ELSEVIER

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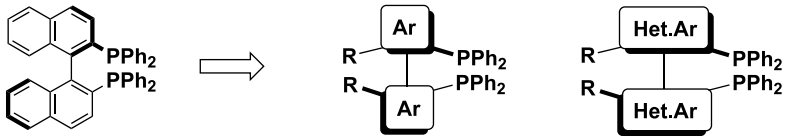
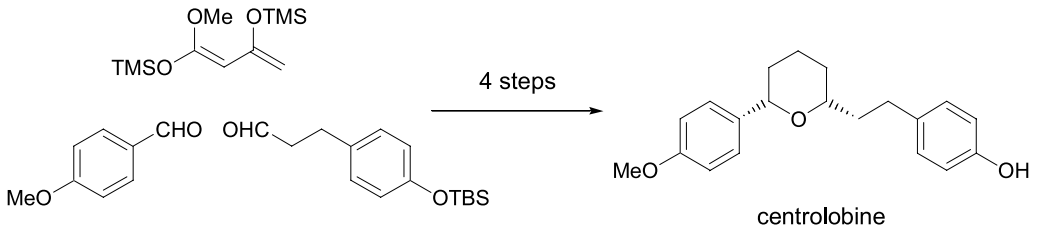
Contents

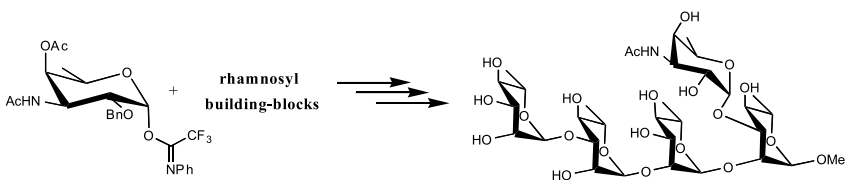
REPORT

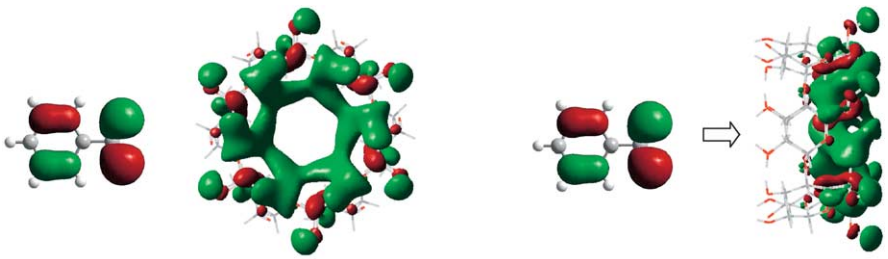


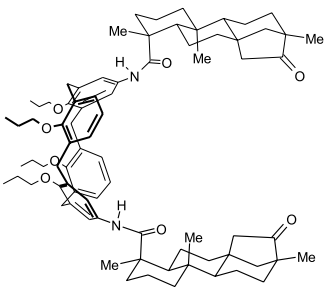
Biaryl-type bisphosphine ligands of recent vintage and their effective applications to asymmetric syntheses are reviewed. The report contains 155 references.

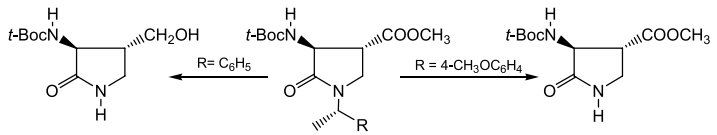
ARTICLES

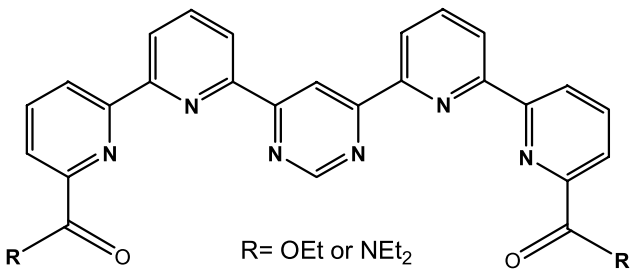


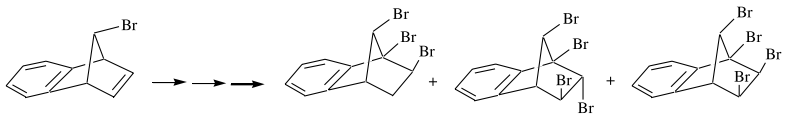




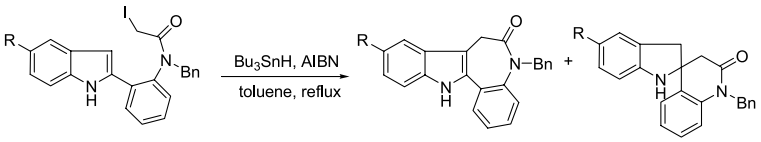


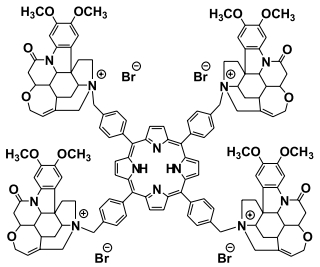


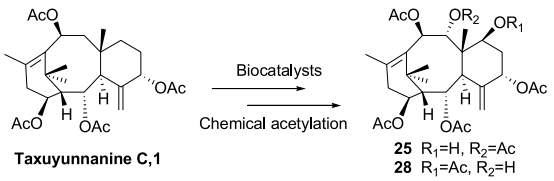




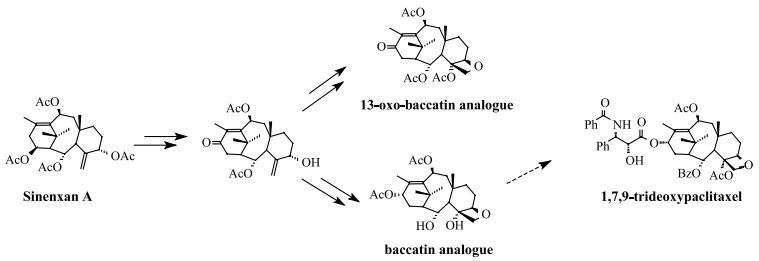
The low and high temperature bromination reactions of bromobenzonorbornadiene derivatives were studied and the possible role of a neighboring group in rearrangements was investigated.

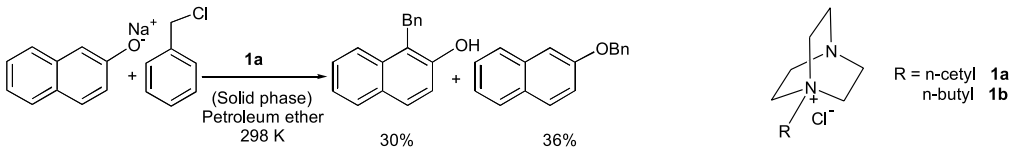




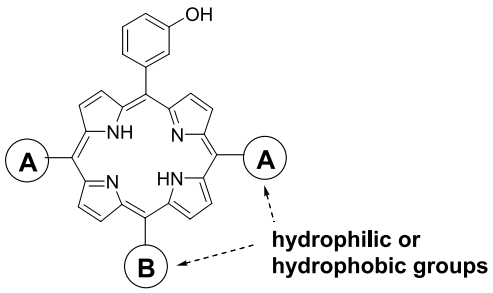


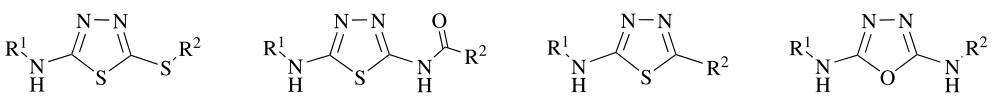
With the aid of chemical acetylation, the selective 9α- and 7β-oxidation of taxuyunnanine C by cell suspension cultures of *Ginkgo biloba* L. and the fungus *Abisidia coerulea* IFO 4011 were successfully combined by subsequent biotransformation.

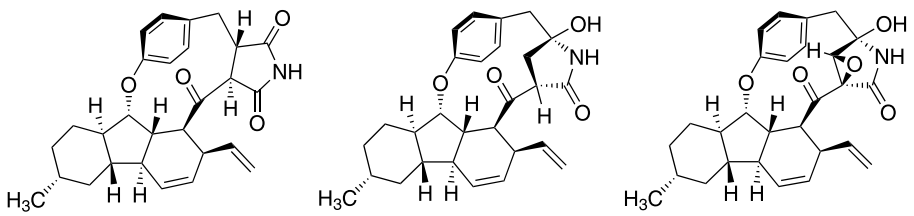




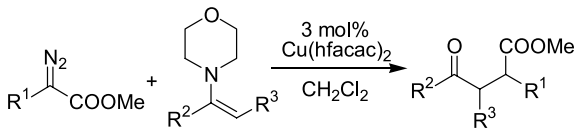
Two triphase catalysts (SLL) **1a**, **1b** have been developed for organic phase–aqueous phase reactions by suitable modified clay (solid phase). These triphase catalysts have been applied to nucleophilic displacement reactions.



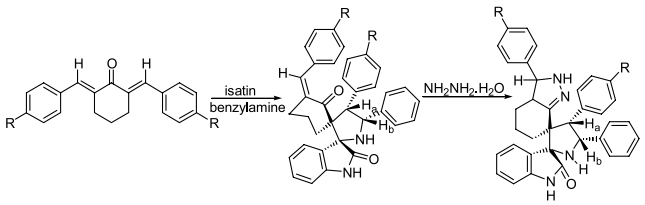


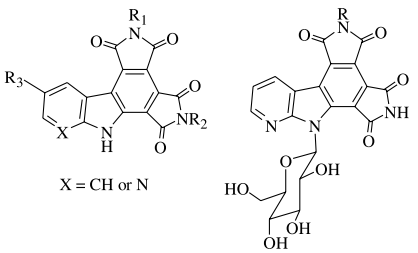


hirsutellone A (**1**) hirsutellone B (**2**) hirsutellone C (**3**)

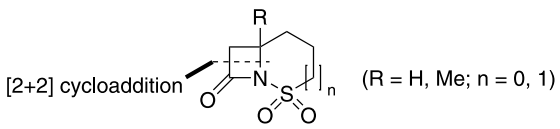


The reaction of aryldiazoacetates with enamines, catalyzed by copper and dirhodium complexes provides exclusively gamma-ketoesters in high yield.

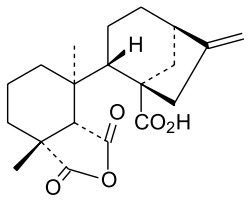




X = CH or N



The microbiological transformation of 7-oxo-*ent*-kaur-16-ene by *Gibberella fujikuroi* gave fujenoic acid (**27**) as the main compound, whilst the incubation of 18-hydroxy-7-oxo-*ent*-kaur-16-ene and 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene afforded the corresponding 6β-hydroxy derivatives. These facts indicated that the formation of fujenoic acid in this biotransformation should occur via a 7-oxo-6β-hydroxy derivative.



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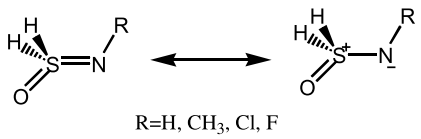
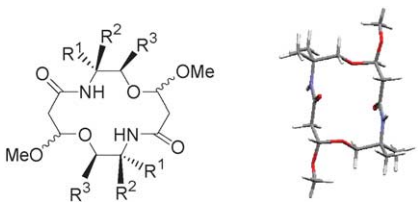
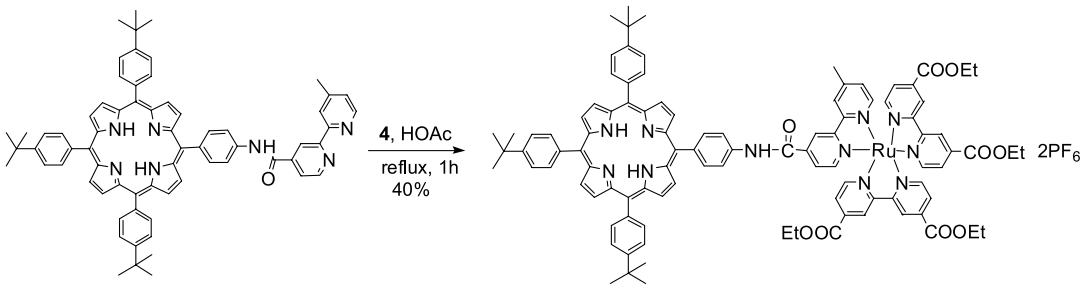
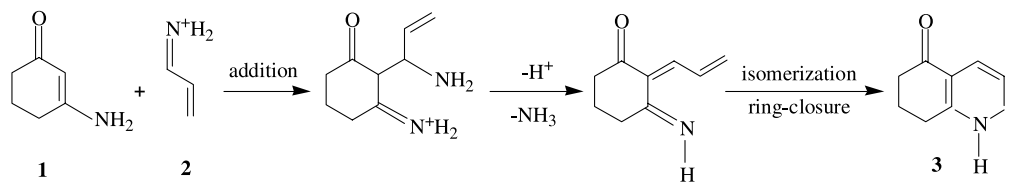
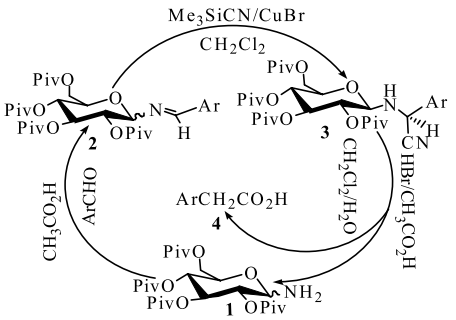
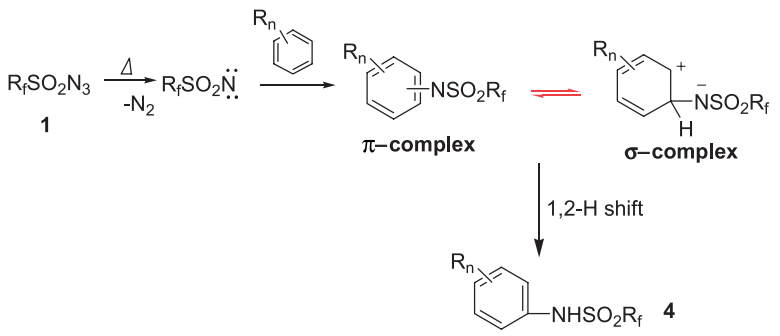


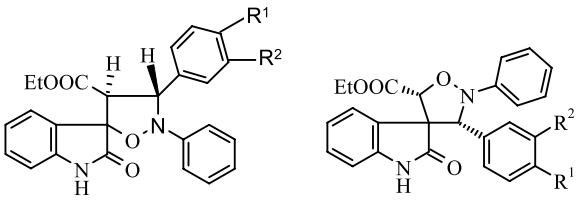




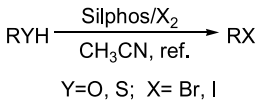








Microwave mediated synthesis of regioisomeric spiro-(indoline-isoxazolidines) has been described. These compounds were found to exhibit moderate anti-mycobacterial and anti-invasive activities.



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Recent advances in biaryl-type bisphosphine ligands

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Contents

1. Introduction

The demand for optically active compounds is increasing in the pharmaceutical, agrochemical, fragrances, and flavors industries, among others.[1] Requirements by the U.S. FDA for 'chiral drugs', along with an increasing demand for atom

Keywords: Bisphosphine ligands; Biaryl ligands; Chiral ligands.
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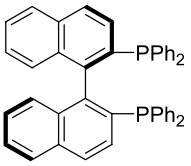
economy and efficiency, have accelerated intense interest to this day.[2] In meeting the demand, asymmetric synthesis has played a significant role that is on a par with other methods, including optical and enzymatic resolutions.[3] Acknowledgement of the importance of this field led to the recent awarding of the 2001 Nobel Prize to W. S. Knowles, R. Noyori, and K. B. Sharpless for their exceptional contributions to asymmetric syntheses.[4]

Striking progress in this area has been made due to developments in organometallic chemistry, in particular where a chiral ligand creates an asymmetric environment around a metal. Researchers worldwide have designed and synthesized large numbers of ligands aiming for greater levels of selectivity, among which chiral diphosphines represent a large category.[1b,5] BINAP, **1a**, developed by Noyori and Takaya,[6] is one the most effective, affording high enantioselectivities in an exceptionally wide variety of reaction types, forming complexes with various metal atoms.[7]



BINAP **1a**

For more than a quarter of a century, since its appearance, BINAP has been the ligand of choice in the majority of asymmetric syntheses. The scaffold that imparts high levels of chiral induction is based on a chiral biaryl backbone. Inspired by the success of BINAP, analogues with various biaryl skeleta have been prepared using several working hypotheses anticipated to lead to enhanced activities and enantioselectivities. These modifications of the biaryl framework are essential if further improvements in their steric and electronic environment are to be realized.

In this paper, we review the efforts to develop ligands beyond BINAP, focusing on biaryl ligands. We discuss chiral bisphosphine ligands post-BINAP; that is, newer ligands that contain a biaryl backbone, the design concepts behind them, as well as their applications to asymmetric syntheses.

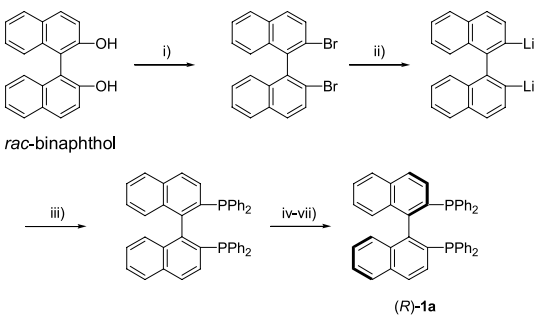
The next section presents a short historical overview of the monumental ligand, BINAP. The background leading to its development along with some of its prominent applications are discussed. The third section elucidates the rationale behind BINAP's selectivity, which forms the basis for further progress in ligand design. In the fourth section, we deal with biaryl ligands of more recent vintage. The fifth section summarizes applications of newly introduced biaryl ligands, and is intended to identify trends resulting from ligand fine-tuning. Attention focuses on BINAP 'descendants' that vary in terms of the nature of the backbone to which is attached two dialkyl- or diaryl-phosphino groups, and their applications to homogenous asymmetric catalysis. Other types of phosphorus-based substituents, such as phosphine-oxide–phosphine,[8] or related ligands aimed at applications of BINAP chemistry to other media[9] have already been reviewed.

2. Historical overview

As BINAP was originally designed for asymmetric hydrogenation, it is inevitable to start with the development of this reaction type and associated early chiral ligands.

In the 1960s many new discoveries were reported which had great impact on later asymmetric hydrogenations; for example, homogeneous catalytic hydrogenation with Ru(II) by Halpern[10] and [$RhCl(PPh_3)_3$] by Wilkinson[11] as well as heterogeneous asymmetric hydrogenation using fibroin supported Pd catalysts.[12] These findings led to the first homogeneous catalytic hydrogenations using a Rh catalyst ligated by chiral phosphines of moderate selectivity, independently developed by Knowles[13] and Horner.[14] The first breakthrough was made by Kagan using a DIOP–Rh complex, yielding a 72% ee in asymmetric hydrogenation of dehydroamino acid derivatives.[15] DIOP not only attracted researchers' attention to this reaction, but also provided an important guideline for future developments; that is, using bidentate phosphines with C_2 symmetry. Of the many chiral bidentate ligands subsequently prepared, DIPAMP, developed by Knowles, displayed outstanding catalytic activity along with high enantioselectivity, observations which were soon applied to the industrial production of L-DOPA.[16]

Meanwhile, the binaphthyl framework was attracting attention as a chiral template.[17] Optical resolution using chiral crown ethers by Cram[18] and reductions using BINAL-H by Noyori[19] are some notable examples. Several groups were simultaneously working to synthesize a diphosphine analogue within the binaphthyl framework. In 1980, Noyori and Takaya finally succeeded in synthesizing enantiomerically pure BINAP.[6a] Although its early application was limited to conventional Rh-catalyzed hydrogenations, Noyori soon made several breakthroughs including development of a BINAP–Ru complex,[20] which afforded high enantioselectivity in asymmetric hydrogenations of a wide range of olefins[21] and functionalized ketones.[22] In

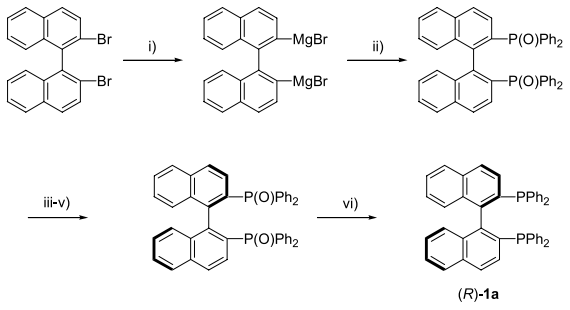


i) Br_2, PPh_3; ii) *t*-BuLi; iii) $ClPPh_2$
iv) di-μ-Cl-bis[(*S*)-dimethyl(α-methylbenzyl)aminato-C^2N]Pd_2
v) $NaBPh_4$; vi) fractional recrystallization; vii) $LiAlH_4$

Scheme 1. Synthesis of BINAP **1a** (Noyori and Takaya).

1995, the Ru-BINAP/diamine complex was discovered as an efficient catalyst for unfunctionalized ketones.[23]

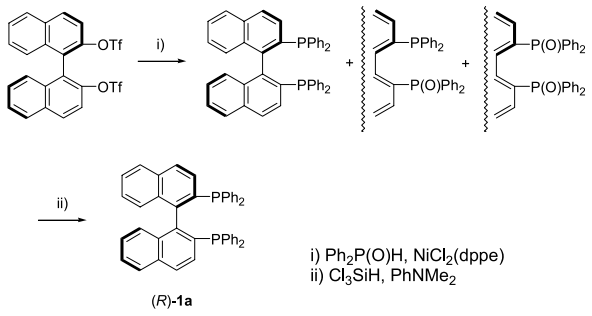
The synthesis of BINAP has continued to evolve. Initially, the ligand was prepared via optical resolution using a derived Pd complex.[6] Racemic BINAP was synthesized by exposing a dilithio species formed from 2,2′-dibromo-1,1′-binaphthyl with chlorodiphenylphosphine (Scheme 1). This method was then replaced by a more economical approach: optical resolution of the corresponding diphosphine oxide of BINAP using camphorsulfonic acid or 2,3-*O*,*O*-dibenzoyl tartaric acid (Scheme 2).[24] This method, which exploits the weak basicity of a phosphine oxide, still remains as one of the standard methods for the optical resolution of chiral bisphosphines.



i) Mg; ii) ClP(O)Ph_2
iii) (+)-camphorsulfonic acid/ acetic acid or (2*R*,3*R*)-di-*O*,*O*-benzoyltartaric acid
iv) fractional recrystallization; v) NaOH; vi) Cl_3SiH, $PhNMe_2$

Scheme 2. Synthesis of BINAP **1a** via optical resolution of the corresponding phosphine dioxide.

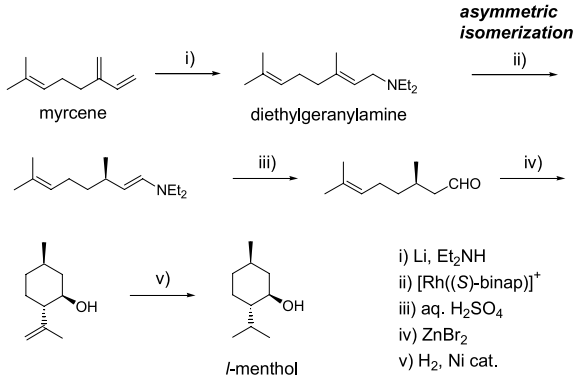
The demand for easier, more efficient access to enantiomerically pure BINAP led to synthetic methods with direct introduction of phosphinyl groups onto an optically active binaphthyl framework. Cai developed a Ni-catalyzed coupling reaction between the ditriflate of optically active binaphthol and diphenylphosphine,[25] whereas Laneman used the optically active ditriflate and chlorodiphenylphosphine.[26] Kumobayashi developed a method using the ditriflate and easy-to-handle diphenylphosphine oxide, giving a mixture of BINAP, its monoxide and its dioxide.[3b,27] The mixture was then reduced with trichlorosilane to give BINAP in high yield (Scheme 3). These methods enjoy a synthetic advantage because the same procedure can be used for syntheses of BINAP variants with different phosphine pendants, using the corresponding phosphine oxides in place of the parent diphenylphosphine oxide.



i) $Ph_2P(O)H$, $NiCl_2(dppe)$
ii) Cl_3SiH, $PhNMe_2$

Scheme 3. Synthesis of BINAP **1a** via ditriflate derived from optically active binaphthol.

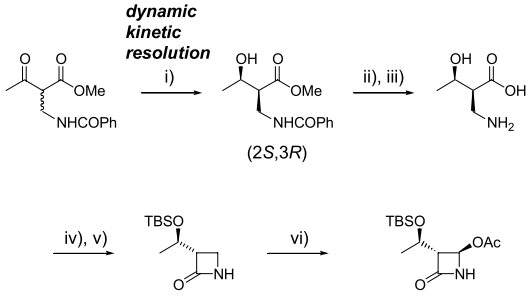
The first industrial process using BINAP was for the purpose of asymmetric isomerization of diethylgeranylamine. Using the finding by Tani and Otsuka,[28] Takasago International Corporation started production of *l*-menthol in 1984. The catalyst turnover number for this asymmetric isomerization exceeds 300,000. This process currently supplies 1000–1500 tons of the product per year, one third of the world supply of synthetic *l*-menthol[3a,29] (Scheme 4).



Scheme 4. Commercial process for *l*-menthol.

Several asymmetric hydrogenations have been developed for use on an industrial scale.[3] Shown below is a synthetic scheme to arrive at a key intermediate of the carbapenem antibiotics.[3a] The key reaction is an asymmetric hydrogenation accompanied by a dynamic kinetic resolution (Scheme 5).[30]

Inspired by the academic and industrial success of BINAP, numerous ligands with different biaryl frameworks have been designed and synthesized in attempts to achieve higher enantioselectivities, greater catalytic activity, and easier access. Biaryl ligands now represent a considerable share in the area of chiral ligands.



i) H_2, (*R*)-Tol-BINAP-Ru(II); ii) HCl; iii) NaOH
iv) *N*-*t*-butyl-2-benzothiazolesufenamide, PPh_3
v) TBSCl, imidazole; vi) $RuCl_3{\cdot}nH_2O$, AcO_2H, AcONa

Scheme 5. Industrial process to prepare a chiral intermediate en route to carbapenem antibiotics.

3. Structural features of biaryl ligands

With respect to the structural background of biaryl ligands, the salient, fundamental requirement for chiral ligands is atropisomerism:[31] the phenomenon of axial chirality caused by restricted rotation about a single C–C bond (Figure 1). Extensive studies on atropisomerism of biphenyls showed that most tetra-*ortho*-substituted biphenyls are quite stable towards racemization, unless at least two of the groups are fluorine or methoxy.[31] As has been empirically shown by their existence in enantioenriched form, with few exceptions, tetra-*ortho*-substituted biaryl and heteroaryl bisphosphine ligands display atropisomerism, which enables them to serve as chiral ligands.

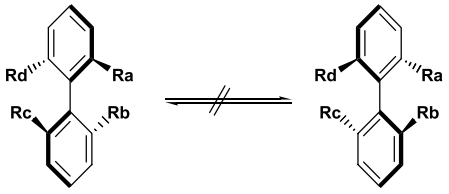


Figure 1. Atropisomerism.

BINAP forms complexes with an exceptional number of metal atoms, a phenomenon attributable to its key features: flexibility of its C(1)–C(1′) binaphthyl axis, and flexibility to control the electronic properties of the appended diarylphosphine residue. Taking advantage of these two features, BINAP has been used in a variety of applications in organic synthesis. The potential for variations in BINAP was seen in X-ray structures that showed different dihedral angles for different metal complexes. For example, the dihedral angle of a BINAP–Rh complex is 74.4°[32] whereas that of a related BINAP–Ru complex is 65.6°.[33]

X-ray analyses also show some of the common structural features of metal complexes ligated by biaryl ligands. In the case of BINAP, X-ray determinations of its Rh,[6,32,34] Ru,[24a,33,35] and Pd[36] complexes have been reported. All show images similar to that illustrated in Figure 2. These crystal structures provide an insight regarding the origin of enantioselectivity. A seven-member chelate is formed by coordination of both phosphine atoms to a metal center. The four phenyl groups on phosphorus are arranged in an edge-face style: two phenyl groups being in an axial array, whereas the other two counterparts are located on an equatorial side. Those in the axial orientation place the phenyl groups parallel to the naphthyl ring of the biaryl skeleton. Equatorial phenyl groups are arranged accordingly to yield selectivities.[37]

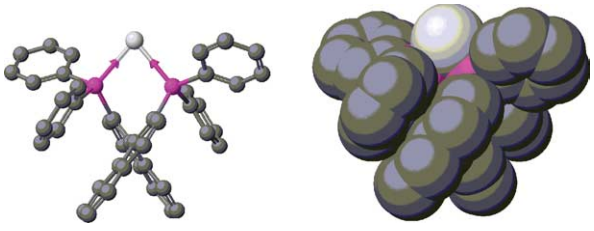


Figure 2. Top view of the (*R*)-BINAP–Ru complex.

The origin of enantioselectivity is well accounted for on the basis of the quadrant rule.[38] When looking at the BINAP complex from the side, the two equatorial phenyl groups spatially occupy, and thus block, two opposite quadrants. In the case of (*R*)-BINAP, two equatorial phenyl groups shield the second and the fourth quadrants (Fig. 3), whereas in (*S*)-BINAP it is the first and the third quadrants that are occupied.

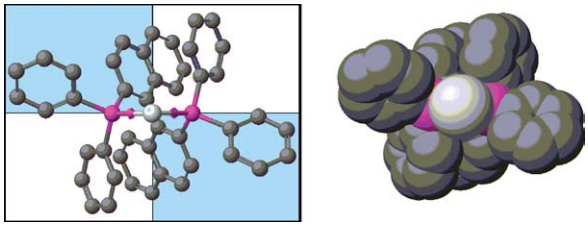


Figure 3. Side view of the (*R*)-BINAP–Ru complex.

During a reaction, a substrate approaches a metal so as to minimize steric interactions with the equatorial phenyl groups. Figure 4 illustrates the favored and disfavored transition states of Ru-catalyzed asymmetric hydrogenation of a β-ketoester. Transition state 2 (TS-2) suffers from steric repulsion between the alkyl group of the substrate and an equatorial phenyl group. Transition state 1 (TS-1) avoids this steric repulsion, allowing the reaction to proceed, yielding the (*R*)-isomer as the major product.[4b]

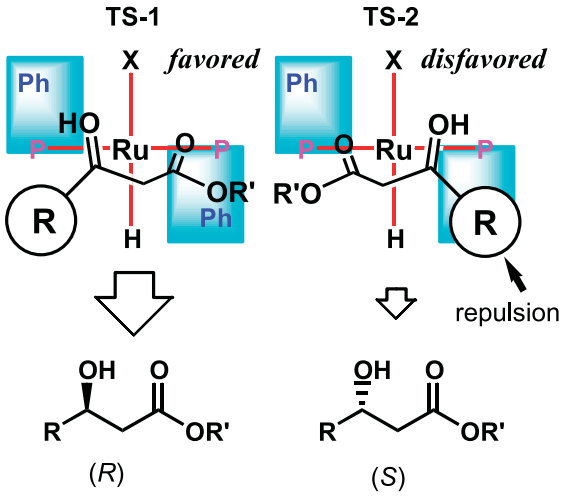


Figure 4. Transition state model for asymmetric hydrogenation of a β-ketoester.

4. Biaryl ligands reported to date

Many different rationales lie behind the development of new biaryl bisphosphine ligands. New ligands are generally developed in an effort to (1) afford higher enantioselectivities; (2) enhance catalytic activity; (3) increase

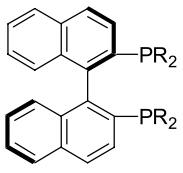
synthetic accessibility; and (4) circumvent patents on existing ligands. In most cases, the ligands are targeted for use in asymmetric hydrogenation, asymmetric isomerization, and asymmetric Heck reactions.

This section offers an up-to-date, yet abridged view of the design, synthesis, and properties of many biaryl bisphosphine ligands. For convenience, all ligands will be illustrated as their (*R*)-isomers unless otherwise noted.

4.1. C_2 symmetric ligands

As is the case with the majority of newly introduced chiral ligands, the concept of C_2 symmetry has been adopted as a basic principle in the development of biaryl bisphosphine ligands.[39] The advantage of C_2 symmetry is that it reduces the number of possible diastereomeric transition states that would compete during a reaction.

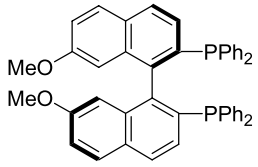
4.1.1. Binaphthyl backbones. Since BINAP's initial synthesis, a considerable number of analogues have been synthesized.[40] The most convenient and straightforward way of modifying BINAP is to replace the 2- and 2′-diphenylphosphino groups with other disubstituted phosphino groups. Representative examples **1b–1k** are shown in Figure 5. Replacement of the 2- and 2′-diphenylphosphino groups serves to either augment or attenuate both the steric and electronic properties of the ligand, thus impacting on its catalytic character. This type of modification, in principle, is applicable to most of the ligands in the biaryl family and is one way to tailor each ligand to maximize its capability for a specific application.



R = 4-MeC_6H_4:	Tol-BINAP **1b**
4-*t*-BuC_6H_4:	*t*-Bu-BINAP **1c**
4-$MeOC_6H_4$:	MeO-BINAP **1d**
3,5-$Me_2C_6H_3$:	DM-BINAP **1e**
3,5-(*t*-Bu)$_2C_6H_3$:	DB-BINAP **1f**
4-MeO-3,5-$Me_2C_6H_2$:	DMM-BINAP **1g**
c-Cy:	Cy-BINAP **1h**
2-furyl:	TetFu-BINAP **1i**
4-FC_6H_4:	*p*-F-BINAP **1j**
4-ClC_6H_4:	*p*-Cl-BINAP **1k**

Figure 5. BINAP variants.

Many groups have attempted to further extend the versatility of BINAP by attaching the ligand to a solid support or by functionalizing the ligand with hydrophobic or hydrophilic groups.[9] Various functionalized BINAP species were created as intermediates en route to the ligands described above. The utility of these intermediates was tested in homogeneous media. Originally developed by Cai et al. as an intermediate in the construction of immobilized BINAP,[41] the 7,7′-dimethoxy analogue of BINAP, **2** was investigated in asymmetric Heck reactions by Keay et al.[42] Use of the 7,7′-disubstituted ligand resulted in either an increase or a decrease in enantioselectivity when compared with BINAP, depending on the coupling partners. *Diam*-BINAPs **3–5**,[43] intermediates in the synthesis of the heterogeneous catalyst, *poly*-NAP, also afforded comparable enantioselectivities when utilized in asymmetric hydrogenations in homogeneous media.



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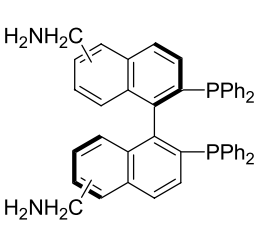
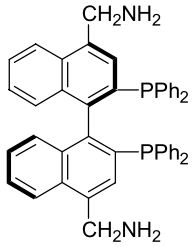
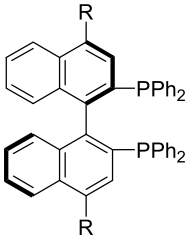


6,6′-*diam*-BINAP: **3**
5,5′-*diam*-BINAP: **4**



4,4′-*diam*-BINAP: **5**

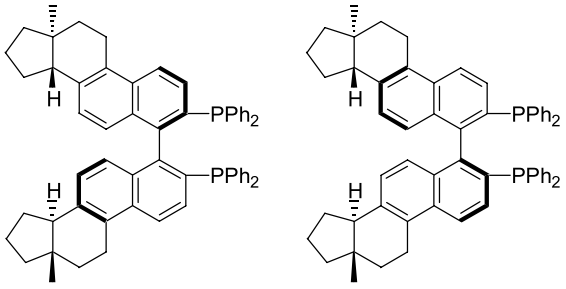
Recently, Lin et al. reported on the efficiency of 4,4′-disubstitution of BINAP in asymmetric hydrogenations.[44] They discovered that the 4,4′-derivatives **6**, some initially developed for biphasic catalysis,[45] have a considerable impact on enantioselectivity in asymmetric hydrogenation of β-aryl-β-ketoesters[44a] and aryl ketones.[44b]



6

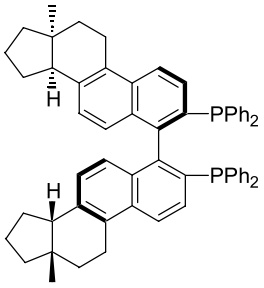
R = $P(O)(OH)_2$, $SiMe_3$, $CPh_2(OH)$, $P(O)(OEt)_2$, I, Br, Cl, Ph, etc.

Utilizing the naturally occurring steroid, equilenin, Mohr et al. were able to synthesize bis-steroidal BINAP analogues **7** and **8**.[46] Diastereomers can easily be separated via column chromatography, avoiding troublesome optical resolution steps. However, as the stereochemistry of the steroidal moieties is not expected to impact on the enantioselective functionality of the ligands, diastereomers **7** and **8** can essentially be treated as axial enantiomers. Ligands **9** and **10** were also synthesized, showcasing alternative stereochemical patterns at the bridgehead positions of the [4.3.0]-bicyclic system.[47]

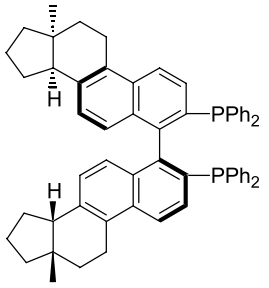


7 (*aR*)

8 (*aS*)



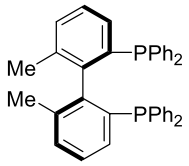
9 (*aR*)



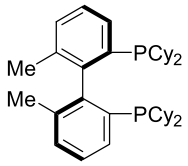
10 (*aS*)

4.1.2. Biphenyl backbones. The biphenyl framework has two major advantages over its binaphthyl counterpart. One is that the dihedral angles of the biaryls may be easily fine tuned by controlling the size of the substituents at the 6- and 6′-positions. Another advantage is that the basicity at phosphorus can be adjusted simply by introducing substituents with differing electronic properties onto the biaryl. Based on these ideas, numerous ligands in this category have been designed. Since so many biphenyl ligands have been synthesized, these will be roughly classified into three categories: (1) biphenyl ligands with carbon atoms at the 6,6′-positions (BIPHEMP type); (2) those with oxygen atoms at the 6,6′-positions (MeO-BIPHEP type); and (3) other ligands.

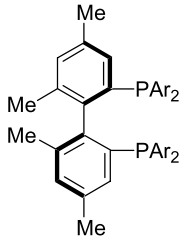
4.1.2.1. BIPHEMP type. The first ligand in this category, ligand **11a**, was developed in the mid-1980s independently by both Schmid[48] and Frejd:[49] referred to as BIPHEMP and BIMEP, respectively. The ligand is effective in a variety of reactions such as asymmetric hydrogenations[50] and asymmetric isomerization.[48b] At this time, Schmid also synthesized ligand **12a** with added methyl groups, ligand **13** with dimethylamino groups, and bridged ligand **14** designed specifically to lock the dihedral angle and afford a more rigid framework. These ligands all afforded enantioselectivities comparable to those of BINAP when applied to asymmetric isomerizations.[48b] A dicyclohexyl analogue of **11a**, BICHEP **11b**, was developed by Takaya,[51] and a bis(3,5-dimethylphenyl)phosphino analogue of **12a**, Xyl-TetraPHEMP **12b**, was recently developed by Moran.[52] The latter has the synthetic advantage of being prepared from *tris*(3,5-dimethylphenyl)phosphine oxide.



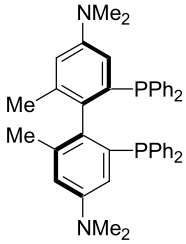
BIPHEMP (BIMEP) **11a**



BICHEP **11b**



Ar = Ph: **12a**
3,5-$Me_2C_6H_3$:
Xyl-TetraPHEMP **12b**



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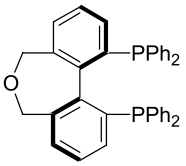
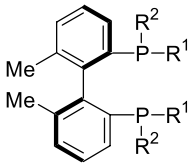


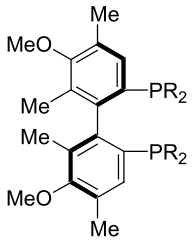
14

Cereghetti has synthesized similar ligands with chirality on the phosphorus atom, **11c** and **11d**[53] although applications have yet to appear in the literature.

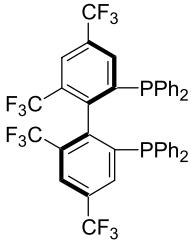


R^1 = Ph, R^2 = *c*-Cy: **11c**
R^1 = Ph, R^2 = *t*-Bu: **11d**

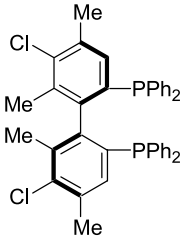
Based on evidence that installation of electron-donating groups, such as methyl or methoxy, on phenyl residues in BPPM and DIOP result in higher catalytic activity in asymmetric hydrogenations,[54] Achiwa synthesized BIMOPs **15a**–**15c**.[55] BIMOP gave slightly higher ees than BINAP in the asymmetric hydrogenations of methyl 3-oxobutanoate and tiglic acid.[55a] Achiwa also prepared BIFUP **16**, an electron-deficient ligand with CF_3 groups on the backbone.[55b,56] As expected, Ru complexes ligated by BIFUP resulted in low catalytic activity. Takasago patented a related ligand, CM-BIPHEMP **17**.[57]



R = Ph: BIMOP **15a**
4-$MeOC_6H_4$:
p-MeO-BIMOP **15b**
c-Cy: Cy-BIMOP **15c**



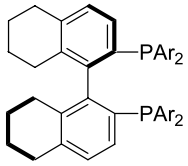
BIFUP **16**



CM-BIPHEMP **17**

The partially hydrogenated BINAP analogue, H_8-BINAP **18a** and relating **18b** were developed by Takaya.[58] The most interesting feature of this ligand is its wide dihedral angle, most likely a result of steric repulsion generated by the sp^3

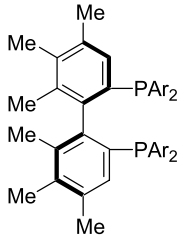
carbon atoms of each tetralin moiety. An X-ray crystallographic study shows the dihedral angle between the two aryls in its Rh complex to be 80.3°, which is considerably larger than that in BINAP (74.4°) or BIPHEMP (71.8°). H_8-BINAP generally gives higher enantioselectivity and catalytic activity than similar ligands when applied to asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[59] An explanation for the effect of large dihedral angles is this: a larger dihedral angle results in a more crowded equatorial coordination and a less crowded apical site. That is, increased steric hindrance around the equatorial site contributes to a more selective approach of an olefin substrate to the Ru metal, while decreased hindrance around the apical site accelerates the hydrogenolysis of the Ru–C bond by hydrogen.[59b]



Ar = Ph: H_8-BINAP **18a**

3,5-$Me_2C_6H_3$: DM-H_8-BINAP: **18b**

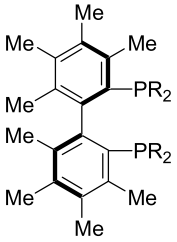
Chirotech Technology Ltd. recently described HexaPHEMP **19a** as a practical ligand.[60] This bisphosphine gives comparable enantioselectivities with BINAP in asymmetric hydrogenations of β-enamides and imines.[60b,61]



Ar = C_6H_5: HexaPHEMP **19a**

3,5-$(CH_3)_2C_6H_3$: Xyl-HexaPHEMP**19b**

Imamoto synthesized ligands **20a**–**20c** with additional methyl groups at the 3- and 3′ positions and applied these to Rh-catalyzed asymmetric hydrogenations of an enamide.[62] The diethylphosphine ligand **20c** was synthesized based on the idea that the stereochemical influence by the backbone should be maximized in a ligand with smaller phosphine pendants.



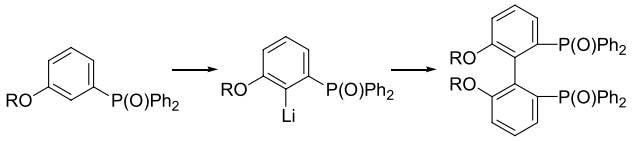
R = Ph: **20a**

c-Cy: **20b**

Et: **20c**

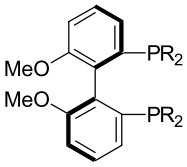
4.1.2.2. MeO-BIPHEP type. The large number of ligands synthesized in this category is likely to be due to their ease of preparation. Biphenyl frameworks are prepared through directed lithiation, made feasible due to an adjacent alkoxy group, followed by biaryl coupling[63] (Scheme 6).

Schmid developed the first ligand within this category, MeO-BIPHEP **21a**.[63,64] As with BINAP, it can be utilized in a wide variety of applications, some of which are amenable



Scheme 6. Directed lithiation followed by biaryl coupling.

to scale up. Hoffmann-La Roche has extensively developed this ligand framework, with more than 60 variations of substituents at phosphorus (e.g., **21b**–**21h**).[64b]



R = Ph: MeO-BIPHEP **21a**

4-MeC_6H_4: **21b**

3,5-$Me_2C_6H_3$: **21c**

3,5-(t-Bu)$_2C_6H_3$: **21d**

4-MeO-3,5-$Me_2C_6H_2$: **21e**

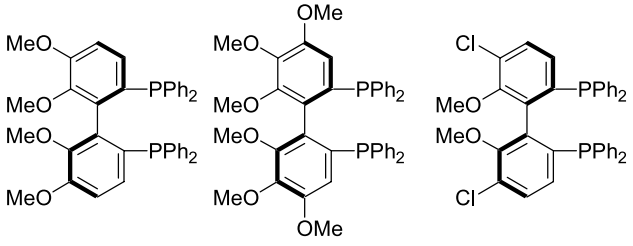
4-MeO-3,5-(t-Bu)$_2C_6H_2$: **21f**

c-Cy: **21g**

2-furyl: **21h**

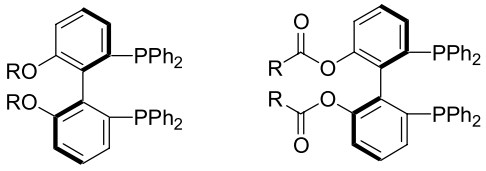
> 60 analogues

At the time MeO-BIPHEP was being synthesized, other ligands with more methoxy groups on the biphenyl backbone **22** and **23** were also under development.[63] Later, Bayer AG developed Cl-MeO-BIPHEP **24**.[65]



22 **23** Cl-MeO-BIPHEP **24**

The dihydroxy **25** and di(trimethylsilyloxy) **26** analogues were originally used for further functionalization, although they have been applied to asymmetric isomerizations of geranyl- and neryl-amine.[66] They gave high, yet slightly lower, enantioselectivities than those realized using BINAP and MeO-BIPHEP. On the other hand, PPG-Sipsy developed carbonyloxy analogues, Soniphos **27** and **28**.[67]



R = H: **25**

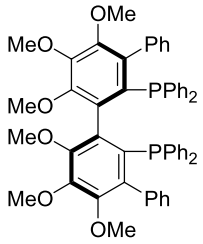
$SiMe_3$: **26**

R = Me: Methyl Soniphos **27**

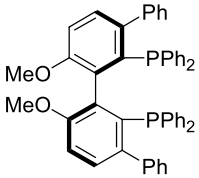
c-Cy: Cyclohexyl Soniphos **28**

Zhang reported a ligand substituted by phenyl groups at the 3,3′-positions, *o*-Ph-hexaMeO-BIPHEP **29**.[68] It was postulated that the phenyl groups not only restricted rotation of the equatorial phenyl group, but also made their protrusion larger compared to those in ligand **23**. The *o*-substitution dramatically increased enantioselectivities in Rh-catalyzed asymmetric hydrogenations of cyclic enamides.[68] Recently,

they also reported *o*-Ph-MeO-BIPHEP **30**, which is very effective for asymmetric hydrogenations of enamides.[69]

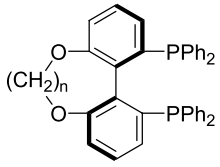


o-Ph-hexaMeO-BIPHEP **29**



o-Ph-MeO-BIPHEP **30**

Recently, dihedral angle control is attracting more attention in an effort to explain observed enantioselectivities. Zhang proposed that BINAP and MeO-BIPHEP occasionally fail to achieve high chiral induction due to their non-rigid biaryl backbones. To determine the importance of the dihedral angle, they synthesized a series of bridged ligands with different alkyl linkers (C_n-TunaPHOS **31**–**36**).[70] They examined the relationship between dihedral angles of the ligands and enantioselectivities in asymmetric hydrogenations.[70a,71] The ligand which gave the highest ees varied by substrates: C_4-TunaPHOS for β-ketoesters,[70b] C_1 and C_2-TunaPHOS for enol acetates,[71a] C_3-TunaPHOS for α-phthalimideketones,[71b] and C_2–C_5-TunaPHOS for β-acylaminoacrylates.[71c]

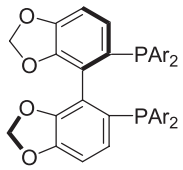


n =1: C_1-TunaPHOS **31**
2: C_2-TunaPHOS **32**
3: C_3-TunaPHOS **33**
4: C_4-TunaPHOS **34**
5: C_5-TunaPHOS **35**
6: C_6-TunaPHOS **36**

ligand	**31**	**32**	**33**	**34**	**35**	**36**	**1a**
Calc. dihedral angle (deg)	60	74	77	88	94	106	87

Saito et al. focused on the dihedral angle of metal-ligand complexes. They noticed a tendency for ligands with narrower dihedral angles to give higher enantioselectivities in asymmetric hydrogenations of hydroxyacetone (BINAP (73.5°), 89% ee; BIPHEMP (72.1°), 93% ee; MeO-BIPHEP (68.6°), 96% ee). Based on their working hypothesis that narrower dihedral angles would make protrusion of equatorial phenyl groups larger (Fig. 6), they sought a ligand with a dihedral angle narrower than MeO-BIPHEP. This led to the SEGPHOS system **37a** (calculated dihedral angle 65.0°).[72] As expected, the parent ligand gave higher enantioselectivities (>99% ee) in the hydrogenation reaction. SEGPHOS generally gives higher levels of chiral induction in asymmetric hydrogenations of functionalized ketones. Ligands in the SEGPHOS series have also been applied to a variety of reactions, in many cases exceeding results obtained earlier using BINAP.

Chan synthesized BisbenzodioxanPhos **38** as a modifier of H_8-BINAP.[73] The ligand was independently developed by Genêt as SYNPHOS.[74] On the other hand, Solvias developed a ligand with a bis(2*H*-1,4-benzooxazine) framework, Solphos **39**.[75]



Ar = Ph: SEGPHOS **37a**
4-MeC_6H_4: T-SEGPHOS **37b**
3,5-$Me_2C_6H_3$: DM-SEGPHOS **37c**
4-MeO-3,5-$Me_2C_6H_2$: DMM-SEGPHOS **37d**
4-MeO-3,5-(*t*-Bu)$_2C_6H_2$: DTBM-SEGPHOS **37e**

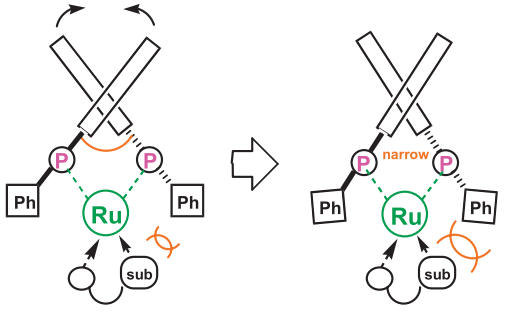
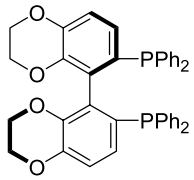
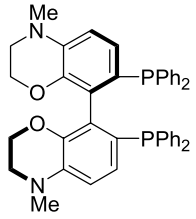


Figure 6. Dihedral angle control.

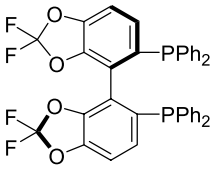


BisbenzodioxanPhos **38**
(SYNPHOS)

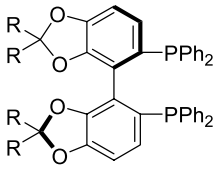


Solphos **39**

Genêt and Schlosser independently developed a ligand with two fluorine atoms on the methylenedioxy moiety **40**.[76,77] The ligand was designed to have more electron deficiency keeping the narrower dihedral angle of **37a**. The ligand gives uniquely higher enantioselectivities in asymmetric hydrogenations of α,α,α-trifluoroketones.[76] The dialkyl analogues on methylenedioxy moiety, **41**–**43**, were also developed recently.[78]

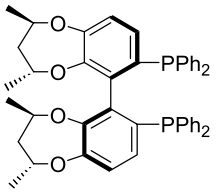


Difluorophos **40**

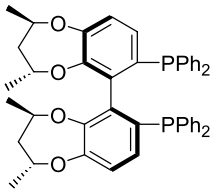


R = Me: **41**
-$(CH_2)_4$-: **42**
-$(CH_2)_5$-: **43**

Chan synthesized an alkylenedioxy-type ligand with an additional sp^3 chiral center at the carbon atoms adjacent to oxygen, illustrated in **44** and **45**.[79] The results of asymmetric hydrogenation of dehydronaproxen showed some impact of the chirality on enantioselectivity.[79]

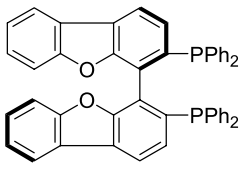


(*R*,*R*,*aR*)-**44**

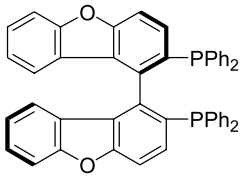


(*R*,*R*,*aS*)-**45**

4.1.2.3. Others. Ligands with bis(dibenzofuran) frameworks have also been designed. Laue et al. synthesized BIBFUP **46**,[80] while Hiemstra et al. synthesized BIFAP **47**.[81] Both ligands gave enantioselectivities practically identical to those of BINAP in asymmetric hydrogenations of β-ketoesters.

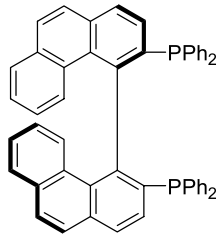


BIBFUP **46**

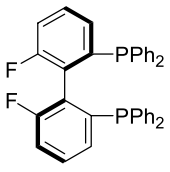


BIFAP **47**

Sumitomo Chemical Co. have patented **48**, a ligand with a bisphenanthrene framework.[82] Jendralla synthesized a 6,6′-difluorinated biphenyl ligand **49**.[83] This electron-deficient ligand was applied to several reactions, but so far catalytic activities have not been satisfactory.



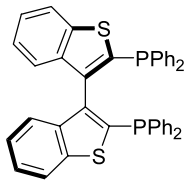
48



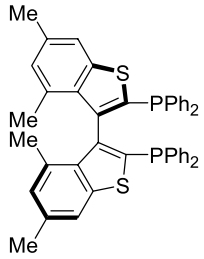
49

4.1.3. Biheteroaryl backbones. Since the mid-1990s a new category of ligands based on biheteroaryl frameworks was introduced. Features of this ligand category are as follows:[84] (1) a wider variety of frameworks is feasible as compared to biaryl ligands; (2) the possibility to synthesize ligands with a variety of electronic properties, as electronic properties of heteroaryl rings impact directly on the electronic properties of the phosphine ligators; and (3) syntheses of these ligands are generally more flexible than those of biaryl ligands.

The ligands in this category were initially developed by Sannicolò et al. They were the first to synthesize BITIANP **50** and TetraMe-BITIANP **51**.[84,85] The ligands are relatively easy to prepare and gave the same or slightly higher enantioselectivities as compared with BINAP in asymmetric hydrogenations of α- and β-ketoesters.[84,85b,86] Furthermore, the ligands gave high enantioselectivities and excellent product selectivities in asymmetric Heck reactions.[87]

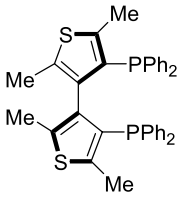


BITIANP **50**

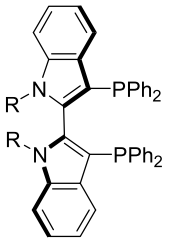


TetraMe-BITIANP **51**

Sannicolò et al. developed TMBTP (tetraMe-BITIOP) **52**,[88] in conjunction with BINPs **53** and **54**,[89] which gave high enantioselectivities in asymmetric hydrogenations.

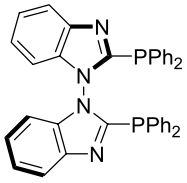


TMBTP **52**
(tetraMe-BITIOP)

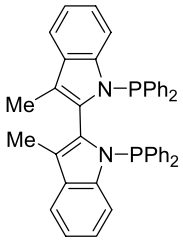


R = Me: N-Me-2-BINP **53**
CH_2OMe: N-MOM-2-BINP **54**

They also synthesized the BIMIP **55** and BISCAP **56** with bisbenzimidazole and bisindole frameworks, respectively.[90] The enantiomers of BIMIP, a ligand with hindered rotation around a N–N bond, have been resolved,[91] although **56** has yet to be isolated in enantiomerically enriched forms.

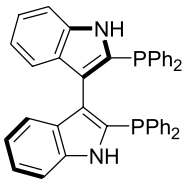


BIMIP **55**



BISCAP **56**

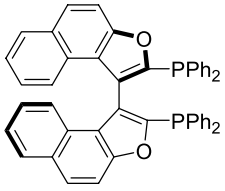
Selke synthesized a 3,3′-bisindolyl ligand **57**, for which no application has been reported thus far.[92]



57

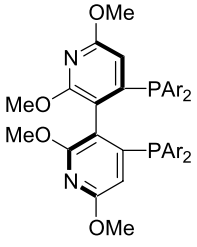
Keay et al. designed BINAPFu **58**, based on the knowledge that trifurylphosphine has a tendency to give a higher catalytic activity than triphenylphosphine in the intermolecular Heck reaction.[93] This ligand proved to be less basic than BINAP, and it is stable towards oxygen. Furthermore, BINAPFu also displays a higher catalytic activity as well as a higher enantioselectivity than BINAP in the asymmetric Heck reaction between dihydrofuran and

phenyl triflate.[93]



BINAPFu **58**

Chan et al. developed ligands with bipyridine backbones, P-PHOS **59a** and its derivatives **59b** and **59c**,[94] during their study on the application of pyridylphosphines to asymmetric hydrogenations. Ru complexes of these ligands gave high enantioselectivities in asymmetric hydrogenations of various substrates, including β-ketoesters,[94] unsaturated α- and β-amino acid derivatives,[95] and arylketones.[96]

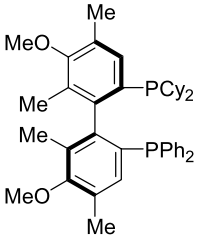


Ar = Ph: P-Phos **59a**
4-MeC_6H_4: T-P-Phos **59b**
3,5-$Me_2C_6H_3$: Xyl-P-Phos **59c**

4.2. C_1 symmetric ligands

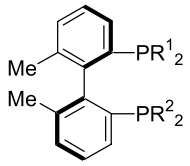
Normally, aside from the presence of a biaryl subunit, the main characteristic of a chiral ligand is that it possesses some element of symmetry. In the majority of cases, this involves C_2 symmetry, but ligands without this feature were synthesized in the early 1990s and can show high enantioselectivity.[97] When developing biaryl ligands, there are two possible means of achieving a highly selective ligand: one is to have a C_2 symmetric backbone with two different phosphino groups, and the other is to have a C_1 symmetric backbone.

4.2.1. With C_2 symmetric backbone. In the early stages of biaryl ligand development, Achiwa synthesized MOC-BIMOP, **15d**, which contains diphenylphosphino and dicyclohexyl groups on the ligand backbone.[98]



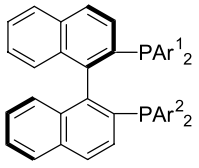
MOC-BIMOP **15d**

Schmid developed BIPHEMP and MeO-BIPHEP ligands, which employ a variety of combinations of phosphino groups.[64b] Specifically, a BIPHEMP ligand with PPh_2 and PCy_2 (**11e**) give the highest catalytic activity and enantioselectivity in Rh-catalyzed asymmetric hydrogenation of a heteroaryl ketone.

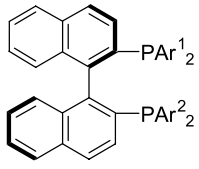


R^1 = Ph, 4-MeC_6H_4
R^2 = 2-furyl, 2-thienyl, *c*-Cy, Cp, *t*-Bu, Et
R^1 = Ph, R^2 = *c*-Cy: **11e**

Gladiali contributed by developing BINAPP′ **1l** containing PPh_2 and P(4-tolyl)$_2$ as the phosphino groups.[99] This ligand has shown slightly higher enantioselectivity than BINAP in asymmetric hydrogenations and allylic alkylations. Hayashi found that *u*-BINAP **1m** gave slightly higher catalytic activity and enantioselectivity in Rh-catalyzed 1,4-additions.[100]

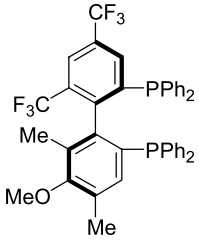


Ar^1 = 4-MeC_6H_4
Ar^2 = Ph
BINAPP' **1l**



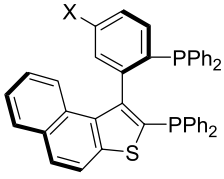
Ar^1 = 4-MeO-3,5-$Me_2C_6H_2$
Ar^2 = Ph
u-BINAP **1m**

4.2.2. With C_1 symmetric backbone. Achiwa developed a ligand with a C_1 symmetric biaryl backbone, FUPMOP **60**.[56,101] The framework of this ligand consists of an electron-rich aryl moiety as well as an electron-deficient bis(trifluoromethyl)benzene moiety. FUPMOP was found to give enantioselectivities comparable to BINAP in asymmetric hydrogenations of β-ketoesters.[56]

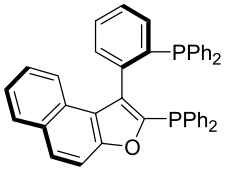


FUPMOP **60**

Sannicolò also developed a series of C_1 symmetric ligands, which can be synthesized in a convenient and inexpensive manner, **61**–**63**.[102] These involve combinations of electron-rich and -poor phosphines.

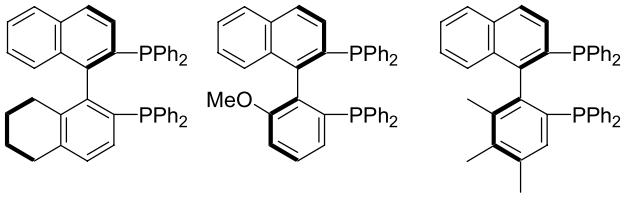


X = H: **61**
OMe: **62**



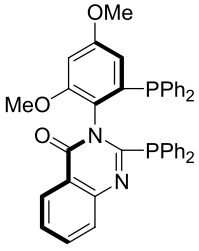
63

Some ligand designs based on previously developed ligands have shown excellent results. For example, Lin synthesized 4*H*-BINAP, **64**,[103] and Genêt developed MeO-NAPhePHOS, **65**[104] and TriMe-NAPhePHOS, **66**.[105] These ligands were found to give comparable enantioselectivity to BINAP in asymmetric hydrogenations.



4H-BINAP **64** MeO-NAPhePHOS **65** TriMe-NAPhePHOS **66**

Lastly, Dai synthesized a ligand with a quinazolinone framework, **67**,[106] although this ligand has yet to be applied to asymmetric reactions.



67

5. Effects of ligand modifications

Although some newly developed biaryl ligands find application to reactions other than asymmetric hydrogenations, isomerizations, or asymmetric Heck reactions, most are designed to be compared with, or exceed, BINAP as the ligand of choice regarding selectivity. In this section, the effects correlated with modification of the biaryl ligands are summarized.

It is well known that the same ligand can evoke different results in a certain reaction, due to different reaction conditions (e.g., different temperature, solvent, additives etc.). Therefore, an effort will be made to evaluate modified biaryl ligands while comparing data obtained using identical reaction conditions throughout the ligand evaluation process. Using the asymmetric hydrogenation of ethyl 4-chloro-3-oxobutanoate as an example, an enantiomeric excess below 70% can be obtained by the use of a BINAP–Ru complex as catalyst at room temperature, whereas carrying out the reaction at 100 °C affords an enantiomeric excess of 97%.[107] Accordingly, the comparison of two different ligands applied in the same reaction but under different reaction conditions would not necessarily reflect the effect caused by the ligand modification. Fortunately, BINAP is mostly used as a standard to examine the impact of newly developed ligands. Based on this data, general tendencies regarding ligand modifications will be discussed. Nevertheless, it remains important to analyze the results obtained with those ligands for which no directly comparable data are available. Therefore, reactions showing excellent results will be emphasized.

In order to better understand the trends caused by ligand modifications, it is helpful to emphasize important ligand characteristics. For the biaryl ligands discussed, three features are considered to be major characteristics in the modification process: the dihedral angle of the biaryl backbone, the electronic properties of the backbone, and the phosphine residue.

Dihedral angles. The dihedral angle has an impact on both the protrusion of the equatorial phenyl groups and the natural bite angle[108] in the respective metal complexes. These are believed to cause both a difference in enantioselectivity and in the catalytic activity in many asymmetric reactions.

Therefore, the dihedral angles of various ligands have been determined and/or calculated in order to establish a relationship with experimental results. The reported values are listed below.

As free ligands

Ligand (dihedral angle):

C_6-TunaPHOS **36** (106°) > C_5-TunaPHOS **35** (94°) > C_4-TunaPHOS **34** (88°) ~ BINAP **1a** (87°) ~ MeO-BIPHEP **21a** (87°) > C_3-TunaPHOS **33** (77°) > C_2-TunaPHOS **32** (74°) > C_1-TunaPHOS **31** (60°); calc.[70b]

1a (86°) > **21a** (72°) > SYNPHOS **38** (71°) > SEGPHOS **37a** (67°) ~ Difluorophos **40** (67°); calc.[76]

BIPHEMP **11a** (88.7°) > **14** (60.5°); X-ray[48b]

BIFAP **47** (81.4°); X-ray[81]

BIMIP **55** (84.2°); X-ray[90]

As Ru complexes

BINAP **1a** (75.7°); as $[RuCl(C_6H_6)(L^*)]BF_4$, X-ray[35b]

1a (74°); as $Ru(L^*)(OCOCMe{=}CHMe)_2$, X-ray[35c]

1a (68.4–70.9°); as $RuHCl(L^*)_2$, X-ray[35a]

1a (65.6°); as $Ru(OCO\text{-}t\text{-}Bu)_2(L^*)$, X-ray[33]

1a (73.5°) > BIPHEMP **11a** (72.1°) > MeO-BIPHEP **21a** (68.6°) > SEGPHOS **37a** (65.0°); calc.[72b]

1a (80°) > **21a** (76°) > SYNPHOS **38** (75°); as intermediates, calc.[74b]

As Rh complexes

BINAP **1a** (74.4°); as $[Rh(L^*)(nbd)]ClO_4$, X-ray[32]

BIPHEMP **11a** (71.8°) > **14** (55.9°); as $[Rh(L^*)(nbd)]BF_4$, X-ray[48b]

H_8-BINAP **18a** (80.3°); as [Rh(L*)(cod)]ClO_4, X-ray[58c]

As Pd complexes

BIFAP **47** (76.2°); $PdCl_2$(L*), X-ray[81]

TetraMe-BITIANP **51** (75.6°) > BITIANP **50** (69.6°), as $PdCl_2$(L*), X-ray[84]

BINAP **1a** (70.2°) > SEGPHOS **37a** (60.1°), as $PdCl_2$(L*), X-ray[109]

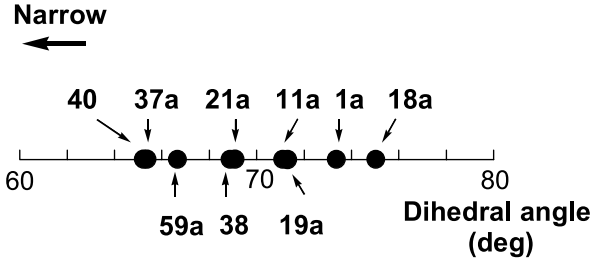
MeO-BIPHEP **21a** (70.3°); as [Pd(L*)($Me_2NCHMeC_6H_4$)]-BF_4, X-ray[63]

BIMIP **55** (67.3°); as $PdCl_2$(L*), X-ray[90]

49 (67.6°); as [Pd(L*)($Me_2NCHMeC_6H_4$)]BF_4, X-ray[83a]

As can be seen from these examples, the orders of magnitude of the dihedral angles are similar, although their values can differ for the same ligand in different complexes.

In this section, the effects caused by the difference in dihedral angle will be discussed. These values are referred to standardized values gained by MM2 calculations.[110] Ru complexes, the most applied complexes in this type of chemistry, were used as a representative series for the calculations. The calculated values for some ligands that found frequent applications to asymmetric hydrogenations are shown in Figure 7. The general magnitude of width is well correlated with those reported above.



L* (calculated dihedral angle: deg):
1a: BINAP (73.5); **11a**: BIPHEMP (71.2);
18a: H_8-BINAP (74.9); **19a**: HexaPHEMP (71.7);
21a: MeO-BIPHEP (69.1); **37a**: SEGPHOS (65.6);
38: BisbenzodioxanPHOS (SYNPHOS) (68.5);
40: Difluorophos (65.4); **59a**: P-PHOS (66.5)

Figure 7. Calculated dihedral angles of L*–Ru complexes.

Electronic properties. The electronic properties of both the backbones and phosphine pendants can affect reactivity. Several methods to measure the electronic properties of phosphorus atoms are known, such as ^{31}P NMR (based on the coupling constants ^{31}P–^{77}Se),[111] IR (increase of CO stretching frequency of their Rh carbonyl complexes)[112] and cyclic voltammetry (electrochemical oxidation potentials)[113] The reported orders of electron abundance are:

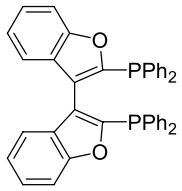
7,7′-dimethoxy-BINAP **2** > BINAP **1a**; ^{31}P NMR[42]

Cy-BINAP **1h** > **1a** > *p*-F-BINAP **1j** ~ *p*-Cl-BINAP **1k**; IR[30b]

1a > BINAPFu **58** > TetFu-BINAP **1i**; ^{31}P NMR[40c]

SYNPHOS **38** > MeO-BIPHEP **21a** > SEGPHOS **37a** ~ **1a** > Difluorophos **40**; IR[76]

N-Me-2-BINP **53** > TMBTP **52** > N-MOM-2-BINP **54** > BINAP **1a** > TetraMe-BITIANP **51** > BISCAP **56** > BICUMP **68**;[84] cyclic voltammetry[89]



BICUMP **68**

Phosphine pendants. In addition to modifying the framework, altering substituents on phosphorus atoms is an effective way to create a variety of steric and electronic environments, which give options for optimizing a reaction. Variations in phosphine pendants are often carried out to maximize the utility of a ligand with a specific backbone. The general impact of electronic or steric properties of the pendants is presumably similar to those of the backbones or triarylphophines.[114] Aside from tuning the framework, it is difficult to establish parameters that affect the outcome from tuning substituents on the biaryl. It often happens that a ligand giving a high enantioselectivity for a specific substrate gives disappointing results with similar substrates. Thus, some examples are discussed where variations in the phosphine afford excellent results.

5.1. Asymmetric hydrogenation

As is the case in other categories of phosphine ligands, the majority of biaryl ligands were developed for application to asymmetric hydrogenations. The most important theme in biaryl ligand development is how to improve upon BINAP in asymmetric hydrogenations. In this section, results from a series of modified ligands in Ru- and Rh-catalyzed asymmetric hydrogenations are discussed.

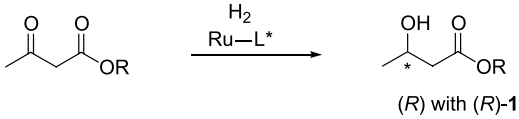
This section is not intended to be a comprehensive review of asymmetric hydrogenation. An excellent review by Zhang on this subject has recently appeared.[5a]

5.1.1. With Ru catalysts. One of the important features of biaryl ligands is their excellent compatibility with Ru for use in asymmetric hydrogenations.[115] Indeed, there are other examples of Ru-catalyzed asymmetric hydrogenations with unrelated types of ligands, such as BPE[116] or BisP*,[117] seen in the literature, and such ligands are mainly used in Rh-catalyzed reactions. As Ru is a much less expensive metal than Rh (Ru: $ 43-68/troy ounce, Rh: $ 520–715/troy ounce; prices of February 2004),[118] the use of Ru is advantageous from an industrial point of view.

5.1.1.1. Ketones. *β-Ketoesters*. Asymmetric hydrogenation of β-ketoesters is one of the specialities of biaryl ligand–Ru complexes. Many biaryl ligands show promise in the hydrogenation, and there exists a review dedicated to asymmetric hydrogenation of 1,3-dicarbonyl systems with biarylbisphosphine–Ru catalysts.[119]

β-Alkyl-β-ketoesters. Biaryl ligands generally afford the corresponding β-hydroxyesters in high enantioselectivities. Besides BINAP, a considerable number of ligands give enantioselectivities >95% ee. Examples that have appeared in the literature are given in Table 1.

Table 1. Asymmetric hydrogenation of alkyl acetoacetates



(*R*) with (*R*)-**1**

R	L* % ee								Ref.
Me				**1a** 99	**3** 98				43a
Me	**15a** 99			**1a** 98			**15b** 95		55a
Me	**15a** 100		**60** >99	**1a** >99			**16** 95 (conv. 15%[a])		56
Me	**34** 99.1	**1a** 98.4	**21a** 97.9	**33** 97.7	**35** 97.1	**36** 96.5	**31** 90.9	**32** 90.8	70b
Me	**45** 99.4		**44** 99.3	**1a** 97.7					79
Me	**47** 100			**1a** 99					81
Et	**5** 98		**1a** 98			**4** 96			43b
Et	**1a** >99		**51** 99	**50** 99					84
Et	**1a** 99		**51** 99	**52** 98		**53** 95	**54** 91		89
cf. Me	**1a**[22a] >99	**11a**[50b] >99	**37a**[120] >99	**46**[80b] >99	**8**[46] 99	**40**[76] 99			
Me	**59a**[94b] 98.5	**38**[73] 98.1	**7**[46] 97	**9**[47] 95	**10**[47] 95				
Et	**41**[78] 99.9	**42**[78] 99.9	**43**[78] 99.9	**62**[102c] 99.9	**52**[88] 98	**65**[104b] 97	**61**[102b] 96		

1a: BINAP, **3**: 6,6′-*diam*-BINAP, **11a**: BIPHEMP, **15a**: BIMOP, **15b**: *p*-MeO-BIMOP, **16**: BIFUP, **21a**: MeO-BIPHEP, **31**: C_1-TunaPHOS, **32**: C_2-TunaPHOS, **33**: C_3-TunaPHOS, **34**: C_4-TunaPHOS, **35**: C_5-TunaPHOS, **36**: C_6-TunaPHOS, **37a**: SEGPHOS, **38**: BisbenzodioxanPhos, **40**: Difluorophos, **46**: BIBFUP, **47**: BIFAP, **59a**: P-PHOS, **60**: FUPMOP; **1a**: BINAP, **5**:4,4′-*diam*-BINAP, **50**: BITIANP, **51**: TetraMe-BITIANP, **52**: TMBTP, **53**: N-Me-2-BINP, **54**: N-MOM-2-BINP, **65**: MeO-NAPhePHOS.
[a] Higher H_2 pressure.

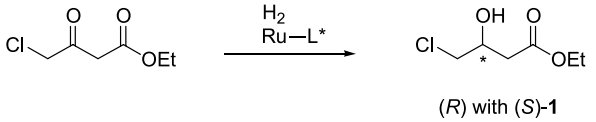
Sannicolò and co-workers proposed that the electrochemical oxidative potential (E^o) should reflect the electronic property of the phosphorus atoms. That is, the greater the oxidative potential, the less electron rich the ligand. They performed a detailed kinetic study on asymmetric hydrogenation of ethyl 3-oxobutanoate and found that both the electronic oxidative potential and the reaction rate have linear relationships. Ligands with a lower oxidation potential (electron-rich ligands) afford faster reactions[89] (Table 2).

Table 2. Effect of electrochemical oxidative potential (E^o) on reaction rate

Ligand	E° (V)	k_{obs}/k_{obs}^{binap}	% ee
N-Me-2-BINP **53**	0.52	2.67	95
TMBTP **52**	0.57	2.89	98
N-MOM-2-BINP **54**	0.60	2.56	91
BINAP **1a**	0.63	1	99
TetraMe-BITIANP **51**	0.76	0.83	99
BISCAP **56**	0.90	0.17	N.A.
BICUMP **68**	1.03	0.017	N.A.

With BINAP, the presence of a halogen atom at the γ-position of the β-ketoester results in a lower enantioselectivity. This occurs due to competition between the ester group and the halogen atom for coordination to the Ru center. Although reaction at higher temperatures solves the problem to a considerable extent,[107] the use of ligands with narrower dihedral angles such as SEGPHOS **37a** and P-PHOS **59a** affords higher enantioselectivities (Table 3).

Table 3. Asymmetric hydrogenation of ethyl 4-chloro-3-oxobutanoate



(*R*) with (*S*)-**1**

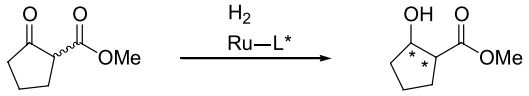
L* % ee						Ref.
	1a (at 100 °C) 97			**1a** (at rt) 70		107
37a 98.5	**1a** 95.9					72b
43 96.8	**41** 96.5			**42** 95.3		78
	1a 90	**66** 86	**65** 83	**21a** 78		105
cf.	**59a**[94b] 98	**38**[73] 97.0	**40**[76] 97	**43**[78] 96.8	**41**[78] 96.5	**42**[78] 95.3	**11a**[50b] 81

1a: BINAP, **11a**: BIPHEMP, **21a**: MeO-BIPHEP, **37a**: SEGPHOS, **38**: BisbenzodioxanPhos, **40**: Difluorophos, **59a**: P-PHOS, **65**: MeO-NAPhePHOS, **66**: TriMe-NAPhePHOS.

α-Substituted-β-alkyl-β-ketoesters. The asymmetric hydrogenations of α-substituted-β-alkyl-β-ketoesters are accompanied by dynamic kinetic resolution. In this case, diastereoselectivity is as important as enantioselectivity. Biaryl ligands usually give higher diastereoselectivities compared to BPE[115] and BisP*.[116] In the case of 2-methoxycarbonylcyclopentanone, the *anti* product is favored.

SEGPHOS gave higher values than did BINAP both in enantioselectivity and diastereoselectivity.[120] Biheteroaryl ligands such as TetraMe-BITIANP **51** and BITIANP **50** also afforded higher enantioselectivities than BINAP with good des.[84] TMBPT **52**, using CF_3CO_2H as additive, also affords excellent ees and des. Moreover, MeO-BIPHEP **21a** and C_4-TunaPHOS **34** gave higher enantioselectivities as well[70b] (Table 4).

Table 4. Asymmetric hydrogenation of 2-(methoxycarbonyl)cyclopentanone



(*R*,*R*) with (*R*)-**1**

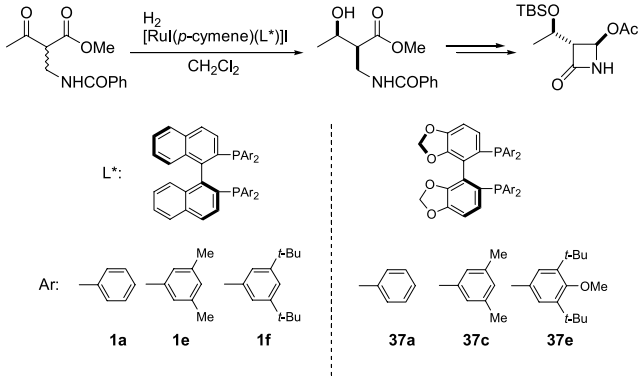
L* % ee (de)								Ref.
37a 99.5 (97.7% de)				**1a** 95.3 (94.4% de)				120
51 99 (86% de)			**50** 97 (78% de)		**1a** 88			84
21a 97.5	**34** 96.8	**33** 95.2	**35** 94.7	**1a** 93.4	**36** 91.9	**32** 89.7	**31** 87.9	70b[a]
cf.	**52**[88] 99 (84% de)				**1a**[30a] 93 (98% de)			

1a: BINAP, **21a**: MeO-BIPHEP, **31**: C_1-TunaPHOS, **32**: C_2-TunaPHOS, **33**: C_3-TunaPHOS, **34**: C_4-TunaPHOS, **35**: C_5-TunaPHOS, **36**: C_6-TunaPHOS, **37a**: SEGPHOS, **50**: BITIANP, **51**: TetraMe-BITIANP, **52**: TMBTP.

[a] Ethyl ester was adopted as substrate.

The key reaction in the synthesis of a carbapenem intermediate is the Ru-catalyzed asymmetric hydrogenation of methyl 2-(benzamidomethyl)-3-oxobutanoate. With BINAP or SEGPHOS ligands, moderate des of the reduced material resulted. However, when 3,5-dimethylphenyl-analogues of BINAP or SEGPHOS were used, des increased. The highest des and ees were observed when phosphine pendants consisted of either 3,5-di(*t*-butyl)-phenyl or 3,5-di(*t*-butyl)-4-methoxyphenyl groups (Table 5).[30b,72b,121]

Table 5. Asymmetric hydrogenation of 2-(benzamidomethyl)-3-oxobutanoate

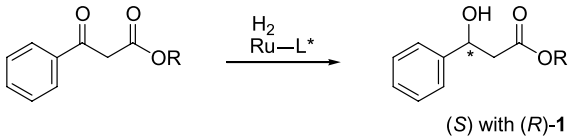


L*	**1a**	**1e**	**1f**[a]	**37a**	**37c**	**37e**
% de	74	95	98	80	94	99
% ee	90	99	99	N.A.	98	99

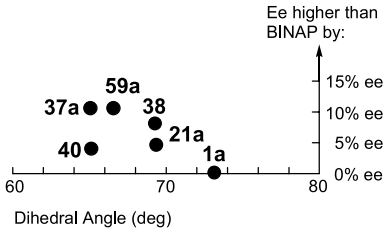
[a] CH_2Cl_2/MeOH (7/1) was used as solvent.

β-Aryl-β-ketoesters. Asymmetric hydrogenation of β-aryl-β-ketoesters, unlike β-alkyl-β-ketoesters, is remarkably influenced by the ligand. In general, ligands with narrow dihedral angles such as SEGPHOS,[72b] SYNPHOS **38**,[74b] MeO-BIPHEP[105] and P-PHOS[94b] give higher enantioselectivity. In the TunaPHOS series, C_4-TunaPHOS ligands generate the highest ees of reduced products[70b] (Table 6).

Table 6. Asymmetric hydrogenation of alkyl 3-oxo-3-phenylpropionates



(*S*) with (*R*)-**1**



R	L* % ee							Ref.
Me	**37a** 97.6			**21a** 93.5		**1a** 87.0		72b
Et	**34** 82.3	**35** 78.5	**1a** 78.4	**31** 76.8	**21a** 74.8	**33** 72.0	**32** 71.4	70b
Et	**38** 97		**21a** 93		**1a** 87			74b
Et	**45** 97.7				**1a** 89.3		**44** 82.4	79
Et	**21a** 97	**66** 93		**65** 92	**1a** 90			105
Et	**59a** 95.2				**1a** 85			94b
Et	**40** 92				**1a** 88			76
Et	**41** 97.9			**43** 96.3		**42** 96.2		78
cf.	**21a**[122] 96			**51**[85b] 90		**1a**[22a] 85		
Et	**52**[88] 93			**61**[102b] 73		**62**[102c] 70		

1a: BINAP, **21a**: MeO-BIPHEP, **31**: C_1-TunaPHOS, **32**: C_2-TunaPHOS, **33**: C_3-TunaPHOS, **34**: C_4-TunaPHOS, **35**: C_5-TunaPHOS, **36**: C_6-TunaPHOS, **37a**: SEGPHOS, **38**: SYNPHOS, **40**: Difluorophos, **51**: TetraMe-BITIANP, **52**: TMBTP, **59a**: P-PHOS.

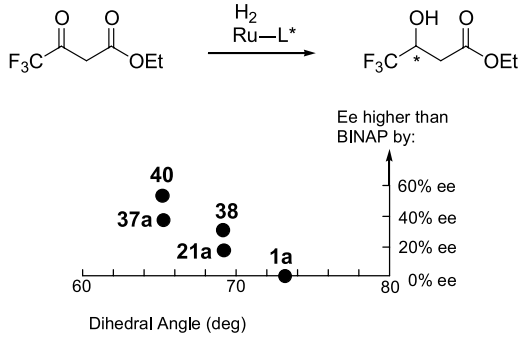
4,4′-Disubstituted BINAP analogues **6** also exhibit high enantioselectivities. With substituents on **6** such as $SiMe_3$, $CPh_2(OH)$, and 1-cyclopentanol, almost single enantiomers were virtually obtained. Lin attributes the reduced enantioselectivity of BINAP to π–π stacking interactions between a phenyl group in the ligand and the substrate. This interaction slightly stabilizes the disfavored transition state, thus lowering the overall enantioselectivity. Substitutions at the 4,4′-positions deter this interaction, leading to higher enantioselectivity[44a] (Table 7).

Table 7. Effects of substituents at the 4,4′-positions

R in **6** % ee						
$SiMe_3$ 99.5	$CPh_2(OH)$ 99.3		1-Cyclopentanol 99.2		$P(O)(OEt)_2$ 98.8	
$Si(i\text{-}Pr)_3$ 98.6	$P(O)(OH)_2$ 97.2	I 86.5	H 85.0	Br 80.8	Cl 77.0	Ph 71.8

β-Trifluoromethyl-β-ketoesters. Enantioselectivities for the reduction of β-trifluoromethyl-β-ketoesters are low to moderate. A general trend to higher enantioselectivities with narrower dihedral angle ligands and lower electron abundance can be established.[74b,76] TMBTP, in particular, affords high enantioselectivity[88] (Table 8).

Table 8. Asymmetric hydrogenation of ethyl 3-oxo-4,4,4-trifluorobutylate

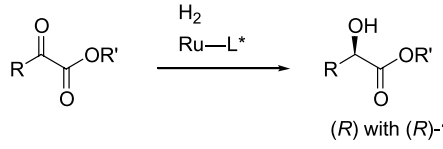


	L* % ee				Ref.
40	**37a**	**38**	**21a**	**1a**	74b
70	59	49	40	23	76
	21a	**66**	**65**	**1a**	105
	42	32	32	25	
cf.	**52**[88]				
	85				

1a: BINAP, **21a**: MeO-BIPHEP, **37a**: SEGPHOS, **38**: SYNPHOS, **40**: Difluorophos, **52**: TMBTP, **65**: MeO-NAPhePHOS, **66**: TriMe-NAPhePHOS.

α-Alkyl-α-ketoesters. α-Ketoesters are hydrogenated with slightly lower enantioselectivities than β-ketoesters. However, ees are within an acceptable range (Table 9).

Table 9. Asymmetric hydrogenation of α-ketoesters



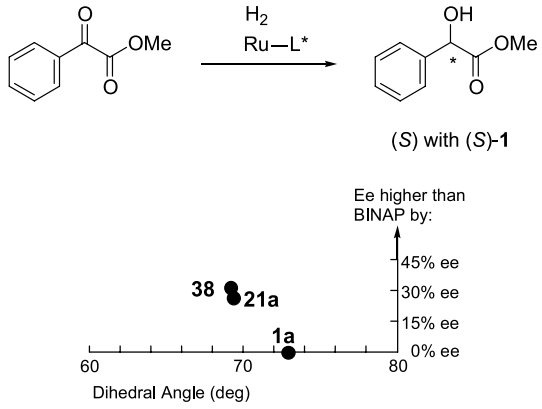
R	R′	L* % ee		Ref.
Me	Me	**51**	**1a**	30b
		88	88	84
$Ph(CH_2)_2$	Et	**37a**	**1a**	72b
		93.7	90	
cf.	Et	**51**[102b]	**52**[88]	
$Ph(CH_2)_2$		93	91	

1a: BINAP, **37a**: SEGPHOS, **51**: TetraMe-BITIANP, **52**: TMBTP.

α-Aryl-α-ketoesters. BICHEP **11b** uniquely affords excellent ees,[51c] whereas triarylphosphine-type ligands such as BINAP give moderate to acceptable ees of the opposite enantiomer. Among the latter, ligands rich in electron density seem to give higher enantioselectivity as the dihedral angles taper (Table 10).

γ-Ketoesters. High enantioselectivities are achieved using

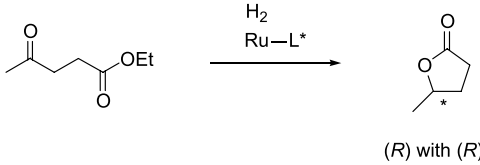
Table 10. Asymmetric hyrogenation of methyl phenylglyoxylate



	L* % ee				Ref.
11b				**1a**	51c
>99				45	
38	**21a**			**1a**	74b
92	90			72	
				1a	**51** 84
				79	78
	21a	**66**	**65**	**1a**	105
	90	85	75	72	
cf.	**1a**[30b]	**52**[88]	**21a**[50b]	**61**[102b]	
	89	89	86	85	

1a: BINAP, **11b**: BICHEP, **21a**: MeO-BIPHEP, **38**: SYNPHOS, **51**: TetraMe-BITIANP, **52**: TMBTP, **65**: MeO-NAPhePHOS, **66**: TriMe-NAPhePHOS.

biaryl ligands with γ-ketoesters, although less attention has been paid to these substrates. In asymmetric hydrogenation of ethyl 4-oxopentanoate, SEGPHOS,[72b] TMBTP[124] as well as BINAP[123] afford excellent enantioselectivities, yielding ethyl 4-hydroxypentanoate (Scheme 7).



	L* % ee		Ref.
	37a	**1b**	72b
	99.0	97.2	120
cf.	**1a**[123]	**52**[124]	
	>98	98	

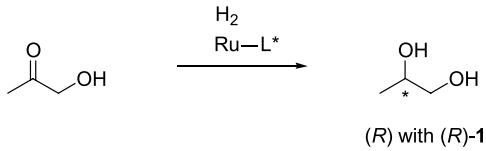
1b:Tol-BINAP, **37a**:SEGPHOS, **52**:TMBTP

Scheme 7. Asymmetric hydrogenation of 4-oxopentanoate.

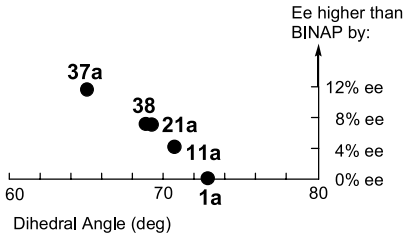
Hydroxyacetone. Hydroxyacetone is the most typical substrate in hydrogenation, illustrating the close relationship between dihedral angle and enantioselectivity. The narrower the ligand's dihedral angle, the higher the enantioselectivity[72b] (Table 11).

α-Amidoketones. α-Phthalimide ketones are precursors to the corresponding amino alcohol derivatives. Asymmetric

Table 11. Asymmetric hydrogenation of hydroxyacetone



(*R*) with (*R*)-**1**

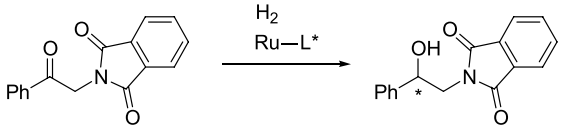


L* % ee				Ref.
37a	**21a**	**11a**	**1a**	72b
99.5	96	93	89	
38	**21a**		**1a**	74c
97	97		89	
cf.		**1a**[22b]		
		92		

1a: BINAP, **11a**: BIPHEMP, **21a**: MeO-BIPHEP, **37a**: SEGPHOS, **38**: SYNPHOS.

hydrogenation of these substrate types was performed with TunaPHOS ligands. For the substrate below, C_3-TunaPHOS **33** gave the highest enantioselectivity[71b] (Table 12).

Table 12. Asymmetric hydrogenation of *N*-phenacyl-phthalimide



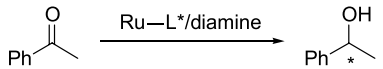
L* % ee								Ref.
33	**1a**	**35**	**34**	**21a**	**31**	**36**	**32**	71b
98.5	96.1	95.3	95.1	94.3	91.3	90.7	90.3	

1a: BINAP, **21a**: MeO-BIPHEP, **31**: C_1-TunaPHOS, **32**: C_2-TunaPHOS, **33**: C_3-TunaPHOS, **34**: C_4-TunaPHOS, **35**: C_5-TunaPHOS, **36**: C_6-TunaPHOS.

Aryl ketones. In reactions developed following the discovery of the Ru-bisphosphine/diamine system,[23] phosphine pendants appear to play an important role. Besides binaphthyl-type arrays, reactions were carried out with P-PHOS,[96a] TetraPHEMP[52b] **12a** and HexaPHEMP **19a**[60b] frameworks. As in the BINAP series, 3,5-dimethylphenyl groups gave the highest enantioselectivities in every case (Table 13).

Ligands with diphenylphosphino groups as pendant also give a comparable enantioselectivity when they possess some substituents at the 4,4′-positions. According to a study by Lin et. al., BINAP analogues having $P(O)(OH)_2$ or trimethylsilyl groups at these sites considerably improve enantioselectivity[44b] (Table 14).

Table 13. Asymmetric hydrogenation of acetophenone



(*R*) with (*S*)-**1e**

L* % ee			Ref.
1e	**1b**	**1a**	23e
99	91	87	
19b	**19a**	**1a**	60b
99	90	86	
59c	**59b**	**59a**	96a
99.1	84.9	83.3	
cf.		**12b**[52b]	
		99	

1a: BINAP, **1b**: Tol-BINAP, **1e**: DM-BINAP, **12b**: Xyl-TetraPHEMP, **19a**: HexaPHEMP, **19b**: Xyl-HexaPHEMP, **59a**: P-PHOS, **59b**: T-P-PHOS, **59c**: Xyl-P-PHOS.

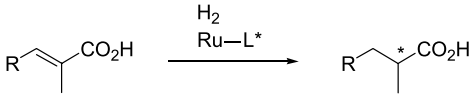
Table 14. Effects of substituents at the 4,4′-positions

R in **6** % ee						
$P(O)(OH)_2$	$SiMe_3$		$P(O)(OEt)_2$		1-*cyclo*pentanol	
97.1	96.0		94.1		91.5	
$CPh_2(OH)$	CH_3	Ph	Br	I	Cl	H
91.5	89.9	88.9	88.8	88.1	85.7	83.0

5.1.1.2. Olefins. *α,β-Unsaturated carboxylic acids*. Ru-diacetate complexes ligated by biaryl phosphine play a leading role in asymmetric hydrogenation of substrates in this category.[21] In contrast to the case of ketones, trends seen in the literature for these adducts are less clear, although H_8-BINAP **18a** generally gives higher enantioselectivity than does BINAP.

In asymmetric hydrogenations of tiglic acid and related compounds, enantioselectivities depend on the type of

Table 15. Asymmetric hydrogenation of tiglic acid



(*R*) with (*R*)-**1**

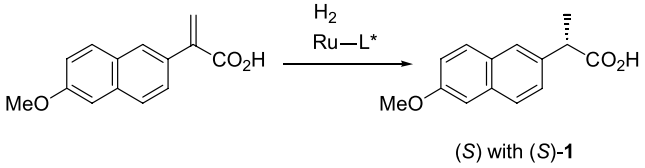
R	L* % ee				Ref.
Me	**18a**	**1b**			3a
	96	91			59a,b
Me	**15a**	**1a**	**15b**	**15c**	55a
	91	87	86	60 (10% conv.)	125
Me	**7**	**1a**			46
	90.4	87.5 (44% conv.)			
Et	**18a**	**1a**			59a,b
	96	84			
cf.	**11a**[50b]	**52**[88]	**21a**[50b]	**51**[84]	**1a**[21b]
Me	98	94	92	92	91

1a: BINAP, **1b**: Tol-BINAP, **11a**: BIPHEMP, **15a**: BIMOP, **15b**:*p*-MeO-BIMOP, **15c**: Cy-BIMOP, **18a**: H_8-BINAP, **21a**: MeO-BIPHEP, **51**: TetraMe-BITIANP, **52**: TMBTP.

complex involved. H_8-BINAP afforded higher enantioselectivities than BINAP under identical conditions.[59a,b] Interestingly, the bis-steroidal ligand **7** reported to occupy similar asymmetric space to BINAP gives significantly higher enantioselectivities[46] (Table 15).

Naproxen is synthesized via asymmetric hydrogenation of the corresponding olefin. H_8-BINAP in this case gave better selectivities than BINAP;[3b] P-PHOS **59a**[94b] and **44**[96] also afforded slightly higher ees (Table 16).

Table 16. Asymmetric hydrogenation of 2-(6-methoxy-2-naphthalen-2-yl)propenoic acid



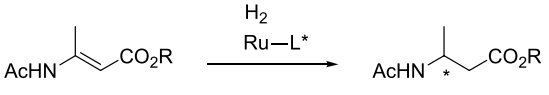
(*S*) with (*S*)-**1**

	L* % ee		Ref.
18a	**1a**		3b
90	88		
38	**1a**		73
91	89		
44	**1a**	**45**	79
96	94	93	
59a	**1a**		94b
96.2	94.8		
cf.	**1a**[21b]	**18a**[64a,b]	
	97	97	

1a: BINAP, **18a**: H_8-BINAP, **38**: BisbenzodioxanPhos, **59a**: P-PHOS.

β-Acylaminoacrylates. Numerous Rh complexes ligated by various alkylphosphine ligands such as DuPHOS[126] and BisP*[127] are known to afford higher enantioselectivities. In this competitive area, Ru complexes with BINAP,[128] HexaPHEP **19a**,[60b] and Xyl-P-PHOS **59c**[95b] hydrogenate β-acetaminocrotonates with comparable enantioselection (Table 17).

Table 17. Asymmetric hydrogenation of (*E*)-alkyl β-acetamidocrotonates



R = Me, Et

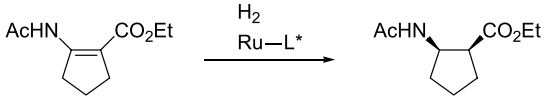
(*S*) with (*R*)-**1**

R		L* % ee		Ref.
Et	**19a**	**1a**		60b
	95	95		
Et	**59c**	**59b**	**59a**	95b
	97.4	93.8	89.4	
Cf.		**1a**[128]		
Me		96		

1a: BINAP, **19a**: HexaPHEMP, **59a**: P-PHOS, **59b**: T-P-PHOS, **59c**: Xyl-P-PHOS.

Cyclic β-acylaminoacrylates. Zhang developed an asymmetric hydrogenation of tetrasubstituted olefins that provides cyclic β-amino acids.[71c] In this hydrogenation, biaryl ligands such as BINAP, MeO-BIPHEP **21a** and TunaPHOS **31**–**36** gave significantly higher enantioselectivities relative to other types of ligands (e.g., DIOP (34% ee), DuPHOS (69% ee)) (Table 18).

Table 18. Asymmetric hydrogenation of 2-acetylamino-cyclopent-1-enecarboxylic acid ethyl ester



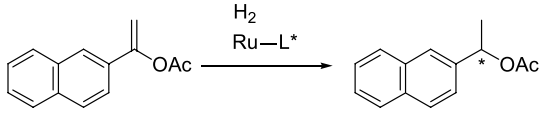
(1*S*, 2*R*) with (*S*)-**1a**

L* % ee								Ref.
1a	**21a**	**32**	**33**	**34**	**35**	**31**	**36**	71c
99	99	99	99	99	99	98	97	

1a: BINAP, **21a**: MeO-BIPHEP, **31**: C_1-TunaPHOS, **32**: C_2-TunaPHOS, **33**: C_3-TunaPHOS, **34**: C_4-TunaPHOS, **35**: C_5-TunaPHOS, **36**: C_6-TunaPHOS.

Enol acetates. Zhang performed Ru-catalyzed asymmetric hydrogenation using TunaPHOS ligands. Among the ligands examined, C_1- and C_2-TunaPHOS afforded the highest enantioselectivities[71a] (Table 19).

Table 19. Asymmetric hydrogenation of an enol acetate

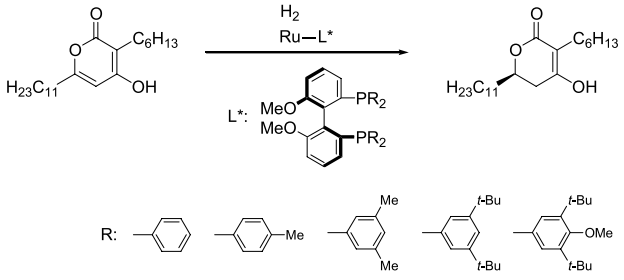


(*S*) with (*S*)-**31**

L* % ee						Ref.
31	**32**	**36**	**33**	**35**	**34**	71a
95.9	95.9	92.3	92.1	91.9	88.9	

31: C_1-TunaPHOS, **32**: C_2-TunaPHOS, **33**: C_3-TunaPHOS, **34**: C_4-TunaPHOS, **35**: C_5-TunaPHOS, **36**: C_6-TunaPHOS.

Table 20. Asymmetric hydrogenation of pyrone



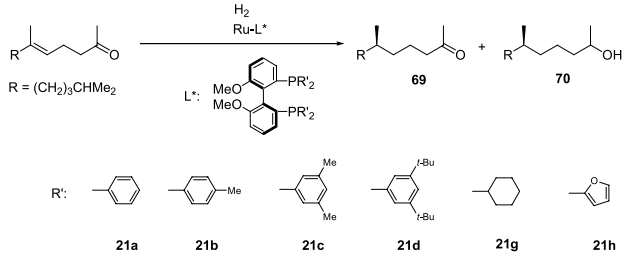
21a **21b** **21c** **21d** **21f**

L*	**21a**	**21b**	**21c**	**21d**	**21f**
Conv. (%)	<1	3	10	84	54
% ee	nd	86	86	93	94

Other olefins. In asymmetric hydrogenation of 2-pyrone using analogues of MeO-BIPHEP, a strong dependence on the residue attached to phosphorus was observed.[64b] Ligands with more sterically hindered phosphines gave not only higher ees, but also showed greater catalytic activity (Table 20).

Dihydrogeranylactone. Schmid performed asymmetric hydrogenations of dihydrogeranylacetone screening numerous ligands from their MeO-BIPHEP libraries.[64b] In addition to enantioselectivity, the chemoselectivity relating to hydrogenation of the C=C bond over the C=O bond present was evaluated. MeO-BIPHEP gave the hydrogenated ketone **69** in higher chemoselectivity, albeit with moderate ees. The more electron donating the phosphine pendant, the greater the percentage of undesired reduction of the C=O bond took place. When the cyclohexyl analogue was used, the over-reduced product **70** was by far the major pathway. In this case, a furyl analogue achieved the highest enantioselectivity together with the best chemoselectivity (Table 21).

Table 21. Asymmetric hyrogenation of dihydrogeranylacetone

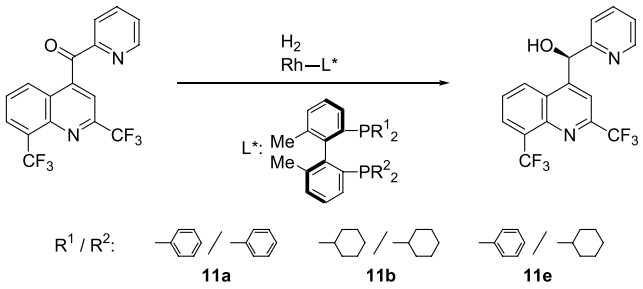


L*	21a	21b	21c	21d	21g	21h
% **69**	97	80	69	33	3	98
% **70**	3	20	28	65	96	2
% ee of **69**	77	75	54	89	73	91

5.1.2. With Rh catalysts. As the initial BINAP chemistry has documented,[6a] biaryl ligands are also effective in Rh catalysis. The stereochemical course is accounted for by mechanisms proposed by Halpern,[129] Brown[130] and Imamoto.[131] In Rh-catalyzed asymmetric hydrogenation, it is commonly believed that high electron density is essential for high enantioselectivity. This notion derives from observations involving alkyl-substituted phosphine ligands in BPE,[132] DuPHOS,[133] BisP*[134] and their descendants that complex well with Rh and afford exceptional enantioselectivities. The situation with biaryl ligands is the same: ligands with dialkylphosphino groups tend to be more successful in terms of enantioselectivity than those with biarylphosphino counterparts. A recent study by Zhang et al. shows 3,3′-substitution of triaryl-type bisphosphine ligands is also effective to improve enantioselectivity.[68,69]

5.1.2.1. Ketones. Asymmetric hydrogenation of a heteroaryl ketone that yields the intermediate of mefloquine, an antimalarial drug, is affected by ligands bearing phosphine residues on the biaryl nucleus. Hydrogenation with BIPHEMP **11a** led to a low rate of conversion compared to that with the Cy analogue **11b**, which afforded improved conversion levels and enantioselectivities. Interestingly, the highest conversion and enantioselectivity was achieved with the hybrid ligand consisting of the diphenylphosphino and the dicyclohexylphosphino group attached to the backbone[64b] (Table 22).

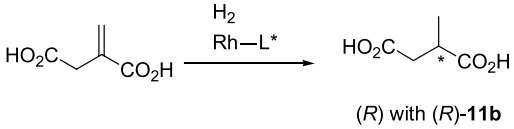
Table 22. Asymmetric hydrogenation of a heteroaryl ketone



R^1/R^2	11a	11b	11e
Conv. (%)	5	75	86
% ee	61	78	92

5.1.2.2. Olefins. *α,β-Unsaturated carboxylic acids*. Itaconic acid is hydrogenated using Rh catalysis. Biaryl ligands gave high enantioselectivities when Rh complexes ligated by dialkylphosphino-types were used[51b,55c,98] (Table 23).

Table 23. Asymmetric hydrogenation of itaconic acid



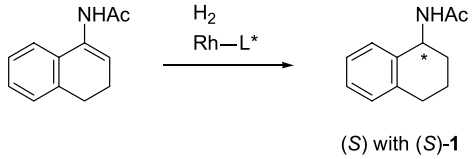
L* % ee					Ref.
15c	**15d**	**15b**[a]	**15a**[a]	**1a**	55c
80	71	57	51	~0	98
cf.			**11b**[51b] 96		

1a: BINAP, **11b**: BICHEP, **15a**: BIMOP, **15b**:*p*-MeO-BIMOP, **15c**: Cy-BIMOP, **15d**: MOC-BIMOP.
[a] The opposite sense of enantioselectivity to **11b** was observed.

Cyclic enamides. Zhang discovered that 3,3′-disubstitution of the biaryl framework led to effective asymmetric hydrogenation of a cyclic enamide.[68b] In the hydrogenation, *o*-Ph-hexaMeO-BIPHEP **29** afforded exceptionally high ees due to extended protrusion of the equatorial phenyl pendants caused by the 3,3′-substitution pattern (Table 24).

Dehydro-α-amino acids. In asymmetric hydrogenation of α-acetaminocinnamic acid, use of ligands with greater electron abundance is more advantageous both in catalytic activity and enantioselectivity. A 3,3′-substitution of a ligand is also effective in improving enantioselectivity.[69] Cy-BIMOP **15c** afforded the complementary enantiomer to that of the Ph substituted analogue.[55c] In a benzoyl-type substrate, BINAP gave excellent ees[6a] (Table 25).

Table 24. Asymmetric hydrogenation of a cyclic enamide

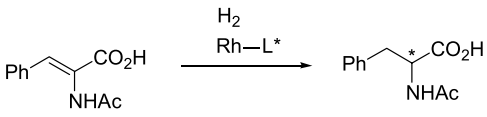


(*S*) with (*S*)-**1**

L*				Ref.
		% ee		
29	**21a**	**23**	**1a**	68b
98	67	65	55	

1a: BINAP, **21a**: MeO-BIPHEP, **23**: HexaMeO-BIPHEP, **29**:*o*-Ph-hexaMeO-BIPHEP.

Table 25. Asymmetric hydrogenation of α-acetaminocinnamic acid



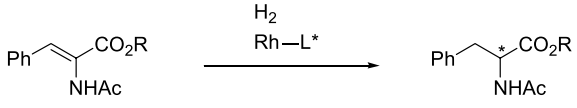
(*R*) with (*S*)-**1**

L*				Ref.
		% ee		
15c	**15b**	**15a**	**1a**	55c
79	44	30	15	
	30	**21a**		69
	96	36		
cf.	**52**[89]	**1a**[6a]	**1a**[6a,a]	
	87	84	>96	

1a: BINAP, **15a**: BIMOP, **15b**:*p*-MeO-BIMOP, **15c**: Cy-BIMOP, **21a**: MeO-BIPHEP, **30**:*o*-Ph-MeO-BIPHEP, 52:TMBTP.
[a] *N*-Benzoyl analogue was adopted as substrate.

Dehydro-α-amino acid esters. This substrate is one of the earliest to have been subject to asymmetric hydrogenation. High enantioselectivities were achieved with various types of ligands.[5a] Thus, there has been much competition for ligands using this class of substrate. Rh complexes ligated by biaryl ligands are generally less effective than those comprising electron-rich ligands such as DuPHOS and BisP*. Nonetheless, high enantioselectivities are feasible using ligands with substituents at the 3,3′-position[69] or with dialkylphosphino groups (Table 26).[51b]

Table 26. Asymmetric hydrogenation of alkyl α-acetamidocinnamates

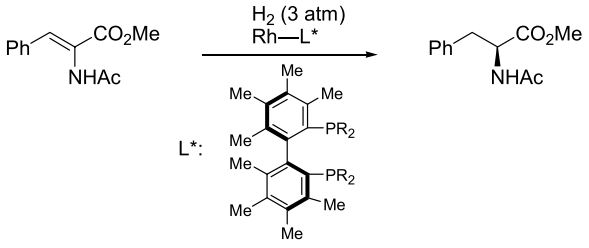


R	L*		Ref.
	% ee		
Me	**30**	**21a**	69
	98	21	
cf.	**59a**[95a]		
Me	90		
Et	**11b**[51b]		
	97		

11b: BICHEP, **21a**: MeO-BIPHEP, **30**: *o*-Ph-MeO-BIPHEP, **59a**: P-PHOS.

Imamoto presumed that smaller alkylphosphine pendants decrease steric repulsion around the reaction center, thereby increasing catalytic activity. Based on that idea, they synthesized a ligand with diethylphosphino groups. In the asymmetric hydrogenation of methyl 2-acetamino-cinnamate, the diphenylphosphino analogue gave low catalytic activities, while the dicyclohexyl analogue required milder reaction conditions to give comparable catalytic activity. Use of the diethylphosphine counterpart resulted in complete reaction within 10 min. The high catalytic activity also enables the reaction temperature to be lowered to −40 °C with an observed improvement of enantioselectivity[62] (Table 27).

Table 27. Asymmetric hydrogenation of methyl α-acetamidocinnamate

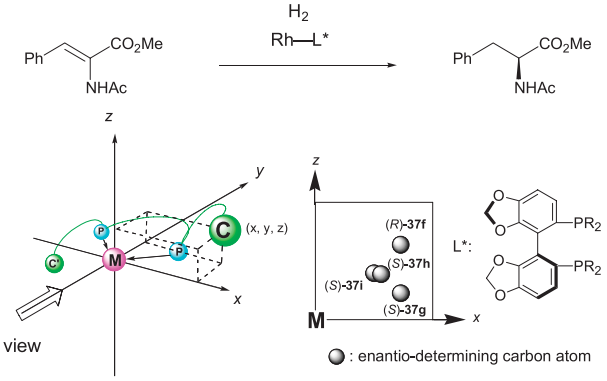


R	Ph[a] **20a**	Cy[b] **20b**	Et **20c**	Et **20c**
Temp (°C)	50	Rt	rt	−40
Time (h)	15	15	<10 min	60
% ee	88	N.A.	74	89

[a] H_2 (50 atm) was used.
[b] Racemate was used.

Saito assumed that a substrate should have its own 'sweet spot' to be shielded during asymmetric hydrogenation to achieve high enantioselectivity. Based on this hypothesis, several ligands placing enantio-determining groups in various positions were synthesized. Asymmetric hydrogenation of methyl 2-acetaminocinnamate revealed that the

Table 28. 'Sweet spots' and enantioselectivities



PR$_2$:				
L*	(*R*)-**37f**	(*S*)-**37g**	(*S*)-**37h**	(*S*)-**37i**
(*x*, *z*)[a]	(3.4, 2.3)	(3.3, 1.6)	(3.1, 2.0)	(3.0, 2.0)
% ee	63	75	97	95

[a] Calculated grid point from the side view of the Rh complexes.

highest enantioselectivity is obtained when the enantio-determining groups are indeed localized at a specific site[135] (Table 28).

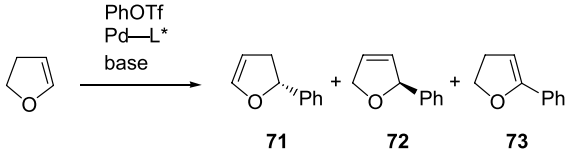
5.2. Asymmetric Heck reaction

The asymmetric Heck reaction between 2,3-dihydrofuran and phenyl triflate is often adopted as a test reaction. In this reaction enantioselectivity is highly affected by the base used.[136]

TetFuBINAP **1i** and BINAPFu **58** give considerably higher enantioselectivities than does BINAP under identical conditions.[40c,93a] BITIANP **50** showed excellent enantioselectivity, whereas another bithienyl ligand TMBTP **52** afforded much lower regioselectivity with poorer ee[87a] (Table 29).

When pyrroline was used as substrate, the same tendency as seen with the case of dihydrofuran was observed: BITIANP gave much higher enantioselectivity with higher regioselectivity, while TMBTP preferred the other regioisomer. Both ligands have much greater catalytic activity relative to BINAP[87c] (Table 30).

Table 29. Asymmetric Heck reaction of dihydrofuran



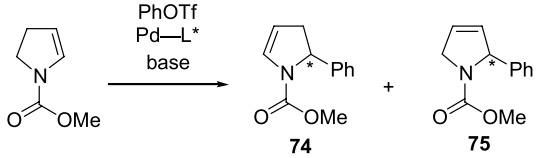
71 **72** **73**

(*R*) with (*R*)-**1a**

L*	% ee of **71** (**71**/**72**/**73**)	Ref.
1a (proton sponge as base)	**1a** (Et_3N as base)	136
>96 (71/29/0)	75 (98/2/0)	
2	**1a**	42
60	54	
21d	**21a**	137
99	87	
1i	**1a**	40b
89 (17/5/0)	66 (53/2/1)	
58	**1a**	93a
>97 (61/9/2)	73 (43/2/2)	
50	**1a**	87a
91 (100/0/0)	42 (3/1/0)	
50	**52**	87a
90 (100/0/0)	4 (1/2/0)	

1a: BINAP, **1i**: TetraFu-BINAP, **21a**: MeO-BIPHEP, **50**: BITIANP, **52**: TMBTP, **58**: BINAPFu.

Table 30. Asymmetric Heck reaction of pyrroline



74 **75**

(*S*) with (*S*)-**50**

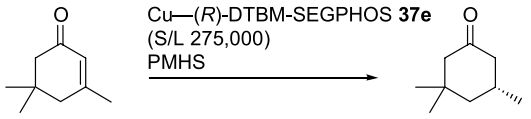
L*	BITIANP **50**	TMBTP **52**
74/**75**	31/1	1/4
% ee of **74**	93	2

cf. BINAP **1a**: conv. 45%.

5.3. Other asymmetric reactions

Although most BINAP descendants are designed for applications to asymmetric hydrogenations and Heck reactions, some have found increased utility. Representative examples over the past decade of modified biaryl ligands that have led to outstanding results are discussed below.

5.3.1. Reduction. *Hydrosilylation*. Catalytic asymmetric hydrosilylation with copper hydride ligated by chiral bisphosphine ligands has been extensively studied by several groups. Buchwald reported the first copper catalysis using nonracemic biaryl ligands (BINAP, T-BINAP and BIPHEMP), reducing acyclic enoates and cyclic α,β-unsaturated ketones in good ees.[138] Recently, Lipshutz established hydrosilylation of cyclic enones using DTBM-SEGPHOS that recorded an unprecedented substrate/ligand ratio (S/L) up to 275,000:1, along with high enantioselectivities[139] (Scheme 8).

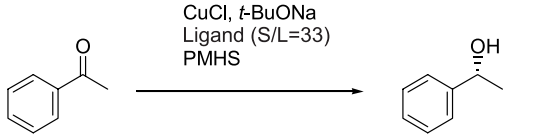


98.5% ee (*R*)

Scheme 8. Cu-catalyzed asymmetric hydrosilylation of isophorone.

Lipshutz expanded the scope of the reaction to aromatic ketones.[140] In the case of acetophenone, DTBM-SEGPHOS gives the highest enantioselectivity and the shortest reaction time (Table 31). The substrate-to-ligand ratio of this reaction exceeded 100,000:1.[140b]

Table 31. Cu-catalyzed asymmetric hydrosilylation of acetophenone



(*R*) with (*R*)-**37e**

L* % ee			
37e	**37c**	**21c**	**21f**
96, 92[a]	95	94	90[b]

21c:3,5-Xyl-MeO-BIPHEP, **21f**:4-MeO-3,5-DTB-MeO-BIPHEP, **37c**: DM-SEGPHOS, **37e**: DTBM-SEGPHOS.
[a] S/L >100,000.
[b] Conv. 50%.

The combination of CuH and DTBM-SEGPHOS also works well as an asymmetric catalyst in the case of heteroaromatic ketones[141] and phosphinylimines,[142] affording high enantioselectivities (Fig. 8).

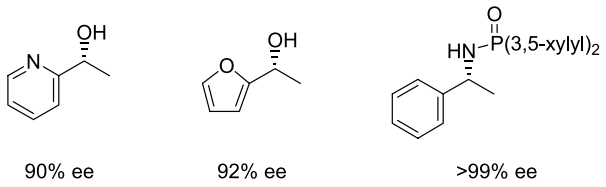
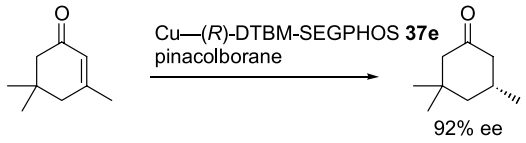


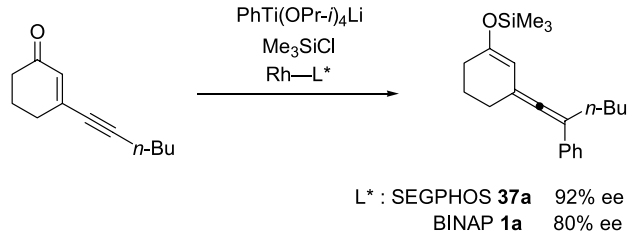
Figure 8. Applications of asymmetric hydrosilylation.

Hydroboration. Asymmetric hydroboration of an enone is achieved using a Cu complex with DTBM-SEGPHOS. Exposure of isophorone to pinacolborane in the presence of the complex afforded the 1,4-reduction product with high ee[143] (Scheme 9).



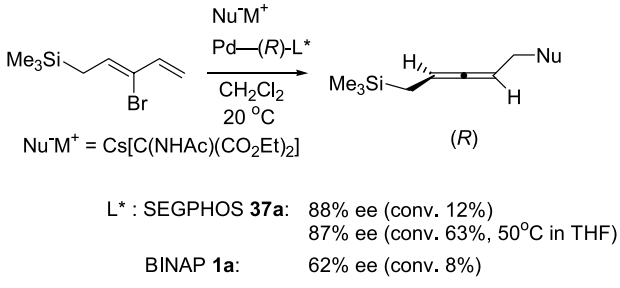
Scheme 9. Cu-catalyzed asymmetric hydroboration.

5.3.2. C–C bond formation. *Allene synthesis via 1,6-addition*. Hayashi developed a 1,6-addition reaction of an aryltitanate to 3-alkynyl-2-en-1-ones that provides axially chiral allenes catalyzed by a bisphosphine–Rh complex.[144] In this reaction, SEGPHOS gave a higher selectivity relative to BINAP (Scheme 10).



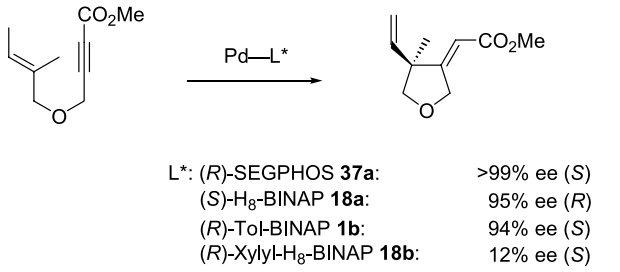
Scheme 10. Allene synthesis via Rh-catalyzed asymmetric 1,6-addition.

Hayashi also developed a novel reaction to prepare allenylmethylsilanes in an S_E' fashion using a Pd catalyst.[145] SEGPHOS afforded higher selectivity than did the corresponding BINAP complex, although yields were low. The yield was improved at higher temperature with little loss of enantioselectivity (Scheme 11).



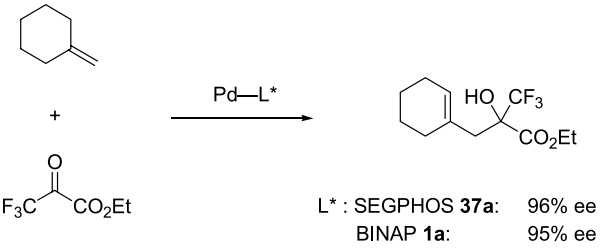
Scheme 11. Pd-catalyzed asymmetric synthesis of axially chiral allenylmethylsilane.

Ene reaction. Mikami et al. investigated ligand effects in Pd-catalyzed asymmetric ene-type cyclizations of a 1,6-enyne.[146] The highest enantioselectivity could be obtained when SEGPHOS was used as the ligand. The apparent drop in enantioselectivity in the Xylyl-H_8-BINAP case was attributed to the assumed dissociation of the ligand from its Pd complex caused by its bulkiness (Scheme 12).



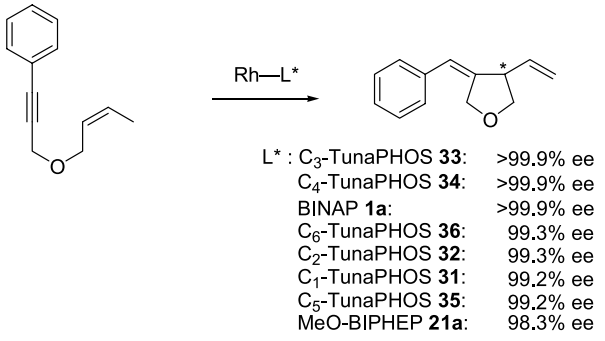
Scheme 12. Pd-catalyzed asymmetric ene-type cyclization.

Mikami et al. also applied that catalytic system to a carbonyl-ene reaction.[109] Here, SEGPHOS was slightly superior to BINAP insofar as enantioselectivity is concerned (Scheme 13).



Scheme 13. Pd-catalyzed asymmetric carbonyl-ene reaction.

Zhang et al. have developed a Rh-catalyzed asymmetric Alder-ene reaction.[147] They utilized predominantly C_n-TunaPHOS ligands, which all afforded high enantioselectivities. Among those studied, C_3- and C_4-TunaPHOS, as well as BINAP, provided almost a single enantiomer (Scheme 14).

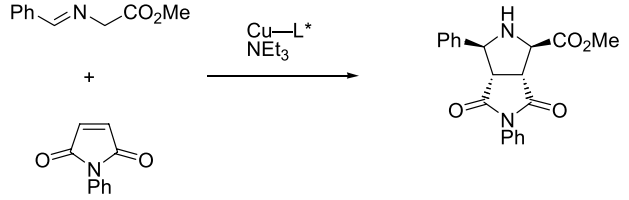


Scheme 14. Rh-catalyzed asymmetric Alder-ene reaction.

1,3-Dipolar addition. Komatsu et al. applied chiral biaryl ligands to a Cu-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with alkenes.[148] However, there are no general tendencies to be revealed for a certain type of ligand as the induced enantioselectivities differed depending on the choice of substrate. For *N*-benzylideneglycine as substrate, SEGPHOS induced the highest

enantioselectivity, but with concomitant loss of *exo* selectivity (Table 32).

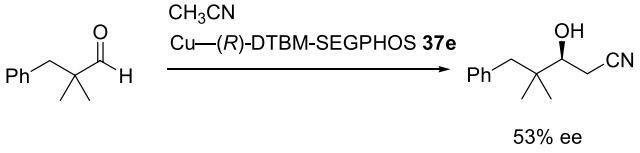
Table 32. Cu-catalyzed asymmetric 1,3-dipolar cycloaddition



L*	**37a**	**1a**	**18a**	**1b**
Yield (%)	78	71	25	24
Exo/*endo*	85/15	>95/<5	93/7	>95/<5
% ee	72	64	60	47

1a: BINAP, **1b**: Tol-BINAP, **18a**: H_8-BINAP, **37a**: SEGPHOS.

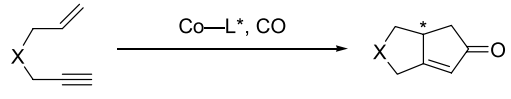
Direct cyanomethylation. Shibasaki et al. developed a novel direct catalytic enantioselective cyanomethylation using DTBM-SEGPHOS as ligand.[149] Starting from acetonitrile and an aldehyde, a copper catalyst associated with the ligand afforded the corresponding β-hydroxynitrile in 53% ee (Scheme 15).



Scheme 15. Cu-catalyzed direct asymmetric cyanomethylaion.

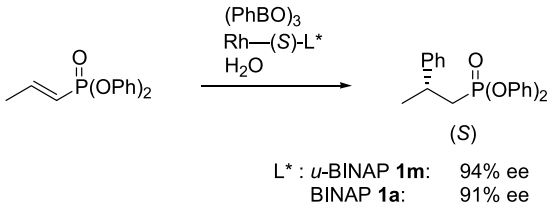
Pauson–Khand reactions. Gibson et al. reported that ligands with axial chirality could afford significant chiral inductions in Co-catalyzed asymmetric Pauson–Khand reactions.[150] Of the ligands examined, only the biaryl-type ligands yielded high enantioselectivity. The obtained asymmetric inductions are not only dependent on the choice of ligand, but also on the choice of substrate (Table 33).

Table 33. Co-catalyzed asymmetric Pauson–Khand reactions



X	Tol-BINAP **1b** (% ee)	HexaPHEMP **19a** (% ee)	BINAP **1a** (% ee)
$C(CO_2Me)_2$	96	93	89
CMe_2	82	59	72
NTs	95	80	88
NCH_2Ph	96	74	92

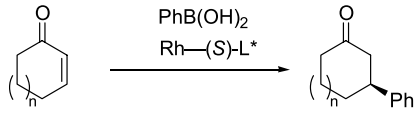
1,4-Addition of boronic acid. Hayashi et al. developed Rh-catalyzed asymmetric 1,4-additions of arylboroxines to α,β-unsaturated phosphonates.[100] In their study, they showed that *u*-BINAP, an unsymmetrical ligand, generally afforded a slightly higher level of enantioselection than did BINAP (Scheme 16).



Scheme 16. Rh-catalyzed asymmetric 1,4-addition.

Chan et al. applied a P-PHOS-containing Rh catalyst to asymmetric 1,4-additions of arylboronic acids to enones.[151] They found that the catalyst gave comparable or even better enantioselectivities and catalytic activities relative to reactions employing BINAP as the ligand. NAPhePHOSes as well as MeO-BIPHEP also gave high enantiomeric excesses[152] (Table 34).

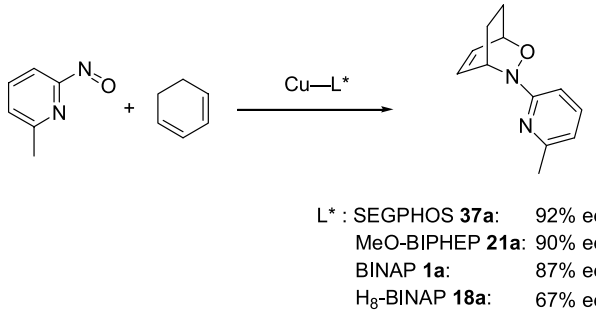
Table 34. Rh-catalyzed asymmetric 1,4-addition



	L* % ee				Ref.
$n=1$	**59a**		**1a**		151
	99		97		152
$n=1$	**66**	**65**	**21a**	**1a**	105
	98	98	98	98	
$n=2$	**59a**		**1a**		151
	98 (88% yield)		93 (51% yield)		152

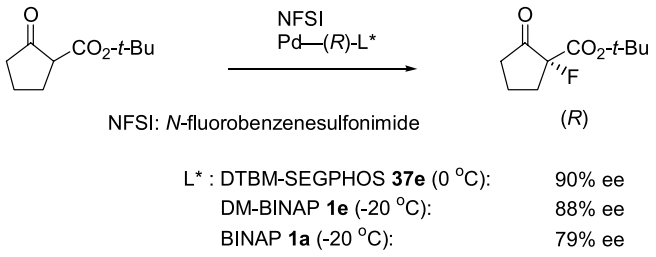
1a: BINAP, **21a**: MeO-BIPHEP, **59a**: P-PHOS, **65**: MeO-NAPhePHOS, **66**: TriMe-NAPhePHOS.

5.3.3. Other reactions. *Nitroso Diels–Alder reactions*. Yamamoto et al. surveyed ligand effects in Cu-catalyzed asymmetric nitroso Diels–Alder reactions.[153] Among the ligands examined, those with narrower dihedral angles tended to give higher enantioselectivities. The best results were obtained using SEGPHOS (92% ee) (Scheme 17).



Scheme 17. Cu-catalyzed asymmetric nitroso Diels–Alder reaction.

Fluorination. Sodeoka et al. developed an asymmetric fluorination reaction using Pd–aquo complexes containing biaryl ligands.[154] They found that substituents in the *meta* position of the phenyl pendants are crucial for high enantioselectivities. The highest enantioselectivities were obtained employing DTBM-SEGPHOS (Scheme 18).

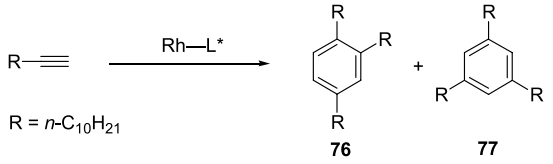


Scheme 18. Pd-catalyzed asymmetric fluorination.

5.4. Non-asymmetric catalysis

The efficiency of ligand optimization was also proven to be valuable in non-asymmetric catalysis.

Tanaka et al. studied Rh-catalyzed regioselective intermolecular cyclotrimerization of terminal alkynes. In the case of 1-dodecyne as substrate, DTBM-SEGPHOS as ligand led to a higher regioselectivity (**76/77**) than that observed using Tol-BINAP[155] (Scheme 19).



L*	DTBM-SEGPHOS **37e**	Tol-BINAP **1b**
76/**77**	83/17	64/36

Scheme 19. Rh-catalyzed intermolecular cyclotrimerization.

6. Concluding remarks

A quarter century has passed since BINAP was first reported. During this time, more than 60 frameworks based on a biarylbisphosphine theme have been developed worldwide. If additional substitution at phosphorus is taken into account, the number grows exponentially. Taken together, these ligands today play a pivotal role in asymmetric hydrogenation. Hypotheses have been advanced to account for their effectiveness, proposals that have spawned even newer and more selective ligands. Nonetheless, there has yet to appear a set of universal guidelines that provide the 'perfect' ligand for any given synthetic situation. Indeed, much more research in this area remains to be done.

For now, the number of applications of these newly developed ligands remains rather limited, compared to those which rely on BINAP. The difference is presumably due to their limited availability. As illustrated in the latter part of this review, some of these ligands are very recent arrivals, yet have already shown great promise in selected reactions, compared to BINAP. If the ligands can be prepared in a large scale and provided conveniently, their scope would expand further. It is of great interest to see how this chemistry will progress in the future.

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Biographical sketch

Hideo Shimizu was born in Yamanashi, Japan, in 1972. He received his M.S. degree in 1997 from Tokyo Institute of Technology under the supervision of Professor Takeshi Nakai before he joined Takasago International Corporation. He spent the year 2002–2003 at University of California, Santa Barbara with Professor Bruce H. Lipshutz, working on asymmetric hydrosilylation of imines. He is currently involved in development of chiral catalysts and their application to production of fine chemicals.

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Exploiting the Maitland–Japp reaction: a synthesis of (±)-centrolobine☆

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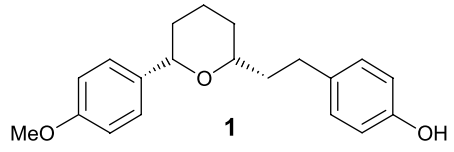
Abstract—Application of our one-pot, three-component variation of the Maitland–Japp reaction has led to the formation of a tetrahydropyran-4-one, which was converted in three steps to the antiparasitic and antibiotic natural product (±) centrolobine.

1. Introduction

(−)-Centrolobine **1** was isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile*.[1,2] Recently, (−)-centrolobine **1** and related natural products, have been shown to be active against *Leishmania amazonensis promastigotes*; a parasite associated with *leishmaniasis*, a major health problem in Brazil.[3,4]



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Leishmania is a parasitic disease transmitted by the sand fly, and is related to Indian dum dum fever. Once in its human host, the parasite attacks the spungiform organs of the body, especially the liver and spleen, where the initial symptoms include a high fever, meaning that the disease is often mistaken for malaria. If the parasite attacks the skin, similar symptoms to leprosy arise, again, often leading to the wrong treatment being given to the patient. For the past 80 years, the only available drug for this distressing disease has been the pentavalent antimonials, which have been recently, linked to cardiac and renal toxicity.[3] It is for this reason that Leon and co-workers, conducted a screen of traditional remedies from the Amazon rainforest to find new anti-leishmanial compounds.[3,4] Interestingly, (−)-centrolobine **1** had already been shown to be one of the active ingredients in a herbal tea made from the wood of *Centrolobum robustum* that is used by the native peoples of the Amazon as a tonic cure for a variety of ailments.

(−)-Centrolobine **1** is a 2,6 *cis*-substituted tetrahydropyran and its simple structure has made it a test-bed for pyran-forming methodologies in recent years. The structure of **1** was proven with the synthesis of the racemic methyl ether in 1964,[1] but it was not until 2002, that the absolute configuration was assigned by the asymmetric total synthesis of **1** by Colobert and co-workers.[5,6] Three further, asymmetric syntheses followed from the groups of Rychnovsky,[7] Evans[8] and Cossy.[9]

The first, total synthesis by Colobert et al.[5] featured the reduction of a β-ketosulfoxide followed by an intramolecular cyclisation and yielded the natural product in nine steps. The second synthesis by Rychnovsky[7] utilised a Prins cyclisation as the key step and furnished (−)-centrolobine in seven steps. A synthesis by Evans,[8] formed the tetrahydropyran ring by an intramolecular reductive etherification strategy and provided the natural product in five steps from aldehyde **5**. Finally, Cossy reported a four step synthesis of (−)-centrolobine in an overall yield of 7%.[9]

2. Results and discussion

We were of the opinion that the existing syntheses of centrolobine were either unduely long or produced centrolobine in an unacceptably low yield, and that our renaissance of the Maitland–Japp reaction may provide a way to synthesise centrolobine in a more expedient and higher yielding

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Keywords: Multi-component; Tetrahydropyran; Maitland–Japp; Centrolobine.
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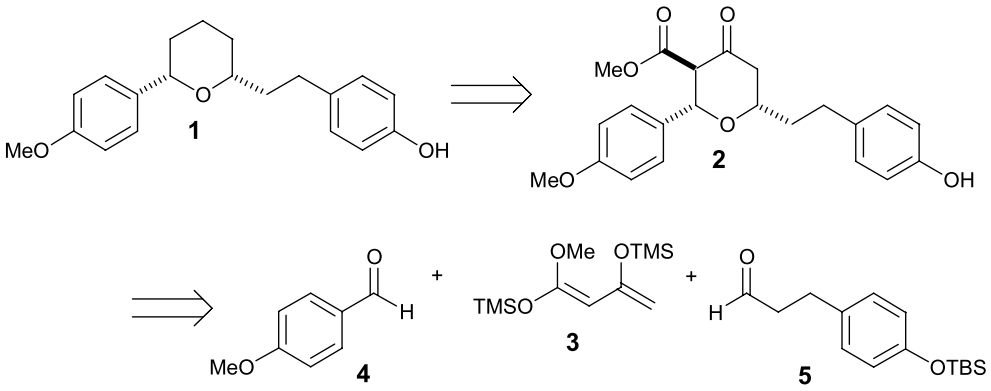


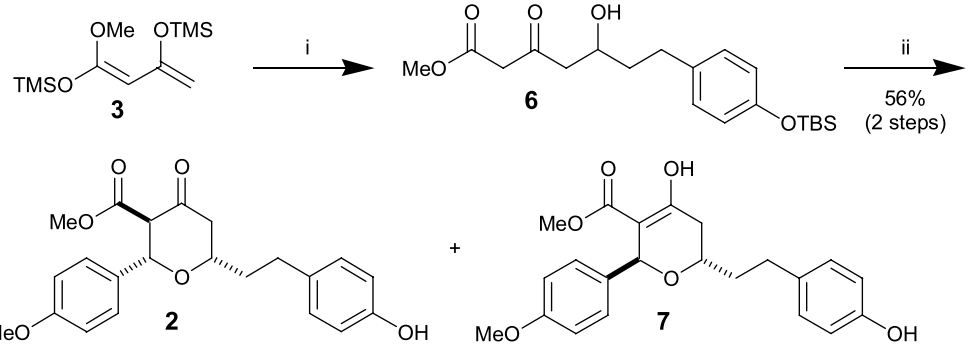
Scheme 1. Retrosynthetic analysis of centrolobine.

manner. Retrosynthetically, it was hypothesised that centrolobine **1** could be obtained by reduction and decarboxylation of the tetrahydropyran-4-one **2**, which would be the result of the Lewis acid mediated Maitland–Japp reaction of Chan's diene **3** and the two aldehydes **4** and **5** (Scheme 1).

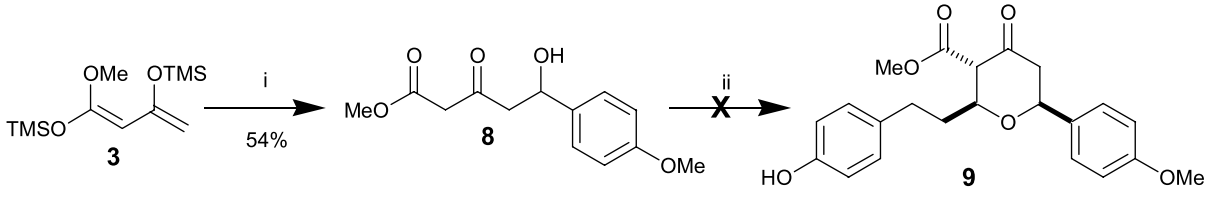
2.1. The two-pot construction of tetrahydropyran-4-one 2

Initially, construction of the tetrahydropyran-4-one **2** by our original two-pot procedure was investigated.[10] It was decided to use aldehyde **5** as the aldol reaction coupling partner, as it had been used previously as a starting point in Evans' synthesis of centrolobine.[8] Aldehyde **5** was prepared according to the procedure of Jones[11] and was subjected to a Mukaiyama aldol reaction with Chan's diene **3**, to give aldol adduct **6**, which was used without any further, purification. With the δ-hydroxy β-ketoester **6** in hand, the boron trifluoride mediated pyran-forming reaction was investigated. Pyran formation appeared to be rapid by TLC analysis but prolonged reaction times were necessary to effect in situ TBS deprotection. This led to the isolation of two diastereomeric tetrahydropyran-4-ones **2** and **7** in a 1.0:0.6 ratio and in a combined overall yield of 56% from the aldehyde **5** (Scheme 2).

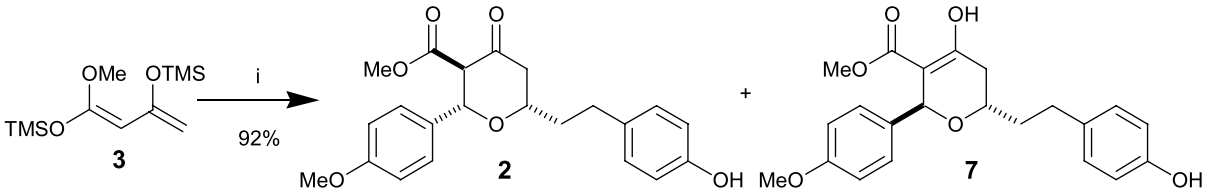
In an attempt to increase, the yield and the selectivity of the Maitland–Japp cyclisation reaction, it was decided to investigate introduction of the side chains in the reverse order, to give pyranone **9**. Therefore, aldol adduct **8** was synthesised in an unoptimised 54% yield by reaction of Chan's diene **3** with anisaldehyde **4**. The cyclisation reaction between **8** and the aldehyde **5** was attempted under the standard boron trifluoride diethyl etherate mediated conditions,[10] however, none of the desired product **9** was isolated. In a further, experiment it was found that the δ-hydroxy β-ketoester **8** was unstable to the Lewis acidic reaction conditions (Scheme 3), probably as the hydroxyl centre is activated by the 4-methoxy group on the aromatic ring.



Scheme 2. Reagents and conditions: (i) **5**, $TiCl_4$, CH_2Cl_2, -78 °C; (ii) anisaldehyde, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temperature, 24 h, 56% over two steps.



Scheme 3. Reagents and conditions: (i) anisaldehyde, $TiCl_4$, CH_2Cl_2, -78 °C, 54%; (ii) **5**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, room temperature.



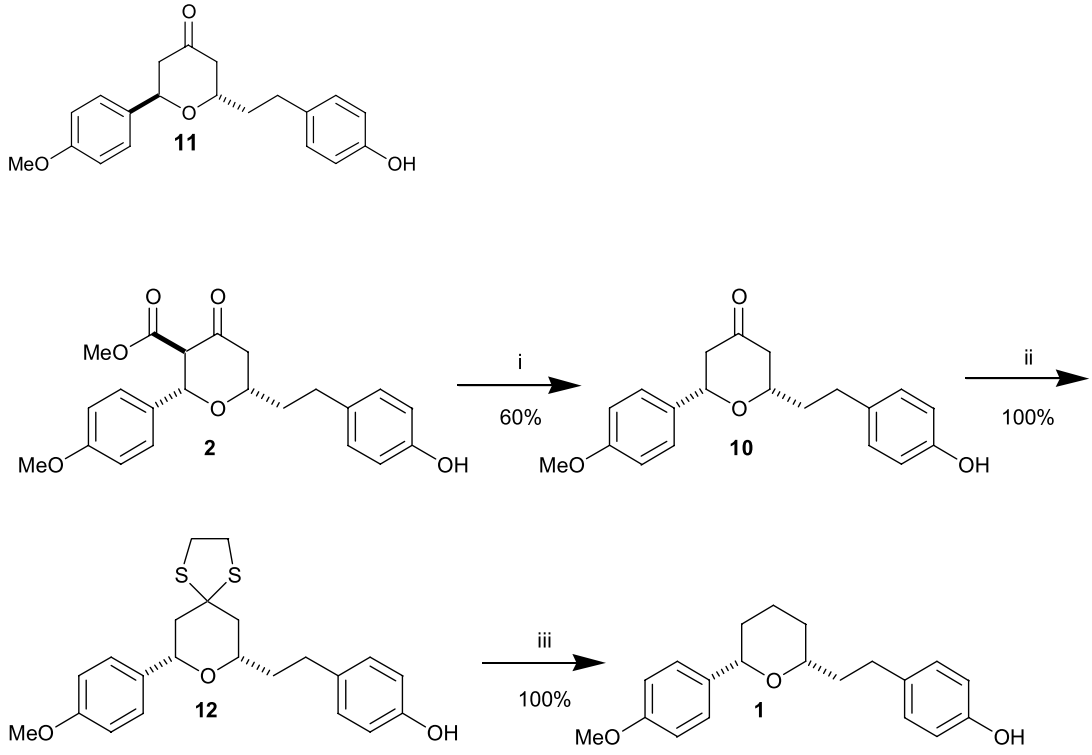
Scheme 4. Reagents and conditions: (i) $Yb(OTf)_3$, **5**, −78 °C, 1 h, then TFA, anisaldehyde, −78 °C to room temperature, 12 h, 92%.

2.2. The one-pot construction of tetrahydropyran-4-one 2

The one-pot pyran-forming methodology[12] was also applied to the synthesis of tetrahydropyran-4-one **2**.[13] It had previously been found that ytterbium (III) triflate favoured the formation of the 2,6 *cis*-isomer over the 2,6 *trans*-isomer, and using the optimised reaction conditions the 2,6 *cis*-isomer **2** was formed in a 2:1 ratio to the 2,6 *trans*-isomer **7** and in an excellent 92% yield (Scheme 4). It was possible to separate and then resubmit the *trans*-diastereomer to the reaction conditions and hence, re-equilibrate to a 2:1 mixture of **2**:**7**, thus, increasing the isolated yield of **2** to 82%.

With a reasonably efficient route to the desired 2,6 *cis*-isomer **2** in hand, the final stages of the synthesis were investigated. Decarboxylation of the pyranone **2** was attempted using LiOH, however, the product of a retro-Michael reaction was formed exclusively, rather than that, of decarboxylation. Decarboxylation was achieved by use of LiOH and H_2O_2, which provided **10** in 60% yield. The remaining mass balance of the reaction was an enone arising from a retro-Michael reaction. We rationalised that the less basic, more nucleophilic hydroperoxide anion favoured saponification of the methyl ester via nucleophilic attack at the carboxyl group, rather than enolate formation, which led to the competing retro-Michael reaction. For the purposes of comparison and to establish that epimerisation at the C6 position had not taken place during the decarboxylation process, the 2,6 *trans*-isomer **11** was formed by decarboxylation of the *trans* pyranone **7** using the same $LiOH/H_2O_2$ conditions employed for the *cis*-isomer **2**. The two compounds, **10** and **11**, had markedly different ^1H NMR spectra with **10** having an ABX system with $J^3=10.7$, 3.4 Hz for H2 coupling to H3α and H3β, and $J^3=10.7$, 3.8 Hz for H6 coupling to H5α and H5β, indicating the 2,6 *cis* stereochemistry whereas **11** had $J^3=5.7$, 5.4 Hz for H6 coupling to H5α and H5β, consistent with a 2,6 *trans* structure in rapid conformational equilibrium. The fact that no epimerisation occurred during the decarboxylation of either pyranone indicates that, under these conditions, decarboxylation is more facile than the retro-Michael reaction and that the decarboxylation of **7** must proceed via tautomerisation of **7** to its keto-tautomer.

The final synthetic challenge was to effect the reduction of the carbonyl of **10** to a methylene group. The first method investigated was the Wolff–Kischner reaction, but upon work-up this was found to have returned only starting



Scheme 5. Reagents and conditions: (i) H_2O_2, LiOH, THF, H_2O, room temperature, 5 h, then 70 °C, 30 min, then room temperature, 12 h, 60%; (ii) $HSCH_2CH_2SH$, $BF_3\cdot OEt_2$, CH_2Cl_2, room temperature, 100%; (iii) Raney nickel, H_2, EtOH, 30 °C, 100%.

material. Analysis by TLC suggested that the hydrazone was formed readily, which implied that the base-mediated elimination was the problematic step. The phenolic hydroxyl group would have been deprotonated under the reaction conditions giving an anionic species that would perhaps be less susceptible to elimination of the hydrazone. With the failure of the Wolff–Kischner reaction it was decided to effect the carbonyl removal in two steps via formation of the dithiane. To this end the carbonyl in **10** was treated with ethane dithiol and boron trifluoride diethyl etherate to give the dithiane **12** in quantitative yield. Raney Nickel reduction of **12** proceeded under an atmosphere of hydrogen at 70 °C to give (±)-centrolobine **1** quantitatively (Scheme 5).

3. Conclusions

We have applied our variation of a one-pot, three-component Maitland–Japp reaction to the synthesis of (±)-centrolobine. The synthesis was achieved in four steps and in 50% yield from aldehyde **5**, which compares extremely favourably with those syntheses already reported.

4. Experimental

4.1. General

All melting points are uncorrected. Reaction progress was monitored using glass-backed TLC plates pre-coated with silica UV_{254} and visualised by using either UV radiation (254 nm), ceric ammonium molybdate or anisaldehyde stains. Column chromatography was performed using silica gel 60 (220–240 mesh), with the solvent systems indicated in the relevant experimental procedures. Dichloromethane was distilled from calcium hydride, tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl, dimethyl formamide was stirred with calcium hydride and distilled prior to use. Benzene, DMSO and MeCN were all distilled from calcium hydride prior to use. Hexane was distilled prior to use. All other reagents were used as received from commercial suppliers unless stated otherwise in the appropriate text.

4.2. The two-pot procedure for the synthesis of 4-hydroxy-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 2 and 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)tetrahydro-pyran-3-carboxylic acid methyl ester 7

To a solution of 3-(4-*tert*-butyldimethlsilyloxyphenyl) propanal **5** (264 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added titanium tetrachloride (111 μL, 1.00 mmol). The black solution was stirred for 2 min and then Chan's diene **3** (570 μL, 2.00 mmol) was added over a 1 min period. The black solution was stirred at −78 °C for 1 h and then 5% aq, $NaHCO_3$ soln (20 mL) was added and the reaction allowed to warm to room temperature. The solution was taken up in Et_2O (30 mL) and washed with 5% aq, $NaHCO_3$ soln (3×30 mL), and brine (2×30 mL), dried ($MgSO_4$), and concentrated in vacuo. The product **6** was used without further purification in the next reaction.

To a stirred mixture of 5-hydroxy-3-oxo-7-(4-tertbutyldimethlsilyloxyphenyl) heptanoic acid methyl ester **6** (1.00 g, 2.63 mmol) in CH_2Cl_2 (40 mL) at room temperature was added anisaldehyde (383 μL, 3.16 mmol) followed by boron trifluoride diethyletherate (333 μL, 2.63 mmol). The yellow solution was stirred at room temperature for 48 h and was then taken up in Et_2O (60 mL) and washed with brine (2×30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:10 EtOAc–petroleum ether) gave **2** and **7** in a ratio of 1.0:0.6 in favour of **2** (566 mg, 56%).

Compound **2**. Oil ν_{max} (film) 3598, 2955, 2930, 1744 (C═O), 1714 (C═O), 1614, 1514, 1251, 1176 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 7.32 (2H, d, J=8.4 Hz), 7.00 (2H, d, J=8.4 Hz), 6.89 (2H, d, J=8.8 Hz), 6.74 (2H, d, J=8.4 Hz), 5.37 (1H, br s), 4.81 (1H, d, J=10.7 Hz), 3.81 (3H, s), 3.81 (1H, dddd, J=11.2, 7.4, 4.4, 2.4 Hz), 3.62 (1H, d, J=10.7 Hz), 3.60 (3H, s), 2.70–2.64 (2H, m), 2.56 (1H, dd, J=14.6, 2.4 Hz), 2.46 (1H, dd, J=14.6, 11.2 Hz), 2.03 (1H, m), 1.85 (1H, m) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.0, 168.0, 154.0, 133.0, 130.9, 129.4, 128.1, 115.3, 114.0, 80.4, 76.0, 55.2, 46.9, 37.8, 30.9, 30.2 ppm; *m/z* (CI+) 384 (40%, M^+), 325 (33%, M^+–CO_2Me), 107 (100%, $MeOPh^+$); HRMS: found (M^+), 384.1561. $C_{22}H_{24}O_6$ requires (M^+) 384.1573.

Compound **7**. Oil ν_{max} (film) 3354, 2924, 2853, 1714 (C═O), 1612, 1414, 1259, 1216, 1173, 1097, 1031 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 12.29 (1H, s), 7.28 (2H, d, J=8.8 Hz), 6.93 (2H, d, J=8.8 Hz), 6.68 (2H, d, J=8.8 Hz), 6.61 (2H, d, J=8.3 Hz), 5.64 (1H, s), 3.88 (3H, s), 3.65 (3H, s), 3.52 (1H, m), 2.60 (1H, ddd, J=13.7, 8.3, 4.9 Hz), 2.40–2.30 (2H, m), 2.22 (1H, dd, J=18.1, 3.9 Hz), 1.81 (1H, dddd, J=17.1, 14.1, 7.8, 4.9 Hz), 1.62 (1H, dddd, J=17.1, 11.7, 8.3, 3.4 Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.2, 171.0, 159.2, 153.5, 133.1, 133.1, 129.8, 129.5, 115.0, 113.5, 99.0, 72.4, 64.7, 55.3, 51.6, 37.6, 34.8, 30.2 ppm; *m/z* (TOF ES+) 448 (69%, M^++Na+CH_3CN), 407 (100%, M^++Na), 385 (36%, M^++H); HRMS: found (M^++Na), 407.1459. $C_{22}H_{24}O_6$ requires (M^++Na) 407.1471.

4.3. The one-pot procedure for the synthesis of 4-hydroxy-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester 2 and 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)tetrahydro-pyran-3-carboxylic acid methyl ester 7

To a suspension of ytterbium (III) triflate (310 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added 3-(4-*tert*-butyldimethlsilyloxyphenyl) propanal **6** (130 mg, 0.50 mmol) followed by Chan's diene (285 μL, 1.00 mmol). The white mixture was stirred at −78 °C for 180 min and then trifluoroacetic acid (158 μL, 2 mmol) was added followed by the anisaldehyde (75 μL, 0.60 mmol). The mixture was warmed to room temperature over 5 min and then stirred at room temperature for 5 h. The mixture was then diluted with Et_2O (40 mL) and washed with 5% aq, $NaHCO_3$ soln, (3×30 mL) and brine (2×30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:10 EtOAc–petroleum ether)

pyran products **2** (115 mg, 60%) and **7** (62 mg, 32%), which were spectroscopically identical to those made via the method above.

4.3.1. 2,6-*cis*-6-(2-(4-Hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-4-oxo-tetrahydropyran 10. To a solution of 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-tetrahydro-pyran-3-carboxylic acid methyl ester **2** (70 mg, 0.18 mmol) in THF/H_2O (4:1, 2 mL) at room temperature was added hydrogen peroxide (90 μL, 0.72 mmol) followed by lithium hydroxide (9 mg, 0.28 mmol). The solution was stirred at 60 °C for 2 h and then taken up in Et_2O (30 mL) and washed with 5% aq, sodium metabisulfite soln, (3× 330 mL), and brine (2×20 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (1:10 EtOAc–petroleum ether) gave the title compound **10** as an oil (36 mg, 60%) ν_{max} (film) 3414, 2856, 1714 (C=O), 1660, 1514, 1444, 1250, 1032 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.31 (2H, d, J=8.4 Hz), 7.03 (2H, d, J=8.4 Hz), 6.93 (2H, d, J=8.8 Hz), 6.74 (2H, d, J=8.8 Hz), 4.92 (1H, s), 4.56 (1H, dd, J=10.7, 3.8 Hz), 3.82 (3H, s), 3.71 (1H, dddd, J=10.7, 8.1, 4.3, 3.4 Hz), 2.77 (1H, ddd, J=14.1, 9.5, 5.5 Hz), 2.71 (1H, ddd, J=14.1, 8.5, 7.7 Hz), 2.61 (1H, ddd, J=14.5, 3.8, 1.3 Hz), 2.57 (1H, dd, J=14.5, 10.7 Hz), 2.44 (1H, ddd, J=14.1, 3.4, 1.3 Hz), 2.39 (1H, dd, J=14.1, 10.7 Hz), 2.04 (1H, dddd, J=13.6, 8.5, 8.1, 5.5 Hz), 1.84 (1H, dddd, J=13.6, 9.4, 7.7, 4.3 Hz) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.2 (s), 159.3 (s), 153.8 (s), 133.5 (s), 133.0 (s), 129.5 (d), 127.0 (d), 115.2 (d), 114.0 (d), 112.7 (s), 78.2 (d), 76.1 (d), 55.3 (q), 49.3 (t), 47.7 (t), 38.1 (t) ppm; m/z (CI+) 326 (38%, M^+), 107 (30%, $C_6H_4OMe^+$) 84 (100%); HRMS: found (M^+), 326.1505. $C_{20}H_{22}O_4$ requires (M^+) 326.1518.

4.3.2. 2,6-*trans*-6-(2-(4-Hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-4-oxo-tetrahydropyran 11. To a solution of 4-hydroxy-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-2,3-dihydro-2*H*-pyran-3-carboxylic acid methyl ester **7** (40 mg, 0.10 mmol) in THF/H_2O (1 mL, 4:1), was added hydrogen peroxide (75 μL, 0.416 mmol) followed by lithium hydroxide (7 mg, 0.166 mmol). The reaction was stirred at room temperature for 5 h. No change was seen by TLC analysis so the temperature was raised to 70 °C for 3 h and the reaction was then stirred for a further, 15 h at room temperature. The reaction mixture was taken up in ether (30 mL), and then washed with 5% aq sodium metabisulfite soln, (3×20 mL), and brine (2×20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash column chromatography (1:10 EtOAc–petroleum ether) gave the title compound **11** as an oil (21 mg, 65%) ν_{max} (film) 3598, 3019, 2929, 2856, 1714 (C=O), 1612, 1514, 1181, 1034 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.29 (2H, d, J=8.8 Hz), 6.94 (2H, J=8.4 Hz), 6.89 (2H, d, J=8.8 Hz), 6.69 (2H, d, J=8.4 Hz), 5.24 (1H, dd, J=5.7, 5.4 Hz), 4.73 (1H, br s), 3.89 (1H, m), 3.82 (3H, s), 2.84 (1H, ddd, J=14.9, 5.4, 1.1 Hz), 2.79 (1H, ddd, J=14.9, 5.7, 1.1 Hz), 2.69 (1H, ddd, J=14.1, 9.6, 5.0 Hz), 2.54–2.48 (2H, m), 2.35 (1H, ddd, J=14.5, 7.6, 1.1 Hz), 1.96 (1H, dddd, J=18.4, 14.1, 9.2, 5.0 Hz), 1.67 (1H, dddd, J=18.4, 14.2, 7.3, 4.2 Hz) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.4, 159.4, 133.5, 132.1, 129.5, 128.4, 115.2, 114.0, 114.0, 73.4, 70.6, 55.3, 47.3, 45.9, 36.7, 30.6 ppm; m/z (CI+) 326 (83%, M^+), 205 (10%, M^+–$CH_2CH_2C_6H_4OH$) 134 (80%), 107 (30%, $C_6H_4OMe^+$); HRMS: found (M^+), 326.1509. $C_{20}H_{22}O_4$ requires (M^+) 326.1518.

4.3.3. 4-Dithiane-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-tetrahydropyran 12. To a solution of 6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-4-oxo-tetrahydropyran **10** (20 mg, 0.061 mmol), in CH_2Cl_2 (1 mL), was added ethane dithiol (5.6 μL, 0.07 mmol), followed by boron trifluoride etherate (8.5 μL, 0.06 mmol). The solution was stirred at room temperature for 20 min then taken up in Et_2O (30 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the title compound as an oil (25 mg, 100%). ν_{max} (film) 3389, 2922, 2852, 1814, 1613, 1442, 1248, 1176, 1033 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.31 (2H, d, J=8.8 Hz), 7.03 (2H, d, J=8.8 Hz), 6.89 (2H, d, J=8.8 Hz), 6.73 (2H, d, J=8.8 Hz), 4.52 (1H, dd, J=11.1, 2.0 Hz), 3.80 (3H, s), 3.67 (1H, dddd, J=11.1, 6.7, 4.4, 2.0 Hz), 3.37–3.35 (4H, m), 2.77 (1H, ddd, J=14.0, 9.9, 5.6 Hz), 2.67 (1H, ddd, J=14.0, 9.6, 6.7 Hz), 2.31 (1H, ddd, J=13.5, 2.4, 2.4 Hz), 2.15 (1H, dd, J=13.5, 11.1 Hz) 2.15 (1H, ddd, J=13.5, 4.1, 2.0 Hz) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 159.0 (s), 153.7 (s), 134.3 (s), 134.2 (s), 129.5 (d), 127.3 (d), 115.2 (d), 113.8 (d), 78.1 (d), 76.4 (d), 65.8 (s), 55.4 (q), 49.7 (t), 47.4 (t), 39.3 (t), 37.9 (t), 37.8 (t), 30.8 (t) ppm; m/z (CI+) 402 (47%, M^+), 309 (100%, M^+-PhOH), 135 (45%), 107 (91%, $C_6H_4OMe^+$); HRMS: found (M^+), 402.1315. $C_{22}H_{26}O_3S_2$ requires (M^+) 402.1323.

4.3.4. (±) Centrolobine 1. To a solution of 4-dithiane-6-(2-(4-hydroxyphenyl)-ethane)-2-(4-hydroxyphenyl)-tetrahydropyran **12** (20 mg, 0.05 mmol) in EtOH (2 mL), was added Raney nickel (150 mg, 50% slurry in H_2O). The heterogeneous mixture was heated at 35 °C for 18 h under an atmosphere of H_2 and then passed through celite. The solvent was removed under reduced pressure to give (±) centrolobine as a white solid (15 mg, 100%) The data were in agreement with the literature values.[5–8] Mp 87–89 °C (lit.[1,5,6] 85–87 °C); ν_{max} (film) 3348, 2924, 2851, 1613, 1514, 1454, 1246, 1174, 1080, 1035, 827 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.31 (2H, d, J=8.5 Hz), 7.05 (2H, d, J=8.8 Hz), 6.88 (2H, d, J=8.5 Hz), 6.74 (2H, d, J=8.8 Hz), 4.29 (1H, dd, J=11.1, 2.0 Hz), 3.80 (3H, s), 3.44 (1H, dddd, J=12.6, 6.4, 4.7, 1.8 Hz), 2.73 (1H, m), 2.65 (1H, m), 1.95–1.22 (8H, m) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 158.7, 153.5, 135.9, 134.7, 129.6, 127.2, 115.1, 113.7, 79.1, 77.2, 55.4, 38.4, 33.4, 31.3, 30.8, 24.1 ppm; m/z (TOF ES+) 335 (50%, M^+ +Na), 233 (100%); HRMS: found (M^+ +Na), 335.1623. $C_{20}H_{24}O_3$ requires (M^+ + Na) 335.1626.

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First synthesis of an α-D-Fuc*p*3NAc containing oligosaccharide: a study on D-Fuc*p*3NAc glycosylation

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Abstract—3-Acetamido-3,6-dideoxy-D-galactopyranose (D-Fuc*p*3NAc) is an aminosugar almost exclusively found in phytopathogenic *O*-antigens. The glycosylation reaction involving D-Fuc*p*3NAc donors was studied with several rhamnosyl acceptors, revealing that the best yields and highest α-stereoselectivity were obtainable by coupling a *N*-phenyl trifluoroacetimidate glycosyl donor in a ternary mixture (dioxane/DME/toluene 4:1:1) as solvent. For the first time a synthetic access to α-D-Fuc*p*3NAc containing oligorhamnans, that are interesting molecules for studying the effects of *O*-antigen model oligosaccharides on the modulation of plant response to bacteria, was reported. An example is the pentasaccharide repeating unit of the major *O*-antigen component from *Pseudomonas syringae* pv. *holci* IMV 8300, which was synthesized as its methyl glycoside.

1. Introduction

Lipopolysaccharides (LPSs) are amphiphilic macromolecules that are located on the external membrane of Gram-negative bacteria.[1] They consist of three different domains:[2] a lipid part, named Lipid-A, an oligosaccharide region, named Core and a polysaccharide portion (*O*-specific chain, or simply *O*-chain), consisting of a 1–8 sugar residues repeating unit, and extends out from the bacterial membrane surface. The role of LPSs in bacterial interactions both with animals and plants is surely crucial, as they cover almost 80% of the cell surface; therefore, they have been the object of many studies, especially in relation to Gram-negative bacteria that are pathogenic to humans and mammals.[3] These studies elucidated that most of the biological activities of LPS are played by Lipid-A, nevertheless *O*-chain is also involved in interactions between bacterial cells and their eukaryotic hosts with its antigenic properties.

However, the effects of LPSs on plant cells have still been poorly elucidated. The only extensive study is on the ability of LPS to prevent the hypersensitive response (HR) caused in plants by avirulent bacteria.[4,5] Even if the molecular basis of the LPS-plant interaction is still very far from completely known, the *O*-chain should be highly involved in the interaction mechanism,[5] because of its extension out from the bacterial cell.

The *O*-chain from phytopathogenic bacteria is typically made of a repeating unit with a linear L- and/or D-rhamnosyl skeleton. This backbone usually bears, as a branch, a single monosaccharide, that can be a common monose (L- or D-Xyl*p*, L- or D-Rha*p*, D-Glc*p*NAc, D-Fuc*f*) or a peculiar aminosugar, 3-acetamido-3,6-dideoxy-D-galactopyranose (D-Fuc*p*3NAc), that is almost exclusively found in LPS from phytopathogenic bacteria.[6] Interestingly, the linkage between D-Fuc*p*3NAc and the rhamnosyl backbone occurs in natural oligosaccharides exclusively as the α-glycoside.

In a recent study, synthetic linear oligorhamnans, mimicking the common structure of the *O*-chain backbones from phytopathogenic bacteria, have been proved to be effective in preventing HR,[7] demonstrating in this way that oligosaccharides are also plant-recognizable pathogen-associated molecular patterns (PAMPs).[8] In order to investigate deeper the effects of oligosaccharides on the modulation of plant response to bacteria, the synthesis of model oligosaccharides, related to the repeating units of *O*-chain, has recently become a topic of interest in carbohydrate synthesis.[9]

In particular, in this paper we have studied the coupling reaction between D-Fuc*p*3NAc trihaloacetimidate donors and some L- and D-rhamnosyl acceptors, in order to open a

Keywords: *O*-chain; Repeating unit; D-Fuc*p*3NAc; Glycosylation; *N*-Phenyl trifluoroacetimidate; *Pseudomonas holci*.
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synthetic access to α-D-Fuc*p*3NAc containing oligorhamnans, which are model oligosaccharides of the repeating units of *O*-chain from phytopathogenic bacteria. To demonstrate the effectiveness of this route, we have synthesized the methyl glycoside of the pentasaccharide repeating unit of the major *O*-antigen component from *Pseudomonas syringae* pv. *holci* IMV 8300[10] (Fig. 1). To the best of our knowledge, this is the first synthesis of an α-D-Fuc*p*3NAc containing oligosaccharide.

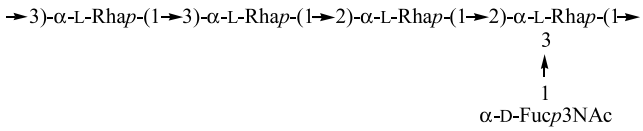
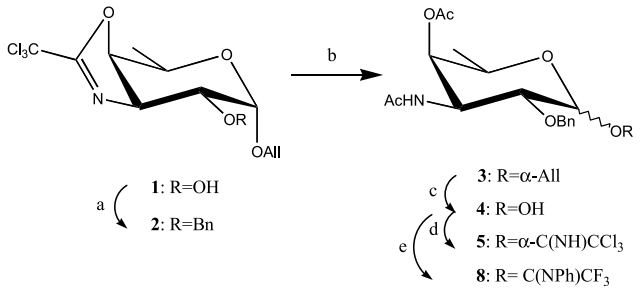


Figure 1. The repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300.

2. Results and discussion

2.1. Study on D-Fuc*p*3NAc glycosidation reaction

The preparative synthesis of the D-Fuc*p*3N building-block **1** from D-fucose has recently been reported.[11] This molecule could be further elaborated to afford D-Fuc*p*3N donors, firstly by protecting position *O*-2. Since D-Fuc*p*3NAc exclusively occurs in the natural polysaccharides as the α-glycoside, a non-participating protecting group, such as the benzyl group, was chosen. Thus, **1** was benzylated to give **2** (68%) that was then subjected to cleavage of the oxazoline ring by acid hydrolysis, and subsequent acetylation of the obtained amino-alcohol (63% over two steps) (Scheme 1). Also the use of an acyl group in position *O*-4 was in accordance with the required α-stereoselectivity in D-Fuc*p*3N glycosidations. Actually, a long range participation effect was firstly postulated[12] and then evidenced[13] to be active in glycosylations involving 4-*O*-acyl-galactose donors; nevertheless it has not been observed in two recent works regarding the coupling of 4-*O*-acyl-thioglycosides.[14,15] We therefore decided to activate D-Fuc*p*3N as trichloroacetimidate, since the use of this kind of glycosyl donor for performing fucosylations with high α-selectivities has been already reported.[16]



Scheme 1. Reagents and conditions: (a) BnBr, NaH, DMF, rt, 68%; (b) (i) 1 M HCl, THF, rt, (ii) Ac_2O, py, rt, 63% over two steps; (c) $PdCl_2$, 1:1 CH_2Cl_2/MeOH, rt, 84% (α/β=1:1.5 as determined by ^1H NMR analysis); (d) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 53%; (e) $CF_3C(NPh)Cl$, NaH, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 74% (α/β=3:1 as determined by ^1H NMR analysis).

The anomeric allyl protecting group of **3** was removed with $PdCl_2$ (84%); the conversion of the resulting hemi-acetal **4** into the α-trichloroacetimidate **5** by treatment with Cl_3CCN and DBU proceeded with only moderate yield (53%). The coupling of **5** with the rhamnosyl acceptors **6**[17] and **7**[18] in CH_2Cl_2 using catalytic TMSOTf (0.01 equiv) as activator led to the consumption of the donor in few min, even working at −50 °C, affording only traces of the desired disaccharides (Fig. 2 and Table 1, entries 1 and 2). A milder activator ($BF_3\cdot OEt_2$), was unfortunately not able to activate **5**, even when used in a more than stoichiometric amount in CH_2Cl_2 at reflux (entry 3).

The rapid decomposition of a 4-*O*-acyl-2-benzylated fucosyl trichloroacetimidate with catalytic TMSOTf in CH_2Cl_2 has been recently reported;[19] moreover, a trimethylated fucosyl trichloroacetimidate revealed a high instability towards many activation conditions,[20] demonstrating in this way the difficulty, in some cases, in glycosylating armed fucosyl-trichloroacetimidates. The difficulty in coupling a D-Fuc*p*3N TCAI-donor as **5** and the not very satisfying yield in obtaining it from **4**, suggested the use of a different glycosyl donor.

Recently, a different trihaloacetimidate, the *N*-phenyl trifluoroacetimidate leaving group, has been installed on the anomeric position of carbohydrates to act as novel glycosyl donor.[21] Since fucosyl *N*-phenyl trifluoroacetimidates have been already successfully glycosylated,[22] the use of this donor also in the D-Fuc*p*3N case has been attempted. Thus, **4** was treated with $CF_3C(NPh)CCl$ and NaH[23] giving **8** in a better yield (74%; α/β 3:1) than **5**.

Gratifyingly, the coupling of **8** respectively with **6** and **7** in CH_2Cl_2 proceeded smoothly, giving disaccharides **9** and **10** in good yields but with moderate α-selectivity (Table 1, entries 4 and 5). Interestingly, 0.1 equiv of TMSOTf were necessary to perform the couplings, but the use of so much activator did not cause significant glycosyl donor decomposition. In order to enhance the α-selectivity of the couplings, we turned to different solvent systems. In particular, α-selectivity is generally favored in electron-donating solvents such as ethers, even if their use can sometimes decrease the total yield of the glycosylation;[24] nevertheless, the use of an 'ether-based' ternary mixture (dioxane/DME/toluene 4:1:1) as solvent for glycosylations involving armed *N*-phenyl trifluoroacetimidate donors, led to higher stereoselectivities of 1,2-*cis*-adducts without affecting the yield of the reactions.[22,25] Actually, performing the coupling between **8** and **7** in this solvent system, the α-stereoselectivity was highly enhanced without a noticeable decrease of the yield (entry 6).

2.2. Synthesis of the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300

The optimization of the conditions for the α-stereoselective coupling between a D-Fuc*p*3N donor as **8** and rhamnosyl acceptors led us to perform the first synthesis of an α-Fuc*p*-3NAc containing repeating unit of *O*-chain from phytopathogenic bacteria, in order to demonstrate the effectiveness of this synthetic approach to this kind of

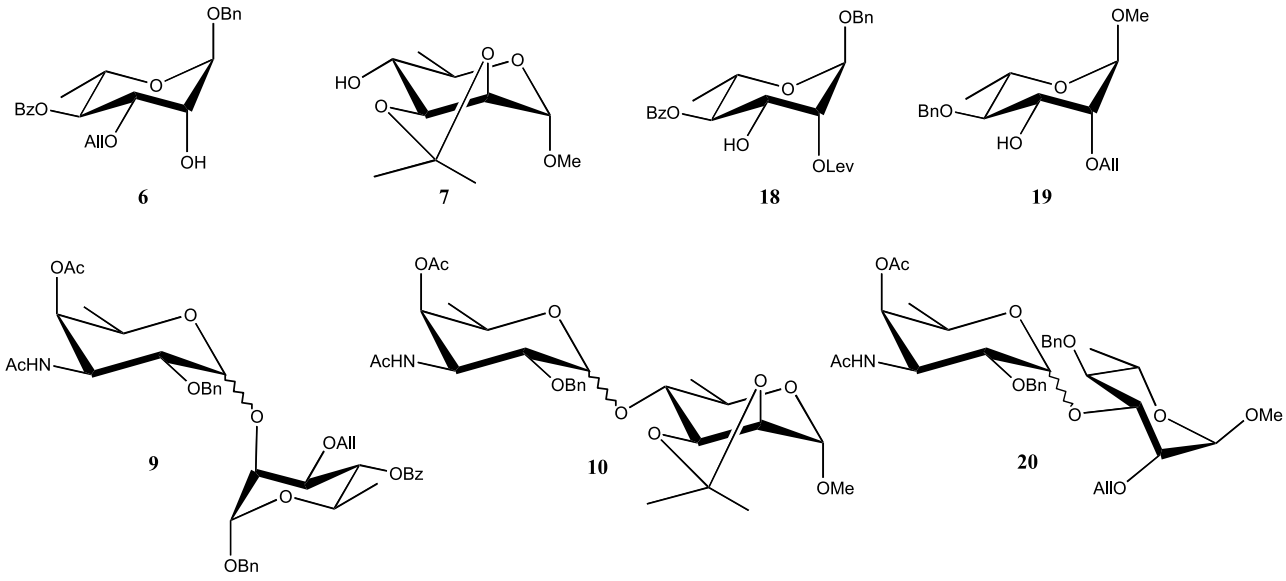


Figure 2. Glycosyl acceptors and products of Table 1 (reaction conditions of the glycosidations are described therein).

Table 1. Glycosylations with D-Fuc*p*3N trihaloacetimidate donors

Entry	Acceptor	Donor	Solvent	Activator	Yield[a] (α/β)	Product
1	**6**	**5** (2.0 equiv)	CH_2Cl_2	TMSOTf	Traces	**9**
2	**7**	**5** (2.0 equiv)	CH_2Cl_2	TMSOTf	Traces	**10**
3	**6**	**5** (2.0 equiv)	CH_2Cl_2	$BF_3 \cdot OEt_2$	No product	—
4	**6**	**8** (2.0 equiv)	CH_2Cl_2	TMSOTf	65% (62:38)[b]	**9**
5	**7**	**8** (2.0 equiv)	CH_2Cl_2	TMSOTf	61% (68:32)[b]	**10**
6	**7**	**8** (1.5 equiv)	Dioxane/DME/ toluene 4:1:1	TMSOTf	55% (88:12)[b]	**10**
7	**18**	**8** (1.5 equiv)	Dioxane/DME/ toluene 4:1:1	TMSOTf	No product	—
8	**19**	**8** (1.8 equiv)	CH_2Cl_2	TMSOTf	70% (82:18)[c]	**20**
9	**19**	**8** (1.5 equiv)	Dioxane/DME/ toluene 4:1:1	TMSOTf	63% (89:11)[c]	**20**

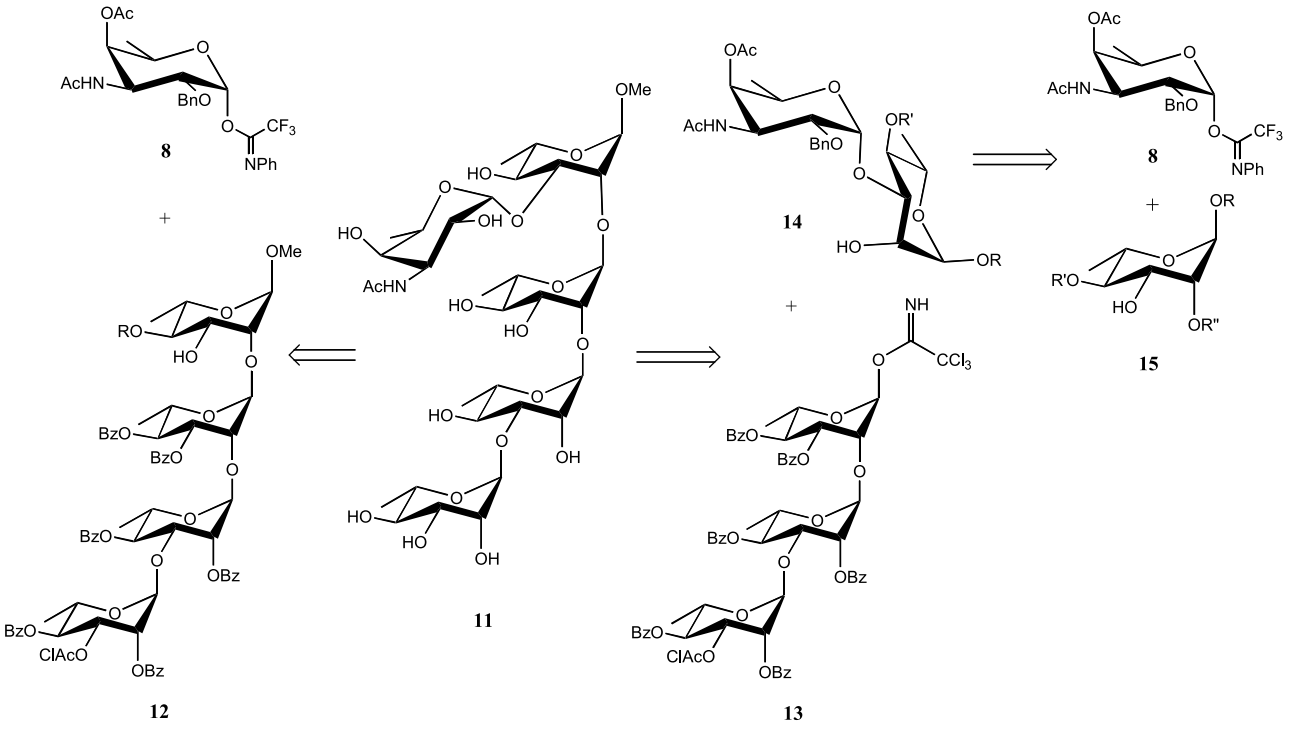
[a] Isolated yield.
[b] Measured by ^{1}H NMR.
[c] Measured after separation of the two anomers.

oligosaccharides. Among the several repeating units that characterise each serotype of phytopathogenic lipopolysaccharides, the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300[10] was chosen (Fig. 1).

For the synthesis of the branched pentasaccharide **11**, two paths could be planned: retrosynthetic analysis suggested either a (4+1) approach, involving the coupling between **8** and a linear rhamnosyl tetrasaccharide **12**,[17] or a (3+2) strategy, in, which the key-glycosylation regards the trisaccharide donor **13**[17] and the disaccharide acceptor **14**, which could be obtained by coupling **8** with a suitable rhamnosyl *O*-3 acceptor **15** (Scheme 2).

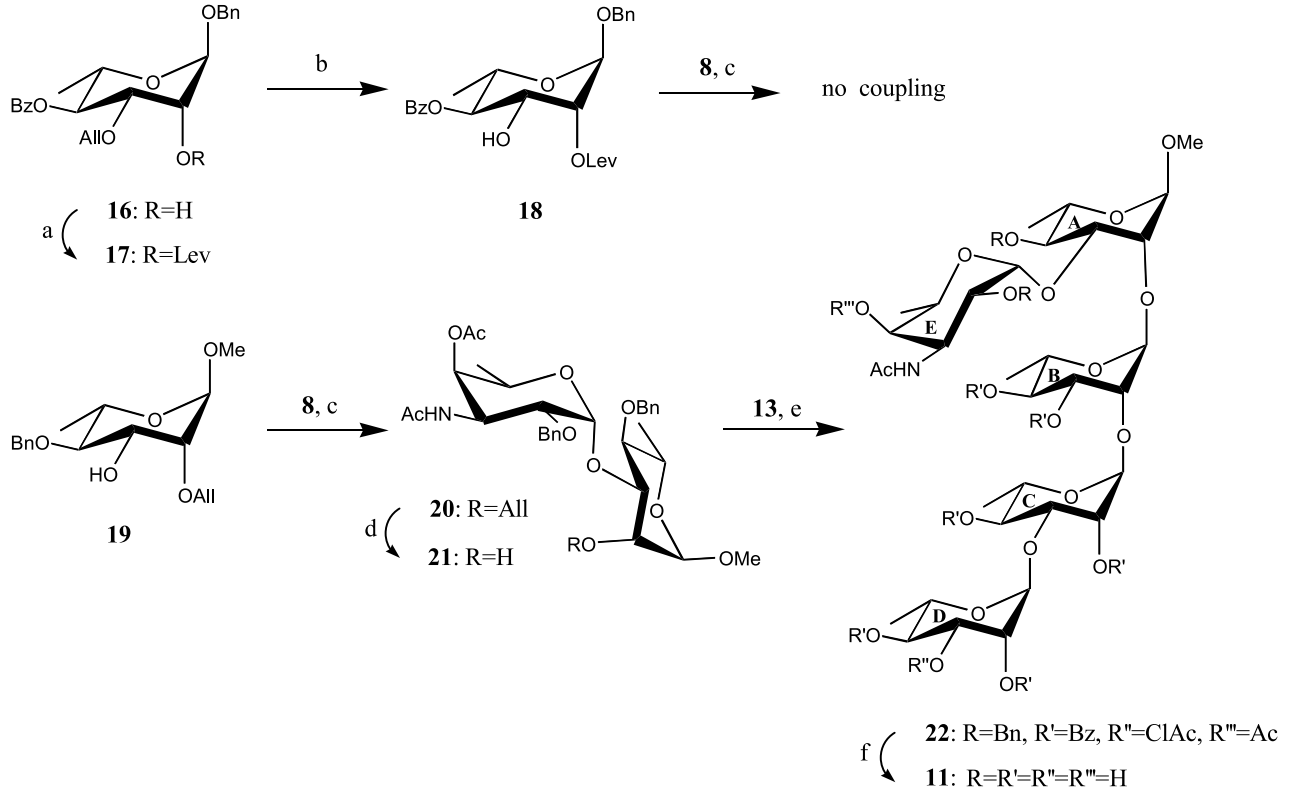
In the synthesis of an analogous pentasaccharide, the major component from *P. syringae* pv. *ribicola* NVPPB 1010, in which the D-Fuc*p*3N branch is replaced by a D-Glc*p*NAc unit,[26] a (4+1) strategy was chosen.[17] It revealed that the (4+1) key-coupling needed a large excess of the aminosugar donor, because of the very poor reactivity of the acceptor **12** (with R=Bz). Since donor **8** was quite 'precious', the other strategy, the (3+2) approach, was chosen for the synthesis of **11**. It required the synthesis of the rhamnosyl *O*-3 acceptor **15**, whose position 2 would be protected with an orthogonal protecting group. Firstly levulinoyl (Lev) was chosen as protecting group for this position. Thus, the known benzyl 3-*O*-allyl-4-*O*-benzoyl-α-L-rhamnopyranoside **16**[17] was subjected to levulination with LevOH in presence of *N*,*N*′-diisopropylcarbodiimide (DIPC) and 4-dimethylaminopyridine (DMAP) (99%) and subsequent de-*O*-allylation with $PdCl_2$ (78%): no acyl migration was observed during the allyl cleavage to obtain **18** (Scheme 3).[27] Unfortunately, the coupling between **8** and **18** was unsuccessful, revealing that the coupling of the D-Fuc*p*3NAc donor **8** probably works only with armed acceptors. Actually, when **8** was coupled with the armed 2-*O*-allylated rhamnosyl *O*-3 acceptor **19**,[28,29] disaccharide **20** was obtained in satisfying yield both in CH_2Cl_2 and in dioxane/DME/toluene 4:1:1 (Table 1, entries 8 and 9). In order to obtain a suitable disaccharide glycosyl acceptor, **20** was subjected to de-*O*-allylation to give **21** in high yield (93%).

The coupling between **21** and the trisaccharide trichloroacetimidate donor **13** was performed in CH_2Cl_2 with



Scheme 2. Retrosynthetic analysis of the methyl glycoside of the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300.

$BF_3 \cdot OEt_2$ as activator, giving **22** in 51% yield. As expected, the new glycosidic bond was formed with total α-stereoselectivity, as ascertained by the value of the heteronuclear $^1J_{C,H}$ coupling constant ($^1J_{C,H}$ = 173 Hz),[30] measured in a coupled HMQC-COSY experiment. Besides, even if the 2-OH group of the glycosyl acceptor **14** was considered to be poorly reactive due to its steric hindrance, and therefore susceptible to competition by the NHAc group as a



Scheme 3. Reagents and conditions: (a) LevOH, DIPC, DMAP, CH_2Cl_2, rt, 99%; (b) $PdCl_2$, 3:2 CH_2Cl_2/MeOH, rt, 78%; (c) see Table 1, entries 7–9; (d) $PdCl_2$, 1:1 CH_2Cl_2/MeOH, rt, 93%; (e) $BF_3 \cdot OEt_2$, AW-300 4 Å molecular sieves, CH_2Cl_2, −20 °C, 51%; (f) (i) Pd/C, 9:1 MeOH/HCOOH, ultrasound bath, rt, (ii) 1 M NaOMe, MeOH, rt, 78% over two steps.

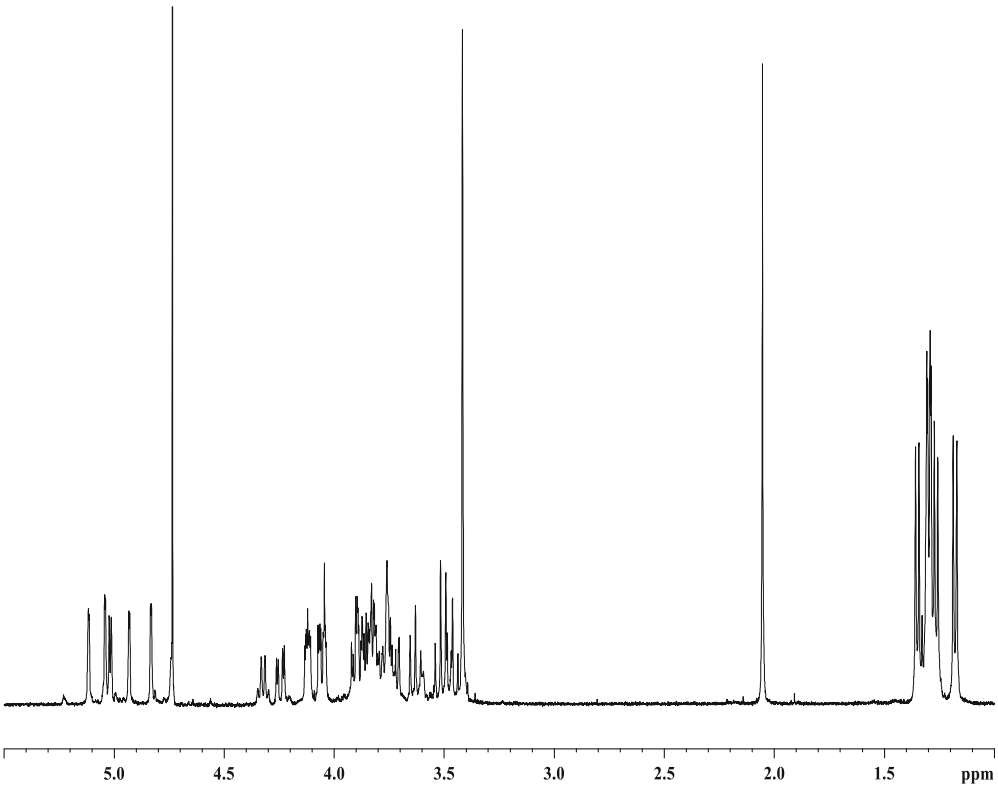


Figure 3. ^{1}H NMR spectrum (D_2O, 400 MHz) of the target pentasaccharide **11**.

nucleophile in the glycosylation,[31] no imidate adducts were detected during the reaction course. Finally, a two-step deprotection of **22** (debenzylation by transfer hydrogenation under Perlin's conditions,[32] and subsequent de-*O*-acylation with sodium methoxide) afforded the target pentasaccharide **11** in 78% yield (^{1}H NMR spectrum of **11** reported in Fig. 3).

3. Summary

The study on the glycosylation reaction involving a D-Fuc*p*3N donor here reported revealed that the *N*-phenyl trifluoroacetimidate of D-Fuc*p*3N gives good yields with several armed rhamnosyl acceptors and a high α-stereoselectivity is achievable by using a ternary mixture (dioxane/DME/toluene 4:1:1) as solvent. This study opens a route to the synthesis of α-D-Fuc*p*3NAc containing oligorhamnans, that are interesting molecules for studying the effects of *O*-antigen model oligosaccharides on the modulation of plant response to bacteria. An example of the synthetic accessibility to these molecules is the first reported synthesis of an α-D-Fuc*p*3NAc containing oligosaccharide, the methyl glycoside of the pentasaccharide repeating unit of the major *O*-antigen component from *P. syringae* pv. *holci* IMV 8300.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on Varian XL-200 (^{1}H: 200 MHz, ^{13}C: 50 MHz) or Bruker DRX-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) instruments in $CDCl_3$ ($CHCl_3$ as internal standard, ^{1}H: C*H*Cl_3 at δ 7.26; ^{13}C: *C*DCl_3 at δ 77.0) and in D_2O (acetone as internal standard, ^{1}H: (CH_3)$_2$CO at δ 2.05; ^{13}C: (CH_3)$_2$CO at δ 31.5). Assignment of proton chemical shifts were based on 1D HOHAHA and COSY experiments. For pentasaccharides **11** and **22**, 2D NMR experiments such as TOCSY, NOESY, HSQC and HMQC-COSY were also performed to assign proton and carbon chemical shifts. Positive ESI-MS spectra were recorded on a Finnigan LCQ-DECA ion trap mass spectrometer. IR spectra were recorded on a JASCO-FT/IR-430 spectrometer. Optical rotations were measured on a JASCO P-1010 polarimeter. Analytical thin layer chromatographies (TLC) were performed on aluminium plates precoated with Merck Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130 °C. Column chromatographies were performed on Merck Kieselgel 60 (63–200 mesh), except where differently specified. Gel-filtration chromatography was performed on a Sephadex G-10 column (1.0×20 cm) with water as eluant.

4.1.1. Allyl 2-*O*-benzyl-3-deoxy-4,3-(2-trichloromethyl-1-oxa-3-azaprop-2-eno)-α-D-fucopyranoside (2). A solution of **1** (903 mg, 2.74 mmol) in DMF (20 mL) was treated with BnBr (3.4 mL, 28.6 mmol) and NaH (60% oil suspension; 353 mg, 14.7 mmol). The solution was stirred at rt for 90 min, the solution was then diluted with CH_2Cl_2 (300 mL) and washed with water (300 mL). The organic layer was collected, dried and concentrated to give a residue that, after chromatography (11:1 petroleum ether/EtOAc), afforded pure **2** (840 mg, 68%) as a yellowish oil. $[\alpha]_D$

+70.2 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3035, 2944, 1677, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36 (m, 5H, H-Ar), 5.91 (m, 1H, $OCH_2CH{=}CH_2$), 5.32 (dd, 1H, $J_{vic}=17.2$ Hz, $J_{gem}=1.6$ Hz, $OCH_2CH{=}CHH$ *trans*), 5.20 (dd, 1H, $J_{vic}=10.4$ Hz, $J_{gem}=1.6$ Hz, $OCH_2CH{=}CHH$ *cis*), 4.85 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.76–4.69 (m, 3H, H_1, H_4, OC*H*HPh), 4.55 (dd, 1H, $J_{3,4}=9.0$ Hz, $J_{3,2}=5.4$ Hz, H_3), 4.30 (m, 2H, H_5, OC*H*HCH=CH_2), 4.05 (m, 1H, OC*H*HCH=CH_2), 3.77 (dd, 1H, $J_{2,3}=5.4$ Hz, $J_{2,1}=4.0$ Hz, H_2), 1.33 (d, 3H, $J_{6,5}=6.6$ Hz, H_6); ($CDCl_3$, 50 MHz) δ 164.1 (*C*=N), 138.0 (C_{ipso}), 134.0 ($OCH_2CH{=}CH_2$), 128.5 (C-Ar), 117.2 ($OCH_2CH{=}CH_2$), 96.1 (C_1), 84.7 (C_4), 74.0, 73.8, 68.7, 66.8, 64.2 (C_2, C_3, C_5, $OCH_2CH{=}CH_2$, OCH_2Ph), 16.1 (C_6). ESI-MS for $C_{18}H_{20}Cl_3NO_4$ (*m*/*z*): M_r (calcd) 419.05, M_r (found) 442.28 $(M+Na)^+$. Anal. Calcd: C, 51.39; H, 4.79; N, 3.33. Found: C, 51.55; H, 4.70; N, 3.32.

4.1.2. Allyl 4-*O*-acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranoside (3). To a solution of **2** (689 mg, 1.64 mmol) in THF (10 mL), 1 M HCl was added (1.57 mL). The mixture was vigorously stirred at rt for 30 min, after that 1 M $NaHCO_3$ (200 mL) was added. Stirring was continued for additional 10 min, then EtOAc (200 mL) was added. The organic layer was collected, dried and concentrated to afford an oily residue that was subsequently dissolved in pyridine (3 mL). The solution was treated with acetic anhydride (3 mL) and stirred at rt overnight. The solution was then concentrated and the residue dissolved in CH_2Cl_2 (100 mL) and extracted with 1 M HCl (100 mL) and water (100 mL). The organic layer was collected, dried and concentrated to afford a residue, that, after chromatography (3:2 petroleum ether/EtOAc), gave pure **3** (403 mg, 63%) as a white foam. $[\alpha]_D$ +126.8 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3055, 2951, 1735, 1664, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.36 (m, 5H, H-Ar), 5.897 (m, 1H, $OCH_2CH{=}CH_2$), 5.35–5.14 (m, 4H, H_4, NH, $OCH_2CH{=}CH_2$), 4.95 (d, 1H, $J_{1,2}=2.7$ Hz, H_1), 4.65 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.53 (m, 1H, H_3), 4.47 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.13 (m, 2H, H_5, $OCH_2CH{=}CH_2$), 3.97 (m, 2H, $OCH_2CH{=}CH_2$), 3.67 (dd, 1H, $J_{2,3}=11.4$ Hz, $J_{2,1}=2.7$ Hz, H_2), 2.06 (s, 3H, OAc), 1.79 (s, 3H, NAc), 1.03 (d, 3H, $J_{6,5}=6.6$ Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0 (2 *C*OCH_3), 138.0 (C_{ipso}), 133.7 ($OCH_2CH{=}CH_2$), 128.5 (C-Ar), 117.8 ($OCH_2CH{=}CH_2$), 95.4 (C_1), 73.1, 72.7, 71.6, 68.4, 64.8 (C_2, C_4, C_5, $OCH_2CH{=}CH_2$, OCH_2Ph), 48.2 (C_3), 23.0, 20.6 (2 CO*C*H_3), 16.1 (C_6). ESI-MS for $C_{20}H_{27}NO_6$ (*m*/*z*): M_r (calcd) 377.18, M_r (found) 400.37 $(M+Na)^+$. Anal. Calcd: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.80; H, 7.00; N, 3.65.

4.1.3. 4-*O*-Acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranose (4). A suspension of **3** (357 mg, 0.92 mmol) and $PdCl_2$ (27 mg, 0.15 mmol) in 1:1 CH_2Cl_2/MeOH (10 mL) was vigorously stirred at rt for 5 h. The mixture was filtered over a Celite pad, then diluted with CH_2Cl_2 (150 mL) and washed with 5 M NaCl (150 mL). The organic layer was collected, dried and concentrated. The resulting residue was chromatographed (1:1 petroleum ether/EtOAc) to afford **4** (270 mg, 84%; $\alpha/\beta=1{:}1.5$) as a yellowish oil. IR (thin film, NaCl) 3517, 3009, 1743, 1666, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.40 (d, 1H, $J_{1,2}=3.6$ Hz, H-1$^{\alpha}$), 5.27 (d, 1H, $J_{4,3}=2.8$ Hz, H-4$^{\alpha}$), 5.21 (d, 1H, $J_{4,3}=2.8$ Hz, H-4$^{\beta}$), 5.01–4.83 (m, 4H, H-1$^{\beta}$, NH$^{\alpha}$, NH$^{\beta}$, OC*H*HPh), 4.76 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.68 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.53 (m, 2H, H-3$^{\alpha}$, OC*H*HPh), 4.38 (q, 1H, $J_{5,6}=6.6$ Hz, H-5$^{\alpha}$), 4.17 (m, 1H, H-3$^{\beta}$), 3.84 (q, 1H, $J_{5,6}=6.6$ Hz, H-5$^{\beta}$), 3.63 (dd, 1H, $J_{2,3}=10.2$ Hz, $J_{2,1}=3.6$ Hz, H-2$^{\alpha}$), 3.33 (dd, 1H, $J_{2,3}=10.2$ Hz, $J_{2,1}=7.2$ Hz, H-2$^{\beta}$), 2.08 (s, 3H, OAc), 2.04 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.79 (s, 3H, NAc), 1.13 (d, 3H, $J_{6,5}=6.6$ Hz, H-5$^{\beta}$), 1.07 (d, 3H, $J_{6,5}=6.6$ Hz, H-5$^{\alpha}$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0 (4 *C*OCH_3), 138.1 (C_{ipso}), 137.4 (C_{ipso}), 128.4 (C-Ar), 98.0 (C-1$^{\alpha}$), 90.5 (C-1$^{\beta}$), 76.0, 73.7, 72.8, 72.1, 71.9, 70.2, 65.0, 60.4 (C-2$^{\alpha}$, C-2$^{\beta}$, C-4$^{\alpha}$, C-4$^{\beta}$, C-5$^{\alpha}$, C-5$^{\beta}$, 2 OCH_2Ph), 52.0, 47.8 (C-3$^{\alpha}$, C-3$^{\beta}$), 23.2 (2 *C*OCH_3), 21.0, 20.7 (2 CO*C*H_3), 16.5, 16.3 (C-6$^{\alpha}$, C-6$^{\beta}$). ESI-MS for $C_{17}H_{23}NO_6$ (*m*/*z*): M_r (calcd) 337.15, M_r (found) 360.22 $(M+Na)^+$. Anal. Calcd: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.89; H, 6.80; N, 4.00.

4.1.4. 4-*O*-Acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranosyl trichloroacetimidate (5). Compound **4** (77 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (3.0 mL) under an argon atmosphere and to the 0 °C cooled solution Cl_3CCN (115 μL, 1.21 mmol) and DBU (3.3 μL, 6.6 μmol) were added. The solution was stirred at 0 °C for 4 h and then concentrated. The resulting residue was chromatographed (1:1 petroleum ether/EtOAc) over neutral alumina gel to afford **5** (57 mg, 53%) as a white foam. $[\alpha]_D$ +99.2 (*c* 0.8, CH_2Cl_2). IR (thin film, NaCl) 3022, 2979, 1739, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.60 (s, 1H, N*H*CCl_3), 7.36 (m, 5H, H-Ar), 6.60 (d, 1H, $J_{1,2}=3.4$ Hz, H_1), 5.41 (d, 1H, $J_{4,3}=2.4$ Hz, H_4), 5.02 (d, 1H, $J_{H,NH}=6.6$ Hz, NH), 4.75 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.55 (m, 1H, H_3), 4.46 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.33 (q, 1H, $J_{5,6}=6.6$ Hz, H_5), 3.81 (dd, 1H, $J_{2,3}=11.4$ Hz, $J_{2,1}=3.4$ Hz), 2.08 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.09 (d, 3H, $J_{6,5}=6.6$ Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.1, 169.9 (2 *C*OCH_3), 161.4 (Cl_3CC=NH), 137.4 (C_{ipso}), 128.3 (C-Ar), 93.5 (C-1), 72.0, 71.9, 71.8, 67.8 (C_2, C_4, C_5, OCH_2Ph), 48.7 (C_3), 23.1, 20.6 (2 CO*C*H_3), 16.3 (C_6). ESI-MS for $C_{19}H_{23}Cl_3N_2O_6$ (*m*/*z*): M_r (calcd) 480.06, M_r (found) 513.30 $(M+Na)^+$. Anal. Calcd: C, 47.37; H, 4.81; N, 5.81. Found: C, 47.60; H, 4.89; N, 5.75.

4.1.5. 4-*O*-Acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranosyl *N*-phenyl-trifluoroacetimidate (8). A mixture of **4** (251 mg, 0.72 mmol) and freshly powdered 4 Å molecular sieves was suspended under argon in CH_2Cl_2 (5 mL) and cooled to 0 °C under stirring. CF_3C(NPh)Cl (53 μL, 0.42 mmol) and NaH (60% oil suspension; 17 mg, 0.42 mmol) were added and stirred was continued at 0 °C for 3 h, after that the mixture was filtered over Celite and the filtrate concentrated. Neutral alumina (Brockman grade 1) column chromatography (3:2 petroleum ether/EtOAc) on the residue, afforded **8** (277 mg, 74%; $\alpha/\beta=3{:}1$) as a colourless oil. IR (thin film, NaCl) 3040, 1738, 1670, 1656, 1260 cm^{-1}; ^1H NMR NMR ($CDCl_3$, 200 MHz) (α-anomer) δ 7.42–6.73 (H-Ar), 6.60 (m, 1H, H-1), 5.38 (d, 1H, $J_{4,3}=2.4$ Hz, H-4), 4.83 (m, 2H, NH, OC*H*HPh), 4.50 (m, 2H, H_3, OC*H*HPh), 4.28 (q, 1H, $J_{5,6}=6.6$ Hz, H-5), 3.75 (dd, 1H, $J_{2,3}=10.2$ Hz, $J_{2,1}=3.4$ Hz, H-2), 2.07 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.11 (dd, 3H, $J_{6,5}=6.6$ Hz, H-6); ^{13}C NMR ($CDCl_3$, 50 MHz) (α-anomer) δ 170.1, 169.9 (2 *C*OCH_3),

143.5, 137.4 (2 C_{ipso}), 129.3–119.4 (C-Ar), 92.5 (C-1), 72.3, 71.9, 71.8, 67.9 (C_2, C_4 C_5, OCH_2Ph), 48.5 (C_3), 23.2, 20.6 (2 COCH_3), 16.4 (C_6). ESI-MS for $C_{25}H_{27}F_3N_2O_6$ (*m/z*): M_r (calcd) 508.18, M_r (found) 531.38 $(M+Na)^+$. Anal. Calcd: C, 59.05; H, 5, 35; N, 5.51. Found: C, 59.10; H, 5.45; N, 5.43.

4.2. General procedure for D-Fuc*p*3NAc couplings in CH_2Cl_2

A mixture of donor **8** (37 mg, 0.074 mmol) and rhamnosyl acceptor (0.037 mmol) was co-evaporated three times with toluene, the residue was then mixed with freshly powdered AW-300 4 Å molecular sieves and suspended under argon in CH_2Cl_2 (1.0 mL). The mixture was cooled and stirred at 0 °C, TMSOTf (1.2 μL, 7.4 μmol) was added and the temperature was allowed to gradually rise to rt. After completion of the reaction (TLC analysis), the mixture was neutralized by adding pyridine. The mixture was then filtered over Celite and concentrated to give a residue, that was purified by column chromatography.

4.3. General procedure for D-Fuc*p*3NAc couplings in dioxane/toluene/DME 4:1:1 v/v/v

A mixture of donor **8** (37 mg, 0.074 mmol) and rhamnosyl acceptor (0.049 mmol) was co-evaporated three times with toluene, the residue was then mixed with freshly powdered AW-300 4 Å molecular sieves and suspended under argon in 4:1 dioxane/toluene (1.5 mL). The mixture was cooled and stirred at 0 °C, a 0.025 M DME solution of TMSOTf (0.3 mL, 7.4 μmol) was added and the temperature was allowed to gradually raise to rt After completion of the reaction (TLC analysis), the mixture was neutralized by adding pyridine. The mixture was then filtered over Celite and concentrated to give a residue, that was purified by column chromatography.

4.3.1. Benzyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranosyl)-(1→3)-3-*O*-allyl-4-*O*-benzoyl-α-L-rhamnopyranoside (9).

See the general procedure for D-Fuc*p*3-NAc couplings in CH_2Cl_2 and in dioxane/toluene/DME 4:1:1 v/v/v. IR (thin film, NaCl) 3025, 2980, 2933, 1744, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11–7.26 (m, 30H, H-Ar), 5.73 (m, 2H, 2 OCH$_2$C*H*=CH$_2$), 5.50 (t, 1H, $J_{4,3}=J_{4,5}=10.0$ Hz, H-4$^{\beta}_{A}$), 5.41 (d, 1H, $J_{4,3}=1.8$ Hz, H-4$^{\alpha}_{B}$), 5.35 (t, 1H, $J_{4,3}=J_{4,5}=10.0$ Hz, H-4$^{\alpha}_{A}$), 5.20–5.10 (m, 5H, H-1$^{\beta}_{A}$, H-4$^{\beta}_{B}$, OC*H*HPh, 2 OCH$_2$CH=C*H*H *trans*), 5.08–4.97 (m, 4H, H-1$^{\alpha}_{B}$, NH$^{\alpha}$, 2 OCH$_2$CH=C*H*H *cis*), 4.91 (bs, 1H, H-1$^{\alpha}_{A}$), 4.77 (m, 4H, NH$^{\beta}$, 3 OC*H*HPh), 4.65 (d, 1H, $J_{1,2}=7.4$ Hz, H-1$^{\beta}_{B}$), 4.61–4.50 (m, 6H, H-3$^{\alpha}_{B}$, H-5$^{\alpha}_{A}$, 4 OC*H*HPh), 4.12–4.03 (m, 5H, H-2$^{\alpha}_{A}$, H-2$^{\beta}_{A}$, H-3$^{\beta}_{B}$, 2 OC*H*HCH=CH$_2$), 4.01–3.94 (m, 6H, H-3$^{\alpha}_{A}$, H-3$^{\beta}_{A}$, H-5$^{\alpha}_{A}$, H-5$^{\beta}_{A}$, 2 OC*H*HCH=CH$_2$), 3.78 (dd, 1H, $J_{2,3}=10.3$ Hz, $J_{2,1}=3.4$ Hz, H-2$^{\alpha}_{B}$), 3.69 (q, 1H, $J_{5,6}=6.4$ Hz, H-5$^{\beta}_{B}$), 3.34 (dd, 1H, $J_{2,3}=10.7$ Hz, $J_{2,1}=7.4$ Hz, H-2$^{\beta}_{B}$), 2.078 (s, 3H, OAc) 2.05 (s, 3H, OAc), 1.84 (s, 3H, NAc), 1.79 (s, 3H, NAc), 1.29 (m, 6H, H-6$^{\alpha}_{A}$, H-6$^{\beta}_{A}$), 1.01 (d, 3H, $J_{6,5}=6.4$ Hz, H-6$^{\alpha}_{B}$), 0.98 (m, 6H, $J_{6,5}=6.4$ Hz, H-6$^{\beta}_{B}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.9 (4 *C*OCH$_3$), 165.5, 165.4 (*C*OPh), 134.4–128.1 (2 OCH$_2$*C*H=CH$_2$, C-Ar), 116.7, 116.6 (2 OCH$_2$CH=*C*H$_2$), 105.8 (C-1$^{\beta}_{B}$), 98.7, 96.6, 96.4 (C-1$^{\alpha}_{A}$, C-1$^{\beta}_{A}$, C-1$^{\alpha}_{B}$), 76.9, 76.0, 75.8, 74.4, 74.2, 73.6, 73.5, 73.4, 72.6, 71.5, 71.3, 71.2, 70.9, 70.5, 69.1, 69.0, 68.9, 67.3, 66.7, 65.1 (C-2$^{\alpha}_{A}$, C-2$^{\beta}_{A}$, C-2$^{\beta}_{B}$, C-2$^{\beta}_{B}$, C-3$^{\alpha}_{A}$, C-3$^{\beta}_{A}$, C-4$^{\alpha}_{A}$, C-4$^{\beta}_{A}$, C-4$^{\alpha}_{B}$, C-4$^{\beta}_{B}$, C-5$^{\alpha}_{A}$, C-5$^{\beta}_{A}$, C-5$^{\alpha}_{B}$, C-5$^{\beta}_{B}$, 2 OC*H*$_2$CH=CH$_2$, 4 OC*H*$_2$Ph,), 23.0, 22.9, 20.6, 20.4 (4 CO*C*H$_3$), 17.6, 17.5, 16.3, 16.1 (C-6$^{\alpha}_{A}$, C-6$^{\beta}_{A}$, C-6$^{\alpha}_{B}$, C-6$^{\beta}_{B}$). ESI-MS for $C_{40}H_{47}NO_{11}$ (*m/z*): M_r (calcd) 717.31, M_r (found) 740.51 $(M+Na)^+$. Anal. Calcd: C, 66.93; H, 6.60; N, 1.95. Found: C, 67.10; H, 6.47; N, 1.99.

4.3.2. Methyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-D-fucopyranosyl)-(1→3)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (10).

See the general procedure for D-Fuc*p*3-NAc couplings in CH_2Cl_2 and in dioxane/toluene/DME 4:1:1 v/v/v. IR (thin film, NaCl) 3042, 1748, 1680, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.26 (m, 10H, H-Ar$^{\alpha,\beta}$), δ 5.73 (d, 1H, $J_{1,2}=3.5$ Hz, H-1$^{\alpha}_{B}$), 5.33 (d, 1H, $J_{4,3}=2.2$ Hz, H-4$^{\alpha}_{B}$), 5.14 (d, 1H, $J_{4,3}=2.2$ Hz, H-4$^{\beta}_{B}$), 4.86 (m, 5H, H-1$^{\alpha}_{A}$, H-1$^{\beta}_{B}$, NH$^{\alpha}$, 2 OC*H*HPh), 4.67–4.54 (m, 4H, H-1$^{\beta}_{B}$, H-5$^{\beta}_{B}$, NH$^{\beta}$, OC*H*HPh), 4.44 (d, 1H, $J_{gem}=$ 12.0 Hz, OC*H*HPh), 4.40 (m, 1H, H-3$^{\alpha}_{B}$), 4.31 (t, 1H, $J_{4,3}=J_{4,5}=7.1$ Hz, H-3$^{\beta}_{A}$), 4.24 (t, 1H, $J_{4,3}=J_{4,5}=7.1$ Hz, H-3$^{\alpha}_{A}$), 4.20–4.07 (m, 4H, H-2$^{\alpha}_{A}$, H-2$^{\beta}_{A}$, H-3$^{\beta}_{B}$, H-5$^{\alpha}_{B}$), 3.72 (m, 2H, H-5$^{\alpha}_{A}$, H-5$^{\beta}_{A}$), 3.65 (dd, 1H, $J_{2,3}=11.4$ Hz, $J_{2,1}=3.5$ Hz, H-2$^{\alpha}_{B}$), 3.56 (dd, 1H, $J_{4,5}=9.9$ Hz, $J_{4,3}=7.1$ Hz, H-4$^{\alpha}_{A}$), 3.51 (dd, 1H, $J_{4,5}=9.9$ Hz, $J_{4,3}=7.1$ Hz, H-4$^{\beta}_{A}$), 3.36 (m, 7H, H-2$^{\beta}_{B}$ OMe$^{\alpha}$, OMe$^{\beta}$), 2.08 (2 s, 6H, 2 OAc), 1.85 (s, 3H, NAc), 1.76 (s, 3H, NAc), 1.57 (s, 6H, 2 CH_3), 1.36 (s, 6H, 2 CH_3), 1.34 (d, 3H, $J_{6,5}=6.2$ Hz, H-6$^{\alpha}_{A}$), 1.24 (d, 3H, $J_{6,5}=$ 6.6 Hz, H-6$^{\beta}_{B}$), 1.15 (d, 3H, $J_{6,5}=6.2$ Hz, H-6$^{\beta}_{A}$), 1.09 (d, 3H, $J_{6,5}=6.6$ Hz, H-6$^{\alpha}_{B}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8 (*C*OCH$_3$), 137.6 (C_{ipso}), 126.5–125.7 (C-Ar), 104.2 (C-1$^{\beta}_{B}$), 97.9 C-1$^{\alpha}_{A}$, C-1$^{\beta}_{A}$), 94.5 (C-1$^{\alpha}_{B}$), 82.2, 78.4, 78.2, 76.4, 76.0, 75.8, 75.2, 73.8, 72.3, 72.1, 71.2, 70.5, 67.3, 65.0, 63.7 (C-2$^{\alpha}_{A}$, C-2$^{\beta}_{A}$, C-2$^{\alpha}_{B}$, C-2$^{\beta}_{B}$, C-3$^{\alpha}_{A}$, C-3$^{\beta}_{A}$, C-4$^{\alpha}_{A}$, C-4$^{\beta}_{A}$, C-4$^{\alpha}_{B}$, C-4$^{\beta}_{B}$, C-5$^{\alpha}_{A}$, C-5$^{\beta}_{A}$, C-5$^{\alpha}_{B}$, C-5$^{\beta}_{B}$, OC*H*HPh), 54.5 (OMe), 51.8 (C-3$^{\beta}_{B}$), 47.9 (C-3$^{\alpha}_{B}$), 27.8 (CH_3), 26.1 (CH_3), 22.9, 22.8, 20.6, 20.5 (4 CO*C*H$_3$), 17.8, 17.5, 16.3, 15.9 (C-6$^{\alpha}_{A}$, C-6$^{\beta}_{A}$, C-6$^{\alpha}_{B}$, C-6$^{\beta}_{B}$). ESI-MS for $C_{27}H_{39}NO_{10}$ (*m/z*): M_r (calcd) 537.26, M_r (found) 538.20 $(M+H)^+$. Anal. Calcd: C, 60.32; H, 7.31; N, 2.61. Found: C, 60.40; H, 7.19; N, 2.51.

4.3.3. Benzyl 3-*O*-allyl-4-*O*-benzoyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (17).

To a solution of **16** (152 mg, 0.382 mmol) in CH_2Cl_2 (3.0 mL), levulinic acid (245 μL, 2.28 mmol), DMAP (23 mg, 0.190 mmol) and then DIPC (220 μL, 2.48 mmol) were added. After 4 h stirring at rt, the mixture was filtered over a Celite pad, diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL). The organic layer was collected, dried and concentrated to give a residue, which after chromatography (8:1 petroleum ether/EtOAc) afforded **17** (187 mg, 99%) as an oil. $[\alpha]_D$ −12.7 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3028, 2935, 1749, 1725, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.05–7.36 (m, 10H, H-Ar), 5.67 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.36 (dd, 1H, $J_{2,3}=3.4$ Hz, $J_{2,1}=1.6$ Hz, H$_2$), 5.24 (t, 1H, $J_{4,3}=J_{4,5}=$ 9.8 Hz, H$_4$), 5.14 (d, 1H, $J_{vic}=17.2$ Hz, $J_{gem}=1.8$ Hz, OCH$_2$CH=C*H*H *trans*), 5.01 (d, 1H, $J_{vic}=10.4$ Hz, $J_{gem}=$ 1.8 Hz, OCH$_2$CH=C*H*H *cis*), 4.88 (d, 1H, $J_{1,2}=1.6$ Hz, H$_1$), 4.72 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.54 (d, 1H, $J_{gem}=12.0$ Hz, OC*H*HPh), 4.07–3.76 (m, 4H, H$_3$, H$_5$, OC*H*$_2$CH=CH$_2$), 2.84–2.68 (m, 4H, C*H*$_2$C*H*$_2$), 2.20 (s, 3H, C*H*$_3$CO), 1.24 (d, 3H, $J_{6,5}=6.4$ Hz, H$_6$); ^{13}C NMR

($CDCl_3$, 50 MHz) δ 206.1 (CH_3C=O), 171.7 (C=O Lev), 166.5 (C=O Bz), 136.4 (C_{ipso}), 134.1 (OCH_2CH=CH_2), 133.2 (C_{ipso}), 130.0–127.5 (C-Ar), 117.5 (OCH_2CH=CH_2), 97.6 (C-1), 74.8, 73.2, 70.9, 69.0, 68.9, 66.6 (C-2, C-3, C-4, C-5, OCH_2CH=CH_2, OCH_2Ph), 37.9, 29.8, 28.2 (CH_2CH_2, CH_3C=O), 17.5 (C-6). ESI-MS for $C_{28}H_{32}O_8$ (*m*/*z*): M_r (calcd) 496.21, M_r (found) 519.22 $(M+Na)^+$. Anal. Calcd: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.65.

4.3.4. Benzyl 4-*O*-benzoyl-2-*O*-levulinoyl-α-L-rhamnopyranoside (18). Compound **17** (189 mg, 0.381 mmol) was dissolved in 3:2 MeOH/CH_2Cl_2 (5.0 mL), $PdCl_2$ (27 mg, 0.30 mmol) was then added and the mixture was vigorously stirred at rt overnight, after that it was filtered over a Celite pad, diluted with CH_2Cl_2 (50 mL) and washed with 5 M NaCl (50 mL). The organic layer was collected, dried and concentrated to give a residue, which, after chromatography (4:1 petroleum ether/EtOAc), afforded **18** (135 mg, 78%) as an oil. $[\alpha]_D$ −41.4 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3517, 3039, 1731, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.05–7.34 (m, 10H, H-Ar), 5.26 (dd, 1H, $J_{2,3}$=3.6 Hz, $J_{2,1}$=1.8 Hz, H_2), 5.12 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.8 Hz, H_4), 4.91 (d, 1H, $J_{1,2}$=1.8 Hz, H_1), 4.74 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.55 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.22 (dd, 1H, $J_{3,4}$=9.8 Hz, $J_{2,1}$=3.6 Hz, H_3), 4.04 (dq, 1H, $J_{5,4}$=9.8 Hz, $J_{5,6}$=6.2 Hz, H_5), 2.87–2.63 (m, 4H, CH_2CH_2), 2.22 (s, 3H, CH_3CO), 1.27 (d, 3H, $J_{6,5}$=6.2 Hz, H_6); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 207.2 (CH_3C=O), 172.2 (C=O Lev), 166.7 (C=O Bz), 136.8, 133.4 (2 C_{ipso}), 129.8–127.8 (C-Ar), 96.9 (C-1), 75.1, 72.7, 69.6, 68.9, 66.4 (C-2, C-3, C-4, C-5, OCH_2Ph), 38.2, 29.7, 28.2 (CH_2CH_2, CH_3C=O), 17.5 (C-6). ESI-MS for $C_{25}H_{28}O_8$ (*m*/*z*): M_r (calcd) 456.18, M_r (found) 479.49 $(M+Na)^+$. Anal. Calcd: C, 65.78; H, 6.18. Found: C, 65.78; H, 6.25.

4.3.5. Methyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranosyl)-(1→3)-2-*O*-allyl-4-*O*-benzyl-α-L-rhamnopyranoside (20). See the general procedure for D-Fuc*p*3-NAc couplings in CH_2Cl_2 and in dioxane/toluene/DME 4:1:1 v/v/v. (α-anomer). $[\alpha]_D$ +20.4 (*c* 0.6, CH_2Cl_2). IR (thin film, NaCl) 3019, 2956, 1747, 1665, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.27 (m, 10H, H-Ar), 5.87 (m, 1H, OCH_2CH=CH_2), 5.24 (dd, 1H, J_{vic}=17.3 Hz, J_{gem}=1.7 Hz, OCH_2CH=C*H*H *trans*), 5.21 (d, 1H, $J_{1,2}$=3.4 Hz, H-1_B), 5.14 (dd, 1H, J_{vic}=10.2 Hz, J_{gem}=1.7 Hz, OCH_2CH=C*H*H *cis*), 5.07 (d, 1H, $J_{4,3}$=3.0 Hz, H-4_B), 4.86 (d, 1H, J_{gem}=10.5 Hz, OC*H*HPh), 4.81–4.60 (m, 5H, H-1_A, H-3_B, NH, 2 OC*H*HPh), 4.43 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.27–4.09 (m, 3H, H-5_B, OCH_2CH=CH_2), 4.05 (dd, 1H, $J_{3,4}$=8.7 Hz, $J_{3,2}$=2.7 Hz, H-3_A), 3.79 (bs, 1H, H-2_A), 3.71 (m, 2H, H-2_B, H-5_A), 3.61 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.3 Hz, H-4_A), 3.33 (m, 3H, OMe), 2.04 (s, 3H, OAc), 1.79 (s, 3H, NAc), 1.37 (d, 3H, $J_{6,5}$=6.0 Hz, H-6_A), 0.78 (d, 3H, $J_{6,5}$=6.6 Hz, H-6_B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 ($COCH_3$), 138.1, 138.0 (2 C_{ipso}), 134.9 (OCH_2CH=CH_2), 129.6–127.7 (C-Ar), 117.2 (OCH_2CH=CH_2), 98.9 (C-1_A), 93.6 (C-1_B), 79.8, 75.5, 74.4, 72.9, 72.8, 72.2, 71.6, 68.1, 68.0, 65.1 (C-2_A, C-2_B, C-3_A, C-4_A, C-4_B, C-5_A, C-5_B, OCH_2Ph, OCH_2CH=CH_2), 54.7 (OMe), 48.1 (C-3_B), 23.1, 20.6 (2 $COCH_3$), 18.1, 15.9 (C-6_A, C-6_B). ESI-MS for $C_{34}H_{45}NO_{10}$ (*m*/*z*): M_r (calcd) 627.72, M_r (found) 650.50 $(M+Na)^+$. Anal. Calcd: C, 65.05; H, 7.23; N, 2.23. Found: C, 65.20; H, 7.19; N, 2.32.

4.3.6. Methyl(4-*O*-acetyl-3-acetamido-2-*O*-benzyl-α-D-fucopyranosyl)-(1→3)-4-*O*-benzyl-α-L-rhamnopyranoside (21). A mixture of compound **20**-α (56 mg, 0.089 mmol) and $PdCl_2$ (7.8 mg, 44 μmol) was suspended in 1:1 CH_2Cl_2/MeOH (2.0 mL) under vigorous stirring. After 4 h the mixture was filtered on a Celite pad, then diluted with CH_2Cl_2 (25 mL) and washed with 5 M NaCl (30 mL). The organic layer was collected, dried and concentrated to give an oily residue that, after column chromatography (1:2 petroleum ether/EtOAc) afforded **21** (49 mg, 93%) as an oil. $[\alpha]_D$ +32.3 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3509, 3030, 1741, 1669, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.29 (m, 10H, H-Ar), 5.07 (d, 1H, $J_{4,3}$=3.0 Hz, H-4_B), 5.04 (bs, 1H, H-1_A), 4.80–4.71 (m, 4H, H-1_B, 3 OC*H*HPh), 4.53 (m, 1H, H-3_B), 4.44 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.06 (q, 1H, $J_{5,6}$=6.6 Hz, H-5_B), 3.99 (m, 2H, H-2_A, H-3_A), 3.75 (dq, 1H, $J_{5,4}$=9.3 Hz, $J_{5,6}$=6.0 Hz, H-5_A), 3.63 (dd, 1H, $J_{2,3}$=11.4 Hz, $J_{2,1}$=3.3 Hz, H-2_B), 3.52 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.3 Hz, H-4_A), 3.36 (s, 3H, OMe), 2.05 (s, 3H, OAc), 1.79 (s, 3H, NAc), 1.38 (d, 3H, $J_{6,5}$=6.0 Hz, H-6_A), 0.73 (d, 3H, $J_{6,5}$=6.6 Hz, H-6_B); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 ($COCH_3$), 138.1, 137.1 (2 C_{ipso}), 128.7–127.5 (C-Ar), 99.9 (C-1_A), 93.3 (C-1_B), 79.3, 77.1, 75.5, 73.1, 73.0, 72.7, 67.6, 67.2 (C-2_A, C-2_B, C-3_A, C-4_A, C-4_B, C-5_A, C-5_B, 2 OCH_2Ph), 54.6 (OMe), 48.1 (C-3_B), 23.1, 20.5 (2 $COCH_3$), 17.9 (C-6_A), 15.8 (C-6_B). ESI-MS for $C_{31}H_{41}NO_{10}$ (*m*/*z*): M_r (calcd) 587.27, M_r (found) 610.00 $(M+Na)^+$. Anal. Calcd: C, 63.36; H, 7.03; N, 2.38. Found: C, 63.55; H, 6.96; N, 2.34.

4.3.7. Methyl(2,4-di-*O*-benzoyl-3-*O*-chloroacetyl-α-L-rhamnopyranosyl)-(1→3)-(2,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-(3,4-di-*O*-benzoyl-α-L-rhamnopyranosyl)-(1→2)-[4-*O*-acetyl-3-acetylamino-2-*O*-benzyl-α-D-fucopyranosyl-(1→3)]-4-*O*-benzyl-α-L-rhamnopyranoside (22). A mixture of **21** (20 mg, 34.1 μmol) and **13** (66 mg, 50.8 μmol) was co-evaporated three times with toluene, the residue was then mixed with freshly powdered AW-300 4 Å molecular sieves, suspended under argon in CH_2Cl_2 (2.0 mL) and stirred at −20 °C. $BF_3{\cdot}OEt_2$ (3.2 μL, 25.4 μmol) was then added. After 24 h, an additional aliquot of **13** (44 mg, 33.9 μmol) and $BF_3{\cdot}OEt_2$ (2.1 μL, 16.9 μmol) was added. After an additional day the reaction was quenched with a drop of Et_3N. After filtration over a Celite pad, the mixture was concentrated to give a residue, that, after column chromatography (1:1 petroleum ether/EtOAc), afforded **22** (30 mg, 51%) as a white foam. $[\alpha]_D$ +113.3 (*c* 1.0, CH_2Cl_2). IR (thin film, NaCl) 3052, 3028, 1739, 1656, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18–7.10 (m, 40H), 5.83 (dd, 1H, $J_{3,4}$=9.6 Hz, $J_{3,2}$=2.8 Hz, H-3_B), 5.72 (d, 1H, $J_{2,3}$=3.0 Hz, H-2_C), 5.59 (t, 1H, $J_{4,3}$=$J_{4,5}$=10.0 Hz, H-4_B), 5.56 (t, 1H, $J_{4,3}$=$J_{4,5}$=9.6 Hz, H-4_C), 5.44 (dd, 1H, $J_{3,4}$=9.8 Hz, $J_{3,2}$=2.8 Hz, H-3_D), 5.34 (m, 2H, H-1_B, H-4_D), 5.18 (m, 3H, H-1_D, H-1_E, H-2_D), 5.11 (d, 1H, $J_{4,3}$=2.8 Hz, H-4_E), 5.06 (bs, 1H, H-1_C), 4.90 (d, 1H, J_{gem}=10.8 Hz, OC*H*HPh), 4.87 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.84 (bs, 1H, H-1_A), 4.76 (d, 1H, J_{gem}=10.8 Hz, OC*H*HPh), 4.63 (m, 2H, H-3_C, NH), 4.50 (m, 1H, H-3_E), 4.42 (d, 1H, J_{gem}=12.0 Hz, OC*H*HPh), 4.34 (bs, 1H, H-2_B),

4.30–4.20 (m, 4H, H-5_B, H-5_C, H-5_D, H-5_E), 4.13 (dd, 1H, $J_{3,4}=9.6$ Hz, $J_{3,2}=2.8$ Hz, H-3_A), 4.08 (bs, 1H, H-2_A), 3.79–3.64 (m, 5H, H-2_E, H-4_A, H-5_A, CH_2Cl), 3.37 (s, 3H, OMe), 1.96 (s, 3H, OAc), 1.54 (s, 3H, NAc), 1.42 (d, 3H, $J_{6,5}=6.0$ Hz, H-6_A), 1.33 (m, 6H, H-6_B, H-6_C), 1.18 (d, 3H, $J_{6,5}=6.2$ Hz, H-6_D), 0.77 (d, 3H, $J_{6,5}=6.6$ Hz, H-6_E); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9 (*C*OCH$_2$Cl), 165.4–164.5 (*C*OCH$_3$, *C*OPh), 138.2, 137.1 (2 C_{ipso}), 133.4–128.0 (C-Ar), 100.5 (C-1_B), 99.8 (C-1_C, $^1J_{C,H}=173$ Hz), 99.6 (C-1_A), 98.9 (C-1_E), 94.2 (C-1_E), 79.8 (C-4_A), 78.7 (C-2_B), 76.6 (C-2_A), 75.7 (C-3_A), 75.5 (O*C*H$_2$Ph), 74.4 (C-3_C), 73.5 (C-4_C), 72.7 (C-4_E), 72.2 (C-2_E), 72.0 (C-4_B), 71.8 (C-2_C), 71.5 (C-4_D, O*C*H$_2$Ph), 70.4 (C-3_B), 70.3 (C-3_D), 68.2 (C-5_A), 67.8–67.2 (C-5_B, C-5_C, C-5_D, C-5_E), 55.0 (OMe), 48.1 (C-3_E), 40.2 (CO*C*H$_2$Cl), 22.9, 20.4 (2 CO*C*H$_3$), 18.1 (C-6_A), 17.7 (C-6_B, C-6_C), 17.3 (C-6_D), 15.8 (C-6_E). ESI-MS for $C_{93}H_{96}ClNO_{29}$ (*m*/*z*): M_r (calcd) 1725.58, M_r (found) 1748.05 $(M+Na)^+$. Anal. Calcd: C, 64.67; H, 5.60; N, 0.81. Found: C, 64.57; H, 5.80; N, 0.75.

4.3.8. Methyl α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-[3-acetamido-α-D-fucopyranosyl-(1→3)]-α-L-rhamnopyranoside (11). Compound **22** (13.0 mg, 7.54 μmol) was dissolved in 9:1 MeOH/HCOOH (2.0 mL) under argon. Pd/C (8 mg) was added and the mixture was kept in an ultrasound bath for 1 h, after that it was filtered on a Celite pad and concentrated. The residue was dissolved in MeOH (2.0 mL) and NaOMe 1 M in MeOH (250 μL) was added. After 48 h the solution was neutralized with Amberlist-15 H^+, filtered and concentrated. The residue was purified by gel filtration to obtain **11** (4.7 mg, 78%) as a white wax. $[\alpha]_D$ +11 (*c* 0.3, D_2O); ^{1}H NMR (D_2O, 400 MHz) δ 5.12 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_B), 5.04 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_D), 5.02 (d, 1H, $J_{1,2}=4.0$ Hz, H-1_E), 4.93 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_C), 4.83 (d, 1H, $J_{1,2}=1.6$ Hz, H-1_A), 4.33 (q, 1H, $J_{5,6}=6.5$ Hz, H-5_E), 4.25 (dd, 1H, $J_{3,2}=11.1$ Hz, $J_{3,4}=2.9$ Hz, H-3_E), 4.12 (m, 2H, H-2_A, H-2_C), 4.07 (dd, 1H, $J_{2,3}=3.6$ Hz, $J_{2,1}=1.6$ Hz, H-2_D), 4.04 (dd, 1H, $J_{2,3}=3.6$ Hz, $J_{2,1}=1.6$ Hz, H-2_B), 3.92–3.73 (m, 10H, H-2_E, H-3_A, H-3_B, H-3_C, H-3_D, H-4_E, H-5_A, H-5_B, H-5_C, H-5_D), 3.63 (t, 1H, $J_{4,3}=J_{4,5}=9.6$ Hz, H-4_A), 3.52 (t, 1H, $J_{4,3}=J_{4,5}=9.5$ Hz, H-4_C), 3.49 (t, 1H, $J_{4,3}=J_{4,5}=9.8$ Hz, H-4_B), 3.46 (t, 1H, $J_{4,3}=J_{4,5}=9.8$ Hz, H-4_D), 3.42 (s, 3H, OMe), 2.05 (s, 3H, Ac), 1.35 (d, 3H, $J_{6,5}=6.2$ Hz, H-6_A), 1.29 (2d, 6H, $J_{6,5}=6.2$ Hz, H-6_B, H-6_D), 1.26 (d, 3H, $J_{6,5}=6.2$ Hz, H-6_C), 1.18 (d, 3H, $J_{6,5}=6.6$ Hz, H-6_E); ^{13}C NMR (D_2O, 100 MHz) δ 165.5 (CO*C*H$_3$), 102.4 (C-1_D), 101.8 (C-1_C), 100.5 (C-1_B), 99.4 (C-1_A), 94.5 (C-1_E), 78.5 (C-2_B), 78.0 (C-3_C), 75.0 (C-2_A), 74.0 (C-3_A), 72.1 (C-4_B), 72.0 (C-4_D), 71.3 (C-4_C), 70.4 (C-4_A), 70.3 (C-4_E), 70.1 (C-2_D), 70.0 (C-3_D), 69.9 (C-2_C), 69.8 (C-3_B), 69.2 (C-5_B), 69.0 (C-5_C), 68.9 (C-5_D), 68.3 (C-5_A), 66.8 (C-5_E), 65.5 (C-2_E), 54.9 (OMe), 51.1 (C-3_E), 22.0 (CO*C*H$_3$), 16.7–16.6 (C-6_A, C-6_B, C-6_C, C-6_D), 15.1 (C-6_E). ESI-MS for $C_{33}H_{57}NO_{21}$ (*m*/*z*): M_r (calcd) 803.34, M_r (found) 826.53 $(M+Na)^+$. Anal. Calcd: C, 49.31; H, 7.15; N, 1.74. Found: C, 49.49; H, 7.10; N, 1.85.

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The role of charge transfer interactions in the inclusion complexation of anionic guests with α-cyclodextrin

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Abstract—Two-parameter correlation models for the inclusion complexation of 30 carboxylic acids and their conjugated basis with α-cyclodextrin were obtained in terms of guest desolvation free energy (G_{desolv}), guest global softness (S) and a host–guest charge transfer parameter (ΔN) defined in the frame of Density Functional Theory (DFT). From the obtained models, it was concluded that charge transfer interactions are relevant in the stabilization of anionic inclusion complexes with α-cyclodextrin. Finally, an orbital picture is proposed in order to account for the charge transfer process between α-cyclodextrin and anionic species.

1. Introduction

Cyclodextrins are cyclic oligomers of α-D-glucose formed by the action of certain enzymes on starch (Fig. 1).[1] Due to the conformation of the monomeric units in the cyclic structure, the three dimensional form of cyclodextrins is similar to a truncated cone, where all the hydroxyl groups point outside the molecule, conferring a highly polar character to the molecular exterior. On the other hand, the glycosidic linkages that delimit the molecular inside are responsible for the hydrophobic character of the molecular cavity. One of the most important features about cyclodextrins is their ability to form inclusion complexes by allowing the penetration of organic and inorganic guests into their well defined molecular cavity.[1–4] Due to this particular ability, cyclodextrins have been the subject of extensive experimental and theoretical research and have been employed in a wide range of applications.[1–4]

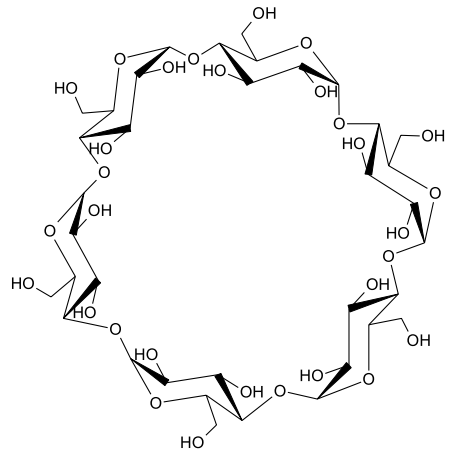

Figure 1. α-Cyclodextrin structure.

Both the determination of inclusion association constants and the identification of the main forces involved in complexation phenomena are central issues in the field of cyclodextrin research. Usually molecular inclusion is made not possible by a single interaction but through the simultaneous cooperation of several weak forces[5–7] Although, the nature and the specific role of each interaction have not been well stated yet, it has been customarily accepted that the high affinity of cyclodextrins upon organic apolar guests arises from the hydrophobic character of their molecular cavity.[1–4] Even though this general idea applies in most cases, hydrophobicity of guests cannot always explain the energetic or orientation features of inclusion complexes. For instance, the inclusion complexation with anionic species is expected to be poor in accordance to their hydrophilic character, however, there are several examples where the inclusion complexation with anions leads to similar or even larger association constants than those observed for their corresponding neutral species.[7–10] Those cases have been considered as exceptions to the general behavior of cyclodextrins and no further explanation has been attained yet.[7–10]

Keywords: Anionic guests; Charge transfer interactions; α-Cyclodextrin; DFT.
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With the aim of getting a better insight on inclusion complexation phenomena, several quantitative correlation models have been developed in order to account for inclusion complexation constants in terms of molecular descriptors related to structural and molecular properties of the guests.[11–19] The main achievements of these models have been to obtain numerical correlations between molecular descriptors and inclusion association constants and to find appropriate relationships between the employed molecular descriptors and the nature of host–guest interactions involved in complexation phenomena. In spite of these attainments, none of the reported models have dealt with the somewhat intriguing inclusion complexation with anionic substrates. Therefore, the search for a quantitative model that can account for the complexation of anions is still to be developed.

In a recent attempt to rationalize the inclusion complexation of some organic anions, Liu and Guo suggested that charge transfer interactions play a relevant role in the stabilization of their inclusion complexes.[20] However, up to now, no quantitative relationship between charge transfer interactions and inclusion association constants have been reported and no further characterization of host–guest charge transfer has been attained.

In the present work, we propose the building of correlation models for the inclusion complexation of 30 carboxylic acids and their corresponding conjugated bases with α-cyclodextrin in aqueous solution. Assuming that molecular descriptors can provide useful insights into physicochemical phenomena,[22] we expect to find a suitable set of descriptors that can account for the nature of the intermolecular forces that determine and differentiate the inclusion complexation with neutral and anionic substrates. In order to evaluate the role of charge transfer interactions on inclusion phenomena, we propose the use of a Density Functional Theory (DFT) approach in terms of global reactivity descriptors of host and guests.[21]

2. Theoretical background

According to DFT,[21] the ground state energy of an atom or molecule is written in terms of its electron density $\rho(r)$ as:

$$E[\rho] = F[\rho] + \int \mathrm{d}r v(r)\rho(r) \tag{1}$$

where $v(r)$ is the external potential and $F[\rho]$ is the Hosenberg–Kohn functional composed of electron kinetic energy and electron–electron repulsion. The first and the second partial derivatives of $E[\rho]$ with respect to the number of electrons N under constant external potential $v(r)$ are known as the electronic chemical potential (α) and the global chemical hardness (η) of the system, respectively.

$$\left(\frac{\partial E[\rho]}{\partial N}\right)_v = \mu, \quad \frac{1}{2}\left(\frac{\partial^2 E[\rho]}{\partial N^2}\right)_v = \eta \tag{2}$$

Both μ and η are reactivity descriptors that determine the global response of the energy of a system to the change in the number of electrons at fixed external potential. Electronic chemical potential measures the escaping tendency of the electron cloud of atoms or molecules. On the other hand, η can be seen as the resistance of an atom or molecule to undergo charge transfer processes.

In order for μ and η to be evaluated, the following operational definitions are currently employed.

$$\mu \approx \frac{\varepsilon_{\mathrm{HOMO}} + \varepsilon_{\mathrm{LUMO}}}{2} \tag{3}$$

$$\eta \approx \frac{\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO}}}{2} \tag{4}$$

Due to the inconsistence of Eq. 4 for anions, η can be calculated by the following expression suggested by Komorowski:[23]

$$\eta_b \approx \frac{\varepsilon_{\mathrm{LUMO}} - \varepsilon_{\mathrm{HOMO-1}}}{2} \tag{5}$$

Another important global reactivity descriptor is global softness (S), which is defined as the inverse of the global hardness.

$$S = \frac{1}{\eta} \tag{6}$$

S has been known as an indicator of the overall stability of a chemical system. In addition, S has been customarily related to macroscopic variables such as polarizability and molar refractivity,[21] which in turn account for the ease of deformation of the electron cloud of a molecule.

By expressing energy as a functional of number of electrons and external potential, the charge transfer process between two atoms or molecules, A and B, can be expressed in terms of global reactivity descriptors of the isolated species as follows:[21,24,25]

$$\Delta E = (\mu_{\mathrm{A}} - \mu_{\mathrm{B}})\Delta N + (\eta_{\mathrm{A}} + \eta_{\mathrm{B}})\Delta N^2 \tag{7}$$

The charge transfer process between A and B proceeds at constant external potential through the equalization of the chemical potentials between the reacting species. In addition, charge transfer is expected to occur from the species with the highest electronic chemical potential to the one that has the least.

By operating over Eq. 7, an expression for the maximum amount of charge transferred between A and B can be obtained:

$$\Delta N = -\frac{(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})}{2(\eta_{\mathrm{A}} + \eta_{\mathrm{B}})} \tag{8}$$

ΔN is a very useful parameter whose magnitude reflects the extension of the charge transfer between the reacting species.

3. Data set and computational aspects

The inclusion association constants (K) between α-cyclodextrin and a set of 30 carboxylic acids and their corresponding conjugated bases in aqueous solution were selected from experimental reports compiled by Connors.[26] It is important to stress that no further experimental data is

available for the inclusion complexation of acid–base conjugated pairs with α-cyclodextrin, under pH conditions where α-cyclodextrin remains essentially neutral.

Geometry optimization of isolated guests was performed by ab initio calculations at HF/6-31g(d) level using Gaussian 94W program.[27] Desolvation free energies (G_{desolv}) for neutral and anionic guests were calculated by using PCM solvation model[28] at HF/6-31g(d) level. α-Cyclodextrin structure was fully optimized at HF/6-31g(d) level, without any symmetry constraint.

DFT molecular descriptors (μ, η, S, and ΔN) for isolated guests and α-cyclodextrin were obtained from gas phase calculations at HF/6-31g(d) level, assuming that errors due to the neglect of solvation effects can be overcome by performing studies over structurally related compounds.[30]

Three molecular descriptors (S, ΔN and G_{desolv}) were employed to build multi-linear correlation models that account for the inclusion complexation constants between α-cyclodextrin and the selected set of 30 carboxylic acids and their corresponding conjugated basis. Other descriptors (dipole moment, electronic chemical potential, chemical hardness) were tried without any satisfactory result. S was included in the correlations as a relative value (S_{rel}) calculated according to Eq. 9:

$$S_{rel} = \frac{S_{guest}}{S_{CD}} \tag{9}$$

where S_{guest} and S_{CD} are the softness of guest and α-cyclodextrin, respectively. On the other hand, ΔN was calculated from Eq. 8 taking A as α-cyclodextrin and B as the guest molecule. The absolute values of ΔN were employed to build the correlation models. The calculated values of S_{rel}, ΔN and G_{desolv} for neutral and anionic guests along with their corresponding association constants with α-cyclodextrin in aqueous solution (ln K) are reported in Table 1.

STATGRAPHICS program was employed to find the best multi-linear correlation between the set of descriptors and the experimental data. Before building the model there was discarded any significant statistical correlation among the employed molecular descriptors in order to ensure the statistical relevance of the obtained results. Several statistical parameters were taken into account to asses the statistical quality of the models: squared correlation coefficient (r^2), T-test, Fischer ratio (F) and cross validation regression coefficient (r^2_{cv}).

Table 1. Calculated molecular descriptors for isolated guests

Guest	G_{desolv}		S_{rel}		ΔN		ln K	
	Neutral	Anionic	Neutral	Anionic	Neutral	Anionic	Neutral	Anionic
4-Acetylbenzoic acid	8.1	67.4	1.438	1.461	−0.088	0.213	6.80	4.10
4-Aminobenzoic acid	10.3	76.2	1.421	1.303	0.015	0.282	6.45	2.20
Benzoic acid	6.4	71.2	1.350	1.295	−0.041	0.283	5.82	2.40
3-Bromocinnamic acid	8.0	70.4	1.518	1.500	−0.062	0.229	7.24	5.69
4-Bromocinnamic acid	7.8	69.7	1.549	1.505	−0.056	0.230	9.42	6.36
2-Chlorocinnamic acid	6.6	71.1	1.471	1.466	−0.056	0.240	6.33	5.65
3-Chlorocinnamic acid	8.0	69.5	1.515	1.498	−0.063	0.231	7.87	6.05
4-Chlorocinnamic acid	7.7	69.7	1.538	1.498	−0.057	0.233	8.44	5.66
Cinnamic acid	7.6	72.7	1.516	1.464	−0.041	0.257	8.15	4.70
3-Cyanobenzoic acid	9.1	64.4	1.373	1.376	−0.093	0.213	5.90	4.10
4-Cyanobenzoic acid	8.3	63.6	1.420	1.404	−0.111	0.206	6.08	4.37
3,4-Dihydroxycinnamic acid	15.6	86.4	1.490	1.448	−0.588	0.264	7.69	5.51
4-Fluorobenzoic acid	6.6	68.5	1.374	1.290	−0.048	0.273	6.22	2.65
3-Hydroxybenzoic acid	12.9	76.2	1.430	1.293	−0.023	0.285	6.12	1.84
4-Hydroxybenzoic acid	12.2	76.2	1.368	1.285	−0.014	0.619	6.08	2.40
3-Hydroxycinnamic acid	13.2	78.4	1.505	1.479	−0.040	0.250	7.19	4.50
4-Hydroxycinnamic acid	13.7	79.1	1.515	1.439	−0.017	0.272	7.60	4.70
2-Methoxybenzoic acid	8.6	76.1	1.250	1.286	−0.011	0.283	3.45	1.97
3-Methoxybenzoic acid	8.5	73.1	1.434	1.297	−0.014	0.289	6.75	2.70
4-Methoixybenzoic acid	8.2	73.9	1.414	1.285	−0.008	0.298	6.78	1.25
3-Methoxycinnamic acid	9.3	74.5	1.547	1.468	−0.033	0.253	7.82	4.26
4-Methooxycinnamic acid	9.4	75.3	1.557	1.436	−0.012	0.273	9.24	5.62
4-*N*-Methylaminobenzoic acid	10.4	76.2	1.447	1.287	0.027	0.314	7.17	1.81
3-Methylbenzoic acid	6.4	70.9	1.380	1.293	−0.027	0.286	5.53	2.70
4-Methylbenzoic acid	6.2	71.4	1.412	1.308	−0.031	0.286	6.99	1.89
3-Methylcinnamic acid	7.6	72.7	1.519	1.471	−0.035	0.257	8.03	4.88
4-Methylcinnamic acid	7.5	73.3	1.540	1.464	−0.029	0.262	9.52	5.87
3-Nitrobenzoic acid	9.1	63.4	1.340	1.492	−0.122	0.180	4.69	6.19
4-Nitrobenzoic acid	8.1	61.5	1.435	1.506	−0.136	0.169	5.86	5.88
2-Hidroxybenzoic acid	6.8	64.2	1.300	1.279	−0.023	0.295	4.14	2.05
α-Cyclodextrin			1.000	1.000				

G_{desolv} is given in Kcal mol^{-1}. S_{rel} and ΔN are given in atomic units. ln K is reported in log units calculated from data in Ref. 26.

Table 2. Summary of statistical results for the obtained correlation models

Number of descriptors	Descriptor	Name	Coefficient	*T*-test	r^2	r^2_{cv}	Fischer test
Neutral guests							
0	Intercept	—	−17.10	−9.51	—	—	—
1	S_{rel}	Guest global relative softness	16.78	13.39	0.7846	0.7412	150.36
2	S_{rel}	Guest global relative softness	16.81	13.35			
	G_{desolv}	Guest desolvation free energy	−0.39	0.93	0.8697	0.8598	90.12
	S_{rel}	Guest global relative softness	16.81	13.35			
3	G_{desolv}	Guest desolvation free energy	−0.39	0.93	0.8697	0.8598	57.85
	ΔN	Host–guest charge transfer parameter	0.03	0.03			
Anionic guests							
0	Intercept	—	−20.68	−13.08	—	—	—
1	S_{rel}	Guest global relative softness	17.32	15.70	0.7754	0.7144	241.35
2	S_{rel}	Guest global relative softness	17.57	15.70			
	ΔN	Host–guest charge transfer parameter	0.52	0.32	0.8997	0.8891	119.47
	S_{rel}	Guest global relative softness	17.57	15.69			
3	ΔN	Host–guest charge transfer parameter	0.52	0.34	0.9001	0.8894	78.88
	G_{desolv}	Guest desolvation free energy	0.01	0.03			

4. Results and discussion

Table 2 shows a statistical summary of the best correlation models obtained for the inclusion complexation of 30 neutral and anionic carboxylic acids with α-cyclodextrin in terms of S_{rel}, ΔN and G_{desolv}. The first parameter reported is the coefficient corresponding to each molecular descriptor in the correlations. Positive regression coefficients indicate that an increase in the descriptor value produce an increase in the predicted ln *K*. On the other hand, negative regression coefficients indicate that the higher the value of the descriptor the lower the value of ln *K*. The second parameter reported is *T*-test, which is useful to determine the statistical significance of each descriptor in the correlations. The next parameters are the squared correlation coefficient (r^2) and the cross-validated correlation coefficient (r^2_{cv}). Essentially, r^2 measures the linear relationship between the considered descriptors and the experimental data, whereas r^2_{cv} describes the stability of the regression model obtained by focusing on the sensitivity of the model to the elimination of any single data point.

From *T*-test, r^2 and r^2_{cv} values it was determined that no significant statistical improvement was attained by employing more than two molecular descriptors. In the case of neutral guests the most important descriptors are S_{rel} and G_{desolv}, whereas in the case of anions, the most significant descriptors are S_{rel} and ΔN. Eqs. 10 and 11 represent the best correlation models obtained for the inclusion complexation of neutral and anionic species, respectively.

For neutral guests:

$$\ln K = -17.10 + 16.81 S_{rel} - 0.39 G_{desolv}, \quad (10)$$

$$N = 30, \quad r^2 = 0.8697, \quad r^2_{CV} = 0.8598$$

For anionic guests:

$$\ln K = -20.68 + 17.57\ S_{rel} + 0.52 \Delta N, \quad (11)$$

$$N = 30, \quad r^2 = 0.8997, \quad r^2_{CV} = 0.8891$$

It is interesting to stress that the most significant descriptor in both models is S_{rel}, while G_{desolv}, and ΔN appear as key factors that determine and differentiate the inclusion complexation between neutral and anionic species. A plot between experimental and predicted ln *K* for the inclusion complexation of neutral and anionic guests is shown in Figure 2.

4.1. Physical interpretation

The nature of the molecular descriptors found in the structure–property correlations can provide valuable information about the physicochemical phenomena involved the inclusion complexation with α-cyclodextrin. According to the obtained models, the most important descriptor for neutral and anionic complexation appears to be S_{rel}. This parameter can be related to the ease of distortion of the electron cloud of the molecules,[21] which in turn can be associated to the ease of the establishment of van der Waals interactions between host and guests. The high *T*-statistical value of S_{rel} in the correlations can be taken as an indicator of the relevance of van der Waals interactions in the inclusion complexation with neutral and anionic guests.[5] On the other hand, the positive coefficients of S_{rel} in both models are in agreement with the attractive nature of van der Waals forces,[29] since, an increase in S_{rel} is directly related to an increase in ln *K*. When analyzing the effect of chemical substitution on S_{rel} it can be seen that the incorporation of larger and more polarizable atoms or groups leads to an increase in S_{rel} as well as an increase in ln *K* for both neutral

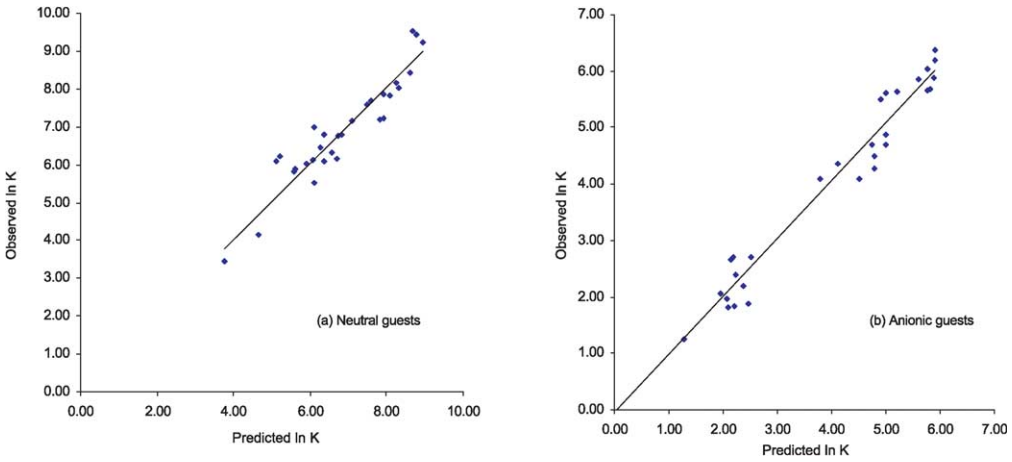

Figure 2. Observed versus predicted ln K for the inclusion complexation of (a) neutral guests and (b) anionic guests. Experimental data obtained from Ref. 26.

and anionic guests. This general trend is observed, for example, when comparing benzoic acid, 4-hydroxybenzoic acid, 4-methoxybenzoic acid (see Table 1). Another example in this sense is given by the series of substituted cinnamic acids, where an increase in global softness and ln K is observed when comparing cinnamic acid, 4-hydroxicinnamic acid, 4-chlorocinnamic acid and 4-bromocinnamic acid. The observation that more polarizable substituents are related to higher association constants is in agreement with several experimental reports and empirical models,[5,11–19] however, the relationship between softness and association constants has not been previously reported. Finally, since, the calculated values of S_{rel} (Table 1) reveal no significant differences between neutral and anionic guests and the T-test and correlation coefficient of S_{rel} in both correlations are very similar (Table 2), it should be expected that van der Waals forces play similar roles in the stabilization of anionic and neutral inclusion complexes.

On the other hand, G_{desolv} can be related to guest hydrophobicity.[5] That this descriptor only appears in the correlation for neutral species can be interpreted in terms of a major contribution of hydrophobic interactions in the inclusion complexation with neutral substrates than in the case of anions. This interpretation seems reasonable, since, anionic species are expected to be less hydrophobic than neutral ones. In addition, the negative coefficient for G_{desolv} in the neutral guests' correlation suggests that lesser desolvation free energies lead to higher association constants, in agreement to chemical intuition. Table 1 contains the calculated G_{desolv} for the isolated neutral and anionic guests. As expected from the obtained correlations, the desolvation of anionic species is highly unfavorable and neutral species appear to be prone to the establishment of hydrophobic interactions.

Finally, the charge transfer parameter ΔN accounts for the extension of the electron transfer between two reacting species.[21] According to the obtained models, ΔN is only of importance in anion complexation with α-cyclodextrin. Since, absolute values for ΔN have been considered to build the correlations, the positive coefficient of ΔN in the model for anions suggests that charge transfer interactions positively contribute to increase the host–guest association constant. As seen in Table 1, ΔN markedly differs from neutral to anionic species, both in sign and magnitude. All neutral guests have small and negative ΔN values, therefore, charge transfer should be of minor importance in their complexation with α-cyclodextrin and a small amount of electron density is expected to flow from host to guest. On the other hand, the large and positive ΔN values for anions indicate that charge transfer is relevant in the stabilization of their inclusion complexes with α-cyclodextrin and that electron density is expected to flow from guest to host. Same conclusions can be attained by analyzing the calculated values of μ and η for isolated host and guests (Table 3). Since, anionic species have larger electronic chemical potentials than α-cyclodextrin they are stronger donor species compared to it and the charge transfer is expected to occur from guest to host. On the other hand, neutral molecules have lesser α values than μ-cyclodextrin; therefore, they are expected to behave as electron acceptors in the inclusion complexation interaction. In the case of η, no significant differences are observed when comparing neutral and anionic guests, hence, they oppose in the same extent to charge transfer processes.

According to the previous analysis and to the obtained models, charge transfer interactions appear as key factors that determine the inclusion complexation with anionic substrates. Up to now, charge transfer has been rarely mentioned as a factor that contributes to inclusion complexation with cyclodextrins.[20] To our knowledge, none of the reported correlation models for the inclusion with cyclodextrins deals with the effect of charge transfer in complexation phenomena.

It is important to stress that the obtained correlations do not mean that other interactions (e.g., electrostatic interactions) do not participate in inclusion complexation. They only state that those factors should not be as important as to produce significant differences among the considered guests. This fact should arise from the structural similarity within the selected set of guests.[31]

It is also important to emphasize that our correlation models do not consider explicitly the contribution of hydrogen bonding to the inclusion complexation. Strictly speaking,

Table 3. Electronic chemical potential (α) and chemical hardness (η) for host and guests. All values are reported in atomic units

Guests	α		η[a]	η_b[a]
	Neutral	Anionic	Neutral	Anionic
4-Acetylbenzoic acid	−0.147	0.004	0.207	0.204
4-Aminobenzoic acid	−0.095	0.046	0.209	0.228
Benzoic acid	−0.124	0.046	0.220	0.230
3-Bromocinnamic acid	−0.134	0.011	0.196	0.198
4-Bromocinnamic acid	−0.130	0.011	0.192	0.198
2-Chlorocinnamic acid	−0.131	0.017	0.202	0.203
3-Chlorocinnamic acid	−0.134	0.012	0.196	0.199
4-Chlorocinnamic acid	−0.131	0.013	0.194	0.199
Cinnamic acid	−0.123	0.026	0.196	0.203
3-Cyanobenzoic acid	−0.150	0.007	0.217	0.216
4-Cyanobenzoic acid	−0.159	0.002	0.211	0.212
3,4-Dihydroxycinnamic acid	−0.110	0.030	0.188	0.206
4-Fluorobenzoic acid	−0.128	0.041	0.224	0.231
3-Hydrzoxybenzoic acid	−0.114	0.048	0.208	0.230
4-Hydroxybenzoic acid	−0.110	0.225	0.217	0.232
3-Hydroxycinnamic acid	−0.123	0.022	0.194	0.201
4-Hydroxycinnamic acid	−0.111	0.034	0.192	0.207
2-Methoxybenzoic acid	−0.108	0.047	0.209	0.231
3-Methoxybenzoic acid	−0.110	0.049	0.207	0.229
4-Methoixybenzoic acid	−0.107	0.055	0.215	0.232
3-Methoxycinnamic acid	−0.119	0.024	0.191	0.203
4-Methooxycinnamic acid	−0.108	0.035	0.191	0.207
4-*N*-Methylaminobenzoic acid	−0.089	0.063	0.206	0.231
3-Methylbenzoic acid	−0.117	0.048	0.216	0.230
4-Methylbenzoic acid	−0.119	0.047	0.218	0.228
3-Methylcinnamic acid	−0.120	0.026	0.196	0.202
4-Methylcinnamic acid	−0.117	0.028	0.193	0.203
3-Nitrobenzoic acid	−0.165	−0.013	0.214	0.199
4-Nitrobenzoic acid	−0.171	−0.019	0.205	0.198
2-Hidroxybenzoic acid	−0.114	0.053	0.206	0.233
α-Cyclodextrin	−0.103		0.298	

[a] η and η_b refers to the hardness of neutral and anionic species. η and η_b were calculated from Eqs. 4 and 5, respectively.

hydrogen bonding cannot be considered as an individual type of interaction, since, it is composed by the simultaneous cooperation of several forces (electrostatic, induction, dispersion and charge transfer interactions).[29] Therefore, hydrogen bond has been implicitly considered by the S_{rel} and ΔN terms in the obtained correlations.

4.2. Orbital picture for charge transfer interactions

Charge transfer interactions are short-range and site specific forces, that arise from orbital overlap between the reacting species. Since, it has been found that charge transfer is relevant in the stabilization of anionic inclusion complexes with α-cyclodextrin, it is very helpful to visualize these interactions in terms of the orbitals involved in the host–guest charge transfer.

From DFT molecular descriptor analysis it has been already stated that anions act as electron donor species in the inclusion interaction with α-cyclodextrin. Therefore, according to the Frontier Molecular Orbitals reactivity theory,[32] one can expect that charge transfer is governed by the maximum overlap between the HOMO of the anionic guests (donor species) and the LUMO of the α-cyclodextrin molecule (acceptor species). Three dimensional plots of the corresponding HOMO of anions and LUMO of α-cyclodextrin were constructed from ab initio calculations at HF/6-31g(d) level and were employed to build a pictorial representation of the orbital interaction that leads to host–guest charge transfer. Figure 3 shows the calculated HOMO for three anionic guests and the LUMO for α-cyclodextrin. In all cases, the HOMO of anions is located at the carboxylate end of the molecules, whereas the LUMO of α-cyclodextrin is located near the primary rim of the molecule. In order to charge transfer to be favored, the carboxylate group of the anions must deeply penetrate the α-cyclodextrin cavity (see Fig. 3). The proposed orbital interaction for host–guest charge transfer is in agreement with experimental reports, which show that the carboxylate group of the guests protrudes from the primary rim of α-cyclodextrin.[33] Therefore, both the energetic criteria given by the correlation model (11) and the geometrical approach given by the orbital picture for host–guest charge transfer are in agreement with the existence of stabilizing charge transfer interactions between α-cyclodextrin and anionic species. These interactions should be helpful to understand why highly hydrophilic species such as anions can penetrate the hydrophobic cavity of cyclodextrins.

5. Conclusion

The inclusion complexation of 30 carboxylic acids and their conjugated basis with α-cyclodextrin was described by simple two-parameter correlation models containing easily interpretable molecular descriptors (S_{rel}, G_{desolv} and ΔN). According to these models van der Waals forces seem to dominate the inclusion complexation with neutral and anionic species, whereas hydrophobic and charge transfer interactions appear as key factors that determine and differentiate the inclusion complexation between neutral and anionic species, respectively.

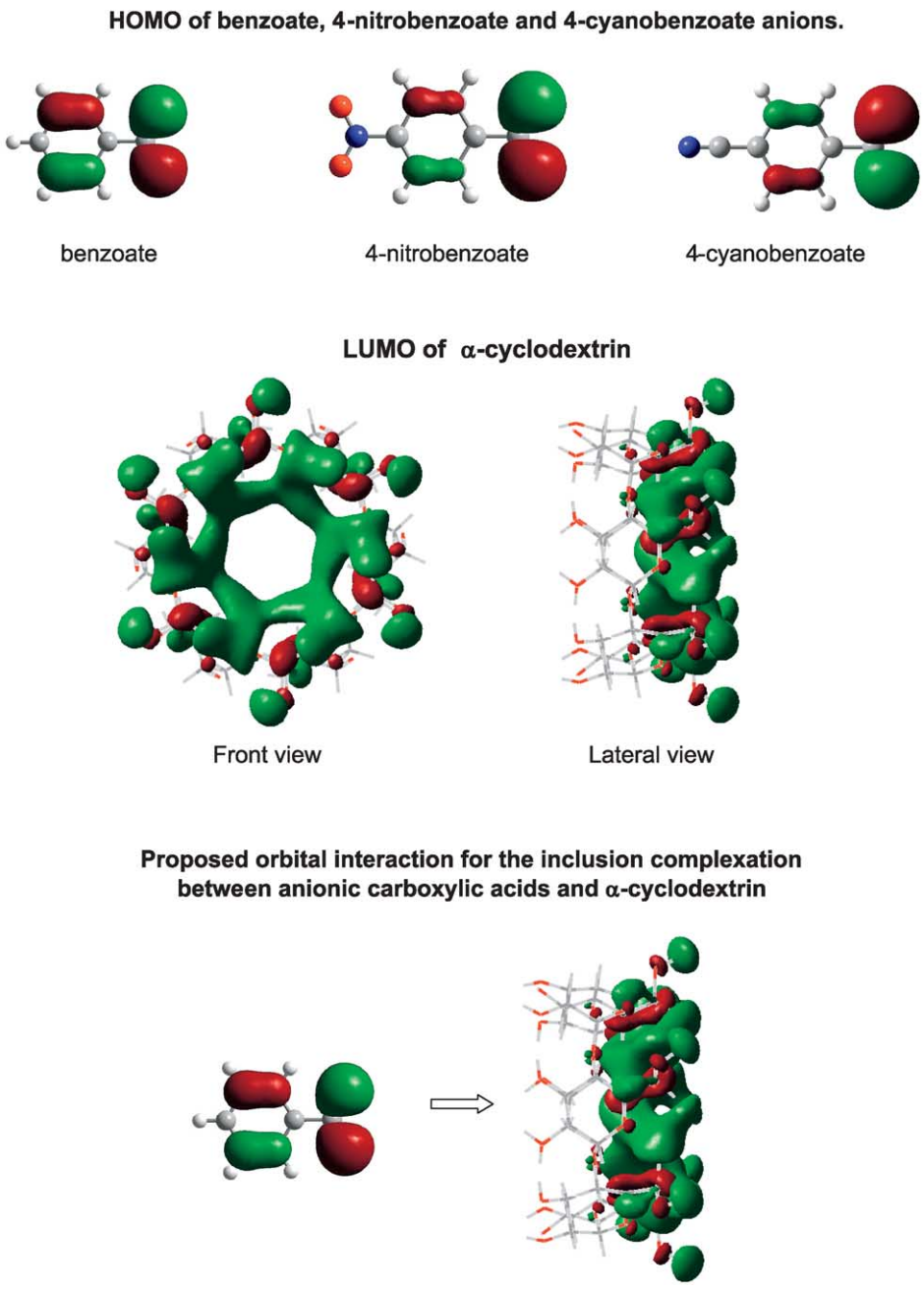

Figure 3. Orbital picture for charge transfer interactions involved in the inclusion complexation of anionic substrates with α-cyclodextrin.

In spite of the restriction of the obtained models to a limited number of compounds, they give a useful picture to understand the differences and similarities between inclusion complexation of neutral species and their corresponding conjugated bases. In addition, they should be helpful to predict and understand the changes in inclusion complexation constants due to guest deprotonation for new series of compounds.

In addition, the use of DFT global molecular descriptors instead of full calculations on inclusion complexes provides a useful strategy to approach to supramolecular interactions. In the case of large systems like cyclodextrins and their inclusion complexes, this approach seems even more advantageous.

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Synthesis and spectroscopic studies of isosteviol-calix[4]arene and -calix[6]arene conjugates

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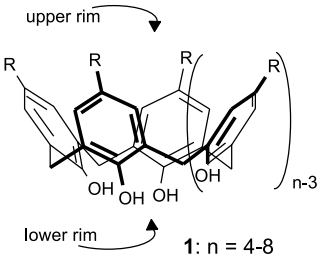
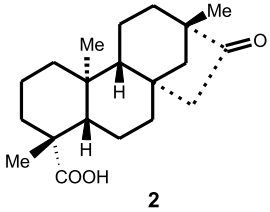
Abstract—Novel calix[4]arene derivatives functionalized with two or four isosteviol units at the upper rim and a new calix[6]arene having six isosteviol moieties at the lower rim have been synthesized. The structures of these compounds have been confirmed by NMR and mass spectrometry data. All ^{1}H and ^{13}C NMR chemical shifts of isosteviol were fully assigned by extensive NMR spectroscopic methods, and used to clarify the structures and conformations of isosteviol-calixarene conjugates.

1. Introduction

Calixarenes (**1**) have been widely used as scaffolds for the synthesis of receptors for cations, anions and neutral molecules.[1] The main reason for the increasing importance of the use of calixarenes in supramolecular and bioorganic chemistry is the possibility of their easy functionalisation both at the lower and at the upper rim.[2] Recently, the calix[4]arene scaffold was functionalized with amino acids at the upper rim and a novel series of biomimetic macrocyclic hybrid receptors possessing both polar groups and hydrophobic cavities as binding sites was elaborated. These compounds exhibit interesting complexation properties towards amino acids, small peptides[3a–d] and sugars.[3e] Calixarenes were also adorned at the upper[3d,f,g] or lower rim[3h] with glycoside units, thus obtaining receptors for anions and molecules able to efficiently and specifically interact with lectins thanks to the glycoside cluster effect. Calixarenes were also functionalized with steroidal derivatives and interesting receptors, able to act as artificial ion channels or enantioselective receptors for organic anions, obtained.[3i–k]



1: n = 4-8



2

The isosteviol **2** (*ent*-16-oxobeyran-19-oic acid)[4] is a diterpenoid which is obtained by acid-catalysed hydrolysis of stevioside,[5a] has anti-feeding action and inhibits the biosynthesis of gibberellins.[6] Although the biotransformations of isosteviol are widely studied (see e.g., Ref. 7) only a few papers[8] are devoted to its chemical transformations. Isosteviol **2** possesses a rigid tetracyclic framework with hydrophobic external and internal surfaces and polar groups at the ends of the molecule. It was found that tweezer-like structures based on isosteviol have hydrophobic internal cavities and form flaky-like structures having alternating hydrophobic and hydrophilic regions in the crystal.[9] In solution these isosteviol derivatives behave as receptors and transport amino acids through liquid chloroform membranes.[10] Moreover, isosteviol **2** itself appeared to bind small aromatic molecules forming crystal inclusion complexes whose supramolecular structure looks like a double chiral helix.[11]

Keywords: Calixarenes; Isosteviol; NMR spectroscopy; Molecular modelling; Ab initio calculations.
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2. Results and discussion

2.1. Full assignment of the isosteviol (2) NMR spectra

First of all we assigned carefully the NMR spectra of isosteviol **2** because there are still some uncertainties in the literature. The ^{1}H NMR spectrum shows signals for three methyl groups at $\delta=1.26$ (s, 3H, 18-H_3), $\delta=0.99$ (s, 3H, 17-H_3) and $\delta=0.80$ (s, 3H, 20-H_3) as well as a number of multiplets in the range from 2.67 up to 0.93 ppm, where the only doublet of doublets at 2.65 (1H, dd, $J=18.7$, 3.7 Hz) is unambiguously assigned to 15-H_α.[5a,9b,12] Nevertheless, the full correlation of signals is necessary for analysis of the more complicated isosteviol-calixarene conjugates. The ^{13}C NMR spectrum of isosteviol **2** shows 20 signals. Two of them correspond to the two carbonyl groups with characteristic chemical shifts $\delta=222.7$ ppm (C-16) and $\delta=183.6$ ppm (C-19). The ^{13}C NMR chemical shifts of all the hydrogenated carbons can be assigned unambiguously by HSQC experiments. The complete elucidation of the isosteviol **2** structure was achieved by the HMBC experiment. The HMBC correlations (Fig. 1a) between the proton signals at $\delta=0.99$ (17-H_3) and the carbon resonances at 222.7 ppm (C-16), 37.3 ppm (C-12) and 54.3 ppm (C-14); between the protons at 1.26 ppm (18-H_3) and the carbon resonances at 183.6 ppm (C-19), 37.7 ppm (C-3) and 57.0 ppm (C-5); between the proton signals at 0.80 ppm (20-H_3) and the carbon resonances at 39.8 ppm (C-1), 57.0 ppm (C-5) and 54.8 ppm (C-9) allowed us to carry out the full assignment of the proton and of the carbon spectra. The results are summarised in Table 1. The ^{13}C NMR chemical shifts coincide with previously reported values.[5a,7] It is worth noting that the assignment of all protons of diterpenoids is very rare in the chemistry of diterpenes, and for diterpenoid isosteviol **2** it has been accomplished for the first time. We know of only one paper concerning the analysis of the ^{1}H NMR spectrum of isosteviol **2**[5a] where signals were assigned only to methyl groups and to the 12-H, 14-H, 15-H protons. However, the discrepancy in the assignment of the doublet at $\delta=2.18$ appeared when comparing our results with previously published data[5a] which were based only on NOE experiment.[5b] This signal was previously assigned[5a] to 12-H_{ax}, whereas we now attribute it to 3-H_{eq}. According to our NOE (Fig. 1b) and particularly HMBC experiments (Fig. 1a) the assignments of 3-H and 12-H protons have to be exchanged (Table 1) in comparison with data from Ref. 5a.

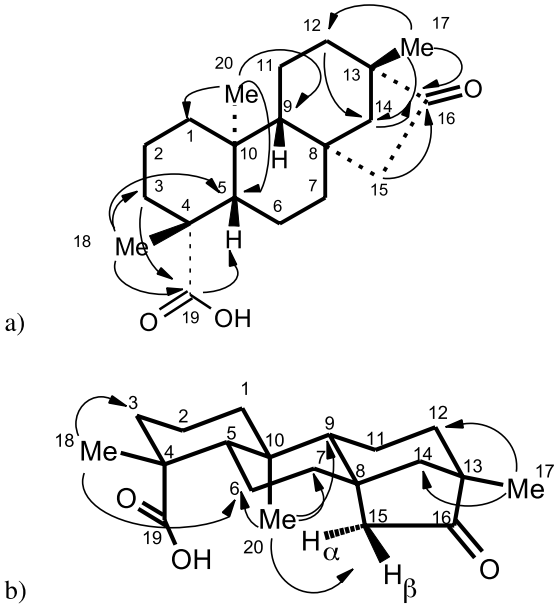


Figure 1. Diagnostic correlations for isosteviol **2**: (a) HMBC, (b) NOESY.

Table 1. ^{13}C and ^{1}H NMR chemical shifts of isosteviol **2** ($CDCl_3$, TMS as internal standard, 303 K, 150.86 and 600.13 MHz, respectively)

C	δ (^{13}C)	δ (^{1}H)	
1	39.8	0.93 (1H, dd, $J=13.3$, 3.9 Hz, 1-H_{ax})	1.75 (1H, d, 1-H_{eq})
2	18.9	1.85 (1H, d, 2-H_{ax})	1.46 (1H, d, 2-H_{eq})
3	37.7	1.04 (1H, dd, $J=13.7$, 4.3 Hz, 3-H_{ax})	2.18 (1H, d, $J=13.4$ Hz, 3-H_{eq})
4	43.7		
5	57.0	1.16 (1H, d, $J=12.1$ Hz, 5-H)	
6	21.6	1.77 (1H, d, 6-H_{ax})	1.90 (1H, d, $J=13.8$ Hz, 6-H_{eq})
7	41.5	1.50 (1H, dd, $J=13.4$, 3.6 Hz, 7-H_{ax})	1.68 (1H, d, $J=13.4$ Hz, 7-H_{eq})
8	48.73		
9	54.8	1.20 (1H, d, $J=14.2$ Hz, 9-H)	
10	38.2		
11	20.3	1.24 (1H, d, 11-H_{ax})	1.71 (1H, d, 11-H_{eq})
12	37.3	1.38 (1H, dd, $J=12.4$, 5.8 Hz, 12-H_{ax})	1.63 (1H, d, $J=13.1$ Hz, 12-H_{eq})
13	39.5		
14	54.3	1.42 (1H, dd, $J=11.5$, 3.4 Hz, 14-H_{ax})	1.56 (1H, dd, $J=11.7$, 2.4 Hz, 14-H_{eq})
15	48.75	2.65 (1H, dd, $J=18.7$, 3.7 Hz, 15-H_α)	1.82 (1H, d, $J=18.5$ Hz, 15-H_β)
16	222.7		
17	19.8	0.99 (3H, s, 17-H_3)	
18	29.0	1.26 (3H, s, 18-H_3)	
19	183.6		
20	13.3	0.80 (3H, s, 20-H_3)	

These conclusions are supported by DFT GIAO 6-31G(d)[13] calculations of ^{1}H and ^{13}C chemical shifts of isosteviol **2** (with preliminary MM minimized geometry) performed with the help of GAUSSIAN 98.[14] The calculated values both for 3-H and 12-H are very close to the experimental ones (Table 2), as well as a good correlation being observed between calculated and experimental values of ^{13}C chemical shifts (Fig. 2). Interestingly, the assignment of 3-H_{eq} to the signal at 2.18 ppm indicates that this proton is deshielded by C=O group and that the conformational preference of the carboxylic group in solution is quite close to that found in the crystal according to X-ray data[15] (schematically represented in Fig. 1b).

2.2. Coupling of isosteviol to calixarenes

As a starting material for introducing the isosteviol

Table 2. Experimental and calculated values of some ^{1}H chemical shifts of isosteviol **2**

	δ_{exp} (ppm)	δ_{calc} (ppm)
3-H_{ax}	1.04	1.17
3-H_{eq}	2.18	2.26
12-H_{ax}	1.38	1.30
12-H_{eq}	1.63	1.68

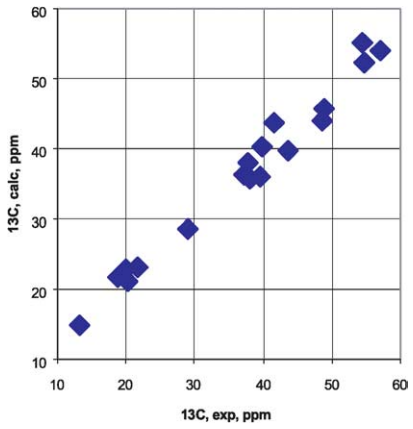
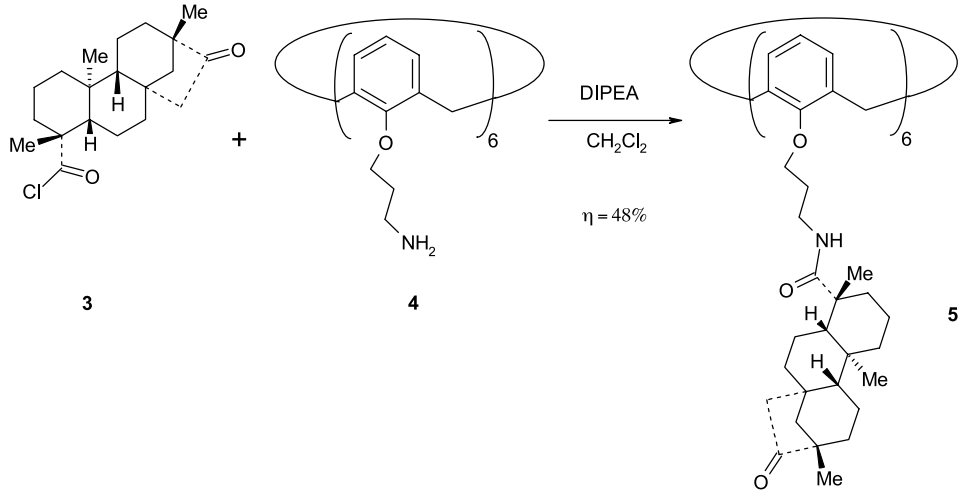
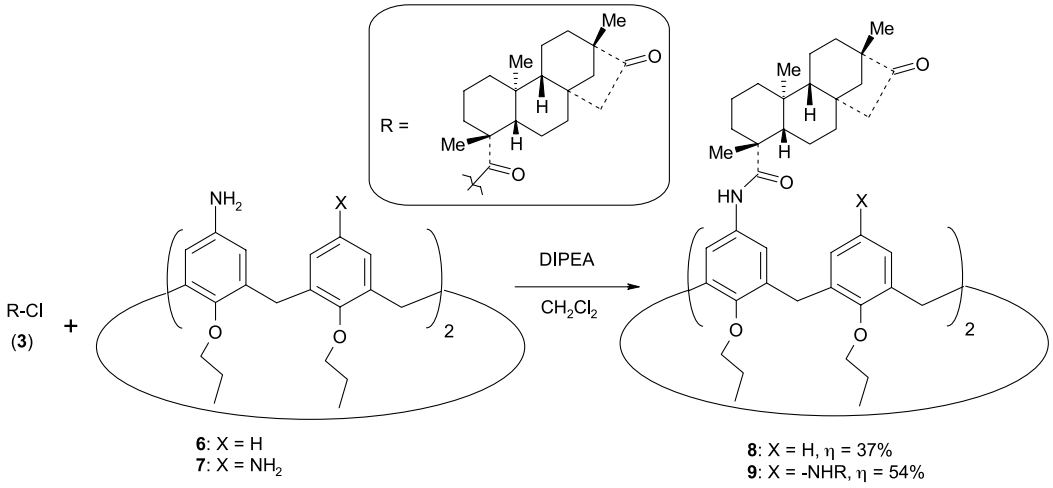


Figure 2. Correlation between calculated and experimental ^{13}C NMR chemical shifts of isosteviol **2**.

framework onto the calixarene system we used isostevioyl chloride **3**, which was synthesized by the reaction of isosteviol **2** with an excess of thionyl chloride. We first, explored the possibility of introducing six isosteviol units at the lower rim of calix[6]arene. By reacting hexaamino-calix[6]arene **4** with isostevioyl chloride **3** and *N*,*N*-diisopropylethyl amine (DIPEA) in dry CH_2Cl_2 we isolated the lower rim isosteviol conjugate **5** in 48% yield (Scheme 1). The ^1H NMR spectrum of **5** shows the equivalence of the six isosteviol units (three signals of methyl groups without splitting) and clear signals (doublet and triplet) in the aromatic part of the spectrum. The singlet at $\delta=3.90$ for the $ArCH_2Ar$ protons indicates that the macrocycle is rapidly interconverting among different conformations. The mass spectrum, showing the presence of the peak corresponding to the molecular weight of compound **5**, confirms that all six isosteviol units are linked to the calixarene scaffold. In order to introduce the isosteviol moieties on the calix[4]arene scaffold we used the upper rim diamino- (**6**) and tetraamino- (**7**) tetrapropoxy-calix[4]arenes. Thus, by reacting diterpenoid **3** with (**6**) or (**7**) and DIPEA in dry CH_2Cl_2, we obtained the di- (**8**) or tetra- (**9**) functionalized compounds (Scheme 2) in 37 and 54% isolated yield, respectively. The electrospray mass spectra of both compounds **8** and **9** show peaks corresponding to the molecular ions plus sodium. Compound **9** shows the typical ^1H NMR spectrum of a tetrafunctionalized calix[4]arene in the cone conformation in which equatorial and axial methylene protons resonate as two distinct doublets at $\delta=3.16$ and 4.41 ppm, respectively. Calixarene



Scheme 1.



Scheme 2.

aromatic protons give rise to two doublets at $\delta=6.75$ and 6.86 ppm due to *meta* couplings with $J=2.4$ Hz, as a consequence of the chirality of isosteviol. The ^{1}H NMR spectrum of **8** shows that the two isosteviol moieties are equivalent as clearly indicated by the three singlets (0.89, 0.98, 1.35 ppm) of the methyl groups of the diterpenoid.

In $CDCl_3$ the relative position of the signals due to the aromatic protons of the substituted (doublets at $\delta=7.16$ and 7.21 ppm) and unsubstituted (doublet and triplet at $\delta=6.17$ and 6.25 ppm, respectively) aromatic nuclei, indicates[3b] that compound **8** adopts an open flattened cone conformation with the two unsubstituted aromatic rings pointing inwards and the other two aromatic rings bearing the isosteviol units pointing outwards from the aromatic cavity. The signals of equatorial and axial methylene protons resonate as doublets at $\delta=3.10$ and 4.41 ppm, respectively, with the signal of the equatorial methylene bridge protons being splitted into two distinct doublets. This splitting, as well as that observed for the protons of substituted aromatic rings (two doublets at $\delta=7.16$ and 7.21 ppm) are caused by the presence of the chiral isosteviol units. The ^{13}C NMR spectrum of calix[4]arene **8** shows full set of signals both for the calixarene moiety and for the isosteviol fragment. The final elucidation of the structure was achieved by the use of 2D HMBC and 2D NOESY experiments.

The diagnostic HMBC correlations (Fig. 3a) between the proton signals at $\delta=1.35$ ppm (18-H_3), $\delta=7.24$ ppm (NH) and $\delta=1.26$ ppm (3-H_{ax}) with the carbon resonance at 174.7 ppm (C-19), as well as the HMBC correlation between proton signals at $\delta=7.24$ ppm (NH) and the carbon resonance at 121.2 ppm (C-4′, C-6′) gave additional proofs of the connection between the isosteviol moieties and the calixarene skeleton. NOE data (Fig. 3b) allowed us to fully assign all the signals of the calix[4]arene moiety and its propyloxy substituents at the lower rim (see Section 4 for **8**). We failed to grow single crystals for X-ray study of compound **8** and modeled its conformation in vacuo using MM computations[16] through Chem3D Ultra 6.0 program (CambridgeSoft Corp). The minimized open flattened cone conformation[17] obtained is shown in Figure 4. According to semiclassical model of anisotropy effect calculations[18] performed for the open flattened cone conformer (MM optimized geometry), the protons H-10′, H-12′, H-11′ of unsubstituted aromatic rings are indeed shielded if compared with benzene protons (0.74 and 0.66 ppm, respectively) by the substituted aromatic rings while the H-4′ and H-6′ protons are slightly deshielded (0.2 ppm). This is in a good agreement with the experimental data. The OCH_2 fragments of the propoxy groups attached to the unsubstituted aromatic rings of **8** give rise to a clear and simple triplet ($\delta=3.64$), while the analogous protons belonging to the other propoxy groups at $\delta=3.98$ are slightly split and appear as a doublet of doublets with $J=8.1$, 8.4 Hz, implying the non-equivalence of the geminal protons. Our computations are in good agreement with these experimental data. In fact, the minimized open flattened cone structure of calix[4]arene **8** (Fig. 4) shows that C_{Ar}–O–CH_2–CH_2–CH_3 moieties have different preferred conformations, namely *anti*,*anti* for moieties attached to unsubstituted aromatic rings and *gauche*,*anti* for moieties attached to aromatic rings functionalized with isosteviol fragments.

3. Conclusions

In conclusion, we have reported an efficient and easy synthetic procedure to introduce isosteviol moieties both at the lower and upper rims of calix[6]- or calix[4]arenes. Also thanks to the complete assignment of the ^{1}H and ^{13}C NMR

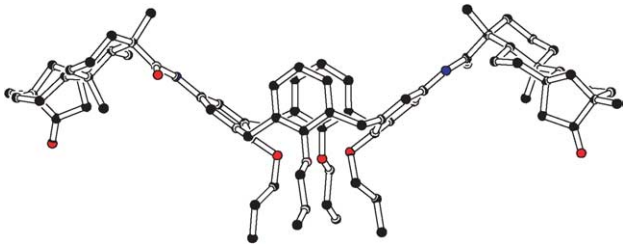


Figure 4. The open flattened cone conformation of functionalized calix[4]arene **8** in vacuo simulated by MM; hydrogen atoms are omitted.

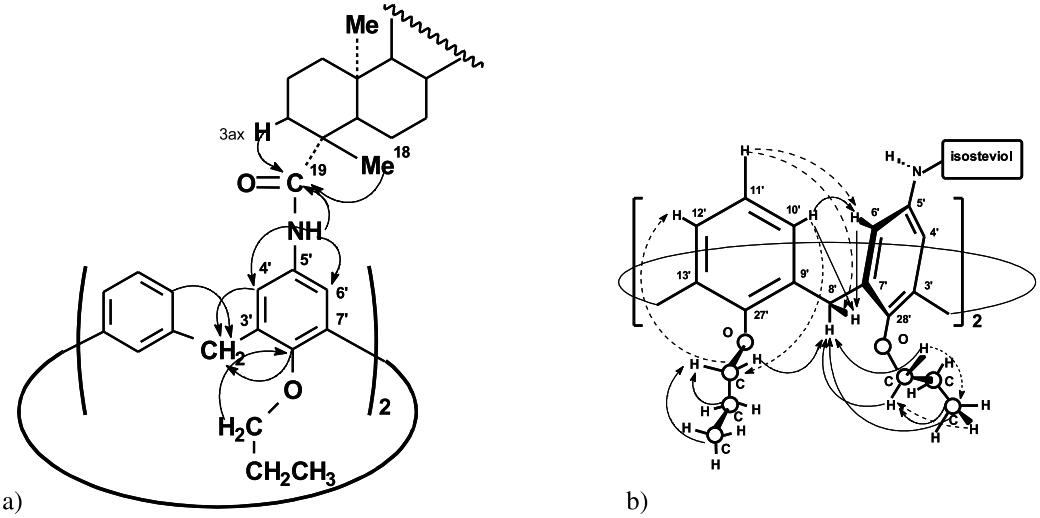


Figure 3. Diagnostic HMBC (a) and 2D NOESY correlations (b) for difunctionalized calyx[4]arene. **8**. Numbering of calixarene atoms according to Ref. 17, the apex prime notation being used to distinguish calixarene carbon atoms from isosteviol ones.

spectra of isosteviol **2**, which was obtained for the first time, it was also possible to assign all the ^{1}H and ^{13}C NMR signals in the spectra of the isosteviol-calixarene conjugates. A detailed conformational analysis of the disubstituted calix[4]arene **8** both in solution and in silico has been also carried out. We are currently investigating the potential of this class of neo-conjugates in the recognition of saccharides and organic anions of biological interest together with their capability to form artificial ion channels and act as transmembrane ionophores.

4. Experimental

4.1. Materials and methods

Most of the solvents and all reagents were commercial and used without further purification. All dry solvents were prepared according to standard procedures and stored over molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 300, Bruker MSL 400 and Avance 600 spectrometers. NMR experiments on Avance 600 spectrometer were performed in dilute $CDCl_3$ solutions at 303 K, the spectrometer being equipped with a 5 mm diameter broad band inverse probehead working at 600.13 MHz in ^{1}H and 150.86 MHz in ^{13}C experiments. Chemical shifts were referenced to the residual signal of $CDCl_3$. Complete assignments of the ^{1}H and ^{13}C NMR spectra of the title compounds were accomplished by 2D COSY, HSQC, HMBC and NOESY experiments. In some cases 1D DPFGNOE method was used to measure NOE's. Mass spectra by electrospray ionization (ESI) were recorded on a Micromass ZMD. Analytical TLC was performed using Merck prepared plates (silica gel 60 F-254 on aluminum). Merck silica gel (40–60 μm) was used for flash chromatography. 5,17-Diamino-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (**6**) and 5,11,17,23-tetraamino-25,26,27,28-tetra-*n*-propyloxycalix[4]arene (**7**) were synthesized according to literature procedures.[19,20] Calix[6]arene fuctionalized with six *n*-propyloxy moieties at lower rim was synthesized according to Ref. 21. Molecular mechanics (employing the MM2 force field[16]) were performed with CS Chem3D Ultra 6.0 (CambridgeSoft Corp.) on a AuthenticAMD Athlon (Im)computer. Ab initio electronic structure calculations were performed using GAUSSIAN 98.[14]

4.1.1. Isostevioyl chloride (3). A mixture of isosteviol **2** (0.5 g, 1.57 mmol) and freshly distilled thionyl chloride (0.5 ml, 2.5 mmol) was refluxed for 1 h. The unreacted excess of thionyl chloride was removed at reduced pressure. The residue was recrystallized from hexane to give **3** (yield 0.41 g, 77%). Mp 143–145 °C. IR-spectrum (mineral oil, ν/cm^{-1}): 1740 (C=O, ketone), 1800 (ClC=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 3H, 20-H_3), 0.97 (s, 3H, 17-H_3), 1.35 (s, 3H, 18-H_3), 0.90–1.90 (m, 18H, 1H_2, 2H_2, 3-H_{ax}, 5-H, 6-H_2, 7-H_2, 9-H, 11-H_2, 12-H_2, 14-H_2, 15-H_β), 2.35 (d, 1H, 3-H_{eq}, J=14.3 Hz), 2.63 (dd, 1H, 15-H_α, J=18.8, 3.9 Hz). Found (%): Cl, 9.93. Calcd for $C_{20}H_{29}ClO_2$ (%): Cl, 10.52.

4.1.2. Synthesis of 37′,38′,39′,40′,41′,42′-hexakis(isostevioylamido)-propyloxycalix[6]arene (5). A solution of calix[6]arene **4** (0.05 g, 0.07 mmol) in 1.5 ml of dry CH_2Cl_2 and DIPEA (0.054 ml, 0.3 mmol) was added to the solution of isostevioyl chloride **3** (0.1 g, 0.3 mmol) in 5 ml of dry CH_2Cl_2. The reaction mixture was heated with stirring in a sealed tube at 80 °C for 48 h. The solvent was removed on rotary evaporator. The residue was purified by column chromatography (hexane/ethyl acetate 5:2). Yield 48%. Mp 208–210 °C. ^{1}H NMR (300 MHz, [D_6]DMSO, 363 K): δ 0.73 (s, 18H, 20-H_3), 0.91 (s, 18H, 17-H_3), 1.11 (s, 18H, 18-H_3), 0.92–1.90 (m, 120H, 1H_2, 2H_2, 3-H_{ax}, 5-H, 6-H_2, 7-H_2, 9-H, 11-H_2, 12-H_2, 14-H_2, 15-H_β, $OCH_2CH_2CH_2$), 2.10 (d, 6H, 3-H_{eq}, J=14.1 Hz), 2.42 (d, 6H, 15-H_α, J=16.2 Hz), 3.42 (s, 12H, CH_2NH), 3.79 (s, 12H, CH_2O), 3.90 (s, 12H, $ArCH_2Ar$ ax), 6.74 (t, 6H, ArH_{para}, J=7.8 Hz), 6.85 (d, 12H, J=7.8 Hz, ArH_{meta}). ^{13}C NMR ($CDCl_3$): δ 222.4 (C-16), 176.8 (C-19), 154.3 (Ar-*ipso*), 134.6 (Ar-*ortho*), 128.9 (Ar-*para*), 124.1 (Ar-*meta*), 70.9 (OCH_2CH_2-CH_2–), 57.7 (C-5), 54.8 (C-9), 54.3 (C-14), 48.8 (C-8), 48.2 (C-15), 43.8 (C-4), 41.8 (C-7), 40.3 (C-1), 39.5 (C-13), 38.2 (C-10), 38.1 (C-3), 37.4 (C-12 and $OCH_2CH_2CH_2$–), 30.4 ($OCH_2CH_2CH_2$–), 30.3 (C-18), 29.7 ($ArCH_2Ar$), 22.3 (C-6), 20.4 (C-11), 19.9 (C-17), 19.3 (C-2), 13.8 (C-20). MS (ESI, CH_3OH) m/z: 2802 $[M+Na]^+$. $C_{180}H_{246}N_6O_{18}$ (2781.98).

4.1.3. 5′,17′-Bis(isostevioylamido)-25′,26′,27′,28′-tetra-*n*-propyloxycalix[4]arene (8). Isostevioyl chloride (**3**) (0.42 g, 1.2 mmol) and compound **6** (0.3 g, 0.48 mmol) were dissolved in dry CH_2Cl_2 (10 ml) and DIPEA (0.2 ml, 1.2 mmol) was added. The reaction mixture was heated with stirring in a sealed tube at 80 °C for 48 h. The solvent was evaporated and the residue purified by column chromatography (hexane/ethyl acetate 5:2) to give 0.21 g (37%) of **8**. Mp 210–220 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.86 (t, 6H, $C^{26'}OCH_2CH_2CH_3$, $C^{28'}OCH_2CH_2CH_3$, J=7.4 Hz), 0.89 (s, 6H, 20-H_3), 0.98 (s, 6H, 17-H_3), 1.08 (t, 6H, $C^{25'}OCH_2CH_2CH_3$, $C^{27'}OCH_2CH_2CH_3$, J=7.4 Hz), 1.35 (s, 6H, 18-H_3), 1.86 (m, 4H, $C^{25'}OCH_2CH_2CH_3$, $C^{27'}OCH_2CH_2CH_3$), 0.90–1.90 (m, 34H, 1H_2, 2H_2, 3-H_{ax}, 5-H, 6-H_{ax}, 7-H_2, 9-H, 11-H_2, 12-H_2, 14-H_2, 15-H_β), 1.95 (m, 4H, $C^{26'}OCH_2CH_2CH_3$, $C^{28'}OCH_2CH_2CH_3$), 2.08 (d, 2H, 6-H_{eq}, J=13.0 Hz), 2.21 (d, 2H, 3-H_{eq}, J=14.0 Hz), 2.69 (dd, 2H, 15-H_α, J=18.8, 3.6 Hz), 3.10 (2d, 4H, $ArCH_2Ar$ eq, J=13.3, 13.3 Hz), 3.64 (t, 4H, $C^{25'}OCH_2CH_2CH_3$, $C^{27'}OCH_2CH_2CH_3$, J=6.6 Hz), 3.98 (dd, 4H, $C^{26'}OCH_2CH_2CH_3$, $C^{28'}OCH_2CH_2CH_3$, J=8.1, 8.4 Hz), 4.41 (d, 4H, $ArCH_2Ar$ ax, J=13.3 Hz), 6.17 (d, 4H, ArH-10′,12′, ArH-24′,22′, J=7.8 Hz), 6.25 (t, 2H, ArH-11′, ArH-23′, J=7.6 Hz), 7.16 (d, 2H, ArH-6′, ArH-16′, J=2.6 Hz), 7.21 (d, 2H, ArH-4′, ArH-18′, J=2.6 Hz), 7.24 (s, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 222.1 (C-16), 174.7 (C-19), 155.2 (Ar-*ipso*: C-25′, C-27′), 154.9 (Ar-*ipso*: C-26′, C-28′), 137.9 (Ar-*ortho*: C-3′, C-7′, C-15′, C-19′), 132.9 (Ar-*ortho*: C-1′, C-9′, C-13′, C-21′), 131.4 (Ar-*para*: C-5′, C-17′), 127.4 (Ar-*meta*: C-10′, C-12′, C-22′, C-24′), 122.1 (Ar-*para*: C-11′, C-23′), 121.2 (Ar-*meta*: C-4′, C-6′, C-16′, C-18′), 77.0 ($C^{25'}OCH_2CH_2CH_3$, $C^{27'}OCH_2CH_2CH_3$), 76.5 ($C^{26'}OCH_2CH_2CH_3$, $C^{28'}OCH_2CH_2CH_3$), 57.9 (C-5), 54.9 (C-9), 54.3 (C-14), 48.7 (C-15), 48.4 (C-8), 44.6 (C-4), 41.8 (C-7), 40.2 (C-1), 39.6 (C-13), 38.4 (C-10), 38.2 (C-3), 37.3 (C-12), 31.1 ($ArCH_2Ar$), 30.1 (C-18), 23.5 ($C^{25'}OCH_2CH_2CH_3$, $C^{27'}OCH_2CH_2CH_3$), 22.9 ($C^{26'}OCH_2CH_2CH_3$, $C^{28'}OCH_2CH_2CH_3$), 22.4 (C-6), 20.4 (C-11), 19.8 (C-17), 19.1 (C-2), 13.8 (C-20), 10.8 ($C^{25'}OCH_2CH_2CH_3$, $C^{27'}OCH_2CH_2CH_3$), 9.7 ($C^{26'}OCH_2CH_2CH_3$,

$C^{28'}OCH_2CH_2CH_3$). MS (ESI, CH_3OH) *m/z*: 1246.1 $[M+Na]^+$. $C_{80}H_{106}N_2O_8$ (1223.74).

4.1.4. 5′,11′,17′,23′-Tetrakis(isostevioylamido)-25′,26′,27′,28′-tetra-*n*-propyloxycalix[4]arene (9). Compound (**9**) was synthesized by the same procedure used for (**5**) from isostevioyl chloride (**3**) and calix[4]arene (**7**). The crude residue was purified by silica gel column chromatography eluting with a mixture of hexane and ethyl acetate with successive increases of ethyl acetate and affording the corresponding product **9** as white solid. Yield: 0.076 g (54%). Mp 140–145 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76 (s, 12H, 20-H_3), 0.96 (s, 12H, 17-H_3), 1.00 (t, 12H, $OCH_2CH_2CH_3$, $J=5.7$ Hz), 1.23 (s, 12H, 18-H_3), 1.67 (m, 8H, $OCH_2CH_2CH_3$), 0.90–1.90 (m, 72H, 1H_2, 2H_2, 3-H_{ax}, 5-H, 6-H_2, 7-H_2, 9-H, 11-H_2, 12-H_2, 14-H_2, 15-H_β), 2.08 (d, 4H, 3-H_{eq}, $J=16.2$ Hz), 2.61 (dd, 4H, 15-H_α, $J=18.6$, 3.3 Hz), 3.16 (d, 4H, $ArCH_2Ar$ eq, $J=12.9$ Hz), 3.83 (t, 8H, $OCH_2CH_2CH_3$, $J=7.6$ Hz), 4.41 (d, 4H, $ArCH_2Ar$ ax, $J=12.9$ Hz), 6.75 (d, 4H, ArH, $J=2.4$ Hz), 6.86 (d, 4H, ArH, $J=2.4$ Hz), 7.21 (s, 4H, NH). ^{13}C NMR ($CDCl_3$): δ 219.4 (C-16), 175.2 (C-19), 153.5 (Ar-*ipso*), 134.9 (Ar-*ortho*), 131.4 (Ar-*para*), 122.3 (Ar-*meta*), 77.0 ($OCH_2CH_2CH_3$), 57.7 (C-5), 54.6 (C-9), 54.2 (C-14), 48.6 (C-15), 48.2 (C-8), 44.1 (C-4), 41.6 (C-7), 40.1 (C-1), 39.4 (C-13), 38.0 (C-10), 37.9 (C-3), 37.2 (C-12), 31.0 ($ArCH_2Ar$), 30.0 (C-18), 23.0 ($OCH_2CH_2CH_3$), 22.2 (C-6), 20.3 (C-11), 19.8 (C-17), 19.1 (C-2), 13.7 (C-20), 10.2 ($OCH_2CH_2CH_3$). MS (ESI, CH_3OH) *m/z*: 1876.9 $[M+Na]^+$. $C_{120}H_{164}N_4O_{12}$ (1854.65).

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Conformationally restricted analogues of both (*S*)-β-homoserine and (*S*)-aspartic acid from chiral 3-acylamino pyrrolidin-2-ones

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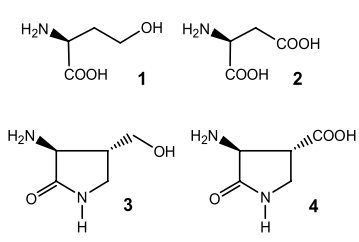
Abstract—Starting from chiral 3,4-*trans*-disubstituted pyrrolidin-2-ones **11a** and **11b**, obtained from a Baylis–Hillman adduct, conformationally restricted analogues of both (*S*)-β-homoserine, **17**, and (*S*)-aspartic acid, **21**, were synthesized, respectively, and these compounds are suitable either for introduction in peptidomimetics or for synthesis of novel β-foldamers.

1. Introduction

Properly substituted pyrrolidin-2-ones (γ-lactams) can be isosteres of natural amino acids. Thus, they can give rise to conformational constrictions useful to both restrict the flexibility of the peptide molecules and to provide informations on the topographical requirements of receptors,[1] when they are introduced in bioactive peptides. Moreover, the incorporation of these units in a peptide lead to analogues that display a lot of advantages such as increased biostability and bioselectivity against the natural biological target of the parent peptide. Therefore, they are interesting target compounds,[2] useful for the synthesis of both terminally constrained or internally constrained peptidomimetics[3] and their availability in an enantiomerically pure form is important for applications in medicinal chemistry.[4] In this field, our attention was focused to the pyrrolidin-2-ones **3** and **4**, that are constrained analogues of (*S*)-β-homoserine **1** and (*S*)-aspartic acid, **2**, respectively (Scheme 1).

2. Results and discussion

We already demonstrated the viability of the approach involving (C-3)–(C-4) bond formation for construction of the pyrrolidin-2-one ring, leading to conformationally restricted amino acids in the enantiomerically pure form.[5] As a further development, we recently, devised a conjugate addition/ring closure sequence starting from the Baylis–Hillman adduct **5** and (*S*)-phenylethylamine, leading to formation of both (N-1)–(C-5) and (N-1)–(C-2) bonds of the γ-lactam ring, and this synthetic approach was directed toward the synthesis of chiral 3-hydroxypyrrolidin-2-ones, intermediates for the preparation of an inhibitor of glycosidases.[6] Our previous investigations concerning the chemistry of Baylis–Hillman adducts disclosed a straightforward general procedure for the preparation of 3-acylamino-2-methylene alkanoates, by exploiting the corresponding acyl carbamates.[7] In this report, the acyl carbamates **7a**,**b** were prepared in quantitative yield by reaction of the adduct **5** and the appropriate acyl isocyanate **6a**,**b** (Scheme 2).[8] However, whereas treating the 1-naphthoyl carbamate **7b** with DABCO in DCM gave the corresponding 1-naphthoylamino derivative **8b** in good yield, the trichloroacetylamino derivative **8a** was obtained only in a disappointing 20% yield from **7a** under the same reaction conditions. The other products of this reaction were a complex, inseparable mixture of polar products. To overcome this problem, an alternative approach to compound **8a** was devised, starting from the trichloroacetimidate **9**. The preparation of this compound, however, turned



Scheme 1.

Keywords: Amino acids; Analogues; Baylis–Hillman; Peptidomimetics; Conformational constrictions.
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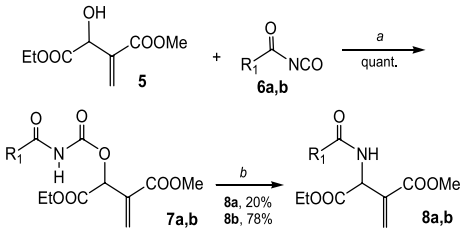
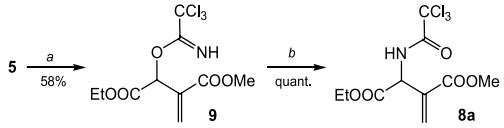


Scheme 2. Reagents and conditions: (a) DCM, rt (b) 10% DABCO, DCM, 0 °C; **8a**, $R_1=CCl_3$; **8b**, $R_1=$1-naphthyl.

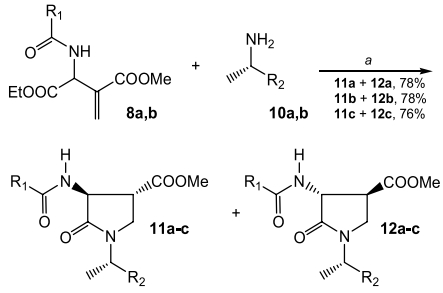


Scheme 3. Reagents and conditions: (a) CCl_3CN, DBU, −15 °C. (b) 10% DABCO, DCM, 0 °C, 2 min.

out to be far from routine. In fact, only traces of the desired product **9** were obtained by following the standard procedures.[9]

On the other hand, when the reaction was carried out by using CCl_3CN as the solvent and DBU as the base, the trichloroacetimidate **9** was obtained in moderate yield. Subsequent treatment with DABCO in DCM afforded the trichloroacetylamino derivative **8a** in quantitative yield (Scheme 3).[10]

By analogy with the synthesis of chiral hydroxypyrrolidin-2-ones from the Baylis–Hillman adduct **5**,[6] condensation of *N*-acylamino derivatives **8a**,**b** with (*S*)-phenylethylamine, **10a**, or (*S*)-4-MeO-phenylethylamine, **10b**, was carried out in MeOH from rt to 60 °C. Although a diastereomeric mixture of four 3,4-disubstituted pyrrolidin-2-ones was formed at first, as evidenced by the corresponding peaks for the methyl esters in the ^{1}H NMR spectrum of the crude reaction, direct treatment of the diastereomeric mixture with DBU in toluene at rt afforded in good yield the 3,4-*trans*-disubstituted derivatives **11a–c** and **12a–c**, exclusively, which were easily separated by flash chromatography on silica gel (Scheme 4).[11] The determination of the absolute configurations of 4-monosubstituted pyrrolidin-2-ones with nitrogen bearing a chiral phenylethyl group was described elsewhere.[5] Thus, ^{1}H NMR analysis was diagnostic for structural assignment at C-4 of **11a–c** and **12a–c**, as



Scheme 4. Reagents and conditions: (a) MeOH, rt to 60 °C, then DBU, toluene at rt. **a** $R_1=CCl_3$, $R_2=C_6H_5$; **b** $R_1=CCl_3$, $R_2=$4-$CH_3OC_6H_4$; **c** $R_1=$1-naphthyl, $R_2=C_6H_5$.

evidenced by the shielding effects on H-5 and H-5′ due to both the phenyl group and the substituent at C-4 (Table 1).

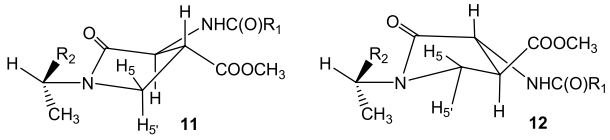
The configuration at C-3 was also assigned by ^{1}H NMR analysis, being significantly supported by the quite large $J_{3,4}$ coupling constant values ($J_{3,4}>9.0$ Hz) (Table 1), and further, confirmed by NOE difference data. In fact, by irradiation of H-3 only a very small enhancement (<1%) was observed to H-4, consistent with the *trans* relative stereochemistry. Eventually, compound **11a** was crystallized from methanol and from the single-crystal X-ray data its absolute configuration was definitely ascertained as (3*S*,4*R*,1′*S*), in full agreement with ^{1}H NMR spectral data (Fig. 1).[12,13]

Our first goal was to find a simple and straightforward access to the constrained β-homoserine derivative **3**,[14] but some difficulties arose in the removal of the naphthoyl group in both **11c** and **12c**. Therefore, since the trichloroacetyl group can be more easily cleaved, we considered as starting materials for further transformations the trichloroacetylamino derivatives **11a**,**b**, that are homochiral at C-3 with the same absolute configuration as the natural amino acids.

In fact, we treated the pyrrolidin-2-one **11a** with $NaBH_4$ in dry ethanol and we were pleased to obtain in good yield the corresponding *trans*-3-amino-4-hydroxymethyl derivative **13**, the reaction proceeding through simultaneous reduction of the methoxycarbonyl group and removal of the trichloroacetamido moiety (Scheme 5).

Prior to the removal of the phenylethyl group, both the

Table 1. Selected ^{1}H NMR data for compounds **11** and **12**



Entry	δ H-3 (ppm)	δ H-5 (ppm)	δ H-5′ (ppm)	$J_{3,4}$ (Hz)	$J_{4,5}$ (Hz)	$J_{4,5'}$ (Hz)
11a	4.65	3.45	3.28	9.5	9.1	8.7
12a	4.58	3.05	3.60	9.4	8.8	9.2
11b	4.65	3.43	3.28	9.6	9.2	8.7
12b	4.71	3.13	3.62	9.2	8.9	9.4
11c	4.84	—[a]	—[a]	9.2	—[a]	—[a]
12c	4.71	3.13	3.62	9.2	8.8	9.4

[a] H-5 and H-5′ give rise to a complex pattern, in agreement with a single shielding for each proton.

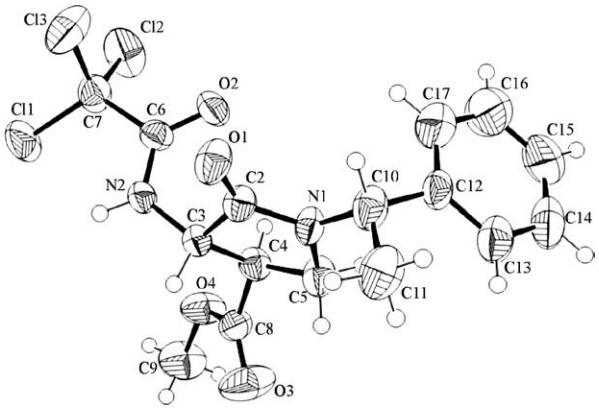
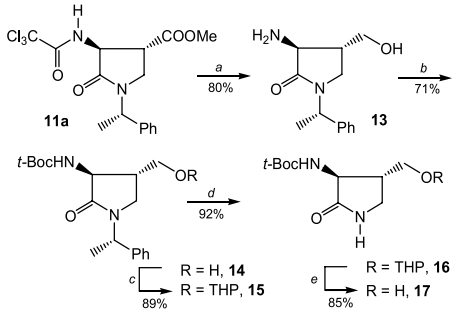


Figure 1. ORTEP drawing of compound **11a**.

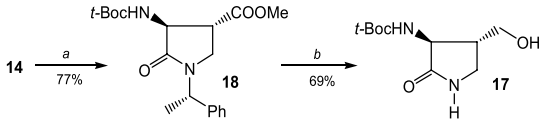


Scheme 5. Reagents and conditions: (a) $NaBH_4$ (4 equiv), dry EtOH, rt; (b) *t*-Boc_2O, MeOH, rt; (c) DHP, DCM, H 15, rt, (d) Li, NH_3, −78 °C; (e) Amberlyst H 15, MeOH, 40 °C.

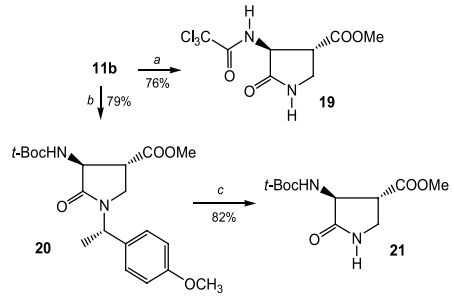
derivatives **14** and **15** were subsequently prepared. Cleavage of the phenylethyl group was easily performed by treating **15** with Li in liquid ammonia at −78 °C, leading to the unsubstituted pyrrolidin-2-one **16** in good yield. Eventually, removal of the THP group afforded **17**, the *N*-protected derivative of **3**, the analogue of β-homoserine (Scheme 5).[15,16]

Then, we started the synthesis of the analogue of the aspartic acid, **4**, but when compound **17** was treated with the Jones' reagent in order to obtain a carboxy group at C-5, only a complex mixture of products resulted from the reaction. In addition, when the compound **18**, easily prepared starting from **14**, underwent cleavage of the phenylethyl group with Li in liquid ammonia, compound **17** was exclusively obtained in moderate yield (Scheme 6).[17]

Thus, an alternative starting substrate to the compound **4** was pyrrolidin-2-one **11b**. In fact, by treatment with CAN in acetonitrile–water[18] this compound underwent rapid cleavage of the 4-methoxyphenylethyl group, to give in good yield the enantiomeric 3,4-*trans*-disubstituted pyrrolidin-2-one **19**, a diprotected form of the constrained analogue **4** (Scheme 7). In addition, the trichloroacetyl group was



Scheme 6. Reagents and conditions: (a) Jones' reagent, acetone, then CH_2N_2; (b) Li, NH_3, −78 °C.



Scheme 7. Reagents and conditions: (a) CAN, CH_3CN–H_2O; (b) 6 M NaOH; then *t*-Boc_2O, TEA, MeOH; then CH_2N_2, diethyl ether; (c) CAN, CH_3CN–H_2O.

removed from **11b** and the amino functionality at C-3 was protected as *t*-Boc derivative to give **20**. Eventually, by treatment with CAN in acetonitrile–water, the protected constrained analogue **21** was obtained in good yield.[19]

3. Conclusion

In summary, by reaction of either (*S*)-phenylethylamine **10a** or (*S*)-(4-methoxyphenyl)ethylamine **10b** and the acyl-amino derivatives **8a**,**b**, obtained from the Baylis–Hillman adduct **5**, the chiral 3,4-*trans*-disubstituted pyrrolidin-2-ones **11a**,**b** and **12a**,**b** were produced in good yield. Then, **17** and **21**, conformationally restricted analogues of (*S*)-β-homoserine and (*S*)-aspartic acid, were obtained starting from compounds **11a** and **11b**, respectively, and it is worth mentioning that both *ent*-**17** and *ent*-**21** can be accessible starting from **12a**,**b**. In addition, **21** and *ent*-**21** will be employed as units for the preparation of novel β-foldamers[20,21] having a constriction due to the sp^2 carbon of the pyrrolidin-2-one and work along this line is currently in progress in our laboratory.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal IA 9000 apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using $CDCl_3$ as a solvent. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Mass spectra (MS) were obtained by electron impact on a Hewlett-Packard spectrometer 5890, series II. Column chromatography was performed with silica gel 60 (230–400 mesh). Compound **5** was synthesized as reported the literature.[22] Trichloroacetyl isocyanate **6a** was purchased from Aldrich, whereas 1-naphthoyl isocyanate **6b** was prepared according to a literature method starting from 1-naphthoyl chloride[8b] and used without purification.

4.2. General procedure for the preparation of acyl carbamates (7a,b)

To a solution containing the adduct **5** (1.9 g, 10 mmol) in dry DCM (50 mL), the appropriate acyl isocyanate **6** (12 mmol) dissolved in dry DCM (10 mL) was added at 0 °C and the mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (cyclohexane–ethyl acetate 80:20 as eluent) to give in quantitative yield the acyl carbamates **7a**,**b**.

4.2.1. 1-Ethyl 4-methyl 2-(1-trichloroacetylaminocarbonyloxy)-3-methylenebutanedioate (7a). According to the above reported procedure and starting from **5** and commercially available trichloroacetyl isocyanate **6a**, the compound **7a** was obtained as a viscous oil: IR ($CHCl_3$) ν 3355, 1741, 1724, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, $J=7.2$ Hz, 3H), 3.79 (s, 3H), 4.22 (q, $J=7.2$ Hz, 2H), 5.98 (s, 1H), 6.11 (s, 1H), 6.55 (s, 1H), 8.78 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 52.4, 62.3, 72.4, 91.4, 132.3, 133.7, 148.5, 157.5, 164.5, 166.7; MS: *m/z* 377–375 (2, M^+), 143 (22), 116 (40), 84 (100). Anal. Calcd for $C_{11}H_{12}Cl_3NO_7$: C, 35.08; H, 3.21; N, 3.72. Found: C, 35.02; H, 3.15; N, 3.64.

4.2.2. 1-Ethyl 4-methyl 2-(1-naphthoylaminocarbonyloxy)-3-methylenebutanedioate (7b). According to the above reported procedure and starting from **5** and 1-naphthoyl isocyanate **6b**, the compound **7b** was obtained as a viscous oil: IR ($CHCl_3$) ν 3350, 1734, 1724, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, $J=7.3$ Hz, 3H), 3.74 (s, 3H), 4.18 (q, $J=7.3$ Hz, 2H), 5.97 (s, 1H), 6.04 (s, 1H), 6.48 (s, 1H), 7.36–7.94 (m, 6 ArH), 8.21–8.29 (m, 1 ArH), 8.64 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 52.2, 62.0, 71.5, 124.3, 124.8, 125.9, 126.6, 127.6, 128.3, 128.4, 129.9, 131.7, 132.1, 133.5, 134.1, 149.5, 164.6, 166.9, 167.2; MS: *m/z* 385 (3, M^+), 197 (29), 155 (100), 127 (76), 83 (88), 43 (70). Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.27; H, 5.03; N, 3.59.

4.3. General procedure for the preparation of acylamino derivatives (8a,b)

To a solution containing **7** (15.0 mmol) in DCM (20 mL) at 0 °C, DABCO (0.2 g, 1.5 mmol) was added and the mixture was stirred for 15 min at 0 °C. The mixture was then diluted with ethyl acetate (150 mL) and the organic layer washed with 1 M HCl (30 mL) and brine (100 mL). After drying (Na_2SO_4), the solvents were removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 80:20 as eluent), to give pure compounds **8a**,**b**.

4.3.1. 1-Ethyl 4-methyl 2-trichloroacetylamino-3-methylenebutanedioate (8a). According to the above reported procedure and starting from **7a**, the title compound was obtained as a colorless oil (1.0 g; 20%), followed by a substantial amount of trichloroacetamide (1.8 g): IR ($CHCl_3$) ν 3351, 1732, 1722, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, $J=7.1$ Hz, 3H), 3.80 (s, 3H), 4.25 (q, $J=7.1$ Hz, 2H), 5.25 (d, $J=7.9$ Hz, 1H), 6.10 (s, 3H), 6.47 (s, 1H), 7.81 (d, $J=7.9$ Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.9, 52.3, 56.0, 62.5, 92.0, 131.7, 134.1, 161.2, 165.3, 168.2; MS: *m/z* 334–332 (4, MH^+), 318–316 (12), 260 (22), 198 (18), 158 (44), 99 (100). Anal. Calcd for $C_{10}H_{12}Cl_3NO_5$: C, 36.12; H, 3.64; N, 4.21. Found: C, 36.16; H, 3.57; N, 4.16.

4.3.2. 1-Ethyl 4-methyl 2-(1-naphthoylamino)-3-methylenebutanedioate (8b). According to the above reported procedure and starting from **7b**, the title compound was obtained as a colorless oil (4.0 g, 78%): IR ($CHCl_3$) ν 3350, 1735, 1720, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, $J=7.4$ Hz, 3H), 3.75 (s, 3H), 4.25 (q, $J=7.4$ Hz, 2H), 5.72 (d, $J=8.5$ Hz, 1H), 6.19 (s, 1H), 6.48 (s, 1H), 7.14 (d, $J=8.5$ Hz, 1H, NH), 7.40–7.94 (m, 6 ArH), 8.31–8.42 (m, 1 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 52.2, 51.8, 62.2, 124.7, 125.4, 125.5, 126.4, 127.2, 128.3, 128.5, 130.2, 130.8, 131.0, 133.5, 136.0, 165.9, 168.7, 169.6; MS: *m/z* 341 (3, M^+), 268 (20), 155 (100), 127 (56), 43 (12). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.79; H, 5.57; N, 4.14.

4.3.3. 1-Ethyl 4-methyl 2-trichloroacetiminoxy-3-methylenebutanedioate (9). To a solution of the adduct **5** (2.8 g, 15 mmol) in CCl_3CN (7.5 g, 75.0 mmol), DBU (0.63 mL, 4.5 mmol) was directly added in three portions (every 15 min) at −15 °C under vigorous stirring. After 1 h the mixture was directly purified by silica gel chromatography (cyclohexane–ethyl acetate 95:5 as eluent) to give the trichloroacetimidate **9** (2.9 g; 58% yield) as a colorless oil: IR ($CHCl_3$) ν 3339, 1732, 1720, 1671 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, $J=7.3$ Hz, 3H), 3.82 (s, 3H), 4.25 (q, $J=7.3$ Hz, 2H), 6.12 (s, 1H), 6.13 (s, 1H), 6.55 (s, 1H), 8.53 (br s, 1H, =NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 53.0, 61.5, 73.4, 90.3, 129.7, 134.1, 160.8, 164.5, 166.8; MS: *m/z* 334 (MH^+, 5), 332 (MH^+, 5), 318 (6), 316 (6), 170 (32), 161 (24), 144 (100). Anal. Calcd for $C_{10}H_{12}Cl_3NO_5$: C, 36.12; H, 3.64; N, 4.21. Found: C, 36.06; H, 3.58; N, 4.27.

4.3.4. 1-Ethyl 4-methyl 2-trichloroacetylamino-3-methylenebutanedioate (8a). To a solution containing the trichloroacetimidate **9** (1.7 g, 5.0 mmol) in DCM (20 mL) at 0 °C, DABCO (65 mg, 0.5 mmol) was added and the mixture was stirred for 2 min at 0 °C. After dilution with ethyl acetate (150 mL), the organic layer was washed with 1 M HCl (30 mL) and brine (100 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure to give the pure trichloroacetylamino derivative **8a** (1.7 g; quantitative yield) as a colorless oil.

4.4. General procedure for the preparation of pyrrolidin-2-ones (11) and (12)

To a solution containing compound **8** (15 mmol) in methanol (20 mL), (*S*)-phenylethylamine **10a** or (*S*)-4-methoxyphenylethylamine **10b** (16 mmol) was added and the mixture was stirred for 12 h at rt and then for 2 h at 60 °C. Methanol was evaporated under reduced pressure, the residue was dissolved ethyl acetate (50 mL) and the organic layer washed with 1 M HCl (20 mL) and brine. After drying (Na_2SO_4) and removal of the solvent under reduced pressure, the residue was dissolved in toluene (20 mL), DBU (2.28 g, 15 mmol) was added and the

solution was stirred at rt for 12 h. After removal of the solvent, the residue was dissolved in ethyl acetate (40 mL) and the organic layer was washed with 2 M HCl (10 mL). After drying (Na_2SO_4) and removal of the solvent, the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 90:10), to give in equimolar amount pure separated diastereomers **11** and **12** as white crystalline solids.

4.4.1. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-1-(1′-phenylethyl)-3-trichloroacetylaminopyrrolidin-2-one (11a) and its (3*R*,4*S*,1′*S*)-isomer (12a). Starting from **8a** and **10a**, the diastereomers **11a** and **12a** were obtained after chromatographic separation in 78% overall yield according to the above reported procedure: IR ($CHCl_3$) ν 3347, 1725, 1670 cm^{-1}. Anal. Calcd for $C_{16}H_{17}Cl_3N_2O_4$: C, 47.14; H, 4.20; N, 6.87. Found: C, 47.06; H, 4.16; N, 6.82. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-1-(1′-phenylethyl)-3-trichloroacetylaminopyrrolidin-2-one (**11a**). Colorless crystals: mp 196–198 °C (dec); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J=7.3 Hz, 3H), 3.09–3.21 (m, 1H), 3.28 (dd, J=8.7, 8.7 Hz, 1H), 3.45 (dd, J=8.7, 9.0 Hz, 1H), 3.75 (s, 3H), 4.65 (dd, J=5.6, 9.6 Hz, 1H), 5.50 (q, J=7.3 Hz, 1H), 7.25–7.48 (m, 6H, 5 ArH+NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 42.2, 44.0, 50.2, 52.7, 56.4, 127.0, 128.0, 128.8, 138.6, 162.3, 167.7, 171.6; $[\alpha]_D$ −75.0 (*c* 0.5, $CHCl_3$). MS: *m*/*z* 408 (4, M^+), 406 (4, M^+), 269 (4), 271 (4), 246 (8), 186 (18), 132 (21), 105 (100), 77 (25). (3*R*,4*S*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-(1′-phenylethyl)pyrrolidin-2-one (**12a**). Colorless crystals: mp 138–140 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J=7.0 Hz, 3H), 3.06 (dd, J=8.8, 9.2 Hz, 1H), 3.22–3.41 (m, 1H), 3.63 (dd, J=9.2, 9.2 Hz, 1H), 3.69 (s, 3H), 4.57 (dd, J=5.9, 9.1 Hz, 1H), 5.48 (q, J=7.0 Hz, 1H), 7.21–7.39 (m, 5 ArH), 7.84 (d, J=5.9 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 42.2, 43.2, 50.3, 52.6, 56.2, 91.7, 126.8, 127.0, 128.0, 128.7, 138.6, 162.4, 167.9, 171.6; $[\alpha]_D$ −82.5 (*c* 1.06, $CHCl_3$); MS: *m*/*z* 408 (4, M^+), 406 (4, M^+), 269 (5), 271 (5), 246 (11), 186 (16), 132 (24), 105 (100), 77 (25).

4.4.2. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-[1′-(4″-methoxyphenyl)ethyl]pyrrolidin-2-one (11b) and its (3*R*,4*S*,1′*S*)-isomer (12b). Starting from **8a** and **10b**, the diastereomers **11b** and **12b** were obtained after chromatographic separation in 78% overall yield according to the above reported procedure: IR ($CHCl_3$) ν 3345, 1724, 1668 cm^{-1}. Anal. Calcd for $C_{17}H_{19}Cl_3N_2O_5$: C, 46.65; H, 4.38; N, 6.40. Found: C, 46.61; H, 4.34; N, 6.44. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-[1′-(4″-methoxyphenyl)ethyl]pyrrolidin-2-one (**11b**). Colorless crystals: mp 178–180 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (d, J=7.2 Hz, 3H), 3.06–3.31 (m, 1H), 3.28 (dd, J=8.7, 9.2 Hz, 1H), 3.43 (dd, J=9.2, 9.2 Hz, 1H), 3.76 (s, 3H), 3.81 (s, 3H), 4.65 (dd, J=4.5, 9.6 Hz, 1H), 5.47 (q, J=7.2 Hz, 1H), 6.90 (d, J=8.7 Hz, 2 ArH), 7.26 (d, J=8.7 Hz, 2 ArH), 7.41 (d, J=4.5 Hz, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 42.0, 43.9, 49.7, 52.7, 55.3, 56.5, 114.1, 128.2, 130.6, 159.2, 162.3, 167.6, 171.7; $[\alpha]_D$ −73.0 (*c* 0.6, $CHCl_3$); MS: *m*/*z* 436 (3, M^+), 434 (3, M^+), 301 (5), 299 (5), 216 (20), 162 (23), 135 (100), 77 (24). (3*R*,4*S*,1′*S*)-4-Methoxycarbonyl-3-trichloroacetylamino-1-[1′-(4″-methoxyphenyl)ethyl]pyrrolidin-2-one (**12b**). Colorless crystals: mp 46–48 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58 (d, J=7.2 Hz, 3H), 3.05 (dd, J=8.8, 9.4 Hz, 1H), 3.20–3.56 (m, 1H), 3.60 (dd, J=9.2, 9.4 Hz, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 4.58 (dd, J=5.8, 9.4 Hz, 1H), 5.47 (q, J=7.2 Hz, 1H), 6.87 (d, J=8.6 Hz, 2 ArH), 7.21 (d, J=8.6 Hz, 2 ArH), 7.42 (d, 1H, NH, J=5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 42.1, 43.1, 49.8, 52.6, 55.2, 56.2, 91.7, 114.0, 128.2, 130.6. 159.2, 162.3, 167.7, 171.6; $[\alpha]_D$ −65.0 (*c* 2.0, $CHCl_3$); MS: *m*/*z* 436 (3, M^+), 434 (3, M^+), 301 (7), 299 (7), 216 (23), 162 (22), 135 (100), 77 (24).

4.4.3. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-(1″-naphthoylamino)-1-(1′-phenylethyl)pyrrolidin-2-one (11c) and its (3*R*,4*S*,1′*S*)-isomer (12c). Starting from **8b** and **10a**, the diastereomers **11c** and **12c** were obtained after chromatographic separation in 76% overall yield according to the above reported procedure: IR ($CHCl_3$) ν 3351, 1722, 1658 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 72.04; H, 5.87; N, 6.68. (3*S*,4*R*,1′*S*)-4-Methoxycarbonyl-3-(1″-naphthoylamino)-1-(1′-phenylethyl)pyrrolidin-2-one (**11c**). Colorless crystals: mp 132–134 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.56 (d, J=7.0 Hz, 3H), 3.12–3.59 (m, 3H), 3.76 (s, 3H), 4.84 (dd, J=5.9, 9.2 Hz, 1H), 5.56 (q, J=7.0 Hz, 1H), 6.82 (d, J=5.9 Hz, 1H, NH), 7.21–7.73 (m, 9 ArH), 7.81–7.96 (m, 2 ArH), 8.31–8.48 (m, 1 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 42.2, 45.0, 50.0, 52.6, 56.1, 124.6, 125.4, 125.5, 125.6, 126.4, 127.0, 127.1, 127.8, 128.2, 128.3, 128.4, 128.8, 131.0, 133.2, 133.7, 139.1, 169.2, 170.1, 172.4; $[\alpha]_D$ −177.8 (*c* 0.6, MeOH); MS: *m*/*z* 416 (11, M^+), 261 (8), 245 (9), 186 (13), 172 (16), 155 (100), 127 (74), 105 (67). (3*R*,4*S*,1′*S*)-4-Methoxycarbonyl-3-(1″-naphthoylamino)-1-(1′-phenylethyl)pyrrolidin-2-one (**12c**). Colorless crystals: mp 176–178 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58 (d, J=7.0 Hz, 3H), 3.13 (dd, J=8.8, 8.9 Hz, 1H), 3.35–3.51 (m, 1H), 3.62 (dd, J=9.4, 8.9 Hz, 1H), 3.73 (s, 3H), 4.71 (dd, J=6.2, 9.2 Hz, 1H), 5.50 (q, J=7.0 Hz, 1H), 6.89 (d, J=6.2 Hz, 1H), 7.22–7.72 (m, 9 ArH), 7.78–7.95 (m, 2 ArH), 8.34–8.44 (m, 1 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9, 42.3, 44.5, 50.2, 52.5, 55.9, 124.5, 125.3, 126.3, 127.0, 127.2, 127.8, 128.1, 128.7, 130.1, 130.9, 133.1, 133.5, 138.9, 169.2, 170.0, 172.2; $[\alpha]_D$ −115.2 (*c* 0.4, $CHCl_3$); MS: *m*/*z* 416 (15, M^+), 261 (8), 245 (7), 186 (10), 172 (18), 155 (100), 127 (75), 105 (67).

4.4.4. (3*S*,4*R*,1′*S*)-3-Amino-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (13). To a solution of **11a** (2.0 g; 5.0 mmol) in dry ethanol (10 mL) sodium borohydride (0.76 g; 20.0 mmol) was added at 0 °C. Then the ice-bath was removed and the reaction was stirred for 12 h at rt. Water (10 mL) was added, ethanol was removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (2×70 mL). The combined organic phases were dried over sodium sulphate and filtered. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (ethyl acetate as eluent) to give **13** (0.94 g, 80%) as a viscous oil: IR ($CHCl_3$) ν 3350, 1671 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (d, J=7.0 Hz, 3H), 1.90–2.08 (m, 1H), 2.82 (br s, 3H, OH+NH_2), 2.97–3.02 (m, 2H), 3.38 (d, J=9.9 Hz, 1H), 3.70 (d, J=5.5 Hz, 2H), 5.40 (q, J=7.0 Hz, 1H), 7.17–7.38 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 41.6, 44.3, 49.3, 56.0, 62.3, 126.7, 126.8, 127.5, 128.5, 128.6, 139.6, 174.6; $[\alpha]_D$

−160.9 (*c* 0.5, $CHCl_3$). MS: *m/z* 218 (2, M^+-NH_2), 217 (4), 203 (4), 187 (5), 122 (11), 106 (13), 85 (18), 82 (48) 70 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.59; H, 7.69; N, 12.02.

4.4.5. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-hydroxymethyl-1-(1′-phenylethyl)pyrrolidin-2-one (14). To the compound **13** (0.94 g, 4.0 mmol) dissolved in methanol (10 mL), di-*tert*-butyl dicarbonate (0.96 g, 4.4 mmol) was added and the mixture was stirred at rt for 12 h. Removal of the solvent and purification of the residue by chromatography on silica gel (cyclohexane–ethyl acetate 50:50 as eluent) gave the product **14** (0.95 g, 71%) as a colorless oil: IR ($CHCl_3$) ν 3345, 1730, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.54 (d, $J=7.0$ Hz, 3H), 2.07–2.25 (m, 1H), 2.98 (dd, $J=5.8$, 7.2 Hz, 1H), 3.05 (dd, $J=7.2$, 7.2 Hz, 1H), 3.63–3.76 (m, 2H, 1H+OH), 4.02–4.15 (m, 1H), 4.21 (dd, $J=5.4$, 10.3 Hz, 1H), 5.41 (d, $J=5.4$ Hz, 1H, NH), 5.49 (q, $J=7.0$ Hz, 1H), 7.22–7.43 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 28.2, 41.4, 45.8, 49.7, 55.4, 61.6, 80.7, 126.8, 127.7, 128.6, 139.4, 157.5, 171.0; $[\alpha]_D$ −141.3 (*c* 1.5, $CHCl_3$); MS: *m/z* 335 (2, MH^+), 279 (48), 218 (15), 187 (46), 156 (32), 134 (30), 106 (100), 70 (44), 58 (87). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.59; H, 7.79; N, 8.42.

4.4.6. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-1-(1′-phenyl-ethyl)-4-tetrahydropyranyloxymethylpyrrolidin-2-one (15). To a solution of **14** (1.0 g; 3.0 mmol) and DHP (0.5 g; 6.0 mmol) in DCM (20 mL), acidic resin H 15 (1.0 g) was added at 0 °C.[23] After 3 h at 0 °C, the resin was filtered off, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 70:30 as eluent) to give the title compound (1.12 g, 89%) as a colorless oil: IR ($CHCl_3$) ν 3341, 1728, 1666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.41–1.79 (m, 6H), 1.45 (d, $J=7.0$ Hz, 3H), 2.18–2.39 (m, 1H), 3.01–3.22 (m, 2H), 3.38–3.56 (m, 2H), 3.62–4.02 (m, 2H), 4.16 (dd, $J=5.3$, 10.1 Hz, 1H), 4.54 (m, 1H), 5.03 (d, $J=5.3$ Hz, 1H, NH), 5.46 (q, $J=7.0$ Hz, 1H), 7.21–7.36 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 19.4 (50%), 19.5 (50%), 25.1, 28.1, 30.3, 41.2 (50%), 41.5 (50%), 42.3 (50%), 42.8 (50%), 49.3, 54.4 (50%), 54.7 (50%), 62.2 (50%), 62.4 (50%), 66.9 (50%), 67.5 (50%), 79.4, 98.8 (50%), 99.4 (50%), 126.7, 127.3, 128.3, 139.5, 155.6, 171.0 (50%), 171.1 (50%).

4.4.7. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-tetrahydropyranyloxymethylpyrrolidin-2-one (16). After NH_3 (40 mL) was condensed in a three-necked flask at −78 °C, Li shots (140 mg, 20.0 mmol) were added and the blue solution was stirred at this temperature for 20 min. Then compound **15** (1.25 g, 3.0 mmol) was dissolved in a mixture of THF (9 mL) and *t*-BuOH (1 mL), and the solution was added in one portion. After 3 min, the reaction mixture was quenched by addition of solid NH_4Cl (2 g) and warmed to rt. Ammonia was removed, ethyl acetate (40 mL) and water (10 mL) were added, the mixture was extracted with ethyl acetate (2×50 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by silica gel chromatography (cyclohexane–ethyl acetate 40:60 as eluent) to give the compound **16** (0.87 g; 92%) as a colorless oil: IR ($CHCl_3$) ν 3341, 1728, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35–1.82 (m, 6H), 1.41 (s, 9H), 2.47–2.71 (m, 1H), 3.15–3.29 (m, 1H), 3.38–3.71 (m, 3H), 3.74–4.16 (m, 3H), 4.59 (m, 1H), 5.10 (br s, 1H, NH), 6.65 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0 (50%), 19.2 (50%), 25.1, 28.0, 30.2, 42.0 (50%), 42.5 (50%), 42.8 (50%), 43.1 (50%), 53.2 (50%), 53.6 (50%), 61.8 (50%), 62.2 (50%), 66.6 (50%), 66.9 (50%), 79.3, 98.4 (50%), 99.1 (50%), 155.6, 175.4 (50%), 175.5 (50%).

4.4.8. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-hydroxymethylpyrrolidin-2-one (17). Compound from **16** (0.79 g, 2.5 mmol) was dissolved in MeOH (20 mL), acidic resin Amberlyst H 15 (1.0 g) was added and the mixture was heated at 45 °C for 3 h.[23] After filtration, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70 as eluent) to give title compound (0.49 g, 85% yield) as a white solid: mp 128–130 °C: IR ($CHCl_3$) ν 3345, 1728, 1671 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.32–2.52 (m, 1H), 3.13 (m, 1H), 3.36 (m, 1H), 3.65 (dd, $J=6.1$, 12.1 Hz, 1H), 3.77 (dd, $J=4.3$, 12.1 Hz, 1H), 4.14 (dd, $J=5.9$, 10.3 Hz, 1H), 5.31 (d, $J=5.9$ Hz, 1H, NH), 6.36 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.2, 41.1, 47.5, 54.3, 61.7, 80.8, 157.4, 175.0; $[\alpha]_D$ −49.2 (*c* 0.6, MeOH); MS: *m/z* 230 (1, M^+), 203 (3), 174 (5), 149 (17), 81 (45), 69 (88), 57 (51), 43 (100). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.11; H, 7.85; N, 12.21.

4.4.9. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-methoxycarbonyl-1-(1′-phenylethyl)pyrrolidin-2-one (18). To a solution containing compound **14** (1.0 g, 3.0 mmol) in acetone (10 mL), the Jones' reagent (1.5 mL) was added at 0 °C and the mixture was stirred for 5 min. Then ethyl acetate (20 mL) and subsequently saturated aqueous Na_2CO_3 solution (15 mL) were added at 0 °C. After extraction of the aqueous phase with ethyl acetate (50 mL), organics were discarded and pH of the aqueous layer raised to 2 by slow addition of 1 M HCl under stirring. Then, extraction with ethyl acetate (2×50 mL) followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure gave a residue which was dissolved in methanol (5 mL). This solution was treated with an ethereal solution of CH_2N_2 in ether [CAUTION: Diazomethane is an explosive and a highly toxic gas. Explosions may occur if the substance is dry and undiluted. All operations involving diazomethane should be carried out in an efficient fumehood following appropriate precautions] until nitrogen evolution ceased. Then, the solvent was evaporated under reduced pressure, to give a residue which was purified by silica gel chromatography (cyclohexane–acetate 70:30 as eluent) affording the ester **18** (0.84 g, 77% yield) as a colorless oil: IR ($CHCl_3$) ν 3341, 1733, 1725, 1664 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.40 (s, 9H), 1.51 (d, $J=7.2$ Hz, 3H), 2.93–3.12 (m, 1H), 3.15 (dd, $J=8.8$, 9.3 Hz, 1H), 3.39 (dd, $J=9.2$, 9.3 Hz, 1H), 3.69 (s, 3H), 4.43 (dd, $J=6.5$, 9.5 Hz, 1H), 5.31 (d, $J=6.5$ Hz 1H, NH), 5.46 (q, $J=7.2$ Hz, 1H), 7.21–7.35 (m, 5 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.0, 28.1, 41.6, 45.3, 49.7, 52.2, 56.3, 80.0, 126.9, 127.6, 128.5, 139.0, 155.2, 169.3, 172.3; $[\alpha]_D$ −53.8 (*c* 1.0, $CHCl_3$); MS: *m/z* 363 (2, MH^+), 306 (26, MH^+-57), 245 (6), 186 (25), 133 (20), 105 (93), 69 (57), 57 (100). Anal. Calcd for

$C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found: C, 62.94; H, 7.19; N, 7.69.

4.4.10. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-hydroxymethylpyrrolidin-2-one (17). After NH_3 (30 mL) was condensed in a three-necked flask at −78 °C, Li shots (70 mg, 10.0 mmol) were added and the blue solution was stirred at this temperature for 20 min. Then compound **18** (0.38 g, 1.0 mmol) was dissolved in a mixture of THF (4 mL) and *t*-BuOH (1 mL), and the solution was added in one portion. After 3 min, the reaction mixture was quenched by addition of solid NH_4Cl (2 g) and warmed to rt. After removal of ammonia, ethyl acetate (40 mL) and water (10 mL) were added, the mixture was extracted with ethyl acetate (2×50 mL) and the combined organic layers were dried over Na_2SO_4. After the solvent was removed in vacuo, the crude product was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70 as eluent) to give the compound **17** (0.18 g; 69%) as a white solid: mp 128–130 °C; $[\alpha]_D$ −49.2 (*c* 0.6, MeOH); MS: *m/z* 230 (1, M^+), 203 (3), 174 (5), 149 (17), 81 (45), 69 (88), 57 (51), 43 (100). Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.11; H, 7.85; N, 12.21.

4.4.11. (3*S*,4*R*)-3-Trichloroacetylamino-4-methoxycarbonylpyrrolidin-2-one (19). A solution of **11b** (1.31 g, 3.0 mmol) in CH_3CN (5 mL) was treated at rt with cerium ammonium nitrate (CAN) (3.3 g, 6.0 mmol) dissolved in water (10 mL), and the reaction mixture was stirred for 3 h. The aqueous layer was extracted with ethyl acetate (3× 25 mL), the organic layers were combined, washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure provided a crude residue, which was purified by silica gel chromatography (cyclohexane–EtOAc 80:20 as eluent) on silica gel to give **19** (0.7 g, 76%) as a white solid: mp 73–75 °C: IR ($CHCl_3$) ν 3347, 1728, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.39–3.57 (m, 2H), 3.59–3.71 (m, 1H), 3.76 (s, 3H), 4.62 (dd, J=7.3, 9.1 Hz, 1H), 7.43 (s, 1H, NH), 8.12 (d, J=7.3 Hz 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 41.7, 45.1, 52.8, 55.0, 91.7, 162.6, 171.6, 172.2; $[\alpha]_D$ −46.1 (*c* 1.9, $CHCl_3$); MS: *m/z* 302 (3, M^+), 304 (3, M^+), 269 (34), 267 (34), 185 (45), 141 (56), 110 (82), 82 (100), 55 (80). Anal. Calcd for $C_8H_9Cl_3N_2O_4$: C, 31.66; H, 2.99%; N, 9.23. Found: C, 31.63; H, 2.26; N, 9.18.

4.4.12. (3*S*,4*R*,1′*S*)-3-*t*-Butoxycarbonylamino-4-methoxy-carbonyl-1-[1′-(4-methoxyphenyl)ethyl]pyrrolidin-2-one (20). In a flask containing compound **11b** (0.5 g, 1.14 mmol), 6 M NaOH (5 mL) was added at rt and the resulting mixture was stirred for 24 h. The pH of the homogeneous solution was adjusted to 7 by addition of 6 M HCl, then water was removed under reduced pressure and methanol (10 mL) was added in order to precipitate the salts that were removed by filtration and filter was washed with methanol (5 mL). The combined filtrates were partially evaporated under reduced pressure and Boc_2O (0.33 g, 1.5 mmol) and TEA (0.4 mL, 3.0 mmol) were added at rt. After 12 h water (5 mL) was added, methanol was removed in vacuo and the solution was acidified with 1 M HCl (0.3 mL). After extraction with ethyl acetate (3×10 mL), the organic layer was dried (Na_2SO_4) and removal of the solvent under reduced pressure gave a residue that was taken off in methanol (5 mL). Subsequent esterification by excess diazomethane in ethyl ether [CAUTION: Diazomethane is an explosive and a highly toxic gas. Explosions may occur if the substance is dry and undiluted. All operations involving diazomethane should be carried out in an efficient fumehood following appropriate precautions] followed by removal of the solvent and purification of the residue by silica gel chromatography (cyclohexane–ethyl acetate 70:30 as eluent) gave compound **20** (0.36 g, 79%) as a viscous oil: IR ($CHCl_3$) ν 3341, 1731, 1725, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H), 1.50 (d, J= 7.2 Hz, 3H), 2.91–3.10 (m, 1H), 3.16 (dd, J=8.8, 9.5 Hz, 1H), 3.38 (dd, J=9.3, 9.5 Hz, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 4.43 (dd, J=6.3, 9.6 Hz, 1H), 5.20 (d, J=6.3 Hz, 1H, NH), 5.44 (q, J=7.2 Hz, 1H), 6.86 (d, J=8.8 Hz, 2 ArH), 7.22 (d, J=8.8 Hz, 2 ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.1, 28.1, 41.5, 45.2, 49.2, 52.2, 55.1, 56.3, 79.9, 113.8, 128.1, 131.0, 155.2, 160.0, 169.2, 172.3; $[\alpha]_D$ −117.1 (*c* 1.9, $CHCl_3$); MS: *m/z* 393 (1, MH^+), 336 (19, MH^+-57), 321 (10), 275 (7), 216 (33), 135 (100), 69 (42), 57 (67). Anal. Calcd for $C_{20}H_{28}N_2O_6$: C 61.21; H 7.19; N 7.14. Found: C, 61.24; H, 7.16; N, 7.09.

4.4.13. (3*S*,4*R*)-3-*t*-Butoxycarbonylamino-4-methoxycarbonylpyrrolidin-2-one (21). A solution of **20** (0.39 g, 1.0 mmol) in CH_3CN (5 mL) was treated at rt with cerium ammonium nitrate (CAN) (1.1 g, 2.0 mmol) dissolved in H_2O (5 mL), and the reaction mixture was stirred for 3 h. The aqueous layer was extracted with ethyl acetate (3× 25 mL), the organic layers were combined, washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure provided a crude residue, which was purified by silica gel chromatography (cyclohexane–ethyl acetate 30:70) to give **21** (0.21 g, 82%) as white solid: mp 131–133 °C: IR ($CHCl_3$) ν 3340, 1733, 1725, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 9H), 3.24–3.65 (m, 3H), 3.75 (s, 3H), 4.31 (dd, J=7.3, 9.2 Hz, 1H), 5.44 (d, J= 7.3 Hz, 1H, NH), 7.12 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.2, 31.3, 46.6, 52.4, 55.1, 80.3, 155.4, 172.2, 173.5; $[\alpha]_D$ −36.7 (*c* 0.6, $CHCl_3$); MS: *m/z* 258 (1, M^+), 202 (16, MH^+-57), 185 (10), 143 (13), 81 (28), 69 (56), 57 (100), 43 (98). Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.16; H, 7.02; N, 10.85. Found: C, 51.12; H, 6.97; N, 10.79.

4.5. Crystal data for 11a

$C_{16}H_{17}Cl_3N_2O_4$: Mw=407.67, colorless crystal 0.35× 0.28×0.15 mm, a=8.594(4) Å, b=8.188(3) Å, c= 19.262(6) Å, α=90.00(3)°, β=90.00(3)°, γ=90.00(3)°, V=1841.5(11) $Å^3$, D_{calc}=1.470 mg/m^3, α=0.095 mm^{-1}, Z=4, Orthorhombic, space group $P2_12_12_1$, λ=0.71069 Å, T=223 K, ω and ϕ scans, 11413 reflections collected, 2245 independent (R_{int}=0.0251), 242 refined parameters, $R1/wR2$ [$I \geq 2\sigma(I)$]=0.0499/0.1308 and $R1/wR2$ (all data)=0.0516/0.1329, maximum (minimum) residual electron density 0.497 (−0.392) e $Å^{-3}$.

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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.2005.03.129

Crystallographic data for the structural analysis of compound **11a** have been deposited at the Cambridge Crystallographic Data Centre. The CCDC no. 261070 has been assigned for the compound **11a**. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

^{1}H and ^{13}C NMR spectra of compounds **11a–c**, **12a–c**, **17**, **19** and **21**, can be found, in the online version, at doi:10.1016/j.tet.2005.03.129.

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Preparation of new heterotopic ligands

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Abstract—A six-step synthesis of two new heterotopic ligands, each possessing two unusual N,N,N,O tetradentate binding subunits, has been developed. This work presents a particularly facile and rapid synthetic protocol for the preparation of these ligands, which one expected to act as useful components in inorganic self-assembly for the preparation of various types of complexes.

1. Introduction

The synthesis of ligands comprising terpyridine units is an area of great interest in organic and supramolecular chemistry due to their interesting metal binding properties.[1] The complexes of lanthanides with terpyridine type ligands are used as highly efficient actinide(III) extracting agents.[2] Transistors incorporating complexes containing a cobalt ion bonded to polypyridyl ligands have been reported, which is expected to be important in molecular electronics and in the study of the physics of nanoscale systems.[3] Multitopic ligands with N,O-donor sets may be employed in the metal ion directed assembly of coordination architectures.[4]

Ligands with five aromatic rings have been successfully demonstrated to form many types of compounds such as racks,[5] grids,[6] clefts[7] and cylindrical architectures,[8] but similar ligand systems with bis(tetradentate) subunits have never been applied. These complexes were found to present interesting electronic, magnetic, and structural properties. Single grids with ligands containing five aromatic rings could be removed from the ordered surface architecture in a controlled way.[9] These well-defined assemblies may be useful models for the study of biological charge transport systems.[10]

In previous studies, we have found that bis(tridentate) ligands with N,N,O donor atoms are good substrates for obtaining grids with metal ions that prefer octahedral coordination geometry[11] and dinuclear complexes with lanthanides.[12] Looking for better complexing agents for lanthanides, we have designed new ligands that include bis(tetradentate) subunits. Coordination is provided by the nitrogen atoms from the bipyridine and pyrimidine rings, while the fourth coordination site is the oxygen atom from the carbonyl donor group. The coordination number of 8 is known for the lanthanides.[13] Supramolecular complexes of lanthanides, especially polymetallic architectures, have been the subject of much interest.[14]

Herein, we describe the syntheses of new octadentate ligands **7** and **8**. The ligand syntheses are straightforward and their precursors have been accessed in good overall yield.

2. Results and discussion

Ligands **7** and **8** were synthesised as outlined in Scheme 1.

2-Methyl-6-trimethylstannylpyridine **1** was obtained from 2-bromo-6-methylpyridine by a halogen/lithium exchange protocol at low temperature in THF with *n*-butyl lithium, followed by quenching the pyridyllithium intermediate with $ClSnMe_3$.[15] The Stille-type[16] coupling reaction of **1** with 2,6-dibromopyridine in toluene using $[Pd(PPh_3)_4]$ as a catalyst furnished **2** in 64% yield after workup (the unsymmetrical compound **2** was obtained by the substitution of 2-ethylsulfinyl-6-methylpyridine with bromo derivative of 2-pyridyllithium in 57% yield).[17] The structure of **2** was confirmed by X-ray structure analysis (Fig. 1). Two almost perfectly planar pirydine rings (maximum deviation from the least-squares plane is 0.005(2) Å) are coplanar and disposed in *trans* arrangement. The molecules lie at the centre of symmetry as the result of disorder in the crystal structure (which is the case, for example, in the structure of biphenyl).[18] However, the shapes and sizes of anisotropic

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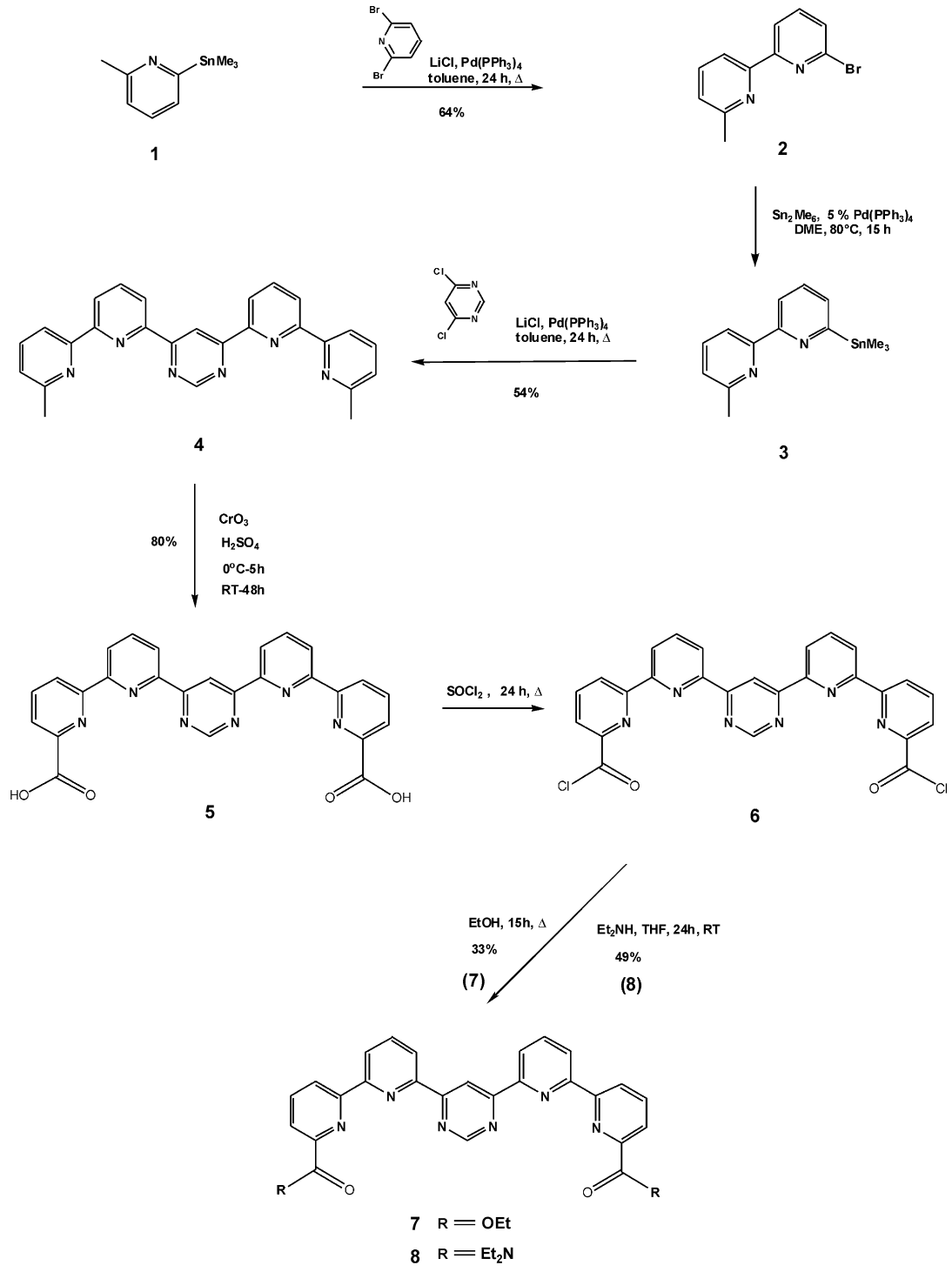

Scheme 1.

displacement ellipsoids do not suggest that the coplanar arrangement is the result of the averaging of two twisted conformations. In the crystal structure the columns of planar molecules (interplanar distance of ca. 3.4 Å) are connected by very weak C–H···Br interactions.

The reaction mixture of **2**, hexamethylditin and 3–5% of $[Pd(PPh_3)_4]$ was degassed. Dry DME was added and heated at 80 °C for 15 h.[19] The solvent was evaporated and the residue was left under vacuum overnight. Without purification, compound **3** was treated with 4,6-dichloropirymidine in the two-fold Stille coupling that resulted in obtaining compound **4** in 55% yield. The methyl groups of **4** were further oxidized with CrO_3 in concentrated H_2SO_4 to afford diacid **5** in 80% yield. The acid is insoluble in most organic solvents and only scarcely in DMSO. Precursor **5** was converted into diacid dichloride **6** upon refluxing in $SOCl_2$, which was used subsequently in further transformations without purification. Thus when **6** was refluxed with EtOH or stirred with Et_2NH in THF, ligands **7** and **8** were

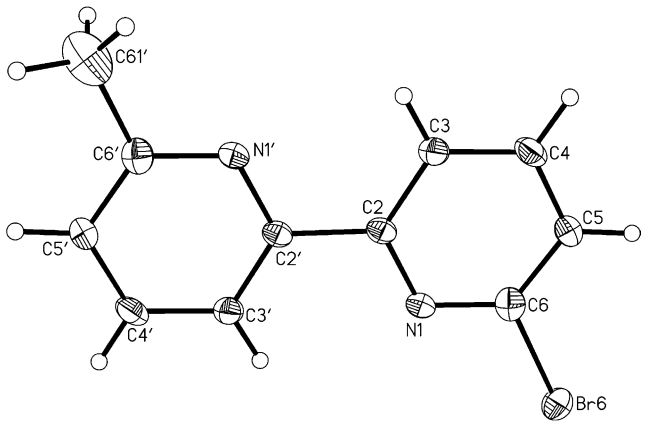

Figure 1. Perspective view of compound **2** with the atomic numbering scheme. The thermal ellipsoids are drawn at 50% probability level; hydrogen atoms are depicted as spheres with arbitrary radii.

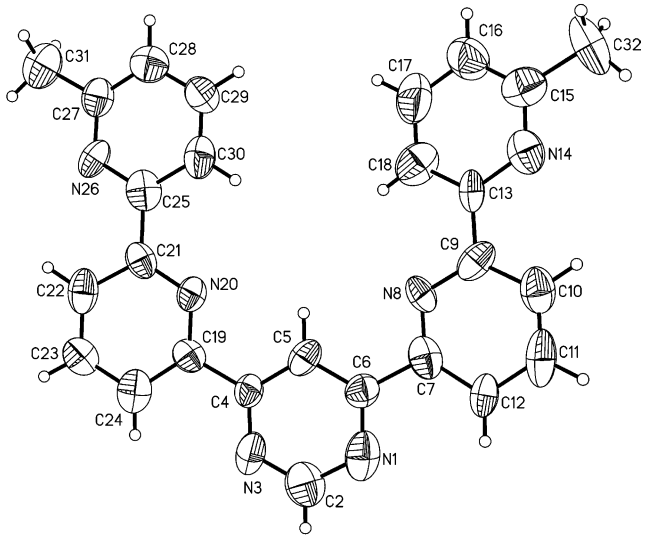

Figure 2. Perspective view of compound **4** with the atomic numbering scheme. The thermal ellipsoids are drawn at 50% probability level; hydrogen atoms are depicted as spheres with arbitrary radii.

obtained in 33 and 49% yields, respectively, after purification. The structure of **7** and **8** and precursors were confirmed by NMR, IR, FAB-MS and elemental analysis. The structures of **4** and **7** have been ascertained on the basis of X-ray crystallography (Figs. 2 and 3). A literature survey reveals that there are only a few X-ray structures of ligands containing five aromatic rings.[20]

In both compounds, the nitrogen atoms are disposed in the all-*trans* manner (N–C–C–N torsion angles are close to 180°). The same disposition of hetero atoms was observed in smaller ligands, 2,2′-bis(4,6-pyrimidinediyl)pyridine derivatives.[11] For steric reasons this conformation is energetically favored; it also allows for many weak intramolecular C–H···N hydrogen bonds to be formed. Also the carbonyl oxygen atoms in **7** are *trans* with respect to the nitrogen atoms of the neighbouring rings. The aromatic rings are almost coplanar, the dihedral angle between the planes of the terminal rings is 10.6° in **4** and ranges from 1.1 to 4.4° in the four symmetry-independent molecules of **7**. In **7**, the COOC groups are almost planar, and their planes are almost parallel to the molecular planes; the maximum angle between the least squares planes of the COOC group and the neighbouring pyridine ring plane is 7.0°. In the analogous structure with a three-ring system,[11] the ethoxy fragments on either side of the molecule were differently oriented (C–O–C–C torsion angles were ca. 160 and 90°), as the result of steric interactions between the ethyl groups. In the case of **7**, the presence of additional rings in *transoid* conformations causes different disposition of ethoxy groups; they are on the other side of the bay region of the molecule (Fig. 3), and, therefore, there is no steric stress connected with these groups. All the eight ethoxy groups (there are four symmetry-independent molecules in the crystal structure) are in the same conformation—the absolute values of the COCC torsion angles are in the range 170–178°. The crystal structures of **4** and **7** are governed by van der Waals interactions and some weak C–H···N and C–H···O hydrogen bonds.

In summary, further investigation on the synthesis of the d- and f-metal complexes and their crystallization is in progress. Transition metal complexes of multidentate

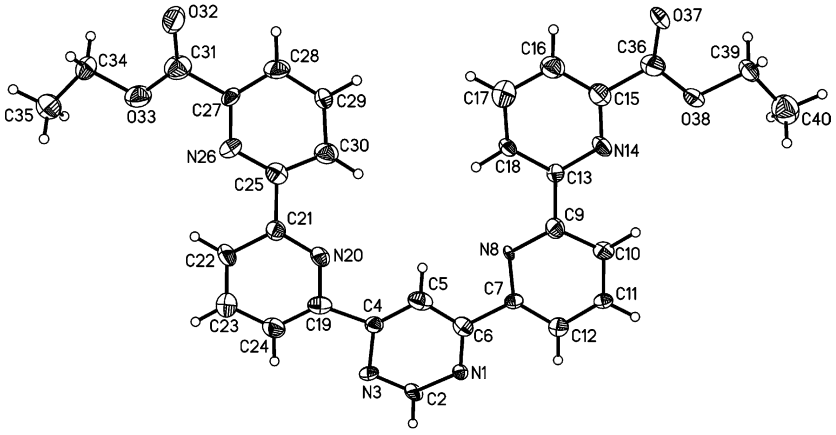

Figure 3. Perspective view of one of the four symmetry-independent molecules of the compound **7** with the atomic numbering scheme. The thermal ellipsoids are drawn at 50% probability level; hydrogen atoms are depicted as spheres with arbitrary radii.

ligands have been widely used in modern chemical applications including supramolecular self-assembly, anion recognition, and catalyst development.[21]

3. Experimental

3.1. General

CH_3CN was freshly distilled under argon from CaH_2. 2-Methyl-6-trimethylstannylpyridine **1** was prepared according to the literature.[15] The reagents from Aldrich or Acros were used without further purification. The NMR spectroscopic data were recorded on a Bruker AC 200 at 200.1 MHz, a Varian Gemini 300, and 500 MHz spectrometer, and were calibrated against residual protonated solvent signal ($CDCl_3$: $\delta=7.24$, [D_6]DMSO: $\delta=2.50$) and are given in ppm. Mass spectra were determined by FAB^+ using a ZAB-HF VG apparatus in an *m*-nitrobenzyl alcohol matrix. The IR spectra were obtained with a Perkin–Elmer 580 spectrophotometer and are reported in cm^{-1}. Microanalyses were obtained using a Perkin Elmer 2400 CHN microanalyzer. Melting points were recorded on an Electrothermal Digital melting point apparatus.

3.1.1. 2-Bromo-6-(6-methylpyridin-2-yl)pyridine (2). 2-Methyl-6-trimethylstannylpyridine **1** (3.26 g, 12.7 mmol) and degassed toluene (45 mL) were added consecutively by syringe to a mixture of 2,6-dibromopyridine (3.01 g, 12.7 mmol), LiCl (1 g, 23.5 mmol) and $Pd(PPh_3)_4$ (0.23 g, 0.2 mmol), under an argon atmosphere. The reaction was refluxed and stirred at 120 °C for 24 h, and the toluene evaporated on a waterbath under reduced pressure. The residue was then purified by column-chromatography on silica gel and eluted with dichloromethane, to afford pale yellow powder −2.03 g (64%) **2**. Mp 150 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=8.41$ (d, 1H, H3, $J=7.6$ Hz), 8.20 (d, 1H, H3′, $J=7.6$ Hz), 7.68 (m, 2H, H4, H4′, $J=8.8$ Hz), 7.48 (d, 1H, H5, $J=7.3$ Hz), 7.20 (d, 1H, H5′, $J=7.0$ Hz), 2.53 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=157.99$ (C6), 157.66 (C2′), 153.83 (C2), 141.48 (C6′), 139.11 (C4′), 137.11 (C4), 127.72 (C5′), 123.83 (C3′), 119.71 (C5), 118.46 (C3), 24.59 (CH_3). IR (KBr, cm^{-1}): $\nu=3041$, 2917, 1973, 1798, 1595, 1576, 1418, 1260, 1153, 1127, 1074, 985, 848, 777, 649, 630, 513, 419. FABMS: $m/z=249.0$ (M^+, 100). Anal. Calcd for $C_{11}H_9N_2Br$ C, 53.04; H, 3.64; N 11.25. Found: C, 53.03; H, 3.58; N, 11.30.

3.1.2. 2-(6-Methylpyridin-2-yl)-6-(trimethylstannyl)pyridine (3). The compound **2** (1.35 g, 5.4 mmol), hexamethylditin (1.78 g, 5.4 mmol) and 5% of $Pd(PPh_3)_4$ (0.32 g, 0.27 mmol) was degassed for 10 minutes, the dry DME (30 mL)was then added and the reaction mixture was heated at 80 °C for 15 h. The solvent was evaporated and the residue was pumped overnight. The crude **3** was then used immediately for the subsequent synthesis of compound **4**.

3.1.3. 4,6-Bis(6-(6-methylpyridin-2-yl)pyridin-2-yl)pyrimidine (4). To a mixture of **3** (1.54 g, 4.8 mmol), 4,6-dichloropirymidine (0.28 g, 1.9 mmol), LiCl (0.5 g, 11.8 mmol) and $Pd(PPh_3)_4$ (0.10 g, 0,1 mmol), under an argon atmosphere, degassed toluene (25 mL) was added gradually by syringe. The reaction was refluxed and stirred at 120 °C for 24 h, and the toluene evaporated on a waterbath under reduced pressure. After alumina column-chromatography with dichloromethane:hexane (7:3), compound **4** was further purified by recrystallization from acetonitrile giving 0.42 g (55%). Mp 220 °C. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta=9.80$ (s, 1H, H2″), 9.40 (s, 1H, H5″), 8.68 (d, 2H, H3, $J=7.9$ Hz), 8.64 (d, 2H, H3′, $J=7.9$ Hz), 8.58 (d, 2H, H5′, $J=7.6$ Hz), 8.07 (t, 2H, H4′, $J=7.8$ Hz), 7.78 (t, 2H, H4, $J=7.8$ Hz), 7.21 (d, 2H, H5, $J=5.8$ Hz), 2.69 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=163.84$ (C4″), 158.38 (C2″), 157.86 (C6′), 155.91 (C2′), 155.13 (C2), 153.15 (C6), 137.93 (C4), 136.75 (C4′), 123.44 (C3), 122.52 (C3′), 121.32 (C5′), 118.11 (C5), 113.98 (C5″), 24.77 (CH_3). IR (KBr, cm^{-1}): $\nu=3413$, 2923, 1646, 1568, 1438, 1381, 1261, 1114, 1076, 996, 909, 828, 772, 642, 608, 470, 420. FABMS: $m/z=417.1$ (M^+, 100). Anal. Calcd for $C_{26}H_{20}N_6$: C, 74.98; H, 4.84; N, 20.18. Found: C, 74.52; H, 4.87; N, 19.91.

3.1.4. 6-(6-(6-(6-(6-Carboxypyridin-2-yl)pyridin-2-yl)pyrimidin-4-yl)pyridin-2-yl)pyridine-2-carboxylic acid (5). Product **4** (0.23 g, 0.55 mmol) was added to concentrated H_2SO_4 (5 mL) and cooled to 0 °C with stirring in an ice-bath. Chromium(VI) oxide (0.33 g, 0.55 mmol) was then added in 0.1 g portions to the stirred solution of **4** at a rate that maintained the reaction temperature below 3 °C. When the addition of CrO_3 was completed (about 5 h) the mixture was stirred for 48 h at room temperature. The viscous reaction solution was then poured onto excess crushed ice with stirring. The precipitated product was finally isolated by filtration under reduced pressure, washed with distilled water and air dried to yield 0.21 g (80%) of **5**. Mp 150 °C. ^1H NMR (300 MHz, DMSO, 25 °C): $\delta=9.66$ (s, 1H, H2″), 9.47 (s, 1H, H5″), 8.88 (d, 2H, H3, $J=7.3$ Hz), 8.76 (d, 2H, H3′, $J=7.7$ Hz), 8.56 (d, 2H, H5, $J=7.7$ Hz), 8.30 (t, 4H, H4, 4′, $J=8.2$ Hz), 8.20 (d, 2H, H5′, $J=7.3$ Hz). IR (KBr, cm^{-1}): $\nu=3410$, 2930, 2256, 2127, 1720, 1586, 1529, 1445, 1380, 1305, 1250, 1148, 1030, 991, 817, 758, 667, 649, 443, 421. Anal. Calcd for $C_{26}H_{16}N_6O_4\cdot H_2O$: C, 63.16; H, 3.67; N, 17.00. Found C, 63.18; H, 3.64; N, 16.88.

3.1.5. 6-(6-(6-(6-(6-(Chlorocarbonyl)pyridin-2-yl)pyridin-2-yl)pyrimidin-4-yl)pyridin-2-yl)pyridine-2-carbonyl chloride (6). Compound **5** (0.04 g, 0.08 mmol) was refluxed for 24 h in thionyl chloride (20 mL) and then the $SOCl_2$ evaporated under reduced pressure on a water bath. The crude **6** was then used immediately for the subsequent synthesis of diester **7** and diamide **8** without further purification.

3.1.6. Ethyl 6-(6-(6-(6-(6-(ethoxycarbonyl)pyridin-2-yl)pyridin-2-yl)pyrimidin-4-yl)pyridin-2-yl)pyridine-2-carboxylate (7). EtOH (10 mL) was added to **6** (34.7 mg, 0.07 mmol) and the resulting mixture refluxed for 15 h and subsequently cooled to room temperature. The reaction was then reduced in volume to 8 mL under pressure on a waterbath, and the mixture cooled in an ice-bath. The blue-green solid was isolated by filtration under vacuum, washed with a small quantity of ice-cold EtOH and air dried to yield 11.9 mg (33%) **7**. Mp 178 °C. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=9.72$ (s, 1H, H2″), 9.42 (s, 1H, H5″), 8.94 (d, 2H,

H3, $J=5.5$ Hz), 8.77 (d, 2H, H3′, $J=5.2$ Hz), 8.64 (d, 4H, H5, H5′, $J=4.6$ Hz), 8.18 (t, 2H, H4, $J=8.4$ Hz), 8.04 (t, 2H, H4′, $J=9.2$ Hz), 4.50 (q, 4H, CH_2, $J=7.0$ Hz), 1.51 (t, 6H, CH_3, $J=6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=167.95$ (CO), 156.76 (C4″), 155.56 (C2″), 154.93 (C6′), 154.50 (C2′), 154.21 (C2), 153.94 (C6), 138.34 (C4), 137.76 (C4′), 127.56 (C3), 122.28 (C3′), 121.19 (C5′), 121.01 (C5), 49.33 (CH_2), 29.70 (CH_3). IR (KBr, cm^{-1}): $\nu=3339$, 2963, 1763, 1666, 1588, 1380, 1260, 1107, 1019, 867, 799, 700, 661, 618, 513, 449. FABMS $m/z=533.2$ (M^+, 100). Anal. Calcd for $C_{30}H_{24}O_4N_6$: C, 67.66; H, 4.54; N, 15.78. Found: C, 67.98; H, 4.67; N, 15.89.

3.1.7. 6-(6-(6-(6-(6-(Diethylcarbamoyl)pyridin-2-yl)pyridin-2-yl)pyrimidin-4-yl)pyridin-2-yl)-*N*,*N*-diethylpyridine-2-carboxamide (8). Anhydrous THF (5 mL), and a solution of Et_2NH (10 mL) in anhydrous THF (50 mL), were added consecutively by syringe to **6** (0.13 g, 2.6 mmol) under an atmosphere of argon. The resulting mixture (brown-purple suspended solid) was then stirred for 24 h at ambient temperature, and filtered under gravity. The filtrate was evaporated to dryness and the remaining solid dissolved in boiling *n*-hexane (100 mL), filtered under gravity, and left to stand overnight. The crystalline solid which formed was isolated by filtration under vacuum, washed with *n*-hexane and air dried to yield 0.08 g (49%) **8**. Mp 207 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=9.77$ (s, 1H, H2″), 9.41 (s, 1H, H5″), 8.84 (d, 2H, H5, $J=7.6$ Hz), 8.58 (d, 4H, H3, 3′, $J=7.6$ Hz), 8.04 (t, 2H, H4, $J=7.8$ Hz), 7.98 (t, 2H, H4′, $J=7.8$ Hz), 7.71 (d, 2H, H5′, $J=7.6$ Hz), 3.62 (q, 4H, CH_2, $J=7.3$ Hz), 3.50 (q, 4H, CH_2, $J=6.8$ Hz), 1.33 (t, 12H, CH_3, $J=7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=168.25$ (CO), 163.76 (C4″), 158.51 (C2″), 155.23 (C6′), 154.59 (C2′), 154.25 (C2), 153.29 (C6), 138.14 (C4), 137.57 (C4′), 123.57 (C3), 122.79 (C3′), 121.79 (C5′), 121.41 (C5), 43.38 (CH_2), 40.37 (CH_2), 14.67 (CH_3), 13.02 (CH_3). IR (KBr, cm^{-1}): $\nu=3558$, 2926, 1633, 1566, 1533, 1425, 1379, 1113, 812, 763, 632, 474. FABMS $m/z=587.1$ (M^+, 100). Anal. Calcd for $C_{34}H_{34}O_2N_8$: C, 69.61; H, 5.84; N, 19.10. Found: C, 69.67; H, 5.69; N, 19.19.

3.2. Crystal structure determination of 2

$C_{11}H_9BrN_2$, colourless plates, dimensions 0.4 mm×0.2 mm×0.07 mm, measured on an Oxford Diffraction KM4CCD diffractometer[22] with Mo K_α radiation, $T=120(1)$ K. Monoclinic, space group $C2/c$, $a=22.323(3)$ Å, $b=3.8396(5)$ Å, $c=11.7068(11)$ Å, $\beta=98.335(11)°$, $V=992.8(2)$ Å^3, $Z=4$, $d_{calcd}=1.67$ g cm^{-3}, $\mu=4.098$ mm^{-1} (absorption corrections were applied with SORTAV[23]), 2135 reflections collected, 1114 independent ($R_{int}=0.038$). Structure solution with direct methods (SHELXS[24]), full-matrix least-squares refinement on F^2 (SHELXL97[25]), the hydrogen atom positions were calculated and refined as riding groups with U_{iso} set at 1.2 times U_{eq} of carrier atom (1.3 for methyl group). $R1=0.052$, $wR2=0.146$, maximum residual electron density 0.57 e Å^{-3}/−0.72 e Å^{-3}. The structure is disordered: the molecule apparently lies at the centre of symmetry, and bromine and methyl substituent appear at the same positions; the attempts to refine this structure in a non-centrosymmetric space group gave no satisfactory results (the model was similar and huge correlations made refinement unreliable). Weak constraints were applied to the thermal parameters of the C-methyl atom.

3.3. Crystal structure determination of 4

$C_{26}H_{20}N_6\cdot 1/2H_2O$, poorly diffracting, thin colorless needles, dimensions 0.4 mm×0.05 mm×0.05 mm, measured on an Oxford Diffraction KM4CCD diffractometer[22] with Mo K_α radiation. $T=120(1)$ K. Monoclinic, space group $P2_1/n$, $a=3.816(1)$ Å, $b=23.153(4)$ Å, $c=23.877(4)$ Å, $\beta=90.74(1)°$, $V=2109.6(7)$ Å^3, $Z=4$, $d_{calcd}=1.34$ g cm^{-3}, $\mu=0.084$ mm^{-1}, 11,412 reflections collected, 4941 independent ($R_{int}=0.129$). Structure solution with direct methods (SHELXS[24]), full-matrix least-squares refinement on F^2 (SHELXL97[25]), the hydrogen atom positions were calculated and refined as riding groups with the U_{iso} set at 1.2 times U_{eq} of carrier atom (1.3 for methyl groups). $R1=0.118$, $wR2=0.157$, maximum residual electron density 0.30 e Å^{-3}/−0.30 e Å^{-3}.

3.4. Crystal structure determination of 7

$C_{30}H_{24}N_6O_4$, poorly diffracting, colorless crystals, dimensions 0.2 mm×0.08 mm×0.05 mm, measured on an Oxford Diffraction KM4CCD diffractometer[22] with Mo K_α radiation. $T=130(1)$ K. Monoclinic, space group $C2/c$, $a=29.984(3)$ Å, $b=15.076(1)$ Å, $c=46.067(4)$ Å, $\beta=96.49(1)°$, $V=20691(3)$ Å^3, $Z=32$, $d_{calcd}=1.37$ g cm^{-3}, $\mu=0.094$ mm^{-1}, 49,466 reflections collected, 22,497 independent ($R_{int}=0.120$). Structure solution with direct methods (SHELXS[24]), full-matrix least-squares refinement on F^2 (SHELXL97[25]), the hydrogen atom positions were calculated and refined as riding groups with the U_{iso} set at 1.2 times U_{eq} of carrier atom (1.3 for methyl groups). $R1=0.068$, $wR2=0.158$, maximum residual electron density 0.19 e Å^{-3}/−0.19 e Å^{-3}. The structure was solved in non-centrosymmetric space group Cc (the attempts of solving it in $C2/c$ were unsuccessful) and then transformed to the centrosymmetric $C2/c$. Different constraints were applied during the refinement: SADI, SIMU, DELU, ISOR, DFIX, because of the low quality of the crystal.

CCDC-257389 (**2**) CCDC-257390 (**4**) and CCDC-235550 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internet.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

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High temperature bromination. Part 18: Bromination of benzonorbornadiene derivatives: Polybrominated benzonorbornenes and benzonorbornadienes☆

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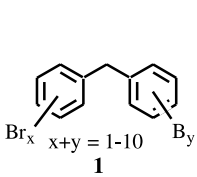
Abstract—The low and high temperature bromination reactions of bromobenzonorbornadiene derivatives were studied and the possible role of a neighboring group in rearrangements was investigated. New polybrominated benzonorbornadiene and benzonorbornene derivatives were synthesized. All compounds were characterized properly using NMR spectroscopy.

1. Introduction

Polymeric materials and synthetic fibers are extensively used in many areas. The demand for non-burning or flame-retardant polymers is strong in various industries. Some of these flame retardant products contain brominated organic compounds such as polybrominated diphenyl ethers (PBDEs) **1**, hexabromocyclododecane (HBCD) **2**, tetrabromobisphenol A (TBBPA) **3**.[2] The compound **4** is also flame-retardant and it contains a brominated benzonorbornadiene moiety.[3]



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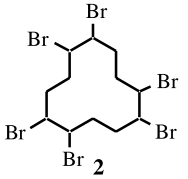

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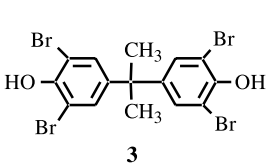

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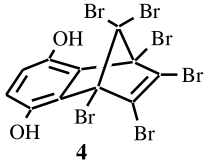

4

Aside from the numerous industrial applications of these highly brominated compounds, such as pesticides, plastics, fire-retardants and pharmaceutical chemicals, they also play an important role as key compounds for the synthesis of other derivatives.[4] Great interest has been focused on the halogenation of norbornadiene[5] and benzonorbornadiene[6] derivatives. In a previous report, we showed that bromination of benzonorbornadiene **5** at a low temperature gives only rearranged product **6**.[6a] However, the bromination reaction of this molecule at 150 °C gave the rearranged **6** and non-rearranged products **7** in a ratio of 1:4 (Scheme 1).[6a]

In this paper, we report the synthesis of poly-brominated benzonorbornadiene derivatives and the mode of the bromination reactions of compounds such as **8** having a bromine atom in the *exo*-position, which blocks the *exo*-face of the double bond. Furthermore, we report the effect bromine atoms bonded to the vinyl carbon atom as well as to the bridgehead carbon atoms in **8** on the mode of bromination reaction.

2. Results and discussion

Firstly, the starting material, monobromide **8** was prepared by way of the potassium *t*-butoxide promoted elimination of **6** according to the published method.[6e] The electrophilic addition of bromine to *anti*-7-bromobenzonorbornadiene **8** was first, reported by Caple et al.[6g] The reaction was performed in chloroform solution at −10 °C and the

☆ See Ref. 1.

Keywords: Benzonorbornadiene; Bromination; Wagner–Meerwein rearrangement; Polybromides.
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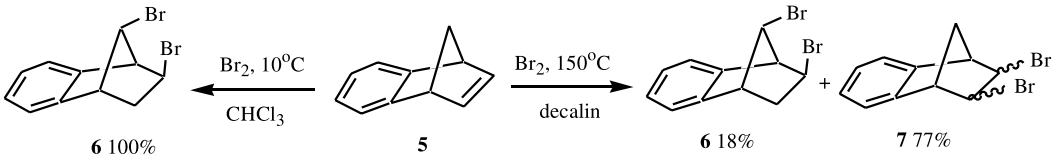
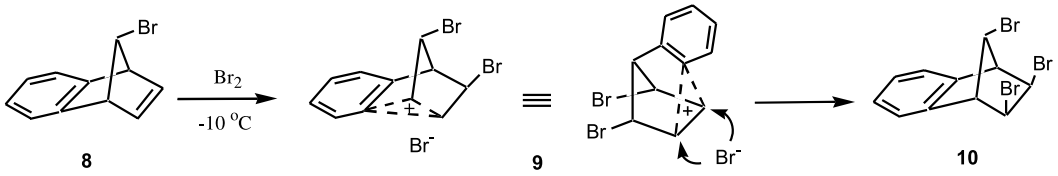


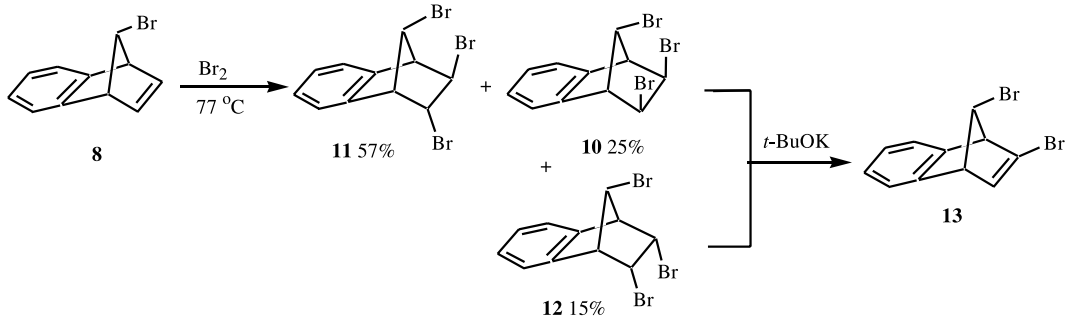
Scheme 1.



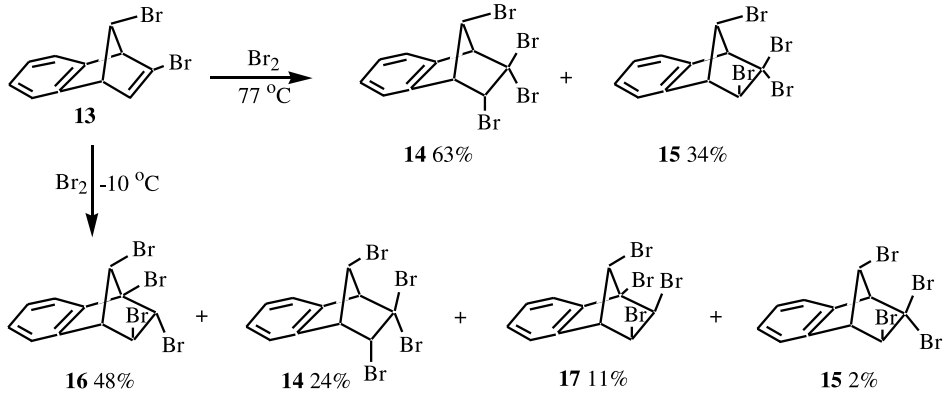
Scheme 2.

symmetrical *cis-exo*-addition product **10** was isolated in a quantitative yield (Scheme 2). The exclusively formation of the *cis-exo*-tribromide **10** can be explained only by the Wagner–Meerwein rearrangement where the symmetrical non-classical carbocation **9** is involved as the intermediate. This reaction clearly demonstrates that even in a case where a bulky group such as a bromine atom located in the *exo*-face of the molecule **8**, the *exo*-selectivity of the electrophiles is not affected during the addition of bromine.

In the course of studying the bromination reaction, it was noticed that the reaction temperature has a dramatic influence on the product distribution.[5d–e,6a–c,7] This factor encouraged us to raise the bromination temperature higher in order to search for the ratio of non-rearranged bromination products derived from **8**. A hot solution of bromine in CCl_4 was added directly to the refluxing solution of **8** in CCl_4. The NMR analysis of the crude product indicated that the reaction mixture consisted mainly of three products. After column chromatography, three isomeric compounds; *trans*-tribromide **11**, *exo-cis*-tribromide **10** and *endo-cis*-tribromide **12** were isolated. The isolated products **10–12** were submitted to the same reaction conditions and it was noticed that the formed product did not undergo any isomerization reactions. Therefore, we assume that all formed products are primary products. It is clear from the structures that the tribromides **11** and **12** are non-rearranged products, however, it is difficult to predict whether the tribromide **10** is formed by Wagner–Meerwein rearrangement or by the direct *exo*-collapse of the bromine with **8**. The elimination reaction of a mixture of tribromides **10–12** allows us the synthesis of 2,9-dibromobenzonorbornadiene



Scheme 3.

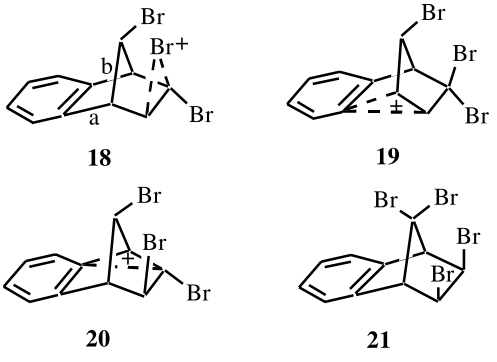


Scheme 4.

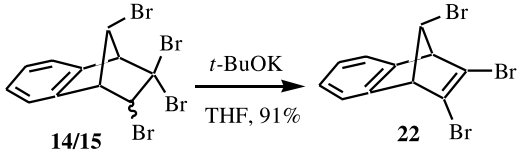
(**13**). The HBr elimination from **11** takes place via *syn*-elimination. Gronert[8] showed that *syn*-elimination occurs more readily than *anti*-elimination in bicyclic systems (scheme 3).

The bromination of **13** at −10 °C resulted in the formation of four products; the rearranged products **16** (48%) and **17** (11%) and the non-rearranged product **14** (24%) and **15** (2%) (Scheme 4). On the other hand, the high temperature bromination of **13** only formed the non-rearranged products **14** and **15** approximately in a ratio of 1:2.

Since, the *exo*-attack intermediate **18** is unsymmetrical, there are two possible aryl shifts involving aryl bonds 'a' and 'b'. The shift of the aryl bond 'a' should form the dibromo compound **21**. However, careful inspection of the reaction mixture did not show the formation of any trace of this dibromide **21**. However, the rearranged products **17** and its isomer **16** were formed in a total yield of 59%. This indicates that the shift of the aryl bond 'b' is predominating, which can be explained by way of the stabilization of the non-classical carbocation **20** by the bromine atom over **19**. The formation of **16** with the unexpected configuration of the bromine atom at C-2 can be attributed to the steric crowdedness, which causes a configurational isomerization. The non-rearranged products **14** and **15** were formed together in a 26% yield.



Comparison of the low temperature bromination reactions of **8** and **13** show that the attachment of an additional bromine atom to the double bond (**13**) changes the amount of the non-rearranged products from 0% (in the case of **8**) up to 30% (in the case of **13**). This means a vinylic bromine atom in benzonorbornadiene partly prevent the skeletal rearrangement during the bromination reaction.



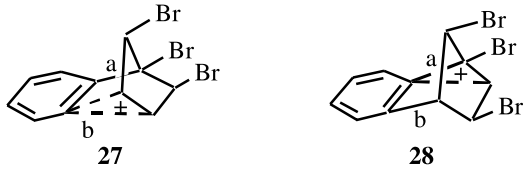
Scheme 5.

HBr elimination from tetrabromides **14** and **15** with potassium *t*-butoxide at room temperature gave tribromide **22** in high yield (Scheme 5). This route allowed the effective synthesis of the symmetrical 2,3,9-tribromobenzonorbornadiene (**22**).

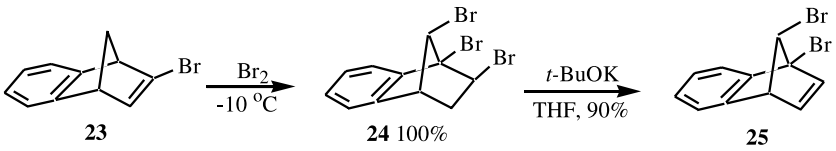
After the completion of the bromination reaction of **13** at different temperatures, we focused on the bromination reaction of bridgehead substituted benzonorbornadiene **25** to investigate the effect of a bromine atom attached to one of the bridgehead carbon atoms on the tendency of skeletal rearrangement during bromination reaction. Elimination of tribromide **24**, which was obtained by the bromination of monobromide **23**,[4a] gave the starting material, dibromide **25** in 90% yield (Scheme 6).

The bromination of **25** at −10 °C resulted in the formation of the tetrabromide **17** in 98% yield (Scheme 7). This product may be either a Wagner–Meerwein rearranged product or a non-rearranged product. Since, the tetrabromide **17** is formed as a single isomer and in high yield, it is likely that it is a rearranged product. In the case of a normal bromine addition to the double bond in **25**, the corresponding *trans*-addition products **26** and **16** should also be formed in some amounts. However, no trace of these products was detected at a low temperature bromination reaction.

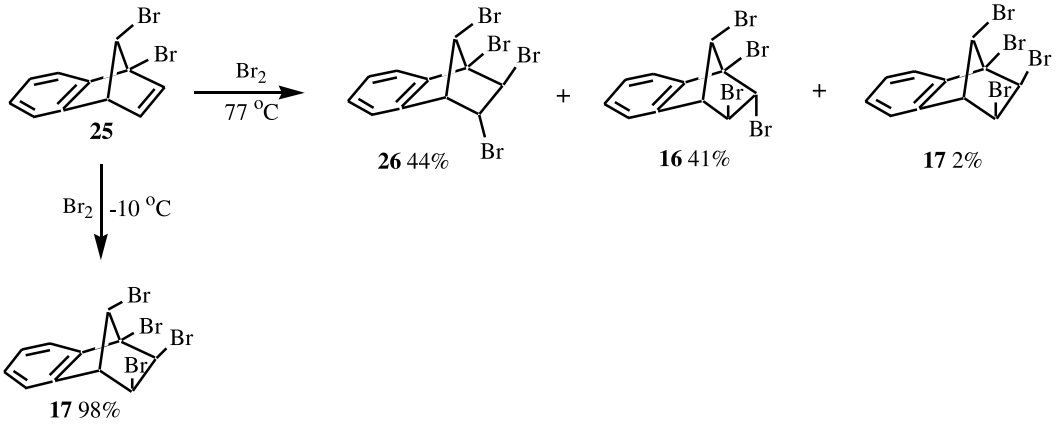
Because of the unsymmetrical structure of the starting material **25**, the initially formed bromonium ion can involve two different aryl shifts during the Wagner–Meerwein rearrangement (non-classical cations **27** and **28**). The sole formation of **17** shows that the non-classical carbocation **27** determines the mode of the reaction. If the shift of the aryl bond 'a' would be the predominating one, a geminal dibromide would be formed. We assume the bromide anion cannot attack the cation **28** due to the crowdedness of the bulky bromine atom. However, the cation **27** can be attacked easily by the bromide anion to form the tetrabromide **17**.



Comparison of these results with those obtained by the bromination reaction of **8** and **13** shows that the position of the bromine atom plays an important role in determination of the mode of the bromination reaction. A bromine atom



Scheme 6.

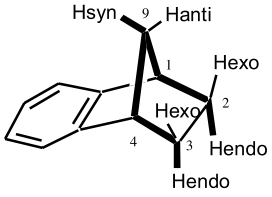


Scheme 7.

attached to the bridgehead carbon atom as in the case of **25** does not prevent the skeletal rearrangement, whereas a vinylic bromine atom in **13** partly hinders the skeletal rearrangement. On the other hand, the high temperature bromination of **25** gave the expected non-rearranged products **16**, **17** and **26** (Scheme 7).

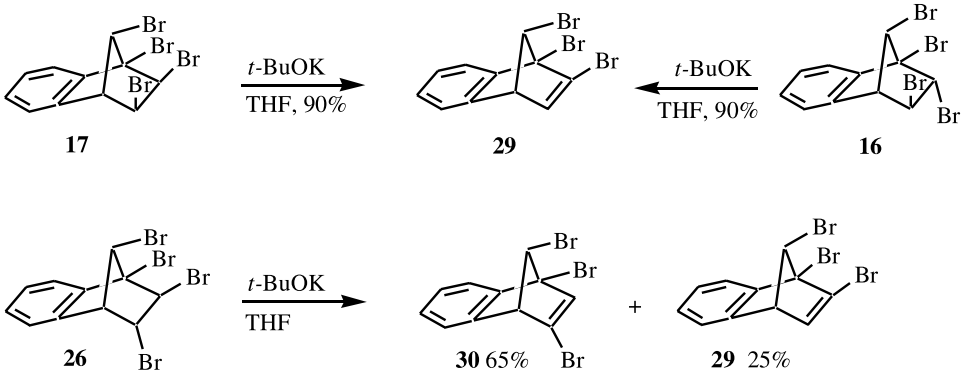
The HBr elimination from tetrabromides **16** and **17** with potassium *tert*-butoxide at room temperature selectively gave tribromide **29** in 90% yield. This route allowed us the effective synthesis of 1,2,9-tribromobenzonorbornadiene **29**. On the other hand, the HBr elimination from **26** gave a mixture of tribromides **30** and **29** in 65 and 25% yields, respectively (Scheme 8).

NMR spectral studies and configuration assignments. The structures of the above mentioned compounds were elucidated on the basis of ^{1}H and ^{13}C NMR spectral data and extensive double resonance experiments.[1]



We mainly used the coupling constants between the relevant protons to assign the relative configuration of the bromine-bearing carbon atoms. The configuration of the atoms at the ethano bridge was determined by measuring the coupling constants between H_1, H_2 and H_3, H_4, respectively. The high value of $J_{1,2}$ ($J_{3,4}$) (3.5–5.0 Hz) is uniquely accommodated by the *exo* orientation of the protons (*endo* orientation bromine atoms) at C_2 and C_3 carbon atoms. On the other hand, the absence of any coupling between the related protons confirms the *endo* orientation of protons at C_2 and C_3, which in turn proves the *exo*-orientaion of the bromine atoms. The existence of a coupling between the bridgehead proton H_9 and CHBr protons (W or M arrangement of the coupled protons) or the lack of a coupling between related protons give information about the orientation of the atoms at the C_2 and C_3 carbon atoms, as well as at the C_9 carbon atom. Monobromide **8** and tribromides **10**, **12** and **22** exhibit an AA′BB′ system for the aromatic protons, which supports the symmetrical structures. Furthermore, a six-line in ^{13}C NMR is also in agreement with the proposed structures.

As a result, the low and high temperature bromination reactions of bromobenzonorbornadiene derivatives were studied and the possible role of neighboring groups on the mode of the rearrangement was investigated. The effect of the newly synthesized polybrominated benzonorbornadiene



Scheme 8.

and benzonorbornene derivatives as fire-redartants will be tested.

3. Experimental

3.1. General

Melting points are uncorrected. Infrared spectra were obtained from solution in 0.1 mm cells or KBr pellets on a regular instrument. The ^{1}H and ^{13}C NMR spectra were recorded on 200 MHz (Varian) spectrometers. All solvents were dried and distilled before use. Column chromatography (CC) was performed on silica gel (60-mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates. All substances reported in this paper, are in their racemic form.

Caution. It has been reported[9] that out of three laboratory workers who have used dibromides and a bromohydrin derived from norbornadiene, two later developed similar pulmonary disorders, which contributed to their subsequent deaths. The third exhibited minor skin sensitivity reactions. In the case of dibromide derived from benzonorbornadiene there is no report in the literature about the toxicological effect. However, we recommend that the compounds must be handled only with extreme caution.

3.2. General procedure for the bromination of olefins at −10 °C

To a magnetically stirred solution of alkene (30.0 mmol) in dry $CHCl_3$ (60 mL) at −10 °C was added dropwise to a solution of bromine (5.0 g, 31.25 mmol) in $CHCl_3$ (5 mL) over 5 min. The color of bromine disappeared immediately. The solvent was evaporated and the crude was purified as the procedure described properly below.

3.3. General procedure for bromination of olefins at 77 °C

To a magnetically stirred solution of alkene (30.0 mmol) in refluxed CCl_4 (60 mL) was added dropwise to a hot solution of bromine (5.71 g, 35.68 mmol) in hot CCl_4 (3 mL) during 5 min. The resulting reaction mixture was heated for 1 min at reflux temperature. After being cooled to room temperature, the solvent was evaporated and the residue was chromatographed on silica gel (100 g) eluting with *n*-hexane.

3.4. General procedure for the elimination of bromides

To a stirred solution of the bromide (3.0 mmol) in dry THF (20 mL) was added a solution of potassium *tert*-butoxide (500 mg, 4.4 mmol) in dry THF (5 mL). The resulting reaction mixture was stirred overnight at room temperature The solvent was evaporated, the mixture was diluted with water and the aqueous solution was extracted with ether (3×50 mL). Combined organic layers, washed with water, dried over $MgSO_4$ and concentrated. The residue was filtered on a short silica gel column (10 g) eluting with *n*-hexane to give olefin.

3.4.1. Synthesis of (1*R*(*S*),4*S*(*R*))-9-*anti*-bromo-1,4-dihydro-1,4-methano-naphthalene (8). The reaction was carried out by the general procedure using **6** (2.0 g, 6.62 mmol) and potassium *t*-butoxide (800 mg, 7.14 mmol). The monobromide **8** (1.40 g, 95%) was obtained. Colorless crystals from CH_2Cl_2/*n*-pentane (1:5); mp 52–53 °C, lit.[6e] 53–54 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27–7.00 (AA′BB′ system, 4H, H_{aryl}), 6.72 (m, 2H, H_2 and H_3), 4.40 (m, 1H, H_9), 4.08 (m, 2H, H_1 and H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.1, 141.5, 127.6, 124.0, 76.19, 59.4.

3.4.2. Bromination of monobromide 8 at −10 °C. The reaction was carried out by the general procedure using monobromide **8** (1.0 g, 4.52 mmol), bromine (730 mg, 4.57 mmol) and $CHCl_3$ (10 mL). After 5 min, the solvent was evaporated and tribromide **10** was obtained as the sole product (1.72 g, 100%).

anti-(1S(R),2R(S), 3S(R),4R(S))-2,3,9-Tribromo-1,2,3,4-tetrahydro-1,4-methano-naphthalene (**10**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:5); mp 188–189 °C, lit.[6g] mp 192–192.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29–7.17 (AA′BB′ system, 4H, H_{aryl}), 4.32 (d, $J_{2,9}=J_{3,9}=1.3$ Hz, 2H, H_2 and H_3), 4.27 (qui, $J_{1,9}=J_{4,9}=J_{3,9}=J_{2,9}=1.3$ Hz, 1H, H_9), 3.91 (d, $J_{1,9}=J_{4,9}=1.3$ Hz, 2H, H_1 and H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 130.4, 124.0, 59.7, 55.1, 52.6. IR: (KBr, cm^{-1}): 3081, 3030, 3004, 2978, 1447, 1268, 1243, 1217, 1166, 885, 834, 731. Anal. Calcd for $C_{11}H_9Br_3$: C, 34.69; H, 2.38; found: C, 34.32; H, 2.25. MS (EI, 70 eV) *m/z* 384/382/380/378 (M^+, 6), 303/301/299 (M^+-Br, 100), 221/219 (M^+-2Br, 56), 141 (M^+-3Br, 76), 115 (indenyl cation, 71), 109 (13), 70 (21%).

3.4.3. Bromination of monobromide 8 at 77 °C. The reaction was carried out by the general procedure using monobromide **8** (1.0 g, 4.52 mmol), bromine (868 mg, 5.42 mmol) and CCl_4 (20 mL). After 5 min, the solvent was evaporated and the residue was purified by column chromatography on silica gel (100 g) using *n*-hexane as eluent. The first fraction was tribromide **11** (983 mg, 57%).

anti-(1S(R),2R(S),3R(S),4R(S))-2,3,9-Tribromo-1,2,3,4-tetrahydro-1,4-methano-naphthalene (**11**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:3); mp 88–89 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.26 (m, 4H, H_{aryl}), 5.18 (t, $J_{2,3}=J_{3,4}=4.0$ Hz, 1H, H_3), 4.25 (m, 1H, H_9), 3.74 (m, 2H, H_1 and H_2), 3.68 (m, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 142.1, 130.4, 129.9, 126.4, 123.0, 60.1, 58.9, 56.1, 55.8, 54.8. IR: (KBr, cm^{-1}): 3081, 3055, 3030, 3004, 2978, 1472, 1294, 1268, 1242, 885, 731. Anal. Calcd for $C_{11}H_9Br_3$: C, 34.69; H, 2.38; found: C, 34.84; H, 2.35. MS (EI, 70 eV) *m/z* 384/382/380/378 (M^+, 11), 303/301/299 (M^+-Br, 100), 222/220 (M^+-2Br, 63), 141/139 (M^+-3Br, 75), 115 (indenyl cation, 58), 89 (8), 70 (16%).

The second fraction was tribromide **12**. (260 mg, 15%) *anti*-(1*S*(*R*),2*S*(*R*),3*R*(*S*),4*R*(*S*))-2,3,9-tribromo-1,2,3,4-tetrahydro-1,4-methano-naphthalene (**12**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:3); mp 160 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.30 (AA′BB′ system, 4H, H_{aryl}), 5.18 (AA′ part of AA′XX′ system, 2H, H_2 and H_3), 4.26 (t, $J_{1,9}=J_{4,9}=$ 1.8 Hz, 1H, H_9), 3.72 (XX′ part of AA′BB′ system, 2H, H_1 and H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 129.6, 126.4,

58.8, 57.3, 52.2. IR: (KBr, cm^{-1}): 3081, 3055, 3029, 2979, 1472, 1243, 1217, 834, 757, 731. Anal. Calcd for $C_{11}H_9Br_3$: C, 34.69; H, 2.38; found: C, 34.75; H, 2.30. MS (EI, 70 eV) *m/z* 384/382/380/378 (M^+, 8), 303/301/299 (M^+-Br, 100), 222/220 (M^+-2Br, 65), 141/139 (M^+-3Br, 76), 115 (indenyl cation, 98), 109 (17), 70 (21%).

The third fraction was identified as tribromide **10** (431 mg, 25%). For the spectral data see above.

3.4.4. Synthesis of (1*S*(*R*),4*R*(*S*),9*R*(*S*))-2,9-dibromo-1,4-dihydro-1,4-methano-naphthalene (13). The reaction was carried out by the general procedure using a mixture of tribromides **10–12** (0.58 g, 1.52 mmol), potassium *t*-butoxide (200 mg, 1.78 mmol) and THF (25 mL). The dibromide **13** (401 mg, 88%) was obtained as the sole product. Colorless crystals from CH_2Cl_2/*n*-pentane (1:6); mp 60 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.38–7.07 (m, 4H, H_{aryl}), 6.68 (bd, $J_{3,4}=3.2$ Hz, 1H, H_3), 4.42 (m, 1H, H_9), 4.11 (m, 1H, H_4), 3.99 (m, 1H, H_1). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5, 147.1, 138.5, 135.6, 128.6, 128.0, 124.5, 124.1, 74.6, 66.8, 60.5. IR: (KBr, cm^{-1}): 3081, 3055, 3004, 2979, 1574, 1446, 1268, 1217, 1140, 1013, 808, 757. Anal. Calcd for $C_{11}H_8Br_2$: C, 44.04; H, 2.69; found: C, 43.77; H, 2.66. MS (EI, 70 eV) *m/z* 302/300/298 (M^+, 11), 221/219 (M^+-Br, 100), 140/139 (M^+-2Br, 73), 115 (indenyl cation, 16), 70 (22%).

3.4.5. Bromination of dibromide 13 at −10 °C. The reaction was carried out by the general procedure using dibromide **13** (1.36 g, 4.52 mmol), bromine (730 mg, 4.57 mmol) and $CHCl_3$ (10 mL). After 10 min, the solvent was evaporated. The ^1H NMR spectrum of the mixture shows the formation of the tetrabromides, **16** (48%), **14** (24%), **17** (11%), **15** (2%) (for the isolation and characterization of these compounds see below).

3.4.6. Bromination of dibromide 13 at 77 °C. The reaction was carried out by the general procedure using dibromide **13** (1.36 g, 4.52 mmol), bromine (868 mg, 5.42 mmol) and CCl_4 (20 mL). After 5 min, the solvent was evaporated and the residue was purified by column chromatography on silica gel (100 g) using *n*-hexane as eluent. The first fraction was tetrabromide **14** (1.31 g, 63%).

(1S(R),3S(R),4R(S),9R(S))-2,2,3,9-Tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**14**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:4); mp 149–150 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.36–7.24 (m, 4H, H_{aryl}), 5.64 (d, $J_{3,4}=3.3$ Hz, 1H, H_3), 4.48 (t, $J_{1,9}=J_{4,9}=1.5$ Hz, 1H, H_9), 4.26 (m, 1H, H_1), 3.66 (m, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.4, 140.5, 130.3, 129.7, 126.6, 126.4, 67.6, 65.3, 62.9, 60.9, 53.8. IR: (KBr, cm^{-1}): 3081, 3055, 3030, 3004, 2978, 1472, 1242, 1217, 936, 834, 732. Anal. Calcd for $C_{11}H_8Br_4$: C, 28.73; H, 1.75; found: C, 29.06; H, 1.76. MS (EI, 70 eV) *m/z* 383/381/379/378 (M^+-Br, 3), 300/299/297 (M^+-2Br, 15), 221/219 (M^+-3Br, 16), 140/139 (100), 115 (indenyl cation, 38), 70 (67%).

The second fraction was identified as tetrabromide **15**. (707 mg, 34%): (1*S*(*R*),3*R*(*S*),4*R*(*S*),9*R*(*S*))-2,2,3,9-tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**15**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:4); mp 117 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.44–7.23 (m, 4H, H_{aryl}), 4.65 (d, $J_{3,9}=2.0$ Hz, 1H, H_3), 4.44 (m, 1H, H_9), 4.31 (m, 1H, H_1), 3.84 (m, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.3, 144.4, 130.8, 129.8, 127.1, 123.4, 68.5, 66.4, 63.7, 60.7, 53.6. IR: (KBr, cm^{-1}): 3081, 3055, 3030, 3004, 2979, 1447, 1268, 1243, 1217, 1191, 910, 834. Anal. Calcd for $C_{11}H_8Br_4$: C, 28.73; H, 1.75; found: C, 28.40; H, 1.70. MS (EI, 70 eV) *m/z* 464//462/460/458/456 (M^+, 3), 383/381/379/377 (M^+-Br, 69), 302/300/299 (M^+-2Br, 51), 221/219 (M^+-3Br, 74), 140/139 (100), 115 (indenyl cation, 63), 70 (81%).

3.4.7. Elimination of the mixture of tetrabromides 14 and 15. The reaction was carried out by the general procedure using the mixture of tetrabromides **14** and **15** (0.70 g, 1.52 mmol), potassium *t*-butoxide (200 mg, 1.78 mmol) and THF (25 mL). The tribromide **22** (524 mg, 91%) was obtained as the sole product.

anti-(1S(R),4R(S))-2,3,9-Tribromo-1,4-dihydro-1,4-methanonaphthalene (**22**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:3); mp 158–159 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.41–7.09 (AA′BB′ system, 4H, H_{aryl}), 4.49 (t, $J_{1(4),9}=1.8$ Hz, 1H, H_9), 4.08 (d, $J_{1(4),9}=1.8$ Hz, 2H, H_1 and H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.8, 132.92, 128.9, 124.5, 72.7, 67.1. IR: (KBr, cm^{-1}): 3081, 3055, 3030, 2978, 1574, 1447, 1243, 1217, 1140, 1064, 1038, 1013, 834, 783, 757. Anal. Calcd for $C_{11}H_7Br_3$: C, 34.87; H, 1.86; found: C, 35.10; H, 1.88. MS (EI, 70 eV) *m/z* 382/380/378/376 (M^+, 33), 301/299/297 (M^+-Br, 100), 219/218/217 (M^+-2Br, 14), 140/139 (72), 110 (17), 69 (30%).

3.4.8. Synthesis of (1*R*(*S*),4*R*(*S*),9*R*(*S*))-1,9-dibromo-1,4-dihydro-1,4-methano-naphthalene (25). The reaction was carried out by the general procedure using tribromide **24**[4a] (0.58 g, 1.52 mmol), potassium *t*-butoxide (250 mg, 2.2 mmol) and THF (25 mL). The dibromide **25** was obtained as the sole product (410 mg, 90%). Pale yellow wax. ^1H NMR (200 MHz, $CDCl_3$) δ 7.47–7.07 (m, 4H, H_{aryl}), 6.72 (dd, $J_{2,3}=5.4$ Hz, $J_{3,4}=3.4$ Hz, 1H, H_3), 4.50 (m, 1H, H_9), 4.15 (m, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.3, 147.0, 144.7, 141.9, 128.8, 128.5, 124.5, 123.9, 83.8, 72.1, 57.8. Anal. Calcd for $C_{11}H_8Br_2$: C, 44.04; H, 2.69; found: C, 43.79; H, 2.64.

3.4.9. Bromination of dibromide 25 at −10 °C. The reaction was carried out by the general procedure using dibromide **25** (1.36 g, 4.52 mmol), bromine (730 mg, 4.57 mmol) and $CHCl_3$ (10 mL). After 5 min, the solvent was evaporated and tetrabromide **17** was obtained (2.04 g, 98%).

(1R(S),2S(R),3S(R),4S(R),9R(S))-1,2,3,9-Tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**17**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:2); mp 186–187 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 7.51–7.24 (m, 4H, H_{aryl}), 4.41 (m, 1H), 4.38 (m, 1H), 4.35 (m, 1H), 3.99 (m, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 143.4, 131.6, 131.0, 124.94, 123.4, 69.8, 62.5, 59.2, 57.2, 52.0. IR: (KBr, cm^{-1}): 3030, 3004, 2979, 1472, 1447, 1294, 1268, 1243, 1166, 987, 910, 757. Anal. Calcd for $C_{11}H_8Br_4$: C, 28.73; H, 1.75; found: C, 28.53; H, 1.69. MS (EI, 70 eV) *m/z* 464/462/460/468/456 (M^+, 1), 383/381/379/377 (M^+-Br, 100), 302/

300/298 (M^+-2Br, 74), 221/219 (M^+-3Br, 92), 195/193 (34), 140/139 (86), 109 (26), 70 (59%).

3.4.10. Bromination of dibromide 25 at 77 °C. The reaction was carried out by the general procedure using dibromide **25** (2.0 g, 6.66 mmol), bromine (1.28 g, 8.00 mmol) and CCl_4 (20 mL). After 5 min, the solvent was evaporated and the residue was crystallized from CH_2Cl_2/*n*-pentane (1:2) and tribromide pure **16** was obtained (700 mg). After filtration of **16**, the residue was chromatographed on silica gel (100 g) using *n*-hexane as eluent. The first fraction was a mixture of tetrabromides **26** and **16**. The solution allowed to stand for a while in refrigerator. The formed crystals were identified as tetrabromide **26**. After filtration of crystals, the residue was analyzed by NMR.

Tetrabromide **26** (600 mg, crystals, 750 mg mixture, total 44% yield).

Tetrabromide **16** (700 mg, crystals, 555 mg mixture, total 41% yield).

The second fraction (from silica gel column) was identified as tetrabromide **17** (61 mg, 2%).

(1R(S),2S(R),3R(S),4S(R),9R(S))-1,2,3,9-Tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**26**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:3); mp 65 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.32 (m, 4H, H_{aryl}), 5.26 (t, $J_{2,3}=J_{3,4}=4.0$ Hz, 1H, H_3), 4.37 (dd, $J_{4,9}=1.9$ Hz, $J_{2,9}=1.7$ Hz 1H, H_9), 3.89 (dd, $J_{3,4}=4.0$ Hz, $J_{4,9}=1.9$ Hz, 1H, H_4), 3.73 (dd, $J_{2,3}=4.0$ Hz, $J_{2,9}=1.7$ Hz, 1H, H_2). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.5, 140.8, 131.0 (2C), 126.4, 123.8, 69.5, 63.8, 61.0, 57.6, 56.1. IR: (KBr, cm^{-1}): 3081, 3055, 3004, 2978, 1472, 1447, 1421, 1293, 1268, 1243, 1217, 1191, 1140, 1013, 859, 757, 731. Anal. Calcd for $C_{11}H_8Br_4$: C, 28.73; H, 1.75; found: C, 28.96; H, 1.75. MS (EI, 70 eV) *m/z* 464/462/460/458/456 (M^+, 3), 383/381/379/377 (M^+-Br, 100), 302/300/298 (M^+-2Br, 82), 221/219 (M^+-3Br, 91), 193/191 (21), 140/139 (86), 114 (indenyl cation, 19), 70 (85%).

(1R(S),2R(S),3S(R),4S(R),9R(S))-1,2,3,9-Tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**16**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:3); mp 173–174 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51–7.24 (m, 4H, H_{aryl}), 5.12 (d, $J_{2,3}=4.2$ Hz, 1H, H_2), 4.37 (t, $J_{4,9}=J_{3,9}=1.9$ Hz, 1H, H_9), 3.80 (m, 2H, H_3 and H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 142.0, 131.5, 130.6, 127.5, 122.7, 71,7, 62.8, 62.5, 56.3, 53.6. IR: (KBr, cm^{-1}): 3055, 3030, 2979, 1447, 1421, 1396, 1294, 1268, 1242, 1165, 1140, 1012, 859. Anal. Calcd for $C_{11}H_8Br_4$: C, 28.73; H, 1.75; found: C, 29.02; H, 1.76. MS (EI, 70 eV) *m/z* 464/462/460/458/456 (M^+, 4), 383/381/379/377 (M^+-Br, 100), 302/300/298 (M^+-2Br, 71), 221/219 (M^+-3Br, 87), 193/191 (29), 140/139 (85), 114 (indenyl cation, 19), 70 (75%).

3.4.11. Elimination of the mixture of tetrabromides 17 and 16. The reaction was carried out by the general procedure using, either a the mixture of tetrabromides **17** and **16** or pure isomers (0.70 g, 1.52 mmol), potassium *t*-butoxide (250 mg, 2.23 mmol) and THF (25 mL). The tribromide **29** (519 mg, 90%) was obtained.

(1R(S),4R(S),9R(S))-1,2,9-Tribromo-1,4-dihydro-1,4-methanonaphthalene (**29**). Colorless crystals from CH_2Cl_2/*n*-pentane (1:4); mp 115–116 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.15 (m, 4H, H_{aryl}), 6.80 (dd, $J_{3,4}=3.6$ Hz, $J_{3,9}=1.2$ Hz, 1H, H_3), 4.60 (dd, $J_{4,9}=1.8$ Hz, $J_{3,9}=1.2$ Hz, 1H, H_9), 4.21 (dd, $J_{3,4}=3.6$ Hz, $J_{4,9}=1.8$ Hz, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.1, 145.7, 139.2, 138.2, 129.6, 128.7, 124.9, 123.8, 81.6, 77.8, 58.1. IR: (KBr, cm^{-1}): 3080, 3055, 3030, 3029, 2979, 1574, 1523, 1447, 1243, 1217, 1063, 1012. Anal. Calcd for $C_{11}H_7Br_3$: C, 34.87; H, 1.86; found: C, 34.81; H, 1.83. MS (EI, 70 eV) *m/z* 382/380/378/376 (M^+,12), 301/299/297 (M^+-Br, 100), 220/219/218/217 (M^+-3Br, 10), 193/191 (10), 140/139 (79), 69 (26%).

3.4.12. Elimination of tetrabromide 26. The reaction was carried out by the general procedure using, tetrabromide **26** (0.70 g, 1.52 mmol), potassium *t*-butoxide (250 mg, 2.23 mmol) and THF (25 mL). After the usual work up, the residue was purified by column chromatography on silica gel (100 g) using *n*-hexane as eluent. The first fraction was tribromide **30** (374 mg, 65%).

(1R(S),4R(S),9R(S))-1,3,9-Tribromo-1,4-dihydro-1,4-methanonaphthalene (**30**). Pale yellow wax. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47–711 (m, 4H, H_{aryl}), 6.55 (m, 1H, H_2), 4.54 (m, 1H, H_9), 4.06 (m, 1H, H_4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.0, 144.9, 141.1, 135.5, 129.3, 129.1, 124.4, 124.2, 71.5, 65.3. IR: (KBr, cm^{-1}): 3080, 3055, 3030, 3004, 2978, 2928, 1574, 1243, 1191, 936, 757. Anal. Calcd for $C_{11}H_7Br_3$: C, 34.87; H, 1.86; found: C, 34.76; H, 1.82.

The second fraction was tribromide **29** (144 mg, 25%).

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An iodoacetamide-based free radical cyclisation approach to the 7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one (paullone) system

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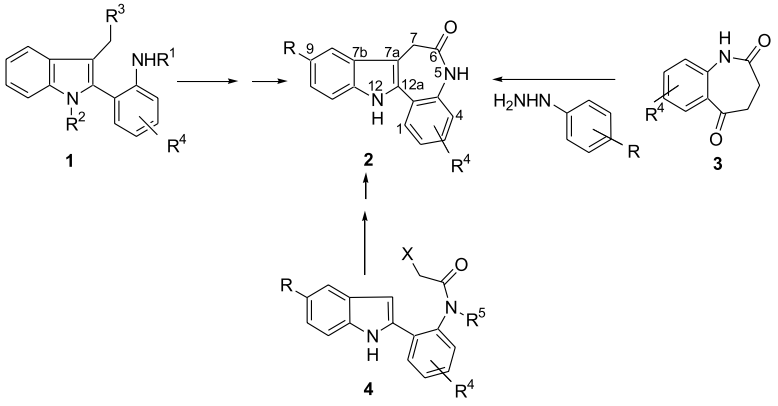
Abstract—A potentially versatile route to 2-(2-aminoaryl)indoles is described based on a palladium-mediated cyclisation of *N*-substituted indoles, together with free radical cyclisation of their *N*-benzyliodoacetamide derivatives to the 7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one system.

1. Introduction

Paullones, named after the late Ken Paull, are of considerable interest as potent cyclin dependent kinase (CDK) inhibitors[1–3] and as inhibitors of glycogen synthase kinase 3.[4] As a result, these 7,12-dihydro-indolo[3,2-*d*][1]-benzazepin-6(5*H*)-ones, also exhibit in vitro antitumour activity and alsterpaullone (**2**, R=NO_2, R^4=H) was reported[5] to be in preclinical development as a potential anti-tumour agent; kenpaullone (**2**, R=Br, R^4=H) is in clinical trials.[6] While structure-CDK inhibitory activity relationships have been undertaken,[2] further, studies in this area and the correlation between such inhibitory activity and anti-tumour activity are still being pursued. In this context, and as part of a programme aimed at the development of synthetic methods for indole-fused 7- and 8-membered ring[7] systems, we were attracted to these paullones and the possible development of a different synthetic approach to them and their derivatives.

Previous approaches to the paullone system (**2**) have been based on two strategies. The first, involves an indole precursor (**1**) and completion of the 7-membered ring by N5–C6 bond formation (Scheme 1). The second strategy



Scheme 1. Approaches to the synthesis of the paullones.

Keywords: Indolobenzazepinones; Iodoacetamides; Radical cyclisation; 7-Membered ring.
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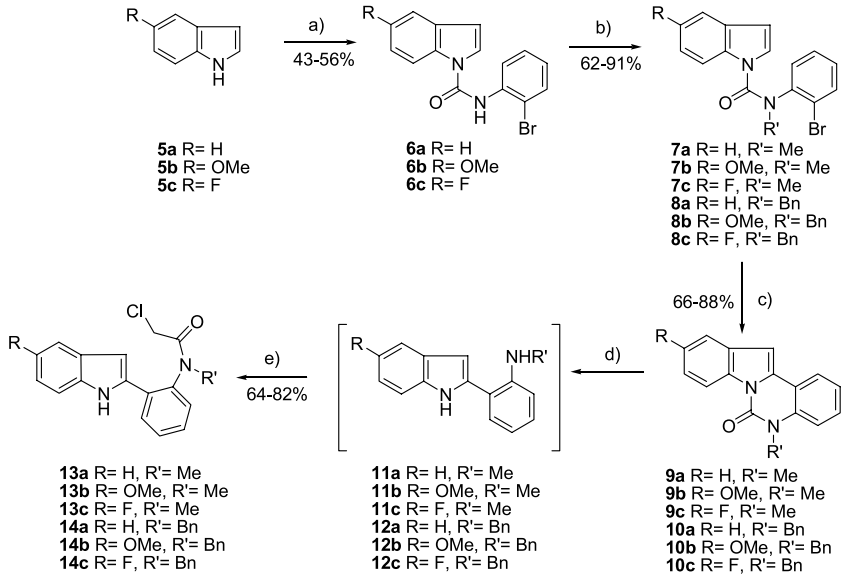


Scheme 2. (a) (i) NaH, DMF (ii) 2-BrPhNCO; (b) (i) NaH, THF (ii) R′-X; (c) $Pd(OAc)_2$, $P(Ph)_3$, $Bu_4N^+Br^-$, K_2CO_3, DMF, 120 °C; (d) 25% NaOH, EtOH; (e) $ClCH_2COCl$, K_2CO_3, THF.

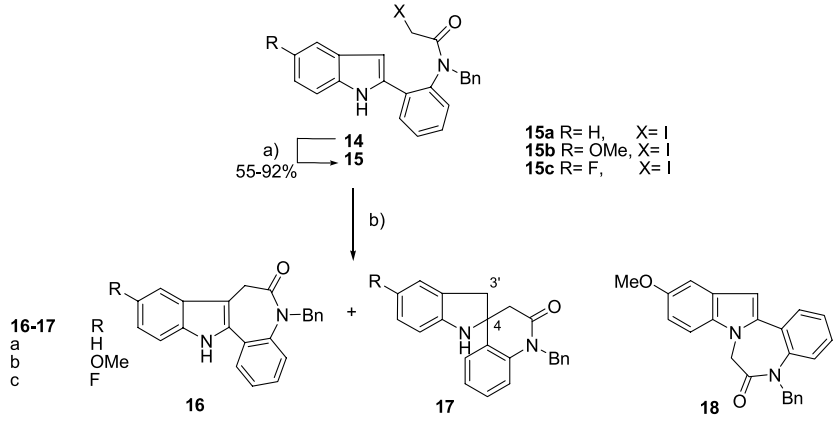
relies on a preformed 7-membered ring (**3**) and construction of the fused indole moiety by formation of the N12–C12a and C7a–C7b bonds by Fischer indolisation with phenylhydrazines (Scheme 1). Examples of the first, strategy include cyclisation[8] of (**1**, R^1=Tos, R^2=H, R^3=COOH, R^4=Et and Me) with HBr/AcOH to afford (**2**) with a 4-ethyl and 3-methyl substituent, and of (**1**, R^1=H, R^2=H, R^3=CN, R^4=H), with NaOH/MeOH/H_2O to give[9] (**2**, R=H, R^4=H) in 51% yield. In the latter case, assembly of the 2-arylindole precursor (**1**) was based on a borylation/Suzuki coupling strategy. Examples of the second paullone synthesis strategy include the preparation[10,11] of the benzazepinedione (**3**, R^4=7-I) in a few step synthesis from 5-iodoanthranilic acid and Fischer indolisation with 4-trifluoromethylphenylhydrazine to give (**2**, R=CF_3, R^4=2-I) in 50% yield from (**3**), a subsequent Heck reaction was used to prepare other substituted derivatives of (**2**).

The key benzazepinedione precursor of (**2**) has also been accessed by ring expansion of 1,4-naphthoquinone[12] or 7-methoxytetralone.[11] A new alternative approach to the paullone system and derivatives (**2**), based on a free radical cyclisation of an indole-haloacetamide precursor to form the 7-membered ring via C7–C7a bond formation, is now reported in this paper.

2. Results and discussion

The indolyl substrates (**13**, **14**) (Scheme 2) required ultimately for the radical cyclisation were prepared from the amines **11** and **12**, which in turn were accessed via a new route developed for 2-(2-aminoaryl)indoles.

This route began with reaction of the appropriate indole **5** with 2-bromophenyl isocyanate to give the ureas **6** in moderate yields, these ureas were then *N*-alkylated to give the *N*-methyl (**7**) or *N*-benzyl (**8**) derivatives, respectively. Palladium-mediated cyclisation of **7** and **8** then gave the indolo[1,2-*c*]quinazolinones **9** and **10** in good yields.[13] The loss of the indole H-2 proton and the bromo substituent in these products was apparent from the ^1H and ^{13}C NMR spectra, together with the mass spectrometric data. Base-induced hydrolysis and decarboxylation of the quinazoline ring then afforded the intermediate amines **11** and **12**. These amines tended to be unstable[14] and contained coloured



Scheme 3. (a) NaI, CH_3CN; (b) Bu_3SnH, AIBN, boiling solvents.

Table 1. Free radical cyclisation of iodoacetamides **15a–c** with Bu_3SnH/AIBN in boiling solvents

Entry	Substrate	mmol	Solvent	Product (%)	
				16	**17**
1	**15a**	0.13	Toluene	25	—
2	**15a**	0.36	Toluene	—	10
3	**15a**	0.15	Toluene	8	13
4	**15a**	0.13	Mesitylene	52	—
5	**15b**	0.11	Mesitylene	25[a]	—
6	**15c**	0.10	Mesitylene	45	—

[a] Compound **18** was also isolated in 30% yield.

contaminants so they were acylated directly by reaction with chloroacetyl chloride to give the chloroacetamides **13** and **14**, which could be readily purified. In the ^{1}H NMR spectra of **13** and **14**, a diagnostic signal appeared at δ 6.40–6.64 for the H-3 proton, while the methylene of the chloroacetmide was ascribed to a signal at ca. δ 3.8.

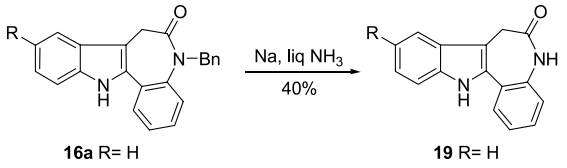
In order to increase the proportion of *cisoid* indoacetamide rotamer required for cyclisation,[7] only the more bulky *N*-benzyliodoacetamides **15** were subjected to free radical cyclisation. Thus, conversion of the chloroacetamides **14** to the iodoacetamides **15** by iodide exchange followed by reaction with tributyltin hydride (Bu_3SnH) in the presence of azobisisobutyronitrile (AIBN) then afforded the *N*-benzylated paullone derivatives **16a–c**. The product of spirocyclisation **17a**, a new heterocyclic derivative, was also observed (Scheme 3) in the case of the reaction of **15a** in toluene.

At higher reaction temperatures (boiling mesitylene), yields of the required paullone system were significantly increased. In the case of **15b**, reaction in mesitylene also afforded some of the indolo[1,2-*d*][1,4]benzodiazepine-6-one **18**, from nucleophilic cyclisation at the indolic nitrogen. Other related compounds containing this ring system have been reported previously (Table 1).[15]

In the ^{1}H NMR spectra of **16a–c**, no signal which could be attributed to an indolic H-3 proton was seen, while a new quaternary carbon signal appeared downfield at ca. δ 110–111 in the ^{13}C NMR spectra. With the spiro derivative **17a**, both the ^{1}H and ^{13}C NMR spectra had signals consistent with the presence of three methylene groups, while the molecular formula was supported by the high resolution mass spectrum.

Mechanistically, the paullone system **16** could arise either via a 7-*endo-trig* addition of the amidomethyl radical (from the *cisoid* iodoacetamide), followed by oxidation, or by 6-*exo-trig* addition at the indole C-2 position followed by rearrangement and oxidation. Rearrangement could compete with hydrogen atom abstraction by the indolic C-3 radical which would afford **17**. A related 5-*exo-trig* spirocyclisation of a carbon centred radical onto the C-2 position of indole, resulting in dearomatisation after hydrogen abstraction, has been reported recently.[16]

In order to access the paullone system itself in which the lactam moiety is not *N*-substituted, the feasibility of chemoselective *N*-debenzylation with sodium in liquid ammonia was investigated in the case of **16a**. Reaction of



Scheme 4.

16a with sodium in liquid ammonia at −60 °C for 10 min afforded the known[17] paullone **19** (R=H) in 40% yield (Scheme 4).

3. Conclusions

It has been shown that free radical cyclisation of indolyl iodoacetamide derivatives is a viable new approach to the pharmacologically significant paullone ring system. New palladium-mediated methodology for the construction of 2-(2-aminoaryl)indoles has also been developed as part of this work. Both this methodology and free radical cyclisation have the potential for synthesis of a variety of new paullone analogues and derivatives.

4. Experimental

4.1. General

Melting points were determined using a Reichert hot-stage melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Unity-300 Fourier transform NMR spectrometer. Unless otherwise stated, the spectra were obtained from solutions in $CDCl_3$ and referenced to TMS (proton) and chloroform mid-line (77 ppm) (carbon). Chemical shifts are reported in parts per million (δ). Where on aromatic proton signal appeared as a triplet of doublets (td) in the ^{1}H NMR, the first, coupling constant given is for both identical *ortho* couplings. MS were obtained using a Shimadzu QP-5000 spectrometer. High resolution MS were run using a Fisons/VG Autospec-TOF spectrometer. IR spectra were recorded on a BOMEM MB-100 FTIR. TLC and preparative thin layer chromatography was performed using Merck silica gel 60 F_{254}. All chromatographic solvent proportions are volume to volume. Column chromatography (silica gel; flash column or normal column) was performed using Merck Kieselgel 60 (0.063–0.200 nm particle size). Solvents were removed under reduced pressure by a Büchi rotary evaporator, and organic solvent extracts were dried with anhydrous Na_2SO_4. Solvent mixtures are v/v ratios.

Petroleum spirit (pet. spirit) refers to the boiling point range 40–60 °C.

4.2. General procedure for the preparation of ureas (6a–c)

To a stirred suspension of sodium hydride (NaH) (60% dispersion in mineral oil, 1.1 equiv) in dry DMF (10 mL) at 0–5 °C was added a solution of the indole **5** (1.0 equiv) in dry DMF (40 mL) under a nitrogen atmosphere and the solution was then stirred at rt for 2 h. An excess of DMF (20 mL) was then added and the mixture was cooled to −60 °C. 2-Bromophenyl isocyanate (1.2 equiv) in DMF (20 mL) was slowly added and the reaction mixture was stirred at rt overnight. Solvent was evaporated and DCM (30 mL) was added and then washed with water several times. The organic layer was dried, concentrated and chromatographed on a column by elution with 10% EtOAc/pet. spirit.

4.2.1. *N*-(2-Bromophenyl)-1*H*-indole-1-carboxamide (6a). Following the general procedure, NaH (0.12 g, 2.80 mmol) was reacted with a solution of **5a** (0.30 g, 2.56 mmol) and 2-bromophenyl isocyanate (0.40 mL, 3.28 mmol) to give **6a** (0.35 g, 43%) as white needles; mp 120–121 °C; IR (KBr) ν_{max}: 3258 (NH), 1676 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.73 (dd, $J=3.3$, 0.9 Hz, 1H, H-3), 7.05 (td, $J=7.2$, 1.5 Hz, 1H, H-4′), 7.29 (dd, $J=8.1$, 0.9 Hz, 1H, H-4), 7.36 (m, 2H, H-6 and H-5′), 7.60 (m, 3H, H-2, H-5 and H-3′), 8.00 (br s, 1H, NH), 8.25 (d, $J=8.1$ Hz, 1H, H-7), 8.36 (dd, $J=8.7$, 1.5 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 108.6 (C-3), 113.9 (C-2′), 114.5 (C-7), 121.7 (C-6′), 121.8 (ArC–H), 123.1 (C-4), 124.1 (ArC–H), 125.0 (ArC–H), 125.6 (C-4′), 128.9 (ArC–H), 130.7 (C-3a), 132.6 (ArC–H), 135.4 (C-7a), 135.5 (C-1′), 149.2 (CO); CI-MS *m/z* 315 ([M+H; $^{79}Br]^+$, 100%), 317 ([M+H; $^{81}Br]^+$, 99%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{15}H_{12}N_2O^{79}Br$: 315.0133, found: 315.0091.

4.2.2. *N*-(2-Bromophenyl)-5-methoxy-1*H*-indole-1-carboxamide (6b). Following the general procedure, NaH (0.18 g, 4.49 mmol) was reacted with a solution of **5b** (0.60 g, 4.08 mmol) and 2-bromophenyl isocyanate (0.64 mL, 5.22 mmol) to give **6b** (0.80 g, 56%) as white needles; mp 117–118 °C; ^1H NMR ($CDCl_3$) δ 3.82 (s, 3H, OCH_3), 6.67 (dd, $J=3.6$, 0.9 Hz, 1H, H-3), 7.02 (dd, $J=9.0$, 2.4 Hz, 1H, H-6), 7.04 (td, $J=7.8$, 2.4 Hz, 1H, H-4′), 7.10 (d, $J=3.0$ Hz, 1H, H-4), 7.40 (td, $J=8.7$, 1.5 Hz, 1H, H-5′), 7.58 (d, $J=3.9$ Hz, 1H, H-2), 7.60 (dd, $J=8.4$, 1.2 Hz, 1H, H-3′), 7.95 (br s, 1H, NH), 8.14 (d, $J=9.0$ Hz, 1H, H-7), 8.35 (dd, $J=8.1$, 1.5 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 55.7 (OCH_3), 103.8 (C-4), 108.2 (C-3), 113.6 (C-2′), 113.7 (C-6), 115.1 (C-7), 121.5 (C-6′), 124.3 (C-2), 125.3 (C-4′), 128.7 (C-5′), 130.3 (C-3a), 131.3 (C-7a), 132.4 (C-3′), 135.3 (C-1′), 148.7 (*C*OCH_3), 156.0 (CO); CI-MS *m/z* 345 ([M+H; $^{79}Br]^+$, 100%), 347 ([M+H; $^{81}Br]^+$, 99%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{16}H_{14}N_2O_2^{81}Br$: 347.0218, found: 347.0204.

4.2.3. *N*-(2-Bromophenyl)-5-fluoro-1*H*-indole-1-carboxamide (6c). Following the general procedure, NaH (0.39 g, 8.14 mmol) was reacted with a solution of **5c** (1.0 g, 7.40 mmol) and 2-bromophenyl isocyanate (1.20 mL, 9.62 mmol) to give **6c** (1.3 g, 53%) as white needles; mp 108–110 °C; ^1H NMR ($CDCl_3$) δ 6.70 (d, $J=3.6$ Hz, 1H, H-3), 7.06 (t, $J=8.4$ Hz, 1H, H-4′), 7.14 (td, $J=9.0$, 2.7 Hz, 1H, H-6), 7.29 (dd, $J=9.0$, 2.4 Hz, 1H, H-4), 7.41 (t, $J=7.8$ Hz, 1H, H-5′), 7.63 (m, 2H, H-2 and H-3′), 7.93 (br s, 1H, NH), 8.23 (dd, $J=9.0$, 4.5 Hz, 1H, H-7), 8.34 (d, $J=8.1$ Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 106.9 (d, $J=23.8$ Hz, ^{13}C–^{19}F, C4–F), 108.5 (d, $J=3.9$ Hz, ^{13}C–^{19}F, C3–F), 113.0 (d, $J=25.2$ Hz, ^{13}C–^{19}F, C6–F), 114.0 (C-2′), 115.8 (d, $J=9.2$ Hz, ^{13}C–^{19}F, C7–F), 121.8 (C-6′), 125.1 (C-2), 125.7 (C-4′), 128.9 (C-5′), 131.3 (C-3a), 132.1 (C-7a), 132.6 (C-3′), 135.3 (C-1′), 148.9 (CO), 159.5 (d, $J=238.0$ Hz, ^{13}C–^{19}F, C5–F); CI-MS *m/z* 333 ([M+H; $^{79}Br]^+$, 100%), 335 ([M+H; $^{81}Br]^+$, 95%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{15}H_{11}N_2O_2F^{81}Br$: 335.0018, found: 335.0006.

4.3. General procedure for the *N*-methylation of the ureas (6a–c)

To a stirred suspension of sodium hydride (NaH) (60% dispersion in mineral oil, 1.1 equiv) in dry THF (10 mL) at 0–5 °C was added a solution of the urea **6a–c** (1.0 equiv) in dry THF (40 mL) under a nitrogen atmosphere. The solution was stirred at rt for 2 h., and a solution of methyl iodide (2.5 equiv) in THF (10 mL) was added, and then the reaction mixture was stirred at rt overnight. THF was evaporated and water (15 mL) was added and the mixture extracted with DCM (3×20 mL). The combined DCM extracts were dried, concentrated and chromatographed on a column by elution with 10% EtOAc/pet. spirit.

4.3.1. *N*-(2-Bromophenyl)-*N*-methyl-1*H*-indole-1-carboxamide (7a). NaH (60% dispersion in mineral oil, 13 mg, 0.33 mmol) was reacted with a solution of **6a** (94 mg, 0.30 mmol) and methyl iodide (38 μL, 0.60 mmol) to give **7a** (73 mg, 76%) as a white solid; mp 136–137 °C; IR (KBr) ν_{max}: 1688 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_3), 6.25 (dd, $J=3.3$, 0.9 Hz, 1H, H-3), 6.79 (d, $J=3.9$ Hz, 1H, H-2), 7.08–7.13 (m, 2H, H-5 and H-5′), 7.15–7.25 (m, 2H, H-3′ and H-4′), 7.32 (td, $J=7.8$, 1.2 Hz, 1H, H-6), 7.46 (dd, $J=7.8$, 0.6 Hz, 1H, H-4), 7.61 (dd, $J=7.8$, 1.8 Hz, 1H, H-6′), 8.11 (dd, $J=7.2$, 0.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.0 (CH_3), 106.5 (C-3), 114.9 (C-7), 120.8 (C-4), 122.3 (C-2′), 122.5 (C-5), 124.1 (C-6), 125.9 (C-2), 129.1 (C-3′), 129.3 (C-4′), 129.36 (C-5′), 129.4 (C-3a), 134.4 (C-6′), 136.6 (C-7a), 143.6 (C-1′), 154.1 (CO); CI-MS *m/z* 329 ([M+H; $^{79}Br]^+$, 100%), 331 ([M+H; $^{81}Br]^+$, 97%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{16}H_{14}N_2O^{79}Br$: 329.0289, found: 329.0283.

4.3.2. *N*-(2-Bromophenyl)-5-methoxy-*N*-methyl-1*H*-indole-1-carboxamide (7b). NaH (60% dispersion in mineral oil, 34 mg, 0.70 mmol) was reacted with a solution of **6b** (0.22 g, 0.64 mmol) and methyl iodide (0.10 mL, 1.60 mmol) to give **7b** (0.20, 88%) as a white solid; mp 130–132 °C; IR (KBr) ν_{max}: 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 6.18 (dd, $J=3.6$, 0.6 Hz, 1H, H-3), 6.74 (d, $J=3.6$ Hz, 1H, H-2), 6.92 (s, 1H, H-4), 6.93 (dd, $J=8.4$, 2.4 Hz, 1H, H-6), 7.07–7.12 (m, 2H, H-4′ and H-5′), 7.19 (dd, $J=6.9$, 1.2 Hz, 1H, H-3′), 7.60 (dd, $J=7.8$, 1.8 Hz, 1H, H-6′), 8.00 (dd, $J=8.7$, 0.6 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.0 (CH_3), 55.9 (OCH_3), 103.1 (C-4), 106.4 (C-3), 113.3 (C-6), 115.7 (C-7),

122.3 (C-2′), 126.5 (C-2), 129.1, 129.2 (C-4′ or C-5′), 129.4 (C-3′), 130.1 (C-3a), 131.4 (C-7a), 134.4 (C-6′), 143.7 (C-1′), 154.1 (*C*OCH$_3$), 155.9 (CO); CI-MS *m/z* 359 ([M+H; ^{79}Br]$^+$, 100%), 361 ([M+H; ^{81}Br]$^+$, 95%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{17}H_{15}N_2O_2^{79}Br$: 359.0395, found: 359.0391.

4.3.3. *N*-(2-Bromophenyl)-5-fluoro-*N*-methyl-1*H*-indole-1-carboxamide (7c). NaH (60% dispersion in mineral oil, 40 mg, 0.83 mmol) was reacted with a solution of **6c** (0.25 g, 0.75 mmol) and methyl iodide (0.12 mL, 1.88 mmol) to give **7c** (0.18 g, 69%) as a white solid; mp 133–134 °C; IR (KBr) ν_{max}: 1689 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H, CH_3), 6.22 (dd, J=3.6, 0.6 Hz, 1H, H-3), 6.83 (d, J=3.3 Hz, 1H, H-2), 7.04 (td, J=9.0, 2.7 Hz, 1H, H-6), 7.09–7.16 (m, 3H, Ar), 7.24 (td, J=6.9, 1.5 Hz, 1H, H-5′), 7.61 (td, J=7.5, 0.6 Hz, 1H, H-6′), 8.06 (dd, J=8.7, 4.2 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 39.1 (CH_3), 106.1 (d, J=23.6 Hz, ^{13}C–^{19}F, C6–F), 106.3 (d, J=3.9 Hz, ^{13}C–^{19}F, C3–F), 112.4 (d, J=25.2 Hz, ^{13}C–^{19}F, C4–F), 115.9 (d, J=9.2 Hz, ^{13}C–^{19}F, C7–F), 122.4 (C-2′), 127.5 (C-2), 129.1, 129.4, 129.45 (all ArC–H), 130.1 (d, J=10.3 Hz, ^{13}C–^{19}F, C3a–F), 133.0 (C-7a), 134.5 (C-6′), 143.4 (C-1′), 155.8 (d, J=286.3 Hz, ^{13}C–^{19}F, C5–F), 160.9 (CO); CI-MS *m/z* 347 ([M+H; ^{79}Br]$^+$, 100%), 349 ([M+H; ^{81}Br]$^+$, 95%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{16}H_{13}N_2O_2F^{79}Br$: 347.0195, found: 347.0194.

4.4. General procedure for the *N*-benzylation of the ureas (6a–c)

To a suspension of NaH (ca. 50% dispersion in mineral oil, 1.3 equiv) in dry DMF (10 mL) at 0 °C was added a solution of the urea **6a–c** (1.0 equiv) in DMF (30 mL) followed by addition of a catalytic amount of *tert*-butylammonium iodide. After 30 min, a solution of benzyl bromide (1.5 equiv) in DMF (20 mL) was added and the reaction mixture was stirred for 16 h at rt. The DMF was then evaporated, DCM (20 mL) was added to the residue and the solution washed with water several times. The DCM phase was dried, concentrated and subjected to flash column chromatography (silica gel, 10% EtOAc/pet. spirit).

4.4.1. *N*-Benzyl-*N*-(2-bromophenyl)-1*H*-indole-1-carboxamide (8a). A suspension of NaH (ca. 50% dispersion in mineral oil, 88 mg, 1.80 mmol) was reacted with a solution of **6a** (0.44 g, 1.40 mmol), *tert*-butylammonium iodide (7 mg) and benzyl bromide (0.26 mL, 2.10 mmol) to give **8a** (0.35 g, 62%) as a while solid; mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 4.63 (br s, 1H, C*H*H), 5.38 (br s, 1H, CH*H*), 6.21 (d, J=3.9 Hz, 1H, H-3), 6.74 (m, 1H, H-3′), 6.80 (d, J=3.6 Hz, 1H, H-2), 7.00–7.04 (m, 2H, H-4′ and H-5′), 7.14 (td, J=7.5, 0.6 Hz, 1H, H-5), 7.20–7.27 (m, 3H, H-6, H-3″ and H-5″), 7.30–7.34 (m, 3H, H-2″, H-4″ and H-6″), 7.42 (dd, J=7.5, 0.3 Hz, 1H, H-4), 7.53 (m, 1H, H-6′), 8.11 (d, J=8.4 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 54.3 (CH_2), 106.5 (C-3), 115.1 (C-7), 120.9 (C-4), 122.6 (C-5), 123.0 (C-2′), 124.1 (C-6), 125.9 (C-2), 128.1 (C-4″), 128.7 (C-3″ and C-5″), 128.9, 129.3 (C-4′ and C-5′), 129.4 (C-3a), 129.7 (C-2″ and C-6″), 130.7 (C-3′), 134.4 (C-6′), 136.5 (C-7a), 136.8 (C-1″), 141.4 (C-1′), 153.9 (CO); EI-MS *m/z* 404 ([M; ^{79}Br]$^+$, 49%), 406 ([M; ^{81}Br]$^+$, 52%); HREI-MS *m/z* calcd for [M]$^+$ $C_{22}H_{17}N_2O^{79}Br$: 404.0524, found: 404.0525.

4.4.2. *N*-Benzyl-*N*-(2-bromophenyl)-5-methoxy-1*H*-indole-1-carboxamide (8b). A suspension of NaH (ca. 50% dispersion in mineral oil, 44 mg, 0.91 mmol) was reacted with a solution of **6b** (0.24 g, 0.70 mmol), *tert*-butylammonium iodide (3.5 mg) and benzyl bromide (0.13 mL, 1.05 mmol) to give **8b** (0.25 g, 81%) as a while solid; mp 117–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.79 (s, 3H, CH_3), 4.66 (br s, 1H, C*H*H), 5.34 (br s, 1H, CH*H*), 6.08 (dd, J=3.5 Hz, 1H, H-3), 6.69–6.71 (m, 2H, H-2 and Ar), 6.82 (s, 1H, H-4), 6.83 (dd, J=9.0, 2.5 Hz, 1H, H-6), 6.95–6.98 (m, 2H, H-5′ and Ar), 7.17–7.19 (m, 3H, H-3″, H-5″ and Ar), 7.24 (dd, J=6.5, 2.5 Hz, 2H, H-2″ and H-6″), 7.46 (dd, J=6.5, 2.5 Hz, 1H, H-6′), 7.94 (d, J=9.0 Hz, 1H, H-7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 54.0 (CH_2), 55.6 (CH_3), 102.8 (C-4), 106.1 (C-3), 113.0 (C-6), 115.6 (C-7), 122.6 (C-2′), 126.1 (C-2), 127.7 (ArC–H), 128.3 (C-3″ and C-5″), 128.4, 128.8, 129.3 (all ArC–H), 129.8 (C-3a), 130.3 (C-2″ and C-6″), 131.3 (C-7a), 134.0 (C-6′), 136.2 (C-1″), 141.3 (C-1′), 153.5 (CO), 155.6 (*C*OCH$_3$); CI-MS *m/z* 335 ([M+H; ^{79}Br]$^+$, 100%), 337 ([M+H; ^{81}Br]$^+$, 95%); HRCI-MS *m/z* calcd for [M+H]$^+$ $C_{23}H_{20}N_2O_2^{81}Br$: 437.0688, found: 437.0669.

4.4.3. *N*-Benzyl-*N*-(2-bromophenyl)-5-fluoro-1*H*-indole-1-carboxamide (8c). A suspension of NaH (ca. 50% dispersion in mineral oil, 44 mg, 0.91 mmol) was reacted with a solution of **6c** (0.23 g, 0.70 mmol), *tert*-butylammonium iodide (3.5 mg) and benzyl bromide (0.13 mL, 1.05 mmol) to give **8c** (0.27 g, 91%) as a while solid; mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 4.64 (br s, 1H, C*H*H), 5.36 (br s, 1H, CH*H*), 6.14 (d, J=3.6 Hz, 1H, H-3), 6.77 (m, 1H, H-3′), 6.80 (d, J=3.6 Hz, 1H, H-2), 6.94–7.06 (m, 4H, Ar), 7.20–7.25 (m, 3H, H-3″, H-5″ and Ar), 7.29–7.32 (m, 2H, H-2″ and H-6″), 7.50 (m, 1H, H-6′), 8.05 (d, J=9.0, 4.5 Hz, 1H, H-7); ^{13}C NMR ($CDCl_3$) δ 54.4 (CH_2), 106.11 (d, J=20.0 Hz, ^{13}C–^{19}F, C6–F), 106.3 (C-3), 112.1 (d, J=25.2 Hz, ^{13}C–^{19}F, C4–F), 116.1 (d, J=9.2 Hz, ^{13}C–^{19}F, C7–F), 113.0 (C-2′), 127.4 (C-2), 128.2 (ArC–H), 128.7 (C-3″ and C-5″), 129.0 (ArC–H), 129.4 (ArC–H), 129.7 (C-2″ and C-6″), 130.1 (d, J=9.8 Hz, ^{13}C–^{19}F, C3a–F), 130.6 (ArC–H), 133.2 (C-7a), 134.4 (C-6′), 136.4 (C-1″), 154.0 (C-1′), 159.9 (d, J=285.0 Hz ^{13}C–^{19}F, C5–F), 171.8 (CO); CI-MS *m/z* 423 ([M+H; ^{79}Br]$^+$, 100%), 425 ([M+H; ^{81}Br]$^+$, 95%); HREI-MS *m/z* calcd for [M]$^+$ $C_{22}H_{16}N_2OF^{81}Br$: 424.0410, found: 424.0415.

4.5. Palladium cyclisation procedure

A mixture of the urea **7–8** (1 equiv), palladium acetate ($Pd(OAc)_2$) (0.33 equiv), triphenylphosphine ($P(Ph)_3$) (0.2 equiv), *tert*-butylammonium bromide (Bu_4NBr) (1 equiv) and K_2CO_3 (2 equiv) in dry DMF (13 mL) was heated at 120 °C under an Ar atmosphere for 3 h. After cooling, the DMF was evaporated, and then DCM (15 mL) was added and washed with water several times. The DCM layer was washed with brine, dried, evaporated and subjected to flash column chromography (silica gel, 9:1 pet. spirit/EtOAc).

4.5.1. 5-Methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (9a). Treatment of **7a** (50 mg, 0.15 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), $P(Ph)_3$ (8 mg, 0.03 mmol), Bu_4NBr (49 mg, 0.15 mmol) and K_2CO_3 (42 mg, 0.30 mmol) gave **9a**

(31 mg, 87%) as white needles; mp 181–183 °C; IR (KBr) ν_{max}: 1677 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H, CH_3), 7.03 (d, J=0.6 Hz, 1H, H-12), 7.22 (td, J=8.1, 0.9 Hz, 1H, H-3), 7.24 (td, J=7.5, 0.9 Hz, 1H, H-10), 7.35–7.46 (m, 3H, H-2, H-9, H-10), 7.68 (ddd, J=6.0, 2.1, 0.9 Hz, 1H, H-1), 7.92 (dd, J=8.1, 1.8 Hz, 1H, H-4), 8.69 (ddd, J=5.7, 2.7, 0.9 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 98.3 (C-12), 114.5 (C-8), 115.6 (C-12b), 116.5 (C-11), 120.3 (C-9), 123.3, 123.7, 123.9 (all ArC–H), 124.0 (C-1), 129.4 (C-3), 130.1 (C-12a), 133.3 (C-11a), 134.6 (C-4a), 135.8 (C-7a), 148.2 (CO); CI-MS m/z 249 ($[M+H]^+$, 100%); HRCI-MS m/z calcd for $[M+H]^+$ $C_{16}H_{13}N_2O$: 249.1028, found: 249.1021.

4.5.2. 10-Methoxy-5-methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (9b). Treatment of **7b** (0.15 g, 0.42 mmol), $Pd(OAc)_2$ (40 mg, 0.18 mmol), $P(Ph)_3$ (22 mg, 0.08 mmol), Bu_4NBr (0.14 g, 0.42 mmol) and K_2CO_3 (0.12 g, 0.84 mmol) gave the title compound **9b** (65 mg, 55%); mp 146–147 °C; ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 6.99 (s, 1H, H-12), 7.00 (dd, J=9.0, 2.7 Hz, 1H, H-9), 7.12 (d, J=2.7 Hz, 1H, H-11), 7.22–7.28 (m, 2H, H-1 and H-3), 7.44 (td, J=7.5, 1.5 Hz, 1H, H-2), 7.94 (dd, J=7.8, 1.5 Hz, 1H, H-4), 8.57 (d, J=9.3 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 55.8 (OCH_3), 98.1 (C-12), 102.2 (C-8), 113.0 (C-11), 114.5 (C-9), 115.5 (C-12b), 117.3, 123.3, 123.9 (all ArC–H), 129.4 (C-12a), 131.0 (C-11a), 133.9 (C-4a), 135.8 (C-7a), 148.2 (CO), 156.8 ($COCH_3$); CI-MS m/z 279 ($[M+H]^+$, 100%); HRCI-MS m/z calcd for $[M+H]^+$ $C_{17}H_{15}N_2O_2$: 279.1134, found: 279.1122.

4.5.3. 10-Fluoro-5-methylindolo[1,2-*c*]quinazolin-6(5*H*)-one (9c). Treatment of **7c** (0.10 g, 0.29 mmol), $Pd(OAc)_2$ (24 mg, 0.10 mmol), $P(Ph)_3$ (16 mg, 0.06 mmol), Bu_4NBr (49 mg, 0.15 mmol), and K_2CO_3 (42 mg, 0.30 mmol) gave compound **9c** (59 mg, 76%) as offwhite needles; mp 188–189 °C; ^1H NMR ($CDCl_3$) δ 3.66 (s, 3H, CH_3), 6.89 (s, 1H, H-12), 7.05 (td, J=9.0, 2.7 Hz, 1H, H-9), 7.16 (d, J=8.7 Hz, 1H, H-1), 7.19–7.25 (m, 2H, H-2 and H-11), 7.41 (ddd, J=8.1, 7.5, 1.2 Hz, 1H, H-3), 7.84 (dd, J=7.8, 1.2 Hz, 1H, H-4), 8.57 (dd, J=9.0, 5.1 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 30.4 (CH_3), 97.8 (d, J=4.3 Hz, ^{13}C–^{19}F, C12–F), 105.3 (d, J=23.8 Hz, ^{13}C–^{19}F, C11–F), 111.6 (d, J=25.2 Hz, ^{13}C–^{19}F, C9–F), 114.5 (C-4), 115.0 (C-12b), 117.5 (d, J=9.4 Hz, ^{13}C–^{19}F, C8–F), 123.7 (C-2), 124.0 (C-3), 129.7 (C-1), 130.8 (C-11a), 131.0 (C-12a), 134.7 (C-4a), 135.8 (C-7a), 147.8 (CO), 160.0 (d, J=238.5 Hz, ^{13}C–^{19}F, C10–F); CI-MS m/z 267 ($[M+H]^+$, 100%); HRCI-MS m/z calcd for $[M+H]^+$ $C_{17}H_{12}N_2OF$: 267.0934, found: 267.0926.

4.5.4. 5-Benzylindolo[1,2-*c*]quinazolin-6(5*H*)-one (10a). Treatment of **8a** (0.30 g, 0.74 mmol), $Pd(OAc)_2$ (66 mg, 0.30 mmol), $P(Ph)_3$ (52 mg, 0.20 mmol), Bu_4NBr (0.31 g, 0.95 mmol), and K_2CO_3 (0.27 g, 1.92 mmol) gave **10a** (0.16 g, 66%) as a white solid; mp 141–143 °C; IR (KBr) ν_{max}: 1685 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 2H, CH_2), 7.12–7.16 (m, 2H, H-12 and H-9), 7.22 (td, J=7.5 Hz, 1H, H-10), 7.26–7.34 (m, 6H, Ar), 7.39–7.41 (m, 2H, Ar), 7.72 (dd, J=7.5, 2.1 Hz, 1H, H-11), 7.98 (d, J=7.5 Hz, 1H, H-4), 8.74 (dd, J=8.0, 1.5 Hz, 1H, H-8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.0 (CH_2), 98.6 (C-12), 115.5 (C-9), 115.9 (C-12b), 116.7 (C-8), 120.3 (C-11), 123.5, 123.9, 124.10 (all ArC–H), 124.12 (C-4), 126.7 (C-2′ and C-6′), 127.7 (ArC–H), 129.1 (C-3′ and C-5′), 129.4 (ArC–H), 130.2 (C-11a), 133.4 (C-12a), 134.7 (C-4a), 135.2 (C-7a), 136.5 (C-1′), 148.6 (CO); EI-MS m/z 324 ($[M]^+$, 50%); HREI-MS m/z calcd for $[M]^+$ $C_{22}H_{16}N_2O$: 324.1263, found: 324.1261.

4.5.5. 5-Benzyl-10-methoxyindolo[1,2-*c*]quinazolin-6(5*H*)-one (10b). Treatment of **8b** (0.25 g, 0.57 mmol), $Pd(OAc)_2$ (52 mg, 0.23 mmol), $P(Ph)_3$ (39 mg, 0.15 mmol), Bu_4NBr (0.24 g, 0.73 mmol) and K_2CO_3 (0.20 g, 1.48 mmol) gave compound **10b** (0.18 g, 89%) as a while solid; mp 214–215 °C; ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 7.02 (dd, J=9.0, 2.7 Hz, 1H, H-9), 7.03 (s, 1H, H-12), 7.14 (s, 1H, H-11), 7.15 (t, J=9.3 Hz, 1H, H-3), 7.02–7.33 (m, 7H, Ar), 7.94 (dd, J=7.8, 1.2 Hz, 1H, H-4), 8.61 (d, J=9.0 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 47.0 (CH_2), 55.9 (CH_3), 98.3 (C-12), 102.3 (C-8), 113.1 (C-11), 115.5 (C-9), 115.7 (C-12b), 117.4, 123.4, 124.0 (all ArC–H), 126.7 (C-2′ and C-6′), 127.7 (ArC–H), 129.1 (C-3′and C-5′), 129.3 (ArC–H), 129.5 (C-11a), 131.2 (C-12a), 134.0 (C-4a), 135.1 (C-7a), 136.5 (C-1′), 148.0 (CO), 157.0 ($COCH_3$); CI-MS m/z 355 ($[M+H]^+$, 100%); HREI-MS m/z calcd for $[M]^+$ $C_{23}H_{18}N_2O_2$: 354.1368, found: 354.1386.

4.5.6. 5-Benzyl-10-fluoroindolo[1,2-*c*]quinazolin-6(5*H*)-one (10c). Treatment of **8c** (0.27 g, 0.64 mmol), $Pd(OAc)_2$ (58 mg, 0.26 mmol), $P(Ph)_3$ (45 mg, 0.0917 mmol), Bu_4NBr (0.26 g, 0.82 mmol) and K_2CO_3 (0.22 g, 1.66 mmol) gave the title compound **10c** (0.15 g, 69%) as a white solid; mp 185–186 °C; ^1H NMR ($CDCl_3$) δ 5.45 (s, 2H, CH_2), 6.97 (s, 1H, H-12), 7.03 (td, J=9.0, 2.4 Hz, 1H, H-9), 7.07 (d, J=8.1 Hz, 1H, H-1), 7.15 (t, J=8.1 Hz, 1H, H-3), 7.18–7.28 (m, 7H, Ar), 7.87 (d, J=7.5 Hz, 1H, H-4), 8.59 (dd, J=9.0, 5.1 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$), δ 47.1 (CH_2), 98.2 (d, J=4.6 Hz, ^{13}C–^{19}F, C12–F), 105.5 (d, J=23.8 Hz, ^{13}C–^{19}F, C11–F), 111.8 (d, J=25.2 Hz, ^{13}C–^{19}F, C9–F), 115.4 (C-12b), 115.6 (C-4), 117.8 (d, J=9.4 Hz, ^{13}C–^{19}F, C8–F), 123.6 (ArC–H), 124.2 (ArC–H), 126.7 (C-2′ and C-6′), 127.8 (ArC–H), 129.2 (C-3′ and C-5′), 129.8 (ArC–H), 131.1 (C-11a), 131.2 (C-12a), 134.9 (C-4a), 135.2 (C-7a), 136.3 (C-1′), 148.4 (CO), 160.2 (d, J=238.5 Hz, ^{13}C–^{19}F, C10–F); CI-MS m/z 343 ($[M+H]^+$, 100%); HRCI-MS m/z calcd for $[M+H]^+$ $C_{22}H_{16}N_2OF$: 343.1247, found: 343.1249.

4.6. General procedure for preparation of the chloroacetamides (13a–c)

Compounds **9**–**10** were heated at reflux in 25% NaOH and EtOH for 24 h. or until no starting material was observed (determined by TLC; silica gel, 10% EtOAc/pet. spirit). The EtOH was then evaporated and water (15 mL) was added and extracted with DCM (3×15 mL). The organic layer was separated, dried and concentrated to give a blue solid. The solid was dried on a high pressure vacuum pump for 2–3 h and then K_2CO_3 (3.6 equiv) and dry THF (10 mL) were added. The reaction mixture was stirred at 0–5 °C under a N_2 atmosphere for 30 min and a solution of chloroacetyl chloride (2.5 equiv) in THF (3 mL) was then added and the mixture stirred overnight at rt. The THF was

evaporated to dryness and DCM (20 mL) was then added. The reaction mixture was washed with water (3×10 mL) and the DCM layer was separated, dried and concentrated. The residue was subjected to preparative thin layer chromatography (silica gel, 10% EtOAc/pet. spirit) to isolate the chloroacetamide products.

4.6.1. *N*-(2-(1*H*-Indol-2-yl)phenyl)-*N*-methylchloro acetamide (13a). A mixture of **9a** (26 mg, 0.10 mmol), 25% NaOH (6 mL) and EtOH (10 mL) was heated at reflux for 24 h. After work up, the crude solid product was then reacted with K_2CO_3 (50 mg, 0.43 mmol) and chloroacetyl chloride (23 μL, 0.30 mmol) to give the title compound **13a** (21 mg, 70%) as a yellow solid; mp 84–86 °C; IR (KBr) ν_{max}: 3310 (NH), 1655 (C=O), 747 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.16 (s, 3H, CH_3), 3.81 (d, J=12.6 Hz, 1H, C*H*HCl), 3.87 (d, J=14.1 Hz, 1H, CH*H*Cl), 6.56 (s, 1H, H-3), 7.08 (t, J=7.8 Hz, 1H, H-5), 7.18–7.59 (m, 2H, Ar), 7.30–7.39 (m, 2H, Ar), 7.45 (t, J=7.8 Hz, 1H, H-5′), 7.58 (d, J=7.8 Hz, 1H, H-4), 7.69 (d, J=8.1 Hz, 1H, H-6′), 8.37 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 37.2 (CH_3), 41.9 (CH_2Cl), 103.6 (C-3), 111.3 (C-7), 120.8 (C-5), 121.3 (C-4), 123.5 (C-6), 129.0 (C-3a), 129.35, 129.4, 129.65, 129.7 (all ArC–H), 132.0 (C-1′), 133.5 (C-2), 135.0 (C-7a), 140.0 (C-2′), 167.3 (CO); CI-MS *m/z* 299 ([M+H; $^{35}Cl]^+$, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{17}H_{16}N_2O_2^{35}Cl$: 299.0951, found: 299.0945.

4.6.2. *N*-(2-(5-Methoxy-1*H*-indol-2-yl)phenyl)-*N*-methyl chloroacetamide (13b). A mixture of **9b** (35 mg, 0.14 mmol), 25% NaOH (10 mL) and EtOH (25 mL) was heated at reflux for 48 h. After work up, the crude solid product was then reacted with K_2CO_3 (0.10 g, 0.74 mmol) and chloroacetyl chloride (42 μL, 0.53 mmol) to give the title compound **13b** (29 mg, 64%) as a yellow solid; mp 88–89 °C; IR (KBr) ν_{max}: 3314 (NH), 1653 (C=O), 763 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 3.89 (d, J=5.1 Hz, 2H, CH_2Cl), 6.40 (d, J=1.2 Hz, 1H, H-3), 6.90 (dd, J=8.7, 2.4 Hz, 1H, H-6), 7.08 (d, J=2.1 Hz, 1H, H-4), 7.30 (d, J=8.7 Hz, 2H, H-7 and H-3′), 7.41 (td, J=8.1, 0.9 Hz, 1H, H-4′), 7.49 (t, J=7.8 Hz, 1H, H-5′), 7.73 (d, J=7.8 Hz, 1H, H-6′), 8.32 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ 37.3 (CH_3), 41.9 (CH_2Cl), 55.8 (OCH_3), 102.2 (C-3), 103.2 (C-4), 112.3 (C-6), 113.9 (C-7), 128.4 (C-3′), 129.1 (C-3a), 129.4, 129.7, 129.8 (all ArC–H), 130.7 (C-1′), 132.0 (C-2), 135.0 (C-7a), 139.0 (C-2′), 155.0 (*C*OCH_3), 167.0 (CO); CI-MS *m/z* 329 ([M+H; $^{35}Cl]^+$, 32%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{18}H_{18}N_2O_2^{37}Cl$: 331.1027, found: 331.1032.

4.6.3. *N*-(2-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-methyl chloroacetamide (13c). A mixture of **9c** (50 mg, 0.19 mmol), 25% NaOH (10 mL) and EtOH (25 mL) was heated at reflux for 24 h. After work up, the solid product was then reacted with K_2CO_3 (0.10 g, 0.74 mmol) and chloroacetyl chloride (42 μL, 0.53 mmol) to give the title compound **13c** (46 mg, 79%) as a yellow solid; mp 175–176 °C; IR (KBr) ν_{max}: 3315 (NH), 1654 (C=O), 764 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.21 (s, 3H, NCH_3), 3.84 (d, J=12.9 Hz, 1H, C*H*HCl), 3.91 (d, J=12.9 Hz, 1H, CH*H*Cl), 6.64 (d, J=2.1 Hz, 1H, H-3), 6.95 (td, J=9.3, 2.4 Hz, 1H, H-6), 7.23–7.35 (m, 3H, Ar), 7.40–7.51 (m, 2H, Ar), 7.76 (dd, J=7.5, 1.5 Hz, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 37.3 (CH_3), 41.9 (CH_2Cl), 103.3 (d, J=4.6 Hz, ^{13}C–^{19}F, C3–F), 105.9 (d, J=23.5 Hz, ^{13}C–^{19}F, C4–F), 111.9 (d, J=26.3 Hz, ^{13}C–^{19}F, C6–F), 112.2 (d, J=9.5 Hz, ^{13}C–^{19}F, C7–F), 129.2 (d, J=10.4 Hz, ^{13}C–^{19}F, C3a–F), 129.5 (C-6′), 129.6, 129.7, 129.8 (all ArC–H), 130.2 (C-1′), 133.7 (C-2), 135.0 (C-7a), 139.2 (C-2′), 158.4 (d, J=234.2 Hz, ^{13}C–^{19}F, C5–F), 167.2 (CO); CI-MS *m/z* 317 ([M+H; $^{35}Cl]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{17}H_{14}N_2OF^{35}Cl$: 316.0779, found: 316.0778.

4.6.4. *N*-(2-(1*H*-Indol-2-yl)phenyl)-*N*-benzylchloro acetamide (14a). A mixture of **10a** (0.14 g, 0.10 mmol), 25% NaOH (27 mL) and EtOH (40 mL) was heated at reflux for 24 h. After work up, the crude solid product was then reacted with K_2CO_3 (0.23 g, 1.7 mmol) and chloroacetyl chloride (96 μL, 1.20 mmol) to give the chloroacetamide **14a** (0.20 g, 79%) as a yellow solid; mp 139–141 °C; IR (KBr) ν_{max}: 3311 (NH), 1638 (C=O), 745 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (d, J=13.5 Hz, 1H, C*H*HCl), 3.87 (d, J=13.2 Hz, 1H, C*H*HCl), 4.58 (d, J=14.1 Hz, 1H, C*H*H), 5.17 (d, J=13.8 Hz, 1H, CH*H*), 6.69 (d, J=2.4 Hz, 1H, H-3), 7.03 (dd, J=8.1, 1.2 Hz, 1H, H-3′), 7.12 (m, 2H, Ar), 7.19 (m, 2H, Ar), 7.25 (m, 2H, Ar), 7.31 (m, 3H, Ar), 7.46 (td, J=7.8, 1.5 Hz, 1H, H-5′), 7.61 (dd, J=7.5, 0.9 Hz, 1H, H-4), 7.71 (dd, J=7.8, 1.2 Hz, 1H, H-6′), 7.86 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.4 (CH_2Cl), 53.7 (CH_2), 103.6 (C-3), 111.4 (C-7), 120.6 (C-4), 121.1 (C-6), 123.3 (C-5), 128.5 (C-3′), 128.6 (C-3a), 129.0 (C-2″ and C-6″), 129.1 (ArC–H), 129.6 (C-3″ and C-5″), 129.9 (ArC–H), 130.1 (ArC–H), 131.0 (C-1′), 133.6 (C-2), 136.2 (C-7a), 136.8 (C-2′), 137.2 (C-1″), 166.8 (CO); CI-MS *m/z* 375 ([M+H; $^{35}Cl]^+$, 11%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{23}H_{20}N_2O^{35}Cl$: 375.1264, found: 375.1267.

4.6.5. *N*-(2-(5-Methoxy-1*H*-indol-2-yl)phenyl)-*N*-benzyl-chloroacetamide (14b). A mixture of **10b** (0.12 g, 0.22 mmol), 25% NaOH (30 mL) and EtOH (40 mL) was heated at reflux for 48 h. After work up, the solid product was then reacted with K_2CO_3 (0.11 g, 0.79 mmol) and chloroacetyl chloride (71 μL, 0.55 mmol) to give the title compound **14b** (97 mg, 71%) as a yellow solid; mp 109–111 °C; IR (KBr) ν_{max}: 3297 (NH), 1655 (C=O), 736 (C–Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (d, J=13.5 Hz, 1H, C*H*HCl), 3.84 (s, 3H, CH_3), 3.88 (d, J=13.8 Hz, 1H, CH*H*Cl), 4.44 (d, J=13.8 Hz, 1H, C*H*H), 5.26 (d, J=14.1 Hz, 1H, CH*H*), 6.61 (dd, J=2.1, 0.9 Hz, 1H, H-3), 6.85 (dd, J=9.0, 2.4 Hz, 1H, H-6), 6.97 (dd, J=8.1, 1.5 Hz, 1H, H-3′), 7.06 (d, J=2.4 Hz, 1H, H-4), 7.13 (d, J=8.7 Hz, 1H, H-7), 7.21–7.32 (m, 6H, Ar), 7.42 (td, J=7.5, 1.2 Hz, 1H, H-5′), 7.73 (dd, J=7.8, 1.3 Hz, 1H, H-6′), 8.17 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.5 (CH_2Cl), 53.4 (CH_2), 56.0 (OCH_3), 102.2 (C-3), 103.2 (C-4), 112.3 (C-6), 114.0 (C-7), 128.5 (ArC–H), 128.9 (ArC–H), 129.0 (C-2″ and C-6″), 129.2 (C-3a), 129.6 (ArC–H), 129.8 (ArC–H), 129.9 (C-3″ and C-5″), 130.7 (C-6′), 130.9 (C-1′), 132.2 (C-2), 134.1 (C-7a), 136.3 (C-2′), 137.0 (C-1″), 154.7 (*C*OCH_3), 167.0 (CO); CI-MS *m/z* 405 ([M+H; $^{35}Cl]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{24}H_{21}N_2O_2^{37}Cl$: 406.1262, found: 406.1208.

4.6.6. *N*-(2-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-benzyl chloroacetamide (14c). A mixture of **10c** (0.13 g, 0.38 mmol), 25% NaOH (30 mL) and EtOH (40 mL) was

heated at reflux for 24 h. After work up, the solid product was then reacted with K_2CO_3 (0.19 g, 1.37 mmol) and chloroacetyl chloride (76 μL, 0.53 mmol) to give the title compound **14c** (90 mg, 82%) as a yellow solid; mp 202–203 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (d, J=13.2 Hz, 1H, C*H*HCl), 3.82 (d, J=13.2 Hz, 1H, CH*H*Cl), 4.64 (d, J=14.1 Hz, 1H, C*H*H), 5.07 (d, J=13.8 Hz, 1H, CH*H*), 6.60 (d, J=1.8 Hz, 1H, H-3), 6.91 (td, J=9.0, 2.4 Hz, 1H, H-6), 7.04–7.08 (m, 2H, H-4 and Ar), 7.19–7.31 (m, 6H, Ar), 7.34 (td, J=7.8, 1.8 Hz, 1H, H-4′), 7.44 (td, J=7.2, 0.9 Hz, 1H, H-5′), 7.68 (dd, J=7.8, 1.5 Hz, 1H, H-6′), 7.77 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 42.3 (CH_2Cl), 53.8 (CH_2), 103.6 (d, J=4.8 Hz, ^{13}C–^{19}F, C3–F), 105.7 (d, J=23.5 Hz, ^{13}C–^{19}F, C4–F), 111.8 (d, J=26.3 Hz, ^{13}C–^{19}F, C6–F), 112.2 (d, J=9.8 Hz, ^{13}C–^{19}F, C7–F), 128.7 (ArC–H), 129.2 (C-2″ and C-6″), 129.5 (ArC–H), 129.7 (ArC–H), 130.1 (C-3″ and C-5″), 130.1 (ArC–H), 130.6 (ArC–H), 130.8 (C-1′), 133.4 (C-2), 135.4 (C-7a), 136.1 (C-2′), 137.3 (C-1″), 159.2 (d, J=240.0 Hz, ^{13}C–^{19}F, C5–F), 166.9 (CO); CI-MS m/z 393 ([M+H; ^{35}Cl]$^+$, 100%); HREI-MS m/z calcd for [M]$^+$ $C_{23}H_{18}N_2OF^{35}Cl$: 392.1092, found: 392.1091.

4.7. General procedure for the preparation of iodoacetamides (15a–c)

A solution of **14a–c** (1.0 equiv) in acetonitrile containing sodium iodide (10 equiv) was heated at reflux for 2 h. The solution was then cooled and water (10 mL) was added. The solution was then extracted with EtOAc (3×20 mL). The organic extracts were combined, dried, concentrated, and chromatographed on a column by elution with DCM to isolate the iodoacetamide products. The following compounds were prepared by this method.

4.7.1. *N*-(2-(1*H*-Indol-2-yl)phenyl)-*N*-benzyl iodoacetamide (15a). Treatment of **14a** (0.20 g, 0.53 mmol) with NaI (0.78 g, 5.30 mmol) in acetonitrile (20 mL) at reflux gave **15a** as a yellow solid (0.23 g, 92%); mp 168–169 °C; IR (KBr) ν_{max}: 3312 (NH), 1637 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 (d, J=9.9 Hz, 1H, C*H*HI), 3.59 (d, J=10.2 Hz, 1H, C*H*HI), 4.54 (d, J=13.8 Hz, 1H, C*H*H), 5.17 (d, J=13.8 Hz, 1H, CH*H*), 6.69 (dd, J=2.1, 0.6 Hz, 1H, H-3), 7.12 (m, 2H, Ar), 7.20 (m, 2H, Ar), 7.25 (m, 2H, Ar), 7.32 (m, 4H, Ar), 7.44 (td, J=8.7, 1.2 Hz, 1H, H-5′), 7.61 (d, J=7.8 Hz, 1H, H-4), 7.70 (dd, J=7.8, 1.2 Hz, 1H, H-6′), 7.94 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ −1.9 (CH_2I), 53.3 (CH_2), 103.3 (C-3), 111.1 (C-7), 120.3 (C-4), 120.8 (C-6), 122.9 (C-5), 128.2 (C-3′), 128.4 (C-3a), 128.7 (ArC–H), 128.8 (C-2″ and C-6″), 129.2 (ArC–H), 129.6 (C-3″ and C-5″), 129.7 (ArC–H), 130.1 (ArC–H), 130.5 (C-1′), 133.4 (C-2), 136.2 (C-7a), 136.6 (C-2′), 137.8 (C-1″), 168.1 (CO); CI-MS m/z 467 ([M+H]$^+$, 15%); HRCI-MS m/z calcd for [M+H]$^+$ $C_{23}H_{20}N_2OI$: 467.0620, found 467.0612.

4.7.2. *N*-(2-(5-Methoxy-1*H*-indol-2-yl)phenyl)-*N*-benzyl iodoacetamide (15b). Treatment of **14b** (97 mg, 0.24 mmol) with NaI (0.36 g, 2.40 mmol) in acetonitrile (20 mL) at reflux gave **15b** as a yellow solid (65 mg, 55%); mp 138–139 °C; IR (KBr) ν_{max}: 3311 (NH), 1637 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.50 (d, J=9.9 Hz, 1H, C*H*HI), 3.56 (d, J=10.2 Hz, 1H, CH*H*I), 3.84 (s, 3H, OCH_3), 4.44 (d, J=13.8 Hz, 1H, C*H*H), 5.24 (d, J=13.8 Hz, 1H, CH*H*), 6.62 (d, J=2.4 Hz, 1H, H-3), 6.84 (dd, J=9.0, 2.4 Hz, 1H, H-6), 7.03–7.13 (m, 3H, Ar), 7.24–7.32 (m, 6H, Ar), 7.42 (t, J=7.5 Hz, 1H, H-5′), 7.71 (dd, J=7.8, 1.5 Hz, 1H, H-6′), 8.05 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ −1.5 (CH_2I), 53.5 (CH_2), 56.0 (OCH_3), 102.3 (C-3), 103.3 (C-4), 112.3 (C-6), 113.9 (C-7), 128.4 (ArC–H), 128.8 (ArC–H), 129.0 (C-2″ and C-6″), 129.2 (C-3a), 129.5 (ArC–H), 129.7 (ArC–H), 129.8 (C-3″ and C-5″), 130.4 (ArC–H), 130.8 (C-1′), 132.2 (C-2), 134.3 (C-7a), 136.5 (C-2′), 138.0 (C-1″), 154.7 (*C*OCH$_3$), 168.5 (CO); CI-MS m/z 497 ([M+H]$^+$, 14%); HREI-MS m/z calcd for [M]$^+$ $C_{24}H_{21}N_2O_2I$: 496.0648, found: 496.0643.

4.7.3. *N*-(2-(5-Fluoro-1*H*-indol-2-yl)phenyl)-*N*-benzyl-iodoacetamide (15c). Treatment **14c** (90 mg, 0.31 mmol) with NaI (0.46 g, 3.10 mmol) in acetonitrile (10 mL) at reflux gave the title compound **15c** (0.10 g, 68%) as a yellow solid; mp 172–173 °C; IR (KBr) ν_{max}: 3297 (NH), 1636 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (d, J=10.2 Hz, 1H, C*H*HI), 3.53 (d, J=10.2 Hz, 1H, CH*H*I), 4.62 (d, J=14.1 Hz, 1H, C*H*H), 5.11 (d, J=14.1 Hz, 1H, CH*H*), 6.63 (d, J=2.1 Hz, 1H, H-3), 6.92 (td, J=9.3, 2.7 Hz, 1H, H-6), 7.09 (dd, J=8.7, 4.5 Hz, 1H, H-7), 7.16 (dd, J=7.8, 1.2 Hz, 1H, H-3′), 7.21–7.33 (m, 6H, Ar), 7.36 (td, J=7.5, 1.5 Hz, 1H, H-4′), 7.46 (td, J=7.8, 1.5 Hz, 1H, H-5′), 7.70 (dd, J=7.8, 1.5 Hz, 1H, H-6′), 7.91 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ −1.8 (CH_2I), 53.8 (CH_2), 103.6 (d, J=5.2 Hz, ^{13}C–^{19}F, C3–F), 105.7 (d, J=23.5 Hz, ^{13}C–^{19}F, C4–F), 111.7 (d, J=26.6 Hz, ^{13}C–^{19}F, C6–F), 112.1 (d, J=9.7 Hz, ^{13}C–^{19}F, C7–F), 128.6 (ArC–H), 129.0 (d, J=10.5 Hz, ^{13}C–^{19}F, C3a–F), 129.1 (C-2″ and C-6″), 129.4 (ArC–H), 129.5 (ArC–H), 129.6 (C-3″ and C-5″), 130.2 (ArC–H), 130.3 (ArC–H), 130.6 (C-1′), 133.4 (C-2), 135.5 (C-7a), 136.3 (C-2′), 138.1 (C-1″), 158.4 (d, J=221.1 Hz, ^{13}C–^{19}F, C5–F), 168.4 (CO); CI-MS m/z 485 ([M+H]$^+$, 25%); HREI-MS m/z calcd for [M]$^+$ $C_{23}H_{18}N_2OFI$: 484.0448, found: 484.0497.

4.8. General procedure for radical cyclisation

A solution of tributyltin hydride (Bu_3SnH) (2.0 equiv) and AIBN (1.0 equiv) in an appropriate solvent (8 mM) was added dropwise to a solution of the iodoacetamide (**15a–c**) (1.0 equiv) in boiling solvent (14 mM) over 4 h, and the mixture was then heated at reflux overnight. After removal of the solvent in vacuo, diethyl ether (20 mL) and saturated potassium fluoride solution (20 mL) were added and the mixture was stirred vigorously at rt for 2–3 h. The organic layer was separated, dried, concentrated and the residue column chromatographed.

4.8.1. Radical cyclisation of 15a in toluene. Compound **15a** (60 mg, 0.13 mmol) in toluene (9 mL) was treated with Bu_3SnH (70 μL, 0.26 mmol) and AIBN (21 mg, 0.13 mmol) in toluene (33 mL). The crude material was chromatographed (hexane/AcOEt, 70:30) to give 5-benzyl-7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one **16a** (11 mg, 25%) as yellow needles; mp 214–216 °C; IR (KBr) ν_{max}: 3270 (NH), 1646 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.37 (d, J=13.5 Hz, 1H, C*H*H-7), 3.73 (d, J=14.0 Hz, 1H, C*H*H-7), 4.88 (d, J=16.0 Hz, 1H, C*H*H), 5.08 (d, J=16.0 Hz, 1H, CH*H*), 6.76 (d, J=7.0 Hz, 2H, H-2′ and H-6′), 7.00 (m, 3H, H-3′, H-4′ and H-5′), 7.11 (t, J=8.0 Hz,

1H, H-9), 7.16 (t, J=7.5 Hz, 1H, H-10), 7.21 (td, J=8.0, 1.5 Hz, 1H, H-2), 7.27 (t, J=7.5 Hz, 1H, H-3), 7.47 (m, 2H, H-4 and H-11), 7.72 (d, J=7.5 Hz, 1H, H-8), 7.75 (dd, J=8.0, 1.5 Hz, 1H, H-1), 11.62 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 35.3 (CH_2-7), 53.2 (CH_2), 110.1 (C-7a), 112.7 (C-11), 118.7 (C-8), 121.2 (C-10), 122.5 (C-9), 125.0 (C-4), 125.3 (C-7b), 126.7 (C-2), 126.8 (C-2′ and C-6′), 127.5 (C-3), 128.2 (C-1), 128.9 (C-3′ and C-5′), 130.2 (C-12b), 133.4 (C-12a), 137.0 (C-11a), 138.2 (C-4a), 138.5 (C-1′), 169.4 (CO); CI-MS m/z 339 ([M+H]$^+$, 100%); HRCI-MS m/z calcd for [M+H]$^+$ $C_{23}H_{19}N_2O$: 339.1497, found: 339.1498.

4.8.2. Radical cyclisation of 15a in de-gassed toluene. *Compound* **15a** (70 mg, 0.15 mmol) in boiling de-gassed toluene (11 mL) under an Ar atmosphere was treated with Bu_3SnH (80 μL, 0.30 mmol) and AIBN (24 mg, 0.15 mmol) in de-gassed toluene (38 mL). After work up, the residue was chromatographed on silica gel (hexane/AcOEt, 70:30). The first, fraction gave 1,2,3,4-tetrahydroquinolin-2-one-4-spiro-2′-indoline **17a** (6.4 mg, 13%) and the second fraction gave **16a** (4 mg, 8%).

Compound **17a** was obtained as a yellow solid, mp 89–91 °C; IR (KBr) ν_{max}: 3350 (NH), 1654 (C=O) cm^{-1}; ^{1}H ($CDCl_3$) δ 2.89 (d, J=15.3 Hz, 1H, C*H*H-3), 3.03 (d, J=15.9 Hz, 1H, C*H*H-3′), 3.09 (d, J=15.6 Hz, 1H, CH*H*-3), 3.31 (d, J=15.6 Hz, 1H, CH*H*-3′), 3.95 (br s, 1H, NH), 5.13 (d, J=16.2 Hz, 1H, C*H*H), 5.33 (d, J=16.2 Hz, 1H, CH*H*), 6.70 (d, J=8.1 Hz, 1H, H-7′), 6.74 (t, J=7.2 Hz, 1H, H-5′), 6.95 (d, J=8.1 Hz, 1H, H-8), 7.00 (t, J=7.8 Hz, 1H, H-6), 7.04–7.11 (m, 2H, H-10 and H-12), 7.16 (td, J=7.5, 1.2 Hz, 1H, H-7), 7.22–7.26 (m, 3H, H-2′, H-4′ and H-6′), 7.30–7–36 (m, 2H, H-3′ and H-5′), 7.54 (dd, J=7.5, 0.1 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$) δ 42.4 (CH_2-3), 44.8 (CH_2), 46.3 (CH_2-3′), 63.7 (C-4 or C-2′), 109.3 (C-7′), 116.3 (C-5′), 119.5 (C-8), 123.9 (C-6), 124.7 (C-7), 125.5 (C-5), 126.1 (C-3′), 126.8 (C-2′ and C-6′), 127.5, 128.1, 128.8 (all ArC–H), 129.0 (C-3′ and C-5′), 133.5 (C-4a), 137.0 (C-8a), 138.2 (C-1′), 149.4 (C-7a), 168.9 (CO); EI-MS m/z 340 ([M]$^+$, 100%); HRCI-MS m/z calcd for [M+H]$^+$ $C_{23}H_{21}N_2O$: 341.1654, found: 341.1638.

4.8.3. Cylisation of 15a in toluene on a larger scale. Compound **15a** (0.17 g, 0.36 mmol) in toluene (25 mL) was treated with Bu_3SnH (0.20 mL, 0.73 mmol) and AIBN (59 mg, 0.36 mmol) in toluene (92 mL). The crude product was chromatographed (hexane/AcOEt, 70:30) to give the spiro derivative **17a** (12 mg, 10%) and some unidentified compounds.

4.8.4. Cycilzation of 15a in mesitylene. Compound **15a** (60 mg, 0.13 mmol) in mesitylene (9 mL) was treated with Bu_3SnH (70 μL, 0.26 mmol) and AIBN (21 mg, 0.13 mmol) in mesitylene (30 mL). The crude product was chromatographed (hexane/AcOEt, 70:30) to give compound **16a** (23 mg, 52%).

4.8.5. Radical cyclisation of 15b. Compound **15b** (55 mg, 0.11 mmol) in mesitylene (20 mL) was treated with Bu_3SnH (59 μL, 0.22 mmol) and AIBN (18 mg, 0.11 mmol) in mesitylene (60 mL). The crude material was chromatographed on silica gel (AcOEt/pet. spirit, 9:1).

The first, fraction gave 5-benzyl-11-methoxy-5*H*-indolo[1,2-*d*][1,4]benzodiazepin-6(7*H*)-one **18** (12 mg, 30%) as a yellow solid, mp 153–154 °C; IR (KBr) ν_{max}: 1670 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H, OCH_3), 4.56 (d, J=13.0 Hz, 1H, C*H*H), 4.97 (d, J=15.0 Hz, 1H, CH*H*), 5.01 (d, J=16.0 Hz, 1H, C*H*H-7), 5.10 (d, J=14.5 Hz, 1H, CH*H*-7), 6.69 (s, 1H, H-13), 6.95 (dd, J=9.0, 2.5 Hz, 1H, H-10), 7.00 (d, J=7.5 Hz, 1H, H-4), 7.14 (d, J=2.5 Hz, 1H, H-12), 7.16–7.20 (m, 2H, H-3, H-2′ and H-6′), 7.27 (td, J=8.5, 1.5 Hz, 1H, H-2), 7.31–7.34 (m, 3H, H-3′, H-4′ and H-5′), 7.43 (d, J=8.5 Hz, 1H, H-9), 7.65 (dd, J=7.5, 1.5 Hz, 1H, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.7 (CH_2), 52.6 (CH_2-7), 55.9 (OCH_3), 99.5 (C-13), 102.3 (C-12), 110.0 (C-9), 112.8 (C-10), 123.4 (C-4′), 126.4 (C-2), 126.8 (C-2′ and C-6′), 127.1 (C-4), 127.2 (C-13b), 128.5 (C-3′ and C-5′), 128.7 (C-13a), 129.0 (C-3), 130.4 (C-1), 131.7 (C-12a), 136.8 (C-1′), 137.5 (C-8a), 139.2 (C-4a), 154.6 ($COCH_3$), 167.2 (CO); EI-MS m/z 368 ([H]$^+$, 100%); HREI-MS m/z calcd for [M]$^+$ $C_{24}H_{20}N_2O_2$: 368.1525, found: 368.1529.

The second fraction gave 5-benzyl-7,12-dihydro-9-methoxy-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one **16b** (10 mg, 25%) as an offwhite solid, mp 213–215 °C; IR (KBr) ν_{max}: 3300 (NH), 1647 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.54 (br s, 2H, CH_2-7), 3.08 (s, 3H, CH_3), 5.08 (br s, 2H, CH_2), 6.83 (dd, J=8.5, 2.5 Hz, 1H, H-10), 6.90 (d, J=6.5 Hz, 2H, H-2′ and H-6′), 7.10–7.15 (m, 3H, H-3′, H-4′ and H-5′), 7.21 (d, J=2.5 Hz, H-8), 7.29 (t, J=7.0 Hz, 1H, H-2), 7.32–7.36 (m, 2H, H-11 and H-3), 7.55 (d, J=8.5 Hz, 1H, H-4), 7.65 (dd, J=7.5, 1.5 Hz, 1H, H-1), 11.57 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.7 (CH_2-7), 52.1 (CH_2), 55.4 (OCH_3), 99.7 (C-8), 109.7 (C-7a), 112.4 (C-11), 112.8 (C-10), 124.2 (C-4), 125.1 (C-2), 126.3 (C-2′ and C-6′), 126.3 (C-7b), 126.4 (C-12b), 126.6 (C-4′), 127.2 (C-1), 127.8 (C-3), 128.2 (C-3′ and C-5′), 132.6 (C-11a), 133.0 (C-12a), 137.9 (C-1′), 138.9 (C-4a), 153.6 (*C*OCH$_3$), 170.3 (CO); CI-MS m/z 369 ([M+H]$^+$, 100%); HREI-MS m/z calcd for [M]$^+$ $C_{24}H_{20}N_2O_2$: 368.1525, found: 368.1531.

4.8.6. Radical cyclisation of 15c. Compound **15c** (50 mg, 0.10 mmol) in mesitylene (20 mL) was treated with Bu_3SnH (54 μL, 0.20 mmol) and AIBN (16 mg, 0.10 mmol) in mesitylene (60 mL). The crude material was chomatographed on silica gel (AcOEt/pet. spirit, 9:1) to give 5-benzyl-9-fluoro-7,12-dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one **16c** as off white needles (16 mg, 45%); mp 247–248 °C; IR (KBr) ν_{max}: 3277 (NH), 1641 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.50 (d, J=13.5 Hz, 1H, C*H*H-7), 3.91 (d, J=13.8 Hz, 1H, CH*H*-7), 5.05 (d, J=15.6 Hz, 1H, C*H*H), 5.14 (d, J=15.4 Hz, 1H, CH*H*), 6.95 (td, J=8.7, 2.4 Hz, 1H, H-10), 7.03–7.05 (m, 2H, H-2′ and H-6′), 7.15–7.17 (m, 2H, H-3′ and H-5′), 7.23–7.27 (m, 2H, H-11 and Ar), 7.30–7.39 (m, 2H, H-2 and Ar), 7.43–7.51 (m, 2H, H-8 and Ar), 7.83 (d, J=7.2 Hz, 1H, H-1), 10.09 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 35.6 (CH_2-7), 54.6 (CH_2), 103.9 (d, J=24.1 Hz, ^{13}C–^{19}F, C8–F), 110.5 (d, J=25.8 Hz, ^{13}C–^{19}F, C10–F), 111.1 (C-7a), 112.7 (d, J=9.8 Hz, ^{13}C–^{19}F, C11–F), 124.4 (ArC–H), 125.7 (d, J=10.0 Hz, ^{13}C–^{19}F, C7b–F), 126.4 (ArC–H), 126.5 (ArC–H), 126.8 (C-2′ and C-6′), 127.2 (C-4′), 128.0 (C-1), 128.7 (C-3′ and C-5′), 129.1 (C-12b), 129.8 (C-12a), 133.2 (C-11a), 137.6

(C-1′), 138.8 (C-4a), 159.0 (d, $J=230.6$ Hz, ^{13}C–^{19}F, C9–F), 169.4 (CO); CI-MS *m/z* 357 ($[M+H]^+$, 100%); HREI-MS *m/z* calcd for $[M]^+$ $C_{23}H_{17}N_2OF$: 356.1325, found: 356.1381.

4.8.7. 7,12-Dihydro-indolo[3,2-*d*][1]benzazepin-6(5*H*)-one 19 (R=H). Sodium metal (ca. 30 mg) was added to dry THF (2 mL) under a N_2 atmosphere and then the mixture was frozen using a liquid N_2 bath. Liquid ammonia (condensed at −70 °C, ca. 7 mL) and a solution of **16a** (26 mg, 0.08 mmol) in dry THF (2 mL) was then added. The frozen mixture was warmed to −60 °C and the reaction mixture was stirred at this temperature for 10 min. Solid ammonium chloride was then added until the colour dissipated at which point the reaction was allowed to warm to room temperature. The residue was dissolved in ethyl acetate (30 mL), extracted with water (3×20 mL), dried and concentrated to give a yellow residue. The residue was purified using preparative thin layer chromatography (silica gel, 1% MeOH/DCM) to give the title compound **19** (R=H) (8 mg, 40%) as a yellow solid; mp >272 °C (lit.[17] >315 °C); IR (KBr) ν_{max}: 3356 (NH), 1655 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.54 (s, 2H, CH_2), 7.11 (ddd, $J=7.2$, 6.9, 1.5 Hz, 1H, H-9), 7.16 (ddd, $J=7.5$, 6.9, 1.5 Hz, 1H, H-10), 7.23–7.29 (m, 3H, H-2, H-3 and H-4), 7.44 (dd, $J=7.2$, 1.5 Hz, 1H, H-11), 7.80 (d, $J=6.9$ Hz, 1H, H-8), 7.85 (m, 1H, H-1), 10.08 (s, 1H, NH), 11.62 (br s, 1H, indole NH); ^{13}C NMR ($CDCl_3$) δ 35.7 (CH_2), 109.7 (C-7a), 112.5 (C-11), 118.7 (C-8), 120.7 (C-9), 122.1 (C-10), 123.3 (ArC–H), 124.8 (ArC–H), 125.9 (C-12b), 126.3 (ArC–H), 126.9 (C-7b), 128.2 (C-1), 132.2 (C-12a), 134.8 (C-4a), 136.9 (C-11a), 170.3 (CO); EI-MS *m/z* 248 ([M]+, 100%); HRCI-MS *m/z* calcd for $[M+H]^+$ $C_{16}H_{13}N_2O$: 249.1028, found: 249.1032.

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New chiral porphyrin–brucine gelator characterized by methods of circular dichroism

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Abstract—Herein, we report the first use of chiral alkaloid brucine to synthesize novel porphyrin–brucine conjugate capable of acting as a gelator of methanol and acetonitrile at extremely low level of concentration. The synthesis, characterization and spectral properties of gelator based on a novel structural motif, quaternized alkaloid conjugates, are described. Different spectroscopic methods (^{1}H NMR spectroscopy, Raman and infrared spectroscopy, and spectroscopy of electronic and vibrational circular dichroism) were used for characterization of the prepared organogel. The aggregation of the gelator studied by UV–vis spectroscopy and electronic circular dichroism showed the formation of chiral *J*-aggregates in water and water–methanol (1:1) mixture. A new methodology for the determination of functional groups involved in gel formation based on vibrational circular dichroism is presented.

1. Introduction

The immobilization of organic solvents by low-molecular weight organic compounds called gelators continues to be a widely studied topic of supramolecular chemistry.[1] Unlike macromolecular gels, the fibers of the resulting organogel consist of non-covalent assemblies of gelator molecules and the organogel prepared contains even more than 99% of an organic solvent.[2] The self-assembly of the gelator molecules into supramolecular structures can find numerous applications in biocatalysis, preparation of microparticles, and separation science.[3] Gels can also be used in molecular recognition,[4,5] cosmetics, food processing, drug delivery or as templates for the creation of inorganic structures.[5–12] Unfortunately, currently there is no reliable procedure suitable to predict capability of an individual low-molecular weight compound to immobilize organic solvents, despite several attempts being published.[13] However, it is known that a potential gelator must have several specific properties. It has to contain a multi-functional system providing interactions among individual gelator molecules (i.e., gelator–gelator interactions). These interactions are responsible for the formation of a three-dimensional network where the molecules of the gelator are bound by non-covalent interactions such as hydrogen bonding, electrostatic interactions, π–π interactions, and metal ligand coordination. The solvent is then physically trapped inside this network through non-covalent interactions.

According to the chemical structure used, low-molecular weight gelators can be divided into several categories[1] including fatty acid derivatives,[14] steroid derivatives,[2,15–23] anthryl derivatives,[24,25] urea derivatives,[26–29] gelators containing steroidal and condensed aromatic rings (ALS),[18] amino acid-type gelators,[30,31] sugar-integrated gelators,[32–41] and organometallic compounds. One discrete group of gelators includes porphyrin-based derivatives.[20,41–43] During the last decade, considerable attention has been paid to the design and synthesis of new gelators of organic solvents.[4,13,29–31,33,34,37,44–48]

Rheological and thermodynamic properties of organogels can be investigated using techniques such as differential scanning calorimetry and rheometry.[24,49,50] The gel-to-sol transition temperature (T_g) is one of the most often reported characteristics of a gel system.

Multiple methods can be used to determine this value,

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including test-tube-tilting method[51,52] and the ball-dropping method.[51,52] By the test-tube-tilting method (also called the inverted test-tube method), the temperature, at which the organogel starts to flow when the test tube is inverted upside down, is measured.[26–28,53] The ball-dropping method exploits the destruction of the organogel by the steel ball placed upon the surface of the organogel. As the organogel melts the ball starts to penetrate the gel structure and the temperature at which the ball reaches the bottom of the tube is called the gel-to-sol transition temperature. However, different authors use steel balls of various weights and diameters, therefore, it is very complicated to compare the results of particular experiments.

On the other hand, results obtained by spectroscopic methods,[18,24,33,34,39] including ^{1}H NMR and electronic circular dichroism (ECD) spectroscopy, are easily reproducible. However, the value of T_g obtained by these methods does not always correspond with that obtained either by the test-tube-tilting method or the ball-dropping method.[1]

As another chiroptical method for studying the structure of supramolecular assemblies and sol–gel transition processes, vibrational circular dichroism (VCD)[54–56] spectroscopy has been newly utilized.[57] This technique combines the advantages of vibrational spectroscopy (rich structural fingerprint region of IR absorption spectra) with the conformational sensitivity of widely used circular dichroism in UV–vis region and is therefore potentially useful in studies of the spatial organization of chiral compounds irrespective of their size. The absolute conformation of small molecules[55,56,58–61] can be determined with a high degree of accuracy. Semiempirical VCD correlations also enable the conformational and structural studies of large biomolecules and supramolecular assemblies.[54,57,62–64]

The focus of our work was to bind up a novel structural motif for gelators together with using novel methodology for gel characterization.

2. Results and discussion

2.1. Gelation ability

We designed, synthesized and characterized a novel brucine-based gelator consisting of porphyrin molecule and four brucine moieties, which forms organogel with methanol even at extremely low concentration of the gelator.

A lot of the advantages accompanying the use of the porphyrin skeleton, known to us from our previous work,[65] were also exploited in this case. The possibility of **1** to act as a potential gelator for hydroxylated solvents (e.g., alcohols) is apparent from its chemical structure (Fig. 1). There are many sites where non-covalent interactions can take place. Due to the presence of the porphyrin moiety, there is the possibility of hydrophobic interactions and π–π stacking, which are the driving forces of the aggregation of the gelator molecules into the supramolecular structures. Moreover, four brucine moieties contain several heteroatoms, which can provide hydrogen bonding with hydroxylated solvents. Finally, the inherent chirality of alkaloid brucine accompanied with the exchange of bromide anion in combination with other interactions can be potentially used for chiral sensing.

Besides compound **1**, other derivatives (**2**–**4**) (Fig. 1) were prepared to clarify necessary structure requirements for the preparation of a gelator. The ability of derivatives **1**–**3** to create an organogel was tested with the test-tube-tilting method for six solvents. We compared dipolar aprotic solvents (acetonitrile, dimethylsulfoxide) with protic solvents (methanol, ethanol, 2-propanol, and water). The results summarized in Table 1 are unambiguous. Only the combination of porphyrin and brucine moieties led to the preparation of a gelator and, moreover, only the special design of porphyrin–brucine conjugate gives gelation properties (see below).

As can be seen from Table 1, **1** is a gelator for methanol. In

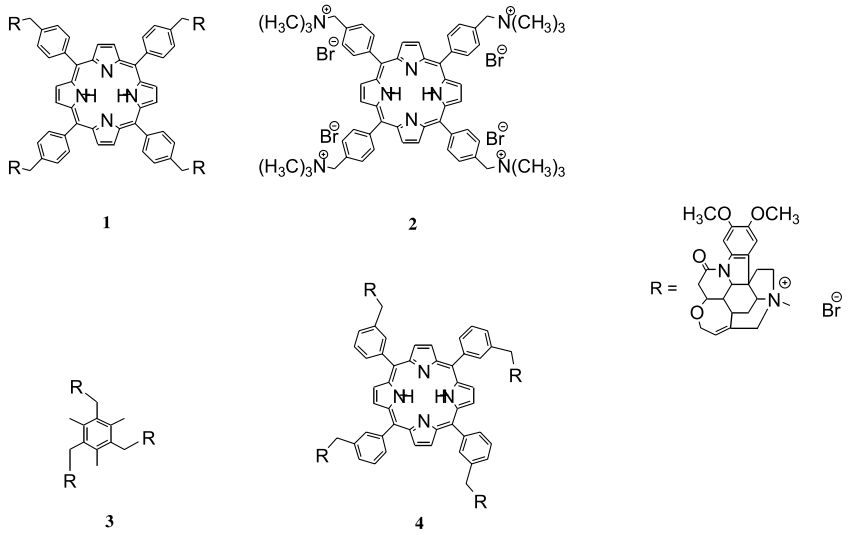

Figure 1. Chemical structures of prepared derivatives **1**–**4**.

Table 1. Results of gelation test on **1–3**

Solvent	Compound **1**	Compounds **2–3**
Acetonitrile	G	S
Dimethylsulfoxide	S	S
Methanol	G	S
Ethanol	S	S
2-Propanol	I	I
Water	S	S

S, solution; G, gel; I, insoluble. Concentration of **1–3** up to 0.22 wt%, temperature 20 °C.

fact, it forms organogel even at very low concentration, specifically at 0.67 mmol L^{-1} (0.22 wt%). The gelator can also immobilize acetonitrile, although the procedure for the preparation of the organogel in acetonitrile is different from that for methanol (for details see Section 4).

In contrast to **1**, derivative **4** is based on meso-tetrakis(*meta*-bromomethylphenyl)porphyrin. The slight change of the position of bromomethyl group from *para*- to *meta*- led to complete loss of gelating properties. Since **1** forms gels in methanol and **4** does not, a high level of structural organization of individual molecules of **1** in gel is presumed.

2.2. ^{1}H NMR study of gel-to-sol transition process

^{1}H NMR spectroscopy was used for determination of T_g of **1**. As the molecular motion of the gelator molecules significantly changes at T_g, the linewidth of β-pyrrolic protons in ^{1}H NMR spectrum strongly depends on the temperature. However, the experiment is complicated by the fact that the signals of the gelator in organogel phase are broadened to such an extent that it is impossible to determine the linewidth reliably at temperatures below 45 °C. As the temperature increases, the signals narrow and the gel to sol transition occurs (Fig. 2).

In order to consider solely the influence of rheological properties of the system on ^{1}H NMR spectrum it was necessary to take into account the natural width of the signals and also the effect of inhomogeneity of magnetic field on the linewidth. On that account the linewidths of β-pyrrolic protons of **2** (ν_3) along with those of **1** (ν_2) were measured. The molar concentration of **1** and **2** was kept the same in the experiments. Since **2** does not form an organogel with methanol, the linewidth of **2** exclusively represents the natural linewidth and the effect of inhomogeneity of magnetic field. Thus, the difference $\Delta\nu = \nu_2 - \nu_3$ reflects the contribution of the gelation process to the linewidth of the signals. Plot of $\Delta\nu$ *versus* temperature (Fig. 3) shows the transition at about 50 °C, where the gel phase becomes the sol.

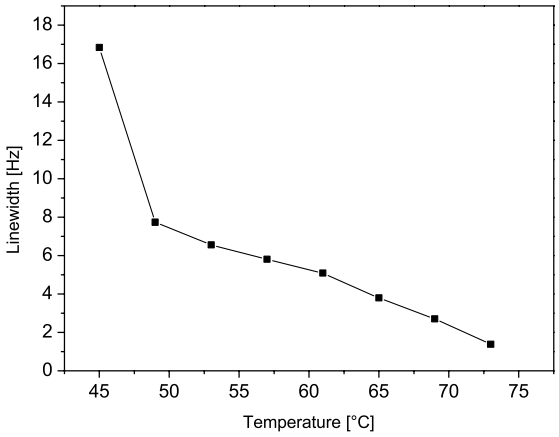

Figure 3. Temperature dependence of the corrected linewidth of ^{1}H NMR signals of β-pyrrolic protons of **1** (2.5 mg mL^{-1}).

2.3. FT Raman measurements

FT Raman spectra of the organogel of **1** in methanol and its solution in [D_6]DMSO were measured (Fig. 4). The bands at 1610 and 1550 cm^{-1} were assigned to stretching vibrational modes of aromatic and pyrrolic rings.[66–69] A comparison of the spectra of the organogel and the solution revealed a different intensity ratio for the two mentioned bands. This effect can be explained by the change in orientation of the aromatic rings with respect to the macrocyclic skeleton caused by the gelation process.[66,69]

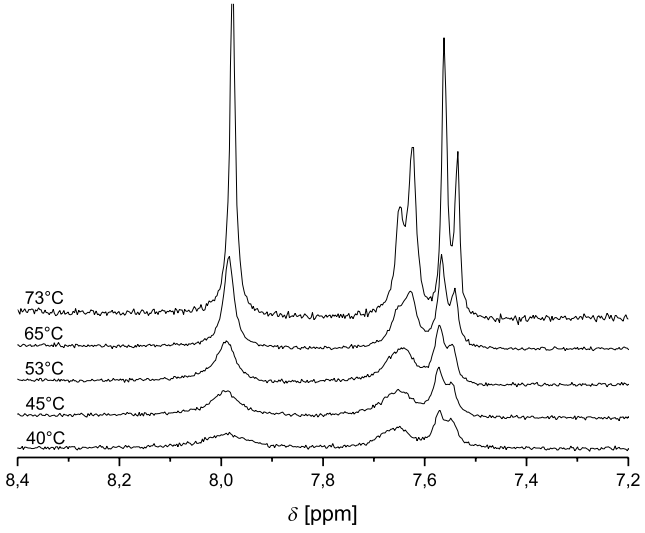

Figure 2. Temperature dependence of ^{1}H NMR spectra of [D_4]methanol gel of **1** (2.5 mg mL^{-1}).

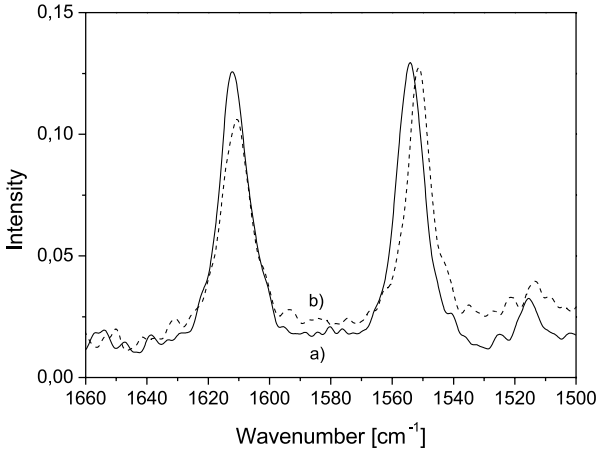

Figure 4. FT Raman spectra of (a) methanol organogel of **1** and (b) [D_6]DMSO solution of **1** (in both cases at concentration 1.0 mmol L^{-1}; signals of pure methanol and [D_6]DMSO, were subtracted from spectra (a) and (b), respectively).

2.4. VCD and FT IR study

In our previous work,[57] VCD proved to be profitable tool for the characterization of chiral gels. The identification of specific parts of molecule the configuration of which is influenced by chiral supramolecular aggregation is the advantage of VCD. In Figure 5, VCD and IR absorption spectra of organogel of **1** in [D_4]methanol, [D_6]DMSO, and brucine in the [D_4]methanol solution are shown in the region of ν(C═O) characteristic vibrations. The sign of the VCD band corresponding to C═O vibrations is inverted to positive in organogel with [D_4]methanol compared with the negative VCD signal of **1** in the [D_6]DMSO solution where the gel is not formed. In addition, the magnitude of VCD signal in the gel phase is significantly enhanced compared with that of sol in [D_6]DMSO. These facts demonstrate that the changes of molecular chirality of **1** connected with C═O groups are induced by the sol-gel transition. While the negative VCD signal at ν(C═O) is given by the inherent chirality of the single molecule **1**, the enhanced positive VCD band (Fig. 5, spectrum a) observed in the gel phase indicates the coupling in the C═O stretching modes, and therefore, the formation of the highly ordered chiral assemblies.[57] The brucine, which is the chiral agent in **1**, reveals a significantly smaller negative VCD signal in the methanol solution (Fig. 5A, spectrum c) originating in the inherent chirality of a single brucine molecule.

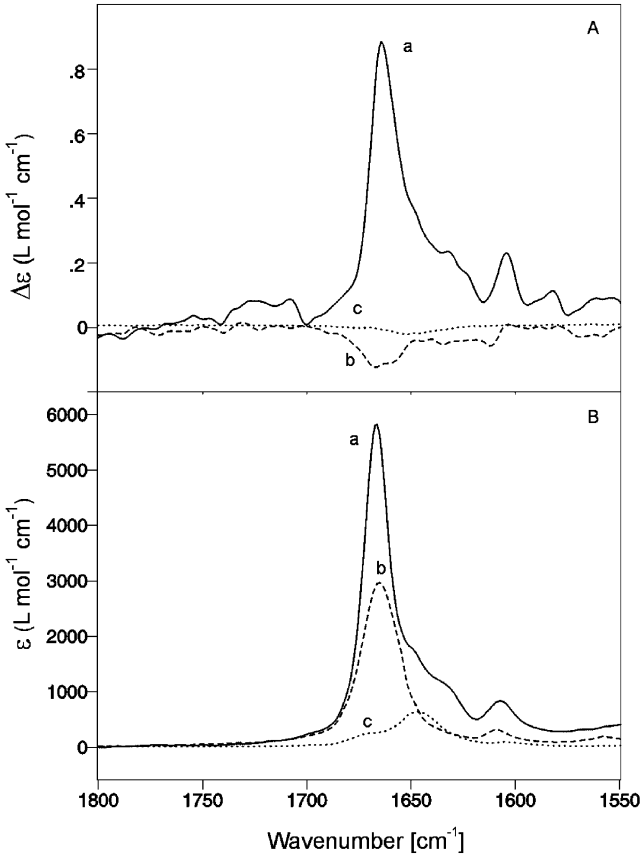

Figure 5. VCD (A) and FTIR absorption (B) spectra of (a) organogel of **1** with methanol, (b) [D_6]DMSO solution of **1**, and (c) brucine in [D_4]methanol (7.7 mmol L^{-1} for **1**, 0.19 mol L^{-1} for brucine; the solvent spectra were used as subtracted baselines).

The absorption maxima of the organogel in [D_4]methanol and the solution of **1** in [D_6]DMSO have almost the same position. On the contrary, the ν(C═O) band observed for brucine in [D_4]methanol (Fig. 5B) shows a frequency shift and a band splitting. This can be explained by the different solvation of brucine molecule than of molecule **1**.

The extremely high sensitivity of the VCD in the ν(C═O) region to gel formation was used to monitor the temperature induced gel–sol transitions (Fig. 6). The [D_4]methanol/[D_6]DMSO=4/1 mixture was used as a solvent to achieve higher temperature than in pure methanol. The decrease of the dissymmetry factor is observed at 40 °C and its sign inverts between 60 and 70 °C, where the sol phase is achieved. The temperature dependence of the VCD dissymmetry factor corresponds very well with the result obtained by the NMR technique (cf. Figs. 3 and 6).

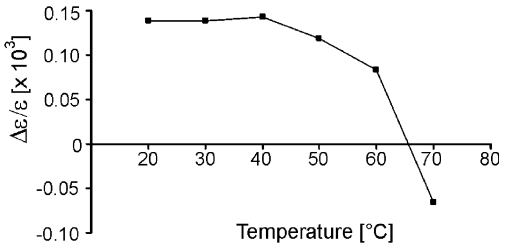

Figure 6. The temperature dependence of the dissymmetry factor of the ν(C═O) band of organogel of **1** in [D_4]methanol/[D_6]DMSO=4/1 (v/v); 7.7 mmol L^{-1}.

2.5. UV–vis and ECD study of aggregation

We investigated the behavior of **1** in water. Porphyrins have a strong characteristic absorption band at about 420 nm (Soret band) and, therefore, they can be studied even at low concentration levels. Furthermore, gelator **1** also contains four chiral brucine moieties that enable the use of ECD spectroscopy. We measured UV–vis and ECD spectra of **1** in various solvents (Figs. 7 and 8). Whereas the level of absorbance in UV–vis spectra (Fig. 7) was about the same independently on the solvent used, the large enhancement of ECD signal was observed only in water. Such spectral patterns imply the formation of chiral aggregates in this solvent. Only a slight decreasing of molar ellipticity with

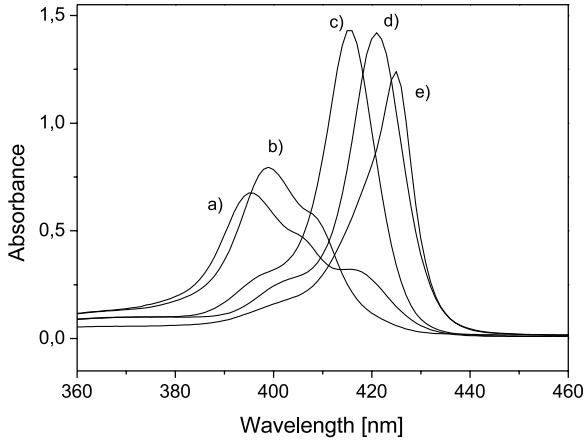

Figure 7. UV–vis spectra of **1** (2.0 μmol L^{-1}) in (a) acetone, (b) dichloromethane, (c) methanol, (d) dimethylsulfoxide, and (e) water.

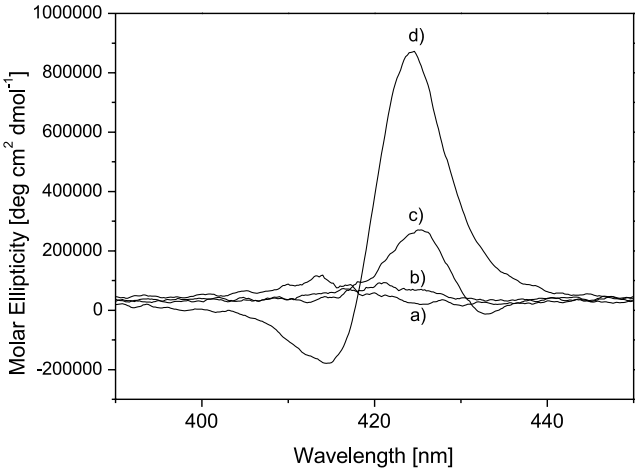

Figure 8. CD spectra of **1** (4.3 μmol L^{-1}) in (a) methanol, (b) dimethylsulfoxide, (c) isopropyl alcohol, and (d) water.

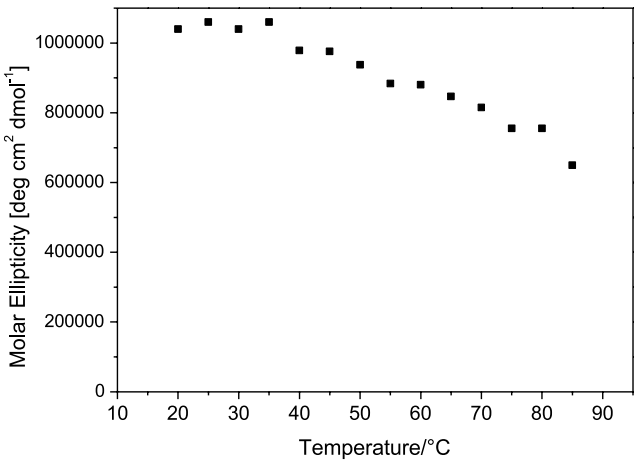

Figure 9. Thermal stability of chiral structure of **1** (4.3 μmol L^{-1}) in water. Dependence of molar ellipticity of **1** at 424 nm on temperature.

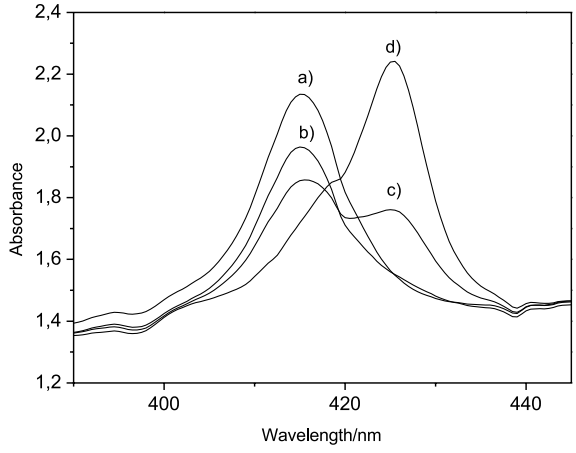

Figure 10. Dependence of UV–vis spectra of **1** (1.4 μmol L^{-1}) on methanol/water ratio (v/v): (a) 2/1, (b) 1/1, (c) 1/2, and (d) 1/6.

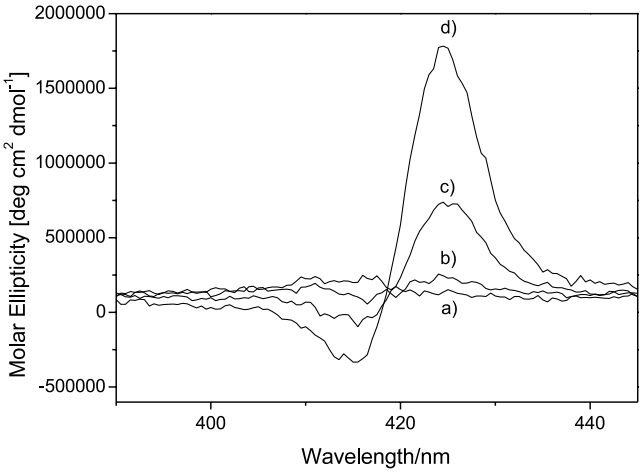

Figure 11. Dependence of CD spectra of **1** (1.4 μmol L^{-1}) on methanol/water ratio (v/v): (a) 2/1, (b) 1/1, (c) 1/2, and (d) 1/6.

increasing temperature (Fig. 9) indicates the high thermal stability of prepared aggregates.

Next, we investigated the aggregation process in a solvent mixture methanol/water. The red shift of the Soret band in UV–vis and increasing ECD intensity with increasing amount of water in the mixed solvent can be observed in Figures 10 and 11, respectively. It is known that the Soret band of higher edge-to-edge aggregates (*J*-aggregates) appears at longer wavelengths.[70–72]

3. Conclusion

The synthesis, characterization and spectral properties of the new gelator, porphyrin with four quaternized brucines on the periphery, were described. We observed the organogels composed of the gelator and methanol or acetonitrile even though low gelator concentration was used. Besides traditional spectral methods, the applicability of VCD spectroscopy for monitoring of the sol–gel transition process of chiral compounds was demonstrated. The VCD spectra showed remarkable sensitivity to the gel formation and provide valuable information on the involvement of specific segments of molecules in the formation of chiral self-assemblies and sensitively reveal the parts of molecules whose optical activity is influenced by the organogel formation.

4. Experimental

4.1. Apparatus for spectroscopy measurements

^{1}H NMR spectra were measured with a Varian Gemini 300 spectrometer using solvent as a reference. Chemical shifts are reported in ppm (δ-scale), the linewidths in Hz. The standard used for temperature calibration was PEG.

Mass spectra were recorded with Bruker Esquire 3000 with electrospray ionization, ion trap analysator and conversion dynode based system (Daly detector).

CD and UV–vis spectra were taken with JASCO 400 and Varian Cary 400, respectively.

FT Raman spectra were obtained with Bruker Equinox 55/S with module FRA 106/S.

VCD and IR absorption spectra were recorded with spectral resolution of 4 cm^{-1} on the IFS 66/S spectrometer equipped with VCD/IRRAS module PMA 37 (Bruker, Germany) by procedure described elsewhere.[73]

4.2. Chemicals

Brucine was purchased from Lachema Chemical Company (Czech Republic). [D_4]methanol (99.8% D) was purchased from Isosar. [D_6]DMSO (99.8% D) was purchased from Chemotrade. $CDCl_3$ (99% D) was purchased from Merck.

5,10,15,20-Tetrakis(*p*-bromomethylphenyl)porphyrin (*p*-**BP**) and 5,10,15,20-tetrakis(*m*-bromomethylphenyl)-porphyrin (*m*-**BP**) were prepared similarly to the procedure described elsewhere.[74]

4.2.1. Compound 1. The title compound was prepared by *N*-alkylation of brucine molecules with *p*-**BP**. The solution of *p*-**BP** (48.6 mg, 0.05 mmol) in chloroform (20 mL) was mixed with the solution of brucine (10 equiv) in chloroform (10 mL). The mixture was stirred under reflux for 24 h. The resulting suspension was filtered off and the insoluble part was washed with chloroform and dried at 80 °C under vacuum. Yield: 77%; deep blue crystals. ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ=8.89 (s, 8H, β-pyrrole), 8.42 (dd, 16H, phenyl), 7.69 (s, 4H, brucine phenyl), 7.26 (s, 4H, brucine phenyl), 6.51 (m, 4H, brucine), 5.25 (s, 8H, phenyl-CH_2), 4.93-4.00 (m, 31H, brucine), 3.75 (s, 12H, OCH_3), 3.62 (s, 12H, OCH_3), 2.94–1.57 (m, 37H, brucine), −2.90 (s, 2H, NH); MS (ESI; exact mass (M^{4+} + $4Br^-$)=2558.71): *m/z* (%): 1202.4 (3) [M^{4+} + $2Br^-$], 774.8 (35) [M^{4+} + Br^-], 561.2 (100) [M^{4+}]; elemental analysis calcd (%) for $C_{140}H_{138}N_{12}O_{16}Br_4 \cdot 3CHCl_3 \cdot 4H_2O$ (2994,5): C, 57.36; H, 5.02; N, 5.61; found: C, 57.39; H, 5.44; N, 5.41.

Note: elemental analysis did not provide accurate results. This was probably due to the fact that the charged porphyrins often retain significant amounts of solvent molecules.[75] Elemental analysis showed that the most likely constitution is: $C_{140}H_{138}N_{12}O_{16}Br_4 \cdot 3CHCl_3 \cdot 4H_2O$.

4.2.2. Compound 2. The title compound was prepared similarly to the procedure described elsewhere.[74]

4.2.3. Compound 3. The title compound was prepared by *N*-alkylation of brucine molecules with 1,3,5-tris(bromomethyl)mesitylene (MES). The solution of MES (100 mg, 0.25 mmol) in acetonitrile (20 mL) was added into the solution of brucine (6 equiv) in acetonitrile (30 mL). The mixture was stirred under argon for 1 day. The resulting white precipitate was filtered off, washed with acetonitrile (5 mL) and ethylacetate (20 mL) and dried at 40 °C under vacuum. Yield: 82%; white crystals. ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ=7.67 (s, 3H, brucine phenyl), 7.65 (s, 3H, brucine phenyl), 6.82 (s, 3H, brucine), 5.43 (s, 6H, phenyl-CH_2), 4.86 (d, 3H, J=11.8 Hz, brucine), 4.58 (s, 3H, brucine), 4.37 (m, 3H, brucine), 4.15–4.00 (m, 12H, brucine), 3.86 (s, 9H, OCH_3), 3.75 (s, 9H, OCH_3), 3.70 (m, 3H, brucine), 3.28 (m, 6H, brucine), 3.0–2.8 (m, 12H, brucine + CH_3 of MES), 2.63 (d, 3H, J=15.7 Hz, brucine), 2.4–2.0 (m, 9H, brucine), 1.71 (d, 3H, J=14.4 Hz, brucine), 1.44 (d, 3H, J=10.5 Hz, brucine); ^{13}C NMR (75.5 MHz, [D_6]DMSO, 25 °C, TMS): δ=168.4, 149.7, 146.9, 145.9, 135.8,135.6, 133.4, 129.1, 120.0, 108.5, 100.2, 76.0, 75.7, 63.2, 58.8, 57.8, 57.0, 55.7, 55.2, 52.0, 46.5, 41.6, 39.9, 39.3, 29.2, 24.6, 21.7; MS (ESI; exact mass (M^{3+} + $3Br^-$)=1578.44): *m/z* (%): 1499.5 (5) [M^{3+} + $2Br^-$], 710.3 (40) [M^{3+} + Br^-]; 447.23 (100) [M^{3+}] elemental analysis calcd (%) for $C_{81}H_{93}N_6O_{12}Br_3 \cdot CH_3CN \cdot 4H_2O$ (1698.5): C, 58.69; H, 6.35; N, 5.77; found: C, 52.6; H, 6.1; N, 4.5.

4.2.4. Compound 4. The title compound was prepared by the same procedure as in the case of the compound **1**. Yield: 48%; deep blue crystals. ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C, TMS): δ=8.80 (s, 8H, β-pyrrole), 8.45–8.32 (m, 16H, phenyl), 7.69 (s, 4H, brucine), 7.26 (s, 4H, brucine), 6.47 (s, 4H, brucine), 5.27 (s, 8H, phenyl-CH_2), 4.80–4.00 (m, 29H, brucine), 3.75 (s, 12H, OCH_3), 3.64 (s, 12H, OCH_3), 3.3–2,6 (m, 26H, brucine), 2,4–1,5 (m, 13H, brucine), −2.91 (s, 2H, NH); MS (ESI; exact mass (M^{4+} + $4Br^-$)=2558.71): *m/z* (%): 1202.4 (5) [M^{4+} + $2Br^-$], 774.6 (43) [M^{4+} + Br^-], 561.3 (100) [M^{4+}]; elemental analysis calcd (%) for $C_{140}H_{138}N_{12}O_{16}Br_4 \cdot 3CHCl_3$ (2922.5): C, 58.77; H, 4.86; N, 5.75; found: C, 58.57; H, 5.84; N, 5.57.

4.3. Gelation test

Solvent (1 mL) was added to 1.7 mg of **1** in the test tube and the mixture was then sonicated and warmed until the gelator was dissolved. The solution was then cooled to 20 °C and after 24 h the tube was inverted. If a stable gel was observed, it was classified as G in Table 1. In the case of acetonitrile, a stable gel was formed using the following procedure: 1 mL of the solvent was added to 1.7 mg of **1**. As this compound is poorly soluble the mixture was sonicated and the suspension was left in the closed tube at the room temperature until the solvent had evaporated to about 1/3 of its initial volume.

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Combined biotransformations of 4(20),11-taxadienes

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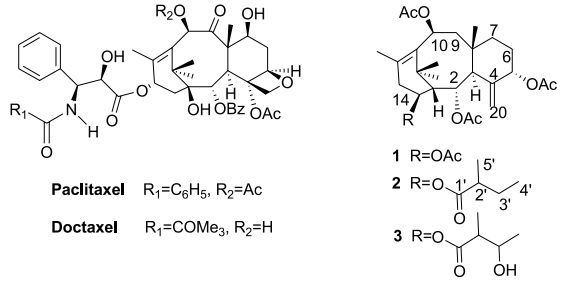
Abstract—Taxuyunnanine C (**1**) and its analogs (**2** and **3**), the C-14 oxygenated 4(20), 11-taxadienes from callus cultures of *Taxus* sp., were regio- and stereo-selectively hydroxylated at the 7β position by a fungus, *Abisidia coerulea* IFO 4011, and it was interesting that the longer the alkyl chain of the acyloxyl group at C-14 became, the higher the yield of 7β-hydroxylated product was. Besides the three 7β-hydroxylated products (**5**, **9**, **17**), other nine new products (**7**, **11**, **12**, **14**, **15**, **16**, **18**, **20** and **21**) and six known products (**4**, **6**, **8**, **10**, **13** and **19**) were obtained. Subsequently, the acetylated derivatives (**24** and **27**) of 7β-and 9α-hydroxylated products of **1** were regio- and stereo-specifically hydroxylated at the 9α position by *Ginkgo* cells and 7β position by *A. coerulea*, respectively. Thus, the two specific oxidations have been combined. These bioconversions would provide not only valuable intermediates for the semi-synthesis of paclitaxel or other bioactive taxoids from **1** and its analogs, but also some useful hints for the biosynthetic pathway of taxoid in the natural *Taxus* plant.

1. Introduction

The diterpenoid paclitaxel (Taxol®, Scheme 1), originally isolated from the Pacific yew (*Taxus brevifolia* Nutt.) in 1971,[1] exhibited remarkably high cytotoxicity and strong antitumor activity against different tumors resistantly treated by existing anticancer drugs.[2] It has been approved for the treatment of advanced ovarian and breast cancers,[3,4] and it is currently in clinical trials for treatment of lung, skin, head and neck cancers with encouraging results.[5] Since the discovery of paclitaxel in the late 1960s, its unique chemical structure, significant biological activity, as well as its novel mechanism of action[6,7] have led to research by scientists from different fields.[8,9]



Scheme 1. The structures of paclitaxel, docetaxel and taxanes from cell cultures of *T. chinensis*.

The source of paclitaxel has been a serious problem all the time since its only approved source was the bark of *T. brevifolia*, which yielded very low amount of paclitaxel (approximately 0.01% of the dry weight). Nowadays, the demand in clinics increases largely because its anticancer spectrum has been broadened and the wild *Taxus* trees have been forbidden to cut for the supply of paclitaxel by the governments of most countries in the world. This situation illustrates a serious resource crisis that has to be alleviated by using various approaches to produce alternate sources of paclitaxel, such as total synthesis, semisynthesis, nursery production of *Taxus* trees, fungal production, plant cell culture, etc.[10] Among them, plant tissue and cell culture of *Taxus* species is considered as one of the most promising approaches to produce paclitaxel and related taxanes. In the past decade, there have been a lot of successful reports and patents on the production of paclitaxel by callus or cell culture of various *Taxus* species, but the paclitaxel content was substantially different according to the particular *Taxus* species being investigated.[11–15] However, for most of these cases, only paclitaxel accumulation was reported, and its content was generally too low to scale-up industrially.

Keywords: *Ginkgo biloba* L.; *Abisidia coerulea* IFO 4011; Cell suspension cultures; 4(20), 11-Taxadiene; Biotransformation; Combination of 7β-and 9α-oxidations.

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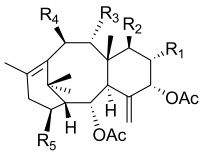
More than 10 years ago, a high and stable taxane-yielding callus strain of *T. chinensis*, (ca. 5–6% of the dry weight of cell cultures) was screened out of various callus strains of different *Taxus* species in our laboratory, which lost the ability to produce paclitaxel and other C-13 oxygenated taxoids, however, possessed the ability to produce C-14 oxygenated 4(20), 11-taxadienes only.[16,17] The three major taxanes are taxuyunnanine C [2α,5α,10β,14β-tetraacetoxytaxa-4(20),11-diene, **1**], 2α,5α,10β-triacetoxy- 14β-(2-methylbutyryl)oxytaxa-4(20),11-diene (**2**), and yunnanxane {2α,5α,10β-triacetoxy-14β-[3 (s)-hydroxy-2 (*R*)-methylbutyryl]oxytaxa- 4(20),11-diene, **3**} (Scheme 1). Their high contents in the cultures and their taxane-skeleton endow them with valuable potential for the semi-synthesis of paclitaxel or other bioactive taxoids. Unfortunately, these compounds have fewer functional groups with the skeleton in comparison with paclitaxel and other bioactive taxoids, such as at C-1, C-7, C-9 and C-13 positions. A number of studies on their structural modification by chemical and biocatalytic approaches were reported, and have achieved a lot of intriguing results.[18–25] However, the regio- and stereoselective introduction of oxygen functional groups at these positions seems to be very difficult through conventional chemical methods. In this context, the enzymatic conversion by employing microorganisms or plant cell suspension cultures is an alternative. In our previous investigation, 9α and 7β selectively hydroxylated products of these taxadeines were obtained successfully by cell suspension cultures of *G. biloba* and the fungus *A. coerulea*, respectively.[22–27] However, could these two selective oxidations be combined by the above two biocatalysts? So, as a part of our ongoing investigations, herein, we report the successful combination of the two reactions by subsequent biotransformation with the aid of chemical modification of the substrates. In addition, in our recent communication, only specific 7β-hydroxylations of **1**, **2** and **3** by *A. coerulea* were reported,[24] however, there are other fifteen products yielded from those bioprocesses, and nine of them are new compounds. These results will be presented in detail, and the effects of different substituents on the biotransformation will also be discussed.

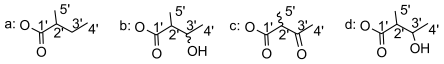
2. Results and discussion

After incubation with cell cultures of fungus *A. coerulea* for 7 days, five more polar metabolites were obtained from **1** by the combination of open silica gel chromatography and semi-prep. HPLC (Scheme 2). On the basis, of the physical and spectroscopic data, their structures were identified as 9α-hydroxy-2α,5α,10β,14β-tetraacetoxytaxa-4(20),11-diene (**4**, 1%),[22] 7β-hydroxy-2α,5α,10β,14β-tetraacetoxytaxa-4(20),11-diene (**5**, 5%),[24] 10β-hydroxy-2α,5α,14β-triacetoxytaxa-4(20),11-diene (**6**, 15%),[19–21,26] 6α-hydroxy-2α,5α,10β,14β-tetraacetoxytaxa-4(20),11-diene (**7**, 2%), 6α,10β-dihydroxy-2α,5α,14β-triacetoxytaxa-4(20),11-diene (**8**, 1%).[19–21,23] Among them, only **7** was a new compound.

The HREIMS, ^{1}H and ^{13}C NMR spectral data of **7** exhibited an elemental composition of $C_{28}H_{40}O_9$ (see Section 4.4.1), suggesting that a hydroxyl group may be introduced. The presence of an OH group in **7** was supported by the IR absorption at 3620 cm^{-1}. ^{1}H NMR spectrum of **7** was similar to that of **1** except that the signals of H-6α or H-6β (2H, δ 1.82, m) in **1** had disappeared, while a new oxymethine proton signal at δ 3.92 (1H, ddd, J=4.1, 5.1, 11.8 Hz) was observed, which was correlated with H-7 and H-5 in ^{1}H–^{1}H COSY spectrum, suggesting that the introduced OH group was at C-6 position. It was confirmed by the signal of C-6 which was substantially shifted downfield at δ 69.11 (d) compared with δ 28.88 (t) in **1**, and by the signal of H-6 which was correlated with C-5 and C-7 in HMBC spectrum. The stereochemistry of 6-OH was determined to be α-configuration by the NOE difference spectrum, in which the integration values of H-5, H-7β and H-19 were enhanced when H-6 was irradiated. Therefore, the structure of **7** was determined as 6α-hydroxy-2α,5α,10β,14β-tetraacetoxytaxa-4(20),11-diene. Although 6α hydroxylation of **1** occurred in the cases of fungus *Cunninghamella echinulata*, cell suspension cultures of *Catharanthus roseus* and *Ginkgo biloba* as the biocatalysts,[19–21,23] but in all cases, the C-10 acetyl group was simultaneously removed to afford **8**, thus this was the first time to get **7** from **1** by biotransformation.



Compounds	R_1	R_2	R_3	R_4	R_5
4	H	H	OH	OAc	OAc
5	H	OH	H	OAc	OAc
6	H	H	H	OH	OAc
7	OH	H	H	OAc	OAc
8	OH	H	H	H	OAc
9	H	OH	H	OAc	a
10	H	H	OH	OAc	a
11	OH	H	H	OAc	a
12	H	OH	H	OH	a
13 and 14 (isomer)	H	H	H	OAc	b
15 and 16 (isomer)	H	H	H	OAc	c
17	H	OH	H	OAc	d
18	H	H	OH	OAc	d
19	H	H	H	OH	d
20	OH	H	H	OAc	d
21	H	OH	H	OH	d



Scheme 2. The transformed products of **1**, **2** and **3** by *A. coerulea*.

Incubation of **2** with *A. coerulea* for 7 days yielded six metabolites (Scheme 2). By combination of ^{1}H NMR, ^{1}H–^{1}H COSY, ^{13}C NMR, DEPT, HMQC, HMBC, NOE, HREIMS and IR spectral analyses, their structures were determined to be 7β-hydroxy-2α,5α,10β-triacetoxy-14β-(2-methylbutyryl)oxytaxa-4(20),11-diene (**9**, 10%),[24] 9α-hydroxy-2α,5α,10β-triacetoxy-14β-(2-methylbutyryl)oxytaxa-4(20),11-diene (**10**, trace),[26] 6α-hydroxy-2α,5α,10β-triacetoxy-14β-(2-methylbutyryl)oxytaxa-4(20),11-diene (**11**, 2%), 7β,10β-dihydroxy-2α,5α-diacetoxy-14β-(2-methylbutyryl)oxytaxa-4(20),11-diene (**12**, trace), 2α,5α,10β-triacetoxy-14β-[3 (s)-hydroxy-2 (*R*)-methylbutyryl]oxytaxa-

4(20),11-diene (**13**, yunnanxane[28]) and 2α,5α,10β-triacetoxy-14β-[3(*R*)-hydroxy-2(*R*)-methylbutyryl]oxytaxa-4(20),11-diene (**14**, 3′-epimer of **13**, obtained as a mixture with **13**, totally in 5% yield). Among them, **11**, **12** and **14** were three new compounds.

The HREIMS spectrum of **11** showed a molecular ion peak $[M]^+$ at *m/z* 562.3154, consistent with the molecular formula of $C_{31}H_{46}O_9$, suggesting that an OH group may be introduced in comparison with **2**. The presence of an OH group in **11** was supported by the IR absorption at 3620 cm^{-1}. ^1H NMR spectrum of **11** was similar to that of **2** except that the signals of H-6α or H-6β (2H, δ 1.82, m) had disappeared, while an additional oxymethine signal at δ 3.96 (1H, ddd, $J=3.9$, 5.1, 11.8 Hz) was observed, suggesting that the OH group may be introduced at C-6 position. It was further supported by the signal of C-6 which was significantly shifted downfield to δ 68.16 (d) when compared with δ 28.88 (t) in **2**, and the correlations of this proton signal with C-5 and C-7 in HMBC spectrum. The stereochemistry of 6-OH was determined to be α-configuration by the NOE difference spectral experiment, in which the integration values of H-5, H-7β and H-19 were enhanced when H-6 was irradiated. Therefore, the structure of **11** was determined as 6α-hydroxy-2α,5α,10β-triacetoxy-14β-(2-methylbutyryl)oxytaxa-4(20),11-diene.

HRESIMS (negative) and HRESIMS (positive) of **12** displayed two quasi molecular ion peaks at *m/z* 519.3019 $[M-H]^+$ and 543.2963 $[M+Na]^+$, respectively, consistent with the molecular formula of $C_{29}H_{44}O_8$. The ^1H NMR spectrum of **12** was similar to that of **9**, but only two OAc signals were observed. The C-10 proton signal was shifted upfield to 0.9 ppm as compared with that of **9**, strongly suggesting a free OH group at C-10 in **12**. The ^1H NMR spectrum of **12** further showed that the resonances corresponding to H-7α or 7β [δ 1.24 (m); 1.98 (m)] in **2** had disappeared, and one new oxygen-bearing methine signal appeared at δ 3.83 (dd, $J=5.1$, 12.2 Hz), suggesting an insertion of an OH group at C-7 position in **12**. It was further supported by the HMBC experiment that this proton was correlated to C-5, C-6, C-8, C-9 and C-19. The stereochemistry of 7-OH was determined to be β-configuration by the NOE difference spectral analysis, in which the integration values of H-3, H-6α, H-10 and H-18 were enhanced when H-7 was irradiated. Thus, the structure of **12** was determined as 7β,10β-dihydroxy-2α,5α-diacetoxy-14β-(2-methylbutyryl)oxytaxa-4(20),11-diene, which could be biosynthesized from **9** via C-10 specific deacetylation.

13 and **14** were obtained as a mixture, clearly as a pair of isomers according to the ^1H and ^{13}C NMR spectra. The separation of these two isomers was tried by normal and reverse phase HPLC, however, it was troublesome and failed to give positive results. The ratio of this pair of isomers was 1:1 by the analysis of ^1H NMR. The NMR and IR spectral data of **13** were in good agreement with those of yunnanxane {2α,5α,10β-triacetoxy-14β-[3 (s)-hydroxy-2 (*R*)-methylbutyryl]oxytaxa- 4(20),11-diene}, and it was also supported by the HRMS experimental data.[28] The NMR data of **14** were very similar to those of **13** except that the signals of C-3′ and H-3′ were at δ 68.01 (δ 69.47 in yunnanxane) and δ 4.04 (δ 3.86 in yunnanxane), therefore, the structure of **14** was determined to be 2α,5α,10β-triacetoxy-14β-[3 (*R*)-hydroxy-2 (*R*)-methylbutyryl]oxytaxa- 4(20),11-diene, the 3′-epimer of yunnanxane. The result showed that **2** could not be specifically hydroxylated at C-3′ position by this fungus. To some extent, this result indicated that **3** was biosynthesized from **2** through C-3′ hydroxylation in the cell cultures of *T. chinensis*, however, in a specific manner.

3 was administered to 2-day-old cell cultures of *A. coerulea* and seven products were isolated by chromatographic methods after additional 7 days of incubation. Based upon the spectral and chemical data, their structures (Scheme 2) were identified as 2α,5α,10β-triacetoxy-14β-(2-methyl-3-keto)-butyryloxytaxa-4(20),11-diene (C-2′ diastereoisomers, **15** and **16**, totally in 10% yield), 7β-hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (**17**, 15%),[24] 9α-hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (**18**, 2%), 10β-hydroxy-2α,5α-diiacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (**19**, 5%),[29] 6α-hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (**20**, 2%), 7β,10β-dihydroxy-2α,5α-diacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (**21**, trace). Among them, **15**, **16**, **18**, **20** and **21** were five new compounds.

15 and **16** were obtained as a mixture of C-2′ diastereoisomers. Normal and reverse phase HPLC had been used for their separation, unfortunately, both efforts failed. The ratio of this pair of isomers was 1:1 by the analysis of ^1H NMR. The HREIMS spectrum showed a molecular ion peak $[M]^+$ at *m/z* 560.2987, consistent with the molecular formula of $C_{31}H_{44}O_9$. However, the OH absorption at 3572 cm^{-1} in **3** was not observed in IR spectrum, suggesting that C-3′ OH group probably oxidized to keto group. The ^1H and ^{13}C NMR spectral data were very similar to those of **3** except that the signals of H-3′ at δ 3.86 (dq, $J=7.0$, 6.8 Hz) had disappeared, and the signal of C-3′ was shifted downfield to δ 203.47 (s) as compared with that of **3** at δ 69.47 (d), solidly indicating the presence of C=O group at C-3′ in **15** and **16** rather than an OH group. But how was **3** with a single stereochemistry at C-2′ converted to a pair of isomers with 2′ (*R*) and 2′ (s) configurations? There was no evidence for the mechanism of this conversion yet.

HREI mass spectrum of **18** exhibited a molecular ion peak $[M]^+$ at *m/z* 578.3102, consistent with the molecular formula of $C_{31}H_{46}O_{10}$, indicating the substitution of an additional OH group as compared with **3**. The ^1H NMR spectral data were very similar to those of **3** except that the signals corresponding to H-9α (δ 1.64, dd, $J=5.6$, 14.9 Hz) or H-9β (δ 2.38, m) in **3** had disappeared, while an oxygen-bearing methine signal was observed at δ 4.14 (d, $J=$ 9.8 Hz). And the signals of H-10α (δ 6.06, dd, $J=5.6$, 11.5 Hz) in **3** were shifted upfield to δ 5.75 (d, $J=9.8$ Hz). All of these suggested that an OH group might be introduced at C-9 position. It was confirmed by the signal of C-9 which was significantly shifted downfield to δ 76.23 (d) when compared with δ 43.88 (t) in **3**, and the correlations of this proton to C-3, C-7, C-8, C-10 and C-19 in HMBC spectrum.

The stereochemistry of 9-OH was determined to be α-configuration by the NOE difference spectrum, in which the integration values of H-16 and H-19 were enhanced when H-9 was irradiated. Accordingly, the structure of **18** was identified as 9α-hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene.

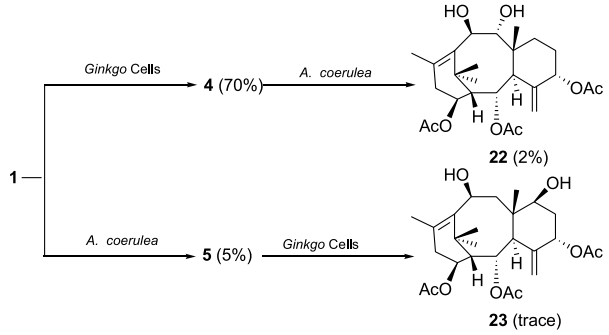
The HREIMS spectrum of **20** showed a molecular ion peak $[M]^+$ at *m/z* 578.3084, consistent with the molecular formula of $C_{31}H_{46}O_9$, suggesting that an OH group may be introduced in comparison with **3**. The ^{1}H NMR spectrum of **20** was similar to that of **3** except that the free methylene signals of H-6α or H-6β (2H, δ 1.80, m) had disappeared, while a new oxymethine signal at δ 3.96 (1H, ddd, J=3.9, 5.1, 11.8 Hz) was observed. In addition, in its ^{13}C NMR spectrum, the signal of C-6 was shifted downfield to δ 68.16 (d) as compared with that of **3** at δ 28.88 (t). These indicated that OH group was introduced at C-6 position. It was further confirmed by the observed correlations of this proton to C-5 and C-7 in HMBC spectrum. The stereochemistry of 6-OH was determined to be α-configuration by the NOE difference spectrum experiment, in which the integration values of H-5, H-7β and H-19 were enhanced when H-6 was irradiated. Therefore, the structure of **20** was determined as 6α-hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene.

The HRFABMS spectrum of **21** exhibited a quasi molecular ion $[M+Na]^+$ at *m/z* 559.2886, consistent with the molecular formula of $C_{29}H_{44}O_9$. The ^{1}H NMR spectrum of **21** was similar to that of **17** except that only two OAc groups were observed. The C-10 proton signal was shifted upfield to 0.9 ppm as compared with that of **17**, strongly suggesting the existence of a free OH group at C-10 in **21**. The ^{1}H NMR spectrum of **21** further showed that the resonances corresponding to H-7α or 7β [δ 1.24 (m); 1.96 (m)] in **3** had disappeared, and one additional oxygen-bearing methine signal appeared at δ 3.82 (dd, J=5.0, 11.4 Hz), indicating an insertion of an OH group at C-7 position in **21**. This was further supported by the HMBC experiment that this proton signal was correlated to C-5, C-6, C-8 and C-19. The stereochemistry of 7-OH was unambiguously determined to be β-configuration based on the NOE difference spectrum, in which the integration values of H-3, H-6α, H-10 and H-18 were enhanced when H-7 was irradiated. Therefore, the structure of **21** was determined to be 7β,10β-dihydroxy-2α,5α-diacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (**21**), which might be biosynthesized from **17** by specific deacetylation at C-10.

From the above results, all of the substrates (**1**, **2** and **3**) could be regio- and stereo-selectively hydroxylated at 7β, 9α and 6α positions by the fungus *A. coerulea*, which suggested that the enzymes responsible for these reactions were highly substrate-specific. It was interesting that the longer the alkyl chain of acyloxyl group at C-14 became, the higher the yield of 7β-hydroxylated product was. Additionally, some other reactions also occurred, such as selective deacetylation at C-10 position for all of them, hydroxylation at C-3′ position for **2**, oxidation of OH group to C=O group for **3**. These results indicated that there were several types of enzymes involved in the bioprocess, in other words, biotransformation is an efficient approach to diversify natural products.

Thus, both 7β and 9α hydroxylations of this type of taxanes could be achieved by fungus *A. coerulea* and cell suspension cultures of *G. biloba*,[22,23] respectively. Clearly, 7β and 9α hydroxylations of **1** were constituted two key steps to the semi-synthesis of paclitaxel or other bioactive taxoids from **1** and /or its analogs, therefore, the combination of two oxidations would be of interest and importance, and the further efforts were carried out.

First, 9α and 7β hydroxylated products (**4**, **5**) were prepared as described before,[22–24] and bioconverted directly as the substrates by fungus *A. coerulea* and cell suspension cultures of *Ginkgo* following the method described as in Section 4, respectively. However, not as expected, the desired reactions-7β or 9α hydroxylation did not occur while 10-deacetylation occurred in the both cases and yielded products **22** and **23** (Scheme 3). Their structures were identified as 9α,10β-dihydroxy-2α,5α,14β-triacetoxy-taxa-4(20), 11-diene (**22**) and 7β,10β-dihydroxy-2α,5α,14β-triacetoxy-taxa-4(20),11-diene (**23**)[4] by IR, NMR, HRMS analyses. **22** was a known compound obtained firstly from the biotransformation of **1** by *Ginkgo* cells,[22] and **23** was a new compound.



Scheme 3. Subsequent biotransformation of **4** and **5** by *A. coerulea* and *Ginkgo* cells.

The HRFABMS spectrum of **23** exhibited a quasi molecular ion peak $[M+Na]^+$ at *m/z* 501.2472, consistent with the molecular formula of $C_{26}H_{38}O_8$, suggesting the removal of one acetyl group in comparison with the molecular of **5**. The presence of three acetoxyl groups in ^{1}H and ^{13}C NMR spectra of **23** confirmed the deduction. The ^{1}H NMR spectrum of **23** was similar to that of **5** except that the signal of H-10β was shifted to an upper field at δ 5.08 (dd, J=5.1, 12.0 Hz) as compared with that of **5** at δ 5.97 (dd, J=5.1, 12.0 Hz), suggesting the existence of an OH group rather than an OAc group at C-10. It was supported by its ^{13}C NMR spectrum in which the signal of C-10 was shifted to an upper field at δ 66.90 (d) compared with that of **5** at δ 69.58 (d). Therefore, **23** was elucidated to be 7β,10β-dihydroxy-2α,5α,14β-triacetoxy-taxa-4(20),11-diene, the 10-deacetyl derivative of **5**, might be formed through specific deacetylation.

The above results indicated somewhat that the enzymes responsible for 7β and 9α hydroxylations were strictly substrate-specific. Considering the effects of the structure of

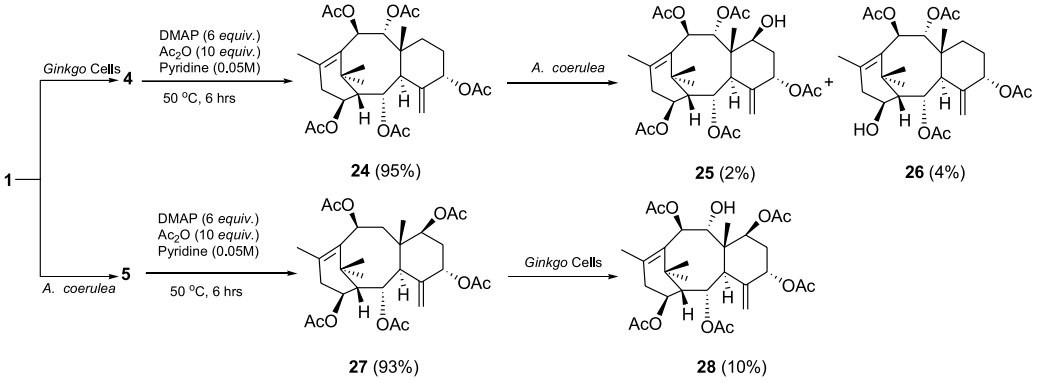
the substrate (substituent, polarity, conformation, etc.) on the biotransformation, we tried the following strategies. **4** and **5** were first acetylated by routinely chemical method, their acetylated products (**24**, **27**; Scheme 4) were subsequently biotransformed by fungus *A. coerulea* and cell suspension cultures of *Ginkgo*, respectively. Intriguingly, the desired hydroxylations took place in both cases, and their corresponding 7β and 9α hydroxylated products (**25** and **28**) were obtained in about 2 and 10% yields, respectively. Also one byproduct, compound **26** (4%) was formed in the former incubation. Their structures were determined on the basis of the ^{1}H NMR, ^{1}H–^{1}H COSY, ^{13}C NMR, DEPT, HMQC, HMBC, NOE, HRMS and IR spectral data.

The HRFABMS spectrum of **25** showed two quasi molecular ion peaks $[M+Na]^+$ and $[M+H]^+$ at *m/z* 601.2630 and 579.2736, respectively, consistent with the molecular formula of $C_{30}H_{42}O_{11}$, suggesting that an OH group may be introduced. The presence of an OH group in **25** was confirmed by the IR absorption at 3614 cm^{-1}. The ^{1}H NMR spectrum of **25** was similar to that of **24** except that the signals of H-7α or H-7β [2H, δ 1.68, m] in **24** had disappeared, while an additional oxymethine signal at δ 3.90 (dd, $J=5.4$, 11.5 Hz) was observed, indicating an OH introduction at C-7 position. It was supported by the signal of C-7 which was shifted to a downfield at δ 71.67 (d) as compared with δ 27.27 (t) in **24**, and by the correlations of this proton with C-5, C-6, C-8, C-9 and C-19 in HMBC. The stereochemistry of 7-OH was determined to be β-configuration by the NOE difference spectrum, in which the integration values of H-3, H-6α, H-10 and H-18 were enhanced when H-7 was irradiated. Thus, the structure of **25** was determined as 7β-hydroxy-2α,5α,9α,10β,14β-pentaacetoxy-taxa- 4(20),11-diene.

The HRFABMS spectrum of **26** exhibited two quasi molecular ion peaks $[M+Na]^+$ and $[M+H]^+$ at *m/z* 543.2571 and 521.2751, respectively, consistent with the molecular formula of $C_{28}H_{40}O_9$. The ^{1}H NMR spectrum of **26** was similar to that of **24** except that four OAc groups were observed, indicating that one acetyl group may be eliminated, and it was supported by the IR absorption at 3624 cm^{-1}. It was further confirmed by which the signals of H-14α and C-14 in ^{1}H NMR and ^{13}C NMR spectra of **26** were shifted upfield at δ 4.08 (dd, $J=5.0$, 9.0 Hz) and δ 67.56 (d) as compared with those of **24** at δ 4.97 (dd, $J=4.9$, 9.0 Hz) and δ 68.87 (d), respectively. So, compound **26** was identified to be 14β-hydroxy-2α,5α,9α,10β-tetraacetoxy-taxa-4(20),11-diene, the 14-deacetyl derivative of compound **24**.

The HRFABMS spectrum of **28** displayed two quasi molecular ion peaks $[M+Na]^+$ and $[M+H]^+$ at *m/z* 601.2626 and 579.2742, respectively, consistent with the molecular formula of $C_{30}H_{42}O_{11}$, implying that an OH group may be introduced. The presence of an additional OH group in **28** was confirmed by the IR absorption at 3620 cm^{-1}. The ^{1}H NMR of **28** was similar to that of **27** except that the signal of H-9α or H-9β (1H, δ 2.10, m; 1H, δ 1.98, m) in **27** had disappeared, however, a new oxymethine signal at δ 4.20 (1H, d, $J=11.5$ Hz) was observed, suggesting the introduction of an OH group at C-9 position. It was supported by the fact that the signal of C-9 was shifted downfield at δ 76.24 (d) in ^{13}C NMR spectrum of **28** as compared with that of **27** at δ 37.18 (t), and by the correlations of this activated carbon with H-3, H-7, H-10 and H-19 in HMBC spectrum. The stereochemistry of 9-OH was determined to be α-configuration by the NOE difference spectrum, in which the integration values of H-16 and H-19 were enhanced when H-9 was irradiated. Therefore, the structure of **28** was elucidated to be 9α-hydroxy-2α,5α,7β,10β,14β-pentaacetoxy-taxa-4(20),11-diene.

Thus, with the aid of simple chemical acetylation, the two selective 9α and 7β bio-oxidations of taxuyunanine C were combined by the cell cultures of *G. biloba* and fungus *A. coerulea*. The results suggested that the structure of the substrate (substituent, polarity, etc.) had influenced on the enzymatic process, and there have already been a great many of reports on it.[26,30–33] On the other hand, it was implied that subtle modification to the structure of substrate (i.e. substrate engineering) was one of the most efficient and simplest methods for obtaining helpful changes (e.g. biotransformation mode, yield, etc.) in biotransformation. Furthermore, the biotransformation of taxanes by employing plant and/or microbial cells may biomimic some steps of taxoid biosynthesis, not only extensive oxidations of the taxane skeleton, but also the order(s) of these functionalizations. It is well known that 9α and 7β oxidations are the two key steps in the taxoid biosynthesis, however, the order of the two steps of taxoids biosynthesis still remains unclear. Our results might somewhat provide a hypothesis that the 7β hydroxylation would occur before 9α functionalization or



Scheme 4. Combination of 9α and 7β oxidations of **1** by *A. coerulea* and *Ginkgo* cells.

after 9α acetoxylation, while, 9α hydroxylation would occur before 7β functionalization or after 7β acetoxylation. To some extent, the results were in good accordance with the results reported by Croteau and his colleagues recently.[34]

3. Conclusion

In conclusion, three C-14 oxygenated taxanes with different substitution groups at C-14 position could be regio- and stereo-selectively hydroxylated at 7β position by fungus *A. coerulea* in different yields. Moreover, nine new taxoids of the 18 products were obtained from these biotransformatios. Most importantly, the combination of 7β- and 9α-oxidations by two different biocatalytic systems, *A. coerulea* and *Ginkgo* cells, has been achieved with the aid of simple chemical modification of the substrates. The results would supply the very useful intermediates for the semi-synthesis of paclitaxel and other bioactive taxoids from readily available natural products—taxuyunanine C and/or its analogs, although in low yields. Additionally, these results might provide a useful tool to probe some important biosynthetic steps of taxoids and/or the order of these steps in *Taxus* plant.

4. Experimental

4.1. General

Optical rotations were obtained using a Horiba SEPA-200 polarimeter. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with a Varian Unity-PS instrument using $CDCl_3$ as solvent and internal standard. ^{1}H NMR and ^{13}C NMR assignments were determined by ^{1}H–^{1}H COSY, DEPT, HMQC and HMBC experiments. HRFABMS were carried out on a JEOL-HX 110 FAB-mate instrument and HREIMS on a JEOL-HX 110 instrument. HRESIMS were performed on a Bruker Daltonics APEX II with a 7 T magnet, compounds formed sodiated ions under the ESI condition with a resolution range from 31,000 to 60,000. IR spectra were taken on a Hitachi 270-30 spectrometer in $CHCl_3$. Semi-preparative HPLC was performed on a Hitachi L-6200 HPLC instrument with an Inertsil Prep-sil (GL Science, 25 cm×10 mm i.d.) stainless steel column and an YRU-883 RI/UV bi-detector, the flow rate was 5.0 mL/min unless otherwise mentioned. Silica gel (230–300 mesh) was employed for flash column chromatography, analytical TLC plates (silica gel 60 F_{254}, Merck) were visualized at UV_{254} and by spraying 5% H_2SO_4 (in EtOH) followed by heating. Pyridine for acetylation was distilled from CaH_2, and the reactions were run under an atmosphere of N_2.

4.2. Substrates

Compounds **1**–**3** (purities: >95% by HPLC analyses) were isolated from callus cultures (Ts-19 strain) of *T. chinensis* and identified by chemical and spectral methods.[16,17] the substrates were dissolved in EtOH (50 mg/mL) before use.

4.3. Organisms, media and cultivation conditions

The cell suspension cultures of *G. biloba* were cultivated in 500 mL Erlenmeyer flask with 150 mL of liquid MS medium supplemented with 0.5 mg/L of naphthalene acetic acid, 0.5 mg/L of 6-benzylaminopurine and 0.2 mg/L of 2,4-dichlorophenoxy acetic acid on the rotary shaker at 110 rpm at (25±2) °C in the dark.[35] The inoculum size was 5 g/L of cell cultures (dry weight) and subcultured every 21 days. The cell cultures were maintained in the above conditions before use for the biotransformation. The fungus, *A. coerulea* IFO4011was purchased from Institute for Fermentation, Osaka, Japan (IFO), and kept on solid PDA medium containing potato (200 g/L), sucrose (20 g/L) and agar (2%) at 4 °C. The seed cultures were prepared in 500 mL flask with 150 mL of liquid medium (PDA medium without agar) and incubated for 2 days. Seed cultures (5 mL) was added to 500 mL flask and shaken at 110 rpm at (25±2) °C in the dark for the use of biotransformation.

4.4. Biotransformation of 1 with *A. coerulea*

1 (400 mg) was dissolved in EtOH (8.0 mL), distributed among forty flasks of 2-day-old cultures and incubated for additional 7 days, after which the cultures were filtered under vacuum, and the filtrate was saturated with NaCl and extracted 5 times with ethyl acetate. All the extracts were pooled, dried with anhydrous Na_2SO_4, and concentrated under vacuum at 40 °C to give 700 mg of residue. The dried cell cultures were extracted thrice by sonication with ethyl acetate, the resulting extracts were pooled and concentrated under vacuum at 40 °C to afford 136.9 mg of residue. The above two parts of extracts were combined and separated by combination of open silica gel chromatography and normal phase semi-prep. HPLC to afford **1** (260 mg, 65%; analyzed by TLC and ^{1}H NMR), **4** (4.5 mg, ca. 1%; t_R=7.6 min; mobile phase: hexane/ethyl acetate=50/50, v/v), **5** (20 mg, ca. 5%; t_R=11.3 min; mobile phase: hexane/ethyl acetate=50/50, v/v), **6** (60 mg, ca. 15%; t_R=8.1 min; mobile phase: hexane/ethyl acetate=50/50, v/v), **7** (9.0 mg, ca. 2%; t_R=19.6 min; mobile phase: hexane/ethyl acetate=50/50, v/v), and **8** (4.0 mg, ca. 1%; t_R=11.7 min; mobile phase: hexane/ethyl acetate=30/60, v/v).

4.4.1. 6α-Hydroxy-2α,5α,10β,14β-tetraacetoxy-taxa-4(20),11-diene (7). White powder; $[\alpha]_D^{20}$ +44.9° (*c* 0.5, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3620, 2936, 1732, 1436, 1240, 1102, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (1H, d, *J*=2.0 Hz, H-1), 5.35 (1H, dd, *J*=2.1, 6.4 Hz, H-2), 2.89 (1H, d, *J*=6.3 Hz, H-3), 5.43 (1H, d, *J*=3.7 Hz, H-5), 3.92 (1H, ddd, *J*=4.1, 5.1, 11.8 Hz, H-6), 1.82 (1H, dd, *J*=12.4, 12.4 Hz, H-7β), 1.56 (1H, dd, *J*=5.1, 12.7 Hz, H-7α), 2.35 (1H, dd, *J*=12.2, 14.6 Hz, H-9β), 1.68 (1H, dd, *J*=5.4, 14.9 Hz, H-9α), 6.03 (1H, dd, *J*=5.6, 12.2 Hz, H-10), 2.81 (1H, dd, *J*=9.0, 19.0 Hz, H-13β), 2.44 (1H, dd, *J*=4.9, 19.0 Hz, H-13α), 4.99 (1H, dd, *J*=4.9, 9.3 Hz, H-14), 1.65 (3H, s, H-16), 1.12 (3H, s, H-17), 2.11 (3H, br s, H-18), 0.86 (3H, s, H-19), 5.38 (1H, s, H-20a), 4.94 (1H, s, H-20b), 2.24, 2×2.05, 2.02 [3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.8 (d, C-1), 70.4 (d, C-2), 41.2 (d, C-3), 140.0 (s, C-4), 80.4 (d, C-5), 69.1 (d, C-6), 42.2 (t, C-7), 38.0 (s, C-8), 43.5 (t, C-9), 69.9 (d, C-10), 135.4 (s, C-11), 134.9 (s, C-12), 39.4 (t, C-13), 70.2 (d, C-14), 37.3 (s, C-15), 25.4 (q,

C-16), 31.8 (q, C-17), 21.0 (q, C-18), 23.4 (q, C-19), 119.7 (t, C-20), 21.7, 2×21.42, 21.4 [q, OAc (CH_3)], 171.0, 170.1, 170.0, 169.9 [s, OAc (CO)]; HREIMS *m/z* 520.2666 $[M]^+$ (calcd 520.2672 for $C_{28}H_{40}O_9$).

4.5. Biotransformation of 2 with *A. coerulea*

The procedures were performed as described in Section 4.4, except that 540 mg of **2** was used, finally 1162 mg of extract (472 mg for filtrate, 690 mg for cell cultures) was afforded. The extract was fractionated and separated by combination of open silica gel chromatography and normal phase semi-prep. HPLC (in this experiment the flow rate was 4 mL/min) to give **2** (360 mg, 66.7%; analyzed by TLC and ^{1}H NMR), **9** (60 mg, ca. 10%; t_R=34.6 min; mobile phase: hexane/ethyl acetate=70/30, v/v), **10** (4 mg; t_R=23.8 min; mobile phase: hexane/ethyl acetate=75/25, v/v), **11** (12 mg, ca. 2%; t_R=28.1 min; mobile phase: hexane/ethyl acetate=60/40, v/v), **12** (3 mg; t_R=15.9 min; mobile phase: hexane/ethyl acetate=60/30,v/v), **13** and **14** (isomers, 28 mg, ca.5%; t_R=31.7 min; mobile phase: hexane/ethyl acetate=70/30, v/v).

4.5.1. 6α-Hydroxy-2α,5α,10β-triacetoxy-14β-(2-methyl)-butyryloxytaxa-4(20),11-diene (11). White powder; $[\alpha]_D^{20}$ +47.9° (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3620, 2936, 1732, 1436, 1374, 1240, 1102, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (1H, d, *J*=2.0 Hz, H-1), 5.39 (1H, dd, *J*=2.2, 6.6 Hz, H-2), 2.94 (1H, d, *J*=6.4 Hz, H-3), 5.47 (1H, d, *J*=3.9 Hz, H-5), 3.96 (1H, ddd, *J*=3.9, 9.3, 16.1 Hz, H-6), 1.86 (1H, dd, *J*=12.5, 12.5 Hz, H-7β), 1.59 (1H, dd, *J*=5.6, 12.5 Hz, H-7α), 2.35–2.45 (1H, m, H-9β), 1.72 (1H, dd, *J*=5.9, 14.9 Hz, H-9α), 6.07 (1H, dd, *J*=5.6, 12.2 Hz, H-10), 2.88 (1H, dd, *J*=9.2, 19.0 Hz, H-13β), 2.42 (1H, dd, *J*=4.4, 19.0 Hz, H-13α), 5.02 (1H, dd, *J*=4.6, 9.0 Hz, H-14), 1.70 (3H, s, H-16), 1.16 (3H, s, H-17), 2.15 (3H, br s, H-18), 0.90 (3H, s, H-19), 5.41 (1H, s, H-20a), 4.94 (1H, s, H-20b), 2.37 (1H, dq, *J*=6.8, 7.3 Hz, H-2′), 1.68 (1H, dq, *J*=6.8, 7.3 Hz, H-3′a), 1.49 (1H, dq, *J*=7.1, 7.3 Hz, H-3′b), 0.92 (3H, t, *J*=7.3 Hz, H-4′), 1.15 (3H, d, *J*=7.3 Hz, H-5′), 2.29, 2.09, 2.05 [3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.1 (d, C-1), 70.2 (d, C-2), 41.3 (d, C-3), 140.0 (s, C-4), 80.3 (d, C-5), 69.2 (d, C-6), 42.2 (t, C-7), 38.0 (s, C-8), 43.6 (t, C-9), 69.9 (d, C-10), 135.4 (s, C-11), 135.0 (s, C-12), 39.7 (t, C-13), 70.0 (d, C-14), 37.3 (s, C-15), 25.4 (q, C-16), 31.7 (q, C-17), 21.0 (q, C-18), 23.4 (q, C-19), 119.6 (t, C-20), 175.7 (s, C-1′), 41.1 (d, C-2′), 26.8 (t, C-3′), 11.6 (q, C-4′), 16.6 (q, C-5′), 21.8, 21.3, 21.4 [q, OAc (CH_3)], 171.0, 170.1, 169.9 [s, OAc (CO)]; HREIMS *m/z* 562.3154 $[M]^+$ (calcd 562.3142 for $C_{31}H_{46}O_9$).

4.5.2. 7β,10β-Dihydroxy-2α,5α-diacetoxy-14β-(2-methyl)-butyryloxytaxa-4(20),11-diene (12). White powder; $[\alpha]_D^{20}$ +59.5° (*c* 0.3, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3624, 2972, 2940, 1732, 1460, 1376, 1244, 1214, 1154, 1084, 1058, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.87 (1H, d, *J*=2.0 Hz, H-1), 5.42 (1H, dd, *J*=2.2, 6.6 Hz, H-2), 2.83 (1H, d, *J*=6.6 Hz, H-3), 5.33 (1H, t, *J*=3.4 Hz, H-5), 2.05–2.15 (1H, m, H-6α), 1.58–1.62 (1H, m, H-6β), 3.83 (1H, dd, *J*=5.1, 12.2 Hz, H-7), 2.25–2.35 (1H, m, H-9β), 2.10–2.16 (1H, m, H-9α), 5.08 (1H, dd, *J*=5.4, 11.7 Hz, H-10), 2.83 (1H, dd, *J*=9.3, 19.0 Hz, H-13β), 2.37 (1H, dd, *J*=5.1, 19.0 Hz, H-13α), 4.95 (1H, dd, *J*=4.9, 9.3 Hz, H-14), 1.76 (3H, s, H-16), 1.19 (3H, s, H-17), 1.95 (3H, br s, H-18), 0.76 (3H, s, H-19), 5.28 (1H, s, H-20a), 4.88 (1H, s, H-20b), 2.26–2.38 (1H, m, H-2′), 1.64–1.72 (1H, m, H-3′a), 1.45–1.52 (1H, m, H-3′b), 0.89 (3H, t, *J*=7.3 Hz, H-4′), 1.12 (3H, d, *J*=6.8 Hz, H-5′), 2.18, 2.07 [3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.4 (d, C-1), 70.1 (d, C-2), 40.4 (d, C-3), 140.4 (s, C-4), 77.5 (d, C-5), 37.5 (t, C-6), 69.3 (d, C-7), 44.4 (s, C-8), 40.5 (t, C-9), 66.9 (d, C-10), 139.0 (s, C-11), 132.2 (s, C-12), 37.0 (t, C-13), 70.2 (d, C-14), 37.4 (s, C-15), 25.4 (q, C-16), 32.0 (q, C-17), 21.2 (q, C-18), 16.7 (q, C-19), 117.9 (t, C-20), 175.7 (s, C-1′), 41.1 (d, C-2′), 26.8 (t, C-3′), 11.6 (q, C-4′), 16.6 (q, C-5′), 21.8, 21.4 [q, OAc (CH_3)], 169.8, 169.9 [s, OAc (CO)]; HRESIMS (negative) *m/z* 519.3019 $[M-H]^+$ (calcd 519.2958 for $C_{29}H_{43}O_8$) and HRESIMS (positive) *m/z* 543.2963 $[M+Na]^+$ (calcd 543.2934 for $C_{29}H_{44}O_8Na$).

4.5.3. 2α,5α,10β-Triacetoxy-14β-[3(*R*)-hydroxy-2(*R*)-methyl]-butyryloxytaxa-4(20),11-diene (14). White powder (mixed with **13**); IR ν_{max} ($CHCl_3$): 3620, 2994, 2936, 1728, 1646, 1240, 1102, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (1H, d, *J*=2.0 Hz, H-1), 5.34 (1H, dd, *J*=2.2, 6.6 Hz, H-2), 2.93 (1H, d, *J*=6.4 Hz, H-3), 5.29 (1H, br s, H-5), 1.76–1.86 (2H, m, H-6), 1.97 (1H, ddd, *J*=6.3, 13.0, 13.0 Hz, H-7α), 1.20–1.26 (1H, m, H-7β), 2.35–2.45 (1H, m, H-9β), 1.64 (1H, dd, *J*=5.8, 13.9 Hz, H-9α), 6.06 (1H, dd, *J*=5.6, 11.9 Hz, H-10), 2.85 (1H, dd, *J*=9.3, 19.0 Hz, H-13β), 2.38–2.46 (1H, m, H-13α), 5.03 (1H, dd, *J*=4.6, 9.0 Hz, H-14), 1.67 (3H, s, H-16), 1.13 (3H, s, H-17), 2.10 (3H, s, H-18), 0.85 (3H, s, H-19), 5.28 (1H, s, H-20a), 4.83 (1H, s, H-20b), 2.40–2.45 (1H, m, H-2′), 4.04 (1H, dq, *J*=6.3, 5.6 Hz, H-3′), 1.16 (3H, d, *J*=7.3 Hz, H-4′), 1.17 (3H, d, *J*=7.0 Hz, H-5′), 2.18, 2.06, 2.04 [s, 3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.2 (d, C-1), 70.5 (d, C-2), 42.1 (d, C-3), 142.2 (s, C-4), 78.2 (d, C-5), 28.9 (t, C-6), 33.8 (t, C-7), 39.7 (s, C-8), 43.9 (t, C-9), 70.0 (d, C-10), 135.4 (s, C-11), 134.6 (s, C-12), 39.5 (t, C-13), 70.8 (d, C-14), 37.3 (s, C-15), 25.4 (q, C-16), 31.7 (q, C-17), 20.9 (q, C-18), 22.5 (q, C-19), 116.9 (t, C-20), 174.7 (s, C-1′), 46.6 (d, C-2′), 68.0 (d, C-3′), 19.9 (q, C-4′), 11.0 (q, C-5′), 21.9, 21.4, 20.9 [q, OAc (CH_3)], 170.2, 170.0, 169.8 [s, OAc (CO)]; HREIMS *m/z* 562.3143 $[M]^+$ (calcd 562.3142 for $C_{31}H_{46}O_9$).

4.6. Biotransformation of 3 with *A. coerulea*

The procedures were carried out as described in Section 4.4, except that 500 mg of **3** was used, finally 973 mg of extract (500 mg for filtrate, 473 mg for cell cultures) was afforded. The extract was fractionated and separated by combination of open silica gel chromatography and normal phase semi-prep. HPLC to yield 300 mg of **3** (ca. 60%; analyzed by TLC and ^{1}H NMR), 50 mg of the mixture of **15** and **16** (ca. 10%; isomers, t_R=13.1 min; mobile phase: hexane/ethyl acetate=7/3, v/v), 76 mg of **17** (ca. 15%; t_R=16.8 min; mobile phase: hexane/ethyl acetate=50/50, v/v), 2 mg of **18** (t_R=12.9 min, mobile phase: hexane/ethyl acetate=50/50, v/v), 25.0 mg of **19** (ca. 5%; t_R=14.7 min; mobile phase: hexane/ethyl acetate=50/50,v/v), 10 mg of **20** (ca. 2%; t_R=18.0 min; mobile phase: hexane/ethyl acetate=1/2, v/v), and 2 mg of **21** (t_R=20.5 min; mobile phase: hexane/ethyl acetate=1/4, v/v).

4.6.1. 2α,5α,10β-Triacetoxy-14β-(2-methyl-3-keto)-butyryloxytaxa-4(20),11-diene (isomers, 15 and 16, the

ratio was 1:1 by ^{1}H NMR analysis). White powder; IR ν_{max} ($CHCl_3$): 3000, 2940, 1730, 1646, 1456, 1376, 1320, 1246, 1230, 1156, 1106, 1072, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (1H, br s, H-1), 5.35 (1H, dd, J=2.4, 6.6 Hz, H-2), 2.910 and 2.904 (1H, d, J=6.1 Hz, H-3, **15** and **16**), 5.28 (1H, br s, H-5), 1.75–1.85 (2H, m, H-6), 1.90–2.02 (1H, m, H-7β), 1.20–1.28 (1H, m, H-7α), 2.32–2.44 (1H, m, H-9β), 1.60–1.70 (1H, m, H-9α), 6.04 (1H, dd, J=5.5, 11.9 Hz, H-10), 2.84 (1H, dd, J=9.3, 19.3 Hz, H-13β), 2.36–2.44 (1H, m, H-13α), 5.033 and 5.024 (1H, dd, J=5.1, 9.8 Hz, H-14, **15** and **16**), 1.65 (3H, s, H-16), 1.08 and 1.07 (3H, s, H-17, **15** and **16**), 2.09 (3H, br s, H-18), 0.84 (3H, s, H-19), 3.471 and 3.465 (1H, q, J=7.2 Hz, H-2′, **15** and **16**), 2.22 and 2.21 (3H, s, H-4′, **15** and **16**), 1.32 (3H, d, J=7.3 Hz, H-5′), 2.086 (3H, s, 2-OAc), 2.176 and 2.168 (3H, 5-OAc, **15** and **16**), 2.043 and 2.035 (3H, s, 10-OAc, **15** and **16**); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.02 and 59.00 (d, C-1, **15** and **16**), 70.39 and 70.33 (d, C-2, **15** and **16**), 42.13 and 42.11 (d, C-3, **15** and **16**), 142.19 and 142.14 (s, C-4, **15** and **16**), 78.2 (d, C-5), 29.0 (t, C-6), 33.80 and 33.77 (t, C-7, **15** and **16**), 39.7 (s, C-8), 43.8 (t, C-9), 70.00 and 69.98 (d, C-10, **15** and **16**), 135.44 and 135.34 (s, C-11, **15** and **16**), 134.53 and 134.44 (s, C-12, **15** and **16**), 39.27 and 39.16 (t, C-13, **15** and **16**), 71.7 (d, C-14), 37.20 and 37.18 (s, C-15, **15** and **16**), 25.3 (q, C-16), 31.6 (q, C-17), 21.4 (q, C-18), 22.5 (q, C-19), 116.94 and 116.91 (t, C-20, **15** and **16**), 169.43 and 169.35 (s, C-1′, **15** and **16**), 53.59 and 53.57 (d, C-2′, **15** and **16**), 203.47 and 203.33 (s, C-3′, **15** and **16**), 28.64 and 28.57 (q, C-4′, **15** and **16**), 12.7 (q, C-5′), 21.4 (q, 2-OAc), 21.9 (q, 5-OAc), 20.92 and 20.90 (q, 10-OAc, **15** and **16**), 169.98 and 169.91 (s, 2-OAc, **15** and **16**), 169.76 and 169.73 (s, 5-OAc, **15** and **16**), 170.23 and 170.21 (s, 10-OAc, **15** and **16**); HREIMS m/z 560.2987 $[M]^+$ (calcd 560.2985 for $C_{31}H_{44}O_9$).

4.6.2. 9α-Hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (18). White powder; $[\alpha]_D^{20}$ +45.8° (c 0.4, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3624, 3540, 3036, 2988, 1726, 1644, 1456, 1374, 1248, 1178, 1108, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.81 (1H, d, J=2.0 Hz, H-1), 5.28 (1H, dd, J=2.2, 6.6 Hz, H-2), 2.87 (1H, d, J=6.6 Hz, H-3), 5.25 (1H, br s, H-5), 1.73–1.79 (2H, m, H-6), 1.60–1.70 (1H, m, H-7β), 1.49 (1H, dd, J=5.5, 13.6 Hz, H-7α), 4.14 (1H, d, J=9.8 Hz, H-9), 5.75 (1H, d, J=9.8 Hz, H-10), 2.81 (1H, dd, J=9.0, 19.0 Hz, H-13β), 2.28–2.35 (1H, m, H-13α), 4.94 (1H, dd, J=4.6, 9.0 Hz, H-14), 1.53 (3H, s, H-16), 1.05 (3H, s, H-17), 2.07 (3H, br s, H-18), 0.99 (3H, s, H-19), 5.25 (1H, s, H-20a), 4.81 (1H, s, H-20b), 2.32 (1H, dq, J=7.0, 7.4 Hz, H-2′), 3.79 (1H, dq, J=7.0, 6.4 Hz, H-3′), 1.13 (3H, d, J=6.4 Hz, H-4′), 1.08 (3H, d, J=7.4 Hz, H-5′), 2.12, 2.05, 1.96 [3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.9 (d, C-1), 70.0 (d, C-2), 44.1 (d, C-3), 141.8 (s, C-4), 78.6 (d, C-5), 28.5 (t, C-6), 25.9 (t, C-7), 44.1 (s, C-8), 76.2 (d, C-9), 76.0 (d, C-10), 136.8 (s, C-11), 133.3 (s, C-12), 39.6 (t, C-13), 70.5 (d, C-14), 37.1 (s, C-15), 26.2 (q, C-16), 31.5 (q, C-17), 21.0 (q, C-18), 17.5 (q, C-19), 117.7 (t, C-20), 174.8 (s, C-1′), 47.0 (d, C-2′), 69.5 (d, C-3′), 20.9 (q, C-4′), 14.0 (q, C-5′), 21.9, 21.4, 21.3 [q, OAc (CH_3)], 170.5, 169.9, 170.0 [s, OAc (CO)]; HREIMS m/z 578.3102 $[M]^+$ (calcd 578.3091 for $C_{31}H_{46}O_{10}$).

4.6.3. 6α-Hydroxy-2α,5α,10β-triacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (20). White powder; $[\alpha]_D^{20}$ +44.4° (c 1.0, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3612, 2940, 1730, 1606, 1458, 1376, 1320, 1240, 1166, 1112, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (1H, d, J=2.2 Hz, H-1), 5.35 (1H, dd, J=2.2, 6.6 Hz, H-2), 2.89 (1H, d, J=6.6 Hz, H-3), 5.43 (1H, d, J=3.9 Hz, H-5), 3.92 (1H, ddd, J=3.9, 5.3, 12.0 Hz, H-6), 1.82 (1H, dd, J=12.4, 12.4 Hz, H-7β), 1.56 (1H, dd, J=5.1, 12.5 Hz, H-7α), 2.35 (1H, dd, J=12.2, 14.9 Hz, H-9β), 1.68 (1H, dd, J=5.6, 14.9 Hz, H-9α), 6.03 (1H, dd, J=5.6, 12.0 Hz, H-10), 2.84 (1H, dd, J=9.2, 19.0 Hz, H-13β), 2.39 (1H, dd, J=4.6, 19.0 Hz, H-13α), 5.02 (1H, dd, J=4.6, 9.3 Hz, H-14), 1.63 (3H, s, H-16), 1.12 (3H, s, H-17), 2.11 (3H, br s, H-18), 0.86 (3H, s, H-19), 5.38 (1H, s, H-20a), 4.91 (1H, s, H-20b), 2.39 (dq, J=7.0, 7.3 Hz, H-2′), 3.86 (1H, dq, J=6.3, 7.0 Hz, H-3′), 1.20 (3H, d, J=6.3 Hz, H-4′), 1.15 (3H, d, J=7.3 Hz, H-5′), 2.25, 2.05, 2.02 [3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.9 (d, C-1), 70.2 (d, C-2), 41.3 (d, C-3), 134.0 (s, C-4), 80.3 (d, C-5), 69.1 (d, C-6), 42.2 (t, C-7), 38.0 (s, C-8), 43.5 (t, C-9), 69.8 (d, C-10), 135.4 (s, C-11), 134.8 (s, C-12), 39.5 (t, C-13), 70.6 (d, C-14), 37.2 (s, C-15), 25.3 (q, C-16), 31.7 (q, C-17), 22.0 (q, C-18), 23.4 (q, C-19), 119.7 (t, C-20), 174.8 (s, C-1′), 47.0 (d, C-2′), 69.5 (d, C-3′), 20.9 (q, C-4′), 14.0 (q, C-5′), 21.8, 21.4, 21.4 [q, OAc (CH_3)], 171.0, 170.1, 169.9 [s, OAc (CO)]; HREIMS m/z 578.3084 $[M]^+$ (calcd 578.3091 for $C_{31}H_{46}O_{10}$).

4.6.4. 7β,10β-Dihydroxy-2α,5α-diacetoxy-14β-(3-hydroxy-2-methyl)-butyryloxytaxa-4(20),11-diene (21). White powder; $[\alpha]_D^{20}$ +45.0° (c 0.3, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3624, 2992, 2944, 1732, 1644, 1456, 1376, 1320, 1242, 1220, 1168, 1114, 1048, 1004 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (1H, d, J=2.0 Hz, H-1), 5.42 (1H, dd, J=2.2, 6.6 Hz, H-2), 2.89 (1H, d, J=6.4 Hz, H-3), 5.23 (1H, t, J=3.9 Hz, H-5), 2.08–2.16 (1H, m, H-6α), 1.60–1.70 (1H, m, H-6β), 3.82 (1H, dd, J=5.0, 11.4 Hz, H-7), 2.29 (1H, dd, J=5.4, 14.9 Hz, H-9β), 1.68 (1H, dd, J=10.7, 14.9 Hz, H-9α), 5.08 (1H, dd, J=5.4, 10.7 Hz, H-10), 2.80 (1H, dd, J=9.3, 18.8 Hz, H-13β), 2.39 (1H, dd, J=4.9, 18.8 Hz, H-13α), 4.99 (1H, dd, J=4.9, 9.3 Hz, H-14), 1.75 (3H, s, H-16), 1.19 (3H, s, H-17), 1.95 (3H, br s, H-18), 0.76 (3H, s, H-19), 5.29 (1H, s, H-20a), 4.89 (1H, s, H-20b), 2.39 (1H, dq, J=7.0, 7.3 Hz, H-2′), 3.86 (1H, dq, J=7.0, 6.3 Hz, H-3′), 1.21 (3H, d, J=7.3 Hz, H-4′), 1.16 (3H, d, J=7.3 Hz, H-5′), 2.19, 2.03 [3H each, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.2 (d, C-1), 70.1 (d, C-2), 40.4 (d, C-3), 140.9 (s, C-4), 77.6 (d, C-5), 37.5 (t, C-6), 69.2 (d, C-7), 44.4 (s, C-8), 40.5 (t, C-9), 66.9 (d, C-10), 139.1 (s, C-11), 132.0 (s, C-12), 39.5 (t, C-13), 70.8 (d, C-14), 37.4 (s, C-15), 25.4 (q, C-16), 31.9 (q, C-17), 21.1 (q, C-18), 16.7 (q, C-19), 118.0 (t, C-20), 174.8 (s, C-1′), 47.0 (d, C-2′), 69.5 (d, C-3′), 14.1 (q, C-4′), 20.9 (q, C-5′), 21.8, 21.4 [q, OAc (CH_3)], 169.8, 169.6 [s, OAc (CO)]; HRFABMS m/z 559.2886 $[M+Na]^+$ (calcd 559.2883 for $C_{29}H_{44}O_9Na$).

4.7. Biotransformation of 4 by *A. coerulea*

The procedures were followed as described in Section 4.4, except that 200 mg of **4** (prepared from biotransformation of **1** by *Ginkgo* cells[23]) was used, finally 373 mg of extract (200 mg for filtrate, 173 mg for cell cultures) was resulted. The extract was fractionated and separated by combination of open silica gel chromatography and normal phase semi-prep. HPLC. **4** (160 mg) (80%; t_R=11.9 min) and 4.0 mg of

22 (ca. 2%; t_R=15.3 min) were obtained, the HPLC mobile phase was the mixture of hexane and ethyl acetate (70/30, v/v).

4.8. Biotransformation of 5 by cell suspension cultures of *G. biloba*

Compound **5** (20 mg) was dissolved in EtOH (0.4 mL), distributed between 2 flasks of 15-day-old cell cultures and incubated for 6 days, after which the cultures were filtered under vacuum and the filtrate was saturated with NaCl and extracted 5 times with ethyl acetate. All the extracts were pooled, dried with anhydrous Na_2SO_4, and concentrated under vacuum at 40 °C to give 30 mg of residue. The dried cell cultures were extracted 3 times by sonication with ethyl acetate, the resulting extracts were pooled and concentrated under vacuum at 40 °C to afford 40 mg of residue. 12 mg of **5** (60%; t_R=12.3 min) and 2.0 mg of **23** (ca. 10%; t_R=14.2 min) were obtained by combination of open silica gel column chromatography and semi-prep. HPLC (mobile phase: hexane/ethyl acetate=70/30, v/v).

4.8.1. 7β,10β-Dihydroxy-2α,5α,14β-triacetoxy-taxa-4(20),11-diene (23). White powder; $[\alpha]_D^{20}$ +42.5° (*c* 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3624, 2992, 2944, 1732, 1644, 1456, 1376, 1242, 1114, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.87 (1H, d, *J*=2.0 Hz, H-1), 5.42 (1H, dd, *J*=2.2, 6.6 Hz, H-2), 2.83 (1H, d, *J*=6.1 Hz, H-3), 5.33 (1H, t, *J*=3.4 Hz, H-5), 2.06–2.14 (1H, m, H-6α), 1.58–1.64 (1H, m, H-6β), 3.83 (1H, dd, *J*=5.1, 11.7 Hz, H-7), 2.30 (1H, dd, *J*=5.1, 15.1 Hz, H-9β), 2.09–2.24 (1H, m, H-9α), 5.08 (1H, dd, *J*=5.1, 12.0 Hz, H-10), 2.83 (1H, dd, *J*=9.3, 19.3 Hz, H-13β), 2.37 (1H, dd, *J*=4.9, 19.0 Hz, H-13α), 4.95 (1H, dd, *J*=4.9, 9.3 Hz, H-14), 1.76 (3H, s, H-16), 1.19 (3H, s, H-17), 1.95 (3H, br s, H-18), 0.75 (3H, s, H-19), 5.28 (1H, s, H-20a), 4.88 (1H, s, H-20b), 2.18, 2.07, 2.03 [3H each, s, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.3 (d, C-1), 70.1 (d, C-2), 40.4 (d, C-3), 140.9 (s, C-4), 77.5 (d, C-5), 37.6 (t, C-6), 69.2 (d, C-7), 44.4 (s, C-8), 40.5 (t, C-9), 66.9 (d, C-10), 139.2 (s, C-11), 132.3 (s, C-12), 39.6 (t, C-13), 70.2 (d, C-14), 37.4 (s, C-15), 25.5 (q, C-16), 31.9 (q, C-17), 21.2 (q, C-18), 16.7 (q, C-19), 118.0 (t, C-20), 21.8, 21.5, 21.4 [q, OAc (CH_3)], 170.2, 169.8, 169.6 [s, OAc (CO)]; HRFABMS *m/z* 501.2472 $[M+Na]^+$ (calcd 501.2464 for $C_{26}H_{38}O_8Na$).

4.9. Acetylation of 4 and 5

Into 50 mL of egg-plant flask, 195 mg of **4** (0.375 mmol) and 274.5 mg (2.25 mmol) of 4-(dimethylamino)-pyridine (DMAP) were added and dissolved with 7.5 mL of dry pyridine at ambient temperature by stirring, then 0.352 mL of Ac_2O (3.75 mmol) was added. After 7 h incubation at 50 °C, the reaction was quenched by adding 20 mL of sat. NaCl aq and extracted with ethyl acetate (4×20 mL). The extract was washed with 2 M HCl (3×20 mL) until the pH<5, followed with sat. $NaHCO_3$ aq (2×15 mL) until the pH 7–8, then with sat. NaCl aq (2×10 mL), dried over anhydrous $NaSO_4$ and concentrated to afford 257 mg of residue. The resulting residue was applied to an open silica gel column and eluted with the mixture of hexane and ethyl acetate (7/3, v/v) to afford 200 mg of **24**. The same procedure was performed in the acetylation of **5** (50 mg, 0.096 mmol), finally 50 mg of **27** was obtained.

4.9.1. 2α,5α,9α,10β,14β-Pentaacetoxy-taxa-4(20),11-diene (24). White powder; $[\alpha]_D^{20}$ +50.8° (*c* 1.2, $CHCl_3$); IR ν_{max} ($CHCl_3$): 2964, 1734, 1436, 1374, 1236, 1224, 1114, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.93 (1H, d, *J*=2.2 Hz, H-1), 5.40 (1H, dd, *J*=2.4, 6.6 Hz, H-2), 2.96 (1H, d, *J*=6.6 Hz, H-3), 5.30 (1H, t, *J*=3.6 Hz, H-5), 1.78–1.85 (1H, m, H-6a), 1.65–1.75 (1H, m, H-6b), 1.64–1.72 (2H, m, H-7), 5.79 (1H, d, *J*=10.3 Hz, H-9), 6.01 (1H, d, *J*=10.5 Hz, H-10), 2.84 (1H, dd, *J*=9.0, 19.0 Hz, H-13β), 2.43 (1H, dd, *J*=4.9, 19.0 Hz, H-13α), 4.97 (1H, dd, *J*=4.9, 9.0 Hz, H-14), 1.71 (3H, s, H-16), 1.12 (3H, s, H-17), 2.14 (3H, br s, H-18), 0.84 (3H, s, H-19), 5.32 (1H, s, H-20a), 4.87 (1H, s, H-20b), 2.17, 2.04, 2.03, 2.01, 2.00 [3H each, s, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.5 (d, C-1), 70.2 (d, C-2), 44.1 (d, C-3), 141.4 (s, C-4), 78.3 (d, C-5), 28.3 (t, C-6), 27.3 (t, C-7), 44.4 (s, C-8), 72.5 (d, C-9), 76.8 (d, C-10), 137.3 (s, C-11), 132.8 (s, C-12), 39.4 (t, C-13), 68.9 (d, C-14), 37.0 (s, C-15), 25.8 (q, C-16), 31.6 (q, C-17), 21.8 (q, C-18), 17.3 (q, C-19), 118.1 (t, C-20), 21.4, 21.3, 21.1, 21.0, 20.8 [q, OAc (CH_3)], 170.0, 169.9, 169.8, 169.7, 169.6 [s, OAc(CO)]; HRFABMS *m/z* 585.2676 $[M+Na]^+$ (calcd 585.2676 for $C_{30}H_{42}O_{10}Na$); 563.2857 $[M+H]^+$ (calcd 563.2856 for $C_{30}H_{43}O_{10}$).

4.9.2. 2α,5α,7β,10β,14β-Pentaacetoxy-taxa-4(20),11-diene (27). White powder; $[\alpha]_D^{20}$ +35.5° (*c* 1.4, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3004, 2940, 1730, 1650, 1432, 1374, 1250, 1222, 1216, 1182, 1104, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.90 (1H, d, *J*=2.2 Hz, H-1), 5.39 (1H, dd, *J*=2.2, 6.6 Hz, H-2), 2.85 (1H, d, *J*=6.6 Hz, H-3), 5.34 (1H, t, *J*=2.4 Hz, H-5), 2.04–2.12 (1H, m, H-6α), 1.65–1.74 (1H, m, H-6β), 2.05–2.15 (1H, m, H-9β), 1.94–2.12 (1H, m, H-9α), 5.85 (1H, dd, *J*=6.0, 11.5 Hz, H-10), 2.82 (1H, dd, *J*=9.3, 19.0 Hz, H-13β), 2.42 (1H, dd, *J*=4.9, 19.0 Hz, H-13α), 4.95 (1H, dd, *J*=4.9, 9.0 Hz, H-14), 1.66 (3H, s, H-16), 1.14 (3H, s, H-17), 2.08 (3H, br s, H-18), 0.83 (3H, s, H-19), 5.32 (1H, s, H-20a), 4.94 (1H, s, H-20b), 2.19, 2.10, 2.06, 2.02, 2.01 [3H each, s, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.8 (d, C-1), 69.7 (d, C-2), 41.0 (d, C-3), 140.5 (s, C-4), 76.8 (d, C-5), 33.8 (t, C-6), 70.6 (d, C-7), 43.1 (s, C-8), 37.2 (t, C-9), 69.8 (d, C-10), 135.2 (s, C-11), 134.9 (s, C-12), 39.4 (t, C-13), 70.4 (d, C-14), 37.4 (s, C-15), 25.4 (q, C-16), 31.6 (q, C-17), 21.3 (q, C-18), 17.8 (q, C-19), 118.4 (t, C-20), 21.7, 21.5, 2×21.4, 21.0 [q, OAc (CH_3)], 170.4, 170.0, 169.9, 169.9, 169.5 [s, OAc(CO)]; HRFABMS *m/z* 585.2676 $[M+Na]^+$ (calcd 585.2676 for $C_{30}H_{42}O_{10}Na$); 563.2857 $[M+H]^+$ (calcd 563.2856 for $C_{30}H_{43}O_{10}$).

4.10. Biotransformation of 24 by *A. coerulea*

Compound **24** (200 mg) was used as substrate in this experiment, and the procedures were performed as described in Section 4.4, finally 321 mg of extract was obtained (210 mg for filtrate, 101 mg for cells). 162 mg of **24** (81%; t_R=9.6 min), 4.2 mg of **25** (ca. 2%; t_R=11.1 min) and 8.5 mg of **26** (ca. 4%; t_R=15.16 min) were obtained by combination of open silica gel chromatography and normal phase semi-prep. HPLC (mobile phase: hexane/ethyl acetate=70/30, v/v).

4.10.1. 7β-Hydroxy-2α,5α,9α,10β,14β-pentaacetoxy-taxa-4(20),11-diene (25). White powder; $[\alpha]_D^{20}$ +38.4° (*c* 0.2, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3614, 2972, 2884, 1732,

1646, 1436, 1374, 1240, 1102, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.88 (1H, d, J=2.2 Hz, H-1), 5.41 (1H, dd, J=2.2, 6.0 Hz, H-2), 2.81 (1H, d, J=6.2 Hz, H-3), 5.31 (1H, t, J=2.6 Hz, H-5), 2.09–2.15 (1H, m, H-6α), 1.67–1.73 (1H, m, H-6β), 3.90 (1H, dd, J=5.4, 11.5 Hz, H-7), 5.80 (1H, d, J=11.0 Hz, H-9), 6.05 (1H, d, J=11.5 Hz, H-10), 2.86 (1H, dd, J=9.0, 19.0 Hz, H-13β), 2.40 (1H, dd, J=4.9, 19.0 Hz, H-13α), 4.95 (1H, dd, J=4.9, 9.0 Hz, H-14), 1.71 (3H, s, H-16), 1.21 (3H, s, H-17), 2.15 (3H, br s, H-18), 1.31 (3H, s, H-19), 5.30 (1H, s, H-20a), 4.88 (1H, s, H-20b), 2.17, 2.04, 2.03, 2.01, 2.00 [3H each, s, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.9 (d, C-1), 70.4 (d, C-2), 45.2 (d, C-3), 140.2 (s, C-4), 83.2 (d, C-5), 31.3 (t, C-6), 71.7 (d, C-7), 45.6 (s, C-8), 73.6 (d, C-9), 70.3 (d, C-10), 135.5 (s, C-11), 133.2 (s, C-12), 39.4 (t, C-13), 68.9 (d, C-14), 37.4 (s, C-15), 26.1 (q, C-16), 31.7 (q, C-17), 21.9 (q, C-18), 12.7 (q, C-19), 117.7 (t, C-20), 21.4, 21.3, 21.1, 21.0, 20.8 [q, OAc (CH_3)], 170.4, 170.1, 169.9, 169.3, 168.8 [s, OAc (CO)]; HRFABMS m/z 601.2630 $[M+Na]^+$ (calcd 601.2625 for $C_{30}H_{42}O_{11}Na$); 579.2796 $[M+H]^+$ (calcd 579.2805 for $C_{30}H_{43}O_{11}$).

4.10.2. 14β-Hydroxy-2α,5α, 9α,10β-tetraacetoxy-taxa-4(20),11-diene (26). White powder; $[\alpha]_D^{20}$ +35.8° (c 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3624, 2940, 1736, 1376, 1226, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.80 (1H, d, J=2.0 Hz, H-1), 5.48 (1H, dd, J=2.2, 6.3 Hz, H-2), 2.92 (1H, d, J=6.3 Hz, H-3), 5.27 (1H, t, J=2.9 Hz, H-5), 1.80–1.88 (1H, m, H-6a), 1.65–1.71 (1H, m, H-6b), 1.68–1.75 (2H, m, H-7), 5.81 (1H, d, J=10.3 Hz, H-9), 6.02 (1H, d, J=10.5 Hz, H-10), 2.76 (1H, dd, J=9.0, 18.5 Hz, H-13a), 2.54 (1H, dd, J=4.4, 18.0 Hz, H-13b), 4.08 (1H, dd, J=5.0, 9.0 Hz, H-14), 1.72 (3H, s, H-16), 1.18 (3H, s, H-17), 2.16 (3H, s, H-18), 0.85 (3H, s, H-19), 5.33 (1H, s, H-20a), 4.91 (1H, s, H-20b), 2.16, 2.08, 2.04, 2.02 [3H each, s, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 63.1 (d, C-1), 70.5 (d, C-2), 44.1 (d, C-3), 141.9 (s, C-4), 78.7 (d, C-5), 28.4 (t, C-6), 27.2 (t, C-7), 44.4 (s, C-8), 76.8 (d, C-9), 72.5 (d, C-10), 137.9 (s, C-11), 132.8 (s, C-12), 42.2 (t, C-13), 67.6 (d, C-14), 37.5 (s, C-15), 26.1 (q, C-16), 31.3 (q, C-17), 20.8 (q, C-18), 17.3 (q, C-19), 118.0 (t, C-20), 22.0, 21.6, 21.5, 21.1 [q, OAc (CH_3)], 170.1, 170.0, 169.7, 169.4 [s, OAc (CO)]; HRFABMS m/z 543.2571 $[M+Na]^+$ (calcd 543.2570 for $C_{28}H_{40}O_9Na$); 521.2751 $[M+H]^+$ (calcd 521.2751 for $C_{28}H_{41}O_9$).

4.11. Biotransformation of 27 by cell suspension cultures of *G. biloba*

Compound **27** (50 mg) was used as the substrate in this experiment, and the procedures were performed as described in Section 4.8, finally 95 mg of extract was afforded (63 mg for filtrate, 32 mg for cells). 31 mg of **27** (ca. 60%; t_R=10.1 min), 6.2 mg of **28** (ca. 10%; t_R=12.9 min) were obtained by combination of open silica gel chromatography and normal phase semi-prep. HPLC (mobile phase: hexane/ethyl acetate=70/30, v/v).

4.11.1. 9α-Hydroxy-2α,5α,7β,10β,14β-pentaacetoxy-taxa-4(20),11-diene (28). White powder; $[\alpha]_D^{20}$ +40.6° (c 0.1, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3620, 3026, 2974, 1734, 1644, 1436, 1240, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.87 (1H, d, J=2.3 Hz, H-1), 5.34 (1H, dd, J=2.3, 6.5 Hz, H-2), 2.93 (1H, d, J=6.5 Hz, H-3), 5.33 (1H, t, J=2.6 Hz, H-5), 2.05–2.15 (1H, m, H-6α), 1.60–1.70(1H, m, H-6β), 5.40 (1H, dd, J=5.4, 11.5 Hz, H-7), 4.20 (1H, d, J=11.0 Hz, H-9), 5.85 (1H, d, J=11.5 Hz, H-10), 2.80 (1H, dd, J=9.0, 19.0 Hz, H-13β), 2.38 (1H, dd, J=4.9, 19.0 Hz, H-13α), 4.94 (1H, dd, J=4.9, 9.0 Hz, H-14), 1.65 (3H, s, H-16), 1.16 (3H, s, H-17), 2.13 (3H, s, H-18), 1.25 (3H, s, H-19), 5.25 (1H, s, H-20a), 4.88 (1H, s, H-20b), 2.19, 2.15, 2.06, 2.01, 2.00 [3H each, s, OAc (CH_3)]; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 59.0 (d, C-1), 70.2 (d, C-2), 43.6 (d, C-3), 142.1 (s, C-4), 77.2 (d, C-5), 31.3 (t, C-6), 70.8 (d, C-7), 44.3 (s, C-8), 76.2 (d, C-9), 76.0 (d, C-10), 136.5 (s, C-11), 133.3 (s, C-12), 39.4 (t, C-13), 68.7 (d, C-14), 37.2 (s, C-15), 26.2 (q, C-16), 31.7 (q, C-17), 21.9 (q, C-18), 12.0 (q, C-19), 118.6 (t, C-20), 21.4, 2×21.3, 21.1, 20.6 [q, OAc (CH_3)], 170.5, 2×170.0, 169.9, 168.6 [s, OAc (CO)]; HRFABMS m/z 601.2626 $[M+Na]^+$ (calcd 601.2625 for $C_{30}H_{42}O_{11}Na$); 579.2806 $[M+H]^+$ (calcd 579.2805 for $C_{30}H_{43}O_{11}$).

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Synthesis of 7,9-dideoxybaccatin IV analogs from sinenxan A

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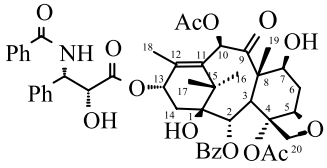
Abstract—Sinenxan A, a taxoid isolated from callus tissue cultures of *Taxus yunnanensis* was converted into 13-oxo-7,9-dideoxy-2-debenzoyl-2-acetyl-baccatin IV and 7,9-dideoxy-2-debenzoyl-4-deacetyl-baccatin IV, a key framework of 1,7,9-trideoxypaclitaxel. Several special steps in this transformation are worthy of note: (1) deoxygenation by treatment with hypophosphorous acid at C-14 position; (2) a highly regioselective *O*-deacetylation of taxanes at C-5 position; and (3) stereoselective reduction of the 13-carbonyl group by transannular assistance from the C-4-hydroxyl.

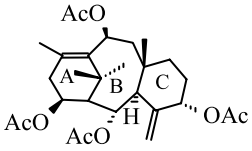
1. Introduction

The diterpenoid paclitaxel (taxol), isolated from the Pacific yew (*Taxus brevifolia Nutt.*) in 1971,[1] is currently one of the most promising antitumor agents available in clinical trials for the treatment of skin, head and neck cancers and has been approved for the treatment of advanced ovarian, breast and lung cancer by FDA. For a long time, paclitaxel, due to its complex molecular structure, significant biological activity and its unique mechanism of action, has been the subject of extensive chemical and biological studies.

Recently, the study of taxanes has been focused on the treatment of multidrug-resistance (MDR) cancer cells, which is mainly caused by the overexpression of P-glycoprotein (P-gp). The overexpression of P-gp results in decreased accumulation of the drug within the cancer cells. Taxane-like multidrug-resistant reversal agents have been discovered that could increase cellular accumulation of vincristin (VCR) in MDR tumor cell, such as taxinine and its derivatives.[2] The 'second-generation' taxoid anticancer agents that would not be recognized by P-gp have also been developed and have displayed a notable activity against the MDR cancer cells, such as SB-RA 4001, IDN-5109, etc.[3]



Paclitaxel



Sinenxan A (SIA)

Sinenxan A that possesses the typical 6/8/6 taxoid ring and lack of 1, 7, and 9 oxygen groups is readily available as a biosynthetic taxane in good yield.[4] The development of a procedure using sinenxan A as the starting material for preparation of 1,7,9-trideoxypaclitaxel and 'second-generation' taxoid anticancer agents will be of significance. Recently, we reported the synthesis of 7,9-dideoxy-2-debenzoyl-4-deacetyl-baccatin IV, a secondary target of 1,7,9-trideoxypaclitaxel via sinenxan A.[5] Herein, we provide a complete account of our work in this area.

2. Results and discussion

2.1. Synthesis of 13-oxo-baccatin IV analogue (10)

Our synthesis (Scheme 1) was started with the functional group manipulation on ring A. Initial attempts to introduce oxygen group at C-13 by treatment with PCC or SeO_2 was failed. It was probably due to the steric hindrance of the acetyl group at C-14. Thus, C-14 oxygen group was designed to be removed above all. 14-Deacetyl-sinenxan A was readily available according to the method of the literature.[6] Although, the yield of *O*-deacetyl of C-14 was

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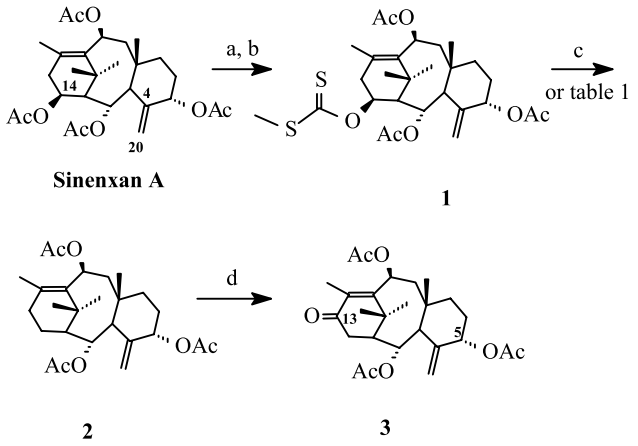


Scheme 1. (a) K_2CO_3/MeOH, 40%; (b) NaH/CS_2/THF, then MeI, 95%; (c) Bu_3SnH/AIBN/toluene, 82%; (d) PCC/NaOAc/Celite/benzene, 65% based on 75% conversion.

only 40%, due to the poor selectivity, this could be overcome by reacetylation of the other hydrolysates back to sinenxan A by treatment with Ac_2O/pyridine. The C-14 deoxy compound **2** was prepared from **1**, via the *S*-methyl-dithiocarbonate, using Barton's deoxygenation procedure (NaH/CS_2, then with MeI, heat, 95%, followed by Bu_3SnH-AIBN, heat, 82%). Because of toxicity of tin compounds, an alternative deoxygenation method was utilized to prepare **2** by treatment of **1** with hypophosphorous acid. Studies indicated addition of an olefin was necessary to raise the yield of **2** (Table 1). It could be explained that the additional olefin would quench the excess phosphorus radical produced in the reaction, which may further, react with $\Delta^{4,20}$ double bond of taxane. After C-14 oxygen group was removed, compound **3** was successfully obtained in moderate yield by allylic oxidation (PCC in refluxing benzene) at C-13. In this step, the reaction time had to be controlled because the newly formed **3** in reaction mixture would be diminished after a long time of heating.

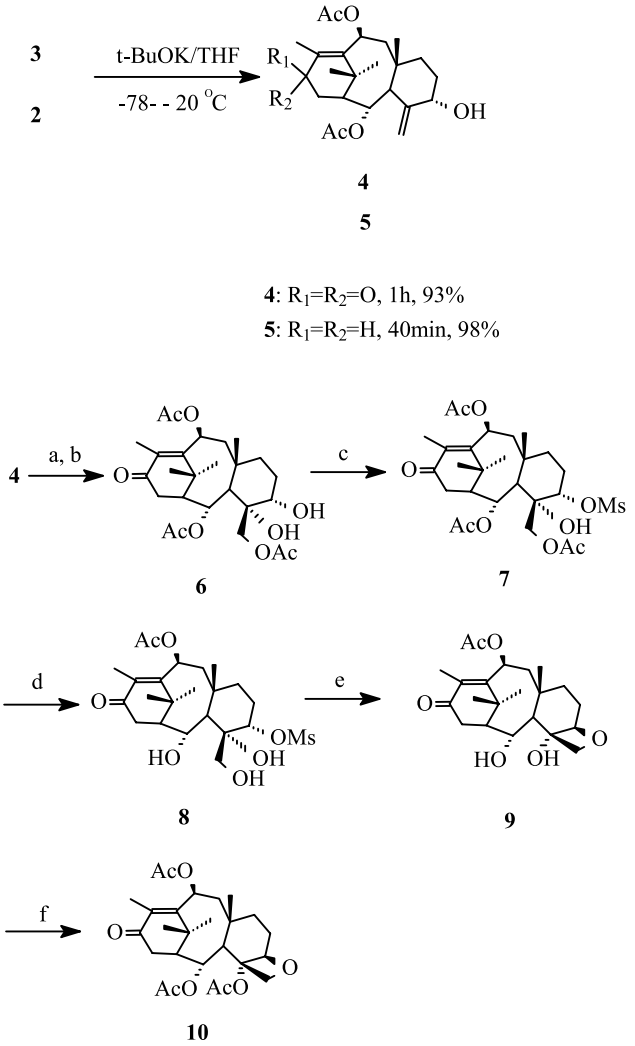
Table 1. Deoxygenation of C-14 *S*-methyl-dithiocarbonate with hypophosphorous acid

Entry	Conditions	**2** (%)
1	50% H_3PO_2, AIBN, Et_3N, 1,4-dioxane	42
2	50% H_3PO_2, AIBN, i-Pr_2EtN, 1,4-dioxane	39
3	50% H_3PO_2, AIBN, Et_3N, cyclohexene, 1,4-dioxane	74
4	50% H_3PO_2, AIBN, Et_3N, 1-dodecene, 1,4-dioxane	75

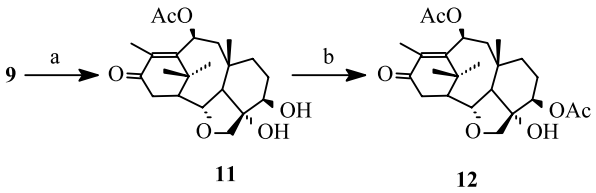
Various methods for preparation of 7-deoxypaclitaxel from 13-oxo taxane such as taxine B have been reported. A similar synthetic route was designed following literature methods.[7] Thus, the next target was the construction of ring D. *O*-Deacetyl of the three acetyl groups of **3** with K_2CO_3/MeOH was in the order of C-10 > C-2 > C-5. Thus, initial synthetic strategy of thorough hydrolysis and then selective acetylation was used to deal with **3** to obtain compound **4**, but the yield was low. Fortuitously, we found that the 5-*O*-acetate of **3** could be selectively cleaved by *t*-BuOK in THF to give **4** in 93% yield. And this regioselective deacetylation by *t*-BuOK could also be used to remove 5-*O*-acetyl group of compound **2** in good yield. A possible mechanism involving the formation of ketene has been proposed in our previous study.[8]

In an attempt to construct an oxetane moiety, treatment of **4** with OsO_4/NMO, followed by Ac_2O afforded **6** as the major product. The configuration of 4-β-CH_2OH was confirmed by NOE differential spectra. The secondary hydroxyl group at C-5 was mesylated to give **7**. Because of intramolecular acetyl transfer, 2-acetyl and 20-acetyl were removed at the same time to provide compound **8** in quantitative yield. The oxetane ring was formed according to Potier's procedure[9] to give **9** in 36% yield. To protect **9** from opening of the oxetane ring, the newly formed **9** was immediately converted into **10** by treatment with Ac_2O/DMAP (Scheme 2).

Noticeably, compound **9** was very sensitive to acidic medium so that a trace of acidic impurities in $CDCl_3$, which did not be processed by K_2CO_3 would convert the oxetane ring to a furan ring (**11**) (Scheme 3). The protons at C-20 position of **11** had a characteristic coupling constant $J = 10$ Hz of furan ring, which was in agreement with the literature.[10] And **12**, obtained from **11**, was observed a evident H-5 shift from 3.96 to 4.99 ppm, which indicated an acetylation at 5-hydroxy.



Scheme 2. (a) OsO_4/NMO, then $NaHSO_3$; (b) Ac_2O/CH_2Cl_2/pyridine, two steps 85%; (c) MsCl/pyridine, 86%; (d) K_2CO_3/MeOH, quantitative; (e) DBU/toluene, 36%; (f) Ac_2O/DMAP/pyridine, 63%.



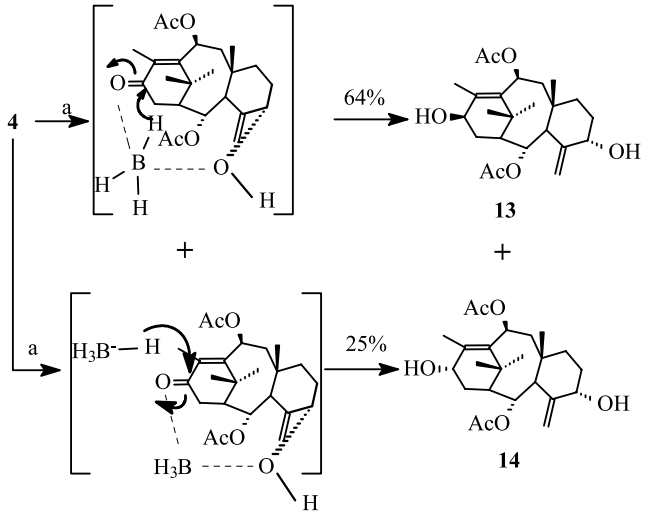
Scheme 3. (a) $CDCl_3$, quantitative; (b) Ac_2O/pyridine, 90%.

Although, we have had 13-oxo-baccatin IV analogue (**10**), all attempts to reduce 13-oxo of **10** to 13-α-hydroxy, including using $NaBH_4$, K-selectride as reductants, were unsuccessful.

2.2. Reduction of 13-ketone

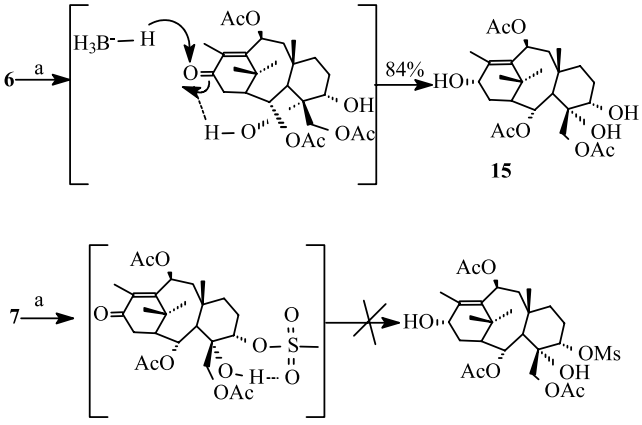
Since the oxetane ring is unstable under certain reaction conditions, we considered to study the reduction of 13-ketone prior to ring closure. $NaBH_4$, as a mild reductant, which hardly attacks other functional groups on the taxane skeleton, was employed to investigate reduction of 13-ketone. Compound **3** and **4** were used to study the reduction of 13-ketone. Like **10**, reduction of **3** using $NaBH_4$ was also failed to yield any expected alcohol product. When **4** was treated with an excess $NaBH_4$, both 13-α-OH (25%) and 13-β-OH (64%) products were obtained (Scheme 4). A transannular delivery of borohydride reagent[11] may explain the formation of 13-β-OH product. The exposed 5-OH of **4** was bonded to borohydride and this borohydride was conjugated to the C-13 ketone, and then attacked 13-ketone below the face to give 13-β-OH product. It was interesting that the 13-α-OH product **14** was also formed. It was very difficult to give an exact explanation, because the conformation of **3** is hardly different from that of **4** from their molecular models. Maybe the borohydride bonding to the C-13 ketone and the C-5 hydroxy caused a little tortion of the carbonyl group of **4** toward inside of the 'cup' and then excess borohydride reagent attacked the 13-ketone from the top face.

Compound **6** with free 4-OH and 5-OH was also chosen to study the reduction of 13-ketone under the same conditions.



Scheme 4. Reduction of 13-ketone by transannular assistance from the C-5-hydroxyl. (a) $NaBH_4/CeCl_3 \cdot 7H_2O$.

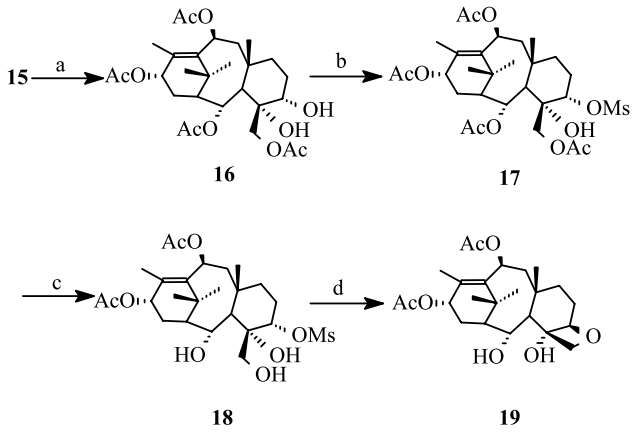
Excitingly, 13-α-alcohol **15** was generated as the major product in 84% yield. From a molecular model of **6**, compound **6** has a ABC ring skeleton, which is quite more flexible than the rigid ABCD ring skeleton of 13-oxo-baccatin III and the distance between C-13-O and C-4-O is so close that a slight torsion of B ring will make the 4-hydroxy group and the 13-oxo group to form a hydrogen bond. Thus, we hypothesized a possible mechanism of the C-13 oxo reduction (Scheme 5). The reason of 13-α-alcohol **15** as the major product could be explained that, on one hand the formation of a hydrogen bond changed the conformation of the A-ring making the C-13 carbonyl vulnerable to the borohydride reagent from top, and on the other hand it also hindered borohydride reagent from conjugating to C-13-O and C-4-O and attacking 13-carbonyl from below. An indirect proof happened to be the same view. When **7** was treated with $NaBH_4/CeCl_3 \cdot 7H_2O$ under the same conditions, the C-13-hydroxyl product was not obtained because the C-4-hydroxyl group formed a hydrogen bond with the 5-mesyl rather than with C-13-oxo group. Thus, without the assistance of the 4-hydroxyl group, the C-13 ketone could not be reduced (Scheme 5).



Scheme 5. Reduction of 13-ketone by transannular assistance from the C-4-hydroxyl. (a) $NaBH_4/CeCl_3 \cdot 7H_2O$.

2.3. Synthesis of 7,9-dideoxy-2-debenzoyl-4-deacetyl-baccatin IV

Having successfully performed the selective reduction of C-13 carbonyl group, we changed our synthetic strategy (Scheme 6). An acetyl group was chosen for protection of 13-hydroxy since, the acetyl group at C-13 could be selectively removed with Red-Al.[12] **16**, prepared from **15** by treatment with Ac_2O in pyridine, was converted into **17** in moderate yield. Because of the steric hindrance extended from the group at C-13 position, the mesylation of C-5-hydroxy was a hard procedure. The reaction conditions needed to be controlled carefully. A higher temperature and a stronger base such as Et_3N resulted in the formation of some byproducts.[13] The acetyl groups at C-20 and C-2 position were selectively removed to give intermediate **18** followed by treatment with DBU in toluene to produce **19** in 93% yield. ^1H NMR spectrum showed that ^2J of H-20 changed from 11 Hz for **15** to 8 Hz for **19**, which indicated the formation of the oxetane ring. Compound **19** has all the desired configuration of the chiral centers of 1,7,9-trideoxypalitaxel, without the amino acid side-chain.



Scheme 6. (a) Ac_2O/pyridine, 87%; (b) MsCl/pyridine, 90% based on 59% conversion; (c) K_2CO_3/MeOH, 97%; (d) DBU/toluene, 93%.

Currently, the synthesis of 1,7,9-trideoxypaclitaxel and its analogs are underway in our group.

3. Conclusion

In conclusion, starting from sinenxan A, we have developed a facile and practical synthetic strategy to fabricate the key framework, 7,9-dideoxy-2-debenzoyl-4-deacetyl-baccatin IV (**19**). The strategy was capitalized on regioselective removal of C-5-acetyl and stereoselective reduction of the 13-carbonyl group by transannular assistance from the C-4-hydroxy. Compound **19** was obtained in 12 steps and 3.5% overall yield from sinenxan A.

4. Experimental

4.1. General

Melting points were obtained on a Yamaco micrometer and all of the temperatures were uncorrected. NMR spectra were recorded on a Bruker AM 300 and Varian INOVA 500 spectrometers (300 and 500 MHz for ^1H and 125 MHz for ^{13}C in $CDCl_3$ unless otherwise noted, TMS as an internal standard). Mass spectra and accurate mass data were obtained on an Autospec-Ultima ETOF spectrometer. Optical rotation was recorded on a Perkin–Elmer 241 polarimeter. TLC analysis was performed on silica gel (GF254) plates and column chromatography over silica gel (200–300 mesh), which were both obtained from Qingdao Ocean Chemicals. Tetrahydrofuran, toluene and benzene were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane was dried with anhydrous potassium carbonate. Pyridine and triethylamine were dried with potassium hydroxide. Commercially available reagents were used as received except as indicated. Sinenxan A was provided by Biosynthetic Laboratory of Institute of Materia Medica.

4.1.1. 4β-*S*-Methyl-dithiocarboxy-2α,5α,10β-triacetoxy-4(20), 11-taxadiene (1). To a solution of 14-deacetylsinenxan A (1.6 g, 3.46 mmol) in 45 mL of THF was added NaH (0.83 g, 20.78 mmol, 60% suspension in mineral oil) and CS_2 (4.1 mL, 69.30 mmol). The resulting red-orange solution was refluxed for 12 h under N_2. The reaction mixture was then cooled to room temperature and treated with methyl iodide (1 mL, 17.32 mmol). After stirred at 40 °C for an additional 2 h, the reaction mixture was filtered through a short silica column. The filtrate was poured into aqueous saturated NH_4Cl (25 mL) and extracted with EtOAc (25 mL×3). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude residue was subjected to chromatography to give corresponding xanthate **1** (1.82 g, 95%) as a light yellow solid.

Compound **1**. Mp: 44–46 °C; ^1H NMR (300 MHz $CDCl_3$, δ ppm) 6.07 (dd, 1H, J=5.7, 12 Hz, H-10), 5.80 (dd, 1H, J=4.5, 9.0 Hz, H-14), 5.39 (dd, 1H, J=2.1, 6.6 Hz, H-2), 5.29 (t, 1H, J=2.7 Hz, H-5), 5.27 (s, 1H, H-20), 4.84 (s, 1H, H-20), 3.02 (dd, 1H, J=9.0, 18.9 Hz, H-13), 2.90 (d, 1H, J=6.3 Hz, H-3), 2.52 (s, 3H, OS_2CMe14), 2.49 (dd, 1H, J=3.9, 18.9 Hz, H-13), 2.39 (dd, 1H, J=12.0, 14.7 Hz, H-13), 2.18 (s, 3H, OAc-CH_3), 2.10 (s, 3H, CH_3-18), 2.07 (s, 3H, OAc-CH_3), 2.01 (s, 3H, OAc-CH_3), 2.10–1.91 (m, 2H, H-6, H-1), 1.76–1.82 (m, 2H, H-6, H-7), 1.69 (s, 3H, CH_3-16), 1.63 (dd, 1H, J=5.4, 15.0 Hz, H-9), 1.21–1.24 (m, 1H, H-7), 1.16 (s, 3H, CH_3-17), 0.84 (s, 3H, CH-19$_3$).

4.1.2. 2α,5α,10β-Triacetoxy-4(20), 11-taxadiene (2).

4.1.2.1. Barton's deoxygenation procedure. Under argon, to a solution of thiocarbamate **1** (250 mg, 0.45 mmol) in degassed toluene (35 mL) stirred at 80 °C was added tributyltin hydride (Bu_3SnH, 1.22 mL, 4.53 mmol) and azobis(isobutyronitrile) (AIBN, 8 mg, 0.05 mmol). After the reaction mixture was stirred at this temperature for 7 h, the solvent was removed under reduced pressure. The crude residue was purified through flash chromatography (silica, 10–15% EtOAc in petroleum ether) to produce the deoxygenated compound **3** (165 mg, 82%).

4.1.2.2. Deoxygenation by treatment with hypophosphorous acid. *Method A: in the absence of olefin*. Under argon, to a solution of **1** (40 mg, 0.075 mmol) in degassed dioxane (3 mL) was added Et_3N (54 μL, 0.39 mmol), 50% aqueous H_3PO_2 (38 μL, 0.37 mmol). The reaction solution was refluxed and treated with AIBN (16 mg in 0.8 mL of dioxane, 0.1 mmol) added in eight portions. After being stirred for 4 h, the reaction mixture was diluted with EtOAc (20 mL), and then washed with H_2O (5 mL), aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over Na_2SO_4, concentrated in vacuo. The crude residue was purified by flash chromatography (silica, 10% acetone in petroleum ether) to give compound **3** (14 mg, 42%).

Method B: in the presence of olefin. Under argon, to a solution of **1** (23 mg, 0.043 mmol) in degassed dioxane (2.5 mL) was added Et_3N (35 μL, 0.25 mmol), 50% aqueous H_3PO_2 (24 μL, 0.23 mmol), cyclohexene (20 μL) and AIBN (2 mg in 0.1 mL of dioxane, 0.012 mmol).The reaction mixture was stirred at reflux for 0.5 h. After dilution with EtOAc (15 mL), the organic layer was washed with H_2O (5 mL), aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over Na_2SO_4, concentrated in vacuo. The crude residue was purified by flash chromatography (silica, 10% acetone in petroleum ether) to give compound **3** (14 mg, 74%).

Compound **2**. $[\alpha]_D^{20}$ +54° (*c* 0.8, $CHCl_3$). Mp: 128–131 °C; HR-FAB-MS (Gly+NaCl): found 469.2562, calcd 469.2567, $C_{26}H_{38}O_6+Na^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.06 (dd, 1H, *J*=5.3, 12.3 Hz, H-10), 5.38 (dd, 1H, *J*=2.0, 6.3 Hz, H-2), 5.27 (t, 1H, *J*=3.0 Hz, H-5), 5.25 (s, 1H, H-20), 4.89 (s, 1H, H-20), 3.08 (d, 1H, *J*=6.0 Hz, H-3), 2.44–2.40 (m, 1H, H-13), 2.37 (dd, 1H, *J*=12.0, 14.5 Hz, H-9), 2.12 (s, 3H, OAc-CH_3), 2.06 (s, 3H, CH_3-18), 2.04 (s, 3H, OAc-CH_3), 2.03 (s, 3H, OAc-CH_3), 2.09–1.87 (m, 3H, H-7, 13-H, H-14), 1.82–1.78 (m, 3H, 1-H, 2×H-6), 1.70–1.64 (m, 1H, H-14), 1.59 (s, 3H, CH_3-16), 1.61–1.54 (m, 1H, H-9), 1.25–1.20 (m, 1H, H-7), 1.05 (s, 3H, CH_3-17), 0.85 (s, 3H, CH_3-19); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 170.2 (OAc-C=O), 169.6 (OAc-C=O), 169.6 (OAc-C=O), 144.4 (C-4), 137.0 (C-12), 133.9 (C-11), 116.4 (C-20), 78.7 (C-5), 72.3 (C-2), 70.5 (C-10), 52.0 (C-1), 43.8 (C-9), 41.2 (C-3), 39.7 (C-8), 37.1 (C-15), 33.7 (C-7), 31.7 (C-17), 30.1 (C-13), 29.0 (C-6), 25.3 (C-16), 22.5 (19-CH_3), 22.0 (OAc-CH_3), 21.7 (OAc-CH_3), 21.7 (OAc-CH_3), 21.2 (18-CH_3), 18.3 (C-14).

4.1.3. 2α,5α,10β-Triacetoxy-4(20), 11-taxadien-13-one (3). Under nitrogen, a solution of **2** (1.26 g, 2.83 mmol) in benzene (50 mL) was treated with anhydrous NaOAc (6.95 g, 84.75 mmol), anhydrous Celite (18.2 g) and pyridium chlorochromate (18.2 g, 84.75 mmol), and stirred at reflux for 7 h. The reaction mixture was filtered through silica gel, eluted with Et_2O (500 mL), concentrated, and the residue was purified by flash chromatography (silica, 12% acetone in petroleum ether) to give **3** (650 mg) and recover **2** (300 mg), 65% yield based on 75% conversion.

Ketone **3**. $[\alpha]_D^{20}$ +69° (*c* 0.6, $CHCl_3$). Mp: 72–74 °C; HR-FAB-MS (Gly+NaCl): found 483.2346, calcd 483.2359, $C_{26}H_{36}O_7+Na^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.06 (dd, 1H, *J*=12.0, 5.5 Hz, H-10), 5.46 (dd, 1H, *J*=2.0, 6.5 Hz, H-2), 5.27 (s, 1H, H-20), 5.23 (t, 1H, *J*=3.0 Hz, H-5), 4.82 (s, 1H, H-20), 3.19 (d, 1H, *J*=6.0 Hz, H-3), 2.87 (dd, 1H, *J*=6.7, 19.7 Hz, H-14), 2.48 (dd, 1H, *J*=12.0, 15 Hz, H-9), 2.33 (d, 1H, *J*=19.5 Hz, H-14), 2.20 (s, 3H, OAc-CH_3-10), 2.14 (dd, 1H, *J*=2, 6.7 Hz, H-1), 2.10 (s, 3H, OAc-CH_3-2), 2.06 (s, 3H, OAc-CH_3-5), 1.99 (s, 3H, CH_3-18), 2.14–1.85 (m, 1H, H-7), 1.82–1.74 (m, 3H, 2×H-6, H-9), 1.69 (s, 3H, CH_3-16), 1.25–1.20 (m, 1H, H-7), 1.13 (s, 3H, CH_3-17), 0.90 (s, 3H, CH_3-19); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 199.4 (13-C=O), 170.3 (OAc-C=O), 170.0 (OAc-C=O), 169.8 (OAc-C=O), 153.6 (C-11), 142.5 (C-4), 136.0 (C-12), 116.4 (C-20), 77.8 (C-5), 71.0 (C-10), 70.4 (C-2), 49.0 (C-1), 42.8 (C-9), 40.9 (C-3), 39.6 (C-8), 37.3 (C-15), 36.0 (C-17), 33.7 (C-14), 29.7 (C-7), 29.0 (C-6), 24.7 (C-16), 22.7 (C-19), 21.5 (OAc-CH_3), 21.4 (OAc-CH_3), 21.3 (OAc-CH_3), 13.8 (C-18).

4.1.4. Regioselective deacetylation by treatment with *t*-BuOK.

4.1.4.1. 5α-Hydroxy-2α,10β-diacetoxy-4(20), 11-taxadien-13-one (4). Under nitrogen, to a solution of **4** (80 mg, 0.17 mmol) in dry THF (3 mL) was added *t*-BuOK (78 mg, 0.70 mmol) at −78 °C. The reaction mixture was stirred at −20 °C for 1 h, then diluted with EtOAc (20 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (25% EtOAc in petroleum ether) to yield compound **4** (68 mg, 93%).

Compound **4**. Mp: 153 °C; ESIMS *m/z* 419 (M+1), 441 (M+Na), 457 (M+K); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.11 (dd, 1H, *J*=12.0, 5.5 Hz, H-10), 5.47 (dd, 1H, *J*=2.0, 6.5 Hz, H-2), 5.09 (s, 1H, H-20), 4.75 (s, 1H, H-20), 4.16 (br s, 1H, H-5), 3.52 (d, 1H, *J*=6.0 Hz, H-3), 2.77 (dd, 1H, *J*=7.0, 19.5 Hz, H-14), 2.44 (dd, 1H, *J*=12.3, 14.7 Hz, H-9), 2.37 (d, 1H, *J*=20.0 Hz, H-14), 2.17 (s, 3H, OAc-CH_3-10), 2.12 (dd, 1H, *J*=1.7, 6.7 Hz, H-1), 2.09 (s, 3H, OAc-CH_3-2), 2.07 (s, 3H, CH_3-18), 2.12–2.06 (m, 1H, H-7), 1.76–1.70 (m, 3H, 2×H-6, H-9), 1.69 (s, 3H, CH_3-16), 1.19–1.15 (m, 1H, H-7), 1.13 (s, 3H, CH_3-17), 0.87 (s, 3H, CH_3-19); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 199.9 (13-C=O), 170.0 (OAc-C=O), 169.7 (OAc-C=O), 152.8 (C-11), 147.75 (C-4), 136.8 (C-12), 113.1 (C-20), 76.1 (C-5), 71.1 (C-10), 70.9 (C-2), 49.1 (C-1), 42.9 (C-9), 39.8 (C-3), 39.1 (C-8), 38.0 (C-15), 37.3 (C-17), 36.10 (C-14), 32.9 (C-7, 31.0 (C-6), 24.8 (C-16), 22.5 (C-19), 21.5 (OAc-CH_3), 21.3 (OAc-CH_3), 13.9 (C-18).

4.1.4.2. 5α-Hydroxy-2α,10β-diacetoxy-4(20), 11-taxadiene (5). Under nitrogen, to a solution of **2** (43 mg, 0.096 mmol) in dry THF (3 mL) was added *t*-BuOK (44 mg, 0.39 mmol) at −78 °C. The reaction mixture was stirred at −20 °C for 40 min. The resulting mixture was diluted with EtOAc (20 mL) and poured into saturated aqueous $NaHCO_3$ (5 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (10% acetone in petroleum ether) to yield compound **5** (38 mg, 98%).

Compound **5**. Mp: 53–55 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.11 (dd, 1H, *J*=12.0, 5.5 Hz, H-10), 5.38 (d, 1H, *J*=6.0 Hz, H-2), 5.10 (s, 1H, H-20), 4.80 (s, 1H, H-20), 4.20 (br s, 1H, H-5), 3.35 (d, 1H, *J*=6.0 Hz, H-3), 2.40–2.36 (m, 1H, H-13), 2.33 (dd, 1H, *J*=12.0, 15.0 Hz, H-9), 2.19–2.04 (m, 2H, H-7, H-13), 2.06–2.04 (3s, 9H, 2×OAc-CH_3, CH_3-18), 1.96–1.84 (m, 1H, H-14), 1.78–1.65 (m, 4H, H-1, 2×H-6, H-14), 1.60 (s, 3H, CH_3-16), 1.59 (dd, 1H, *J*=5.5, 15.0 Hz, H-9), 1.20–1.13 (m, 1H, H-7), 1.06 (s, 3H, CH_3-17), 0.83 (s, 3H, CH_3-19).

4.1.5. 4α,5α-Dihydroxy-2α,10β,20-triacetoxy-11-taxen-13-one (6). To a solution of **5** (12 mg, 0.029 mmol) in a mixture of THF (3 mL) acetone (4.5 mL) and water (1.2 mL) under nitrogen was added 4-methylmorpholine *N*-oxide (NMO, 17 mg, 0.14 mmol) and 4% aqueous OsO_4 (18 μL, 0.0029 mmol). After the mixture was vigorously stirred at room temperature for 4 h, 0.5 mL of saturated aqueous $NaHSO_3$ was added and stirring was continued for additional 4 h. The reaction mixture was concentrated in vacuo, poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (15 mL×3). The combined organic phase was washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo to give crude product (14 mg).

To a stirred solution of this crude triol compound in a mixed solvent of CH_2Cl_2 (3 mL) and pyridine (2 mL) was added Ac_2O (0.032 mL, 0.34 mmol). After the mixture was stirred at room temperature for 4 h, methanol (0.05 mL) was added to quench the reaction. The resulting mixture was

neutralized with 1 mol/L aqueous HCl and diluted with EtOAc (20 mL). The organic layer was separated, washed with 1 mol/L aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated and purified by TLC (60% EtOAc in petroleum ether) to give desired diol **6** (12 mg, 85%) as a white powder.

Diol **6**. $[\alpha]_D^{20}$ +90° (*c* 1.0, $CHCl_3$). Mp: 198–200 °C; HR-FABMS (Gly+NaCl): found 517.2400, calcd 517.2414, $C_{26}H_{38}O_9+Na^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.04 (dd, 1H, *J*=12.0, 5.0 Hz, H-10), 5.49 (dd, 1H, *J*=2.0, 5.0 Hz, H-2), 4.49 (d, 1H, *J*=11.5 Hz, H-20), 4.04 (d, 1H, *J*=12.0 Hz, H-20), 3.80 (t, *J*=2.7 Hz, 1H, H-5), 3.14 (d, 1H, *J*=19.7 Hz, H-14), 2.99 (d, 1H, *J*=5.0 Hz, H-3), 2.72 (dd, 1H, *J*=6.7, 19.7 Hz, H-14), 2.40 (dd, 1H, *J*=12.5, 15 Hz, H-9), 2.24 (s, 3H, OAc-CH_3-20), 2.19–2.16 (m, 1H, H-1), 2.12 (s, 3H, OAc-CH_3-10), 2.08 (s, 3H, OAc-CH_3-2), 2.07 (s, 3H, CH_3-18), 2.04–1.98 (m, 1H, H-7), 1.81–1.72 (m, 2H, 2×H-6), 1.68 (s, 3H, CH_3-16), 1.54 (dd, 1H, *J*=5.5, 15 Hz, H-9), 1.13 (s, 3H, CH_3-17), 1.11–1.07 (m, 1H, H-7), 0.89 (s, 3H, CH_3-19); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 200.4 (C=O-13), 171.3 (OAc-C=O), 169.9 (OAc-C=O), 169.8 (OAc-C=O), 152.2 (C-11), 137.2 (C-12), 77.1 (C-5), 72.6 (C-4), 70.9 (C-10), 69.4 (C-2), 65.5 (C-20), 48.4 (C-1), 44.2 (C-9), 41.4 (C-3), 38.2 (C-8), 37.5 (C-15), 37.3 (C-17), 35.8 (C-14), 31.0 (C-7), 24.6 (C-6), 24.5 (C-16), 24.2 (C-19), 21.6 (OAc-CH_3), 21.2 (OAc-CH_3), 20.8 (OAc-CH_3), 13.3 (C-18).

4.1.6. 5α-Methanesulfonyloxy-4α-hydroxy-2α,10β,20-triacetoxy-11-taxen-13-one (7). To a solution of **6** (10 mg, 0.02 mmol) in pyridine (2 mL) was added methanesulfonyl chloride (8 μL, 0.1 mmol). The reaction mixture was stirred at room temperature for 2.5 h, and then warmed to 30–40 °C for additional 4 h. The reaction was quenched with ice-water (0.2 mL). The mixture was diluted with EtOAc (20 mL) and adjusted to pH 6–7 with 1 mol/L aqueous HCl. The organic layer was separated, washed with 1 mol/L aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, concentrated and purified by TLC (30% acetone in petroleum ether) to give compound **7** (10 mg, 86%).

Mesylate **7**. ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 6.04 (dd, 1H, *J*=12.0, 5.1 Hz, H-10), 5.30 (dd, 1H, *J*=2.1, 4.8 Hz, H-2), 4.97 (br s, 1H, H-5), 4.71 (d, 1H, *J*=12.3 Hz, H-20), 3.96 (d, 1H, *J*=12.6 Hz, H-20), 3.06 (d, 1H, *J*=19.5 Hz, H-14), 3.01 (s, 3H, CH_3SO_2), 2.86 (d, 1H, *J*=4.5 Hz, H-3), 2.75 (dd, 1H, *J*=6.9, 19.5 Hz, H-14), 2.43 (dd, 1H, *J*=12.0, 15.3 Hz, H-9), 2.24 (s, 3H, OAc-CH_3-20), 2.18 (s, 3H, OAc-CH_3-10), 2.12 (s, 3H, OAc-CH_3-2), 2.08 (s, 3H, CH_3-18), 2.19–2.05 (m, 2H, H-1,H-7), 1.97–1.95 (m, 2H, 2×H-6), 1.68 (s, 3H, CH_3-16), 1.59 (dd, 1H, *J*=5.7, 15.0 Hz, H-9), 1.27–1.25 (m, 1H, H-7), 1.149 (s, 3H, CH_3-17), 0.93 (s, 3H, CH_3-19).

4.1.7. 5α-Methanesulfonyloxy-2α,4α,20-triihydroxy-10β-acetoxy-11-taxen-13-one (8). To a solution of **7** (70 mg, 0.12 mmol) in methanol (2 mL) was added 1 mol/L aqueous K_2CO_3 (0.25 mL, 0.25 mmol). The reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with 1 mol/L aqueous HCl, and the resulting mixture was concentrated and extracted with EtOAc (10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography to give compound **8** (59 mg, 99%).

Triol **8**. FABMS *m/z* 489 (M+1), 511 (M+Na), 527 (M+K); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.00 (dd, 1H, *J*=12.0, 5.5 Hz, H-10), 4.89 (br s, 1H, H-5), 4.28 (d, 1H, *J*=11.0 Hz, H-20), 4.14 (dd, 1H, *J*=2.0, 5.0 Hz, H-2), 3.67 (d, 1H, *J*=11.0 Hz, H-20), 3.06 (s, 3H, CH_3SO_2), 2.92 (d, 1H, *J*=19.5 Hz, H-14), 2.78 (dd, 1H, *J*=6.7, 19.7 Hz, H-14), 2.59 (d, 1H, *J*=5.0 Hz, H-3), 2.35 (dd, 1H, *J*=12.5, 15 Hz, H-9), 2.26 (dd, 1H, *J*=2.0, 6.5 Hz, H-1), 2.17 (s, 1H, OH), 2.16 (s, 3H, OAc-CH_3-10), 2.08 (s, 3H, CH_3-18), 1.98–1.85 (m, 3H, H-7, 2×H-6), 1.61 (s, 3H, CH_3-16), 1.55 (dd, 1H, *J*=5.5, 14.5 Hz, H-9), 1.27–1.24 (m, 1H, H-7), 1.18 (s, 3H, CH_3-17), 0.955 (s, 3H, CH_3-19); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 200.45 (C=O-13), 169.76 (OAc-C=O), 153.75 (C-11), 136.39 (C-12), 79.84 (C-5), 76.98 (C-4), 70.89 (C-10), 70.74 (C-2), 64.99 (C-20), 51.69 (C-1), 44.07 (C-9), 42.42 (C-3), 38.73 (CH_3SO_2), 38.04 (C-8), 37.83 (C-17), 37.28 (C-15), 35.22 (C-14), 31.98 (C-7), 25.68 (C-6), 24.81 (C-16), 24.26 (C-19), 21.19 (OAc-CH_3), 13.28 (C-18).

4.1.8. 5β,20-Epoxy-2α,4α-dihydroxy-10β-acetoxy-11-taxen-13-one (9). Under argon, to a stirred solution of **8** (14 mg, 0.029 mmol) in dry toluene (2 mL) was added DBU (6.5 μL, 0.043 mmol). The reaction solution was heated to reflux for 2 h, and then cooled to room temperature. The resulting solution was column chromatographed (50–70% EtOAc in petroleum ether) to yield oxetane **9** (4 mg, 36%).

Oxetane **9**. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 5.95 (dd, 1H, *J*=12.0, 5.5 Hz, H-10), 4.73 (d, 1H, *J*=8.5 Hz, H-20), 4.67 (dd, 1H, *J*=3.0, 9.0 Hz, H-5), 4.35 (d, 1H, *J*=8.0 Hz, H-20), 4.22–4.18 (m, 1H, *J*=3.0, 5.5, 9 Hz, H-2), 3.216 (s, 1H, OH), 2.56 (d, 1H, *J*=9.5 Hz, OH-2), 2.74 (d, 2H, *J*=3.5 Hz, H-14), 2.44 (dd, 1H, *J*=12.0, 14.7 Hz, H-9), 2.22 (dd, 1H, *J*=3.5, 6.5 Hz, H-1), 2.14–2.09 (m, 1H, H-6), 2.081 (s, 3H, OAc-CH_3-10), 2.01 (s+m, 4H, H-6, CH_3-18), 1.97 (d, 1H, *J*=5.5 Hz, H-3), 1.65 (s, 3H, CH_3-16), 1.64–1.57 (m, 3H, H-9, 2×H-7), 1.38 (s, 3H, CH_3-19), 1.17 (s, 3H, CH_3-17).

4.1.9. 5β,20-Epoxy-2α,4α,10β-triacetoxy-11-taxen-13-one (10). To a solution of **9** (50 mg, 0.12 mmol) in pyridine (1 mL) was added Ac_2O (0.2 mL, 2.12 mmol) and DMAP (120 mg, 0.98 mmol). The reaction mixture was stirred at room temperature for 12 h, and then diluted with EtOAc (15 mL) and 1 mol/L aqueous HCl (15 mL). The organic layer was separated, washed with aqueous $CuSO_4$ (10 mL×2), aqueous $NaHCO_3$ (10 mL), brine (5 mL), concentrated, and purified by TLC (25% EtOAc in petroleum ether) to give **10** (38 mg, 63%) as a colorless foam.

Compound **10**. $[\alpha]_D^{20}$ +98° (*c* 0.5, $CHCl_3$); HR-FABMS (Gly+NaCl): found 499.2302, calcd 499.2308, $C_{26}H_{36}O_8+Na^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 5.98 (dd, 1H, *J*=12.0, 5.5 Hz, H-10), 5.48 (dd, 1H, *J*=2.5, 6.0 Hz, H-2), 4.93 (d, 1H, *J*=9.0 Hz, 1H, H-5), 4.50 (d, 1H, *J*=8.0 Hz, H-20), 4.18 (d, 1H, *J*=8.0 Hz, H-20), 2.87 (d, 1H, *J*=6.5 Hz, H-3),

2.73 (dd, 1H, J=7.0, 19.5 Hz, H-14), 2.51 (dd, 1H, J=12.0, 15.0 Hz, H-9), 2.31 (d, 1H, J=20.5 Hz, H-14), 2.24–2.17 (m, 1H, H-6), 2.10 (dd, 1H, J=6.5, 2.5 Hz, H-1), 2.08 (s, 3H, OAc-CH_3-10), 2.073 (s, 3H, OAc-CH_3-4), 2.04 (s, 3H, OAc-CH_3-2), 2.02 (s, 3H, CH_3-18), 1.98–1.89 (m, 1H, H-6), 1.69 (s, 3H, CH_3-16), 1.67 (dd, 1H, J=5.5, 15.0 Hz, H-9), 1.59–1.55 (m, 2H, 2×H-7), 1.37 (s, 3H, CH_3-19), 1.13 (s, 3H, CH_3-17); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 199.0 (C=O-13), 169.9 (OAc-C=O), 169.7 (2×OAc-C=O), 153.6 (C-11), 137.1 (C-12), 84.9 (C-4), 82.4 (C-5), 76.3 (C-10), 70.9 (C-20), 70.9 (C-2), 47.2 (C-1), 44.0 (C-9), 41.2 (C-3), 38.0 (C-8), 37.6 (C-17), 36.9 (C-15), 35.3 (C-14), 35.1 (C-7), 27.4 (C-6), 24.5 (C-16), 21.8 (OAc-CH_3), 21.6 (OAc-CH_3), 21.5 (C-19), 21.2 (OAc-CH_3), 13.5 (C-18).

4.1.10. 2α,20-Epoxy-4α,5β-dihydroxy-10β-acetoxy-11-taxen-13-one (11) and 2α,20-epoxy-4α-hydroxy-5β,10β-diacetoxy-11-taxen-13-one (12). Compound **9** (2 mg) was dissolved in $CDCl_3$ (1 mL), which was not processed by K_2CO_3 and maintained at room temperature for 2 min. The solvent was removed in vacuo to give **11** (2 mg).

To a solution of **11** (2 mg, 0.0051 mmol) in pyridine (0.5 mL) was added Ac_2O (0.018 mL, 0.19 mmol). The reaction mixture was stirred at room temperature for 6 h, and then quenched with 1 mol/L aqueous HCl. After the dilution of EtOAc (6 mL), the organic layer was separated, washed with aqueous $CuSO_4$ (5 mL), aqueous $NaHCO_3$ (5 mL) and brine (5 mL), concentrated in vacuo, and purified by TLC (45% acetone in petroleum ether) to give **12** (2 mg, 90%).

Compound **11**. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.09 (t, 1H, J=4.0 Hz, H-10), 4.37 (br d, 1H, J=4.5 Hz, H-2), 3.90 (dd, 1H, J=6.0, 11.5 Hz, H-5), 3.69 (d, 1H, J=10.0 Hz, H-20), 3.51 (d, 1H, J=10.0 Hz, H-20), 2.77 (dd, 1H, J=7.5, 19.5 Hz, H-14), 2.60 (d, 1H, J=19.5 Hz, H-14), 2.36 (dd, 1H, J=2.0, 7.0 Hz, H-1), 2.11 (s, 3H, OAc-CH_3-10), 2.1–2.06 (m, 1H, H-6), 1.90 (s, 3H, CH_3-18), 1.86 (d, J=5.5 Hz, 1H, H-3), 1.78–1.70 (m, 3H, OH, H-9, H-6), 1.57 (s, 3H, CH_3-16), 1.54–1.36 (m, 3H, H-9, 2×H-7), 1.24 (s, 3H, CH_3-19), 1.19 (s, 3H, CH_3-17); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 199.3 (C=O-13), 170.3 (OAc-C=O), 156.2 (C-12), 132.8 (C-11), 84.2, 82.1, 76.2, 73.0, 72.7 (5×*C*–O), 53.1 (C-1), 47.9 (C-9), 46.8 (C-3), 41.7 (C-17), 39.3 (C-8), 37.0 (C-15), 36.5 (C-14), 35.3 (C-7), 27.9 (C-6), 25.3 (C-16), 24.2 (C-19), 21.4 (OAc-CH_3), 14.3 (C-18).

Compound **12**. FABMS *m/z* 435 (M+1), 457 (M+Na); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.09 (t, 1H, J=5.0 Hz, H-10), 4.94 (dd, 1H, J=7.0, 11.0 Hz, H-5), 4.34 (dd, 1H, J=2.0, 6.0 Hz, H-2), 3.49 (d, 1H, J=10.0 Hz, H-20), 3.45 (d,1H, J=10.0 Hz, H-20), 2.87 (d, 1H, J=20.0 Hz, H-14), 2.71 (dd, 1H, J=7.5, 20.0 Hz, H-14), 2.35 (dd, 1H, J=2.5, 7.0 Hz, H-1), 2.10 (s, 3H, OAc-CH_3-10), 2.07 (s, 3H, OAc-CH_3-5), 1.99 (d, J=6.0 Hz, 1H, H-3), 1.93 (s, 3H, CH_3-18), 1.91–1.81 (m, 3H, H-9, 2×H-6), 1.57 (s, 3H, CH_3-16), 1.54–1.46 (m, 3H, H-9, 2×H-7), 1.21 (s, 3H, CH_3-19), 1.18 (s, 3H, CH_3-17).

4.1.11. 5α,13β-Dihydroxy-2α,10β-diacetoxy-4(20), 11-taxadiene (13) and 5α,13α-dihydroxy-2α,10β-diacetoxy-4(20), 11-taxadiene (14). To a solution of **4** (20 mg, 0.048 mmol) in a mixture of methanol (1 mL) and THF (0.5 mL) was added $CeCl_3\cdot 7H_2O$ (71 mg, 0.19 mmol) and $NaBH_4$ (180 mg, 4.86 mmol). The reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with saturated aqueous NH_4Cl (2 mL). After dilution with EtOAc (15 mL), the organic layer was separated, washed with 1 mol/L aqueous HCl, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (25–35% EtOAc in petroleum ether) to give 13-β-hydroxy compound **13** (13 mg, 64%) and 13-α-hydroxy compound **14** (5 mg, 25%).

13-β-Hydroxy compound **13**. $[\alpha]_D^{20}$ +36° (*c* 0.3, $CHCl_3$); FABMS *m/z* 443 (M+Na); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.06 (dd, 1H, J=6.0, 12.3 Hz, H-10), 5.41 (dd, 1H, J=2.0, 6.5 Hz, H-2), 5.11 (s, 1H, H-20), 4.69 (t, 1H, J=1.5 Hz, H-20), 4.30 (dd, 1H, J=4.0, 9.5 Hz, H-13), 4.20 (t, 1H, J=2.7 Hz, H-5), 3.17 (d, 1H, J=7.0 Hz, H-3), 2.40 (dd, 1H, J=12.0, 14.7 Hz, H-9), 2.19 (dd, 1H, J=9.5, 15.5 Hz, H-14), 2.12 (s, 3H, 18-CH_3), 2.09–2.03 (m, 1H, H-14), 2.05–2.04 (2s, 6H, 2×OAc-CH_3), 1.98 (dd, 1H, J=2.0, 7.5 Hz, H-1), 1.76–1.71 (m, 2H, H-6, H-7), 1.61–1.57 (m+s, 5H, H-6, H-9, 16-CH_3), 1.28 (s, 3H, 17-CH_3), 1.15–1.12 (m, 1H, H-7), 0.85 (s, 3H, 19-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 170.2 (OAc-C=O), 169.7 (OAc-C=O), 147.9 (C-4), 139.1 (C-12), 137.3 (C-11), 113.1 (C-20), 76.2 (C-5), 71.2 (C-10), 70.9 (C-2), 70.5 (C-2), 56.8 (C-1), 43.1 (C-9), 40.3 (C-3), 40.1 (C-8), 36.7 (C-15), 36.5 (C-17), 33.1 (C-14), 31.3 (C-7), 29.9 (C-6), 25.4 (C-16), 22.4 (C-19), 21.5 (OAc-CH_3), 21.4 (OAc-CH_3), 18.8 (C-18).

13-α-Hydroxy compound **14**. FABMS *m/z* 443 (M+Na); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.09 (dd, 1H, J=5.5, 12 Hz, H-10), 5.61 (dd, 1H, J=1.5, 6.0 Hz, H-2), 5.15 (s, 1H, H-20), 4.83 (t, 1H, J=1.5 Hz, H-20), 4.35 (dd, 1H, J=3.3, 10.2 Hz, H-13), 4.28 (br s, 1H, H-5), 3.40 (d, 1H, J=5.5 Hz, H-3), 2.70 (dt, 1H, J=10.0, 15.5 Hz, H-14), 2.32 (dd, 1H, J=12.0, 14.5 Hz, H-9), 2.20 (s, 3H, 18-CH_3), 2.18–2.12 (m, 1H, H-7), 2.05 (br s, 6H, 2×OAc-CH_3), 1.81–1.71 (m, 3H, 2×H-6, H-1), 1.63 (dt, 1H, J=3.0, 15.5 Hz, H-14), 1.59 (s, 3H, 16-CH_3), 1.47–1.41 (m, 1H, H-9), 1.19–1.16 (m, 1H, H-7), 0.93 (s, 3H, 17-CH_3), 0.84 (s, 3H, 19-CH_3).

4.1.12. 13α,4α,5α-Trihydroxy-2α,10β,20-triacetoxy-11-taxene (15). To a solution of **6** (38 mg, 0.077 mmol) in a mixture of methanol (1.6 mL) and THF (0.8 mL) was added $CeCl_3\cdot 7H_2O$ (71 mg, 0.19 mmol) and $NaBH_4$ (15 mg, 0.41 mmol). The reaction mixture was stirred at room temperature for 1 h, and then quenched with saturated aqueous NH_4Cl (2 mL). After dilution with EtOAc (25 mL), the organic layer was separated, washed with 1 mol/L aqueous HCl, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (30–50% EtOAc in petroleum ether) to give desired 13-α-hydroxy compound **15** (32 mg, 84%).

Compound **15**. $[\alpha]_D^{20}$ +61° (*c* 0.8, $CHCl_3$); HR-FABMS (Gly+NaCl): found 519.2558, calcd 519.2570, $C_{26}H_{40}O_9+Na^+$; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 6.02 (dd, 1H, J=10.7, 6.0 Hz, H-10), 5.41 (dd, 1H, J=1.8, 4.8 Hz, H-2), 4.40 (d, 1H, J=11.7 Hz, H-20), 4.34 (br d,

1H, J=8.7 Hz, H-13), 4.02 (d, 1H, J=11.7 Hz, H-20), 3.95 (br s, 1H, H-5), 3.10 (d, 1H, J=5.1 Hz, H-3), 2.60 (dt, 1H, J=7.8, 15.0 Hz, H-14), 2.27 (dd, 1H, J=12.6, 15.6 Hz, H-9), 2.19–2.04 (5s+m, 14H, 4×OAc-CH_3, CH_3-18, H-14, H-7), 1.82–1.76 (m, 2H, 2×H-6), 1.67 (dd, 1H, J=2.0, 8.0 Hz, H-1), 1.58 (s, 3H, CH_3-16), 1.43 (dd, 1H, J=5.5, 15 Hz, H-9), 1.10–1.04 (m, 1H, H-7), 0.92 (s, 3H, CH_3-17), 0.86 (s, 3H, CH_3-19).

4.1.13. 4α,5α-Dihydroxy-2α,10β,13α,20-tetraacetoxy-11-taxene (16). To a solution of **15** (240 mg, 0.48 mmol) in pyridine (15 mL) was added Ac_2O (0.8 mL, 8.49 mmol) and DMAP (100 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 1 h, and then quenched with methanol (1 mL). The resulting mixture was diluted with EtOAc (100 mL), poured into 1 mol/L aqueous HCl (50 mL) and extracted with EtOAc (50 mL×2). The combined organic phase was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated in vacuo, purified by flash chromatography (50% EtOAc in petroleum ether) to yield corresponding compound **16** (225 mg, 87%).

Compound **16**. Mp: 81–83 °C; $[\alpha]_D^{20}$ +69° (*c* 0.4, $CHCl_3$); FABMS *m/z* 561 (M+Na); ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.04 (dd, 1H, J=12.0, 5.5 Hz, H-10), 5.59 (dd, 1H, J=7.0, 8.5 Hz, H-13), 5.41 (dd, 1H, J=2.0, 5.0 Hz, H-2), 4.45 (d, 1H, J=12.0 Hz, H-20), 4.06 (d, 1H, J=12.0 Hz, H-20), 3.89 (t, 1H, J=2.7 Hz, H-5), 3.19 (s, 1H, OH), 3.06 (d, 1H, J=5.0 Hz, H-3), 2.95 (d, 1H, J=2.0 Hz, OH), 2.63–2.58 (m, 1H, H-14), 2.30 (dd, 1H, J=12.5, 14.5 Hz, H-9), 2.17–2.04 (5s, 4×OAc-CH_3, CH_3-18), 2.16 (dd, 1H, J=3.0, 15.5 Hz, H-14), 2.12–2.01 (m, 1H, H-7), 1.84–1.75 (m, 2H, 2×H-6), 1.72 (dd, 1H, J=2.0, 8.0 Hz, H-1), 1.62 (s, 3H, CH_3-16), 1.45 (dd, 1H, J=5.5, 15 Hz, H-9), 1.09–1.07 (m, 1H, H-7), 0.99 (s, 3H, CH_3-17), 0.86 (s, 3H, CH_3-19).

4.1.14. 5α-Methanesulfonyloxy-4α-hydroxy-2α,10β,13α,20-tetraacetoxy-11-taxene (17). To a solution of **16** (120 mg, 0.22 mmol) in pyridine (8 mL) was added dropwise methanesulfonyl chloride (0.35 mL, 4.51 mmol). The reaction solution was stirred at 30 °C for 60 h, and then diluted with EtOAc (40 mL), poured into 1 mol/L aqueous HCl (20 mL) and extracted with EtOAc (20 mL×2). The combined organic phase was washed with aqueous $CuSO_4$, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography (20% acetone in petroleum ether) to yield 73 mg (90% based on 59% conversion) of corresponding mesylate **17** and 49 mg of recovered alcohol **16** (41%).

Mesylate **17**. Mp: 130–133 °C; $[\alpha]_D^{20}$ +64° (*c* 0.3, $CHCl_3$); HR-FABMS (Gly+NaCl): found 639.2440, calcd 639.2451, $C_{29}H_{44}O_{12}S+Na^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 5.99 (dd, 1H, J=12.0, 5.5 Hz, H-10), 5.78 (dd, 1H, J=7.0, 8.5 Hz, H-13), 5.40 (d, 1H, J=5.0 Hz, H-2), 4.75 (s, 1H, H-5), 4.51 (d, 1H, J=12.5 Hz, H-20), 3.92 (d, 1H, J=12.5 Hz, H-20), 3.01 (s, 3H, CH_3SO_2), 2.87 (d, 1H, J=5.0 Hz, H-3), 2.42 (dt, 1H, J=9.7, 14.7 Hz, H-14), 2.30 (dd, 1H, J=12.5, 15.0 Hz, H-9), 2.16–1.92 (5s+m, 19H, 4×OAc-CH_3, CH_3-18, H-7, H-14, 2×H-6), 1.73 (d, 1H, J=9.0 Hz, H-1), 1.59 (s, 3H, CH_3-16), 1.42 (dd, 1H, J=5.5, 15.0 Hz, H-9), 1.29–1.23 (m, 1H, H-7), 1.03 (s, 3H, CH_3-17), 0.84 (s, 3H, CH_3-19).

4.1.15. 5α-Methanesulfonyloxy-2α,4α,20-trihydroxy-10β,13α-diacetoxy-11-taxene (18). To a solution of **17** (115 mg, 0.19 mmol) in a mixed solvent of methanol (4 mL) and THF (3 mL) was added 1 mol/L aqueous K_2CO_3 (0.3 mL, 0.3 mmol). The reaction mixture was stirred at 0 °C for 0.5 h. The reaction was quenched with 1 mol/L aqueous HCl. The resulting solution was concentrated and diluted with 40 mL of EtOAc. The organic phase was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (60% EtOAc in petroleum ether) to yield triol **18** (96 mg, 97%).

Triol **18**. ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 6.02 (dd, 1H, J=12.0, 5.5 Hz, H-10), 5.84 (dd, 1H, J=6.5, 9.0 Hz, H-13), 4.77 (s, 1H, H-5), 4.26 (d, 1H, J=11.5 Hz, H-20), 4.08 (br d, 1H, J=6.0 Hz, H-2), 4.03 (s, 1H, OH), 3.62 (dd, 1H, J=8.0, 11.0 Hz, H-20), 3.45 (d, 1H, J=8.0 Hz, OH), 3.10 (s, 3H, CH_3SO_2), 2.74 (d, 1H, J=6.0 Hz, OH-2), 2.65 (d, 1H, J=5.0 Hz, H-3), 2.58 (dt, 1H, J=9.5, 15.5 Hz, H-14), 2.28 (dd, 1H, J=12.5, 14.5 Hz, H-9), 2.20 (s, 3H, CH_3-18), 2.03–1.92 (2s+m, 11H, 2×OAc-CH_3, H-7, H-1, H-14, 2×H-6), 1.57 (s, 3H, CH_3-16), 1.43 (dd, 1H, J=5.5, 15.0 Hz, H-9), 1.25–1.22 (m, 1H, H-7), 1.10 (s, 3H, CH_3-17), 0.93 (s, 3H, CH_3-19); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 171.1 (OAc-C=O), 167.0 (OAc-C=O), 136.0 (C-12), 135.2 (C-11), 81.2 (C-5), 77.5 (C-4), 72.3 (C-2), 67.0 (C-10), 69.8 (C-13), 65.6 (C-20), 51.2 (C-1), 44.9 (C-9), 43.6 (C-3), 38.2 (C-8), 37.7 (C-15), 37.1 (CH_3SO_2), 32.3 (C-14), 31.9 (C-17), 27.1 (C-7), 26.1 (C-6), 25.4 (C-16), 24.2 (C-19), 21.4 (OAc-CH_3), 21.2 (OAc-CH_3), 14.9 (C-18).

4.1.16. 7,9-Dideoxy-2-debenzoyl-4-deacetyl-baccatin IV (19). Under argon, to a solution of **18** (85 mg, 0.16 mmol) in dry toluene (5 mL) was added DBU (30 μL, 0.2 mmol). The reaction solution was stirred at reflux for 1 h, and then cooled to room temperature. The resulting solution was column chromatographed (50–70% EtOAc in petroleum ether) to yield baccatin IV analogue **19** (65 mg, 93%).

Compound **19**. Mp: 71–73 °C; $[\alpha]_D^{20}$ +46 (*c* 0.6, $CHCl_3$); HR-FABMS (Gly+NaCl): found 459.2349, calcd 459.2359, $C_{24}H_{36}O_7+Na^+$; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm) 5.91 (dd, 1H, J=12.0, 5.5 Hz, H-10), 5.64 (d, 1H, J=9.5 Hz, H-13), 4.70 (d, 2H, J=8.5 Hz, H-2, H-20), 4.39 (d, 1H, J=8.0 Hz, H-20), 4.10–4.06 (m, 1H, H-5), 2.76 (s, 1H, OH), 2.68–2.60 (m, 2H, H-3, H-14), 2.32 (dd, 1H, J=12.5, 15.0 Hz, H-9), 2.17–2.15 (m, 2H, 2×H-6), 2.12 (s, 3H, OAc-CH_3), 2.05 (s, 3H, OAc-CH_3), 2.04–1.96 (m, 1H, H-7), 1.89 (s, 3H, CH_3-18), 1.85 (dd, 1H, J=2.5, 8.0 Hz, H-1), 1.77 (dd, 1H, J=3.0, 15.6 Hz, H-14), 1.67–1.60 (m, 1H, H-7), 1.57 (s, 3H, CH_3-16), 1.52 (dd, 1H, J=5.5, 15.0 Hz, H-9), 1.33 (s, 3H, CH_3-19), 1.01 (s, 3H, CH_3-17); ^{13}C NMR (125 MHz, $CDCl_3$, δ ppm) 170.0 (OAc-C=O), 169.7 (OAc-C=O), 138.6 (C-12), 133.9 (C-11), 87.5 (C-5), 80.33 (C-4), 77.5 (C-10), 70.5 (C-20), 70.3 (C-13), 69.8 (C-2), 49.4 (C-1), 47.6 (C-9), 44.3 (C-3), 37.2 (C-8), 36.6 (C-15), 35.7 (C-14), 33.8 (C-17), 27.5 (C-7), 27.0 (C-6), 25.1 (C-16), 22.0 (C-19), 21.4 (OAc-CH_3), 21.1 (OAc-CH_3), 15.7 (C-18).

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Applications of surfactant-modified clays to synthetic organic chemistry

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Abstract—Two triphase catalysts (SLL) have been developed for organic phase–aqueous phase reactions catalyzed by suitable modified clay (solid phase). These triphase catalysts have been applied to nucleophilic displacement on activated (benzylic) as well as unactivated organic halides and provide a convenient and effective method of preparation of the corresponding products. Other useful transformations to, which these triphase catalysts have been successfully applied are the synthesis of 9,9-dichloro bicyclo[6.1.0]nonane, O-alkylation and C-alkylation of β-naphthol.

1. Introduction

A significant and recurring problem in organic synthesis stems from use, or desired use, of a water-soluble reagent in chemically altering a water-insoluble organic substrate. If the reaction is conducted as a heterogeneous process (e.g., organic phase–aqueous phase reaction) observed reaction rates are normally very slow owing to the low concentration of at least one of the reactants in each phase. Techniques available to circumvent this problem rely on the use of rapid stirring, co-solvent, and phase-transfer methods. If a chemical reaction takes place at a liquid–liquid phase boundary, rapid stirring may have an accelerating effect by increasing interfacial contact.[1] Alternatively, the addition of a co-solvent can bring about a homogeneous state and thereby completely eliminate phase separation. Although this latter approach is often useful, product mixtures are necessarily made more complex and the resulting work-up made difficult. In addition, with aqueous phase–organic phase reactions, use of a co-solvent not only renders the organic substrate accessible to the reagent, but also increases the substrates contact with water and can promote competing hydrolytic pathways. Previously, another technique was developed, which appeared to have considerable potential; this method has been referred to as phase-transfer catalysis.[2,3] In brief, an organic-soluble, partially water-soluble catalyst (most commonly a tetraalkylammonium or tetraalkylphosphonium salt) accelerate an aqueous–organic phase reaction, presumably, by extracting a given ionic reagent out of water and into the bulk organic phase where reaction can ensue.[4,5] One practical limitation to the phase-transfer method, however, is that many of the catalysts employed promote the formation of stable emulsions.

Regen developed a technique centering around the use of a solid phase catalyst to accelerate aqueous–organic phase reactions (triphase catalysis), which had a considerable advantages over those methods described above.[6] In this technique, not only would catalyst recovery and product isolation be greatly simplified, but also, owing to the three-phase nature of the system, a continuous flow method could be employed, making the technique particularly attractive for industrial applications. In this respect, another promising field of application of triphase catalysis is that of certain organic clays, as triphase catalysts in nucleophilic displacement reactions. For example, the methyltrioctylammonium exchanged form of hectorite gives very high yields over a wide range of nucleophiles.[7]

We previously demonstrated the feasibility of triphase catalysis for the oxidation of 2-ethylhexanol (organic phase) by dichromate ion (aqueous phase) catalyzed by a suitable modified clay (solid phase).[8] The work described in this paper, was carried out to expand the scope of these modified clays by applying them to a variety of useful synthetic transformations.

2. Results and discussion

2.1. Modified clays

Natural bentonite from salafchegan, Iran, gray in color was

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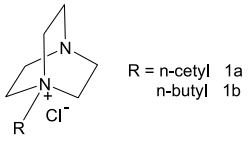
used. It had the following chemical composition (in wt%): SiO_2 (65.04), Fe_2O_3 (1.67), MgO (1.87), Al_2O_3 (13.61), CaO (2.01), TiO_2 (0.19), Na_2O (2.26), K_2O (0.75).[9] Since, XRD analysis revealed the presence of significant amounts of quartz and feldespar, the raw material was purified with the following procedure. A 4 wt% bentonite slurry in water was prepared and swollen at room temperature under continuous stirring. After 5 h, the concentration of the suspension was diluted to 2 wt% by addition of 0.1 M NaCl solution. The suspension was stirred overnight followed by decantation. The ion exchange procedure was repeated three times with fresh NaCl solution. Finally, the solid was washed free of chloride ions. At the last washing, stirring was stopped; the particles contained in the suspension were separated from the quartz deposits and centrifuged. The cake was dried at room temperature. The BET surface area of the unmodified Na-bentonite was 63 m^2/g.

1-Cetyl-4-aza-1-azonia bicyclo[2.2.2]octane chloride (**1a**) and 1-butyl-4-aza-1-azonia bicyclo[2.2.2]octane (**1b**) were selected as the surfactants for modifying the bentonite. The reason for choosing these surfactants for modification of bentonite was that they could be synthesized very easily, and the polar heads of the surfactants have free nitrogen that is able to participate in hydrogen bonding, in addition, to electrostatic interaction between positive charge of surfactant with negative site of the bentonite surface. PTC supported on bentonite was prepared by loading 0.1 g (2.4 mmol of **1a** or 4.0 mmol of **1b**) of surfactant on 1 g of bentonite. The catalysts obtained from this modification are identified hereafter by **1a**-clay and **1b**-clay.



Based on the physical analysis of the adsorption system and adsorption process, it is recognized[10] that the radical characteristics of the adsorption of surfactant at the solid/liquid interface should include two main points. First, according to the nature of adsorption there must be some attraction between surfactant molecules and the bentonite surface, which forces the surfactant molecules to transfer from bulk solution to the bentonite surface. The second one comes from the character of surfactant. It is well known that a surfactant is a kind of organic compound consisting of a hydrophilic part and a hydrophobic part. The tail exhibits the hydrophobic effect,[11] and in aqueous surfactant solutions above the critical micelle concentration, individual surfactant molecules will aggregate and form micelles. If the molecules of surfactant are adsorbed at the solid/liquid interface, they should also exhibit the hydrophobic effect to some extent, hence, form aggregates at solid/liquid interface with other molecules of surfactant, in the range of concentration of bulk solution. Therefore, the formation of surface aggregates can be envisaged as a superficial analogue of micellization in the bulk solution, these surface aggregates may be of different shape and size, including the so-called hemimicelles.[12,13]

It occurred to us to develop an old technique[14] centering on the use of solid phase catalysts, which show different degree of hydrophobicity. These new phase-transfer catalysts[8] would have considerable advantages over the previously mentioned triphase-catalysts.

2.2. Synthesis of nitriles

Nucleophilic displacement by cyanide ion on organic halides represent the most commonly used method for the preparation of nitriles. Despite the usefulness of this approach, however, the required used of water and/or other polar and potentially nucleophilic solvent needed to dissolve both the cyanide salt and the organic substrate introduces distinct limitations. In particular, competing hydrolysis and ether formation can lead to low yield of nitrile.[15] Phase-transfer catalysis procedures have been successfully utilized in cyanide displacement reactions involving simple alkyl halides.[4,5,16] Durst in the past reported that phase-transfer catalyzed cyanide displacement on activated halides, e.g., benzyl chloride (or bromide), gave significantly higher yields of nitrile when conducted as liquid–solid rather than liquid–liquid system.[17]

A physical phenomenon, which, if present, may make important contribution to certain triphase catalysis transformation refers to as 'surface area catalysis'.[14] On the basis of this phenomenon, it is possible that these modified clays generating microscopic aqueous and organic pools, the composition of which is either similar or identical to the external bulk phases. Modified clays used in this work may operate in part by generating extensive 'pool/pool phase boundary' thereby increasing the rate of interfacial reaction. We have found that by choosing an appropriate condition in the microenvironment of the reactive site in the 'pool', the displacement of nucleophile (e.g., cyanide ion) on alkyl halide, provides a simple and effective means for converting activated as well as unactivated organic halides to their corresponding products (Table 1). As can be seen in the Table 1, if we modify the clay material with **1a**, benzyl chloride converts very easily to benzyl cyanide at room temperature in petroleum ether. But displacement of cyanide ion on 1,6-dibromohexane does not occur in this condition. Even by changing the solvent to toluene and conducting the reaction at 90 °C, after 24 h, the displacement leads to 7-bromoheptanenitrile in less than 5%. One could help the microenvironment of the reactive site in the 'pool', by substituting toluene or petroleum ether with a more polar solvent. 1,6-Dibromohexane reacts with cyanide ion in the presence of **1a**-clay, in chloroform as solvent at 58 °C and produces 7-bromoheptanenitrile (37%) and 1,6-hexanedicarbonitrile (39%). Furthermore, by using a less hydrophobic environment, i.e., using **1b**-clay and increasing the polarity of microenvironment, this reaction could be done in toluene (Table 1).

2.3. Halogen exchange

Although many procedures are available for exchanging halogen in organic halides, we have found that the modified clay as the triphase catalyst furnishes a convenient method for carrying out such transformations. Examples illustrating the utility of these modified clays to catalyze halogen exchange are provided in Table 1. The fact that catalyst

Table 1. Synthetic applications of modified clay

Reactant	Product	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
Cyanide displacement						
Benzyl chloride	Benzyl cyanide	**1a**-clay	Pet. ether	25	24	86
1,6-Dibromohexane	—	**1a**-clay	Pet. ether	25	24	NR
1,6-Dibromohexane	7-Bromoheptanenitrile	**1a**-clay	Toluene	90	24	<5
1,6-Dibromohexane	7-Bromoheptanenitrile	**1a**-clay	$CHCl_3$	58	24	37
	1,6-Dicyanohexane					39
1,6-Dibromohexane	7-Bromoheptanenitrile	**1b**-clay	Toluene	90	24	18
	1,6-Dicyanohexane					50
n-Cetyl bromide	*n*-Cetyl cyanide	**1a**-clay	Toluene	90	24	5
n-Cetyl bromide	*n*-Cetyl cyanide	**1b**-clay	Toluene	90	24	75
Halogen exchange						
Benzyl chloride	Benzyl iodide	**1a**-clay	Pet. ether	25	24	50
Benzyl chloride	Benzyl bromide	**1a**-clay	Pet. ether	25	24	25
Benzyl chloride	Benzyl bromide	**1a**-clay	Toluene	90	6	80
1,6-Dibromohexane	1-Bromo-6-iodohexane	**1a**-clay	Pet. ether	25	24	<5
1,6-Dibromohexane	1-Bromo-6-iodohexane	**1a**-clay	$CHCl_3$	25	24	<5
1,6-Dibromohexane	1-Bromo-6-iodohexane	**1a**-clay	$CHCl_3$	58	24	39
	1,6-Diodohexane					41
1,6-Dibromohexane	1-Bromo-6-iodohexane	**1b**-clay	$CHCl_3$	58	24	<5
n-Cetyl bromide	—	**1a**-clay	Pet. ether	25	24	NR
n-Cetyl bromide	*n*-Cetyl iodide	**1b**-clay	$CHCl_3$	58	24	58

[a] Yields are determined by GLC based upon the reactant.

activity of the modified clays change with their hydrophilicity and the polarity of solvent, suggests that in the microenvironment of the reactive site all of the components of the system play their role.

2.4. Synthesis of dichloro bicyclo[6.1.0]nonane

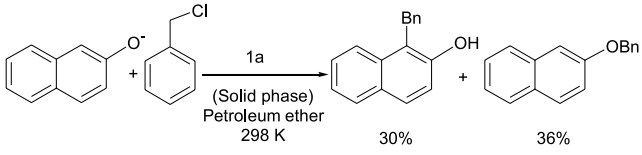
Dichlorocarbene addition to the alkenes provides an attractive route to dichlorocyclopropanes.[18,19,20] We have found that dichlorocarbene can be conveniently generated by the addition of **1a**-clay to mixture of 50% aqueous sodium hydroxide and chloroform at 58 °C. When cyclooctene is added to the mixture, the high yield of the corresponding dichlorocyclopropane is formed (Table 2).

2.5. Synthesis of thiocyanate

We have found that these modified clays provide a simple and effective means for converting organic halides to their corresponding thiocyanates (Table 2).

2.6. C-Alkylation and O-alkylation of naphtoxide

Phenoxides undergo O-alkylation in solvents such as DMSO, DMF, ethers and alcohols. In water and trifluoroethanol, however, selective C-alkylation occurs.[21,22] On the basis of the percentage of the C-alkylated and O-alkylated products it is possible to make a justifiable statement about the polarity of the microenvironment of the active site in our triphase system that is something between the polarity of aprotic and protic solvents, although the solvent is petroleum ether (Scheme 1).



Scheme 1.

An essential part of such a study was to establish the value of including the bentonite. In this respect, we compared the results obtained in the triphasic reactions with a series of

Table 2. Synthetic applications of modified clay

Reactant	Product	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
Dichlorocarbene addition						
Cyclooctene	9,9-Dichloro-bicyclo[6.1.0]nonane	**1a**-clay	$CHCl_3$	58	24	96
Cyclooctene	9,9-Dichloro-bicyclo[6.1.0]nonane	**1a**-clay	$CHCl_3$	25	24	NR
Thiocyanate displacement						
n-Cetyl bromide	*n*-Cetyl thiocyanate	**1b**-clay	Pet. ether	25	24	NR
n-Cetyl bromide	*n*-Cetyl thiocyanate	**1a**-clay	$CHCl_3$	58	24	60
	n-Cetyl isothiocyanate					<2
n-Cetyl bromide	*n*-Cetyl thiocyanate	**1b**-clay	Toluene	90	24	50
	n-Cetyl isothiocyanate					<1
C-alkylation and O-alkylation						
2-Naphthol	1-Benzyl-2-naphthol	**1a**-clay	Pet. ether	25	15	30[b]
	Benzyl-2-naphthyl ether					36[b]

[a] Yields are determined by GLC based upon the reactant.
[b] Isolated yield.

Table 3. Control experiments

Entry	Reactant	Product	Time (h)	Temperature (°C)	Solvent	Exp. condition			
						Without surfactant and clay	Clay alone	Surfactant alone	Catalysts
1	Benzyl chloride	Benzyl cyanide	24	25	Pet. ether	NR	NR	4%	86%[a]
2	1,6-Dibromohexane	7-Bromoheptanenitrile 1,6-Dicyanohexane	24	58	$CHCl_3$	0.5% NR	0.5% NR	21% 9%	37%[a] 39%
3	1,6-Dibromohexane	7-Bromoheptanenitrile 1,6-Dicyanohexane	24	90	Toluene	6.6% 3.3%	0.6% NR	6.6% 3.3%	18%[b] 50%
4	*n*-Cetyl bromide	*n*-Cetyl cyanide	24	90	Toluene	<1%	<1%	<1%	75%[b]
5	Benzyl chloride	Benzyl bromide	6	90	Toluene	17%	21%	21%	80%[a]
6	1,6-Dibromohexane	1-Bromo-6-iodohexane 1,6-Diodohexane	24	58	$CHCl_3$	8.5% 0.3%	1% NR	35.6% 8.6%	39%[a] 41%
7	*n*-Cetyl bromide	*n*-Cetyl iodide	24	58	$CHCl_3$	<1%	<1%	<1%	58%[b]
8	Cyclooctene	9,9-Dichloro-bicyclo-[6.1.0]nonane	24	58	$CHCl_3$	4%	0.5%	80%	96%[a]
9	*n*-Cetyl bromide	*n*-Cetyl thiocyanate *n*-Cetyl isothiocyanate	24	58	$CHCl_3$	0.5% 1%	NR 1.1%	11% 13%	60%[a] <2%
10	*n*-Cetyl bromide	*n*-Cetyl thiocyanate *n*-Cetyl isothiocyanate	24	58	$CHCl_3$	<1%	<1%	<1%	50%[b] <1%

[a] **1a**-clay.
[b] **1b**-clay.

control experiments in, which the bentonite has been omitted (i.e., a two-phase system with only the quaternary ammonium salt as the catalyst). Table 3 compares the yield, and product ratio of different control reactions on the most appropriate conditions cited in Table 1. Data in Table 3 shows that phase-transfer catalyzed displacement reactions on activated and unactivated halides gave significantly higher yields when conducted as liquid–solid rather than liquid–liquid system. An interesting point with regard to the nucleophilic substitution reactions in the presence of **1b**, was that this quaternary ammonium salt is completely soluble in water and does not show any catalytic activity in the absence of bentonite (entries 3c, 4c, 7c and 10c in Table 3). But when this quaternary ammonium salt supported on bentonite, it shows a good catalytic activity in some conditions. For example, cyanide displacement on unactivated bromide (e.g., entry 4) gave significantly higher yield of nitrile (75%) when **1b** supported on bentonite.

The results reported here demonstrate that these modified bentonites possess considerable advantages over traditional procedures for nucleophilic substitution reactions. The reactions are clean, good yielding, and work-up is simple, and the catalysts stay active for at least five times after first used.

3. Experimental

3.1. General methods

Unless stated otherwise, all reagents were obtained commercially and were used without further, purification. All alkyl and benzyl halides as well as cyclooctene and 2-naphthol were purchased from Merck Chemical Co. and used as obtained. Product mixtures were analyzed by GLC (Shimadzo Gas Chromatograph, GC 6A) flame ionization instrument using a OV-17 column (2 m) or a Carbowax 20M column (2 m) and a FID detector. Appropriate response factors relative to an internal standard were determined for each different substance analyzed. HRMS (EI) of all new compounds were performed on a Finnigan MAT 95 double focusing mass spectrometer, equipped with an EI ion source operated at 70 eV.

3.2. Displacement of cyanide ion on organic halides

To a Morton flask (100 ml) containing 0.5 g of **1a**-clay was added a solution of 0.4 g (8.5 mmol) of sodium cyanide dissolved in 25 ml of distilled water followed by 1 ml (8.5 mmol) of benzyl chloride plus 25 ml petroleum ether. An internal standard (*n*-dodecane) was added to the reaction mixture and the mixture stirred with mechanical stirrer.

3.3. Halogen exchange

Procedure similar to that described for the conversion of benzyl chloride to benzyl iodide was followed for all of the halogen exchange reactions described in Table 1. To a Morton flask containing 0.5 g of **1a**-clay was added a solution of 1.4 g (8.5 mmol) of potassium iodide dissolved in 25 ml of distilled water followed by 1 ml (8.5 mmol) of benzyl chloride plus 25 ml petroleum ether. An internal standard (*n*-dodecane) was added to the reaction mixture and the flask heated in an oil bath maintained at 25 °C for 24 h, and the reaction mixture was stirred with a mechanical stirrer.

3.4. Naphthoxide displacement on benzyl chloride

To a Morton flask containing 0.5 g of **1a**-clay was added 5 ml of 5.2 M sodium hydroxide followed by 1.2 g (8.7 mmol) 2-naphthol in 25 ml petroleum ether, 1 ml (8.7 mmol) of benzyl chloride, and an internal standard (*n*-dodecane). The mixture was stirred with a mechanical stirrer and placed in an oil bath maintained at 25 °C for 15 h.

3.5. Dichlorocarbene addition to cyclooctene

Cyclooctene (2 ml, 7.7 mmol) dissolved in 25 ml of chloroform was added to 25 ml of 50% aqueous sodium hydroxide solution, plus **1a**-clay (0.5 g) contained in a Morton flask. After addition of an internal standard (*n*-dodecane) the mixture was stirred with a mechanical stirrer and allowed to remain at 58 °C for 24 h. Analysis of the organic phase by GLC (SE-30 column) indicated a 96% yield of 9,9-dichlorobicyclo[6.1.0]nonane.

3.6. Displacement of thiocyanate ion on organic halides

Procedures similar to that described for the conversion of *n*-cetyl bromide to *n*-cetyl thiocyanate was followed for all of the thiocyanate forming reactions described in Table 2. To a Morton flask containing 0.5 g of **1a**-clay was added a solution of 0.32 g (3.2 mmol) of potassium thiocyanate dissolved in 25 ml of distilled water followed by 1 ml (3.2 mmol) of *n*-cetyl bromide plus 25 ml chloroform. An internal standard (*n*-dodecane) was added to the reaction mixture and the flask was stirred with a mechanical stirrer, placed in an oil bath maintained at 58 °C for 24 h.

3.6.1. 9,9-Dichloro-bicyclo[6.1.0]nonane.[22] ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.3 (4H), 1.24 (4H), 1.13 (4H), 0.82 (2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 27.4, 28.2, 28.8, 66.1. MS (EI), *m/z* (%): 192 (M^+, 10), 124 (50.7), 122 (84.9), 109 (25.9), 96 (44.3), 81 (99.9), 68 (33.9), 67 (83.6), 55 (63.9), 41 (76.7), 39 (51.6). IR (KBr): 685, 790, 875, 920, 1020, 1050, 1180, 1190, 1465, 1450, 1410, 2798, 2850, 2920 cm^{-1}. Anal. Calcd for $C_9H_{14}Cl_2$: C, 55.96; H, 7.25. Found; C, 55.98; H, 7.29.

3.6.2. 1-Benzyl-2-naphthol. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (2H), 5.0 (1H), 6.84 (1H), 7.07 (1H), 7.14 (2H), 7.18 (1H), 7.29 (1H), 7.46 (1H), 7.6 (3H), 7.63 (1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.9, 120.4, 122.5, 123.2, 126.3, 128.3, 129.3, 133.5, 133.9, 141.6, 153.5. IR (KBr): 621, 741, 813, 844, 905, 958, 1172, 1216, 1276, 1406, 1466, 1512, 1600, 1630, 2923, 3050, 3200–3500 (bs) cm^{-1}. Mp 110–112 °C (lit.[23] 110–111 °C).

3.6.3. Benzyl-2-naphthyl ether. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.3 (2H), 6.97 (1H), 7.04 (1H), 7.19 (5H), 7.21 (1H), 7.3 (1H), 7.6 (2H), 7.64 (1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.9, 105.9, 118.8, 124, 126.7, 126.9, 127.2, 127.7, 127.8, 129, 129.5, 129.6, 134.8, 141.2, 157.3. IR (KBr): 632, 751, 843, 905, 959, 1277, 1378, 1466, 1511, 1630, 1701, 2922, 3055 cm^{-1}. Mp 98–100 °C (lit.[23] 98–99.5 °C).

3.6.4. *n*-Cetyl thiocyanate.[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H), 1.29 (24H), 1.33 (2H), 1.66 (2H), 2.44 (2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.8, 28.6, 29, 29.4, 29.7, 29.9, 31.9, 32.1, 117.3. MS (EI), *m/z* (%): 99 (13.4), 85 (43.7), 71 (63.8), 57 (99.9), 55 (24.2). Anal. Calcd for $C_{17}H_{33}NS$: C, 72.08; H, 11.66; N, 4.95; S, 11.31. Found: C, 72.15; H, 11.71; N, 4.91; S, 11.28.

3.6.5. *n*-Cetyl isothiocyanate.[25] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H), 1.29 (24H), 1.3 (2H), 1.33 (2H), 3.6 (2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1; 22.8, 26.6; 29; 29.4; 29.7; 30.2; 31.9, 53.8, 130.7. MS (EI), *m/z* (%): 283 (M^+, 0.6), 251 (17.6), 250 (86.1), 115 (91.9), 83 (17), 72 (20.9), 69 (38.3), 57 (44.1), 55 (88.5), 43 (92.6), 41 (99.1), 29 (45.3). Anal. Calcd for $C_{17}H_{33}NS$: C, 72.08; H, 11.66; N, 4.95; S, 11.31. Found: C, 72.21: H, 11.76; N, 4.89; S, 11.26.

3.6.6. *n*-Cetyl cyanide.[26] ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H), 1.29 (24H), 1.33 (2H), 1.66 (2H), 2.41 (2H).^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 17.5, 22.8, 25.5, 28.6, 28.9, 29.4, 29.7, 31.9, 117.7. MS (EI), *m/z* (%): 208 (9.3), 138 (13.8), 110 (27), 97 (46.1), 96 (22), 70 (26.6), 57 (74.7), 55 (52.5), 43 (99.9), 41 (89.4), 29 (57.5). IR (KBr): 718, 1471, 2245, 2873, 2915, 2948, 2977 cm^{-1}. Anal. Calcd for $C_{17}H_{33}N$: C, 81.27; H, 13.15; N, 5.78. Found: C, 81.30; H, 13.18; N, 5.75.

3.6.7. *n*-Cetyl iodide. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (3H), 1.29 (24H), 1.33 (2H), 1.86 (2H), 3.13 (2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.8, 14.1, 22.8, 28.5, 29.4, 29.7, 30.4, 31.9, 33.6. MS (EI), *m/z* (%): 225 (10.3), 85 (54.6), 71 (75.5), 57 (99.9), 43 (60.8), 29 (8.6). IR (KBr) 604, 719, 1179, 1204, 1377, 1369, 1377, 1467, 2853, 2918, 2966 cm^{-1}. Bp 130 °C/0.2 mm (lit.[27] 152–154 °C/0.7 mm).

3.6.8. 1,6-Diiodohexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (4H), 1.86 (4H), 3.13 (4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.8, 29.2, 33.6. MS (EI), *m/z* (%): 338 (M^+, 0.4), 211 (29.4), 169 (28.5), 155 (45.5), 128 (12.5), 127 (24.9), 83 (61.5), 55 (99.1), 43 (18.1), 41 (88.5), 39 (46.8), 29 (29.2), 27 (60). IR (KBr): 596, 719, 1179, 1216, 1425, 1456, 2950, 2953 cm^{-1}. Bp 72–74 °C/0.2 mm (lit.[28] 141–142 °C/10 mm).

3.6.9. 1-Bromo-6-iodohexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (4H), 1.79 (2H), 1.86 (2H), 3.13 (2H), 3.3 (2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ: 6.8, 26.9, 29.4, 32.7, 33.6, 33.7. MS (EI), *m/z* (%): 292 (M^+, 1.9), 165 (25.7), 163 (25.4), 123 (17.9), 121 (19.1), 109 (16.7), 107 (17.3), 84 (16.3), 83 (98.3), 56 (16.7), 55 (99.9), 43 (80.3), 41 (83.9), 39 (68.7). Anal. Calcd for $C_6H_{12}BrI$: C, 24.74; H, 4.12. Found: C, 24.71; H, 4.05.

3.6.10. 1,6-Dicyanohexane. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (4H), 1.66 (4H), 2.41 (4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5, 25.5, 27.8, 117.7. MS (EI), *m/z* (%): 137 (M^+, 1.2), 96 (99.9), 83 (16.3), 82 (26.5), 69 (63.4), 68 (16.9), 55 (84.7), 54 (54.5), 42 (34.7), 41 (87.9). IR: 850, 1398, 1440, 2225, 2840, 2950 cm^{-1}. Anal. Calcd for $C_8H_{12}N_2$: C, 70.59; H, 8.82; N, 20.59. Found: C, 70.68; H, 8.91; N, 20.68.

3.6.11. 7-Bromoheptanenitrile. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (4H), 1.66 (2H), 1.79 (2H), 2.41 (2H), 3.3 (2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5, 25.5, 27.3, 27.6, 32.7, 33.7, 117.7. MS (EI), *m/z* (%): 190 (M^+, 0.2), 110 (99.9), 109 (10.7), 83 (44.9), 82 (44.3), 69 (92.9); 55 (66.2), 54 (47.8), 43 (15.1), 42 (22.9), 41 (87.6), 39 (44.2). Bp 96–98 °C/2 mm (lit.[29] 140–141 °C/14 mm).

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Lead structures for applications in photodynamic therapy. Part 1: Synthesis and variation of *m*-THPC (Temoporfin) related amphiphilic A_2BC-type porphyrins

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Abstract—Photodynamic therapy (PDT) is a developing modality for the treatment of certain tumorous and other diseases. Considerable progress has been made in recent years in the search for new photosensitizers, in particular elucidating the role of localization of the photosensitizer. Known successful photosensitizers of the tetrapyrrole type are amphiphilic molecules, preferably localizing in cellular membrane structures. Thus, the quest for new photosensitizers requires the synthesis of unsymmetrically substituted (amphiphilic) tetrapyrroles. In this article, we describe strategies for the de novo synthesis of amphiphilic tetrapyrroles using a 3-hydroxyphenyl substituted tetrapyrrolic system (Temoporfin) as the lead structure. From an applied science-oriented approach, such a set of amphiphilic porphyrins is best synthesized by combining well-developed condensation methods with subsequent functionalization via organolithium compounds or transition metal catalyzed coupling protocols. Starting from simple A_2- or AB-porphyrins, the synthesis of A_2B-, A_3-, A_3B-, and A_2BC-porphyrins with a mixed hydrophilic/hydrophobic substitution pattern is described. Because of the versatility of this approach to unsymmetrically substituted porphyrins it is also applicable to other areas where porphyryns with a tailor-made substitution patterns are needed, for example, catalysts or molecular electronic devices based on tetrapyrroles.

1. Introduction

Photodynamic therapy (PDT) is a method of medicinal treatment that uses the combination of a dye (a photosensitizer) and light to generate reactive oxygen species, most prominently singlet oxygen, to damage unwanted tissue or cells.[1] Originally applied for the treatment of tumors,[2] PDT has gained an increasing number of potential applications, for example, antiviral and antibacterial PDT,[3] for the treatment of psoriasis[4] or for certain forms of the age-related macular degeneration (AMD).[5] Numerous substances have been tested for their suitability as photosensitizers but until today only a few photosensitizers have gained approval of the legal authorities in Europe and/or the United States, namely Photofrin® (or similar mixtures of hematoporphyrin derivatives), Verteporfin® (benzoporphyrin derivative), ALA (δ-amino levulinic acid), and Temoporfin [5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin **1**].[6] All of these are tetrapyrrolic systems (or—as ALA—a biosynthetic precursor of a porphyrin, that is, protoporphyrin **2**), and indeed tetrapyrrolic systems are the most widely tested class of photosensitizers.[7]

Another property shared by these drugs is their amphiphilic structure, as the molecular frameworks have hydrophilic and hydrophobic parts. This amphiphilicity has been identified as an important criterion for the action of photosensitizers in vivo as it facilitates localization in membrane structures of the cells. It is here, where the reactive oxygen species generated initiate the complex reaction cascade eventually leading to cell death via necrosis and/or apoptosis.[8] Strongly hydrophilic photosensitizers have been shown to lack high PDT efficacy, most probably due to the fact that the singlet oxygen is generated in an aqueous environment, too far away from sensitive cellular structures, given the lifetime of singlet oxygen (2 μs) and the resulting low diffusion distance.[7]

Thus, when developing new photosensitizers for PDT, the

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target should be a series of compounds differing in the extent of hydrophilic/hydrophobic substitution but related to a common lead structure. This will allow a systematic assessment of membrane affinity to establish quantitative structure activity relationships (QSAR). Such an approach has already been successfully applied to compounds of the pheophorbide or hypocrellin series.[9]

Taking these requirements into account, the search for new photosensitizers requires the synthesis of unsymmetrically substituted tetrapyrrolic systems with mixed hydrophilic/hydrophobic substitution pattern (**3**, Fig. 1). One possibility to obtain such systems is to modify the ubiquitous occurring natural tetrapyrroles (chlorophylls, heme), the other possibility is the complete de novo synthesis of appropriate tetrapyrrolic systems. In the quest for potential new photosensitizer structures, both have been employed intensively. Among the approved PDT drugs, Verteporfin is an example for the first approach, the latter is exemplified by 5,10,15,20-tetrakis(3-hydroxyphenyl)-chlorin (**1**, Temoporfin). Additionally, from an industrial perspective the syntheses should be simple, facile, involve only a few synthetic steps, and be simple enough to easily pass the regulatory approval process. In order to simplify the optimization of and search for lead structures the synthetic methodology used in the development process should be simple and versatile to allow the preparation of series of compounds with minimal changes in the reaction conditions. In order to test how much present synthetic methods allow improvements on compounds that have already given promising medicinal results we decided to use Temoporfin, that is, a 3-hydroxyphenyl substituted tetrapyrrolic system as lead structure for our initial studies.

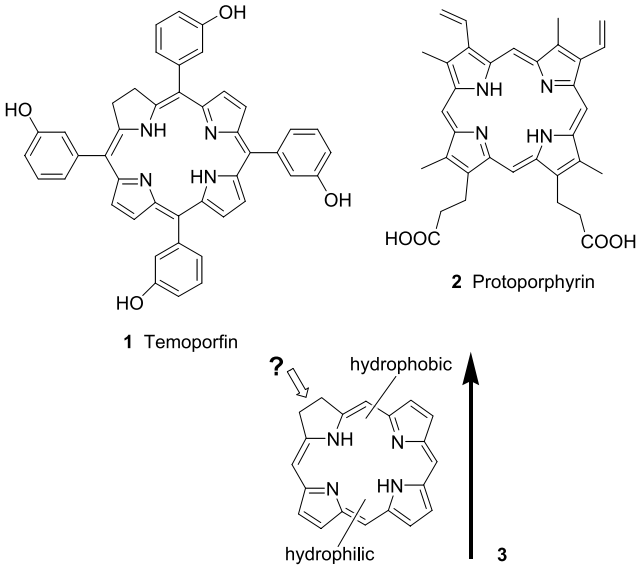


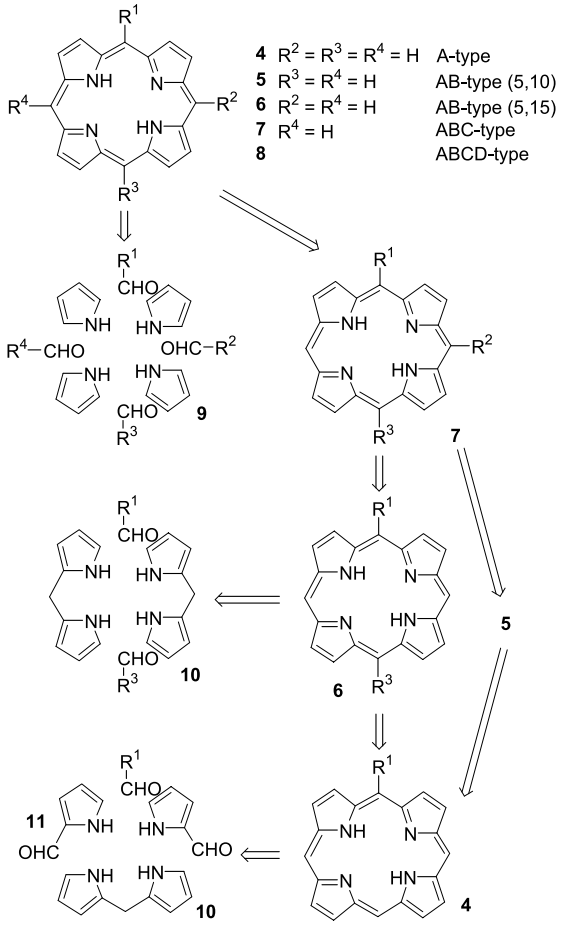
Figure 1. Temoporfin **1** and protoporphyrin **2** as typical photosensitzers and schematic illustration of the basic structure of porphyrins suitable for PDT.

The de novo synthesis of unsymmetrically substituted (amphiphilic) tetrapyrroles may in principle be achieved by condensation of pyrroles or dipyrromethanes with different aldehydes. But, of course, this 'combinatorial' approach results in complex product mixtures, which require tedious chromatographic workup procedures. Thus, more promising is the combination of those classical condensation reactions with subsequent functionalization via organometallic compounds or transition metal catalyzed coupling protocols. In the present work we exemplify how this combination of synthetic methods can be used to obtain—in a straightforward way—unsymmetrically substituted porphyrins with two, three or four substituents. Though the present examples focuses on tetrapyrroles for amphiphilicity studies in PDT, this combination of methods is also suited for preparing unsymmetrically substituted porphyrins for other application protocols, for example, push–pull porphyrins for nonlinear optics, chiral oxidation catalysts, etc.

2. Results and discussion

2.1. Synthetic rational

The most basic retrosynthetic approach for various unsymmetrically substituted porphyrins (**5**–**8**) is the disconnection into pyrrole **9** and aldehydes, where the latter provide the *meso* substitutents (Scheme 1). However, this approach is only successful when the differences in polarity of the individual porphyrins formed are large enough to allow chromatographic separation and it fails for ABC **7** or ABCD **8** porphyrins due to the large number of regioisomers



Scheme 1. Retrosynthetic analysis of ABCD-type porphyrins.

formed. Thus, while easily performed this strategy it is limited to selected types of substituents.[10,11]

A more general approach towards ABCD porphyrins is currently under development by Lindsey's group.[12] However, at present this approach has mainly been elaborated for the synthesis of porphyrins with *meso*-aryl substituents and not for *meso*-alkyl-substituted porphyrins a requirement for us to yield amphiphilic porphyrins. In addition, these methods require more synthetic steps and thus will be more suitable for large-scale synthesis when suitable candidates for further testing have been identified. Additionally, the mixed alkyl/aryl-substituted porphyrins resulting from the mixed-aldehyde–pyrrole condensation reactions usually differ strongly in their polarity, thus making chromatographic separation feasible.

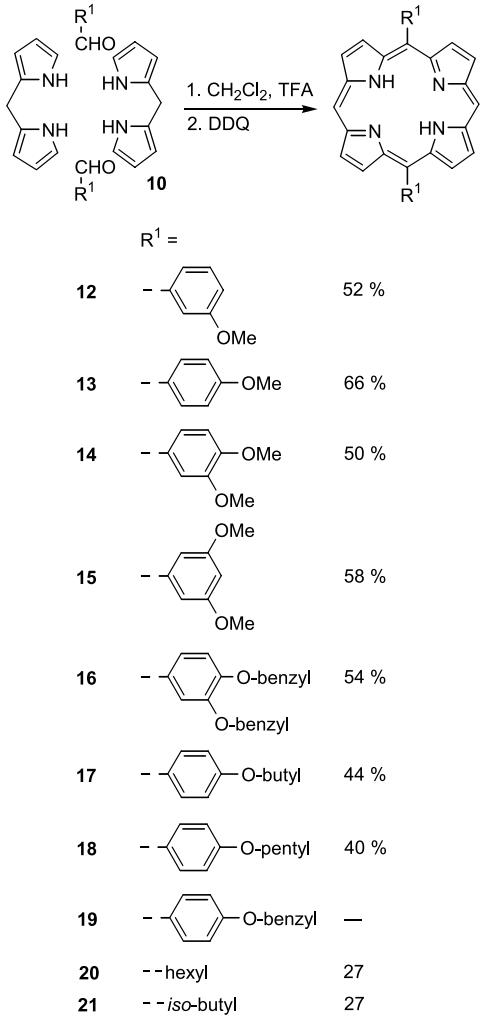
Therefore we decided to utilize a mix of the well-developed condensation reactions and newer methods like our nucleophilic substitution reactions[13] for the preparation of the target compounds. The individual syntheses will be discussed in order of increasing number of substituents and complexity.

2.2. Starting materials—A_2- and AB-porphyrins via condensation reactions

A rational synthesis of A_2BC porphyrins has to start with the respective mono- or disubstituted porphyrins. The easiest approach is the use of A_2-type porphyrins as starting materials for subsequent modifications. A_2-type porphyrins are easily accessible via a 2+2 condensation reaction using dipyrromethane **10** and an appropriate aldehyde.[14]

First, a number of compounds with methoxy groups was prepared (**12**–**15**) in yields of 50–66% using standard type condensation reactions (Scheme 2). As these compounds often had a low solubility, we also prepared the ether derivatives **16**–**19** with longer alkyl chains in order to improve the solubility. Yields ranged from 40 to 54%. However, the benzyl ether **19** proved to be so insoluble to preclude characterization. In order to later introduce individual methoxy residues we also prepared the two dialkylporphyrins **20** and **21** in yields of 27%, each.

Using similar condensation methods we also prepared a number of 5,15-AB-type porphyrins (Scheme 3). While different methods have been described for these[15] we chose mixed condensations for the initial generation of starting materials and prepared compounds **22**–**24** in 14–17% yield. Formation of these compounds was always accompanied by formation of the two symmetric A_2 porphyrins. In the case of using 4-methoxy- or 3,5-dimethoxybenzaldehyde separation of the mixtures is quite easy as the low solubility of the respective A_2-type disubstituted porphyrins retains these on the column. For subsequent functionalization reactions some of the 5,15-AB- and A_2-type porphyrins were converted into the respective nickel(II) complexes. Metallation was performed using the DMF-method[16] to yield compounds **25**–**29** mostly in quantitative yields (Scheme 4).

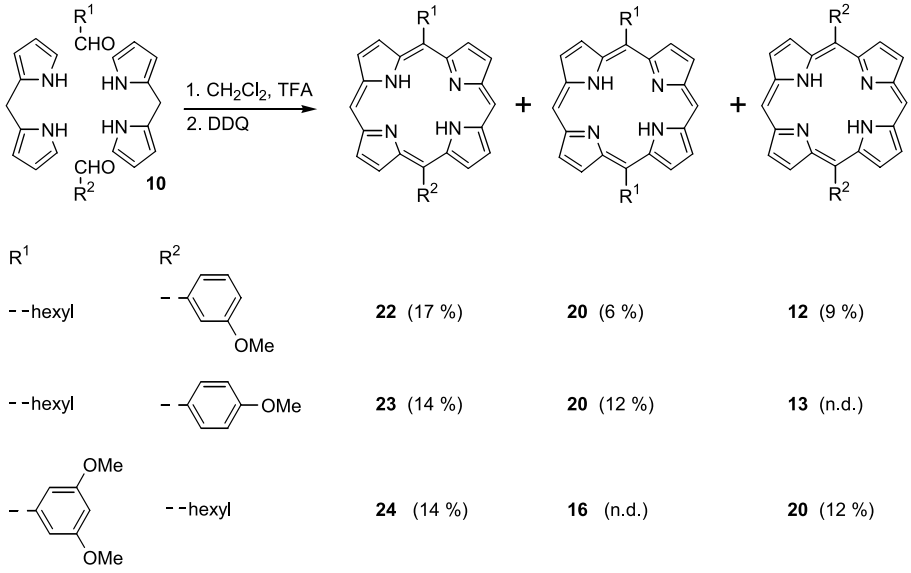


Scheme 2. Synthesis of A_2-type porphyrins.

2.3. A_2B- and A_3-type porphyrins via S_NAr reactions

The first series of target compounds related to *m*-THPC and suitable for biological studies were compounds carrying both precursors for hydroxyphenyl groups and alkyl chains in various combinations. As outlined in Scheme 2 the method of choice for the preparation of porphyrins with three *meso* substituents is the functionalization of the A_2- and AB-type porphyrins described above via electrophilic or nucleophilic substitution reactions.

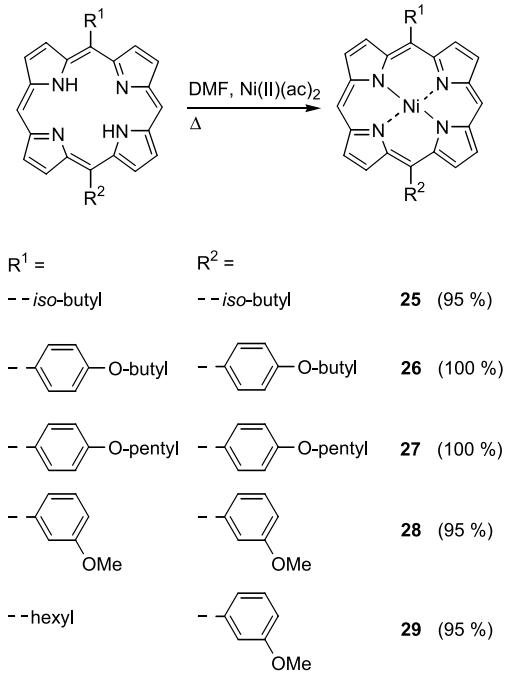
As we have developed the latter method over the last years[17,18] and the present study was intended as a test case of its applicability for a medicinal problem, we reacted a number of free base porphyrins with organolithium reagents as shown in Scheme 5. The reaction works well for both the introduction of aryl or alkyl residues and the A_3 porphyrin **30** and a wide range of A_2B-type porphyrins **32**–**40** could be prepared in yields from 50 to 91%. Only the reaction of bis(4-methoxyphenyl)porphyrin **13** with *n*-hexyl lithium (yielding compound **31**) gave an unsatisfactory yield of 35%, presumably, due to the low solubility of the starting material. This method can also be applied towards the synthesis of 5,10-A_2B-type porphyrins. For example, the



Scheme 3. Synthesis of AB-type porphyrins.

5,15-AB porphyrin **24** was reacted with *n*-hexyl lithium to yield the 5,10-A_2B porphyrin **38** in 60% yield. Alternatively, this compound could be prepared in 80% yield by direct disubstitution of the monosubstituted porphyrin **41**[19] using a method developed for the synthesis of 5,10-disubstituted porphyrins.[20] Thus, S_NAr reactions are useful methods for the preparation of both 5,15- and 5,10-A_2B-type porphyrins.

Again, some porphyrins were converted into the nickel(II) complexes (e.g., **42** and **43**); compound **44** was obtained as side product during the syntheses of **30**.



Scheme 4. Synthesis of metalloporphyrins.

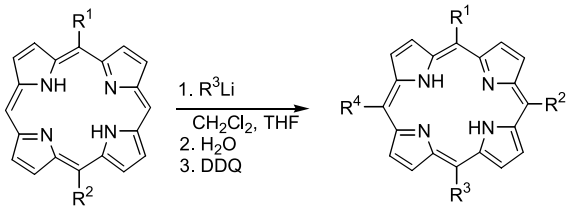
2.4. A_3B-type porphyrins via condensation reactions

The next series involved the mixing of *meso* alkyl and hydroxyphenyl precursor residues at all four *meso* positions to yield A_3B porphyrins. While we had already shown that such compounds can be prepared via reaction of 5,15-disubstituted nickel(II) porphyrins with RLi/RI combinations,[21] this reaction is yet only applicable to metalloporphyrins. As condensations have been utilized for the preparation of tetraarylporphyrins with different aryl residues[22] we investigated the utility of mixed condensation for this purpose.

As shown in Scheme 6, mixed condensation of an aliphatic and aromatic aldehyde yields a mixture of tetrasubstituted A_xB_y porphyrins. All possible combinations are formed, however, the different solubilities of the products allow separation via a single chromatographic column to yield the A_3B target compounds in yields of 6 to 10%. Purification is simpler when the aliphatic aldehyde is utilized as the A, that is, the major component. In this case, the A_4 and A_3B porphyrin show higher solubility and elute first. Thus, for **53** and **58** only the target compounds and the A_4 porphyrins **52** and **57** were isolated, making this a practical method for mixed A_3B porphyrins.

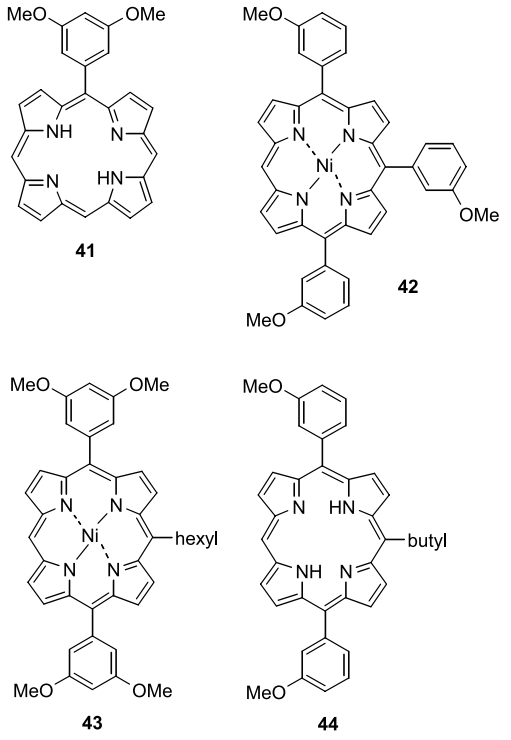
2.5. A_2BC-type porphyrins via S_NAr reactions

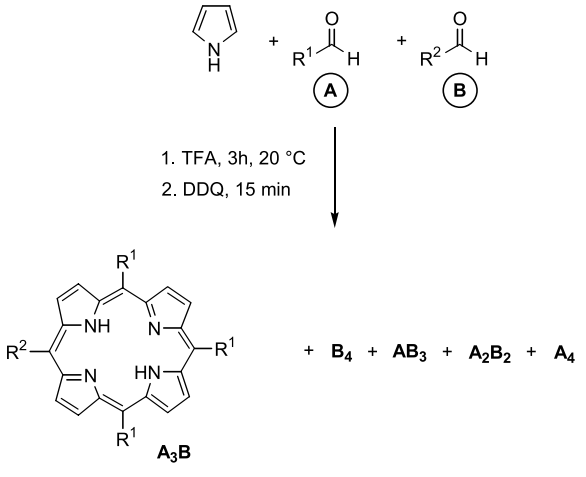
A_2BC free base porphyrins can be prepared via reaction of *meso* trisubstituted porphyrins (A_2B) with an appropriate organolithium reagent introducing the 'C' group. While this reaction often gives excellent yields with lithium aryl reagents and β substituted porphyrins,[13] utilization of *meso* trisubstituted porphyrins **7** as starting materials gave mixed results (Scheme 7). If **7** carries an alkyl residue in the B (R^2) position reaction with LiAr generally gives better yields than alkyl lithium reagents. Likewise, attacking a *meso* position opposite to one carrying an aryl group generally gives lower yields, due to steric hindrance of the mesomeric benzylic anion stabilization, as established by earlier



R^1 =	R^2 =	R^3 =	R^4 =		
3-MeO-Ph	3-MeO-Ph	3-MeO-Ph	H	**30**	(79 %)
hexyl	4-MeO-Ph	H	4-MeO-Ph	**31**	(35 %)
3-MeOPh	hexyl	3-MeO-Ph	H	**32**	(65 %)
4-Butyloxy-Ph	hexyl	4-Butyloxy-Ph	H	**33**	(51 %)
hexyl	4-Pentyloxy-Ph	H	4-Pentyloxy-Ph	**34**	(91 %)
3,5-DiMeO-Ph	hexyl	3,5-DiMeO-Ph	H	**35**	(58 %)
hexyl	*iso*-butyl	H	*iso*-butyl	**36**	(50 %)
hexyl	hexyl	4-MeO-Ph	H	**37**	(53 %)
hexyl	hexyl	3,5-DiMeO-Ph	H	**38**	(60 %)
4-NH_2-Ph	3-MeO-Ph	H	3-MeO-Ph	**39**	(73 %)
hexyl	Ph	H	Ph	**40**	(71 %)

Scheme 5. Synthesis of A_3- and A_2B-type porphyrins via S_NAr reactions.





R^1 =	R^2 =						
3-MeO-Ph	pentyl	**45**	(9 %)	**46**	**47**	**48/49**	**50**
3-MeO-Ph	hexyl	**51**	(8 %)	**52**	**53**	**54/55**	**50**
hexyl	3-MeO-Ph	**53**	(8 %)	-	-	-	**52**
3-MeO-Ph	heptyl	**56**	(10 %)	**57**	**58**	**59/60**	**50**
heptyl	3-MeO-Ph	**58**	(6 %)	-	-	-	**57**

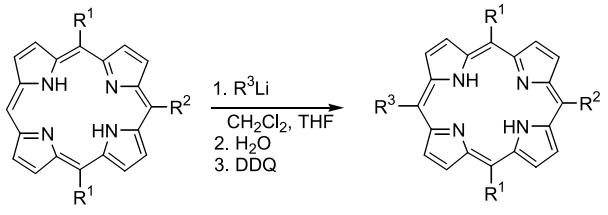
Scheme 6. Synthesis of A_3B-type porphyrins via condensation reactions.

mechanistic studies.[17b] Nevertheless, this method allows the preparation of the target compounds **61–68** in acceptable yields and two steps from the respective A_2 porphyrins. We are currently investigating improvements of these reactions by using various cocatalysts.

The most significant result is, that hydroxyphenyl residues can be introduced directly and in good to excellent yields using the respective dilithio species. For example, the *m*-hydroxyphenylporphyrin **63** could be prepared in 83% yield. As discussed in Section 2.8 currently most strategies involve first preparation of, for example, methoxyarylporphyrins and then demethylation to the desired hydroxyphenylporphyrins. The ease of the direct substitution reaction indicates that the use of protected alcohols followed by deprotection can be circumvented. Bonnett and Martinez recently described a method that allows the conversion of *m*-hydroxyphenyl groups into 3,5-dihydroxyphenyl groups in *m*-THPC derivatives via sensitization reactions offering the possibility to further increase the polarity of such compounds.[23]

2.6. Vinylogous formylation reactions

Alternatively, electrophilic substitution reactions have been utilized for a long time for the modification of porphyrins and as an entry into more elaborate photosensitizer structures.[24] One such example are the benzochlorins,[25] which can be prepared via acid-catalyzed cyclization of

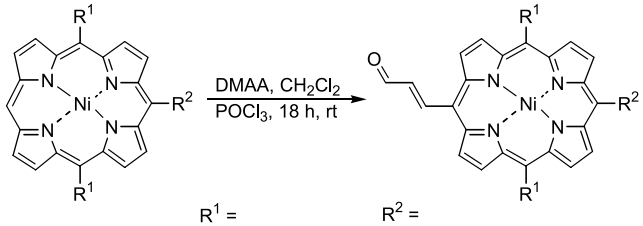


R^1 =	R^2 =	R^3 =		
Ph	hexyl	butyl	**61**	(31 %)
Ph	hexyl	4-Me_2N-Ph	**62**	(54 %)
Ph	hexyl	3-HO-Ph	**63**	(83 %)
Ph	hexyl	4-HO-Ph	**64**	(65 %)
Ph	hexyl	2-MeO-Ph	**65**	(40 %)
Ph	hexyl	2,5-DiMeO-Ph	**66**	(29 %)
Ph	4-H_2N-Ph	4-Me_2N-Ph	**67**	(20 %)
3-MeO-Ph	4-H_2N-Ph	hexyl	**68**	(44 %)

Scheme 7. Synthesis of A_2BC-type porphyrins via S_NAr reactions.

meso acrolein substituted porphyrins.[26,27] In order to test, whether this method is also applicable to the unsymmetric porphyrins targeted here, a number of nickel(II) porphyrins were subjected to a vinylogous Vilsmeier formylation to yield the acroleinporphyrins.

Like classic formylation reactions,[28] the vinylogous Vilsmeier reactions proceed quite well with A_2- and A_2B-type porphyrins. As shown in Scheme 8 the trisubstituted porphyrins **69–71** were accessible in about 60% yield from the respective A_2 porphyrins. The disubstitution products **72–74** were formed in small amounts during these reactions. Likewise the A_2BC porphyrins **75** and **76** could be prepared in good yields. Most vinylogous formylation reactions of porphyrins found in the literature have been performed with β-substituted porphyrins, namely octaethylporphyrin and its derivatives. Yields are in general quite good, often exceeding 80%. Vinylogous formylation reactions on β-unsubstituted porphyrins have — to the best of our knowledge — been described only twice with yields between 29 and 55%.[27,28a] This is in line with our findings which also gave lower yields for β-unsubstituted porphyrins. One reason for this may be a higher reactivity of the β-unsubstituted porphyrins, resulting in side-reactions. This higher reactivity is also supported by the occurrence of bis-vinylogously formylated products for all 5,15-disubstituted porphyrins.



R^1 =	R^2 =		
4-butyloxy-Ph	H	**69**	(63 %)
4-pentyloxy-Ph	H	**70**	(63 %)
3-MeO-Ph	H	**71**	(56 %)
4-butyloxyphenyl	-CH=CH-CHO	**72**	side prod.
4-pentyloxyphenyl	-CH=CH-CHO	**73**	side prod.
3-MeO-Ph	-CH=CH-CHO	**74**	side prod.
3-MeO-Ph	3-MeO-Ph	**75**	(77 %)
3,5-DiMeO-Ph	hexyl	**76**	(55 %)

Scheme 8. Vinylogous formylation reactions.

An interesting feature of the vinylogously formylated porphyrins is a strong bathochromic shift (~35 nm) in the long-wavelength absorption band, most probably due to the extension of the conjugated system. The bathochromic shift is nearly the same starting from 5,15-di- as well as from 5,10,15-trisubstituted porphyrins. As a bathochromically shifted absorption is a prerequisite for a promising photosensitizer (cf. also Section 2.7), these vinylogously formylated porphyrins - after removal of the central metal ion by standard methods - themselves could have potential as photosensitizers.

Unfortunately, we were unable to accomplish subsequent acid-catalyzed cyclization reactions in a rational manner. Although the synthesis of benzochlorins has been widely used with β-substituted porphyrins,[25] only one compound derived from β-unsubstituted 5,15-disubstituted porphyrins has been reported.[28] However, in all present cases complex product mixtures (>10 compounds) were obtained, that could not be separated. Spectroscopic evidence points towards the formation of different cyclization products, the occurrence of dealkylation reactions and a general instability of the products formed.[29a] Such an anomalous cyclization behavior has also been observed for *meso* 3-methoxyphenyl-substituted β-formyl porphyrins.[29b]

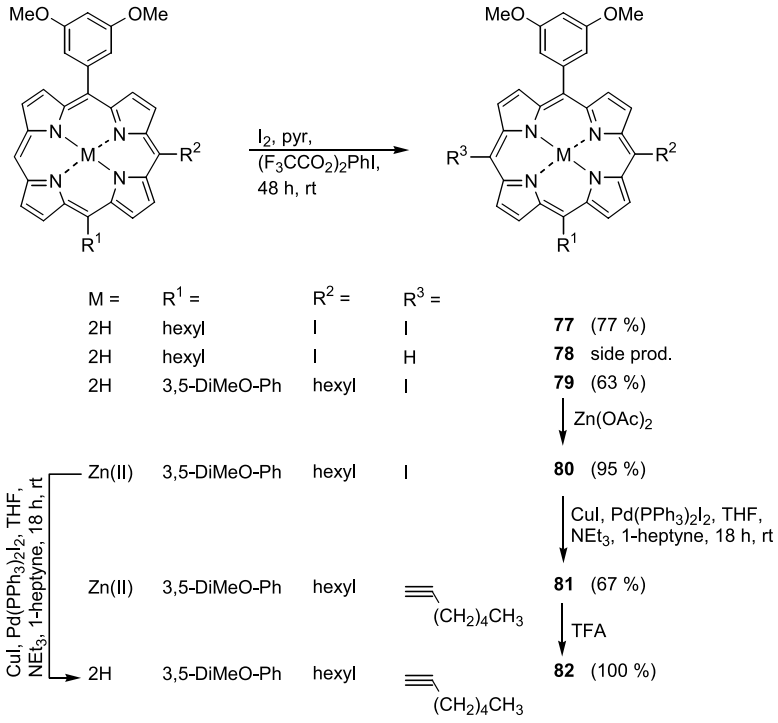
2.7. Alkynyl substituted porphyrins

Another approach for facile *meso* modifications is the preparation of *meso* halogenoporphyrins followed by subsequent coupling reactions.[24b] We were especially interested in functionalization methods that allowed both a modulation of amphiphilicity and the electronic properties of the target compounds. Porphyrins carrying ethynyl residues exhibit bathochromically shifted absorption bands, with each alkynyl system typically accounts for a 15 nm shift.[30] This is a desirable effect for photosensitizers in PDT due to the deeper tissue penetration of the exciting light.

As reasoned above, the basic framework of the porphyrin system should contain both potentially polar and apolar side chains to assure amphiphilicity. As the polar groups are provided here by the hydroxyphenyl groups related to the original Temoporfin framework, this required introduction of the C≡C group in a long aliphatic chain to maintain an amphiphilic system.

Using the A_2B porphyrin **35** as a test bed this compound was *meso* iodinated[31] to give **79** in 63% yield on a 100 mg scale. Longer reaction times led to an increase in yield. However, this was accompanied by the formation of more side products. Metallation with zinc(II) acetate gave the corresponding metalloporphyrin **80** in almost quantitative yield and this compound was then subjected to a palladium-catalyzed coupling[32] with 1-heptyne to give the alkynylated porphyrin **81** in 67% yield (Scheme 9). The reaction sequence was completed by quantitative demetallation of **81** to **82**. For practical purposes the reaction sequence coupling–demetallation (e.g., **80**→**81**→**82**) can be performed in a one-pot procedure by addition of TFA to the crude mixture of the coupling reaction. This gave **82** in 50% yield with respect to **80**. Similar reactions using diiodinated AB porphyrins (e.g., **77**) as starting materials are possible and will be reported elsewhere.

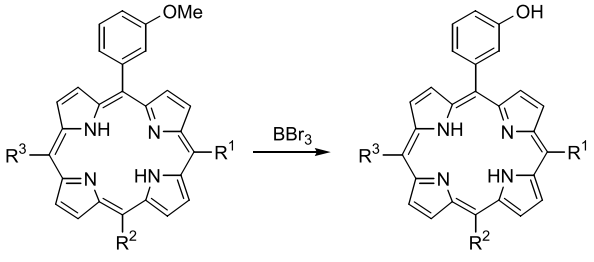
Compounds derived from **82** possessing free hydroxyl groups and the alkynyl chain are very promising candidates as photosensitizers by combining a bathochromically shifted absorption with an amphiphilic molecular structure. Moreover, the alkynyl chain is chemically more stable than, for example, simple chlorin structures, which are easily reoxidized to the corresponding porphyrins, thus loosing their decisive absorption features. As discussed below (cf. Section 2.8) such compounds possessing three free hydroxyl groups and a lipophilic carbon chain also exhibit special features in a biomimetic environment such as liposomes.



Scheme 9. Synthesis of alkynyl substituted porphyrins.

2.8. Hydroxyphenylporphyrins and preliminary biological studies

In order to have truly amphiphilic porphyrins a number of A_2-, AB-, A_3-, A_2B-, and A_3B-type porphyrins carrying methoxyphenyl groups were converted into the respective hydroxyphenyl porphyrins **83**–**92**. The results are summarized in Scheme 10. Demethylation with BBr_3[33] generally proceeds well in yields of 80–90%. Only **83** gave a very low isolated yield, presumably due to the very low solubility of the compound.



R^1 =	R^2 =	R^3 =		
H	3-HO-Ph	H	**83**	(21 %)
H	hexyl	H	**84**	(83 %)
3-HO-Ph	3-HO-Ph	H	**85**	(81 %)
hexyl	3-HO-Ph	H	**86**	(84 %)
3-HO-Ph	3-HO-Ph	pentyl	**87**	(85 %)
hexyl	3-HO-Ph	3-HO-Ph	**88**	(89 %)
heptyl	3-HO-Ph	3-HO-Ph	**89**	(86 %)
hexyl	hexyl	hexyl	**90**	(92 %)
heptyl	heptyl	heptyl	**91**	(87 %)
3-HO-Ph	3-HO-Ph	3-HO-Ph	**92**	(90 %)

Scheme 10. Preparation of hydroxyphenylporphyrins.

In order to test the influence of an amphiphilic substitution pattern on the PDT properties detailed in vitro and in vivo tests are currently ongoing. Initial results on the PDT-related photophysical properties for a number of selected porphyrins were determined in isotropic solution and in liposome membrane model systems and have already been communicated.[34] Absorption, fluorescence, and singlet oxygen quantum yields were determined in isotropic solution and in DPPC liposomes.

In isotropic ethanol solution, the compounds showed properties typical for *meso* substituted porphyrins, that is, fluorescence lifetimes of about 8–9 ns, singlet oxygen quantum yields of 0.6–0.7, and singlet oxygen luminescence lifetimes of 14 μs. Only the *p*-aminophenyl substituted porphyrins **39** and **68** exhibited a smaller singlet oxygen quantum yield. Due to the differences in solubility, with the *m*-hydroxyphenyl-substituted porphyrins having a much higher solubility. As expected, high concentrations in liposomes could only be achieved with compounds having free hydroxy or amino groups. The highest concentration in liposomes was obtained with compounds **87**–**89** (i.e., those that have three 3-hydroxyphenyl substituents and one alkyl chain) and for 5,10,15,20-tetrakis(3-hydroxyphenyl)-porphyrin **92**.

In addition, compounds **87**–**89** exhibited a striking difference to all other compounds studied. Their fluorescence lifetime in liposomes was significantly reduced as was the singlet oxygen quantum yield. Both parameters are indicators of the localization of the dyes in the lipid bilayer and we concluded that the amphiphilic *m*-THPC congeners with one hydrophobic alkyl chain and three 3-hydroxyphenyl residues differ in their localization behavior in the

liposome bilayer from all other compounds studied. Most likely is a preferable localization at the hydrophobic/hydrophilic interface of the liposomes indicating that, compared to Temoporfin, a more specific in vivo localization of unsymmetrically substituted amphiphilic photosensitizers may be achieved using this strategy. Indeed, for related chlorins (not shown) the increasing amphiphilicity of the sensitizer molecules could be correlated with an increased uptake into lysosomes and an increased ratio of necrotic versus apoptotic cells.[35]

3. Conclusions

Starting from an applied-science oriented approach, we have shown how the present tools of synthetic porphyrin chemistry can be combined to obtain a wide variety of unsymmetrically substituted amphiphilic porphyrins as potential photosensitizers and as probes for assessing membrane affinity.

The porphyrin starting materials (such as A_2- or AB-porphyrins) are best prepared by simple condensation reactions of dipyrromethane and suitable aldehydes. These porphyrins are then easily functionalized by an S_NAr reaction with organolithium compounds, allowing the introduction of, for example, alkyl chains, protected phenolic functions, free hydroxyphenyl residues, or aminophenyl substituents. Other methods were complementarily used to further tune the properties of the tetrapyrrolic system, for example, introduction of alkynyl-substituents that exert a bathochromic shift, thus, improving the absorption properties.

Future work will be concentrated on utilizing these principles for the synthesis of photosensitizers with optimized membrane affinity and targeting properties. In particular, the direct introduction of *m*, *o*, and *p*-hydroxyphenyl groups into the tetrapyrrolic system via organolithium chemistry (thus, circumventing deprotection procedures) poses a promising route to compounds with a tailored degree of hydrophilicity. We are currently investigating the synthesis of ABCD porphyrins carrying up to four hydroxyphenyl groups via direct S_NAr reactions.

Further work will be directed towards the construction of combinatorial libraries with these multi-functionalized porphyrins and their extension to chlorin systems. An unsymmetrically substituted chlorin of this type has already been shown to give promising results in Jurkat cell suspensions.[35]

4. Experimental

4.1. General methods

All chemicals used were of analytical grade and were purchased from Aldrich Co. unless stated otherwise. Reactions with organolithium reagents were performed using standard Schlenk techniques and glassware. Melting points were measured on a Reichert Thermovar apparatus and are uncorrected. Silica gel 60 (0.04–0.063 mm, 230–400 mesh ASTM, Merck) was used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 plates (precoated sheets, 0.2 mm thick, with and without fluorescence indicator F254) or alumina plates (Alox 60, Machery & Nagel). Alternatively, neutral alumina (60 mesh, Alfa), normally deactivated with water (7%= Brockmann grade III), was used for column chromatography. Proton NMR spectra were recorded at a frequency of 250 MHz (AC 250) or 500 MHz (Bruker, AMX 500), ^{13}C NMR spectra at a frequency of 125 MHz. All chemical shifts are given in ppm, referenced on the δ scale downfield from the TMS signal as internal standard. Electronic absorption spectra were recorded on a Specord S10 (Carl Zeiss) spectrophotometer using dichloromethane as solvent. Mass spectra were recorded using a Varian MAT 711 or MAT 112 S mass spectrometer using the EI technique with a direct insertion probe and an excitation energy of 80 eV. FAB spectra were recorded with CH-5 DF instrument from Varian. Elemental analyses were performed with a Perkin–Elmer 240 analyzer. Preparative HPLC was performed with columns (23×15 and 23×30 mm, respectively) filled with silica gel [Merck, Nucleosil 50 (5 μm)] using a Knauer-pump (Knauer MPLC Pump and Knauer HPLC Pump 64, respectively). The solvent flow rate was 64 mL/min (P= 23 bar$=23\times10^5$ Pa). UV detection (Knauer Variable Wavelength Monitor) was performed at 420 nm for the porphyrins. Analytical HPLC was performed using a Spectra Physics pump (SP 8810) and an analytical column (4×250 mm) filled with silica gel (Merck, Nucleosil 50, 5 μm). The solvent flow rate was 1 mL/min, with UV/vis detection typically at 420 nm for the porphyrins.

4.2. Starting materials

5-(3,5-Dimethoxyphenyl)porphyrin **41**[19] 5,15-diphenylporphyrin,[14a] 5-(*p*-aminophenyl)-10,20-diphenylporphyrin,[18b] dipyrromethane **10**[12b] and 5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin **50**[36] (which is also obtained as a by-product in the synthesis of **45**, **51**, and **56**) were prepared according to published procedures. Pyrrole-2-carbaldehyde **11** was obtained from Fluka. 4-Pentyloxybenzaldehyde was obtained from Lancaster.

4.3. A_2-type porphyrins

4.3.1. 5,15-Bis(3-methoxyphenyl)porphyrin (12). Dry dichloromethane (1 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (Ar) and a reflux condenser. Dipyrromethane **10** (593 mg, 4.06 mmol) and 3-methoxybenzaldehyde (530 μL, 4.35 mmol) were added. The flask was shielded from ambient light and then 70 μL (0.9 mmol) of TFA were added and the reaction mixture was stirred for 18 h at 20 °C. After this time, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h, followed by addition of 15 mL of triethylamine. The reaction mixture was concentrated in vacuo to about 100 mL and filtered through 600 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluate was evaporated to dryness and the residue resuspended in 100 mL of dichloromethane and then layered with a 2-fold excess of methanol. After 24 h, the precipitated solid was

removed by suction filtration through a D3 frit and dried in vacuo. Yield: 550 mg (1.05 mmol; 52%) of purple crystals: mp >350 °C, sublimation >300 °C; R_f=0.58 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.16 (s, br., 2H, N*H*), 4.01 (s, 6H, OCH_3), 7.35 (m, 2H, Ph-*H*), 7.67 (m, 2H, Ph-*H*), 7.84 (m, 4H, Ph-*H*), 9.11 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 9.38 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 10.31 ppm (s, 2H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.57, 105.26, 113.55, 120.82, 127.78, 127.92, 131.05, 131.58, 142.75, 145.30, 147.10, 153.64, 158.29 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 (4.30), 361 (4.49), 390 (4.95), 410 (5.57), 474 (3.77), 502 (4.30), 536 (3.88), 575 (3.84), 628 nm (3.56); MS (EI, 80 eV, 250 °C) *m/z* (%): 522 (100) [M^+], 507 (2) [M^+-CH_3], 491 (3) [M^+-CH_3O], 261 (7) [M^{2+}]; HRMS (EI) [$C_{34}H_{26}N_4O_2$]: calcd 522.20558, found 522.20642; [$C_{34}H_{26}N_4O_2$, 522.61 g mol^{-1}]. Anal. Calcd C 78.14, H 5.01, N 10.72. Anal. Calcd for [$C_{34}H_{26}N_4O_2\cdot0.5H_2O$, 531.62 g mol^{-1}]. Anal. Calcd C 76.82, H 5.12, N 10.54, found C 76.80, H 4.90, N 10.53.

4.3.2. 5,15-Bis(4-methoxyphenyl)porphyrin (13). Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and 4-methoxybenzaldehyde (1 mL, 8.2 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of trifluoroacetic acid were added and the reaction mixture stirred for 18 h at 20 °C. Subsequently, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 6 mL of triethylamine were added and the reaction mixture was concentrated in vacuo to about 150 mL. Methanol (150 mL) was added and the reaction mixture was filtered through a D3 frit. The residue in the frit was thoroughly washed with acetone and methanol until the washing solution becomes nearly colorless. Finally it was washed with 100 mL of dichloromethane. The filtrate was discarded and the residue in the frit was dried in vacuo to yield 1.42 g (2.7 mmol; 66%) of the title compound as a purple amorphous solid: mp >330 °C; R_f=0.54 (CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.11 (s, br., 2H, N*H*), 4.12 (s, 6H, OCH_3), 7.34 (m, 4H, phenyl-*H*), 8.18 (m, 4H, phenyl-*H*), 9.09 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 9.38 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 10.29 ppm (s, 2H, *meso-H*); UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 (4.26), 391 (4.86), 410 (5.54), 505 (4.22), 540 (3.93), 577 (3.82), 634 nm (3.56); MS (EI, 80 eV, 300 °C) *m/z* (%): 522 (100) [M^+], 507 (6) [M^+-CH_3], 416 (2) [$M^+-C_6H_7O$], 261 (10) [M^{2+}]; HRMS (EI) [$C_{34}H_{26}N_4O_2$]: calcd 522.20558, found 522.20392; [$C_{34}H_{26}N_4O_2$, 522.61 g mol^{-1}]. Anal. Calcd C 78.14, H 5.01, N 10.72, found C 77.80, H 4.98, N 10.63.

4.3.3. 5,15-Bis(3,4-dimethoxyphenyl)porphyrin (14). Dry dichloromethane (2 L) was placed in a three-necked-flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and 3,4-dimethoxybenzaldehyde (1.35 g, 8.1 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of trifluoroacetic acid were added and the reaction mixture was stirred for 18 h at 20 °C. After this time 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 6 mL of triethyl amine were added and the reaction mixture was stirred for 15 min. The reaction mixture was filtered through 100 g of silica, washing with dichloromethane (approximately 4 L). The eluted porphyrin fractions were evaporated to dryness. The porphyrin was resuspended in 100 mL of dichloromethane and then layered with a 2-fold excess of methanol. After 48 h, the precipitated purple solid was removed by suction filtration through a D4 frit and dried in vacuo to yield 1.23 g of a purple amorphous solid (2.1 mmol; 50%): mp >340 °C; R_f=0.65 (SiO_2, CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); ^{1}H NMR (250 MHz, $CDCl_3$) δ=−3.10 (s, 2H, N*H*), 4.03 (s, 6H, OCH_3), 4.19 (s, 6H, OCH_3), 7.31 (m, 2H, phenyl-*H*), 7.81 (m, 4H, phenyl-*H*), 9.12 (d, *J*=5 Hz, 4H, β-pyrrole-*H*), 9.38 (d, *J*=5 Hz, 4H, β-pyrrole-*H*), 10.30 ppm (s, 2H, *meso-H*); UV/vis (CH_2Cl_2): λ_{max} (log ε)=411 (5.60), 505 (4.24), 541 (3.87), 577 (3.74), 633 nm (3.32); MS (EI, 80 eV, 240 °C) *m/z* (%): 582 (100) [M^+], 567 (5) [M^+-CH_3], 551 (6) [M^+-CH_3O], 445 (1) [$M^+-C_8H_9O_2$], 291 (5) [M^{2+}]; HRMS (EI) [$C_{36}H_{30}N_4O_4$]: calcd 582.22668, found 582.22745; [$C_{36}H_{30}N_4O_4$, 582.66 g mol^{-1}]. Anal. Calcd C 74.21, H 5.19, N 9.62, found C 74.11, H 5.05, N 9.97.

4.3.4. 5,15-Bis(3,5-dimethoxyphenyl)porphyrin (15). Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (Ar) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and 3,5-dimethoxybenzaldehyde (1.4 g, 8.4 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of TFA were added and the reaction mixture was stirred for 18 h at 20 °C. After this time, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 6 mL of triethylamine were added and the reaction mixture was concentrated in vacuo to about 200 mL. Methanol (50 mL) was added and the reaction mixture was filtered through a D3 frit. The residue in the frit was thoroughly washed with dichloromethane, acetone, and methanol until the washing solution became nearly colorless. The wash solutions were discarded and the residue in the frit was dried in vacuo to yield 1.4 g (2.4 mmol; 58%) of a purple amorphous solid: mp >340 °C; R_f=0.5 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.16 (s, br., 2H, N*H*), 4.01 (s, 12H, OCH_3), 6.94 (m, 2H, phenyl-H_{para}), 7.46 (m, 4H, phenyl-H_{ortho}), 9.18 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 9.39 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 10.32 ppm (s, 2H, *meso-H*); UV/vis (CH_2Cl_2): λ_{max} (log ε)=300 (4.37), 361 (4.52), 391 (4.96), 407 (5.36), 502 (4.33), 533 (3.93), 573 (3.93), 628 nm (3.61); MS (EI, 80 eV, 250 °C) *m/z* (%): 582 (100) [M^+], 567 (3) [M^+-CH_3], 531 (4) [M^+-CH_3O], 446 (2) [$M^+-C_8H_8O_2$], 291 (11) [M^{2+}]; HRMS (EI) [$C_{36}H_{30}N_4O_4$]: calcd 582.22671, found 582.22833; [$C_{36}H_{30}N_4O_4$, 582.66 g mol^{-1}]. Anal. Calcd C 74.21, H 5.19, N 9.62, found C 74.55, H 5.18, N 9.78.

4.3.5. 5,15-Bis(3,4-dibenzyloxyphenyl)porphyrin (16). Dry dichloromethane (2000 mL) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and 3,4-dibenzyloxybenzaldehyde (2.58 g, 8.1 mmol) were added. The flask was shielded from ambient

light and then 140 μL (1.8 mmol) of TFA were added and the reaction mixture was stirred for 18 h at 20 °C. After this time, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 6 mL of triethylamine were added and the reaction mixture was stirred for 15 min. The reaction mixture was filtered through 100 g of silica, washing with dichloromethane (~1 L). The eluted porphyrin fractions were evaporated to dryness. The porphyrin was resuspended in 100 mL of dichloromethane and then layered with a twofold excess of methanol. After 24 h, the precipitated purple solid was removed by suction filtration through a D3 frit. This solid was thoroughly washed with dichloromethane (the filtrate was discarded) and then dried in vacuo. Yield: 1967 mg of a purple amorphous solid (2.2 mmol; 54%); mp 319–321 °C; R_f=0.65 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.44 (SiO_2, CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.16 (s, 2H, N*H*), 5.36 (s, 4H, OCH_2), 5.48 (s, 4H, OCH_2), 7.33–7.55 (m, 12H, phenyl-*H*), 7.65–7.75 (m, 6H, phenyl-*H*), 7.88 (m, 2H, phenyl-*H*), 8.95 (d, *J*=5 Hz, 4H, β-pyrrole-*H*), 9.31 (d, *J*=5 Hz, 4H, β-pyrrole-*H*), 10.25 ppm (s, 2H, *meso*-*H*); UV/vis (CH_2Cl_2): λ_{max} (log ε)=412 (5.66), 505 (4.13), 542 (3.78), 578 (5.39), 633 nm (3.14); MS (FAB+, CH_2Cl_2/*m*-NO_2-Bzl-OH/Xe), *m/z* (%): 887 (6) [(M+H)$^+$], 796 (1) [(M+H)$^+$−C_7H_7], 443 (0.2) [M^{2+}]; HRMS (EI) [$C_{60}H_{38}N_4O_4$]: calcd 886.35191, found 886.35134; [$C_{60}H_{38}N_4O_4$, 887.05 g mol^{-1}]. Anal. Calcd C 81.24, H 5.23, N 6.32, found C 81.21, H 5.29, N 6.45.

4.3.6. 5,15-Bis(4-butyloxyphenyl)porphyrin (17). Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and 4-butyloxybenzaldehyde (1.4 mL, 8.25 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of TFA were added and the reaction mixture was stirred for 18 h at 20 °C. After this time, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. After addition of 6 mL of triethylamine the reaction mixture was filtered through 50 g of silica (washing with dichloromethane) and then concentrated in vacuo to about 150 mL. The flask was ultrasonicated for 2 min and then layered with a 2-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 1.1 g (1.81 mmol; 44%) of the title porphyrin as a purple amorphous powder: mp >340 °C; R_f=0.60 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.09 (s, br., 2H, N*H*), 1.11 (t, 6H, *J*=7 Hz, $OCH_2CH_2CH_2CH_3$), 1.68 (m, 4H, $OCH_2CH_2CH_2$-CH_3), 1.99 (m, 4H, $OCH_2CH_2CH_2CH_3$), 4.28 (t, 4H, *J*=6 Hz, $OCH_2CH_2CH_2CH_3$), 7.32 (m, 4H, phenyl-*H*), 8.15 (m, 4H, phenyl-*H*), 9.09 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 9.38 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 10.28 ppm (s, 2H, *meso*-H); UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 nm (4.36), 360 (4.44), 391 (4.93), 410 (5.50), 474 (3.85), 505 (4.29), 541 (4.03), 578 (3.89), 633 (3.65); MS (EI, 80 eV, 320 °C) *m/z* (%): 606 (100) [M^+], 549 (5) [M^+−C_4H_9], 458 (12) [M^+−$C_{10}H_{12}O$], 303 (1) [M^{2+}]; HRMS (EI) [$C_{40}H_{38}N_4O_2$]: calcd 606.29948, found 606.29663; [$C_{40}H_{38}N_4O_2$, 606.77 g mol^{-1}]: C 79.18, H 6.31, N 9.23, [$C_{34}H_{26}N_4O_2\cdot 1H_2O$, 615.78 g mol^{-1}]. Anal. Calcd C 76.90, H 6.45, N 8.97, found C 76.36, H 6.05, N 8.81.

4.3.7. 5,15-Bis(4-pentyloxyphenyl)porphyrin (18). Dry dichloromethane (2 L) was placed in a three-necked-flask equipped with magnetic stirrer, gas inlet (Ar) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and 4-pentyloxybenzaldehyde (1.56 mL, 8.25 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of TFA acid were added and the reaction mixture was stirred for 18 h at 20 °C. After this time, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h, followed by addition of 6 mL triethylamine. The reaction mixture was concentrated in vacuo to about 200 mL, ultrasonicated for 2 min and then filtered through 600 mL of silica (column diameter 5 cm), washing with dichloromethane (ca. 2 L). The eluate was evaporated to dryness and the residue resuspended in 100 mL of dichloromethane and then layered with a 2-fold excess of methanol. After 24 h the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo. Yield: 1.05 g (1.65 mmol; 40%) of purple crystals: mp 314–316 °C; R_f=0.64 (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.48 (CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.08 (s, br., 2H, N*H*), 1.04 (t, 6H, *J*=7 Hz, $OCH_2CH_2CH_2CH_2$-CH_3), 1.45–1.70 (m, 8H, $OCH_2CH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2CH_3$), 2.01 (m, 4H, $OCH_2CH_2CH_2CH_2$-CH_3), 4.27 (t, 4H, *J*=6 Hz, $OCH_2CH_2CH_2CH_2CH_3$), 7.32 (m, 4H, phenyl-*H*), 8.15 (m, 4H, phenyl-*H*), 9.09 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 9.38 (d, 4H, *J*=5 Hz, β-pyrrole-*H*), 10.28 ppm (s, 2H, *meso*-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.13, 22.62, 28.44, 29.25, 68.44, 105.12, 113.15, 118.96, 131.03, 131.46, 133.60, 135.87, 145.12, 147.58, 159.14 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 nm (4.33), 360 (4.40), 391 (4.91), 410 (5.54), 474 (3.69), 505 (4.23), 541 (3.93), 578 (3.74), 633 (3.36); MS (EI, 80 eV, 320 °C) *m/z* (%): 634 (100) [M^+], 563 (6) [M^+−C_5H_{11}], 472 (2) [M^+−$C_{11}H_{14}O$], 317 (1) [M^{2+}]; HRMS (EI) [$C_{42}H_{42}N_4O_2$]: calcd 634.330777, found 634.33423; [$C_{42}H_{42}N_4O_2$, 634.82 g mol^{-1}]. Anal. Calcd C 79.47, H 6.67, N 8.83, found C 78.95, H 6.56, N 8.80.

4.3.8. 5,15-Bis(4-benzyloxyphenyl)porphyrin (19). Synthetic procedure similar to that for compound **18** (Section 4.3.7). However, the crude product obtained was completely insoluble in common solvents. Although roughly 300 mg crude material were obtained, no characterization could be performed.

4.3.9. 5,15-Dihexylporphyrin (20). Dry dichloromethane (2 L) was placed in a three-necked-flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol) and heptanal (1.17 mL, 8.4 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of trifluoroacetic acid were added and the reaction mixture was stirred for 18 h at 20 °C. After this time 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 3 mL of triethylamine were added and the reaction mixture was concentrated in vacuo to about 150 mL. The reaction mixture was filtered through

600 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated purple needles were removed by suction filtration through a D3 frit and dried in vacuo. Yield: 534 mg (1.1 mmol; 27%). Purple needles: mp 214–216 °C; R_f=0.87 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.90 (s, br., 2H, N*H*), 0.96 (t, J=7 Hz, 6H, 5^6-CH_3 and 15^6-CH_3), 1.43 (m, 4H, 5^5-CH_2 and 15^5-CH_2), 1.54 (m, 4H, 5^4-CH_2 and 15^4-CH_2), 1.84 (m, 4H, 5^3-CH_2 and 15^3-CH_2), 2.57 (m, 4H, 5^2-CH_2 and 15^2-CH_2), 5.02 (t, J=8 Hz, 4H, 5^1-CH_2 and 15^1-CH_2), 9.41 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.58 (d, J=5 Hz, 4H, β-pyrrole-*H*), 10.17 ppm (s, 2H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.12, 22.73, 29.70, 30.24, 31.93, 34.65, 38.59, 48.33, 104.22, 118.82, 127.77, 131.83, 144.21, 147.49, 153.08 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=300 (4.21), 360 (4.41), 388 (4.91), 404 (5.45), 475 (3.34), 504 (4.19), 535 (3.56), 578 (3.59), 633 nm (3.18); MS (EI, 80 eV, 220 °C), *m/z* (%): 478 (100) [M^+], 407 (65) [$M^+-C_5H_{11}$], 336 (29) [$M^+-2\times C_5H_{11}$], 239 (4) [M^{2+}]; HRMS (EI) [$C_{32}H_{38}N_4$]: calcd 478.30965, found 478.30755; [$C_{32}H_{38}N_4$, 478.68 g mol^{-1}]. Anal. Calcd C 80.29, H 8.00, N 11.70, found C 80.10, H 7.85, N 11.66.

4.3.10. 5,15-Di(*iso*-butyl)porphyrin (21). The reaction was performed using the conditions given in Section 4.3.9 using 3-methyl butanal (920 μL, 8.5 mmol). After concentration of the reaction mixture it was filtered through 600 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness and the residue redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated purple needles were removed by suction filtration through a D3 frit and dried in vacuo to yield 470 mg of purple crystals (1.1 mmol; 27%) of the title compound: mp 265–267 °C; R_f=0.57 (CH_2Cl_2/C_6H_{14}, 2:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.91 (s, br., 2H, N*H*), 1.22 (d, 12H, J=6 Hz, $CH_2CH(CH_3)_2$), 2.82 (m, 2H, $CH_2CH(CH_3)_2$), 4.86 (d, 4H, J=8 Hz, $CH_2CH(CH_3)_2$), 9.38 (d, 4H, J=5 Hz, β-pyrrole-*H*), 9.54 (d, 4H, J=5 Hz, β-pyrrole-*H*), 10.17 ppm (s, 2H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=22.37, 36.73, 43.04, 104.35, 117.64, 128.28, 131.71, 144.13, 148.00 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)= 300 nm (4.22), 342 (4.34), 360 (4.45), 402 (5.44), 475 (3.41), 504 (4.22), 535 (3.66), 577 (3.69), 632 (3.33); MS (EI, 80 eV, 230 °C), *m/z* (%): 422 (67) [M^+], 379 (100) [$M^+-C_3H_7$], 336 (47) [$M^+-2\times C_3H_7$], 211 (4) [M^{2+}]; HRMS (EI) [$C_{28}H_{30}N_4$]: calcd 422.24705, found 422.24734; [$C_{28}H_{30}N_4$, 422.57 g mol^{-1}]. Anal. Calcd C 79.59, H 7.16, N 13.26, found C 79.13, H 6.96, N 13.30.

4.3.11. [5,15-Di(*iso*-butyl)porphyrinato]nickel(II) (25). 5,15-Di(*iso*-butyl)porphyrin **21** (200 mg, 0.47 mmol) was placed in a round-bottomed flask equipped with a reflux condenser. DMF (100 mL) and nickel(II) acetate (1.2 g, 6.8 mmol) were added and the flask was heated at 150 °C (bath temperature) for 2 h. The solvent was evaporated to dryness and the residue taken up in dichloromethane. The mixture was ultrasonicated for 2 min and then filtered through silica (50 g), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness and the residue redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated crystals were removed by suction filtration through a D3 frit and dried in vacuo to yield 210 mg (0.44 mmol, 93%) of the title compound as red needles: mp 226 °C; R_f=0.81 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); HPLC (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/C_6H_{14}, 1:1; v/v, flow rate: 1 mL/min, detection at 420 nm): retention time: 2.95 min (90.0%), (same conditions but detection at 254 nm) retention time: 3.02 min (94.4%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.95 (d, 12H, J= 6 Hz, $CH_2CH(CH_3)_2$), 2.42 (m, 2H, $CH_2CH(CH_3)_2$), 4.62 (d, 4H, J=7 Hz, $CH_2CH(CH_3)_2$), 9.14 (d, 4H, J=5 Hz, β-pyrrole-*H*), 9.41 (d, 4H, J=5 Hz, β-pyrrole-*H*), 9.68 ppm (s, 2H, *meso-H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ=23.11, 34.97, 42.43, 103.94, 116.11, 130.19, 132.09, 141.38, 143.09 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=292 (4.08), 322 (3.95), 402 (5.32), 518 (4.16), 549 nm (3.70); MS (EI, 80 eV, 300 °C) *m/z* (%): 478 (88) [M^+], 435 (100) [$M^+-C_3H_7$], 392 (79) [$M^+-2\times C_3H_7$], 239 (6) [M^{2+}]; HRMS (EI) [$C_{28}H_{28}N_4Ni$]: calcd 478.16674, found 478.16619; [$C_{28}H_{28}N_4Ni$, 479.25 g mol^{-1}]. Anal. Calcd C 70.17, H 5.89, N 11.69, found C 69.88, H 5.71, N 11.79.

4.3.12. [5,15-Bis(4-butyloxyphenyl)porphyrinato]-nickel(II) (26). The free base **17** (100 mg, 0.16 mmol) was placed in a round-bottomed flask equipped with a reflux condenser. DMF (50 mL) and 600 mg (3.4 mmol) of nickel(II)acetate were added and the flask was heated at 150 °C (bath temperature) for 1.5 h. The solvent was evaporated to dryness and the residue was taken up in dichloromethane. The mixture was ultrasonicated for 2 min and then filtered through silica (30 g), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness and the residue resuspended in 50 mL of dichloromethane and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated red crystals were removed by suction filtration through a D3 frit and dried in vacuo and gave the title porphyrin in quantitative yield: mp 325 °C; R_f=0.74 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.09 (t, J=7 Hz, 6H, $OCH_2CH_2CH_2CH_3$), 1.66 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.96 (m, 4H, $OCH_2CH_2CH_2CH_3$), 4.23 (t, J=6 Hz, 4H, $OCH_2CH_2CH_2CH_3$), 7.20 (m, 4H, phenyl-*H*), 7.95 (m, 4H, phenyl-*H*), 8.96 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.16 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.90 ppm (s, 2H, *meso-H*); UV/vis (CH_2Cl_2): λ_{max} (log ε)=323 (4.25), 404 (5.37), 516 (4.28), 547 nm (3.94); MS (EI, 80 eV, 290 °C), *m/z* (%): 662 (100) [M^+], 605 (4) [$M^+-C_4H_9$], 549 (2) [$M^+-C_4H_9$-C_4H_8], 514 (17) [$M^+-C_{10}H_{12}O$], 331 (1) [M^{2+}]; HRMS (EI) [$C_{40}H_{36}N_4NiO_2$]: calcd 662.21917, found 662.21679; [$C_{40}H_{36}N_4NiO_2$, 663.44 g mol^{-1}]. Anal. Calcd C 72.42, H 5.47, N 8.44, [$C_{40}H_{36}N_4NiO_2\cdot\frac{1}{2}H_2O$, 672.45 g mol^{-1}] C 71.45, H 5.55, N 8.33, found C 71.32, H 5.26, N 8.37.

4.3.13. [5,15-Bis(4-pentyloxyphenyl)porphyrinato]-nickel(II) (27). The free base **18** (100 mg, 0.16 mmol) was treated in a similar manner as described in Section 4.3.12. After workup the compound was obtained in quantitative yield; mp 302–304 °C; R_f=0.76 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: C_6H_{14}/CH_2Cl_2, 60:40, v/v, flow: 1 mL/min, detection at

420 nm) retention time: 5.36 min (93.6%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.02 (t, J=7 Hz, 6H, OCH_2CH_2-$CH_2CH_2CH_3$), 1.45–1.66 (m, 8H, $OCH_2CH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2CH_3$), 1.97 (m, 4H, $OCH_2CH_2CH_2$-CH_2CH_3), 4.22 (t, J=6 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_3$), 7.21 (m, 4H, phenyl-*H*), 7.94 (m, 4H, phenyl-*H*), 8.95 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.15 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.89 ppm (s, 2H, *meso*-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.10, 22.58, 28.40, 29.19, 68.36, 104.94, 112.97, 118.15, 131.85, 132.43, 133.20, 134.86, 142.52, 143.30, 159.03 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=323 (4.10), 404 (5.36), 516 (4.25), 547 nm (3.83); MS (EI, 80 eV, 280 °C), *m*/*z* (%): 690 (100) [M^+], 619 (4) [$M^+-C_5H_{11}$], 528 (12) [$M^+-C_{11}H_{14}O$], 345 (1) [M^{2+}]; HRMS (EI) [$C_{42}H_{40}N_4NiO_2$]: calcd 690.25047, found 690.25433; [$C_{42}H_{40}N_4NiO_2$, 691.50 g mol^{-1}]. Anal. Calcd C 72.95, H 5.83, N 8.10, found C 72.68, H 5.66, N 8.09.

4.3.14. [5,15-Bis(3-methoxyphenyl)porphyrinato]-nickel(II) (28). The free base **12** (200 mg, 0.38 mmol) was treated in a similar manner as described in Section 4.3.11 to yield 210 mg red crystals (0.36 mmol, 95%): mp 340 °C; R_f=0.51 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.69 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.95 (s, 6H, OCH_3), 7.23–7.32 (m, 2H, phenyl-*H*), 7.57–7.68 (m, 6H, phenyl-*H*), 8.96 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.17 (d, J=5 Hz, 4H, β-pyrrole-*H*), 9.92 ppm (s, 2H, 10-*meso*-*H* and 20-*meso*-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.48, 105.08, 113.55, 119.85, 126.90, 127.71, 132.00, 132.43, 142.37, 142.64, 142.79, 153.49, 158.17 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=317 (3.93), 400 (5.34), 514 (4.19), 546 nm (3.90); MS (EI, 80 eV, 400 °C), *m*/*z* (%): 578 (100) [M^+], 289 (3) [M^{2+}]; HRMS (EI) [$C_{34}H_{24}N_4NiO_2$]: calcd 578.125273, found 578.12732; [$C_{34}H_{24}N_4NiO_2$, 579.28 g mol^{-1}]. Anal. Calcd C 70.50, H 4.18, N 9.67, found C 70.78, H 4.48, N 9.73.

4.4. 5,15-AB-type porphyrins

4.4.1. 5-Hexyl-15-(3-methoxyphenyl)porphyrin (22). Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Dipyrromethane **10** (1.2 g, 8.2 mmol), 3-methoxybenzaldehyde (0.56 mL, 4.6 mmol), and heptanal (0.64 mL, 4.6 mmol) were added. The flask was shielded from ambient light and then 140 μL (1.8 mmol) of TFA were added and the reaction mixture was stirred for 18 h at 20 °C. After this time, 2.77 g (12.2 mmol) of DDQ suspended in 100 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 6 mL of triethylamine were added and the reaction mixture was concentrated in vacuo to about 200 mL. The reaction mixture was filtered through 500 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The porphyrins were separated by column chromatography on silica (3×60 cm) using dichloromethane/hexane (3:1, v/v) as eluent. The first fraction was 5,15-dihexylporphyrin **20** (120 mg, 0.25 mmol, 6%), the second fraction 5-hexyl-15-(3-methoxyphenyl)porphyrin **22** (370 mg, 0.7 mmol, 17%), and the third fraction 5,15-bis(3-methoxyphenyl)porphyrin **12** (200 mg, 0.38 mmol, 9%). The porphyrins were redissolved/suspended in dichloromethane and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated purple crystals were removed by suction filtration through a D3 frit and dried in vacuo. Title compound: mp 215 °C; R_f=0.39 (SiO_2, CH_2Cl_2/C_6H_{14}, 3:1, v/v); R_f=0.69 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.06 and −3.03 (each s, 1H, N*H*), 0.94 (t, J=7 Hz, 3H, 5^6-CH_3), 1.33–1.59 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.83 (m, 2H, 5^3-CH_2), 2.57 (m, 2H, 5^2-CH_2), 4.00 (s, 3H, 15-OCH_3), 5.02 (t, J=8 Hz, 2H, 5^1-CH_2), 7.34 (m, 1H, phenyl-*H*), 7.68 (m, 1H, phenyl-*H*), 7.81–7.86 (m, 2H, phenyl-*H*), 9.07 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.33 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.41 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.59 (d, J=5 Hz, 2H, β-pyrrole-*H*), 10.21 ppm (s, 2H, 10- and 20-*meso*-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.15, 22.74, 30.28, 31.92, 34.81, 38.75, 55.51, 104.75, 113.38, 117.94, 119.78, 120.73, 127.78, 127.86, 127.99, 130.69, 131.64, 131.78, 142.71, 144.53, 144.77, 147.20, 147.25, 158.24 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=301 (4.10), 366 (4.21), 3.88 (4.68), 406 (5.29), 475 (3.19), 503 (3.99), 536 (3.55), 576 (3.47), 631 nm (3.07); MS (EI, 80 eV, 220 °C), *m*/*z* (%): 500 (100) [M^+], 429 (70) [M^+-71 (C_5H_{11})], 250 (8) [M^{2+}]; MS (FAB+, CH_2Cl_2/*m*-NO_2-Bzl-OH/Xe), *m*/*z* (%): 501 (6) [$(M+H)^+$], 430 (2) [$\{M+H\}^+-C_5H_{11}$]; HRMS (EI) [$C_{33}H_{32}N_4O$]: calcd 500.25761, found 500.25473; [$C_{33}H_{32}N_4O$, 500.64 g mol^{-1}]. Anal. Calcd C 79.17, H 6.44, N 11.19, found C 79.04, H 6.31, N 11.18.

4.4.2. 5-Hexyl-15-(4-methoxyphenyl)porphyrin (23). Dry dichloromethane (2 L) was placed in a three-necked flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. The reaction flask was charged with dipyrromethane **10** (1.2 g, 8.2 mmol), 4-methoxybenzaldehyde (500 μL, 4.15 mmol), and heptanal (580 μL, 4.15 mmol). Further reaction conditions were as described in Section 4.4.1. After concentration the reaction mixture was filtered through a D3 frit. The filtrate was filtered through 600 mL of silica (column diameter 5 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The residue in the frit was thoroughly washed with dichloromethane, acetone, and methanol and then dried in vacuo. It consisted largely of 5,15-bis(4-methoxyphenyl)-porphyrin **13** and was discarded. The eluted porphyrin fractions were separated by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. The first fraction was 5,15-dihexylporphyrin **20** (240 mg, 0.5 mmol, 12%), the second fraction the title compound **23**. Each of the two porphyrins was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated crystals were removed by suction filtration through a D3 frit and dried in vacuo. Yield 5-hexyl-15-(4-methoxyphenyl)porphyrin **23**: 300 mg (0.6 mmol; 14%) of purple crystals: mp 238–240 °C; R_f=0.52 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.11 and −3.07 (each s, 1H, N*H*), 0.93 (t, J=7 Hz, 3H, 5^6-CH_3), 1.41 (m, 2H, 5^5-CH_2), 1.52 (m, 2H, 5^4-CH_2), 1.82 (m, 2H, 5^3-CH_2), 2.56 (m, 2H, 5^2-CH_2), 4.10 (s, 3H, OCH_3), 5.01 (t, J=8 Hz, 2H, 5^1-CH_2), 7.32 (m, 2H, phenyl-*H*), 8.14 (m, 2H, phenyl-*H*), 9.04 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.33 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.40 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.58 (d, J=5 Hz, 2H, β-pyrrole-*H*), 10.30 (s, 2H, *meso*-*H*); UV/vis (CH_2Cl_2): λ_{max} (log ε)=301 (4.05), 360

(4.35), 390 (4.91), 406 (5.53), 474 (3.28), 505 (4.20), 539 (3.70), 578 (3.69), 632 (3.17); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.13, 22.75, 30.28, 31.94, 34.82, 38.74, 55.61, 104.70, 112.60, 118.19, 119.54, 127.97, 130.73, 131.54, 131.82, 133.77, 135.81, 144.54, 144.77, 147.32, 147.70, 159.49; MS (EI, 80 eV, 250 °C), *m/z* (%): 500 (100) [M^+], 429 (66) [$M^+-C_5H_{11}$], 250 (8) [M^{2+}]; HRMS (EI) [$C_{33}H_{32}N_4O$]: calcd 500.257612, found 500.25561; [$C_{33}H_{32}N_4O$, 500.64 g mol^{-1}]. Anal. Calcd C 79.17, H 6.44, N 11.19, found C 78.85, H 6.10, N 11.03.

4.4.3. 5-(3,5-Dimethoxyphenyl)-15-hexylporphyrin (24). Reaction and workup of dipyrromethane (**10**) (1.2 g, 8.2 mmol), 3,5-dimethoxybenzaldehyde (700 mg, 4.1 mmol), and heptanal (580 μL, 4.1 mmol) as described in Section 4.4.2. Yields: 240 mg (0.5 mmol, 12%) purple needles of 5,15-dihexylporphyrin (**20**) and 300 mg purple crystals (0.6 mmol, 14%) of the title compound **24**: mp 295–297 °C; R_f=0.78 (CH_2Cl_2), 0.44 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2 with 0.1% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm) retention time: 2.99 min (97.9%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.04 (s, br., 2H, N*H*), 0.93 (t, *J*=7 Hz, 3H, 5^6-C*H*$_3$), 1.41 (m, 2H, 5^5-C*H*$_2$), 1.52 (m, 2H, 5^4-C*H*$_2$), 1.83 (m, 2H, 5^3-C*H*$_2$), 2.57 (m, 2H, 5^2-C*H*$_2$), 3.98 (s, 6H, OC*H*$_3$), 5.03 (t, *J*=8 Hz, 2H, 5^1-C*H*$_2$), 6.91 (m, 1H, phenyl-*H*$_{para}$), 7.42 (m, 2H, phenyl-*H*$_{ortho}$), 9.11 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.33 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.41 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.60 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.21 (s, 2H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.12, 22.72, 30.25, 31.90, 34.77, 38.70, 55.63, 100.06, 104.71, 105.26, 114.05, 117.90, 119.79, 127.93, 130.67, 131.62, 131.71, 143.34, 144.54, 144.85, 147.17, 159.20; UV/vis (CH_2Cl_2): λ_{max} (log ε)=300 (4.22), 360 (4.40), 390 (4.93), 404 (5.54), 474 (3.38), 504 (4.17), 535 (3.61), 578 (3.69), 633 (3.05); MS (EI, 80 eV, 250 °C), *m/z* (%): 530 (100) [M^+], 459 (57) [$M^+-C_5H_{11}$], 429 (3) [$M^+-C_5H_{11}-2\times CH_3$], 265 (11) [$M^{2+}$]; HRMS (EI) [$C_{34}H_{34}N_4O_2$]: calcd 530.268177, found 530.26574; [$C_{34}H_{34}N_4O_2$, 530.67 g mol^{-1}]. Anal. Calcd C 76.95, H 6.46, N 10.56, found C 77.03, H 6.35, N 10.49.

4.4.4. [5-Hexyl-15-(3-methoxyphenyl)porphyrinato]-nickel(II) (29). 5-Hexyl-15-(3-methoxyphenyl)porphyrin **22** (150 mg, 0.3 mmol) was placed in a round-bottomed flask equipped with a reflux condenser. DMF (50 mL) and 900 mg (5.1 mmol) of nickel(II) acetate were added and the flask was heated at 150 °C (bath temperature) for 1.5 h. The solvent was evaporated to dryness and the residue was taken up in dichloromethane. The mixture was filtered through silica (30 g), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The porphyrin was resuspended in 50 mL of dichloromethane and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated red crystals were removed by suction filtration through a D3 frit and dried in vacuo to give the title compound in quantitative yield: mp 228 °C; R_f=0.68 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.93 (t, *J*=7 Hz, 3H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.29–1.51 (m, 4H, $CH_2CH_2CH_2CH_2CH_2CH_3$ and $CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 1.66 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.37 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 3.94 (s, 3H, OCH_3), 4.58 (t, *J*=7 Hz, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 7.28 (m, 1H, phenyl-*H*), 7.60 (m, 3H, phenyl-*H*), 8.89 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.05 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.09 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.38 ppm (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.69 ppm (s, 2H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.11, 22.69, 30.15, 31.80, 34.36, 37.74, 55.42, 104.42, 113.43, 117.25, 118.07, 119.80, 126.84, 127.68, 129.40, 131.85, 132.12, 141.87, 142.03, 142.39, 142.52, 142.71, 158.16; MS (EI, 80 eV, 305 °C), *m/z* (%): 556 (100) [M^+], 485 (65) [$M^+-C_5H_{11}$], 278 (2) [M^{2+}]; UV/vis (CH_2Cl_2): λ_{max} (log ε)=401 (5.11), 516 (3.94), 548 nm (3.55); HRMS (EI) [$C_{33}H_{28}N_4NiO$]: calcd 554.16166, found: 554.16169.

4.5. A_3- and A_2B-type porphyrins via S_NAr

4.5.1. 5,10,15-Tris(3-methoxyphenyl)porphyrin (30). 3-Methoxybromobenzene (760 μL, 6 mmol) was dissolved in diethyl ether in a septum equipped Schlenk flask under argon. The flask was cooled in an ice-bath and 4 mL of a 2.5 M solution of *n*-butyl lithium (6 mmol) were added through the septum via a syringe. The solution was stirred for 1 h in the ice bath. The solution gradually becomes turbid. The solution of the lithio-3-methoxybenzene was then cooled to −70 °C. At the same time, in a second Schlenk flask 200 mg (0.38 mmol) of 5,15-bis(3-methoxyphenyl)porphyrin **12** were dried in vacuo for 2 h. THF (40 mL, abs.) was added under argon. The porphyrin suspension was cooled to −70 °C and poured all at once into the flask containing the lithio-3-methoxybenzene. The cold bath was removed and the reaction mixture was stirred for 60 min at 20 °C. The solution gradually changed its color from red to green-brown. Water (3 mL) was added and the solution was stirred for 20 min. On addition of water the reaction mixture changed its color to dark-green. After this time, 3 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 0.78 mmol) were added, upon which the solution became dark red again. The reaction mixture was filtered through silica (3×50 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/hexane (7:3, v/v) as eluent. As the first fraction, a small amount (~15 mg) of 5-butyl-10,20-bis(3-methoxyphenyl)porphyrin **44** was isolated, which was identified by ^{1}H NMR and mass spectrometry (Section 4.5.14). The title compound was eluted as the second fraction. The porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo: 190 mg (0.3 mmol; 79%) purple crystals; mp 253–255 °C; R_f=0.15 (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.44 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.04 (s, br., 2H, N*H*), 3.96 (s, 3H, 10-OC*H*$_3$), 3.99 (s, 6H, 5-OC*H*$_3$ and 15-OC*H*$_3$), 7.30–7.60 (m, 3H, phenyl-*H*), 7.64 (m, 3H, phenyl-*H*), 7.76–7.84 (m, 6H, phenyl-*H*), 8.91 (m [AB-spectrum], 4H, β-pyrrole-*H*), 9.04 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.32 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.20 ppm (s, 1H, 20-*meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.52, 104.83, 113.58, 119.37, 120.24, 120.53, 120.65, 127.34, 127.62, 127.77, 130.70, 131.25, 131.38, 143.12, 143.90, 145.98, 146.87, 157.89, 158.15 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.22), 374 (4.43), 395 (4.89), 413 (5.60), 478 (3.34), 508 (4.27),

541 (3.60), 582 (3.66), 637 nm (3.05); MS (EI, 80 eV, 290 °C), *m/z* (%): 628 (100) [M^+], 613 (3) [M^+-CH_3], 597 (2) [M^+-CH_3O], 314 (14) [M^{2+}]; HRMS (EI) [$C_{41}H_{32}N_4O_3$]: calcd 628.24744, found 628.24714; [$C_{41}H_{32}N_4O_3$, 628.73 g mol^{-1}]. Anal. Calcd C 78.32, H 5.13, N 8.91, found C 78.05, H 4.82, N 8.71.

4.5.2. 5-Hexyl-10,20-bis(4-methoxyphenyl)porphyrin (31). 5,15-Bis(4-methoxyphenyl)porphyrin **13** (220 mg, 0.42 mmol) was dried in vacuo in a septum equipped Schlenk flask for 2 h and then abs. THF (50 mL) was added under argon. The porphyrin suspension was cooled to −70 °C and *n*-hexyl lithium (1100 μL of a 2.5 M solution, 2.75 mmol) was added via a syringe. The cold bath was removed and the reaction mixture was stirred for 15 min at 20 °C. The solution changed its color from red to green-brown. Water (8 mL) was added in two portions and the solution was then stirred for 60 min. Upon addition of water the reaction mixture changed its color to dark-green. Next, 6 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 1.6 mmol) were added in two portions, upon which the solution turned dark-red again. The mixture was stirred for 15 min at 20 °C followed by filtration through silica (column diameter 3 cm, filling height 50 cm), washing with dichloromethane. The filtrate was evaporated to dryness and the product purified by column chromatography on silica (3×70 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. To remove a small amount of a yellow-brown by-product, the porphyrin was again chromatographed on silica (3×70 cm) using dichloromethane as eluent. After evaporation of the solvent the porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 90 mg (0.15 mmol; 35%) of brown microcrystals: mp 251–252 °C; R_f=0.31 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.99 (s, br., 2H, N*H*), 0.91 (t, *J*=7 Hz, 3H, 5^6-C*H*$_3$), 1.38 (m, 2H, 5^5-C*H*$_2$), 1.50 (m, 2H, 5^4-C*H*$_2$), 1.84 (m, 2H, 5^3-C*H*$_2$), 2.55 (m, 2H, 5^2-C*H*$_2$), 4.10 (s, 6H, OC*H*$_3$), 5.05 (t, *J*=8 Hz, 2H, 5^1-C*H*$_2$), 7.30 (m, 4H, phenyl-*H*), 8.12 (m, 4H, phenyl-*H*), 8.97 (m, 4H, β-pyrrole-*H*), 9.24 (d, *J*=4 Hz, 2H, β-pyrrole-*H*), 9.52 (d, *J*=4 Hz, 2H, β-pyrrole-*H*), 10.06 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.10, 22.71, 30.28, 31.91, 35.99, 38.99, 55.61, 103.86, 112.30, 118.75, 121.07, 128.12, 130.79, 131.18, 131.43, 134.49, 135.61, 146.27, 159.47 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.18), 369 (4.35), 397 (4.92), 415 (5.56), 484 (3.56), 511 (4.25), 547 (3.93), 587 (3.73), 642 nm (3.60); MS (EI, 80 eV, 300 °C), *m/z* (%): 606 (100) [M^+], 535 (55) [$M^+-C_5H_{11}$], 303 (10) [M^{2+}]; HRMS (EI) [$C_{40}H_{38}N_4O_2$]: calcd 606.29948, found 606.29742; [$C_{40}H_{38}N_4O_2$, 606.77 g mol^{-1}]. Anal. Calcd C 79.18, H 6.31, N 9.23, found C 79.12, H 6.25, N 9.10.

4.5.3. 10-Hexyl-5,15-bis(3-methoxyphenyl)porphyrin (32). 5,15-Bis(3-methoxyphenyl)porphyrin **12** (160 mg, 0.31 mmol) was dried in vacuo in a septum-equipped Schlenk-flask for 2 h. THF (30 mL, abs.) was then added under argon. The porphyrin suspension was cooled to −70 °C. *n*-Hexyl lithium (550 μL of a 2.5 M solution, 1.35 mmol) was added via a syringe through the septum. The cold bath was removed and the reaction mixture was stirred for 15 min at 20 °C. The solution changed its color from red to green-brown. Water (4 mL) was added and the solution was then stirred for 60 min. On addition of water the reaction mixture changed its color to dark-green. After this time, 3 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 0.78 mmol) were added, upon which the solution became dark red again. The reaction mixture was filtered through silica (3×50 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. The porphyrin was again dissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 120 mg (0.2 mmol; 65%) of red-brown microcrystals: mp 226–227 °C; R_f=0.32 (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.55 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.03 (s, 2H, N*H*), 0.91 (t, *J*=7 Hz, 3H, 5^6-C*H*$_3$), 1.30–1.56 (m, 4H, 5^5-C*H*$_2$ and 5^4-C*H*$_2$), 1.81 (m, 2H, 5^3-C*H*$_2$), 2.55 (m, 2H, 5^2-C*H*$_2$), 4.00 (s, 6H, 10-OC*H*$_3$ and 20-OC*H*$_3$), 5.06 (t, *J*=8 Hz, 2H, 5^1-C*H*$_2$), 7.34 (m, 2H, phenyl-*H*), 7.66 (m, 2H, phenyl-*H*), 7.78–7.83 (m, 4H, phenyl-*H*), 9.00 (m [AB-spectrum], 4H, β-pyrrole-*H*), 9.24 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.52 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.07 ppm (s, 1H, 15-*meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.13, 22.72, 30.29, 31.92, 35.97, 39.04, 55.54, 103.99, 113.49, 118.76, 120.56, 121.24, 127.53, 127.72, 143.39, 158.04 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.17), 372 (4.39), 393 (4.87), 413 (5.53), 478 (3.39), 509 (4.24), 543 (3.74), 584 (3.67), 639 nm (3.40); MS (EI, 80 eV, 310 °C), *m/z* (%): 606 (22) [M^+], 535 (9) [$M^+-C_5H_{11}$], 303 (2) [M^{2+}], 18 (100) [H_2O^+, cf. elem. anal.]; HRMS (EI) [$C_{40}H_{38}N_4O_2$]: calcd 606.29948, found 606.29907; [$C_{40}H_{38}N_4O_2$, 606.77 g mol^{-1}]. Anal. Calcd C 79.18, H 6.31, N 9.23, [$C_{40}H_{38}N_4O_2\cdot\frac{1}{2}H_2O$, 615.78 g mol^{-1}]. Anal. Calcd C 78.02, H 6.38, N 9.10, found C 78.37, H 6.07, N 8.79.

4.5.4. 5,15-Bis(4-butyloxyphenyl)-10-hexylporphyrin (33). Reaction and workup as described in Section 4.5.3 using 5,15-bis(4-butyloxyphenyl)porphyrin **17** (240 mg, 0.4 mmol) as starting material. Yield 140 mg (0.2 mmol; 51%) of brown microcrystals: mp 203 °C; R_f=0.54 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.99 (s, br., 2H, N*H*), 0.91 (t, *J*=7 Hz, 3H, 10^6-C*H*$_3$), 1.11 (t, *J*=7 Hz, 6H, OCH$_2$CH$_2$CH$_2$C*H*$_3$), 1.33–1.55 (m, 4H, 10^4-C*H*$_2$ and 10^5-C*H*$_2$), 1.67 (m, 4H, OCH$_2$CH$_2$C*H*$_2$-CH$_3$), 1.81 (m, 2H, 10^3-C*H*$_2$), 1.99 (m, 4H, OCH$_2$C*H*$_2$CH$_2$-CH$_3$), 2.55 (m, 2H, 10^2-C*H*$_2$), 4.26 (t, *J*=6 Hz, 4H, OC*H*$_2$CH$_2$CH$_2$CH$_3$), 5.05 (t, *J*=8 Hz, 2H, 10^1-C*H*$_2$), 7.28 (m, 4H, phenyl-*H*), 8.10 (m, 4H, phenyl-*H*), 8.98 (m, 4H, β-pyrrole-*H*), 9.24 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.52 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.06 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=13.98, 14.11, 9.46, 22.71, 30.29, 31.61, 31.92, 35.99, 68.09, 103.83, 112.85, 118.64, 121.02, 128.07, 130.73, 131.17, 131.47, 134.26, 135.62, 146, 159.04 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.24), 367 (4.33), 397 (4.90), 415 (5.52), 485 (3.53), 511 (4.23), 548 (3.92), 587 (3.69), 644 nm (3.56); MS (EI, 80 eV, 270 °C), *m/z* (%): 690 (100) [M^+], 633 (3) [$M^+-C_4H_9$], 619 (24) [$M^+-C_5H_{11}$], 345 (3) [M^{2+}]; HRMS (EI) [$C_{46}H_{50}N_4O_2$]: calcd 690.39338, found 690.39654;

[$C_{46}H_{50}N_4O_2$, 690.93 g mol^{-1}]. Anal. Calcd C 79.97, H 7.29, N 8.11, [$C_{46}H_{50}N_4O_2 \cdot ½H_2O$]. Anal. Calcd C 78.94, H 7.34, N 8.00 found C 78.48, H 7.33, N 7.99.

4.5.5. 5-Hexyl-10,20-bis(4-pentyloxyphenyl)porphyrin (34). 5,15-Bis(4-pentyloxyphenyl)porphyrin **18** (270 mg, 0.45 mmol) was dried in vacuo in a septum equipped Schlenk flask for 2 h. THF abs. (40 mL) was then added under argon and the suspension was cooled to −70 °C. *n*-Hexyl lithium (1100 μL of a 2.5 M solution, 2.75 mmol) was added via a syringe through the septum, the cold bath removed, and the reaction mixture was stirred for 20 min at 20 °C. The solution changed its color from red to green-brown and water (8 mL) was added in two portions and the solution was stirred for 60 min. Upon addition of 10 mL water the reaction mixture changed its color to dark-green and was stirred for 45 min. Subsequently, 5 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 1.3 mmol) were added in two portions and the solution turned dark-red again. Further workup was as described in Section 4.5.3 to yield 300 mg (0.41 mmol; 91%) of brown microcrystals: mp 174 °C; R_f=0.56 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.98 (s, br., 2H, N*H*), 0.91 (t, J=7 Hz, 3H, 5^6-C*H*$_3$), 1.04 (t, J=7 Hz, 6H, OCH$_2$CH$_2$-CH$_2$CH$_2$C*H*$_3$), 1.33–1.70 (m, 12H, 5^4-C*H*$_2$, 5^5-C*H*$_2$, OCH$_2$-CH$_2$C*H*$_2$CH$_2$CH$_3$, and OCH$_2$CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.81 (m, 2H, 5^3-C*H*$_2$), 2.01 (m, 4H, OCH$_2$C*H*$_2$CH$_2$CH$_2$CH$_3$), 2.55 (m, 2H, 5^2-C*H*$_2$), 4.26 (t, J=6 Hz, 4H, OC*H*$_2$CH$_2$CH$_2$CH$_2$-CH$_3$), 5.06 (t, J=8 Hz, 2H, 5^1-C*H*$_2$), 7.28 (m, 4H, phenyl-*H*), 8.10 (m, 4H, phenyl-*H*), 8.98 (m, 4H, β-pyrrole-*H*), 9.24 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.52 (d, J=5 Hz, 2H, β-pyrrole-*H*), 10.06 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.11, 22.61, 22.71, 28.42, 29.24, 30.29, 31.92, 35.99, 38.99, 68.40, 103.83, 112.85, 118.86, 121.02, 128.07, 130.80, 131.19, 131.46, 134.26, 135.62, 146.82, 159.03 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.34), 370 (4.45), 398 (4.90), 415 (5.59), 482 (3.71), 511 (4.28), 548 (3.99), 587 (3.79), 643 nm (3.56); MS (EI, 80 eV, 270 °C), *m*/*z* (%): 718 (100) [M$^+$], 647 (26) [M$^+$−C_5H_{11}], 359 (1) [M^{2+}]; HRMS (EI) [$C_{48}H_{54}N_4O_2$]: calcd 718.42468, found 718.42767; [$C_{48}H_{54}N_4O_2$, 718.98 g mol^{-1}]. Anal. Calcd C 80.19, H 7.57, N 7.79, [$C_{48}H_{54}N_4O_2 \cdot ½H_2O$]. Anal. Calcd C 79.19, H 7.62, N 7.70, found C 79.36, H 7.56, N 7.80.

4.5.6. 5,15-Bis(3,5-dimethoxyphenyl)-10-hexylporphyrin (35). 5,15-Bis(3,5-dimethoxyphenyl)porphyrin **15** (240 mg, 0.41 mmol) was suspended in 60 mL THF and reacted with *n*-hexyl lithium (1.1 mL of a 2.5 M solution, 2.75 mmol) in a similar manner as described in Section 4.5.3. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. The porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 160 mg (0.24 mmol; 58%) of brown microcrystals: mp 319–320 °C; R_f=0.25 (CH_2Cl_2/C_6H_{14}, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.02 (s, br., 2H, N*H*), 0.92 (t, J=7 Hz, 3H, 5^6-C*H*$_3$), 1.40 (m, 2H, 5^5-C*H*$_2$), 1.51 (m, 2H, 5^4-C*H*$_2$), 1.82 (m, 2H, 5^3-C*H*$_2$), 2.56 (m, 2H, 5^2-C*H*$_2$), 3.98 (s, 12H, OC*H*$_3$), 5.06 (t, J=8 Hz, 2H, 5^1-C*H*$_2$), 6.91 (m, 2H, phenyl-H_{para}), 7.41 (m, 4H, phenyl-H_{ortho}), 9.04 (m, 4H, β-pyrrole-*H*), 9.23 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.52 (d, J=5 Hz, 2H, β-pyrrole-*H*), 10.06 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.14, 22.72, 30.30, 31.91, 35.95, 39.04, 55.65, 100.12, 103.98, 113.93, 118.73, 121.21, 128.24, 131.25, 143.98, 146.23, 158.96 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.07), 370 (4.39), 396 (4.92), 414 (5.39), 480 (3.45), 509 (4.25), 543 (3.60), 584 (3.65), 640 nm (3.41); MS (EI, 80 eV, 270 °C), *m*/*z* (%): 666 (100) [M$^+$], 595 (41) [M$^+$−C_5H_{11}], 565 (2) [M$^+$−C_5H_{11}−2×CH_3], 333 (20) [M^{2+}]; HRMS (EI) [$C_{42}H_{42}N_4O_4$]: calcd 666.32061, found 666.32360; [$C_{42}H_{42}N_4O_4$, 666.82 g mol^{-1}]. Anal. Calcd C 75.65, H 6.35, N 8.40, found C 75.61, H 6.31, N 8.39.

4.5.7. 5-Hexyl-10,20-di(*iso*-butyl)porphyrin (36). 5,15-Di(*iso*-butyl)porphyrin **21** (100 mg, 0.24 mmol) was dried in vacuo in a septum equipped Schlenk flask for 2 h and 25 mL dry THF abs. were then added under argon. The porphyrin solution was cooled to −60 °C and *n*-hexyl lithium (520 μL of a 2.5 M solution, 1.29 mmol) was added via a syringe. The cold bath was removed and the reaction mixture was stirred for 15 min at 20 °C accompanied by a color change from red to green-brown. Water (3 mL) was added and the solution was then stirred for 30 min. Upon addition of water the reaction mixture turned dark-green. Next, 3 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 0.78 mmol) were added, upon which the solution changed color to dark-red again. The mixture was stirred for 15 min at 20 °C and filtered through silica (column diameter 3 cm, filling height 30 cm), washing with dichloromethane. The filtrate was evaporated to dryness and the residue purified by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. The porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield: 60 mg (0.12 mmol; 50%) of brown microcrystals: mp 201–203 °C; R_f=0.72 (CH_2Cl_2/*n*-hexane, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.87 (s, br., 2H, N*H*), 0.95 (t, J=7 Hz, 3H, 5^6-C*H*$_3$), 1.19 (d, J=6 Hz, 12H, CH$_2$CH(C*H*$_3$)$_2$), 1.43 (m, 2H, 5^5-C*H*$_2$), 1.56 (m, 2H, 5^4-C*H*$_2$), 1.86 (m, 2H, 5^3-C*H*$_2$), 2.57 (m, 2H, 5^2-C*H*$_2$), 2.77 (m, 2H, CH$_2$C*H*(CH$_3$)$_2$), 4.83 (d, J=8 Hz, 4H, C*H*$_2$CH(CH$_3$)$_2$), 5.05 (t, J=8 Hz, 2H, 5^1-C*H*$_2$), 9.27 (d, J=4 Hz, 2H, β-pyrrole-*H*), 9.50 (m, 4H, β-pyrrole-*H*), 9.58 (d, J=4 Hz, 2H, β-pyrrole-*H*), 9.95 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.16, 22.79, 23.37, 30.40, 31.95, 36.36, 36.71, 39.08, 43.40, 103.07, 117.49, 120.03, 128.33, 128.53, 128.74, 131.17, 145.14, 147.16 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 (4.23), 363 (4.34), 394 (4.79), 412 (5.64), 479 (3.44), 512 (4.18), 545 (3.85), 589 (3.74), 645 nm (3.66); MS (EI, 80 eV, 250 °C), *m*/*z* (%): 506 (100) [M$^+$], 463 (76) [M$^+$−C_3H_7], 435 (6) [M$^+$−C_5H_{11}], 392 (3) [M$^+$−C_3H_7−C_5H_{11}], 253 (4) [M^{2+}]; HRMS (EI) [$C_{34}H_{42}N_4$]: calcd 506.34095, found 506.34353; [$C_{34}H_{42}N_4$, 506.73 g mol^{-1}]. Anal. Calcd C 80.59, H 8.35, N 11.06, [$C_{34}H_{42}N_4$×½CH_3OH]. Anal. Calcd C 79.27, H 8.48, N 10.72, found C 79.76, H 8.09, N 10.72.

4.5.8. 5,10-Dihexyl-15-(4-methoxyphenyl)porphyrin (37). 5-Hexyl-15-(4-methoxyphenyl)porphyrin **23** (210 mg, 0.42 mmol) was suspended in 50 mL THF and

reacted with *n*-hexyl lithium (1100 μL of a 2.5 M solution, 2.75 mmol) in a similar manner as described in Section 4.5.3. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. After recrystallization from CH_2Cl_2/CH_3OH 130 mg (0.22 mmol; 53%) of brown microcrystals were obtained: mp 131–132 °C; R_f=0.58 (CH_2Cl_2/*n*-hexane, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.93 (s, br., 2H, N*H*), 0.94 (m, 6H, 5^6-C*H*$_3$ and 10^6-C*H*$_3$), 1.35–1.59 (m, 8H, 5^5-C*H*$_2$, 10^5-C*H*$_2$, 5^4-C*H*$_2$, and 10^4-C*H*$_2$), 1.85 (m, 4H, 5^3-C*H*$_2$ and 10^3-C*H*$_2$), 2.55 (m, 4H, 5^2-C*H*$_2$ and 10^2-C*H*$_2$), 4.10 (s, 3H, OC*H*$_3$), 5.02 (m, 4H, 5^1-C*H*$_2$ and 10^1-C*H*$_2$), 7.27 (m, 2H, phenyl-*H*), 8.09 (m, 2H, phenyl-*H*), 8.92 (m, 2H, β-pyrrole-*H*), 9.21 (d, *J*=5 Hz, 1H, β-pyrrole-*H*), 9.29 (d, *J*=5 Hz, 1H, β-pyrrole-*H*), 9.48–9.61 (m, 4H, β-pyrrole-*H*), 9.98 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ= 14.12, 22.75, 30.32, 31.93, 35.31, 36.11, 38.77, 39.02, 55.59, 103.42, 112.32, 118.07, 119.39, 120.49, 127.96, 128.26, 128.45, 130.88, 131.12, 134.41, 135.57, 159.41 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 (4.18), 364 (4.35), 395 (4.89), 413 (5.53), 480 (3.50), 511 (4.22), 547 (3.85), 591 (3.66), 644 nm (3.55); MS (EI, 80 eV, 250 °C), *m*/*z* (%): 584 (100) [M^+], 513 (65) [$M^+-C_5H_{11}$], 442 (9) [$M^+-2\times C_5H_{11}$], 292 (8) [M^{2+}]; HRMS (EI) [$C_{39}H_{44}N_4O$]: calcd 584.351512, found 584.35431; [$C_{39}H_{44}N_4O$, 584.80 g mol^{-1}]. Anal. Calcd C 80.10, H 7.58, N 9.58, found C 79.89, H 7.64, N 9.36.

4.5.9. 5,10-Dihexyl-15-(3,5-dimethoxyphenyl)porphyrin (38). *Method a.* 5-(3,5-Dimethoxyphenyl)porphyrin 41[19] (100 mg, 0.22 mmol) was dried in vacuo in a septum equipped Schlenk-flask for 2 h and then treated with 25 mL abs. THF. The porphyrin suspension was cooled to −70 °C and *n*-hexyl lithium (550 μL of a 2.5 M solution, 1.38 mmol) was added via a syringe through the septum. The cold bath was removed and the reaction mixture was stirred for 20 min at 20 °C. The solution changed its color from red to green-brown and then to dark-blue. Water (5 mL) was added and the solution was then stirred for 60 min resulting in a color change to dark-green. Next; 5 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 1.3 mmol) were added, upon which the solution turned dark-red again. The mixture was stirred for 15 min at 20 °C and then filtered through silica (3×20 cm), washing with dichloromethane. The filtrate was evaporated to dryness and the product purified by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. After evaporation of the solvent the porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 110 mg (0.18 mmol; 80%) of brown microcrystals.

Method b. 5-(3,5-Dimethoxyphenyl)-15-hexylporphyrin **24** (100 mg, 0.19 mmol) was dried in vacuo in a septum equipped Schlenk flask for 2 h. THF abs. (25 mL) was then added under argon and the porphyrin suspension was cooled to −70 °C. *n*-Hexyl lithium (520 μL of a 2.5 M solution, 1.29 mmol) was added via a syringe, the cold bath was removed and the reaction mixture was stirred for 15 min at 20 °C. The solution changed its color from red to green-brown. Water (4 mL) was added and the solution was then stirred for 30 min. Upon addition of water the reaction mixture changed its color to dark-green. Subsequently, 3 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 0.78 mmol) were added, upon which the solution turned dark-red again. Subsequent purification steps were as described before. To remove a small amount of a yellow-brown by-product, the porphyrin was chromatographed a second time on silica (3×70 cm) using the same conditions as before. After recrystallization from CH_2Cl_2/CH_3OH 70 mg of brown crystals (0.11 mmol, 60%) of the title compound were obtained. Mp 133–134 °C; R_f=0.48 (CH_2Cl_2/*n*-hexane, 3:1, v/v), 0.75 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.93 (s, br., 2H, N*H*), 0.96 (m, 6H, 5^6-C*H*$_3$ and 10^6-C*H*$_3$), 1.35–1.60 (m, 8H, 5^5-C*H*$_2$, 10^5-C*H*$_2$, 5^4-C*H*$_2$, and 10^4-C*H*$_2$), 1.83 (m, 4H, 5^3-C*H*$_2$ and 10^3-C*H*$_2$), 2.55 (m, 4H, 5^2-C*H*$_2$ and 10^2-C*H*$_2$), 3.97 (s, 6H, OC*H*$_3$), 5.00 (m, 4H, 5^1-C*H*$_2$ and 10^1-C*H*$_2$), 6.93 (m, 1H, phenyl-H_{para}), 7.42 (m, 2H, phenyl-H_{ortho}), 9.03 (m, 2H, β-pyrrole-*H*), 9.21 (d, *J*=5 Hz, 1H, β-pyrrole-*H*), 9.27 (d, *J*=5 Hz, 1H, β-pyrrole-*H*), 9.48–9.62 (m, 4H, β-pyrrole-*H*), 9.98 ppm (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ= 14.14, 22.75, 30.30, 31.93, 35.29, 36.05, 38.77, 39.02, 55.63, 100.08, 103.47, 113.91, 117.80, 119.68, 120.55, 127.97, 128.41, 130.92, 131.07, 131.21, 143.98, 145.88, 159.02 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=302 (4.20), 366 (4.38), 394 (4.89), 413 (5.51), 479 (3.59), 510 (4.23), 544 (3.80), 586 (3.72), 642 nm (3.56); MS (EI, 80 eV, 310 °C), *m*/*z* (%): 614 (100) [M^+], 543 (53) [$M^+-C_5H_{11}$], 307 (9) [M^{2+}]; HRMS (EI) [$C_{40}H_{46}N_4O_2$]: calcd 614.36208, found 614.36262; EA [$C_{40}H_{46}N_4O_2$, 614.83 g mol^{-1}]. Anal. Calcd C 78.14, H 7.54, N 9.11, found C 77.81, H 7.51, N 9.10.

4.5.10. 5-(4-Aminophenyl)-10,20-bis(3-methoxyphenyl)-porphyrin (39). 4-Bromoaniline (1 g, 5.8 mmol) was dissolved in 20 mL of absolute diethylether in a septum-equipped Schlenk flask under argon. The solution was cooled in an ice bath. *n*-Butyl lithium (7 mL of a 2.5 M solution, 17.5 mmol) was added dropwise via a syringe through the septum over a period of approximately 1 h. The reaction mixture was stirred for 1 h in the ice bath and then for 45 min at 20 °C. The ethereal solution of this organometallic compound was cooled to −70 °C. To this solution was added, under argon, a cooled (−70 °C) suspension of 210 mg (0.4 mmol) of 5,15-bis(3-methoxyphenyl)porphyrin **12** in 30 mL of absolute THF. The cold bath was removed and the reaction mixture was stirred for 60 min at 20 °C. The solution gradually changed its color from red to green-brown. Water (4 mL) was added and the solution was then stirred for 20 min. On addition of water the reaction mixture changed its color to dark-green. After this time, 3 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 0.78 mmol) were added, upon which the solution became dark red again. After 15 min, the reaction mixture was filtered through silica (3×50 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated until a viscous brown oil was obtained which was then dried in vacuo at 75 °C for 3 h to remove aniline. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/methanol (20:1, v/v) as eluent. The porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated

solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 180 mg (0.29 mmol; 73%) of an amorphous purple solid: mp 271–272 °C; R_f=0.7 (CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.01 (s, 2H, N*H*), 3.98 (s, 6H, OCH_3), 4.80 (s, br., 2H, NH_2), 7.02 (m, 2H, 5-phenyl-*H*), 7.31 (m, 2H, 10,20-phenyl-*H*), 7.63 (m, 2H, 10,20-phenyl-*H*), 7.83 (m, 2H, 10,20-phenyl-*H*), 7.97 (m, 2H, 5-phenyl-*H*), 8.91 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 8.95 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.03 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.29 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.16 ppm (s, 1H, 15-*meso*-H); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.50, 104.41, 105.30, 113.28, 113.52, 119.21, 120.63, 121.30, 127.57, 127.78, 130.47, 131.09, 131.34, 131.64, 132.76, 135.58, 143.22, 146.01, 146.66, 152.81, 153.61, 158.09 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=369 (4.44), 397 (4.97), 415 (5.53), 483 (3.55), 511 (4.25), 546 (3.80), 585 (3.72), 638 nm (3.42); MS (EI, 80 eV, 280 °C), *m*/*z* (%): 613 (100) [M^+], 307 (%) [M^{2+}]; HRMS (EI) [$C_{40}H_{31}N_5O_2$]: calcd 613.24778, found 613.24682; [$C_{40}H_{31}N_5O_2$, 613.72 g mol^{-1}]. Anal. Calcd C 78.28, H 5.09, N 11.41, found C 78.26, H 4.87, N 11.27.

4.5.11. 5-Hexyl-10,20-diphenylporphyrin (40). *n*-Hexyl lithium (1.7 mL of a 2.5 M solution in hexane, 3.4 mmol) was added under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of 5,15-diphenylporphyrin (220 mg, 0.47 mmol) in 40 mL of dry THF at −80 °C. The color of the mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 5 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. The mixture was filtered through silica gel (Merck) and the organic solvent was removed under vacuum or washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with ethyl acetate/*n*-hexane (1:7, v/v) yielding the title compound (185 mg, 0.34 mmol, 71%) as purple crystals, mp >300 °C; R_f=0.62 (ethyl acetate/*n*-hexane, 1:4, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=−2.95 (s, 2H, 2×N*H*), 0.92 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.38 (m, 2H, $CH_2CH_2CH_2CH_2$-CH_2CH_3), 1.55 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.83 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.52 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 5.02 (t, 2H, *J*=8.1 Hz, CH_2-$CH_2CH_2CH_2CH_2CH_3$), 7.78 (m, 6H, *o*,*p*-Ph-H), 8.23 (m, 2H, *m*-Ph-H), 8.26 (m, 2H, *m*-Ph-H), 8.91 (m, 4H, β-pyrrole-H), 9.24 (d, 2H, *J*=5.0 Hz, β-pyrrole-H), 9.59 (d, 2H, *J*=5.0 Hz, β-pyrrole-H), 10.18 (s, 1H, *meso*-H); ^{13}C NMR (300 MHz, $CDCl_3$): δ=14.54 (5^6-C), 23.13 (5^5-C), 28.16 (5^4-C), 30.11 (5^3-C), 32.33 (5^2-C), 39.45 (5^1-C), 119.45, 121.64, 127.14, 128.07, 135.03, 142.49 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=412 (5.02), 510 (3.69), 544 (3.23), 583.59 (3.28), 655 nm (3.41); MS (EI, 80 eV): *m*/*z* (%): 546 (90) [M^+], 475 (100) [$M^+-C_5H_{11}$], 273 (26) [M^{++}]; HRMS [$C_{46}H_{43}N_5$]: calcd 546.2783, found 546.2759.

4.5.12. [5,10,15-Tris(3-methoxyphenyl)porphyrinato]-nickel(II) (42). 5,10,15-Tris(3-methoxyphenyl)porphyrin **30** (150 mg, 0.24 mmol) was placed in a round-bottomed flask equipped with a reflux condenser. DMF (70 mL) and nickel(II) acetate (1.07 g, 6.1 mmol) were added and the flask was heated at 150 °C (bath temperature) for 2 h. The solvent was evaporated to dryness and the residue was taken up in dichloromethane. The mixture was ultrasonicated for 2 min and then filtered through silica (50 g), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The porphyrin was again dissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated red crystals were removed by suction filtration through a D3 frit and dried in vacuo: 135 mg (0.2 mmol, 83%); mp 239 °C; R_f=0.43 (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.61 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.91 (s, 3H, 10-OCH_3), 3.93 (s, 6H, 5-OCH_3 and 15-OCH_3), 7.20–7.28 (m, 3H, phenyl-*H*), 7.51–7.65 (m, 6H, phenyl-*H*), 8.81 (m, 4H, β-pyrrole-*H*), 8.91 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.11 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.82 ppm (s, 1H, 20-*meso*-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.45, 86.18, 104.65, 113.57, 118.42, 119.16, 119.68, 119.76, 126.79, 126.82, 127.64, 127.72, 132.10, 132.57, 142.31, 142.38, 142.44, 142.66, 142.77, 142.87, 158.08, 158.15 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=317 (4.04), 407 (5.39), 520 (4.97), 551 nm (3.77); MS (EI, 80 eV, 400 °C), *m*/*z* (%): 684 (100) [M^+], 562 (8) [$M^+-(C_7H_7O+CH_3)$], 342 (19) [M^{2+}]; HRMS (EI) [$C_{41}H_{30}N_4NiO_3$]: calcd 684.16713, found 684.16773; [$C_{41}H_{30}N_4NiO_3$, 685.40 g mol^{-1}]. Anal. Calcd C 71.85, H 4.41, N 8.17, found C 71.71, H 4.29, N 7.95.

4.5.13. [5,15-Bis(3,5-dimethoxyphenyl)-10-hexyl-porphyrinato]nickel(II) (43). 5,15-Bis(3,5-dimethoxyphenyl)-10-hexylporphyrin **35** (200 mg, 0.3 mmol) was placed in a round-bottomed flask equipped with a reflux condenser. DMF (70 mL) and 1.2 g (6.8 mmol) of nickel(II) acetate were added and the flask was heated at 150 °C (bath temperature) for 2 h. The solvent was evaporated to dryness and the residue was taken up in dichloromethane. The mixture was ultrasonicated for 2 min and then filtered through silica (50 g), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness and the residue was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated red crystals were removed by suction filtration through a D3 frit and dried in vacuo to yield: 195 mg (0.27 mmol, 90%) of the metalloporphyrin: mp 272 °C; R_f=0.46 (CH_2Cl_2/*n*-hexane, 3:1, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/0.05% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm) retention time: 3.3 min (92.3%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.88 (t, *J*=7 Hz, 3H, 5^6-CH_3), 1.25–1.47 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.62 (m, 2H, 5^3-CH_2), 2.34 (m, 2H, 5^2-CH_2), 3.92 (s, 12H, OCH_3), 4.64 (t, *J*=7 Hz, 2H, 5^1-CH_2), 6.83 (m, 2H, phenyl-H_{para}), 7.20 (m, 4H, phenyl-H_{ortho}), 8.92 (m, 4H, β-pyrrole-*H*), 9.04 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.35 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.68 ppm (s, 1H, *meso*-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.06, 22.62, 30.09, 31.78, 34.53, 37.66, 55.55, 100.10, 103.84, 112.98, 117.34, 119.31, 129.29, 131.93, 132.33, 132.51, 141.90, 141.96, 142.19, 142.91, 159.12 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=325 (3.98), 410 (5.34), 523 (4.17), 551 nm (3.68); MS (EI, 80 eV, 300 °C), *m*/*z* (%): 722 (100) [M^+], 651 (41) [$M^+-C_5H_{11}$], 361 (11) [M^{2+}]; HRMS (EI) [$C_{42}H_{40}N_4NiO_4$]: calcd 722.2403, found 722.24334;

[$C_{42}H_{40}N_4NiO_4$, 723.49 g mol^{-1}]. Anal. Calcd C 69.73, H 5.57, N 7.74, found C 69.41, H 5.31, N 7.54.

4.5.14. 5-Butyl-10,20-bis(3-methoxyphenyl)porphyrin (44). Side product from the synthesis of 5,10,15-tris(3-methoxyphenyl)porphyrin **30** (Section 4.5.1): purple crystals, mp = 272 °C; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = -3.01$ (s, 2H, N*H*), 1.14 (t, 3H, $J_{5-6} = 7$ Hz, 6-H), 1.77–1.92 (m, 2H, 5-H), 2.51–2.63 (m, 2H, 4-H), 4.03 (s, 6H, MeO), 5.10 (t, 2H, $J_{3-4} = 7.7$ Hz, 3-H), 7.35–7.39 (m, 2H, Ph), 7.65–7.72 (m, 2H, Ph), 7.81–7.86 (m, 4H, Ph), 9.02 (m, each 2H, 1-H, 8-H), 9.28 (d, 2H, $J_{1-7} = 4.3$ Hz, 7-H), 9.56 (d, 2H, $J_{1-2} = 5.2$, 2-H), 10.11 (s, 1H, *meso-H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta = 14.61$, 24.07, 36.04, 41.51, 55.93, 104.41, 113.91, 119.17, 120.97, 121.57, 127.94, 143.80, 158.45 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 412 (5.19), 439 (3.89), 509 (4.01), 540 (3.75), 586 (3.72), 640 nm (3.68); MS (EI, 80 eV, 300 °C); *m/z* (%): 684 (2.25), 639 (15.68) [$M^+ + Cu$], 595 (10.75) [$M^+ + Cu - C_3H_7$], 578 (100) [M^+], 535 (77.35) [$M^+ - C_3H_7$], 518 (3.96) 495 (5.39), 289 (14.46) [$M^+/2$]; MS (EI, 80 eV, 280 °C); *m/z* (%): 578 (12) [M^+], 535 (34) [$M^+ - C_3H_7$], 289 (20) [M^{++}]; HRMS (EI) [$C_{38}H_{34}N_4O_2$]: calcd 578.268177, found 578.268234.

4.6. A_3B-type porphyrins

4.6.1. 5,10,15-Tris(3-methoxyphenyl)-20-pentylporphyrin (45). Dry dichloromethane (1500 mL) was placed in a three-necked-flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Hexanal (0.46 mL, 3.75 mmol), 3-methoxybenzaldehyde (1.37 mL, 11.25 mmol), and pyrrole (1.04 mL, 15 mmol) were added. The flask was shielded from ambient light and then 1.16 mL (15 mmol) of trifluoroacetic acid were added and the reaction mixture was stirred for 3 h at 20 °C. After this time, 2.55 g (11.25 mmol) of DDQ suspended in 200 mL of dry dichloromethane were added and the mixture was stirred for 1 h. Then, 6 mL of triethylamine were added and the reaction mixture was stirred for 15 min. The reaction mixture was filtered through 100 g of silica, washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The eluted porphyrin fractions were separated by column chromatography on silica (3× 60 cm) using gradient elution with dichloromethane/hexane (2:1 to 3:1, v/v). The desired 5,10,15-tris(3-methoxyphenyl)-20-pentylporphyrin was obtained as the fourth fraction, preceded by 5,10,15,20-tetrapentylporphyrin **46** (traces), 5-(3-methoxyphenyl)-10,15,20-tripentylporphyrin **47** (<20 mg) and the (non-separable) isomeric mixture of 5,10-bis(3-methoxyphenyl)-15,20-dipentylporphyrin **48** and 5,15-bis(3-methoxyphenyl)-10,20-dipentylporphyrin **49**. The fifth fraction was 5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin **50** (160 mg, 0.22 mmol, 6%). The title porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated crystals were removed by suction filtration through a D3 frit and dried in vacuo to yield 240 mg (0.34 mmol; 9%) of purple crystals: mp 233–235 °C; $R_f = 0.17$ (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.48 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = -2.76$ (s, 2H, N*H*), 0.96 (t, $J = 7$ Hz, 3H, 20^5-CH_3), 1.55 (m, 2H, 20^4-CH_2), 1.78 (m, 2H, 20^3-CH_2), 2.55 (m, 2H, 20^2-CH_2), 3.96 (s, 3H, 10-OCH_3), 3.98 (s, 6H, 5-OCH_3 and 15-OCH_3), 5.00 (t, $J = 8$ Hz, 2H, 20^1-CH_2), 7.28–7.35 (m, 3H, phenyl-*H*), 7.58–7.66 (m, 3H, phenyl-*H*), 7.74–7.82 (m, 6H, phenyl-*H*), 8.82 (s, 4H, β-pyrrole-*H*), 8.94 (d, $J = 5$ Hz, 2H, β-pyrrole-*H*), 9.47 ppm (d, $J = 5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta = 14.12$, 22.78, 32.75, 35.52, 38.55, 55.51, 113.55, 119.00, 119.27, 120.46, 120.80, 127.41, 127.51, 127.64, 127.91, 130.01, 130.76, 131.25, 143.43, 143.78, 146.78, 157.96, 158.03 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 303 (4.25), 374 (4.39), 401 (4.92), 418 (5.61), 484 (3.51), 516 (4.28), 550 (3.89), 592 (3.74), 648 nm (3.64); MS (EI, 80 eV, 250 °C), *m/z* (%): 698 (100) [M^+], 641 (39) [$M^+ - C_4H_9$], 349 (12) [M^{2+}]; HRMS (EI) [$C_{46}H_{42}N_4O_3$]: calcd 698.32569, found 698.32348; [$C_{46}H_{42}N_4O_3$, 698.86 g mol^{-1}]. Anal. Calcd C 79.06, H 6.06, N 8.02, found C 78.77, H 5.87, N 7.80.

4.6.2. 5-Hexyl-10,15,20-tris(3-methoxyphenyl)porphyrin (51). Preparation and workup as described in Section 4.6.1 using heptanal (0.52 mL, 3.75 mmol). Column chromatography gave the desired monohexylated porphyrin **51** as the fourth fraction, preceded by 5,10,15,20-tetrahexylporphyrin **52** (traces), 5,10,15-trihexyl-20-(3-methoxyphenyl)-porphyrin **53** (<20 mg) and the (non-separable) isomeric mixture of 5,10-dihexyl-15,20-bis(3-methoxyphenyl)-porphyrin **54** and 5,15-dihexyl-10,20-bis(3-methoxyphenyl)porphyrin **55**. The fifth fraction was 5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin **50** (170 mg, 0.23 mmol, 6%). The title porphyrin was again dissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated crystals were removed by suction filtration through a D3 frit and dried in vacuo to yield 210 mg (0.29 mmol; 8%) of purple crystals: mp 206–208 °C; $R_f = 0.19$ (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.52 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = -2.74$ (s, 2H, N*H*), 0.93 (t, $J = 7$ Hz, 3H, 5^6-CH_3), 1.32–1.57 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.81 (m, 2H, 5^3-CH_2), 2.55 (m, 2H, 5^2-CH_2), 3.97 (s, 3H, 15-OCH_3), 3.99 (s, 6H, 10-OCH_3 and 20-OCH_3), 5.00 (t, $J = 8$ Hz, 2H, 5^1-CH_2), 7.29–7.36 (m, 3H, phenyl-*H*), 7.59–7.68 (m, 3H, phenyl-*H*), 7.76–7.83 (m, 6H, phenyl-*H*), 8.85 (s, 4H, β-pyrrole-*H*), 8.96 (d, $J = 5$ Hz, 2H, β-pyrrole-*H*), 9.47 ppm (d, $J = 5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta = 14.12$, 22.71, 30.25, 31.92, 35.56, 38.85, 55.50, 113.54, 119.01, 119.27, 120.47, 120.81, 127.40, 127.50, 127.64, 131.20, 143.43, 143.78, 157.96, 158.04 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε) = 304 (4.23), 374 (4.39), 401 (4.94), 418 (5.59), 484 (3.48), 516 (4.28), 550 (3.88), 592 (3.72), 648 nm (3.57); MS (EI, 80 eV, 310 °C), *m/z* (%): 712 (100) [M^+], 641 (51) [$M^+ - C_5H_{11}$], 356 (19) [M^{2+}]; HRMS (EI) [$C_{47}H_{44}N_4O_3$]: calcd 712.34134, found 712.34332; [$C_{47}H_{44}N_4O_3$, 712.89 g mol^{-1}]. Anal. Calcd C 79.19, H 6.22, N 7.86, found C 78.83, H 5.93, N 7.69.

4.6.3. 5,10,15,20-Tetrahexylporphyrin (52). Obtained as purple needles (5%, 130 mg, 0.2 mmol) during the synthesis of 5,10,15-trihexyl-20-(3-methoxyphenyl)porphyrin (Section 4.6.4, **53**): mp 120 °C; $R_f = 0.52$ (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = -2.67$ (s, 2H, N*H*), 0.96 (t, $J = 7$ Hz, 12H, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 1.30–1.60 (m, 16H, $CH_2CH_2CH_2CH_2CH_2CH_3$ and

$CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81 (m, 8H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.51 (m, 8H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 4.90 (t, $J=8$ Hz, 8H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 9.44 ppm (s, 8H, β-pyrrole-H); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=14.14$, 22.76, 30.29, 31.70, 31.95, 32.89, 35.55, 38.66, 118.38, 128.08, ~145 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.04), 349 (4.18), 367 (4.27), 400 (4.86), 418 (5.46), 485 (3.44), 520 (4.14), 555 (3.96), 601 (3.55), 660 nm (3.80); MS (EI, 80 eV, 260 °C): *m/z* (%): 646 (100) [M^+], 575 (27) [M^+-71 (C_5H_{11})], 323 (9) [M^{2+}]; HRMS (EI) [$C_{44}H_{62}N_4$]: calcd 646.49745, found 646.44920; [$C_{44}H_{62}N_4$, 647.01 g mol^{-1}]. Anal. Calcd C 81.68, H 9.66, N 8.66, found C 81.41, H 9.59, N 8.70.

4.6.4. 5,10,15-Trihexyl-20-(3-methoxyphenyl)porphyrin (53). Dry dichloromethane (1500 mL) was placed in a three-necked-flask equipped with magnetic stirrer, gas inlet (argon) and a reflux condenser. Heptanal (1.57 mL, 11.25 mmol), 3-methoxybenzaldehyde (0.46 mL, 3.75 mmol), and pyrrole (1.04 mL, 15 mmol) were added. Further conditions and workup as described in Section 4.6.1 followed by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (1:1, v/v) as eluent. The desired 5,10,15-trihexyl-20-(3-methoxyphenyl)porphyrin **53** was obtained as the second fraction, preceded by 5,10,15,20-tetrahexylporphyrin **52** (130 mg, 0.2 mmol, 5%). Efforts to recrystallize the 5,10,15-trihexyl-20-(3-methoxyphenyl)porphyrin were unsuccessful; yield: 200 mg (0.3 mmol; 8%) of a purple amorphous solid: mp 91 °C; $R_f=0.48$ (CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^1H NMR (250 MHz, $CDCl_3$): $\delta=-2.61$ (s, 2H, N*H*), 1.05 (m, 9H, 5^6-, 10^6-, and 15^6-C*H*$_3$), 1.29–1.63 (m, 12H, 5^5-, 10^5-, and 15^5-C*H*$_2$, 5^4-, 10^4-, and 15^4-C*H*$_2$), 1.85 (m, 6H, 5^3-, 10^3-, and 15^3-C*H*$_2$), 2.56 (m, 6H, 5^2-, 10^2-, and 15^2-C*H*$_2$), 4.02 (s, 3H, OC*H*$_3$), 4.91 (m, 6H, 5^1-, 10^1-, and 15^1-C*H*$_2$), 7.40 (m, 1H, phenyl-*H*), 7.70 (m, 1H, phenyl-*H*), 7.87 (m, 2H, phenyl-*H*), 8.95 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.42 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.47 ppm (m [AB-spectrum], 4H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=14.18$, 22.75, 30.23, 30.28, 31.93, 35.35, 35.72, 38.65, 38.82, 55.44, 113.35, 117.70, 119.06, 119.39, 120.47, 127.36, 127.62, 131.19, 144.08, 145.53, 158.00 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=349 (4.23), 367 (4.30), 398 (4.79), 418 (5.55), 485 (3.39), 519 (4.15), 553 (3.88), 597 (3.64), 655 nm (3.70); MS (EI, 80 eV, 240 °C), *m/z* (%): 668 (100) [M^+], 597 (36) [$M^+-C_5H_{11}$], 334 (4) [M^{2+}]; HRMS (EI) [$C_{45}H_{56}N_4O$]: calcd 668.44541, found 668.44287.

4.6.5. 5-Heptyl-10,15,20-tris(3-methoxyphenyl)porphyrin (56). Preparation and workup as described in Section 4.6.1 using octanal (0.59 mL, 3.75 mmol). Column chromatography gave the desired 5-heptyl-10,15,20-tris(3-methoxyphenyl)porphyrin **56** as the fourth fraction, preceded by 5,10,15,20-tetraheptylporphyrin **57** (traces), 5,10,15-triheptyl-20-(3-methoxyphenyl)porphyrin **58** (<20 mg) and the (non-separable) isomeric mixture of 5,10-diheptyl-15,20-bis(3-methoxyphenyl)porphyrin **59** and 5,15-diheptyl-10,20-bis(3-methoxyphenyl)porphyrin **60**. The fifth fraction was 5,10,15,20-tetrakis(3-methoxyphenyl)-porphyrin **50** (160 mg, 0.22 mmol, 6%). The target fraction was again dissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated crystals were removed by suction filtration through a D3 frit and dried in vacuo to yield 270 mg (0.37 mmol; 10%) of purple crystals: mp 203–205 °C; $R_f=0.23$ (CH_2Cl_2/C_6H_{14}, 3:1, v/v), 0.56 (CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$): $\delta=-2.76$ (s, 2H, N*H*), 0.89 (t, $J=7$ Hz, 3H, 5^7-C*H*$_3$), 1.30–1.39 (m, 4H, 5^6-C*H*$_2$ and 5^5-C*H*$_2$), 1.51 (m, 2H, 5^4-C*H*$_2$), 1.80 (m, 2H, 5^3-C*H*$_2$), 2.54 (m, 2H, 5^2-C*H*$_2$), 3.96 (s, 3H, 15-OC*H*$_3$), 3.98 (s, 6H, 10-OC*H*$_3$ and 20-OC*H*$_3$), 5.00 (t, $J=8$ Hz, 2H, 5^1-C*H*$_2$), 7.28–7.35 (m, 3H, phenyl-*H*), 7.59–7.67 (m, 3H, phenyl-*H*), 7.75–7.82 (m, 6H, phenyl-*H*), 8.83 (s, 4H, β-pyrrole-*H*), 8.95 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.47 ppm (d, $J=5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=14.08$, 22.69, 29.37, 30.56, 31.89, 35.56, 38.90, 55.49, 113.52, 118.97, 119.24, 120.42, 120.80, 127.39, 127.49, 127.62, 127.88, 130.68, 131.18, 143.40, 143.75, 145.94, 157.91, 157.99 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=304 (4.17), 373 (4.35), 401 (4.86), 418 (5.59), 485 (3.45), 516 (4.24), 550 (3.84), 592 (3.67), 648 nm (3.56); MS (EI, 80 eV, 250 °C), *m/z* (%): 726 (100) [M^+], 641 (36) [$M^+-C_6H_{13}$], 363 (17) [M^{2+}]; HRMS (EI) [$C_{48}H_{46}N_4O_3$]: calcd 726.35699, found 726.35633; [$C_{48}H_{46}N_4O_3$, 726.92 g mol^{-1}]. Anal. Calcd C 79.31, H 6.38, N 7.71, found C 79.12, H 6.18, N 7.62.

4.6.6. 5,10,15,20-Tetraheptylporphyrin (57). Obtained as purple needles (5%, 140 mg, 0.2 mmol) during the synthesis of 5,10,15-triheptyl-20-(3-methoxyphenyl)porphyrin (Section 4.6.7, **58**): mp 103 °C; $R_f=0.58$ (SiO_2, CH_2Cl_2/C_6H_{14}, 1:1, v/v); ^1H NMR (250 MHz, $CDCl_3$): $\delta=-2.66$ (s, 2H, N*H*), 0.90 (t, $J=7$ Hz, 12H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.35 (m, 16H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ and $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.52 (m, 8H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.79 (m, 8H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 2.50 (m, 8H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 4.91 (t, $J=8$ Hz, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 9.44 ppm (s, 8H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=14.12$, 22.72, 29.41, 30.60, 31.96, 35.56, 38.73, 118.40 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=350 (4.18), 366 (4.27), 400 (4.87), 418 (5.60), 489 (3.40), 520 (4.13), 555 (3.96), 601 (3.54), 660 nm (3.78); MS (EI, 80 eV, 320 °C), *m/z* (%): 702 (100) [M^+], 617 (22) [M^+-85 (C_6H_{13})], 351 (5) [M^{2+}]; HRMS (EI) [$C_{48}H_{70}N_4$]: calcd 702.56005, found 702.56445; [$C_{48}H_{70}N_4$, 703.11 g mol^{-1}]. Anal. Calcd C 82.00, H 10.03, N 7.97, found C 81.95, H 9.95, N 7.69.

4.6.7. 5,10,15-Triheptyl-20-(3-methoxyphenyl)porphyrin (58). Preparation, observations, chromatography and workup as described in Section 4.6.4 using octanal (1.76 mL, 11.25 mmol). Yield of 5,10,15-triheptyl-20-(3-methoxyphenyl)porphyrin **58**: 170 mg (recrystallization unsuccessful, 0.24 mmol; 6%) as a purple amorphous solid; yield of 5,10,15,20-tetraheptylporphyrin **57**: 140 mg (0.2 mmol; 5%) as purple needles. Analytical data for the title compound: mp 144 °C; $R_f=0.52$ (CH_2Cl_2/C_6H_{14}, 1:1, v/v): 0.52; ^1H NMR (250 MHz, $CDCl_3$): $\delta=-2.67$ (s, 2H, N*H*), 0.92 (m, 9H, 5^7-, 10^7-, and 15^7-C*H*$_3$), 1.30–1.41 (m, 12H, 5^6-, 10^6-, and 15^6-C*H*$_2$, 5^5-, 10^5-, and 15^5-C*H*$_2$), 1.53 (m, 6H, 5^4-, 10^4-, and 15^4-C*H*$_2$), 1.79 (m, 6H, 5^3-, 10^3-, and 15^3-C*H*$_2$), 2.51 (m, 6H, 5^2-, 10^2-, and 15^2-C*H*$_2$), 3.98 (s, 3H, OC*H*$_3$), 4.93 (m, 6H, 5^1-, 10^1-, and 15^1-C*H*$_2$), 7.33 (m, 1H, phenyl-*H*), 7.63 (m, 1H, phenyl-*H*), 7.75 (m, 2H, phenyl-*H*), 8.86 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.37 (d, $J=5$ Hz, 2H,

β-pyrrole-*H*), 9.50 (m [AB-spectrum], 4H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.12, 22.72, 29.39, 30.54, 30.59, 31.93, 31.97, 35.39, 35.76, 38.69, 38.86, 55.46, 113.37, 117.68, 119.06, 119.41, 120.44, 127.35, 127.58, 127.79, 131.25, 143.55, 145.71, 157.97 ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ=14.12, 14.15, 22.71, 22.74, 29.39, 29.42, 30.55, 30.64, 31.93, 31.97, 35.41, 35.82, 38.72, 38.93, 55.47, 113.35, 117.65, 119.11, 119.47, 120.33, 127.34, 127.55, ~128.5, ~131.5, 143.97, 157.89 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=349 (4.27), 367 (4.35), 401 (4.86), 418 (5.60), 485 (3.37), 518 (4.20), 553 (3.94), 597 (3.65), 654 nm (3.71); MS (EI, 80 eV, 200 °C), *m*/*z* (%): 710 (100) [M^+], 625 (28) [$M^+-C_6H_{13}$]; HRMS (EI) [$C_{48}H_{62}N_4O$]: calcd 710.49236, found 710.4945.

4.7. A_2BC-type porphyrins via S_NAr

4.7.1. 5-Butyl-15-hexyl-10,20-diphenylporphyrin (61). *n*-Butyl lithium (2 mL of a 2.5 M solution in hexane, 5 mmol) was added under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of 5-hexyl-10,20-diphenylporphyrin **40** (100 mg, 0.18 mmol) in 40 mL of dry THF at −80 °C. The mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 1 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. Subsequently, the mixture was filtered through silica gel and the organic solvent was removed under vacuum or washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with dichloromethane/*n*-hexane (2:1, v/v) and yielded the title compound (34 mg, 0.05 mmol, 31%) as purple crystals, mp >300 °C; R_f=0.77 (dichloromethane/*n*-hexane, 2:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=−2.67 (s, 2H, 2×N*H*), 0.94 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.13 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.27 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.52 (m, 2H, $CH_2CH_2CH_2CH_2$-CH_2CH_3),1.81 (m, 4H, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 2.48 (m, 4H, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_2CH_2CH_3$), 4.99 (t, 4H, *J*=8.1 Hz, CH_2-$CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_2CH_2CH_3$), 7.75 (m, 6H, phenyl-*H*), 8.21 (m, 4H, phenyl-*H*), 8.85 (m, 4H, β-pyr-pyrrole-*H*), 9.43 ppm (m, 4H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=13.71 (15^6-C), 22.27 (15^5-C), 23.15 (5^4-C), 29.28 (5^3-C), 29.76 (15^4-C), 31.46 (15^3-C), 34.54 (5^2-C), 34.85 (15^2-C), 38.23 (15^1-C), 40.31 (5^1-C), 118.45, 119.36, 126.08, 127.14, 133.99, 142.26, 143.84, 146.70 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=417 (4.96), 438 (4.03), 515 (3.87), 550 (3.72), 592 (3.59), 651 nm (3.69); MS (EI, 80 eV) *m*/*z* (%): 602 (60) [M^+], 559 (50) [$M^+-C_3H_7$], 531 (64) [$M^+-C_5H_{11}$], 488 (38) [$M^+-C_5H_{11}-C_3H_7$], 301 (26) [M^{++}]; HRMS [$C_{42}H_{42}N_4$]: calcd 602.3409, found 602.3383.

4.7.2. 5-(4-Dimethylaminophenyl)-15-hexyl-10,20-diphenylporphyrin (62). *n*-Butyl lithium (1.2 mL of a 2.5 M solution in hexane, 3 mmol) was slowly added (ca. 1 h) under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of *p*-(dimethylamino)bromobenzene (0.5 g, 2.5 mmol) in 10 mL of dry diethyl ether at 0 °C. After addition of *n*-butyl lithium the cold bath was removed and stirring was continued for another 1 h at room temperature. The solution became yellow and opaque. To the vigorously stirred mixture was added rapidly a solution of 5-hexyl-10,20-diphenylporphyrin **40** (100 mg, 0.18 mmol) in 40 mL of dry THF under an argon atmosphere. The color of the mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 3 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. Subsequently, the mixture was filtered through silica gel (Merck) and the organic solvent was removed under vacuum or washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with ethyl acetate/*n*-hexane (1:4, v/v) yielded the title compound (66.1 mg, 0.1 mmol, 54%) as purple crystals, mp >300 °C; R_f=0.42 (ethyl acetate/*n*-hexane, 1:4, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=−2.61 (s, 2H, 2×N*H*), 0.92 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2$-CH_3), 1.39 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.55 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.79 (m, 2H, $CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 2.53 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 3.22 (s, 6H, $N(CH_3)_2$), 5.02 (t, 2H, *J*=8.1 Hz, CH_2CH_2-$CH_2CH_2CH_2CH_3$), 7.11 (d, 2H, *J*=7.5 Hz, Ph-H), 7.76 (m, 6H, Ph-H), 8.06 (d, 2H, *J*=7.5 Hz, Ph-H), 8.22 (m, 4H, Ph-H), 8.81 (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*), 8.92 (m, 4H, β-pyrrole-*H*), 9.46 ppm (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=13.72, 22.28, 29.81, 31.47, 35.04, 38.36, 40.25, 110.29, 118.85, 119.64, 126.12, 127.13, 128.33, 134.07, 135.25, 142.18, 149.45 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=419 (4.91), 517 (3.76), 564 (3.47), 595 (3.16), 653 nm (3.33); MS (EI, 80 eV) *m*/*z* (%): 665 (24) [M^+], 594 (25) [$M^+-C_5H_{11}$], 578 (10) [$M^+-C_5H_{12}-CH_3$], 333 (20) [M^{++}]; HRMS [$C_{46}H_{43}N_5$]: calcd 665.3518, found 665.3491.

4.7.3. 5-Hexyl-15-(3-hydroxyphenyl)-10,20-diphenylporphyrin (63). *n*-Butyl lithium (3 mL of a 2.5 M solution in hexane, 7.5 mmol) was added under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of *m*-bromophenol (0.87 g, 5 mmol) in 10 mL of dry diethyl ether at 0 °C. After addition of *n*-butyl lithium the cold bath was removed and stirring was continued for 18 h at room temperature. The solution slowly became opaque yellow. To the vigorously stirred mixture was added rapidly a solution of 5-hexyl-10,20-diphenylporphyrin **40** (100 mg, 0.18 mmol) in 40 mL of dry THF under an argon atmosphere. The mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 2 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. Subsequently, the mixture was filtered through silica gel and the organic solvent was removed under vacuum or washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with ethyl acetate/*n*-hexane (1:4, v/v) yielding the title compound (97 mg, 0.15 mmol, 83%) as purple crystals,

mp >300 °C; R_f=0.55 (ethyl acetate/*n*-hexane, 1:3, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=0.96 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.27 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.40 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.72 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 2.51 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 4.92 (t, 2H, *J*=8.1 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 6.41 (m, 1H, phenyl-*H*), 6.69 (m, 1H, phenyl-*H*), 6.95 (m, 1H, phenyl-*H*), 7.45 (m, 1H, phenyl-*H*), 7.67 (s, 1H, O*H*), 7.78 (m, 6H, phenyl-*H*), 8.24 (m, 4H, phenyl-*H*), 8.77 (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*), 8.82 (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*), 8.95 (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*), 9.45 ppm (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=13.68, 22.24, 29.75, 31.42, 35.06, 38.37, 113.61, 118.16, 119.20, 120.49, 121.25, 122.13, 123.19, 126.18, 127.22, 130.08, 134.08, 141.90, 142.89, 153.26, 155.77 ppm; UV/Vis (CH_2Cl_2): λ_{max} (log ε)=417 (4.97), 443 (4.22), 514 (3.76), 549 (3.55), 593 (3.48), 657 nm (3.56); MS (EI, 80 eV): *m*/*z* (%): 638 (16) [M^+], 567 (30) [$M^+-C_5H_{11}$], 319 (18) [M^{++}]; HRMS [$C_{44}H_{38}N_4O$]: calcd 638.3045, found 638.3025; [$C_{44}H_{38}N_4O$, 638.81 g mol^{-1}]. Anal. Calcd C 82.73, H 6.00, N 8.77, found C 82.71, H 5.98, N 8.43.

4.7.4. 5-Hexyl-15-(4-hydroxyphenyl)-10,20-diphenylporphyrin (64). *n*-Butyl lithium (3 mL of a 2.5 M solution in hexane, 7.5 mmol) was added under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of *p*-bromophenol (0.87 g, 5 mmol) in 10 mL of dry diethyl ether at 0 °C. Further reaction and work-up followed the procedure given in Section 4.7.3 to yield the title compound (76 mg, 0.12 mmol, 65%) as purple crystals, mp >300 °C; R_f=0.33 (ethyl acetate/*n*-hexane, 1:4, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=0.94 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.36 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.51 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.55 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 4.99 (t, 2H, *J*=8.1 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 6.46–6.49 (m, 3H, Ph-H), 6.99 (d, 2H, *J*=7.5 Hz, Ph-H), 7.23–7.26 (m, 3H, Ph-H), 7.76 (m, 2H, Ph-H), 7.78 (s, 1H, O*H*), 7.98 (d, 2H, *J*=7.5 Hz, Ph-H), 8.20–8.23 (d, 2H, *J*=7.5 Hz, Ph-H), 8.82 (m, 4H, β-pyrrole-*H*), 8.95 (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*), 9.48 ppm (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.54 (5^6-C), 23.11 (5^5-C), 30.65 (5^4-C), 32.29 (5^3-C), 35.58 (5^2-C), 39.26 (5^1-C), 113.10, 117.45, 120.03, 121.16, 127.05, 128.10, 132.71, 134.95, 136.06, 142.72, 154.81 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=417 nm (4.96), 445 (4.51), 514 (4.28), 595 (4.14), 653 nm (4.15); MS (EI, 80 eV) *m*/*z* (%): 638 (18) [M^+], 567 (34) [$M^+-C_5H_{11}$], 319 (17) [M^{++}]; HRMS [$C_{44}H_{38}N_4O$]: calcd 638.3045, found 638.3027; [$C_{44}H_{38}N_4O$, 638.81 g mol^{-1}]. Anal. Calcd C 82.73, H 6.00, N 8.77, found C 82.58, H 6.15, N 8.85.

4.7.5. 5-Hexyl-15-(2-methoxyphenyl)-10,20-diphenylporphyrin (65). *n*-Butyl lithium (2 mL of a 2.5 M solution in hexane, 5 mmol) was added under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of *o*-bromoanisole (0.5 g, 2.7 mmol) in 10 mL of dry THF at −78 °C. After addition of *n*-butyl lithium the cold bath was removed and stirring was continued for 1 h at room temperature. To the vigorously stirred mixture was added rapidly a solution of 5-hexyl-10,20-diphenylporphyrin **40** (50 mg, 0.09 mmol) in 40 mL of dry THF under an argon atmosphere. The mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 12 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. Subsequently, the mixture was filtered through silica gel and the organic solvent was removed under vacuum or washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with ethyl acetate/*n*-hexane (1:4, v/v) yielding the title compound (24 mg, 0.04 mmol, 40%) as purple crystals, mp >300 °C; R_f=0.25 (ethyl acetate/*n*-hexane, 1:4, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=−2.64 (s, 2H, 2×N*H*), 0.96 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.28 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.55 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.85 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 2.56 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 3.8 (s, 3H, OCH_3), 5.04 (t, 2H, *J*=8.1 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 7.01 (m, 1H, phenyl-*H*), 7.37 (m, 2H, phenyl-*H*), 7.79 (m, 6H, phenyl-*H*), 8.01 (m, 1H, phenyl-*H*), 8.22 (m, 4H, phenyl-*H*), 8.76 (m, 4H, β-pyrrole-*H*), 8.92 (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*), 9.49 ppm (d, 2H, *J*=5.0 Hz, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.14, 22.71, 30.23, 31.90, 35.58, 38.81, 55.66, 111.06, 115.18, 119.23, 120.74, 126.54, 127.55, 128.58, 130.88, 131.44, 135.56, 157.01, 159.42 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=416 (4.93), 443 (4.20), 514 (4.00), 565 (3.86), 594 (3.63), 649 nm (3.86); MS (EI, 80 eV): *m*/*z* (%): 652 (20) [M^+], 581 (35) [$M^+-C_5H_{11}$], 489 (18) [$M^+-C_5H_{11}-C_6H_5-CH_3$], 326 (15) [$M^{++}$]; HRMS [$C_{45}H_{40}N_4O$]: calcd 652.3202, found 652.3176.

4.7.6. 5-(2,5-Dimethoxyphenyl)-15-hexyl-10,20-diphenylporphyrin (66). *n*-Butyl lithium (2 mL of a 2.5 M solution in hexane, 5 mmol) was added under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of 1-bromo-2,5-dimethoxybenzene (0.5 g, 2.4 mmol) in 10 mL of dry THF at −80 °C. After addition of *n*-butyl lithium the cold bath was removed and stirring was continued for 1 h at room temperature. To the vigorously stirred mixture was added rapidly a solution of 5-hexyl-10,20-diphenylporphyrin **40** (50 mg, 0.09 mmol) in 40 mL of dry THF under an argon atmosphere. The mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 5 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. Subsequently, the mixture was filtered through silica gel and the organic solvent was removed under vacuum and washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with ethyl acetate/*n*-hexane (1:4, v/v) yielded the title compound (18 mg, 0.03 mmol, 29%) as purple crystals, mp >300 °C; R_f=0.22 (ethyl acetate/*n*-hexane, 1:4, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ=−2.66 (s, 2H, 2×N*H*), 0.95 (t, 3H, *J*=7.2, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.26 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.52 (m,

2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.89 (m, 2H, $CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 2.55 (m, 2H, $CH_2CH_2CH_2CH_2CH_2CH_3$), 3.50–3.91 (m, 6H, $2\times OCH_3$), 5.05 (t, 2H, $J=8.1$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 6.77 (m, 1H, phenyl-*H*), 7.28 (m, 1H, phenyl-*H*), 7.58 (m, 1H, phenyl-*H*), 7.77 (m, 6H, phenyl-*H*), 8.20 (m, 4H, phenyl-*H*), 8.77 (m, 4H, β-pyrrole-*H*), 8.89 (d, 2H, $J=5.0$ Hz, β-pyrrole-*H*), 9.49 ppm (d, 2H, $J=5.0$ Hz, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=$ 13.71, 22.28, 29.83, 31.48, 35.58, 38.41, 55.48, 56.27, 111.60, 114.37, 117.30, 118.85, 120.96, 126.13, 127.15, 131.50, 134.00, 142.02, 151.99, 153.69 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=417 (4.97), 440 (3.97), 514 nm (3.83), 545 (3.61), 590 (3.57), 649 nm (3.61); MS (EI, 80 eV) *m/z* (%): 682 (20) [M^+], 611 (36) [$M^+-C_5H_{11}$], 341 (14) [M^{++}]; HRMS [$C_{45}H_{40}N_4O$]: calcd 682.3307, found 682.3275.

4.7.7. 5-(4-Aminophenyl)-15-(4-dimethylaminophenyl)-10,20-diphenylporphyrin (67). *n*-Butyl lithium (0.6 mL of a 2.5 M solution in hexane, 0.6 mmol) was slowly added (ca. 1 h) under an argon atmosphere to a 100 mL Schlenk flask charged with a solution of *p*-(dimethylamino)bromobenzene (0.25 g, 1.25 mmol) in 10 mL of dry diethylether at 0 °C. After addition of *n*-butyl lithium the cold bath was removed and stirring was continued for another 1 h at room temperature. The solution became bright yellow and opaque. To the vigorously stirred mixture was added rapidly a solution of 5-(*p*-aminophenyl)-10,20-diphenylporphyrin (50 mg, 0.09 mmol) in 40 mL of dry THF under an argon atmosphere. The mixture changed from deep purple to brown within 30 min. The reaction mixture was stirred for 4 h (TLC control). Subsequently, a mixture of 2 mL of water in 3 mL of THF was added for hydrolysis. After stirring of the mixture for 20 min, a solution of 10 equiv of DDQ in THF (0.06 M) was added and the reaction mixture was stirred for another 60 min at room temperature. Subsequently, the mixture was filtered through silica gel and the organic solvent was removed under vacuum or washed with enough *n*-hexane. Final purification was achieved by column chromatography and elution with ethyl acetate/*n*-hexane (1:2, v/v) yielded the title compound (12 mg, 0.017 mmol, 20%) as purple crystals, mp >300 °C; $R_f=0.72$ (ethyl acetate/*n*-hexane, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta=-2.65$ (s, 2H, 2×NH), 3.23 (s, 6H, $N(CH_3)_2$), 7.02 (d, 2H, $J=7.5$ Hz, Ph-H), 7.11 (d, 2H, $J=7.5$ Hz, phenyl-*H*), 7.77 (m, 6H, phenyl-*H*), 7.97 (d, 2H, $J=7.5$ Hz, phenyl-*H*), 8.07 (d, 2H, $J=7.5$ Hz, phenyl-*H*), 8.24 (m, 4H, phenyl-*H*), 8.83 (d, 2H, $J=5.0$ Hz, β-pyrrole-*H*), 8.84 (d, 2H, $J=5.0$ Hz, β-pyrrole-*H*), 8.92 (d, 2H, $J=5.0$ Hz, β-pyrrole-*H*), 8.95 ppm (d, 2H, $J=5.0$ Hz, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=40.27$, 110.28, 113.01, 119.31, 120.54, 126.183, 127.14, 134.13, 142.03, 145.52, 149.54 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=421 (5.09), 518 (4.03), 560 (3.90), 597 (3.79), 655 nm (3.97); MS (EI, 80 eV) *m/z* (%): 658 (4) [M^+-CH_2], 336 (6) [M^{++}], 149 (100) [4-Me_2N–C_6H_4–CHO]; [$C_{46}H_{36}N_6$ 672.83 g mol^{-1}]. Anal. Calcd C 82.11, H 6.15, N 8.85, found C 82.45, H 6.52, N 8.71.

4.7.8. 5-(4-Aminophenyl)-15-hexyl-10,20-bis(3-methoxyphenyl)porphyrin (68). 5-(4-Aminophenyl)-10,20-bis(3-methoxyphenyl)porphyrin **39** (65 mg, 0.11 mmol) was dried in vacuo in a septum-equipped Schlenk-flask for 2 h. 20 mL of abs. THF were then added under argon. The porphyrin solution was cooled to −70 °C. *n*-Hexyl lithium (250 μL of a 2.5 M solution, 6.25 mmol) was added via a syringe through the septum. The cold bath was removed and the reaction mixture was stirred for 15 min at 20 °C. The solution changed its color from red to green-brown. Water (4 mL) was added and the solution was then stirred for 20 min. Upon addition of water the reaction mixture changed its color to dark-green. After this time, 3 mL of a solution of DDQ (0.6 g DDQ in 10 mL THF, ca. 0.78 mmol) were added, upon which the solution becomes dark red again. The reaction mixture was filtered through silica (column 3×50 cm), washing with dichloromethane. The eluted porphyrin fractions were evaporated to dryness. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/methanol (20:1, v/v) as eluent. The porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 33 mg (0.047 mmol; 44%) of purple microcrystals; mp 129–130 °C; $R_f=0.74$ ($CH_2Cl_2/CH_3C(O)OCH_2CH_3$, 95:5, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=-2.74$ (s, 2H, N*H*), 0.91 (t, $J=7$ Hz, 3H, 15^6-CH_3), 1.30–1.52 (m, 4H, 15^5-CH_2 and 15^4-CH_2), 1.80 (m, 2H, 15^3-CH_2), 2.53 (m, 2H, 15^2-CH_2), 3.98 (s, 6H, OCH_3), 4.99 (t, $J=8$ Hz, 2H, 15^1-CH_2), 7.02 (m, 2H, 5-phenyl-*H*), 7.32 (m, 2H, 10,20-phenyl-*H*), 7.63 (m, 2H, 10,20-phenyl-*H*), 7.80 (m, 2H, 10,20-phenyl-*H*), 7.94 (m, 2H, 5-phenyl-*H*), 8.81 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 8.86 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 8.93 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.45 ppm (d, $J=5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): $\delta=14.14$, 22.72, 30.26, 31.92, 35.51, 38.82, 55.50, 113.48, 119.05, 120.00, 120.29, 120.38, 127.36, 127.62, ~130, 132.29, 135.60, 143.87, 145.95, 157.88 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=370 (4.35), 401 (4.84), 420 (5.52), 489 (3.61), 518 (4.22), 555 (3.93), 594 (3.65), 651 nm (3.65); MS (EI, 80 eV, 200 °C), *m/z* (%): 697 (100) [M^+], 349 (18) [M^{2+}]; HRMS (EI) [$C_{46}H_{43}N_5O_2$]: calcd 697.34168, found 697.34424.

4.8. Vinylogous formylation reactions

4.8.1. [5,15-Bis(4-butyloxyphenyl)-10-(2-formylethenyl)-porphyrinato]nickel(II) (69). 3-Dimethylamino acrolein (1.2 mL, 12 mmol) together with 12 mL of dry dichloromethane were placed in a 100 mL three-necked flask equipped with magnetic stirrer and gas inlet and cooled in an ice-bath. Then, 1.2 mL (12.8 mmol) of $POCl_3$ were added dropwise via a syringe under argon. Initially, a white precipitate formed upon addition of $POCl_3$, which dissolved again on further addition of the reagent. At the end a viscous, red-brown solution was formed which was stirred for 15 min at 0 °C. This solution was then transferred to a second flask (also cooled in an ice bath) containing 220 mg (0.33 mmol) [5,15-bis(4-butyloxyphenyl)porphyrinato]-nickel(II) **26** dissolved in 200 mL of dry dichloromethane. The cold bath was removed and the reaction mixture stirred for 18 h at 20 °C. After this time, 200 mL of a saturated sodium carbonate solution were added and the mixture was stirred for 12 h. Then, the phases were separated and the organic phase was washed with brine (3×200 mL) and then with water (4–5×200 mL) up to neutral reaction of the

water phase. The organic phase was dried with sodium sulfate and then evaporated to dryness. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/acetic acid ethylester (50:1, v/v) as eluent. The red-green product was eluted first, followed by a second fraction containing the doubly formylated product (72, <5%). The target porphyrin fractions were evaporated to dryness and redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated green-purple crystals were removed by suction filtration through a D4 frit and dried in vacuo to yield 150 mg (0.21 mmol, 63%) of the title compound: mp 211 °C; R_f=0.64 (CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/0.05% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm) retention time: 6.5 min (95%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.08 (t, J=7 Hz, 6H, $OCH_2CH_2CH_2CH_2CH_3$), 1.54–1.71 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.96 (m, 4H, $OCH_2CH_2CH_2CH_3$), 4.20 (t, J=7 Hz, 4H, $OCH_2CH_2CH_2CH_3$), 6.59 (dd, J_1=15 Hz, J_2=8 Hz, 1H, 10^2-C*H*), 7.19 (m, 4H, phenyl-*H*), 7.82 (m, 4H, phenyl-*H*), 8.76 (d, J=5 Hz, 2H, β-pyrrole-*H*), 8.83 (d, J=5 Hz, 2H, β-pyrrole-*H*), 8.99 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.24 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.59 (d, J=15 Hz, 1H, 10^1-C*H*), 9.63 (s, 1H, *meso-H*), 10.01 ppm (d, J=8 Hz, 1H, 10^3-C*H*O); ^{13}C NMR (60 MHz, $CDCl_3$): δ=13.96, 19.42, 31.53, 68.05, 106.29, 108.67, 113.16, 119.45, 130.37, 132.27, 132.66, 132.76, 133.83, 134.68, 140.91, 141.40, 142.19, 142.25, 143.57, 151.82, 159.23, 192.03 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=318 (4.49), 430 (5.24), 542 (4.10), 587 (4.06) nm; MS (EI, 80 eV, 300 °C), *m/z* (%): 716 (100) [M^+], 688 (20) [M^+-CO], 631 (2) [$M^+-CO-C_4H_9$], 358 (1) [M^{2+}]; HRMS (EI) [$C_{43}H_{38}N_4NiO_3$]: calcd 716.22974, found 716.22766; [$C_{43}H_{38}N_4NiO_3$, 717.49 g mol^{-1}]. Anal. Calcd C 71.98, H 5.34, N 7.81, found C 71.51, H 5.22, N 7.67.

4.8.2. [5-(2-Formylethenyl)-10,20-bis(4-pentyloxyphenyl)porphyrinato]nickel(II) (70). 3-(Dimethylamino)acrolein (0.6 mL, 6 mmol) and 6 mL of dry dichloromethane were placed in a 100 mL three-necked flask equipped with magnetic stirrer and gas inlet and cooled in an ice-bath. Then, 0.6 mL (6.4 mmol) of $POCl_3$ were added dropwise via a syringe under argon. Upon addition of the $POCl_3$ a white precipitate formed, which dissolved again on further addition of the reagent. Eventually, a viscous, red-brown solution was formed which was stirred for 15 min at 0 °C. This solution was then transferred to a second flask (also cooled in an ice bath) containing 120 mg (0.17 mmol) [5,15-bis(4-pentyloxyphenyl)porphyrinato]-nickel(II) **27** dissolved in 100 mL dry dichloromethane. Further conditions and workup were similar to those given in Section 4.8.1. Yield: 80 mg (0.11 mmol, 63%) of green-purple crystals: mp 160 °C; R_f=0.67 (CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/0.05% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm) retention time 5.80 min (96.5%), (same conditions but detection at 254 nm) retention time 5.87 min (94.9%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.01 (t, J=7 Hz, 6H, $OCH_2CH_2CH_2CH_2CH_3$), 1.43–1.66 (m, 8H, $OCH_2CH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2CH_3$), 1.96 (m, 4H, $OCH_2CH_2CH_2CH_2CH_3$), 4.19 (t, J=7 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_3$), 6.63 (dd, J_1=15 Hz, J_2=8 Hz, 1H, 5^2-C*H*), 7.19 (m, 4H, phenyl-*H*), 7.85 (m, 4H, phenyl-*H*), 8.77 (d, J=5 Hz, 2H, β-pyrrole-*H*), 8.86 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.01 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.29 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.65 (d, J=15 Hz, 1H, 5^1-C*H*), 9.65 (s, 1H, *meso-H*), 10.05 ppm (d, J=8 Hz, 1H, 5^3-C*H*O); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.09, 22.57, 28.38, 29.16, 68.36, 106.27, 108.65, 113.15, 119.42, 130.35, 132.26, 132.65, 132.74, 133.80, 134.66, 140.87, 141.38, 142.17, 142.23, 143.55, 151.79, 159.21, 192.02 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=317 (4.24), 429 (5.18), 544 (3.98), 590 nm (3.91); MS (EI, 80 eV, 300 °C), *m/z* (%): 744 (100) [M^+], 716 (27) [M^+-CO], 673 (10) [$M^+-C_5H_{11}$], 645 (9) [$M^+-CO-C_5H_{11}$], 574 (5) [$M^+-CO-2\times C_5H_{11}$], 545 (12) [$M^+-CO-2\times C_5H_{11}-CHO$], 372 (2) [$M^{2+}$]; HRMS (EI) [$C_{45}H_{42}N_4NiO_3$]: calcd 744.261039, found 744.26446; [$C_{45}H_{42}N_4NiO_3$, 745.54 g mol^{-1}]. Anal. Calcd C 72.50, H 5.68, N 7.51, found C 72.22, H 5.23, N 7.43.

4.8.3. [5-(2-Formylethenyl)-5,15-bis(3-methoxyphenyl)porphyrinato]nickel(II) (71). 3-(Dimethylamino)acrolein (600 μL, 6 mmol) together with 6 mL of dry dichloromethane were placed in a 100 mL-three-necked-flask equipped with magnetic stirrer and gas inlet. The flask was cooled in an ice-bath. Then, 600 μL (6.4 mmol) of phosphoroxytrichloride were added dropwise via a syringe under argon. At first, a white precipitate was formed on addition of the phosphoroxytrichloride, which dissolved again on further addition of the reagent. Eventually, a viscous, red-brown solution was formed which was stirred for 15 min at 0 °C. This solution was then transferred to a second flask (also cooled in an ice bath) containing 100 mg (0.17 mmol) [5,15-bis(3-methoxyphenyl)porphyrinato]-nickel(II) **28** dissolved in 100 mL of dry dichloromethane. The cold bath was removed and the reaction mixture stirred for 18 h at 20 °C. After this time, 100 mL of a saturated sodium carbonate solution were added and the mixture was stirred for 12 h. Then, the phases were separated and the organic phase was washed with brine (3×100 mL) and then with water (4–5×100 mL) up to neutral reaction of the water phase. The organic phase was dried with sodium sulfate and then evaporated to dryness. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/acetic acid ethylester (50:1, v/v) as eluent. First, the red-green product was eluted. As a second fraction, a small amount (~10 mg) of the doubly formylated product **74** was isolated. The eluted porphyrin fractions were evaporated to dryness. The monoformylated porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of methanol. After 24 h, the precipitated crystals were removed by suction filtration through a D4 frit and dried in vacuo to yield 60 mg (0.09 mmol, 56%) of green-purple crystals; mp 233 °C; R_f=0.6 (CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.94 (s, 6H, OCH_3), 6.58 (dd, J_1=15 Hz, J_2=8 Hz, 1H, 5^2-C*H*), 7.23–7.30 (m, 2H, phenyl-*H*), 7.49–7.61 (m, 6H, phenyl-*H*), 8.77 (d, J=5 Hz, 2H, β-pyrrole-*H*), 8.83 (d, J=5 Hz, 2H, β-pyrrole-*H*), 8.97 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.21 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.55 (d, J=15 Hz, 1H, 5^1-C*H*), 9.60 (s, 1H, *meso-H*), 10.01 ppm (d, J=8 Hz, 1H, 5^3-C*H*O); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.46, 106.31, 108.85, 113.62, 119.21, 119.72, 126.59, 127.91, 130.47, 132.76, 133.77, 140.91, 141.46, 141.49, 141.67, 142.35, 142.99,

151.66, 158.26, 191.97 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=313 (4.25), 370 (4.16), 427 (5.18), 538 (4.03), 584 nm (3.95); MS (EI, 80 eV, >300 °C), *m/z* (%): 632 (55) [M^+], 630 (100) [M^+-2H], 602 (50) [M^+-CH_2O, 523 (14) [$M^+-2H-C_7H_7O$], 495 (15) [$M^+-CH_2O-C_7H_7O$], 315 (9) [$(M\text{-}2H)^{2+}$]; MS (FAB+, CH_2Cl_2/*m*-NO_2-Bzl-OH/Xe), *m/z* (%): 633 (1) [$(M+H)^+$]; HRMS (EI) [$C_{37}H_{26}N_4NiO_3$]: calcd 632.13584, found 632.13579; [$C_{37}H_{26}N_4NiO_3$, 633.33 g mol^{-1}]: calcd C 70.17, H 4.14, N 8.85, found C 69.75, H 3.97, N 9.26.

4.8.4. [5,15-Bis(4-butyloxyphenyl)-10,20-bis(2-formylethenyl)porphyrinato]nickel(II) (72). Obtained in trace amounts during the synthesis of [5,15-bis(4-butyloxyphenyl)-10-(2-formylethenyl)porphyrinato]nickel(II) **69** (Section 4.8.1): ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.02 (t, *J*=7 Hz, 6H, $OCH_2CH_2CH_2CH_3$), 1.52–1.65 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.88 (m, 4H, $OCH_2CH_2CH_2CH_3$), 4.13 (t, *J*=7 Hz, 4H, $OCH_2CH_2CH_2CH_3$), 6.52 (dd, J_1=15 Hz, J_2=8 Hz, 1H, 10^2-*H*), 7.12 (m, 4H, phenyl-*H*), 7.72 (m, 4H, phenyl-*H*), 8.66 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.12 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.42 (d, *J*=15 Hz, 1H, 10^1-*H*), 9.96 ppm (d, *J*=8 Hz, 1H, 10^3-C*H*O); MS (EI, 80 eV, 320 °C), *m/z* (%): 770 (100) [M^+], 742 (40) [M^+-CO], 714 (38) [$M^+-2\times CO$]; HRMS (EI) [$C_{46}H_{40}N_4NiO_4$]: calcd 770.24030, found 578.25138.

4.8.5. [5,15-Bis(2-formylethenyl)-10,20-bis(4-pentyloxyphenyl)porphyrinato]nickel(II) (63). Obtained in traces during the synthesis of [5-(2-formylethenyl)-10,20-bis(4-pentyloxyphenyl)porphyrinato]nickel(II) **70** (Section 4.8.2). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.00 (t, *J*=7 Hz, 6H, $OCH_2CH_2CH_2CH_2CH_3$), 1.43–1.66 (m, 8H, $OCH_2CH_2CH_2CH_2CH_3$ and $OCH_2CH_2CH_2CH_2CH_3$), 1.95 (m, 4H, $OCH_2CH_2CH_2CH_2CH_3$), 4.18 (t, *J*=7 Hz, 4H, $OCH_2CH_2CH_2CH_2CH_3$), 6.57 (dd, J_1=15 Hz, J_2=8 Hz, 2H, 10^2-*H*), 7.17 (m, 4H, phenyl-*H*), 7.77 (m, 4H, phenyl-*H*), 8.71 (d, *J*=5 Hz, 4H, β-pyrrole-*H*), 9.17 (d, *J*=5 Hz, 4H, β-pyrrole-*H*), 9.48 (d, *J*=15 Hz, 1H, 10^1-*H*), 10.00 ppm (d, *J*=8 Hz, 2H, 10^3-C*H*O); HRMS (EI) [$C_{48}H_{44}N_4NiO_4$]: calcd 798.27160, found 578.27377.

4.8.6. [5,15-Bis(2-formylethenyl)-10,20-bis(3-methoxyphenyl)porphyrinato]nickel(II) (74). Obtained in traces during the synthesis of [5-(2-formylethenyl)-10,20-bis(3-methoxyphenyl)porphyrinato]nickel(II) **71** (Section 4.8.3). ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.95 (s, 6H, OCH_3), 6.63 (dd, 1H, J_{2-3}=15.4 Hz, J_{1-2}=7.7 Hz, –CH=C*H*–CHO), 7.25–7.30 (m, 2H, phenyl-*H*), 7.46 (m, 2H, phenyl-*H*), 7.52–7.64 (m, 4H, phenyl-*H*), 8.79 (d, 4H, J_{4-5}=5.2 Hz, β-pyrrole-*H* 2), 9.25 (d, 4H, J_{4-5}=5.2 Hz, β-pyrrole-*H* 3), 9.57 (d, 1H, J_{2-3}=15.4 Hz, –C*H*=CH–CHO), 10.08 (d, 1H, J_{1-2}=7.7 Hz, -C*H*O).

4.8.7. [5-(2-Formylethenyl)-10,15,20-tris(3-methoxyphenyl)porphyrinato]nickel(II) (75). 3-(Dimethylamino)-acrolein (600 μL, 6 mmol) together with 6 mL of dry dichloromethane were placed in a 100 mL three-necked flask equipped with magnetic stirrer and gas inlet. The flask was cooled in an ice bath. Then, 600 μL (6.4 mmol) of $POCl_3$ were added dropwise via a syringe under argon. At first, a white precipitate was formed on addition of the phosphoroxytrichloride, which dissolves again on further addition of the reagent. At the end a viscous, red-brown solution was formed which was stirred for 15 min at 0 °C. This solution was then transferred to a second flask (also cooled in an ice bath) containing 100 mg (0.15 mmol) [5,10,15-tris(3-methoxyphenyl)porphyrinato]nickel(II) **42** dissolved in 100 mL of dry dichloromethane. Further conditions and workup were similar to those given in Section 4.8.3. Yield 80 mg (0.11 mmol, 72%) of purple-green crystals: mp 163 °C; R_f=0.6 (CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.90 (s, 3H, OCH_3), 3.92 (s, 6H, OCH_3), 6.66 (dd, J_1=15 Hz, J_2=8 Hz, 1H, 5^2-C*H*), 7.18–7.28 (m, 3H, phenyl-*H*), 7.45–7.50 (m, 3H, phenyl-*H*), 7.51–7.62 (m, 6H, phenyl-*H*), 8.66 (m [AB-spectrum], 4H, β-pyrrole-*H*), 8.85 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.29 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.45 (d, *J*=15 Hz, 1H, 5^1-C*H*), 10.07 (d, *J*=8 Hz, 1H, 5^3-C*H*O); ^{13}C NMR (60 MHz, $CDCl_3$): δ=55.46, 108.44, 113.72, 119.56, 119.62, 119.76, 120.86, 126.53, 127.89, 127.97, 130.80, 132.43, 133.01, 134.06, 141.40, 141.47, 142.23, 143.03, 151.45, 158.30, 192.03 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=315 (4.18), 434 (5.14), 548 (3.99), 593 nm (3.94); MS (EI, 80 eV, 350 °C), *m/z* (%): 738 (58) [M^+], 736 (100) [M^+-2H], 708 (36) [M^+-CH_2O], 629 (9) [$M^+-2H-C_7H_7O$)], 601 (11) [$M^+-CH_2O-C_7H_7O$)], 368 (11) [$(M-2H)^{2+}$]; MS (FAB+, CH_2Cl_2/*m*-NO_2-Bzl-OH/Xe), *m/z* (%)=739 (1) [$(M+H)^+$]; HRMS (EI) [$C_{44}H_{32}N_4NiO_4$]: calcd 738.17770, found 738.17779.

4.8.8. [5,15-Bis(3,5-dimethoxyphenyl)-10-(2-formylethenyl)-20-hexylporphyrinato]nickel(II) (76). Reaction of 3-dimethylaminoacrolein (1.2 mL, 12 mmol) in 12 mL of dry dichloromethane, 1.2 mL (12.8 mmol) $POCl_3$, and 240 mg (0.33 mmol) [5,15-bis(3,5-dimethoxyphenyl)-10-hexylporphyrinato]nickel(II) **43** dissolved in 200 mL of dry dichloromethane as described in Section 4.8.1. Yield 140 mg (0.18 mmol, 55%) of green-purple crystals: mp 223 °C; R_f=0.58 (CH_2Cl_2/$CH_3C(O)OCH_2CH_3$, 95:5, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/0.05% CH_3OH, v/v, flow: 2 mL/min, detection at 420 nm) retention time: 11.39 min (100%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.88 (t, *J*=7 Hz, 3H, 15^6-CH_3), 1.23–145 (m, 4H, 15^5- and 15^4-CH_2), 1.54 (m, 2H, 15^3-CH_2), 2.22 (m, 2H, 15^2-CH_2), 3.93 (s, 12H, OCH_3), 4.48 (t, *J*=7 Hz, 2H, 15^1-CH_2), 6.63 (dd, J_1=15 Hz, J_2=8 Hz, 1H, 5^2-C*H*), 6.83 (m, 2H, phenyl-H_{para}), 7.14 (m, 4H, phenyl-H_{ortho}), 8.76 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 8.86 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.19 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.25 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.58 (d, *J*=15 Hz, 1H, 5^1-C*H*), 10.01 ppm (d, *J*=8 Hz, 1H, 5^3-C*H*O); ^{13}C NMR (60 MHz, $CDCl_3$): δ=13.96, 22.50, 29.86, 31.61, 33.99, 37.15, 55.49, 100.09, 107.52, 112.67, 119.21, 121.58, 130.24, 130.62, 132.57, 134.00, 140.56, 140.78, 141.48, 141.84, 141.96, 142.13, 151.29, 153.26, 158.26, 159.20, 191.98 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=320 (4.26), 437 (5.22), 555 (4.01), 598 nm (4.00); MS (EI, 80 eV, 280 °C), *m/z* (%): 776 (100) [M^+], 748 (31) [M^+-CO], 705 (31) [$M^+-C_5H_{11}$], 677 (23) [$M^+-CO-C_5H_{11}$], 662 (8) [$M^+-CO-CH_3-C_5H_{11}$], 639 (7) [$M^+-C_8H_9O_2$], 568 (3) [$M^+-C_8H_9O_2-C_5H_{11}$], 388 (6) [M^{2+}]; HRMS (EI) [$C_{45}H_{42}N_4NiO_5$]: calcd 776.25087, found 776.25433; [$C_{45}H_{42}N_4NiO_5$, 777.54 g mol^{-1}]. Anal. Calcd C 69.51, H 5.44, N 7.21, found C 69.50, H 5.15, N 7.02.

4.9. Alkynyl substituted porphyrins

4.9.1. 5-(3,5-Dimethoxyphenyl)-15-hexyl-10,20-diiodoporphyrin (77). 5-(3,5-Dimethoxyphenyl)-5-hexylporphyrin **24** (53 mg, 0.1 mmol) was dissolved in 80 mL of dry chloroform under argon. Iodine (36 mg, 0.14 mmol) and 4 drops of pyridine were added, followed by 42 mg (0.1 mmol) of [bis(trifluoroacetoxy)iodo]benzene. The reaction flask was then shielded from ambient light and the reaction mixture was stirred for 48 h at 20 °C, followed by filtration through silica (40 g), washing with dichloromethane. The filtrate was evaporated to dryness. The recovered solvent was red-colored, due to the presence of unreacted iodine. The product was purified by column chromatography on silica (3×60 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. The diiodinated porphyrin was isolated as the first fraction, as the second fraction a small amount of the monoiodinated porphyrin **78** (Section 4.9.2). The title porphyrin was dissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of hexane. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield: 60 mg (0.077 mmol; 77%) of purple crystals: mp 204 °C; R_f=0.86 (CH_2Cl_2/*n*-hexane, 3:1, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: C_6H_{14}/CH_2Cl_2, 75:25, v/v, flow: 1 mL/min, detection at 420 nm) retention time: 3.66 min (95.9%), (same conditions but detection at 254 nm) retention time 3.01 min (97.9%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.89 (s, br., 2H, N*H*), 0.92 (t, J=7 Hz, 3H, 5^6-CH_3), 1.31–1.51 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.75 (m, 2H, 5^3-CH_2), 2.37 (m, 2H, 5^2-CH_2), 3.96 (s, 6H, OCH_3), 4.67 (t, J=8 Hz, 2H, 5^1-CH_2), 6.89 (m, 1H, phenyl-H_{para}), 7.30 (m, 2H, phenyl-H_{ortho}), 8.82 (d, J=4 Hz, 2H, β-pyrrole-*H*), 9.24 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.53 (d, J=4 Hz, 2H, β-pyrrole-*H*), 9.57 ppm (d, J=5 Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.09, 22.67, 30.17, 31.80, 35.55, 38.96, 55.63, 100.21, 113.87, 120.31, 122.36, 143.31, 158.87 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=295 (4.28), 378 (4.40), 407 (4.89), 426 (5.58), 494 (3.63), 526 (4.18), 562 (4.13), 605 (3.63), 664 nm (3.87); MS (EI, 80 eV, 270 °C), *m/z* (%): 782 (2) [M^+], 711 (1) [$M^+-C_5H_{11}$], 656 (4) [M^+-I], 530 (100) [$M^+-2\times I$], 459 (66) [$M^+-2\times I-C_5H_{11}$], 265 (10) [$(M-2\times I)^{2+}$]; MS (FAB+, CH_2Cl_2/*m*-NO_2-Bzl-OH/Xe), *m/z* (%): 783 (6) [$(M+H)^+$], 711 (2) [$M^+-C_5H_{11}$], 656 (2) [M^+-I], 585 (1) [$M^+-I-C_5H_{11}$], 530 (0.4) [$M^+-2\times I$]; HRMS (EI) [$C_{34}H_{32}I_2N_4O_2$] calcd 782.06148, found 782.06445; [$C_{34}H_{32}I_2N_4O_2$, 782.46 g mol^{-1}]. Anal. Calcd C 52.17, H 4.12, N 7.16, found C 52.38, H 4.39, N 7.45.

4.9.2. 5-(3,5-Dimethoxyphenyl)-15-hexyl-10-iodoporphyrin (78). Obtained in traces during the synthesis of 5-(3,5-dimethoxyphenyl)-15-hexyl-10,20-diiodoporphyrin **77** (Section 4.9.1). R_f=0.77 (CH_2Cl_2/*n*-hexane, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.22 (s, br., 2H, N*H*), 0.93 (t, J=7 Hz, 3H, 5^6-CH_3), 1.31–1.51 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.77 (m, 2H, 5^3-CH_2), 2.42 (m, 2H, 5^2-CH_2), 3.97 (s, 6H, OCH_3), 4.75 (t, J=8 Hz, 2H, 5^1-CH_2), 6.92 (m, 1H, phenyl-H_{para}), 7.38 (m, 2H, phenyl-H_{ortho}), 8.98 (m, 2H, β-pyrrole-*H*), 9.17 (m, 2H, β-pyrrole-*H*), 9.33 (m, 2H, β-pyrrole-*H*), 9.71 (m, 2H, β-pyrrole-*H*), 9.94 ppm (s, 1H, *meso*-*H*).

4.9.3. 5,15-Bis(3,5-dimethoxyphenyl)-10-hexyl-20-iodoporphyrin (79). 5,15-Bis(3,5-dimethoxyphenyl)-10-hexylporphyrin **32** (134 mg, 0.2 mmol) was dissolved in 160 mL of dry chloroform under argon and treated with iodine (72 mg, 0.28 mmol), 8 drops of pyridine, and 84 mg (0.2 mmol) of [bis(trifluoroacetoxy)iodo]benzene. The reaction flask was then shielded from ambient light and the reaction mixture was stirred for 48 h at 20 °C. The reaction mixture was filtered through silica (40 g), washing with dichloromethane. The recovered solvent was red-colored, due to the presence of unreacted iodine. The filtrate was evaporated to dryness and the residue was purified by column chromatography on silica (3×50 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. After evaporation of the solvent, the porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of hexane. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit, dried in vacuo and yielded 100 mg (0.13 mmol; 63%) of green-purple microcrystals: mp 251 °C; R_f=0.43 (CH_2Cl_2/*n*-hexane, 3:1, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/0.1% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm), retention time: 3.01 min (98.1%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.67 (s, br., 2H, N*H*), 0.91 (t, J=7 Hz, 3H, 5^6-CH_3), 1.38 (m, 2H, 5^5-CH_2), 1.50 (m, 2H, 5^4-CH_2), 1.78 (m, 2H, 5^3-CH_2), 2.49 (m, 2H, 5^2-CH_2), 3.96 (s, 12H, OCH_3), 4.91 (t, J=8 Hz, 2H, 5^1-CH_2), 6.91 (m, 2H, phenyl-H_{para}), 7.35 (m, 4H, phenyl-H_{ortho}), 8.90 (d, J=5 Hz, 2H, β-pyrrole-*H*), 8.94 (d, J=4 Hz, 2H, β-pyrrole-*H*), 9.40 (d, J=4 Hz, 2H, β-pyrrole-*H*), 9.57 ppm (d, J=5 Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.12, 22.69, 30.22, 31.87, 35.44, 38.77, 55.63, 100.19, 113.84, 119.99, 121.98, 143.97, 158.79 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=306 (4.20), 380 (4.38), 407 (4.93), 424 (5.56), 485 (3.68), 521 (4.24), 556 (3.97), 597 (3.74), 654 nm (3.63); MS (EI, 80 eV, 270 °C), *m/z* (%): 792 (12) [M^+], 666 (100) [M^+-I], 595 (38) [$M^+-I-C_5H_{11}$], 333 (12) [$(M-I)^{2+}$]; MS (FAB+, CH_2Cl_2/*m*-NO_2-Bzl-OH/Xe), *m/z* (%): 793 (100) [$(M+H)^+$], 721 (25) [$M^+-C_5H_{11}$], 667 (11) [$(M+H)^+-I$], 595 (11) [$M^+-I-C_5H_{11}$]; HRMS (EI) [$C_{42}H_{41}IN_4O_4$]: calcd 792.21726, found 792.21924; [$C_{42}H_{41}IN_4O_4$, 792.72 g mol^{-1}]. Anal. Calcd C 63.64, H 5.21, N 7.07, [$C_{42}H_{41}IN_4O_4\cdot\frac{1}{2}H_2O$]: C 62.92, H 5.28, N 6.99, found C 62.66, H 4.94, N 6.65.

4.9.4. [5,15-Bis-(3,5-dimethoxyphenyl)-10-hexyl-20-iodoporphyrinato]zinc(II) (80). The corresponding free base porphyrin **79** (90 mg, 0.11 mmol) was dissolved in 70 mL of dichloromethane and treated with a solution of zinc(II) acetate (230 mg, 1.25 mmol) in methanol. The mixture was stirred until the reaction was complete (TLC control, dichloromethane/*n*-hexane, 3:1, v/v, approximately 15 min). The reaction mixture was transferred to a separatory funnel and washed with water (3×100 mL). The organic phase was filtered through 100 g of silica, washing with dichloromethane, and then evaporated to dryness. The residue was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of hexane. After 24 h, the precipitated dark-purple microcrystals were removed by suction filtration through a D3 frit and dried in vacuo to yield 90 mg (0.105 mmol, 95%) of the zinc(II) complex: mp >280 °C (dec.); R_f=0.42 (CH_2Cl_2); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2, flow: 1 mL/

min, detection at 420 nm) retention time: 4.86 min (99.8%), (same conditions but detection at 254 nm) retention time: 4.93 min (100%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.92 (t, J=7 Hz, 3H, 5^6-CH_3), 1.28–1.56 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.82 (m, 2H, 5^3-CH_2), 2.52 (m, 2H, 5^2-CH_2), 3.93 (s, 12H, OCH_3), 4.95 (t, J=7 Hz, 2H, 5^1-CH_2), 6.86 (m, 2H, phenyl-H_{para}), 7.33 (m, 4H, phenyl-H_{ortho}), 8.99 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.03 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.51 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.70 ppm (d, J=5 Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.12, 22.71, 30.35, 31.90, 35.83, 39.04, 55.62, 100.12, 113.81, 120.97, 122.88, 129.32, 132.59, 133.48, 137.50, 144.39, 149.73, 150.56, 150.63, 152. 33, 158.75 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=312 (4.19), 350 (4.02), 406 (4.63), 424 (5.60), 518 (3.38), 554 (4.29), 592 nm (3.61); MS (EI, 80 eV, 305 °C), *m/z* (%): 854 (26) [M^+], 783 (18) [$M^+-C_5H_{11}$], 728 (100) [M^+-I], 657 (89) [$M^+-I-C_5H_{11}$], 364 (4) [$(M-I)^{2+}$]; HRMS (EI) [$C_{42}H_{39}IN_4O_4Zn$]: calcd 854.13063, found 854.13021.

4.9.5. [5,15-Bis(3,5-dimethoxyphenyl)-10-(hept-1-ynyl)-20-hexylporphyrinato]zinc(II) (81). [5,15-Bis(3,5-dimethoxyphenyl)-10-hexyl-20-iodoporphyrinato]zinc(II) **80** (28 mg, 0.033 mmol) was dissolved in 20 mL of dry THF (filtered through basic alumina) under argon. Copper(I) iodide (6 mg, 0.032 mmol), dichlorobis(triphenylphosphine)palladium(II) (3 mg, 0.0042 mmol), triethylamine (50 μL, 0.3 mmol), and 1-heptyne (50 μL, 0.38 mmol) were added and the reaction mixture was stirred for 18 h at 20 °C in the dark. The reaction mixture was filtered through silica (50 g), washed with dichloromethane and the filtrate evaporated to dryness. The product was purified by column chromatography on silica (3×50 cm) using dichloromethane/*n*-hexane (3:1, v/v), as eluent. First a small non-uniform red fraction (according to TLC) was obtained whose NMR-spectrum showed complicated multiplets for the porphyrin β-protons and inequivalent methoxy groups, suggesting the presence of phenyl-ring substituted products. The alkyne-substituted porphyrin was obtained as the second fraction. After evaporation of the solvent the porphyrin was redissolved in as little dichloromethane as possible and then layered with a 2–3-fold excess of hexane. After 24 h, the precipitated solid was removed by suction filtration through a D3 frit and dried in vacuo to yield 18 mg (0.022 mmol; 67%) of green-purple microcrystals: mp 274 °C; R_f=0.49 (CH_2Cl_2); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/0.1% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm) retention time: 3.41 min (100%), (same conditions but detection at 254 nm) retention time: 3.48 min (100%); ^{1}H NMR (250 MHz, $CDCl_3$): δ=0.92 (t, J=7 Hz, 3H, 15^6-CH_3), 1.05 (t, J=7 Hz, 3H, 5^7-CH_3), 1.32–1.64 (m, 6H, 15^4-CH_2, 15^5-CH_2, and 5^6-CH_2), 1.81 (m, 4H, 15^3-CH_2 and 5^5-CH_2), 2.04 (m, 2H, 5^4-CH_2), 2.53 (m, 2H, 15^2-CH_2), 2.99 (t, J=7 Hz, 2H, 5^3-CH_2), 3.95 (s, 12H, OCH_3), 4.97 (t, J=8 Hz, 2H, 15^1-CH_2), 6.87 (m, 2H, phenyl-H_{para}), 7.36 (m, 4H, phenyl-H_{ortho}), 9.01 (m, 4H, β-pyrrole-*H*), 9.49 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.65 ppm (d, J=5 Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.14, 20.50, 22.46, 22.73, 28.99, 30.38, 31.58, 31.93, 35.86, 38.99, 55.64, 82.88, 97.21, 100.11, 113.72, 120.77, 122.88, 128.98, 130.95, 132.14, 132.52, 144.62, 149.24, 149.56, 150.14, 152.81, 158.83 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=311 (4.22), 348 (4.05), 409 (4.69), 428 (5.60), 432 (5.55), 523 (3.60), 562 (4.29), 598 nm (4.03); MS (EI, 80 eV, 300 °C), *m/z* (%): 822 (19) [M^+], 751 (6) [$M^+-C_5H_{11}$], 694 (1) [$M^+-C_4H_9$], 411 (1) [M^{2+}], 44 (100) [CO_2^+]; HRMS (EI) [$C_{49}H_{50}N_4O_4Zn$]: calcd 822.31235, found 822.31567.

4.9.6. 5,15-Bis(3,5-dimethoxyphenyl)-10-(hept-1-ynyl)-20-hexylporphyrin (82). The zinc(II) complex of 5,15-bis(3,5-dimethoxyphenyl)-10-hexyl-20-iodoporphyrin **80** (28 mg, 0.033 mmol) was dissolved in 20 mL of dry THF (filtered through basic alumina) under argon and initially reacted using the conditions and reagents given in Section 4.9.5. The product fraction was evaporated to dryness, dissolved again in 15 mL of dichloromethane, 13 drops of TFA were added (from a 1 mL syringe) and the mixture was stirred for 2 min. After this time, 20 mL of water were added and the mixture was transferred to a separatory funnel. The phases were separated and the organic phase was washed with water (2×15 mL), saturated sodium bicarbonate solution (1×15 mL), and again with water (1×15 mL). The organic phase was dried over sodium sulfate and then evaporated to dryness, followed by chromatography on silica (2×30 cm) using dichloromethane/*n*-hexane (3:1, v/v) as eluent. The eluted porphyrin fraction was evaporated to dryness, recrystallized from dichloromethane/hexane, removed by suction filtration through a D3 frit and dried in vacuo to yield 12 mg (0.016 mmol; 50%) of green-purple microcrystals. Alternatively, the present free base can be obtained from the respective zinc(II) complex **81** by stirring with TFA for a few minutes in quantitative yield: mp 217 °C; R_f=0.45 (CH_2Cl_2/*n*-hexane, 3:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.39 (s, br., 2H, N*H*), 0.97 (t, J=7 Hz, 3H, 15^6-CH_3), 1.11 (t, J=7 Hz, 3H, 5^7-CH_3), 1.33–1.70 (m, 6H, 15^4-CH_2, 15^5-CH_2, and 5^6-CH_2), 1.86 (m, 4H, 15^3-CH_2 and 5^5-CH_2), 2.10 (m, 2H, 5^4-CH_2), 2.55 (m, 2H, 15^2-CH_2), 3.05 (t, J=7 Hz, 2H, 5^3-CH_2), 4.02 (s, 12H, OCH_3), 4.99 (t, J=8 Hz, 2H, 15^1-CH_2), 6.95 (m, 2H, phenyl-H_{para}), 7.41 (m, 4H, phenyl-H_{ortho}), 8.96 (m, 4H, β-pyrrole-*H*), 9.44 (d, J=5 Hz, 2H, β-pyrrole-*H*), 9.60 ppm (d, J=5 Hz, 2H, β-pyrrole-*H*); MS (EI, 80 eV, 305 °C), *m/z* (%): 760 (100) [M^+], 689 (44) [$M^+-C_5H_{11}$], 380 (4) [M^{2+}]; HRMS (EI) [$C_{49}H_{52}N_4O_4$]: calcd 760.39886, found 760.39827.

4.10. Preparation of hydroxyphenyl porphyrins

4.10.1. 5,15-Bis(3-hydroxyphenyl)porphyrin (83). 5,15-Bis(3-methoxyphenyl)porphyrin **12** (100 mg, 0.19 mmol) was suspended in 150 mL of dry dichloromethane in a three-necked flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 25 mL-dropping funnel. The mixture was cooled to −50 °C. The flask was shielded from ambient light and the dropping funnel was charged with 7 mL (7 mmol) of a 1 M solution of boron tribromide. The BBr_3 solution was added dropwise to the porphyrin solution over a period of approximately 15 min. Then, the reaction mixture was stirred for 18 h and slowly warmed to 20 °C. After this time, the reaction mixture was cooled again to −30 °C and 3 mL of an acetone/water-mixture (2:1, v/v) were added dropwise. The mixture was slowly warmed to 20 °C and then 10 g of sodium bicarbonate were added. The mixture was stirred for 2 h until it changed its color from green to red. Then, 0.5 mL of triethylamine and 10 g of

anhydrous sodium sulfate were added and the mixture was stirred for 18 h at 20 °C. After this time, the mixture was filtered. Despite intensive washing, a large amount of the deprotected porphyrin could not be isolated due its extremely low solubility. The isolated porphyrin was finally purified by column chromatography on silica (3×40 cm) using dichloromethane/methanol (10:1, v/v) as eluent to yield 20 mg (0.04 mmol; 21%) of a purple amorphous solid: mp >340 °C; R_f=0.49 (CH_2Cl_2/CH_3OH, 9:1, v/v); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−3.12 (s, 1H, N*H*), 7.35 (m, 1H, phenyl-*H*), 7.67 (m, 1H, phenyl-*H*), 7.75 (m, 2H, phenyl-*H*), 9.14 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.57 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.54 (s, 2H, *meso-H*); UV/vis (CH_2Cl_2):[37] λ_{max} (rel. int.)=365 (0.11), 389 (0.26), 406 (1.00), 503 (0.06), 536 (0.03), 574 (0.02), 631 (0.01); MS (EI, 80 eV, 310 °C), *m/z* (%): 494 (100) [M^+], 477 (2) [M^+−17 (OH)], 401 (2) [M^+−93 (C_6H_5O)], 247 (11) [M^{2+}]; HRMS (EI) [$C_{32}H_{22}N_4O_2$]: calcd 494.17428, found 494.17743.

4.10.2. 5-Hexyl-15-(3-hydroxyphenyl)porphyrin (84). 5-Hexyl-15-(3-methoxyphenyl)porphyrin **22** (100 mg, 0.2 mmol) was dissolved in 90 mL of dry dichloromethane in a three-necked-flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 25 mL-dropping funnel. The mixture was cooled to −50 °C. The flask was shielded from ambient light and the dropping funnel was charged with 3.6 mL (3.6 mmol) of a 1 M solution of boron tribromide. The boron tribromide solution was added dropwise to the porphyrin solution over a period of approximately 5 min. Then, the reaction mixture was stirred for 18 h and slowly warmed to 20 °C. After this time, the reaction mixture was cooled again to −30 °C and 3 mL of an acetone/water-mixture (2:1, v/v) were added dropwise. The mixture was slowly warmed to 20 °C and then 10 g of sodium bicarbonate were added. The mixture was stirred for 2 h until it changed color from green to red. Then, 0.5 mL of triethylamine and 10 g of anhydrous sodium sulfate were added and the mixture was stirred for 18 h at 20 °C. After this time, the mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved again in a mixture of acetic acid ethylester and water (2:1, v/v). The organic phase was washed with brine (1×50 mL), and with water (2×50 mL). The organic phase was dried over anhydrous sodium sulfate and then evaporated to dryness. Final purification was achieved by column chromatography on silica (3×40 cm) using dichloromethane/methanol (10:1, v/v) as eluent. Yield: 80 mg (0.16 mmol; 83%) of a purple, amorphous solid; mp 193 °C; R_f=0.15 (SiO_2, CH_2Cl_2/CH_3OH, 9:1, v/v), 0.41 (CH_2Cl_2); ^{1}H NMR (250 MHz, acetone-d_6): δ=−3.03 (s, 2H, N*H*), 0.89 (t, *J*=7 Hz, 3H, 5^6-CH_3), 1.38 (m, 2H, 5^5-CH_2), 1.52 (m, 2H, 5^4-CH_2), 1.83 (m, 2H, 5^3-CH_2), 2.56 (m, 2H, 5^2-CH_2), 5.11 (t, *J*=8 Hz, 2H, 5^1-CH_2), 7.31 (m, 1H, phenyl-*H*), 7.60–7.74 (m, 3H, phenyl-*H*), 9.00 (s, br., 1H, O*H*), 9.06 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.49 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.57 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.78 ppm (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.41 (s, 2H, 10- and 20-*meso-H*); ^{13}C NMR (60 MHz, acetone-d_6): δ=14.33, 23.37, ∼30 (superposition with solvent signal), 32.65, 35.12, 39.73, 105.67, 115.77, 119.04, 120.69, 123.02, 127.33, 128.87, 129.25, 131.35, 132.84, 133.08, 143.34, 145.67, 148.05, 148.27, 157.20 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=301 (4.13), 364 (4.38), 3.88 (4.87), 406 (5.47), 474 (3.33), 503 (4.16), 536 (3.62), 576 (3.65), 631 nm (3.05); MS (EI, 80 eV, 250 °C), *m/z* (%): 486 (100) [M^+], 415 (97) [M^+−71 (C_5H_{11})], 243 (5) [M^{2+}]; HRMS (EI) [$C_{32}H_{30}N_4O$]: calcd 486.24196, found 486.24533.

4.10.3. 5,10,15-Tris(3-hydroxyphenyl)porphyrin (85). 5,10,15-Tris(3-methoxyphenyl)porphyrin **30** (105 mg, 0.17 mmol) was dissolved in 90 mL of dry dichloromethane in a three-necked flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 25 mL-dropping funnel. The mixture was cooled to −50 °C. The flask was shielded from ambient light and the dropping funnel was charged with 9 mL (9 mmol) of a 1 M solution of boron tribromide. The BBr_3 solution was added dropwise to the porphyrin solution over a period of approximately 15 min. Then, the reaction mixture was stirred for 18 h and slowly warmed to 20 °C. After this time, the reaction mixture was cooled again to −30 °C and 3 mL of an acetone/water-mixture (2:1, v/v) were added dropwise. The mixture was slowly warmed to 20 °C and then 10 g of sodium bicarbonate were added. The mixture was stirred for 2 h until it changed its color from green to red, followed by addition of 0.5 mL of triethylamine and 10 g of anhydrous sodium sulfate and stirring for 18 h at 20 °C. After this time, the mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved again in a mixture of acetic acid ethylester and water (2:1, v/v). The organic phase was washed with brine (1×50 mL), and with water (2×50 mL). The organic phase was dried over anhydrous sodium sulfate and then evaporated to dryness. Final purification was achieved by column chromatography on silica (3×40 cm) using dichloromethane/methanol (10:1, v/v) to yield 80 mg (0.14 mmol; 81%) of a purple amorphous solid: mp 233–235 °C; R_f=0.29 (CH_2Cl_2/CH_3OH, 9:1, v/v); ^{1}H NMR (250 MHz, acetone-d_6): δ=−3.02 (s, 2H, N*H*), 7.33 (m, 3H, phenyl-*H*), 7.58–7.75 (m, 9H, phenyl-*H*), 8.97 (m [AB-spectrum], 4H, β-pyrrole-*H*), 9.07 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.51 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 10.44 ppm (s, 1H, 20-*meso-H*); ^{13}C NMR (60 MHz, acetone-d_6): δ=115.87, 120.40, 121.25, 122.94, 127.27, 128.41, 128.70, ∼132, 143.73, 144.54, 156.73, 156.98 ppm; UV/vis (CH_2Cl_2): λ_{max} (log εlog ε)=371 (4.18), 392 (4.58), 413 (5.29), 480 (3.27), 508 (3.95), 542 (3.41), 581 (3.44), 637 nm (3.01); MS (EI, 80 eV, 320 °C), *m/z* (%): 586 (100) [M^+], 569 (1) [M^+−OH], 493 (1) [M^+−C_6H_5O], 293 (12) [M^{2+}]; HRMS (EI) [$C_{38}H_{26}N_4O_3$]: calcd 586.20049, found 586.20001.

4.10.4. 5-Hexyl-10,20-bis(3-hydroxyphenyl)porphyrin (86). 5-Hexyl-10,20-bis(3-methoxyphenyl)porphyrin **32** (100 mg, 0.16 mmol) was dissolved in 90 mL of dry dichloromethane in a three-necked flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 25 mL-dropping funnel. The mixture was cooled to −50 °C. The flask was shielded from ambient light and the dropping funnel was charged with 6 mL (6 mmol) of a 1 M solution of boron tribromide. The BBr_3 solution was added dropwise to the porphyrin solution over a period of approximately 15 min. Further conditions and purification as described in Section 4.10.3 to yield 80 mg (0.14 mmol; 84%) of a purple amorphous solid: mp 169 °C; R_f=0.64 (CH_2Cl_2/CH_3OH, 9:1, v/v); ^{1}H NMR (250 MHz, acetone-d_6): δ=−3.02 (s,

2H, N*H*), 0.86 (t, $J=7$ Hz, 3H, 5^6-CH_3), 1.30–1.52 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.83 (m, 2H, 5^3-CH_2), 2.51 (m, 2H, 5^2-CH_2), 5.06 (t, $J=8$ Hz, 2H, 5^1-CH_2), 7.32 (m, 2H, phenyl-*H*), 7.58–7.72 (m, 6H, phenyl-*H*), 8.99 (m [AB-spectrum], 6H, β-pyrrole-*H* and 2O*H*), 9.38 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.66 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 10.25 ppm (s, 1H, 15-*meso*-*H*); ^{13}C NMR (60 MHz, acetone-d_6): $\delta=14.13$, 23.34, ~30 (superposition with solvent signal), 32.61, 36.24, 40.00, 104.97, 115.81, 119.79, 122.09, 122.91, 127.22, 128.62, 129.49, 132.08, 144.03, ~147, 156.90 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.13), 372 (4.37), 395 (4.95), 413 (5.54), 480 (3.47), 509 (4.22), 543 (3.70), 584 (3.67), 640 nm (3.36); MS (EI, 80 eV, 315 °C), *m/z* (%): 578 (100) [M^+], 521 (2) [$M^+-C_4H_9$], 507 (95) [$M^+-C_5H_{11}$], 289 (10) [M^{2+}]; HRMS (EI) [$C_{38}H_{34}N_4O_2$]: calcd 578.26818, found 578.26434.

4.10.5. 5,10,15-(3-Hydroxyphenyl)-20-pentylporphyrin (87). 5,10,15-Tris(3-methoxyphenyl)-20-pentylporphyrin **45** (120 mg, 0.17 mmol) was dissolved in 90 mL of dry dichloromethane in a three-necked-flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 25 mL-dropping funnel. The mixture was cooled to −50 °C. The flask was shielded from ambient light and the dropping funnel was charged with 9 mL (9 mmol) of a 1 M solution of boron tribromide. Further conditions and purification as described in Section 4.10.3 to yield 95 mg (0.14 mmol; 85%) of a purple amorphous solid: mp 201 °C; $R_f=0.43$ (CH_2Cl_2/CH_3OH, 9:1, v/v); ^{1}H NMR (250 MHz, acetone-d_6): $\delta=-2.74$ (s, 2H, N*H*), 0.93 (t, $J=7$ Hz, 3H, 20^5-CH_3), 1.51 (m, 2H, 20^4-CH_2), 1.79 (m, 2H, 20^3-CH_2), 2.52 (m, 2H, 20^2-CH_2), 5.01 (t, $J=8$ Hz, 2H, 20^1-CH_2), 7.27–7.34 (m, 3H, phenyl-*H*), 7.55–7.72 (m, 9H, phenyl-*H*), 8.88 (s, 4H, β-pyrrole-*H*), 8.96 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.05 (br s, 3H, O*H*), 9.63 ppm (d, $J=5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, acetone-d_6): $\delta=14.37$, 23.40, 33.27, 35.79, 39.52, 115.79, 120.07, 120.32, 121.70, 122.80, 127.11, 128.49, ~129, ~132, 144.06, 144.41, 156.79, 156.87; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.20), 374 (4.38), 401 (4.89), 418 (5.62), 482 (3.49), 515 (4.26), 550 (3.86), 591 (3.67), 647 nm (3.60); MS (EI, 80 eV, 310 °C), *m/z* (%): 656 (83) [M^+], 599 (70) [$M^+-C_4H_9$], 328 (11) [M^{2+}], 172 (100); HRMS (EI) [$C_{43}H_{36}N_4O_3$]: calcd 656.27874, found 656.27630.

4.10.6. 5-Hexyl-10,15,20-tris(3-hydroxyphenyl)-porphyrin (88). Reaction, workup and chromatography using 5-hexyl-10,15,20-tris(3-methoxyphenyl)porphyrin **51** (120 mg, 0.17 mmol) as described in Section 4.10.5 gave 100 mg (0.15 mmol; 89%) of the title compound as a purple amorphous solid: mp 150–151 °C; $R_f=0.43$ (CH_2Cl_2/CH_3OH, 9:1, v/v); ^{1}H NMR (250 MHz, acetone-d_6): $\delta=-2.73$ (s, 2H, N*H*), 0.86 (t, $J=7$ Hz, 3H, 5^6-CH_3), 1.22–1.41 (m, 4H, 5^5-CH_2 and 5^4-CH_2), 1.76 (m, 2H, 5^3-CH_2), 2.47 (m, 2H, 5^2-CH_2), 4.94 (t, $J=8$ Hz, 2H, 5^1-CH_2), 7.26–7.34 (m, 3H, phenyl-*H*), 7.54–7.75 (m, 9H, phenyl-*H*), 8.88 (s, 4H, β-pyrrole-*H*), 8.95 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.03 (br s, 3H, O*H*), 9.58 ppm (d, $J=5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, acetone-d_6): $\delta=14.30$, 23.30, ~30 (superposition with solvent signal), 32.57, 35.78, 39.75, 115.78, 120.05, 120.30, 121.68, 122.80, 127.09, 128.47, 129.19, 131.48, 144.04, 144.39, 156.77, 156.85 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (3.73), 374 (3.92), 399 (4.44), 418 (5.18), 483 (3.10), 515 (3.79), 550 (3.43), 591 (3.28), 647 nm (3.15); MS (EI, 80 eV, 300 °C), *m/z* (%): 670 (100) [M^+], 599 (50) [$M^+-C_5H_{11}$], 335 (8) [M^{2+}]; HRMS (EI) [$C_{44}H_{38}N_4O_3$]: calcd 670.29439, found 670.29493.

4.10.7. 5-Heptyl-10,15,20-tris(3-hydroxyphenyl)-porphyrin (89). Reaction, workup and chromatography using 5-heptyl-10,15,20-tris(3-methoxyphenyl)porphyrin **56** (125 mg, 0.17 mmol) as described in Section 4.10.5 yielded 100 mg of the title compound as a purple amorphous solid (0.15 mmol; 86%): mp 180 °C; $R_f=0.48$ (CH_2Cl_2/CH_3OH, 9:1, v/v); ^{1}H NMR (250 MHz, acetone-d_6): $\delta=-2.74$ (s, 2H, N*H*), 0.85 (t, $J=7$ Hz, 3H, 5^7-CH_3), 1.25–1.37 (m, 4H, 5^6-CH_2 and 5^5-CH_2), 1.50 (m, 2H, 5^4-CH_2), 1.81 (m, 2H, 5^3-CH_2), 2.53 (m, 2H, 5^2-CH_2), 5.04 (t, $J=8$ Hz, 2H, 5^1-CH_2), 7.27–7.34 (m, 3H, phenyl-*H*), 7.55–7.72 (m, 9H, phenyl-*H*), 8.88 (s, 4H, β-pyrrole-*H*), 8.96 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.04 (s, br., 3H, O*H*), 9.65 ppm (d, $J=5$ Hz, 2H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, acetone-d_6): $\delta=14.26$, 23.29, ~30 (superposition with solvent signal), 31.04, 32.61, 35.84, 39.85, 115.79, 120.05, 120.30, 121.70, 122.79, 127.08, 128.48, 129.14, 131.77, 144.02, 144.38, 156.73, 156.87 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=303 (4.12), 374 (4.34), 401 (4.85), 418 (5.57), 483 (3.48), 515 (4.22), 550 (3.82), 591 (3.67), 647 nm (3.57); MS (EI, 80 eV, 340 °C), *m/z* (%): 684 (100) [M^+], 599 (66) [$M^+-C_6H_{13}$], 342 (8) [M^{2+}]; HRMS (EI) [$C_{45}H_{40}N_4O_3$]: calcd 684.31004, found 684.31433.

4.10.8. 5,10,15-Trihexyl-20-(3-hydroxyphenyl)porphyrin (90). 5,10,15-Trihexyl-20-(3-methoxyphenyl)porphyrin **53** (100 mg, 0.15 mmol) was dissolved in 60 mL of dry dichloromethane in a three-necked flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 25 mL-dropping funnel. The mixture was cooled to −50 °C. The flask was shielded from ambient light and the dropping funnel was charged with 2.7 mL (2.7 mmol) of a 1 M solution of boron tribromide. The BBr_3 solution was added dropwise to the porphyrin solution over a period of approximately 5 min. Then, the reaction mixture was stirred for 18 h and slowly warmed to 20 °C. After this time the reaction mixture was cooled again to −30 °C and 3 mL of an acetone/water-mixture (2:1, v/v) were added dropwise. The mixture was slowly warmed to 20 °C and 50 mL of water were added. The phases were separated and the organic phase was washed with water (1×50 mL), saturated sodium bicarbonate solution (1×50 mL), brine (2×50 mL), and again with water (1×50 mL). The organic phase was dried over anhydrous sodium sulfate and then evaporated to dryness. Final purification was achieved by column chromatography on silica (3×60 cm) using dichloromethane as eluent to yield 90 mg (0.14 mmol; 92%) of a purple amorphous solid: mp 84 °C; $R_f=0.21$ (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta=-2.73$ (s, br., 2H, N*H*), 0.93 (m, 9H, 5^6-, 10^6-, and 15^6-CH_3), 1.29–1.58 (m, 12H, 5^5-, 10^5-, and 15^5-CH_2, 5^4-, 10^4-, and 15^4-CH_2), 1.77 (m, 6H, 5^3-, 10^3-, and 15^3-CH_2), 2.50 (m, 6H, 5^2-, 10^2-, and 15^2-CH_2), 4.89 (m, 6H, 5^1-, 10^1-, and 15^1-CH_2), 7.13 (m, 1H, phenyl-*H*), 7.39 (m, 1H, phenyl-*H*), 7.51 (m, 1H, phenyl-*H*), 7.69 (m, 1H, phenyl-*H*), 8.76 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.31 (d, $J=5$ Hz, 2H, β-pyrrole-*H*), 9.46 ppm (m [AB-spectrum], 4H, β-pyrrole-*H*); ^{13}C NMR (60 MHz,

$CDCl_3$): δ=14.14, 14.16, 22.72, 22.76, 30.22, 30.31, 31.90, 31.93, 35.38, 35.78, 38.65, 38.85, 114.46, 117.24, 119.11, 119.50, 121.62, 127.47, 127.51, 143.96, 153.73 ppm; UV/vis (CH_2Cl_2): λ_{max} (log ε)=350 (4.19), 367 (4.27), 398 (4.80), 418 (5.53), 485 (3.53), 518 (4.14), 553 (3.90), 597 (3.60), 654 nm (3.75); MS (EI, 80 eV, 250 °C), *m/z* (%): 654 (100) [M^+], 583 (35) [$M^+-C_5H_{11}$], 512 (2) [$M^+-(2\times C_5H_{11})$], 327 (6) [M^{2+}]; HRMS (EI) [$C_{44}H_{54}N_4O$]: calcd 654.42976, found 654.42657.

4.10.9. 5,10,15-Triheptyl-20-(3-hydroxyphenyl)-porphyrin (91). Reaction, workup and chromatography using 5,10,15-triheptyl-20-(3-methoxyphenyl)porphyrin **58** (100 mg, 0.14 mmol) as described in Section 4.10.8 yielded 85 mg of the title compound as a purple amorphous solid (0.12 mmol; 87%): mp 98 °C; R_f=0.25 (CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$): δ=−2.70 (s, 2H, N*H*), 0.91 (m, 9H, 5^7-, 10^7-, and 15^7-CH_3), 1.30–1.39 (m, 12H, 5^6-, 10^6-, and 15^6-CH_2, 5^5-, 10^5-, and 15^5-CH_2), 1.50 (m, 6H, 5^4-, 10^4-, and 15^4-CH_2), 1.76 (m, 6H, 5^3-, 10^3-, and 15^3-CH_2), 2.49 (m, 6H, 5^2-, 10^2-, and 15^2-CH_2), 4.93 (m, 6H, 5^1-, 10^1-, and 15^1-CH_2), 7.17 (m, 1H, phenyl-*H*), 7.47 (m, 1H, phenyl-*H*), 7.53 (m, 1H, phenyl-*H*), 7.70 (m, 1H, phenyl-*H*), 8.78 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.33 (d, *J*=5 Hz, 2H, β-pyrrole-*H*), 9.48 (m [AB-spectrum], 4H, β-pyrrole-*H*); ^{13}C NMR (60 MHz, $CDCl_3$): δ=14.10, 22.70, 29.39, 30.54, 30.62, 31.92, 35.41, 35.82, 38.69, 38.90, 114.52, 117.21, 119.14, 119.54, 121.74, 127.60, ~128, 131.14, 144.14, 153.78; UV/vis (CH_2Cl_2): λ_{max} (log ε)=350 (4.34), 365 (4.40), 401 (4.93), 418 (5.59), 483 (3.49), 518 (4.21), 552 (3.97), 597 (3.69), 655 nm (3.79); MS (EI, 80 eV, 300 °C), *m/z* (%): 696 (100) [M^+], 611 (26) [$M^+-C_6H_{13}$], 348 (8) [M^{2+}]; HRMS (EI) [$C_{47}H_{60}N_4O$]: calcd 696.47671, found 696.47937.

4.10.10. 5,10,15,20-Tetrakis(3-hydroxyphenyl)porphyrin (92).[38] *Modified literature procedure*. 5,10,15,20-Tetrakis(3-methoxyphenyl)porphyrin (400 mg, 0.54 mmol) was dissolved in 200 mL of dry dichloromethane in a three-necked flask equipped with magnetic stirrer, gas inlet (argon), drying tube, and a 100 mL dropping funnel. The mixture was cooled to −50 °C and the flask shielded from ambient light. The dropping funnel was charged with 70 mL (70 mmol) of a 1 M solution of boron tribromide and this was added dropwise to the porphyrin solution over a period of approximately 1 h. The reaction mixture was stirred for 18 h and slowly warmed to room temperature. Subsequently, the reaction mixture was cooled again to −30 °C and 5 mL of an acetone/water mixture (4.5:1) were added dropwise. The mixture was slowly warmed to 20 °C and treated with 25 g of sodium bicarbonate. The mixture was stirred for 3 h until its color changed from green to red. After addition of 2 mL of triethylamine and 25 g of anhydrous sodium sulfate the mixture was stirred for 18 h at 20 °C, filtered and the filtrate evaporated to dryness. The residue was redissolved in a mixture of acetic acid ethylester and water (2:1). The organic phase was washed with brine (2×100 mL), sodium bicarbonate solution (2×100 mL), and with water (2×100 mL), dried over anhydrous sodium sulfate and then evaporated to dryness. to yield 330 mg (0.49 mmol; 90%) of a purple amorphous solid: R_f=0.37 (CH_2Cl_2/CH_3OH, 9:1, v/v); HPLC: (Nucleosil 50, 5 μm, eluent: CH_2Cl_2/10% CH_3OH, v/v, flow: 1 mL/min, detection at 420 nm) retention time: 3.57 min (91.8%), (same conditions but detection at 254 nm) retention time: 3.64 min (90.7%); the ^{1}H NMR was identical with that given in the literature; ^{13}C NMR (60 MHz, acetone-d_6): δ=115.86, 120.91, 122.82, 127.13, 128.57, 131.86, 144.10, 156.83; MS (EI, 80 eV, 320 °C), *m/z* (%): 678 (100) [M^+], 585 (1) [$M^+-C_6H_5O$], 339 (9) [M^{2+}]; HRMS (EI) [$C_{44}H_{30}N_4O_4$]: calcd 678.22677, found 678.22845.

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Versatile strategies for the solid phase synthesis of small heterocyclic scaffolds: [1,3,4]-thiadiazoles and [1,3,4]-oxadiazoles

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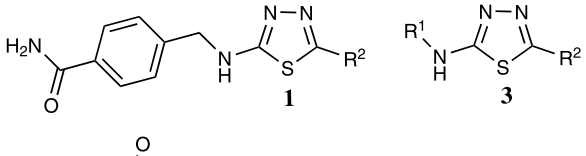
Abstract—New robust protocols for the solid phase synthesis of 5-alkylthio-, 5-alkyl/aryl-, and 5-acylamino-2-alkylamino-[1,3,4]-thiadiazoles are described based on a common resin bound thiosemicarbazide. A protocol for the solid phase synthesis of 2-alkyl/aryl-amino-5-alkylamino-[1,3,4]-oxadiazoles from a resin bound semicarbazide is likewise reported. The protocols have been verified by the preparation of four small libraries that all gave products in good to excellent yields and purity.

1. Introduction

Parallel synthesis has over the last 20 years evolved into a well established and essential medicinal chemist's tool for the rapid preparation of screening libraries as well as accelerating the lead optimization process.[1] Initially screening libraries were designed with focus on diversity and number of compounds,[2] but later Lipinski invited awareness towards the importance of their 'drug-like' physiochemical properties.[3] More recently the concept of 'lead-like' was introduced by Teague et al.[4,5] They investigated a number of drugs and their corresponding leads and found that size and lipophilicity in general increases through the lead-optimization process. Based on these findings they suggest that screening libraries should consist of lead-like compounds with physiochemical properties in the range $M_w < 350$ and $1 < c \log P < 3$.



In recent publications we have described several novel solid phase synthesis strategies for the preparation of [1,3,4]-thiadiazoles[6] **1** and [1,3,4]-oxadiazoles[7] **2**. However, the reported strategies proceeded with the aid of a relatively large 'spacer' and thus the products were inapplicable in the context of lead-like criteria and investigations were thus directed towards reducing the generic scaffold size. In this communication we would like to present both new and revised solid phase synthesis strategies for the formation of substituted [1,3,4]-thiadiazoles **3** and [1,3,4]-oxadiazoles **4**.

2. Results and discussion

An obvious attachment point to a solid support for thiadiazole **3** and oxadiazole **4** is the secondary heteroarylamine. One possible approach for such an attachment is to use a backbone amide linker (BAL)[8] either as a di- or a trialkoxybenzyl amine. In general the resin bound tertiary amines formed when employing such resins do not undergo acidolytic cleavage. However, a few examples are known where substituted anilines[9] or aminothiazoles[10] have been released under acidic conditions. Due to the heteroaromatic character of the thiadiazole- and oxadiazole amines we expected that these would undergo acidolytic cleavage.

Hence, the commercially available 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene[11] was treated with a range of primary amines under standard reductive amination conditions to yield the respective resin bound benzyl amine derivates **5** as depicted in Scheme 1. In our previous paper we reported the transformation of a resin bound primary amine to an isothiocyanate upon treatment with di-(2-pyridyl)-thionocarbonate (DPT).[6] The

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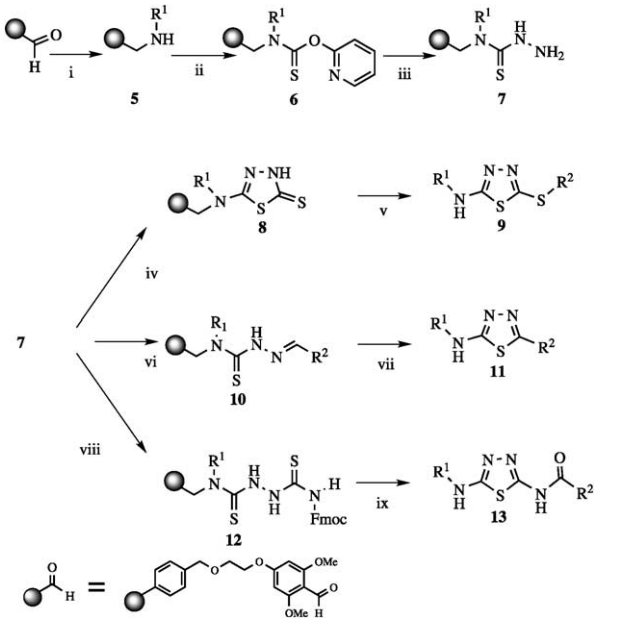


Scheme 1. Reagents and condition. (i) (a) R^1NH_2, 5% AcOH, NMP/MeOH, 1 h; (b) $NaBH_3CN$, NMP/MeOH, 12 h; (ii) DPT, NMP, 50 °C, 16 h; (iii) $H_2NNH_2 \cdot H_2O$, DMSO, 50 °C 14 h; (iv) DPT, DCM, 3 h; (v) (a) 1,4-dioxane/MeOH/$NaOH_{aq}$ (1 N), 30 min; (b) R^2Br, 1,4-dioxane, 14 h; (c) TFA/DCM, 2 h (vi) R^2CHO, TMOF/NMP, (2+14) h; (vii) (a) $FeCl_3$, DCM/MeOH, (2+14) h; (b) TFA/DCM, 2 h; (viii) FmocNCS, DCM, DIPEA, 14 h; (ix) (a) EDC, NMP, 50 °C, 14 h; (b) DMF/piperidine (2+20) min; (c) R^2COOH, DIIC, DMAP, DIPEA, NMP/DCM; (d) TFA/DCM, 2 h.

isothiocyanate was subsequently reacted with hydrazine to give a thiosemicarbazide.

In this approach, where the immobilized secondary amine has to be converted to the thiosemicarbazide **7**, the intermediate can not be an isothiocyanate. It has been reported that secondary amines react with DPT to give the corresponding 2-pyridyl thiocarbamates.[12] However, the conversion of this to a thiosemicarbazide by treatment with a hydrazine has to our knowledge not been reported and therefore reaction conditions for this transformation had to be developed.

The immobilized amines **5** were treated with DPT under a range of conditions to investigate the formation of the reactive species **6**. A small amount of resin **6** was cleaved with TFA/DCM (50:50) but due to lack of stability of the intermediate released from resin **6** under the cleavage conditions the reaction could not be monitored directly. Instead the reaction was investigated by treatment of resin **6** with hydrazine hydrate and monitoring the formation of thiosemicarbazide **7** by cleavage of a small amount of the resin with TFA/DCM (50:50). LC–MS analysis was performed on the crude residue. When applying the conditions we previously developed for conversion of a resin bound primary amine to a thiosemicarbazide only minimal conversion was observed. Replacing the solvent with 1,3-dichloropropane (DCP) and heating to 50 °C did not improve the result. However, when the reaction was performed in *N*-methyl-2-pyrrolidinone (NMP) for 16 h, almost complete conversion was suggested as interpreted by a negative chloranil test result. The resin bound benzyl-

Table 1. Conditions used to convert resin bound benzyl amine **5a** into benzyl-thiocarbamic acid *O*-pyridin-2-yl ester **6a**

Reagents and conditions	% Purity **7a**		
	20 °C	50 °C	80 °C
5 equiv DPT in DCM	20	—	—
5 equiv DPT in DCP	0	20	—
5 equiv DPT in DMSO	16	57	10
5 equiv DPT in NMP	15	85	73
10 equiv DPT in NMP	22	95	71

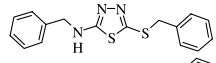
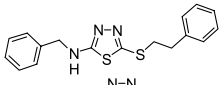
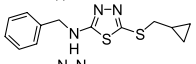
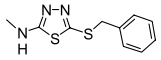
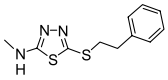
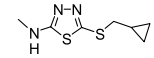
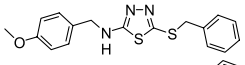
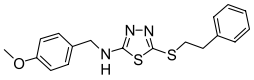
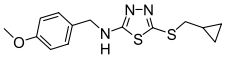
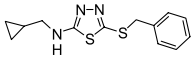
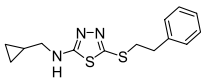
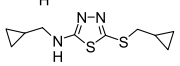
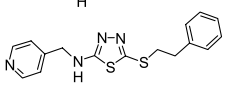
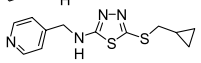
All reactions were run for 12 h. Results are given as percentage purity of the corresponding formation of **7a** (LC–MS, UV peak integration at 214 nm).

thiocarbamic acid *O*-pyridin-2-yl ester **6** was subsequently substituted by treatment with hydrazine in DMSO at 50 °C to form the pivotal thiosemicarbazide **7**. The results are given in Table 1.

Thiosemicarbazide **7** is a versatile intermediate and several derivatisations leading to heterocyclic systems could be imagined from this intermediate. As depicted in Scheme 1 we have investigated three different transformations of thiosemicarbazide **7** to substituted [1,3,4]-thiadiazoles.

Resin bound thiosemicarbazide **7** was treated with 10 equiv DPT in DCM to give immobilized thione **8**.[6] Alkylation of

Table 2. Representative results and structures from the library of 2-alkylthio-5-alkylamino-[1,3,4]-thiadiazoles (**9**)

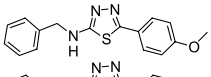
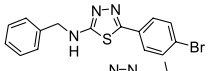
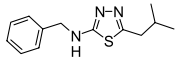
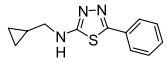
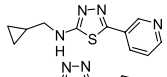
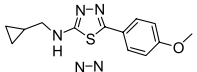
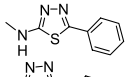
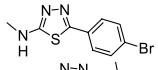
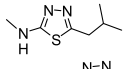
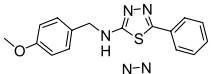
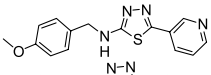
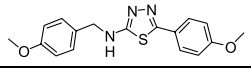
		Purity (%)	Yield (%)
9a[13]		70	65
9b		70	60
9c		70	56
9d[14]		95	72
9e		95	50
9f		90	81
9g		90	71
9h		95	82
9i		90	78
9j		90	73
9k		90	72
9l		60	45
9m		90	64
9n		90	58

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.

thione **8** with primary alkyl- or benzyl bromides in 1,4-dioxane yielded a mixture *N*- and *S*-alkylated products. Applying DIPEA in the alkylation procedure did not improve the selectivity for S-alkylation. However, when the resin was treated with a mixture of 1,4-dioxane, methanol and aqueous sodium hydroxide prior to alkylation, only S-alkylation was observed. Employing this procedure thione **8** was treated with a range of alkylating agents to give the corresponding monoalkylated products. Subsequent cleavage with TFA/DCM yielded [1,3,4]-thiadiazoles **9**. The results are given in Table 2.

Intermediate resin bound thiosemicarbazide **7**, was an ideal starting point for the synthesis of substituted 5-alkyl-[1,3,4]thiadiazol-2-yl amines **11**. The formation of imine **10** by reaction with aldehydes was therefore investigated. Treatment with aldehydes in a mixture of trimethyl orthoformate (TMOF), NMP and acetic acid (5:5:1) yielded a mixture of products. When applying the same conditions in the absence of acid, the intermediate resin bound thiosemicarbazone **10** was formed. Cyclization of **10** was achieved by treating the resin with a solution of iron(III) chloride in DCM/MeOH.[6] Subsequent cleavage with TFA/DCM yielded substituted 5-alkyl-[1,3,4]thiadiazol-2-yl amines **11**. The results are given in Table 3.

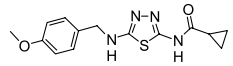
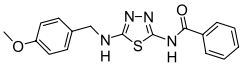
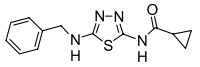
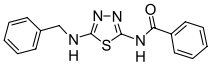
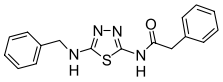
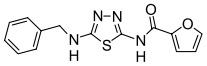
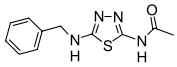
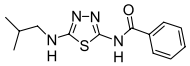
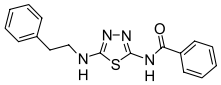
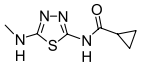
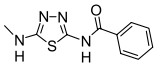
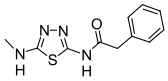
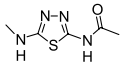
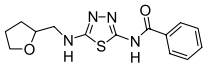
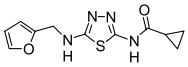
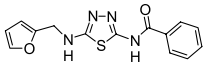
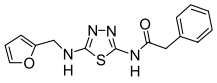
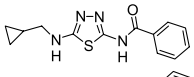
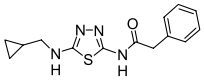
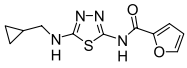
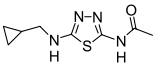
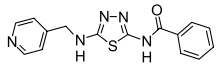
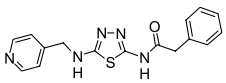
Table 3. Representative results and structures from the library of substituted 5-alkyl-[1,3,4]thiadiazol-2-yl amines (**11**)

		Purity (%)	Yield (%)
11a		95	73
11b		91	69
11c[15]		86	72
11d		98	61
11e		81	65
11f		65	47
11g		92	70
11h		98	71
11i		99	76
11j		99	73
11k		98	66
11l		95	61

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.

The chemistry discussed above yields substituted 5-thio-1,3,4-thiadiazoles **9** and substituted 5-alkyl-1,3,4-thiadiazoles **11**. As a continuation of this work we sought to synthesize substituted 5-carboxamide-1,3,4-thiadiazoles **13**. To our knowledge, a solid phase synthesis of this scaffold

Table 4. Representative results and structures from the library of *N*-(5-alkylamino-[1,3,4]thiadiazol-2-yl)-amide (**13**)

		Purity (%)	Yield (%)
13a		95	63
13b		91	73
13c		82	59
13d[16]		78	65
13e[16]		90	71
13f		90	80
13g		89	64
13h		85	60
13i		87	86
13j		90	74
13k		94	75
13l		90	71
13m		70	71
13n		90	49
13o		67	51
13p		72	43
13q		59	48
13r		96	72
13s		95	66
13t		61	31
13u		70	59
13v		90	66
13x		95	85

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.

has never been reported. Treatment of thiosemicarbazide **7** with a mixture of fmoc-isothiocyanate and DIPEA in DCM yielded resin bound hydrazine-1,2-dicarbothioamide **12**. A range of different conditions were applied in an attempt to cyclizise intermediate **12** as shown in Table 5. 1,3-Diisopropyl carbodiimide (DIIC) in dry DMSO or NMP resulted only in partial cyclization. A mixture of triphenylphosphine and hexachloroethane in dry THF gave good conversion, but the reagent generated acidic conditions resulting in partial resin cleavage. Addition of DIPEA to minimize cleavage resulted in incomplete cyclization. However, treating the resin with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) in DMSO at 80 °C gave almost complete conversion and good yield, similarly EDC·HCl in NMP gave complete conversion and good yield at 50 °C. The latter procedure was chosen for cyclization in the library synthesis due to the lower temperature associated with NMP as the solvent. Immobilized 5-fmoc-amino-1,3,4-thiadiazoles were subsequently deprotected with 20% piperidine in NMP. The resulting 5-amino-1,3,4-thiadiazoles were then acylated with different carboxylic acids using DIIC in DCM/NMP. Cleavage with TFA/DCM yielded substituted 5-carboxamide-1,3,4-thiadiazoles **13**. A small library based on this protocol was prepared. The results are given in Table 4.

Encouraged by the results obtained with the [1,3,4]-thiadiazole scaffolds we decided to investigate the possibility of preparing the analogous [1,3,4]-oxadiazole derivative **16** (Scheme 2). Hence, a resin bound amine **5** was treated with triphosgene and DIPEA in DCM, followed by reaction of the formed reactive intermediate with hydrazine hydrate in DMSO to yield semicarbazide intermediate **14**.

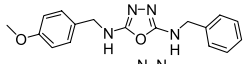
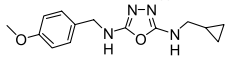
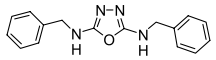
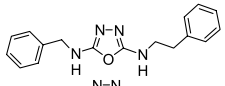
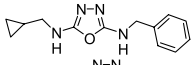
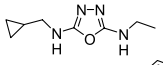
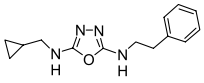
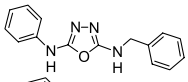
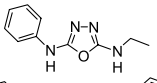
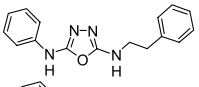
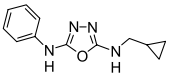
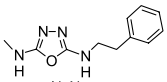
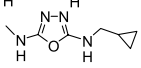
Subsequent addition of various thiocyanates under basic conditions gave the substituted thiobisurea **15**. Again, a range of conditions for the cyclization were investigated. The results are given in Table 5. As for the cyclization of **12**, EDC·HCl in dry NMP were the preferred reaction conditions to convert resin bound **15** into 2,5-diamino-1,3,4-oxadiazole **16**. Cleavage was realized upon treatment with TFA/DCM. The developed protocol was used to generate a small library of substituted 2,5-diamino-1,3,4-oxadiazoles **16**. The results are displayed in Table 6.

Table 5. Selected results for the cyclization of **12** and for the cyclization of **15**

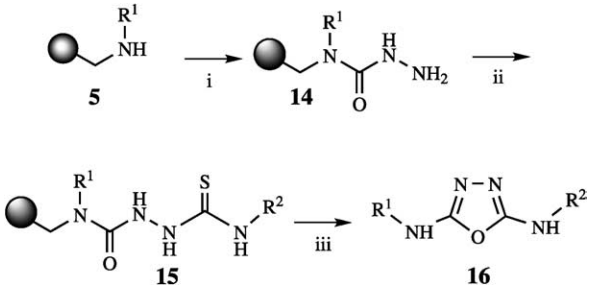
	Reagents and conditions	Cyclization of **12** (%)	Cyclization of **15** (%)
1	DIIC in dry NMP (20 °C)	25	0
2	DIIC in dry NMP (80 °C)	63	33
3	DIIC in dry DMSO (80 °C)	12	5
4	PPh_3 and C_2Cl_6 in THF (20 °C)	95	67
5	PPh_3 and C_2Cl_6 in THF/DIPEA (20 °C)	42	23
6	EDC·HCl in dry DMSO (50 °C)	71	54
7	EDC·HCl in dry DMSO (80 °C)	96	89
8	EDC·HCl in dry NMP (50 °C)	99	97

Results are given as percentage purity of product determined by using LC–MS of the crude cleavage product (UV peak integration at 214 nm). All reactions were run over 14 h.

Table 6. Representative results and structures from library of *N*,*N*-dialkyl-[1,3,4]oxadiazoles-2,5-diamine (**16**)

		Purity (%)	Yield (%)
16a		95	81
16b		95	76
16c		90	73
16d		95	83
16e		83	73
16f		75	58
16g		90	60
16h[17]		95	85
16i[17]		95	87
16j		95	81
16k		95	89
16l		95	72
16m		95	65

Purity is determined by LC–MS of the crude cleavage product (UV peak integration at 214 nm) and yield is determined by NMR with internal reference.



Scheme 2. Reagent and conditions. (i) (a) $CO(OCCl_3)_2$, DIPEA, DCM, 5 h; (b) $H_2NNH_2 \cdot H_2O$, DMSO, 14 h; (ii) R^2NCS; DCM, DIPEA, 6 h; (iii) (a) EDC·HCl, dry NMP, 50 °C, 14 h, (b) TFA/DCM, 2 h.

3. Conclusion

In conclusion, we have studied and developed four new versatile solid phase synthesis protocols for the preparation of 'lead-like' substituted [1,3,4]-oxadiazoles and [1,3,4]-thiadiazoles. Treating the highly applicable resin bound thiosemicarbazide with a variety of reagents and conditions yielded, after TFA-mediated cleavage, 5-alkylthio-, 5-alkyl, and 5-acylamino-2-alkylamino-[1,3,4]-thiadiazoles in good yield and purity. In another investigation resin

bound semicarbazide was treated with isothiocyanates and the resulting intermediates after cyclodehydration and TFA-mediated cleavage yielded substituted 2,5-dialkyl-amino-[1,3,4]-oxadiazoles in good yield and purity.

4. Experimental

4.1. General

All reactions where performed in standard glassware or Teflon apparatus suitable for solid-phase synthesis. Starting materials were commercially available and used without further purification. 2-(3,5-Dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene, (200–400 mesh, polystyrene-divinylbenzene 1%, 0.45 mmol/g) was purchased from Novabiochem. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 spectrometer. Chemical shifts (δ) are given in parts per million (ppm) and are relative to TMS as internal standard. Coupling constants are given in Hertz (J values in Hz). The following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet, dd = double of doublets. IR spectra were recorded on a FT/IR Perkin–Elmer spectrometer, model Spectrum one. Electrospray (ES) mass spectra and LC–MS analyses were recorded on a PE Sciex API 3000 instrument with an HP1100 HPLC equipped with binary pump, column compartment, diode array detector, single quadrupole mass spectrometer detector and a C18 column ((Waters Xterra MS C-18X) 3 mm) at 40 °C with a flow of 1.0 mL/min. Two mobile phases (mobile phase A, 100% water, 0.01% TFA; mobile phase B, 100% acetonitrile, 0.01% TFA) were employed to run a gradient condition from 10–100% B in 7.5 min with UV detection at 210 nm and MS scanning range from 100–1000 amu. Injections of 1 μL were used. Unless stated, all reactions were carried out at 20 °C and washing was performed at a ratio of 1 mL solvent per 100 mg resin. Unless stated, reactions were monitored by cleaving small portion of the resin and analyzing the crude cleavage product on LC–MS. Yields were determined by NMR studies using 2,5-dimethyl-furan as internal standard.

4.2. General procedure for reductive amination of 2-(3,5-dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene (5)

Typical procedure. A solution of benzyl amine (480 mg, 4.50 mmol) in NMP/MeOH/AcOH (10 mL, 5:5:1 v/v) was added to 2-(3,5-dimethoxy-4-formylphenoxy) ethoxymethyl polystyrene resin (1.0 g, 0.45 mmol) pre-swollen in NMP. The mixture was agitated for 30 min before a solution of $NaBH_3CN$ (422 mg, 6.75 mmol) in MeOH/NMP (10 mL, 1:1 v/v) was added. The mixture was shaken for a further 18 h. Excess reagents were removed by filtration and the resin was washed with NMP (3×), MeOH/THF (1:1 v/v) (2×) and DCM (3×). The resin was dried in vacuo overnight at 40 °C.

4.3. Formation of thiosemicarbazide (7)

Typical procedure. A solution of DPT (1.04 g, 4.50 mmol) in dry NMP (15 mL) was added to resin **5** (1.0 g, 0.45 mmol) and the mixture was shaken for 12 h at 50 °C. The resin was filtered before washing with DMSO (3×). A solution of hydrazine hydrate (216 mg, 4.50 mmol) in DMSO (15 mL) was added and the resin was then agitated 14 h at 50 °C before excess reagent was removed by filtration. The resin was washed with DMSO (3×), MeOH/THF (1:1 v/v) (2×), and DCM (3×).

4.4. Synthesis of 5-amino-3H-1,3,4-thiadiazole-2-thione (8)

A solution of DPT (97 mg, 0.42 mmol) in DCM (3 mL) was added to a portion of resin **7** (100 mg, 0.042 mmol). The mixture was agitated for 3 h before excess reagent was removed by filtration and washing using NMP (3×) and DCM (3×).

4.5. Formation of 2-alkylthio-5-alkylamino-[1,3,4]-thiadiazole (9) and resin cleavage

Typical procedure. Resin **8** (100 mg, 0.042 mmol) pre-swollen in 1,4-dioxane was treated with a mixture of 1,4-dioxane/MeOH/$NaOH_{(aq)}$(1 N) (2 mL, 7:3:1, v/v) for 30 min, before a solution of benzylbromide (22 mg, 0.126 mmol) in 1,4-dioxane (3 mL) was added. The resin was agitated 14 h, filtered to remove excess reagents and washed with NMP (3×), MeOH/THF (1:1 v/v) (2×) and DCM (3×). The resin was subsequently cleaved with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding the title compounds **9**.

4.5.1. Benzyl-(5-benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9a). White solid, mp 95.2–95.9 °C; ν_{max} (KBr) 703, 1027, 1092, 1207, 1357, 1426, 1452, 1479, 1547, 3029, 3248 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 4.30 (s, 2H, PhCH_2S), 4.40 (d, J = 5.2 Hz, 2H, PhCH_2NH), 7.33 (m, 10H, ArH), 8.29 (t, J = 5.2 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 38.7 (SCH_2), 48.2 (NHCH_2), 127.5, 127.8, 127.9, 128.7, 128.8, 129.4, 137.4, 138.8, 150.0, 169.9 (ArC). HR-MS (Q-TOF-ES) m/z = 314.0780, calcd for $[C_{33}H_{34}N_4OS + H]^+$ 314.0785.

4.5.2. Benzyl-(5-phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9b). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ = 2.92 (t, J = 7.5 Hz, 2H, PhCH_2CH_2S), 3.31 (t, J = 7.5 Hz, 2H, PhCH_2CH_2S), 4.47 (d, J = 4.9 Hz, 2H, PhCH_2-NH), 7.26 (m, 6H, ArH), 7.35 (d, J = 4.3 Hz, 4H, ArH), 8.31 (t, J = 4.9 Hz, 1H, PhCH_2NH). ES-MS m/z 328 MH^+.

4.5.3. Benzyl-(5-cyclopropylmethylsulfanyl-1,3,4] thiadiazol-2-yl)-amine (9c). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ = 0.25 (m, 2H, CH(CH_2CH_2)), 0.51 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH_2CH_2)), 3.02 (d, J = 7.1, 2H, SCH_2cPr), 4.46 (d, J = 5.6 Hz, 2H, PhCH_2NH), 7.29 (m, 1H, ArH), 7.34 (d, J = 4 Hz, 4H, ArH), 8.29 (t, J = 5.6 Hz, 1H, PhCH_2NH). ES-MS m/z 278 MH^+.

4.5.4. (5-Benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-methyl-amine (9d).[14] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.83 (d, J=3.9 Hz, 3H, CH_3NH), 4.30 (s, 2H, SCH_2Ph), 7.32 (m, 5H, ArH), 7.71 (q, J=3.9 Hz, 1H, CH$_3$NH). ES-MS m/z 238 MH$^+$.

4.5.5. Methyl-(5-phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9e). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.86 (d, J=4.8 Hz, 2H, CH_3NH), 2.94 (t, J=7.6 Hz, 2H, PhCH_2CH$_2$), 3.31 (t, J=7.6, 2H, PhCH$_2$CH_2), 7.26 (m, 5H, ArH), 7.74 (q, J=4.8 Hz, 1H, CH$_3$NH). ES-MS m/z 252 MH$^+$.

4.5.6. (5-Cyclopropylmethylsulfanyl-[1,3,4]thiadiazol-2-yl)-methyl-amine (9f). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.26 (m, 2H, CH(CH_2CH_2)), 0.53 (m, 2H, CH(CH_2CH_2)), 1.05 (m, 1H, CH(CH$_2$CH$_2$)), 2.85 (d, J=4.7 Hz, 3H, CH_3NH), 3.01 (d, J=7.0 Hz, SCH_2), 7.71 (q, J=4.7 Hz, 1H, NH). ES-MS m/z 202 MH$^+$.

4.5.7. (5-Benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-(4-methoxy-benzyl)-amine (9g). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.73 (s, 3H, CH_3O), 4.30 (s, 2H, SCH_2Ph), 4.35 (d, J=5.5 Hz, 2H, CH_2NH), 6.89 (d, J=6.6 Hz, 2H ArH), 7.30 (m, 7H, ArH), 8.21 (t, J=5.5 Hz, NH). ES-MS m/z 344 MH$^+$.

4.5.8. (4-Methoxy-benzyl)-(5-phenethylsulfanyl-1,3,4]thiadiazol-2-yl)-amine (9h). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.94 (t, J=7.6 Hz, 2H, PhCH_2CH$_2$), 3.31 (t, J=7.5 Hz, 2H, PhCH$_2$CH_2), 3.73 (s, 3H, CH_3O), 4.38 (d, J=5.6 Hz, 2H, CH_2NH), 6.91 (d, J=8.6 Hz, 2H, ArH), 7.25 (m, 7H, ArH), 8.23 (t, J=5.6 Hz, 1H, NH). ES-MS m/z 358 MH$^+$.

4.5.9. (5-Cyclopropylmethylsulfanyl-[1,3,4]thiadiazol-2-yl)-(4-methoxy-benzyl)-amine (9i). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.26 (m, 2H, CH(CH_2CH_2)), 0.53 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH$_2$CH$_2$)), 3.01 (d, J=7.1 Hz, 2H, SCH_2), 3.73 (s, 3H, CH_3O), 4.37 (d, J=6.4 Hz, CH_2NH), 6.89 (d, J=8.6 Hz, 2H, ArH), 7.27 ((d, J=8.6 Hz, 2H, ArH), 8.21 (t, J=6.4 Hz, 1H NH). ES-MS m/z 307 MH$^+$.

4.5.10. (5-Benzylsulfanyl-[1,3,4]thiadiazol-2-yl)-cyclopropylmethyl-amine (9j). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.20 (m, 2H, CH(CH_2CH_2)), 0.45 (m, 2H, CH(CH_2CH_2)), 1.03 (m, 1H, CH(CH$_2$CH$_2$)), 3.11 (dd, J_1=6.6 Hz, J_2=5.6 Hz, CHCH_2NH), 4.30 (s, 2H, SCH_2), 7.23 (m, 5H, ArH), 7.89 (t, J=5.6 Hz, 1H NH). ES-MS m/z 278 MH$^+$.

4.5.11. Cyclopropylmethyl-(5-phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9k). White solid, mp 66.9–67.2 °C; ν_{max} (KBr) 1045, 1205, 1278, 1327, 1542, 3003, 3232 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=0.22 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH$_2$CH$_2$)), 2.94 (t, J=7.4 Hz, 2H, PhCH_2CH$_2$), 3.13 (dd, J_1=5.5 Hz, J_2=7.1 Hz, 2H, cPrCH_2NH), 3.31 (t, J=7.4 Hz, 2H, PhCH$_2$CH_2), 7.25 (m, 5H, ArH), 7.91 (t, J=5.5 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6): δ=3.3, 10.3, 34.96, 36.40, 50.0, 126.3, 128.3, 128.5, 139.4, 149.4, 169.3. HR-MS (Q-TOF-ES) m/z=292.0937, calcd for [C$_{33}$H$_{34}$N$_4$OS+H]$^+$ 292.0942.

4.5.12. Cyclopropylmethyl-(5-yclopropylmethyl-sulfanyl-[1,3,4]thiadiazol-2-yl)-amine (9l). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.25 (m, 4H, CH(CH_2CH_2)), 0.50 (m, 4H, CH(CH_2CH_2)), 1.07 (m, 2H, CH(CH$_2$CH$_2$)), 3.01 (d, J=7.1 Hz, 2H, SCH_2cPr), 3.12 (dd, J_1=5.5 Hz, J_2=6.6 Hz, 2H, cPrCH_2NH), 7.89 (t, J=5.5 Hz, 1H, NH). ES-MS m/z 242 MH$^+$.

4.5.13. (5-Phenethylsulfanyl-[1,3,4]thiadiazol-2-yl)-pyridin-4-ylmethyl-amine (9m). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.94 (t, J=7.3 Hz, 2H, CH$_2$CH_2Ph), 3.33 (t, J=7.3 Hz, 2H, CH_2CH$_2$Ph), 4.58 (d, J=5.8 Hz, 2H, CH_2NH), 7.24 (m, 5H, ArH), 7.46 (d, J=5.5 Hz, 2H, ArH), 8.44 (t, J=5.8 Hz, NH), 8.58 (d, J=6.1 Hz, 2H, ArH). ES-MS m/z 329 MH$^+$.

4.5.14. (5-Cyclopropylmethylsulfanyl-[1,3,4]thiadiazol-2-yl)-pyridin-4-ylmethyl-amine (9n). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.25 (m, 2H, CH(CH_2CH_2)), 0.55 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, CH(CH$_2$CH$_2$)), 3.01 (d, J=7.1 Hz, 1H, SCH_2cPr), 3.03 (d, J=7.5 Hz, 1H, SCH_2cPr), 4.57 (d, J=5.2, 2H, PyCH_2NH), 7.45 (br s, 2H, ArH), 8.43 (t, J=5.2 Hz, 1H, NH), 8.59 (br s, 2H, ArH). ES-MS m/z 279 MH$^+$.

4.6. Formation of substituted thiosemicarbazide (10)

General procedure. A solution of 4-methoxybenzaldehyde (57 mg, 0.42 mmol) in TMOF/NMP (1:1, v/v, 3 mL) was added to resin **7** (100 mg, 0.042 mmol) and the resulting mixture agitated for 2 h. Excess reagents were removed by filtration before a new portion of aldehyde was added to the resin and the mixture was agitated for 14 h. Excess reagents were removed by filtration and the resin was washed with NMP (3×), THF/MeOH (1:1 v/v) (2×) and DCM (3×).

4.7. Formation of 5-alkyl-[1,3,4]thiadiazol-2-yl) alkyl amine (11)

General procedure. $FeCl_3$ (34 mg, 0.21 mmol) dissolved in DCM/MeOH (2 mL, 2:1 v/v) was added to resin **10** and agitated for 2 h. Excess reagents were removed by filtration and the, a new protion of $FeCl_3$ was added and the mixture aggitated for 14 h. The resin was filtered and washed with DCM (2×), NMP (2×), MeOH/DCM (1:1 v/v) (2×) and DCM (5×). The resin was subsequently treated with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding title products **11**.

4.7.1. Benzyl-[5-(4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11a). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.30 (s, 3H, OCH_3), 4.52 (d, J=5.8 Hz, 2H, NHCH_2), 7.02 (d, J=9.1 Hz, 2H, ArH), 7.28 (m, 1H, ArH), 7.37 (m, 4H, ArH), 7.67 (d, J=9.1 Hz, 2H, ArH), 8.35 (t, J=5.8 Hz, 1H, NHCH$_2$). ES-MS m/z 298 MH$^+$.

4.7.2. Benzyl-[5-(4-bromo-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11b). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=4.54 (d, J=5.8 Hz, 2H, NHCH_2), 7.28 (m, 1H, ArH), 7.38 (m, 4H, ArH), 7.69 (m, 4H, ArH), 8.53 (t, J=5.8 Hz, 1H, NHCH$_2$). ES-MS m/z 346 MH$^+$.

4.7.3. Benzyl-(5-isobutyl-[1,3,4]thiadiazol-2-yl)-amine (11c).[15] White solid, mp 119.2–119.9 °C; ν_{max} (KBr) ν_{max} (KBr) 721, 1138, 1201, 1433, 1454, 1598, 1649, 2962, 3366 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=0.91 (d, J=6.5 Hz, 6H, CH(CH_3)$_2$), 1.90 (m, 1H, CH(CH$_3$)$_2$), 2.69 (d, J=7.1 Hz, 2H, CH_2CH(CH$_3$)$_2$), 4.48 (s, 2H, NHCH_2), 7.28 (m, 1H, ArH), 7.38 d, J=4.5 Hz, 4H, ArH), 8.52 (s, 1H, NHCH$_2$); ^{13}C NMR (DMSO-d_6): δ=21.8, 28.6, 38.1, 48.2, 127.3, 127.6, 128.4, 138.1, 157.3, 168.3. HR-MS (Q-TOF-ES) m/z=248.1216, calcd for [C$_{33}$H$_{34}$N$_4$OS+H]$^+$ 248.1221.

4.7.4. Cyclopropylmethyl-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine (11d). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.27 (m, 2H, CH(CH_2CH_2)), 0.50 (m, 2H, CH(CH_2-CH_2)), 1.12 (m, 1H, CH(CH$_2$CH$_2$)), 3.21 (d, J=6.6 Hz, 2H, CH_2CH(CH$_2$CH$_2$)), 7.46 (m, 3H, ArH), 7.75 (m, 2H, ArH), 8.27 (s, 1H, NHCH$_2$). ES-MS m/z 232 MH$^+$.

4.7.5. Cyclopropylmethyl-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-yl)-amine (11e). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.27 (m, 2H, CH(CH_2CH_2)), 0.50 (m, 2H, CH(CH_2CH_2)), 1.13 (m, 1H, CH(CH$_2$CH$_2$)), 3.24 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 7.61 (m, 1H, ArH), 8.27 (m, 2H, ArH), 8.32 (br s, 1H, NHCH$_2$), 8.67 (d, J=4.1 Hz, 1H, ArH), 9.01 (s, 1H, ArH). ES-MS m/z 233 MH$^+$.

4.7.6. Cyclopropylmethyl-[5-(4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11f). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.26 (m, 2H, CH(CH_2CH_2)), 0.49 (m, 2H, CH(CH_2CH_2)), 1.10 (m, 1H, CH(CH$_2$CH$_2$)), 3.19 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 3.81 (s, 3H, OCH_3), 7.04 (d, J=8.6 Hz, 2H, ArH), 7.69 (d, J=9.0 Hz, 2H, ArH), 8.11 (br s, 1H, NHCH$_2$). ES-MS m/z 262 MH$^+$.

4.7.7. Methyl-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine (11g). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.95 (s, 3H, NHCH_3), 7.47 (m, 3H, ArH), 7.77 (m, 2H, ArH), 8.10 (s, 1H, NHCH$_3$). ES-MS m/z 192 MH$^+$.

4.7.8. [5-(4-Bromo-phenyl)-[1,3,4]thiadiazol-2-yl]-methyl-amine (11h). Isolated as a pale oil; ν_{max} (KBr) 824, 976, 1067, 1154, 1202, 1399, 1497, 1553, 1678, 3283 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.95 (d, J=4.0 Hz, 3H, NHCH_3), 7.69 (m, 4H, ArH), 7.98 (s, 1H, NHCH$_3$); ^{13}C NMR (DMSO-d_6): δ=31.3, 122.7, 128.1, 130.1, 132.1, 154.6, 169.5. HR-MS (Q-TOF-ES) m/z=269.9695, calcd for [C$_{33}$H$_{34}$N$_4$OS+H]$^+$ 269.9701.

4.7.9. (5-Isobutyl-[1,3,4]thiadiazol-2-yl)-methyl-amine (11i). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.92 (d, J=6.6 Hz, 6H, CH(CH_3)$_2$), 1.91 (m, 1H, CH(CH$_3$)$_2$), 2.70 (d, J=7.1 Hz, 2H, CH_2CH(CH$_3$)$_2$), 2.90 (s, 3H, NHCH_3) 8.34 (s, 1H, NHCH$_3$). ES-MS m/z 172 MH$^+$.

4.7.10. (4-Methoxy-benzyl)-(5-phenyl-[1,3,4]thiadiazol-2-yl)-amine (11j). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.74 (s, 3H, OCH_3), 4.75 (d, J=5.1 Hz, 2H, NHCH_2), 6.92 (d, J=8.5 Hz, 2H, ArH), 7.32 (d, J=8.6 Hz, 2H, ArH), 7.46 (m, 3H, ArH), 7.75 (d, J=8.1 Hz, 2H, ArH), 8.46 (t, J=5.1 Hz, 1H, NHCH$_2$). ES-MS m/z 298 MH$^+$.

4.7.11. (4-Methoxy-benzyl)-(5-pyridin-3-yl-[1,3,4]thiadiazol-2-yl)-amine (11k). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.74 (s, 3H, OCH_3), 4.58 (d, J=5.1 Hz, 2H, NHCH_2), 6.93 (d, J=9.1 Hz, 2H, ArH), 7.32 (d, 2H, J=8.5 Hz, 2H, ArH), 7.58 (m, 1H, ArH), 8.23 (m, 1H, ArH), 8.58 (t, J=5.1 Hz, 1H, NHCH$_2$), 8.65 (m, 1H, ArH),), 8.99 (s, 1H, ArH). ES-MS m/z 299 MH$^+$.

4.7.12. (4-Methoxy-benzyl)-[5-(4-methoxy-phenyl)-[1,3,4]thiadiazol-2-yl]-amine (11l). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=3.73 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3) 4.44 (d, J=5.6 Hz, 2H, NHCH_2), 6.92 (d, J=8.6 Hz, 2H, ArH), 7.01 (d, 2H, J=9.1 Hz, 2H, ArH), 7.31 (d, J=8.5 Hz, 2H, ArH), 7.67 (d, J=8.5 Hz, 2H, ArH), 8.34 (t, J=5.6 Hz, 1H, NHCH$_2$). ES-MS m/z 328 MH$^+$.

4.8. Formation of hydrazine-1,2-dicarbothioamide (12)

To resin **7** (100 mg, 0.042 mmol pre-swollen in DCM was added a mixture of fmoc-isothiocyanate (60 mg, 0.21 mmol) and DIPEA (47 μL, 0.27 mmol) in DCM (2 mL) and the resulting mixture was agitated for 14 h. The resin was subsequently washed with DMF (3×) and DCM (2×).

4.9. Formation of *N*-(5-alkylamino-[1,3,4]thiadiazol-2-yl)-alkylamide (13)

General procedure. To resin **12** (100 mg, 0.042 mmol) pre-swollen in dry NMP was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol) in dry NMP (3 mL) and the mixture was agitated for 14 h at 50 °C. Excess reagent was removed by filtration and the resin was washed with NMP (2×), MeOH/THF (1:1 v/v) (2×), DCM (2×) and NMP (2×). Subsequently the resin was de-protected by treatment with NMP/piperidine (2 mL, 80:20 v/v) for 20 min, the de-protection procedure was repeated a further time. Excess reagents were removed by filtration and the resin was washed with NMP (3×) yielding the resin bound [1,3,4]thiadiazol-2-yl) amine. A solution of benzoic acid (49 mg, 0.40 mmol) in NMP/DCM (2 mL, 1:1 v/v) was added to the resin followed by DIPEA (75 μL, 0.44 mmol), DIIC (26 mg, 0.20 mmol) and a catalytic amount of DMAP (2 mg, 1.6 μmol). The mixture was agitated for 14 h before the excess reagents were removed by filtration followed by washing with NMP (3×), MeOH/THF/AcOH (10:10:1 v/v) (2×), MeOH/THF (1:1 v/v) (2×) and DCM (4×). The resin was subsequently treated with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding the title compounds **13**.

4.9.1. Cyclopropanecarboxylic acid [5-(4-methoxy-benzylamino)-[1,3,4]thiadiazol-2-yl]-amide (13a). White solid, mp 185.3–186.1 °C; ν_{max} (KBr) 957, 1032, 1174, 1317, 1407, 1512, 1542, 1586, 1662, 2744, 3334 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta=0.88$ (m, 4H, CH(CH_2CH_2)), 1.89 (m, 1H, C*H*(CH_2CH_2)), 3.73 (s, 3H, OCH_3), 4.37 (s, 2H, $NHCH_2$), 6.91 (d, $J=8.6$ Hz, 2H, Ar*H*), 7.27 (d, $J=9.1$ Hz, 2H, Ar*H*), 8.08 (s, 1H, $NHCH_2$), 12.30 (s, 1H, CON*H*); ^{13}C NMR (DMSO-d_6): $\delta=10.3$, 15.4, 49.1, 57.0, 115.8, 130.9, 132.3, 150.8, 160.5, 166.1, 173.4. HR-MS (Q-TOF-ES) $m/z=305.1076$, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 305.1072.

4.9.2. *N*-[5-(4-Methoxy-benzylamino)-[1,3,4]thiadiazol-2-yl]-benzamide (13b). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=3.74$ (s, 3H, OCH_3), 4.42 (br s, 2H, $NHCH_2$), 6.93 (d, $J=8.5$ Hz, 2H, Ar*H*), 7.31 (d, $J=8.6$ Hz, 2H, Ar*H*), 7.53 (t, $J=8.5$ Hz, 2H, Ar*H*), 7.63 (t, $J=7.3$ Hz, 2H, Ar*H*), 8.06 (d, $J=7.1$ Hz, 2H, Ar*H*), 8.14 (br s, 1H, $NHCH_2$), 12.5 (br s, 1H, CON*H*). ES-MS *m/z* 305 MH^+.

4.9.3. Cyclopropanecarboxylic acid (5-benzylamino-[1,3,4]thiadiazol-2-yl)-amide (13c). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.89$ (m, 4H, CH(CH_2CH_2)), 1.89 (m, 1H, C*H*(CH_2CH_2)), 4.47 (s, 2H, $NHCH_2$), 7.32 (m, 4H, Ar*H*), 8.35 (s, 1H, $NHCH_2$), 12.38 (s, 1H, CON*H*). ES-MS *m/z* 275 MH^+.

4.9.4. *N*-(5-Benzylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13d).[16] White solid, mp 235.9–237.1 °C; ν_{max} (KBr) 671, 694, 752, 892, 1304, 1492, 1539, 1649, 3366 cm^{-1}; ^1H NMR (DMSO-d_6): $\delta=4.48$ (d, $J=6.1$ Hz, 2H, $NHCH_2$), 7.27 (m, 1H, Ar*H*), 7.37 (m, 4H, Ar*H*), 7.52 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.62 (t, $J=7.1$ Hz, 1H, Ar*H*), 7.89 ((t, $J=6.1$ Hz, 1H, CH_2NH), 8.05 (d, $J=7.0$ Hz, Ar*H*), 12.45 (br s, 1H, CON*H*); ^{13}C NMR (DMSO-d_6): $\delta=46.6$, 126.3, 126.8, 127.5, 127.7, 127.8, 131.8, 138.2, 163.6. HR-MS (Q-TOF-ES) $m/z=311.0961$, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 311.0967.

4.9.5. *N*-(5-Benzylamino-[1,3,4]thiadiazol-2-yl)-2-phenyl-acetamide (13e).[16] Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=3.70$ (s, 2H, PhCH_2CO), 4.43 (d, $J=5.6$ Hz, 2H, $NHCH_2$), 7.30 (m, 10H, Ar*H*), 7.82 (t, $J=5.6$ Hz, 1H $NHCH_2$), 12.17 (br s, 1H, N*H*CO). ES-MS *m/z* 325 MH^+.

4.9.6. Furan-2-carboxylic acid (5-benzylamino-[1,3,4]-thiadiazol-2-yl)-amide (13f). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=4.47$ (d, $J=5.6$ Hz, 2H, $NHCH_2$), 6.71 (m, 1H, C(OCHC*H*CH)), 7.27 (m, 1H, Ar*H*), 7.36 (m, 4H, Ar*H*), 7.57 (br s, 1H, C(OCHCHC*H*)), 7.94 (t, $J=5.6$ Hz, 1H $NHCH_2$), 7.98 (s, 1H, C(OC*H*CHCH)), 12.47 (br s, 1H, N*H*CO). ES-MS *m/z* 301 MH^+.

4.9.7. *N*-(5-Benzylamino-[1,3,4]thiadiazol-2-yl)-acetamide (13g). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.10$ (s, 3H, CH_3O), 7.47 (s, 2H, $NHCH_2$), 7.29 (m, 1H, Ar*H*), 7.35 (d, $J=4.1$ Hz, 4H, Ar*H*), 8.27 (br s, 1H, $NHCH_2$), 12.06 (br s, 1H, N*H*CO). ES-MS *m/z* 249 MH^+.

4.9.8. *N*-(5-Isobutylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13h). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.93$ (d, $J=6.5$ Hz, 6H, CH(CH_3)$_2$), 1.91 (hept, $J=6.5$ Hz, 1H, C*H*(CH_3)$_2$), 3.13 (t, $J=4.6$ Hz, 2H, CH_2NH), 7.55 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.65 (t, $J=7.1$ Hz, 2H, Ar*H*), 8.07 (d, $J=7.1$ Hz, 2H, Ar*H*), 8.25 (br s, 1H, $NHCH_2$), 12.68 (br s, 1H, N*H*CO). ES-MS *m/z* 277 MH^+.

4.9.9. *N*-(5-Phenethylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13i). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.90$ (t, $J=7.1$ Hz, 2H, $NHCH_2CH_2$), 3.52 (t, $J=5.1$ Hz, 2H, $NHCH_2CH_2$), 7.28 (m, 5H, Ar*H*), 7.53 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.63 (t, $J=7.1$ Hz, 1H, Ar*H*), 7.74 (br s, 1H, $NHCH_2$), 8.05 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.49 (br s, 1H, N*H*CO). ES-MS *m/z* 325 MH^+.

4.9.10. Cyclopropanecarboxylic acid (5-methylamino-[1,3,4]thiadiazol-2-yl)-amide (13j). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.84$ (m, 4H, CH(CH_2CH_2)), 1.86 (m, 1H, C*H*(CH_2CH_2)), 2.80 (d, $J=4.9$ Hz, 3H, $NHCH_3$), 7.17 (q, $J=4.9$ Hz, 1H, $NHCH_3$), 12.14 (s, 1H, N*H*CO). ES-MS *m/z* 199 MH^+.

4.9.11. *N*-(5-Methylamino-[1,3,4]thiadiazol-2-yl)-benzamide (13k). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.88$ (s, 3H, $NHCH_3$), 7.52 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.62 (t, $J=7.6$ Hz, 1H, Ar*H*), 7.66 (br s, 1H, $NHCH_3$), 8.04 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.54 (s, 1H, N*H*CO). ES-MS *m/z* 235 MH^+.

4.9.12. *N*-(5-Methylamino-[1,3,4]thiadiazol-2-yl)-2-phenyl-acetamide (13l). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.88$ (s, 3H, $NHCH_3$), 3.74 (s, 2H, $COCH_2$), 7.29, (m, 5H, Ar*H*), 8.25 ($NHCH_3$), 12.50 (br s, 1H, N*H*CO). ES-MS *m/z* 249 MH^+.

4.9.13. *N*-(5-Methylamino-[1,3,4]thiadiazol-2-yl)-acetamide (13m). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=2.08$ (s, 3H, $COCH_3$), 2.82 (d, $J=4.4$ Hz, 3H, $NHCH_3$), 7.21 (q, $J=4.4$ Hz, 1H, $NHCH_3$), 11.88 (s, 1H, N*H*CO). ES-MS *m/z* 173 MH^+.

4.9.14. *N*-{5-[(Tetrahydro-furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-benzamide (13n). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=1.57$ (m, 1H, CH(OCH_2-CH_2CH_2)), 1.86 (m, 2H, CH($OCH_2CH_2CH_2$), 1.97 (m 1H, CH($OCH_2CH_2CH_2$), 3.39 (dd, $J_1=6.0$ Hz, $J_2=6.8$ Hz, 2H, $NHCH_2$), 3.66 (q, $J=7.1$ Hz, 1H, CH($OCH_2CH_2CH_2$)), 3.79 (q, $J=7.1$ Hz, 1H, CH($OCH_2CH_2CH_2$)), 4.04 (m, 1H, C*H*($OCH_2CH_2CH_2$)), 7.55 (t, $J=7.6$ Hz, 2H, Ar*H*), 7.65 (t, $J=7.1$ Hz, 2H, Ar*H*), 8.07 (d, $J=7.1$ Hz, 2H, Ar*H*), 8.34 (d, $J=6.8$ Hz, 1H, $NHCH_2$), 12.68 (br s, 1H, N*H*CO). ES-MS *m/z* 305 MH^+.

4.9.15. Cyclopropanecarboxylic acid {5-[(furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-amide (13o). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=0.85$ (m, 4H, CH(CH_2CH_2)), 1.89 (m, 1H, C*H*(CH_2CH_2)), 4.42 (d, $J=5.0$ Hz, 2H, $NHCH_2$), 6.33 (d, $J=3$ Hz, 1H, C(OCHC*H*CH)), 6.41 (q, $J=1.5$ Hz, 1H, C(OCHCHC*H*)), 7.61 (m, 1H, C(OC*H*CHCH)), 7.71 (t, $J=5.0$ Hz, 1H $NHCH_2$), 12.20 (s, 1H, CON*H*). ES-MS *m/z* 265 MH^+.

4.9.16. *N*-{5-[(Furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-benzamide (13p). Isolated as a pale oil; ^1H NMR (DMSO-d_6): $\delta=4.47$ (d, $J=5.0$ Hz, $NHCH_2$), 6.35

(d, $J=3.0$ Hz, 1H, C(OCHC*H*CH)), 6.42 (m, 1H, C(OCHCHC*H*)), 7.53 (m, 2H, Ar*H*), 7.62 (m, 2H, Ar*H* and C(OC*H*CHCH)), 7.82 (t, $J=5.0$ Hz, 1H, N*H*CH_2) 8.05 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.49 (s, 1H, N*H*CO). ES-MS *m/z* 301 MH^+.

4.9.17. *N*-{5-[(Furan-2-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-2-phenyl-acetamide (13q). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=3.71$ (s, 2H, COCH_2), 4.42 (d, $J=5.6$ Hz, NHCH_2), 6.32 (d, $J=3.0$ Hz, 1H, C(OCHC*H*CH)), 6.40 (m, 1H, C(OCHCHC*H*)), 7.31 (m, 5H, Ar*H*), 7.60 (m, 1H, 1H, C(OC*H*CHCH)), 7.74 (t, $J=5.6$ Hz, NHCH$_2$), 12.20 (s, 1H, N*H*CO). ES-MS *m/z* 315 MH^+.

4.9.18. *N*-[5-(Cyclopropylmethyl-amino)-[1,3,4]thiadiazol-2-yl]-benzamide (13r). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.22$ (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.08 (m, 1H, C*H*(CH_2CH_2)), 3.13 (t, $J=6.8$ Hz, 2H, NHCH_2*c*Pr), 7.51 (m, 3H Ar*H*), 7.61 (t, $J=6.8$ Hz, 1H, CH$_2$N*H*), 8.05 (d, $J=7.0$ Hz, 2H, Ar*H*), 12.42 (br s, 1H, CON*H*). ES-MS *m/z* 275 MH^+.

4.9.19. *N*-[5-(Cyclopropylmethyl-amino)-[1,3,4]thiadiazol-2-yl]-2-phenyl-acetamide (13s). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.19$ (m, 2H, CH(CH_2CH_2)), 0.43 (m, 2H, CH(CH_2CH_2)), 1.03 (m, 1H, C*H*(CH_2CH_2)), 3.08 (t, $J=6.0$ Hz, 2H, NHCH_2*c*Pr), 3.69 (s, 2H, CH_2Ph) 7.29 (m, 5H Ar*H*), 7.38 (t, $J=6.0$ Hz, 1H, CH$_2$N*H*), 12.11 (s, 1H, CON*H*). ES-MS *m/z* 289 MH^+.

4.9.20. Furan-2-carboxylic acid [5-(cyclopropylmethyl-amino)-[1,3,4]thiadiazol-2-yl]-amide (13t). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.24$ (m, 2H, CH(CH_2-CH_2)), 0.51 (m, 2H, CH(CH_2CH_2)), 1.10 (m, 1H, C*H*(CH$_2$-CH$_2$)), 3.16 (t, $J=6.6$ Hz, 2H, NHCH_2*c*Pr), 6.73 (m, 1H, Ar*H*), 7.59 (m, 1H, Ar*H*), 8.01 (m, 1H, Ar*H*) 8.11 (br s, 1H, CH$_2$N*H*), 12.66 (s, 1H, CON*H*). ES-MS *m/z* 265 MH^+.

4.9.21. *N*-[5-(Cyclopropylmethyl-amino)-[1,3,4] thiadiazol-2-yl]-acetamide (13u). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=0.21$ (m, 2H, CH(CH_2CH_2)), 0.46 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, C*H*(CH$_2$CH$_2$)), 2.08 (s, 3H, CH_3CO) 3.10 (t, $J=6.6$ Hz, 2H, NHCH_2*c*Pr), 7.35 (t, $J=6.6$ Hz, 1H, CH$_2$N*H*), 11.84 (s, 1H, CON*H*). ES-MS *m/z* 213 MH^+.

4.9.22. *N*-{5-[(Pyridin-4-ylmethyl)-amino]-[1,3,4] thiadiazol-2-yl}-benzamide (13v). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=4.76$ (d, $J=4.6$ Hz, 2H CH_2), 7.53 (m, 3H, Ar*H*), 7.82 (d, $J=6.7$ Hz, 2H, Ar*H*), 8.06 (d, $J=7.0$ Hz, 2H, Ar*H*), 8.24 (m, 1H, CH$_2$N*H*), 8.78 (d, $J=6.7$ Hz, 2H, Ar*H*), 11.84 (s, 1H, CON*H*). ES-MS *m/z* 312 MH^+.

4.9.23. 2-Phenyl-*N*-{5-[(pyridin-4-ylmethyl)-amino]-[1,3,4]thiadiazol-2-yl}-acetamide (13x). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=3.72$ (s, 2H, COCH_2) 4.71 (d, $J=4.3$ Hz, CH_2NH), 7.31 (m, 6H, Ar*H*), 7.78 (d, $J=6.0$ Hz, Ar*H*), 8.16 (m, 1H, CH$_2$N*H*), 8.77 (d, $J=6.6$ Hz, Ar*H*), 12.27 (s, 1H, CON*H*). ES-MS *m/z* 326 MH^+.

4.10. Formation of semicarbazide (14)

Typical procedure. Resin **5** (1.0 g, 0.42 mmol) swollen in DCM (15 mL) and DIPEA (2 mL) was agitated for 10 min before a solution of triphosgene (380 mg, 1.3 mmol) in DCM (10 mL) was added. The resulting mixture was agitated for 5 h before excess reagents were removed by filtration and the resin was washed with DCM (3×). A solution of hydrazine hydrate (210 mg, 4.2 mmol) in DMSO (15 mL) was added and the mixture was agitated for 14 h before the resin was filtered and washed with DMSO (3×), MeOH/THF/AcOH (10:10:1, v/v) (2×), MeOH/THF (1:1, v/v) (2×) and DCM (4×). The resin was dried in vacuo overnight at 40 °C to yield resin bound semicarbazide **14**.

4.11. Formation of carbamoyl thiosemicarbazide (15)

Typical procedure. A solution of isothiocyanate (0.21 mmol) dissolved in DCM (2 mL) and DIPEA (50 μL, 0.29 mmol) was added to resin **14** and the mixture was agitated for 6 h. Excess reagents were removed by filtration and the resin was washed with DCM (2×), NMP (3×), MeOH/THF (1:1, v/v) (2×) and DCM (3×) yielding resin bound carbamoyl thiosemicarbazide **15**.

4.12. Formation of *N*,*N*-dialkyl-[1,3,4]oxadiazoles-2,5-diamine (16)

Typical procedure. To resin **15** (100 mg, 0.042 mmol) preswollen in dry NMP was added a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol,) in dry NMP (3 mL) and the mixture was agitated for 14 h at 60 °C. Excess reagents were removed by filtration and the resin was washed with NMP (2×), MeOH/THF (1:1, v/v) (2×) and DCM (4×). The resin was subsequently treated with TFA/DCM (2 mL, 1:1 v/v) for 2 h before the liquors were transferred to a 10 mL round bottom flask and concentrated in vacuo. The residue was re-dissolved in acetonitrile (5 mL) and a sample (1 mL) was removed and concentrated in vacuo for NMR concentration studies and LC–MS analysis. The rest of the crude products were purified by preparative HPLC yielding the title compounds **15**.

4.12.1. *N*-Benzyl-*N′*-(4-methoxy-benzyl)-[1,3,4]oxadiazole-2,5-diamine (16a). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): $\delta=3.72$ (s, 3H, OCH_3), 4.16 (d, $J=6.1$ Hz, 2H, NHCH_2), 4.24 (d, $J=6.1$ Hz, 2H, NHCH_2), 6.87 (d, $J=9.1$ Hz, 2H, Ar*H*), 7.24 (d, $J=8.6$ Hz, 2H, Ar*H*), 7.32 (m, 5H, Ar*H*), 7.40 (t, $J=6.1$ Hz, 1H, N*H*), 7.48 (t, $J=6.1$ Hz, 1H, N*H*). ES-MS *m/z* 311 MH^+.

4.12.2. *N*-Cyclopropylmethyl-*N′*-(4-methoxy-benzyl)-[1,3,4]oxadiazole-2,5-diamine (16b). White solid, mp 104.7–105.2 °C; ν_{max} (KBr) 823, 1034, 1177, 1252, 1302, 1515, 1569, 1660, 2927, 3298 cm^{-1}; ^{1}H NMR (DMSO-d_6): $\delta=0.23$ (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2-CH_2)), 1.04 (m, 1H, C*H*(CH$_2$CH$_2$)), 3.01 (m, 2H, CH_2-CH(CH$_2$CH$_2$)), 3.74 (s, 3H, OCH_3), 4.25 (br s, 2H, NHCH_2), 6.91 (d, $J=9.1$ Hz, 2H, Ar*H*), 7.29 (d, $J=7.4$ Hz, 2H, Ar*H*), 7.52 (br s, 1H, N*H*), 7.57 (br s, 1H, N*H*); ^{13}C NMR (DMSO-d_6): $\delta=3.39$, 10.3, 45.3, 47.1, 55.1, 113.8, 129.0, 129.8, 156.8, 158.4, 158.6. HR-MS

(Q-TOF-ES) m/z=275.1503, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 275.1508.

4.12.3. *N*,*N*′-Dibenzyl-[1,3,4]oxadiazole-2,5-diamine (16c). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=4.32 (d, J=6.1 Hz, 4H, NHCH_2), 7.25 (m, 2H, Ar*H*), 7.35 (m, 8H, Ar*H*), 8.61 (br s, 2H, N*H*). ES-MS m/z 281 MH^+.

4.12.4. *N*-Benzyl-*N*′-phenethyl-[1,3,4]oxadiazole-2,5-diamine (16d). White solid, mp 134.8–135.9 °C; ν_{max} (KBr) 697, 1136, 1201, 1263, 1359, 1452, 1598, 1680, 2983, 3170 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ=2.82 (t, J=7.6 Hz, 2H, PhCH_2CH_2), 3.28 (m, 2H, PhCH_2CH_2), 4.26 (d, J=6.3 Hz, PhCH_2NH), 7.27 (m, 11H, Ar*H* and N*H*), 8.17 (t, J=6.3 Hz 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ=34.5, 43.9, 45.8, 126.0, 126.9, 127.3, 128.2, 128.2, 128.6, 138.8, 139.1, 157.8, and 157.9. HR-MS (Q-TOF-ES) m/z=295.1553, calcd for $[C_{33}H_{34}N_4OS+H]^+$ 295.1559.

4.12.5. *N*-Benzyl-*N*′-cyclopropylmethyl-[1,3,4]oxadiazole-2,5-diamine (16e). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.22 (m, 2H, CH(CH_2CH_2)), 0.46 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH_2CH_2)), 2.99 (m, 2H, CH_2CH(CH_2CH_2)), 4.31 (d, J=6.1 Hz, 2H, NHCH_2Ph), 7.30 (m, 5H, Ar*H*), 8.32 (br s, 1H, N*H*), 8.43 (br s, 1H, N*H*). ES-MS m/z 245 MH^+.

4.12.6. *N*-Cyclopropylmethyl-*N*′-ethyl-[1,3,4]oxadiazole-2,5-diamine (16f). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH_2CH_2)), 1.14 (t, J=7.1 Hz, 3H, CH_2CH_3), 3.00 (m, 2H, NHCH_2CH_2), 3.15 (m, 2H, CH_2CH(CH_2CH_2)), 8.20 (br s, 1H, N*H*), 8.37 (br s, 1H, N*H*). ES-MS m/z 183 MH^+.

4.12.7. *N*-Cyclopropylmethyl-*N*′-phenethyl-[1,3,4]oxadiazole-2,5-diamine (16g).[15] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH_2CH_2)), 2.85 (t, J=7.2 Hz, 2H, PhCH_2CH_2), 3.00 (m, 2H, CH_2-CH(CH_2CH_2)), 3.35 (m, 2H, PhCH_2CH_2), 7.25 (m, 5H, Ar*H*), 8.31 (br s, 1H, N*H*), 8.37 (br s, 1H, N*H*). ES-MS m/z 259 MH^+.

4.12.8. *N*-Benzyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16h).[17] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=4.33 (d, J=6.1 Hz, 2H, NHCH_2), 6.91 (t, J=7.1 Hz, 1H, Ar*H*), 7.28 (m, 3H, Ar*H*), 7.37 (m, 4H, Ar*H*), 7.45 (d, J=7.6 Hz, 2H, Ar*H*), 7.82 (t, J=6.1 Hz, 1H, N*H*CH_2), 9.95 (s, 1H, PhN*H*). ES-MS m/z 266 MH^+.

4.12.9. *N*-Ethyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16i).[17] Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=1.18 (t, J=7.6 Hz, 3H, CH_2CH_3), 3.20 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 6.95 (t, J=7.6 Hz, 1H, Ar*H*), 7.31 (t, J=8.6 Hz, 2H, Ar*H*), 7.44 (d, J=7.6 Hz, 2H, Ar*H*), 8.07 (br s, 1H, N*H*CH_2), 10.21 (s, 1H, PhN*H*). ES-MS m/z 205 MH^+.

4.12.10. *N*-Phenethyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16j). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.87 (t, J=7.0 Hz, 2H, CH$_2$CH_2Ph), 3.45 (m, 2H, CH_2CH$_2$Ph), 6.92 (t, J=7.5 Hz, 1H, Ar*H*), 7.29 (m, 9H, Ar*H* and N*H*CH_2), 7.47 (d, J=7.6 Hz, 2H, Ar*H*), 9.91 (s, 1H, PhN*H*). ES-MS m/z 281 MH^+.

4.12.11. *N*-Cyclopropylmethyl-*N*′-phenyl-[1,3,4]oxadiazole-2,5-diamine (16k). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.46 (m, 2H, CH(CH_2CH_2)), 1.07 (m, 1H, C*H*(CH$_2$CH$_2$)), 3.01 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 6.93 (t, J=7.6 Hz, 1H, Ar*H*), 7.29 (t, J=8.4 Hz, 2H, Ar*H*), 7.44 (d, J=7.6 Hz, 2H, Ar*H*), 7.91 (br s, 1H, N*H*CH$_2$), 10.10 (s, 1H, PhN*H*). ES-MS m/z 231 MH^+.

4.12.12. *N*-Methyl-*N*′-phenethyl-[1,3,4]oxadiazole-2,5-diamine (16l). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=2.76 (d, J=2.0 Hz, NHCH_3), 2.84 (t, J=7.1 Hz, 2H, PhCH_2CH$_2$), 3.34 (m, 2H, PhCH$_2$CH_2), 7.25 (m, 5H, Ar*H*), 8.17 (br s, 1H, N*H*), 8.24 (s, 1H, N*H*). ES-MS m/z 219 MH^+.

4.12.13. *N*-Cyclopropylmethyl-*N*′-methyl-[1,3,4]oxadiazole-2,5-diamine (16m). Isolated as a pale oil; ^{1}H NMR (DMSO-d_6): δ=0.23 (m, 2H, CH(CH_2CH_2)), 0.47 (m, 2H, CH(CH_2CH_2)), 1.04 (m, 1H, C*H*(CH$_2$CH$_2$)), 2.76 (s, 3H, NHCH_3), (3.00 (m, 2H, CH_2CH(CH$_2$CH$_2$)), 8.17 (br s, 1H, N*H*), 8.29 (br s, 1H, N*H*). ES-MS m/z 169 MH^+.

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Hirsutellones A–E, antimycobacterial alkaloids from the insect pathogenic fungus *Hirsutella nivea* BCC 2594

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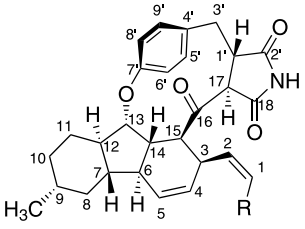
Abstract—Five new alkaloids, hirsutellones A–E, were isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594. Their structures were elucidated by spectroscopic analysis and X-ray crystallography. Hirsutellones displayed significant growth inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Ra$.

1. Introduction

Tuberculosis, caused by *Mycobacterium tuberculosis*, has again become a serious endemic disease. It is estimated that one-third of the world's population is infected with the tubercule bacillus, causing each year eight million new cases of developing clinical tuberculosis and two million deaths.[1] Due to this burgeoning problem caused by the emergence of a multi-drug resistance strain, there is an urgent need to search for new chemical class of anti-tubercular drugs.[2] As a part of our ongoing research program on the identification of novel bioactive compounds from fungi in Thailand,[3] we have extensively screened extracts from fungal cultures for in vitro antimycobacterial activity. Herein, we report the isolation and structure elucidation of novel antitubercular alkaloids, hirsutellones A–E (**1**–**5**), from the insect pathogenic fungus *Hirsutella nivea* BCC 2594. Hirsutellones possess unique structural features: a highly strained 12- or 13-membered ring containing a γ-lactam or succinimide, a *para*-substituted phenyl ether, and a tricyclic polyketide moieties. The genus *Hirsutella* has rarely been chemically explored, only a toxic protein, hirsutellin A, from *H. thompsonii*,[4] and a cyclohexadepsipeptide, hirsutellide A, from *H. kobayasii* BCC 1660,[5] have been reported.



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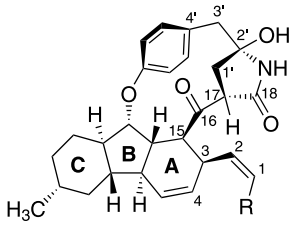
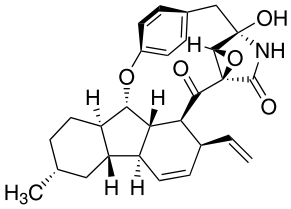
4 : R = CH_3



2 : R = H
5 : R = CH_3



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2. Results and discussion

Mycelia from liquid fermentation in Erlenmeyer flasks (10 L) were extracted with MeOH, and the extract after concentration in vacuo was subjected to a combination of column chromatography, using Sephadex LH20, silica gel, and reversed-phase preparative HPLC, to obtain

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Table 1. ^{1}H NMR data for compounds **1–5** in $CDCl_3$

Position	Hirsutellone A (**1**)	Hirsutellone B (**2**)	Hirsutellone C (**3**)	Hirsutellone D (**4**)	Hirsutellone E (**5**)
1	4.98 (d, 10.0)	4.84 (m)	4.91 (dd, 9.7, 1.6)	5.21 (ddq, 10.9, 0.9, 6.8)	5.30 (m)[a]
	4.83 (d, 17.0)	4.92 (dd, 16.7, 1.4)	4.94 (dd, 16.4, 1.6)	—	—
2	5.20 (ddd, 17.0, 10.3, 6.5)	5.22 (dt, 16.8, 9.6)	5.23 (dt, 16.9, 1.6)	4.88 (m)	4.82 (tq, 10.5, 1.0)
3	4.17 (ddd, 5.6, 5.4, 5.2)	3.50 (m)	3.82 (m)	4.37 (m)	4.00 (m)
4	5.49 (ddd, 9.7, 5.6, 2.4)	5.34 (ddd, 9.7, 4.7, 2.5)	5.39 (ddd, 9.8, 3.9, 2.9)	5.58 (ddd, 9.6, 5.6, 2.3)	5.30 (m)[a]
5	5.91 (d, 9.8)	5.81 (d, 9.8)	5.88 (d, 9.9)	5.74 (d, 9.6)	5.77 (d, 9.8)
6	2.23 (dt, 1.0, 11.2)	2.13 (m)	2.15 (m)	2.18 (m)	2.11 (m)
7	0.73 (dq, 2.3, 11.2)	0.82 (dq, 2.4, 11.1)	0.90 (m)	0.76 (dq, 2.3, 11.3)	0.82 (dq, 2.2, 11.3)
8	0.94 (m)	0.90 (m)	0.94 (m)	0.90 (m)	0.89 (m)
	1.98 (m)	1.96 (m)	2.01 (m)	1.94 (m)	1.97 (m)
9	1.43 (m)	1.43 (m)	1.44 (m)	1.40 (m)	1.45 (m)
10	1.12 (dq, 4.0, 12.3)	1.12 (dq, 3.5, 12.5)	1.11 (m)	1.12 (dq, 4.1, 12.5)	1.12 (dq, 4.0, 12.3)
	1.84 (m)	1.85 (m)	1.85 (m)	1.84 (m)	1.85 (m)
11	1.35 (dq, 3.5, 12.3)	1.41 (dq, 3.3, 12.5)	1.41 (dq, 3.7, 12.3)	1.36 (dq, 3.6, 12.4)	1.42 (m)
	2.13 (m)	2.16 (m)	2.12 (m)	2.15 (m)	2.17 (m)
12	1.68 (m)	1.64 (m)	1.65 (m)	1.68 (m)	1.66 (m)
13	4.46 (dd, 3.4, 3.3)	4.86 (m)	4.63 (dd, 3.8, 3.6)	4.55 (t, 3.6)	4.87 (t, 4.0)
14	1.48 (dt, 4.1, 11.3)	1.47 (dt, 4.6, 11.5)	1.71 (dt, 4.4, 11.8)	1.58 (m)	1.48 (m)
15	3.13 (dd, 10.9, 4.8)	3.45 (dd, 11.0, 5.9)	3.72 (dd, 12.0, 5.9)	3.17 (dd, 11.0, 5.8)	3.43 (dd, 11.5, 6.1)
17	3.52 (d, 6.4)	2.94 (dd, 12.3, 3.7)	—	3.44 (d, 6.1)	2.80 (dd, 12.3, 3.8)
1-C*H*$_3$	—	—	—	1.56 (dd, 6.7, 1.4)	1.6[b]
9-C*H*$_3$	0.96 (d, 6.6)	0.96 (d, 6.6)	0.97 (d, 6.4)	0.95 (d, 6.4)	0.95 (d, 6.5)
1′	3.36 (dt, 12.1, 6.0)	1.94 (dd, 14.8, 12.6)	3.69 (d, 2.4)	3.33 (dt, 12.1, 5.8)	1.91 (dd, 15.0, 12.0)
	—	2.70 (dd, 14.9, 3.7)	—	—	2.71 (dd, 15.0, 3.8)
3′	2.41 (t, 12.4)	2.86 (d, 13.0)	3.14 (d, 13.3)	2.38 (t, 12.3)	2.86 (d, 13.1)
	3.65 (dd, 12.7, 6.5)	3.00 (d, 13.0)	3.18 (d, 13.3)	3.64 (dd, 12.6, 5.6)	2.97 (d, 13.1)
5′	6.95 (dd, 8.1, 1.8)	6.91 (dd, 8.4, 1.5)	6.98 (s)[a]	6.94 (dd, 8.1, 1.9)	6.89 (dd, 8.4, 1.7)
6′	7.02 (dd, 8.1, 2.3)	6.86 (dd, 8.3, 2.2)	6.98 (s)[a]	7.03 (dd, 8.1, 2.4)	6.87 (dd, 8.3, 2.0)
8′	7.05 (dd, 8.6, 1.8)	7.05 (dd, 8.4, 2.3)	6.93 (d, 8.4)	7.06 (dd, 8.6, 2.4)	7.06 (dd, 8.4, 2.1)
9′	7.16 (dd, 8.6, 1.8)	7.10 (dd, 8.4, 1.7)	7.10 (d, 8.4)	7.08 (dd, 8.5, 1.9)	7.09 (dd, 8.4, 1.5)
N*H*	8.24 (br s)	6.15 (br s)	6.00 (d, 2.2)	7.53 (br s)	5.73 (br s)

[a] The proton signals were superimposed.
[b] The proton signal of this methyl group was overlapped with H_2O peak.

hirsutellones A–E. Structural elucidation of the new compounds was first, conducted for the most abundant constituent, hirsutellone B (**2**). The molecular formula of hirsutellone B (**2**) was determined as $C_{28}H_{33}NO_4$, by HRMS (ESI-TOF) and ^{13}C NMR spectroscopy. The IR spectrum of **2** showed a strong absorption band at ν_{max} 1683 (broad) cm^{-1} with shoulders at 1703 and 1670 cm^{-1}, consistent with the ^{13}C NMR signals assigned to a ketone (δ_C 200.9) and an amide (δ_C 172.1). The planar structure of **2** was deduced by analysis of ^{1}H and ^{13}C NMR, DEPT, COSY, HMQC and HMBC spectral data (Table 1). Thus, the tricyclic moiety of **2**, from C-3 through C-15, was a perhydrofluorene attached to a vinyl group (C-1, C-2) at C-3 and a methyl substituent at C-9. This ring system was connected at C-15 to a γ-lactam moiety via a ketone (C-16), as indicated by the HMBC correlations from H-15, H-17 and two H-1′ protons to the carbonyl (C-16). The γ-lactam system was deduced from the chemical shifts data and HMBC correlations from an amide proton (δ_H 6.15, D_2O exchangeable) to C-17 and C-1′, and from H-17 and H-1′ to a carbonyl carbon at δ_C 172.1 (C-18). HMBC correlations from H-17 methine, H-1′ and H-3′ methylene protons to a quaternary carbon at δ_C 87.6 led to the assignment of this carbon for the γ-position of the lactam ring (C-2′), and its up-field shift indicated the attachment of a hydroxyl group. HMBC correlations also revealed the presence of a *para*-substituted benzene ring (C-4′ to C-9′) attached to the C-3′ methylene carbon on one side and an oxygen atom on the other (C-7′, δ_C 158.3). The non-symmetrical appearance of the four aromatic protons (H-5′, H-6′, H-8′ and H-9′) and corresponding carbons indicated the restricted rotation of this benzene ring. This question was solved by the formation of the 13-membered ring resulted from the connection of C-7′ (of the benzene ring) with C-13 (of B-ring) via an ether linkage. HMBC correlation from H-13 to C-7′ clearly indicated this unusual linkage system, and it was strongly supported by the NOESY correlation between H-13 and one of the aromatic protons, H-8′ (Table 2).

Relative stereochemistry of hirsutellone B (**2**) was elucidated by analysis of NOESY spectral data (Fig. 1) and vicinal *J*-values. The cyclohexane moiety (C-ring) of the tricyclic system adopts a chair conformation. The vicinal coupling constants of $J_{12,7}=J_{7,8ax}=11.1$ Hz, $J_{9,10ax}=J_{10ax,11ax}=J_{11ax,12}=12.5$ Hz demonstrated the antiperiplanar relationships (axial orientations) of these six protons. This assignment was strongly supported by the NOESY correlations: H-7 to H-9, and H-12 to H-8ax and H-10ax, which revealed the *trans*-junction between B- and C-rings, with a β-orientation of H-7 and an α-orientation of H-12. H-14 showed NOESY correlations with H-2, H-7 and H-13, indicated the β-orientations of H-13, H-14 and the vinyl group (C-1, C-2). On the other hand, H-6 showed NOESY cross signals with H-8ax, H-12 and H-15, which placed both H-6 and H-15 on the α-face. The vicinal coupling constants of $J_{7,6}=11.1$ Hz, $J_{6,14}=J_{14,15}=11.5$ Hz demonstrated the connectivity for these four protons, all with antiperiplanar relationships. This data reveals a *trans*-junction between A- and B-rings. Relative stereochemistry and the approximate conformation of the 13-membered ring moiety were further, addressed by NOESY spectral analysis. Correlations between H-13 to H-8′, and H-15 to H-6′ enabled the

Table 2. ^{13}C NMR data for hirsutellones A–D (**1**–**4**) in $CDCl_3$

Position	**1**	**2**	**3**	**4**	**7** [lit.][a]	**10** [lit.][b]
1	118.6 (t)	116.4 (t)	116.7 (t)	125.0 (d)	112.0 (t)	114.1 (t)
2	136.9 (d)	137.3 (d)	138.0 (d)	128.1 (d)	146.3 (d)	141.5 (d)
3	37.97 (d)	44.0 (d)	41.4 (d)	33.7 (d)	41.6 (s)	36.7 (d)
4	127.4 (d)	128.7 (d)	128.9 (d)	128.0 (d)	130.7 (d)	121.7 (d)
5	127.7 (d)	127.2 (d)	127.1 (d)	125.3 (d)	138.5 (s)	136.1 (s)
6	43.1 (d)	42.4 (d)	41.6 (d)	42.7 (d)	53.0 (d)	52.9 (d)
7	50.5 (d)	50.0 (d)	49.7 (d)	50.3 (d)	41.5 (s)	46.9 (s)
8	38.02 (t)	38.0 (t)	37.9 (t)	37.9 (t)	49.0 (t)	47.5 (t)
9	33.2 (d)	33.1 (d)	33.1 (d)	33.1 (d)	28.0 (d)	27.7 (d)
10	36.6 (t)	36.5 (t)	36.5 (t)	36.5 (t)	45.5 (t)	44.5 (t)
11	29.4 (t)	29.4 (t)	29.3 (t)	29.5 (t)	27.3 (d)	26.7 (d)
12	56.0 (d)	55.7 (d)	55.7 (d)	55.7 (d)	60.9 (d)	52.2 (d)
13	87.1 (d)	84.5 (d)	82.9 (d)	86.9 (d)	90.7 (d)	90.8 (d)
14	48.0 (d)	47.2 (d)	45.8 (d)	48.9 (d)[c]	50.6 (d)	43.5 (d)
15	54.2 (d)	48.9 (d)	49.8 (d)	53.2 (d)	56.7 (d)	49.7 (d)
16	198.6 (s)	200.9 (s)	199.5 (s)	198.6 (s)	200.2 (s)	209.6 (s)
17	59.9 (d)	54.0 (d)	58.5 (s)	59.7 (d)	56.7 (d)	53.3 (d)
18	170.2 (s)	172.1 (s)	167.8 (s)	169.1 (s)	171.8 (s)	172.3 (s)
1-CH_3	—	—	—	13.4 (q)	—	—
3-CH_3	—	—	—	—	25.7 (q)	—
5-CH_3	—	—	—	—	20.9 (q)	24.8 (q)
7-CH_3	—	—	—	—	16.0 (q)	22.9 (q)
9-CH_3	22.5 (q)	22.5 (q)	22.5 (q)	22.5 (q)	22.8 (q)	22.8 (q)
11-CH_3	—	—	—	—	19.8 (q)	19.8 (q)
1′	49.6 (d)	34.5 (t)	65.4 (d)	48.8 (d)[c]	33.4 (t)	36.7 (t)
2′	176.2 (s)	89.1 (s)	84.5 (s)	175.6 (s)	88.8 (s)	87.6 (s)
3′	35.6 (t)	46.7 (t)	44.0 (t)	35.8 (t)	47.0 (t)	44.6 (t)
4′	132.8 (s)	127.5 (s)	126.2 (s)	132.6 (s)	127.9 (s)	132.2 (s)
5′	129.9 (d)	131.4 (d)	131.1 (d)	130.3 (d)	133.3 (d)	133.1 (d)
6′	123.3 (d)	121.8 (d)	122.2 (d)	122.6 (d)	118.8 (d)	121.8 (d)
7′	158.6 (s)	158.3 (s)	158.6 (s)	158.9 (s)	159.8 (s)	157.3 (s)
8′	123.8 (d)	121.5 (d)	119.5 (d)	123.4 (d)	124.4 (d)	124.0 (d)
9′	130.7 (d)	131.7 (d)	131.9 (d)	130.8 (d)	131.5 (d)	131.7 (d)

[a] Literature data, in $CDCl_3$; Ref. 10.
[b] Literature data, in DMSO-d_6; Ref. 9.
[c] The assignment can be interchanged.

assignments of the aromatic protons. One of the C-1′ methylene protons situated at δ_H 1.94 showed an intense correlation to H-17. The large vicinal *J*-value (12.3 Hz) of these protons indicated the *cis*-relationship with a dihedral angle of approximately 0°. The NOESY correlations from another C-1′ methylene proton (δ_H 2.70) to H-9′ and Hβ-3′, and the correlations of the amide proton (NH) with Hα-3 (δ_H 3.00) and H-5′ strongly suggested that C-1′ methylene carbon of the γ-lactam situated on the β-face and the amide moiety on the opposite. On the basis of this spectral data, the relative stereochemistry of hirsutellone B (**2**) was proposed as depicted in the figure.

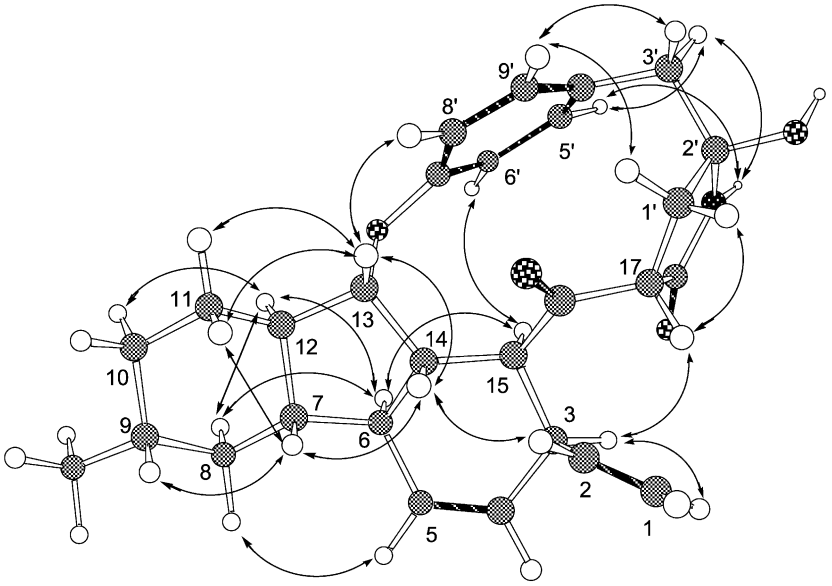


Figure 1. Plausible stereo structure of hirsutellone B (**2**). Selected NOESY correlations are illustrated with solid arrows.

The molecular formula of hirsutellone A (**1**) was determined as $C_{28}H_{31}NO_5$ by HRMS (ESI-TOF) and ^{13}C NMR data, possessing two hydrogen atoms less than hirsutellone B (**2**). Spectral analysis of **1** revealed that this compound contained a succinimide moiety instead of the γ-lactam, as in **2**. Thus, two amide carbonyl carbons were present (δ_C 176.2 and 170.2), which was consistent with the IR absorptions for carbonyls at ν_{max} 1769 and 1726 cm^{-1} in addition to another carbonyl (C-16, ketone) at 1702 cm^{-1}. Instead, the hemi-aminal carbon, as found in **2** (C-2′), was absent in hirsutellone A (**1**). Analysis of COSY and HMQC spectra of **1** indicated that benzylic methylene protons (H-3′) at δ_H 3.65 (dd, J=12.7, 6.5 Hz) and 2.41 (t, J=12.4 Hz) were vicinally coupled with a methine proton situated at δ_H 3.36 (dt, J=12.1, 6.0 Hz attached to C-1′, δ_C 49.6), which was connected to another methine (δ_H 3.52, d, J=6.4 Hz δ_C 59.9, C-17). The succinimide structure was confirmed by HMBC correlations from the imide proton (N*H*) to C-1′ and C-17. One of the imide carbonyl carbon, δ_C 176.2 (C-2′), was correlated from H-1′ and H-3′α (δ_H 2.41), while the other (δ_H 170.2, C-18) was correlated from H-17. The connectivity between the succinimide and the tricyclic ring moiety via a ketone (δ_C 198.6, C-16) was established by HMBC correlations to this carbonyl carbon from H-15, H-17 and H-1′. Stereochemistry of the succinimide moiety was revealed by the NOESY spectral data: H-17 showed correlation with H-3, H-3′α and H-5′, while H-1′ exhibited cross signals with H-3′β and H-9′. Finally, the proposed relative stereochemistry of hirsutellone A (**1**) was confirmed by X-ray crystallographic analysis (Fig. 2). The most interesting feature concerning the crystal structure of hirsutellone A is the 'bent' *para*-substituted benzene ring. This is due to the high ring strain, the aromatic nucleus can be viewed as part of an [8]paracyclophane system.[6]

Hirsutellone C (**3**), molecular formula $C_{28}H_{31}NO_5$ (HRMS, ^{13}C NMR), exhibited similar ^1H and ^{13}C NMR spectra to those of hirsutellone B (**2**), except for the part of γ-lactam moiety. Proton and carbon signals for methine of C-17 and methylene of C-1′ in **2** were lacking in **3**, instead, a quaternary carbon (δ_C 58.5, C-17) and a methine (δ_C 65.4, δ_H 3.69, C-1′) were present. In the HMBC spectrum of **3**, correlations from the amide proton (δ_H 6.00) to both of these carbons (C-17 and C-1′) were observed. Additional HMBC data, that is, benzylic protons (H-3′) to C-1′, and H-1 to C-18 (δ_C 167.8) and C-2′ (δ_C 84.5), indicated the presence of an epoxide in the γ-lactam moiety. Stereochemistry of the epoxide was addressed based on the NOESY correlations from H-1′ to H-3′β and H-9′, and the amide proton (N*H*) to H-3′α and H-5′.

The IR and UV spectra of hirsutellone D (**4**), a minor constituent, were very similar to those of hirsutellone A (**1**). The HRMS experiment and ^{13}C NMR data revealed its molecular formula as $C_{29}H_{33}NO_4$, having additional CH_2 unit to **1**. ^1H and ^{13}C NMR spectra of **4** indicated the presence of a *cis*-1-propenyl group replacing the vinyl group (C-1, C-2) observed in **1**. Thus, the signal attributable to the allylic methyl protons appeared as a doublet of doublets (δ_H 1.56, J=6.7, 1.4 Hz), and was vicinally coupled with H-1 (J=6.7 Hz). The *cis*-olefinic geometry was evident from the $J_{1,2}$-value of 10.9 Hz. NOESY correlations from the methyl protons to H-3, and H-2 to H-14, further, confirmed this partial structure. Other NOESY correlation data for **4** were similar to those of **1**. On the basis of these spectral data, hirsutellone D (**4**) was assigned as 1-methyl derivative of hirsutellone A (**1**).

Hirsutellone E (**5**) was obtained in very low quantity, 0.24 mg, from 10 L fermentation. UV spectrum of **5** (in MeCN–H_2O), acquired during its purification by semi-preparative HPLC/UV, was similar to that of **2**. ^1H NMR, COSY and NOESY spectral data of **5** strongly suggested that this compound was the 1-methyl analog of hirsutellone B (**2**). The HRMS data for **5**, *m/z* 460.2483 $[M-H]^-$ (Calcd for $C_{29}H_{34}NO_4$ 460.2488), indicated its molecular formula as $C_{29}H_{35}NO_4$, which was consistent with the proposed structure.

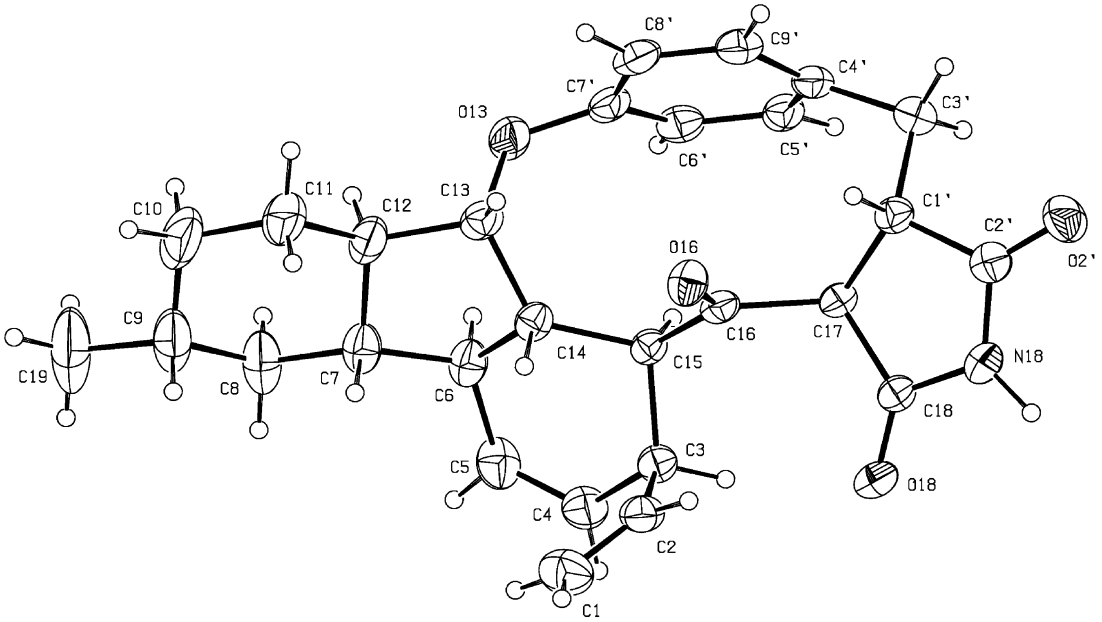
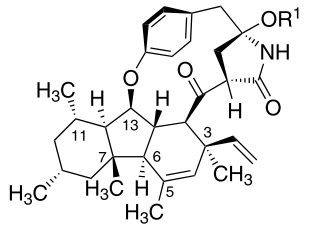
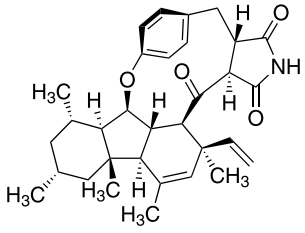


Figure 2. X-ray crystal structure of hirsutellone A (**1**). Thermal elipsoids given at 50% probability level.

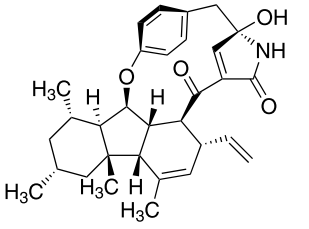
The structures of hirsutellones are related to those of GKK1032A$_1$ (**6**), GKK1032A$_2$ (**7**) and GKK1032B (**8**) isolated from *Penicillium* sp. GKK1032.[7,8] These compounds possess four additional methyl groups at C-3, C-5, C-7 and C-11. It is interesting to note that the relative stereochemistry of GKK1032s differs from that of hirsutellones at the C-13 position. Pyrrocidines A (**9**) and B (**10**), recently, isolated from an unidentified filamentous fungus *LL*-Cyan426,[9] also share a similar molecular framework, although their proposed relative stereochemistry on the tricyclic ring moiety differ from those of hirsutellones.



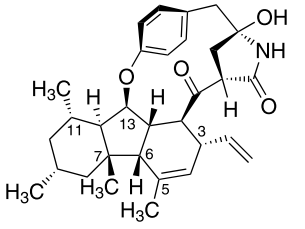
6: R^1 = CH$_3$ (GKK1032A$_1$)
7: R^1 = H (GKK1032A$_2$)



8 (GKK1032B)

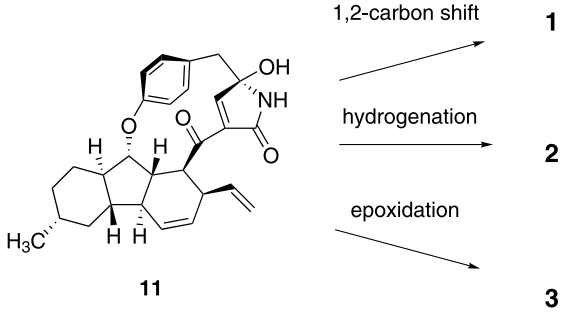


9 (pyrrocidine A)



10 (pyrrocidine B)

Biosynthesis of GKK 1032A$_2$ (**7**) has recently, been studied by administration of isotopically labeled (^{13}C and ^{2}H) precursors to *Penicillium* sp. GKK1032.[10] Thus, the backbone of **7** is constructed from L-tylosine and a nonaketide chain flanked by five methyl groups, probably by a polyketide synthase and a nonribosomal peptide synthetase hybrid. It is not unreasonable to assume that the proposed biosynthetic pathway could be applied to hirsutellones production by *H. nivea* BCC 2595. Final transformations may also be similar to those for GKK1032s. Thus, a 1,2-carbon shift from C-1′ to C-2′ in the plausible intermediate **11** should give rise to hirsutellone A (**1**), while hirsutellone B (**2**) could be produced by hydrogenation of **11**. The occurrence of the epoxide derivative, hirsutellone C (**3**), can also be reasonably explained by the same precursor (Scheme 1).



Scheme 1. Proposed biogenetic conversion from the plausible precursor **11** to **1**, **2** and **3**.

Hirsutellones A–D exhibited potent antitubercular activity (*Mycobacterium tuberculosis* H$_{37}$Ra) with MIC values of 0.78–3.125 μg/mL, while they were not or only weakly cytotoxic to Vero cells and three cancer cell-lines (KB, BC, NCI-H187) (Table 3). Amongst these compounds, hirsutellone A displayed the best selectivity index. Compounds **1**–**3** were inactive in our antimalarial (*Plasmodium falciparum* K1) activity assay at a concentration of 20 μg/mL, and they were also inactive against *Candida albicans* at a concentration of 50 μg/mL. Related compounds, pyrrocidines A and B, are known to exhibit antibiotic activities against Gram-positive bacteria,[9] whilst weak anti-tumor activity (Hela S3) was reported for GKK01032s.[7] Although the antimycobacterial activities of hirsutellones were much weaker than standard drugs, example isoniazid (MIC 0.06 μg/mL, in our assay system), the unique and rare chemical skeleton and good selectivity index deserve further, studies on structural modification.

3. Experimental

3.1. General experimental procedures

Melting points were measured with an Electrothermal IA9100 digital melting point apparatus and were uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. UV spectra were recorded on a Varian CARY 1E UV–Visible spectrophotometer. FT-IR spectra were taken on a Bruker VECTOR22 spectrometer. Mass spectra (ESI-TOF) were measured with a Micromass LCT mass spectrometer. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), DEPT and 2D NMR spectra (COSY, NOESY, HMQC and HMBC) were taken on a Bruker DRX400 spectrometer.

Table 3. Antimycobacterial and cytotoxic activities of hirsutellones A–D

Compound	Anti-tuberculosis (MIC, μg/mL) *M. tuberculosis* H$_{37}$Ra	cytotoxicity (IC$_{50}$, μg/mL)			
		KB	BC	NCI-H187	Vero
Hirsutellone A (**1**)	0.78	>20	>20	>20	>50
Hirsutellone B (**2**)	0.78	>20	>20	6.0	>50
Hirsutellone C (**3**)	0.78	4.6	3.2	8.3	12
Hirsutellone D (**4**)	3.125	>20	>20	7.3	—[b]
Isoniazid[a]	0.06	—[b]	—[b]	—[b]	—[b]

[a] Standard antitubercular drug.
[b] Not tested.

3.2. Fungal material

Hirsutella nivea Hywel-Jones (Ascomycota, Mitosporic, Hypocreales, Clavicipitaceae)[11] was collected, identified and isolated from Homoptera-leaf-hopper, Khao Yai National Park, Central Thailand, by Dr. Nigel. L. Hywel-Jones. This fungus was deposited at the BIOTEC Culture Collection as BCC 2594.

3.3. Fermentation, extraction and isolation

BCC 2594 was maintained on potato dextrose agar at 25 °C for 16 days, the agar was cut into pieces (1×1 cm) and inoculated into 4×250 mL Erlenmeyer flasks containing 25 mL of potato dextrose broth (PDB; composition, potato starch 4.0 g, dextrose 20.0 g/L). After incubation at 25 °C for 8 days on a rotary shaker (200 rpm), each primary culture was transferred into a 1 L Erlenmeyer flask containing 250 mL of the same liquid medium (PDB), and incubated at 25 °C for 8 days on a rotary shaker (200 rpm). Each 25 mL portion of the secondary cultures (in 4 flasks) was transferred into 32×1 L Erlenmeyer flasks each containing minimum salt medium (composition; glucose 20.0 g, NH_4NO_3 3.0 g, KH_2PO_4 0.5 g, $MgSO_4 \cdot 7H_2O$ 0.5 g, $CaCl_2$ 0.5 g and yeast extract 1.0 g/L), and static fermentation was carried out at 25 °C for 40 days. The cultures were filtered and the residue (mycelial cake) was extracted with MeOH (1000 mL, rt, 2 days). After filtration, H_2O (50 mL) was added to the filtrate, washed with hexane (400 mL), and the aqueous MeOH layer was concentrated under reduced pressure. The residual oil was dissolved in EtOAc (500 mL), washed with H_2O (150 mL), and concentrated to obtain a brown gum (1.57 g). This mycelial extract was passed through a Sephadex LH-20 column (3×25 cm; MeOH as eluent). Fractions containing hirsutellones were combined and subjected to column chromatography on silica gel ($MeOH/CH_2Cl_2$, step gradient elution) to obtain three fractions, Fr-A (a mixture of **1** and **4**, 140 mg), Fr-B (contained **3**, 35 mg), Fr-C (a mixture of **2**, **3** and **5**, 153 mg). Fr-A was subjected to preparative HPLC using a reversed-phase column (Prep Nova-Pak HR C_{18}, 6 μm, 40×100 mm) with $MeCN/H_2O$=75:25 as eluent at a flow rate of 20 mL/min to yield hirsutellones A (**1**; 76.1 mg, t_R 18 min) and D (**4**; 2.9 mg, t_R 23 min). Preparative HPLC ($MeCN/H_2O$ =65:35) of Fr-B provided hirsutellone C (**3**, 13.6 mg, t_R 19 min). Trituration of Fr-C in MeOH (1 mL, r.t., 5 h) gave colorless solid of hirsutellone B (**2**, 92.0 mg). The filtrate was subjected to preparative HPLC ($MeCN/H_2O$=65:35) to obtain **2** (35.9 mg, t_R 16 min), **3** (1.6 mg, t_R 19 min) and hirsutellone E (**5**; 0.24 mg, t_R 21 min).

3.3.1. Hirsutellone A (1). Colorless solid; mp 155–157 °C; $[\alpha]^{29}_D$ +168° (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.42), 228 sh (3.72), 281 sh (2.99) nm; IR (KBr) ν_{max} 3473, 2920, 1769, 1726 (sh), 1702, 1505, 1359, 1239, 1192 cm^{-1}; HRMS (ESI-TOF, negative) *m/z* 444.2183 $[M-H]^-$ (Calcd for $C_{28}H_{30}NO_4$ 444.2175; Δ=1.8 ppm); ^1H and ^{13}C NMR data in $CDCl_3$, Tables 1 and 2.

3.3.2. Hirsutellone B (2). Colorless solid; mp 261–263 °C (dec); $[\alpha]^{27}_D$ +256° (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 203 (4.37), 227 sh (3.78), 276 sh (2.99) nm; IR (KBr) ν_{max} 3405, 3647, 2917, 1708 (sh), 1683, 1670 (sh), 1508, 1241, 1093 cm^{-1}; HRMS (ESI-TOF, negative) *m/z* 446.2336 $[M-H]^-$ (Calcd for $C_{28}H_{32}NO_4$ 446.2332; Δ= 0.9 ppm); ^1H and ^{13}C NMR data in $CDCl_3$, Tables 1 and 2.

3.3.3. Hirsutellone C (3). Colorless solid; mp 234–235 °C (dec); $[\alpha]^{29}_D$ +129° (*c* 0.20, MeOH); UV (MeOH) λ_{max} (MeOH) 203 (4.42), 230 (3.93), 277 (3.12) nm; IR (KBr) ν_{max} 3396, 3264, 2921, 1713, 1698 (sh), 1687 (sh), 1507, 1241, 1134, 923 cm^{-1}; HRMS (ESI-TOF, negative) *m/z* 460.2121 $[M-H]^-$ (Calcd for $C_{28}H_{30}NO_5$ 460.2124; Δ= 0.7 ppm); ^1H and ^{13}C NMR data in $CDCl_3$, Tables 1 and 2.

3.3.4. Hirsutellone D (4). Colorless amorphous solid; mp 106–109 °C; $[\alpha]^{29}_D$ +214° (*c* 0.07, MeOH); UV (MeOH) λ_{max} (log ε) 204 (4.46), 229 sh (3.78), 283 sh (3.07) nm; IR (KBr) ν_{max} 3226, 2914, 1780, 1723, 1707, 1504, 1353, 1246, 1183 cm^{-1}; HRMS (ESI-TOF, negative) *m/z* 458.2325 $[M-H]^-$ (Calcd for $C_{29}H_{32}NO_4$ 458.2332; Δ=1.5 ppm); ^1H and ^{13}C NMR data in $CDCl_3$, Tables 1 and 2.

3.3.5. Hirsutellone E (5). Colorless amorphous solid; UV ($MeCN/H_2O$) λ_{max} 227 (sh), 276 nm; HRMS (ESI-TOF, negative) *m/z* 460.2483 $[M-H]^-$ (Calcd for $C_{29}H_{34}NO_4$ 460.2488; Δ=1.1 ppm); ^1H NMR data in $CDCl_3$, Table 1.

3.4. X-ray crystallographic analysis of hirsutellone A (1)

Crystal data for compound **1** at 298 (2) K: $C_{28}H_{31}NO_4 \cdot H_2O$, M_r=463.57, orthorhombic, space group $P2_12_12_1$ (No. 19) with *a*=9.3530 (3) Å, *b*=15.8703 (7) Å, *c*=34.1922 (14) Å, *V*=5075.3 (3) $Å^3$, *Z*=8, D_{calc}=1.169 Mg/m^3. F_{000}=1912, λ (Mo Kα)=0.71073 Å, μ=0.077 mm^{-1}. Data collection and reduction: crystal size 0.10×0.15×0.20 mm, θ range 1.02–21.49°, 17033 reflection collected, 3318 independent reflections (R_{int}=0.053), final *R* indices ($I>2\sigma(I)$: 0.0433, wR_2=0.1054 for 615 parameters, GOF=1.091. Intensity data were measured on a Bruker–Nonius kappa CCD diffractometer. Crystallographic data for the structure **1** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 257861. 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].

3.5. Biological assays

Growth inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Ra$ was performed using the Microplate Alamar Blue Assay (MABA) described by Collins and Franzblau.[12] Cytotoxic activities of the purified compound to Vero cells (African green monkey kidney fibroblast) and three cancer cell-lines, KB (human epidermoid carcinoma on the mouth), BC (human breast cancer) and NCI-H187 (human small cell lung cancer), were evaluated using the colorimetric method.[13]

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New reaction of enamines with aryldiazoacetates catalyzed by transition metal complexes

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Abstract—The reaction of aryldiazoacetates with enamines catalyzed by copper and rhodium complexes provided γ-keto esters in good yields. A full investigation of the effects of solvents, catalysts, enamines and aryldiazoacetates on the reaction was carried out. Careful analysis of the crude reaction mixture revealed a substituted enamine as the primary product, which was hydrolyzed over silica gel to give a γ-keto ester as the final product. A reaction mechanism involving nucleophilic addition of an enamine to a metal carbene and subsequent hydrogen transfer was proposed. Chiral dirhodium and copper catalysts were examined and found to provide γ-keto esters with no enantioselectivity. The result could be rationalized based on the proposed reaction mechanism. Attempts to trap the enamine intermediate with several electrophilic reagents were not successful.

1. Introduction

Transition metal catalyzed reactions of diazo compounds have been widely used in organic synthesis in the past two decades.[1] The reactions of diazo compounds with electron-rich olefins usually provide cyclopropanes in good yields. However, in the reaction of diazo compounds with some polarizable olefins such as enol ethers, dihydrofurans and enamines, the formation of other abnormal products has been reported. Wenkert et al. reported the cyclopropanation of enol ether with diazoacetates catalyzed by copper salts provided oxycyclopropanes,[2] but Alonso found that the reaction of enol ethers with diazomalonates afforded 'apparent' vinyl insertion product.[3] The reaction of enamines with ethyl diazoacetate (EDA) in the presence of cuprous chloride or silver oxide unexpectedly gave α-diazo-β-amino-ester in good yield.[4] The reaction was probably proceeded via a nucleophilic addition of EDA to iminium cation formed by isomerization of enamine under the reaction conditions. The addition of EDA to enamine catalyzed by *N*-α-(4-chlorophenyl)isobutyl-(salicylaldimino)copper complex was reported to give aminocyclopropane product in low yield,[5] however, the addition of diazomethane to enamine catalyzed by cuprous chloride could provide aminocyclopropane derivatives in good yields.[6] The reaction of semicyclic enaminocarbonyl compounds with EDA provided enamino esters probably via the rearrangement of the 2-acyl-3-aminocyclopropane-1-carboxylate intermediates.[7] On the other hand, the reaction of semicyclic enaminocarbonyl compounds with vinyldiazoacetates was found to afford betaines as major products.[8] In the absence of transition metal catalysts, the addition of EDA to enamines could provide either dihydropyrazoles or azo coupling products depending on the structure of the enamine.[9] In our preliminary study of the catalyzed reaction of enamines with aryldiazoacetates, we have found the reaction could provide γ-keto esters in excellent yields.[10] In this paper, we report the full investigation of this new reaction.

2. Results and discussion

The reaction of methyl phenyldiazoacetate (**1a**) with *N*-(1-styryl)morpholine (**2a**) was studied in the presence of 1 mol% $Rh_2(OAc)_4$. Disappearance of **1a** was observed in less than 1 h. Purification of reaction mixture via column chromatography over silica gel provided a white solid in good yield, which was unambiguously confirmed as methyl 4-oxo-2,4-diphenylbutanoate (**3a**) by combination of ^1H, ^{13}C NMR and mass spectral analyses (Scheme 1).[11] None of the expected aminocyclopropane product was found after careful examination of the reaction mixture. This unusual result promoted us to study the new reaction in detail.

Keywords: Enamine; Diazo compound; Catalysis; γ-Keto esters; Dirhodium tetraacetate; Copper salt.
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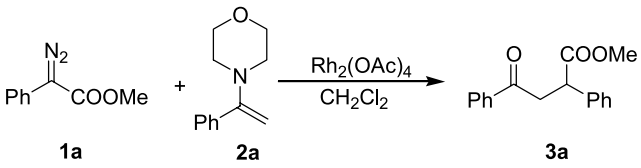


Scheme 1.

2.1. Catalysts

The reaction of methyl phenyldiazoacetate (**1a**) with *N*-(1-styryl)morpholine (**2a**) did not occur in the absence of a catalyst. In addition to $Rh_2(OAc)_4$, a variety of dirhodium and copper catalysts were also examined in this transformation and the results were summarized in Table 1. Most of tested dirhodium and copper catalysts showed very good catalytic activity. $Cu(hfacac)_2$ was preferred due to its excellent chemical yield and relative low price. It was noticeable that in previous studies copper catalysts were found to be less effective than $Rh_2(OAc)_4$ for the reaction involving aryldiazoacetates.[12] The ratio of enamine to diazo compound also played an important role for the yield of the reaction. The use of excess enamine efficiently increases the yield probably due to partly decomposition of enamine under reaction conditions (entry 6 vs entry 3).

Table 1. Reaction of **1a** with **2a** catalyzed by copper and dirhodium complexes[a]

Entry	Catalyst (mol%)	**2a**:**1a** (mol/mol)	Time (h)	Yield (%)[b]
1	$Rh_2(OAc)_4$ (1 mol%)	1:1	0.5	63
2	$Cu(hfacac)_2$ (1 mol%)[c]	1:1	0.5	58
3	$Cu(hfacac)_2$ (3 mol%)	1:1	0.5	63
4	$Cu(OTf)_2$ (3 mol%)[d]	1:1	1	59
5	CuI (3 mol%)	1:1	10	50
6	$Cu(hfacac)_2$ (3 mol%)	1.5:1	0.5	80
7	$CuPF_6$ (3 mol%)	1.5:1	0.5	78
8	$Cu(acac)_2$ (3 mol%)	1.5:1	6	78
9	**4** (1 mol%)	1.5:1	3.5	84
10	**5**/$Cu(hfacac)_2$ (1.1/1 mol%)	1.5:1	1	60
11	**5**/$Cu(OTf)_2$ (1.1/1 mol%)	1.5:1	4	46
12	**5**/$CuPF_6$ (1.1/1 mol%)	1.5:1	1	60
13	**6**/$Cu(hfacac)_2$ (1.1/1 mol%)	1.5:1	9.5	0

[a] The reactions were carried out with 1 mmol **1a** in refluxing dichloromethane.
[b] Isolated yields after column chromatography.
[c] $Cu(hfacac)_2$=bis-hexafluoroacetoacetonato copper (II).
[d] $Cu(OTf)_2$=copper (II) bis-trifluoromethanesulfonate

Chiral dirhodium and copper catalysts were also examined in the reaction to achieve enantioselectivity (Scheme 2). Davies' catalyst **4** provided **3a** in excellent yield (entry 9). Readily available chiral diimine ligand **5** combined with $Cu(hfacac)_2$, $Cu(OTf)_2$ or $CuPF_6$ could also give **3a** in good yield (entries 10–12). However, in these reactions the product **3a** was found to be racemic after determination by chiral HPLC. On the other hand, the complex of chiral salen **6** and copper salt did not show any catalytic activity (entry 13).

2.2. Solvent choice

The reaction of **1a** with **2a** was carried out in a variety of solvents using $Cu(hfacac)_2$ as the catalyst and the results were summarized in Table 2. It is amazing that all tested solvents provided good yields of **3a**, despite in the hexane $Cu(hfacac)_2$ and $Rh_2(OAc)_4$ were almost insoluble. The extremely high reactivity of enamines toward the carbenoid may overturn the possible solvent effects.

Table 2. Solvent effect in the reaction of **1a** with **2a**[a]

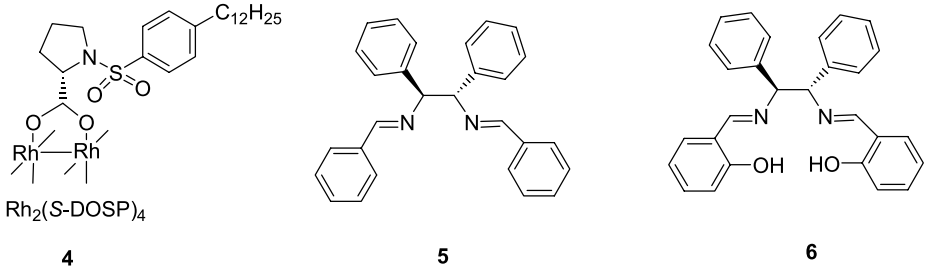
Solvent	Yield (%)[b]
CH_2Cl_2	80
Hexane	72
Hexane[c]	75
Benzene	78
Toluene	78
THF	77
$ClCH_2CH_2Cl$	77

[a] The reactions were carried out with 1 mmol **1a**, 1.5 mmol **2a** and 0.03 mmol $Cu(hfacac)_2$ under refluxing.
[b] Isolated yields after column chromatography.
[c] 1 mol% $Rh_2(OAc)_4$ was used as catalyst.

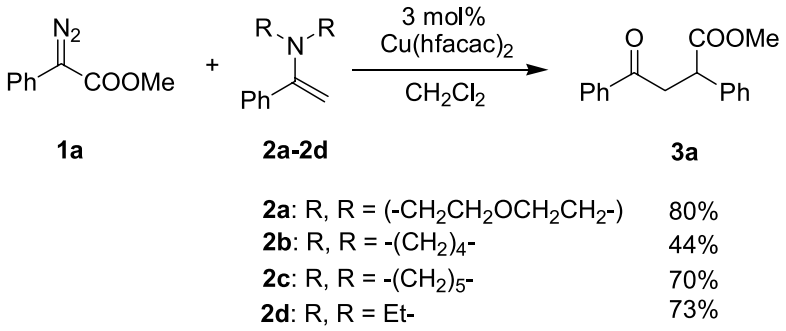
2.3. The effect of enamines

Enamines **2a**–**2d** were prepared from acetophenone and several secondary amines and examined in the reaction with methyl phenyldiazoacetate **1a** (Scheme 3). Both cyclic and acyclic secondary amines could be used for this transformation and provided variable yields of **3a**. Enamine **2a** derived from morpholine afforded best yield of **3a**.

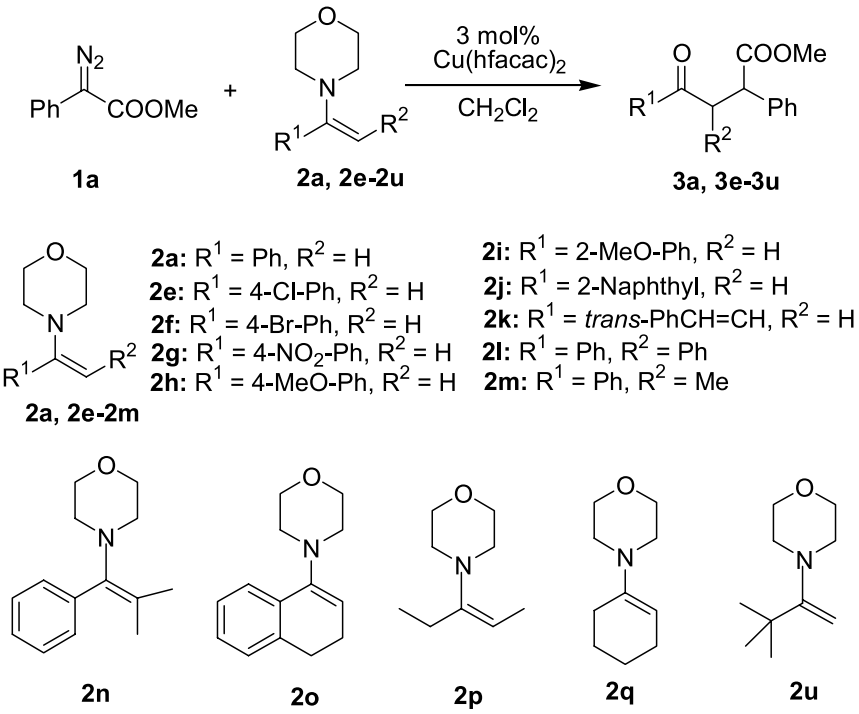
Enamines **2e**–**2u** derived from morpholine and different ketones were also examined in the reaction with **1a** (Scheme 4). The experiment results were summarized in Table 3. Enamines **2a**, **2e**–**2h** derived from unhindered aryl methyl ketone provided good yields of γ-keto esters. However, low yields were observed with enamines **2i** and **2j**, presumably due to their intense steric hindrance. β-Phenyl or methyl substituted enamines **2l** or **2m** also gave good yield of γ-keto esters as a mixture of two diastereomers. β,β-Disubstituted enamine **2n** and sterically demanding enamine **2o** did not afford substantial amount of



Scheme 2.



Scheme 3.



Scheme 4.

Table 3. Reaction of enamines **2a**, **2e**–**2u** with **1a**[a]

Entry	Enamine	Time (h)	Yield (%)[b]
1	**2a**	0.5	80
2	**2e**	1	67
3	**2f**	0.5	60
4	**2g**	1	54
5	**2h**	1	79
6	**2i**		33
7	**2j**	1	50
8	**2k**	3	0
9	**2l**	3.5	78[c]
10	**2m**	1	79[d]
11	**2n**	0.5	0
12	**2o**	1	0
13	**2p**	0.5	0
14	**2q**	1	0
15	**2u**	1	0

[a] The reactions were carried out with 1 mmol **1a**, 1.5 mmol enamine and 0.03 mmol $Cu(hfacac)_2$ in refluxing CH_2Cl_2.
[b] Isolated yields after column chromatography.
[c] The product was obtained as a mixture of two diastereomer (2:1).
[d] The product was obtained as a mixture of two diastereomer (1.5:1).

γ-keto esters. It is unexpected that the dialkyl ketone derived enamines **2p**–**2u** could not react with methyl phenyldiazoacetate, although these enamines were found to be good nucleophilic reagents in previous studies. No reliable explanation can be proposed at the present time.

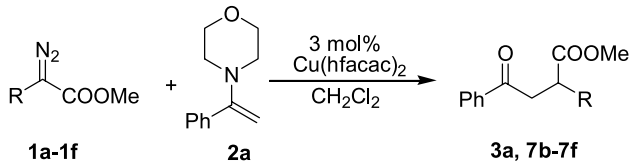
2.4. The effect of diazo compounds

Several methyl aryldiazoacetates **1a**–**1f** were prepared and tested in the reaction with enamine **2a**. The results were summarized in Table 4. All aryl- and heteroaryl-diazoacetates examined in the reaction gave good yields of γ-keto esters. In another study, we also found the reaction of enamines with ethyl diazoacetate (EDA) provided corresponding γ-keto esters in excellent yields.[13]

2.5. Asymmetric synthesis of γ-keto esters

To the best of our knowledge, no efficient synthesis of chiral 2-aryl γ-keto esters had been reported. Our present studies

Table 4. The reactions of methyl aryldiazoacetates **1a–1f** with enamine **2a**[a]



R	Time (h)	Yield (%)[b]
Ph (**1a**)	0.5	80
4-BrC_6H_4 (**1b**)	1.5	85
β-Naphthyl (**1c**)	1	83
α-Naphthyl (**1d**)	1	76
2-Thiophyl (**1e**)	1	55
3-Indolyl (**1f**)	1	60

[a] The reactions were carried out with 1 mmol **1a–1f**, 1.5 mmol **2a** and 0.03 mmol $Cu(hfacac)_2$ in refluxing CH_2Cl_2.
[b] Isolated yields after column chromatography.

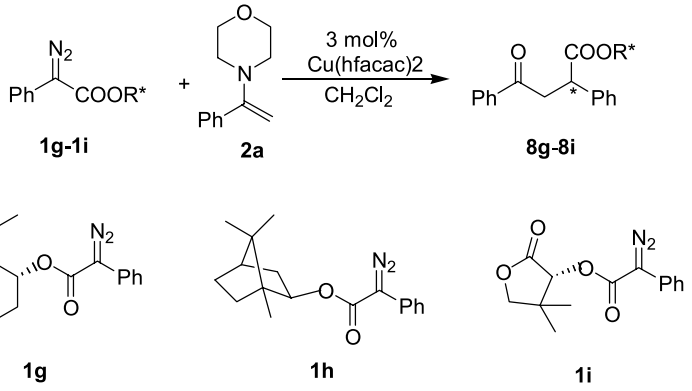
provided two possible pathways for the asymmetric synthesis of γ-keto esters. Davies catalyst **4** and chiral diimine-copper catalysts were studied, but the resulting γ-keto esters were found to be racemic (vide anti). Alternatively, phenyldiazoacetates derived from several commercially available chiral alcohols were prepared and studied in the reaction (Scheme 5). The structure of chiral alcohols showed profound effect on the results of the reactions. **1g** and **1h** did not react with enamine **2a** using $Cu(hfacac)_2$ or $Rh_2(OAc)_4$ as the catalyst, but **1i** could react with **2a** to give γ-keto ester **8i** in good yield using $Cu(hfacac)_2$ as the catalyst. The low reactivity of **1g** and **1h** may be resulted from larger steric hindrance than **1i**.

Other two copper salts and $Rh_2(OAc)_4$ were also examined as the catalyst in the reaction of **1i** with **2a** and the results were summarized in Table 5. The catalysts showed significant effects on the chemical yields of the reactions. The product **8i** obtained from the copper catalysts showed the same diastereoisomer ratio about 2:1 via the ^1H NMR analysis. It is very interesting that $Rh_2(OAc)_4$ was inefficient for the reaction of **1i** with **2a**.

In recent years, proline catalyzed asymmetric aldol reactions received much attention.[14] The formation of chiral enamine intermediate from proline and ketones was thought to be the key step in this methodology. We studied the possible formation of the enamine intermediate in situ from acetophenone and proline, which could undergo a consequent reaction with diazo compound to provide chiral γ-keto esters. Unfortunately, the reaction failed to give γ-keto ester **3a** (Scheme 6).

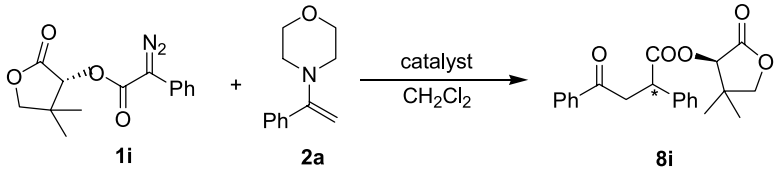
2.6. Reaction mechanism

In the reaction of enamine **2a** with methyl phenyldiazoacetate **1a** catalyzed by $Rh_2(OAc)_4$, analysis of the crude reaction mixture with ^1H NMR revealed only very weak



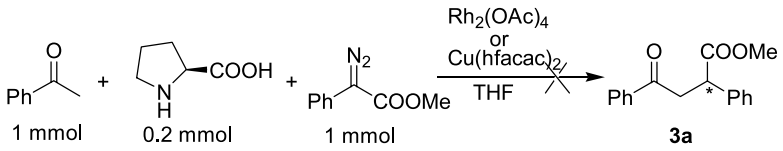
Scheme 5.

Table 5. The reaction of **1i** with **2a**[a]



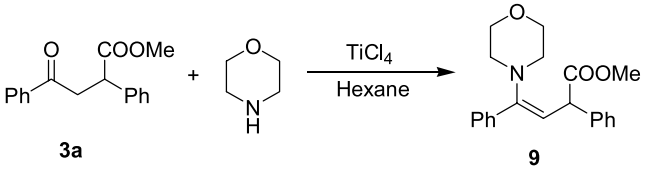
Catalyst (mol%)	Time (h)	Yield (%)[b]	Diastereomer ratio[c]
$Cu(hfacac)_2$ (3 mol%)	0.5	70	2:1
$CuPF_6$ (3 mol%)	2.5	40	2:1
$Cu(CF_3SO_3)_2$(3 mol%)	6	30	2:1
$Rh_2(OAc)_4$(1 mol%)	8	N.R.[d]	N.A.[e]

[a] The reactions were carried out with 1 mmol **1i** and 1.5 mmol **2a** in refluxing CH_2Cl_2.
[b] Isolated yields after column chromatography.
[c] Determined by the ^1H NMR of crude product.
[d] No reaction.
[e] Not applicable.



Scheme 6.

signals assigned for γ-keto ester **3a**. Instead another compound was found to be the major component, which provided the following ^{1}H NMR spectrum: 7.36–7.19 (comp, 10H), 5.08 (d, J=10.4 Hz, 1H), 4.18 (d, J=10.4 Hz, 1H), 3.87–3.78 (comp, 2H), 3.71–3.65 (comp, 2H), 3.63 (s, 3H), 3.10–2.96 (comp, 2H), 2.83–2.74 (comp, 2H). Its IR spectrum revealed two strong absorption bands at 1731.38 and 1615 cm^{-1}, indicating existence of a carbonyl group and a double bond. According to these data this compound was assigned as the enamine **9**. Further attempt to purify and characterize **9** was unsuccessful due to its unstable property. A control test was carried out to verify the structure of **9**. Treatment of **3a** with morpholine in the presence of $TiCl_4$ gave a crude product, which provided identical ^{1}H NMR and IR spectra with **9** obtained above (Scheme 7).



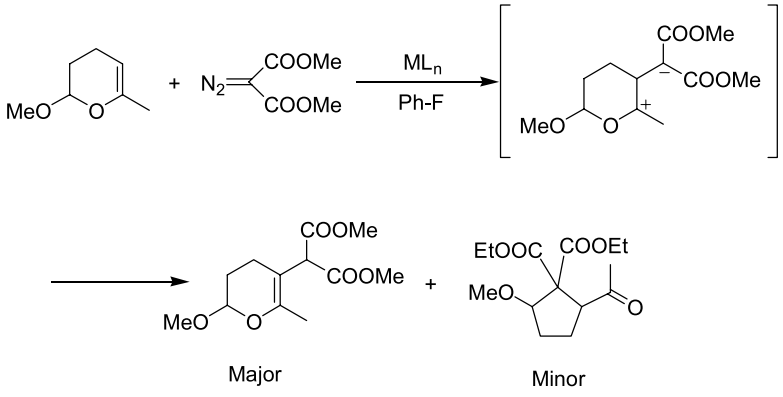
Scheme 7.

Transition metal catalyzed reactions of olefins with diazo compounds usually provide cyclopropanes in good yield. The early proposed reaction mechanism of involving metallocyclobutane has been discarded.[15] Instead a concert reaction mechanism was suggested, in which no considerable charge buildup was occurred in the transition state.[16] However, in the reaction of some polarizable olefins with diazo compounds, formation of abnormal products was observed. Alonso et al. found a vinyl C–H insertion in the reaction of vinyl ether with diazomalonates and suggested an addition–elimination mechanism through highly polarized zwitterionic intermediates (Scheme 8).[3] Doyle suggested a similar explanation, in which a competitive hydrogen transfer step was proposed.[1a] Davies suggested the involvement of zwitterionic intermediates in rhodium-catalyzed reaction of vinyldiazoacetates with electron-rich dienes.[17] Mass also proposed an addition-proton transfer mechanism to rationalize the formation of 'apparent' enaminic C–H insertion products in the reaction of enaminocarbonyl compounds with vinyldiazoacetates.[8]

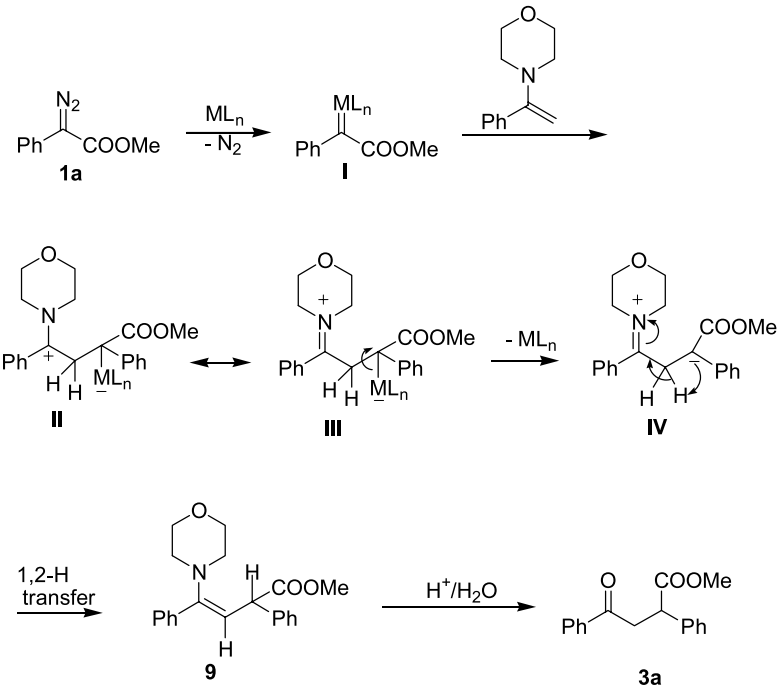
Based on these suggestions and our present experiment results, a possible mechanism for the reaction of enamine **2a** with methyl phenyldiazoacetate **1a** was proposed (Scheme 9). Nucleophilic addition of **2a** to the highly electron-deficient metal carbene (**I**) produced a zwitterionic intermediate (**II**). The developed positive charge at the carbon could be stabilized efficiently by nitrogen atom through resonance structure (**III**). The observed results, which chiral dirhodium and copper catalysts did not provide any enantioselectivity, supported the occurrence of an intermediate **IV** without association of chiral catalysts. The **IV** underwent a proton transfer with complete preference over the competitive cyclopropanation process to provide enamine **9**, which was hydrolyzed over silica gel to give γ-keto ester **3a** as the final product.

2.7. Trapping the enamine intermediate 9

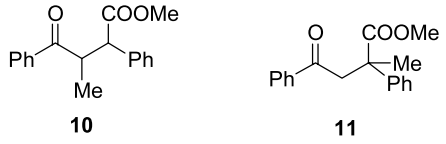
The enamine intermediate **9** may be trapped by electrophilic reagents. For this purpose, the reaction of enamine **2a** with methyl phenyldiazoacetate **1a** was carried out in the presence of excess methyl iodide (3 equiv). The reaction still gave γ-keto ester **3a** in good yield. No alkylation product **10** (from enamine intermediate **9**) or **11** (from intermediate **IV**) was observed (Scheme 10). Other electrophilic reagents such as allyl bromide and benzaldehyde were also examined and no addition product from enamine **9** could be determined.



Scheme 8.



Scheme 9.



Scheme 10.

3. Conclusions

In conclusion, we have found an unusual reaction of aryldiazoacetates with enamines leading to γ-keto esters. A reaction mechanism involving nucleophilic addition of enamines to metal carbenes and subsequent hydrogen transfer was proposed. Enamines derived from aryl alkyl ketone underwent this transformation to provide γ-keto esters in good yield, however, enamines derived from dialkyl ketones and α,α-disubstituted aryl alkyl ketones were not applicable for this reaction. On the other hand, the reaction tolerated many aryl and heteroaryl diazoacetates. Enantioselectivity of the reaction could not be achieved with chiral dirhodium and copper catalysts. The result could be rationalized based on the proposed reaction mechanism. Further studies are under the way to expand the reaction to other types of diazo compounds.

4. Experimental

4.1. General

All reactions were carried out in oven-dried glassware using standard Schlenk technique under argon atmosphere. Hexane, THF, benzene and toluene were distilled from sodium–benzophenone. Dichloromethane and 1,2-dichloroethane were distilled over CaH_2. Other solvents were used as their commercial anhydrous grade. The Flash column chromatography was carried out on Merck Silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer as solutions in d_3-chloroform. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm, δ) downfield from the internal standard Me_4Si (TMS). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal ($\delta = 77.00$ ppm). Infrared spectra were recorded on a Nicolet FT-IR500 spectrometer using KBr pellets and absorption is reported in wave-numbers (cm^{-1}). High-resolution mass spectra were obtained with a GCT-TOF instrument. Elemental analyses were performed on a Carlo–Erba EA1110 CNNO-S analyzer. Unless otherwise stated, all chemicals were purchased from Aldrich or Acros chemical company and used thus, without further purification. *p*-Acetamidobenzenesulfonyl azide (ABSA),[18] aryldiazoacetates[19] and enamines[20] were prepared according to known procedures.

4.1.1. Representative procedure for the preparation of methyl aryldiazoacetates. To a solution of methyl phenylacetate (600 mg, 4 mmol) and ABSA (4-acetamidobenzenesulfonyl azide) (1.06 g, 4.4 mmol) in anhydrous acetonitrile (8 mL) under an ice-bath, was added DBU (0.64 mL, 4.4 mmol) over 15 min. The resulting solution was stirred under an ice-bath for 2 h. The solution was passed through a short silica gel plug and eluted with dichloromethane until all red color had been collected. The filtrate was concentrated under reduced pressure at 20 °C and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15/1) to afford methyl phenyldiazoacetate (**1a**) as red oil (539 mg, 76.6%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.20 (comp, 5H), 3.86 (s, 3H).

4.1.2. Representative procedure for the preparation of phenyldiazoacetates derived from chiral alcohols. To a solution of (*R*)-pantolactonyl phenylacetate (0.78 g, 3.14 mmol) and ABSA (0.98 g, 4.08 mmol) in acetonitrile (30 mL), was added dropwise DBU (0.47 mL, 3.14 mmol) at 0 °C. The solution was stirred at room temperature for 15 h and quenched with saturated solution of NH_4Cl (30 mL). The aqueous layer was extracted with ether (30 mL×3). The combined organic layer was washed with brine and dried over $MgSO_4$. After the solvent was evaporated in vacuum, the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=4/1) to afford **1i** as brown oil (0.64 g, 75%). IR ($CHCl_3$) (ν_{max}): 2100 (m), 1745 (s), 1705 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51–7.19 (m, 5H), 5.55 (s, 1H), 4.09 (s, 2H), 1.28 (s, 3H), 1.15 (s, 3H).

4.1.3. Representative procedure for the preparation of enamines. To a solution of acetophenone (5 mL, 43 mmol) and morpholine (22.4 mL, 257 mmol) in anhydrous hexane (100 mL), was added $TiCl_4$ (2.6 mL, 23 mmol) over 10 min. The reaction mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated under vacuum to give colorless oil, which was distilled under reduced pressure (0.03 mmHg, 85–90 °C) to give *N*-(1-styryl)morpholine (**2a**) as a pale yellow liquid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56–7.26 (comp, 5H), 4.33 (s, 1H), 4.20 (s, 1H), 3.77 (s, 4H), 2.85 (s, 4H).

4.1.4. Representative procedure for the reaction of aryldiazoacetates with enamines. To a round-bottomed flask equipped with a stirrer and an addition funnel under argon atmosphere, was charged *N*-(styryl)morpholine (**2a**) (0.284 g, 1.5 mmol), $Cu(hfacac)_2$ (14.3 mg, 0.03 mmol) and dichloromethane (3 mL). The reaction solution was heated in an oil-bath and kept refluxing. The addition funnel was charged with a solution of methyl phenyldiazoacetate (**1a**) (0.176 g, 1 mmol) in dichloromethane (3 mL), which was added dropwise to the reaction solution over 30 min. The reaction mixture was refluxed for additional 30 min. After the solvent was evaporated under vacuum, the crude product was purified by flash column chromatography (petroleum ether/ethyl acetate=10/1) over silica gel to give methyl 4-oxo-2,4-diphenylbutanoate (**3a**) as a white powder (0.214 g, 80%). IR (KBr): 3449 (w), 3062 (w), 2991 (w), 2951 (w), 1733 (s), 1685 (s), 1446 (m), 1336 (s), 1226 (m), 1202 (m), 1161 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, J=7.2 Hz, 2H), 7.57 (t, J=7.2, 6.8 Hz, 1H), 7.48–7.45 (comp, 2H), 7.32–7.27 (comp, 5H), 4.30 (dd, J=4.4, 10.4 Hz, 1H), 3.96 (dd, J=10.4, 19.2 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, J=4.4, 19.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 174.2, 138.7, 136.7, 133.7, 129.3, 129.0, 128.4, 128.2, 127.9, 52.7, 46.7, 43.2. HRMS (EI^+) calcd for $C_{17}H_{16}O_3$ (M^+): 268.1099; found: 268.1112. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 75.99; H, 6.11.

4.1.5. Methyl-4-oxo-4-(4-chlorophenyl)-2-phenylbutanoate (3e). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, J=8.4 Hz, 2H), 7.42 (d, J=8.4 Hz, 2H), 7.34–7.25 (comp, 5H), 4.28 (dd, J=2.8, 10.4 Hz, 1H), 3.92 (dd, J=10.4, 17.6 Hz, 1H), 3.69 (s, 3H), 3.22 (dd, J=3.2, 17.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.2, 174.2, 140.2, 138.6, 135.1, 129.9, 129.4, 129.39, 128.2, 128.1, 52.9, 46.7, 43.2. HRMS (EI^+) calcd for $C_{17}H_{15}O_3Cl(35)$ (M^+): 302.0710; found: 302.0698.

4.1.6. Methyl-4-oxo-4-(4-bromophenyl)-2-phenylbutanoate (3f). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J=8.8 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 7.34–7.25 (comp, 5H), 4.28 (dd, J=4.0, 10.0 Hz, 1H), 3.91 (dd, J=11.2, 18.4 Hz, 1H), 3.69 (s, 3H), 3.21 (dd, J=4.0, 18.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.1, 174.2, 138.5, 135.4, 132.3, 130.0, 129.4, 128.9, 128.2, 128.1, 52.8, 46.7, 43.1. HRMS (EI^+) calcd for $C_{17}H_{15}O_3Br(79)$ (M^+): 346.0205; found: 346.0197.

4.1.7. Methyl-4-oxo-4-(4-nitrophenyl)-2-phenyl-butanoate (3g). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, J=8.8 Hz, 2H), 8.13 (d, J=8.8 Hz, 2H), 7.38–7.26 (comp, 5H), 4.32 (dd, J=3.6, 10.4 Hz, 1H), 3.99 (dd, J=11.8, 18.0 Hz, 1H), 3.70 (s, 3H), 3.29 (dd, J=4.0, 18.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 174.0, 150.8, 141.1, 138.2, 129.6, 129.5, 128.2, 128.1, 124.3, 52.9, 46.7, 43.7. HRMS (EI^+) calcd for $C_{17}H_{15}NO_5$(M^+): 313.0950; found: 313.0965.

4.1.8. Methyl 4-oxo-4-(4-methoxyl-phenyl)-2-phenylbutanoate (3h). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, J=8.8 Hz, 2H), 7.35–7.26 (comp, 5H), 6.92 (d, J=8.8 Hz, 2H), 4.29 (dd, J=4.4, 10.4 Hz, 1H), 3.91 (dd, J=10.4, 17.6 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.23 (dd, J=4.4, 17.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.6, 174.4, 164.0, 138.9, 130.8, 129.8, 129.3, 128.2, 127.9, 114.1, 55.9, 52.8, 46.8, 42.9. HRMS (EI^+) calcd for $C_{18}H_{18}O_4$ (M^+): 298.1205; found: 298.1204. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.45; H, 6.09; found: C, 72.69; H, 6.24.

4.1.9. Methyl 4-oxo-4-(2-methoxyl-phenyl)-2-phenylbutanoate (3i). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, J=8.0 Hz, 1H), 7.47 (t, J=8.0, 7.6 Hz, 1H), 7.35–7.26 (comp, 5H), 7.01–6.94 (comp, 2H), 4.26 (dd, J=4.0, 10.8 Hz, 1H), 3.93 (dd, J=10.8, 19.6 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 3H), 3.36 (dd, J=4.0, 19.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.7, 174.6, 159.4, 139.0, 134.4, 131.0, 129.2, 128.3, 127.8, 127.5, 121.0, 111.9, 55.9, 52.7, 48.4, 47.2. HRMS (EI^+) calcd for $C_{18}H_{18}O_4$ (M^+): 298.1205; found: 298.1218.

4.1.10. Methyl-4-oxo-4-(2-naphthyl)-2-phenyl-butanoate (3j). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H), 8.03 (s, 1H), 7.93–7.86 (comp, 3H), 7.57 (d, J=5.2 Hz, 2H), 7.39–7.24 (comp, 5H), 4.37 (dd, J=4.0, 8.0 Hz, 1H), 4.10 (dd, J=8.0, 18.0 Hz, 1H), 3.72 (s, 3H), 3.42 (dd, J=18.0, 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 174.4, 138.8, 136.1, 134.1, 132.8, 130.3, 130.0, 129.4, 129.0, 128.9, 128.0, 127.2, 124.1, 52.8, 46.9, 43.3. HRMS (EI^+) calcd for $C_{21}H_{18}O_3$ (M^+): 318.1256; found: 318.1251.

4.1.11. Methyl 4-oxo-2,3,4-triphenylbutanoate (3l). *Major isomer*: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J=7.2 Hz, 2H), 7.53–7.22 (comp, 10H), 7.20–6.96 (comp, 3H), 5.18 (d, J=11.6 Hz, 1H), 4.43 (d, J=10.4 Hz, 1H), 3.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.9, 174.7, 129.7, 129.65, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1,

128.7, 128.5, 128.1, 128.0, 58.6, 56.0, 53.1. HRMS (EI^+) calcd for $C_{23}H_{20}O_3$ (M^+): 344.1412; found: 344.1416.

Minor isomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, J=7.2 Hz, 2H), 7.53–7.22 (comp, 10H), 7.20–6.96 (comp, 3H), 5.49 (d, J=11.6 Hz, 1H), 4.66 (d, J=11.6 Hz, 1H), 3.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 172.9, 131.3, 130.7, 130.0, 129.9, 129.63, 129.6, 129.4, 129.23, 129.2, 128.5, 128.4, 128.3, 56.9, 55.9, 52.6. HRMS (EI^+) calcd for $C_{23}H_{20}O_3$ (M^+): 344.1412; found: 344.1416.

4.1.12. Methyl 4-oxo-3-methyl-2,4-diphenylbutanoate (3m). *Major isomer*: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J=7.6 Hz, 2H), 7.50–7.23 (comp, 6H), 7.19 (t, J=7.2, 10.8 Hz, 2H), 4.20–4.07 (comp, 2H), 3.70 (s, 3H), 1.27 (d, J=6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.1, 172.9, 137.4, 136.5, 133.4, 129.0, 128.8, 128.6, 128.5, 127.7, 55.2, 52.5, 44.4, 16.4. HRMS (EI^+) calcd for $C_{18}H_{18}O_3$(M^+): 282.1256; found: 282.1250.

Minor isomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 8.06 (d, J=7.2 Hz, 2H), 7.60–7.23 (comp, 6H), 7.12 (t, J=6.8, 14.0 Hz, 2H), 4.41–4.34 (comp, 2H), 3.54 (s, 3H), 0.90 (d, J=6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.0, 174.4, 137.3, 136.1, 133.5, 129.2, 128.9, 128.6, 128.5, 128.0, 55.2, 52.5, 44.6, 14.5. HRMS (EI^+) calcd for $C_{18}H_{18}O_3$ (M^+): 282.1256; found: 282.1250.

4.1.13. Methyl 4-oxo-4-phenyl-2-(4-bromophenyl)-butanoate (7b). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, J=7.2 Hz, 2H), 7.58 (t, J=7.2 Hz, 1H), 7.48–7.44 (comp, 4H), 7.26–7.23 (comp, 2H), 4.26 (dd, J=4.0, 9.6 Hz, 1H), 3.92 (dd, J=9.6, 18.0 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, J=4.0, 18.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.7, 173.9, 137.7, 136.6, 133.9, 132.4, 130.0, 129.1, 128.5, 122.0, 53.0, 46.2, 42.9. HRMS (EI^+) calcd for $C_{17}H_{15}O_3Br(81)$ (M^+): 348.0184; found: 348.0216. HRMS (EI^+) calcd for $C_{17}H_{15}O_3Br(79)$ (M^+): 346.0205; found: 346.0226. Anal. Calcd for $C_{17}H_{15}O_3Br$: C, 58.96; H, 4.37. Found: C, 58.88; H, 4.51.

4.1.14. Methyl 4-oxo-4-phenyl-2-(2-naphthyl)-butanoate (7c). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J=7.6 Hz, 2H), 7.84–7.81 (comp, 4H), 7.56 (t, J=6.8, 4.0 Hz, 1H), 7.45–7.24 (comp, 5H), 4.47 (dd, J=4.4, 10.0 Hz, 1H), 4.06 (dd, J=10.0, 18.0 Hz, 1H), 3.70 (s, 3H), 3.36 (dd, J=4.4, 18.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.0, 174.3, 136.7, 136.1, 133.87, 133.84, 133.1, 129.1, 129.0, 128.5, 128.2, 128.1, 127.1, 126.8, 126.5, 126.2, 52.9, 46.8, 43.2. HRMS (EI^+) calcd for $C_{21}H_{18}O_3$ (M^+): 318.1256; found: 318.1275.

4.1.15. Methyl 4-oxo-4-phenyl-2-(1-naphthyl)-butanoate (7d). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.14 (d, J=8.8 Hz, 1H), 7.97 (d, J=7.6 Hz, 2H), 7.87 (d, J=8.0 Hz, 1H), 7.79 (d, J=7.6 Hz, 1H), 7.56–7.39 (comp, 7H), 5.19 (dd, J=4.0, 10.0 Hz, 1H), 4.10 (dd, J=10.0, 17.6 Hz, 1H), 3.69 (s, 3H), 3.31 (dd, J=4.0, 17.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.2, 174.7, 136.6, 135.1, 134.5, 133.8, 131.4, 129.5, 129.0, 128.59, 128.54, 127.1, 126.3, 125.9, 125.4, 123.3, 52.9, 42.9, 42.2. HRMS (EI^+) calcd for $C_{21}H_{18}O_3$ (M^+): 318.1256; found: 318.1242.

4.1.16. Methyl 4-oxo-4-phenyl-2-(2-thiophenyl)-butanoate (7e). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, J=7.6 Hz, 2H), 7.58 (t, J=8.0 Hz, 1H), 7.49–7.45 (comp, 2H), 7.23 (s, 1H), 7.01 (s, 1H), 6.98 (s, 1H), 4.59 (dd, J=5.2, 10.4 Hz, 1H), 3.97 (dd, J=10.4, 18.0 Hz, 1H), 3.74 (s, 3H), 3.42 (d, J=18.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.6, 173.4, 140.6, 136.5, 133.9, 129.1, 128.5, 127.4, 126.0, 125.2, 53.1, 43.6, 41.9. HRMS (EI^+) calcd for $C_{15}H_{14}O_3S$ (M^+): 274.0664; found: 274.0692.

4.1.17. Methyl-4-oxo-4-phenyl-2-(1-*tert*-butyloxycarbonyl-indol-3-yl)-butanoate (7f). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, J=6.8 Hz, 1H), 8.0 (d, J=8.0 Hz, 2H), 7.70 (d, J=7.6 Hz, 1H), 7.58–7.55 (comp, 2H), 7.47–7.44 (comp, 2H), 7.35 (d, J=7.2 Hz, 1H), 7.27 (d, J=7.2 Hz, 1H), 4.57 (dd, J=4.0, 10.0 Hz, 1H), 4.08 (dd, J=10.0 Hz, 18.4 Hz, 1H), 3.71 (s, 3H), 3.37 (dd, J=4.0, 18.4 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 174.0, 149.9, 136.7, 133.8, 129.5, 129.1, 128.5, 125.2, 123.9, 123.2, 119.8, 118.0, 115.8, 84.4, 52.9, 41.6, 37.9, 28.6. HRMS (EI^+) calcd for $C_{24}H_{25}NO_5$ (M^+): 407.1733; found: 407.1740.

4.1.18. (*R*)-Pantolactonyl 4-oxo-2,4-diphenylbutanoate (8i). *Major isomer*: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, J=7.6 Hz, 2H), 7.60 (d, J=7.6 Hz, 1H), 7.47–7.41 (comp, 4H), 7.37–7.34 (comp, 2H), 7.28 (d, J=12 Hz, 1H), 5.38 (s, 1H), 4.47 (dd, J=5.2, 9.6 Hz, 1H), 3.95 (dd, J=9.6, 15.2 Hz, 1H), 3.92 (s, 2H), 3.41 (dd, J=5.2, 15.2 Hz, 1H), 1.03 (s, 3H), 0.71 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.4, 172.6, 172.5, 138.4, 136.6, 133.8, 129.4, 129.1, 128.5, 128.4, 128.3, 76.5, 75.6, 46.9, 42.6, 40.9, 23.3, 19.7. HRMS (ESI) calcd for $C_{22}H_{22}NaO_5$ ($M+Na^+$): 389.1365; found: 389.1346. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.10; H, 6.06. Found: C, 72.03; H, 6.01.

Minor isomer: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, J=7.6 Hz, 2H), 7.58 (d, J=6.0 Hz, 1H), 7.47–7.41 (comp, 4H), 7.37–7.34 (comp, 2H), 7.27 (d, J=6.8 Hz, 1H), 5.35 (s, 1H), 4.38 (dd, J=3.6, 10.8 Hz, 1H), 4.07 (dd, J=16.0, 10.8 Hz, 1H), 3.94 (s, 2H), 3.37 (dd, J=16.0, 3.6 Hz, 1H), 1.26 (s, 3H), 1.24 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 197.8, 172.5, 172.3, 137.5, 136.6, 133.82, 128.4, 128.2, 128.1, 76.4, 75.8, 46.5, 43.4, 40.9, 23.2, 20.2. HRMS (ESI) calcd for $C_{22}H_{22}NaO_5$ ($M+Na^+$): 389.1365; found: 389.1346. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.10; H, 6.06. Found: C, 72.03; H, 6.01.

4.1.19. Preparation of 4-morpholin-4-yl-2,4-diphenyl-but-3-enoic acid methyl ester (9). To a solution of methyl 4-oxo-2,4-diphenylbutanoate (**3a**) (0.268 g, 1 mmol) and morpholine (0.522 g, 6 mmol) in 10 mL anhydrous hexane, was added $TiCl_4$ (0.06 mL, 0.55 mmol) over 10 min. The reaction mixture was stirred at room temperature for 24 h and was filtered. The filtrate was evaporated under vacuum to give a light yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 7.36–7.19 (comp, 10H), 5.08 (d, J=10.4 Hz, 1H), 4.18 (d, J=10.4 Hz, 1H), 3.82 (m, 2H), 3.68 (m, 2H), 3.63 (s, 3H), 3.04 (m, 2H), 2.78 (m, 2H). IR (KBr): 2962 (s), 2910 (s), 2717 (m), 2443 (w), 1731 (s), 1615 (s), 1599 (s), 1495 (s) cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{24}O_3N$ ($M+H^+$): 338.1756; found: 338.1739.

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A regioselective synthesis of dispiro[oxindole-cyclohexanone]pyrrolidines and dispiro[oxindole-hexahydroindazole]pyrrolidines by sequential 1,3-dipolar cycloaddition and annulation through a microwave induced solvent-free approach

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Abstract—The 1,3-dipolar cycloaddition of an azomethine ylide, generated from isatin and benzylamine by a 1,5-prototopic shift route with various *p*-substituted 2,6-bis(arylmethylidene)cyclohexanones under different conditions, proceeded regioselectively to give novel dispiroheterocycles. The product on subsequent annulation with hydrazine hydrate afforded 4-aryl-5-phenyl(spiro[2.3″]oxindole)3′-aryl-3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolospiro[7′.3]pyrrolidines in good yield.

1. Introduction

1,3-Dipolar cycloaddition are fundamental processes in organic chemistry, and have taken a prominent place as a synthetic strategy for the synthesis of complex heterocyclic systems,[1] natural products and alkaloids.[2] The reaction of azomethine ylides with various dipolarophiles results in highly substituted five membered nitrogen heterocycles.[3,4] Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties.[5,6] Spirooxindole ring systems are found in a number of alkaloids like horsifiline, spirotryprostatin and (+)elacomine.[7] The derivatives of the spirooxindole ring systems find wide biological applications as antimicrobial, and antitumuor agents and as inhibitors of the human NKI receptor.[8] In the past few years there have been reports of novel spiropyrrolidines synthesized through a decarboxylative route[9,10] in moderate to good yield. The synthesis of dispiroheterocycles through 1,5-prototropic shift is less studied.[11]

As a part of our endeavour to synthesise novel dispiroheterocycles[12,13] containing the spiropyrrolidinyl oxindole moiety through cycloaddition methodology, we herein report for the first time the synthesis of a rare class of novel dispiroheterocycles through 1,3-dipolar cycloaddition reaction of azomethine ylides generated from isatin and benzylamine through 1,5-prototropic shift. The azomethine ylides so generated readily react with various *p*-substituted 2,6-bis(arylmethylidine)cyclohexanones to give novel spiropyrrolidinyl oxindole derivatives. The oxindole derivatives on subsequent annulation using hydrazine hydrate afford 4-aryl-5-phenyl(spiro[2.3″] oxindole)3′-aryl-3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolo spiro[7′.3]pyrrolidines in good yield.

2. Results and discussion

Condensation of benzylamine with isatin could give rise to two configurationally distinct azomethine ylides, **3a** and **3b**. The transition state leading to the azomethine ylide **3a** is favored over **3b** due to the developing steric interaction between the carbonyl moiety and the phenyl group.[11] Thus, **3a** preferentially interacts with the dipolarophile. It reacts with bis-arylmethylidene cyclohexanones **4a–e** to give a series of novel dispiro oxindole derivatives in a regioselective manner. The reaction had occurred at one of the

Keywords: 1,3-Dipole; Cycloaddition; Dispiroheterocycles; Annulation.
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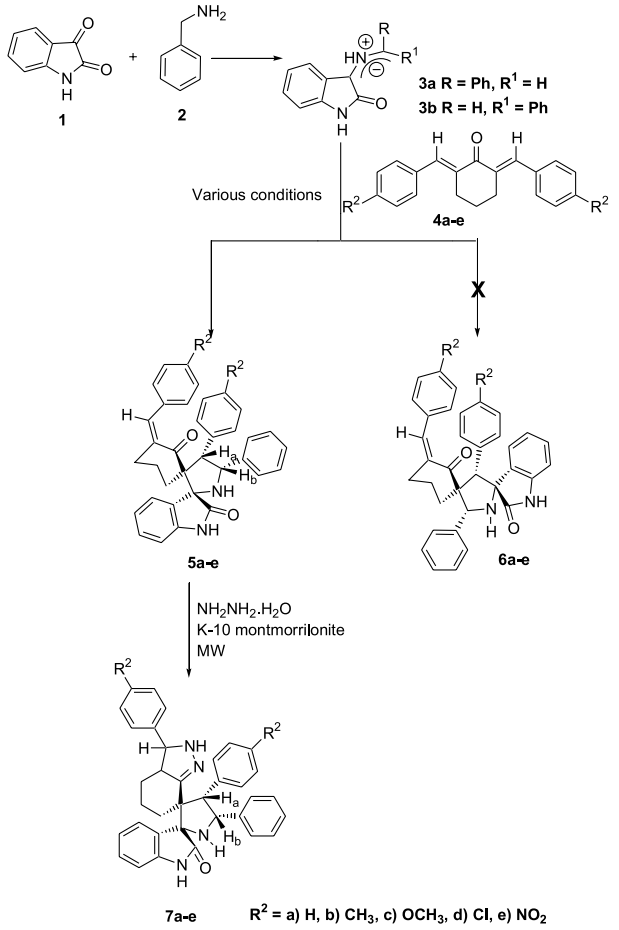
exocyclic double bonds of **4a–e**. With excess 1,3-dipole and prolonged reaction time, the other double bond remained unaffected, which may be attributed to steric hindrance of the spiropyrrolidinyloxindole moiety, which prevents the attack of the 1,3-dipole on the other exocyclic double bond.

As can be seen in Scheme 1 the reaction was carried out under three different conditions. When the reaction was conducted in methanol or acetonitrile at reflux yield of the products were found to be low with a long reaction time. However, when the above reaction was carried out under solvent-free conditions, by grinding together the reactants with K-10 montmorillonite under microwave irradiation (600 W), the products were obtained in good yield with high regioselectivity in a short duration of time. Thus the reaction of **4a–e** with the azomethine ylide generated through 1,5-prototropic shift afforded a series of novel dispiro-oxindole derivatives in good yield. The structures of the dispiro-pyrrolidinyl-oxindole derivatives were confirmed through spectral analysis.



Scheme 1.

The IR spectrum of **5a** reveals the presence of a carbonyl stretching vibration band at 1668 cm^{-1}, showing an increase of 10 cm^{-1} from the normal value observed for the bis-benzylidene-cyclohexanone indicating the loss of conjugation. It also exhibited a peak at 1711 cm^{-1} due to the carbonyl group of the oxindole moiety.

The approach of the ylide with the configuration shown in **3a** can lead to the formation of the products **5a–e** with high regio- and stereoselectivity as shown in Scheme 1. The high regioselectivity obtained in the formation of products **5a–e** can be attributed to the regioselective approach of the dipole towards the termini of the dipolarophile. The other approach in forming the products **6a–e** can lead to severe steric interaction between the phenyl and oxindole group. The regiochemistry of **5a** was apparent from the ^{1}H NMR spectrum. The benzylic protons gave rise to two doublets, δ 4.19 and 5.72, $J=10.0$ Hz indicating *cis* stereochemistry at pyrrolidine ring position 4 and 5. If the other isomer **6a** were formed, one would expect a singlet instead of a doublet for the benzylic proton. The ^{13}C NMR spectrum of **5a** exhibited peaks at δ 67.5 and 76.1 ppm for the two spiro-carbons. The peaks at δ 166.2 ppm and at δ 203.3 ppm are due to the oxindole and ketone carbonyl carbons, respectively. The mass spectrum of **5a** showed a molecular ion peak at *m/z* 509 (M^+) which further confirms the formation of mono-adduct. Identical results were obtained for other compounds **5b–e** with identical stereochemistry as was obtained for **5a** which was corroborated to the X-ray structure of a similar type of compound.[9]

The dispiro[oxindole/cyclohexanone]pyrrolidines were further annulated by grinding the mono-adduct and hydrazine hydrate with K-10 montmorillonite thoroughly and irradiating under microwave conditions to afford a series of novel 4-aryl-5-phenyl(spiro[2.3″]oxindole)3′-aryl-3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolospiro[7′.3] pyrrolidines (**7a–e**). The structures of the annulated products were confirmed by spectral analysis. The IR spectrum of **7a** reveals the disappearance of carbonyl group of the cyclohexanone and exhibited a peak 1709 cm^{-1} due to the carbonyl group of the oxindole and 3282 cm^{-1} due to NH stretching. The ^{1}H NMR spectrum of **7a** shows a multiplet in the region δ 0.90–2.12 for the cyclohexylprotons.

The benzylic protons of the pyrrolidine moiety exhibited doublets at δ 4.20 and 5.21. The benzylic proton of the indazole moiety showed a doublet at δ 4.56. The NH protons of the indazole and oxindole moieties appeared as singlets at δ 6.23 and δ 8.32, respectively. The aromatic protons showed a multiplet in the region δ 6.66–7.72. The ^{13}C NMR spectrum of **7a** showed peaks at δ 68.7 and δ 70.0 for the two spirocarbons. The C=NH group of the indazole showed a peak at δ 155.6 ppm. The oxindole carbonyl carbon exhibited a peak at δ 172.0 ppm. The mass spectrum of **7a** showed a molecular ion peak at *m/z* 524 (M^+).

In conclusion, we have carried out an efficient synthesis of rare class of novel dispiroheterocycles using 1,3-dipolar cycloaddition methodology in which the 1,3-dipole generated by 1,5-prototropic shift is reacted with bis-arylmethylidene cyclohexanones for the first time as dipolaraphiles and subsequent annulation under solvent-free conditions. This method provides an easy access to the spiropyrrolidinyloxindole framework with high regio- and stereoselectivity, which occurs in many alkaloids.

Table 1. Comparative study on the reactivity of 1,3-dipolar cycloaddition reaction

5	Methanol/reflux		Acetonitrile/reflux		K-10 Montmorrilonite/MW	
	Time h	Yield (%)	Time (h)	Yield (%)	Time (s)	Yield (%)
a	36	25	26	34	80	87
b	28	20	20	30	72	75
c	34	27	25	32	70	80
d	20	23	17	27	68	92
e	18	30	14	38	40	97

3. Experimental

3.1. General

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU FT-IR 8300 instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL 400 spectrometer at 400 MHz and 100 MHz, respectively. Mass spectra were recorded on a JEOL DX 303 HF spectrometer. Elemental analyses were carried out on a Perkin–Elmer 240 B instrument.

(*E*,*E*)-2,6-bis(arylmethylidene)cyclohexanones (**4a–e**) were prepared according to a literature procedure.[14]

3.2. Synthesis of dispiroheterocycles 4-aryl-5-phenyl-pyrrolo-(spiro[2.3″]-oxindole)-spiro[3.2′]6′-arylmethylidene cyclohexanones 5a–e

Method A. A solution of isatin (1 mmol), benzylamine (1 mmol) and 2,6-bis(arylmethylidene)cyclohexanone (1 mmol) was heated to reflux in methanol or acetonitrile for the time as given in the Table 1. The solvent was then removed in vacuo. The crude product was subjected to column chromatography using petroleum ether/ethyl acetate (8:2) as eluent.

Method B. A mixture of isatin (1 mmol), benzylamine (1 mmol) and 2,6-bis(arylmethylidene)cyclohexanone (1 mmol) were ground with K-10 Montmorillonite clay and irradiated under microwave (600 W) for the time as given in the Table 1. The reaction mixture was extracted with dichloromethane and the solution was dried over $MgSO_4$. The solvent was removed in vacuo and the residue obtained was subjected to column chromatography using petroleum ether/ethyl acetate (8:2) as eluent.

3.2.1. 4,5-Diphenylpyrrolo(spiro[2.3″]oxindole)spiro [3.2′]6′-phenylmethylidenecyclohexanone (5a). White solid, mp 120 °C; [Found: C, 82.5; H, 6.0; N, 5.2. $C_{35}H_{30}N_2O_{20}$ requires C, 82.3; H, 5.9; N, 5.5%]; ν_{max} (KBr) 1668, 1711, 3258 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.21 (1H, s, N*H*–CO), 6.80–7.83 (19H, m, Ph), 7.24 (1H, s, N*H*–N=C), 5.72 (1H, d, J=10.0 Hz, C*H*Ph), 4.19 (1H, d, J=10.0 Hz, C*H*Ph), 1.83 (1H, br s, N*H*CH$_2$), 1.62–2.43 (6H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 203.3, 166.2, 143.9, 142.1, 131.6, 130.0, 128.3, 127.9, 127.7, 127.6, 126.9, 126.2, 125.7, 124.6, 122.5, 120.9, 76.1, 67.5, 59.8, 54.8, 33.7, 29.0, 25.4; *m*/*z* 509 (M$^+$).

3.2.2. 4-Methylphenyl-5-phenylpyrrolo(spiro[2.3″] oxindole)spiro[3.2′]6′-(4-methylphenyl)methylidene cyclohexanone (5b). Pale yellow solid, mp 115 °C; [Found: C, 82.4; H, 6.6; N, 5.0. $C_{37}H_{34}N_2O_2$ requires C, 82.5; H, 6.3; N, 5.2%]; ν_{max} (KBr) 1670, 1701, 3252 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.29 (1H, s, N*H*CO), 6.61–7.80 (17H, m, Ph), 7.33 (1H, s, N*H*–N=C), 5.71 (1H, d, J=10.5 Hz, C*H*Ph), 4.24 (1H, d, J=10.5 Hz, C*H*Ph), 2.22 (6H, s, *Me*), 1.90 (1H, br s, N*H*CH$_2$), 1.24–2.11 (6H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 213.8, 172.3, 143.1, 141.2, 132.7, 131.0, 129.6, 128.7, 128.4, 127.8, 127.5, 126.8, 126.0, 124.3, 119.7, 117.8, 115.7, 75.3, 63.7, 60.0, 54.7, 31.6, 28.1, 24.3, 20.9; *m*/*z* 538 (M$^+$).

3.2.3. 4-Methoxyphenyl-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.2′]6′-(4-methoxyphenyl)methylidene cyclohexanone (5c). Yellow solid, mp 130 °C; [Found: C, 78.2; H, 5.8; N, 4.7. $C_{37}H_{34}N_2O_4$ requires C, 77.9; H, 6.0; N, 4.9%]; ν_{max} (KBr) 1672, 1710, 3249 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.28 (1H, s, N*H*CO), 6.90–7.84 (17H, m, Ph), 6.91 (1H, s, N*H*–N=C), 5.53 (1H, d, J=10.2 Hz, C*H*Ph), 4.31 (1H, d, J=10.2 Hz, C*H*Ph), 3.40 (6H, s, *OMe*), 1.41 (1H, br s, N*H*CH$_2$), 1.35–2.38 (6H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 209.7, 168.1, 159.2, 141.9, 136.7, 132.9, 130.9, 130.5, 129.4, 127.1, 126.9, 126.4, 125.9, 125.2, 123.2, 122.9, 119.3, 75.0, 64.6, 56.0, 55.9, 54.6, 32.3, 28.6, 22.3; *m*/*z* 570 (M$^+$).

3.2.4. 4-Chlorophenyl-5-phenylpyrrolo(spiro[2.3″] oxindole)spiro[3.2′]6′-(4-chlorophenyl)methylidene cyclohexanone (5d). Yellow solid, mp 124 °C; [Found: C, 72.3; H, 4.6; N, 5.2. $C_{35}H_{28}N_2O_2Cl_2$ requires C, 72.5; H, 4.8; N, 4.8%]; ν_{max} (KBr) 1669, 1709, 3256 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.10 (1H, s, N*H*CO), 6.89–7.63 (17H, m, Ph), 7.44 (1H, s, N*H*–N=C), 5.62 (1H, d, J=10.0 Hz, C*H*Ph), 4.36 (1H, d, J=10.0 Hz, C*H*Ph), 2.07 (1H, br s, N*H*CH$_2$), 0.62–2.33 (6H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 205.6, 169.1, 144.6, 142.3, 132.9, 132.0, 131.4, 131.2, 130.0, 128.9, 128.6, 127.9, 127.1, 123.7, 120.6, 116.3, 113.1, 74.1, 65.3, 54.4, 52.8, 32.1, 26.8, 21.2, 20.6; *m*/*z* 580 (M$^+$).

3.2.5. 4-Nitrophenyl-5-phenylpyrrolo(spiro[2.3″] oxindole)spiro[3.2′]6′-(4-nitrophenyl)methylidene cyclohexanone (5e). White solid, mp 135 °C; [Found: C, 70.3; H, 4.5; N, 9.1. $C_{35}H_{28}N_4O_6$ requires C, 70.0; H, 4.7; N, 9.3%]; ν_{max} (KBr) 672, 1706, 3248 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.26 (1H, s, N*H*CO), 6.77–7.90 (17H, m, Ph), 7.34 (1H, s, N*H*–N=C), 5.57 (1H, d, J=10.2 Hz, C*H*Ph), 4.30 (1H, d, J=10.2 Hz, C*H*Ph), 1.74 (1H, br s, N*H*CH$_2$), 1.23–2.32 (6H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 208.0, 177.1, 149.3, 144.3, 143.1, 132.1, 131.6, 129.4, 128.0, 127.6, 127.3, 126.8, 126.6, 125.2, 124.7, 123.6, 120.2, 72.9, 69.8, 59.5, 57.3, 34.8, 28.9, 23.6; *m*/*z* 600 (M$^+$).

3.3. Synthesis of 4-aryl-5-phenyl(spiro[2.3″]oxindole)3′-aryl-3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolospiro[7′.3] pyrrolidines 7a–e

A mixture of 4-aryl-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.2′]6′-aryl methylidenecyclohexanone **5a–e** (1 mmol), hydrazine hydrate (2 mmol) and K-10 montmorillonite were ground and irradiated under microwave (600 W) for the time as given in the Table 1. The reaction mixture was extracted with dichloromethane and the solution was dried over $MgSO_4$. The solvent was removed in vacuo and the residue obtained was crystallized from ethanol.

3.3.1. 4,5-Diphenyl(spiro[2.3″]oxindole)3′-(4-phenyl) 3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolospiro[7′.3] pyrrolidine (7a). 88% white solid, mp 125 °C; [Found: C, 80.4; H, 6.3; N, 10.4. $C_{35}H_{32}N_4O$ requires C, 80.1; H, 6.1; N, 10.7%]; ν_{max} (KBr) 1709, 3282 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.32 (1H, s, N*H*CO), 6.66–7.72 (19H, m, Ph), 6.23 (1H, s, N*H*–N=C), 5.21 (1H, d, $J=10.8$ Hz, C*H*Ph), 4.56 (1H, d, $J=12.2$ Hz, C*H*Ph), 4.20 (1H, d, $J=10.8$ Hz, C*H*Ph), 1.80 (1H, br s, N*H*CH_2), 0.90–2.12 (7H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 172.0, 155.6, 140.6, 139.4, 139.0, 131.3, 128.3, 128.0, 126.0, 125.9, 125.7, 123.9, 120.2, 70.0, 68.7, 56.3, 54.8, 52.0, 43.2, 25.9, 25.6, 23.5; *m/z* 524 (M^+).

3.3.2. 4-Methylphenyl-5-phenyl(spiro[2.3″]oxindole)3′-(4-methylphenyl)3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolospiro[7′.3]pyrrolidine (7b). 90% white solid, mp 119 °C; [Found: C, 80.6; H, 6.2; N, 10.3. $C_{37}H_{36}N_4O$ requires C, 80.4; H, 6.5; N, 10.1%]; ν_{max} (KBr) 1712, 3278 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, s, N*H*CO), 6.69–7.83 (17H, m, Ph), 6.62 (1H, s, N*H*–N=C), 5.40 (1H, d, $J=10.9$ Hz, C*H*Ph), 4.79 (1H, d, $J=12.3$ Hz, C*H*Ph), 4.13 (1H, d, $J=11$ Hz, C*H*Ph), 2.42 (6H, s, *Me*), 1.89 (1H, br s, N*H*CH_2), 1.31–2.63 (7H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 169.8, 154.0, 141.1, 138.9, 138.6, 131.9, 131.0, 128.5, 128.1, 128.0, 126.8, 125.2, 124.9, 121.3, 115.1, 75.1, 67.3, 56.9, 56.7, 55.2, 41.3, 25.1, 24.9, 22.4, 20.8; *m/z* 552 (M^+).

3.3.3. 4-Methoxyphenyl-5-phenyl(spiro[2.3″]oxindole) 3′-(4-methoxyphenyl)3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolospiro[7′.3]pyrrolidine (7c). 94% pale yellow solid, mp 125 °C; [Found: C, 75.8; H, 6.3; N, 9.7. $C_{37}H_{36}N_4O_3$ requires C, 76.0; H, 6.2; N, 9.6%]; ν_{max} (KBr) 1715, 3273 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.28 (1H, s, N*H*CO), 6.63–7.84 (17H, m, Ph), 6.13 (1H, s, N*H*–N=C), 5.94 (1H, d, $J=11.2$ Hz, C*H*Ph), 4.76 (1H, d, $J=13.0$ Hz, C*H*Ph), 4.42 (1H, d, $J=11.2$ Hz, C*H*Ph), 3.83 (6H, s, *OMe*), 1.42 (1H, br s, N*H*CH_2), 0.61–2.28 (7H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 173.7, 155.0, 142.1, 138.0, 134.9, 130.4, 129.2, 127.6, 127.5, 127.0, 126.2, 124.8, 124.6, 121.9, 119.2, 113.0, 72.5, 63.1, 56.7, 56.3, 55.8, 51.1, 42.0, 25.6, 25.2, 24.1; *m/z* 584 (M^+).

3.3.4. 4-Chlorophenyl-5-phenyl(spiro[2.3″]oxindole)3′-(4-chlorophenyl)3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolo spiro[7′.3]pyrrolidine (7d). 85% yellow solid, mp 132 °C; [Found: C, 71.1; H, 5.2; N, 9.2. $C_{35}H_{30}N_4OCl_2$ requires C, 70.8; H, 5.1; N, 9.4%]; ν_{max} (KBr) 1710, 3269 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, s, N*H*CO), 6.80–7.89 (17H, m, Ph), 6.51 (1H, s, N*H*–N=C), 5.72 (1H, d, $J=11.0$ Hz, C*H*Ph), 4.70 (1H, d, $J=12.8$ Hz, C*H*Ph), 4.33 (1H, d, $J=11.0$ Hz, C*H*Ph), 2.01 (1H, br s, N*H*CH_2), 0.63–2.44 (7H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 168.7, 153.1, 143.1, 139.7, 133.5, 132.3, 131.1, 130.9, 130.6, 129.0, 126.8, 126.7, 124.9, 120.3, 115.9, 74.0, 69.9, 59.1, 57.3, 56.1, 44.8, 24.7, 24.1, 19.6; *m/z* 593 (M^+).

3.3.5. 4-Nitrophenyl-5-phenyl(spiro[2.3″]oxindole)3′-(4-nitrophenyl)3′,3a′,4′,5′,6′,7′-hexahydro-2*H*-indazolo spiro[7′.3]pyrrolidine (7e). 90% yellow solid, mp 129 °C; [Found: C, 68.1; H, 5.1; N, 13.9. $C_{35}H_{30}N_6O_5$ requires C, 68.4; H, 4.9; N, 13.7%]; ν_{max} (KBr) 1708, 3272 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.19 (1H, s, N*H*CO), 6.64–7.34 (17H, m, Ph), 6.53 (1H, s, N*H*–N=C), 5.09 (1H, d, $J=11.0$ Hz, C*H*Ph), 4.48 (1H, d, $J=13.2$ Hz, C*H*Ph), 4.14 (1H, d, $J=11.0$ Hz, C*H*Ph), 1.69 (1H, s, N*H*CH_2), 1.13–2.11 (7H, m, cyclohexyl); δ_C (100.4 MHz, $CDCl_3$) 174.0, 153.7, 143.7, 142.2, 139.1, 138.5, 131.5, 130.0, 129.6, 129.3, 128.0, 127.9, 126.7, 124.7, 121.2, 74.9, 63.8, 59.2, 50.6, 50.1, 39.7, 25.2, 23.5, 22.3; *m/z* 614 (M^+).

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Synthesis of granulatimide bis-imide analogues

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Abstract—The synthesis of dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones, structurally related to granulatimide is reported. These compounds can be considered as granulatimide analogues in which a maleimide heterocycle replaces the imidazole moiety. The synthesis of pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraones is also reported. In these compounds, a 7-azaindole unit replaces the indole moiety present in the granulatimide and isogranulatimide structures.

1. Introduction

Many antitumor compounds from natural sources contain a carbazole maleimide or maleamide framework. Rebeccamycin is a topoisomerase I inhibitor[1] whereas staurosporine is a non specific kinase inhibitor interacting with the ATP binding site of the enzymes.[2] UCN-01, structurally related to staurosporine, also inhibits various kinases. Moreover, like granulatimide and isogranulatimide, natural compounds isolated from an ascidian, UCN-01 inhibits the cell cycle checkpoint in the G2 phase which is activated in response to DNA damage (Fig. 1).[3–6] This cell cycle checkpoint is mainly regulated by the two kinases Chk1 and Chk2.

Compounds structurally related to granulatimide, isogranulatimide isomers and analogues bearing modified heterocycles, have been recently synthesized.[7–11]

To get an insight into the possible interactions of granulatimide and isogranulatimide with the ATP binding site of the target kinases, a detailed computational study was performed.[12] The electronic density in specific regions of the molecules appears to play a pivotal role toward activity. Both granulatimide and isogranulatimide are almost planar. The molecular planarity creates a broad negative electrostatic potential on the two sides which are lypophilic sites whereas the positive potential resulting from a low electron density in the central core increases their hydrophilicity.

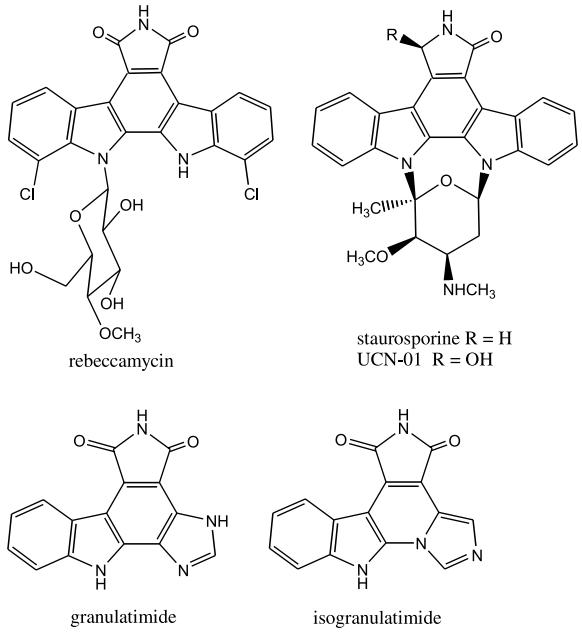

Figure 1. Chemical structures of rebeccamycin, staurosporine, UCN-01, granulatimide and isogranulatimide.

In a previous brief communication, we reported the synthesis of the first granulatimide analogues bearing a maleimide instead of an imidazole heterocycle.[13] In this paper, the synthesis of new analogues in this series **7a–7l** is described (Fig. 2).

Keywords: Granulatimide; Pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone; Dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone; 7-Azaindole.
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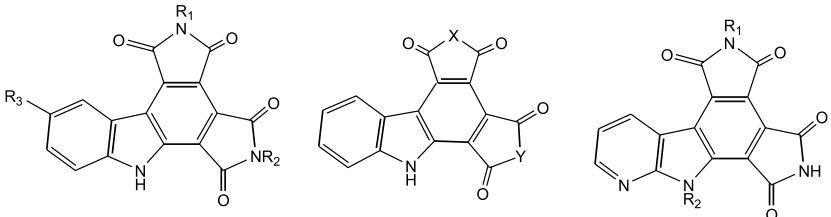


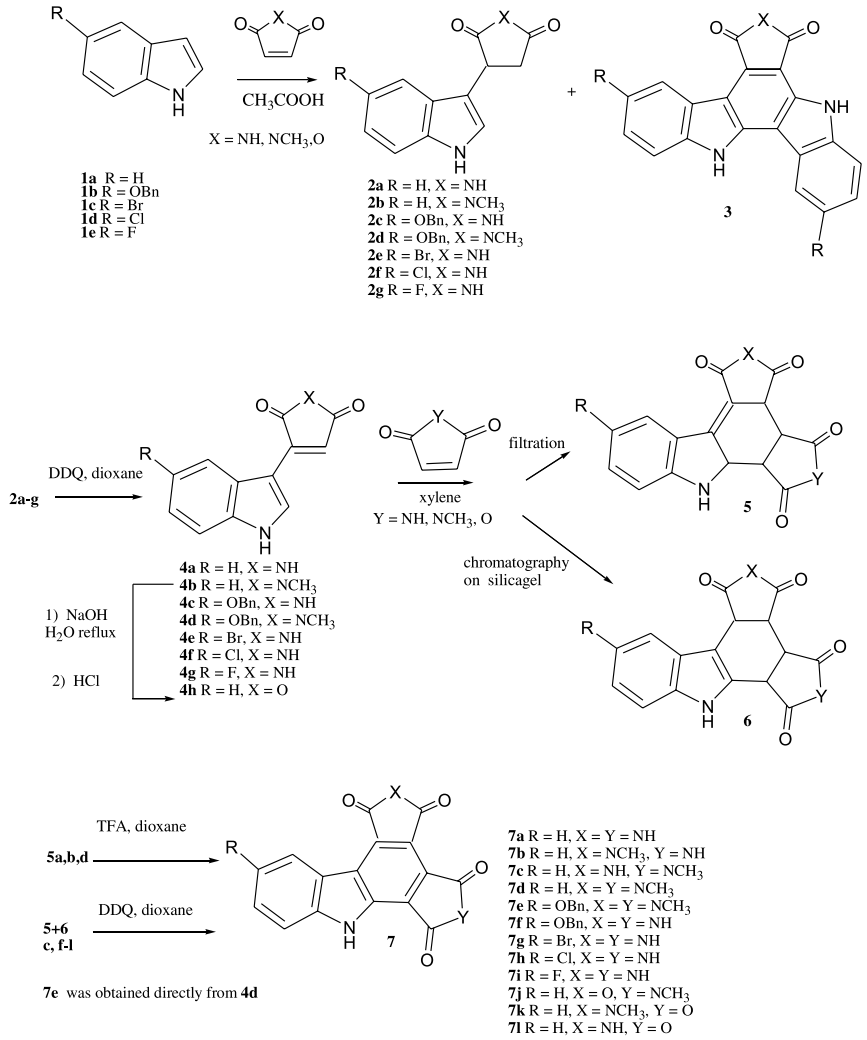
7a $R_1 = R_2 = R_3 = H$
7b $R_1 = CH_3$, $R_2 = R_3 = H$
7c $R_1 = R_3 = H$, $R_2 = CH_3$
7d $R_1 = R_2 = CH_3$, $R_3 = H$
7e $R_1 = R_2 = CH_3$, $R_3 = OBn$
7f $R_1 = R_2 = H$, $R_3 = OBn$
7m $R_1 = R_2 = H$, $R_3 = OH$
7g $R_1 = R_2 = H$, $R_3 = Br$
7h $R_1 = R_2 = H$, $R_3 = Cl$
7i $R_1 = R_2 = H$, $R_3 = F$
7n $R_1 = CH_3$, $R_2 = -(CH_2)_2-NEt_2,HCl$, $R_3 = H$
7o $R_1 = -(CH_2)_2-NEt_2,HCl$, $R_2 = CH_3$, $R_3 = H$

7j X = O, Y = NCH_3
7k X = NCH_3, Y = O
7l X = NH, Y = O

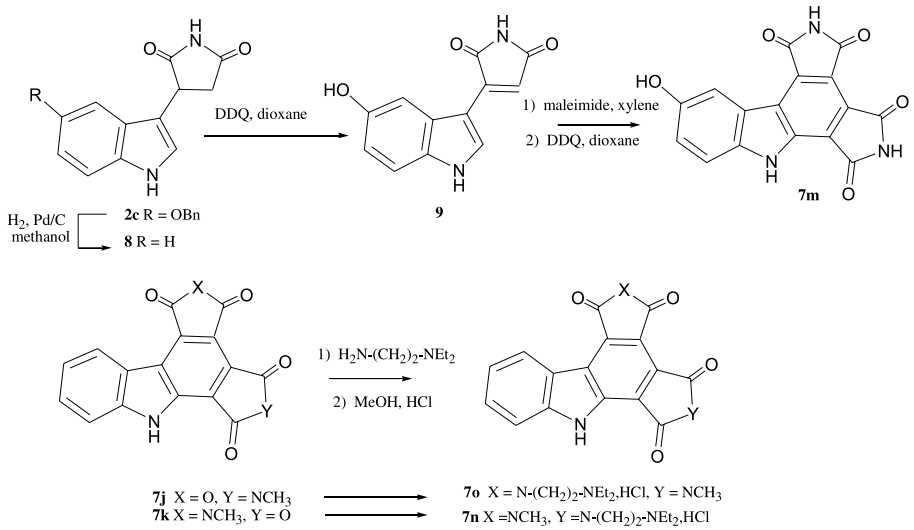
13a $R_1 = CH_3$, $R_2 = H$
13b $R_1 = CH_2OH$, $R_2 = H$
13c $R_1 = R_2 = H$
20 R_1 =H, R_2 = β-glucosyl

Figure 2. Granulatimide bis-imide analogues and related compounds.

Azaindoles, biosters of indole, are found in many natural and synthetic compounds of biological interest.[14–16] The replacement of a carbon atom by a nitrogen atom could increase the affinity for the binding site on the target enzyme(s) and also modify the electronic distribution of the aromatic framework and the lipophilicity of the molecule. In this paper, the synthesis of new bis-imide analogues in which a 7-azaindole replaces the indole unit is also reported **13a–c** (Fig. 2). To mimic the sugar part present in UCN-01 and ATP, compound **20** in which a β-glucopyranosyl moiety is attached to the azaindole was also synthesized.



Scheme 1. Synthesis of compounds **7a–7l**.

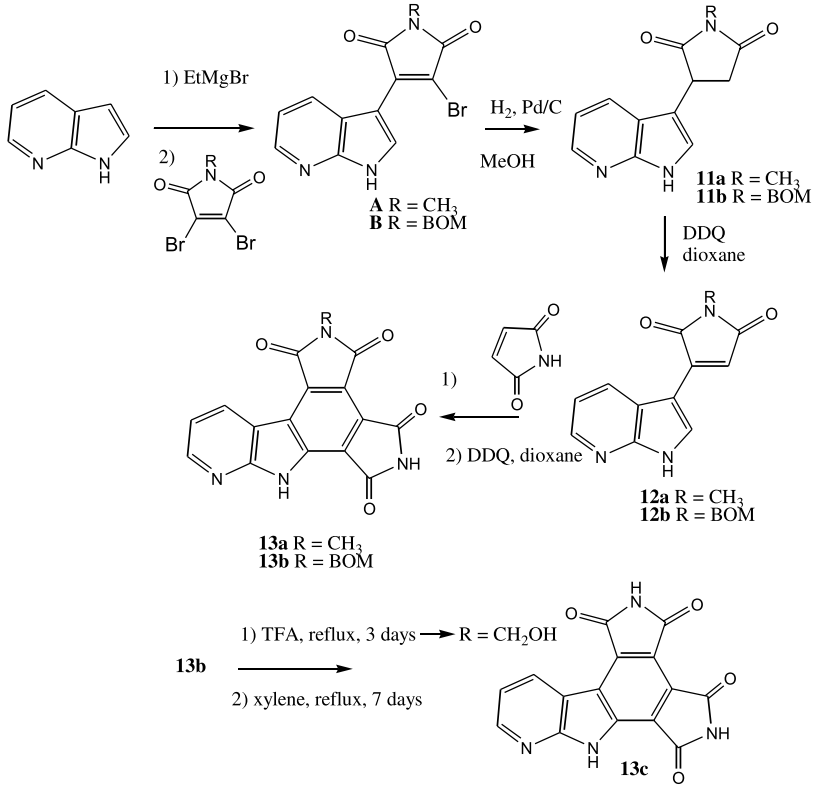


Scheme 2. Synthesis of **7m**–**7o**.

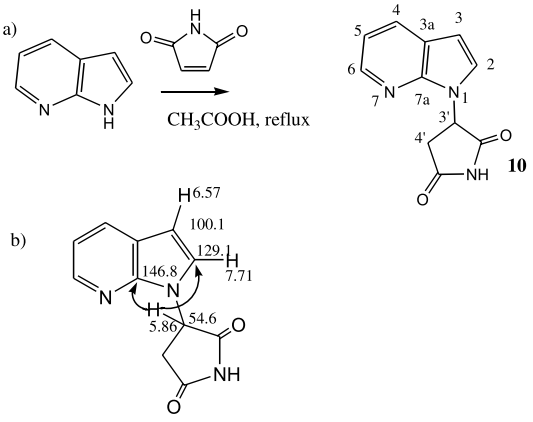
2. Results and discussion

In our previous communication, we described the synthetic pathways to access to compound **7a** and its analogues **7b**, **7d**, **7e**, **7j** and **7o**.[13] The key step consists in a Diels–Alder reaction between 3-indolylmaleimides and maleimides or maleic anhydride.[17] The 3-indolylmaleimides or maleic anhydrides **4a**–**g** were obtained either by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) of the corresponding 3-(indol-3-yl)-succinimides or succinic anhydrides **2a**–**g** resulting from acid induced addition of indoles to maleimides[18] (Scheme 1). In some cases, together with compound **2a**–**g**, small amounts of compounds **3** have been isolated. According to the work-up (filtration or chromatography on silicagel), the Diels–Alder cycloadduct **5a** or its isomer **6a** were isolated. The non-aromatic intermediates were further oxidized in the presence of either TFA or DDQ to yield **7a**–**7l**. Compound **4h** was obtained from **4b** by opening of the imide heterocycle in a basic medium followed by acidic treatment.

To synthesize the analogue **7m** bearing a hydroxy substituent (Scheme 2), hydrogenolysis of **2c** led to succinimide **8**. The same sequence of reactions as described in Scheme 1 from compounds **2a**–**g** yielded **7m**. To obtain more soluble compounds, a *N*,*N*-diethylaminoethyl



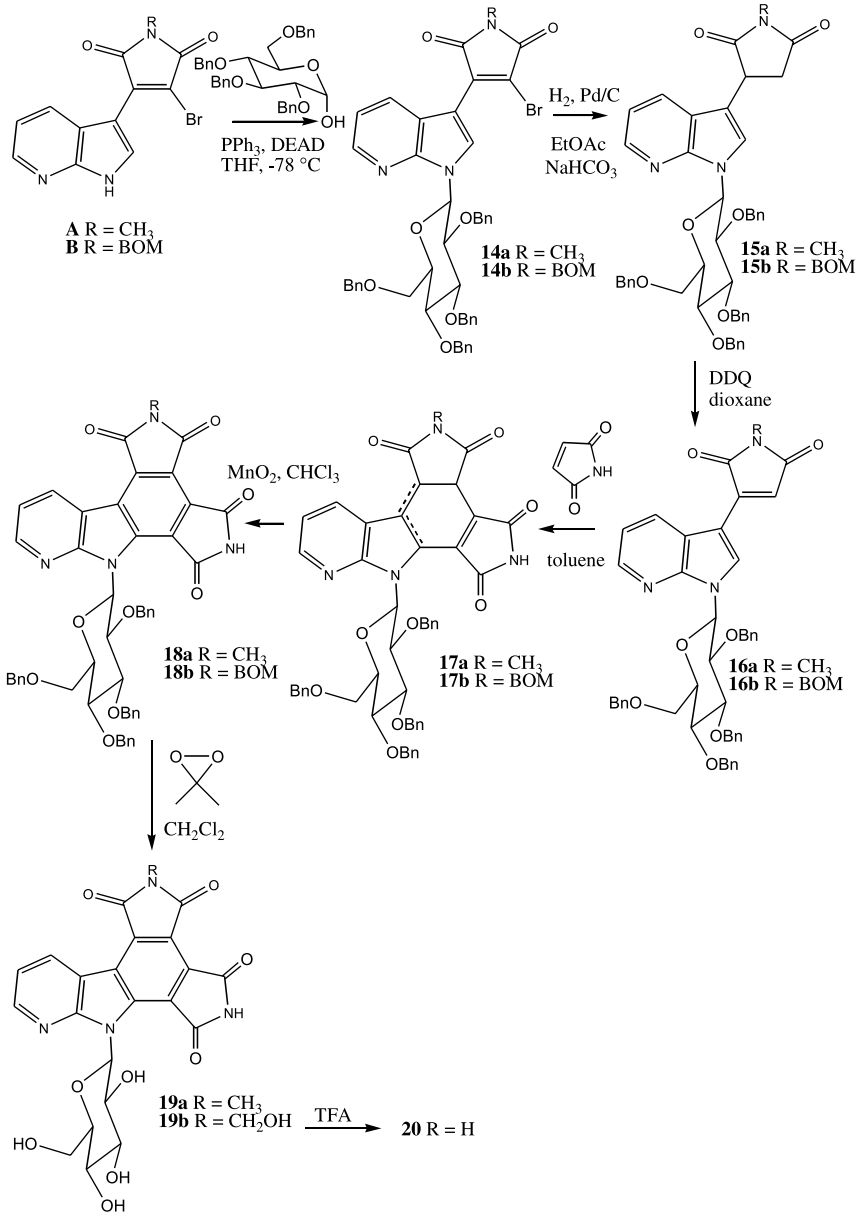
Scheme 3. Synthesis of **13c**.



Scheme 4. (a) Reaction of 7-azaindole with maleimide. (b) Long range $^{1}H–^{13}C$ coupling (chemical shifts in ppm).

substituent was introduced on one of the imide nitrogens via the corresponding anhydrides according to a method previously developed in indolocarbazole series (Scheme 2).[1]

In the aza series, the method used for the synthesis of compounds **12a** and **12b** (Scheme 3) was a little bit different from that previously described for the synthesis of the non aza analogues. The advantage of the Michael addition used for the non aza compounds was to avoid the steps of hydrogenolysis/hydrogenation then oxidation (compare Schemes 1 and 3). Unfortunately, in aza series, the reaction between 7-azaindole and maleimide in refluxing acetic acid afforded compound **10** (Scheme 4). The structure of compound **10** was assigned from NMR $^{1}H–^{1}H$ COSY correlations, HMBC and HSQC experiments (Scheme 4). Consequently, the strategy described on Scheme 3 was chosen. Moreover, the presence of an electron-withdrawing



Scheme 5. Synthesis of compound **20**.

group such as Br is necessary to increase the reactivity of the Mitsunobu reaction used for the coupling of the sugar part (Scheme 5).[19,20]

Compounds **A** and **B** were prepared as previously described.[16] Hydrogenolysis with Pd/C in methanol led to **11a** and **11b** in 90 and 68% yields, respectively, from **A** and **B**. Oxidation of **11a** and **11b** with DDQ gave **12a** and **12b** in 94 and 100% yields, respectively. Diels–Alder reactions were carried out in refluxing *p*-xylene leading to a mixture of isomers which were further oxidized with DDQ to give **13a** and **13b** in 83 and 77% yields, respectively. For the removal of the benzyloxymethyl protective group of compound **13b**, the classical method by hydrogenolysis then aminolysis could not be performed due to, firstly the insolubility of **13b** which could not be separated from the catalyst and secondly to the sensitivity of the maleimide units to basic media which often led to the opening of the maleimide heterocycles. The BOM group was eliminated in two steps: reaction with trifluoroacetic acid[21,22] which led to the *N*-hydroxymethyl-tetraone followed by refluxing in xylene[23] to give the required compound **13c**. A glucose moiety was attached to the azaindolic nitrogen. The carbohydrate could reinforce the hydrogen bond net in the target enzyme(s) (Scheme 5). A Mitsunobu reaction was carried out with compounds **A** and **B** and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose leading to **14a** and **14b** as the major products of the reactions in 46 and 64% yields, respectively. Hydrogenolysis/hydrogenation was performed using 10% Pd/C in EtOAc and $NaHCO_3$[24] affording **15a** and **15b** in 48 and 46% yields, respectively, as a mixture of two diastereoisomers. Oxidation with DDQ gave **16a** and **16b** in 61 and 64% yields, respectively. Diels–Alder reaction with maleimide in refluxing toluene afforded **17a** and **17b** in 41 and 85% yields, respectively, as a mixture of isomers. Oxidation with DDQ only gave degradation products whereas using MnO_2 in chloroform[25] **18a** and **18b** were isolated in 61 and 86% yields, respectively. For debenzylation, several methods were tried. Reaction with boron tribromide[26] or trimethylsilyliodide[27] led to a mixture of partially debenzylated compounds which could not be easily recovered from an aqueous phase during the work-up. Classical hydrogenolysis using Pd/C or $Pd(OH)_2$/C as catalysts reduced the pyridine moiety. A method for the removal of the protective groups carried out from **18b** using trifluoroacetic acid led to **19b** in 73% yield. Surprisingly, in these conditions, **20** was not directly obtained from **18b**. After isolation **19b** could be converted to **20** with TFA in 43% yield. A second method for debenzylation using dimethyldioxirane[28,29] led to **19a** and **19b** in 59 and 76% yields from **18a** and **18b**, respectively.

3. Conclusion

In conclusion, this work reports the synthesis of dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones and pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraones, bearing or not a methyl group on the nitrogen of the upper maleimide heterocycle. These compounds are structurally related to granulatimide.

In the first series, various substituents were introduced on the indole moiety and a diethylaminoethyl chain was attached to the imide nitrogen of the upper heterocycle. In the aza series, in contrast to what observed in non aza series, the Michael addition between 7-azaindole and maleimide did not work. A different sequence of reactions has to be performed from dibromomaleimide. An analogue in which a glucose moiety is attached to the 7-azaindole unit was prepared. According to the presence or the absence of a sugar part, the methods carried out for the oxidation of the Diels–Alder adducts were different. The classical methods usually used for the deprotection of the benzyl groups did not afford the required compounds and the debenzylation procedures were modified. The biological evaluation of these new compounds is now under investigation

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer 881 spectrometer (ν in cm^{-1}). NMR spectra were performed on a Bruker AVANCE 400 and AVANCE 500 (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), broad singlet (br s), doublet (d), doubled doublet (dd), triplet (t), pseudo triplet (pt), multiplet (m), tertiary carbons (C tert), quaternary carbons (C quat). The signals were assigned from ^1H–^1H COSY and ^{13}C–^1H correlation. Low resolution mass spectra (ESI+, CI) were determined on a Hewlett Packard MS engine. HRMS (FAB+) were determined at CESAMO (Talence, France) on a high resolution Fisons Autospec-Q spectrometer. Chromatographic purifications were performed by flash silicagel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography.

4.1.1. 3-(Indol-3-yl)-succinimide (2a). A mixture of indole (2.34 g, 20 mmol) and maleimide (1.96 g, 20 mmol) in acetic acid (18 mL) was refluxed for 36 h. After evaporation, the residue was purified by flash chromatography (eluent: EtOAc/cyclohexane from 1:1 to 4:1) to give **2a** (3.33 g, 15.6 mmol, 74% yield) as a pale yellow solid.

Mp 196–197 °C. IR (KBr): $\nu_{C=O}$ 1696 cm^{-1}, ν_{NH} 3292–3370 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 2.78 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.18 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.33 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.00 (1H, t, $J=7.0$ Hz), 7.10 (1H, t, $J=7.0$ Hz), 7.33 (1H, d, $J=2.5$ Hz), 7.38 (1H, d, $J=8.0$ Hz), 7.42 (1H, d, $J=8.0$ Hz), 11.07 (1H, s, NH), 11.34 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.5 (CH_2), 39.1 (CH), 111.8, 118.5, 118.9, 121.5, 123.5 (C tert arom), 110.0, 126.0, 136.6 (C quat arom), 178.2, 180.1 (C=O).

4.1.2. 1-Methyl-3-(indol-3-yl)-pyrrolidine-2,5-dione (2b) and 2-methyl-1,3-dihydro-2*H*,4*H*,9*H*-indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-1,3-dione (3b). A mixture of indole (2.34 g, 20 mmol) and *N*-methylmaleimide (2.22 g, 20 mmol) in acetic acid (18 mL) was refluxed for 48 h. After evaporation, the residue was purified by flash

chromatography (eluent: EtOAc/cyclohexane from 3:7 to 7:3) to give **3b** (66 mg, 0.195 mmol, 1% yield) as an orange solid and **2b** (2.50 g, 11 mmol, 55% yield) as a pale yellow solid.

Compound **2b**: Mp 172–174 °C. IR (KBr): $\nu_{C=O}$ 1670, 1680 cm^{-1}, ν_{NH} 3340 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 2.83 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 2.96 (3H, s, CH_3), 3.27 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.40 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 7.03 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 7.13 (1H, dt, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 7.37 (1H, d, $J=2.5$ Hz), 7.41 (1H, d, $J=8.0$ Hz), 7.43 (1H, d, $J=7.5$ Hz), 11.12 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (CH_3), 36.1 (CH_2), 37.6 (CH), 110.7, 125.9, 136.4 (C quat arom), 111.7, 118.4, 118.8, 121.3, 123.4 (C tert arom), 176.6, 178.4 (C=O).

Compound **3b**: ^1H NMR (400 MHz, DMSO-d_6): 3.21 (3H, s, CH_3), 7.40 (1H, t, $J=7.0$ Hz), 7.45 (1H, t, $J=8.0$ Hz), 7.55 (1H, d, $J=5.5$ Hz), 7.59 (1H, d, $J=6.5$ Hz), 7.77 (1H, d, $J=8.0$ Hz), 7.80 (1H, d, $J=8.0$ Hz), 8.80 (1H, d, $J=8.0$ Hz), 8.98 (1H, d, $J=8.0$ Hz), 12.22 (1H, s, NH), 12.35 (1H, s, NH).

4.1.3. 3-(5-Benzyloxy-indol-3-yl)-pyrrolidine-2,5-dione (2c). Identical method as described for the preparation of **2b** gave from 5-benzyloxyindole (1.79 g, 8.0 mmol) and maleimide (776 mg, 8.0 mmol) compound **2c** (1.01 g, 3.16 mmol, 39% yield) as a pale yellow solid.

Mp 175 °C. IR (KBr) $\nu_{C=O}$ 1690, 1780 cm^{-1}, ν_{NH} 3210, 3420 cm^{-1}.

HRMS (FAB+) $[M]^+$ calcd. for $C_{19}H_{16}N_2O_3$ 320.1161, found 320.1168.

^1H NMR (400 MHz, DMSO-d_6): 2.76 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.33 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 5.10 (2H, s), 6.88 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.06 (1H, d, $J=2.5$ Hz), 7.31 (1H, d, $J=9.0$ Hz), 7.31 (1H, d, $J=2.5$ Hz), 7.36 (1H, m), 7.43 (2H, m), 7.51 (2H, m), 10.92 (1H, d, $J=2.0$ Hz, NH), 11.32 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.3, 69.9 (CH_2), 38.9 (CH), 102.2, 111.8, 112.3, 123.9, 127.6, 127.7 (2C), 128.3 (2C) (C tert arom), 110.6, 126.4, 131.7, 137.6, 152.1 (C quat arom), 178.0, 179.8 (C=O).

4.1.4. 1-Methyl-3-(5-benzyloxy-indol-3-yl)-pyrrolidine-2,5-dione (2d) and 2-methyl-7,12-dibenzyloxy-4*H*,9*H*-indolo[3,2-*a*]pyrrolo[3,4-*c*]-carbazole-1,3-dione (3d). Identical procedure as described for the synthesis of **2b** and **3b** gave from 5-benzyloxy-indole (1.79 g, 8 mmol) and *N*-methylmaleimide (0.89 g, 8 mmol) compound **3d** (68 mg, 0.123 mmol, 2% yield), and **2d** (1.10 g, 3.29 mmol, 41% yield) as a light brown solid.

Compound **2d**: Mp 49–53 °C. IR (KBr): $\nu_{C=O}$ 1690, 1700 cm^{-1}, ν_{NH} 3300–3500 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{20}H_{19}N_2O_3$ 335.1396, found 335.1397.

^1H NMR (400 MHz, DMSO-d_6): 2.79 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 2.96 (3H, s, CH_3), 3.26 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.35 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 5.11 (2H, s, CH_2), 6.88 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.00 (1H, d, $J=2.0$ Hz), 7.30–7.38 (3H, m), 7.43 (2H, t, $J=7.5$ Hz), 7.49 (2H, d, $J=7.0$ Hz), 10.95 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (CH_3), 36.0 (CH_2), 37.5 (CH), 69.8 (CH_2), 102.0, 111.9, 112.3, 124.0, 127.6 (3C), 128.3 (2C) (C tert arom), 110.4, 126.3, 131.7, 137.7, 152.2 (C quat arom), 176.6, 178.4 (C=O).

Compound **3d**: Mp 286 °C. IR (KBr): $\nu_{C=O}$ 1680, 1790 cm^{-1}, ν_{NH} 3300–3400 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 3.18 (3H, s, CH_3), 5.26 (2H, s, CH_2), 5.32 (2H, s, CH_2), 7.28 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.30 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.39–7.51 (6H, m), 7.62 (4H, t, $J=7.0$ Hz), 7.68 (1H, d, $J=9.0$ Hz), 7.70 (1H, d, $J=9.0$ Hz), 8.42 (1H, d, $J=2.0$ Hz), 8.65 (1H, d, $J=2.5$ Hz), 12.01 (1H, s, NH), 12.14 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.6 (CH_3), 69.9, 70.5 (CH_2), 106.3, 110.5, 111.7, 120.6, 121.8, 123.8, 132.9, 135.8, 136.0, 137.3, 137.4, 138.7, 153.0, 153.3 (C quat arom), 106.0, 107.8, 112.0, 112.7, 115.6, 115.8, 127.6 (2C), 127.8 (2C), 128.1 (2C), 128.4 (4C) (C tert arom), 168.9, 169.7 (C=O).

4.1.5. 3-(5-Bromo-indol-3-yl)-pyrrolidine-2,5-dione (2e). Identical method as described for the preparation of **2b** gave from 5-bromo-indole (1.0 g, 5.10 mmol) and maleimide (495 mg, 5.10 mmol) compound **2c** (647 mg, 2.21 mmol, 43% yield) as a pale yellow solid.

Mp 208–215 °C. IR (KBr) $\nu_{C=O}$ 1700, 1775 cm^{-1}, ν_{NH} 3420 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_{10}N_2O_2Br$ 292.9926 found 292.9915.

^1H NMR (400 MHz, DMSO-d_6): 2.84 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.20 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.40 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.25 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 7.38 (1H, d, $J=8.5$ Hz), 7.45 (1H, d, $J=2.5$ Hz), 7.68 (1H, d, $J=2.0$ Hz), 11.30 (1H, s, NH), 11.35 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 34.0 (CH_2), 35.6 (CH), 113.7, 120.9, 123.8, 124.8 (C tert arom), 110.8, 111.3, 128.1, 135.1 (C quat arom), 177.9, 179.7 (C=O).

4.1.6. 3-(5-Chloro-indol-3-yl)-pyrrolidine-2,5-dione (2f). Identical method as described for the preparation of **2b** gave from 5-chloro-indole (1,0 g, 6.6 mmol) and maleimide (640 mg, 6.6 mmol) compound **2f** (412 mg, 1.66 mmol, 25% yield) as an amorphous orange solid.

IR (KBr) $\nu_{C=O}$ 1700, 1780 cm^{-1}, ν_{NH} 3200–3500 cm^{-1}.

HRMS (FAB+) $[M]^+$ calcd. for $C_{12}H_9N_2O_2Cl$ 248.0353, found 248.0354.

^{1}H NMR (400 MHz, DMSO-d_6): 2.84 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.40 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.14 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 7.43 (1H, d, $J=8.5$ Hz), 7.46 (1H, d, $J=2.5$ Hz), 7.53 (1H, d, $J=2.0$ Hz), 11.29 (1H, s, NH), 11.34 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.0 (CH_2), 38.6 (CH), 113.2, 117.9, 121.3, 125.0 (C tert arom), 110.8, 123.4, 127.3, 134.9 (C quat arom), 177.9, 179.7 (C=O).

4.1.7. 3-(5-Fluoro-indol-3-yl)-pyrrolidine-2,5-dione (2g). Identical method as described for the preparation of **2b** gave from 5-fluoro-indole (1.0 g, 7.40 mmol) and maleimide (718 mg, 7.40 mmol) compound **2g** (679 mg, 2.92 mmol, 40% yield) as an orange solid.

Mp 190–195 °C. IR (KBr) $\nu_{C=O}$ 1690, 1775 cm^{-1}, ν_{NH} 3360 cm^{-1}.

HRMS (FAB+) $[M]^+$ calcd. for $C_{12}H_9N_2O_2F$ 232.0648, found 232.0644.

^{1}H NMR (400 MHz, DMSO-d_6): 2.83 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.37 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 6.99 (1H, dt, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.24 (1H, dd, $J_1=10$ Hz, $J_2=2.5$ Hz), 7.40 (1H, dd, $J_1=9.0$ Hz, $J_2=4.5$ Hz), 7.45 (1H, d, $J=2.5$ Hz), 11.18 (1H, s, NH), 11.33 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.1 (CH_2), 38.7 (CH), 103.3 (d, $J_{C,F}=23$ Hz), 109.5 (d, $J_{C,F}=26$ Hz), 112.6 (d, $J_{C,F}=9.5$ Hz), 125.2 (C tert arom), 111.2 (d, $J_{C,F}=4.5$ Hz), 126.4 (d, $J_{C,F}=10$ Hz), 133.1, 156.7 (d, $J_{C,F}=232$ Hz) (C quat arom), 177.9, 179.7 (C=O).

4.1.8. 2,5-Dihydro-1-methyl-3-(indol-3-yl)-pyrrole-2,5-dione (4b). A solution of DDQ (456 mg, 2 mmol) in dioxane (20 mL) was slowly added to a solution of **2b** (454 mg, 2 mmol) in dioxane (20 mL). The mixture was stirred at room temperature for 12 h. After filtration and removal of the solvent, the residue was dissolved in isopropanol (23 mL). After cooling for 12 h at 0 °C, the precipitate was filtered off, and the solid was washed with isopropanol before purification by flash chromatography (eluent: EtOAc/cyclohexane 3:7) to give **4b** (112 mg, 0.496 mmol, 25% yield). The filtrate was concentrated and purified by flash chromatography (eluent: EtOAc/cyclohexane 3:7) to give **4b** (197 mg, 0.872 mmol, 44% yield), total yield: 69%.

Mp 188 °C. IR (KBr) $\nu_{C=C}$ 1610 cm^{-1}, $\nu_{C=O}$ 1680, 1690 cm^{-1}, ν_{NH} 3220 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): 2.95 (3H, s, CH_3), 6.92 (1H, s), 7.24 (1H, t, $J=7.5$ Hz), 7.30 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 7.56 (1H, d, $J=8.0$ Hz), 8.01 (1H, d, $J=8.0$ Hz), 8.44 (1H, d, $J=3.0$ Hz), 12.10 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 105.5, 125.4, 136.7, 139.0 (C quat), 112.6, 114.0, 120.4, 121.4, 123.0, 131.0 (C tert), 171.6, 171.9 (C=O).

4.1.9. 3-(5-Benzyloxy-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4c). A solution of DDQ (339 mg, 1.49 mmol) in dioxane (15 mL) was slowly added to a solution of **2c** (456 mg, 1.42 mmol) in dioxane (15 mL). The mixture was stirred at room temperature for 12 h. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) to give **4c** (409 mg, 1.28 mmol, 90% yield) as an orange solid.

Mp 211 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1705, 1755 cm^{-1}, ν_{NH} 3150–3450 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{19}H_{15}N_2O_3$ 319.1083, found 319.1089.

^{1}H NMR (400 MHz, DMSO-d_6): 5.25 (2H, s), 6.86 (1H, s), 6.99 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.36 (1H, m), 7.44 (2H, m), 7.46 (1H, d, $J=9.0$ Hz), 7.50 (1H, d, $J=2.5$ Hz), 7.54 (2H, m), 8.35 (1H, s), 10.77 (1H, br s, NH), 11.93 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 69.9 (CH_2), 103.9, 113.3, 113.5, 114.7, 127.6, 127.7 (2C), 128.4 (2C), 131.2 (C tert), 105.3, 126.2, 131.6, 137.6, 139.4, 154.2 (C quat), 173.3, 173.5 (C=O).

4.1.10. 2,5-Dihydro-1-methyl-3-(5-benzyloxy-indol-3-yl)-pyrrole-2,5-dione (4d). Identical method as described for the preparation of **4b** gave from **2d** (668 mg, 2 mmol) compound **4d** (442 mg, 1.33 mmol, 67% yield).

Mp 176–182 °C. IR (KBr): $\nu_{C=O}$ 1690, 1700 cm^{-1}, ν_{NH} 3300–3440 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{20}H_{17}N_2O_3$ 333.1239, found 333.1238.

^{1}H NMR (400 MHz, DMSO-d_6): 2.98 (3H, s, CH_3), 5.28 (2H, s, CH_2), 6.98 (1H, s), 7.00 (1H, dd, $J_1=9.0$ Hz, $J_2=2.0$ Hz), 7.36 (1H, t, $J=7.5$ Hz), 7.41 (1H, d, $J=7.5$ Hz), 7.45 (2H, t, $J=8.5$ Hz), 7.53 (1H, d, $J=2.0$ Hz), 7.56 (2H, d, $J=7.5$ Hz), 8.39 (1H, d, $J=3.0$ Hz), 11.96 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 69.9 (CH_2), 103.9, 113.4, 113.6 (2C), 127.6 (2C), 127.7, 128.3 (2C), 131.3 (C tert), 105.4, 126.1, 131.6, 137.6, 138.9, 154.3 (C quat), 171.7, 172.1 (C=O).

4.1.11. 3-(5-Bromo-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4e). Identical method as described for the preparation of **4c** gave from **2e** (499 mg, 1.70 mmol) compound **4e** (476 mg, 1.64 mmol, 96% yield) as an orange solid.

Mp 268 °C. IR (KBr) $\nu_{C=C}$ 1595 cm^{-1}, $\nu_{C=O}$ 1705, 1750 cm^{-1}, ν_{NH} 3200, 3340 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_8N_2O_2Br$ 290.9769, found 290.9766.

^{1}H NMR (400 MHz, DMSO-d_6): 6.95 (1H, d, J=1.0 Hz), 7.41 (1H, dd, J_1=8.5 Hz, J_2=2.0 Hz), 7.52 (1H, d, J=8.5 Hz), 8.19 (1H, d, J=2.0 Hz), 8.41 (1H, d, J=2.5 Hz), 10.82 (1H, s, NH), 12.19 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 114.4, 116.5, 122.5, 125.6, 131.9 (C tert), 104.9, 114.2, 127.2, 135.4, 138.7 (C quat), 173.0, 173.2 (C=O).

4.1.12. 3-(5-Chloro-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4f). Identical method as described for the preparation of **4c** gave from **2f** (394 mg, 1.58 mmol) compound **4f** (219 mg, 0.89 mmol, 56% yield) as an orange solid.

Mp 254–264 °C. IR (KBr) $\nu_{C=C}$ 1605 cm^{-1}, $\nu_{C=O}$ 1710, 1750 cm^{-1}, ν_{NH} 3100–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_8N_2O_2Cl$ 247.0274, found 247.0278.

^{1}H NMR (400 MHz, DMSO-d_6): 6.95 (1H, d, J=1.0 Hz), 7.29 (1H, dd, J_1=8.5 Hz, J_2=2.0 Hz), 7.57 (1H, d, J=8.5 Hz), 8.06 (1H, d, J=2.0 Hz), 8.43 (1H, d, J=3.0 Hz), 10.82 (1H, s, NH), 12.18 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 114.0, 116.4, 119.6, 123.0, 132.1 (C tert), 105.1, 126.2, 126.6, 135.1, 138.7 (C quat), 173.0, 173.3 (C=O).

4.1.13. 3-(5-Fluoro-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4g). Identical method as described for the preparation of **4c** gave from **2g** (569 mg, 2.45 mmol) compound **4g** (464.5 mg, 2.02 mmol, 82% yield) as an orange solid.

Mp 255–265 °C. IR (KBr) $\nu_{C=C}$ 1605 cm^{-1}, $\nu_{C=O}$ 1720, 1750 cm^{-1}, ν_{NH} 3150–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_8N_2O_2F$ 231.0570, found 231.0567.

^{1}H NMR (400 MHz, DMSO-d_6): 6.91 (1H, d, J=0.5 Hz), 7.14 (1H, dt, J_1=9.0 Hz, J_2=2.5 Hz), 7.56 (1H, dd, J_1=9.0 Hz, J_2=4.5 Hz), 7.83 (1H, dd, J_1=10 Hz, J_2=2.5 Hz), 8.44 (1H, d, J=2.5 Hz), 10.81 (1H, s, NH), 12.13 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 105.7 (d, $J_{C,F}$=25 Hz), 111.0 (d, $J_{C,F}$=26 Hz), 113.6 (d, $J_{C,F}$=10 Hz), 115.8, 132.4 (C tert), 105.5, 125.9 (d, $J_{C,F}$=11 Hz), 133.2, 139.0, 158.3 (d, $J_{C,F}$=234 Hz) (C quat), 173.1, 173.3 (C=O).

4.1.14. 2,5-Dihydro-3-(indol-3-yl)-furane-2,5-dione (4h). A mixture of **4b** (200 mg, 0.884 mmol) and NaOH (500 mg) in water (100 mL) was refluxed for 2 h. After cooling, concentrated HCl was added dropwise until formation of a yellow precipitate. The precipitate was filtered off, washed with water to give **4h** (125 mg, 0.59 mmol, 66% yield) as a yellow solid.

Mp 210–214 °C. IR (KBr) $\nu_{C=O}$ 1740, 1800 cm^{-1}, ν_{NH} 3320 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): 7.30 (1H, t, J=7.3 Hz), 7.32 (1H, s), 7.35 (1H, t, J=7.2 Hz), 7.60 (1H, d, J=7.7 Hz), 8.08 (1H, d, J=7.7 Hz), 8.46 (1H, d, J=2.9 Hz), 12.38 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 105.0, 125.2, 136.9, 141.3 (C quat), 112.9, 113.9, 120.5, 122.1, 123.6, 133.0 (C tert), 166.1, 166.6 (C=O).

4.1.15. 1,3,4,6-Tetrahydro-2-methyl-5*H*,7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7b). A mixture of **4b** (226 mg, 1 mmol) and maleimide (106 mg, 1.10 mmol) in *p*-xylene (17 mL) was refluxed for 48 h. After cooling, the yellow precipitate was filtered off, washed with xylene and dried. The residue was purified by flash chromatography (eluent: EtOAc/cyclohexane from 1:1 to 100% EtOAc, then EtOAc/methanol 98:2) to give an orange solid. A mixture of this solid in dioxane (40 mL) and trifluoroacetic acid (636 μL) was refluxed for 48 h. After evaporation, EtOAc was added to the residue, and the mixture was successively washed with saturated aqueous $NaHCO_3$ and brine. The solid at the interface was filtered off to give **7b** (48 mg, 0.150 mmol, 15% yield) as an orange solid.

Mp>300 °C. IR (KBr): $\nu_{C=O}$ 1710, 1720, 1760, 1780 cm^{-1}, ν_{NH} 3260, 3395 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_{10}N_3O_4$ 320.0671, found 320.0666.

^{1}H NMR (400 MHz, DMSO-d_6): 3.16 (3H, s, CH_3), 7.45 (1H, t, J=6.5 Hz), 7.70 (1H, t, J=6.0 Hz), 7.78 (1H, d, J=7.5 Hz), 9.00 (1H, br s), 11.59 (1H, s, NH), 12.76 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.0 (CH_3), 117.5, 118.5, 119.3, 124.3, 125.5, 130.6, 136.8, 144.1 (C quat arom), 112.9, 121.6, 125.4, 130.1 (C tert arom), 165.1, 166.3, 167.9, 168.5 (C=O).

4.1.16. 1,3,4,6-Tetrahydro-5-methyl-2*H*,7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7c). A mixture of **4a** (193 mg, 0.91 mmol) and *N*-methylmaleimide (121 mg, 1.09 mmol) in *p*-xylene (19 mL) was refluxed for 12 h. After cooling, the mixture was filtered off and the orange solid was washed with xylene and dried. This solid (223 mg) was dissolved in dioxane (12 mL). DDQ (344 mg, 1.52 mmol) was added and the mixture was refluxed for 3 days. After cooling, water and EtOAc were added. The solid at the interface was filtered off and washed with water then EtOAc to give compound **7c** (187 mg, 0.586 mmol, 64% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1695, 1725, 1765, 1775 cm^{-1}, ν_{NH}=3220, 3330 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_{10}N_3O_4$ 320.0671, found 320.0677.

^{1}H NMR (400 MHz, DMSO-d_6): 3.16 (3H, s, NCH_3), 7.48 (1H, t, J=7.5 Hz), 7.73 (1H, dt, J_1=7.5 Hz, J_2=1.0 Hz),

7.82 (1H, d, J=8.0 Hz), 9.04 (1H, d, J=8.0 Hz), 11.65 (1H, s, NH), 12.83 (1H, s, NH).

4.1.17. 1,3,4,6-Tetrahydro-2,5-dimethyl-7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7d). A mixture of **4b** (226 mg, 1 mmol) and *N*-methylmaleimide (122 mg, 1.10 mmol) in xylene (17 mL) was refluxed for 24 h. After cooling, the precipitate was filtered off, washed with xylene and dried. The solid residue was purified by flash chromatography (eluent: EtOAc/cyclohexane from 1:1 to 100% EtOAc then EtOAc/methanol 98:2) to give an orange solid (156 mg). A mixture of this solid (156 mg, 0.465 mmol) in dioxane (25 mL) and trifluoroacetic acid (480 μL) was refluxed for 84 h. After evaporation, EtOAc was added to the residue. Identical work-up as for **7b** gave **7d** (91 mg, 0,271 mmol, 27% yield) as an orange solid.

Mp 300 °C. IR (KBr): $\nu_{C=O}$ 1695–1720 cm^{-1}, ν_{NH} 3410 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{18}H_{12}N_3O_4$ 334.0828, found 334.0825.

^1H NMR (400 MHz, DMSO-d_6): 3.12 (3H, s, CH_3), 3.13 (3H, s, CH_3), 7.41 (1H, t, J=7.5 Hz), 7.68 (1H, t, J=7.0 Hz), 7.73 (1H, d, J=8.0 Hz), 8.88 (1H, d, J=8.0 Hz), 12.67 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.0 ($2CH_3$), 116.5, 118.4, 119.3, 124.4, 124.6, 131.2, 136.6, 144.2 (C quat arom), 112.9, 121.7, 125.4, 130.2 (C tert arom), 165.0, 166.8, 167.2, 167.8 (C=O).

4.1.18. 2,5-Dimethyl-10-benzyloxy-1,3,3a,3b,4,6,6a,6b-octahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (5 R=OBn, X=Y=NCH_3) and 1,3,4,6-tetrahydro-2,5-dimethyl-10-benzyloxy-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7e). A mixture of **4d** (216 mg, 0.650 mmol) and *N*-methylmaleimide (80 mg, 0.715 mmol) in *p*-xylene (17 mL) was refluxed for 48 h. After cooling, the yellow precipitate was filtered off, washed with *p*-xylene and dried. The solid was washed with CH_2Cl_2 to give **7e** (20 mg, 0.046 mmol, 7% yield) as a yellow solid. The filtrate was evaporated and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane from 3:2 to 100% EtOAc then EtOAc/methanol 95:5) to give **5** (R=OBn, X=Y=NCH_3) (59 mg, 0.133 mmol, 21% yield) as an orange solid.

Compound **5** (R=OBn, X=Y=NCH_3): Mp 173–174 °C. IR (KBr): $\nu_{C=O}$ 1700, 1710, 1760, 1770 cm^{-1}, ν_{NH} 3400 cm^{-1}. Mass (EI) $[M+H]^+$: 444.

^1H NMR (400 MHz, DMSO-d_6): 2.56 (3H, s, CH_3), 3.00 (3H, s, CH_3), 3.64 (4H, s, CH), 5.00 (2H, s, CH_2), 6.92 (1H, d, J=9.0 Hz), 7.13 (1H, dd, J_1=9.0 Hz, J_2=2.5 Hz), 7.36 (1H, t, J=7.0 Hz), 7.42 (2H, t, J=7.0 Hz), 7.48 (2H, d, J=7.0 Hz), 7.53 (1H, d, J=2.5 Hz), 8.01 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (2C) (NCH_3), 41.2 (2C), 45.7 (2C), 69.8 (CH_2), 108.8, 117.7, 137.0, 146.8, 150.4, 153.4 (C quat), 109.0, 111.6, 125.2, 127.9 (3C), 128.3 (2C) (C tert arom), 164.0, 172.1, 172.6, 173.9 (C=O).

Compound **7e**: Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1700, 1720, 1775 cm^{-1}, ν_{NH} 3480 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{25}H_{18}N_3O_5$ 440.1246, found 440.1246.

^1H NMR (400 MHz, DMSO-d_6): 3.08 (3H, s, CH_3), 3.10 (3H, s, CH_3), 5.16 (2H, s, CH_2), 7.33 (1H, d, J=8.5 Hz), 7.43 (1H, d, J=7.0 Hz), 7.47 (2H, t, J=7.0 Hz), 7.55 (1H, d, J=9.0 Hz), 7.63 (2H, d, J=7.5 Hz), 8.35 (1H, s), 12.40 (1H, br s, NH).

4.1.19. 10-Benzyloxy-1,3,4,6-tetrahydro-7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7f). Identical method as described for the preparation of **7c** gave from **4c** (190 mg, 0.597 mmol) and maleimide (64 mg, 0.66 mmol) compound **7f** (172.5 mg, 0.419 mmol, 70% yield) as a red solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1725, 1755, 1780 cm^{-1}, ν_{NH} 3150–3500 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{23}H_{14}N_3O_5$ 412.0933, found 412.0933.

^1H NMR (400 MHz, DMSO-d_6): 5.24 (2H, s), 7.38 (1H, m), 7.42 (1H, dd, J_1=9.0 Hz, J_2=2.5 Hz), 7.46 (2H, m), 7.60 (2H, m), 7.67 (1H, d, J=9.0 Hz), 8.60 (1H, d, J=2.5 Hz), 11.54 (1H, br s, NH), 11.56 (1H, br s, NH), 12.58 (1H, br s, NH).

^{13}C NMR (125 MHz, DMSO-d_6): 69.9 (CH_2), 108.6, 113.6, 120.0, 127.8, 127.9 (2C), 128.4 (2C) (C tert arom), 117.9, 119.0, 119.8, 124.1, 125.5, 131.5, 136.9, 137.0, 139.0, 153.5 (C quat arom), 166.4, 166.5, 168.6, 169.3 (C=O).

4.1.20. 10-Bromo-1,3,4,6-tetrahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7g). Identical method as described for the preparation of **7c** gave from **4e** (150 mg, 0.515 mmol) and maleimide (55 mg, 0.567 mmol) compound **7g** (125 mg, 0.325 mmol, 63% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1710, 1720, 1760 cm^{-1}, ν_{NH} 3150–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_3O_4Br$ 383.9620, found 383.9619.

^1H NMR (400 MHz, DMSO-d_6): 7.75 (1H, d, J=8.5 Hz), 7.86 (1H, d, J=8.5 Hz), 9.15 (1H, s), 11.64 (1H, s, NH), 11.69 (1H, s, NH), 12.93 (1H, s, NH).

4.1.21. 10-Chloro-1,3,4,6-tetrahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7h). Identical method as described for the preparation of **7c** gave from **4f** (158 mg, 0.64 mmol) and maleimide (62 mg, 0.64 mmol) compound **7h** (104 mg, 0.306 mmol, 48% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1710, 1720, 1760 cm^{-1}, ν_{NH} 3120–3380 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_3O_4Cl$ 340.0125, found 340.0121.

^{1}H NMR (400 MHz, DMSO-d_6): 7.75 (1H, dd, $J_1=9.0$ Hz, $J_2=2.0$ Hz), 7.81 (1H, d, $J=9.0$ Hz), 9.01 (1H, d, $J=2.0$ Hz), 11.64 (1H, s, NH), 11.69 (1H, s, NH), 12.94 (1H, s, NH).

4.1.22. 10-Fluoro-1,3,4,6-tetrahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7i). Identical method as described for the preparation of **7c** gave from **4g** (347 mg, 1.51 mmol) and maleimide (146 mg, 1.51 mmol) compound **7i** (464 mg containing 11.4% dioxane (w/w) measured from ^{1}H NMR spectrum, 1.27 mmol, 84% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1710, 1780 cm^{-1}, ν_{NH} 3100–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_3O_4F$ 324.0421, found 324.0424.

^{1}H NMR (400 MHz, DMSO-d_6): 7.57 (1H, dt, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.75 (1H, dd, $J_1=9.0$ Hz, $J_2=4.5$ Hz), 8.63 (1H, dd, $J_1=9.5$ Hz, $J_2=2.5$ Hz), 10.61 (2H, br s, 2 NH), 12.77 (1H, br s, NH).

^{13}C NMR (125 MHz, DMSO-d_6): 110.2 (d, $J_{C,F}=25$ Hz), 114.2 (d, $J_{C,F}=9$ Hz), 118.0 (d, $J_{C,F}=26$ Hz) (C tert arom), 118.4, 119.4, 119.6 (d, $J_{C,F}=11$ Hz), 123.5 (d, $J_{C,F}=4.5$ Hz), 126.2, 131.9 137.3, 140.5, 157.2 (d, $J_{C,F}=236$ Hz) (C quat arom), 166.2, 166.3, 168.4, 169.2 (C=O).

4.1.23. 2-Methyl-1,3,4,6-tetrahydro-7*H*-furo[3,4-*c*]pyrrolo[3,4-*a*]carbazole-1,3,4,6-tetraone (7j). Identical method as described for the preparation of **7c** gave from **4h** (213 mg, 0.997 mmol) and *N*-methylmaleimide (122 mg, 1.26 mmol) compound **7j** (40 mg, 0.125 mmol, 13% yield) as an orange solid.

Mp 294 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1775, 1840 cm^{-1}, ν_{NH} 3370 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_9N_2O_5$ 321.0511, found 321.0494.

^{1}H NMR (400 MHz, DMSO-d_6): 3.20 (3H, s, NCH_3), 7.58 (1H, t, $J=8.0$ Hz), 7.82 (1H, t, $J=8.0$ Hz), 7.90 (1H, d, $J=8.0$ Hz), 8.91 (1H, d, $J=8.0$ Hz), 13.20 (1H, s, NH).

4.1.24. 1,3,4,6-Tetrahydro-2-methyl-7*H*-furo[3,4-*a*]pyrrolo[3,4-*c*]carbazole-1,3,4,6-tetraone (7k). Identical procedure as described for the preparation of **7c** gave from **4b** (315 mg, 1.39 mmol) and maleic anhydride (164 mg, 1.67 mmol) compound **7k** (235 mg, 0.734 mmol, 53% yield) as a yellow solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1705, 1760, 1835 cm^{-1}, ν_{NH} 3370 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_9N_2O_5$ 321.0511, found 321.0513.

^{1}H NMR (400 MHz, DMSO-d_6): 3.20 (3H, s, NCH_3), 7.51 (1H, ddd, $J_1=8.0$ Hz, $J_2=6.0$ Hz, $J_3=2.0$ Hz), 7.78 (2H, m), 8.99 (1H, d, $J=8.0$ Hz), 13.22 (1H, s, NH).

^{13}C NMR (125 MHz, DMSO-d_6): 23.9 (CH_3), 113.0, 121.2, 124.8, 129.1 (C tert arom), 112.6, 117.8, 119.3, 120.2, 128.5, 130.4, 142.6, 143.0 (C quat arom), 166.0, 167.0, 167.1, 167.6 (C=O).

4.1.25. 1,3,4,6-Tetrahydro-2*H*,7*H*-furo[3,4-*a*]pyrrolo-[3,4-*c*]carbazole-1,3,4,6-tetraone (7l). Identical method as described for the preparation of **7c** gave from **4a** (200 mg, 0.942 mmol) and maleic anhydride (111 mg, 1.13 mmol) compound **7l** (235 mg, 0.767 mmol, 81% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=C}$ 1610 cm^{-1}, $\nu_{C=O}$ 1700–1850 cm^{-1}, ν_{NH} 3240, 3380 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_2O_5$ 307.0355, found 307.0357.

^{1}H NMR (400 MHz, DMSO-d_6): 7.55 (1H, t, $J=7.5$ Hz), 7.79 (1H, t, $J=7.5$ Hz), 7.85 (1H, d, $J=8.0$ Hz), 9.06 (1H, d, $J=8.0$ Hz), 11.86 (1H, br s, NH), 13.28 (1H, br s, NH).

4.1.26. 2,5-Dihydro-3-(5-hydroxy-indol-3-yl)-1*H*-pyrrole-2,5-dione (9). A mixture of compound **2c** (450 mg, 1.40 mmol), methanol (90 mL) and Pd/C 10% (135 mg) was hydrogenated (1 bar) for 3 h. After filtration over celite, the filtrate was evaporated to give compound **8** as a grey oil. A solution of DDQ (318 mg, 1.40 mmol) in dioxane (15 mL) was slowly added to a solution of **8** (323 mg, 1.40 mmol) in dioxane (15 mL). The mixture was stirred at room temperature overnight then filtered off. After removal of the solvent, the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 1:1) to give **9** (166 mg, 0.73 mmol, 52% yield) as an orange solid.

Compound **8**: IR (film) $\nu_{C=O}$ 1700 cm^{-1}, $\nu_{NH,OH}$ 3000–3700 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): 2.75 (1H, dd, $J_1=18$ Hz, $J_2=5.0$ Hz), 3.18 (1H, dd, $J_1=18$ Hz, $J_2=9.5$ Hz), 4.26 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 6.65 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 6.75 (1H, d, $J=2.0$ Hz), 7.20 (1H, d, $J=8.5$ Hz), 7.24 (1H, d, $J=2.5$ Hz), 8.74 (1H, s, OH), 10.74 (1H, s, NH), 11.34 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.2 (CH_2), 39.1 (CH), 102.3, 111.7, 112.1, 123.9 (C tert arom), 109.9, 126.4, 131.0, 150.4 (C quat arom), 178.1, 180.0 (C=O).

Compound **9**: Mp 292–298 °C. IR (KBr) $\nu_{C=C}$ 1610 cm^{-1}, $\nu_{C=O}$ 1690, 1760 cm^{-1}, $\nu_{NH,OH}$ 3260, 3370, 3430 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_9N_2O_3$ 229.0613, found 229.0609.

^{1}H NMR (400 MHz, DMSO-d_6): 6.47 (1H, s), 6.80 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 7.20 (1H, d, $J=2.0$ Hz), 7.36 (1H, d, $J=8.5$ Hz), 8.29 (1H, d, $J=3.0$ Hz), 9.09 (1H, s, OH), 10.74 (1H, s, NH), 11.85 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 104.7, 112.7, 113.1, 113.5, 131.1 (C tert), 104.6, 126.7, 130.7, 139.9, 152.8 (C quat), 173.1, 173.3 (C=O).

4.1.27. 1,3,4,6-Tetrahydro-10-hydroxy-7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7m). Identical method as described for the preparation of **7c** gave from **9** (79.5 mg, 0.348 mmol) and maleimide (33.8 mg, 0.348 mmol) compound **7m** (38.5 mg, 0.120 mmol, 34% yield) as a brown solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1715, 1770 cm^{-1}, $\nu_{NH,OH}$ 3100–3650 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_8N_3O_5$ 322.0464, found 322.0460.

^{1}H NMR (400 MHz, DMSO-d_6): 7.21 (1H, dd, J_1=2.5 Hz, J_2=9.0 Hz), 7.63 (1H, d, J=9.0 Hz), 8.45 (1H, d, J=2.5 Hz), 9.52 (1H, br s, OH), 11.49 (1H, s, NH), 11.52 (1H, s, NH), 12.51 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 109.7, 113.4, 120.0 (C tert arom), 117.7, 118.7, 120.2, 124.2, 125.4, 131.6, 137.1, 138.1, 152.5 (C quat arom), 166.5, 166.6, 168.8, 169.4 (C=O).

4.1.28. 2-(2-*N*,*N*-Diethylaminoethyl)-1,3,5,6-tetrahydro-5-methyl-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone hydrochloride (7o). To a solution of **7j** (28.3 mg, 0.088 mmol) in THF (5.2 mL) was added dropwise *N*-*N*-diethylethylenediamine (19 μL, 0.132 mmol). The light-protected mixture was stirred at 65 °C for 4 days. After cooling, 1 N HCl (40 mL) was added. The mixture was washed with EtOAc and the aqueous phase was adjusted to pH 8 by addition of saturated aqueous $NaHCO_3$ then extracted with EtOAc. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduce pressure at 20 °C to give the free amine (29 mg) as a yellow solid. To a solution of the amine at 0 °C in methanol (400 μL) was added dropwise 1 N HCl (190 μL). The mixture was stirred for 30 min. The solvent was removed to give hydrochloride **7o** (32.3 mg, 0.071 mmol, 81% yield) as a yellow solid.

Mp 184 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1710, 1720, 1765, 1775 cm^{-1}, ν_{NH} 3300–3600 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{23}H_{23}N_4O_4$ 419.1719, found 419.1713.

^{1}H NMR (400 MHz, DMSO-d_6): 1.27 (6H, t, J=7.0 Hz), 3.18 (3H, s, NCH_3), 3.35 (4H, m), 3.50 (2H, m), 4.09 (2H, t, J=6.5 Hz), 7.51 (1H, t, J=8.0 Hz), 7.75 (1H, t, J=8.0 Hz), 7.84 (1H, d, J=8.5 Hz), 9.04 (1H, d, J=8.5 Hz), 9.43 (1H, br s), 12.95 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 8.2 (2C) (CH_3), 24.0 (NCH_3), 32.6, 46.1 (2C), 47.9 (CH_2), 113.0, 121.8, 125.4, 130.4 (C tert arom), 116.7, 118.2, 119.2, 124.5, 124.7, 130.1, 136.6, 144.3 (C quat arom), 164.8, 165.0, 167.1, 167.6 (C=O).

4.1.29. 5-(2-*N*,*N*-Diethylaminoethyl)-1,3,4,6-tetrahydro-2-methyl-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone hydrochloride (7n). To a solution of **7k** (30 mg, 0.094 mmol) in THF (5.5 mL) was added dropwise *N*,*N*-diethylethylenediamine (20 μL, 0.142 mmol). The light-protected mixture was stirred at 65 °C for 4 days. After cooling, the solvent was removed. Acetic anhydride (1 mL) and NaOAc (75 mg, 0.91 mmol) were added to the residue. The mixture was stirred at 90 °C for 4 h. After cooling, 1 N HCl (40 mL) then EtOAc were added. After extraction, EtOAc and saturated aqueous $NaHCO_3$ were added to the aqueous phase. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure without heating. The free amine (33 mg) was obtained as a yellow solid. To a solution of the free amine in methanol (1 mL) at 0 °C was added dropwise 1 N HCl (172 μL). The mixture was stirred for 30 min. The solvent was removed to give **7n** (31 mg, 0.068 mmol, 72% yield) as a yellow-orange solid.

Mp 278–280 °C. IR (KBr) $\nu_{C=O}$ 1710, 1770 cm^{-1}, ν_{NH} 3200, 3600 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{23}H_{23}N_4O_4$ calcd. for 419.1719, found 419.1720.

^{1}H NMR (400 MHz, DMSO-d_6): 1.29 (6H, t, J=7.0 Hz), 3.19 (3H, s, NCH_3), 3.31 (4H, m), 3.46 (2H, m), 4.08 (2H, t, J=6.5 Hz), 7.48 (1H, t, J=7.5 Hz), 7.74 (1H, t, J=7.5 Hz), 7.81 (1H, d, J=8.0 Hz), 9.00 (1H, d, J=8,0 Hz), 10.04 (1H, br s), 12.87 (1H, s).

^{13}C NMR (100 MHz, DMSO-d_6): 8.2 (2C), 24.0 (CH_3), 32.5, 46.1 (2C), 47.9 (CH_2), 112.9, 121.8, 125.4, 130.3 (CH arom), 116.3, 118.3, 119.1, 124.3 (2C), 130.0, 136.5, 144.2 (C quat arom), 164.7, 164.9, 166.8, 167.5 (C=O).

4.1.30. 1-(2,5-Dioxopyrrolidin-3-yl)-pyrrolo[2,3-*b*]pyridine 10. A solution of 7-azaindole (1 g, 8.47 mmol) and maleimide (904 mg, 9.32 mmol) in acetic acid (10 mL) was refluxed for 60 h. Acetic acid was evaporated and EtOAc was added. The solution was washed with saturated aqueous $NaHCO_3$ then dried over Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography (eluent EtOAc/cyclohexane from 1:2 to 7:3) to give a solid which was washed with EtOAc then with Et_2O to give **10** (184 mg, 0.86 mmol, 10% yield) as a white solid.

Mp > 200 °C (sublimation). IR (KBr) $\nu_{C=O}$ 1720, 1780 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{11}H_{10}N_3O_2$ 216.0773, found 216.0770.

^{1}H NMR (400 MHz, DMSO-d_6): 3.14 (1H, dd, J_1=17.5 Hz, J_2=6.0 Hz), 3.26 (1H, dd, J_1=17.5 Hz, J_2=9.5 Hz), 5.86 (1H, dd, J_1=9.5 Hz, J_2=6.0 Hz), 6.57 (1H, d, J=3.5 Hz), 7.16 (1H, dd, J_1=8.0 Hz, J_2=4.5 Hz), 7.71 (1H, d, J=3.5 Hz), 8.04 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=4.5 Hz), 11.69 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 36.4 (CH_2), 54.6, 100.1, 116.2, 129.0, 129.1, 142.5 (CH), 120.5, 146.8 (C quat arom), 175.8, 176.3 (C=O).

4.1.31. 1-Methyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrolidine-2,5-dione 11a. A mixture of **A** (199 mg, 0.65 mmol) and 10% Pd/C (20 mg) in methanol (40 mL) was hydrogenated (1 bar) for 3.5 h. The mixture was filtered over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent from EtOAc 100% to EtOAc/MeOH 9:1) to give **11a** (135 mg, 0.59 mmol, 90% yield) as a white solid.

Mp 199–202 °C. IR (KBr) $\nu_{C=O}$ 1690, 1770 cm^{-1}, ν_{NH} 3250–3500 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_2$ 230.0930, found 230.0925.

^1H NMR (400 MHz, DMSO-d_6): 2.92 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 2.95 (3H, s, NCH_3), 3.25 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.42 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.10 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 7.53 (1H, d, $J=2.5$ Hz), 7.92 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.26 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 11.64 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.6 (CH_3), 37.5 (CH_2), 35.6 (CH), 115.2, 123.8, 127.0, 142.9 (C tert arom), 109.5, 118.4, 148.6 (C quat arom), 176.5, 178.1 (C=O).

4.1.32. 1-Benzyloxymethyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrolidin-2,5-dione 11b. A mixture of **B** (607 mg, 1.47 mmol), $NaHCO_3$ (618 mg, 7.36 mmol) and 10% Pd/C (607 mg) in EtOAc (57 mL) was hydrogenated (1 bar) for 24 h. The mixture was filtered over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 3:7) to give **11b** (334 mg, 1.00 mmol, 68% yield) as a white solid.

Mp 136–138 °C. IR (KBr) $\nu_{C=O}$ 1707, 1776 cm^{-1}, ν_{NH} 3143 cm^{-1}.

Mass (ESI+) $[M+H]^+$ 336. ^1H NMR (400 MHz, DMSO-d_6): 3.00 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.30 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.47 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 4.60 (2H, s, CH_2), 4.99 (2H, s, CH_2), 7.07 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 7.30–7.42 (5H, m), 7.54 (1H, d, $J=2.5$ Hz), 7.93 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.26 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 11.66 (1H, br s, NH).

^{13}C NMR (100 MHz, $CDCl_3$): 35.9, 68.0, 72.4 (CH_2), 38.2 (CH), 116.0, 123.1, 127.6 (2C), 127.8, 127.9, 128.5 (2C), 143.1 (C tert arom), 109.4, 118.8, 137.5, 149.0 (C quat arom), 175.8, 177.4 (C=O).

4.1.33. 2,5-Dihydro-1-methyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione 12a. A solution of DDQ (138 mg, 0.61 mmol) in dioxane (10 mL) was added dropwise to a solution of **11a** (133 mg, 0.581 mmol) in dioxane (5 mL). After stirring for 15 h at room temperature, the solvent was removed and CH_2Cl_2 was added to the residue. After filtration, the solid was washed with CH_2Cl_2 then with methanol to give **12a** (124 mg, 0.546 mmol, 94% yield) as a white solid.

Mp > 250 °C. IR (KBr) $\nu_{C=O}$ 1700, 1760 cm^{-1}, ν_{NH} 3300–3600 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{12}H_{10}N_3O_2$ 228.0773, found 228.0774.

^1H NMR (400 MHz, DMSO-d_6): 2.98 (3H, s, NCH_3), 7.08 (1H, s), 7.29 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 8.40 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.47 (1H, d, $J=2.5$ Hz), 8.52 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 12.59 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 115.9, 117.4, 128.9, 130.9, 144.3 (C tert), 104.3, 117.7, 138.3, 149.1 (C quat), 171.3, 171.8 (C=O).

4.1.34. 1-Benzyloxymethyl-2,5-dihydro-3-(1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione 12b. DDQ (234 mg, 1.03 mmol) was added slowly to a solution of **11b** (329 mg, 0.98 mmol) in dioxane (20 mL). The mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 1:1 then THF/cyclohexane 1:1) to give **12b** (327 mg, 0.98 mmol, 100% yield) as a yellow solid.

Mp 186 °C. IR (KBr): $\nu_{C=C}$ 1585, 1600 cm^{-1}, $\nu_{C=O}$ 1705, 1760 cm^{-1}. Mass (ESI+) $[M+H]^+$ 334, $[M+Na]^+$ 356.

^1H NMR (400 MHz, DMSO-d_6): 4.60 (2H, s, CH_2), 5.02 (2H, s, CH_2), 7.16 (1H, s), 7.31 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 7.31 (1H, m), 7.37 (4H, m), 8.41 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.51 (1H, d, $J=3.0$ Hz), 8.54 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 12.66 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 66.4, 70.3 (CH_2), 116.0, 117.5, 127.4 (2C), 127.5, 128.2 (2C), 129.0, 131.4, 144.4 (C tert), 104.1, 117.7, 137.7, 138.5, 149.1 (C quat), 171.0, 171.2 (C=O).

4.1.35. 2-Methyl-1,3,4,6-tetrahydro-5*H*,7*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 13a. A mixture of **12a** (55 mg, 0.242 mmol) and maleimide (26 mg, 0.267 mmol) in *p*-xylene (5 mL) was refluxed for 20 h. After cooling, then filtration, the solid was washed with *p*-xylene. A mixture of the solid (70.8 mg) and DDQ (116 mg, 0.509 mmol) in dioxane (5 mL) was refluxed for 3 days. After removal of the solvent, water was added. After filtration, the residue was washed with water then with EtOAc affording **13a** (64.7 mg, 0.202 mmol, 83% yield) as a yellow-orange solid.

Mp > 300 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1710, 1730, 1770, 1780 cm^{-1}, ν_{NH} 3200 cm^{-1}.

Mass (FAB+) $[M+H]^+$ 321.

^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 7.56 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 8.77 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 9.29 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.67 (1H, s, NH), 13.39 (1H, s, NH).

Due to its insolubility, the ^{13}C NMR spectrum could not be recorded.

4.1.36. 2-Benzyloxymethyl-5*H*,7*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 13b. A mixture of

12b (329 mg, 0.99 mmol) and maleimide (101 mg, 1.04 mmol) in *p*-xylene (17 mL) was refluxed for 24 h. After cooling, then filtration, the solid was washed with *p*-xylene. A mixture of the solid (361 mg) and DDQ (417 mg, 1.84 mmol) in dioxane (15 mL) was refluxed for 40 h. After filtration, the residue was washed with water then with EtOAc affording **13b** (325 mg, 0.76 mmol, 77% yield) as a pale-yellow solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1715, 1780 cm^{-1}, ν_{NH} 3200 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{23}H_{14}N_4O_5$ 427.1042, found 427.1042.

^1H NMR (400 MHz, DMSO-d_6): 4.69 (2H, s, CH_2), 5.22 (2H, s, CH_2), 7.28 (1H, m), 7.32–7.42 (4H, m), 7.54 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 8.74 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 9.21 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.70 (1H, s, NH), 13.39 (1H, s, NH).

Due to its insolubility, the ^{13}C NMR spectrum could not be recorded.

4.1.37. 1,3,4,6-Tetrahydro-2*H*,5*H*,7*H*-pyridino[2,3-*b*]-dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 13c. A solution of compound **13b** (100 mg, 0.234 mmol) in TFA (14 mL) was refluxed for 3 days. After removal of the solvent, water was added. After fitration the solid residue was washed with EtOAc then dried under vacuum. A mixture of the solid residue in *p*-xylene (3 mL) was refluxed for 7 days. After cooling then filtration, the solid was washed with *p*-xylene, water, EtOAc, and finally with THF to give **13c** (45 mg, 0.147 mmol, 63% yield) as a green-yellow solid.

Mp > 300 °C. IR (KBr) $\nu_{C=C}$ 1590 cm^{-1}, $\nu_{C=O}$ 1718, 1780 cm^{-1}, ν_{NH} 3000–3300 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{15}H_6N_4O_4$ 307.0467, found 307.0477.

^1H NMR (400 MHz, DMSO-d_6): 7.53 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 8.74 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 9.24 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.63 (1H, br s, NH), 11.68 (1H, br s, NH), 13.32 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 117.9, 134.0, 150.5 (C tert arom), 112.4, 118.8, 120.3, 122.1, 126.8, 132.4, 136.2, 155.4 (C quat arom), 166.2, 166.3, 167.9, 169.1 (C=O).

4.1.38. 3-Bromo-2,5-dihydro-1-methyl-4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]-pyridin-3-yl]-pyrrole-2,5-dione 14a. To a solution of **A** (50 mg, 0.172 mmol) in THF (4 mL) were added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (264 mg, 0.488 mmol) and triphenylphosphine (128 mg, 0.488 mmol). The mixture was cooled to −78 °C then diisopropyl azodicarboxylate (DIAD, 97 μL, 0.488 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred at room temperature for 15 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **14a** (65 mg, 0.078 mmol, 46% yield) as the major product of the reaction and as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1710, 1760 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{46}H_{43}N_3O_7Br$ 828.2284, found 828,2283.

^1H NMR (400 MHz, $CDCl_3$): 3.21 (3H, s, NCH_3), 3.74–3.87 (3H, m), 3.74 (1H, t, $J=9.5$ Hz), 3.97–4.05 (2H, m), 4.51 (1H, d, $J=11.0$ Hz), 4.53 (1H, d, $J=12.0$ Hz), 4.63 (1H, d, $J=12.0$ Hz), 4.70 (1H, d, $J=10.5$ Hz), 4.92 (1H, d, $J=10.5$ Hz), 4.98 (3H, s), 6.17 (1H, d, $J=7.5$ Hz, $H_{1'}$), 6.60 (2H, d, $J=7.0$ Hz), 6.99 (2H, t, $J=7.5$ Hz), 7.06 (1H, t, $J=7.5$ Hz), 7.22–7.40 (15H, m), 8.27 (1H, s), 8.47 (1H, d, $J=5.0$ Hz), 8.49 (1H, d, $J=8.0$ Hz).

RMN ^{13}C (100 MHz, $CDCl_3$): 24.9 (N–CH_3), 68.5 ($C_{6'}$), 73.5, 74.9, 75.2, 75.8 (CH_2), 77.5, 78.0, 81.7, 82.2, 85.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.0, 127.6–128.5, 130.0, 132.0, 144.4, 152.6 (C tert arom), 104.7, 116.2, 118.2, 136.4, 136.9, 137.9, 138.0, 138.3, 148.0 (C quat arom), 166.4, 169.0 (C=O).

4.1.39. 3-Bromo-1-benzyloxymethyl-2,5-dihydro-4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 14b. To a solution of **B** (774 mg, 1.88 mmol) in THF (5 mL) were added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (3.04 g, 5.62 mmol) and triphenylphosphine (1.74 g, 5.62 mmol). The mixture was cooled to −78 °C then DIAD (1.12 mL, 5.62 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred at room temperature for 15 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2 then CH_2Cl_2/EtOAc 95:5) to give **14b** (1.12 mg, 1.20 mmol, 64% yield) as the major product of the reaction and as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1720–1780 cm^{-1}.

Mass (ESI+) $[M+Na]^+$ 956, 958, $[M+K]^+$ 972, 974.

^1H NMR (400 MHz, $CDCl_3$): 3.66 (1H, m), 3.72 (2H, d, $J=9.0$ Hz), 3.83 (1H, m), 3.89–3.93 (3H, m), 4.42 (1H, d, $J=11.0$ Hz), 4.43 (1H, d, $J=12.0$ Hz), 4.52 (1H, d, $J=12.0$ Hz), 4.59 (1H, d, $J=11.0$ Hz), 4.60 (2H, s), 4.82 (1H, d, $J=11.0$ Hz), 4.87 (2H, s), 5.09 (2H, s), 6.09 (1H, br s, $H_{1'}$), 6.49 (2H, d, $J=7.0$ Hz), 6.86–6.97 (3H, m), 7.10–7.25 (21H, m), 8.14 (1H, s), 8.36–8.42 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$): 67.6, 68.6, 72.0, 73.6, 74.9, 75.3, 75.8 (CH_2), 77.6, 78.1, 81.5, 82.2, 85.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.1, 127.7–128.5, 130.5, 132.4, 132.5, 144.1 (C tert arom), 118.6, 125.3, 136.9, 137.4, 138.0 (2C), 138.4 (C quat arom), 165.5, 168.0 (C=O).

4.1.40. 1-Methyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-gluco-pyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrolidine-2,5-dione 15a. To a suspension of **14a** (65 mg, 0.078 mmol)

in EtOAc (10 mL) were added $NaHCO_3$ (66 mg, 0.93 mmol) and 10% Pd/C (65 mg). The mixture was hydrogenated (1 bar) at room temperature for 24 h. After filtration over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **15a** (28 mg, 0.037 mmol, 48% yield) as a colourless oil and as a mixture of two diastereoisomers (diastereoisomeric ratio: 1:1 calculated from ^{1}H NMR spectrum on signals at 3.04 and 3.05 ppm).

IR (NaCl film) $\nu_{C=O}$ 1700–1750 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{46}H_{46}N_3O_7$ 752.3335, found 752.3333.

^{1}H NMR (400 MHz, $CDCl_3$): 2.80 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 2.83 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 3.04 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 3.18 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.65–3.94 (14H, m), 4.21 (2H, m), 4.34 (2H, d, $J=11.0$ Hz), 4.45 (2H, d, $J=12.0$ Hz), 4.54 (2H, d, $J=12.0$ Hz), 4.60 (2H, d, $J=11.0$ Hz), 4.84 (2H, d, $J=11.0$ Hz), 4.87–4.91 (4H, m), 6.03 (1H, br s, $H_{1'}$), 6.55 (4H, d, $J=7.0$ Hz), 6.98 (4H, t, $J=7.5$ Hz), 7.00–7.18 (8H, m), 7.20–7.33 (28H, m), 7.82 (1H, d, $J=8.0$ Hz), 7.85 (1H, d, $J=8.0$ Hz), 8.35 (2H, d, $J=5.0$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 25.0 (NCH_3), 35.4, 35.9 (CH_2), 38.0, 38.1 (CH), 68.6 ($C_{6'}$), 73.5, 74.4, 74.5, 75.1, 75.6, 75.7 (CH_2), 77.7, 81.5, 81.7, 82.0, 85.7, 85.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.8, 122.2, 127.4–128.4, 144.0 (C tert arom), 110.7, 110.8, 119.2, 119.3, 137.2, 138.0, 138.5, 148.3 (C quat arom), 175.3, 175.8, 175.9, 176.5 (C=O).

4.1.41. 1-Benzyloxymethyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrolidine-2,5-dione 15b. To a suspension of **14b** (117 mg, 0.125 mmol) in EtOAc (10 mL) were added $NaHCO_3$ (53 mg, 0.625 mmol) and 10% Pd/C (117 mg). The mixture was hydrogenated (1 bar) at room temperature for 24 h. After filtration over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **15b** (50 mg, 0.058 mmol, 46% yield) as a colourless oil and as a mixture of two diastereoisomers (diastereoisomeric ratio: 1:1 calculated from ^{1}H NMR spectrum on signals at 7.77 and 7.81 ppm).

IR (NaCl film) $\nu_{C=O}$ 1715–1780 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 880, $[M+K]^+$ 896.

^{1}H NMR (400 MHz, $CDCl_3$): 2.71 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 2.73 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.04 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.07 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.64–3.89 (12H, m), 4.00–4.10 (2H, m), 4.31 (2H, d, $J=11.0$ Hz), 4.42 (2H, d, $J=12.0$ Hz), 4.51 (2H, d, $J=12.0$ Hz), 4.57 (2H, d, $J=11.0$ Hz), 4.60 (2H, s), 4.83 (2H, d, $J=11.0$ Hz), 4.86 (2H, dd, $J_1=5.0$ Hz, $J_2=3.5$ Hz), 5.03 (2H, d, $J=3.5$ Hz), 6.00 (2H, br s), 6.50 (4H, d, $J=7.5$ Hz), 6.90–6.95 (4H, m), 6.98–7.10 (4H, m), 7.12–7.15 (4H, m), 7.18–7.31 (36H, m), 7.76 (1H, d, $J=8.0$ Hz), 7.81 (1H, d, $J=8.0$ Hz), 8.32 (2H, d, $J=4.5$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 35.2, 35.8 (CH_2), 37.9, 38.1 (CH), 68.0, 68.1, 68.6, 72.4, 73.5, 74.4, 74.6, 75.2, 75.6, 75.7 (CH_2), 77.6, 81.5, 81.7, 85.6, 85.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 110.3, 110.4, 119.2, 137.2, 137.5, 137.9, 138.0, 138.5 (C quat arom), 116.8, 122.4, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 129.7, 144.0 (C tert arom), 175.4, 175.5, 176.6, 176.7 (C=O).

4.1.42. 2,5-Dihydro-1-methyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 16a. To a solution of **15a** (420 mg, 0.56 mmol) in dioxane (20 mL) was slowly added a solution of DDQ (227 mg, 0.98 mmol) in dioxane (20 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **16a** (270 mg, 0.360 mmol, 61% yield) as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1710, 1770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 3.04 (3H, s, NCH_3), 3.63–3.75 (3H, m), 3.79 (1H, t, $J=9.5$ Hz), 3.87–3.98 (2H, m), 3.91 (1H, d, $J=11.0$ Hz), 4.41 (1H, d, $J=10.5$ Hz), 4.44 (1H, d, $J=12.0$ Hz), 4.52 (1H, d, $J=12.0$ Hz), 4.59 (1H, d, $J=10.5$ Hz), 4.83 (1H, d, $J=11.0$ Hz), 4.87 (2H, s), 6.02 (1H, d, $J=8.0$ Hz, $H_{1'}$), 6.49 (2H, d, $J=7.5$ Hz), 6.55 (1H, s), 6.87 (2H, t, $J=7.5$ Hz), 6.96 (1H, t, $J=7.5$ Hz), 7.12–7.30 (16H, m), 7.99 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.38 (1H, dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz), 8.44 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 23.8 (NCH_3), 68.6, 73.5, 74.9, 75.3, 75.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 77.7, 78.0, 81.6, 82.1, 85.8 (CH_2 of OBn, $C_{6'}$), 105.7, 119.0, 136.9, 137.9, 138.0, 138.4, 138.6, 148.5 (C quat arom), 116.8, 118.3, 127.5–128.6, 144.7 (C tert arom), 171.2, 171.8 (C=O).

4.1.43. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]-pyridin-3-yl]-pyrrole-2,5-dione 16b. To a solution of **15b** (420 mg, 0.490 mmol) in dioxane (20 mL) was slowly added a solution of DDQ (227 mg, 0.98 mmol) in dioxane (20 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **16b** (270 mg, 0.315 mmol, 64% yield) as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1710, 1770 cm^{-1}.

Mass (ESI+) $[M+Na]^+$ 878, $[M+K]^+$ 894.

^{1}H NMR (400 MHz, $CDCl_3$): 3.76–3.95 (4H, m), 3.98–4.08 (2H, m), 4.04 (1H, d, $J=11.0$ Hz), 4.53 (1H, d, $J=11.0$ Hz), 4.56 (1H, d, $J=11.0$ Hz), 4.64 (1H, d, $J=12.0$ Hz), 4.71 (1H, d, $J=10.0$ Hz), 4.72 (2H, s), 4.95 (1H, d, $J=11.0$ Hz), 5.00 (2H, s), 5.17 (2H, s), 6.15 (1H, d, $J=7.0$ Hz, $H_{1'}$), 6.60 (2H, d, $J=7.5$ Hz), 6.69 (1H, s), 6.97 (2H, t, $J=7.5$ Hz), 7.06 (1H, t, $J=7.5$ Hz), 7.23–7.46 (21H, m), 8.08 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 8.49 (1H, dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz), 8.55 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 66.7, 68.6, 71.5, 73.5, 74.8, 75.3, 75.7 (CH_2), 77.7, 78.0, 81.5, 82.0, 85.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$,

$C_{4'}$, $C_{5'}$), 116.9, 118.4, 126.5–128.6, 130.5, 144.8 (C tert arom), 105.4, 118.9, 136.9, 137.5, 137.9 (2C), 128.4, 138.6, 148.5 (C quat arom), 170.8, 171.2 (C=O).

4.1.44. 2-Methyl-7-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 18a. A mixture of **16a** (605 mg, 0.790 mmol) and maleimide (384 mg, 3.95 mmol) in toluene (12 mL) was refluxed for 14 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give the mixture of isomers **17a** (277 mg, 0.327 mmol, 41% yield) as a pale yellow solid. To a solution of **17a** (277 mg, 0.327 mmol) in $CHCl_3$ (13 mL) was added MnO_2 (491 mg, 5.65 mmol). The mixture was refluxed for 24 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) to give **18a** (168 mg, 0.199 mmol, 61% yield) as a pale yellow solid.

Mp 68–70 °C.

IR (KBr) $\nu_{C=O}$ 1710, 1720, 1735, 1780 cm^{-1}, ν_{NH} 3280 cm^{-1}.

Mass (ESI+) $[M+Na]^+$ 865.

^1H NMR (400 MHz, $CDCl_3$): 3.17 (3H, s), 3.72–3.80 (2H, m), 3.81 (1H, d, $J=9.5$ Hz), 3.85 (1H, d, $J=8.0$ Hz), 3.93 (1H, t, $J=9.0$ Hz), 4.12 (1H, m), 4.43 (1H, d, $J=12.0$ Hz), 4.47 (1H, d, $J=12.0$ Hz), 4.60 (2H, d, $J=12.0$ Hz), 4.85–4.95 (3H, m), 5.43 (1H, t, $J=9.0$ Hz), 6.26 (2H, d, $J=7.5$ Hz), 6.60 (2H, t, $J=7.5$ Hz), 6.71 (1H, t, $J=7.5$ Hz), 7.00–7.30 (16H, m), 7.34 (1H, d, $J=9.0$ Hz), 8.54 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 9.20 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 9.34 (1H, s,NH).

^{13}C NMR (100 MHz, $CDCl_3$): 24.5 (CH_3), 69.1, 73.1, 74.4, 75.0, 75.2, 75.9 (CH_2), 59.1, 69.3, 76.8, 78.1, 78.5 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 86.3, 87.0, 119.0, 126.9–129.5, 135.2, 150.4 (C tert arom), 114.5, 118.3, 119.8, 123.7, 131.0, 137.0, 137.6, 137.8, 138.0, 138.4, 140.2, 154.1 (C quat arom), 163.4, 164.1, 166.4, 167.1 (C=O).

4.1.45. 2-Benzyloxymethyl-7-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino-[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 18b. A mixture of **16b** (100 mg, 0.117 mmol) and maleimide (56.6 mg, 0.584 mmol) in toluene (2 mL) was refluxed for 14 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give the mixture of isomers **17b** (95 mg, 0.100 mmol, 85% yield) as a pale yellow solid. To a solution of **17b** (192 mg, 0.202 mmol) in $CHCl_3$ (9 mL) was added MnO_2 (352 mg, 4.06 mmol). The mixture was refluxed for 24 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane:EtOAc 7:3) to give **18b** (166 mg, 0.174 mmol, 86% yield) as a pale yellow solid.

Mp 59–61 °C. IR (KBr) $\nu_{C=O}$ 1725, 1770, 1790 cm^{-1}, ν_{NH} 3200–3300 cm^{-1}.

Masse (ESI+) $[M+H]^+$ 949.

^1H NMR (400 MHz, $CDCl_3$): 3.84 (1H, d, $J=11.0$ Hz, $H_{6'}$), 3.92 (1H, dd, $J_1=12.0$ Hz, $J_2=5.0$ Hz, $H_{6'}$), 3.95 (1H, d, $J=12.0$ Hz), 4.01–4.05 (2H, m, $H_{3'}+H_{4'}$), 4.17 (1H, m, $H_{5'}$), 4.51 (1H, d, $J=12.0$ Hz), 4.59 (1H, d, $J=12.0$ Hz), 4.71 (2H, d, $J=12.0$ Hz), 4.75 (2H, s), 4.97 (1H, d, $J=11.0$ Hz), 4.99 (1H, d, $J=11.0$ Hz), 5.02 (1H, d, $J=11.0$ Hz), 5.34 (2H, s), 5.50 (1H, m, $H_{2'}$), 6.38 (2H, d, $J=7.5$ Hz), 6.60–6.75 (2H, m), 6.83 (1H, t, $J=7.5$ Hz), 7.15–7.50 (22H, m), 8.65 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 8.82 (1H, s, NH), 9.37 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 67.4, 68.9, 72.1, 73.2, 74.4, 75.2, 75.9 (CH_2), 77.2, 78.1, 78.2, 86.4, 87.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.2, 126.9, 127.1, 127.4–128.5, 135.3, 150.5 (C tert arom), 114.5, 119.0, 119.8, 124.2, 130.9, 137.3, 137.8, 138.0, 138.1, 138.5, 140.5, 154.1 (C quat arom), 163.5, 164.0, 166.2, 166.9 (C=O).

4.1.46. 2-Methyl-7-(β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 19a. To a solution of **18a** (168 mg, 0.199 mmol) in CH_2Cl_2 (6 mL) was added during 48 h a solution of dimethyldioxirane (0.8 1.0 M, 56 mL). After evaporation, EtOAc was added. After filtration, the solid residue was washed with EtOAc, then with CH_2Cl_2 and finally with acetone to give **19a** (57 mg, 0.118 mmol, 59% yield) as a yellow solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1700, 1710, 1720, 1770 cm^{-1}, $\nu_{NH,\ OH}$ 3000–3660 cm^{-1}.

HRMS (FAB+) $[M+Na]^+$ calcd for $C_{22}H_{18}N_4O_9Na$ 505.0971, found 505.0981.

^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 3.30–3.39 (2H, m), 3.51 (1H, m), 3.66–3.82 (2H, m), 4.56 (1H, pt, $J=5.5$ Hz), 5.01 (1H, d, $J=5.5$ Hz, OH), 5.08–5.17 (2H, m, 2OH), 5.19 (1H, d, $J=4.0$ Hz, OH), 7.27 (1H, d, $J=9.0$ Hz, $H_{1'}$), 7.64 (1H, m), 8.82 (1H, d, $J=3.5$ Hz), 9.48 (1H, d, $J=7.5$ Hz), 11.93 (1H, s).

^{13}C NMR (100 MHz, DMSO-d_6): 24.2 (CH_3), 61.2 ($C_{6'}$), 68.8, 70.3, 78.1, 79.4, 87.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.8, 134.1, 150.1 (C tert arom), 113.9, 120.3, 122.3 (2C), 128.5, 131.8, 140.1, 153.7 (C quat arom), 164.4, 165.2, 167.4, 167.8 (C=O).

4.1.47. 2-Hydroxymethyl-7-(β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 19b. To a solution of **18b** (20 mg, 0.021 mmol) in CH_2Cl_2 (1.5 mL) was added during 72 h a solution of dimethyldioxirane (0.8–1.0 M, 13 mL). After evaporation, EtOAc was added. After filtration, the solid residue was washed with EtOAc, then with CH_2Cl_2 and finally with acetone to give **19b** (8 mg, 0.016 mmol, 76% yield) as a yellow solid.

Mp>250 °C (decomposition).

HRMS (FAB+) $[M+Na]^+$ calcd for $C_{22}H_{18}N_4O_{10}Na$ 521.0921, found 521.0938.

IR (KBr) $\nu_{C=O}$ 1710, 1720, 1760, 1780 cm^{-1}, $\nu_{NH,\ OH}$ 2900–3600 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 3.34–3.45 (2H, m), 3.52 (1H, m), 3.71 (1H, m), 3.77 (1H, m), 4.55 (1H, t, $J=5.5$ Hz, OH), 5.01 (1H, d, $J=5.5$ Hz, $H_{2'}$), 5.10–5.16 (4H, m, CH_2OH +2OH), 5.18 (1H, d, $J=4.0$ Hz, OH), 6.55 (1H, t, $J=7.5$ Hz), 7.29 (1H, d, $J=8.5$ Hz, $H_{1'}$), 7.65 (1H, dd, $J_1=7.0$ Hz, $J_2=5.0$ Hz), 8.83 (1H, d, $J=3.0$ Hz), 9.50 (1H, d, $J=8.0$ Hz), 11.94 (1H, s).

^{13}C NMR (100 MHz, DMSO-d_6): 60.6, 61.2 ($C_{6'}$, CH_2OH), 68.8, 70.3, 78.1, 79.5, 87.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.8, 134.1, 150.2 (C tert arom), 113.9, 119.5, 120.0, 122.6, 129.0, 131.3, 140.2, 153.7 (C quat arom), 163.7, 165.1, 166.9, 167.7 (C=O).

4.1.48. 7-(β-D-Glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 20. A solution of **19b** (32 mg, 0.064 mmol) in TFA (2.5 mL) was refluxed for 3 days. After evaporation, the residue was purified by flash chromatography (eluent EtOAc 100%) to give a solid to which was added EtOAc. The precipitate was filtered off washed with EtOAc, then with CH_2Cl_2 and finally with Et_2O to give **20** (13 mg, 0.028 mmol, 43% yield) as a yellow solid.

Mp>260 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1720, 1740, 1755, 1780 cm^{-1}, $\nu_{NH,\ OH}$ 3100–3600 cm^{-1}.

HRMS (FAB+) $[M+Na]^+$ calcd for $C_{21}H_{16}N_4O_9Na$ 491.0815, found 491.0818.

^1H NMR (400 MHz, DMSO-d_6): 3.32–3.48 (2H, m), 3.51 (1H, m), 3.67–3.80 (2H, m), 4.55 (1H, t, $J=6.0$ Hz, $OH_{6'}$), 4.99 (1H, d, $J=5.5$ Hz), 5.13 (1H, m, $H_{2'}$), 5.12 (1H, d, $J=4.5$ Hz, OH), 5.18 (1H, d, $J=4.5$ Hz, OH), 7.28 (1H, d, $J=9.0$ Hz, $H_{1'}$), 7.62 (1H, dd, $J_1=8.0$ Hz, $J_2=5.0$ Hz), 8.81 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 9.47 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.79 (1H, s, NH), 11.80 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 61.2 ($C_{6'}$), 68.8, 70.3, 78.1, 79.4, 87.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.7, 134.3, 150.0 (C tert arom), 113.9, 119.2, 121.3, 122.4, 128.7, 132.7, 140.1, 153.7 (C quat arom), 165.3, 165.7, 167.9, 168.7 (C=O).

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Synthetic and computational studies on intramolecular [2+2] sulfonyl isocyanate-olefin cycloadditions

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Abstract—Novel unsaturated sulfonyl isocyanates were prepared using a boron trichloride promoted thermal cleavage of the corresponding sulfonylcarbamates. Due to their moisture sensitivity, the isocyanates were directly converted into sulfonylureas in good yields. An intramolecular cycloaddition of the olefinic sulfonyl isocyanates to give β-lactam-sulfonamide hybrids was not observed experimentally. Investigation of this cycloaddition by DFT-calculations using the 6-31G* and 6-311+G** basis sets showed it to be endergonic.

1. Introduction

β-Lactams are still the most important pharmacophores for treatment of diseases caused by bacterial infections.[1] Next, to their significance as antibacterial agents, β-lactams show other interesting biological properties. They are potent inhibitors of mammalian serine proteases and of cholesterol absorption.[2,3] These biological activities, different from the classical antibacterial action of β-lactams, combined with the emergence of new types of bacteria resistant to the more commonly used β-lactam antibiotics,[4] provide the motivation to explore new methodologies for the synthesis of bioactive substances based on the azetidin-2-one core.[5,6] Due to their versatile biological properties, sulfonamides also play a key role in pharmaceutical research.[7] Recently, cyclic sulfonamides (sultams) have been shown to be highly useful heterocycles for medicinal chemistry as well.[8,9] Thus, hybrids of β-lactams and sulfonamides might well display synergetic biological effects.

As part of a program initiated to develop novel methods for the preparation and synthetic elaboration of sultones and sultams, we have recently reported a concise access to the heterobicyclic compounds **1c–h**, which can be viewed as β-lactam-sulfonamide hybrids (Fig. 1).[10,11]

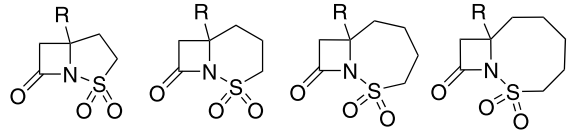
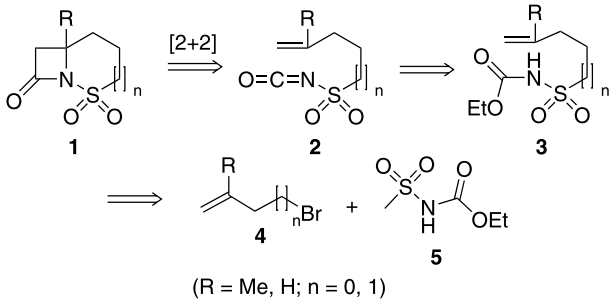


Figure 1. β-Lactam-sulfonamide hybrids **1a–h**.

Here we report our investigations towards the synthesis of **1** by intramolecular[12] [2+2] cycloaddition of olefinic sulfonyl isocyanates **2**, generated in situ from sulfonylcarbamates **3** (Scheme 1). This approach was inspired by the well established intramolecular cycloaddition of ketenes as closely related heterocumulenes to olefins.[13]



Scheme 1. Synthetic strategy for β-lactam-sulfonamide hybrids **1a–d**.

Keywords: Cycloaddition; Sulfonyl isocyanates; β-Lactams; Sultams; Sulfonylureas; Density functional theory.
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† X-ray diffraction analysis.

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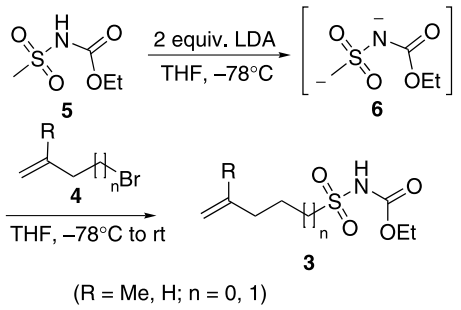
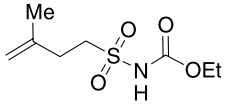
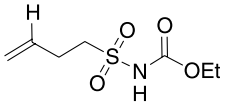
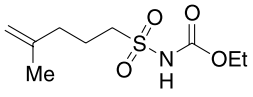
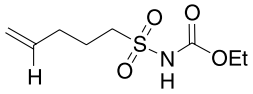


Scheme 2.

protocol reported by Butler and Alper[17] gave the best results.

An intramolecular [2+2] cycloaddition to give β-lactam-sulfonamide hybrids **1** was not observed under the conditions (benzene, reflux) applied for formation of the unsaturated sulfonyl isocyanates **2**. These compounds turned out to be very moisture sensitive and thus, they were immediately converted into sulfonylureas **8** for characterization purposes by treatment with excess aniline (Scheme 3, Table 2). The sulfonylurea moiety is interesting in its own right, since this structural motif is frequently encountered in antidiabetic drugs[18] and is present in antitumor reagents as well.[19]

Table 1. Preparation of sulfonylcarbamates **3**

4	R	*n*	**3**	Yield **3** (%)[a]
a	Me	0		98
b	H	0		93
c	Me	1		49[b]
d	H	1		54[b]

[a] Isolated yield after flash chromatography.
[b] HMPA (2 equiv) was used as cosolvent.

2. Results and discussion

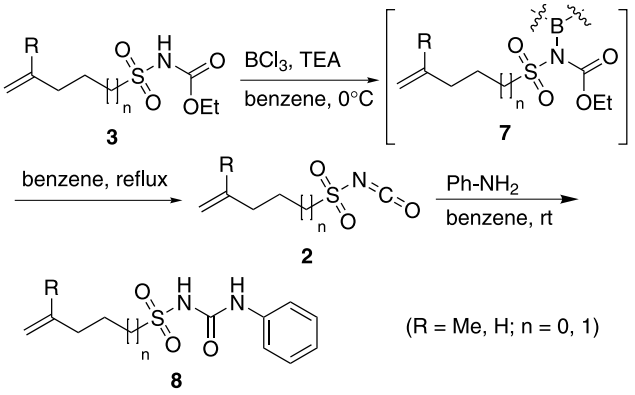
2.1. Experimental work

Ethyl-*N*-(methylsulfonyl) carbamate **5** was synthesized by acylation of methanesulfonamide with ethyl chloroformate using triethylamine as base and catalytic amounts of *N*,*N*-dimethylaminopyridine according to a published procedure.[14] Deprotonation of **5** using an excess of lithium diisopropylamide gave rise to dianion **6**,[15] which was alkylated with several unsaturated bromides **4** (Scheme 2, Table 1) to yield sulfonylcarbamates **3**.

While alkylation of **5** with allylic bromides **4a**,**b** produced carbamates **3a**,**b** in excellent yields, the use of homoallylic bromides **4c**,**d** to furnish **3c**,**d** was less efficient, probably due to competing elimination of the bromides **4**. Employment of hexamethylphosphoric triamide as a cosolvent in order to increase the nucleophilicity of **6** was essential for achieving synthetically useful yields.

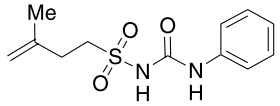
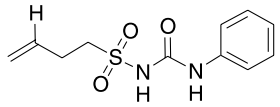
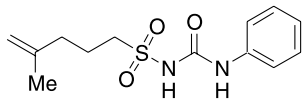
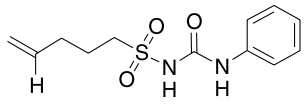
The thermal cleavage of carbamates to give isocyanates is a commonly applied process. Usually, *N*-silylated carbamates serve as the starting materials.[16] However, the synthesis of unsaturated sulfonyl isocyanates such as **2** has not been reported in the literature so far. In our hands, utilization of *N*-borylated carbamates **7** (Scheme 3) according to a

A small amount of **2b** was isolated and analyzed by IR. The typical absorption at 2239 cm^{-1} confirmed the successful generation of the isocyanate function. In addition, a control experiment was run to rule out a direct conversion of carbamates **3** into sulfonylureas **8** by nucleophilic attack of aniline. To this end, **3b** was treated with triethyl borate, triethylamine hydrochloride and aniline. From this experiment, the carbamate **3b** was completely recovered, which

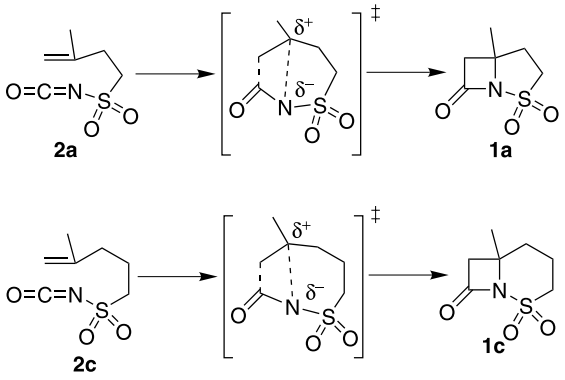


Scheme 3.

Table 2. Preparation of sulfonylureas **3**

8		Yield **8** (%)[a]
a		74
b		66
c		65
d		64

[a] Isolated yield after recrystallization.



Scheme 4.

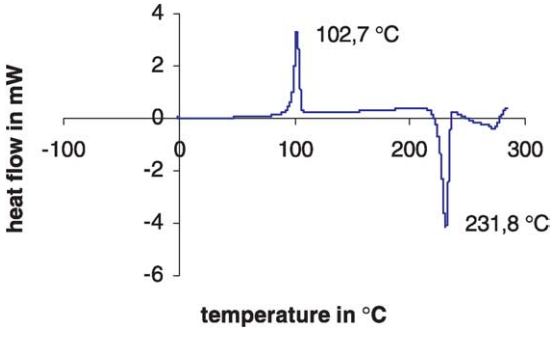


Figure 2. DSC analysis of **1c**.

clearly points to the formation of sulfonyl isocyanates **2** after thermal cleavage.

The mechanism of the envisaged intramolecular [2+2] sulfonyl isocyanate-olefin cycloaddition is expected to be asynchronous and pseudo-concerted (Scheme 4).[20] In order to stabilize the anticipated polar transition state, a series of cycloaddition experiments was performed using **2c** as a test substrate in solvents that have a higher polarity than benzene. Thus, after conversion of **3c** to **2c**, the solvent benzene was removed, and crude **2c** was heated to 110 °C in dichloromethane (sealed tube), reflux in tetrahydrofuran or reflux in *N*,*N*-dimethylformamide. However, formation of β-lactam-sulfonamide hybrid **1c** was not observed in any of these reactions. Similarly, subjecting a solution of crude **2c** in dichloromethane to extremely high pressure (13 kbar) at room temperature,[21] did not yield **1c** either.

Analysis of **1c**[10] by differential scanning calorimetry (DSC) showed the melting point at 102.7 °C as an endothermic event and an irreversible exothermic reaction at 231.8 °C (Fig. 2) indicating that the corresponding intramolecular cycloaddition could be an endergonic process.

To gain additional insight, we investigated the intramolecular cycloaddition by density functional calculations.

2.2. Density functional calculations

We calculated the reaction pathways for cyclization of sulfonyl isocyanate **2a** and **2c** to give the corresponding β-lactam-sulfonamide hybrids **1a** and **1c**, respectively, at two different levels of theory.[22] Table 3 summarizes the gas phase energies (ΔH and ΔG) obtained for the transition state (TS) and the product (prod) relative to the starting material.

Both reactions were calculated to be endergonic at standard conditions. Only the formation of the [2.4]bicyclic product **1c** is exothermic by −5.9 kcal/mol (BS1) and by −1.5 kcal/mol (BS2). The formation of the [2.3]bicyclic system **1a** is endothermic by +0.1 kcal/mol (BS1) and +4.1 kcal/mol (BS2) and correspondingly proceeds via a higher barrier in the gas phase.

From the atomic distances shown in Table 4, it is obvious that the calculated transition states (Fig. 3, Table 3) are very early on the reaction coordinate corresponding to high barriers of 40–50 kcal/mol.

The atomic distances listed in Table 4 describe the transition state TS**2c**→**1c** with prolonged bonds between N1–C1 and C2–C3, while the developing bonds are very long, an indication of an early transition state. We also confirmed by IRC calculations[22] the concerted nature of this ring closure,

Table 3. Enthalpy and free energy in kcal/mol

Reaction	ΔH (TS)	ΔG (TS)	ΔH (prod)	ΔG (prod)
2a→**1a**	BS1: +43.4	BS1: +48.2	BS1: +0.1	BS1: +5.7
	BS2: +45.1	BS2: +50.1	BS2: +4.1	BS2: +9.7
2c→**1c**	BS1: +38.2	BS1: +43.0	BS1: −5.9	BS1: +0.5
	BS2: +40.2	BS2: +45.2	BS2: −1.5	BS2: +4.6

Table 4. Selected bond lengths of the calculated transition states and products in Å (B3LYP/6-31G*) as well as bond lengths obtained from the solid state structure of **1c**

	N1–C1	C2–C3	C1–C2	N1–C3
TS**2a**→**1a**	1.36	1.45	1.64	2.47
1a	1.43	1.56	1.54	1.51
TS**2c**→**1c**	1.31	1.40	1.90	2.34
1c	1.41	1.56	1.54	1.51
1c (exp.)[a]	1.40	1.55	1.51	1.51

[a] See Ref. 23.

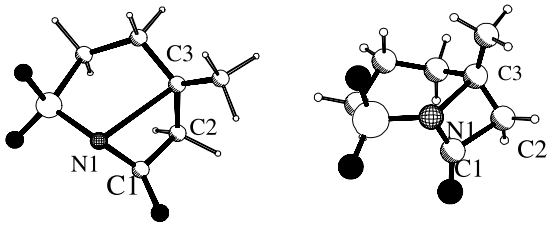


Figure 3. Calculated transition states (B3LYP/6–31G*): TS**2a**→**1a** (left) and TS**2c**→**1c** (right).

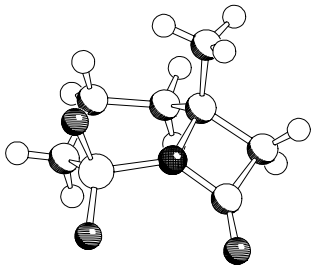


Figure 4. Crystal structure of hybrid **1c**.[23,24]

although the degree of bond formation between C2–C1 (1.90 Å) and N1–C3 (2.34 Å) seems to be very different. The formation of **1a** shows an even larger degree of asynchronicity in the transition state structure. The C1–C2 distance is relatively short (1.64 Å), while the N1–C3 distance is unusually long (2.47 Å). To exclude a possible biradical character of the polarized transition state, we conducted several tests, but did not find any indications. The corresponding triplet ground state of the seven-membered ring is energetically much more unfavorable compared to **1a** (by +63.4 kcal/mol, ΔG). Nevertheless, closure of the seven-membered ring is almost complete in TS**2a**→**1a**. As this structural feature is not as distinct in TS**2c**→**1c**, it explains why the barrier is about 5 kcal/mol lower in the latter case.

The calculated geometry of the β-lactam-sulfonamide hybrid **1c** (Table 4) corresponds well to its solid state structure depicted in Figure 4.[23]

To allow a better comparison to the experimental conditions, solvation calculations using the PCM model[22] were performed (Table 5). We investigated the effect of the three solvents dichloromethane, tetrahydrofuran and *N*,*N*-dimethylformamide as used experimentally.

From the calculated electronic energies, it can be shown that a more polar solvent can lower the barrier of both reactions. It also leads to a decrease of the reaction energies. The similar polarity of dichloromethane and tetrahydrofuran explains why they show a comparable effect in the solvent calculations. It is interesting to note that the more polar solvent *N*,*N*-dimethylformamide lowers the barrier for formation of the smaller ring system (TS**2a**→**1a**) much more compared to the calculated barrier for formation of the larger ring via transition state TS**2c**→**1c**. This might be explained by a more polar transition state for the smaller ring system.

3. Conclusion

Using a combination of alkylation and thermal cleavage methodologies, an efficient route to several unsaturated sulfonyl isocyanates **2** has been developed. The highly moisture sensitive isocyanates **2** were immediately transformed into sulfonylureas **8**. An intramolecular [2+2] cycloaddition of **2** could not be achieved under any of the reaction conditions applied. Experimental and theoretical data agree well and confirm that the ring closure for the systems investigated is expected to be endergonic and therefore difficult to accomplish. We could also confirm the asynchronous character of the transition states reported earlier[20] for similar systems.

4. Experimental

4.1. General methods

All reactions were carried out under argon atmosphere using anhydrous solvents and flame-dried glassware. Commercially available compounds were used without further purification. Benzene was refluxed with Na/K and freshly

Table 5. Solvation effects (BS1, with respect to the corresponding starting materials in kcal/mol)[a]

	TS**2a**→**1a**	**1a**	TS**2c**→**1c**	**1c**
$\Delta\varepsilon$ (gas phase)	+44.9	−0.3	+39.6	−6.8
$\Delta\varepsilon$ (CH_2Cl_2)	+33.4	−6.5	+32.5	−12.0
$\Delta\varepsilon$ (THF)	+33.6	−6.1	+32.6	−12.0
$\Delta\varepsilon$ (DMF)	+25.3	−9.5	+27.9	−14.4

[a] PCM only corrects electronic energies ($\Delta\varepsilon$).

destilled prior to use. Other solvents were dried according to standard procedures. Analytical TLC was performed on precoated Merck Si 254 F plates, and the products were visualized with a solution of $KMnO_4$. Merck silica gel 60 (40–63 μm) was used for flash chromatography. Melting points were determined on a Kofler microscope desk. IR spectra were measured with a ThermoNicolet AVATAR 360 FT-IR. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 using $CDCl_3$ as the solvent and are reported in ppm downfield from TMS ($\delta=0$) for ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta=77.7$) for ^{13}C NMR. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra (LC/ESI) were recorded with a Hewlett Packard Esquire-LC. Elemental analysis were carried out with a EuroVector EA-3000. The DSC of **1c** was performed with a TA Instruments MSDC (Modulated Differential Scanning Calorimeter) using a heating rate of 5 K/min.

4.2. Ethyl-*N*-(methylsulfonyl) carbamate (5)

To a cooled (0 °C) suspension of methanesulfonamide (4.75 g, 50.0 mmol) in CH_2Cl_2 (150 mL) was added triethylamine (9.1 mL, 65.0 mmol) and DMAP (0.61 g, 5.00 mmol). To the resulting mixture a solution of ethyl chloroformate (5.49 mL, 57.5 mmol) in CH_2Cl_2 (100 mL) was added slowly over a period of 30 min. After 3 h stirring at ambient temperature, all volatile parts of the mixture were removed in vacuo, the residue was dissolved in EtOAc (570 mL) and washed with 1 N HCl (380 mL), water (250 mL) and brine (250 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude product as a yellow oil. Recrystallization (hexane/Et_2O) yielded **5** as a white solid. Yield 36% (2.98 g, 17.8 mmol); mp 55–57 °C; IR (neat) 1710, 1327, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, $J=7.1$ Hz), 3.29 (s, 3H, 1-H), 4.27 (q, 2H, $J=7.1$ Hz), 7.51 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.13, 41.19, 63.44, 151.08; MS (LC/MS) *m/z* (%) 168 (26) [$M+H^+$], 185 (25) [$M+NH_4^+$], 190 (25) [$M+Na^+$], 357 (100) [$2\times M+Na^+$]. Anal. Calcd for $C_4H_9NO_4S$: C, 28.74; H, 5.43; N, 8.38; S 19.18. Found: C, 28.86; H 5.44; N, 8.34; S, 19.28.

4.3. General procedure for allylation

To a cooled (−78 °C) solution of diisopropylamine (1.14 mL, 8.00 mmol) in THF (8 mL) was added *n*-BuLi (5.00 mL, 8.00 mmol, 1.6 M in *n*-hexane). After stirring the resulting mixture for 10 min, a solution of carbamate **5** (668.0 mg, 4.00 mmol) in THF (8 mL) was added dropwise over a period of 20 min and stirred for additional 20 min. The resulting white suspension was treated successively with a solution of allyl derivatives **4a**,**b** (5.00 mmol) in THF (5 mL) over a period of 30 min. The reaction mixture was slowly warmed to ambient temperature (16 h) and poured onto a mixture of 2 N HCl and ice water (50 mL, 1:4). The aqueous layer was extracted three times with CH_2Cl_2 (100 mL), and the organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc 5:1) to afford **3a**,**b**.

4.3.1. Ethyl-*N*-(3-methyl-3-butenylsulfonyl) carbamate (3a). Yield 98% (862 mg, 3.90 mmol); colorless oil; R_f 0.58 (CH_2Cl_2/EtOAc 5/1); IR (neat) 1746, 1346, 1144 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, 3H, $J=7.1$ Hz), 1.77 (s, 3H), 2.54 (t, 2H, $J=8.1$ Hz), 3.53–3.59 (m, 2H), 4.27 (q, 2H, $J=7.1$ Hz), 4.78 (d, 1H, $J=1.0$ Hz), 4.86 (d, 1H, $J=0.6$ Hz), 7.34 (s, NH); ^{13}C NMR ($CDCl_3$) δ 14.15, 22.15, 31.00, 51.45, 63.43, 112.58, 140.91, 150.94; MS (LC/MS) *m/z* (%)=222 (3) [$M+H^+$], 244 (28) [$M+Na^+$], 465 (100) [$2\times M+Na^+$]. Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.33; S, 14.49. Found: C, 43.57; H, 6.91; N, 6.38; S, 14.51.

4.3.2. Ethyl-*N*-(3-butenylsulfonyl) carbamate (3b). Yield 93% (770 mg, 3.72 mmol); colorless oil; R_f 0.45 (CH_2Cl_2/EtOAc 5/1); IR (neat) 1723, 1342, 1138 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, $J=7.1$ Hz), 2.57–2.70 (m, 2H), 3.51 (dt, 2H, $J=7.8$, 9.7 Hz), 4.27 (q, 2H, $J=7.1$ Hz), 5.11–5.22 (m, 2H), 5.74–5.88 (m, 1H), 7.56 (s, NH); ^{13}C NMR ($CDCl_3$) δ 14.11, 27.34, 52.18, 63.40, 117.66, 133.29, 150.99; MS (LC/MS) *m/z* (%)=208 (8) [$M+H^+$], 230 (100) [$M+Na^+$], 437 (95) [$2\times M+Na^+$]. Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.57; H, 6.32; N, 6.76; S, 15.47. Found: C, 40.60; H, 6.38; N, 6.89; S, 15.13.

4.4. General procedure for homoallylation

To a cooled (−78 °C) solution of diisopropylamine (0.57 mL, 4.00 mmol) in THF (4 mL) was added *n*-BuLi (2.50 mL, 4.00 mmol, 1.6 M in *n*-hexane). After stirring the resulting mixture for 10 min and addition of HMPA (0.7 mL, 4.00 mmol), a solution of carbamate **5** (334.0 mg, 2.00 mmol) in THF (4 mL) was added dropwise during 20 min, and stirring was continued for additional 20 min. The resulting white suspension was treated successively with a solution of homoallyl derivatives **4c–d** (4.00 mmol) in THF (2.5 mL) over a period of 30 min. The reaction mixture was slowly warmed to ambient temperature (16 h) and poured onto a mixture of 2 N HCl and ice water (70 mL, 2:5). The aqueous layer was extracted three times with Et_2O (25 mL), the organic extracts were treated with water (75 mL), and saturated aqueous Na_2CO_3 solution was added until pH 10. The aqueous layer was extracted twice with Et_2O (25 mL), and more Et_2O (25 mL) was added. The mixture was acidified (pH 2) through addition of 2 N HCl and extracted three times with Et_2O (25 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Et_2O) to afford **3c**,**d**.

4.4.1. Ethyl-*N*-(4-methyl-4-pentenylsulfonyl) carbamate (3c). Yield 49% (228 mg, 0.97 mmol); pale yellow oil; R_f 0.59 (Et_2O); IR (neat) 1744, 1342, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, 3H, $J=7.1$ Hz), 1.72 (s, 3H), 1.95–2.06 (m, 2H), 2.17 (t, 2H, $J=7.3$ Hz), 3.38–3.45 (m, 2H), 4.27 (q, 2H, $J=7.1$ Hz), 4.72 (d, 1H, $J=0.8$ Hz), 4.81 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.14, 20.94, 21.97, 35.72, 52.48, 63.39, 111.81, 143.18, 150.98; MS (LC/MS) *m/z* (%)=236 (9) [$M+H^+$], 258 (41) [$M+Na^+$], 493 (100) [$2\times M+Na^+$]. Anal. Calcd for $C_9H_{17}NO_4S$: C, 45.94; H, 7.28; N, 5.95; S, 13.63. Found: C, 45.75; H, 7.34; N, 5.97; S, 13.58.

4.4.2. Ethyl-*N*-(4-pentenylsulfonyl) carbamate (3d). Yield 54% (239 mg, 1.08 mmol); colorless oil; R_f 0.58 (Et_2O); IR (neat) 1743, 1339, 1138 cm^{-1}; ^1H NMR

($CDCl_3$) δ 1.32 (t, 3H, $J=7.1$ Hz), 1.91–2.01 (m, 2H), 2.22 (dt, 2H, $J=7.0$, 7.0 Hz), 3.40–3.50 (m, 2H), 4.27 (q, 2H, $J=7.1$ Hz), 5.05–5.12 (m, 2H), 5.69–5.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.29, 31.74, 52.35, 63.37, 116.66, 136.05, 150.99; MS (LC/MS) *m/z* (%) = 222 (7) [M+H$^+$], 244 (24) [M+Na$^+$], 465 (100) [2×M+Na$^+$]. Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.33; S, 14.49. Found: C, 43.56; H, 7.10; N, 6.27; S, 14.17.

4.5. General procedure for thermal cleavage

A two-necked flask was charged with a solution of sulfonylcarbamate **3** (0.5 mmol) in benzene (10 mL) and cooled to 0 °C. Triethylamine (77 μL, 0.55 mmol) and a 1.0 M solution of BCl_3 in *n*-hexane (0.17 mL, 0.17 mmol) were added slowly, the mixture was stirred for 30 min at 0 °C and then refluxed for 8 h. The resulting bright yellow suspension was cooled to ambient temperature and aniline (0.52 mL, 5.7 mmol) was added in one portion. After additional stirring for 8 h, water (5 mL) was added. The reaction mixture was acidified (pH 2) with 2 N HCl and extracted with CH_2Cl_2 (40 mL). The organic extracts were dried over anhydrous $MgSO_4$ and evaporated in vacuo to give a bright yellow crude product, which was purified by recrystallization (hexane/EtOAc).

4.5.1. *N*-Phenyl-*N′*-(3-methyl-3-butenylsulfonyl) urea (8a). Yield 74% (105 mg, 0.37 mmol); white solid; mp 139–140 °C; R_f 0.51 (CH_2Cl_2/EtOAc 3/1); IR (neat) 1685, 1334, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H), 2.58 (t, 2H, $J=8.0$ Hz), 3.51 (dt, 2H, $J=8.0$, 10.8 Hz), 4.78 (s, 1H), 4.86 (s, 1H), 7.14 (t, 1H, $J=7.3$ Hz), 7.29–7.41 (m, 4H), 8.24 (s, NH), 8.33 (s, NH); ^{13}C NMR ($CDCl_3$) δ 22.13, 31.09, 53.12, 112.82, 120.54, 125.02, 129.20, 136.40, 140.67, 149.54; MS (LC/MS) *m/z* (%) 269 (6) [M+H$^+$], 291 (71) [M+Na$^+$], 559 (100) [2×M+Na$^+$]. Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44; S 11.95. Found: C, 53.50; H 6.04; N, 10.43; S, 11.68.

4.5.2. *N*-Phenyl-*N′*-(3-butenylsulfonyl) urea (8b). Yield 66% (84 mg, 0.33 mmol); pale yellow solid; mp 135–136 °C; R_f 0.42 (CH_2Cl_2/EtOAc 3/1); IR (neat) 1677, 1334, 1133 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.63 (dt, 2H, $J=6.6$, 7.8 Hz), 3.47 (dt, 2H, $J=7.9$, 9.9 Hz), 5.10–5.18 (m, 2H), 5.72–5.86 (m, 1H), 7.12 (t, 1H, $J=7.2$ Hz), 7.25–7.38 (m, 4H), 8.17 (s, NH); ^{13}C NMR ($CDCl_3$) δ 27.46, 53.78, 117.95, 120.59, 125.00, 129.17, 133.11, 136.39, 149.82; MS (LC/MS) *m/z* (%) 255 (100) [M+H$^+$], 277 (65) [M+Na$^+$]. Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02; S 12.61. Found: C, 51.99; H 5.57; N, 10.82; S, 12.53.

4.5.3. *N*-Phenyl-*N′*-(4-methyl-4-pentenylsulfonyl) urea (8c). Starting material **3c** (97.7 mg, 0.42 mmol) was used. Yield 65% (77 mg, 0.27 mmol); white solid; mp 113 °C; R_f 0.49 (Et_2O); IR (neat) 1664, 1340, 1147 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.98–2.08 (m, 2H), 2.16 (t, 2H, $J=7.1$ Hz), 3.56 (dt, 2H, $J=7.8$, 16.1 Hz), 4.70 (s, 1H), 4.78 (s, 1H), 7.13 (t, 1H, $J=7.3$ Hz), 7.28–7.41 (m, 4H), 8.27 (s, NH), 8.50 (s, NH); ^{13}C NMR ($CDCl_3$) δ 20.99, 21.95, 35.65, 53.97, 111.96, 120.51, 124.93, 129.16, 136.49, 142.99, 149.79; MS (LC/MS) *m/z* (%) 283 (100) [M+H$^+$], 300 (15) [M+NH$_4^+$], 321 (48) [M+K$^+$]. Anal. Calcd for $C_{13}H_{18}N_2O_3S$: C, 55.30; H, 6.43; N, 9.92; S 11.36. Found: C, 55.42; H 6.67; N, 9.76; S, 11.56.

4.5.4. *N*-Phenyl-*N′*-(4-pentenylsulfonyl) urea (8d). Yield 69% (92 mg, 0.34 mmol); pale yellow solid; mp 129–130 °C; R_f 0.59 (CH_2Cl_2/EtOAc 5/1); IR (neat) 1667, 1339, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.94–2.06 (m, 2H), 2.21 (dt, 2H, $J=7.0$, 7.0 Hz), 3.30–3.40 (m, 2H), 5.03–5.09 (m, 2H), 5.66–5.80 (m, 1H), 7.14 (t, 1H, $J=7.2$ Hz), 7.26–7.40 (m, 4H), 8.12 (s, NH), 8.25 (s, NH); ^{13}C NMR ($CDCl_3$) δ 22.40, 31.73, 53.98, 116.89, 120.48, 124.94, 129.18, 135.88, 136.48, 149.64; MS (LC/MS) *m/z* (%) 269 (100) [M+H$^+$], 286 (19) [M+NH$_4^+$], 307 (5) [M+K$^+$]. Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44; S 11.95. Found: C, 53.55; H 6.06; N, 10.49; S, 11.79.

4.6. Control experiment

A solution of **3b** (103.5 mg, 0.50 mmol) in benzene (10 mL) was treated with triethylamine×HCl (75.7 mg, 0.55 mmol), $B(OEt)_3$ (28.9 μL, 0.17 mmol) and aniline (0.52 mL, 5.7 mmol). The resulting mixture was stirred at ambient temperature (8 h), and then water (5 mL) was added. The solution was acidified (pH 2) with 2 N HCl and extracted with CH_2Cl_2 (40 mL). The organic extracts were dried over anhydrous $MgSO_4$ and after evaporation in vacuo, the colorless oil **3b** was completely recovered.

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Biotransformation of 7-oxo-*ent*-kaur-16-ene derivatives by *Gibberella fujikuroi*

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Abstract—The microbiological transformation of 7-oxo-*ent*-kaur-16-ene by the fungus *Gibberella fujikuroi* gave fujenoic acid as the main compound, whilst the incubation of 18-hydroxy-7-oxo-*ent*-kaur-16-ene and 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene afforded the corresponding 6β-hydroxy-derivatives. These facts indicate that the formation of fujenoic acid in this biotransformation should occur via a 7-oxo-6β-hydroxy derivative. In the three biotransformations, an 11β-hydroxylation was also produced, in low yield, indicating that a 7-oxo-group also directs hydroxylation at C-11.

1. Introduction

The biotransformation of diterpenes by the fungus *Gibberella fujikuroi* has been one of the subjects of our studies, in relation to the specificity in the substrate of the enzymes involved in the metabolism of this fungus, and of the characteristics of the receptors taken part in these processes. The triacid **1** is a metabolite of this fungus, which is formed from 7β-hydroxy-*ent*-kaur-16-en-19-oic acid (**3**), via the 6β,7β-diol **4**.[1,2] On the other hand, **1** is also produced in the incubation with *G. fujikuroi* of 7-oxo-*ent*-kaur-16-en-19-oic (**6**), which does not appear to be a natural metabolite of this fungus.[3] In this last work, MacMillan et al. showed that compound **6** was transformed exclusively into the triacid **1** in very good yield, but the mechanism of formation was not studied. Thus, we think that the incubation of other 7-oxo-*ent*-kaur-16-ene derivatives with the fungus should afford some insight in this respect. In this way, we incubated *G. fujikuroi* with three types of substrates: (a) 7-oxo-*ent*-kaur-16-ene (**9**), a compound where the C-19 oxidation must not be inhibited; (b) 7-oxo-18-hydroxy-*ent*-kaur-16-ene (**8**), where this oxidation must be partially inhibited by the 18-hydroxy group[4] and (c) 3α,18-dihydroxy-*ent*-kaur-16-ene (**9**) where a total inhibition of the C-19 oxidation must exist due to the presence of the 3α-hydroxy group.[5]

2. Results and discussion

The incubations with *G. fujikuroi* were carried out in the presence of AMO 1618, a substance that inhibits the formation of *ent*-kaurene without perturbing the post-kaurene metabolism.[6,7] The substrates were obtained in the following ways: (a) substrate **9**. Partial hydrolysis of epicandicandiol diacetate[8–10] (**12**) gave the monoacetates **13** and **14**. The latter was treated with triphenylphosphine and carbon tetrachloride to afford the 18-chloro derivative **16**, which by hydrolysis gave the corresponding alcohol **17**. Treatment of this with tri-*n*-butyltin hydride led to candol A (**18**).[11] Oxidation of **20** with Jones reagent led to the first, substrate, 7-oxo-*ent*-kaur-16-ene (**7**). (b) Substrate **8**. Partial acetylation of epicandicandiol[8–10] (**15**) gave the two monoacetates **13** and **14**, the former being oxidized to afford the 7-oxo derivative **10**. Hydrolysis of this last compound led to the required second substrate, 18-hydroxy-7-oxo-*ent*-kaur-16-ene (**8**). (c) Substrate **9**. The diterpene foliol[12] (**19**) was treated with acetone and copper sulphate to form the acetonide **20**. Oxidation of this with Jones reagent afforded the 7-oxo-derivative **21**, which was hydrolyzed with 10% aqueous ethanolic hydrochloric acid to give the third substrate, 3α,18-dihydroxy-*ent*-7-oxo-kaur-16-ene (**9**).

The microbiological transformation of **7** gave 11β,19-dihydroxy-7-oxo-*ent*-kaur-16-ene (**22**), 17,19-dihydroxy-11β,16β-epoxy-7-oxo-*ent*-kaurane (**23**), 11β,13-dihydroxy-7-oxo-*ent*-kaur-16-ene (**24**) and fujenoic acid (**25**). The main compound obtained was **25** and its structure was determined as follows: its high resolution MS showed the

Keywords: *Gibberella fujikuroi*; Microbiological transformations; Diterpenes; 7-Oxo-*ent*-kaur-16-ene derivatives.
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Table 1. ^{13}C NMR data of **4**, **9**–**13** and **24**–**28**

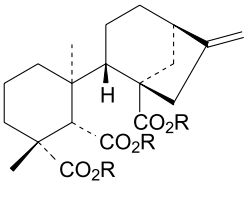
C	4	9	10	11	12	13	24	25	26	27	28
1	37.7	40.2	39.7	38.0	39.3	38.0	39.7	40.3	39.5	33.4	33.4
2	20.3	18.4	17.6	26.1	17.2	22.8	17.8	17.9	18.1	17.8	17.8
3	33.6	41.7	34.9	73.3	35.4	73.7	35.7	35.6	41.4	28.8	28.9
4	45.8	33.5	38.8	42.4	38.6	40.7	38.5	38.2	35.5	44.6	44.6
5	60.1	53.2	45.9	45.4	46.7	44.8	53.2	53.5	53.0	56.4	56.5
6	173.8	37.4	36.9	36.7	36.8	36.3	37.3	37.8	37.0	171.6	171.6
7	180.1	213.7	214.2	214.2	212.4	212.2	211.7	211.6	211.1	183.0	178.2
8	54.3	57.3	57.3	57.0	56.6	56.8	56.1	55.9	53.3	52.6	52.6
9	53.1	56.4	56.2	55.6	55.8	55.4	65.1	59.3	64.0	46.2	46.2
10	43.7	39.1	37.9	38.6	36.4	38.4	38.1	36.7	38.0	42.0	41.8
11	20.9	17.5	17.5	17.7	17.2	17.8	65.5	76.4	67.1	19.7	19.7
12	36.3	32.6	32.5	32.4	32.2	32.4	42.7	41.0	48.8	31.7	31.8
13	52.4	42.4	42.2	42.1	41.7	42.0	40.9	41.4	78.1	43.6	43.6
14	37.9	38.2	38.6	37.9	37.6	37.5	38.5	43.2	45.6	34.2	34.4
15	48.2	41.8	41.8	41.7	41.7	42.0	40.7	46.2	39.0	46.5	46.3
16	154.4	154.2	154.0	153.6	153.8	153.6	154.0	89.4	154.8	151.8	152.1
17	105.3	104.5	104.6	104.8	104.4	104.9	106.5	65.5	105.8	104.5	104.3
18	20.9	32.8	70.5	67.0	71.7	64.5	26.5	26.7	32.7	29.8	29.9
19	178.0	21.0	16.9	11.2	16.4	16.8	65.2	65.2	20.9	176.0	176.1
20	20.3	16.3	16.6	16.7	16.2	12.4	16.6	16.1	16.2	19.0	18.9

molecular ion at *m/z* 346.1788 ($C_{20}H_{26}O_5$). The IR spectrum showed absorptions of an acid function [3440 (br) and 1700 cm^{-1}], an anhydride group (1815 and 1785 cm^{-1}) and an exocyclic double bond (3050 and 890 cm^{-1}). The ^1H NMR showed two methyl groups at δ 0.98 and 1.09, the H-5 as a singlet at δ 2.52 (s) and signals of the two H-17 at δ 4.82 and 4.90. This anhydride-acid **25** is probably formed from the triacid **1**, during the chromatography of the extract. This triacid is also a natural metabo-lite of *G. fujikuroi*,[13–15] and, as mentioned above, had also been obtained in the incubation of the keto-acid **6**.[3] This last compound **6** must also be an intermediate in the feeding of our substrate **9**.

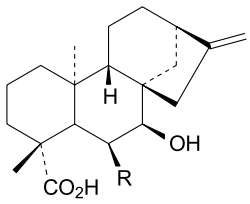
The second substance obtained was **22** ($C_{20}H_{30}O_3$), which was formed by the introduction of two oxygen atoms during the feeding. These must form a part of two new hydroxyl groups, because its ^1H NMR spectrum showed characteristic signals of a hydroxymethylene group at δ 3.51 and 3.70 (each 1H, d, $J=11.9$ Hz), and of a proton geminal to a hydroxyl group at δ 3.94 (1H, t, $J=7$ Hz). The primary alcohol was assigned at C-19 for biogenetic reasons and then confirmed by 2D NMR data. The secondary hydroxyl was located at C-11 (β), considering ^{13}C NMR data (Table 1) and the coupling constant observed in the ^1H NMR spectrum. Thus, the structure of this metabolite was determined as 11β,19-dihydroxy-7-oxo-*ent*-kaur-16-ene (**22**). To another compound isolated from this feeding the structure of 17,19-dihydroxy-11β,16β-epoxy-7-oxo-*ent*-kaurane (**23**) was assigned. Its HRMS was in accordance with the structure $C_{20}H_{30}O_4$. Its ^1H NMR spectrum, in comparison with that of the substrate **7**, showed a new primary alcohol, which was assigned to C-17, considering the disappearance of the double bond resonances and the absence of a new methyl group signal. The form of resonance of this new hydroxymethylene group indicated that C-16 was a tetrasubstituted carbon. Thus, we located an oxygen bridge between C-11 (β) and C-16. The stereochemistry at C-11 was assigned considering the form and coupling constant observed for H-11. The fourth metabolite **24** showed the molecular ion at *m/z* 318.2165 ($C_{20}H_{30}O_3$). The new oxygen introduced in the molecule during the feeding must be a part of a tertiary hydroxyl group, which we assigned to C-13, considering the disappearance of the characteristic signal of H-13 in the substrate (δ 2.64), and the observed shift of the two H-17 at a lower field, in comparison with the spectra of **7** or **22**. This location was confirmed by the unambiguous assignment of the ^{13}C NMR spectrum using 2D NMR data. Therefore, the structure of 11β,13-dihydroxy-7-oxo-*ent*-kaur-16-ene (**24**) was assigned to this substance.

The incubation of the second substrate 18-hydroxy-7-oxo-*ent*-kaur-16-ene (**8**) afforded the metabolites 18,19-dihydroxy-7-oxo-*ent*-kaur-16-ene (**27**), 11β,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**29**), 11α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**30**), 18-hydroxy-11β,16β-epoxy-7-oxo-*ent*-kaurane (**31**), 6β,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**32**), 18-hydroxy-16α,17-epoxy-7-oxo-*ent*-kaurane (**33**), 1α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**35**) and 7-oxo-*ent*-kaur-16-en-18,6β-olide (**37**).

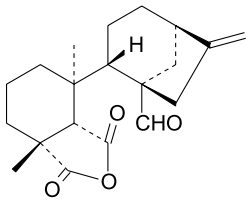
Compound **27** was obtained in low yield and identified as its diacetate **28**, by acetylation of the fraction containing it. In its high resolution MS, the molecular ion appears at *m/z* 402.2403 ($C_{24}H_{34}O_5$). Its ^1H NMR showed only one methyl group of the two present in the substrate. Thus, a methyl group has been substituted by one additional $-CH_2-O-$ group, which resonates as a pair of doublets, at δ 4.07 and 4.28 ($J=11$ Hz). This was located at C-19 for biosynthetic reasons, and confirmed by assignment of its ^{13}C NMR spectrum (Table 1). In this feeding, three related compounds, with the same molecular formula $C_{20}H_{30}O_3$, were also obtained. Two of them, **29** and **30**, showed a similar ^1H NMR spectra. The additional oxygen present in both molecules was located at C-11 by ^{13}C NMR data as a hydroxyl group. Thus, the substances are epimeric at this carbon. The β-epimer **29**, obtained in a greater amount, shows the geminal proton to the hydroxyl group at δ 3.97 (d, $J=4.7$ Hz), while in the α-epimer **30** the geminal hydrogen appears at δ 4.26 (br m, $W_{1/2}=18$ Hz). To the third of these metabolites the structure **31** was assigned. In its ^1H NMR spectrum do not appear the hydrogens of the C-17 double bond, which have been substituted by a new angular methyl signal. In consequence, we located an ether bridge between



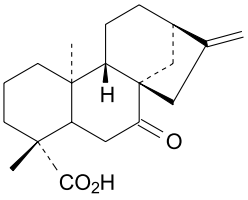
1 R = H
2 R = Me



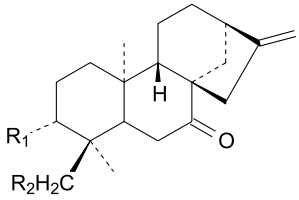
3 R = H
4 R = OH



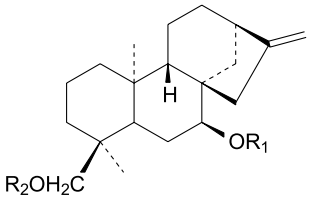
5



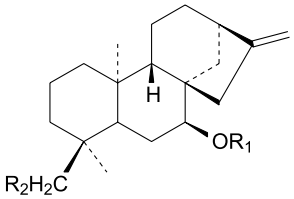
6



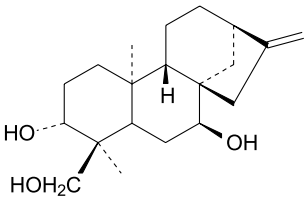
7 $R_1 = R_2 = H$
8 $R_1 = H$ $R_2 = OH$
9 $R_1 = R_2 = OH$
10 $R_1 = H$ $R_2 = OAc$
11 $R_1 = R_2 = OAc$



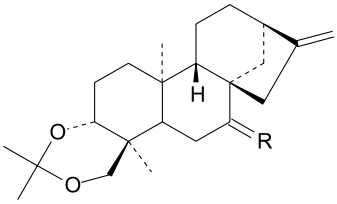
12 $R_1 = R_2 = Ac$
13 $R_1 = H$ $R_2 = Ac$
14 $R_1 = Ac$ $R_2 = H$
15 $R_1 = R_2 = H$



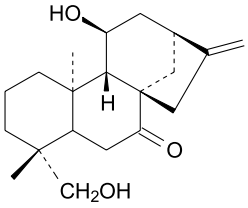
16 $R_1 = Ac$ $R_2 = Cl$
17 $R_1 = H$ $R_2 = Cl$
18 $R_1 = R_2 = H$



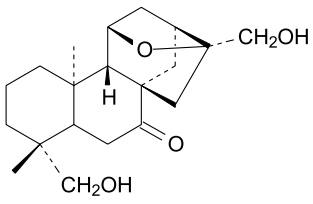
19



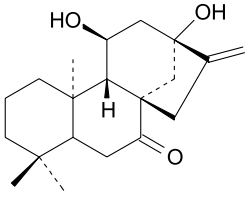
20 R = β–OH
21 R = O



22



23



24

C-11 (β) and C-16 (β). The stereochemistry of this group derives from its probable origin from **29**, which should have occurred via protonation of the double bond and neutralization of the ion formed at C-16 by the 11β-OH. The resonance of the geminal hydrogen at C-11 (δ 4.39, br s) was similar to that observed for compound **23** (δ 4.50, br s). The ^{13}C NMR spectrum (Table 2) confirmed its structure as 18-hydroxy-11β,16β-epoxy-7-oxo-*ent*-kaurane (**31**). Another substance obtained was 1α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**35**), which was obtained in very low yield and identified as its diacetate **36**. The HRMS was in accordance with the molecular formula $C_{24}H_{34}O_5$. Its ^{1}H NMR, compared with that of the acetate of substrate (**10**), showed a geminal proton to an acetoxyl group resonating at δ 4.56 (dd, $J=10.3$, 5.5 Hz). Considering the observed coupling, this acetoxyl group must be situated at C-1 (α) or C-3 (α). The 1α position was chosen considering its ^{13}C NMR spectrum (Table 2), and later confirmed because this compound was different from **11** (see below).

One of the main compounds isolated in this feeding was 6β,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**32**). Its ^{1}H NMR spectrum showed the signal of a geminal hydrogen to a new alcohol group at δ 4.48 (d, $J=13$ Hz). Its form of resonance and the disappearance of the signals at δ 2.31 and 2.48 of the two H-6, observed in the spectrum of the substrate, indicated the location of this new hydroxyl group at the 6β-position. The structure **32** was confirmed using 2D NMR

Table 2. ^{13}C NMR data of **31–35**, **37**, **39–42** and **44**

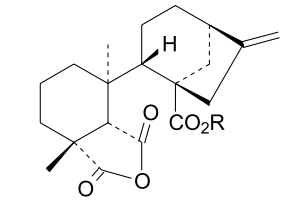
C	31	32	33	34	35	37	38	40	41	42	44
1	39.7	38.9	40.8	39.6	40.2	39.8	81.9	40.7	38.0	37.4	38.6
2	17.3	17.5	17.6	17.4	17.8	17.6	24.1	18.1	26.3	22.4	22.6
3	31.1	34.9	34.8	34.7	38.3	35.0	32.9	32.2	73.3	73.9	73.2
4	40.1	37.9	38.1	36.4	39.8	38.9	36.5	42.1	43.7	40.5	37.8
5	48.1	45.8	45.1	45.9	54.8	46.3	45.1	58.7	52.0	47.1	44.5
6	37.5	36.8	36.7	37.3	73.0	36.6	36.1	76.2	72.8	74.9	36.0
7	214.0	212.8	213.1	213.4	208.7	212.2	212.0	211.0	212.7	204.8	210.8
8	57.3	56.1	56.9	56.4	55.8	58.4	56.9	50.0	55.5	56.7	55.8
9	56.0	65.0	61.0	58.5	55.1	56.1	56.4	57.2	54.5	54.4	61.2
10	39.0	37.8	39.8	37.5	39.1	37.9	42.8	32.2	39.4	40.0	40.6
11	17.6	65.5	67.9	76.0	17.6	18.6	19.0	18.5	17.7	17.8	67.1
12	32.5	42.5	43.5	40.4	32.5	28.5	32.3	31.7	32.3	32.3	36.9
13	42.4	40.9	41.0	44.8	42.6	41.5	41.0	43.0	42.3	42.0	39.2
14	38.2	38.5	36.2	43.8	38.5	37.2	37.0	37.6	38.5	37.8	41.0
15	41.4	41.0	43.1	50.4	41.3	40.9	42.9	39.4	41.4	41.2	40.2
16	153.6	154.1	154.3	86.1	152.2	66.3	154.2	151.3	152.0	152.2	152.5
17	104.7	106.6	105.6	22.9	104.9	50.1	105.1	105.2	105.0	104.9	104.8
18	68.7	70.6	71.1	70.9	74.5	70.7	70.9	178.6	68.9	66.6	64.3
19	63.8	17.0	17.2	17.1	17.2	16.8	16.9	15.5	11.7	13.0	12.4
20	16.7	16.6	17.8	18.0	18.3	16.7	12.4	17.0	18.1	18.0	17.0

data. Another metabolite obtained was the epoxide **33**. Its HRMS indicated that during the feeding a new oxygen atom had been introduced in the substrate **7**. Comparison of the ^1H NMR spectrum with that of the substrate showed the disappearance of the signals corresponding to the two hydrogens of the exocyclic double bond and the presence of new resonances of two protons at δ 2.79 and 2.89 (each 1H, d, $J=4.7$ Hz). These last signals are typical of H-17 hydrogens in a 16,17-oxyranic ring. The α-stereochemistry assigned to this epoxide was given considering that in this type of compounds the epoxidation occurs by the α-face. Its structure **33** was confirmed by epoxidation of **7** with *m*-chloroperbenzoic acid.

The molecular ion of compound **37** at *m*/*z* 314, compared to that of the substrate (*m*/*z* 302), informed us that in the molecule of the latter several reactions had occurred during the incubation. Its IR spectrum showed an absorbance characteristic of a lactone (1775 cm^{-1}). The ^1H NMR spectrum showed the disappearance of the ABX system of the two H-6, and also of the hydroxymethylene signals. In their place the presence of a new signal of a geminal hydrogen to an oxygen function was observed at δ 4.98 ($J=$ 14 Hz). Thus, we assigned the lactonic structure 7-oxo-*ent*-kaur-16-ene-18,6β-olide (**37**) to this compound, which was confirmed by 2D NMR studies.

The feeding of the third substrate **9** gave 3α,6β,18-trihydroxy-7-oxo-*ent*-kaur-16-ene (**38**) and 3α,11β,18-trihydroxy-7-oxo-*ent*-kaur-16-ene (**40**). The arguments used above in the assignment of the hydroxyl group at C-6 (β) in **32** were the same ones now utilized for **38**, and consequently we will not repeat them. Compound **40** was identified as its triacetate **41** by acetylation of the fractions containing it. The geminal proton to the new acetoxy group resonates at δ 5.12 as a doublet ($J=5.3$ Hz). These values are typical of a hydrogen geminal to an acetate group at C-11 (β).[16] This location was confirmed by assignment of ^{13}C NMR data.

Several conclusions may be deduced from the results obtained in the microbiological transformations of the substrates **7–9**. (1) A 7-oxo group in *ent*-kaur-16-ene derivatives does not inhibit oxidation at C-19, which is characteristic of the biosynthesis of gibberellins and kaurenolides.[17] The inhibition produced in the feeding of **8** is due to the presence of the 3α-hydroxyl group, which confirmed previous results obtained by us.[5] (2) The incubation of 7-oxo-*ent*-kaurene derivatives by this fungus, when the oxidation at C-19 is not inhibited by a specific substituent in the molecule, is a good procedure to prepare seco-ring B compounds. (3) The isolation of the 6β-hydroxy derivatives **32** and **39** in the incubations of **8** and **9**, respectively, indicates that the formation of fujenoic acid (**27**) in the biotransformation of **9** should occur via a 7-oxo-6β-hydroxy derivative. This also should be applied to the formation of the metabolite **1** from the substrate **6**,[3] where a 6β-hydroxy-7-oxo intermediate (**42**) may be involved. (4) The main bioreaction observed in these feedings was the 6β-hydroxylation, with the best yield in the formation of **38** from **9**, where the inhibition of the oxidation at C-19 was complete. (5) In the biotransformations of epicandicandiol[4] (**15**) and foliol[5] (**19**) the 6-hydroxylation was not observed, nor the ring contraction to form gibberellins, indicating that the reactions at C-6 were inhibited by the presence of the 18-hydroxyl group. However, hydroxylation at C-6 (β) has now been produced in the incubations of **8** and **9**, which can be explained considering the different conformation of ring B in these compounds, due to the presence of the 7-oxo group. (6) We did not detect the presence of any compounds with a seco-ring B in the incubation of **8** or **9**, indicating that the possible subsequent step(s) to **32** or **38**, respectively, cannot be produced by the absence of an acid group at C-19 or, alternatively, due to the existence of an 18-hydroxyl group. (7) A 7-oxo group also directs hydroxylation at C-11. This effect was analogous to that produced by a 15-oxo group, previously reported by us.[18,19] (8) The oxidation of C-18 at the acid level that takes place in the formation of **37** from **8** is very interesting, because this is the first, time that it is observed in a biotransformation with *G. fujikuroi*, being probably due to the different conformation of ring B adopted by the presence of the 7-oxo group. The oxidation of the 18-hydroxyl did not occur in the feeding of **9**, probably due to the presence of a 3α-alcohol.



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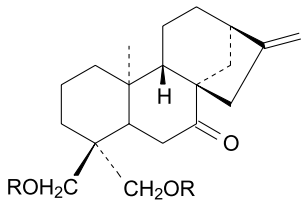
26 R = Me



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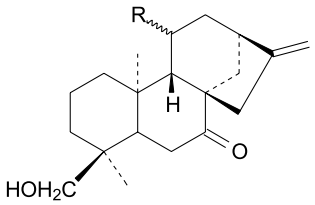
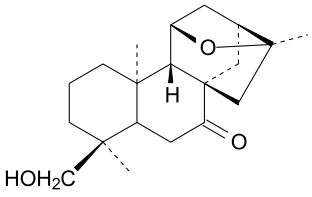
28 R = Ac



29 R = β–OH
30 R = α–OH



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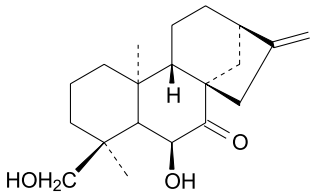
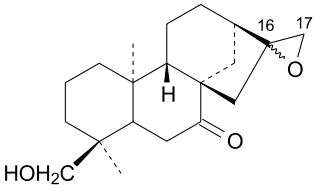
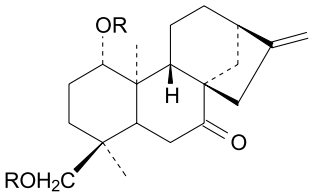


32



33 16,17-α-epoxide
34 16,17-β-epoxide



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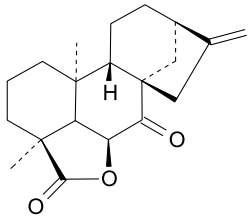
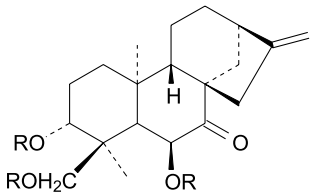


37



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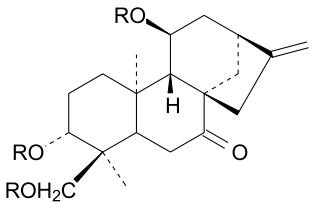

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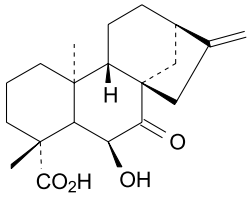
41 R = Ac



42

3. Experimental

3.1. General procedures

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500.1 and 125.8 MHz, respectively, with a Bruker AMX-500 spectrometer. Mass spectra were taken in a Micromass Autospect instrument at 70 eV (probe). Dry column chromatographies were made on silica gel Merck 0.02–0.063 mm. When further, purification was required, semipreparative HPLC in a Beckman System Gold with a Beckman ultrasphere Si 1×25 cm column was used. The substances were crystallized from petrol–EtOAc except where otherwise indicated.

3.2. Preparation of the substrate 7-oxo-*ent*-kaur-16-ene (7)

3.2.1. Epicandicandiol diacetate (12). Mp, $[\alpha]_D$ and IR see Ref. 9; $[M-COCH_2]^+$ at *m/z* 346.2510, $C_{22}H_{34}O_3$ requires 346.2508; ^{1}H NMR (500 MHz) δ 0.78 (3H, s, H-19), 1.03 (3H, s, H-20), 0.80 (1H, td, $J=13$, 3.8 Hz, H-1β), 1.79 (1H, dt, $J=13$, 3.1 Hz, H-1α), 1.86 (1H, dd, $J=11$, 2.1 Hz, H-14), 1.99 (6H, s), 2.04 (1H, dt, $J=17.1$, 2.6 Hz, H-15), 2.13 (1H, dd, $J=17.1$, 1.5 Hz, H-15), 2.64 (1H, br s, H-13), 3.61 and 3.66 (each 1H, d, $J=11$ Hz, H-18), 4.71 (1H, br s, H-7), 4.74 and 4.76 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 388 $[M]^+$ (0.2), 346 (1), 328 (46), 313 (8), 268 (100), 255 (38), 253 (51), 239 (18), 225 (10).

3.2.2. 7β-Hydroxy-18-acetoxy-*ent*-kaur-16-ene (13). Prepared by partial acetylation of epicandicandiol (**15**).[11] mp,

$[\alpha]_D$, IR see Refs. 11 and 20; $[M]^+$ at *m/z* 346.2513, $C_{22}H_{34}O_3$ requires 346.2507; ^1H NMR (500 MHz) δ 0.80 (3H, s, H-19), 0.82 (1H, td, $J=13.5$, 3.7 Hz, H-1β), 1.04 (3H, s, H-20), 1.13 (1H, dd, $J=11$, 4.9 Hz, H-5), 2.05 (3H, s), 2.24 (2H, s, H-15), 2.65 (1H, br s, H-13), 3.45 and 4.06 (each 1H, d, $J=11$ Hz, H-18), 3.55 (1H, br s, H-7), 4.77 and 4.79 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 346 $[M]^+$ (4), 328 (23), 313 (6), 286 (7), 268 (70), 255 (100), 253 (29), 239 (13), 225 (8), 211 (5), 199 (11), 187 (13).

3.2.3. 7β-Acetoxy-18-hydroxy-*ent*-kaur-16-ene (14). This compound had been obtained by partial acetylation of epicandicandiol (**15**)[11] and partial hydrolysis of epicandicandiol diacetate (**12**).[21] Mp, $[\alpha]_D$, IR and MS see Refs. 11 and 21; ^1H NMR (500 MHz) δ 0.62 (3H, s, H-19), 0.75 (1H, td, $J=13.5$, 2.7 Hz, H-1β), 0.97 (3H, s, H-20), 1.62 (1H, br d, $J=12.7$ Hz, H-5), 1.69 (2H, m, H-1α and H-6), 1.80 (1H, br d, $J=11.2$ Hz, H-14), 1.94 (3H, s), 1.98 and 2.10 (each 1H, br d, $J=17$ Hz, H-15), 2.59 (1H, br s, H-13), 2.90 and 3.18 (each 1H, d, $J=10.8$ Hz, H-18), 4.59 (1H, br s, H-7), 4.66 and 4.71 (each 1H, br s, H-17).

3.2.4. 7β-Acetoxy-18-chloro-*ent*-kaur-16-ene (16). Compound **14** (1.4 g) in CCl_4 (60 ml) and C_5H_5N (20 ml) was treated with Ph_3P (3 g) under reflux for 2 h. Evaporation of the solvent and chromatography (petroleum ether–EtOAc, 10%) gave **16** (1.24 g). Colourless needles, mp 110–113 °C (petroleum ether). Found: C, 72.08; H, 9.57; calcd for $C_{22}H_{33}O_2Cl$: C, 72.40; H, 9.11%; $[M]^+$ at *m/z* 460.2424, $C_{22}H_{33}O_2Cl$ requires 460.2461; ^1H NMR (500 MHz) δ 0.81 (3H, s, H-19), 0.83 (1H, br t, $J=12.3$ Hz, H-1), 1.18 (2H, m, H-3 and H-14), 1.03 (3H, s, H-20), 1.79 (1H, br d, $J=12.6$ Hz, H-5), 1.85 (1H, dd, $J=11.3$, 2 Hz, H-14), 2.00 (3H, s), 2.03 and 2.27 (each 1H, br d, $J=17.3$ Hz, H-15), 2.64 (1H, br s, H-13), 3.02 and 3.37 (each 1H, d, $J=11$ Hz, H-18), 4.65 (1H, br s, H-7), 4.72 and 4.76 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 364 $[M]^+$ (0.3), 322 (2), 304 (100), 289 (39), 269 (16), 255 (40), 224 (25), 199 (15), 185 (20), 173 (15), 159 (11).

3.2.5. 7β-Hydroxy-18-chloro-*ent*-kaur-16-ene (17). The monoacetate **16** (1.4 g) in methanolic KOH (5%) was refluxed for 30 min and treated in the usual way giving **17** (1.2 g). Colourless needles, mp 118–119 °C (petroleum–EtOAc). Found: C, 74.15; H, 9.89; calcd for $C_{20}H_{31}OCl$: C, 74.39; H, 9.68%; $[M]^+$ at *m/z* 322.2057. $C_{20}H_{31}OCl$ requires 322.2063; ^1H NMR (500 MHz) δ 0.82 (1H, td, $J=13.1$, 16.9 Hz, H-1β), 0.87 (3H, s, H-19), 1.03 (3H, s, H-20), 1.13 (1H, dd, $J=11.3$, 5.1 Hz, H-14), 1.28 (1H, m, H-3), 1.80 (2H, m, H-1α and H-14), 1.84 (1H, dd, $J=13$, 1.8 Hz, H-5), 2.25 (2H, br s, H-15), 2.65 (1H, br s, H-13), 3.18 and 3.43 (each 1H, d, $J=11.1$ Hz, H-18), 3.57 (1H, br s, H-7), 4.78 and 4.79 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 322 $[M]^+$ (7), 304 (100), 289 (34), 268 (10), 255 (54), 239 (7), 224 (17), 213 (8), 199 (15), 185 (16), 173 (14), 164 (29).

3.3. Reduction of 17

Compound **17** (1.2 g) in dry toluene (30 ml) was treated with tri-*n*-butyltin hydride (4.5 ml) and azobisisobutyronitrile (traces) under reflux for 18 h. The solution was diluted with Et_2O and H_2O saturated with KF and left with stirring for 30 min. After filtration the solution was dried and evaporated to afford candol A[11] (**18**) (810 mg).

3.3.1. Oxidation of candol A (18). A solution of **18** (430 mg) in Me_2CO was treated with a slight excess of Jones reagent and left at room temperature for 5 min. Then MeOH was added to destroy the excess reagent. The mixture was diluted with H_2O and extracted with EtOAc affording 7-oxo-*ent*-kaur-16-ene (**7**), mp 63–64 °C. Found: C, 83.83; H, 10.47; calcd for $C_{20}H_{30}O_2$: C, 83.86; H, 10.57%; IR ν_{max} cm^{-1} 3030, 2925, 2860, 1700, 1660, 1460, 1385, 1300, 1260, 1200, 1115, 975, 880; $[M]^+$ at *m/z* 286.2296, $C_{20}H_{30}O$ requires 286.2297; ^1H NMR (500 MHz) δ 0.80 (1H, td, $J=12.8$, 3.4 Hz, H-1β), 0.84 (6H, s, H-18 and H-19), 1.12 (3H, s, H-20), 1.15 (1H, dd, $J=13.8$, 4.1 Hz, H-3β), 1.25 (1H, dd, $J=13.8$, 3.4 Hz, H-5), 1.51 and 1.75 (each 1H, m, H-12), 1.83 (1H, ddd, $J=12.8$, 2.8, 2.1 Hz, H-1α), 1.95 (1H, dd, $J=11$, 2.7 Hz, H-14), 2.10 (1H, dd, $J=17$, 1.9 Hz, H-15), 2.37 (1H, dd, $J=14$, 3.4 Hz, H-6β), 2.43 (1H, t, $J=14$ Hz, H-6α), 2.69 (1H, br s, H-13), 3.09 (1H, dt, $J=17$, 2.9 Hz, H-15), 4.81 and 4.85 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 286 $[M]^+$ (100), 271 (9), 253 (5), 245 (25), 201 (6), 175 (4), 163 (8), 148 (12), 123 (27).

3.4. Preparation of the substrate 18-hydroxy-7-oxo-*ent*-kaur-16-ene (8)

3.4.1. Partial acetylation of epicandicandiol (15). To a solution of **15** (1.3 g) in pyridine (25 ml) at 0 °C Ac_2O (9 ml) was added, and the mixture left at this temperature for 10 min. Chromatography of the residue with petroleum ether–EtOAc (10%) afforded diacetate **12** (36 mg), 18-monoacetate **13** (440 mg), 7β-monoacetate **14** (230 mg) and starting material (580 mg).

3.4.2. Oxidation of 13. The alcohol **13** (440 mg) was oxidized as described above for **18** to afford 18-acetoxy-7-oxo-*ent*-kaur-16-ene (**10**) (412 mg), $[M]^+$ at *m/z* 344.2351, $C_{22}H_{32}O_3$ requires 344.2351; ^1H NMR (200 MHz) δ 0.80 (3H, s, H-19), 1.08 (3H, s, H-20), 2.02 (3H, s), 2.62 (1H, br s, H-13), 2.98 (1H, br d, $J=16.8$ Hz; H-15), 3.55 and 3.67 (each 1H, d, $J=11$ Hz, H-18), 4.74 and 4.79 (each 1H, br, s, H-17); EIMS *m/z* (rel. int.) 344 $[M]^+$ (31), 284 (21), 269 (9), 255 (4), 189 (13), 174 (13), 161 (6), 147 (100).

3.4.3. Hydrolysis of 10. Compound **10** (400 mg) was dissolved in 5% methanolic KOH (20 ml) and left overnight at room temperature. The solution was neutralized and the product recovered in EtOAc to afford 18-hydroxy-7-oxo-*ent*-kaur-16-ene (**8**) (340 mg). Colourless prisms, mp 132–134 °C (petroleum ether–EtOAc). Found: C, 79.42; H, 10.00; calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 9.88%; $[M]^+$ at *m/z* 302.2245, $C_{20}H_{30}O_2$ requires 302.2245; ^1H NMR (500 MHz) δ 0.78 (3H, s, H-19), 0.83 (1H, td, $J=13.2$, 3.8 Hz, H-1β), 1.17 (3H, s, H-20), 1.29 (1H, m, H-3), 1.43 (2H, m, H-9 and H-14), 1.67 (1H, dd, $J=14$, 3.2 Hz, H-5), 1.78 (1H, m, H-12), 1.85 (1H, dt, $J=12.7$, 2 Hz, H-1α), 1.97 (1H, dd, $J=11.2$, 2.5 Hz, H-14), 2.03 (1H, br d, $J=17.1$ Hz, H-15), 2.31 (1H, dd, $J=14.5$, 3.1 Hz, H-6β), 2.48 (1H, t, $J=14.5$, H-6α), 3.05 and 3.37 (each 1H, d, $J=11$ Hz, H-18), 3.08 (1H, dt, $J=17.1$, 2.8 Hz, H-15), 4.83 and 4.87 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 302 $[M]^+$ (100),

284 (5), 271 (35), 261 (8), 253 (17), 189 (34), 175 (33), 147 (39).

3.5. Preparation of the substrate 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (9)

3.5.1. Acetonide of 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (21). The preparation of this compound has been described.[5] $[M]^+$ at *m/z* 358.2502, $C_{23}H_{34}O_3$ requires 358.2508; ^1H NMR (500 MHz) δ 1.03 (1H, td, $J=13$, 4 Hz, H-1β), 1.08 (3H, s, H-19), 1.19 (3H, s, H-20), 1.27 (1H, dd, $J=14.1$, 3.1 Hz, H-5), 1.39 and 1.40 (each 3H, s, acetonide), 1.49 (1H, m, H-2), 1.53 and 1.73 (each 1H, m, H-12), 1.60 (2H, m, H-11), 1.68 (1H, dd, $J=12$, 3.5 Hz, H-2), 1.99 (1H, br d, $J=17$, H-15), 2.05 (1H, dd, $J=14.7$, 3.1 Hz, H-6), 2.54 (1H, t, $J=14.7$, H-6), 2.71 (1H, br s, H-13), 3.12 (1H, dt, $J=17$, 2.8 Hz, H-15), 3.40 and 3.44 (each 1H, d, $J=11$ Hz, H-18), 3.48 (1H, dd, $J=11.9$, 3.8 Hz, H-3), 4.83 and 4.86 (each 1H, s, H-17); EIMS *m/z* (rel. int.) 358 $[M]^+$ (4), 343 (100), 300 (14), 283 (23), 270 (8), 243 (5), 215 (6), 189 (5), 175 (8), 147 (10).

3.5.2. Hydrolysis of 21. The acetonide **21** (300 mg) in EtOH (50 ml) was treated with 10% aqueous ethanolic HCl (0.5 ml) for 1 h. Extraction with EtOAc in the usual way afforded 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**9**) (214 mg). Found: C, 75.66; H, 9.62; calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%; $[M]^+$ at *m/z* 318.2217, $C_{20}H_{30}O_3$ requires 318.2195; IR ν_{max} cm^{-1} 3400, 2930, 2860, 1690, 1470, 1390, 1300, 1080, 1040; ^1H NMR (500 MHz) δ 0.74 (1H, s, H-19), 0.92 (1H, br m, H-1β), 1.23 (3H, s, H-20), 1.34 (2H, m, H-9 and H-14), 1.50 (1H, dd, $J=13.9$, 2.9 Hz, H-5), 1.77 (1H, dt, $J=13.4$, 3.2 Hz, H-1α), 1.91 (1H, br d, $J=11.1$ Hz, H-14), 1.95 (1H, br d, $J=17$ Hz, H-15β), 2.21 (1H, dd, $J=14.4$, 2.9 Hz, H-6β), 2.49 (1H, t, $J=14.4$ Hz, H-6α), 2.67 (1H, br s, H-13), 3.00 (1H, dt, $J=17$, 2.2 Hz, H-15α), 3.22 and 3.47 (each 1H, d, $J=11$ Hz, H-18), 3.60 (1H, t, $J=8.5$ Hz, H-3), 4.78 and 4.83 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 318 $[M]^+$ (85), 300 (50), 288 (17), 282 (14), 270 (43), 241 (21), 227 (7), 215 (12), 201 (9), 188 (12), 175 (14), 173 (11), 161 (10), 147 (100). Diacetate **11**: mp 106–107 °C (petroleum ether–EtOAc); $[M]^+$ at *m/z* 402.2418, $C_{24}H_{34}O_5$ requires 402.2406; IR ν_{max} cm^{-1} 2935, 2865, 1740, 1700, 1650, 1470, 1370, 1300, 1030, 930, 875; ^1H NMR (200 MHz) δ 0.87 (3H, s, H-19), 1.06 (1H, td, $J=13$, 4 Hz, H-1β), 1.17 (3H, s, H-20), 1.99 and 2.01 (each 3H, s), 2.27 (1H, dd, $J=14$, 3.4 Hz, H-6β), 2.51 (1H, t, $J=14$ Hz, H-6α), 3.09 (1H, dt, $J=16.8$, 2.1 Hz, H-15α), 3.59 and 3.83 (each 1H, d, $J=11$ Hz, H-18), 4.73 (1 h, dd, $J=11.6$, 3.2 Hz, H-3), 4.83 and 4.88 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 402 $[M]^+$ (3), 342 (8), 300 (7), 282 (21), 267 (6), 241 (7), 188 (6), 147 (100).

3.6. Incubation experiments

The fungus *Gibberella fujikuroi* (IMI 58289), inhibited with 5×10^{-5} M AMO 1618, was grown in shake culture at 25° for 2 days in 65–75 conical flasks (250 ml) each containing sterile medium (50 ml).[22] The substrate in EtOH (13–15 ml) was distributed equally between the flasks and the incubation allowed to continue for a further, 6 days. The broth was filtered, adjusted to pH 2 with diluted HCl, and extracted with EtOAc.

3.6.1. Incubation of 7-oxo-*ent*-kaur-16-ene (7). The feeding of **7** gave starting material, **22** (1.2 mg), **23** (9 mg), **24** (1.7 mg) and fujenoic acid (**25**) (11 mg).

3.6.2. β,19-Dihydroxy-7-oxo-*ent*-kaur-16-ene (22). Colourless gum; $[M]^+$ at *m/z* 318.2206, $C_{20}H_{30}O_3$ requires 318.2195; IR ν_{max} cm^{-1} 3425, 2925, 2855, 1700, 1650, 1460, 1370, 1300, 1250, 1180, 1125, 1085, 1035, 995, 890; ^1H NMR (500 MHz) δ 0.98 (3H, s, H-18), 1.09 (3H, s, H-20), 1.44 (1H, d, $J=11.1$ Hz, H-14), 1.73 (br s, H-9), 1.87 (1H, dd, $J=11.1$, 2.6 Hz, H-14), 2.33 (1H, br d, $J=17.5$ Hz, H-15), 2.55 (2H, m, H-6), 2.78 (1H, br s, H-13), 3.32 (1H, dt, $J=17.5$, 2.7 Hz, H-15), 3.51 and 3.70 (each 1H, d, $J=11.9$ Hz, H-19), 3.94 (1H, t, 7 Hz, H-11), 4.94 and 5.08 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 318 $[M]^+$ (22), 300 (13), 287 (18), 269 (100), 255 (6), 199 (6), 187 (6), 173 (7), 161 (34), 147 (22).

3.6.3. 17,19-Dihydroxy-11β,16β-epoxy-7-oxo-*ent*-kaurane (23). $[M]^+$ at *m/z* 334.2144, $C_{20}H_{30}O_4$ requires 334.2144; IR ν_{max} cm^{-1} 3420, 2925, 1695, 1465, 1370, 1315, 1195, 1155, 1120, 1080, 1030, 975, 945; ^1H NMR (500 MHz) δ 0.98 (3H, s, H-18), 1.05 (1H, td, $J=13.5$, 4.5 Hz, H-3β), 1.19 (1H, td, $J=13.6$, 4.3 Hz, H-1β), 1.28 (3H, s, H-20), 1.43 (1H, dd, $J=11.4$, 5.8 Hz, H-5), 1.55 (3H, m, 2H-2 and H-14), 1.69 (1H, dd, $J=11.7$, 3.4 Hz, H-15), 1.83 (1H, br d, $J=14$ Hz, H-3α), 1.88 (1H, br s, H-9), 11.93 (2H, m, H-1 and H-12), 2.06 (1H, d, $J=11.7$ Hz, H-15), 2.10 (1H, dd, $J=11.6$, 3.4 Hz, H-14), 2.17 (1H, d, $J=11.6$ Hz, H-12), 2.52 (2H, m, H-6), 2.64 (1H, t, $J=6.5$ Hz, H-13), 3.54 and 3.77 (each 1H, d, $J=10.9$ Hz, H-19), 3.65 and 3.84 (each 1H, d, $J=11.6$ Hz, H-17), 4.50 (1H, br s, H-11); EIMS *m/z* (rel. int.) 334 $[M]^+$ (20), 316 (100), 304 (84), 291 (11), 273 (10), 267 (8), 255 (7), 224 (47), 215 (7), 201 (7), 187 (9), 173 (11), 161 (14), 147 (23).

3.6.4. β,13-Dihydroxy-7-oxo-*ent*-kaur-16-ene (24). Colourless needles, mp 155–157 °C (petroleum ether–EtOAc); $[M]^+$ at *m/z* 318.2165, $C_{20}H_{30}O_3$ requires 318.2195; IR ν_{max} cm^{-1} 3430, 2925, 1690, 1465, 1080, 890; ^1H NMR (500 MHz) δ 0.87 (3H, s, H-19), 0.90 (3H, s, H-18), 1.12 (3H, s, H-20), 1.13 (1H, td, $J=13.3$, 3.3 Hz, H-1β), 1.23 (1H, td, $J=13.1$, 4 Hz, H-3β), 1.33 (1H, dd, $J=10.9$, 6,1 Hz, H-5), 1.47 (1H, dd, $J=10.8$, 2.9 Hz, H-14), 1.54 (1H, m, H-3), 1.98 (1H, dd, $J=13.9$, 2 Hz, H-12α), 2.02 (1H, dt, $J=13.3$, 2 Hz, H-1α), 2.07 (1H, dd, $J=10.8$, 2.8 Hz, H-14), 2.27 (1H, dd, $J=13.9$, 6.0 Hz, H-12β), 2.35 (1H, dd, $J=17.8$, 2.4 Hz, H-15), 2.47 (2H, m, H-6), 3.50 (1H, dt, $J=17.8$, 2.8 Hz, H-15), 4.23 (1H, t, $J=6.0$ Hz, H-11), 5.04 (1H, br s, H-17), 5.21 (1H, t, $J=2.8$ Hz, H-17); EIMS *m/z* (rel. int.) 318 $[M]^+$ (23), 300 (56), 285 (95), 275 (12), 267 (8), 260 (8), 257 (11), 207 (), 176 (28), 162 (14), 151 (15).

3.6.5. Fujenoic acid (25). $[M]^+$ at *m/z* 346.1788, $C_{20}H_{26}O_5$ requires 346.1780; IR ν_{max} cm^{-1} 3433 (br), 2940, 1815, 1785, 1700, 1460, 1205, 1005, 920, 890; ^1H NMR (500 MHz) δ 1.08 (3H, s, H-20), 1.20 (1H, m, H-3β), $J=$ 1.36 Hz (3H, s, H-18), 1.75 (d, $J=10.4$ Hz, H-14), 1.85 (1H, d, $J=10.4$, 2.5, H-1), 1.93 (1H, m, H-11), 1.98 (1H, dd, $J=12.5$, 5.1 Hz, H-14), 2.36 (1H, dt, $J=14.9$, 2.8 Hz, H-3α), 2.50 (1H, dt, $J=17.6$, 2.4 Hz, H-15), 2.56 (1H, s, H-5), 2.68 (1H, dd, $J=17.6$, 1.5 Hz, H-15), 2.70 (1H, d, $J=6.7$, H-9),

2.80 (1H, br s, H-13), 4.82 and 4.90 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 346 $[M-H_2O]^+$ (1), 328 (37), 300 (12), 256 (17), 256 (17), 254 (10), 241 (14), 181 (6), 166 (27), 165 (21), 153 (19), 148 (12). Methyl ester (**28**), $[M]^+$ at *m/z* 360.1919. $C_{21}H_{28}O_5$ requires 360.1937; ^{1}H NMR (500 MHz) δ 0.90 (3H, s, H-20), 1.18 (1H, m, H-3β), 1.33 (3H, s, H-18), 1.70 (1H, dd, J=12.2, 2.4 Hz, H-14), 1.81 (1H, dd, J=10.6, 3.3 Hz, H-1), 1.88 (1H, m, H-11), 1.96 (1H, dd, J=12.2, 5.0 Hz, H-14), 2.32 (1H, dt, J=17.2, 3.3 Hz, H-3α), 2.37 (1H, dt, J=17.6, 2.3 Hz, H-15), 2.50 (1H, s, H-5), 2.60 (1H, dd, J=17.6, 1.3 Hz, H-15), 2.66 (1H, d, J=7.6 Hz, H-9), 2.75 (1H, br s, H-13), 3.62 (3H, s, –OMe), 4.76 and 4.85 (each 1H, s, H-17); EIMS *m/z* (rel. int.) 360 $[M]^+$ (4), 328 (53), 300 (18), 179 (57), 147 (28), 137 (8).

3.6.6. Preparation of the trimethylester 2. Fujenoic acid (**25**) (5 mg) was refluxed with dry MeOH (5 ml) for 40 h. The solvent was evaporated and the residue treated with ethereal diazomethane to afford **2** (5 mg), $[M]^+$ at *m/z* 406.2348, $C_{23}H_{34}O_6$ requires 406.2355; ^{1}H NMR (500 MHz) δ 1.07 (3H, s, H-20), 1.25 (3H, s, H-18), 2.35 (1H, dt, J=17.3, 2.5 Hz, H-15), 2.47 (1H, d, J=17.3 Hz, H-15), 2.53 (1H, s, H-5), 2.70 (1H, br s, H-13), 3.61, 3.63 and 3.67 (each 3H, s, –OMe), 4.72 and 4.81 (each 1H, s, H-17), EIMS *m/z* (rel. int.) 406 $[M]^+$ (2), 388 (1), 375 (6), 342 (2), 315 (3), 283 (2), 255 (5), 247 (1), 227 (69), 195 (100), 167 (62).

3.6.7. Incubation of 18-hydroxy-7-oxo-*ent*-kaur-16-ene (8). The feeding of **8** (250 mg) gave starting material (95 mg), **27** (0.8 mg), **29** (11 mg), **31** (1 mg), (**30**) (1.4 mg), **32** (4 mg), **33** (0.9 mg), **35** (0.7 mg) and **37** (1.0 mg).

3.6.8. 18,19-Dihydroxy-7-oxo-*ent*-kaur-16-ene (27). Obtained as its diacetate **28**, $[M]^+$ at *m/z* 402.2403, $C_{24}H_{34}O_5$ requires 402.240; ^{1}H NMR (500 MHz) δ 1.23 (3H, s, H-20), 2.03 and 2.04 (each 3H, s), 2.49 (1H, dd, J=14.4, 2.9 Hz, H-6β), 2.61 (1H, t, J=14.4 Hz, H-6α), 2.73 (1H, br d, H-13), 3.14 (1H, dt, J=17, 3 Hz, H-15), 3.90 and 3.95 (each 1H, d, J=11 Hz, H-18), 4.07 and 4.28 (each 1H, d, J=11 Hz, H-19), 4.83 and 4.87 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 402 $[M]^+$ (49), 360 (21), 342 (43), 300 (19), 282 (40), 147 (100).

3.6.9. 11β,18-Dihydroxy-7-oxo-*ent*-kaur-16-ene (29). $[M]^+$ at *m/z* 318.2206, $C_{20}H_{30}O_3$ requires 318.2195; ^{1}H NMR (500 MHz) δ 0.78 (3H, s, H-19), 1.12 (3H, s, H-20), 1.33 (1H, dd, J=Hz, H-14), 1.71 (1H, dd, J=Hz, H-5), 1.78 (1H, br s, H-9), 2.47 (1H, t, J=14.4 Hz, H-6), 2.79 (1H, br s, H-13), 3.07 and 3.39 (each 1H, d, J=11 Hz, H-18), 3.31 (1H, dt, J=17.5, 3 Hz, H-15), 3.97 (1H, d, J=4.7 Hz; H-11), 4.95 and 5.10 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 318 $[M]^+$ (8), 300 (7), 285 (7), 269 (100), 205 (6), 187 (7), 161 (15).

3.6.10. 11α,18-Dihydroxy-7-oxo-*ent*-kaur-16-ene (31). $[M]^+$ at *m/z* 318.2194, $C_{20}H_{30}O_3$ requires 318.2195; ^{1}H NMR (500 MHz) δ 0.82 (3H, s, H-19), 1.04 (1H, dd, J=13.1, 3.8 Hz, H-1β), 1.29 (3H, s, H-20), 1.30 (1H, m, H-3), 1.51 (3H, m, H-2, H-3 and H-14), 1.66 (1H, dt, J=13.5, 3.5 Hz, H-2α), 1.74 (1H, d, J=5.9 Hz, H-9), 1.81 (2H, m, H-5 and H-12), 1.99 (1H, m, H-12), 2.07 /1H, br d, J=16 Hz, H-15), 2.20 (1H, dd, J=12, 2.7 Hz, H-14), 2.34 (1H, dd, J=15.2, 4.5 Hz, H-6β), 2.41 (1H, dt, J=13.1, 2 Hz, H-1α), 2.48 (1H, dd, J=15.2, 13.4, H-6α), 2.78 (1H, br s, H-13), 2.80 (1H, dt, J=16, 2.7 Hz, H-15), 3.05 and 3.35 (each 1H, d, J=11 Hz, H-18), 4.26 (1H, m, $W_{1/2}$=18 Hz, H-11), 4.80 and 4.91 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 318 $[M]^+$ (80), 300 (24), 287 (20), 285 (11), 277 (15), 269 (54), 249 (10), 229 (11), 187 (12), 178 (20), 165 (22), 147 (30).

3.6.11. 18-Hydroxy-11β,16β-epoxy-7-oxo-*ent*-kaurane (31). Colourless needles, mp 171–173 °C (petroleum ether–CH_2Cl_2); $[M]^+$ at *m/z* 318.2192, $C_{20}H_{30}O_3$ requires 318.2195; ^{1}H NMR (500 MHz) δ 0.80 (3H, s, H-19), 1.14 (1H, td, J=12.6, 3.5 Hz, H-1β), 1.27 (3H, s, H-20), 1.31 and 1.46 (each 1H, m, H-3), 1.40 (3H, s, H-17), 1.58 (2H, m, H-2 and H-14), 1.64 (2H, m, H-2 and H-5), 1.70 (1H, dd, J=11.5, 3.5 Hz, H-15), 1.83 (1H, br d, J=12.6 Hz, H-1α), 1.85 (1H, br s, H-9), 1.95 (1H, m, H-12), 2.06 (3H, m, H-12, H-14 and H-15), 2.30 (1H, t, J=14.4 Hz, H-6α), 2.32 (1H br s, H-13), 2.39 (1H, br d, J=14.4 Hz, H-6β), 3.04 and 3.32 (each 1H, d, J=11 Hz, H-18), 4.39 (1H, br s, H-11); EIMS *m/z* (rel. int.) 318 $[M]^+$ (100), 300 (22.6), 289 (31), 274 (19), 269 (15), 247 (14), 215 (10), 178 (12), 161 (11), 150 (21).

3.6.12. 6β,18-Dihydroxy-7-oxo-*ent*-kaur-16-ene (32). $[M]^+$ at *m/z* 318.2192, $C_{20}H_{30}O_3$ requires 318.2195; ^{1}H NMR (500 MHz) δ 0.83 (1H, td, J=13.1, 3.7 Hz, H-1β), 1.03 (3H, s, H-19), 1.35 (3H, s, H-20), 1.39 (1H, dd, J=13.7, 4.4 Hz, H-14), 1.42 (1H, s, H-5), 1.86 (1H, dt, J=13.1, 2 Hz, H-1), 2.07 (1H, dd, J=13.7, 2.5 Hz, H-14), 2.10 (1H, dd, J=17.7, 2.5 Hz, H-15), 2.78 (1H, br s, H-13), 3.06 and 3.53 (each 1H, d, J=11 Hz, H-18), 3.30 (1H, dt, J=17.7, 3.0 Hz, H-15), 3.35 and 4.23 (each 1H, –OH), 4.48 (1H, d, J=13.0 Hz, H-6), 4.88 and 4.90 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 318 $[M]^+$ (3), 300 (14), 288 (10), 285 (8), 270 (61), 255 (12), 201 (9), 189 (36), 173 (6), 167 (11), 151 (8).

3.6.13. 18-Hydroxy-16α,17-epoxy-7-oxo-*ent*-kaurane (33). $[M]^+$ at *m/z* 318.2181, $C_{20}H_{30}O_3$ requires 318.2195; ^{1}H NMR (500 MHz) δ 0.77 (3H, s, H-19), 1.23 (3H, s, H-20), 0.84 (1H, td, J=15, 5 Hz, H-1β), 1.44 (1H, d, J=7 Hz, H-9), 1.59 (1H, dd, J=14.8, 2.2 Hz, H-15), 2.05 (1H, dd, J=11.3, 2.2 Hz, H-14), 2.32 (1H, dd, J=14.2, 2.7 Hz, H-6α), 2.50 (1H, t, J=14.2 Hz, H-6β), 2.74 (1H, d, J=14.8 Hz, H-15), 2.79 and 2.89 (each 1H, d, J=4.7 Hz, H-17), 3.04 and 3.36 (each 1H, d, J=11 Hz, H-18), EIMS *m/z* (rel. int.) 318 $[M]^+$ (42), 300 (9), 290 (57), 288 (100), 269 (44), 255 (8), 231 (16), 217 (9), 205 (35), 199 (9), 191 (30), 187 (25), 173 (11), 165 (27), 161 (16), 150 (23).

3.6.14. Epoxidation of 7. The substrate (**7**) (15 mg) in CH_2Cl_2 (2 ml) was treated with *m*-chloroperbenzoic acid (12 mg) and Na_2HPO_4 (30 mg) in H_2O (0.75 ml). Extraction with CH_2Cl_2 and chromatography afforded a mixture 85:15 (11 mg) of the α- and β-epoxides, **33** and **34**, respectively. The ^{1}H NMR signals of the main compound **33** was identical to the metabolite obtained in the incubation and the minor component was identified as the β-isomer **34**: ^{1}H NMR (500 MHz) δ 0.78 (3H, s, H-19), 1.20 (3H, s, H-20),

2.07 (1H, dd, $J=13$, 6 Hz, H-14), 2.32 (1H, dd, $J=14.2$, 2.7 Hz, H-6a), 2.47 (1H, t, $J=14.2$ Hz, H-6a), 2.82 and 2.85 (each 1H, d, $J=5$ Hz, H-17), 3.05 and 3.35 (each 1H, d, $J=11$ Hz, H-18).

3.6.15. 1α,18-Dihydroxy-7-oxo-*ent*-kaur-16-ene (35). Obtained as its diacetate (**36**), $[M]^+$ at *m/z* 402.2401, $C_{24}H_{34}O_5$ requires 402.2406; ^1H NMR (500 MHz) δ 0.89 (3H, s, H-19), 1.25 (3H, s, H-20), 1.35 (1H, dt, $J=13.5$, 3 Hz, H-3), 1.70 (2H, m, H-2 and H-9), 1.75 (1H, dd, $J=13.5$, 4 Hz, H-5), 1.83 (2H, m, H-11 and H-14), 2.02 and 2.04 (each 3H, s), 2.29 (1H, dd, $J=15.1$, 4 Hz, H-6), 2.53 (1H, dd, $J=15.1$, 13.5 Hz, H-6), 2.67 (1H, br s, H-13), 2.90 (1H, dt, $J=16.8$, 2.6 Hz, H-15), 3.62 and 3.74 (each 1H, d, $J=11$ Hz, H-18), 4.56 (1H, dd, $J=10.3$, 5.5 Hz, H-1), 4.81 and 4.88 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 402 $[M]^+$ (83), 342 (45), 327 (11), 300 (8), 282 (40), 269 (61), 253 (13), 239 (10), 225 (6), 213 (9), 201 (12), 188 (25), 187 (23), 175 (12), 173 (15), 161 (17), 147 (100).

3.6.16. 7-Oxo-*ent*-kaur-16-en-18,6β-olide (37). $[M]^+$ at *m/z* 314.1873, $C_{20}H_{26}O_3$ requires 314.1881; IR ν_{max} cm^{-1} 2930, 2850, 1775, 1720, 1460, 1390, 1130, 1060, 1045, 955, 875; ^1H NMR (500 MHz) δ 0.86 (1H, m, H-1β), 1.29 and 1.31 (each 3H, s, H-19 and H-20), 1.44 (1H, td, $J=12.4$, 5.8 Hz, H-3α), 1.74 (1H, d, $J=14.0$ Hz, H-5), 1.85 (1H, dt, $J=13.0$, 3.2 Hz, H-1β), 1.91 (1H, dt, $J=13.0$, 3.2 Hz, H-3β), 2.09 (1H, br d, $J=17.7$ Hz, H-15), 2.82 (1H, br s, H-13), 3.28 (1H, dt, $J=17.7$, 2.7 Hz, H-15), 4.87 and 4.91 (each 1H, br s, H-17), 4.98 (1H, d, $J=14.0$ Hz, H-6); EIMS *m/z* (rel. int.) 314 $[M]^+$ (10), 286 (87), 268 (12), 253 (20), 243 (15), 225 (17), 213 (6), 199 (6), 187 (15), 173 (11), 147 (50), 139 (100).

3.6.17. Incubation of 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (9). The feeding of **9** (214 mg) gave starting material (29 mg), **38** (64 mg) and **40**, identified as its triacetate **41** (14 mg).

3.6.18. 3α,6β,18-Trihydroxy-7-oxo-*ent*-kaur-16-ene (38). Colourless gum; $[M]^+$ at *m/z* 334.2151, $C_{20}H_{30}O_4$ requires 334.2144; ^1H NMR (500 MHz) δ 0.93 (1H, td, $J=13.4$, 5.6 Hz, H-1β), 0.98 (3H, s, H-19), 1.30 (1H, s, H-20), 1.88 (1H, dt, $J=13.4$, 3.3 Hz, H-1α), 2.04 (1H, br d, $J=11.1$ Hz, H-14), 2.08 (1H, br d, $J=17.4$ Hz, H-15β), 2.76 (1H, br s, H-13), 3.27 (1H, br d, $J=17.4$ Hz, H-15α), 3.53 (1H, dd, $J=10.6$, 6 Hz, H-3), 3.66 and 3.76 (each 1H, d, $J=11$ Hz, H-18), 4.23 (1H, br s, –OH), 4.51 (1H, d, $J=12.8$ Hz, H-6), 4.87 and 4.89 (each 1H, br s, H-17); EIMS *m/z* (rel. int.) 334 $[M]^+$ (12), 316 (53), 304 (100), 298 (28), 286 (65), 268 (36), 255 (19), 241 (18), 201 (15), 189 (59), 183 (44), 167 (14), 147 (21). Triacetate (**42**) $[M]^+$ at *m/z* 460.2469. $C_{26}H_{36}O_7$ requires 460.2461; ^1H NMR (500 MHz) δ 0.95 (3H, s, H-19), 1.10 (1H, td, $J=13.7$, 3.4 Hz, H-1β), 1.37 (3H, s, H-20), 1.42 (1H, d, $J=6.8$ Hz, H-9), 1.51 (1H, dd, $J=11.2$, 5 Hz, H-14), 1.56 (1H, m, H-12), 1.82 (1H, ddd, $J=13.3$, 9.1, 4.4 Hz, H-2), 1.94 (1H, dt, $J=13.7$, 3.4 Hz, H-1α), 2.01, 2.02 and 2.10 (each 3H, s), 2.74 (1H, br s, H-13), 3.13 (1H, dt, $J=17.5$ Hz, 3.3 Hz, H-15), 3.59 and 4.17 (each 1H, d, $J=11.45$ Hz, H-18), 4.76 (1H, dd, $J=12$, 4.9 Hz, H-3), 4.85 (1H, d, $J=13.3$ Hz, H-6), 5.54 and 5.56 (each 1H, s, H-17); EIMS *m/z* (rel. int.) 460 $[M]^+$ (0.5), 400 (2), 358 (5), 340 (1), 325 (2), 316 (1), 298 (12), 280 (9), 252 (8), 147 (8), 91 (100).

3.6.19. 3α,11β,18-Trihydroxy-7-oxo-*ent*-kaur-16-ene (40). Obtained by acetylation as its triacetate **41**. Colourless gum; ^1H NMR (500 MHz) δ 0.87 (3H, s, H-19), 1.20 (3H, s, H-20), 1.65 (1H, s, H-9), 1.76 (1H, dd, $J=14.4$, 2.5 Hz, H-5), 1.94, 2.01 and 2.03 (each 3H, s), 2.50 (1H, t, $J=14.4$ Hz, H-6β), 2.72 (1H, br s, H-13), 3.28 (1H, dt, $J=17.3$, 2.4 Hz, H-15α), 3.58 and 3.83 (each 1H, d, $J=12.2$ Hz, H-18), 4.75 (1H, dd, $J=11.7$, 4.8 Hz, H-3), 4.80 and 4.91 (each 1H, br s, H-17), 5.12 (1H, d, $J=5.3$ Hz, H-11); EIMS *m/z* (rel. int.) 460 $[M]^+$ (23), 400 (46), 358 (15), 340 (50), 325 (6), 298 (42), 280 (100), 265 (50), 239 (33), 225 (10), 213 (11), 205 (35), 200 (23), 173 (11), 161 (25), 147 (54).

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Theoretical studies on the S–N interactions in sulfoximine

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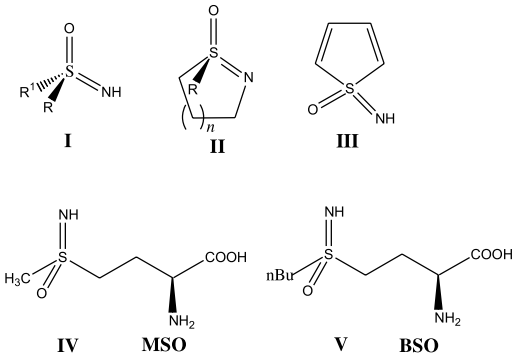
Abstract—The potential energy surface of sulfoximines has been searched using ab initio MO and Density Functional Calculations. The electronic structures of the isomers of sulfoximine have been studied using HF/6-31+G*, MP2(full)/6-31+G* and B3LYP/6-31+G* levels. Final energies of these molecules have been calculated at the high accuracy G2 and CBS-Q levels. Though a formal S=N double bond is generally considered between sulfur and nitrogen in these systems, theoretical studies do not show any π interaction between them. S–N rotational barriers, bond dissociation energies, atomic charge analysis, and NBO analysis all indicate only a single bond across S–N with a very strong ionic interaction.

1. Introduction

Sulfoximines ($R_2S(=O)=NR$), **I** also known as sulfoximides, are an extremely versatile class of compounds with several functional characteristics.[1] Chiral sulfoximines have found applications not only in asymmetric synthesis but also in biological and physiological studies.[1b] These compounds can be synthesised using: (a) oxidative imination of sulfoxides,[2a–e] (b) oxidation of sulfilimines[3] (c) nucleophilic substitution at sulfur[4] and (d) rearrangement of λ^6-sulfanenitriles.[5] Based on the centre of reactivity, sulfoximines are classified as C-nucleopiles, electrophiles and also serve as a ligand. Medicinal applications of sulfoximines have been reported in many cases.[6] Several cyclic sulfoximines with an exocyclic/endocyclic (**II–III** Scheme 1) S=N moiety have been prepared and a few of them have been tested for dihydrorotase inhibitor activity.[6i] Methionine sulfoximine MSO (**IV**)[7a–c] is a potent inhibitor for glutamate synthetase and γ-glutamyl synthase. Buthionine sulfoximine BSO (**V**)[8] inhibits the intracellular generation of glutathione and enhances the efficiency of cytotoxic agents.[9] β-sulfoximinopropionic acids were found to be potent inhibitors of carboxypeptidase A.[6f,g] Other medicinal applications of sulfoximine derivatives includes carboxylate kinase mediated phosphorylation,[6l,m] as anti-viral agents,[6d,n] anti-fungal agents,[6o,p] and anti-herpetic agents,[6d] and as radiation induced drugs for the treatment of malignant melanoma.[6k,q] Pseudopeptides bearing sulfoximines have been used as proteinase K chiral backbone modifying agents.[6c]



Scheme 1.

It is important to study S–N interactions in these systems because the stereoelectronic control across this bond is important in asymmetric reactions involving sulfoximines. Though a few conformational studies have been reported on sulfoximines most studies concentrate on S–C interactions in these systems rather than S–N interactions.[10] No mention about *cis–trans* (*anti–syn*) isomerisation across this S=N double bond has been made. Is there a dπ–pπ bond between sulfur and nitrogen? What is the charge distribution across the S–N bond? How does the S–N interaction in sulfoximines compare with that of sulfilimines? The S–N interactions in sulfilimines, sulfonamides, thionylimide, etc. have been shown to be strongly influenced by negative hyperconjugative interactions as well as ionic interactions.[11] Are there any negative hyperconjugative interactions across the S–N bond in sulfoximines ($R_2S=NR$)? These questions

Keywords: Sulfoximines; Ab initio calculations; Negative hyperconjuction; Rearrangements.
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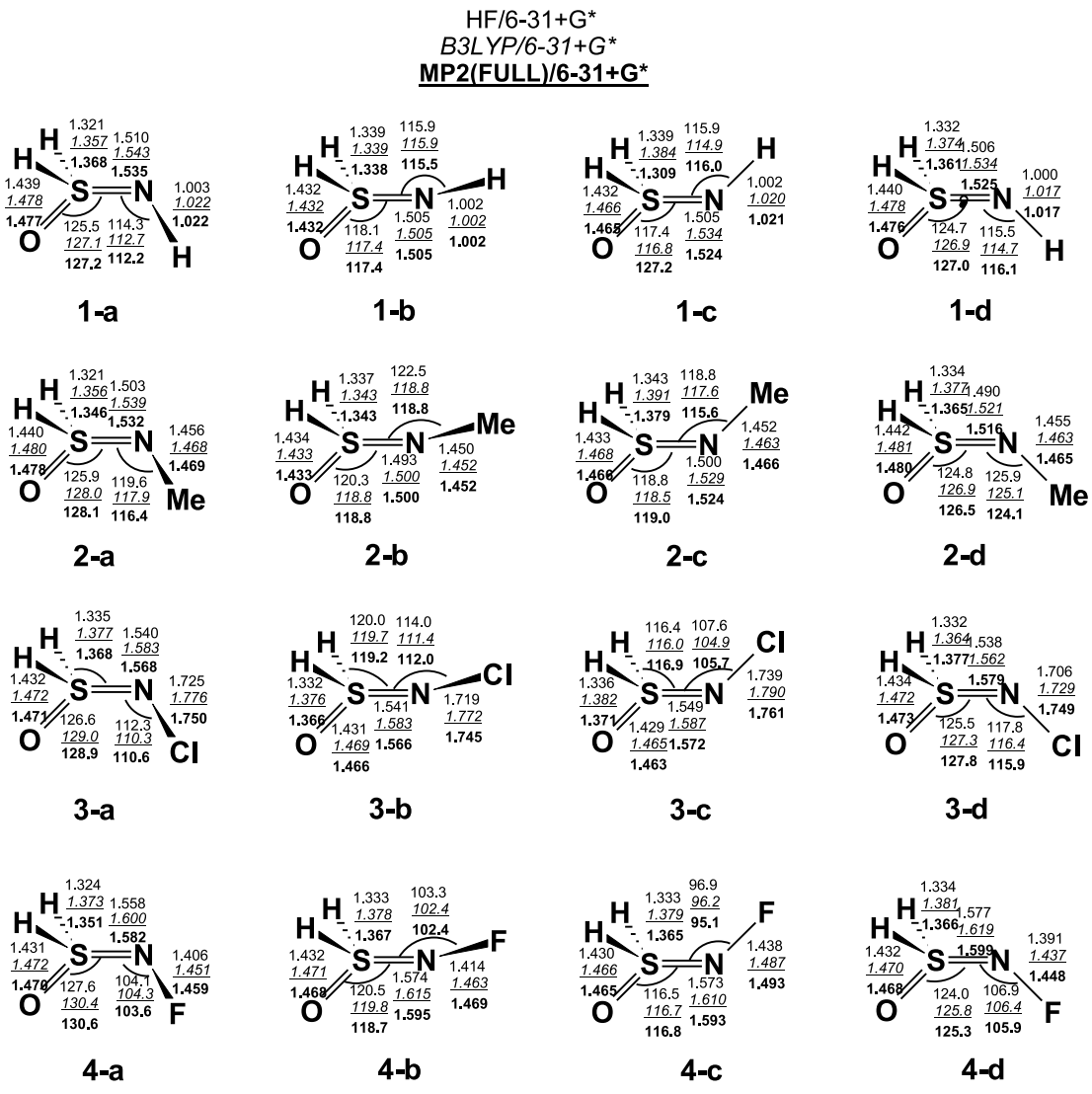


Figure 1. The structure and the geometrical parameters of the various isomers of sulfoximines **1**–**4** at HF, B3LYP and MP2(Full) (using 6-31+G* basis set) (distances in Angstrom units, angles in degrees).

have not been addressed by previous workers. In this paper, we report the electronic structure of sulfoximines with the aim of understanding S–N interactions. We also report the relative stability of $H_2(O)S{=}NH$ on its PE surface and the 1,3-shift processes in these systems to give λ^6-sulfanenitriles.

2. Methods of calculations

Ab initio MO[12] and density functional (DFT)[13] calculations have been carried out using the GAUSSIAN03 package.[14] Complete optimisations have been performed on sulfoximinines **1**, and its conformers using the HF/6-31G*, B3LYP/6-31+G* and MP2(full)/6-31+G* levels (Fig. 1). Frequency calculations have been performed in order to characterize each stationary point as a minimum or a transition state and to determine the zero point vibrational energies (ZPE). In order to obtain accurate values, the calculations have been performed at higher level of ab initio calculations including CBS-Q[15a] and G2[15b] method as shown in Table 1. Atomic charges in all the structures were obtained using the Natural Population Analysis (NPA) method within the Natural Bond Orbital approach[16] with MP2 densities using MP2(FULL)/6-31+G* geometries to understand the electron distribution in these molecules. To study the substituent effect on the structure and conformations ab initio MO, DFT and NPA calculations have been performed on $H_2S(O)$–NR, **2**–**4** in which R is CH_3, Cl and F (Fig. 1). Second order energy analysis has been carried out using the NBO method to understand the delocalisation present in different sulfoximines (**1**–**4**). The geometric parameters obtained at MP2(full)/6-31+G* level and the G2 (thermal free) energy values are employed in this discussion unless otherwise specifically mentioned.

3. Results and discussion

3.1. $H_2S(=O)=NH$

The absolute energies of sulfoximine (**1a**–**d**), and their conformational isomers, including transition state, along the rotational path are given in Tables 1 and 2. Figure 1

Table 1. The absolute energy (in a.u.) of the various isomers of sulfoximines **1**–**4** at different levels

Molecular conformation	O–S–N–R torsional angle[a]	HF/6-31+G*	MP2(full)/6-31+G*	B3LYP/6-31+G*	CBS-Q	G2
1a	56.4	−528.413769	−528.92661	−529.838619	−529.261202	−529.273259
1b	158.6	−528.402852	—	—	—	—
1c	176.7	−528.402880	−528.912413	−529.826732	−529.252347	−529.262673
1β	0.0	−528.409009	−528.919069	−529.832388	−529.254998	−529.265209
2a	61.1	−567.439701	−568.090936	−569.146348	−568.473711	−568.487889
2b	141.9	−567.429395	—	—	—	—
2c	180.0	−567.429911	−568.077259	−569.135533	−568.465528	−568.47792
2β	0.0	−567.432515	−568.079996	−569.137415	−568.465607	−568.478952
3a	66.2	−987.264620	−987.922659	−989.391719	−988.373496	−988.378098
3b	130.8	−987.253131	−987.908495	−989.379850	−988.364652	−988.368449
3c	179.8	−987.258071	−987.910960	−989.383135	−988.368658	−988.373304
3β	0.0	−987.251283	−987.904297	−989.375307	−988.358269	−988.362875
4a	70.1	−627.179107	−627.875634	−629.002792	−628.337562	−628.341111
4b	128.6	−627.167383	−627.860958	−628.990865	−628.325417	−628.329783
4c	180.0	−627.172593	−627.861891	−628.991822	−628.327600	−628.332551
4β	0.0	−627.158502	−627.848340	−628.979321	−628.315914	−628.318973

[a] O–S–N–R torsional angle at HF/6-31+G* level, in degrees. On the PE surface of each of these molecules there is another set of transition states (degenerate with **1b**, **2b**, **3b**, **4b** and with negative value of O–S–N–R). Similarly there is a set of minima (degenerate with **1c**, **2c**, **3c**, **4c** and with negative O–S–N–R torsions).

shows the important geometric parameters obtained at HF/6-31+G*, B3LYP/6-31+G* and MP2(full)/6-31+G* levels. On the potential energy (PE) surface of sulfoximine **1** three minima and three transition states could be located. The three minima are defined by O–S–N–H torsional angles of ∼60, ∼180, and ∼300° (all with staggered arrangement). A structure with an O–S–N–H torsional angle of 60° (**1**–**a**) (which is degenerate with structure with ∼300° torsional angle) has been found to be a global minimum at all levels. The three transition states are characterised by O–S–N–H torsional angles of ∼120, ∼240 and ∼360° at MP2 level all with eclipsed arrangement. This PE surface clearly points out the absence of S–N π interactions (neither pπ–pπ nor dπ–pπ). Figure 2 shows the PE surface of **1**. The overall energy barrier for S–N bond rotation is 8.92 kcal/mol at MP2 level. It is really surprising to note that the barrier for the S–N rotational path is very high at 8.90 kcal/mol in the absence of S–N double bond. NBO analysis showed that there are two lone pairs on nitrogen in **1**. Hence, the Newman projections of the various conformers can be shown as given in Scheme 2. Such representations show that **1a** is characterised by $n_N \rightarrow \sigma^*_{S-O}$ negative hyperconjugative interactions with estimated second order delocalisation energy of $E^{(2)} = 31.93$ kcal/mol. The electron density in the delocalised lone pair is 1.92, much less than that in the other lone pair (1.99). The greater stability of **1a** is due to anomeric π strength arising due to $n_N \rightarrow \sigma^*_{S-O}$ negative hyperconjugative interactions. In the rotational transition state **1b** there is a strong lone-pair(N) lone-pair(O) repulsion, and also the anomeric π interaction is negligible. Hence, in sulfoximines, the S–N barrier is very high due to lone-pair lone-pair repulsions and breaking of anomeric π interaction, but not due to S–N π bond breaking (Table 2).

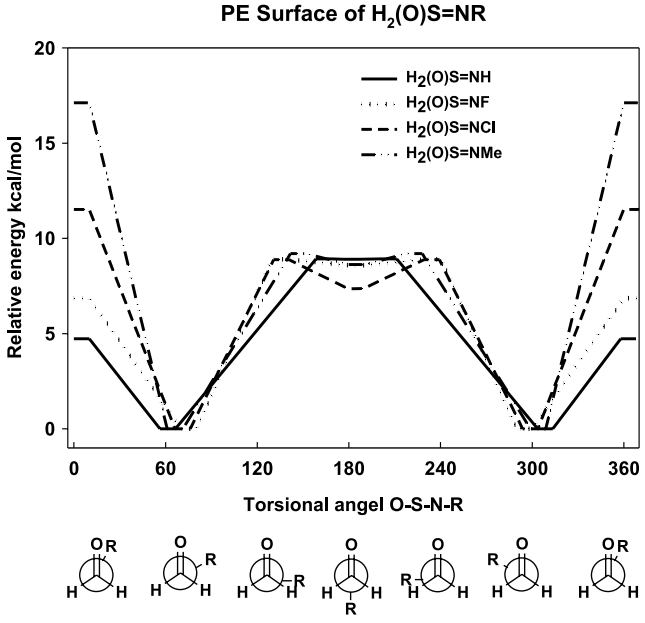
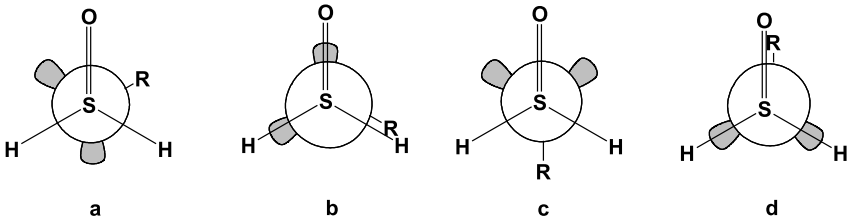


Figure 2. PE surface of various isomers of sulfoximines **1**–**4** at MP2(full)/6-31+G*level.[19]

The S–N interactions in sulfoximine should be compared to that of S=NH, (O)S=NH, (HN)S=NH and H_2S=NH, where a formal double bond is usually drawn. Table 3 gives comparative data on these systems. The S–N bond length in **1** is the smallest though there is no formal S–N double bond.



Scheme 2. Newman projections of the various conformers of sulfoximines. (R=H, CH_3, Cl, F).

Table 2. The relative energy (in kcal/mol.) of the various isomers of sulfoximines **1–4** at different levels

Molecule	HF/6-31+G*	MP2(full)/6-31+G*	B3LYP/6-31+G*	CBS-Q	G2
1a	0.0	0.0	0.0	0.0	0.0
1b[a]	6.85	8.92	7.47	5.56	6.65
1c	6.83	8.90	7.45	5.55	6.64
1d	2.98	4.73	3.91	3.89	5.05
2a	0.0	0.0	0.0	0.0	0.0
2b[a]	6.46	8.90	7.10	5.14	6.26
2c	6.14	8.58	6.78	4.82	5.94
2d	4.50	6.86	5.60	4.42	5.60
3a	0.0	0.0	0.0	0.0	0.0
3b	7.20	8.88	7.44	5.54	6.05
3c	4.10	7.34	5.38	3.03	3.00
3d	8.36	11.52	10.29	9.55	9.55
4a	0.0	0.0	0.0	0.0	0.0
4b	7.35	9.20	7.48	7.62	7.10
4c	4.08	8.62	6.88	6.25	5.37
4d	12.92	17.12	14.72	13.58	13.89

[a] Ref. 19.

Table 3. Comparative data containing S–N bond distance, rotational barrier (RB), charge on S and N, Nitrogen lone pair occupancy ($\rho n_{(N)}$)

Molecules	S–N[a]	RB[b]	Charges		$\rho n_{(N)}$	S–N BDE[b]
			S	N		
S=NH	1.594	—	0.336	−0.722	1.995	188.2
OS=NH	1.550	18.58	1.558	−1.005	1.942	170.8
HN=S=NH	1.569	20.42	1.355	−1.072	1.941	142.6
H_2S=NH	1.588	6.23	0.738	−1.220	1.952	117.4
H_2OS=NH(1)	1.535	4.73	1.764	−1.253	1.922	51.35
H_2OS=NMe(2)	1.532	10.85	1.775	−1.066	1.907	41.28
H_2OS=NCl(3)	1.568	11.52	1.735	−0.999	1.956	69.18
H_2OS=NF(4)	1.582	17.12	1.686	−0.554	1.972	66.40

All the values at MP2(full)/6-31+G* level.
[a] Bond length in Å units.
[b] Rotational barriers (RB) and bond dissociation energies (BDE) in kcal/mol.

This is due to the strong ionic interaction between sulfur and nitrogen in **1**. Whereas S=NH, (O)S=NH and (HN)S=NH are characterised by a regular S–N π bonds, H_2S=NH is characterised by very weak S–N π bond, H_2(O)S=NH is characterised by no π bond. The estimated S–N bond dissociation energies (BDE) also support this observation. The S–N BDE in **1** (51.35 kcal/mol) much smaller than that in S=NH (188.2) > OS=NH (170.8) > (NH)S=NH (142.6) > H_2S=NH (117.4 kcal/mol). This indicates that the S–N bond in sulfoximine is quiet weak, and the release of nitrene from these systems is practical, in fact the S–N breaking in sulfoximine during organic reactions has been reported experimentally.[17]

3.2. Substituent effect: $H_2S(=O)=NR$ (R=Me, Cl, F)

To estimate the influence of substituents on the S–N interaction, calculations have been performed on **1**, **2**, **3**, **4** and their S–N rotational path. Three minima have been identified on the S–N rotational path on each of **2–4**, confirming that *cis–trans* isomerisation should not be expected across this formal S–N double bond. The S–N rotational path in **2–4** is characterised by severe lone-pair lone-pair repulsions, that is, all the transition states along the S–N rotational path are due to lone-pair lone-pair repulsions only. The overall rotational barriers are 8.90, 11.52 17.12 kcal/mol for **2–4**, respectively at MP2(full)/6-31+G* level. PE surfaces of the rotational paths shown in Figure 2 reveal that with an increase in the electronegativity on the substituents, a structure with a *syn* periplanar arrangement across O–S–N–X becomes very unstable, and hence influences the PE surface strongly. This is mainly due to the increased lone-pair lone-pair repulsions between substituent (R) and oxygen rather than due to the electronegativity of the substituents. The S–N bond dissociation energies in **1–4** (51.35, 41.28, 69.18, 66.40 kcal/mol, respectively) are all smaller than the other systems with formal S=N double bond (Table 3). Substituents on nitrogen strongly influence the S–N bond dissociation energy, electronegative substituents showing larger S–N dissociation energies. This may in part be explained on the basis of the smaller stability of the nitrene generated due to S–N bond cleavage in sulfoximines.[17a]

3.3. H-shift in $H_2S(=O)=NH$

Sulfoximines are prone to undergo rearrangements.[5,17] For example, allylic sulfoximines are involved in sulfoximine ⇌ sulfinamide rearrangement.[17c] Literature reports suggest that sulfoximines are rearranged to the corresponding λ^6-sulfanenitriles.[5] Such a process in **1** is equivalent to a 1,3-H shift as in keto ⇌ enol tautomerism.[18] Ab initio calculations have been carried out to study this process. Figure 4 shoes the PE surface for the 1,3-H shift from **1** ⇌ **5**. Compound **5** is less stable than **1** by about 25.6 kcal/mol at

Table 4. Absolute energy (a.u.) of various isomers **5**–**7** obtained by 1,2-H shift and 1,3-H shift

Molecule	HF	B3LYP	MP2
1	−528.4137696	−529.8386196	−528.9266100
5	−528.3537304	−529.7938878	−528.8857997
6	−528.4541378	−529.8823638	−528.9680439
7	−528.4907287	−529.9103099	−528.9969436
TS-5	−528.2840846	−529.7349788	−528.8239275
TS-6	−528.3017653	−529.7593553	−528.8452699
TS-7	−528.3247543	−529.7810431	−528.8673065

MP2(full)/6-31+G* level. The barrier for this 1,3-H shift is about 64.4 kcal/mol at the same level. This 1,3-H shift barrier is relatively less than that in CH_3–CHO⇌ H_2C=CH–OH tautomerisation (~80–110) kcal/mol and the H_3C–CH=NH⇌H_2C=CH–NH_2 (~80–110 kcal/mol).[18] However, this barrier is significantly large enough, suggesting that the observed 1,3-shift takes place via an ionic path (Table 4).

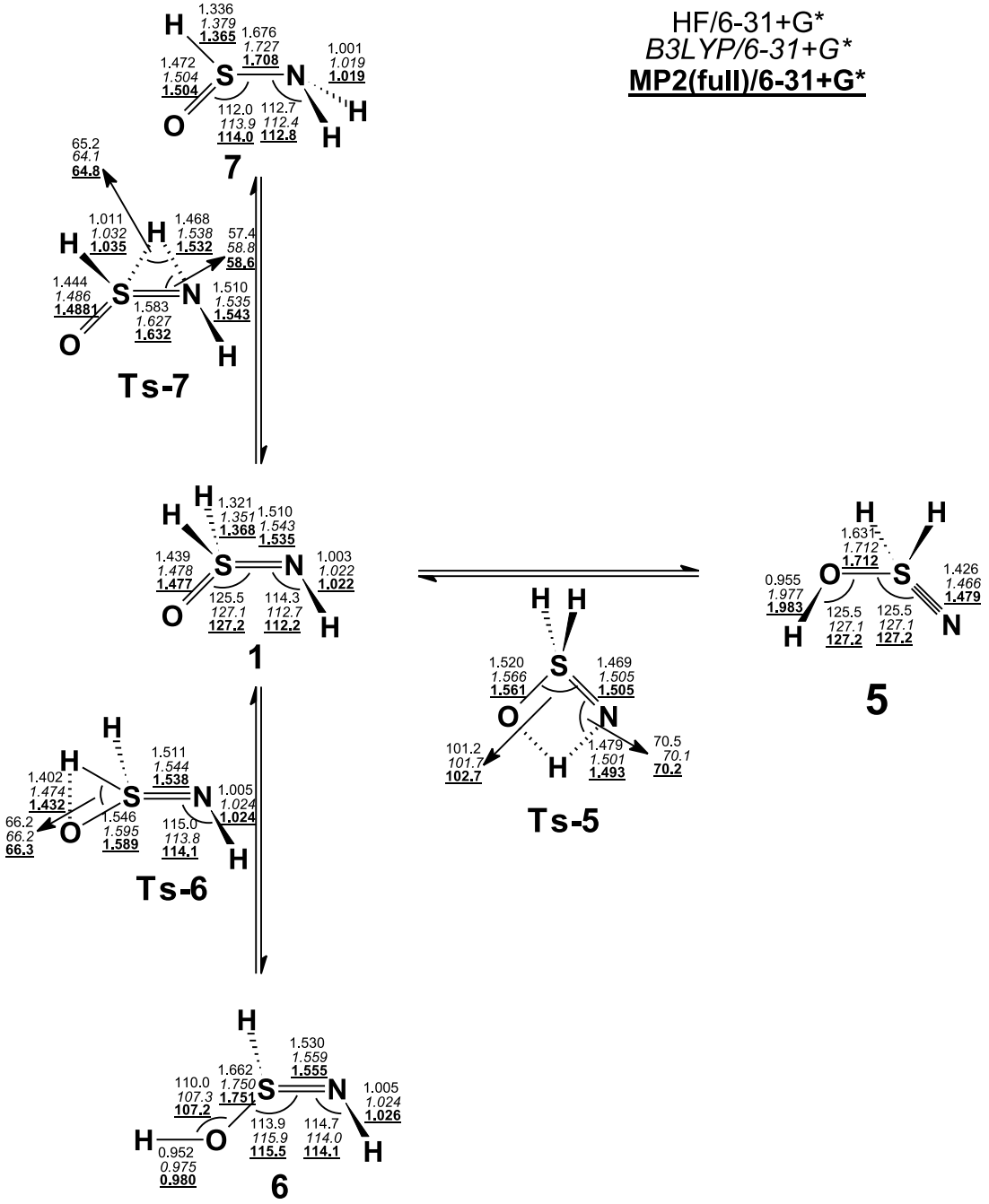


Figure 3. The structure and the geometrical parameters of the various isomers obtained from sulfoximines through 1,2-H shift (**6**, **7**) and 1,3-shift (**5**) at HF, B3LYP and MP2(Full) (using 6-31+G* basis set) (distances in a.u, angles in degrees).

There are many other isomers of **1** with well defined structures. For example, **6** is a sulfilimine and **7** is a sulfinamide. Sulfilimine **6** is more stable than **1** by about 26.00 kcal/mol. 1,2-H Shift between **1** and **6** goes through a barrier of 51.04 kcal/mol MP2(full)/6-31+G* level. Similarly, sulfinamide **7** is more stable than **1** by about 44.13 kcal/mol and the corresponding 1,2-H shift goes through a barrier of 37.21 kcal/mol (Figs. 3 and 4, Table 5). It is intriguing to note that in **1**, 1,2-H shift barriers are less than 1,3-H shift barrier. This can be attributed to the hypervalent nature of sulfur. Considering this, it may be suggested that performing gas phase rearrangements under matrix isolated conditions on **1** may be taken up similar to the studies on thionylimide.[20]

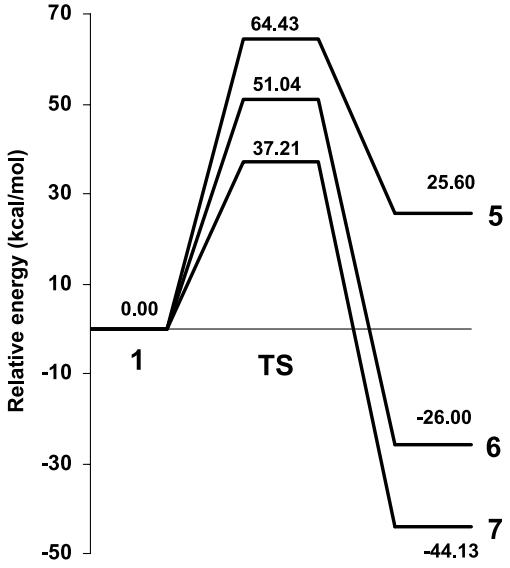


Figure 4. PE surface representing **1**⇌**5**, **1**⇌**6** and **1**⇌**7** rearrangement processes at MP2(full)/6-31+G* level. See Table 5.

Table 5. Relative energy (kcal/mol) of various isomers **5**–**7** obtained by 1,2-H shift and 1,3-H shift

Molecule	HF	B3LYP	MP2
1	0.0	0.0	0.0
5	37.67	28.06	25.60
6	−25.33	−27.44	−26.00
7	−48.29	−44.98	−44.13
TS-5	81.37	65.03	64.43
TS-6	70.28	49.73	51.04
TS-7	55.85	36.12	37.21

4. Conclusions

The structural aspects, charge distribution and S–N rotational barrier in sulfoximine $R_2S(=O)=NR$ **1**–**4** have been studied using ab initio molecular orbital calculations. The estimated S–N rotational barriers are ~6–14 kcal/mol at G2 level. The short S–N distances (1.535–1.582 Å) observed in these molecules can be attributed to the electrostatic attractions between S (1.764) and N (−1.253) rather than π character. This explains the shortening of S–N bond length in sulfoximine in relation to other systems with formal S=N double bond. The high rotational barriers in sulfoximines are due to severe lone-pair lone-pair repulsions between oxygen and nitrogen as well as due to the breaking of anomeric π interaction. Sulfoximines have a tendency to prefer a torsional angle of 60° between O–S–N–R, which can be attributed to stabilisation due to negative hyperconjugation in these systems arising from the two lone pairs on nitrogen. Computational studies on 1,2-H shift (**6**, **7**) and 1,3-shift (**5**) rearrangement on the model of sulfoximine **1** also have been studied. The ΔE between **1** and its isomers **5**, **6** and **7** are 25.6, −26.00 and −44.13 kcal/mol, respectively. The barriers for **1**→**5**, **1**→**6** and **1**→**7** isomerisation are 64.43, 51.04 and 37.21 kcal/mol, respectively.

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19. The stationary points near 0, 60 and 180° could be easily located on all the systems. Stationary points near 120° could be located for all systems at HF/6-31+G* level. However, the stationary points at ~120° could not be successfully located for $H_2(O)S{=}NH$ and $H_2(O)S{=}NMe$ at MP2 and B3LYP levels using any of the transition state (Berny, EF, QST2, QST3) location options in Gaussian package. This is because of a very shallow minimum available at about ~180° for O–S–N–R using MP2 and B3LYP methods. Since the two minima near 60 and 180° could be successfully located at all methods, but the TS at ~120° could be located at only HF method, the reported energies for the ~120° structure for $H_2(O)S{=}NH$ and $H_2(O)S{=}NMe$ are using extrapolated values. For **1b**, extrapolated relative energy values at B3LYP and MP2 levels have been obtained by adding 0.02 (ΔE **1c**–**1b** at HF/6-31+G* level) to relative energy of **1c**. Similarly for **2b** the extrapolated relative energy values at B3LYP and MP2 levels have been obtained by adding 0.32 (ΔE **2c**–**2b** at HF/6-31+G* level) to the relative energy of **2c**.
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Conformational analysis of new 14-membered ring diketal dilactam macrocycles: molecular mechanics, liquid and solid state NMR studies

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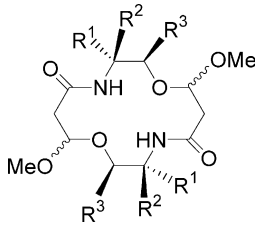
Abstract—A conformational study of new diversely substituted 14-membered diketal dilactam macrocycles was conducted by NMR spectroscopy in liquid and solid states, molecular mechanics calculations and, for one compound, a previous X-ray analysis. The results obtained by the different techniques show that the conformations depend closely on whether the molecules are chiral or achiral and on the stereochemistry of the ketal OMe groups. In achiral compounds, the most stable conformation of each compound has, in both the liquid and solid states, the two NH–CO links positioned perpendicular to the macrocycle plane, lending to the *trans*-7,7′–OMe macrocycles **6b** and **7b** a rectangular [3434]-type structure. In contrast, in chiral compounds, the most stable conformations are not the same in the liquid and solid phases. In the liquid state the conformations are set by the presence of one or two N_4–H···$O_{1'}$, $N_{4'}$–H···O_1 intramolecular hydrogen bonds that position the amide group parallel to the macrocycle plane, whereas in the solid state the amide moieties again adopt a perpendicular position which can be stabilized, when the 3-R substituent is not too bulky, by intermolecular N–H···O=C bonds between parallel sheets, and exceptionally, in the *cis*-7,7′-OMe-3,3′-Ph compound **1c**, by a π–π stacking effect between the phenyl groups.

1. Introduction

In the last four decades, conformational analysis of macrocyclic compounds has attracted increasing interest, partly because of the insight it brings on the physical and chemical properties of these systems.

For some years we have been interested in the synthesis[1] and in cationic recognition properties[2] of new diversely substituted 14-membered ring compounds bearing diketal and dilactam functions (Scheme 1). The conformational preferences of these macrocycles according to the nature of their substituents should help to account for the differences observed in their binding abilities. The complexity of the molecules, due to the presence of two different functions and of various substituents, prompted us first to search the literature for proposed shapes for these structures, beginning with the unsubstituted 14-membered ring cycloalkane, cyclotetradecane.



Scheme 1.

The conformation of cyclotetradecane was thoroughly investigated using, successively, qualitative analysis,[3] semi-quantitative enthalpy calculations,[4] low temperature NMR,[5] X-ray diffraction,[6] solid state ^{13}C NMR,[7] molecular mechanics methods[8] and vibrational spectroscopy.[9] These studies show that c-$C_{14}H_{28}$ occurs in the solid state as an ordered crystalline phase with a single conformation,[6,7] but in the liquid state the cycloalkane ring loses its conformational homogeneity and occurs in several conformations, among which the crystal conformation is largely

Keywords: Diketal dilactam macrocycles; Conformational analysis; Computational studies; Liquid and solid state NMR.
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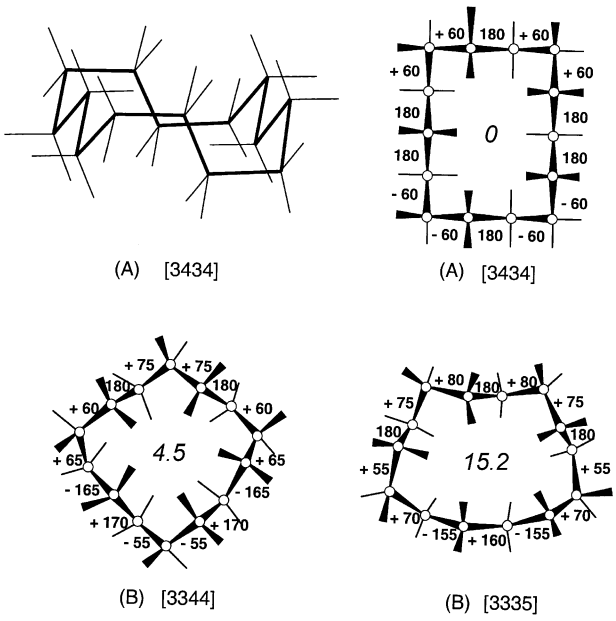


Figure 1. Representations of cyclotetradecane: (A) Side view and top view of the [3434] rectangular conformer;[3a,4] (B) Top views of the [3344] and [3335] quadrangular conformers.[3a] Positive and negative numbers refer to the ring torsion angles[3a] and italic numbers to the relative conformational strain energies (kJ mol^{-1}) given by Snyder[9] after readjustment of the first values calculated by Dale.[4a]

predominant.[4,5,8,9] This first conformer of lowest energy, designated [3434][†] or gtggttg′g′tg′g′ttg[‡] according to Dale′s[4] and Snyder′s[9] respective conventions, possesses the ideal strain-free 'rectangular' diamond lattice structure,[3,4,10a] with four 'corners' corresponding to gg or g′g′ sequences and two parallel long chains roughly at van der Waals distance linked at each end by C_2 bridges in a perspective drawing (Fig. 1).[3] Among the conformers detected at higher energy, the second and the eighth ones, named [3344] or gtggtggttg′g′ttg and [3335] or gtggtggtggtttg, respectively, present a 'quadrangular' conformation.[4a,9] The unsymmetrical arrangement gg′ or g′g of two *gauche* bonds of opposite sign, generally excluded in open chains by the 1,5 pentane interaction,[4a] but apparently very common in medium rings,[8] is encountered in several conformers, from the fourth to the seventh, with an increase to $\approx 100°$ of one of the two dihedral angles.[8,9]

Simple substituents on cyclotetradecane are assumed not to influence the conformation of the ring itself, except by their bulk.[3a] An alkyl group, particularly a *gem*-dimethyl group, would be preferentially located in a corner position of the rectangular cyclotetradecane and a symmetrical bi-*gem*-dimethyl substitution would favour the diamond-lattice conformation.[11,12] Replacement of a $–CH_2–$ group by –O–, –NR–, –C═O, –C═N–OH, etc. is considered to cause minimal perturbations[3a] and gives the same [3434] conformational preference for: (i) 1-oxa-,[13] 1,3,8,10-tetraoxa-,[14] 1,8-diaza-,[10b,15] and 1,8-dihydroxy-1,8-diaza-[10b,16] cyclotetradecanes, (ii) cyclotetradecanone,[17,18] cyclotetradecane-1,8-dione,[11,19] cyclotetradecane oxime[20] and tridecanolactone.[21]

Insertion, into the saturated ring chain, of an amide linkage which presents a partial double-bond character, induces some strain in the molecule. The torsion angles adjacent to the amide group are expected to be about 60 and 120° for the extreme case.[22,23] Between the two possible configurations of the NH–CO function, the *trans* one (H *anti* to the carbonyl oxygen atom) is strongly favoured[3b] and is in fact the exclusive conformation for *n*-membered ring lactams in which $n \geq 11$.[24] Studies of 1-azacyclotetradecane-2-one by low temperature NMR point to the presence in solution of at least two main conformers, while molecular mechanics calculations describe four possible structures (Fig. 2).[24] The two conformers **A** and **B** of lowest energy present a [3434] shape with a *trans* amide group located on a 'four-bond' side. In contrast, in the two structures **C** and **D**, the amide function is accommodated in a 'three-bond' side and the conformation **D**, deriving from **C** by a NH–CO moiety rotation eliminating two corners, is considered less favourable. Similarly, X-ray studies of substituted 14-ring monolactams reveal conformations derivable from the above shapes, as described by reports on two naturally-occurring substances.[25,26]

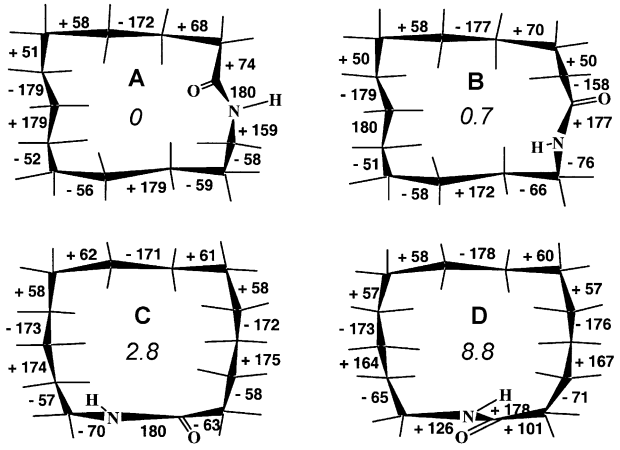


Figure 2. Top view representations of the 1-azacyclotetradecane-2-one conformers.[24] Positive and negative numbers refer to the ring torsion angles and italic numbers to the relative conformational strain energies (kJ mol^{-1}).

The X-ray diffraction of the symmetrical dilactam 1,8-diazacyclotetradecane-2,9-dione shows a centrosymmetric ring structure with the opposite NH–CO links on the short 'sides' and adjacent angle values close to those observed in the monolactam conformer **D**.[27,28] The planes containing the amide groups are perpendicular to the average macrocyclic ring and the molecules are linked together in

[†] In Dale′s convention,[4] the numbers in brackets indicate the number of C–C bonds between corner carbon atoms starting with the shortest.[4,9] Thus the [3434] conformer has two 'three-bond' sides and two 'four-bond' sides.

[‡] In Snyder′s designation,[9] the letters g, g', t, corresponding to *gauche* and *trans* bonds, refer to dihedral angles varying significantly from +60°, −60°, 180°. They include the following ranges: [+45°≤g ≤ +105°, −45° ≤ g' ≤ −105°, ±165°≤ t≤ ±180°] for cyclotetradecane[8,9] and [+50°≤g≤+126°, −50°≤g'≤ −126°, ±158° ≤t≤ ±180°] for 1-azacyclotetradecan-2- one (14-membered ring monolactam) (vide infra).[24] In our study, we have adopted the following convention: +20°≤g≤ +116–120°, −20°≤g' ≤ −116–120°, ±116–120°≤t≤ ±180°.

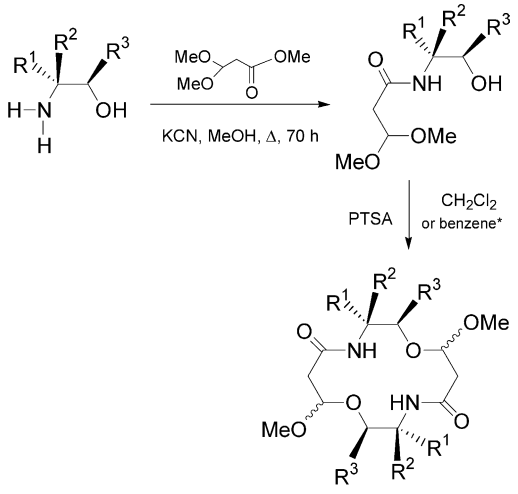
parallel sheets by intermolecular N–H···O═C hydrogen bonds.

Concerning the 14-membered ring compounds we are interesting on, they include, besides the two symmetrical lactam functions, two infrequently encountered hybrid ketal groups with endo- and exo-cyclic oxygens that would be expected to have a strong influence on the shape of the molecules (Scheme 1). Conformational investigations were conducted by: (i) NMR spectroscopy both in solution (^{13}C and ^{1}H NMR, NOE difference) and in the solid state (^{13}C SSNMR), (ii) molecular mechanics calculations (Monte Carlo simulations) using the AMBER force field, (iii) X-ray crystallography of one macrocycle. The data obtained in this last case were compared with those deduced from the SSNMR study of the same compound. This powerful technique,[29] which offers the advantage of being easier to handle than XR diffraction, is particularly useful for studying molecular conformations that rapidly equilibrate in solution but are 'frozen out' in the crystalline state. The results obtained by the different approaches will be compared.

2. Results and discussion

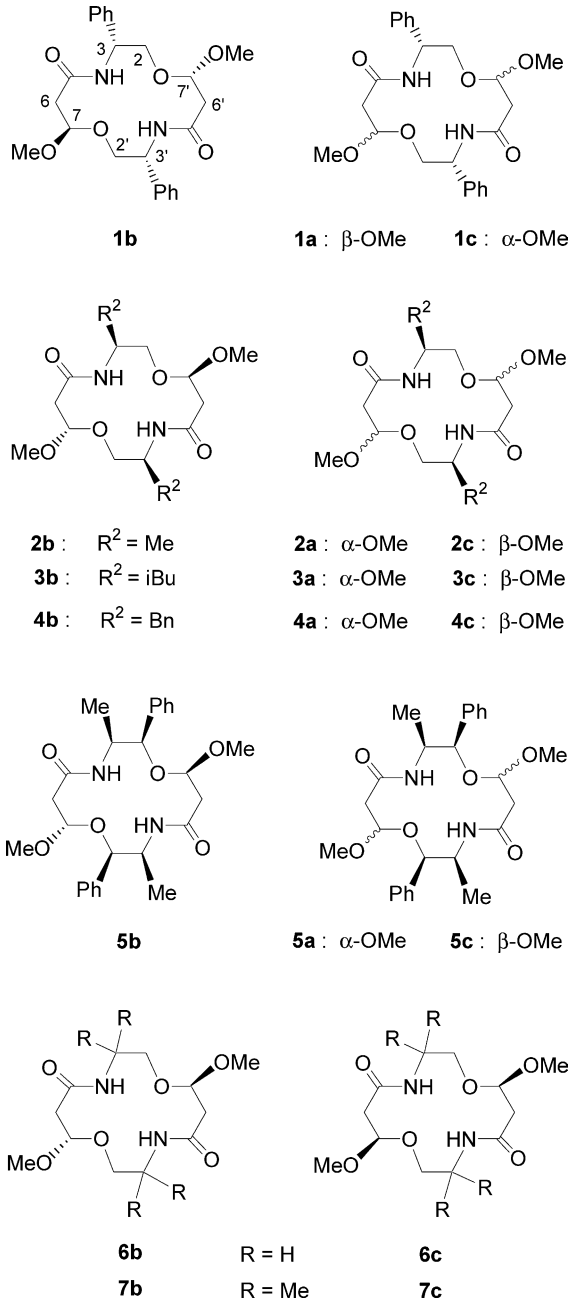
Macrocyclic diketal dilactams **1–7** were prepared in two steps from β-aminoalcohols.[1] The macrocyclization strategy was based on a [1+1] cyclocondensation by *trans*-acetalization in acidic conditions of hydroxyamidoketals bearing a *trans*-amide group (Scheme 2).[1b]

Fourteen-membered macrocycles were generated under different diastereoisomeric forms depending on the chiral



R-(-)-phenylglycinol	: R^1 = Ph; R^2 = R^3 = H	**1**
S-(+)-alaninol	: R^2 = Me; R^1 = R^3 = H	**2**
S-(+)-leucinol	: R^2 = iBu; R^1 = R^3 = H	**3**
S-(-)-phenylalaninol	: R^2 = Bn; R^1 = R^3 = H	**4**
1*R*,2*S*-(-)-norephedrine	: R^1 = H; R^2 = Me; R^3 = Ph	**5**
Aminoethanol	: R^1 = R^2 = R^3 = H	**6**
Dimethylaminoethanol	: R^1 = R^2 = Me; R^3 = H	*7

Scheme 2.



Scheme 3.

or achiral character of the starting β-aminoalcohols (Scheme 3).

The chiral series provided three diastereoisomers: an unsymmetrical isomer **b**, in which the two OMe substituents are in a *trans* configuration and two isomers **a** and **c** of C_2 symmetry, in which the two OMe groups are in a *cis* arrangement, **a** and **c** differing from each other, respectively, by the *trans* or *cis* relationship of the OMe and R groups. The achiral series led to two isomers **b** and **c** that both possessed some symmetry (center in **b**, C_2 axis in **c**).

2.1. Liquid NMR studies

Complete assignments of the liquid NMR spectra of all the macrocycles were previously reported.[1] In ^{13}C and ^{1}H

Table 1. Liquid ^{13}C NMR chemical shifts (δ in ppm) of macrocycles **1–7**

Compound	Carbon					
	C_6	C_3	OMe	C_2	C_7	CO
1a	40.0	52.5	54.5	67.6	100.1	167.9
1b chain 1	39.8	51.9	53.8	70.1	99.8	168.0
chain 1′	41.3	52.4	52.7	67.1	101.0	168.4
1c	41.2	52.5	53.2	70.5	101.2	168.4
2a	39.9	44.8	54.4	66.8	99.9	167.9
2b chain 1	39.4	44.2	54.2[a]	71.0	99.7	167.8
chain 1′	41.9	44.6	52.8[a]	65.7	101.3	168.3
2c	41.5	44.7	52.7	70.4	100.9	168.3
3a	39.4	46.7	54.9	64.6	99.7	167.8
3b chain 1	39.0	46.9	54.8[a]	70.3	99.6	167.7
chain 1′	42.1	46.3	52.6[a]	63.8	101.5	168.5
3c	41.6	47.0	52.8	69.6	101.2	168.4
4a	40.3	50.1	54.4	65.4	100.3	168.0
4b chain 1	39.9	49.6	53.8[a]	68.3	100.0	167.9
chain 1′	42.1	49.6	53.7[a]	65.1	101.6	168.5
4c	41.5	50.1	53.8	67.7	101.4	168.3
5a	40.6	50.1	56.5	78.0	98.6	167.9
5b chain 1	40.8	50.8	54.9	81.6	98.1	168.2
chain 1′	41.8	49.0	55.1	77.5	102.2	168.5
5c	40.9	47.9	54.6	80.7	100.0	167.8
6b	40.6	39.0	53.9	64.6	100.6	168.8
6c	41.1	39.2	53.4	66.1	100.9	169.1
7b	42.2	53.6	53.0	73.3	100.8	168.6
7c	41.9	53.5	54.2	72.8	101.3	168.5

[a] Values which may be inverted.

NMR, chiral isomers **a** and **c** and achiral compounds **b** and **c** showed one signal for each pair of identical groups of the macrocycle, while chiral isomers **b** exhibited double signals owing to the asymmetry of the two ring chains, which could be clearly distinguished using two-dimensional NMR and INEPT long-range experiments.[1b,30]Comparison of these NMR data (chemical shifts, coupling constants, NOE difference) was used in a first approach to the conformation of the diketal dilactams studied.

2.1.1. ^{13}C NMR. Chemical shifts are collected in Table 1. For each carbon, a small variation in shielding is observed depending on the nature of the substituents R^1, R^2 and R^3 and on the stereochemistry of the OMe group. The 3-monosubstituted compounds **1**–**4** display the following features: (i) the ring carbons C_6, C_2, C_7 and CO appear at higher field and the OMe groups at lower field in isomers **a** than in isomers **c**, (ii) identical effects occur between chain 1 and chain 1′ of isomers **b** except for carbons C_2, which show

Table 2. Liquid NMR chemical shifts and patterns of protons H_7, H_{6A}, H_{6B} in compounds **1–7**

Compound	H_7 δ (ppm)	H_{6A} δ (ppm)	H_{6B} δ (ppm)	Pattern[a]	$\Delta\nu=\nu_{6A}-\nu_{6B}$ (Hz)
1a	4.77	2.80	2.58	3dd	89.0
1c	4.78	2.64	2.62	ABX	5.0
1b chain 1	4.77	2.86	2.56	3dd	120.3
chain 1′	4.82	2.60	2.59	ABX	3.7
2a	4.77	2.74	2.55	3dd	98.0
2c	4.69	2.58	2.54	ABX	17.4
2b chain 1	4.74	2.77	2.50	3dd	108.0
chain 1′	4.75	2.56	2.53	ABX	11.6
3a	4.78	2.75	2.54	3dd	87.0
3c	4.65	2.55	2.53	ABX	10.9
3b chain 1	4.74	2.79	2.50	3dd	114.0
chain 1′	4.73	2.55	2.51	ABX	14.3
4a	4.64	2.70	2.47	3dd	92.0
4c	4.63	2.55	2.55	ABX≈d+t	0
4b chain 1	4.63	2.76	2.47	3dd	115.0
chain 1′	4.65	2.52	2.45	ABX	28.3
5a	4.55	2.78	2.76	ABX	6.1
5c	4.95	2.77	2.65	ABX≈3dd	47.6
5b chain 1	4.49	2.83	2.65	3dd	72.6
chain 1′	4.89	2.77	2.65	ABX≈3dd	49.8
6b	4.77	2.66	2.56	ABX≈3dd	43.1
6c	4.69	2.63	2.59	ABX	34.5
7b	4.70	2.55	2.45	ABX	39.8
7c	4.70	2.60	2.49	ABX≈3dd	44.1

[a] ABX system for $\Delta\nu<5\times J_{6A-6B}$ with $J_{6A-6B}=13.4$–16.1 Hz.

Table 3. Coupling constants (J in Hz) of compounds **1-7** in liquid ^{1}H NMR

Compound[a]	$\lvert J_{3\text{-}2A}\rvert$	$\lvert J_{3\text{-}2B}\rvert$	$\lvert J_{7\text{-}6A}\rvert$	$\lvert J_{7\text{-}6B}\rvert$
1a	3.2	4.4	7.2	2.1
1b chain 1	3.1	3.3	8.4	1.7
chain 1′	3.2	5.5	1.6	9.0
1c	4.9	3.3	9.7	0.3
2a	3.2	4.3	7.5	2.1
2b chain 1	2.1	2.7	8.6	1.8
chain 1′	2.7	4.3	1.9	9.3
2c	3.2	2.9	8.5	2.2
3a	2.8	2.8	7.9	2.2
3b chain 1	1.4	2.7	8.7	1.7
chain 1′	2.6	0.5	2.1	9.3
3c	2.6	2.6	8.3	1.8
4a	3.0	4.0	6.6	2.0
4b chain 1	2.5	3.0	7.9	1.8
chain 1′	3.0	4.8	2.1	8.7
4c	3.2	3.0	4.7	4.7
5a	2.7		3.6	1.2
5b chain 1	2.0		6.1	0.5
chain 1′	3.0		6.7	1.8
5c	2.9		2.6	5.2
6b[b]	3.0	6.8	8.3	2.0
	6.0	2.6		
6c[b]	4.5	2.1	8.2	1.8
	2.9	9.2		
7b	-	-	8.3	1.9
7c	-	-	7.1	2.2

[a] For all compounds $\lvert J_{2A\text{–}2B}\rvert$ = 8.8–10.0 Hz; $\Delta\nu = \nu_{2A} - \nu_{2B}$ = 76–184 Hz.
[b] First line: $J_{3A\text{–}2X}$; second line: $J_{3B\text{–}2X}$.

an upfield shift in chain 1′, (iii) in isomers **b**, chemical shift values of carbons C_6, C_7, CO and OCH_3 (chain 1) are nearly identical to those of isomers **a**, while carbon δ values of chain 1′ are close to those of isomers **c**.

These observations suggest that in each series, the variations in shielding depend essentially on the stereochemistry of the OMe group. Thus a *trans* relationship between OMe and the R^1 or R^2 substituents as it exists in isomers **a** and in chain 1 of isomers **b** induces shielding of the nearest carbons C_7, C_6, C_5 and $C_{2'}$ while a *cis* relationship as it exists in isomers **c** and in chain 1′ of isomers **b** causes deshielding of carbons $C_{7'}$, $C_{6'}$, $C_{5'}$ and C_2.

2.1.2. ^{1}H NMR. Firstly, a careful analysis of the splitting of H_{6A} and H_{6B} due to coupling with the H_7 proton (Table 2) reveals that in 3-monosubstituted compounds **1**–**4**, these hydrogens appear as a doublet of doublet in each isomer **a** and as an ABX system in each isomer **c**. An identical splitting difference of protons H_{6A} and H_{6B} is also observed between the two chains of isomers **b**. In fact, H_{6A} hydrogens in **1a**–**4a** and **1b**–**4b** (chain 1) are curiously deshielded ($\Delta\delta \approx +0.16 - +0.30$ ppm) compared with all the other H_6 protons. This effect may be due to a greater proximity of H_{6A} and the OMe oxygen lone pair in these cases. This hypothesis is supported below. In the norephedrine series in which the macrocycles have two substituents (R^2 = Me and R^3 = Ph), the same observations can be made regarding the two chains of compound **5b**. In contrast, and surprisingly, an inversion occurs in the splitting of **5a** and **5c** that is a real ABX system for **5a** and an ABX system close to 3dd ($\Delta\nu \approx 3 \times J_{6A\text{-}6B}$) for **5c**. This last pattern is also present in achiral compounds **6b** and **7c**.

Secondly, examination of coupling constants of H_3 and H_7 with their vicinal hydrogens provides information on their position in the ring (Table 3). Thus, in all the compounds, H_3 hydrogens whose both coupling constants have small values ($J_{3\text{-}2A}$ = 1.4–4.9 and $J_{3\text{-}2B}$ = 0.5–5.5 Hz) probably occupy an equatorial position bisecting the dihedral angle H_{2A}–C–H_{2B}. Similarly, H_7 protons, which in most compounds have widely different J values ($J_{7\text{-}6ax}$ = 4.7–9.7, $J_{7\text{-}6eq}$ = 0.3–4.7 Hz), very likely occupy an axial position with axial–axial and axial–equatorial coupling constants, respectively. One exception is, however, observed for **5a** in which H_7 protons show closer J values (3.6 and 1.2 Hz) corresponding to a pseudo-axial or equatorial position of H_7 due to a modification of the ring shape.

Thirdly, a complementary study by the ^{1}H–^{1}H nuclear Overhauser effect (NOE) was made on compounds **1c**, **2c**, **6c** and **7c** to obtain further information on the spatial interactions. Irradiation of H_7 produces nuclear Overhauser enhancements on: (i) H_{6B} for which a differentiated effect with regard to H_{6A} is clearly visible on compounds **6c** and **7c** but not on compounds **1c** and **2c**, the $\Delta\nu$ values being

Table 4. (a) In normal characters: nuclear Overhauser effects (%) observed on protons H_x by irradiation of H_7 for compounds **1c**, **2c**, **6c**, **7c**; (b) in italic characters: interatomic distances $d_{H_7\text{–}H_x}$ (Å) measured by molecular modeling

Compound	Proton		
	H_{2A}	H_{2B}	H_{6B}
1c	0.0%	3.6%	5.0%
	2.93	*2.41*	*2.52*
2c	1.0%	3.7%	4.2%
	2.89	*2.42*	*2.52*
6c	0.5%	4.0%	3.1%
	2.92	*2.38*	*2.53*
7c	0%	3.9%	5.2%
	2.91	*2.36*	*2.53*

large in the first case and small in the second case (Table 2), (ii) H_{2B} whereas no appreciable effect is observed on H_{2A} (Table 4). This last result points to a partial strain in the assumed high flexibility of the macrocycles which would produce an effect on both H_2 protons. In contrast, the observed NOE indicates that H_7 must be *cis* to H_{2B} and *trans* to H_{2A}. Taking into account the axial position of H_7 and the equatorial position of H_3 in **1c** and **2c** (see above), these results identify H_{2A} as H_{2eq} and H_{2B} as H_{2ax} in all isomers **c**, in particular in the 3-disubstituted compound **7c**, for which J_{3-2} coupling constants are not available.

2.2. Molecular modeling

The Monte-Carlo calculations indicate a certain flexibility of these macrocyclic ligands, for which ten conformations are generally observed within 4–13 kJ mol^{-1} of the global minimum (Supplementary material SM). However, in around 60% of cases (11/19), a greater energy difference is observed between the first two conformers than between the five following ones taken two by two ($\Delta E_{2-1} > \Delta E_{3-2}$ or ΔE_{4-3} or ΔE_{5-4}). Hence, because a detailed comparison of all the conformers would have been tedious and difficult, the modeling study was conducted, for most of the compounds, on the first conformer of lowest energy, and only exceptionally on the following ones.

The calculated H–H dihedral angles (SM) for conformer **1** of most of the chiral compounds (**1a–c**, **2a–c**, **3b**,**c**, **4c**, **5a**,**c**) point to: (i) an equatorial position of H_3 bisecting the angle H_{2ax}–C–H_{2eq} ($\theta_{H_3,H_{2ax}} = 33–63°$ and $\theta_{H_3,H_{2eq}} = 54–85°$) and corresponding to an axial position of the 3,3′-R groups (α-axial in **1**, β-axial in **2–5**) and to an equatorial position of the 2,2′-Ph substituents in macrocycles **5a** and **5c**, (ii) an axial position of H_7 ($\theta_{H_7,H_{6ax}} = 168–180°$) corresponding to an energetically favourable equatorial position of the α or β-OMe groups. These observations, not made in the first conformer of **3a** and **4a**, are consistent, however, with the second conformer. These results agree with the above ^1H NMR data: equatorial and axial characters of H_3 and H_7, respectively. The preferential 3-R substituent axial position and the preferential OMe group equatorial situation may produce a partial strain in these otherwise flexible compounds, as suggested by the NOE results (vide supra). Two exceptions are, however, to be noted for the chain 1′ of macrocycles **4b** and **5b**, in which $H_{3'}$ or $H_{7'}$ or both protons occupy an opposite situation on the first conformers, while the above conformation ($H_{3'eq}$ and $H_{7'ax}$) occurs only on conformer 5 of **4b** and on conformer 8 of **5b**. In the NMR spectrum of **4b**, the $J_{3'\text{-}2'B}$ value (4.8 Hz), which corresponds to the maximum of the observed $J_{3\text{-}2}$ values, is consistent with an equilibrium between the conformers of lowest energy. Also, the assumed equatorial position of H_7 in compound **5a** (see above) is confirmed for the chain 1′ of the second conformer ($\theta_{H_{7'},H_{6'ax}} = 55°$ and $\theta_{H_{7'},H_{6'eq}} = 62°$).

Measurements of the H_6–OMe interatomic distances indicate a shorter $d_{H_{6ax}-OMe}$ for compounds **a** and **b** (chain 1) (2.69–2.76 Å) than for compounds **c** and **b** (chain 1′) (2.80–2.87 Å) (SM). These indications are evidenced in most of conformers 1 (**1a–c**, **2a–c**, **3b–c**, **4c**, **5a**,**c**), in conformer 2 of **3a** and **4a**, in conformer 5 of **4b** and in conformer 8 of **5b**. They are consistent with the deshielding observed for H_{6A} in compounds **a** and **b** (chain 1) (see above) that is to say in the chain in which the 7-OMe group is in a *trans* relationship with the 3-R substituent. C–C dihedral angles of the 19 macrocycles are given in Table 5. All exhibit invariable transoid conformations along the two bonds C_3–N_4–CO–C_6 corresponding to the amide links (torsions: 172–180°) and the two bonds $C_{7'}$–O_1–C_2–C_3 (torsions: 121–180°), and *gauche* conformations along the bonds O_1–C_2–C_3–N_4 (torsions: 34–72°) and C_5–C_6–C_7–$O_{1'}$ (torsions: 50–75°). In contrast, the values of the C_2–C_3–N_4–C_5, N_4–C_5–C_6–C_7 and C_6–C_7–$O_{1'}$–$C_{2'}$ angles range from 22 to 180° and correspond to *gauche* or *trans* (*anti*) conformations depending on the macrocycle stereochemistry and the nature of the substituents.

In the achiral compounds, structures of the [3434]-type are observed for the symmetry center macrocycles **6b** and **7b** (structure Ib) in which the *trans*-OMe groups are accommodated in the two opposite corners C_7, $C_{7'}$, while the C_3, $C_{3'}$ carbons form the other two corners (Fig. 3). The O_1, $O_{1'}$ atoms, located on the 'three-bond' sides, point inwards into the ring. The *trans*-amide functions, situated on the 'four-bond' sides, are set perpendicular to the macrocyclic plane and display the conformationally more stable opposite orientation.[27] The rectangular diamond-lattice structure is magnified in compound **7b** (N_4–C_5–C_6–C_7, $N_{4'}$–$C_{5'}$–$C_{6'}$–$C_{7'}$ dihedral angles = ±145° in **6b**, ±172° in **7b**) by the presence in C_3, $C_{3'}$ of *gem*-dimethyl groups (see above).[11,12] In the *cis*-OMe isomers **6c** and **7c** (structure IIc), the potential rectangular shape is distorted compared with **6b** and **7b** by a ≈180° rotation of one NH-CO group, eliminating the C_7, $C_{7'}$ corners and causing the appearance in C_6 and $C_{6'}$ of g′g sequences accompanied by an increase to 95 or 119° of one of the corresponding dihedral angles as indicated above for some conformers of cyclotetradecane.[8] The NH–CO links are still perpendicular to the macrocycle, but in this case they are located on the pseudo three-bond sides and oriented in the same direction, in agreement with a C_2 symmetry, while the O_1 and $O_{1'}$ atoms, still pointing into the ring, now occupy the middle position of the four-bond side (Fig. 3).

In the chiral compounds **1–5**, the conformation of the molecules is modified, compared with the above shapes, by a 90° rotation of one or both NH–CO links, which take a position parallel to the average macrocycle plane, with the C═O and N–H bonds directed outwards from and inwards into the ring respectively. This arrangement allows the formation of intramolecular hydrogen bonds between the NH hydrogens and the endocyclic ketal oxygens of the other chain, which are invariably oriented inwards into the ring (Fig. 3). Thus while most of *trans* compounds **b** (**2b–5b**), exhibit only one N_4–H···$O_{1'}$ bond, *cis* macrocycles **a** and **c** are characterized in most cases [**1a–3a**, **1c–3c**, **4a** (conformer 2), **4c** (conformer 5), **5a**, **5c**] by the presence of two hydrogen bonds N_4–H···$O_{1'}$ and $N_{4'}$–H···O_1 consistent with a C_2 symmetry (SM).

All these molecules show gg′ or g′g arrangements for C_6, $C_{6'}$ with N_4–C_5–C_6–C_7 and C_5–C_6–C_7–$O_{1'}$ angles ranging from ±22 to ±122° (Table 5). They differ essentially in the values of the dihedral angles C_2–C_3–N_4–C_5 and

Table 5. C–C torsional angles ϕ (°) for macrocycles **1**–**7** ($+20° < g < +116$–$126°$; $-20° < g' < -116$–$126°$; ± 116–$126° < t < \pm 180°$

Macrocycle	ϕ														Nomemclature	Structure
	C7′–O1–C2–C3	O1–C2–C3–N4	C2–C3–N4–C5	C3–N4–C5–C6	N4–C5–C6–C7	C5–C6–C7–O1′	C6–C7–O1′–C2′	C7–O1′–C2′–C3′	O1′–C2′–C3′–N4′	C2′–C3′–N4′–C5′	C3′–N4′–C5′–C6′	N4′–C5′–C6′–C7′	C5′–C6′–C7′–O1	C6′–C7′–O1–C2		
1a conf 1	+153	+34	+152	−172	−62	+59	+177	+153	+34	+152	−172	−61	+59	+177	tgttg′gttgttg′gt	Enan Ia[a]
2a conf 1	−174	−52	−148	+179	+29	−62	−69	−174	−52	−148	+180	+29	−62	−69	tg′ttgg′g′tg′ttgg′g′	IIa
3a conf 1	+171	−53	−131	+177	+40	−69	+170	+172	+51	−160	−178	−49	+55	+167	tg′ttgg′ttgttg′gt	I′a
3a conf 2	−179	−54	−148	−179	+36	−64	−71	−174	−57	−130	−179	+22	−61	−72	tg′ttgg′g′tg′ttgg′g′	IIa
4aconf 1	−174	−48	−150	+175	+49	−69	+177	+174	+63	−165	+177	−66	+54	+169	tg′ttgg′ttgttg′gt	I′a
4a conf 2	+168	−62	−106	−178	+28	−64	−80	+168	−60	−109	+179	+32	−65	−80	tg′g′tgg′g′tg′g′tgg′g′	IIIa
5a conf 1	+138	−61	−80	+180	+40	−64	−78	+138	−61	−80	+180	+40	−64	−78	tg′g′tgg′g′tg′g′tgg′g′	IIIa
5a conf 2	+162	−49	−135	+175	+45	−68	+177	+167	+46	−166	−179	−44	+59	+166	tg′ttgg′ttgttg′gt	I′a
1b conf 1	−176	+49	+152	+178	−47	+66	+70	+170	+47	+156	+176	+58	−68	+177	tgttg′ggtgttgg′t	Enan IIb[a]
2b conf 1	+179	−54	−143	+180	+43	−66	−68	−168	−50	−147	−179	−65	+68	−174	tg′ttgg′g′tg′ttg′gt	IIb
3b conf 1	+177	−55	−143	−180	+48	−68	−68	−166	−53	−128	−179	−78	+68	−173	tg′ttgg′g′tg′ttg′gt	IIb
4b conf 1	+172	−60	−154	+177	+52	−69	+176	+174	+64	−159	+180	−76	+69	−180	tg′ttgg′ttgttg′gt	IIIb
4b conf 5	+166	−60	−99	−180	+28	−63	−76	+177	−62	−140	−172	−47	+67	+179	tg′g′tgg′g′tg′ttg′gt	IVb
5b conf 1	+143	−52	−151	+175	+62	−73	+177	+158	+59	−93	+179	−122	+70	−171	tg′ttgg′ttgg′tg′gt[c]	Vb[c]
5b conf 8	+116	−52	−74	+175	+47	−64	−79	+142	−72	−83	−170	−45	+68	−171	tg′g′tgg′g′tg′g′tg′gt[c]	VIb[c]
6b conf 1	+179	+60	+83	−179	+145	−60	−72	−180	−60	−83	+179	−145	+60	+72	tggttg′g′tg′g′tt′gg	Ib [3434]
7b conf 1	−172	+55	+61	−178	+172	−62	−75	+172	−55	−61	+178	−172	+62	+75	tggttg′g′tg′g′ttgg	Ib [3434]
1c conf 1	+176	+51	+155	+178	+47	−71	+175	+176	+51	+155	+178	+47	−71	+175	tgttgg′ttgttgg′t	Enan Ic[a]
1c XR[b]	−84	−62	+143	−179	+93	−70	+176	−84	−62	+143	−179	+93	−70	+176	g′g′ttgg′tg′g′ttgg′t	
2c conf 1	−174	−54	−147	−179	−50	+71	−174	−174	−54	−147	−179	−50	+71	−174	tg′ttg′gttg′ttg′gt	Ic
3c conf 1	−175	−58	−128	−178	−59	+71	−175	−175	−58	−128	−178	−59	+71	−175	tg′ttg′gttg′ttg′gt	Ic
4c conf 1	+170	−61	−127	−176	−45	+70	+179	−179	−64	−86	+178	−82	+73	−179	tg′ttg′gttg′g′tg′gt	IIIc
4c conf 5	+172	−62	−134	−175	−44	+69	−179	+180	−64	−116	−179	−58	+72	−180	tg′ttg′gttg′ttg′gt[c]	Ic[c]
5c conf 1	+121	−60	−78	−177	−41	+68	−176	+121	−60	−78	−177	−41	+68	−176	tg′g′tg′gttg′g′tg′gt[c]	IIc[c]
6c conf 1	−178	−59	−80	−180	−95	+72	−172	−178	−59	−79	−180	−95	+72	−172	tg′g′tg′gttg′g′tg′gt	IIc
7c conf 1	−179	−54	−59	+179	−119	+72	−172	−179	−54	−59	+179	−119	+72	−172	tg′g′tg′gttg′g′tg′gt	IIc

[a] Enan = Enantiomer of structure.

[b] X-ray angle data.

[c] Hybride structure for: **5b** conformer 1: tg′ttgg′ttgg′tg′gt (Vb) or tg′ttgg′ttgg′ttgt due to one hybride angle of 122°; **5b** conformer 8: tg′g′tgg′g′tg′g′tg′gt (VIb) or gg′g′tgg′g′tg′g′tg′gt due to one hybride angle of 116°; **4c** conformer 5: tg′ttg′gttg′ttg′gt (Ic) or tg′ttg′gttg′g′tg′gt (IIIc) due to one hybride angle of 116°; **5c** conformer 1: tg′g′tg′gttg′g′tg′gt (IIc) or gg′g′tg′gtgg′g′tg′gt due to two hybride angles of 121°.

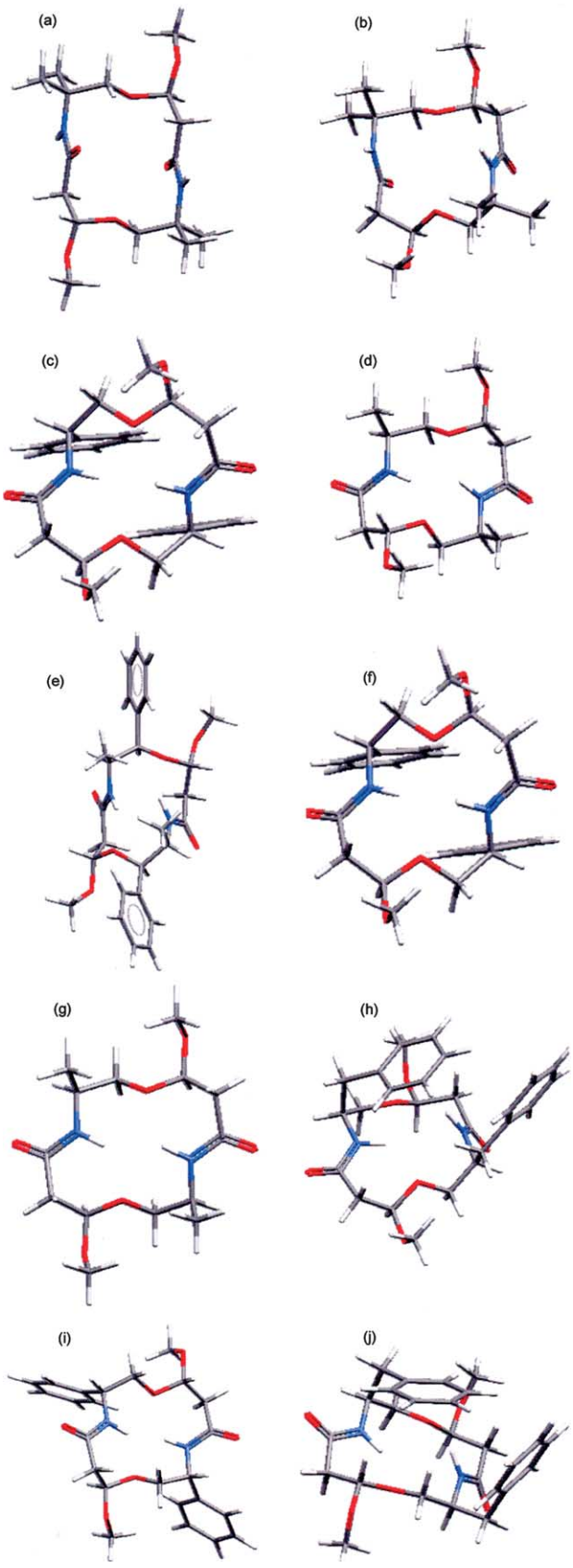


Figure 3. Top view representations of some diketal dilactam macrocycles (conformer 1) by molecular modeling: (a) **7b**: structure Ib, (b) **7c**: structure IIc, (c) **1a**: enantiomer of structure Ia, (d) **2a**: structure IIa, (e) **5a**: structure IIIa, (f) **1c**: enantiomer of structure Ic, (g) **2c**: structure Ic, (h) **4c**: structure IIIc, (i) **1b**: enantiomer of structure IIb, (j) **4b**: structure IIIb.

C_6–C_7–$O_{1'}$–$C_{2'}$ which can correspond to either a *trans* or a *gauche* conformation.

Thus chiral macrocycles **a** present four different structures: (i) structure Ia: tg′ttgg′ttg′ttgg′t (enantiomer of **1a**)[§] and structure I′a: tg′ttgg′ttgttg′gt (**3a** conformer 1, **4a** conformer 1, **5a** conformer 2) neither of which have a corner, and which present an identical chain 1, but which differ in the sign of the chain 1′ *gauche* angles, causing a loss of symmetry in I′a, (ii) structure IIa: tg′ttgg′g′tg′ttgg′g′ (**2a** conformer 1, **3a** conformer 2) characterized by the presence of corners at C_7, $C_{7'}$, (iii) structure IIIa: tg′g′tgg′g′tg′g′tgg′g′ (**4a** conformer 2, **5a** conformer 1) which has corners at C_3, $C_{3'}$ and C_7, $C_{7'}$.

Chiral compounds **c** present three different structures: (i) structure Ic: tg′ttg′gttg′ttg′gt, the most frequently observed (enantiomer of **1c**,[§] **2c**, **3c**, **4c** conformer 5), which has no corner; (ii) structure IIc: tg′g′tg′gttg′g′tg′gt (**5c** conformer 1) characterized by the presence of two corners at C_3, $C_{3'}$ as previously observed in achiral macrocycles **6c** and **7c**; the three compounds differ essentially in some lower dihedral angle values in **5c**: N_4-C_5—C_6-C_7', $N_{4'}$-$C_{5'}$—$C_{6'}$-$C_{7'}$ (95 and 119° in **6c** and **7c**, 41° in **5c**) and $C_{7'}$–O_1–C_2–C_3, C_7–$O_{1'}$–$C_{2'}$-$C_{3'}$ (178–179° in **6c** and **7c**, 121° in **5c** (limit value between *trans* and *gauche* conformations)]; (iii) structure IIIc: tg′ttg′gttg′g′tg′gt (**4c** conformers 1–4), which has a single corner at $C_{3'}$ with no symmetry, and which is composed of chain 1 of Ic and chain 1′ of IIc. Structures Ic, IIc and IIIc differ in the values of the four angles C_2–C_3–N_4–C_5, $C_{2'}$–$C_{3'}$–$N_{4'}$–$C_{5'}$ and C_6–C_7—$O_{1'}$–$C_{2'}$, $C_{6'}$–$C_{7'}$–O_1–C_2, as seen above.

Chiral macrocycles **b**, whose chain 1 possesses the stereochemistry of compounds **a** and chain 1′ the stereochemistry of compounds **c**, can adopt various combinations between structures Ia–IIIa and Ic–IIIc to give five different conformations IIb–VIb.

The representation of compounds with identical stereochemistry, for example macrocycles **c**, along a horizontal C_7–$C_{7'}$ axis, with the OMe groups at each extremity, allows an interesting comparison of the global shape of the skeletons in function of the nature of the substituent (Fig. 4). Thus, all molecules of structure Ic [enantiomer of **1c**, **2c**, **3c** (conformers 1) and **4c** (conformer 5)] adopt a nearly identical pseudo-planar shape, while molecules with structure IIc show a convex form, slight in **6c** and **7c**, and marked in **5c**.

2.3. X-ray crystallography

The previously determined crystal structure[1a] of macrocycle **1c** presents Ph and OMe substituents in an equatorial position. It shows a g′g′ttgg′tg′g′ttgg′t conformation close to that observed for **6c** and **7c** in molecular modeling (see

[§] Macrocycle **1a** with an *R* stereochemistry at C-3 and C-3′ corresponds to a tgttg′gttgttg′gt structure. To establish comparison with the 3-*S* compounds **2a**, **3a**, **4a** and **5a**, we have to consider the 3-*S* enantiomer of **1a**, the designation of which would be tg′ttgg′ttg′ttgg′t. Identical modifications have to be made for **1b** (tgttg′ggtgttgg′t) and **1c** (tgttgg′ttgttgg′t), enantiomers of which would have tg′ttgg′g′tg′ttg′gt and tg′ttg′gttg′ttg′gt structures, respectively.

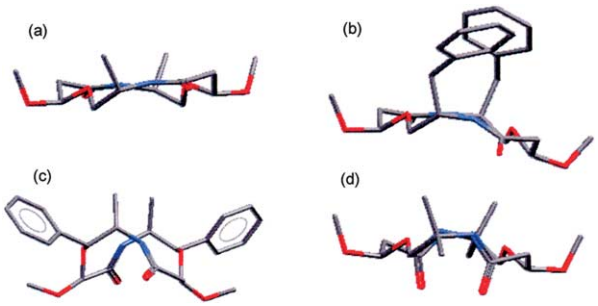


Figure 4. Representation by molecular modeling of some macrocycles **c** with a horizontal C_7–$C_{7'}$ axis: (a) **2c** conformer 1: structure Ic, (b) **4c** conformer 5: structure Ic, (c) **5c** conformer 1: structure IIc, (d) **7c** conformer 1: structure IIc.

above) and characterized by a C_2 symmetry, gg′ sequences at C_6, $C_{6'}$ and corners at C_2, $C_{2'}$ instead of C_3, $C_{3'}$, consequent to a shift of the pseudo three- and four-bond sides (Table 5). Besides, in comparison with **1c** (conformer 1), transoid conformations are also observed along the bonds C_2–C_3–N_4–C_5, C_6–C_7–$O_{1'}$–$C_{2'}$ and of course along the amide links, but in the crystal, the two $C_{7'}$–O_1–C_2–C_3 bonds correspond to a *gauche* conformation. Also, the O_1, $O_{1'}$ atoms still point into the ring but the NH–CO links, located on the pseudo four-bond sides are now perpendicular to the macrocyclic plane and oriented in the same direction (Fig. 5). This arrangement in the crystal allows, the formation of N–H···O=C intermolecular hydrogen bonds (2.95 Å) that link the molecules together into sheets parallel to the binary axis,[1a] while π–π stacking interactions between the phenyl groups may also reinforce the cohesion of the structure.

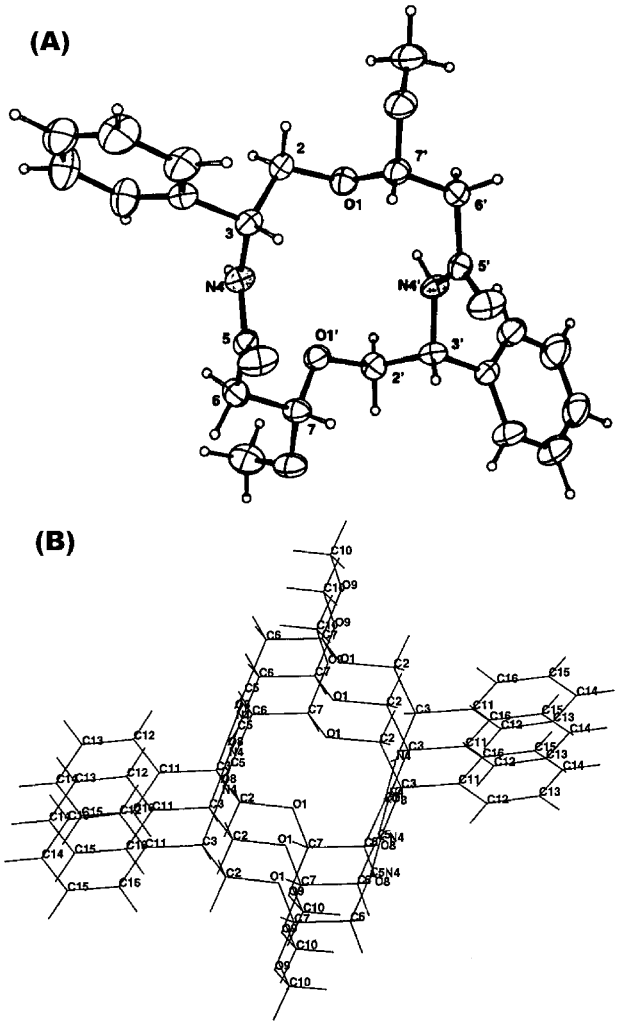


Figure 5. Phenyl macrocycle **1c**: (A) X-ray structure;[1a] (B) Stacking of the molecules in parallel layers.[1a]

2.4. Solid state NMR analysis

When no suitable crystals are available for an X-ray study, structural information concerning the solid state can be obtained by SSNMR. This technique, which unlike liquid NMR does not reflect an averaged conformation, permits the analysis of conformational constraints and polymorphic forms. Associated with magic angle spinning, the most common NMR experiment designed for this purpose is certainly the cross-polarization pulse scheme (CP-MAS), which allows a marked sensitivity enhancement and reduced acquisition time. Thus SSNMR spectra were first recorded for compounds **1a**, **1b** and **1c** to evaluate the effect of the relative positions of the 3,3′-R substituents (Ph in the present case) and the 7,7′–OMe groups on the ring conformation. Compounds **2c**, **3c**, **4c**, **6b** and **6c** were then analyzed to study the effect of the nature of the 3,3′-R substituent. Unfortunately, no suitable solid for NMR analysis was obtained for macrocycles **5**.

The solid state NMR spectra of the three phenyl isomers **1a–c** were recorded in the same conditions and compared with the corresponding liquid state ^{13}C NMR spectra, and for **1c** to its X-ray diffraction data.[1a] In agreement with the liquid state ^{13}C NMR spectra, isomers **a** and **c** show one signal for each pair of identical groups of the macrocycle, while isomer **b** exhibits double signals (Table 6).

Concerning isomer **1c**, the presence of a high symmetry is readily apparent in its ^{13}C CP-MAS spectrum which shows 10 signals for the twenty carbons (SM). Several very interesting singularities can be noted in comparison with the ^{13}C liquid spectrum: (i) deshielding ($\Delta\delta$+1.5 ppm) of the CO peak, which confirms the presence of intermolecular C=O···HN hydrogen bonds[31,32] as observed by X-ray diffraction analysis; (ii) shielding of the methoxy groups ($\Delta\delta$ −6.4 ppm), which can be distinguished from C_3 carbons by dipolar dephasing experiments[¶,33] and by comparison of the signal shape (sharp singlet for OMe and broadened singlet for C_3 due to a quadrupolar coupling with the a ^{14}N atom);[34] (iii) shielding of C_7 ($\Delta\delta$ −6.2 ppm) and C_3 ($\Delta\delta$ −1.2 ppm) carbon signals due to a γ-*gauche* effect known to give substantially shielded ^{13}C resonances[35–37] and resulting from $C_{7'}$–O_1–C_2–C_3 *gauche* conformations, present in the solid state (torsions: 84° from X-ray data) and not in the liquid state (torsions: 176° from molecular modeling data). Complementary NMR experiments were conducted on this isomer by varying the

¶ Dipolar dephasing induces fast dephasing of protonated carbon signals (CH, CH_2) except for those of CH_3 groups which have a higher 'mobility'.

Table 6. SSNMR ^{13}C chemical shifts (δ in ppm) of compounds **1a**-**c**, **2c**-**4c** and **6b**,**c**. Values in *italic* correspond to chemical shift differences between solid and liquid states ($\Delta\delta = \delta_{sol.} - \delta_{liq.}$)

Compound	Carbon					
	C_6	C_3	O–CH_3	C_2	C_7	C=O
1a	43.2	54.0[a]	54.0[a]	74.7	102.6	169.4
	+3.2	*+1.5*	*−0.5*	*+7.1*	*+2.5*	*+1.5*
1b chain 1	43.2[a]	54.0[a]	54.0[a]	74.7	103.5	169.4[a]
	+3.4	*+2.1*	*+0.2*	*+4.6*	*+3.7*	*+1.4*
chain 1′	43.2[a]	51.1	46.8	67.1	94.6	169.4[a]
	+1.9	*−1.3*	*−5.9*	*0.0*	*−6.4*	*−1.0*
1c	42.9	51.3	46.8	67.3	94.9	169.9
	+1.7	*−1.2*	*−6.4*	*−3.2*	*−6.3*	*+1.5*
2c	40.1	46.1/45.4[b]	48.7	71.1	100.9	171.0/170.2[b]
	−1.4	*+1.4/+0.7*	*−4.0*	*+0.7*	*0.0*	*+2.7/+1.9*
3c polymorph 1[c]	42.0	47.9	54.5	72.3	103.5	169.0
	+0.4	*+0.9*	*+1.7*	*+2.7*	*+2.3*	*+0.6*
polymorph 2[c]	42.3	47.8	54.0/54.4	69.9/70.4	103.1	168.6
	+0.7	*+0.8*	*+1.2/+1.6*	*+0.3/+0.8*	*+1.9*	*+0.2*
4c[d]	40.9/43.1	51.8[a]	55.1/56.8	64.4/71.5	100.5/104.9	169.1[a]
	−0.6/+1.6	*+1.7*	*+1.3/+3.0*	*−3.3/+3.8*	*−0.9/+3.5*	*+0.8*
6b	39.2	37.6	56.8	61.0	102.2	168.5
	−1.4	*−1.4*	*+2.9*	*−3.6*	*+1.6*	*−0.3*
6c	40.7	40.1	47.9	64.4	100.6	170.9
	−0.4	*+0.9*	*−5.5*	*−1.7*	*−0.3*	*+1.8*

[a] Values corresponding to unresolved and/or broad signals.
[b] Asymmetric doublet resulting from the quadrupolar moment of ^{14}N.
[c] Polymorphs 1 and 2 present the same solution spectrum.
[d] Compound **4c** does not show any difference between the two chains in liquid NMR.

temperature in the solid and liquid states. The aim of these studies was to explore potential conformational changes by: (i) increasing the temperature in the solid state to enhance the flexibility of the ring and ultimately approach $C_{7'}$–O_1–C_2–C_3, C_7–$O_{1'}$–$C_{2'}$–$C_{3'}$ *trans* conformations, (ii) decreasing the temperature in the liquid state to obtain a more constrained conformation. At 130 °C (maximum temperature technically available), no change was detected in the SSNMR spectra. In contrast, at −80 °C (minimum temperature available in CD_2Cl_2)[‖] all resonances, except the CO one, were shielded from about 0.6–1.0 ppm, in particular the C_7 resonance ($\Delta\delta$ −0.8 ppm), shielding of which is consistent with possible *gauche* conformations at low temperature in the liquid state.

As noted for isomer **1c**, the symmetry of isomer **1a** is conserved in the solid state NMR spectrum. Compared with the liquid NMR spectrum, the deshielding of the CO carbon ($\Delta\delta$ +1.5 ppm) underlines again the presence of intermolecular CO···HN hydrogen bonds. Besides, the C_7 shift variation ($\Delta\delta$ +2.5 ppm) indicates that no γ-*gauche* effect occurs in the solid state of this compound.

Concerning isomer **1b**, its ^{13}C SSNMR spectrum, which should exhibit two signals for each pair of identical groups, is characterized by 11 resolved lines: in fact, only the OMe, C_3, C_2 and C_7 carbons are split. Intermolecular CO···HN hydrogen bonds are present once more as shown by the shift of the CO carbons ($\Delta\delta$ +1.4 and +1.0 ppm). Besides, as previously observed in the liquid NMR spectrum, the ^{13}C chemical shifts of chain 1 are nearly identical to those of **1a**, and the δ values of chain 1′ are close to those of **1c** (Table 6). These results indicate that a *trans* relationship between the 3-phenyl substituents and the OMe groups (as occurs in isomer **a**) implies *trans* or *anti* $C_{7'}$–O_1–C_2–C_3 conformations, while a *cis* relationship (as occurs in isomer **c**) implies *gauche* $C_{7'}$–O_1–C_2–C_3 conformations in the solid state in contrast with the *anti* conformations observed in the liquid phase.

Consequently if a positive difference in chemical shifts between the solid and liquid spectra ($\Delta\delta = \delta_{solid} - \delta_{liquid} \geq 0$) is observed for the C_7 carbon, a *trans* conformation may be expected. In contrast, if $\Delta\delta < 0$, a degree of conformational constraint, such as a *gauche* conformation, may be expected. The results obtained for the other compounds will be discussed on this basis.

The SSNMR spectrum of compound **2c** which presents seven resonances for 14 carbons, indicates that the symmetry is also preserved in the solid phase (Table 6). The CO downfield effect ($\Delta\delta = +1.9 - +2.7$ ppm) may be due, as seen above, to the presence of intermolecular CO···HN hydrogen bonds. Besides, the C_7 chemical shift variation ($\Delta\delta$ 0 ppm) is broadly indicative of a globally non-constrained conformation for **2c** in the solid state. Thus, the simple presence of a methyl group in the C_3 position appears insufficient to produce a constrained conformation.

The symmetry of the compound **3c** in the solid phase is maintained: nine intense peaks are visible for 20 carbons (C_9 and one OCH_3 being superimposed). Surprisingly, a polymorphic transformation occurs with time, while a such kinetic/thermodynamic evolution has never been observed for the other compounds. The thermodynamic polymorph spectrum shows a partial absence of symmetry as underlined by the splitting of C_2, C_9, CH_3 and OCH_3 carbons (SM). This asymmetry may be explained by a movement of the isobutyl side chain. It has to be noted that the two polymorphs give the same ^{13}C liquid state NMR spectrum.

[‖] Low temperature liquid state experiments were run in CD_2Cl_2 instead of chlorofluorocarbons generally used for this purpose but in which the studied macrocycles were not soluble.

Moreover, the *quasi* absence of intermolecular hydrogen bonding ($\Delta\delta_{CO} = +0.2 - +0.6$ ppm) may be explained by the bulkiness of the two isobutyl substituents while the slight C_7 downfield shift ($\Delta\delta = +1.9 - +2.3$ ppm) agrees with a *trans* conformation, previously assigned by calculations.

The solid state spectrum of compound **4c**, compared with the liquid phase, shows an unsymmetrical conformation in regard to the C_2 axis. While the sites are conformationally averaged in solution to give one resonance, in the solid phase spectrum two resonances of nearly equal intensity are observed for each carbon, except for the C_3 and Ar–CH carbons, the peaks of which are broadened. The asymmetry could be due to different orientations or dynamic motions of the two phenyl rings, which could undergo a staccato-like rotation (or π-flip)[36] and their non-equivalence could result from a lattice deformation corresponding to a minimum space occupation and a minimum repulsion. This observed asymmetry is consistent with the molecular modeling results that indicate for **4c**: (i) different N_4–C_5–C_6–C_7 dihedral angles values between the two chains (Table 5), (ii) the presence of a single NH···$O_{1'}$ intramolecular hydrogen bond up to conformer 5 (SM).

Finally, the spectra of the two achiral 3-unsubstitued macrocycles (**6b** and **6c**) were recorded to investigate the influence of the methoxy groups on the 14-membered ring. For these two compounds, the symmetry is conserved in the solid state. The comparison for both compounds of liquid and solid state chemical shifts indicates that in the solid state: (i) intermolecular CO···HN hydrogen bonding occurs only in isomer **6c** (**6c**: $\Delta\delta_{CO}$ +1.8 ppm; **6b**: $\Delta\delta_{CO}$ 0 ppm), (ii) a *trans* conformation is conserved along the two bonds $C_{7'}$–O_1–C_2–C_3, while a small γ-*gauche* effect is observed along the two bonds $C_{6'}$–$C_{7'}$–O_1–C_2 referring to the C_2 and C_6 chemical shift variations (Table 6).

Thus it appears from these results that the γ-*gauche* effect observed for **1c** in the solid state is not dictated by the methoxy groups but is induced by the presence of the 3-phenyl substituent.

In summary, ^{13}C SS CPMAS NMR is a simple and useful tool for obtaining conformational data in the solid state. For compound **1c**, the NMR results are consistent with those obtained by the X-ray analysis. More specifically, the NMR technique enabled us to show the presence of: (i) a symmetry in compounds **1c**–**3c**, **6b** and **6c**, and an asymmetry in compound **4c** in the solid state, (ii) intermolecular CO···HN hydrogen bonds for compounds **1a**, **1c**–**4c** and **6c**, the strength of which decreases with the bulkiness of the substituents, (iii) strong *gauche* conformations for the two $C_{7'}$–O_1–C_2–C_3 bonds in **1c**, and weaker *gauche* conformations for the two $C_{6'}$–$C_{7'}$–O_1–C_2 bonds in **6b** and **6c**, (iv) polymorphic forms for compound **3c**, probably due to the high degree of freedom of the isobutyl side chain.

3. Conclusion

In the liquid state, the conformations of the 14-membered diketal dilactam macrocycles, which all show gg′ or g′g arrangements for C_6, $C_{6'}$, seem to depend strongly on whether the molecules are chiral or achiral, and whether the OMe groups are in a *cis* or *trans* configuration. In achiral compounds, the more stable conformation has the two NH–CO links perpendicular to the macrocyclic plane, with orientation either same (in **6c**, **7c**) or opposite (in **6b**, **7b**); this latter arrangement lends to **6b** and **7b** a rectangular [3434]-type structure with the four corners at C_3, $C_{3'}$, C_7, $C_{7'}$. In contrast, in the chiral compounds **1**–**5**, the conformations are governed: (i) by the presence of one (in most isomers **b**) or two (in most isomers **a** and **c**) N_4–H···$O_{1'}$, $N_{4'}$–H···O_1 intramolecular hydrogen bonds, which sets the amide function parallel to the macrocyclic plane, (ii) by the position of the OMe groups in regard to the 3-R substituents, (iii) by the nature of the 3-R substituent. Thus the structure tg′ttg′gttg′ttg′gt (Ic), which has no corner, is most frequently observed for 3,3′-monosubstituted compounds **1c**–**4c**, while no predominant structure appears for the corresponding isomers **a** and **b**.

In the solid state, only slight changes in conformation seem to occur for the achiral compounds **6b** and **6c** in regard to the liquid state; they probably retain the more stable shape found in molecular modeling studies that is the NH–CO link perpendicular to the macrocyclic plane, with, however, in the present case, NH···O=C intermolecular hydrogen bonds between successive sheets, H bonds underlined by a small γ effect on the C_2 and C_6 carbons and, in **6c**, slight deshielding of the CO carbon. This orientation of the amide moieties is probably present in the solid state of chiral compounds **1a**, **1b**, **2c**–**4c** with, however, the cohesive force of any intermolecular H bonds strongly weakened (**1a**, **1b**, **2c**) or cancelled (**3c**, **4c**) by the presence of 3-R substituents. In contrast, in compound **1c**, the cohesion of the NH···O=C intermolecular H bonds, revealed by the X-ray analysis, is reinforced by a π–π stacking effect between the phenyl groups, which adopt a position parallel to the macrocyclic plane and thus give to the molecule a constrained shape with an unusual *gauche* conformation along the two $C_{7'}$–O_1–C_2–C_3 bonds.

4. Experimental

4.1. Synthesis

The 14-membered ring diketal dilactam syntheses were previously reported.[1]

4.2. Liquid NMR

Proton and carbon NMR spectra were recorded in deuteriochloroform solutions using a Bruker AC 400 spectrometer (^1H: 400 MHz; ^{13}C: 100 MHz), equipped with a DUAL $^1H/^{13}C$ probe, at 303 K. Chemical shifts are given in parts per million (ppm) and referenced to chloroform ($\delta =$ 7.27 ppm for ^1H and 77.1 ppm for ^{13}C) as internal standard.

The NOE measurements were made on a Bruker spectrometer, model DSX 300, equipped with a double resonance probe, at 303 K with 10 mM $CDCl_3$ solutions. Samples were degassed by bubbling dry argon through the solution in the

NMR tube for 30 min. NOE difference spectra were recorded after presaturation of the signal to irradiate using the 'NOEmult' pulse sequence. The following conditions were used: proton relaxation delay 1 s, irradiation period 2.5 s (50 presaturation cycles of 50 ms), total measuring time 7 s. Each FID corresponds to the average of 64 acquisitions and the NOE difference spectra to the average of 8 FID.

4.3. Molecular modeling

The MACROMODEL molecular modeling program (version 7.0) developed by Still and co-workers[38] was used to determined the global minimum conformations of the macrocyclic diketals dilactams. The AMBER force field[39] implemented in the program and well-suited to the study of compounds incorporating amide functions was chosen. The method known as Monte-Carlo Multiple Minimum Search (MCMM) was applied. The starting structure was the previously determined XR structure of the macrocycle **1c**.[1a] All other structures were written from the **1c** minimum conformation. A minimum of 5000 conformations were minimized for every compound. Detection conditions for hydrogen bonds: interatomic distances $d<2.5$ Å, angles: N–H···O $<90°$ and H···O–R $<60°$.

4.4. Solid state NMR

The high-resolution ^{13}C solid state spectra were recorded at 75.46 MHz on a Bruker Avance DSX-300 spectrometer with a double bearing magic angle spinning (MAS) probehead. The samples were packed in 4 mm zirconia rotors fitted with Kel-F caps, and when the amount of macrocycle was not sufficient, the sample volume was reduced in the center of the rotor using a Teflon insert. The samples were spun at the magic angle with a speed of 10 kHz at ambient temperature. A ramped cross polarization (RACP) from protons to carbon was carried out at a proton nutation frequency of 70 kHz over a contact time of 1.5 ms and a recycle delay of 3 s. The proton CW decoupling field strength was 68 kHz, and when necessary a TPPM decoupling[40] with a ^{1}H nutation frequency of 70 kHz, a pulse length of 6.0 μs and a phase shift of 15° was used to resolve the asymmetric doublet due to the large ^{14}N quadrupolar coupling. Dipolar dephased spectra were obtained by turning off the ^{1}H decoupling for a short time after the cross-polarization pulse. Also, to suppress the movable methyl groups, the delay was set between 25 and 150 μs depending on the structure. Free induction decays (FID) were digitized into 6 K data points and Fourier-transformed after applying 5 Hz exponential line broadening. The number of transients (200–4096) was fitted to reach optimal signal-to-noise ratios. ^{13}C chemical shifts were measured relative to an external reference (carbonyl of glycine: 176.03 ppm, Aldrich), set carefully before each spectrum.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.073

Tables of: (1) Relative energy (kJ mol^{-1}) of the 10 first conformers of compounds **1–7**; (2) H_3–C_3–C_2–H_2 and H_7–C_7–C_6–H_6 dihedral angles; (3) Interatomic distances between the H_6 hydrogens and the OMe oxygens; (4) Interatomic distances between the NH hydrogens and the endocyclic acetalic oxygens.

Solid state ^{13}C NMR chemical shifts of macrocycles **1a–c**, **2c–4c**, **6b–c** and spectra of **1a–c**.

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Synthesis, characterization and some properties of amide-linked porphyrin–ruthenium(II) tris(bipyridine) complexes

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Abstract—A new molecular dyad, comprised of a zinc-porphyrin and a ruthenium(II) tris(bipyridine) complex linked through an amide bond has been synthesized and characterized by ^{1}H, ^{13}C NMR, UV–vis, mass-spectrometry and elemental analysis. The electrochemistry as well as the steady-state emission properties were investigated. The redox behavior of the dyad exhibits a favorable reversible characteristic. Substantial quenching of porphyrin emission was found when the Q band of **5** and **5-Zn** was selectively photoexcited. This observation suggests a quenching mechanism with possible intramolecular electron transfer or energy transfer between the $Ru(bpy)_3$ moiety and the porphyrin free-base or Zn porphyrin moieties.

1. Introduction

In nature, many processes convert the solar energy into chemical energy, for instance, the photosynthesis. This process involves with a complicated mechanism: sunlight is captured by chlorophyll arrays, funnels the excited energy to the reaction center, and converts it to chemical potential in the form of a long-lived charge-separated state.[1] Up to now, many types of supramolecular systems have been designed and studied as model systems to mimic the natural process of sunlight conversion.[2] Among these, porphyrinoid arrays, dyads, triads and higher order arrays, linked by covalent bonds and non-covalent forms have been extensively studied.[3] Porphyrin is the most widely used chromophore.[4] Other elaborate systems include porphyrins–quinone assemblies,[5] with porphyrin or metalloporphyrins as donor and quinones as acceptors.

Polypyridine,[6] on the other hand, especially ruthenium(II) tris-(2,2′-bipyridine), is another kind of important chromophore. It has an absorption maximum in the range of 400–500 nm with increased absorptive cross sections at the wavelength of the porphyrins. Such complementary absorption spectra of porphyrin and ruthenium(II) tris-bipyridine provide us with an extended absorption range favorable for the collection of light. In addition, an intramolecular electron transfer from porphyrin to the Ru-complex occurs on the excitation of the porphyrin moiety or Ru moiety.[7] Ruthenium(II) tris-bipyridine derivatives have favourable photophysical and redox properties, which make them ideal candidates for photosensitizer.[6,7]

A previous work have shown intramolecular electron transfer from the higher excited state S_2 of a zinc porphyrin to a covalently linked ruthenium complex was possible.[8] Related studies for such porphyrin–Ru systems have been reported by a few research groups.[9] Based on these analyses, $[Ru(bpy)_3]^{2+}$ was used here for constructing some electron donor–acceptor systems based on $Ru(bpy)_3$–porphyrin conjugates. We present here the synthesis, electrochemical and photophysical studies of porphyrin–$Ru(bpy)_3$ conjugates as well as related reference compounds. The deliberate introduction of electron-withdrawing substituents (carboxylate ester) on the bipyridine rings is expected to have some effects on electron transfer and energy transfer,[10] because the oxidation potential is different from the unsubstitutied $Ru(bpy)_3$.

2. Results and discussion

2.1. Synthesis

This work started with the preparation of mono nitro-substituted porphyrin **1** according to Lindsey's method[11] by condensation of aldehydes with pyrroles in the presence of

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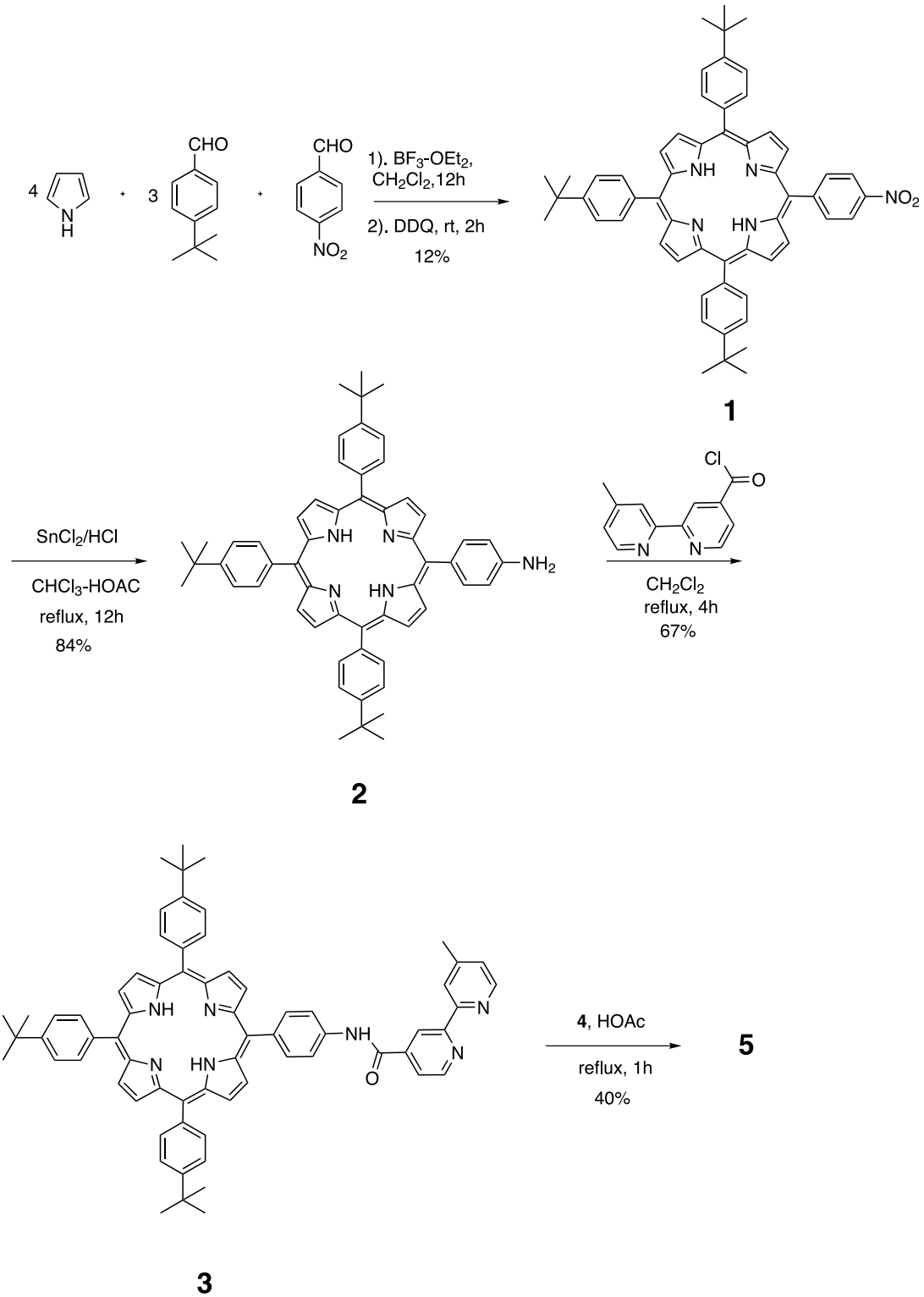
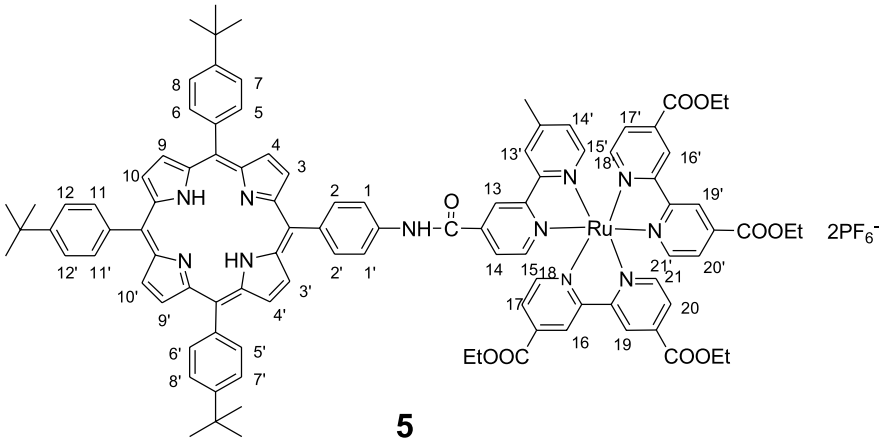
BF_3/etherate, followed by oxidation with DDQ, outlined in Scheme 1. Pyrrole, 4-*tert*-butylbenzaldehyde and 4-nitrobenzaldehyde in a ratio of 4/3/1 reacted in CH_2Cl_2 at room temperature to afford **1** after usual workup and repeated column chromatography on silica gel, with bis-, tris-, and tetra-nitrophenyl analogues as the side products. The reduction of nitro group was carried out in $CHCl_3$/HOAc by usual $SnCl_2$/HCl procedure[12] to give the amino substituted phenylporphyrin **2** in good yield. It was further treated with 4′-methyl-2,2′-bipyridinyl-4-carbonyl chloride (which was prepared from 4,4′-dimethyl-2,2′-bypyridine according to literature[13]) in the presence of Et_3N to form porphyrin–bipyridine ligand **3** in 67% yield. By refluxing the mixture of **4** and **3** in acetic acid, ruthenium(II) complex **5** was obtained. ^{1}H NMR assignments for **5** (Fig. 1) were based on peak intensity, peak multiplicity, and were verified



Scheme 1. Synthetic route for compound **5**.



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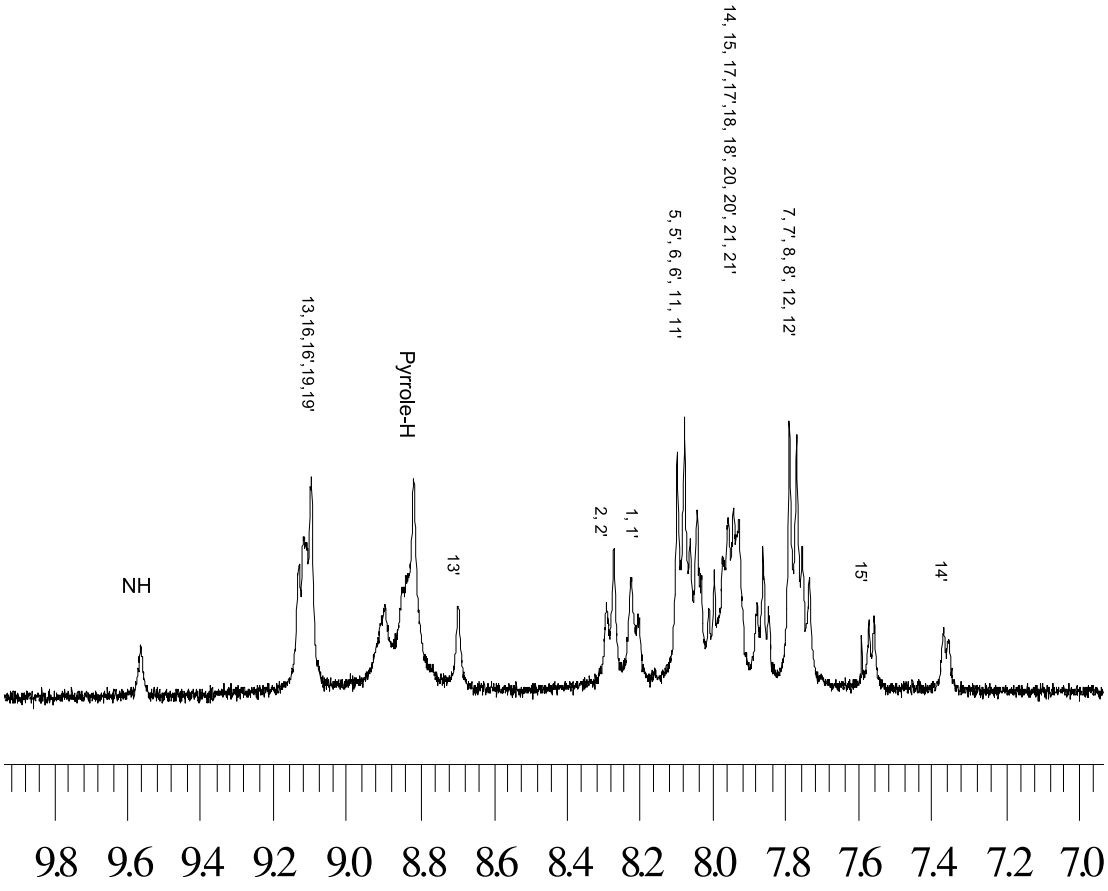
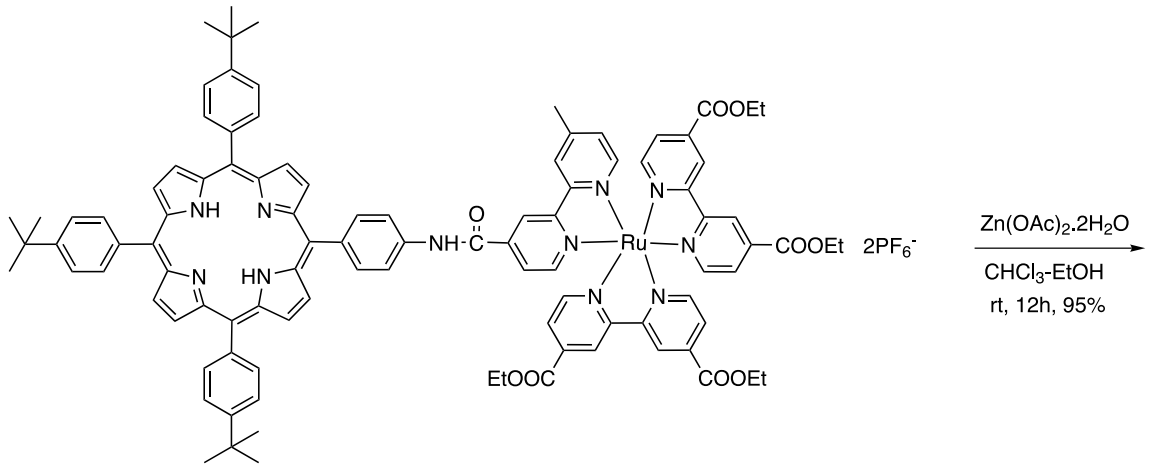


Figure 1. The aromatic region of the ^{1}H NMR (400 MHz) spectrum of **5** in CD_3CN.

by 2D NMR spectroscopy. Particularly diagnostic in ^{1}H NMR were three resonance signals at δ −2.81 (internal NH-pyrrolic resonance), 1.55 (H from *t*-butyl) and 9.56 (amide H). Obviously ruthenium(II) has just coordinated to the bipyridine rather than inserting into the porphyrin ring. This can be confirmed by ^{1}H NMR, which shows a broad singlet at δ −2.81 corresponding to the NH proton of the free base porphyrin. The dinuclear complex **5**-**Zn** was then formed by stirring the mixture of $Zn(OAc)_2$ and **5** in chloroform with minor EtOH at room temperature (Scheme 2). This reaction is facile but has to be performed under N_2 in the dark. The target dinuclear complex **5**-**Zn** can be prepared by two synthetic approaches: Zn(II) was inserted into the porphyrin free base first, then ruthenium(II) was coordinated to the bpy ligand **3**; or ruthenium(II) was used to coordinate to the bpy ligand before the Zn(II) was inserted. Of the two possibilities, the former seems to be problematic for the coordination of ruthenium(II) to the bipyridine ligand, partly due to the coordination of bipyridine to the Zn-porphyrin as an axial ligand. To overcome this problem, we chose the latter approach for the preparation of **5**-**Zn**.

2.2. Steady-state absorption spectra

The ground-state absorption spectrum is shown in Figure 2. It exhibits the Soret band at ca. 420 nm and Q-bands ranging



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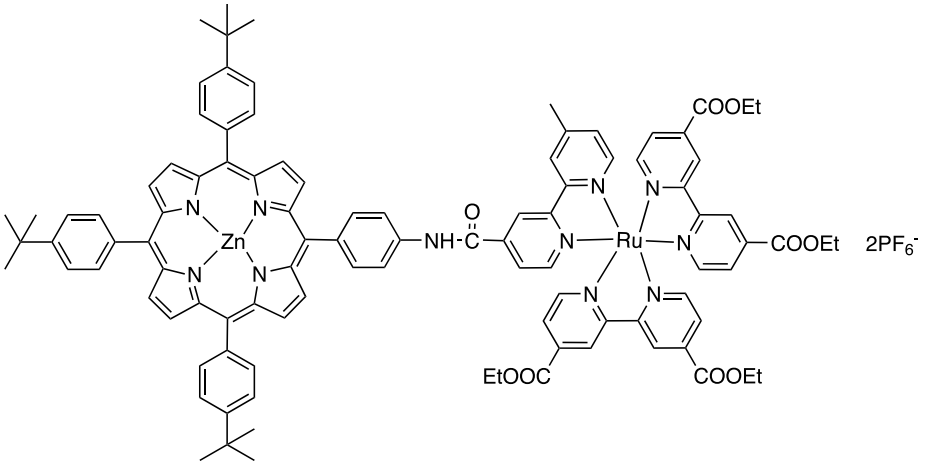
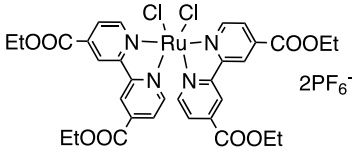


5-Zn



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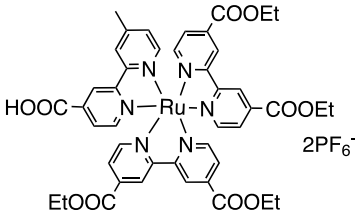

6

Scheme 2. Synthetic route for complex **5**-**Zn**.

from 500 to 650 nm for the porphyrin subunit, in addition to the absorption bands for the $[Ru(bpy)_3]^{2+}$ moiety at 300 nm (bipy $\pi \rightarrow \pi^*$) and 475 nm (MLCT transition). The Soret band characterizes promotion to the second-excited singlet state of porphyrin, while the Q-bands correspond to the first-excited singlet state of the porphyrin. The two Q-bands absorption of compound **5**-**Zn** arrised from the increasing molecular symmetry to $D_{4\,h}$, which is a typical pattern of regular metal porphyrins. The metal to ligand charge transfer (MLCT) transition is red shifted (25 nm) corresponding to the absorption of $[Ru(bpy)_3]^{2+}$,[14] which is caused by esterification in the pyridine rings. The other main absorption bands of the **5**-**Zn** display also a slight red shift, compared to the relevant transitions for the absorption

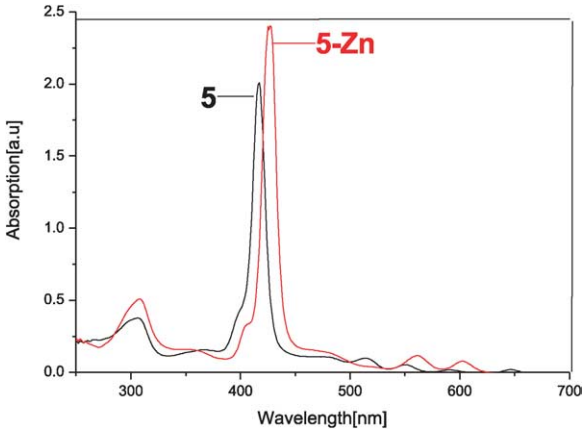

Figure 2. UV–vis absorption spectra of **5**-**Zn**, **5** in CH_3CN [5×10^{-6} M].

derived from the comparisons of the optical absorption and emission characteristics of such assemblies. The steady state emission spectra are shown in Figure 3. An emission profile was obtained upon excitation of the MLCT band of **5**-**Zn**, the free base and the ruthenium(II) tris-bipyridine subunit **6**. The emission spectrum of **5**-**Zn** shows a mixture of fluorescence from porphyrin and luminescence from the $Ru(bpy)_3$ unit (Fig. 3a). However, we find that the emission from **5** is solely due to the fluorescence of porphyrin unit, and there is substantial quenching of porphyrin and $Ru(bpy)_3$ unit emission in **5**-**Zn** compared to **5** and **6**. The detailed data are listed in Table 1. This implies that there are completely different electron or energy transfer paths in the compounds **5**-**Zn** and **5**. On the other hand, when selectively exciting the Q bands in **5**-**Zn** (558 nm) and **5** (551 nm), the fluorescent emission of **5**-**Zn** is blue-shifted (0–0 and 0–1

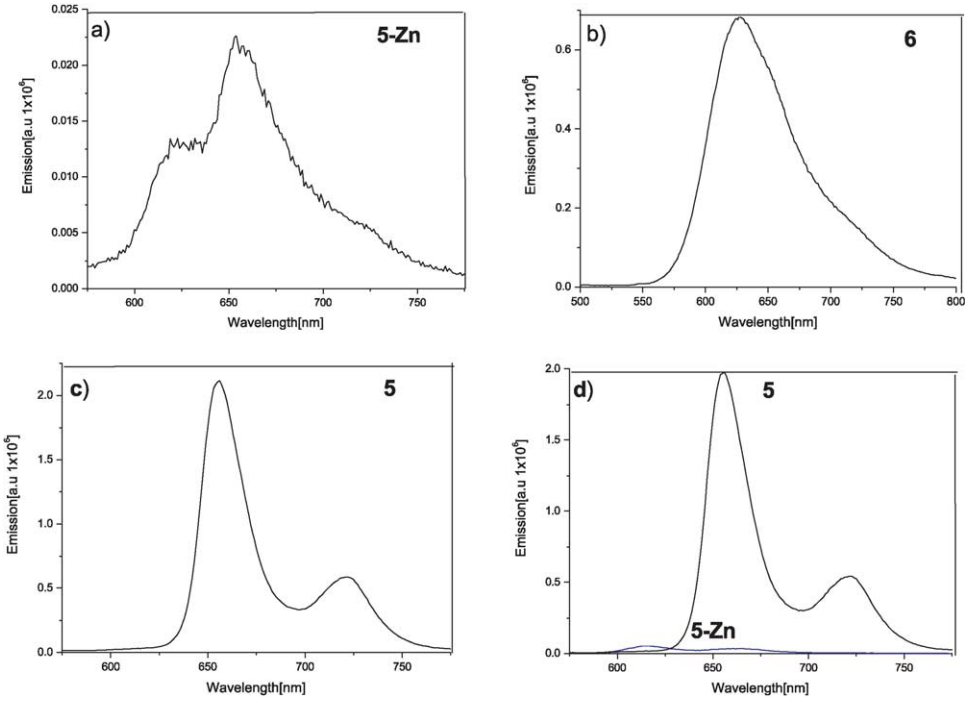

Figure 3. Steady-state emission spectra of (a) **5**-**Zn** ($\lambda_{ex}=471$ nm); (b) **6** ($\lambda_{ex}=468$ nm); (c) **5** ($\lambda_{ex}=471$ nm); (d) **5**-**Zn** ($\lambda_{ex}=558$ nm), **5** ($\lambda_{ex}=551$ nm) with excitation of Porphyrin's Q band in deoxygenated CH_3CN [5×10^{-6} M].

band of **5**, suggesting some interaction between the intramolecular porphyrin and $[Ru(bpy)_3]^{2+}$ chromophores (Scheme 2).[15]

2.3. Emission measurements

Evidence for excited state interactions in our molecule is

band at 619 and 654 nm) with respect to **5**, but their emission profile is very similar. There is also a classic oxidizing quenching with electron transfer from porphyrin to the Ru complex. The emission from **5**-**Zn** was found to be 3% relative to that of **5**. Such transformation is more effective for the zinc porphyrin due to its lower oxidation potential (Table 1).

Table 1. Steady-state emission spectroscopic data of **5**, **6** and **5**-**Zn** in CH_3CN at 298 K [5×10^{-6} M]

Compd.	MLCT band			Soret band		
	λ_{ex} (nm)	λ_{em} (nm)	$I_{em}\times10^{-3}$(a.u.)	λ_{ex} (nm)	λ_{em} (nm)	$I_{em}\times10^{-3}$ (a.u.)
5-**Zn**	471	654	22.7	558	617	50.8
5	471	656	2100	551	656	1980
6	470	627	683			

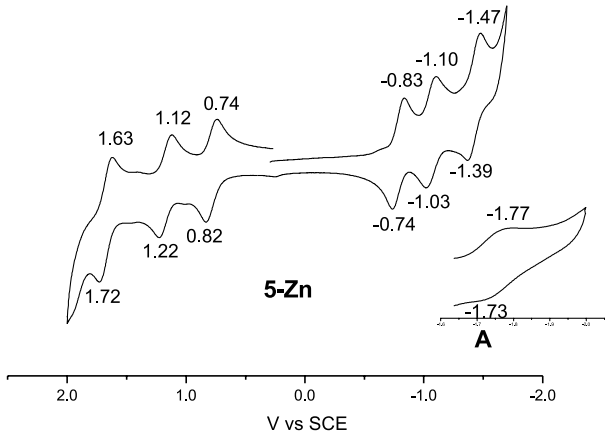

Figure 4. Cyclic voltammogram for complex **5-Zn** in 10^{-3} M CH_2Cl_2/0.1 M $TBAPF_6$ on a glassy carbon disc electrode at a scan rate of 50 mV/s. Inset A was recorded in CH_3CN/0.05 M $TBAPF_6$ at a glass carbon working electrode with a scan rate of 50 mV/s and reported relative to SCE.

On the reduction side, there were also three reversible peaks: $E_{1/2}=-0.79$, -1.07, and -1.43 V, corresponding to the first reduction of the Zn porphyrin unit (**2**) and the first and second reduction of the $Ru(bpy)_3^{2+}$ unit. Inset A in Figure 4 was one part of the CV recorded in CH_3CN, which was not observed in CH_2Cl_2.[16,17] The new reduction peak which occurs at $E_{1/2}=-1.75$ V is assigned to the third reduction of the $Ru(bpy)_3^{2+}$ unit. To ensure a more accurate comparison between the porphyrins and ruthenium complexes, all measurements were performed in CH_2Cl_2 as a solvent.[18] All six redox peaks (Fig. 4) are reversible one-electron processes.

The cyclic voltammogram for **5** was recorded in CH_2Cl_2 and 0.05 M $TBAPF_6$ (Fig. 5). In Figure 5, the oxidation part of the cyclic voltammogram for complex **5** exhibited two reversible one-electron process peaks: $E_{1/2}=1.18$ and 1.47 V assigned to the oxidation of its porphyrin unit and the metal-based oxidation (Ru^{II}/Ru^{III}) couple respectively,

Table 2. Electrochemical data versus SCE for complexes and model compounds

Complexes	Oxidations						Reductions					
	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p	$E_{1/2}$	ΔE_p
5-Zn	1.68	0.09	1.17	0.1	0.78	0.08	−0.79	0.09	−1.07	0.07	−1.43	0.08
5	1.47	0.11	1.18	0.12			−1.04	0.19	−1.56		−1.87	
$Ru(bpy)_3^{2+}$	1.35	0.07					−1.32	0.07	−1.51	0.07	−1.76	0.07

Recorded in CH_2Cl_2 0.05 M $TBAPF_6$ with a scan rate of 50 mV/s.

2.4. Electrochemistry

The cyclic voltammogram for the ruthenium complex **5-Zn** recorded in CH_2Cl_2 0.1 M $TBAPF_6$ (Fig. 4) exhibited a favorable reversible process. Reversible oxidation peaks of **5-Zn** were observed at $E_{1/2}=0.78$ V and $E_{1/2}=1.17$ V versus SCE assigned to the first and second oxidation of Zn porphyrin unit, and $E_{1/2}=1.68$ V assigned to metal-based oxidation (Ru^{II}/Ru^{III}) couple, being obviously shifted from the value observed for that in $Ru(bpy)_3^{2+}$ (see Table 2). The introduction of carboxylic groups to the bipyridyl ligands affects the redox potential values. Increasing the number of electron-withdrawing groups on the ligands makes the metal oxidation more difficult and the reduction of the ligands easier.[10]

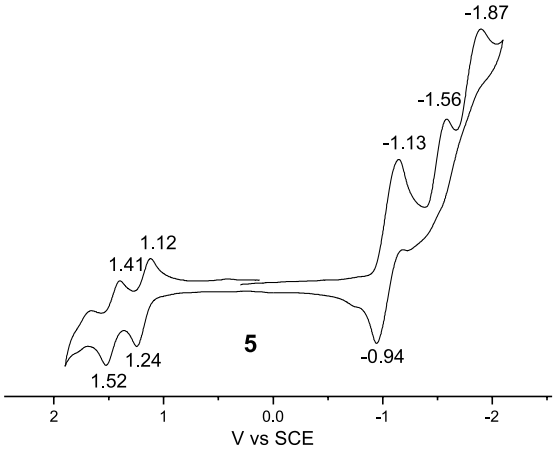

Figure 5. Cyclic voltammogram for complex **5** in 10^{-3} M CH_2Cl_2/0.1 M $TBAPF_6$ on a glassy carbon disc electrode at 50 mV/s.

which has one less oxidation peak than that in the case of **5-Zn**, and the potential value of Ru^{II}/Ru^{III} couple was obviously lower than that of **5-Zn**.

On the other hand, there are great differences between **5** and **5-Zn** in the reduction region. The diagram of **5** exhibited three consecutive reduction waves, of which the second and third ones were not reversible, corresponding to the first and second reduction of the $Ru(bpy)_3^{2+}$ units. We also leave out here the part of the third reduction of the $Ru(bpy)_3^{2+}$ units in acetonitrile. The presence of a reversible two-electron reduction peak at $E_{1/2}=-1.04$ V is worthy of note, corresponding to the reduction of the porphyrin subunit, and suggesting the occurrence of a chemical reaction of the two-electron-reduced species.

In summary, the free base porphyrin and the Zn-porphyrin are covalently linked to a Ru(II) tris-bipyridine complex which bears four carboxylate ester groups on the bipyridine ligands. From the electrochemical study, it has been indicated that photogenerated Ru(III), which has a higher oxidation potential than normal $Ru(bpy)_3$, oxidize the porphyrin moiety thermodynamically. This observation could lead to an interesting photo-induced electron transfer or energy transfer process.

3. Experimental

3.1. General

All reagents were purchased from Aldrich, and all solvents were purified according to standard methods. Pyrrole was freshly distilled before use. All of the manipulations were

performed under N_2. ^1H NMR spectra were recorded on a Varian 400 spectrometer and reported in ppm downfield from TMS. CH_2Cl_2 (Aldrich, spectroscopy grade) used for performance of electrochemistry was dried with molecular sieves (4 Å) and then freshly distilled from CaH_2 under N_2. Cyclic voltammograms were recorded at a scan rate of 50 mV/s in 10^{-3} M CH_2Cl_2 solutions using 0.05 M Bu_4NPF_6 as supporting electrolyte. Electrochemical measurements were recorded using a BAS-100W electrochemical potentiostat. The electrolyte solution was degassed by bubbling with dry argon for 10 min before measurements. Cyclic voltammograms were obtained in a three-electrode cell under argon. The working electrode was a glassy carbon disc (diameter 3 mm) successively polished with 3 and 1 μm diamond pastes and sonicated in ion-free water for 10 min. The reference electrode was a non-aqueous Ag/Ag^+ electrode (0.01 M $AgNO_3$ in CH_3CN) and the auxiliary electrode was a platinum wire. The measured potentials in Figures 4 and 5 were corrected to the values of SCE by adding 0.30 V.

3.1.1. 5-(4-Nitrophenyl)-10,15,20-tris(4-*tert*-butylphenyl)porphyrin (1). Pyrrole (0.28 mL, 4.0 mmol), 4-nitrobenzaldehyde (153 mg, 1.0 mmol) and 4-*tert*-butylbenzaldehyde (0.52 mL, 3.0 mmol) were added to CH_2Cl_2 (500 mL) which was degassed with N_2 for 30 min. After the mixture was stirred and purged with N_2 for a further 30 min, a BF_3/etherate solution (0.5 mL, 2 M in CH_2Cl_2, 1.0 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. 2,3-Dichloro-5,6-dicyanobenzo-quinone (DDQ) (0.91 g, 4.0 mmol) was added to the red-brown solution, and the resulting black mixture was refluxed for 2 h. Et_3N (0.56 mL, 4.0 mmol) was added, and the solution was concentrated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel, pentane /CH_2Cl_2=60/40) to give the desired porphyrin product in 12% yield: Mp >300 °C; ^1H NMR ($CDCl_3$) δ −2.78 (s, br, 2H, –NH), 1.60 (s, 27H, *tert*-butyl-H), 7.74 (d, J=8.4 Hz, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$, H_{12}, $H_{12'}$), 8.11 (dd, J=8.0 Hz, J=2.4 Hz, 6H, H_5, $H_{5'}$ H_6, $H_{6'}$ H_{11}, $H_{11'}$), 8.37 (d, J=8.4 Hz, 2H, H_1, $H_{1'}$), 8.60 (d, J=8.8 Hz, 2H, H_2, $H_{2'}$), 8.68 (d, J=4.0 Hz, 2H, H_3, $H_{3'}$), 8.86 (s, 4H, H_4, $H_{4'}$, H_9, $H_{9'}$), 8.90 (d, J=4.8 Hz, 2H, H_{10}, $H_{10'}$); UV–vis in methylene chloride λ_{max} [nm]=422.0, 518.0, 554.0, 593.0, 650.0; APCI-MS Positive: $[M+H]^+$ (m/z=828.5); Anal. Calcd for $C_{56}H_{53}N_5O_2\cdot 0.75C_6H_{14}$: C, 81.40; H, 7.17; N, 7.85. Found: C, 80.91; H, 7.02; N, 7.56.

3.1.2. 5-(4-Aminophenyl)-10,15,20-tris(4-*tert*-butylphenyl)porphyrin (2). To a solution of **1** (335 mg, 0.405 mmol) in 1:2 $CHCl_3$/HOAc (30 mL) was added a solution of $SnCl_2\cdot 2H_2O$ (366 mg, 1.62 mmol) in concentrated HCl (10 mL). The mixture was vigorously stirred in a preheated oil bath (65–70 °C) for 30 min, refluxed overnight, then neutralized with ammonia solution (25%) to pH 8–9. Chloroform (100 mL) was added, and the mixture was stirred for 1 h. The organic phase was separated, and the water phase was extracted with $CHCl_3$ (2×100 mL). The combined organic layer was washed once with dilute ammonia solution, three times with water, then concentrated to dryness. The residue was purified by column chromatography (silica gel, chloroform). Yield: 84%. Mp >300 °C; ^1H NMR ($CDCl_3$): δ −2.72 (s, br, 2H, –NH), 1.60 (s, 27H, *tert*-butyl-H), 3.91 (s, br, 2H, $-NH_2$), 6.99 (d, J=8.0 Hz, 2H, H_1, $H_{1'}$), 7.74 (d, J=8.0 Hz, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$, H_{12}, $H_{12'}$), 7.98 (d, J=8.4 Hz, 2H, H_2, $H_{2'}$), 8.14 (d, J=8.0 Hz, 6H, H_5, $H_{5'}$, H_6, $H_{6'}$, H_{11}, $H_{11'}$), 8.86 (s, 6H, H_3, $H_{3'}$, H_4, $H_{4'}$, H_9, $H_{9'}$), 8.91 (d, J=4.8 Hz, 2H, H_{10}, $H_{10'}$); ^{13}C NMR ($CDCl_3$) δ 31.9, 35.1, 113.6, 120.1, 120.2, 120.7, 123.8, 131.3, 132.7, 134.7, 135.9, 139.5, 146.1, 150.6; UV–vis in methylene chloride λ_{max} [nm]=421.0, 517.0, 555.0, 591.0, 650.0; APCI-MS Positive: $[M+H]^+$ (m/z=798.4). Anal. Calcd for $C_{56}H_{55}N_5\cdot 0.25H_2O$: C, 83.81; H, 6.97; N, 8.73. Found: C, 83.83; H, 7.02; N, 8.47.

3.1.3. Porphyrin-NHCO-bpy (3). A mixture of 4-carboxy-4′-methyl-2,2′-bipyridine (146 mg, 0.680 mmol) and $SOCl_2$ (10 mL) was refluxed for 2 h. After removing excess $SOCl_2$ by distillation under reduced pressure, the acid chloride product was obtained and further dried in vacuum at 70 °C for 1 h. Then anhydrous CH_2Cl_2 (5 mL) was added and the mixture was stirred for 5 min at 50 °C. The resulting light yellow solution was added dropwise to the CH_2Cl_2 solution of **2** (0.27 g, 0.33 mmol) in which 2 drops of Et_3N had been pre-added. White smoke was observed in the reaction flask. The mixture was refluxed for 4 h, washed with 5% aqueous ammonia solution then with water. After removing the solvent, the residue was dissolved in $CHCl_3$ (10 mL) then CH_3CN (100 mL) was added dropwise. Precipitate was formed by slowly evaporating $CHCl_3$ under vacuum. The desired product was obtained after column chromatography on silica gel with a mixture of CH_2Cl_2/MeOH (94:6) as eluent to give purple solid (221 mg, 67%): mp >250 °C; ^1H NMR ($CDCl_3$): δ −2.74 (s, br, 2H –NH), 1.61 (s, 27H, *tert*-butyl-H), 2.46 (s, 3H, bpy-CH_3) 7.23–7.25 (m, 1H, $H_{14'}$), 7.73–7.77 (m, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$, H_{12}, $H_{12'}$), 8.02–8.04 (m, 1H, H_{14}), 8.12–8.16 (m, 8H, H_1, $H_{1'}$, H_5, $H_{5'}$, H_6, $H_{6'}$, H_{11}, $H_{11'}$), 8.26 (d, J=8.4 Hz, 2H, H_2, $H_{2'}$), 8.36 (s, 1H, $H_{13'}$), 8.60 (d, J=4.8 Hz, 1H, $H_{15'}$), 8.82 (s, br, 1H, amide H), 8.86–8.92 (m, 9H, H_{13}, H_3, $H_{3'}$, H_4, $H_{4'}$, H_9, $H_{9'}$, H_{10}, $H_{10'}$), 8.94 (s, 1H, H_{15}); ^{13}C NMR ($CDCl_3$) δ 21.5, 31.9, 35.1, 117.8, 118.7, 119.1, 120.4, 122.2, 122.6, 123.7, 125.5, 131.4, 134.6, 135.4, 137.4, 139.2, 143.2, 148.9, 150.5, 155.1, 157.0, 164.3; UV–vis in methylene chloride λ_{max} [nm]=420.0, 517.0, 553.0, 591.0, 649.0; APCI-MS Positive: $[M+H]^+$ (m/z=994.5); Anal. Calcd for $C_{68}H_{63}N_7O\cdot 0.75\ CH_2Cl_2$: C, 78.05; H, 6.14; N, 9.27. Found: C, 77.82; H, 6.53; N, 8.95.

3.1.4. Porphyrin-NHCO-bpy-Ru[(bpy)(COOEt)$_2$]$_2$-[PF$_6$]$_2$ (5). A mixture of **3** (50 mg, 0.050 mmol) and $Ru[bpy(COOEt)_2]_2Cl_2$ (40 mg, 0.050 mmol) in acetic acid (10 mL) was refluxed for 1 h under N_2 in the dark. After removing the solvent, the product was loaded onto a column of silica gel with a mixture of CH_2Cl_2/MeOH (10:1) as eluent, and the anion was exchanged with NH_4PF_6. The desired product was obtained as a red-brown solid (40 mg, 40%): mp >250 °C; ^1H NMR (CD_3CN): δ −2.81 (s, br, 2H, –NH), 1.42–1.46 (m, 12H, $-COOCH_2CH_3$), 1.55 (s, 9H, *tert*-butyl), 1.57 (s, 18H, *tert*-butyl), 2.64 (s, 3H, bpy-CH_3), 4.49–4.51 (m, 8H, $-COOCH_2CH_3$), 7.36 (d, J=4.8 Hz, 1H, $H_{14'}$), 7.56–7.59 (m, 1H, $H_{15'}$), 7.73–7.79 (m, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$, H_{12}, $H_{12'}$), 7.85–7.88 (m, 2H, H_{14}, H_{15}), 7.94–8.03 (m, 8H, H_{17}, $H_{17'}$, H_{18}, $H_{18'}$, H_{20}, $H_{20'}$, H_{21}, $H_{21'}$), 8.04–8.10 (m, 6H, H_5, $H_{5'}$, H_6, $H_{6'}$, H_{11}, $H_{11'}$), 8.21 (d, J=8.0 Hz, 2H, H_1, $H_{1'}$), 8.27 (d, J=8.0 Hz, 2H, H_2, $H_{2'}$), 8.69 (s, 1H, $H_{13'}$),

8.82–8.89 (m, 8H, H_3, $H_{3'}$, H_4, $H_{4'}$, H_9, $H_{9'}$, H_{10}, $H_{10'}$), 9.09–9.13 (m, 5H, H_{13}, H_{16}, $H_{16'}$, H_{19}, $H_{19'}$), 9.56 (s, br, 1H, amide-H); ^{13}C NMR (CD_3CN): δ 13.9, 21.3, 31.3, 34.9, 63.3, 119.3, 120.6, 121.5, 122.7, 123.8, 123.9, 124.3, 125.7, 126.5, 127.1, 129.5, 130.6, 131.3, 131.8, 131.9, 134.4, 135.3, 137.8, 138.2, 138.9, 139.0, 139.8, 139.9, 144.3, 151.1, 151.5, 152.2, 153.0, 153.2, 153.3, 153.5, 155.9, 157.7, 157.9, 162.6, 163.7.); UV–vis in methylene chloride λ_{max} [nm]=421.0, 450.0, 555.0, 650.0; API-ES-MS *m/z*: $[M\text{-}PF_6]^+$ 1840.6, $[M\text{-}2PF_6]^{2+}$ 847.4; Anal. Calcd for $C_{100}H_{95}F_{12}N_{11}O_9P_2Ru\cdot 1.5CH_2Cl_2$: C, 57.69; H, 4.67; N, 7.29. Found: C, 57.56; H, 4.99; N, 6.95.

3.1.5. Zn-Porphyrin-NHCO-bpy-Ru[(bpy)(COOEt)$_2$]$_2$-[PF$_6$]$_2$ (5-Zn). A solution of $Zn(OAc)_2\cdot 2H_2O$ (10 mg, 0.050 mmol) in ethanol (1 mL) was added to a solution of **5** (50 mg, 0.025 mmol) in chloroform (10 mL), and stirred at rt overnight under N_2 in the dark. This mixture was washed with water and then evaporated to dryness and purified by CH_2Cl_2/MeOH (10:1). The desired product was obtained as a red-brown solid: (49 mg, 95%) mp >250 °C; ^{1}H NMR (CD_3CN) δ 1.42–1.45 (m, 12H, –COOCH$_2$*CH*$_3$), 1.56 (s, 9H, *tert*-butyl), 1.58 (s, 18H, *tert*-butyl), 2.64 (s, 3H, bpy-CH_3), 4.47–4.51 (m, 8H, –COO*CH*$_2$CH$_3$), 7.37 (d, J= 5.2 Hz, 1H, $H_{14'}$), 7.56–7.59 (m, 1H, $H_{15'}$), 7.73–7.78 (m, 6H, H_7, $H_{7'}$, H_8, $H_{8'}$, H_{12}, $H_{12'}$), 7.86–7.90 (m, 2H, H_{14}, H_{15}), 7.92–8.04 (m, 8H, H_{17}, $H_{17'}$, H_{18}, $H_{18'}$, H_{20}, $H_{20'}$, H_{21}, $H_{21'}$), 8.06–8.15 (m, 8H, H_1, $H_{1'}$ H_5, $H_{5'}$, H_6, $H_{6'}$, H_{11}, $H_{11'}$), 8.26 (d, J=7.6 Hz, 2H, H_2,$H_{2'}$), 8.68 (s, 1H, $H_{13'}$), 8.83–8.89 (m, 8H, H_3, $H_{3'}$, H_4, $H_{4'}$, H_9, $H_{9'}$, H_{10}, $H_{10'}$), 9.06–9.13 (m, 5H, H_{13}, H_{16}, $H_{16'}$, H_{19}, $H_{19'}$), 9.49 (s, br, 1H, amide-H); ^{13}C NMR (CD_3CN) δ 14.4, 21.4, 31.8, 35.3, 63.8, 118.3, 119.4, 120.6, 121.7, 123.1, 124.2, 124.3, 124.9, 126.1, 126.9, 127.7, 130.1, 132.3, 132.6, 135.1, 135.8, 138.2, 140.3, 140.4, 140.9, 141.2, 144.5, 150.7, 150.9, 151.2, 152.0, 152.8, 153.5, 153.8, 153.9, 154.2, 156.5, 158.3, 158.5, 163.1, 164.4; UV–vis in methylene chloride λ_{max} [nm]=422.0, 549.0, 468.0. API-ES-MS *m/z*: $[M\text{-}PF_6]^+$ 1904.7, $[M\text{-}2PF_6]^{2+}$, 879.0 Anal. Calcd for $C_{100}H_{93}F_{12}N_{11}O_9P_2RuZn\cdot 1.2CH_2Cl_2$: C, 56.50; H, 4.47; N, 7.16. Found: C, 56.85; H, 4.51; N, 6.78.

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Theoretical studies on formal hetero [3+3] cycloaddition reaction between vinylogous amide and α,β-unsaturated imine cation

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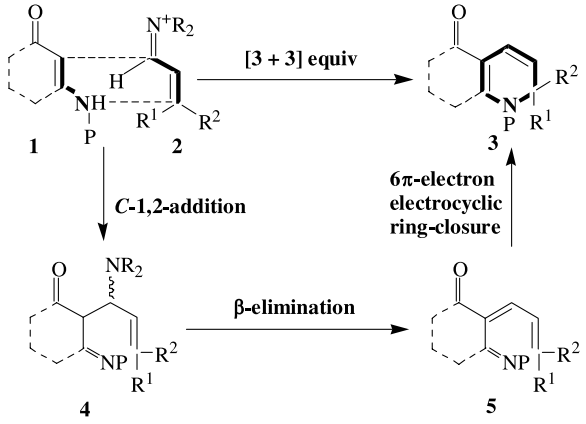
Abstract—Density functional theory (DFT) calculations at B3LYP/6-31G** level have been carried out to study the mechanism of title reaction. The whole picture for the possible mechanism has been explored and verified both in gas phase and $C_6H_5CH_3$ solvent. The calculated results show that this reaction proceeds via the following several steps: (1) addition of two reactant molecules; (2) removing of $\mathbf{H}^+$ and succedent elimination of $\mathbf{NH_3}$ from intermediates; (3) isomerization and final cyclization of intermediates, in which the elimination step of $\mathbf{NH_3}$ is the rate-controlling one in the whole reaction process. The final product has two competitive parallel paths, in which the 6π-electron electrocyclic ring closure is not reversible.

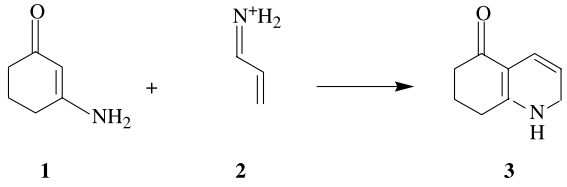
1. Introduction

Cycloaddition and annulation reactions are very important methods for the synthesis of monocyclic or polycyclic carbocycles and heterocycles through a concerted, stepwise, or sequential process. Extensive attention has been paid to this field, including experimental and theoretical studies. Recently, the experimental chemists have investigated the reactions of vinylogous amides with α,β-unsaturated iminium salts leading to 1,2-dihydropyridines, including intermolecular[1] and intramolecular[2] reactions. These reactions can be seen as formal hetero [3+3] cycloaddition reactions[3] and are useful for synthesis of complicated heterocycles. The experimental investigations suggested that these reactions involve a sequence that consists of a *C*-1,2-addition to an iminium salt followed by β-elimination that gives an 1-azatriene and a 6π-electron electrocyclic ring-closure of 1-azatriene[4] as shown in Scheme 1.



Scheme 1.

However, it remains to be answered for several questions, for example, how and when the H^+ and R_2NH are to be removed? What is the whole reaction pattern? Which step is the rate-controlling one? The theoretical investigations will shed light on the mechanistic details of these reactions. Therefore, the model reaction, shown in Scheme 2, is considered in this paper for simplicity.



Scheme 2.

2. Computational methods

All calculations included in this work have been performed with the Gaussian03 program package.[5] The geometries of reactants, products, complexes, intermediates, and transition states have been fully optimized by using Density

Keywords: [3+3] Cycloaddition; Vinylogous amide; α,β-Unsaturated imine cation; Calculations; DFT.
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functional theory (DFT) methods. All the geometric parameters of the possible stationary points have been located at the B3LYP/6-31G** level and characterized by the number of imaginary frequencies. For some key reaction pathways, the Intrinsic Reaction Coordinate (IRC)[6] has also been traced to confirm the **TS** connecting with the corresponding two minima. In order to simulate the real reaction condition, the Polarized Continuum (overlapping spheres) model (PCM)[7] and $C_6H_5CH_3$ as the solvent have been employed to study the solvent effects at the temperature of 298.15 K.

The bonding character and charge distribution for some stationary points have been studied with Bader's AIM theory,[8] which is very suitable for studying the properties of the weak bonds, such as hydrogen bonds. The topological properties of the electron density distribution of a molecule are based on the gradient vector field of the electron density $\rho(\mathbf{r})$ and on the Laplacian of the electron density $\nabla^2\rho(\mathbf{r})$, where $\mathbf{r}$ is the positional vector of an electron in three-dimensional space.

The AIM98PC package,[9] a PC version of AIMPAC,[10] has been employed for the electron density topological analysis, using the wave functions obtained with the B3LYP/6-31G** calculations.

3. Results and discussions

The calculation results indicate that the title reaction take place via a sequential mechanism (see Scheme 3). The first step is the addition reaction between two reactants **1** and **2** with formation of a cation intermediate **INT1**. The removing of $\mathbf{H}^+$ is promoted by the nucleophilic attack of $\mathbf{AcO}^-$ to the H atom and the succedent 1,4-elimination of $\mathbf{NH_3}$ from **INT1** affords the molecular intermediate **INT4**. The subsequent isomerization of **INT4** and the final electrocyclic ring-closure yield the product **3**.

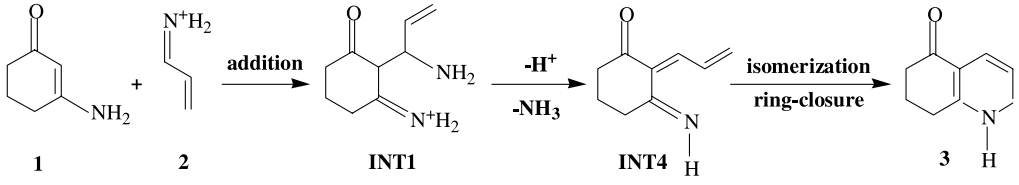
3.1. The addition reaction step of two reactants 1 and 2

Reactant **2** has two isomers, only *trans*-isomer was considered in the present discussion because it is about 4.9 kcal/mol below the *cis*-one. On this addition path, complex (**COM1**), transition state (**TS1**), and intermediate (**INT1**) formed from **1** and **2** have been located (see Scheme 4) and the connection between **COM1** and **INT1** through **TS1** is confirmed by IRC calculations. A hydrogen bond complex **COM1** is first formed when reactant **1** approaches **2**, in which most frame atoms are basically on the same plane except C1 as in reactant **1**. The O2–H5 bond distance is 1.884 Å, indicating that a typical C–H···O hydrogen bond[11] is involved in such complex. The bond lengths of H5–C4 and O2–C6 are 1.101 and 1.251 Å respectively, about 0.012, and 0.023 Å longer than the corresponding ones in **1** and **2**. In the formation of **INT1**, the bond distance of C4–C3 changes dramatically, which ranges from 4.769 (in **COM1**) to 2.014 (in **TS1**), and to 1.568 Å (in **INT1**). There exists a N–H···N hydrogen bond in **INT1**, whose hydrogen-bond length H···N is 1.695 Å. The geometries of **COM1** and **TS1** are displayed in Figure 1.

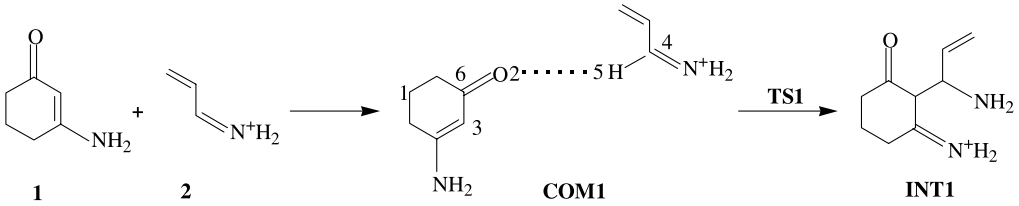
The schematic potential energy surface for the addition reaction step is shown in Figure 2, from which one can realize that the stationary points along this reaction pathway are well below the reactant's asymptote due to the formation of **COM1** (with a stabilization energy of 27.4 kcal/mol in gas phase). Such large interaction is far away from the general hydrogen bond for neutral molecules. However, the charge transfer through the hydrogen bond is obvious (0.13e from **1** to **2**), which disperses the positive charge. Transition state **TS1** lays 22.1 kcal/mol above **COM1**, but still 5.3 kcal/mol below the reactants. Complexation of two reactant molecules makes the addition step easy to proceed.

Topological analysis, shown in Figure 3a, indicates that there is a hydrogen bond interaction between two portions of reactants in **COM1**, i.e. C–H···O type hydrogen bond interaction, and the electron density at this bond critical point is 0.03 au. The **INT1** is of N–H···N hydrogen bond, in which the electron density of bond critical point is 0.06 au.

We have also considered the solvent effect with $C_6H_5CH_3$ as solvent. The geometric parameters obtained for the possible stationary points are similar to those in the gas phase, accordingly, the geometric data involved below are for the gas phase unless stated in particular. But **COM1** has only



Scheme 3.



Scheme 4.

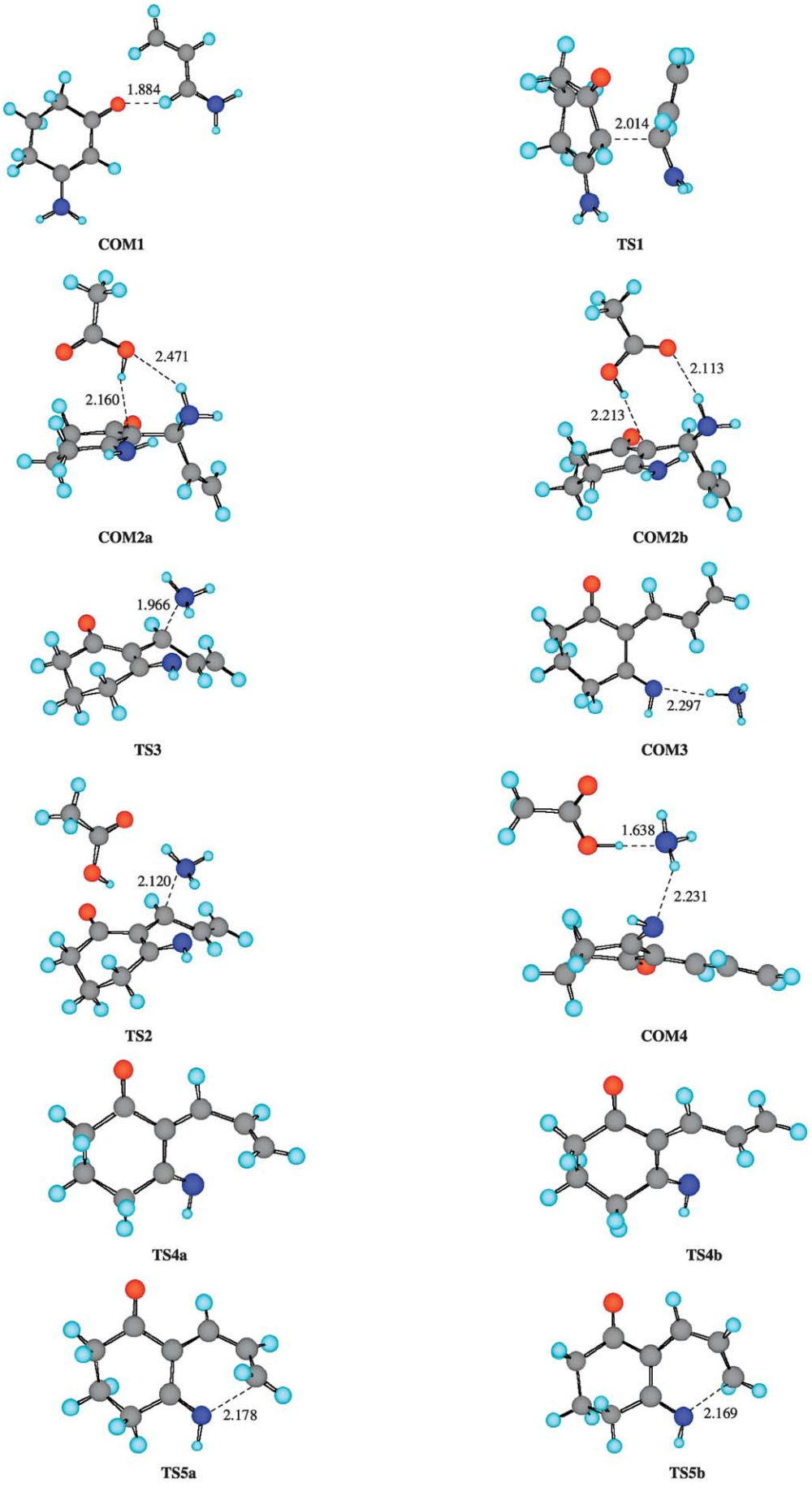


Figure 1. Geometric structures of the optimized stationary points, along with the values of the bond lengths directly involved in the process.

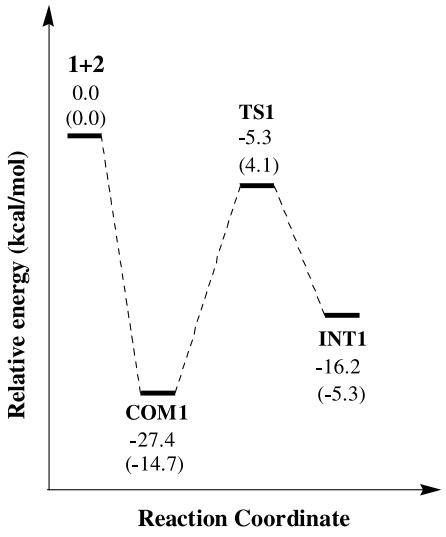
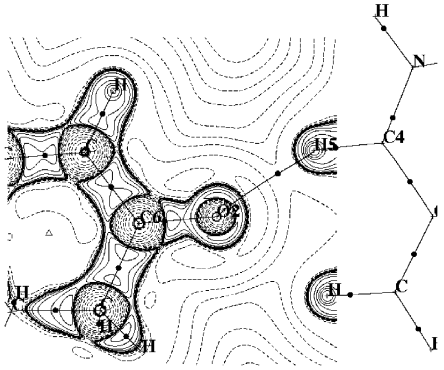


Figure 2. The schematic potential energy profile for the formation of **INT1** (the data in parentheses are for solution phase).

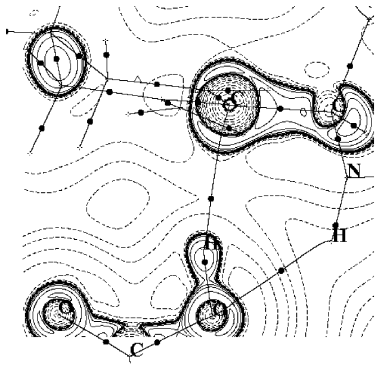
14.7 kcal/mol in energy lower than the reactants, 12.7 kcal/mol less stable than that in the gas phase (see Fig. 2). Meanwhile, **TS1** becomes about 4.1 kcal/mol above the reactants, which is also different from the value in gas phase. This reflects the fact that reactant **2** is more susceptible to solvent effect than **COM1**, **TS1** and **INT1** although it becomes more stable for both cation and anion systems in solution than in gas phase generally.

3.2. Removing of H^+ and succedent elimination of NH_3

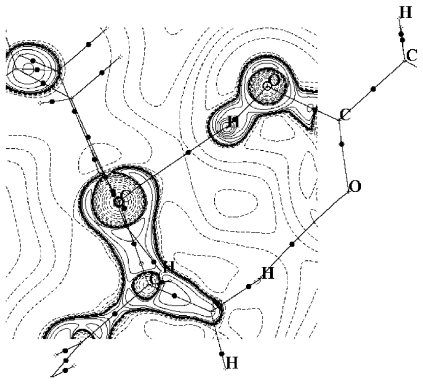
There are two hydrogen atoms in the adduct **INT1** (see Scheme 5), which may be removed, i.e. H atom on C1 or H5 on N2. According to experimental suggestions, H5 on N2 should be removed from **INT1** before the 1,2-elimination of **NH_3** molecule, but we found that if H5 on N2 is removed to form intermediate **INT2**, it always fails to locate the transition state to eliminate NH_3 molecule from **INT2**. In fact, once H atom on C1 approaches toward N3, one of hydrogen atoms on N3 will shift to N2 to form intermediate **INT3**, which is much more stable than **INT2** (20.3 kcal/mol below **INT2** at B3LYP/6-31G** level in gas phase). In addition, the H atom on N2 is on the crowded position, which is difficult for the attacking of **AcO^-** in the reaction solution. The obtained reaction pathway to remove **H^+** is shown in Scheme 5, from which one can realize that the O atom in **AcO^-** attacks H atom on C1 in **INT1** to form **COM2a** or **COM2b** without any energy barrier. **COM2a** and **COM2b** are typical molecular complexes between **AcOH** and **INT3**, in which the C–H bond lengths to be broken are 2.160 and 2.213 Å respectively (see Fig. 1). All the possible reaction pathways for the NH_3 elimination process are explored, in which **COM3**(from **INT4** and **NH_3**) could be formed via the 1,4-elimination of **NH_3** from **INT3**, which originates from either **COM2a** or **COM2b**. Two types of hydrogen bonds could be found for **COM2a** and **COM2b** as shown in Figure 3b and c. The electron density for bond critical point of O–H···C in **COM2a** and



(a) **COM1**

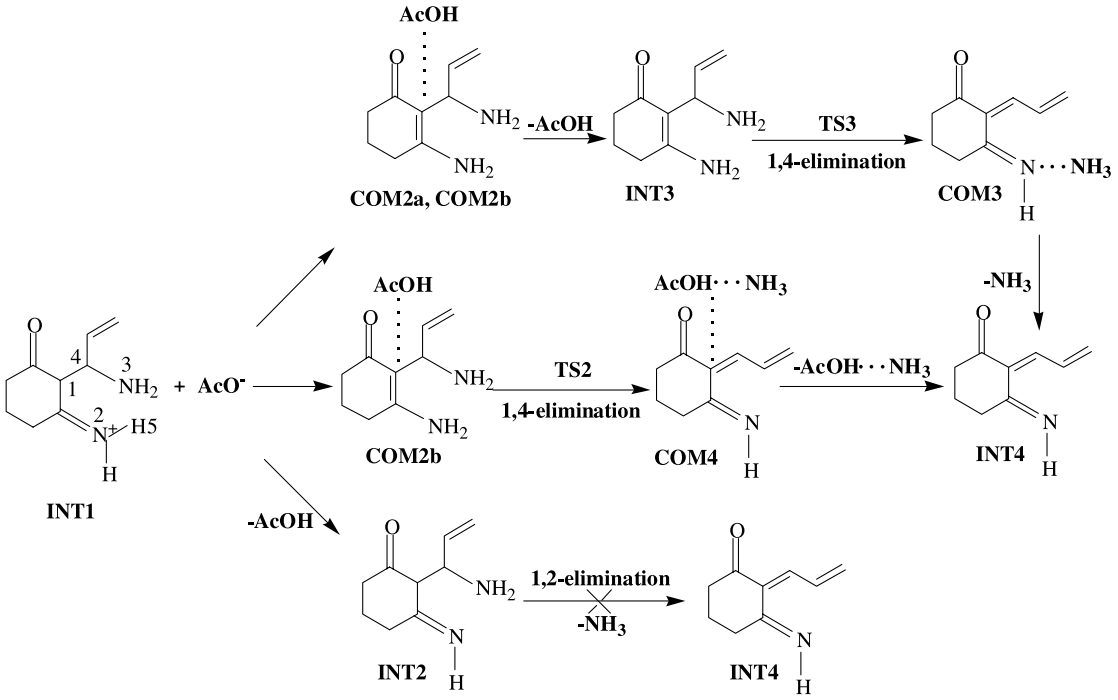


(b) **COM2a**



(c) **COM2b**

Figure 3. The molecular graphs and Laplacian distribution of some stationary points. In these figures, dashed lines denote positive value of $\nabla^2\rho_b$ and full lines stand for negative values of $\nabla^2\rho_b$. The bonded charge concentrations are indicated by solid squares. In addition, bond paths (heavy solid lines), bond critical points (solid circle), and ring critical points (triangle) are shown for $\rho(\mathbf{r})$.



Scheme 5.

COM2b are 0.02 and 0.02 au, respectively. As for N–H···O, the values of ρ_b are 0.01 and 0.02 au, respectively, which reveal the weaker interaction. In **INT3**, an intramolecular N–H···N hydrogen bond is formed and the bond distance of H···N is only 1.969 Å. When N3–C4 bond is lengthened, H5 approaches N3 gradually to form a complex **COM3** via **TS3**, in which the bond distances of N3–C4, H5–N3 and H5–N2 are 1.966, 1.034 and 2.007 Å respectively. **COM3** is also an intermolecular hydrogen bond complex between intermediate **INT4** and $\mathbf{NH_3}$, with the bond length of H5–N2 being 2.297 Å. Another pathway is the 1,4-elimination of $\mathbf{NH_3}$ from **COM2b** via **TS2** directly, which is similar to the former, but the structure of **COM4** is different from that of **COM3** as shown in Figure 1. The intermediate **INT4** can react further, which would be discussed in Section 3.3.

The schematic potential energy surface for the removing of $\mathbf{H^+}$ and elimination of $\mathbf{NH_3}$ is given in Figure 4, from which

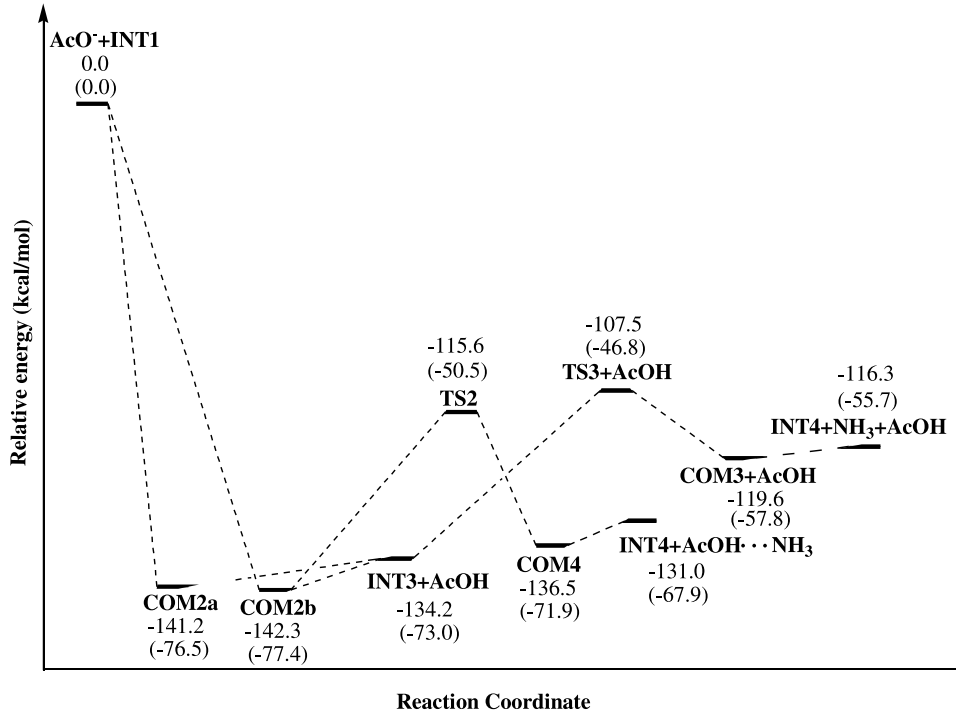
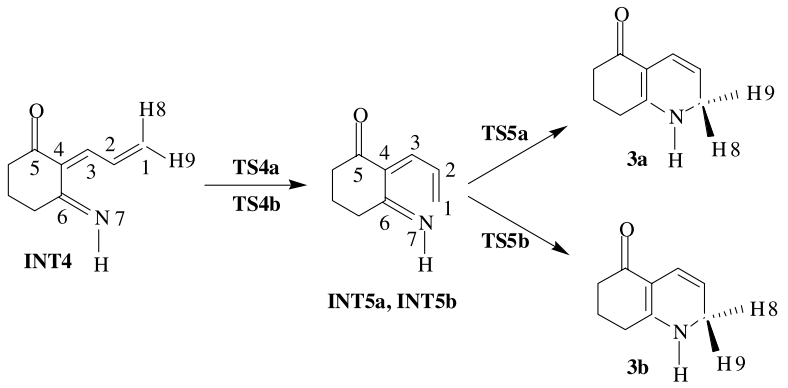


Figure 4. Schematic description of the potential energy profile for the elimination of $\mathbf{H^+}$ and $\mathbf{NH_3}$ (the data in parentheses are for solution phase).



Scheme 6.

one can realize that $\mathbf{AcO}^-$ collides with **INT1** cation to form **COM2a** or **COM2b** directly without climbing up any energy barrier. From the data in Figure 4, one can also see that the relative energies of stationary points are comparable both in gas and $C_6H_5CH_3$ solution, except that of $\mathbf{AcO}^-$ + **INT1** in solution phase differs remarkably from that in gas phase. However, the solvent $C_6H_5CH_3$ has only negligible influence on the energy barriers of the elimination processes of $\mathbf{NH_3}$. The energy of **COM2a** is 141.2 kcal/mol lower than that of $\mathbf{AcO}^-$ + **INT1** in gas phase, but it becomes only 76.5 kcal/mol with $C_6H_5CH_3$ solvent. Such dramatic change comes from the lowering of energy for $\mathbf{AcO}^-$, which has the same trend for ion system as pointed out in previous section. The formation of **COM2a** and **COM2b** need not to overcome any activation barrier, therefore, the elimination of $\mathbf{H}^+$ is very easy. In addition, considering $\mathbf{AcO}^-$ as an anion, calculations with diffuse basis sets for $\mathbf{AcO}^-$, **INT1** and **COM2a** may be necessary. Because the energies of B3LYP/6-31+G**//B3LYP/6-31G** single-point calculations are very close to those of the optimized geometries at B3LYP/6-31+G** level in gas phase, so only SCRF-B3LYP/6-31+G**//B3LYP/6-31G** single-point calculations were taken into account. It was found that the relative energy of **COM2a** becomes −128.8 (in gas phase) or −64.5 kcal/mol (in $C_6H_5CH_3$ solvent), about 12 kcal/mol higher than those with 6-31G** and the results for other stationary points are also similar. Accordingly, we can draw the conclusion that the basis set effect makes the whole energy profile a little upward shift, but solvent effect takes more important role in our present systems. However, they do not change the reaction mechanism. After removing of $\mathbf{H}^+$, the elimination of $\mathbf{NH_3}$ needs to overcome an energy barrier of about 27 kcal/mol from either **INT3** or **COM2b**. However, due to the release of an excess energy from the formation of **COM2a** and **COM2b**, such process should proceed easily.

3.3. The isomerization of INT4 and final cyclization

In this section, we will discuss the isomerization of **INT4** and cyclization reaction. The C4–C3 and C2–C1 bonds in **INT4** are of double bond character (C4–C3 = 1.366 and C2–C1 = 1.346 Å) and are in *trans*-structure (the dihedral angle C4–C3–C2–C1 = −179.8°, see Scheme 6). In order to get the final product, the *trans* structure of **INT4** should isomerize into *gauche* structures of **INT5a** or **INT5b** first. Two transition states **TS4a** and **TS4b**, corresponding to two opposite rotations around C3–C2 single bond, have been located for the isomerization process of **INT4**. The torsional angles of C4–C3–C2–C1 for **TS4a**, **TS4b**, **INT5a** and **INT5b** are −78.5, 94.6, −29.0 and 29.9°, respectively, and the angles of N7–C6–C4–C5 for **INT5a** and **INT5b** are −151.7 and 151.0°, respectively. In **INT5a** and **INT5b**, the bond distances of N7–C1 are 2.946 and 2.948 Å, while they

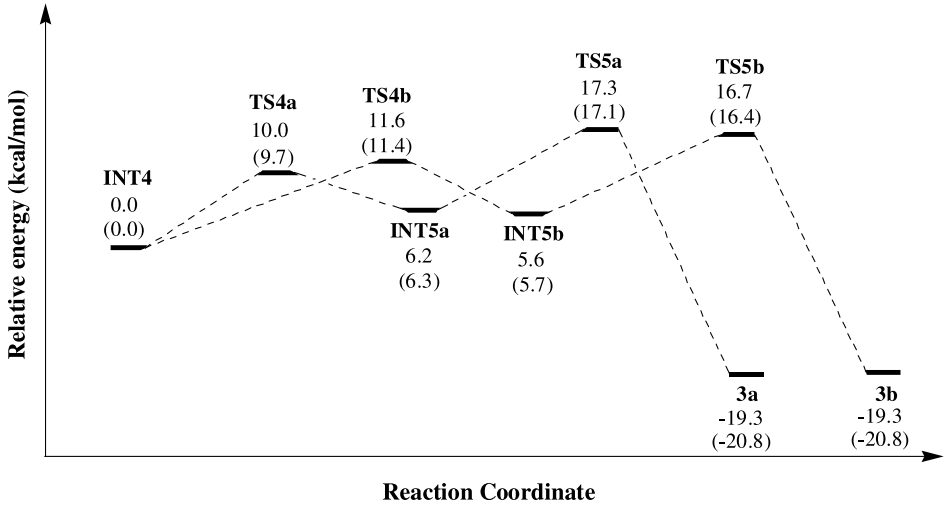


Figure 5. Schematic potential energy profile for the isomerization of **INT4** and final cyclization (the data in parentheses are for solution phase).

become 2.178 and 2.169 Å in **TS5a** and **TS5b** (see Fig. 1). For present model system, final cyclization products **3a** and **3b** are identical. But if a substituent group displaces the position of H9 atom as in real experiments, **3a** and **3b** will be different, i.e. such reactions will yield two isomers. Further works will be done on this subject.

The relative energies for the stationary points are given in Figure 5, from which one can see that the solvent $C_6H_5CH_3$ has also only negligible influence on the relative energies of the stationary points. **INT4** is of about 6 kcal/mol more stable than **INT5a** and **INT5b** due to less steric hindrance. The **TS4a** is about 1.6 kcal/mol more stable than **TS4b**, but the energy barrier from **INT5a** to **3a** is almost the same as that from **INT5b** to **3b**. It should be indicated that a transition state connecting **INT5a** with **INT5b** is located, which is only 0.3 or 0.9 kcal/mol higher than **INT5a** or **INT5b**, which means that **INT5a** and **INT5b** can be converted freely. In addition, the energy barrier for the reverse process is about 36 kcal/mol, which indicates that the cyclization step for the model reaction is not reversible unless in unusual condition.

4. Conclusions

The mechanism for the formal [3+3] cycloaddition reaction between vinylogous amide and α,β-unsaturated imine cation has been studied by using DFT methods. This reaction takes place via the following several steps: (1) addition of two reactant molecules; (2) removing of $\mathbf{H}^+$ and succedent elimination of $\mathbf{NH_3}$ from intermediates; (3) isomerization and final cyclization of intermediates. The formation of final products has parallel pathway of mutual competition. The addition step and the elimination of $\mathbf{H}^+$ are easy to proceed and the elimination of $\mathbf{NH_3}$ is the rate-controlling step for the whole reaction. The solvent $C_6H_5CH_3$ has notable influence on the potential energy surface of the reaction steps involving cation and anion species, but it has a trivial effect on the steps involving only neutral molecules.

Acknowledgements

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A novel method for synthesis of arylacetic acids from aldehydes, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine and trimethylsilylcyanide

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Abstract—A novel synthetic approach for the preparation of arylacetic acids via the reaction of aldehydes, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine and trimethylsilylcyanide was developed, in which the *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine can be recycled conveniently and reused efficiently.

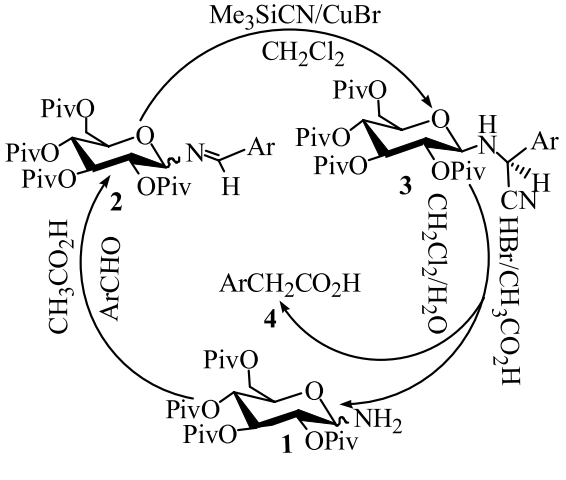
1. Introduction

In recent years, arylacetic acids and their derivatives have received much more attention because they are versatile intermediates in the synthesis of a vast range of pharmaceuticals, cosmetics, and fragrances.[1]

As a consequence of the potent biological activity associated with arylacetic acids and their derivatives, many synthetic methodologies have been developed over the past decade, including carbonylation, addition hydrolysis and electrolysis, oxidation etc.[2] However, most of them need harsh reaction conditions such as use of expensive catalysts, high pressure, high temperature etc., especially some of them suffered from long reaction time, unsatisfactory yields, tedious work-up or cumbersome product isolation procedures etc. Therefore, it is highly desirable to develop an operationally simple, effective and benign synthetic procedure for the synthesis of arylacetic acids and their derivatives from readily available materials.

Our considerable current research interest is in the asymmetric synthesis, which is enlightened by Kunz's work, etc.,[3] using *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)aldimine as chiral template. During the course of our studies on stereoselective synthesis of α-amino acids, unexpectedly, instead of the desirable formation of α-amino acids, only arylacetic acids were obtained from the reaction of aldehydes, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine and trimethylsilylcyanide. To the best of our knowledge, such transformation for synthesis of arylacetic acids has not been reported previously.

Herein, we report a successful and novel synthesis of arylacetic acids by the reaction of aldehydes, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine and TMSCN at ambient temperature (shown in Scheme 1).



Piv =(CH_3)$_3$CCO-

Scheme 1. (a) Ar=C_6H_5; (b) Ar=C_6H_5-4-CH_3; (c) Ar=C_6H_5-2-OH; (d) Ar=C_6H_5-4-OCH_3; (e) Ar=C_6H_5-4-Cl; (f) Ar=C_6H_5-4-F; (g) Ar=C_6H_5-2-F; (h) Ar=C_6H_5-4-NO_2; (i) Ar=C_6H_5-3-NO_2; (j) Ar=2-furyl.

Keywords: Arylacetic acids; *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopryanosyl)amine; Aldehyde; Triethylsilylcyanide.
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2. Results and discussion

2.1. Preparation of *N*-(2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosyl)aldimines

Imines are readily accessible by simple condensation of aldehydes with amines, which act as important intermediates in the synthesis of amino acids, β-lactams, heterocycles, alkaloids, aziridines, and amines etc.[4]

In order to prepare *N*-(2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosyl)aldimines, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine **1** was reacted with aldehydes in the presence of acetic acid in 2-propanol. The reactions were proceeded smoothly within a short period of time at room temperature under extremely mild conditions to afford desired products **2a**–**j** in yields of 90% or higher. The results were listed in Table 1.

Based on the experiments, it was found that the rates of the condensation of the electron-poor aromatic aldehydes with **1** were much higher than those of the electron-rich aromatic aldehydes. To further, explore the structure of **2**, a single-crystal X-ray diffraction study of **2c** was performed (CCDC 264908). The molecular structure of **2c** was shown in Figure 1, and the structure was consistent with that of 2-hydroxyl-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine.[5]

Table 1. The condensation of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine **1** with aldehydes at room temperature

Product **2**	Ar	Time (h)	Yield (%)	^{13}C NMR of C=N
2a	C_6H_5	0.5	90	161.1
2b	C_6H_4–CH_3	1.0	93	161.7
2c	C_6H_4-2-OH	1.5	92	165.2
2d	C_6H_4-4-OCH_3	2.5	90	162.7
2e	C_6H_4-4-Cl	1.0	92	159.9
2f	C_6H_4-4-F	0.5	93	162.7
2g	C_6H_4-2-F	0.5	91	161.9
2h	C_6H_4-4-NO_2	0.25	95	158.0
2i	C_6H_4-3-NO_2	0.25	96	157.4
2j	2-Furyl–	2.0	90	151.7

2.2. The Strecker reaction of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)aldimines with trimethylsilylcyanide: synthesis of α-amino nitriles 3

The nucleophilic addition reaction of the imine needs to be promoted by Lewis acids,[6] especially for the Strecker reaction. So several kinds of Lewis acid were first examined for the Strecker reaction of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)aldimines with trimethylsilylcyanide. In the case of the synthesis of **3a**, Lewis acids such as $SnCl_4$, $TiCl_4$, $AlCl_3$, CuBr, $ZnCl_2$ and ZnI_2 were studied for this transformation, the results were summarized in Table 2.

Table 2. Effects of the catalysts for the conversion from **2a** to **3a**

Entry	Lewis acid (equiv)	Reaction period (h)	Yield of **3a** (%)
1	$SnCl_4$ (1.0)	3.0	71
2	$TiCl_4$ (1.0)	3.0	60
3	$AlCl_3$ (1.0)	3.0	58
4	$ZnCl_2$ (1.0)	3.0	42
5	ZnI_2 (1.0)	3.0	45
6	CuBr (1.0)	3.0	81
7	CuBr (0.1)	4.0	40
8	CuBr (0.25)	3.5	60
9	CuBr (0.5)	3.5	72
10	CuBr (1.25)	3.0	90
11	CuBr (2.5)	3.0	89
12	CuBr (5.0)	3.0	90

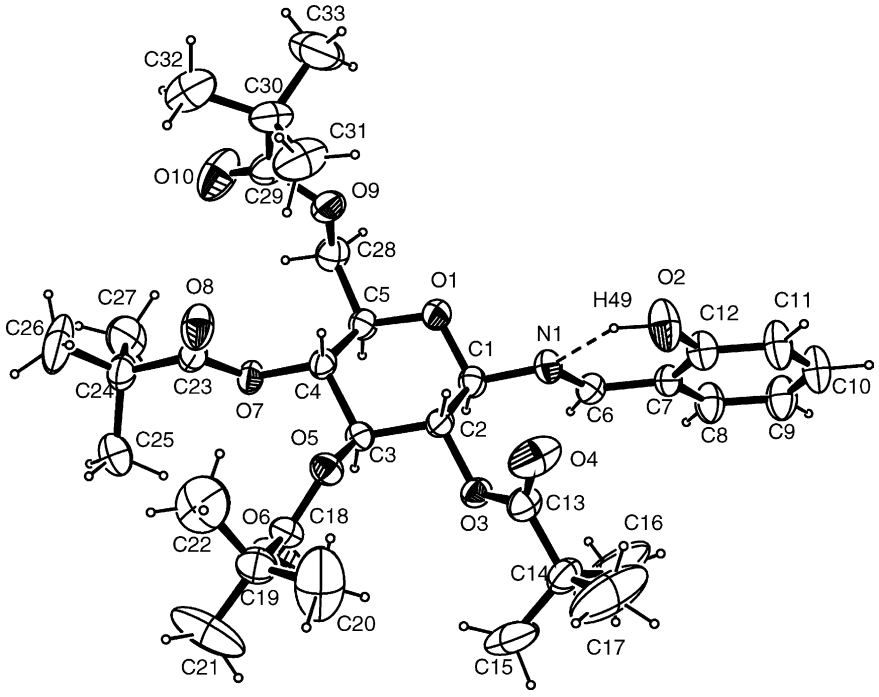


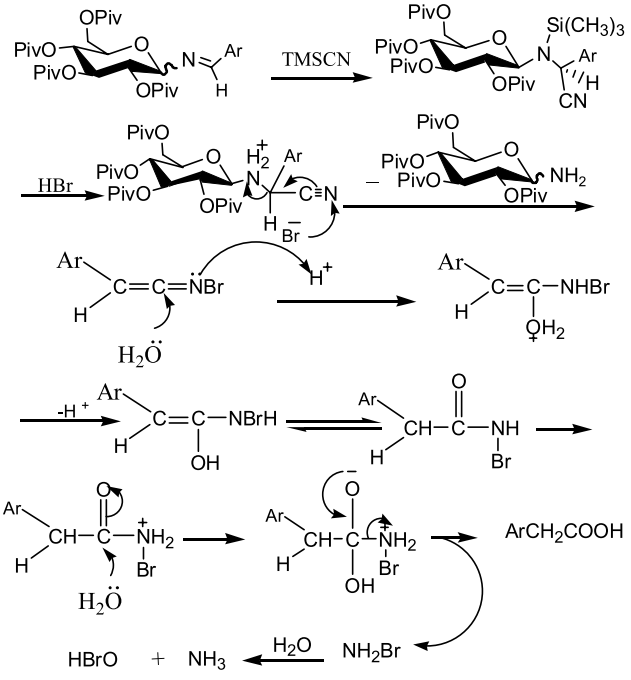
Figure 1. Crystal structure of **2c**.

It was found that the conversion of **3a** in low yields with $TiCl_4$, $AlCl_3$, $ZnCl_2$ and ZnI_2. On the other hand, $SnCl_4$ and CuBr were found to be more effective in terms of conversion and reactivity for **3a**, however, $SnCl_4$ is more sensitive to the moisture than CuBr. Therefore, CuBr was addressed as the most efficient Lewis acid in this reaction.

Under optimal condition, 1.0 mmol of **2a–j** was treated with TMSCN (1.0 mmol) in the presence of CuBr (1.25 mmol) at room temperature, using dichloromethane as the solvent.

Table 3. The Strecker reaction of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)aldimines **2a–j** at room temperature

Product **3**	Ar	Time (h)	Yield (%)	^{13}C NMR of CN
3a	C_6H_5	3.0	90	114.3
3b	C_6H_4–CH_3	3.5	92	114.7
3c	C_6H_4-2-OH	5.0	89	113.4
3d	C_6H_4-4-OCH_3	6.0	85	114.3
3e	C_6H_4-4-Cl	4.0	86	114.7
3f	C_6H_4-4-F	2.5	88	114.3
3g	C_6H_4-2-F	3.0	90	114.5
3h	C_6H_4-4-NO_2	2.0	89	115.5
3i	C_6H_4-3-NO_2	2.0	91	116.7
3j	2-Furyl–	4.0	85	114.9



Scheme 2.

The reactions were completed in 2–8 h and gave **3a–j**, which were verified by ^{1}H NMR, ^{13}C NMR, MS and IR, in excellent yields (Table 3).

2.3. Synthesis of arylacetic acids

Acid-catalyzed hydrolysis of α-amino nitriles[5d] is the key step of the generation of arylacetic acids. Our original objective was to detach the α-amino acids from the carbohydrate moiety by the treatment of the α-amino nitriles **3** with hydrogen bromide in acetic acid at room temperature. However, during our research, we found when α-amino nitriles **3** were treated with hydrogen bromide (45%) in acetic acid/dichloromethane in the presence of water at room temperature, an unexpected process of rupture of N–C bond took place and gave arylacetic acids rather than the amino acids (Scheme 2), in which the amine **1** was regenerated.

In our process, after the hydrolysis reaction was accomplished, the arylacetic acids could be separated by a simple phase separation process and 2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosylamine **1** could be recycled conveniently from the filtrate and reused efficiently.

To evaluate the scope and generality of this transformation, various substituted arylacetic acids have been synthesized successfully by the same strategy. The results were listed in Table 4.

The possible mechanism we deduced was shown in Scheme 2.

3. Conclusion

In conclusion, we have developed a method for the synthesis of arylacetic acids from the reaction of aldehydes, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)amine and TMSCN, which has the advantages of recycling of the template amine **1** thus, high efficiency and the mild reaction conditions as well. Hence, this method could provide a convenient access to arylacetic acids, in which the imine could be transformed into methylene, a new carbon–carbon bond formed to extend the carbon chain. Further studies along this line are now in progress in our laboratory.

Table 4. Synthesis of arylacetic acids from α-amino nitriles **3**

Product **4**	Ar	Time (h)	Yield (%)	Mp (°C)	^{13}C NMR of CO_2H	^{13}C NMR of α-C
4a	Phenyl–	1.0	91	76–78	191.8	45.2
4b	C_6H_4–CH_3	1.0	89	91–92	191.9	45.8
4c	C_6H_4-2-OH	1.5	87	145–148	192.2	45.6
4d	C_6H_4-4-OCH_3	2.0	85	85–87	192.5	46.0
4e	C_6H_4-4-Cl	1.0	92	104–106	191.2	45.3
4f	C_6H_4-4-F	1.5	90	82–85	192.5	45.2
4g	C_6H_4-2-F	1.0	91	60–63	194.1	50.9
4h	C_6H_4-4-NO_2	0.5	92	153–155	193.0	46.0
4i	C_6H_4-3-NO_2	0.5	93	118–120	192.7	46.2
4j	2-Furyl–	1.5	90	90–92	181.9	44.3

4. Experimental

4.1. General

Commercially available chemicals were reagent grade and CH_2Cl_2 was distilled from CaH_2 freshly prior to use. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or D_2O on a Bruker AVANCE DRX-500 NMR spectrometer, using TMS as the internal standard. ESIMS were acquired on a Bruker Esquire 3000 plus spectrometer. IR spectra were determined on a Nicolet NEXUS-470 FT-IR spectrometer as KBr pellets. Melting points were determined on an X4-Data microscopic melting point apparatus. Analytical TLC was performed on a Merck precoated TLC (silica gel 60 F254) plate. Elemental analyses were performed on Carlo-Erba 1106. X-ray measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo Kα.

4.2. Typical procedure for the preparation of *N*-(2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosyl)aldimines 2a–j

To a solution of **1** (0.515 g, 1 mmol) and aldehyde (1.3 mmol) in 2-propanol (2.5 mL), 2–3 drops of acetic acid were added and the mixture was stirred at room temperature for 20 min to 3 h. The appearance of a precipitate from the solution indicated the formation of **2**, which was filtered and washed rapidly with ice cold 2-propanol and dried in vacuum.

4.2.1. *N*-(2,3,4,6-Tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2a). Mp 142–145 °C; yield 90%; *m/z* (ESI): 604.3 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.19 (s, 1H), 7.71 (d, $J=7.0$ Hz, 2H), 7.52 (t, $J=6.9$ Hz, 1H), 7.39 (t, $J=6.6$ Hz, 2H), 5.46 (t, $J=9.4$ Hz, 1H), 5.25 (t, $J=9.7$ Hz, 1H), 5.05 (t, $J=4.5$ Hz, 1H), 4.72 (d, $J=8.8$ Hz, 1H), 4.29 (d, $J=12.1$ Hz, 1H), 4.19 (q, $J=4.7$ Hz, 1H), 3.91 (t, $J=3.6$ Hz, 1H), 1.03–1.29 (m, 36H); ^{13}C NMR ($CDCl_3$) δ 178.3, 177.2, 177.0, 176.3, 161.1, 134.7, 131.4, 128.9, 128.5, 91.5, 72.8, 71.9, 69.2, 67.9, 61.8, 38.6, 27.0–27.1; IR (KBr, cm^{-1}) ν: 2980, 1740, 1648, 1580, 1481, 1459, 1398, 1366, 761. Anal. Calcd for $C_{33}H_{49}NO_9$: C, 65.65; H, 8.18; N, 2.32. Found: C, 65.68; H, 8.16; N, 2.33.

4.2.2. 4-Methyl-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2b). Mp 169–170 °C; yield 93%; *m/z* (ESI): 618.5 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.36 (s, 1H), 7.61 (d, $J=7.9$ Hz, 2H), 7.20 (d, $J=7.9$ Hz, 2H), 5.47 (t, $J=9.5$ Hz, 1H), 5.25 (t, $J=9.6$ Hz, 1H), 5.06 (t, $J=9.2$ Hz, 1H), 4.86 (d, $J=8.8$ Hz, 1H), 4.27 (d, $J=10.9$ Hz, 1H), 4.18 (q, $J=4.9$ Hz, 1H), 3.90–39.2 (m, 1H), 2.38 (s, 3H), 1.03–1.25 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.5, 176.6, 176.4, 161.6, 142.2, 132.8, 129.5, 129.0, 93.8, 74.4, 73.1, 72.2, 68.2, 62.1, 38.9–39.1, 27.2–27.4, 21.8; IR (KBr, cm^{-1}): ν 2973, 1743, 1647, 1480, 1380, 1282, 1140, 1075, 763. Anal. Calcd for $C_{34}H_{51}NO_9$: C, 66.10; H, 8.32; N, 2.27. Found: C, 66.08; H, 8.29; N, 2.36.

4.2.3. 2-Hydroxyl-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2c). Mp 195–197 °C; yield 92%; *m/z* (ESI): 620.2 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.54 (s, 1H), 7.34 (t, $J=7.3$ Hz, 1H), 7.28 (d, $J=7.8$ Hz, 1H), 6.94 (d, $J=7.6$ Hz, 1H), 6.89 (t, $J=7.0$ Hz, 1H), 5.49 (t, $J=9.3$ Hz, 1H), 5.24 (t, $J=9.6$ Hz, 1H), 5.06 (t, $J=9.2$ Hz, 1H), 4.97 (d, $J=8.8$ Hz, 1H), 4.31 (d, $J=12.3$ Hz, 1H), 4.18 (q, $J=4.7$ Hz, 1H), 3.92 (t, $J=4.4$ Hz, 1H), 1.07–1.29 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.3, 177.5, 176.7, 176.6, 165.2, 161.0, 133.6, 132.7, 119.2, 118.4, 117.5, 90.3, 74.6, 73.0, 72.4, 68.0, 61.8, 39.0–39.2, 27.3–27.4; IR (KBr, cm^{-1}): ν 3480, 2990, 1750, 1625, 1614, 1495, 1530, 1300, 1250, 750. Anal. Calcd for $C_{33}H_{49}NO_{10}$: C, 63.95; H, 7.97; N, 2.26. Found: C, 63.93; H, 7.95; N, 2.30.

4.2.4. 4-Methoxy-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2d). Mp 150–153 °C; yield 90%; *m/z* (ESI): 634.2 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.31 (s, 1H), 7.66 (d, $J=8.0$ Hz, 2H), 6.90 (d, $J=8.0$ Hz, 2H), 5.45 (t, $J=9.4$ Hz, 1H), 5.25 (t, $J=9.6$ Hz, 1H), 5.06 (t, $J=9.2$ Hz, 1H), 4.81 (d, $J=8.5$ Hz, 1H), 4.26 (d, $J=11.9$ Hz, 1H), 4.18 (q, $J=7.5$ Hz, 1H), 3.89 (d, $J=5.8$ Hz, 1H), 3.83 (s, 3H), 1.04–1.22 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.6, 176.7, 176.5, 162.6, 161.5, 130.8, 128.3, 114.3, 94.5, 74.4, 73.1, 72.2, 68.2, 62.2, 55.6, 38.9–39.1, 27.2–27.4; IR (KBr, cm^{-1}): ν 2973, 1738, 1649, 1607, 1578, 1513, 1481, 1397, 1281, 1253, 1150, 762. Anal. Calcd for $C_{34}H_{51}NO_{10}$: C, 64.43; H, 8.11; N, 2.21. Found: C, 64.45; H, 8.08; N, 2.25.

4.2.5. 4-Chloro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2e). Mp 178–180 °C; yield 92%; *m/z* (ESI): 638.1 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.36 (s, 1H), 7.65 (d, $J=8.3$ Hz, 2H), 7.37 (d, $J=8.3$ Hz, 2H), 5.47 (t, $J=9.5$ Hz, 1H), 5.23 (t, $J=9.6$ Hz, 1H), 5.00 (t, $J=9.2$ Hz, 1H), 4.91 (d, $J=8.9$ Hz, 1H), 4.30 (d, $J=1.3$ Hz, 1H), 4.17 (q, $J=4.9$ Hz, 1H), 3.90 (q, $J=3.5$ Hz, 1H), 1.02–1.25 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.4, 176.7, 176.6, 159.8, 137.8, 134.1, 130.1, 129.2, 92.9, 74.5, 73.0, 72.2, 68.2, 62.1, 39.0–39.1, 27.3–27.4; IR (KBr, cm^{-1}) ν: 2945, 1742, 1646, 1616, 1577, 1505, 1450, 822. Anal. Calcd for $C_{33}H_{48}ClNO_9$: C, 62.11; H, 7.58; N, 2.19. Found: C, 62.16; H, 7.57; N, 2.21.

4.2.6. 4-Fluoro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2f). Mp 170–171 °C; yield. 93%; *m/z* (ESI): 622.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.37 (s, 1H), 7.71 (q, $J=5.6$ Hz, 2H), 7.09 (t, $J=8.5$ Hz, 2H), 5.47 (t, $J=9.5$ Hz, 1H), 5.24 (t, $J=9.6$ Hz, 1H), 5.15 (t, $J=4.7$ Hz, 1H), 4.90 (d, $J=8.9$ Hz, 1H), 4.29 (d, $J=12.1$ Hz, 1H), 4.17 (q, $J=4.9$ Hz, 1H), 3.91 (q, $J=3.5$ Hz, 1H), 1.00–1.25 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.3 177.5, 176.7, 176.5, 164.0, 162.7, 159.9, 130.9, 116.1, 93.1, 74.4, 73.0, 72.2, 68.1, 62.0, 38.9–39.1, 27.3–27.4; IR (KBr, cm^{-1}): ν 2973, 1730, 1643, 1603, 1509, 1480, 1365, 1138, 831, 763. Anal. Calcd for $C_{33}H_{48}FNO_9$: C, 63.75; H, 7.78; N, 2.25. Found: C, 63.73; H, 7.80; N, 2.26.

4.2.7. 2-Fluoro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2g). Mp 140–142 °C; yield 91%; *m/z* (ESI): 622.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.73 (s, 1H), 7.92 (t, $J=6.8$ Hz, 1H), 7.41 (q, $J=6.0$ Hz, 1H), 7.16 (t, $J=7.5$ Hz, 1H), 7.07 (q, $J=9.0$ Hz, 1H), 5.48 (t, $J=9.5$ Hz, 1H), 5.24 (t, $J=9.6$ Hz, 1H), 5.03 (t, $J=9.3$ Hz, 1H), 4.92 (d, $J=8.9$ Hz, 1H), 4.28 (d, $J=12.1$ Hz, 1H), 4.19 (m, 1H), 3.92 (q, $J=3.5$ Hz, 1H), 0.99–1.36 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.3, 177.4, 176.7, 176.5, 163.9, 161.9, 154.7, 133.3, 128.1, 124.7, 115.9, 93.3, 74.3, 73.0, 72.1,

68.2, 62.1, 38.9–39.1, 27.2–27.4; IR (KBr, cm^{-1}): ν 2969, 1733, 1639, 1614, 1582, 1481, 1397, 1281, 1141, 941, 754. Anal. Calcd for $C_{33}H_{48}FNO_9$: C, 63.75; H, 7.78; N, 2.25. Found: C, 63.71; H, 7.76; N, 2.28.

4.2.8. 4-Nitro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2h). Mp 180–185 °C; yield 95%; *m/z* (ESI): 649.2 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.50 (s, 1H), 8.26 (d, $J=8.4$ Hz, 2H), 7.85 (d, $J=8.4$ Hz, 2H), 5.50 (t, $J=9.5$ Hz, 1H), 5.23 (t, $J=9.7$ Hz, 1H), 5.00 (t, $J=9.2$ Hz, 1H), 4.96 (t, $J=9.2$ Hz, 1H), 4.31 (d, $J=12$ Hz, 1H), 4.18 (q, $J=4.9$ Hz, 1H), 3.92 (t, $J=5.9$ Hz, 1H), 1.02–1.23 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.5, 176.8, 176.7, 157.9, 150.0, 141.1, 129.5, 124.2, 91.6, 74.5, 72.9, 72.2, 68.0, 61.9, 39.0–39.1, 27.3–27.4; IR (KBr, cm^{-1}): ν 2940, 1735, 1600, 1578, 1528 1480, 1457, 1342, 832. Anal. Calcd for $C_{33}H_{48}N_2O_{11}$: C, 61.10; H, 7.46; N, 4.32. Found: C, 61.08; H, 7.49; N, 4.30.

4.2.9. 3-Nitro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)benzylideneamine (2i). Mp 211–213.9 °C; yield 96%; *m/z* (ESI): 649.2 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.73 (s, 1H), 8.50 (s, 1H), 8.28 (d, $J=8.0$ Hz, 1H), 7.99 (d, $J=7.6$ Hz, 1H), 7.60 (t, $J=7.8$ Hz, 1H), 5.52 (t, $J=9.6$ Hz, 1H), 5.22 (t, $J=9.6$ Hz, 1H), 5.07 (d, $J=9.1$ Hz, 1H), 4.95 (t, $J=9.3$ Hz, 1H), 4.33 (d, $J=12$ Hz, 1H), 4.19 (q, 1H), 3.93 (q, 1H), 1.04–1.26 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.3, 177.5, 176.9, 176.7, 157.3, 148.8, 137.5, 134.5, 129.9, 125.8, 123.2, 91.3, 77.5, 77.30, 77.0, 74.6, 72.9, 72.3, 68.1, 61.9, 27.33; IR (KBr, cm^{-1}): ν 2945, 1746, 1644, 1614, 1580, 1530, 1490, 1462, 1356, 794. Anal. Calcd for $C_{33}H_{48}N_2O_{11}$: C, 61.10; H, 7.46; N, 4.32. Found: C, 61.11; H, 7.43; N, 4.28.

4.2.10. *N*-(2,3,4,6-Tetra-*O*-pivaloylated-D-glucopyranosyl)-2-furylideneamine (2j). Mp 95–98 °C; yield 90%; *m/z* (ESI): 594.2 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.21 (s, 1H), 7.53 (d, $J=3.3$ Hz, 1H), 6.86 (d, $J=2.5$ Hz, 1H), 6.48 (t, $J=1.8$ Hz, 1H), 5.45 (t, $J=9.4$ Hz, 1H), 5.23 (t, $J=9.6$ Hz, 1H), 5.00 (t, $J=9.62$ Hz, 1H), 4.88 (d, $J=8.6$ Hz, 1H), 4.26 (d, $J=12$ Hz, 1H), 4.16–4.18 (m, 1H), 3.89 (d, $J=5.8$ Hz, 1H), 1.06–1.29 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.5, 176.6, 176.6, 151.6, 149.8, 145.8, 115.6, 112.3, 93.2, 74.5, 73.1, 72.3, 68.1, 62.1, 39.0–39.1, 27.3–27.4; IR (KBr, cm^{-1}): ν 2974, 1741, 1648, 1480, 1397, 1368, 1283, 1140, 1070, 896, 761. Anal. Calcd For $C_{31}H_{47}NO_{10}$: C, 62.71; H, 7.98; N, 2.36. Found: C, 62.76; H, 7.88; N, 2.38.

4.3. General procedure for the preparation of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)-amino nitriles 3a–j[5]

To a solution of trimethylsilylcyanide (0.186 g, 1.875 mmol) and cuprous bromide (0.488 g, 1.875 mmol) in dichloromethane (20 mL) at 0 °C, a solution of imine **2** (1.5 mmol) in dichloromethane (1 mL) was added slowly. After half an hour, the solution was allowed to slowly warm to room temperature. The reaction was monitored by TLC, after accomplished, the mixture was quenched with 2 N HCl (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL×3) and water (10 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from heptane to give *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)-amino nitriles **3**.

4.3.1. *N*-(2,3,4,6-Tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3a). Mp 152–155 °C; yield 90%; *m/z* (ESI): 631.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.70 (d, $J=7.2$ Hz, 2H), 7.41 (t, $J=6.8$ Hz, 2H), 7.31 (t, $J=6.5$ Hz, 1H), 5.45 (t, $J=9.4$ Hz, 1H), 5.26 (t, $J=9.6$ Hz, 1H), 5.14 (t, $J=9.2$ Hz, 1H), 4.75 (d, $J=8.8$ Hz, 1H), 4.58 (s, 1H) 4.29–4.32 (m, 2H), 3.92 (d, $J=1.6$ Hz, 1H), 1.07–1.33 (m, 36H); ^{13}C NMR ($CDCl_3$) δ 178.5, 177.9, 176.8, 176.5, 130.1, 129.5, 128.8, 127.9, 114.2, 73.5, 72.3, 71.6, 68.2, 67.8.3, 66.8, 48.7, 39.0–39.2, 27.3–27.4; IR (KBr, cm^{-1}): ν 2979, 2245, 1744, 1633, 1481, 1398, 1279, 1139, 1033, 941, 893. Anal. Calcd for $C_{34}H_{50}N_2O_9$: C, 64.74; H, 7.99; N, 4.44. Found: C, 64.73; H, 7.96; N, 4.47.

4.3.2. 4-Methyl-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3b). Mp 195–197 °C; yield 92%; *m/z* (ESI): 645.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.63 (d, $J=7.9$ Hz, 2H), 7.23 (d, $J=7.9$ Hz, 2H), 5.73 (t, $J=9.5$ Hz, 1H), 5.56 (t, $J=9.6$ Hz, 1H), 5.08 (t, $J=9.2$ Hz, 1H), 4.86 (d, $J=8.8$ Hz, 1H), 4.79 (s, 1H), 4.27 (d, $J=10.9$ Hz, 1H), 4.18 (q, $J=4.9$ Hz, 1H), 3.80–3.82 (m, 1H), 2.39 (s, 3H), 1.03–1.25 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.5, 176.7, 176.4, 142.2, 132.1, 129.7, 129.2, 114.7, 70.5, 68.9, 68.6, 60.7, 59.2, 58.2, 48.5, 39.6–39.4, 27.2–27.4, 21.8; IR (KBr, cm^{-1}): ν 2976, 2254, 1747, 1609, 1575, 147–81, 1398, 1368, 1138, 762. Anal. Calcd for $C_{35}H_{52}N_2O_9$: C, 65.20; H, 8.13; N, 4.34. Found: C, 65.23; H, 8.10; N, 4.13.

4.3.3. 2-Hydroxyl-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3c). Mp 205–208 °C; yield 89%; *m/z* (ESI): 647.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.34 (t, $J=7.3$ Hz, 1H), 7.28 (d, $J=8.0$ Hz, 1H), 6.96 (d, $J=8.2$ Hz, 1H), 6.89 (t, $J=7.0$ Hz, 1H), 5.61 (d, $J=9.6$ Hz, 1H), 5.50 (t, $J=3.5$ Hz, 1H), 5.34 (d, $J=9.9$ Hz, 1H), 4.89 (s, 1H), 4.60 (d, $J=9.9$ Hz, 1H), 4.13 (t, $J=4.4$ Hz, 1H), 3.87 (d, $J=3.0$ Hz, 1H), 3.75 (q, $J=1.5$ Hz, 1H), 1.07–1.29 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 179.1, 178.9, 177.6, 176.3, 160.7, 134.4, 132.9, 119.7, 117.8, 113.3, 69.8, 68.3, 68.6, 67.2, 64.3, 60.3, 49.1, 39.0–39.2, 27.3–27.4. IR (KBr, cm^{-1}): ν 3490, 2950, 2246, 1720, 1600, 1498, 1250, 1125, 750. Anal. Calcd for $C_{34}H_{50}N_2O_{10}$: C, 63.14; H, 7.79; N, 4.33. Found: C, 63.18; H, 7.75; N, 4.31.

4.3.4. 4-Methoxy-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3d). Mp 182–185 °C; yield 85%; *m/z* (ESI): 661.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.76 (d, $J=8.4$ Hz, 2H), 6.96 (d, $J=8.4$ Hz, 2H), 5.74 (t, $J=9.6$ Hz, 1H), 5.28 (t, $J=9.6$ Hz, 1H), 5.06 (t, $J=9.2$ Hz, 1H), 4.81 (s, 1H), 4.26 (d, $J=5.3$ Hz, 1H), 4.13–4.16 (m, 2H), 3.89 (s, 3H), 3.85 (d, $J=5.8$ Hz, 1H), 1.04–1.22 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.6, 177.3, 176.8, 162.8, 130.9, 128.0, 114.9, 114.3, 75.1, 74.4, 73.1, 72.2, 68.2, 62.2, 55.6, 49.5, 38.9–39.1, 27.2–27.4; IR (KBr, cm^{-1}): ν 2976, 2246, 1739, 1607, 1580, 1520, 1481, 1396, 1284, 1254, 1150, 763. Anal. Calcd for $C_{35}H_{52}N_2O_{10}$: C, 63.62; H, 7.93; N, 4.24. Found: C, 63.58; H, 7.96; N, 4.21.

4.3.5. 4-Chloro-*N*-(2,3,4,6-tetra-*O*-pivaloyl-D-glucopyranosyl)phenylglycinonitrile (3e). Mp 210–212 °C; yield

86%; *m/z* (ESI): 665.2 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.76 (d, $J=8.3$ Hz, 2H), 7.42 (d, $J=8.3$ Hz, 2H), 5.44 (t, $J=7.3$ Hz, 1H), 5.21 (d, $J=10$ Hz, 1H), 4.93 (d, $J=1.9$ Hz, 1H), 4.80 (s, 1H), 4.12 (d, $J=7.0$ Hz, 1H), 3.56–3.58 (m, 2H), 3.10–3.13 (m, 1H), 1.05–1.30 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 179.0, 177.4, 177.2, 176.6, 138.6, 133.3, 130.3, 129.3, 114.7, 69.6, 68.8, 67.5, 65.8, 59.5, 57.8, 45.17, 39.1–39.5, 27.1–27.5; IR (KBr, cm^{-1}): ν 2980, 2248, 1760, 1550, 1450, 1300, 150, 870. Anal. Calcd for $C_{34}H_{49}ClN_2O_9$: C, 61.39; H, 7.42; N, 4.21. Found: C, 61.36; H, 7.46; N, 4.19.

4.3.6. 4-Fluoro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3f). Mp 192–195 °C; yield 88%; *m/z* (ESI): 649.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.76 (t, $J=5.5$ Hz, 2H), 7.11 (t, $J=8.5$ Hz, 2H), 5.76 (t, $J=9.5$ Hz, 1H), 5.57 (t, $J=9.6$ Hz, 1H), 5.13 (d, $J=4.7$ Hz, 1H), 4.88 (s, 1H), 4.05 (d, $J=8.9$ Hz, 1H), 3.80–3.82 (m, 2H), 3.54–3.57 (m, 1H), 0.930–1.38 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.2, 177.3, 176.8, 176.4, 166.2, 131.3, 130.3, 116.1, 114.3, 70.3, 68.9, 64.5, 60.4, 59.0, 58.1, 48.1 39.0–39.5, 26.9–27.4; IR (KBr, cm^{-1}) ν: 2976, 1746, 1603, 1510, 1481, 1398, 1368, 1276, 1139, 763. Anal. Calcd for $C_{34}H_{49}FN_2O_9$: C, 62.95; H, 7.61; N, 4.32. Found: C, 62. 91; H, 7.65; N, 4.28.

4.3.7. 2-Fluoro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3g). Mp 166–168 °C; yield. 90%; *m/z* (ESI): 649.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.9 (t, $J=6.8$ Hz, 1H), 7.46 (q, $J=6.0$ Hz, 1H), 7.17 (t, $J=7.5$ Hz, 1H), 7.09 (q, $J=9.0$ Hz, 1H), 5.73 (t, $J=9.5$ Hz, 1H), 5.56 (t, $J=9.6$ Hz, 1H), 5.14 (d, $J=9.3$ Hz, 1H), 4.86 (s, 1H), 4.25 (d, $J=8.9$ Hz, 1H), 3.82–3.84 (m, 2H), 3.54 (t, $J=12.6$ Hz, 1H), 0.85–1.34 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.5, 176.7, 176.3, 161.8, 158.7, 134.3, 129.1, 124.7, 116.3, 114.5, 74.3, 70.4, 69.8, 68.9, 61.4, 60.7, 49.3, 39.1–39.6, 27.2–27.4; IR (KBr, cm^{-1}): ν 2914, 1731, 1614, 1583, 1486, 1396, 1281, 1128, 762. Anal. Calcd for $C_{34}H_{49}FN_2O_9$: C, 62.95; H, 7.61; N, 4.32. Found: C, 62.93; H, 7.63; N, 4.30.

4.3.8. 4-Nitro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3h). Mp 223–226 °C; yield 89%; *m/z* (ESI): 676.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.67 (d, $J=8.4$ Hz, 2H), 8.15 (d, $J=8.4$ Hz, 2H), 5.45 (t, $J=9.4$ Hz, 1H), 5.25 (t, $J=9.5$ Hz, 1H), 5.06 (t, $J=9.1$ Hz, 1H), 4.90 (s, 1H), 4.81 (d, $J=8.5$ Hz, 1H), 4.26 (d, $J=11.9$ Hz, 1H), 3.89–3.91 (m, 2H), 1.0–1.22 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 178.4, 177.6, 176.7, 176.5, 147.7, 136.2, 129.9, 122.8, 115.4, 74.4, 73.1, 72.2, 68.3, 62.2, 55.6, 46.04, 39.1–38.9, 27.3–27.4; IR (KBr, cm^{-1}): ν 2976, 2240, 1739, 1605, 1529, 1481, 1462, 1398, 1279, 1136, 856. Anal. Calcd for $C_{34}H_{49}N_3O_{11}$: C, 60.43; H, 7.31; N, 6.22. Found: C, 60.39; H, 7.28; N, 6.26.

4.3.9. 3-Nitro-*N*-(2,3,4,6-tetra-*O*-pivaloylated-D-glucopyranosyl)phenylglycinonitrile (3i). Mp 248–251 °C; yield 91%; *m/z* (ESI): 676.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 8.41 (s, 1H), 8.33 (d, $J=8.0$ Hz, 1H), 8.03 (d, $J=7.6$ Hz, 1H), 7.69 (t, $J=7.8$ Hz, 1H), 5.99 (t, $J=1.8$ Hz, 1H), 5.76 (t, $J=9.6$ Hz, 1H), 5.40 (t, $J=9.6$ Hz, 1H), 5.21 (d, $J=9.1$ Hz, 1H), 4.95 (s, 1H), 4.07 (t, $J=9.3$ Hz, 2H), 3.58–3.60 (m, 1H), 1.08–1.30 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 179.3, 178.1, 177.9, 176.6, 149.2, 135.5, 134.2, 130.5, 125.2, 123.3, 116.6, 71.2, 70.3, 69.8, 60.2, 59.3, 52.3, 46.17, 39.4, 27.3–27.4. IR (KBr, cm^{-1}): ν 2975, 2238, 1736, 1536, 1481, 1399, 1352, 1279, 1139, 1036, 940, 809. Anal. Calcd for $C_{34}H_{49}N_3O_{11}$: C, 60.43; H, 7.31; N, 6.22. Found: C, 60.47; H, 7.28; N, 6.24.

4.3.10. *N*-(2,3,4,6-Tetra-*O*-pivaloylated-D-glucopyranosyl)-2-furylglycinonitrile (3j). Mp 129–132 °C; yield 85%; *m/z* (ESI): 621.4 $[M+H]^+$; ^1H NMR ($CDCl_3$): δ 7.43 (d, $J=3.3$ Hz, 1H), 6.75 (d, $J=2.5$ Hz, 1H), 6.39 (t, $J=1.8$ Hz, 1H), 5.32 (t, $J=9.4$ Hz, 1H), 5.28 (t, $J=9.6$ Hz, 1H), 5.14 (d, $J=8.6$ Hz, 1H), 4.98 (t, $J=9.62$ Hz, 1H), 4.80 (s, 1H), 4.55 (d, $J=12$ Hz, 1H), 4.16–4.18 (m, 2H), 3.88 (d, $J=12$ Hz, 1H), 1.06–1.24 (m, 36H); ^{13}C NMR ($CDCl_3$): δ 177.4, 176.3, 175.8, 175.2, 152.6, 114.9, 148.6, 111.0, 106.2, 75.3, 71.5, 70.3, 69.2, 654.5, 59.3, 45.1, 38.7–39.0, 25.1–27.3; IR (KBr cm^{-1}): ν 2979, 2250, 1740, 1650, 1482, 1380, 1283, 1177, 893. Anal. Calcd for $C_{32}H_{48}N_2O_{10}$: C, 61.92; H, 7.79; N, 4.51. Found: C, 61.86; H, 7.80; N, 4.49.

4.4. General procedure for preparation of aromatic acetic acids 4a–j

To a solution of **3** (2.0 mmol) in dichloromethane (20 mL) was added 0.5 mL of 45% HBr in acetic acid in presence of H_2O (0.1 mL) at room temperature, forming deposits in the solution, which were filtered and washed with ethyl acetate, to give the product **4** in excellent yields. The filtrate was concentrated by rotary evaporation. Recrystallization of the residue from petroleum ether furnished **1** which was restored as the starting material.

4.4.1. Phenylacetic acid (4a). Mp 76–78 °C (lit.[7a] 75–78 °C); yield 91%; *m/z* (ESI): 137.1 $[M+H]^+$; ^1H NMR (D_2O): δ 7.89 (d, $J=7.6$ Hz, 2H), 7.64 (t, $J=7.0$ Hz, 1H), 7.49 (t, $J=7.6$ Hz, 2H), 4.60 (s, 2H); ^{13}C NMR (D_2O): δ 191.76, 135.21, 131.43, 129.08, 128.17, 45.17; IR (KBr, cm^{-1}): ν 3300–2200, 1698, 1500, 1460, 1402, 1299, 1225, 1180, 925, 756.

4.4.2. 4-Methyl-phenylacetic acid (4b). Mp 91–92 °C (lit.[7b] 90–93 °C); yield 89%; *m/z* (ESI): 151.1 $[M+H]^+$; ^1H NMR (D_2O): δ 7.76 (d, $J=8.0$ Hz, 2H), 7.28 (d, $J=8.0$ Hz, 2H); 4.54 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (D_2O): δ 191.9, 142.3, 132.9, 129.7, 129.3, 45.8, 21.9; IR (KBr, cm^{-1}): ν 3300–2500, 1699, 1525, 1410, 1330, 1250, 760.

4.4.3. 2-Hydroxyl-phenylacetic acid (4c). Mp 145–148 °C (lit.[7c] 143–147 °C); yield 87%; *m/z* (ESI): 153.1 $[M+H]^+$ ^1H NMR (D_2O): δ 7.36 (t, $J=8.0$ Hz, 1H), 7.29 (d, $J=7.8$ Hz, 1H), 6.95 (d, $J=7.7$ Hz, 1H), 6.89 (t, $J=7.0$ Hz, 1H), 4.60 (s, 2H); ^{13}C NMR (D_2O): δ 191.2, 161.0, 133.6, 132.7, 119.2, 118.4, 117.5, 45.6; IR (KBr, cm^{-1}): ν 3400, 3300–2500, 1720, 1610, 1500, 1470, 1380, 1310, 1100, 760.

4.4.4. 4-Methoxy-phenylacetic acid (4d). Mp 85–87 °C (lit.[7d] 85–88 °C); yield 85%; *m/z* (ESI): 167.1 $[M+H]^+$; ^1H NMR (D_2O): δ 7.78 (d, $J=8.4$ Hz, 2H), 6.97 (d, $J=8.4$ Hz, 2H), 4.62 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (D_2O): δ 192.5, 162.8, 130.9, 128.0, 114.3, 55.6, 46.0; IR (KBr, cm^{-1}): ν 3400–2500, 1710, 1610, 1520, 1240, 1180, 1020, 820.

4.4.5. 4-Chloro-phenylacetic acid (4e). Mp 104–106 °C

(lit.[7e] 103–107 °C); yield 92%; *m/z* (ESI): 171.0 $[M+H]^+$; ^1H NMR (D_2O): δ 8.10 (d, $J=8.5$ Hz, 2H), 7.64 (d, $J=8.5$ Hz, 2H), 4.69 (s, 2H); ^{13}C NMR (D_2O): δ 191.2, 140.9, 132.5, 129.9, 129.3, 45.3; IR (KBr, cm^{-1}): ν 3400–2300, 1700, 1600, 1495, 1445, 1350, 1249, 1099, 930, 820.

4.4.6. 4-Fluoro-phenylacetic acid (4f). Mp 82–85 °C (lit.[7f] 82–86 °C); yield 90%; *m/z* (ESI): 155.1 $[M+H]^+$; ^1H NMR (D_2O): δ 7.91 (q, $J=5.4$ Hz, 2H), 7.14 (t, $J=8.5$ Hz, 2H), 4.52 (s, 2H); ^{13}C NMR (D_2O): δ 192.5, 165.7, 131.4, 129.7, 116.3, 45.1; IR (KBr, cm^{-1}): ν 3300–2500, 1700, 1490, 1420, 1338, 1255, 1080, 1020, 805.

4.4.7. 2-Fluoro-phenylacetic acid (4g). Mp 60–63 °C (lit.[7g] 60–645 °C; yield 91%; *m/z* (ESI): 155.1 $[M+H]^+$; ^1H NMR (D_2O): δ 7.85 (q, $J=7.5$ Hz, 1H), 7.59–7.62 (m, 1H), 7.24 (t, $J=7.7$ Hz, 1H), 7.18 (q, $J=8.7$ Hz, 1H), 4.48 (s, 2H); ^{13}C NMR (D_2O): δ 194.1, 166.1 140.2, 132.9, 127.8, 124.0, 119.6, 50.9; IR (KBr, cm^{-1}): ν 3400– 2500, 1710, 1600, 1500, 1470, 1415, 1295, 1240, 1100, 760.

4.4.8. 4-Nitro-phenylacetic acid (4h). Mp 153–155 (lit.[7h] 153–156 °C); yield 92%; *m/z* (ESI): 182.0 $[M+H]^+$; ^1H NMR (D_2O): δ 8.28 (br, 2H), 8.13 (br, 2H), 4.75 (s, 2H); ^{13}C NMR (D_2O): δ 193.0, 151.1, 138.0, 129.8, 124.5, 46.0; IR (KBr, cm^{-1}): ν 3400–2450, 1720, 1600, 1520, 1430, 1350, 1310, 1260, 1200, 1110, 950, 830.

4.4.9. 3-Nitro-phenylacetic acid (4i). Mp 118–120 °C (lit.[7i] 116–120 °C); yield 93%; *m/z* (ESI): 182.0 $[M+H]^+$; ^1H NMR (D_2O): δ 8.69 (s, 1H), 8.43 (d, $J=8.1$ Hz, 1H), 8.30 (d, $J=7.8$ Hz, 1H), 7.75 (t, $J=8.0$ Hz, 1H), 4.72 (s, 2H); ^{13}C NMR (D_2O): δ 192.7, 148.7, 134.8, 131.2, 129.7, 123.7, 46.2; IR (KBr, cm^{-1}): ν 3440–2460, 1746, 1620, 1543, 1455, 1353, 1300, 1270, 1125, 980, 828.

4.4.10. 2-Furyl-acetic acid (4j). Mp 90–92 °C; yield 90%; *m/z* (ESI): 127.0 $[M+H]^+$; ^1H NMR (D_2O): δ 7.94 (s, 1H), 7.62 (d, $J=3.3$ Hz, 1H), 6.80 (t, $J=1.8$ Hz, 1H), 4.57 (s, 2H); ^{13}C NMR (D_2O): δ 181.9, 149.9, 149.3, 121.9, 113.5, 44.3; IR (KBr, cm^{-1}): ν 3460–2400, 1748, 1680, 1618, 1469, 1400, 129, 1168, 972, 910, 796.

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Studies on the reactions of fluoroalkanesulfonyl azide with aromatic compounds

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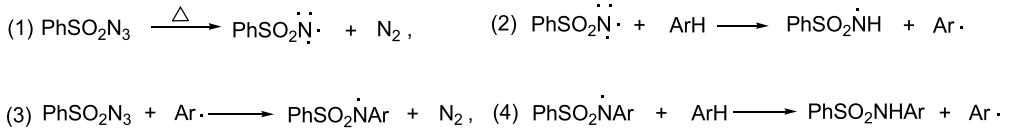
Abstract—The thermal decomposition reactions of fluoroalkanesulfonyl azides $R_fSO_2N_3$ (**1**) in the presence of various substituted benzene $X_nC_6H_{6-n}$ [X: CH_3 ($n=1$, 2, 4, 6), OCH_3 ($n=1$, 2), $C_6H_5CH_2$ ($n=1$), F, Cl, Br] were studied in detail. The *N*-aryl fluoroalkanesulfonyl amides [$R_fSO_2NHC_6H_{5-n}X_n$] were produced as the major products. The *ortho*/*para* ratio resembled that of an electrophilic aromatic substituted reaction. An ionic π- or σ-complex was postulated as the intermediate for these reactions.

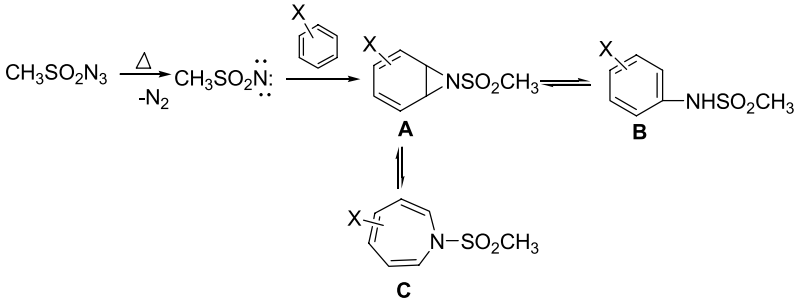
1. Introduction

Reactions of nitrenes with benzene and its derivatives are among the most studied reactions of nitrenes. These reactions involve an electron-deficient nitrogen carbene species that abstracts electron from aromatic nuclei.[1–3] The thermal decomposition of sulfonyl azides in aromatic solvents was first, reported by Curtius and Schmidt,[4,5] who proposed a radical intermediate was involved. In some early studies, Dermer and Edmison[6] found that methyl acrylate or acrylonitrile were polymerized at 110 °C in the presence of benzene sulfonyl azide. DeTar and Sagmanli[7] proposed a radical mechanism for the formation of *N*-aryl phenylsulfonylamide from the thermal reaction of phenylsulfonyl azide in aromatic solvents (Scheme 1).

Later, Abramovitch et al.[8] reported the reactions of methanesulfonyl azide with benzene and its derivatives



Scheme 1.



Scheme 2.

Keywords: Fluoroalkanesulfonyl azide; Aromatic compound; σ-Complex; Thermal decomposition reaction.
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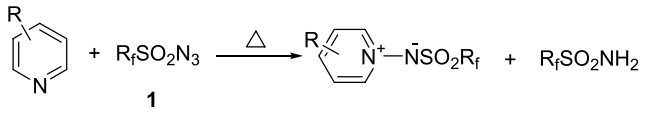


Scheme 3.

and rationalized these results in terms of the addition of the singlet nitrene to the aromatic molecules and formation of a benzaziridine intermediate **A**, which gave *N*-mesylazepine **C** or *N*-mesylanilines **B**, respectively, under kinetic or thermodynamic conditions (Scheme 2).

Comparing with the hydrocarbon analogues, the reactions of fluorinated sulfonyl azides have been studied rarely. In 1984, Kamigata et al.[9] first, reported the thermolysis of trifluoromethanesulfonyl azide in benzene, toluene and anisole; they assumed a similar reaction pathway as proposed by Abramovitch, that is through the *N*-trifluoromethanesulfonyl aziridine intermediates. During our continuous study on the fluoroalkanesulfonyl azide $R_fSO_2N_3$ **1** (R_f: $X(CF_2)_2O(CF_2)_2$, C_4F_9) since 1992,[10] we have reported its reaction with pyridines, alkanes, alkenes, triphenylphosphine, DMSO and, etc. We found that the reaction of **1** with pyridine and its derivatives gave pyridinium *N*-fluoroalkanesulfonylimides. In these reactions pyridine and its derivatives acted as electron donor to capture the electron-deficient fluoroalkanesulfonyl nitrenes (Scheme 3).[11]

While literature reported the phenylsulfonyl azide reacted with pyridine derivatives gave three products (Scheme 4).[12]

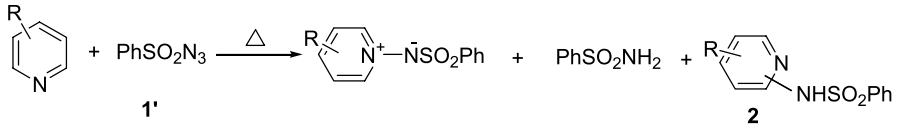
The product **2** was also produced from the corresponding aziridine intermediate. The formation of similar product in the reaction of **1** with pyridine indicated that the more electron deficient fluoroalkanesulfonyl nitrene [R_fSO_2N:] seems more favorable to be trapped by an electron donor rather than its addition to pyridine ring.

As an extension of the exploration of fluorosulfonyl nitrenes, recently we systematically studied the thermolysis reaction of **1** with substituted benzene and found that, no corresponding aziridiene or azepene was formed in any of these reaction. We postulated that in these reactions an ionic π- or σ- complex intermediate may be formed first, by the donor–acceptor interaction between the aromatic compounds and the electron-deficient singlet nitrene [R_fSO_2N:]. Herein, we wish to report these results.

2. Results and discussion

Thermal reaction of fluoroalkanesulfonyl azide **1a** in an excess (5.0 equiv) anisole **3a** at 120 °C in a degassed sealed tube was investigated firstly. The reaction was finished within 48 h (monitored by TLC), and the isomers' ratio of fluoroalkanesulfonanilides **4aa** was determined by ^{19}F NMR spectrometry. Unfortunately, the isomers could not be separated by column chromatography under various eluent-separating conditions. Finally, the isomers were successfully isolated by TLC. The *ortho* and *para* isomers were identified from the coupling pattern of the aromatic CH observed in ^1H NMR. For example, a typical AA′BB′ system was observed at δ 7.25 and 6.89 ppm in the ^1H NMR spectrum of the product with higher polarity, which indicated to be a *para*-methoxylfluoroalkanesulfonylanilide **4aa**. Meanwhile, a complicated ABCD system observed in ^1H NMR spectrum of the other isomer indicating an *ortho*-isomer. The overall isolated yield of fluoroalkanesulfonanilide **4aa** was 75%.

To our surprise, in the case of toluene **3b** with **1a**, all the



Scheme 4.

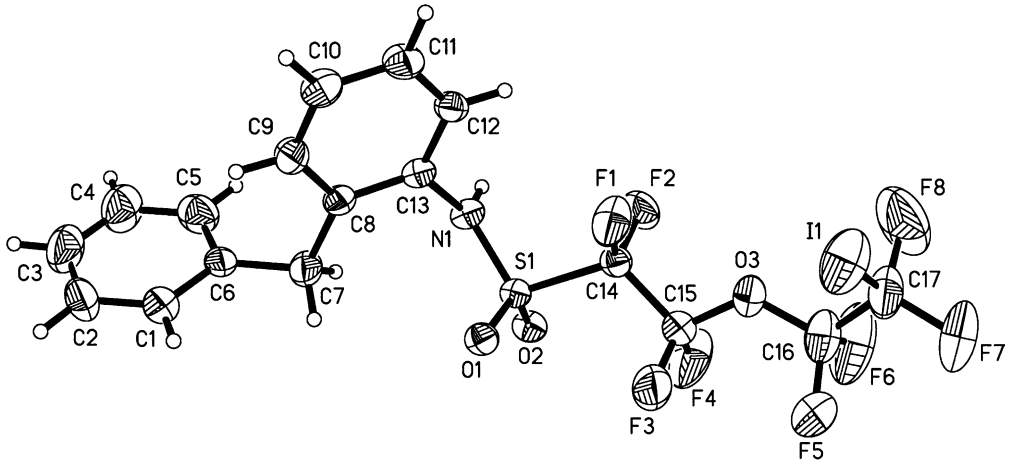
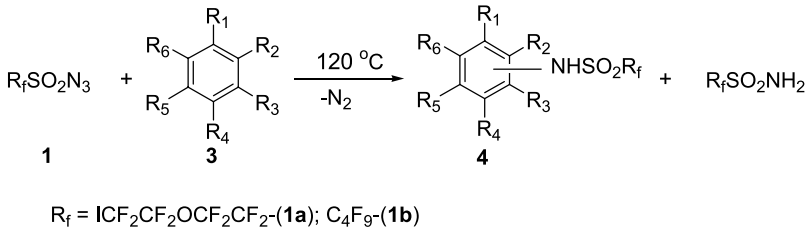


Figure 1. The molecular structure of *ortho*-**4ac**.

Table 1. Thermal reaction results of fluoroalkanesulfonyl azides and aromatic compounds

Entry	Azides	ArX (X=)	Time (h)	Products distribution[a]			Yields (%)[b]
				o-	*p*-	*m*-	
1	**1a**	OMe **3a**	48	49	51	—	**4aa** (75)
2	**1a**	Me **3b**	24	52	34	14	**4ab** (61)
3	**1a**	Bn **3c**	48	40	60	—	**4ac** (31)
4	**1b**	Bn **3c**	36	44	56	—	**4bc** (39)
5	**1a**	1,4-diMe **3d**	48	100	—	—	**4ad** (35)
6	**1a**	1,4-diMeO **3e**	48	100	—	—	**4ae** (33)
7	**1a**	1,2,4,5-tetraMe **3f**	72	100	—	—	**4af** (23)
8	**1b**	1,2,4,5-tetraMe **3f**	60	100	—	—	**4bf** (25)
9	**1a**	F **3g**	4	42	58	—	**4ag** (58)
10	**1a**	Cl **3h**	6	61	39	—	**4ah** (31)
11	**1a**	Br **3i**	4	65	35	—	**4ai** (29)
12	**1b**	Br **3i**	4	45	55	—	**4bi** (28)

[a] Determined by ^{19}F NMR.
[b] Isolated yields of **4** based on **1**.



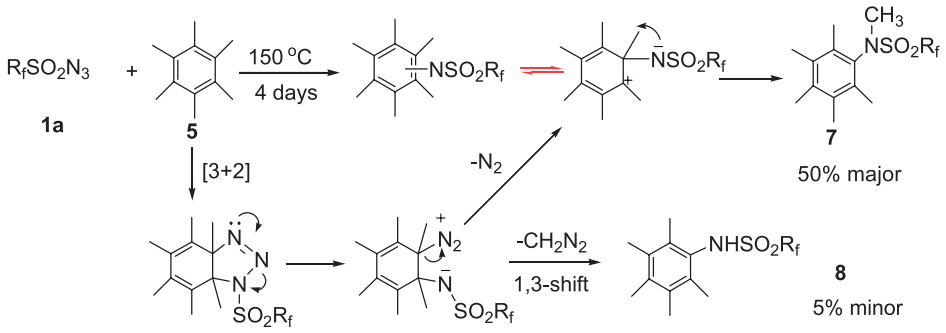
Scheme 5.

ortho-, *meta*- and *para*- isomers were observed in the following ^{19}F NMR spectrometry. However, we could not separate them, as described by Kamigata et al.[9] Meanwhile, we noticed that in the case of **1a** with diphenyl methane Ph_2CH_2 **3c** bearing two reactive methylene protons, no *meta*-isomer was detected according to the ^1H and ^{19}F NMR spectra of the reaction mixture upon the complete consumption of **1a**. The hydrogen abstraction product $Ph_2CHNHSO_2R_f$ was not obtained either, but the *ortho* and *para* isomers **4ac** were separated along with the corresponding $R_fSO_2NH_2$. Due to the two aromatic nuclei in the compound, the relative complicated peak shape in low field resulted in the difficult assignment to the *ortho* or *para* isomers. To assign which is the *ortho* or *para* isomer, the accurate relative configuration of the lower polarity isomer was further elucidated by a single crystal X-ray diffraction analysis. Its molecular structure showed an *ortho* correlation between the fluoroalkanesulfonyl and benzyl groups (Fig. 1). So the other *ortho*/*para* isomers **4** were easily assigned by their NMR pattern compared with **4ac**.

Other azides and aromatic compounds also reacted smoothly under the similar reaction conditions and the results were summarized in Table 1 (Scheme 5).

As seen in Table 1, both the substitutes and the steric hindrance of aromatic compounds have significant impact on the product distribution and the overall isolated yields. In most cases, the *para*-fluoroalkanesulfonanilide was the major products and the *ortho*/*para* ratio resembles that of an electrophilic aromatic substituted reaction. It was observed that the more electron-rich the groups on aromatic nuclei, the longer reaction time is required (entries 1, 2, 5, and 6). However, in the case of aromatic halide ArX, the reaction time was notably shorter (entries 10–12). Moreover, we noticed that the stronger steric hindrance, the longer time is required along with the lower overall yields of the corresponding fluoroalkanesulfonanilide (entries 5–8).

In addition, the thermal reactions of fluoroalkanesulfonyl azide **1a** with electron-rich hexamethylbenzene **5** or the



Scheme 6.

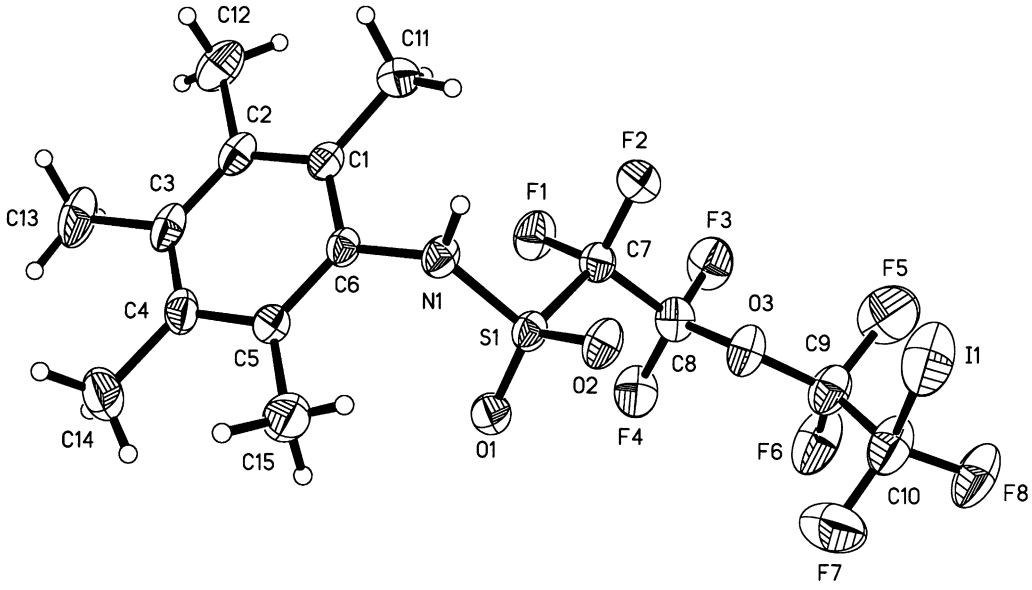
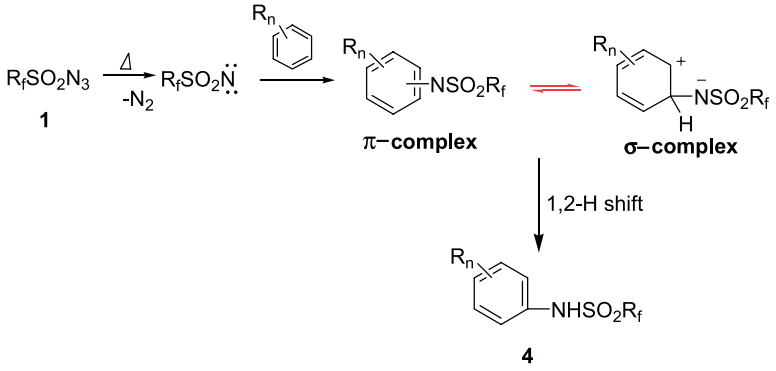


Figure 2. The molecular structure of compound **8**.

electron-deficient nitrobenzene **6** were also investigated. In the case of nitrobenzene, the reaction proceeded smoothly and finished within 2 h, however, the fluoroalkanesulfonylamide $R_fSO_2NH_2$ was obtained as a major product up to 80%. Upon heated to 150 °C, the reaction of fluoroalkanesulfonyl azide **1a** with **5** proceeded very slowly and it completed within 4 days. It was found that the *N*-methyl-*N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-pentamethylaniline **7** was obtained as major product in 50% yield along with the demethylated product *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-pentamethylaniline **8** in 5% yield. A possible mechanism for the formation of **7** and **8** was proposed in Scheme 6. According to our previous studies, at 150 °C it is almost impossible for the cycloaddition process to occur, so other possible mechanisms for the formation of **8** may be postulated. Product **8** was further, confirmed by a single crystal X-ray diffraction analysis (Fig. 2). The further efforts to a clear explanation of the formation of **8** were underway in our lab.

Considering the results reported by Abramovitch and those summarized in Table 1, we proposed another possible mechanism for the formation of fluoroalkanesulfonanilide. From the above studies, we noticed that in the case of **3c** with **1**, no corresponding hydrogen abstraction products from the methylene position $Ph_2CHNHSO_2R_f$ were isolated, which indicated the resulting fluoroalkanesulfonyl nitrene [R_fSO_2N:] intermediate did not react in a triplet state, that is, it did not act as a radical species for the formation of the product **4**. This point was further, substantiated in the reactions of **3f** or **5** with **1**, while no hydrogen abstraction products from the ArH or phenylmethyl groups were observed. Abramovitch proposed that a benzaziridine intermediate could be involved for the formation of ring-opening product *N*-mesylaniline under conditions of thermodynamic control and ring-expansion product *N*-mesylazepine under kinetic control conditions. Trapping the benzaziridine intermediate was accomplished by adding tetracyanoethylene (TCNE) to the reaction mixture, and the expected [4+2] cycloadduct was isolated.

However, in the case of fluoroalkanesulfonyl azides, corresponding aziridines or azepenes were not isolated or detected during the reaction process. A similar trapping experiment using TCNE failed to give the corresponding adduct of the azepene. Based on these results, an ionic π- or σ-complex was postulated as the intermediate for these reactions. That is to say, in the reactions the three membered ring aziridiene was not formed, instead, an ionic π- or σ-complex may be formed first, by the donor–acceptor



Scheme 7.

interaction between the aromatic compounds and the electron-deficient singlet nitrenes [R_fSO_2N:] (Scheme 7). The same mechanism can be well applied for the explanation of the previous studies of the reactions between pyridine and **1**, where no corresponding 2-, 3- or 4-aminopyridine derivatives R_fSO_2NHAr was found but the donor–acceptor products *N*-fluoroalkanesulfonyl pyridinium imide were isolated. It may be attributed to the electron-deficient [R_fSO_2N:], which is liable to combine with donors rather than add to the double bond of aromatic compounds or pyridine.

3. Conclusion

In summary, the thermal decomposition reactions of fluoroalkanesulfonyl azides $R_fSO_2N_3$ **1** with various substituted benzene $X_nC_6H_{6-n}$ [CH_3 ($n=1$, 2, 4, 6), OCH_3 ($n=1$, 2), $C_6H_5CH_2$ ($n=1$), X: F, Cl, Br,] were studied in detail. All the reactions gave corresponding *N*-aryl fluoroalkanesulfonyl amides $R_fSO_2NHC_6H_{5-n}X_n$ as the major products. The *ortho*/*para* ratio resembled that of an electrophilic aromatic substituted reaction. An ionic π- or σ-complex was postulated as the intermediate for these reactions.

4. Experimental

Melting points were measured in a melting point apparatus and were uncorrected. ^1H and ^{19}F NMR spectra were recorded in $CDCl_3$ Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum or high resolution mass spectra (HRMS) were obtained on a Finnigen GC–MS 4021 or a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 eV), respectively. Elemental analyses were performed by this Institute. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument.

4.1. General procedure for the thermal reaction of fluoroalkanesulfonyl azide with aromatic compounds

A solution of fluoroalkanesulfonyl azide **1a** in excess anisole **3a** (5.0 equiv) was heated at 120 °C in a degassed sealed tube for 48 h. The reaction was monitored by TLC analysis. After removal of the excess anisole, the reaction mixture was subjected to flash column chromatography using petroleum ether/ethyl acetate (10:1) as eluent to afford fluoroalkanesulfonanilide **4aa** (*o*, *p*-mix) in 75% overall yield. The isomer ratio of the products was determined by ^{19}F NMR when the reaction was completed. Further, thin layer preparation chromatography was applied to isolate *ortho*- and *para*- isomer.

4.1.1. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2-methoxylaniline (*o*-4aa). Colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.57–6.92 (4H, m), 3.90 (3H, s), 1.61 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.9 (CF_2, t, $J=6$ Hz), −81.6 (CF_2, t, $J=13$ Hz), −85.4 (CF_2, m), −115.0 (CF_2, s). IR (KBr) cm^{-1}: 3280, 2943, 2848, 1602, 1503, 1200, 1143. MS (70 eV, EI) *m*/*z* (%): 530 ($M^+ +1$, 46), 529 (M^+, 47), 227 ($IC_2F_4^+$, 4), 177 (ICF_2^+, 4), 122 ($M^+ - R_fSO_2$, 100), 94 ($M^+ +1 - R_fSO_2$–HCN, 16). HRMS for $C_{11}H_8NF_8SO_4I$ Calcd 528.9091; Found 528.9094.

4.1.2. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-4-methoxylaniline (*p*-4aa). White solid. Mp 54–56 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25 (2H, d, $J=2.0$ Hz, AA′BB′ system), 6.89 (2H, d, $J=2.4$ Hz, AA′BB′ system), 3.81 (3H, s), 2.29 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.9 (CF_2, t, $J=6$ Hz), −81.6 (CF_2, t, $J=13$ Hz), −85.4 (CF_2, m), −113.9 (CF_2, s). IR (KBr) cm^{-1}: 3235, 1610, 1514, 1365, 1295, 1140. MS (70 eV, EI) *m*/*z* (%): 530 ($M^+ +1$, 46), 529 (M^+, 47), 227 ($IC_2F_4^+$, 4), 177 (ICF_2^+, 4), 122 ($M^+ - R_fSO_2$, 100), 94 ($M^+ +1 - R_fSO_2$–HCN, 16). Anal. Calcd for $C_{11}H_8F_8NO_4SI$: C, 24.97; H, 1.52; N, 2.65%; Found: C, 25.03; H, 1.74; N, 2.64%.

4.1.3. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2(or 3,4)-methylaniline (4ab). Slightly red oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.10 (4H, m), 6.28 (1H, br), 2.36 (3H, m). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.9 (CF_2, t, $J=6$ Hz), −81.5 (CF_2, t, $J=13$ Hz), −85.4 (CF_2, m), −114.8 (CF_2, m). IR (KBr) cm^{-1}: 3293, 2928, 1511, 1417, 1294, 1143, 1093. MS (70 eV, EI) *m*/*z* (%): 514 ($M^+ +1$, 30), 513 (M^+, 32), 227 ($IC_2F_4^+$, 4), 177 (ICF_2^+, 3), 106 ($M^+ - R_fSO_2$, 100). HRMS for $C_{11}H_8NF_8SO_3I$ Calcd 512.9142; Found 512.9118.

4.1.4. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2-benzylaniline (*o*-4ac). White solid. Mp 70–72 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47–7.13 (9H, m), 6.41 (1H, br), 4.10 (2H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.9 (CF_2, t, $J=6$ Hz), −81.4 (CF_2, t, $J=13$ Hz), −85.4 (CF_2, m), −115.1 (CF_2, s). IR (KBr) cm^{-1}: 3245, 1493, 1419, 1371, 1294, 1197, 1134. MS (70 eV, EI) *m*/*z* (%): 589 (M^+, 9), 227 ($IC_2F_4^+$, 3), 182 ($M^+ - R_fSO_2$, 100), 177 (ICF_2^+, 2), 167 ($M^+ - R_fSO_2NH_2$, 15). Anal. Calcd for $C_{17}H_{12}F_8NO_3SI$: C, 34.65; H, 2.05; N, 2.38%; Found: C, 34.70; H, 2.07; N, 2.37%.

4.1.5. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-4-benzylaniline (*p*-4ac). White solid. Mp 50–52 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33–7.16 (9H, m), 6.82 (1H, br), 3.98 (2H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.4 (CF_2, t, $J=6$ Hz), −82.1 (CF_2, t, $J=13$ Hz), −85.9 (CF_2, m), −114.4 (CF_2, s). IR (KBr) cm^{-1}: 3239, 1510, 1413, 1366, 1295, 1197, 1137, 1095. MS (70 eV, EI) *m*/*z* (%): 589 (M^+, 35), 227 ($IC_2F_4^+$, 5), 182 ($M^+ - R_fSO_2$, 100), 177 (ICF_2^+, 4), 167 ($M^+ - R_fSO_2NH_2$, 12). Anal. Calcd for $C_{17}H_{12}F_8NO_3SI$: C, 34.65; H, 2.05; N, 2.38%; Found: C, 34.75; H, 2.12; N, 2.38%.

4.1.6. *N*-Perfluorobutylsulfonyl-2-benzylaniline (*o*-4bc). White solid. Mp 104–106 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.50–7.14 (9H, m), 6.50 (1H, br), 4.11 (2H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −80.9 (CF_3, t, $J=10$ Hz), −111.8 (CF_2, t, $J=13$ Hz), −121.2 (CF_2, d, $J=5$ Hz), −126.2 (CF_2, t, $J=17$ Hz). IR (KBr) cm^{-1}: 3258, 1423, 1354, 1240, 1203, 1137, 1036. MS (70 eV, EI) *m*/*z* (%): 465 (M^+, 9), 182 ($M^+ - R_fSO_2$, 100), 167 ($M^+ - R_fSO_2NH_2$, 23). Anal. Calcd for $C_{17}H_{12}F_9NO_2S$: C, 43.88; H, 2.60; N, 3.01%; Found: C, 44.26; H, 2.78; N, 2.81%.

4.1.7. *N*-Perfluorobutylsulfonyl-4-benzylaniline (*p*-4bc). White solid. Mp 58–60 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.17 (9H, m), 6.96 (1H, br), 4.00 (2H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −80.9 (CF_3, t, J=6 Hz), −110.7 (CF_2, t, J=13 Hz), −121.3 (CF_2, s), −126.2 (CF_2, t, J=13 Hz). IR (KBr) cm^{-1}: 3270, 1411, 1355, 1235, 1189, 1140, 1036. MS (70 eV, EI) *m/z* (%): 465 (M^+, 27), 182 ($M^+-R_fSO_2$, 100), 167 ($M^+-R_fSO_2NH_2$, 13). Anal. Calcd for $C_{17}H_{12}F_9NO_2S$: C, 43.88; H, 2.60; N, 3.01%; Found: C, 43.83; H, 2.70; N, 2.77%.

4.1.8. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2,5-dimethylaniline (4ad). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.23–7.05 (3H, m), 6.82 (1H, br), 2.35 (3H, s), 2.32 (3H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.9 (CF_2, t, J=6 Hz), −81.4 (CF_2, t, J=13 Hz), −85.4 (CF_2, m), −115.0 (CF_2, s). IR (KBr) cm^{-1}: 3295, 2928, 1511, 1422, 1294, 1202, 1144, 1093. MS (70 eV, EI) *m/z* (%): 527 (M^+, 25), 227 ($IC_2F_4^+$, 3), 177 (ICF_2^+, 2), 120 ($M^+-R_fSO_2$, 100). HRMS for $C_{12}H_{10}NF_8SO_3I$ Calcd 526.9298; Found 526.9284.

4.1.9. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2,5-dimethoxylaniline (4ae). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18–6.71 (3H, m), 5.78 (1H, s), 3.84 (3H, s), 3.76 (3H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.8 (CF_2, t, J=6 Hz), −82.9 (CF_2, t, J=13 Hz), −86.4 (CF_2, m), −115.8 (CF_2, s). IR (KBr) cm^{-1}: 3274 (N–H), 1421 (SO_2), 1221–1046 (C–F). MS (70 eV, EI) *m/z* (%): 560 (M^++1, 28), 559 (M^+, 100), 227 ($IC_2F_4^+$, 3), 152 ($M^+-R_fSO_2$, 49), 125 ($M^+-R_fSO_2$–HCN, 16). HRMS for $C_{12}H_{10}NF_8SO_5I$ Calcd 558.9197; Found 558.9174.

4.1.10. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2,3,5,6-tetramethylaniline (4af). White solid. Mp 89–90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04 (1H, s), 6.46 (1H, s), 2.20–2.30 (12H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.7 (CF_2, t, J=6 Hz), −82.8 (CF_2, t, J=13 Hz), −86.4 (CF_2, m), −116.9 (CF_2, s). IR (KBr) cm^{-1}: 3272 (N–H), 1410 (SO_2), 1205 −1095 (C–F). MS (70 eV, EI) *m/z* (%): 555 (M^+, 16), 227 ($IC_2F_4^+$, 4), 177 (ICF_2^+, 3), 148 ($M^+-R_fSO_2$, 100), 133 ($M^+-R_fSO_2NH$, 11). Anal. Calcd for $C_{14}H_{14}F_8NO_3SI$: C, 30.29; H, 2.54; N, 2.52%; Found: C, 30.61; H, 2.52; N, 2.50%.

4.1.11. *N*-Perfluorobutylsulfonyl-2,3,5,6-tetramethylaniline (4bf). White solid. Mp 64–66 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.03 (1H, s), 6.52 (1H, br), 2.33 (6H, s), 2.25 (6H, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.1 (CF_3, t, J=10 Hz), −112.7 (CF_2, t, J=13 Hz), −121.4 (CF_2, s), −126.4 (CF_2, s). IR (KBr) cm^{-1}: 3287 (N–H), 1424 (SO_2), 1223 −1033 (C–F). MS (70 eV, EI) *m/z* (%): 431 (M^+, 11), 148 ($M^+-R_fSO_2$, 100). Anal. Calcd for $C_{14}H_{14}F_9NO_2S$: C, 38.99; H, 3.27; N, 3.25%; Found: C, 38.64; H, 3.34; N, 3.06%.

4.1.12. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl- 2- or 4-fluoroaniline (4ag). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.61–7.06 (4H, m), 2.32 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.3 (CF_2, t, J=6 Hz), −81.8/−81.9 (CF_2, t, J=13 Hz), −85.7 (CF_2, m), −113.5/−114.2 (ArF, s), −114.3/−115.0 (CF_2, s). IR (KBr) cm^{-1}: 3288, 1509, 1414, 1295, 1201, 1144, 1095, 915. MS (70 eV, EI) *m/z* (%): 517 (M^+, 19), 227 ($IC_2F_4^+$, 5), 177 (ICF_2^+, 5), 110 ($M^+-R_fSO_2$, 100). HRMS for $\{[M+H]-F\}^+$ $C_{10}H_6NF_8O_3SI$ Calcd 498.8985; Found 498.9029.

4.1.13. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2-or 4-chloroaniline (4ah). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68–7.20 (4H, m), 6.98 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.4 (CF_2, t, J=6 Hz), −81.9/−82.0 (CF_2, t, J=13 Hz), −85.8 (CF_2, m), −114.8 (CF_2, m). IR (KBr) cm^{-1}: 3284, 2928, 1593, 1492, 1336, 1295, 1202, 1144, 1094. MS (70 eV, EI) *m/z* (%): 535/533 (M^+, 8/21), 227 ($IC_2F_4^+$, 5), 177 (ICF_2^+, 5), 126 ($M^+-R_fSO_2$, 100). HRMS for $C_{10}H_5NClF_8SO_3I$ Calcd 532.8596; Found 532.8585.

4.1.14. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-2-bromoaniline (*o*-4ai). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69–7.13 (4H, m), 5.76 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.4 (CF_2, t, J=6 Hz), −81.9 (CF_2, t, J=13 Hz), −85.9 (CF_2, m), −115.2 (CF_2, s). IR (KBr) cm^{-1}: 3280, 2928, 2855, 1589, 1480, 1428, 1294, 1203, 1144, 1093. MS (70 eV, EI) *m/z* (%): 579/577 (M^+, 28/28), 227 ($IC_2F_4^+$, 10), 177 (ICF_2^+, 9), 172/170 ($M^+-R_fSO_2$, 98/100). HRMS for $C_{10}H_5NBrF_8SO_3I$ Calcd 576.8091; Found 576.8068.

4.1.15. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-4-bromoaniline (*p*-4ai). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50 (2H, m, AA′BB′ system), 7.22 (2H, m, AA′BB′ system), 5.27 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.4 (CF_2, s), −82.0 (CF_2, t, J=13 Hz), −85.8 (CF_2, m), −114.4 (CF_2, s). IR (KBr) cm^{-1}: 3280, 2928, 2855, 1589, 1480, 1428, 1294, 1203, 1144, 1093. MS (70 eV, EI) *m/z* (%): 579/577 (M^+, 28/28), 227 ($IC_2F_4^+$, 10), 177 (ICF_2^+, 9), 172/170 ($M^+-R_fSO_2$, 98/100). HRMS for $C_{10}H_5NBrF_8SO_3I$ Calcd 576.8091; Found 576.8068.

4.1.16. *N*-Perfluorobutylsulfonyl-4-bromoaniline (*p*-4bi). White solid. Mp 85–87 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.57 (2H, d, J=1.6 Hz, AA′BB′ system), 7.20 (2H, d, J=1.2 Hz, AA′BB′ system), 3.04 (1H, br). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.0 (CF_3, t, J=10 Hz), −110.6 (CF_2, t, J=13 Hz), −121.3 (CF_2, t, J=6 Hz), −126.2 (CF_2, m). IR (KBr) cm^{-1}: 3282, 1489, 1400, 1228, 1191, 1142, 1035. MS (70 eV, EI) *m/z* (%): 455/453 (M^+, 28/27), 172/170 ($M^+-R_fSO_2$, 97/100). Anal. Calcd for $C_{10}H_5NBrF_9O_2S$: C, 26.45; H, 1.11; N, 3.08%; Found: C, 26.69; H, 1.27; N, 3.04%.

4.1.17. *N*-Methyl-*N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-pentamethylaniline (7). White solid. Mp 88–90 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.62 (3H, NCH_3, s), 2.33 (6H, 2×CH_3, s), 2.27 (3H, *p*-CH_3, s), 2.25 (6H, 2×CH_3, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (CF_2, t, J=6 Hz), −82.0 (CF_2, t, J=13 Hz), −85.7 (CF_2, m), −115.8 (CF_2, s). IR (KBr) cm^{-1}: 2954, 2925, 2869, 1459, 1376, 1174, 1151, 1091, 917. MS (70 eV, EI) *m/z* (%): 583 (M^+, 5), 227 ($IC_2F_4^+$, 2), 160 ($M^+-R_fSO_2$–CH_3, 100). Anal. Calcd for $C_{16}H_{18}F_8NO_3SI$: C, 32.95; H, 3.11; N, 2.40%; Found: C, 33.02; H, 3.31; N, 2.33%.

4.1.18. *N*-(5′-Iodo-3′-oxa-octafluoropentyl)-sulfonyl-pentamethylaniline (8). White solid. Mp 138–140 °C. ^{1}H

Table 2. X-ray data collection and processing parameters for compounds *o*-**4ac** and **8**

Compound	*o*-**4ac**	**8**
Formula	$C_{17}H_{12}F_8NO_3SI$	$C_{15}H_{16}F_8NO_3SI$
Size (mm)	0.36×0.18×0.06	0.52×0.49×0.40
Space group	*P*2 (1)/*C*	*P*−1
Crystal system	Monoclinic	Triclinic
a (Å)	16.412 (19)	8.505 (9)
b (Å)	5.773 (7)	11.261 (12)
c (Å)	22.601 (3)	11.287 (12)
α (°)	90.00	106.880 (2)
β (°)	95.663 (2)	90.885 (2)
γ (°)	90.00	97.488 (2)
V (Å^3)	2130.9 (4)	1024.00 (19)
Z-value	4	2
D_{calcd} (g cm^{-3})	1.837	1.846
μ (mm^{-1})	1.688	1.753
T (K)	293(2)	293(2)
2θ range (degree)	4–56	4–56
Total reflections	12128	6283
F(000)	1144	556
Independent reflections	4948	4559
R_{int}	0.0633	0.0648
$I>2\sigma(I)$	2052	3260
Parameters	293	272
Goodness of fit	0.853	1.103
Final *R* indices ($I>2\sigma(I)$)	0.0594; 0.1374	0.0581; 0.1657
R indices (all data)	0.0502; 0.0939	0.1043; 0.1684

NMR ($CDCl_3$, 300 MHz): δ 6.43 (1H, NH, s), 2.32 (6H, 2×CH_3, s), 2.23 (3H, *p*-CH_3, s), 2.22 (6H, 2×CH_3, s). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −64.8 (CF_2, t, J=7 Hz), −81.3 (CF_2, t, J=13 Hz), −85.4 (CF_2, m), −116.0 (CF_2, s). IR (KBr) cm^{-1}: 3250, 1414, 1364, 1332, 1291, 1179, 1147, 1093. MS (70 eV, EI) *m/z* (%): 569 (M^+, 8), 227 ($IC_2F_4^+$, 2), 177 (ICF_2^+, 1), 162 ($M^+-R_fSO_2$, 100). HRMS(+ESI) for $[M+Na]^+$ $C_{15}H_{16}F_8INO_3SNa$ Calcd 591.9660; Found 591.9665.

4.2. X-ray crystal structure data of compounds *o*-4ac (CCDC 260074) and 8 (CCDC 260075).

Intensity data were collected at 293(2) K on Bruker P4 diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of full matrix least-squares refinement was based on F^2, respectively. All calculations were performed using SHELXS-97 and SHELXL-97 programs. X-ray data for compounds *o*-**4ac** and **8** are listed in Table 2.

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Microwave mediated synthesis of spiro-(indoline-isoxazolidines): mechanistic study and biological activity evaluation☆

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Abstract—Regioisomeric spiro-(indoline-isoxazolidines) have been synthesized in moderate yields by the cycloaddition reaction between ethyl (3-indolylidene)acetate and various substituted α,*N*-diphenylnitrones, using environmentally benign microwave technology. A novel concerted reaction mechanism is described that explains the preferential formation of the regioisomeric spiro-(indoline-isoxazolidine) analogs **6** over **5**. These compounds were screened for anti-mycobacterial and anti-invasive activities against tumor cells.

1. Introduction

The 1,3-dipolar cycloaddition reactions belong to the most important and versatile methods for building five membered heterocycles; they have been applied to the synthesis of natural products such as sugar derivatives,[1] β-lactams,[2] amino acids[3] and alkaloids.[4] Among dipoles, nitrile oxides and nitrile imines have been used extensively. The 1,3-dipolar cycloaddition of nitrones with alkenes in particular has received considerable attention over the past few years in the synthesis of isoxazolidines.[5–9] One of the reasons for the success of the synthetic applications of nitrones is that, contrary to the majority of other 1,3-dipoles, most nitrones are stable compounds which readily undergo cycloadditions to a wide variety of alkenes, affording isoxazolidines and isoxazolines, extremely useful classes of heterocycles.[10]

Recently, a number of publications and reviews have advocated the use of microwave technology in organic synthesis.[11–13] Microwave radiation generally results in enhanced reaction rates and higher product yields as compared to those by conventional heating.[14,15]

In view of above, we have investigated the reaction of indolylidene acetate with a series of nitrones yielding a large number of isomeric spiro-(indoline-isoxazolidines) in a one-pot reaction sequence using microwave radiation. Several of these compounds exhibited interesting anti-tubercular and anti-invasive activities against MCF 7/6 cancer cells.

2. Results and discussion

Spiro-(indoline-isoxazolidines) were synthesized by the cycloaddition reaction between ethyl (3-indolylidene)-acetate (**3**)[16] and various substituted α,*N*-diphenylnitrones **4a–4j** (Scheme 1). The ethoxycarbonylmethylenetriphenyl phosphorane (**2**) was synthesized by the Wittig reaction of triphenylphosphine and ethyl bromoacetate in benzene,[17] which on condensation with the commercially available indoline-2,3 dione (**1**) in acetic acid (glacial) at 80 °C afforded the ethyl (3-indolylidene)acetate (**3**). The nitrones **4a–4j**[18–22] were prepared by the condensation of appropriately substituted aromatic aldehydes with phenylhydroxylamine in ethanol at room temperature. Though, all the nitrones **4a–4j** are known compounds, the spectral

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Keywords: Nitrone; Cycloaddition reaction; Microwave; Spiro-(indoline-isoxazolidines); Anti-mycobacterial; Anti-invasive.
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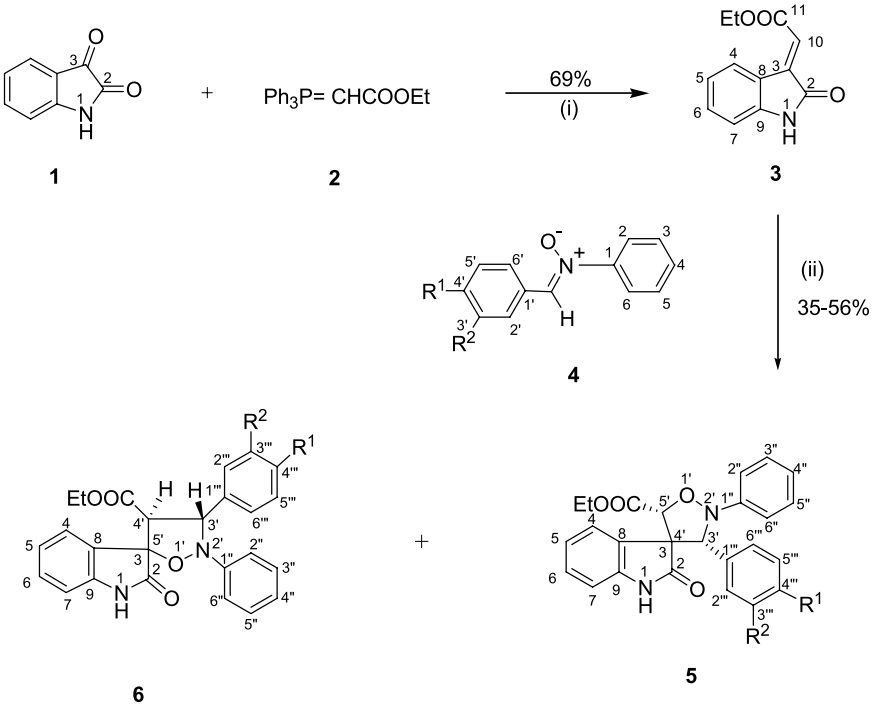


(i) CH_3COOH (glacial), 80 °C, 4 h, 69% yield
(ii) Microwave irradiation, 35 to 56% yield

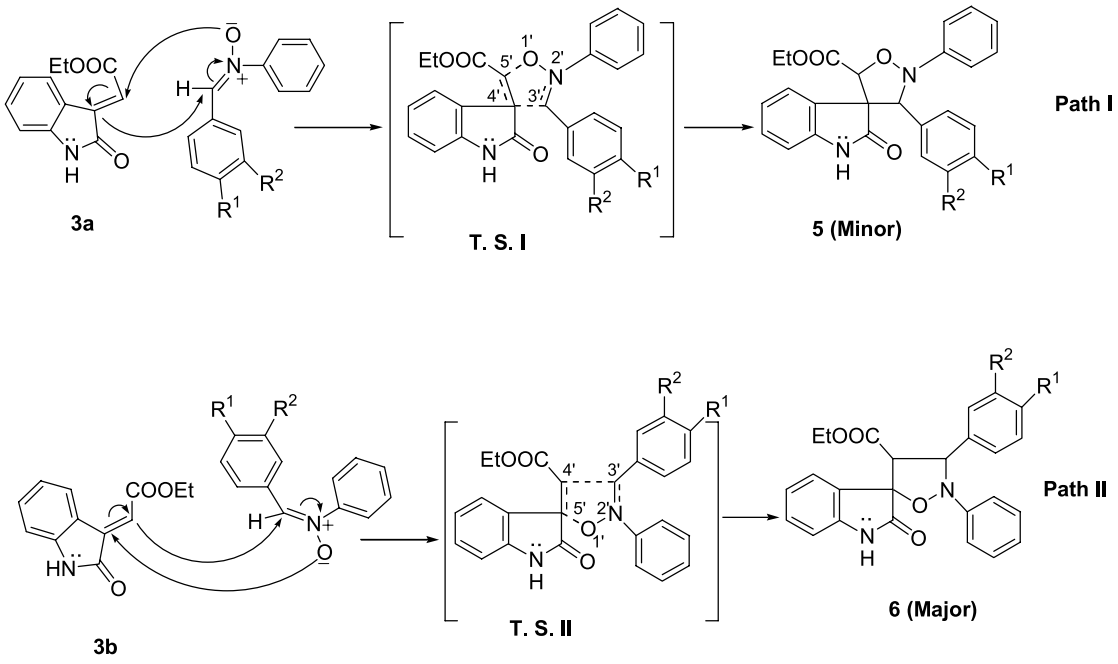
4-6	R^1	R^2	Yield 5 (%)	Yield 6 (%)	MW Irradiation Time (min)
a	Cl	H	22.7	33.8	4.0
b	Br	H	12.1	38.5	4.0
c	NO_2	H	12.8	27.1	5.0
d	F	H	10.0	43.7	4.0
e	CH_3	H	15.6	39.2	4.0
f	H	Cl	21.4	33.0	5.0
g	H	Br	9.1	44.4	4.0
h	H	NO_2	12.1	42.1	4.0
i	H	F	11.7	23.2	5.0
j	H	CH_3	15.8	36.1	4.0

Scheme 1.

data and melting point for α-(3-fluorophenyl)-*N*-phenylnitrone (**4i**) have not been reported earlier. The cycloaddition reaction between the nitrones **4a**–**4j** and ethyl (3-indolylidene)acetate (**3**) in benzene at 60 °C afforded a mixture of two regioisomeric spiro-(indoline-isoxazolidines), that is **5a**–**5j** and **6a**–**6j** in just 10–15% combined yields even after 150–180 h of stirring.

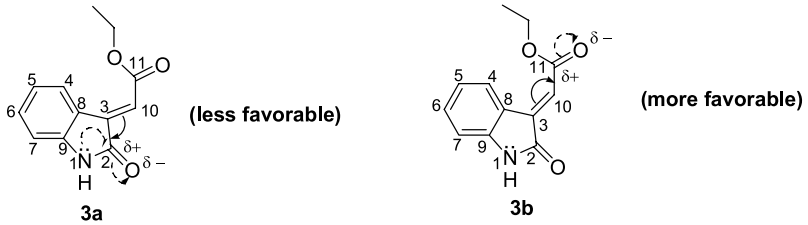
To increase the yield of the spiro-(indoline-isoxazolidines), different reaction conditions and methodologies were attempted, of which a solvent-free reaction coupled with microwave activation provided the desired spiro-(indoline-isoxazolidines) in better yields. Thus, under microwave conditions, spiro compounds **5a**–**5j** and **6a**–**6j** have been prepared just by irradiating the mixture of ethyl (3-indolylidene)acetate (**3**) and the α,*N*-diphenylnitrones **4a**–**4j** in the absence of any solvent for 4–5 min (1 min at a time with 10 s interval) in 35–56% combined yields. The temperature of the reaction mixture under these conditions was observed to reach between 55 and 60 °C. However, by irradiating the reaction mixture in a single attempt for 4–5 min led to a charred mass with the temperature reaching 132–140 °C. The reaction did not proceed when the two reactants were heated (without solvent) in an oil bath at 55 °C for 20 h. Thus, the use of microwave irradiation in dry media resulted in drastic reduction of reaction time and enhancement in yields in comparison to classical heating conditions. In addition, the microwave methodology developed here possesses the currently much demanded 'Green Appeal' and avoids the use of hazardous and toxic solvent(s).

The nitrone addition to the olefinic bond of ethyl (3-indolylidene)acetate (**3**) seems to follow a concerted cyclization mechanism (Scheme 2). The preferential formation of isomers **6** (23–44% yields) over **5** (9–22% yields) indicates that path II is more favorable over path I (Scheme 2). The isomer **6** was found to be the major product in all the cases. This was ascertained by recording the ^{1}H NMR spectra of



Scheme 2.

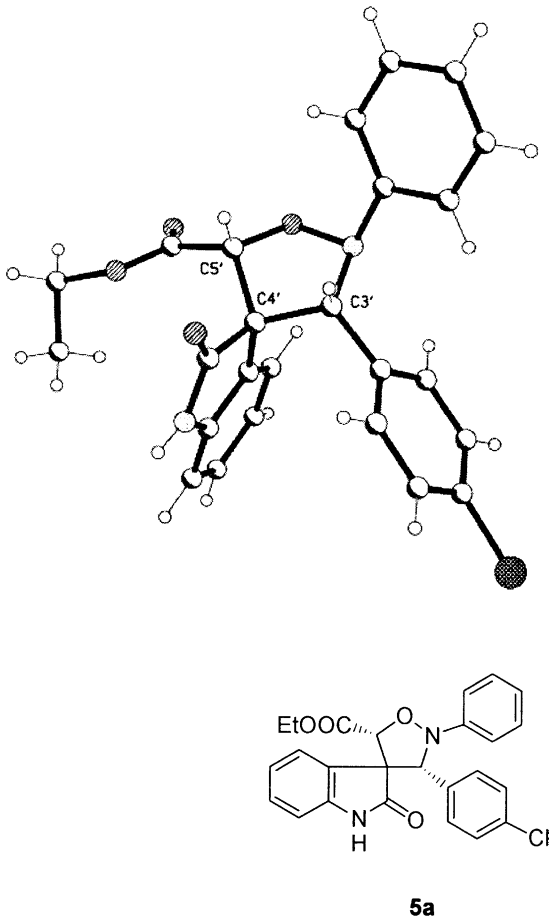
the reaction products containing both the regioisomers **5** and **6**. This mixture was then subjected to isomeric separation by column chromatography, compounds of both the series were obtained in pure forms along with their inseparable mixtures. The relative ratios of the two isomers in the mixtures were determined from ^{1}H NMR spectral analysis and this information was used to calculate the yields of the two isomers, **5** and **6**. The formation of two regioisomeric spiro-(indoline-isoxazolidines) **5a–5j** and **6a–6j** can be explained on the basis of the intermolecular cycloaddition involving exocyclic double bond shifting in **3** in two different modes as depicted mechanistically in Scheme 3. The partial negative charge calculated using the Cache Pro 5.04 (PM3) programme[23] was found to be higher on C-10 (−0.091) as compared to that on C-3 (−0.028). This may be due to the consequence of having an (equivalent of) *o*-aminophenyl substituent on C-3 in **3** conjugated to the ester carbonyl group on C-10, thus the shifting (or polarizability) of the π-electrons towards C-10 is favored over that towards C-3 (Scheme 3). This explains higher yields of the spiro-(indoline-isoxazolidine) isomers **6** over those of **5** (cf. Section 5 and Table 1). Additionally **6** is also calculated to be thermodynamically preferred over **5**. The two regioisomeric spiro-(indoline-isoxazolidines) were well characterized on the basis of their ^{1}H and ^{13}C NMR spectra. In case of the regioisomers **5a–5j**, the two isoxazolidine ring protons appeared as two distinct singlets in the ranges δ 5.24–5.28 and δ 5.30–5.45 (Table 1), indicating them to be on non-adjacent positions. On the other hand, in the case of the regioisomers **6a–6j**, the two isoxazolidine ring protons coupled with each other and appeared as two distinct doublets with J values in the range of 9.0–9.7 Hz (Table 1), suggesting them to be on adjacent ring carbon atoms. Furthermore, the C-3′H appeared quite downfield in **6a–6j** (δ 5.20–5.41, Table 1) as compared to the C-4′H (δ 4.16–4.24, Table 1). The structures of the two regioisomeric spiro derivatives were also compatible with their respective ^{13}C NMR spectra. In the case of regioisomers **6a–6j**, the spiro carbon, that is the C-5 appeared downfield (δ 82.96–83.67) in comparison to the spiro carbon, that is C-4 in compounds **5a–5j** (δ 66.34–68.87, Table 1) because in the former, C-5 is directly attached to the ring oxygen in the isomers **6a–6j**. The structures of two regioisomeric spiro-(indoline-isoxazolidines) were finally confirmed by X-ray crystallographic studies of two compounds, one representative example from each series of two regioisomers, that is of the compounds **5a** and **6c** (Diagrams 1 and 2).[24] Interestingly, the X-ray structures clearly indicate the preference for the C-5′ side chain in **5a** and the C-4′ side chain in **6c** to be *cis* to the larger group at the adjacent spiro carbon (Diagrams 1 and 2).[24] Since both these groups are present in the common starting compound **3**, that is 3-(indolylidene)acetate for both the isomers, the formation of *cis*-products of both the series



Scheme 3.

Table 1. Yields and ^{1}H and ^{13}C NMR chemical shift values of key protons and carbon atoms of spiro compounds **5a–5j** and **6a–6j**

Compound	Yield (%)	δ Value of C-3H	δ Value of C-5H	δ Value of C-4	Compound	Yield (%)	δ Value of C-3H (*J* value in Hz)	δ Value of C-4H (*J* value in Hz)	δ Value of C-5
5a	22.7	5.25	5.32	66.34	**6a**	33.8	5.22 (9.5)	4.16 (9.5)	83.51
5b	12.1	5.25	5.30	66.78	**6b**	38.5	5.21 (9.4)	4.16 (9.4)	83.21
5c	12.8	5.26	5.44	68.86	**6c**	27.1	5.41 (9.1)	4.18 (9.2)	83.03
5d	10.0	5.25	5.33	66.55	**6d**	43.7	5.23 (9.5)	4.18 (9.4)	83.23
5e	15.6	5.25	5.32	66.91	**6e**	39.2	5.20 (9.7)	4.21 (9.7)	83.16
5f	21.4	5.24	5.32	68.87	**6f**	33.0	5.23 (9.5)	4.17 (9.5)	82.98
5g	9.1	5.24	5.32	66.58	**6g**	44.4	5.25 (9.5)	4.20 (9.5)	83.67
5h	12.1	5.28	5.45	66.90	**6h**	42.1	5.40 (9.1)	4.17 (9.0)	83.18
5i	11.7	5.24	5.35	66.55	**6i**	23.2	5.27 (9.3)	4.19 (9.3)	83.13
5j	15.8	5.24	5.32	67.08	**6j**	36.1	5.22 (9.7)	4.24 (9.7)	82.96



5a

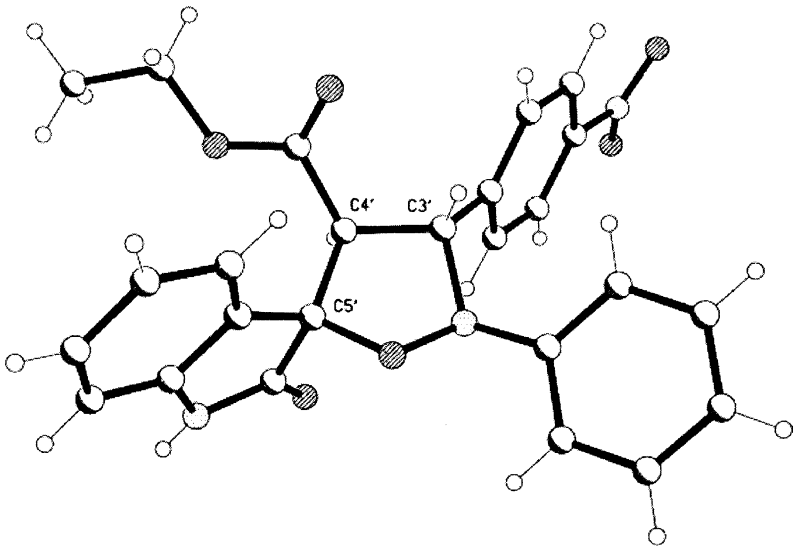
Diagram 1. X-ray crystallography of **5a**.

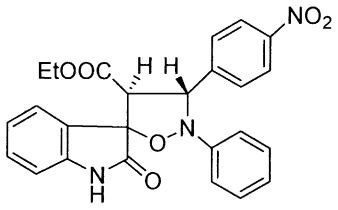
can only be explained if the two groups also have *cis* relationship in the precursor **3**. To establish the geometry, we carried out the NOE experiments on compound **3** but were not able to ascertain the stereo-chemical features in the compound. However, the X-ray crystallographic study on compound **3** (Diagram 3)[24] fully established that ethoxycarbonyl group and phenyl group are in *cis* configuration, this further supports the proposed concerted mechanism.

The ^{1}H and ^{13}C NMR spectra of the spiro-(indoline-isoxazolidines) **5a–5j** and **6a–6j** exhibited only one set of peaks, thereby confirming the formation of single diastereoisomers during the cycloaddition reactions. All 20 spiro-(indoline-isoxazolidines) are new compounds in the literature and have been fully characterized from their spectral data (cf. Section 5).

3. Anti-mycobacterial and anti-invasive activity evaluation of 5a–5j and 6a–6j

All the spiro compounds, viz. **5a–5j** and **6a–6j** were submitted to the NIH Center at SRI (Birmingham, Alabama) for ascertaining their anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294);[25] the spiro-(indoline-isoxazolidines) having structures belonging to series **6** showed better anti-tubercular activities (15–29% inhibition of *Mycobacterium tuberculosis*) than those of the





6c

Diagram 2. X-ray crystallography of **6c**.

spiro compounds belonging to the series **5** (2–8% inhibition, Table 2).

Furthermore, we tested the spiro compounds **5a**–**5j** and **6a**–**6j** in an organotypic assay for invasion. The assay of anti-invasive activity was based on confrontation of invasive human MCF-7/6 mammary carcinoma cells with embryonic chick heart fragments.[26–29] The spiro compounds **5b**, **5c**, **5d**, **5e**, **5g**, **5j**, **6c** and **6e** (Table 3) showed significant inhibition of invasion at 100 μM concentration. The compounds **5c**, **5e** and **6e** showed activity at 10 μM concentration also; none of the compounds exhibited any activity at further dilutions. It is interesting to note that unlike the anti-tubercular activity, the compounds of the series **5** exhibited better anti-invasive activities against tumor cells than the spiro-(indoline-isoxazolidines) **6**.

4. Conclusions

We have synthesized 20 novel spiro compounds taking advantage of the complementarity of the eco-friendly microwave technology under solvent-free conditions. The use of microwave technique resulted in drastic reduction of reaction time and enhancement in yields in comparison to the classical heating method. Furthermore, these compounds showed moderate anti-mycobacterial and anti-invasive activities.

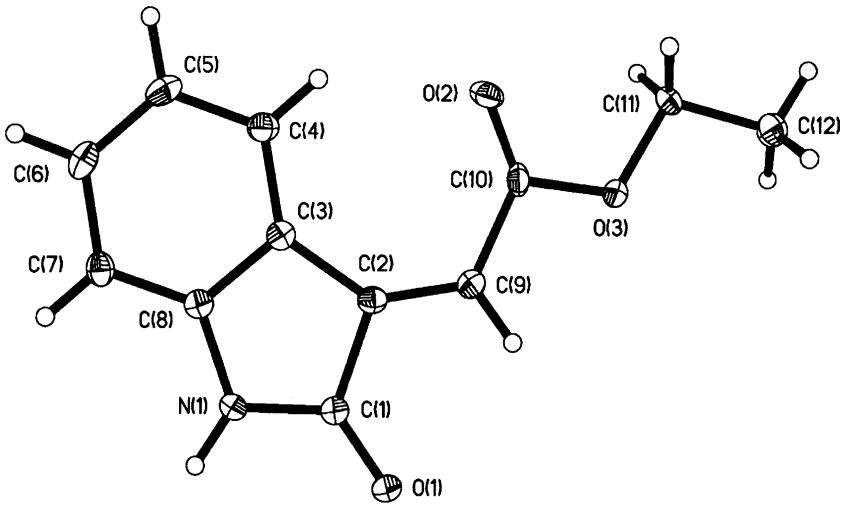
5. Experimental

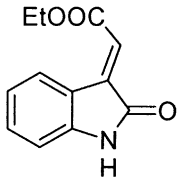
5.1. General

Materials were obtained from commercial suppliers and were used without further purification unless otherwise noted. Petroleum ether (60–80 °C) and ethyl acetate were distilled over P_2O_5 and K_2CO_3, respectively prior to use. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR spectrometer. The ^1H NMR and ^{13}C NMR spectra (in $CDCl_3$) were recorded on a Bruker Avance 300 spectrometer at 300 MHz and at 75.5 MHz, respectively using TMS as internal standard. The chemical shifts values are on δ scale and the coupling constants (J) are in Hz. The HRMS determinations were made in FAB positive mode on a JEOL JMS-AX505W high-resolution mass spectrometer using bis-hydroxyethyldisulfide (HEDS) doped with sodium acetate as matrix. All flash chromatographic separations were performed on 100–120 mesh silica gel. Analytical TLCs were performed on Merck silica gel 60 F_{254} plates. Microwave reactions were performed in a domestic microwave oven of 850 W 1.2 Cft (33 L, Infodisplay, Sharp Carosel). Melting points were recorded in a sulphuric acid bath and are uncorrected.

5.2. Preparation of ethyl 2-oxo-3(2*H*)-indolylidene acetate (3)

A mixture of indolin-2,3-dione (**1**, 7.3 g, 50.0 mmol),





3

Diagram 3. X-ray crystallography of **3**.

ethoxycarbonylmethylene-triphenylphosphorane (**2**, 17.3 g, 50.0 mmol) and glacial acetic acid (60 mL) was heated for 4 h at 80 °C.[16] Acetic acid was removed under vacuum, and the residue was washed onto a filter funnel with a small quantity of methanol. Recrystallization from ethanol gave compound **3** (17.6 g, 69%) as an orange solid, mp 168–170 °C (lit.[30] mp 169–170 °C).

5.3. General method for preparation of α,*N*-diphenylnitrones 4a–4j

Phenylhydroxylamine (1 mmol)[31] and appropriately substituted benzaldehydes (1 mmol) were dissolved in ethyl alcohol (20 mL). The reaction mixture was stirred overnight at room temperature when a solid precipitated out; the desired compounds **4a–4j**[18–22] after recrystallization from ethyl alcohol were obtained as crystalline solids in 69–85% yields.

5.3.1. α-(3-Fluorophenyl)-*N*-phenylnitrone (4i). Obtained as a white solid (3.63 g, 74%), mp 100–102 °C (from ethanol); R_f: 0.45 (petroleum ether–ethyl acetate 4:1); ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.46–7.51 (3H, m, C-2H, C-4H and C-6H), 7.58–7.62 (2H, m, C-3H and C-5H), 7.74–7.78 (2H, m, C-2′H and C-5′H), 7.89 (1H, s, α-H) and 8.28 (2H,

Table 2. Anti-tuberculosis activity data of spiroisoxazolidines in Alamar assay at 6.25 μg/mL MIC level

Compound	% Inhibition
5c	5
5d	4
5e	5
5f	8
5i	5
5j	2
6a	16
6b	26
6c	15
6d	27
6e	20
6f	29

Table 3. Effect of Spiroisoxazolidines on invasion of MCF-7/6 Cells in vitro

Compound no.	100 μM	10 μM	1 μM
5a	−	0	0
5b	+	0	0
5c	+	+	−
5d	+	−	−
5e	+	+	−
5f	0	−	−
5g	+	0	0
5h	−	0	0
5i	−	0	0
5j	+	−	−
6a	−	0	0
6b	−	0	0
6c	+	0	0
6d	−	0	0
6e	+	+	0
6f	−	0	0
6g	Toxic	0	0
6h	0	0	0
6i	0	0	0
6j	0	0	0

+, anti-invasive; −, not anti-invasive; 0, not tested.

d, $J=8.6$ Hz, C-4′H and C-6′H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 115.5 (d, $J=24.7$ Hz, C-2′), 118.1 (d, $J=21.7$ Hz, C-4′), 122.0 (C-4), 125.4 (d, $J=2.4$ Hz, C-6′), 129.6 (C-3 and C-5), 130.3 (d, $J=6.9$ Hz, C-5′), 130.5 (C-2 and C-6), 132.9 (d, $J=7.2$ Hz, C-1′), 133.75 (C-α), 149.3 (C-1) and 162.9 (d, $J=245.47$ Hz, C-3′). HRMS Calcd for $C_{13}H_{10}FNO$: 215.0746. Found: 215.0735.

5.4. General method of preparation of spiro-(indoline-3,4′/3,5′-isoxazolidines)

(a) By conventional heating. To a solution of ethyl (3-indolylidene)acetate (**3**, 9.21 mmol) in benzene (50 mL), various substituted α,*N*-diphenylnitrones **4a–4j** (9.21 mmol) were added, and the reaction mixture was heated at 60 °C. Progress of the reaction was monitored by TLC; after 150–180 h, the reaction mixture was concentrated under reduced pressure. Crude products were chromatographed over silica gel using ethyl acetate–petroleum ether as eluent to afford **5a–5j** and **6a–6j** as light yellow solids, which were recrystallized from ethyl acetate–petroleum ether to afford the white to light yellow crystals of regioisomeric spiro derivatives in combined yields of 10–15%.

(b) By microwave method. A mixture of ethyl (3-indolylidene)acetate (**3**, 1.84 mmol) and variously substituted α,*N*-diphenylnitrones **4a–4j** (1.84 mmol) were irradiated in a microwave (850 W 1.2 Cft). The progress of the reaction was monitored by TLC; after irradiating the reaction mixture for 4–5 min (1 min at a time with 10 s interval), the mixture was chromatographed over silica gel using ethyl acetate–petroleum ether as eluent to afford the spiro compounds **5a–5j** and **6a–6j** as light yellow solids, which were recrystallized from ethyl acetate–petroleum ether to afford the white to light yellow crystals of regioisomeric spiro derivatives in combined yields of 35–56%.

5.4.1. 3′-(4-Chlorophenyl)-5′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5a). Obtained as a white solid (188 mg, 22%), mp 158–159 °C (from petroleum ether–ethyl acetate), R_f: 0.34 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3272 (NH), 1737 ($COOC_2H_5$), 1616 (CONH), 1486, 1230, 1078, 1011 and 751 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.68 (1H, d, $J=7.7$ Hz, C-7H), 6.93 (1H, t, $J=7.1$ Hz, C-4″H), 7.00–7.13 (6H, m, C-2″H, C-3″H, C-5″H, C-6″H, C-2‴H and C-6‴H), 7.21–7.29 (4H, m, C-5H, C-6H, C-3‴H and C-5‴H), 7.53 (1H, d, $J=7.4$ Hz, C-4H) and 7.78 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.4 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 66.3 (C-4′), 77.5 (C-3′), 81.9 (C-5′), 109.3 (C-4″), 115.7 (C-2″ and C-6″), 122.6 (C-7), 123.1 (C-5), 124.6 (C-9), 126.9 (C-6), 127.9 (C-3″ and C-5″), 128.4 (C-2‴ and C-6‴), 128.9 (C-3‴ and C-5‴), 129.2 (C-4), 133.8 (C-8 and C-1‴), 140.0 (C-1″), 150.8 (C-4‴), 165.5 (CONH) and 173.7 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1205.

5.4.2. 3′-(4-Chlorophenyl)-4′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6a). Obtained as a white solid (280 mg, 33%), mp 159–160 °C (from petroleum ether–ethyl acetate), R_f: 0.37 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3205 (NH), 1729 ($COOC_2H_5$), 1621 (CONH), 1491, 1339, 1192, 1031 and 903 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.69 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.65–3.82 (2H, m, $COOCH_2CH_3$), 4.16 (1H, d, $J=9.5$ Hz, C-4′H), 5.22 (1H, d, $J=9.5$ Hz, C-3′H), 6.87 (1H, d, $J=7.8$ Hz, C-7H), 6.92–6.99 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.09–7.19 (3H, m, C-5H, C-6H and C-4‴H), 7.35 (2H, d, $J=8.4$ Hz, C-2‴H and C-6‴H) and 7.63–7.66 (3H, m, C-4H, C-3‴H and C-5‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2CH_3$), 61.7 ($COOCH_2CH_3$), 64.8 (C-4′), 71.2 (C-3′), 83.5 (C-5′), 110.9 (C-4″), 117.5 (C-2″ and C-6″), 123.4 (C-7), 123.9 (C-5), 126.0 (C-9), 126.6 (C-6), 129.0 (C-3″ and C-5″), 129.6 (C-2‴ and C-6‴), 129.7 (C-3‴ and C-5‴), 131.1 (C-4), 134.6 (C-1‴), 137.2 (C-8), 141.8 (C-1″), 149.8 (C-4‴), 167.8 (CONH) and 176.0 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1187.

5.4.3. 3′-(4-Bromophenyl)-5′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5b). Obtained as a light yellow solid (111 mg, 12%), mp 170–171 °C (from petroleum ether–ethyl acetate), R_f: 0.41 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3274 (NH), 1737 ($COOC_2H_5$), 1618 (CONH), 1476, 1399, 1230, 1075 and 750 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.30 (1H, s, C-5′H), 6.69 (1H, d, $J=7.7$ Hz, C-7H), 6.93 (1H, t, $J=7.5$ Hz, C-4″H), 7.03–7.10 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.15–7.17 (2H, m, C-2‴H and C-6‴H), 7.23–7.29 (4H, m, C-5H, C-6H, C-3‴H and C-5‴H) and 7.53 (1H, d, $J=7.4$ Hz, C-4′H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.9 ($COOCH_2CH_3$), 61.8 ($COOCH_2CH_3$), 66.7 (C-4′), 78.0 (C-3′), 82.5 (C-5′), 102.9 (C-4″), 109.9 (C-2″ and C-6″), 122.5 (C-9), 123.1 (C-7), 123.6 (C-5), 125.1 (C-1‴), 127.4 (C-6), 128.7 (C-3″ and C-5″), 129.4 (C-2‴ and C-6‴), 129.7 (C-4), 131.9 (C-3‴ and C-5‴), 134.8 (C-8), 140.5 (C-1″), 151.2 (C-4‴), 166.0 (CONH) and 174. 2 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{79}BrO_4$: 492.0685. Found: 492.0670.

5.4.4. 3′-(4-Bromophenyl)-4′-ethoxycarbonyl-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6b). Obtained as a light yellow solid (351 mg, 39%), mp 161–162 °C (from petroleum ether–ethyl acetate), R_f: 0.43 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3426 (NH), 1729 ($COOC_2H_5$), 1619 (CONH), 1474, 1190, 1023 and 755 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.69–3.78 (2H, m, $COOCH_2CH_3$), 4.16 (1H, d, $J=9.4$ Hz, C-4′H), 5.21 (1H, d, $J=9.4$ Hz, C-3′H), 6.85 (1H, d, $J=7.5$ Hz, C-7H), 6.93–6.97 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.09–7.19 (3H, m, C-5H, C-6H and C-4″H) and 7.49–7.60 (5H, m, C-4H, C-2‴H, C-3‴H, C-5‴H and C-6‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2CH_3$), 61.6 ($COOCH_2CH_3$), 64.8 (C-4′), 71.2 (C-3′), 83.2 (C-5′), 110.5 (C-4″), 117.6 (C-2″ and C-6″), 122.8 (C-1‴), 123.4 (C-7), 123.9 (C-5), 126.0 (C-9), 126.7 (C-6), 128.9 (C-3″ and C-5″), 130.0 (C-2‴ and C-6‴), 131.1 (C-4), 132.5 (C-3‴ and C-5‴), 137.8 (C-8), 141.5 (C-1″), 149.7 (C-4‴), 167.8 (CONH) and 175.2 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2^{79}BrO_4$: 492.0685. Found: 492.0682.

5.4.5. 5′-Ethoxycarbonyl-3′-(4-nitrophenyl)-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5c). Obtained as a light yellow solid (109 mg, 12%), mp 169–170 °C (from petroleum ether–ethyl acetate), R_f: 0.34 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3280 (NH), 1724 ($COOC_2H_5$), 1619 (CONH), 1474, 1344, 1230, 1075 and 834 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.81–3.99 (2H, m, $COOCH_2CH_3$), 5.26 (1H, s, C-3′H), 5.44 (1H, s, C-5′H), 6.68 (1H, d, $J=7.7$ Hz, C-7H), 6.91–6.94 (1H, m, C-4″H), 7.00–7.10 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.27–7.31 (2H, m, C-2‴H and C-6‴H), 7.47–7.50 (4H, m, C-5H, C-6H, C-3‴H and C-5‴H) and 7.98–8.01 (2H, m, C-4′H and NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 15.9 ($COOCH_2CH_3$), 63.9 ($COOCH_2CH_3$), 68.8 (C-4′), 79.9 (C-3′), 84.7 (C-5′), 111.9 (C-4″), 117.9 (C-2″ and C-6″), 125.3 (C-7), 125.9 (C-5), 126.0 (C-3″ and C-5″), 126.6 (C-9), 129.2 (C-6), 129.8 (C-2‴ and C-6‴), 131.5 (C-3‴ and C-5‴), 132.0 (C-4), 142.4 (C-1‴), 145.4 (C-8), 150.0 (C-1″), 152.9 (C-4‴), 167.6 (CONH) and 175.8 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1435.

5.4.6. 4′-Ethoxycarbonyl-3′-(4-nitrophenyl)-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6c). Obtained as a light yellow solid (229 mg, 27%), mp 171–172 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3203 (NH), 1729 ($COOC_2H_5$), 1621 (CONH), 1599, 1472, 1243, 1029 and 855 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.1$ Hz, $COOCH_2CH_3$), 3.68–3.85 (2H, m, $COOCH_2CH_3$), 4.18 (1H, d, $J=9.2$ Hz, C-4′H), 5.41 (1H, d, $J=9.1$ Hz, C-3′H), 6.90–7.01 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.08 (1H, d, $J=7.3$ Hz, C-4″H), 7.15–7.20 (2H, m, C-5H and C-6H), 7.25–7.31 (1H, m, C-4H), 7.91 (2H, d, $J=8.7$ Hz, C-2‴H and C-6‴H), 8.12 (1H, br s, NH) and 8.26 (2H, d, $J=8.7$ Hz, C-3‴H and C-5‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.2 ($COOCH_2CH_3$), 61.4 ($COOCH_2CH_3$), 64.3 (C-4′), 70.2 (C-3′), 83.0 (C-5′), 110.2 (C-4″), 116.9 (C-2″ and C-6″), 123.0 (C-7), 123.6 (C-5), 124.1 (C-3″ and C-5″), 125.2 (C-9), 126.1 (C-6), 128.6 (C-2‴ and C-6‴), 128.7 (C-3‴ and C-5‴), 130.8 (C-4), 141.1 (C-1‴), 145.8 (C-8), 147.9 (C-1″), 148.7 (C-4‴), 167.1 (CONH) and 174.4 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1451.

5.4.7. 5′-Ethoxycarbonyl-3′-(4-florophenyl)-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5d). Obtained as a white solid (80 mg, 10%), mp 154–155 °C (from petroleum ether–ethyl acetate), R_f: 0.42 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3277 (NH), 1738 ($COOC_2H_5$), 1617 (CONH), 1473, 1226, 1153, 908 and 754 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.33 (1H, s, C-5′H), 6.66 (1H, d, $J=7.6$ Hz, C-7H), 6.77–6.95 (3H, m, C-4″H, C-2‴H and C-6‴H), 7.00–7.12 (5H, m, C-2″H, C-3″H, C-5″H, C-6″H and C-3‴H), 7.23–7.29 (3H, m, C-5H, C-6H and C-5‴H), 7.48 (1H, br s, NH) and 7.54 (1H, d, $J=7.3$ Hz, C-4H); ^{13}C NMR (300 MHz; $CDCl_3$): δ 13.5 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 66.5 (C-4′), 77.7 (C-3′), 82.0 (C-5′), 109.3 (C-4″), 115.1 (d, $J=7.2$ Hz, C-6‴), 115.4 (d, $J=22.4$ Hz, C-5‴), 115.9 (C-2″ and C-6″), 122.6 (C-7), 123.2 (C-5), 124.9 (C-9), 127.1 (d, $J=6.9$ Hz, C-2‴), 128.2 (C-6), 128.4 (d, $J=21.8$ Hz, C-3‴), 128.9 (C-3″ and C-5″), 129.2 (C-4), 131.1 (d, $J=2.9$ Hz, C-1‴), 140.1 (C-8), 150.9 (C-1″), 162.3 (d, $J=247.0$ Hz, C-4‴), 165.7 (CONH), 173.9 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1505.

5.4.8. 4′-Ethoxycarbonyl-3′-(4-florophenyl)-2′-phenyl-spiro[indoline-3,5′-isoxazolidine]-2-one (6d). Obtained as a light yellow solid (348 mg, 43%), mp 149–150 °C (from petroleum ether–ethyl acetate), R_f: 0.45 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3449 (NH), 1729 ($COOC_2H_5$), 1621 (CONH), 1473, 1193 and 754 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.69 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 3.69–3.80 (2H, m, $COOCH_2CH_3$), 4.18 (1H, d, $J=9.5$ Hz, C-4′H), 5.23 (1H, d, $J=9.5$ Hz, C-3′H), 6.88 (1H, d, $J=7.8$ Hz, C-7H), 6.92–6.99 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.04–7.19 (5H, m, C-4H, C-5H, C-6H, C-2‴H and C-6‴H), 7.23–7.29 (1H, m, C-4″H), 7.66–7.70 (2H, m, C-3‴H and C-5‴H) and 7.83 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2CH_3$), 61.6 ($COOCH_2CH_3$), 64.8 (C-4′), 71.2 (C-3′), 83.2 (C-5′), 110.6 (C-4), 116.1 (d, $J=6.8$ Hz, C-6‴), 116.4 (d, $J=21.8$ Hz, C-5‴), 117.6 (C-2″ and C-6″), 123.4 (C-7), 123.8 (C-5), 126.0 (C-9), 126.6 (d, $J=7.1$ Hz, C-2‴), 128.9 (C-3″ and C-5″), 129.9 (C-6), 130.0 (d, $J=22.6$ Hz, C-3‴), 131.0 (C-4), 134.3 (d, $J=3.1$ Hz, C-1‴), 141.5 (C-8), 149.7 (C-1″), 163.2 (d, $J=247.0$ Hz, C-4‴), 167.8 (CONH) and 175.5 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1494.

5.4.9. 5′-Ethoxycarbonyl-3′-(4-methylphenyl)-2′-phenyl-spiro[indoline-3,4′-isoxazolidine]-2-one (5e). Obtained as a light yellow solid (123 mg, 15%), mp 155–156 °C (from petroleum ether–ethyl acetate), R_f: 0.46 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 2924 (NH), 1739 ($COOC_2H_5$), 1593 (CONH), 1475, 1401, 1233, 1074 and 742 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 2.17 (3H, s, C_6H_4–CH_3), 3.79–3.97 (2H, m, $COOCH_2CH_3$), 5.25 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.64 (1H, d, $J=7.7$ Hz, C-7H), 6.89–6.93 (3H, m, C-4″H, C-2‴H and C-6‴H), 7.00–7.08 (4H, m, C-3″H, C-5″H, C-6″H and C-2″H), 7.15 (2H, d, $J=8.0$ Hz, C-3‴H and C-5‴H), 7.21–7.24 (2H, m, C-5H and C-6H), 7.39 (1H, br s, NH) and 7.58 (1H, d, $J=7.2$ Hz, C-4H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.9 ($COOCH_2CH_3$), 21.4 ($C_6H_4CH_3$), 61.7 ($COOCH_2CH_3$), 66.9 (C-4′), 78.5 (C-3′), 82.3 (C-5′), 109.6 (C-4″), 116.2 (C-2″ and C-6″), 122.9 (C-7), 123.3 (C-5), 125.5 (C-9), 126.9 (C-3″ and C-5″), 127.5 (C-6), 129.2 (C-4) 129.3 (C-3‴, C-5‴, C-2‴, C-6‴), 132.5 (C-1‴), 138.1 (C-8), 140.5 (C-1″), 151.6 (C-4‴), 166.2 (CONH) and 174. 5 ($COOC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1725.

5.4.10. 4′-Ethoxycarbonyl-3′-(4-methylphenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6e). Obtained as a light yellow solid (309 mg, 39%), mp 160–162 °C (from petroleum ether–ethyl acetate), R_f: 0.48 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 2924 (NH), 1728 ($COOC_2H_5$), 1619 (CONH), 1471, 1376, 1243, 1027 and 828 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.69 (3H, t, $J=7.0$ Hz, $COOCH_2CH_3$), 2.34 (3H, s, $C_6H_4CH_3$), 3.63–3.80 (2H, m, $COOCH_2CH_3$), 4.21 (1H, d, $J=9.7$ Hz, C-4′H), 5.20 (1H, d, $J=9.7$ Hz, C-3′H), 6.84

(1H, d, $J=7.7$ Hz, C-7H), 6.92–6.98 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.12–7.23 (6H, m, C-4H, C-5H, C-6H, C-4‴H, C-2‴H and C-6‴H), 7.44 (1H, br s, NH) and 7.58 (2H, d, $J=8.0$ Hz, C-3‴H and C-5‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.7 ($COOCH_2\mathit{C}H_3$), 21.5 ($C_6H_4\mathit{C}H_3$), 61.4 ($COO\mathit{C}H_2CH_3$), 64.9 (C-4′), 71.7 (C-3′), 83.1 (C-5′), 110.4 (C-4″), 117.6 (C-2″ and C-6″), 123.3 (C-7), 123.6 (C-5), 126.2 (C-9), 126.7 (C-6), 128.2 (C-3″ and C-5″), 128.8 (C-2‴ and C-6‴), 130.0 (C-3‴ and C-5‴), 130.9 (C-4), 135.5 (C-1‴), 138.5 (C-8), 141.5 (C-1″), 150.1 (C-4‴), 167.9 (CONH) and 175.5 ($\mathit{CO}OC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1721.

5.4.11. 3′-(3-Chlorophenyl)-5′-ethoxycarbonyl-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5f). Obtained as a light yellow solid (177 mg, 21%), mp 158–159 °C, (from petroleum ether–ethyl acetate), R_f: 0.35 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3317 (NH), 1741 ($COOC_2H_5$), 1619 (CONH), 1595, 1399, 1230, 1075 and 750 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, t, $J=7.0$ Hz, $COOCH_2C\mathit{H}_3$), 3.80–3.98 (2H, m, $COOC\mathit{H}_2CH_3$), 5.24 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.68 (1H, d, $J=7.7$ Hz, C-7H), 6.91–6.96 (1H, m, C-5‴H), 7.01–7.17 (7H, m, C-2″H, C-3″H, C-4″H, C-5″H, C-6″H, C-2‴H and C-6‴H), 7.25–7.31 (3H, m, C-5H, C-6H and C-4‴H), 7.51 (1H, d, $J=7.4$ Hz, C-4H) and 7.62 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 15.94 ($COOCH_2$-$\mathit{C}H_3$), 63.8 ($COO\mathit{C}H_2CH_3$), 68.8 (C-4′), 80.0 (C-3′), 84.5 (C-5′), 111.75 (C-4″), 117.9 (C-2″ and C-6″), 125.0 (C-7), 125.5 (C-5), 127.0 (C-6), 127.2 (C-9), 129.0 (C-5‴), 129.4 (C-6‴), 130.7 (C-4), 131.4 (C-3″ and C-5″), 131.7 (C-4‴), 131.9 (C-2‴), 136.7 (C-1‴), 140.0 (C-8), 142.4 (C-1″), 153.3 (C-3‴), 167.9 (CONH) and 176.0 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1182.

5.4.12. 3′-(3-Chlorophenyl)-4′-ethoxycarbonyl-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6f). Obtained as a light yellow solid (272 mg, 33%), mp 159–160 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3205 (NH), 1729 ($COOC_2H_5$), 1620 (CONH), 1472, 1339, 1292, 1033, 1097 and 841 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.1$ Hz, $COOCH_2C\mathit{H}_3$), 3.69–3.82 (2H, m, $COOC\mathit{H}_2CH_3$), 4.17 (1H, d, $J=9.5$ Hz, C-4′H), 5.23 (1H, d, $J=9.5$ Hz, C-3′H), 6.89–6.99 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.05 (1H, d, $J=7.4$ Hz, C-6‴H) 7.15–7.20 (2H, m, C-4″H and C-5‴H), 7.23–7.33 (3H, m, C-5H, C-6H and C-4‴H), 7.60–7.62 (1H, m, C-4H), 7.73 (1H, br s, C-2‴H) and 8.13 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.3 ($COOCH_2\mathit{C}H_3$), 61.3 ($COO\mathit{C}H_2CH_3$), 64.4 (C-4′), 70.6 (C-3′), 82.9 (C-5′), 110.1 (C-4″), 116.8 (C-2″ and C-6″), 123.0 (C-7), 123.3 (C-5), 125.4 (C-9), 125.9 (C-6), 126.3 (C-5‴), 127.8 (C-6‴), 128.6 (C-4, C-3″ and C-5″), 130.2 (C-4‴), 130.6 (C-2‴), 134.8 (C-1‴), 140.5 (C-8), 141.0 (C-1″), 149.4 (C-3‴), 167.2 (CONH) and 174.6 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{35}ClO_4$: 448.1190. Found: 448.1183.

5.4.13. 3′-(3-Bromophenyl)-5′-ethoxycarbonyl-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5g). Obtained as a light yellow solid (83 mg, 9%), mp 160–161 °C (from petroleum ether–ethyl acetate), R_f: 0.36 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3284 (NH), 1739 ($COOC_2H_5$), 1618 (CONH), 1469, 1231, 1073, 753 and 694 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, $J=7.0$ Hz, $COOCH_2C\mathit{H}_3$), 3.80–3.98 (2H, m, $COOC\mathit{H}_2CH_3$), 5.24 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.69 (1H, d, $J=7.7$ Hz, C-7H), 6.91–7.12 (6H, m, C-2″H, C-3″H, C-5″H, C-6″H, C-2‴H and C-6‴H), 7.19–7.23 (2H, m, C-4″H and C-5‴H), 7.25–7.30 (2H, m, C-5H and C-6H) 7.47–7.51 (2H, m, C-4H and C-4‴H) and 7.89(1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.5 ($COOCH_2\mathit{C}H_3$), 61.4 ($COO\mathit{C}H_2CH_3$), 66.5 (C-4′), 77.6 (C-3′), 82.2 (C-5′), 109.4 (C-4″), 115.5 (C-2″ and C-6″), 122.5 (C-7), 123.1 (C-5), 124.7 (C-9), 125.1 (C-6), 127.0 (C-4), 129.0 (C-3″ and C-5″), 129.3 (C-6‴), 129.6 (C-5‴), 129.8 (C-4‴), 131.2 (C-2‴), 137.9 (C-8 and C-1‴), 140.1 (C-1″), 150.9 (C-3‴), 165.5 (CONH) and 173.8 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{79}BrO_4$: 492.0685. Found: 492.0696.

5.4.14. 3′-(3-Bromophenyl)-4′-ethoxycarbonyl-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6g). Obtained as a light yellow solid (402 mg, 44%) mp 145–146 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3206 (NH), 1730 ($COOC_2H_5$), 1620 (CONH), 1474, 1338, 1192, 1027 and 834 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, $J=7.0$ Hz, $COOCH_2C\mathit{H}_3$), 3.67–3.84 (2H, m, $COOC\mathit{H}_2CH_3$), 4.20 (1H, d, $J=9.5$ Hz, C-4′H), 5.25 (1H, d, $J=9.5$ Hz, C-3′H), 6.90–7.00 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.04 (1H, d, $J=7.2$ Hz, C-6‴H), 7.15–7.20 (2H, m, C-4″H and C-5‴H), 7.23–7.29 (2H, m, C-5H and C-6H), 7.44–7.47 (1H, m, C-4‴H), 7.65 (1H, d, $J=7.7$ Hz, C-4H), 7.89–7.90 (1H, m, C-2‴H) and 8.47 (1H, br s, NH); ^{13}C NMR (300 MHz; $CDCl_3$): δ 13.7 ($COOCH_2\mathit{C}H_3$), 61.7 ($COO\mathit{C}H_2CH_3$), 64.8 (C-4′), 71.1 (C-3′), 83.6 (C-5′), 110.9 (C-4″), 117.2 (C-2″ and C-6″), 123.4 (C-7), 123.7 (C-5), 125.9 (C-9), 126.6 (C-6), 126.9 (C-4), 129.0 (C-3″ and C-5″), 130.9 (C-6‴), 131.1 (C-5‴), 131.1 (C-4‴), 132.0 (C-2‴), 141.2 (C-8 and C-1‴), 141.7 (C-1″), 149.9 (C-3‴), 167.6 (CONH) and 175.6 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_2\ ^{79}BrO_4$: 492.0685. Found: 492.0704.

5.4.15. 5′-Ethoxycarbonyl-3′-(3-nitrophenyl)-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5h). Obtained as a light yellow solid (123 mg, 12%), mp 165–166 °C (from petroleum ether–ethyl acetate), R_f: 0.28 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3310 (NH), 1741 ($COOC_2H_5$), 1619 (CONH), 1474, 1348, 1231, 1076 and 830 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, t, $J=$ 7.0 Hz, $COOCH_2C\mathit{H}_3$), 3.81–3.99 (2H, m, $COOC\mathit{H}_2CH_3$), 5.28 (1H, s, C-3′H), 5.45 (1H, s, C-5′H), 6.68 (1H, d, $J=$ 7.7 Hz, C-7H), 6.87–6.93 (1H, m, C-5‴H), 7.03–7.10 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H),7.29–7.35 (3H, m, C-5H, C-6H and C-4″H), 7.49 (1H, d, $J=7.3$ Hz, C-4H), 7.63–7.67 (2H, m, C-2‴H and C-6‴H), 7.95–7.98 (1H, m, C-4‴H) and 8.16 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.9 ($COOCH_2\mathit{C}H_3$), 61.9 ($COO\mathit{C}H_2CH_3$), 66.9 (C-4′), 77.9 (C-3′), 82.7 (C-5′), 109.9 (C-4″), 116.0 (C-2″ and C-6″), 121.9 (C-7), 123.2 (C-5), 123.5 (C-6), 123.9 (C-6‴), 124.7 (C-9), 127.2 (C-5‴), 129.5 (C-3″ and C-5″), 129.8 (C-4‴), 129.9 (C-2‴), 132.9 (C-4), 138.5 (C-1‴), 140.4 (C-8), 148.5 (C-1″), 150.9 (C-3‴), 165.7 (CONH) and 173.8 ($\mathit{C}OOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1438.

5.4.16. 4′-Ethoxycarbonyl-3′-(3-nitrophenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6h). Obtained as a light yellow solid (356 mg, 42%), mp 159–160 °C (from petroleum ether–ethyl acetate), R_f: 0.32 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3093 (NH), 1730 ($COOC_2H_5$), 1619 (CONH), 1472, 1351, 1198, 1024 and 906 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.68 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 3.66–3.83 (2H, m, $COOCH_2CH_3$), 4.17 (1H, d, J=9.0 Hz, C-4′H), 5.40 (1H, d, J=9.1 Hz, C-3′H), 6.86–6.97 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.05 (1H, d, J=7.3 Hz, C-4″H), 7.12–7.27 (3H, m, C-5H, C-6H and C-6‴H), 7.55 (1H, t, J=7.9 Hz, C-5‴H), 7.87 (1H, br s, NH), 8.07–8.17 (2H, m, C-4H and C-4‴H) and 8.53 (1H, br s, C-2‴H); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.2 ($COOCH_2CH_3$), 61.4 ($COOCH_2CH_3$), 64.2 (C-4′), 70.3 (C-3′), 83.1 (C-5′), 110.3 (C-4″), 116.9 (C-2″ and C-6″), 122.9 (C-7), 123.0 (C-5), 123.3 (C-6), 123.6 (C-6‴), 125.3 (C-9), 126.1 (C-5‴), 128.6 (C-3″ and C-5″), 129.9 (C-4), 130.8 (C-4‴), 133.8 (C-2‴), 140.8 (C-1‴), 141.1 (C-8), 148.6 (C-1″), 148.8 (C-3‴), 167.1 (CONH) and 174.6 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}N_3O_6$: 459.1430. Found: 459.1425.

5.4.17. 5′-Ethoxycarbonyl-3′-(3-florophenyl)-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5i). Obtained as a light yellow solid (93 mg, 11%), mp 169–170 °C (from petroleum ether–ethyl acetate), R_f: 0.35 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3296 (NH), 1741 ($COOC_2H_5$), 1615 (CONH), 1484, 1379, 1296, 1024 and 904 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 3.81–3.98 (2H, m, $COOCH_2CH_3$), 5.24 (1H, s, C-3′H), 5.35 (1H, s, C-5′H), 6.67 (1H, d, J=7.7 Hz, C-7H), 6.78–6.80 (1H, m, C-4″H), 6.92 (1H, t, J=7.0 Hz, C-5‴H), 7.04–7.06 (7H, m, C-4H, C-2″H, C-3″H, C-5″H, C-6″H, C-4‴H and C-6‴H), 7.26–7.30 (2H, m, C-5H and C-6H) and 7.50–7.52 (2H, m, C-2‴H and NH); ^{13}C NMR (300 MHz; $CDCl_3$): δ 13.6 ($COOCH_2CH_3$), 61.4 ($COOCH_2CH_3$), 66.5 (C-4′), 77.7 (C-3′), 82.2 (C-5′), 109.4 (C-4″), 113.7 (d, J=2.9 Hz, C-6‴), 115.1 (d, J=8.2 Hz, C-5‴), 115.6 (C-2″ and C-6″), 122.1 (d, J=22.9 Hz, C-4‴), 122.7 (C-7), 123.2 (C-5), 124.8 (C-9), 127.8 (C-6), 129.0 (C-3″ and C-5″), 129.3 (C-4), 129.9 (d, J=22.4 Hz, C-2‴), 138.3 (d, J=7.9 Hz, C-1‴), 140.2 (C-8), 151.0 (C-1″), 162.7 (d, J=246.8 Hz, C-3‴), 165.6 (CONH) and 173.9 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1492.

5.4.18. 4′-Ethoxycarbonyl-3′-(3-florophenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6i). Obtained as a light yellow solid (185 mg, 23%), mp 144–145 °C (from petroleum ether–ethyl acetate), R_f: 0.38 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3210 (NH), 1730 ($COOC_2H_5$), 1618 (CONH), 1473, 1341, 1229, 1132, 1090 and 961 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.71 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 3.67–3.80 (2H, m, $COOCH_2CH_3$), 4.19 (1H, d, J=9.3 Hz, C-4′H), 5.27 (1H, d, J=9.3 Hz, C-3′H), 6.87 (1H, d, J=7.7 Hz, C-7H), 6.90–7.01 (4H, m, C-2″H, C-3″H, C-5″H and C-6″H), 7.03–7.08 (2H, m, C-4″H and C-5‴H), 7.14–7.19 (2H, m, C-5H and C-6H), 7.31–7.38 (1H, m, C-4‴H) and 7.42–7.50 (3H, m, C-4H, C-2‴H and C-6‴H); ^{13}C (75.5 MHz; $CDCl_3$): δ 13.3 ($COOCH_2CH_3$), 61.3 ($COOCH_2CH_3$), 64.4 (C-4′), 70.7 (C-3′), 83.1 (C-5′), 110.3 (C-4″), 114.8 (d, J=2.9 Hz, C-6‴), 115.4 (d, J=8.0 Hz, C-5‴), 116.9 (C-2″ and C-6″), 123.0 (C-7), 123.3 (C-5), 123.4 (d, J=22.6 Hz, C-4‴), 125.5 (C-9), 126.3 (C-6), 128.6 (C-3″ and C-5″), 130.5 (d, J=21.2 Hz, C-2‴),130.7 (C-4), 141.1 (d, J=6.4 Hz, C-1‴), 141.2 (C-8), 149.4 (C-1″), 162.9 (d, J=246.7 Hz, C-3‴), 167.4 (CONH) and 175.0 ($COOC_2H_5$); HRMS Calcd for $C_{25}H_{21}FN_2O_4$: 432.1485. Found: 432.1464.

5.4.19. 5′-Ethoxycarbonyl-3′-(3-methylphenyl)-2′-phenylspiro[indoline-3,4′-isoxazolidine]-2-one (5j). Obtained as a light yellow solid (126 mg, 15%), mp 158–160 °C (from petroleum ether–ethyl acetate), R_f: 0.32 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3304 (NH), 1733 ($COOC_2H_5$), 1617 (CONH), 1378, 1227, 1076 and 750 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.80 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 2.17 (3H, s, $C_6H_4CH_3$), 3.80–3.98 (2H, m, $COOCH_2CH_3$), 5.24 (1H, s, C-3′H), 5.32 (1H, s, C-5′H), 6.64 (1H, d, J=7.7 Hz, C-7H), 6.87–7.00 (3H, m, C-4″H, C-5‴H and C-6‴H), 7.03–7.10 (5H, m, C-2″H, C-3″H, C-5″H, C-6″H and C-2‴H), 7.22–7.28 (3H, m, C-5H, C-6H and C-4‴H) and 7.54–7.56 (2H, m, C-4H and NH); δ (75.5 MHz; $CDCl_3$) 13.9 ($COOCH_2CH_3$), 21.6 ($C_6H_4CH_3$), 61.6 ($COOCH_2CH_3$), 67.0 (C-4′), 78.6 (C-3′), 82.4 (C-5′), 109.6 (C-4″), 116.0 (C-2″ and C-6″), 122.7 (C-7), 123.2 (C-5), 124.0 (C-6), 125.5 (C-9), 127.5 (C-5‴), 127.6 (C-6‴), 128.4 (C-4‴), 129.1 (C-3″ and C-5″), 129.2 (C-2‴), 129.4 (C-4), 135.6 (C-1‴), 138.2 (C-8), 140.7 (C-1″), 151.7 (C-3‴), 166.2 (CONH) and 174.8 ($COOC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1720.

5.4.20. 4′-Ethoxycarbonyl-3′-(3-methylphenyl)-2′-phenylspiro[indoline-3,5′-isoxazolidine]-2-one (6j). Obtained as a light yellow solid (287 mg, 36%), mp 139–140 °C (from petroleum ether–ethyl acetate), R_f: 0.35 (petroleum ether–ethyl acetate, 3:2); IR (KBr): 3216 (NH), 1732 ($COOC_2H_5$), 1618 (CONH), 1470, 1377, 1293, 1110, 1051 and 906 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$): δ 0.70 (3H, t, J=7.0 Hz, $COOCH_2CH_3$), 2.37 (3H, s, $C_6H_4CH_3$), 3.64–3.81 (2H, m, $COOCH_2CH_3$), 4.24 (1H, d, J=9.7 Hz, C-4′H), 5.22 (1H, d, J=9.7 Hz, C-3′H), 6.87–6.97 (5H, m, C-7H, C-2″H, C-3″H, C-5″H and C-6″H), 7.07–7.17 (4H, m, C-5H, C-6H, C-4″H and C-5‴H), 7.22–7.29 (2H, m, C-4‴H and C-6‴H), 7.48–7.54 (2H, m, C-4H and C-2‴H) and 8.00 (1H, br s, NH); ^{13}C NMR (75.5 MHz; $CDCl_3$): δ 13.2 ($COOCH_2CH_3$), 21.3 ($C_6H_4CH_3$), 61.0 ($COOCH_2CH_3$), 64.5 (C-4′), 71.3 (C-3′), 82.9 (C-5′), 110.1 (C-4″), 116.8 (C-2″ and C-6″), 122.8 (C-7), 122.9 (C-5), 124.9 (C-6), 125.7 (C-9), 126.3 (C-4), 128.2 (C-6‴), 128.3 (C-3″ and C-5″), 128.7 (C-5‴), 129.0 (C-4‴), 130.5 (C-2‴), 138.1 (C-1‴), 138.6 (C-8), 141.1 (C-1″), 149.8 (C-3‴), 167.3 (CONH) and 175.1 ($COOC_2H_5$); HRMS Calcd for $C_{26}H_{24}N_2O_4$: 428.1736. Found: 428.1718.

6. X-ray crystallography

The crystallographic measurements on compounds **3**, **5a** and **6c** were made using a Siemens SMART area-detector diffractometer. Graphite monochromated Mo-K_α radiation was used in all cases. The structures were solved using SHELXTL-PLUS[32] and refined with SHELXL-96.[33]

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Silicaphosphine (Silphos): a filterable reagent for the conversion of alcohols and thiols to alkyl bromides and iodides

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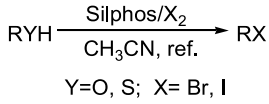
Abstract—Silicaphosphine (Silphos), $[P(Cl)_{3-n}(SiO_2)_n]$, as a new heterogeneous reagent is introduced. This reagent converts alcohols and thiols to their corresponding bromides and iodides in the presence of X_2 (X = Br, I) in refluxing CH_3CN in high to quantitative yields. Use of Silphos provides a highly practical method for the easy separation of the Silphos oxide byproduct by a simple filtration.

1. Introduction

The conversion of alcohols to alkyl halides with tertiary phosphines and different sources of halogens has widely been studied.[1–9] A common drawback of all these systems is the formation of a stoichiometric amount of phosphine-oxide as a byproduct, of which its separation from the reaction mixture is usually a difficult task and requires time consuming column or more frequently plate chromatography techniques. As a solution to this problem, the use of expensive and not easily available reagents such as polymer-supported triphenylphosphine,[5a,10–12] or tris[4-(1*H*,1*H*-perfluorooctyloxyphenyl)] phosphine[13] is reported. The use of diphos-1,2-bis (diphenylphosphino-ethane),[14] as another source of phosphine for this purpose still has the technical problem that only 75% of diphos oxide can be removed under the most suitable conditions.

2. Results and discussion

Recently, we reported on the application of Ph_3P in the presence of *N*-halosuccinimides[15] or DDQ[16] for the conversion of alcohols and thiols into alkyl halides. In continuation of this work on the use of phosphines in organic synthesis, and in order to advance the problems encountered with the isolation process of the byproduct phosphine oxide, we now introduce silicaphosphine (Silphos), $[P(Cl)_{3-n}(SiO_2)_n]$, as a cheap, easily prepared, and stable reagent which can be used as a new source of filterable phosphine. This reagent was successfully applied for the efficient conversion of alcohols and thiols to their corresponding bromides and iodides with molecular bromine and iodine in refluxing CH_3CN as the most suitable solvent (Scheme 1).



Scheme 1. Conversion of alcohols and thiols to their corresponding bromides and iodides.

In order to select the best supporting bed and conditions for the preparation of a suitable phosphine reagent, we first reacted different types of silica and alumina with excess of $P(OEt)_3$ under argon atmosphere. The obtained results are shown in Table 1. From all these reactions, the reagent which was obtained after filtration, washing with dry CH_2Cl_2 and drying, showed a considerable weight increase. As demonstrated in Table 1, the weight increase in the cases of using plate silica gel is considerably higher. The use of these supported phosphine reagents (Table 1, entries 1–4), in conjunction with molecular bromine for the conversion of benzyl alcohol to benzyl bromide was found to be unsuitable, since the formation of some undesired products also occurred as side reactions. We then chose plate silica gel and reacted it with $P(OEt)_3$ with stoichiometry of 3:1. The maximum replacement of –OEt groups with hydroxyl groups of silica was obtained after 6 days heating in an oil bath at 100–110 °C. The reagent which was obtained under

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Table 1. Preparation of different supported reagents using $P(OEt)_3$ and their uses for transformation of benzyl alcohol to benzyl bromide

Entry	Supporting bed[a]	Molar ratio of supporting bed/ $P(OEt)_3$[b]	Reaction time (day)	% of weight increase	Reaction time and conversion yield for transformation of benzyl alcohol to benzyl bromide
1	Aluminum oxide 150, basic	Excess of $P(OEt)_3$	7	22–25	3 h, mixture of benzyl bromide (45%)+side products [d] (30%)
2	Column SiO_2-gel	Excess of $P(OEt)_3$	7	16–18	3 h, mixture of benzyl bromide (40%) +side products [d] (35%)
3	Activated plate SiO_2-gel[c]	Excess of $P(OEt)_3$	7	28–31	3 h, mixture of benzyl bromide (45%) +side products[d] (25%)
4	Plate SiO_2-gel	Excess of $P(OEt)_3$	7	38–42	1 h, mixture of benzyl bromide (70%) +side products[d] (30%)
5	Dried plate SiO_2-gel	3:1[$P(OEt)_3$]	4	28–32	45 min, mixture of benzyl bromide (70%)+side products[d] (30%)
6	Dried plate SiO_2-gel	3:1[$P(OEt)_3$]	5	24–26	0.5 h, mixture of benzyl bromide (90%)+side products[d] (10%)
7	Dried plate SiO_2-gel	3:1[$P(OEt)_3$]	6	20–22	20 min (100%)
8	Dried plate SiO_2-gel	3:1[$P(OEt)_3$]	7	20–22	20 min (100%)

[a] Plate SiO_2-gel (type 60, 15–40 μm) and column SiO_2 gel (type 60, 63–200 μm) were used.
[b] The mixture was heated at 100–110 °C in an oil bath under argon atmosphere. The filtered cake was then washed with CH_2Cl_2, and dried under vacuum.
[c] Silica-gel was activated by refluxing in concentrated HCl for 4 h. It was filtered, washed with CH_2Cl_2 and dried at 200 °C under vacuum.
[d] A mixture of benzaldehyde and dibenzyl ether was produced.

these conditions (Table 1, entry 7) converted benzyl alcohol to benzyl bromide quantitatively in the presence of molecular bromine after 20 min in refluxing acetonitrile. Increase of the reaction time for the preparation of Silphos did not show any change in the efficiency of the reagent (Table 1, entry 8).

Activation and drying of plate silica gel did not lead to a considerable difference in the capacity and reactivity of the obtained reagent.

To reduce the reaction time for the preparation of the reagent, we turned our attention to the use of more reactive PCl_3 instead of $P(OEt)_3$. The optimized conditions for the reaction of plate silica gel and PCl_3 with a stoichiometry of 3:1 are shown in Table 2. The results of this study show that the reaction time for the preparation of Silphos using PCl_3 compared to $P(OEt)_3$ is considerably shorter (30 min and 6 days, respectively). A quantitative conversion of benzyl alcohol to benzyl bromide was observed with this reagent and bromine after 5 min in refluxing acetonitrile.

The structure of Silphos obtained from the reaction of plate silica gel and PCl_3 is not very clear to us. The presence of a Cl atom in the structure of Silphos was determined by titration of the produced HCl by aqueous NaOH. This

Table 2. Preparation of Silphos from silica-gel (type 60, 15–40 μm) and PCl3 with stoichiometry of 3:1 under different conditions and its use for transformation of benzyl alcohol to benzyl bromide

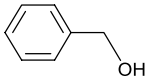
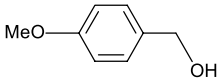
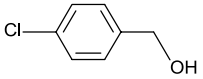
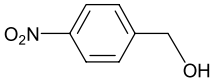
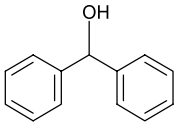
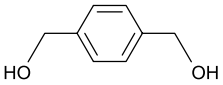
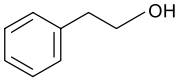
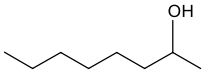
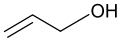
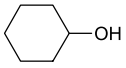
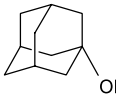
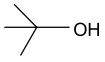
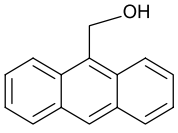
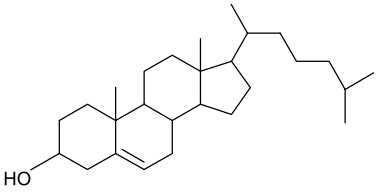
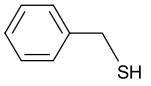
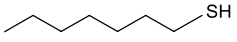
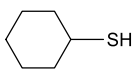
Entry	Different conditions for preparation of Silphos[a]			% Conversion of benzyl alcohol to benzyl bromide after 5 min[b]
	Temperature	Time (h)	% of weight increase	
1	rt	0.5	23–25	100
2	rt	1	23–25	100
3	rt	2	23–25	100
4	50–55 °C	0.5	20–23	100
5	50–55 °C	1	20–23	100
6	50–55 °C	2	22–24	100

[a] Reactions were performed under argon atmosphere.
[b] Molar ratio of benzyl alcohol to bromine is 1:1.4 and 1.0 g of Silphos is used in CH_3CN under reflux condition.

Table 3. Different conditions for the reaction of benzyl alcohol (1.0 mmol) with different quantities of Br_2 and Silphos in refluxing acetonitrile

Entry	Br_2 (mmol)+Silphos (g)	Temperature	Time	Conversion (%) to benzyl bromide
1	1+0.2	rt	10 h	20
2	1+0.4	rt	10 h	30
3	1+0.6	rt	10 h	55
4	1.0+1.0	rt	10 h	80
5	1.2+1.0	rt	10 h	100
6	1.2+1.0	Reflux	45 min	100
7	1.4+1.0	Reflux	5 min	100

Table 4. Conversion of alcohols to their corresponding bromides and iodides using 1 g of Silphos in refluxing acetonitrile

Entry	Substrate	Molar ratio of ROH/Br_2 ROH/I_2	Time	Isolated yield (%)[a]
1		1:1.4 1:1.4	5 min 2 min	97 94
2		1:1.4 1:1.4	1 min $<$1 min	99 98
3		1:1.4 1:1.4	3 h 2.5 h	89 90
4		1:2.2[b] 1:2.2[b]	40 min 35 min	92 89
5		1:1.4 1:1.4	30 min 1 h	98 95
6		1:2[c] 1:2[c]	10 min 5 min	97 95
7		1:1.4 1:1.4	25 min 40 min	96 94
8		1:2[c] 1:2[c]	2 h 2 h	91 87
9		1:1.4 1:1.4	10 min 8 min	84 78
10		1:1.4 1:1.4	25 min 20 min	93 91
11		1:1.4 1:1.4	30 min 45 min	95 95
12		1:1.4 1:1.4	35 min 40 min	90 91
13		1:2[c] 1:2[c]	45 min 50 min	97 96
14		1:1.4 1:1.4	40 min 40 min	99 94
15		1:1.4 1:1.4	10 min 5 min	92 95
16		1:1.4 1:1.4	45 min 30 min	90 93
17		1:1.4 1:1.4	40 min 30 min	92 90

[a] All the products are known compounds. The spectral data of the products were compared with those of known samples prepared according to the literature.[16–20]
[b] The amount of Silphos used was 1.4 g.
[c] The amount of Silphos used was 1.2 g.

analysis showed that not all the Cl atoms of PCl_3 are replaced with silica and the general structure of Silphos could be represented as $P(Cl)_{3-n}(SiO_2)_n$. The amount of active phosphorus content of the reagent was determined by reacting Silphos with an excess of molecular bromine in refluxing acetonitrile until the consumption of Br_2 was stopped. On the basis of titration of unreacted bromine by sodium thiosulfate, the phosphorus content of Silphos was determined to be 1 mmol per 0.6 g of the reagent. The IR spectrum (400–4000 cm^{-1}) of the Silphos and plate silica gel are similar and both show a very strong and broad band centered about 1100 cm^{-1} and a strong band centered at 1000 cm^{-1}. However, Silphos oxide which was obtained from the transformation of benzyl alcohol to benzyl halides is similar to the one which was obtained from oxidation of Silphos by aqueous hydrogen peroxide and showed the additional characteristic P═O band as a shoulder about 1300 cm^{-1}.

Since the introduced filterable Silphos $[P(Cl)_{3-n}(SiO_2)_n]$ as an inorganic silica based polymeric phosphine showed excellent reactivity for the conversion of benzyl alcohol to its bromide and provided very simple and practical isolation of the product, we decided to study its applicability as a general reagent for the conversion of different classes of alcohols into their bromides and iodides. We optimized the conditions for the conversion of benzyl alcohol to its corresponding bromide using different ratios of bromine and Silphos (Table 3).

We then applied the optimized conditions for the reaction of structurally different alcohols. By this method, primary, secondary, and tertiary alcohols were converted into their bromides and iodides with excellent yield (Table 4). The presence of electron-withdrawing groups such as –Cl or $–NO_2$ in the substrates increases the reaction time but the yields are still excellent. We also used Silphos for the successful conversion of thiols to their corresponding bromides and iodides in excellent yields under the same reaction conditions as applied for alcohols (Table 4, entries 15–17).

In order to have more insight into the applicability of this method, some competitive reactions were performed between structurally different alcohols in binary mixtures. The results which are tabulated in Table 5 show high selectivity between 1° aliphatic and 1° benzylic alcohols, benzyl alcohol and 4-nitrobenzyl alcohol, and also between 1° and 2° alcohols.

3. Conclusion

The use of Silphos as a cheap, stable and very easily prepared supported reagent provides an attractive and practical method for the clean conversion of alcohols and thiols to their corresponding alkyl bromides and iodides. The work-up is by simple filtration to isolate the product without interference from the Silphos oxide byproduct. The filterable nature of produced Silphos oxide provides a potential application for Silphos as a heterogeneous oxophilic reagent in organic synthesis.

4. Experimental

4.1. General comments

Chemicals were obtained from Merck and Fluka chemical companies. Infrared spectra were recorded on a Perkin–Elmer 781 spectrometer. Nuclear magnetic resonance spectra were recorded on a Brucker Advanced DPX-250 MHz spectrometer using tetramethylsilane as internal standard. The plate silica-gel used for the preparation of Silphos was type 60 (15–40 μm) which was dried in a vacuum oven at 200 °C for 24 h before use.

4.2. General procedure for the preparation of Silphos

Under an argon atmosphere, to a flask containing dried silica-gel (type 60, 15–40 μm) (18.0 g, 0.3 mol) was added PCl_3 (13.8 g, 0.1 mol) at rt and stirred slowly with a mechanical stirrer for 30 min. The mixture was then heated to 60 °C while it was stirring (400 cycle/min) under pressure of argon for 3 h to remove all HCl. The reaction mixture was washed with 50 mL of dry CH_2Cl_2 and dried under vacuum. Silphos was obtained as a white solid (21.6–22.3 g), which was stored in a capped bottle. The reagent can be kept without any change for months. The presence of chloride in the reagent was determined by titration of the produced HCl from the above reaction with 0.1 M aq NaOH. The results obtained from several runs showed the formation of 0.156–0.165 mol of HCl. This shows that not all the chlorine atoms of PCl_3 are replaced and each mole of Silphos could contain 1.35–1.44 mol of chloride atom in its structure. In order to determine the amount of active phosphorus content of the reagent, Silphos was reacted with excess of bromine in acetonitrile and stirred for 1 h under reflux conditions. On the basis of titration of unreacted bromine with an aqueous solution of sodium thiosulfate, the amount of active phosphorus content was determined to be 1 mmol per

Table 5. Competitive reactions of different binary mixtures with Silphos (1 g) and molecular bromine or iodine (1.4 mmol) in refluxing acetonitrile

Entry	Binary mixture of alcohols	Halogen	Time (min)	Conversion % to alkyl halide[a]
1	$PhCH_2OH + PhCH_2CH_2OH$	Br_2	5	90:10
2	$PhCH_2OH + PhCH_2CH_2OH$	I_2	3	85:15
3	$PhCH_2OH + CH_3(CH_2)_5CH(OH)CH_3$	Br_2	5	90:10
4	$PhCH_2OH + CH_3(CH_2)_5CH(OH)CH_3$	I_2	3	88:12
5	$PhCH_2OH$ + 4-NO_2-$C_6H_4CH_2OH$	Br_2 or I_2	5	100:0
6	$PhCH_2CH_2OH + CH_3(CH_2)_5CH(OH)CH_3$	Br_2	5	80:20
7	$PhCH_2CH_2OH + CH_3(CH_2)_5CH(OH)CH_3$	I_2	3	75:25

[a] GC yield using *n*-octane or *n*-nonane as an internal standard.

0.6 g of Silphos; IR (KBr disk) ν (cm^{-1}): 3200, 1100, 1000, 800, 680, and 500.

4.3. A typical procedure for the conversion of benzyl alcohol to benzyl bromide

To a flask containing a stirring mixture of Silphos (3.0 g) and Br_2 (0.67 g, 4.2 mmol) in refluxing dry acetonitrile (20 mL), was added benzyl alcohol (0.324 g, 3 mmol). The orange color of the reaction mixture became yellow after 5 min and GC analysis showed the completion of the reaction. Then, enough powdered sodium thiosulfate was added in portions to the reaction mixture and stirred vigorously to decolorize the unreacted bromine. The mixture was then filtered and the solvent was evaporated under vacuum in a rotary evaporator. Benzyl bromide was obtained as a colorless liquid (0.265 g, 97%, bp 195 °C, lit.[19] bp 196–198 °C). The product was found to be highly pure by GC and NMR analysis. Spectral data for benzyl bromide [100-39-0]; IR (neat) ν (cm^{-1}): 3070, 3060, 3025, 1500, 1440, 1220, 1200, 1050, 1000, 750, 690, 600, ^{1}H NMR ($CDCl_3$) δ (ppm) 7.19–7.36 (5H, m), 4.52 (2H, s); ^{13}C NMR ($CDCl_3$) δ (ppm) 137.4, 129.0, 128.6, 128.3, 33.5.

4.4. A typical procedure for the conversion of allyl alcohol to 3-iodo-1-propene

To a flask containing a stirring mixture of 1 g of Silphos and I_2 (0.36 g, 1.4 mmol) in refluxing dry acetonitrile, was added allyl alcohol (0.06 g, 1 mmol). The progress of the reaction was monitored by GC. After the completion of the reaction (10 min), enough powdered sodium thiosulfate was added with vigorous stirring to react with the unreacted iodine. The mixture was then filtered and the solvent was removed under vacuum. Pure 3-iodo-1-propene was obtained (0.13 g, 78%), bp 100 °C, lit.[19] bp 102 °C. The product was found to be highly pure by GC and NMR analysis. Spectral data for 3-iodo-1-propene [556-56-9], IR (neat) ν (cm^{-1}): 3050, 2970, 2960, 1640, 1430, 1400, 1145, 990, 910, 840, 670. ^{1}H NMR ($CDCl_3$) δ (ppm) 6.0–6.1 (1H, m), 5.27–5.33 (1H, m), 5.09–5.12 (1H, m), 3.89 (2H, d, J= 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm) 135.2, 117.1, 5.3.

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20. Registry number and H NMR ($CDCl_3$, 250 MHz) of the products: **benzyl iodide** [620-05-3], δ (ppm) 7.23–7.39 (5H, m), 4.43 (2H, s); **4-methoxy-benzyl bromide** [2746-25-0], δ (ppm) 6.83–7.27 (4H, m), 4.38-4.50 (2H, s), 3.79 (3H,s); **4-methoxy benzyl iodide** [70887-29-5], δ (ppm) 6.79–7.32 (4H, m), 4.46 (2H, s), 3.78 (3H, s); **4-chloro benzyl bromide** [622-95-7], δ (ppm) 7.22–7.28 (4H, m), 4.42 (2H, s); **4-chloro-benzyl iodide** [35424-56-7], δ (ppm) 7.23–7.32 (4H, m), 4.49 (2H, s); **4-nitro benzyl bromide** [100-1108], δ (ppm) 7.50–8.12 (4H, m), 4.45 (2H, s); **4-nitro benzyl iodide** [3145-86-6], δ (ppm) 7.50–8.23 (4H, m), 4.48 (2H, s); **1,1-diphenyl methyl bromide** [776-74-9], δ (ppm) 7.44–7.50 (10H, m), 6.04 (1H, s); **1,1-diphenyl methyl iodide** [Ref. No. 17,18] δ (ppm) 7.20–7.32 (10H, m), 6.17 (1H, s); **α,α'-dibromo-p-xylene** [623-24-5], δ (ppm) 7.20–7.28 (4H, m), 4.43 (4H, s); **α,α'-diiodo-p-xylene**, δ (ppm) 7.15–7.18 (4H, m), 4.39 (4H, s); **1-bromo-2-phenyl ethane** [103-63-9], δ (ppm) 7.08–7.17 (5H, m), 3.36–3.42 (2H, m), 2.99–3.15 (2H, m); **1-iodo-2-phenyl-ethane** [17376-04-4], δ (ppm) 7.00–7.12 (5H, m), 3.30–3.35 (2H, m), 2.91–2.95 (2H, d, m); **2-bromo octane** [557-35-7], δ (ppm) 3.82–3.91 (1H, m), 1.66–1.68 (3H, m), 1.43–1.63 (2H, m), 1.07 (2H, m), 1.28–1.30 (6H, m), 0.85–0.87 (3H, m); **2-iodo octane** [557-36-8], δ (ppm) 3.85–3.92 (1H, m), 1.66–1.69 (3H, m), 1.45–1.65 (2H, m), 1.09 (2H, m), 1.28–1.31 (6H, m), 0.87–0.89 (3H, m); **3-bromo-1-propene** [106-95-6], δ (ppm) 5.96–6.02 (1H, m), 5.26–5.31 (1H, m), 5.09-5.12 (1H, m), 3.87 (2H, d, J=7.2); **bromo-cyclohexane** [108-85-0], δ (ppm) 3.32 (1H, m), 1.38–1.72 (6H, m), 0.81–0.96 (4H, m); **iodo cyclohexane** [626-62-0], δ (ppm) 3.89 (1H, m), 1.40–1.75 (6H, m), 0.85-0.99 (4H, m); **adamantyl bromide** δ (ppm) 2.31 (6H, s), 2.08 (3H, s), 1.73 (6H, s); **adamantyl iodide** [768-90-1], δ (ppm) 2.40 (6H, s), 2.20 (3H, s), 1.85 (6H, s); **2-bromo-2-methyl propane** [507-19-7], δ (ppm) 1.76 (9H, s); **2-iodo-2-methyl propane** [558-17-8], δ (ppm) 1.81 (9H, s); **9-bromomethyl anthracene** [2417-77-8], δ (ppm) 8.43 (1H, s), 7.72–7.76 (4H,

m), 7.58–7.61 (2H, m), 7.23–7.27 (2H, m), 4.98 (2H, s); **9-iodomethyl-anthracene** [260365-89-7], δ (ppm) 8.44 (1H, s), 7.72–7.77 (4H, m), 7.58–7.62 (2H, m), 7.25–7.30 (2H, m), 5.05 (2H, s); **3-bromocholest-5-ene** [516-91-6], δ (ppm) 5.42 (1H, s), 4.01 (1H, s), 2.50–2.70 (2H, m), 0.70-2.20 (41H, complex); **3-iodocholest-5-ene** [2930-80-5], δ (ppm) 5.45 (1H, s), 4.03 (1H, s), 2.60-2.85 (2H, m), 0.78–2.31 (41H, complex); **1-bromo octane** [111-83-1], δ (ppm) 3.36–3.38 (2H, m), 1.21–1.32 (12H, m), 0.90–0.94 (3H, m); **1-iodo octane** [629-27-6], δ (ppm) 3.29–3.32 (2H, m), 1.27–1.35 (12H, m), 0.91–0.94 (3H, m).