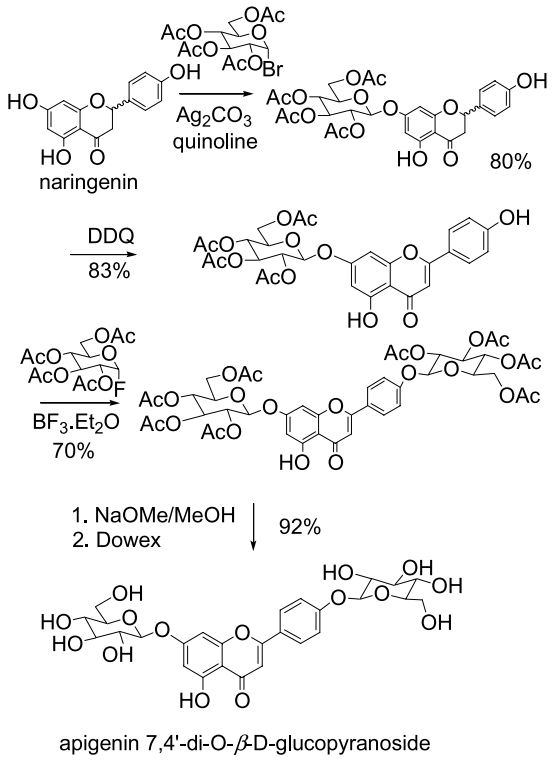
Scheme 32. Synthesis of quercetin-3-*O*-β-D-glucuronide.



Scheme 33. Synthesis of calabricoside.

used in folk medicine in Turkey as a diuretic and as an antihypertensive agent (Scheme 36).[70]

A glycosidation with L-daunosamyl chloride was the key step of the total synthesis of a novel analogue of the antitumour agent 4-demethoxydaunorubicin reported by Mitscher et al. (Scheme 37).[71]



Scheme 34. Synthesis of apigenin 7,4′-di-*O*-β-D-glucopyranoside.

The first total synthesis of the fungal metabolite caloporoside, a strong and selective inhibitor of phospholipase C, was developed by Fürstner et al. (Scheme 38).[72] The glycosylation was performed in the presence of Ag^+ on silica/alumina as the promoter.

The natural antibiotic, BE-12406 A, which has a structure close to those of the gilvocarcin–ravidomycin class of antibiotics, was synthesised by Suzuki et al., using a selective *O*-glycosylation of naphthol with L-rhamnopyranosyl fluoride as the key step (Scheme 39).[73]

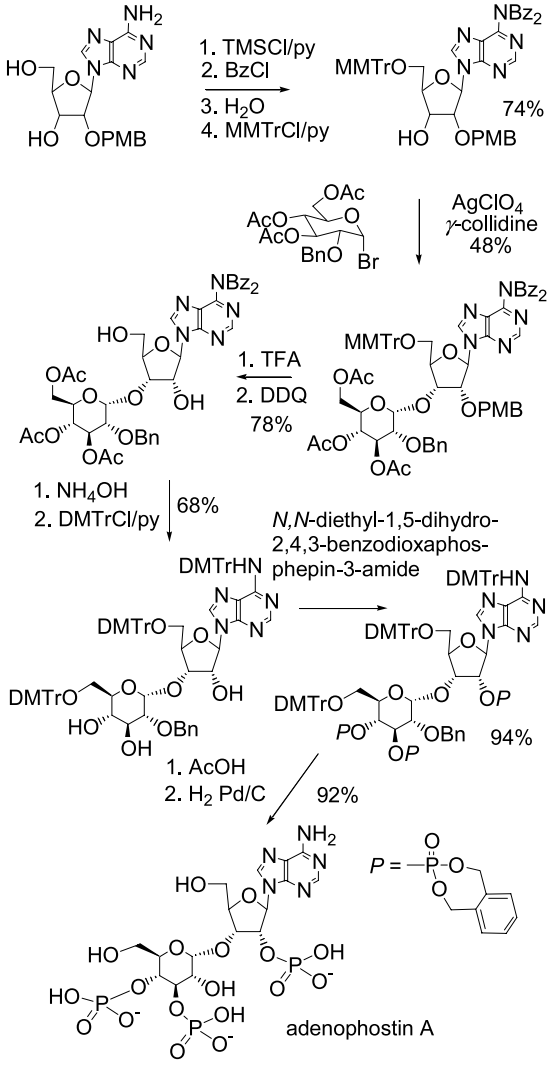
The enantioselective total synthesis of fluvirucin B_1, an antifungal agent, was based on a glycosylation process with a glycosyl fluoride, followed by a Mo-catalysed macrocyclisation (Scheme 40).[74]

In 2003, Nicolaou proposed a general strategy for the total synthesis of the antitumour agent apoptolidin, involving several glycosylations, amongst which was a coupling with a disaccharide fluoride activated by $SnCl_2$ (Scheme 41).[75]

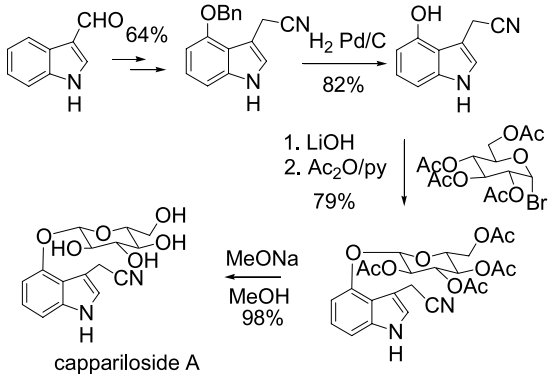
3. 1-*O*-Derivatives as glycosyl donors

3.1. 1-*O*-Imidates

Trichloroimidate-mediated glycosylation was reported by Schmidt et al.[76] in 1980 as an alternative useful method to

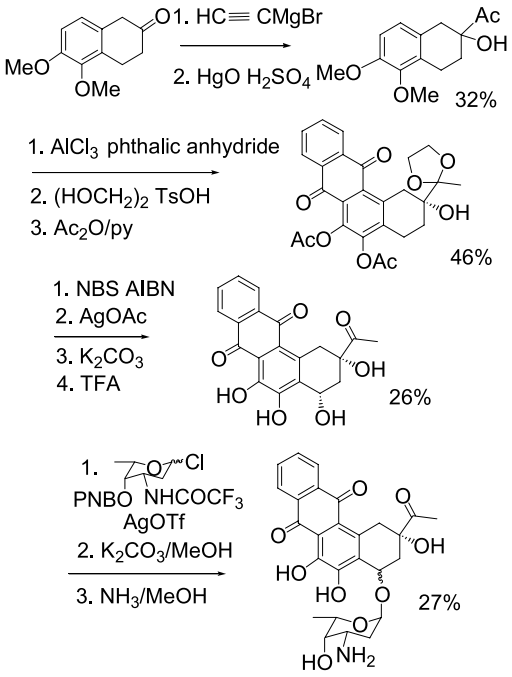


Scheme 35. Synthesis of adenophostin A.

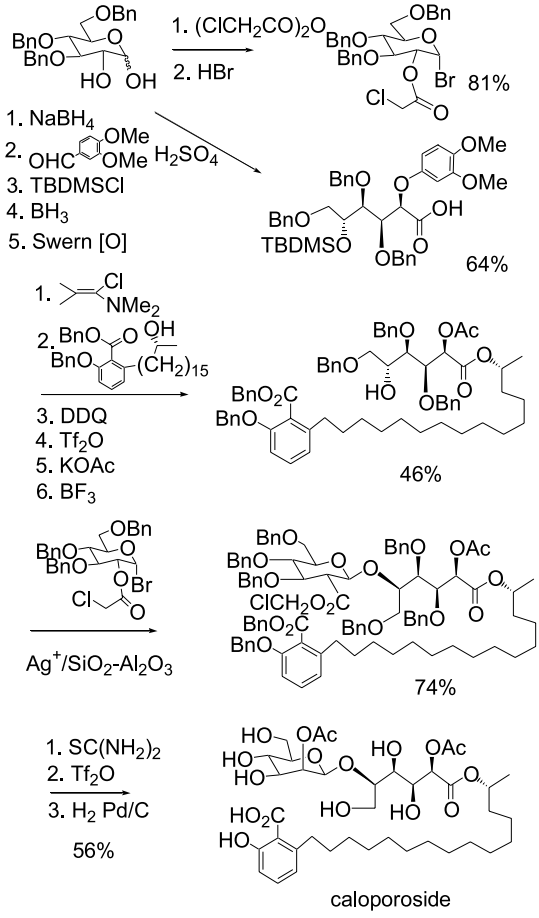


Scheme 36. Synthesis of cappariloside A.

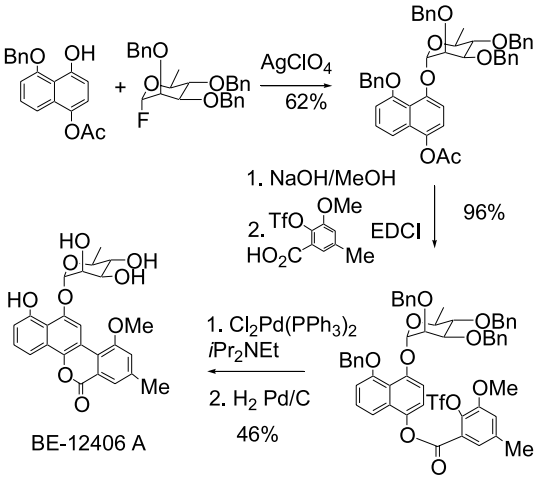
the classical Koenigs–Knorr procedure and now appears to be one of the most ideal glycosylation protocols. This type of glycosylation reaction is generally smoothly promoted by the catalytic use of $BF_3.Et_2O$ or TMSOTf. Some advantages of this reaction are the very mild conditions, its irreversible



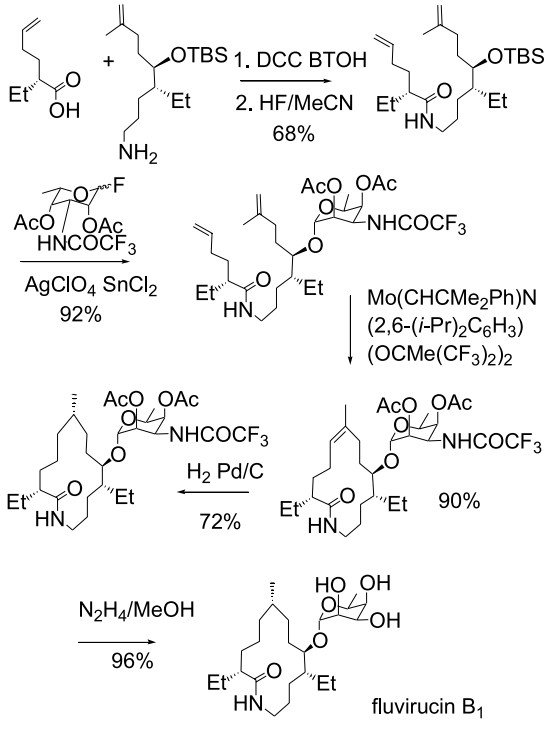
Scheme 37. Synthesis of antitumour agent 4-demethoxydaunorubicin analogue.



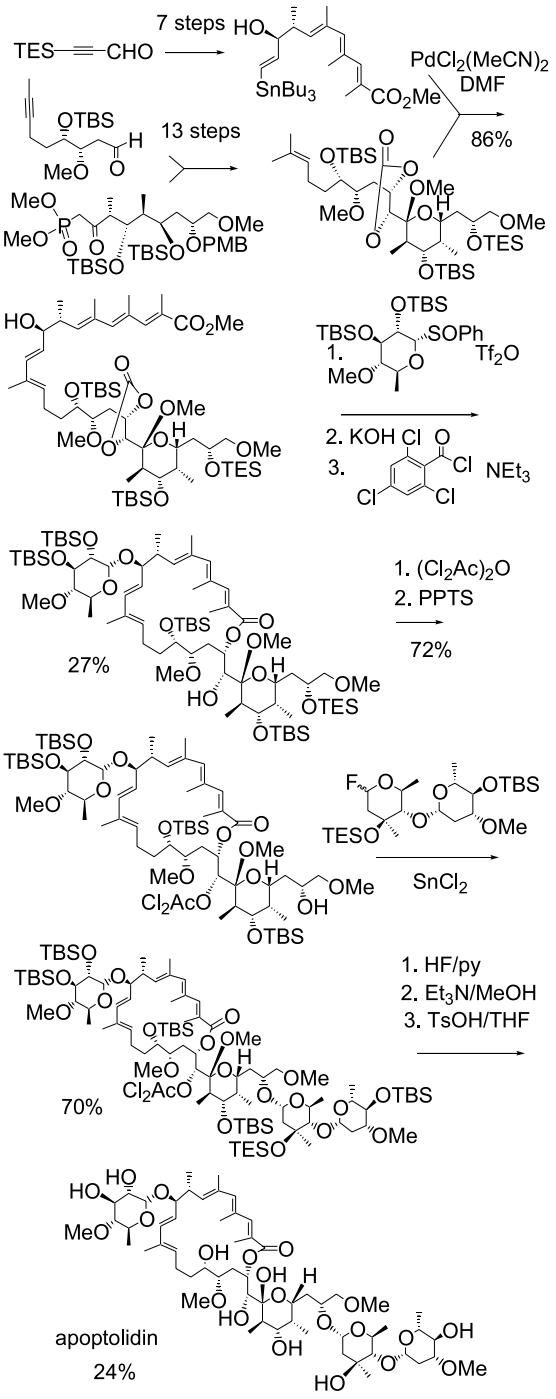
Scheme 38. Synthesis of caloporoside.



Scheme 39. Synthesis of BE-12406 A.



Scheme 40. Synthesis of fluvirucin B_1.



Scheme 41. Synthesis of apoptolidin.

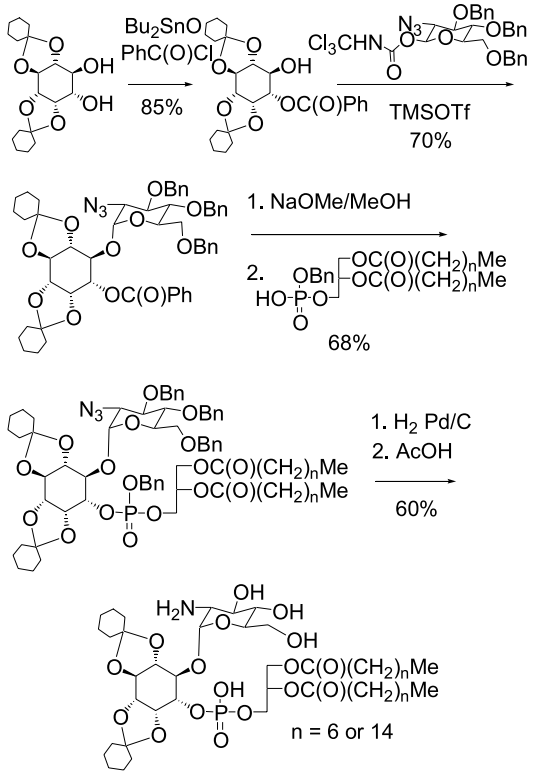
nature, the thermal stability and ease of preparation of the trichloroacetimidate, the usually good chemical yield, the good stereocontrol and the lack of effect on other glycosidic bonds.

3.1.1. Synthesis of glycolipids. In 1996, Falck et al. reported the synthesis of aminoglucosyl phosphatidylinositol core analogues from a chiral inositol (Scheme 42).[77]

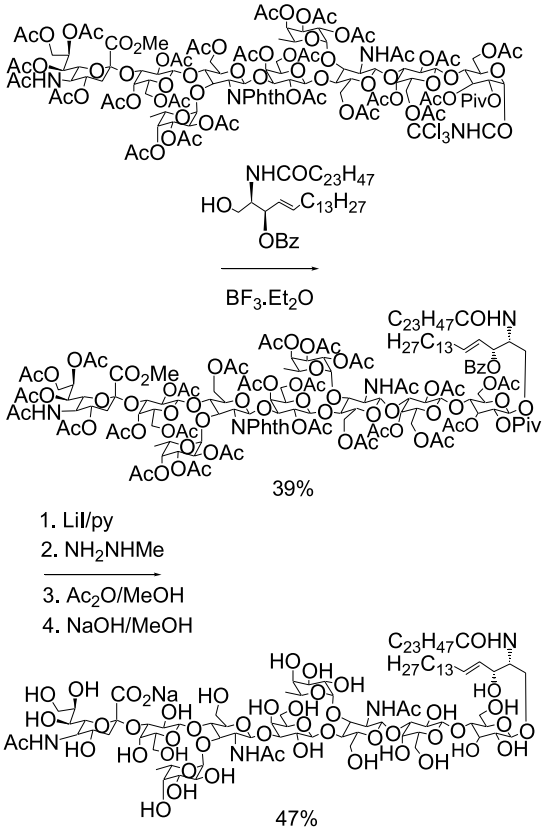
An unambiguous total synthesis of sialyl dimeric Le^x glycononaosyl ceramide was exploited for the first time by Nunomura et al.[78] Only the crucial coupling of a glycononaosyl trichloroacetimidate with 3-*O*-benzoyl-2-*N*-tetracosanoylsphingenine is depicted in Scheme 43.

In 1997, Tietze et al. described the synthesis of a novel stable GM_3-lactone analogue as hapten for a possible immunization against cancer (Scheme 44).[79] The strategy involved a $BF_3 \cdot Et_2O$-mediated glycosylation between an azidosphingosine and a trisaccharide trichloroacetimidate.

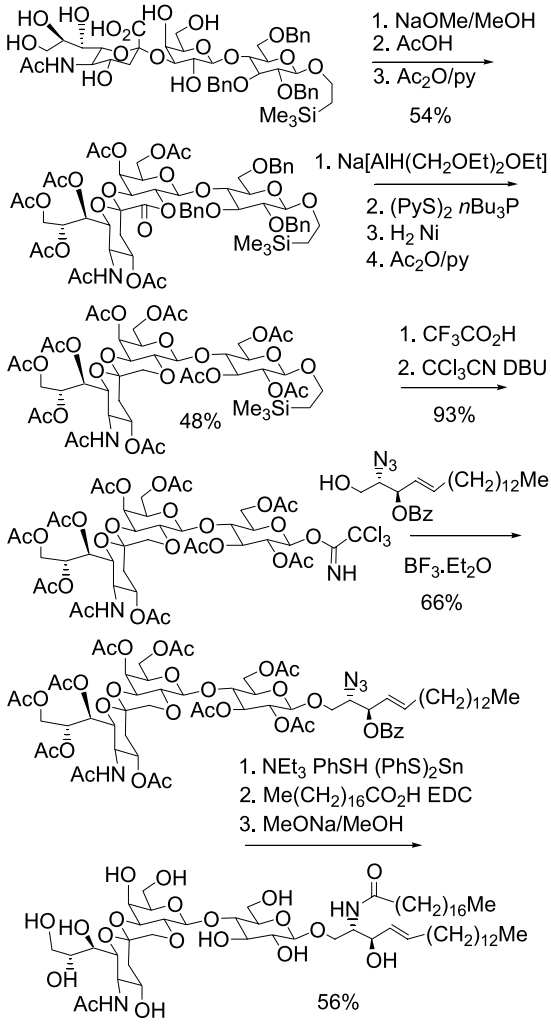
The same procedure was applied by Chida et al. to elaborate the first total synthesis of acanthacerebroside A, a novel



Scheme 42. Synthesis of aminoglucosyl phosphatidylinositol core analogues.



Scheme 43. Synthesis of a glycononaosyl ceramide with a sialyl dimeric Le^x sequence.



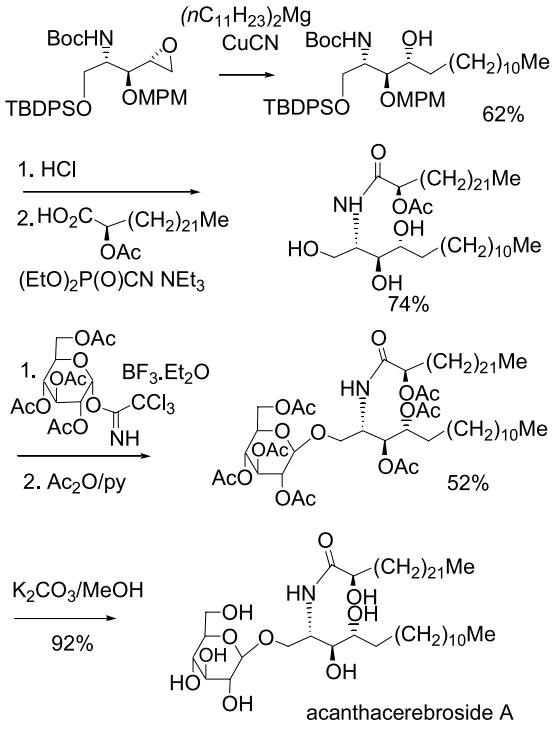
Scheme 44. Synthesis of a GM_3-lactone analogue.

glycosphingolipid isolated from starfish, exhibiting significant antitumour, immunostimulatory, neuritogenic and growth-inhibitory activities (Scheme 45).[80]

The power of the trichloroacetimidate method was particularly showcased in the development of the first total synthesis of one of the most complex resin glycosides known to date, woodrosin I (Scheme 46).[81]

In addition, the total synthesis of the natural herbicide tricolorin A constituted a major challenge due to the presence of a macrolide entity formed by (11*S*)-hydroxyhexadecanoic acid spanning two units of its sugar backbone.[82] Scheme 47 summarizes the synthesis of tricolorin A reported by Heathcock in 1997.[83]

In 2004, Fürstner reported another synthesis of tricolorin A based on a macrocyclisation by ring-closing metathesis for the formation of the large ring instead of a macrolactonisation similar to that depicted in Scheme 47. This methodology was generalised to the synthesis of tricolorin G.[84] The total synthesis by the same author and co-workers of another complex glycolipid exhibiting pronounced antiviral activity, cycloviracin B_1, was a remarkable target, which



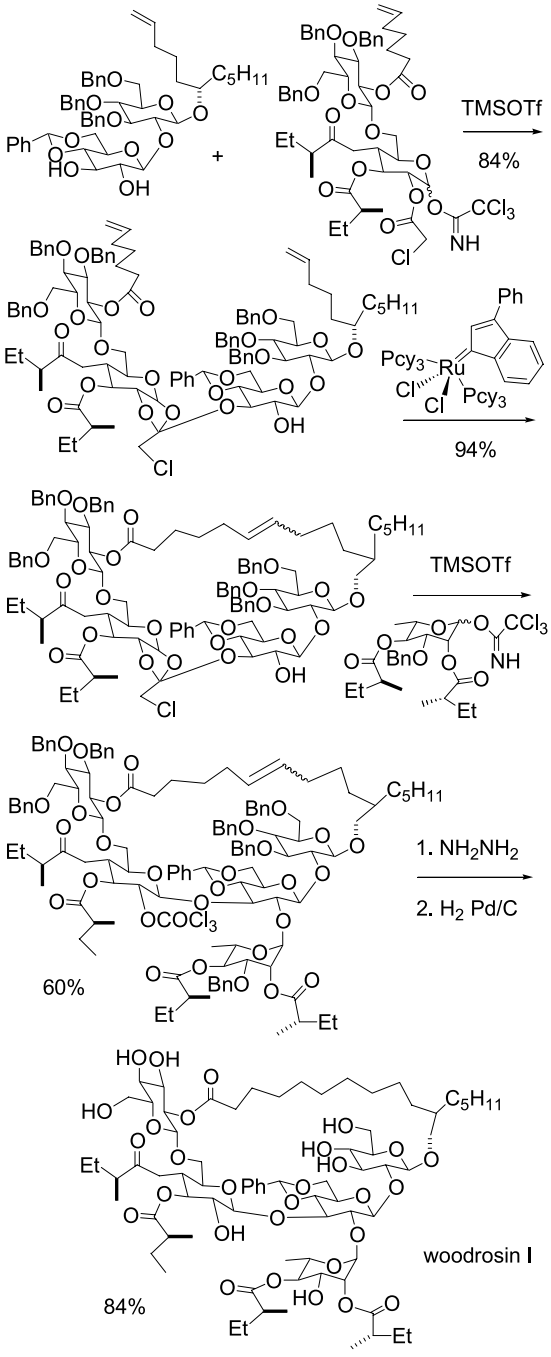
Scheme 45. Synthesis of acanthacerebroside A.

involved a trichloroacetimidate-mediated glycosylation as the final step (Scheme 48).[85]

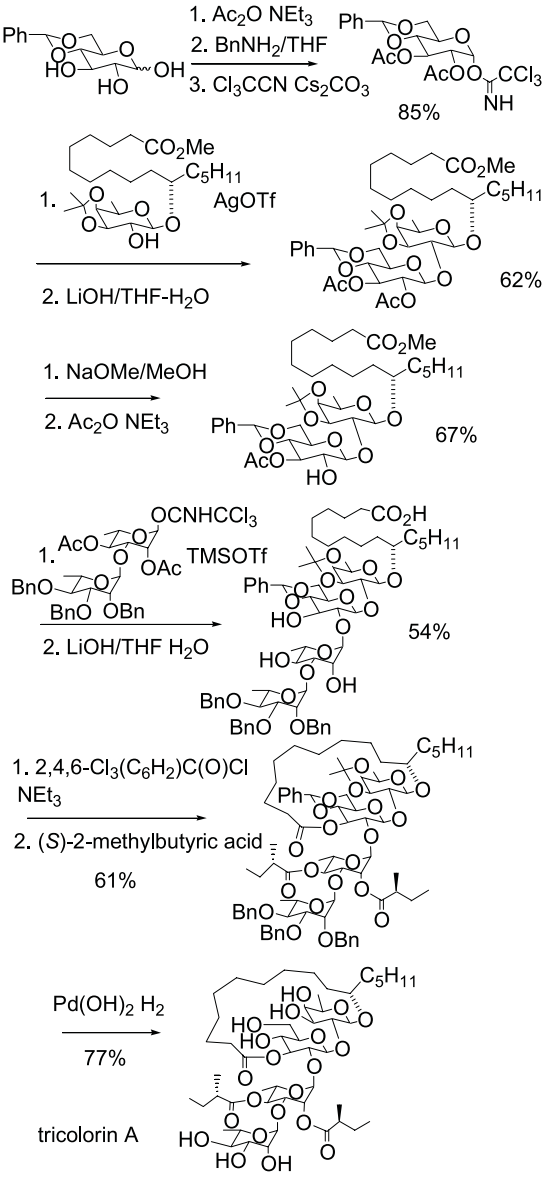
In 2004, Fürstner et al. reported the first total synthesis of another antiviral complex glycolipid, macroviracin D, which can be considered as a constitutional isomer of cycloviracin B_1, with respect to their core structures.[86] The blueprint of the synthesis of cycloviracin B_1 outlined above could be easily adapted to the synthesis of the related macrodiolide glucolipsin A, a natural glucokinase inhibitor.[87] Moreover, Schmidt et al. have reported the syntheses of various glycolipids such as the macrolidic glycolipid calonyctin A, a plant-growth regulator,[88] and synthetic glycolipids in which the synthetic carbohydrate antigen was linked to an appropriate synthetic immunostimulatory carrier.[89] On the other hand, in 2001, an efficient synthesis of fluorescence-labelled sialyl Lewis^x glycosphingolipids was performed on the basis of several trichloroacetimidate donors and an azidosphingosine glycosylation procedure for the attachment of the labelled fatty acids (Scheme 49).[90]

In order to clarify the mode of the biological action of lipid A, various lipid A analogues have been prepared.[91] As an example, Kusumoto et al. have described the synthesis of a fluorescence-labelled lipid A analogue in 15 steps from D-glucosamine in total 16% yield (Scheme 50).[92]

3.1.2. Synthesis of oligosaccharides. The trichloroacetimidate methodology has been widely employed for the synthesis of oligosaccharides, in particular those corresponding to the regular sequence of heparin.[93–95] This methodology was also applied to the synthesis of hyaluronic acid, an extracellular carbohydrate polymer regulating various biological processes.[96] Moreover, trichloroacetimidates were used as intermediates in the synthesis of the naphthyl disaccharides corresponding to olivomycin A and mithramycin, which are the most well-known members of the aureolic acid antitumour antibiotic family.[97] In the same way, a ribofuranosyl trichloroacetimidate derivative has proved to be an excellent precursor for the synthesis of the key monomer unit for the preparation of oligosaccharides of *Haemophilus influenzae* type B (a major cause of meningitis).[98] In 2003, various trichloroacetimidoyl derivatives were also employed in the synthesis of the antitumour agent laminarin, a hexasaccharide having D-arabinofuranosyl side chains.[99] In order to study the binding properties of calicheamicin's oligosaccharides to



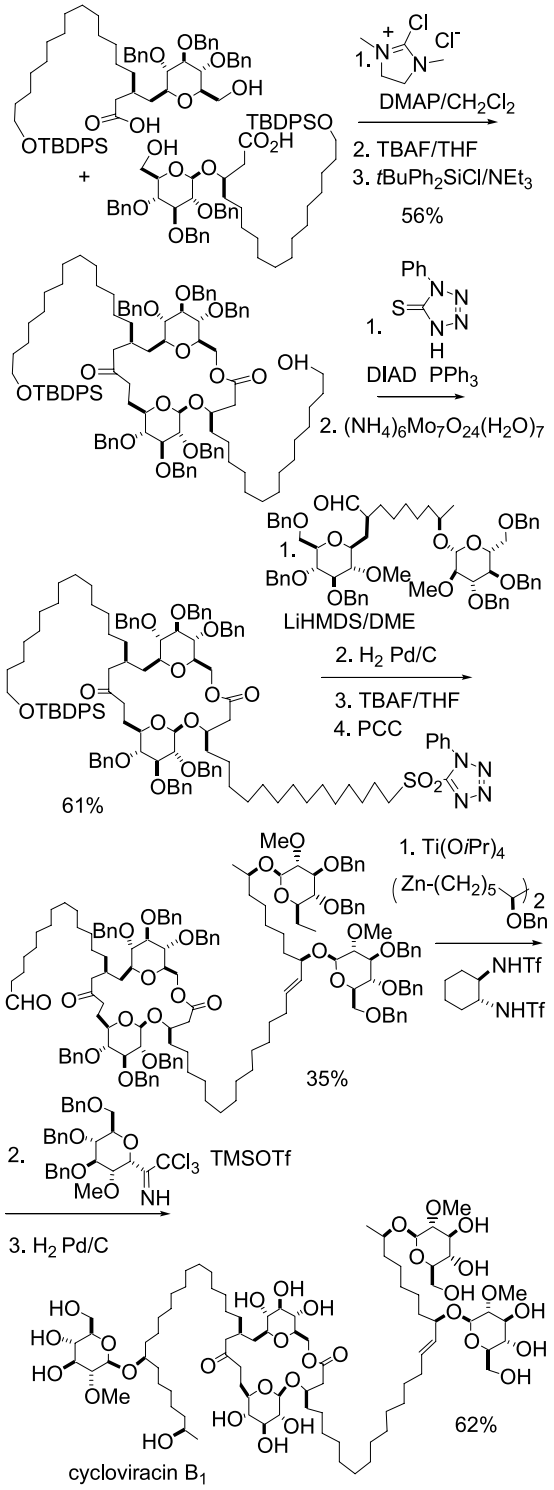
Scheme 46. Synthesis of woodrosin I.



Scheme 47. Synthesis of tricolorin A.

DNA, Nicolaou et al. have prepared a series of analogues of these natural antitumour antibiotic oligosaccharides by the use of trichloroacetimidates.[100] During a program directed towards the total synthesis of the everninomicin oligosaccharide antibiotics, the same group has developed the stereoselective construction of 1,1′-disaccharides and 1,1′;1″,2-trisaccharides by tin acetal technology involving trichloroacetimidates (Scheme 51).[101]

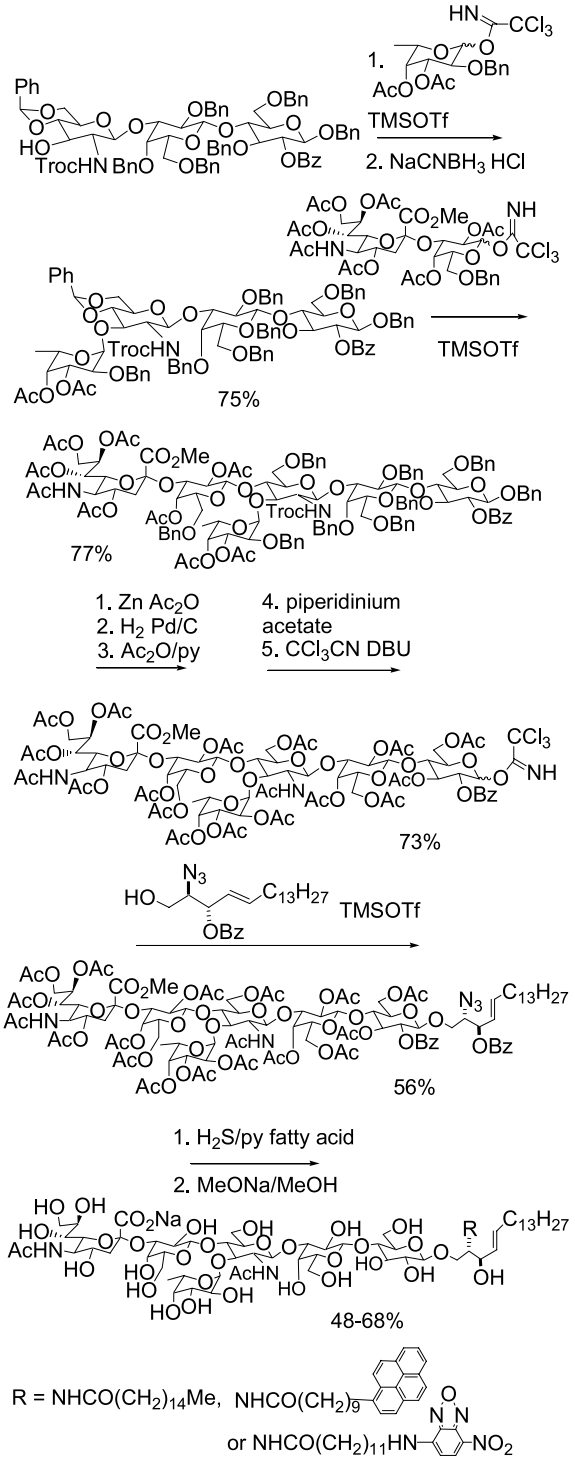
α(1→2)-Linked disaccharides are key subunits of numerous biologically potent oligosaccharides such as antigens, antibiotics, glycoproteins, and glycolipids. In 2002, Hung et al. reported the synthesis of biologically potent α1→2-linked disaccharide derivatives via regioselective one-pot protection–glycosylation (Scheme 52).[102] As an example, compounds **7** and **8** are the protected versions of biologically potent disaccharides, which are, respectively, a typical constituent of the cell membrane of halophilic



Scheme 48. Synthesis of antiviral glycolipid cycloviracin B_1.

bacteria and the major component of the glycolipids extracted from *Lactobacillus casei* A.T.C.C. 7469.

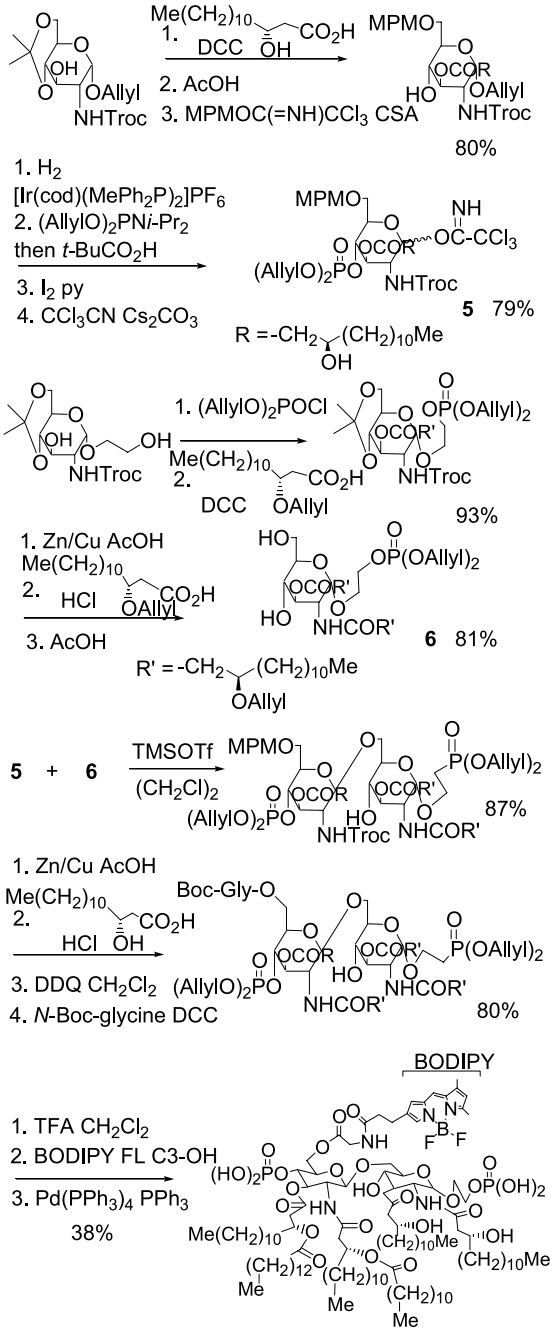
More recently, Kong et al. reported the synthesis of the glycosylphosphatidylinositol (GPI) anchor glycans from *Saccharomyces cerevesiae* and *Aspergillus fumigatus*, which are human pathogens.[103] Scheme 53 illustrates the synthesis of the pentasaccharide from *S. cerevesiae* as its



Scheme 49. Synthesis of sialyl Lewis^x glycosphingolipids.

methyl ether, which involves several trichloroacetimidations performed in the presence of TMSOTf.

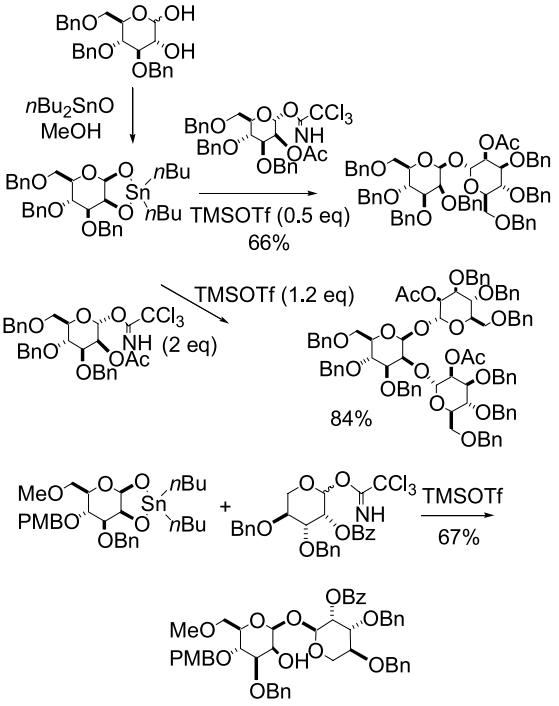
3.1.3. Synthesis of glycopeptides and glycoproteins. The trichloroacetimidate method has been widely applied for the synthesis of glycosylated peptides and proteins such as the antibiotics bulgecins,[104] antifreeze glycoproteins,[49] the mucin-related F1α antigen,[105] and various glycosyl amino acid derivatives involved as building blocks for solid-phase



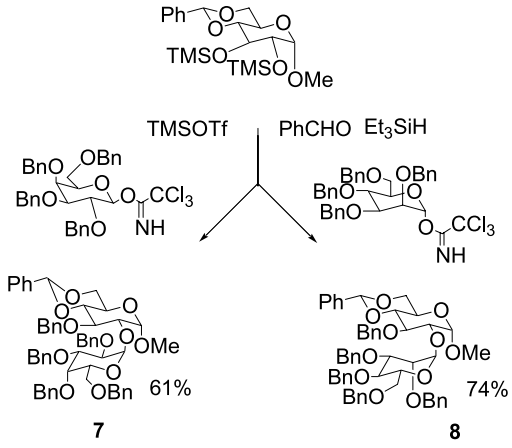
Scheme 50. Synthesis of a fluorescence-labelled analogue of lipid A.

glycopeptide synthesis.[106] Thus, Koganty et al. have developed the synthesis of cancer-associated carbohydrates core 2, core 6, core 5, sialyl core 5, and another structure, F1-α, in order to use them as building blocks for the synthesis of mucin glycopeptides involved in cancer immunotherapy.[107] As an example, Scheme 54 depicts the synthesis of core 5. On the other hand, Kanemitsu et al. also involved trichloroacetimidate donors in their synthesis of suppresein A.[108]

In 2003, Barchi et al. reported a highly efficient preparation of tumour antigen-containing glycopeptide building blocks from novel pentenyl glycosides (Scheme 55).[109]



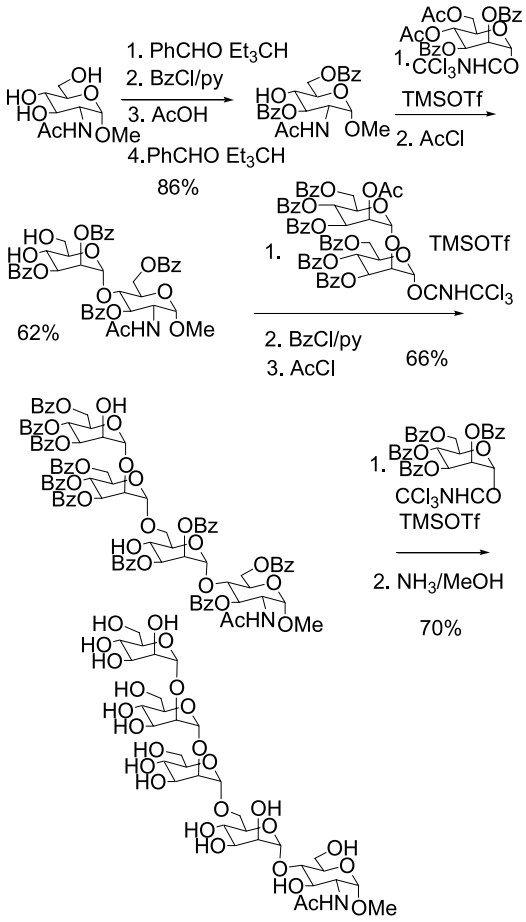
Scheme 51. Synthesis of everninomicin oligosaccharides by tin acetal technology.



Scheme 52. Synthesis of α-linked disaccharides by one-pot benzylation-glycosylation.

In order to prepare new types of glycoconjugates such as *O*-glycosylated-isoserine derivatives, Burger et al. studied the incorporation of isoserine directly at the interface of the carbohydrate/peptide (Scheme 56).[110]

3.1.4. Synthesis of natural products. Up to now, the powerful trichloroacetimidate-mediated glycosidation procedure has been widely used in complex molecule construction, for example, in Hatakeyama's paeoniflorin synthesis,[111] Knapp's capuramycin synthesis,[112] Kocevar's novobiocin-related compounds synthesis,[113] and Nakamura's anti-inflammatory drug DUP-697 metabolite



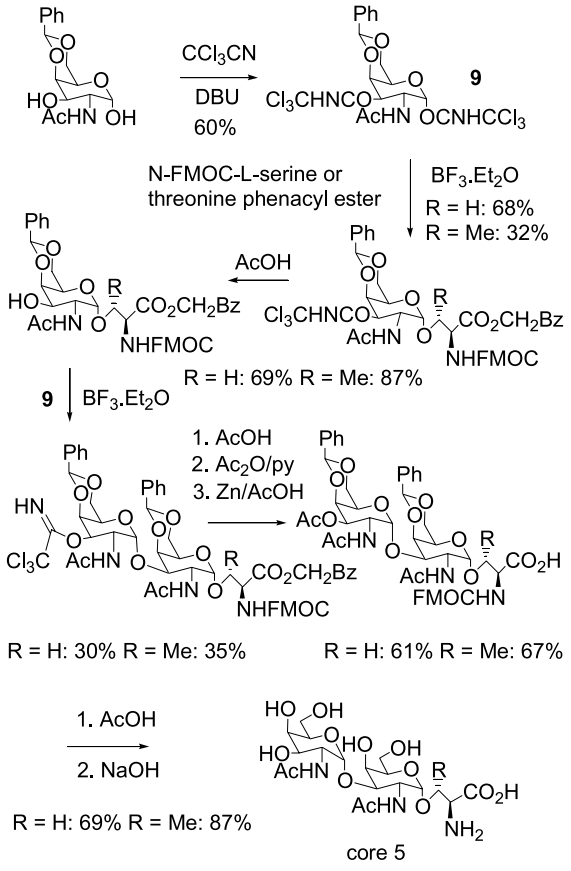
Scheme 53. Synthesis of the GPI anchor pentasaccharide from *S. cerevesiae*.

synthesis.[114] More recently, Yu et al. and Baï et al. have successfully applied the glycosylation protocol to their synthetic studies of anti-allergic cassiaside C_2,[115] and antiviral sarmentosin (Scheme 57), respectively.[116]

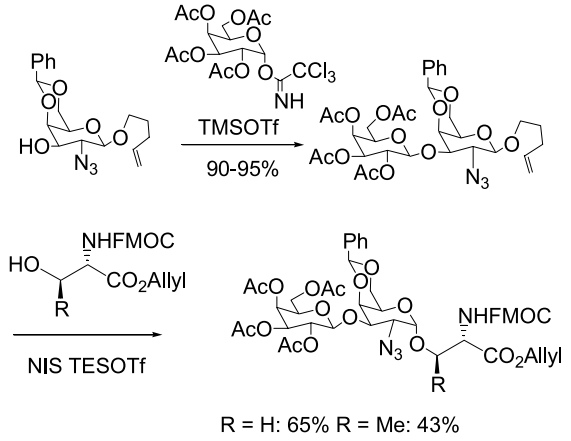
Eleutherobin is a recently discovered antitumour agent isolated from an *Eleutherobia* species of soft coral, and exhibiting a taxol-like mechanism of action in polymerizing and stabilizing microtubules. The total syntheses of eleutherobin and its relatives, eleutherosides A and B, from D-arabinose imidate were reported by Nicolaou (Scheme 58).[117]

Callipeltoside A is a rare cytotoxic polyketide, recently isolated from the lithistida sponge, *Callipelta* sp., and presenting excellent prospects for the study and treatment of cancer. Trost[118] and, more recently, Paterson[119] (Scheme 59) have elaborated total syntheses of this structurally unique class of bioactive marine macrolides. The glycosylation step was suitable for the final stage of Paterson's synthesis.

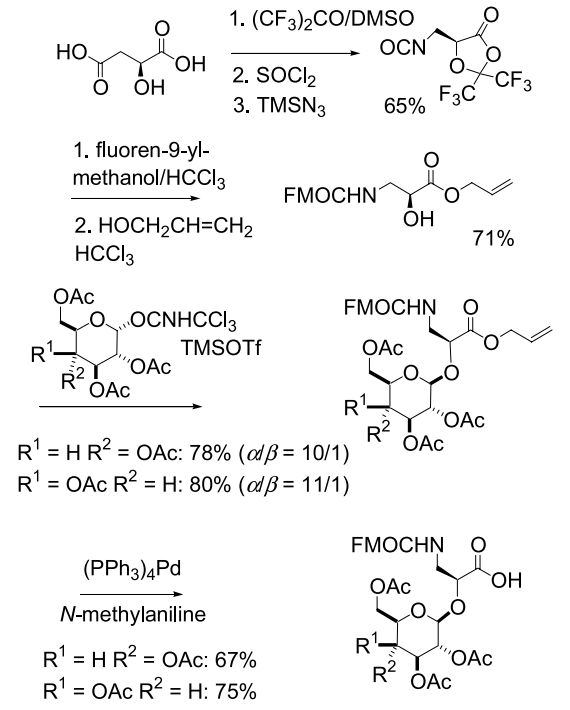
The first total synthesis of olivomycin A, a prominent member of the aureolic acid family of antitumour antibiotics, was achieved in 1999 by a route featuring three highly stereoselective β-glycosidation reactions (Scheme 60)[120,121]



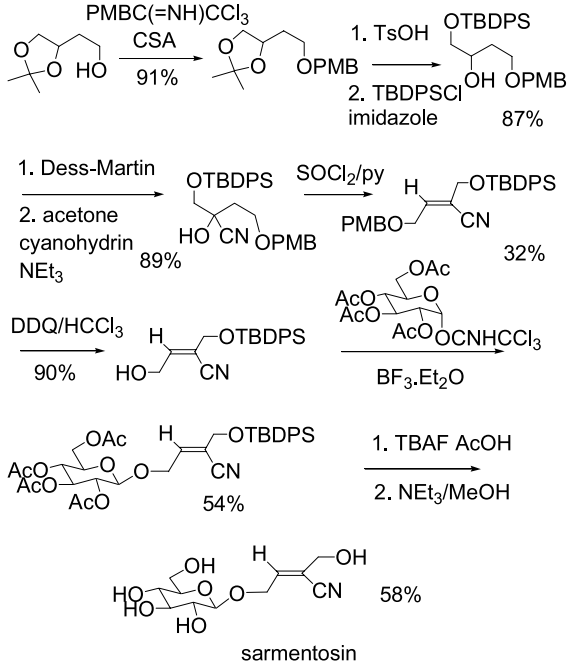
Scheme 54. Synthesis of core 5.



Scheme 55. Synthesis of tumour antigen-containing glycopeptide building blocks.



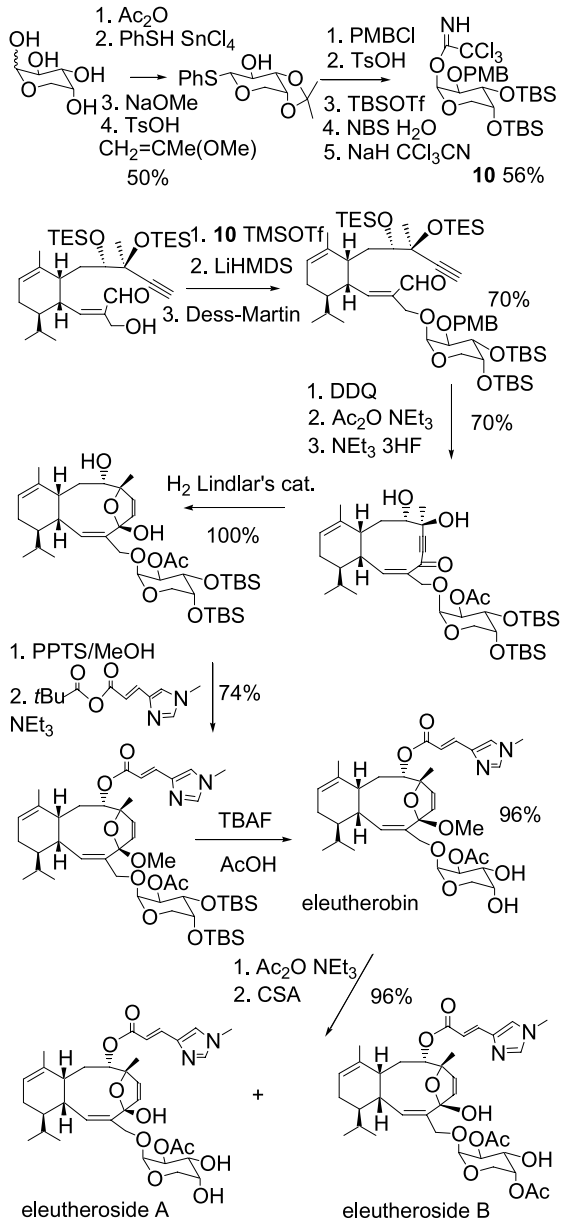
Scheme 56. Synthesis of *O*-glycosylated-isoserine derivatives.



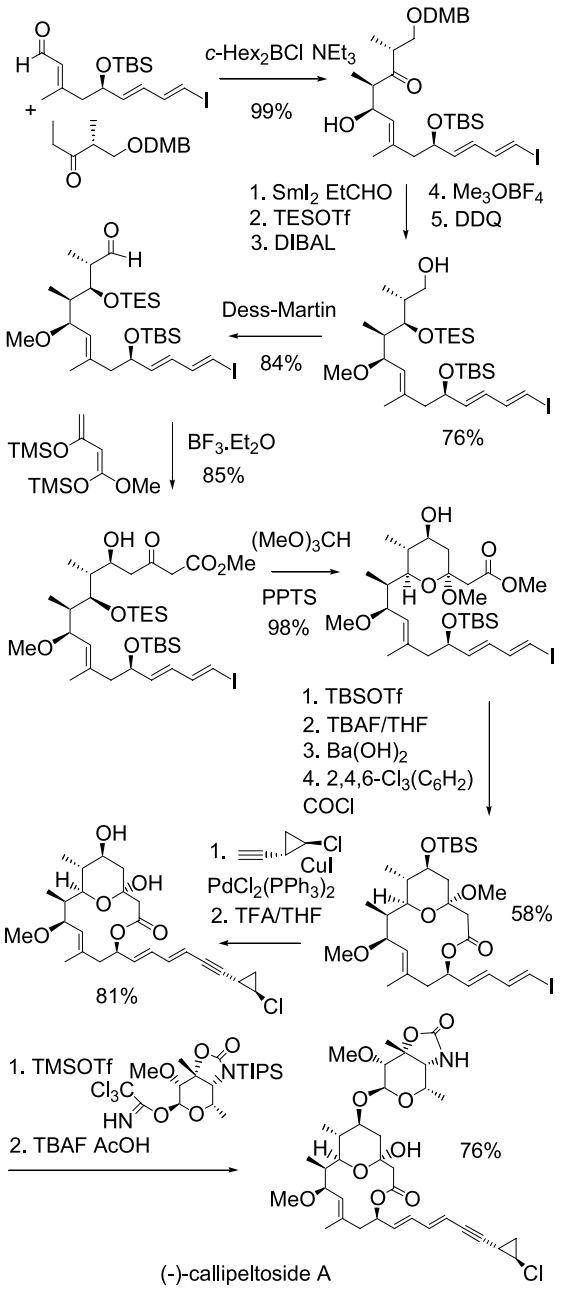
Scheme 57. Synthesis of sarmentosin.

Phenylethyl glycosides constitute an interesting group of natural products, which are widely distributed in the plant kingdom. Verbascoside, which belongs to this class of compounds, is a potent inhibitor of protein kinase C and aldose reductase. In addition, it possesses antibacterial, antiviral, and antitumour activity, as well as cytotoxic and immunomodulatory properties. Scheme 61 depicts the first synthesis of verbascoside developed by van Boom in 1999, on the basis of a disaccharide imidate couplage.[122]

Neocarzinostatin was the first natural enediyne antitumour antibiotic identified and is the prototypical member of the chromoprotein class. Members of the chromoprotein class are composed of a 1:1 complex of a small-molecule chromophore component and a binding protein. In 2002, Myers et al. described the first synthesis of neocarzinostatin chromophore involving a $BF_3 \cdot Et_2O$-mediated glycosylation



Scheme 58. Synthesis of eleutherobin and eleutherosides A and B.



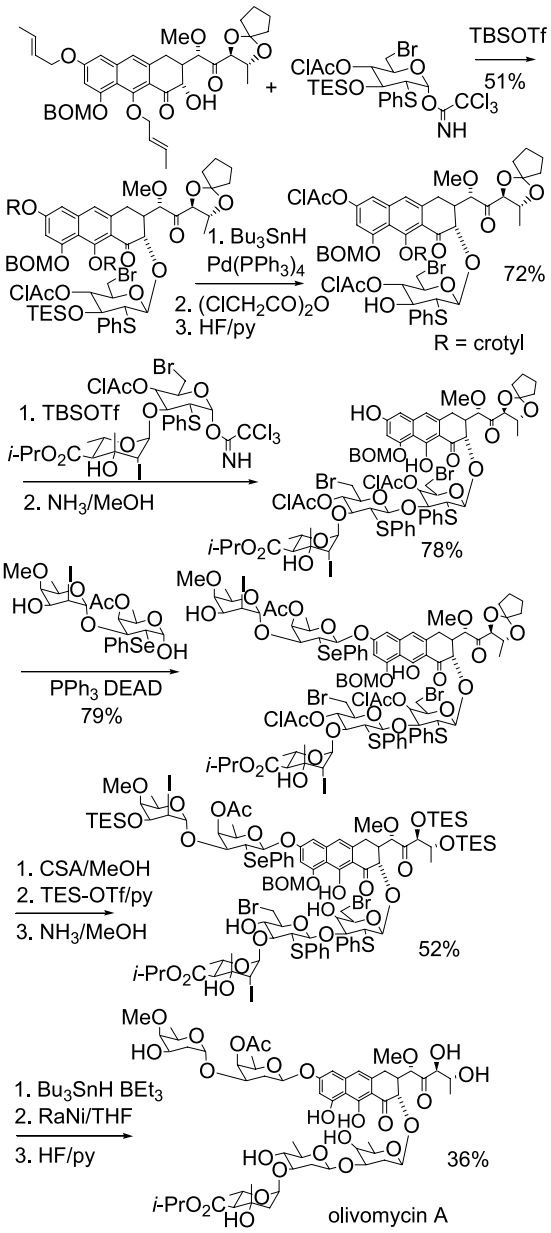
Scheme 59. Synthesis of (−)-callipeltoside A.

of a trichloroacetimidate containing a free *N*-methylamino group (Scheme 62).[123]

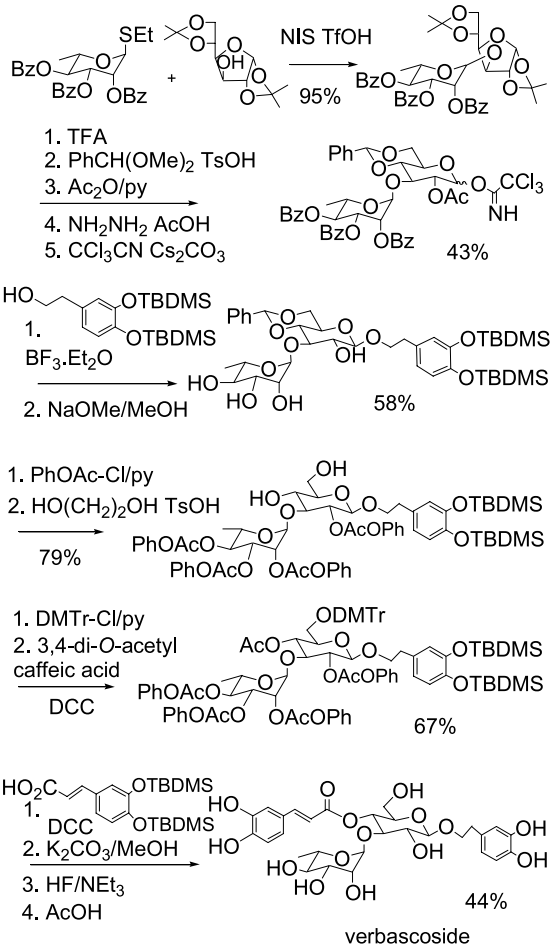
The enediyne antibiotic family can be broadly divided into a chromoprotein subclass including neocarzinostatin, and a non-proteinaceous group, exemplified the calicheamicins and typified by calicheamicin γ_1. The trichloroacetimidate methodology was already involved by Nicolaou in his first total synthesis of this fascinating and unusual molecule.[124] In 1995, Danishefsky et al. developed another total synthesis of calicheamicin γ_1 based on a similar glycosylation reaction. Their own efforts were deployed towards determining the latest point in the synthesis in which coupling between the calicheamicinone derivative and the trichloroacetimidate could be accomplished (Scheme 63).[125]

Paclitaxel (taxol) can be considered as the anticancer wonder drug of the 1990s. One of the major drawbacks of this drug is its extremely low aqueous solubility. In order to prepare taxane glycoconjugates, similar to those found in nature, which maintained the antitumour efficacy, but which would be more soluble in water than paclitaxel, Zamir et al. reported in 2003 the semisynthesis of an *O*-glycosylated docetaxel analogue by glycosylation of a natural taxane with an imidate derivative (Scheme 64).[126]

On the other hand, the trichloroacetimidate procedure was also used to synthesise more simple compounds[127] such as the causative agents of favism, vicine and convicine,[128] various monosaccharide-linked cationic amphiphiles to deliver genes into cells,[129] an important metabolite,



Scheme 60. Synthesis of olivomycin A.



Scheme 61. Synthesis of verbascoside.

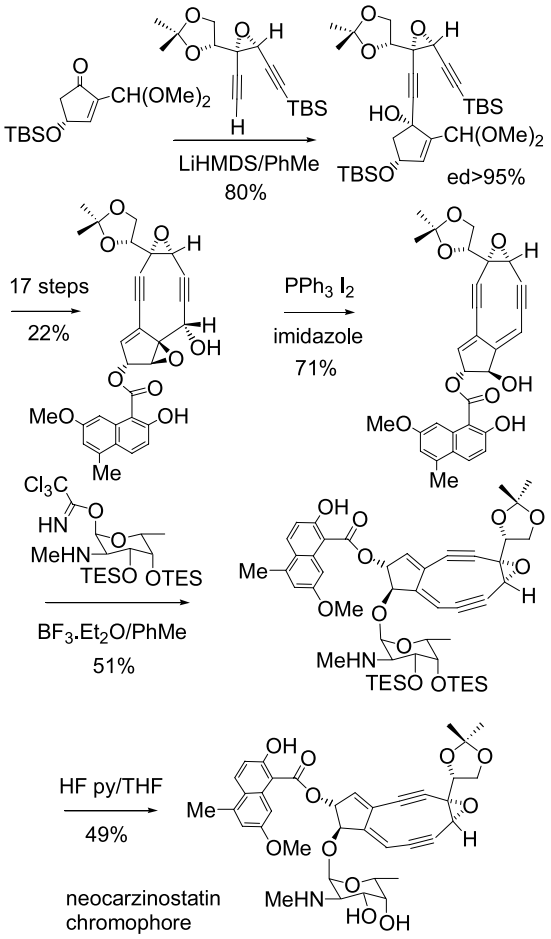
7-hydroxycoumarin glucuronide,[130] and glycosylinositol phosphates related to putative insulin mimetics.[131] Moreover, flavonoid 7-*O*-glycosides were prepared by coupling glycosyl trifluoroacetimidates with flavonoid derivatives under the promotion of $BF_3 \cdot Et_2O$.[132] The same methodology was applied by Boubekeur et al. in 2004 to provide the first total synthesis of the potent glycosidase inhibitors, 1-*O*-β-D-glucopyranosyl-5-deoxyadenophorine and its aglycon congener.[133]

3.2. 1-*O*-Acyl sugars

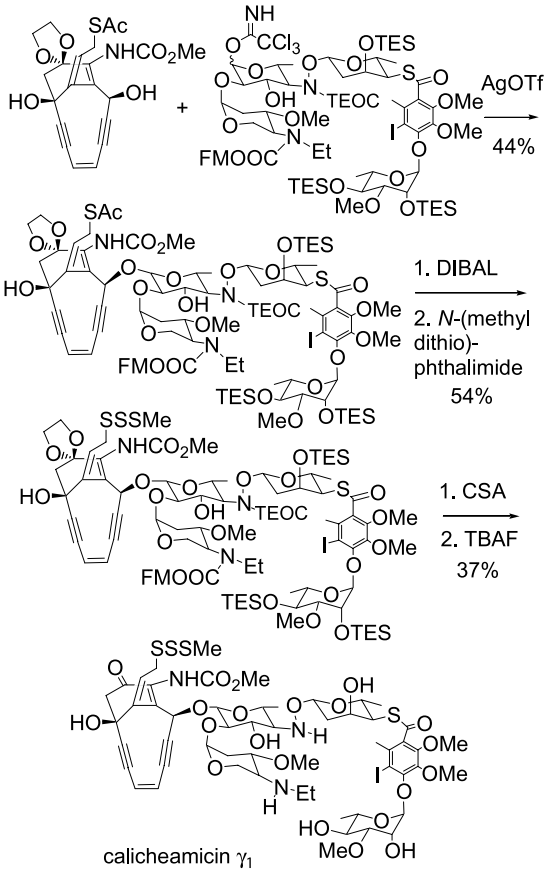
An advantage of the 1-*O*-acylated glycosyl donors in the glycosylation method is undoubtedly the ease of their preparation. Generally, the activation of these compounds is achieved in the presence of a Lewis acid, traditionally $SnCl_4$, $BF_3 \cdot Et_2O$, or TMSOTf. Elofsson et al. discovered that anomeric acetates could be used to glycosylate amino acids in which the carboxylic acid was unprotected.[134] This was a major breakthrough, because the approach circumvents the deprotection of that carboxylic acid prior to incorporation into a peptide. Steffan et al. showed that coupling peracetylated glucose with *N*-FMOC-protected serine provided the corresponding glycosylated amino acid (Scheme 65).[135] In 2004, this glycosyl donor was involved in a rapid, high-yield and stereoselective synthesis of *O*-glycopeptides.[136] The glycosylation reaction mixture (peracetylated glucose, protected amino acid and $BF_3 \cdot Et_2O$) was used directly to couple to the amino group of the peptide resin without isolation and purification.

In 1994, Satoh et al. used this glycosyl donor in order to prepare 4-alkoxyphenyl β-D-glucopyranosides, showing strong inhibitory effects on concanavalin A-induced histamine release.[137] A similar methodology was applied for the preparation of sannamycin-type aminoglycoside antibiotics.[138] In 1994, Krausz et al. reported the synthesis of bioactive nucleoside analogues with a spacer arm linking the sugar and the base via $SnCl_4$-mediated glycosylation of 3-alkyl N^4-(3-hydroxypropyl) 2-piperazinones with protected 1-*O*-acetyl ribofuranoses (Scheme 66).[139]

In 1996, this group reported the synthesis of novel *meso*-glycosylarylporphyrins, where the carbohydrate moiety was



Scheme 62. Synthesis of neocarzinostatin chromophore.



Scheme 63. Synthesis of calicheamicin γ_1.

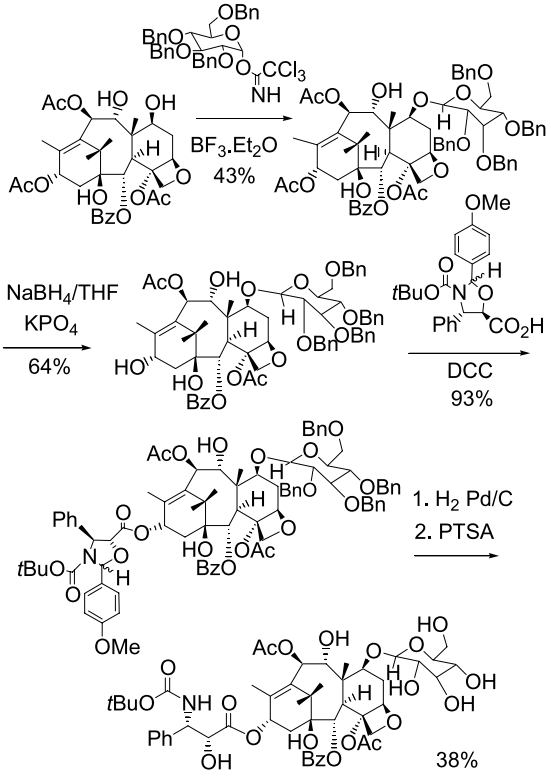
separated from the aryl substituent by a spacer arm, by a similar methodology.[140] These compounds were of considerable interest for photodynamic therapy. The first synthesis of the complex macrolide insecticide, lepicidin A, was developed by Evans and involved an acid-catalysed glycosidation with a glycosyl acetate in the presence of catalytic quantities of trityl perchlorate (Scheme 67).[141]

In 2002, Kakinuma et al. achieved the enantioselective total synthesis of an antitumour antibiotic, vicenistatin, featuring a 20-membered macrocyclic lactam glycoside with the aminosugar vicenisamine.[142] A penultimate glycosidation of the previously prepared *O*-TMS-aglycone with the appropriately protected 1-*O*-acetyl aminosugar, followed by final deprotection, allowed the accomplishment of the total synthesis (Scheme 68).

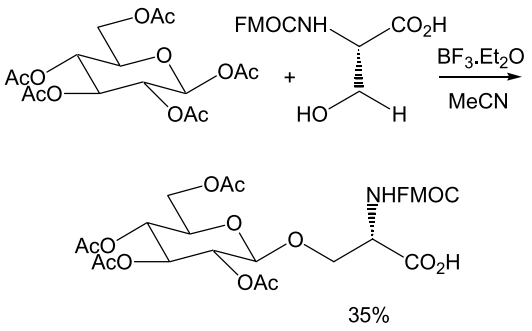
Normal glycosidation methods applied to furanosides showed generally low stereoselectivities. In this way, Trost developed a new palladium-catalysed glycosidation with elaborated phenols, and applied it as the key step in the enantioselective synthesis of the *C*-2 epimer of hygromycin A, a fermentation-derived natural product exhibiting peptidyltransferase inhibition (Scheme 69).[143]

3.3. Phosphate derivatives

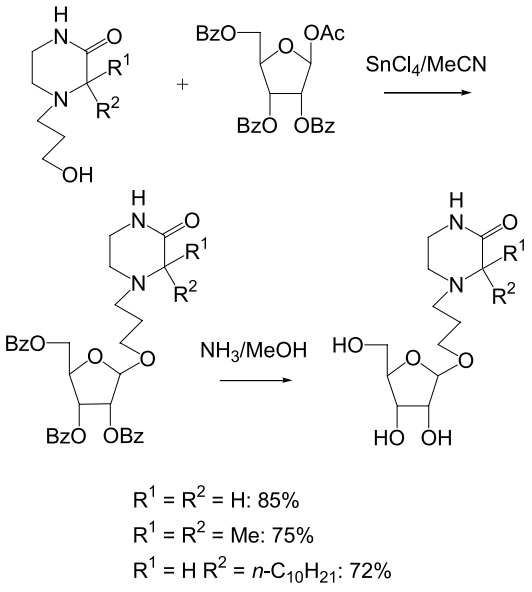
Several glycosyl donors possessing a phosphorus atom in



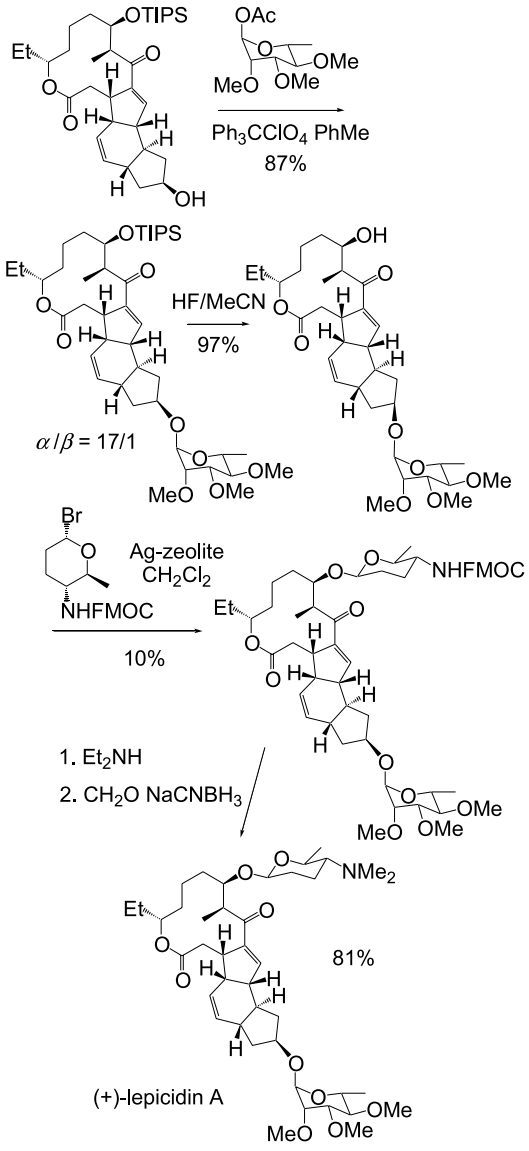
Scheme 64. Semisynthesis of *O*-glycosylated docetaxel analogue.



Scheme 65. Synthesis of a glycosylated amino acid.



Scheme 66. Synthesis of nucleoside analogues.

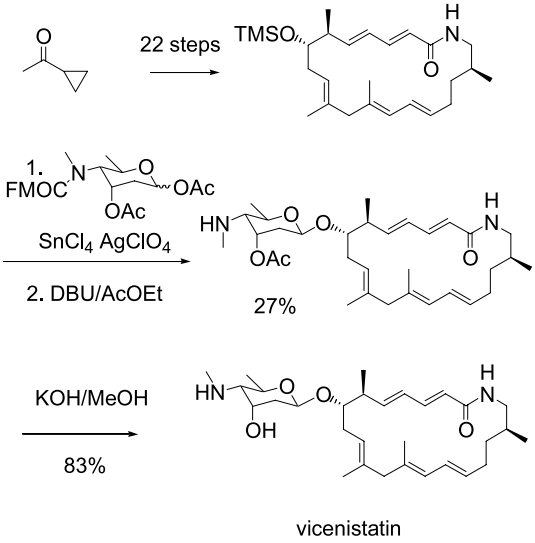


Scheme 67. Synthesis of (+)-lepicidin A.

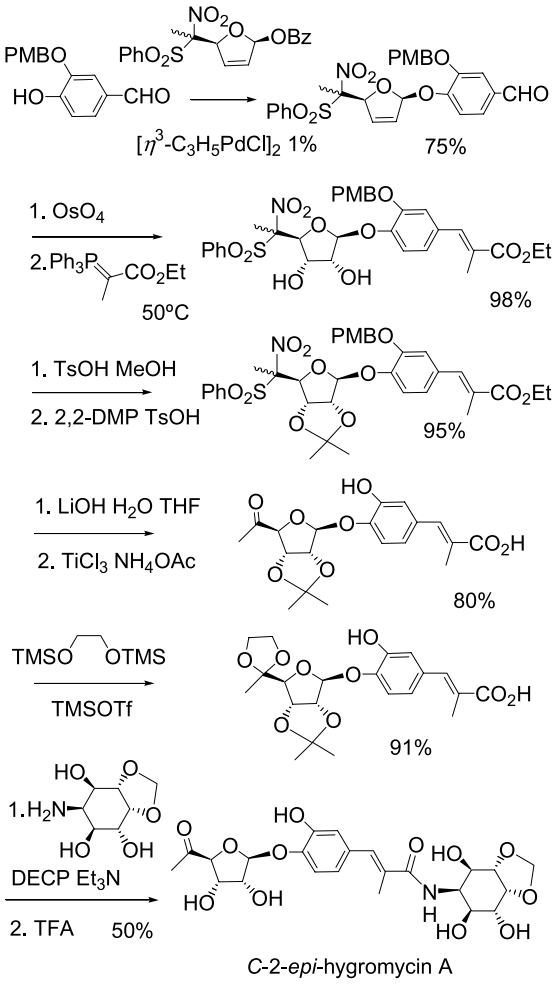
the leaving group at the anomeric centre have been investigated for the glycosylation procedure. Since phosphorus compounds can be easily modified by several kinds of other atoms, a wide variety of leaving groups (phosphates, phosphites, phosphoramidates) with different properties can be designed. As an example, Boger involved two glycosylations with glycosyl diphenyl phosphates as key steps in his total synthesis of bleomycin A_2, a major constituent of a family of glycopeptide antitumour antibiotics (Scheme 70).[144]

In 1999, Singh et al. demonstrated that activation of the anomeric centre of suitably protected L-fucopyranose and D-galactopyranose with propane-1,3-diyl phosphate allowed the synthesis of disaccharide fucosidase substrates (Scheme 71).[145] These compounds occur as part of the carbohydrate motif of the blood group-specific glycoproteins and glycolipids, and are also present in human milk.

In 1994, Schmidt et al. showed the utility of glycosyl phosphites as glycosyl donors by involving fructofuranosyl and 2-deoxyhexopyranosyl phosphites in glycoside bond



Scheme 68. Synthesis of antitumour antibiotic vicenistatin.

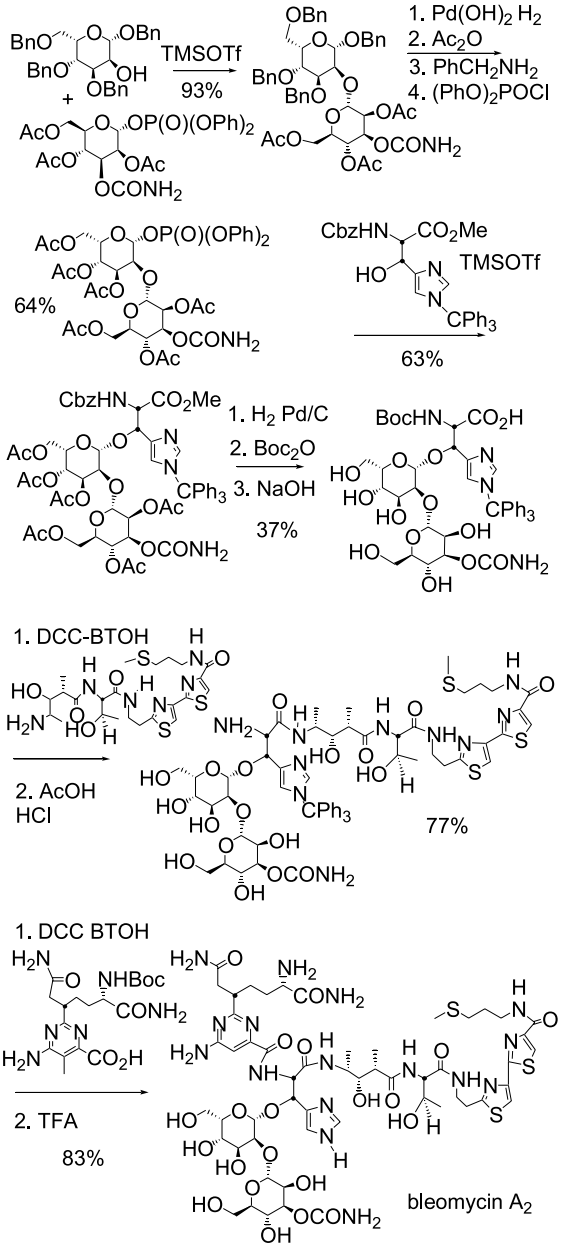


Scheme 69. Synthesis of *C*-2-*epi*-hygromycin A.

formation.[146] A similar methodology was applied by Wong et al. to prepare sialyl Lewis X mimetics exhibiting inhibitory activities against E-selectin.[147] In 2000, Danishefsky developed a cleaner method using diisopropyl phosphoramidite as the source of the phosphite group and applied this method to the total synthesis of the methyl glycoside of ganglioside GM_1 (Scheme 72).[148]

In 1997, Hashimoto et al. accomplished a stereocontrolled synthesis of globotriaosylceramide (Gb_3) by linear and convergent routes based on the glycosylation methodology, where the dual role of the tetramethylphosphoroamidate group as an anomeric protective group as well as a leaving group was crucial to the success of the strategy (Scheme 73).[149]

Several new classes of glycoproteins have been recently identified and an intriguing group contains oligosaccharides linked to a serine moiety via a phosphodiester linkage, this type of protein modification having been referred to as protein phosphoglycosylation. In order to study the biological significance of protein phosphoglycosylation, reasonable quantities of the compounds were required. In this context, Boons et al. demonstrated that benzyl and cyanoethyl phosphochloroamidites were convenient



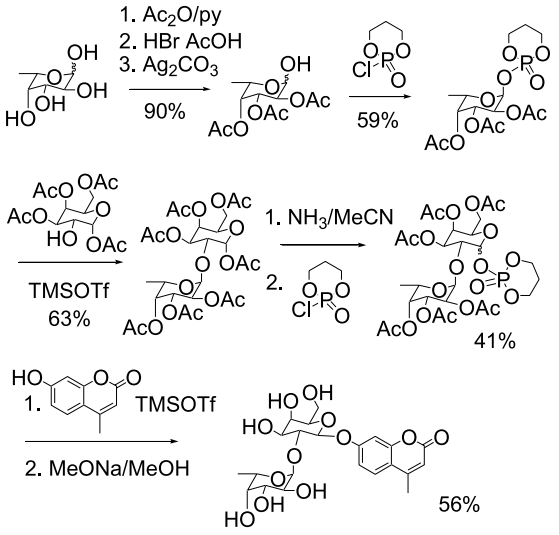
Scheme 70. Synthesis of bleomycin A_2.

reagents for the preparation of a wide range of α-D-mannosylphosphate serine derivatives that could be used for the synthesis of glycosylphosphopeptides (Scheme 74).[150]

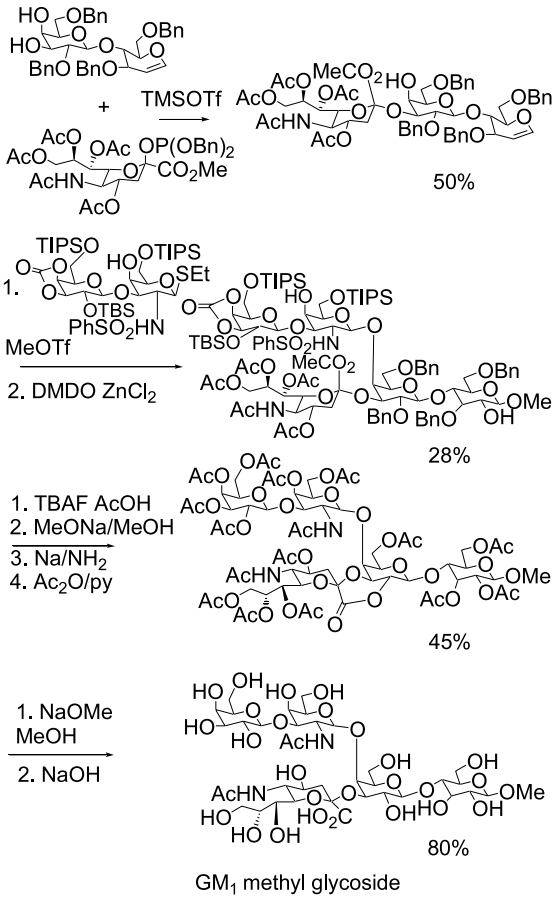
3.4. 1-Hydroxyl sugars

The Fischer–Helferich method comprises the direct formation of a glycosidic bond from the 1-hydroxyl sugar through an acid-catalysed acetalisation procedure. This direct method was employed by Saulnier et al. for the semi-synthesis of the anticancer compound, etoposide phosphate, a water-soluble clinically active prodrug of etoposide (Scheme 75).[151]

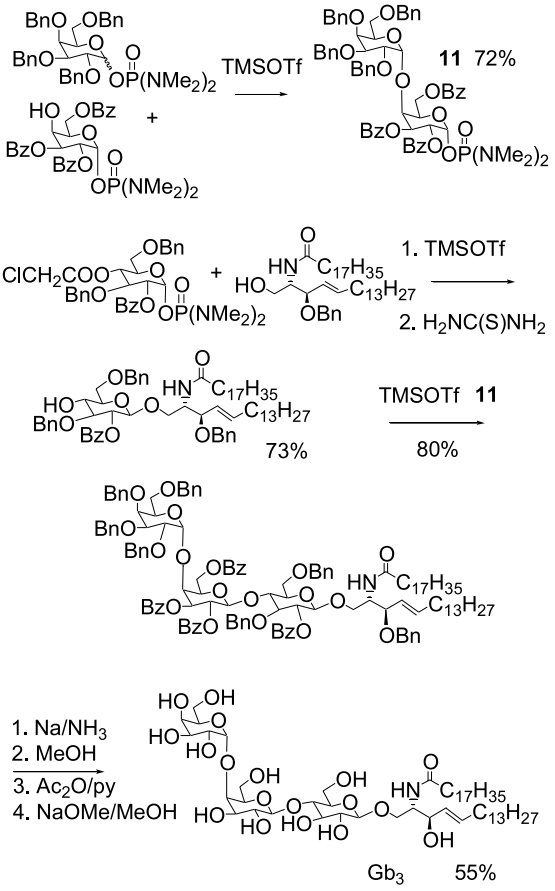
In order to prepare analogues of the natural antimalarial agent, artemisinin, more suitable for intravenous



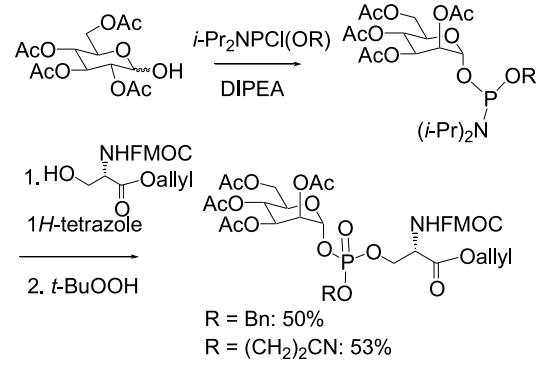
Scheme 71. Synthesis of fucosidase substrate.



Scheme 72. Synthesis of methyl glycoside of GM_1.



Scheme 73. Synthesis of globotriaosylceramide Gb_3.

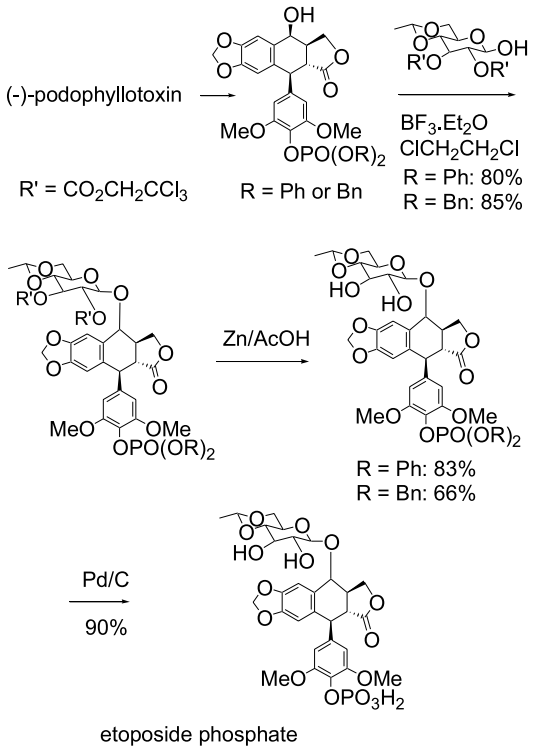


Scheme 74. Synthesis of α-D-mannosylphosphate serine derivatives.

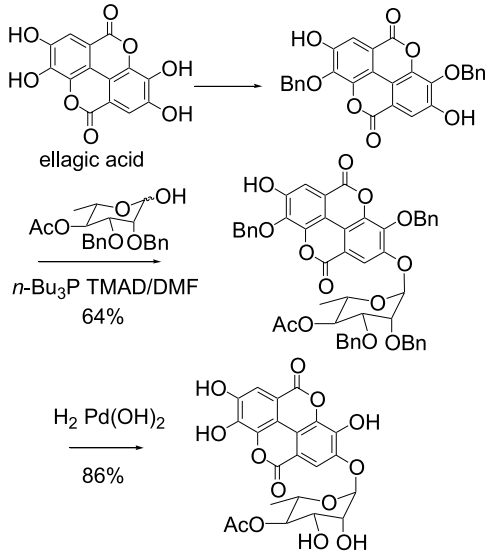
administration, Ramu has applied a similar procedure to that depicted in Scheme 75.[152] On the other hand, Tatsuta et al. reported in 2003 the total synthesis of a new bioactive ellagic acid derivative by involving the glycosylation of 3,3′-di-*O*-benzylellagic acid with 4-*O*-acetyl-2,3-di-*O*-benzyl-L-rhamnose as the key step (Scheme 76).[153]

3.5. Other 1-*O*-derivatives

An unusual *O*-glycosidic linkage was designed and synthesised by Kim et al. in their preparation of glycopeptoids related to the cancer T_N antigen.[154] Reaction of GalNAc with allyl alcohol under Lewis acid catalysis led to an *O*-glycoside, which was then transformed into the expected peptoid building block (Scheme 77).

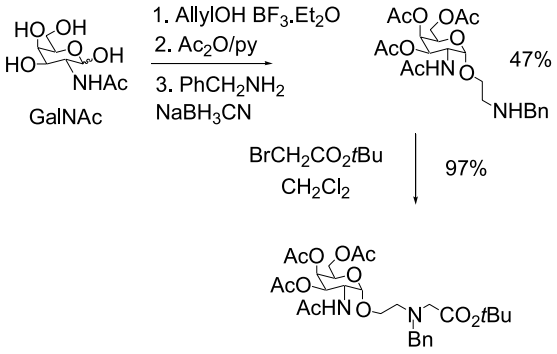


Scheme 75. Synthesis of etoposide phosphate.



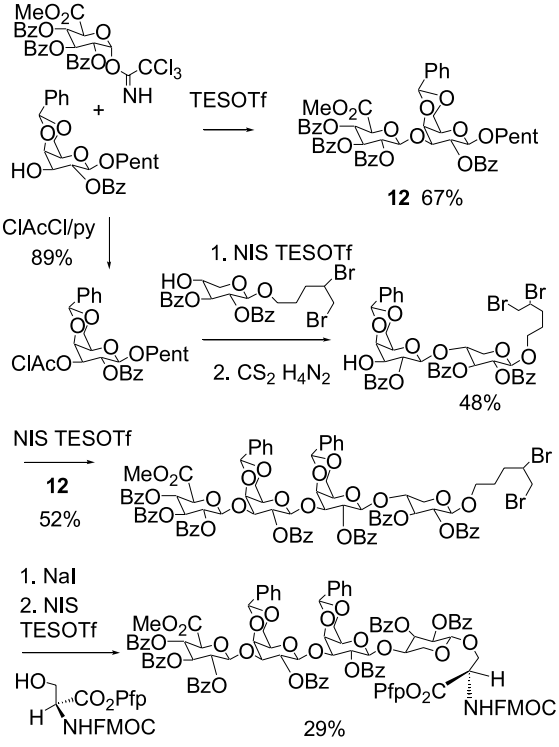
Scheme 76. Synthesis of a new bioactive ellagic acid derivative.

In 1988, Fraser–Reid introduced a 4-pentenyl group as a new and effective leaving group at the anomeric centre of the glycosyl donor.[155] The *n*-pentenyl group allows a wide variety of manipulations on the building blocks. The glycosylation reactions with 4-pentenylglycosides are usually promoted by IDCP or the more reactive NIS–TfOH or NIS–Et_3SiOTf, and are generally effected within minutes, depending on the promoter that is used. Moreover, all 4-*n*-pentenylated intermediates can be stored indefinitely. Fraser–Reid has widely developed the 4-*n*-



Scheme 77. Synthesis of a glycopeptoid.

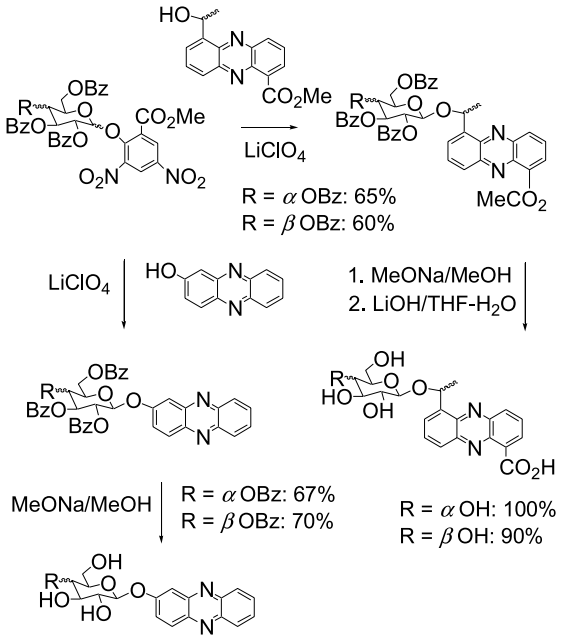
pentenylglycoside chemistry in the context of preparing biologically important oligosaccharides such as the pentasaccharide core of glycophosphatidylinositol anchors of membrane-bound proteins,[156] and the tetraglycosylserine corresponding to the proteoglycan linkage region (Scheme 78).[157] The 4-*n*-pentenyl glycoside method was also employed by Danishefsky et al. in order to develop a synthesis of fucosyl GM_1, a highly tumour-specific antigen associated with small-cell lung carcinoma.[158]



Scheme 78. Synthesis of the proteoglycan linkage region.

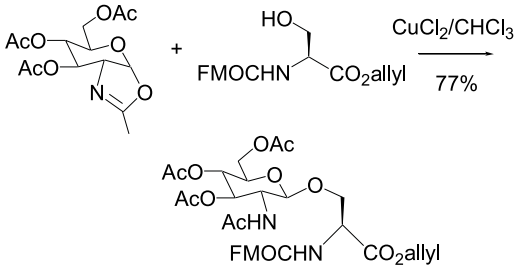
In order to elucidate the precise epitope structures of a number of monoclonal antibodies, Madsen et al. have recently applied the same procedure for the synthesis of hexasaccharide fragments of pectin.[159] Indeed, all glycosylation reactions implicated in this synthesis of hexagalacturonates were carried out with 4-*n*-pentenyl glycosides, providing good yields and selectivities.

On the other hand, Nielsen et al. have developed a new and efficient method for glycosylation under neutral, mildly basic, or very mild acidic conditions, in which the anomeric leaving group was methyl 3,5-dinitrosalicylate (DISAL), combining high reactivity with stability on prolonged storage. This methodology was successfully applied to the synthesis of glycosylated phenazine natural products and analogues (Scheme 79).[160]



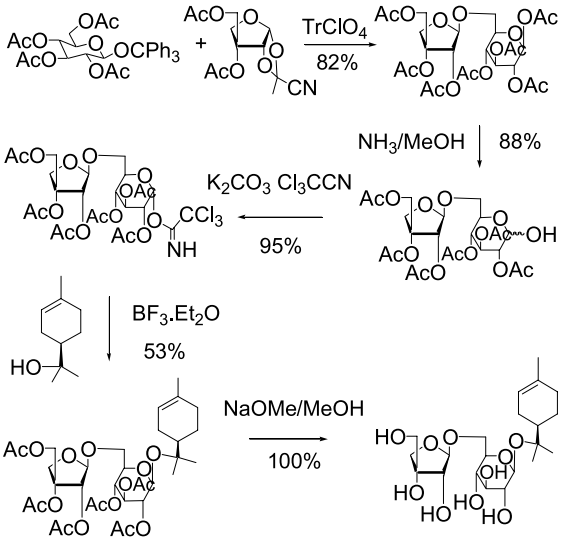
Scheme 79. Synthesis of glycosylated phenazines.

The oxazoline procedure has allowed the successful synthesis of 1,2-*trans*-2-acetamido-2-deoxyglycosides and oligosaccharides. The most commonly used sugar oxazolines are the methyl oxazolines. These are reactive intermediates upon activation by an acid or Lewis acids, allowing nucleophilic attack by a glycosyl acceptor to afford anomerically pure β-glycosides possessing the natural *N*-acetyl function, which is an extremely useful feature. This approach was applied by Arsequell et al. in order to prepare 2-acetamido-2-deoxyglycosides of amino acids for solid-phase peptide synthesis.[161] The same methodology was used for the synthesis of a partial structure of the large subunit of mammalian RNA polymerase II.[162] More recently, Wittmann et al. have reported the copper(II)-mediated glycosylation with glucosamine-derived oxazolines, providing various β-glycosides bearing the natural 2-acetamido functionality (Scheme 80). Compared to the usual procedures, the reactivity of the oxazoline was not enhanced, but the reaction conditions were milder, allowing higher yields without decomposition of the products.[163]



Scheme 80. Glycosylation of serine derivatives by the oxazoline method.

In 2002, Backinowsky reported that the cyanoethylidene derivative of a branched trisaccharide was an efficient glycosyl donor, allowing the assembly of a variety of 3,6-branched manno-oligosaccharides.[164] The Kochetkov method was also applied to the synthesis of natural 6-*O*-β-D-apiofuranosyl-β-D-glucopyranosides having terpineyl as the aglycon moiety (Scheme 81).[165]



Scheme 81. Synthesis of apiosyl-glucosides.

In 2003, Crich et al. developed the synthesis of the trisaccharide building block of the *N*-linked glycans of *N*-linked glycoproteins via a triflate-mediated direct β-mannosylation.[166] The triflate was generated from the corresponding thiomannoside donor in the presence of benzenesulfinylpiperidine and triflic anhydride.

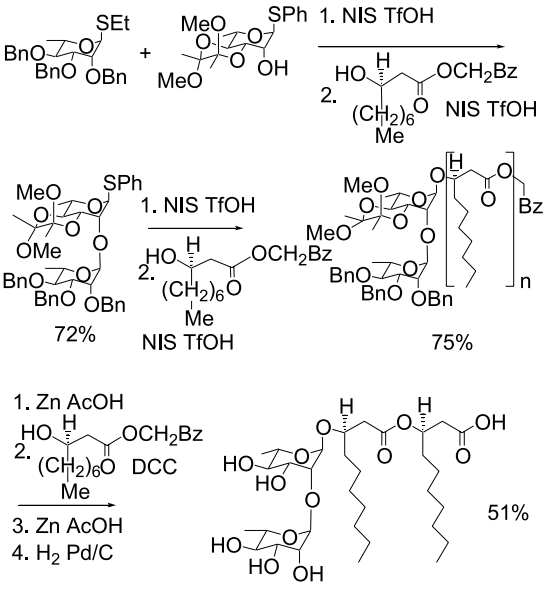
On the other hand, the *p*-methoxyphenyl group was shown to be a useful leaving group in a glycosylation performed for the synthesis of the macrocyclic trisaccharide binding with the lectin LOLI complex.[167]

4. 1-*S*-Derivatives as glycosyl donors

4.1. Thioglycosides

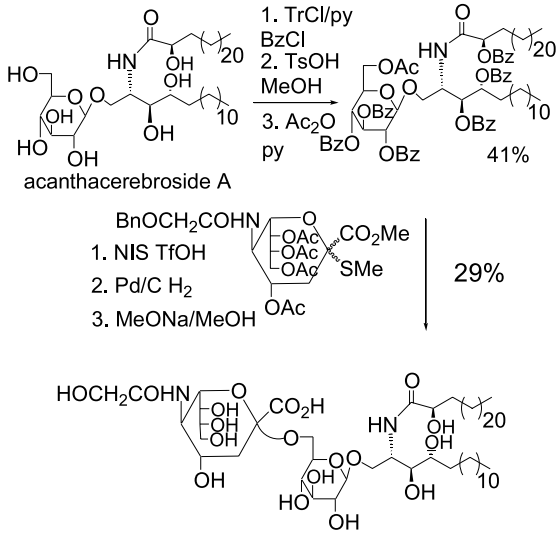
Thioglycosides are amongst the most widely used glycosyl donors.[168] Their popularity is partly due to their ready synthesis and partly to their easy conversion into other common glycosyl donors such as sulfoxides, imidates, bromides, etc.

4.1.1. Synthesis of glycolipids. A number of glycosylations with thioglycosides have constituted key steps in the syntheses of various glycolipids such as the heterocyst glycolipid present in cells of cyanobacteria,[169] and gangliosides GQ1b,[170] VIM-2[171] and GM3.[172] The thioglycoside methodology was also applied by van Boom to the synthesis of naturally occurring biologically interesting rhamnolipids (Scheme 82).[173]



Scheme 82. Synthesis of rhamnolipids.

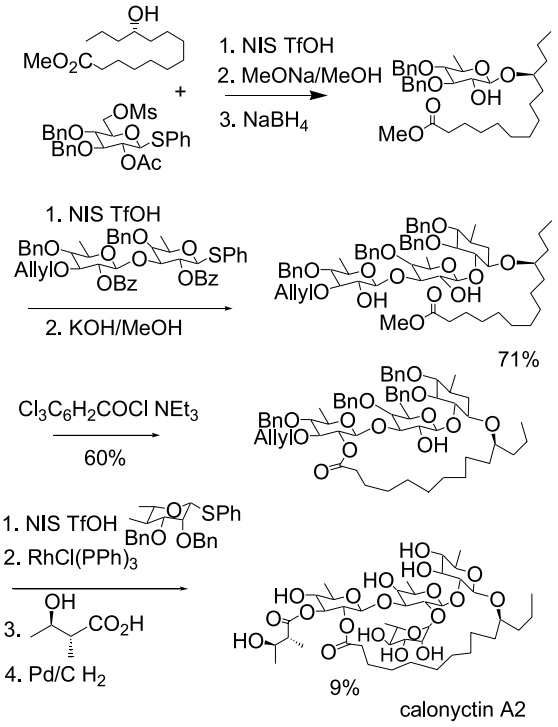
In 1999, Higuchi et al. reported the synthesis of a ganglioside analogue containing a phytosphingosine as a long-chain base and an α-hydroxy fatty acid, starting from the known acanthacerebroside A (Scheme 83).[174]



Scheme 83. Synthesis of a ganglioside analogue.

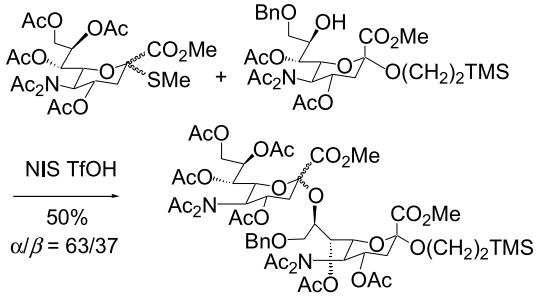
Calonyctin A2, a tetrasaccharide glycolipid having a 22-membered macrolidic structure, was synthesised by the assembly of three 6-deoxygenated thioglycoside intermediates (Scheme 84).[175]

4.1.2. Synthesis of oligosaccharides. Glycosylations with thioglycosides have allowed the synthesis of various oligosaccharides such as the extended blood group B determinant,[176] the tetrasaccharide core structure of lipopolysaccharides of Gram-negative bacteria,[177] phytoalexin-elicitor active oligosaccharides,[178,179] the oligosaccharide domain of the hypoglycemic agent, acarbose,[180] the trisaccharide moiety of the antitumour antibiotic, olivomycin A,[181] the disaccharide moiety of the antibiotic



Scheme 84. Synthesis of calonyctin A2.

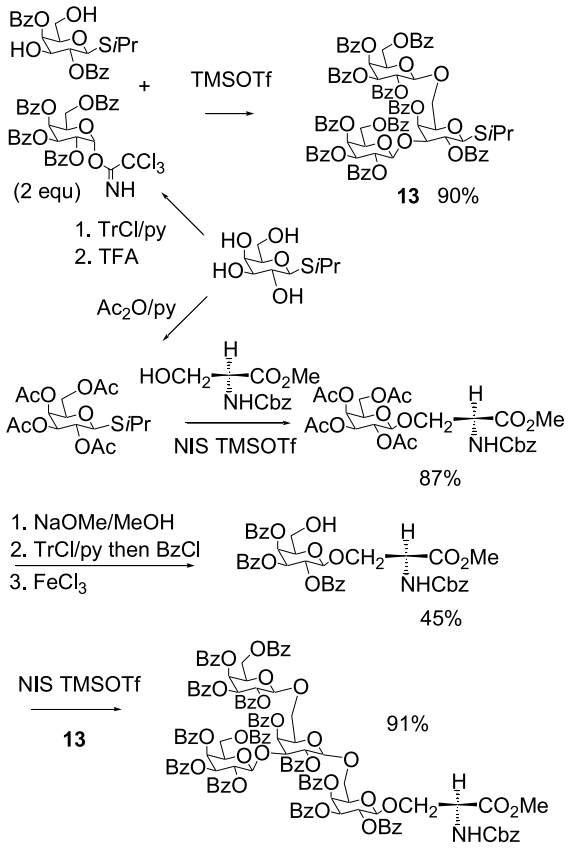
avermectins,[181] conformationally restricted trisaccharides lectin ligands,[182] the cororubicin trisaccharide,[183] bioactive verbascoside,[122] the core heptasaccharyl *myo*-inositol,[184] and a buffalo milk pentasaccharide derivative.[185] Moreover, Boons et al. reported the efficient synthesis of dimers of *N*-acetylneuraminic acid, important constituents of tumour-associated antigens, by using a novel and highly reactive 2-methylthioneuraminyl donor (Scheme 85).[186]



Scheme 85. Synthesis of dimers of *N*-acetylneuraminic acid.

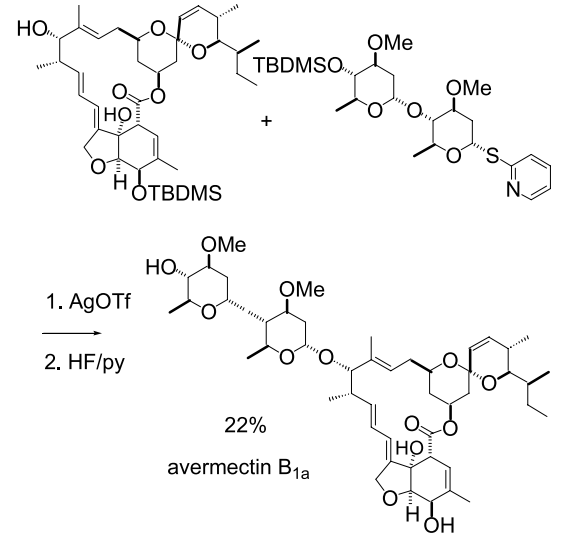
4.1.3. Synthesis of glycopeptides and glycoproteins. In 2001, Du et al. reported an efficient synthesis of galactopyranosyl-containing 3,6-branched oligosaccharides by using, for the first time, isopropyl thioglycosides as glycosyl donors.[187] This method was applied for the preparation of a glycopeptide that relates to *Lycium barbarum* L (Scheme 86).

Thioglycosides have also been involved in the synthesis of more complex neoglycoproteins,[188] and were successfully applied in 2004 to the first chemical synthesis of gp120 glycopeptide fragments in pursuit of carbohydrate-based HIV vaccines.[189]



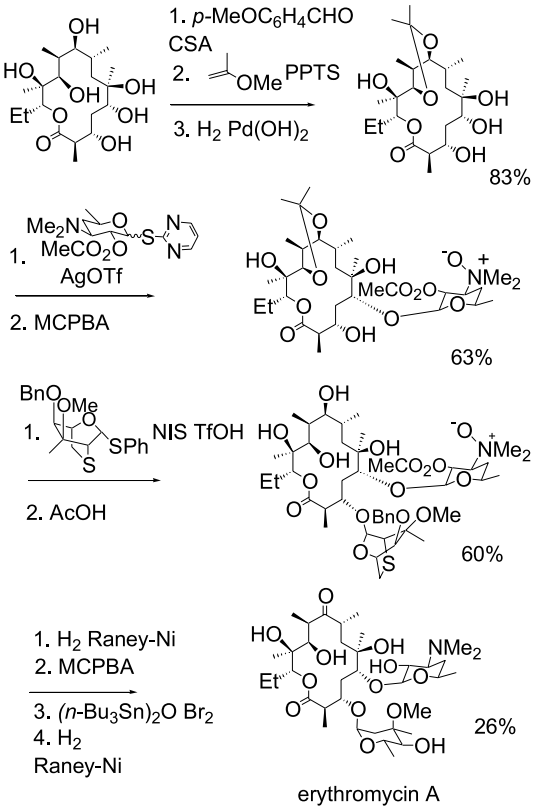
Scheme 86. Synthesis of a glycopeptide containing a 3,6-branched tetrasaccharide.

4.1.4. Synthesis of natural products. The use of thioglycosides has allowed the synthesis of a number of bioactive natural products such the antibiotics ezomycin[190] and neocarzinostatin,[191] adenophostin A,[192] the glycosidase inhibitor, gualamycin,[193] tricolorin A,[194] and the pesticide, emamectin.[195] Another application of this methodology was the synthesis of the complex antiparasitic agent, avermectin B_{1a}, achieved by attachment to the aglycon of the L-oleandrosyl-L-oleandrose disaccharide via a pyridylthioglycoside (Scheme 87).[196]



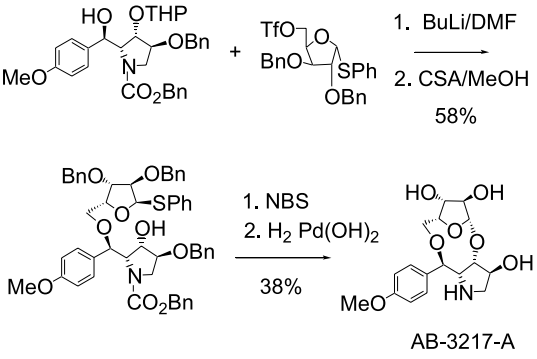
Scheme 87. Synthesis of avermectin B_{1a}.

A most typical and medicinally important macrolide antibiotic, erythromycin A, was synthesised by Toshima et al. by the successful involvement of stereocontrolled glycosidations using 2,6-anhydro-2-thio sugars (Scheme 88).[197]



Scheme 88. Synthesis of erythromycin A.

Intramolecular glycosylations have been rarely used in the synthesis of natural products. This reaction was, however, performed as the ultimate step in the first total synthesis of AB-3217-A, an acaricidal substance (Scheme 89).[198]

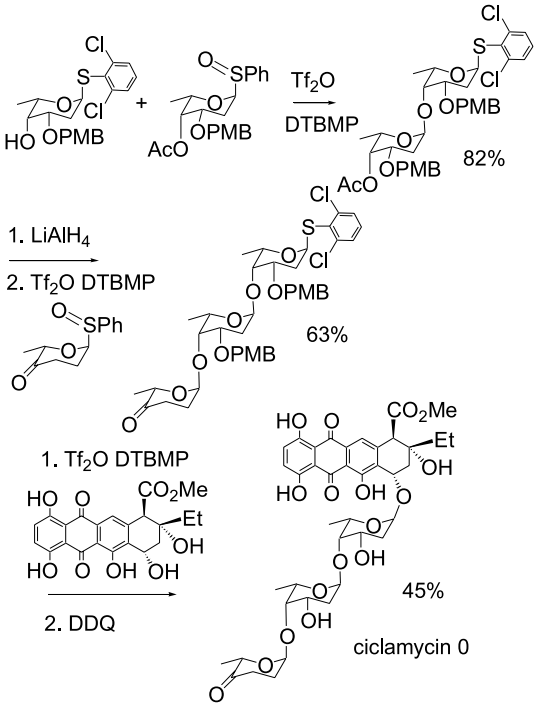


Scheme 89. Synthesis of AB-3217-A.

4.2. Sulfoxides

Anomeric sulfoxides, prepared by thioglycoside oxidation, have been introduced by Kahne as versatile glycosylation agents when activated with Tf_2O.[199] It was established that these reactions proceeded via three possible different intermediates, an oxonium ion, a glycosyl triflate, and a

glycosyl sulfenate.[200] Glycosyl sulfoxides are more reactive than thioglycosides and are prepared by the oxidation of thioglycosides using *m*-chloroperbenzoic acid just before the glycosylation reaction. Activation of glycosyl sulfoxides is generally achieved under mild conditions using triflic anhydride in the presence of an acid scavenger such as 2,6-di-*t*-butyl-4-methylpyridine. Kahne et al. have applied this method to the synthesis of a variety of saccharide structures such as the glycopeptide antibiotic, vancomycin,[201] the anthracycline antibiotic, ciclamycin 0 (Scheme 90),[202] DNA-binding oligosaccharides,[203] and also glycopeptides.[204]

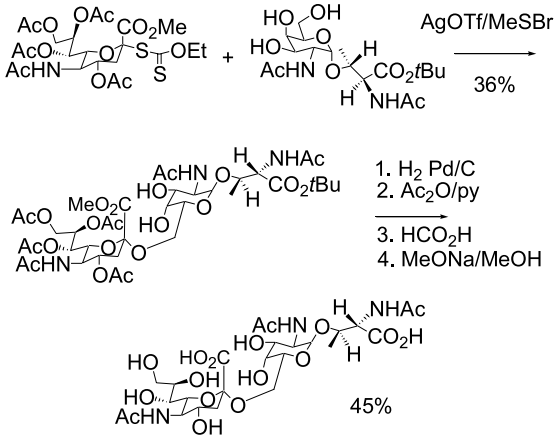


Scheme 90. Synthesis of ciclamycin 0.

The advantages of Kahne's sulfoxide glycosylation strategy were further extended by Crich for the synthesis of β-mannosides[205] such as the caloporoside disaccharide[206] and the trisaccharide component of a glycosphingolipid.[207] Nicolaou et al. have also involved sulfoxides amongst various other glycosyl donors in the synthesis of apoptolidin[75a] and the very complex antibiotic, everninomicin 13,384-1, exhibiting a 1,1′-disaccharide bridge, 13 rings combined and 35 stereogenic centres.[208] Moreover, in 2003, Danishefsky et al. reported a concise route to the core pentasaccharide of *N*-linked glycoproteins using Crich's direct coupling protocol.[209]

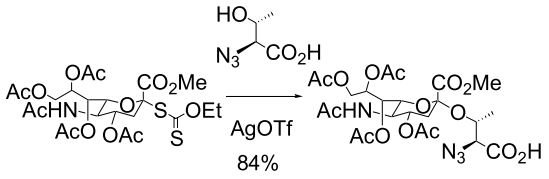
4.3. Xanthates

Glycosyl xanthates were initially introduced as glycosyl donors for the synthesis of 2-amino-2-deoxyglycosides.[210] This approach was then extended to the synthesis of 1,2-*cis* furanosides in the presence of AgOTf.[211] In 1994, Kunz et al. reported the synthesis of a sialyl-T_N antigen conjugate by reacting a xanthate glycosyl donor with a galactosamine threonine derivative (Scheme 91).[212]



Scheme 91. Synthesis of a sialyl-T_N antigen.

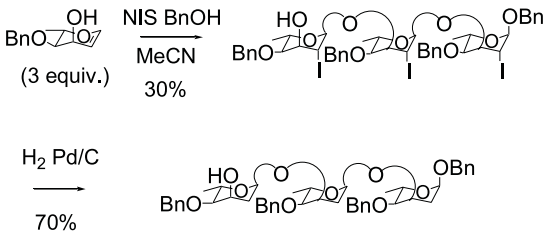
The ganglioside LM1 is of great importance in the pathogenesis and treatment of cancer. Its synthesis was performed by the glycosidation of a neuraminic xanthate in the presence of the promoter, phenylsulfenyl triflate.[213] This protocol, established by Whitesides et al.,[214] was employed in the synthesis of a GM3-lactone analogue.[79,215] The same methodology was also applied to the synthesis of various sialylated threonine building blocks, in order to be used in solid-phase glycopeptide synthesis (Scheme 92).[216] These compounds were the first reported sialylated amino acids to be *O*-linked via the glycosidic bond.



Scheme 92. Synthesis of sialylated threonine building blocks.

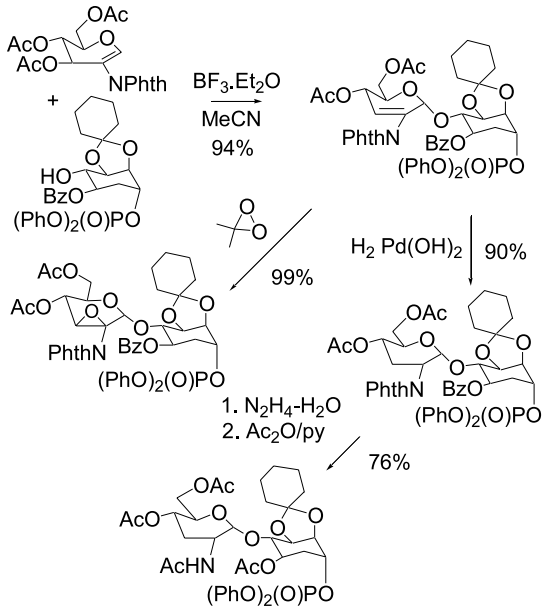
5. Glycals as glycosyl donors

Glycal is a very versatile synthetic intermediate, especially in the synthesis of 2-deoxyglycosides. A thorough and useful review of the general glycal methodology has been published by Danishefsky.[217] In this methodology, it appeared that the complexities associated with differential hydroxyl protection would be significantly reduced. Indeed, in a hexose glycal, only three hydroxyl groups need to be distinguished. In addition, each hydroxyl moiety could well differ from the others in its expected reactivity, since one is primary, one is allylic, and the other is a more hindered secondary alcohol. It seemed, therefore, that the need for selective protection could be lessened and those protections which are needed could be simplified in the context of glycals. The glycal methodology was applied to the total synthesis of various natural products such as vancomycin,[218] osmundalactone,[219] the potential anticancer vaccine, KH-1 adenocarcinoma antigen,[220] the MBr1 carbohydrate antigen,[9] and calicheamicin.[221] Moreover, Köpper et al. reported a one-pot synthesis of an α-linked deoxy sugar trisaccharide, part of the antibiotic, kijanimicin. This one-pot procedure afforded the trisaccharide directly from the monosaccharide glycal precursor in 30% yield in the presence of NIS (Scheme 93).[222]

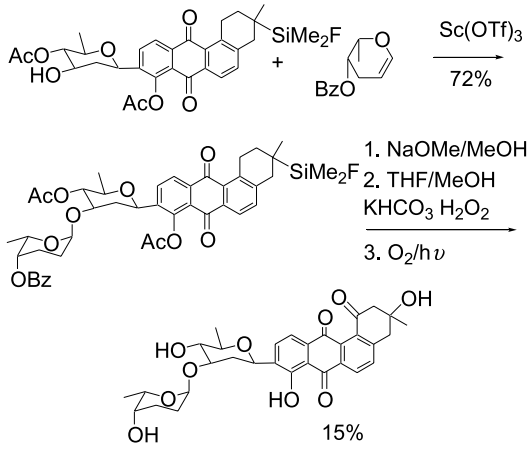


Scheme 93. One-pot synthesis of a trisaccharide from glycal.

The TMS triflate-promoted *O*-glycosylation of numerous amino acids, and linear and cyclic peptides with 3-amino-glycals afforded L-acosamine and L-ristosamine derivatives. In comparison with the *N*-iodosuccinimide (NIS) method, activation with TMS triflate leads directly to 2-deoxy-glycosides in shorter reaction times.[223] On the other hand, Cleophax et al. involved $BF_3 \cdot Et_2O$ as a promoter in the synthesis of glycosylphosphatidylinositol (GPI) analogues (Scheme 94).[224]



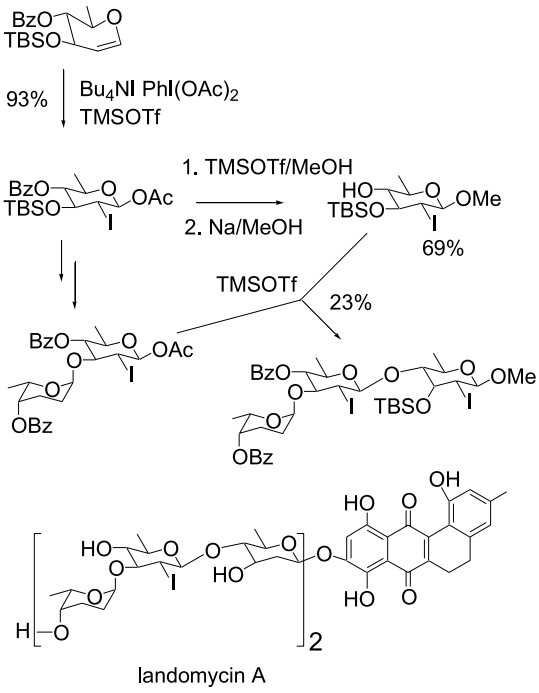
Scheme 94. Synthesis of analogues of insulin-like inositol glucans.



Scheme 95. Synthesis of angucycline antibiotics.

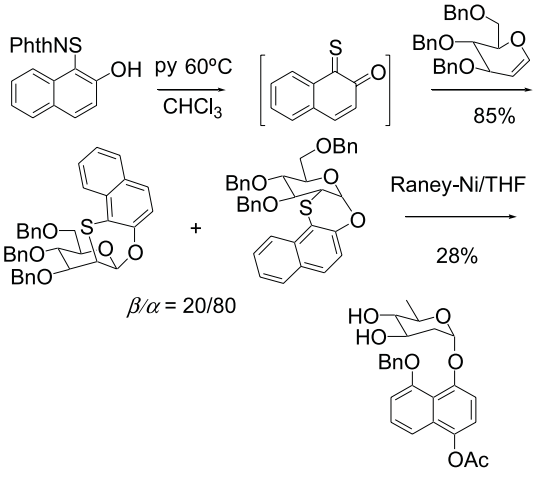
In 1998, McDonald et al. activated L-aculose-α-L-rhodinose disaccharide glycal under acidic catalysis (TsOH) in order to prepare precursors to the aquayamycin class of platelet aggregation inhibitor natural products.[225] More recently, Krohn et al. have reported the total synthesis of angucycline antibiotics using benzoyl rhamnal as the glycoside donor and scandium triflate as the promoter (Scheme 95).[226]

The synthesis of the trisaccharide monomer of another angucyclin antibiotic, landomycin A, was accomplished by Weber et al.,[227] using the iodoacetoxylation of a glycal performed in the presence of $PhI(OAc)_2$, Bu_4NI and TMSOTf (Scheme 96).[228]



Scheme 96. Synthesis of trisaccharide monomer of landomycin A.

Capozzi et al. have shown that α-hydroxynaphthylthio-phthalimide was a suitable precursor of reactive *o*-thio-quinone, which could be generated in situ and trapped by glycals. This new methodology was applied to the synthesis



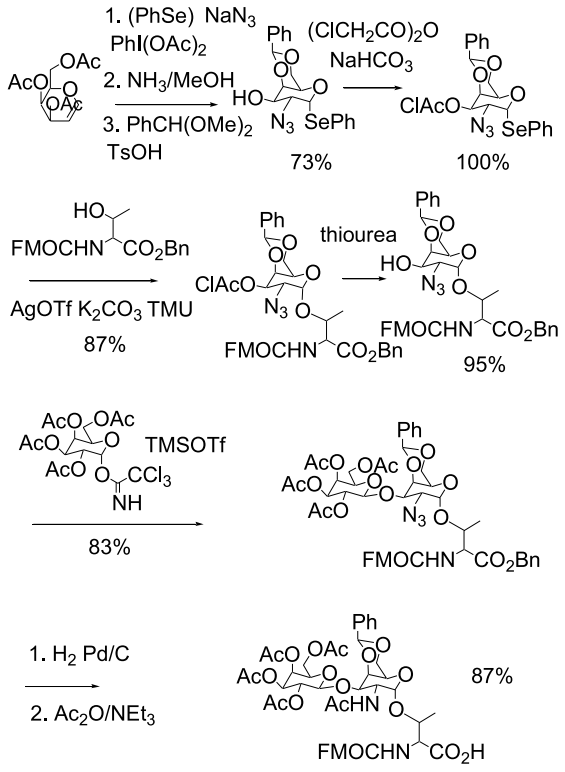
Scheme 97. Synthesis of aryl 2-deoxy-*O*-glycosides.

of aryl *O*-glycoside antibiotics such as those of the aureolic acid antibiotic family (Scheme 97).[229]

While iodoglycosylation provides valuable capabilities for the conversion of glycals into various glycosides, there was a need for a general route to convert glycals into the common glycosides of glucose, galactose, and mannose. In this way, glycals were converted into the corresponding epoxides by treatment with 2,2-dimethyldioxirane (DMDO). These latter compounds were involved by Danishefsky et al. as glycosyl donors activated by $ZnCl_2$ in the synthesis of various products such as gangliosides,[230] and the complex saponin, desgalactotigonin.[231] Moreover, the same group has more recently reported the synthesis of glycosylamino acids containing tumour-associated carbohydrate antigens, in which the key glycosylation reaction was actually carried out with a glycal epoxide donor generated by the treatment of glycal with DMDO.[232]

6. Selenoglycosides as glycosyl donors

Selenoglycosides have proved to be versatile glycosyl donors closely related in their behaviour to thioglycosides. Pinto et al. have demonstrated, however, the possible selective activation of phenyl selenoglycosides over ethyl thioglycosides by AgOTf and K_2CO_3.[233] Selenoglycosides have the added advantage that they are inert during the activation of glycosyl halides and trichloroacetimidates.[234] They can be prepared from peracetylated sugars or by azidoselenylation of glycals.[235] In 2000, Chen et al. reported a new glycosylation methodology for synthesising a protected TF antigen.[236] The key step was to use a phenyl selenoglycoside as a glycosyl donor, thereby successfully establishing an *O*-linked FMOC-protected threoninyl monosaccharide in excellent yield and high α-selectivity (Scheme 98). The FMOC-protected glycopeptide thus formed was a suitable building block to synthesise long-chain glycopeptides or glycoproteins via solid-phase synthesis.



Scheme 98. Synthesis of glycosylated amino acid from a phenyl selenoglycoside.

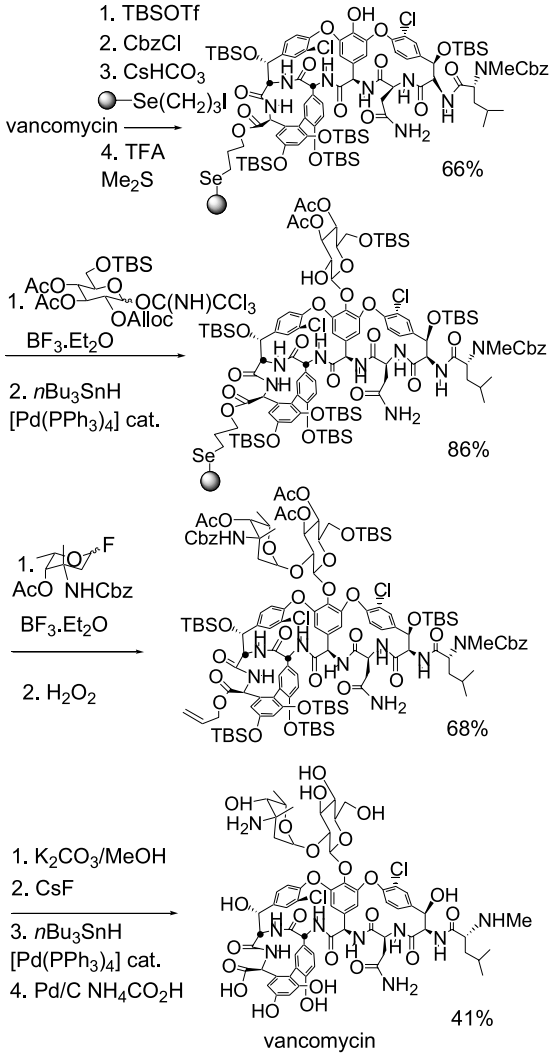
In 2000, Ley et al. reported the synthesis of high-mannose-type neoglycolipids to be used for the active targeting of liposomes to macrophages in gene therapy. Several starting materials in the synthesis were α-1,3-linked seleno disaccharides.[237] The reactivity of selenium glycosides was also employed by this group for the syntheses of a glycosylphosphatidylinositol anchor,[238] and of glycans from the glycodelins, human glycoproteins isolated from amniotic fluid and seminal plasma.[239] A chemoselective glycosylation of a selenoglycosyl donor with a thioglycosyl acceptor was the key aspect of a recently reported synthesis of bioactive *Rhizobial sin*-1 lipopolysaccharides.[240]

7. Miscellaneous chemical methods

7.1. Solid-phase synthesis

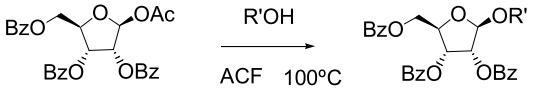
With the emergence of combinatorial chemistry as a powerful tool in the drug discovery process, solid-phase chemistry has assumed a central position in organic synthesis.[241] Solid-phase synthesis requires repetitive glycosylations and deprotection reactions in excellent yields, thus obviating the need for purification at each stage. Hence, the chemistry of the various re-iterations must be sufficiently efficient that a single purification at the final stage affords a product of the required homogeneity. Inspired by the success of solid-phase peptide and oligonucleotide syntheses in the early 1970s, several groups have developed the solid-supported oligosaccharide synthesis. In 1994, Kahne et al. described the solid-supported synthesis of oligosaccharides using anomeric sulfoxides as donors.[242] In this procedure, the anomeric centre of the saccharide was linked to the solid support (polystyrene) and glycosyl donors were added to the growing chain. An inverse approach is also possible using the incoming sugars as glycosyl acceptors. This methodology, reported by Danishefsky in order to synthesise an oligosaccharide, was initiated by attaching a suitably protected glycal to a solid support.[243] The double bond of the glycal was then activated by epoxidation and glycosylation occurred between a solution-based glycal acceptor and the epoxide linked to the solid support. The last sugar was introduced as a non-glycal to terminate the process and the oligosaccharide was released from the solid support by TBAF treatment. This methodology was applied to the synthesis of *N*-linked glycopeptides.[243c] An account of the use of glycal methodology in the solid phase has been published.[244] The rate of reactions on a solid support is generally reduced, compared to the solution-based methods. Krepinsky et al. have addressed this problem by polymer-supported solution synthesis of oligosaccharides.[245] This strategy was based on a polyethylene polymer-supported saccharide being soluble under the conditions of glycosylation, but insoluble during the work-up procedure. Poly(ethylene glycol) monomethyl ether (PEG) was bound to the anomeric centre of a

saccharide via an α,α′-dioxyxylyl glycoside.[246] This linkage was stable under many chemical conditions including glycosylation, but could be cleaved by hydrogenolysis. The PEG-based methodology was used for the preparation of a heptaglucoside having phytoalexin elicitor activity[247] and other oligosaccharides.[248] On the other hand, Schmidt and Rademann have designed a linker system that relies on a thioglycosyl linkage.[249] Merrifield's resin was functionalised to form either an O or S ether, leaving a free thiol that was glycosylated with a trichloroacetimidate donor. Nicolaou et al. have demonstrated the synthesis of a heptasaccharide phytoalexin elicitor[179] and a corresponding β-gluco dodecasaccharide[250] on Merrifield resin using linear sugar-by-sugar and re-iterative block-type construction strategies, respectively, starting from oligosaccharides tethered at the reducing-end anomeric centre. This dodecasaccharide represents one of the largest oligosaccharides to be synthesised in the solid phase. The use of orthogonally protected thioglycosides, activated by DMTST, has allowed the construction of a trisaccharide block, which was cleaved from the resin to give a trisaccharide thioglycoside. Iterative reaction of this trisaccharide with a resin-bound tri-, hexa- and then a nonasaccharide yielded the final product, which was cleaved through irradiation with UV light, due to the presence of a photolabile linker. Solid-phase pentenyl glycoside has also been described.[251] Wong et al. have developed the first examples of a non-destructive monitoring method for oligosaccharide synthesis and of the chemical synthesis of the tetrasaccharide motif of sLe^x in the solid phase.[252] In 2000, Nicolaou reported a solid-phase synthesis of the glycopeptide antibiotic, vancomycin (Scheme 99).[253] A key factor in the success of this strategy was the use of a selenium-based safety-catch linker, in which a resin-bound seleno ether was cleaved with H_2O_2 to furnish an allyl ester, which was subsequently removed with nBu$_3$SnH and [Pd(PPh$_3$)$_4$].



Scheme 99. Solid-phase synthesis of vancomycin.

A similar methodology was applied to the synthesis of peracetyl macrophylloside D, a derivative of a natural chromene glycoside.[254] A carboxylic acid resin was treated with a trichloroacetimidate in the presence of $BF_3 \cdot Et_2O$ to smoothly furnish the corresponding ester (91%). Selective deprotection with HF·py (89%), followed by a second coupling between the resin-bound monosaccharide and a trichloroacetimidate, afforded the expected disaccharide as a single anomer in 57% yield. Finally, the disaccharide was cleaved from the resin (H_2O_2) to give hepta-acetylated macrophylloside in 18% overall yield. On the other hand, Jensen et al. have reported the application to solid-phase oligosaccharide synthesis of the DISAL (methyl 3,5-dinitrosalicylate) glycosyl donors carried out under mild activation by $LiClO_4$.[160] The key step was the glycosylation of a D-glucosamine derivative anchored by the 2-amino group through a backbone amide linker to a polystyrene support.[255] In 2004, Krausz et al. reported a new system for solvent-free *O*-glycosylation by using activated carbon fiber (ACF) as a solid acid promoter. This practical solid-state protocol was applied to the synthesis of bioactive sterol and triterpene *O*-glycosides, as well as nucleoside analogues (Scheme 100).[256]



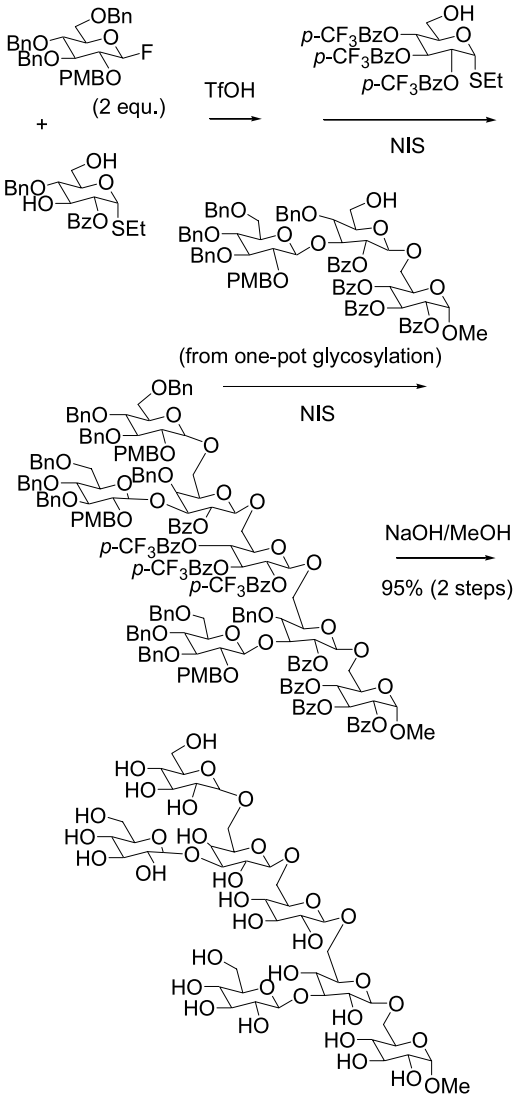
Scheme 100. Solid-phase *O*-glycosylation with ACF as promoter.

It must be added that many glycosylated amino acid building blocks prepared by the usual glycosylation methods have been engaged in the solid-phase synthesis of glycopeptides.[257]

7.2. One-pot sequential glycosylation

There are several strategies for the one-pot synthesis of oligosaccharides.[202a,258] One-pot sequential glycosylation is one of the most effective solution-phase methodologies, not only for the high-speed synthesis of a target oligosaccharide, but also for the combinatorial synthesis of an oligosaccharide library.[259] In particular, programmed one-pot oligosaccharide synthesis facilitates the convenient assembly of glycan structures,[260] and has been used in the synthesis of such complex molecules as Globo H,[261] Lewis

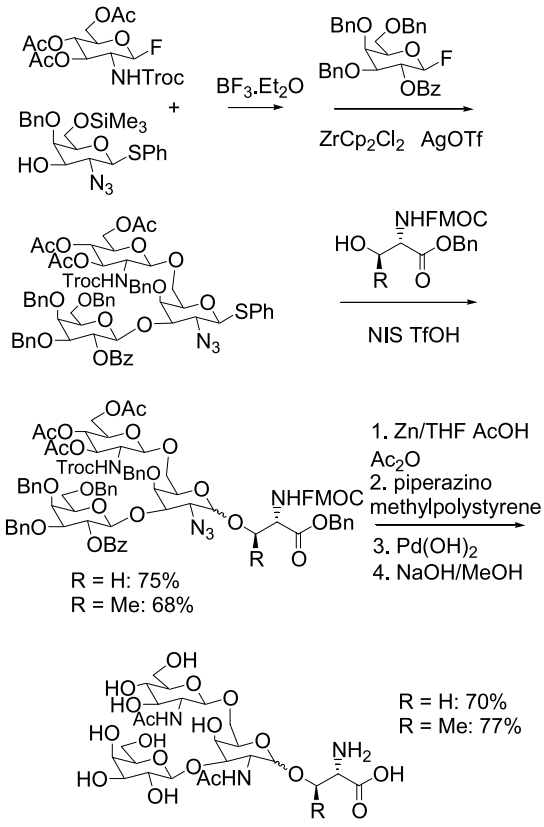
Y,[262] fucosyl GM_1,[263] and an elicitor-active hexaglucoside analogue.[258a] A phytoalexin elicitor-active heptasaccharide was also synthesised by way of two one-pot sequential glycosylation reactions by Mukaiyama et al. (Scheme 101).[264]



Scheme 101. Synthesis of a phytoalexin elicitor-active heptasaccharide.

The same methodology was recently applied to the synthesis of F1α antigen, a member of the tumour-associated *O*-linked mucin glycosylamino acids.[265] In 2004, Takahashi et al. demonstrated an effective one-pot synthesis of core 2 class branched glycosylamino acids, initiated by chemoselective glycosylation of a silyl ether at the 6-position of a galactoside with a glycosyl fluoride in the presence of $BF_3 \cdot Et_2O$. No *O*- or *S*-glycosylation at position 3 was observed (Scheme 102).[266]

In order to investigate the exact role of the glycan portion of natural bioactive products such as vancomycin, an efficient strategy for the glycosylation of the vancomycin aglycon was still required, no examples of direct chemical glycosylation of the aglycon to provide vancomycin



Scheme 102. Synthesis of core 2 class glycosylamino acids.

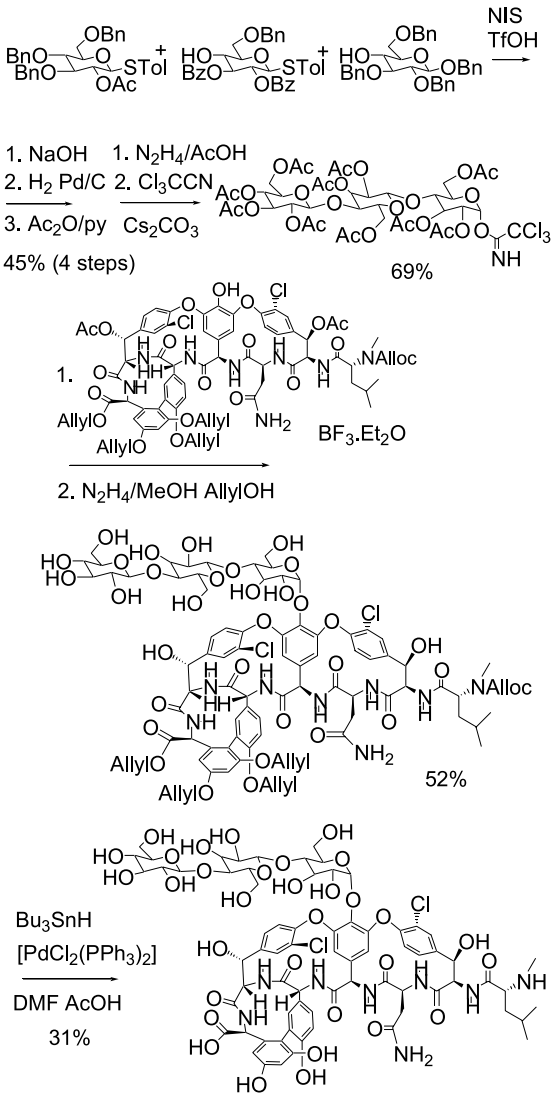
derivatives bearing non-natural di- or oligosaccharide substituents having been reported. Wong et al. have implemented a programmable one-pot oligosaccharide strategy in order to construct a set of such derivatives.[267] Scheme 103 summarizes an example of the programmable one-pot oligosaccharide synthesis for diversifying the sugar domains of vancomycin.

7.3. Other chemical methods

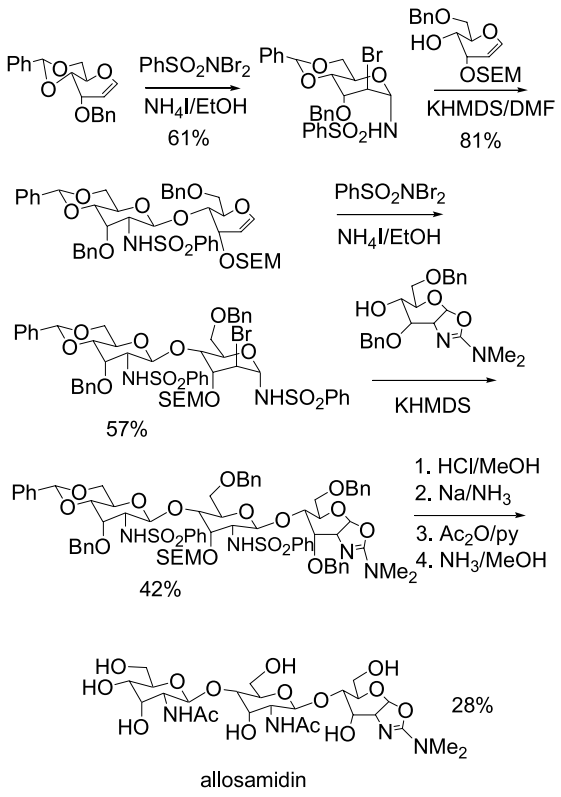
Danishefsky et al. have developed the sulfonamidoglycosylation reaction of glycal by the combinational use of IDCP and benzenesulfonamide or the use of *N*,*N*-dibromobenzenesulfonamide to prepare 2-amino-2-deoxy-β-glycosides.[268] This method, derived from the glycal methodology, was elegantly applied to the total synthesis of allosamidin (Scheme 104),[269] a powerful and selective chitinase inhibitor, the Le^y determinant,[270] the Le^b determinant,[271] the Le^x determinant,[272] and tumour-associated carbohydrate antigens.[273]

An original approach to heterocyclic anthracycline antibiotics was developed by Xu et al., based on DDQ-induced, anomeric-specific, and diastereoselective benzylic glycosidation carried out under neutral conditions.[274] The direct oxidative introduction of the sugar was an interesting feature of this glycosidation procedure, because it did not require the glycosyl acceptor in its higher oxidation stage (Scheme 105).

In 2003, Lin et al. reported the first stereoselective



Scheme 103. Synthesis of vancomycin derivative.

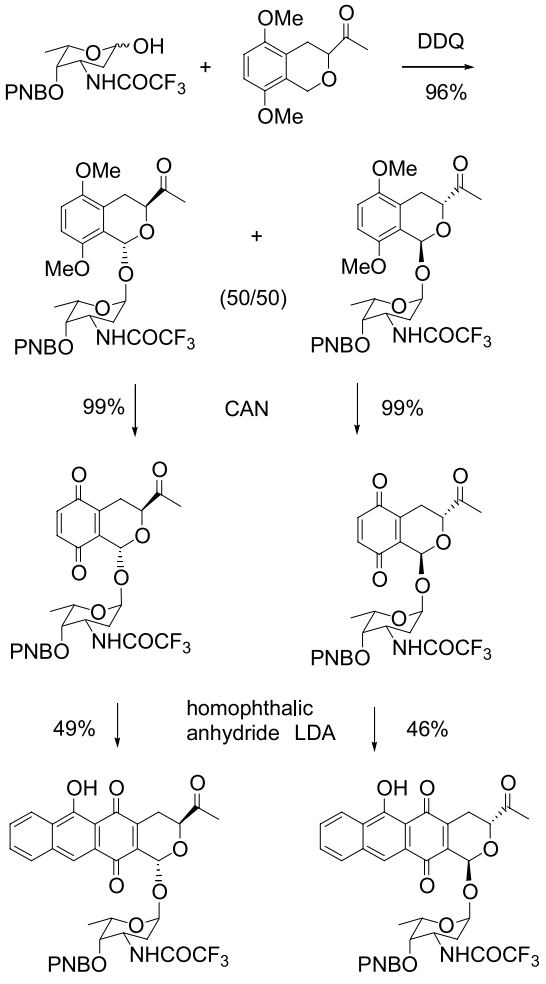


Scheme 104. Synthesis of allosamidin.

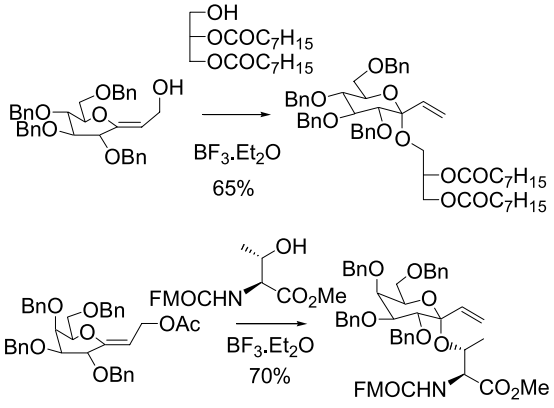
glycosylation of *exo*-glycals, allowing the synthesis of disaccharides, glycolipids and glycopeptides mimicking the essential core structure of T_N antigen (Scheme 106).[275] All functional groups on the sugar ring remained intact, contrary to the analogous reactions of *endo*-glycals in which two chiral centres at C2 and C3 are always missing. Moreover, the glycosylation product contains a vinyl group that can be further elaborated for general purposes.

8. Enzymatic and semisynthetic methods

The reader is referred to an excellent review, published in 2000, that has previously covered aspects of enzyme-based synthesis of glycoconjugates.[276] Consequently, this section will be limited to some selected examples reported in the literature from 2000. The need for increasingly efficient methods for oligosaccharide synthesis has stimulated the development of enzymatic methods and two basic approaches are available.[277] In the first approach, glycosyltransferases and sugar nucleotide diphosphates are used for glycosidic bond formation. This method is very powerful, especially when the sugar nucleotides are regenerated in situ. Indeed, glycosyltransferases are enzymes that catalyse the regio- and stereospecific transfer of monosaccharides from activated nucleotide donor substrates to oligosaccharide acceptors. This transfer specificity is advantageous in oligosaccharide synthesis employing glycosyltransferases, since protection and deprotection of saccharides are not necessary. One of the greatest advantages of using glycosyltransferases is that complex glycoconjugates such as lipids, peptides, proteins and even cell surfaces can be glycosylated. In the second approach, the reverse hydrolytic activity of glycosidases can be exploited in glycosidic bond formation. In contrast to glycosyltransferases, glycosidases are able to glycosylate many 'xeno-substrates' with primary and secondary hydroxyl groups. Most glycosidases that have been used as biocatalysts are exoglycosidases, which hydrolyse or synthesise terminal glycosidic linkages. On the other hand, a number of endoglycosidases are known to assemble larger oligosaccharides. In 2000, Seto et al. reported an enzymatic synthesis of blood group A and B trisaccharide analogues.[278] Recombinant human glycosyltransferase A was used to synthesise the blood group A analogue by transferring GlcNAc from the donor UDP-GlcNAc to the precursor. Recombinant human glycosyltransferase B was used to synthesise the blood group B analogue by transferring Glc from the donor UDP-Glc to the same precursor. More recently, glycosyltransferases were employed in a chemo-enzymatic approach to the synthesis of DNA glycoconjugates.[279] A phosphoramidite derivative of *N*-acetylglucosamine (GlcNAc) was prepared and used to attach GlcNAc sugars to the 5′-terminus of DNA oligonucleotides by solid-phase DNA synthesis. The resulting

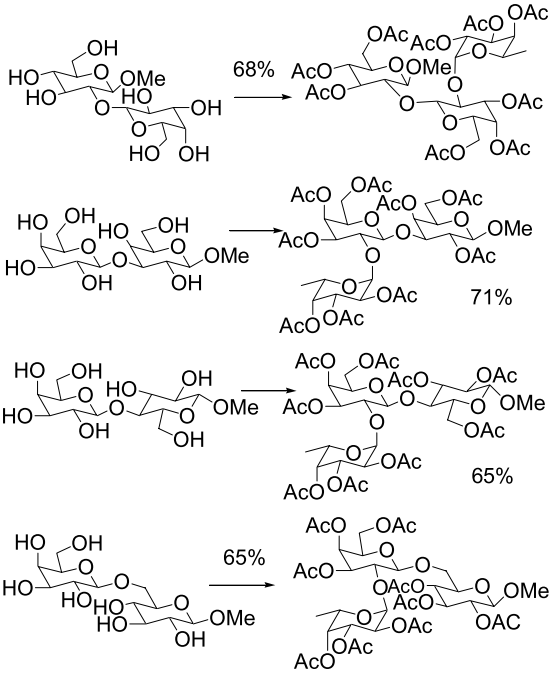


Scheme 105. Synthesis of heterocyclic anthracycline antibiotics.



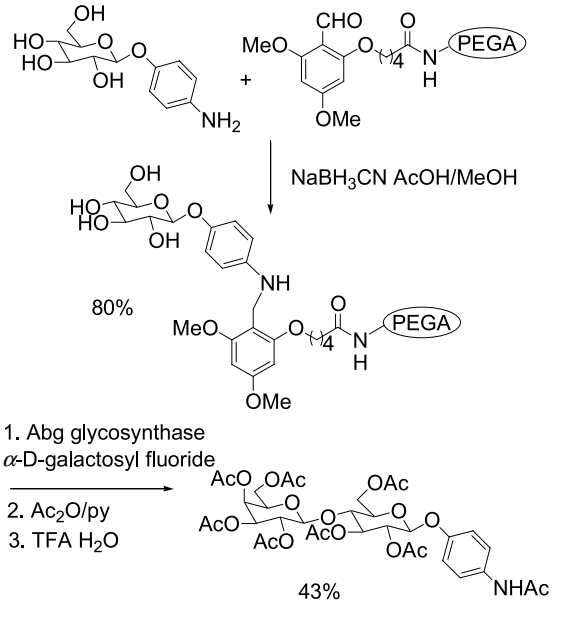
Scheme 106. Glycosylation of *exo*-glycal.

GlcNAc-DNA conjugates were used as substrates for glycosyltransferase enzymes to synthesise DNA glycoconjugates. A galactosyltransferase exhibiting fucosyltransferase activity has been employed to transfer L-fucose from GDP-L-fucose to terminal, non-reducing D-galactose residues of an oligosaccharide, thus providing facile access to a range of H-antigen-containing oligosaccharides (Scheme 107).[280]



Scheme 107. Enzymatic synthesis of H-antigen-containing oligosaccharides.

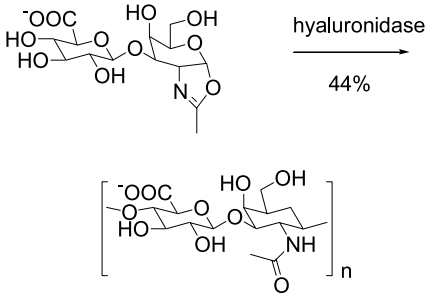
Nishimura has reported the chemo-enzymatic synthesis of glycopolymers and sequential glycopeptides bearing lactosamine and sialyl Lewis^x unit pendant chains by the use of glycosyltransferases. The obtained compounds were useful tools in the study of sugar–lectin interactions and as selectin inhibitors.[281] In 2003, Wang et al. introduced the creatine phosphate–creatine kinase system as a novel and practical energy source in carbohydrate synthesis. This system was



Scheme 108. Solid-phase oligosaccharide synthesis using glycosynthases.

successfully demonstrated in the production of bioactive oligosaccharides with different sugar nucleotide regeneration systems.[282] A multi-enzyme system towards sialyllactosides was constituted by sialyltransferases combined with five other enzymes. A fast and efficient enzymatic glycosylation for cyclodextrins based on the use of an α-galactosidase was recently reported by Rabiller et al.[283] The first application of glycosynthases, mutated retaining glycosidases, to solid-phase oligosaccharide synthesis was reported by Jensen et al. in 2002 (Scheme 108).[284] Acceptors were linked to PEGA resin (poly(ethylene glycol)/polyacrylamide copolymers) through a backbone amide linker and, using the enzymes, a galactose moiety was transferred from a donor sugar, α-D-galactosyl fluoride, with high efficiency. In addition, it was demonstrated that a resin-bound model glycopeptide was also an acceptor for the glycosynthase.

Finally, Kobayashi et al. described enzymatic polymerization to provide chondroitin and its derivatives, which are naturally occurring heteropolysaccharides belonging to the family of glycosaminoglycans. The reaction was catalysed by hyaluronidase, a hydrolysis enzyme of chondroitin (Scheme 109).[285]



Scheme 109. Enzymatic synthesis of chondroitin.

9. Conclusions

The abundance of carbohydrates in nature and their diverse roles in biological systems make them attractive subjects for chemical and biological research. This review shows the power of the *O*-glycosylation reaction for the synthesis of biologically active natural products and related compounds. It concentrates on the new progress in *O*-glycosylation methods applied to the total syntheses of complex glycoconjugates after 1993. Since glycosylation chemistry does not offer a general solution and is still not a routine, predictable or generally accessible technique, chemists will find reviews on this topic of considerable value. Thus, the glycosylation reaction is well represented in this review as an important synthetic tool for total synthesis.

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Biographical sketch

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Tetrapyrazolic tripods. Synthesis and preliminary use in metal ion extraction

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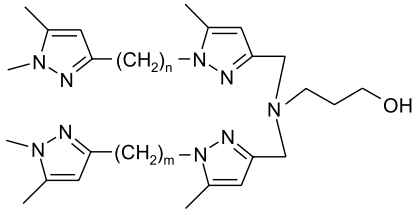
Abstract—The synthesis of two new tetrapyrazolic tripods with a side-arm bearing a functionalized donor-group is reported. The complexing properties of these compounds towards heavy metal ions (Hg^{2+}, Cd^{2+}, Pb^{2+}) and alkaline metal ions (K^{+}, Na^{+}, Li^{+}) was studied by a liquid–liquid extraction process and the extracted cation percentage was determined by atomic absorption measurements.

1. Introduction

For many years, the ability of pyrazole and its derivatives to act as ligands with sp^2 hybrid nitrogen donors has been the research subject of many coordination chemists. This is evident from the large number of articles, several of them being reviews.[1,2] Moreover, polydentate pyrazolic receptors are well known for their ability to complex not only alkali cations[3–7] but also to form stable complexes with transition metal ions.[8–11] These complexes are so stable that it is often difficult to obtain the free macrocycles from them.

In our recent work, a series of acyclic pyrazole compounds containing one, two, three or four pyrazole rings were prepared and demonstrated to extract only transition metal cations[12–14] whereas macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals.[15,16]

In this paper we describe the synthesis of two new tetrapyrazolic tripods (Fig. 1) containing a mobile chain with a donor heteroatom and their binding ability towards alkali and transition metal ions. The presence of a functional mobile chain also provides these structures with the possibility of being immobilised on the surface of a solid material (organic resin or silica gel) by covalent bonding.



6 n = m = 0
7 n = 0, m = 1
8[12] n = m = 1

Figure 1. Structures of synthesised tetrapyrazolic tripods.

2. Results and discussion

The route used by us to prepare the pyrazole compounds is shown in Scheme 1. Compounds **1**, **2**, **4** and **8** are already reported.[12,17] Compound **3** was prepared from **1** using thionyl chloride. The reaction of synthon **3** with commercially available 3-aminopropanol in a 2:1 ratio under reflux condition using sodium carbonate as base afforded a mixture of mono-alkylation product **5** and bisalkylation compound **6** in a 1:4 ratio. These compounds were separated using silica gel column chromatography. The minor product **5** was equally obtained from **3** by reacting an excess of 3-aminopropanol at room temperature to form only the mono-alkylated produit in a 75% yield. Compound **5** was then added to synthon **4** using sodium carbonate as base to give **7** in a 68% yield.

Structures of all compounds were determined on the basis of the corresponding analytical and spectroscopic data.

2.1. Liquid–liquid extraction of individual cations

We used this method in order to study the relative capabilities of these new tetrapyrazolic tripods **6** and **7**

Keywords: Tetrapyrazolic tripods; Liquid–liquid extraction; Cations.
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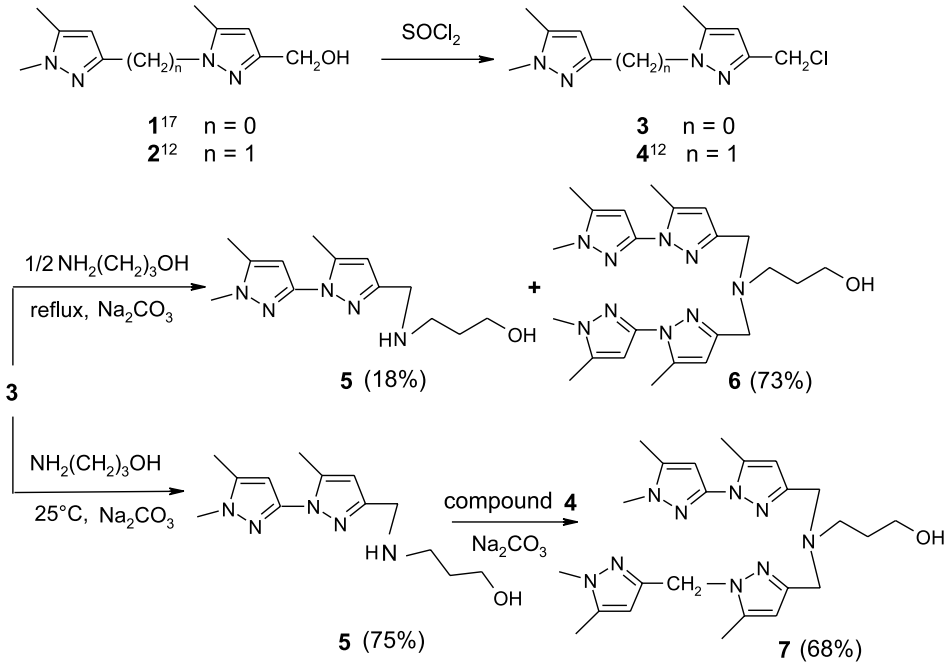
doi:10.1016/j.tet.2005.01.122



Scheme 1.

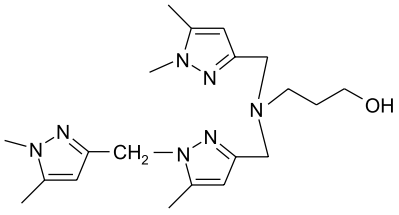


Figure 2. Tripyrazolic compound **9**.

compared to the known tetrapyrazolic compound **8**,[12,13] tripyrazolic compound **9**[13] (Fig. 2) and bipyrazolic group **1** in extracting Hg^{2+}, Cd^{2+}, Pb^{2+}, K^{+}, Na^{+} and Li^{+} cations. Metal picrates were extracted into the organic phase by complex formation with tripods and with compound **1**. The last compound was also studied here for its complexation properties for the first time. The percentage limits of extraction determined by atomic absorption measurements are given in Table 1.

Results in Table 1 show that in analogy to our previous work[12–16] in which acyclic pyrazoles extract only the transition metal cations when the macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals, we demonstrate also here an affinity of these new acyclic tripods only with the transition metal cations, with no complexation being observed toward alkali cations. The same result was also observed for a bipyrazolic group **1**.

The affinity of these hosts is especially high for mercury. This is not surprising if the high donor properties of nitrogen towards this metal are considered.

We notice for all transition metal under study that the extraction yield increases with the number of pyrazoles rings and is a maximum for compounds with four pyrazole rings.

We also notice an increase in complexation ability towards Cd^{2+} and Pb^{2+} when going from compound **8** with two CH_2 junctions to compound **7** with one CH_2 junction and from **7** to compound **6** without a CH_2 junction due to the chelating effect. Indeed, in most cases, bipyrazole groups act as convergent chelating bidentate donors. The term convergent refers to the nitrogen donor atoms coordinating to the same metal centre. The intervening CH_2 junction forms a six-membered ring with the complexated metal cation, while absence of the CH_2 junction leads to a five-membered ring which is thus part of several such rings when the whole ligand is considered. It is well known[18] that five-membered ring chelates are more stable than six-membered and four-membered ones. Thus, N–C–C–N arrangements are preferable to the homologous N–C–C–C–N and N–C–N ones.

Table 1. Yields of extraction of various heavy and alkali metal ions

	Mercury (1.10 Å)	Cadmium (0.92 Å)	Lead (1.20 Å)	Potassium (1.33 Å)	Sodium (0.98 Å)	Lithium (0.60 Å)
1	24	7	0	0	0	0
9[13]	38	10	10	0	0	0
6	50	30	35	0	0	0
7	52	25	30	0	0	0
8[13]	55	15	26	0	0	0

1, bipyrazolic compound; **9**, tripyrazolic compound; **6**, **7** and **8**, tetrapyrazolic compounds.

It is thus interesting to propose a use of these bipyrazolic tripods without a CH_2 junction which forms stable complexes to prepare electrodes for detecting the corresponding metals. Whereas bipyrazolic tripods with the CH_2 junction could be used in solid membranes for example, because of their easy decomplexation.

A linear bipyrazolic ligand **1** forms chelate type complexes which may be one-dimensional when tetrapyrazolic tripods **6–8** are expected to form stable sandwich complexes (bi-dimensional). The increased yield of complexation when going from linear ligand **1** to tripod ligand **6** is then clear.

According to the similar pyrazolic structures possessing tertiary amines,[19] any protonation was detected since identical results were obtained for picrate solution and hydroxide solution.

3. Conclusion

In conclusion, metal cations and macrocyclic pyrazolic compounds are expected to form stable complexes both with transition and alkali metals, while the new acyclic tripod ligands reported here only form complexes with transition metal cations. They do not complex alkali metal cations at all.

4. Experimental

4.1. General

4.1.1. Synthesis of 3. A solution of thionyl chloride (6 ml) in methylene chloride (15 ml) was slowly added to compound **1** (4 g, 2×10^{-2} mol) in 80 ml of methylene chloride. This mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 100 ml of ether. The mixture was then neutralized with about 20 ml of saturated sodium bicarbonate solution and the ether solution was dried over anhydrous sodium sulfate. After evaporating the mixture, the residue was filtered through a short alumina column to give a 85% yield of **3** as a white solid: mp=72–75 °C; ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H); 2.42 (s, 3H); 3.70 (s, 3H); 4.55 (s, 2H); 6.18 (s, 2H); IR: ν(C–Cl)=1260 cm^{-1}.

4.1.2. Synthesis of 5. A mixture of **3** (3 g, 13.3×10^{-3} mol) and 3-aminopropanol in a 1:5 ratio in acetonitrile (50 ml) was added to a sodium carbonate (5.5 g, 66.5×10^{-3} mol) in 50 ml of acetonitrile. The resulting mixture was stirred at room temperature for 24 h. After filtering and evaporating, the residue was chromatographed on alumina using 97/3 CH_2Cl_2/MeOH as eluant to give a 75% yield of compound **5** as a viscous oil: R_f=0.3 (CH_2Cl_2/MeOH, 97/3); ^{1}H NMR ($CDCl_3$) δ: 1.75 (m, 2H); 2.25 (s, 3H); 2.35 (s, 3H); 2.75 (t, 2H, J=6.2 Hz); 3.58 (m, 4H); 3.74 (s, 3H); 6.01 (s, 1H); 6.08 (s, 1H). Anal. Calcd for $C_{13}H_{21}N_5O$: C, 59.31; H, 7.98; N, 26.61. Found: C, 59.35; H, 7.93; N, 26.66; *m/z*: 264 (MH^+); IR: ν(OH, NH)=3300 cm^{-1}.

4.1.3. Synthesis of 6. To a mixture of compound **3** (3 g, 13.3×10^{-3} mol) and sodium carbonate (5.6 g, 67.5×10^{-3} mol) in acetonitrile (150 ml) was added slowly 3-aminopropanol (0.5 g, 6.68×10^{-3} mol). The mixture was stirred under reflux for 12 h. The solid material was filtered and the filtrate was concentrated under reduced pressure. The residue was separated on alumina using 98/2 CH_2Cl_2/MeOH as eluant to give a 73% yield of **6** as a white solid and an 18% yield of **5** as a viscous oil. Compound **6**: R_f=0.6 (CH_2Cl_2/MeOH, 97/3); mp=82–84 °C; ^{1}H NMR ($CDCl_3$) δ: 1.76 (m, 2H); 2.28 (s, 6H); 2.40 (s, 6H); 2.76 (t, 2H, J=6.2 Hz); 3.68 (m, 6H); 3.76 (s, 6H); 6.15 (s, 2H); 6.18 (s, 2H). Anal. Calcd for $C_{23}H_{33}N_9O$: C, 61.19; H, 7.32; N, 27.94. Found: C, 61.22; H, 7.33; N, 27.90; *m/z*: 452 (MH^+); IR: ν(OH)=3200 cm^{-1}, ν(tertiary nitrogen)=1120 cm^{-1}.

4.1.4. Synthesis of 7. A mixture of **5** (3.4 g, 13×10^{-3} mol) and **4** (3.1 g, 13×10^{-3} mol) in acetonitrile (100 ml) in the presence of sodium carbonate (5.4 g, 65×10^{-3} mol) as base was refluxed for 6 h. The resulting mixture was filtered, evaporated and purified to give a 68% yield of **7** as a viscous oil: R_f=0.62 (CH_2Cl_2/MeOH, 97/3); ^{1}H NMR ($CDCl_3$) δ: 1.86 (m, 2H); 2.20 (s, 3H); 2.25 (s, 3H); 2.30 (s, 3H); 2.48 (s, 3H); 2.85 (br s, 2H); 3.70 (br s, 7H); 3.72 (s, 3H); 3.78 (m, 2H); 5.15 (s, 2H); 5.35 (s, 1H); 5.75 (s, 1H); 6.18 (s, 2H). Anal. Calcd for $C_{24}H_{35}N_9O$: C, 61.93; H, 7.52; N, 27.09. Found: C, 61.95; H, 7.54; N, 27.87; *m/z*: 466 (MH^+); IR: ν(OH)=3200 cm^{-1}, ν(tertiary nitrogen)=1120 cm^{-1}.

4.2. Extraction experiments

A solution of 7×10^{-5} M of tripod or bipyrazolic group in CH_2Cl_2 (50 ml) was stirred for 2 h with an aqueous solution (50 ml) of metal picrates (7×10^{-5} M); the complexation was followed by measuring the concentration of cations in an aqueous solution by atomic absorption. The temperature remained constant during all the experiments at 25 °C and at pH 7 measured by a pH-meter. This was explained by the absence of nitrogen protons in ligands and by the low alkalinity and concentration of picrate ions exchanged.

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Intramolecular 1,3-dipolar nitrone and nitrile oxide cycloaddition of 2- and 4-*O*-allyl and propargyl glucose derivatives: a versatile approach to chiral cyclic ether fused isoxazolidines, isoxazolines and isoxazoles

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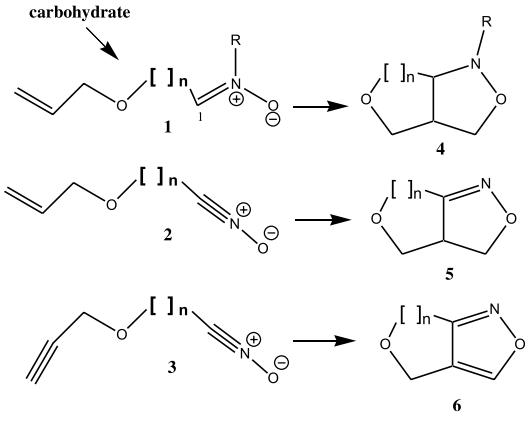
Abstract—2-*O*- and 4-*O*-Allyl and -propargyl glucose and the corresponding oxime derivatives were prepared from readily available glucose dithioacetals. Intramolecular 1,3-dipolar cycloaddition of the *N*-benzyl and *N*-methyl nitrones of the above acyclic 2-*O*-allyl glucose derivatives led to the diastereoselective formation of chiral isoxazolidines incorporating the tetrahydrofuran ring. The EI mass spectra revealed a characteristic cleavage of the C-alkyl group adjacent to the furan oxygen atom. An enantiopure trisubstituted tetrahydrofuran was obtained by the reductive cleavage of the isoxazolidine ring of one of the cycloadducts. In contrast, the nitrile oxide cycloaddition of the 2-*O*-allyl derivatives afforded diastereomeric mixtures of the corresponding dihydroisoxazolines, the stereochemistry of which was tentatively assigned on the basis of the principle of optical superposition. The exclusive formation of a tetrahydrofuran ring from pentaallyl nitrone or nitrile oxide demonstrated the preferred formation of a five-membered ring to that of six or seven-membered rings. The nitrile oxide generated from a 3,4,5,6,7-pentaallyloxy-1-nitroheptane derivative obtained from pentaallylglucose underwent diastereoselective cycloaddition to give an isoxazoline fused to a pyran ring. Enantiopure isoxazoles containing tetrahydrofuran and oxepane rings were also prepared in good yields by the nitrile oxide cycloaddition of the 2-*O*- and 4-*O*-propargyl derivatives.

1. Introduction

One of the frequently used strategies employed for the synthesis of heterocyclic compounds is the 1,3-dipolar cycloaddition reactions involving a nitrone or nitrile oxide and an alkene or alkyne.[1–4] Recently, these two cycloaddition reactions have been successfully applied to *O*- and *N*-alkenylcarbohydrate derivatives leading to the synthesis of enantiomerically pure cyclic ethers and amines fused to isoxazolidine and dihydroisoxazoline rings.[5–7] Most of these cycloadditions have been applied to 3-*O*-allyl carbohydrate derivatives giving rise to pyran and oxepane rings.[8] Examples of the synthesis of tetrahydrofuran rings from carbohydrate derivatives by employing these cycloadditions have remained scarce.[9–11] Earlier, we reported the formation of tetrahydrofuran rings via the nitrone cycloaddition of acyclic 2-*O*-allyl glucose derivatives.[9] Herein, we describe in detail the earlier work[9] and hitherto unreported nitrile oxide cycloaddition of acyclic 2-*O*- and 4-*O*-allyl and propargyl glucose derivatives leading to enantiopure isoxazolidine, dihydroisoxazoline and isoxazole ring fused tetrahydrofuran, pyran and oxepane derivatives.

The general strategy for the above cycloaddition reactions is depicted in Scheme 1. A nitrone or nitrile oxide



Scheme 1. *O*-Allyl and -propargylcarbohydrate nitrone and nitrile oxide cycloaddition strategy.

Keywords: Nitrone; Nitrile oxide; Cycloaddition; Glucose; Isoxazolidine; Isoxazoline; Isoxazole.
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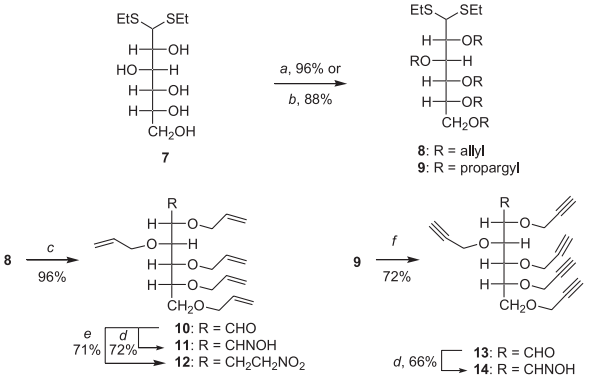
functionality is generated at the 1-C of an acyclic glucose derivative having a 2-*O*- or 4-*O*-allyl or propargyl moiety corresponding to the values of $n=1$ and 3. The nitrone **1** or the nitrile oxides **2** and **3** formed in this manner undergo cycloaddition to afford an isoxazolidine **4**, a dihydroisoxazoline **5** and an isoxazole **6**, respectively. A noteworthy feature of this strategy is the availability of different sizes of cyclic ethers fused to diverse types of heterocyclic rings.

2. Results and discussion

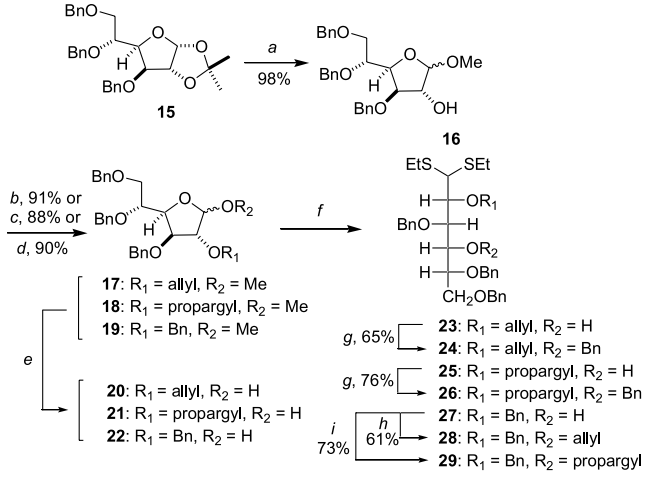
2.1. Preparation of the nitrone and nitrile oxide precursors

The nitrones used in this work were prepared from the reaction of the corresponding aldehydes and *N*-benzylhydroxylamine or *N*-methylhydroxylamine, whereas nitrile oxides were generated from the corresponding aldoximes using chloramine-T,[12] and in one case from a primary nitro compound using 4-chlorophenyl isocyanate.[13] The starting acyclic aldehydes were prepared by the cleavage of the corresponding dithioacetals, which were obtained from readily available glucose derivatives according to Scheme 2. The glucose dithioacetal **7**[14] was converted to the pentaallyl and pentapropargyl derivatives **8** and **9** by alkylation with allyl bromide and propargyl bromide using sodium hydride in DMF. The dithioacetal **8** was converted to the aldehyde **10** by treatment with $HgCl_2$ and $CaCO_3$ in aqueous acetonitrile.[15] The aldehyde **10** and other aldehyde intermediates in this study were used directly for the next steps, because they were found to be sensitive to chromatographic purification. The penta-*O*-propargyl glucose dithioacetal **9** was converted to the aldehyde **13** by a two-step procedure involving oxidation with $NaIO_4$ followed by treatment of the crude sulfoxide intermediate with H_2SO_4 and THF,[16,17] because the direct $HgCl_2$ mediated cleavage of **9** failed to afford **13**. The aldehydes **10** and **13** were converted to the respective oximes **11** and **14** by treatment with $NH_2OH.HCl$ in pyridine–methanol. The primary nitro derivative **12** was prepared from **10** by following a known protocol[18] involving treatment with nitromethane and acetylation followed by reduction with $NaBH_4$ without isolation of the intermediates (Scheme 2).

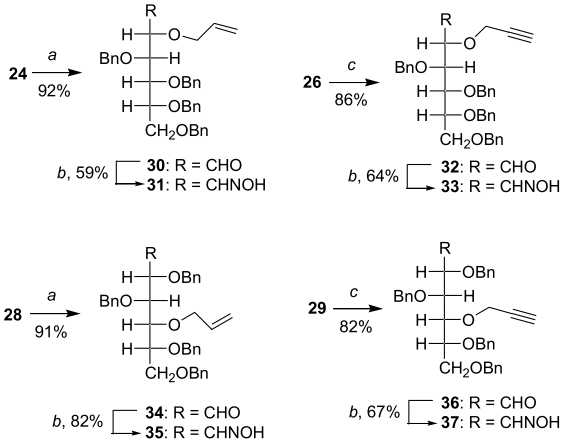


Scheme 2. Synthesis of penta-*O*-allyl and penta-*O*-propargyl glucose, their respective oximes and the nitro derivative **12**. Reagents and conditions: (a) NaH, allylbromide, DMF, 25 °C, 12 h; (b) NaH, propargylbromide, DMF, 25 °C, 12 h; (c) $HgCl_2$, $CaCO_3$, CH_3CN–H_2O (4:1), 25 °C, 6 h; (d) $NH_2OH.HCl$, pyridine, MeOH, reflux, 8 h; (e) (i) CH_3NO_2, KF, 2-propanol, 25 °C, 15 h, (ii) Ac_2O, DMAP, CH_2Cl_2, 25 °C, 12 h, (iii) $NaBH_4$, EtOH, 0–25 °C, 6 h; (f) (i) $NaIO_4$, EtOH, 25 °C, 10 h, (ii) THF, conc H_2SO_4, 25 °C, 12 h.

Another set of acyclic intermediates were prepared from the 1,2-isopropylidene glucose derivative **15**,[19] which was converted to the methyl glycoside **16** as an anomeric mixture, alkylation of which with allyl bromide, propargyl bromide and benzyl bromide separately afforded the anomeric mixtures of the 2-*O*-allyl, 2-*O*-propargyl and 2-*O*-benzyl derivatives **17**, **18** and **19**, respectively (Scheme 3). Although, the respective α and β anomers in the mixtures could be separated by column chromatography, in this study the mixtures were used without separation for the next steps viz. deglycosylation to **20**, **21** and **22** and dithioacetylation to **23**, **25** and **27** followed by alkylation of the 4-OH with either benzyl or allyl or propargyl bromide giving rise to the dithioacetal derivatives **24**, **26**, **28** and **29**.



Scheme 3. Synthesis of 2-*O*- and 4-*O*-allyl and -propargyl glucose dithioacetals. Reagents and conditions: (a) *p*-TsOH, MeOH, reflux, 6 h; (b) allylbromide, Bu_4NBr, CH_2Cl_2, 50% aq NaOH, 25 °C, 12 h; (c) propargylbromide, Bu_4NBr, CH_2Cl_2, 50% aq NaOH, 25 °C, 12 h; (d) benzylbromide, Bu_4NBr, CH_2Cl_2, 50% aq NaOH, 25 °C, 12 h; (e) 50% aq TFA, 25 °C, 24 h, **20** (96%), **21** (94%), **22** (89%); (f) EtSH, conc H_2SO_4, 0 °C, 20 h, **23** (81%), **25** (76%), **27** (73%); (g) NaH, benzylbromide, THF, 25 °C, 12 h; (h) NaH, allylbromide, THF, 25 °C, 12 h; (i) NaH, propargylbromide, THF, 25 °C, 12 h.



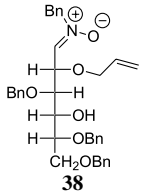
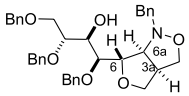
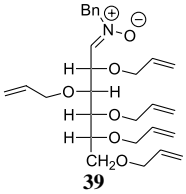
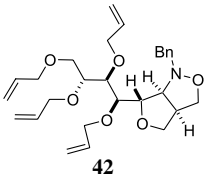
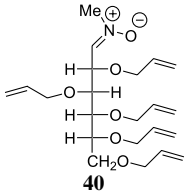
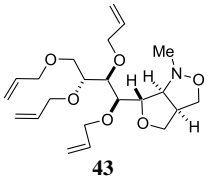
Scheme 4. Synthesis of 2-*O*- and 4-*O*-allyl and -propargyl glucose oximes from their dithioacetals. Reagents and conditions: (a) $HgCl_2$, $CaCO_3$, CH_3CN:H_2O (4:1), 25 °C, 6 h; (b) $NH_2OH.HCl$, pyridine, MeOH, reflux, 8 h; (c) (i) $NaIO_4$, EtOH, 25 °C, 10 h, (ii) THF, conc H_2SO_4, 25 °C, 12 h.

The *O*-allylcarbohydrate aldehydes **30** and **34** were obtained from the corresponding dithioacetal derivatives **24** and **28** by treatment with $HgCl_2$ and $CaCO_3$ in aqueous acetonitrile (Scheme 4). The *O*-propargyl aldehydes **32** and **36** were obtained in good yields from the *O*-propargyl dithioacetals **26** and **29** via the earlier mentioned oxidative method using $NaIO_4$ followed by treatment with an acid. The aldehydes **30**, **32**, **34** and **36** were converted to the corresponding oximes **31**, **33**, **35** and **37**, respectively, as described before (Scheme 4).

2.2. 2-*O*-Allyl carbohydrate nitrone cycloaddition

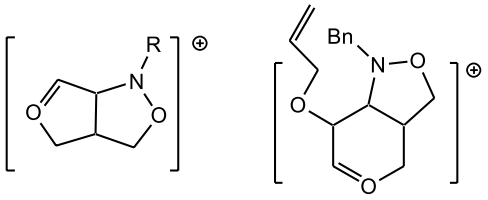
As reported earlier the *N*-benzyl nitrones **38** and **39** prepared from 3,5,6-tri-*O*-benzylglucofuranose **20** and **10** by treatment with *N*-benzylhydroxylamine in refluxing ethanol afforded via in situ cycloaddition the fused isoxazolidines **41** (70%) and **42** (75%), respectively, as exclusive products (Table 1).[9] The presence of a one-proton multiplet at δ 3.36 (3a-H) in the ^{1}H NMR spectrum and a peak at δ 47.5 (3a-C) in the ^{13}C NMR spectrum clearly indicated **41** to be a fused isoxazolidine.[20] The mass spectrum of **41** exhibited besides the molecular ion at *m/z* 595 a strong peak at *m/z* 204 due to the fragment **44**, which is indicative of the presence of the furoisoxazolidine skeleton. The presence of multiple allyl groups in **42** caused extensive overlapping of signals in its ^{1}H NMR spectrum. However, the occurrence of cycloaddition was evident from the appearance of peaks in the spectrum due to the phenyl group as well as the ratio (5:4) of the relative integrations of the aromatic protons and the vinylic methine protons. The ^{13}C NMR spectrum, however, appeared to be more helpful, and clearly indicated the ring juncture 3a-C and 6a-C at δ 48.4 (CH) and 71.9 (CH), respectively.

Table 1. 2-*O*-Allyl carbohydrate nitrone cycloaddition[a]

Nitrone precursor	Nitrone	Product	Yield[b]
20	 **38**	 **41**	70%
10	 **39**	 **42**	75%
10	 **40**	 **43**	75%

[a] Conditions: for *N*-benzyl nitrones–*N*-benzyl hydroxylamine, benzene, reflux; for *N*-methyl nitrone **40**–*N*-methyl hydroxylamine hydrochloride, $NaHCO_3$, 80% aq EtOH, reflux.
[b] Yields refer to chromatographically isolated products.

However, it was more difficult to ascertain whether **42** was a tetrahydrofuran derivative arising out of the cycloaddition to the 2-*O*-allyl group or a tetrahydropyran derivative due to the cycloaddition to the 3-*O*-allyl group of **39**. The problem was resolved by the analysis of the EI mass spectrum

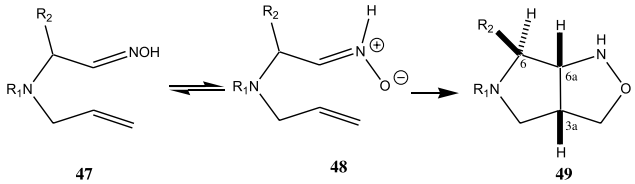


44: R = Bn *m/z* 204
45: R = Me *m/z* 128

46: *m/z* 274

of **42**, in which the fragment **44** at *m/z* 204 appeared besides the molecular ion at *m/z* 485 indicating the presence of the tetrahydrofuran skeleton. The absence of any peak corresponding to the mass spectral fragment **46** (*m/z* 274) in the mass spectrum ruled out the alternative pyran structure. The occurrence of the furoisoxazolidine fragment appeared to be a characteristic of the EI mass spectra of furoisoxazolidines, because the mass spectrum of **43**, formed in 75% yield by the cycloaddition of the *N*-methyl nitrone **40**, also exhibited a strong peak at *m/z* 128 corresponding to the furoisoxazolidine fragment **45**.

The assignment of the ring-junction stereochemistry in **41**, **42** and **43** proved difficult by NMR spectral analysis due to the presence of a number of allyl and benzyl moieties. Hassner et al. reported a number of tetrahydropyrroloisoxazolidine derivatives of the type **49** by the oxime-olefin cycloaddition of **47** (Scheme 5).[21,22] It is generally believed that oxime-olefin cycloaddition proceeds via the formation of the NH nitrone such as **48**. The *cis–trans* stereochemistry of the sequence 3a–6a–6 in **49** was established on the basis of NMR spectral analysis.[22] This stereochemical assignment was also corroborated by MM2 calculations, which revealed a 3.8 kcal difference in energy between the *cis–cis* and the *cis–trans* isomers in favor of the latter.[22] Due to close structural resemblance, the transition state geometries of the nitrones **38**–**40** are not expected to be much different from that of **48**, and the sequence 3a–6a–6 in **41**–**43** was accordingly assigned the *cis–trans* stereochemistry.



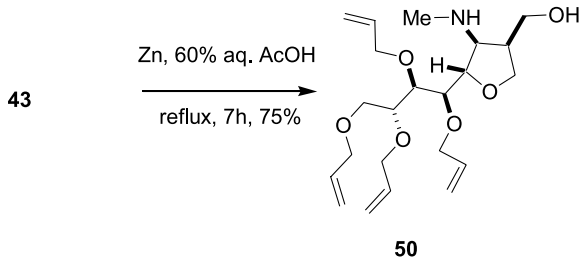
47 **48** **49**

Scheme 5. Reported examples of isoxazolidines prepared by oxime-olefin cycloaddition.

An interesting feature of the cycloaddition of the pentaallyl nitrones **39** and **40** is that although they contain three potentially reactive alkenes viz. 2-, 3- and 4-*O*-allyl residues available for cycloaddition to the dipole, the tetrahydrofuran ring was formed exclusively. The result reflected the great

propensity of the formation of five-membered rings compared to six- and seven-membered rings.

The cleavage of the isoxazolidine ring is frequently a necessary step in any synthetic exercise involving the application of the cycloaddition strategy. Although attempted reaction of **43** with $LiAlH_4$ led to intractable products, Zn and aqueous acetic acid successfully cleaved **43** to the trisubstituted tetrahydrofuran derivative **50** in 75% yield (Scheme 6).

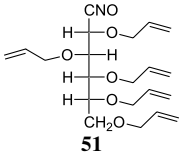
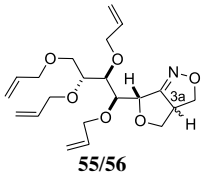
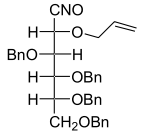
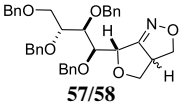
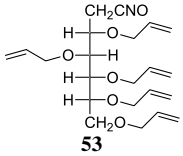
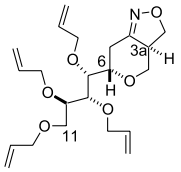
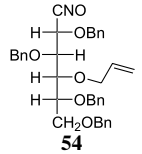
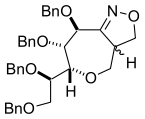


Scheme 6. Cleavage of the isoxazolidine ring of **43**.

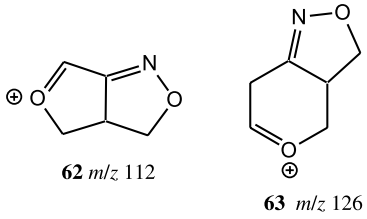
2.3. *O*-Allyl and -propargyl nitrile oxide cycloaddition

The results of the hitherto unreported application of the intramolecular nitrile oxide cycloaddition to acyclic 2-*O*-allyl and 4-*O*-allyl carbohydrate derivatives are presented in Table 2. In contrast to the diastereoselective nitrone cycloaddition of the 2-*O*-allyl carbohydrate derivatives, the corresponding nitrile oxide cycloaddition appeared to furnish mixtures of diastereomers. The nitrile oxide **51**, generated from the pentaallyl carbohydrate oxime **11** by treatment with chloramine-T in ethanol under reflux, underwent in situ cycloaddition giving rise to a separable mixture of the diastereomeric dihydrofuro[3,4-*c*]isoxazoles **55** and **56**. The presence of the isoxazoline rings in these compounds was evident from the appearance of 3a-C signals at δ 44.7 and δ 50.4 as well as quaternary carbon signals due to C=N at δ 156.1 and δ 157.7 in their ^{13}C NMR spectra. The furoisoxazole nature of the rings in **55** and **56** was evident from the appearance of strong peaks at *m*/*z* 112 corresponding to the ion **62** in their mass spectra.

Table 2. *O*-Allyl carbohydrate nitrile oxide cycloaddition[a]

Nitrile oxide precursor	Nitrile oxide	Product[b]	Yield (%)[c]
11	 **51**	 **55/56**	61
31	 **52**	 **57/58**	54
12	 **53**	 **59**	68
35	 **54**	 **60/61**	64

[a] Conditions: nitrile oxides from (a) oximes–chloramine-T, ethanol, reflux; (b) the nitro derivative **12**–4-chlorophenyl isocyanate, triethylamine, benzene, 25 °C.
[b] Except for **59**, all the cycloadducts were isolated as mixtures of diastereomers.
[c] Yields refer to chromatographically isolated mixtures.

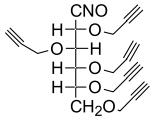
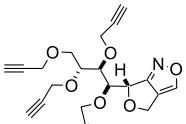
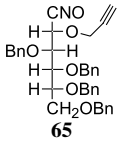
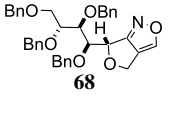
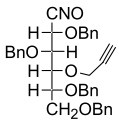
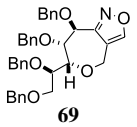


The formation of epimeric pairs of racemic dihydroisoxazolines fused to tetrahydrofuran rings has also been observed in the cycloaddition of nitrile oxides generated from 2-allyloxynitroethanes.[23] The configurations at the newly formed chiral center 3a-C could not be established by NMR spectral analysis, for example, NOESY due to extensive overlapping of relevant signals in the ^{1}H NMR spectrum. However, a tentative assignment was made on the basis of an empirical correlation of optical rotation with configuration, which will be described later in this study. The cycloaddition of the tetra-*O*-benzyl-2-*O*-allyl nitrile oxide **52** prepared from the oxime **31** afforded an inseparable mixture of the diastereomers **57** and **58**. The ^{1}H and ^{13}C NMR spectra of the enriched chromatographic fractions of the mixture had closely similar features, which indicated that they were indeed 3a-epimers. In contrast, the pentaallyl nitrile oxide **53**, the homolog of the nitrile oxide **51** and generated from the nitro derivative **12** by treatment with 4-chlorophenyl isocyanate, underwent cycloaddition to give exclusively the pyran-fused isoxazoline **59** in 68% yield. The pyranoisoxazoline ring in **59** was characterized by the facile cleavage of the substituent at 6-C in the EI mass spectrum, which exhibited a strong peak at *m*/*z* 126 corresponding to the ion **63**. The 500 MHz ^{1}H NMR spectrum exhibited the 3a-H as a multiplet centered around δ 3.42. The gross structure of **59** was established by DQFCOSY and HMQC spectra. The NOESY spectrum of **59** revealed cross peaks between 3a-H and 11-CH_2, and hence the stereochemistry of 3a-C was assigned as shown. The cycloaddition of the 4-*O*-allyl carbohydrate nitrile oxide **54** prepared from the oxime **35** by treatment with chloramine-T led to the formation of a diastereomeric mixture of the oxepanoisoxazolines **60** and **61**, which were separated by column chromatography and characterized. The appearance of 3a-C signals at δ 52.7 and 50.2 as well as quaternary C=N carbon signals at δ 159.7 and 157.7 in the ^{13}C NMR spectra indicated the presence of the isoxazoline ring in the above compounds.

The general yields of the abovementioned nitrile oxide cycloadditions were found to be rather poor compared to the results observed for the corresponding nitrone cycloaddition. Although nitrile oxides are known to be susceptible to dimerization, no dimeric products were detected in the reactions. Intractable polymeric products were observed, and the reasons for the inefficiency of the reaction in these cases are not known to us.

The approach described above for the synthesis of chiral isoxazolines from 2-*O*- and 4-*O*-allyl nitrile oxides was also suitable for preparing chiral isoxazole derivatives by the nitrile oxide cycloaddition of the corresponding *O*-propargyl derivatives. Although the synthesis of chiral isoxazolopyrans and isoxazolooxepanes from 3-*O*-propargyl carbohydrate derivatives has been reported,[24] to our knowledge synthesis of similar systems from the acyclic counterparts is not yet known. In Table 3 are presented the results of the cycloaddition of the nitrile oxides **64**, **65** and **66**. The 2-*O*-propargyl nitrile oxides generated from the corresponding oximes **14** and **33** by treatment with chloramine-T smoothly underwent cycloaddition giving rise to the isoxazoles **67** and **68** in yields of 72 and 77%, respectively. The cycloaddition of 4-*O*-propargyl nitrile oxide **66** obtained from the oxime **37** led to the formation of the oxepinoisoxazole derivative **69** in 80% yield. The presence of the isoxazole ring in **67**–**69** was clearly evident from the appearance of singlets at δ 8.05, 7.96 and 8.18 in their ^{1}H NMR spectra due to the isoxazole protons. The ^{13}C NMR spectra also exhibited peaks due to C=N and quaternary C=C at δ 170.5/123.6, 171.1/124.0 and 160.3/118.5, respectively. The yields encountered in the alkyne-nitrile oxide cycloadditions in the present study were found to be considerably higher than those of the corresponding alkene-nitrile oxide reactions, and reflected the high efficiency of the reaction leading to the formation of a stabilized heterocyclic ring.

Table 3. *O*-Propargyl carbohydrate nitrile oxide cycloaddtion[a]

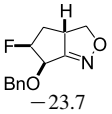
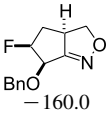
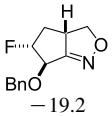
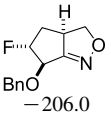
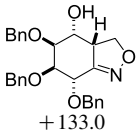
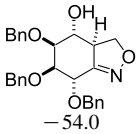
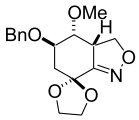
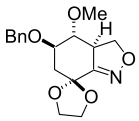
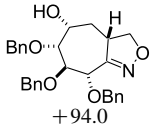
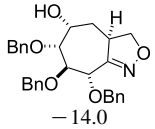
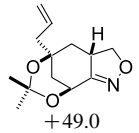
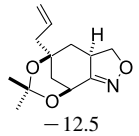
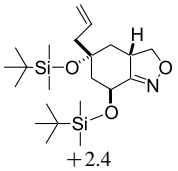
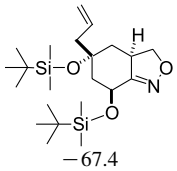
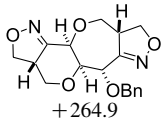
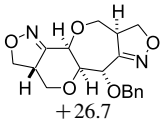
Nitrile oxide precursor	Nitrile oxide	Product	Yield (%)[b]
14	 **64**	 **67**	72
33	 **65**	 **68**	77
37	 **66**	 **69**	80

[a] Conditions: chloramine-T, ethanol, reflux.
[b] Yields refer to chromatographically isolated products.

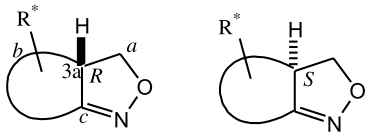
2.4. Empirical assignment of stereochemistry of the 3a-epimeric pairs of isoxazolines 55/56 and 60/61

As mentioned earlier that although individual components of the epimeric pairs of the isoxazolines **55/56** and **60/61** were available, the stereochemistry of the newly formed chiral centres in these compounds could not be established by NOE due to overlapping of signals. The application of X-ray diffraction analysis was precluded by their liquid nature. In the past several attempts were made to empirically assign stereochemistry on the basis of the comparison of optical rotation values.[25,26] With recourse to such an assignment a survey of literature revealed that a number of epimeric pairs of enantiomerically pure isoxazolines with known optical rotation values exist, and are listed in Table 4.[27–32] It is apparent if the isoxazolines are represented by **70** and **71**, the former with the *R*

Table 4. Examples of epimeric dihydroisoxazolines and their $[\alpha]_D$ values reported in the literature

Entry	3a *R*-isoxazoline $[\alpha]_D$	3a *S*-isoxazoline $[\alpha]_D$	Reference
1	 −23.7	 −160.0	27
2	 −19.2	 −206.0	27
3	 +133.0	 −54.0	28
4	 +34.7	 −20.4	29
5	 +94.0	 −14.0	30
6	 +49.0	 −12.5	31
7	 +2.4	 −67.4	31
8	 +264.9	 +26.7	32

configuration of the newly formed center 3a-C (with the arbitrarily assigned sequence priority as shown) has the higher positive rotation. An interesting feature of the optical rotation values is that the difference in the specific rotation values of epimers is appreciable and ranges from +55.1 to +238.2, although the magnitude of the differences does not conform to any correlation with the structural



70 **71**

pattern. Following this trend, the isoxazolines **55**, **56**, **60** and **61** were empirically assigned the stereochemistry shown in Figure 1.

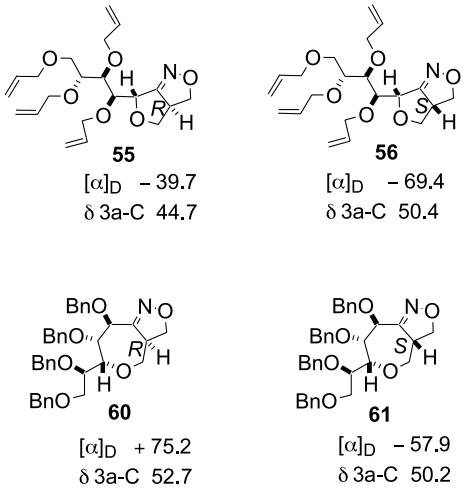


Figure 1. Empirically assigned stereochemistry of isoxazolines.

In conclusion, the work described here demonstrated that intramolecular nitrone and nitrile oxide cycloaddition of readily available acyclic 2- and 4-*O*-allyl and -propargyl carbohydrate derivatives can furnish diverse types of chiral cyclic ether fused isoxazolidine, isoxazoline and isoxazole rings.

3. Experimental

3.1. General

Melting points are uncorrected. Unless otherwise mentioned ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Assignment of CH_3, CH_2, CH and quaternary (q) carbon atoms in ^{13}C NMR spectra was based on DEPT analysis. Elemental analyses were performed at the Indian Association for the Cultivation of Science, Kolkata. Reactions were monitored by thin layer chromatography using Merck 60 F_{254} precoated silica gel plate (No. 1.05554). Organic extracts were dried over anhydrous sodium sulfate. Unless otherwise mentioned 60–120 mesh silica gel was used for column chromatography. Solvents were distilled and dried immediately prior to use. Petroleum ether refers to a fraction boiling between 60 and 80 °C. Room temperature refers to 25 °C.

3.1.1. Penta-*O*-allylglucose diethyl dithioacetal 8. The glucose dithioacetal **7**[14] (4.00 g, 14.00 mmol) was added in portions to a stirred suspension of NaH (2.00 g, 83.00 mmol) in DMF (60 mL) at 0 °C. After the addition was over, the mixture was stirred at 25 °C for 1 h. A solution of allyl bromide (7.5 mL, 87.00 mmol) in DMF (20 mL) was added dropwise to the mixture at 0 °C and the stirring was continued for 30 min. The mixture was then stirred for another 12 h at 25 °C. The whole reaction mixture was poured into water (500 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with water, dried and concentrated in vacuo affording a yellowish liquid, which on chromatography (EtOAc–petroleum ether, 1:24) gave **8** (6.50 g, 96%) as a light yellow liquid, $[\alpha]_D^{25}$ +13.2 (*c* 0.97, $CHCl_3$); IR (Neat): 3080, 3013, 1645, 1455 cm^{-1}; MS (FAB): *m/z* 487 (M+H); ^{1}H NMR: δ 6.03–5.85 (m, 5H), 5.37–5.09 (m, 10H), 4.34–3.97 (m, 12H), 3.88–3.80 (m, 2H), 3.73–3.56 (m, 3H), 2.82–2.61 (m, 4H), 1.25 (t, 6H, *J*=7.6 Hz); ^{13}C NMR: δ 135.1 (CH), 134.9 (CH), 134.7 (2×CH), 134.5 (CH), 116.5 (CH_2), 116.4 (CH_2), 116.0 (2×CH_2), 115.8 (CH_2), 82.7 (CH), 80.4 (CH), 78.8 (CH), 78.1 (CH), 74.2 (CH_2), 73.7 (CH_2), 72.5 (CH_2), 71.9 (CH_2), 70.6 (CH_2), 69.2 (CH_2), 52.9 (CH), 24.7 (CH_2), 24.6 (CH_2), 14.2 (2×CH_3). Anal. Calcd for $C_{25}H_{42}O_5S_2$: C, 61.69; H, 8.70. Found: C, 61.61; H, 8.39.

3.1.2. Penta-*O*-propargylglucose diethyl dithioacetal 9. The above procedure using **7** (1.50 g, 5.24 mmol) and propargyl bromide (4.84 mL, 32.50 mmol) as the alkylating agent yielded after chromatography of the crude product (EtOAc–petroleum ether, 1:19) **9** (2.20 g, 88%) as a pale yellow liquid, $[\alpha]_D^{25}$ −12.0 (*c* 0.76, $CHCl_3$); IR (Neat): 3291, 2117, 1449 cm^{-1}; MS (EI): *m/z* 476 (M), 415 (M−SEt); ^{1}H NMR: δ 4.51 (t, 2H, *J*=2.4 Hz), 4.49 (d, 2H, *J*=2.1 Hz), 4.41 (d, 2H, *J*=2.2 Hz), 4.36 (t, 2H, *J*=2.4 Hz), 4.22–4.21 (m, 2H), 4.11 (t, 2H, *J*=4.5 Hz), 4.00–3.96 (m, 3H), 3.88 (t, 1H, *J*=4.3 Hz), 3.73 (dd, 1H, *J*=11.3, 6.1 Hz), 2.81–2.68 (m, 4H), 2.47–2.45 (m, 5H), 1.28 (t, 6H, *J*=7.4 Hz); ^{13}C NMR: δ 81.9 (CH), 80.0 (CH), 79.7 (CH), 79.6 (2×CH), 79.3 (CH), 79.2 (CH), 78.2 (CH), 77.4 (CH), 74.8 (q), 74.6 (q), 74.5 (2×q), 74.4 (q), 68.5 (CH_2), 60.0 (CH_2), 59.8 (CH_2), 58.8 (CH_2), 58.1 (CH_2), 57.2 (CH_2), 52.5 (CH), 25.1 (CH_2), 24.8 (CH_2), 14.2 (CH_3), 14.1 (CH_3). Anal. Calcd for $C_{25}H_{32}O_5S_2$: C, 63.00; H, 6.77. Found: C, 63.24; H, 6.68.

3.2. General procedure for the cleavage of diethyl dithioacetals by $HgCl_2$

Preparation of the aldehydes **10**, **30** and **34**. The general procedure for the cleavage of the dithioacetals by $HgCl_2$ is illustrated by the preparation of **10**.

A mixture of **8** (1.00 g, 2.00 mmol) in 80% aq CH_3CN (30 mL), $HgCl_2$ (1.20 g, 4.40 mmol) and $CaCO_3$ (0.45 g, 4.40 mmol) were added and stirred at 25 °C for 6 h. After completion of the reaction as revealed by TLC, the resulting precipitate was filtered and washed with CH_3CN. The combined filtrate and washings were evaporated under reduced pressure. The residue obtained was extracted with CH_2Cl_2 and the combined organic extracts were washed

with water and dried. Removal of solvent yielded **10** (0.76 g, 96%) as a light yellow liquid, which was used without purification for the next step.

The aldehydes **30** and **34** prepared by this method were also used without purification.

3.3. General procedure for the cleavage of diethyl dithioacetals by $NaIO_4$–H_2SO_4

Preparation of the aldehydes **13**, **32** and **36**. The general procedure for the cleavage of the dithioacetals is illustrated by the preparation of **13**.

To a solution of **9** (1.00 g, 2.10 mmol) in EtOH (40 mL) was added with stirring a solution of $NaIO_4$ (1.12 g, 5.23 mmol) in water (10 mL) and the mixture was stirred at 25 °C for 10 h. It was then filtered and the filtrate was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 and the combined organic extracts were washed with water, dried and removal of solvent afforded a syrupy material. A solution of the above material in THF (20 mL) containing a catalytic amount of conc H_2SO_4 was stirred at 25 °C for 12 h. The reaction mixture was neutralised with saturated $NaHCO_3$ solution and solvent was removed until a syrupy residue was obtained. The residue was extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried and concentrated to give **13** (0.56 g, 72%) as a colorless liquid, which was immediately used without purification for the next step.

The aldehydes **32** and **36** prepared by the above method was also used without purification.

3.4. General procedure for the preparation of aldoximes 11, 14, 31, 33, 35 and 37

The general procedure is illustrated by the preparation of **11**.

A mixture of **10** (0.80 g, 2.10 mmol), pyridine (0.4 mL, 5.00 mmol), $NH_2OH.HCl$ (0.22 g, 3.15 mmol) and MeOH (20 mL) was heated under reflux for 8 h. After removal of solvent, the residue was extracted with CH_2Cl_2. The organic extract was washed with water, dried and evaporated under reduced pressure. The residue was repeatedly co-evaporated with dry toluene, and then chromatographed (EtOAc–petroleum ether, 1:16–1:12) to give the oxime **11** (0.60 g, 72%, mixture of *syn* and *anti* isomers) as a pale yellow syrup, IR (Neat): 3363, 3081, 3014, 1646, 1457, 1424 cm^{-1}; MS (FAB): *m/z* 396 (M+H); ^1H NMR: δ 7.48 (d, 0.75H, J=7.5 Hz), 6.95 (d, 0.25H, J=6.5 Hz), 5.96–5.83 (m, 5H), 5.30–5.10 (m, 10H), 4.88 (dd, 0.25H, J=6.4, 4.6 Hz), 4.33–3.54 (m, 15.75H); ^{13}C NMR: δ 150.9 (CH), 149.4 (CH), 135.2 (CH), 134.9 (2×CH), 134.8 (CH), 134.7 (CH), 134.6 (CH), 134.5 (CH), 134.3 (CH), 134.0 (CH), 133.9 (CH), 117.4 (CH_2), 117.2 (CH_2), 117.0 (CH_2), 116.9 (CH_2), 116.8 (CH_2), 116.7 (CH_2), 116.5 (CH_2), 116.4 (CH_2), 116.3 (CH_2), 116.2 (CH_2), 80.3 (CH), 79.5 (CH), 79.1 (CH), 78.5 (CH), 78.2 (CH), 77.8 (2×CH), 76.8 (CH), 74.2 (CH_2), 73.9 (CH_2), 73.6 (CH_2), 73.2 (CH_2), 72.1 (CH_2), 71.4 (CH_2), 71.0 (CH_2), 70.7 (CH_2), 70.1 (CH_2), 68.8 (CH_2), 68.4 (CH_2), 68.3 (CH_2). Anal. Calcd for $C_{21}H_{33}NO_6$: C, 63.78; H, 8.41; N, 3.54. Found: C, 63.59; H, 8.47; N, 3.42.

3.4.1. Aldoxime 14. Pale yellow syrup; yield: 66%; mixture of *syn* and *anti* isomers; IR (Neat): 3362, 3293, 2119, 1445 cm^{-1}; MS (FAB): *m/z* 386 (M+H), 330 (M−OCH_2CCH); ^1H NMR: δ 7.97 (br s, 1H), 7.54 (d, 0.8H, J=7.6 Hz), 6.99 (d, 0.2H, J=6.5 Hz), 5.09 (dd, 0.2H, J=6.4, 3.7 Hz), 4.46–4.12 (m, 10.8H), 4.01–3.86 (m, 4H), 3.77–3.73 (m, 1H), 2.49–2.44 (m, 5H); ^{13}C NMR: δ 149.8 (CH), 148.6 (CH), 79.8 (CH), 79.7 (CH), 79.6 (2×CH), 79.5 (CH), 79.3 (CH), 79.2 (CH), 79.0 (CH), 78.9 (CH), 78.3 (CH), 77.9 (CH), 77.7 (CH), 77.3 (CH), 75.8 (CH), 75.4 (q), 75.3 (q), 75.0 (q), 74.9 (q), 74.8 (q), 74.7 (q), 74.6 (q), 74.4 (q), 70.6 (CH), 67.8 (CH_2), 67.7 (CH_2), 59.8 (CH_2), 59.7 (CH_2), 59.6 (CH_2), 59.5 (CH_2), 58.2 (CH_2), 57.4 (CH_2), 57.2 (CH_2), 56.3 (CH_2). Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.57; H, 6.23; N, 3.53.

3.4.2. Aldoxime 31. Colorless syrup; yield: 59%; mixture of *syn* and *anti* isomers; IR (Neat): 3354, 3062, 3031, 1644, 1603, 1494, 1454 cm^{-1}; MS (FAB): *m/z* 596 (M+H); ^1H NMR: δ 7.41 (d, 0.75H, J=7.6 Hz), 7.31–7.26 (m, 20H), 6.89 (d, 0.25H, J=6.2 Hz), 5.89–5.76 (m, 1H), 5.24 (dd, 1H, J=17.2, 1.4 Hz), 5.14 (dd, 1H, J=10.3, 1.4 Hz), 4.88 (dd, 0.25H, J=6.2, 4.5 Hz), 4.74–4.43 (m, 7.75H), 4.24 (dd, 1H, J=7.4, 6.3 Hz), 4.11–4.05 (m, 1H), 4.00–3.96 (m, 1H), 3.91–3.82 (m, 4H), 3.70–3.66 (m, 1H); ^{13}C NMR: δ 151.3 (CH), 149.6 (CH), 138.4 (q), 138.36 (q), 138.2 (q), 138.0 (q), 134.0 (CH), 133.9 (CH), 128.3 (CH), 128.2 (CH), 128.16 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.36 (CH), 117.7 (CH_2), 117.5 (CH_2), 79.8 (CH), 78.4 (CH), 78.3 (CH), 76.9 (CH), 75.0 (CH_2), 74.6 (CH_2), 74.1 (CH_2), 73.2 (CH_2), 71.9 (CH_2), 71.7 (CH_2), 71.1 (CH_2), 70.3 (CH_2), 69.3 (CH_2), 68.8 (CH_2). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.82; H, 6.97; N, 2.21.

3.4.3. Aldoxime 33. Colorless syrup; yield: 64%; mixture of *syn* and *anti* isomers; IR (Neat): 3362, 3292, 3062, 3031, 2117, 1604, 1495, 1453 cm^{-1}; MS (FAB): *m/z* 616 (M+Na), 594 (M+H), 576 (M−OH), 538 (M−OCH_2CCH), 486 (M−OBn); ^1H NMR: δ 7.40 (d, 0.8H, J=7.4 Hz), 7.31–7.25 (m, 20H), 6.91 (d, 0.2H, J=6.0 Hz), 5.07 (dd, 0.2H, J=5.9, 3.8 Hz), 4.76–4.59 (m, 5H), 4.57–4.41 (m, 3.8H), 4.26–3.99 (m, 3H), 3.92–3.83 (m, 3H), 3.75 (dd, 0.2H, J=10.3, 5.8 Hz), 3.69 (dd, 0.8H, J=10.1, 4.6 Hz), 2.36 (t, 1H, J=2.2 Hz); ^{13}C NMR: δ 149.0 (CH), 138.5 (q), 138.3 (q), 138.1 (q), 128.3 (CH), 128.24 (CH), 128.22 (CH), 128.19 (CH), 128.16 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.44 (CH), 127.39 (CH), 79.7 (CH), 79.5 (CH), 79.2 (CH), 78.7 (CH), 78.3 (CH), 76.1 (CH), 75.1 (q), 74.8 (CH_2), 74.3 (CH_2), 73.2 (CH_2), 71.9 (CH_2), 68.9 (CH_2), 56.3 (CH_2). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.77; H, 6.87; N, 2.16.

3.4.4. Aldoxime 35. Colorless syrup; yield: 82%; mixture of *syn* and *anti* isomers; IR (Neat): 3354, 3063, 3031, 1644, 1604, 1495, 1454 cm^{-1}; MS (FAB): *m/z* 634 (M+K), 618 (M+Na), 596 (M+H); ^1H NMR: δ 7.49 (d, 0.75H, J=7.6 Hz), 7.31–7.25 (m, 20H), 6.93 (d, 0.25H, J=6.6 Hz), 5.94–5.81 (m, 1H), 5.18 (dd, 1H, J=17.2, 1.4 Hz), 5.08 (dd, 1H, J=10.2, 1.4 Hz), 4.98 (dd, 0.25H, J=6.2, 4.0 Hz), 4.72 (d, 1H, J=11.5 Hz), 4.65–4.46 (m, 4.75H), 4.43–4.27 (m, 3H), 4.19–4.11 (m, 2H), 3.91–3.76 (m, 4H), 3.67–3.60 (m, 1H); ^{13}C NMR: δ 150.8 (CH), 149.4 (CH), 138.4 (q), 138.3

(q), 138.2 (q), 138.1 (q), 138.0 (q), 137.5 (q), 137.4 (q), 135.1 (CH), 134.8 (CH), 128.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 116.5 (CH_2), 116.3 (CH_2), 79.3 (CH), 79.1 (CH), 78.7 (CH), 78.5 (CH), 78.0 (CH), 77.9 (CH), 76.8 (CH), 74.8 (CH_2), 74.3 (CH_2), 73.5 (CH_2), 73.2 (CH_2), 73.1 (CH_2), 72.0 (CH_2), 71.7 (CH_2), 71.6 (CH_2), 71.2 (CH_2), 69.0 (CH_2), 68.4 (CH_2). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.46; H, 7.12; N, 2.16.

3.4.5. Aldoxime 37. Colorless syrup; yield: 67%; mixture of *syn* and *anti* isomers; IR (Neat): 3363, 3292, 3061, 3032, 2119, 1604, 1495, 1453 cm^{-1}; MS (FAB): *m/z* 594 (M+H), 576 (M−OH), 486 (M−OBn); ^1H NMR: δ 7.54 (d, 0.7H, J=7.6 Hz), 7.31–7.26 (m, 20H), 6.98 (d, 0.3H, J=6.2 Hz), 4.95 (dd, 0.3H, J=6.4, 4.4 Hz), 4.71–4.46 (m, 6H), 4.43–4.27 (m, 4.7H), 4.03 (dd, 0.3H, J=5.6, 4.3 Hz), 3.96–3.81 (m, 2.7H), 3.77–3.72 (m, 1H), 3.67–3.62 (m, 1H), 2.39 (t, 1H, J=2.3 Hz). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.69; H, 6.59; N, 2.32.

3.4.6. (3*S*,4*R*,5*R*,6*R*)-3,4,5,6,7-Pentaallyloxy-1-nitroheptane (12). A mixture of the aldehyde **10** (1.76 g, 4.63 mmol) prepared as described above, nitromethane (5.1 mL, 92.60 mmol), anhydrous KF (0.40 g, 6.90 mmol) and isopropanol (20 mL) was stirred at 25 °C for 15 h. The mixture was then filtered and the filtrate was concentrated to afford a syrupy liquid. To a solution of this material in CH_2Cl_2 (20 mL) at 0 °C, Ac_2O (1 mL) and 4-dimethylaminopyridine (DMAP) (50 mg) were added, and the mixture was kept at 25 °C for 12 h. After addition of water (25 mL), the mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with 10% HCl (5 mL), water, dried and concentrated to yield an oil. The latter was dissolved in ethanol (10 mL) and added dropwise to a stirred suspension of $NaBH_4$ (1.00 g) in EtOH (30 mL) at 0 °C and the resulting mixture was stirred for 6 h at 25 °C. Excess $NaBH_4$ was destroyed by the addition of 10% aqueous AcOH, and the residue obtained after removal of solvent was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried and concentrated under reduced pressure to give a syrupy residue, which was chromatographed (EtOAc–petroleum ether, 1:12) to give **12** (1.40 g, 71%) as a light yellow syrupy liquid, $[\alpha]_D^{25}$ −16.7 (*c* 0.86, $CHCl_3$); IR (Neat): 3081, 1646, 1553 cm^{-1}; MS (FAB): *m/z* 426 (M+H); ^1H NMR: δ 5.98–5.82 (m, 5H), 5.30–5.13 (m, 10H), 4.55 (dd, 1H, J=13.3, 7.4 Hz), 4.46 (dd, 1H, J=13.3, 6.4 Hz), 4.23–3.96 (m, 10H), 3.78–3.53 (m, 6H), 2.47–2.39 (m, 1H), 2.17–2.09 (m, 1H); ^{13}C NMR: δ 134.7 (CH), 134.64 (CH), 134.62 (CH), 134.4 (CH), 134.2 (CH), 117.0 (CH_2), 116.7 (2×CH_2), 116.5 (CH_2), 116.2 (CH_2), 79.5 (CH), 77.8 (CH), 77.5 (CH), 75.4 (CH), 73.5 (CH_2), 72.8 (CH_2), 72.2 (CH_2), 72.0 (CH_2), 71.9 (CH_2), 70.5 (CH_2), 68.0 (CH_2), 28.6 (CH_2). Anal. Calcd for $C_{22}H_{35}NO_7$: C, 62.10; H, 8.29; N, 3.29. Found: C, 62.02; H, 8.14; N, 3.35.

3.4.7. (α,β)-Methyl-3,5,6-tri-*O*-benzylglucofuranoside (16). A solution of **15** (4.5 g, 9.18 mmol) in dry MeOH (75 mL) containing TsOH (0.22 g, 1.41 mmol) was heated at reflux for 6 h. The reaction mixture was neutralised with saturated $NaHCO_3$ solution and solvent was removed until a syrupy residue was obtained. The residue was extracted with CH_2Cl_2 and the combined organic layers were washed with water, dried and concentrated to give **16** (4.2 g, 98%) as a light yellow viscous oil, which was a mixture of the α and β anomers and used as such for the next steps. The mixture was separated by chromatography (100–200 mesh; EtOAc–petroleum ether, 1:9) to give the α-**16** as a colorless syrup, $[\alpha]_D^{28}$ +28.9 (*c* 0.32, $CHCl_3$); IR (Neat): 3517, 3062, 3031, 1604 cm^{-1}; MS (FAB): *m/z* 487 (M+Na), 465 (M+H), 447 (M−OH), 433 (M−OCH_3); ^1H NMR: δ 7.33–7.25 (m, 15H), 5.02 (d, 1H, J=4.5 Hz), 4.78 (d, 1H, J=11.5 Hz), 4.69 (d, 1H, J=11.7 Hz), 4.61–4.57 (m, 2H), 4.54 (d, 1H, J=11.5 Hz), 4.51 (d, 1H, J=11.7 Hz), 4.30 (dd, 1H, J=8.2, 4.4 Hz), 4.24 (dd, 1H, J=4.1, 1.4 Hz), 4.06–4.00 (m, 2H), 3.86 (dd, 1H, J=10.5, 1.9 Hz), 3.69 (dd, 1H, J=10.6, 5.8 Hz), 3.46 (s, 3H).

Further elution with EtOAc–petroleum ether (1:7) afforded the β-**16** as a colorless syrup, $[\alpha]_D^{28}$ −54.9 (*c* 0.25, $CHCl_3$); IR (Neat): 3431, 3062, 3031, 1604 cm^{-1}; MS (FAB): *m/z* 487 (M+Na), 465 (M+H), 447 (M−OH), 433 (M−OCH_3); ^1H NMR: δ 7.36–7.25 (m, 15H), 4.79 (s, 1H), 4.75 (d, 1H, J=11.4 Hz), 4.62–4.58 (m, 3H), 4.53 (d, 1H, J=11.9 Hz), 4.50 (d, 1H, J=11.4 Hz), 4.39 (dd, 1H, J=8.9, 4.9 Hz), 4.18 (s, 1H), 4.06 (ddd, 1H, J=8.7, 5.1, 1.9 Hz), 3.96 (dd, 1H, J=4.8, 1.1 Hz), 3.89 (dd, 1H, J=10.7, 1.9 Hz), 3.72 (dd, 1H, J=10.7, 5.2 Hz), 3.36 (s, 3H).

3.5. General procedure for the alkylation of 16

The procedure is illustrated by the preparation of methyl-2-*O*-allyl-3,5,6-tri-*O*-benzylglucofuranoside (**17**).

3.5.1. Methyl-2-*O*-allyl-3,5,6-tri-*O*-benzylglucofuranoside (17). A mixture of **16** (3.3 g, 7.11 mmol) in CH_2Cl_2 (50 mL), 50% aq NaOH solution (40 mL), tetrabutylammoniumbromide (15 mol%) and allyl bromide (0.92 mL, 10.66 mmol) was vigorously stirred for 12 h at 25 °C. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried and the solvent was removed under reduced pressure to afford **17** (3.26 g, 91%) as a colorless syrup, which was a mixture of the α and β anomers and used as such for the next steps. The mixture was separated by chromatography (EtOAc–petroleum ether, 1:19) to give the β-**17** as a colorless syrup, $[\alpha]_D^{25}$ −39.1 (*c* 2.15, $CHCl_3$); IR (Neat): 3063, 3031, 1644, 1603 cm^{-1}; MS (FAB): *m/z* 527 (M+Na), 505 (M+H), 473 (M−OCH_3); ^1H NMR: δ 7.37–7.24 (m, 15H), 5.87–5.76 (m, 1H), 5.26–5.14 (m, 2H), 4.85 (s, 1H), 4.78 (d, 1H, J=11.4 Hz), 4.59–4.57 (m, 4H), 4.51 (d, 1H, J=11.4 Hz), 4.31 (dd, 1H, J=9.0, 4.6 Hz), 4.08 (ddd, 1H, J=9.0, 5.3, 2.0 Hz), 4.02 (dd, 1H, J=4.5, 0.7 Hz), 3.92–3.87 (m, 4H), 3.72 (dd, 1H, J=10.7, 5.3 Hz), 3.38 (s, 3H); ^{13}C NMR: δ 138.8 (q), 138.5 (q), 137.8 (q), 133.9 (CH), 128.2 (2×CH), 128.16 (2×CH), 128.1 (2×CH), 127.8 (2×CH), 127.6 (CH), 127.5 (2×CH), 127.4 (2×CH), 127.3 (CH), 127.2 (CH), 117.3 (CH_2), 108.5 (CH), 85.4 (CH), 80.4 (CH), 80.1 (CH), 76.5 (CH), 73.2 (CH_2), 72.2 (CH_2), 72.1 (CH_2), 70.7 (CH_2), 70.5 (CH_2), 55.8 (CH_3). Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.56; H, 7.28.

Further elution with EtOAc–petroleum ether (1:16) afforded the α-**17** as a colorless syrup, $[\alpha]_D^{25}$ +43.2 (*c* 1.20, $CHCl_3$);

IR (Neat): 3063, 3031, 1644, 1602 cm^{-1}; MS (FAB): *m/z* 505 (M+H); ^1H NMR: δ 7.33–7.27 (m, 15H), 5.97–5.84 (m, 1H), 5.27 (d, 1H, J=17.3 Hz), 5.20 (d, 1H, J=10.3 Hz), 4.95 (d, 1H, J=4.2 Hz), 4.79 (d, 1H, J=11.6 Hz), 4.63 (d, 1H, J=11.8 Hz), 4.56 (s, 2H), 4.55 (d, 1H, J=11.5 Hz), 4.54 (d, 1H, J=11.3 Hz), 4.33 (t, 1H, J=6.4 Hz), 4.21 (dd, 1H, J=5.7, 4.0 Hz), 4.12–3.98 (m, 3H), 3.94 (t, 1H, J=4.0 Hz), 3.86 (dd, 1H, J=10.6, 1.7 Hz), 3.71 (dd, 1H, J=10.5, 6.1 Hz), 3.41 (s, 3H); ^{13}C NMR: δ 138.8 (q), 138.5 (q), 138.0 (q), 134.4 (CH), 129.7 (CH), 128.9 (CH), 126.8 (CH), 117.7 (CH_2), 101.4 (CH), 83.6 (CH), 81.9 (CH), 76.8 (CH), 76.7 (CH), 73.3 (CH_2), 72.5 (CH_2), 72.2 (CH_2), 71.7 (CH_2), 71.2 (CH_2), 55.4 (CH_3). Anal. Calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.68; H, 7.36.

3.5.2. Methyl-2-*O*-propargyl-3,5,6-tri-*O*-benzylglucofuranoside (18). The above procedure using propargyl bromide as the alkylating agent gave **18** (88%) as a mixture of anomers, which was used without separation for the next step. The mixture was separated by chromatography (EtOAc–petroleum ether, 1:19) to give the β-**18** as a colorless syrup, $[\alpha]_D^{25}$ −54.0 (*c* 1.49, $CHCl_3$); IR (Neat): 3285, 3062, 3031, 2117, 1602 cm^{-1}; MS (FAB): *m/z* 525 (M+Na), 503 (M+H), 471 (M−OCH_3); ^1H NMR: δ 7.37–7.25 (m, 15H), 4.87 (s, 1H), 4.77 (d, 1H, J=11.4 Hz), 4.64 (d, 1H, J=12.0 Hz), 4.59 (s, 2H), 4.57 (d, 1H, J=12.0 Hz), 4.51 (d, 1H, J=11.4 Hz), 4.29 (dd, 1H, J=9.0, 4.7 Hz), 4.15–4.01 (m, 5H), 3.89 (dd, 1H, J=10.7, 2.0 Hz), 3.71 (dd, 1H, J=10.7, 5.3 Hz), 3.39 (s, 3H), 2.44 (t, 1H, J=2.5 Hz); ^{13}C NMR: δ 138.8 (q), 138.5 (q), 137.7 (q), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.8 (2×CH), 127.6 (CH), 127.5 (4×CH), 127.3 (CH), 127.2 (CH), 108.3 (CH), 84.9 (CH), 80.0 (CH), 79.9 (CH), 79.0 (CH), 76.4 (CH), 75.1 (q), 73.3 (CH_2), 72.3 (CH_2), 72.0 (CH_2), 70.6 (CH_2), 57.0 (CH_2), 55.9 (CH_3). Anal. Calcd for $C_{31}H_{34}O_6$: C, 74.08; H, 6.82. Found: C, 73.84; H, 6.73.

Further elution with EtOAc–petroleum ether (1:16) afforded the α-**18** as a colorless syrup, $[\alpha]_D^{25}$ +39.5 (*c* 1.04, $CHCl_3$); IR (Neat): 3285, 3063, 3032, 2119, 1602 cm^{-1}; MS (FAB): *m/z* 525 (M+Na), 503 (M+H), 471 (M−OCH_3); ^1H NMR: δ 7.35–7.21 (m, 15H), 5.02 (d, 1H, J=3.9 Hz), 4.79 (d, 1H, J=11.6 Hz), 4.68 (d, 1H, J=11.7 Hz), 4.56 (s, 2H), 4.55 (d, 1H, J=11.6 Hz), 4.53 (d, 1H, J=11.7 Hz), 4.35–4.16 (m, 5H), 4.03 (ddd, 1H, J=8.2, 6.1, 2.2 Hz), 3.86 (dd, 1H, J=10.6, 2.2 Hz), 3.70 (dd, 1H, J=10.6, 6.1 Hz), 3.41 (s, 3H), 2.46 (t, 1H, J=2.5 Hz); ^{13}C NMR: δ 138.8 (q), 138.5 (q), 137.9 (q), 128.4 (CH), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.6 (2×CH), 127.5 (2×CH), 127.4 (2×CH), 127.3 (CH), 127.2 (CH), 101.3 (CH), 82.7 (CH), 81.6 (CH), 79.2 (CH), 76.8 (CH), 76.5 (CH), 75.3 (q), 73.3 (CH_2), 72.5 (CH_2), 72.0 (CH_2), 71.1 (CH_2), 57.6 (CH_2), 55.4 (CH_3). Anal. Calcd for $C_{31}H_{34}O_6$: C, 74.08; H, 6.82. Found: C, 74.26; H, 6.68.

3.5.3. Methyl-2,3,5,6-tetra-*O*-benzylglucofuranoside (19). The above procedure using benzyl bromide as the alkylating agent gave **19** (90%) as a mixture of anomers, which was used without separation for the next step. The mixture was separated by chromatography (EtOAc–petroleum ether, 1:16) to give the β-**19** as a colorless syrup, $[\alpha]_D^{25}$ −30.4 (*c* 1.35, $CHCl_3$); IR (Neat): 3062, 3031, 1603 cm^{-1}; MS (EI): *m/z* 554 (M); ^1H NMR: δ 7.36–7.26 (m, 20H), 4.90 (s, 1H), 4.77 (d, 1H, J=11.4 Hz), 4.59 (s, 2H), 4.52 (s, 2H), 4.51 (d, 1H, J=11.2 Hz), 4.43 (s, 2H), 4.35 (dd, 1H, J=9.0, 4.6 Hz), 4.11–4.06 (m, 2H), 3.92 (s, 1H), 3.88 (d, 1H, J=1.7 Hz), 3.72 (dd, 1H, J=10.7, 5.3 Hz), 3.37 (s, 3H); ^{13}C NMR: δ 138.8 (q), 138.6 (q), 137.8 (q), 137.4 (q), 128.4 (2×CH), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.9 (2×CH), 127.8 (CH), 127.6 (CH), 127.5 (6×CH), 127.3 (CH), 127.2 (CH), 108.6 (CH), 85.6 (CH), 80.5 (CH), 80.1 (CH), 76.5 (CH), 73.3 (CH_2), 72.3 (CH_2), 72.1 (CH_2), 71.7 (CH_2), 70.7 (CH_2), 55.8 (CH_3). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.91; H, 6.83.

Further elution with EtOAc–petroleum ether (1:14) afforded the α-**19** as a colorless syrup, $[\alpha]_D^{25}$ +40.6 (*c* 1.19, $CHCl_3$); IR (Neat): 3062, 3031, 1603 cm^{-1}; MS (EI): *m/z* 554 (M); ^1H NMR: δ 7.34–7.19 (m, 20H), 4.87 (d, 1H, J=4.2 Hz), 4.77 (d, 1H, J=11.6 Hz), 4.63 (d, 1H, J=12.0 Hz), 4.55–4.45 (m, 6H), 4.35 (t, 1H, J=6.2 Hz), 4.23 (dd, 1H, J=5.7, 3.9 Hz), 4.02–3.95 (m, 2H), 3.85 (dd, 1H, J=10.5, 2.0 Hz), 3.69 (dd, 1H, J=10.5, 6.1 Hz), 3.39 (s, 3H); ^{13}C NMR: δ 138.8 (q), 138.5 (q), 137.9 (q), 137.5 (q), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 128.0 (2×CH), 127.9 (2×CH), 127.8 (CH), 127.5 (3×CH), 127.4 (2×CH), 127.3 (2×CH), 127.2 (CH), 127.1 (CH), 101.3 (CH), 83.5 (CH), 81.9 (CH), 76.7 (CH), 76.5 (CH), 73.2 (CH_2), 72.5 (CH_2), 72.4 (CH_2), 72.0 (CH_2), 71.1 (CH_2), 55.3 (CH_3). Anal. Calcd for $C_{35}H_{38}O_6$: C, 75.79; H, 6.91. Found: C, 75.72; H, 6.74.

3.6. General procedure for the deglycosylation of the methylfuranosides 20, 21, 22

The general deglycosylation procedure is illustrated by the preparation of **20**.

3.6.1. 2-*O*-Allyl-3,5,6-tri-*O*-benzylglucofuranose (20). A solution of the α/β mixture **17** (2.60 g) in 50% aq TFA (30 mL) was stirred at 25 °C for 24 h. The reaction mixture was neutralized with solid $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 and the combined organic extract was washed with water, dried and concentrated to give a syrupy liquid, which on chromatography (EtOAc–petroleum ether, 1:9) gave an anomeric mixture of **20** (2.42 g, 96%) as a colorless syrup, IR (Neat): 3508, 3062, 3031, 1644, 1603 cm^{-1}; MS (FAB): *m/z* 513 (M+Na), 491 (M+H), 473 (M−OH); ^1H NMR: δ 7.36–7.21 (m, 15H), 5.88–5.77 (m, 1H), 5.48 (d, 0.4H, J=3.3 Hz), 5.28–5.17 (m, 2.6H), 4.84 (d, 0.6H, J=11.4 Hz), 4.83 (d, 0.4H, J=11.4 Hz), 4.63–4.47 (m, 5H), 4.31 (dd, 0.6H, J=9.4, 3.7 Hz), 4.23 (dd, 0.4H, J=9.1, 3.3 Hz), 4.12–3.89 (m, 5.6H), 3.78 (d, 0.4H, J=3.7 Hz), 3.72 (dd, 0.6H, J=10.6, 5.5 Hz), 3.70 (dd, 0.4H, J=10.6, 5.8 Hz).

3.6.2. 2-*O*-Propargyl-3,5,6-tri-*O*-benzylglucofuranose (21). The same procedure starting from the α/β mixture of **18** (2.95 g) yielded an anomeric mixture of **21** (2.70 g, 94%) as a colorless syrup, IR (Neat): 3435, 3287, 3062, 3031, 2117, 1603 cm^{-1}; MS (FAB): *m/z* 511 (M+Na), 471 (M−OH), 411 (M−Ph); ^1H NMR: δ 7.35–7.25 (m, 15H), 5.50 (d, 0.35H, J=3.4 Hz), 5.22 (s, 0.65H), 4.82 (d, 0.65H, J=11.5 Hz), 4.81 (d, 0.35H, J=11.4 Hz), 4.64–4.47 (m, 6H), 4.30–4.22 (m, 1H), 4.18–4.12 (m, 3H), 4.07–3.99 (m, 1H),

3.94–3.88 (m, 1H), 3.72 (dd, 0.65H, $J=10.7$, 5.4 Hz), 3.69 (dd, 0.35H, $J=10.7$, 5.9 Hz), 2.45 (t, 1H, $J=2.5$ Hz).

3.6.3. 2,3,5,6-Tetra-*O*-benzylglucofuranose (22). The same procedure starting from the α/β mixture of **19** (2.00 g) yielded an anomeric mixture of **22** (1.73 g, 89%) as a colorless syrup, IR (Neat): 3508, 3062, 3031, 1603 cm^{-1}; MS (FAB): *m/z* 563 (M+Na), 523 (M−OH); ^1H NMR: δ 7.36–7.17 (m, 20H), 5.48 (br s, 0.4H), 5.25 (br s, 0.6H), 4.83 (d, 0.6H, $J=11.4$ Hz), 4.81 (d, 0.4H, $J=11.3$ Hz), 4.63–4.41 (m, 7H), 4.34 (dd, 0.6H, $J=9.4$, 3.7 Hz), 4.26 (dd, 0.4H, $J=9.1$, 3.3 Hz), 4.12–3.83 (m, 4H), 3.73 (dd, 0.6H, $J=10.5$, 5.4 Hz), 3.69 (dd, 0.4H, $J=10.5$, 5.5 Hz).

3.7. General procedure for the preparation of the diethyl dithioacetal derivatives 24, 26, 28 and 29

The general procedure for the preparation of the above compounds is illustrated by the preparation of **24**.

A solution of **20** (2.40 g) in conc HCl (18 mL) was cooled to 0 °C with stirring for 15 min. To the mixture was added EtSH (9 mL) dropwise and the resulting solution was stirred for another 4 h at 0 °C. The solution was kept in a freezer for 16 h. The reaction mixture was neutralised with solid $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layers were washed with water, dried and evaporated under reduced pressure yielding a light yellow syrup, which was chromatographed (EtOAc–petroleum ether, 1:11) to give **23** (2.37 g, 81%) as a colorless syrup, $[\alpha]_D^{25}-46.7$ (*c* 0.14, $CHCl_3$); IR (Neat): 3539, 3063, 3030, 1604, 1496, 1453 cm^{-1}; MS (FAB): *m/z* 619 (M+Na), 597 (M+H), 535 (M−SEt); ^1H NMR: δ 7.34–7.26 (m, 15H), 6.01–5.88 (m, 1H), 5.25 (dd, 1H, $J=17.2$, 1.6 Hz), 5.12 (dd, 1H, $J=10.5$, 1.4 Hz), 4.83 (d, 1H, $J=11.2$ Hz), 4.72 (d, 1H, $J=11.6$ Hz), 4.57 (s, 2H), 4.43 (d, 1H, $J=11.2$ Hz), 4.34–4.28 (m, 3H), 4.19 (d, 1H, $J=7.5$ Hz), 3.98–3.87 (m, 3H), 3.75–3.62 (m, 3H), 2.76–2.61 (m, 4H), 1.25 (t, 3H, $J=7.4$ Hz), 1.23 (t, 3H, $J=7.4$ Hz).

A solution of **23** (2.30 g, 3.86 mmol) in THF (20 mL) was added dropwise to a stirred suspension of NaH (60% suspension in mineral oil; 0.232 g, 5.79 mmol) in THF (20 mL) at 0 °C. After the addition was over, the mixture was stirred at 25 °C for 1 h. To this mixture was added dropwise with stirring a solution of benzyl bromide (0.70 mL, 5.79 mmol) in THF (20 mL) at 0 °C and stirring was continued for 30 min. The mixture was heated at 25 °C for 12 h. It was then cooled to 0 °C and few drops of water were added to destroy excess NaH. After concentration of the mixture, the residue was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried, concentrated and the residue was chromatographed (EtOAc–petroleum ether, 1:10) to give **24** (1.72 g, 65%) as a colorless syrup, $[\alpha]_D^{25}-2.4$ (*c* 0.11, $CHCl_3$); IR (Neat): 3062, 3030, 1644, 1604, 1495, 1453 cm^{-1}; MS (FAB): *m/z* 709 (M+Na), 625 (M−SEt), 579 (M−OBn); ^1H NMR: δ 7.33–7.25 (m, 20H), 5.99–5.87 (m, 1H), 5.22 (d, 1H, $J=17.2$ Hz), 5.08 (d, 1H, $J=10.3$ Hz), 4.82–4.61 (m, 5H), 4.51–4.48 (m, 3H), 4.29–4.26 (m, 2H), 4.17–4.14 (m, 1H), 3.95–3.83 (m, 5H), 3.76–3.73 (m, 1H), 2.66 (q, 2H, $J=7.4$ Hz), 2.56–2.48 (m, 2H), 1.20 (t, 3H, $J=7.4$ Hz), 1.14 (t, 3H, $J=7.4$ Hz); ^{13}C NMR: δ 138.6 (q), 138.5 (q), 138.2 (q), 135.0 (CH), 128.1 (CH), 128.08 (CH), 128.03 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 127.44 (CH), 127.4 (CH), 127.36 (CH), 127.2 (CH), 116.1 (CH_2), 82.9 (CH), 80.7 (CH), 79.4 (CH), 78.6 (CH), 75.2 (CH_2), 73.8 (CH_2), 73.4 (CH_2), 73.1 (CH_2), 71.8 (CH_2), 70.0 (CH_2), 53.3 (CH), 24.9 (CH_2), 24.7 (CH_2), 14.3 (CH_3), 14.2 (CH_3). Anal. Calcd for $C_{41}H_{50}O_5S_2$: C, 71.68; H, 7.34. Found: C, 71.57; H, 7.17.

3.7.1. Dithioacetal 26. The same procedure starting from **21** (2.69 g) yielded after chromatography (EtOAc–petroleum ether, 1:10) **25** (2.48 g, 76%) as a light yellow syrup, $[\alpha]_D^{25}-33.2$ (*c* 0.64, $CHCl_3$); IR (Neat): 3536, 3288, 3062, 3031, 2120, 1603, 1496, 1452 cm^{-1}; MS (FAB): *m/z* 633 (M+K), 617 (M+Na), 595 (M+H), 533 (M−SEt); ^1H NMR: δ 7.34–7.26 (m, 15H), 4.86 (d, 1H, $J=11.1$ Hz), 4.73 (d, 1H, $J=11.7$ Hz), 4.57 (s, 2H), 4.48 (d, 2H, $J=1.7$ Hz), 4.43 (d, 1H, $J=11.1$ Hz), 4.34 (d, 1H, $J=11.7$ Hz), 4.22–4.20 (m, 1H), 4.09 (dd, 1H, $J=7.4$, 2.9 Hz), 3.97 (d, 1H, $J=2.9$ Hz), 3.89 (dd, 1H, $J=10.4$, 2.4 Hz), 3.75–3.70 (m, 2H), 3.66–3.62 (m, 1H), 2.72 (q, 2H, $J=7.3$ Hz), 2.70 (q, 2H, $J=7.3$ Hz), 2.40 (t, 1H, $J=2.4$ Hz), 1.26 (t, 3H, $J=7.3$ Hz), 1.23 (t, 3H, $J=7.3$ Hz); ^{13}C NMR: δ 138.2 (q), 138.1 (q), 138.0 (q), 128.2 (CH), 128.15 (CH), 128.11 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 83.0 (CH), 79.8 (CH), 78.0 (CH), 77.8 (CH), 74.6 (q), 74.6 (CH_2), 73.3 (CH_2), 71.4 (CH_2), 70.6 (CH), 69.8 (CH_2), 60.1 (CH_2), 52.7 (CH), 25.6 (CH_2), 25.5 (CH_2), 14.3 (2×CH_3).

Alkylation of **25** (1.07 g, 1.80 mmol) with benzyl bromide (0.32 mL, 2.70 mmol) using the procedure described for the convertion of **23** to **24** gave after chromatography (EtOAc–petroleum ether, 1:16) **26** (0.93 g, 76%) as a colorless syrup, $[\alpha]_D^{25}+1.0$ (*c* 0.20, $CHCl_3$); IR (Neat): 3289, 3062, 3031, 2120, 1603, 1495, 1452 cm^{-1}; MS (FAB): *m/z* 685 (M+H), 623 (M−SEt), 577 (M−OBn); ^1H NMR: δ 7.36–7.23 (m, 20H), 4.81 (d, 1H, $J=11.2$ Hz), 4.76 (d, 1H, $J=11.3$ Hz), 4.72 (d, 1H, $J=11.2$ Hz), 4.68 (d, 1H, $J=11.2$ Hz), 4.66 (d, 1H, $J=11.4$ Hz), 4.55–4.51 (m, 3H), 4.47–4.45 (m, 2H), 4.20–4.17 (m, 1H), 3.96–3.87 (m, 5H), 3.76–3.70 (m, 1H), 2.64 (q, 2H, $J=7.4$ Hz), 2.59–2.50 (m, 2H), 2.37 (t, 1H, $J=2.2$ Hz), 1.20 (t, 3H, $J=7.4$ Hz), 1.15 (t, 3H, $J=7.4$ Hz); ^{13}C NMR: δ 138.5 (2×q), 138.2 (q), 138.1 (q), 128.2 (3×CH), 128.1 (3×CH), 128.0 (4×CH), 127.9 (2×CH), 127.5 (2×CH), 127.4 (3×CH), 127.3 (CH), 127.27 (CH), 127.2 (CH), 82.0 (CH), 80.2 (CH), 80.0 (CH), 79.2 (CH), 78.8 (CH), 75.1 (CH_2), 74.5 (q), 73.6 (CH_2), 73.1 (CH_2), 71.8 (CH_2), 69.8 (CH_2), 59.5 (CH_2), 52.8 (CH), 25.1 (CH_2), 24.7 (CH_2), 14.3 (CH_3), 14.1 (CH_3). Anal. Calcd for $C_{41}H_{48}O_5S_2$: C, 71.89; H, 7.06. Found: C, 71.82; H, 7.24.

3.7.2. Dithioacetal 28. Dithioacetylation of **22** (1.54 g) afforded after chromatography (EtOAc–petroleum ether, 1:11) **27** (1.34 g, 73%) as a colorless syrup, $[\alpha]_D^{28}-18.9$ (*c* 0.23, $CHCl_3$); IR (Neat): 3538, 3062, 3031, 1604, 1496, 1452 cm^{-1}; MS (FAB): *m/z* 669 (M+Na), 585 (M−SEt); ^1H NMR: δ 7.37–7.18 (m, 20H), 4.86 (d, 1H, $J=11.1$ Hz), 4.80 (d, 1H, $J=11.2$ Hz), 4.78 (d, 1H, $J=11.1$ Hz), 4.71 (d, 1H, $J=11.6$ Hz), 4.57 (s, 2H), 4.42 (d, 1H, $J=11.1$ Hz), 4.30 (d, 1H, $J=11.6$ Hz), 4.22 (d, 1H, $J=7.7$ Hz), 4.09 (dd, 1H, $J=7.7$, 2.7 Hz), 3.96 (d, 1H, $J=2.7$ Hz), 3.90 (dd, 1H, $J=10.7$, 2.8 Hz), 3.76–3.71 (m, 2H), 3.66–3.61 (m, 1H), 2.74–2.59 (m, 4H), 1.24 (t, 3H, $J=7.4$ Hz), 1.20 (t, 3H,

$J=7.4$ Hz); ^{13}C NMR: δ 138.2 (3×q), 138.0 (q), 128.1 (CH), 128.03 (CH), 127.99 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 83.3 (CH), 78.1 (CH), 77.9 (CH), 75.1 (CH_2), 74.4 (CH_2), 73.2 (CH_2), 71.3 (CH_2), 70.5 (CH), 69.8 (CH_2), 53.3 (CH), 25.6 (CH_2), 25.2 (CH_2), 14.2 (2×CH_3).

Alkylation of **27** (1.70 g, 2.63 mmol) with allyl bromide (0.34 mL, 3.95 mmol) gave after chromatography (EtOAc–Petroleum ether, 1:16) **28** (1.10 g, 61%) as a colorless syrup, $[\alpha]_D^{25}+3.8$ (*c* 0.39, $CHCl_3$); IR (Neat): 3063, 3030, 1644, 1604, 1496, 1453 cm^{-1}; MS (FAB): *m/z* 685 (M−H), 625 (M−SEt), 579 (M−OBn); ^{1}H NMR: δ 7.44–7.26 (m, 20H), 5.95–5.82 (m, 1H), 5.20 (d, 1H, $J=17.2$ Hz), 5.12 (d, 1H, $J=10.3$ Hz), 4.86 (d, 1H, $J=11.0$ Hz), 4.80 (d, 1H, $J=11.2$ Hz), 4.79 (d, 1H, $J=10.8$ Hz), 4.66 (d, 1H, $J=11.1$ Hz), 4.62 (d, 1H, $J=11.6$ Hz), 4.51 (s, 2H), 4.37 (d, 1H, $J=11.8$ Hz), 4.24–4.20 (m, 2H), 4.13–4.04 (m, 3H), 3.91–3.83 (m, 2H), 3.77 (t, 1H, $J=4.4$ Hz), 3.67 (dd, 1H, $J=9.9$, 4.7 Hz), 2.77–2.59 (m, 4H), 1.22 (t, 3H, $J=7.3$ Hz), 1.20 (t, 3H, $J=7.3$ Hz); ^{13}C NMR: δ 138.6 (q), 138.5 (q), 138.4 (q), 138.2 (q), 134.8 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 116.8 (CH_2), 82.7 (CH), 80.5 (CH), 78.9 (CH), 78.7 (CH), 75.1 (CH_2), 74.5 (CH_2), 73.1 (CH_2), 72.8 (CH_2), 71.6 (CH_2), 69.5 (CH_2), 53.4 (CH), 24.8 (2×CH_2), 14.3 (2×CH_3). Anal. Calcd for $C_{41}H_{50}O_5S_2$: C, 71.68; H, 7.34. Found: C, 71.52; H, 7.32.

3.7.3. Dithioacetal 29. Alkylation of **27** (1.30 g, 2.01 mmol) with propargyl bromide (0.45 mL, 3.02 mmol) yielded after chromatography (EtOAc–Petroleum ether, 1:16) **29** (1.00 g, 73%) as a colorless syrup, $[\alpha]_D^{28}-11.2$ (*c* 0.27, $CHCl_3$); IR (Neat): 3289, 3062, 3031, 2120, 1604, 1496, 1452 cm^{-1}; MS (FAB): *m/z* 707 (M+Na), 684 (M), 623 (M−SEt), 577 (M−OBn); ^{1}H NMR: δ 7.38–7.22 (m, 20H), 4.89 (d, 1H, $J=11.0$ Hz), 4.80 (d, 1H, $J=11.1$ Hz), 4.79 (d, 1H, $J=11.4$ Hz), 4.66 (d, 1H, $J=11.3$ Hz), 4.61 (d, 1H, $J=11.8$ Hz), 4.50 (s, 2H), 4.42–4.37 (m, 3H), 4.21–4.08 (m, 3H), 3.97–3.90 (m, 2H), 3.84–3.79 (m, 1H), 3.65 (dd, 1H, $J=10.5$, 5.4 Hz), 2.77–2.63 (m, 4H), 2.44 (t, 1H, $J=2.3$ Hz), 1.23 (t, 3H, $J=7.4$ Hz), 1.22 (t, 3H, $J=7.4$ Hz); ^{13}C NMR: δ 138.3 (q), 138.2 (q), 138.1 (q), 137.9 (q), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 82.5 (CH), 80.3 (CH), 79.9 (CH), 79.0 (CH), 77.8 (CH), 75.0 (CH_2), 74.7 (q), 74.5 (CH_2), 72.9 (CH_2), 71.5 (CH_2), 69.3 (CH_2), 58.5 (CH_2), 53.2 (CH), 24.7 (CH_2), 24.5 (CH_2), 14.2 (2×CH_3). Anal. Calcd for $C_{41}H_{48}O_5S_2$: C, 71.89; H, 7.06. Found: C, 71.97; H, 7.12.

3.8. General procedure for the preparation of the *N*-benzyl nitrones 38 and 39 and their cycloaddition to (1′*R*,2′*R*,3′*R*,3a*R*,6*S*,6a*S*)-6-(2′-hydroxy-1′,3′,4′-tribenzyloxy)butyltetrahydrofuro[3,4-*c*]isoxazole (41) and (1′*R*,2′*R*,3′*R*,3a*R*,6*S*,6a*S*)-1-benzyl-6-(1′,2′,3′,4′-tetraallyloxy)butyltetrahydrofuro[3,4-*c*]isoxazole (42)

The general procedure is illustrated by the preparation of **39** and its cycloaddition to **42**.

A solution of the aldehyde **10** (0.38 g, 1.00 mmol) and BnNHOH (0.19 g, 1.54 mmol) in benzene (10 mL) was heated under reflux in the presence of 3 Å molecular sieves (0.21 g) for 8 h. It was then filtered and washed with benzene. The combined filtrate and the washings were evaporated to afford a syrupy residue, which on chromatography (EtOAc–petroleum ether, 1:7) gave **42** (0.36 g, 75%) as a colorless syrup, $[\alpha]_D^{25}+21.8$ (*c* 1.42, $CHCl_3$); IR (Neat): 3079, 3013, 1645 cm^{-1}; MS (EI): *m/z* 485 (M), 204; ^{1}H NMR: δ 7.39–7.24 (m, 5H), 6.00–5.83 (m, 3H), 5.77–5.64 (m, 1H), 5.33–5.00 (m, 8H), 4.30–4.24 (m, 1H), 4.18–4.00 (m, 9H), 3.82–3.48 (m, 9H), 3.38–3.28 (m, 3H); ^{13}C NMR: δ 136.6 (q), 135.3 (CH), 135.0 (CH), 134.8 (CH), 134.7 (CH), 129.0 (2×CH), 128.3 (2×CH), 127.4 (CH), 116.4 (CH_2), 116.3 (CH_2), 116.0 (CH_2), 115.9 (CH_2), 83.2 (CH), 80.5 (CH), 78.5 (CH), 78.2 (CH), 73.9 (CH_2), 73.4 (CH_2), 73.2 (CH_2), 72.0 (CH_2), 71.9 (CH), 70.6 (CH_2), 69.7 (CH_2), 69.2 (CH_2), 59.9 (CH_2), 48.4 (CH). Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.09; N, 2.88. Found: C, 68.95; H, 7.99; N, 2.72.

Compound **41**. The same procedure starting from **20** (0.42 g, 0.86 mmol) with BnNHOH (0.16 g, 1.30 mmol) yielded after chromatography (EtOAc–petroleum ether, 1:5) **41** (0.36 g, 70%) as a white solid, mp 98–99 °C, $[\alpha]_D^{25}-16.4$ (*c* 1.40, $CHCl_3$); IR (KBr): 3508, 3061, 3031, 1604 cm^{-1}; MS (EI): *m/z* 595 (M), 204; ^{1}H NMR (100 MHz): δ 7.36–7.28 (m, 20H), 4.74 (d, 1H, $J=12.0$ Hz), 4.58 (s, 2H), 4.42 (s, 2H), 4.32–4.08 (m, 2H), 3.96–3.52 (m, 12H), 3.36 (m, 1H), 1.64 (br s, 1H); ^{13}C NMR (25 MHz): δ 138.6 (2×q), 138.4 (q), 136.2 (q), 129.2 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 85.4 (CH), 77.7 (CH), 77.4 (CH), 73.7 (CH_2), 73.6 (CH_2), 73.3 (CH_2), 72.7 (CH), 71.7 (CH_2), 71.3 (CH), 70.0 (2×CH_2), 59.8 (CH_2), 47.5 (CH). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.48; H, 7.23; N, 2.18.

3.8.1. Preparation of the *N*-methyl nitrone 40 and its cycloaddition to (1′*R*,2′*R*,3′*R*,3a*R*,6*S*,6a*S*)-1-methyl-6-(1′,2′,3′,4′-tetraallyloxy)butyltetrahydrofuro[3,4-*c*]-isoxazole (43). A solution of **10** (1.16 g, 3.05 mmol), MeNHOH.HCl (0.33 g, 3.95 mmol) and $NaHCO_3$ (0.39 g, 4.64 mmol) in 80% aqueous EtOH (40 mL) was heated under reflux for 12 h. After it was cooled to 25 °C, the mixture was concentrated under reduced pressure to give a residue, which was extracted with CH_2Cl_2. The organic layer was washed with water, dried and concentrated to give a reddish yellow syrupy residue, which on chromatography (EtOAc–petroleum ether, 1:6) gave **43** (0.94 g, 75%) as a pale yellow syrup. $[\alpha]_D^{25}+19.8$ (*c* 0.65, $CHCl_3$); IR (Neat): 3079, 1645 cm^{-1}; MS (FAB): *m/z* 410 (M+H), 128; ^{1}H NMR: δ 6.00–5.85 (m, 4H), 5.30–5.09 (m, 8H), 4.35–3.99 (m, 10H), 3.84–3.81 (m, 2H), 3.72–3.51 (m, 7H), 3.34–3.29 (m, 1H), 2.63 (s, 3H); ^{13}C NMR: δ 135.0 (CH), 134.7 (CH), 134.6 (CH), 134.4 (CH), 116.3 (CH_2), 116.1 (CH_2), 116.0 (CH_2), 115.5 (CH_2), 82.6 (CH), 79.7 (CH), 78.7 (CH), 77.9 (CH), 75.1 (CH), 73.5 (CH_2), 73.0 (2×CH_2), 71.7 (CH_2), 70.4 (CH_2), 69.1 (CH_2), 68.8 (CH_2), 48.4 (CH), 43.4 (CH_3). Anal. Calcd for $C_{22}H_{35}NO_6$: C, 64.52; H, 8.61; N, 3.42. Found: C, 64.53; H, 8.77; N, 3.22.

3.8.2. (1′*R*,2′*R*,3′*R*,2*S*,3*S*,4*S*)-3-Methylamino-4-hydroxymethyl-2-(1′,2′,3′,4′-tetraallyloxy)butyltetrahydrofuran (50). A mixture of the isoxazolidine **43** (2.06 g, 5.01 mmol) and Zn dust (1.31 g, 20.04 mmol) in 60% aqueous AcOH (35 mL) was heated under reflux for 7 h. After completion

of the reaction as revealed by TLC, the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 and the combined organic extracts were washed with $NaHCO_3$, water, dried and concentrated under reduced pressure to give a syrupy residue, which was chromatographed (MeOH–CH_2Cl_2, 1:49) to give **50** (1.40 g, 75%) as a colorless syrup, $[\alpha]_D^{28}+2.1$ (*c* 0.81, $CHCl_3$); IR (Neat): 3331, 3080, 3012, 1645 cm^{-1}; MS (EI): *m/z* 412 (M+H), 130; ^1H NMR: δ 6.01–5.84 (m, 4H), 5.30–5.11 (m, 8H), 4.34–4.25 (m, 2H), 4.18–4.05 (m, 4H), 4.01–3.96 (m, 3H), 3.85–3.66 (m, 8H), 3.58–3.51 (m, 2H), 3.29 (t, 1H, *J*=7.3 Hz), 2.85 (br s, 2H, exchangeable with D_2O), 2.49 (s, 3H); ^{13}C NMR: δ 135.1 (CH), 134.9 (CH), 134.6 (CH), 134.4 (CH), 116.7 (CH_2), 116.4 (2×CH_2), 115.8 (CH_2), 82.6 (CH), 79.9 (CH), 79.2 (CH), 77.7 (CH), 74.0 (CH_2), 72.5 (CH_2), 71.9 (CH_2), 70.7 (CH_2), 69.5 (CH_2), 69.1 (CH_2), 64.0 (CH), 61.4 (CH_2), 42.0 (CH), 35.7 (CH_3). Anal. Calcd for $C_{22}H_{37}NO_6$: C, 64.21; H, 9.06; N, 3.40. Found: C, 63.96; H, 8.78; N, 3.13.

3.9. General procedure for the generation of *O*-allyl and *O*-propargyl nitrile oxides from oximes and their cycloaddition

A mixture of chloramine-T hydrate (0.64 mmol) and the oxime (0.25 mmol) in EtOH (10 mL) was heated under reflux for 9 h. After completion of the reaction as revealed by TLC, the resulting precipitate was filtered and the filtrate was evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 and the combined organic layer was washed successively with water, 1 M aq NaOH solution and water. The organic extract was then dried, and removal of solvent afforded a syrupy residue, which on chromatography over silicagel (100–200 mesh; EtOAc–petroleum ether) gave the dihydroisoxazoline as a mixture of 3a-epimers or the isoxazole. The yields of the mixture of 3a-epimeric dihydroisoxazolines are presented in Table 2. The individual epimers **55**, **56**, **60** and **61** could be isolated by column chromatography. The mixture of **57** and **58** on preparative TLC gave enriched fractions of the two compounds.

3.9.1. (1′*R*,2′*R*,3′*R*,3a*R*,6*S*)-6-(1′,2′,3′,4′-Tetraallyloxy)-butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (55). $[\alpha]_D^{25}-39.7$ (*c* 0.21, $CHCl_3$); IR (Neat): 3080, 1645 cm^{-1}; MS (EI): *m/z* 393 (M), 112; ^1H NMR: δ 6.02–5.81 (m, 4H), 5.34–5.11 (m, 8H), 4.51 (dd, 1H, *J*=10.2, 8.3 Hz), 4.41 (s, 1H), 4.38 (dd, 1H, *J*=10.6, 6.7 Hz), 4.29 (dd, 1H, *J*=12.5, 5.8 Hz), 4.21 (dd, 1H, *J*=12.5, 5.8 Hz), 4.10–3.97 (m, 6H), 3.89–3.81 (m, 2H), 3.74–3.64 (m, 3H), 3.59–3.55 (m, 1H), 3.50 (dd, 1H, *J*=7.8, 1.3 Hz), 3.34 (t, 1H, *J*=10.8 Hz); ^{13}C NMR: δ 156.1 (q), 135.6 (CH), 134.8 (CH), 134.5 (CH), 133.3 (CH), 118.4 (CH_2), 116.8 (CH_2), 116.6 (CH_2), 116.4 (CH_2), 82.5 (CH), 78.7 (CH), 77.4 (CH), 74.3 (CH_2), 72.2 (CH_2), 71.9 (CH_2), 70.7 (CH_2), 70.0 (CH_2), 69.9 (CH_2), 69.9 (CH), 68.9 (CH_2), 44.7 (CH). Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.87; H, 7.93; N, 3.43.

3.9.2. (1′*R*,2′*R*,3′*R*,3a*S*,6*S*)-6-(1′,2′,3′,4′-Tetraallyloxy)-butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (56). $[\alpha]_D^{25}-69.4$ (*c* 0.46, $CHCl_3$); IR (Neat): 3081, 1646 cm^{-1}; MS (EI): *m/z* 393 (M), 112; ^1H NMR: δ 6.01–5.81 (m, 4H), 5.32–5.14 (m, 8H), 4.75 (d, 1H, *J*=4.7 Hz), 4.59 (dd, 1H, *J*=10.7, 8.1 Hz), 4.28–4.20 (m, 2H), 4.11–3.82 (m, 10H), 3.76–3.59 (m, 5H); ^{13}C NMR: δ 157.7 (q), 135.0 (CH), 134.9 (CH), 134.6 (CH), 133.7 (CH), 117.6 (CH_2), 117.5 (CH_2), 116.8 (CH_2), 116.6 (CH_2), 80.5 (CH), 76.3 (CH), 75.4 (CH), 73.6 (CH_2), 72.3 (CH_2), 72.2 (CH), 71.4 (CH_2), 71.2 (CH_2), 70.8 (CH_2), 69.8 (CH_2), 68.3 (CH_2), 50.4 (CH). Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 63.87; H, 7.88; N, 3.63.

3.9.3. (1′*R*,2′*R*,3′*R*,3a*R*,6*S*)-6-(1′,2′,3′,4′-Tetrabenzyloxy)-butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (57) and (1′*R*,2′*R*,3′*R*,3a*S*,6*S*)-6-(1′,2′,3′,4′-tetrabenzyloxy)butyl-3a,4-dihydro-3*H*,6*H*-furo[3,4-*c*]isoxazole (58). NMR and mass spectra of the preparative TLC fractions enriched in either **57** or **58** were obtained. Data for the fraction enriched in the faster moving compound **57** in TLC (EtOAc–petroleum ether, 1:3): MS (FAB): *m/z* 594 (M+H); ^1H NMR (peaks assignable to **57** are presented): δ 7.32–7.29 (m), 4.83 (d, *J*=3.3 Hz), 4.76 (s), 4.67 (d, *J*=11.9 Hz), 4.62 (d, *J*=10.7 Hz), 4.56 (d, *J*=12.2 Hz), 4.52 (s), 4.27 (t, *J*=7.9 Hz), 4.08 (dd, *J*=6.1, 4.2 Hz), 3.67 (dd, *J*=9.6, 4.7 Hz), 3.59 (t, *J*=9.0 Hz); ^{13}C NMR (peaks assignable to **57** are presented): δ 170.3 (q), 138.7 (q), 138.4 (q), 138.2 (q), 138.1 (q), 128.4–127.4 (aromatic CH), 80.6 (CH), 79.8 (CH), 78.6 (CH), 75.3 (CH_2), 74.6 (CH_2), 73.43 (CH_2), 73.36 (CH_2), 73.1 (CH), 72.0 (CH_2), 69.8 (CH_2), 69.3 (CH_2), 56.0 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.73; H, 6.69; N, 2.25. Data for the fraction enriched in the slower moving compound **58** in TLC (EtOAc–petroleum ether, 1:3): MS (FAB): *m/z* 594 (M+H); ^1H NMR (peaks assignable to **58** are presented): δ 7.32–7.28 (m), 4.86 (d, *J*=3.1 Hz), 4.76–4.68 (m), 4.58 (d, *J*=11.8 Hz), 4.52 (s), 4.23 (dd, *J*=5.9, 4.5 Hz), 4.15 (dd, *J*=5.9, 3.8 Hz), 3.70 (dd, *J*=9.9, 5.1 Hz); ^{13}C NMR (peaks assignable to **58** are presented): δ 170.4 (q), 138.8 (q), 138.6 (q), 138.5 (q), 138.3 (q), 128.4–127.4 (aromatic CH), 81.3 (CH), 79.6 (CH), 79.1 (CH), 75.5 (CH_2), 74.5 (CH_2), 73.4 (CH_2), 72.4 (CH), 72.0 (CH_2), 69.7 (CH_2), 56.6 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.95; H, 6.53; N, 2.23.

3.9.4. (1′*R*,3a*R*,6*R*,7*R*,8*R*)-6-(1′,2′-Dibenzyloxy)ethyl-7,8-dibenzyloxy-3a,4,7,8-tetrahydro-3*H*,6*H*-2,5-dioxa-1-azaazulene (60). $[\alpha]_D^{25}+75.2$ (*c* 0.37, $CHCl_3$); IR (Neat): 3061, 3031, 1602 cm^{-1}; MS (FAB): *m/z* 594 (M+H); ^1H NMR: δ 7.31–7.20 (m, 18H), 7.09–7.07 (m, 2H), 4.79 (d, 1H, *J*=12.3 Hz), 4.70 (d, 1H, *J*=11.6 Hz), 4.63–4.42 (m, 6H), 4.25 (d, 1H, *J*=12.0 Hz), 4.21 (d, 1H, *J*=12.0 Hz), 4.10–4.04 (m, 2H), 3.93–3.79 (m, 3H), 3.73–3.65 (m, 3H), 3.52 (t, 1H, *J*=10.7 Hz); ^{13}C NMR: δ 159.7 (q), 138.5 (2×q), 137.5 (q), 137.4 (q), 128.4 (4×CH), 128.3 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 128.0 (2×CH), 127.9 (CH), 127.8 (CH), 127.6 (2×CH), 127.5 (2×CH), 127.4 (2×CH), 77.7 (CH), 77.0 (CH), 75.5 (CH), 73.4 (CH_2), 72.5 (CH_2), 71.7 (CH_2), 71.1 (CH_2), 70.9 (CH), 70.4 (CH_2), 69.3 (CH_2), 69.0 (CH_2), 52.7 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.62; H, 6.86; N, 1.99.

3.9.5. (1′*R*,3a*S*,6*R*,7*R*,8*R*)-6-(1′,2′-Dibenzyloxy)ethyl-7,8-dibenzyloxy-3a,4,7,8-tetrahydro-3*H*,6*H*-2,5-dioxa-1-azaazulene (61). $[\alpha]_D^{25}-57.9$ (*c* 0.52, $CHCl_3$); IR (Neat):

3061, 3031, 1607 cm^{-1}; MS (FAB): *m/z* 616 (M+Na), 594 (M+H); ^1H NMR: δ 7.33–7.22 (m, 20H), 4.81 (d, 1H, *J*= 4.5 Hz), 4.68–4.46 (m, 7H), 4.31 (d, 1H, *J*=3.3 Hz), 4.27 (d, 1H, *J*=3.6 Hz), 4.09–4.03 (m, 3H), 3.82–3.75 (m, 4H), 3.68–3.58 (m, 2H); ^{13}C NMR: δ 157.7 (q), 138.4 (q), 138.3 (q), 137.4 (q), 137.0 (q), 128.4 (2×CH), 128.3 (2×CH), 128.2 (6×CH), 127.9 (CH), 127.6 (5×CH), 127.4 (2× CH), 127.4 (CH), 127.3 (CH), 80.3 (CH), 76.4 (CH), 75.2 (CH), 73.6 (CH_2), 73.2 (CH_2), 72.0 (CH), 71.8 (CH_2), 71.7 (2×CH_2), 69.6 (CH_2), 68.2 (CH_2), 50.2 (CH). Anal. Calcd for $C_{37}H_{39}NO_6$: C, 74.85; H, 6.62; N, 2.36. Found: C, 74.54; H, 6.87; N, 2.14.

3.9.6. (1′*R*,2′*R*,3′*R*,6*S*)-6-(1′,2′,3′,4′-Tetrapropargyloxy)-butyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (67). 72%; $[\alpha]_D^{28}+10.4$ (*c* 0.25, $CHCl_3$); IR (Neat): 3289, 2120 cm^{-1}; MS (EI): *m/z* 383 (M); ^1H NMR: δ 8.05 (s, 1H), 5.42 (d, 1H, *J*=6.1 Hz), 4.96 (d, 1H, *J*=11.7 Hz), 4.86 (d, 1H, *J*=11.7 Hz), 4.51–4.38 (m, 4H), 4.33–4.31 (m, 2H), 4.26–4.23 (m, 2H), 4.05 (dd, 1H, *J*=6.2, 3.7 Hz), 3.99–3.96 (m, 3H), 3.79 (dd, 1H, *J*=11.4, 4.9 Hz), 2.48–2.43 (m, 4H); ^{13}C NMR: δ 170.5 (q), 148.0 (CH), 123.6 (q), 79.9 (CH), 79.7 (2×CH), 79.4 (CH), 78.8 (CH), 77.9 (CH), 77.3 (CH), 76.7 (CH), 74.8 (q), 74.7 (q), 74.6 (q), 74.4 (q), 67.8 (CH_2), 64.1 (CH_2), 60.1 (CH_2), 59.7 (CH_2), 58.4 (CH_2), 57.3 (CH_2). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.58; H, 5.87; N, 3.38.

3.9.7. (1′*R*,2′*R*,3′*R*,6*S*)-6-(1′,2′,3′,4′-Tetrabenzyloxy)-butyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (68). 77%; $[\alpha]_D^{28}+13.5$ (*c* 0.40, $CHCl_3$); IR (Neat): 3062, 3031, 1602 cm^{-1}; MS (FAB): *m/z* 592 (M+H), 500 (M−Bn), 484 (M−OBn); ^1H NMR: δ 7.96 (s, 1H), 7.34–7.21 (m, 18H), 7.09–7.07 (m, 2H), 5.39 (d, 1H, *J*=3.8 Hz), 4.92 (d, 1H, *J*=11.5 Hz), 4.81–4.77 (m, 3H), 4.70–4.53 (m, 6H), 4.21 (t, 1H, *J*= 4.9 Hz), 4.01–3.87 (m, 3H), 3.71 (dd, 1H, *J*=10.0, 5.0 Hz); ^{13}C NMR: δ 171.1 (q), 147.6 (CH), 138.7 (q), 138.5 (q), 138.4 (q), 138.2 (q), 128.3 (2×CH), 128.25 (2×CH), 128.2 (2×CH), 128.1 (2×CH), 127.8 (2×CH), 127.74 (2×CH), 127.7 (2×CH), 127.6 (2×CH), 127.5 (CH), 127.4 (CH), 127.3 (2×CH), 124.0 (q), 81.2 (CH), 79.5 (CH), 78.7 (CH), 76.2 (CH), 75.1 (CH_2), 74.5 (CH_2), 73.3 (CH_2), 72.0 (CH_2), 69.4 (CH_2), 64.3 (CH_2). Anal. Calcd for $C_{37}H_{37}NO_6$: C, 75.11; H, 6.30; N, 2.37. Found: C, 74.97; H, 6.38; N, 2.26.

3.9.8. (1′*R*,6*R*,7*R*,8*R*)-6-(1′,2′-Dibenzyloxy)ethyl-7,8-dibenzyloxy-7,8-dihydro-4*H*,6*H*-2,5-dioxa-1-aza-azulene (69). 80%; $[\alpha]_D^{28}+6.7$ (*c* 0.24, $CHCl_3$); IR (Neat): 3061, 3031, 1603 cm^{-1}; MS (FAB): *m/z* 592 (M+H), 500 (M−Bn), 484 (M−OBn); ^1H NMR: δ 8.18 (s, 1H), 7.34–7.05 (m, 20H), 4.87 (d, 1H, *J*=5.4 Hz), 4.72 (d, 1H, *J*= 13.8 Hz), 4.69 (d, 1H, *J*=11.6 Hz), 4.64 (d, 1H, *J*= 12.3 Hz), 4.54–4.18 (m, 9H), 3.86 (dd, 1H, *J*=12.4, 4.1 Hz), 3.75–3.70 (m, 2H); ^{13}C NMR: δ 160.3 (q), 154.1 (CH), 138.5 (2×q), 137.3 (q), 137.2 (q), 128.5 (2×CH), 128.4 (3×CH), 128.37 (3×CH), 128.2 (2×CH), 127.9 (CH), 127.8 (2×CH), 127.74 (CH), 127.68 (2×CH), 127.6 (2×CH), 127.5 (CH), 127.4 (CH), 118.5 (q), 79.2 (CH), 77.0 (CH), 73.9 (CH), 73.3 (CH_2), 72.2 (CH_2), 71.8 (CH_2), 70.8 (CH_2), 69.8 (CH), 69.1 (CH_2), 62.5 (CH_2). Anal. Calcd for $C_{37}H_{37}NO_6$: C, 75.11; H, 6.30; N, 2.37. Found: C, 75.27; H, 6.47; N, 2.23.

3.9.9. Preparation of the nitrile oxide 53 and its cycloaddition to (1′*R*,2′*R*,3′*R*,3a*R*,6*S*)-6-(1′,2′,3′,4′-tetra-allyloxy)butyl-3a,4,6,7-tetrahydro-3*H*-pyrano[4,3-*c*]-isoxazole (59). To a solution of **12** (0.19 g, 0.45 mmol) in benzene (10 mL) was added 4-chlorophenyl isocyanate (0.69 g, 4.50 mmol) and Et_3N (0.6 mL, 4.50 mmol), and the mixture was stirred at 25 °C for 50 h under N_2 atmosphere. Water (5 mL) was added and the mixture was stirred for 24 h. It was then filtered and the residue was washed repeatedly with benzene. The organic layer of the filtrate was separated and the aqueous layer was extracted with benzene. The combined organic extracts were washed with water and dried. Removal of solvent yielded a residue, which was chromatographed over silicagel (100–200 mesh; EtOAc–petroleum ether, 1:10) to afford **59** (0.12 g, 68%) as a colorless syrup, $[\alpha]_D^{25}+49.1$ (*c* 2.33, $CHCl_3$); IR (Neat): 3079, 1645 cm^{-1}; MS (EI): *m/z* 407 (M), 126; ^1H NMR (500 MHz): δ 6.01–5.83 (m, 4H), 5.28–5.12 (m, 8H), 4.47 (dd, 1H, *J*=10.3, 8.3 Hz), 4.36 (dd, 1H, *J*=10.6, 6.8 Hz), 4.30 (ddt, 1H, *J*=12.2, 5.7, 1.3 Hz), 4.24 (ddt, 1H, *J*=12.6, 5.5, 1.3 Hz), 4.20–4.14 (m, 2H), 4.13 (ddt, 1H, *J*=12.9, 5.5, 1.3 Hz), 4.05 (ddt, 1H, *J*=12.9, 5.5, 1.4 Hz), 4.00–3.99 (m, 2H), 3.88 (dd, 1H, *J*=6.2, 4.0 Hz), 3.74–3.69 (m, 3H), 3.63 (dd, 1H, *J*=8.9, 4.8 Hz), 3.57–3.52 (m, 2H), 3.45–3.38 (m, 1H), 3.26 (t, 1H, *J*=10.7 Hz), 2.68–2.59 (m, 2H); ^{13}C NMR (125 MHz): δ 157.3 (q), 135.2 (CH), 134.9 (2×CH), 134.5 (CH), 117.5 (CH_2), 116.9 (CH_2), 116.8 (CH_2), 116.5 (CH_2), 80.4 (CH), 79.5 (CH), 78.03 (CH), 78.0 (CH), 74.7 (CH_2), 73.5 (CH_2), 72.2 (CH_2), 71.6 (CH_2), 70.8 (CH_2), 69.3 (CH_2), 68.8 (CH_2), 47.3 (CH), 28.0 (CH_2). Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16; N, 3.44. Found: C, 64.61; H, 8.36; N, 3.32.

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Isoaurostatin: total synthesis and structural revision☆

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Abstract—Isoaurostatin, a topoisomerase I inhibitor isolated from *Thermomonospora alba* has been synthesized for the first time from 2,4-dihydroxyacetophenone via 6-methoxybenzo-2(3*H*)-furanone in five steps. The *E*-isomer was converted into *Z*-isomer, but spectroscopic data of either of these two isomers did not match with those of the natural product. The structure of isoaurostatin has been revised to a known isoflavone, daidzein (**2**), based on careful analysis of spectroscopic data.

1. Introduction

Isoaurostatin, a novel topoisomerase I inhibitor was recently isolated from the culture filtrate of *Thermomonospora alba* strain No. 1520.[1] Isoaurostatin inhibited the relaxation activity of calf thymus topoisomerase I in a noncompetitive manner and did not inhibit the relaxation and decatenation of human placenta topoisomerase II. Structure of isoaurostatin was determined as **1** based on interpretation of spectroscopic data. Aurones and isoaurones, are naturally occurring yellow pigments of plants and are structurally related to flavonoids.[2] Aurones have limited natural occurrence and fewer methods of synthesis,[3–5] and naturally occurring isoaurones are extremely rare and only two compounds have been reported[6,7] so far. Structures of these compounds have been deduced on the basis of NMR data and confirmed by partial synthesis.[8,9] Pterocarposide, the only isoaurone C-glucoside reported so far, was isolated from *Pterocarpus marsupium* and its structure was deduced from spectroscopic data.[10] In this paper, we wish to report a total synthesis of the proposed structure of isoaurostatin (**1**) and its structural revision into daidzein (**2**).

2. Results and discussion

The general synthetic route to isoaurones involves the acid or base catalyzed condensation of substituted 2(3*H*)-benzofuranone with aromatic aldehydes. We, therefore, synthesized the desired 6-methoxybenzo-2(3*H*)-furanone (**9**) as follows. Willgerodt–Kindler reaction of 2-hydroxy-4-methoxyacetophenone (**7**) with sulfur and morpholine under phase transfer catalytic conditions[11] gave phenylacetic acid derivative **8**, in 66% yield. Lactonization of **8** in the presence of phosphorous oxychloride[12] yielded 6-methoxy-2(3*H*)-furanone (**9**) in 90% yield. Acid catalyzed condensation of **9** with 4-hydroxybenzaldehyde afforded 4′-hydroxy-6-methoxyisoaurone (**10**), which was demethylated using pyridine hydrochloride[13] to give 4′,6-dihydroxyisoaurone (**1**) in 63% yield (Scheme 1). The ^{1}H NMR spectrum showed that it is a mixture of two isomers and this was also confirmed by HPLC (*E*/*Z*—90:10). Attempts to purify further were not successful. In order to assign the stereochemistry unambiguously, we sought the *Z*-isomer also. Therefore, **1** was photoisomerised to **5** using a medium pressure mercury lamp. Again, it was obtained as a mixture of two isomers in the ratio of *Z*/*E*—90:10, after repeated crystallizations.

In (*E*) and (*Z*)-isoaurones, the configuration was assigned based on the differences in chemical shifts of olefinic protons (H-10) and *ortho* protons (H-2′ and H-6′) of the pendant aryl unit. These protons are deshielded by the carbonyl group and are expected to give downfield signals.[14] In *E*-isomers, H-2′, H-6′ protons of the aryl unit appear as doublet in the range of δ 7.0–7.8, whereas in *Z*-isomers the corresponding protons appear in the range of δ 8.0–8.2.[14] The chemical shifts of synthetic **1**, gave a doublet at δ 7.65 (H-2′, H-6′) supporting the *E*-configuration and in **5**, these protons resonated at δ 8.16 (H-2′, H-6′) confirming a *Z*-configuration. The olefinic protons (H-10) in

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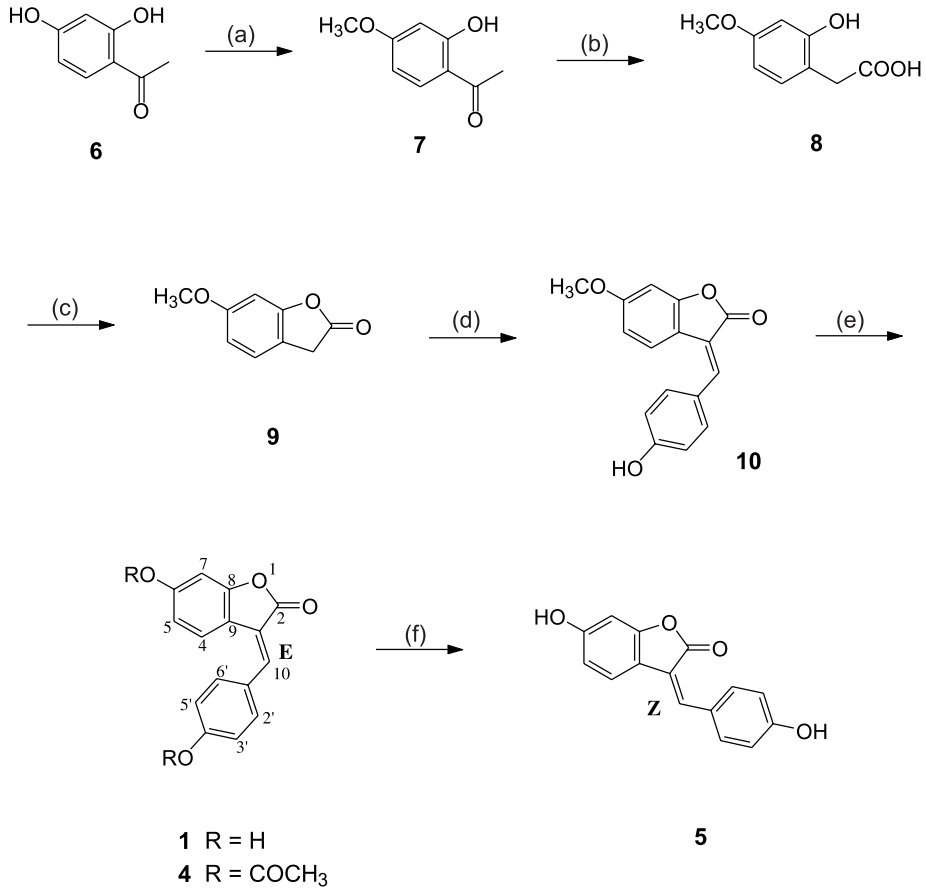

Scheme 1. Reagents and conditions: (a) DMS, K_2CO_3, acetone, rt, 5 h, 91%; (b) S, morpholine, *p*-TSA, 20% NaOH, PTC, reflux, 16 h, 66%; (c) $POCl_3$, DCE, rt, 15 h, 90%; (d) 4-hydroxybenzaldehyde, Ac_2O, 90 °C, 3 h, 61%; (e) pyridine HCl, 180–190 °C, 3 h, 63%; (f) UV, THF, rt, 10 h, 70%.

Table 1. ^1H and ^{13}C NMR data of **1**, **5** and isoaurostatin[1]

Position	**1**-*E*[a]		**5**-*Z*[a]		Isoaurostatin[b]	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2		169.4		166.5		174.8
3		117.8		116.9		123.6
4	7.69 (d, 8.5)	123.4	7.58 (d, 8.3)	125.2	7.94 (d, 8.5)	127.3
5	6.58 (d, 8.5)	111.1	6.63 (dd, 2.1, 8.3)	111.1	6.91 (dd, 2.4, 8.5)	115.3
6		159.9		160.3		162.8
7	6.64 (s)	98.5	6.59 (d, 2.1)	97.9	6.83 (d, 2.4)	102.2
8		154.9		152.9		157.6
9		112.9		116.3		116.6
10	7.50 (s)	137.1	7.72 (s)	137.9	8.25 (s)	152.9
1′		124.8		120.6		122.6
2′,6′	7.65 (d, 8.4)	132	8.16 (d, 8.7)	134.3	7.36 (d, 8.5)	130.1
3′,5′	6.92 (d, 8.4)	115.8	6.88 (d, 8.7)	115.5	6.79 (d, 8.5)	115
4′		159.8		159		157.2

[a] ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) in DMSO-d_6.
[b] ^1H NMR data (500 MHz) and ^{13}C NMR data (125 MHz) in DMSO-d_6 are taken from Ref. 1.

these isomers gave a singlet at δ 7.50 (for *E*-isomer) and at δ 7.72 (for *Z*-isomer).

However, the olefinic proton in isoaurostatin was reported to resonate at δ 8.25 and the other proton and carbon NMR chemical shifts (Table 1) are also not consistent with either *E*-isomer **1** or *Z*-isomer **5**. Furthermore, the proton NMR data of acetyl derivative **4** of the *E*-isomer are also not consistent with the reported data on isoaurostatin diacetate.[1] Obviously, isoaurostatin does not posses an isoaurone structure. So, we have carefully reanalyzed the spectroscopic

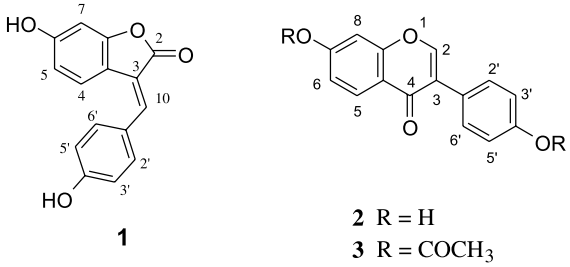

Figure 1. Structures of isoaurostatin (**1**) and daidzein (**2**).

Table 2. ^{1}H and ^{13}C NMR data of reassigned isoaurostatin, isoaurostatin diacetate, daidzein (**2**) and daidzein diacetate (**3**)

Position	Isoaurostatin[a]		Isoaurostatin diacetate[b]	Daidzein (**2**)[c]		Daidzein diacetate **3**[d]
	δ_H	δ_C	δ_H	δ_H	δ_C	δ_H
OAc			2.32 (s), 2.36 (s)			2.32 (s), 2.37 (s)
2	8.25 (s)	152.9	8.01 (s)	8.28 (s)	152.3	8.01 (s)
3		123.6			122.7	
4		174.8			178.6	
5	7.94 (d, 8.5)	127.3	8.32 (d, 8.5)	7.95 (d, 8.7)	127.2	8.33 (d, 8.7)
6	6.91 (dd, 2.4, 8.5)	115.3	7.18 (dd, 1.8, 8.5)	6.92 (dd, 2.1, 8.7)	115.1	7.18 (dd)[e]
7		162.8			162.6	
8	6.83 (d, 2.4)	102.2	7.32 (d, 1.8)	6.84 (d, 2.1)	102.2	7.32 (d, 2.1)
9		157.6			157.6	
10		116.6			116.9	
1′		122.6			123.9	
2′,6′	7.36 (d, 8.5)	130.1	Not reported	7.36 (d, 8.6)	130	7.59 (d, 8.6)
3′,5′	6.79 (d, 8.5)	115	7.17 (d, 8.5)	6.79 (d, 8.6)	115.1	7.17 (d, 8.6)
4′		157.2			157.3	

[a] ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) in DMSO-d_6 are taken from Ref. 1 and reassigned.
[b] ^{1}H NMR (500 MHz) data in $CDCl_3$ is taken from Ref. 1 and reassigned.
[c] ^{1}H NMR (300 MHz) in DMSO-d_6 and ^{13}C NMR (15 MHz) in $CDCl_3$/DMSO-d_6 are taken from Refs. 15 and 16.
[d] ^{1}H NMR (400 MHz) in $CDCl_3$.
[e] Merged with H-3′,5′ doublet.

data reported for natural isoaurostatin and found that the data agrees well with an isomeric structure **2** (Fig. 1). The carbonyl absorptions in IR for isoaurostatin was reported at 1630 cm^{-1}, which is in good agreement with those of reported for **2**, but not to the isoaurones ($\sim$1750 cm^{-1}). Further, the singlet at δ 8.25 in the ^{1}H NMR data of isoaurostatin agrees well with the chemical shift reported for H-2 in **2**, but not to the olefinic proton in isoaurones (δ 7.0–7.8).[10,14] Based on the above, the proton and carbon NMR data reported for isoaurostatin have been reassigned and the data are found to be in good agreement with the reported proton[15] and carbon[16] NMR data of daidzein (**2**) (Table 2). Furthermore, the reassigned proton NMR data reported for isoaurostatin diacetate are also identical with those of daidzein diacetate, **3** (Table 2) prepared by us. From the foregoing, the novel inhibitor of topoisomerase I isolated from the culture filtrate of *Thermomonospora alba* is, in fact, daidzein (**2**), a known isoflavone.

3. Conclusions

In summary, we have accomplished the first total synthesis of the proposed structure of isoaurostatin (**1**), a novel topoisomerase I inhibitor from *Thermomonospora alba* in five steps starting from 2,4-dihydroxyacetophenone. The *E*-isomer **1** was converted into *Z*-isomer **5** and the spectral data of these isomers did not match with those reported for isoaurostatin. The reported spectral data of natural product have been reassigned and found to match well with those recorded for daidzein (**2**).

4. Experimental

4.1. General

Melting points were recorded on a Mel-Temp melting point apparatus, in open capillaries and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX1 FTIR Spectrophotometer. ^{1}H NMR (400 MHz), ^{13}C NMR-DEPT (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer using TMS as internal reference and the values for chemical shifts (δ) being given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were recorded on Agilent 1100 LC/MSD. HPLC was recorded by a Shimadzu SCL-10A instrument under the following conditions: column, Altima C18; flow rate, 1 mL/min; detection at 384 nm; mobile phase, 0.1% phosphoric acid: acetonitrile (65:35, v/v); retention time for **1**, 20.91 and for **5**, 22.51 min. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively.

4.1.1. 2-Hydroxy-4-methoxyacetophenone (7). A mixture of **6** (6 g, 39.5 mmol), dimethyl sulfate (4.1 mL, 43.4 mmol), potassium carbonate (8.2 g, 59.2 mmol) and acetone (100 mL) was stirred at rt for 5 h. After completion of reaction, the solid was filtered off and the solvent was evaporated. The residue obtained was chromatographed over silica gel column using mixtures of petroleum ether–ethyl acetate (90:10) as eluent to give **7** (6 g, 91%) as a white solid, mp 46–48 °C (lit.[17] mp 49–50 °C) and its spectroscopic data are consistent with those reported in the literature.[17]

4.1.2. 2-(2-Hydroxy-4-methoxyphenyl)acetic acid (8). A mixture of **7** (1.66 g, 10 mmol), sulfur (0.64 g, 20 mmol), morpholine (3 mL, 30 mmol) and *p*-toluenesulfonic acid (0.06 g, 0.32 mmol) was refluxed under constant stirring at 120–130 °C for 8 h. After completion of reaction, the mixture was allowed to cool and 20% NaOH (10 mL) and tetrabutylammonium bromide (16 mg, 0.05 mmol) were added and continued hydrolysis for further 8 h at 100 °C. The cooled reaction mixture was filtered and the filtrate was acidified with HCl to pH 2. The precipitated solid was filtered and chromatographed over silica gel column using hexane–EtOAc (80:20) as eluents to give **8** (1.2 g, 66%) as a light yellow solid, mp 130–132 °C (lit.[18] mp 130 °C) and its spectroscopic data are consistent with those reported in the literature.[18]

4.1.3. 6-Methoxy-3-hydrobenzo[*b*]furan-2-one (9). A mixture of **8** (340 mg) and phosphorous oxychloride (1.5 mL) in dichloroethane (10 mL) was stirred at rt for 15 h. The reaction mixture was diluted with water (50 mL) and extracted with chloroform (3×30 mL) and the combined chloroform layer was washed with water (2× 20 mL), sodium bicarbonate (20 mL) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using petroleum ether–EtOAc (90:10) as eluents to give **9** (270 mg, 90%) as a light yellow solid, mp 58–60 °C (lit.[18] mp 55–56 °C) and its spectroscopic data are consistent with those reported in the literature.[18]

4.1.4. 3-[(4-Hydroxyphenyl)methylene]6-methoxybenzo-[*b*]furan-2-one (10). A mixture of **9** (0.5 g, 3.05 mmol), 4-hydroxybenzaldehyde (0.372 g, 3.05 mmol) in acetic anhydride (7.5 mL, 79.4 mmol) and triethylamine (0.5 mL) was heated at 90 °C for 2 h. The cooled reaction mixture was poured into ice-cooled water (50 mL) and extracted with diethyl ether (3×30 mL). The organic layer was washed with water (2×20 mL), brine (20 mL) and dried over sodium sulfate, and the solvent was removed under vaccum. The residue was dissolved in methanol (10 mL), HCl (20%, 10 mL) and refluxed for 2 h. The cooled reaction mixture was poured into ice-cooled water (50 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with water (2×20 mL), brine (20 mL) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using petroleum ether–EtOAc (80:20) to give **10** (500 mg, 61%), which was recrystallized from chloroform to give the product as a yellow crystalls, mp 152–154 °C; ν_{max} (KBr): 3310, 1743, 1594, 1286, 1226, 1074, 967, 826 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.83 (3H, s, $-OCH_3$), 6.76 (1H, d, J=8.5 Hz, H-5), 6.95 (2H, d, J=8.2 Hz, H-3′,5′), 6.96 (1H, s, H-7), 7.60 (1H, s, =CH), 7.70 (2H, d, J=8.2 Hz, H-2′,6′), 7.79 (1H, d, J=8.5 Hz, H-5), 10.30 (1H, brs, Ar-OH); MS (ESI, negative scan): *m/z* 267 $(M-H)^-$. HRMS (*m/z*): Calcd for $C_{16}H_{12}O_4$ (M+Na): 291.0633. Found: 291.0636.

4.1.5. 6-Hydroxy-3-[(4-hydroxyphenyl)methylene]benzo-[*b*]furan-2-one (1*E*). A mixture of **10** (100 mg) and pyridine hydrochloride (1.5 g) was stirred at 180–190 °C for 3 h. The cooled reaction mixture was diluted with water (20 mL), acidified with dil HCl and extracted with EtOAc (3×20 mL). The combined EtOAc layer was washed with brine (20 mL) and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over silica gel column using chloroform–methanol (94:6) as eluents to give **1**-*E* (60 mg, 63%), which was recrystallized from chloroform–methanol to give the product as a yellow crystalls, *E*/*Z*–90:10. Mp 258–260 °C; ν_{max} (KBr): 3350, 1733, 1582, 1374, 1280, 1241, 1069, 959 cm^{-1}; ^1H and ^{13}C NMR (DMSO-d_6): see Table 1; MS (ESI, negative scan): *m/z* 253 $(M-H)^-$. HRMS (*m/z*): Calcd for $C_{15}H_{10}O_4$ (M+Na): 277.0477. Found: 277.0484.

4.1.6. 6-Acetyloxy-3-[(4-acetyloxyphenyl)methylene]-benzo[*b*]furan-2-one (4). A mixture of **1** (20 mg), acetic anhydride (1 mL), and pyridine (1 mL) was kept standing at room temperature for 16 h and diluted with diethyl ether (20 mL). The mixture was washed successively with water (20 mL), dil HCl (20 mL), water (20 mL) and brine (20 mL) and dried over sodium sulfate. The solution was filtered and the residue obtained after evaporation of the solvent was chromatographed over silica gel column using hexane–EtOAc (80:20) as eluents to give **4** (20 mg) as a light yellow solid, mp 128–130 °C; ν_{max} (neat): 1767, 1617, 1598, 1195, 1168, 1118, 1078, 1013 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.32 (3H, s, OAc), 2.35 (3H, s, OAc), 6.80 (1H, dd, J=2.2, 8.4 Hz, H-5), 6.96 (1H, d, J=2.2 Hz, H-7), 7.24 (2H, d, J= 8.7 Hz, H-3′,5′), 7.70 (2H, d, J=8.7 Hz, H-2′,6′), 7.73 (1H, d, J=8.4 Hz, H-4), 7.81 (1H, s, H-10); ^{13}C NMR ($CDCl_3$): δ 169.1, 168.9, 168.6, 155.0, 152.4, 152.2, 139.7, 131.5, 130.7, 123.3, 122.3, 121.6, 119.4, 117.1, 105.8, 21.2, 21.1; MS (ESI, positive scan): *m/z* 339 $(M+H)^+$. Analysis found: C, 67.38; H, 4.21%. Calcd for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17%.

4.1.7. 6-Hydroxy-3-[(4-hydroxyphenyl)methylene]benzo-[*b*]furan-2-one (5*Z*). A solution of **1** (100 mg) in THF (90 mL) was irradiated using a medium pressure mercury lamp for 10 h and the residue obtained after evaporation of the solvent was recrystallized from chloroform–methanol to give **5** (70 mg, 70%) as a yellow solid, *Z*/*E*—90:10; mp 258–260 °C; ^1H and ^{13}C NMR (DMSO-d_6): see Table 1; MS (ESI, negative scan): *m/z* 253 $(M-H)^-$.

4.1.8. Daidzein diacetate (3). A mixture of daidzein (96%, 40 mg), acetic anhydride (1 mL), and pyridine (1 mL) was kept standing at room temperature for 16 h and diluted with diethyl ether (20 mL). The mixture after usual work-up as described above, gave diacetate **3** (45 mg, 85%) as a white solid, mp 186–188 °C (lit.[19] mp 188–190 °C); ν_{max} (neat): 1750, 1644, 1616, 1222, 1017 cm^{-1}; ^1H NMR ($CDCl_3$): see Table 2; MS (ESI, positive scan): *m/z* 339 $(M+H)^+$.

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Clean and efficient microwave-solvent-free conversion of homochiral amines, α-amino alcohols and α-amino acids to their chiral 2-substituted pyrrole derivatives

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Abstract—Efficient synthesis of 1,2-disubstituted homochiral pyrroles has been achieved by a two-component coupling of chloroenones and amine compounds on the surface of silica gel without any solvent under microwave irradiation.

1. Introduction

Compounds containing a pyrrole ring can be found in many naturally occurring compounds and have been found to be useful for applications in medicine and agriculture.[1] Chiral pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of many different biologically active compounds. Several useful variants of classical methods can be found in the literature.[2] A stereoselective approach to the synthesis of indolizidine alkaloids, based on the reaction of pyrrole derivatives of amino acids has been reported.[3] C-2 substituted pyrrole derivatives provide access to substituted indolizidine alkaloids (**A**), hydroxylactams (**B**) unsaturated γ-lactams (**C**) and bicyclic lactams (**D**) (Fig. 1).

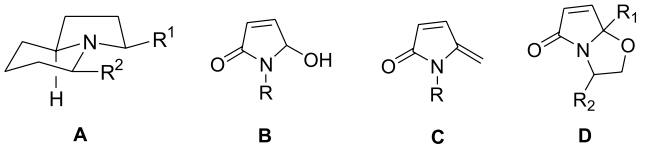

Figure 1.

The most widely used approach to pyrrole synthesis is the Paal–Knorr method in which 1,4-dicarbonyl compounds[4] and their masked equivalents such as tetrahydro-2,5-dimethoxyfuran, are converted to pyrrole derivatives with primary amines.[3] During the condensation reaction for the formation of the pyrrole ring with amino acids, partial racemization often occurs. Therefore, the development of a flexible and selective method to obtain such compounds is desirable. As we described in our previous paper,[5] we have designed a convenient new route to 2-alkyl substituted pyrrole rings from amines, amino alcohols and amino acids with chloroenones. The use of microwaves for carrying out these reactions under solvent free conditions provides advantages for the synthesis of numerous types of pyrroles. As part of our continued interest in the chemistry of substituted pyrroles, we wish to report here an efficient microwave-assisted one-pot synthesis of pyrroles by coupling chloroenones and amine compounds onto the surface of silica gel.

2. Results and discussion

Haloenones are valuable intermediates for the construction of nitrogen heterocycles. Chloroenones **2a–d** provide a four carbon unit with a carbonyl and halide functionality to form pyrrole rings with primary amines. As we previously reported, the refluxing of amine compounds with chloroenone in benzene-triethylamine and water for 4–6 h furnished the 2-substituted pyrrole derivatives in 71–95% yields (Table 1).[5] The use of microwaves for carrying out reactions in the laboratory provides advantages for the synthesis of numerous types of compounds. When the technique is applied successfully, the most evident improvements are reduced time of reaction, cleaner reactions due to fewer side-reactions, and the use of minimal quantities of solvent. Thus, microwave assisted

Keywords: Pyrrole; Microwave; Silica gel; Chloroenone.
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Table 1. The synthesis of 2-substituted pyrroles

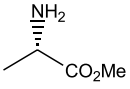
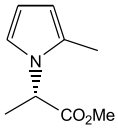
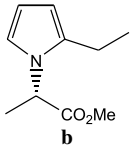
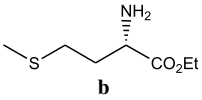
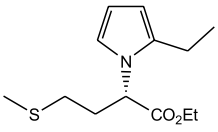
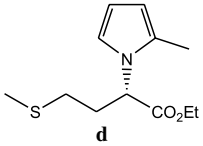
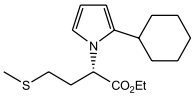
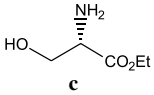
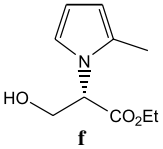
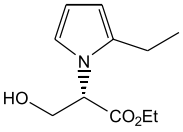
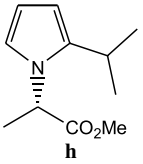
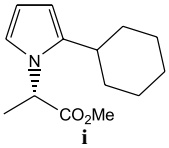
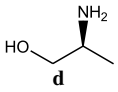
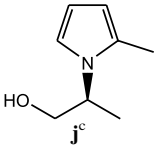
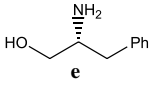
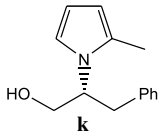
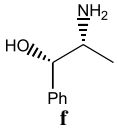
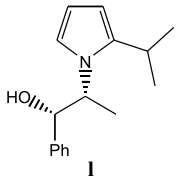
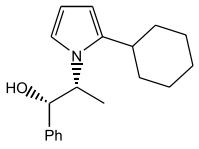
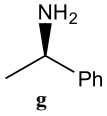
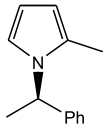
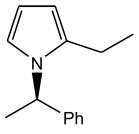
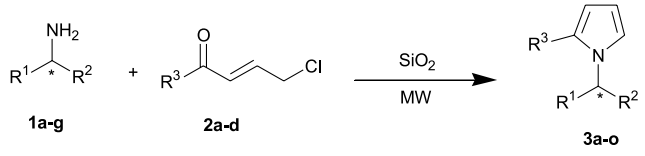
Amine **1**	Chloroenone **2** R=	Pyrrole **3**[a]	Heating method		Microwave	
			Reaction time (h)	Yield[b] (%)[ref]	Reaction time (min)	Yield[b] (%)
 **a**	CH_3 **a**	 **a**	6	80[5b,c]	5	79
a	C_2H_5 **b**	 **b**	6	74	4	68
 **b**	**b**	 **c**	5	80	6	82
b	**a**	 **d**	5	71	4	70
b	C_6H_{11} **c**	 **e**	6	73	6	74
 **c**	**a**	 **f**	6	75[5d,e]	5	83
c	**b**	 **g**	4	79	4	77
a	$(CH_3)_2CH$ **d**	 **h**	5	76[5b,c]	5	84
a	**c**	 **i**	5	72[5b,c]	5	83
 **d**	**a**	 **j**[c]	5	95[5d,e]	5	88

Table 1 (*continued*)

Amine **1**	Chloroenone **2** R=	Pyrrole **3**[a]	Heating method		Microwave	
			Reaction time (h)	Yield[b] (%)[ref]	Reaction time (min)	Yield[b] (%)
 **e**	**a**	 **k**	5	84[5d,e]	5	87
 **f**	**d**	 **l**	4	85[5b,c]	6	83
f	**c**	 **m**	4	81[5b,c]	5	87
 **g**	**a**	 **n**	6	90[5b,c]	5	88
g	**b**	 **o**	5	72	4	84

[a] The compounds **3a**,**f**,**h**,**i**,**j**,**k**,**l**,**m**,**n** are known and have been identified by comparison of spectral data with those reported in the literature.
[b] Isolated yields.
[c] $[\alpha]_D^{20}=9.9$ (*c* 1.2, $CHCl_3$); lit.[5d] $[\alpha]_D^{20}=-9.6$ (*c* 1.2, $CHCl_3$) for (*R*)-**3j**.

synthesis can be considered to be more economical and environmentally friendly.[6] We have explored the use of microwaves in the pyrrole formation reaction. We tried different reaction conditions to carry out this reaction under microwave irradiation and found when the irradiation of chloroenone with amine compounds was carried out on the surface of silica gel without solvent the pyrroles were quickly furnished in good yield (Scheme 1). In a typical procedure, a mixture of chloroenone, amine compound and triethylamine adsorbed on the surface of silica gel was irradiated in a microwave oven for a certain period of time as required to complete the reaction. Elution of the reaction mixture with ether followed by the evaporation of solvent furnished the crude product which was purified by column chromatography. Conventional heating in dry media in place of microwave leads to a messy product with the formation of tarry material.

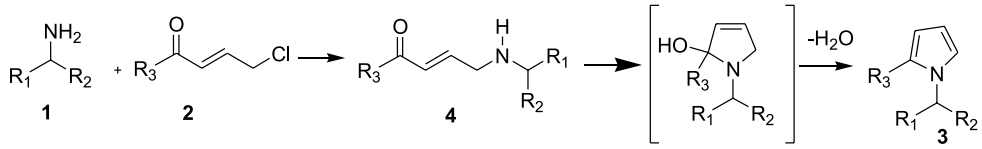


Scheme 1.

A wide range of chiral amine compounds were coupled with various chloroenones by this procedure through a single step operation to produce the corresponding alkyl substituted pyrroles as summarized in Table 1.

The reaction of alanine methyl ester (**1a**) with 5-chloro-3-pentene-2-one (**2a**) gave the 2-methylpyrrole derivative of alanine methyl ester (**3a**) in 79–80% yield. Under similar conditions 2-aminopropan-1-ol (**1d**) with **2a** gave the pyrrole derivative **3j** in 88–95% yield. The compound (*S*)-**3j** was also synthesized from the LAH reduction of (*S*)-**3a** in 81% yield. The pyrrole derivative **3j**, synthesized from different ways showed the same optical rotation value. This result showed that the formation of pyrrole derivative from alanine ester works without racemization.

The pyrrole derivative of amino acid esters and amino alcohols showed excellent separation properties by chiral HPLC column.[7] Control of the optical purity of the products by comparing racemic mixtures using chiral HPLC column



Scheme 2.

gave the same result as the formation of a pyrrole ring from amino acids esters in which no racemization occurs.

In general, the microwave assisted reactions are very fast and clean. The yields are reasonably good for a two-component coupling reaction. None of these operations involves any strong acid, base or solvent.

The suggested mechanism for the formation of pyrroles **3** is outlined in Scheme 2. It seems reasonable to suggest that the amine reacts initially with the allylic chloride to form **4** and the cyclisation onto the ketone occurs as the ring closing step, followed by elimination of water to give the product **3**.

3. Conclusion

In conclusion, the present microwave-assisted one-pot procedure provides an efficient methodology for the synthesis of alkyl-substituted pyrroles on the surface of silica gel from easily available starting materials by a condensation reaction. The notable advantages of this procedure are: (a) reasonably good yields; (b) fast reaction; (*c*) mild reaction conditions; (d) no racemization; (e) general applicability and (f) above all, green synthesis avoiding toxic reagents and solvents. Thus, it provides a better and more practical alternative to the existing methodologies.

4. Experimental

All reagents were of commercial quality and reagent quality solvents were used without further purification. IR spectra were determined on a Perkin Elmer 1600 spectrometer. NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: $\delta=7.27$), $CDCl_3$ (^{13}C: $\delta=77.0$) and CCl_4 (^{13}C: $\delta=96.4$) as internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda=254$ nm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column. MS: Thermo Quest Finnigan multi Mass (EI, 70 eV). Optical rotations were measured with Krüss P3002RS automatic polarimeter. The reactions are carried out in Milestone-Start microwave instrument. Haloenones **2a–d** are synthesized according to the literature.[8]

4.1. Representative example

4.1.1. (*S*)-Methyl 2-(2-methyl-1*H*-pyrrol-1-yl)propanoate (*S*)-3a.[5b,c] A mixture of amine (103 mg, 1.0 mmol), chloroenone (153 mg, 1.3 mmol) and triethylamine (1.0 mmol) were uniformly adsorbed on the surface of silica gel (5 g) in a pyrex round bottomed flask at rt. The flask was then placed on a bed of silica gel in a porcelain basin and irradiated by a microwave oven at 500 W for 5 min (TLC). The reaction mass was eluted with ether and the ether extract was evaporated to leave the crude product which was purified by column chromatography over silica gel (EtOAc/hexane 1:2, 1:6 or 1:10) to afford the pure product as a viscous oil (133 mg, 79%). $[\alpha]_D^{20}=-49.4$ (*c* 2, CH_3OH), [lit.[5b] $[\alpha]_D^{20}=-48.1$(*c* 2, CH_3OH)]; IR(neat): ν 2897, 1778, 1463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.70 (d, $J=7.2$ Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 4.80 (q, $J=7.0$, 1H, CH), 5.95 (m, 1H, =CH), 6.10 (m, 1H, =CH), 6.75 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$):δ 12.4, 18.5, 53.1, 54.2, 108.2, 108.5, 118.0, 129.7, 173.3. The spectroscopic data are in accordance with the literature.[5b]

4.1.2. (*S*)-Methyl 2-(2-ethyl-1*H*-pyrrol-1-yl)propanoate (*S*)-3b. Light yellow oil (123 mg, 68%). $[\alpha]_D^{20}=-30.7$ (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): ν 2954, 1742, 1434, 1203 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, $J=7.5$ Hz, 3H, CH_3), 1.60 (d, $J=7.2$ Hz, 3H, CH_3), 2.45 (q, $J=7.5$ Hz, 2H, CH_2), 3.62 (s, 3H, CH_3), 4.67 (q, $J=7.2$ Hz, 1H, CH), 5.78 (br s, 1H, =CH), 5.99 (t, $J=3.2$ Hz, 1H, =CH), 6.58 (br s, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 18.3, 19.4, 52.3, 53.1, 105.3, 107.9, 117.1, 134.5, 171.6; MS (*m*/*z*) (rel abund): 181 [M^+] (13), 165 (32), 122 (80), 106 (65), 94 (100), 80 (51). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.11): C, 66.27; H, 8.34; N, 7.73. Found: C, 66.15; H, 8.29; N, 7.85.

4.1.3. (*S*)-Ethyl 2-(2-ethyl-1*H*-pyrrol-1-yl)-4-(methylthio)butanoate (*S*)-3c. Yellow oil (209 mg, 82%). $[\alpha]_D^{20}=-46.0$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν 2966, 1736, 1428, 1215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (m, 6H, CH_3), 1.99 (s, 3H, CH_3), 2.28 (m, 4H, CH_2), 2.51 (q, $J=7.5$ Hz, 2H, CH_2), 4.09 (m, 2H, CH_2), 4.78 (m, 1H, CH), 5.76 (br s, 1H, =CH), 6.00 (t, $J=3.2$ Hz, 1H, =CH), 6.56 (br s, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 14.1, 15.3, 19.5, 30.2, 31.6, 55.9, 61.3, 105.1, 108.3, 117.2, 135.2, 170.4; MS (*m*/*z*) (rel abund): 255 [M^+] (15), 180 (95), 152 (70), 134 (58), 108 (100), 93 (50). Anal. Calcd for $C_{13}H_{21}NO_2S$ (255.13): C, 61.14; H, 8.29; N, 5.48; S, 12.56. Found: C, 61.31; H, 8.22; N, 5.56; S, 12.43.

4.1.4. (*S*)-Ethyl 2-(2-methyl-1*H*-pyrrol-1-yl)-4-(methylthio)butanoate (*S*)-3d. Yellow oil (169 mg, 70%). $[\alpha]_D^{20}=-39.5$ (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): ν 2978, 2910, 1738, 1420, 1295 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, $J=7.2$ Hz, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 2.31 (m, 4H, CH_2), 4.11 (m, 2H, CH_2), 4.78 (m, 1H, CH), 5.74 (br s, 1H, =CH), 5.96 (m, 1H, =CH), 6.54 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 14.2, 15.3, 30.1, 31.2, 56.1, 61.4, 107.1, 108.3, 117.2, 128.9,

170.4; MS (*m*/*z*) (rel abund): 241 [M^+] (13), 196 (5), 166 (84), 137 (57), 120 (91), 94 (100), 80 (40). Anal. Calcd for $C_{12}H_{19}NO_2S$ (241.11): C, 59.72; H, 7.93; N, 5.80; S, 13.29. Found: C, 59.64; H, 8.06; N, 5.71; S, 13.16.

4.1.5. (*S*)-Ethyl 2-(2-cyclohexyl-1*H*-pyrrol-1-yl)-4-(methylthio)butanoate (*S*)-3e. Dark yellow oil (229 mg, 74%). $[\alpha]_D^{20} = -34.8$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): ν 2927, 1735, 1444, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, $J=7.5$ Hz, 3H, CH_3), 1.30 (m, 4H, CH_2), 1.75 (m, 6H, CH_2), 1.99 (s, 3H, CH_3), 2.17 (m, 2H, CH_2), 2.31 (m, 2H, CH_2), 2.45 (m, 1H, CH), 4.10 (m, 2H, CH_2), 4.81 (m, 1H, CH), 5.75 (m, 1H, =CH), 5.99 (m, 1H, =CH), 6.51 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 15.3, 26.2, 26.7, 26.8, 30.3, 31.9, 33.8, 34.3, 35.4, 55.8, 61.3, 103.8, 108.4, 116.8, 139.5, 170.5; MS (*m*/*z*) (rel abund): 309 [M^+] (8), 292 (13), 260 (14), 234 (67), 205 (21), 191 (34), 179 (80), 166 (82), 152 (59), 147 (34), 118 (55), 106 (100), 81 (27). Anal. Calcd for $C_{17}H_{27}NO_2S$ (309.18): C, 65.98; H, 8.79; N, 4.53; S, 10.36. Found: C, 66.12; H, 8.67; N, 4.45; S, 10.44.

4.1.6. (*S*)-Ethyl 2-(2-ethyl-1*H*-pyrrol-1-yl)-3-hydroxypropanoate (*S*)-3g. Light yellow oil (162 mg, 77%). $[\alpha]_D^{20} = -27.1$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): ν 3451, 2973, 2927, 1735, 1479, 1287 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (m, 6H, CH_3), 2.48 (q, $J=7.5$ Hz, 2H, CH_2), 2.53 (br s, 1H, OH), 3.80 (m, 1H, CH_A), 3.98 (m, 1H, CH_B), 4.10 (m, 2H, CH_2), 4.63 (t, $J=6.7$ Hz, 1H, CH), 5.78 (m, 1H, =CH), 5.98 (t, $J=3.2$ Hz, 1H, =CH), 6.56 (m, 1H, =CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.1, 14.1, 19.4, 59.3, 61.6, 63.0, 105.3, 108.3, 117.7, 135.3, 169.5; MS (*m*/*z*) (rel abund): 211 [M^+] (15), 195 (38), 137 (38), 106 (55), 94 (100), 80 (82). Anal. Calcd for $C_{11}H_{17}NO_3$ (211.12): C, 62.54; H, 8.11; N, 6.63. Found: C, 62.49; H, 8.24; N, 6.54.

4.1.7. (*R*)-2-Ethyl-1-(1-phenylethyl)-1*H*-pyrrole (*R*)-3o. Light yellow oil (167 mg, 84%). $[\alpha]_D^{20} = -20.7$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): ν 3055, 2985, 2927, 1450, 1211 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, $J=7.5$ Hz, 3H, CH_3), 1.70 (d, $J=7.1$ Hz, 3H, CH_3), 2.23 (m, 1H, CH_A), 2.40 (m, 1H, CH_B), 5.17 (q, $J=7.1$ Hz, 1H, CH), 5.82 (br s, 1H, =CH), 6.02 (t, $J=3.2$ Hz, 1H, =CH), 6.66 (m, 1H, =CH), 7.00 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0, 19.6, 22.7, 54.5, 105.3, 107.1, 116.9, 125.3, 125.6, 127.1, 128.6, 135.0, 144.1; MS (*m*/*z*) (rel abund): 199 [M^+] (15), 105 (100), 95 (67), 80 (93). Anal. Calcd for $C_{14}H_{17}N$ (199.14): C, 84.37; H, 8.60; N, 7.03. Found: C, 84.23; H, 8.56; N, 7.15.

Acknowledgements

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Base-assisted intramolecular 6-acetoxypyranone-acetylene [5+2] cycloaddition. Synthesis and reactivity of novel oxa-tricyclo[5.3.1.0^{1,5}]undecenones

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Abstract—The synthesis of 3,11-dioxatricyclo[5.3.1.0^{1,5}]undeca-5,9-dien-8-ones is reported from suitable 5-substituted furfuryl alcohols bearing an acetylenic side-chain. Successive peracid-mediated oxidative rearrangement of furan carbinols and base-assisted intramolecular 1,3-dipolar cycloaddition afforded oxygen-bridged tricyclo-undecane derivatives. Stereoselective transformations of cycloadducts are also discussed.

1. Introduction

The synthesis and reactivity of oxygen-bridged compounds remain a significant synthetic challenge to organic chemists targeting medium-size ring systems,[1] highly valuable building blocks for natural product synthesis.[2] In this way, [5+2] cycloadditions have long been recognized as a method of choice in the synthesis of sophisticated molecules[3] such as phorbol,[4] phomoidribe B[5] or taxane diterpenes.[6] It is noteworthy that subsequent ring-opening of a bridged ether, as a latent hydroxyl function, has proved effective in natural tropolone synthesis.[1,7]

Recently, we reported a biomimetic approach to epolone B (**2**, Figure 1)[8] via a tropolone quinone methide derived from the highly functionalized oxabicyclo[3.2.1]octane **1**. Key steps in the synthesis of **1** included an intermolecular [5+2] cycloaddition reaction. Based on our commitment to new methodologies connecting cycloadditions and biomimetic synthesis,[9] we decided to investigate the scope of the intramolecular [5+2] cycloaddition towards oxygen-bridged compounds such as 3,11-dioxatricyclo[5.3.1.0^{1,5}] undeca-5,9-dien-8-one model **3**, a potential precursor of naturally occurring bicyclic tropolones.[10]

2. Results and discussion

One of the most commonly used procedures to achieve this goal relies on a [5+2] cycloaddition of carbonyl ylides **5** or **6** with dipolarophiles, in either inter- or intramolecular pathways; likewise the intermolecular cycloadditions of furans are of synthetic interest (Scheme 1).[11] Intermediates **5** or **6** can be generated in situ as follows: the 6-acetoxy-3-pyranones **7**[12] and 3-hydroxy-4-pyrones **8**[13] are converted to a common 3-oxidopyrilium ylide **5** upon thermolysis, acid or base-assisted reactions, whereas intermediate **6** is involved during a rhodium-catalyzed cyclization of α-diazoketones **9**.[14] Extensive studies of [5+2] cycloadditions report the

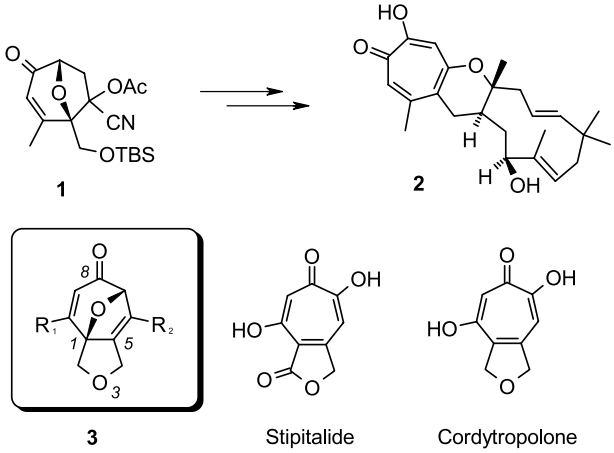

Figure 1.

Keywords: Intramolecular [5+2] cycloaddition; 3-Oxidopyrilium ylide; Acetylenic dipolarophiles; Tricyclo[5.3.1.0]undecane; Tropolone.
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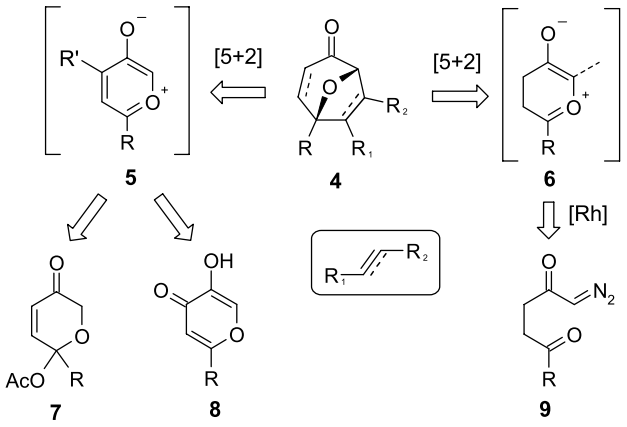


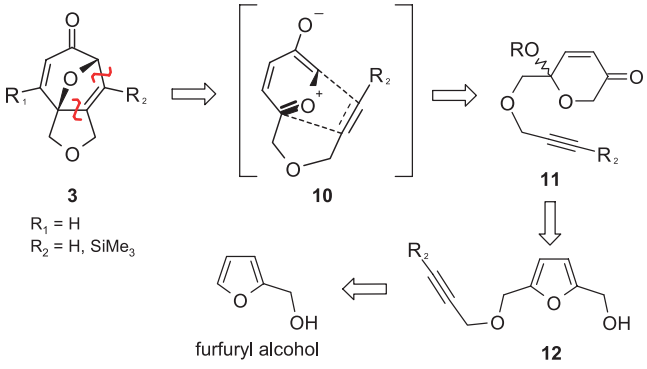
Scheme 1.

effectiveness of electron-rich or electron-deficient alkenes in open or strained-form as dipolarophiles.[15] Recently, substituted allenes[16] and dienes[17] have been successfully engaged as dipolarophiles in intra- and intermolecular reactions, and functionalized acetylenes have proved to be excellent reaction partners with substrates **8** and **9**.[18]

We now report the first base-assisted intramolecular [5+2] cycloaddition of 6-acetoxy-3-pyranones **7** with unsubstituted acetylenes.

2.1. Retrosynthetic analysis of 3

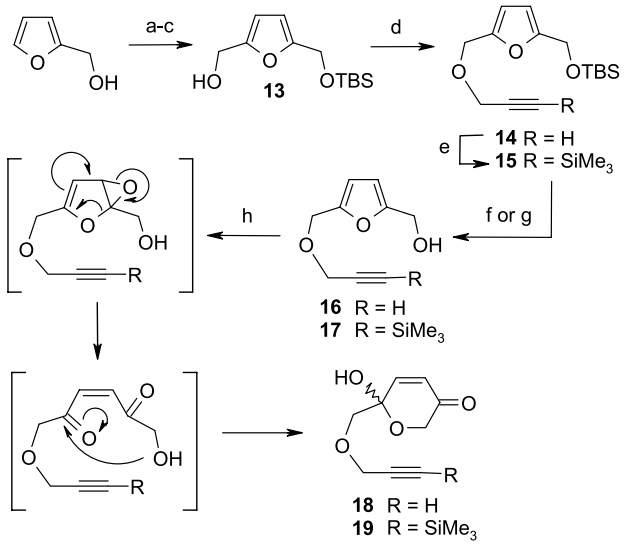
The desired dioxa-tricyclo-undecenone model **3** was disconnected using an intramolecular 1,3-dipolar cycloaddition between the 3-oxidopyrilium ylide and the acetylene functionalities of intermediate **10** as the key step (Scheme 2). The 3-oxidopyrilium ylide **10** would be obtained from the corresponding pyranulose acetate **11**, which in turn would be derived from 5-substituted furan carbinol **12** via a peracid-mediated oxidative rearrangement.[19]



Scheme 2.

2.2. Synthesis of hydroxypyranulose 18 and 19

The synthesis started with the preparation of 2,5-disubstituted furyl alcohol **16** and **17** (Scheme 3). Hydroxyl protection of furfuryl alcohol as a TBS–ether, followed by formylation at C-5 using *n*-BuLi and DMF, and subsequent reduction with sodium borohydride afforded alcohol **13** in very good yield over three steps. *O*-Alkylation under phase



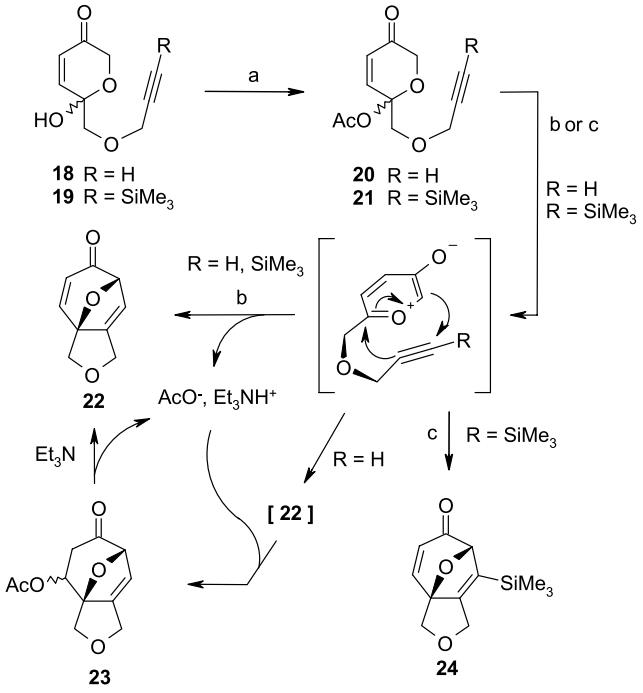
Scheme 3. (a) TBDMSCl, imidazole, DMF, rt, 91%; (b) *n*-BuLi, DMF, THF, −78 °C to rt, 98%; (c) $NaBH_4$, MeOH, 0 °C to rt, 98%; (d) propargyl bromide, cat. Bu_4NHSO_4, 15 N NaOH, toluene, 0 °C to rt, 99%; (e) *n*-BuLi, TMSCl, THF, −78 °C to rt, 90%; (f) TBAF, THF, 0 °C to rt, 91%; (g) cat. *p*-TSA, H_2O, MeOH, 0 °C, 10 min, 93%; (h) *t*-BuO_2H, cat. $VO(acac)_2$, CH_2Cl_2, 0 °C to rt, 86% (**18**) and 68% (**19**).

transfer catalysis using *n*-Bu_4NBr, 15 N NaOH and propargyl bromide provided the acetylene **14** quantitatively. Deprotection of silyl ether **14** with TBAF at 0 °C gave alcohol **16** in 91% yield. The silyl acetylene derivative **17** was easily obtained via direct lithiation of terminal acetylene **14** using *n*-BuLi at −78 °C, quenching with TMSCl, followed by acid-catalyzed deprotection of silyl ether **15**.

The first key step of our strategy relies on the oxidative rearrangement of furylmethanols, commonly induced by the reaction of peracids[20] or direct bromination.[21] However, the use of *m*-CPBA in the furan-ring expansion of our substrate **16** at low temperature furnished unreproducible results on small to larger scale and only gave modest yield after purification (40–50%). It was found that the most suitable method for the oxidative rearrangement of furans **16** and **17** was the system using *tert*-butylhydroperoxide (1.5 equiv) and catalytic vanadyl acetylacetonate ($VO(acac)_2$),[22] the latter reagent being used as a useful colour-indicator during the reaction. Hydroxy-pyranuloses **18** and **19** were relatively unstable and rapid purification on silica gel is highly recommended.

2.3. Intramolecular [5+2] dipolar cycloadditions

The intramolecular 1,3-dipolar cycloaddition of the hydroxypyranulose **18** was first tested to evaluate the reactivity of internal acetylene with the in situ generated 3-oxidopyrilium ylide (Scheme 4). Initially, pyranulose acetate **20** was generated from **18** using a standard protocol (Ac_2O, cat. DMAP, pyridine or Et_3N), followed by the addition of excess 5-diazabicyclo[5.4.0]undec-5-ene (DBU) at reflux in toluene to perform the cycloaddition. Our first results were unsuccessful as multiple degraded products were observed. Gratifyingly, when acetate **20** was isolated and engaged after purification in the cyclisation step using a



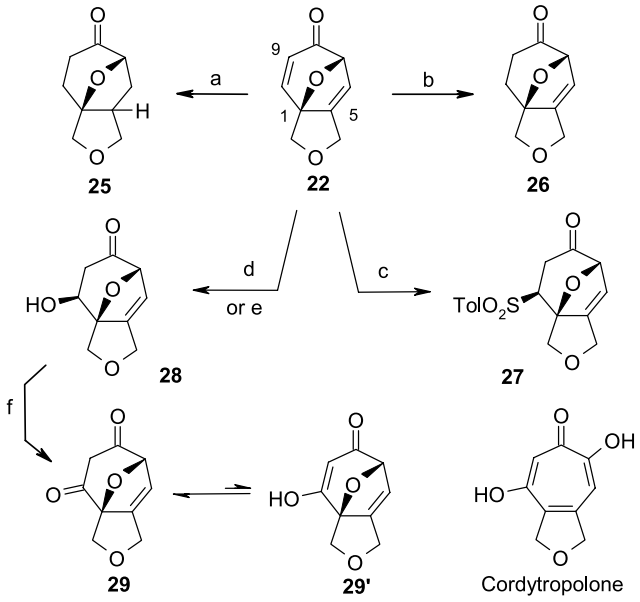
Scheme 4. (a) Ac_2O, DMAP, Et_3N, 0 °C to rt, 83% (**20**) and 78% (**21**); (b) Et_3N, toluene, reflux, 86% (from **20**), 74% (from **21**); (c) Et_3N, CH_3CN, reflux, 86% (from **21**).

stoichiometric amount of Et_3N as a base in refluxing toluene, cycloadduct **22** was cleanly obtained in 86% yield. However, using an excess of Et_3N or longer reaction time led to the formation of a side-product **23**. Curiously, silyl derivative **21** underwent conversion to **22** in refluxing toluene, via a desilylation process. The use of acetonitrile as solvent however gave the desired silyl cycloadduct **24** in good yield.

2.4. Reactivity of oxa-tricyclic adduct 22

Interestingly, the observation of contaminated acetoxy side-product **23** in crude **22** produced during the cyclisation step prompted us to investigate the reactivity of the enone moiety (Scheme 5). With the oxygen-bridged compound **22** in hand, we firstly hydrogenated using 5% Pd/C to afford a single cycloheptanone **25**. Surprisingly, L-selectride in THF at −78 °C selectively reduced the $C_{9,10}$ double-bond to give the cycloheptan-2-en-7-one **26** without affecting the carbonyl function. 1,4-Addition-type reactions were also briefly examined. Indeed, the addition of sodium *para*-toluenesulfinate in the presence of acetic acid onto the enone **22** stereoselectively afforded the β-keto-sulfone **27** in 70% yield,[23] in which the *cis*-relationship of the sulfone group, with respect to the oxygen bridge, has been confirmed by NOE experiments (Fig. 2).

Although the transformation of an enone function into the corresponding β-hydroxy-ketone has been well documented (requiring several steps via an α,β-epoxy ketone),[24] we found that the simple treatment of water in basic (Et_3N) or acidic-media (6 N HCl, dioxane) afforded the desired β-hydroxy ketone **28** in good to excellent yields. NMR studies confirmed a high stereoselectivity (>95:5, β-/α-OH) in which the stereochemistry has been defined by 2D NMR and



Scheme 5. (a) H_2, Pd/C, MeOH, rt, 92%; (b) L-selectride, THF, −78 °C, 86%; (c) *p*-$TolSO_2Na$, AcOH, rt, 70%; (d) Et_3N, H_2O, 0 °C to rt, 1 h, 98% (one single diastereomer β-OH-**28**); (e) 6 N HCl, dioxane, reflux, 80% (ratio β/α-OH-**28** >95:5); (f) Jones' reagent, acetone, 0 °C, 76%.

NOE experiments (Fig. 2). Finally, alcohol **28** was in turn submitted to low temperature Jones oxidation to give β-diketone **29** in 76% yield.[25] According to NMR data, we observed that the diketone/conjugated enol form equilibrium was shifted towards the diketone **29**, an oxygen-bridged isomer of the natural cordytropolone. First attempts to transform compound **29** into cordytropolone have proved to be challenging.

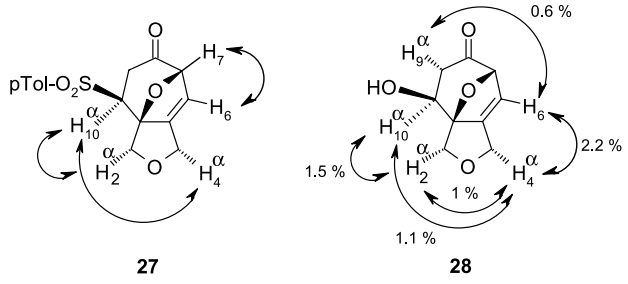


Figure 2. Selected NOE for compounds **27** and **28**.

3. Conclusion

In summary, we have described the first base-assisted intramolecular [5+2] cycloaddition of 6-acetoxy-3-pyranones with appropriate acetylenic functions to access 3,11-dioxatricyclo[5.3.1.$0^{1,5}$]undeca-5,9-dien-8-ones **22** and **24**. Some stereoselective transformations of tricyclic adduct **22** were also investigated. Further explorations of this methodology will be reported in due course.

4. Experimental

4.1. General techniques

All reactions requiring anhydrous conditions were

conducted in flame-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 100 °C and allowed to cool in a dessicator over P_2O_5 before use. THF was obtained by distillation over sodium benzophenone under N_2. Anhydrous DCM was obtained by distillation from CaH_2 under N_2. Petroleum ether referred to the fraction with bp 40–60 °C.

TLC was performed on Merck aluminium foil-backed sheets precoated with 0.2 mm Kieselgel 60 F_{254}. Product spots were visualised by the quenching of UV fluorescence (λ_{max}, 254 nm), or by staining with a solution of 5% (w/v) dodecamolybdophosphoric acid in EtOH or KMnO4 in EtOH, H_2SO_4, followed by heating. Flash column chromatography was performed using silica gel (Sorbisil™ C_{60} 40–60 μm).

NMR spectra were recorded on Bruker DPX 250 (250 MHz), DPX400 (400 MHz) and AMX500 (500 MHz) spectrometers ^{13}C NMR were recorded on Bruker DPX 250 (63 MHz), DPX400 (100 MHz) and AMX500 (125 MHz) spectrometers. Chemical shifts (δ) are reported in ppm, and are referenced to the residual solvent peak. Coupling constant (J) are quoted to the nearest 0.5 Hz. IR spectra were recorded as a thin film between NaCl plates on a Perkin–Elmer 1750 FTIR spectrometer. Only selected peaks and strong absorbed peaks are reported, absorption maxima being recorded in cm^{-1}. Low resolution mass-spectra (m/z) were recorded on a Fisons Platform (EI) or a Fisons AutoSpec-oaTof (EI, CI) mass spectrometer, m/z values of major peaks are reported in Daltons, with intensities quoted as percentages of the base peak. High resolution mass spectra were recorded on a Fisons AutoSpec-oaTof (EI, CI) or a Micromass GCT (EI, CI) mass spectrometer.

4.2. Experimental procedures and data

4.2.1. 2-*tert*-Butyldimethylsilyloxymethyl furan. The title compound was prepared on multigram scale according to Corey's procedure.[26] NMR ^1H (400 MHz, $CDCl_3$) δ 7.39 (d, 1H, $J=0.5$ Hz), 6.32 (dd, 1H, $J=0.5$, 2 Hz), 6.36 (d, 1H, $J=2$ Hz), 4.56 (s, 2H, CH_2), 0.93 (s, 9H, *t*-Bu-Si), 0.10 (s, 6H, $(CH_3)_2$-Si)). NMR ^{13}C (100 MHz, $CDCl_3$) δ 154.3 (C), 142.1 (CH), 110.7 (CH), 107.2 (CH), 58.2 (CH_2), 25.9 (($CH_3)_3$), 18.5 (C), −5.2 (CH_3). CI-MS m/z 230 (40), 172 (45); HRMS calcd for $C_{11}H_{24}NO_2Si$ ($[M+NH_4]^+$) 230.1576, found 230.1571.

4.2.2. 2-*tert*-Butyldimethylsilyloxymethyl-5-formyl furan. To a stirred solution of the above furan (26.54 g, 125 mmol) in THF (200 ml) at −78 °C was added dropwise 55 ml of *n*-BuLi (2.5 M, 137.5 mmol, 1.1 equiv). The solution was stirred 1.5 h at −78 °C, then 30 min at 0 °C and cooled to −78 °C before the dropwise addition of 19.3 ml of distilled DMF (250 mmol, 2 equiv, neat). The solution was stirred for 1 h at −78 °C, then allowed to warm at room temperature, and stirred for a further 30 min. The solution was quenched with water (100 ml) and diluted with ether (200 ml). The aqueous phase was extracted with ether (3×100 ml) and the combined organic extracts were washed with water (3×20 ml), then brine; dried ($MgSO_4$) and concentrated in vacuo. The pure aldehyde (29.46 g, 98%) was used in the next step without further purification. NMR ^1H (400 MHz, $CDCl_3$) δ 9.58 (s, 1H, CHO), 7.21 (d, 1H, $J=3.5$ Hz), 6.48 (d, 1H, $J=3.5$ Hz), 4.77 (s, 2H), 0.92 (s, 9H), 0.11 (s, 6H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 177.5 (CHO), 161.4 (C), 152.2 (C), 109.4 (2CH), 58.6 (CH_2), 25.8 (CH_3), 18.3 (C), −5.4 (CH_3). IR (NaCl plates) 2938–2858, 1683 (C=O). CI-MS m/z 258 (100), 241 (68); HRMS calcd for $C_{12}H_{21}O_3Si$ ($[M+H]^+$) 241.1260, found 241.1263.

4.2.3. 5-*tert*-Butyldimethylsilyloxy-2-furan methanol (13). To a stirred solution of the above aldehyde (6.01 g, 25.0 mmol) in MeOH (120 ml) at 0 °C was added portionwise 1.6 g of sodium borohydride (powder, 40 mmol). The solution was stirred 30 min at 0 °C, then 4 h at room temperature. The solution was concentrated under reduced pressure, and water followed by ethyl acetate were added successively. The aqueous phase was adjusted to pH 9 by addition of 1 M NaOH solution, and extracted with ethyl acetate (3×50 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% EtOAc in petroleum ether) afforded alcohol **13** as a pale yellow oil (5.97 g, 98%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.21 (d, 1H, $J=3.5$ Hz), 6.18 (d, 1H, $J=3.5$ Hz), 4.63 (s, 2H), 4.57 (s, 2H), 2.20 (br s, 1H, OH), 0.91 (s, 9H), 0.10 (s, 6H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 154.3 (C), 153.7 (C), 108.4 (CH), 108.0 (CH), 58.3 (CH_2), 57.5 (CH_2), 25.9 (CH_3), 18.4 (C), −5.2 (CH_3). IR (NaCl plates) 3307 (O–H), 2930–2858 (C–H), 1686 (C=C). CI-MS m/z 260 (7), 225 (71); HRMS calcd for $C_{12}H_{26}NO_3Si$ ($[M+NH_4]^+$) 260.1682, found 260.1695.

4.2.4. 2-*tert*-Butyldimethylsilyloxymethyl-5-[(2-propynyloxy)-methyl]furan (14). To a vigourously stirred solution of alcohol **13** (5.88 g, 24.3 mmol) in toluene (25 ml) at 0 °C was added water (10 ml), tetrabutylamonium hydrogen-sulfate monohydrate (424 mg, 1.21 mmol, 0.05 equiv) and portionwise sodium hydroxide (4 g, 97 mmol, 4 equiv, pearls). The solution was stirred 15 min at 0 °C, 1 h at room temperature, and cooled to 0 °C before the dropwise addition of propargyl bromide (80% w/w in toluene, 36.37 mmol, 1.5 equiv). The solution was vigorously stirred for 30 min at 0 °C and at room temperature until completion of the reaction. The solution was diluted with ether (100 ml) followed by the addition of water (20 ml). The aqueous phase was extracted with ether (3× 40 ml). The organic extracts were washed with saturated aqueous NH_4Cl, brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 5% EtOAc in petroleum ether) afforded propargyl ether **14** as a pale yellow oil (6.74 g, 99%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.31 (d, 1H, $J=3$ Hz), 6.19 (d, 1H, $J=3$ Hz), 4.64 (s, 2H), 4.54 (s, 2H), 4.16 (d, 2H, $J=2.5$ Hz), 2.47 (t, 1H, $J=2.5$ Hz), 0.91 (s, 9H), 0.10 (s, 6H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 155.1 (C), 150.2 (C), 110.9 (CH), 107.9 (CH), 79.4 (C), 74.8 (CH), 63.1 (CH_2), 58.3 (CH_2), 56.6 (CH_2), 25.9 (CH_3), 18.4 (C), −5.2 (CH_3). IR (NaCl plates) 3307 (O–H), 2930–2860 (C–H), 2117 (C≡C). CI-MS m/z 298 (7), 225 (43); HRMS calcd for $C_{15}H_{28}NO_3Si$ ($[M+NH_4]^+$) 298.1838, found 298.1826.

4.2.5. 5-[(2-Propynyloxy)methyl]-2-furan methanol (16). To a stirred solution of silyl ether **14** (6.68 g, 23.8 mmol) in THF (180 ml) at 0 °C was added dropwise tetrabutylammonium fluoride (1 M in THF, 26.2 ml, 26 mmol, 1.1 equiv). A red color was instantaneously observed and the solution was

stirred a further 30 min before quenching with water (60 ml). The solution was diluted with ether (150 ml) and washed with water (3×20 ml). The organic extracts were washed with saturated aqueous NH_4Cl, brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 30% EtOAc in petroleum ether) afforded alcohol **16** as a colorless oil (3.60 g, 91%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.32 (d, 1H, $J=3$ Hz), 6.23 (d, 1H, $J=3$ Hz), 4.57 (s, 2H), 4.52 (s, 2H), 4.16 (d, 2H, $J=2.5$ Hz), 2.48 (t, 1H, $J=2.5$ Hz), 2.38 (br s, 1H, OH). NMR ^{13}C (100 MHz, $CDCl_3$) δ 154.7 (C), 150.6 (C), 111.5 (CH), 109.0 (CH), 79.2 (C), 74.9 (CH), 63.2 (CH_2), 57.4 (CH_2), 56.8 (CH_2). IR (NaCl plates) 3398 (O–H), 2926–2961 (C–H). CI-MS *m/z* 184 (7), 167 (2) 149 (100); HRMS calcd for $C_9H_{11}O_3$ ($[M+H]^+$) 167.0708, found 167.0711.

4.2.6. 2-*tert*-Butyldimethylsilyloxymethyl-5-({[3-(trimethylsilyl)prop-2-ynyl]oxy}methyl)furan (15). To a stirred solution of alkyne **14** (2.00 g, 7.14 mmol) in THF (70 ml) was added dropwise 3.30 ml of *n*-BuLi (2.3 M/ hexanes, 7.49 mmol, 1.05 equiv) at −78 °C. The resulting yellow-green solution was stirred for 30 min at −78 °C and a solution of chlorotrimethylsilane (1.4 ml, 10.70 mmol, 1.5 equiv) in THF (1.5 ml) was added dropwise. The reaction mixture was kept at −78 °C for 90 min, allowed to warm slowly to room temperature and stirred for a further 1 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3×50 ml). The organic layer was washed with saturated aqueous NH_4Cl, brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 2% EtOAc in petroleum ether) afforded silyl **15** as a colorless oil (2.25 g, 90%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.30 (d, 1H, $J=3$ Hz), 6.19 (d, 1H, $J=3$ Hz), 4.63 (s, 2H), 4.52 (s, 2H), 4.17 (s, 2H), 0.91 (s, 9H), 0.20 (s, 9H). 0.10 (s, 6H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 155.0 (C), 150.4 (C), 110.8 (CH), 107.8 (CH), 101.1 (C), 92.9 (C), 63.1 (CH_2), 58.3 (CH_2), 57.5 (CH_2), 25.9 (CH_3), 18.4 (C), −0.2 (CH_3), −5.2 (CH_3). IR (NaCl plates) 2957–2930–2858 (C–H), 2175 (C≡C), 1251, 1080, 841. CI-MS *m/z* 370 (35), 295 (14); HRMS calcd for $C_{18}H_{36}NO_3Si_2$ ($[M+NH_4]^+$) 370.2234, found 370.2216.

4.2.7. 5-({[3-(Trimethylsilyl)prop-2-ynyl]oxy}methyl)-2-furan-methanol (17). To a stirred solution of silyl ether **15** (2.04 g, 5.78 mmol) in anhydrous MeOH (50 ml) at 0 °C was added 55 mg of *para*-toluenesulfonic acid monohydrate (0.289 mmol, 0.05 equiv). After complete reaction (1 h), the solvent was evaporated and the residue was taken up with EtOAc (60 ml) and washed with 10% aqueous solution of $NaHCO_3$. The aqueous layer was back extracted with EtOAc (3×20 ml) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% EtOAc in petroleum ether) afforded alcohol **17** as a pale yellow oil (1.28 g, 93%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.30 (d, 1H, $J=3$ Hz), 6.26 (d, 1H, $J=3$ Hz), 4.58 (s, 2H), 4.51 (s, 2H), 4.18 (s, 2H), 2.49 (br s, 1H, OH), 0.15 (s, 9H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 154.7 (C), 150.7 (C), 110.8 (CH), 108.3 (CH), 100.9 (C), 92.0 (C), 63.1 (CH_2), 57.6 (CH_2), 57.4 (CH_2), −0.2 (CH_3). IR (NaCl plates) 3399 (O–H), 2961–2857 (C–H) 2174 (C≡C), 1250, 1075, 844. CI-MS *m/z* 256 (19), 221 (27); HRMS calcd for $C_{12}H_{22}NO_3Si$ ($[M+NH_4]^+$) 256.1369, found 256.1373.

4.2.8. 6-Hydroxy-6-[(2-propynyloxy)methyl]-2*H*-pyran-3(6*H*)-one (18). To a stirred solution of alcohol **16** (1.01 g, 6.10 mmol) in CH_2Cl_2 (30 ml) at 0 °C was added in one portion $VO(acac)_2$ (170 mg, 0.6 mmol, 0.1 equiv). The solution became instantaneously green and 1.95 ml of *tert*-butylhydroperoxide (5–6 M/ nonane, 9.15 mmol, 1.5 equiv) was added dropwise. The dark-red solution was stirred for 1.5 h at 0 °C, then at room temperature until total consumption of the starting material (TLC: two successive elutions (EtOAc-PE 9:1 then 7:3). The final green solution was slowly filtered through a pad of celite and the filtrate concentrated in vacuo. The crude alcohol was directly subjected to a short flash chromatography (silica gel, 20% EtOAc in petroleum ether) to provide pure alcohol **18** as a white crystalline product (956 mg, 86%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.88 (d, 1H, $J=10.5$ Hz), 6.18 (d, 1H, $J=10.5$ Hz), 4.61 and 4.19 (m, 2H, *AB*-system, $J_{AB}=17$ Hz), 4.37 and 4.28 (m, 2H, *AB*-system, $J_{AB}=14$ Hz), 3.79 (br s, 1H, O–H), 3.72 (m, 2H, *AB*-system, $J_{AB}=10$ Hz), 2.21 (t, 1H, $J=2.5$ Hz). NMR ^{13}C (100 MHz, $CDCl_3$) δ 194.7 (C=O), 145.4 (CH), 133.5 (CH), 92.5 (C), 78.6 (C), 75.7 (CH), 73.4 (CH_2), 66.5 (CH_2), 59.1 (CH_2). IR (NaCl plates) 3390 (O–H), 3303, 2895 (C–H), 2110 (C≡C), 1692 (conjugated C=O). EI-MS *m/z* 181 (100); HRMS calcd for $C_9H_9O_4$ ($[M-H]^-$) 181.0501, found 181.0500.

4.2.9. 5-Oxo-2-[(2-propynyloxy)methyl]-5,6-dihydro-2*H*-pyran-2-yl-pyran-2-yl acetate (20). To a stirred solution of alcohol **18** (1.737 g, 9.53 mmol) in CH_2Cl_2 (60 ml) at 0 °C was added DMAP (60 mg, 0.48 mmol, 0.05 equiv) followed by the dropwise addition of pyridine (0.925 ml, 11.44 mmol, 1.2 equiv) and acetic anhydride (1.82 ml, 19.07 mmol, 2 equiv). The solution was stirred 30 min at 0 °C, then 6 h at room temperature. The resulting mixture was quenched by H_2O (10 ml) and extracted with CH_2Cl_2 (3×20 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification through short column chromatography (silica gel, 20% EtOAc in petroleum ether) afforded acetate **20** as a colorless oil (1.77 g, 83%). NMR ^1H (400 MHz, $CDCl_3$) δ 7.21 (d, 1H, $J=10.5$ Hz), 6.14 (d, 1H, $J=10.5$ Hz), 4.52 and 4.22 (m, 2H, *AB*-system, $J_{AB}=17$ Hz), 4.19 (d, 2H, $J=2.5$ Hz), 3.98 and 3.83 (m, 2H, *AB*-system, $J_{AB}=10.5$ Hz), 2.48 (t, 1H, $J=2.5$ Hz), 2.02 (s, 3H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 193.4 (C=O enone), 169.3 (C=O acetate), 145.3 (CH), 127.6 (CH), 98.1 (C), 78.7 (C), 75.5 (CH), 71.1 (CH_2), 67.8 (CH_2), 58.9 (CH_2), 21.2 (CH_3). IR (NaCl plates) 2930 (C–H), 2117 (C≡C), 1740 (C=O acetate), 1702 (conjugated C=O). CI-MS *m/z* 225 (14); HRMS calcd for $C_{11}H_{13}O_5$ ($[M+H]^+$) 225.0763, found 225.0768.

4.2.10. 3,11-Dioxatricyclo[5.3.1.0^{1,5}]undeca-5,9-dien-8-one (22). To a stirred solution of acetate **20** (1.8 g, 8.03 mmol) in toluene (80 ml) at 0 °C was added dropwise triethylamine (1.23 ml, 8.83 mmol, 1.1 equiv) and the resulting red solution was heated at reflux for 10 h. After cooling at room temperature, the solvent was removed and the residue was directly purified by flash chromatography (silica gel, 20% EtOAc in petroleum ether) to give cycloadduct **22** as a deliquescent yellow solid (1.13 g, 86%). NMR ^1H (400 MHz, $CDCl_3$) δ 7.41 (d, 1H, H_{10}, –C*H*=CH–CO, $J^{10-9}=9.5$ Hz), 6.10–6.05 (d, 1H, H_6, –CH=C<, $J^{6-7}=2.5$ Hz), 5.76 (dd, 1H, H_9,CH=C*H*–CO, $J^{9-7}=1.5$, $J^{9-10}=$

9.5 Hz), 5.29–5.24 (m, 1H, H_7, CO–C*H*–CH=C, $J^{7-9}=1.5$, $J^{7-6}=2.5$ Hz), 4.50 and 4.40 (m, 2H, *AB*-system, H_4, –O–CH_2–C=C, $J_{gem}=14$ Hz), 4.19–3.81 (m, 2H, *AB*-system, H_2, >C–CH_2–O–, $J_{gem}=9.5$ Hz). NMR ^{13}C (100 MHz, $CDCl_3$) δ 198.9 (C=O enone), 170.0 (C), 154.7 (CH), 121.8 (CH), 121.6 (CH), 96.2 (CH), 95.7 (C), 68.5 (CH_2), 67.1 (CH). IR (NaCl plates) 2937–2869 (C–H), 1694 (conjugated C=O). CI-MS *m/z* 182 (72), 164 (15); HRMS calcd for $C_9H_{12}NO_3$ ($[M+NH_4]^+$) 182.0817, found 182.0809.

4.2.11. 6-Hydroxy-6-({[3-(trimethylsilyl)prop-2-ynyl]oxy}-methyl)-2*H*-pyran-3(6*H*)-one (19). To a stirred solution of alcohol **17** (1.40 g, 5.87 mmol) in CH_2Cl_2 (50 ml) at 0 °C was added in one portion $VO(acac)_2$ (160 mg, 0.06 mmol, 0.1 equiv). The solution became instantaneously green and 1.77 ml of *tert*-butylhydroperoxide (5–6 M/nonane, 8.8 mmol, 1.5 equiv). was added dropwise. The dark-red solution was stirred for 30 min at 0 °C, then at room temperature until total consumption of the starting material (TLC: two successive elutions (EtOAc-PE 9:1 then 7:3)). The final green solution was slowly filtered through a pad of celite and the filtrate concentrated in vacuo. The crude alcohol was directly subjected to a short flash chromatography (silica gel, 20% EtOAc in petroleum ether) to provide pure alcohol **19** as a pale yellow oil (1.02 g, 68%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.88 (d, 1H, $J=10.5$ Hz), 6.18 (d, 1H, $J=10.5$ Hz), 4.63 and 4.19 (m, 2H, *AB*-system, $J_{AB}=17$ Hz), 4.40 and 4.28 (m, 2H, *AB*-system, $J_{AB}=14$ Hz), 3.70 (m, 2H, *AB*-system, $J_{AB}=10$ Hz), 3.59 (br s, 1H, O–H), 0.19 (s, 9H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 194.6 (C=O), 145.3 (CH), 128.5 (CH), 100.1 (C), 92.9 (C), 92.5 (C), 73.4 (CH_2), 66.5 (CH_2), 60.0 (CH_2), −0.3 (CH_3). IR (NaCl plates) 3402 (O–H), 2960–2290 (C–H), 2175 (C≡C), 1703 (conjugated C=O). EI-MS *m/z* 253 (62); HRMS calcd for $C_{12}H_{17}O_4Si$ ($[M-H]^-$) 253.0896, found 253.0896.

4.2.12. 5-Oxo-2-({[3-(trimethylsilyl)prop-2-ynyl]oxy}-methyl)-5,6-dihydro-2*H*-pyran-2-yl acetate (21). To a stirred solution of alcohol **19** (1.00 g, 3.94 mmol) in CH_2Cl_2 (40 ml) at 0 °C was added DMAP (25 mg, 0.2 mmol, 0.05 equiv) followed by the dropwise addition of triethylamine (0.6 ml, 4.32 mmol, 1.1 equiv) and acetic anhydride (0.45 ml, 4.7 mmol, 1.2 equiv). The solution was stirred 30 min at 0 °C, then 5 h at room temperature. The resulting mixture was quenched by saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3×20 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 10% EtOAc in petroleum ether) afforded acetate **21** as a colorless oil (912 mg, 78%). NMR ^1H (400 MHz, $CDCl_3$) δ 7.30 (d, 1H, $J=10.5$ Hz), 6.21 (d, 1H, $J=10.5$ Hz), 4.60 and 4.31 (m, 2H, *AB*-system, $J_{AB}=17$ Hz), 4.26 (s, 2H), 4.07 and 3.90 (m, 2H, *AB*-system, $J_{AB}=10.5$ Hz), 2.10 (s, 3H), 0.19 (s, 9H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 193.5 (C=O enone), 169.3 (C=O acetate), 144.4 (CH), 127.6 (CH), 100.3 (C), 98.3 (C), 92.5 (C), 71.1 (CH_2), 67.9 (CH_2), 59.8 (CH_2), 21.3 (CH_3), −0.3 (CH_3). IR (NaCl plates) 2960 (C–H), 2175 (C≡C), 1741 (C=O acetate), 1703 (conjugated C=O). EI-MS *m/z* 281 (30), 237 (1); HRMS calcd for $C_{12}H_{17}O_3Si$ ($[M-AcO]^+$) 237.0947, found 237.0956.

4.2.13. 3,11-Dioxa-6-trimethylsilyl-tricyclo[5.3.1.0^{1,5}]undeca-5,9-dien-8-one (24). To a stirred solution of acetate **21** (759 mg, 2.57 mmol) in CH_3CN (25 ml) at 0 °C was added dropwise triethylamine (0.38 ml, 2.70 mmol, 1.05 equiv) and the resulting red solution was heated at 80 °C for 6 h. After cooling at room temperature, EtOAc (30 ml) and water (10 ml) were added successively. The separated aqueous layer was extracted with EtOAc (3× 15 ml) and the combined organic extracts were washed with saturated aqueous NH_4Cl, brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 10% EtOAc in petroleum ether) afforded cycloadduct **24** as a white powder (522 mg, 86%). mp 52–53 °C. NMR ^1H (400 MHz, $CDCl_3$) δ 7.35 (d, 1H, H_{10}, C*H*=CH–CO, $J=9.5$ Hz), 5.71 (dd, 1H, H_9, CH=C*H*–CO, $J^{9-10}=9.5$, $J^{9-7}=1$ Hz), 5.31 (m, 1H, H_7), 4.42 (m, 2H, H_4, $J=15$ Hz), 4.08 and 3.75 (m, 2H, *AB*-system, H_2, $J_{gem}=9$ Hz), 0.12 (s, 9H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 193.1 (C=O), 168.6 (C), 152.4 (CH), 130.3 (C), 125.0 (CH), 101.7 (CH), 95.4 (C), 69.9 (CH_2), 63.4 (CH_2), −1.40 ((CH_3)$_3$). IR (NaCl plates) 2957–2870, 1700 (C=O), 1251. EI-MS *m/z* 236 (M^+, 50), 269 (M+Na, 100). CI-MS *m/z* 237 (98), 221 (73); HRMS calcd for $C_{12}H_{17}O_3Si$ ($[M+H]^+$) 237.0947, found 237.0938.

4.2.14. 3,11-Dioxatricyclo[5.3.1.0^{1,5}]undecan-8-one (25). To a stirred solution of compound **22** (100 mg, 0.61 mmol) in MeOH (10 ml), purged twice with argon, was added 5% palladium on carbon (120 mg, 10 mol%) and the system was purged twice with hydrogen. The solution was stirred at room temperature under hydrogen until complete reaction. The solution was filtered through celite, washed with MeOH and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% EtOAc in petroleum ether) afforded ketone **25** as a colorless oil (94 mg, 92%). NMR ^1H (500 MHz, $CDCl_3$) δ 4.48 (d, 1H, H_7, $J=7.5$ Hz), 4.06 and 3.59 (m, 2H, *AB*-system, $J_{gem}=10.5$ Hz), 4.05–3.98 (m, 1H, $H_{4\alpha}$), 3.72–3.65 (m, 1H, $H_{4\beta}$), 2.70 (m, 1H, $H_{5\alpha}$), 2.59–2.52 (m, 1H, $H_{9\beta}$), 2.49–2.40 (m, 1H, $H_{9\alpha}$), 2.37–2.29 (m, 1H, $H_{10\beta}$), 2.25–2.19 (m, 1H, $H_{2\beta}$), 2.05–1.98 (m, 1H, $H_{10\alpha}$). NMR ^{13}C (100 MHz, $CDCl_3$) δ 208.2 (C=O), 92.5 (C), 85.2 (CH), 75.2 (CH_2), 74.8 (CH_2), 46.9 (CH), 36.5 (CH_2), 33.5 (CH_2), 29.0 (CH_2). IR (NaCl plates) 2947–2868 (C–H), 1726 (C=O). CI-MS *m/z* 186 (2), 169 (2); HRMS calcd for $C_9H_{13}O_3$ ($[M+H]^+$) 169.0865, found 169.0861.

4.2.15. 3,11-Dioxatricyclo[5.3.1.0^{1,5}]undec-5-en-8-one (26). To a stirred solution of compound **22** (80 mg, 0.49 mmol) in THF (5 ml) at −78 °C was added dropwise 510 µl of L-selectride (1 M in THF, 0.51 mmol). The solution was stirred for 1 h at this temperature, quenched with water before it was allowed to warm to room temperature. The solution was diluted with EtOAc, successively washed with 10% aqueous NaOH and brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% EtOAc in petroleum ether) afforded ketone **26** as a colorless oil (70 mg, 86%). NMR ^1H (400 MHz, $CDCl_3$) δ 6.00–5.97 (m, 1H, H_6, $J=2$ Hz), 4.95–4.94 (m, 1H, H_7, $J=2$ Hz), 4.44 (m, 2H, *AB*-system, H_4, $J_{gem}=15$ Hz), 3.83 (m, 2H, *AB*-system, H_2, $J_{gem}=9.0$ Hz), 2.96–2.85 (m, 1H), 2.67–2.58 (m, 1H), 2.47–2.39 (m, 1H), 2.18–2.11 (m, 1H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 201.9 (C=O), 154.5 (C), 119.7 (CH), 95.5 (CH),

94.7 (C), 71.9 (CH_2), 63.2 (CH_2), 32.8 (CH_2), 26.8 (CH_2). IR (NaCl plates) 1710 (C=O). CI-MS *m/z* 184 (8), 150 (19); HRMS calcd for $C_9H_{14}NO_3$ ($[M+NH_4]^+$) 184.0974, found 184.0972.

4.2.16. 3,11-Dioxa-10β-*p*-tolylsulfonyl-tricyclo[5.3.1.0^{1,5}] undec-5-en-8-one (27). To a stirred solution of sodium *para*-toluenesulfinate monohydrate (45 mg, 0.25 mmol, 1.1 equiv) in THF/H_2O (1:2) at 0 °C was added dropwise acetic acid (15 μl, 0.25 mmol, 1.1 equiv). A solution of enone **22** (38 mg, 0.23 mmol) in THF (0.5 ml) was added at this temperature. The yellow solution was stirred for 5 h and quenched with H_2O and extracted with EtOAc (3×10 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was recrystallized in a little volume of EtOAc to give β-sulphoxy-ketone **27** as highly hygroscopic crystals (52 mg, 70%). NMR ^{1}H (400 MHz, $CDCl_3$) δ 7.80 and 7.36 (2d, 2× 2H, H_{tolyl}, $J=8.5$ Hz), 6.12–6.09 (m, 1H, H_6), 5.00 and 3.90 (2d, 2H, *AB*-system, H_2, $J_{gem}=10$ Hz), 4.88 (d, 1H, H_7, $J=2.0$ Hz), 4.50 and 4.36 (m, 2H, *AB*-system, H_4, $J_{gem}=14.5$ Hz, $J=2.0$ Hz), 3.87 (dd, 1H, $H_{10\alpha}$, C*H*–SO_2Tol, $J=2$ (*cis*), 8.5 Hz (*trans*)), 3.13–2.95 (m, 2H, H_9), 2.45 (s, 3H, CH_3). NMR ^{13}C (100 MHz, $CDCl_3$) δ 196.9 (C=O), 155.2 (C), 145.5 (C), 134.7 (C), 129.9 (2×CH), 129.4 (2×CH), 123.1 (CH), 95.8 (CH), 94.4 (C), 69.9 (CH_2), 62.8 (CH_2), 61.3 (*C*H–SO_2Tol), 34.5 (CH_2), 21.7 (CH_3). IR (NaCl plates) 2946–2873 (C–H), 1732 (C=O). EI-MS *m/z* 338 (90), 321 (8); HRMS calcd for $C_{16}H_{20}NO_5S$ ($[M+NH_4]^+$) 338.1062, found 338.1067.

4.2.17. 3,11-Dioxa-10β-hydroxytricyclo[5.3.1.0^{1,5}]undec-5-en-8-one (28). To a stirred solution of enone **22** (165 mg, 1 mmol, 1 equiv) in H_2O (8 ml) at 0 °C was added dropwise Et_3N (125 μl, 0.5 mmol, 0.9 equiv). The solution was stirred at room temperature for 2 h, until complete and slow dissolution of enone **22** in the aqueous mixture. The solution was extracted with $CHCl_3$ (3×10 ml). The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification through short column chromatography (silica gel, 50% EtOAc in petroleum ether) afforded β-hydroxy ketone **29** as a colorless oil (179 mg, 98%). Main diastereomer **29** (β-OH): NMR ^{1}H (400 MHz, $CDCl_3$) δ 6.01–5.99 (m, 1H, H_6), 5.07–5.04 (m, 1H, H_7), 4.48–4.39 (m, 2H, H_4), 4.23–3.71 (m, 2H, H_2, $J_{gem}=9$ Hz), 4.18 (dd, 1H, $H_{10\beta}$, CH–OH, $J=1.5$ (*cis*), 7 Hz (*trans*)), 3.31–2.64 (m, 2H, H_9), 3.05 (br s, 1H, O–H). NMR ^{13}C (100 MHz, $CDCl_3$) δ 200.7 (C=O), 154.0 (C), 120.9 (CH), 98.0 (C), 96.1 (CH), 68.5 (CH_2), 66.1 (CH–OH), 63.3 (CH_2), 43.5 (CH_2). IR (NaCl plates) 2945–2870 (C–H), 1730 (C=O). EI-MS *m/z* 181 (100), 163 (50); HRMS calcd for $C_9H_{11}O_4$ ($[M+H]^+$) 183.0657, found 183.0660.

4.2.18. 3,11-Dioxatricyclo[5.3.1.0^{1,5}]undecan-8,10-dione (29). To a stirred solution of compound **28** (165 mg, 0.91 mmol) in dry acetone (10 ml) at 0 °C was added dropwise a solution of Jones reagent until the red color persisted (3 h). At this time, *i*-PrOH was added in excess to reduce Cr(IV) and the resulting mixture was partitioned with water and CH_2Cl_2. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification through short column chromatography (silica gel, 50% EtOAc in petroleum ether) afforded diketone **29** as a colorless oil (124 mg, 76%). NMR ^{1}H (400 MHz, $CDCl_3$) δ 6.1–6.05 (m, 1H, H_6), 5.50 (d, 1H, H_7, $J=2.5$ Hz), 4.49 and 4.17 (m, 2H, *AB*-system, H_4, $J_{gem}=14$ Hz), 4.40 and 3.82 (m, 2H, *AB*-system, H_2, $J_{gem}=9.5$ Hz), 3.95 and 3.60 (m, 2H, *AB*-system, H_9, $J_{gem}=9.5$ Hz). NMR ^{13}C (100 MHz, $CDCl_3$) δ 198.2 and 196.3 (2×C=O), 153.05 (C), 121.6 (CH), 101.5 (C), 96.1 (CH), 66.3 (CH_2), 62.8 (CH_2), 53.0 (CH_2). IR (NaCl plates) 2960, 1720 and 1711 (C=O). EI-MS *m/z* 181 (1), 163 (3); HRMS calcd for $C_9H_9O_4$ ($[M+H]^+$) 181.0501, found 181.0505.

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Synthesis of the end-capped 5-(*N*,*N*-dimethylamino)naphthyl-1-ethynyl derivatives and their 1,4-di[5-(*N*,*N*-dimethylamino)naphthyl]-1,3-butadiynes: *anti* rotamer structure

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Abstract—A new family of the end-capped 5-(*N*,*N*-dimethylamino)naphthylethynyl chains were synthesized, as terminal acetylenes or poly(yne) structures, by heterocoupling between 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine and 2-methyl-3-butyn-2-ol or 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol, catalyzed by the palladium–copper system. Catalytic homocoupling of the terminal acetylenes, affords to 1,4-dinaphthyl-1,3-butadiyne nanostructures. X-ray diffraction analysis of 1,4-di(α-naphthyl)-1,3-butadiyne shows that the naphthalene rings are in the *anti* configuration along the acetylene axis. All the conjugated compounds show an important fluorescent emission radiation.

1. Introduction

Molecular electronics is currently a topic of considerable interest among a diverse community of scientists and engineers.[1] Many molecular structures have been synthesized for use as molecular devices, including switches, wires, controllers and gates.[2]

Interest in organic compounds for second- and third-order non-linear optical (NLO) applications has increased considerably.[3–7] Typical NLO chromophores studied are one-dimensional, conjugated π-systems with donor and acceptor moieties as terminal substituents.

Afterwards, π-conjugated oligomers and polymers have attracted increasing attention in recent years owing to their applications as light-emitting layers in organic light-emitting diodes (OLEDs).[8] Those materials offer the possibility of tuning both the characteristics of the emitted light and the efficiency of the devices by means of simple chemical modifications of their structures. The most commonly followed strategies for chemical modification consist of a) the introduction of lateral chains that can improve the solubility of the compounds and effect the conjugation of the system by steric hindrance,[9] b) the introduction of electron-withdrawing substituents which increase the electron affinity of the molecules[10] or c) the replacement of the phenylene ring by other aromatic structures.[11]

Naphthalene-containing conjugated oligomers and polymers are a unique class of electrically active materials.[12–15] In particular, conjugated polymers incorporating the naphthalene units through the 1,5-positions have shown electroluminescence properties.[15]

On the other hand, solid state polymerization of some 1,3-diynes to form crystalline conjugated poly(en-yne) structures has attracted much attention by the electronic and optical properties of the poly(1,3-diynes).[16]

The naphthalene conjugated system as the 1,4-diethynylnaphthalene unit has been designed in binaphthyl-based oligomers,[17] as spacer-phenylene or diporphyrins connector, and applied for studies of intramolecular energy transfer.[18,19] However, the 1,5-diethynylnaphthalene unit has been used less, although it has been integrated in di- and trinuclear alkyne-rhodium(I) complexes.[20]

The synthesis and the structure analysis of the novel rigid conjugated nanostructures based on 1,5-diethynylnaphthalene units are now reported.

Keywords: 1,4-Di[5-(*N*,*N*-dimethylamino)naphthyl]-1,3-butadiynes; X-ray structure; Sonogashira reaction; Fluorescence.
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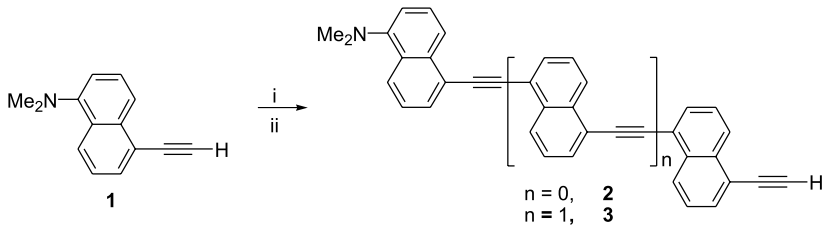
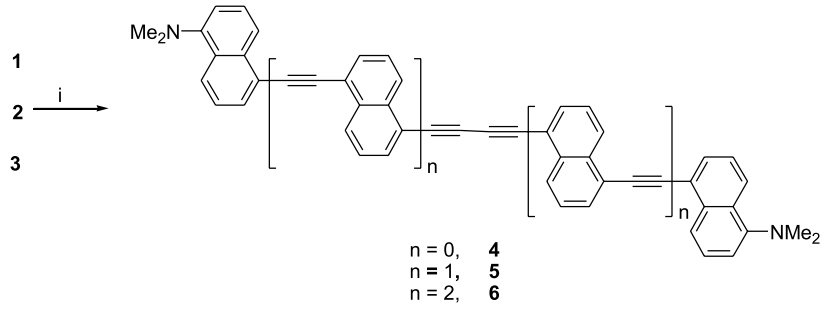


Scheme 1. (i) 4-(5-Iodo-1-naphthyl)-2-methyl-3-butyn-2-ol, $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3, (ii) NaOH, toluene, reflux.



Scheme 2. (i) Cu_2Cl_2, pyridine, at 40 °C, oxygen atmosphere.

2. Results and discussion

The syntheses of the terminal naphthylacetylenes (**1**–**3**) was carried out by the heterocoupling between 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine[21] and 2-methyl-3-butyn-2-ol or 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol,[22] in presence of dichloro bis(triphenylphosphine)palladium and cuprous iodide system, in triethylamine,[23] Scheme 1.

To increase the conjugation of the terminal acetylenes the 1,4-dinaphthyl-1,3-butadiynes were prepared. Synthesis of the 1,3-butadiynes (**4**, **5** and **6**) were carried out by oxidative dimerization of the corresponding 5-(*N*,*N*-dimethylamino)-naphthylethynyl derivatives **1**–**3** respectively under adapted Glaser conditions, using cuprous chloride as the catalyst under oxygen atmosphere in dry pyridine at 40 °C, in practically quantitative yield: Compound **4** was isolated as a dark-amber solid; Compound **5** was isolated as an orange solid; Compound **6** was isolated as a dark-yellow solid in more modest yield (65%), Scheme 2.

Structure of the naphthylethynyl units along the conjugated polyacetylene chain in the 1,3-butadiyne networks, was analyzed for 1,4-di(α-naphthyl)-1,3-butadiyne (**7**). This compound was obtained by homocoupling of α-naphthylacetylene, catalyzed by cuprous chloride, in pyridine under oxygen atmosphere, giving a yellow solid, in practically quantitative yield. Prismatic crystals adequate for X-ray diffraction analysis were selected.

The X-ray molecular structure of the compound and the numbering scheme are shown in Figure 1.[24] Although there is no sterical H8-H22 hydrogen–hydrogen repulsion, due to the large distance, it is noticeable that the molecule adopts the centre symmetric *anti* configuration of the naphthalene rings around the 1,3-diyne axis.

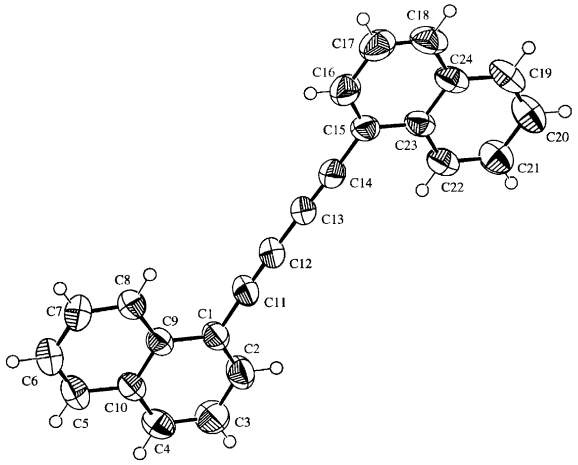


Figure 1. X-ray molecular structure of 1,4-di(α-naphthyl)-1,3-butadiyne (**7**).

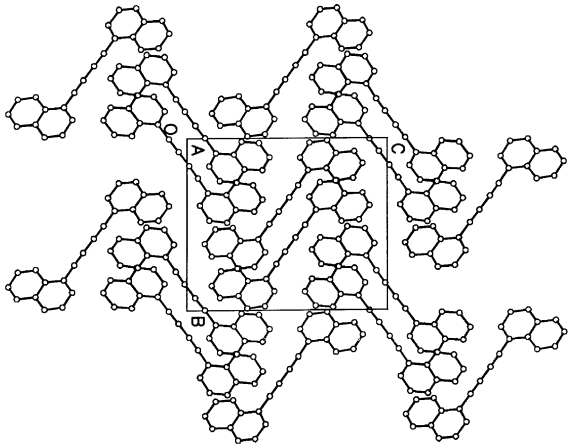


Figure 2. View of the molecular packing of the molecules of 1,4-di(α-naphthyl)-1,3-butadiyne (**7**).

Table 1. UV–visible and fluorescence spectra of terminal acetylenes **1–3** and 1,3-butadiynes **4–6**

Compound	UV/vis[a] λ_{max} (nm)	ε (M^{-1} cm^{-1})	F[b] λ_{max} (nm)	Φ_f
1	336	2200	463	0.63[c]
2	343	23,100	397	0.55[d]
3	363	26,600	398 and 414	0.65[d]
4	378	17,700	526	0.18[c]
5	377	55,300	533	0.10[c]
6	366	62,800	526	0.18[c]

[a] At room temperature in dichloromethane.
[b] $\lambda_{exc}=365$ nm, at room temperature in dichloromethane and $[c]\cong 10^{-8}$ M.
[c] Fluorescence quantum yield was in dichloromethane relative to 2-aminopyridine in 0.1 N H_2SO_4.
[d] Fluorescence quantum yield in dichloromethane relative to quinine sulfate in 1 N H_2SO_4.

The distances in the structure range from 1.344 (4) to 1.438 (3) Å (naphthalene rings 1.362–1.426 Å).[25] The naphthalene rings are rather planar (maximum deviations −0.010(2) Å for C5 and 0.036(3) Å for C16 atoms); both naphthalenes form a dihedral angle of 3.25(4)°, so the whole molecule may be considered as planar. The packing presents a typical segregation pattern of slabs parallel to the *a*,*b* plane, alternating those formed by the naphthalene rings (at 1/4, 3/4 along *c*-axis) and those of the butadiyne links (at 0, 1/2 along *c*-axis), Figure 2.

The terminal acetylenes **1–3**, exhibit fluorescence emission radiation which for **1** and **2** consists of one broad band, while **3** shows two broad bands. Compound **1** shows a large anomalous Stokes shift and a considerable quantum yield value,[26] while compounds **2** and **3** show a normal Stokes shift, Table 1 and Figures 3–4.

However, the 1,3-butadiyne derivatives **4–6** show fluorescence emission but with lowest quantum yield than the corresponding terminal acetylene, Table 1 and Figures 5–6. Thus, compounds **4** and **6** show identical quantum yield value, while compound **5** shows an appreciable decreasing. However, it is remarkable in the 1,3-butadiynes **4–6** the large Stokes shift of the fluorescence emission and a decreasing of the quantum yields, which can be explained

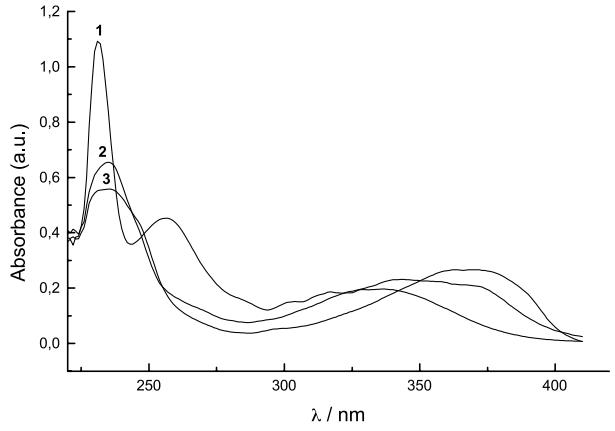


Figure 3. UV–visible absorption spectra for the compounds **1–3** in CH_2Cl_2 at room temperature and $[c]=10^{-5}$ M.

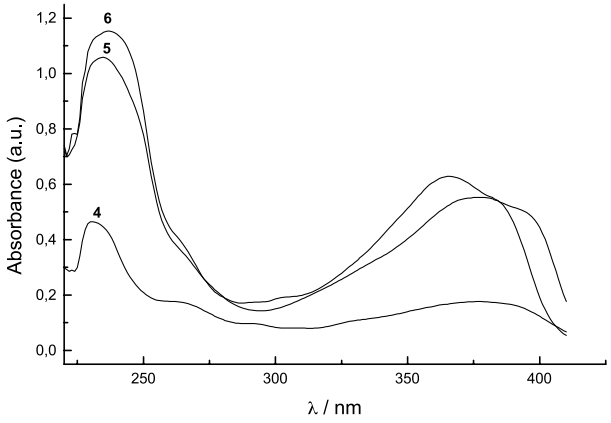


Figure 5. UV–visible absorption spectra for the compounds **4–6** in CH_2Cl_2 at room temperature and $[c]=10^{-5}$ M.

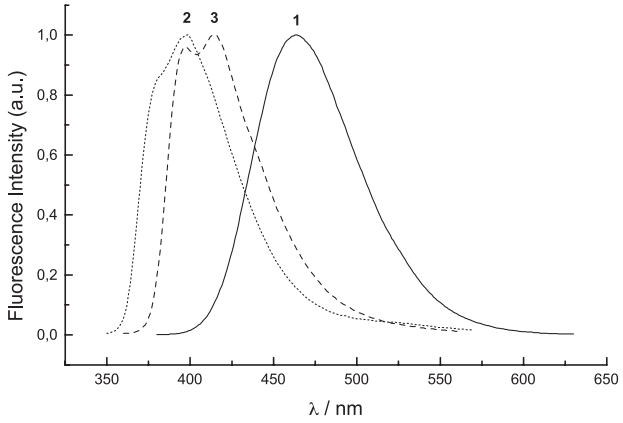


Figure 4. Normalized emission spectra for the compounds **1–3** in CH_2Cl_2 at room temperature.

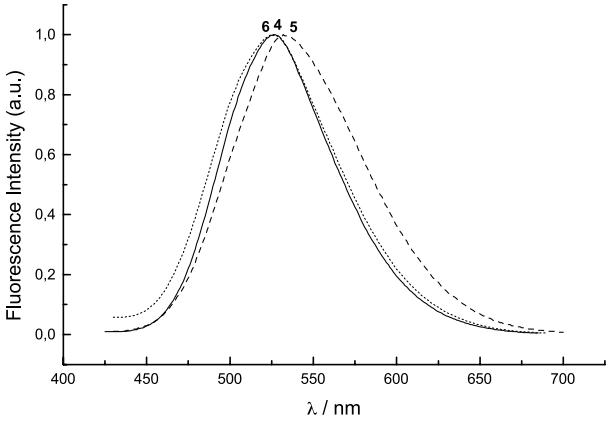
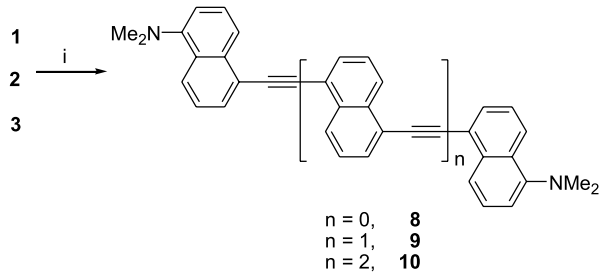
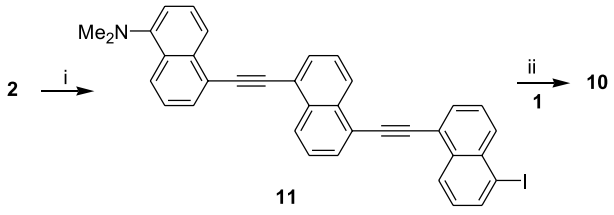


Figure 6. Normalized emission spectra for the compounds **4–6** in CH_2Cl_2 at room temperature.



Scheme 3. (i) 5-Iodo-*N*,*N*-dimethylnaphthalen-1-amine, $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3.



Scheme 4. (i) 1,5-Diiodonaphthalene, $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3, (ii) $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3.

by an intramolecular charge transfer (ICT) or twisted ICT (TICT) interactions due to the presence of the *N*,*N*-dimethylamino group.[27]

The doubly end-capped *N*,*N*-dimethylnaphthyl symmetrical units **8**–**10**, were obtained by the heterocoupling between the adequate terminal acetylene **1**–**3** and 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine, in the presence of the palladium–copper catalyst system, Scheme 3. Thus, **8** was obtained by the heterocoupling between the terminal acetylene **1** and 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine, under a carbon dioxide atmosphere, to avoid the homocoupling reaction.[21] Compound **8** was isolated as a dark-amber solid in excellent yield (95%). Compound **9** was obtained by heterocoupling between the acetylene **2** and 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine, under an argon atmosphere, as a yellow solid in good yield (87%). However, the heterocoupling between the terminal acetylene **3** and 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine provides **10** as a yellow solid in very low yield (6%), which can be due to the size of the terminal acetylene **3**, which confers low solubility and mobility, avoiding the incorporation of the acetylene on the palladium complex coordination sphere, following the Sonogashira mechanism.[28]

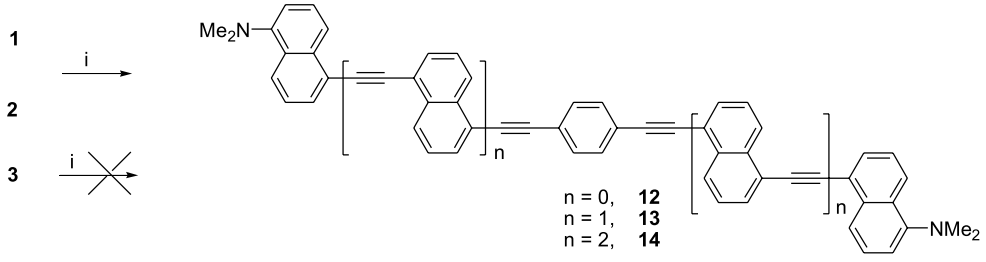
A retrosynthetic alternative for **10** changing the terminal acetylene and the iodoarene sizes, was developed, Scheme 4. Thus, compound **10** was obtained by the heterocoupling between the terminal acetylene **1** and the iodoarene **11**, under a carbon dioxide atmosphere to avoid the homocoupling reaction. Thus, compound **10** was isolated as a yellow solid in good yield (76%), Scheme 4. Compound **11** was prepared by heterocoupling between the terminal acetylene **2** and 1,5-diiodonaphthalene, in presence of the palladium–copper system, as an orange solid in good yield (80%).

The doubly symmetrical end-capped *N*,*N*-dimethylaminonaphthyl derivatives **8**–**10** show fluorescence emission radiation, which wavelength and quantum yield are summarized in Table 2. The large anomalous Stoke shift and the quantum yield decreasing with the separation distance of the end-capped *N*,*N*-dimethylamino groups would be interpreted by a (TIC or TICT) mechanism. It has been reported that some donor–acceptor substituted naphthalenes show a large anomalous Stokes shifts and a decreasing in quantum yield.[27] Hence, the *N*,*N*-dimethylaminonaphthyl conjugated structures show a broad fluorescence band which contains strongly overlapping of locally excited (LE) and dynamics of intramolecular charge transfer interaction (ICT) emission bands,[27] which agrees well with the large anomalous Stokes shifts observed.

Table 2. UV–visible and fluorescence spectra of the end-capped *N*,*N*-dimethylamino **8**–**10** and **12**–**14**

Compound	UV/vis[a] λ_{max} (nm)	ε (M^{-1} cm^{-1})	F[b] λ_{max} (nm)	Φ_f[c]
8	363	17,900	504	0.32
9	373	33,000	525	0.21
10	375	29,700	527	0.13
12	369	36,200	524	0.30
13	375	60,300	528	0.15
14	371	87,500	529	0.08

[a] At room temperature in dichloromethane.
[b] $\lambda_{exc}=365$ nm, at room temperature in dichloromethane and $[c]\cong 10^{-8}$ M.
[c] Fluorescence quantum yield in dichloromethane relative to quinine sulfate in 1 N H_2SO_4.



Scheme 5. (i) 1,4-Diiodobenzene, $Cl_2Pd(PPh_3)_2$, Cu_2I_2, NEt_3.

To improve the fluorescent properties of the naphthylethynyl derivatives **8–10**, a conjugated phenylethynyl spacer was introduced in the sequence of the naphthylethynyl chains.

Compounds **12–14**, containing a 1,4-phenylethynyl unit in the middle of the chain, has been obtained by heterocoupling between the terminal acetylene derivatives **1–3** and 1,4-diiodobenzene, catalyzed by the palladium–copper system, Scheme 5. Thus, 1,4-di[(5-{*N*,*N*-dimethylamino}-1-naphthyl)ethynyl]benzene (**12**) was prepared by the heterocoupling reaction between **1** and 1,4-diiodobenzene, under a carbon dioxide atmosphere to avoid the homocoupling reaction,[21] catalyzed by the palladium–copper system, as yellow solid in good yield (90%); compound **13** was obtained by heterocoupling between **2** and 1,4-diiodobenzene, under argon atmosphere, as yellow solid in good yield (81%). However, the heterocoupling between the terminal acetylene **3** and 1,4-diiodobenzene to obtain the poly(yne) **14** fails, under the same conditions of preparation of **13**, or under more drastic conditions, using pyridine or quinoline, at the reflux temperature. The inactivity of the acetylene **3** would be due to its molecular size, which confers low solubility and mobility, necessary for the acetylene coordination to the palladium complex sphere,[28] Scheme 5.

A retrosynthetic alternative for the preparation of **14** by heterocoupling reaction was developed, changing the terminal acetylene and the iodoarene sizes. Thus, by heterocoupling between 1,4-diethynylbenzene and the iodoarene **11** in pyridine, catalyzed by the palladium–copper system, was obtained **14** as yellow solid in moderate-good yield (58%).

The doubly end-capped *N*,*N*-dimethylaminonaphthyl derivatives **8–10** and these with the phenylethynyl spacer **12–14**, show fluorescence emission radiation, Table 2 and Figures 7–10. Both families of compounds show a large Stokes shift and the quantum yield decreasing with the separation distance between the end-capped *N*,*N*-dimethylamino groups. The quantum yield of **12–14** slightly diminishes with respect to their naphthylethynyl parents **8–10**.

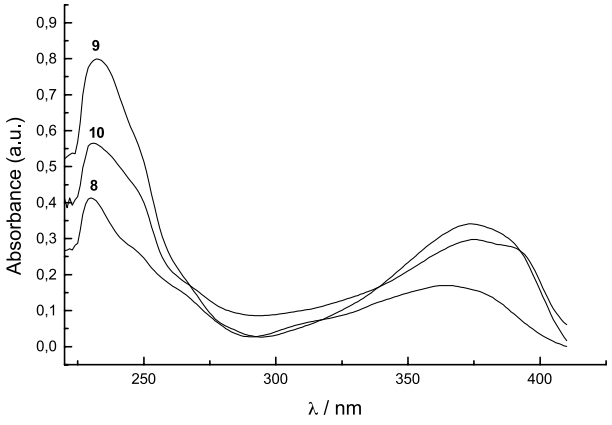


Figure 7. UV–visible absorption spectra for the compounds **8–10** in CH_2Cl_2 at room temperature and $[c]=10^{-5}$ M

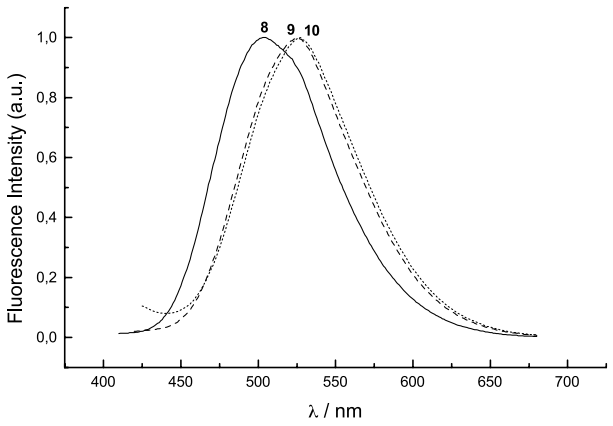


Fig. 8. Normalized emission spectra for the compounds **8–10** in CH_2Cl_2 at room temperature.

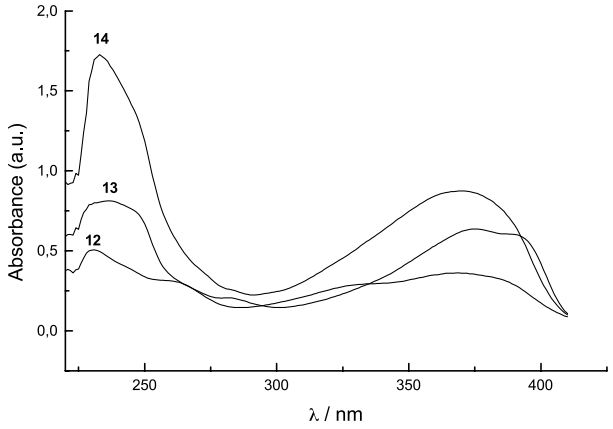


Fig. 9. UV–visible absorption spectra for the compounds **12–14** in CH_2Cl_2 at room temperature and $[c]=10^{-5}$ M.

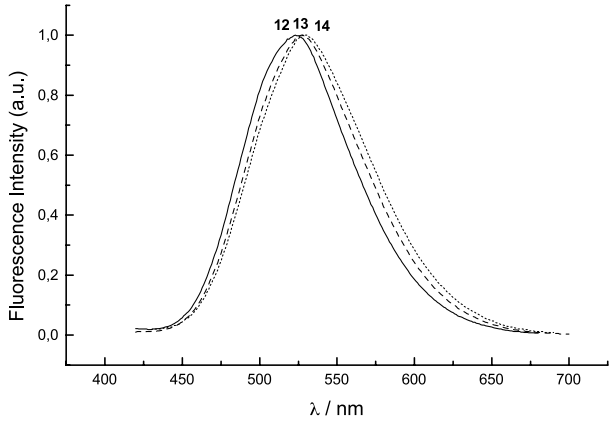


Fig. 10. Normalized emission spectra for the compounds **12–14** in CH_2Cl_2 at room temperature.

The UV–vis and fluorescence emission spectra obtained for the naphthylethynyl chains are relevant because they can be applied to the analyses of large oligomers or polymers obtained from the 1,5-naphthyl difunctional units.

3. Conclusions

End-capped 5-(*N*,*N*-dimethylamino)naphthylethynyl chains **1**–**3** and double end-capped 1,5-(*N*,*N*-dimethylamino)-naphthylethynyl **8**–**10** can be efficiently synthesized, by heterocoupling between 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine and 2-methyl-3-butyn-2-ol or 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol, catalyzed by the palladium–copper system, followed of catalytic treatment with powdered sodium hydroxide. A new family of the end-capped 1,4-dinaphthyl-1,3-butadiyne nanostructures **4**–**6** were efficiently obtained by homocoupling of the terminal acetylenes, catalyzed by cuprous chloride in pyridine. The *anti* configuration structure of the naphthalene rings along the molecular acetylene axis has been observed by X-ray diffraction analysis of 1,4-di(α-naphthyl)-1,3-butadiyne. The heterocoupling reaction fails for long terminal acetylene chains **3** by low solubility or low mobility of the molecule. All the conjugated compounds show an important fluorescent emission radiation with large anomalous Stokes shift due to a ICT or TICT effect.

4. Experimental

4.1. General

Melting points were determined in open capillaries using a Buchi or Reichert hot stage microscope and are uncorrected. IR spectra of solids were recorded as KBr pellets and IR spectra of oils were recorded as thin films on NaCl plates with a Bruker Vector 22 spectrophotometer, and the wave numbers are given in cm^{-1}. ^1H NMR spectra and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker Aspect spectrometer. Chemical shifts are given in δ with TMS as an internal reference and constants coupling J are given in Hz, the solvent is $CDCl_3$. Mass spectra were recorded on a VG AutoSpec spectrometer at 70 eV. The UV–vis spectra were recorded on a Hewlett Packard 8453 spectrometer, frequencies are given in nm and ε in L mol^{-1} cm^{-1}. All fluorescence spectra were recorded at room temperature at 10^{-8} M on a SLM Aminco Bowman series 2, the fluorescence quantum yield was determined in dichloromethane on freshly prepared samples (air-equilibrated) with absorbances at the excitation wavelength (365 nm for the standard quinine sulfate). The samples quinine sulfate in 1 N H_2SO_4 and 2-aminopyridine in 0.1 N H_2SO_4 were employed as a standard ($\Phi_f=0.55$ and $\Phi_f=0.66$ respectively) to measure the fluorescence quantum yields, which were corrected taking into account the refractive indices of the solvents used. Yields are given after chromatography column separation on silica gel 60 (200–400 mesh) using the indicated solvents or solvent crystallization.

4.1.1. 5-Ethynyl-*N*,*N*-dimethylnaphthalen-1-amine (1).

4.1.1.1. 4-[5-(*N*,*N*-Dimethylamino)-1-naphthyl]-2-methyl-3-butyn-2-ol (1a). General procedure for the cross-coupling reaction. To a solution of 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine (1 g, 3.4 mmol) and 2-methyl-3-butyn-2-ol (314 mg, 3.74 mmol) in freshly distilled diethylamine (or triethylamine) (40 mL), under argon atmosphere and at room temperature, was added dichloro bis(triphenylphosphine)palladium (24 mg, 0.034 mmol) and copper iodide (0.5 mg, 0.003 mmol). The mixture was stirred for 15 h (monitored by TLC) and then, the amine was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution with a little amount of KCN, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration, the solvent was removed to give a brown solid, which was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (3:1). Compound **1a** was isolated as a dark amber oil, 840 mg (98%) yield. IR (film, cm^{-1}): 3398, 2220, 1409, 1165, 791. ^1H NMR ($CDCl_3$): δ 8.24 (d, 1H, $J=8.7$ Hz), 7.99 (d, 1H, $J=8.7$ Hz), 7.63 (d, 1H, $J=6.9$ Hz), 7.47 (t, 1H, $J=8.1$ Hz), 7.41 (dd, 1H, $J=6.9$, 8.7 Hz), 7.11 (d, 1H, $J=7.8$ Hz), 2.89 (s, 6H), 1.73 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.24, 134.64, 130.32, 128.58, 126.61, 125.01, 124.28, 120.75, 120.52, 114.49, 98.48, 80.69, 65.85, 45.29, 31.64. $C_{17}H_{19}NO$ (253.34): Anal. Calcd: C 80.60, H 7.56, N 5.53. Found: C 80.74, H 7.44, N 5.68.

4.1.1.2. 5-Ethynyl-*N*,*N*-dimethylnaphthalen-1-amine (1). General procedure for arylacetylenes. To a solution of **1a** (700 mg, 2.8 mmol) in anhydrous toluene (40 mL) was added finely powdered sodium hydroxide (12 mg, 0.28 mmol), under argon atmosphere, and the mixture was warmed at the reflux temperature for 10 h (monitored by TLC), and then filtered. The solvent was removed at reduced pressure and the solid residue was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:2) giving **1** as a dark amber solid, mp 50–51 °C, 545 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 229 (ε, 12,300), 254 (ε, 4800), 336 (ε, 2200). Fluorescence (CH_2Cl_2), λ_{max} (nm): 463 ($\phi=0.63$). IR (KBr, cm^{-1}): 3299, 2294, 1402, 791. ^1H NMR ($CDCl_3$): δ 8.46 (d, 1H, $J=9.0$ Hz), 8.31 (d, 1H, $J=8.4$ Hz), 7.93 (d, 1H, $J=7.2$ Hz), 7.64 (t, 1H, $J=7.8$ Hz), 7.56 (dd, 1H, $J=9.0$, 7.2 Hz), 7.21 (d, 1H, $J=7.5$ Hz), 3.65 (s, 1H), 2.89 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.15, 134.81, 131.05, 128.44, 126.77, 125.44, 124.10, 120.63, 119.92, 114.50, 82.21, 81.82, 45.06. COSY ($^1H/^1H$): 8.46/7.56/7.93, 8.31/7.64/7.21. HETCORR ($^{13}C/^1H$): 131.05/7.93, 126.77/7.64, 125.44/8.46, 124.10/7.56, 120.63/8.31, 114.50/7.21. MS (70 eV): 195 (M^+, 100), 194 (43), 179 (7), 165 (3), 152 (31). $C_{14}H_{13}N$ (195.26): Anal. Calcd: C 86.12, H 6.71, N 7.17. Found: C 85.92, H 6.86, N 7.02.

4.1.2. 5-[(5-Ethynyl-1-naphthyl)ethynyl]-*N*,*N*-dimethylnaphthalen-1-amine (2).

4.1.2.1. 4-(5-{[5-(*N*,*N*-Dimethylamino)-1-naphthyl]-ethynyl}-1-naphthyl)-2-methyl-3-butyn-2-ol (2a). General procedure for the cross-coupling reaction in CO_2 atmosphere. A dispersion of the components in dry triethylamine was placed in a Schlenk: compound **1** (100 mg, 0.51 mmol), 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol (171 mg, 0.51 mmol), triethylamine (30 mL), dichloro bis(triphenylphosphine)palladium (36 mg, 0.051 mmol) and copper iodide (1 mg, 0.0051 mmol). Then, carbonic dry-ice rods were added and maintained in slow sublimation until a white dense cloud was formed. The carbonic anhydride atmosphere was slowly displaced with an external stream of carbonic anhydride, bubbled through the dry triethylamine solution. The mixture was stirred at

room temperature for 15 h (monitored by TLC) and then, the amine was removed under reduced pressure. The crude residue was washed with a saturated aqueous ammonium chloride solution with a little amount of KCN, and extracted with dichloromethane. The extracts were dried on anhydrous sodium sulfate and after filtration, the solvent was removed to give a brown solid, which was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (2:1). Compound **2a** was isolated as a pale yellow solid, mp 120–121 °C, 180 mg (87%) yield. IR (KBr, cm^{-1}): 3280, 2224, 1418, 1152, 782. ^1H NMR ($CDCl_3$): δ 8.57 (d, 1H, $J=8.4$ Hz), 8.34 (d, 1H, $J=7.5$ Hz), 8.32 (d, 1H, $J=7.8$ Hz), 8.26 (d, 1H, $J=8.7$ Hz), 7.92 (d, 1H, $J=6.9$ Hz), 7.88 (d, 1H, $J=7.5$ Hz), 7.72 (d, 1H, $J=7.2$ Hz), 7.62–7.49 (m, 4H), 7.16 (d, 1H, $J=7.5$ Hz), 2.93 (s, 6H), 1.76 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.41, 134.65, 133.18, 133.07, 130.99 (2C), 130.61, 128.75, 127.15, 126.87, 126.80, 126.19, 126.09, 125.30, 124.50, 121.67, 121.09, 120.99, 120.82, 114.65, 99.19, 93.37, 91.90, 80.10, 65.76, 45.34, 31.50. $C_{29}H_{25}NO$ (403.52): Anal. Calcd: C 86.32, H 6.24, N 3.47. Found: C 86.49, H 6.34, N 3.56.

4.1.2.2. 5-[(5-Ethynyl-1-naphthyl)ethynyl]-*N*,*N*-dimethylnaphthalen-1-amine (2). Following the general method used for the synthesis of **1**, a mixture of compound **2a** (100 mg, 0.25 mmol), anhydrous toluene (50 mL), and finely powdered sodium hydroxide (1 mg, 0.03 mmol) was stirred for 5 h and then filtered. The residual solid was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:1) giving **2** as a yellow solid, mp 145–147 °C, 86 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 235 (ε, 65,500), 343 (ε, 23,100). Fluorescence (CH_2Cl_2), λ_{max} (nm): 397 ($\phi=0.55$). IR (KBr, cm^{-1}): 3293, 2188, 2099, 1402, 787. ^1H NMR ($CDCl_3$): δ 8.61 (d, 1H, $J=8.4$ Hz), 8.42 (d, 1H, $J=8.4$ Hz), 8.32 (d, 1H, $J=8.7$ Hz), 8.26 (d, 1H, $J=8.1$ Hz), 7.93 (d, 1H, $J=6.9$ Hz), 7.88 (d, 1H, $J=7.5$ Hz), 7.82 (d, 1H, $J=7.5$ Hz), 7.64–7.49 (m, 4H), 7.17 (d, 1H, $J=7.8$ Hz), 3.52 (s, 1H), 2.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.40, 134.65, 133.43, 133.01, 131.80, 131.05, 130.61, 128.79, 127.68, 126.88, 126.82, 126.37, 126.03, 125.34, 124.49, 121.69, 121.07, 120.95, 120.26, 114.66, 93.43, 91.78, 82.39, 81.56, 45.36. HMQC ($^1H/^{13}C$): 8.61/127.68, 8.42/126.82, 8.32/125.34, 8.26/120.95, 7.93/131.05, 7.88/130.61, 7.82/131.80, 7.61/126.37, 7.58/126.03, 7.56/126.88, 7.52/124.49, 7.17/114.66. COSY ($^1H/^1H$): 8.61/7.58/7.82, 8.42/7.61/7.93, 8.32/7.52/7.88, 8.26/7.56/7.17. MS (70 eV): 345 (M^+, 100), 344 (19), 328 (10), 300 (21), 172 (12), 150 (18). $C_{26}H_{19}N$ (345.44): Anal. Calcd: C 90.40, H 5.54, N 4.05. Found: C 90.48, H 5.28, N 4.89.

4.1.3. 5-({5-[(5-Ethynyl-1-naphthyl)ethynyl]-1-naphthyl}-ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (3).

4.1.3.1. 4-{5-[(5-{[5-(*N*,*N*-Dimethylamino)-1-naphthyl]-ethynyl}-1-naphthyl)ethynyl]-1-naphtyl}-2-methyl-3-butyn-2-ol (3a). Following the general method used for the synthesis of **1a**, a mixture of dichloro bis(triphenylphosphine)palladium (173 mg, 0.25 mmol), copper iodide (5 mg, 0.025 mmol), compound **2** (850 mg, 2.46 mmol), 4-(5-iodo-1-naphthyl)-2-methyl-3-butyn-2-ol (826 mg, 2.46 mmol), and triethylamine (200 mL) was stirred for 20 h. A flash chromatography on silica gel, eluting with hexane/ethyl acetate (2:1) giving **3a** as an orange solid, mp 238–240 °C, 1.2 g (88%) yield. IR (KBr, cm^{-1}): 3287, 2274, 2217, 1421, 1151, 780. ^1H NMR ($CDCl_3$): δ 8.65 (d, 1H, $J=8.1$ Hz), 8.61 (d, 1H, $J=7.8$ Hz), 8.58 (d, 1H, $J=8.4$ Hz), 8.38 (d, 1H, $J=8.4$ Hz), 8.34 (d, 1H, $J=8.4$ Hz), 8.29 (d, 1H, $J=7.8$ Hz), 7.97 (d, 2H, $J=6.3$ Hz), 7.96 (d, 1H, $J=6.6$ Hz), 7.91 (d, 1H, $J=7.2$ Hz), 7.76 (d, 1H, $J=7.5$ Hz), 7.70–7.51 (m, 6H), 7.19 (d, 1H, $J=6.9$ Hz), 2.96 (s, 6H), 1.77 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.49, 134.73, 133.24 (3C), 133.07, 131.23, 131.19, 131.12, 131.07, 130.66, 128.56, 127.45 (2C), 127.09 (2C), 126.92, 126.41, 126.31 (2C), 126.22, 125.39, 124.52, 121.86, 121.45 (2C), 121.15, 121.00, 120.95, 114.70, 99.28, 93.51, 92.67, 92.59, 91.90, 80.10, 65.94, 45.39, 31.68. $C_{41}H_{31}NO$ (553.70): Anal. Calcd: C 88.94, H 5.64, N 2.53. Found: C 89.02, H 5.50, N 2.78.

4.1.3.2. 5-({5-[(5-Ethynyl-1-naphthyl)ethynyl]-1-naphthyl}ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (3). Following the general method used for the synthesis of **1**, a mixture of compound **3a** (200 mg, 0.36 mmol), anhydrous toluene (40 mL), and finely powdered sodium hydroxide (1.4 mg, 0.036 mmol) was stirred for 10 h and then filtered. The residual solid was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:3) giving **3** as a pale orange solid, mp 210–211 °C, 177 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 235 (ε, 55,800), 363 (ε, 26,600). Fluorescence (CH_2Cl_2), λ_{max} (nm): 398, 414 ($\phi=0.65$). IR (KBr, cm^{-1}): 3293, 2219, 2083, 1420, 790. ^1H NMR ($CDCl_3$): δ 8.63 (d, 1H, $J=8.4$ Hz), 8.60 (d, 1H, $J=8.4$ Hz), 8.59 (d, 1H, $J=8.4$ Hz), 8.44 (d, 1H, $J=8.4$ Hz), 8.33 (d, 1H, $J=8.7$ Hz), 8.27 (d, 1H, $J=8.4$ Hz), 7.96 (d, 2H, $J=7.2$ Hz), 7.95 (d, 1H, $J=7.2$ Hz), 7.89 (d, 1H, $J=7.5$ Hz), 7.83 (d, 1H, $J=7.2$ Hz), 7.68–7.50 (m, 6H), 7.18 (d, 1H, $J=7.5$ Hz), 3.53 (s, 1H), 2.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.57, 134.74, 133.52, 133.22 (2C), 133.04, 131.90, 131.25 (2C), 131.17, 130.70, 128.82, 127.63, 127.49, 127.10, 127.05, 126.93, 126.44 (2C), 126.32, 126.18, 125.36, 124.56, 121.89, 121.50, 121.44, 121.16, 121.07, 120.42, 114.74, 93.53, 92.75, 92.53, 91.93, 82.47, 81.60, 45.42. MS (70 eV): 495 (M^+, 100), 494 (9), 441 (15), 316 (12), 277 (7), 247 (22). $C_{38}H_{25}N$ (495.62): Anal. Calcd: C 92.09, H 5.08, N 2.83. Found: C 91.02, H 5.34, N 2.78.

4.1.4. 1,4-Di(5-{*N*,*N*-dimethylamino}-1-naphthyl)buta-1,3-diyne (4) by homocoupling reaction of arylacetylene. General procedure. To a solution of cuprous chloride (11 mg, 0.052 mmol) in dry pyridine (50 mL), under oxygen atmosphere at 40 °C, was added a solution of the arylacetylene **1** (200 mg, 1.03 mmol) in dry pyridine (10 mL) and stirred for 6h. After, solvent was removed, to give a residual solid that was washed with ammonium hydroxide, till the blue color disappears, and then extracted with dichloromethane. The organic layer was dried on anhydrous magnesium sulfate and after filtration and solvent evaporation was obtained a brown solid, that was purified by silica gel column chromatography, eluting with hexane/dichloromethane (1:1) giving **4** as a dark amber solid, mp 176–178 °C, 194 mg (100%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 231 (ε, 46,500), 259s (ε, 18,400), 291s (ε, 10,100), 378 (ε, 17,700). Fluorescence (CH_2Cl_2), λ_{max} (nm): 526 ($\phi=0.18$). IR (KBr, cm^{-1}): 2134, 1402, 785. ^1H NMR ($CDCl_3$): δ 8.32 (d, 2H, $J=8.4$ Hz), 8.15 (d, 2H, $J=8.4$ Hz), 7.83 (d, 2H, $J=6.9$ Hz), 7.55 (t, 2H,

J=7.7 Hz), 7.47 (t, 2H, J=8.0 Hz), 7.15 (d, 2H, J=7.5 Hz), 2.91 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.44, 135.33, 131.97, 128.60, 127.15, 126.02, 124.35, 120.85, 119.76, 114.83, 81.39, 78.57, 45.33. MS (70 eV): 388 (M^+, 100), 373 (2), 358 (2), 328 (10), 300 (8), 193 (17), 150 (10). $C_{28}H_{24}N_2$ (388.51): Anal. Calcd: C 86.56, H 6.23, N 7.21. Found: C 86.72, H 6.18, N 7.48.

4.1.5. 1,4-Di(5-{[5-(*N*,*N*-dimethylamino)-1-naphthyl]-ethynyl}-1-naphthyl)buta-1,3-diyne (5). Following the general method used for the synthesis of **4**, a mixture of cuprous chloride (3 mg, 0.015 mmol) in dry pyridine (30 mL) and a solution of compound **2** (100 mg, 0.29 mmol) in dry pyridine (10 mL), was stirred for 7 h. The extraction was carried out with abundant dichloromethane (200 mL). A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:1) giving **5** as an orange solid, mp 219–221 °C, 97 mg (100%) yield. UV–vis (CH_2Cl_2), λ max (nm): 235 (ε, 105,900), 377 (ε, 55,300). Fluorescence (CH_2Cl_2), λ_{max} (nm): 533 (ϕ=0.10). IR (KBr, cm^{-1}): 2210, 2189, 1414, 787. ^{1}H NMR ($CDCl_3$): δ 8.64 (d, 2H, J=8.7 Hz), 8.48 (d, 2H, J=8.7 Hz), 8.32 (d, 2H, J=8.4 Hz), 8.25 (d, 2H, J=8.7 Hz), 7.95 (d, 2H, J=7.2 Hz), 7.92 (d, 2H, J=7.2 Hz), 7.89 (d, 2H, J=7.2 Hz), 7.69–7.49 (m, 8H), 7.17 (d, 2H, J=7.2 Hz), 2.94 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.43, 134.68, 133.90, 133.09, 132.69, 131.28, 130.67, 128.83, 126.90 (2C), 126.74, 126.20, 125.42, 124.50 (2C), 122.00, 121.04, 120.98, 120.02, 114.71, 93.66, 91.72, 81.06, 79.05, 45.36. MS (70 eV): 688 (M^+, 100), 673 (1), 344 (19). $C_{52}H_{36}N_2$ (688.87): Anal. Calcd: C 90.67, H 5.27, N 4.07. Found: C 90.75, H 5.08, N 4.24.

4.1.6. 1,4-Di{5-[(5-{[5-(*N*,*N*-dimethylamino)-1-naphthyl]-ethynyl}-1-naphthyl)ethynyl]-1-naphthyl}buta-1,3-diyne (6). Following the general method used for the synthesis of **4**, a mixture of cuprous chloride (2 mg, 0.01 mmol) in dry pyridine (30 mL) and a solution of compound **3** (100 mg, 0.20 mmol) in dry pyridine (10 mL), was stirred for 5h. The extraction was carried out with abundant dichloromethane (600 mL). A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **6** as a dark yellow solid, mp 169–170 °C, 64 mg (65%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 237 (ε, 115,300), 383s (ε, 54,700), 366 (ε, 62,800). Fluorescence (CH_2Cl_2), λ_{max} (nm): 526 (ϕ=0.18). IR (KBr, cm^{-1}): 2200, 1421, 797. ^{1}H NMR ($CDCl_3$): δ 8.63 (d, 2H, J=8.4 Hz), 8.60 (d, 2H, J=8.4 Hz), 8.57 (d, 2H, J=8.4 Hz), 8.43 (d, 2H, J=8.7 Hz), 8.32 (d, 2H, J=9.0 Hz), 8.27 (d, 2H, J=8.7 Hz), 7.96 (d, 4H, J=7.2 Hz), 7.95 (d, 2H, J=7.2 Hz), 7.89 (d, 2H, J=8.4 Hz), 7.83 (d, 2H, J=7.2 Hz), 7.68–7.48 (m, 12H), 7.17 (d, 2H, J=7.5 Hz), 2.93 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.77, 134.94, 133.73, 133.42 (2C), 133.24, 132.10, 131.45 (2C), 131.36, 130.89, 128.99, 127.83, 127.69, 127.30 (2C), 127.12, 126.63 (2C), 126.52, 126.39, 125.55, 124.55, 122.09, 121.70 (2C), 121.36, 121.26, 120.41, 114.94, 93.76, 92.95, 92.73, 91.93, 81.80, 45.62. MS (FAB+): 988.5 $C_{76}H_{48}N_2$ (989.23): Anal. Calcd: C 92.28, H 4.89, N 2.83. Found: C 92.39, H 5.00, N 2.64.

4.1.7. 1,4-Di(α-naphthyl)-1,3-butadiyne (7). Following the general method used for the synthesis of **4**, a mixture of cuprous chloride (96 mg, 0.99 mmol) in dry pyridine (10 mL) and a solution of 1-ethynylnaphthalene (150 mg, 0.99 mmol) in dry pyridine (5 mL), was stirred for 5h. The extraction was carried out with abundant dichloromethane (600 mL). A flash chromatography on silica gel, eluting with hexane/dichloromethane (3:2) giving **7** as a yellow solid, mp 177–180 °C, 286 mg (96%) yield. IR (KBr, cm^{-1}): 3054, 2138, 795. ^{1}H NMR ($CDCl_3$): δ 8.44 (d, 2H, J=8.3 Hz), 7.90 (d, 2H, J=8.3 Hz), 7.85 (d, 2H, J=8.3 Hz), 7.84 (dd, 2H, J=7.2, 1.3 Hz), 7.64 (ddd, 2H, J=8.3, 7.0, 1.3 Hz), 7.56 (ddd, 2H, J=8.3, 7.0, 1.3 Hz), 7.47 (dd, 2H, J=8.3, 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 133.8, 133.0, 132.0, 129.7, 128.4, 127.2, 126.6, 126.1, 125.2, 119.5, 80.9, 78.6. MS (70 eV): 302 (M^+, 100), 151 (22). $C_{24}H_{14}$ (302.35): Anal. Calcd: C 95.33, H 4.67. Found: C 95.15, H 4.54.

A crystal of 0.33×0.47×0.17 mm was selected for data collection in a Seifert XRDD3000 S diffractometer, using graphite-monochromated Cu Kα radiation and ω-2θ scan. The lattice parameters were refined on the setting angles of 56 reflections in the range $5\leq\theta\leq32°$. The intensities of 2049 reflections were measured, 1735 observed ($I>2\sigma(I)$), in the range $2\leq\theta\leq65°$. Two standard reflections were measured every 100 reflections; a linear decay correction was made to allow for an overall 9% decrease in diffracted power. All calculations were performed on a VAX 3100 computer. Lorentz and polarization corrections but not absorption corrections were applied. The structure was solved by direct methods.[29] Refinement was carried out by least-squares methods,[30] and all non-H atoms were refined anisotropically. H atoms were placed in geometrically calculated positions with C–H=0.93 Å riding on the C atoms to which they were attached, with their isotropic temperature factors held constant (1.2 times those of the H equivalent of the riding carbon atom). The final R values together with other experimental and crystallographic data are given in Table 3. Geometrical calculations were performed.[31]

Table 3. Crystal data and structure refinement for 1,4-di(α-naphthyl)-1,3-butadiyne (**7**)

Identification code	NAF
Empirical formula	$C_{24}H_{14}$
Formula weight	302.35
Temperature	293 (2) K
Wavelength	1.54180 Å
Crystal system, space group	Monoclinic, $P2_1/n$
Unit cell dimensions	a=8.352(1) Å, α=90° b=12.747(2) Å, β=100.83(1)° c=15.316(2) Å, γ=90°
Volume	1601.5(4) Å^3
Z, calculated density	4, 1.254 mg/m^3
Absorption coefficient	0.541 mm^{-1}
F(000)	632
Crystal size, mm	0.33×0.47×0.17
Theta range for data collection	4.55–64.97°
Index ranges	$0\leq h\leq9$, $0\leq k\leq14$, $-18\leq l\leq17$
Reflections collected/independent	2409/2409
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2409/0/218
Goodness-of-fit on F^2	1.092
Final R indices [$I>2\sigma(I)$]	$R1$=0.0558, $wR2$=0.1528
R indices (all data)	$R1$=0.0709, $wR2$=0.1757
Extinction coefficient	0.010(2)
Largest diff. peak and hole	0.331 and −0.265 e Å^{-3}

4.1.8. 5-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)ethynyl]-*N*,*N*-dimethylnaphthalen-1-amine (8). Following the general method used for the synthesis of **2a**, a mixture of dichloro bis(triphenylphosphine)palladium (36 mg, 0.051 mmol), copper iodide (1 mg, 0.005 mmol), compound **1** (100 mg, 0.51 mmol), 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine (151 mg, 0.51 mmol), and triethylamine (30 mL) was stirred for 15 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **8** as a dark amber solid, mp 99–101 °C, 176 mg (95%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 230 (ε, 41,400), 315s (ε, 8400), 363 (ε, 17,900). Fluorescence (CH_2Cl_2), λ_{max} (nm): 504 (ϕ=0.32). IR (KBr, cm^{-1}): 1413, 785. ^1H NMR ($CDCl_3$): δ 8.30 (d, 2H, J=7.5 Hz), 8.27 (d, 2H, J=7.5 Hz), 7.87 (d, 2H, J=6.6 Hz), 7.57–7.48 (m, 4H), 7.16 (d, 2H, J=7.2 Hz), 2.92 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.37, 134.70, 130.46, 128.78, 126.74, 125.05, 124.51, 121.45, 121.14, 114.60, 92.67, 45.37. MS (70 eV): 364 (M^+, 100), 349 (3), 304 (10), 276 (10), 181 (20). $C_{26}H_{24}N_2$ (364.48): Anal. Calcd: C 85.68, H 6.64, N 7.69. Found: C 86.59, H 6.50, N 7.82.

4.1.9. 5-({5-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)-ethynyl]-1-naphthyl}ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (9). Following the general method used for the synthesis of **1a**, a mixture of dichloro bis(triphenylphosphine)palladium (20 mg, 0.030 mmol), copper iodide (0.6 mg, 0.003 mmol), compound **2** (100 mg, 0.30 mmol), 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine (86 mg, 0.30 mmol), and triethylamine (30 mL) was stirred for 16 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **9** as a yellow solid, mp 214–216 °C, 130 mg (87%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 237 (ε, 60,700), 373 (ε, 33,000). Fluorescence (CH_2Cl_2), λ_{max} (nm): 525 (ϕ=0.21). IR (KBr, cm^{-1}): 2198, 1418, 790. ^1H NMR ($CDCl_3$): δ 8.64 (d, 2H, J=8.7 Hz), 8.34 (d, 2H, J=9.0 Hz), 8.31 (d, 2H, J=8.4 Hz), 7.97 (d, 2H, J=6.6 Hz), 7.92 (d, 2H, J=7.2 Hz), 7.69–7.52 (m, 6H), 7.18 (d, 2H, J=6.9 Hz), 2.95 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.42, 134.68, 133.20, 131.06, 130.61, 128.80, 127.14, 126.88, 126.28, 125.30, 124.50, 121.74, 121.16, 120.99, 114.67, 93.41, 91.99, 45.32. MS (70 eV): 514 (M^+, 100), 257(13), 207 (8). $C_{38}H_{30}N_2$ (514.66): Anal. Calcd: C 88.68, H 5.88, N 5.44. Found: C 88.72, H 5.69, N 5.52.

4.1.10. 5-{[5-({5-[(5-{*N*,*N*-Dimethylamino}-1-naphthyl)-ethynyl]-1-naphthyl}ethynyl)-1-naphthyl]ethynyl}-*N*,*N*-dimethylnaphthalen-1-amine (10). Following the general method used for the synthesis of **1a**, a mixture of dichloro bis(triphenylphosphine)palladium (21 mg, 0.030 mmol), copper iodide (0.5 mg, 0.003 mmol), compound **3** (150 mg, 0.30 mmol), 5-iodo-*N*,*N*-dimethylnaphthalen-1-amine (89 mg, 0.30 mmol), and triethylamine (30 mL) was stirred for 20 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **10** as a yellow solid, mp 262–264 °C, 12 mg (6%) yield.

4.1.10.1. Between 5-ethynyl-*N*,*N*-dimethylnaphthalen-1-amine (1) and the iodoarene 11. Following the general method used for the synthesis of **2a**, a mixture of dichloro bis(triphenylphosphine)palladium (5.6 mg, 0.008 mmol), copper iodide (0.15 mg, 0.0005 mmol), compound **11** (50 mg, 0.08 mmol), compound **1** (31 mg, 0.16 mmol), and triethylamine (30 mL) was stirred for 15 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **10** as a yellow solid, mp 262–264 °C, 40 mg (76%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 231 (ε, 56,600), 375 (ε, 29,700). Fluorescence (CH_2Cl_2), λ_{max} (nm): 527 (ϕ=0.13). IR (KBr, cm^{-1}): 2220, 1421, 784. ^1H NMR ($CDCl_3$, 55 °C): δ 8.61 (d, 2H, J=8.4 Hz), 8.42 (d, 2H, J=8.4 Hz), 8.32 (d, 2H, J=8.4 Hz), 8.26 (d, 2H, J=8.7 Hz), 7.93 (d, 2H, J=7.2 Hz), 7.88 (d, 2H, J=7.8 Hz), 7.82 (d, 2H, J=7.5 Hz), 7.64–7.49 (m, 8H), 7.16 (d, 2H, J=7.5 Hz), 2.93 (s, 12H). ^{13}C NMR ($CDCl_3$, 55 °C): δ 151.38, 134.64, 133.36, 132.98, 131.78, 131.03, 130.58, 128.77, 127.66, 126.84, 126.79, 126.34, 126.01, 125.31, 124.47, 121.68, 121.04, 120.93, 120.26, 114.64, 93.42, 91.76 (2C), 81.53, 45.33. MS (70 eV): 664 (M^+, 100), 648 (2), 332 (16). $C_{50}H_{36}N_2$ (664.84): Anal. Calcd: C 90.33, H 5.46, N 4.21. Found: C 90.51, H 5.28, N 4.13.

4.1.11. 5-({5-[(5-Iodo-1-naphthyl)ethynyl]-1-naphthyl}-ethynyl)-*N*,*N*-dimethylnaphthalen-1-amine (11). Following the general method used for the synthesis of **1a**, a mixture of dichloro bis(triphenylphosphine)palladium (41 mg, 0.058 mmol), copper iodide (1.1 mg, 0.006 mmol), compound **2** (200 mg, 0.58 mmol), 1,5-diiodonaphthalene (1.3 g, 3.48 mmol), and triethylamine (30 mL) was stirred for 15 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:1) giving **11** as an orange solid, mp 191–192 °C, 275 mg (80%) yield. IR (KBr, cm^{-1}): 2220, 2197, 1403, 966, 787. ^1H NMR ($CDCl_3$): δ 8.63 (d, 1H, J=8.4 Hz), 8.61 (d, 1H, J=8.7 Hz), 8.57 (d, 1H, J=9.0 Hz), 8.32 (d, 1H, J=9.0 Hz), 8.27 (d, 1H, J=8.7 Hz), 8.18 (d, 1H, J=7.2 Hz), 8.17 (d, 1H, J=8.7 Hz), 7.96 (d, 2H, J=7.2 Hz), 7.95 (d, 1H, J=7.2 Hz), 7.89 (d, 1H, J=7.5 Hz), 7.68–7.50 (m, 5H), 7.34 (dd, 1H, J=8.7, 9.0 Hz), 7.17 (d, 1H, J=7.8 Hz), 2.93 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 151.47, 138.25, 134.66, 134.19, 134.01, 133.23 (3C), 131.44, 131.28, 131.14, 130.64, 128.83, 127.80, 127.53, 127.36, 127.07, 126.94, 126.89, 126.43, 126.29, 125.36, 124.48, 121.88 (2C), 121.29, 121.10, 120.99, 114.68, 99.99, 93.50, 92.85, 92.10, 91.88, 45.37. MS (70 eV): 597 (M^+, 100), 471(44), 424 (12), 298 (18). $C_{36}H_{24}NI$ (597.49): Anal. Calcd: C 72.37, H 4.05, N 2.34. Found: C 72.46, H 3.96, N 2.20.

4.1.12. 1,4-Di[(5-{*N*,*N*-dimethylamino}-1-naphthyl)-ethynyl]benzene (12). Following the general method used for the synthesis of **2a**, a mixture of dichloro bis(triphenylphosphine)palladium(II) (72 mg, 0.10 mmol), copper iodide (2 mg, 0.01 mmol), compound **1** (100 mg, 0.51 mmol), 1,4-diiodobenzene (84 mg, 0.26 mmol), and triethylamine (40 mL) was stirred for 15 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:1) giving **12** as a yellow solid, mp 173–175 °C, 106 mg (90%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 231 (ε, 50,600), 234s (ε, 29,300), 259s (ε, 31,400), 369 (ε, 36,200). Fluorescence (CH_2Cl_2), λ_{max} (nm): 524 (ϕ=0.30). IR (KBr, cm^{-1}): 2929, 2213, 1401, 842, 783. ^1H NMR ($CDCl_3$): δ 8.28 (d, 2H, J=8.4 Hz), 8.14 (d, 2H, J=8.4 Hz), 7.77 (d, 2H, J=6.9 Hz), 7.66 (s, 4H), 7.52 (dd, 2H, J=8.4, 7.5 Hz), 7.47 (dd, 2H, J=8.4, 6.9 Hz), 7.15 (d, 2H, J=7.5 Hz), 2.91 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.39, 134.68, 131.60, 130.52, 128.80, 126.80, 125.32, 124.48, 123.41, 120.95 (2C), 114.68, 93.85, 90.03, 45.39. MS (70 eV): 464 (M^+, 100), 441 (10), 296 (7).

$C_{34}H_{28}N_2$ (464.60): Anal. Calcd: C 87.90, H 6.07, N 6.03. Found: C 88.05, H 6.21, N 6.24.

4.1.13. 1,4-Di({5-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)-ethynyl]-1-naphthyl}ethynyl)benzene (13). Following the general method used for the synthesis of **1a**, a mixture of dichloro bis(triphenylphosphine)palladium (20 mg, 0.029 mmol), copper iodide (0.6 mg, 0.003 mmol), compound **2** (100 mg, 0.29 mmol), 1,4-diiodobenzene (48 mg, 0.15 mmol), and triethylamine (30 mL) was stirred for 18 h. A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:1) giving **13** as a yellow solid, mp 234–235 °C, 90 mg (81%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 236 (ε, 81,300), 375 (ε, 63,700), 390s (ε, 60,300). Fluorescence (CH_2Cl_2), λ_{max} (nm): 528 ($\phi=0.15$). IR (KBr, cm^{-1}): 2220, 1403, 927, 780. ^1H NMR ($CDCl_3$): δ 8.61 (d, 2H, $J=8.4$ Hz), 8.51 (d, 2H, $J=8.4$ Hz), 8.32 (d, 2H, $J=8.1$ Hz), 8.27 (d, 2H, $J=8.4$ Hz), 7.95 (d, 2H, $J=7.5$ Hz), 7.89 (d, 2H, $J=6.0$ Hz), 7.87 (d, 2H, $J=6.3$ Hz), 7.71 (s, 4H), 7.68–7.49 (m, 8H), 7.17 (d, 2H, $J=6.3$ Hz), 2.93 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 151.46, 134.65, 133.17 (2C), 131.71, 131.13 (2C), 130.63, 128.82, 126.89 (3C), 126.33, 126.25, 125.36, 124.48, 123.32, 121.77, 121.18, 121.13, 120.97, 114.68, 94.44, 93.46, 91.90, 89.42, 45.36. MS (70 eV): 764 (M^+, 100), 688 (21), 596 (9), 429 (3), 382 (10), 355 (62). $C_{58}H_{40}N_2$ (764.96): Anal. Calcd: C 91.07, H 5.27, N 3.66. Found: C 91.27, H 5.04, N 3.99.

4.1.14. 1,4-Di{[5-({5-[(5-{*N*,*N*-dimethylamino}-1-naphthyl)ethynyl]-1-naphthyl}ethynyl)-1-naphthyl]-ethynyl}benzene (14). Following the general method used for the synthesis of **1a**, a mixture of dichloro bis(triphenylphosphine)palladium (9 mg, 0.013 mmol), copper iodide (0.3 mg, 0.001 mmol), compound **11** (80 mg, 0.13 mmol), 1,4-diethynylbenzene (9 mg, 0.07 mmol), and triethylamine (25 mL) was stirred for 48 h at reflux. The extraction was carried out with abundant dichloromethane (400 mL). A flash chromatography on silica gel, eluting with hexane/dichloromethane (1:2) giving **14** as a yellow solid, mp 204–206 °C, 41 mg (58%) yield. UV–vis (CH_2Cl_2), λ_{max} (nm): 233 (ε, 172,600), 371 (ε, 87,500). Fluorescence (CH_2Cl_2), λ_{max} (nm): 529 ($\phi=0.08$). IR (KBr, cm^{-1}): 2223, 2198, 1420, 927, 780. ^1H NMR ($CDCl_3$): 8.82 (d, 2H, $J=8.7$ Hz), 8.65 (d, 2H, $J=8.4$ Hz), 8.54 (d, 2H, $J=8.4$ Hz), 8.33 (d, 2H, $J=8.7$ Hz), 8.30 (d, 2H, $J=8.4$ Hz), 8.26 (d, 2H, $J=8.4$ Hz), 8.03 (d, 2H, $J=6.9$ Hz), 8.02 (d, 2H, $J=6.9$ Hz), 7.96 (d, 4H, $J=6.9$ Hz), 7.88 (d, 2H, $J=6.9$ Hz), 7.77–7.50 (m, 16H), 7.17 (d, 2H, $J=6.9$ Hz), 2.94 (s, 12H). ^{13}C NMR ($CDCl_3$): 151.157, 134.71, 133.28, 133.18 (2C), 132.94, 132.45, 132.04, 131.73, 131.46, 131.22, 130.71, 128.89, 128.14, 127.88, 126.96, 126.80, 126.58, 126.29 (2C), 125.99, 125.91, 125.48, 124.54 (C-3), 122.25 (2C), 122.02 (3C), 121.09, 117.68, 114.75, 93.81, 93.70 (2C), 91.80 (2C) 91.47, 45.41. MS (FAB+): 1064.6 $C_{82}H_{52}N_2$ (1065.32): Anal. Calcd: C 92.45, H 4.92, N 2.63. Found: C 92.30, H 4.84, N 4.15.

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Oligothienylenevinylenes incorporating 3,4-ethylenedioxythiophene (EDOT) units

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Abstract—A new series of π-conjugated oligomers based on various combinations of thiophene and EDOT units and double bonds has been synthesized by Wittig–Horner reactions from phosphonate anions carrying EDOT or bis-EDOT units. Optical and electrochemical results evidence the crucial role of the EDOT moiety for modulating the electronic properties of the oligomers. The insertion of bis-EDOT unit in the middle of the molecule leads to a self-rigidification of the conjugated system due to non covalent S···O intramolecular interactions. The strong electron donor effect of the EDOT units explains the determining role of the relative position of the EDOT units on the localization and stabilization of the positive charges in the radical cation or dication states.

1. Introduction

Monodisperse thiophene-based oligomers represent one of the most widely investigated classes of functional π-conjugated systems.[1,2] In addition to their use as model compounds for the analysis of the relationships between the structure and electronic properties of the parent polydisperse polymers,[1,2] π-conjugated oligomers have acquired a growing importance as organic semi-conducting materials for the fabrication of various kinds of electronic and optoelectronic devices such as field-effect transistors,[3] light-emitting diodes[4] and solar cells.[5,6]

In recent years the structural control of the energy level of the frontier orbitals (HOMO and LUMO), of conjugated oligomers and thus of the band gap (Eg) of the resulting molecular materials has been a focus of considerable attention.[7] In fact these quantities are keys to modulate parameters such as ionization potential, electron affinity, absorption and emission spectra which are of course crucial for technological applications.

We have already described various series of extended oligothienylenevinylenes (nTVs) and we have shown that these oligomers present the smallest HOMO-LUMO gap (ΔE) value and longest convergence limit of ΔE among all classes of known extended π-conjugated oligomers.[8,9] Although the insertion of double bonds of controlled *trans* configuration between the thiophene rings implies more complex synthetic approaches, the synergistic effects of planarization and reduction of the overall aromaticity of the π-conjugated system induced by this structural modification leads to a significant decrease of ΔE compared to oligothiophenes involving the same number of sp^2 carbons.[10] More recently, we have synthesized various classes of linear π-conjugated systems based on 3,4-ethylenedioxythiophene (EDOT). The analysis of the structure and electronic properties of NLO-phores,[11] fluorophores,[12] extended π-donors[13] or conjugated oligomers[14,15] has demonstrated that the combination of the strong electron donor properties of EDOT with the self-rigidification effect resulting from non covalent intramolecular sulfur-oxygen interactions with adjacent EDOT or thiophene units makes EDOT a unique building block for the design of advanced functional π-conjugated systems.

In this general context, we report here the synthesis and characterization of a new series of conjugated oligomers based on various combinations of thiophene, EDOT and ethylenic units (**1**–**6**) (Chart 1).

2. Synthesis

The various oligomers were synthesized using Wittig–Horner reactions as shown in Schemes 1–3. Cava and co-workers have described the synthesis of a triphenylphosphonium salt bearing the EDOT moiety but the Wittig

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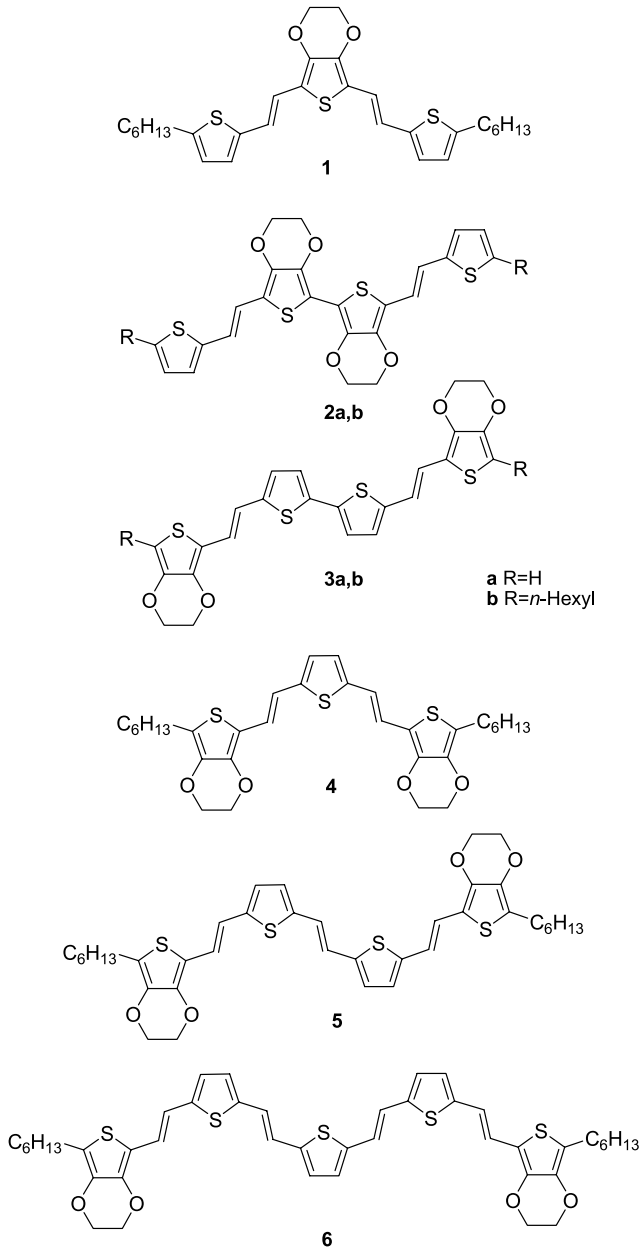
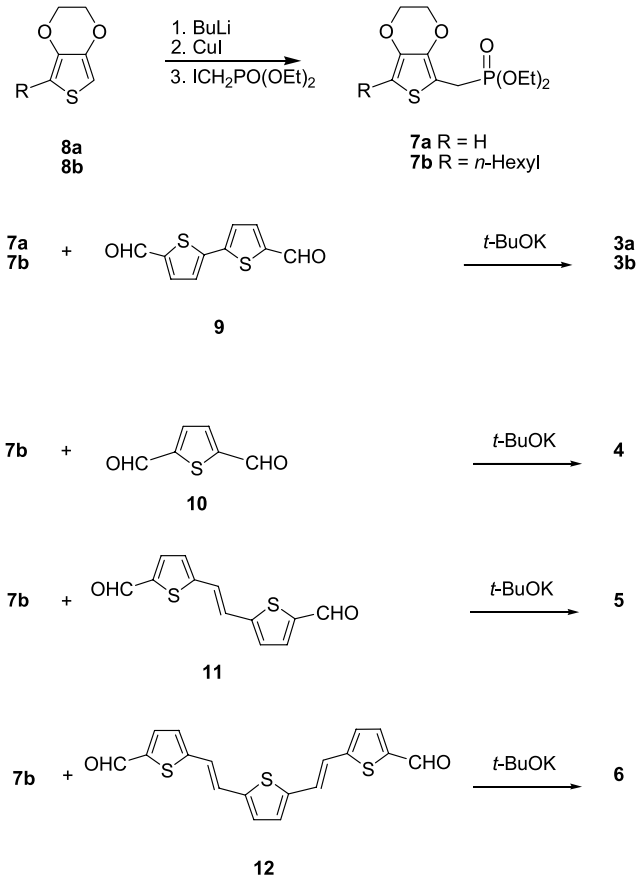


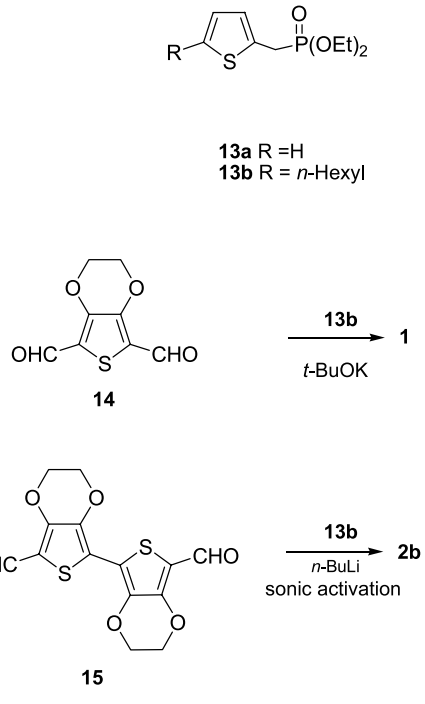
Chart 1.

reactions involving the corresponding ylide led to very low yields of the expected olefins (less than 5%).[16] We have developed the synthesis of the EDOT derivatives **7a**,**b** containing methylphosphonate groups which were expected to give more reacting phosphonate anions. Compounds **7a**,**b** were obtained in 56 and 31% yield, respectively, in a one-step reaction from EDOT **8a** or *n*-hexyl-EDOT **8b** by successive addition of *n*-BuLi, CuI and diethyl-iodomethyl-phosphonate at −78 °C.[17] The formation of the intermediate 2-thienyl copper reactants allows to decrease the basic character of the organometallic compound and thus to favour the nucleophilic substitution with iodinated phosphonate by avoiding the acid-base reaction. Twofold Wittig–Horner olefination with diformyl derivatives **9**–**12** and phosphonates **7a** or **7b** in the presence of *t*-BuOK at room temperature gave oligomers **3**–**6** in 50–65% yields (Scheme 1).

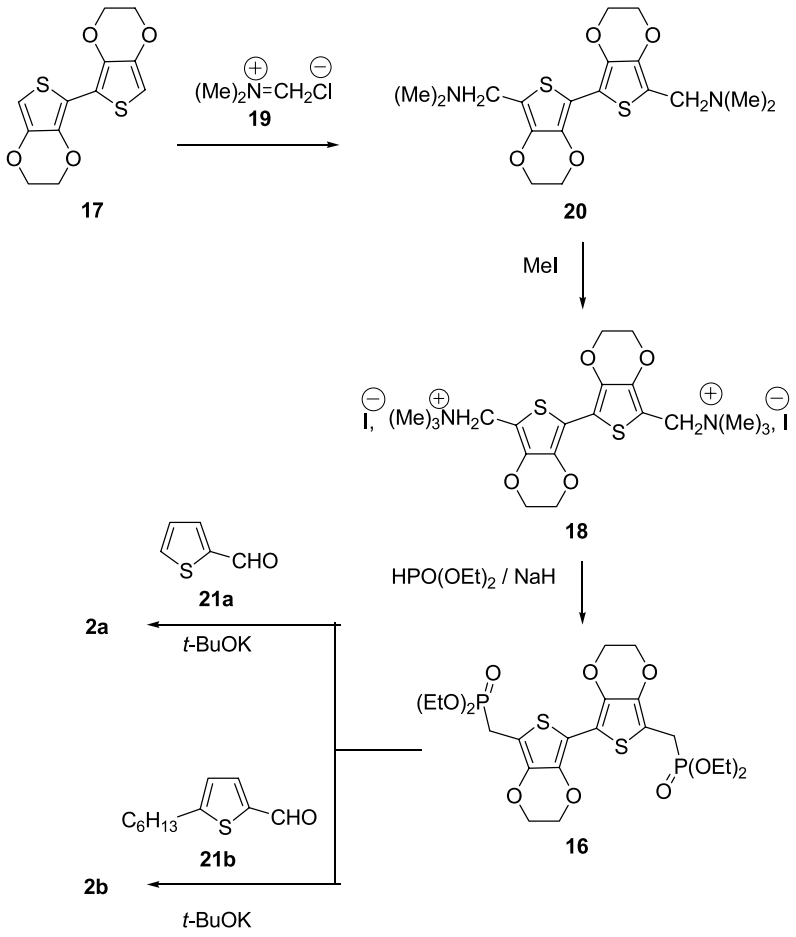


Scheme 1.

Compounds **1** and **2** with median EDOT units were obtained by twofold Wittig–Horner reaction of phosphonate **13b** with EDOT or bis-EDOT dialdehydes **14** and **15**, respectively (Scheme 2).



Scheme 2.



Scheme 3.

Due to the very low solubility of **15**[14] the Wittig–Horner reaction was carried out using an unusual procedure involving the dropwise addition of *n*-BuLi to a suspension of the dialdehyde in the presence of a slight excess of phosphonates **13b** under ultra-sound at room temperature. Sonication favoured solubilisation of the dialdehyde while the fast reaction of phosphonate anions on the carbonyl groups led to the desired oligomers. It should be noted that with the unsubstituted thienylmethylphosphonate **13a**, the poor solubility of the resulting oligomer **2a** did not allow a clean reaction and this method led to a mixture of several compounds difficult to separate. On the other hand, attempts to react dialdehydes **14** and **15** with phosphonate **7b**, in order to obtain oligomers containing EDOT rings only failed probably due to the low stability of such oligomers.

Compounds **2a**,**b** were also synthesized by a different method using the bis-phosphonate **16** carrying the bis-EDOT moiety. Two synthetic pathways starting from bis-EDOT **17** were explored for the formation of **16**. The direct reaction based on the sequence *n*-BuLi/CuI followed by addition of a slight excess of diethyl-iodomethyl-phosphonate was tried first but gave only low yield (less than 10%).[14] The second procedure, based on the methodology developed by Cava and coworkers for the synthesis of the phosphonium salt of EDOT,[16] involved the reaction of the diammonium salt **18** with the diethylphosphite anion. This method gave compound **16** in 55% yield. A twofold Mannich reaction of dimethylimminium cation **19**[18] with bis-EDOT **17** gave the bis-amino derivative **20** which, after treatment with a slight excess of methyliodide led to compound **18** in 64% overall yield. Phosphonate **16** was then reacted with the thiophene aldehydes **21a**,**b** in the presence of *t*-BuOK to give **2a**,**b** in 60–65% yield.

3. Crystal structure of 3a

The crystallographic structure of single crystals of **3a** obtained by slow evaporation of chloroform-ethanol solutions has been analyzed by X-ray diffraction. **3a** crystallizes in the monoclinic *P*2/1*n* space group and the structure is defined from a half molecule due to an inversion centre (Fig. 1). The structure of the molecule reveals that the two ethylenic bonds adopt a *E* configuration. Furthermore, the two thiophene rings present an *anti* conformation which confers a good planarity to the molecule with a median twist angle smaller than 5°. The molecules stack along the *b* axis with an overlapping mode where each molecule bridges two others with intermolecular distances of 3.98 Å (Fig. 1).

4. UV–vis spectroscopy

The electronic absorption data of the various oligomers in dichloromethane are listed in Table 1. The table also

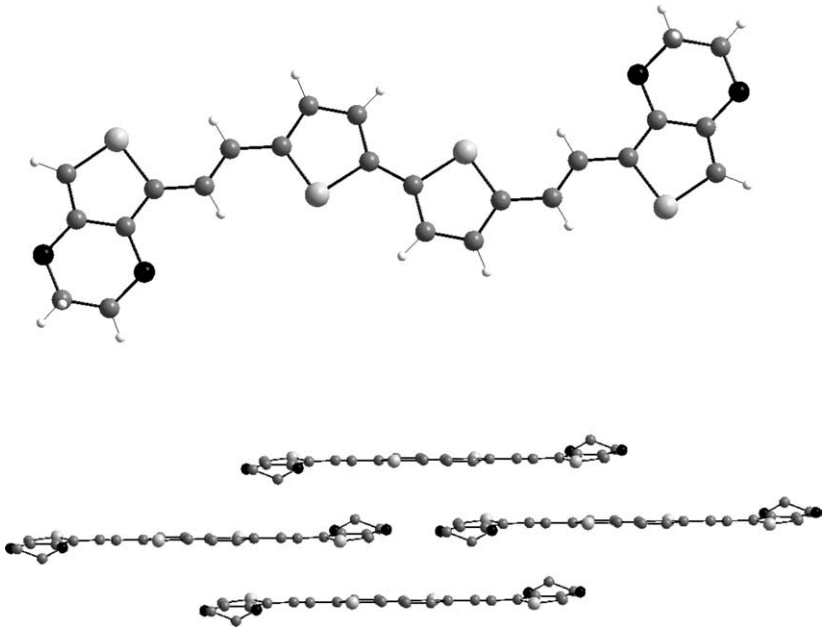
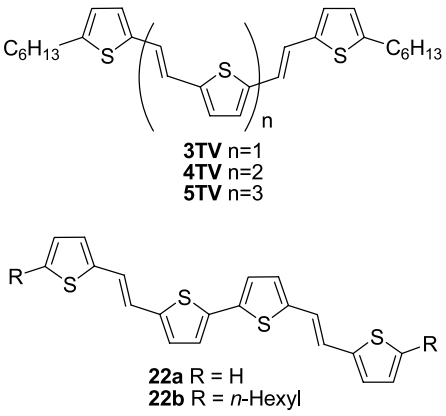


Figure 1. Molecular structure (top) and packing mode (bottom) of **3a** in a single crystal.

Table 1. Electronic absorption data of oligomers (10^{-5} M in CH_2Cl_2)

Compound	λ_{max} (nm)	$\lambda_{0\text{-}0}$ (nm)	ΔE (eV)
2a	461	490	2.53
3a	454	481	2.58
22a[10]	435	448	2.77
1	455	485	2.65
2b	472	503	2.46
3b	468	493	2.52
22b[10]	449	477	2.60
4	448	479	2.58
5	487	517	2.40
6	512	545	2.28
3TV[10]	423	454	2.73
4TV[10]	465	495	2.51
5TV[10]	493	526	2.36

includes data corresponding to oligothienylenevinylenes (nTVs) and hybrid oligomers **22a**,**b** for comparison (Scheme 4).[10]



Scheme 4.

Figure 2 shows the UV–vis spectra of oligomers **2b** and **3b**. The spectra are characterised by a well resolved fine structure in particular for compound **2b** with a bis-EDOT median core. As already shown, the bis-EDOT block adopts a δ-*trans* conformation stabilized by non bonded S···O intramolecular interactions.[11,13] Based on this self-structuration of the central part of the molecule, oligomers **2a**,**b** possess a more rigid structure than their thiophene-based isomers **3a**,**b**. In addition, the insertion of the EDOT units in the centre of the molecule for **2a**,**b** produces also a slight bathochromic shift of the absorption bands compared to **3a**,**b**. On the other hand, comparison of these data to those for oligomers **22a**,**b** shows that replacement of thiophene by EDOT units produces a 20–25 nm red shift of the absorption bands indicating a decrease of the HOMO–LUMO gap ΔE.

The same difference is observed when comparing the data for **1** and **3TV**. The decrease of ΔE between oligomers **1** and

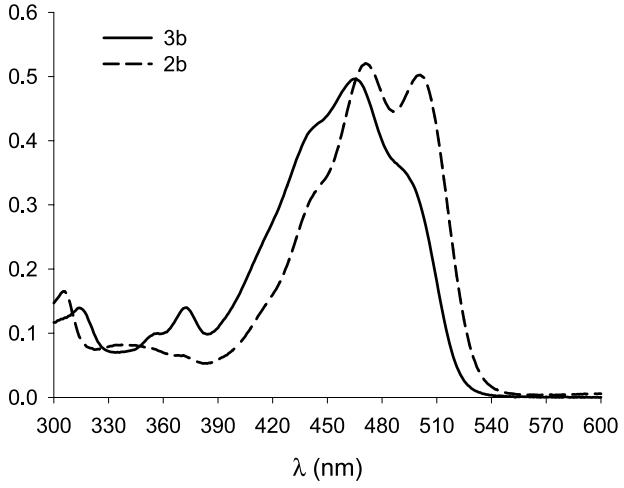


Figure 2. Electronic absorption spectra of **2b** and **3b** (10^{-5} M in CH_2Cl_2).

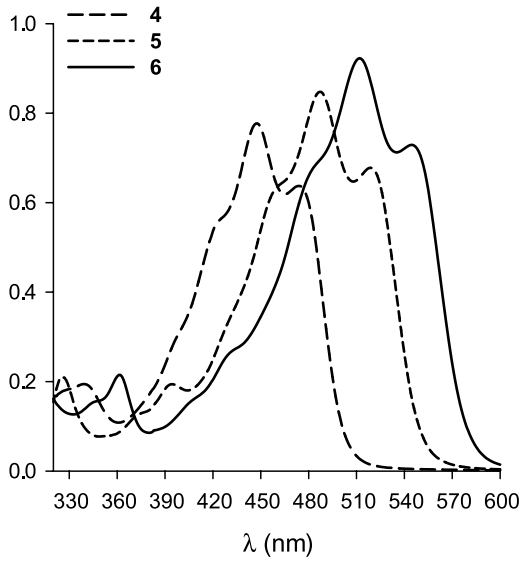


Figure 3. Electronic absorption spectra of **4**, **5** and **6** (10^{-5} M in CH_2Cl_2).

2b, from 2.65 to 2.46 eV is due to the combined effects of the lengthening of the conjugated chain and the enhanced donor effect of the two ethylenedioxy group. It is worth noting that in the thiophene series the insertion of an additional thiophene unit between **3TV** and **22b** leads to a decrease of the ΔE of 0.13 eV only.

Figure 3 shows the UV–vis spectra of compounds **4**, **5** and **6**. All spectra show a well-resolved vibronic fine structure characteristic of a planar rigid system. As expected chain extension leads to a bathochromic shift of the absorption bands and hence to a decrease of ΔE. On the other hand, comparison with the data for nTVs containing the same number of sp^2 carbons shows that replacement of thiophene by EDOT induces a decrease of ΔE. The magnitude of the donor effect decreases with chain extension, as already observed for other substituted nTVs.[19] Thus, ΔE decreases by 0.15 eV between **4** and **3TV** but only of 0.08 eV between **6** and **5TV**.

5. Electrochemical properties of oligomers

The cyclic voltammetric (CV) data of the various oligomers are gathered in Table 2 and are compared to the analogs nTV derivatives.

Table 2. Cyclic voltammetric data of oligomers, 10^{-4} mol L^{-1} (* saturated solution) in 0.1 M Bu_4NPF_6/CH_2Cl_2, scan rate 100 mV s^{-1}, reference AgCl/Ag

Compound	E_1 (V)	E_2 (V)	$\Delta E = E_2 - E_1$ (mV)
2a*	0.59	1.00	410
3a*	0.71[a]	–	–
1	0.61	0.85	240
2b	0.44	0.80	360
3b	0.55	0.70	150
4	0.56	0.78	220
5	0.55	0.65	100
6	0.50	0.54	40
3TV[10]	0.76	0.97	220
4TV[10]	0.67	0.80	130
5TV[10]	0.62	0.70	80

[a] Irreversible peak.

Figure 4 shows the cyclic voltammograms for compounds **2a** and **3a**. The CV of compound **2a** with the bis-EDOT median unit presents two reversible one-electron oxidation waves at 0.59 and 1.00 V corresponding to the successive generation of the radical cation and dication. For isomer **3a**, only an irreversible oxidation peak at 0.71 V is observed. In this latter case, application of successive potential scans leads to the emergence of a new redox system at lower potential. These results indicate that the electrogenerated cation radical undergoes a subsequent coupling leading to the deposition of a more extensively conjugated system on the anode. The process results from the donor effect of the ethylenedioxy groups which contributes to localize the positive charge of the radical cation on a terminal EDOT moiety, thus giving a high reactivity to the terminal α-positions.

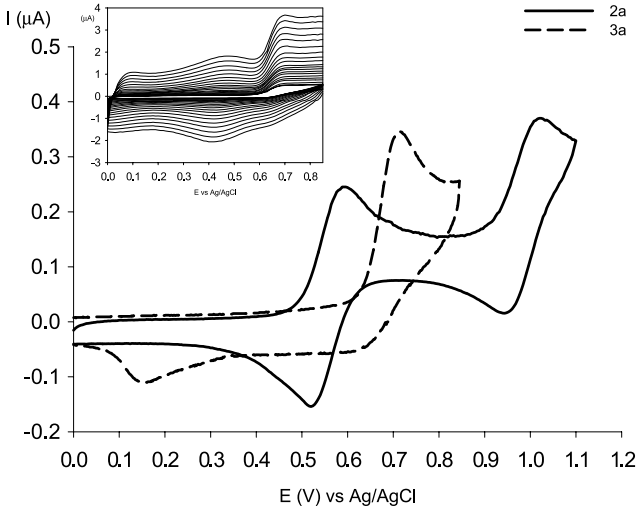


Figure 4. CV of oligomers **2a** and **3a** (saturated solution in 0.1 M Bu_4NPF_6/CH_2Cl_2), scan rate 100 mV s^{-1}; insert) electropolymerisation of **3a** by application of successive potential scans.

In contrast, when the EDOT units are inserted in the middle of the molecule, the localisation of the positive charge on the EDOT rings stabilizes the radical cation. Similar effects of the EDOT position have already been observed for hybrid EDOT-thiophene oligomers.[14]

By blocking the end α-positions by *n*-hexyl groups prevents the coupling of the cation radical and the cyclic voltammogram of compounds **2b** and **3b** presents two reversible oxidation waves. Nevertheless the potentials of the two successive oxidation steps of these two oligomers strongly depend on the relative position of the EDOT moieties in the conjugated chain. The lowest E_1 value of 0.44 V is obtained for **2b** with the EDOT moieties in the middle of the molecule, while E_1 increases to 0.55 V for **3b**.

This effect can be interpreted by structural and electronic effects. Indeed as previously discussed, the bis-EDOT core tends to increase the rigidity of the conjugated system by developing S···O intramolecular interactions. In addition,

the contribution of the electron-releasing effect of the ethylenedioxy groups on the HOMO level must be more important when EDOT units are located inside the conjugated chain.

In contrast, the value of the second oxidation potential E_2 is lower for **3b** (0.70 V) than for **2b** (0.80 V) leading to a strong variation of the difference $\Delta E_p = E_2 - E_1$ between the two oxidation peaks with the position of the EDOT moieties. Moving the EDOT units from outer to the inner positions of the molecule provokes a strong increase of ΔE_p from 150 mV for **3b** to 360 mV for **2b**. As the magnitude of ΔE_p reflects the Coulombic repulsion between positive charges in the dicationic state, this result indicates a higher localization of the positive charges on the median EDOT units for **2b** due to the electron-releasing character of the ethylenedioxy groups.

Such effects, already observed for EDOT or bis-EDOT end-capped by dithiafulvalenyl[13,20] or 2-thienylmesitylsulfanyl groups,[21] reveal an increase of the thermodynamic stability of the radical cation to the detriment of the dication state when bis-EDOT units are inserted in the middle of the molecule.

As shown in Figure 5, compounds **4** and **5** present two distinct oxidation processes corresponding to the successive formation of cation radical and dication species. For compound **6** which shows a single oxidation peak, the width at half maximum of 60 mV is larger than the 28.5 mV expected for an ideal two electron transfer, indicating that the oxidation process involves two very close one-electron steps. The difference ΔE_p of 40 mV between the two oxidation potentials was evaluated from Myers and Shain's method.[22] As expected, the lengthening of the conjugated chain produces both a decrease of the oxidation potentials and a strong reduction of the difference ΔE_p by decreasing the intramolecular Coulombic repulsion. Comparison of these results to those of nTV oligomers[10] shows that the insertion of the EDOT units produces a negative shift of the first oxidation potential reflecting an increase of the HOMO level due to the electron releasing effect of the ethylenedioxy groups. On the other hand, the decrease of ΔE_p upon replacement of the terminal thiophenes by EDOT units indicates an easier access to the dication state for **4–6** than for **nTVs**. Such an effect can be interpreted by a preferential localization of the positive charges on the terminal EDOT moieties.

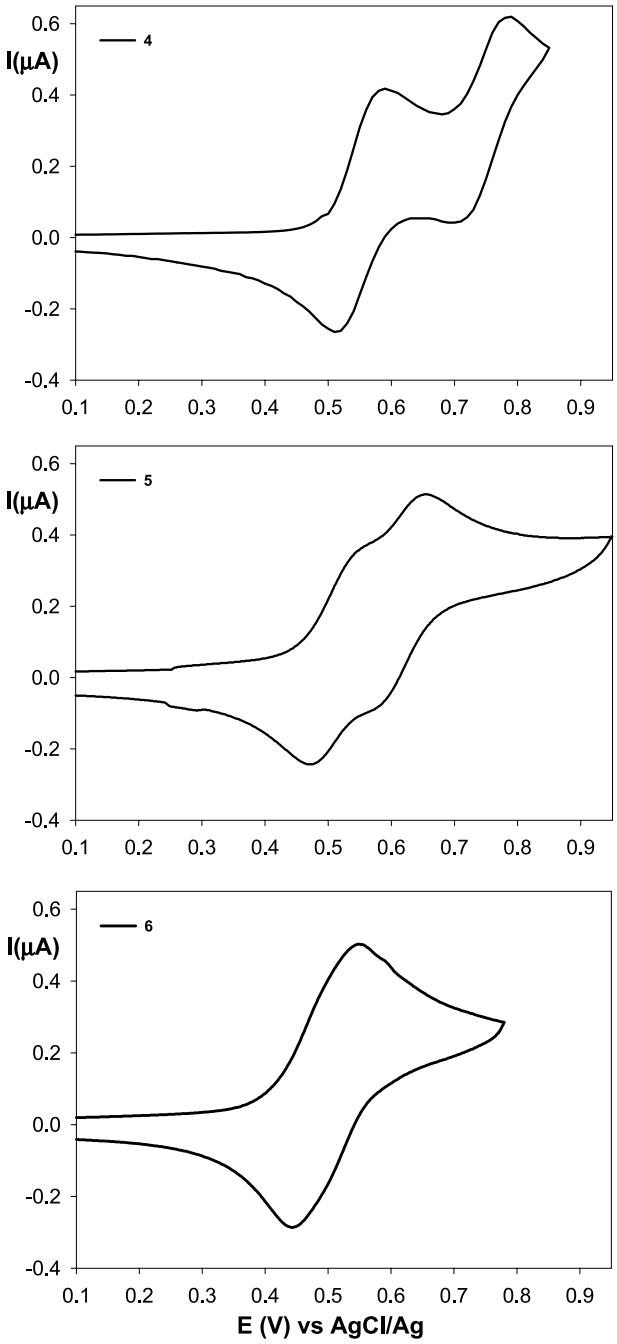


Figure 5. CV of oligomers **4–6** (10^{-4} mol L^{-1} in 0.1 M Bu_4NPF_6/CH_2Cl_2), scan rate 100 mV s^{-1}.

6. Conclusion

A new series of oligomers based on various combinations of thiophene and EDOT units and double bonds has been synthesized by Wittig–Horner reactions from phosphonate anions carrying EDOT or bis-EDOT units. The role of the EDOT moieties and of their relative position in the conjugated chain on the modulation of the electronic properties of the oligomers has been evidenced. Optical and electrochemical results show that the electron releasing effect the EDOT unit provokes a decrease of the HOMO–LUMO gap and an increase of the HOMO level of the oligomers. The insertion of bis-EDOT unit in the middle of the molecule leads to self-rigidification of the conjugated systems due to non covalent S···O intramolecular interactions. The strong electron donor effect of the EDOT units explains the determining role of the relative position of the EDOT units on the localization and stabilization of the positive charges in the radical cation or dication states. The introduction of EDOT units in the middle of the conjugated chain stabilizes the cation radical thus preventing subsequent chemical coupling while making the access to the dication state more difficult. These results thus confirm that a judicious use of the number and position of EDOT building block allows a fine tuning of the electronic properties of extended conjugated oligomers.

7. Experimental

7.1. General

The solvents are purified and/or dried according to the usual protocols. ^{1}H NMR spectra were recorded on Bruker AVANCE DRX 500 (500 MHz) and Jeol GSX 270 WB (270 MHz) instruments. MALDI-TOF MS spectra were recorded on Bruker Biflex-IIITM apparatus, equipped with a 337 nm N_2 laser. The high-resolution mass spectra (HRMS) obtained by electronic impact (EI), fast atoms bombardment (FAB) or electrospray (ESI), were recorded on a double focusing mass spectrometer Jeol JMS 700 with magneto-electrostatic analyzers. UV/visible spectra were recorded on a Lambda 19 instrument. The elemental analyses were carried out by the service of CNRS in Vernaison. The cyclic voltamperometry studies were carried out with a potentiostat-galvanostat EG and G PARK model 273. Compounds (c.a. 10^{-4} mol L^{-1}) were dissolved in a solvent containing the hexafluorophosphate tetrabutylammonium (0.1 mol L^{-1}). The electrolysis cell was equipped with three electrodes: a platinum working electrode, a platinum counter electrode and a reference (Ag/AgCl). The scanning rate was 100 mV s^{-1}.

7.2. Preparation of phosphonate 7a and 7b

To a solution of 5 mmol of EDOT **8a** (0.71 g) or hexyl-EDOT **8b**[15] (1.13 g) in dry THF (15 mL) at −70 °C under nitrogen atmosphere, was slowly added 2 ml of *n*-BuLi in *n*-hexane (2.5 M, 5 mmol) then the solution was stirred for 1 h. The mixture was allowed to warm to −50 °C and 5 mmol of dry CuI (950 mg) was added in small portion. After stirring 1 h at −20 °C, 1 equiv of diethyl-iodomethyl-phosphonate was slowly added and the mixture was allowed to warm to room temperature. After stirring overnight, the mixture was washed with a saturated solution of $NaHCO_3$ then the aqueous phase was extracted with diethyl ether (2×50 mL) and the organic phase was dried over $MgSO_4$. Removal of the solvent at reduced pressure and purification by chromatography on silica gel (eluent: AcOEt/Petroleum ether 1/1) afforded the phosphonates **7a** or **7b** as brown oils.

7.2.1. Diethyl (3,4-ethylenedioxy-2-thienyl)methylphosphonate: 7a. 56% yield, MS (EI) m/z=292 [$M^{+\cdot}$]. ^{1}H NMR ($CDCl_3$) δ 6.20 (d, 1H, $^5J_{H\text{-}P}$=2.8 Hz); 4.18 (m, 4H); 4.10 (m, 4H); 3.20 (d, 2H, $^2J_{H\text{-}P}$=20 Hz); 1.30 (t, 6H, ^3J=7.0 Hz).

7.2.2. Diethyl (3,4-ethylenedioxy-5-hexyl-2-thienyl)-methylphosphonate: 7b. 31% yield, MS (EI) m/z=376 [$M^{+\cdot}$]. ^{1}H NMR ($CDCl_3$) δ 4.16 (m, 4H); 4.10 (m, 4H); 3.20 (d, 2H, $^2J_{H\text{-}P}$=20 Hz); 2.59 (m, 2H), 1.58 (m, 2H), 1.30 (m, 12H); 0.88 (t, 3H, ^3J=6.8 Hz). Anal. (Calcd): C, 54.23 (54.24); H, 7.71 (7.76); O, 21.11 (21.25); S, 8.39 (8.52).

7.2.3. 2,2′-Bi[(5-dimethylaminomethyl-3, 4-ethylenedioxy)thiophene]: 20. To a solution of bis-EDOT **17**[16] (500 mg, 1.77 mmol) in dichloroethane (20 mL) at room temperature was added under nitrogen atmosphere, a solution of 365 mg of chloride dimethylimminium **19**[18] in 10 ml of acetonitrile. A white precipitate appeared in the solution and at the end of the addition, the mixture was refluxed for 1 h. The reaction mixture was cooled at room temperature, diluted with dichloroethane (50 mL) then 10 mL of Et_3N was added. After stirring 30 min at room temperature, 50 mL of water was added and the organic phase was separated and dried over $MgSO_4$. Removal of the solvent at reduced pressure and purification by chromatography on silica gel (eluent CH_2Cl_2/AcOEt, 3/2+1% of Et_3N) gave 350 mg of a yellow pale solid (64% yield) which was rapidly engaged for the next step.

Mp 184 °C dec. ^{1}H NMR ($CDCl_3$) δ 4.32 (m, 4H); 4.22 (m, 4H); 3.51(s, 4H); 2.28 (s, 12H). MS MALDI-TOF for $C_{18}H_{24}N_2O_4S_2$: calculated 396.12, observed 396.11.

7.2.4. 2,2′-Bi[(5-trimethylaminomethyl)-3,4-ethylenedioxythiophene]: 18. To a solution of 330 mg of **20** (0.83 mmol) in 10 mL of $CHCl_3$ and 15 mL of Et_2O was added 1.83 mmol of methyliodide (2.2 equiv) at room temperature. After stirring 12 h in the darkness, the precipitate obtained was filtered and washed twice with diethyl ether to give 550 mg of a white powder (95% yield).

Dec from 200 °C. ^{1}H NMR ($CDCl_3$) δ 4.57 (s, 4H); 4.42 (m, 4H); 4.36(m, 4H); 3.50 (s, 18H). Anal. (Calcd): C, 35.45 (35.30); H, 4.35 (4.44).

7.2.5. 2,2′-Bi[(5-diethylphosphomethyl)-3,4-ethylenedioxythiophene]: 16. Under nitrogen atmosphere, a suspension of 3 mmol of NaH (60% in oil, washed with twice 5 mL of dry THF) in 5 mL of THF was cooled at 0 °C. A solution of 2 mmol (0.3 mL) of diethyl phosphite in 5 mL of THF was added dropwise. After 15 min of stirring, a solution of 550 mg of ammonium salt **18** in 15 mL of acetonitrile was added and then the mixture was warmed at 60 °C for 10 h. The red solution obtained, was washed with 20 mL of water, extracted with CH_2Cl_2 and the organic phase was dried over $MgSO_4$. Removal of the solvent at reduced pressure and purification by chromatography on silica gel (eluent CH_2Cl_2/AcOEt, 1/1) gave 260 mg of a white solid (64% yield).

Mp <60 °C. ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 8H); 4.12 (q, 8H, ^3J=7.3 Hz); 3.22(d, 4H, $^2J_{H\text{-}P}$=20 Hz); 1.30 (t, 12H, ^3J=7.3 Hz). MS MALDI-TOF for $C_{22}H_{32}P_2O_{10}S_2$: calculated 582.09, observed 581.98.

7.3. General procedure for the Wittig–Horner olefination

Under nitrogen atmosphere, potassium *tert*-butoxide was added portionwise to a mixture containing the dialdehyde and the phosphonate (2.5 equiv) in dry THF at 0 °C. The mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was taken with MeOH/water mixture to give a precipitate. The solid was filtered then was washed twice with MeOH. The crude product was purified by recrystallization.

7.3.1. (*E*,*E*)-2, 5-Bis[3,4-ethylenedioxy-5-hexyl-2-thienyl)-1-ethenyl]thiophene: 4. Orange powder recrystallized from methanol, 53% yield. Mp 165 °C. ^{1}H NMR ($CDCl_3$) δ 6.86 (d, 2H, ^3J=15.8 Hz); 6.79 (d, 2H, ^3J=15.8 Hz); 6.78 (s, 2H); 4.25 (m, 8H); 2.63 (t, 4H,

$^3J=7.4$ Hz); 1.60 (m, 4H); 1.36 (m, 12H); 0.91 (t, 6H, $^3J=6.9$ Hz). MS MALDI-TOF for $C_{32}H_{40}O_4S_3$: calculated 584.21, observed 584.03. Anal. (Calcd): C, 65.75 (65.72); H, 6.81 (6.89).

7.3.2. (*E*,*E*,*E*)-1, 2-Bis[5-[2-(3,4-ethylenedioxy-5-hexyl-2-thienyl)-1-ethenyl]-2-thienyl]ethene: 5. Red-purple powder recrystallized from methanol, 55% yield. Mp 178 °C. ^{1}H NMR ($CDCl_3$) δ 6.89 (s, 2H); 6.88 (d, 2H, $^3J=15.8$ Hz); 6.85 (d, 2H, $^3J=3.8$ Hz); 6.81 (d, 2H, $^3J=3.8$ Hz); 6.80 (d, 2H, $^3J=15.8$ Hz); 4.26 (m, 4H); 4.20 (m, 4H); 2.62 (t, 4H, $^3J=7.5$ Hz); 1.58 (m, 4H); 1.32 (m, 12H); 0.89 (t, 6H, $^3J=6.9$ Hz). MS MALDI-TOF for $C_{38}H_{44}O_4S_4$: calculated 692.21, observed 692.09. Anal. (Calcd): C, 65.61 (65.86); H, 6.55 (6.40).

7.3.3. (*E*,*E*,*E*,*E*)-2,5-Bis[2-[5-(3,4-ethylenedioxy-5-hexyl-2-thienyl)-2-thienyl]-1-ethenyl]-2-thienyl]thiophene: 6. Purple powder recrystallized from methanol, 50% yield. Mp 188 °C dec. ^{1}H NMR ($CDCl_3$) δ 6.95–6.80 (m, 14H); 4.26 (m, 4H); 4.22 (m, 4H); 2.64 (t, 4H, $^3J=7.5$ Hz); 1.55 (m, 4H); 1.30 (m, 12H); 0.90 (t, 6H, $^3J=6.9$ Hz). MS MALDI-TOF for $C_{44}H_{48}O_4S_5$: calculated 800.22, observed 800.01.

7.3.4. (*E*,*E*)-2,5-Bis[2-(5-hexyl-2-thienyl)-1-ethenyl]- 3,4-ethylenedioxythiophene: 1. Orange powder recrystallized from methanol, 53% yield. Mp 165 °C. ^{1}H NMR ($CDCl_3$) δ 6.87 (d, 2H, $^3J=15.8$ Hz); 6.80 (d, 2H, $^3J=15.8$ Hz); 6.78 (d, 2H, $^3J=3.5$ Hz); 6.62 (d, 2H, $^3J=3.5$ Hz) 4.27 (s, 4H); 2.76 (t, 4H, $^3J=7.5$ Hz); 1.65 (m, 4H); 1.30 (m, 12H); 0.89 (t, 6H, $^3J=7.5$ Hz). MS MALDI-TOF for $C_{30}H_{38}O_2S_3$: calculated 526.20, observed 526.20. Anal. (Calcd): C, 68.22 (68.40); H, 7.07 (7.27).

7.3.5. (*E*,*E*)-5,5′-bis[2-(3,4-ethylenedioxy-2-thienyl)-1-ethenyl]-2,2′-bithiophene: 3a. Orange powder recrystallized from chloroform–methanol solution, 67% yield. Mp 205 °C. ^{1}H NMR (C_6D_6) δ 7.22 (d, 2H, $^3J=15.9$ Hz); 7.11 (d, 2H, $^3J=15.9$ Hz); 6.80 (d, 2H, $^3J=3.7$ Hz); 6.52 (d, 2H, $^3J=3.7$ Hz); 6.01 (s, 2H); 3.36 (m, 8H). HRMS (EI) for $C_{24}H_{18}O_4S_4$: calculated 498.0088, observed 498.0085.

7.3.6. (*E*,*E*)-5,5′-bis[2-(3,4-ethylenedioxy-5hexyl-2-thienyl)-1-ethenyl]-2,2′-bithiophene: 3b. Orange powder recrystallized from methanol, 55% yield. Mp 210 °C. ^{1}H NMR (CDCl3) δ 6.88 (d, 2H, $^3J=15.8$ Hz); 6.85 (d, 2H, $^3J=3.8$ Hz); 6.81 (d, 2H, $^3J=15.8$ Hz); 6.79 (d, 2H, $^3J=3.8$ Hz); 4.24 (m, 8H); 2.64 (t, 4H, $^3J=7.4$ Hz); 1.61 (m, 4H); 1.34 (m, 12H); 0.90 (t, 6H, $^3J=6.8$ Hz). MS MALDI-TOF for $C_{36}H_{42}O_4S_4$: calculated 666.20, observed 665.96. Anal. (Calcd): C, 64.72 (64.83); H, 6.25 (6.35).

7.3.7. (*E*,*E*)-5,5′-bis[(2-thienyl)-1-ethenyl]-2,2′-bis((3,4-ethylenedioxythiophene): 2a. Under nitrogen atmosphere, potassium *tert*-butoxide (0.3 mmol) was added portionwise to a mixture containing 117 mg of phosphonate **16** (0.2 mmol) and an excess of thiophenecarbaldehyde **21a** (120 mg, 1,05 mmol) in dry THF (10 mL) at 0 °C. The red mixture was stirred at room temperature for 1 h then 20 mL of water was added to give a precipitate. The solid was filtered then was washed twice with MeOH to give 65 mg of orange powder recrystallized from methanol, 65% yield. Mp >260 °C. ^{1}H NMR (C_6D_6) δ 7.39 (d, 2H, $^3J=15.9$ Hz); 7.21 (d, 2H, $^3J=15.9$ Hz); 6.71 (d, 2H, $^3J=3.4$ Hz); 6.68 (d, 2H, $^3J=4.9$ Hz); 6.64 (dd, 2H, $^3J=3.4$, 4.9 Hz); 6.01 (s, 2H); 3.49 (m, 4H); 3.33 (m, 4H). HRMS (EI) for $C_{24}H_{18}O_4S_4$: calculated 498.0088, observed 498.0066.

7.3.8. (*E*,*E*)-5,5′-bis[(5-hexyl-2-thienyl)-1-ethenyl]-2,2′-bis((3,4-ethylenedioxythiophene): 2b.

Method A. Starting from phosphonate **13b** and dialdehyde **15**.

A suspension of dialdehyde **15** (135 mg, 0.4 mmol) in dry THF with 4 equiv of phosphonate **13b** (510 mg, 1.6 mmol) under nitrogen atmosphere, was treated dropwise with 4 equiv of BuLi (1.6 M in hexane) at room temperature and under sonic activation. The solution was immediately turned red and was stirred for about 20 min at room temperature. The solution was concentrated in vacuo and was treated with a MeOH/water mixture to give a precipitate. The solid was filtered then was washed twice with MeOH to give 95 mg of red powder recrystallized from methanol, 35% yield.

Method B. Starting from phosphonate **16** and aldehyde **21b**

Under nitrogen atmosphere, potassium *tert*-butoxide (0.3 mmol) was added portionwise to a mixture containing 125 mg of phosphonate **16** (0.21 mmol) and an excess of aldehyde **21b** (215 mg, 1,1 mmol) in dry THF (10 mL) at 0 °C. The red mixture was stirred at room temperature for 1 h. The solution was concentrated in vacuo and was treated with a MeOH/water mixture to give a precipitate which was filtered and washed with MeOH (84 mg, 60% yield).

Mp 200 °C. ^{1}H NMR ($CDCl_3$) δ 6.90 (d, 2H, $^3J=15.8$ Hz); 6.83 (d, 2H, $^3J=15.8$ Hz); 6.77 (d, 2H, $^3J=3.4$ Hz); 6.62 (d, 2H, $^3J=3.4$ Hz); 4.32 (m, 4H); 4.32 (m, 4H); 2.76 (t, 4H, $^3J=7.4$ Hz); 1.65 (m, 4H); 1.30 (m, 12H); 0.87 (t, 6H, $^3J=6.8$ Hz). MS MALDI-TOF for $C_{36}H_{42}O_4S_4$: calculated 666.20, observed 666.08. Anal. (Calcd): C, 64.52 (64.83); H, 6.40 (6.35).

7.4. X-ray structure of compound 3a

Single crystals of **3a** were mounted on an Enraf-Nonius MACH3 diffractometer with graphite monochromator and Mo Kα ($\lambda=0.71073$ Å) radiation at $T=294$ K. The data collections were performed with the $\omega/2\theta$ scan technique. The crystal structures were solved by direct method (SIR) and refined by full matrix least squares techniques using MolEN software.

Crystal data of **3a**
Formula : $C_{24}H_{18}O_4S_4$
Molecular weight : 498.66
Crystal system : monoclinic
Space group : P 1 21/n 1
a (Å) : 10.82(1)
b (Å) : 8.584(2)
c (Å) : 13.04(1)
α (deg) : 90
β (deg) : 112.4(1)
γ (deg) : 90
V (Å^3) : 1119(2)

Z: 2
Dcalc(gcm^{-3}) : 1.48
F_{000} : 516
μ (mm^{-1}) : 0.455
Trans. min and max : 0.3663/1.0000
Temperature (K) : 294
Wavelength (Å) : 0.71073
Radiation : Mo Kα graphite monochromated
Scan mode: $\omega/2\theta$
hkl limits : −12,0/−10,0/−14,15
Theta limits (deg): 2.5/24.96
Number of data meas.: 2228
Number of data with: 420
$I>3\ \sigma(I)$
Weighting scheme: $4Fo^2/(\sigma 2(Fo^2) + 0.0064\ Fo^4)$
Number of variables: 65
R: 0.069
Rw: 0.083
GOF: 1.438
Largest peak in final: 0.352
difference (e $Å^{-3}$)

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre under reference CCDC 252152

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Understanding the catalytic role of flexible chiral δ-amino alcohols: the 1-(2-aminoethyl)norbornan-2-ol model

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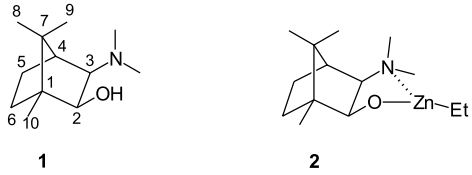
Abstract—An empiric first approach to the knowledge about the structural factors influencing the catalytic behavior of conformationally flexible δ-amino-alcohol-based ligands, for the enantioselective addition of dialkylzincs to prochiral carbonyl groups, has been applied using the 1-(2-aminoethyl)norbornan-2-ol moiety as the model chiral system, and the asymmetrically catalyzed addition of diethylzinc to benzaldehyde as the test reaction. For this purpose, a selected small library of seven norbornane-based chiral ligands, bearing well-defined structural variations to allow a comparative study, that is, variation of the relative configuration and steric hindrance at the C(2), C(3) and/or C(7) norbornane positions, has been synthesized and probed in the mentioned test reaction. The experimental results obtained have been rationalized empirically using diastereomeric Noyori-like transition states, demonstrating that the conformational flexibility of the δ-amino-alcohol ligands, contrary to the more studied and rigid β-amino-alcohols, plays a crucial role on the catalytic behavior of such ligands (stereochemical sense and degree of the stereodifferentiation in the asymmetric process), which makes such structural factors, important for the improved design of new related chiral catalysts. In this sense, a robust crude empirical model for the prediction of the catalytic behavior of such δ-amino-alcohol-based ligands is proposed.

1. Introduction

Asymmetric synthetic methods involving C–C bond formation have gained great importance in organic synthesis.[1] In this sense, the catalyzed enantioselective addition of dialkylzinc reagents to prochiral carbonyl groups must be outlined,[2] since it produces valuable enantiomerically pure or enriched alcohols, which can be used as key *chirons* (chiral building blocks)[3] for the preparation of a large number of biologically active molecules, that is, enantiopure natural products with pharmacological activity.[4]

Since Noyori et al. demonstrated the high efficiency of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) (**1** in Fig. 1) as chiral ligand for the catalyzed asymmetric addition of diethylzinc to benzaldehyde,[5] and suggested a mechanistic model for the catalytic cycle, based on an in situ formation of a stable five-membered Zn-chelate catalyst **2** (Fig. 1),[6] many other chiral β-amino alcohols have been synthesized and employed as chiral ligands for this asymmetrically catalyzed C–C bond-formation process.[7,8]



1 **2**

Figure 1. Noyori's DAIB (**1**) and corresponding Zn-chelate catalyst (**2**) for the asymmetric addition of diethylzinc to carbonyl groups.

Noyori's studies on DAIB[6] have served as a model for the prediction of the catalytic role of other related β-amino alcohols. Thus, the catalytic role of a great number of chiral β-amino alcohols has been extensively outlined and explained on the basis of the formation of five-membered Zn chelates.[8] Nevertheless, the applicability of γ- and δ-amino alcohols as chiral ligands for such an interesting asymmetric process has been less studied and, therefore, their catalytic role is still not totally understood.[9,10] In these latter cases, the Zn atom is part of a more flexible six- or seven-membered ring in the corresponding Zn chelate (Fig. 2) and, therefore, the rigidity of the chiral

Keywords: Camphor; Diethylzinc addition; Asymmetric reactions; Chiral ligands; Ligand design.
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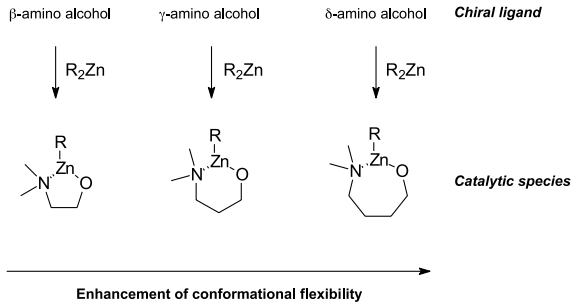


Figure 2. Relationship between chiral-ligand type and catalytic-specie flexibility.

amino-alcohol ligand plays an important role in limiting the conformational freedom of such catalytic species, particularly around the oxygen and nitrogen atoms.[11]

Among the broad group of chiral δ-amino alcohols, δ-amino norbornanols are favored candidates to act as chiral ligands for the asymmetric process under consideration, due to the rigidity imposed by the bicyclic framework. In this sense, some δ-amino norbornanols have been recently described as good chiral ligands for the catalyzed enantioselective addition of dialkylzinc to benzaldehyde, for example, **3**,[10d] **4**[11a] and **5**[10f] in Figure 3: restricted torsion angles are highlighted.

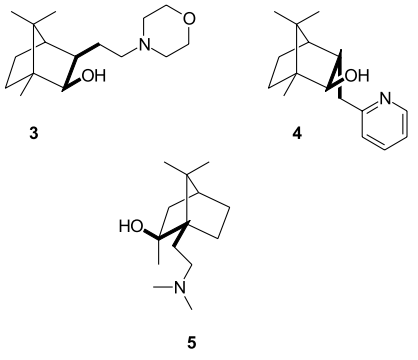


Figure 3. Some norbornane-based δ-amino alcohols described previously.

Unfortunately, the lack of general synthetic methods for enantiopure flexible δ-amino norbornanols has prevented the systematic study of the catalytic behavior of this interesting family of chiral δ-amino-alcohol-based ligands, as well as the establishment of their catalytic role. As an exception to the last, the recently-described accessibility to enantiopure 1-(2-aminoethyl)norbornan-2-ols (**6** to **9** in Fig. 4), by specific routes based on selective stereocontrolled Wagner–Meerwein rearrangements of camphor- or fenchone-derived intermediates,[10e–g,12] makes such flexible δ-amino 2-norbornanols, with additional limited conformational flexibility around the oxygen atom, to be interesting models to study the catalytic role of other related δ-amino alcohols.

In this sense, Fujita et al. were the first authors to develop an elegant synthetic strategy to enantiopure *N*,*N*-dialkyl-substituted 1-(2-aminoethyl)norbornan-2-*exo*-ols (**6** and **7** in Fig. 4).[10e–g] This fact allowed the authors to make a study of the role played by the alkyl substitution on the nitrogen

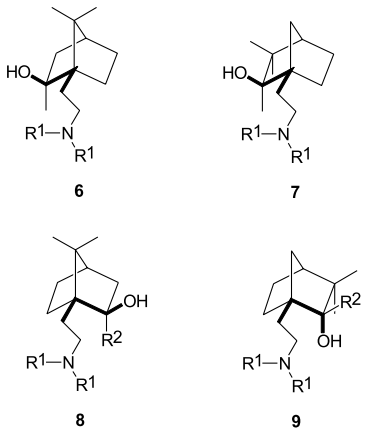
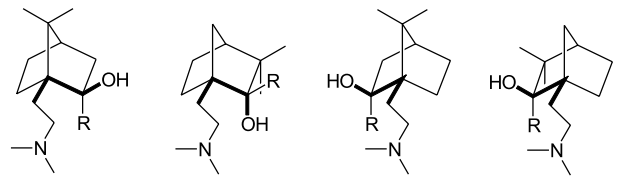


Figure 4. Some easily accessible 1-(2-aminoethyl)norbornan-2-ols.

atom (R^1), as well as by the *gem*-dimethyl substitution on the norbornane framework (7,7-dimethyl substitution in **6** vs 3,3-dimethyl in **7**), on the catalytic activity of such flexible ligands.

Continuing along these lines, we have recently developed an alternative synthetic route for the preparation of enantiopure *N*,*N*-dialkyl-substituted 1-(2-aminoethyl)norbornan-2-ols (**8** and **9** in Fig. 4), allowing variation of the substitution and relative configuration of the hydroxyl-bearing C(2) norbornane position (note R^2 groups and hydroxyl disposition of **8** and **9** in Fig. 4). The preliminary results on the influence of such structural factors on the catalytic behavior of the corresponding norbornane-based ligand have been recently reported by us in previous communications.[12]

In this paper we provide a crude empiric insight into the catalytic role of δ-amino alcohols, using the 1-(2-aminoethyl)norbornan-2-ol moiety as a model system and the asymmetrically catalyzed addition of diethylzinc to benzaldehyde as the test reaction. For this purpose, we have joined together our previously reported ligands[12] with some new ones, to form a selected small library of seven 1-(2-aminoethyl)norbornan-2-ols (**10** to **16** in Fig. 5) with well-defined structural variations [relative configuration and steric hindrance at the C(2), C(3) and/or C(7) norbornane positions]. Additionally, two previous results reported by Fujita on the catalytic behavior of *ent*-**11** (enantiomer of **11**) and *dia*-**16** [C(1)-epimeric diasteromer of **16**] of have been taken into account for comparison (Fig. 5).[10e–g] The comparative study on the catalytic activity of the library's individuals has allowed us to get valuable information on



10 (R = H)
11 (R = Me)
12 (R = Et)
13 (R = *i*Pr)
14 (R = *t*Bu)

15 (R = H)
16 (R = Me)

***ent*-11** (R = Me)

***dia*-16** (R = Me)

Figure 5. Selected library of 1-(2-aminoethyl)norbornan-2-ols.

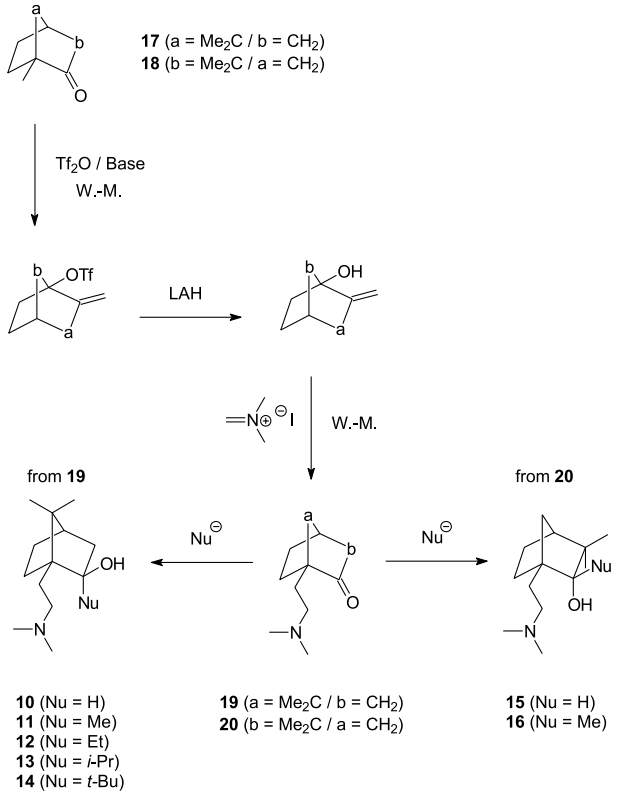
the influence exerted by combined structural factors on the catalytic activity, as well as to propose a rationalized empirical model for the catalytic role of such δ-amino-alcohol-based catalysts.

2. Results and discussion

2.1. Library preparation

7,7-Dimethylnorbornane-based ligands (**10** to **14** in Fig. 5) and 3,3-dimethylnorbornane-based ones (**15** and **16** in Fig. 5) were prepared from readily available natural (+)-(1*R*)-camphor (**17**) and (−)-(1*R*)-fenchone (**18**) respectively, according to our previously described four step route based in two stereocontrolled 2-norbornyl-cation Wagner-Meerwein rearrangements (Scheme 1).[13,14]

The key intermediates of the described synthetic route are the corresponding camphor- and fenchone-derived 1-(2-aminoethyl)norbornan-2-ones **19** and **20**.[14] These δ-amino 2-norbornanones are able to react with different nucleophilic reagents in a different highly diastereoselective form (due to the different topicity imposed by the rigid camphor and fenchone frameworks), to generate the corresponding desired δ-amino 2-norbornanols (2-*exo*-norbornanols from camphor-derived **19** and 2-*endo*-norbornanols from fenchone-derived **20**). The nucleophilic reagents used, as well as the yields obtained after purification by elution-chromatography, are summarized in Table 1.



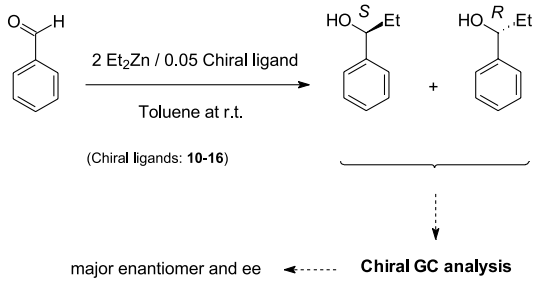
Scheme 1. Library preparation.

Table 1

2-Norbornanone	Nucleophilic reagent	2-Norbornanol (yield)
19	LAH	**10** (95%)
19	MeMgI	**11** (75%)
19	EtMgBr	**12** (75%)
19	*i*PrMgCl	**13** (79%)
19	*t*BuLi	**14** (71%)
20	LAH	**15** (76%)
20	MeMgI	**16** (70%)

2.2. Catalytic-behavior test

The chosen test reaction, that is, enantioselective addition of diethylzinc to benzaldehyde, was performed in the same conditions reported previously by Fujita et al. for testing *ent*-**11** and *dia*-**16**,[10f] in order to make possible a posterior comparison study (Scheme 2).



Scheme 2. Catalytic-behavior test.

After reaction, the mixture obtained was analyzed by chiral GC, to determine the configuration of the major alcohol enantiomer obtained as well as the ee reached. The retention time for each enantiomer was previously assigned by comparison of the chromatogram obtained for a scalemic mixture of such enantiomers with the rotation sign of such mixture.[15] The results obtained on the catalytic behavior of δ-amino 2-norbornanols **10** to **16** are summarized in Table 2. Previous Fujita's results on ligands *ent*-**11** and *dia*-**16** has been also included for comparison.[10f]

As Table 2 shows, the ligands studied exhibit a wide range of catalytic efficiency. Thus, Fujita's 3,3-dimethylated ligand *dia*-**16** exhibits the best catalytic stereodifferentiation with a pro-S behavior. On the other hand, 7,7-dimethylated ligands **10** to **12** and *ent*-**11**[16] exhibit a moderate stereodifferentiation and, whereas ligand **10** has a pro-R behavior, ligands **11**[16] and **12** shows a pro-S one. Finally, 7,7-dimethylated pro-R ligands **13** and **14**, and 3,3-dimethylated pro-S ligand **16** exhibit the worst stereodifferentiations.

2.3. Empiric rationalization

To explaining the catalytic behavior of the δ-amino 2-norbornanols studied, stereodifferentiation's sense (absolute configuration for the major 1-phenylpropan-1-ol obtained) and stereodifferentiation efficiency (reached ee), we have taken into account the next two preliminary considerations:

(1) In analogy to that established by Noyori for β-amino alcohols,[6] a catalytic seven-membered Zn-chelate species is

Table 2. Catalytic behavior of lignads **10–16**, *ent*-**11** and *dia*-**16** in the asymmetric addition of diethylzinc to benzaldehyde

Chiral ligand		1-Phenylpropan-1-ol		
Entry	$[\alpha]_D^{20a}$	Yield (%)[b]	ee (%)	Config.
10	+7.1	98	66[c]	*R*
11	−18.0	98	61[c]	*S*
ent-**11**[d]	+16.0[d]	99[d]	56[d,e]	*R*[d]
12	−13.0	97	62[c]	*S*
13	−13.6	98	6[c]	*R*
14	−19.1	95	8[c]	*R*
15	+10.6	98	67[c]	*S*
16	+15.4	97	13[c]	*S*
dia-**16**[d]	−19.4[d]	98[d]	91[d]	*S*[d]

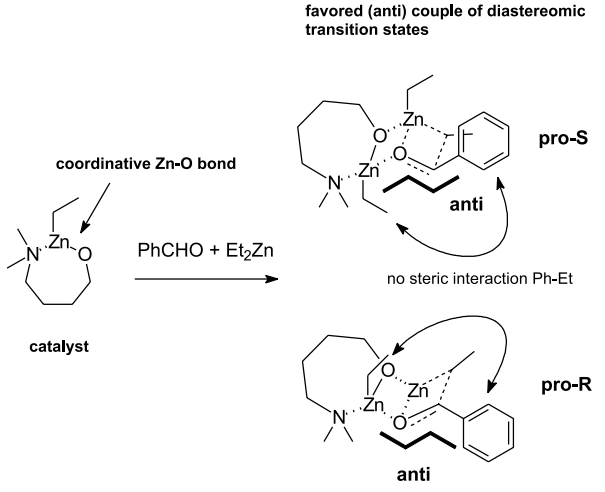
[a] Measured in $CHCl_3$ solution.
[b] Determined by GC.
[c] Determined by chiral GC using a Cyclodex-B column.
[d] Previous reported results (Ref. 10f)
[e] Determined by chiral GC using a OD-H column.

formed initially by reaction of a molecule of the chiral δ-amino-alcohol ligand with a molecule of diethylzinc (Fig. 2). This chiral catalyst coordinates diastereoselectively to a new molecule of dialkylzinc and a molecule of aldehyde by the catalyst's O and Zn atoms, respectively (Scheme 3). Such coordination activates and approximates the reactive molecules to give the enantioselective addition reaction, through a sterically-favored couple of diastereomeric tricyclic 7/4/4-membered Noyori's *anti*-type transition states (Scheme 3).[6] Therefore, controlled by the stereodifferentiation which occurs when the catalyst Zn–O bond coordinates to the aldehyde and a new molecule of diethylzinc.

(2) Since the topology around the catalyst's Zn–O bond changes with the catalyts conformation, due to the flexibility of the seven-membered Zn-chelate, only the more favored catalyst conformation has been taken into consideration for the empiric rationalization.

For the family of the δ-amino-2-*exo*-norbornanol-based catalysts, three more-favored conformations (*exo*-**I**, *exo*-**II** and *exo*-**III** in Scheme 4) would be possible,[17] due to the *exo*-bending disposition imposed by the rigid norbornane system to the seven-membered Zn chelate, as well as to a differential steric interaction exerted by the groups located at the C(2)-*endo* and C(7)-*syn* norbornane position on the dimethylamino group.

In these conformations, the three possible β-alkyl substituents of the C(2)-*endo* alkyl group (L, M and S = large, medium and small) would be disposed as shown in Figure 6 to minimize steric interactions. Thus, a large β-alkyl rest (L) would be situated at the less sterically congested



Scheme 3. Favored diasatereomeric Noyori's *anti*-type transition states for δ-amino-alcohol-based ligands.

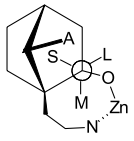
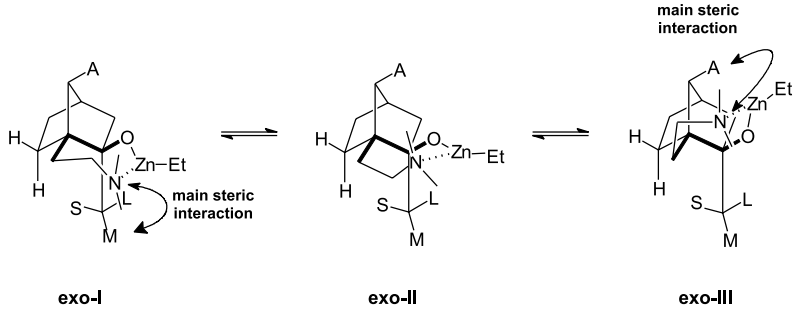
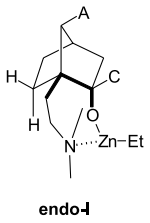


Figure 6. Favored disposition of the C(2)-*endo*-group substituents in a δ-amino-2-*exo*-norbornanol-based Zn-chelate catalyst.



Scheme 4. Favored conformations for δ-amino-2-*exo*-norbornanol-based Zn-chelate catalysts.



endo-I

Figure 7. Favored conformation for δ-amino-2-*endo*-norbornanol-based Zn-chelate catalyst.

These preliminary considerations make it possible to predict the most favored catalyst conformation from some key structural features which are present in the starting chiral ligand: C(2)-*exo* versus C(2)-*endo* hydroxyl group, C(7)-*syn* group and C(2)-*endo* group (Table 3).

Thus, for the 2-*exo*-norbornanol-based ligands **10** to **14** and *ent*-**11**, the existence of a voluminous C(7)-*syn*-methyl group makes catalyst conformation *exo*-**III** to be disfavored.

Table 3. Prediction of the favored catalyst conformation

Chiral ligand	Structural features						Favored catalyst conformation
	C(7)-*syn* group	C(2)-OH disposition	C(2)-group	L[a]	M[a]	S[a]	
10	Me	*exo*	*endo*-H				*exo*-**I**
11	Me	*exo*	*endo*-Me	H	H	H	*exo*-**I**
ent-**11**	Me	*exo*	*endo*-Me	H	H	H	*ent-exo*-**I**
12	Me	*exo*	*endo*-Et	Me	H	H	*exo*-**I**
13	Me	*exo*	*endo*-*i*-Pr	Me	Me	H	*exo*-**II**
14	Me	*exo*	*endo*-*t*-Bu	Me	Me	Me	*exo*-**II**
15	H	*endo*	*exo*-H				*endo*-**I**
16	H	*endo*	*exo*-Me				*endo*-**I**
dia-**16**	H	*exo*	*endo*-Me	H	H	H	*ent-exo*-**III**

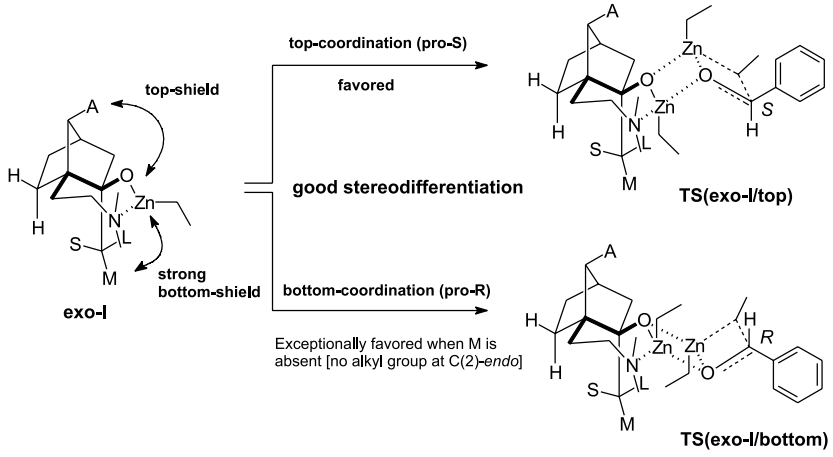
[a] Corresponding L, M, S (large, medium and small) β-substituents of the C(2)-*endo* alkyl groups.

'out-norbornane' zone, whereas a small one (S) would be located at the more congested 'under-norbornane' zone (Fig. 6 *N*-methyl and Zn-ethyl groups have been eliminated to clarify the figure). On the other hand, conformation *exo*-**I** is disfavored when important steric interactions between M and dimethylamino groups are possible, whereas conformation *exo*-**III** is disfavored for strong steric interactions between the C(7)-*syn* A and *gem*-dimethylamino groups (see Scheme 4).

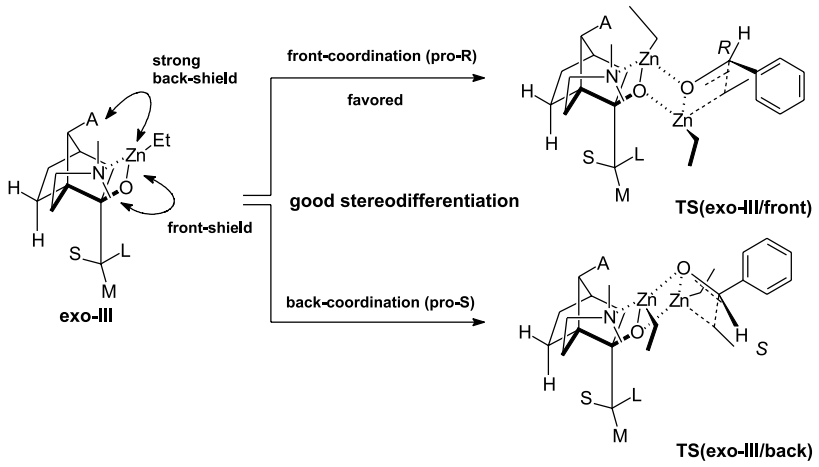
Contrarily to δ-amino-2-*exo*-norbornanol-based catalysts, the δ-amino-2-*endo*-norbornanol-based family would present a single more-favored conformation, due to the *endo*-bending disposition imposed by the rigid norbornane system to the seven-membered Zn chelate, as well as to the steric hindrance exerted by the norbornane *endo* face, mainly by the C(6)-*endo* hydrogen atom (Fig. 7).

Additionally, for ligands **10** to **12** and *ent*-**11**, a weak steric interaction by the C(2)-*endo* group (M = H) makes *exo*-**I** the favored conformation for the corresponding Zn chelate (cf. Table 3 and Scheme 4). Nevertheless, when the steric bulk of M increases, for example, from H to Me as in **12** to **13**, the preferred catalyst conformation changes from *exo*-**I** to *exo*-**II** (Scheme 4) to minimize steric interaction with the dimethylamino group. On the other hand, the lack of a C(7)-*syn*-methyl group in the 2-*exo*-norbornanol-based ligand *dia*-**16**, makes *exo*-**III** the favored conformation for the corresponding catalyst (cf. Table 3 and Scheme 4).

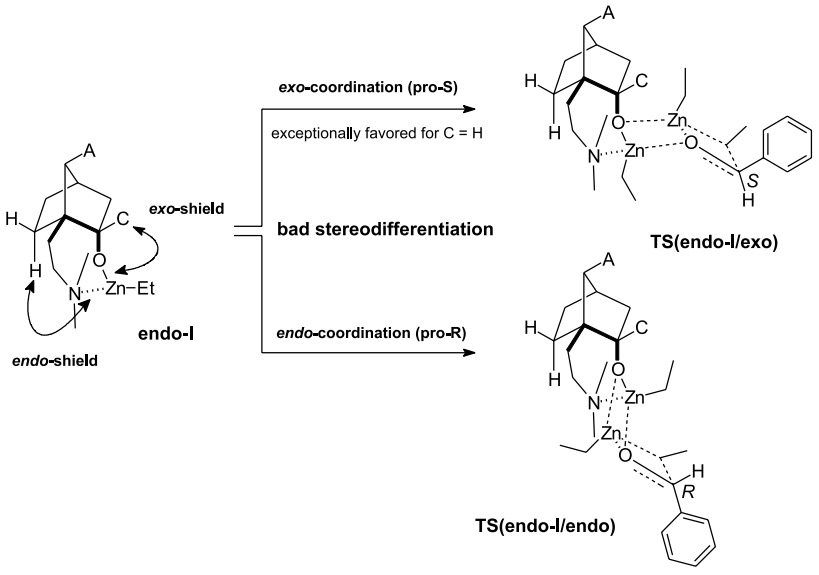
Finally, for the 2-*endo*-norbornanol-based ligands **15** and **16**, the preferred catalyst conformations the *endo*-**I** one, as commented before. Once the preferred catalyst conformation for a given δ-amino-alcohol-based ligand has been established, it is easy to predict empirically the sense and



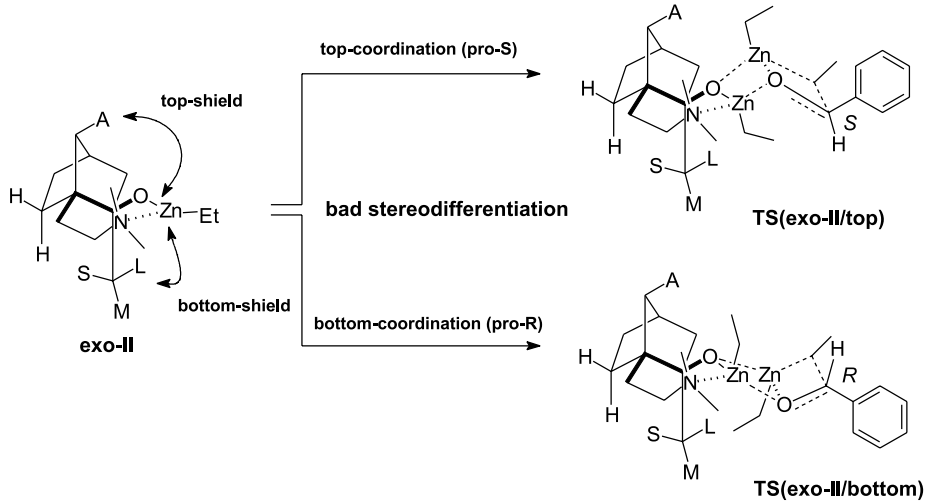
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

Table 4. Empirical prediction of the degree and sense of the stereodifferentiation

Ligand	Empiric prediction			Experimental results	
	Favored catalyst conformation [C(2) group]	Stereodifferentiation		Stereodifferentiation	
		Degree	Sense	Degree (ee)	Sense
10	*exo*-**I** [hydrogen]	Good	pro-R	66	*R*
11	*exo*-**I** [alkyl]	Good	pro-S	61	*S*
12	*exo*-**I** [alkyl]	Good	pro-S	62	*S*
13	*exo*-**II** [alkyl]	Bad		6	*R*
14	*exo*-**II** [alkyl]	Bad		8	*R*
15	*endo*-**I** [hydrogen]	Good	pro-S	67	*S*
16	*endo*-**I** [alkyl]	Bad		13	*S*
ent-dia-**16**[a]	*ent-exo*-**III** [alkyl]	Good	pro-R	91	*R*

[a] *ent-dia*-**16** has been considered instead of its enantiomer *dia*-**16** to facilitate the correlation with the correct enantiomer for the catalyst's conformation.

degree of stereodifferentiation for the asymmetric addition reaction.

Thus, for conformation *exo*-**I**, with a bottom Zn–O face strongly shielded by a near M substituent of a C(2)-*endo* alkyl group, even for M=H (see Scheme 5), the coordination takes preferably place (with a good degree of differentiation) at the top face, giving rise to a pro-S transition state [**TS**(*exo*-**I/top**) in Scheme 5]. An exception occurs when M=H, coordination taking place preferebly, and also with a good degree of stereodifferentiation, at the bottom Zn–O face and, therefore, giving rise to a pro-R trasnsition state [**TS**(*exo*-**I/bottom**) in Scheme 5].

On the other hand, conformation *exo*-**III**, with a back Zn–O face strongly shielded by the nearby A group, and a front Zn–O face softly shielded by an aminomethyl group, coordination takes place preferably (with a good degree of stereodifferentiation) at the front Zn–O face, giving rise to a pro-R transition state [**TS**(*exo*-**III/front**) in Scheme 6].

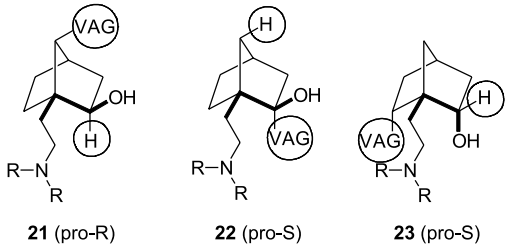
Conformation *exo*-**II** results to be an intermediate case between *exo*-**I** and *exo*-**III**. In such case, the Zn–O bond is placed in an intermediate position between the stereodifferentiating C(7)-*syn* and C(2)-*endo* alkyl groups (Scheme 7). Therefore, the degree of stereodifferentiation upon coordination of the Zn–O bond by the reactive aldehyde and dialkylzinc molecules is predicted to be low.

Finally, in conformation *endo*-**I** the *exo* Zn–O face is protected by the C(2)-*exo* alkyl group, whereas the *endo* face is shielded by the C(6)-*endo* hydrogen, giving rise to a low stereodifferentiation. On the other hand, the absence of the shielding C(2)-*exo* alkyl group, that is, when C=H, makes the *exo* Zn–O face the favored one for the coordination, giving rise to a good degree of pro-S stereodifferentiation (Scheme 8).

These crude empiric catalytic-behavior predictions (Schemes 5 to 8) are robust enough, agreeing with the obtained experimental results shown in Table 2. The obtained qualitative correlation is shown in Table 4.

This reasonable correlation between the experimental catalytic behavior and the crude proposed empirical model (Table 4), which is based on the variation of some crucial structural features of the starting chiral δ-amino-alcohol-based ligand (see Table 3), may allow a rational design of new improved 1-(2-aminoethyl)norbornan-2-ol-based ligands.[18]

Thus, a good 2-*exo*-norbornanol-based ligand should have some basic structural features which force the corresponding seven-membered Zn chelate to adopt a well stereodifferentiated *exo*-**I** or *exo*-**III** conformation (see Table 4). Such basic structural features which freeze the conformational flexibility of the catalyst at a stereodifferentiated *exo*-**I** conformation are: (a) a hydrogen atom at the C(2)-*endo* position and (b) a voluminous alkyl group (VAG) at the C(7)-*syn* position (see **21** in Fig. 8). To favor a well stereodifferentiated *exo*-**III** conformation, the optimum structural features are: (a) a VAG at the C(2)-*endo* position and, (b) a hydrogen at the C(7)-*syn* position (see **22** in Fig. 8).



21 (pro-R) **22** (pro-S) **23** (pro-S)

Figure 8.

On the other hand, a good 2-*endo*-norbornanol-based ligand will need to have some basic structural features to force the seven-membered Zn chelate to adopt a well stereodifferentiated *endo*-**I** conformation. Such structural features are: (a) a hydrogen atom at the C(2)-*exo* position and (b) a VAG at the C(6)-*endo* position (see **23** in Fig. 8).

Either way, the synthetic approach to such improved structures is not trivial, specially the C(6)-*endo*-substituted **22**. This synthetic effort would be necessary to validate the realized empiric chiral-ligand design.

3. Conclusion

High flexibility in δ-amino-alcohol-based catalysts leads to conformational flexibility in the seven-membered Zn chelate, which needs to be restricted so that good catalytic

behavior can be achieved. This conformational restriction has to be directed towards a specific favored conformation with a high degree of stereodifferentiation around the coordinative Zn–O bond. In this sense, previous empiric conformational analysis of the corresponding Zn chelate can serve as a valuable empirical tool to determine the basic structural features necessary in the starting ligand to limit conformational freedom towards the optimum conformation. The presence of some restricted torsion angle in the chelate, for example, C–C(1)–C(2)–O in the herewith studied δ-amino-norbornanol-based ligands, as well as a well-positioned couple of stereodifferentiating substituents, formed by a small group (e.g., hydrogen) and a shielding voluminous group, are more essential structural factors than alkyl substitution at the nitrogen atom.[19]

In conclusion, the developed empiric model enables a crude robust prediction of the ligand's catalytic behavior, but it should hopefully in the future be backed up by further computational and experimental verifications.

4. Experimental

4.1. General information

All starting materials and reagents were obtained from commercial suppliers and were used without further purification. Ether and toluene were dried by distillation over sodium/benzophenone, under an argon atmosphere, immediately prior to use. CH_2Cl_2 and $CHCl_3$ were dried by distillation over P_2O_5. Chromatography was performed on silica gel (flash) or neutral aluminum oxide (150 mesh). ^1H and ^{13}C NMR were recorded on 200 and 300-MHz spectrometers. Chemical shifts (δ) for ^1H and ^{13}C NMR were recorded in ppm downfield relative to the internal standard tetramethylsilane (TMS), and coupling constants (J) are in Hz. IR spectra were recorded on a FT spectrometer. Mass spectra were recorded on a 60 eV mass spectrometer. High resolution mass spectra (HRMS) were recorded using the FAB technique (deviations from the corresponding calculated mass are within ± 0.003). For gas–liquid chromatography (GC), chromatographs equipped with a capillary silicon-gum column (TRB-1) or Cyclodex-B column (chiral GC) were used.

4.1.1. (1*S*)-10-[(Dimethylamino)methyl]camphor (19) and (1*S*)-10-[(dimethylamino)methyl]fenchone (20). Amino 2-norbornanones **19** and **20** were prepared from commercial (1*R*)-camphor and (1*S*)-fenchone, respectively, according to our previously-described three step route.[14]

4.1.2. (1*S*)-1-[2-(Dimethylamino)ethyl]-7,7-dimethylnorbornan-2-*exo*-ol (10). Prepared from 2-norbornanone **19** by standard reaction with LAH.[12a] Yield: 95%. Colorless oil: $[\alpha]_D^{20} = +7.1$ (0.80, $CHCl_3$). FTIR (film) ν 3000–3500 (br) cm^{-1}. MS m/z 183 ($M^+ - 28$, 3), 58 (100). HRMS 211.1932 (calcd 211.1936 for $C_{13}H_{25}NO$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) $\delta = 0.79$ (s, 3H), 1.09 (s, 3H), 1.39–1.00 (m, 4H), 1.87–1.64 (m, 5H), 2.30 (m, 1H), 2.35 (s, 6H), 2.68 (ddd, $J = 12.9$, 9.9, 3.0 Hz, 1H), 3.74 (dd, $J = 8.0$, 3.9 Hz, 1H), 4.21 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) $\delta = 20.1$, 20.5, 25.1, 27.3, 31.9, 38.7, 45.4 (two signals), 45.5, 46.6, 52.7, 56.2, 76.8 ppm.

4.1.3. (1*S*)-1-[2-(Dimethylamino)ethyl]-2,7,7-trimethylnorbornan-2-*exo*-ol (11). Prepared from 2-norbornanone **19** by standard reaction with methylmagnesium iodide.[12a] Yield: 75%. Colorless oil: $[\alpha]_D^{20} = -18.0$ (1.01, $CHCl_3$). Spectroscopic data agree with that previously reported for the enantiomer.[10f]

4.1.4. (1*S*)-1-[2-(Dimethylamino)ethyl]-2-ethyl-7,7-dimethylnorbornan-2-*exo*-ol (12). Prepared from 2-norbornanone **19** by standard reaction with ethylmagnesium bromide.[12a] Yield: 75%. Colorless oil: $[\alpha]_D^{20} = -13.0$ (1.23, $CHCl_3$). FTIR (film) ν 3000–3500 (br) cm^{-1}. MS m/z 224 ($M^+ - 15$, 2), 210 ($M^+ - 29$, 1), 58 (100). HRMS 239.2227 (calcd 239.2249 for $C_{15}H_{29}NO$). ^1H NMR (200 MHz, $CDCl_3$, 22 °C) $\delta = 0.84$ (s, 3H), 0.93 (t, $J = 7.2$ Hz, 3H), 1.24 (s, 3H), 1.78–0.90 (m, 10H), 1.85 (m, 1H), 2.19 (s, 6H), 2.36 (dd, $J = 6.2$, 5.0 Hz, 2H), 5.40 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C) $\delta = 8.7$, 21.2, 22.4, 26.7, 27.0, 30.3, 32.7, 44.5, 44.6 (two signals), 46.1, 50.2, 55.4, 56.0, 79.6 ppm.

4.1.5. (1*S*)-1-[2-(Dimethylamino)ethyl]-2-isopropyl-7,7-dimethylnorbornan-2-*exo*-ol (13). Prepared from 2-norbornanone **19** by standard reaction with isopropylmagnesium chloride.[12a] Yield: 79%. Colorless oil: $[\alpha]_D^{20} = -13.6$ (2.61, $CHCl_3$). FTIR (film) ν 3000–3500 (br) cm^{-1}. MS m/z 235 ($M^+ - 18$, 1), 210 ($M^+ - 43$, 3), 58 (100). HRMS 253.2403 (calcd 253.2406 for $C_{16}H_{31}NO$). ^1H NMR (300 MHz, $CDCl_3$, 22 °C) $\delta = 0.90$ (s, 3H), 0.96 (d, $J = 7.6$ Hz, 6H), 1.79–0.80 (m, 8H), 1.41 (s, 3H), 2.07–1.93 (m, 3H), 2.24 (s, 6H), 2.83 (td, $J = 12.5$, 2.4 Hz, 1H), 6.48 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C) $\delta = 18.8$, 19.1, 21.3, 24.2, 27.1, 29.5, 31.7, 38.0, 45.2 (two signals), 47.0, 50.6, 55.7, 55.8, 80.9 ppm.

4.1.6. (1*S*)-2-*tert*-Butyl-1-[2-(dimethylamino)ethyl]-7,7-dimethylnorbornan-2-*exo*-ol (14). Prepared from 2-norbornanone **19** by standard reaction with *tert*-butyllithium.[12a] Yield: 71%. Colorless oil: $[\alpha]_D^{20} = -19.1$ (1.32, $CHCl_3$). FTIR (film) ν 3000–3500 (br) cm^{-1}. MS m/z 210 ($M^+ - 57$, 1), 58 (100). HRMS 267.2548 (calcd 267.2562 for $C_{17}H_{33}NO$). ^1H NMR (200 MHz, $CDCl_3$, 22 °C) $\delta = 0.87$ (s, 3H), 1.08 (s, 9H), 1.42 (s, 3H), 2.15–1.03 (m, 10H), 2.25 (s, 6H), 2.84 (m, 1H), 5.70 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C) $\delta = 21.0$, 24.6, 25.8, 29.0 (three signals), 29.4, 31.4, 41.0, 41.6, 45.1 (two signals), 46.6, 51.4, 55.9, 58.1, 83.6 ppm.

4.1.7. (1*S*)-1-[2-(Dimethylamino)ethyl]-3,3-dimethylnorbornan-2-*endo*-ol (15). Prepared from 2-norbornanone **20** by reaction with LAH.[12b] Yield: 76%. Colorless oil: $[\alpha]_D^{20} = +10.6$ (3.51, $CHCl_3$). FTIR (film) ν 3000–3500 (br) cm^{-1}. MS m/z 211 (M^+, 2), 58 (100). HRMS 211.1943 (calcd 211.1936 for $C_{13}H_{25}NO$). ^1H NMR (200 MHz, $CDCl_3$, 22 °C) $\delta = 0.84$ (s, 3H), 0.96 (s, 3H), 1.92–0.80 (m, 9H), 2.03 (ddd, $J = 12.8$, 3.4, 3.4 Hz, 1H), 2.17 (s, 6H), 2.44 (td, $J = 12.7$, 2.6 Hz, 1H), 3.21 (d, $J = 2.3$ Hz, 1H), 6.88 (brs, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C) δ 20.5, 22.4, 25.7, 31.1, 33.6, 39.6, 41.6, 44.6 (two signals), 47.7, 53.2, 56.8, 83.3 ppm.

4.1.8. (1*S*)-1-[2-(Dimethylamino)ethyl]-2,3,3-trimethylnorbornan-2-*endo*-ol (16). Prepared from 2-norbornanone **20** by standard reaction with methylmagenesium iodide.[12b] Characterization data, including molecular rotation have been previously described by us.[12b]

Acknowledgements

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15. As an example, in chiral GLC with a Cyclodex-B column, the peak at lower retention time corresponds to (+)-(*R*)-1-phenylpropan-1-ol.
16. The difference in stereodifferentiation obtained by the use of ligands **11** and *ent*-**11** is probably due to the different enantiopurity of such ligands (note different measured rotations in Table 2), which is probably due to the different purity of the starting natural products used for the preparation of such ligands.
17. Fujita et al. were the first to assign different conformational dispositions in the Zn–O bonds for the Zn chelates of *ent*-**11** and *dia*-**16**, in order to explain their different catalytic behavior (see Ref. 10f).
18. Soai, K. On the importance of this type of structure–activity design, see:. *Enantiomer* **1999**, *4*, 591–598.
19. Fujita et al. have previously demonstrated the low role played by the different *N*-gem-dialkyl substitution on the catalytic behavior of 1(2-aminoethyl)norbornan-2-ols (see Ref. 10f).

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Regioselective enzymatic acylation of vicinal diols of steroids

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Abstract—Monoacylated derivatives of a complete set of 2,3- and 3,4-vicinal diols of steroids were prepared by regioselective lipase-catalysed transesterification reactions. The enzymes displayed different selectivities towards the vicinal diols depending on the configuration of the hydroxyl groups.

1. Introduction

Polyhydroxylated steroids bearing vicinal diols on the A-ring are frequently found in Nature and some of them have relevant biological activities. For instance, the *trans*-diaxial 2β,3α-di-hydroxy pattern is present in natural sulphated sterols with antiviral[1] or anti-angiogenic[2] action, while 2α,3α-diols isolated from marine sources hold cytotoxic activity.[3] Steroidal saponins displaying *trans*-diequatorial 2α,3β-vicinal diols are quite frequent as gitogenin derivatives with antitumor properties.[4] In turn, the 3β,4β-diol functionality is present in a variety of steroids like in the agosterols, which induce reversal of multidrug resistance[5] and proteasome inhibition,[6] as well as in formestane metabolites[7] and in volkendousins, which are potent antitumor agents.[8] Finally, the 3α,4β-vicinal diol pattern has been identified in contignasterol, a natural anti-inflammatory compound[9] and, recently, in a steroid possessing chemotaxis activity.[10]

The discovery that lipases and proteases are able to act in organic solvents opened the way to an intensive synthetic exploitation of these biocatalysts, which, as shown in hundreds of papers and several industrial applications, display remarkable chemo-, regio- and stereoselectivity.[11]

Specifically in the steroids field, enzyme catalysis can play an important role for the mild and selective interconversion of functional groups via regioselective transformations.[12–19] Studies on the transesterification of polyfunctionalyzed steroids have shown that hydrolases can have access to substituents either on the A-ring or on the D-ring and/or on the side-chain of steroids. Several lipases showed a preference for C-3 hydroxyl groups,[13,14] whereas the protease subtilisin Carlsberg catalysed the acylation of C-17 OH.[14] Moreover, stereoselective resolutions of epimeric alcohols located on the steroid side-chain have been carried out by lipase PS[15] and, more recently, by subtilisin.[16]

Concerning the modifications of A-ring substituents, the selectivity of lipases for 3-hydroxysteroids has been applied to the chemoenzymatic synthesis of pharmacologically relevant tibolone metabolites.[17] Quite recently, we have reported a highly selective lipase-catalysed preparation of epimerically pure 5α,6α- and 5β,6β-epoxysteroids through acylation or deacylation reactions at the C-3 OH.[18] Finally, the ability to discriminate among different hydroxyl groups on the A-ring has been demonstrated in the esterification of ecdysteroids catalysed by *Candida antarctica* lipase, which afforded the 2β-monoacyl derivatives in good yields.[19]

In this context, to further explore the enzymatic transformations of steroids, we endeavoured a systematic study on the selectivity of commercially available lipases towards a complete set of stereoisomeric 2,3- and 3,4-vicinal diols, to provide a new tool for the selective transformation of these molecules and of related natural compounds.

2. Results and discussion

Different synthetic strategies were used to afford the

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Table 1. Lipase-catalysed monoacylation of vicinal diols[a]

Substrate	Novozym 435	*C. rugosa* lipase	Lipase AY	Lipase PS	Lipase AK	*C. viscosum* lipase	Porcine pancreatic lipase	Lipozyme IM 20	Lipase CE
1	−	++	+	+	+	+	−	−	−
2	−	+	+	++	+	+	−	−	−
3	++	−	−	−	−	−	−	−	−
4	++	+[b]	+[b]	++	−	−	−	−	−
5	+	++	++	+	+	+	−	−	−
6	+	+	+	+	+	++	−	−	−
7	−	+	−	++	+	+	−	−	−
8	−	−	−	−	−	−		−	−

[a] Conversion and product(s) formation was evaluated by TLC.
[b] The formation of two products was observed.

requested stereoisomeric vicinal diols **1**–**8**. Woodward's *cis*-dihydroxylation method, which is known to be selective for the more hindered β-face of 5α-steroids,[20] was applied to Δ^2- or Δ^3-unsaturated precursors affording the *cis*-β diols **1** and **5** (Scheme 2). Complementarily, the *cis*-α diols **3** and **7** were accessed through osmium tetroxide-mediated dihydroxylation on the same olefins.[21] *Trans*-diequatorial diols **2** and **6** were obtained by two different approaches. Starting from cholestan-3-one, α-acetoxylation by lead tetracetate,[22] followed by stereoselective reduction by $NaBH_4/CeCl_3$ and deacetylation rendered the diol **2**. On the other hand, the 3β,4α-diol **6** was directly accessed by hydroboration of the Δ^4-3-one precursor.[23] Finally, *trans*-diaxial diols **4** and **8** were obtained by epoxide opening reactions.

As shown in the formula, the 2,3-diols were prepared by modifying the cholestane skeleton, whereas the difficulties found on separating the 5α- and 5β-epimers of Δ^3-cholestane by sequential crystallizations led us to prepare the set of 3,4-diols in the androstane series. The cholestane derivative **9** was also synthesised to confirm that lipases selectivity towards the A-ring OH was not affected by different substituents on the D-ring.

The performances of a panel of 9 commercial lipases were evaluated for the esterification of the vicinal diols **1**–**9**, using vinyl acetate as the acyl donor and toluene or acetone/THF as solvents for the cholestane or the androstane derivatives, respectively. TLC monitoring allowed the identification, for each substrate, of the lipase(s) able to promote the monoacylation of the substrates. As shown in Table 1, all the stereoisomeric vicinal diols were accepted as substrates by some of the enzymes tested with the exception of compound **8**.

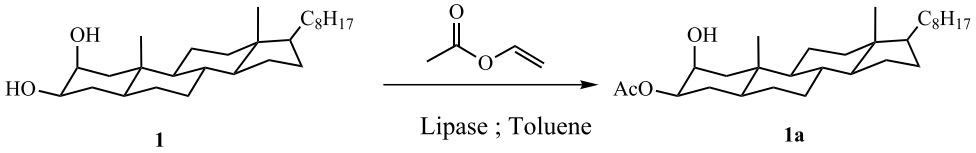
Lipases from different sources (*Candida antarctica*, column 2; *Candida rugosa*, columns 3 and 4; *Pseudomonas* strains, columns 5 and 6; *Chromobacterium viscosum*, column 7) were able to acylate the target compounds. Usually more than one enzyme was acting on the same substrate, with the notable exception of compound **3** (2α,3α-diol) acylated only by Novozym 435 (immobilized lipase B from *Candida antarctica*). Enzymatic acylations were highly regioselective, showing the formation of only one product by TLC, with the exception of *Candida rugosa* lipase (from Sigma or Amano) acting on compound **4**. Noteworthy, lipase PS and Novozym 435 showed complementary regioselectivity towards compound **4**.

For each substrate the best performing lipase (evaluated by TLC) was chosen for scale-up reactions, allowing the isolation of the corresponding monoester in good yields (Scheme 1). Products identification was easily done by NMR analysis (downfield shift of the signals due to the proton geminal to the acylated OH) and, when possible, by comparison with literature data.

The general preference of lipases for the C-3 OH[13,14] was observed with most of the substrates (Scheme 2). Specifically, the diequatorial vicinal diols **2** and **6** were converted into the corresponding 3β-acetate, showing a common preference of different lipases toward a 3β-equatorial OH in the presence of 2α-equatorial OH (substrate **2**) or of 4α-equatorial OH (substrate **6**).

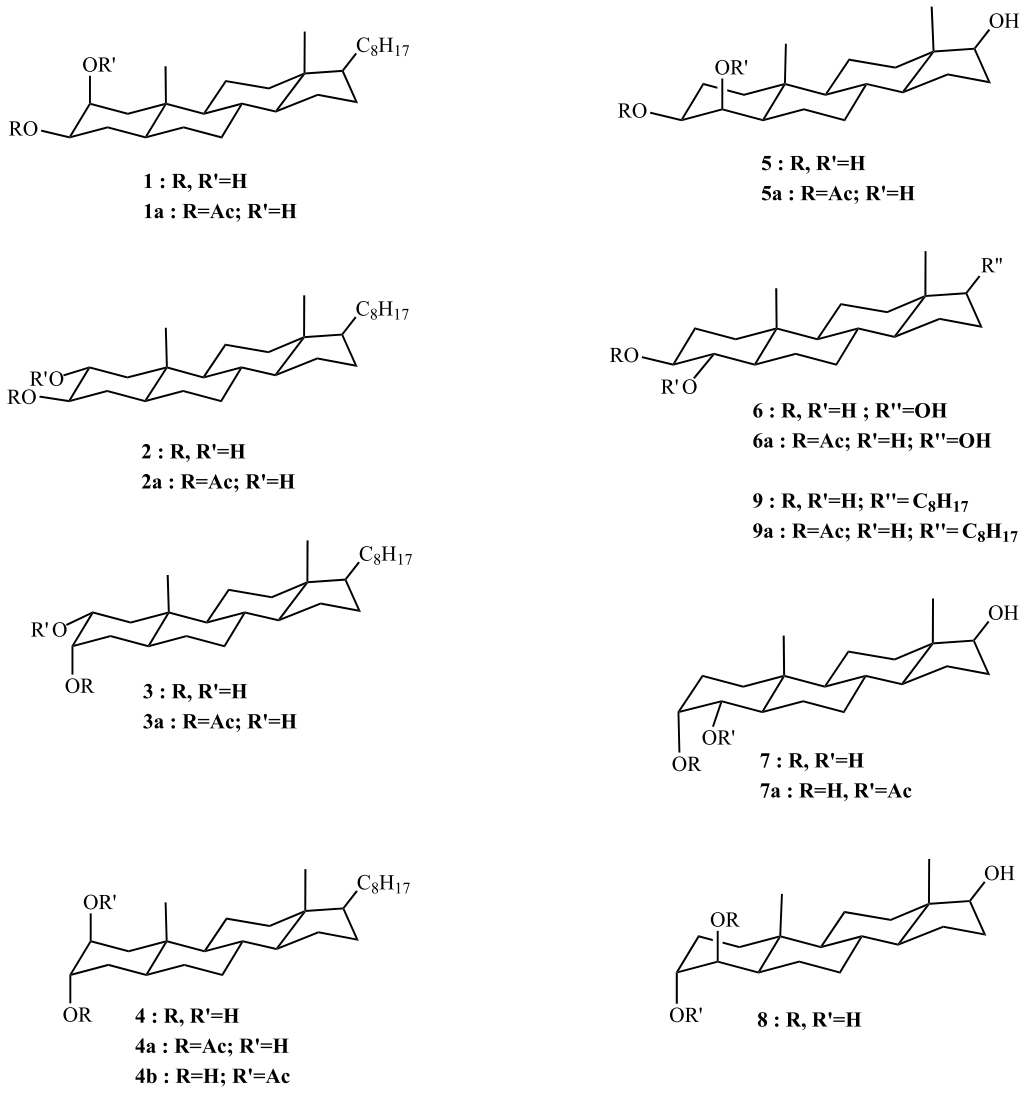
Concerning the diaxial 2β,3α- and 3α,4β-diols (substrates **4** and **8**), different outcomes were noticed. The diaxial 2β,3α-diol was differently accepted by the lipases tested. Whereas Novozym 435 converted this diol exclusively into the 3α-acetate **4a**, lipase PS showed opposite selectivity rendering the 2β-acyl derivative **4b** as the only product. Moreover, acylations catalysed by *Candida rugosa* lipases were not regioselective with this substrate. Conversely, the diaxial 3α,4β diol (**8**) was not accepted by any of the enzymes tested.

Finally, the equatorial/axial 2α,3α-diol (**3**), only accepted by Novozym 435, was acylated at the axial 3α-position, while, at variance, the 3α,4α-dihydroxy steroid (**7**) displaying axial/equatorial configuration, was acylated by different lipases at its equatorial 4α-OH.



1 **1a**

Scheme 1.



Scheme 2.

Moreover, in agreement with previous observations, the lipases tested did not catalyse any acylation of the 17β-OH (substrates **5**–**8**), that was found unaffected in each of the isolated products.

The ability of Novozym 435 to accept axial 3α-OH as a nucleophile has been reported previously.[13d] Herein, we noticed that this lipase catalyses the acylation of the 3α-OH even when a second hydroxyl is located at C-2 (substrates **3** and **4**), whereas the enzyme is inactive when the other OH is located at C-4 (substrates **7** and **8**).

Concerning lipase PS, the ability of this enzyme to esterify 3-hydroxy steroids has been previously observed with 3β-hydroxy-5,6-epoxy derivatives.[18] In the present work, lipase PS was found able to acylate most of the substrates (Table 1), catalysing their regioselective modification, not only at equatorial C-3 (product **2a**), but also at equatorial C-4 (product **7a**) and axial C-2 (product **4a**). Noteworthy, among the panel of tested enzymes, lipase PS was the only one able to acylate hydroxy groups located at the latter positions.

Candida rugosa lipase accepted most of the substrates. Specifically, this enzyme catalysed the acetylation of substrates **1**, **2**, **5** and **6** at their 3β-OH, as was expectable from previous studies.[13b,c] However, the 3α,4α-diol **7** was also acylated by *Candida rugosa* lipase at the C-4 OH, and the 2β,3α-diol **4** was acylated at both its hydroxy groups, showing that this enzyme has a quite variable affinity and selectivity pattern.

Chromobacterium viscosum lipase, which is known to have a strict selectivity for the 3β-hydroxyl of 5α-steroids,[14] showed the expected preference for diols carrying this OH (substrates **1**, **2**, **5** and **6**). In addition, acylation of the substrate **7** was also noticed, but at the 4α-OH.

Finally, the substrate **9**, a cholestane displaying 3β,4α-diequatorial configuration, was converted into the 3β-monoacetate **9a**, a result which confirmed that the differences in the steroid side chain do not influence the selectivity of lipases.

3. Conclusions

The reported results clearly show that lipases are able to

discriminate vicinal hydroxy groups located on the A-ring of steroids, being sensitive to the configuration of the different diols and affording the monoesters with high regioselectivity and good yields.

Considering the occurrence of steroidal vicinal diols in Nature, some of which being mono-acylated,[3,6] -glycosylated[4] or -sulphated,[1,10] these findings can offer useful synthetic tools for the preparation of these compounds and of related derivatives.

4. Experimental

4.1. General

All commercially available chemicals were used as supplied by the manufacturers. Steroids, porcine pancreatic lipase (13.3 U/mg) and crude *Candida rugosa* lipase (665 U/mg) were from Sigma. Novozym 435 (8600 PLU/g) and Lipozyme IM 20 (24 BIU/g) were from Novozymes. Lipase PS (30.8 U/mg, from *Pseudomonas cepacia*) was purchased from Amano and adsorbed on celite as described elsewhere.[16] Lipases AK (20 U/mg, from *Pseudomonas fluorescens*), CE (5.5 U/mg, from *Humicola lanuginosa*) and AY (30 U/mg, from *Candida rugosa*) were from Amano. *Chromobacterium viscosum* lipase (100 U/mg) was supplied by Finnsugar. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 at 300 M Hz and at 75.47 M Hz, respectively, using $CDCl_3$ and CD_3OD as solvents. Chemical shifts are reported on the δ (ppm) scale and are relative to tetramethylsilane as internal standard. Infrared spectra were recorder on a Jasco FT/IR-420 spectrometer. Mass spectra were recorded on a GCT Micromass spectrometer. Melting points were measured in a Büchi B-540. Flash chromatography was performed using silica gel (230–400 Mesh) from Merck and petroleum ether/ethyl acetate mixtures as eluents. TLC monitoring was done in petroleum ether/ethyl acetate as eluent and detected with the Komarowsky's reagent.[24]

4.2. Chemical synthesis of the diols

4.2.1. Cholestane-2β,3β-diol (1). According to a known procedure,[25] silica gel (70–230 Mesh, 100 g) was added to a solution of *p*-toluenesulfonic acid (3 g) in acetone (20 ml). The mixture was stirred, then evaporated under reduced pressure and left in a vacuum oven for 2 days. A mixture of cholestan-3β-ol (1.17 g, 3 mmol), *p*-toluenesulfonic acid/silica (15 g) and anhydrous toluene (200 ml) was stirred under reflux, until the consumption of the starting material (24 h). After cooling, diethyl ether was added and the silica was removed by filtration. The organic solution was washed with water, saturated bicarbonate solution and brine. Upon evaporation, cholest-2-ene (1.0 g, 90%) was recovered as a single product.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.66 (3H, s, CH_3-18), 0.75 (3H, s, CH_3-19), 0.86 (6H, two d, $J=6.6$ Hz, CH_3-26 and CH_3-27), 0.90 (3H, d, $J=6.5$ Hz, CH_3-21), 5.59 (2H, m, H-2 and H-3). ^{13}C NMR δ: 125.96, 125.85, 56.49, 56.27, 54.07, 42.47, 41.45, 40.03, 39.78, 39.51, 36.17, 35.79, 35.61, 34.69, 31.82, 30.31, 28.77, 28.22, 28.00, 24.20, 23.82, 22.82, 22.56, 20.90, 18.68, 11.98, 11.67.

To a solution of cholest-2-ene (420 mg, 1.15 mmol) in glacial acetic acid (35 ml), I_2 (600 mg) and $Cu(OAc)_2$ (500 mg) were added and the reaction mixture was refluxed under magnetic stirring. After 6 h the reaction was complete (TLC control). Then, toluene and NaCl were added and the insoluble salts were filtered off. Diethyl ether was added to the filtrate and the organic phase was washed with water and saturated sodium bicarbonate solution. Evaporation of the solvents under reduced pressure rendered the crude product, which was dissolved in ethanol/chloroform (4:1) (20 ml), and treated with NaOH 16% aqueous solution (1 ml) for 2 h. Finally, upon addition of chloroform, the organic layers were washed with water, HCl 5%, and brine and evaporated to dryness. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 4:1), affording pure cholestane-2β,3β-diol (**1**, 270 mg, 58%), which was crystallized from *n*-hexane, mp 173–175 °C (lit. 174–177[21a] and 175–176[26] °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.86 (6H, two d, $J=6.6$ Hz, CH_3-26 and CH_3-27), 0.89 (3H, d, $J=6.5$ Hz, CH_3-21), 1.00 (3H, s, CH_3-19), 3.63 (1H, dt, $J=4.6$, 10.8 Hz, H-3α), 4.02 (1H, brq, H-2α). ^{13}C NMR δ: 72.42, 70.22, 56.41, 56.26, 55.24, 45.33, 43.17, 42.62, 40.03, 39.50, 36.16, 35.78, 35.23, 34.83, 32.54, 31.96, 28.34, 28.22, 27.99, 24.17, 23.81, 22.80, 22.55, 21.29, 18.64, 14.56, 12.09. FTIR (ATR): ν_{max} 1049.1, 2850.3–2931.3, 3311.2 cm^{-1}.

4.2.2. Cholestane-2α,3β-diol (2). Glacial acetic acid (60 ml) was refluxed with acetic anhydride (5 ml) for 10 min, then cholestan-3-one (769 mg, 2 mmol) was added and, finally, lead tetracetate (1.5 g, 3.4 mmol) was slowly added. The reaction was heated under reflux, with magnetic stirring until the consumption of the starting material (24 h). After cooling, diethyl ether was added and the organic solution was washed with HCl 5%, saturated bicarbonate solution and brine. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 5:1) affording pure 3-oxocholestan-2α-yl acetate (710 mg, 80%), as a white amorphous powder, mp 120–122 °C (lit.[27] 124.7–125.2 °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.67 (3H, s, CH_3-18), 0.85 0.91 (9H, CH_3-21, CH_3-26 and CH_3-27), 1.12 (3H, s, CH_3-19), 2.15 (3H, s, CH_3CO), 5.29 (1H, dd, $J=6.6$, 12.9 Hz, H-2β). ^{13}C NMR δ: 204.3, 170.15, 74.46, 56.16, 56.06, 53.78, 47.84, 44.82, 43.57, 42.56, 39.71, 39.47, 37.18, 36.10, 35.74, 34.67, 31.56, 28.38, 28.20, 27.99, 24.16, 23.78, 22.80, 22.54, 21.60, 20.79, 18.63, 12.75, 12.04. FTIR (ATR): ν_{max} 1222.7, 1727.9, 1750.1 cm^{-1}.

To a solution of 3-oxocholestan-2α-yl acetate (700 mg, 1.6 mmol) in THF/methanol 2:1, $CeCl_3 \cdot 7H_2O$ (745 mg, 2 mmol) was added and the mixture was stirred for 10 min at room temperature before $NaBH_4$ (120 mg, 3.2 mmol, 8 equiv) was slowly added. After 30 min, the reaction was complete (TLC monitoring) and HCl 5% was added dropwise. The mixture was poured into water and extracted with diethyl ether. The organic solution was washed with

HCl 5%, saturated bicarbonate solution and brine, and evaporated to dryness, yielding 3β-hydroxycholestan-2α-yl acetate (641 mg, 91%), as a white powder, mp 73–75 °C.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.64 (3H, s, CH_3-18), 0.84–0.90 (12H, CH_3-19, CH_3-21, CH_3-26, CH_3-27), 2.08 (3H, s, CH_3CO), 3.59 (1H, ddd, J=5.4, 9.5, 11.1 Hz, H-3α), 4.82 (1H, ddd, J=4.8, 9.4, 11.6 Hz, H-2β). ^{13}C NMR δ: 171.59, 76.49, 73.53, 56.28, 56.17, 54.17, 44.43, 42.52, 42.12, 39.81, 39.47, 37.27, 36.11, 35.89, 35.73, 34.70, 31.79, 28.19, 27.97, 27.77, 24.15, 23.77, 22.79, 22.53, 21.38, 18.63, 13.09, 12.02.

3β-Hydroxycholestan-2α-yl acetate (500 mg, 1.12 mmol) was treated with NaOH as described in Section 4.2.1. The crude product was purified by flash chromatography (petroleum ether/ethyl acetate 4:1), rendering cholestane-2α,3β-diol (**2**, 370 mg, 82%), which was crystallized from methanol, mp 196.0–197.5 °C (lit.[22b] 204 °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.64 (3H, s, CH_3-18), 0.84–0.91 (12H, CH_3-19, CH_3-21, CH_3-26, CH_3-27), 3.40 (1H, ddd, J=5.1, 8.9, 10.9 Hz, H-3α), 3.59 (1H, ddd, J=4.7, 9.0, 11.5 Hz, H-2β). ^{13}C NMR δ: 73.11, 72.3, 56.30, 56.20, 54.26, 45.03, 44.83, 39.89, 39.48, 38.14, 37.46, 36.13, 35.77, 35.57, 34.73, 31.88, 28.23, 28.00, 27.91, 24.17, 23.80, 22.81, 22.55, 21.36, 18.64, 13.50, 12.04. FTIR (ATR): ν_{max} 1051.0, 2850.1–2930.3, 3312.9 cm^{-1}.

4.2.3. Cholestane-2α,3α-diol (3). A solution of $K_3Fe(CN)_6$ (1 g), Et_3N (7 μl), K_2CO_3 (420 mg) and methanesulphonamide (96 mg) in 20 ml of *t*-BuOH/H_2O (3:2) was prepared. Cholest-2-ene (370 mg, 1 mmol), (Section 4.2.1) was dissolved in 30 ml THF/*t*-BuOH/H_2O (10:3:2) and added to the previous solution. Then, 30 μl of OsO_4 solution (0.1 mg/μl in CH_3CN) was added and the reaction was stirred at room temperature until the total consumption of the starting material (48 h). Sodium sulphite 5% was added and the mixture was stirred for 5 h. Upon addition of diethyl ether, the organic layer was washed with HCl 5%, saturated bicarbonate solution and brine, and then, evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 4:1), rendering cholestane-2α,3α-diol (**3**, 242 mg), which was crystallized from *n*-hexane, mp 217–218 °C (lit.[22b] 216–219 °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.80 (3H, s, CH_3-19), 0.86 (6H, two d, J=6.6 Hz, CH_3-26 and CH_3-27), 0.90 (3H, d, J=6.6 Hz, CH_3-21), 3.77 (1H, br d, J=11.0 Hz, 2β-H), 3.96 (1H, br s, 3β-H). ^{13}C NMR δ: 69.27, 69.12, 56.35, 56.16, 54.16, 42.55, 40.93, 39.90, 39.49, 38.14, 36.90, 36.13, 35.78, 34.76, 34.22, 31.82, 28.22, 28.00, 27.65, 24.17, 23.80, 22.81, 22.55, 20.90, 18.65, 12.40, 12.06. FTIR (ATR): ν_{max} 1048.7, 2852.2–2930.0, 3315.0 cm^{-1}.

4.2.4. Cholestane-2β,3α-diol (4). A mixture of cholest-2-ene (400 mg, 1.1 mmol), $CHCl_3$ (15 ml) and 3-chloroperoxybenzoic acid (400 mg, 2.3 mmol) was stirred at room temperature. After the disappearance of the starting material (24 h), the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic phase was washed with sodium sulphite 5%, water and brine, dried with $MgSO_4$ and evaporated at reduced pressure, affording 2α,3α-epoxycholestane (395 mg, 93%).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.64 (3H, s, CH_3-18), 0.75 (3H, s, CH_3-19), 0.86 (6H, two d, J=6.6 Hz, CH_3-26 and CH_3-27), 0.90 (3H, d, J=6.5 Hz, CH_3-21), 3.14 (2H, m, H-2β and H-3β).

According to a known procedure,[28] to a solution of 2α,3α-epoxycholestane (374 mg, 0.9 mmol) in acetone (30 ml), periodic acid (350 mg) in acetone/water (1:1.5 ml) was added and the mixture was heated to reflux for 5 min, then concentrated until 1/3 of the initial volume and kept at room temperature for 30 min. This mixture was refluxed again while water (2 ml) was added dropwise for 30 min. Finally, the mixture was cooled, concentrated under vacuum and purified by flash chromatography (petroleum ether/ethyl acetate 4:1), yielding cholestane-2β,3α-diol (**4**, 309 mg, 85%), which was crystallized from methanol, mp 183–185 °C (lit. 178–180[1b] and 197–200[21a] °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.86 (6H, two d, J=6.6 Hz, CH_3-26 and CH_3-27), 0.90 (3H, d, J=6.5 Hz, CH_3-21), 0.99 (3H, s, CH_3-19), 3.87 (2H, m, H-2α and H-3β). ^{13}C NMR δ: 71.82, 70.61, 56.41, 56.19, 55.10, 42.60, 40.54, 40.01, 39.49, 38.93, 36.14, 35.78, 35.73, 34.88, 31.90, 31.71, 28.20, 28.01, 24.13, 23.80, 22.82, 22.55, 20.86, 18.64, 14.59, 12.10. FTIR (ATR): ν_{max} 1047.9, 2843.2–2930.9, 3310.1 cm^{-1}.

4.2.5. Androstane-3β,4β,17β-triol (5). A mixture of testosterone acetate (661 mg, 2 mmol), glacial acetic acid (30 ml) and zinc dust (4 g) was stirred at room temperature. After disappearance of the starting material (5 h), diethyl ether was added and the suspension was filtered through a celite pad. The filtrate was evaporated under reduced pressure, then dissolved in diethyl ether and washed with water, saturated sodium bicarbonate solution and brine. After drying with $MgSO_4$, the organic phase was evaporated, affording an epimeric mixture of 5α- and 5β-androst-3-en-17β-yl acetate (595 mg, 94%).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.78 (3H, s, 18-CH_3), 0.80 and 0.96 (3H, two s, 19-CH_3), 2.03 (3H, s, CH_3CO), 4.56 (1H, m, H-17α), 5.29 (1H, dq, H-4), 5.54 and 5.66 (1H, two m, H-3). The 5α- and 5β- epimeric ratio, evaluated by the integration of the H-3 multiplets,[29] was 0.8:1. Epimerically pure 5α-androst-3-en-17β-yl acetate was obtained after 3 sequential crystallizations in *n*-hexane.

5α-Androst-3-en-17β-yl acetate (200 mg, 0.63 mmol) reacted with I_2/$Cu(OAc)_2$, the product obtained was treated with NaOH (Section 4.2.1) and purified by flash chromatography (petroleum ether/ethyl acetate 1:2), rendering androstane-3β,4β,17β-triol (**5**, 95 mg), as a white amorphous powder, mp 257–260 °C (lit.[30] 263–265 °C).

Selected data: ^{1}H NMR ($CDCl_3$/CD_3OD) δ: 0.72 (3H, s, CH_3-18), 1.04 (3H, s, CH_3-19), 3.50 (1H, m, H-3α), 3.57 (1H, t, J=8.6 Hz, H-17α), 3.68 (1H, br t, J=2.30 Hz, H-4α). ^{13}C NMR δ: 81.89, 75.12, 72.67, 56.03, 51.64, 43.42, 37.66, 37.17, 36.12, 36.05, 32.54, 30.09, 26.34, 25.80,

23.79, 20.69, 14.98, 11.42. FTIR (ATR): ν_{max} 1064.6, 2845.5–2934.2, 3308.3 cm^{-1}.

4.2.6. Androstane-3β,4α,17β-triol (6). Testosterone (288.4 mg, 1 mmol) was dissolved in THF (10 ml) and cooled to 0 °C. Then, BH_3 in THF (1.0 M, 5 ml) was added slowly. The mixture was stirred for 3 h, then warmed to room temperature over 2.5 h and cautiously quenched with a 10 N NaOH aqueous solution (2 ml), followed by slow addition of a 30% H_2O_2 aqueous solution (2 ml). This mixture was stirred overnight, then poured into water and extracted with diethyl ether. The organic layers were washed with HCl 5%, saturated bicarbonate solution and brine. After drying with $MgSO_4$, the solvent was evaporated at reduced pressure and the residue purified by flash chromatography (petroleum ether/ethyl acetate 1:2), rendering androstane-3β,4α,17β-triol (**6**, 246 mg, 80%), which was crystallized from methanol, mp 253.3–255.8 °C (lit. 248–250[23a] and 258–259[30] °C).

Selected data: ^{1}H NMR ($CDCl_3/CD_3OD$) δ: 0.72 (3H, s, CH_3-18), 0.85 (3H, s, CH_3-19), 3.20 (1H, t, $J=8.7$ Hz, H-4β), 3.29 (1H, m, H-3α), 3.59 (1H, t, $J=8.5$ Hz, H-17α). ^{13}C NMR δ: 81.87, 76.52, 75.53, 55.24, 51.53, 51.48, 43.38, 37.75, 37.23, 36.85, 35.68, 31.76, 30.13, 28.78, 23.77, 23.10, 21.10, 13.89, 11.47. FTIR (ATR): ν_{max} 1066.0, 2847.5–2932.0, 3309.1 cm^{-1}.

4.2.7. Androstane-3α,4α,17β-triol (7). 5α-Androst-3-en-17β-yl acetate (200 mg, 0.63 mmol) (Section 4.2.5) was oxidized by OsO_4 (Section 4.2.3). The product was treated with NaOH (Section 4.2.1) and purified by flash chromatography (petroleum ether/ethyl acetate 1:2), affording androstane-3α,4α,17β-triol (**7**, 110.6 mg, 57%).

Selected data: ^{1}H NMR ($CDCl_3/CD_3OD$) δ: 0.72 (3H, s, CH_3-18), 0.85 (3H, s, CH_3-19), 3.45 (1H, d, $J=10.2$ Hz, H-4β), 3.6 (1H, t, $J=8.5$ Hz, H-17α), 3.97 (1H, s, H-3β). ^{13}C NMR δ: 82.40, 73.56, 70.14, 54.19, 50.76, 42.52, 37.50, 37.11, 36.89, 34.90, 31.76, 31.10, 23.47, 22.58, 21.20, 20.30, 12.70, 11.49. FTIR (ATR): ν_{max} 1065.0, 2846.1–2933.3, 3307.8 cm^{-1}.

4.2.8. Androstane-3α,4β,17β-triol (8). 5α-Androst-3-en-17β-yl acetate (290 mg, 0.92 mmol) obtained as described above (2.5) reacted with 3-chloroperoxybenzoic (Section 4.2.4). The product obtained was treated with periodic acid (Section 4.2.4), deacetylated with NaOH (Section 4.2.1) and purified by flash chromatography (petroleum ether/ethyl acetate 1:2), affording androstane-3α,4β,17β-triol (**8**, 142 mg), which was crystallized from methanol, mp 263–264.3 °C.

Selected data: ^{1}H NMR ($CDCl_3/CD_3OD$) δ: 0.71 (3H, s, CH_3-18), 1.03 (3H, s, CH_3-19), 3.49 (1H, br s, H-4α), 3.55 (1H, t, $J=8.6$ Hz, H-17α), 3.75 (1H, br q, $J=2.6$ Hz, H-3β). ^{13}C NMR δ: 82.54, 76.56, 71.24, 56.94, 52.51, 45.24, 44.08, 37.99, 37.09, 36.96, 33.32, 33.21, 30.61, 26.60, 25.11, 24.31, 20.97, 14.85, 11.67. FTIR (ATR): ν_{max} 1064.9, 2849.8–2935.1, 3309.5 cm^{-1}. FD-MS $m/z=308.2386$ (100%, M^+), 309.2424 (27%, M^++1), 290.2237 (17%, M^+-H_2O).

4.2.9. Cholestane-3β,4α-diol (9). Hydroboration of cholest-4-en-3-one (384 mg, 1 mmol) under the conditions described in Section 4.2.8 rendered cholestane-3β,4α-diol (**9**, 352 mg, 87%), which was crystallized from *n*-hexane, mp 235–237 °C (lit.[31] 237 °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.62 (3H, s, CH_3-18), 0.79–0.87 (12H, CH_3-19, CH_3-21, CH_3-26, CH_3-27), 3.18 (1H, t, $J=10.2$ Hz, H-4β), 3.29 (1H, m, H-3α). ^{13}C NMR δ: 76.24, 75.25, 56.54, 56.37, 54.6, 50.86, 42.63, 40.08, 39.62, 37.28, 36.36, 36.27, 35.92, 35.16, 31.74, 28.37, 28.26, 28.11, 24.28, 23.93, 22.83, 22.78, 22.58, 21.08, 18.70, 13.58, 12.11. FTIR (ATR): ν_{max} 1047.1, 2851.2–2930.2, 3315.0 cm^{-1}.

4.3. Enzymatic acylation of 2,3- and 3,4-vicinal diols

In a typical screening assay, a solution of the substrate (2 mg), in 0.9 ml of solvent (toluene for the cholestane diols or acetone/THF for the androstane diols) and vinyl acetate (0.1 ml) was prepared. This solution was added to the enzyme (30 mg of crude enzymes, 10 mg of Lipozyme IM 20 or 5 mg of Novozym 435) in 3 ml vials, which were stopped with a cap and shaken at 250 rpm at 45 °C. The reactions were monitored by TLC (see Table 1).

4.3.1. 2β-Hydroxycholestan-3β-yl acetate (1a). To a solution of cholestane-2β, 3β-diol (**1**, 25 mg, 0.062 mmol) in toluene (8 ml) and vinyl acetate (2 ml), *Candida rugosa* lipase (100 mg) was added and the reaction was shaken at 250 rpm, at 45 °C. After 24 h the reaction was complete. The enzyme was filtered off and the solvent was evaporated, the residue was purified by flash chromatography (petroleum ether/ethyl acetate 5:1) yielding 2β-hydroxycholestan-3β-yl acetate (**1a**, 22 mg, 80%), which was crystallized from methanol, mp 147–148 °C (lit.[26] 154 °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.86 (6H, two d, $J=6.5$ Hz, CH_3-26 and CH_3-27), 0.89 (3H, d, $J=6.5$ Hz, CH_3-21), 1.03 (3H, s, CH_3-19), 2.08 (3H, s, CH_3CO), 4.09 (1H, br q, $J=2.6$ Hz, H-2α), 4.78 (1H, ddd, $J=3.34$, 4.71, 11.75 Hz, H-3α). ^{13}C NMR δ: 170.13, 75.58, 68.72, 56.30, 56.19, 55.15, 45.40, 42.90, 42.59, 39.95, 39.47, 36.12, 35.76, 35.30, 34.77, 31.86, 28.58, 28.20, 28.13, 27.98, 24.13, 23.79, 22.80, 22.54, 21.34, 21.22, 18.62, 14.51, 12.07. FTIR (ATR): ν_{max} 1025.1, 1259.3, 1721.8, 2858.0–2950.2, 3510.8 cm^{-1}. FD-MS $m/z=$ 386.3462 (100%, M^+-CH_3COOH), 447.3828 (83%, M^++1), 404.3776 (67%, M^++1-CH_3CO), 448.3870 (25%, M^++2), 61.0324 (8%, $CH_3COOH+1$).

4.3.2. 2α-Hydroxycholestane-3β-yl acetate (2a). To a solution of cholestane-2α, 3β-diol (**2**, 50 mg, 0.124 mmol) in toluene (8 ml), vinyl acetate (1 ml) and lipase PS (100 mg) were added and the reaction mixture was shaken for 24 h, under the conditions described above. After usual work-up and purification by flash chromatography, 2α-hydroxycholestane-3β-yl acetate was recovered (**2a**, 48 mg, 87%) as a white powder, mp 157–159 °C. The TLC R_f of **2a** and of 3β-hydroxycholestan-2α-yl acetate (synthesised in Section 4.2.2) using petroleum ether/ethyl acetate (2:1) as eluent were 0.47, and 0.39, respectively.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.84–0.90 (12H, CH_3-19, CH_3-21, CH_3-26, CH_3-27), 2.08 (3H, s, CH_3CO), 3.77 (1H, ddd, J=4.8, 9.4, 11.5 Hz, H-2β), 4.59 (1H, ddd, J=5.4, 9.5, 10.9 Hz, H-3α). ^{13}C NMR δ: 171.37, 78.99, 69.85, 56.13, 56.09, 54.03, 45.28, 44.34, 42.46, 39.75, 39.39, 36.81, 36.03, 35.68, 34.62, 32.53, 31.69, 30.82, 28.13, 27.90, 27.63, 24.08, 23.70, 22.70, 22.44, 21.25, 18.54, 13.17, 11.94. FTIR (ATR): ν_{max} 1025.9, 1259.8, 1718.8, 2857.0–2951.3, 3512.1 cm^{-1}. FI-MS m/z= 386.3553 (100%, M^+-CH_3COOH), 446.3842 (54%, M^+), 387.3591 (35%, M^++1-CH_3COOH), 447.3853 (33%, M^++1), 61.0251 (1%, $CH_3COOH+1$).

4.3.3. 2α-Hydroxycholestane-3α-yl acetate (3a). To a solution of cholestane-2α,3α-diol (**3**, 40 mg, 0.1 mmol) in toluene (8 ml), vinyl acetate (1 ml) and Novozym 435 (80 mg) were added and the reaction mixture was shaken for 2 days, under the conditions described above. After usual work-up and purification by flash chromatography, 2α-hydroxycholestane-3α-yl acetate was recovered (**3a**, 33 mg, 75%) and crystallized from methanol, mp 163–164 °C.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.82 (3H, s, CH_3-19), 0.87 (6H, two d, J=6.5 Hz, CH_3-26 and CH_3-27), 0.90 (3H, d, J=6.5 Hz, CH_3-21), 2.12 (3H, s, CH_3CO) 3.84 (1H, dt, J=4.2, 11.4 Hz, H-2β), 5.12 (1H, br q, J=2.6 Hz, H-3β). ^{13}C NMR δ: 171.58, 73.03, 68.11, 56.33, 56.23, 54.14, 42.57, 41.70, 39.88, 39.47, 39.29, 36.74, 36.13, 35.78, 34.71, 32.21, 31.77, 28.23, 27.99, 27.45, 24.16, 23.83, 22.81, 22.54, 21.38, 20.89, 18.63, 12.55, 12.04. FTIR (ATR): ν_{max} 1027.4, 1259.8, 1714.7, 2859.0 2952.5, 3516.3 cm^{-1}. FI-MS m/z=446.3828 (100%, M^+), 386.3293 (91%, M^+-CH_3COOH), 447.3842 (29%, M^++1), 387.3349 (23%, M^++1-CH_3COOH).

4.3.4. 2β-Hydroxycholestane-3α-yl acetate (4a). To a solution of cholestane-2β,3α-diol (**4**, 50 mg, 0.124 mmol) in toluene (10 ml), vinyl acetate (1 ml) and Novozym 435 (80 mg) were added and the reaction mixture was shaken for 3 days, under the conditions described above. After usual work-up and purification by flash chromatography, 2β-hydroxycholestane-3α-yl acetate was recovered as a single product (**4a**, 47.6 mg, 86%), mp 110–111 °C (lit.[1b] 106–107 °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.86 (6H, two d, J=6.6 Hz, CH_3-26 and CH_3-27), 0.90 (3H, d, J=6.5 Hz, CH_3-21), 0.99 (3H, s, CH_3-19), 2.07 (3H, s, CH_3CO), 3.88 (1H, br s, H-2α), 4.82 (1H, br s, H-3β). ^{13}C NMR δ: 170.52, 72.92, 68.65, 56.43, 56.25, 54.97, 42.58, 40.46, 39.99, 39.89, 39.46, 36.13, 35.77, 35.34, 34.81, 31.85, 28.66, 28.21, 27.97, 24.11, 23.83, 22.80, 22.53, 21.40, 20.81, 18.62, 14.18, 12.06. FTIR (ATR): ν_{max} 1033.1, 1261.2, 1714.2, 2860.1–2953.8, 3500.3 cm^{-1}.

4.3.5. 3α-Hydroxycholestane-2β-yl acetate (4b). To a solution of cholestane-2β,3α-diol (**4**, 50 mg, 0.124 mmol) in toluene (9 ml), vinyl acetate (1 ml) and lipase PS (200 mg) were added and the reaction mixture was shaken for 3 days, under the conditions described above. After usual work-up and purification by flash chromatography, 3α-hydroxycholestane-2β-yl acetate was recovered as a single product (**4b**, 37 mg, 67%), mp 115.7–116.2 °C (lit. 85–86[1b] and 113[27] °C).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.64 (3H, s, CH_3-18), 0.86 (6H, two d, J=6.6 Hz, CH_3-26 and CH_3-27), 0.89 (3H, d, J=5.3 Hz, CH_3-21), 0.90 (3H, s , CH_3-19), 2.04 (3H, s, CH_3CO), 3.84 (1H, br q, J=2.3 Hz, H-3β), 4.87 (1H, br q, H-2α). ^{13}C NMR δ: 170.30, 73.15, 67.59, 56.35, 56.17, 54.85, 42.55, 39.92, 39.48, 38.52, 37.10, 36.12, 35.77, 35.56 34.94, 31.84, 31.74, 28.19, 28.11, 27.99, 24.12, 23.81, 22.80, 22.54, 21.44, 20.20, 18.63, 13.64, 12.06. FTIR (ATR): ν_{max} 1034.5, 1263.2, 1716.4, 2862.8–2928.4, 3481.8 cm^{-1}.

4.3.6. 4β,17β-Dihydroxyandrostane-3β-yl acetate (5a). To a solution of androstane-3β,4β,17β-triol (**5**, 35 mg, 0.114 mmol) in toluene (5 ml), THF (5 ml) and vinyl acetate (1 ml), *Candida rugosa* lipase (100 mg) was added and the reaction mixture was shaken for 3 days, under the conditions described above. After usual work-up and purification by flash chromatography (petroleum ether/ethyl acetate 2:1), 4β,17β-dihydroxyandrostan-3β-yl acetate was recovered (**5a**, 29.3 mg, 74%).

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, s, CH_3-18), 1.06 (3H, s, CH_3-19), 2.09 (3H, s, CH_3CO), 3.63 (1H, t, J= 8.7 Hz, H-17α), 3.83 (1H, br t, H-4α), 4.72 (1H, ddd, J= 3.2, 4.8, 8.0 Hz, H-3α). ^{13}C NMR δ: 170.27, 81.87, 75.53, 72.88, 55.29, 50.98, 48.71, 42.93, 36.85, 36.54, 35.61, 35.44, 31.82, 30.45, 25.55, 23.34, 22.13, 21.34, 20.11, 14.71, 11.11. FTIR (ATR): ν_{max} 1041.5, 1258.2, 1709.3, 2840.9–2943.0, 3442.0 and 3530.1 cm^{-1}. FD-MS m/z=351.2470 (100%, M^++1), 290.2104 (78%, M^+-CH_3COOH), 350.2468 (37%, M^+).

4.3.7. 4α,17β-Dihydroxyandrostane-3β-yl acetate (6a). To a solution of androstane-3β,4α,17β-triol (**6**, 30 mg, 0.1 mmol) in acetone (6 ml), THF (3 ml) and vinyl acetate (1 ml), *Chromobacterium viscosum* lipase (200 mg) was added and the reaction mixture was shaken for 3 days, under the conditions described above. After usual work-up and purification by flash chromatography, 4α,17β-dihydroxyandrostan-3β-yl acetate was recovered (**6a**, 20.2 mg, 60%), and crystallized from methanol, mp 182–184 °C.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.73 (3H, s, CH_3-18), 0.86 (3H, s, CH_3-19), 2.09 (3H, s, CH_3CO), 3.46 (1H, t, J= 9.5 Hz, H-4β), 3.64 (1H, t, J=8.5 Hz, H-17α), 4.58 (1H, ddd, J=5.4, 9.2, 11.6 Hz, H-3α). ^{13}C NMR δ: 171.51, 81.85, 79.23, 72.48, 54.32, 51.29, 50.83, 42.88, 36.58, 36.01, 35.05, 31.00, 30.50, 25.62, 23.32, 22.48, 21.37, 20.54, 15.26, 13.51, 11.11. FTIR (ATR): ν_{max} 1035.6, 1262.2, 1707.7, 2841.6–2940.9, 3443.3 and 3522.3 cm^{-1}. FI-MS m/z=290.2061 (100%, M^+-CH_3COOH), 350.2541 (39%, M^+), 291.2042 (12%, M^++1-CH_3COOH).

4.3.8. 3α,17β-Dihydroxyandrostan-4α-yl acetate (7a). To a solution of 3α,4α,17β-trihydroxyandrostane (**7**, 118 mg, 0.38 mmol) in acetone (18 ml), THF (4 ml) and vinyl acetate (2 ml), lipase PS (500 mg) was added and the reaction mixture was shaken for 4 days, under the conditions described above. After usual work-up and purification by

flash chromatography, 3α,17β-dihydroxyandrostan-4α-yl acetate was recovered (**7a**, 102.3 mg, 76%) as a white powder.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.72 (3H, s, CH_3-18), 0.87 (3H, s, CH_3-19), 2.09 (3H, s, CH_3CO), 3.64 (1H, t, J=8.5 Hz, H-17α), 4.01 (1H, q, J=2.9, 2.7 Hz, H-3β). 4.85 (1H, dd, J=11.8, 2.9 Hz, H-4β). ^{13}C NMR δ: 171.24, 82.76, 75.20, 67.58, 54.11, 50.67, 42.83, 42.48, 37.68, 36.80, 34.79, 31.14, 30.84, 27.48, 26.75, 23.41, 22.42, 21.13, 20.27, 12.82, 11.51. FTIR (ATR): ν_{max} 1039.2, 1265.1, 1710.7, 2841.6, 3445.7 and 3528.1 cm^{-1}. FI-MS m/z= 308.2328 (100%, $M^+ + 1 - CH_3CO$), 290.2052 (71%, $M^+ - CH_3COOH$), 350.2441 (62%, M^+), 332.2306 (26%, $M^+ - H_2O$), 351.2468 (12%, $M^+ + 1$).

4.3.9. 4α-Hydroxycholestane-3β-yl acetate (9a). To a solution of cholestane-3β,4α-diol (**9**, 50 mg, 0.124 mmol) in acetone (9 ml), vinyl acetate (1 ml) and *Chromobacterium viscosum* lipase (500 mg) were added and the reaction mixture was shaken under the conditions described above for 6 days. The usual work-up and flash chromatography yielded 4α-hydroxycholestane-3β-yl acetate (**9a**, 42.3 mg, 76%), mp 169–170 °C.

Selected data: ^{1}H NMR ($CDCl_3$) δ: 0.65 (3H, s, CH_3-18), 0.84–0.91 (12H, CH_3-19, CH_3-21, CH_3-26, CH_3-27), 2.08 (3H, s, CH_3CO), 3.45 (1H, t, J=9.7 Hz, H-4β), 4.57 (1H, ddd, J=5.3, 9.1, 11.5 Hz, H-3α). ^{13}C NMR δ: 171.49, 79.24, 72.47, 56.30, 56.18, 54.21, 51.23, 42.45, 39.85, 39.46, 36.83, 36.10, 35.96, 35.76, 34.97, 31.44, 28.22, 27.97, 25.65, 24.12, 23.80, 22.79, 22.60, 21.53, 21.36, 20.94, 18.61, 13.46, 12.01. FTIR (ATR): ν_{max} 1036.6, 1263.2, 1715.4, 2860.9–2930.2, 3549.3 cm^{-1}. FI-MS m/z= 386.3400 (100%, $M^+ - CH_3COOH$), 446.3787 (33%, M^+), 387.3417 (27%, $M^+ + 1 - CH_3COOH$), 447.3893 (13%, $M^+ + 1$).

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Ultrasound-assisted convenient synthesis of hypolipidemic active natural methoxylated (*E*)-arylalkenes and arylalkanones☆

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Abstract—An ultrasound-assisted convenient method was developed for the conversion of toxic methoxylated *cis*-isomer of arylalkenes into its hypolipidemic active *trans*-isomer. Treatment of *cis*-isomer or mixture of all three isomers (**1a**–**1j**) with ammonium formate and 10% Pd/C gave arylalkanes (**2a**–**2j**), which upon oxidation with DDQ in anhydrous dioxane containing a little amount of silica gel, provided (*E*)-arylalkenes (**3a**–**3g**) in 42–72% yield depending upon the substituents attached at the aryl ring. The same method, upon addition of a few drops of water, provided hypolipidemic active arylalkanones (**3h**–**3j**) in 59–65% yield.

1. Introduction

Hypercholesterolemia[1] appears to be a serious risk factor for coronary heart diseases (CHDs). High level of low-density lipoprotein (LDL) are recognized as the initiating event in CHDs. LDL can undergo extensive lipid peroxidation, resulting in the generation of modified LDL and the formation of atheromatic lesions. Hence, implementation of hypolipidemic drugs in any heart disease prevention therapy is an imperative strategy. In this regards, various hypolipidemic drugs[2] such as statins, clofibrate, niacins etc. are found effective. On the other side, a large number of plant extracts[3] as well as natural molecules[4] including phenylpropanoids[5] and phenylbutanoids[5b,6] have also shown promising results. Among them, some methoxylated phenylpropanoids and phenylbutanoids like (*E*)-arylalkenes[7] (such as α-asarone) (**3a**–**3g**) and arylalkanones[7,8] (such as isoacoramone) (**3h**–**3j**) are reported to be active hypolipidemic agents. Besides possessing hypolipidemic activities, these natural compounds (**3a**–**3j**) are known to have a wide range of biological[9] activities such as neuroleptic, anti-ulcerogenic, anti-atherogenic, anti-inflammatory, anti-choleretic, anti-PAF, anti-fungal and anti-platelet activities. Various synthetic methods are reported for (*E*)-arylalkenes which involve Grignard,[10] Wittig–Horner,[11] Aldol–Grob,[12] Wittig,[6] Friedel–Crafts[7] and photochemical isomerization[13] reactions. However, all the above methods result in formation of some amount of unwanted toxic[14] *cis*-isomer[15] along with the desired *trans*-isomer and it becomes difficult to separate them through column purification[16] due to resemblance in R_f values of both the isomers. Recent development of disodium iron tetracarbonyl, iridium and palladium(II) catalyzed isomerization of *gamma*[17] and *cis*-arylalkenes[18] is a very useful entry to (*E*)-arylalkene synthesis. However, expensive reagents limit its scope for a large scale synthesis. As for the synthesis of aforementioned hypolipidemic arylalkanones **3h**–**3j**, a lot of methods[19] are reported which mainly involve Grignard[10] and Friedel–Crafts[7] approaches. Overall, all the synthetic methods mentioned above suffer from some drawbacks such as long reaction time, tedious workups, expensive and hazardous reagents and starting materials. Keeping this in mind, it would, therefore, be useful to utilize inexpensive and abundantly available isomeric mixture of arylalkenes in a reliable, mild, economical and environment friendly manner for the synthesis of title compounds. In this context, we, herein, report an ultrasound-assisted[20] convenient method for the preparation of methoxylated (*E*)-arylalkenes (**3a**–**3g**) and arylalkanones (**3h**–**3j**) via DDQ-assisted oxidation of arylalkanes (**2a**–**2j**) obtained by hydrogenation of isomeric mixture of arylalkenes (**1a**–**1j**) (Scheme 1).

2. Results and discussion

As per our continuing efforts towards chemical modification of abundantly[15] available toxic[14] (*Z*)-1-(2′,4′,5′-trimethoxyphenyl)prop-1-ene (commonly known as β-asarone) (**1a**) into value added products,[21] synthesis of hypolipidemic (*E*)-1-(2′,4′,5′-trimethoxyphenyl)prop-1-ene

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Keywords: Hypolipidemic; Ultrasound; (*E*)-Arylalkenes; Arylalkanones; DDQ.
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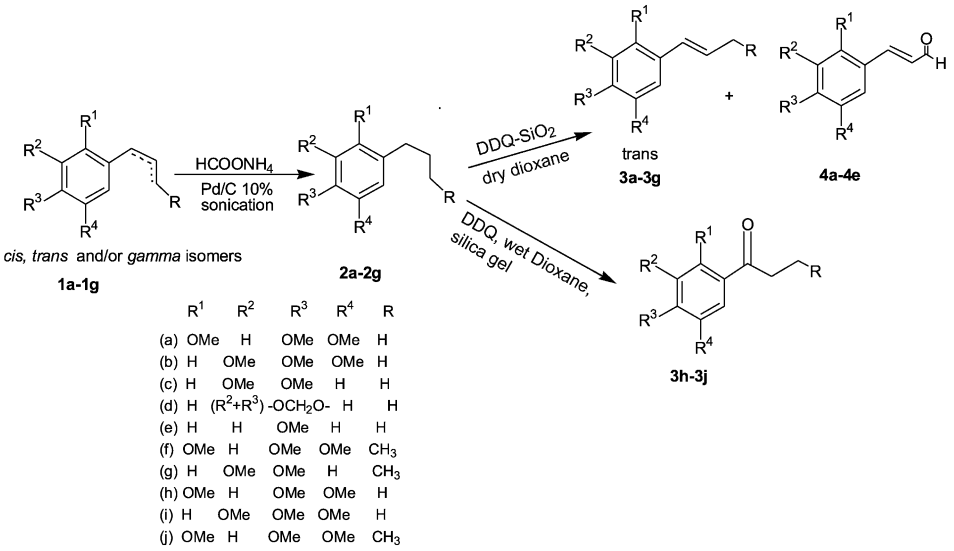


Scheme 1.

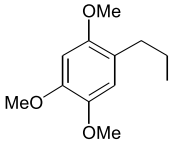
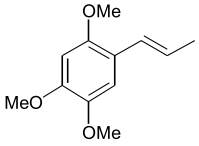
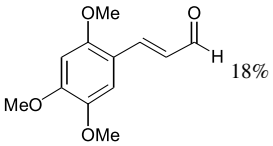
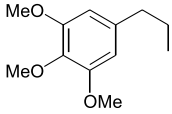
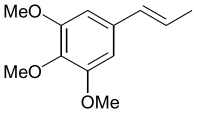
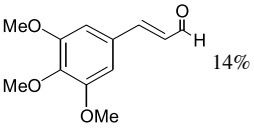
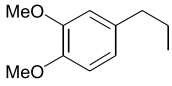
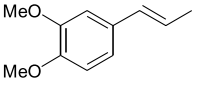
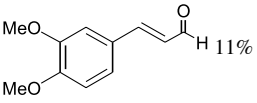
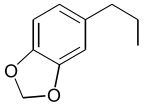
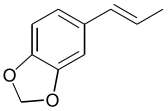
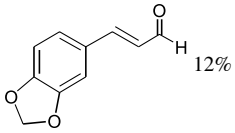
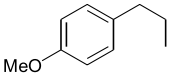
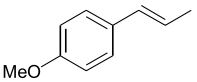
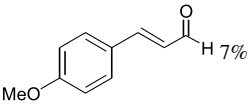
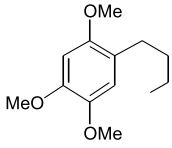
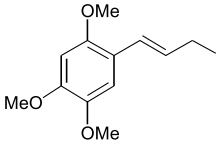
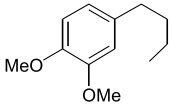
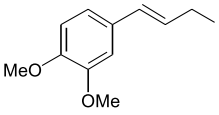
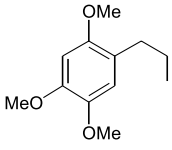
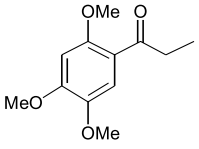
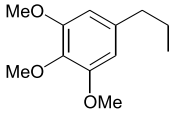
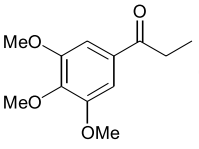
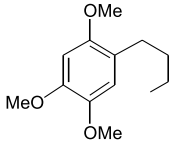
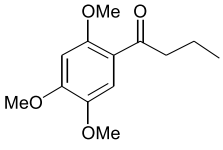
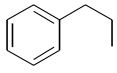
α-asarone) (**3a**) was undertaken from **1a** as a starting compound. Treatment of **1a**, containing an isomeric mixture of α- and/or γ-asarone (3-(2′,4′,5′-trimethoxyphenyl)prop-1-ene), with ammonium formate[22] and Pd/C provided 1-(2′,4′,5′-trimethoxyphenyl)propane[23] (dihydroasarone) (**2a**) in quantitative yield in 30 min while conventional method required 10–12 h for complete hydrogenation of **1a** into **2a**. In the next step, dehydrogenation of **2a** into **3a** was attempted with various dehydrogenating reagents[24] such as Pd–C in diphenylether, SeO_2 and chloranil but none were successful. In all the above conditions, the reaction did not go to completion, and mostly the starting **2a** remained unreacted. Later on, the attention was shifted to the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[25] and reaction of **2a** with 1.0–1.1 M equiv of DDQ in dry toluene under nitrogen atmosphere, furnished the corresponding dehydrogenated product **3a** in 32% yield with a large amount of unreacted starting compound **2a**. Use of 1.25 M equiv of DDQ in toluene provided **3a** in 45% yield and it did not improve further, even when using excess of DDQ and refluxing the mixture for 20 h. Similarly, the above reaction was carried out in MeOH which afforded 23% of the product **3a** and rest of the starting **2a** remained unreacted. However, in 1,4-dioxane as solvent, reaction of **2a** with 1.25 equiv DDQ increased the yield of **3a** up to 52% along with a yellow coloured side product, that is, (*E*)-3-(2′,4′,5′-trimethoxyphenyl)prop-2-en-1-al[26] (**4a**, 12% yield). There was no further improvement in the yield of **3a** with increasing the amount of DDQ. The spectroscopic analysis and comparison with the reported[7,26] data clearly indicated both **3a** and **4a** exclusively with *trans* selectivity. Interestingly, when a catalytic amount of pre-activated silica gel was added to the above reaction mixture, the yield of **3a** increased up to 72% with 18% yield of **4a** at room temperature under nitrogen atmosphere. This incremental effect due to silica gel was presumed to be due to its mild acidic nature which, in catalytic amounts, would initiate the protonation of DDQ and facilitate the reaction (Table 1). In order to increase the yield of **3a** further, we performed the same dehydrogenation reaction of **2a** under sonication[20] for 40 min. However, instead of increasing yield of **3a**, it increased the yield of **4a** up to 29% at the cost of desired **3a** which got reduced to 48%. Increase in the yield of **4a** could be due to the presence of atmospheric oxygen/moisture in the reaction mixture during sonication, which would form highly reactive peroxy radicals[27] to further oxidize **3a** into **4a**. It is evident from the fact that maintenance of nitrogen atmosphere during conventional method limits the yield of **4a** to 18% only.

Having been successful with the synthesis of **3a**, the combination of DDQ–silica-dioxane successfully converted **2b–2g**, dihydro products[23] of **1b–1g**, into **3b–3g** with a little amount of corresponding (*E*)-arylalkenals[26] (**4b–4e**) and no arylalkenals were detected in case of **2f–2g** (Table 2). After successful synthesis of a series of hypolipidemic (*E*)-arylalkenes (**3a–3g**), we shifted our focus towards synthesis of hypolipidemic arylalkanones **3h–3j**. In the same method of treatment of **2a** with DDQ–silica-dioxane, a few drops of water were added which provided **3h** in 43% yield with mere 7% of **3a**, without formation of any **4a**, within 10 h. Reaction conditions were optimized and 2.2 equiv of

Table 1. Oxidation of arylalkane (**2a**) into (*E*)-arylalkene (**3a**) with varying amounts of DDQ in different solvents

Entry	DDQ (in M equiv)	Solvents	Yield of **3a** (%)
1	1.0–1.1	Toluene	32
2	1.25	Toluene	45
3	1.50	Toluene	43
4	1.25	MeOH	23
5	1.25	1,4-Dioxane	52
6	1.25 + silica gel (cat.)	1,4-Dioxane	72
7	1.25 + silica gel (cat.) (under sonication)	1,4-Dioxane	48

Table 2. DDQ assisted oxidation of arylalkanes (**2**) into (*E*)-arylalkenes/arylalkanones (**3**) and (*E*)-arylalkenal (**4**)

Entry	Arylalkane (**2**)	Method[a]	*E*-Arylalkene/arylalkanone (**3**)	*E*-Arylalkenal (**4**)
a		A	 72%	 18%
b		A	 70%	 14%
c		A	 63%	 11%
d		A	 56%	 12%
e		A	 42%	 7%
f		A	 54%	—
g		A	 49%	—
h		B	 64%	—
i		B	 65%	—
j		B	 59%	—
k		A or B	—	—

[a] Method A: DDQ (1.25 equiv)/dry dioxane/silica gel; Method B: DDQ (2.2 equiv)/wet dioxane/silica gel.

DDQ[25] was found most suitable with **2a** and silica-dioxane-water to provide maximum yield of **3h** up to 57% within 10 h, whereas the same reaction provided 64% of **3h** in 20 min under sonication. No more increase in the yield of **3h** was observed by increasing either the sonication period or the heating temperature of the reaction mixture. Similarly, **3i**–**3j** got formed in 65 and 59%, yield respectively under sonication during oxidation of **2i**–**2j**. It was interesting that, oxidation of **2k** did not provide corresponding (*E*)-alkene or alkanone (**3k**) with either DDQ–silica-dioxane or DDQ–silica-dioxane-water-sonication, and mostly the starting material was recovered. This indicates that the presence of

methoxy group in the aryl ring plays an important role in the oxidation of **2a–2j** (Table 2). However, further studies regarding this mechanistic aspect influenced by the structural variation of the starting compounds is under progress. It is worth mentioning that the use of DDQ has so far been reported in the formation of arylpropenals[26] from arylpropenes, but removal of double bond of arylpropenes by conversion into arylpropanes followed by oxidation with DDQ is a new method for the formation of various bioactive compounds, including hypolipidemic (*E*)-arylalkenes (**3a–3g**) and arylalkanones (**3h–3j**).

3. Conclusion

In conclusion, we have realized an ultrasound-assisted convenient semi-synthetic approach towards preparation of a number of natural hypolipidemic compounds (**3a–3j**) from commercially available isomeric mixture of substituted arylalkenes (**1a–1j**) via intermediate arylalkanes (**2a–2j**). Moreover, our studies strongly emphasize the change in the products from arylalkenes (**3a–3g**) on one side to arylalkanones (**3h–3j**) on the other, with a little change in the ratio of DDQ and the reaction conditions from anhydrous to aqueous medium.

4. Experimental

4.1. General methods

Melting points were determined with a Mettler FP80 micromelting point apparatus and are uncorrected. Column chromatography was performed on silica gel (60–120 mesh size). ^{1}H (300 MHz) NMR spectra was recorded in $CDCl_3$ on a Bruker Avance-300 spectrometer. Sonication (20 kHz, 400 W; Pulse length:10 s; 75% duty) was used for all the given reactions.

4.2. General procedure for ultrasound-assisted conversion of toxic methoxylated *cis*-arylalkenes containing an isomeric mixture of *trans* and *gamma*-isomers (1a–1k) into arylalkanes (2a–2k)

The isomeric mixture of methoxylated arylalkenes **1a–1k** (0.044 mol), 10% Pd/C (0.75–1.20 g) and ammonium formate (0.41 mol) in ethanol (200 mL) was sonicated for 30–40 min. After completion of the reaction, the catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between ethyl acetate (70 mL) and water (15 mL) and the ethyl acetate layer was washed with water (2×10 mL), 10% HCl (2×5 mL), brine (2×10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated and the obtained residue was purified by column chromatography (silica gel, hexane:ethyl acetate::9:1) to afford arylalkane **2a–2k** in quantitative yield whose spectra were found matching with the reported values.[23]

4.3. General procedure for dehydrogenation of methoxylated arylalkanes (2a–2g) into (*E*)-arylalkenes (3a–3g)

Arylalkane **2a–2g** (2.4 mmol), DDQ (3.0 mmol), silica gel (0.2–0.3 g, kept at 110–120 °C for 3–4 h before use) in anhydrous dioxane (30 mL) was stirred at room temperature for 12–14 h under nitrogen atmosphere till completion of the reaction. The precipitated $DDQH_2$ was filtered and the filtrate was evaporated and subsequently chromatographed on silica gel (hexane:ethyl acetate::7:3) to provide **3a–3g** in 42–72% yield along with some amount of (*E*)-arylalkenal (**4a–4e**) (Table 2). The spectral data of compounds (**3a–3g** and **4a–4e**) agreed well with the reported values.[7,8,10,17c,18,21,23,28]

4.3.1. 1-(2′,4′,5′-Trimethoxyphenyl)prop-1-ene (3a).[7b] Yield 72%; white solid; mp 44–45 °C (lit.[7b] mp 44–45 °C); ^{1}H NMR ($CDCl_3$): δ 6.91 (1H, s, H-6′), 6.64 (1H, dq, J=16.0, 1.5 Hz, H-1), 6.45 (1H, s, H-3′), 6.02 (1H, dq, J=16.0, 6.2 Hz, H-2), 3.84, 3.81 and 3.77 (each 3H, s, three OCH_3),1.87 (3H, dd, J=6.2, 1.5 Hz, H-3).

4.3.2. 1-(3′,4′,5′-Trimethoxyphenyl)prop-1-ene (3b).[7b] Yield 70%; liquid; ^{1}H NMR ($CDCl_3$): δ 6.50 (2H, s, H-2′ and H-6′), 6.31 (1H, dq, J=15.7, 1.4 Hz, H-1), 6.12 (1H, dq, J=15.7, 6.3 Hz, H-2), 3.81 (3H, s, OCH_3), 3.78 (6H, s, two OCH_3), 1.82 (3H, dd, J=6.3, 1.4 Hz, H-3).

4.3.3. 1-(3′,4′-Dimethoxyphenyl)prop-1-ene (3c).[17c] Yield 63%; liquid; ^{1}H NMR ($CDCl_3$): δ 6.90–6.78 (3H, m, H-2′, H-5′ and H-6′), 6.35 (1H, d, J=16.2 Hz, H-1), 6.22–6.11 (1H, m, H-2), 3.87 and 3.83 (each 3H, s, two OCH_3), 1.87 (3H, d, J=6.2 Hz, H-3).

4.3.4. 1-(3′,4′-Dioxymethylenephenyl)prop-1-ene (3d).[8] Yield 56%; Liquid; ^{1}H NMR ($CDCl_3$): δ 6.92–6.77 (3H, m, H-2′, H-5′ and H-6′), 6.35 (1H, d, J=16.2 Hz, H-1), 6.25–6.11 (1H, m, H-2), 5.95 (2H, s, –OCH_2O–), 1.95 (3H, d, J=6.2 Hz, H-3).

4.3.5. 1-(4′-Methoxyphenyl)prop-1-ene (3e).[17c] Yield 42%; liquid; ^{1}H NMR ($CDCl_3$): δ 7.07–6.96 (2H, m, H-2′ and H-6′), 6.88–6.80 (2H, m, H-3′ and H-5′), 6.39 (1H, d, J=16.2 Hz, H-1), 6.18–6.11 (1H, m, H-2), 3.83 (3H, s, OCH_3), 1.87 (3H, d, J=6.2 Hz, H-3).

4.3.6. 1-(2′,4′,5′-Trimethoxyphenyl)-1-butene (3f).[6a] Yield 54%; mp 40–41 °C (reported as a pale yellow liquid in literature[6a]); ^{1}H NMR ($CDCl_3$): δ 6.82 (1H, s, H-6′), 6.54 (1H, d, J=16.2 Hz, H-1), 6.29 (1H, s, H-3′), 5.96 (1H, m, H-2), 3.66 (6H, s, two OCH_3), 3.60 (3H, s, OCH_3), 2.08 (2H, m, H-3), 0.93 (3H, t, J=7.1 Hz, H-4).

4.3.7. 1-(3′,4′-Dimethoxyphenyl)-1-butene (3g).[6a] Yield 49%; liquid; ^{1}H NMR ($CDCl_3$): 6.90–6.79 (3H, m, H-2′, H-5′ and H-6′), 6.51 (1H, d, J=16.1 Hz, H-1), 5.42 (1H, m, H-2), 3.84 and 3.81 (each 3H, s, two OCH_3), 2.21 (2H, m, H-3), 1.02 (3H, t, J=7.0 Hz, H-4).

4.3.8. 3-(2′,4′,5′-Trimethoxyphenyl)prop-2-en-1-al (4a).[26] Yield 18%; yellow solid; mp 139–140 °C (lit.[26] 140–142 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.65 (1H, d, J=7.8 Hz, H-1), 7.81 (1H, d, J=15.8 Hz, H-3), 7.03 (1H, s, H-6′), 6.64 (1H, dd, J=15.8, 7.8 Hz, H-2), 6.51 (1H, s, H-3′), 3.95, 3.91 and 3.87 (each 3H, s, three OCH_3).

4.3.9. 3-(3′,4′,5′-Trimethoxyphenyl)-prop-2-en-1-al (4b).[26] Yield 14%; yellow solid; mp 110 °C (lit.[26] 109–111 °C); ^{1}H NMR ($CDCl_3$): δ 9.68 (1H, d, J=7.8 Hz, H-1), 7.58 (1H, d, J=15.8 Hz, H-3), 6.63 (1H, dd, J=15.8, 7.8 Hz, H-2), 6.26 (2H, s, H-2′ and H-6′), 3.73 (9H, s, three OCH_3).

4.3.10. 3-(3′,4′-Dimethoxyphenyl)prop-2-en-1-al (4c). Yield 11%; mp 78 °C (lit.[28] mp 78–79 °C); ^{1}H NMR ($CDCl_3$): δ 9.67 (1H, d, J=7.8 Hz, H-1), 7.43 (1H, d, J=15.8 Hz, H-3), 7.15 (1H, d, J=8.1 Hz, H-6′), 7.08 (1H, s, H-2′), 6.91 (1H, d, J=8.1 Hz, H-5′), 6.61 (1H, dd, J=15.8, 7.8 Hz, H-2), 3.94 and 3.93 (each 3H, s, two OCH_3).

4.3.11. 3-(3′,4′-Dioxymethylenephenyl)prop-2-en-1-al (4d). Yield 12%; mp 78 °C (lit.[28] mp 77 °C); ^{1}H NMR ($CDCl_3$): δ 9.88 (1H, d, J=7.8 Hz, H-1), 7.38 (1H, d, J=15.8 Hz, H-3), 6.75 (1H, d, J=8.2 Hz, H-6′), 6.70 (1H, s, H-2′), 6.63 (1H, d, J=8.2 Hz, H-5′), 6.56 (1H, dd, J=15.8, 7.8 Hz, H-2), 6.10 (2H, s, –OCH_2O–).

4.3.12. 3-(4′-Methoxyphenyl)prop-2-en-1-al (4e).[28] Yield 7%; white solid, mp 58–59 °C (lit.[28] mp 59 °C); ^{1}H NMR ($CDCl_3$): δ 9.68 (1H, d, J=7.8 Hz, H-1), 7.58 (1H, d, J=15.8 Hz, H-3), 7.19 (2H, m, H-2′ and H-6′), 6.72 (2H, m, H-3′ and H-5′), 6.63 (1H, dd, J=15.8, 7.8 Hz, H-2), 3.73 (3H, s, OCH_3).

4.4. General procedure for ultrasound-assisted synthesis of methoxylated arylalkanones (3h–3j) from oxidation of arylalkanes (2a–2b and 2f) with DDQ

A mixture of substituted arylalkane (**2a**–**2b** and **2f**) (2.4 mmol), DDQ (4.8–5.24 mmol), 10% HCl (1–2 drops) in wet dioxane (30 mL, dioxane:water::90:10) was stirred under sonication for 20 min. The precipitated $DDQH_2$ was filtered and the red coloured filtrate was evaporated and subsequently chromatographed on silica gel (hexane:ethyl acetate 7:3) to provide **3h**–**3j** in 59–65% yield (Table 2). The spectral data of compounds (**3h**–**3j**) agreed well with the reported values.[7,8,21]

4.4.1. 1-(2′,4′,5′-Trimethoxyphenyl)-1-propanone (also known as isoacoramone) (3h).[7] Yield 64%; White solid; mp 108–109 °C (lit.[7] mp 109 °C); ^{1}H NMR ($CDCl_3$) δ 7.45 (1H, s, H-6′), 6.77 (1H, s, H-3′), 3.96, 3.93 and 3.89 (each 3H, s, three –OCH_3), 2.99 (2H, q, J=6.9 Hz, H-2), 1.18 (3H, t, J=6.9 Hz, H-3).

4.4.2. 1-(3′,4′,5′-Trimethoxyphenyl)-1-propanone (3i).[7] Yield 65%; White solid; mp 52–53 °C (lit.[7] mp 53 °C); ^{1}H NMR ($CDCl_3$) δ 7.23 (2H, s, H-2′ and H-6′), 3.90 (9H, s, three –OCH_3), 2.95 (2H, q, J=7.2 Hz, H-2), 1.22 (3H, t, J=7.2 Hz, H-3).

4.4.3. 1-(2′,4′,5′-Trimethoxyphenyl)-1-butanone (3j). Yield 59%; White solid; mp 75–76 °C (lit.[7] mp 75–77 °C); ^{1}H NMR ($CDCl_3$) δ 7.34 (1H, s, H-6′), 6.41 (1H, s, H-3′), 3.85, 3.82 and 3.78 (each 3H, s, three –OCH_3), 2.87 (2H, t, J=7.4 Hz, H-2), 1.67–1.55 (2H, m, H-3), 0.89 (3H, t, J=7.4 Hz, H-4).

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15. A large number of arylalkenes mostly phenylpropenes are found in high concentration (up to 90%) in many essential oil bearing plants as an isomeric mixture of three isomers namely *trans* (α), *cis* (β) and *gamma* (γ) isomers. Purification of these isomers into a pure single isomer by column chromatography is tedious.[16] Among three isomers, *cis*-arylalkenes are recently proved to be carcinogenic and toxic[14] which overall restrict the market potential of an essential oil rich in *cis*-isomer. Therefore, utilization of an isomeric mixture of arylalkenes via arylalkanes is an added benefit towards formation of useful products including (*E*)-arylalkenes (**3a**–**3g**) and arylalkanones (**3h**–**3j**).
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Cross-linked poly(4-vinylpyridine/styrene) copolymers as a support for immobilization of ytterbium triflate

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Abstract—Eight cross-linked poly(4-vinylpyridine/styrene) (P/S) resins (as beads) were prepared by radical suspension polymerization. Ytterbium triflate was immobilized in the range of 0.10–0.24 mmol/g by mixing with the P/S resins. The ytterbium triflate-immobilized P/S resins exhibited good activity in two Lewis acid-catalyzed reactions. Low pyridine containing resins were recycled with no loss of activity, while a slight loss of activity was observed with the higher pyridine containing resins.

1. Introduction

Rare earth metal triflates ($RE(OTf)_3$) including lanthanide (III) triflates ($Ln(OTf)_3$) have been employed as mild Lewis acid in many organic transformations including aldol, Diels–Alder, Michael addition, aziridination, oxidation/reduction, rearrangement and protection/deprotection reactions.[1] The use of these compounds has gained prominence not only due to their chemical versatility but also because of their stability in the presence of most polar functional groups and organic solvents including aqueous media. Moreover, $RE(OTf)_3$ are catalytically active in the presence of Lewis bases containing nitrogen, oxygen, phosphorous and sulfur atoms. These catalysts are used as homogeneous catalysts in organic solvents in most applications and since $RE(OTf)_3$ are more soluble in water than in common organic solvents, they can be recovered by aqueous extraction and reused.[2] Alternatively, immobilization of these catalysts on solid supports affords improved recycling and facile use in synthetic schemes, a consummate goal in catalyst development. Several methods for the immobilization of $RE(OTf)_3$ on polymer supports have been developed,[3] including microencapsulation using soluble polystyrene and lightly cross-linked polystyrene-supported scandium triflate. These immobilized catalysts were recycled without any loss of catalytic activity. However, while the microencapsulated catalysts has very good activity, a drawback to its use is the required precipitation of the polymer for recovery of the catalyst.[3c] Similarly, the insoluble lightly cross-linked polystyrene/divinylbenzene (PS/DVB) copolymer-supported $Sc(OTf)_3$ has a shortcoming in that it requires an intricate six step synthesis.[3d] Therefore, the development of solid polymeric support, that can be readily synthesized, possesses good activity and stability, and can be recycled efficiently would be of synthetic utility.

Recently, highly cross-linked polystyrene resins with pendant pyridine functional groups have been reported for immobilization of dirhodium tetracarboxylates.[4,5] The immobilization was considered to be due to both ligand coordination and physical encapsulation. Another example of catalyst immobilization on a pyridine-based polymer is the commercially available poly(4-vinylpyridine) supported osmium catalysts.[6] These two examples led us to speculate that cross-linked pyridine/styrene polymers could serve as potential supports for $Ln(OTf)_3$. Herein, we describe the synthesis of a series of cross-linked poly(4-vinylpyridine/styrene) copolymers, immobilization of $Yb(OTf)_3$ on these polymers, and their catalytic activity and reusability in two model reactions.

2. Results and discussion

A series of cross-linked poly(4-vinylpyridine/styrene) copolymers (abbreviated as ^{x}P/S resins, where superscript x equates to % pyridine content) with varying ratios of styrene, 4-vinylpyridine and (cross-linker) 1,4-bis(4-vinylphenoxy)butane[7] were synthesized as beads by aqueous

Keywords: Lanthanide triflate; Poly(4-vinylpyridine/styrene); Catalyst immobilization.
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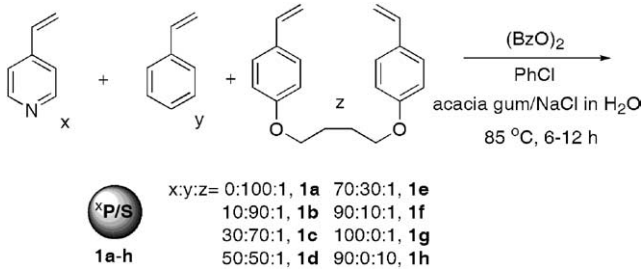
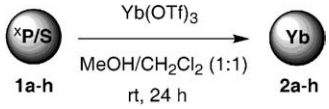
suspension radical polymerization in the presence of benzoyl peroxide (Scheme 1). Low cross-linked P/S resins **1a–1g** were prepared using 1 mol% of the 1,4-bis(4-vinylphenoxy)butane cross-linker. A highly cross-linked poly(4-vinylpyridine) (abbreviated as ^{90}P/DVB) resin **1h**, was prepared with 10% divinylbenzene as the cross-linker. All resins were sieved to a range of 40–400 mesh.



Scheme 1. The preparation of P/S resins. Actual nitrogen (pyridine) content (mmol/g) found in experimental section (Table 5).

For lightly cross-linked resins, swelling in common organic solvents is an important factor in the success of solid-phase reactions.[8] The swollen volumes for these resins were determined by the syringe method[9] in several organic solvents (Table 1). All P/S resins displayed outstanding swelling in dichloromethane and modest swelling in methanol and acetonitrile. As expected the swelling of the high cross-linked PS/DVB resin **1h** was low and unaffected by the choice of solvent.

Immobilization of $Yb(OTf)_3$, a representative $Ln(OTf)_3$ having relatively high acidity due to its small ionic radii,[10] onto P/S resins was achieved by shaking a suspension of P/S resins and $Yb(OTf)_3$ for 24 h in a 1:1 mixture of methanol/dichloromethane (Scheme 2). This mixture is an optimal solvent for immobilization since $Yb(OTf)_3$ has good solubility and the resins also exhibit good swelling. The loading of $Yb(OTf)_3$ was determined by measuring the increase in the weight of the resulting resins, and verified by measuring the residual $Yb(OTf)_3$ in the filtrate. Yttebium triflate was immobilized into 200 mg of ^{x}P/S resins **1b–1g** and ^{90}P/DVB resin **1h** resulting in a loading of 0.10–0.24 mmol/g of ^{x}P/S(Yb) **2b–2g** and ^{90}P/DVB(Yb) **2h** (Table 1). Loading of $Yb(OTf)_3$ increased from ^{10}P/S to ^{70}P/S, and then decreased as the pyridine content was raised in ^{90}P/S and ^{100}P/S. The corresponding N/Yb ratio ranged between 9.2 and 52.0. No change in swelling of the ^{x}P/S(Yb) resins was observed relative to the starting ^{x}P/S resins.



Scheme 2. Immobilization of $Yb(OTf)_3$ into P/S resins.

Prior reports using soluble polymer supported $Sc(OTf)_3$ have described that the interaction between $Sc(OTf)_3$ and the phenyl groups of polystyrene may contribute to catalyst encapsulation.[3c] We prepared an insoluble cross-linked polystyrene resin **2a**, and applied the immobilization technique used to prepare resins **2b–2h**. However, no $Yb(OTf)_3$ was detected in this resin, confirming that phenyl groups residing within the resin do not play a major role in the immobilization, and the $Yb(OTf)_3$ immobilization on the ^{x}P/S resin occurs primarily by the ligand interaction between the metal and the pyridine moieties of each of the resins (Fig. 1).

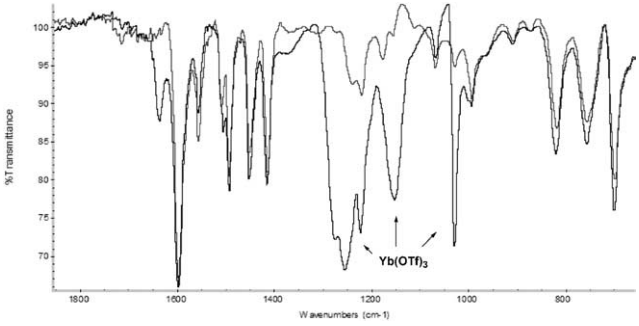


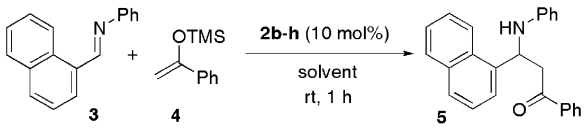
Figure 1. IR spectrum of ^{50}P/S (**1d**, gray) and ^{50}P/S(Yb) (**2d**, black).

The key to the successful development of an immobilized catalyst requires that the twin goals of high activity and good stability be achieved. In the context of immobilized metal catalysts, contamination of the product by the homogeneous catalyst is a significant issue, therefore catalyst leaching should be kept to a minimum. Two preliminary tests were performed to determine the extent $Yb(OTf)_3$ leaching from P/S resins and to determine the activity of the immobilized catalyst. First, the effect of solvent on catalyst leaching was determined by suspending

Table 1. Swollen volume of P/S resins and loading amounts of $Yb(OTf)_3$

	Swollen volume (mL/g)				Loading[a]	N/Yb
	CH_2Cl_2	MeOH	MeCN			
1a	23.8	5.6	2.6	**2a**	0	—
1b	19.6	4.6	2.7	**2b**	0.10	9.2
1c	10.5	3.2	3.2	**2c**	0.15	18.9
1d	18.3	6.5	2.9	**2d**	0.20	23.1
1e	10.4	6.6	4.1	**2e**	0.24	26.9
1f	9.5	10.2	4.1	**2f**	0.23	35.7
1g	10.7	11.7	5.2	**2g**	0.18	52.0
1h	—	—	—	**2h**	0.23	36.5

[a] mmol/g, Determined by weight increase.



Scheme 3. β-Amino ketone synthesis.

Table 2. Leaching test[a]

Entry	Solvent	(%) Conversion[b]	Loss of IR signal[c] (%)
1	CH_2Cl_2	3	0
2	MeCN	96	8
3	MeOH	100	49
4	MeCN/CH_2Cl_2 (1:1)	91	0
5	MeOH/CH_2Cl_2 (1:1)	95	47

[a] All reactions were carried out on a 0.1 mmol scale.
[b] Determined by HPLC.
[c] Calculated by IR integration of used P/S(Yb) resins.

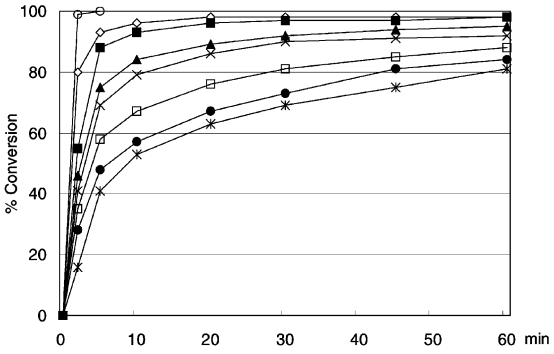


Figure 2. Kinetics for the synthesis of **5** with resins (**2b–2h**) and $Yb(OTf)_3$ (10 mol%).—(○, $Yb(OTf)_3$), (◇, ^{10}P/S(Yb)), (■, ^{30}P/S(Yb)), (▲, ^{50}P/S(Yb)), (×, ^{70}P/S(Yb)), (◆, ^{90}P/S(Yb)), (*, ^{100}P/S(Yb)), (□, ^{90}P/DVB(Yb)).

the immobilized catalyst in solvent for 30 min, followed by filtration, washing and drying. An IR technique was used as a semi-quantitative tool to determine the extent of leaching.[†] The degree of leaching was determined by comparing the IR spectrums before and after the test. The ^{x}P/S(Yb) and ^{90}P/DVB(Yb) resins were found to be stable in dichloromethane, acetonitrile, and methanol. In DMF, significant $Yb(OTf)_3$ was leached out from low pyridine-content ^{x}P/S(Yb) resins **2b** and **2c**, while no leaching was observed in high pyridine-containing resins **2d–2h**. However, in 10% pyridine/dichloromethane, almost all the $Yb(OTf)_3$ was removed from all tested resins, further confirming the chelation of $Yb(OTf)_3$ by the pyridine moieties of the polymer.

Second, the activity of the catalyst and leaching of the catalyst was investigated in the context of a β-amino ketone synthesis[11] (Scheme 3) on ^{50}P/S(Yb) resin **2d** (Table 2). Since the resins contain pyridine moieties, the activity of the catalyst could be adversely affected by pyridine-catalyst interactions. However, we determined that the catalytic activity of $Yb(OTf)_3$ is retained in a homogenous version of the probe reaction even in the presence of pyridine. In a non-polar solvent such as methylene chloride, catalytic activity was low, but no discernable leaching of the catalyst was observed. In contrast, significant catalytic activity was obtained in acetonitrile and methanol solvents, but unacceptable levels of catalyst leaching were also observed. Since good activity is achieved in polar solvents and the catalyst is more stable in non-polar solvents, a mixed solvent system was required to optimize activity and stability. Using methanol/dichloromethane (1:1) or acetonitrile/dichloromethane (1:1), relatively low leaching of the catalyst was observed and 95% conversion to the desired β-amino ketone was obtained. An optimal solvent ratio of acetonitrile and dichloromethane was found to be 3:1, resulting in 95% conversion in 1 h with no apparent leaching of the catalyst; by comparison the homogeneous reaction was complete in 10 min under similar reaction conditions.

The entire array of the immobilized catalysts **2b–2h** were tested using the probe β-amino ketone synthesis consisting of aromatic imine **3** and vinyl silyl ether **4**. The kinetics (Fig. 2) and the conversion (Table 3) reveal that the reactivity of the $Yb(OTf)_3$-immobilized catalyst is related to the ratio of N/Yb: higher activity is obtained at lower N/Yb ratios. Although lanthanides have weak interactions with heteroatoms, high pyridine concentration surrounding the metal might limit the accessibility of the metal to the substrate resulting in lower activity at high N/Yb ratios. This observation is comparable to the reported decrease in catalytic activity for a palladium/monophosphine polystyrene catalyst as the ligand to metal ratio was increased.[12]

Table 3. Recycling results for the synthesis of **5**[a]

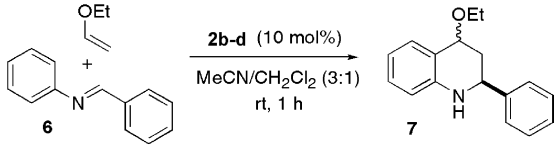
Resin	1st	2nd	3rd	4th	5th	6th	7th	Ave.
2b	98	98	98	97	98	98	98	98
2c	99	98	98	98	98	97	98	98
2d	95	95	95	95	95	95	95	95
2e	96	96	95	93	93	88	92	93
2f	89	85	82	79	83	72	84	82
2g	86	82	80	76	74	72	81	79
2h	91	75	84	86	89	89	88	87

[a] All reactions were carried out on a 1 mmol scale, and conversion yield (%) was determined by HPLC.

[†] In addition to the IR bands of the ^{x}P/S resins, ^{x}P/S(Yb) and ^{90}P/DVB(Yb) resins show two broad bands 1252, 1154 cm^{-1} and one sharp band at 1029 cm^{-1} in the IR spectrum due to the triflate ligand.[3c] Since these $Yb(OTf)_3$-specific IR bands do not overlap with the IR bands of the resins, the extent of leaching of $Yb(OTf)_3$ could be determined by relative comparison to polymer specific bands. To validate this IR technique, we prepared $Yb(OTf)_3$-immobilized ^{50}P/S(Yb) resins with six different loadings (The loading amount was obtained by weight increase of the resin and confirmed by the amount of $Yb(OTf)_3$ in filtrates after immobilization), followed by an IR (1252 cm^{-1}) integration. A linear correlation between the IR integration and ytterbium loading was obtained.

Resins **2b**, **2c** and **2d** containing 10–50% pyridine showed good activity and were recycled six times with no loss of activity (Table 3). However, resins **2e**, **2f** and **2g** (70, 90 and 100% pyridine, respectively) had lower reactivity and exhibited a small decrease in activity after the sixth recycle. The highly cross-linked resin **2h** was also recycled six times with no loss of activity. In particular, for the case of resin **2d**, filtrates from the first three recycled reactions were analyzed for ytterbium by ICP-AES analysis to quantitate catalyst retention and leaching. A very small amount of ytterbium (detection limit corresponded to $<0.2\%$ of ytterbium on the catalyst) was observed in the three filtrates. Further corroboration was obtained by IR spectroscopy; integration of the IR spectra of resin **2d** before and after use yielded no change. Finally, reaction curves and rates from six recycled reactions revealed that the activity of the immobilized catalyst is not altered after recycling. These observations show that there is no leaching of $Yb(OTf)_3$ during the reaction, as well as no loss of activity.

To demonstrate the versatility of the immobilized $Yb(OTf)_3$ resin, we chose to study its application in a second model reaction; the Diels–Alder reaction of imine **6** and ethyl vinyl ether for the synthesis of tetrahydroquinolines[13] (Scheme 4, Table 4). Three ^{x}P/S(Yb) resins with low N/Yb ratio (**2b**, **2c**, **2d**) were used under identical reaction conditions as that for β-amino ketone synthesis (Table 4). As observed in the former example, the order of reactivity was **2b**>**2c**>**2d**. Furthermore, these resins could be used five times without any loss of activity or alteration of the *trans*/*cis* ratio of products. These results show that the immobilized catalyst is not substrate-dependant, as the optimum conditions developed for the β-amino ketone synthesis were successfully employed in the synthesis of tetrahydroquinoline.



Scheme 4. Imino Diels–Alder reaction.

Table 4. Recycling results for the synthesis of **7**[a]

Resin	1st	2nd	3rd	4th	5th	Ave. ratio *trans*/*cis*[b]
2b	93	94	93	93	92	13/87
2c	90	92	91	92	92	13/87
2d	69	82	79	83	82	13/87

[a] All reactions were carried out on a 0.1 mmol scale, and data in table is % conversion determined by HPLC.
[b] The ratio was determined by HPLC and major product was proven to have *cis* configuration on the basis of correlation between coupling constants of four aliphatic protons.

3. Conclusion

A series of P/S resins were prepared by suspension polymerization and used as polymeric supports to immobilize $Yb(OTf)_3$. These resins are inexpensive and can be readily prepared and the immobilized catalysts can be recycled without any loss of activity. Although we have demonstrated the use of these resins in preparation of a β-amino ketone and tetrahydroquinoline, the development of immobilized lanthanide triflate clearly provides a clean route for preparing many potentially useful compounds. With the current emphasis on green chemistry, the use of pyridine-based polymers to immobilize other metal-based catalysts affords an interesting area for further research.

4. Experimental

4.1. General methods

All chemicals were obtained from commercial suppliers and were used without further purification unless otherwise stated. All of the glassware used in the solid-phase reactions was silanized by treating with Sigmacote®. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh). Preparative TLC was carried out on Merck 60 F254 plates (0.5 mm) eluting with ethyl acetate/hexanes. FT-IR spectra were recorded using a Thermo Nicolet AVATA 360 spectrometer equipped with a Golden Gate single reflection diamond ATR accessory. ^{1}H and ^{13}C NMR spectra were recorded using a Varian INOVA-399 (400 MHz) and calibrated using residual undeuterated solvent as an internal reference. High performance liquid chromatography (HPLC) was performed using a Hitachi system: L-5000 LC controller, 655A variable wavelength UV monitor, 655A-12 liquid chromatograph, and D-2000 chromato-integrator. HPLC conditions: Vydac 201SP column (5 μm RP C18) 4.6 mm ×250 mm, acetonitrile/water isocratic 65:35 (for compound **5**), 50:50 (for compound **7**), flow: 1 mL min^{-1}, detection UV ($\lambda=254$ nm), injection loop 20 μL. High-resolution mass spectra (HRMS) were recorded at The Scripps Research Institute using an IonSpec Ultima high-resolution FTMS instrument (MALDI-FTMS) and low-resolution mass spectra were obtained using electrospray ionization (ESI).

4.2. General procedure for synthesis of P/S resins

^{50}P/S resin (**1d**). The aqueous phase used for the suspension polymerization reactions was prepared by dissolving acacia gum (30 g) and NaCl (10 g) in deionized water (1 L). This solution was then filtered to remove insoluble impurities, and degassed for 15 min under vacuum while being sonicated. A 300 mL flange flask equipped with 3-necked lid and mechanical stirrer was charged with 250 mL of the above aqueous solution. To this preheated solution at 50 °C was added a homogeneous solution of styrene (13.81 mL, 120.6 mmol), freshly-distilled 4-vinylpyridine (13.00 mL, 120.6 mmol), di(4-vinylphenoxy)-butane (710 mg, 2.41 mmol), benzoyl peroxide (292 mg, 1.21 mmol) and chlorobenzene (8 mL) prepared by gentle warming. The suspension was stirred at 500 rpm and 50 °C for about 3–5 min with monitoring droplet size. Once the desired droplet size was formed, the stirring rate was reduced to 250 rpm and the reaction flask was heated to 80 °C for 6 h. After cooling, the polymer was filtered with 400-meshed sieve and washed several times with warm water, followed by a methanol. The resultant beads were washed by continuous extraction in Soxhlet apparatus with THF overnight and sequentially washed with 50% MeOH/THF

and MeOH and dried under vacuum to give 12.76 g of pale yellow resin. The dried resin was sieved to give 11.54 g of the ^{50}P/S resin (**1d**, 49%) in the 40–400 mesh size. Nitrogen content (mmol/g) of **1d** was obtained from elemental analysis to be 4.48 mmol/g (Table 5); FTIR: ν_{max} (cm^{-1}) 3024, 2920, 1596, 1557, 1493, 1451, 1414; Anal. Calcd for $C_{7.70}H_{7.72}N_{0.50}O_{0.02}$: C, 85.96; H, 7.23; N, 6.51. Found: C, 82.99; H, 7.35; N, 6.28: other P/S resins were prepared in the same manner.

^{0}P/S resin (**1a**). 17.28 g (64%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3025, 2920, 1601, 1492, 1451;

^{10}P/S resin (**1b**). 9.05 g (36%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3025, 2918, 1598, 1493, 1451; Anal. Calcd for $C_{8.10}H_{8.12}N_{0.10}O_{0.02}$: C, 90.76; H, 7.64; N, 1.30. Found: C, 89.85; H, 8.10; N, 1.73:

^{30}P/S resin (**1c**). 16.15 g (67%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3025, 2919, 1597, 1557, 1493, 1452, 1415; Anal. Calcd for $C_{7.90}H_{7.92}N_{0.30}O_{0.02}$: C, 88.36; H, 7.43; N, 3.91. Found: C, 84.97; H, 7.12; N, 3.75:

^{70}P/S resin (**1e**). 13.06 g (51%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3025, 2920, 1596, 1557, 1493, 1452, 1414; Anal. Calcd for $C_{7.50}H_{7.52}N_{0.70}O_{0.02}$: C, 83.59; H, 7.03; N, 9.10. Found: C, 81.13; H, 7.20; N, 7.68:

^{90}P/S resin (**1f**). 14.10 g (55%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3025, 2920, 1596, 1557, 1414; Anal. Calcd for $C_{7.30}H_{7.32}N_{0.90}O_{0.02}$: C, 81.20; H, 6.83; N, 11.67. Found: C, 76.95; H, 7.39; N, 10.98:

^{100}P/S resin (**1g**). 14.40 g (57%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3025, 2920, 1596, 1557, 1414; Anal. Calcd for $C_{7.20}H_{7.22}N_{1.00}O_{0.02}$: C, 80.01; H, 6.73; N, 12.96. Found: C, 74.74; H, 6/97; N, 11.99:

^{90}P/DVB resin (**1h**). 3.85 g (51%, 40–400 mesh). FTIR: ν_{max} (cm^{-1}) 3026, 2925, 1597, 1557, 1415; Anal. Calcd for $C_{8.30}H_{8.50}N_{0.90}O_{0.20}$: C, 80.85; H, 6.91; N, 10.16. Found: C, 74.82; H, 7.49; N, 10.92:

4.3. Immobilization procedure

Each 200 mg of eight resins (**1a–1h**) was placed in 5 mL-vial containing 50 mg of $Yb(OTf)_3$. 4 mL of methanol/dichloromethane (1:1) cosolvent was added to the vial. After being tightly capped, these vials were shaken for 24 h at room temperature. The resultant resins were collected in a plastic syringe equipped with a polyethylene frit and washed with methanol/dichloromethane (1:1) solvent several times, and dried under reduced pressure to give $Yb(OTf)_3$-immobilized resins (**2a**: 200 mg, **2b**: 213 mg, **2c**: 220 mg, **2d**: 229 mg, **2e**: 235 mg, **2f**: 233 mg, **2g**: 225 mg, **2h**: 233 mg).

4.3.1. 3-(Naphthalen-1-yl)-1-phenyl-3-phenylamino-propan-1-one (5). Compound **3** (23 mg, 0.10 mmol) and **4** (29 mg, 0.15 mmol) were added to a vial containing acetonitrile/dichloromethane (3 mL, 3:1, v/v) and 0.01 mmol of ^{x}P/S(Yb) resins (**2b**, 100 mg; **2c**, 68 mg; **2d**, 50 mg; **2e**, 41 mg; **2f**, 43 mg; **2g**, 56 mg; **2h**, 44 mg). After shaking for 1 h at room temperature, reaction mixture was filtered with a plastic syringe equipped with a polyethylene frit. The filtrate was used for HPLC analysis and purified with preparative TLC for further analysis. The filtered ^{x}P/S(Yb) resins was washed with acetonitrile/dichloromethane (v/v=3:1) three times, and dried under reduced pressure. These recovered ^{x}P/S(Yb) resins were reused up to six times more in the same procedure. After six-time reuse, the filtrate was used for another leaching test (as mentioned below) as well as HPLC analysis: ^{1}H NMR ($CDCl_3$) δ 3.53 (dd, J=16.8, 8.4 Hz, 1H), 3.62 (dd, J=16.6, 4.2 Hz, 1H), 4.80–5.20 (br s, 1H), 5.81 (dd, J=8.2, 4.2 Hz, 1H), 6.53 (dd, J=8.6, 1.0 Hz, 2H), 6.63 (tt, J=8.0, 0.9 Hz, 1H), 7.03 (dd, J=8.6, 7.4 Hz, 2H), 7.34–7.41 (m, 3H), 7.48–7.58 (m, 3H), 7.69 (d, J=7.2 Hz, 1H), 7.73 (d, J=8.4 Hz, 1H), 7.85–7.90 (m, 3H), 8.19 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.9, 50.8, 114.0, 118.1, 122.3, 123.6, 125.6, 125.8, 126.5, 127.9, 128.2, 128.7, 129.1, 129.3, 130.5, 133.5, 134.1, 136.6, 137.4, 198.2; HRMS (MALDI-FTMS) m/z =35275.1514 $[M+Na]^+$, calcd for $C_{25}H_{21}NONa$ =374.1515.

4.3.2. 4-Ethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline (7).[13] Compound **6** (18 mg, 0.10 mmol) and ethyl vinyl ether (29 μL, 0.30 mmol) were used as reactants. The procedure and reaction scale was the same as the synthesis of **5**. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J=7.0 Hz, 3H), 2.06 (ddd, J=12.0, 12.0, 12.0 Hz, 1H), 2.39 (ddd, J=12.4, 5.7, 2.7 Hz, 1H), 3.50–3.58 (m, 1H), 3.64–3.72 (m, 1H), 3.97 (br s, 1H), 4.51 (dd, J=11.6, 2.8 Hz, 1H), 4.80 (dd, J=10.4, 5.6 Hz, 1H), 6.49 (dd, J=8.0, 0.8 Hz, 1H), 6.72 (td, J=7.4, 1.1 Hz, 1H), 7.03 (tm, J=7.2 Hz, 1H), 7.28–7.46 (m, 6H); MS (ESI) m/z 254 $[M+H]^+$, 208. (see Ref. 13 for ^{13}C NMR).

4.4. Activity and leaching tests

4.4.1. Test I (ligand-exchange with solvent). One millilitre of dichloromethane was added to 2 mL vial containing 20 mg of **2d**. After shaking for 30 min, the resin was collected in a plastic syringe equipped with a polyethylene frit and quickly washed with the same solvent twice, and dried under reduced pressure. A small amount of the resin was employed to obtain IR spectra. Leaching tests in methanol, acetonitrile, DMF and 10% pyridine/dichloromethane were performed in the same manner as described above.

4.4.2. Test II (activity and ligand-exchange with substrates and products). To a suspension of **2d** (50 mg, 0.01 mmol) and dichloromethane (2.5 mL) in a reaction vial was added **3** (23 mg, 0.10 mmol) and **4** (29 mg, 0.15 mmol).

Table 5. Nitrogen (pyridine) content (mmol/g)

	1b	1c	1d	1e	1f	1g	1h
Theoretical	0.92	2.79	4.65	6.49	8.30	9.25	8.36
Experimental	1.24	2.68	4.48	5.48	7.84	8.56	7.79

After shaking for 1 h, the resin was collected in a plastic syringe equipped with a polyethylene frit and quickly washed with the same solvent twice, and dried under reduced pressure. A small amount of the resin was employed to obtain IR spectra. Leaching tests in methanol, acetonitrile, methanol/dichloromethane (1:1) and acetonitrile/dichlromethane (1:1) were performed in the same manner as described above (% Conversion was determined by HPLC).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.01.068.

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An intriguing reaction of 4-hydroxycoumarins with 2,3-dichloro-5,6-dicyanobenzoquinone

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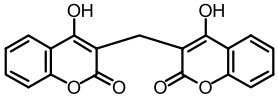
Abstract—An intriguing reaction of 4-hydroxycoumarins with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) occurred in the presence of catalytic acetic acid in ethanol at reflux with the products being obtained in high yields.

1. Introduction

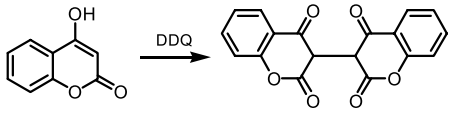
4-Hydroxycoumarins, a large and highly diverse class of natural products, possess a wide range of biological activities including anticoagulant and HIV protease inhibition effects.[1] The dimeric coumarin dicoumarol, 3,3′-methylenebis-(4-hydroxycoumarin), is the principle haemorrhagic component of fermented sweet clover and was once widely prescribed as an oral anticoagulant (Scheme 1).[2]



Scheme 1.

An analogue of the dicoumarol, the dehydroy-dimer, was obtained when 4-hydroxycoumarin was treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in methanol (Scheme 2).[3]

Herein we present a different reaction of 4-hydroxy-coumarins with DDQ and five spiro compounds prepared via[X1] this reaction.



Scheme 2.

2. Results and discussion

Due to the enol lactone structure [X2] of 4-hydroxy-coumarins, 3-C shows[X3] nucleophilicity, and a number of the 4-hydroxycoumarins derivatives can be synthesized through the Michael addition of 4-hydroxycoumarins to αα, ββ-unsaturated carbonyl compounds utilizing this nucleophilicity[X4].[4] Very recently, the methods via the nucleophilicity for the asymmetric synthesis of several 4-hydroxycoumarins derivatives have also been described.[5]

DDQ is one of the most useful reagents for several organic transformations,[6] such as dehydrogenation, oxidation of allylic and benzylic alcohols,[7] and the oxidative removal of protecting groups from alcohols.[8] Additionally, DDQ is relative stability[X5] and does not react with halide, alkoxy, acyl,[X6] or carboxy functional groups.[8,9]

During our investigations of the nucleophilicity of 4-hydroxycoumarin (**Ia**), we found an interesting reaction of **Ia** with DDQ, which occurred in the presence of catalytic

Keywords: 4-Hydroxycoumarins; 1,2-Dichloro-5,6-dicyanobenzoquinone (DDQ); X-ray diffraction.
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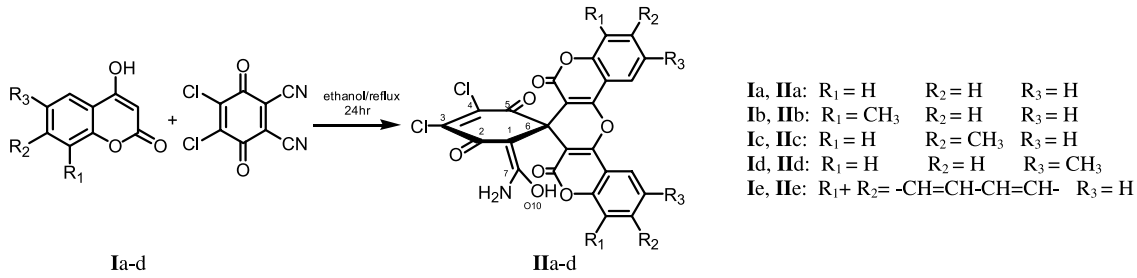


Scheme 3.

[X7]acetic acid in ethanol after refluxing for 24 h. Product **IIa** was obtained in high yield (Scheme 3). Other analogues (**IIb–e**) were obtained under similar conditions from substituted comarins[X8] (**Ib–e**).

The molecular structures of **IIa–e** were established by MASS[X9], IR, ^{1}H NMR and ^{13}C NMR spectroscopy. In the case of **IIa**, the molecular structure was unambiguously determined by single crystal X-ray diffraction[X10] (Fig. 1) (CCDC No. 247047).

It is interesting that[X11] C7 mainly exists in the enol form, rather than the conventional carbonyl form. The C1–C7 bond [1.413(4) Å] is shorter than a typical single Csp^2–Csp^3 [X12]bond in presence of a carbon oxygen double bond [1.516 Å].[10] The C7–O10 bond [1.322(3) Å] is longer than the double Csp^2[X13]–O bond in carboxylic amides [1.23 Å][10] and was similar into the length[X14] Csp^2–O[X15] bond in salicylic acid [1.36 Å].[10] Moreover, the dihedral angles for C7–C1–C2–C3, C2–C1–C7–N1 and C6–C1–C7–O10 are 179.5, −1.9 and −1.5°, respectively. It is possible that the conjugated nature of the enol form makes this tautomer more stable than the corresponding amide tautomer. A check with the Cambridge Structural Database lists only six examples, five of these being drugs: tetracycline hydrochloride,[11] 6-methyleneoxytetracycline hydrobromide,[12] 6-deoxyoxy-tetracyclinehydrochloride,[13] 4-deamino-4-hydroxy-4,11a-anhydrotetracyclinemethanol solvate[14] and 5a-*epi*-6-thia-tetracycline DMF solvate.[15] The exception is nitro-malonamide, (NH2)(OH)C–C(NO2)C(O)NH2[X16].[16]

Although [X17] the exact mechanism of these reactions is not yet clear, a[X18] possible pathway is proposed in Scheme 4. Thus, an[X19] initial addition of **Ia** to DDQ is[X20] followed by the elimination of a molecule of hydrogen cyanide, to form[X21] **3**. The protonation of **3** generates **4**, which may readily react with another molecule of **Ia**, to give **5**. The intramolecular nucleophilic attack of **5** can produce[X22] **6**, which may undergo proton transfer to form **7**. Dehydration of **7**, then produces compound **8**[X23]. The hydrolysis of **8** affords **9**, which was converted to **IIa** through tautomerization.

3. Conclusion

To summarize, we have described here an unexpected and interesting reaction of 4-hydroxycoumarins with DDQ. Five new products, which were not the dehydro-dimers,[5][X24] were synthesized via this reaction. This study also shed light onto the reaction properties of DDQ.

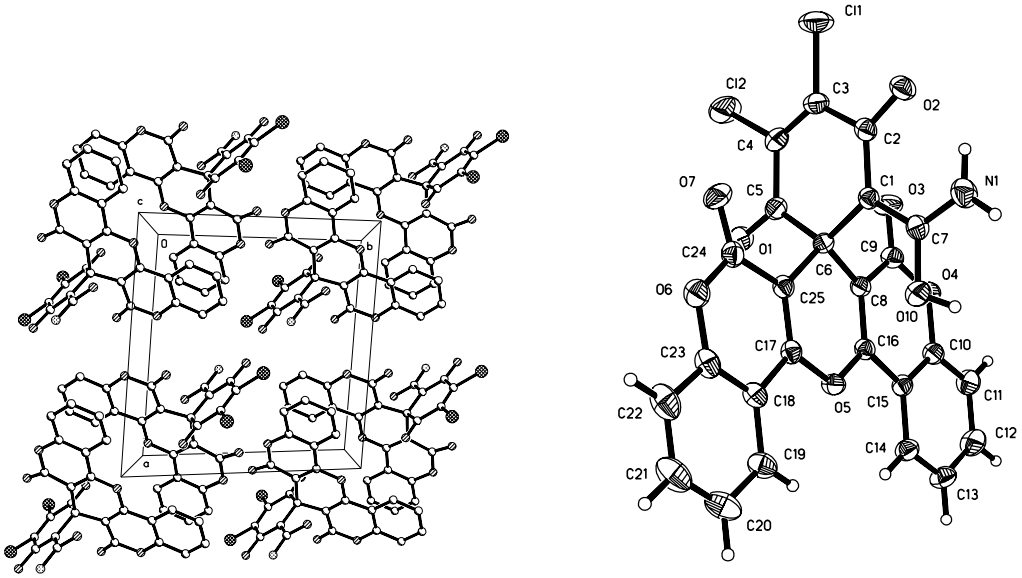
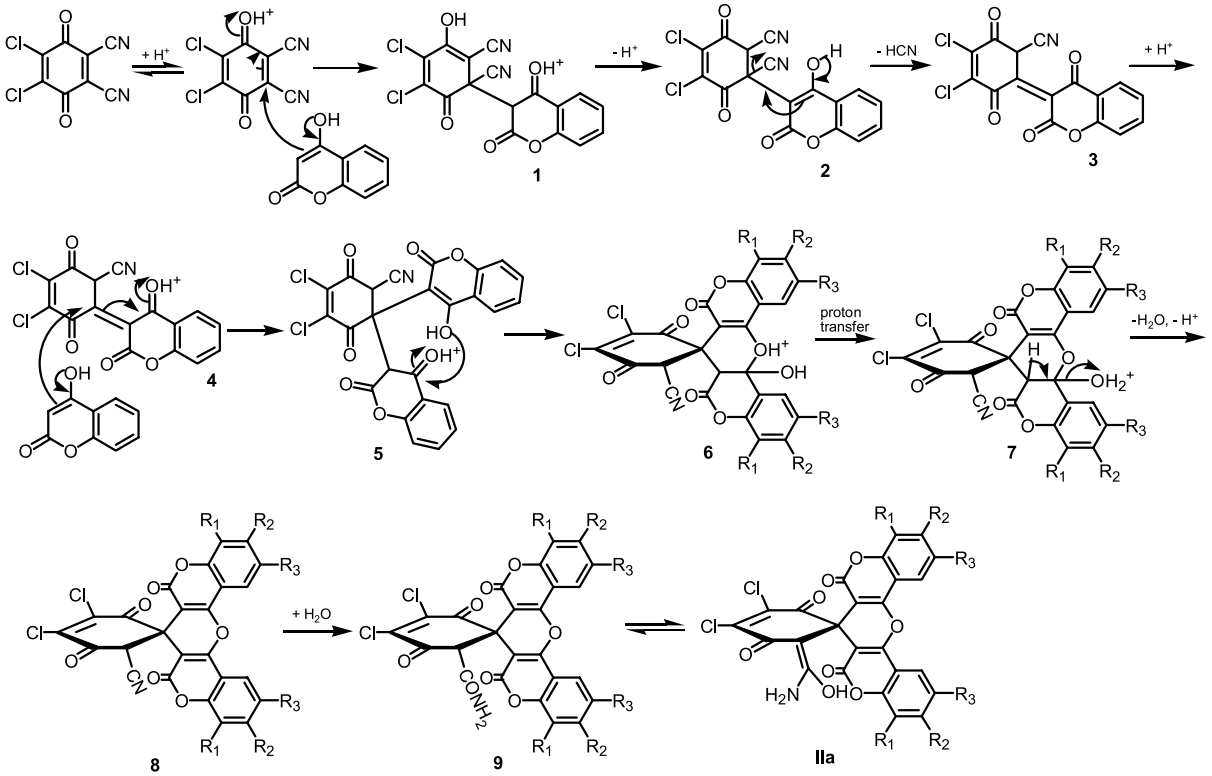


Figure 1. X-ray structure of compound **IIa**.



Scheme 4.

4. Experimental

Melting points were determined using a XT-4 apparatus and were uncorrected. ^{1}H NMR, ^{13}C NMR[X25] spectra were measured on a Varian UNITY INOVA 500 MHz spectrometer using TMS as an internal standard. For the electrospray (ESI) MS analysis, a Finnigan LCQ Deca XP ion trap mass spectrometer equipped with a Microsoft Windows NT data system and an ESI interface was used. Elementary analysis was recorded on an Elementar Vario EL elementary analysis device. IR absorption was recorded on a Bruker TENSOR 37 spectrophotometer.

4.1. General procedure

A mixture of **Ia** (400 mg, 2.5 mmol), DDQ (568 mg[X26], 2.5 mmol) and a drop of glacial acetic acid (about 40 μL) in anhydrous ethanol (30 mL) was magnetically[X27] stirred under reflux for 24 h. After cooling, the reaction mixture was filtered[X28] to afford a crude product which was purified by column chromatography (silica gel, methanol–trichloromethane = 1:5). Compound **IIa** (410 mg) was obtained as a pale yellow solid in 63% yield.

4.1.1. Spiro[(7*H*-pyrano[3,2-*c*;5,6-*c*′]dichromene-6,8-dione)-7,6′-(5′-(amino-hydroxy-methylene-2′,3′-dichlorocyclohex-2′-ene-1′,4′-dione)] (IIa). Reaction[X29] of 4-hydroxycoumarin (**Ia**) (400 mg, 2.5 mmol) with DDQ (568 mg, 2.5 mmol) in anhydrous ethanol (30 mL) afforded **IIa** 410 mg, 63%) as a yellow solid. Mp 208–210 °C (decomposes). IR ν_{max} (KBr) 3458, 1719, 1669, 1609, 1578 cm^{-1}. ESI-MS *m*/*z* (rel. int.)[X30] 522 ($M^{+}-2$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (d, 2H, J=8.0 Hz), 7.81 (t, 2H, J=7.0 Hz), 7.55–7.59 (m, 4H), 7.21 (br, s, 1H), 4.49 (br, s, 2H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 188.5, 184.9, 184.8, 184.6, 169.4, 159.1, 152.8, 151.3, 145.5, 132.6, 124.8, 123.1, 116.3, 112.9, 107.3, 95.4. Anal. Calcd for $C_{25}H_{11}Cl_2NO_8$: C, 57.27%; H, 2.11%; N, 2.67%. Found: C, 57.13%; H, 2.37%; N, 2.72%.

4.1.2. Spiro[(4,10-dimethyl-7*H*-pyrano[3,2-*c*;5,6-*c*′]dichromene-6,8-dione)-7,6′-(5′-(amino-hydroxy-methylene-2′,3′-dichlorocyclohex-2′-ene-1′,4′-dione)] (IIb). Reaction[X31] of 4-hydroxycoumarin (**Ib**) (440 mg, 2.5 mmol) with DDQ (568 mg, 2.5 mmol) in anhydrous ethanol (30 mL) afforded **IIb** (360 mg, 52%) as a yellow solid. Mp 215–218 °C (decomposes[X32]). IR ν_{max} (KBr) 3449, 1750, 1708, 1624, 1495 cm^{-1}. ESI-MS *m*/*z* (rel. int.)[X33] 550 ($M^{+}-2$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (d, 2H, J=8.0 Hz), 7.64 (d, 2H, J=7.5 Hz), 7.43 (t, 2H, J=8.0 Hz), 7.18 (br, s, 1H), 4.52 (br, s, 2H), 2.38 (s, 6H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 193.8, 184.9, 184.6, 184.5, 169.4, 159.0, 152.9, 149.5, 133.3, 131.6, 125.2, 124.2, 120.6, 112.7, 107.1, 98.3, 14.9. Anal. Calcd for $C_{27}H_{15}Cl_2NO_8$: C, 58.72%; H, 2.74%; N, 2.54%. Found: C, 58.55%; H, 2.81%; N, 2.65%.

4.1.3. Spiro[(3,11-dimethyl-7*H*-pyrano[3,2-*c*;5,6-*c*′]dichromene-6,8-dione)-7,6′-(5′-(amino-hydroxy-methylene-2′,3′-dichlorocyclohex-2′-ene-1′,4′-dione)] (IIc). Reaction[X34] of 4-hydroxycoumarin (**Ic**) (440 mg, 2.5 mmol) with DDQ (568 mg, 2.5 mmol) in anhydrous ethanol (30 mL) afforded **IIc** (390 mg, 57%) as a yellow solid. Mp 217–219 °C (decomposes). IR ν_{max} (KBr) 3409, 1707, 1664, 1622, 1514 cm^{-1}. ESI-MS *m*/*z* (rel. int.)[X35] 550 ($M^{+}-2$). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (d,

2H, $J=8.0$ Hz), 7.37 (d, 2H, $J=8.5$ Hz), 7.34 (s, 2H), 7.17 (br, s, 1H), 4.47 (br, s, 2H), 2.50 (s, 6H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 193.9, 184.9, 169.4, 162.2, 159.2, 158.9, 152.4, 151.4, 143.2, 131.8, 128.1, 125.9, 116.5, 112.0, 107.5. Anal. Calcd for $C_{27}H_{15}Cl_2NO_8$: C, 58.72%; H, 2.74%; N, 2.54%. Found: C, 58.63%; H, 2.78%; N, 2.63%.

4.1.4. Spiro[(2,12-dimethyl-7*H*-pyrano[3,2-*c*;5,6-*c*′]dichromene-6,8-dione)-7,6′-(5′-(amino-hydroxy-methylene-2′,3′-dichlorocyclohex-2′-ene-1′,4′-dione)] (IId). Reaction[X36] of 4-hydroxycoumarin (**Id**) (440 mg, 2.5 mmol) with DDQ (568 mg, 2.5 mmol) in anhydrous ethanol (30 mL) afforded **IId** (460 mg, 67%) as a solid. Mp 221–213 °C (decomposes[X37]). IR ν_{max} (KBr) 3419, 1717, 1703, 1611, 1586 cm^{-1}. ESI-MS *m*/*z* (rel. int.)[X38] 550 (M^+-2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.08 (s, 2H), 7.54 (d, 2H, $J=7.5$ Hz), 7.26 (d, 2H, $J=8.5$ Hz), 7.15 (br, s, 1H), 4.43 (br, s, 2H), 2.45 (s, 6H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 187.4, 184.8, 184.7, 184.5, 181.9, 158.9, 153.4, 152.3, 149.3, 134.8, 134.1, 124.6, 121.8, 116.3, 111.6, 105.9, 18.4. Anal. Calcd for $C_{27}H_{15}Cl_2NO_8$: C, 58.72%; H, 2.74%; N, 2.54%. Found: C, 58.67%; H, 2.83%; N, 2.62%.

4.1.5. Spiro[(7*H*-dibenzo[*c*,*n*]pyrano[3,2-*c*;5,6-*c*′]dichromene-6,8-dione)-7,6′-(5′-(amino-hydroxy-methylene-2′,3′-dichlorocyclohex-2′-ene-1′,4′-dione)] (IIe). Reaction of 4-hydroxycoumarin (**Ie**) (530 mg, 2.5 mmol) with DDQ (568 mg, 2.5 mmol) in anhydrous ethanol (30 mL) afforded **IIe** (420 mg, 54%) as a yellow solid. Mp 232–234 °C (decomposes). IR ν_{max} (KBr) 3445, 1701, 1673, 1624, 1717 cm^{-1}. ESI-MS *m*/*z* (rel. int.)[X39] 622 (M^+-2). ^{1}H NMR (500MHz, DMSO-d_6) δ 9.78 (br, s, 1H), 8.39 (d, 2H, $J=8.5$ Hz), 8.29 (d, 2H, $J=7.0$ Hz), 8.13 (d, 2H, $J=7.5$ Hz), 8.02 (d, 2H, $J=8.5$ Hz), 7.71–7.77 (4H, m), 5.29 (br, s, 1H). ^{13}C NMR (500 MHz, DMSO-d_6) δ 192.1, 185.5, 185.2, 185.1, 169.5, 162.4, 157.4, 154.2, 153.6, 148.3, 134.3, 128.9, 128.1, 127.6, 122.9, 121.7, 118.5, 115.7, 107.2, 98.4. Anal. Calcd for $C_{33}H_{15}Cl_2NO_8$: C, 63.48%; H, 2.42%; N, 2.24%. Found: C, 63.56%; H, 2.55%; N, 2.37%.

Acknowledgements

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Synthesis of novel pyrido[2,3-*e*][1,3]oxazines

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Abstract—The preparation of novel pyrido[2,3-*e*][1,3]oxazines starting from 3-hydroxy-pyridine-2-carbonitrile, *N*-aralkoxy-3-hydroxy-pyridine-2-carboxamides and 3-hydroxy-pyridine-2-carboxylic acid hydrazides is described.

1. Introduction

Development of novel synthetic methods for the construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Due to their broad spectrum of biological activities, including analgesic, antipyretic, bacteriostatic, fungistatic and monoaminoxidase inhibitory activity, pyrido[2,3-*e*][1,3]oxazine-2,4-diones are an interesting class of compounds for further structural modifications (Fig. 1).[1,2]

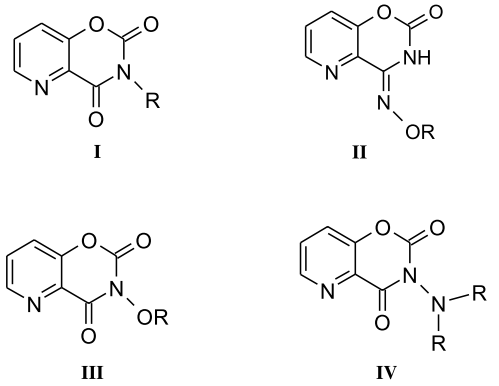

Figure 1. Pyrido[2,3-*e*][1,3]oxazines.

Compounds **I** have previously been prepared by reactions of 3-hydroxypicolinic acid amides and chloroformates, by treatment of 3-hydroxypicolinates with isocyanates and by oxidation of 5-(2-furyl)hydantoins.[1–4] Surprisingly, only very few structural modifications of the 1,3-oxazin-2,4-dione moiety have been reported in the literature so far. Most of the publications relate to simple modifications of the alkyl, alkylaryl and aryl substituents at the 1,3-oxazine nitrogen.[1–4]

In this paper, the synthesis of 4-methoxy(aralkoxy)imino-pyrido[2,3-*e*][1,3]oxazin-2-ones (**II**), 3-aralkoxypyrido[2,3-*e*][1,3]oxazin-2,4-diones (**III**) and *N*-disubstituted 3-amino-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (**IV**), as novel analogs of **I**, is described (Fig. 1).

The retrosynthetic analysis prompted us to investigate the applicability of 3-hydroxy-pyridine-2-carbonitrile (**1**) and 3-hydroxypicolinic acid (**6**) as starting materials for the synthesis of **II**–**IV**.[5]

2. Results and discussion

2.1. Synthesis of 4-methoxy(aralkoxy)imino-pyrido[2,3-*e*][1,3]oxazin-2-ones

Reaction of 3-hydroxy-pyridine-2-carbonitrile (**1**) with 1,1′-carbonyl-di-(1,2,4-triazole) in dry THF at room temperature smoothly led to the triazolide intermediate (**2**), which was treated with *O*-substituted hydroxylamines[6] to give the open-chained alkoxycarbamate intermediates (**3**). Ring closure of **3** took place in refluxing toluene in the presence of triethylamine and led to pyrido[2,3-*e*][1,3]oxazines (**4**), which underwent base catalyzed Dimroth rearrangement to give **5a**–**g** (Table 1).[7–9] During the reaction, the formation of intermediates **3**, which are characterized by a sharp (C=O) band at 1745–1755 cm^{-1} was monitored by IR spectroscopy. The disappearance of the (CN) band in the IR-spectra at 2233 cm^{-1} and precipitation of greenish solids

Keywords: Pyrido[2,3-*e*][1,3]oxazin-2-ones; 3-Hydroxy-pyridine-2-carbonitrile; 1,1′-Carbonyl-di-(1,2,4-triazole); 3-Hydroxy-picolinic acid; Diphosgene.
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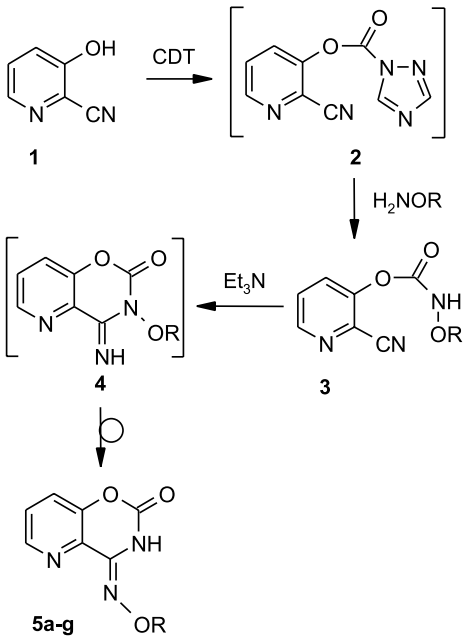


Scheme 1. Synthesis of methoxy(aralkoxy)imino-pyrido[2,3-*e*][1,3]oxazin-2-ones (**5a**–**g**).

Table 1. Synthesis of methoxy(aralkoxy)imino-pyrido[2,3-*e*][1,3]oxazin-2-ones (**5a**–**g**)

	R	**5** yield [%]
5a	4-Br–C_6H_4–CH_2	72
5b	4-CH_3–C_6H_4–CH_2	68
5c	CH_3	51
5d	$C_6H_5(CH_2)_2$	55
5e	$C_6H_5CH_2$	62
5f	$C_6H_5(CH_2)_3$	58
5g	4-F–C_6H_4–CH_2	66

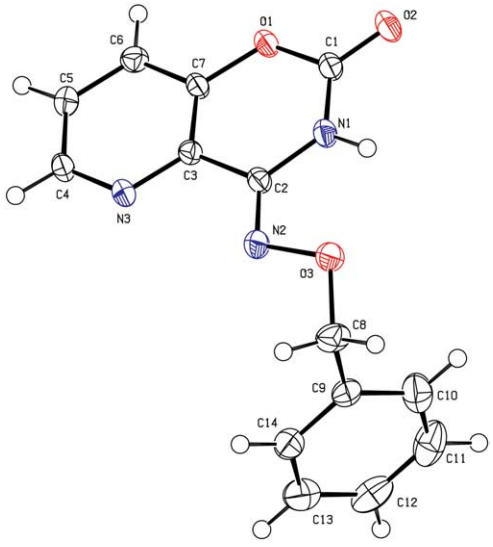


Figure 2. Perspective view of the X-ray crystal structure of **5e**.

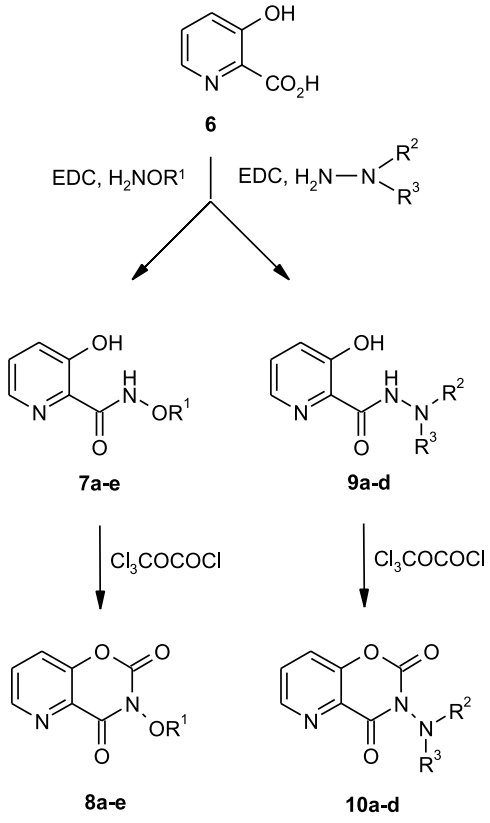
from refluxing toluene/triethylamine clearly indicated in all cases the formation of **5**. Interestingly, according to X-ray crystal structure analysis, CHN analysis and NMR spectroscopy the target heterocycles (**5a**–**g**) precipitated together with 1,2,4-*1H*-triazole in a 1:1 ratio. Finally, treatment of **5a**–**g** with $KHCO_3$ solution, extraction with $CHCl_3$ and crystallization from EtOAc/hexane provided analytical pure samples of **5a**–**g** in 51–72% overall yield (Scheme 1).

The structure of compund **5e** was elucidated by X-ray crystallography. The crystal structure showed a semicyclic amidoxime moiety, in which the benzyloxymino group is located at the carbon atom 2 of the 1,3-oxazine nucleus (Fig. 2).

2.2. Synthesis of 3-aralkoxy-pyrido[2,3-*e*][1,3]oxazin-2,4-diones (8a–e) and *N*-disubstituted 3-amino-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (10a–d)

N-Aralkoxy-3-hydroxy-pyridine-2-carboxamides (**7a**–**e**) and *N′*,*N′*-disubstituted 3-hydroxy-pyridine-2-carboxylic acid hydrazides (**9a**–**d**) have been prepared by a 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) mediated coupling reaction of 3-hydroxypicolinic acid (**6**) with aralkoxyamines and *N′*,*N′*-disubstituted hydrazines in 45–52% (**7a**–**e**) and 28–41% (**9a**–**d**) yield, respectively.

Initial attempts to get access to compound **8d** starting from **7d** and 1,1′-carbonyldiimidazole failed. Although the reaction of **7d** with ethyl chloroformate afforded the target



Scheme 2. Synthesis of 3-aralkoxy-pyrido[2,3-*e*][1,3]oxazin-2,4-diones (**8a**–**e**) and *N′*-disubstituted 3-amino-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (**10a**–**d**).

Table 2. *N*-Aralkoxy-3-hydroxy-pyridine-2-carboxamides (**7a–e**) and 3-aralkoxy-pyrido[2,3-*e*][1,3]oxazin-2,4-diones (**8a–e**)

	R^1	**7** yield [%]	**8** yield [%]
7a, **8a**	4-Br–C_6H_4–CH_2	51	95
7b, **8b**	4-CH_3–C_6H_4–CH_2	52	93
7c, **8c**	$C_6H_5(CH_2)_2$	45	91
7d, **8d**	$C_6H_5CH_2$	51	93
7e, **8e**	$C_6H_5(CH_2)_3$	50	94

Table 3. Synthesis of (**9a–d**) and (**10a–d**)

	R^2	R^3	**9** yield [%]	**10** yield [%]
9a, **10a**	CH_3	CH_3	34	86
9b, **10b**	CH_3	Ph	41	87
9c, **10c**	–$(CH_2)_2$O–$(CH_2)_2$–		39	90
9d, **10d**	–$(CH_2)_5$–		28	84

compound **8d**, the yield was low and various by-products were detected by TLC.

Next we turned our attention to phosgene as a carbonylating agent, which provided **8d** in a somewhat higher yield of 65%. Finally, treatment of **7a–e** with diphosgene in dry dichloromethane smoothly led to **8a–e** in high yields of 91–95%.

Furthermore, reactions of **9a–d** with diphosgene under similar conditions afforded *N*-disubstituted 3-amino-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (**10a–d**) in 84–90% yield.

The structures of all compounds were confirmed by IR, ^{1}H, ^{13}C NMR spectroscopy and elemental analysis (Scheme 2, Tables 2 and 3).

3. Conclusion

In this paper, the synthesis of three novel classes of pyrido[2,3-*e*][1,3]oxazines is described. A practical one-pot protocol for the synthesis of 4-methoxy(aralkoxy)imino-pyrido[2,3-*e*][1,3]oxazin-2-ones (**5a–g**) as well as a convenient pathway for the preparation of 3-aralkoxy-pyrido[2,3-*e*][1,3]oxazin-2,4-diones (**8a–e**) and *N*-disubstituted 3-amino-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (**10a–d**) have been developed.

4. Experimental

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analysis were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Shimadzu FT-IR 8300. ^{1}H NMR (400 MHz) und ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-d_6 and $CDCl_3$ as solvents.

4.1. General procedure for the preparation of 4-alkoxy-(aralkoxy)imino-pyrido[2,3-*e*][1,3]-oxazin-2-ones (5a–l)

To a suspension of 1,1′-carbonyl-di-(1,2,4-triazole) (3.3 mmol) in anhydrous THF (10 mL) were added triethylamine (2 drops) and 2-cyano-3-hydroxy pyridine (**2**) (0.36 g, 3.0 mmol) portionwise over a period of 10 min at room temperature. After stirring for 10 min a solution of the appropriate hydroxylamine in THF was added dropwise and the reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, toluene (5 mL) and triethylamine (5 mL) was added and the reaction mixture was refluxed for 1–2 h. After cooling to room temperature, the solid was filtered, suspended in diluted $KHCO_3$ solution (15 mL) and extracted twice with $CHCl_3$ (15 mL). The organic layer was dried over $MgSO_4$, concentrated and the remaining solid was recrystallized from EtOAc/hexane to give **5a–g** as colorless solids in 51–72% yield.

4.1.1. 4-(4-Bromobenzyloxy)imino-pyrido[2,3-*e*][1,3]-oxazin-2-one (5a). Colorless crystals (72%). Mp 180.2 °C (EtOAc/hexane); IR (KBr): ν=3253, (NH) 1743 (C=O), 1641 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 5.16 (s, 2H), 7.42–7.44 (m, 2H), 7.54–7.59 (m, 3H), 7.69 (dd, J=1, 27, 8.39 Hz, 1H), 8.43 (dd, J=1, 27, 4.57 Hz, 1H), 11.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 75.2, 121.1, 124.9, 127.4, 130.2, 130.3, 131.4, 137.7, 140.2, 145.3, 146.7, 147.9. Anal. Calcd for $C_{14}H_{10}BrN_3O_3$: C, 48.30; H, 3.03; N, 12.65; Found C, 48.30; H, 3.03; N, 12.65.

4.1.2. 4-(4-Methylbenzyloxy)imino-pyrido[2,3-*e*][1,3]-oxazin-2-one (5b). Colorless crystals (68%). Mp 176.8 °C (EtOAc/hexane); IR (KBr): ν=3224 (NH) 1751 (C=O), 1641 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 2.29 (s, 3H), 5.14 (s, 2H), 7.17 (d, J=7.88 Hz, 2H), 7.34 (d, J=7.89 Hz, 2H), 7.55 (d, J=4.33, 8.40 Hz, 1H), 7.68 (dd, J=1.02, 8.39 Hz, 1H), 8.44 (dd, J=1.02, 4.58 Hz, 1H), 11.18 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 21.1, 76.0, 124.9, 127.4, 128.3, 129.1, 131.4, 135.2, 137.2, 139.7, 145.2, 146.7, 147.8. Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83; Found C, 48.30; H, 3.03; N, 12.65.

4.1.3. 4-Methoxyimino-pyrido[2,3-*e*][1,3]oxazin-2-one (5c). Colorless crystals (51%). Mp 246.3 °C (EtOAc/hexane); IR (KBr): ν=3205 (NH), 1751 (C=O), 1647 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.91 (s, 3H), 7.58 (dd, J=4.58, 8.39 Hz, 1H) 7.70 (dd, J=1, 27, 8.39 Hz, 1H), 8.44 (dd, J=1, 52, 4.38 Hz, 1H), 11.06 (s, 1H);. ^{13}C NMR (DMSO-d_6) δ (ppm): 62.0, 124.5, 126.9, 131.0, 139.0, 144.8, 146.3, 147.4. Anal. Calcd for $C_8H_7N_3O_3$: C, 49.75; H, 3.65; N, 21.75; Found C, 49.77; H, 3.83; N, 21.75.

4.1.4. 4-Phenethyloxyimino-pyrido[2,3-*e*][1,3]oxazin-2-one (5d). Colorless crystals (55%). Mp 133.4 °C (EtOAc/hexane); IR (KBr): ν=3201 (NH), 1745 (C=O), 1651 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.05 (t, J=7.12 Hz, 2H), 4.32 (t, J=7.12 Hz, 2H), 7.19–7.24 (m, 1H), 7.29–7.34 (m, 4H), 7.58 (dd, J=4.58, 8.39 Hz, 1H), 7.71 (dd, J=1, 27, 8.39 Hz, 1H), 8.49 (dd, J=1.27, 4.58 Hz, 1H), 11.09 (s, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 34.7, 74.8, 124.5, 126.1, 127.0, 128.2, 129.0, 131.1, 138.4, 139.3, 145.0, 146.3, 147.1. Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83; Found C, 63.63; H, 4.66; N, 14.89.

4.1.5. 4-Benzyloxyimino-pyrido[2,3-*e*][1,3]oxazin-2-one (5e). Colorless crystals (62%). Mp 156.1 °C (EtOAc/

hexane); IR (KBr): ν=3234 (NH), 1741 (C=O), 1647 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.19 (s, 2H), 7.28–7.32 (m, 1H), 7.34–7.41 (m, 2H), 7.44–7.48 (m, 2H), 7.55 (dd, J=4.57, 8.39 Hz, 1H), 7.69 (dd, J=1, 27, 8.39 Hz, 1H), 8.44 (dd, J=1, 27, 4.57 Hz, 1H), 11.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 75.7, 124.5, 126.9, 127.5, 127.7, 128.1, 131.0, 137.8, 139.4, 144.8, 146.2, 147.4. Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61; Found C, 62.32; H, 4.10; N, 15.66.

Crystallographic data for compound **5e** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 232948. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.6. 4-(4-Fluorobenzyloxy)imino-pyrido[2,3-*e*][1,3]-oxazin-2-one (5f). Colorless crystals (58%). Mp 164.7 °C (EtOAc/hexane); IR (KBr): ν=3244 (NH), 1739, (C=O), 1647 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): δ=5.20 (s, 2H), 7.18–7.22 (m, 2H), 7.51–7.59 (m, 3H), 7.70 (d, J=8.40 Hz, 1H), 8.44 (d, J=4.07 Hz, 1H), 11.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 75.0, 124.5, 127.0, 130.0, 130.1, 134.0, 139.6, 144.9, 146.3, 147.5, 160.5, 126.9. Anal. Calcd for $C_{14}H_{10}FN_3O_3$: C, 58.54; H, 3.51; N, 14.63; Found C, 48.30; H, 3.03; N, 12.65.

4.1.7. 4-Phenypropyloxyimino-pyrido[2,3-*e*][1,3]oxazin-2-one (5g). Colorless crystals (66%). Mp 122.5 °C (EtOAc/hexane); IR (KBr): ν=3253 (NH), 1739 (C=O), 1653 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.99 (dt, J=6.35, 7.35 Hz, 2H), 2.75 (t, J=7.35 Hz, 2H), 4.13 (t, J=6.35 Hz, 2H), 7.17–7.32 (m, 3H), 7.57 (dd, J=4.32, 8.39 Hz, 1H), 7.71 (dd, J=1, 02, 8.39 Hz, 1H), 8.46 (dd, J=1.02, 4.32 Hz, 1H), 11.10 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 30.3, 31.3, 73.3, 124.5, 125.6, 126.9, 128.2, 128.3, 131.1, 139.0, 141.7, 145.0, 146.3, 147.4. Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 64.64; H, 5.09; N, 14.13; Found C, 64.66; H, 5.15; N, 14.26.

4.2. General procedure for the preparation of *N*-aralkoxy-3-hydroxy-pyridine-2-carboxamides and (7a–e) and *N′*,*N′*-disubstituted 3-hydroxy-pyridine-2-carboxylic acid hydrazides (9a–d)

To a solution of 3-hydroxypicolinic acid (**6**) (10 mmol), 4-(dimetylamino)-pyridine (2 mmol) and aralkoxyamine or *N*,*N′*-disubstituted hydrazine (10.5 mmol) in dry dichloromethane (50 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) at room temperature. After stirring at ambient temperature overnight, the solvent was removed under reduced pressure and the remaining residue was treated with EtOAc (50 mL) and 10% citric acid solution (30 mL). The organic layer was extracted twice with citric acid solution (10%, 20 mL), washed with water and once with sodium carbonate solution (30 mL). Afterwards the organic layer was dried over $MgSO_4$, filtered and concentrated to a volume of 10 mL. Addition of hexane provided **7a–e** and **9a–d** as solid compounds.

4.2.1. *N*-(4-Bromobenzyloxy)-3-hydroxy-pyridine-2-carboxamide (7a). Colorless crystals (51%). Mp 157.8 °C (EtOAc/hexane); IR (KBr): ν=3303 (NH, OH), 1654 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 4.95 (s, 2H), 7.41–7.46 (m, 3H), 7.53 (dd, J=4.33, 8.65 Hz, 1H), 7.57–7.61 (m, 2 H), 8.13 (dd, J=1, 28, 4.32 Hz, 1 H), 12.05, (s, 1H), 12.45 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 76.6, 121.8, 126.1, 129.3, 130.8, 131.2, 131.4, 135.1, 140.1, 157.1, 165.8. Anal. Calcd for $C_{13}H_{11}BrN_2O_3$: C, 48.32; H, 3.43; N, 8.67; Found: C, 48.21; H, 3.44; N, 8.35.

4.2.2. 3-Hydroxy-*N*-(4-methylbenzyloxy)-pyridine-2-carboxamide (7b). Colorless crystals (57%). Mp 139.2 °C (EtOAc/hexane); IR (KBr): ν=3309 (NH, OH), 1654 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.37 (s, 3H), 5.00 (s, 2H), 7.19 (d, J=7.63 Hz, 2H), 7.29–7.35 (m, 4H), 7.97–7.98 (m, 1H), 12.05, (s, 1H), 12.45 (s, 1H), ^{13}C NMR ($CDCl_3$) δ (ppm): 21.3, 78.8, 126.3, 128.9, 129.4, 130.4, 131.8, 138.9, 139.8, 157.6, 166.1; Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85; Found: C, 64.87; H, 5.56; N, 10.87.

4.2.3. 3-Hydroxy-*N*-phenylethyloxy-pyridine-2-carboxamide (7c). Colorless crystals (45%). Mp 57.7 °C (EtOAc/hexane); IR (KBr): ν=3280 (NH, OH), 1658 (C=O), cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.97 (t, J=6.87 Hz, 2H), 4.16 (t, J=6.87 Hz, 2H), 7.18–7.24 (m, 1H), 7.26–7.35 (m, 4H), 7.43 (dd, J=1.27, 8.65 Hz, 1H), 7.52 (dd, J=4.32, 8.65 Hz, 1H), 8.14 (dd, J=1, 27, 4.32 Hz, 1H), 12.13, (s, 1H), 12.38 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 34.1, 76.1, 126.0, 126.4, 126.5, 129.0, 129.2, 131.0, 138.2, 140.0, 157.1, 165.7. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85; Found: C, 65.02; H, 5.51; N, 10.83.

4.2.4. *N*-Benzyloxy-3-hydroxy-pyridine-2-carboxamide (7d). Colorless crystals (58%). Mp 102.4 °C (EtOAc/hexane); IR (KBr): ν=3294 (NH, OH), 1656 (C=O), cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 4.98 (s, 2H), 7.34–7.44 (m, 4H), 7.45–7.49 (m, 2H), 7.53 (dd, J=4.33, 8.40 Hz, 1H), 8.13 (dd, J=1, 27, 4.32 Hz, 1H), 12.08, (s, 1H), 12.45 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 77.2, 125.9, 128.2, 128.2, 128.8, 129.0, 130.6, 135.3, 139.8, 156.8, 165.5; Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47; Found: C, 63.88; H, 5.01; N, 11.24.

4.2.5. 3-Hydroxy-*N*-phenylpropyloxy-pyridine-2-carboxamide (7e). Colorless crystals (55%). Mp 49.2 °C (EtOAc/hexane); IR (KBr): ν=3323 (NH, OH), 1658 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.90 (dt, J=6.36, 7.88 Hz, 2H), 2.73 (t, J=7.88 Hz, 2H), 3.95 (t, J=6.36 Hz, 2H), 7.16–7.21 (m, 1H), 7.25–7.31 (m, 4H), 7.43 (dd, J=1.27, 8.65 Hz, 1H), 7.54 (dd, J=4, 32, 8.65 Hz, 1H), 8.14 (dd, J=1, 27, 4.32 Hz, 1H), 12.15, (s, 1H), 12.37 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 29.8, 31.6, 75.1, 125.9, 126.1, 128.4, 128.5, 129.2, 130.9, 140.0, 141.8, 157.1, 165.8. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29; Found: C, 66.12; H, 6.03; N, 10.37.

4.2.6. *N′*,*N′*-Dimethyl-3-hydroxy-picolinohydrazide (9a). Colorless crystals (34%). Mp 85.7 °C (EtOAc/hexane); IR (KBr): ν=3200 (OH), 3054 (NH), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.60 (s, 6H), 7.41 (dd, J=1, 27, 8.65 Hz, 1H), 7.52 (dd, J=4.32, 8.65 Hz, 1H), 8.14 (dd, J=1.27, 4.32 Hz, 1H), 10.05 (s, 1H), 12.56 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 46.1, 125.7, 128.9, 131.1, 139.5,

157.2, 165.9. Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19; Found C, 53.00; H, 6.15; N, 23.29.

4.2.7. *N′*-Methyl-*N′*-phenyl-3-hydroxy-picolinohydrazide (9b). Brown crystals (41%). Mp 109.4 °C (EtOAc/hexane); IR (KBr): ν=3371 (OH), 3059 (NH), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 3.20 (s, 3H), 6.83–6.77 (m, 3H), 7.20–7.24 (m, 2H), 7.47 (dd, J=1, 27, 8.65 Hz, 1H), 7.58 (dd, J=4.32, 8.65 Hz, 1H), 8.22 (dd, J=1.27, 4.32 Hz, 1H), 11.17 (s, 1H), 12.03 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 39.9, 112.5, 118.5, 125.9, 128.8, 129.3, 130.9, 140.0, 149.4, 157.1, 167.9. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27; Found C, 64.13; H, 5.41; N, 17.36.

4.2.8. 3-Hydroxy-*N*-(morpholine-4-yl)-pyridine-2-carboxamide (9c). Yellow crystals (39%). Mp 111.9 °C (EtOAc/hexane); IR (KBr): ν=3296 (OH), 3205 (NH), 1661 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.91 (t, J=4, 58 Hz, 4H), 3.68 (t, J=4, 58 Hz, 4H), 7.41 (dd, J=1, 27, 8.40 Hz, 1H), 7.54 (dd, J=4, 32, 8, 64 Hz, 1H), 8.16 (dd, J=1, 27, 4.32 Hz, 1H), 10.24 (s, 1H), 12.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 54.1, 65.8, 125.8, 129.0, 131.0, 139.6, 157.2, 166.0. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82; Found C, 53.76; H, 5.86; N, 18.84.

4.2.9. 3-Hydroxy-*N*-(piperidine-1-yl)-pyridine-2-carboxamide (9d). Colorless crystals (28%). Mp 69.5 °C (EtOAc/hexane); IR (KBr): ν=3211 (OH), 3059 (NH), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.31–1.41 (m, 2H), 1.57–1.64 (m, 4H), 2.83 (t, J=5.34 Hz, 4H), 7.41 (dd, J=1.27, 8.40 Hz, 1H), 7.51 (dd, J=4.32, 8.39 Hz, 1H), 8.13 (dd, J=1.27, 4.32 Hz, 1H), 9.99 (s, 1H), 12.57 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.8, 25.2, 55.0, 125.7, 128.9, 131.1, 139.5, 157.2, 165.6. Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99; Found C, 59.77; H, 6.84; N, 17.92.

4.3. General procedure for the preparation of 3-aralkoxy-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (8a–e) and *N*-disubstituted 3-amino-pyrido[2,3-*e*][1,3]-oxazin-2,4-diones (10a–d)

To a solution of **7a–e** or **9a–d** (2 mmol) in dry THF (15 mL) was added diphosgene (4.5 mmol) dropwise under ice cooling. After stirring for 5 h the solvent was evaporated and the remaining residue was treated with cold $NaHCO_3$ solution. The solid was filtered, dried and recrystallized to give **8a–e** and **10a–d** as colorless solids.

4.3.1. 3-(4-Bromobenzyloxy)-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (8a). Colorless crystals (95%). Mp 221.9 °C ($CHCl_3$/hexane); IR (KBr): ν=1780, 1728 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.14 (s, 2H), 7.55 (d, J=7.36 Hz, 2H), 7.65 (d, J=7.36 Hz, 2H), 7.85 (dd, J=4.32, 8.39 Hz, 1H), 8.00 (dd, J=1.27, 8.39 Hz, 1H), 8.71 (dd, J=1, 27, 4.32 Hz, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 76.7, 122.2, 125.3, 129.9, 131.4, 131.6, 132.4, 133.4, 145.1, 147.2, 149.8, 156.3. Anal. Calcd for $C_{14}H_9BrN_2O_4$: C, 48.16; H, 2.60; N, 8.02; Found: C, 47.96; H, 2.60; N, 8.16.

4.3.2. 3-(4-Methylbenzyloxy)-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (8b). Colorless crystals (93%). Mp 198.6 °C ($CHCl_3$/hexane); IR (KBr): ν=1774, 1724 (C=O) cm^{-1}; ^1H NMR NMR (DMSO-d_6) δ (ppm): 2.34 (s, 3H), 5.10 (s, 2H), 7.25 (d, J=7.36 Hz, 2H), 7.46 (d, J=7.36 Hz, 2H), 7.86 (dd, J=4.32, 8.39 Hz, 1H), 8.00 (d, J=8.39 Hz, 1H), 8.71 (d, J=3.82 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm): 20.8, 77.4, 125.3, 128.9, 129.6, 129.9, 130.9, 132.4, 138.4, 145.1, 147.2, 149.8, 156.3. Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85; Found: C, 63.26; H, 4.32; N, 9.78.

4.3.3. 3-Phenylethyloxy-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (8c). Colorless crystals (91%). Mp 126.7 °C (EtOAc/hexane); IR (KBr): ν=1774, 1735 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 3.07 (t, J=6.87 Hz, 2H), 4.37 (t, J=6.87 Hz, 2H), 7.18–7.24 (m, 1H), 7.29–7.35 (m, 4H), 7.83 (dd, J=1.27, 8.65 Hz, 1H), 7.97 (dd, J=4.32, 8.65 Hz, 1H), 8.69 (dd, J=1, 27, 4.32 Hz, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 33.7, 75.9, 125.2, 126.2, 128.2, 128.7, 129.8, 132.5, 137.3, 145.1, 147.1, 149.7, 156.3. Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85; Found: C, 63.22; H, 4.05; N, 9.56.

4.3.4. 3-Benzyloxy-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (8d). Colorless crystals (93%). Mp 216 °C ($CHCl_3$/hexane); IR (KBr): ν=1770, 1722 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.16 (s, 2H), 7.41–7.47 (m, 3H), 7.57–7.60 (m, 2H), 7.85 (dd, J=4.32, 8.39 Hz, 1H), 8.00 (dd, J=1.27, 8.39 Hz, 1H), 8.72 (dd, J=1, 27, 4.32 Hz, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 77.5, 125.2, 128.5, 129.0, 129.5, 129.9, 132.5, 133.9, 145.1, 147.2, 149.8, 156.3; Calcd for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37; Found: C, 62.02; H, 3.75; N, 10.17.

4.3.5. 3-Phenylpropyloxy-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (8e). Colorless crystals (94%). Mp 118.5 °C ($CHCl_3$/hexane); IR (KBr): ν=1772, 1735 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.98 (dt, J=6.36, 7.88 Hz, 2H), 2.78 (t, J=7.88 Hz, 2H), 4.16 (t, J=6.36 Hz, 2H), 7.16–7.23 (m, 1H), 7.26–7.32 (m, 4H), 7.84 (dd, J=4.32, 8.39 Hz, 1H), 7.96 (d, J=8.39 Hz, 1H), 8.70 (d, J=4.32 Hz, 1H) ^{13}C NMR (DMSO-d_6) δ (ppm): 29.4, 31.2, 75.1, 125.2, 125.8, 128.2, 128.3, 129.8, 132.5, 141.3, 145.1, 147.1, 149.7, 156.4. Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39; Found: C, 64.44; H, 4.79; N, 9.36.

4.3.6. 3-Dimethylamino-pyrido-[2,3-*e*][1,3]-oxazin-2,4-dione (10a). Colorless crystals (86%). Mp 171.3 °C (EtOAc/hexane); IR (KBr): ν=1728, 1778 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.85 (s, 6H), 7.80 (dd, J=4.33, 8.39 Hz, 1H), 7.91 (dd, J=1.27, 8.40 Hz, 1H), 8.86 (dd, J=1.27, 4.32 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 42.2, 124.9, 129.6, 132.6, 146.1, 146.9, 149.9. 158.8. Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28; Found C, 52.28; H, 4.61; N, 20.30.

4.3.7. 3-(Methyl-phenylamino)-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (10b). Yellow crystals (87%). Mp 175.5 °C (EtOAc/hexane); IR (KBr): ν=1728, 1789 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 3.30 (s, 3H), 6.80–6.90 (m, 3H), 7.19–7.23 (m, 2H), 7.88 (dd, J=4.32, 8.39 Hz, 1H), 8.01 (dd, J=1.27, 8.39 Hz, 1H), 8.71 (dd, J=1.27, 4.32 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 37.6, 111.7, 119.0, 125.2, 128.9, 130.0, 132.4, 146.5, 147.0, 147.1, 150.5, 158.4. Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61; Found C, 62.45; H, 4.40; N, 15.63.

4.3.8. 3-(Morpholin-4-yl)-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (10c). Colorless crystals (90%). Mp 258.8 °C (EtOAc/hexane); IR (KBr): $\nu = 1728$, 1772 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.28 (s, 4H), 3.70 (t, $J = 4$, 83 Hz, 4H), 7.81 (dd, $J = 4$, 32, 8.65 Hz, 1H), 7.91 (dd, $J = 1$, 27, 8, 65 Hz, 1H), 8.67 (dd, $J = 1$, 27, 4.32 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 50.1, 66.5, 124.9, 129.7, 132.6, 146.2, 146.9, 149.8, 158.7. Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86; Found C, 52.96; H, 4.62; N, 16.92.

4.3.9. 3-(Piperidin-1-yl)-pyrido[2,3-*e*][1,3]-oxazin-2,4-dione (10d). Colorless crystals (84%). Mp 240.2 °C (EtOAc/hexane); IR (KBr): $\nu = 1726$, 1777 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 1.31–1.54 (m, 2H), 1.60–1.64 (m, 4H), 3.16–3.27 (m, 4H), 7.78 (dd, $J = 4.32$, 8.40 Hz, 1H), 7.90 (dd, $J = 1.28$, 8.40 Hz, 1H), 8.65 (dd, $J = 1.28$, 4.33 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.1, 25.8, 50.8, 124.8, 129.6, 132.6, 146.2, 146.8, 149.9, 158.8. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99; Found C, 58.09; H, 5.44; N, 17.04.

Acknowledgements

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Synthesis of isomerically pure carboxylate- and sulfonate-substituted xanthene fluorophores

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Abstract—Xanthene-based fluorophores such as fluorescein and rhodamine are typically prepared by acid-catalyzed condensation of the appropriate resorcinol or 3-aminophenol with phthalic anhydride. Condensation of substituted phthalic anhydride species results in functionalized fluorophores that are formed as mixed isomers. Crystallization approaches to isomer separation have been reported elsewhere for symmetric fluorescein carboxylates. We describe crystallization-based separation of protected fluorescein sulfonates and coupling conditions to form sulfonamides, precursors for carboxylate-substituted rhodamines, and precursors for asymmetrically substituted fluoresceins and rhodafluors.

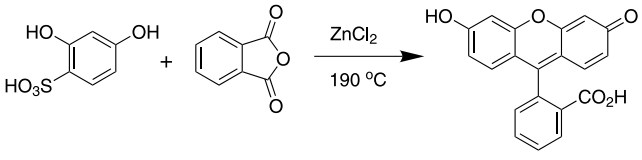
1. Introduction

Xanthene-based dyes such as rhodamines and fluoresceins are widely used in sensing applications owing to their brightness, high quantum yields, low-energy excitation and emission wavelengths, and biocompatibility. Functional handles are typically incorporated into the benzoic acid ring of these fluorophores. Bottom-ring-substituted rhodamines and fluoresceins form by acid-catalyzed condensation of a 3-aminophenol or resorcinol with a substituted phthalic acid species. This reaction affords the desired product as an equal mixture of two isomers, substituted at the 5- and 6-positions[1] of the benzoic acid ring. Crystallization-based separations of protected fluorescein carboxylate isomeric mixtures have been described,[1,2] and we now report similar methods in the separation of fluorescein 5(6) sulfonic acid isomers. However, there is no general method for separating rhodamine 5- and 6-carboxylate mixtures by crystallization. Chromatographic separation of isomers is particularly tedious with these polar, charged compounds.[3,4] Finally, asymmetrically substituted fluoresceins[5–8] and various hybrid rhodamine-fluorescein compounds,[9–13] termed rhodafluors or rhodols, have been prepared by our group and others. These compounds share a 2′,4′-dihydroxybenzophenone-2-carboxylate as a synthon, but the preparation of isomerically pure dicarboxy-substituted analogues of these benzophenones has not been reported. We now describe methodology for the synthesis of isomerically pure carboxylic or sulfonic acid-substituted analogues of these fluorophores.

2. Results and discussion

2.1. Fluorescein sulfonamides

In the course of our efforts to produce fluorescent sensors for Zn^{2+}, the synthesis of fluorescein sulfonamides was of interest owing to the many reported sulfonamide-based Zn^{2+} sensors. Sulfonation of the xanthene system was considered most likely to afford a derivative that would exhibit a metal-induced change in fluorescence. Direct sulfonation of unsubstituted fluorescein with fuming sulfuric acid provided only unreacted starting material, however. Reaction of sulfonated resorcinol with phthalic anhydride provided unsubstituted fluorescein as the major product (Scheme 1). Condensation of resorcinol with 4-sulfophthalic acid was explored next. As expected, this reaction produced a mixture of two isomers (**1a**, **b**, Scheme 2) in roughly equal amounts, a mixture that is available



Scheme 1.

Keywords: Fluorescein sulfonic acid; Rhodamine carboxylate; Isomer resolution; Fractional crystallization; Dibromofluoran; Asymmetric fluorescein carboxylate.
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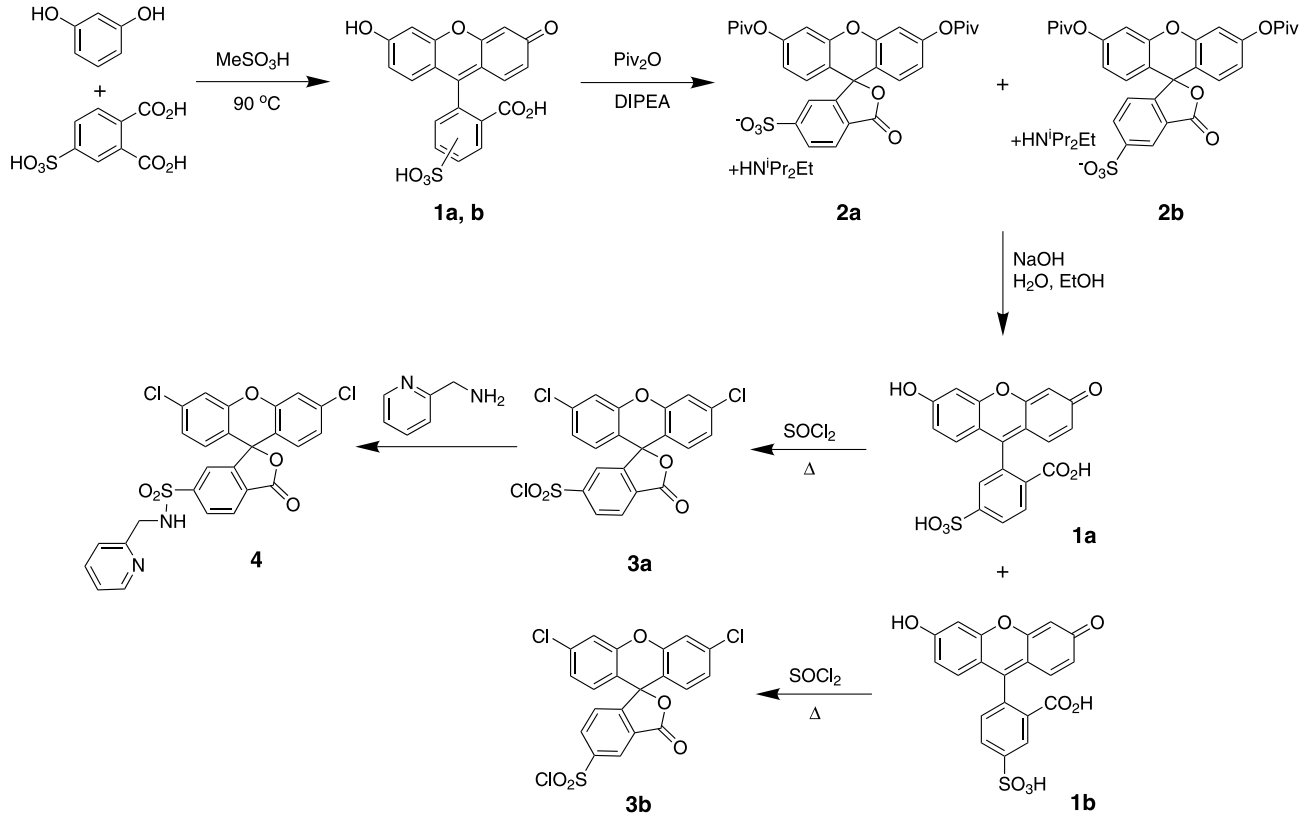


Scheme 2.

commercially.[14] The separation of fluorescein-5(6)-sulfonic acid isomers, reported previously, claimed isomeric purity based on infrared spectroscopy and paper chromatography.[15,16] The analytical sensitivity of these techniques is relatively low. We were able to separate the mixed isomers by protection as the dipivaloyl esters and subsequent crystallization of the 6-isomer **2a** followed by crystallization of the 5-isomer **2b**, each as its diisopropylethylammonium salt. Isomeric purity of **2a** and **2b** was greater than 95% based on NMR spectroscopy. Basic hydrolysis of the isomerically pure dipivaloates **2a** and **2b** yielded the deprotected fluorescein sulfonic acids **1a** and **1b**.

A crystal structure of fluorescein-6-sulfonic acid (**1a**) was obtained (Fig. 1). The crystal formed under strongly acidic conditions and, consequently, the fluorescein is in the

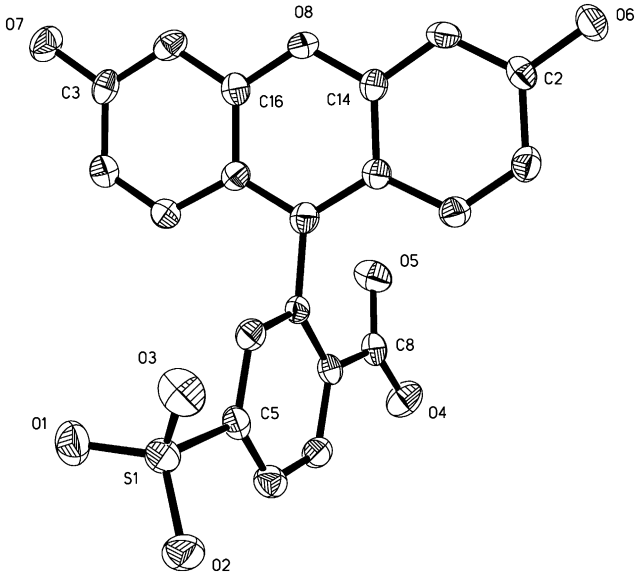


Figure 1. ORTEP diagram of fluorescein-6-sulfonic acid (**1a**) showing 50% probability thermal ellipsoids. The solvent molecules have been omitted for clarity.

Table 1. Crystallographic information

	1a·3H$_2$O	**4**
Empirical formula	$C_{20}H_{18}O_{11}S$	$C_{26}H_{16}N_2O_5SCl_2$
Molecular weight	466.40	539.37
Space group	$P2_1/c$	$P\bar{1}$
a (Å)	10.4324(12)	9.997(4)
b (Å)	16.854(2)	11.067(2)
c (Å)	11.9615(14)	11.401(2)
α, deg		95.65(3)
β, deg	109.516(2)	100.55(3)
γ, deg		106.81
V, Å^3	1982.3(4)	1171.6(4)
Z	4	2
ρ_{calc}, g/cm^3	1.563	1.529
T, °C	−85	−100
μ (Mo Kα), mm^{-1}	0.228	0.409
θ limits, deg	2.07–28.29	1.84–28.29
Total number of data	12393	10559
Number of unique data points	4568	5363
Number of parameters	316	352
R^a	0.0670	0.0433
wR^{2b}	0.1341	0.1070
max, min peaks, e/Å^3	0.464, −0.488	0.663, −0.199

[a] $R=\Sigma||F_o|-F_c||/\Sigma|F_o|$.
[b] $wR^2=\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$.

lactone-opened form, presumably with a positive charge delocalized over the xanthene system. The charge is neutralized by the anionic sulfonate group. The C–O bonds of the phenolic hydroxyls are approximately the same length (1.34, 1.33 Å) and are each consistent with a single bond, rather than a ketone tautomer. Three water molecules were present in the asymmetric unit, with 12 in the unit cell. Crystallographic parameters are listed in Table 1 and selected bond lengths and angles for **1a**, in Table 2.

Table 2. Selected bond lengths and angles for **1a**

Bond lengths	(Å)	Bond angles	(Deg)
S(1)–O(2)	1.442(3)	O(2)–S(1)–O(1)	113.08(15)
S(1)–O(1)	1.451(3)	O(2)–S(1)–O(3)	112.75(17)
S(1)–O(3)	1.456(3)	O(1)–S(1)–O(3)	112.10(16)
S(1)–C(5)	1.780(3)	O(4)–C(8)–O(5)	124.7(3)
O(8)–C(14)	1.355(4)		
O(8)–C(16)	1.360(4)		
O(7)–C(3)	1.342(4)		
O(6)–C(2)	1.326(4)		
O(5)–C(8)	1.309(4)		
O(4)–C(8)	1.219(4)		

Coupling of the sulfonic acids with amines was first attempted following activation with thionyl chloride (Scheme 2). Reaction of both protected and unprotected fluoresceins under these conditions gave a non-fluorescent material **3a** or **3b**, however, which was determined to be the

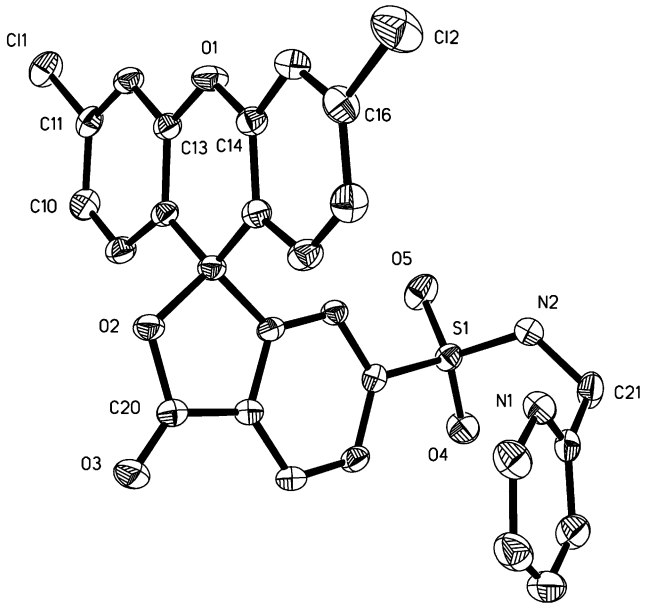


Figure 2. ORTEP diagram of fluorescein-6-sulfonamidopicoline (**4**) showing 50% probability thermal ellipsoids.

Table 3. Selected bond lengths and angles for **4**

Bond lengths	(Å)	Bond angles	(Deg)
Cl(1)–C(11)	1.7313(18)	O(5)–S(1)–O(4)	121.11(9)
Cl(2)–C(16)	1.7362(19)	O(5)–S(1)–N(2)	106.95(9)
S(1)–O(5)	1.4263(14)	O(4)–S(1)–N(2)	107.75(9)
S(1)–O(4)	1.4294(14)	C(21)–N(2)–S(1)	122.30(13)
S(1)–N(2)	1.5958(16)	O(3)–C(20)–O(2)	121.94(16)
O(1)–C(13)	1.371(2)	C(10)–C(11)–Cl(1)	119.33(14)
O(1)–C(14)	1.374(2)	C(13)–O(1)–C(14)	118.12(13)
N(2)–C(21)	1.456(2)		

3′, 6′-dichlorofluoran by X-ray crystallographic analysis of the 2-picolylamine adduct **4** (Fig. 2; selected bond lengths and angles listed in Table 3). The dihedral angle between the two extended aromatic ring systems is 86.6°, indicating a nearly perpendicular orientation. Use of the milder oxalyl chloride as an activating agent to generate sulfonyl chloride **5** and subsequent reaction with an amine affords the desired sulfonamide product as a mixture of unprotected (**6**) and protected (**7**) products (Scheme 3).

2.2. Rhodamines and rhodamine carboxylates

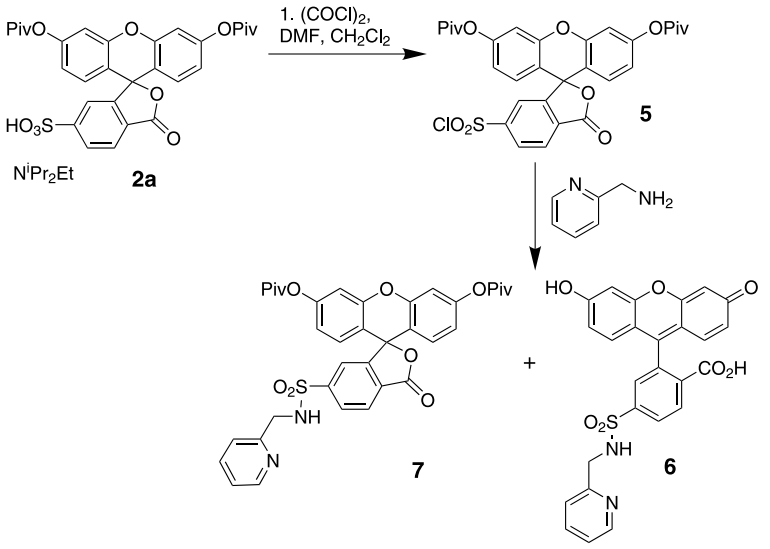
3′,6′-Dichlorofluoran can be converted into rhodamines by direct $ZnCl_2$-catalyzed condensation with excess amine.[17,18] This reaction suggested that, since 3′,6′-dihalofluorans share with 3′,6′-diacetyl- or -dipivaloyl-fluorescein the fluorescein motif that has been trapped in the lactone form, it might be possible to synthesize 3′,6′-dihalofluoran-5(6)-carboxylates by acid-catalyzed condensation and subsequently resolve the isomers by selective crystallization. Alternatively, reaction of previously resolved fluorescein carboxylates with thionyl chloride or thionyl bromide could provide the desired isomerically pure dihalofluoran carbonyl halide (vide supra). Subsequent condensation with amines under appropriate conditions might afford isomerically pure rhodamine carboxylates.[19]

We chose to work with the more reactive dibromofluoran species, rather than the reported dichlorofluran substrate. 3′,6′-Dibromofluoran **8** was synthesized by acid-catalyzed condensation of 3-bromophenol with phthalic anhydride and used as a model for the less readily available dibromofluoran carboxylates. 3′,6′-Dibromofluoran reacted smoothly with excess pyrrolidine under literature conditions to afford the desired rhodamine **9**. Palladium-catalyzed reductive coupling under reaction conditions described in the literature[20] also furnished **9**. This chemistry is summarized in Scheme 4.

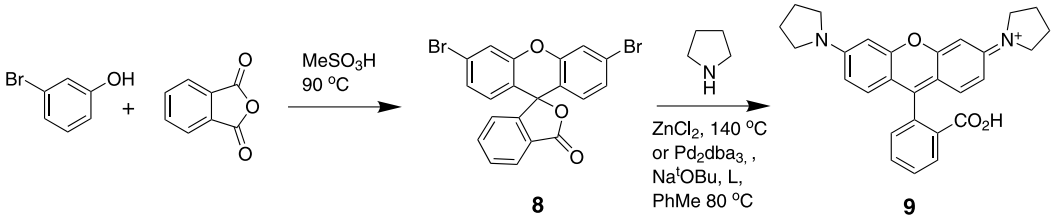
3′,6′-Dibromo-5(6)-carboxylate (**10a**, **b**) was synthesized similarly (Scheme 5). Selective crystallization from pyridine and acetic anhydride afforded the pure 6-isomer pyridinium salt **10c** in 15% yield, and further recrystallization of the mother liquor furnished the pure 5-isomer **10b** in 11% yield. Unsurprisingly, palladium-catalyzed coupling conditions were not compatible with a carboxylate-containing substrate. Nevertheless, heating **10c** at 140 °C with 5 equiv of $ZnCl_2$ and 10 equiv of pyrrolidine, followed by treatment with hydrochloric acid, afforded the desired rhodamine **11** in >94% yield with no apparent mixing of isomers. The strongly acidic workup is necessary in order to hydrolyze any amide byproduct that arises from carboxylate-amine condensation. The harsh conditions required for the reaction preclude the use of all but the most robust amines in the condensation.

2.3. Isomerically pure synthons for asymmetric carboxy-substituted xanthene dyes

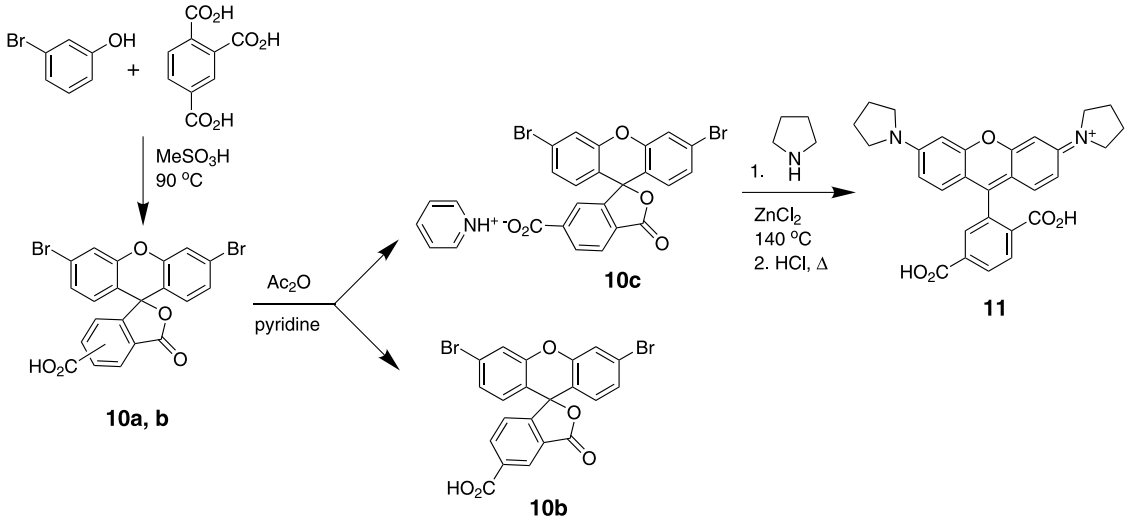
The syntheses of symmetrically substituted fluorescein-based zinc(II) biosensors containing a carboxylate or an amide functionality have been described previously.[21,22] To date, no such methodology exists for preparing similarly



Scheme 3.



Scheme 4.

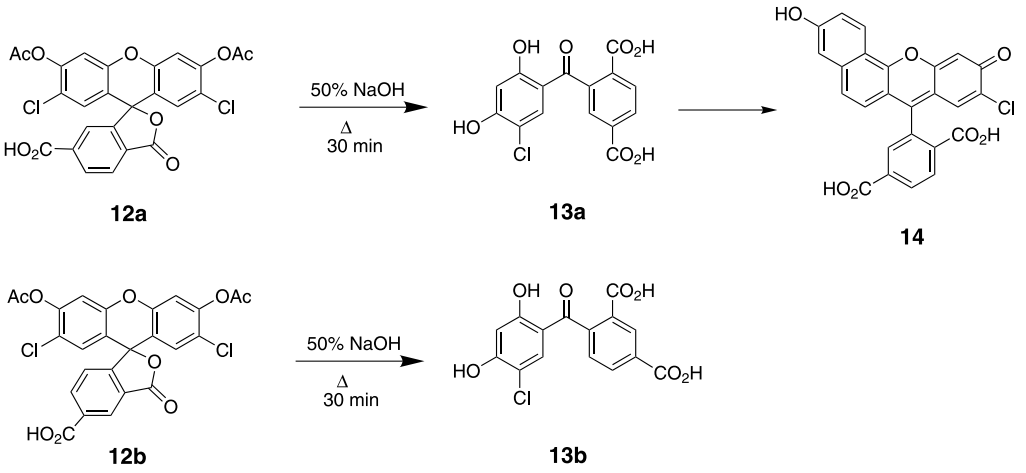


Scheme 5.

functionalized sensors based on asymmetric fluorescein scaffolds.[5,8,6] We, therefore, turned our attention to the synthesis of dihydroxydicarboxybenzophenones, which would be the logical starting material for the synthesis of asymmetric carboxylate-containing fluoresceins. Although subjecting 1,2,4-benzenetricarboxylic acid to aluminum chloride-catalyzed condensation with 4-chlororesorcinol[13] resulted in quantitative recovery of starting material, the hydrolysis of previously-resolved fluorescein carboxylates **12a** and **12b** under harshly basic conditions furnished the desired benzophenones **13a**, **13b** as isomerically pure compounds (Scheme 6). Results from condensation of **13a** with 1,6-dihydroxynaphthalene indicate that seminaphthofluorescein **14** can be obtained in excellent yield with no apparent scrambling of isomers.

3. Conclusions

We describe here the synthesis and separation of



Scheme 6.

fluorescein 5(6)-sulfonic acid. The structural assignment of fluorescein-6-sulfonic acid was confirmed in an X-ray crystallographic structure determination. Oxalyl chloride activation of the separated isomers affords the fluorescein sulfonyl chloride, whereas thionyl chloride converts the phenolic hydroxyls to chlorine atoms. Such dihalofluorans may also be synthesized by acid-catalyzed condensation of 3-halophenol with phthalic anhydride or analogues and can be converted to rhodamines via Lewis acid- or palladium-catalyzed reaction with simple amines. Carboxylate-substituted dihalofluorans are similar to diacetyl- or dipivaloyl-fluoresceins in that they are formed as a mixture of isomers, are trapped in lactone form, and may be separated by fractional crystallization. This methodology can be applied as a route to isomerically pure carboxylate-substituted rhodamines. Strongly basic hydrolysis of previously resolved fluorescein carboxylates affords the appropriate synthon for isomerically pure asymmetric fluorescein or rhodafluor carboxylates.

4. Experimental

4.1. Materials and methods

Reagents were obtained from Aldrich, except for 4-sulfophthalic acid, which was obtained from Lancaster, and palladium dibenzylideneacetone, sodium *tert*-butoxide, and 2′-dimethylamino-2-dicyclohexyl-phosphinobiphenyl, which were obtained from Strem. 4-Sulforesorcinol[23] and isomerically pure 3′,6-diacetyl-2′,7′-dichlorofluorescein-5(6)-carboxylates[22] were prepared as previously described. The purity of all compounds reported here was judged to be >95% by NMR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on a 300 or 500 MHz Varian or 400 MHz Bruker instrument. HRMS data were acquired by personnel at the MIT DCIF. Low-resolution electrospray mass spectra were obtained on an Agilent Technologies 1100 Series LCMS. Single crystals suitable for X-ray crystallography were covered with Infineum V8512 (formerly called Paratone N oil) and mounted on a quartz fiber. Data were collected by using a Bruker CCD X-ray diffractometer with Mo Kα radiation (λ=0.71073 Å) using the SMART software package[24] and corrected for absorption using SADABS v 6.2.[25] Data were integrated using the SAINT-PLUS software package,[26] and structures were solved and refined using SHELXTL.[27] Procedures for data collection and structural work have been reported in detail elsewhere.[28] All non-hydrogen atoms were refined anisotropically using least-squares methods and Fourier syntheses. Hydrogen atoms were assigned idealized positions and given thermal parameters of 1.2 times the thermal parameter of the carbon or nitrogen atom to which they were attached. All structure solutions were checked for higher symmetry with the PLATON program.[29]

4.2. Synthetic procedures

4.2.1. Condensation of 4-sulforesorcinol with phthalic anhydride. 4-Sulforesorcinol (424 mg, 2 mmol) was ground together with phthalic anhydride (148 mg, 1 mmol) and $ZnCl_2$ (41 mg, 0.3 mmol) with a mortar and pestle, and the resulting mixture was heated in a 190 °C oil bath for 30 min. Water and MeOH were added and the resulting solution was extracted with 3×20 mL portions of CH_2Cl_2. The combined organic layers were washed with 1×20 mL of brine, dried over $MgSO_4$, and evaporated to afford a dark orange-brown solid residue. ^{1}H NMR analysis indicated unsubstituted fluorescein as the major product. ^{1}H NMR (MeOH-d_4): δ 8.05 (d, 1H, J=7.5 Hz); 7.77 (td, 1H, J=7.5, 2.1 Hz); 7.70 (td, 1H, J=7.5, 2.1 Hz); 7.21 (d, 1H, J=7.5 Hz); 6.70 (d, 2H); 6.60 (d, 2H, J=3.2 Hz); 6.61–6.52 (m, 4H).

4.2.2. Fluorescein-5(6)-sulfonic acid (1). A 1.14 mL portion of a 50% aqueous solution of 4-sulfophthalic acid (0.736 g, 3 mmol, 80% pure) was neutralized with potassium hydroxide (45% w/v in water) and the solvent was evaporated to give a purple semi-solid residue, which was combined with resorcinol (0.661 g, 6 mmol) in 6 mL of methanesulfonic acid. The reaction mixture was stirred in an 85 °C oil bath for 18 h, then poured into 40 mL of H_2O. A reddish-brown precipitate was filtered and dried under vacuum to afford 696 mg of a brown powder (71% yield), which was carried on without further purification. ^{1}H NMR (MeOH-d_4): δ 8.81 (s, 1H, J=1.8 Hz); 8.46 (d, 1H, J=8.1 Hz); 8.23–8.30 (m, 2H); 7.84 (d, 1H, J=1.8 Hz); 7.5 (d,

1H, $J=8.1$ Hz); 7.5 (s, 2H); 7.46 (s, 2H); 7.36 (t, 4H, $J=3.0$ Hz); 7.2 (m, 4H). MS(M-H): calcd 411.0; Found 411.4.

4.2.3. Diisopropylethylammonium salt of 3′,6′-dipivaloylfluorescein-6-sulfonate (2a). Fluorescein-5(6)-sulfonic acid (9.08 g, 22 mmol) was dissolved in 35 mL of trimethylacetic anhydride, 17.5 mL of diisopropylethylamine, and 30 mL of DMF. The solution was heated to reflux for 4 h and then quenched by addition of ethanol. The solvents were removed on the rotary evaporator and the resulting light brown viscous oil was taken up in 200 mL of CH_2Cl_2 and 400 mL of ethyl acetate, and washed with 3× 300 mL of 1 M phosphate buffer (pH 7.0). The organic phase was dried over $MgSO_4$ and evaporated. Diethyl ether was added, and a heavy fine precipitate formed. The filtered solid was recrystallized from dichloromethane and diethyl ether to give 2.10 g (13.5%) of fluorescein 6-sulfonic acid dipivaloate diisopropylethylammonium salt; mp 227–229 °C. ^{1}H NMR ($CDCl_3$): δ 9.00 (br s, 1H); 8.17 (d, 1H, $J=8.1$ Hz); 8.04 (d, 1H, $J=8.1$ Hz); 7.64 (s, 1H); 7.04 (d, 2H, $J=2.1$ Hz); 6.84 (d, 2H, $J=8.7$ Hz); 6.76 (dd, 2H, $J=8.7$, 2.1 Hz); 3.60 (m, 2H); δ 3.03 (m, 2H); 1.36 (s, 18H); 1.30–1.34 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 176.8, 169.6, 154.1, 152.6, 151.6, 147.0, 131.4, 129.1, 125.1, 124.4, 123.4, 117.8, 116.6, 110.4, 81.4, 39.4, 27.3, 22.3. HRMS(M-HN^{i}Pr$_2$Et): calcd 579.1325; Found 579.1330.

4.2.4. Diisopropylethylammonium salt of 3′,6′-dipivaloylfluorescein-5-sulfonate (2b). The filtrate from **2a** was allowed to stand at room temperature overnight, and the resulting light yellow crystals were filtered to give 0.91 g (5.8% overall) of the diisopropylethylammonium salt of fluorescein 5-sulfonic acid dipivaloate; mp 154–156 °C. ^{1}H NMR ($CDCl_3$): δ 9.25 (br s, 1H); 8.33 (s, 1H); 8.06 (d, 1H, $J=6.6$ Hz); 6.97 (d, 1H, $J=8.1$ Hz); 6.86 (d, 2H, $J=1.8$ Hz); 6.61–6.56 (m, 4H); 3.56 (m, 2H); 2.98 (m, 2H); 1.35 (m, 9H); 1.26 (d, 6H, $J=6.6$ Hz); 1.17 (s, 18H). ^{13}C NMR (DMSO-d_6): δ 176.0, 168.1, 152.4, 152.2, 150.8, 150.8, 133.4, 129.3, 125.2, 123.9, 121.5, 118.5, 115.9, 110.4, 81.1, 53.6 41.9, 38.7, 27.0, 26.7, 18.1, 16.7, 12.5. MS(M-HN^{i}Pr$_2$Et): Calcd 579.1; Found 579.2. Continued fractional crystallization brought the final yields to 3.31 g, 21% for the 6-isomer; and 1.59 g, 10.1% for the 5-isomer.

4.2.5. Optimized purification of diisopropylethylammonium salt of 3′,6′-dipivaloyl-fluorescein-6-sulfonate (2a). Fluorescein 5(6)-sulfonic acid (6.20 g, 15 mmol) was combined with trimethylacetic anhydride (35 mL) and diisopropylethylamine (18 mL) in DMF (20 mL) and heated to reflux 4 h. The reaction was allowed to cool, then taken up in 200 mL of CH_2Cl_2 and 400 mL of ethyl acetate. The organic solution was washed with 3×300 mL of phosphate buffer (1 M, pH 7.0), dried over $MgSO_4$, evaporated, and the resulting residue was crystallized from diethyl ether and CH_2Cl_2 at −25 °C overnight. Filtration gave 2.49 g (23.4%) of the desired product. The mother liquor was placed in the freezer and a second crop of crystals was obtained (800 mg) for a total yield of 3.29 g (31% overall).

4.2.6. Fluorescein 6-sulfonic acid (1a). The diisopropylethylammonium salt of 3′,6′-dipivaloylfluorescein 6-sulfonic acid (177 mg, 0.25 mmol) was dissolved in 10 mL of 50:50 v/v ethanol/H_2O. Potassium hydroxide was added (0.40 g) and the reaction was heated to reflux overnight. The ethanol was then removed under reduced pressure, the dark red solution was acidified, and the resulting orange precipitate (71 mg, 69%) was collected by filtration and dried overnight; mp >338 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 1H, $J=7.8$ Hz); 7.87 (d, 1H, $J=9.3$ Hz); 7.25 (s, 1H); 6.70 (s, 2H); 6.55–6.62 (m, 4H). IR: 3400–2500 cm^{-1} (br, s), 1707 cm^{-1} (m), 1638 cm^{-1} (m), 1603 cm^{-1} (s), 1457 cm^{-1} (s), 1314–1122 cm^{-1} (br, s), 1037 cm^{-1} (s). ^{13}C NMR (DMSO-d_6): δ 168.4, 160.0, 154.9, 152.0, 129.3, 127.7, 125.9, 125.0, 120.6, 113.1, 109.5, 102.3. HRMS(M+H): Calcd 413.0331; Found 413.0320. The acidic filtrate obtained was allowed to stand at RT for 2 weeks, at the end of which time small bright-orange X-ray quality crystals of **1a** had formed.

4.2.7. 3′,6′-Dichlorofluoran-6-sulfonyl chloride (3a). Fluorescein 6-sulfonic acid (412 mg, 1 mmol) was added to thionyl chloride (2.6 mL, 6 g, 5 mmol) and dimethylformamide (6 mg, 6 μL, 82 μmol) and the reaction was heated to reflux under Ar for 4 h. The resulting solution was poured into 150 mL of stirred ice water and stirred for an additional 10 min. The yellow grainy solid obtained was lyophilized to give a final mass of 360 mg (87% yield); mp >210 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 8.02 (d, 1H, $J=8.1$ Hz); 7.94 (d, 2H, $J=1.2$ Hz); 7.92 (d, 1H, $J=2.4$ Hz); 7.58 (s, 2H); 7.39 (s, 1H); 7.22 (dd, 2H, $J=8.6$, 1.8 Hz), 6.94 (d, 2H, $J=8.4$ Hz). ^{13}C NMR (DMSO-d_6): δ 168.1, 155.6, 152.6, 150.6, 135.4, 129.9, 128.3, 125.3, 125.0, 124.9, 120.5, 117.4, 117.1, 80.3. FTIR (KBr, cm^{-1}): 3422 (br, m), 1777 (s), 1599 (m), 1566 (w), 1482 (m), 1411 (s), 1266–1060 (br, s), 955 (m). MS(M–Cl+OH): Calcd 446.9; Found 447.0.

4.2.8. Fluorescein 5-sulfonic acid (1b). 3′,6′-Dipivaloylfluorescein 5-sulfonic acid diisopropylethyl ammonium salt (1.42 g, 2 mmol) and potassium hydroxide (3.2 g) were dissolved in 30 mL of 50:50 v/v ethanol/H_2O and heated to reflux overnight. The ethanol was removed under reduced pressure, and the aqueous solution was acidified with concentrated HCl, causing the product to precipitate. Filtration and drying overnight afforded the desired product as 696 mg (84%) of a yellow solid; mp >330 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 1H); 7.98 (d, 1H, $J=9.3$ Hz); 7.22 (d, 1H, $J=8.1$ Hz); 6.67 (d, 2H, $J=2.1$ Hz); 6.61–6.55 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 168.3, 160.3, 152.3, 150.2, 133.0, 129.5, 126.2, 124.3, 121.6, 113.2, 109.8, 102.3. FTIR (KBr, cm^{-1}): 3500–2500 (br, s), 1714 (s), 1639–1538 (br, s) 1463 (s), 1383 (m), 1326 (s), 1220–1126 (s), 1039 (m). HRMS(M-H): Calcd 411.0175; Found 411.0155.

4.2.9. 3′,6′-Dichlorofluoran-5-sulfonyl chloride (3b). Fluorescein 5-sulfonic acid (618 mg, 1.5 mmol) was combined with thionyl chloride (4 mL) and dimethylformamide (10 μL) and heated to reflux for 4 h. The reaction was poured into 150 mL of stirred ice water, affording a dark yellow solid that was filtered and lyophilized to give a final mass of 549 mg (82% yield); mp >232 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 8.10 (s, 1H); 8.00 (d, 1H, $J=9.6$ Hz); 7.58 (d, 2H, $J=2.1$ Hz); 7.33 (d, 1H, $J=8.7$ Hz); 7.20 (dd, 2H, $J=8.6$, 2.4 Hz); 6.95 (d, 2H, $J=8.4$ Hz). ^{13}C NMR (DMSO-d$_6$): δ 168.1, 152.3, 150.9, 150.7, 135.4, 133.6,

130.1, 125.0, 124.0, 121.7, 117.5, 117.1, 80.4. IR: 3091 cm^{-1} (br, w), 1779 cm^{-1} (s), 1599 cm^{-1} (s), 1564 cm^{-1} (s), 1481 cm^{-1} (s), 1425–1384 cm^{-1} (br, s), 1318 cm^{-1} (m), 1251–1083 cm^{-1} (br, m), 954 cm^{-1} (s). HRMS(M–Cl+OH): Calcd 446.9497; Found 446.9503.

4.2.10. 3′, 6′-Dichlorofluoran-6-sulfonamido-2-methylpyridine (4). 3′,6′-Dichlorofluoran-6-sulfonyl chloride (**4**, 86 mg, 0.2 mmol) was dissolved in 15 mL of CH_2Cl_2 and added dropwise to a stirred suspension of 2-aminomethylpyridine (43 mg, 0.4 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in CH_2Cl_2. After stirring overnight, the reaction suspension was filtered and evaporated; the product was purified by flash chromatography on silica gel (10 mm×17 cm) eluting with 9:1 $CHCl_3$:MeOH, and then recrystallized from methanol to give 30 mg (30%) of an off-white powder; mp 236–238 °C. ^{1}H NMR (DMSO-d_6): δ 8.59 (t, 1H, J=5.7 Hz), 8.31 (d, 1H,, J=4.8 Hz), 8.20 (d, 1H, J=8.4 Hz), 8.08 (dd, 1H, J=8.7, 0.6 Hz), 7.76 (s, 1H), 7.66 (td, 1H, J=7.8, 2.1 Hz), 7.61 (d, 2H, J=1.8 Hz), 7.15–7.26 (m, 3H), 6.91 (d, 2H, J=8.4 Hz), 4.12 (d, 2H, J=6.0 Hz). ^{13}C NMR (DMSO-d_6): δ 168.2, 157.5, 153.6, 151.8, 149.8, 149.3, 137.9, 136.7, 131.1, 130.0, 129.3, 127.6, 126.1, 123.7, 123.2, 122.8, 118.2, 118.0, 81.9, 48.9. MS(M-H): Calcd 537.0; Found 537.1. X-ray quality crystals were obtained by slow evaporation of a saturated acetonitrile solution of **4** at RT over 2 days.

4.2.11. 3′,6′-Dipivaloylfluorescein-6-sulfonyl chloride (5). 3′,6′-Dipivaloylfluorescein-6-sulfonate diisopropylethylammonium salt (708 mg, 1 mmol) was stirred in 10 mL of ethyl acetate (dried over $MgSO_4$) in an ice bath. Oxalyl chloride (1 mL of 2 M solution in CH_2Cl_2) was added, followed by 200 μL of DMF. The ice bath was removed, and the reaction was stirred for 16 h. The reaction was then placed on ice and quenched with 10 mL of H_2O. The layers were separated, and the organic layer was washed with 1×10 mL H_2O and 1×10 mL brine, dried, and evaporated to give a yellow solid residue; mp >160 °C (decomp.). ^{1}H NMR ($CDCl_3$): δ 8.68 (s, 1H); 8.31 (d, 1H, J=6.8 Hz); 7.45 (d, 1H, J=6.5 Hz); 7.18 (s, 2H); 6.84 (s, 2H); 1.37 (s, 18H). HRMS(M+H): Calcd 599.1143; Found 599.1114.

4.2.12. 6-Fluoresceinsulfonamido-2-methylpyridine (6). The product from **5** was dissolved in 20 mL of $CHCl_3$ and stirred in an ice bath. 2-Aminomethylpyridine (300 μL) was added and the reaction was stirred overnight. The reaction was then extracted with 2×20 mL of H_2O, the combined aqueous layers were washed with 1×20 mL $CHCl_3$, concentrated on the rotary evaporator to 5 mL, and the bright red viscous solution was acidified with 2 mL of 1 N HCl. The resulting yellow precipitate was filtered and the resulting solid (485 mg) was chromatographed on silica (20 mm×16 cm), eluting with 89:10:1 $CHCl_3$:MeOH:AcOH. The desired product (43 mg, 8.5%) was isolated as a bright yellow–orange solid; mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ 8.40–8.36 (m, 2H); 8.10 (dd, 1H, J=8.1, 1.5 Hz); 7.74 (td, 1H, J=7.8, 1.5 Hz); 7.43 (d, 1H, J=7.8 Hz); 7.31–7.23 (m, 2H); 6.69 (t, 2H, J=0.9 Hz); 6.59 (s, 4H); 4.34 (s, 2H). ^{13}C NMR (DMSO-d_6): δ 167.4, 156.7, 152.4, 148.8, 142.8, 136.8, 136.5, 129.5, 129.3, 122.5, 122.4, 122.0, 109.1, 102.5, 102.3, 48.0. HRMS(M+H): Calcd 503.0913; Found 503.0912. The dipivaloyl-protected sulfonamide product **7** was also isolated from the organic reaction extract by flash chromatography on silica eluted with 94:6 $CHCl_3$:MeOH; mp 184–186 °C. ^{1}H NMR (MeOH-d_4): δ 8.38 (m, 2H); 8.09 (dd, 1H, J=8.1, 1.8 Hz); 7.61 (td, 1H, J=7.8, 2.1 Hz); 7.25 (s, 1H); 7.21–7.12 (m, 3H), 7.05 (d, 1H, J=2.1 Hz); 6.84–6.77 (m, 3H); 6.70 (d, 2H, J=8.4 Hz); 4.40 (s, 2H); 1.36 (s, 18H). ^{13}C NMR (DMSO-d_6): δ 176.1, 167.1, 156.5, 155.0, 152.7, 150.9, 148.8, 143.6, 136.8, 133.7, 129.4, 126.1, 125.2, 123.5, 122.6, 122.2, 118.7, 115.3, 110.5, 81.4, 48.0, 38.8, 26.7. HRMS (M+H): Calcd 671.2063; Found 671.2071.

4.2.13. 3′,6′-Dibromofluoran (8). 3-Bromophenol (1.73 g, 10 mmol) and phthalic anhydride (740 mg, 5 mmol) were combined in 5 mL of methanesulfonic acid and heated in a 140 °C oil bath for 16 h. The reaction was poured into 120 mL of stirred ice water, stirred for 20 min, and then filtered. The resulting damp gray solid was taken up in $CHCl_3$ and filtered through a short plug of silica gel, evaporated, and recrystallized from CH_2Cl_2 and MeOH to afford the desired product as 990 mg of off-white crystals (43% yield); mp 277–280 °C. ^{1}H NMR ($CDCl_3$): δ 8.05 (dd, 1H, J=7.8, 1.5 Hz); 7.67 (p, 2H, J=1.2 Hz); 7.50 (d, 2H, J=1.8 Hz); 7.20 (dd, 2H, J=10.5, 2.1 Hz); 7.14 (d, 1H, J=7.8 Hz); 6.71 (d, 2H, J=8.4 Hz). ^{13}C NMR ($CDCl_3$): δ 169.4, 153.2, 151.5, 135.9, 130.7, 129.6, 127.9, 126.2, 125.9, 124.6, 124.1, 120.8, 118.3, 81.5. HRMS(M+H): Calcd 456.9075; Found 456.9084.

4.2.14. 3′,6′-Pyrrolidinorhodamine (9)—method A. 3′,6′-Dibromofluoran (46 mg, 0.1 mmol) was combined with $ZnCl_2$ (68 mg, 0.5 mmol) and pyrrolidine (83 μL, 71 mg, 1 mmol) and heated in a 170 °C oil bath for 4 h. The reaction was removed from heat, and allowed to cool. Water and concentrated HCl were added; the suspension was stirred, filtered, and the solid was washed twice with dilute HCl to afford a purple solid (42 mg, 95% yield); mp >220 °C (decomp.). ^{1}H NMR (MeOH-d_4): δ 8.34 (d, 1H, J=7.5 Hz); 7.81 (m, 2H); 7.41 (d, 1H, J=8.7 Hz); 7.12 (d, 2H, J=9.3 Hz); 6.90 (dd, 2H, J=6.9, 1.8 Hz); 6.82 (d, 2H, J=2.1 Hz); 3.61 (m, 8H); 2.14 (s, 8H). ^{13}C NMR (DMSO-d_6): δ 169.0, 152.7, 152.3, 152.3, 149.2, 135.3, 129.8, 128.9, 128.5, 128.3, 126.7, 125.4, 124.5, 124.0, 108.8, 105.4, 97.4, 85.4, 47.4, 25.0. MS(M+H): Calcd 439.2; Found 439.4.

4.2.15. 3′,6′-Pyrrolidinofluoran (9)—method B. 3′,6′-Dibromofluoran (229 mg, 0.5 mmol) was combined with palladium dibenzylideneacetone (11.5 mg, 0.0125 mmol; 0.025 mmol Pd), sodium *tert*-butoxide (101 mg, 1.05 mmol), and 2′-dimethylamino-2-dicyclohexyl-phosphinobiphenyl (10.3 mg, 0.025 mmol) in a thick-walled tube fitted with a rubber septum. The tube was thrice evacuated and back-filled with N_2, and 1.5 mL of dry toluene was added, followed by 90 μL (77 mg, 1.08 mmol) of pyrrolidine. The septum was replaced with a Teflon screw cap and the reaction was stirred in an 80 °C oil bath for 15 h, then removed from heat and allowed to cool. Hexanes were added to the purple slurry, and a purple solid was isolated by filtration (350 mg, wet) LCMS and ^{1}H NMR analysis of the solid supported a single product identical to those produced by method A.

4.2.16. Pyridinium salt of 3′,6′-dibromo-6-carboxyfluoran (10c). 3-Bromophenol (3.46 g, 20 mmol) and 1, 2, 4-benzenetricarboxylic acid (2.10 g, 10 mmol) were combined in 10 mL of methanesulfonic acid and heated in a 140 °C oil bath for 3 days. The reaction was poured into 200 mL of stirred ice water, stirred vigorously with warming for 30 min, and then filtered to yield a greenish solid which was dried in air to give 3.83 g of **10a** and **10b** as a mixture of isomers. Crystallization from 30 mL of acetic anhydride and 10 mL of pyridine afforded 1.35 g of white solid, which was recrystallized from 2:1 Ac_2O:pyridine to furnish the desired compound **10c** as 1.07 g (18%) of fine white crystals; mp >327 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 8.58 (m, 2H); 8.25 (d, 1H, J=6.5 Hz); 8.16 (d, 1H, J=6.4 Hz); 7.86 (s, 1H); 7.76 (m, 1H); 7.43 (m, 2H); 6.87 (d, 2H, J=6.4 Hz); 6.67 (d, 2H, J=6.3 Hz). ^{13}C NMR (DMSO-d_6): δ 172.1, 167.6, 166.0, 152.2, 150.8, 149.6, 137.9, 136.2, 131.5, 130.1, 128.6, 127.7, 125.7, 124.8, 124.0, 123.8, 119.9, 117.5, 80.8. HRMS(M-pyH): Calcd 498.8817; Found 498.8804.

4.2.17. 3′,6′-Dibromo-5-carboxyfluoran (10b). The filtrate from the initial crystallization of **10c** was concentrated and recrystallized from pyridine to afford 906 mg of an off-white solid. Further recrystallization from $CHCl_3$:MeOH afforded the desired product as 571 mg of white crystals (11.4% yield); mp >324 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 8.44 (s, 1H); 8.31 (d, 1H, J=8.0, 1.2 Hz); 7.72 (d, 2H, J=2.0 Hz); 7.51 (d, 1H, J=8.0 Hz); 7.34 (dd, 2H, J=8.6, 2.0 Hz); 6.90 (d, 2H, J=8.4 Hz). ^{13}C NMR (DMSO-d_6): δ 167.5, 165.9, 155.5, 150.6, 136.5, 133.4, 130.8, 127.8, 127.7, 126.0, 125.9, 124.6, 123.9, 119.9, 117.4, 80.6. MS(M+H): Calcd 500.9; Found 501.0.

4.2.18. 3′,6′-Dipyrrolidino-6-carboxyrhodamine (11). 3′,6′-Dibromo-6-carboxyfluoran (116 mg, 0.2 mmol) was combined with $ZnCl_2$ (136 mg, 1 mmol) and pyrrolidine (332 μL, 5 mmol) and heated in a 140 °C oil bath for 4 h. The dark purple residue was dissolved in 15 mL of concentrated HCl, and the resulting dark red solution was filtered and then diluted with 30 mL of H_2O, allowed to stand at rt for 2 h, and filtered to yield 98 mg (94%) of the desired product HCl salt; mp >310 °C (decomp.). ^{1}H NMR (MeOH-d_4): δ 8.42 (s, 1H); 8.39 (d, 1H, J=5.8 Hz); 7.98 (s, 1H); 7.11 (d, 2H, J=6.4 Hz); 6.94–6.84 (m, 4H); 3.62 (br s, 8H); 2.14 (s, 8H). HRMS(M-H): Calcd 481.1763; Found 481.1744.

4.2.19. 2,5-Dicarboxy-5′-chloro-2′,4′-dihydroxybenzophenone (13a). 3′,6′-Diacetyl-2′,7′-dichlorofluorescein-6-carboxylic acid pyridinium salt (2.44 g, 4 mmol) was suspended in 60 mL of 50% aqueous NaOH (w/v) and heated at 165 °C for 60 min. The reaction was removed from the heating bath, poured into 400 mL of cold H_2O, acidified with conc HCl, and allowed to stand at rt for 2 h. The suspension was filtered, and the pale yellow solid was taken up in MeOH, filtered to remove residual NaCl, and evaporated to afford 1.19 g of the desired product (89% yield); mp >250 °C (decomp.). ^{1}H NMR (MeOH-d_4): δ 8.20 (m, 2H); 7.98 (s, 1H); 6.97 (s, 1H); 6.49 (s, 1H). ^{13}C NMR (MeOH-d_4): δ 201.2, 168.0, 168.0, 164.8, 162.0, 141.6, 135.7, 134.6, 134.5, 132.1, 132.0, 129.6, 115.4, 113.5, 105.0. MS(M-H): Calcd 335.0; Found 335.0.

4.2.20. 2,4-Dicarboxy-5′-chloro-2′,4′-dihydroxybenzophenone (13b). 3′,6′-Diacetyl-2′,7′-dichlorofluorescein-5-carboxylic acid (2.12 g, 4 mmol) was suspended in 60 mL of 50% aqueous NaOH (w/v) and heated at 165 °C for 60 min. The reaction was removed from heat, poured into 400 mL of cold H_2O, acidified with conc. HCl, and allowed to stand at rt overnight. The suspension was filtered, and the dirty-brown solid was resuspended in 50 mL of H_2O, stirred, and filtered again. The resulting solid was then taken up in MeOH, filtered to remove residual NaCl, and evaporated to afford 1.14 g of the desired product (85% yield); mp >265 °C (decomp.). ^{1}H NMR (MeOH-d_4): δ 8.72 (s, 1H); 8.34 (d, 1H, J=5.7 Hz); 7.51 (d, 1H, J=4.8 Hz); 6.95 (s, 1H); 6.49 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 201.4, 168.1, 167.9, 164.8, 162.0, 145.2, 134.7, 134.6, 133.8, 132.9, 131.2, 129.1, 115.4, 113.6, 105.0. HRMS(M-H): Calcd 334.9959; Found 334.9944.

4.2.21. 6-Carboxy-2′-chloroseminaphthofluorescein (14). 1,6-Dihydroxynaphthofluorescein (24 mg, 0.15 mmol) was combined with benzophenone **13a** (34 mg, 0.1 mmol) in 200 μL of methanesulfonic acid in a 180 °C oil bath. After 14 h, 5 mL of H_2O was added and the resulting suspension was filtered and washed twice with H_2O. The resulting purple solid was dissolved in MeOH, the solution was filtered, and H_2O was added to the filtrate to induce precipitation. The product was collected by filtration and dried in air to give 42 mg (91%) of the desired compound; mp >256 °C (sublimed). ^{1}H NMR (DMSO-d_6): δ 11.2 (br s, 1H); 10.2 (br s, 1H); 8.40 (d, 1H, J=8.8 Hz); 8.24 (d, 1H, J=1.2 Hz); 8.16 (d, 1H, J=8.0 Hz); 7.72 (s, 1H); 7.38 (d, 1H, J=8.8 Hz); 7.27 (d, 1H, J=9.0 Hz); 7.15 (s, 1H); 7.14 (s, 1H); 6.91 (s, 1H); 6.62 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 167.9, 166.1, 157.5, 155.2, 152.7, 145.0, 146.4, 137.5, 136.0, 131.2, 129.3, 128.6, 125.6, 124.6, 123.8, 122.5, 119.2, 117.0, 116.6, 110.0, 109.4, 108.7, 103.9, 82.8. MS(M-H): Calcd 459.0; Found 459.0.

Acknowledgements

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Synthesis of substituted uracils by the reactions of halouracils with selenium, sulfur, oxygen and nitrogen nucleophiles under focused microwave irradiation

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Abstract—Under microwave irradiation, the nucleophilic substitution reactions of halouracils with selenium, sulfur, oxygen and nitrogen nucleophiles was complete within several minutes with yields up to 99%. The method using microwave irradiation is superior to those conducted under conventional heating processes.

1. Introduction

Several of the 5- and 6-substituted uracils exhibit significant antitumor activity against experimental mouse tumor.[1] Therefore, an efficient synthetic methodology for the preparation of these uracil derivatives will be crucial in developing new antitumor drugs. Our previous results have shown that the reaction rates of nucleophilic aromatic and heteroaromatic substitution can be accelerated under microwave irradiation.[2,3] We have been interested in developing new, more efficient, and synthetically useful reactions for the synthesis of biologically active molecules via microwave acceleration. As a result the development of more practical synthesis of 5-substituted and 6-substituted uracils will be examined in this proposal to further expand the utility and scope of our previous studies.

2. Results and discussion

Study was initiated of 5-bromouracil with amine nucleophiles. Microwave irradiation of 10 equiv of benzylamine and 5-bromouracil at 110 °C is found to yield 5-benzylaminouracil in 95% (Table 1, entry 1). The nucleophilic substituted reactions of 5-iodouracil, 5-chlorouracil and 5-fluorouracil were similarly performed. Of the four halouracils studied, the relative reactivity of 5-halouracils toward nitrogen-containing nucleophile (benzylamine) appeared to decrease in the order of Br > Cl > F > I (compared entries 1, 2, 4 with 5 in Table 1). There is little regularity in the relative replaceabilities of these substituents. The reason might be that iodine is too soft to react with hard nitrogen nucleophile.[4] As a comparison (entry 3, Table 1), 5-chlorouracil was heated with 20 equiv of benzylamine at 150 °C in an oil bath for 20 min to give only 34% yield of 5-benzylaminouracil, far less than 88% in microwave irradiation (entry 2, Table 1). We have now found that 5-substituted aminouracils were prepared by reaction of 5-bromouracil with appropriate amine in 95–98% yield within 10 min under microwave irradiation (Table 1, entries 8–12). Weak nucleophilic aromatic amine such as aniline also can react with 5-bromouracil to give 5-anilinouracil (92% yield) at 180 °C within 15 min (Table 1, entry 13). By conventional heating process, 5-anilinouracil was prepared at 195 °C in refluxing ethylene glycol for 2 h (76% yield).[5]

In order to investigate the efficacy of nucleophilic substitutions in different reaction conditions, we examined the solvent effect in the displacement reaction. 5-Chlorouracil, 5-bromouracil and 5-iodouracil were studied. When reacted with PhSNa under microwave irradiation, the substitution reaction could be realized by using NMP (*N*-methylpyrrolidone), HMPA, DMSO, DMF and DMAC (dimethylacetamide) as the solvent (Table 2). The better yields were obtained in HMPA for 5-chlorouracil and 5-bromouracil (93 and 86%, respectively. Table 2, entries 2 and 7). However, the reaction of 5-iodouracil with 2.2 equiv of PhSNa proceeded smoothly at 130 °C under microwave

Keywords: Microwave irradiation; Nucleophilic substitution; Halouracils.
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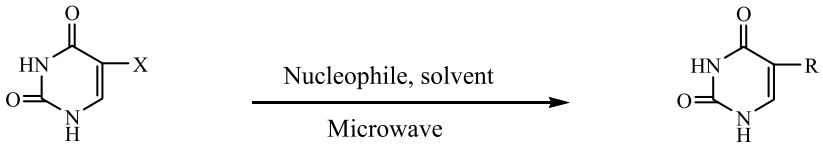
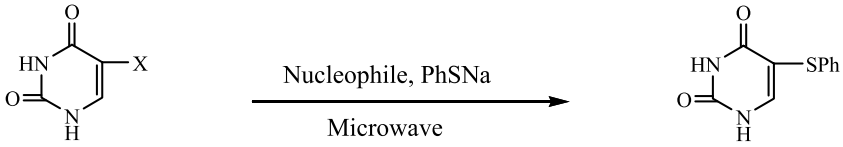
Table 1. Substitution of 5-halouracils with amines



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	Br	NH_2CH_2Ph	[a]	10	110	12	$NHCH_2Ph$	95
2	Cl	NH_2CH_2Ph	[a]	20	150	20	$NHCH_2Ph$	88
3	Cl	NH_2CH_2Ph	[a]	20	150	20	$NHCH_2Ph$	34[b]
4	F	NH_2CH_2Ph	[a]	20	170	20	$NHCH_2Ph$	76
5	I	NH_2CH_2Ph	[a]	20	130	10	$NHCH_2Ph$	0
6	I	NH_2CH_2Ph	[a]	10	100	10	$NHCH_2Ph$	18
7	I	NH_2CH_2Ph	DMF	3.5	130	10	$NHCH_2Ph$	16
8	Br	$NH_2(CH_2)_3CH_3$	[a]	20	90	10	$NH(CH_2)_3CH_3$	96
9	Br	Piperidine	[a]	20	90	9	Piperidyl	95
10	Br	Morpholine	[a]	20	90	5	N-Morpholyl	96
11	Br	Cyclohexylamine	[a]	20	110	7	Cyclohexylamino	98
12	Br	$NH(CH_3)CH_2$ Ph	[a]	15	120	5	N (CH_3) CH_2 Ph	97
13	Br	$PhNH_2$	[a]	15	180	15	NHPh	92

[a] No solvent was used.
[b] Heating in an oil bath.

Table 2. Reaction conditions of 5-halorouracils

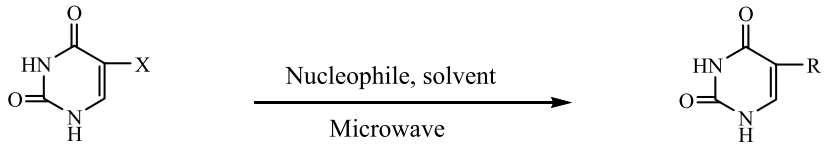


Entry	X	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	Cl	NMP	4	140	5	SPh	81
2	Cl	HMPA	4	140	5	SPh	93
3	Cl	DMSO	4	140	5	SPh	56
4	Cl	DMF	4	140	5	SPh	74
5	Cl	DMAC	4	140	5	SPh	74
6	Br	NMP	4	140	5	SPh	75
7	Br	HMPA	4	140	5	SPh	86
8	Br	DMSO	4	140	5	SPh	65
9	Br	DMF	4	140	5	SPh	77
10	Br	DMAC	4	140	5	SPh	75
11	I	NMP	2.2	130	5	SPh	82
12	I	HMPA	2.2	130	5	SPh	72
13	I	DMSO	2.2	130	5	SPh	80
14	I	DMF	2.2	130	5	SPh	84

irradiation for 5 min in different solvents (Table 2, entries 11–14). Interestingly, the result indicated that DMF was the best solvent.

A detailed study of the reactions of 5-halouracils with O, S and Se containing nucleophiles in various amounts, reaction times, temperatures and solvents was investigated in order to find the optimized conditions for the preparation of uracil derivatives (Table 3). When 5-fluorouracil was treated with the oxygen, sulfur and selenium nucleophiles (PhONa, PhSNa and PhSeH) under microwave irradiation, the corresponding 5-substituted uracils were obtained in low yield (0–14%). The nucleophilic substitution reactions of 5-chlorouracil, 5-bromouracil and 5-iodouracil were similarly carried out (Table 3, entries 4–29). We might expect that with 5-iodouracil the order of reactivity is PhSeH > PhSNa > PhONa (compared entries 17, 21 with 29 in Table 3). Different 5-halouracils were studied in an attempt to appreciate the leaving group effect on reactivity and yields. Of the four halouracil tested, the relative reactivity of 5-halouracils toward selenium nucleophile (PhSeH) appeared to decrease in the order of I > Br > Cl > F (compared entries 3, 10, 15 with 29 in Table 3). The relative reactivity of 5-halouracils toward sulfur nucleophile (PhSNa) appeared to decrease in the order of I > Cl ~ Br > F (compared entries 2, 4, 12 with 22 in Table 3). Se and I are more polarizable in nucleophiles and halogens. The iodine would be expected to be easily attacked by nucleophilic

Table 3. Reactions of 5-halouracil with nucleophiles



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	F	PhONa	NMP	4	140	5	OPh	0
2	F	PhSNa	HMPA	4	180	30	SPh	17
3	F	PhSeH	HMPA	4	180	20	SePh	14
4	Cl	PhSNa	NMP	2	130	5	SPh	51
5	Cl	PhSNa	NMP	4	130	5	SPh	84
6	Cl	PhSNa	HMPA	4	130	5	SPh	86
7	Cl	PhSNa	HMPA	4	140	5	SPh	93
8	Cl	PhSNa	HMPA	4	150	5	SPh	97
9	Cl	PhSNa	HMPA	4	150	5	SPh	36[a]
10	Cl	PhSeH	HMPA	4	150	5	SePh	52
11	Cl	PhSeH	HMPA	4	160	10	SePh	43
12	Br	PhSNa	NMP	2	130	5	SPh	47
13	Br	PhSNa	NMP	4	140	5	SPh	75
14	Br	PhSNa	HMPA	4	140	5	SPh	86
15	Br	PhSeH	HMPA	4	150	5	SePh	70
16	Br	PhSeH	DMF	4	130	5	SePh	29
17	I	PhONa	NMP	3	160	20	OPh	0
18	I	PhSNa	NMP	4	130	5	SPh	39
19	I	PhSNa	NMP	3	130	5	SPh	69
20	I	PhSNa	NMP	2.5	130	5	SPh	81
21	I	PhSNa	NMP	2.2	130	5	SPh	82
22	I	PhSNa	NMP	2	130	5	SPh	82
23	I	PhSNa	HMPA	2	130	5	SPh	77
24	I	PhSNa	DMSO	2	130	5	SPh	76
25	I	PhSNa	DMF	2.2	130	5	SPh	84
26	I	PhSNa	DMF	2	130	5	SPh	82
27	I	PhSeH	DMF	3	130	5	SePh	58
28	I	PhSeH	DMF	2.5	130	5	SePh	75
29	I	PhSeH	DMF	2.3	130	5	SePh	96

[a] Heating in an oil bath.

selenium. So the trend of 5-halouracils toward selenium nucleophile is predictable.

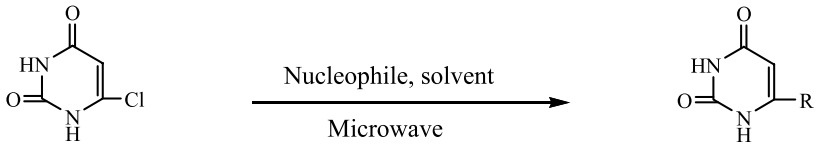
The product yield could be improved by running the reaction in a more polar solvent. The reaction of 5-chlorouracil with PhSNa afforded 5-phenylthiouracil in the yield up to 97% (Table 3, entry 8). The dipolar solvent HMPA might facilitate the substitution reaction. For comparing the efficacy of microwave irradiation with conventional heating, a HMPA solution of 5-chlorouracil and PhSNa (4 equiv) was heated at 150 °C in an oil bath for 5 min to give only 36% yield of 5-phenylthiouracil, far less than 97% in microwave irradiation (Table 3, entry 9). The reaction with PhONa nucleophile failed to give any appreciable quantities of the 5-phenoxyuracil in various reaction conditions.

When 2.2 equiv of PhSNa or 2.3 equiv of PhSeH were used, 5-iodouracil was converted to 5-phenylthiouracil or 5-(phenylselenenyl)uracil in good yields (84 and 96%, respectively. Table 3, entries 25 and 29). However, the yield of 5-phenylthiouracil or 5-(phenylselenenyl)uracil deteriorated when greater quantities of PhSNa or PhSeH were applied (Table 3, entries 18–22 and 27–29). Because iodine is the most replaceable of the halogens, it does not need too much amount of nucleophile.

Under microwave irradiation, 6-chlorouracil also reacted with PhSNa, PhSeH and some amino nucleophiles to give the corresponding 6-substituted uracils in varied yields (38–98%, Table 4). The reaction with PhSNa (4 equiv) in HMPA and DMSO at 90 °C for 3 min afforded an excellent yield of 6-phenylthiouracil (98 and 96%, respectively. Table 4, entries 11 and 12). The substitution with PhSeH was achieved in DMF to provide an 86% yield of 6-phenylselenenyluracil (entry 18, Table 4). The results indicated that the reactivity is 6-chlorouracil > 5-chlorouracil. For example, the substitution reaction of 6-chlorouracil with PhSNa occurred at 90 °C in 3 min (98% yield, Table 4, entry 11), whereas the reaction of 5-chlorouracil occurred at 150 °C in 5 min (97% yield, Table 3, entry 8).

Similar experiments were performed with another two substrates, 1,3-dimethyl-5-bromouracil and 1,3-dimethyl-6-chlorouracil (Tables 5 and 6). 1,3-Dimethyl-5-bromouracil was less reactive than 5-bromouracil toward nitrogen-containing nucleophiles. Only the reaction with piperidine gave the desired substitution product in a good yield of 94% (entry 8, Table 5). When 1,3-dimethyl-6-chlorouracil was treated with the sulfur, oxygen and nitrogen nucleophiles (PhSNa, PhONa, EtONa, MeONa, aniline, benzylamine and piperidine) under microwave irradiation, the corresponding

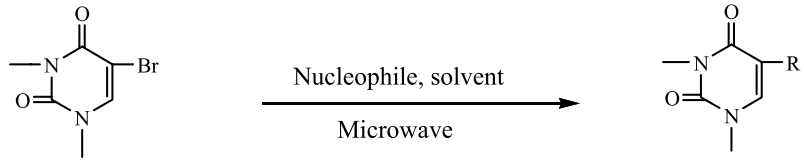
Table 4. Substitutions of 6-chlorouracil with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	NH_2CH_2Ph	[a]	15	130	15	$NHCH_2Ph$	94
2	NH_2CH_2Ph	[a]	15	130	15	$NHCH_2Ph$	41[b]
3	$NH_2(CH_2)_3CH_3$	[a]	15	90	20	$NH(CH_2)_3CH_3$	62
4	Cyclohexylamine	[a]	20	130	35	Cyclohexylamino	88
5	Piperidine	[a]	20	100	15	Piperidyl	96
6	Morpholine	[a]	20	100	15	N-Morpholyl	94
7	NH (CH_3) CH_2 Ph	[a]	10	130	20	N (CH_3) CH_2 Ph	92
8	$PhNH_2$	[a]	30	160	20	NHPh	95
9	PhONa	NMP	4	90	3	OPh	0
10	PhSNa	NMP	4	90	3	SPh	86
11	PhSNa	HMPA	4	90	3	SPh	98
12	PhSNa	DMSO	4	90	3	SPh	96
13	PhSNa	DMF	4	90	3	SPh	90
14	PhSNa	DMAC	4	90	3	SPh	85
15	PhSeH	NMP	4	90	3	SePh	83
16	PhSeH	HMPA	4	90	4	SePh	63
17	PhSeH	DMSO	4	90	4	SePh	38
18	PhSeH	DMF	4	90	4	SePh	86

[a] No solvent was used.
[b] Heating in an oil bath.

Table 5. Substitutions of 1,3-dimethyl-5-bromouracil with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	PhSNa	NMP	3	130	3	SPh	79
2	PhSNa	HMPA	3	130	3	SPh	52
3	PhSNa	DMSO	3	130	3	SPh	45
4	PhSNa	DMF	3	130	3	SPh	78
5	PhONa	NMP	3	130	2	OPh	0
6	$PhNH_2$	[a]	20	180	30	NHPh	0
7	NH_2CH_2Ph	[a]	20	180	30	$NHCH_2Ph$	0
8	Piperidine	[a]	15	100	40	Piperidyl	94

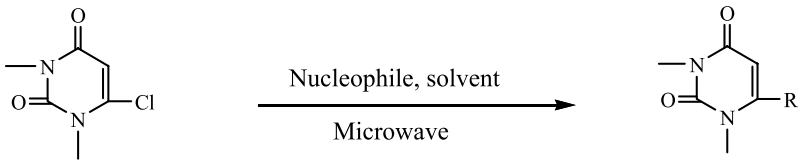
[a] No solvent was used.

6-substituted uracils were obtained in excellent yields (90–99%, Table 6).

3. Conclusion

In conclusion, our present study demonstrated that microwave irradiation can greatly facilitate the synthesis of various substituted uracils by nucleophilic substitution. This new synthetic tool is definitely valuable for the quick access of these bioactive compounds. The substitution reactions under conventional heating take many hours and low yields desired products were obtained. For example, the substitution reaction of 5-bromouracil with PhSNa by heating at 140 °C for 2 h gave a low yield (11%) of 5-phenylthiouracil,[6] whereas the reaction was promoted significantly by microwave irradiation at 140 °C for 5 min gave a good yield (86%) of the desired product (Table 3, entry 14). The relative reactivity of halouracils in substitution reactions follows 1,3-dimethyl-6-chlorouracil > 5-bromouracil > 6-chlorouracil > 1,3-dimethyl-5-bromouracil. For example, the reaction of 1,3-dimethyl-6-chlorouracil with PhONa afforded 90% yield of the desired product under microwave irradiation at 60 °C for 0.5 min (Table 6, entry 2).

Table 6. Substitutions of 1,3-dimethyl-6-chlorouracil with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temp (°C)	Time (min)	Product, R=	Yield (%)
1	PhSNa	NMP	3	60	0.5	SPh	93
2	PhONa	NMP	3	60	0.5	OPh	90
3	EtONa	EtOH	3	60	0.5	OEt	97
4	MeONa	MeOH	3	60	0.5	OMe	99
5	$PhNH_2$	[a]	15	160	30	NHPh	98
6	NH_2CH_2Ph	[a]	5	130	3	$NHCH_2Ph$	98
7	piperidine	[a]	15	60	0.5	piperidyl	99
8	NH (CH_3) CH_2 Ph	[a]	5	130	1	N (CH_3) CH_2 Ph	94

[a] No solvent was used.

4. Experimental

^{1}H NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions on a Bruker 300 spectrometer. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F-254 (0.2 mm layer thickness). Flash chromatography was carried out by utilizing silica gel 60 (70–230 mesh ASTM).

4.1. General procedure for reaction of halouracil nucleophile

In a reaction vessel (12 mL) were placed a nucleophile and a halouracil (0.1 mmol) in an appropriate solvent (1 mL). *t*-BuOK (1.1 equiv vs. nucleophile) could be added as the base if needed. The reaction vessel was then placed into the cavity of a focused monomode microwave reactor (CEM Discover) and irradiated for the period listed in the tables. The reaction temperature was maintained by modulating the power level of the reactor. The desired product precipitates after the pH was adjusted to 6 with 6 N HCl. The product was collected, washed with H_2O. Then was purified by recrystallization. Products **19**, **21**, **22**, **23**, **24**, **26** and **27** were purified by silica gel chromatography eluting with a mixture of hexane, ethyl acetate and acetone.

4.1.1. 5-Benzylaminouracil.[7] Pale white solid, mp 301–305 °C (dec) (lit. 285 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.34 and 10.02 (2s, 2H, 2NH), 7.31–7.19 (m, 5H, Ph), 6.08 (s, 1H, 6-H), 4.97 (t, J=6.2 Hz, 1H, NH), 4.08 (d, J=6.2 Hz, 2H).

4.1.2. 5-Butylaminouracil.[8] Pale yellow solid, mp 285–288 °C (dec) (lit. 286–288 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.11 and 10.13 (2s, 2H, 2NH), 6.26 (d, J=6.0 Hz, 1H, 6-H), 4.10 (t, J=5.8 Hz, 1H, NH), 2.76 (m, 2H), 1.47 (m, 2H), 1.30 (m, 2H), 0.87 (t, J=7.4 Hz, 3H).

4.1.3. 5-Piperidyluracil.[8] White solid, mp 303–305 °C (dec) (lit. 285–290 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.89 and 10.40 (2s, 2H, 2NH), 6.66 (s, 1H, 6-H), 2.71 (m, 4H), 1.54–1.43 (m, 6H).

4.1.4. 5-Morpholinouracil.[8] White solid, mp 329–334 °C (dec) (lit. >310 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 and 10.46 (2s, 2H, 2NH), 6.72 (s, 1H, 6-H), 3.63 (t, J=4.5 Hz, 4H), 2.77 (t, J=4.5 Hz, 4H).

4.1.5. 5-Cyclohexylaminouracil.[8] Pale yellow solid, mp 327–333 °C (dec) (lit. >305 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.13 and 10.15 (2s, 2H, 2NH), 6.36 (d, J=5.2 Hz, 1H, 6-H), 3.78 (d, J=8.4 Hz, 1H, NH), 2.87 (m, 1H), 1.84–1.05 (m, 10H).

4.1.6. 5-(Benzylmethylamino)uracil.[8] White solid, mp 269–271 °C (lit. 267–269 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.08 and 10.40 (2s, 2H, 2NH), 7.33–7.20 (m, 5H, Ph), 6.60 (s, 1H, 6-H), 4.04 (s, 2H), 2.39 (s, 3H).

4.1.7. 5-Anilinouracil.[5] Pale white solid, mp 318–320 °C (dec) (lit. 317–319 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.25 (s, H, NH), 10.63 (d, J=4.8 Hz, 1H, NH), 7.29 (d, J=5.8 Hz, 1H, 6-H), 7.12–6.62 (m, 5H, Ph), 6.90 (s, 1H, NH).

4.1.8. 5-Phenylthiouracil.[9] White solid, mp 273–274 °C (lit. 269–271 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.40 (s, 2H, 2NH), 7.92 (s, 1H, 6-H), 7.29–7.14 (m, 5H, SPh).

4.1.9. 5-Phenylselenenyluracil.[9] White solid, mp 250–252 °C (lit. 249–251 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 and 11.01 (2s, 2H, 2NH), 7.79 (s, 1H, 6-H), 7.36–7.19 (m, 5H, SePh).

4.1.10. 6-Benzylaminouracil.[10] Pale white solid, mp 318–320 °C (dec) (lit. 316–317 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.19 and 10.03 (2s, 2H, 2NH), 7.38–7.24 (m, 5H, Ph), 6.60 (t, J=5.7 Hz, 1H, NH). 4.37 (s, 1H, 5-H). 4.25 (d, J=5.7 Hz, 2H, –CH_2Ph).

4.1.11. 6-Cyclohexylaminouracil.[11] Yellow solid, mp 327–329 °C (lit. 327–328 °C); ^{1}H NMR (300 MHz,

DMSO-d_6) δ 10.15 and 9.66 (2s, 2H, 2NH), 6.03 (d, J= 7.9 Hz, 1H, NH), 4.43 (s, 1H, 5-H), 3.18 (m, 1H), 1.83–1.14 (m, 10H).

4.1.12. 6-Piperidyluracil.[12] White solid, mp 307–309 °C (dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 and 10.22 (2s, 2H, 2NH), 4.60 (s, 1H, 5-H), 3.23 (m, 4H), 1.51 (m, 6H).

4.1.13. 6-Morpholinouracil.[13] White solid, mp 322–326 °C (dec) (lit. >310 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 and 10.24 (2s, 2H, 2NH), 4.65 (s, 1H, 5-H), 3.61 (t, J=4.8 Hz, 4H), 3.12 (t, J=4.8 Hz, 4H).

4.1.14. 6-(Benzylmethylamino)uracil.[11] White solid, mp 273–275 °C (lit. 273–275 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.35 and 10.13 (2s, 2H, 2NH), 7.40–7.15 (m, 5H, Ph), 4.58 (s, 2H), 4.47 (s, 1H, 5-H), 2.92 (s, 3H).

4.1.15. 6-Anilinouracil.[10] Pale white solid, mp 326–327 °C (dec) (lit. 325–327 °C dec); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.46 and 10.17 (2s, 2H, 2NH), 8.25 (s, 1H, NH). 7.29 (d, J=5.8 Hz, 1H, 6-H), 7.40–7.12 (m, 5H, Ph), 4.68 (s, 1H, 5-H).

4.1.16. 6-Phenylthiouracil.[9] White solid, mp 272–274 °C (lit. 270–272 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.58 and 10.98 (s, 2H, 2NH), 7.65–7.51 (m, 5H, SPh), 4.51 (s, 1H, 5-H).

4.1.17. 6-Phenylselenenyluracil.[9] White solid, mp 241–243 °C (lit. 238–240 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.54 and 10.97 (2s, 2H, 2NH), 7.70–7.47 (m, 5H, SePh), 4.68 (s, 1H, 5-H).

4.1.18. 1,3-Dimethyl-5-phenylthiouracil.[14] White solid, mp 134–136 °C (lit. 136 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.34 (s, 1H, 6-H), 7.29–7.12 (m, 5H, SPh), 3.35 (s, 3H), 3.18 (s, 3H).

4.1.19. 1,3-Dimethyl-5-piperidyluracil. Colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.10 (s, 1H, 6-H), 3.27 (s, 3H), 3.14 (s, 3H), 2.76 (t, J=5.1 Hz, 4H), 1.60–1.45 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 150.2, 130.1, 126.7, 51.1 (2C), 36.2, 27.7, 25.5 (2C), 23.8; IR (MeOH): 2931, 1700, 1650 cm^{-1}; MS *m/e* 223 (M^+), 194, 140, 84, 69; HRMS *m/e* calcd for 223.2782, found 223.1329.

4.1.20. 1,3-Dimethyl-6-phenylthiouracil.[15] Colorless needles, mp 131–132 °C (lit. 129–130 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66–7.56 (m, 5H, SPh), 4.71 (s, 1H, 5-H), 3.45 (s, 3H), 3.10 (s, 3H).

4.1.21. 1,3-Dimethyl-6-phenoxyuracil.[15] Colorless needles, mp 109–110 °C (lit. 107–108 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56–7.30 (m, 5H, OPh), 4.44 (s, 1H, 5-H), 3.41 (s, 3H), 3.13 (s, 3H).

4.1.22. 1,3-Dimethyl-6-ethoxyuracil.[16] White solid, mp 136–137 °C (lit. 134 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.19 (s, 1H, 5-H), 4.12 (q, J=7.0 Hz, 2H), 3.20 (s, 3H), 3.11 (s, 3H), 1.34 (t, J=7.0 Hz, 3H).

4.1.23. 1,3-Dimethyl-6-methoxyuracil.[17] Colorless needles, mp 164–166 °C (lit. 165–166 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.21 (s, 1H, 5-H), 3.86 (s, 3H), 3.20 (s, 3H), 3.12 (s, 3H).

4.1.24. 1,3-Dimethyl-6-anilinouracil.[18] Yellow solid, mp 186–188 °C (lit. 187 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (s, 1H, NH), 7.45–7.21 (m, 5H, Ph), 4.62 (s, 1H, 5-H), 3.42 (s, 3H), 3.10 (s, 3H).

4.1.25. 1,3-Dimethyl-6-benzylaminouracil.[19] Colorless needles, mp 159–163 °C (lit. 158–159 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (t, J=5.9 Hz, NH), 7.34–7.21 (m, 5H, Ph), 4.49 (s, 1H, 5-H), 4.32 (d, J= 5.9 Hz, 2H), 3.36 (s, 3H), 3.04 (s, 3H).

4.1.26. 1,3-Dimethyl-6-piperidyluracil.[20] Colorless solid, mp 78–79 °C (lit. 77 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.10 (s, 1H, 5-H), 3.24 (s, 3H), 3.11 (s, 3H), 2.84 (t, J= 4.7 Hz, 4H), 1.62–1.52 (m, 6H).

4.1.27. 1,3-Dimethyl-6-(benzylmethylamino)uracil. Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.24 (m, 5H, Ph), 5.27 (s, 1H, 5-H), 4.10 (s, 2H), 3.4 7 (s, 3H), 3.34 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ163.3, 160.0, 153.3, 135.4, 129.0 (2C), 128.2 (3C), 88.7, 58.1, 39.4, 33.4, 27.9; IR (MeOH): 2924, 2854, 1699, 1655, 1606 cm^{-1}; MS *m/e* 259 (M^+), 244, 137, 91, 69; HRMS *m/e* calcd for 259.2989, found 259.1322.

Acknowledgements

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The reaction between 3-aminocrotonates and oxindole-3-ylidene derivatives: synthesis of highly substituted pyrroles

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Abstract—The reaction between 3-aminocrotonates and 3-acetonylideneoxindole in refluxing toluene resulted in 2-pyrrolo-3′-yloxindoles in high yields (around 90%). At room temperature the 2-pyrrolo-3′-yloxindoles exists as keto–enol tautomers. Treatment with $POCl_3$ yielded the 2-chloro-3-pyrrolyl indole, which gave the pyrrolo annulated indolopyran-2-one upon basic hydrolysis of 2-chloro-3-pyrrolyl indole methyl ester.

1. Introduction

The chemistry of enaminones, for example, 3-aminocrotonates, has been used to synthesize a multitude of heterocycles, as is evident from a recent review.[1] Classical use of 3-amino-enones can be exemplified with the Nenitzescu indole synthesis, whereby an indole is constructed from an enaminone and a quinone.[2] Another area of synthetic usefulness of 3-aminocrotonates involves in the Hantzsch cyclocondensation, wherein 3-aminocrotonates together with 1,3-dicarbonyl compounds and aldehydes will give 1,4 dihydropyridines[3] which can be smoothly dehydrogenated to pyridines.[4] Several pyridine derivatives have also been synthesized in good yields from 3-amino-enones and the appropriate alkynones.[5]

In 1976 Tacconi et al.,[6] studied the reaction between 2-oxoindolin-3-ylidene derivatives and 1-pyrrolidinocyclopentene. The enamine added in a Michael fashion yielding a new enamine **1** via the zwitterionic intermediate **2**. Hydrolysis and treatment with aniline yielded the 2,3-disubstituted-4-(3′-oxindolyl)-pyrrole **3**. Recently, a study incorporating a discussion on the stereochemical outcome of the addition of 1-pyrrolidinocyclohexene to *N*-methyl-3-phenacylideneoxindole yielding the oxindole **4** was published.[7] The structure of compound **4** was supported by extensive ^{1}H NMR studies and finally confirmed by X-ray diffraction analysis (Fig. 1).

The reaction patterns of oxindole-3-ylidene derivatives have previously caught our interest, and recently we have studied the reaction between ethyl 3-methylene-oxindole acetate **6** and *p*-toluenesulfonylmethyl isocyanide (TosMIC), whereupon an initially formed spiro pyrrolo-oxindole underwent rearrangement to finally yield the pyrroloquinolone **5** in 74% yield.[8]

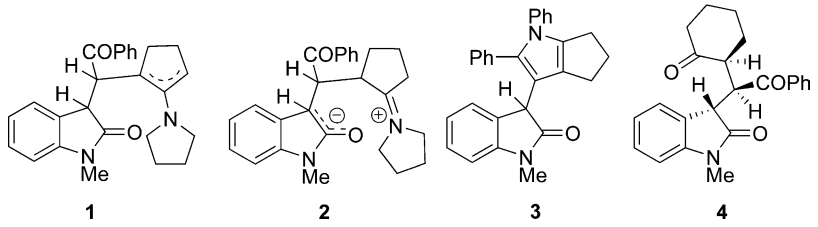

Figure 1. Enamine adducts based upon 3-phenacylideneoxindole.

Keywords: Pyrrole synthesis; Keto–enol tautomers; Indolopyrano-2-one.
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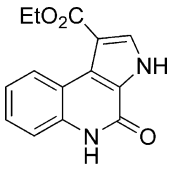

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Therefore, we wanted to explore this type of reactivity further, and in this paper we report the outcome of reactions between 3-aminocrotonates and oxindole-3-ylidene derivatives.

2. Results and discussion

We expected that the 3-aminocrotonates would attack the oxindole 3-ylidene derivatives at the exocylic methylene carbon, and at an early stage yield a zwitterionic intermediate in accordance with what have been discussed earlier in this paper. The 3-aminocrotonates behave as 1,3 di-nucleophiles when utilized in ring closure reactions such as the Hantzsch pyrrole synthesis. Thus, upon mixing 3-aminocrotonates with oxindole-3-ylidene derivatives a cyclocondensed product ought to be formed.

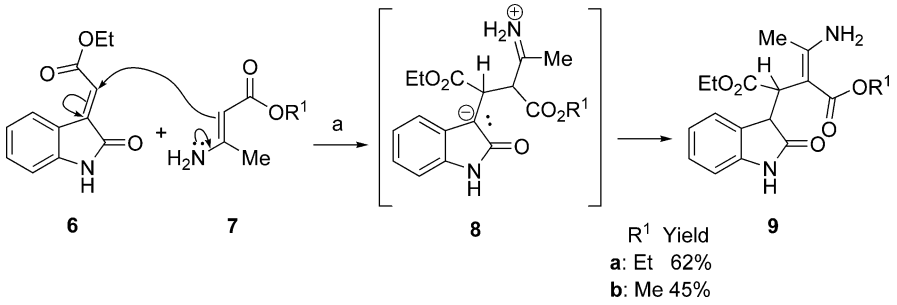
2.1. 3-Aminocrotonates and 3-methyleneoxindole acetic acid ethyl ester

When 2 mol equiv of the ethyl 3-aminocrotonate **7a** was added to a suspension of the oxindole derivative **6** in pentane, following the procedure reported by Avendaño et al.,[7] no reaction occurred. By changing the conditions to refluxing ethanol for 3 h, however, a colourless solid could be isolated after partial evaporation of the solvent (Scheme 1).

The product from this reaction was the adduct **9**, in 62% yield when ethyl 3-aminocrotonate was used and in 45% yield when methyl 3-aminocrotonate was used. Thus in no case a cyclocondensed product was obtained. The ^{1}H NMR spectrum of compound **9a** showed the presence of two isomers, namely the *E*, *Z*-pair. The location of the double bond is as presented in formula **9**, since the signal corresponding to the methyl appeared as a singlet. Thus no splitting occurs because there is no neighbouring hydrogen atom to the methyl group. On the other hand, the spectrum of compound **9b** indicated that only one isomer was present. The stereochemistry of the double bond was deduced when irradiation of the methyl signal at 1.94 ppm gave rise to a NOE interaction at 3.96 ppm, which corresponds to the α-proton of the ethyl ester.[9] To cause this NOE effect, the amino functionality should be *cis* to the carbomethoxy group, and when the methoxy signal at 3.22 ppm was irradiated no NOE interaction could be detected at 1.94 ppm, which excludes *E*-configuration of the double bond. From the proton NMR spectrum, only one of the two amine protons appeared and then as a very broad singlet. It seems likely that the other signal could be hidden among the aromatic signals. Nevertheless, heating of the sample to 90 °C brought the two signals rising from the amino protons to merge into one signal that resonated at 7.41 ppm. When the ethyl ester **9a** was recrystallized from ethyl acetate only one regioisomer could be isolated, and in the case of compound **9b** only one amino proton could be observed (as a very broad singlet in the proton NMR spectrum). Unfortunately, when compound **9a** was heated in an attempt to detect the two amino protons as previously done for compound **9b**, it only resulted in decomposition of compound **9a**.

2.2. 3-Aminocrotonates and 3-acetonylideneoxindole

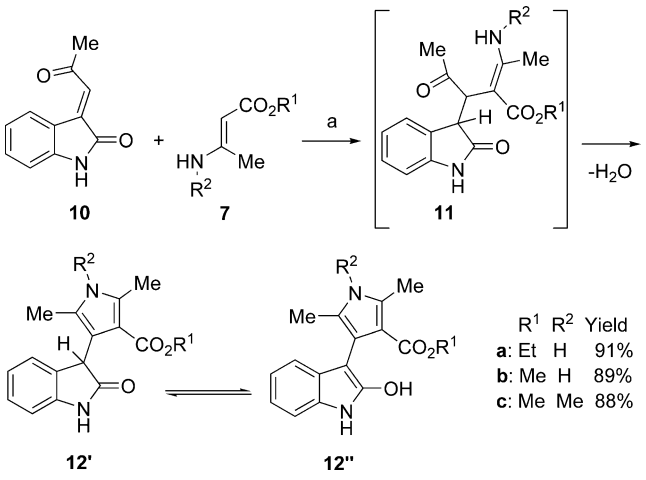
Now, we turned our attention to 3-acetonylideneoxindole **10**, which having an α,β-unsaturated carbonyl function with a lower oxidation state than the 3-methyleneoxindole acetic acid ethyl ester **6**, it would together with 3-aminocrotonates initially yield a product similar to those described above. After an initial attack on the methylidene carbon atom in Michael fashion, it would lead to a compound analogous to **9** via an adduct like **8**. In contrast to the reaction with the ethyl ester **6**, the reaction with 3-acetonylideneoxindole **10** would yield an adduct with a more reactive keto functionality, which ought to cyclise to a pyrrolo oxindole. A similar reaction path has been described by Kaupp et al.[10] when they mixed 3-aminocrotonates with dibenzoylethylene to yield highly substituted pyrroles. The mechanism resembles the classical Hantzsch pyrrole synthesis where 3-aminocrotonates, formed by an initial condensation between ammonia and β-ketoesters (or β-diketones), are alkylated by α-haloketones (or α-haloaldehydes) and finally a cyclocondensation to yield pyrroles.[11] Although 2-pyrrolo-3′-yloxindoles have been prepared previously by reaction between 3-diazooxindoles and pyrroles in the presence of a rhodium(II) acetate catalyst,[12] the reaction between 3-aminocrotonate esters and oxindole-3-ylidene



Scheme 1. Addition of 3-aminocrotonates to 3-methyleneoxindole acetic acid ethyl ester. (a) Ethanol, reflux 3 h.

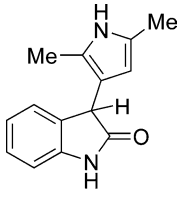
derivatives should yield a more highly substituted pyrrole moiety.

When 3-acetonylideneoxindole **10** and ethyl 3-aminocrotonate **7a** were heated in ethanol, as discussed above, the expected pyrrolo-oxindole **12a** was formed. The reaction proceeded more smoothly in toluene, and the final product **12a** could be collected in very good yield (91%). Methyl 3-aminocrotonate **7b** worked as well to yield the pyrrolo-oxindole **12b** (89%). Usually the product could be collected from the cooled suspension. However, better yields were obtained when the solvent was evaporated followed by trituration with hot dichloromethane. Purification by dry flash chromatography was applied in the few cases when trituration failed. Reaction of methyl 3-(methylamino)crotonate **7c** with 3-acetonylideneoxindole **10** yielded the pyrrolo-oxindole **12c** (88%), which demonstrated that the extra methyl group did not substantially affect the reaction result (Scheme 2).



Scheme 2. Synthesis of pyrrolo oxindole. (a) Toluene, reflux.

Removal of the carbethoxy group in **12a** (heating in 45% $KOH_{(aq)}$ in ethanol) gave the pyrrolo-oxindole **13**, exclusively in the keto form.



13

At the first glance, the proton NMR spectrum of **12a** appeared to be complex because two sets of signals were observed, that is, the characteristic pattern of an ethyl group was doubled (with the approximate proportion 2/3). We believe that the structure of the carboxylated pyrrolo-oxindole **12** facilitates the existence of the keto–enol pair, **12′** and **12″**, since the proton NMR spectrum of the non carboxylated pyrrolo-oxindole **13** only displayed one set of signals. The proton signals from the different tautomers (**12′** and **12″**) were easy to distinguish, except the aromatic signals, but the carbon signals were not discernible at 25 °C. However, when the temperature was raised to 125 °C, both the proton NMR spectrum and the carbon NMR spectrum displayed only one set of signals. The heating did not have any disruptive influence on the structure, because a comparison between two 25 °C spectra, one before heating and one after heating showed no discrepancy.

Thus, in solution three different species are present; the enol **12c″** and the two enantiomers **12c′**(*S*) and **12c′**(*R*) but in the solid state the racemic keto form **12c′** was the tautomer present. This is unambiguous from the X-ray structure[13] of compound **12c** (Fig. 2).

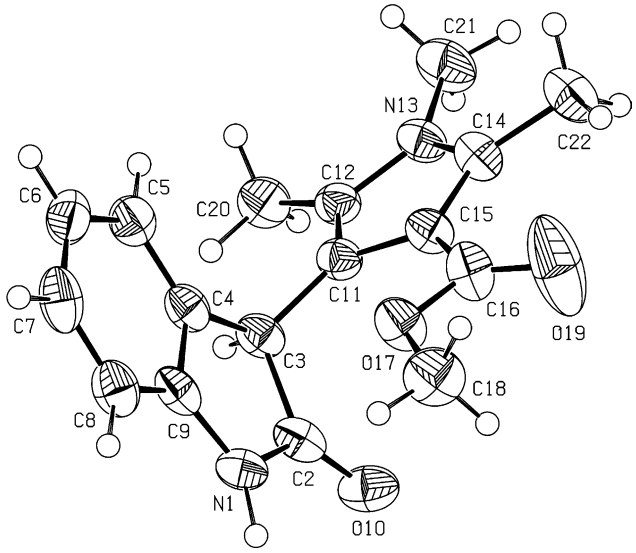


Figure 2. The racemic compound **12c**. Here the atom-labelling scheme of molecule A is shown.

However, the unit cell established from single crystal X-ray structure analysis contained three independent molecules (A, B and C) where both enantiomers were represented (Fig. 3).

The three independent molecules can be explained by the packing arrangement where the hydrogen bonding contacts are revealed. In the solid state the molecules are joined as dimers, the indolic NH in contact with the amide oxygen.

3-Phenacylideneoxindole **14** was similarly reacted with methyl 3-aminocrotonate **7b** in toluene at reflux. The final pyrrolo-oxindole **15** was collected in 92% yield by direct collection from the cooled reaction mixture (Scheme 3).

Interestingly at room temperature the keto form was the prevailing tautomer (90%) in contrast to the pyrrolo oxindole **12a** where the equilibrium at room temperature is close to 2/3. Why this equilibrium exists can be explained in terms of π-stacking between the oxindole nucleus and the phenyl ring. In the keto structure **15′**, carbon 3 (in the oxindole) forms a tetrahedral sp^3 carbon that directs the pyrrole ring with the phenyl out of the plane with the possibility of π-stacking. Thus, in the enol structure **15″**

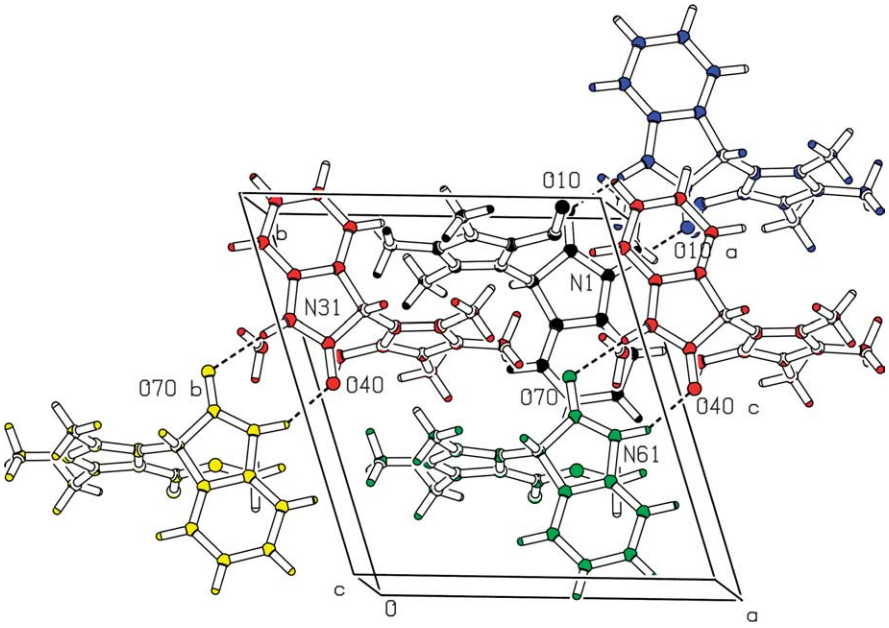
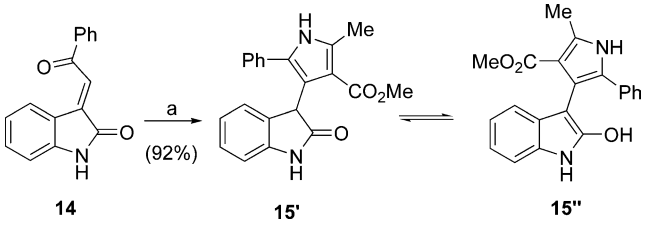


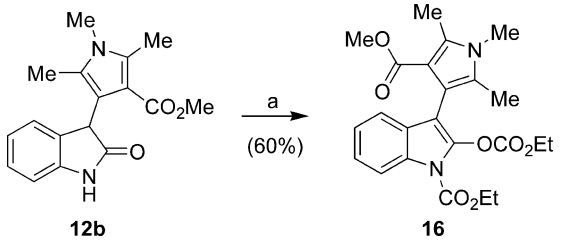
Figure 3. Detailed H-bonding scheme for (±)-**12c′**. Compound **12c** is a racemate, with three independent molecules: A, B and C in the asymmetric crystallographic unit.



Scheme 3. (a) Methyl 3-amino crotonate **7b**, toluene, reflux, 3 h.

carbon 3 forms a plane sp^2 carbon, which levels the oxindole and the pyrrole moiety. In this respect, the possibility of π-stacking between the phenyl ring and the oxindole will diminish.

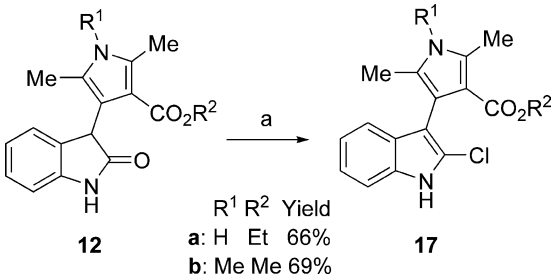
The same observation involving transformation between tetrahedral sp^3 carbon and planar sp^2 carbons could be observed when the pyrrolo-oxindole **12b** was treated with ethyl chloroformate to yield the pyrrolo-indole **16** (Scheme 4).



Scheme 4. (a) Ethyl chloroformate, Et_3N, CH_2Cl_2.

Proton 4 in the indole ring was shifted downfield approximately 1 ppm in the pyrrolo-indole **16**, as compared with the corresponding proton in compound **12b**. In addition he doubling of signals that appears in the ^1H NMR spectra of pyrrolo-oxindole **12b** was absent. Shielding from the carbonyl in the methyl ester causes a downshift of the proton signal. The reason for the proximity of the carbonyl can be found in the conversion of carbon 3 from a tetrahedral sp^3 carbon to a planar sp^2 carbon, which will cause the carbomethoxy group on the pyrrole ring to bend toward the indole moiety.

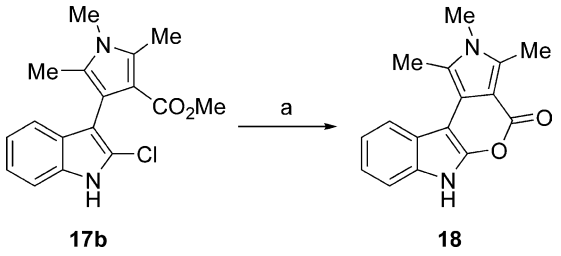
Treatment with $POCl_3$ ought to convert the pyrrolo-oxindole **12** to the corresponding 2-chloroindoles and in this way trap the indolic tautomer. Thus pyrrolo-oxindole **12a** was treated with this reagent and the conversion to a 2-chloroindole was accomplished albeit the yield was low. When the conditions were changed to 2 equiv of $POCl_3$ and a slight excess of Et_3N in acetonitrile at reflux, the yield reached 66 and 64% for pyrrolo 2-chloroindoles **17a** and **17b**, respectively, (Scheme 5).



Scheme 5. (a) $POCl_3$, Et_3N, MeCN reflux over night.

In the efforts to chlorinate pyrrolo oxindole **12b** with neat $POCl_3$, the reaction mixture was quenched with an ice/water mixture and made alkaline with 45% $KOH_{(aq)}$. From the reaction mixture the desired 2-chloroindolyl substituted pyrrole **17b** could be isolated, albeit in a very low yield, but the main product obtained was the pyrrolo annulated indolo-2-pyranone **18**. We believe that during the addition of $KOH_{(aq)}$ the methyl ester was hydrolyzed and ring closure

was affected by the carboxylate anion attacking the 2-chloroindole moiety. To further comprehend the formation of the annulated indolo-2-pyranone **18**, the methyl ester of 2-chloroindole **17b** was subjected to hydrolytic conditions, whereby the annulated indolo pyrane **18** could be isolated in almost quantitative yield (Scheme 6).



17b **18**

Scheme 6. (a) 45% $KOH_{(aq)}$, MeOH, reflux.

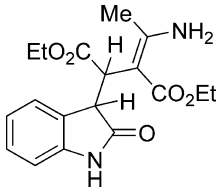
Although indolo-pyrones such as pyrano[3,4-*b*]indol-3-one **19**[14] and the isomeric pyrano[4,3-*b*]indol-3-one **20**[15] have been described, the isomeric ring system pyrano[2,3-*b*]indol-2-one **21** is hitherto unknown. There are, however, a few scattered reports of 3- and 4-substituted derivatives of **21**.[16,17] In contrast, the 4-keto cousin of **21**, that is, **22**, is well represented with a number of well described derivatives[18] (Fig. 4).

In conclusion, we have synthesized the pyrrolo-oxindole **12** in good yields by reacting 3-acetonylideneoxindole **10** with 3-aminocrotonates **7**. These oxindolyl pyrroles exists as keto–enol tautomers at room temperature. Furthermore, by treating the oxindolyl pyrrole **12** with $POCl_3$ we afforded the 2-chlorinated indolopyrrole **17** which could be cyclized to the most uncommon pyrrolo annulated indolo-2-pyranone **18**.

3. Experimental

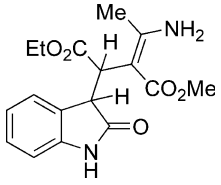
3.1. General remarks

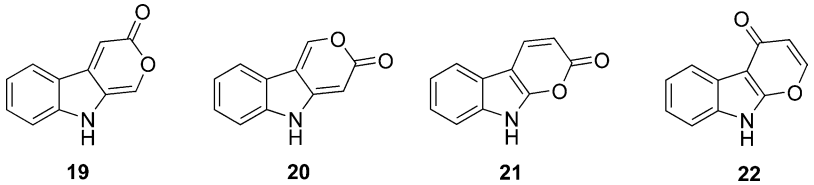
The 3-aminocrotonates and solvents (PA grade) are commercially available and were used without further purification. The oxindoles, 3-methyleneoxindole acetic acid ethyl ester **6**,[19] 3-acetonylideneoxindole **10**,[20] and 3-phenacylideneoxindole **14**[21] were prepared according to literature procedures. NMR spectra were recorded in DMSO-d_6 solutions at 25 °C, unless otherwise stated, on a Bruker Avance DPX 300 spectrometer, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, δ values are reported in ppm and *J* values in Hertz. IR spectra were recorded on a Thermo Nicolet Avatar 330 FT-IR instrument using single-reflection ATR. Mass spectra were recorded on a Micromass Platform II spectrometer, using the direct-inlet system operating in the electron impact (EI) mode at 70 eV. Only fragment peaks larger than 20% of the base peak are given. Single crystal X-ray diffraction analysis was performed by Birgitta Stensland (Preformulation and Biopharmaceutics, Solid State Analysis, AstraZeneca PAR and D/SBBG B341:3, SE-151 85 Södertälje, Sweden), HRMS-determinations (FAB) were performed by Dr Einar Nilsson, University of Lund, Sweden. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were determined with a Büchi melting point B-545 apparatus and are uncorrected.



3.1.1. 2-(1-Amino-ethylidene)-3-(2-oxo-2,3-dihydro-1*H*-indole-3-yl)-succinic acid diethyl ester, 9a. A mixture of 3-methyleneoxindole acetic acid ethyl ester **6** (2.17 g, 10 mmol) and ethyl 3-aminocrotonate **7a** (1.29 g, 10 mmol) was heated to reflux in ethanol (25 ml). After 3 h the red mixture was concentrated to half of the initial volume, whereupon a solid started to precipitate. The white solid formed (2.16 g, 62%) was collected after 2 h. The analytically pure substance was obtained by recrystallization from ethyl acetate.

Mp 157–159 °C. IR (neat) 3436, 3323, 2982, 1733, 1691, 1609, 1253, 1226, 1170, 1098, 1018, 673, 591 cm^{-1}. δ_H 1.06 (3H, t, J=7.1 Hz), 1.17 (3H, t, J=7.1 Hz), 1.89 (3H, s), 3.53–3.64 (1H, m), 3.84–3.93 (2H, m), 3.99–4.17 (3H, m), 6.73 (1H, d, J=7.6 Hz), 6.84 (1H, t, J=7.5 Hz), 7.07–7.14 (2H, m), 8.29 (1H, bs), 10.28 (1H, s). δ_C 14.05 (q), 14.15 (q), 20.4 (q), 44.7 (d), 47.4 (d), 57.8 (t), 60.1 (t), 88.0 (s), 108.8 (d), 120.4 (d), 126.6 (d), 127.40 (d), 127.42 (s), 143.0 (s), 161.2 (s), 168.5 (s), 173.0 (s), 178.3 (s). MS (EI) *m/z* 346 (1) $[M]^+$, 217 (63), 214 (47), 172 (53), 168 (20), 144 (41), 129 (39), 117 (28), 116 (44), 89 (29), 84 (100), 83 (21), 68 (20), 57 (49). Anal. calcd for: $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.35; H, 6.49; N, 7.99.



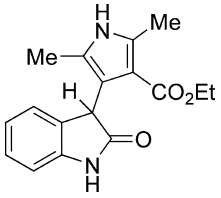


19 **20** **21** **22**

Figure 4. Pyrano-indolones.

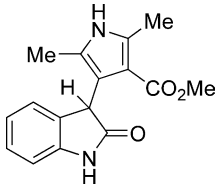
3.1.2. 2-[1-Amino-eth-(*Z*)-ylidene]-3-(2-oxo-2,3-dihydro-1*H*-indole-3-yl)-succinic acid 4-ethyl ester 1-methyl ester, 9b. A mixture of 3-methyleneoxindole acetic acid ethyl ester **6** (1.28 g, 6 mmol) and methyl 3-aminocrotonate **7b** (0.68 g, 6 mmol) was heated to reflux in ethanol (12 ml). After 3 h of reflux, the red mixture was concentrated to half of the initial volume whereupon a solid started to precipitate. After 2 h a white solid (0.43 g) was collected. The filtrate was evaporated and the resulting solid was recrystallized from ethanol yielding a further 0.45 g of **9b**, which gave a total yield 0.89 g (45%).

Mp 171–173 °C. IR (neat) 3433, 3319, 3247, 1736, 1690, 1614, 1228, 1184, 1170, 595 cm^{-1}. δ_H 1.16 (3H, t, J=7.0 Hz), 1.94 (3H, s), 3.22 (3H, s), 3.96–3.98 (1H, m), 4.01–4.21 (3H, m), 6.71–6.74 (1H, m), 6.83–6.88 (1H, m), 7.07–7.12 (1H, m), 7.15–7.17 (1H, m), 8.26 (1H, bs), 10.27 (1H, s). δ_C 14.2 (q), 20.4 (q), 44.6 (d), 47.7 (d), 49.2 (q), 60.1 (t), 87.8 (s), 108.8 (d), 120.4 (d), 126.9 (d), 127.3 (d), 127.4 (s), 143.0 (s), 161.3 (s), 168.7 (s), 173.1 (s), 178.2 (s). MS (EI) *m/z* 332 (1) $[M]^+$, 217 (68), 200 (47), 172 (57), 145 (67), 144 (46), 117 (31), 116 (51), 115 (58), 89 (32), 84 (100), 83 (30). Anal. calcd for: $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.52; H, 6.10; N, 8.54.



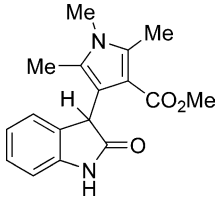
3.1.3. 2,5-Dimethyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylic acid ethyl ester, 12a. 3-Acetonylideneoxindole **10** (2.20 g, 12 mmol) and ethyl 3-aminocrotonate **7a** (1.67 g, 13 mmol) were heated at reflux for 3 h in toluene (40 ml). The mixture was allowed to reach rt, the solvent was evaporated, and the resulting crude pyrrolo oxindole was triturated with hot CH_2Cl_2 to yield 3.19 g (91%) of a yellowish solid of the keto–enol tautomer in a 2:3 ratio (^{1}H NMR analysis of the CH_3 protons).

Mp 220–221 °C. IR (neat) 3338, 3253. 3205, 1697, 1668, 1471, 1265, 1129, 758, 746 cm^{-1}. δ_H (major tautomer) 0.83 (3H, t, J=7.0 Hz), 2.22 (3H, s), 2.33 (3H, s), 3.69–3.75 (2H, m), 4.52 (1H, s), 6.70–7.13 (4H, m), 10.19 (1H, s), 11.05 (1H, s). δ_H (minor tautomer) 1.26 (3H, t, J=7.0 Hz), 1.56 (3H, s), 2.38 (3H, s), 4.16–4.23 (2H, m), 5.46 (1H, s), 6.70–7.13 (4H, m), 10.43 (1H, s), 10.97 (1H, s). δ_C (125 °C)=9.5 (q), 12.2 (q), 13.3 (q), 43.4 (d), 57.2 (t), 108.1 (d), 109.4 (s), 113.4 (s), 120.1 (d), 122.6 (d), 123.7 (s), 126.0 (d), 130.7 (s), 132.6 (s), 141.9 (s), 164.2 (s), 177.2 (s). MS (EI) *m/z* 298 (15) $[M]^+$, 252 (100), 251 (40), 224 (27). Anal. calcd for: $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.42; H, 6.06; N, 9.28.



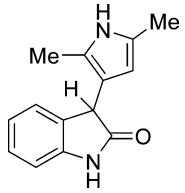
3.1.4. 2,5-Dimethyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylic acid methyl ester, 12b. 3-Acetonylideneoxindole **10** (2.20 g, 12 mmol) and methyl 3-aminocrotonate **7b** (1.53 g, 12 mmol) were heated at reflux for 3 h in toluene (40 ml). The mixture was allowed to reach rt and the solvent was evaporated and the resulting crude pyrrolo oxindole was triturated with hot CH_2Cl_2 to yield 3.05 g (89%) of a yellowish solid constituting the keto–enol tautomer in a 5:3 ratio (^{1}H NMR analysis if the NH protons).

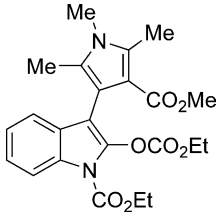
Mp 240–241 °C. IR (neat) 3348, 3233, 3186, 1696, 1667, 1464, 1124, 745, 681 cm^{1}. δ_H (major tautomer) 2.23 (3H, s), 2.32 (3H, s), 3.19 (3H, s), 4.52 (1H, s), 6.70–7.13 (4H, m), 10.20 (1H, s), 11.07 (1H, s). δ_H (minor tautomer) 1.55 (3H, s), 2.38 (3H, s), 3.72 (3H, s), 5.45 (1H, s), 6.70–7.13 (4H, m), 10.43 (1H, s), 10.99 (1H, s). δ_C (125 °C)=9.5 (q), 12.1 (q), 43.4 (d), 48.4 (q), 108.0 (d), 109.1 (s), 113.4 (s), 120.2 (d), 122.6 (d), 123.9 (s), 126.1 (d), 130.8 (s), 132.7 (s), 141.9 (s), 164.5 (s), 177.2 (s). MS (EI) *m/z* 284 (20) $[M]^+$, 253 (20), 252 (100), 251 (56), 224 (33), 126 (20). Anal. calcd for: $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.43; H, 5.78; N, 9.73.



3.1.5. 1,2,5-Trimethyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylic acid methyl ester, 12c. 3-Acetonylideneoxindole **10** (1.87 g, 10 mmol) and methyl 3-(methylamino)crotonate **8c** (1.42 g, 11 mmol) were heated at reflux for 6 h in toluene (40 ml). The solvent was evaporated and the resulting crude pyrrolo-oxindole was purified by dry flash chromatography to yield 2.62 g (88%) of **12c** as a pale orange solid (keto–enol ratio of 2:1) as indicated by the ^{1}H NMR analysis of the NH protons.

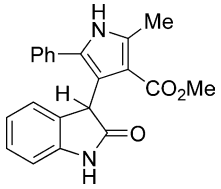
Mp 169–170 °C. IR (neat) 3135, 3081, 2947, 1709, 1693, 1259, 752, 744 cm^{-1}. δ_H (major tautomer) 2.27 (3H, s), 2.40 (3H, s), 3.16 (3H, s), 3.46 (3H, s), 4.62 (1H, s), 6.68–7.15 (4H, m), 10.22 (1H, s). δ_H (minor tautomer) 1.58 (3H, s), 2.47 (3H, s), 3.33 (3H, s), 3.73 (3H, s), 5.51 (1H, s), 6.68–7.15 (4H, m), 10.47 (1H, s). δ_C (125 °C)=8.7 (q), 10.4 (q), 29.3 (q), 43.6 (d), 48.4 (q), 108.0 (d), 108.8 (s), 113.2 (s), 120.1 (d), 122.4 (d), 126.1 (d), 126.4 (s), 130.7 (s), 134.0 (s), 141.9 (s), 164.4 (s), 177.2 (s). MS (EI) *m/z* 298 (15) $[M]^+$, 266 (100), 265 (48), 238 (24). FABHRMS Calcd for $C_{17}H_{18}N_2O_3$ $[M]^+$ 298.1317, found 298.1313.





3.1.6. 3-(2,5-Dimethyl-1*H*-pyrrol-3-yl)-1,3-dihydro-indol-2-one, 13. Pyrrolo-oxindole **12a** (0.62 g, 2 mmol) was heated at reflux in a mixture of 45% $KOH_{(aq)}$ (15 ml) and ethanol (15 ml). After 3 h the reaction mixture was poured into (100 ml) ice/water and acidified with concd HCl. The mixture was kept at 10 °C over night and 0.34 g (72%) of a pale brown solid was collected.

Mp 195–200 °C (dec). IR (neat) 3319, 3173, 3064, 2919, 1685, 1469, 726, 670, 659, 605, 554 cm^{-1}. δ_H 2.04 (3H, s), 2.07 (3H, s), 4.41 (1H, s), 5.15 (1H, s), 6.80–6.97 (3H, m), 7.11–7.16 (1H, m), 10.16 (1H, s), 10.26 (1H, s) δ_C 10.9 (q), 12.6 (q), 44.5 (d), 104.8 (d), 108.9 (d), 113.4 (s), 121.2 (d) 123.0 (s), 124.1 (s), 124.4 (d), 127.3 (d), 131.6 (s), 142.3 (s), 178.4 (s). MS (EI) *m/z* 226 (24) $[M]^+$, 149 (24), 135 (21), 111 (37), 109 (28), 99 (20), 97 (57), 96 (20), 95 (44), 94 (26), 85 (49), 83 (54), 81 (45), 71 (68), 70 (22), 69 (68), 67 (27), 57 (100). FABHRMS Calcd for $C_{14}H_{13}N_2O$ $[M-H]^+$ 225.1028 found 225.1021.

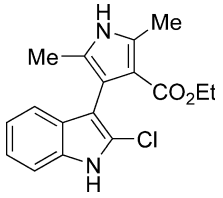


3.1.7. 2-Methyl-5-phenyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylic acid methyl ester, 15. 3-Phenacylideneoxindole **14** (2.47 g, 10 mmol) and methyl 3-aminocrotonate **7b** (1.26 g, 11 mmol) were heated at reflux in toluene (40 ml) for 18 h and then allowed to reach rt whereupon 2.98 g of a beige solid was collected. The filtrate was evaporated and the residue recrystallized from ethanol to yield further 0.20 g of **15** which gave the total yield 3.18 g (92%) of compound **15** (keto–enol tautomer ratio of 10:1) as indicated by ^1H NMR analysis if the NH protons. Only data for the keto tautomer are given.

Mp 317–319 °C (dec). IR (neat) 3353, 1695, 1666, 1462, 1449, 1143, 1091, 748, 695, 681, 630 cm^{-1}. δ_H 2.43 (3H, s), 3.20 (3H, s), 4.58 (1H, s), 6.82–6.85 (3H, m), 7.09–7.13 (1H, m), 7.36–7.38 (1H, m), 7.45–7.50 (2H, m), 7.54–7.57 (2H, m), 10.34 (1H, s), 11.63 (1H, s). δ_C 12.9 (q), 44.6 (d), 49.2 (q), 108.6 (d), 109.4 (s), 113.9 (s), 120.9 (d), 122.4 (d), 127.0 (d), 127.4 (d), 127.8 (d), 128.8 (d), 131.6 (s), 131.7 (s), 131.8 (s), 136.6 (s), 142.9 (s), 164.4 (s), 178.6 (s). MS (EI) *m/z* 346 (35) $[M]^+$, 315 (55), 314 (100), 313 (42), 286 (28), 285 (25), 157 (34), 128 (21). Anal. calcd for: $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.75; H, 5.37; N, 7.99.

3.1.8. 2-Ethoxycarbonyloxy-3-(4-methoxycarbonyl-1,2,5-trimethyl-1*H*-pyrrol-3-yl)-indole-1-carboxylic acid ethyl ester, 16. Triethylamine (0.53 g, 5.2 mmol) followed by ethyl chloroformate (0.43 g, 3.9 mmol) were added to a stirred suspension of pyrrolo-oxindole **12b** (0.39 g, 1.3 mmol) in CH_2Cl_2 (15 ml) at 0 °C. The reaction mixture was then allowed to reach rt, stirred for 18 h, then extracted twice with water (10 ml), brine (10 ml) and finally dried with $MgSO_4$. The pyrrolo-indole obtained was purified by dry flash chromatography (hexane–ethyl acetate, 3:1 to hexane–ethyl acetate, 1:1) to yield 0.35 g (60%) of **16**. An analytically pure sample was obtained by recrystallization from ethanol.

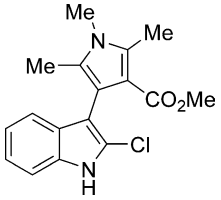
Mp 151–152 °C. IR (neat) 1772, 1744, 1685, 1375, 1225, 1202, 1080, 745 cm^{-1}. δ_H 1.34 (3H, t, J=7.1 Hz), 1.47 (3H, t, J=7.1 Hz), 2.05 (3H, s), 2.58 (3H, s), 3.40 (3H, s), 3.47 (3H, s), 4.29 (2H, q, J=7.1 Hz), 4.50 (2H, q, J=7.1 Hz), 7.17–7.33 (3H, m), 8.13 (1H, d, J=8.3 Hz). δ_C 10.8 (q), 11.7 (q), 14.1 (q), 14.3 (q), 30.6 (q), 50.3 (q), 63.3 (t), 64.4 (t), 106.3 (s), 108.1 (s), 110.8 (s), 115.2 (d), 120.2 (d), 123.1 (d), 124.1 (d), 128.2 (s), 128.9 (s), 131.9 (s), 135.9 (s), 137.4 (s), 150.5 (s), 152.2 (s), 166.1 (s). MS (EI) *m/z* 442 (8) $[M]^+$, 338 (53), 337 (20), 266 (66), 265 (100), 59 (22), 56 (29). Anal. calcd for: $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.28; H, 5.88; N, 6.24.



3.1.9. 4-(2-Chloro-1*H*-indol-3-yl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid ethyl ester, 17a. $POCl_3$ (1.50 g, 10 mmol) and Et_3N (0.53 g, 5.2 mmol) were added at rt to a suspension of oxindolyl-pyrrole **12a** (1.41 g, 4.7 mmol) in acetonitrile (75 ml). The mixture was heated at reflux overnight (16 h) and then allowed to reach rt and evaporated. The black residue was portioned between EtOAc (100 ml) and satd aq $NaHCO_3$ (100 ml), and the aqueous phase was extracted twice with 25 ml EtOAc. The combined organic phases were extracted with H_2O (25 ml) and satd aq NaCl (50 ml), dried ($MgSO_4$), to yield 1.35 g of a greenish solid after evaporation. Purification (dry flash chromatography) using CH_2Cl_2 as eluent yielded 0.99 g of **17a** as white solid in 66% yield.

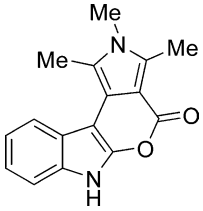
Mp 200 °C (dec). IR (neat) 3390, 3282, 1655, 1425, 1408, 1200, 1092, 746 cm^{-1}. δ_H 0.52 (3H, t, J=8.1 Hz), 1.88

(3H, s), 2.43 (3H, s), 4.00 (2H, q, $J=8.1$ Hz), 7.56 (1H, t, $J=8.4$ Hz), 7.67–7.73 (2H, m), 7.95 (1H, t, $J=9.0$ Hz), 12.39 (1H, s), 12.88 (1H, s). δ_C 11.3 (q), 13.2 (q), 13.6 (q), 58.0 (t), 107.4 (s), 110.3 (s), 110.46 (s), 110.48 (d), 118.95 (d), 119.04 (d), 120.96 (d), 121.04 (s), 124.8 (s), 128.3 (s), 133.7 (s), 134.4 (s), 164.8 (s). MS (EI) *m/z* 318 (23), 316 (68) $[M]^+$, 281 (55), 253 (29), 252 (100), 251 (64). Anal. calcd for: $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84. Found: C, 64.37; H, 5.41; N, 8.74.



3.1.10. 4-(2-Chloro-1*H*-indol-3-yl)-1,2,5-trimethyl-1*H*-pyrrole-3-carboxylic acid methyl ester, 17b. To an acetonitrile (75 ml) solution of oxindolyl-pyrrole **12c** (1.72 g, 6 mmol), $POCl_3$ (1.79 g, 12 mmol) and Et_3N (0.64 g, 6 mmol) were added in sequence at rt. The mixture was heated at reflux over night (16 h) and then allowed to reach rt and quenched with ice followed by satd aq $NaHCO_3$ (100 ml). The black mixture was portioned first by 50 ml CH_2Cl_2 and the aqueous phase was then washed with a further three portions of 25 ml CH_2Cl_2. The combined CH_2Cl_2 phase was washed with 50 ml of satd aq $NaHCO_3$ and brine, respectively, and dried ($MgSO_4$) to yield 1.58 g of a brownish solid after evaporation. Purification (dry flash chromatography) using CH_2Cl_2 as eluent yielded 1.17 g of **17b** as a white solid in 64% yield.

Mp 206 °C (dec). IR (neat) 3298, 1668, 1437, 1427, 1401, 1265, 1229, 1207, 1154, 744 cm^{-1}. δ_H 2.39 (3H, s), 2.93 (3H, s), 3.76 (3H, s), 3.90 (3H, s), 7.34–7.39 (1H, m), 7.47–7.51 (2H, m), 7.70–7.72 (1H, m), 12.08 (1H, s). δ_C 10.7 (q), 11.5 (q), 30.6 (q), 50.0 (q), 107.2 (s), 109.8 (s), 110.2 (s), 110.6 (d), 118.8 (d), 119.1 (d), 121.0 (d), 121.2 (s), 127.3 (s), 128.0 (s), 134.3 (s), 134.8 (s), 162.2 (s). MS (EI) *m/z* 318 (27), 316 (81) $[M]^+$, 281 (100), 266 (96), 265 (50), 249 (24), 142 (20), 133 (40), 56 (20). Anal. calcd for: $C_{17}H_{17}ClN_2O_2$: C, 64.46; H, 5.41; N, 8.84. Found: C, 64.54; H, 5.46; N, 9.04.



3.1.11. 4-Oxo-1,2,3-trimethyl-pyrrolo[3′,4′:3,4]pyrano[6,5-*b*]-1*H*-indole, 18. The methyl ester **17b** (0.32 g, 1 mmol) was heated at reflux in a mixture of MeOH (10 ml) and 45% $KOH_{(aq)}$ (10 ml). After 3 h, the reaction mixture was quenched with ice/water (100 ml) and acidified with concd HCl and a quantitative yield (0.27 g) of the indolo-2-pyranone **18** was collected as a light brown solid. An analytically pure sample was obtained by recrystallization from 2-propanol.

Mp 325–329 °C (dec). IR (neat) 3178, 1679, 1406, 984, 763 cm^{-1}. δ_H 2.57 (3H, s), 2.68 (3H, s), 3.52 (3H, s), 7.09–7.12 (2H, m), 7.34–7.37 (1H, m), 7.87–7.90 (1H, m), 11.86 (1H, s). δ_C 11.0 (q), 12.4 (q), 30.6 (q), 87.9 (s), 100.9 (s), 111.5 (d), 115.4 (s), 117.2 (s), 119.4 (d), 119.9 (d), 120.5 (d), 121.3 (s), 131.1 (s), 135.8 (s), 146.2 (s), 158.2 (s). MS (EI) *m/z* 266 (100) $[M]^+$, 265 (66), 238 (22), 56 (21). FABHRMS Calcd for $C_{16}H_{14}N_2O_2$ $[M]^+$ 266.1055 found 266.1057.

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